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Sex differences in the outcome after percutaneous coronary intervention – A propensity matching analysis

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ABSTRACT

Background: Whether there are sex differences in the outcome of patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) remains controversial. We undertook this study to assess whether there are sex-related differences in the long-term mortality in a large series of patients with CAD after PCI.

Methods: The study included 18,334 patients (4735 women and 13,599 men) with CAD treated with PCI. Propensity matching was performed to obtain a group of patients (3000 women and 3000 men) matched for all characteristics available in database. The primary outcome was a composite of cardiac mortality, myocardial infarction or stroke at 3 years of follow-up.

Results: The primary outcome occurred in 660 women and 1440 men (Kaplan-Meier [KM] estimates, 15.2% in women and 11.6% in men, unadjusted hazard ratio [HR] = 1.35, 95% confidence interval [CI] 1.24 to 1.49; P < 0.001). Women were at higher risk of all-cause mortality (15.4% vs. 12.3%; P < 0.001), cardiac mortality (10.2% vs. 7.6%; P < 0.001) and stroke (2.6% vs. 1.4%; P < 0.001) than men. In matched patients, the primary outcome occurred in 371 women and 322 men (KM estimates, 13.4% vs. 11.6%, HR = 1.18 [1.01–1.36], P = 0.033). Women were at higher risk of myocardial infarction (4.2% vs. 3.1%; P = 0.044) but not cardiac (8.7% vs. 8.2%; P = 0.306) or all-cause death (12.5% vs. 12.9%; P = 0.991) or stroke (1.9% vs. 1.6%; P = 0.550) than men.

Conclusions: After propensity matching, women remained at a higher risk of a composite of cardiac mortality, myocardial infarction or stroke up to 3 years after PCI than men.

1. Introduction

The Framingham Study suggested the existence of striking sex-related differences in the clinical presentation and prognosis of patients with coronary artery disease (CAD) and a distinctly worse prognosis in women than men in terms of higher risk of early mortality or myocardial infarction within 5 years after an acute myocardial infarction [1,2]. Subsequent studies evidenced a plethora of sex-related disparities encompassing almost all aspects of CAD [3,4]. Many changes have occurred in the diagnosis, therapy, risk assessment and secondary prevention after an acute CAD event, yet the knowledge on the sex-related differences in CAD presentation or response to therapy remain controversial. Numerous studies have shown that, compared with men, women have an older age at presentation, present later after symptom, have less obstructive angiographic CAD, have a worse cardiovascular risk profile including more frequent diabetes and chronic kidney disease, are less likely to undergo coronary angiography or receive revascularization procedures or medications known to reduce mortality and have an increased susceptibility to procedure-related complications in case of invasive treatment [3–5]. With respect to the outcome following percutaneous coronary intervention (PCI), an increased risk of mortality or major adverse cardiovascular events (MACE) in women compared with men which is attenuated (or abolished) following adjustment for baseline characteristics has frequently been reported [6–10]. Studies that have assessed sex differences in the long-term outcome after PCI have reported similar [8,11,12] worse [13–15] or even better [16,17] prognostic outcomes in women. Against this background, we undertook this study to assess whether there are sex-related differences in the long-term mortality in patients with CAD undergoing PCI.

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2. Methods

2.1. Study patients

The study included 18,334 consecutive patients (4735 women) with symptomatic CAD admitted for PCI in 2 German hospitals between January 2000 and January 2011. Patients undergoing coronary artery bypass surgery during the index hospitalization were excluded. Clinical and angiographic data were prospectively collected and stored in a dedicated database [18]. By design, the study represents a retrospective analysis. Overall there were 8745 patients presenting with an acute coronary syndrome and 9589 patients presenting with stable CAD. All patients gave written informed consent for angiographic examination and PCI. The study conforms to the Declaration of Helsinki.

2.2. Angiographic examination and PCI

Coronary angiography and PCI were performed according to the standard criteria. Off-line analysis of digital angiograms was performed in the core laboratory using an automated edge detection system (CMS; Medis Medical Imaging Systems, Neuen, the Netherlands) by personnel blinded to the clinical data. Angiographic analysis was performed according to the modified American College of Cardiology/American Heart Association Stenosis Morphology Classification [19]. The B2 and C lesions were considered as complex. Left ventricular ejection fraction was calculated using the area-length method [20]. Coronary stenting was performed as per standard practice. Bare-metal (n = 7605 patients) or drug-eluting (n = 10,729 patients) stents were implanted. All patients received 325 to 500 mg of aspirin and a loading dose of 600 mg of clopidogrel before procedure. Unfractionated heparin or bivalirudin was used periprocedurally as per standard practice. Post-PCI antithrombotic therapy included aspirin (80–325 mg/day continuously) and clopidogrel (150 mg/day until discharge but for no longer than 3 days followed by 75 mg/day for at least 1 month after bare-metal stent, ≥6 months after drug-eluting stent implantation and ≥12 months in patients with acute coronary syndromes). Other medications were left at the discretion of patient's physician.

2.3. Study definitions

The diagnosis of CAD was based on clinical criteria and it was confirmed by coronary angiography in all included patients. Cardiovascular risk factors were defined as follows: arterial hypertension – documentation of the systolic blood pressure of ≥140 mm Hg or the diastolic blood pressure of ≥90 mm Hg or active treatment with anti-hypertensive drugs; hypercholesterolemia – documentation of total cholesterol of 220 mg/dL or greater or prior or ongoing treatment with lipid-lowering agents; diabetes mellitus - history of diabetes with active treatment with oral hypoglycaemic agents or insulin or documentation of an abnormal fasting blood glucose (≥126 mg/dL or ≥7.0 mmol/L) or glucose tolerance test (≥200 mg/dL or ≥11.1 mmol/L) according to the World Health Organization criteria for diabetes or a blood glucose >200 mg/dL at any time; current smoking - regular use of any type of tobacco in the prior 6 months. Patients' weight and height were measured during the index hospitalization and used to calculate the body mass index. Renal function was assessed by calculating the estimated glomerular filtration rate using the Cockcroft–Gault equation [21]. Bleeding events were classified according to the Thrombolysis in Myocardial Infarction group criteria [22]. Periprocedural myocardial infarction was defined as an increase in creatine-kinase myocardial band (CK-MB) >3 times upper limit of normal (50% increase above the most recent level in those with elevated CK-MB) within 24 h of PCI in the presence of ischemic symptoms or new ST-segment abnormalities or Q waves developing after PCI.

2.4. Study outcomes and follow-up

The primary outcome was a composite of 3-year cardiac death, myocardial infarction or stroke. Individual components of primary outcome, target lesion revascularization (repeat PCI or coronary artery bypass surgery), stent thrombosis or all-cause mortality at 3 years were also assessed. All inhospital and 30-day outcomes were analyzed. Cardiac death was defined according to the Academic Research Consortium criteria [23] and included any death due to proximate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. The diagnosis of myocardial infarction required clinic-based documented occurrence of myocardial infarction (including periprocedural myocardial infarction) or development of new abnormal Q waves in ≥2 contiguous precordial or ≥2 adjacent limb leads occurring during the follow-up. The diagnosis of stroke required the development of an acute neurological event of at least 24 h of duration, with focal signs and symptoms and without evidence supporting any alternative explanation; the diagnosis required confirmation by computed tomography or magnetic resonance imaging of the head. Target lesion revascularization was defined as clinically indicated (ischemia-driven) percutaneous or surgical revascularization of the index lesion during the follow-up. Definite stent thrombosis was defined as presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion [23]. Information on mortality was obtained from the hospital records, death certificates, or telephone contact with the referring physician(s), relatives of the patient, insurance companies, or registration of address office.

Patients were visited by their physician or interviewed by telephone at 30 days, 6 months, 1 year and yearly thereafter after the PCI procedure. Patients with cardiac complaints underwent a complete clinical, electrocardiographic, and laboratory evaluation any time during the follow-up. The collection of follow-up information and adjudication of events was performed by medical personnel unaware of patients' clinical data.

2.5. Statistical analysis

Data are presented as mean ± standard deviation, median with 25th to 75th percentiles, counts or proportions (%). The normality of distribution of continuous data was tested with the Kolmogorov-Smirnov test. Continuous data were compared with the *t*-test or Wilcoxon rank-sum test, depending on the sample distribution pattern. Categorical data were compared with the chi-square test. Survival analysis was performed with the Kaplan-Meier method and univariable Cox proportional hazards model. Propensity matching analysis was used to select an equal number of women and men patients (n = 3000 patients per group) who were matched based upon their propensity scores for baseline characteristics available in database. All variables of Table 1 were included in the analysis. Landmark analysis with a prespecified landmark at 30 days was performed to assess early and late risk of primary outcome in women and men. All analyses were performed using the R 2.15.1 Statistical Package (The R foundation for Statistical Computing, Vienna, Austria). A two-sided P-value <0.05 was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

The study included 18,334 patients: 4735 women and 13,599 men. Baseline characteristics of patients are shown in Table 1. As seen, women were older and were more likely to have diabetes, arterial

Table 1
Baseline clinical and angiographic characteristics.

Characteristic	All patients (n = 18,334)		P value	Propensity matching groups (n = 6000)		P value
	Women (n = 4735)	Men (n = 13,599)		Women (n = 3000)	Men (n = 3000)	
Age (years)	71.5 ± 11.2	65.3 ± 10.7	<0.001	67.8 ± 10.5	67.9 ± 10.0	0.604
Body mass index (kg/m^2)	26.6 ± 4.0	27.3 ± 4.9	<0.001	27.0 ± 5.1	27.0 ± 3.8	0.706
Diabetes mellitus	1410 (29.8)	3350 (24.6)	<0.001	797 (26.6)	800 (26.7)	0.930
Arterial hypertension	3447 (72.8)	8294 (61.0)	<0.001	1983 (66.1)	2044 (68.1)	0.100
Hypercholesterolemia (≥220 mg/dL)	2942 (62.1)	8197 (60.3)	0.024	1807 (60.2)	1832 (61.1)	0.509
Current smoker	724 (15.3)	3137 (23.1)	<0.001	595 (19.8)	574 (19.1)	0.494
Previous MI	841 (17.8)	3585 (26.4)	<0.001	685 (22.3)	674 (22.5)	0.734
Previous CABG	369 (7.8)	1761 (12.9)	<0.001	336 (11.2)	345 (11.5)	0.714
Acute coronary syndrome	2372 (50.1)	6373 (46.9)	<0.001	1410 (47.0)	1399 (46.6)	0.776
Stable coronary artery disease	2363 (49.9)	7226 (53.1)		1590 (53.0)	1601(53.4)	
Glomerular filtration rate (ml/min)	65.53 ± 29.3	85.9 ± 33.1	<0.001	76.3 ± 29.7	77.3 ± 26.2	0.175
Number of affected coronary arteries			<0.001			0.955
1	1422 (30.0)	3068 (22.6)		724 (24.1)	716 (23.9)	
2	1415 (29.9)	3930 (28.9)		866 (28.9)	875 (29.2)	
3	1898 (40.1)	6601 (48.5)		1748 (47.0)	1409 (46.9)	
Multivessel disease	3313 (70.0)	10,531 (77.4)	<0.001	2276 (75.9)	2284 (76.1)	0.809
Baseline TIMI flow grade[a]			0.021			0.213
0	527/4569 (11.5)	1713/13079 (13.1)		356/2877 (12.4)	340/2884 (11.8)	
1	210/4569 (4.6)	541/13079 (4.1)		230/2877 (4.5)	121/2884 (4.2)	
2	553/4569 (12.1)	1637/13079 (12.5)		338/2877 (11.7)	390/2884 (13.5)	
3	3279/4569 (71.8)	9188/13079 (70.3)		2053/2877 (71.4)	2033/2884 (70.5)	
Complex lesions (ACC/AHA B2, C class)	3637 (76.8)	10,614 (78.0)	0.077	2319 (77.3)	2307 (76.9)	0.712
Chronic occlusion	167 (6.6)	622 (4.6)	0.002	131 (4.4)	132 (4.4)	0.950
Restenotic lesion	172 (3.6)	542 (4.0)	0.279	118 (3.9)	124 (4.1)	0.694
Stent type						
Bare-metal stent	1892 (40.0)	5713 (42.0)	0.014	1240 (41.3)	1270 (42.3)	0.432
Drug-eluting stent (1st generation)	1024 (21.6)	2826 (20.8)	0.219	624 (20.8)	638 (21.3)	0.657
Drug-eluting stent (2nd generation)	1819 (38.4)	5060 (37.2)	0.139	1136 (37.9)	1092 (36.4)	0.240
Balloon diameter (mm)	3.25 ± 0.54	3.38 ± 0.57	<0.001	3.33 ± 0.55	3.34 ± 0.55	0.604
Maximal balloon pressure (atm)	14.2 ± 3.0	14.5 ± 3.1	<0.001	14.5 ± 3.1	14.4 ± 3.0	0.461
Total stented length (mm)	24.2 ± 12.3	25.2 ± 11.7	< 0.001	24.7 ± 12.0	24.8 ± 12.1	0.781
Left ventricular ejection fraction (%)[b]	58.0 [47.0; 64.0]	55.0 [44.0; 62.0]	<0.001	56.0 [45.0; 63.0]	56.0 [45.0; 63.0]	0.993

Data are median [25th; 75th percentiles] or number of patients (%). ACC/AHA = American College of Cardiology/American Heart Association; CABG = coronary artery bypass graft; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.
[a] Available in in 17,648 patients (5761 patients propensity matching groups).
[b] Available in 4126 women and 11,849 men.

hypertension, hypercholesterolemia and present with an acute coronary syndrome compared with men. Women had a lower body mass index and glomerular filtration rate and were less likely to be a current smoker, have multivesssel disease, chronic occlusion, previous myocardial infarction or coronary artery bypass surgery. Balloon diameter, maximal balloon pressure and total stented length were smaller in women than men. Women had significantly better left ventricular ejection fraction compared with men. In propensity matching groups, characteristics were balanced and none of them differed significantly between women and men (Table 1).

3.2. Inhospital outcome and periprocedural complications

Inhospital outcome is shown in Table 2. Women showed a higher risk of cardiac mortality, all-cause mortality or bleeding even after matching.

Table 2
In hospital outcome and procedural complications.

	All patients		P value	Propensity matching groups		P value
	Women (n = 4735)	Men (n = 13,599)		Women (n = 3000)	Men (n = 3000)	
Cardiac death, MI or stroke	213 (4.5)	425 (3.1)	<0.001	125 (4.2)	91 (3.0)	0.018
Cardiac death or MI	192 (4.1)	389 (2.9)	<0.001	116 (3.9)	81 (2.7)	0.011
Cardiac deaths	102 (2.1)	183 (1.3)	<0.001	62 (2.1)	39 (1.3)	0.021
Myocardial infarction	99 (2.0)	218 (1.6)	0.026	61(2.0)	46 (1.5)	0.143
Stroke	22 (0.5)	38 (0.3)	0.054	9 (0.3)	10 (0.3)	0.818
TLR	28 (0.6)	65 (0.5)	0.344	19 (0.6)	16 (0.5)	0.611
Repeat PCI	22 (0.5)	50 (0.4)	0.358	14 (0.5)	11 (0.4)	0.578
CABG	6 (0.1)	16 (0.1)	0.876	5 (0.2)	5 (0.2)	0.999
Stent thrombosis	11 (0.2)	26 (0.2)	0.587	6 (0.2)	7 (0.2)	0.781
Vessel perforation	27 (0.6)	62 (0.4)	0.329	16 (0.5)	14 (0.4)	0.714
Residual dissection	184 (3.9)	481 (3.5)	0.268	130 (4.3)	104 (3.5)	0.083
Any bleeding	212 (4.4)	272 (2.0)	<0.001	107 (3.6)	65 (2.2)	0.001
Major bleeding	75 (1.6)	97 (0.7)	<0.001	34 (1.1)	19 (0.6)	0.038
All-cause deaths	109 (2.3)	194 (1.4)	<0.001	67 (2.2)	39 (1.3)	0.006

Data are number of patients (%); CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization.

Table 3
Clinical outcome.

Outcome	All patients (n = 18,334)				Propensity matching groups (n = 6000)			
	Events		Unadjusted HR [95% CI]	P value	Events		HR [95% CI]	P value
	Women (n = 4735)	Men (n = 13,599)			Women (n = 3000)	Men (n = 3000)		
Thirty-day outcome								
Cardiac death, MI or stroke	348 (7.4)[a]	703 (5.2)	1.44 [1.27–1.64]	<0.001	197 (6.6)	138 (4.6)	1.45 [1.16–1.80]	<0.001
Cardiac death or MI	296 (6.3)	639 (4.7)	1.34 [1.17–1.54]	<0.001	171 (5.7)	120 (4.0)	1.44 [1.14–1.82]	0.002
Cardiac deaths	197 (4.2)	373 (2.8)	1.53 [1.29–1.82]	<0.001	112 (3.8)	72 (2.4)	1.57 [1.17–2.11]	0.003
Myocardial infarction	121 (2.6)	313 (2.3)	1.12 [0.91–1.38]	0.287	72 (2.4)	57 (1.9)	1.28 [0.90–1.81]	0.169
Stroke	62 (1.4)	76 (0.6)	2.37 [1.69–3.12]	<0.001	30 (1.0)	18 (0.6)	1.69 [0.94–3.02]	0.080
TLR	62 (1.3)	211 (1.6)	0.85 [0.64–1.13]	0.265	41 (1.4)	43 (1.5)	0.96 [0.63–1.48]	0.864
Repeat PCI	52 (1.1)	182 (1.4)	0.83 [0.61–1.13]	0.229	34 (1.2)	36 (1.2)	0.95 [0.60–1.53]	0.844
CABG	11 (0.2)	31 (0.2)	1.03 [0.52–2.05]	0.937	8 (0.3)	7 (0.2)	1.15 [0.42–3.18]	0.783
Stent thrombosis	30 (0.7)	107 (0.8)	0.81 [0.54–1.22]	0.314	17 (0.6)	16 (0.5)	1.07 [0.54–2.13]	0.837
All-cause deaths	240 (5.1)	446 (3.3)	1.56 [1.33–1.82]	<0.001	137 (4.6)	87 (2.9)	1.59 [1.22–2.08]	<0.001
Three-year outcome								
Cardiac death, MI or stroke	660 (15.2)	1440 (11.6)	1.35 [1.24–1.49]	<0.001	371 (13.4)	322 (11.6)	1.18 [1.01–1.36]	0.033
Cardiac death or MI	572 (13.3)	1298 (10.5)	1.30 [1.18–1.43]	<0.001	331 (12.0)	285 (10.3)	1.19 [1.01–1.39]	0.035
Cardiac deaths	434 (10.2)	922 (7.6)	1.39 [1.24–1.56]	<0.001	239 (8.7)	221 (8.2)	1.10 [0.92–1.32]	0.306
Myocardial infarction	182 (4.2)	485 (3.8)	1.10 [0.92–1.30]	0.280	114 (4.2)	87 (3.1)	1.33 [1.01–1.76]	0.044
Stroke	108 (2.6)	170 (1.4)	1.87 [1.47–2.39]	<0.001	49 (1.9)	44 (1.6)	1.13 [0.75–1.70]	0.550
TLR	800 (19.8)	2740 (23.0)	0.85 [0.78–0.92]	<0.001	535 (20.8)	597 (22.5)	0.90 [0.80–1.01]	0.066
Repeat PCI	749 (18.6)	2578 (21.7)	0.84 [0.78–0.92]	<0.001	500 (19.5)	564 (21.4)	0.89 [0.78–1.00]	0.051
CABG	62 (1.5)	199 (1.7)	0.92 [0.70–1.22]	0.569	42 (1.6)	38 (1.4)	1.13 [0.73–1.75]	0.591
Stent thrombosis	57 (1.4)	189 (1.5)	0.88 [0.66–1.19]	0.403	35 (1.4)	32 (1.1)	1.11 [0.69–1.80]	0.665
All-cause deaths	656 (15.4)	1493 (12.3)	1.30 [1.19–1.43]	<0.001	340 (12.5)	346 (12.9)	1.00 [0.86–1.16]	0.991

CABG = coronary artery bypass graft; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization.
[a] Numbers in parentheses are Kaplan-Meier estimates.

3.3. Thirty-day outcome

Thirty-day outcome is shown in Table 3. At 30 days, the composite of cardiac death, myocardial infarction or stroke occurred in 348 women and 703 men (Kaplan-Meier [KM] estimates, 7.4% in women and 5.2% in men, unadjusted hazard ratio [HR] = 1.44, 95% confidence interval [CI] 1.27 to 1.64; P < 0.001). With respect to individual components, women had a significant 53% higher risk of cardiac mortality, a significant 2.37-fold increase in the risk of stroke and a significant 56% increased risk of all-cause mortality compared with men. Any bleeding occurred in 252 women and 324 men (5.3% vs. 2.4%; P < 0.001), major bleeding occurred in 97 women and 123 men (2.0% vs. 0.9%; P < 0.001) and minor bleeding occurred in 155 women and 201 men (3.3% vs. 1.5%; P < 0.001).

In matched groups, the composite of cardiac death, myocardial infarction or stroke occurred in 197 women and 138 men (KM estimates, 6.6% and 4.6% (HR = 1.45 [1.16–1.80]; P < 0.001). As compared with men, women had a significant 57% higher risk of cardiac mortality, a significant 44% higher risk of cardiac death or myocardial infarction and a significant 59% higher risk of all-cause mortality (Table 3). Any bleeding occurred in 130 women and 74 men (4.3% vs. 2.5%; P < 0.001), major bleeding occurred in 48 women and 23 men (1.6% vs. 0.8%; P = 0.003) and minor bleeding occurred in 82 women and 51 men (2.7% vs. 1.7%; P = 0.006).

3.4. Three-year clinical outcome

Three-year clinical outcome is shown in Table 3. The primary outcome occurred in 660 women and 1440 men (KM estimates, 15.2% in women and 11.6% in men; unadjusted HR = 1.35 [1.24–1.49]; P < 0.001, showing a 35% higher risk of cardiac death, myocardial infarction or stroke in women; Fig. 1). Women had a significant 30% higher risk of cardiac death or myocardial infarction, a significant 39% higher risk of cardiac death, a significant 87% higher risk of stroke and a significant 30% higher risk of all-cause mortality compared with men. The risk for target lesion revascularization was 15% lower in women, almost entirely due to less repeat PCI in women. The risk of myocardial infarction, coronary artery bypass surgery or stent thrombosis appears to differ little between women and men.

In matching groups, the primary outcome occurred in 371 women and 322 men (KM estimates, 13.4% in women and 11.6% in men; HR = 1.18 [1.01–1.36], P = 0.033, showing a significant 18% higher risk in women compared with men; Fig. 1). The composite of cardiac death or myocardial infarction was more frequent in women mostly driven by a higher risk of myocardial infarction. There was a strong trend towards lower risk of target lesion revascularization in women almost entirely driven by a lower frequency of repeat PCI in women. No significant difference was observed in women versus men with respect to the risk of cardiac mortality, stroke, coronary artery bypass surgery, all-cause mortality or stent thrombosis (Table 3).

In the whole group of patients, the landmark analysis showed that from 30 days to 3 years the primary outcome occurred in 312 women and 737 men (KM estimates, 8.5% in women and 6.7% in men, HR = 1.27 [1.11–1.45]; P < 0.001) showing a significantly higher risk in women over this time period. In matched groups, from 30 days to 3 years the primary outcome occurred in 174 women and 184 men (KM estimates, 7.3% in women and 7.4% in men, HR = 0.97 [0.79–1.12], P = 0.787) showing a similar risk of adverse events beyond 30 days in women and men (Fig. 2).

4. Discussion

The principal findings of this study may be summarized as follows: 1) Women have a significantly higher unadjusted risk of all-cause mortality, cardiac mortality or stroke up to 3 years following PCI compared with men. 2) After propensity matching with men, women remained at a higher risk of a composite of cardiac mortality, myocardial infarction or stroke up to 3 years after PCI. 3) The excess risk in women was particularly high in the first 30 days after PCI. 4) There was a significant and progressively widening difference in the risk for adverse cardiovascular events from 30 day to 3 years between unmatched women and men; in matched groups, the difference in the risk from 30 days to 3 years after PCI was abolished.

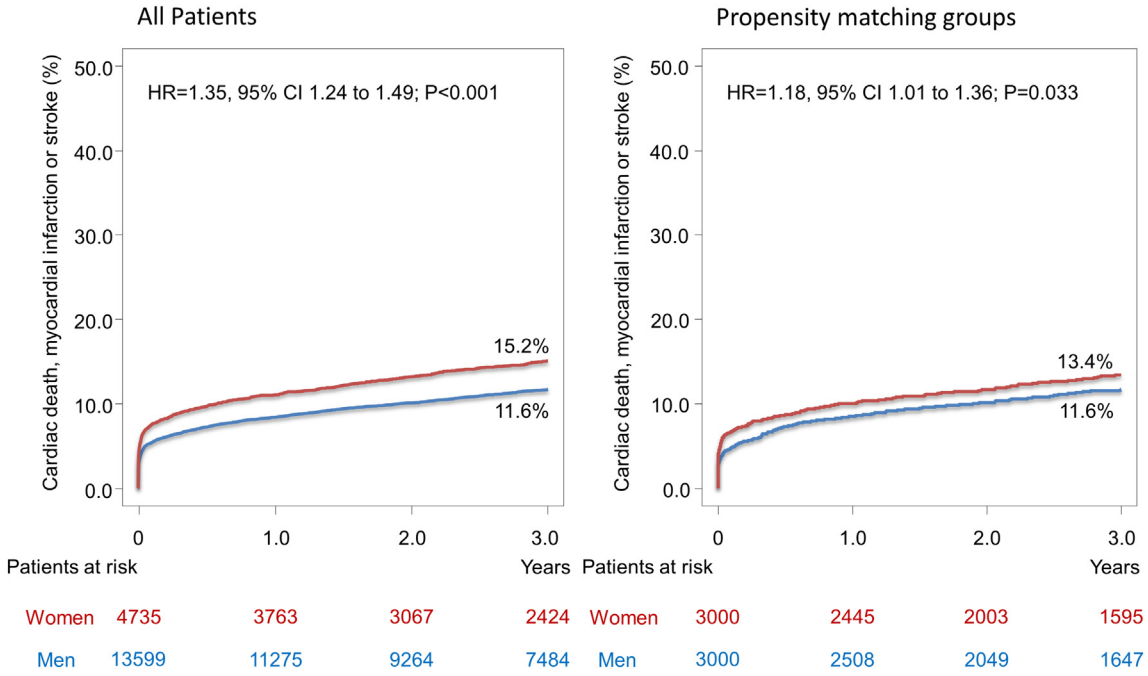

Fig. 1. Kaplan-Meier curves of primary outcome (a composite of cardiac death, myocardial infarction or stroke) in all patients (left panel) and propensity matching groups (right panel). Percentages are Kaplan-Meier estimates; CI = confidence interval; HR = hazard ratio.

The findings of current study support previous studies that have shown a worse prognosis after PCI in women compared with men [13–15]. The excess risk in women has been attributed to a combination of differences in baseline characteristics, received therapy and procedural complications [15]. At the time of PCI, women are older and have a worse cardiovascular risk profile and more comorbidities compared with men [6,7,9,17]. In this regard, our data are consistent with these studies. Multivariable adjustment was commonly used to account for sex differences in baseline data when assessing sex differences in the outcome after PCI. However, the degree of adjustment differs widely across the studies and concerns have been raised that with this approach, residual confounders or hidden comorbidities remain commonly unaccounted for. In the current study we used propensity matching for available characteristics (demographic, clinical and procedural) to create groups of women and men with (propensity score) balanced baseline characteristics. The results of propensity matching-based analyses are conditional only on the observed covariates, so that if many covariates are measured, then one can be fairly confident that unbiased estimates for a given association can be obtained [24]. It may be advantageous to adjustment using multivariable regression particularly because it allows to adjust for a higher number of covariates than in conventional multivariable model [25,26] and depending on the number of variables entered into the propensity analysis, estimates that are rarely statistically different from those obtained by randomization

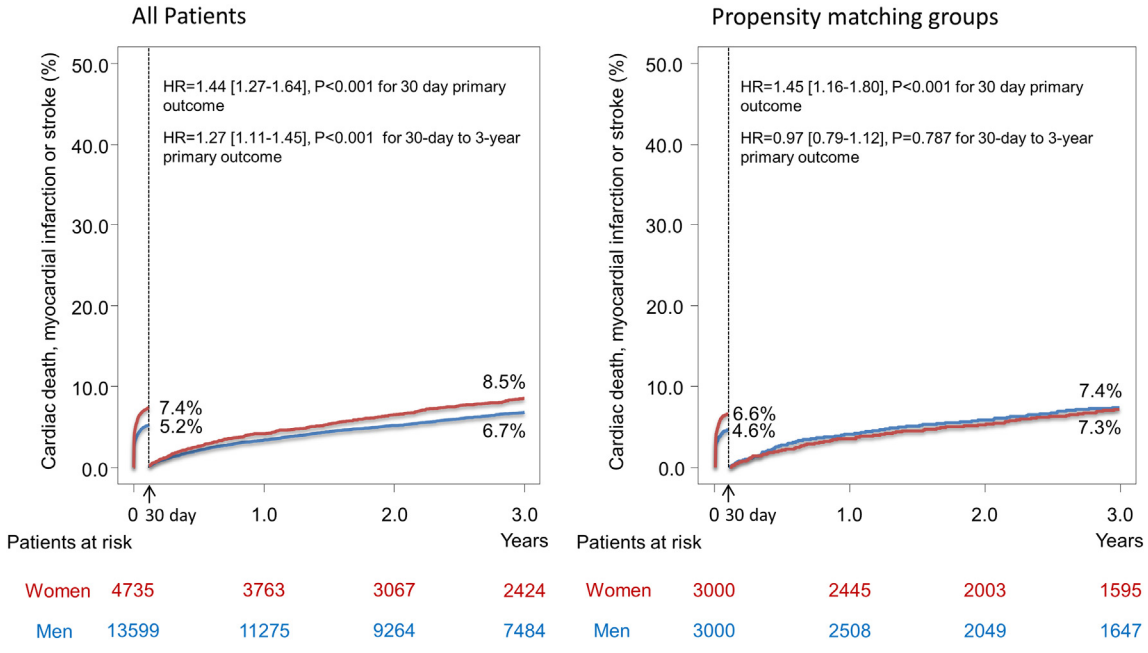

Fig. 2. Landmark analysis with a prespecified analysis of primary outcome at 30 days in all patients (left panel) and matched groups (right panel). HR = hazard ratio.

process can be produced [27]. With regard to the impact of therapy, the predominant finding across the studies is that women are less likely to receive invasive therapy or medications than men [28–30]. A previous study by Hollenbeak et al. [30] showed that among patients presenting with acute myocardial infarction, women had 24% lower odds of receiving PCI after controlling for age, race/ethnicity, severity at admission, infarct location or admission source. Importantly, in propensity matching analysis women that received PCI were less likely to die compared with those who did not. This [30] and other [6] studies suggested that PCI may narrow or even abolish sex differences in mortality. In our study, all patients were treated with PCI, so that no confounding effect in the association between sex and outcome was introduced by this factor. Recent studies have shown that women are at a higher risk of PCI-related complications even in current era of PCI, compared with men [15]. A recent study by Lichtman et al. [31] showed that women, regardless of age, experience more complications than men even in risk-adjusted analyses. A previous study by our group showed that women have a higher adjusted risk of periprocedural bleeding – an important correlate of mortality in post-PCI period –even after matching with men for age, body mass index and type of anticoagulant therapy [32]. In the current study women remained at a higher risk of PCI-related bleeding even after propensity matching with men for all characteristics available.

The analysis of sex-related differences in short- and long-term outcomes in unmatched and matched patients provided interesting data. In current study, women showed a significantly higher unadjusted risk of cardiac mortality, all-cause mortality or stroke within the first 30 days after PCI. The risk of 30-day cardiac or all-cause mortality remained significantly higher in women than men even after propensity matching. This is consistent with previous studies reporting a higher risk of short-term mortality after PCI in women [33]. Conversely, the differences in 3-year cardiac or all-cause mortality were attenuated after matching. Although reasons for this are not entirely clear, the differences in cardiovascular risk factors and procedural complications, between women and men may be responsible for sex difference in short-term and long-term outcome. Procedural complications, particularly bleeding events which were significantly more frequent in women, are associated with increased risk of short-term mortality whereas the association with long-term mortality is diminished [34] or even is abolished [35]. On the other hand, baseline cardiovascular risk factors impact on short- and long-term outcomes. In unmatched patients there was a significant and progressively widening risk difference for adverse events between women and men from 30 days to 3 years, likely reflecting continuation of the deleterious effects of cardiovascular risk factors, which were more prevalent in women. Conversely, in matched patients, the sex differences in the risk for adverse events from 30 days to 3 years were abolished. Thus in matched groups, the higher 30-day risk in women was maintained up to 3 years with no further accentuation in the risk difference beyond the 30-day time point. A higher 30-day risk in women even after matching may be explained by PCI-related bleeding events which were significantly more frequent in women even after matching. A higher frequency of other PCI-related complications in women has also been reported [15,31]. Moreover, even though balanced in terms of risk factors, exposure to the same risk factor like 2 diabetes [36] or obesity [37] may be more deleterious in women than men. However, this hypothesis needs further confirmation.

Two other findings of this study may deserve commenting. First, the frequency of target lesion revascularization remained lower in women compared with men up to 3 years after PCI. This may reflect the hesitancy to perform coronary angiography and PCI in women in the post-PCI period [30]. Alternatively, since women with acute CAD events have a higher risk of mortality, ischemia-driven clinical events may end fatally more often in women than men. If this were the case, it may limit the number of repeat interventions in women. Second, abolition of the sex differences in all-cause mortality after matching may reflect the increasing role of non-cardiac mortality particularly beyond 6 months after PCI [38]. These findings may have implications regarding the outcome assessment after PCI. Since the risk of spontaneous vascular events (cardiac death, myocardial infarction or stroke) and target lesion revascularization may go in opposite directions, their combination in a composite endpoint may be misleading due to mutually neutralizing effect of components with opposite directions. Thus, if composite endpoints are to be used for outcome assessment, each component should be reported separately. Moreover, even though all-cause mortality is most accurately documented and reported outcome, it may be suboptimal as an endpoint to assess the outcome after PCI, due to interference from noncardiac mortality which is becoming the dominant form of death in the current era of PCI [38].

The study has limitations. First, the study has limitations inherent to its retrospective design and somewhat outdated antithrombotic therapy and stents. Second, patients with an event before landmark (30 days) were excluded from further analysis. This is a recognized limitation of this method [39]. However, the principal study finding(s) was not derived by this analysis and thus was not influenced by this factor. Third, the 3-year follow-up was incomplete in some patients. However, there was no difference in follow-up between women and men and the Kaplan-Meier method used for survival analysis compensates at least partially for differences in the length of follow-up.

In conclusion, women have a significantly higher unadjusted risk of all-cause mortality, cardiac mortality or stroke up to 3 years following PCI compared with men. After propensity matching, women remained at a higher risk of a composite of cardiac mortality, myocardial infarction or stroke men up to 3 years following PCI, compared with men. The excess risk in women was particularly high in the first 30 days after PCI.

Disclosures

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