Measuring quality of care in the treatment of acute coronary syndrome

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Chapter 4

A focus on female gender in the treatment of acute coronary syndrome patients; determining differences in the type, nature and preventability of adverse event rates by means of medical record review.

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ABSTRACT:

BACKGROUND: Numerous studies reported that female patients treated for an acute coronary syndrome have poorer cardiovascular outcomes and receive less optimal treatment compared to male patients.

AIM: The aim of this study was to assess whether there is a gender disparity in the nature, occurrence and preventability of harm in patients with an acute coronary syndrome.

METHODS: A structured retrospective patient record review was performed to screen for adverse events during admission for the treatment of a suspicion of acute coronary syndrome warranting coronary angiography. An adverse event was defined as an unintended injury resulting in disability at time of discharge, prolonged hospital stay or death, that was caused by health care management rather than a patient's underlying disease.

RESULTS: In total, 879 patients (age 64 (SD 12) years, 71% male) were included. Female patients were slightly older, were less often diagnosed with a STEMI and were less often treated by percutaneous coronary intervention. Of the 626 male patients, 10% (95%-CI: 7%–12%) experienced an adverse event whereas in the group of 253 female patients, 21% (95%-CI: 16%–26%) patients experienced an adverse event ($p \leq 0.001$). No differences were found in the nature of the AEs between male and female patients ($p = 0.360$), however the causal factors of the adverse events were significantly different between male and female patients (adverse event $p = 0.043$). Female gender remained a significant predictor for adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics (OR=2.4, $p<0.001$).

CONCLUSION: Women experience more adverse events compared to men. Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidity and treatment characteristics.

INTRODUCTION

Adverse events are a major cause of mortality and morbidity among hospitalized patients. Therefore, patient safety is a serious health care issue and research on the incidence, preventability and causes of adverse events is receiving growing attention since the *To Err is Human* report in 1999.[1] Herein, adverse events are defined as medical injuries resulting in disability or death *due to health care management*, rather than attributable to the underlying disease process. Previous studies reported adverse events rates of 2.9 % to 16.6% based on all types of clinical admissions.[2-13] A recent study which focused on adverse events in patients treated for acute coronary syndrome showed that among patients admitted for the treatment of an acute coronary syndrome, 13% experienced an adverse event. Female patients, elderly and patients with an impaired renal function were at increased risk for an adverse event.[14] This poorer outcome in female patients, which has been demonstrated in terms of mortality and complications in previous studies, seems to be at least partly explained by sex differences in baseline characteristics, biomarkers, symptom presentation, prognosis and management of acute coronary syndrome.[15-24] Female patients with a myocardial infarction are older and have more comorbidities (such as hypertension and diabetes mellitus), and therefore have a higher risk of adverse cardiovascular outcomes.[18,23,25] Furthermore, accumulating evidence suggests that also female specific risk factors can influence the onset and outcome of myocardial infarction.[19]

In contrary to the vast amount of knowledge regarding the risk factors and differences in health outcomes (i.e. mortality and complications as bleeding) between male and female myocardial patients there is a scarcity of knowledge regarding potential differences in the underlying causes that lead to these adverse events. Hence, this study adds to the current body of knowledge by examining differences in causal factors, nature and the consequences of adverse events between male and female patients treated for an acute coronary syndrome.

METHODS

Patient population

All patients with a suspicion of acute coronary syndrome warranting coronary angiography, who were evaluated and treated according to a strict evidence-based protocol (the MISSION! Protocol) are included.[26-28] Since the goal of this study was to examine differences in the occurrence, nature and causal factors of experiencing an adverse event in patients with a suspicion of acute coronary syndrome, irrespective of the final treatment that was given, no differentiation was made between patients that did receive or did not receive

a coronary angiography after diagnosis. For the current study, patients were evaluated for the occurrence and preventability of adverse events during the in-hospital program. All patients treated in 2012 and 2013 were extracted from the electronic patient record system (EPD-Vision, LUMC, Leiden The Netherlands) by selecting the diagnose coding of a diagnosis-treatment-combination for unstable angina (UA) (11.203), ST-segment elevation myocardial infarction (STEMI) (11.204) and non-ST-segment elevation myocardial infarction (NSTEMI) (11.205).

Evaluation of adverse event

Through a structured medical record review, patients were assessed for the occurrence of adverse events by trained independent physician reviewers. The method is based on the Harvard Medical Practice Study.[12] A comprehensive description of the method is described in a previous study.[29] Summarized, the first phase focuses on identifying process deviations during the admission. A process deviation was defined as every operation or treatment that differed from the MISSION!-protocol[28], such as additional procedures (a pacemaker implantation or second PCI procedure), prescription of extra medication other than described in the protocol (use of anti-arrhythmics, anti-coagulation, inotropics or diuretics) or omission of a procedure (no diagnostics performed). If a process deviation was present, the medical record was transferred to a second phase which involved an assessment on whether the event resulted in harm to the patient. Patient harm was defined as any disadvantage for the patient that resulted in prolonged or strengthened treatment, temporary or permanent (physical and/or mental) impairment or death. Furthermore, it was rated whether patient harm was caused by medical care (and therefore an adverse event) and if so, whether it was potentially preventable (and therefore caused by an error). In case of doubt the expert panel, consisting of experienced cardiologists, was consulted. When more than one adverse event occurred in a patient, both were registered. Adverse events were classified by severity (leading to possible injury, temporary injury, permanent injury or death), nature (e.g. as a consequence of taken medication, procedural activities, diagnostic activities or other clinical activities) and causal factors (technical, human, organisational or patient-related factors) were noted.[30] Only the first (preventable) event was taken into account when comparing differences in the frequency of nature and causal factors.

Evaluation of gender differences

To examine the potential gender differences in the treatment, number of adverse events and type of adverse events of patients with acute coronary syndrome various factors were taken into account. Information on risk factors and comorbidities was collected, including on hypertension (defined as blood pressure ≥ 140/90 mmHg or previous pharmacological treatment), hyperlipidaemia (defined as total cholesterol ≥ 190 mg/dl or previous pharmacological treatment), smoking, a diagnose of diabetes mellitus (insulin

and non-insulin-dependent), history of coronary artery disease or previous percutaneous coronary intervention, history of pulmonary diseases and renal clearance at admission. Renal clearance was measured by calculating the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[31] The comorbidity score at baseline was calculated using an abbreviated Charlson Comorbidity Index (CCI) with the following comorbid conditions: myocardial infarction, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease, liver disease, renal failure and any malignancy.[32] The abbreviated CCI was computed in accordance with the original CCI in which a weight of 2 was assigned to renal failure and any malignancy, and a weight of 1 to the other comorbid conditions. Because age is a risk factor for mortality independent of the presence of comorbid conditions, the score was adjusted by adding one point to the score for each decade of life over the age of 50 at time of study entry.[33] Moreover, medication use known at admission and discharge was noted for aspirin-species, P2Y12-inhibitors, statins, beta-blockers and angiotensin converting enzyme inhibitor or angiotensine-2-antagonist (ACE/AT2-inhibitors).

Furthermore, infarct characteristics and treatment were collected, such as prior diagnosis (STEMI, NSTEMI and UA), percutaneous treatment, peak Troponin-T and creatine kinase (CK). STEMI was defined in the presence of symptoms of angina lasting longer than 30 minutes with typical electrocardiographic changes (ST-segment elevation $\geq$ 0.2 mV in $\geq$ 2 contiguous leads in V1 through V3, or $\geq$ 0.1 mV in other leads, or presumed new left bundle branch block.[34] In addition, treatment variables as symptom-to-needle-time, diagnosis-to-needle-time and door-to-needle-time were noted. Symptom-to-needle time was defined as the time between the onset of symptoms and first needle puncture during the procedure in the catheterization laboratory. Diagnosis-to-needle time was defined as the time between the first diagnostic ECG, usually the ambulance triage ECG, and the time of the needle puncture.

Statistical analysis

Adverse event rates were calculated by taking the proportion of patients with at least one adverse event and the number of adverse events per 1,000 patient days. For the calculation of the 95% confidence interval for event rates, a Poisson distribution of the observed number of events was presumed. Continuous variables were presented as means with standard deviations or medians with 25th and 75th percentiles. Dichotomous variables were presented as numbers and percentages. Demographic and clinical characteristics were stratified by male and female gender. To examine gender differences in experiencing an adverse event, demographic variables, risk factors, comorbidities and medication use known at baseline were compared by means of T-tests, Mann-Whitney U tests, or chi-squared-test, where appropriate. Logistic regression was used to examine lifestyle factors, comorbidities, medi-

cation at admission, treatment factors as influencing the gender differences in experiencing an adverse event during admission. Due to missing values on symptom-to-needle time (~13%), Troponin-T-peak (~14%) and medication at admission (~4%), multiple imputation was performed by using Predictive Mean Matching (Markov Chain Monte Carlo, 100 imputations). Predictive mean matching is similar to the regression method except that for each missing value, it imputes a value randomly from a set of observed values whose predicted values are closest to the predicted value for the missing value from the simulated regression model.[35] Subsequently, the imputation database was used to perform a logistic regression. Gender was entered in the hierarchical regression analyses using the *enter* method (Model 1). Subsequently, socio-demographic variables (age, body-mass index and smoking), medication (aspirin, P2Y12-inhibitor, statin, beta-blocker and ACE/AT2-inhibitor) were added to the analyses thereby creating Model 2 and Model 3, respectively. To determine if treatment comorbidities or treatment characteristics were predictive of adverse event during admission, Charlson Comorbidity Index, Diagnosis, PCI, symptom-to-needle-time (divided in four groups by quartiles) and Troponin-T (for each gender divided in four groups by quartiles), were added to the logistic regression model (Model 4 and 5). In Model 4, age was excluded because it was already incorporated in the Charlson Comorbidity Index. The explained variance of Model 1 to Model 5 were estimated using block entry of the variable groups and were calculated based on a method for combining R square values from imputed data sets.[36]

Furthermore, of each variable, an odds ratio with standard error and a p-value was calculated. All analyses were performed with IBM SPSS Statistics for Windows, Version 23.0 (SPSS, Armonk, NY, USA) and a p-value < 0.05 was considered statistically significant.

Ethical considerations

The institutional ethical committee of Leiden University Medical Center gave a declaration of "medical-ethical permittance not necessary" for this retrospective records study (reference number P15.133). Data was analysed anonymously.

RESULTS

Population

In total, 879 patients (mean age of 64 (SD = 12) years) were evaluated and treated for an acute coronary syndrome. The majority of the patients was male (71%, n = 626) and 594 (68%) patients experienced a STEMI. During a median stay of three days (25^{th} – 75^{th} percentile: 2 – 4), all patients underwent coronary angiography and 747 (85%) patients were treated by PCI. Further demographic, clinical and medication characteristics are shown in **Table 1**.

Table 1: Patient characteristics

	All patients	Male	Female	p-value
	N = 879	N = 626	N = 253	
Age (years)	64 (SD 12)	63 (SD 12)	65 (SD 13)	0.070
BMI (kg/m2)	27 (SD 4)	27 (SD 4)	26 (SD 5)	0.202
Comorbidities				
Charlson Comorbidity Index	2.7 (SD 2.1)	2.7 (SD 2.1)	2.7 (SD 2.0)	0.560
Current smoker	326 (37%)	243 (39%)	97 (38%)	0.927
Medication use at home				
Aspirin-specie	203 (23%)	138 (22%)	65 (26%)	0.278
P2Y12-inhibitor	51 (6%)	30 (5%)	21 (8%)	0.071
Statin	256 (29%)	180 (29%)	78 (31%)	0.616
Beta-blocker	225 (26%)	140 (22%)	85 (34%)	0.001
ACE- or AT2-inhibitor	243 (28%)	162 (26%)	81 (32%)	0.074
Admission characteristics				
Length of stay (days) (median, IQR)	3 (2 – 4)	2 (3 – 4)	3 (2 – 5)	0.055
Diagnosis				0.006
STEMI	594 (68%)	445 (71%)	149 (59%)	
NSTEMI	135 (15%)	87 (14%)	48 (19%)	
Unstable angina	150 (17%)	94 (15%)	56 (22%)	
Percutaneous coronary intervention	747 (85%)	541 (86%)	206 (81%)	0.060
Symptom-to-needle time (minutes) (median, IQR)	228 (124 – 669)	202 (117 – 556)	320 (149 – 1,045)	0.001
Diagnosis-to-needle time (minutes) (median, IQR)	70 (55 – 192)	69 (54 – 148)	75 (56 – 265)	0.035
Troponin-T-peak (µg/L) (median, IQR)	1.8 (0.3 – 4.8)	2.1 (0.4 – 5.0)	1.1 (0.2 – 3.6)	0.001
CK-peak (U/L) (median, IQR)	705(206 1,665)	882(239 1,723)	488(151 – 1,414)	≤ 0.001
Medication at discharge				
Aspirin-specie	834 (95%)	592 (95%)	243 (96%)	0.493
P2Y12-inhibitor	789 (90%)	567 (91%)	222 (88%)	0.214
Statin	824 (94%)	590 (94%)	233 (92%)	0.276
Beta-blocker	756 (86%)	550 (88%)	206 (81%)	0.016
ACE- or AT2-inhibitor	774 (88%)	561 (90%)	212 (84%)	0.020

SD = standard deviation; BMI = body-mass index; IQR = interquartile rang; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; CK = Creatine kinase.

Gender variety

Gender differences in baseline characteristics are shown in **Table 1**. Female patients were slightly older (65 (SD = 13) years versus 63 (SD = 12) years, p = 0.070), were less often diagnosed with a STEMI (71% versus 59%, p = 0.006), had a lower Troponin-T-peak (female 1.1 (IQR 0.2 – 3.6) vs male 2.1 (IQR 0.4 – 5.0) (p = 0.001) and lower CK peak (female 488

(IQR 151 – 1,414) vs male 882 (IQR 239 – 1,723) ($p \leq 0.001$)). Moreover, female patients had more risk factors compared to male patients, such as hypertension (female 51% versus male 38%, $p \leq 0.001$). Subsequently, differences were found in the treatment of female patients. Female patients were less often treated by PCI (female 81% versus male 86%, $p = 0.060$), were less often treated with a beta-blocker ($p = 0.016$) and ACE- or AT2-inhibitor ($p = 0.020$) at discharge, and also the time from first symptom-to-treatment (females 320 minutes (IQR 149 – 1,045) vs males 202 minutes (IQR 117 – 556) ($p = 0.001$)) and diagnosis-to-treatment (females 75 (56 – 265) vs males 69 (IQR 54 – 148) ($p = 0.035$)) was longer compared to male patients.

Within the group of STEMI patients, the symptom-to-needle time was consistently longer in female patients (166 minutes (IQR 155 – 328) compared to male patients (150 minutes (IQR 102 – 249) ($p = 0.019$)). No differences were observed in diagnosis-to-needle time ((females 62 minutes (IQR 50 – 77) vs males 62 minutes (IQR 51 – 75) ($p = 0.775$)) and PCI-treatment (females 97% versus males 95%, $p = 0.387$).

Adverse events

During 2,999 days of observation, a total of 143 adverse events were observed in 116 patients. In the group of 626 male patients, 63 (10% (95%-CI: 7% – 12%)) patients experienced an adverse event, while in the group of 253 female patients, 53 (21% (95%-CI: 16% – 26%)) patients experienced an adverse event ($p \leq 0.001$). Similarly, a significant difference was seen in the number of patients with at least one preventable adverse event: 6% among female patients (95%-CI: 3% – 9%) compared to 3% among male patients (95%-CI: 2% – 4%) (≤ 0.001).(**Table 2**) The difference in the frequency of adverse events between female and male patients was also observed when the same analysis was performed on the group of STEMI patients (n = 594) (females 19% versus males 11%, $p = 0.006$). In both female (13 events) and male patients (9 events), adverse events were mainly related to bleeding complications.

When examining the nature and causes of all first events in 116 patients, it appears that 72% of all events in the group of female patients were related to procedural activities, compared to 56% in the group of male patients ($p = 0.360$). This difference was also found in the preventable adverse events (male 28% vs female 75% due to procedural activities, $p = 0.042$). The causal factors of (preventable) adverse events were also significantly different between male and female patients (adverse event $p = 0.043$, preventable adverse event $p = 0.021$). Human factors were the primary cause of (preventable) adverse events in female patients (female AE: 68% and female preventable AE: 75% respectively). Human factors (male AE: 51%, male preventable AE: 50%) and patient-related factors (male AE: 43%, male preventable AE: 50%) were found as the primary causes of the (preventable) adverse

Table 2: Occurrence and preventability of adverse events.

	All patients	Male	Female	p-value
	N = 879	N = 626	N = 253	
Days of observation, total	2,999	2,060	939	
Days of observation / per patient	3.4	3.3	3.7	
Number of adverse events	143	78	65	
Number of preventable adverse events	35	18	17	
Event risk				
Number of patients with at least one adverse event	116 (13%) (95%-CI: 11–16%)	63 (10%) (95%-CI: 7– 12%)	53 (21%) (95%-CI: 16– 26%)	≤ 0.001
Number of patients with at least one preventable adverse event	34 (4%) (95%-CI: 3– 5%)	18 (3%) (95%-CI: 2– 4%)	16 (6%) (95%-CI: 3– 9%)	0.021
Event rate				
Adverse event rate	48 per 1,000 patient days	38 per 1,000 patient days	69 per 1,000 patient days	
Preventable adverse event rate	12 per 1,000 patient days	9 per 1,000 patient days	18 per 1,000 patient days	

events in male patients.(**Table 3**) Focussing on preventable adverse events with a human factor, no explicit differences between male and female patients were found. Examples of human factors related to preventable adverse events were delayed percutaneous interventions in an NSTEMI patient despite evolving electrocardiographic changes during the weekends (male gender), traumatic placement of urinary bladder catheter in patients with triple anti platelet therapy resulting in bladder lavage (male gender), and late detection of subcutaneous edema due to intravenous infusion (female gender), late detection and consultation of an NSTEMI at a pulmonary department (female gender).

Risk factors by gender

Between patients with and without an adverse event, stratified by gender (male AE = 63, male non-AE = 563, female AE = 53, female non-AE = 200) data were compared on the same variables as used in **Table 1**. Differences between patients with and without an adverse event were found in both gender groups in age (male AE versus male non-AE, p = 0.001; female AE vs female non-AE, p = 0.002) and Charlson Comorbidity Index (male AE versus male non-AE, p ≤ 0.001; female AE vs female non-AE, p = 0.009). Female gender with an adverse event were less often smokers (21% vs 43%, p = 0.004) compared to female patients without an adverse event. No differences were observed in the type of diagnosis (p-values al above 0.05) in male and female patients. However, symptom-to-needle time was significantly longer in female patients with an adverse event (440 minutes (233 – 1,790) compared to females without an adverse event 317 minutes (144 – 936), p =

Table 3: Adverse event characteristics

	All adverse events	Adverse event Male	Adverse event Female	p-value	All preventable adverse event	Preventable adverse event Male	Preventable adverse event Female	p-value
	N = 116	N = 63	N = 53		N = 34	N = 18	N = 16	
Consequences of the adverse event				**0.308**				**0.109**
Possible injury	15 (13%)	7 (11%)	8 (15%)		1 (3%)	0 (0%)	1 (6%)	
Temporary injury	92 (79%)	51 (81%)	41 (77%)		28 (82%)	15 (83%)	13 (81%)	
Permanent injury	7 (6%)	5 (8%)	2 (4%)		3 (9%)	3 (17%)	0 (0%)	
Deceased	2 (2%)	0 (0%)	2 (4%)		2 (6%)	0 (0%)	2 (13%)	
Nature				**0.360**				**0.042**
Diagnostic activities	2 (2%)	1 (2%)	1 (2%)		2 (6%)	1 (6%)	1 (6%)	
Drug-related adverse event	19 (16%)	14 (22%)	5 (9%)		5 (15%)	4 (22%)	1 (6%)	
Other clinical activities	20 (17%)	12 (19%)	8 (15%)		10 (29%)	8 (44%)	2 (13%)	
Other non-procedural activities	2 (2%)	1 (2%)	1 (2%)		0 (0%)	0 (0%)	0 (0%)	
Procedural activities	73 (63%)	35 (56%)	38 (72%)		17 (50%)	5 (28%)	12 (75%)	
Causal factors				**0.043**				**0.021**
Human factors	68 (59%)	32 (51%)	36 (68%)		21 (62%)	9 (50%)	12 (75%)	
Patient-related factors	38 (33%)	27 (43%)	11 (21%)		10 (29%)	9 (50%)	1 (6%)	
Technical factors	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	
Organizational factors	5 (4%)	1 (2%)	4 (8%)		2 (6%)	0 (0%)	2 (13%)	
Not judgeable	5 (4%)	3 (5%)	2 (4%)		1 (3%)	0 (0%)	1 (6%)	

0.048). Furthermore, male patients with an adverse event were more often treated by PCI (95% vs 85%, p = 0.032) and P2Y12 inhibitors (98% vs 90%, p = 0.033).

Multivariate analyses

The odds of experiencing an adverse event are explained by gender for 3.6% - 4.8%. Gender remained a significant predictor for adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics (OR1 = 2.4, SE = 0.2; OR2 = 2.3, 0.2; OR3 = 2.3, SE = 0.2, OR4 = 2.5, SE = 0.2, OR5 = 2.4, SE = 0.2; all p-values ≤ 0.001).(**Table 4**) The explained variance of the lifestyle and socio-demographic factors (minus age), medication use prior to admission, and comorbidity in Model 4 was 1,7%, 1,7%, and 4,1%, respectively. The explained variance of the lifestyle factors and socio-demographic factors (including age), medication use at home, and treatment variations in Model 5 was 6%, 1,4%, and 2,1%, respectively. In addition to gender, age (Model 2, Model 3 and Model 5 all values OR = 1.0, SE 0.0, P ≤ 0.001), the degree of comorbidity (OR4 = 1.3, SE 0.1, p ≤ 0.001) and the symptom-to-needle time (OR5 = 1.3, SE = 0.3, p = 0.036) remained significant predictors for adverse events.(**Table 4**)

DISCUSSION

In this study on gender disparities in the treatment, number of adverse events and type of adverse events in patients with acute coronary syndrome, the findings can be summarized as follows: (i) Women experience more adverse events compared to men (female patients (21%) vs. males (10%)); (ii) Women have a more unfavourable baseline risk profile (due to age and comorbidities) and are less often treated according to clinical guidelines, which may partly explain the higher odds of having an adverse event; (iii) Adverse events in women are more often related to human factors compared to men; (iv) Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics.

The prevalence of adverse events observed in this study was higher compared to previous national registries and similar to worldwide studies.[2-13,37] The majority of these adverse events were related to bleeding complications. In cardiovascular literature, no previous study focused on examining patient harm caused specifically by health care management. However, previous studies did consistently find a higher risk of bleeding complications in female patients, which could be associated with higher mortality rates.[16,22,24,38,39] Unfortunately, the interaction between gender and baseline characteristics and antithrombotic treatment, that can increase or decrease the risk of having a bleeding event, remains poorly understood. It seems that in women acute myocardial infarction is more frequently caused

Table 4: Multivariate analysis

	Model 1			Model 2			Model 3			Model 4			Model 5		
	OR	SE	p-value	OR	SE	p-value	OR	SE	p-value	OR	SE	p-value	OR	SE	p-value
Gender	**R2 = 0.036**			**R2 = 0.036**			**R2 = 0.036**			**R2 = 0.035**			**R2 = 0.036**		
Gender	2.368	0.204	≤ 0.001	2.270	0.209	≤ 0.001	2.287	0.213	≤ 0.001	2.471	0.215	≤ 0.001	2.362	0.217	≤ 0.001
Lifestyle & socio-demographic factors				**R2 = 0.096**			**R2 = 0.096**			**R2 = 0.052**			**R2 = 0.096**		
Age				1.043	0.009	≤ 0.001	1.043	0.010	≤ 0.001				1.040	0.010	≤ 0.001
BMI				1.029	0.025	0.250	1.025	0.026	0.326	1.014	0.026	0.593	1.028	0.026	0.287
Smoking				0.733	0.243	0.201	0.757	0.248	0.262	0.703	0.243	0.148	0.695	0.252	0.147
Medication at home							**R2 = 0.110**			**R2 = 0.069**			**R2 = 0.110**		
Aspirin							0.540	0.313	0.049	0.483	0.318	0.022	0.526	0.319	0.044
P2Y12-inhibitor							1.533	0.421	0.310	1.467	0.425	0.368	1.513	0.435	0.341
Statin							1.321	0.277	0.316	1.195	0.283	0.528	1.377	0.282	0.256
Beta-blocker							0.905	0.278	0.726	0.860	0.287	0.600	0.965	0.288	0.903
ACE/AT2-inhibitor							1.296	0.252	0.303	1.226	0.258	0.429	1.221	0.256	0.434
Comorbidities										**R2 = 0.110**					
Charlson Comorbidity Index										1.279	0.055	≤ 0.001			
Treatment characteristics													**R2 = 0.131**		
Diagnosis STEMI / NSTEMI													1.372	0.339	0.350
Troponin-T-Peak													1.109	0.122	0.395
Percutaneous coronary intervention													1.751	0.356	0.116
Symptom-To-Needle Time (minutes)													1.326	0.282	0.036

BMI = body-mass index; ACE/AT2-inhibitor = angiotensin converting enzyme or angiotensine-2-inhibitor; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction;

by plaque erosion, and women tend to suffer more from non-obstructive cardiac disease and coronary microvascular dysfunction compared to men.[40,41] Hormonal differences, like the endogenous oestrogen levels in the premenopausal phase of the vascular endothelium, have been described as a protective factor for acute coronary syndrome in women,[17,42] but women do show a higher platelet reactivity compared to men.[43,44]

Although a gender-disparity in baseline biological characteristics exists, studies appear to show a largely comparable efficacy of antithrombotic treatment for acute coronary syndrome.[16] Hochholzer showed in the TRITON-TIMI-38 trial that complications in men were mainly related to gastrointestinal bleeding, whereas those in women were mainly related to the vascular access site of bleeding.[45] Moreover, female gender was a predictor for serious bleeding of any cause.[45]

As confirmed in other registries, demographic and lifestyle risk profile at admission differ between female and male patients. Also in this study, female patients were older and had more comorbidities, such as hypertension. Other registries also showed that diabetes, congestive heart failure, renal insufficiency and cerebrovascular disease were more prevalent in female gender.[39,46-49] Surprisingly, in our study a better renal function was observed in females compared to males. Our findings also indicate that female patients were less often treated according to the guidelines (lower number of PCI procedures and longer symptom-to-needle time), which seems consistent with the "risk-treatment paradox".[25] The "risk-treatment paradox" is a situation in which patients at high risk for adverse events receive less-intensive treatment than do patients at lower risk.[50] This is in concordance to other studies showing that women were more often treated with medical therapy alone compared to men, had a delay in PCI times and were less likely to receive discharge medication according to guidelines or to medication continue after one year follow-up.[48,51-54] Poon et al. showed that the "risk-treatment paradox" could be the result of an underappreciation of the increased risk associated with female gender.[54]

Most predictors of adverse events, such as demographic factors (age), lifestyle factors, comorbidities and treatment patterns were partly associated with the odds of having adverse events in our study. Especially gender seems to be an important independent predictor for experiencing an adverse event. Also in studies focusing on young women with coronary artery disease after PCI, an increased risk of major adverse cardiovascular events (target vessel and target lesion failure) is observed.[55] When focussing on the events itself, the majority of the events in females were caused by human factors, whereas events in males were caused by medication and human factors. Other factors, such as communication and symptom presentation by female patients could play a role in identifying an adverse event to prevent further harm. Often, women present without chest pain or discomfort when

having an acute coronary syndrome.[20] Moreover, women are less aware of having an acute coronary syndrome and underestimate their risk by attributing acute coronary syndrome mainly as a 'male problem'.[56] Women also showed a delay in seeking care, based on the time between the first symptoms and having the first medical contact.[20,51,57]

Limitations

This study is one of the first studies which focusses on gender differences in patient's harm caused by health care management after treatment for an acute coronary syndrome. However, some limitations need to be addressed. This study shares the limitations of a retrospective study. In addition, the chance of experiencing an adverse event can dependent on numerous factors, which could not all be taken into account in this study. Furthermore, judging whether an adverse event is preventable is subjective to potential hindsight bias. Despite this limitation, retrospective medical record review studies are currently one of the best methods available to assess incidence of AEs and discover latent errors.[58]

Future perspectives

In the future, a greater awareness of sex-based differences regarding the treatment and symptom presentation of acute coronary syndrome might be important in preventing adverse events. An increased focus on unravelling the causes of specific adverse events (i.e. bleeding) and whether this is caused by the "risk-treatment paradox" or gender itself seems important, as well as a greater focus on gender-specific treatment during the education of physicians. Furthermore, clinical guidelines should place a greater emphasis on the gender-difference in the treatment of cardiovascular disease, and the pharmaceutical industry and scientific researchers should be encouraged to initiate clinical trials with an equal representation of male and female patients.

CONCLUSION

Gender is an independent predictor of adverse events after adjustment for lifestyle factors, medication, comorbidities and treatment characteristics. More research is needed to disentangle the underlying causes which increase the risk for adverse events in women compared to men.

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