

Female sex is associated with delayed reperfusion by percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction

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Introduction Time delay to reperfusion (TD) is the crucial prognostic factor in patients with acute myocardial infarction (AMI); the delay in reperfusion results in higher morbidity and mortality rates.^{1,2} Previous studies documented a significantly longer TD in women compared with men,^{3,4} attributed mainly to a longer time from symptom onset to the first medical contact.⁵ Most of these studies were performed more than a decade ago. The treatment of ST-elevation myocardial infarction (STEMI) has improved and campaigns to raise public awareness have been conducted, although a registry published in 2011 indicated that women continue to have longer presentation and treatment times.⁴ The aim of this study was to assess the current relation between sex and TD from symptom onset to reperfusion by percutaneous coronary intervention (PCI).

Patients and methods Data from the registry of 745 consecutive patients admitted to our tertiary-care hospital with STEMI and treated by PCI from January 2009 to December 2011 were retrospectively analyzed.

Electrocardiographic (ECG) criteria for entry included ST-segment elevation of more than 2 mm in at least 2 contiguous leads and left or right bundle branch block of new origin. In borderline cases of STEMI (possible misdiagnosis), angiographic findings or autopsy examinations were retrospectively evaluated. Patients not requiring PCI were not included into the registry. Patients with unclear time of symptom onset were excluded from the study (5 of 750 patients).

Time to treatment was calculated as the interval from symptom onset to the first balloon inflation. Data on the time of symptom onset were

collected routinely on patient admission. Medical history, sociodemographic, angiographic, and hemodynamic variables were assessed.

Patients who did not work full or part time were classified as nonworking (mostly retired or physically disabled individuals).

The primary endpoint was the relation between sex and TD from symptom onset to reperfusion in patients with STEMI. The secondary endpoint was the in-hospital mortality in relation to sex.

The study was approved by the institutional review board at the Third Medical Faculty and University Hospital Kralovske Vinohrady, Prague, Czech Republic.

Statistical analysis The location and variability of continuous variables were expressed as arithmetic mean and standard deviation for normally distributed variables or as median (25 and 75 percentile) for nonnormally distributed variables. The 2-sample *t* test and Mann-Whitney test were used to test differences between the groups. Categorical data were described using absolute and relative frequencies (percentages) and analyzed using the Fisher exact test.

Multiple linear regression and multiple logistic regression models were used to compare the study subgroups and to identify independent predictors of the endpoint occurrence. TD was logarithmically transformed in a linear regression analysis due to nonnormal distribution. The results are presented as the ratio of geometric means or the odds ratio, with the corresponding 95% confidence intervals.

The statistical analysis was performed using the Stata, release 13.1, software (Stata Corp LP, College Station, Texas, United States). A *P* value

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TABLE Baseline characteristics of the patients according to sex

		All n = 745	Women n = 180 (24.2%)	Men n = 565 (75.8%)	P value
age, y		63.4 (55.2–84)	71.3 (60–77)	61.5 (54–70)	<0.001
BMI, kg/m ²		27.34 (24.5–26.3)	26.3 (23.4–29.3)	27.8 (25–29.4)	0.009
BSA, m ²		1.95 ± 0.23	1.75 ± 0.17	2.01 ± 0.21	0.009
hypertension		55.2	65.7	51.8	0.001
diabetes mellitus		25.0	32	22.8	0.015
current smoking		52.7	38.5	57.2	0.001
hyperlipoproteinemia		19.0	20.8	18.4	NS
previous MI		15.8	18.0	15.1	NS
previous CABG, PCI		11.5	11.8	11.4	NS
previous stroke		8.1	9.6	7.6	NS
PAD		6.8	9.6	5.9	NS
creatinine clearance <30 ml/min		3.7	8.9	2.0	<0.001
LVEF <45%		39.1	41.6	38.3	NS
LVEF <30%		6.2	5.1	6.6	NS
Killip class >1		25.9	28.3	25.1	NS
Killip class 4		10.93	10.0	11.23	NS
culprit lesion	LAD	47.7	46.7	48.0	NS
	LCx	14.8	13.9	15	NS
	RCA	40.8	42.8	40.2	NS
ECG	ST-segment elevations on ECG	89	90	88.7	NS
	BBB on ECG	11	10	11.3	NS
number of affected arteries	1	34.1	33.0	34.4	NS
	2	30.7	30.2	30.9	
	3	29.9	33	28.9	
	4	5.4	3.9	5.9	
TIMI after PCI <3		13.5	16.1	12.6	NS
TD, h		4.33 (2.51–9.85)	5.74 (3.18–12.17)	3.92 (2.36–8.79)	<0.001
interhospital transport ^a		25.6	28.3	24.7	NS
first contact delay ^b		10.2	11.1	9.9	NS

Data are presented as median (interquartile range), mean ± standard deviation, or percentage of patients.

a interhospital transport: patients transferred to our PCI center from community hospital

b first contact delay: patients who visited primary care physician instead of calling emergency medical service immediately

Abbreviations: BBB, bundle branch block; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass surgery; ECG, electrocardiography; LAD, left anterior descending artery; LCx, left circumflex artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, nonsignificant; number of affected arteries, 4 stands for stenosis >50% of the left main artery; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; TD, time delay to reperfusion; TIMI, Thrombolysis in Myocardial Infarction flow

of less than 0.05 was considered statistically significant.

Results Baseline characteristics Demographic, clinical, and angiographic characteristics in relation to sex are presented in the [TABLE](#).

Of 745 patients, 180 were women (24.2%). Women were significantly older than men (median age, 71.3 years and 61.5 years, respectively, $P < 0.001$). In addition, they had higher prevalence of hypertension and diabetes mellitus and higher incidence of severe renal failure. Considering the social status, women were significantly more often nonworking than men (84% vs 51.9%, $P < 0.001$). They were also more likely to

report shortness of breath without accompanying chest pain ($P = 0.15$). The hemodynamic or angiographic characteristics did not differ significantly between the groups.

Clinical factors associated with time delay to reperfusion In the study population, 35.75% of men ($n = 202$) and 47.78% of women ($n = 86$) underwent PCI after 6 hours from symptom onset. Median TD to PCI was significantly longer in women: 344.4 minutes compared with 235.2 minutes in men ($P < 0.001$).

A multiple linear regression analysis identified the following factors as significantly related to TD: number of affected arteries, shortness

of breath without chest pain, left ventricular dysfunction, transport from community non-PCI hospital or delay by first contact physician, symptom onset at night, bundle branch block on ECG, and collapse in the initial phase of STEMI. Female sex was independently related to prolonged TD after adjustment (mean TD ratio, 1.22; $P < 0.001$). The association of diabetes mellitus, renal failure, and history of ischemic heart disease with TD was not significant after adjustment for baseline covariates.

In a multiple logistic binary model, the estimated odds ratio for delayed reperfusion (TD from symptom onset >6 hours) in women was 1.55 ($P = 0.036$) compared with men.

Interactions Significant interactions of sociodemographic and process-of-care factors were observed in relation to sex and TD. Women older than 65 years underwent PCI 1.54 times later than men in the same age group ($P = 0.007$). In the group of patients who contacted emergency medical service or community hospital emergency immediately, TD to reperfusion in women was 1.43 times longer than in men ($P < 0.001$).

Working women underwent PCI 1.59 times later than working men ($P = 0.019$) and 1.42 times later than nonworking women.

Outcomes The incidence of postprocedural TIMI flow of less than 3 in men was 12.6% and in women, 16.1%; after adjustment, the difference was not significant. The all-cause hospital mortality was 9.14% in men ($n = 51$) and 9.44% in women ($n = 17$); no significant difference was found between the 2 groups after the adjustment for TD and other significant variables (age, Killip class, left ventricular dysfunction, postprocedural TIMI in the culprit vessel).

The rates of hospital mortality among men and women did not differ significantly within different matching TD intervals.

Discussion This study confirms the persistence of prolonged time to treatment in women with STEMI in the current era of PCI. The reasons are probably multifactorial, including demographic and clinical factors, logistic and physician issues, and psychological and socioeconomic status.

Demographic and clinical factors The difference in TD to PCI in this work was largely due to the subgroup of women older than 65 years. In the study of Sheifer et al.,³ over one-fourth of elderly patients with AMI presented to the hospital more than 6 hours after symptom onset. Older persons often suffer from comorbidities, which makes them less likely to attribute their symptoms to cardiac causes or modifies their perception of pain. Diabetes mellitus and renal failure were related to the delayed presentation of patients with AMI.^{3,4} Women frequently present with atypical symptoms such as shortness of breath, back, arm pain, or fatigue.⁶

Socioeconomic factors The socioeconomic status contributes to delayed treatment of patients with AMI.³ An interesting feature observed in this work was the relation between age, working status, and gender. Working women underwent PCI significantly later than nonworking women of the same age group. Psychosocial factors may be involved, such as unawareness of AMI risk in women, especially if they are active, employed, and feel healthy, unwillingness to trouble others, or reluctance to leave the working place during working hours.⁷

Process-of-care and patient factors Compared with men, women tend to receive treatment less often and their treatment is less consistent with evidence. Over the last decade, women were less likely to receive thrombolysis and PCI in the acute phase⁸; women who received primary PCI had longer door-to-balloon times.⁹ It seems that women are unaware of their high cardiovascular risk. In 1997, less than one-third of American women knew that heart disease was the leading cause of death.¹⁰ In 2001–2002, the American Heart Association and National Heart, Lung, and Blood Institute campaigns were initiated to increase women's awareness of heart disease but there was no reduction in time to presentation in AMI and a significant gender gap remained. Similar results were observed in a Canadian study.⁹

Outcomes The adjusted rates of postprocedural Thrombolysis in Myocardial Infarction (TIMI) <3 in the culprit vessel and in-hospital mortality were comparable between men and women in this study. Improved early survival of STEMI patients after PCI in contrast to thrombolysis or a limited number of patients may have contributed to the lack of difference in mortality.

In a French registry,¹¹ female in-hospital mortality in STEMI exceeded that of men independently of study variables including TD and reperfusion technique.

In a study by Benamer et al.,¹² in STEMI patients treated with PCI within 24 hours, female sex was associated with mortality only in the subgroup of patients older than 75 years of age. In a study by Sędkowska et al.,¹³ female sex was an independent risk factor for myocardial reinfarction, stroke, or repeat revascularization but not for mortality in AMI patients with impaired glucose tolerance treated by PCI. The analysis of Kang et al.¹⁴ showed that increased mortality in women became nonsignificant when adjusted for age, medical history, and hemodynamic status.

Limitations The retrospective analysis of a relatively small study population from the tertiary-care center could confound the results and conclusions. The results should be interpreted with regard to possible regional population differences.

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