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Gender-related differences in patients with ST-elevation myocardial infarction

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Summary
Background A decade ago women with ST-elevation myocardial infarction (STEMI) were significantly older than men, with more comorbidities, less likely treated by primary percutaneous coronary intervention (PPCI) and their prognosis was worse. The progress in treatment led to increased survival after STEMI. Our aim was to evaluate the possible current differences between the genders in treatments, mortality and the changes in women over time in STEMI population.

Methods We retrospectively evaluated 307 STEMI patients (224 men, 83 women), admitted between October 1, 2011 and December 31, 2012 and a historic group of 523 STEMI patients from 2008 to 2009 (361 men, 162 women). Reperfusion strategy was PPCI, combined with aspirin and clopidogrel or prasugrel or ticagrelor and a heparin with glycoprotein receptor IIb/IIIa antagonist or bivalirudin. Between the genders and in women over time we compared clinical data, the use and time to PPCI, in-hospital complications, 30-day and 6-month mortality.

Results STEMI patients in recent years were treated by PPCI in 94.5%. Their 30-day mortality was 10.4% and 6-month mortality 14.7%. Between the genders we observed mostly nonsignificant differences (age, comorbidities, treatments, in-hospital complications, 30-day and 6-month mortality). Over the last years in women mean age significantly decreased, the use of PPCI significantly increased, the incidence of heart failure and bleedings decreased significantly, but mortalities nonsignificantly.

Conclusion Women still account for 1/4 of STEMI population, but the gap between the genders in presentation, treatments and outcome in STEMI population is decreasing.

Keywords Acute ST-elevation myocardial infarction · Men · Women · Treatment · Mortality

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Introduction

Contemporary reperfusion therapy by primary percutaneous coronary intervention (PPCI) combined with novel antiplatelet and anticoagulant agents improved prognosis of patients with ST-elevation myocardial infarction (STEMI) significantly and decreased short- and long-term mortality [1, 2].

Some years ago clinical studies demonstrated several significant differences between men and women with STEMI. Women in comparison to men were significantly older—even up to 10 years; they were less likely treated by reperfusion therapy, in particular by PPCI [3, 4]. In women, time to reperfusion therapy was significantly prolonged [4, 5]. In women, STEMI was significantly more likely complicated by in-hospital heart failure and their short- (30-day) and long-term (6-month) mortality was significantly increased in comparison to men [4–6].

Within the last few years women gained more attention in respect to diagnostics and treatment of cardiovascular diseases, in particular in the setting of STEMI [5–8]. Our aim was to evaluate gender differences in the setting of STEMI as well as the differences in women over time regarding clinical presentation, treatments, in particular the use of reperfusion therapy—in our case PPCI—and novel antithrombotic therapies, in-hospital complications and mortality within 30 days and 6 months.

Patients and methods

We retrospectively included all STEMI patients, admitted from October 1, 2011 to December 31, 2012, to the Department of Medical Intensive Care at University Clinical Centre Maribor. The study was approved by the Institutional Ethics Committee (UKC-MB-04/14), who waived the need for informed consent because of the retrospective nature of the study. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Personal data of all the patients were protected according to the Law on personal data protection.

We retrospectively evaluated all the electronic records of patients with discharge diagnoses of ischemic heart disease (I20.0-I.25.0) by the institutional electronic information system. As only discharge diagnoses were considered, all the patients with chest pain of noncoronary origin were excluded. Finally, we included 307 STEMI patients (mean age 64.7 ± 12.4 years, 244 men, 83 women), fulfilling inclusion criteria for STEMI such as rest chest pain of more than 20–30 min, nonresponding to sublingual nitroglycerin and persistent ST-segment elevation of at least 1–2 mm in at least two leads of standard echocardiography (ECG) or presumably new left bundle branch block with later rise and fall of troponin I [9].

Additionally, we included a historic group of 523 STEMI patients, treated from January 1, 2008 to December 31, 2009. National Ethics Committee (RS-KME 102/06/09) approved collection of these data and waived the need for informed consent due to retrospective nature of data collection, which was in accordance with the ethical standards of the Declaration of Helsinki and the Law on personal data protection.

In all STEMI patients in addition to age and gender, we registered prior diseases, known as risk factors for atherosclerosis (prior arterial hypertension, known diabetes, smoking), duration of chest pain to treatment, laboratory data (admission and peak troponin I levels, admission lipid profile, peak NT-proBNP levels), in-hospital treatments (PPCI, antithrombotic medication), ejection fraction (EF), in-hospital complications such as arrhythmias, heart failure, reinfarction, bleedings as well as 30-day and 6-month mortality.

All the registered data were compared between the genders in each time period and finally, all the registered data were compared in women over time—between period 1 (January 1, 2008 to December 31, 2009) and period 2 (October 1, 2011 to December 31, 2012).

After STEMI was diagnosed either on field or in the Emergency Department of University Clinical Centre Maribor by standard ECG, the patients immediately received acetylsalcylic acid (ASA)—loading dose of 300–500 mg orally or i.v., morphine with antiemetic i.v., sublingual nitroglicerine and standard heparin i.v. up to 5000 IE [9].

As soon as STEMI was diagnosed, catheterization laboratory was consulted for PPCI and the majority of STEMI patients also received second oral antiplatelet agent—clopidogrel (loading dose 300–600 mg) or ticagrelor (loading dose 180 mg) or prasugrel (loading dose 60 mg) at the discretion of the consulted physician. The patients were usually immediately transferred to the catheterization laboratory for PPCI [9].

After PPCI was performed STEMI patients were admitted to the Department of Medical Intensive Care for monitoring and treatment [9]. All the patients were noninvasively monitored for at least 24 h by continuous ECG, pulse oxymetry. Blood pressure and pulse were measured noninvasively per hour. Peripheral i.v. catheter was inserted in all the patients [9].

On admission in all STEMI patients, standard ECG was recorded and blood samples were drawn to measure baseline laboratory tests, including troponin I levels, the lipid profile (serum triglicerides, total serum cholesterol, HDL-cholesterol and LDL-cholesterol).

During in-hospital stay standard ECG was recorded and troponin I measured on daily basis. Within the first 24–48 h NT-proBNP was measured and echocardiography performed to measure ejection fraction (EF).

In case of complications, laboratory tests were usually repeated as well as other diagnostic procedures (ECG, chest rentgenograph) [9].

Acute myocardial infarction was confirmed with the rise and fall of troponin I in addition to ECG changes with or without Q wave [9, 10].

Troponin I was measured by colorimetric immuno method (Siemens Healthcare Diagnostics Inc., Newark, USA; normal levels were up to 0.045 μg/l) [9, 10].

Total serum cholesterol, triglicerides, HDL-cholesterola, and LDL-cholesterol were measured by standard enzymatic methods (Olympus, Japan) and NT-proBNP levels by the electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, normal levels up to 20 pmol/l) [9, 10].

During the first few hours after PPCI the patients usually received oxygen by face mask or by nasal canulla, i.v. infusion of fluids to prevent renal injury and i.v. infusion of glycoprotein receptor (GP) IIb/IIIa antagonist or bivalirudin at the discretion of the treating physician [9].

Within the first 24 h treatment with statins, beta blockers and angiotensin-converting enzyme inhibitors was initiated, if indicated. Daily treatment with ASA and clopidogrel or ticagrelor or prasugel was continued [9].

Among in-hospital complications we registered acute heart failure, arrhythmias, reinfarctions, bleedings, and acute renal failure [9].

Arrhythmias, registered by continuous ECG monitoring and standard ECG recordings, were defined as atrial or ventricular or conduction disturbances [9].

Heart failure was defined by the Killip–Kimball classification as classes II–IV. Pulmonary congestion belonged to Killip class II, pulmonary edema to Killip class III, cardiogenic shock to Killip class IV [9].

Reinfarctions were classified as recurrent chest pain with new ECG-changes and recurrent rise and fall of serum troponin I [9, 10].

Bleedings were classified according to severity and localization. Major bleedings were cerebral or symptomatic bleedings of other location with a drop in hemoglobin level of >50 g/l, minor bleedings were symptomatic with a drop in hemoglobin of 30–50 g/l. Minimal bleedings were symptomatic bleedings with a drop in hemoglobin level of <30 g/l [9].

Acute renal failure was defined as a twofold increase in serum creatinine within 48–72 h [9, 11].

In case of complications, invasive monitoring was started by insertion of intraarterial, central venous and urine catheter to measure arterial bood pressure continuously, to estimate arterial blood gas analysis frequently, to measure central venous pressure and diuresis hourly [9].

In case of complications, our patients were treated by the discretion of the treating physician by diuretics, dopamine, dobutamine, noradrenalin, levosimendan, antibiotics, intra-aortic baloon pump, mechanical or noninvasive ventilation, additional infusion of fluids, blood transfusions, etc. [9].

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 22 for Windows. The data were expressed as means ± standard deviations or percentages. Differences between the groups were tested by the two-sided Student's *t*-test for means ± standard deviations and by the chi-squared test for percentages. A *p*-value < 0.05 was considered statistically significant.

Results

Comparison of baseline clinical data, the use of reperfusion therapy and antithrombotics between the genders in period 1 and period 2, as well as comparison of data over time (between period 1 and period 2) are displayed in Table 1. In period 1, we observed some nonsignificant differences between the genders, but women with STEMI were significantly more likely to have prior arterial hypertension, less likely to smoke and less likely to undergo PPCI in the first 12 or 6 or 3 h in comparison to men. In period 2, we observed mainly nonsignificant differences between the genders, except for anterior STEMI, that was significantly less likely to be observed in women than in men. There were nonsignificant differences between the genders in time-intervals to PPCI, in the use of PPCI, stents and antithrombotic treatments.

Over time, in women we observed nonsignificant differences in the incidence of prior arterial hypertension, diabetes, prior myocardial infarctions, smoking, in time-intervals to PPCI < 6 and < 3 h, the use of stents, ASA and second ADP inhibitor. Over time, in women there was a significant increase in survival of out-of-hospital cardiac arrest, the use of PPCIs and bivalirudin, but significant

Table 1 Baseline clinical data, reperfusion therapy and antithrombotic therapy in all STEMI patients, men and women in period 1 and period 2

Baseline clinical data, PPCI, antithrombotics (%)	Period 1				Period 2			
	All (*n* = 523)	Men (*n* = 361)	Women (*n* = 162)	*p*	All (*n* = 307)	Men (*n* = 224)	Women (*n* = 83)	*p*
Arterial hypertension	57.9	52.4	69.9	0.005	55.7	54	60.2	ns
Prior diabetes	21.1	19.2	25.2	ns	17.9	16.5	21.7	ns
Prior MI	14.3	15.4	11.8	ns	13.7	14.3	12	ns
Anterior STEMI	43.6	41.8**	47.5*	ns	47.2	52.7**	32.5*	ns
Survivors of OHCA	8.9**	9.1***	8.6*	ns	16.3**	17.4***	13.5*	ns
Smoking	43.6	48.7***	30.9	0.001	31.3	29.9***	34.9	ns
Time to PPCI < 12 h	86.5***	89.1***	80.7*	0.024	66.1***	66***	66.3*	ns
Time to PPCI < 6 h	68.8***	72.8***	60	0.008	52.8***	52.2***	54.2	ns
Time to PPCI < 3 h	35.4	38.7	28.4	0.043	32.2	30.8	36.1	ns
PPCI	88.9**	89.5	87.7*	ns	94.5**	93.3	97.6*	ns
Stenting	77.4	81.8	76.6	ns	82.4	83.4	79.6	ns
ASA	98.6**	98.6*	98.7	ns	94.4**	94.6*	93.6	ns
Second ADP inhibitor	94.2	95.7	90.8	ns	92.5	92.4	92.8	ns
Heparins	96.3***	96.1	96.7***	ns	83.4***	83.9	81.9***	ns
GP IIb/IIIa inhibitors	89.7***	90.8***	87.1***	ns	51.1***	51.8***	49.4***	Ns
Bivalirudin	0***	0***	0***	ns	35.5***	36.2***	33.7***	ns

MI myocardial infarction, *STEMI* ST-elevation myocardial infarction, *OHCA* out-of-hospital cardiac arrest, *PPCI* primary percutaneous coronary intervention, *ASA* acetylsalicylic acid, *ADP* adenosine diphosphate, *GP* glycoprotein

Within the groups statistical analysis: *; statistically significant ($p < 0.05$; **; statistically significant ($p < 0.01$); ***; statistically significant ($p < 0.001$) for the differences over time in all STEMI patients, in men and women with STEMI (between the period 1 and period 2), ns; statistically nonsignificant ($p > 0.05$)

decrease in the incidence of anterior STEMI, in time-intervals to PPCI < 12 h, significant decrease in the use of heparins and GP IIb/IIIa inhibitors.

Comparison of admission and in-hospital data between the genders in period 1 and period 2, as well as comparison of data in STEMI patients over time are displayed in Table 2. In period 1 we observed mostly nonsignificant differences between the genders, except for mean age, EF and HDL-cholesterol. Women were significantly older, their EF significantly decreased and their HDL-cholesterol significantly increased in comparison to men. In period 2, between the genders there were only nonsignificant differences in admission and in-hospital data.

Over time, mean age and mean NT-proBNP levels in women decreased significantly, but their EF levels significantly improved.

Complications are presented in Table 3. In period 1, women with STEMI were significantly more likely to have in-hospital heart failure (Killip classes II–IV) and bleedings than men, but in period 2 in-hospital complications occurred equally in men and women. Over time, in women the incidence of heart failure, bleedings, and acute renal failure decreased significantly. In period 1, in women with STEMI 30-day and 6-month mortality were significantly increased in comparison to men, but in period 2 the differences between the genders were nonsignificant. Over time, in women 30-day in 6-month mortality decreased nonsignificantly.

Discharge treatments are displayed in Table 4. In period 1, discharge treatments were mostly equal in men and women, but for ASA, that was significantly less likely to be administered in women than in men. In period 2, discharge treatments were equal between the genders, except that men were significantly more likely to be treated by ACE inhibitors than women and women by angiotensin-receptor blockers than men. Over time, in women discharge treatment by prasugrel and ticagrelor increased and by clopidogrel decreased significantly.

Discussion

Among our STEMI patients in recent years (period 2) 73.0 % were men and 27 % women, which was equal as few years ago (period 1). Recently, we observed mainly nonsignificant differences between the genders in baseline clinical and laboratory data on admission and during in-hospital stay, in the use of PPCI and novel antithrombotic medications, in in-hospital complications and in mortality.

Few years ago (period 1), we observed a significant difference in mean age between the genders. Women with STEMI were in average 7 years older than men. The same observations were presented in other studies [12–14]. Recently, our women with STEMI were in average only 8 months older than men. However, mean age of men with STEMI increased at the same time, reflecting aging of population and prolonged life expectancy in general [15].

In spite the younger age of women with STEMI in recent years, comorbidities such as arterial hypertension and diabetes were more likely to be observed in women than in men, but the difference was not significant. Other studies also report increased incidence of arterial hypertension in women with STEMI, but in particular in older ones [2, 3, 15].

Table 2 Admission and in-hospital data in all STEMI patients, men and women in period 1 and period 2

Admission, in-hospital data (mean ± SD)	Period 1				Period 2			
	All (n=523)	Men (n=361)	Women (n=162)	p	All (n=307)	Men (n=224)	Women (n=83)	p
Age (years)	64 ± 12.6	61.8 ± 11.7	68.9 ± 13.1*	< 0.001	64.7 ± 12.4	64.5 ± 11.9	65.3 ± 13.7*	ns
Admission troponin I (μg/l)	11.5 ± 22.1	11.8 ± 23.1	10.6 ± 19.8	ns	9.3 ± 20	9.7 ± 20.4	8.2 ± 19.2	ns
Total cholesterol (mmol/l)	5.2 ± 1.3***	5.1 ± 1.2**	5.2 ± 1.4	ns	4.9 ± 1.4***	4.8 ± 1.4**	4.9 ± 1.4	ns
Triglycerides (mmol/l)	2 ± 5.3	2.3 ± 6.3	1.6 ± 1.3	ns	1.9 ± 2.2	1.9 ± 2.4	1.6 ± 1.3	ns
LDL-cholesterol (mmol/l)	3.4 ± 1*	3.4 ± 0.9*	3.4 ± 1.2	ns	3.2 ± 1.2*	3.2 ± 1.1*	3.3 ± 1.2	ns
HDL-cholesterol (mmol/l)	1.1 ± 0.3***	1.0 ± 0.3	1.2 ± 0.3	0.024	1.4 ± 5***	1.5 ± 5.8	1.2 ± 0.3	ns
Peak troponin I (μg/l)	47.4 ± 34.7	47.0 ± 34.5	48.1 ± 34.9	ns	50.6 ± 39.2	53 ± 38.7	44.1 ± 40.2	ns
Peak NT-proBNP (ng/l)	1116.8 ± 1289.4***	880 ± 1243.3*	1684.8 ± 1279***	ns	668.9 ± 1079.9***	631.7 ± 1045*	767.5 ± 1668.8***	ns
EF (%)	43.4 ± 14.6	44.9 ± 14.4	40 ± 14.7*	0.007	43.4 ± 12.7	43.4 ± 12.3	44.3 ± 13*	ns

STEMI ST-elevation myocardial infarction, *SD* standard deviation, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *EF* ejection fraction
Within the groups statistical analysis: *; statistically significant (p < 0.05); **; statistically significant (p < 0.01; ***; statistically significant (p < 0.001) for the differences over time in all STEMI patients, in men and women with STEMI (between the period 1 and period 2), ns; statistically nonsignificant (p > 0.05)

Table 3 Complications in all STEMI patients, men and women in period 1 and period 2

Complications (%)	Period 1				Period 2			
	All ($n=523$)	Men ($n=361$)	Women ($n=162$)	p	All ($n=307$)	Men ($n=224$)	Women ($n=83$)	p
In-hospital Killip classes II–IV	39.6	36	47.5***	0.016	25	25.9	22.9***	ns
In-hospital arrhythmias	42.2	43.1	40.4	ns	40.4	41.5	37.3	ns
In-hospital bleedings	16.1***	12.6***	23.5***	0.002	2.9***	3.6***	1.2***	ns
In-hospital acute renal failure	10.3***	8.8	13.6*	ns	4.5***	4.9	3.6*	ns
In-hospital reinfarctions	1.9	1.8	2.6	ns	1	1.3	0	ns
In-hospital in-stent thrombosis	1.5	1.5	2	ns	0.7	0.9	0	ns
30-day mortality	12.6	10.5	17.3	0.032	10.4	8.9	14.5	ns
6-month mortality	15.5	13.3	20.4	0.047	14.7	13.4	18.1	ns

Within the groups statistical analysis: *; statistically significant ($p<0.05$); **; statistically significant ($p<0.01$); ***; statistically significant ($p<0.00$)1 for the differences over time in all STEMI patients, in men and women with STEMI (between the period 1 and period 2), ns; statistically nonsignificant ($p>0.05$)

Table 4 Discharge treatment in all STEMI patients, men and women in period 1 and period 2

Discharge therapy (%)	Period 1				Period 2			
	All ($n=523$)	Men ($n=361$)	Women ($n=162$)	p	All ($n=307$)	Men ($n=224$)	Women ($n=83$)	p
ASA	87.4	89.5	82.7	0.032	86.3	87.5	83.2	ns
Clopidogrel	87.4***	89.5***	82.7***	ns	22.1***	20.5***	26.5***	ns
Prasugrel	/	/	/		44.3***	46.4***	38.6***	ns
Ticagrelor	/	/	/		18.2***	19.6***	14.4***	ns
ACE inhibitor	34***	34***	32.7***	ns	65.1***	69.2***	54.2***	0.045
Beta-receptor blockers	31.7***	32.9***	29.1***	ns	60.9***	64.3***	51.8***	Ns
ARBs	/	/	/		13.3***	10.7***	20.4***	0.02
Statins	46***	45.9***	46.3***	ns	85***	86.6***	85.5***	ns

ASA acetylsalicylic acid, *ACE* angiotensin-converting enzyme, *ARB* angiotensin-receptor blockers
Within the groups statistical analysis: *; statistically significant ($p<0.05$); **; statistically significant ($p<0.01$); ***; statistically significant ($p<0.001$) for the differences over time in all STEMI patients, in men and women with STEMI (between the period 1 and period 2), ns; statistically nonsignificant ($p>0.05$)

In recent years we observed increase in smoking in women with STEMI, which may contribute to the onset of STEMI in women at an earlier age. Years ago (period 1) smoking predominated significantly in male STEMI population. Several European studies after 2010 observed a substantial increase in smoking in younger women with STEMI as well [15].

Majority of trials observed a significant time delay from the onset of chest pain to reperfusion therapy in women in comparison to men [12–14, 16]. We observed the same situation few years ago in our women with STEMI (Table 1). Our recent data demonstrated that within the first 3 h of STEMI PPCI was performed even more often in women than in men (36.1 vs. 30.8 %). However, this difference was not significant. Earlier start of reperfusion therapy in our women with STEMI in period 2 could be attributed to younger age of women. Clinical studies in the past demonstrated that elderly patients seeked help in case of STEMI later than the younger ones, in particularly elderly women [15, 17].

PPCI, being most efficient reperfusion strategy, was performed in 94.5 % of our STEMI patients in recent years, what is a significant increase since 2008–2009, when PPCI was performed in approximately 90 % of STEMI patients in our institution.

Years ago several studies reported significant underuse of PPCI in women with STEMI [3, 4, 18]. Since 2010 several studies demonstrated equal treatments of men and women with STEMI by PPCI and antithrombotic drugs [12, 13, 17]. Since 2008 our women and men with STEMI were equally treated by PPCI, oral antiplatelet agents, including novel antiplatelet agents such as prasugrel and ticagrelor, GP IIb/IIIa inhibitors, heparins, and bivalirudin.

Years ago studies and reports observed in women with STEMI, in addition to older age and under treatment by delayed PPCI, a significant increase of in-hospital complications, in particular heart failure and bleedings [13–15, 17]. Some years ago (period 1) we observed the same situation—a significant delay in treatment by PPCI, increased incidence of heart failure and bleedings in women in comparison to men (Table 3). Recently, we observed important improvements. Over time, in women the incidence of in-hospital complications significantly decreased, in particularly heart failure and bleedings. Recently, in-hospital complications were even less likely

to occur in women than in men, but the difference was nonsignificant. Younger age and earlier start of PPCI of women in comparison to men may contribute to these trends.

In recent years (period 2) bleedings were rare in our STEMI patients—in women even in 1.2 % in comparison to 3.6 % in men. The increased use of bivalirudin instead of combination of heparins and GP IIb/IIIa receptor antagonists together with novel oral antiplatelet agents such as prasugrel and ticagrelor could contribute to this finding. In the past, combined use of heparins and GP IIb/IIIa receptor antagonists most probably increased the risk of bleedings significantly in our STEMI patients, in particular in women in comparison to men [3, 9, 12, 15, 19, 20].

In recent years (period 2) we still observed predominating anterior infarcts with nonsignificantly increased peak troponin I levels in men, suggesting larger myocardial infarcts in men than in women. However, mortality in women with STEMI was still nonsignificantly increased—either at 30 days or at 6 months. In addition, NT-proBNP, being a marker of heart failure and of prognosis, was nonsignificantly increased in women as well.

Years ago in our STEMI patients the differences in mortality between men and women were significant. Older age and delayed start of reperfusion therapy were most important risk factors for increased mortality in women with STEMI as observed in several reports [3, 12, 15, 19]. Over time, we observed significant changes in treatments, presentation and in-hospital complications, that could explain a decrease in 30-day and 6-month mortality in STEMI patients in general, including women.

More efficient secondary prevention in recent years contributed additionally to improved survival in STEMI patients in long term, including women. It consisted of significantly increased use of novel dual antiplatelet therapy, statins, beta blockers and blockade of renin–angiotensin–aldosteron system by angiotensin-receptor antagonists or angiotensin-converting enzyme inhibitors [3].

Our conclusions are that the differences between the genders in STEMI patients are decreasing in presentation, treatments, in time to PPCI, the use of PPCI and novel antithrombotics, in-hospital complications and mortalities.

Conflict of interest

All the authors—Andreja Sinkovic, Nejc Piko, Matevz Frangez and Andrej Markota declare that there are no actual or potential conflicts of interest related to this article.

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