

GENDER RELATED DIFFERENCES IN OUTCOMES FOLLOWING PERCUTANEOUS CORONARY INTERVENTIONS IN DIFFERENT AGE GROUPS OF PATIENTS WITH ST – ELEVATION ACUTE MYOCARDIAL INFARCTION

*Gujajaini L.
Sharashidze N.
Pagava Z.
Mamatsahvili M.
Aladashvili L.
Taboridze I.
Saatashvili G.*

Iv. Javakhishvili Tbilisi State University, LTD “ADAPTI”

Abstract

Background: Conflicting evidence exists in respect of gender differences in outcomes after Acute Coronary Syndromes (ACS).

Aim: Evaluation of gender differences in outcomes after ST – elevation Acute Myocardial Infarction (STEMI) in different age groups of patients following percutaneous coronary interventions (PCI).

Methods: We studied consecutive 292 female and consecutive 311 male STEMI patients who underwent PCI with stent implantation. Study individuals were divided into groups by the gender and age (<65, 65-75, >75 years). Patients with total ischemic time >4 hours were excluded from the study. In hospital, 45-day and one year outcomes (death from cardiovascular causes, repeated angiography and revascularization) were evaluated, as well as several factors which may influence disease outcomes.

Results: Total death rate in hospital, during 45-days and one year period: in women - 0.168, 0.250, 0.438, in men - 0.161, 0.289, 0.408, differences were not significant ($p > 0.05$). In hospital death rate in study groups (age groups <65, 65-75, >75 years): in women -0.112, 0.155, 0.257, in men -0.121, 0.176, 0.216. Forty five-day mortality rate in study groups: in women -0.135, 0.279, 0.338, in men- 0.226, 0.279, 0.471; one year mortality rate in study groups: in women -0.315, 0.419, 0.622, in men - 0.347, 0.419, 0.529. Differences are

statistically significant in age group under 65 years ($P < 0.05$). Age under 65 years is associated with lower probability of in hospital and 45 days mortality (OR -0.53, 95% CI 0.9 – 0.25, OR- 0.36, 95% CI 0.18-0.72) in females, as well as with one year mortality in females OR- 0.47 , 95%CI 0.28 -0.80 and 45 days mortality in males OR-0.35, 95%CI 0.59-0.99. Study showed significantly ($P < 0.005$) higher rate of repeated angiography (0.154 vs 0.077) and revascularization (0.127 vs 0.026) in females as compared with men after STEMI following primary PCI with stent implantation,

Conclusions: a) Mortality rates (in hospital, 45 days and one year) after STEMI in patients with ischemic time < 4 hours who underwent PCI with stent implantation did not differ between genders; b) Women younger 65 years with STEMI after timely revascularization have better prognosis as compared with their male counterparts and females of other groups; c) Risk of one year repeated angiography and revascularization in one year is higher in female patients with STEMI following primary PCI with stent implantation.

Keywords: Gender Differences, ST – elevation Acute Myocardial Infarction (STEMI), percutaneous coronary interventions (PCI)

Introduction

Most of earlier studies suggested that female gender is associated with worse prognosis after acute coronary syndromes (ACS) (Greenland P, Reicher-Reiss H, Goldbourt U, et.al., 1991), (Cowley M., Mullin S., Kelsey S. et al., 1985). However, prognosis of AMI improved during the last decades as a result of implementation of innovative treatment strategies (Duvernoy CS, Smith DE, Manohar P, et.al., 2010), (Park JS, Kim YJ, Shin DG, et.al. , 2010), (Singh M, Rihal CS, Gersh BJ, et al., 2008), (Lansky AJ, Hochman JS, Ward PA, et al., 2005). Some studies showed the similar success rate of primary Percutaneous Coronary Intervention (PCI) and in-hospital outcomes in both genders (Singh M, Rihal CS, Gersh BJ, et al., 2008), (Liu Y, Wang LF, Yang XF, et.al., 2008), (Radovanovic D, Erne P, Urban P, et.al., 2007), while others did not (Mehilli J, Kastrati A, Dirschinger J, et. al., 2002), (Jacobs A.K., Johnstone J.M., Haviland A. et al., 2002). Significantly higher unadjusted mortality rate was observed in women (Thompson CA, Kaplan AV, Friedman BJ, et. al. , 2006) - a higher short-term mortality in females with STEMI (Park JS, Kim YJ, Shin DG, et.al., 2010), (Rasoul S, Ottervanger JP, de Boer MJ, et.al., 2009), (Benamer H, Tafflet M, Bataille S, et al., 2011) and female patients with acute STEMI still have a worse prognosis during the long-term follow-up (Liu Y, Wang LF, Yang XF, et.al., 2008), (Wijnbergen I, Tijssen J, van 't Veer M, et.al., 2013), but after adjustment for age and cardiovascular risk factors, the long-term

mortality rate in patients with STEMI did not differ between genders (Singh M, Rihal CS, Gersh BJ, et al., 2008), (Jacobs A.K., Johnstone J.M., Haviland A. et al., 2002), (Thompson CA, Kaplan AV, Friedman BJ, et. al., 2006), or was lower in women (Lee KH, Jeong MH, Ahn YK, et. al., 2008), (De Luca G, Gibson CM, Gyöngyösi M.et.al., 2010), (Bhan V, Cantor WJ, Yan RT, et.al., 2012).

Age was an important determinant for clinical outcomes in the group of consecutive STEMI patients transferred for primary PCI (Dziewierz A. Zbigniew Siudak Z. Rakowski T.et.al., 2012). Age-adjusted hospital mortality was higher in women and was associated with a lower rate of percutaneous coronary intervention (Milcent C, Dormont B, Durand-Zaleski I, et.al., 2007). Whether female gender can be considered as an independent risk factor remains unclear. Older age of women with ACS at presentation is main confounding factor (Rasoul S, Ottervanger JP, de Boer MJ, et.al., 2009), (Berger JS, Brown DL., 2006). Women were underrepresented in most of studies and comparison between genders was difficult due to differences in age between male and female subjects. It is important to clarify possible differences between men and women in a large prospective cohort study, with equal numbers of male and female patients. Furthermore, as age is an important confounding factor, men and women of similar age should be compared (Berger JS, Brown DL., 2006).

The aim of the study was to evaluate gender differences in outcomes after ST – elevation Acute Myocardial infarction (STEMI) in different age groups of patients following percutaneous coronary interventions (PCI).

Patients and methods

Consecutive 292 female and consecutive 311 male STEMI patients (total number - 603) admitted to the hospital during 2009-2010 and underwent PCI with stent implantation were studied. In vast majority of the patients bare metal stents were used. Study individuals were divided into groups by the gender and age: males – I group, females – II group, Ia group -124 (males < 65 years), Ib group -136 (males 65 – 75 years), Ic group -51 (males >75 years), IIa group - 89 (females < 65 years), IIb group -129 (females 65 – 75 years), IIc group -74 (females >75 years). Patients with total ischemic time (defined as time from symptom onset to first coronary intervention) >4 hours were excluded from the study. In hospital, 45-day and one year outcomes were evaluated, as well as several factors (co-morbidities, the initial level of Troponin I - 6 hours later the symptom onset, EF %-examined by echocardiography) which may influence disease outcomes in all groups of patients. All patients were linked to the one year follow up, and follow up was performed by outpatient visits or telephone call.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local Ethics Committee. Written informed consent was obtained from all patients.

STEMI definition

STEMI was defined by symptoms, electrocardiographic changes - ST-segment elevation and/or a new development of LBBB at presentation, cardiac marker elevation (troponin I above individual hospital cut-off levels for MI).

Study endpoints

The primary endpoint was death from cardiovascular causes. Secondary endpoints included repeated angiography and revascularization (PCI or CABG).

Statistics

Continuous variables are expressed as mean \pm SD, and categorical variables as frequencies. Continuous variables were compared with the use of the students' *t* test and categorical variables with the use of the Fisher's Exact Test. All statistical tests were two-tailed, and a **p** value < 0.05 was considered as statistically significant. The odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. All statistical analyses were performed using SPSS version 17.0.

Results

Prevalence of diabetes, CKD and COPD in all study population did not differ significantly between genders (Table1). Prevalence of hypertension was significantly higher in women. Prevalence of diabetes, hypertension and CKD increases with age. Comparison of different age groups showed higher prevalence of diabetes, hypertension and lower prevalence of CKD in males <65 years as compared with age matched females (Table 2). Prevalence of Diabetes and Hypertension was higher in females of 65-75 years than in the same age group of males (Table 2).

Mean EF% in males (47.65 ± 11.136) was higher as compared with females (44.63 ± 12.441) ($p < 0.01$). No difference in mean initial troponin I level between genders was revealed (mean level in males – ($0.311 \text{ ng/ml} \pm 0.195$, in females - $0.332 \text{ ng/ml} \pm 0.211$, $P > 0.05$).

No differences in overall mortality rates between genders were found (Table1). In hospital, 45-day and one year mortality increases with age. In age group <65 mortality was lower in females as compared with males. Mortality rates did not differ between genders in age groups 65-75 (Table2).

Table 1 Mortality and co-morbidities in female and male patients with STEMI

Co - morbidities	Variables	Males	Females	P
		n=311(grII) Abs (freq)	n=292 (grI) Abs (freq)	
Co - morbidities	Diabetes	124 (0.40)	123 (0.42)	0.5775
	hypertension	195 (0.63)	219 (0.75)	0.0011
	CKD	46 (0.15)	58 (0.20)	0.0998
	COPD	63 (0.20)	44 (0.15)	0.0959
mortality	In-hospital mortality	50 (0.161)	49 (0.168)	0.8158
	45-day mortality	90 (0.289)	73 (0.250)	0.2768
	1-year mortality	127(0.408)	128(0.438)	0.4566

***Table 2 Co -morbidities and mortality in different age groups of patients with STEMI**

Co-morbidities	Variables	Females I n=292			Males II n=311		
		IIa (n=89)	IIb (n=129)	IIc (n=74)	Ia (n=124)	Ib n=136	Ic (n=51)
		Abs.(freq)	Abs.(freq)	Abs.(freq)	Abs.(freq)	Abs.(freq)	Abs.(freq)
Co-morbidities	Diabetes	26 (0.29)	60 (0.46)	37(0.50)	39 (0.31)	59 (0.43)	25 (0.49)
	Hypertensio n	53 (0.59)	106(0.82)	60 (0.81)	76 (0.61)	74 (0.54)	45 (0.88)
	CKD	11 (0.12)	21(0.16)	26 (0.35)	13 (0.10)	18 (0.13)	15 (0.29)
	COPD	11 (0.12)	18(0.14)	15 (0.29)	24 (0.19)	24 (0.17)	15 (0.29)
Mortality	In-hospital	10 (0.12)	20 (0.15)	19 (0.25)	15 (0.12)	24 (0.17)	11 (0.29)
	45 -day	12 (0.11)	36 (0.27)	25 (0.33)	28 (0.26)	38 (0.27)	24 (0.47)
	One-year	28 (0.13)	54 (0.41)	46 (0.62)	43 (0.34)	57 (0.41)	27 (0.52)

* p values for data demonstrated in table 2 are given in table 3

Table 3 P values for table 2

groups	P value						
	Diabetes	hypertension	CKD	COPD	In-hospital	45-day	one-year
IIa –Ia	0.0068	0.0031	0.0006	0.1710	0.0167	0.0021	0.0001
IIb- Ib	0.0143	0.0002	0.1775	0.2493	0.4336	0.3309	0.2410
IIc -Ic	0.9145	0.2855	0.5047	0.2414	0.5987	0.1367	0.3059
IIa-IIb	0.0104	0.0002	0.4226	0.7340	0.3697	0.0117	0.1201
IIa-IIc	0.0068	0.0031	0.0006	0.1710	0.0167	0.0021	0.0001
IIb-IIc	0.6329	0.8469	0.0022	0.7235	0.0774	0.3806	0.0055
Ia-Ib	0.0478	0.0005	0.4949	0.1475	0.2115	0.3221	0.2320
Ia-Ic	0.0288	0.0000	0.0020	0.0786	0.1104	0.0013	0.0254
Ib-Ic	0.4912	0.0012	0.0100	0.0958	0.5414	0.0136	0.1780

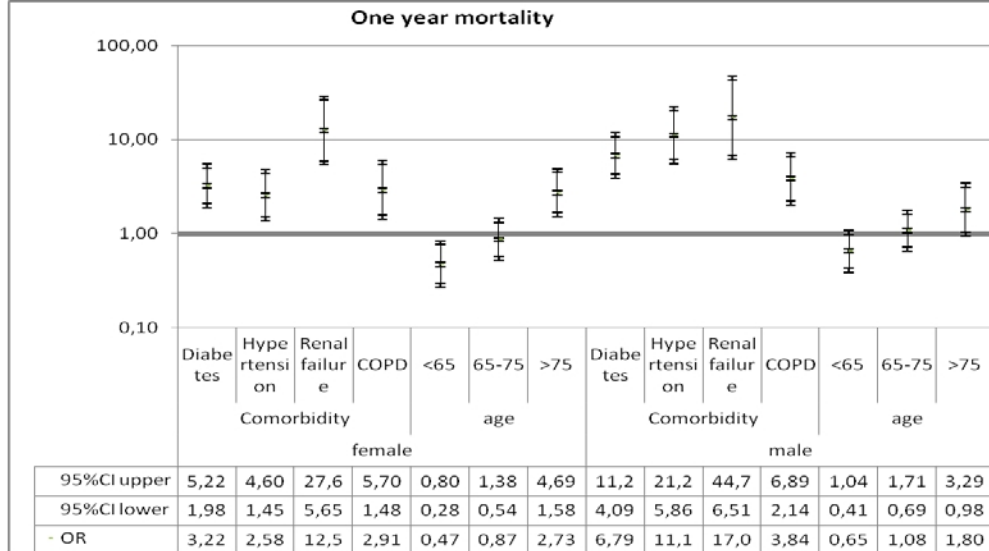
Diabetes, hypertension, CKD and age >75 increases risk of mortality in females (RR- 1.89,95% CI 1.48 - 2.43, RR- 1.39, 95% CI 1.27 - 1.52, RR-4.03, 95% CI 2.66 – 6.11 RR-2.60, 95% CI 1.34- 5.03). Risk of mortality in males is higher in individuals with Hypertension, Diabetes, COPD and CKD (RR 1.70 , 95% CI 1.51- 1.92,RR 2.61, 95% CI 2.09 - 3.26 , RR2.25, 95% CI 1.44- 3.52, RR 6.21 ,95% CI 3.79- 10.19) .

Diabetes, hypertension, CKD and age >75 increases in hospital mortality in females (OR-3.92(95%CI:2.02-7.60), OR-20.21(2.74-14924), OR-7.45(3.80-14.64), OR-4.14(1.13-2.16)., In hospital mortality in males rises with Hypertension - OR=18.61(4.43-78.2), Diabetes – OR=9.4(4.62-21.42), COPD - OR=3.02(1.57(-5.83) and CKD - OR=11.43(5.61-23.28). Age < 65 found to be predictor of favorable prognosis in females. Age under 65 years was associated with lower probability of in hospital and 45 days mortality (OR -0.53, 95% CI 0.9 – 0.25), OR- 0.36, 95%CI (0.18-0.72) , as well as one year mortality in Females (Figure 1).

Age < 65 is associated with lower 45-day mortality in males (OR - 0.35(0.59-0.99). Diabetes, hypertension, CKD and age >75 increases 45-day mortality in females (OR-4.00 95% CI 2.28-7.02, OR-7.94 95%CI 2.78-22.62, OR-9.69 95%CI 5.10-18.43, OR-1.8195%CI 1.01-3.22) as well as in males(OR-5.39 95%CI 3.17-9.17, OR-17.16 95%CI 6.70-17.16, OR-14.07 95% CI 6.57-30.13 and OR-2.61 95%CI 1.41-4.84). COPD, also, is a predictor of adverse outcome in males (OR-4.39 95%CI 2.46-7.84).

Hypertension, Diabetes, CKD, COPD and age above 75 are associated with higher one-year mortality in both genders (Figure 1).

Figure 1 One-year mortality (Odds Ratio) in different groups of patients with STEMI



Repeated angiography and revascularization rates during one year after primary PCI were higher in women (Table 4). Repeated angiography and revascularization rates during one year after primary PCI were significantly higher in women >75 years as compared with age matched man (Table 4). Female gender increases chance of one-year Repeated

Angiography and revascularization in patients aged >75 (OR - 4.29, 95% CI 1.70 -17.63).

Table 4 Repeated Angiography and Revascularization in different age groups of females and males with STEMI

	Repeated Angiography			Repeated revascularization		
	Females Abs,(freq.)	Males Abs,(freq.)	<i>P</i>	Females Abs,(freq.)	Males Abs,(freq.)	<i>P</i>
<i>Age</i>						
<65	1 (0.011)	3 (0.024)	0.8625	1 (0.011)	3 (0.024)	0.8625
65 -75	5 (0.039)	6 (0.044)	0.9203	4 (0.031)	2 (0.015)	0.6172
>75	8 (0.108)	2 (0.039)	0.2943	5 (0.068)	1 (0.020)	0.4101
Total	14 (0.048)	11(0.035)	0.5839	10 (0.034)	6 (0.019)	0.3712
In- Hospital						
<65	1 (0.011)	3 (0.024)	0.8625	1 (0.011)	2 (0.016)	0.7773
65 -75	7 (0.054)	7 (0.051)	0.8625	5 (0.039)	3 (0.022)	0.6548
>75	10 (0.135)	2 (0.039)	0.1380	5 (0.068)	1 (0.020)	0.2059
Total	18 (0.062)	12(0.039)	0.2733	11 (0.031)	6 (0.019)	0.5270
45 days						
<65	6 (0.067)	7 (0.056)	0.9203	1 (0.011)	5 (0.040)	0.4020
65 -75	9 (0.070)	10 (0.074)	0.9203	7 (0.054)	2 (0.015)	0.1516
>75	30 (0.405)	7 (0.137)	0.0027	29 (0.392)	1 (0.020)	0.0000
Total	45 (0.154)	14 (0.077)	0.0043	37 (0.127)	8 (0.026)	0.0000
One year						

Discussion:

Inconsistence of data regarding gender differences in outcomes of ACS may be explained by heterogeneity of population included in different studies: in some of them patients with STEMI were included, while in other studies patients with non-STEMI and unstable angina were also involved. Large variation in mean age of study groups makes difficult to compare results of different studies. In most of studies women are underestimated. By the existed data in several studies the total ischemic time was longer in women (Lee KH, Jeong MH, Ahn YK, et. al., 2008), (De Luca G, Gibson CM, Gyöngyösi M.et.al., 2010), (Lee CY, Hairi NN, Wan Ahmad WA, et.al., 2013). It should be considered that the outcomes may be greatly influenced by the prolongation of ischemic time. To resolve the question whether female gender is an independent risk factor causing worse outcomes in ACS, similar number of patients of different genders with similar characteristics should be compared. In our study relatively homogeneous groups of patients of both genders were investigated (individuals with STEMI and total ischemic time <4 hours, data in the same age groups of patients were compared, all study subjects underwent PCI with stent implantation). Previous studies reported that women younger than 65 years have worse prognosis as compared with men of the same age group (Berger JS, Brown DL., 2006) (Regitz-Zagrosek V., Lehmkuhl E., Hoher B. et al., 2004). It may be caused by high cardiovascular risk burden, as well as delayed hospitalization and less aggressive treatment. According to the data of our research, women under 65 years have better prognosis (in-hospital, 45 days and one year) as compared with their male counterparts. It should be

noted that they were hospitalized within 4 hours from symptom onset, as well as men enrolled in research and received the same treatment as men of similar age group. Hypertension and diabetes were observed in female patients more frequently than in male counterparts (Greenland P, Reicher-Reiss H, Goldbourt U, et.al., 1991), (Singh M, Rihal CS, Gersh BJ, et al., 2008), (Thompson CA, Kaplan AV, Friedman BJ, et. al., 2006). Women were significantly older and had significantly higher rates of diabetes mellitus, hypertension, chronic renal failure (Lee CY, Hairi NN, Wan Ahmad WA, et.al., 2013), (Dey S, Flather MD, Devlin G, et al., 2009). According to the data of our research, rate of hypertension was significantly higher in women, but frequency of diabetes, renal failure and COPD did not differ significantly between genders. Nevertheless, comparison of different age groups showed lower prevalence of co-morbidities in women <65 years and in contrast of it, higher prevalence of concomitant diseases in females 65-75 years as compared with age matched males. No differences in prevalence of co-morbidities between genders above 75 years were revealed. Co-existence of diabetes, hypertension and CKD worsens prognosis after STEMI in both genders.

The higher in-hospital mortality noted in women is likely multifactorial and may be largely due to increased risk profile (advanced age at PCI, more frequent presentation with acute coronary syndrome, and higher prevalence of co -morbid conditions) (Singh M, Rihal CS, Gersh BJ, et al., 2008). Differences in mortality between men and women with STEMI treated with PCI were shown to be age- depended (Otten AM, Maas AH, Ottervanger JP, et.al., 2013), (Presbitero P, Carcagnì A.et.al., 2003). According to our results, overall, in hospital mortality did not differ significantly between genders and one year mortality is lower in women aged <65 as compared with men of the same age group. Higher mortality in males <65 may be due to higher prevalence of co - morbidities as compared with age matched females. Risk of mortality (in hospital, 45 day and one-year) in females increases above the age of 75 years. No differences in mortality rates between genders in age groups 65-75 were noted. Mortality rates did not differ significantly in males and females above 75 years.

By our results female gender is associated with higher rate of both early and later repeated angiography and revascularization after STEMI. Further research (large scale randomized control trials) is needed to confirm this finding and identify possible reasons for it.

Conclusion

a) Mortality rates (in-hospital, 45 days and one year) after STEMI in patients with ischemic time <4 hours who underwent PCI with stent implantation did not differ between genders; b) Women younger 65 years

with STEMI after timely revascularization have better prognosis as compared with their male counterparts and females of the other groups; c) Risk of repeated angiography and revascularization after one year are higher in female patients with STEMI following primary PCI with stent implantation.

Study limitations

Retrospective design, single centre study with limited size of included population; Possible influence of selection bias; Data missing regarding coronary anatomy and severity of lesions, amount of implanted stents, location of infarct , KILLIP class of heart failure, severe arrhythmias, drug treatment regimen during one year period– factors may influence outcomes. We have no data regarding sex differences in STEMI patients with delayed hospitalization and their outcomes, as well as, generally, differences of outcomes in patients treated conservatively.

Further research is needed to define issues regarding sex-specificity features of disease course, treatment efficacy and outcomes in patients with STEMI.

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