

The Impact of Gender on the Outcomes of Invasive versus Conservative Management of Patients with Non-ST-Segment Elevation Myocardial Infarction

Li-Ching Lee,¹ MBBS, MRCP, Kian-Keong Poh,¹ FRCP, FAMS, FACC, Tiffany PL Tang,¹ MBBS, MRCP, Yee-Leng Tan,¹ MBBS, MRCP, Han-Wen Tee,¹ MBBS, Huay-Cheem Tan,¹ FRCP, FAMS, FACC

Abstract

Introduction: Studies have suggested that women who present with non-ST-segment elevation myocardial infarction (NSTEMI) may differ in their clinical response to early invasive strategy compared to male patients. We examined the impact of gender difference in NSTEMI patients on outcomes following invasive versus conservative treatment. **Materials and Methods:** Patients enrolled in our national myocardial infarction (MI) registry between January 2000 and September 2005 with diagnosis of NSTEMI were retrospectively analysed. The study endpoint was the occurrence of major adverse cardiac events (MACE) in the patients at 1 year. **Results:** A total of 1353 patients (62.2% male) with NSTEMI were studied. The mean age of men was 62 ± 14 versus 72 ± 12 years in women in the cohort ($P < 0.001$). The prevalence of hypertension and diabetes mellitus were significantly higher in women. Men were more likely to undergo revascularisation than women (OR, 2.97; 95% CI, 2.18-3.89, $P < 0.001$). Among those who were revascularised, there was no gender difference in survival or recurrent MI rates during hospitalisation and at 1 year. Compared to medical therapy, percutaneous coronary intervention (PCI) was associated with a significant reduction in MACE in both women (OR, 0.44; 95% CI, 0.20-0.95) and men (OR, 0.40; 95% CI, 0.20-0.75). The most important predictor of MACE for females was diabetes mellitus (HR, 1.98; 95% CI, 1.17-3.33). **Conclusions:** There is a gender-based difference in the rate of revascularisation among patients with NSTEMI. Women benefit from an invasive approach as much as men, despite their advanced age, with similar rates of mortality and recurrent MI at 1-year follow-up.

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Key words: Acute coronary syndrome, Major adverse cardiac events, Management strategies, Women

Introduction

Recent studies have suggested differences in clinical outcomes between men and women following acute myocardial infarction (AMI). Some studies have indicated poorer survival of female AMI patients on admission and short-term follow-up, whilst others have shown no difference in outcome.^{1,2} Poorer outcome was often attributed to less aggressive management or underlying co-morbidities,³ and women had consistently been shown to be more likely to receive less invasive treatment compared to men.⁴⁻⁷ In addition, there were studies suggesting that women who presented with non-ST-elevation myocardial infarction (NSTEMI) did not benefit from early invasive strategy.^{8,9} Though there are conflicting data on the impact of gender on the outcome of AMI, the poor outcome in

female patients may be due to higher age at presentation and attendant comorbid conditions.¹⁰

To date, most of the studies conducted on AMI populations either included both STEMI and NSTEMI patients, or solely STEMI patients. We performed a retrospective analysis of all patients admitted to our institution between January 2000 and September 2005 for NSTEMI. Our primary aim was to examine the impact of gender on clinical outcomes. We also aimed to determine the impact of age, cardiovascular risk factors, and invasive treatment (i.e. percutaneous coronary intervention (PCI) versus conservative treatment) on the 2 gender groups and then compare the differential effects of gender. The study endpoint was a composite of major adverse cardiovascular events (MACE) of target vessel revascularisation, mortality and re-infarction at 1-year follow-up.

¹ The Cardiac Department, National University Heart Centre and Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Address for Correspondence: A/Prof Huay-Cheem Tan, National University Heart Centre, Singapore, 5 Lower Kent Ridge Rd, Main Building Level 3, Singapore 119074.
Email: Huay_Cheem_Tan@nuhs.edu.sg

Materials and Methods

Study Patients

Patients who presented at National University Heart Centre, Singapore with NSTEMI between January 2000 and September 2005 were enrolled in our study. Those who underwent coronary artery bypass surgery (CABG) following coronary angiography (119 patients) were excluded. Patients were classified by the type of treatment they received, namely, invasive PCI vs medical therapy, and followed-up for up to 1 year after admission. Out-of-hospital mortality was confirmed with the Singapore Registry of Births and Death.

Statistical Analysis

Univariate analyses were performed to identify gender difference in terms of risk factors and type of interventions. Significant factors were included in logistic regression analysis to assess the impact of gender difference on patient outcomes. Multivariate logistic regression was also performed to determine predictors of 1-year mortality. All analyses were performed using SPSS 13.0 for Windows (SPSS Inc, Chicago, IL). Statistical significance level was set at ≤ 0.05 .

To examine the associations between clinical outcome, gender and use of medication, odd ratios (OR) were evaluated. The 4 groups of medications included in the analyses were antiplatelets, statins, angiotensin-aldosterone blockers and beta-blockers.

Results

A total of 1353 patients (62.2% males) with NSTEMI were studied. The study cohort comprises Chinese (59.3%), Malays (22.5%), Indians (15.9%) and Others (i.e. Eurasian and foreigners) (2.3%).

Cardiovascular Risk Factors

We found that in our series of NSTEMI, women (72 ± 12 years) were significantly older than men (62 ± 14 years). They were more likely to be non-smokers (13.1% vs 61.0%) and had had significantly higher prevalence of hypertension (80.4% vs 63.5%) and diabetes mellitus (63.8% vs 40.4%). However, there were more men with dyslipidaemia (67.5% vs 61.1%) (Table 1).

Intervention

Of the 1353 cases, 539 (39.8%) were offered coronary angiography. A significant proportion of men [410 (48.7%)] underwent coronary catheterisation compared to women [129 (25.2%), $P < 0.001$]. For those who underwent the procedure, 265 men and 70 women subsequently underwent successful PCI (Table 2). Females were less likely to undergo invasive procedure, even after correcting for age (OR, 1.56; 95% CI, 1.18-2.05; $P = 0.002$).

Table 1. Baseline Characteristics of All Patients

	Male (n = 842)	Female (n = 511)	Overall (n = 1353)	P value
Age (y)	62 $\pm$ 14	72 $\pm$ 12	66 $\pm$ 14	<0.001
Race				
Chinese (%)	485 (57.6%)	318 (62.2%)	803 (59.3%)	NS
Malay (%)	194 (23.0%)	110 (21.5%)	304 (22.5%)	NS
Indian (%)	142 (16.9%)	73 (14.3%)	215 (15.9%)	NS
Others (%)	21 (2.5%)	10 (2.0%)	31 (2.3%)	NS
Hypertension (%)	307 (36.5%)	411 (80.4%)	946 (69.9%)	<0.001
Hyperlipidaemia (%)	568 (67.5%)	312 (61.1%)	880 (65.0%)	0.017
Diabetes mellitus (%)	502 (59.6%)	326 (63.8%)	666 (49.2%)	<0.001
Smoker (%)	514 (61.0%)	67 (13.1%)	581 (42.9%)	<0.001
Prior myocardial infarction (%)	133 (15.8%)	65 (12.7%)	198 (14.6%)	NS
Prior PCI (%)	59 (7.0%)	28 (5.5%)	87 (6.4%)	NS
Prior CABG (%)	39 (4.6%)	15 (2.9%)	54 (4.0%)	NS

CABG: coronary artery bypass graft; NS: not significant; PCI: percutaneous coronary intervention

Table 2. Procedural Characteristics of All Patients

Procedure	Total	Male	Female	P value
Coronary angiogram (%)	539 (39.8%)	410 (48.7%)	129 (25.2%)	<0.001
Percutaneous coronary intervention (%)	335 (62.2%)	265 (64.6%)	70 (54.3%)	<0.001

Table 3. In-hospital and Follow-up Crude Mortality Rates of Patients who were Managed Medically and with Percutaneous Coronary Intervention (PCI)

Mortality	Medical treatment (%) (n = 1017)	PCI (%) (n = 336)
During admission	135 (13.3%)	2 (0.6%)
30-day	149 (14.7%)	2 (0.6%)
1 year	208 (20.5%)	2 (0.6%)

Mortality and Re-infarction at 1-year Follow-up

The overall mortality and re-infarction rate at 1 year was 15.5% (n = 210) and 13.8% (n = 142) respectively. Women have a higher rate of re-infarction within the first year (17.5% vs 11.6%; $P = 0.007$). Both genders derived significant benefits from revascularisation. As a whole, crude in-hospital, 30-day and 1-year mortality rates

of patients managed conservatively were significantly higher in comparison with the other group (Table 3). Compared to medical therapy, PCI was associated with a significantly lower re-infarction in women (HR, 7.46; 95% CI, 1.78-31.34) and men (HR, 3.78; 95% CI, 1.95-7.32). Revascularisation reduced MACE in men and women by 2.5 and 2.3 times, respectively (Fig. 1). Multivariate logistic regression identified increased age, presence of diabetes mellitus and dyslipidaemia and non-utility of intervention to be independent predictors of 1-year mortality.

Readmission Rate at 1-year Follow-up

Table 4 showed that revascularisation decreased total re-admission rate from cardiovascular complications, including angina, re-infarction, malignant arrhythmias or congestive heart failure, across the cohort. Females were slightly more likely to be re-admitted compared to their male counterparts, regardless of treatment strategy.

Influence of Cardiovascular Risk Factors by Gender

Older patients and those who had diabetes and hypertension were more likely to die or have a re-infarction within 1 year. This applied to both men and women. Although female gender appeared to confer a poorer outcome, but after correcting for revascularisation, age and diabetes mellitus were the only determinants of poor prognosis (Tables 5A and 5B).

Discharged Medication

Upon discharge, 46.9% of all patients were on all 4 classes of medications analysed in this study (antiplatelets, statins, angiotensin-aldosterone blockers and beta-blockers), while 34.1% were on 3 classes. The median number of medications that men and women were prescribed upon discharge was the same (3 classes). However, women were prescribed less antiplatelet and lipid-lowering medications (75.3% vs 83.7%; 77.4% vs 86.0%; $P < 0.05$). There was also a trend showing that the number of medications correlated negatively with the age of patients.

Discussion

The question of whether higher morbidity and mortality observed in women are due to fundamental differences in the biology and pathophysiology of AMI between gender groups is hotly debated and still unresolved.¹¹⁻¹³ Many of these differences have been explained by the presence of more comorbidities and worse clinical manifestation in women than in men.¹⁴ As expected, we found that females with NSTEMI tend to be older and had a higher burden of comorbidities. They had higher adverse event rates compared to men. However, after adjusting for gender, the difference is no longer significant. Similar results were reported in a study by Mehilli et al.¹⁵

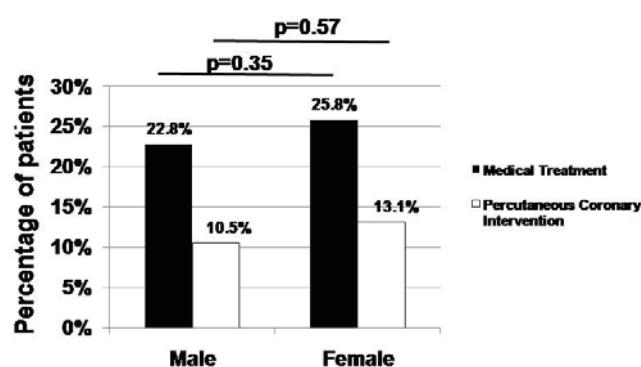


Fig. 1. Percentage of patients with major adverse cardiovascular events at 1 year, stratified by gender and management strategies (medical therapy vs PCI).

Table 4. One Year Re-Admission Rate between the Genders Following Revascularisation or Medical Treatment

	Readmission for cardiovascular complications (%)		
	Male	Female	P
Medical treatment	31.6%	36%	0.20
PCI	14.8%	19.7%	0.35
P	<0.001	0.013	

PCI: percutaneous coronary intervention

Table 5A. Relationship between MACE and Cardiovascular Risk Factors as well as Gender in All Patients

	HR (95% CI)	P
Gender (men vs women)	0.72 (0.53-0.98)	0.037
Age	1.03 (1.02-1.04)	<0.001
Hypertension	1.87 (1.29-2.71)	0.001
Hyperlipidaemia	1.27 (0.89-1.84)	0.193
Diabetes mellitus	1.89 (1.39-2.57)	<0.001
Smoker	0.73 (0.53-1.00)	0.047

95% CI: 95% confidence interval; HR: hazard ratio

Table 5B. Relationship between MACE and Cardiovascular Risk Factors, Gender after Correction for Revascularisation

	Adjusted HR (95% CI)	P
Gender (men vs women)	1.10 (0.76-1.59)	0.62
Age	1.02 (1.01-1.04)	0.001
Hypertension	1.38 (0.93-2.05)	0.11
Diabetes mellitus	1.69 (1.21-2.36)	0.002
Smoker	1.10 (0.76-1.61)	0.61
Smoker	0.73 (0.53-1.00)	0.047

95% CI: 95% confidence interval; HR: hazard ratio

Delay in detection of coronary artery disease in women due to their atypical presentation and older age may have contributed to their worse outcome compared to men. Yet, it appeared that women were 1.6 times less likely to be treated

invasively even after correcting for age. This may be due to inherent gender bias in patient care. Perhaps females, being older at presentation, resulted in lower tendency to prescribed invasive procedures.

Also, there was a proportionally higher number of diabetics among the female patients (63.8% vs 40.4%). Diabetes mellitus is known to be associated with more diffuse disease and poorer left ventricular function post-infarction.^{16,17} In fact, some earlier studies have shown poorer outcomes in women with diabetes mellitus as comorbidity.¹⁸⁻²¹

On the other hand, procedural refusal may have also contributed to the disparity in management between male and female patients. Though we do not have similar data in this Asian setting, based on clinical observation of the authors, elderly female patients tend to refuse invasive procedures in our local culture. However, a study by Rathore and Krumholz²² showed that absolute race and sex differences in rates of procedure refusal postmyocardial infarction in the USA were small and provided only a partial explanation of observed differences in cardiac procedure use.

Aggressive management successfully reduced the unfavourable composite outcomes in women with NSTEMI. More importantly, mortality and re-infarction associated with revascularisation treatment were not significantly different between the 2 genders in this cohort, even though some studies have shown that women treated with very early aggressive revascularisation with PCI have a better long-term outcome compared to men.²³ A possible reason may be that only women with relatively lower risk were offered invasive therapy, whilst women with multiple comorbidities were more likely to be managed conservatively. There is good evidence that use of a higher rate of invasive strategy can improve prognosis for both men and women.^{24,25} Indeed, patients with the highest risk profile including females derive the most benefit from intervention and should be employed in higher frequency. However, not infrequently, reperfusion procedures were performed less often in women.^{26,27}

Hence, although a gender gap indeed existed between men and women with AMI, this gap is only an apparent one, and not truly related to gender alone, after adjusting for other risk factors and revascularisation therapy. More importantly, doctors appear to be hesitant in recommending invasive treatment to female patients in the high-risk group, i.e. those with prior infarction, history of revascularisation and multiple comorbidities. Among all the patients who were managed aggressively, gender disparity in terms of outcome was not observed. In an editorial, Jacobs²⁸ reported that women tend to have worse in-hospital, but not long-term, outcomes than men. Most of these adverse outcomes were explained by the higher risk profile of women, as well as peri-procedural complications. However, in our study,

the in-hospital mortality rate was not significantly higher in women.

Previous studies have demonstrated that patients receiving optimal medical therapy had significantly lower 1-year mortality.²⁹ Women as a whole were given sub-optimal medications in our study. Our study has shown that women were less likely to be discharged with antiplatelet and lipid-lowering medications. A possible reason may be the concern of side-effects of these medications such as higher vascular complication rate, bleeding events, anaemia and renal impairment in female patients. Interestingly, similar findings were reported recently in recent studies where women with acute coronary syndrome were less likely to receive aspirin or statin.^{30,31} Quality improvement strategies are hence needed to enhance the appropriate use of effective therapies, targeting especially the high-risk, but undertreated, female patients who may derive the greatest therapeutic benefit.

Limitations

This is a non-randomised clinical observational study. We did not have the details of patients who died outside the hospital. In addition, the reasons (such as eligibility criteria) for less invasive management of women are not available.

Conclusions

There is a gender-based difference in the rate of invasive procedures, as well as optimal medical therapy, among the NSTEMI patients in this study. Women benefit from an invasive approach as much as men, despite their advanced age. Mortality and re-infarction associated with revascularisation treatment are independent of gender. It is possible that underlying comorbidities contribute significantly to women's mode of management and poorer survival rate. Both men and women should be treated similarly and not be denied invasive therapy. Efforts to optimise medication regimens upon discharge from hospitalisation, and to enhance rates of compliance, are warranted to prevent subsequent death and re-infarction.

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