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Paper

Predictors of excess mortality after myocardial infarction in women

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SUMMARY

Background: Research suggests that women have higher mortality after acute myocardial infarction (AMI) than men. Potential factors to explain this disparity include delay to presentation, less aggressive interventional strategies, and more severe disease at coronary angiography in women.

Methods: Consecutive patients (n=663) presenting to coronary care between Jan 2002 and Jan 2005 with ischemic type chest pain and AMI (troponin T >0.09ng/ml) were recruited. Details of the presentation and management were obtained from the medical notes. The primary endpoint was three month all cause mortality.

Results: Of these patients 31% (205/663) were female. Mean age of women was 70 (SD 11) and 63 (SD 13) for men (p<0.001). There was no difference between the sexes for delay in presentation or treatment or for ST elevation infarction site. Women had prior hypertension more than men (49% 100/205 vs. 38% 174/458, p=0.008). Women were less likely to have diagnostic catheterisation (67% 137/205 vs. 80% 365/458 p<0.001). Both genders had similar coronary artery disease extent and frequencies of LV impairment (EF<45%) and were equally likely to undergo revascularisation (79% 108/137 vs. 81% 295/365 p=NS). There was an excess 3 month mortality among women (11% 23/205 vs. 5% 24/458 in men p=0.006).

Independent predictors of 3 month mortality by logistic regression analysis were age (OR 1.06, 95% CI 1.03 -1.09, p<0.001) and LV impairment (OR 0.28, 95% CI 0.13-0.56, p<0.001).

Conclusion: As LV impairment was comparable in men and women, the excess mortality identified is due to older age at presentation of women.

INTRODUCTION

In this era of primary prevention in the cardiovascular field it is crucial that both health professionals and patients alike recognise coronary heart disease (CHD) as the leading cause of death amongst women. Cardiovascular disease is responsible for one third of female mortality worldwide[1]. Public health initiatives for women have concentrated on the "bikini cancers" with successful outcomes. It follows therefore that highlighting issues associated with CHD in women could have widespread effects on the targeting of health service provision.

Women are significantly more likely than men to die within 1 year of myocardial infarction[1-5]. Several reasons for this gender discrepancy in early mortality have been postulated. Of those patients diagnosed with myocardial infarction, the women are on average 8 years older than the men[6-9]. The diagnosis and management of CHD in women is therefore complicated by age associated comorbidities. Behavioural factors may play a role; the traditional role of the female as the care giver rather than care seeker has been implicated in their reluctance to seek medical assistance for the atypical symptoms that they often develop[10]. Women diagnosed with ischemic heart disease have greater frequencies of hypertension[5,8,9,11] and diabetes mellitus[3,6,8,9, 11,12] than their male counterparts. Also non ST elevation MIs (NSTEMI's) are more common in women than in men[10]. This clearly adds to the difficulty in diagnosing AMI in women and further compounds delay to initiation of appropriate treatment[10,13]. Several studies have demonstrated that the aggressive revascularisation strategies are less likely to be employed in women presenting with acute coronary syndromes[9,10,11,14].

The aim of this study was to clarify the differences in the presentation and management of AMI between males and females and to determine predictors of the excess mortality amongst women presenting to the Royal Victoria Hospital Belfast Coronary Care Unit.

METHODS

Study patients

The recruitment site has a doctor manned mobile coronary care unit, an Accident and Emergency department and is a tertiary facility with on site coronary angiography theatres

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TABLE I.

Baseline Characteristics of Male and Female Patients

	Males (N=458)		Females (N=205)		P value
Age (yr)*	63±13		70±11		<0.001
	No's	**%**	**No's**	**%**	
Family History	220	48	99	48	0.322
Diabetes Mellitus	74	16	42	20	0.166
Hypercholesterolaemia†	198	43	88	43	0.982
Hypertension	174	38	100	49	0.008
Smoking status-					
Never smoked	108	24	80	39	<0.001
Ex-smoker	166	36	51	25	
Current smoker	184	40	73	36	
Body-mass index >25‡	217	47	66	32	0.001
Past Medical History					
Previous angina	180	39	92	45	0.184
Previous infarction	131	29	63	31	0.644
Previous Investigation					
PCI	47	10	14	7	0.155
CABG	40	9	7	3	0.013
Total Cholesterol mmol/L*	4.8±1.2		5.2±1.2		<0.001
HDL mmol/L*	1.2±0.5		1.4±0.5		<0.001
LDL mmol/L*	2.8±1.1		3.2±1.1		0.002
Triglycerides mmol/L§	1.52		1.67		0.327
Creatinine Clearance mls/min*	82±33		63±30		<0.001

*Mean ±SD †>5mmol/L ‡The body-mass index is the weight in kilograms divided by the square of the height in meters. Blood samples are fasting taken on day 2 of admission
§ Median value – differences detected using the non parametric Mann Whitney U test. CABG = Coronary Artery Bypass Grafting, PCI = Percutaneous Coronary Intervention

and a regional cardiac surgery department. The Coronary Care Myocardial Infarction Registry was used to identify consecutive patients presenting during 01 January 2002- 01 January 2005 with a diagnosis of myocardial infarction. Myocardial infarction was defined as typical ischemic or atypical symptoms of at least 20 minutes duration with a cardiac Troponin T > 0.09ng/ml at 12 hours from symptom onset. Atypical symptoms were predefined as breathlessness, upper back pain between the shoulder blades, epigastric discomfort or jaw pain in the absence of chest pain.

Data collection

This study was a retrospective case review. Obtained from the medical notes of these patients were the following:

Demographics: Age, sex, mode of admission (the mobile coronary care unit or via the emergency room etc.)

Risk Factors: History of hypertension, diabetes mellitus, family history of coronary disease, smoking, cholesterol, and body mass index.

Delay Factors: Presentation delay was defined as longer than 2 hours from onset of symptoms to first seeking medical assistance. Treatment delay was defined as longer than 1 hour from when the patient first sought assistance to the initiation of appropriate medical therapy. Time of onset of symptoms (taken from the patient history), time of ambulance call (recorded on emergency room or mobile coronary care unit admission data) and time when seen by medical personnel were used to calculate delays.

Clinical Factors: A prior history of MI or angina, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were noted.

The site of infarction was determined from the admission ECG using standard Minnesota coding criteria. NSTEMI was diagnosed if no ST elevation was present. Echocardiography

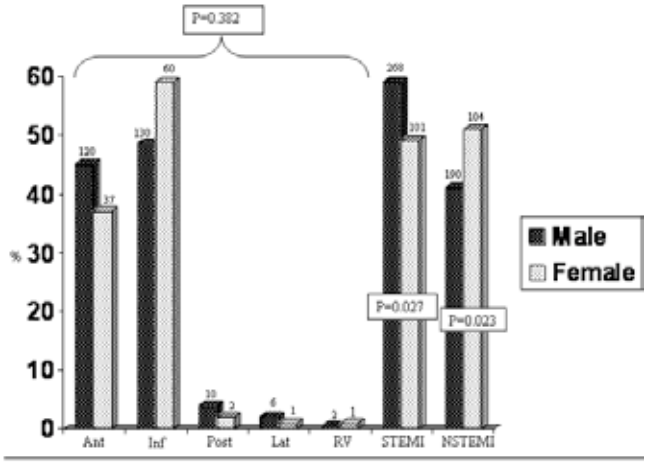

Fig 1. Comparison of infarct location from admission 12 lead ECG in males and females*.

carried out (n = 545) within 48 hours of admission was assessed. LV dysfunction was diagnosed if the Ejection Fraction was <45%.

Laboratory Data: Fasting cholesterol and triglyceride levels on day two after admission and creatinine clearance were recorded for each patient.

Medical Therapy: Antiplatelet therapies including aspirin, clopidogrel and GPIIbIIIa inhibitors were noted. Thrombolytic therapy where appropriate, beta blocking therapy, ACE inhibition and statin therapy were also recorded.

Coronary Angiography: If coronary angiography was performed during admission or within three weeks after discharge it was noted as was revascularisation by PCI or CABG. The extent of disease at angiography i.e. single, double or triple vessel disease was also documented.

Endpoint: The primary endpoint of the study was three month all cause mortality. These data were obtained from the secondary prevention clinics or where this was unavailable, from the general practitioner's records. This endpoint at 3 months post event was chosen to assess an intermediate mortality as other studies have assessed the early in hospital and 1 year mortality; it is however inclusive of in-hospital mortality.

Statistical analysis

All analyses were performed using SPSS version 11 for Windows; SPSS Inc, Chicago, Illinois, USA). Univariate comparison of dichotomous variables firstly by gender and then mortality was carried out using the Pearson's χ^2 statistic. Continuous normally distributed variables are reported as mean ± 1SD; median is quoted for data of skewed distribution. Normally distributed continuous variables were similarly evaluated in terms of gender and then mortality using the Student's t test. Mann Whitney U method was used to compare non parametric continuous variables. A p value of <0.05 was significant.

Three month mortality after myocardial infarction was compared between men and women firstly without adjustment, then with adjustment for age and then with adjustment for age and other candidate variables identified on initial univariate analysis. The models were constructed in a stepwise manner beginning with prehospital variables such as demographics and risk factors, followed by delay factors and clinical variables and finally with treatment given and interventions undertaken. In each case sex was forced into the model. In this way the influence of gender on mortality could be evaluated in conjunction with confounding factors. Results are shown as odds ratios (OR) with corresponding 95% confidence intervals (CI). The goodness of fit of the model was assessed by the Hosmer-Lemeshow statistic.

RESULTS

Baseline and presentation characteristics

Of the 663 AMI patients 31% (205) were female. Females were older (p<0.001), had a greater history of hypertension (p = 0.008) and smoked less than males (p<0.001). A BMI >25 was more frequent in the male group than in females (47% vs. 32%, p=0.001). Also the mean LDL was higher in the female group (3.2mmol/L vs. 2.8mmol/L, p = 0.002) (table I.)

Women more commonly presented with atypical features than men (24% 49/205 versus 9% 41/458, p<0.001). There were no significant differences between males and females in their modes of presentation to coronary care; 63% (288/458) of males compared to 64% (132/205) of females were admitted via the emergency department and 37% (170/458) and 36% (73/205) respectively were admitted via the mobile coronary care unit. Similar numbers of males and females sought initial assistance from their general practitioner (12% 53/458 males versus 16% 33/205 females, p = NS). Similar rates of delay were observed in both groups; 37% (170/458) males and 40% (81/205) females demonstrated a delay to present to medical services and 8% (36/458) males and 8% (16/205) females had some delay in initiation of therapy (p = 0.994). Baseline biochemical analysis for males and females is as shown in table 1. Mean creatinine clearance in the female group was significantly lower than that of the male group (p<0.001) as would be expected given that creatinine clearance is closely related to age.

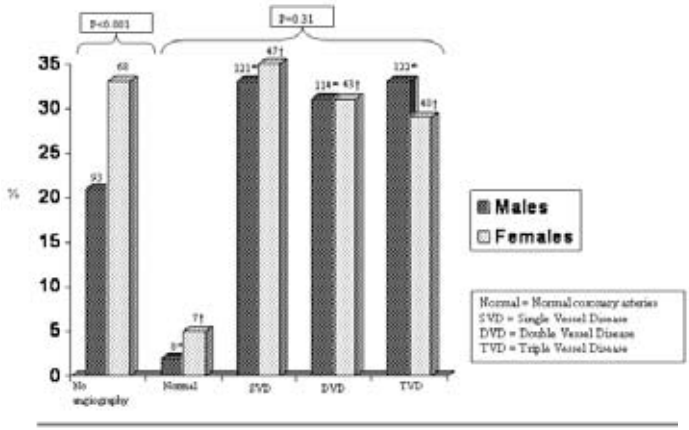

Fig 2. Coronary angiography in males and females.

Table II.

Initial Medical Therapy

Treatment	Male (N=458)		Females (N=205)		P value
	No's	%	No's	%	
Thrombolytic given*	231	94	85	97	0.197
Aspirin therapy	433	95	194	95	0.952
Clopidogrel therapy	402	88	166	81	0.014
GP IIbIIIa Inhibitor therapy	67	15	18	9	0.037
LMWH/UFH	446	97	196	96	0.282
β blocking therapy	429	94	186	91	0.118
ACE inhibitor therapy	401	88	171	83	0.115
Statin therapy	444	97	199	97	0.829

*247 Males and 88 Females met Minnesota criteria for thrombolytic therapy and had no contraindication to thrombolytic therapy. LMWH=Low Molecular Weight Heparin, UFH=Unfractionated Heparin

Clinical factors and management instituted

ST elevation infarct location was similar in males and females. There was however a preponderance of NSTEMI in females (51% 104/205 versus 41% 190/458 in males, p = 0.023) (figure 1).

Females did not receive aggressive antiplatelet therapies as often as males despite the higher prevalence of NSTEMI's in this group (table II).

Also, women did not proceed to diagnostic angiography and hence intervention as frequently as men (see figure 2). This figure also demonstrates that the extent of atherosclerotic disease at catheterisation is similar in males and females. Females who were conservatively managed were significantly older than those males who did not proceed to invasive investigation as shown in figure 3. For those 365 male and 137 female patients who did have diagnostic angiography, similar frequencies of males and females were successfully revascularised by either PCI (69% 253/365 males vs. 71% 97/137 females) or CABG (12% 42/365 males vs. 8% 11/137 females) (p = NS). LV impairment occurred with similar frequency in both genders; 28% 106/377 males compared to 30% 51/168 females, p = 0.594.

Three month mortality in females was 11% (23/205) compared to 5% (24/458) in males (p = 0.006). The age distribution of deceased patients is shown in figure 4.

Factors predictive of three month mortality

Table III summarises the results of a univariate analysis of three month mortality.

Subsequent logistic regression models analysing the influence of gender on mortality in association with pre hospital variables and also with treatment factors were constructed. Table IV demonstrates that the most significant independent predictors of early mortality amongst these models are advanced age and presence of LV impairment. ST elevation infarction site was not included in this analysis as there were no significant differences between the genders for infarction site and to do so would have reduced the numbers of patients for analysis to a much smaller number.

The influence of gender on mortality after AMI

The effect of sex on mortality loses significance when age is added in the first model. As age was such a significant confounding variable it is subsequently included in all models. The frequency of LV impairment was similar in males and females, therefore we conclude that the observed excess in mortality amongst females is due to their advanced age.

DISCUSSION

These results highlight several differences in the presenting characteristics and subsequent management of myocardial infarction in men and women. Potentially this information may be used to establish a gender specific approach to diagnosis and management of CHD, so focusing services to better meet the needs of patients regardless of their gender.

What are the gender differences in presentation and management of AMI? Women and men have different disease perception; it is known that atypical symptoms such as epigastric discomfort, breathlessness and back pain are common presentations in women[12,13]. It is hypothesised that female patients are unaware that these symptoms can represent coronary ischaemia and so may fail to present to medical services in a timely fashion[15,16]. Our results do not support this theory but do show that a large proportion of our patients delay to present for significant periods of time regardless of their gender. For those women who do present, theoretically there may be a delay in making the diagnosis and hence

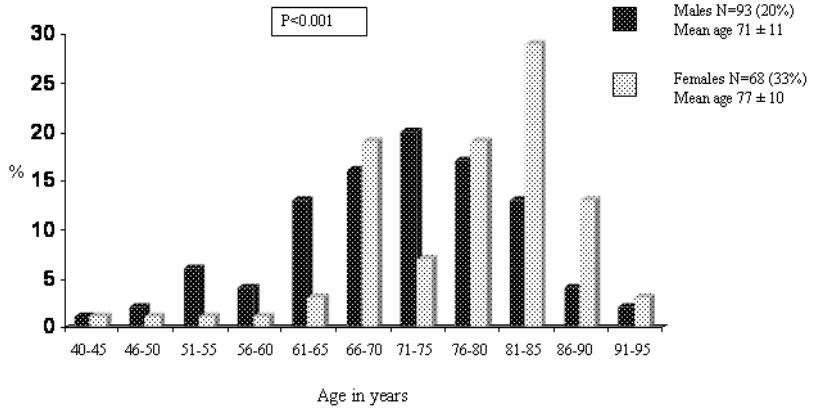

Fig 3. Age distribution of males and females who did not have coronary angiography and were managed conservatively.

TABLE III.

Univariate Analysis of three Month Mortality

	Deceased at 3 months (N=47)		Alive at 3 months (N=616)		P value
Age (yr)*	73±10		64±13		<0.001
	No's	**%**	**No's**	**%**	
Sex					
Male	24	51	434	71	0.006
Female	23	49	182	29	
Risk Factors:					
Family History	20	43	299	48	0.763
Diabetes Mellitus	10	21	106	17	0.435
History of Hypercholesterolaemia†	19	40	267	43	0.788
Hypertension	25	53	249	40	0.047
Smoking status-					
Never smoked	17	36	171	28	
Ex-smoker	19	40	198	32	0.048
Current smoker	10	21	247	40	
Body-mass index >25	14	30	269	44	0.198
Past Medical History:					
Previous angina	23	49	249	40	0.257
Previous infarction	16	34	178	29	0.463
Previous Investigation:					
PCI	3	6	58	9	0.486
CABG	5	11	42	7	0.327
Delay Total Delay	28	60	243	39	0.007
Presentation Delay	27	57	224	36	0.004
Treatment Delay	2	4	50	8	0.341
MI type:					
STEMI	25	53	344	56	0.724
NSTEMI	22	47	272	44	
ST elevation infarct site: N=369					
Anterior	8/25	32	149/344	43	
Inferior	11/25	44	179/344	52	
Posterior	5/25	20	7/344	2	<0.001
Lateral			7/344	2	
Right Ventricular	1/25	4	2/344	1	
LV impairment: N=545	21/36	58	136/509	27	<0.001
Treatment:					
Thrombolytic therapy	16	34	300	49	0.052
Aspirin therapy	43	91	584	95	0.306
Clopidogrel therapy	28	60	540	88	<0.001
LMWH/UFH therapy	44	94	598	97	0.135
GpIIbIIIa inhibition	7	15	78	13	0.659
ACE Inhibitor therapy	30	64	542	88	<0.001
B blocking therapy	35	75	580	94	<0.001
Statin therapy	41	87	602	98	<0.001
Coronary Angiography: N=502	19	4	483	96	<0.001
PCI	8/19	42	342/483	71	<0.001
CABG	4/19	21	49/483	10	0.956
Disease Extent at Angiography:					
Normal Coronaries			15/483	3	
Single Vessel Disease	1/19	5	167/483	35	0.004
Double Vessel Disease	5/19	26	152/483	31	
Triple Vessel Disease	13/19	68	149/483	31	
	N=29		**N=539**		
Total cholesterol mmol/L*	4.4±1.3		5.0±1.3		0.009
LDL mmol/L*	2.6±1.2		3.0±1.1		0.129
HDL mmol/L*	1.2±0.5		1.2±0.5		0.988
Triglycerides mmol/L§	1.2 (0.2)		1.6 (1.3)		0.001
	N=36		**N=585**		
Creatinine Clearance mls/min*	40±31		74±36		<0.001

*Mean ±SD †>5mmol/L §Median (Variance) – Differences detected by the non parametric Mann Whitney U test CABG = Coronary Artery Bypass Grafting, HDL = High Density Lipoprotein, LDL = Low Density Lipoprotein, LMWH = Low Molecular Weight Heparin, PCI = Percutaneous Coronary Intervention, UFH = Unfractionated Heparin

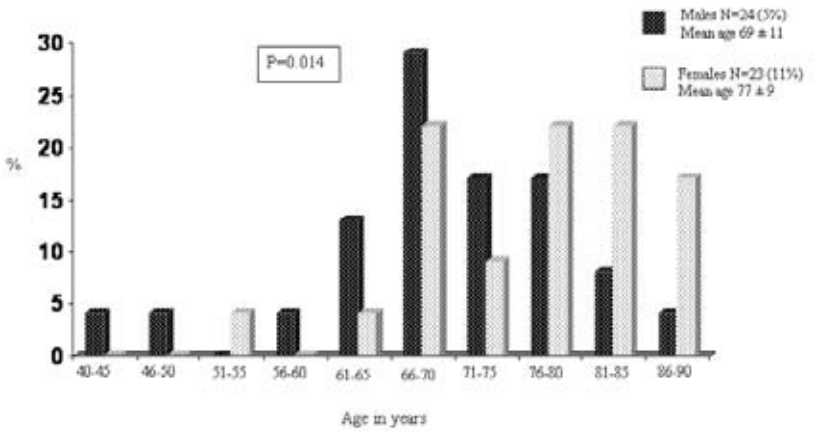

Fig 4. Age distribution of patients deceased at three months.

initiation of therapy due to a combination of atypical histories and more NSTEMI's[13]. Again our results do not support greater treatment delay in females. It is demonstrated that women have more hypertension and proportionately higher LDL and triglyceride levels than the men. Perhaps these risk factors impart more serious consequences to postmenopausal females than males of a similar age particularly when the fact that females tend to have smoked less is considered. Women are more likely to have a definite history of pre-infarct angina than men who tend to present initially with an infarct[2,4]. It is potentially in this pre-infarct stage that intervention, both revascularisation techniques and risk factor management could be optimised in females.

TABLE IV.

*The Influence of Gender on 3 Month Mortality By Logistic Regression**

	P Value	OR (95%CI)	Hosmer-Lemeshow statistic p value
Sex	0.007	2.29 (1.26-4.15)	
Model 1 - Demographics			0.702
Sex	0.121	1.64 (0.88-3.04)	
Age	<0.001	1.06 (1.03-1.09)	
Model 2 – Risk factors			0.733
Sex	0.210	1.51 (0.79-2.89)	
Age	0.001	1.05 (1.02-1.09)	
BP	0.18	1.53 (0.81-2.87)	
Smoking	0.44	0.85 (0.56-1.29)	
Model 3 - Delay			0.381
Sex	0.133	1.62 (0.86-3.02)	
Age	<0.001	1.06 (1.03-1.09)	
Presentation Delay	0.015	2.14 (1.16-3.97)	
Model 4 – Disease factors			0.219
Sex	0.100	1.83 (0.90-3.75)	
Age	0.009	1.05 (1.01-1.08)	
LV impairment	<0.001	0.28 (0.13-0.56)	
Model 5 – Treatment factors			0.410
Sex	0.197	1.54 (0.80-3.00)	
Age	0.002	1.05 (1.02-1.08)	
Clopidogrel therapy	0.010	0.40 (0.20-0.80)	
β Blocking therapy	0.006	0.31 (0.13-0.71)	
ACE Inhibitor therapy	0.005	0.35 (0.17-0.73)	
Statin therapy	0.090	0.32 (0.09-1.20)	
Model 6- Intervention			0.798
Sex	0.147	1.61 (0.85-3.06)	
Age	0.080	1.03 (1.00-1.06)	
Angiography	0.070	0.48 (0.22-1.06)	
PCI	0.030	0.35 (0.13-0.91)	

*Creatinine clearance was not included as its value is largely a function of age.

Is the "discrimination" against women in terms of investigation and management real?

ST elevation infarct site and presence of post infarct LV impairment is similar in men and women. Consistent with previous reports highlighting discrepancies in invasive investigation and management between males and females[10,11,14], this is confirmed in our patient population. This also contributes to the shortfall in the administration of aggressive antiplatelet agents in women. Figure 3 shows that those women who were managed conservatively were much older than males posing the question that perhaps there are younger males who may have benefited from invasive investigation. Contrary to the opinion that women have less intervention potential due to their smaller arteries, distribution of disease and comorbidities, we have demonstrated that those females selected for angiography have similar disease extent and revascularisation outcomes to the males. These women are however a selected group in real practice; this may prove to be the best management approach and not a reflection of "discrimination" towards the female gender.

When adjusted for confounding variables gender no longer has an influence on survival after myocardial infarction regardless of the management strategy. The advanced age of the females largely explains the excess in three month mortality observed in this group.

Implications for future policies on management of CHD in women:

As our Western population continues to age so the burden of ischemic heart disease in women is increasing. Mortality after myocardial infarction is indeed higher in women and so the challenge presents to prevent myocardial infarction where possible by targeting modifiable factors in the pre-infarct stage. Traditionally guidelines on the diagnosis and management of ischemic heart disease have made few allowances for the differences in presentation and natural history of the disease between the genders. In the light of these results and those of previous studies it follows that we as physicians are not adhering to the current guidelines[7,9,11,13,14,17]. Is this appropriate? Until recent years coronary heart disease was predominantly a male disease and the large clinical trial data have reflected this experience with only small numbers of females recruited. Our study has not specifically examined diagnostic investigations, but it is demonstrated in the WISE study[18] and others[19-21] that diagnostic strategies have different sensitivity specificity ratios in females as compared to males, further compounding the confusion in diagnosis and substantiating the myth that females are not at risk of CHD. Also whilst it is reasonable to extrapolate findings from large meta-analyses on the standard pharmacological therapies to female patients, it is important to recognise that gender related differences in metabolism and action of these medications often have important clinical effects[22]. It is also accepted that women have more complications following PCI or CABG however this opinion is based on registry observations and there are few clinical trials powered sufficiently to detect a significant outcome difference between the sexes[23-26]. Some conflicting studies determined that women have equal[5,6] if not more benefit from PCI[27]. Trial data on patients over 75 years of which women make up the majority are scarce. For this reason guidelines based on existing data should be interpreted with caution in the real life scenario, particularly with regard to elderly female patients.

It is likely that when armed with information such as is presented in this study we will appreciate that a gender specific approach to the diagnosis and management of ischemic heart disease will be more effective in the future. One such approach will take account of the diagnostic limitations of the exercise stress test in females and make better use of other more sensitive and specific investigations in this group such as dobutamine stress echocardiography and myocardial perfusion imaging. Very aggressive risk factor modification, in particular hypertension and cholesterol management, may have more marked benefits in women than men in terms of prevention of fatal myocardial infarction. Selection of female patients after myocardial infarction for intervention should take into consideration comorbidities and the risk benefit ratio of intervention in women. Disease perception and awareness is a persistent problem amongst females. The American Heart Association's "Go red for women" and the European Cardiology Society's "Women at heart" initiatives should help to raise awareness of these issues and implement appropriate changes in management strategy.

Study limitations

Several limitations should be recognised. The numbers of patients achieving the endpoint of three month mortality are relatively small in both males and females. This is clearly a reflection of the improved management strategies in recent years but may have implications on regression models for identification of independent predictors of mortality. We do however feel that the model devised is reliable in that advanced age accounted for the vast majority of the gender discrepancy. We did not take account of pre hospital mortality which is recognised to be higher in males than in females[10]. Not all of the patients had a 48 hour echo carried out (82% 545/663) therefore we do not have complete data on LV function. However identical proportions of each gender had an echo completed (82% 377/458 men vs. 82% 168/205 women). Also, the logistic regression models devised on SPSS utilise only patients with complete data for the variable under examination and so we feel the models to be accurate and reliable.

CONCLUSIONS

Three month mortality after myocardial infarction in women is higher than that of men (11% vs. 5%). Women (70 ± 11 years) were significantly older than men (63 ± 13 years). Whilst women after myocardial infarction are less likely than men to undergo invasive cardiac catheterisation (67% 137/205 vs. 80% 365/458) successful revascularisation rates were similar (71% 97/137 women had PCI vs. 69% 255/365 men and 8% 11/137 women had CABG vs. 12% 42/365 men). Independent predictors of three month mortality were age and left ventricular impairment. As left ventricular impairment was comparable in men and women, the excess mortality observed in females was mainly due to their older age at presentation.

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