Pattern of Gender Variations in Acute Coronary Syndrome for Patients in Kuwait (Pagacks Study)

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Abstract

Introduction: Acute coronary syndrome (ACS) is a major cause of morbidity and mortality globally. The world has started laying emphasis on risk stratification based on gender differences. Hence, there seemed to be a void to be filled regarding ACS which aimed to identify patient characteristics (especially gender) and clinical management, as well as angiographic, PCI, and hospital outcomes in Kuwait. Out of 400 consecutive patients, 280 (140 males and 140 females) with the diagnosis of ACS transferred to the Chest Diseases Hospital for cardiac catheterization from Sep 2014 until Sep 2015 were enrolled to this pilot, observational, prospective, open label, double arm study.

Results: Analysis with SPSS 22 showed -Patients were primarily Kuwaitis (n = 206; 73.57%) and with a mean age of 59.93 ± 10.99 years. The manifestation of ACS was predominantly atypical in females. The most common reason for referral among females was non-ST segment myocardial infarction (NSTEMI, n = 84), followed by unstable angina (n = 28) and ST segment myocardial infarction (n = 23). Male presentation of STEMI were higher (n = 74); while NSTEMI and unstable angina were lesser (n = 34 and 32 respectively). 33.9% of patients had multivessel disease, possibly due to the high rate of diabetes and renal disease. While a higher percentage of females could be managed with medical management alone (48.6%), those who had to be referred for CABG (17.9%) were higher, but those who underwent PCI (33.6%) was comparatively lower than males.

Conclusion: High rates of aggressive ACS make primary prevention extremely important especially in females.

Introduction

Gender differences play a role in the treatment of cardiovascular disease (CVD) and affect outcomes. Sex differences are a result of a single chromosomal difference between men (XY) and women (XX). Gender, however, is a social construct that differentiates men from women in a society as they assume their social roles. Gender develops on the basis of cultural norms and is articulated through values, perceptions, psychosocial characteristics, and behaviours [1-3].

Background and Rationale

Despite substantial progress in the diagnosis and management of acute coronary syndrome (ACS) over the past 20 years, ACS remains a major cause of morbidity and mortality globally [4]. In addition to aggressive medical therapy, two treatment pathways have emerged for the treatment of ACS. Using the initial invasive strategy, triaged patients undergo an invasive diagnostic evaluation without first undergoing a noninvasive stress test (i.e., initial conservative diagnostic strategy) otherwise known as selective invasive strategy [5].

Keywords
Cardiac catheterization, Coronary Angiography (CAG), Percutaneous Coronary Intervention (PCI), Gender, Kuwait, ACS- Acute Coronary Syndrome
outcomes of such patients in Kuwait. In this pilot, observational, prospective, double arm study, we evaluated ACS patients who were transferred to the Chest Diseases Hospital for coronary angioplasty over a period of 1 year (01 Sep 2014 to 01 Sep 2015).

**Methodology**

For patients with ACS, angiography is used for invasive risk stratification [6]. It can identify the 10-20% of patients without significant coronary stenosis, 20% with multivessel CAD, and 20% with left main stenosis. This latter group can derive a survival benefit from coronary artery bypass graft (CABG) surgery. In addition, percutaneous coronary intervention (PCI) of the culprit lesion may reduce the risk for subsequent hospitalization and the need for multiple anti-anginal drugs compared with an early conservative strategy [6].

In the state of Kuwait, majority of ACS patients is admitted to a general hospital for diagnosis and initial management, and is subsequently transferred to the Chest Diseases Hospital as a tertiary referral center for cardiac catheterization and coronary angiography (the hub and spoke model with Chest Diseases Hospital as the hub and different referring general hospitals as the spokes). Due to the absence of sufficient published data for patients undergoing coronary angiography after an ACS event emphasizing on gender differences, our aim was to identify the characteristics, clinical management, and the angiographic, PCI, and hospital outcomes of such patients in Kuwait. In this pilot, observational, prospective, double arm study, we evaluated ACS patients who were transferred to the Chest Diseases Hospital for coronary angioplasty over a period of 1 year (01 Sep 2014 to 01 Sep 2015).

**Figure 1**: Methodology.

ACS: Acute Coronary Syndrome; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft.

ACS patients from Ministry of health hospitals and private hospitals

Transfer to Chest diseases hospital

Screening and informed consent process

Baseline data collection

Coronary angiography

Selection of treatment pattern-medical management, PCI or CABG

Subject discharged/transferred back to referring hospital

1. Diagnosed as ACS.
2. Subjects ≥ 18 years of age.
3. Informed consent signed by subject/legally accepted representative.
Alsaddah et al. Int J Clin Cardiol 2017, 4:092

ratio- i.e. 140 each) transferred to the Chest Diseases Hospital in Kuwait for cardiac catheterization and coronary angiography with the diagnosis of ACS from Sep 2014 until Sep 2015 were enrolled into the study. The demographics and clinical characteristics of all subjects and the two cohorts are outlined in table 1. Among the 280 subjects, 206 (73.6%) were Kuwaitis. The mean age were found to be almost similar for both groups, while BMI was higher for females presenting with ACS. Amongst these the following factors were found to be significant- there were significantly higher number of smokers in males than in females (82 vs. 16 respectively; p-value: < 0.001). Even though most of the subjects in both cohorts presented with a Killip class III, the number of males in Killip III were significantly higher compared to the females (72 vs. 46 respectively; p-value: 0.002) while the number of females were significantly higher in the Killip- I category (50 females vs. 30 males; p-value: 0.008).

A huge percentage of patients transferred to the Chest Diseases Hospital from other hospitals were already on the following medications to treat the coronary event: 272 (97.1%) on aspirin, 262 (93.6%) on Plavix, 217 (77.5%) on beta blocker, 86 (30.7%) on intravenous unfractionated

### Table 1: Baseline demographics and clinical characteristics on transfer.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 280)</th>
<th>Male (n = 140)</th>
<th>Female (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>60.10 ± 11.72</td>
<td>60.81 ± 10.76</td>
<td>59.39 ± 12.62</td>
</tr>
<tr>
<td>Kuwaitis, n (%)</td>
<td>206 (73.6%)</td>
<td>103 (73.6%)</td>
<td>103 (73.6%)</td>
</tr>
<tr>
<td>Mean BMI in kg/m²</td>
<td>30.48 ± 7.16</td>
<td>26.76 ± 4.36</td>
<td>34.14 ± 7.51</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>180 (64.3%)</td>
<td>86 (61.4%)</td>
<td>94 (67.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>200 (71.4%)</td>
<td>94 (67.1%)</td>
<td>106 (75.7%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>189 (67.5%)</td>
<td>91 (65%)</td>
<td>98 (70%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>102 (38.6%)</td>
<td>82 (58.6%)</td>
<td>16 (18.6%)</td>
</tr>
<tr>
<td>Positive family history of coronary artery disease</td>
<td>101 (36.1%)</td>
<td>48 (34.3%)</td>
<td>53 (37.9%)</td>
</tr>
<tr>
<td>H/o Percutaneous Coronary Intervention (PCI)</td>
<td>36 (12.9%)</td>
<td>18 (12.9%)</td>
<td>18 (12.9%)</td>
</tr>
<tr>
<td>H/o Coronary Artery Bypass Graft (CABG)</td>
<td>29 (10.4%)</td>
<td>17 (12.1%)</td>
<td>12 (8.6%)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin in gm/dL- Mean</td>
<td>13.13 ± 1.86</td>
<td>14.04 ± 1.61</td>
<td>12.21 ± 1.62</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 gm/dL</td>
<td>13 (4.64%)</td>
<td>1 (0.7%)</td>
<td>12 (8.57%)</td>
</tr>
<tr>
<td>Creatinine-mean in mmol/ dL</td>
<td>106.20 ± 106</td>
<td>102.21 ± 67.66</td>
<td>110.18 ± 106.52</td>
</tr>
<tr>
<td>Creatinine &gt; 120 mmol/ dL</td>
<td>55 (19.64%)</td>
<td>24 (17.14%)</td>
<td>31 (22.1%)</td>
</tr>
<tr>
<td>Fasting blood glucose (mean) in mmol/ dL</td>
<td>11.70 ± 6.08</td>
<td>10.04 ± 4.43</td>
<td>13.35 ± 6.98</td>
</tr>
<tr>
<td>Fasting blood glucose ≥ 7 mmol/ dL</td>
<td>203 (72.5%)</td>
<td>96 (66.57%)</td>
<td>107 (76.43%)</td>
</tr>
<tr>
<td><strong>Killip class</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Killip I</td>
<td>80 (28.6%)</td>
<td>30 (21.4%)</td>
<td>50 (35.7%)</td>
</tr>
<tr>
<td>Killip II</td>
<td>23 (8.2%)</td>
<td>7 (5%)</td>
<td>16 (11.4%)</td>
</tr>
<tr>
<td>Killip III</td>
<td>118 (42.1%)</td>
<td>72 (51.4%)</td>
<td>46 (32.9%)</td>
</tr>
<tr>
<td>Killip IV</td>
<td>59 (21.1%)</td>
<td>31 (22.1%)</td>
<td>28 (20%)</td>
</tr>
<tr>
<td><strong>Medications on transfer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>272 (97.1%)</td>
<td>138 (98.6%)</td>
<td>134 (95.7%)</td>
</tr>
<tr>
<td>Plavix</td>
<td>262 (93.6%)</td>
<td>136 (97.1%)</td>
<td>126 (90%)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>217 (77.5%)</td>
<td>112 (80%)</td>
<td>105 (75%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>86 (30.7%)</td>
<td>38 (27.1%)</td>
<td>48 (34.3%)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>68 (24.3%)</td>
<td>37 (26.4%)</td>
<td>31 (22.1%)</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>272 (97.1%)</td>
<td>138 (98.6%)</td>
<td>134 (95.7%)</td>
</tr>
</tbody>
</table>

ACE: Angiotensin-Converting Enzyme Inhibitors; SD: Standard Deviation.

### Exclusion criteria

1. Subjects < 18 years.
2. Subjects belonging to vulnerable sections of the society.
3. Subjects refusing to give consent.

Patients were examined individually, and data were obtained from the patient and the patient file from the time of admission until discharge. Subjects were divided into two cohorts based on their gender. Demographic and clinical characteristics, as well as angiographic results were recorded in both paper case report forms and then transferred to SPSS format and analyzed using SPSS version 22. Statistical analysis involved estimation of frequencies, measures of central tendencies as well as bi-variate correlations using Karl Pearson’s method. ACS diagnosis and the definition of data variables were based on the American College of Cardiology (ACC) clinical data standards [7].

### Results

#### Baseline demographics, clinical characteristics on transfer

A total of 280 selected patients (male: female in 1:1 ratio- i.e. 140 each) transferred to the Chest Diseases Hospital in Kuwait for cardiac catheterization and coronary angiography with the diagnosis of ACS from Sep 2014 until Sep 2015 were enrolled into the study. The demographics and clinical characteristics of all subjects and the two cohorts are outlined in table 1. Among the 280 subjects, 206 (73.6%) were Kuwaitis. The mean age were found to be almost similar for both groups, while BMI was higher for females presenting with ACS.

Amongst these the following factors were found to be significant- there were significantly higher number of smokers in males than in females (82 vs. 16 respectively; p-value: < 0.001). Even though most of the subjects in both cohorts presented with a Killip class III, the number of males in Killip III were significantly higher compared to the females (72 vs. 46 respectively; p-value: 0.002) while the number of females were significantly higher in the Killip- I category (50 females vs. 30 males; p-value: 0.008).

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Alsaddah et al. Int J Clin Cardiol 2017, 4:092
fraction (defined as EF ≤ 25%) was found in 4 males (2.9%), 2 females (1.4%) also had the same finding. There were no significant variations in the severity of left ventricular dysfunction (classified as normal, mild, moderate and severe) among the two cohorts.

Coronary angiography revealed normal coronaries in 57 patients (20.4%), significant left main disease (> 50% stenosis) in 5 patients (1.8%), single vessel disease in 67 patients (23.9%), double vessel disease in 49 patients (17.5%) and triple vessel disease in 46 patients (16.4%). There was no significant variation among the two cohorts, except for the fact that more left main disease as well as multivessel disease was found in males, than females presenting with ACS.

Of the total number of patients (280) who underwent angiography, 116 patients (41.4%) underwent percutaneous coronary intervention (PCI), 43 patients (15.4%) underwent coronary artery bypass surgery, and 121 patients (43.2%) were treated medically. While most males underwent PCI (49.3%), most females went for medical treatment (48.6%). CABG was higher in female than in males while PCI was higher in males than in females.

As shown in table 3, left ventriculography revealed significant mitral regurgitation in 12 patients (4.3%), showing such significant predominance in females (n = 12, P-value > 0.001). While significantly low ejection fraction (defined as EF ≤ 25%) was found in 4 males (2.9%), 2 females (1.4%) also had the same finding. There were no significant variations in the severity of left ventricular dysfunction (classified as normal, mild, moderate and severe) among the two cohorts.

Coronary Angiography and ECHO Findings, Treatment Adopted and Interventional Data

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115 of the 116 patients (99.1%) who underwent PCI had successful procedure; drug eluting stents were used in 97 (92.2%), whereas bare metal stents were used in 18 (15.5%). More BMS were used in females (21.3%) than in males.
producing 0.4% in-hospital mortality rate; peri-procedural myocardial infarction was experienced by 3 patients (3.1%) and 10 patients (3.6%) had heart failure. Fever was present in 3 patients (1.1%) and 10 patients (3.6%) had contrast-induced nephropathy, 2 patients (0.7%) developed (11.6%). Bifurcation stenting was done in 5 patients (4.3%) while PCI of instent re-stenosis was done in 4 cases (3.4%).

In-hospital outcomes and discharge medication data

As shown in table 4, there were one in-hospital death (0.4%) and 10 patients (3.6%) had heart failure. Fever was present in 3 patients (1.1%) and 10 patients (3.6%) had contrast-induced nephropathy, 2 patients (0.7%) developed
Of the 43 patients who underwent CABG, surgery was performed in-hospital for 17 patients (40%) while the rest were discharged with appointments for CABG at the earliest date. The median in-hospital waiting period for CABG was 3.5 days. There was no surgical mortality. The median hospital stay duration was 3 days. Medications on discharge included aspirin in 279 patients (99.6%), statins in 279 patients (99.6%), beta blockers in 268 patients (95.7%), Plavix in 237 patients (84.6%), angiotensin converting enzyme (ACE) inhibitors in 180 patients (64.3%) and angiotensin receptor blockers (ARBs) in 99 patients (35.40%). There were no significant differences of discharge medications among the two cohorts.

Discussion

In Kuwait, patients with the diagnosis of ACS are admitted to general hospitals for non-invasive cardiology services. Based on the recently published ACS registry in Kuwait, the rates of ACS patients undergoing in-hospital coronary angiography are 21% for NSTEMI, 17% for STEMI, and 15% for UA [8]. However, the Global Registry of Acute Coronary Events (GRACE) reports rates for coronary angiograms as 53% for NSTEMI, 55% for STEMI, and 42% for UA [9]. The low rate of referrals for coronary angiography in our study suggests that a conservative strategy with noninvasive tools is the primary method for risk stratification of ACS patients in Kuwait. Furthermore, studies have shown that hospitals lacking onsite catheterization laboratory have lower rates of coronary angiography and angioplasty [10], suggesting the lack of onsite cardiac catheterization laboratories and only one invasive cardiac center limit the use of coronary angiography in Kuwait.

In elderly cohorts, absence of chest pain seems to be common in both men and women. Women may however have milder or more often absent chest pain than men. It is possible that a higher prevalence of comorbid conditions such as diabetes may explain some of the sex-based differences in ACS presentation in elderly women. Chest pain is the predominant symptom of ACS in both younger (< 55 years) men and women, regardless of ACS type. Women have a higher chance of presenting without chest pain than men [11]. This survey reveals the treatments used and short-term prognosis of ACS patients in our hospital, especially with regards to gender variations. Despite similarities between our group of patients and the Euro Heart Survey II patients [12], some differences were noted (Table 4). Medications on discharge were comparable except for aspirin, 99.6% of our patients were discharged on ASA compared with 95% in Euro Heart Survey II. More patients in the present study had diabetes mellitus and renal impairment. Because heparin is administered within the initial 48 hours, the number of patients who were in the referring hospital since more than a week would have not been able to receive heparin in our hospital. Females presented with more atypical symptoms than males, and were mostly NSTEMI cases; most males presented with Killip III while most females presented with Killip I. Most males had to be treated by PCI while CABG was higher in females.

Drug eluting stents were used in almost 92.2% of patients who received stents, because more than 60% of the patients could obtain drug eluting stents free of charge. 33.9% of our patients had MVD disease, probably due to the high incidence of diabetes (64.3%) and impaired renal function (19.64%). Although we had more patients with MVD and diabetes, almost half of the patients were treated with PCI and 14.3% were treated with CABG. Our patients typically choose PCI over CABG even when they knew that the results could be inferior to surgery. Our findings also demonstrated that we have very competent operators as reflected by high procedural success rate and low complication rate.

Conclusion

From this pilot study, we found a high incidence of aggressive coronary artery disease in our hospital, which makes primary prevention extremely important, especially in females. Because this is a descriptive study with a moderate number of subjects, strong conclusions are limited and a randomized study including a larger number of patients will provide the additional data needed to draw more solid conclusions.

Acknowledgement

This research was conducted by Dr. Jadan Al Saddah, Msc, MD in association with the co-authors. All procedures were done in accordance with the ICH-GCP guidelines and according to the Ethics Committee and Declaration of Helsinki principles. All authors had full access to all of the data in the study and takes responsibility for the integrity of the data in the study and accuracy of data analysis, including and especially any adverse events. All authors contributed substantially to the study design, data analysis and interpretation and writing of the manuscript. There was no conflict of interest involved. The Ministry of Health, Kuwait and Kuwait University sponsored the necessities for conducting the study. However none of the authors have received any grants of any sorts from any institution for this study. We express our gratitude to all supporting staff of Chest Diseases Hospital, Dar Al Shifa Hospital and Al seef Hospital for their time and effort for helping us acquire clean and timely data.
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