International Journal of Clinical Cardiology

Original Article: Open Access

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

Jadan Alsaddah[1]*, Mohammad Almutairi[1], Wael Aboshokka[1], Saad Alkandari[2], PRS Remya[3] and Hany Younan[4]

[1]Department of Cardiology, Chest Diseases Hospital, Kuwait

[2]Department of Cardiology, Dar Alshifa Hospital, Kuwait

[3]Cardiology Research Centre, Chest Diseases Hospital, Kuwait

[4]Department of Cardiology, Alseef Hospital, Kuwait

*Corresponding author: *Jadan AlSaddah, MSc, MD, Department of Cardiology, Chest Diseases Hospital, Kuwait, Tel: +965-55595989, Fax: +965-24919742, E-mail: dr_alsadda7@hotmail.com*

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.

Keywords

Cardiac catheterization, Coronary Angiography (CAG), Percutaneous Coronary Intervention (PCI), Gender, Kuwait, ACS- Acute Coronary Syndrome

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].
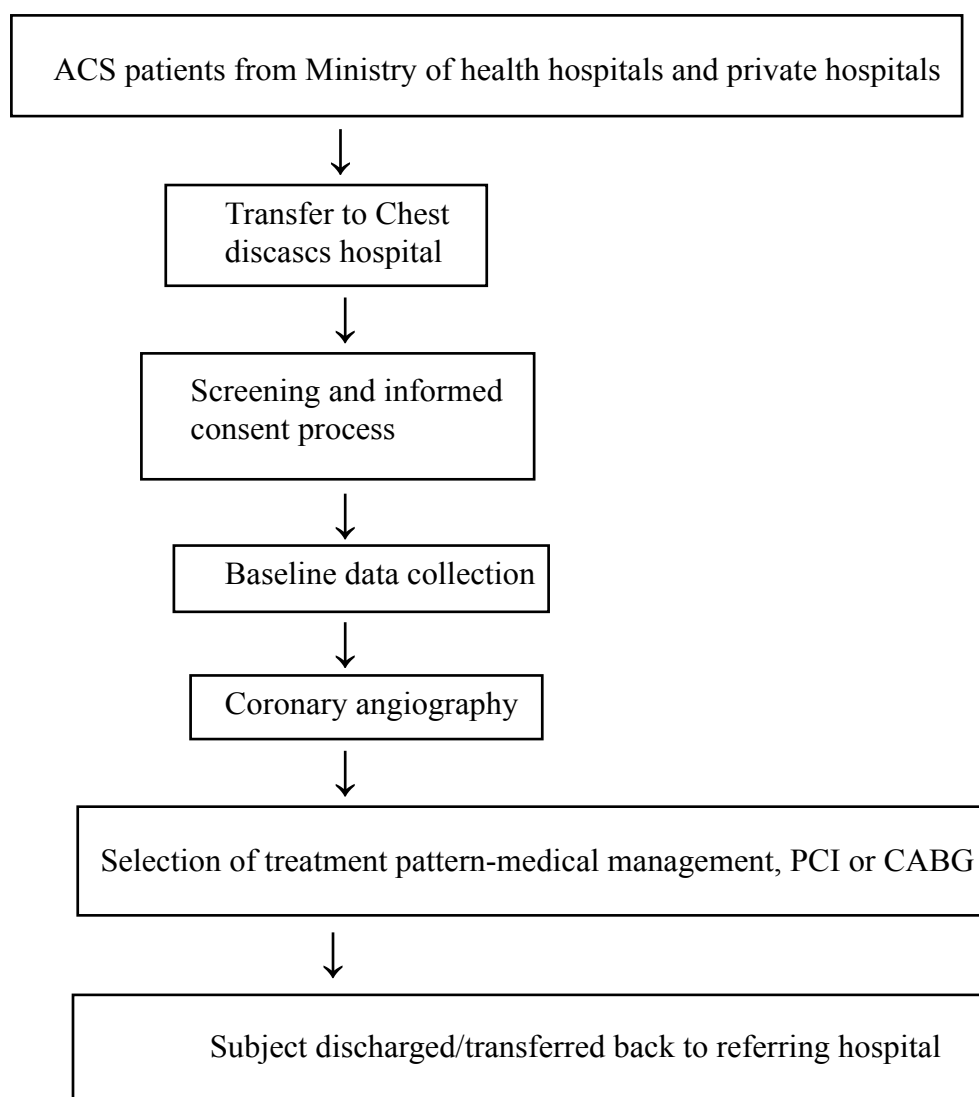
ClinMed International Library

Figure 1: Methodology.

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

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).

Methodology

All consecutive patients transferred to the Chest Diseases Hospital from public sector (Ministry of Health hospitals) as well as Private sector, for cardiac catheterization and coronary angiography with the diagnosis of ACS from 01 Sep 2014 to 01 Sep 2015 were screened, and enrolled into the study after obtaining informed consents which were approved by the Ethics committee (Figure 1).

Inclusion criteria

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

• Page 2 of 7 •

Table 1: Baseline demographics and clinical characteristics on transfer.

Characteristics	Patients (n = 280)	Male (n = 140)	Female (n = 140)
Demographics			
Mean age, years (SD)	60.10 ± 11.72	60.81 ± 10.76	59.39 ± 12.62
Kuwaitis, n (%)	206 (73.6%)	103 (73.6%)	103 (73.6%)
Mean BMI in kg/m²	30.48 ± 7.16	26.76 ± 4.36	34.14 ± 7.51
Cardiovascular risk factors			
Diabetes mellitus	180 (64.3%)	86 (61.4%)	94 (67.1%)
Hypertension	200 (71.4%)	94 (67.1%)	106 (75.7%)
Dyslipidemia	189 (67.5%)	91 (65%)	98 (70%)
Smoking	108 (38.6%)	82 (58.6%)	16 (18.6%)
Positive family history of coronary artery disease	101 (36.1%)	48 (34.3%)	53 (37.9%)
H/o Percutaneous Coronary Intervention (PCI)	36 (12.9%)	18 (12.9%)	18 (12.9%)
H/o Coronary Artery Bypass Graft (CABG)	29 (10.4%)	17 (12.1%)	12 (8.6%)
Clinical characteristics			
Hemoglobin in gm/dL- Mean	13.13 ± 1.86	14.04 ± 1.61	12.21 ± 1.62
Hemoglobin < 10 gm/dL	13 (4.64%)	1 (0.7%)	12 (8.57%)
Creatinine-mean in mmol/ dL	106.20 ± 106	102.21 ± 67.66	110.18 ± 106.52
Creatinine > 120 mmol/ dL	55 (19.64%)	24 (17.14%)	31 (22.1%)
Fasting blood glucose (mean) in mmol/ dL	11.70 ± 6.08	10.04 ± 4.43	13.35 ± 6.98
Fasting blood glucose ≥ 7 mmol/ dL	203 (72.5%)	96 (68.57%)	107 (76.43%)
Killip class			
Killip I	80 (28.6%)	30 (21.4%)	50 (35.7%)
Killip II	23 (8.2%)	7 (5%)	16 (11.4%)
Killip III	118 (42.1%)	72 (51.4%)	46 (32.9%)
Killip IV	59 (21.1%)	31 (22.1%)	28 (20%)
Medications on transfer			
Aspirin	272 (97.1%)	138 (98.6%)	134 (95.7%)
Plavix	262 (93.6%)	136 (97.1%)	126 (90%)
Beta blockers	217 (77.5%)	112 (80%)	105 (75%)
ACE inhibitors	86 (30.7%)	38 (27.1%)	48 (34.3%)
Unfractionated heparin	68 (24.3%)	37 (26.4%)	31 (22.1%)
Low-molecular-weight heparin	272 (97.1%)	138 (98.6%)	134 (95.7%)

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).

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
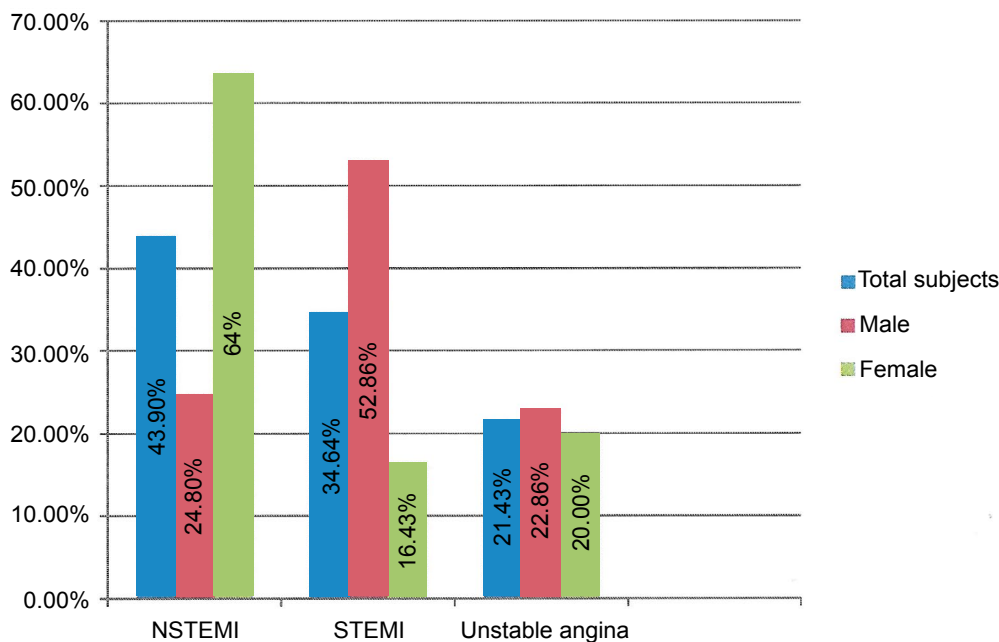
Alsaddah et al. Int J Clin Cardiol 2017, 4:092

• Page 3 of 7 •

Figure 2: CAG indication (ACS sub-classification).

CAG: Coronary Angiography; ACS: Acute Coronary Syndrome; STEMI: ST Segment Elevation Myocardial Infarction; NSTEMI: Non-ST Segment Elevation Myocardial Infarction.

Table 2: Acute coronary syndrome diagnosis sub-classifications.

ACS classification	Patients (n = 280)	Male (n = 140)	Female (n = 140)
NSTEMI	123 (43.9%)	34 (24.80%)	89 (63.57%)
STEMI	97 (34.64%)	74 (52.86%)	23 (16.43%)
UA	60 (21.43%)	32 (22.86%)	28 (20.00%)

NSTEMI: Non-ST elevation Myocardial Infarction; STEMI: ST elevation myocardial infarction; UA: Unstable angina.

heparin, 68 (24.3%) on low-molecular-weight heparin. The median waiting period for angiogram and/or catheterization was 1 day in both groups.

Referring hospital and reasons for referral

More referals came from Mubarak Al-Kabeer (21.3%); followed by Farwania Hospital (19.1%), Sabah Hospital (14.9%), Jahra Hospital (13.8%), Amiri Hospital (12.8%), Adan Hospital (7.4%) and private hospitals (10.7%). The most common indication for referral for coronary angiography - i.e. the sub-classifications of ACS for both groups and all subjects are depicted in figure 2 and details are outlined in table 2.

As observed, majority of both cohorts presented with NSTEMI, the percentage of females who presented with STEMI was significantly higher than males (P-value: 0.001). Most percentage of females presented with atypical symptoms like NSTEMI (63.57%) while most of the males presented with STEMI (52.86%).

Coronary Angiography and ECHO Findings, Treatment Adopted and Interventional Data

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 $\leq$ 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.

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

Table 3: Basic angiographic data and echo findings, treatment provided and interventional data.

Characteristics	Patients (n = 280)	Male (n = 140)	Female (n = 140)
ECHO			
Normal	176 (62.9%)	81 (57.9%)	95 (67.9%)
Mild dysfunction	60 (21.4%)	35 (25%)	25 (17.9%)
Moderate dysfunction	38 (13.6%)	20 (14.3%)	18 (12.9%)
Severe dysfunction	6 (2.2%)	4 (2.8%)	2 (1.4%)
Ejection fraction less than 25%	6 (2.1%)	4 (2.9%)	2 (1.4%)
Mitral regurgitation more than class 3	12 (4.3%)	0	12 (8.6%)
Coronary angiographic findings			
TVD	46 (16.4%)	20 (14.3%)	26 (18.6%)
DVD	49 (17.5%)	33 (23.6%)	16 (11.4%)
SVD	67 (23.9%)	34 (24.3%)	33 (23.6%)
LMD	5 (1.8%)	1 (0.7%)	4 (2.9%)
LMD + DVD	6 (2.1%)	6 (4.3%)	0
LMD + TVD	8 (2.9%)	4 (2.9%)	4 (2.9%)
Mild CAD	42 (15%)	16 (11.4%)	26 (18.6%)
Normal	57 (20.4%)	26 (18.6%)	31 (22.1%)
Treatment selected			
PCI	116 (41.4%)	69 (49.3%)	47 (33.6%)
CABG	43 (15.4%)	18 (12.9%)	25 (17.9%)
Medical	121 (43.2%)	53 (37.9%)	68 (48.6%)
PCPCI angiographic data			
Bare Metal Stent (BMS)	18 (15.5%)	8 (11.6%)	10 (21.3%)
Drug Eluting Stent (DES)	97 (84.5%)	61 (88.4%)	36 (78.7%)
Failure of PCI	1 (0.9%)	0	1 (2.1%)
Bifurcation stenting	5 (4.3%)	1 (1.4%)	4 (8.5%)
PCI of ISR	4 (3.4%)	2 (2.9%)	2 (4.3%)

TVD: Triple Vessel Disease; DVD: Double Vessel Disease; SVD: Single Vessel Disease; LM: Left Main; CAD: Coronary Artery Disease; MR: Mitral Regurgitation; EF: Ejection Fraction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; BMS: Bare Metal Stent; DES: Drug Eluting Stent; ISR: Instent Restenosis.

Table 4: In-hospital outcomes and discharge medication.

Outcomes	Patients (n = 280)	Male (n = 140)	Female (n = 140)
Post procedure pre-discharge events			
Stent thrombosis	1 (0.4%)	1 (1.4%)	0
Heart failure	10 (3.6%)	2 (1.4%)	8 (5.7%)
CIN	10 (3.6%)	9 (6.4%)	1 (0.7%)
VT/VF	2 (0.7%)	1 (0.7%)	1 (0.7%)
Fever	3 (1.1%)	0	3 (2.1%)
MI	3 (1.1%)	1 (0.7%)	2 (1.4%)
CVA	0	0	0
Death	1 (0.4%)	0	1 (0.7%)
Vascular complications			
Pseudo aneurysm	2 (0.7%)	1 (0.7%)	1 (0.7%)
Groin hematoma	3 (1.1%)	2 (1.4%)	1 (0.7%)
Retroperitoneal bleeding	1 (0.4%)	1 (0.7%)	0
Medications on discharge			
Aspirin	279 (99.6%)	140 (100%)	139 (99.3%)
Plavix	237 (84.6%)	122 (87.1%)	115 (82.1%)
Beta blockers	268 (95.7%)	129 (92.1%)	139 (99.3%)
ACE	180 (64.3%)	96 (68.6%)	84 (60.4%)
ARBS	99 (35.4%)	44 (31.4%)	55 (39.3%)
Statins	279 (99.6%)	140 (100%)	139 (99.3%)

MI: Myocardial Infarction; CVA: Cerebrovascular Accident; ACE: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin Receptors Blockers.

(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 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

femoral artery pseudo aneurysm, 3 patients (1.1%) developed groin local hematoma while 1 male (0.4%) developed retroperitoneal bleed. No cerebrovascular accidents occurred. The contrast induced nephropathy was significantly higher in males (10 patients; 6.4%) than in females (1 female, 0.7%) with a p-value of 0.010.

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

Alsaddah et al. Int J Clin Cardiol 2017, 4:092

• Page 6 of 7 •

References

1. Wizemann TM, Pardur ML (2001) Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington, DC: National Academies Press.

2. McGregor AJ, Templeton K, Kleinman MR, Jenkins MR (2013) Advancing sex and gender competency in medicine: Sex & Gender Women's Health Collaborative. Biol Sex Differ 4: 11.

3. Allen J, Szanton S (2005) Gender, ethnicity, and cardiovascular disease. J Cardiovasc Nurs 20: 1-6.

4. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ (2006) Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 367: 1747-1757.

5. De Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, et al. (2005) Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 353: 1095-1104.

6. (1994) Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 89: 1545-1556.

7. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, et al. (2001) American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 38: 2114-2130.

8. Zubaid M, Rashed WA, Saad H, Attiya A, Al-Banat BA, et al. (2007) Kuwait acute coronary syndromes registry: baseline characteristics, management practices and hospital outcomes of patients hospitalized with acute coronary syndromes in Kuwait. Med Princ Pract 16: 407-412.

9. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, et al. (2002) Baseline characteristics, management practices, and hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). Am J Cardiol 90: 358-363.

10. Fox KA, Goodman SG, Klein W, Brieger D, Steg PG, et al. (2002) Management of acute coronary syndromes: variations in practice and outcome; findings from the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 23: 1177-1189.

11. Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, et al. (2013) Sex Differences in Acute Coronary Syndrome Symptom Presentation in Young Patients. JAMA Intern Med 173: 1863-1871.

12. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, et al. (2006) The second Euro Heart survey on acute coronary syndrome: Characteristics, treatment and outcome of patients with ACS in Europe and the mediterranean basin in 2004. Eur Heart J 27: 2285-2293.