Sex Differences in Cardiovascular Risk Factors and Management in a Preventive Cardiology Clinic at a Tertiary Referral Center

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Abstract

Background: Cardiovascular disease is the leading cause of death in both genders worldwide. Gender differences in clinical presentation and treatment have been reported.

Objective: This study aims to describe and compare the cardiovascular risk factors and management strategies for primary prevention among Filipinos.

Methods: An analytical cross-sectional study was done on 2,082 patients at the Preventive Cardiology Clinic of a tertiary referral center in Quezon City, Philippines from January 1, 2002 to December 31, 2017.

Results: Seventy-two percent of the patients were females with a higher mean age compared to males (57.67 $\pm$ 10.50 vs 55.66 $\pm$ 11.82, p 0.002). There were more women who were unemployed (75.2 vs 45.9, *p<0.001*). There was no significant difference in the prevalence of hypertension (68.6% vs 67.9%, *p=0.542*) and type 2 diabetes mellitus (19.8% vs 21.5%, *p=0.437*) in both genders. Beta blockers (24.1%), calcium channel blockers (22.9%) and angiotensin receptor blockers (22.1%) were the most commonly prescribed anti-hypertensive drugs. Biguanides were the most commonly prescribed glucose-lowering drug (11.3%). Compared to men, more women had dyslipidemia (51.8% vs 38.6%, *p<0.001*). Statins were more commonly prescribed in women (22.4 vs 18.1%, *p=0.033*).

Conclusion: There were significantly more women seen in our Preventive Cardiology clinic. Smoking and alcoholic drinking were higher in males. BMI, total cholesterol and HDL were significantly higher in females than in males.

Keywords: Sex differences, cardiovascular risk factors, cardiovascular disease prevention, primary prevention, preventive medicine

Introduction

Cardiovascular disease (CVD) is the most common cause of death in both sexes worldwide due to an increase in the prevalence of the risk factors for coronary artery disease (CAD) such as hypertension, dyslipidemia and diabetes.[1] This accounts for more than 17.3 million deaths per year, thus, imposes a significant disease burden. It is also one of the leading causes of morbidity and mortality in the Philippines.[2]

Differences in the clinical presentation and management of cardiovascular diseases have been reported between genders.[3] Women have been observed to develop ischemic heart disease at a later age than men. This was presumed to be due to the protective effect of hormones in pre-menopausal women which has contributed to the under-recognition of cardiovascular diseases among females. Once CAD is manifested clinically, women lose this apparent prognostic advantage over men.[4] Women have also been reported to be more likely to have non-obstructive CAD amongst those with acute coronary syndrome and often seek medical consultation later in their clinical presentation compared to men. Among patients with heart failure, preserved ejection fraction has also been consistently reported to have a female preponderance.[5] De Smedt *et al.* recently studied gender differences in cardiovascular

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Table I. Baseline characteristics of patients seen at the Primary Preventive Cardiology Out-Patient Department, January to December 2017 (N=2082)

Parameter	Total (N = 2082)	Female (n = 1509, 72.5%)	Male (n=573, 27.5%)	p value
Age (Mean ± SD)	57.12 + 10.9	57.67 + 10.5	55.66 + 11.8	0.0002
Civil Status				
Married	1,401 (67.3)	933 (61.8)	468 (81.7)	<0.001
Widow	337 (16.2)	318 (21.1)	19 (3.3)	<0.001
Single	255 (12.2)	186 (12.3)	69 (12)	<0.001
Separated	52 (2.5)	41 (2.7)	11 (1.9)	<0.001
Employment Status				
Unemployed	1,398 (67.1)	1,135 (75.2)	263 (45.9)	<0.001
Employed	544 (26.1)	294 (19.5)	250 (43.6)	<0.001
Retired	141 (6.8)	80 (5.3)	61 (10.6)	<0.001
Educational Attainment				
Grade school level	255 (12.2)	180 (11.9)	45 (7.8)	0.001
High school level	547 (26.3)	402 (26.6)	145 (25.3)	0.001
College level	613 (29.4)	412 (27.3)	201 (35.1)	0.001
Comorbid illnesses				
Hypertension	1424 (68.4)	1035 (68.6)	389 (67.9)	0.542
Type 2 diabetes	422 (20.3)	299 (19.8)	123 (21.5)	0.437
Dyslipidemia	1,003 (48.2)	782 (51.8)	221 (38.6)	<0.001
Post-menopausal		1,035 (68.6)		
On Hormone Replacement Therapy		13 (0.9)		
Reason for consult				
Shortness of breath or dyspnea	512 (24.6)	386 (25.6)	126 (22)	0.177
Chest pain	484 (23.2)	370 (24.5)	114 (20)	0.023
Bipedal edema	286 (13.7)	219 (14.5)	67 (11.7)	0.090
Palpitations	273 (13.1)	224 (14.8)	49 (8.5)	0.346
Dizziness	259 (12.4)	197 (13.0)	62 (10.8)	0.159
Orthopnea	97 (4.6)	70 (4.6)	27 (4.7)	0.962
Numbness	95 (4.6)	71 (4.7)	24 (4.2)	0.603
Abdominal pain	49 (2.3)	38 (2.5)	11 (1.9)	0.415
Loss of consciousness	30 (1.4)	24 (1.6)	6 (1.0)	0.350
Heredofamilial diseases				
Hypertension	1,128 (54.2)	828 (54.9)	300 (52.3)	0.254
Coronary artery disease	772 (37.1)	571 (37.8)	201 (35.1)	0.230
Type 2 diabetes mellitus	422 (20.3)	299 (19.8)	123 (21.4)	0.437
Smoking history				
Current smoker	334 (16)	85 (5.6)	249 (43.4)	<0.001
Former smoker	107 (5.1)	33 (2.2)	74 (12.9)	<0.001
Alcoholic drinker	270 (13.0)	95 (6.3)	175 (30.6)	<0.001
Former alcoholic drinker	178 (8.5)	45 (3.0)	133 (23.2)	<0.001

risk factors and reported females to have a worse risk factor profile compared to males who were more likely to have on target LDL-cholesterol and HbA1c, to be non-obese and to engage in adequate physical activity.[6]

There is a paucity of data in our local setting comparing gender-specific differences in cardiovascular risk factors and treatment. The findings in our study are believed to provide useful insights in risk factor quantification between genders with implications for individualized gender-specific therapeutic trends in clinical practice.

Objectives

The general objective of our study was the comparison of cardiovascular risk factors and management strategies between men and women. The specific objectives of our study include a comparison of the demographics, anthropometric measures, body mass index, blood pressure, lipid profile, fasting blood glucose and glycosylated hemoglobin levels, and management strategies in both genders.

Methodology

An analytical cross-sectional study was done at the Preventive Cardiology Clinic at a tertiary referral center after the protocol was approved by the Institutional Ethics Review Board. The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. A retrospective review of the medical records of 2,088 patients at the Preventive Cardiology Clinic who were ≥19 years old during their

initial consult from January 1, 2002 to December 31, 2017 was done. Six patients were excluded due to incomplete data. There were 2,082 patients included in the final study. BP levels reported were based on the office blood pressure taken on their first consultation.

Using Epi Info™ 7, a minimum of 44 patients were required for this study based on the 0.8761 effect size of systolic blood pressure between genders with 5% α-level of significance.[7] Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables. Median and interquartile range for non-normally distributed continuous variables, and mean and standard deviation for normally distributed continuous variables were used. Independent Sample T-test, Mann-Whitney U test and Fisher's Exact/Chi-square test were used to determine the difference in mean, rank and frequency, respectively, between male and female. All statistical tests were two-tailed tests. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. *STATA® v13.1* was used for data analysis.

Results

Clinical Characteristics

Baseline Demographics. Table I highlights the baseline characteristics of the 2,082 patients included in this study. Seventy-two percent of the patients were females (1,509 vs 573) with a higher mean age compared to men (57.7 ± 10.50 vs 55.7 ± 11.82, p 0.002). The age distribution per sex is illustrated in *Figure 1*. The majority of females seen were in the 51 to 60 years age group, while the majority of males seen were in the 30 to 50 years old age group.

Comorbid Illnesses. The prevalence of hypertension and diabetes mellitus was 68.4% (1424) and 20.3% (422) respectively with no significant difference between sex (*Table II*). Compared to men, significantly more women had dyslipidemia (51.8% vs 38.6%, *p <0.001*). Only 8.3% were taking statins. Among women, 68.6% were post-menopausal. A family history of hypertension (54.2%), coronary artery disease (37.1%) and type 2 diabetes mellitus (20.3%) were reported in both sexes. Sixteen percent of the patients were cigarette smokers. There were significantly more men who were current smokers (43.4% vs 5.6%, *p<0.001*) and former smokers (12.9% vs 2.2%, *p<0.001*). There were significantly more male patients who continued to drink alcoholic beverages (30.6% vs 6.3%, *p<0.001*) or were former alcoholic drinkers (23.2% vs 3.0, *p<0.001*).

Anthropometric Measurements

Male patients were heavier (67.6 ± 11.9 vs 59 ± 10.9 kg, *p<0.001*) and taller (1.6 ± 0.1 vs 1.5 ± 0.1 m, *p<0.001*) compared to women (*Table II*). However, a higher body mass index was observed among women (25.8 ± 4.3 vs 25.2 ± 4.1 kg/m^2, *p< 0.011*). Compared to women, the waist and hip circumferences of men were significantly increased compared to women (88.4 ± 10.8 vs 84.8 ± 10.2 cm, *p<0.001*, 96.8 ± 8.6 vs 94.6 ± 8.6 cm, *p<0.001*). The WHRs were 0.92 and 0.90 in men and women respectively (*p<0.001*).

Most of the patients in both sexes had pre-hypertension (33.9%, 706) and stage 1 hypertension (32.5%, 676) based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation of

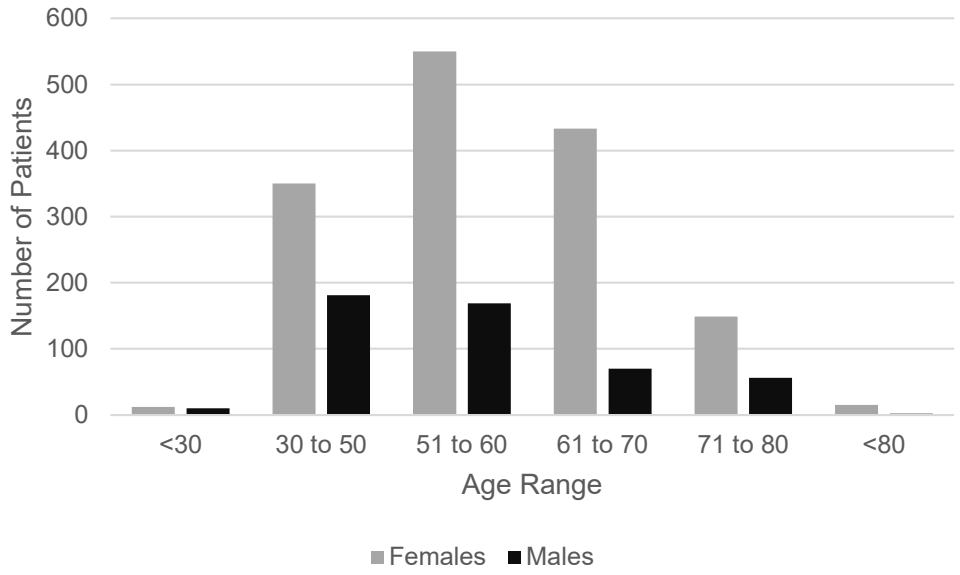

Figure 1. Age and Sex Distribution of Patients Seen at the Philippine Heart Center Primary Preventive Cardiology Unit, 2002-2017 (n=2082)

Table II. Anthropometric measurements, body mass index, blood pressure, cholesterol, fasting blood glucose and glycosylated hemoglobin levels of the patients in the Preventive Cardiology Clinic, 2002 to 2017 (N=2082)

Parameter	Total (N = 2082)	Female (n = 1509)	Male (n = 573)	p value
Weight (kg)	61.4 + 11.8	59 + 10.9	67.6 + 11.9	<0.001
Height (m)	1.6 + 0.1	1.51 + 0.1	1.64 + 0.1	<0.001
Body mass index (kg/m^2)	25.6 + 4.3	25.8 + 4.3	25.2 + 4.1	0.011
Waist (cm)	85.8 + 10.5	84.8 + 10.2	88.4 + 10.8	<0.001
Hip (cm)	95.2 + 8.6	94.6 + 8.6	96.8 + 8.6	<0.001
Waist:Hip ratio (WHR)	0.90	0.90	0.92	<0.001
Blood pressure (mm Hg)				
Systolic	140.41 + 22.3	140.98 + 22.3	138.90 + 22.2	0.057
Diastolic	86.45 + 11.3	86.30 + 11.2	86.85 + 11.7	0.326
JNC Classification (SBP)				
Normal	221 (10.6)	149 (26)	72 (4.8)	0.346
Pre-hypertension	706 (33.9)	512 (33.9)	194 (12.9)	0.346
Stage 1	676 (32.5)	497 (3)	179 (11.9)	0.346
Stage 2	477 (22.9)	349 (23.16)	128 (8.5)	0.346
JNC Classification (DBP)				
Normal	268 (12.9)	199 (13.2)	69 (12)	0.460
Pre-hypertension	750 (36)	543 (36)	207 (36.1)	0.460
Stage 1	644 (30.9)	474 (31.4)	170 (29.6)	0.460
Stage 2	421 (20.2)	293 (19.4)	128 (22.3)	0.460
Total cholesterol (mg/dL)	210.1 + 50.3	215.4 + 50.8	195.0 + 46.2	<0.001
LDL cholesterol (mg/dL)	126 (102 - 160)	127 (103.5-160.6)	124.2 (97.5-156.7)	0.412
HDL cholesterol (mg/dL)	46 (38 - 56)	47 (38.5-57.4)	42.08 (36-51)	0.002
Triglycerides (mg/dL)	136 (98.2 - 186)	136 (100-186)	136.1 (91-183.6)	0.450
Fasting blood glucose (mg/dL)	100 (89-117)	100 (89-116)	101 (90-118.2)	0.682
Glycosylated hemoglobin (%)	7 + 6.5	7 + 2.0	7 + 2.5	0.990

Table III. Management strategies

Parameter	Total N = 2082	Female n = 1509	Male n = 573	p value
Anti-hypertensive agents				
Beta blockers	500 (24.1)	378 (25.1)	122 (21.4)	0.164
Calcium channel blocker	476 (22.9)	348 (23.1)	128 (22.3)	0.684
Angiotensin receptor blocker	459 (22.1)	348 (23.1)	111 (19.3)	0.063
Angiotensin converting enzyme inhibitor	258 (12.4)	173 (11.5)	85 (14.8)	0.042
Hydrochlorothiazide	57 (2.7)	36 (2.4)	21 (3.7)	0.116
Anti-hyperlipidemic agents				
Statins	441 (21.2)	337 (22.4)	104 (18.1)	0.033
Fenofibrates	8 (0.4)	5 (0.3)	3 (0.5)	0.692
Bile acid sequestrants	4 (0.2)	3 (0.2)	1 (0.2)	1.000
Anti-diabetic medications				
Biguanides	235 (11.3)	175 (11.6)	60 (10.5)	0.508
Sulfonylureas	91 (4.4)	29 (1.9)	62 (10.8)	0.406
Insulin	7 (0.3)	3 (0.2)	4 (0.7)	0.416
Thiazolidinediones	16 (9.1)	11 (8.8)	5 (9.8)	0.781

Hypertension (JNC 7).[8] Compared to men, women had significantly higher total cholesterol (215.4 ± 50.8 vs 195.0 ± 46.2 mg/dL, *p<0.001*) and higher high-density lipoprotein levels (47 (38.46-57.36 mg/dL) vs 42.08 (36-51 mg/dL), *p=0.002*).

Management Strategies

Beta blockers (24.1%), calcium channel blockers (22.9%) and angiotensin receptor blockers (22.1%) were the three most commonly prescribed anti-hypertensive medications in both sexes as seen in *Table III*. Angiotensin converting enzyme (ACE) inhibitors were more commonly prescribed among men (12.4% vs 11.5%, *p=0.042*).

In both sexes, biguanides (Metformin) were the most commonly prescribed glucose-lowering medication (11.3%), followed by sulfonylureas (2.6%). Compared to men, statins were more commonly prescribed among women (22.4 vs 18.1%, *p=0.033*).

Discussion

There were more female patients (72.5% vs 27.5%) in our Preventive Cardiology Clinic. While this may reflect cultural and sociodemographic differences and more health-seeking behavior in women, this is contrary to what is usually seen in literature.[9-11] Males have consistently been reported to be the predominant sex involved in cardiovascular diseases (CVD) such as acute myocardial infarction and heart failure.[12,13]

Women had a significantly higher mean body mass index (BMI) in our cohort. These patients had an increased risk of developing CVD, especially women.[14-16] Moreover, Chen *et al.* reported high BMI as a risk factor for mortality from CVD and ischemic or hemorrhagic stroke among East Asians.[15] Similarly, waist circumference and WHR are also significant risk factors for the development of CVD.[17] Abdominal obesity, measured using the WHR, is a strong predictor for the development of CVD, stroke and death particularly if the WHR is >0.98 for men and >0.91 for women. The mean WHR for both sexes was 0.9 $\pm$ 0.1 which is close to the quintile associated with increased risk of cardiovascular events as reported by Megnien *et al.*[18] Intensive lifestyle modification that includes healthy eating habits, exercise and targeted weight loss strategies must be advised in this subset of patients to lower their risk of CVD and its complications.[16]

The prevalence of hypertension in our cohort is higher compared to studies in other countries which *ranged* from 28.5% to 31.5%.[19,20] About a third (33.2%) of the hypertensive patients were on anti-hypertensive medications at the time of consult. This is in contrast to the study of Choi *et al.,* where anti-hypertensive medications were being taken in 88.6% and 92.6% of the male and female hypertensive patient, respectively.[20] This suggests lack of awareness on the need to control hypertension among Filipinos similar to the findings in one large study.[21] This highlights the need to institute preventive measures including lifestyle changes and effective pharmacotherapy.[11,15,21] Equal importance must be given to patients with prehypertension to prevent progression.[11,16,21,22] Although guidelines in clinical practice recommend thiazide-like diuretics as one of the first line agents for hypertension these were only prescribed in 2.7% of the hypertensive patients in our cohort. [11,16,22] Beta blockers (24.1%) were the most commonly prescribed anti-hypertensive drugs similar to another local study probably due to its low cost which makes it attractive in terms of better compliance.[21] Recent data have shown that beta blockers are inferior to other anti-hypertensive drugs for initial treatment with little or no mortality benefit thus, these drugs are no longer recommended in the latest guidelines as first line agents if without compelling indications.[16,22,23] CCBs (22.9%), ARBs (22.1%) and ACEi (12.4%) were the next most commonly prescribed agents as recommended by the guidelines.[16,22]

Type 2 diabetes mellitus was reported in 20.3% of the patients in our study. Biguanides (Metformin) were the most commonly prescribed glucose-lowering medication (11.3%) as recommended in the guidelines.[15] The mean HbA1c of our patients was 7%. To prevent the development of microvascular complications, a level of <7% has been recommended.[16]

Significantly more women had dyslipidemia (51.8% vs 38.6%). Only 8.3% were taking statins at the time of initial consultation. The reasons for suboptimal compliance to a statin may be multifactorial (socioeconomic, awareness, misconceptions, and side effects). Effective interventions that address the concerns of the patients are needed to improve adherence to statin therapy.[24] Women had a higher total baseline cholesterol level (215.4 vs 195.0 mg/dL) congruent with their significantly higher baseline high density lipoprotein (HDL) level (47 vs 42.1 mg/dL). A high HDL level is considered to have cardio-protective effects.[25,26] Gordon *et al.* studied the relationship between HDL and cardiovascular events in four prospective studies and it was found out that a 1 mg/dL increase in HDL decreased coronary heart disease risk by 2% in men and 3% in women, and lowers CVD mortality by 3.7% in men and 4.7% in women.[27] The recommended target level for HDL is >40mg/dL in men and >45mg/dL to 48mg/dL in women.[16] The mean HDL levels in our cohort are in line with the latest recommendations. The mean triglyceride level in both sexes was 136 mg/dL which adheres to the target level of <150 mg/dL for cardiovascular disease prevention.[16, 28]

Completeness of data could not be fully ascertained due to the retrospective nature of this study. The data in this study reflected the patients in our institution. The authors would like to recommend a prospective multicenter study be done to address the said limitations. More research is needed in our setting to determine the long-term clinical impact of these sex-based differences.

The sample size of our cohort was one of the strengths of our study. The insights provided useful information with regards to the quality and conduct of primary cardiovascular care in both sexes. It added knowledge in areas where our practices may be improved upon further investigated.

Conclusion

There were significantly more women seen at our Preventive Cardiology clinic with a male:female ratio of 1:38. Smoking and drinking alcohol were higher in males. BMI, total cholesterol and HDL were higher in females. Understanding contemporary sex differences in risk assessment and management strategies of cardiovascular disease is important to facilitate preventive cardiovascular care.

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