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SEX DIFFERENCES AND DISEASE FACTORS AFFECTING MONOTHERAPY CHOICE FOR HYPERTENSION

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Abstract:
Objective: To investigate the impact of sex differences and disease factors on drug monotherapy choice for hypertension.
Design and Methods: The data for this study were collected from patient's medical files. The sample studied included 876 patients with cardiovascular diseases. Focus was made on the 228 patients with uncomplicated and complicated hypertension who were receiving monotherapy. SPSS was used for data entering and statistical analysis.
Results: 43% (98) of the treated men and 57% (130) of the treated women were on monotherapy for hypertension. Women tend to be treated with diuretics more often than men while men were more often treated with beta blockers. Prevalence of the four major anti-hypertesive drug classes among men and women were as follows: diuretics (men 12%, women 32%), [beta]-blocker (men 45%, women 42%), calcium antagonist (men 15%, women 11%) or an angiotensin converting enzyme inhibitor (men 27%, women 15%). Disease factors that produce significant impact on drug choice include age category, diabetes mellitus, and bronchodilators co-medication. Presence of ischemic heart disease does not have statistically significant impact on BB or CCB antihypertensive drug choice.
Conclusions: The pattern of antihypertensive drug use is influenced by sex and presence of other co-morbid conditions. The influence of sex needs further long term investigation. In general, physicians in Palestine take most known indications and contra-indications into account when they prescribe an antihypertensive drug motherapy.
Running Title: Factors Affecting Hypertension Monotherapy Treatment

Key words: Sex differences, Disease Factors, Hypertension Treatment, Monotherapy.

Introduction:

The choice of antihypertensive drug(s) in general should be guided by several considerations. The *Seventh Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VII) contains the main guidelines for the pharmacotherapy of hypertension [(1)]. Similar therapeutic guidelines were made by the *British Hypertension Society* and the *World Health Organization / International Society of Hypertension* (WHO/ISH) [(2,3)]. The JNC VII recommends that anti-hypertensive drugs documented to reduce cardiovascular morbidity and mortality, like diuretics, BB and ACE-I, be the agents of choice and should be prescribed in their minimum effective dose. The JNC VII further recommends that polypharmacy should be avoided in hypertension therapy as much as possible. The JNC VII recommends that diuretics and β-blockers be used as first-choice agents in the treatment of hypertension 'unless they are contraindicated or unacceptable. These drugs are recommended as first line therapy because they are the only classes of anti-hypertensive drugs that have been shown in long-term controlled clinical trials to reduce cardiovascular morbidity and mortality [(4-6)]. In clinical trials, β-Blockers have not been found to be superior to diuretics in uncomplicated hypertension not associated with concomitant conditions, and most of their prescription has been as step two therapy especially among elderly patients [(7)]. JNC-VI also acknowledges that angiotensin-converting-enzyme (ACE) inhibitors, calcium-channel blockers, -1-receptor blockers, and angiotensin-receptor antagonists are as efficacious as -blockers and diuretics in reducing blood pressure. However, theses drugs are expensive compared to - b l ockers and diuretics. Furthermore, there is no current strong evidence that these drug classes reduce the risk of morbidity and mortality among hypertensive patients and that is why the JNC VI recommendations prefer that ACE inhibitors or calcium channel blockers not to be used as initial therapy for patients with uncomplicated hypertension or those with hypertension without special needs. The JNC VI recommends ACE inhibitors as second-line agents in most patients with hypertension and as first-line choices only in selected patients, including those with left ventricular systolic dysfunction and those with diabetes and microalbuminuria or proteinuria. A new class of antihypertensive drugs are the Angiotensin II receptor antagonist (AT-R1-antagonists). These drugs (e.g. Losartan, Candesartan cilexetil and Valsartan) do not inhibit the synthesis of angiotensin, rather they block the effects of angiotensin at the receptor level [8]. Calcium channel blockers (CCB, e.g. Nifedipine, Verapamil, Diltiazem and Amlodipine) prevent calcium from entering the muscle cells of the heart and blood vessels, thus relaxing blood vessels and decreasing blood pressure and are prefered in elderly patients [9, 10]. Dihydropyridine class of CCB (e.g. Nifedipine and Amlodipine) is the most commonly prescribed for hypertension. Diltiazem (a benzothiazepine) and Verapamil (an aryl alky amine) are CCB belonging to a totally different class and much less frequently as antihypertensive agents, rather they are used as adjunct therapy in angina pectoris and arrythmias. Clinical trials now support the safety and efficacy of the long-acting dihydropyridines for patients with both uncomplicated and diabetic hypertension, although conventional therapies and, in the latter case, angiotensin-converting enzyme inhibitors have superior proof of benefit.

Up until now, there is no compelling reason to suggest that one class of antihypertensive drugs is better than another class with respect to sex as described in JNC VI report. However, in many countries, hypertensive women are more frequently treated with diuretics while hypertensive men were treated with beta blockers (BB), angiotensin converting enzyme inhibitors (ACE-I) and Calcium channel blockers (CCB) [11]. The aim of this study is to investigate the patterns and rationality of prescribing antihypertensive drugs among male and female hypertensive patients and to describe and try to explain the sex differences in anti-hypertensive drug use.

Methodology:

The study was carried out in Nablus district, the largest district in north Palestine, with a population of 325, 269 inhabitants [12]. The medical files of eight hundred and seventy six patients (876) who were diagnosed with cardiovascular diseases were reviewed and analyzed. The patients included in the study were those having the disease for at least the past six months. The files were selected randomly from the four governmental out-patient primary health care centers in Nablus district in north Palestine. These health care centers provide medical services to patients registered at the Ministry of Health (MOH) as chronic patients and who dispense their medications on regular basis. The selection of these files was random. In each primary health care center, every other file was obtained and if it belongs to a patient with a cardiovascular disease, it is considered part of the study. Files that belong to patients suffering from non-cardiovascular diseases were not taken for the study. The total number of files present at the four centers where the study took place was more than eight thousand files. Eight hundred and seventy six medical_files fit the criteria and were considered for the study. In each medical file, the data regarding age, gender, drug history (all drugs prescribed for the patients) and the prescribing physician were obtained and analyzed using Statistical Package for Social Sciences (SPSS) version 10. Chi-Square T test was used as a statistical test of significance. Data collection was made over a period of six months starting April 2003 until October 2003. The researchers took permission from the Ministry of Health officials before starting the collection of data. The correlation test was used to determine the differences between proportions. A "p" value < 0.05 was considered to represent statistical significance.

Results:

A total of 876 patients diagnosed with cardiovascular diseases were studied. The prevalence of complicated or uncomplicated hypertension among the studied sample was 646/876 (73.7%). Of those 646; 228 (35%) patients were receiving anti-hypertensive monotherapy. Among those receiving antihypertensive monotherapy, 57% (130) were women and 43% (98) were men. The mean age of men was 58.78 years (Std. Deviation = 8.73; Range = 29). The mean age of women was 69.81 years (Std. Deviation = 6.54; Range = 15). Chi-Square T-test for the differences in age distribution between males and females gave a *P* value of 0.131 suggesting insignificant difference between men and women in age distribution.

About 32% of the women and 12% of the men were treated with diuretics (Table 1). Cross tabulation of gender versus diuretic prescribing and using a Chi-Square T test gave a value less than 0.005 suggesting that prescribing of diuretics is significantly influenced by gender. Mean weight for men was 88.4 Kg (Std. Deviation = 9.17; Range = 18). Mean weight for women was 73.8 Kg (Std. Deviation = 4.61; Range 13). Analysis of weight distribution among men and women showed that the prescribing of diuretics was not due to weight differences (*P* value = 0.271), rather, was due to gender differences. Cross tabulation of gender with the prescribing of other drug classes showed that gender does not significantly affect the prescribing of other antihypertensive drug classes as seen in Table-1.

Analysis of the effect of age on the prescribing of various antihypertensive drug classes showed that the prescribing of diuretics and ACE-I increased with increasing age while the prescribing of [beta]-blockers and CCB decreased with increasing age. However the cross tabulation between age in general and each drug class showed a Chi-Square T-Test of *P* value greater than 0.005 suggesting insignificant effect of age on prescribing of these drug classes as seen in Table-1. Cross tabulation between age category of 20 – 40 and more than 60 in one hand with the prescribing of various antihypertensive drug classes showed a significant statistical difference (*P* value = 0.002) in prescribing of diuretics and ACE-I (data not shown).

Analysis of the effect of the presence of diabetes mellitus on the prescribing of various antihypertensive drug classes showed that the presence of diabetes mellitus significantly affect the tendency to prescribe ACE-Is where diabetic patients were more likely to be prescribed ACE-I than non-diabetics. Diabetic patients were also significantly less likely to be prescribed BB compared to non diabetics at a *P* value less than 0.05.

Among patients with a history of IHD, there was a tendency to use [beta]-blockers and calcium antagonists more often than ACE inhibitors or diuretics, although these associations gave *P* value greater than 0.05 suggesting statistically insignificant correlation (Table 1). Other factors that have significant statistical correlation with drug choice selection were the use of bronchodilator. Patients using bronchodilators, suggestive of the presence of obstructive pulmonary disease, have high tendency to be prescribed CCB use and low tendency to be prescribed either BB or ACE-I. Finally, the use of either low dose aspirin or lipid lowering agents was not significantly correlated with the choice of anti-hypertensive monotherapy. The prevalence of use of other anti-hypertensive drug classes like alpha blockers, centrally acting sympatholytics and angiotensin receptor antagonists was either zero or less than 1% in most categories studied and that is why they were not included in table 1.

Table 1: Prevalence of Diuretics (D), Beta Blockers (BB), calcium Channel Blockers (CCB), Angiotensin Converting Enzyme-Inhibitors (ACE-I) for hypertension among men and women receiving monotherapy for treatment of complicated or uncomplicated hypertension. D = Diuretics, BB = beta blockers, CCB = calcium channel blockers, ACE-I = angiotensin converting enzyme inhibitors.

Parameter	**Status**	**Frequency (Percentage)**				
		Total No	**D** (Frequency; Percentage)	**BB** (Frequency; Percentage)	**CCB** (Frequency; Percentage)	**ACE-I** (Frequency; Percentage)
Gender						
	Men	98	(12; 12%)	(45; 45%)	(15; 15%)	(26; 27%)
	Women	130	(42; 32%)	(46; 42%)	(14; 11%)	(20; 15%)
	P		0.002	0.249	0.478	0.012
Age						
	20 – 40	42	(5; 12%)	(22; 52%)	(7; 17%)	(8; 19%)
	40 – 60	86	(15; 17%)	(44; 51%)	(9; 11%)	(18; 21%)
	> 60	100	(24; 24%)	(41; 41%)	(10; 10%)	(25; 25%)
	P value		0.098	0.063	0.149	0.671
Diabetes						
	Positive	88	(14; 16%)	(27; 31%)	(19; 21%)	(28; 32%)
	Negative	140	(32; 23%)	(66; 47%)	(17; 12%)	(25; 18%)
	P value		0.061	0.004	0.045	0.001
History of IHD						
	Positive	85	(9, 11%)	(52; 61%)	(16; 19%)	(8; 9%)
	Negative	143	(21; 15%)	(73; 51%)	(17; 12%)	(32; 22%)
	P value		0.598	0.062	0.091	0.008

Use of Organo-nitrates						
	Yes	72	(10; 14%)	(40; 56%)	(8; 11%)	(14; 19%)
	No	156	(30; 19%)	(64; 41%)	(22; 14%)	(40; 26%)
	P value		0.765	0.451	0.795	0.784
Use of Anti-arrhythmic						
	Yes	64	(6, 9%)	(35; 54%)	(19; 29%)	(5; 8%)
	No	164	(23; 14%)	(79; 48%)	(28; 17%)	(34; 21%)
	P value		0.675	0.869	0.320	0.041
Use of Anti-hyperlipidemics						
	Yes	31	(4; 13%)	(13; 42%)	(6; 19%)	(8; 26%)
	No	197	(22; 11%)	(77; 39%)	(39; 20%)	(59; 30%)
	P value		0.819	0.787	0.896	0.934
Use of 100 mg Aspirin						
	Yes	111	(15; 14%)	(46; 41%)	(21; 19%)	(29; 26%)
	No	117	(14; 12%)	(53; 45%)	(19; 16%)	(32; 27%)
	P value		0.813	0.962	0.652	0.783
Use of Bronchodilator						
	Yes	29	(9; 31%)	(6; 21%)	(11; 38%)	(3; 10%)
	No	199	(31; 16%)	(96; 48%)	(32; 16%)	(40; 20%)
	P value		0.09	0.001	0.007	0.098

Discussion:

Recent publications by the Palestinian Bureau of Central Statistics (PCBS) has shown that hypertension is the most prevalent chronic health condition in Palestine, when compared to other chronic diseases like diabetes mellitus, cardiovascular diseases, cancer, ulcers, asthma and epilepsy. This indicates the importance of the proper management and rational selection of antihypertensive drug therapy in order to improve the overall health of the Palestinian population. This study showed that there are significant differences between men and women in use of the four major classes of antihypertensive drugs. Among those receiving monotherapy, women were less likely to use calcium antagonists or ACE inhibitors than diuretics or BB. Among those receiving monotherapy, men were less likely to use diuretics or CCB than BB or ACE-I. One possible explanation for the sex differences in anti-hypertensive drug use include side effects and sex differences in the response to different antihypertensive drug classes. Side effects of antihypertensive drugs, such as sexual dysfunction in men or an ACE inhibitor-induced cough, which is more likely to occur in women, may also have contributed to the sex differences [(13)]. Moreover, in view of evidence of increased fetal wastage with the use of ACE inhibitors during pregnancy' physicians may be less inclined to prescribe these drugs for women of childbearing age who are likely to become pregnant [(14)]. Other possible explanation for the sex differences is that women might respond better to diuretics than ACE-I because women tend to have low renin activity. Furthermore, thiazide diuretics are known to cause hypocalcaemia which reduces risk of bone fracture, given the fact that elderly women are at higher risk of developing osteoporosis. In this study, the prevalence of diuretics was shown to increase with age. This is not surprising, since older patients respond better to diuretics than younger patients [(15)]. Calcium antagonists are more effective in lowering blood pressure in older than in younger hypertensives, yet the prevalence of their use was also declining with age [(15)]. The current study also showed that diabetic hypertensives were more likely to be using ACE inhibitors than diuretics. One possible explanation is that diuretics can induce hypokalemia, which may decrease glucose tolerance, whereas ACE inhibitors have a potentially beneficial effect on micro-albuminuria and renal function in patients with diabetic renal disease [(16, 17)]. This difference between diabetics and nondiabetics in the use of diuretics and ACE inhibitors was not found in two similar studies conducted in other countries [(18, 19)].

Hypertensives with asthma or chronic obstructive pulmonary disease were less likely to be using [beta]-blockers than CCB. This can be explained by the ability of [beta]-blockers to cause bronchoconstriction [20, 21]. Hypertensive patients with a history of hyperlipidemia as indicated by their use of lipid lowering agents were using the four studied anti-hypertensive classes to a similar extent although diuretics can induce small increases in the levels of total plasma cholesterol, triglycerides and low-density lipoprotein cholesterol, while ACE inhibitors have no adverse effects on the levels of serum lipids and lipoprotein [22]. In summary, the findings of our study show that physicians in Palestine take most known indications and contra-indications into account when they prescribe an antihypertensive drug motherapy. However, further investigation may be required to understand the long term effects of anti-hypertensive drug differences among men and women.

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