A study of anti-hypertensive drug prescription patterns in hypertensive post- menopausal women

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ABSTRACT

Background: Drug prescription in menopause is complex as estrogen deficiency, hypertension (HT) and other risk factors, rapidly increase the risk of cardiovascular diseases (CVD) in post-menopausal women (PMW).

Objectives: To evaluate the prescription trends of anti-hypertensive drugs in PMW.

Methods: This was an observational, cross sectional study conducted over a period of 1 year, on hypertensive PMW. The prescriptions were evaluated for antihypertensive drug use patterns and also as per WHO core drug indicators.

Results: 21.82% of prescriptions had monotherapy, amongst which angiotensin receptor blockers (ARB) (10%) and individually, telmisartan (5.45%) were most commonly prescribed. Majority of prescriptions had two drug therapy (44.09%), among which ARB + beta-blockers (BB) (20.91%) and individually, Telmisartan + Metoprolol (13.64%) were most frequently prescribed. ARB + Diuretic (DI) (9.55%) was the most common fixed drug combination (FDC) prescribed. ARB + BB + DI (10.45%), ARB + 2DI + BB (4.09%) and ARB + 2DI + BB + Calcium channel blocker (1.82%) were most commonly prescribed three, four and ≥five drug combinations, respectively. Hypolipidemic drugs (60.45%) were maximally co-prescribed. Percentage of drugs prescribed by generic name was 4.63% and from essential drug list was 32.62%.

Conclusions: A high trend of polypharmacy was observed in hypertensive PMW. HT, being a multifactorial disease, deserves a multidisciplinary and a comprehensive approach in the care of this population subgroup. Knowledge of prescription pattern and thus the rational utilisation of drugs will help achieve better control rates of HT and hence curb down the burden of CVDs in PMW.

Keywords: Hypertension, post-menopausal women, prescription pattern, polypharmacy, anti-hypertensive drugs

Introduction

Menopause is the permanent end of menstruation due to the depletion of functional and viable ovarian follicles.[1] It is a physiological part of ageing that is said to occur 12 months after a woman's last menstrual period. Menopause occurs between 45-50 years of age, the average age of menopause being 47 years.[2] Menopause is associated with an increase in the sympathetic nervous system activity, increase in low-density lipoprotein- cholesterol (LDL-C), lipoprotein-α and triglyceride (TG) and a decrease in high-density lipoprotein- cholesterol (HDL-C), progressive weight gain and consequent increase in blood pressure (BP) and increased cardiovascular risk.[3]

The exact mechanisms causing an increase in post-menopausal BP are yet to be clearly explained. How so ever an interplay of various humoral systems has been seen as the major causal link with post-menopausal hypertension (HT). These include a decline in estrogen/ androgen ratios, activation of renin-angiotensin-aldosterone system (RAAS) and an increase in the levels of endothelin and oxidative stress.[4] After menopause, there is a crossover in the prevalence of HT and post- menopausal women (PMW) have higher HT rates than age matched males. Despite of increasing burden of the disease, HT in women has been paid much less attention when compared to men.[5] Moreover, hypertensive women need more stringent efforts to achieve therapeutic BP goals than the hypertensive men. A cross-sectional study reported that though women are significantly more likely to receive anti-hypertensive therapy (61.4% in women as compared to 56.8% in men), only 44.8% of these women were likely to achieve target BP control as compared to 51.1% of treated men.[6] Since the causal relationship between HT and heart disease

is well established, maintaining low BP is of prime importance for the prevention of heart disease and stroke. It has been estimated that a 5 mm Hg reduction in systolic blood pressure (SBP) can decrease all deaths by 7%, stroke deaths by 14% and coronary deaths by 9%.[7]

The drug prescription in menopause is complex. Factors like polypharmacy, inappropriate medicine use, co-morbid conditions, pharmacokinetic and pharmacodynamic variability, non compliance and irrational prescription pattern make this population subgroup particularly vulnerable to a host of adverse drug reactions. Knowledge of prescription pattern and thus the rational utilisation of drugs will help overcome these adverse reactions. It is therefore necessary to regularly assess the drug utilisation pattern so as to maximise the therapeutic benefits and minimise the adverse effects. Literature has many studies available analysing anti-hypertensive drug prescription pattern in various age groups however, there is paucity of data regarding anti-hypertensive prescription trends among PMW.[8,9]

Material and Methods

This study was a cross sectional and observational study. The study was conducted for the duration of one year. The trial was registered at the Clinical Trial Registry- India [CTRI.nic.in identifier: CTRI/2017/06/008779] and the World Health Organization (WHO) [Universal Trial Number: U1111-1179-3239]. A total of 220 prescriptions prescribed to PMW for diagnosed HT, were collected for one point analysis from the department of Cardiology of a tertiary care teaching hospital. The patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study after obtaining written informed consent. The study population consisted of PMW diagnosed for HT with or without co-morbidities like diabetes, obesity, hypothyroidism. Inclusion and exclusion criteria were as follows.

Inclusion Criteria
- Women with self reported cessation of menstruation for >12 consecutive months.
- PMW with surgically induced menopause.

- Patients with HT in stage I/ stage II.
- Newly diagnosed and old patients of HT.
- Hypertensive patients with or without co-morbidities like diabetes, obesity, hypothyroidism.

Exclusion Criteria
- Women with indeterminate menopausal status.
- Patients with SBP >210 and/or Diastolic Blood Pressure (DBP) >120 mm Hg, requiring emergency care.

Patients underwent an initial evaluation that included HR, height, weight and BP evaluation. Two separate BP readings were taken and averaged. The Joint National Committee-7 (JNC-7) guidelines were used to classify the stages of HT among the patients. All the prescriptions prescribed to PMW for HT were surveyed. The prescriptions collected were evaluated for: WHO core drug indicators, Pattern of usage of a class of anti-hypertensive drugs, Pattern of usage of individual drugs within the class, Pattern of usage of anti-hypertensive drugs in patients treated with multiple drug therapy/ Fixed drug combination (FDC) and presence of any associated co-morbidities. WHO core drug indicators (The permission to use these indicators was taken [ID: 211361]) includes:

- **Average number of drugs per encounter:** Average was calculated by dividing the total number of different drug products prescribed, by the number of encounters surveyed. It was not relevant whether the patient actually received the drugs.
- **Percentage of drugs prescribed by generic name:** Percentage was calculated by dividing the number of drugs prescribed by generic name, by the total number of drugs prescribed, multiplied by 100.
- **Percentage of encounters with an antibiotic prescribed:** Percentage was calculated by dividing the number of patient encounters during which an antibiotic was prescribed, by the total number of encounters surveyed, multiplied by 100.
- **Percentage of encounters with an injection prescribed:** Percentage was calculated by dividing the number of patient encounters

during which an injection was prescribed, by the total number of encounters surveyed, multiplied by 100.

- **Percentage of drugs prescribed from essential drugs list (EDL) or formulary:** Percentage was calculated by dividing the number of products prescribed which were listed on the EDL, by the total number of products prescribed, multiplied by 100.[10,11]

Patients on anti-hypertensive medication with only one active ingredient were defined as receiving monotherapy. Patients taking two active ingredients in a combination pill were defined as receiving FDC therapy. Patients prescribed with two or more active ingredients were considered to be on polytherapy. The observations of individual patients were pooled and analyzed. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 20.0 Chicago, Illinois, United States. Descriptive statistics was applied for the analysis of data. Data was expressed in proportion and percentage form and represented in the form of tables, charts and bar diagrams.

Results

The mean age (± SD) of patients was 59.90±7.34 years. Majority of PMW with HT were of the age-group 61-65 years (27.27%). [Figure 1] The mean age at menopause was 47.85±4.93 years and mean duration since menopause was 12.10±6.88 years. Dyslipidemia (60.45%) followed by anxiety (44.55%), diabetes (39.54%), osteoporosis (34.55%), obesity (28.64%), gastro-esophageal reflux disorder (GERD) (24.09%) and hypothyroidism (6.82%) were the most common co-morbidities associated in PMW.

As per JNC-7 classification, 45.91% had pre-HT, 28.18% had Stage I HT, 15.45% had Stage II HT and only 10.45% of patients had BP in the normal range. 21.82% patients were on anti-hypertensive monotherapy while 78.18% of patients were on anti- hypertensive polytherapy. Overall, ARB (72.27%) was maximally prescribed as the class and telmisartan (44.09%) was most commonly prescribed anti-hypertensive drug, either as monotherapy or polytherapy. [Table 1] In the monotherapy category, angiotensin receptor blockers (ARBs) accounted for 10% of

the total prescriptions followed by, calcium channel blockers (CCBs) (5%), angiotensin converting enzyme inhibitors (ACEIs) (4.54%), beta-blockers (BB) (1.82%), and diuretics (0.45%. ARBs were prescribed the most whereas BBs and diuretics were the least prescribed. However, individually telmisartan was maximally prescribed in 5.45% of cases. Telmisartan and losartan (2.27%) among ARBs, amlodipine (4.09%) among CCBs, ramipril (2.72%) among ACEIs and atenolol (0.91%) and metoprolol (0.91%) among BBs were most commonly prescribed in their respective category. [Table 2]
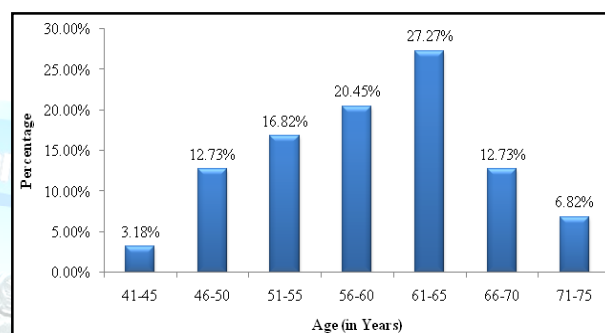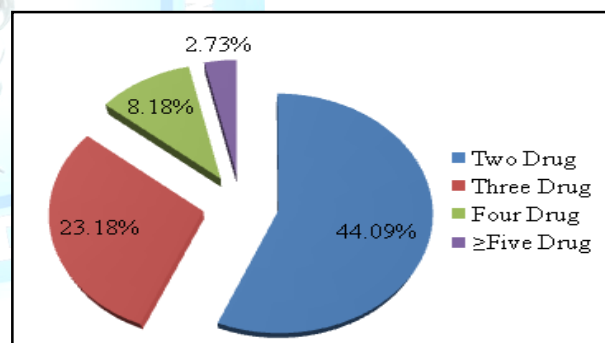

Fig.1 Age distribution

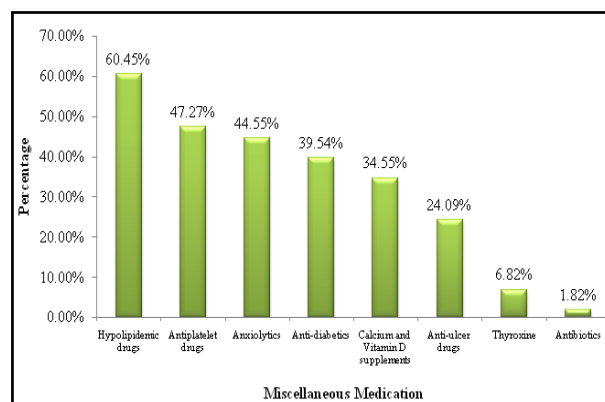**Fig. 2 Frequency distribution of the type of anti-hypertensive polytherapy**

Fig. 3 Frequency distribution of miscellaneous medications

Table 1: Overall drug frequency either as monotherapy or polytherapy

Anti-hypertensive	Monotherapy (%)	Combination (%)	FDC (%)	Total (%age)
ARB				**159(72.27%)**
Telmisartan	12 (5.45%)	58 (26.36%)	27 (12.27%)	97 (44.09%)
Olmesartan	5 (2.27%)	16 (7.27%)	11 (5%)	32 (14.55%)
Losartan	5 (2.27%)	23 (10.45%)	2 (0.91%)	30 (13.64%)
Candesartan	0 (0%)	1 (0.45%)	0 (0%)	1 (0.45%)
BB				**134 (60.90%)**
Metoprolol	2 (0.91%)	74 (33.64%)	20 (9.09%)	96 (43.64%)
Atenolol	2 (0.91%)	13 (5.91%)	0 (0%)	15 (6.82%)
Nebivolol	0 (0%)	10 (4.55%)	3 (1.36%)	13 (5.91%)
Carvedilol	0 (0%)	8 (3.63%)	0 (0%)	8 (3.63%)
Propranolol	0 (0%)	1 (0.45%)	0 (0%)	1 (0.45%)
Bisoprolol	0 (0%)	1 (0.45%)	0 (0%)	1 (0.45%)
DI				**100 (45.45%)**
Chlorthalidone	0 (0%)	22 (10%)	17 (7.72%)	39 (17.73%)
Hydrochlorothiazide	0 (0%)	20 (9.09%)	12 (5.45%)	32 (14.55%)
Spironolactone	0 (0%)	20 (9.09%)	0 (0%)	20 (9.09%)
Torsemide	0 (0%)	18 (8.18%)	0 (0%)	18 (8.18%)
Furosemide	1 (0.45%)	6 (2.73%)	0 (0%)	7 (3.18%)
Indapamide	0 (0%)	1 (0.45%)	1 (0.45%)	2 (0.91%)
CCB				**54 (24.54%)**
Amlodipine	9 (4.09%)	22 (10%)	6 (2.73%)	37 (16.82%)
Cilnidipine	2 (0.91%)	11 (5%)	4 (1.82%	17 (7.73%)
ACEI				**30 (13.63%)**
Ramipril	6 (2.72%)	14 (6.36%)	4 (1.82%)	24 (10.91%)
Enalapril	2 (0.91%)	1 (0.45%)	0 (0%)	3 (1.36%)
Lisinopril	2 (0.91%)	0 (0%)	0 (0%)	2 (0.91%)
Perindopril	0 (0%)	0 (0%)	1 (0.45%)	1 (0.45%)
α₂A				**05 (2.27%)**
Moxonidine	0 (0%)	2 (0.91%)	0 (0%)	2 (0.91%)
α-Blocker				**2 (0.91%)**
Prazosin	0 (0%)	2 (0.91%)	0 (0%)	2 (0.91%)

FDC = Fixed Drug Combination; ARB = Angiotensin receptor blockers; BB = Beta- blockers; DI = Diuretics; CCB = Calcium channel blockers; ACEI = Angiotensin converting enzyme inhibitors; α2A = Alpha2 Agonists; α-Blocker = Alpha Blocker

Table 2: Frequency distribution of anti- hypertensive monotherapy

Anti-hypertensive drug	Frequency	Percentage	Total (%age)
ARB			**22 (10%)**
Telmisartan	12	5.45%	
Losartan	5	2.27%	
Olmesartan	5	2.27%	
CCB			**11 (5%)**
Amlodipine	9	4.09%	
Cilnidipine	2	0.91%	
ACEI			**10 (4.54%)**
Ramipril	6	2.72%	
Lisinopril	2	0.91%	
Enalapril	2	0.91%	
BB			**04 (1.82%)**
Metoprolol	2	0.91%	
Atenolol	2	0.91%	
DI			**01 (0.45%)**
Furosemide	1	0.45%	

ARB = Angiotensin receptor blockers; CCB = Calcium channel blockers; ACEI = Angiotensin converting enzyme inhibitors; BB = Beta- blockers; DI = Diuretics

Table 3: Frequency of anti- hypertensive drugs in two drug therapy

Antihypertensive drugs	Combination		FDC		Total (%age)
	No.	%age	No.	%age	
TWO DRUGS					**97 (44.09%)**
ARB + BB					**46 (20.91%)**
Telmisartan + Metoprolol	15	6.82%	15	6.82%	30 (13.64%)
Losartan + Metoprolol	7	3.18%	0	0%	7 (3.18%)
Losartan + Atenolol	4	1.82%	0	0%	4 (1.82%)
Telmisartan + Nebivolol	4	1.82%	0	0%	4 (1.82%)
Telmisartan + Carvedilol	1	0.45%	0	0%	1 (0.45%)
ARB + Diuretic					**24 (10.91%)**
Olmesartan + Chlorthalidone	0	0%	8	3.64%	8 (3.64%)
Telmisartan + Chlorthalidone	0	0%	5	2.27%	5 (2.27%)
Telmisartan + Hydrochlorothiazide	0	0%	4	1.82%	4 (1.82%)
Olmesartan + Hydrochlorothiazide	2	0.91%	2	0.91%	4 (1.82%)
Losartan + Hydrochlorothiazide	0	0%	2	0.91%	2 (0.91%)
Losartan + Spironolactone	1	0.45%	0	0%	1 (0.45%)
ACEI + Diuretic					**06 (2.73%)**
Ramipril + Hydrochlorothiazide	1	0.45%	3	1.36%	4 (1.82%)
Ramipril + Torsemide	1	0.45%	0	0%	1 (0.45%)
Perindopril + Indapamide	0	0%	1	0.45%	1 (0.45%)
ACEI + BB					**5 (2.27%)**
Ramipril + Metoprolol	3	1.36%	1	0.45%	4 (1.82%)
Ramipril + Carvedilol	1	0.45%	0	0%	1 (0.45%)
BB + Diuretic					**5 (2.27%)**
Nebivolol + Chlorthalidone	0	0.45%	2	0.91%	2 (0.91%)
Metoprolol + Torsemide	1	0.45%	0	0%	1 (0.45%)
Nebivolol + Torsemide	1	0.45%	0	0%	1 (0.45%)
Metoprolol + Chlorthalidone	0	0%	1	0.45%	1 (0.45%)
ARB + CCB					**4 (1.82%)**
Telmisartan + Cilnidipine	0	0%	2	0.91%	2 (0.91%)
Telmisartan + Amlodipine	0	0%	1	0.45%	1 (0.45%)
Olmesartan + Amlodipine	0	0%	1	0.45%	1 (0.45%)
CCB + BB					**4 (1.82%)**
Amlodipine + Metoprolol	0	0%	3	1.36%	3 (1.36%)
Cilnidipine + Nebivolol	0	0%	1	0.45%	1 (0.45%)
CCB + Diuretic					**3 (1.36%)**
Cilnidipine + Chlorthalidone	0	0%	1	0.45%	1 (0.45%)
Amlodipine + Chlorthalidone	1	0.45%	0	0%	1 (0.45%)
Amlodipine + Hydrochlorothiazide	0	0%	1	0.45%	1 (0.45%)

FDC = Fixed Drug Combination; ARB = Angiotensin receptor blockers; CCB = Calcium channel blockers; ACEI = Angiotensin converting enzyme inhibitors; BB = Beta- blockers

About 44.09% prescription had two drug, whereas 23.18% had three drug, 8.18% had four drug and 2.73% had five antihypertensive drug therapy. [Figure 2] Overall, ARB + BB (20.91%) was the most frequent anti-hypertensive class prescribed among polytherapy followed by ARB + DI (10.91%) and ARB + BB + DI (10.45%). Among two drug therapy, overall ARB + BB was most commonly prescribed, accounting for 20.91%; 14.09% of which was prescribed as combination and 6.82% as FDC. Individually, overall Telmisartan + Metoprolol was maximally prescribed, accounting for 13.64%; among which 6.82% was prescribed as combination and 6.82% as FDC. Only two drug FDCs (24.55%) were prescribed to the patients. ARB + DI (9.55%) was the most common FDC of antihypertensive class prescribed. [Table 3] Telmisartan + Metoprolol + Chlorthalidone (3.64%), Telmisartan + Torsemide + Spironolactone + Metoprolol (1.82%) and Telmisartan + Spironolactone + Furosemide + Metoprolol + Cilnidipine (0.91%) were the most

frequently prescribed three drug, four drug and five drug combination therapies. [Table 4,5,6].

Table 4: Frequency of anti-hypertensive drugs in three drug therapy

Antihypertensive	Combination		FDC		Total (%age)
	No.	%age	No.	%age	
THREE DRUGS					**51 (23.18%)**
ARB+BB+Diuretic					**23 (10.45%)**
Telmisartan+Metoprolol+Chlorthalidone	8	3.64%	0	0%	8 (3.64%)
Telmisartan+Metoprolol+Hydrochlorothiazide	5	2.27%	0	0%	5 (2.27%)
Losartan+Atenolol+Hydrochlorothiazide	2	0.91%	0	0%	2 (0.91%)
Olmesartan+Metoprolol+Chlorthalidone	2	0.91%	0	0%	2 (0.91%)
Telmisartan+Carvedilol+Hydrochlorothiazide	1	0.45%	0	0%	1 (0.45%)
Telmisartan+Metoprolol+Torsemide	1	0.45%	0	0%	1 (0.45%)
Olmesartan+Metoprolol+Indapamide	1	0.45%	0	0%	1 (0.45%)
Telmisartan+Nebivolol+Chlorthalidone	1	0.45%	0	0%	1 (0.45%)
Losartan+Carvedilol+Hydrochlorothiazide	1	0.45%	0	0%	1 (0.45%)
Losartan+Carvedilol+Spironolactone	1	0.45%	0	0%	1 (0.45%)
ARB+CCB+BB					**15 (6.82%)**
Losartan+Amlodipine+Atenolol	4	1.82%	0	0%	4 (1.82%)
Telmisartan+Amlodipine+Metoprolol	3	1.36%	0	0%	3(1.36%)
Telmisartan+Cilnidipine+Metoprolol	2	0.91%	0	0%	2 (0.91%)
Telmisartan+Amlodipine+Bisoprolol	1	0.45%	0	0%	1 (0.45%)
Telmisartan+Amlodipine+Nebivolol	1	0.45%	0	0%	1 (0.45%)
Olmesartan+Amlodipine+Metoprolol	1	0.45%	0	0%	1 (0.45%)
Telmisartan+Cilnidipine+Nebivolol	1	0.45%	0	0%	1 (0.45%)
Olmesartan+Cilnidipine+Nebivolol	1	0.45%	0	0%	1 (0.45%)
Losartan+Cilnidipine+Metoprolol	1	0.45%	0	0%	1 (0.45%)
ACEI+Diuretic+BB					**9 (4.09%)**
Ramipril+Hydrochlorothiazide+Metoprolol	6	2.73%	0	0%	6 (2.73%)
Ramipril+Chlorthalidone+Metoprolol	1	0.45%	0	0%	1 (0.45%)
Ramipril+Torsemide+Metoprolol	1	0.45%	0	0%	1 (0.45%)
Enalapril+Hydrochlorothiazide+Propranolol	1	0.45%	0	0%	1 (0.45%)
ARB+Diuretic+CCB					**2 (0.91%)**
Telmisartan+Chlorthalidone+Amlodipine	1	0.45%	0	0%	1 (0.45%)
Telmisartan+Hydrochlorothiazide+Cilnidipine	1	0.45%	0	0%	1 (0.45%)
Diuretic+BB+CCB					**1 (0.45%)**
Chlorthalidone+Metoprolol+Amlodipine	1	0.45%	0	0%	1 (0.45%)
Diuretic+BB					**1 (0.45%)**
Spironolactone+Torsemide+Metoprolol	1	0.45%	0	0%	1 (0.45%)

FDC = Fixed Drug Combination ; ARB = Angiotensin receptor blockers; CCB = Calcium channel blockers; ACEI = Angiotensin converting enzyme inhibitors; BB = Beta- blockers

Of the other drug groups prescribed in the hypertensive PMW, hypolipidemic drugs (60.45%) and anti-platelet drugs (47.27%) were the most frequently prescribed. [Figure 3] The prescriptions were analysed using WHO core prescribing indicators. Average number of drugs per prescription was 5.91; percentage of drugs prescribed by generic name was 4.63% only; percentage of prescriptions with antibiotic was 1.82% and percentage of drugs from EDL was 32.62%. None of the prescription had an injectable drug prescribed. [Table 7]

Table 5: Frequency of anti- hypertensive drugs in four drug therapy

Antihypertensive	Combination		FDC		Total (%age)
	No.	%age	No	%age	
FOUR DRUGS					**18 (8.18%)**
ARB+(2)Diuretic+BB					**9 (4.09%)**
Telmisartan+Torsemide+Spironolactone+Metoprolol	4	1.82%	0	0%	4 (1.82%)
Telmisartan+Furosemide+Spironolactone+Carvedilol	2	0.91%	0	0%	2 (0.91%)
Losartan+Furosemide+Spironolactone+Atenolol	1	0.45%	0	0%	1 (0.45%)
Olmesartan+Furosemide+Spironolactone+Metoprolol	1	0.45%	0	0%	1 (0.45%)
Losartan+Torsemide+Spironolactone+Carvedilol	1	0.45%	0	0%	1 (0.45%)
ARB+Diuretic+BB+CCB					**6 (2.73%)**
Olmesartan+Chlorthalidone+Metoprolol+Amlodipine	3	1.36%	0	0%	3 (1.36%)
Olmesartan+Chlorthalidone+Atenolol+Amlodipine	2	0.91%	0	0%	2 (0.91%)
Telmisartan+Chlorthalidone+Metoprolol+Amlodipine	1	0.45%	0	0%	1 (0.45%)
ARB+(2)Diuretic+CCB					**1 (0.45%)**
Olmesartan+Torsemide+Spironolactone+Amlodipine	1	0.45%	0	0%	1 (0.45%)
(2)ARB+Diuretic+CCB					**1 (0.45%)**
Telmisartan+Candesartan+Torsemide+Cilnidipine	1	0.45%	0	0%	1 (0.45%)
(2)Diuretic+BB+CCB					**1 (0.45%)**
Torsemide+Spironolactone+Nebivolol+Cilnidipine	1	0.45%	0	0%	1 (0.45%)

FDC = Fixed Drug Combination; ARB = Angiotensin receptor blockers; BB = Beta- blockers; DI = Diuretics; CCB = Calcium channel blockers; ACEI = Angiotensin converting enzyme inhibitors

Table 6: Frequency of anti- hypertensive drugs in ≥five drug therapy

Antihypertensive	Combination		FDC		Total (%age)
	No.	%age	No	%	
≥FIVE DRUGS					**6 (2.73%)**
ARB+(2)Diuretic+BB+CCB					**4 (1.82%)**
Telmisartan+Spironolactone+Furosemide+Metoprolol + Cilnidipine	2	0.91%	0	0%	2 (0.91%)
Telmisartan+Spironolactone+Torsemide+Metoprolol+Cilnidipine	1	0.45%	0	0%	1 (0.45%)
Telmisartan+Spironolactone+Torsemide+Metoprolol+Amlodipine	1	0.45%	0	0%	1 (0.45%)
ARB+3DI+α-Blocker+α$_2$A					**1 (0.45%)**
Olmesartan+Chlorthalidone+Torsemide+Spironolactone+Prazosin+ Moxonidine	1	0.45%	0	0%	1 (0.45%)
ARB+2DI+BB+CCB+α-Blocker+α$_2$A Olmesartan+Torsemide+Spironolactone+ Metoprolol+Amlodipine+ Prazosin+Moxonidine	1	0.45%	0	0%	**1 (0.45%)** 1 (0.45%)

FDC = Fixed Drug Combination; ARB = Angiotensin receptor blockers; BB = Beta- blockers; DI = Diuretics; CCB = Calcium channel blockers; ACEI =
 Angiotensin converting enzyme inhibitors; α2A = Alpha2 Agonists; α-Blocker = Alpha Blocker

Table 7: WHO prescribing indicators

WHO prescribing indicators	
Average number of drug per prescription	5.91
Percentage of drugs prescribed by generic name	4.63
Percentage with antibiotic	1.82
Percentage with injection	0.00
Percentage from EDL	32.62

EDL = Essential Drug List

Discussion

The trends of antihypertensive prescription observed in our study are in accordance with the study conducted by Sharma AK et al (2015) in hypertensive population of mean age 58.25 years where 67.97% received combination therapy while only 31.8% received monotherapy.[12] JNC-7 guidelines recommend considering initiation of therapy with two drugs, either as FDC or separate prescriptions, when SBP >20 mm Hg and DBP >10 mm Hg above the goal BP.[13] HT being a multifactorial disease, therapy with a single agent is unlikely to achieve the target BP. This provides the basis of combining a second agent acting by a complimentary mechanism. Moreover, combining the drugs achieves better control rates and reduces the adverse effects by lowering the dose of individual drug component. Combining BB with dihydropyridine CCB counters the tachycardia induced by CCB. ACEI/ ARB by their hyperkalemic effects, counter the hypokalemia caused by potassium loss with DI therapy. BB lower the increased plasma renin activity induced by CCB, ACEI and DI.[14,15]

Tandon VR et al (2014), in a similar study on 500 hypertensive PMW, reported that ARB (24.8%) were prescribed the most in monotherapy followed by CCB (19.4%), ACEI (11%), BB (2.8%) and DI (2%). Individually, amlodipine among CCB accounted for 16.4% of cases followed by ramipril (6.8%) and enalapril (3.4%) among ACEI and atenolol (1.8%) and metoprolol (0.8%) among BB.[8] The findings of this study are in accordance with our study. However, Tiwari et al recorded 46.2% of prescriptions to have BBs, which is extremely high in comparison to 1.82% found in our study.[16] This may be due to the fact that BB are no longer recommended as a first line anti-hypertensive drug class in uncomplicated HT because of inferiority compared to other drugs in prevention of stroke and left ventricular hypertrophy; lack of efficacy in preventing myocardial infarction; less efficacy in controlling SBP, pulse pressure and central aortic pressure; and side effect profile including fatigue, depression, sexual dysfunction and metabolic abnormalities like impaired glucose tolerance and lipid abnormalities. BB are thus preferred to be used only in patients with compelling cardiac indications or as add-on agents in uncontrolled HT. Though JNC-8 recommends an initial anti-hypertensive treatment including a thiazide DI, CCB, ACEI or ARB in nonblack race group whereas a thiazide DI or CCB in black race group, the higher utilization of ARB, CCB and ACEI over DI in the present study might be because of their better tolerance and fewer side effects as compared to the DI in this age group in addition to the cardiovascular and renal protection conferred by ACEI/ ARB.[17,18]

Our findings are similar to those of the study conducted by Jeschke et al on 1320 hypertensive patients (63.5% women) with mean age 64.2 years. This study reported that ACEI + DI (31.2%) and ARB + DI (25.8%) were most frequently prescribed option among the two drug treatments, either as combination or FDC, followed by DI + BB (14.2%). Among combination therapy, BB + anti-hypertensive other than DI or CCB (9.6%) was maximally prescribed followed by ACEI + DI (6.6%) and DI + BB (6.3%). ACEI + DI (24.6%) and ARB + DI (24.5%) were the most common prescribed FDCs.[19] Low dose combination drug treatment increases efficacy and reduces adverse effects. BB are used in combination with ARB/ ACEI to boost BP reduction. BB by their pharmacological actions reduce cardiac output and sympathetic activity, thus complementing the effects of RAAS inhibition by ARB/ ACEI in terms of BP reduction. Moreover, concomitant BB therapy prevents the upregulation of renin that is seen with treatment on ACEI, DI or both. ACEI and BB are also known to significantly reduce plasma homocysteine levels in patients with HT.[15] The combination of ARB/ ACEI with DI was also very frequently prescribed. DI, by causing volume and sodium depletion, stimulate the production of renin and angiotensin leading to a relative increase in BP and sodium retention, thus counteracting some of its own anti-hypertensive effects. ACEI, by decreasing angiotensin II levels, lead to decreased sodium retention and an enhanced anti-hypertensive effect. [20]

When available, FDCs were preferred over combination therapy, accounting for 24.55% of all the two drug therapies in the present study.

This is likely due to the reason that FDCs make dosing format more convenient and improve patient compliance. FDCs when used as an initial therapy, combat therapeutic inertia, which is the physician's failure to either increase the dose of anti-hypertensive medication or add another medication to achieve BP control.[15]

In accordance with our study, Cidda M et al (2014) also reported that ARB + BB + DI (21.27%) and ARB + 2DI + BB (20%) were the most commonly prescribed three drug and four drug combinations.[21] Sivakumar A et al (2014), it was concluded that ARB were the most used anti-hypertensive agent especially Telmisartan. ACEI were the least prescribed anti-hypertensive agent.[22]

As far as the analysis according to WHO core prescribing indicators is concerned, Beg MA et al (2014) reported similar findings where the average number of drugs prescribed per prescription was 2.83, 100% drugs were prescribed by their brand names, 32.28% drugs were prescribed from National Essential Medicine List and 97.43% drugs were prescribed by oral formulations.[23] The WHO expects a 100% prescription of drugs by their generic names. The cost of drugs for the patients can be significantly reduced by increasing generic prescribing of drugs.[24]

Despite being on antihypertensive therapy, only 10.45% of patients had BP in the normal range while majority had pre-HT, stage I HT and stage II HT. These findings reflect the unmet need of the control of BP in this vulnerable population group.

Overall this study stresses upon the need to optimize strategies to improve prescribing of anti-hypertensive therapy in PMW. Our study also had potential limitations. It was a cross-sectional study and no follow up was done. The study analyses a subgroup of population and the prescription trends were not compared with general population. Moreover, the antihypertensive drug prescriptions were not correlated with menopausal parameters. Even the rationality and the adherence of the prescriptions to HT treatment guidelines were not studied. Also, owing to the limited duration, small sample size and region specific nature of

the study, further multi-centric studies with a larger sample size and longer duration are warranted.

In this study, a high trend of polypharmacy in anti-hypertensive prescriptions was observed in PMW. HT is a multifactorial disease and moreover, it coexists with various risk factors including menopause itself, dyslipidemia, diabetes and obesity in PMW. Uncontrolled BP, despite being on anti-hypertensive medications is an area of major concern. Time demands to promote a multidisciplinary, multi-pronged, comprehensive approach to the care of this population subgroup.

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