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Effects of multimorbidity and polypharmacy on blood pressure target attainment in patients with hypertension

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ABSTRACT

Background Hypertension prevalence increases with age, as well as polypharmacy and multimorbidity (P&M), which are the use of multiple medications and the presence of multiple chronic diseases, respectively. Whether P&M affects attaining blood pressure (BP) goals is not clear.

Methods Hypertensive patients in the general internal medicine outpatient clinic were evaluated retrospectively. Data regarding age, gender, comorbidities, medications, office BP (OBP), home BP (HBP), and ambulatory BP (ABP) were obtained. Having two or more diseases was classified as multimorbidity, whereas using five or more drugs was classified as polypharmacy. OBP <140/90 mmHg, HBP <135/85 mmHg, and ABP <130/80 mmHg were considered BP targets. Differences in BP and attaining targets were analyzed according to P&M. Correlation analysis was also performed between BP, age, comorbidities, and medications.

Results Of the 147 patients, 124 (84.4%) had multimorbidity, and 56 (38.1%) had polypharmacy. While systolic BP in OBP and HBP did not differ in the P&M groups (all $p>0.05$), diastolic BP was lower in patients with both (all $p<0.05$). Age, total number of medications, anti-hypertensive tablets, and active substance numbers showed a negative correlation with diastolic BP in both OBP and HBP (all $p<0.05$). There was no difference between BP goal attainments in P&M groups ($p>0.05$).

Conclusion P&M does not affect the achievement of office and home BP targets. Lower diastolic BP with P&M does not reflect better control but reflects the effect of age on diastolic BP.

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INTRODUCTION

Hypertension is one of the most common chronic diseases, with wide adverse implications for cardiovascular, cerebrovascular, and renal outcomes.[1,2] Thanks to anti-hypertensive medications' effect on lowering all-cause mortality, many elderly patients are now continuing their lives without experiencing hypertension-related adverse outcomes.[3,4] However, hypertensive patients generally need two to three medications for their blood pressure (BP) to reach BP goals that prevent adverse outcomes.[5] Besides, patients with hypertension usually have one or more accompanying diseases, such as diabetes, dyslipidemia, chronic kidney disease, and cardiovascular disease, which necessitate multiple medications as well.[6-11] This translates into the fact that patients with hypertension have significant rates of multimorbidity and polypharmacy, two interrelated global challenges with substantial impact on both patients and societies. In Europe, a 2018 study found that the prevalence of polypharmacy ranged from 25 to 40%.[12] Polypharmacy has various imprecise definitions and is subject to debate. The study above defined polypharmacy as "concurrent use of five or more medications per day." However, many other definitions exist as well.[13] Similar to polypharmacy, multimorbidity has multiple definitions, but "having two or more co-existing conditions in an individual" is the most adapted definition by the World Health Organization.[14] Similar to polypharmacy, multimorbidity has a high prevalence and is reported to range from 15 to 43%.[15] It has been demonstrated that patients with multimorbidity and polypharmacy have increased healthcare utilisation, have more frequent hospital admissions, experience longer hospital stays, and have higher rates of falls, cognitive impairment, and mortality.[15,16]

It has been shown that medication non-adherence among patients with hypertension is common and associated with the number of medications prescribed.[17] The recent European Society of Hypertension addresses this issue and recommends single pill combinations to improve adherence.[5] Also, the BP goals of patients with hypertension up to 80 years old are similar to younger patients' goals.[5] However, whether the presence of polypharmacy or multimorbidity impacts BP levels and reaching BP targets. A higher number of medications does not necessarily translate into lower adherence to anti-hypertensive medications. A meta-analysis demonstrated that medication regimen complexity was associated with medication non-adherence in only 2 of 6 observational studies.[18] Moreover, one study in this meta-analysis found that participants with less complex medication regimens were more likely to stop medications when feeling worse.[19] In the context of the current ambiguous literature data, we aimed to investigate whether having multimorbidity or polypharmacy is associated with worse BP control and lower BP goal attainment rates.

MATERIAL AND METHODS

This study was designed as a retrospective case-control study in the Başkent University Ankara Hospital General Internal Medicine outpatient clinic. We evaluated the eligibility of patients with a primary hypertension diagnosis (ICD-10 code: I10) admitted to the clinic between June 2023 and January 2024. Electronic medical records were used for data gathering.

The study included patients with BP readings obtained from either office, home, or ambulatory settings. Age, gender, chronic diseases (grouped as follows: diabetes mellitus, cardiovascular diseases, metabolic diseases, pulmonary diseases, malignancy, rheumatological diseases, neuropsychiatric diseases, and others), number of comorbidities, number of total medications (including over-the-counter pills, vitamins, pain medications, etc.), anti-hypertensive medication's active substance numbers and pill numbers, and systolic and diastolic BP readings of office, home, or ambulatory BPs were acquired. Having multimorbidity was defined as having two or more diseases apart from hypertension, and having polypharmacy was defined as using five or more medications, including anti-hypertensive pills.

The study assigned an anonymous serial number to the patients to ensure confidentiality. The data processing did not require informed consent, and written informed consent was not obtained due to the study's retrospective design. The study complies with the principles outlined in the Declaration of Helsinki, and the study was approved by the Başkent University Review Board (decision number: KA23/454).

Statistical analysis

Continuous variables (i.e., age, BP, number of comorbidities, and medications) were presented by median (interquartile range). In contrast, categorical variables (i.e., gender, comorbidities, multimorbidity, polypharmacy, and BP target attainment) were presented as numbers (percentages). Between-group dif-

ferences were analysed using Pearson's chi-squared test (χ^2 test) or Fisher's exact test for categorical variables. The Mann-Whitney U test was used for continuous variables between two groups and continuous variables between more. Relationships between continuous variables were tested using Spearman's correlation test. Statistics were provided according topatients' multimorbidity and polypharmacy presence. IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL) was used for analyses. We performed two-sided significance testing and considered p-values less than 0.05 as significant.

Table 1. Demographic, clinical and blood pressure values of the patients

Variables	Values
Age (years) median (IQR)	67 (21)
Gender (Female/Male) n (%)	104 (70.7)/43 (29.3)
Comorbidities n (%)	
Diabetes mellitus	60 (40.8)
Cardiovascular disease	30 (20.4)
Metabolic	68 (46.3)
Pulmonary	17 (11.6)
Malignancy	9 (6.1)
Rheumatological	14 (9.5)
Neuropsychiatric	33 (22.4)
Number of chronic diseases n (%)	
0	3 (2)
1	20 (13.6)
2	33 (22.4)
3	32 (21.8)
4	31 (21.1)
5	20 (13.6)
6 and above	8 (5.5)
Multimorbidity n (%)	124 (84.4)
Number of total medications n (%)	
0	16 (10.9)
1-5	85 (57.8)
6-10	34 (23.1)
11 and above	12 (8.1)
Polypharmacy n (%)	56 (38.1)
Number of anti-hypertensive pills n (%)	35 (23.8)
0	55 (37.4)
1	45 (30.6)
2	10 (6.8)
3	2 (1.4)
4	
Number of anti-hypertensive active substances n (%)	
0	35 (23.8)
1	28 (19)
2	41 (27.9)
3	29 (19.7)
4	12 (8.2)
5	2 (1.4)
Blood pressure (mmHg) median (IQR)	
Office (n: 124)	150 (27) / 87 (15)
Home (n: 69)	130 (15) / 75 (13)
Ambulatory (n: 16)	127 (17) / 77 (17)

RESULTS

One hundred and forty-seven patients were included in the study. Of those, the majority were women (70.7%), and the median age was 67 years (21). Metabolic diseases, including diabetes mellitus, constituted the most common co-morbidity (46.3%), followed by neuropsychiatric conditions (22.4%) and cardiovascular diseases (20.4%). One hundred twenty-four patients (84.4%) had multimorbidity. While 16 patients did not use any medications, 85 patients (57.8%) used 1 to 5 medications, 34 (23.1%) used 6 to 10 medications, and 12 (8.1%) used 11 or more medications. Fifty-six patients (38.1%) had polypharmacy. While 55 (37.4%) patients were using one anti-hypertensive medication pill and 45 (30.6%) were on two anti-hypertensive pills, 35 (23.8%) patients were not using anti-hypertensive medications. Regarding the number of anti-hypertensive active substances, 28 (19%) patients were on one medication, 41 (27.9%) were on two medications, and 29 (19.7%) were on three medications. Of the 147 patients, 124 had office BP readings, 69 had home BP readings, and only 16 had ambulatory BP readings. Median systolic and diastolic BP of office, home, and ambulatory readings were 150/87, 130/75, and 127/77 mmHg, respectively. The baseline clinical features of the patients were detailed in Table 1.

The age of patients with multimorbidity was significantly higher (69 vs. 51 years, $p<0.001$) compared to those who did not have multimorbidity. The median number of total medications, the number of anti-hypertensive pills, and active substances were also significantly higher among patients with multimorbidity (4 vs. 1, 1 vs. 0, and 2 vs. 0, respectively, all $p<0.001$). Considering office BP readings, systolic BP was not different (155 vs. 145 mmHg, $p=0.21$); however, diastolic BP was lower among patients with multimorbidity (85 vs. 95 mmHg, $p=0.016$). Regarding home and ambulatory BP readings, both systolic and diastolic BPs did not differ between multimorbidity groups (all $p>0.05$). Goal BP attainment rates using different office, home, or ambulatory BP readings were not

Table 2. Clinical and blood pressure values of the patients according to multimorbidity and polypharmacy

Variables	Multimorbidity			Polypharmacy		
	Absent n: 23	Present n: 124	*P*-value	Absent n: 91	Present n: 56	*P*-value
Age (years) median (IQR)	51 (19)	69 (15)	<0.001	64 (20)	72.5 (15)	<0.001
Number of medications n (%)						
Total medications	1 (2)	4 (6)	<0.001	2 (2)	8 (4)	<0.001
Anti-hypertensive pills	0 (1)	1 (1)	<0.001	1 (1)	2 (1)	<0.001
Anti-hypertensive active substance	0 (1)	2 (2)	<0.001	1 (2)	2.5 (1)	<0.001
Office BP (mmHg) median (IQR)	n: 20	n: 104		n: 77	n: 47	
Systolic	145 (25)	155 (25)	0.21	150 (25)	155 (35)	0.92
Diastolic	95 (15)	85 (15)	0.016	90 (15)	85 (20)	0.015
Office BP target attainment n (%)	7 (35)	33 (31.7)	0.77	24 (31.2)	16 (34)	0.74
Home BP (mmHg) median (IQR)	n: 12	n: 57		n: 41	n: 28	
Systolic	125 (20)	130 (14)	0.4	131.5 (18)	127 (12)	0.13
Diastolic	80 (16)	75 (11)	0.3	80 (15)	70.5 (12)	0.02
Home BP target attainment n (%)	8 (66.7)	40 (70.2)	0.81	25 (61)	23 (82.1)	0.06
Ambulatory BP (mmHg) median (IQR)	n: 2	n: 14		n: 11	n: 5	
Systolic	133.5 (NA)	127 (17)	0.41	128 (12)	121 (36)	0.74
Diastolic	77 (NA)	74 (18)	0.93	78 (15)	68 (14)	0.14
Ambulatory BP target attainment n (%)	1 (50)	8 (57.1)	0.84	6 (54.5)	3 (60)	0.83

BP: blood pressure, NA: not applicable.

among multimorbidity groups (all p>0.05). Table 2 showed the characteristics of patients with multimorbidity in detail.

Patients with polypharmacy had significantly higher ages (72.5 vs. 64 years, p<0.001) as well. The median number of anti-hypertensive pills and active substances was significantly higher among patients with polypharmacy (2 vs. 1 and 2.5 vs. 1, respectively, all p<0.001). Considering office BP readings, systolic BP was not different (150 vs. 155 mmHg, p=0.92); however, diastolic BP was lower among patients with polypharmacy (85 vs. 90 mmHg, p=0.015). Regarding home BP readings, systolic BP was not different (127 vs. 131.5 mmHg, p=0.13); however, diastolic BP was lower among patients with polypharmacy (70.5 vs. 80 mmHg, p=0.02). Regarding ambulatory BP readings, both systolic and diastolic BPs did not differ between polypharmacy groups (all p>0.05). Goal BP attainment rates using different office, home, or ambulatory BP readings were not among the polypharmacy groups (all p>0.05). Table 2 demonstrated the characteristics of patients with polypharmacy in detail.

Systolic BP, whether it is attained via office or home readings, is not correlated with age, number of comorbidities, number of total medications, number of anti-hypertensive pills, or active substances. How-

Table 3. Correlations between blood pressures and clinical features

Variables	Office blood pressure		Home blood pressure		Ambulatory blood pressure	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Age	r=0.17	r= –0.401	r=0.08	r= –0.35	r= –0.19	r= –0.29
	p=0.05	p<0.001	p=0.48	p=0.003	p=0.48	p=0.27
Number of comorbidities	r=0.16	r= –0.19	r= –0.07	r= –0.39	r= –0.23	r= –0.22
	p=0.07	p=0.020	p=0.56	p=0.001	p=0.38	p=0.40
Total medications	r=0.05	r= –0.30	r= –0.13	r= –0.40	r= –0.12	r= –0.33
	p=0.53	p<0.001	p=0.27	p=0.001	p=0.63	p=0.2
Anti-hypertensive pill number	r=0.05	r= –0.29	r= –0.11	r= –0.32	r=0.15	r= –0.25
	p=0.54	p=0.001	p=0.36	p=0.007	p=0.55	p=0.33
Anti-hypertensive active substance number	r=0.007	r= –0.34	r= –0.08	r= –0.33	r= –0.02	r= –0.19
	p=0.94	p<0.001	p=0.46	p=0.005	p=0.91	p=0.47

ever, diastolic BP readings significantly negatively correlated with all these factors. Ambulatory readings of systolic or diastolic BPs are not associated with the characteristics above. Table 3 illustrated the correlations between BPs and clinical features in detail.

DISCUSSION

This study demonstrated that although polypharmacy and multimorbidity are common among patients with hypertension, BP levels and goal BP attainment rates do not differ according to their presence. Moreover, diastolic BP levels are even lower in patients with multimorbidity and polypharmacy. However, this finding is attributable to the age-related diastolic BP drop rather than better BP control.

Patients with hypertension usually need more than one medication to control their BP, as also reflected by our study. Besides, accompanying diseases necessitate further medication. Regarding our patient cohort, 40.8% had diabetes mellitus, which requires at least one medication, and 20.4% had cardiovascular disease, which necessitated more than one medication. The resulting multimorbidity and polypharmacy are associated with adverse health outcomes.[15,16]; however, it is not clear whether worse outcomes are caused by loss of BP control due to an increasing number of pills or whether increased disease and pill burden result in loss of BP control. The HYVET study demonstrated that patients over 80 years old benefit from lowering their BP lowering.[20] Moreover, subgroup analysis of the SPRINT trial illustrated that the benefit of intensive BP control was observed independently of their frailty level.[21] These two studies prove that BP control should not be loosely based on age among elderly patients. Despite these findings, the latest European guideline suggests consideration of monotherapy among hypertensive elderly patients with polypharmacy.[5] Gupta *et al*.'s[17] study found supporting evidence that polypharmacy was an important risk factor for non-adherence to anti-hypertensive medication, a study performed by measuring BP medications or metabolites in blood or urine samples. The results of our study may seem contradictory to Gupta's study at first glance. Polypharmacy has an impact on medication adherence and causes partial non-adherence. However, it is likely that lower adherence-caused reductions of medications' blood levels are not of clinical importance and do not necessarily translate into loss of BP control.

Patients in our cohort with multimorbidity and polypharmacy had significantly lower diastolic BP. The most likely explanation for this finding is that patients with multimorbidity and polypharmacy were significantly older than those without (69 vs. 51 mmHg, $p<0.001$ and 72.5 vs. 64 mmHg, $p<0.001$). Since age itself is associated with diastolic BP fall, this finding is expected.[22]

The level of goal BP attainment in office BP measurements was fairly low compared to attainment rates in home BP measurements. The difference between office and home BP widens as BP rises, yet our findings differ more than expected. Among systolic BP, the highest difference was observed among patients with multimorbidity (155 vs. 130 mmHg), around 20 mmHg. Regarding diastolic BP, the highest differences were observed among patients with polypharmacy and without multimorbidity (85 vs. 70.5 mmHg and 95 vs. 80 mmHg), around 10 to 15 mmHg. Although BP targets derived from randomised controlled trials are mostly based on office BP measurements, office BP measurement does not have the highest concordance with end-organ damage prediction. A recent study demonstrated that home BP measurements were superior to office and ambulatory BP measurements in predicting target organ damage.[23] We demonstrated that multimorbidity and polypharmacy did not affect the gap between office and home BP measurements.

We acknowledge our study's limitations. Firstly, this study was a single-centre retrospective study; thus, findings cannot be confidently generalised. Secondly, the number of patients with office, home, and ambulatory BP readings was not equal, which caused improper comparisons between different BP measurement methods. Thirdly, we defined BP targets roughly but did not define precise targets according to age, frailty, and underlying comorbidities.

CONCLUSIONS

Multimorbidity and polypharmacy are common in the elderly and are important issues to address; however, achieving BP goals does not seem to be affected by the presence of multimorbidity or polypharmacy.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or

publication of this article.

Ethical Approval

The study complies with the principles outlined in the Declaration of Helsinki, and the study was approved by the Başkent University Review Board (Decision Number: KA23/454).

Authors' Contribution

Study Conception: ATG, NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ; Study Design: ATG, NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ; Literature Review: ATG; Critical Review: ATG; Data Collection and/or Processing: NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ,; Analysis and/or Data Interpretation: ATG, NH, AEA; Manuscript preparing: ATG, NH, AEA, CK, TÇ, YAA, EÖ, SK, ZŞ.

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