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HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN EHTIOPIA

Short title: hypertension treatment practices and determinants

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ABSTRACT

Objectives: We examined determinants for achieving blood pressure control in hypertensive patients and for treatment intensification in patients with uncontrolled blood pressure.

Design: A retrospective cohort study in six public hospitals, Ethiopia

Participants: Adult ambulatory hypertensive patients with at least one previous prescribed antihypertensive medication.

Outcome: Controlled BP (<140/90 mm Hg), and treatment intensification for patients with uncontrolled BP.

Results: The study population comprised 897 patients. Their mean age was 57 (SD 14) years, 63% were females, and 35% had one or more cardiometabolic comorbidities mainly diabetes mellitus. BP was controlled in 37% patients. Treatment was intensified for 23% patients with uncontrolled BP. In multivariable (logistic regression) analysis, determinants positively associated with controlled BP were treatment at general hospitals (OR 1.89 [95% CI: 1.26; 2.83]) compared to specialized hospitals, and longer treatment duration (OR 1.04 [95% CI: 1.01; 1.06]). Negatively associated determinants were previously uncontrolled BP (OR 0.30 [95% CI: 0.21; 0.43]), treatment regimens with diuretics (OR 0.68 [95% CI, 0.50; 0.94]), and age (OR 0.99 [95% CI: 0.98; 1.00]). The only significant – positive - determinant for treatment intensification was duration of therapy (OR 1.05 [95% CI: 1.02; 1.09]).

Conclusions: The level of controlled BP and treatment intensification practice in this study was low. Intervention programs to improve BP control should target in particular specialized hospitals, and older patients. Treatment intensification should be initiated earlier.

Key words: hypertension, antihypertensive medication, blood pressure control, treatment intensification, ambulatory patients, Ethiopia, hospital, observational study

STRENGTH AND LIMITATIONS

- This is the first study which gives insight in determinants for hypertension treatment practice (level of BP control and treatment intensification) in a diverse population treated in public hospitals in Ethiopia.
- We analysed BP measurements as recorded in patients' medical records which reflected actual clinical practice, but may be subject to recording and measurement error.
- The finding of this study may not be generalizable to other settings such as private practice, primary health care centers in Ethiopia.

BACKGROUND

Hypertension is a major risk factor for cardiovascular diseases, the leading cause of death and disability globally.[1] The World Health Organization (WHO) recently reported that 80% of deaths due to cardiovascular disease occur in low- and middle-income countries, with the highest death rate reported in African countries. The report also indicated that prevalence of hypertension in adults was highest in the African region (46%) compared to e.g. 35% in the region of the Americas.[1] Hypertension is more prevalent even among the African-origin population living in Western world than among whites.[2] The population of African ancestry is characterized by high vascular contractility, extreme salt sensitivity, and low renin release.[3-5] Hence, over-activation of the sympathetic nervous system and renin-angiotensin-aldosterone system is more prevalent in this population, making them more vulnerable to high blood pressure. In addition, changes in environmental factors such as economic development, urbanization, and lifestyle have resulted in an epidemiological transition from infectious to non-communicable disease such as hypertension in the African region.[6]

Large clinical outcome studies have repeatedly shown that treating hypertension improves cardiovascular outcomes.[7] However, to achieve target blood pressure (BP) using evidence based antihypertensive treatment and by adjusting life style remains a challenge in clinical practice. The majority of studies in Africa have shown that less than a third of patients achieves treatment goals.[8] Generally, four main factors for achieving BP control have been identified. First, there are factors intrinsic to the nature of the disease; in most cases hypertension is initially asymptomatic and this delays early prevention, diagnosis and treatment.[9] Second, poor treatment response may be due to patient-related factors such as age, gender, race, and compliance to medication.[4,10] Third, there are healthcare system-related factors such as lack of effective hypertension prevention and treatment programs, and access to medications. Fourth, prescriber behavior, competences, and large

patient-to-prescriber ratio affect hypertension prevention and treatment outcomes. The majority of these factors have been extensively studied in western society; however, little is known of their impact on BP control in developing nations. Some of these factors may be unique to, or more pronounced in the African setting including low societal awareness, priority to fight infectious diseases, and human resource limitations in particular the number of available healthcare professionals.[6,11]

Effective prevention and treatment strategies have been evaluated in the western world to optimize BP control.[12] Such programs may be relevant for the African setting. However, to guide targeted interventions studies identifying factors contributing to poor BP control in the African setting are urgently needed. Studies conducted to date in Ethiopia, the second largest populous country (approximately 100 million) in Africa, focused on determining prevalence of the disease.[13-15] Although, prevalence was relatively low (10 – 30%),[1,13-15] further data on hypertension treatment practices beyond mere drug utilization are lacking.[16] Therefore, we aimed to assess the proportion of patients treated for hypertension who had controlled BP and identify determinants for achieving BP control. In addition, we aimed to study whether treatment was intensified in those patients with uncontrolled BP and identify the determinants for treatment intensification.

METHODS

Study design and setting

This retrospective cohort study was conducted in outpatient clinics of six public hospitals in Addis Ababa (capital city) and Tigray regional state, Ethiopia. We included two specialized hospitals (Addis Ababa), and four general hospitals, three from Tigray and one from Addis Ababa.

Study population

Participants were approached while waiting for their appointment in the waiting area of the outpatient clinics. They were recruited consecutively after giving consent. Hypertensive patients aged 18 years or above were included, if they had at least one previous antihypertensive medication prescription in the same hospital, and gave informed consent. Patients were identified based on patient report or marked on their pocket-size appointment card (for being hypertensive). These inclusion criteria were verified in each clinic log-book (if available), and individual patient medical record.

Routine practice in the study hospitals was that nurses measured patient's blood pressure, and assigned the patient to a physician. The physician will then consult the patient, confirm the diagnosis and if necessary perform further examinations including rechecking BP, and renew or amend prescribed medication. Patients will then collect their medicine from pharmacy outlets at the same hospital or if not available from private or community pharmacies.

Data collection

Included patients were interviewed in the waiting area to collect data on their socio demographics, treatment duration of antihypertensive medication(s), and medication adherence. Clinical information including BP measurements, medication prescribed, and comorbid illnesses were retrieved from medical records for the current visit (*index visit*) and the previous visit (*prior visit*).

Data were collected by professional nurses or pharmacists who were trained in using a dedicated case-report form. Data were collected between February and August, 2015.

Variables

Outcome measures

We defined two *outcome measures*. First, for *BP control* we used the 'standard' definition of controlled BP, i.e., systolic BP/diastolic BP below 140/90 mm Hg at the index visit.[12] Second, we defined *treatment intensification* as an increase in dose of an antihypertensive drug and/or addition of one or more antihypertensive drug(s). Treatment intensification was calculated for those patients who had a complete medication history (including dose and administration frequency) at both visits and whose BP was not controlled at the index visit. A switch in drug class was not considered as treatment intensification.

Explanatory variables

As *determinants* for BP control or treatment intensification we included socio-demographic variables (age in year], gender, smoking history, alcohol use, marital status, and educational status), hospital type (general/specialized), cardiometabolic comorbid illnesses (diabetes mellitus [DM], dyslipidemia, kidney disease, heart failure/myocardial infarction), uncontrolled BP (≥140/90 mm Hg) at the prior visit, duration of antihypertensive treatment in year, treatment adherence (MMAS ≥ 7: yes/no), revisit schedule in month], and antihypertensive medications prescribed at prior visit.

Antihypertensive medication adherence was measured with the eight-point Morisky Medication adherence scale (MMAS-8), which has been previously validated for hypertensive patients.[17,18] The scale was translated into two Ethiopian languages (Amharic and Tigrigna) according to the method described by Beaton *et al.*[19] A sum score of seven or more (maximum eight) was considered to be adherent to antihypertensive medication; i.e. MMAS ≥ 7.[17] For a sensitivity analyses, we used a lower level of adherence with a cut-off of MMAS ≥ 6. The revisit schedule period

in months was calculated by taking the difference in days between the index and prior visits divided by 30.

Sample size

Achieved sample size was based on an estimated 30% prevalence of controlled BP among treated hypertensive patients in Ethiopia [8,15] and a single proportion sample size calculation formula. The total sample size was 984 (164 per hospital) with 0.80 power, 95% confidence interval, 3% margin of error, and an estimated 10% none response rate, or incomplete/irretrievable patient records.

Statistical analyses

Descriptive statistics were used to summarize socio-demographic, disease characteristics of the study population, and nature and frequency of antihypertensive medications used. Multivariable logistic regression analyses were applied to investigate determinants for achieving target BP at index visit, and determinants for treatment intensification. Statistical significance was considered at p value < 0.05. Potential determinants with p < 0.2 in bivariable analyses were included into the multivariable logistic model. Microsoft access 10 and SPSS version 22.0 statistical software was used for data entry and analyses respectively.

Sensitivity analyses

We performed sensitivity analyses using tighter BP targets at index visit (BP <130/80 mm Hg) for those patients with diabetes mellitus (DM) and/or renal disease, and for all others participants the standard BP target (BP <140/90 mm Hg). In addition, we performed a sensitivity analysis using a different cut off for adherence.

RESULTS

We were able to approach 968 patients at six public hospitals in Ethiopia. Seventy-one patients were excluded from our analyses; eight refused to participate, six were not hypertensive, and 57 patients had no retrievable records or incomplete records (missing BP at index visit), resulting in a study population of 897 patients (Figure 1). The mean (SD) patient age was 57 (14) years, the majority (63%) of patients were female, most patients (65%) were married and 64% had no formal education or only attended primary school. Almost all (94%) had never smoked, nearly half (43%) consumed alcohol regularly or occasionally (Table 1). At index visit, 35% study participants had at least one recorded comorbid illness, predominantly DM (Table 1).

Table 1 Characteristics of ambulatory hypertensive patients at two visits, Ethiopia

Characteristics	Index visit	Prior visit
Demographics		
Age (mean, SD), Year	57 (14)	
Female (n, %)	551 (63)	
Smoking (n, %)	57 (6)	
Alcohol use (n, %)	378 (43)	
Married (n, %)	567 (65)	
Education (n, %)		
University/college education	170 (20)	
Secondary education	141 (16)	
Primary or no formal education	557 (64)	
Setting		
Specialized hospitals: both from Addis Ababa (n, %)		
Tikur Anbessa Hospital	139 (16)	
St. Paul's Hospital	153 (17)	
General hospitals: all from Tigray, except Yekatit 12 from Addis Ababa (n, %)		
St. Mary Axum Hospital	139 (16)	
Mekelle Hospital	152 (17)	
Lemlem Karl Maychew Hospital	155 (17)	
Yekatit 12 Hospital	159 (18)	
Disease characteristics		
Blood pressure (BP)		
Systolic BP (Mean, SD)	139 (21)	144 (22)
Diastolic BP (Mean, SD)	84 (11)	85 (13)
Controlled BP (<140/90 mm Hg) (n, %)	335 (37)	231 (27)
Controlled BP (<130/80 mm Hg for DM &/or kidney diseases, otherwise <140/90 mm Hg) (n, %)	268 (30)	202 (24)
Cardiometabolic comorbid illnesses (n, %)		
Diabetes Mellitus	227 (25)	198 (22)
Dyslipidemia	57 (6)	45 (5)
Renal diseases	25 (3)	23 (3)
Heart failure / myocardial infarction	72 (8)	60 (7)
Antihypertensive treatment characteristics		
Drug class (n, %)		
ACE inhibitors	503 (56)	494 (55)
Enalapril	499 (56)	492 (55)
Lisinopril or captopril	4 (0.4)	2 (0.2)
Beta blockers	167 (19)	166 (19)
Atenolol	148 (17)	147 (16)
Propranolol	9 (1)	8 (1)
Metoprolol or carvedilol	10 (1)	11 (1)
Calcium channel blockers	449 (50)	439 (49)
Nifedipine	381 (43)	389 (43)
Amlodipine or felodipine	68 (8)	50 (6)
Diuretics [#]	498 (56)	486 (54)
Hydrochlorothiazide	428 (48)	421 (47)
Furosemide	76 (9)	71 (8)
Spironolactone	72 (8)	66 (7)
Others (methyldopa, nitrates or losartan)	19 (2)	13 (1)
Duration of therapy years (mean, SD)	6.6 (7)	
Revisit schedule in months (mean, SD)	2.3 (2.0)	
Adherence (MMAS ≥ 7) (n, %)	355 (40)	
Therapy (n, %)		
Monotherapy	*343 (38)*	*363 (41)*
Multidrug therapy	*550 (62)*	*521 (59)*
Treatment intensified in patients with uncontrolled BP at index visit (n=540) * (n, %)	123 (23)	

Mono/Multidrug therapy is limited to antihypertensive medications. *For 22 of 562 patients with uncontrolled BP at the index visit the medication history was not complete. Treatment intensification could thus only be calculated for 540 patients. [#]Some patients had more than one type of diuretics.

Thirty-seven percent (n=335) of the participants had controlled BP at the index visit (Table 1). In our sensitivity analyses, applying the stricter BP target for patients with DM and/or renal disease (BP<130/80 mm Hg), the proportion of patients with controlled BP dropped to 27% (n=231).

Only, 23% of 540 patients with uncontrolled BP and complete medication history had their treatment intensified (Table 1). For 22 (4%) of 562 patients with uncontrolled BP at the index visit, the medication history was not complete, either the dose and/or administration frequency were missing. The antihypertensive medication adherence rate (MMAS ≥ 7) was 40%, (Table 1), and 57% for the lower MMAS ≥ 6 cut off (Supplement Table 1).

Overall, angiotensin-converting-enzyme (ACE) inhibitors were the most commonly prescribed group of drugs (n = 503) followed by diuretics (n = 498) (Table 1). Medication use was quite similar on both visits. At the index visit 62% of included patients were prescribed a multidrug treatment regimens and 45% patients took two antihypertensive agents (Supplement Table 2). Most (38 %) of the 343 patients on monotherapy had diuretics prescription (n=127).

Determinants of BP Control

BP <140/90 mm Hg (primary analysis)

According to our multivariable logistic regression model (Table 2), factors significantly associated with achieving target BP at the index visit were age (OR 0.99 [95% CI: 0.98; 1.00]), follow-up at general hospitals (OR 1.89 [95% CI: 1.26; 2.83]), inadequately controlled BP at prior visit (OR 95% CI: 0.30 [0.21; 0.43]), longer treatment duration per year (OR 1.04 [95% CI: 1.01; 1.06]), and prescribed diuretics (OR 0.68 [95% CI: 0.50; 0.94]).

Table 2 Determinants of achieving target BP (BP < 140/90) at index visit in ambulatory hypertension patients

Variables		Controlled BP		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), year		58 (13)	56 (15)	#0.99 [0.98; 1.00]	*0.99 [0.98; 1.00]
Gender (n, %)	Male	219 (67)	109 (33)	Ref	
	Female	331 (60)	220 (40)	*1.34 [1.00; 1.78]	1.12 [0.80; 1.55]
Smoking (n, %)	No	514 (62)	312 (38)	Ref	
	Yes	37 (65)	20 (35)	0.89 [0.51; 1.56]	
Alcohol use (n, %)	No	310 (63)	184 (37)	Ref	
	Yes	232 (61)	146 (39)	1.06 [0.81; 1.40]	
Marital status (n, %)	Single	187 (60)	124 (40)	Ref	
	Married	359 (63)	208 (37)	0.87 [0.66; 1.16]	
Educational status (n, %)	College/University	110 (65)	60 (35)	Ref	
	Secondary	86 (61)	55 (39)	1.17 [0.74; 1.86]	
	Primary /not formal	345 (62)	212 (38)	1.13 [0.79; 1.61]	
Hospital type (n, %)	Specialized	199 (68)	93 (32)	Ref	
	General	363 (60)	242 (40)	*1.43 [1.06; 1.92]	*1.89 [1.26; 2.83]
Disease characteristics (n, %)					
Diabetes Mellitus	No	413 (62)	257 (38)	Ref	
	Yes	149 (66)	78 (34)	0.84 [0.61; 1.15]	
Dyslipidemia	No	523 (62)	317 (38)	Ref	
	Yes	39 (68)	18 (32)	0.76 [0.43; 1.35]	
Renal disease	No	542 (62)	330 (38)	Reference	
	Yes	20 (80)	5 (20)	#0.41 [0.15; 1.10]	0.58 [0.19; 1.71]
Heart failure/ MI at	No	518 (63)	307 (37)	Ref	
	Yes	44 (61)	28 (39)	1.07 [0.66; 1.76]	
Controlled BP at prior visit	No	424 (68)	199 (32)	*0.37 [0.27; 0.51]	*0.30 [0.21; 0.43]
	Yes	102 (44)	129 (56)	Ref	
Antihypertensive Treatment characteristics					
Duration of therapy, years (mean, SD)		6.2 (6.4)	7. 4 (8.3)	#1.02 [1.00; 1.04]	*1.04 [1.01; 1.06]
Adherent (MMAS $\geq$ 7) (n, %)	No	319 (60)	212 (40)	Ref	
	Yes	233 (66)	122 (34)	#0.79 [0.60; 1.04]	0.80 [0.58; 1.09]
Revisit schedule in months (Mean, SD)		2.2 (1.4)	2.0 (1.2)	*0.89 [0.82 ;0.97]	0.91 [0.82; 1.02]
Therapy at prior visit (n, %)	Monotherapy	225 (62)	138 (38)	Ref	
	Multidrug	326 (63)	195 (37)	0.98 [0.74; 1.29]	
Antihypertensive medications at prior visit					
ACE inhibitors (n, %)	No	259 (64)	144 (36)	Ref	
	Yes	303 (61)	191 (39)	1.13 [0.86; 1.49]	
Beta blockers (n, %)	No	472 (65)	259 (35)	Ref	
	Yes	90 (54)	76 (46)	*1.54 [1.09; 2.16]	1.42 [0.95; 2.10]
Calcium channel blockers (n, %)	No	290 (63)	168 (37)	Ref	
	Yes	272 (62)	167 (38)	1.06 [0.81 ;1.39]	
Diuretics (n, %)	No	243 (59)	168 (41)	Reference	
	Yes	319 (66)	167 (34)	*0.76 [0.58; 0.99]	*0.68 [0.50; 0.94]

Only patients with available data were included in the analyses, therefore numbers may sometimes differ from Table 1. Percentages are calculated per a row. Statistically significant values: *p< 0.05 at 95% CI. Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in the multivariable model. Mono/Multidrug therapy was for antihypertensive medications.

Sensitivity (secondary) analysis

BP <130/80 mm Hg for patients with DM and/or renal disease, for all other patients <140/90 mm Hg.

In this secondary analyses uncontrolled BP at the prior visit had a negative effect on achieving target BP at the index visit (OR 0.25 [95% CI: 0.17; 0.37]). Medications prescribed during the prior visit, except diuretics (OR 0.60 [95% CI: 0.40; 0.90]), were not significantly associated with achieving controlled BP at the index visit. Unlike the primary analyses, age, treatment duration, and hospital type did not show statistically significant effects on index visit BP status (Supplement Table 3).

Determinant of treatment intensification

The only statistically significant determinant for treatment intensification in the multivariable analyses was longer treatment duration (OR 1.05 [95% CI: 1.02; 1.09]), Table 3.

Table 3 Treatment intensification determinants for ambulatory hypertension patients with uncontrolled BP at index visit

Variables		Treatment intensified		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), Year		57 (13)	60 (13)	#1.02 [1.00; 1.03]	1.02 [1.00; 1.04]
Gender (n, %)	Male	167 (80)	41 (20)	Ref	
	Female	241 (75)	80 (25)	#1.35 [0.88; 2.07]	1.47 [0.91; 2.37]
Smoking (n, %)	No	383 (77)	113 (23)	Ref	
	Yes	27 (79)	7 (21)	0.88 [0.37; 2.07]	
Alcohol use (n, %)	No	225 (76)	73 (25)	Ref	
	Yes	180 (80)	44 (20)	0.75 [0.49; 1.15]	
Marital status (n, %)	Single	138 (77)	42 (23)	Ref	
	Married	269 (78)	76 (22)	0.93 [0.60; 1.43]	
Educational status (n, %)	College/University	82 (78)	23 (22)	Ref	
	Secondary	58 (70)	25 (30)	1.54 [0.80; 2.97]	
	Primary /not formal education	262 (79)	70 (21)	0.95 [0.56; 1.62]	
Hospital type (n, %)	Specialized	137 (73)	51 (27)	Ref	
	General	280 (80)	72 (21)	#0.69 [0.46; 1.04]	0.83 [0.51; 1.37]
Disease characteristics (n, %)					
Diabetes Mellitus at index visit	No	311 (79)	84 (21)	Ref	
	Yes	106 (73)	39 (27)	#1.36 [0.88; 2.11]	1.10 [0.67; 1.81]
Dyslipidemia at index visit	No	388 (77)	113 (23)	Reference	
	Yes	29 (74)	10 (26)	1.19 [0.56; 2.50]	
Renal disease at index visit	No	403 (77)	118 (23)	Ref	
	Yes	14 (74)	5 (26)	1.22 [0.43; 3.45]	
Heart Failure / MI at index visit	No	384 (77)	112 (23)	Ref	
	Yes	33 (75)	11 (25)	1.14 [0.56; 2.33]	
Controlled BP at prior visit	No	312 (77)	96 (24)	#1.50 [0.85; 2.66]	1.38 [0.76; 2.50]
	Yes	83 (83)	17 (17)	Ref	
Antihypertensive treatment characteristics					
Duration of therapy yrs (mean SD)		5.7 (6.1)	8.1 (7.4)	*1.05 [1.02; 1.08]	*1.05 [1.02; 1.09]
Adherence (MMAS ≥ 7) (n, %)	No	232 (76)	73 (24)	Ref	
	Yes	178 (78)	49 (22)	0.88 [0.58; 1.32]	
Therapy at prior visit (n, %)	Monotherapy	168 (76)	53 (24)	Ref	
	Multidrug therapy	249 (78)	70 (22)	0.89 [0.59; 1.34]	

Statistically significant values: *p < 0.05 at 95% CI. Variable with #p < 0.2 or *p < 0.05 in the bivariable model were included in the multivariable model. Percentages are calculated per a row. Treatment intensification was calculated for 540 patients who had complete medication history (including dose and frequency) on both visits and uncontrolled BP at index visit.

DISCUSSION

In this study, nearly two-thirds of patients on medication had uncontrolled BP. Drugs were prescribed from four antihypertensive drug classes, ACE-inhibitors, diuretics, CCBs, and BBs. Generally, a single specific agent (over 90%) was prescribed within a class, enalapril, hydrochlorothiazide, nifedipine, and atenolol respectively. Age of patients, uncontrolled BP at prior visit, and a treatment regimen containing diuretics contributed to poorer BP control. Whereas follow-up in a general hospital as compared to a specialized hospital, and longer treatment duration were associated with a better BP control. Duration of therapy on antihypertensive medication was the only, albeit modestly (also for BP control), significant contributing factor for treatment intensification.

Most other studies in Africa, 41 out of 44, showed a lower proportion of patients with controlled BP (these studies reported levels of control ranging from <1% to 33%) than our study.[8] The reported wide variation could be explained by population differences and variation in study set-up. In comparison with studies in western countries, the percentage of patients with adequately controlled BP, and those who received treatment intensification was lower in our study than in North American countries but similar to some European countries.[20,21] These differences may be explained in part by different recommendations between national guidelines. However, as reported elsewhere, it is not only differences between guidelines, but also how much effort countries put in implementation of these recommendations.[21] While the Ethiopian guideline is similar to the USA guidelines [20,22], possible differences in implementation, due to typical African factors including resource limitations, low priority for communicable diseases, and healthcare providers' behavior and skills may in part explain the low level of BP control.[23]

In our study one of the determinants for achieving target BP was the healthcare setting. Patients referred to the specialized hospitals may be more complex – in terms of comorbidities or severity of

hypertension. Hence, it may not be that surprising that patients in these hospitals are more likely to have inadequately controlled BP. Younger age was another significant determinant for achieving target BP. Prescribers in our study may have accepted higher BP in older patients, possibly because of tolerability or perceived lack of need for tight BP control. Recent evidence, however, suggests that ''the lower is the better'' also in older patients.[24,25] Nevertheless, guidelines lack consistency on BP targets for elderly,[26] especially when patients are frail doctors may not aim for tight BP control. Another determinant of BP control was the type of medication prescribed. Most of our study participants received diuretics, the first line antihypertensive agents. We have no data in which order medication was initiated; therefore, we can only speculate why treatment regimens containing these drugs did not show better BP control. Since, three-quarters of diuretics-containing regimens in our study existed of two drugs only (S 2 Tab), patients may need additional therapy. However, physicians may have been reluctant to intensify treatment further, because of fear for risk of too drastic BP lowering (e.g. resulting in dehydration when increasing diuretic doses).

Only one fifth of patients with uncontrolled BP at the index visit had their treatment intensified. Longer treatment duration was the only statistically significant determinant for intensification. Possibly, it took a while before prescribers would intensify treatment. Ultimately, the lack of BP control at the prior visit was the strongest predictor of patients not having controlled BP at index visit. This seems to suggest some level of 'clinical inertia', where doctors are slow to respond to clinical parameters indicating a need to step up therapy. However, it may also be explained by true therapy resistant hypertension (although only 17% of patients received three or more antihypertensive agents at the prior visit) or possibly medication adherence.[27-30] Medication adherence is known as an important determinant for controlling hypertension.[31] In our study using a self-reported scale, less than half of the patients were adherent. Surprisingly, there was no significant association with BP control (Table 2, Supplement Table 1).

An interesting finding was that more hypertensive women than men were included in our study, and that so few patients smoked. The reason why more women were included could be that hypertension is truly more prevalent in Ethiopian females as shown in a recent paper,[13] although a meta-analysis showed almost equal prevalence.[15] Another explanation may be that women with hypertension are seeking care more regularly than man. However, women were not more likely than man to have controlled BP or their treatment intensified. Our study was largely performed in urban areas, which have the highest prevalence of hypertension in Ethiopia that is attributed to adoption of a Western life-style.[15] Still, our patient population looks very different from that in European or USA studies; i.e. with few smokers and few patients with (known) cardiometabolic comorbidities.

Strength and limitations

As far as we are aware, this was the first study of its kind in Ethiopia covering a relatively diverse population. Our data included patients from outpatient clinics of hospitals in the capital city and northern region of Ethiopia.

A limitation of our study was the validity of the BP measure used. We analysed BP measurements as recorded in patients' medical records which reflected actual clinical practice, but may be subject to recording and measurement error. It is not clear how prescribers considered measurement variability or if any attempt was made to avoid 'white-coat' hypertension, e.g. by repeating BP measurement. Still, many observational studies use medical records – with data collected in routine practice - as data source. Future studies may consider using standardized assessment of BP evaluation. Another limitation is that medical records did not include extensive or well-structured patient information. For example, comorbidities may be underreported. For this reason, we limited evaluated comorbidities to cardiometabolic diseases as these are relevant to hypertension prognosis and treatment and are more likely to have been recorded in the charts. This study focused on public

secondary and specialized hospitals, therefore the result may not be generalizable to other settings such as private practices and primary health care centers.

CONCLUSION

Nearly two-thirds of patients on antihypertensive medication did not achieve target BP during routine clinical practice, and only a quarter of them received treatment intensification. Our data suggest that intervention programs to improve BP control may first target patients with repeated lack of BP control and intensify treatment more promptly. Especially, in elderly patients and those treated in specialized hospitals.

Acknowledgments

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Contribution

D.F. Berhe, K. Taxis and P. Mol designed and performed the research, analyzed, and interpreted the data. Flora M Haaijer-Ruskamp, Afework Mulugeta, and Yewondwossen Tadesse Mengistu designed the study. All authors participated in writing the manuscript, also read and approved the final version.

Conflict of Interest: There are no competing interests to declare.

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Ethics approval

This study was approved by Ethiopian Health Research Ethical Review Committees of (i) the College of Health Sciences, Mekelle University, (ii) St Paul's Hospital Millennium Medical College, and (iii) the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University. All individual participants included in this study consented to participation.

Data sharing statement

No additional data are available for this specific study.

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HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN EHTIOPIA

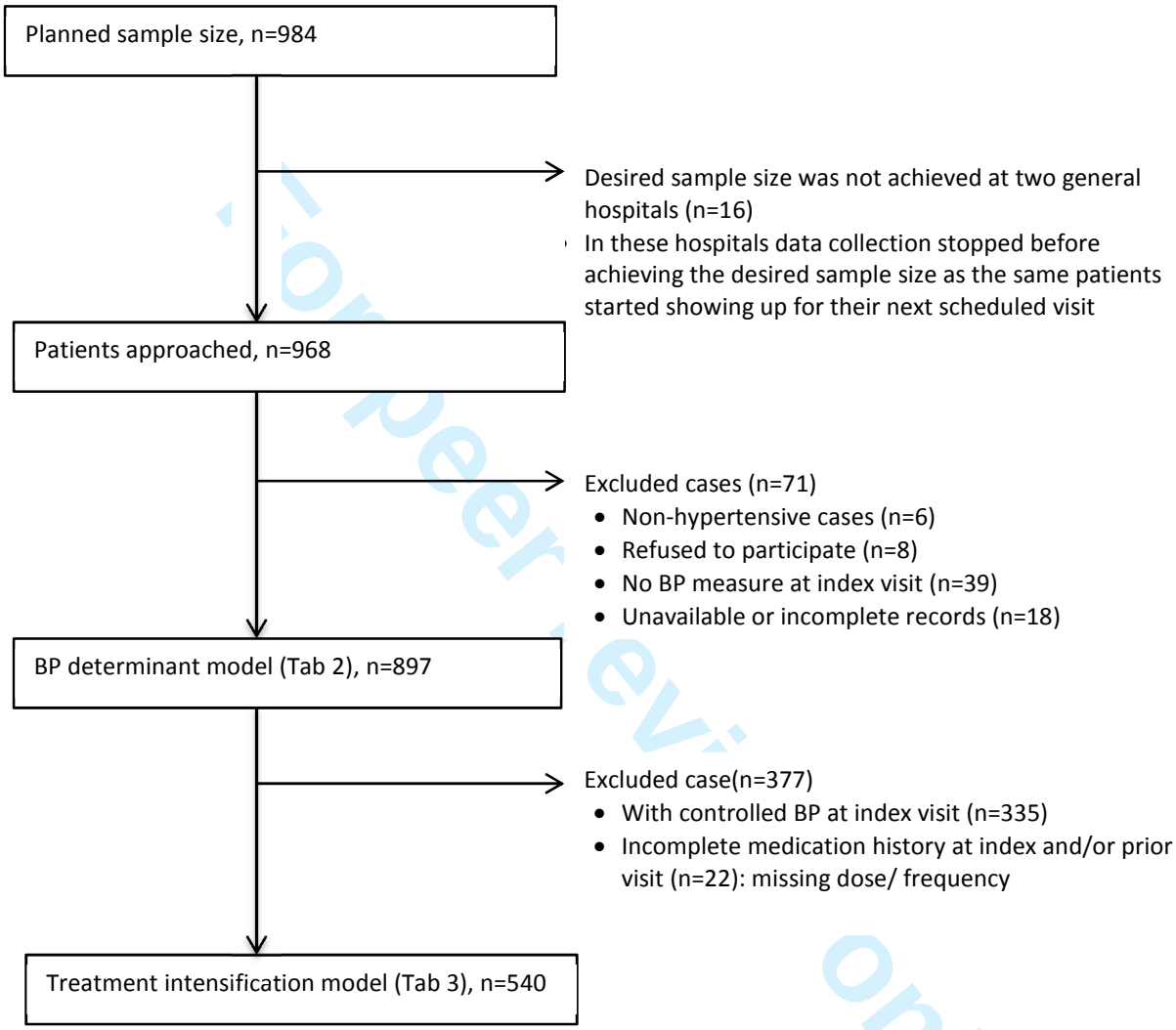

Figure 1 Flow chart for case inclusion for analysis

HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN EHTIOPIA

Supplement Table 1 Determinants of achieving target BP (BP < 140/90) at index visit ambulatory hypertension patients (sensitivity anlysis with adherence definition of MMAS ≥ 6)

Variables		Controlled BP		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), year		58 (13)	56 (15)	#0.99 [0.98; 1.00]	*0.99 [0.98; 1.00]
Gender (n, %)	Male	219 (67)	109 (33)	Ref	
	Female	331 (60)	220 (40)	*1.34 [1.00; 1.78]	1.12 [0.81; 1.55]
Hospital type (n, %)	Specialized	199 (68)	93 (32)	Ref	
	General	363 (60)	242 (40)	*1.43 [1.06; 1.92]	*1.88 [1.25; 2.81]
Disease characteristics at index visit (n, %)					
Renal disease	No	542 (62)	330 (38)	Reference	
	Yes	20 (80)	5 (20)	#0.41 [0.15; 1.10]	0.60 [0.20; 1.79]
Controlled BP at **prior visit**	No	424 (68)	199 (32)	*0.37 [0.27; 0.51]	*0.30 [0.21; 0.43]
	Yes	102 (44)	129 (56)	Ref	
Antihypertensive Treatment characteristics					
Duration of therapy, years (mean, SD)		6.2(6.4)	7. 4 (8.3)	#1.02 [1.00; 1.04]	*1.04 [1.02; 1.06]
Adherent (MMAS ≥ 6) (n, %)	No	237 (63)	140 (37)	Ref	
	Yes	315 (62)	194 (38)	1.04 [0.79; 1.37]	1.14 [0.83; 156]
Revisit schedule in months (Mean, SD)		2.2 (1.4)	2.0 (1.2)	*0.89 [0.82 ;0.97]	0.91 [0.82; 1.02]
Beta blockers (n, %)	No	472 (65)	259 (35)	Ref	
	Yes	90 (54)	76 (46)	*1.54 [1.09; 2.16]	1.45 [0.98; 2.15]
Diuretics (n, %)	No	243 (59)	168 (41)	Reference	
	Yes	319 (66)	167 (34)	*0.76 [0.58; 0.99]	*0.68 [0.50; 0.94]

Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in this multivariable model (sensitivity analysis).

Supplement Table 2 Prescribed antihypertensive medication(s) per patient

Drug prescribed per case	At Index visit (n≠=887), %	At Prior visit (n≠=882), %
D (Diuretics)	14.3	15.0
C (CCBs)	13.0	13.7
A (ACE inhibitors)	9.9	11.0
B (BBs)	0.8	1.4
DC	9.4	8.6
DA	17.0	16.6
CA	11.5	10.2
AB	2.6	2.4
CB	2.4	2.7
DB	2.0	1.5
DCB	1.5	1.1
DCA	6.1	6.1
ACB	3.7	3.5
DAB	2.7	2.5
DABC	3.2	3.7

CCBs, calcium channel blockers; ACE, Angiotensinogen Converting Enzyme; BBs; Beta Blockers

≠The table did not include rarely used medication categories. These drugs were methyldopa, losartan, hydralazine, and nitrates and in combination with others or as a monotherapy.

Supplement Table 3 Sensitivity analyses: determinants for controlled hypertension at alternative BP target (BP <130/80 mm Hg) for patients with DM and/or renal disease, and all other patients BP <140/90 mm Hg)

Variables		Controlled BP		Bivariable OR [95% CI]	Multivariable OR [95% CI]
		No	Yes		
Demographics					
Age (mean. SD)		58 (13)	56 (15)	#0.99 [0.98; 1;00]	0.99 [0.98; 1.00]
Gender (n, %)	Male	244 (74)	84 (26)	Ref	
	Female	373 (68)	178 (32)	*1.39 [1.02; 1.88]	1.30 [0.87; 1.95]
Smoking (n, %)	No	572 (69)	254 (31)	Ref	
	Yes	45 (79)	12 (21)	#0.60 [0.31; 1.16]	1.05 [0.50; 2.24]
Alcohol use (n, %)	No	354 (72)	140 (28)	Ref	
	Yes	254 (67)	124 (33)	#1.23 [0.92; 1.65]	1.54 [1.07; 2.21]
Marital status (n, %)	Single	207 (67)	104 (33)	Ref	
	Married	406 (72)	161 (28)	#0.79 [0.59; 1.06]	0.82 [0.56; 1.18]
Educational status (n, %)	College/University	123 (72)	47 (28)	Ref	
	Secondary	103 (73)	38 (27)	1.21 [0.83; 1.77]	
	Primary /not formal	381 (68)	176 (32)	0.97 [0.59; 1.59]	
Hospital type (n, %)	Specialized	217 (74)	75 (26)	Ref	
	General	412 (68)	193 (32)	1.36 [0.99; 1.85]	1.17 [0.75; 1.82]
Disease characteristics (n, %)					
Dyslipidemia at index visit	No	583 (69)	257(31)	Ref	
	Yes	46 (81)	11 (19)	#0.54 [0.28; 1.06]	0.47 [0.20; 1.10]
Heart Failure / MI at index visit	No	578 (70)	247 (30)	Ref	
	Yes	51 (71)	21 (29)	0.96 [0.57; 1.64]	
Controlled BP at prior visit	No	501 (77)	151 (23)	*0.25 [0.18; 0.35]	*0.25 [0.17; 0.37]
	Yes	92 (46)	110 (55)	Ref	
Antihypertensive treatment characteristics					
Duration of therapy years (mean, SD)		7.0 (7.3)	5.8 (6.9)	#0.98 [0.96; 1.00]	0.99 [0.97; 1.02]
Adherence (MMAS-8 ≥ 7) (n, %)	No	373 (70)	158 (29)	Ref	
	Yes	246 (69)	109 (31)	1.04 [0.78; 1.40]	
Revisit schedule in months (Mean, SD)		2.4 (2.1)	2.0 (1.2)	*0.88 [0.81; 0.97]	0.94 [0.84; 1.06]
Therapy at prior visit (n, %)	Monotherapy	240 (66)	123 (34)	Ref	
	Multidrug therapy	378 (73)	143 (27)	*0.74 [0.55; 0.99]	1.02 [0.69; 1.51]
Antihypertensive medications at prior visit					
ACE inhibitors (n, %)	No	274 (68)	129 (32)	Ref	
	Yes	355 (72)	139 (28)	0.83 [0.62; 1.11]	
Beta blockers (n, %)	No	511 (70)	220 (30)	Ref	
	Yes	118 (71)	48 (29)	0.95 [0.65; 1.37]	
Calcium channel blockers (n, %)	No	312 (68)	146 (32)	Ref	
	Yes	317 (72)	122 (28)	#0.82 [0.62; 1.10]	0.88 [0.59; 1.31]
Diuretics (n, %)	No	276 (67)	135 (33)	Ref	
	Yes	353 (73)	133 (27)	#0.77 [0.58; 1.03]	*0.60 [0.40; 0.90]

Only patients with available data are included in the analyses, therefore numbers may sometimes differ from Table 1. Percentages are calculated per a row. Statistically significant values: *p< 0.05 at 95% CI. Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in the multivariable model. DM: diabetes mellitus

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, also on Figure 1 (Page 24)
		(b) Give reasons for non-participation at each stage	9, also on Figure 1 (Page 24)
		(c) Consider use of a flow diagram	Figure 1 (Page 24)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	10 (Revisit schedule)
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12, 14
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplement Tables (Page 25/27)
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN ETHIOPIA

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HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN EHTIOPIA

Short title: hypertension treatment practices and determinants

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ABSTRACT

Objectives: We examined determinants of achieving blood pressure control in hypertensive patients and of treatment intensification in patients with uncontrolled blood pressure (BP).

Design: A retrospective cohort study in six public hospitals, Ethiopia

Participants: Adult ambulatory hypertensive patients with at least one previously prescribed antihypertensive medication in the study hospital.

Outcome: Controlled BP (<140/90 mm Hg), and treatment intensification of patients with uncontrolled BP.

Results: The study population comprised of 897 patients. Their mean age was 57 (SD 14) years, 63% were females, and 35% had one or more cardiometabolic comorbidities mainly diabetes mellitus. BP was controlled in 37% patients. Treatment was intensified for 23% patients with uncontrolled BP. In multivariable (logistic regression) analysis, determinants positively associated with controlled BP were treatment at general hospitals (OR 1.89 [95% CI: 1.26; 2.83]) compared to specialized hospitals, and longer treatment duration (OR 1.04 [95% CI: 1.01; 1.06]). Negatively associated determinants were previously uncontrolled BP (OR 0.30 [95% CI: 0.21; 0.43]), treatment regimens with diuretics (OR 0.68 [95% CI, 0.50; 0.94]), and age (OR 0.99 [95% CI: 0.98; 1.00]). The only significant – positive - determinant for treatment intensification was duration of therapy (OR 1.05 [95% CI: 1.02; 1.09]).

Conclusions: The level of controlled BP and treatment intensification practice in this study was low. The findings suggest the need for in-depth understanding and interventions of the identified determinants such as uncontrolled BP on consecutive visits, older age, and type of hospital.

Key words: hypertension, antihypertensive medication, blood pressure control, treatment intensification, ambulatory patients, Ethiopia, hospital, observational study

STRENGTH AND LIMITATIONS

- This is the first study that gives insight into determinants of hypertension treatment practice (level of BP control and treatment intensification) in a diverse population treated in public hospitals in Ethiopia.
- We analysed BP measurements as recorded in patient medical records, which reflect actual clinical practice, but may be subject to recording and measurement error.
- The finding of this study may not be generalizable to other settings such as private practice or primary health care centers in Ethiopia.

BACKGROUND

Hypertension is a major risk factor for cardiovascular diseases and it is the leading cause of death and disability globally.[1] The World Health Organization (WHO) recently reported that 80% of deaths due to cardiovascular disease occur in low- and middle-income countries, with the highest death rate reported in African countries. The report also indicated that prevalence of hypertension in adults was higher in Africa (46%) than for instance in the US (35%).[1] Hypertension is also more prevalent among people from Africa living in Western world than among whites.[2] The population of African ancestry is characterized by high vascular contractility, extreme salt sensitivity, and low renin release.[3-5] Hence, over-activation of the sympathetic nervous system and renin-angiotensin-aldosterone system is more prevalent in this population, making them more vulnerable to high blood pressure. In addition, changes in environmental factors such as economic development, urbanization, and lifestyle have resulted in an epidemiological transition from infectious to non-communicable disease such as hypertension in the African region.[6]

Large clinical outcome studies have repeatedly shown that treating hypertension using evidence based antihypertensive treatment and/or adjusting life style improves cardiovascular outcomes.[7] However, achieving target blood pressure (BP) level remains a challenge in clinical practice. The majority of studies in Africa have shown that less than a third of patients achieve treatment goals.[8] Generally, four main factors have been identified that influence achieving controlled BP. First, there are factors intrinsic to the nature of the disease; in most cases hypertension is initially asymptomatic and this delays early prevention, diagnosis and treatment.[9] Second, poor treatment response may be due to patient-related factors such as age, gender, race, awareness and compliance to medication.[4,10] Third, these are healthcare system-related factors such as lack of effective hypertension prevention and treatment programs, and access to medications. Fourth, prescriber behavior, competences, and large patient-to-prescriber ratio affect hypertension prevention and

treatment outcomes. The majority of these factors have been extensively studied in western society; however, little is known of their impact on BP control in developing nations. Some of these factors may be unique to, or more pronounced in the African setting including low societal awareness, priority to fight infectious diseases, and human resource limitations in particular the number of available healthcare professionals.[6,11]

Prevention and treatment strategies have been shown to be effective in optimizing BP control in the western world.[12] Such programs may be relevant for the African setting. In order to guide targeted interventions studies, identifying factors contributing to poor BP control in the African setting are urgently needed. Studies on hypertension conducted to date in Ethiopia, the second largest populous country (approximately 100 million) in Africa, have focused on determining prevalence of the disease.[13-15] Prevalence is relatively low (10 – 30%), [1,13-15], but further data on hypertension treatment practices are lacking.[16,17] Therefore, we aimed to assess the proportion of patients treated for hypertension who had controlled BP and identify determinants for achieving BP control in an Ethiopian setting. Additionally, we aimed to study whether treatment was intensified in those patients with uncontrolled BP and identify the determinants for treatment intensification.

METHODS

Study design and setting

This retrospective cohort study was conducted in outpatient clinics of six public hospitals in Addis Ababa (capital city) and Tigray regional state, Ethiopia. We included two specialized hospitals (Addis Ababa), and four general hospitals, three from Tigray and one from Addis Ababa. Specialized (tertiary) hospitals are at the top tier of Ethiopian public healthcare system and serve up to five million population. The general (secondary) hospitals are estimated to serve 1-1.5 million population. Furthermore, patients including those with hypertension are usually treated first at a primary healthcare center.[18]

Study population

Participants were approached while waiting for their appointment in the waiting area of hypertension outpatient clinics, where known hypertensive patients come for regular follow-up visits. They were recruited consecutively after giving consent. Hypertensive patients aged 18 years or above were included, if they had at least one previous antihypertensive medication prescription in the same hospital, and gave informed consent. Patients were identified based on self-reported hypertension or based on the mark on their pocket-size appointment card as being hypertensive. We verified in each clinic log-book (if available), and from individual patient medical records if patients met the inclusion criteria as they had indicated during the interviews.

Routine practice in the study hospitals is that nurses measure patient's blood pressure and assign the patient to a physician. The physician will then perform a consultation, confirm the hypertension diagnosis, and if necessary perform further examinations including rechecking BP, and renew or amend prescribed medication. Patients then collect their medicine from pharmacy outlets at the same hospital or if not available from private or community pharmacies.

Data collection

Included patients were interviewed in the waiting area before they were seen by the physician. Data collected via interview were socio demographics, medication adherence, and treatment duration of antihypertensive medication(s). The socio demographics variables were age, sex, educational and marital status, alcohol use and smoking habits. Clinical information retrieved from medical records were BP measurements, medication prescribed, and comorbid illnesses, and information was retrieved for the *current visit* and the previous (*prior) visit.* Data were collected by professional nurses or pharmacists who were trained in using a dedicated case-report form. Data were collected between February and August 2015.

Variables

Outcome measures

We defined two *outcome measures*. First, for *BP control* we used the 'standard' definition of controlled BP, i.e., systolic BP/diastolic BP below 140/90 mm Hg at the current visit.[12] Second, we defined *treatment intensification* as an increase in dose of an antihypertensive drug and/or addition of one or more antihypertensive drug(s). Treatment intensification was calculated for those patients who had a complete medication history (including dose and administration frequency) at both current and prior visits and whose BP was not controlled at the current visit. A switch in drug class was not considered as treatment intensification.

Explanatory variables

For *determinants* of BP control or treatment intensification, we included socio-demographic variables (age in year, gender, smoking history, alcohol use, marital status, and educational status), hospital type (general versus specialized), cardiometabolic comorbid illnesses (diabetes mellitus-DM, dyslipidemia, kidney disease, heart failure/myocardial infarction), uncontrolled BP (≥140/90 mm Hg) at the prior visit, duration of antihypertensive treatment in year, treatment adherence with eight-

point Morisky Medication adherence scale, MMAS-8 (≥ 7: yes/no), visit schedule in month, and antihypertensive medications prescribed at prior visit. For alcohol use and smoking habit, participants were asked if they were active smokers or consume alcohol until our survey date, i.e smoking history (Yes: current smokers, and No: never smoke or ex-smoker), alcohol use (Yes: regularly or sometimes, and No: never consume alcohol). The visit schedule was calculated by taking the difference in days between the current and prior visits divided by 30, i.e its indicates length of time (duration) between the two follow-up visit expressed in months.

Antihypertensive medication adherence was measured with the eight-point Morisky Medication adherence scale (MMAS-8), which has been previously validated for hypertensive patients.[19,20] The items of the scale are grouped into three aspects. The first aspect is about forgetting to take medication sometimes (Item 1), and more specifically in the past two weeks (item 2), or under special circumstances during travel/leaving home (item 4), and finally asking if medication was taken yesterday (item 5). The second aspect is about intentionally stopping or cutting back medication because of feeling worse (item 3) or because of a feeling that BP is under control (Item 6). The last aspect relates to convenience (item 7) or inconvenience frequency of difficult times to take medication (item 8). The scale was translated into two Ethiopian languages (Amharic and Tigrigna) according to the method described by Beaton *et al.*[21] A total score of seven or more (maximum eight) was considered to be adherent to antihypertensive medication; i.e. MMAS ≥ 7.[19] For a sensitivity analyses, we used a lower level of adherence with a cut-off of MMAS ≥ 6.

Sample size

Achieved sample size was based on an estimated 30% prevalence of controlled BP among treated hypertensive patients in Ethiopia [8,15] and a single proportion sample size calculation formula. The total sample size was 984 (164 per hospital) with 0.80 power, 95% confidence interval, 3% margin of error, and an estimated 10% none response rate, or incomplete/irretrievable patient records.

Statistical analyses

Descriptive statistics were used to summarize socio-demographic, disease characteristics of the study population, and nature and frequency of antihypertensive medications used. Multivariable logistic regression analyses were applied to investigate determinants for achieving target BP at current visit, and determinants for treatment intensification. Statistical significance was considered at p value < 0.05. Potential determinants with p < 0.2 in bivariable analyses were included into the multivariable logistic model. Microsoft access 10 and SPSS version 22.0 statistical software was used for data entry and analyses respectively.

Sensitivity analyses

We performed four sensitivity analyses. First, tighter BP targets at current visit (BP <130/80 mm Hg) were applied for those patients with diabetes mellitus (DM) and/or renal disease. Standard BP target (BP <140/90 mm Hg) was used for all others participants. Second, we performed a sensitivity analysis for the main outcome measure (controlled BP <140/90) using a different cut off for adherence (MMAS ≥ 6). Third (for controlled BP) and fourth (for treatment intensification) sensitivity analysis were similar with Table 2 and 3 with three modified determinants. Graded hypertension (prior BP) was performed according to the stages defined by the Ethiopian standard treatment guideline for hypertension: normal BP (systolic BP <120 and DBP < 80 mm Hg), pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89 mm Hg), stage-I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm Hg), and stage-II hypertension (systolic BP ≥ 160 or diastolic BP ≥100 mm Hg).[21] These analysis also included the number of cardiometabolic comorbid illnesses as a proxy measure for more severely ill patients and age categorized in to five groups [22]. Patients with higher hypertension stages and multiple comorbid illness were hypothesized to be more difficult to treat.

Ethics approval

This study was approved by Ethiopian Health Research Ethical Review Committees of (i) the College of Health Sciences, Mekelle University, (ii) St Paul's Hospital Millennium Medical College, and (iii) the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University. All individual participants included in this study consented to participation.

RESULTS

We were able to approach 968 patients at six public hospitals in Ethiopia. Seventy-one patients were excluded from our analyses; eight refused to participate, six were not hypertensive, and 57 patients had no retrievable records or incomplete records (missing BP at current visit), resulting in a study population of 897 patients (Figure 1). The majority of included patients (93%) reported to have come for their regular hypertension follow-up visit. The remaining 7% had (perceived) symptoms; uncontrolled hypertension or adverse events. The mean (SD) patient age was 57 (14) years, 63% of patients were female, most patients (65%) were married, and 64% had no formal education or only attended primary school. Almost all (94%) had never smoked, and nearly half (43%) consumed alcohol regularly or occasionally (Table 1). At the current visit, 35% study participants had at least one recorded comorbid illness, predominantly DM (Table 1).

Table 1 Characteristics of ambulatory hypertensive patients at two visits, Ethiopia

Characteristics	Current visit	Prior visit
Demographics		
Age (mean, SD), Year	57 (14)	
Female (n, %)	551 (63)	
Smoking [current smoker] (n, %)	57 (6)	
Alcohol use [regularly or sometimes] (n, %)	378 (43)	
Married (n, %)	567 (65)	
Education (n, %)		
University/college education	170 (20)	
Secondary education	141 (16)	
Primary or no formal education	557 (64)	
Setting		
Specialized hospitals: both from Addis Ababa (n, %)		
Tikur Anbessa Hospital	139 (16)	
St. Paul's Hospital	153 (17)	
General hospitals: all from Tigray, except Yekatit 12 from Addis Ababa (n, %)		
St. Mary Axum Hospital	139 (16)	
Mekelle Hospital	152 (17)	
Lemlem Karl Maychew Hospital	155 (17)	
Yekatit 12 Hospital	159 (18)	
Disease characteristics		
Blood pressure (BP)		
Systolic BP (Mean, SD)	139 (21)	144 (22)
Diastolic BP (Mean, SD)	84 (11)	85 (13)
Controlled BP (<140/90 mm Hg) (n, %)	335 (37)	231 (27)
Controlled BP (<130/80 mm Hg with DM &/or kidney diseases, [#]otherwise <140/90 mm Hg) (n, %)	268 (30)	202 (24)
Cardiometabolic comorbid illnesses (n, %)		
Diabetes Mellitus	227 (25)	198 (22)
Dyslipidemia	57 (6)	45 (5)
Renal diseases	25 (3)	23 (3)
Heart failure / myocardial infarction	72 (8)	60 (7)
Antihypertensive treatment characteristics		
Drug class (n, %)		
ACE inhibitors	503 (56)	494 (55)
Enalapril	499 (56)	492 (55)
Lisinopril or captopril	4 (0.4)	2 (0.2)
Beta blockers	167 (19)	166 (19)
Atenolol	148 (17)	147 (16)
Propranolol, metoprolol or carvedilol	19 (2)	19 (2)
Calcium channel blockers	449 (50)	439 (49)
Nifedipine	381 (43)	389 (43)
Amlodipine or felodipine	68 (8)	50 (6)
Diuretics [¥]	498 (56)	486 (54)
Hydrochlorothiazide	428 (48)	421 (47)
Furosemide	76 (9)	71 (8)
Spironolactone	72 (8)	66 (7)
Others (methyldopa, nitrates or losartan)	19 (2)	13 (1)
Duration of therapy years (Median, interquartile rang)	4 (7)	
Visit schedule in months (mean, SD)	2.3 (2.0)	
Adherence (MMAS ≥ 7) (n, %)	355 (40)	
Therapy (n, %)		
Monotherapy	*343 (38)*	*363 (41)*
Multidrug therapy	*550 (62)*	*521 (59)*
Treatment intensified in patients with uncontrolled BP at current visit (n=540) * (n, %)	123 (23)	

Mono/Multidrug therapy is limited to antihypertensive medications. *For 22 of 562 patients with uncontrolled BP at the current visit the medication history was not complete. Treatment intensification could thus only be calculated for 540 patients. [¥] Some patients had more than one type of diuretics. [#]otherwise: hypertensive patients without DM or kidney disease.

Thirty-seven percent (n=335) of the participants had controlled BP at the current visit (Table 1). Applying the stricter BP target for patients with DM and/or renal disease (BP<130/80 mm Hg), the proportion of patients with controlled BP dropped to 27% (n=231).

Only, 23% of 540 patients with uncontrolled BP and complete medication history had their treatment intensified (Table 1). For 22 (4%) of 562 patients with uncontrolled BP at the current visit, the medication history was not complete, either the dose and/or administration frequency were missing. The antihypertensive medication adherence rate (MMAS ≥ 7) was 40%, (Table 1), and 57% for the lower cut off, MMAS ≥ 6 (Supplement Table 1).

Overall, angiotensin-converting-enzyme (ACE) inhibitors were the most commonly prescribed group of drugs (n = 503), followed by diuretics (n = 498) (Table 1). Medication use was quite similar on both visits. At the current visit 62% of included patients were prescribed a multidrug treatment regimen and 45% patients took two antihypertensive agents (Supplement Table 2). Most (38 %) of the 343 patients on monotherapy were prescribed diuretics (n=127).

Determinants of BP Control

BP <140/90 mm Hg (primary analysis)

According to our multivariable logistic regression model (Table 2), factors significantly associated with achieving target BP at the current visit were age (OR 0.99 [95% CI: 0.98; 1.00]), follow-up at general hospitals (OR 1.89 [95% CI: 1.26; 2.83]), inadequately controlled BP at prior visit (OR 95% CI: 0.30 [0.21; 0.43]), longer treatment duration per year (OR 1.04 [95% CI: 1.01; 1.06]), and prescribed diuretics (OR 0.68 [95% CI: 0.50; 0.94]).

Table 2 Determinants of achieving target BP (BP < 140/90) at current visit in ambulatory hypertension patients

Variables		Controlled BP		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), year		58 (13)	56 (15)	#0.99 [0.98; 1.00]	***0.988 [0.976; 0.997]**
Gender (n, %)	Male	219 (67)	109 (33)	Ref	
	Female	331 (60)	220 (40)	*1.34 [1.00; 1.78]	1.12 [0.80; 1.55]
Smoking (n, %)	No	514 (62)	312 (38)	Ref	
	Yes	37 (65)	20 (35)	0.89 [0.51; 1.56]	
Alcohol use (n, %)	No	310 (63)	184 (37)	Ref	
	Yes	232 (61)	146 (39)	1.06 [0.81; 1.40]	
Marital status (n, %)	Single	187 (60)	124 (40)	Ref	
	Married	359 (63)	208 (37)	0.87 [0.66; 1.16]	
Educational status (n, %)	College/University	110 (65)	60 (35)	Ref	
	Secondary	86 (61)	55 (39)	1.17 [0.74; 1.86]	
	Primary /not formal	345 (62)	212 (38)	1.13 [0.79; 1.61]	
Hospital type (n, %)	Specialized	199 (68)	93 (32)	Ref	
	General	363 (60)	242 (40)	*1.43 [1.06; 1.92]	***1.89 [1.26; 2.83]**
Disease characteristics (n, %)					
Diabetes Mellitus	No	413 (62)	257 (38)	Ref	
	Yes	149 (66)	78 (34)	0.84 [0.61; 1.15]	
Dyslipidemia	No	523 (62)	317 (38)	Ref	
	Yes	39 (68)	18 (32)	0.76 [0.43; 1.35]	
Renal disease	No	542 (62)	330 (38)	Reference	
	Yes	20 (80)	5 (20)	#0.41 [0.15; 1.10]	0.58 [0.19; 1.71]
Heart failure/ MI	No	518 (63)	307 (37)	Ref	
	Yes	44 (61)	28 (39)	1.07 [0.66; 1.76]	
Controlled BP at prior visit	No	424 (68)	199 (32)	*0.37 [0.27; 0.51]	***0.30 [0.21; 0.43]**
	Yes	102 (44)	129 (56)	Ref	
Antihypertensive Treatment characteristics					
Duration of therapy, years (mean, SD)		6.2 (6.4)	7. 4 (8.3)	#1.02 [1.00; 1.04]	***1.04 [1.01; 1.06]**
Adherent (MMAS ≥ 7) (n, %)	No	319 (60)	212 (40)	Ref	
	Yes	233 (66)	122 (34)	#0.79 [0.60; 1.04]	0.80 [0.58; 1.09]
Revisit schedule in months (Mean, SD)		2.2 (1.4)	2.0 (1.2)	*0.89 [0.82 ;0.97]	0.91 [0.82; 1.02]
Therapy at prior visit (n, %)	Monotherapy	225 (62)	138 (38)	Ref	
	Multidrug	326 (63)	195 (37)	0.98 [0.74; 1.29]	
Antihypertensive medications at prior visit					
ACE inhibitors (n, %)	No	259 (64)	144 (36)	Ref	
	Yes	303 (61)	191 (39)	1.13 [0.86; 1.49]	
Beta blockers (n, %)	No	472 (65)	259 (35)	Ref	
	Yes	90 (54)	76 (46)	*1.54 [1.09; 2.16]	1.42 [0.95; 2.10]
Calcium channel blockers (n, %)	No	290 (63)	168 (37)	Ref	
	Yes	272 (62)	167 (38)	1.06 [0.81 ;1.39]	
Diuretics (n, %)	No	243 (59)	168 (41)	Reference	
	Yes	319 (66)	167 (34)	*0.76 [0.58; 0.99]	***0.68 [0.50; 0.94]**

Only patients with available data were included in the analyses, therefore numbers may sometimes differ from Table 1. Percentages are calculated per a row. Statistically significant values: *p< 0.05 at 95% CI. Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in the multivariable model. Mono/Multidrug therapy was for antihypertensive medications.

Determinant of treatment intensification

The only statistically significant determinant for treatment intensification in the multivariable analyses was longer treatment duration (OR 1.05 [95% CI: 1.02; 1.09]), Table 3.

Sensitivity (secondary) analysis

In our first sensitivity analyses, using BP <130/80 mm Hg for patients with DM and/or renal disease, and for all other patients <140/90 mm Hg as cut-offs, uncontrolled BP at the prior visit had a negative effect on achieving target BP at the current visit (OR 0.25 [95% CI: 0.17; 0.37]). Medications prescribed during the prior visit, except diuretics (OR 0.60 [95% CI: 0.40; 0.90]), were not significantly associated with achieving controlled BP at the current visit. Unlike the primary analyses, age, treatment duration, and hospital type did not show statistically significant effects on current visit BP status (Supplement Table 3).

In the sensitivity analyses for BP control (supplement Table 4) and treatment intensification (supplement Table 5), the results were mostly similar with the main analysis (Table 2 and 3) respectively. As expected, more severe hypertension stage was associated with more difficulty to achieve target BP: stage-II hypertension [(OR 0.17 [95% CI 0.09;0.35]), and stage-I hypertension [(OR 0.34 [95% CI 0.17;0.67]. However, number of comorbid illness was not significant determinants. In case of age, older age groups were less likely to achieve target BP than youngest age group (<35 years): 55-64 years old (OR 0.41 [95% CI 0.20; 0.83]) and ≥ 65 years old (OR 0.46 [95 CI: 0.22;0.93]). Supplementary analysis for treatment intensification (Supplement Table 5), gave similar results with main analysis on Table 3, where only duration of therapy was positive significant determinant (OR 1.05 [95% CI: 1.02; 1.08]) of treatment intensification.

Table 3 Treatment intensification determinants for ambulatory hypertension patients with uncontrolled BP at current visit

Variables		Treatment intensified		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), Year		57 (13)	60 (13)	#1.02 [1.00; 1.03]	1.02 [1.00; 1.04]
Gender (n, %)	Male	167 (80)	41 (20)	Ref	
	Female	241 (75)	80 (25)	#1.35 [0.88; 2.07]	1.47 [0.91; 2.37]
Smoking (n, %)	No	383 (77)	113 (23)	Ref	
	Yes	27 (79)	7 (21)	0.88 [0.37; 2.07]	
Alcohol use (n, %)	No	225 (76)	73 (25)	Ref	
	Yes	180 (80)	44 (20)	0.75 [0.49; 1.15]	
Marital status (n, %)	Single	138 (77)	42 (23)	Ref	
	Married	269 (78)	76 (22)	0.93 [0.60; 1.43]	
Educational status (n, %)	College/University	82 (78)	23 (22)	Ref	
	Secondary	58 (70)	25 (30)	1.54 [0.80; 2.97]	
	Primary /not formal education	262 (79)	70 (21)	0.95 [0.56; 1.62]	
Hospital type (n, %)	Specialized	137 (73)	51 (27)	Ref	
	General	280 (80)	72 (21)	#0.69 [0.46; 1.04]	0.83 [0.51; 1.37]
Disease characteristics (n, %)					
Diabetes Mellitus at current visit	No	311 (79)	84 (21)	Ref	
	Yes	106 (73)	39 (27)	#1.36 [0.88; 2.11]	1.10 [0.67; 1.81]
Dyslipidemia at current visit	No	388 (77)	113 (23)	Reference	
	Yes	29 (74)	10 (26)	1.19 [0.56; 2.50]	
Renal disease at current visit	No	403 (77)	118 (23)	Ref	
	Yes	14 (74)	5 (26)	1.22 [0.43; 3.45]	
Heart Failure / MI at current visit	No	384 (77)	112 (23)	Ref	
	Yes	33 (75)	11 (25)	1.14 [0.56; 2.33]	
Controlled BP at prior visit	No	312 (77)	96 (24)	#1.50 [0.85; 2.66]	1.38 [0.76; 2.50]
	Yes	83 (83)	17 (17)	Ref	
Antihypertensive treatment characteristics					
Duration of therapy yrs (mean SD)		5.7 (4.1)	8.1 (7.4)	*1.05 [1.02; 1.08]	***1.05 [1.02; 1.09]**
Adherence (MMAS ≥ 7) (n, %)	No	232 (76)	73 (24)	Ref	
	Yes	178 (78)	49 (22)	0.88 [0.58; 1.32]	
Therapy at prior visit (n, %)	Monotherapy	168 (76)	53 (24)	Ref	
	Multidrug therapy	249 (78)	70 (22)	0.89 [0.59; 1.34]	

Statistically significant values: *p < 0.05 at 95% CI. Variable with #p < 0.2 or *p < 0.05 in the bivariable model were included in the multivariable model. Percentages are calculated per row. Treatment intensification was calculated for 540 patients who had complete medication history (including dose and frequency) on both visits and uncontrolled BP at current visit.

DISCUSSION

In this study, nearly two-thirds of patients on antihypertensive medication had uncontrolled BP. Drugs were prescribed from four antihypertensive drug classes, ACE-inhibitors, diuretics, CCBs, and BBs. Generally, a single specific agent (over 90%) was prescribed within a class, enalapril, hydrochlorothiazide, nifedipine, and atenolol respectively. Age of patients, uncontrolled BP at prior visit, and a treatment regimen containing diuretics contributed to poorer BP control. Follow-up in a general hospital as compared to a specialized hospital, and longer treatment duration were associated with a better BP control. Duration of therapy on antihypertensive medication was the only, albeit modestly, significant contributing factor of treatment intensification (also for control BP).

Most other studies in Africa, 41 out of 44, showed a lower proportion of patients with controlled BP (these studies reported levels of control ranging from <1% to 33%) than our study.[8] The reported wide variation could be explained by population differences and variation in study set-ups. The level of BP control in our study was in between that reported in two studies performed in a Southern Ethiopia hospital.[16,23] Gudina *et al* studied the prevalence of hypertension among patients visiting a hospital for any reason, of patients with known hypertension 44% were controlled.[23] The study by Asgedom *et al* was more similar to ours with 50% of patients visiting an outpatient hypertension clinic who had been treated for at least 12 months in the study hospital.[16] The longer duration of treatment in this latter study compared to ours perhaps may explain the better level of control, considering that duration of therapy was a significant determinant in our study for BP control.

In comparison with studies in western countries, the percentage of patients with adequately controlled BP, and those who received treatment intensification was lower in our study than in North American countries, but similar to some European countries.[24,25] These differences may be explained in part by different recommendations between national guidelines. However, as reported

elsewhere, it is not only differences between guidelines, but also how much effort countries put in implementation of these recommendations.[25] While the Ethiopian guideline is similar to the USA guidelines,[21,24] possible differences in implementation, due to African factors including resource limitations, low priority for communicable diseases, and healthcare providers' behavior and skills may in part explain the low level of BP control.[26] However, comparing our results with population based studies in western countries or those in other part of Africa should be done with caution as we investigated regional Ethiopian hypertensive population treated at a hospital setting.

In our study, one of the determinants for achieving target BP was the healthcare setting. Patients who are referred to specialized hospitals may be more complex – in terms of comorbidities or severity of hypertension. Hence, it is surprising that patients in these hospitals are more likely to have inadequately controlled BP. Younger age was another significant determinant for achieving target BP. Prescribers in our study may have accepted higher BP in older patients, possibly because of tolerability or perceived lack of need for tight BP control. Recent evidence, however, suggests that ''the lower is the better'' also in older patients.[27,28] Nevertheless, guidelines lack consistency on BP targets for elderly,[29] especially when patients are frail and doctors may not aim for tight BP control. Another determinant of BP control was the type of medication prescribed. Most of our study participants received diuretics, the first line antihypertensive agents. We have no data in which order medication was initiated; therefore, we can only speculate why treatment regimens containing these drugs did not show better BP control. Since three-quarters of diuretics-containing regimens in our study existed of two drugs only (Supplement Table 2), patients may need additional therapy.

Only one fifth of patients with uncontrolled BP at the current visit had their treatment intensified. Longer treatment duration was the only statistically significant determinant for intensification. Possibly, it took a while before prescribers would intensify treatment. Ultimately, the lack of BP control at the prior visit was the strongest predictor of patients not having controlled BP at current

visit. This seems to suggest some level of 'clinical inertia', where doctors are slow to respond to clinical parameters indicating a need to step up therapy. However, it may also be explained by true therapy resistant hypertension (although only 17% of patients received three or more antihypertensive agents at the prior visit).[30-33] Moreover, prescribers may not intensify treatment if they suspect that increased BP levels may be related to a suspected or reported poor compliance for a particular patient. (Poor) medication adherence is known as an important determinant for controlling hypertension.[34] The level of adherence we observed (40% and 57% for MMAS-8 with a cut-off at > 6 and ≥ 6 respectively) was close to that reported by Asgedom *et al* (35% and 61% respectively).[16] Two other Ethiopian studies reported low levels of adherence although more difficult to compare as they used a 4-point MMAS.[35, 36] Surprisingly, the level of adherence was not associated with BP control in our main and sensitivity analyses (Supplement Table 1). Similarly in the study by Asgedom *et al,* a hospital-based study in Southern Ethiopia, no relation with adherence and BP control was observed.[16] Self-reported medication adherence may be overestimated and therefore lead to bias.

An interesting finding was that more hypertensive women than men were included in our study, and that so few patients smoked. One reason why more women were included could be that hypertension is more prevalent in Ethiopian females as suggested in a recent community-based study evaluating prevalence of hypertension in Ethiopia.[13] Another explanation may be that women with hypertension seek care more regularly than men. However, a meta-analysis including hospital-based studies showed a higher prevalence of hypertension for males.[15] Another recent hospital-based study also indicated a higher prevalence of males with hypertension.[16] We observed that women were not more likely than men to have controlled BP or their treatment intensified.

Poor hypertension control should be addressed in a holistic approach that includes life style modification and management of comorbid illnesses. Our study was largely performed in urban areas, which have the highest prevalence of hypertension in Ethiopia, which is attributed to adoption of a Western life-style.[15] Still, our patient population looks very different from that in European or USA studies; i.e. with few smokers and few patients with (known) cardiometabolic comorbidities.

Strengths and limitations

As far as we are aware, this was the first study of its kind in Ethiopia covering a relatively diverse population. Our data included patients from hypertension outpatient clinics of six public hospitals in the capital city and northern region of Ethiopia.

A limitation of our study was the validity of the BP measure used. We analysed BP measurements as recorded in patients' medical records that reflected actual clinical practice, but may be subject to recording and measurement error. It is not clear how prescribers considered measurement variability or if any attempt was made to avoid 'white-coat' hypertension, e.g. by repeating BP measurement. Still, many observational studies use medical records – with data collected in routine practice - as a data source. Future studies may consider using standardized assessment of BP evaluation. Another limitation is that medical records did not include extensive or well-structured patient information. For example, comorbidities may be underreported. For this reason, we limited evaluated comorbidities to cardiometabolic diseases as these are relevant to hypertension prognosis and treatment and are more likely to have been recorded in the charts. This study focused on public secondary and specialized hospitals; therefore the result may not be generalizable to other settings such as private practices and primary health care centers. Differences in socioeconomic status did not seem related with type of drug prescribed. This may have affected redeeming prescriptions at the pharmacy but we did not record that information. Nevertheless, educational status – a proxy for socioeconomic status – in our study population was not related to BP control.

CONCLUSION

Nearly two-thirds of patients on antihypertensive medication did not achieve target BP during routine clinical follow-up, and only a quarter of these patients with uncontrolled BP received treatment intensification. To improve care for patients visiting Ethiopian hospital hypertension clinics, focus should be on older patients and interventions may be needed for specialized centers.

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Contribution

D.F. Berhe, K. Taxis and P. Mol designed and performed the research, analyzed, and interpreted the data. Flora M Haaijer-Ruskamp, Afework Mulugeta, and Yewondwossen Tadesse Mengistu designed the study. All authors participated in writing the manuscript, also read and approved the final version.

Conflict of Interest: There are no competing interests to declare.

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Data sharing statement

No additional data are available for this specific study.

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Figure legend

Figure 1 Flow chart for case inclusion for analysis

Figure 1

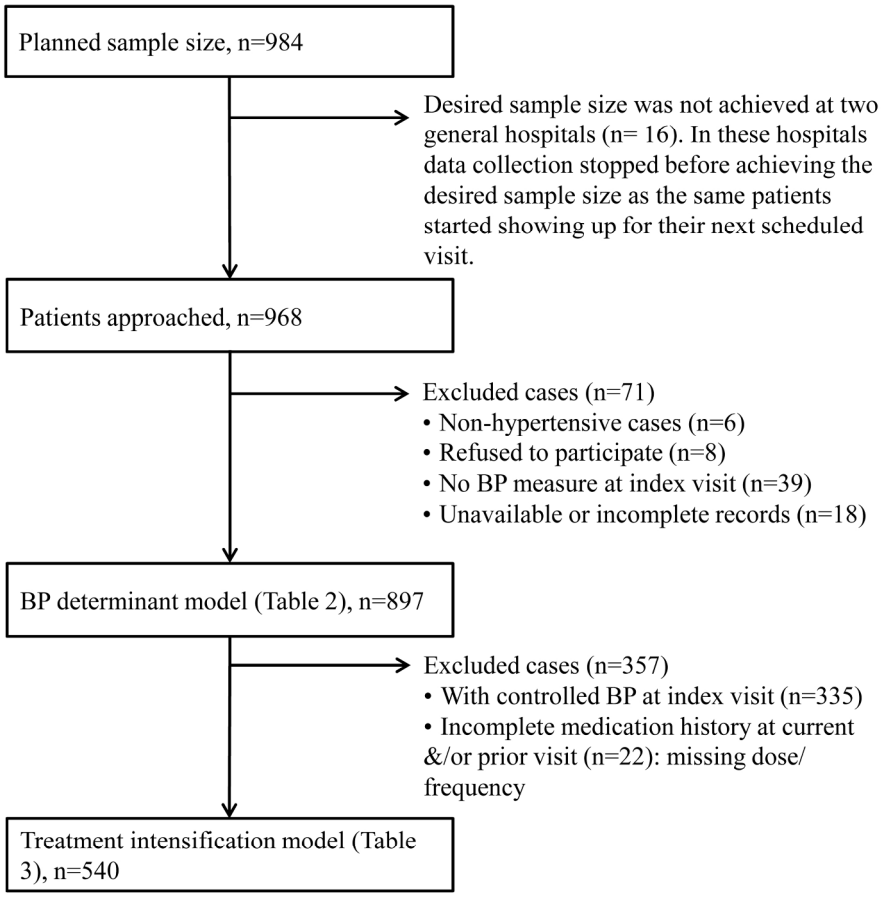

Figure 1 Flow chart for case inclusion for analysis

194x198mm (300 x 300 DPI)

HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS:

A RETROSPECTIVE COHORT STUDY IN EHTIOPIA

Supplement Table 1 Determinants of achieving target BP (BP < 140/90) at index visit ambulatory hypertension patients (sensitivity analysis with adherence definition of MMAS ≥ 6)

Variables		Controlled BP		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), year		58 (13)	56 (15)	#0.99 [0.98; 1.00]	*0.99 [0.98; 1.00]
Gender (n, %)	Male	219 (67)	109 (33)	Ref	
	Female	331 (60)	220 (40)	#1.34 [1.00; 1.78]	1.12 [0.81; 1.55]
Hospital type (n, %)	Specialized	199 (68)	93 (32)	Ref	
	General	363 (60)	242 (40)	*1.43 [1.06; 1.92]	*1.88 [1.25; 2.81]
Disease characteristics at index visit (n, %)					
Renal disease	No	542 (62)	330 (38)	Reference	
	Yes	20 (80)	5 (20)	#0.41 [0.15; 1.10]	0.60 [0.20; 1.79]
Controlled BP at **prior visit**	No	424 (68)	199 (32)	*0.37 [0.27; 0.51]	*0.30 [0.21; 0.43]
	Yes	102 (44)	129 (56)	Ref	
Antihypertensive Treatment characteristics					
Duration of therapy, years (mean, SD)		6.2(6.4)	7. 4 (8.3)	#1.02 [1.00; 1.04]	*1.04 [1.02; 1.06]
Adherent (MMAS ≥ 6) (n, %)	No	237 (63)	140 (37)	Ref	
	Yes	315 (62)	194 (38)	1.04 [0.79; 1.37]	1.14 [0.83; 1.56]
Revisit schedule in months (Mean,		2.2 (1.4)	2.0 (1.2)	*0.89 [0.82 ;0.97]	0.91 [0.82; 1.02]
Beta blockers (n, %)	No	472 (65)	259 (35)	Ref	
	Yes	90 (54)	76 (46)	*1.54 [1.09; 2.16]	1.45 [0.98; 2.15]
Diuretics (n, %)	No	243 (59)	168 (41)	Reference	
	Yes	319 (66)	167 (34)	*0.76 [0.58; 0.99]	*0.68 [0.50; 0.94]

Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in this multivariable model (sensitivity analysis).

Supplement Table 2 Prescribed antihypertensive medication(s) per patient

Drug prescribed per case	At Index visit (n≠=887), %	At Prior visit (n≠=882), %
D (Diuretics)	14.3	15.0
C (CCBs)	13.0	13.7
A (ACE inhibitors)	9.9	11.0
B (BBs)	0.8	1.4
DC	9.4	8.6
DA	17.0	16.6
CA	11.5	10.2
AB	2.6	2.4
CB	2.4	2.7
DB	2.0	1.5
DCB	1.5	1.1
DCA	6.1	6.1
ACB	3.7	3.5
DAB	2.7	2.5
DABC	3.2	3.7

CCBs, calcium channel blockers; ACE, Angiotensinogen Converting Enzyme; BBs; Beta Blockers

≠The table did not include rarely used medication categories. These drugs were methyldopa, losartan, hydralazine, and nitrates and in combination with others or as a monotherapy.

Supplement Table 3 Sensitivity analyses: determinants for controlled hypertension at alternative BP target (BP <130/80 mm Hg) for patients with DM and/or renal disease, and all other patients BP <140/90 mm Hg)

Variables		Controlled BP		Bivariable OR [95% CI]	Multivariable OR [95% CI]
		No	Yes		
Demographics					
Age (mean. SD)		58 (13)	56 (15)	#0.99 [0.98; 1;00]	0.99 [0.98; 1.00]
Gender (n, %)	Male	244 (74)	84 (26)	Ref	
	Female	373 (68)	178 (32)	*1.39 [1.02; 1.88]	1.30 [0.87; 1.95]
Smoking (n, %)	No	572 (69)	254 (31)	Ref	
	Yes	45 (79)	12 (21)	#0.60 [0.31; 1.16]	1.05 [0.50; 2.24]
Alcohol use (n, %)	No	354 (72)	140 (28)	Ref	
	Yes	254 (67)	124 (33)	#1.23 [0.92; 1.65]	1.54 [1.07; 2.21]
Marital status (n, %)	Single	207 (67)	104 (33)	Ref	
	Married	406 (72)	161 (28)	#0.79 [0.59; 1.06]	0.82 [0.56; 1.18]
Educational status (n, %)	College/University	123 (72)	47 (28)	Ref	
	Secondary	103 (73)	38 (27)	1.21 [0.83; 1.77]	
	Primary /not formal	381 (68)	176 (32)	0.97 [0.59; 1.59]	
Hospital type (n, %)	Specialized	217 (74)	75 (26)	Ref	
	General	412 (68)	193 (32)	1.36 [0.99; 1.85]	1.17 [0.75; 1.82]
Disease characteristics (n, %)					
Dyslipidemia at index visit	No	583 (69)	257(31)	Ref	
	Yes	46 (81)	11 (19)	#0.54 [0.28; 1.06]	0.47 [0.20; 1.10]
Heart Failure / MI at index visit	No	578 (70)	247 (30)	Ref	
	Yes	51 (71)	21 (29)	0.96 [0.57; 1.64]	
Controlled BP at prior visit	No	501 (77)	151 (23)	*0.25 [0.18; 0.35]	*0.25 [0.17; 0.37]
	Yes	92 (46)	110 (55)	Ref	
Antihypertensive treatment characteristics					
Duration of therapy years (mean, SD)		7.0 (7.3)	5.8 (6.9)	#0.98 [0.96; 1.00]	0.99 [0.97; 1.02]
Adherence (MMAS-8 ≥ 7) (n, %)	No	373 (70)	158 (29)	Ref	
	Yes	246 (69)	109 (31)	1.04 [0.78; 1.40]	
Revisit schedule in months (Mean, SD)		2.4 (2.1)	2.0 (1.2)	*0.88 [0.81; 0.97]	0.94 [0.84; 1.06]
Therapy at prior visit (n, %)	Monotherapy	240 (66)	123 (34)	Ref	
	Multidrug therapy	378 (73)	143 (27)	*0.74 [0.55; 0.99]	1.02 [0.69; 1.51]
Antihypertensive medications at prior visit					
ACE inhibitors (n, %)	No	274 (68)	129 (32)	Ref	
	Yes	355 (72)	139 (28)	0.83 [0.62; 1.11]	
Beta blockers (n, %)	No	511 (70)	220 (30)	Ref	
	Yes	118 (71)	48 (29)	0.95 [0.65; 1.37]	
Calcium channel blockers (n, %)	No	312 (68)	146 (32)	Ref	
	Yes	317 (72)	122 (28)	#0.82 [0.62; 1.10]	0.88 [0.59; 1.31]
Diuretics (n, %)	No	276 (67)	135 (33)	Ref	
	Yes	353 (73)	133 (27)	#0.77 [0.58; 1.03]	*0.60 [0.40; 0.90]

Supplement Table 4: Determinants of achieving target BP (BP < 140/90) at index visit in ambulatory hypertension patients

Variables		Odds ratio at 95% CI	
		Bivariable estimates	Multivariable estimate
Demographics			
Age [year]			
< 35		Ref	
35-44		0.56 [0.27; 1.18]	0.51 [0.24; 1.10]
45-54		0.51 [0.25; 1.03]	0.53 [0.26; 1.10]
55-64		0.40 [0.20; 0.80]	0.41 [0.20; 0.83]
≥ 65		0.50 [0.25; 0.99]	0.46 [0.22; 0.93]
Gender	Male	Ref	
	Female	*1.34 [1.00; 1.78]	1.15 [0.83; 1.61]
Smoking	No	Ref	
	Yes	0.89 [0.51; 1.56]	
Alcohol use	No	Ref	
	Yes	1.06 [0.81; 1.40]	
Marital status	Single	Ref	
	Married	0.87 [0.66; 1.16]	
Educational status	College/University	Ref	
	Secondary	1.17 [0.74; 1.86]	
	Primary /not formal	1.13 [0.79; 1.61]	
Hospital type	Specialized	Ref	
	General	*1.43 [1.06; 1.92]	*2.05 [1.36;0.09]
Disease characteristics			
Number of cardiometabolic comorbid illnesses		0.86 [0.69; 1.06]	0.84 [0.64; 1.11]
Hypertension severity at prior visit			
Normal BP (systolic BP < 120 and diastolic BP < 80 mm Hg)		Ref	
Pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89 mm Hg)		0.83 [0.45; 1.53]	0.80 [0.40; .62]
Stage I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm Hg)		*0.40 [0.21; 0.72]	*0.34 [0.17; .67]
Stage II hypertension (systolic BP ≥ 160 or diastolic BP ≥ 100 mm Hg)		*0.25 [0.14; 0.46]	*0.17 [0.09; .35]
Antihypertensive Treatment characteristics			
Duration of therapy, years (mean, SD)		#1.02 [1.00; 1.04]	*1.04 [1.02; .07]
Adherent (MMAS ≥ 7)	No	Ref	
	Yes	#0.79 [0.60; 1.04]	0.75 [0.54; 1.04]
Revisit schedule in months (Mean, SD)		*0.89 [0.82 ;0.97]	0.93 [0.83; 1.04]
Therapy at prior visit	Monotherapy	Ref	
	Multidrug therapy	0.98 [0.74; 1.29]	
Antihypertensive medications at prior visit			
ACE inhibitors	No	Ref	
	Yes	1.13 [0.86; 1.49]	
Beta blockers	No	Ref	
	Yes	*1.54 [1.09; 2.16]	*1.63 [1.08; .45]
Calcium channel blockers	No	Ref	
	Yes	1.06 [0.81 ;1.39]	
Diuretics	No	Reference	
	Yes	*0.76 [0.58; 0.99]	*0.68 [0.49;0.94]

Difference with the main analysis (Table 2): Age categorical, prior BP based on severity, and comorbid illness count included.

Supplement Table 5 Treatment intensification determinants for ambulatory hypertension patients with uncontrolled BP at index visit

Variables		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
Demographics			
Age, Year			
	< 35	Ref	
	35-44	1.53 [0.39; 5.99]	1.25 [0.31; 5.02]
	45-54	1.45 [0.39; 5.38]	1.08 [0.28; 4.10]
	55-64	1.95 [0.55; 6.96]	1.20 [0.33; 5.49]
	≥ 65	2.03 [0.57; 7.26]	1.49 [0.41; 2.22]
Gender	Male	Ref	
	Female	#1.35 [0.88; 2.07]	1.40 [0.86; 1.29]
Smoking	No	Ref	
	Yes	0.88 [0.37; 2.07]	
Alcohol use	No	Ref	
	Yes	0.75 [0.49; 1.15]	
Marital status	Single	Ref	
	Married	0.93 [0.60; 1.43]	
Educational status	College/University	Ref	
	Secondary	1.54 [0.80; 2.97]	
	Primary /no formal education	0.95 [0.56; 1.62]	
Hospital type	Specialized	Ref	
	General	#0.68 [0.43; 1.06]	0.78 [0.48 1.29]
Disease characteristics			
Cardiometabolic comorbid illness at current visit		#1.15 [0.86; 1.52]	1.04 [0.74; 1.45]
Hypertension severity at prior visit			
Normal BP (systolic BP < 120 and diastolic BP < 80 mm Hg)		Ref	
Pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89		0. 65 [0.20; 2.07]	
Stage-I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm		0.93 [0.32; 2.68]	
Stage-II hypertension (systolic BP ≥ 160 or diastolic BP ≥ 100 mm Hg)		1.15 [0.40; 3.26]	
Antihypertensive treatment characteristics			
Duration of therapy years (mean SD)		*1.05 [1.02; 1.08]	*1.05 [1.02; 1.08]
Adherence (MMAS ≥ 7)	No	Ref	
	Yes	0.88 [0.58; 1.32]	
Therapy at prior visit	Monotherapy	Ref	
	Multidrug therapy	0.89 [0.59; 1.34]	

Difference with the main analysis (table 3): Age grouped, prior BP based on severity, and comorbid illness count included.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, also on Figure 1
		(b) Give reasons for non-participation at each stage	11 also on Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12 (visit schedule)
Outcome data	15*	Report numbers of outcome events or summary measures over time	12 and 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14 and 16 (Table 2 and 3)
		(*b*) Report category boundaries when continuous variables were categorized	12 (Table 1)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplement Tables 1-5)
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18 and 20
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN ETHIOPIA

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HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS: A RETROSPECTIVE COHORT STUDY IN ETHIOPIA

Short title: hypertension treatment practices and determinants

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References: 36

ABSTRACT

Objectives: We examined determinants of achieving blood pressure control in hypertensive patients and of treatment intensification in patients with uncontrolled blood pressure (BP).

Design: A retrospective cohort study in six public hospitals, Ethiopia

Participants: Adult ambulatory hypertensive patients with at least one previously prescribed antihypertensive medication in the study hospital.

Outcome: Controlled BP (<140/90 mm Hg), and treatment intensification of patients with uncontrolled BP.

Results: The study population comprised of 897 patients. Their mean age was 57 (SD 14) years, 63% were females, and 35% had one or more cardiometabolic comorbidities mainly diabetes mellitus. BP was controlled in 37% patients. Treatment was intensified for 23% patients with uncontrolled BP. In multivariable (logistic regression) analysis, determinants positively associated with controlled BP were treatment at general hospitals (OR 1.89 [95% CI: 1.26; 2.83]) compared to specialized hospitals and longer treatment duration (OR 1.04 [95% CI: 1.01; 1.06]). Negatively associated determinants were previously uncontrolled BP (OR 0.30 [95% CI: 0.21; 0.43]), treatment regimens with diuretics (OR 0.68 [95% CI, 0.50; 0.94]), and age (OR 0.99 [95% CI: 0.98; 1.00]). The only significant – positive – determinant for treatment intensification was duration of therapy (OR 1.05 [95% CI: 1.02; 1.09]).

Conclusions: The level of controlled BP and treatment intensification practice in this study was low. The findings suggest the need for in-depth understanding and interventions of the identified determinants such as uncontrolled BP on consecutive visits, older age, and type of hospital.

Key words: hypertension, antihypertensive medication, blood pressure control, treatment intensification, ambulatory patients, Ethiopia, hospital, observational study

STRENGTH AND LIMITATIONS

- This is the first study that gives insight into determinants of hypertension treatment practice (level of BP control and treatment intensification) in a diverse population treated in public hospitals in Ethiopia.
- We analysed BP measurements as recorded in patient medical records, which reflect actual clinical practice, but may be subject to recording and measurement error.
- The finding of this study may not be generalizable to other settings such as private practice or primary health care centers in Ethiopia.

BACKGROUND

Hypertension is a major risk factor for cardiovascular diseases, and it is the leading cause of death and disability globally.[1] The World Health Organization (WHO) recently reported that 80% of deaths due to cardiovascular disease occur in low- and middle-income countries, with the highest death rate reported in African countries. The report also indicated that prevalence of hypertension in adults was higher in Africa (46%) than for instance in the US (35%).[1] Hypertension is also more prevalent among people from Africa living in the Western world than among whites.[2] The population of African ancestry is characterized by high vascular contractility, extreme salt sensitivity, and low renin release.[3-5] Hence, over-activation of the sympathetic nervous system and renin-angiotensin-aldosterone system is more prevalent in this population, making them more vulnerable to high blood pressure. In addition, changes in environmental factors such as economic development, urbanization, and lifestyle have resulted in an epidemiological transition from infectious to non-communicable disease such as hypertension in the African region.[6]

Large clinical outcome studies have repeatedly shown that treating hypertension using evidence based antihypertensive treatment and/or adjusting lifestyle improves cardiovascular outcomes.[7] However, achieving target blood pressure (BP) level remains a challenge in clinical practice. The majority of studies in Africa have shown that less than a third of patients achieve treatment goals.[8] Generally, four main factors have been identified that influence achieving controlled BP. First, there are factors intrinsic to the nature of the disease; in most cases hypertension is initially asymptomatic and this delays early prevention, diagnosis, and treatment.[9] Second, poor treatment response may be due to patient-related factors such as age, gender, race, awareness, and compliance to medication.[4,10] Third, there are healthcare system-related factors such as lack of effective hypertension prevention and treatment programs, and access to medications. Fourth, prescriber behavior, competences, and large patient-to-prescriber ratio affect hypertension prevention and

treatment outcomes. The majority of these factors have been extensively studied in western societies; however, little is known of their impact on BP control in developing nations. Some of these factors may be unique to, or more pronounced in the African setting, including low societal awareness, priority to fight infectious diseases, and human resource limitations, in particular the number of available healthcare professionals.[6,11]

Prevention and treatment strategies have been shown to be effective in optimizing BP control in the western world.[12] Such programs may be relevant for the African setting. In order to guide targeted interventions studies, identifying factors contributing to poor BP control in the African setting are urgently needed. Studies on hypertension conducted to date in Ethiopia, the second most populous country (approximately 100 million) in Africa, have focused on determining prevalence of the disease.[13-15] Prevalence is relatively low (10 – 30%), [1,13-15], but further data on hypertension treatment practices are lacking.[16,17] Therefore, we aimed to assess the proportion of patients treated for hypertension who had controlled BP and identify determinants for achieving BP control in an Ethiopian setting. Additionally, we aimed to study whether treatment was intensified in those patients with uncontrolled BP and identify the determinants for treatment intensification.

METHODS

Study design and setting

This retrospective cohort study was conducted in outpatient clinics of six public hospitals in Addis Ababa (capital city) and Tigray regional state, Ethiopia. We included two specialized hospitals (Addis Ababa), and four general hospitals, three from Tigray and one from Addis Ababa. Specialized (tertiary) hospitals are at the top tier of Ethiopian public healthcare system and serve approximately five million people. The general (secondary) hospitals are estimated to serve 1-1.5 million people. Furthermore, patients including those with hypertension are usually treated first at a primary healthcare center.[18]

Study population

Participants were approached while waiting for their appointment in the waiting area of hypertension outpatient clinics, where known hypertensive patients come for regular follow-up visits. Participants were recruited consecutively after giving consent. Hypertensive patients aged 18 years or older were included, if they had at least one previous antihypertensive medication prescription in the same hospital, and gave informed consent. Patients were identified based on self-reported hypertension or based on a mark on their pocket-size appointment card as being hypertensive. We verified in each clinic log-book (if available) and from individual patient medical records if patients met the inclusion criteria as they had indicated during the interviews.

Routine practice in the study hospitals is that nurses measure the patient's blood pressure and assign the patient to a physician. The physician then performs a consultation, confirms the hypertension diagnosis, if necessary performs further examinations including rechecking BP, and renews or amends prescribed medication. Patients then collect their medicine from pharmacy outlets at the same hospital or from private or community pharmacies.

Data collection

Included patients were interviewed in the waiting area before they were seen by the physician. Data collected via interview included socio demographics, medication adherence, and duration of antihypertensive treatment with medication. The socio demographics variables were age, sex, educational and marital status, alcohol use, and smoking habits. Clinical information retrieved from medical records were BP measurements, medication prescriptions, and comorbid illnesses, and information was retrieved for the *current visit* and the previous (*prior) visit.* Data were collected by professional nurses or pharmacists who were trained in using a dedicated case-report form. Data were collected between February and August 2015.

Variables

Outcome measures

We defined two *outcome measures*. First, for *BP control* we used the 'standard' definition of controlled BP, i.e., systolic BP/diastolic BP below 140/90 mm Hg at the current visit.[12] Second, we defined *treatment intensification* as an increase in dose of an antihypertensive drug and/or addition of one or more antihypertensive drug(s). Treatment intensification was calculated for those patients who had a complete medication history (including dose and administration frequency) at both current and prior visits and whose BP was not controlled at the current visit. A switch in drug class was not considered as treatment intensification.

Explanatory variables

For determinants of BP control or treatment intensification, we included socio demographic variables (age in year, gender, smoking history, alcohol use, marital status, and educational status), hospital type (general versus specialized), cardiometabolic comorbid illnesses (diabetes mellitus (DM), dyslipidemia, kidney disease, heart failure/myocardial infarction), uncontrolled BP (≥140/90 mm Hg) at the prior visit, duration of antihypertensive treatment in years, treatment adherence with the

eight-point Morisky Medication adherence scale, MMAS-8 (≥ 7: yes/no), visit schedule in month, and antihypertensive medications prescribed at the prior visit. For alcohol use and smoking habit, participants were asked if they were active smokers or consume alcohol up to our survey date, i.e smoking history (Yes: current smokers, and No: never smoke or ex-smoker), alcohol use (Yes: regularly or sometimes, and No: never consume alcohol). The visit schedule was calculated by taking the difference in days between the current and prior visits divided by 30, i.e., indicating the length of time (duration) between the two follow-up visit expressed in months.

Antihypertensive medication adherence was measured with the eight-point Morisky Medication adherence scale (MMAS-8), which has been previously validated for hypertensive patients.[19,20] The items of the scale are grouped into three aspects. The first aspect is about sometimes forgetting or intentionally not taking prescribed medication (item 1), and more specifically in the past two weeks (item 2), or under special circumstances during travel/leaving home (item 4), and finally asking if medication was taken yesterday (item 5). The second aspect is about intentionally stopping or cutting back medication because of feeling worse (item 3) or because of a feeling that BP is under control (item 6). The last aspect relates to convenience (item 7) or inconvenience frequency of difficult times to take medication (item 8). The scale was translated into two Ethiopian languages (Amharic and Tigrigna) according to the method described by Beaton *et al.*[21] A total score of seven or more (maximum eight) was considered to be adherent to antihypertensive medication; i.e., MMAS ≥ 7.[19] For a sensitivity analyses, we used a lower level of adherence with a cut-off of MMAS ≥ 6.

Sample size

Achieved sample size was based on an estimated 30% prevalence of controlled BP among treated hypertensive patients in Ethiopia [8,15] and a single proportion sample size calculation formula. The total sample size was 984 (164 per hospital) with 0.80 power, 95% confidence interval, 3% margin of error, and an estimated 10% none response rate, or incomplete/irretrievable patient records.

Statistical analyses

Descriptive statistics were used to summarize socio demographic, disease characteristics of the study population, and nature and frequency of antihypertensive medications used. Multivariable logistic regression analyses were applied to investigate determinants for achieving target BP at current visit and determinants for treatment intensification. Statistical significance was considered at p value < 0.05. Potential determinants with p < 0.2 in bivariable analyses were included into the multivariable logistic model. Microsoft access 10 and SPSS version 22.0 statistical software was used for data entry and analyses, respectively.

Sensitivity analyses

We performed five sensitivity analyses. First, tighter BP targets at the current visit (BP <130/80 mm Hg) were applied for those patients with diabetes mellitus (DM) and/or renal disease. Standard BP target (BP < 140/90 mm Hg) was used for all others participants. Second, we performed a sensitivity analysis for the main outcome measure (controlled BP < 140/90) using a different cut off for adherence (MMAS ≥ 6). Third (for controlled BP) and fourth (for treatment intensification) sensitivity analysis were similar to the main analysis with three modified determinants. Graded hypertension (prior BP) was performed according to the stages defined by the Ethiopian standard treatment guideline for hypertension: normal BP (systolic BP < 120 and DBP < 80 mm Hg), pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89 mm Hg), stage-I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm Hg), and stage-II hypertension (systolic BP ≥ 160 or diastolic BP ≥ 100 mm Hg).[22] These analysis also included the number of cardiometabolic comorbid illnesses as a proxy measure for more severely ill patients and age categorized in to five groups. Patients with higher hypertension stages and multiple comorbid illness were hypothesized to be more difficult to treat. A fifth sensitivity analysis was performed in patients who had been on medication for at least six months, assuming that these patients were no longer in the initial careful up-titration phase.

Ethics approval

This study was approved by Ethiopian Health Research Ethical Review Committees of (i) the College of Health Sciences, Mekelle University, (ii) St Paul's Hospital Millennium Medical College, and (iii) the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University. All individual participants included in this study consented to participation.

RESULTS

We were able to approach 968 patients at six public hospitals in Ethiopia. Seventy-one patients were excluded from our analyses: eight refused to participate, six were not hypertensive, and 57 patients had no retrievable records or incomplete records (missing BP at current visit). This resulted in a study population of 897 patients (Figure 1). The majority of included patients (93%) reported to have come for their regular hypertension follow-up visit. The remaining 7% had (perceived) symptoms, uncontrolled hypertension, or adverse events. The mean (SD) patient age was 57 (14) years, 63% of patients were female, most patients (65%) were married, and 64% had no formal education or only attended primary school. Almost all (94%) had never smoked, and nearly half (43%) consumed alcohol regularly or occasionally (Table 1). At the current visit, 35% study participants had at least one recorded comorbid illness, predominantly DM (Table 1).

Table 1 Characteristics of ambulatory hypertensive patients at two visits, Ethiopia

Characteristics	Current visit	Prior visit
Demographics		
Age (mean, SD), Year	57 (14)	
Female (n, %)	551 (63)	
Smoking [current smoker] (n, %)	57 (6)	
Alcohol use [regularly or sometimes] (n, %)	378 (43)	
Married (n, %)	567 (65)	
Education (n, %)		
University/college education	170 (20)	
Secondary education	141 (16)	
Primary or no formal education	557 (64)	
Setting		
Specialized hospitals: both from Addis Ababa (n, %)		
Tikur Anbessa Hospital	139 (16)	
St. Paul's Hospital	153 (17)	
General hospitals: all from Tigray, except Yekatit 12 from Addis Ababa (n, %)		
St. Mary Axum Hospital	139 (16)	
Mekelle Hospital	152 (17)	
Lemlem Karl Maychew Hospital	155 (17)	
Yekatit 12 Hospital	159 (18)	
Disease characteristics		
Blood pressure (BP)		
Systolic BP (Mean, SD)	139 (21)	144 (22)
Diastolic BP (Mean, SD)	84 (11)	85 (13)
Controlled BP (<140/90 mm Hg) (n, %)	335 (37)	231 (27)
Controlled BP (<130/80 mm Hg with DM &/or kidney diseases, [#]otherwise <140/90 mm Hg) (n, %)	268 (30)	202 (24)
Cardiometabolic comorbid illnesses (n, %)		
Diabetes Mellitus	227 (25)	198 (22)
Dyslipidemia	57 (6)	45 (5)
Renal diseases	25 (3)	23 (3)
Heart failure / myocardial infarction	72 (8)	60 (7)
Antihypertensive treatment characteristics		
Drug class (n, %)		
ACE inhibitors	503 (56)	494 (55)
Enalapril	499 (56)	492 (55)
Lisinopril or captopril	4 (0.4)	2 (0.2)
Beta blockers	167 (19)	166 (19)
Atenolol	148 (17)	147 (16)
Propranolol, metoprolol or carvedilol	19 (2)	19 (2)
Calcium channel blockers	449 (50)	439 (49)
Nifedipine	381 (43)	389 (43)
Amlodipine or felodipine	68 (8)	50 (6)
Diuretics [¥]	498 (56)	486 (54)
Hydrochlorothiazide	428 (48)	421 (47)
Furosemide	76 (9)	71 (8)
Spironolactone	72 (8)	66 (7)
Others (methyldopa, nitrates or losartan)	19 (2)	13 (1)
Duration of therapy years (Median, interquartile rang)	4 (7)	
Visit schedule in months (mean, SD)	2.3 (2.0)	
Adherence (MMAS ≥ 7) (n, %)	355 (40)	
Therapy (n, %)		
Monotherapy	*343 (38)*	*363 (41)*
Multidrug therapy	*550 (62)*	*521 (59)*
Treatment intensified in patients with uncontrolled BP at current visit (n=540) * (n, %)	123 (23)	

Mono/Multidrug therapy is limited to antihypertensive medications. *For 22 of 562 patients with uncontrolled BP at the current visit the medication history was not complete. Treatment intensification could thus only be calculated for 540 patients. [¥] Some patients had more than one type of diuretics. [#]otherwise: hypertensive patients without DM or kidney disease.

Thirty-seven percent (n = 335) of the participants had controlled BP at the current visit (Table 1). Applying the stricter BP target for patients with DM and/or renal disease (BP<130/80 mm Hg), the proportion of patients with controlled BP dropped to 27% (n = 231).

Only 23% of 540 patients with uncontrolled BP and complete medication history had their treatment intensified (Table 1). For 22 (4%) of 562 patients with uncontrolled BP at the current visit, the medication history was not complete. Either the dose and/or administration frequency were missing. The antihypertensive medication adherence rate (MMAS ≥ 7) was 40%, (Table 1), and 57% for the lower cut off, MMAS ≥ 6 (Supplement Table 1).

Overall, angiotensin-converting-enzyme (ACE) inhibitors were the most commonly prescribed group of drugs (n = 503), followed by diuretics (n = 498) (Table 1). Medication use was quite similar on both visits. At the current visit 62% of included patients were prescribed a multidrug treatment regimen and 45% patients took two antihypertensive agents (Supplement Table 2). Most (38 %) of the 343 patients on monotherapy were prescribed diuretics (n = 127).

Determinants of BP Control

BP <140/90 mm Hg (primary analysis)

According to our multivariable logistic regression model (Table 2), factors significantly associated with achieving target BP at the current visit were age (OR 0.99 [95% CI: 0.98; 1.00]), follow-up at general hospitals (OR 1.89 [95% CI: 1.26; 2.83]), inadequately controlled BP at prior visit (OR 0.30 [95% CI: 0.21; 0.43]), longer treatment duration per year (OR 1.04 [95% CI: 1.01; 1.06]), and prescribed diuretics (OR 0.68 [95% CI: 0.50; 0.94]).

Table 2 Determinants of achieving target BP (BP < 140/90) at current visit in ambulatory hypertension patients

Variables		Controlled BP		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), year		58 (13)	56 (15)	#0.99 [0.98; 1.00]	***0.988 [0.976; 0.997]**
Gender (n, %)	Male	219 (67)	109 (33)	Ref	
	Female	331 (60)	220 (40)	*1.34 [1.00; 1.78]	1.12 [0.80; 1.55]
Smoking (n, %)	No	514 (62)	312 (38)	Ref	
	Yes	37 (65)	20 (35)	0.89 [0.51; 1.56]	
Alcohol use (n, %)	No	310 (63)	184 (37)	Ref	
	Yes	232 (61)	146 (39)	1.06 [0.81; 1.40]	
Marital status (n, %)	Single	187 (60)	124 (40)	Ref	
	Married	359 (63)	208 (37)	0.87 [0.66; 1.16]	
Educational status (n, %)	College/University	110 (65)	60 (35)	Ref	
	Secondary	86 (61)	55 (39)	1.17 [0.74; 1.86]	
	Primary /not formal	345 (62)	212 (38)	1.13 [0.79; 1.61]	
Hospital type (n, %)	Specialized	199 (68)	93 (32)	Ref	
	General	363 (60)	242 (40)	*1.43 [1.06; 1.92]	***1.89 [1.26; 2.83]**
Disease characteristics (n, %)					
Diabetes Mellitus	No	413 (62)	257 (38)	Ref	
	Yes	149 (66)	78 (34)	0.84 [0.61; 1.15]	
Dyslipidemia	No	523 (62)	317 (38)	Ref	
	Yes	39 (68)	18 (32)	0.76 [0.43; 1.35]	
Renal disease	No	542 (62)	330 (38)	Reference	
	Yes	20 (80)	5 (20)	#0.41 [0.15; 1.10]	0.58 [0.19; 1.71]
Heart failure/ MI	No	518 (63)	307 (37)	Ref	
	Yes	44 (61)	28 (39)	1.07 [0.66; 1.76]	
Controlled BP at prior visit	No	424 (68)	199 (32)	*0.37 [0.27; 0.51]	***0.30 [0.21; 0.43]**
	Yes	102 (44)	129 (56)	Ref	
Antihypertensive Treatment characteristics					
Duration of therapy, years (mean, SD)		6.2 (6.4)	7. 4 (8.3)	#1.02 [1.00; 1.04]	***1.04 [1.01; 1.06]**
Adherent (MMAS ≥ 7) (n, %)	No	319 (60)	212 (40)	Ref	
	Yes	233 (66)	122 (34)	#0.79 [0.60; 1.04]	0.80 [0.58; 1.09]
Revisit schedule in months (Mean, SD)		2.2 (1.4)	2.0 (1.2)	*0.89 [0.82 ;0.97]	0.91 [0.82; 1.02]
Therapy at prior visit (n, %)	Monotherapy	225 (62)	138 (38)	Ref	
	Multidrug	326 (63)	195 (37)	0.98 [0.74; 1.29]	
Antihypertensive medications at prior visit					
ACE inhibitors (n, %)	No	259 (64)	144 (36)	Ref	
	Yes	303 (61)	191 (39)	1.13 [0.86; 1.49]	
Beta blockers (n, %)	No	472 (65)	259 (35)	Ref	
	Yes	90 (54)	76 (46)	*1.54 [1.09; 2.16]	1.42 [0.95; 2.10]
Calcium channel blockers (n, %)	No	290 (63)	168 (37)	Ref	
	Yes	272 (62)	167 (38)	1.06 [0.81 ;1.39]	
Diuretics (n, %)	No	243 (59)	168 (41)	Reference	
	Yes	319 (66)	167 (34)	*0.76 [0.58; 0.99]	***0.68 [0.50; 0.94]**

Only patients with available data were included in the analyses, therefore numbers may sometimes differ from Table 1. Percentages are calculated per a row. Statistically significant values: *p< 0.05 at 95% CI. Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in the multivariable model. Mono/Multidrug therapy was for antihypertensive medications.

Determinant of treatment intensification

The only statistically significant determinant for treatment intensification in the multivariable analyses was longer treatment duration (OR 1.05 [95% CI: 1.02; 1.09]) (Table 3).

Sensitivity (secondary) analysis

In our first sensitivity analyses, using BP <130/80 mm Hg for patients with DM and/or renal disease, and for all other patients <140/90 mm Hg as cut-offs, uncontrolled BP at the prior visit had a negative effect on achieving target BP at the current visit (OR 0.25 [95% CI: 0.17; 0.37]). Medications prescribed during the prior visit, except diuretics (OR 0.60 [95% CI: 0.40; 0.90]), were not significantly associated with achieving controlled BP at the current visit. Unlike the primary analyses, age, treatment duration, and hospital type did not show statistically significant effects on current visit BP status (Supplement Table 3).

In the sensitivity analyses for BP control (Supplement Table 4) and treatment intensification (Supplement Table 5), the results were mostly similar with the main analysis (Table 2 and 3, respectively). As expected, more severe hypertension stage was associated with more difficulty to achieve target BP: stage-II hypertension (OR 0.17 [95% CI 0.09;0.35]), and stage-I hypertension (OR 0.34 [95% CI 0.17;0.67]). However, the number of comorbid illness was not a significant determinant of achieving target BP. In case of age, older age groups were less likely to achieve target BP than younger age groups (< 35 years): 55-64 years old (OR 0.41 [95% CI 0.20; 0.83]) and ≥ 65 years old (OR 0.46 [95 CI: 0.22;0.93]). Supplementary analysis for treatment intensification (Supplement Table 5) gave similar results with main analysis on Table 3, where only duration of therapy was a significant determinant (OR 1.05 [95% CI: 1.02; 1.08]) for more treatment intensification. The majority (94%) of participants had been on medication for at least for six months. Exclusion of the 6% of patients who had recently started therapy (< 6 months ago) in the sensitivity analysis (Supplement Table 6) did not

change our findings reported in Table 2. The proportion of patients with controlled BP 303 (39%) remained similar as well. Duration of therapy remained a significant determinant for achieving target BP and for intensifying treatment.

Table 3 Treatment intensification determinants for ambulatory hypertension patients with uncontrolled BP at current visit

Variables		Treatment intensified		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), Year		57 (13)	60 (13)	#1.02 [1.00; 1.03]	1.02 [1.00; 1.04]
Gender (n, %)	Male	167 (80)	41 (20)	Ref	
	Female	241 (75)	80 (25)	#1.35 [0.88; 2.07]	1.47 [0.91; 2.37]
Smoking (n, %)	No	383 (77)	113 (23)	Ref	
	Yes	27 (79)	7 (21)	0.88 [0.37; 2.07]	
Alcohol use (n, %)	No	225 (76)	73 (25)	Ref	
	Yes	180 (80)	44 (20)	0.75 [0.49; 1.15]	
Marital status (n, %)	Single	138 (77)	42 (23)	Ref	
	Married	269 (78)	76 (22)	0.93 [0.60; 1.43]	
Educational status (n, %)	College/University	82 (78)	23 (22)	Ref	
	Secondary	58 (70)	25 (30)	1.54 [0.80; 2.97]	
	Primary /not formal education	262 (79)	70 (21)	0.95 [0.56; 1.62]	
Hospital type (n, %)	Specialized	137 (73)	51 (27)	Ref	
	General	280 (80)	72 (21)	#0.69 [0.46; 1.04]	0.83 [0.51; 1.37]
Disease characteristics (n, %)					
Diabetes Mellitus at current visit	No	311 (79)	84 (21)	Ref	
	Yes	106 (73)	39 (27)	#1.36 [0.88; 2.11]	1.10 [0.67; 1.81]
Dyslipidemia at current visit	No	388 (77)	113 (23)	Reference	
	Yes	29 (74)	10 (26)	1.19 [0.56; 2.50]	
Renal disease at current visit	No	403 (77)	118 (23)	Ref	
	Yes	14 (74)	5 (26)	1.22 [0.43; 3.45]	
Heart Failure / MI at current visit	No	384 (77)	112 (23)	Ref	
	Yes	33 (75)	11 (25)	1.14 [0.56; 2.33]	
Controlled BP at prior visit	No	312 (77)	96 (24)	#1.50 [0.85; 2.66]	1.38 [0.76; 2.50]
	Yes	83 (83)	17 (17)	Ref	
Antihypertensive treatment characteristics					
Duration of therapy yrs (mean SD)		5.7 (4.1)	8.1 (7.4)	*1.05 [1.02; 1.08]	***1.05 [1.02; 1.09]**
Adherence (MMAS ≥ 7) (n, %)	No	232 (76)	73 (24)	Ref	
	Yes	178 (78)	49 (22)	0.88 [0.58; 1.32]	
Therapy at prior visit (n, %)	Monotherapy	168 (76)	53 (24)	Ref	
	Multidrug therapy	249 (78)	70 (22)	0.89 [0.59; 1.34]	

Statistically significant values: *p < 0.05 at 95% CI. Variable with #p < 0.2 or *p < 0.05 in the bivariable model were included in the multivariable model. Percentages are calculated per row. Treatment intensification was calculated for 540 patients who had complete medication history (including dose and frequency) on both visits and uncontrolled BP at current visit.

DISCUSSION

In this study, nearly two-thirds of patients on antihypertensive medication had uncontrolled BP. Drugs were prescribed from four antihypertensive drug classes, ACE-inhibitors, diuretics, calcium channel blockers, and beta blockers. Generally, a single specific agent (over 90%) was prescribed within a class, enalapril, hydrochlorothiazide, nifedipine, and atenolol, respectively. Age of patients, uncontrolled BP at the prior visit, and a treatment regimen containing diuretics contributed to poorer BP control. Follow-up in a general hospital compared to a specialized hospital and longer treatment duration were associated with a better BP control. Duration of therapy on antihypertensive medication was the only, albeit modestly, significant contributing factor of treatment intensification (also for achieving target BP).

When looking at other studies on hypertension awareness, treatment and control in Africa, 41 out of 44 studies showed a lower proportion of patients with controlled BP (these studies reported levels of control ranging from <1% to 33%) than our study.[8] The reported wide variation could be explained by population differences and variation in study set-ups. The level of BP control in our study was between that reported in two studies performed in a Southern Ethiopian hospital.[16,23] Gudina *et al.* studied the prevalence of hypertension among patients visiting a hospital for any reason, and of patients with known hypertension, 44% were controlled.[23] In the other study, 50% of patients had achieved their target BP.*[16].* This study was more of similar to ours; patients were included who visited an outpatient hypertension clinic and who had been treated for at least 12 months in the study hospital.[16] Unfortunately, information on duration of the therapy was not included in these studies.[16,23] In comparison with studies from western countries, the percentages of patients with adequately controlled BP and those who received treatment intensification were lower in our study than in North American countries, but similar to some European countries.[24,25] These differences may be explained in part by different national guidelines recommendations.

However, as reported elsewhere, it is not only differences between guidelines, but also how much effort countries put in implementation of these recommendations.[25] While the Ethiopian guideline is similar to the USA guidelines,[22,24] possible differences in implementation, due to African factors including resource limitations, low priority for non-communicable diseases, and healthcare providers' behavior and skills may in part explain the low level of BP control.[26] However, comparing our results with population-based studies in western countries or those in other parts of Africa should be done with caution as we investigated two regional Ethiopian hypertensive populations treated at a hospital setting only.

In our study, one of the determinants for achieving target BP was the healthcare setting. Patients who are referred to specialized hospitals may be more complex – in terms of comorbidities or severity of hypertension. Numerically, patients received more treatment intensification at specialized hospitals (27%) than at generalized hospitals (21%), although these differences were not significant in our bi-and multivariable analyses (Table 3). Thus, the additional effort provided in these specialized hospitals may have not been sufficient to offset the difficulties in achieving BP control in the more complex patient population. Younger age was another significant determinant for achieving target BP. Prescribers in our study may have accepted higher BP in older patients, possibly because of tolerability or perceived lack of need for tight BP control. Recent evidence, however, suggests that ''the lower is the better'', also in older patients.[27,28] Nevertheless, guidelines lack consistency on BP targets for the elderly,[29] especially when patients are frail and doctors may not aim for tight BP control. Another determinant of BP control was the type of medication prescribed. Most of our study participants received diuretics, the first line antihypertensive agents. We have no data in which order medication was initiated. Therefore, we can only speculate why treatment regimens containing these drugs did not show better BP control. Since three-quarters of diuretics-containing regimens in our

study existed of two drugs only (Supplement Table 2), patients may need additional antihypertensive therapy.

Only one fifth of patients with uncontrolled BP at the current visit had their treatment intensified. Longer treatment duration was the only statistically significant determinant for intensification. Possibly, it took some while before prescribers could intensify treatment. Ultimately, the lack of BP control at the prior visit was the strongest predictor of patients not having controlled BP at current visit. This seems to suggest some level of 'clinical inertia', where doctors are slow to respond to clinical parameters. This practice indicates a need to intensify therapy. Indeed, a lack of achieving BP control may also be explained by true therapy resistant hypertension (although only 17% of patients received three or more antihypertensive agents at the prior visit).[30-33] Moreover, prescribers may not intensify treatment if they suspect that increased BP levels may be related to a suspected or reported poor compliance for a particular patient. (Poor) medication adherence is known as an important determinant for controlling hypertension.[34] The level of adherence we observed (40% and 57% for MMAS-8 with a cut-off at > 6 and ≥ 6 respectively) was close to that reported by Asgedom *et al.* (35% and 61% respectively).[16] Two other Ethiopian studies reported low levels of adherence, although more difficult to compare as they used a 4-point MMAS.[35, 36] Surprisingly, the level of adherence was not associated with BP control in our main and sensitivity analyses (Supplement Table 1). Similarly in the study by Asgedom *et al.,* a hospital-based study in Southern Ethiopia, no relation with adherence and BP control was observed.[16] Self-reported medication adherence may be overestimated and therefore lead to bias.

We found that more hypertensive women than men were included in our study, and that few patients smoked. Our study was not a population study designed to evaluate prevalence of hypertension, and the reason why more women were included could have been that women seek more care than men. Although a recent community-based study evaluating prevalence of

hypertension in Ethiopia suggested more women were hypertensive than men,[13] a meta-analysis including hospital-based studies [15] and another recent hospital-based study reported a higher prevalence of males with hypertension.[16] The higher prevalence of women in our study does not appear to have a strong impact on our study findings, as gender was not a significant determinant for BP control BP or treatment intensification.

Poor hypertension control should be addressed in a holistic approach that includes lifestyle modification and management of comorbid illnesses. Our study was largely performed in urban areas with the highest prevalence of hypertension in Ethiopia, likely attributed to adoption of a Western lifestyle.[15] Still, our patient population looks very different from that in European or USA studies, i.e., few smokers and few patients with (known) cardiometabolic comorbidities.

Strengths and limitations

As far as we are aware, this was the first study of its kind in Ethiopia covering a relatively diverse population. Our data included patients from hypertension outpatient clinics of six public hospitals in the capital city and northern region of Ethiopia.

A limitation of our study was the validity of the BP measure used. We analysed BP measurements as recorded in patients' medical records that reflected actual clinical practice, but these values may be subject to recording and measurement error. It is not clear how prescribers considered measurement variability or if any attempt was made to avoid ''white-coat'' hypertension, e.g., by repeating BP measurement. Still, many observational studies use medical records – with data collected in routine practice – as a data source. Future studies may consider using standardized assessment of BP. In our study, the level of BP control was assessed for two consecutive visits only. Follow-up at more visits may still be needed, as achieving BP control may require more time, and would thus provide a better understanding of doctors truly being slow to intensify treatment.

Another limitation is that medical records did not include extensive or well-structured patient information. For example, comorbidities may be underreported. For this reason, we limited evaluated comorbidities to cardiometabolic diseases as these are relevant to hypertension prognosis and treatment and are more likely to have been recorded in the charts. We did not study if prescribing was in line with guideline recommendations, e.g., based on comorbidities, but focused instead on the actual impact of prescribing on BP. This study focused on public secondary and specialized hospitals; therefore, the results may not be generalizable to other settings such as private practices and primary health care centers. Differences in socio economic status did not seem related with type of drug prescribed. This may have affected redeeming prescriptions at the pharmacy, but we did not have that information. We did not query patients for economic reasons of non-compliance, e.g. if they could afford their medication or that they needed to travel too far to collect medication. We used the validated MMAS-8 questionnaire and did not want to overburden patients further. Nevertheless, educational status – a proxy for socio economic status – in our study population was not related to BP control.

Finally, as in all studies we were not able to include all previously reported potential confounders for achieving BP control [35]. For example, type of prescriber (was difficult to retrieve from medication charts), or medication counseling and patient's own knowledge of hypertension and treatment goals (would have required further interview time) may require further study.

CONCLUSION

Nearly two-thirds of patients on antihypertensive medication did not achieve target BP during routine clinical follow-up, and only a quarter of these patients with uncontrolled BP received treatment intensification. To improve care for patients visiting Ethiopian hospital hypertension clinics, focus should be on older patients, and interventions may be needed for specialized centers.

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Contribution

D.F. Berhe, K. Taxis and P.GM Mol designed and performed the research, analyzed, and interpreted the data. F.M. Haaijer-Ruskamp, A. Mulugeta, and Y.T. Mengistu designed the study. All authors participated in writing the manuscript, also read and approved the final version.

Conflict of Interest: There are no competing interests to declare.

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Data sharing statement

No additional data are available for this specific study.

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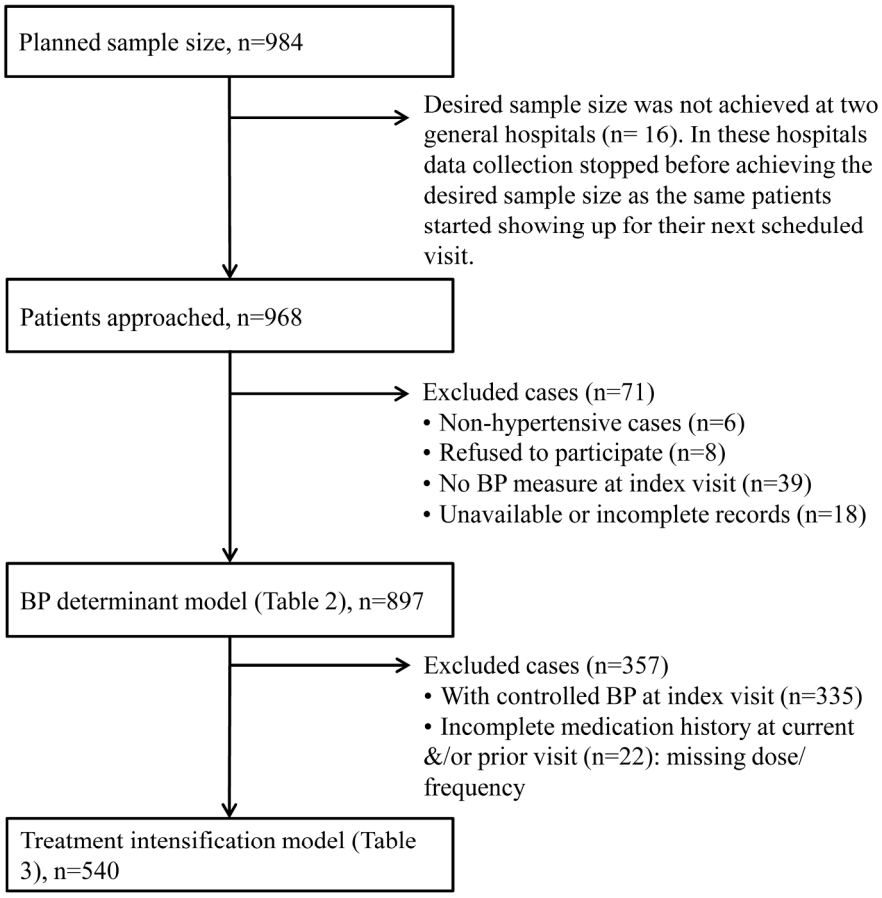
Figure legend

Figure 1 Flow chart for case inclusion for analysis

Figure 1



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HYPERTENSION TREATMENT PRACTICES AND ITS DETERMINANTS AMONG AMBULATORY PATIENTS:

A RETROSPECTIVE COHORT STUDY IN ETHIOPIA

Supplement Table 1 Determinants of achieving target BP (BP < 140/90) at index visit ambulatory hypertension patients (sensitivity analysis with adherence definition of MMAS ≥ 6)

Variables		Controlled BP		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
		No	Yes		
Demographics					
Age (mean, SD), year		58 (13)	56 (15)	#0.99 [0.98; 1.00]	*0.99 [0.98; 1.00]
Gender (n, %)	Male	219 (67)	109 (33)	Ref	
	Female	331 (60)	220 (40)	#1.34 [1.00; 1.78]	1.12 [0.81; 1.55]
Hospital type (n, %)	Specialized	199 (68)	93 (32)	Ref	
	General	363 (60)	242 (40)	*1.43 [1.06; 1.92]	*1.88 [1.25; 2.81]
Disease characteristics at index visit (n, %)					
Renal disease	No	542 (62)	330 (38)	Reference	
	Yes	20 (80)	5 (20)	#0.41 [0.15; 1.10]	0.60 [0.20; 1.79]
Controlled BP at **prior visit**	No	424 (68)	199 (32)	*0.37 [0.27; 0.51]	*0.30 [0.21; 0.43]
	Yes	102 (44)	129 (56)	Ref	
Antihypertensive Treatment characteristics					
Duration of therapy, years (mean, SD)		6.2(6.4)	7. 4 (8.3)	#1.02 [1.00; 1.04]	*1.04 [1.02; 1.06]
Adherent (MMAS ≥ 6) (n, %)	No	237 (63)	140 (37)	Ref	
	Yes	315 (62)	194 (38)	1.04 [0.79; 1.37]	1.14 [0.83; 1.56]
Revisit schedule in months (Mean,		2.2 (1.4)	2.0 (1.2)	*0.89 [0.82 ;0.97]	0.91 [0.82; 1.02]
Beta blockers (n, %)	No	472 (65)	259 (35)	Ref	
	Yes	90 (54)	76 (46)	*1.54 [1.09; 2.16]	1.45 [0.98; 2.15]
Diuretics (n, %)	No	243 (59)	168 (41)	Reference	
	Yes	319 (66)	167 (34)	*0.76 [0.58; 0.99]	*0.68 [0.50; 0.94]

Variables with #p < 0.20 or *p< 0.05 in the bivariable model were included in this multivariable model (sensitivity analysis).

Supplement Table 2 Prescribed antihypertensive medication(s) in the study population

Drug prescribed per case	At Index visit (n≠ = 887), %	At Prior visit (n≠ = 882), %
D (Diuretics)	14.3	15.0
C (CCBs)	13.0	13.7
A (ACE inhibitors)	9.9	11.0
B (BBs)	0.8	1.4
D + C	9.4	8.6
D + A	17.0	16.6
C + A	11.5	10.2
A + B	2.6	2.4
C + B	2.4	2.7
D + B	2.0	1.5
D + C + B	1.5	1.1
D+ C + A	6.1	6.1
A + C + B	3.7	3.5
D + A + B	2.7	2.5
D + A + B + C	3.2	3.7

CCBs, calcium channel blockers; ACE, Angiotensinogen Converting Enzyme; BBs; Beta Blockers

≠The table did not include rarely used medication categories. These drugs were methyldopa, losartan, hydralazine, and nitrates and in combination with others or as a monotherapy.

Supplement Table 3 Sensitivity analyses: determinants for controlled hypertension at alternative BP target (BP < 130/80 mm Hg) for patients with DM and/or renal disease, and all other patients BP < 140/90 mm Hg)

Variables		Controlled BP		Bivariable OR [95% CI]	Multivariable OR [95% CI]
		No	Yes		
Demographics					
Age (mean. SD)		58 (13)	56 (15)	#0.99 [0.98; 1;00]	0.99 [0.98; 1.00]
Gender (n, %)	Male	244 (74)	84 (26)	Ref	
	Female	373 (68)	178 (32)	*1.39 [1.02; 1.88]	1.30 [0.87; 1.95]
Smoking (n, %)	No	572 (69)	254 (31)	Ref	
	Yes	45 (79)	12 (21)	#0.60 [0.31; 1.16]	1.05 [0.50; 2.24]
Alcohol use (n, %)	No	354 (72)	140 (28)	Ref	
	Yes	254 (67)	124 (33)	#1.23 [0.92; 1.65]	1.54 [1.07; 2.21]
Marital status (n, %)	Single	207 (67)	104 (33)	Ref	
	Married	406 (72)	161 (28)	#0.79 [0.59; 1.06]	0.82 [0.56; 1.18]
Educational status (n, %)	College/University	123 (72)	47 (28)	Ref	
	Secondary	103 (73)	38 (27)	1.21 [0.83; 1.77]	
	Primary /not formal	381 (68)	176 (32)	0.97 [0.59; 1.59]	
Hospital type (n, %)	Specialized	217 (74)	75 (26)	Ref	
	General	412 (68)	193 (32)	1.36 [0.99; 1.85]	1.17 [0.75; 1.82]
Disease characteristics (n, %)					
Dyslipidemia at index visit	No	583 (69)	257(31)	Ref	
	Yes	46 (81)	11 (19)	#0.54 [0.28; 1.06]	0.47 [0.20; 1.10]
Heart Failure / MI at index visit	No	578 (70)	247 (30)	Ref	
	Yes	51 (71)	21 (29)	0.96 [0.57; 1.64]	
Controlled BP at prior visit	No	501 (77)	151 (23)	*0.25 [0.18; 0.35]	*0.25 [0.17; 0.37]
	Yes	92 (46)	110 (55)	Ref	
Antihypertensive treatment characteristics					
Duration of therapy years (mean, SD)		7.0 (7.3)	5.8 (6.9)	#0.98 [0.96; 1.00]	0.99 [0.97; 1.02]
Adherence (MMAS-8 ≥ 7) (n, %)	No	373 (70)	158 (29)	Ref	
	Yes	246 (69)	109 (31)	1.04 [0.78; 1.40]	
Revisit schedule in months (Mean, SD)		2.4 (2.1)	2.0 (1.2)	*0.88 [0.81; 0.97]	0.94 [0.84; 1.06]
Therapy at prior visit (n, %)	Monotherapy	240 (66)	123 (34)	Ref	
	Multidrug therapy	378 (73)	143 (27)	*0.74 [0.55; 0.99]	1.02 [0.69; 1.51]
Antihypertensive medications at prior visit					
ACE inhibitors (n, %)	No	274 (68)	129 (32)	Ref	
	Yes	355 (72)	139 (28)	0.83 [0.62; 1.11]	
Beta blockers (n, %)	No	511 (70)	220 (30)	Ref	
	Yes	118 (71)	48 (29)	0.95 [0.65; 1.37]	
Calcium channel blockers (n, %)	No	312 (68)	146 (32)	Ref	
	Yes	317 (72)	122 (28)	#0.82 [0.62; 1.10]	0.88 [0.59; 1.31]
Diuretics (n, %)	No	276 (67)	135 (33)	Ref	
	Yes	353 (73)	133 (27)	#0.77 [0.58; 1.03]	*0.60 [0.40; 0.90]

Supplement Table 4 Determinants of achieving target BP (BP < 140/90) at index visit in ambulatory hypertensive patients

Variables		Odds ratio at 95% CI	
		Bivariable estimates	Multivariable estimate
Demographics			
Age [year]			
< 35		Ref	
35-44		0.56 [0.27; 1.18]	0.51 [0.24; 1.10]
45-54		0.51 [0.25; 1.03]	0.53 [0.26; 1.10]
55-64		0.40 [0.20; 0.80]	0.41 [0.20; 0.83]
≥ 65		0.50 [0.25; 0.99]	0.46 [0.22; 0.93]
Gender	Male	Ref	
	Female	*1.34 [1.00; 1.78]	1.15 [0.83; 1.61]
Smoking	No	Ref	
	Yes	0.89 [0.51; 1.56]	
Alcohol use	No	Ref	
	Yes	1.06 [0.81; 1.40]	
Marital status	Single	Ref	
	Married	0.87 [0.66; 1.16]	
Educational status	College/University	Ref	
	Secondary	1.17 [0.74; 1.86]	
	Primary /not formal	1.13 [0.79; 1.61]	
Hospital type	Specialized	Ref	
	General	*1.43 [1.06; 1.92]	*2.05 [1.36;0.09]
Disease characteristics			
Number of cardiometabolic comorbid illnesses		0.86 [0.69; 1.06]	0.84 [0.64; 1.11]
Hypertension severity at prior visit			
Normal BP (systolic BP < 120 and diastolic BP < 80 mm Hg)		Ref	
Pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89 mm Hg)		0.83 [0.45; 1.53]	0.80 [0.40; .62]
Stage I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm Hg)		*0.40 [0.21; 0.72]	*0.34 [0.17; .67]
Stage II hypertension (systolic BP ≥ 160 or diastolic BP ≥ 100 mm Hg)		*0.25 [0.14; 0.46]	*0.17 [0.09; .35]
Antihypertensive Treatment characteristics			
Duration of therapy, years (mean, SD)		#1.02 [1.00; 1.04]	*1.04 [1.02; .07]
Adherent (MMAS ≥ 7)	No	Ref	
	Yes	#0.79 [0.60; 1.04]	0.75 [0.54; 1.04]
Revisit schedule in months (Mean, SD)		*0.89 [0.82 ;0.97]	0.93 [0.83; 1.04]
Therapy at prior visit	Monotherapy	Ref	
	Multidrug therapy	0.98 [0.74; 1.29]	
Antihypertensive medications at prior visit			
ACE inhibitors	No	Ref	
	Yes	1.13 [0.86; 1.49]	
Beta blockers	No	Ref	
	Yes	*1.54 [1.09; 2.16]	*1.63 [1.08; .45]
Calcium channel blockers	No	Ref	
	Yes	1.06 [0.81 ;1.39]	
Diuretics	No	Reference	
	Yes	*0.76 [0.58; 0.99]	*0.68 [0.49;0.94]

Difference with the main analysis (Table 2): Age categorical, prior BP based on severity, and comorbid illness count included.

Supplement Table 5 Treatment intensification determinants for ambulatory hypertensive patients with uncontrolled BP at index visit

Variables		Bivariable estimates OR [95% CI]	Multivariable estimate OR [95% CI]
Demographics			
Age, Year			
	< 35	Ref	
	35-44	1.53 [0.39; 5.99]	1.25 [0.31; 5.02]
	45-54	1.45 [0.39; 5.38]	1.08 [0.28; 4.10]
	55-64	1.95 [0.55; 6.96]	1.20 [0.33; 5.49]
	≥ 65	2.03 [0.57; 7.26]	1.49 [0.41; 2.22]
Gender	Male	Ref	
	Female	#1.35 [0.88; 2.07]	1.40 [0.86; 1.29]
Smoking	No	Ref	
	Yes	0.88 [0.37; 2.07]	
Alcohol use	No	Ref	
	Yes	0.75 [0.49; 1.15]	
Marital status	Single	Ref	
	Married	0.93 [0.60; 1.43]	
Educational status	College/University	Ref	
	Secondary	1.54 [0.80; 2.97]	
	Primary /no formal education	0.95 [0.56; 1.62]	
Hospital type	Specialized	Ref	
	General	#0.68 [0.43; 1.06]	0.78 [0.48 1.29]
Disease characteristics			
Cardiometabolic comorbid illness at current visit		#1.15 [0.86; 1.52]	1.04 [0.74; 1.45]
Hypertension severity at prior visit			
Normal BP (systolic BP < 120 and diastolic BP < 80 mm Hg)		Ref	
Pre-hypertensive stage (systolic BP 120-139 or diastolic BP 80-89		0. 65 [0.20; 2.07]	
Stage-I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm		0.93 [0.32; 2.68]	
Stage-II hypertension (systolic BP ≥ 160 or diastolic BP ≥ 100 mm Hg)		1.15 [0.40; 3.26]	
Antihypertensive treatment characteristics			
Duration of therapy years (mean SD)		*1.05 [1.02; 1.08]	*1.05 [1.02; 1.08]
Adherence (MMAS ≥ 7)	No	Ref	
	Yes	0.88 [0.58; 1.32]	
Therapy at prior visit	Monotherapy	Ref	
	Multidrug therapy	0.89 [0.59; 1.34]	

Difference with the main analysis (table 3): Age grouped, prior BP based on severity, and comorbid illness count included.

Supplement Table 6 Determinants of achieving target BP (BP < 140/90) at current visit in ambulatory hypertensive patients (For patient with ≥ 6 months on antihypertensive medication).

Variables		Odds ratio at 95% CI	
		Bivariable estimates	Multivariable estimate
Demographics			
Age [year]		#0.99 [0.98; 1.00]	*0.99 [0.98; 1.00]
Gender	Male	Ref	
	Female	#1.26 [0.93; 1.71]	1.09 [0.78; 1.53]
Smoking	No	Ref	
	Yes	0.92 9 [0.51; 1.66]	
Alcohol use	No	Ref	
	Yes	1.06 [0.79; 1.42]	
Marital status	Single	Ref	
	Married	0.87 [0.65; 1.18]	
Educational status	College/University	Ref	
	Secondary	1.31 [0.81; 2.13]	
	Primary /not formal	1.14 [0.79; 1.66]	
Hospital type	Specialized	Ref	
	General	*1.48 [1.08; 2.02]	*2.03 [1.34; 3.06]
Diabetes Mellitus	No	Ref	
	Yes		
Dyslipidemia	No	Ref	
	Yes		
Renal disease	No	Ref	
	Yes	0.59 [0.18; 1.99]	
Heart failure/ MI at	No	Ref	
	Yes		
Controlled BP at prior visit	Yes	Ref	
	No		*0.30 [0.21; 0.44]
Antihypertensive Treatment characteristics			
Duration of therapy, years (mean, SD)		#1.02 [1.00; 1.04]	*1.04 [1.01; 1.06]
Adherent (MMAS ≥ 7)	No	Ref	
	Yes	#0.79 [0.58; 1.05]	0.75 [0.55; 1.07]
Revisit schedule in months (Mean, SD)		*0.87 [0.79 ;0.96]	0.92 [0.82; 1.03]
Therapy at prior visit	Monotherapy	Ref	
	Multidrug therapy	1.01 [0.75; 1.36]	
Antihypertensive medications at prior visit			
ACE inhibitors	No	Ref	
	Yes	1.15 [0.86; 1.55]	
Beta blockers	No	Ref	
	Yes	*1.52 [1.06; 2.17]	1.44 [0.96; 2.15]
Calcium channel blockers	No	Ref	
	Yes	1.06 [0.79 ;1.41]	
Diuretics	No	Reference	
	Yes	*0.75 [0.56; 1.00]	*0.68 [0.49; 0.95]

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, also on Figure 1
		(b) Give reasons for non-participation at each stage	11 also on Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12 (visit schedule)
Outcome data	15*	Report numbers of outcome events or summary measures over time	12 and 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15 and 17 (Table 2 and 3)
		(*b*) Report category boundaries when continuous variables were categorized	12 (Table 1)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplement Tables 1-6)
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19 and 21-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.