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Blood pressure lowering medicines implemented in 12 African countries: The cross-sectional multination EIGHT Study

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Title page:

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Abstract

Objective: In Africa, the number of patients with hypertension is expected to reach 216.8 million by 2030. Large-scale data on antihypertensive medications used in Sub-Saharan Africa (SSA) are scarce.

Here, we describe antihypertensive drug strategies and identify treatment factors associated with blood pressure (BP) control in 12 Sub-Saharan countries.

Setting: We conducted an observational cross-sectional study using data collected during outpatient consultations in cardiology centers of 29 hospitals from 17 cities across 12 SSA countries.

Participants: Patients ≥18 years of age with hypertension were enrolled at any visit during outpatient consultations.

Main outcome measure: We collected sociodemographic and socio economic characteristics, antihypertensive treatment (including traditional medicine) of patients. Seated office BP was measured twice by physicians, and BP control was defined as seated office BP<140/90mmHg. Severity of hypertension was defined according to European Society of Cardiology guidelines (mild, moderate and severe). We used logistic regression with a random effect on countries to assess factors of BP control.

Results: Overall, 2198 hypertensive patients were included and a total of 96.6% (n=2123) were on antihypertensive medications. Among treated patients, 653(30.8%) patients received a monotherapy by calcium channel blocker (n=324, 49.6%), renin angiotensin system blocker (RAS)(n=126, 19.3%) or diuretic (n=122, 18.7%). Two-drug strategies were prescribed in 927(43.6%) patients including mainly diuretics and RAS(n=327, 42% of two-drug strategies). Prescriptions of three-drugs or more were used in 543(25.6%) patients. Overall, among treated patients, 1630(76.7%) had uncontrolled BP, of whom 462(28.3%) had BP levels ≥180/110mmHg, mainly in those on monotherapy. After adjustment for sociodemographic factors, the use of traditional medicine was the only factor significantly associated with uncontrolled BP(OR 1.72 [1.19-2.49] p<0.01).

Conclusion: Our study provided large scale data on antihypertensive prescriptions in the African continent. Among patients declared adherent to drugs, poor BP control was significantly associated with the use of traditional medicine.

Key words: Hypertension, cardiology, antihypertensive medications, developing countries

Strengths and limitations of this study

- We embraced 12 African countries unusually considered in international studies
- A multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from Africa and France conceived and designed the study
- The data in the EIGHT study were derived from urban clinics and likely represents the best-case scenario for BP treatment and control, data from rural area should be collected.
- We probably over estimated cross-sectional associations between drug regimens and BP control because of other unknown cardiovascular indications.
- Use of traditional medicine is strongly associated with uncontrolled blood pressure while we didn't depicted all aspect of traditional medicine (herbal medicines, indigenous healthcare practices, complementary and alternative medicine like acupuncture or chiropractic, consultation of traditional health practitioners).

Introduction

High blood pressure (BP) is one of the leading contributor to the global burden of chronic disease reaching 10 million deaths each year(1). In Africa, 130.2 million people suffer from hypertension and this figure is expected to reach 216.8 million by 2030(2). Hypertension is the leading cause of cardiovascular disease (CVD) in Africa; indeed, it is a major and independent risk factor for heart failure, stroke and kidney failure (3). In Sub-Saharan Africa (SSA), the overall prevalence of hypertension is 30%(4). In developed countries, improvements in hypertension control have led to considerable reduction in overall morbidity and mortality over the last fifty years(3). In SSA, the prevention of CVD is not always in the public health agenda (5).

A combination of lifestyle modification and blood pressure-lowering medications are the cornerstone of hypertension control. Randomized clinical trials conducted in high income countries have shown that antihypertensive medication therapy reduces BP and cardiovascular, cerebrovascular and renal morbidity and mortality(6). Various antihypertensive drug classes including calcium channel blockers, diuretics, renin-angiotensin system blockers, beta-blockers or centrally active drug can be used alone or in combination according to international guidelines to achieve BP control(7,8). Although international guidelines to manage hypertension contain recommendations for black adults who live mostly in high income countries outside of Africa(7), 74% of African countries have no dedicated guidelines for the management of hypertension for the predominantly black populations in these countries(4). Indeed, in SSA countries, five dimensions of access to medicine should be considered including availability, affordability, accessibility, acceptability and quality of medicines. Among these dimensions, acceptability describes how medicines are used in real-world settings, including appropriate prescription by physicians and behavior of patients (adherence and cultural factors)(9). A few studies describe access of medication in SSA and often they examine availability and affordability of antihypertensive medicines but not the acceptability and consequences of these medications on BP control(10).

There is scarce information from SSA(11). Published data are derived from worldwide studies, where SSA countries are poorly represented(12) or estimated(13). Conclusions of such global studies may not always be extrapolated to these SSA countries. Furthermore, most studies in SSA are limited to single countries or centers(14).

Therefore, the purpose of the current study is to describe antihypertensive drug strategies and identify treatment factors associated with uncontrolled BP using a large multinational study conducted in 12 SSA countries: the EIGHT Study (Evaluation of Hypertension in Sub-Saharan Africa)(15).

Methods

Study design and setting

We conducted an observational cross-sectional study using data collected during outpatient consultations for hypertension in cardiology departments of 29 hospitals from 17 cities across 12 SSA countries (Benin, Cameroon, Congo (Brazzaville), Democratic Republic of the Congo, Gabon, Guinea, Côte d'Ivoire, Mauritania, Mozambic, Niger, Senegal, Togo) between January 2014 and November 2015.

A multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from Africa and France conceived and designed The Evaluation of Hypertension among Patients in Africa (EIGHT) study.

The EIGHT team had extensive prior research experience and existing collaborations with a network of physician-scientists in Africa in the field of Rheumatic heart disease(14), sickle cell(17) disease and quality of cardiovascular drugs(18) which aided planning and launch of the present study.

The study was approved by the Ile-de-France III ethics committee (Number 2014-A00710-47) and was declared to the National Commission of Informatics (Number 1762715). This study was exclusively supported by a public grant.

Participants

Patients ≥18 years of age with hypertension were enrolled at any visit during outpatient consultations in the cardiology departments of the participating hospitals. Each patient received an information leaflet about the study. In addition, the on-site physician presented and explained the study in the regional language to all patients meeting eligibility criteria. Patients who agreed to participate completed a standardized questionnaire while waiting for their appointment. Participating physicians at each center received a training note detailing the study and standardized instructions on how they should interact with the patients while completing the questionnaire.

Patient and public involvement

Patients and public were not directly involved in research design, recruitment or conduct of this study.

Measurements

A dedicated questionnaire was conceived for this study(15). A pilot investigation involving 90 patients who tested the questionnaire was conducted in January 2014 in Côte d'Ivoire.

Treatment factors

The first part of the questionnaire was completed by patients and collected data on patient sociodemographic factors (age, sex, and location), use of traditional medicine and adherence to treatment. A patient was defined as non-adherent if she/he reported sometimes forgetting to take medications in his/her self questionnaire.

The second part was filled out by the physician during the consultation and collected data on socioeconomic status (patient wealth index), antihypertensive drugs classes and generic prescriptions, blood pressure values (measured in standardized conditions, see below), and cardiovascular risk factors helping with the medical file if necessary.

Patient wealth index were assessed by the treating physician and classified as low, middle and high :

- "Low" defined poor patients who have difficulties to afford medical consultations
- "Middle" defined patients who can manage with paying medical consultations
- "High" defined patients who have no difficulties to pay medical consultations"

The antihypertensive drug classes recorded were: calcium channel blockers, diuretics, renin-angiotensin system blockers (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), beta-blockers, centrally active drugs and direct vasodilators. Antihypertensive drug strategies were defined according to the number of prescribed drug classes.

Blood pressure measurement

Seated office BP was measured twice by physicians, at least 15 minutes apart; participants were instructed to avoid caffeine and smoking within 30 minutes prior to BP measurement.

Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of the measured office BP values in the clinic(19).

Severity of hypertension was defined according to European Society of Cardiology guidelines(19): Mild hypertension (SBP: 140-159 mmHg and/or DBP: 90-99 mmHg), moderate hypertension (SBP: 160-179 mmHg and/or DBP: 100-109 mmHg) and severe hypertension (SBP≥180 mmHg and/or DBP ≥110 mmHg).

Study power

The study was designed with 90% power to detect a relative difference superior at 5% on BP control between monotherapy and combination therapy group of patients (with a significance level of 5%). A total of 2060 patients were required.

Statistical analysis

Continuous and categorical variables were expressed as mean (standard deviation) and numbers (percentage) where appropriate.

Missing data were not imputed and taken into account in descriptive data. For statistical models, only complete cases were analyzed.

Categorical variables were compared using Chi-square tests.

It is difficult to interpret the potential role of antihypertensive drugs in non-adherent patients. Therefore, the association of treatments factors with uncontrolled hypertension and hypertension severity were assessed in adherent patients only. In this way, we studied the association of treatments factors with BP control in patients who reported actually taking their antihypertensive drugs. The following regression models were analyzed.

First, in univariate analysis, the odds ratio (OR) and 95% confidence intervals of the association of treatment factors (therapeutic strategy using two-drug strategies as the reference categories, antihypertensive drugs classes, prescription of generic drugs and use of traditional medicine) with uncontrolled BP were estimated in separate logistic regression models. A random effect for country was added (generalized estimated equation models) to account for inter-country variability. Interactions between antihypertensive strategies and each antihypertensive drug class were tested as well as interaction between patient wealth index and the use of traditional medicine. Then, in a multivariate analysis, models were adjusted for sociodemographic factors along with all factors with a p value of less than 0.2 in the univariate analysis.

Second, we quantified the association between treatment factors and hypertension severity using separate linear regression models with a random effect for country (generalized estimated equation models). As previously stated, all factors with a p value of less than 0.2 as well as sociodemographic factors were included in a model for multivariable analysis.

A two tailed p value of <0.05 was considered significant. All analyses were performed through scripts developed in the R software (version 3.5.1 (2018-07-02)).

Results

Participants

The EIGHT study included 2198 patients with hypertension in 12 SSA countries between January 2014 and November 2015. Patients' baseline data are reported in Table 1. Mean age of patients was 58.3± 11.8 years. A greater proportion of patients were women (n=1324, 60.2%). Overall, 1017 patients (46.3%) were from low-income countries (Benin, Democratic Republic of the Congo, Guinea, Mozambic, Niger, and Togo), and 1181 (53.7%) were from middle-income countries (Cameroon, Congo [Brazzaville], Gabon, Côte d'Ivoire, Mauritania, and Senegal). Most of the patients were living in urban cities (n=1702, 78.9%) compared to rural areas (n=455, 21.1%). Individual wealth index was low, middle and high in 376 (17.6%), 1053 (49.2%) and 713 patients (33.3%) respectively.

Treatments

Overall, 96.6% (n=2123) of patients were prescribed antihypertensive medications (Table 1). Among treated patients, 653 (30.8%) patients received a monotherapy and 927 (43.6%) patients received two antihypertensive drugs classes (Table 1). Prescriptions of three, four, five and more antihypertensive drugs was found for 425 (20.0%), 107 (4.8%), 11 (0.4%) patients respectively. Characteristics of patients according to therapeutic strategy were detailed in Table 1.

Antihypertensive drug strategies according to country are displayed in Figure 1.

Calcium channel blockers (n=1219, 57.4%), diuretics (n=1167, 55.0%) and angiotensin-converting enzyme inhibitors (n=981, 46.2%) were the most commonly prescribed BP-lowering drugs overall (Table 1). Diuretics and renin-angiotensin system (RAS) blockers were most frequently prescribed as part of a two-drug antihypertensive medication strategy ($p<0.001$) as compared to a one drug or three or more-drug strategy. β-blockers were most frequently prescribed as part of a three or more drug antihypertensive medication strategy as compared to a one or two-drug strategy ($p<0.001$).

Antihypertensive drugs according to medication strategies are presented in Supplemental Table 1. Calcium channel blockers (CCB) were the most widely prescribed monotherapy (n=324, 49.6%) followed by RAS blockers (n=126, 19.3%), diuretics (n=122, 18.7%) and β-blockers (n=67, 10.3%). The three most common two-drug strategies were composed of diuretics + RAS blockers and CCBs + RAS blockers. Among three-drug

strategies, the three most common strategies (CCB + Diuretics + RAS blockers; Diuretics + β blockers + RAS blockers; CCB + β blockers + RAS blockers) represented 84.5% of prescriptions. The triple prescription strategies of Diuretics + CCB + RAS blockers represented almost half of the three-drug strategy prescriptions (n=250, 54.1%). Among four-drug strategies, the most common prescription strategy of CCB + Diuretics + β blockers + RAS blockers constituted 73.8% (n=79) of prescriptions.

About half of patients were prescribed at least one generic drug (n=801, 50%) (Table 1).

Among patients prescribed antihypertensive medication, 64% reported adherence to treatment.

A quarter (n=512, 24.1%) of patients used traditional medicine in addition to other drugs and this proportion was similar whatever the pharmacological antihypertensive drug strategy prescribed (monotherapy, two-drug strategies, three-drug strategies and more; p=0.107). The percentage of patients using traditional medicine varied from 9.9% (17/178) in Congo to 47.7% (82/172) in Guinea.

Factors associated with uncontrolled hypertension

Overall, 1630 (76.7%) had uncontrolled BP. BP control according to countries were depicted in Supplemental table 2. Drugs strategies by BP control are described in Table 1. In univariate analysis among patients who reported adherence to antihypertensive medication, factors associated with uncontrolled BP are detailed in Figure 2. The proportion of patients with uncontrolled BP was significantly increased with individual wealth index (middle versus high as reference), with monotherapy (versus two-drug therapy as reference) and with the use of traditional medicine ($p<0.05$). Patients treated with diuretics (versus patients without diuretics) had more frequently controlled BP (OR 0.72 [0.55-0.94] $p<0.05$); this association was not found for any other class of antihypertensive drugs.

In multivariable analysis among adherent patients adjusted for sociodemographic factors (age, sex, individual wealth index and location (rural or urban)), the use of traditional medicine remained the only factor significantly associated with uncontrolled hypertension (OR 1.72 [1.19-2.49], $p<0.01$). None of the antihypertensive drugs classes alone was associated with uncontrolled hypertension. There was no significant interaction between antihypertensive drug strategy and class, and between patient wealth index and the use of traditional medicine.

Factors associated with severity of hypertension

Drugs strategies are described by hypertension severity in Table 1. Among patients with severe hypertension, 127 (27.5%) were treated with a monotherapy. This proportions varied across countries (Figure 3). In univariate analysis among adherent patients, the proportion of patients with severe hypertension was higher in patients with three-drug and more strategies (versus two-drug therapy), and with CCB, diuretics and the use traditional medicine ($p<0.05$) (Supplemental table 3).

In multivariable analysis among adherent patients adjusted for sociodemographic factors, the use of traditional medicine remained associated with higher grades of hypertension (linear regression coefficient=0.15; [0.029 - 0.28], $p<0.05$).

Discussion

Key results

Overall, 653 (30.8%) patients received antihypertensive medication monotherapy, 927 (43.6%) received two-drug strategies and 543 (25.6%) received three-drugs and more. These proportions varied across countries.

CCB was the most common antihypertensive drug class prescribed among all strategies. However, if angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were considered as one antihypertensive drug class merged into RAS blockers, they represented 68% of all prescriptions.

We found that the use of traditional medicine was an important determinant of poor BP control, beyond the traditional factors including patient wealth index and adherence to medication. Medical staff attention should particularly be provided to these patients.

Antihypertensive drug strategies

The proportion of patients on antihypertensive medications in our study was very high. This is related to the recruitment of patients during outpatient consultations in cardiology departments or urban hospitals. There is scarce data on proportion of patients treated with antihypertensive medication among patients aware of a hypertension diagnosis in SSA. According to the Eighth Joint National Committee, the first recommended line of treatment for black hypertensive patients is diuretics or CCB alone or in combination(20). Accordingly, CCBs alone or in combination were widely prescribed in our study. Surprisingly, RAS blockers and especially ACEI were the second most prescribed treatment alone before diuretics even though these are less effective compared with CCBs in reducing BP in black hypertensive patients(21). Physicians in the EIGHT study seem to follow international guidelines for black patients regarding CCB prescriptions. The high proportion of ACEI prescriptions (usually not recommended for black patients except for compelling indications including heart failure, post-myocardial infarction, diabetes, proteinuric nephropathy) suggests that continuing education of physician would be necessary. Though, our methodology did not allow to completely distinguish indications of some drugs, and particularly to know whether ACEI were prescribed in a compelling indication because of the non-reported patient's comorbidities. Diuretics should be considered, particularly due to their low cost(22) .

Even among patients recruited from tertiary cardiology centers in urban areas in Sub-Saharan countries, BP control remains very poor and monotherapy remains widely prescribed. Some barriers associated with uptitration of treatments could be cited. Access to medicines, defined by availability, affordability, accessibility, quality and

acceptability of antihypertensive drugs varied across low and middle-income countries. These factors are associated with poor blood pressure control (9,23,24).

In low and middle-income countries, a large proportion of communities do not have access to more than one antihypertensive drug and, when available, they are often not affordable. In a multinational study among 68 950 households, the proportion of households unable to afford two blood pressure-lowering medicines was 31% in low-income countries and 9% in middle-income countries (11). Furthermore, we cannot exclude that the pharmaceutical quality of drugs did not contribute to treatment failure. Indeed, we have previously shown in the SEVEN study that 16% of cardiovascular drugs have poor quality in SSA, especially calcium channel blockers, and the proportion of poor quality can reach 50% when drugs produced in Asia are sold in street markets (18).

Among solutions, fixed drug combinations have been shown to enhance adherence and effectiveness of treatment by combining different treatments with different mechanisms of action. Randomized Controlled Trial on adherence to treatment by providing fixed drug combination free of charge in other part of the world achieve to increase blood pressure control (25). However, fixed drug combinations are poorly available and affordable in low and middle-income countries. Nevertheless, using fixed drug combinations had limitations: they may have potentially higher prices versus the cost of the components combined, they may be only available as "branded" medicines in some countries and consequently only available in private pharmacies rather than public facilities and not in rural area (26).

Traditional medicine

Our results underlined the strong association between the use of traditional medicine and uncontrolled BP, after adjusting for well-known factors associated with poor BP control including age, sex, socioeconomic factors, and poor adherence to treatment(27). The WHO define the use of traditional medicine as the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness(28). The prevalence of the use of traditional medicine is rising worldwide and is well documented in both African countries and worldwide to be between 20-80%(29,30). We found that 24.1% of patients (range 9.9% to 47.7%) used traditional medicine, consistent with the literature(31). Several factors have previously been reported to be associated with the use of traditional medicine including socio-demographic characteristics of patients, dissatisfaction with conventional treatments (ineffective treatments or side effects), cultural beliefs that illnesses have a "spiritual" origin, availability and affordability of antihypertensive drugs(31). In our study, conventional medicine and traditional medicine were

concurrently used**.** Studies have shown that patients used traditional medicine along with their conventional treatments(32) but use of traditional medicine was strongly associated with poor adherence to conventional treatments(27). Collaboration between traditional healthcare professionals and physician seems to be essential to improve the management of hypertension(33) in SSA.

Limitation and strength

We acknowledged the following limitations. Caution is needed in extrapolating the information in the current study to other population because the sampling framework in each country was not nationally representative. The data in the EIGHT study were derived from urban clinics and likely represents the best-case scenario for BP treatment and control. Therefore, the magnitude of uncontrolled BP in the general population with hypertension could be underestimated. Although a random selection of centers would be ideal from a methodological perspective, such an approach is not practical given the lack of cardiovascular care in this part of the world. Concerning antihypertensive drugs classes, aldosterone antagonist and thiazide diuretic were not differentiated in our study. For antihypertensive drug strategies, even if a patient has a prescription for single-pill combination, they may be unable to purchase this treatment. We therefore decided not to incorporate this information in our analysis. We probably over estimated cross-sectional associations between drug regimens and BP control because of other unknown cardiovascular indications. Furthermore, this study could not take into account the role of indication bias in interpreting cross-sectional associations between drug regimens and BP control.

This study had many strengths including its multisite design, with over 2000 patients from 29 medical centers in 17 cities from 12 countries. Actual data on management of cardiovascular disease are uncommon in Africa and are usually derived from small, single center studies. The EIGHT study embraced 12 African countries which are usually not considered in international studies, such as the PURE study(11) providing global data on cardiovascular epidemiology. Furthermore, this study was supported by a strong and structured collaborative multidisciplinary network. Active involvement of African cardiologists, who are familiar with the problems of this area, helped derive specific questions and analysis.

Conclusion

Hypertension is a rapidly growing epidemic in low and middle income countries. In this multinational study, we described antihypertensive drugs by classes in Sub-Saharan Africa. Our study provided large scale data on

antihypertensive prescriptions in the African continent. We found that the use of traditional medicine was an important determinant of poor BP control.

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Author's contribution:

All authors have substantial contributions.

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Final approval of the version to be published: all authors

Data availability statement

"P. Cavagna, M. Antignac and X. Jouven had full access to the whole data in the study and take responsibility for integrity of the data and accuracy of data analysis. All data are available on request."

References

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl. 2018 10;392(10159):1923–94.

2. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. PloS One. 2014;9(8):e104300.

3. Kayima J., Wanyenze R.K., Katamba A., Leontsini E., Nuwaha F. Hypertension awareness, treatment and control in Africa: A systematic review. BMC Cardiovasc Disord [Internet]. 2013;13((Kayima J., jkkayima@gmail.com) Department of Medicine, School of Medicine, College of Health Sciences, Makerere University, P.O. Box 7072, Kampala, Uganda). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52715263

4. Kuate Defo B, Mbanya JC, Kingue S, Tardif J-C, Choukem SP, Perreault S, et al. Blood pressure and burden of hypertension in Cameroon, a microcosm of Africa: a systematic review and meta-analysis of population-based studies. J Hypertens. 2019 Jun;1.

5. Twagirumukiza M, De Bacquer D, Kips JG, de Backer G, Stichele RV, Van Bortel LM. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. J Hypertens. 2011 Jul;29(7):1243–52.

6. Mills KT, Obst KM, Shen W, Molina S, Zhang H-J, He H, et al. Comparative Effectiveness of Implementation Strategies for Blood Pressure Control in Hypertensive Patients: A Systematic Review and Meta-analysis. Ann Intern Med. 2018 16;168(2):110–20.

7. Mancia G, Rosei EA, Azizi M, Burnier M, Clement DL, Coca A, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. :98.

8. Whelton Paul K., Carey Robert M., Aronow Wilbert S., Casey Donald E., Collins Karen J., Dennison Himmelfarb Cheryl, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun 1;71(6):e13–115.

9. Wirtz VJ, Kaplan WA, Kwan GF, Laing RO. Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries. Circulation. 2016 May 24;133(21):2076–85.

10. Antignac M, Marijon E, Jouven X. Letter by Antignac et al Regarding Article "Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries." Circulation. 2016 04;134(14):e303–4.

11. Attaei MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet Public

Health. 2017;2(9):e411–9.

12. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJL. Estimates of global and regional premature cardiovascular mortality in 2025. Circulation. 2015 Sep 29;132(13):1270–82.

13. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013 Sep 4;310(9):959–68.

14. Mutua EM, Gitonga MM, Mbuthia B, Muiruri N, Cheptum JJ, Maingi T. Level of blood pressure control among hypertensive patients on follow-up in a regional referral hospital in Central Kenya. Pan Afr Med J. 2014;18:278.

15. Antignac M, Diop IB, Macquart de Terline D, Kramoh KE, Balde DM, Dzudie A, et al. Socioeconomic Status and Hypertension Control in Sub-Saharan Africa: The Multination EIGHT Study (Evaluation of Hypertension in Sub-Saharan Africa). Hypertension. 2018 Apr;71(4):577–84.

16. Marijon E, Ou P, Celermajer DS, Ferreira B, Mocumbi AO, Jani D, et al. Prevalence of Rheumatic Heart Disease Detected by Echocardiographic Screening [Internet]. http://dx.doi.org/10.1056/NEJMoa065085. 2009 [cited 2019 Jun 27]. Available from: https://www.nejm.org/doi/10.1056/NEJMoa065085?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov

17. Ranque B, Menet A, Diop IB, Thiam MM, Diallo D, Diop S, et al. Early renal damage in patients with sickle cell disease in sub-Saharan Africa: a multinational, prospective, cross-sectional study. Lancet Haematol. 2014 Nov;1(2):e64-73.

18. Antignac M, Diop BI, Macquart de Terline D, Bernard M, Do B, Ikama SM, et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. Int J Cardiol. 2017 Sep 15;243:523–8.

19. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013 Oct;31(10):1925–38.

20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507–20.

21. Leenen FHH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertens Dallas Tex 1979. 2006 Sep;48(3):374–84.

22. Kramoh K.E., Aké-Traboulsi E., Konin C., N'Goran Y., Coulibaly I., Adoubi A., et al. Management of hypertension in the elderly patient at Abidjan cardiology institute (Ivory Coast). Int J Hypertens [Internet]. 2012;2012((Kramoh K.E., krakoueul@yahoo.fr; Aké-Traboulsi E.,

evyaket@aviso.ci; Konin C., koninchristophe@yahoo.fr; N'Goran Y., ngoran.yves@yahoo.fr; Coulibaly I., iklo_coulibaly@hotmail.com; Adoubi A., anicetadoubi@yahoo.fr; Koffi J., koffidjinguin@yahoo.fr; Anzouan-Kacou J.B., jb_anzouan@yahoo.fr; Guikahue M., guika_abj_ci@hotmail.com) Institute of Cardiology of Abidjan (Ivory Coast), BPV 206, Abidjan, Cote d'Ivoire). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L365970813

23. Ashigbie PG, Rockers PC, Laing RO, Cabral HJ, Onyango MA, Buleti JPL, et al. Availability and prices of medicines for non-communicable diseases at health facilities and retail drug outlets in Kenya: a cross-sectional survey in eight counties. BMJ Open. 2020 May 15;10(5):e035132.

24. Kaiser AH, Hehman L, Forsberg BC, Simangolwa WM, Sundewall J. Availability, prices and affordability of essential medicines for treatment of diabetes and hypertension in private pharmacies in Zambia. Thet Wai K, editor. PLOS ONE. 2019 Dec 13;14(12):e0226169.

25. Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, et al. Effect on Treatment Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized Clinical Trial. JAMA Intern Med. 2020 Jan 1;180(1):27–34.

26. Godman B, McCabe H, D Leong T. Fixed dose drug combinations - are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries. Expert Rev Pharmacoecon Outcomes Res. 2020 Feb;20(1):1–26.

27. Macquart de Terline D, Kane A, Kramoh KE, Ali Toure I, Mipinda JB, Diop IB, et al. Factors associated with poor adherence to medication among hypertensive patients in twelve low and middle income Sub-Saharan countries. Li Y, editor. PLOS ONE. 2019 Jul 10;14(7):e0219266.

28. World Health Organization, editor. WHO traditional medicine strategy. 2014-2023. Geneva: World Health Organization; 2013. 76 p.

29. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998 Nov 11;280(18):1569–75.

30. Eddouks M, Maghrani M, Lemhadri A, Ouahidi M-L, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol. 2002 Oct;82(2–3):97–103.

31. Osamor PE, Owumi BE. Complementary and alternative medicine in the management of hypertension in an urban Nigerian community. BMC Complement Altern Med. 2010 Jul 19;10:36.

32. Nuwaha F, Musinguzi G. Use of alternative medicine for hypertension in Buikwe and Mukono districts of Uganda: a cross sectional study. BMC Complement Altern Med. 2013 Nov 4;13:301.

33. Krah E, de Kruijf J, Ragno L. Integrating Traditional Healers into the Health Care System: Challenges and Opportunities in Rural Northern Ghana. J Community Health. 2018;43(1):157–63.

Figures: titles and legends

Figure 1: Antihypertensive drugs strategies (%) according to countries level income and countries

Legend: bars represent the percentage of antihypertensive drugs strategies

Figure 2: Proportion of monotherapy in patients with severe hypertension.

Legend: Grey countries were not included in the EIGHT study.

Figure 3: Odds ratio (OR) of sociodemographic and treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications in univariate analysis.

Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. *RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.*

Table 1: Characteristics of participants according to therapeutic strategy

	GLOBAL	No drugs	Monotherapy	Two-drug therapy	Three-drug and +
Overall					
N, (%)	2198	75 (3.4)	653 (29.7)	927 (42.2)	543 (24.7)
Age (year), mean (sd)	58.3 (11.8)	55.3 (14.1)	57.8 (12.12)	58.5 (11.70)	58.9 (11.09)
Male, N (%)	874 (39.8)	22 (29.3)	248 (38.0)	385 (41.5)	219 (40.3)
Patient wealth index, N (%)					
Low	376 (17.6)	15 (22.4)	109 (17.2)	166 (18.3)	86 (16.2)
Middle	1053 (49.2)	36 (53.7)	302 (47.6)	450 (49.5)	265 (49.8)
High	713 (33.3)	16 (23.9)	224 (35.2)	292 (32.2)	181 (34.0)
NA	56	8	18	19	11
Country-level income (Low vs Middle), N (%)	1017 (46.3)	23 (30.7)	361 (55.3)	419 (45.2)	214 (39.4)
Location (Urban vs Rural), N (%)	1702 (78.9)	56 (74.7)	485 (75.7)	729 (80.3)	432 (81.1)
NA	41	0	12	19	10
Cardiovascular risks factors, N (%)					
Tobacco use	84 (5.1)	7 (13.7)	16 (3.4)	45 (6.5)	16 (3.7)
Diabetes mellitus	288 (17.5)	8 (15.7)	74 (15.6)	119 (17.3)	87 (20.2)
Hypercholesterolemia	328 (19.9)	4 (7.8)	75 (15.8)	142 (20.6)	107 (24.9)
Hypertriglyceridemia	88 (5.3)	0 (0.0)	26 (5.5)	43 (6.2)	19 (4.4)
Obesity	340 (20.7)	16 (31.4)	79 (16.6)	144 (20.9)	101 (23.5)
Sedentary Lifestyle	649 (39.5)	29 (56.9)	169 (35.6)	254 (36.9)	197 (45.8)
None	461 (28.0)	8 (15.7)	160 (33.7)	193 (28.0)	100 (23.3)
NA	553	113	24	178	283
Year since hypertension diagnosis (>1 year), N (%)	1816 (84.4)	45 (67.1)	487 (76.1)	802 (87.8)	482 (90.8)
NA	47	8	13	14	12
Among treated patients		-			
Patients on antihypertensive medication, N (%)	2123 (96.6)	-	653 (30.8)	927 (43.6)	543 (25.6)
Antihypertensive drug class, N (%)		-			
Calcium channel blocker	1219 (57.4)	-	324 (26.6)	457 (37.5)	438 (35.9)
Diuretic	1167 (55.0)	-	122 (10.5)	567 (48.5)	478 (41.0)
RAS Blocker : Angiotensin-converting-enzyme inhibitor	981 (46.2)	-	94 (9.6)	505 (51.5)	382 (38.9)
RAS Blocker : Angiotensin II receptor antagonist	321 (15.1)	-	32 (10)	163 (50.8)	126 (39.3)
Beta-blocker	466 (22.0)	-	67 (14.4)	138 (29.6)	261 (56)
Centrally active drug	79 (3.7)	-	12 (15.2)	20 (25.3)	47 (59.5)
Vasodilator	33 (1.6)	-	2 (6.1)	4 (12.1)	27 (81.8)
Prescription of generic drug, N (%)	801 (50.1)	-	225 (48.9)	298 (44.2)	273 (62.5)
NA	599	-	193	253	106
Use of traditional medicine, N (%)	512 (24.1)	-	150 (23.7)	231 (25.5)	107 (20.6)
NA	70	-	21	22	23
Patient reported adherence to antihypertensive medication, N (%)	1359 (64)	-	397 (29.2)	597 (43.9)	365 (26.8)
Office Blood pressure, mean (sd)		-			
Systolic blood pressure, mmHg	148.9 (23.4)	-	147.2 (21.6)	147.1 (22.4)	154 (26.5)
Diastolic blood pressure, mmHg	88.2 (14.2)	-	89.2 (13.9)	87.3 (14)	88.7 (14.7)
Blood pressure control* (Uncontrolled vs controlled), N (%)	1630 (76.7)	-	519 (79.7)	682 (73.9)	429 (79.4)
NA	10	-	2	5	3
Hypertension severity, N (%)		-			
Mild	625 (38.3)	-	212 (40.8)	270 (39.6)	143 (33.3)
Moderate	543 (33.3)	-	180 (34.6)	226 (33.1)	137 (31.9)
Severe	462 (28.3)	-	127 (24.4)	186 (27.3)	149 (34.8)

Legend:* Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic.

Supplemental Digital Content: Titles and legend

Supplemental Table 1. Antihypertensive drugs according to medication strategies

Legend: β blockers: Beta blockers, CCB: Calcium channel blockers, RAS blockers: Renin-Angiotensin System blockers

*Combination therapy recommended

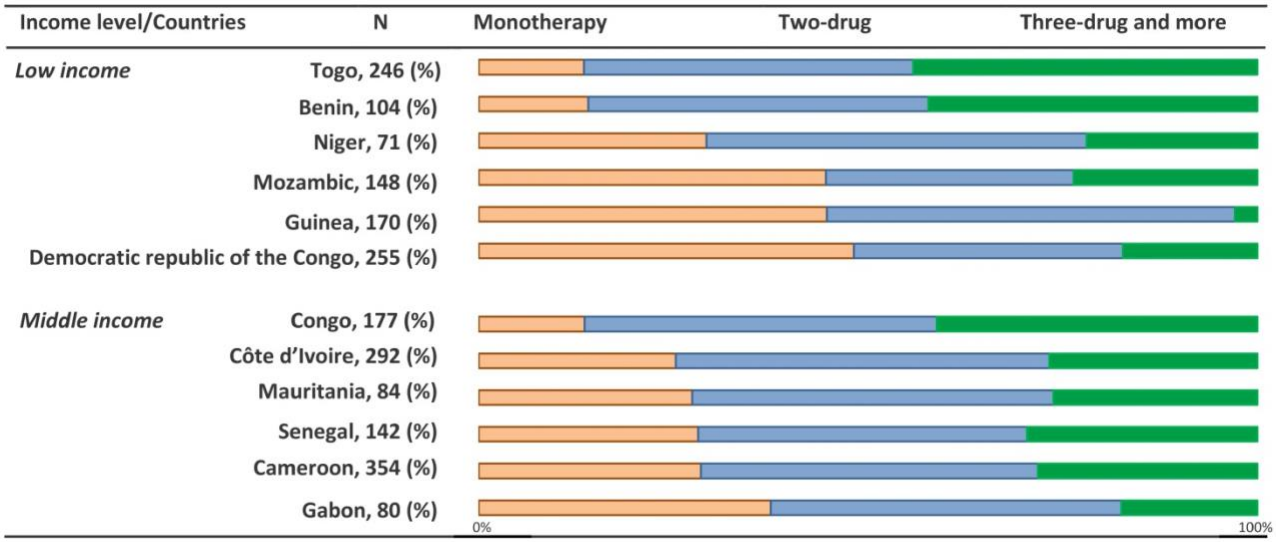
† Patient with six-drug strategies were not presented

Supplemental Table 2: Treatments characteristics by country among treated patients

***** Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic

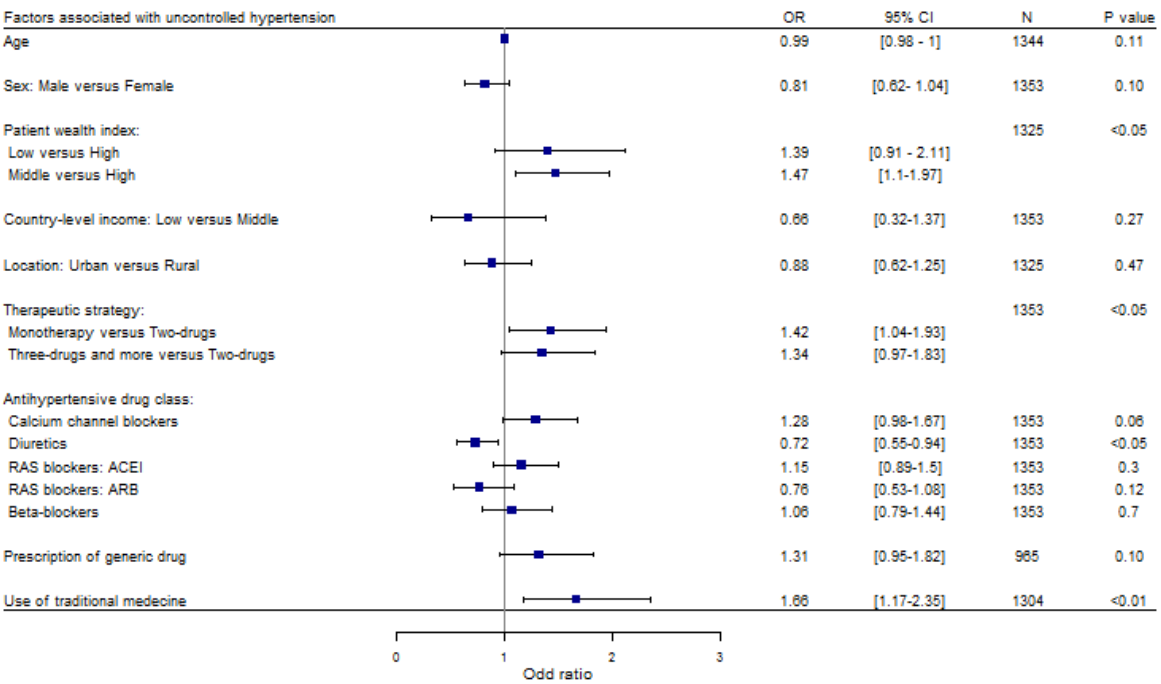
Supplemental Table 3: Linear regression coefficient of sociodemographic and treatments factors for severity of hypertension in univariate analysis.

Figure 1: Antihypertensive drugs strategies (%) according to countries level income and countries



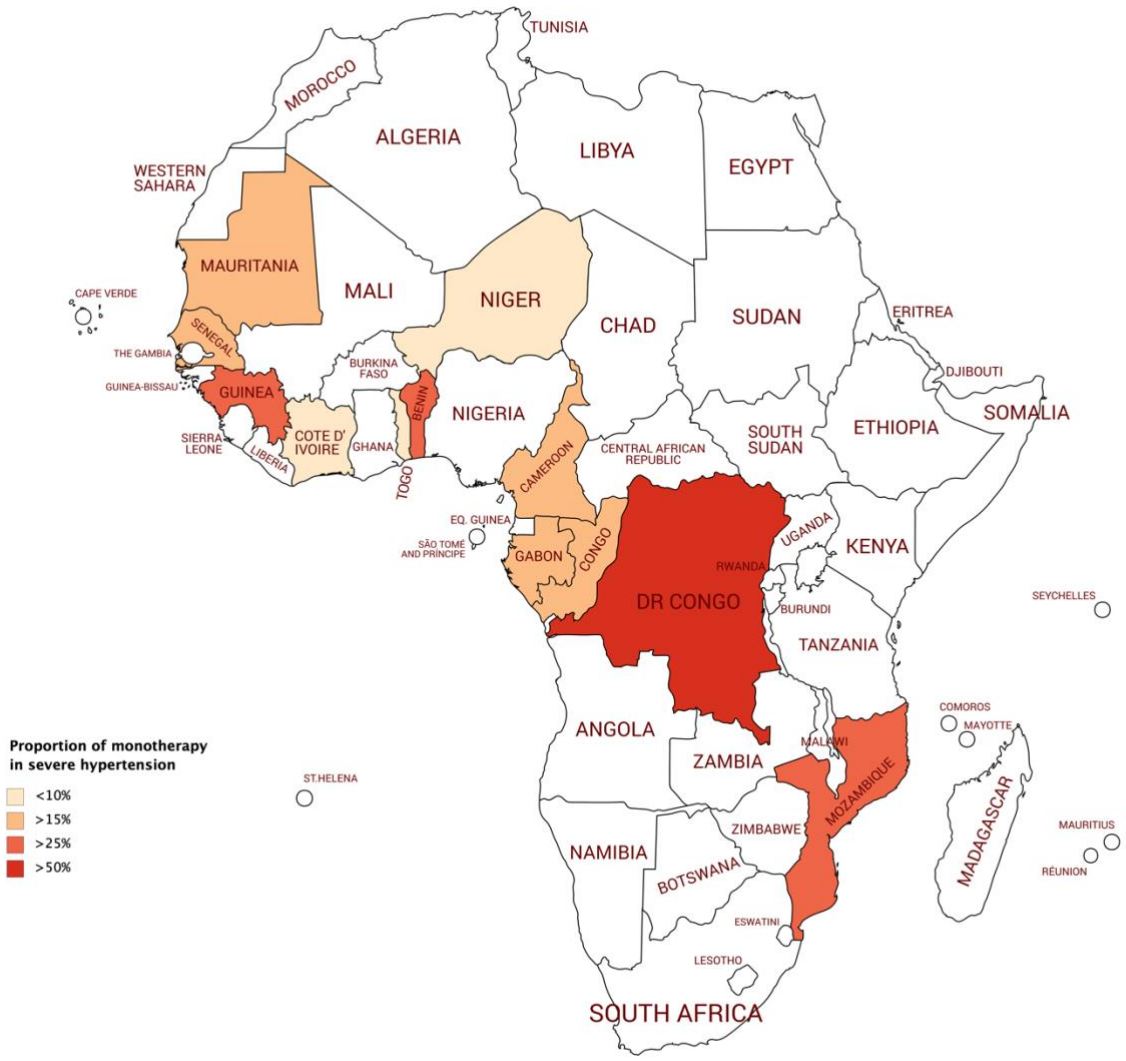
Legend: bars represent the percentage of antihypertensive drugs strategies

Figure 2: Odds ratio (OR) of sociodemographic and treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications in univariate analysis.



Legend: Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.

Figure 3: Proportion of monotherapy in patients with severe hypertension



Legend: White countries were not included in the EIGHT study.

Supplemental Table 1. Antihypertensive drugs according to medication strategies

	N, (%)
Monotherapy	**653 (30.8)**
Calcium channel blockers (CCB)	324 (49.6)
Renin-Angiotensin system (RAS) blockers	126 (19.3)
Diuretics	122 (18.7)
Beta-blockers (β blockers)	67 (10.3)
Centrally active drug	12 (1.8)
Vasodilator	2 (0.3)
Two-drug strategies	**927 (43.6)**
Diuretics + RAS blockers*	387 (41.7)
CCB + RAS blockers*	240 (25.9)
CCB + Diuretics *	140 (15.1)
CCB + β blockers*	61 (6.6)
β blockers + RAS blockers	38 (4.1)
Diuretic + β blockers *	37 (4.0)
Centrally active drug + Other drug class	20 (2.2)
Vasodilator + Other drug class	4 (0.4)
Three-drug strategies	**425 (20.0)**
CCB + Diuretics + RAS blockers*	230 (54.1)
Diuretics + β blockers + RAS blockers	84 (19.8)
CCB + β blockers + RAS blockers	45 (10.6)
CCB + Diuretics + β blockers *	26 (6.1)
Centrally active drug + Other drug class	23 (5.4)
Vasodilator + Other drug class	15 (3.5)
2 RAS blockers + Other drug class	2 (0.4)
Four-drug strategies	**107 (5)**
CCB + Diuretics + β blockers + RAS blockers	79 (73.8)
Centrally active drug + Other drug class	17 (15.9)
Vasodilator + Other drug class	6 (5.6)
2 RAS blockers + Other drug class	4 (3.7)
Five-drug strategies and more †	**11 (0.4)**
CCB + Diuretics + β blockers + RAS blockers + Centrally active drug	4 (40.0)
CCB + Diuretics + β blockers + RAS blockers + Vasodilator	4 (40.0)
CCB + Diuretics + RAS blockers + Centrally active drug + Vasodilator	1 (10.0)
Diuretics + β blockers + 2 RAS blockers + Centrally active drug	1 (10.0)

Legend: β blockers: Beta blockers, CCB: Calcium channel blockers, RAS blockers: Renin-Angiotensin System blockers

*Combination therapy recommended

† Patient with six-drug strategies were not presented

Supplemental Table 2: Treatments characteristics by country among treated patients

	Niger	Togo	Benin	Guinea	Mozambic	Dem. Rep of the Congo	Congo	Senega	Côte d'Ivoire	Cameroon	Mauritania	Gabon
N, (%)	71(3.")	104 (4.9)	246 (11.6)	170 (8.0)	148 (7.0)	255 (12.0)	177 (8.3)	142 (6.7)	292 (13.7)	354 (16.7)	84 (3.9)	80 (3.8)
Blood pressure control* (Uncontrolled vs controlled), N (%)	65 (84.4)	77 (72.6)	142 (57)	125 (73.5)	119 (80.4)	232 (89.2)	134 (75.3)	128 (80.5)	228 (77.8)	285 (76.6)	68 (81)	89 (100
NA	3	0	1	2	0	1	0	1	2	3	0	0
Therapeutic Strategies, N (%)												
Monotherapy	10 (14.1)	14 (13.5)	72 (29.3)	76 (44.7)	66 (44.6)	123 (48.2)	24 (13.6)	40 (28.2)	74 (25.3)	101 (28.5)	23 (27.4)	30 (37.5)
Two-drug strategies	31 (43.7)	44 (42.3)	120 (48.9)	89 (52.4)	47 (31.8)	88 (34.5)	80 (45.2)	60 (42.2)	140 (47.9)	153 (43.0)	39 (46.4)	36 (45.0)
Three and more drugs strategies	30 (42.3)	46 (44.2)	54 (22.0)	5 (2.9)	35 (23.6)	44 (17.3)	73 (41.2)	42 (29.6)	78 (26.7)	100 (28.2)	22 (26.2)	14 (17.5)

***** Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic

Supplemental Table 3: Linear regression coefficient of sociodemographic and treatments factors for severity of hypertension in univariate analysis

	N	Linear regression coefficients	CI 95%	P value
Age	1017	-0.0021	-0.006 – 0.002	0.32
Sex (Male versus Female)	1023	0.087	-0.012 – 0.186	0.08
Patient Wealth index:	1004			0.10
Low versus high		0.15	0.0012 – 0.305	
Middle versus high		0.009	-0.101 – 0.12	
Location : urban versus rural	1001	-0.011	-0.136 – 0.112	0.86
Therapeutic strategy:	1023			<0.01
Monotherapy versus two-drugs		-0.106	-0.22 – 0.007	
Three-drugs and more versus two-drugs		0.155	0.037 – 0.273	
Antihypertensive drug class:				
Calcium channel blockers	1023	0.107	0.008 – 0.207	0.03
Diuretics	1023	0.136	0.039 – 0.233	<0.01
RAS blockers : ACEI	1023	0.043	-0.057 – 0.144	0.39
RAS blockers : ARB	1023	0.090	-0.05 – 0.231	0.21
Beta blockers	1023	-0.015	-0.131 – 0.099	0.797
Prescription of generic drug	731	0.025	-0.099 – 0.147	0.68
Use of traditional medicine	976	0.168	0.045 – 0.291	<0.01

Legend: Linear regression coefficients derived from separated linear regression with a random effect on country

to account for inter-country variability

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional 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	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	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
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
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	7
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	7
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	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*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
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10-11
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	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	16

*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

Blood pressure lowering medicines implemented in 12 African countries: The cross-sectional multination EIGHT Study

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Title page:

Full title: Blood pressure lowering medicines implemented in 12 African countries: The cross-sectional multination EIGHT Study

Short title: Antihypertensive strategies in Africa

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Abstract

Objective: In Africa, the number of patients with hypertension is expected to reach 216.8 million by 2030. Large-scale data on antihypertensive medications used in Sub-Saharan Africa are scarce.

Here, we describe antihypertensive drug strategies and identify treatment factors associated with blood pressure (BP) control in 12 Sub-Saharan countries.

Setting: Outpatient consultations for hypertension in urban tertiary cardiology centers of 29 hospitals from 17 cities across 12 SSA countries between January 2014 and November 2015.

Participants: Patients ≥18 years of age with hypertension were enrolled at any visit during outpatient consultations in the cardiology departments

Main outcome measure: We collected BP levels, demographic characteristics, and antihypertensive treatment use (including traditional medicine) of patients with hypertension attending outpatient visits. BP control was defined as seated office BP<140/90mmHg. We used logistic regression with a random effect on countries to assess factors of BP control.

Results: Overall, 2198 hypertensive patients were included and a total of 96.6% (n=2123) were on antihypertensive medications. Among treated patients, 653(30.8%) patients received a monotherapy by calcium channel blocker (n=324, 49.6%), renin angiotensin system blocker (RAS)(n=126, 19.3%) or diuretic (n=122, 18.7%). Two-drug strategies were prescribed in 927(43.6%) patients including mainly diuretics and RAS(n=327, 42% of two-drug strategies). Prescriptions of three-drugs or more were used in 543(25.6%) patients. Overall, among treated patients, 1630(76.7%) had uncontrolled BP, of whom 462(28.3%) had BP levels ≥180/110mmHg, mainly in those on monotherapy. After adjustment for sociodemographic factors, the use of traditional medicine was the only factor significantly associated with uncontrolled BP(OR 1.72 [1.19-2.49] p<0.01).

Conclusion: Our study provided large scale data on antihypertensive prescriptions in the African continent. Among patients declared adherent to drugs, poor BP control was significantly associated with the use of traditional medicine.

Key words: Hypertension, cardiology, antihypertensive medications, developing countries

Strengths and limitations of this study

- Our study included over 2000 patients from 29 tertiary centers in 17 cities from 12 low and middle countries from Sub-Saharan Africa.
- Caution is needed in extrapolating the information to other population because the sampling framework in each country was not nationally representative.
- We possibly over estimated cross-sectional associations between drug regimens and BP control because of other unknown cardiovascular indications.
- A multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from Africa and France conceived and designed the study
- Our study represents the first multination African report on antihypertensives strategies

Introduction

High blood pressure (BP) is one of the leading contributor to the global burden of chronic disease reaching 10 million deaths each year(1). In Africa, 130.2 million people suffer from hypertension and this figure is expected to reach 216.8 million by 2030(2). Hypertension is the leading cause of cardiovascular disease (CVD) in Africa; indeed, it is a major and independent risk factor for heart failure, stroke and kidney failure(3). In Sub-Saharan Africa (SSA), the overall prevalence of hypertension is 30%(4). In developed countries, improvements in hypertension control have led to considerable reduction in overall morbidity and mortality over the last fifty years(3). In SSA, the prevention of CVD is not always in the public health agenda (5).

A combination of lifestyle modification and blood pressure-lowering medications are the cornerstone of hypertension control. Randomized clinical trials conducted in high income countries have shown that antihypertensive medication therapy reduces BP and cardiovascular, cerebrovascular and renal morbidity and mortality(6). Various antihypertensive drug classes including calcium channel blockers, diuretics, renin-angiotensin system blockers, beta-blockers or centrally active drug can be used alone or in combination according to international guidelines to achieve BP control(7,8). Although international guidelines to manage hypertension contain recommendations for black adults who live mostly in high income countries outside of Africa(7), 74% of African countries have no dedicated guidelines for the management of hypertension for the predominantly black populations in these countries(4). Indeed, in SSA countries, five dimensions of access to medicine should be considered including availability, affordability, accessibility, acceptability and quality of medicines. Among these dimensions, acceptability describes how medicines are used in real-world settings, including appropriate prescription by physicians and behavior of patients (adherence and cultural factors)(9). A few studies describe access of medication in SSA and often they examine availability and affordability of antihypertensive medicines but not the acceptability and consequences of these medications on BP control(10).

There is scarce information from SSA(11). Published data are derived from worldwide studies, where SSA countries are poorly represented(12) or estimated(13). Conclusions of such global studies may not always be extrapolated to these SSA countries. Furthermore, most studies in SSA are limited to single countries or centers(14).

We aimed to explore acceptability by providing light on which antihypertensive drugs were prescribed by physicians and which factors were associated with the effectiveness of treatments. Therefore, the purpose of the current study is to describe antihypertensive drug strategies and identify treatment factors associated with

uncontrolled BP using a large multinational study conducted in 12 SSA countries: the EIGHT Study (Evaluation of Hypertension in Sub-Saharan Africa)(15).

Methods

Study design and setting

We conducted an observational cross-sectional study using data collected during outpatient consultations for hypertension in cardiology departments of 29 hospitals from 17 cities across 12 SSA countries (Benin, Cameroon, Congo (Brazzaville), Democratic Republic of the Congo, Gabon, Guinea, Côte d'Ivoire, Mauritania, Mozambic, Niger, Senegal, Togo) between January 2014 and November 2015.

A multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from Africa and France conceived and designed The Evaluation of Hypertension among Patients in Africa (EIGHT) study.

The EIGHT team had extensive prior research experience and existing collaborations with a network of physician-scientists in Africa in the field of Rheumatic heart disease(16), sickle cell(17) disease and quality of cardiovascular drugs(18) which aided planning and launch of the present study.

The study was approved by the Ile-de-France III ethics committee (Number 2014-A00710-47) and was declared to the National Commission of Informatics (Number 1762715). This study was exclusively supported by a public grant. Due to the observational, non-interventional nature of the study, with anonymized data, written informed consent was not required whereas patient non-opposition was documented, according to legislation. After providing information regarding the study, the investigator notified patient non opposition to participate in the study in the patient file.

Participants

Patients ≥18 years of age with hypertension were enrolled at any visit during outpatient consultations in the cardiology departments of the participating hospitals. Each patient received an information leaflet about the study. In addition, the on-site physician presented and explained the study in the regional language to all patients meeting eligibility criteria. Patients who agreed to participate completed a standardized questionnaire while waiting for their appointment. Participating physicians at each center received a training note detailing the study and standardized instructions on how they should interact with the patients while completing the questionnaire.

Patient and public involvement

Patients and public were not directly involved in research design, recruitment or conduct of this study

Measurements

A dedicated questionnaire was conceived for this study(15). A pilot investigation involving 90 patients who tested the questionnaire was conducted in January 2014 in Côte d'Ivoire.

Treatment factors

The first part of the questionnaire was completed by patients and collected data on patient sociodemographic factors (age, sex, and location), site of purchase of cardiovascular drugs, use of traditional medicine and adherence to treatment. A patient was defined as non-adherent if she/he reported sometimes forgetting to take medications in his/her self questionnaire.

The second part was filled out by the physician during the consultation and collected data on socioeconomic status (patient wealth index), antihypertensive drugs classes and generic prescriptions, blood pressure values (measured in standardized conditions, see below), and cardiovascular risk factors helping with the medical file if necessary.

Patient wealth index were assessed by the treating physician and classified as low, middle and high:

- "Low" defined poor patients who have difficulties to afford medical consultations
- "Middle" defined patients who cannot systematically paying medical consultations
- "High" defined patients who have no difficulties to pay medical consultations"

The antihypertensive drug classes recorded were: calcium channel blockers, diuretics, renin-angiotensin system blockers (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), beta-blockers, centrally active drugs and direct vasodilators. Antihypertensive drug strategies were defined according to the number of prescribed drug classes.

Blood pressure measurement

Seated office BP was measured twice by physicians, at least 15 minutes apart; participants were instructed to avoid caffeine and smoking within 30 minutes prior to BP measurement.

Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of the measured office BP values in the clinic(19).

Severity of hypertension was defined on uncontrolled BP according to European Society of Cardiology guidelines(19). Mild hypertension (SBP: 140-159 mmHg and/or DBP: 90-99 mmHg), moderate hypertension (SBP: 160-179 mmHg and/or DBP: 100-109 mmHg) and severe hypertension (SBP≥180 mmHg and/or DBP ≥110 mmHg).

Study power

The study was designed with 90% power to detect a relative difference superior at 5% on BP control between monotherapy and combination therapy group of patients (with a significance level of 5%). A total of 2060 patients were required.

Statistical analysis

Continuous and categorical variables were expressed as mean (standard deviation) and numbers (percentage) where appropriate.

Missing data were not imputed and taken into account in descriptive data. For statistical models, only complete cases were analyzed.

Categorical variables were compared using Chi-square tests.

It is difficult to interpret the potential role of antihypertensive drugs in non-adherent patients. Therefore, the association of treatments factors with uncontrolled hypertension and hypertension severity were assessed in adherent patients only. In this way, we studied the association of treatments factors with BP control in patients who reported actually taking their antihypertensive drugs. The following regression models were analyzed.

First, in univariate analysis, the odds ratio (OR) and 95% confidence intervals of the association of treatment factors (therapeutic strategy using two-drug strategies as the reference categories, antihypertensive drugs classes, prescription of generic drugs and use of traditional medicine) with uncontrolled BP were estimated in separate logistic regression models. A random effect for country was added (generalized estimated equation models) to account for inter-country variability. Interactions between antihypertensive strategies and each antihypertensive drug class were tested as well as interaction between patient wealth index and the use of traditional medicine. Then, in a multivariate analysis, models were adjusted for sociodemographic factors along with all factors with a p value of less than 0.2 in the univariate analysis.

Second, we quantified the association between treatment factors and hypertension severity using separate linear regression models with a random effect for country (generalized estimated equation models). As previously

stated, all factors with a p value of less than 0.2 as well as sociodemographic factors were included in a model for multivariable analysis.

A two tailed p value of <0.05 was considered significant. All analyses were performed through scripts developed in the R software (version 3.5.1 (2018-07-02)).

Results

Participants

The EIGHT study included 2198 patients with hypertension in 12 SSA countries between January 2014 and November 2015. Patients' baseline data are reported in Table 1. Mean age of patients was 58.3± 11.8 years. A greater proportion of patients were women (n=1324, 60.2%). Overall, 1017 patients (46.3%) were from low-income countries (Benin, Democratic Republic of the Congo, Guinea, Mozambic, Niger, and Togo), and 1181 (53.7%) were from middle-income countries (Cameroon, Congo [Brazzaville], Gabon, Côte d'Ivoire, Mauritania, and Senegal). Most of the patients were living in urban cities (n=1702, 78.9%) compared to rural areas (n=455, 21.1%). Individual wealth index was low, middle and high in 376 (17.6%), 1053 (49.2%) and 713 patients (33.3%) respectively.

Treatments

Overall, 96.6% (n=2123) of patients were prescribed antihypertensive medications (Table 1). Among treated patients, 653 (30.8%) patients received a monotherapy and 927 (43.6%) patients received two antihypertensive drugs classes (Table 1). Prescriptions of three, four, five and more antihypertensive drugs was found for 425 (20.0%), 107 (4.8%), 11 (0.4%) patients respectively. Characteristics of patients according to therapeutic strategy were detailed in Table 1.

Antihypertensive drug strategies according to country are displayed in Figure 1.

Calcium channel blockers (n=1219, 57.4%), diuretics (n=1167, 55.0%) and angiotensin-converting enzyme inhibitors (n=981, 46.2%) were the most commonly prescribed BP-lowering drugs overall (Table 1). Diuretics and renin-angiotensin system (RAS) blockers were most frequently prescribed as part of a two-drug antihypertensive medication strategy ($p<0.001$) as compared to a one drug or three or more-drug strategy. β-blockers were most frequently prescribed as part of a three or more drug antihypertensive medication strategy as compared to a one or two-drug strategy ($p<0.001$).

Antihypertensive drugs according to medication strategies are presented in Supplemental Table 1. Calcium channel blockers (CCB) were the most widely prescribed monotherapy (n=324, 49.6%) followed by RAS blockers (n=126, 19.3%), diuretics (n=122, 18.7%) and β-blockers (n=67, 10.3%). The three most common two-drug strategies were composed of diuretics + RAS blockers and CCBs + RAS blockers. Among three-drug

strategies, the three most common strategies (CCB + Diuretics + RAS blockers; Diuretics + β blockers + RAS blockers; CCB + β blockers + RAS blockers) represented 84.5% of prescriptions. The triple prescription strategies of Diuretics + CCB + RAS blockers represented almost half of the three-drug strategy prescriptions (n=250, 54.1%). Among four-drug strategies, the most common prescription strategy of CCB + Diuretics + β blockers + RAS blockers constituted 73.8% (n=79) of prescriptions.

About half of patients were prescribed at least one generic drug (n=801, 50%) (Table 1).

Among patients prescribed antihypertensive medication, 64% reported adherence to treatment.

A quarter (n=512, 24.1%) of patients used traditional medicine in addition to other drugs and this proportion was similar whatever the pharmacological antihypertensive drug strategy prescribed (monotherapy, two-drug strategies, three-drug strategies and more; p=0.107). The percentage of patients using traditional medicine varied from 9.9% (17/178) in Congo to 47.7% (82/172) in Guinea.

Factors associated with uncontrolled hypertension

Overall, 1630 (76.7%) had uncontrolled BP. BP control according to countries were depicted in Supplemental table 2. Drugs strategies by BP control are described in Table 1. In univariate analysis among patients who reported adherence to antihypertensive medication, factors associated with uncontrolled BP are detailed in Figure 2. The proportion of patients with uncontrolled BP was significantly increased with individual wealth index (middle versus high as reference), with monotherapy (versus two-drug therapy as reference) and with the use of traditional medicine ($p<0.05$). Patients treated with diuretics (versus patients without diuretics) had more frequently controlled BP (OR 0.72 [0.55-0.94] $p<0.05$); this association was not found for any other class of antihypertensive drugs.

In multivariable analysis among adherent patients adjusted for sociodemographic factors (age, sex, individual wealth index and location (rural or urban)), the use of traditional medicine remained the only factor significantly associated with uncontrolled hypertension (OR 1.72 [1.19-2.49], $p<0.01$) (Figure 3). None of the antihypertensive drugs classes alone was associated with uncontrolled hypertension. There was no significant interaction between antihypertensive drug strategy and class, and between patient wealth index and the use of traditional medicine.

Factors associated with severity of hypertension

Drugs strategies are described by hypertension severity in Table 1. Among patients with severe hypertension, 127 (27.5%) were treated with a monotherapy. This proportions varied across countries (Figure 4). In univariate analysis among adherent patients, the proportion of patients with severe hypertension was higher in patients with three-drug and more strategies (versus two-drug therapy), and with CCB, diuretics and the use traditional medicine ($p<0.05$) (Supplemental table 3).

In multivariable analysis among adherent patients adjusted for sociodemographic factors, the use of traditional medicine remained associated with higher grades of hypertension (linear regression coefficient=0.15; [0.029 - 0.28], $p<0.05$).

Discussion

Key results

Overall, 653 (30.8%) patients received antihypertensive medication monotherapy, 927 (43.6%) received two-drug strategies and 543 (25.6%) received three-drugs and more. These proportions varied across countries.

CCB was the most common antihypertensive drug class prescribed among all strategies. However, if angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were considered as one antihypertensive drug class merged into RAS blockers, they represented 68% of all prescriptions.

We found that the use of traditional medicine was an important determinant of poor BP control, beyond the traditional factors including patient wealth index and adherence to medication. Medical staff attention should particularly be provided to these patients.

Antihypertensive drug strategies

The proportion of patients on antihypertensive medications in our study was very high. This is related to the recruitment of patients during outpatient consultations in cardiology departments or urban hospitals. There is scarce data on proportion of patients treated with antihypertensive medication among patients aware of a hypertension diagnosis in SSA. According to the Eighth Joint National Committee, the first recommended line of treatment for black hypertensive patients is diuretics or CCB alone or in combination(20). Accordingly, CCBs alone or in combination were widely prescribed in our study. Surprisingly, RAS blockers and especially ACEI were the second most prescribed treatment alone before diuretics even though these are less effective compared with CCBs in reducing BP in black hypertensive patients(21). Physicians in the EIGHT study seem to follow international guidelines for black patients regarding CCB prescriptions. The high proportion of ACEI prescriptions (usually not recommended for black patients except for compelling indications including heart failure, post-myocardial infarction, diabetes, proteinuric nephropathy) suggests that continuing education of physician could be an avenue for improved care. Though, our methodology did not allow to completely distinguish indications of some drugs, and particularly to know whether ACEI were prescribed in a compelling indication because of the non-reported patient's comorbidities. Diuretics should be considered, particularly due to their low cost(22) .

Even among patients recruited from tertiary cardiology centers in urban areas in Sub-Saharan countries, BP control remains very poor and monotherapy remains widely prescribed. Some barriers associated with uptitration

of treatments could be cited. Access to medicines, defined by availability, affordability, accessibility, quality and acceptability of antihypertensive drugs varied across low and middle-income countries. These factors are associated with poor blood pressure control (9,23,24).

In low and middle-income countries, a large proportion of communities do not have access to more than one antihypertensive drug and, when available, they are often not affordable. In a multinational study among 68 950 households, the proportion of households unable to afford two blood pressure-lowering medicines was 31% in low-income countries and 9% in middle-income countries (11). Furthermore, we cannot exclude that the pharmaceutical quality of drugs did not contribute to treatment failure. Indeed, we have previously shown in the SEVEN study that 16% of cardiovascular drugs have poor quality in SSA, especially calcium channel blockers, and the proportion of poor quality can reach 50% when drugs produced in Asia are sold in street markets (18).

Among solutions, fixed drug combinations have been shown to enhance adherence and effectiveness of treatment by combining different treatments with different mechanisms of action. Randomized Controlled Trial on adherence to treatment by providing fixed drug combination free of charge in other part of the world achieve to increase blood pressure control (25). However, fixed drug combinations are poorly available and affordable in low and middle-income countries. Nevertheless, using fixed drug combinations had limitations: they may have potentially higher prices versus the cost of the components combined, they may be only available as "branded" medicines in some countries and consequently only available in private pharmacies rather than public facilities and not in rural area (26).

Traditional medicine

Our results underlined the strong association between the use of traditional medicine and uncontrolled BP, after adjusting for well-known factors associated with poor BP control including age, sex, socioeconomic factors, and poor adherence to treatment(27). The WHO define the use of traditional medicine as the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness(28). The prevalence of the use of traditional medicine is rising worldwide and is well documented in both African countries and worldwide to be between 20-80%(29,30). We found that 24.1% of patients (range 9.9% to 47.7%) used traditional medicine, consistent with the literature(31). Several factors have previously been reported to be associated with the use of traditional medicine including socio-demographic characteristics of patients, dissatisfaction with conventional treatments (ineffective treatments or side effects), cultural beliefs that illnesses have a "spiritual" origin, availability and

affordability of antihypertensive drugs(31). In our study, conventional medicine and traditional medicine were concurrently used**.** Studies have shown that patients used traditional medicine along with their conventional treatments(32) but use of traditional medicine was strongly associated with poor adherence to conventional treatments(27). Our study methodology does not allow us to describe more specifically patients' behavior towards traditional medicine. The reasons why patients choose to use traditional medicine have been much discussed but not fully understood(33,34). They may lose trust confidence in conventional medicine. In our study, patients declared to use traditional medicine, unfortunately details of traditional medicine were not depicted (herbal medicines, indigenous healthcare practices, complementary and alternative medicine like acupuncture or chiropractic, consultation of traditional health practitioners). Use of natural medicines is one kind of Traditional medicine. Systematic review on traditional herbal medicine use among hypertensive patients in SSA have been published (35) and they find a list of more than 20 different herbal used in different form (extract that needed to be dissolved, steam inhalation, single herbs, and mixtures herbs). We cannot exclude that this preparation of natural medicine could increase blood pressure. In SSA, traditional health practitioner and physicians are cohabiting. To the burden of high blood pressure, they should work together to improve blood pressure control. Interventional models of care to fight hypertension are currently being developed and for us, traditional medicine should be integrated as a part of hypertension management. In a previous analysis of the EIGHT study, the use of traditional medicine was shown to be strongly associated with poor adherence to conventional treatments (27). It would be an interesting and useful addition to include traditional medicine and traditional health practitioners in interventional model of care(36,37).

Limitation and strength

We acknowledged the following limitations. Caution is needed in extrapolating the information in the current study to other population because the sampling framework in each country was not nationally representative. The data in the EIGHT study were derived from urban clinics and likely represents the best-case scenario for BP treatment and control. Therefore, the magnitude of uncontrolled BP in the general population with hypertension could be underestimated. Although a random selection of centers would be ideal from a methodological perspective, such an approach is not practical given the lack of cardiovascular care in this part of the world. We can fear to overestimate blood pressure figures and therefore uncontrolled hypertension because of the white coat effect during one visit. We tried to consider this effect by measuring seated office BP twice by physicians. We chose this measure because it was appropriate for the African setting. Defining uncontrolled hypertension versus controlled hypertension based on office blood pressure readings during one visit was open to criticism but we

cannot be sure that patients will ever come back in outpatient consultation. Concerning antihypertensive drugs classes, aldosterone antagonist and thiazide diuretic were not differentiated in our study. For antihypertensive drug strategies, even if a patient has a prescription for single-pill combination, they may be unable to purchase this treatment. We therefore decided not to incorporate this information in our analysis. We probably over estimated cross-sectional associations between drug regimens and BP control because of other unknown cardiovascular indications. Furthermore, this study could not take into account the role of indication bias in interpreting cross-sectional associations between drug regimens and BP control. We could fear to overestimate adherence because of using self-reported questionnaire. However, self-reported medication adherence is a practical way to measure adherence because of its low cost and potential to be easily implemented into the clinical workflow. Also, evidence pointed out that self- reported adherence is predictive of clinical outcomes and especially in hypertension (38,39).

This study had many strengths including its multisite design, with over 2000 patients from 29 medical centers in 17 cities from 12 countries. Actual data on management of cardiovascular disease are uncommon in Africa and are usually derived from small, single center studies. The EIGHT study embraced 12 African countries which are usually not considered in international studies, such as the PURE study(11) providing global data on cardiovascular epidemiology. Furthermore, this study was supported by a strong and structured collaborative multidisciplinary network. Active involvement of African cardiologists, who are familiar with the problems of this area, helped derive specific questions and analysis.

Conclusion

Hypertension is a rapidly growing epidemic in low and middle income countries. In this multinational study, we described antihypertensive drugs by classes in Sub-Saharan Africa. Our study provided large scale data on antihypertensive prescriptions in the African continent. Among patients declared adherent to drugs, poor BP control was significantly associated with the use of traditional medicine.

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Author's contribution:

All authors have substantial contributions.

P. Cavagna, M. Antignac and X. Jouven had full access to the whole data in the study and take responsibility for integrity of the data and accuracy of data analysis. Those authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Ethical Approval Statement: The study was approved by the Ile-de-France III ethics committee (Number 2014-A00710-47) and was declared to the National Commission of Informatics (Number 1762715).

References

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl. 2018 10;392(10159):1923–94.

2. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. PloS One. 2014;9(8):e104300.

3. Kayima J., Wanyenze R.K., Katamba A., Leontsini E., Nuwaha F. Hypertension awareness, treatment and control in Africa: A systematic review. BMC Cardiovasc Disord [Internet]. 2013;13(54). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52715263

4. Kuate Defo B, Mbanya JC, Kingue S, Tardif J-C, Choukem SP, Perreault S, et al. Blood pressure and burden of hypertension in Cameroon, a microcosm of Africa: a systematic review and meta-analysis of population-based studies. J Hypertens. 2019 Jun;1.

5. Twagirumukiza M, De Bacquer D, Kips JG, de Backer G, Stichele RV, Van Bortel LM. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. J Hypertens. 2011 Jul;29(7):1243–52.

6. Mills KT, Obst KM, Shen W, Molina S, Zhang H-J, He H, et al. Comparative Effectiveness of Implementation Strategies for Blood Pressure Control in Hypertensive Patients: A Systematic Review and Meta-analysis. Ann Intern Med. 2018 16;168(2):110–20.

7. Mancia G, Rosei EA, Azizi M, Burnier M, Clement DL, Coca A, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. :98.

8. Whelton Paul K., Carey Robert M., Aronow Wilbert S., Casey Donald E., Collins Karen J., Dennison Himmelfarb Cheryl, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun 1;71(6):e13–115.

9. Wirtz VJ, Kaplan WA, Kwan GF, Laing RO. Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries. Circulation. 2016 May 24;133(21):2076–85.

10. Antignac M, Marijon E, Jouven X. Letter by Antignac et al Regarding Article "Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries." Circulation. 2016 04;134(14):e303–4.

11. Attaei MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet Public Health. 2017;2(9):e411–9.

12. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJL. Estimates of global and regional premature cardiovascular mortality in 2025. Circulation. 2015 Sep 29;132(13):1270–82.

13. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013 Sep 4;310(9):959–68.

14. Mutua EM, Gitonga MM, Mbuthia B, Muiruri N, Cheptum JJ, Maingi T. Level of blood pressure control among hypertensive patients on follow-up in a regional referral hospital in Central Kenya. Pan Afr Med J. 2014;18:278.

15. Antignac M, Diop IB, Macquart de Terline D, Kramoh KE, Balde DM, Dzudie A, et al. Socioeconomic Status and Hypertension Control in Sub-Saharan Africa: The Multination EIGHT Study (Evaluation of Hypertension in Sub-Saharan Africa). Hypertension. 2018 Apr;71(4):577–84.

16. Marijon E, Ferreira B, Paquet C, Jouven X. Prevalence of Rheumatic Heart Disease Detected by Echocardiographic Screening. N Engl J Med. 2007;357:470–6.

17. Ranque B, Menet A, Diop IB, Thiam MM, Diallo D, Diop S, et al. Early renal damage in patients with sickle cell disease in sub-Saharan Africa: a multinational, prospective, cross-sectional study. Lancet Haematol. 2014 Nov;1(2):e64-73.

18. Antignac M, Diop BI, Macquart de Terline D, Bernard M, Do B, Ikama SM, et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. Int J Cardiol. 2017 Sep 15;243:523–8.

19. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013 Oct;31(10):1925–38.

20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507–20.

21. Leenen FHH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertens Dallas Tex 1979. 2006 Sep;48(3):374–84.

22. Kramoh K.E., Aké-Traboulsi E., Konin C., N'Goran Y., Coulibaly I., Adoubi A., et al. Management of hypertension in the elderly patient at Abidjan cardiology institute (Ivory Coast). Int J Hypertens [Internet]. 2012;2012

23. Ashigbie PG, Rockers PC, Laing RO, Cabral HJ, Onyango MA, Buleti JPL, et al. Availability and prices of medicines for non-communicable diseases at health facilities and retail drug outlets in Kenya: a cross-sectional survey in eight counties. BMJ Open. 2020 May 15;10(5):e035132.

24. Kaiser AH, Hehman L, Forsberg BC, Simangolwa WM, Sundewall J. Availability, prices and affordability of essential medicines for treatment of diabetes and hypertension in private pharmacies in Zambia. Thet Wai K, editor. PLOS ONE. 2019 Dec 13;14(12):e0226169.

25. Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, et al. Effect on Treatment Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized Clinical Trial. JAMA Intern Med. 2020 Jan 1;180(1):27–34.

26. Godman B, McCabe H, D Leong T. Fixed dose drug combinations - are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries. Expert Rev Pharmacoecon Outcomes Res. 2020 Feb;20(1):1–26.

27. Macquart de Terline D, Kane A, Kramoh KE, Ali Toure I, Mipinda JB, Diop IB, et al. Factors associated with poor adherence to medication among hypertensive patients in twelve low and middle income Sub-Saharan countries. Li Y, editor. PLOS ONE. 2019 Jul 10;14(7):e0219266.

28. World Health Organization, editor. WHO traditional medicine strategy. 2014-2023. Geneva: World Health Organization; 2013. 76 p.

29. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative

medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998 Nov 11;280(18):1569–75.

30. Eddouks M, Maghrani M, Lemhadri A, Ouahidi M-L, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol. 2002 Oct;82(2–3):97–103.

31. Osamor PE, Owumi BE. Complementary and alternative medicine in the management of hypertension in an urban Nigerian community. BMC Complement Altern Med. 2010 Jul 19;10:36.

32. Nuwaha F, Musinguzi G. Use of alternative medicine for hypertension in Buikwe and Mukono districts of Uganda: a cross sectional study. BMC Complement Altern Med. 2013 Nov 4;13:301.

33. Lorenc A, Ilan-Clarke Y, Robinson N, Blair M. How parents choose to use CAM: a systematic review of theoretical models. BMC Complement Altern Med. 2009 Dec;9(1):9.

34. James PB, Wardle J, Steel A, Adams J. Traditional, complementary and alternative medicine use in Sub-Saharan Africa: a systematic review. BMJ Glob Health. 2018 Oct;3(5):e000895.

35. Liwa A., Roediger R., Jaka H., Bougaila A., Smart L., Langwick S., et al. Herbal and Alternative Medicine Use in Tanzanian Adults Admitted with Hypertension-Related Diseases: A Mixed-Methods Study. Int J Hypertens [Internet]. 2017;2017

36. Krah E, de Kruijf J, Ragno L. Integrating Traditional Healers into the Health Care System: Challenges and Opportunities in Rural Northern Ghana. J Community Health. 2018;43(1):157–63.

37. Cavagna P, Kramoh KE, Sidy Ali A, Balde DM, Traore AK, Khoury S, et al. The importance of considering cultural and environmental elements in an interventional model of care to fight hypertension in Africa. J Clin Hypertens. 2021 Jun;23(6):1269–70.

38. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013 Oct 7;34(38):2940–8.

39. Korb-Savoldelli V, Gillaizeau F, Pouchot J, Lenain E, Postel-Vinay N, Plouin P-F, et al. Validation of a French Version of the 8-Item Morisky Medication Adherence Scale in Hypertensive Adults: Validation of a French Version of MMAS. J Clin Hypertens. 2012 Jul;14(7):429–34.

Figures: titles and legends

Figure 1: Antihypertensive drugs strategies (%) according to countries level income and countries

Legend: bars represent the percentage of antihypertensive drugs strategies

Figure 2: Odds ratio (OR) of sociodemographic and treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications in univariate analysis.

Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. *RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.*

Figure 3: Odds ratio (OR) of treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications adjusted for sociodemographic factors in multivariate analysis.

Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. *RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.*

Figure 4: Proportion of monotherapy in patients with severe hypertension.

Legend: Grey countries were not included in the EIGHT study.

Table 1: Characteristics of participants according to therapeutic strategy

	GLOBAL	No drugs	Monotherapy	Two-drug therapy	Three-drug and +
Overall					
N, (%)	2198	75 (3.4)	653 (29.7)	927 (42.2)	543 (24.7)
Age (year), mean (sd)	58.3 (11.8)	55.3 (14.1)	57.8 (12.12)	58.5 (11.70)	58.9 (11.09)
Male, N (%)	874 (39.8)	22 (29.3)	248 (38.0)	385 (41.5)	219 (40.3)
Patient wealth index, N (%)					
Low	376 (17.6)	15 (22.4)	109 (17.2)	166 (18.3)	86 (16.2)
Middle	1053 (49.2)	36 (53.7)	302 (47.6)	450 (49.5)	265 (49.8)
High	713 (33.3)	16 (23.9)	224 (35.2)	292 (32.2)	181 (34.0)
NA	56	8	18	19	11
Country-level income (Low vs Middle), N (%)	1017 (46.3)	23 (30.7)	361 (55.3)	419 (45.2)	214 (39.4)
Location (Urban vs Rural), N (%)	1702 (78.9)	56 (74.7)	485 (75.7)	729 (80.3)	432 (81.1)
NA	41	0	12	19	10
Cardiovascular risks factors, N (%)					
Tobacco use	84 (5.1)	7 (13.7)	16 (3.4)	45 (6.5)	16 (3.7)
Diabetes mellitus	288 (17.5)	8 (15.7)	74 (15.6)	119 (17.3)	87 (20.2)
Hypercholesterolemia	328 (19.9)	4 (7.8)	75 (15.8)	142 (20.6)	107 (24.9)
Hypertriglyceridemia	88 (5.3)	0 (0.0)	26 (5.5)	43 (6.2)	19 (4.4)
Obesity	340 (20.7)	16 (31.4)	79 (16.6)	144 (20.9)	101 (23.5)
Sedentary Lifestyle	649 (39.5)	29 (56.9)	169 (35.6)	254 (36.9)	197 (45.8)
None	461 (28.0)	8 (15.7)	160 (33.7)	193 (28.0)	100 (23.3)
NA	553	113	24	178	283
Year since hypertension diagnosis (>1 year), N (%)	1816 (84.4)	45 (67.1)	487 (76.1)	802 (87.8)	482 (90.8)
NA	47	8	13	14	12
Among treated patients		-			
Patients on antihypertensive medication, N (%)	2123 (96.6)	-	653 (30.8)	927 (43.6)	543 (25.6)
Antihypertensive drug class, N (%)		-			
Calcium channel blocker	1219 (57.4)	-	324 (26.6)	457 (37.5)	438 (35.9)
Diuretic	1167 (55.0)	-	122 (10.5)	567 (48.5)	478 (41.0)
RAS Blocker : Angiotensin-converting-enzyme inhibitor	981 (46.2)	-	94 (9.6)	505 (51.5)	382 (38.9)
RAS Blocker : Angiotensin II receptor antagonist	321 (15.1)	-	32 (10)	163 (50.8)	126 (39.3)
Beta-blocker	466 (22.0)	-	67 (14.4)	138 (29.6)	261 (56)
Centrally active drug	79 (3.7)	-	12 (15.2)	20 (25.3)	47 (59.5)
Vasodilator	33 (1.6)	-	2 (6.1)	4 (12.1)	27 (81.8)
Prescription of generic drug, N (%)	801 (50.1)	-	225 (48.9)	298 (44.2)	273 (62.5)
NA	599	-	193	253	106
Use of traditional medicine, N (%)	512 (24.1)	-	150 (23.7)	231 (25.5)	107 (20.6)
NA	70	-	21	22	23
Patient reported adherence to antihypertensive medication, N (%)	1359 (64)	-	397 (29.2)	597 (43.9)	365 (26.8)
Office Blood pressure, mean (sd)		-			
Systolic blood pressure, mmHg	148.9 (23.4)	-	147.2 (21.6)	147.1 (22.4)	154 (26.5)
Diastolic blood pressure, mmHg	88.2 (14.2)	-	89.2 (13.9)	87.3 (14)	88.7 (14.7)
Blood pressure control* (Uncontrolled vs controlled), N (%)	1630 (76.7)	-	519 (79.7)	682 (73.9)	429 (79.4)
NA	10	-	2	5	3
Hypertension severity, N (%)		-			
Mild	625 (38.3)	-	212 (40.8)	270 (39.6)	143 (33.3)
Moderate	543 (33.3)	-	180 (34.6)	226 (33.1)	137 (31.9)
Severe	462 (28.3)	-	127 (24.4)	186 (27.3)	149 (34.8)

Legend:* Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic.

Supplemental Digital Content: Titles and legend

Supplemental Table 1. Antihypertensive drugs according to medication strategies

Legend: β blockers: Beta blockers, CCB: Calcium channel blockers, RAS blockers: Renin-Angiotensin System blockers

*Combination therapy recommended

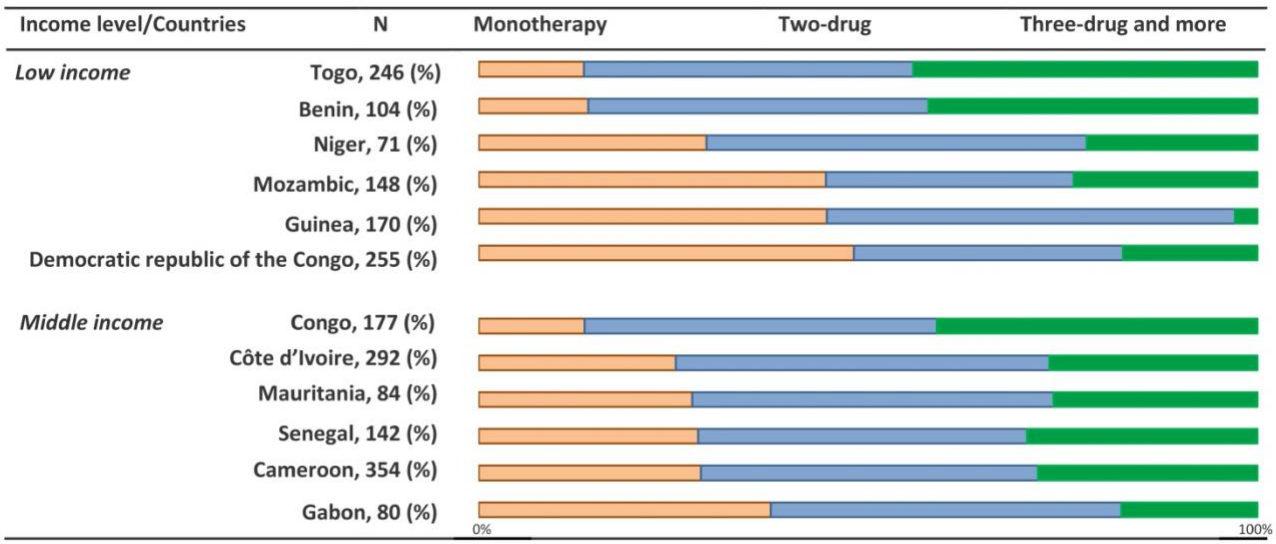
† Patient with six-drug strategies were not presented

Supplemental Table 2: Treatments characteristics by country among treated patients

***** Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic

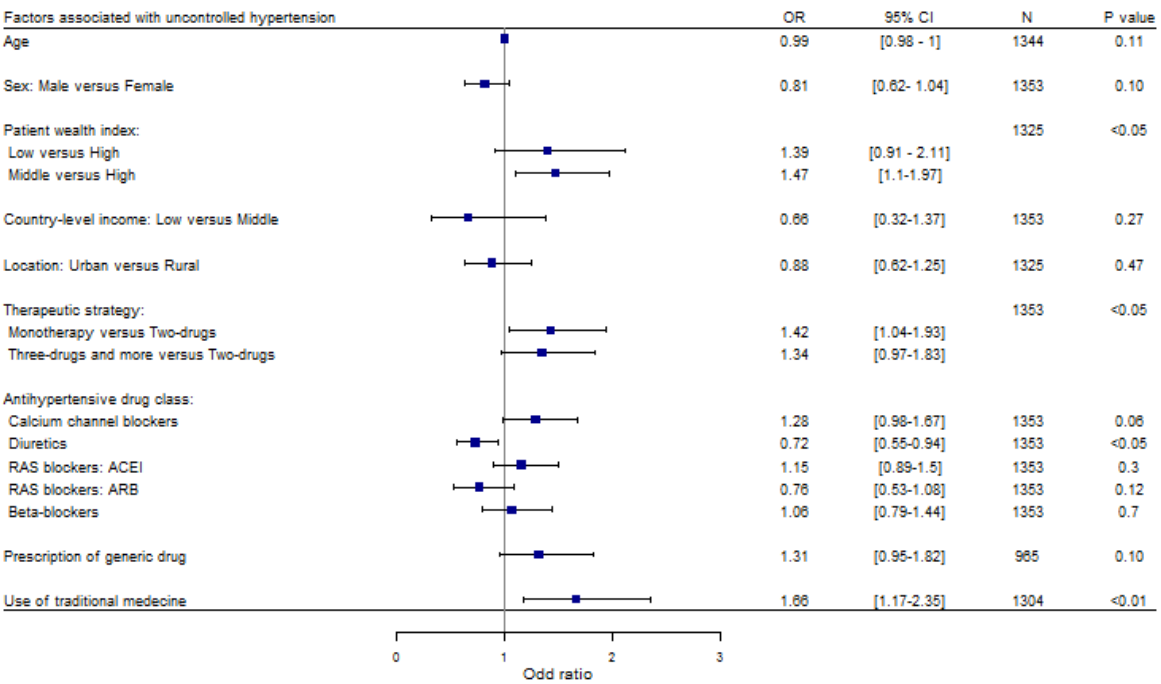
Supplemental Table 3: Linear regression coefficient of sociodemographic and treatments factors for severity of hypertension in univariate analysis.

Figure 1: Antihypertensive drugs strategies (%) according to countries level income and countries



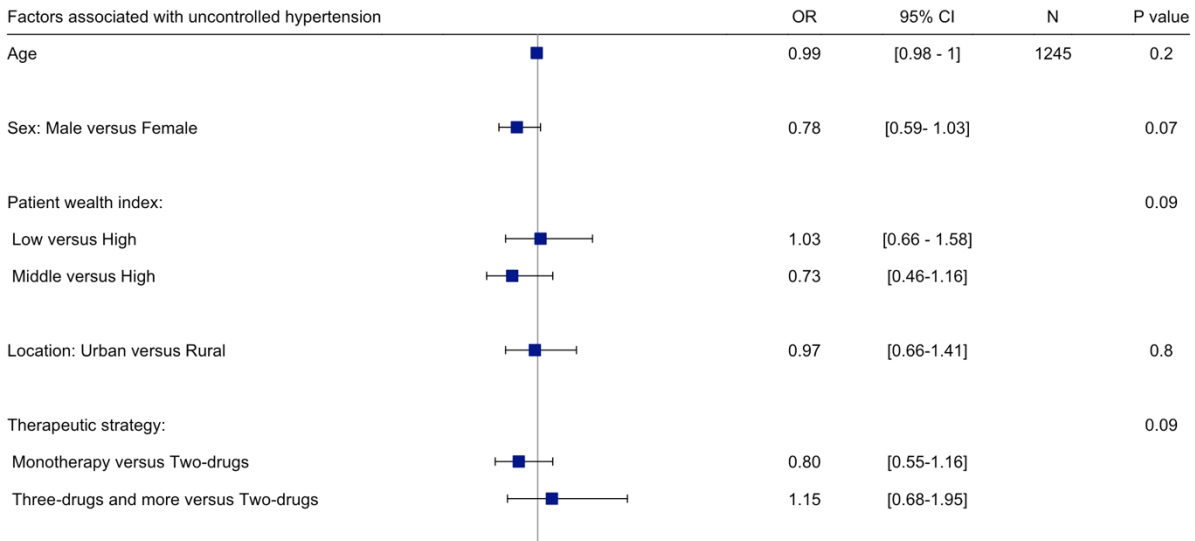
Legend: bars represent the percentage of antihypertensive drugs strategies

Figure 2: Odds ratio (OR) of sociodemographic and treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications in univariate analysis.



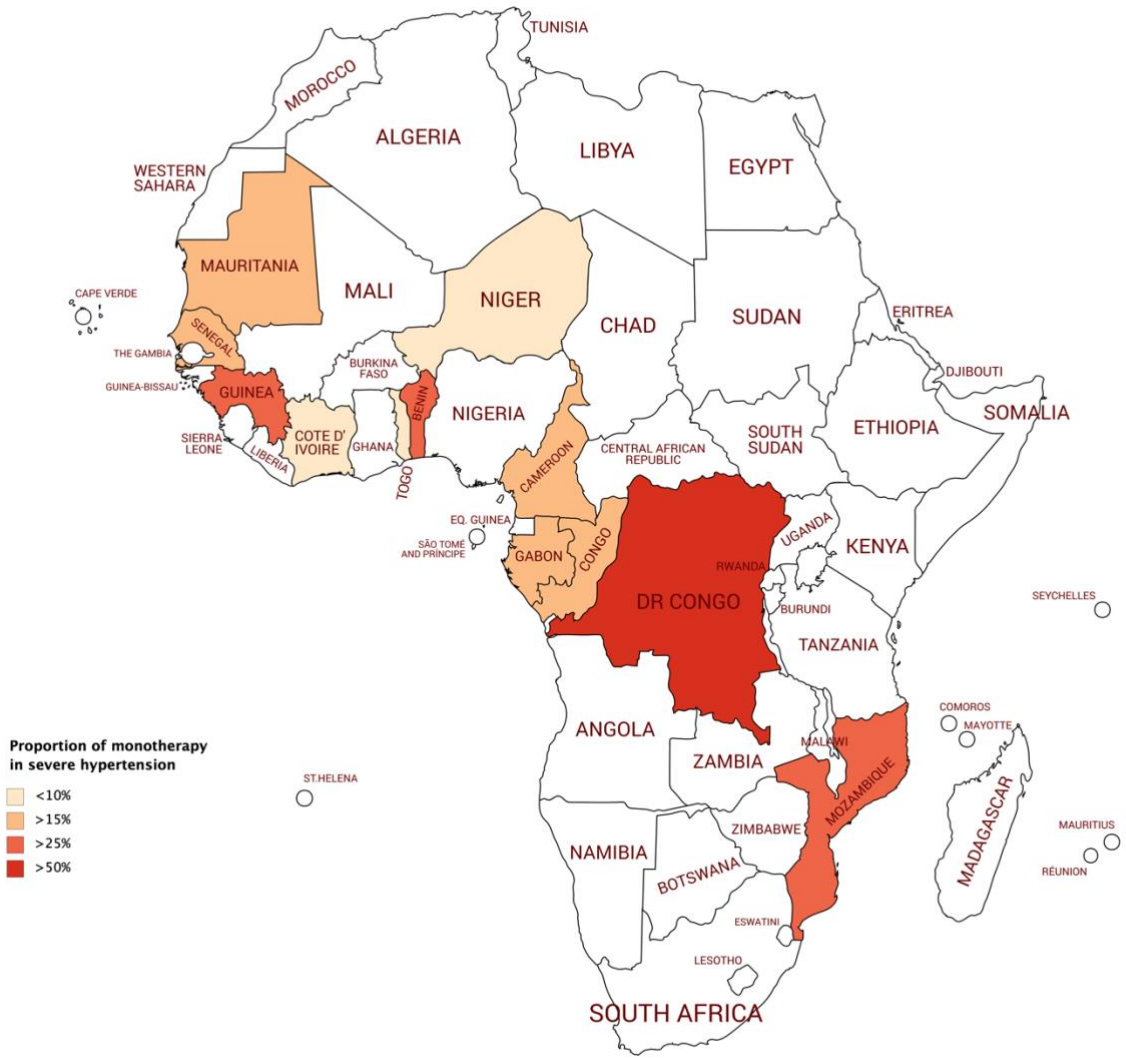
Legend: Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.

Figure 3: Odds ratio (OR) of treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications adjusted for sociodemographic factors in multivariate analysis.



Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.

Figure 4: Proportion of monotherapy in patients with severe hypertension



Legend: White countries were not included in the EIGHT study.

Supplemental Table 1. Antihypertensive drugs according to medication strategies

	N, (%)
Monotherapy	**653 (30.8)**
Calcium channel blockers (CCB)	324 (49.6)
Renin-Angiotensin system (RAS) blockers	126 (19.3)
Diuretics	122 (18.7)
Beta-blockers (β blockers)	67 (10.3)
Centrally active drug	12 (1.8)
Vasodilator	2 (0.3)
Two-drug strategies	**927 (43.6)**
Diuretics + RAS blockers*	387 (41.7)
CCB + RAS blockers*	240 (25.9)
CCB + Diuretics *	140 (15.1)
CCB + β blockers*	61 (6.6)
β blockers + RAS blockers	38 (4.1)
Diuretic + β blockers *	37 (4.0)
Centrally active drug + Other drug class	20 (2.2)
Vasodilator + Other drug class	4 (0.4)
Three-drug strategies	**425 (20.0)**
CCB + Diuretics + RAS blockers*	230 (54.1)
Diuretics + β blockers + RAS blockers	84 (19.8)
CCB + β blockers + RAS blockers	45 (10.6)
CCB + Diuretics + β blockers *	26 (6.1)
Centrally active drug + Other drug class	23 (5.4)
Vasodilator + Other drug class	15 (3.5)
2 RAS blockers + Other drug class	2 (0.4)
Four-drug strategies	**107 (5)**
CCB + Diuretics + β blockers + RAS blockers	79 (73.8)
Centrally active drug + Other drug class	17 (15.9)
Vasodilator + Other drug class	6 (5.6)
2 RAS blockers + Other drug class	4 (3.7)
Five-drug strategies and more †	**11 (0.4)**
CCB + Diuretics + β blockers + RAS blockers + Centrally active drug	4 (40.0)
CCB + Diuretics + β blockers + RAS blockers + Vasodilator	4 (40.0)
CCB + Diuretics + RAS blockers + Centrally active drug + Vasodilator	1 (10.0)
Diuretics + β blockers + 2 RAS blockers + Centrally active drug	1 (10.0)

Legend: β blockers: Beta blockers, CCB: Calcium channel blockers, RAS blockers: Renin-Angiotensin System blockers

*Combination therapy recommended

† Patient with six-drug strategies were not presented

Supplemental Table 2: Treatments characteristics by country among treated patients

	Niger	Togo	Benin	Guinea	Mozambic	Dem. Rep of the Congo	Congo	Senega	Côte d'Ivoire	Cameroon	Mauritania	Gabon
N, (%)	71(3.")	104 (4.9)	246 (11.6)	170 (8.0)	148 (7.0)	255 (12.0)	177 (8.3)	142 (6.7)	292 (13.7)	354 (16.7)	84 (3.9)	80 (3.8)
Blood pressure control* (Uncontrolled vs controlled), N (%)	65 (84.4)	77 (72.6)	142 (57)	125 (73.5)	119 (80.4)	232 (89.2)	134 (75.3)	128 (80.5)	228 (77.8)	285 (76.6)	68 (81)	89 (100
NA	3	0	1	2	0	1	0	1	2	3	0	0
Therapeutic Strategies, N (%)												
Monotherapy	10 (14.1)	14 (13.5)	72 (29.3)	76 (44.7)	66 (44.6)	123 (48.2)	24 (13.6)	40 (28.2)	74 (25.3)	101 (28.5)	23 (27.4)	30 (37.5)
Two-drug strategies	31 (43.7)	44 (42.3)	120 (48.9)	89 (52.4)	47 (31.8)	88 (34.5)	80 (45.2)	60 (42.2)	140 (47.9)	153 (43.0)	39 (46.4)	36 (45.0)
Three and more drugs strategies	30 (42.3)	46 (44.2)	54 (22.0)	5 (2.9)	35 (23.6)	44 (17.3)	73 (41.2)	42 (29.6)	78 (26.7)	100 (28.2)	22 (26.2)	14 (17.5)

***** Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic

Supplemental Table 3: Linear regression coefficient of sociodemographic and treatments factors for severity of hypertension in univariate analysis

	N	Linear regression coefficients	CI 95%	P value
Age	1017	-0.0021	-0.006 – 0.002	0.32
Sex (Male versus Female)	1023	0.087	-0.012 – 0.186	0.08
Patient Wealth index:	1004			0.10
Low versus high		0.15	0.0012 – 0.305	
Middle versus high		0.009	-0.101 – 0.12	
Location : urban versus rural	1001	-0.011	-0.136 – 0.112	0.86
Therapeutic strategy:	1023			<0.01
Monotherapy versus two-drugs		-0.106	-0.22 – 0.007	
Three-drugs and more versus two-drugs		0.155	0.037 – 0.273	
Antihypertensive drug class:				
Calcium channel blockers	1023	0.107	0.008 – 0.207	0.03
Diuretics	1023	0.136	0.039 – 0.233	<0.01
RAS blockers : ACEI	1023	0.043	-0.057 – 0.144	0.39
RAS blockers : ARB	1023	0.090	-0.05 – 0.231	0.21
Beta blockers	1023	-0.015	-0.131 – 0.099	0.797
Prescription of generic drug	731	0.025	-0.099 – 0.147	0.68
Use of traditional medicine	976	0.168	0.045 – 0.291	<0.01

Legend: Linear regression coefficients derived from separated linear regression with a random effect on country

to account for inter-country variability

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional 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	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	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
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
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	7
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	7
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	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*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
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10-11
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	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	16

*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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Blood pressure lowering medicines implemented in 12 African countries: The cross-sectional multination EIGHT Study

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Title page:

Full title: Blood pressure lowering medicines implemented in 12 African countries: The cross-sectional multination EIGHT Study

Short title: Antihypertensive strategies in Africa

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Abstract

Objective: In Africa, the number of patients with hypertension is expected to reach 216.8 million by 2030. Large-scale data on antihypertensive medications used in Sub-Saharan Africa are scarce.

Here, we describe antihypertensive drug strategies and identify treatment factors associated with blood pressure (BP) control in 12 Sub-Saharan countries.

Setting: Outpatient consultations for hypertension in urban tertiary cardiology centers of 29 hospitals from 17 cities across 12 SSA countries between January 2014 and November 2015.

Participants: Patients ≥18 years of age with hypertension were enrolled at any visit during outpatient consultations in the cardiology departments

Main outcome measure: We collected BP levels, demographic characteristics, and antihypertensive treatment use (including traditional medicine) of patients with hypertension attending outpatient visits. BP control was defined as seated office BP<140/90mmHg. We used logistic regression with a random effect on countries to assess factors of BP control.

Results: Overall, 2198 hypertensive patients were included and a total of 96.6% (n=2123) were on antihypertensive medications. Among treated patients, 653(30.8%) patients received a monotherapy by calcium channel blocker (n=324, 49.6%), renin angiotensin system blocker (RAS)(n=126, 19.3%) or diuretic (n=122, 18.7%). Two-drug strategies were prescribed in 927(43.6%) patients including mainly diuretics and RAS(n=327, 42% of two-drug strategies). Prescriptions of three-drugs or more were used in 543(25.6%) patients. Overall, among treated patients, 1630(76.7%) had uncontrolled BP, of whom 462(28.3%) had BP levels ≥180/110mmHg, mainly in those on monotherapy. After adjustment for sociodemographic factors, the use of traditional medicine was the only factor significantly associated with uncontrolled BP(OR 1.72 [1.19-2.49] p<0.01).

Conclusion: Our study provided large scale data on antihypertensive prescriptions in the African continent. Among patients declared adherent to drugs, poor BP control was significantly associated with the use of traditional medicine.

Key words: Hypertension, cardiology, antihypertensive medications, developing countries

Strengths and limitations of this study

- Our study included over 2000 patients from 29 tertiary centers in 17 cities from 12 low and middle countries from Sub-Saharan Africa.
- Caution is needed in extrapolating the information to other population because the sampling framework in each country was not nationally representative.
- We possibly over estimated cross-sectional associations between drug regimens and BP control because of other unknown cardiovascular indications.
- A multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from Africa and France conceived and designed the study
- Our study represents the first multination African report on antihypertensives strategies

Introduction

High blood pressure (BP) is one of the leading contributor to the global burden of chronic disease reaching 10 million deaths each year(1). In Africa, 130.2 million people suffer from hypertension and this figure is expected to reach 216.8 million by 2030(2). Hypertension is the leading cause of cardiovascular disease (CVD) in Africa; indeed, it is a major and independent risk factor for heart failure, stroke and kidney failure(3). In Sub-Saharan Africa (SSA), the overall prevalence of hypertension is 30%(4). In developed countries, improvements in hypertension control have led to considerable reduction in overall morbidity and mortality over the last fifty years(3). In SSA, the prevention of CVD is not always in the public health agenda (5).

A combination of lifestyle modification and blood pressure-lowering medications are the cornerstone of hypertension control. Randomized clinical trials conducted in high income countries have shown that antihypertensive medication therapy reduces BP and cardiovascular, cerebrovascular and renal morbidity and mortality(6). Various antihypertensive drug classes including calcium channel blockers, diuretics, renin-angiotensin system blockers, beta-blockers or centrally active drug can be used alone or in combination according to international guidelines to achieve BP control(7,8). Although international guidelines to manage hypertension contain recommendations for black adults who live mostly in high income countries outside of Africa(7), 74% of African countries have no dedicated guidelines for the management of hypertension for the predominantly black populations in these countries(4). Indeed, in SSA countries, five dimensions of access to medicine should be considered including availability, affordability, accessibility, acceptability and quality of medicines. Among these dimensions, acceptability describes how medicines are used in real-world settings, including appropriate prescription by physicians and behavior of patients (adherence and cultural factors)(9). A few studies describe access of medication in SSA and often they examine availability and affordability of antihypertensive medicines but not the acceptability and consequences of these medications on BP control(10).

There is scarce information from SSA(11). Published data are derived from worldwide studies, where SSA countries are poorly represented(12) or estimated(13). Conclusions of such global studies may not always be extrapolated to these SSA countries. Furthermore, most studies in SSA are limited to single countries or centers(14).

We aimed to explore acceptability by providing light on which antihypertensive drugs were prescribed by physicians and which factors were associated with the effectiveness of treatments. Therefore, the purpose of the current study is to describe antihypertensive drug strategies and identify treatment factors associated with

uncontrolled BP using a large multinational study conducted in 12 SSA countries: the EIGHT Study (Evaluation of Hypertension in Sub-Saharan Africa)(15).

Methods

Study design and setting

We conducted an observational cross-sectional study using data collected during outpatient consultations for hypertension in cardiology departments of 29 hospitals from 17 cities across 12 SSA countries (Benin, Cameroon, Congo (Brazzaville), Democratic Republic of the Congo, Gabon, Guinea, Côte d'Ivoire, Mauritania, Mozambic, Niger, Senegal, Togo) between January 2014 and November 2015.

A multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from Africa and France conceived and designed The Evaluation of Hypertension among Patients in Africa (EIGHT) study.

The EIGHT team had extensive prior research experience and existing collaborations with a network of physician-scientists in Africa in the field of Rheumatic heart disease(16), sickle cell(17) disease and quality of cardiovascular drugs(18) which aided planning and launch of the present study.

The study was approved by the Ile-de-France III ethics committee (Number 2014-A00710-47) and was declared to the National Commission of Informatics (Number 1762715). This study was exclusively supported by a public grant. Due to the observational, non-interventional nature of the study, with anonymized data, written informed consent was not required whereas patient non-opposition was documented, according to legislation. After providing information regarding the study, the investigator notified patient non opposition to participate in the study in the patient file.

Participants

Patients ≥18 years of age with hypertension were enrolled at any visit during outpatient consultations in the cardiology departments of the participating hospitals. Each patient received an information leaflet about the study. In addition, the on-site physician presented and explained the study in the regional language to all patients meeting eligibility criteria. Patients who agreed to participate completed a standardized questionnaire while waiting for their appointment. Participating physicians at each center received a training note detailing the study and standardized instructions on how they should interact with the patients while completing the questionnaire.

Patient and public involvement

Patients and public were not directly involved in research design, recruitment or conduct of this study

Measurements

A dedicated questionnaire was conceived for this study(15). A pilot investigation involving 90 patients who tested the questionnaire was conducted in January 2014 in Côte d'Ivoire.

Treatment factors

The first part of the questionnaire was completed by patients and collected data on patient sociodemographic factors (age, sex, and location), site of purchase of cardiovascular drugs, use of traditional medicine and adherence to treatment. A patient was defined as non-adherent if she/he reported sometimes forgetting to take medications in his/her self questionnaire.

The second part was filled out by the physician during the consultation and collected data on socioeconomic status (patient wealth index), antihypertensive drugs classes and generic prescriptions, blood pressure values (measured in standardized conditions, see below), and cardiovascular risk factors helping with the medical file if necessary.

Patient wealth index were assessed by the treating physician and classified as low, middle and high:

- "Low" defined poor patients who have difficulties to afford medical consultations
- "Middle" defined patients who cannot systematically paying medical consultations
- "High" defined patients who have no difficulties to pay medical consultations"

The antihypertensive drug classes recorded were: calcium channel blockers, diuretics, renin-angiotensin system blockers (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), beta-blockers, centrally active drugs and direct vasodilators. Antihypertensive drug strategies were defined according to the number of prescribed drug classes.

Blood pressure measurement

Seated office BP was measured twice by physicians, at least 15 minutes apart; participants were instructed to avoid caffeine and smoking within 30 minutes prior to BP measurement.

Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of the measured office BP values in the clinic(19).

Severity of hypertension was defined on uncontrolled BP according to European Society of Cardiology guidelines(19). Mild hypertension (SBP: 140-159 mmHg and/or DBP: 90-99 mmHg), moderate hypertension (SBP: 160-179 mmHg and/or DBP: 100-109 mmHg) and severe hypertension (SBP≥180 mmHg and/or DBP ≥110 mmHg).

Study power

The study was designed with 90% power to detect a relative difference superior at 5% on BP control between monotherapy and combination therapy group of patients (with a significance level of 5%). A total of 2060 patients were required.

Statistical analysis

Continuous and categorical variables were expressed as mean (standard deviation) and numbers (percentage) where appropriate.

Missing data were not imputed and taken into account in descriptive data. For statistical models, only complete cases were analyzed.

Categorical variables were compared using Chi-square tests.

It is difficult to interpret the potential role of antihypertensive drugs in non-adherent patients. Therefore, the association of treatments factors with uncontrolled hypertension and hypertension severity were assessed in adherent patients only. In this way, we studied the association of treatments factors with BP control in patients who reported actually taking their antihypertensive drugs. The following regression models were analyzed.

First, in univariate analysis, the odds ratio (OR) and 95% confidence intervals of the association of treatment factors (therapeutic strategy using two-drug strategies as the reference categories, antihypertensive drugs classes, prescription of generic drugs and use of traditional medicine) with uncontrolled BP were estimated in separate logistic regression models. A random effect for country was added (generalized estimated equation models) to account for inter-country variability. Interactions between antihypertensive strategies and each antihypertensive drug class were tested as well as interaction between patient wealth index and the use of traditional medicine. Then, in a multivariate analysis, models were adjusted for sociodemographic factors along with all factors with a p value of less than 0.2 in the univariate analysis.

Second, we quantified the association between treatment factors and hypertension severity using separate linear regression models with a random effect for country (generalized estimated equation models). As previously

stated, all factors with a p value of less than 0.2 as well as sociodemographic factors were included in a model for multivariable analysis.

A two tailed p value of <0.05 was considered significant. All analyses were performed through scripts developed in the R software (version 3.5.1 (2018-07-02)).

Results

Participants

The EIGHT study included 2198 patients with hypertension in 12 SSA countries between January 2014 and November 2015. Patients' baseline data are reported in Table 1. Mean age of patients was 58.3± 11.8 years. A greater proportion of patients were women (n=1324, 60.2%). Overall, 1017 patients (46.3%) were from low-income countries (Benin, Democratic Republic of the Congo, Guinea, Mozambic, Niger, and Togo), and 1181 (53.7%) were from middle-income countries (Cameroon, Congo [Brazzaville], Gabon, Côte d'Ivoire, Mauritania, and Senegal). Most of the patients were living in urban cities (n=1702, 78.9%) compared to rural areas (n=455, 21.1%). Individual wealth index was low, middle and high in 376 (17.6%), 1053 (49.2%) and 713 patients (33.3%) respectively.

Treatments

Overall, 96.6% (n=2123) of patients were prescribed antihypertensive medications (Table 1). Among treated patients, 653 (30.8%) patients received a monotherapy and 927 (43.6%) patients received two antihypertensive drugs classes (Table 1). Prescriptions of three, four, five and more antihypertensive drugs was found for 425 (20.0%), 107 (4.8%), 11 (0.4%) patients respectively. Characteristics of patients according to therapeutic strategy were detailed in Table 1.

Antihypertensive drug strategies according to country are displayed in Figure 1.

Calcium channel blockers (n=1219, 57.4%), diuretics (n=1167, 55.0%) and angiotensin-converting enzyme inhibitors (n=981, 46.2%) were the most commonly prescribed BP-lowering drugs overall (Table 1). Diuretics and renin-angiotensin system (RAS) blockers were most frequently prescribed as part of a two-drug antihypertensive medication strategy ($p<0.001$) as compared to a one drug or three or more-drug strategy. β-blockers were most frequently prescribed as part of a three or more drug antihypertensive medication strategy as compared to a one or two-drug strategy ($p<0.001$).

Antihypertensive drugs according to medication strategies are presented in Supplemental Table 1. Calcium channel blockers (CCB) were the most widely prescribed monotherapy (n=324, 49.6%) followed by RAS blockers (n=126, 19.3%), diuretics (n=122, 18.7%) and β-blockers (n=67, 10.3%). The three most common two-drug strategies were composed of diuretics + RAS blockers and CCBs + RAS blockers. Among three-drug

strategies, the three most common strategies (CCB + Diuretics + RAS blockers; Diuretics + β blockers + RAS blockers; CCB + β blockers + RAS blockers) represented 84.5% of prescriptions. The triple prescription strategies of Diuretics + CCB + RAS blockers represented almost half of the three-drug strategy prescriptions (n=250, 54.1%). Among four-drug strategies, the most common prescription strategy of CCB + Diuretics + β blockers + RAS blockers constituted 73.8% (n=79) of prescriptions.

About half of patients were prescribed at least one generic drug (n=801, 50%) (Table 1).

Among patients prescribed antihypertensive medication, 64% reported adherence to treatment.

A quarter (n=512, 24.1%) of patients used traditional medicine in addition to other drugs and this proportion was similar whatever the pharmacological antihypertensive drug strategy prescribed (monotherapy, two-drug strategies, three-drug strategies and more; p=0.107). The percentage of patients using traditional medicine varied from 9.9% (17/178) in Congo to 47.7% (82/172) in Guinea.

Factors associated with uncontrolled hypertension

Overall, 1630 (76.7%) had uncontrolled BP. BP control according to countries were depicted in Supplemental table 2. Drugs strategies by BP control are described in Table 1. In univariate analysis among patients who reported adherence to antihypertensive medication, factors associated with uncontrolled BP are detailed in Figure 2. The proportion of patients with uncontrolled BP was significantly increased with individual wealth index (middle versus high as reference), with monotherapy (versus two-drug therapy as reference) and with the use of traditional medicine ($p<0.05$). Patients treated with diuretics (versus patients without diuretics) had more frequently controlled BP (OR 0.72 [0.55-0.94] $p<0.05$); this association was not found for any other class of antihypertensive drugs.

In multivariable analysis among adherent patients adjusted for sociodemographic factors (age, sex, individual wealth index and location (rural or urban)), the use of traditional medicine remained the only factor significantly associated with uncontrolled hypertension (OR 1.72 [1.19-2.49], $p<0.01$) (Figure 3). None of the antihypertensive drugs classes alone was associated with uncontrolled hypertension. There was no significant interaction between antihypertensive drug strategy and class, and between patient wealth index and the use of traditional medicine.

Factors associated with severity of hypertension

Drugs strategies are described by hypertension severity in Table 1. Among patients with severe hypertension, 127 (27.5%) were treated with a monotherapy. This proportions varied across countries (Figure 4). In univariate analysis among adherent patients, the proportion of patients with severe hypertension was higher in patients with three-drug and more strategies (versus two-drug therapy), and with CCB, diuretics and the use traditional medicine ($p<0.05$) (Supplemental table 3).

In multivariable analysis among adherent patients adjusted for sociodemographic factors, the use of traditional medicine remained associated with higher grades of hypertension (linear regression coefficient=0.15; [0.029 - 0.28], $p<0.05$).

Discussion

Key results

Overall, 653 (30.8%) patients received antihypertensive medication monotherapy, 927 (43.6%) received two-drug strategies and 543 (25.6%) received three-drugs and more. These proportions varied across countries.

CCB was the most common antihypertensive drug class prescribed among all strategies. However, if angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were considered as one antihypertensive drug class merged into RAS blockers, they represented 68% of all prescriptions.

We found that the use of traditional medicine was an important determinant of poor BP control, beyond the traditional factors including patient wealth index and adherence to medication. Medical staff attention should particularly be provided to these patients.

Antihypertensive drug strategies

The proportion of patients on antihypertensive medications in our study was very high. This is related to the recruitment of patients during outpatient consultations in cardiology departments or urban hospitals. There is scarce data on proportion of patients treated with antihypertensive medication among patients aware of a hypertension diagnosis in SSA. According to the Eighth Joint National Committee, the first recommended line of treatment for black hypertensive patients is diuretics or CCB alone or in combination(20). Accordingly, CCBs alone or in combination were widely prescribed in our study. Surprisingly, RAS blockers and especially ACEI were the second most prescribed treatment alone before diuretics even though these are less effective compared with CCBs in reducing BP in black hypertensive patients(21). Physicians in the EIGHT study seem to follow international guidelines for black patients regarding CCB prescriptions. The high proportion of ACEI prescriptions (usually not recommended for black patients except for compelling indications including heart failure, post-myocardial infarction, diabetes, proteinuric nephropathy) suggests that continuing education of physician could be an avenue for improved care. Though, our methodology did not allow to completely distinguish indications of some drugs, and particularly to know whether ACEI were prescribed in a compelling indication because of the non-reported patient's comorbidities. Diuretics should be considered, particularly due to their low cost(22) .

Even among patients recruited from tertiary cardiology centers in urban areas in Sub-Saharan countries, BP control remains very poor and monotherapy remains widely prescribed. Some barriers associated with uptitration

of treatments could be cited. Access to medicines, defined by availability, affordability, accessibility, quality and acceptability of antihypertensive drugs varied across low and middle-income countries. These factors are associated with poor blood pressure control (9,23,24).

In low and middle-income countries, a large proportion of communities do not have access to more than one antihypertensive drug and, when available, they are often not affordable. In a multinational study among 68 950 households, the proportion of households unable to afford two blood pressure-lowering medicines was 31% in low-income countries and 9% in middle-income countries (11). Furthermore, we cannot exclude that the pharmaceutical quality of drugs did not contribute to treatment failure. Indeed, we have previously shown in the SEVEN study that 16% of cardiovascular drugs have poor quality in SSA, especially calcium channel blockers, and the proportion of poor quality can reach 50% when drugs produced in Asia are sold in street markets (18).

Among solutions, fixed drug combinations have been shown to enhance adherence and effectiveness of treatment by combining different treatments with different mechanisms of action. Randomized Controlled Trial on adherence to treatment by providing fixed drug combination free of charge in other part of the world achieve to increase blood pressure control (25). However, fixed drug combinations are poorly available and affordable in low and middle-income countries. Nevertheless, using fixed drug combinations had limitations: they may have potentially higher prices versus the cost of the components combined, they may be only available as "branded" medicines in some countries and consequently only available in private pharmacies rather than public facilities and not in rural area (26).

Traditional medicine

Our results underlined the strong association between the use of traditional medicine and uncontrolled BP, after adjusting for well-known factors associated with poor BP control including age, sex, socioeconomic factors, and poor adherence to treatment(27). The WHO define the use of traditional medicine as the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness(28). The prevalence of the use of traditional medicine is rising worldwide and is well documented in both African countries and worldwide to be between 20-80%(29,30). We found that 24.1% of patients (range 9.9% to 47.7%) used traditional medicine, consistent with the literature(31). Several factors have previously been reported to be associated with the use of traditional medicine including socio-demographic characteristics of patients, dissatisfaction with conventional treatments (ineffective treatments or side effects), cultural beliefs that illnesses have a "spiritual" origin, availability and

affordability of antihypertensive drugs(31). In our study, conventional medicine and traditional medicine were concurrently used**.** Studies have shown that patients used traditional medicine along with their conventional treatments(32) but use of traditional medicine was strongly associated with poor adherence to conventional treatments(27). Our study methodology does not allow us to describe more specifically patients' behavior towards traditional medicine. The reasons why patients choose to use traditional medicine have been much discussed but not fully understood(33,34). They may lose trust confidence in conventional medicine. In our study, patients declared to use traditional medicine, unfortunately details of traditional medicine were not depicted (herbal medicines, indigenous healthcare practices, complementary and alternative medicine like acupuncture or chiropractic, consultation of traditional health practitioners). Use of natural medicines is one kind of Traditional medicine. Systematic review on traditional herbal medicine use among hypertensive patients in SSA have been published (35) and they find a list of more than 20 different herbal used in different form (extract that needed to be dissolved, steam inhalation, single herbs, and mixtures herbs). We cannot exclude that this preparation of natural medicine could increase blood pressure. In SSA, traditional health practitioner and physicians are cohabiting. To the burden of high blood pressure, they should work together to improve blood pressure control. Interventional models of care to fight hypertension are currently being developed and for us, traditional medicine should be integrated as a part of hypertension management. In a previous analysis of the EIGHT study, the use of traditional medicine was shown to be strongly associated with poor adherence to conventional treatments (27). It would be an interesting and useful addition to include traditional medicine and traditional health practitioners in interventional model of care(36,37).

Limitation and strength

We acknowledged the following limitations. Caution is needed in extrapolating the information in the current study to other population because the sampling framework in each country was not nationally representative. The data in the EIGHT study were derived from urban clinics and likely represents the best-case scenario for BP treatment and control. Therefore, the magnitude of uncontrolled BP in the general population with hypertension could be underestimated. Although a random selection of centers would be ideal from a methodological perspective, such an approach is not practical given the lack of cardiovascular care in this part of the world. The 6-7-year gap between data collection and reporting is not significant in terms of antihypertensive drugs, for which there have been no significant innovations in the last six years. Traditional medicine is ancestral and changes in physicians' practices as well as in antihypertensive medication strategies are elements that evolve slowly. We can fear to overestimate blood pressure figures and therefore uncontrolled hypertension because of

the white coat effect during one visit. We tried to consider this effect by measuring seated office BP twice by physicians. We chose this measure because it was appropriate for the African setting. Defining uncontrolled hypertension versus controlled hypertension based on office blood pressure readings during one visit was open to criticism but we cannot be sure that patients will ever come back in outpatient consultation. Concerning antihypertensive drugs classes, aldosterone antagonist and thiazide diuretic were not differentiated in our study. For antihypertensive drug strategies, even if a patient has a prescription for single-pill combination, they may be unable to purchase this treatment. We therefore decided not to incorporate this information in our analysis. We probably over estimated cross-sectional associations between drug regimens and BP control because of other unknown cardiovascular indications. Furthermore, this study could not take into account the role of indication bias in interpreting cross-sectional associations between drug regimens and BP control. We could fear to overestimate adherence because of using self-reported questionnaire. However, self-reported medication adherence is a practical way to measure adherence because of its low cost and potential to be easily implemented into the clinical workflow. Also, evidence pointed out that self- reported adherence is predictive of clinical outcomes and especially in hypertension (38,39).

This study had many strengths including its multisite design, with over 2000 patients from 29 medical centers in 17 cities from 12 countries. Actual data on management of cardiovascular disease are uncommon in Africa and are usually derived from small, single center studies. The EIGHT study embraced 12 African countries which are usually not considered in international studies, such as the PURE study(11) providing global data on cardiovascular epidemiology. Furthermore, this study was supported by a strong and structured collaborative multidisciplinary network. Active involvement of African cardiologists, who are familiar with the problems of this area, helped derive specific questions and analysis.

Conclusion

Hypertension is a rapidly growing epidemic in low and middle income countries. In this multinational study, we described antihypertensive drugs by classes in Sub-Saharan Africa. Our study provided large scale data on antihypertensive prescriptions in the African continent. Among patients declared adherent to drugs, poor BP control was significantly associated with the use of traditional medicine.

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Author's contribution:

All authors have substantial contributions.

P. Cavagna, M. Antignac and X. Jouven had full access to the whole data in the study and take responsibility for integrity of the data and accuracy of data analysis. Those authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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References

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl. 2018 10;392(10159):1923–94.

2. Adeloye D, Basquill C. Estimating the prevalence and awareness rates of hypertension in Africa: a systematic analysis. PloS One. 2014;9(8):e104300.

3. Kayima J., Wanyenze R.K., Katamba A., Leontsini E., Nuwaha F. Hypertension awareness, treatment and control in Africa: A systematic review. BMC Cardiovasc Disord [Internet]. 2013;13(54). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52715263

4. Kuate Defo B, Mbanya JC, Kingue S, Tardif J-C, Choukem SP, Perreault S, et al. Blood pressure and burden of hypertension in Cameroon, a microcosm of Africa: a systematic review and meta-analysis of population-based studies. J Hypertens. 2019 Jun;1.

5. Twagirumukiza M, De Bacquer D, Kips JG, de Backer G, Stichele RV, Van Bortel LM. Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. J Hypertens. 2011 Jul;29(7):1243–52.

6. Mills KT, Obst KM, Shen W, Molina S, Zhang H-J, He H, et al. Comparative Effectiveness of Implementation Strategies for Blood Pressure Control in Hypertensive Patients: A Systematic Review and Meta-analysis. Ann Intern Med. 2018 16;168(2):110–20.

7. Mancia G, Rosei EA, Azizi M, Burnier M, Clement DL, Coca A, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. :98.

8. Whelton Paul K., Carey Robert M., Aronow Wilbert S., Casey Donald E., Collins Karen J., Dennison Himmelfarb Cheryl, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun 1;71(6):e13–115.

9. Wirtz VJ, Kaplan WA, Kwan GF, Laing RO. Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries. Circulation. 2016 May 24;133(21):2076–85.

10. Antignac M, Marijon E, Jouven X. Letter by Antignac et al Regarding Article "Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries." Circulation. 2016 04;134(14):e303–4.

11. Attaei MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet Public Health. 2017;2(9):e411–9.

12. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJL. Estimates of global and regional premature cardiovascular mortality in 2025. Circulation. 2015 Sep 29;132(13):1270–82.

13. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013 Sep 4;310(9):959–68.

14. Mutua EM, Gitonga MM, Mbuthia B, Muiruri N, Cheptum JJ, Maingi T. Level of blood pressure control among hypertensive patients on follow-up in a regional referral hospital in Central Kenya. Pan Afr Med J. 2014;18:278.

15. Antignac M, Diop IB, Macquart de Terline D, Kramoh KE, Balde DM, Dzudie A, et al. Socioeconomic Status and Hypertension Control in Sub-Saharan Africa: The Multination EIGHT Study (Evaluation of Hypertension in Sub-Saharan Africa). Hypertension. 2018 Apr;71(4):577–84.

16. Marijon E, Ferreira B, Paquet C, Jouven X. Prevalence of Rheumatic Heart Disease Detected by Echocardiographic Screening. N Engl J Med. 2007;357:470–6.

17. Ranque B, Menet A, Diop IB, Thiam MM, Diallo D, Diop S, et al. Early renal damage in patients with sickle cell disease in sub-Saharan Africa: a multinational, prospective, cross-sectional study. Lancet Haematol. 2014 Nov;1(2):e64-73.

18. Antignac M, Diop BI, Macquart de Terline D, Bernard M, Do B, Ikama SM, et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa. Int J Cardiol. 2017 Sep 15;243:523–8.

19. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013 Oct;31(10):1925–38.

20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507–20.

21. Leenen FHH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertens Dallas Tex 1979. 2006 Sep;48(3):374–84.

22. Kramoh K.E., Aké-Traboulsi E., Konin C., N'Goran Y., Coulibaly I., Adoubi A., et al. Management of hypertension in the elderly patient at Abidjan cardiology institute (Ivory Coast). Int J Hypertens [Internet]. 2012;2012

23. Ashigbie PG, Rockers PC, Laing RO, Cabral HJ, Onyango MA, Buleti JPL, et al. Availability and prices of medicines for non-communicable diseases at health facilities and retail drug outlets in Kenya: a cross-sectional survey in eight counties. BMJ Open. 2020 May 15;10(5):e035132.

24. Kaiser AH, Hehman L, Forsberg BC, Simangolwa WM, Sundewall J. Availability, prices and affordability of essential medicines for treatment of diabetes and hypertension in private pharmacies in Zambia. Thet Wai K, editor. PLOS ONE. 2019 Dec 13;14(12):e0226169.

25. Persaud N, Bedard M, Boozary AS, Glazier RH, Gomes T, Hwang SW, et al. Effect on Treatment Adherence of Distributing Essential Medicines at No Charge: The CLEAN Meds Randomized Clinical Trial. JAMA Intern Med. 2020 Jan 1;180(1):27–34.

26. Godman B, McCabe H, D Leong T. Fixed dose drug combinations - are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries. Expert Rev Pharmacoecon Outcomes Res. 2020 Feb;20(1):1–26.

27. Macquart de Terline D, Kane A, Kramoh KE, Ali Toure I, Mipinda JB, Diop IB, et al. Factors associated with poor adherence to medication among hypertensive patients in twelve low and middle income Sub-Saharan countries. Li Y, editor. PLOS ONE. 2019 Jul 10;14(7):e0219266.

28. World Health Organization, editor. WHO traditional medicine strategy. 2014-2023. Geneva: World Health Organization; 2013. 76 p.

29. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative

medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998 Nov 11;280(18):1569–75.

30. Eddouks M, Maghrani M, Lemhadri A, Ouahidi M-L, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol. 2002 Oct;82(2–3):97–103.

31. Osamor PE, Owumi BE. Complementary and alternative medicine in the management of hypertension in an urban Nigerian community. BMC Complement Altern Med. 2010 Jul 19;10:36.

32. Nuwaha F, Musinguzi G. Use of alternative medicine for hypertension in Buikwe and Mukono districts of Uganda: a cross sectional study. BMC Complement Altern Med. 2013 Nov 4;13:301.

33. Lorenc A, Ilan-Clarke Y, Robinson N, Blair M. How parents choose to use CAM: a systematic review of theoretical models. BMC Complement Altern Med. 2009 Dec;9(1):9.

34. James PB, Wardle J, Steel A, Adams J. Traditional, complementary and alternative medicine use in Sub-Saharan Africa: a systematic review. BMJ Glob Health. 2018 Oct;3(5):e000895.

35. Liwa A., Roediger R., Jaka H., Bougaila A., Smart L., Langwick S., et al. Herbal and Alternative Medicine Use in Tanzanian Adults Admitted with Hypertension-Related Diseases: A Mixed-Methods Study. Int J Hypertens [Internet]. 2017;2017

36. Krah E, de Kruijf J, Ragno L. Integrating Traditional Healers into the Health Care System: Challenges and Opportunities in Rural Northern Ghana. J Community Health. 2018;43(1):157–63.

37. Cavagna P, Kramoh KE, Sidy Ali A, Balde DM, Traore AK, Khoury S, et al. The importance of considering cultural and environmental elements in an interventional model of care to fight hypertension in Africa. J Clin Hypertens. 2021 Jun;23(6):1269–70.

38. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013 Oct 7;34(38):2940–8.

39. Korb-Savoldelli V, Gillaizeau F, Pouchot J, Lenain E, Postel-Vinay N, Plouin P-F, et al. Validation of a French Version of the 8-Item Morisky Medication Adherence Scale in Hypertensive Adults: Validation of a French Version of MMAS. J Clin Hypertens. 2012 Jul;14(7):429–34.

Figures: titles and legends

Figure 1: Antihypertensive drugs strategies (%) according to countries level income and countries

Legend: bars represent the percentage of antihypertensive drugs strategies

Figure 2: Odds ratio (OR) of sociodemographic and treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications in univariate analysis.

Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. *RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.*

Figure 3: Odds ratio (OR) of treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications adjusted for sociodemographic factors in multivariate analysis.

Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. *RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.*

Figure 4: Proportion of monotherapy in patients with severe hypertension.

Legend: Grey countries were not included in the EIGHT study.

Table 1: Characteristics of participants according to therapeutic strategy

	GLOBAL	No drugs	Monotherapy	Two-drug therapy	Three-drug and +
Overall					
N, (%)	2198	75 (3.4)	653 (29.7)	927 (42.2)	543 (24.7)
Age (year), mean (sd)	58.3 (11.8)	55.3 (14.1)	57.8 (12.12)	58.5 (11.70)	58.9 (11.09)
Male, N (%)	874 (39.8)	22 (29.3)	248 (38.0)	385 (41.5)	219 (40.3)
Patient wealth index, N (%)					
Low	376 (17.6)	15 (22.4)	109 (17.2)	166 (18.3)	86 (16.2)
Middle	1053 (49.2)	36 (53.7)	302 (47.6)	450 (49.5)	265 (49.8)
High	713 (33.3)	16 (23.9)	224 (35.2)	292 (32.2)	181 (34.0)
NA	56	8	18	19	11
Country-level income (Low vs Middle), N (%)	1017 (46.3)	23 (30.7)	361 (55.3)	419 (45.2)	214 (39.4)
Location (Urban vs Rural), N (%)	1702 (78.9)	56 (74.7)	485 (75.7)	729 (80.3)	432 (81.1)
NA	41	0	12	19	10
Cardiovascular risks factors, N (%)					
Tobacco use	84 (5.1)	7 (13.7)	16 (3.4)	45 (6.5)	16 (3.7)
Diabetes mellitus	288 (17.5)	8 (15.7)	74 (15.6)	119 (17.3)	87 (20.2)
Hypercholesterolemia	328 (19.9)	4 (7.8)	75 (15.8)	142 (20.6)	107 (24.9)
Hypertriglyceridemia	88 (5.3)	0 (0.0)	26 (5.5)	43 (6.2)	19 (4.4)
Obesity	340 (20.7)	16 (31.4)	79 (16.6)	144 (20.9)	101 (23.5)
Sedentary Lifestyle	649 (39.5)	29 (56.9)	169 (35.6)	254 (36.9)	197 (45.8)
None	461 (28.0)	8 (15.7)	160 (33.7)	193 (28.0)	100 (23.3)
NA	553	113	24	178	283
Year since hypertension diagnosis (>1 year), N (%)	1816 (84.4)	45 (67.1)	487 (76.1)	802 (87.8)	482 (90.8)
NA	47	8	13	14	12
Among treated patients		-			
Patients on antihypertensive medication, N (%)	2123 (96.6)	-	653 (30.8)	927 (43.6)	543 (25.6)
Antihypertensive drug class, N (%)		-			
Calcium channel blocker	1219 (57.4)	-	324 (26.6)	457 (37.5)	438 (35.9)
Diuretic	1167 (55.0)	-	122 (10.5)	567 (48.5)	478 (41.0)
RAS Blocker : Angiotensin-converting-enzyme inhibitor	981 (46.2)	-	94 (9.6)	505 (51.5)	382 (38.9)
RAS Blocker : Angiotensin II receptor antagonist	321 (15.1)	-	32 (10)	163 (50.8)	126 (39.3)
Beta-blocker	466 (22.0)	-	67 (14.4)	138 (29.6)	261 (56)
Centrally active drug	79 (3.7)	-	12 (15.2)	20 (25.3)	47 (59.5)
Vasodilator	33 (1.6)	-	2 (6.1)	4 (12.1)	27 (81.8)
Prescription of generic drug, N (%)	801 (50.1)	-	225 (48.9)	298 (44.2)	273 (62.5)
NA	599	-	193	253	106
Use of traditional medicine, N (%)	512 (24.1)	-	150 (23.7)	231 (25.5)	107 (20.6)
NA	70	-	21	22	23
Patient reported adherence to antihypertensive medication, N (%)	1359 (64)	-	397 (29.2)	597 (43.9)	365 (26.8)
Office Blood pressure, mean (sd)		-			
Systolic blood pressure, mmHg	148.9 (23.4)	-	147.2 (21.6)	147.1 (22.4)	154 (26.5)
Diastolic blood pressure, mmHg	88.2 (14.2)	-	89.2 (13.9)	87.3 (14)	88.7 (14.7)
Blood pressure control* (Uncontrolled vs controlled), N (%)	1630 (76.7)	-	519 (79.7)	682 (73.9)	429 (79.4)
NA	10	-	2	5	3
Hypertension severity, N (%)		-			
Mild	625 (38.3)	-	212 (40.8)	270 (39.6)	143 (33.3)
Moderate	543 (33.3)	-	180 (34.6)	226 (33.1)	137 (31.9)
Severe	462 (28.3)	-	127 (24.4)	186 (27.3)	149 (34.8)

Legend:* Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic.

Supplemental Digital Content: Titles and legend

Supplemental Table 1. Antihypertensive drugs according to medication strategies

Legend: β blockers: Beta blockers, CCB: Calcium channel blockers, RAS blockers: Renin-Angiotensin System blockers

*Combination therapy recommended

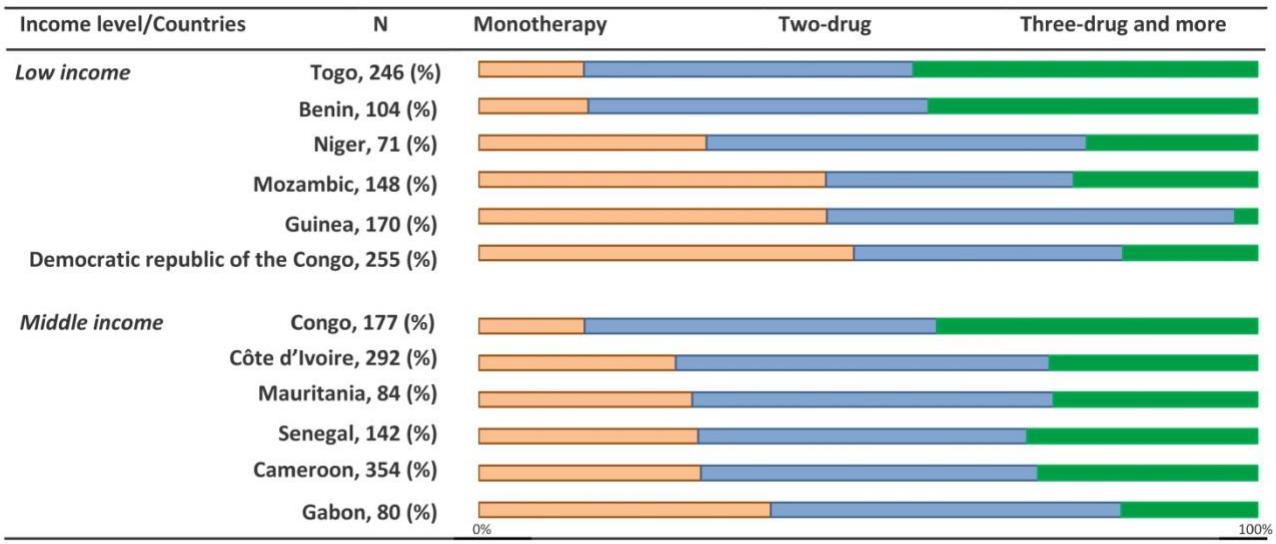
† Patient with six-drug strategies were not presented

Supplemental Table 2: Treatments characteristics by country among treated patients

***** Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic

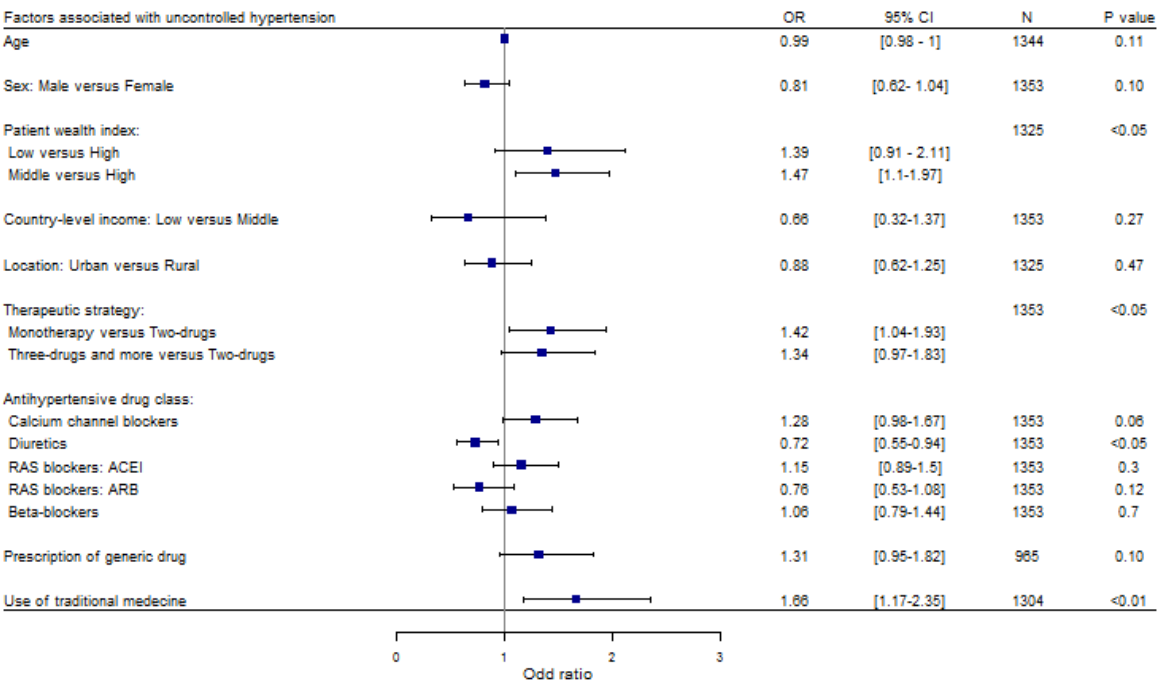
Supplemental Table 3: Linear regression coefficient of sociodemographic and treatments factors for severity of hypertension in univariate analysis.

Figure 1: Antihypertensive drugs strategies (%) according to countries level income and countries



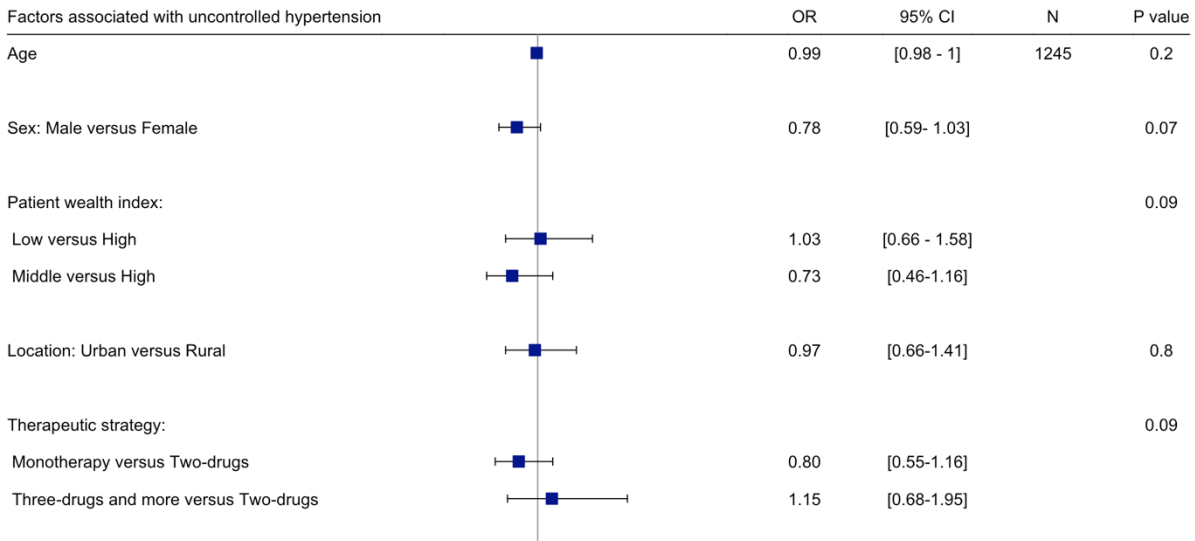
Legend: bars represent the percentage of antihypertensive drugs strategies

Figure 2: Odds ratio (OR) of sociodemographic and treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications in univariate analysis.



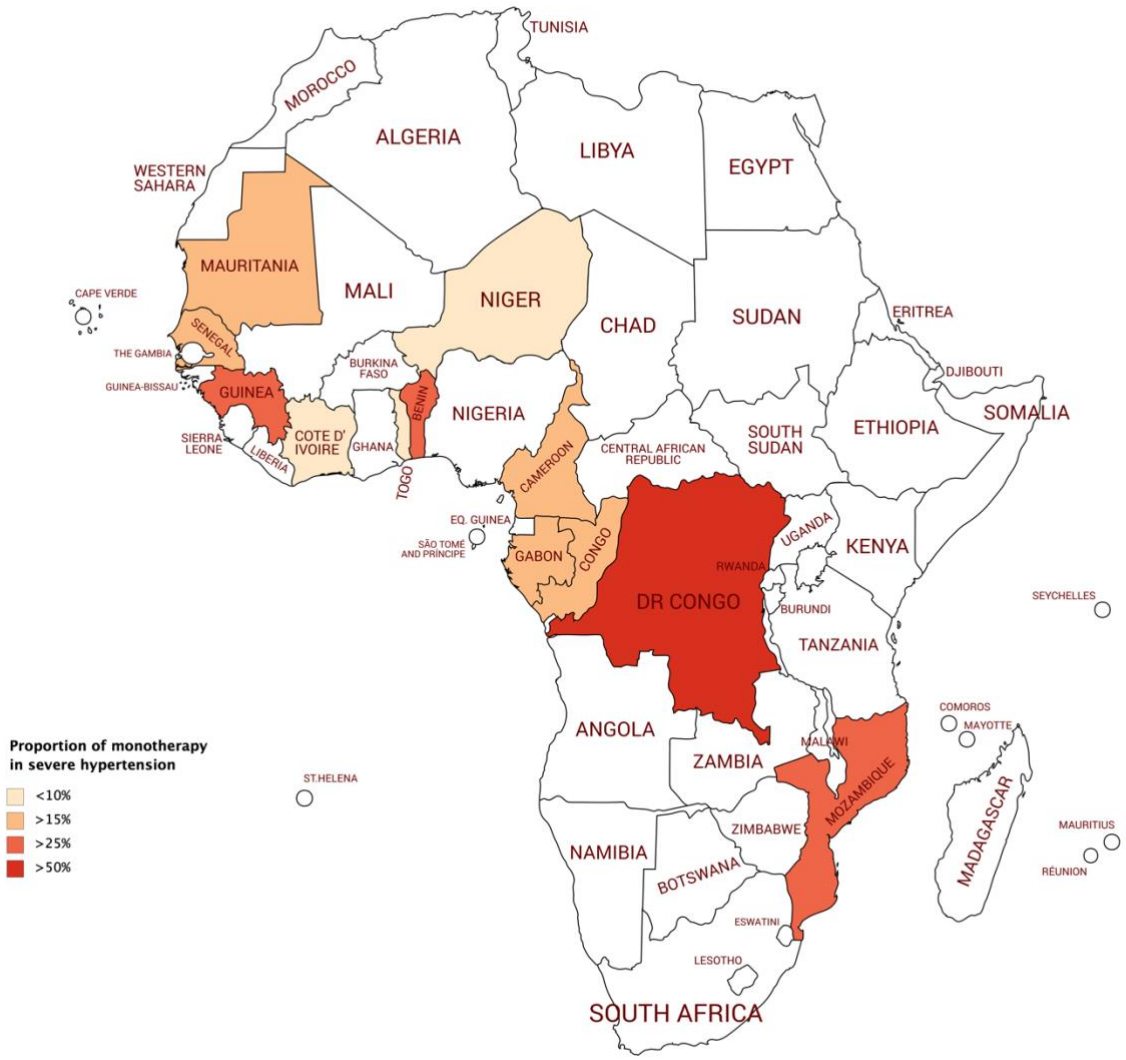
Legend: Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.

Figure 3: Odds ratio (OR) of treatments factors for uncontrolled hypertension among patients who declared to be adherent to medications adjusted for sociodemographic factors in multivariate analysis.



Legend*:* Squares represent OR and lines, 95% confidence interval (CI). ORs derived from separated logistic regression with a random effect on country to account for inter-country variability. N represents overall for each variable. RAS: Renin-angiotensin system ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blockers.

Figure 4: Proportion of monotherapy in patients with severe hypertension



Legend: White countries were not included in the EIGHT study.

Supplemental Table 1. Antihypertensive drugs according to medication strategies

	N, (%)
Monotherapy	**653 (30.8)**
Calcium channel blockers (CCB)	324 (49.6)
Renin-Angiotensin system (RAS) blockers	126 (19.3)
Diuretics	122 (18.7)
Beta-blockers (β blockers)	67 (10.3)
Centrally active drug	12 (1.8)
Vasodilator	2 (0.3)
Two-drug strategies	**927 (43.6)**
Diuretics + RAS blockers*	387 (41.7)
CCB + RAS blockers*	240 (25.9)
CCB + Diuretics *	140 (15.1)
CCB + β blockers*	61 (6.6)
β blockers + RAS blockers	38 (4.1)
Diuretic + β blockers *	37 (4.0)
Centrally active drug + Other drug class	20 (2.2)
Vasodilator + Other drug class	4 (0.4)
Three-drug strategies	**425 (20.0)**
CCB + Diuretics + RAS blockers*	230 (54.1)
Diuretics + β blockers + RAS blockers	84 (19.8)
CCB + β blockers + RAS blockers	45 (10.6)
CCB + Diuretics + β blockers *	26 (6.1)
Centrally active drug + Other drug class	23 (5.4)
Vasodilator + Other drug class	15 (3.5)
2 RAS blockers + Other drug class	2 (0.4)
Four-drug strategies	**107 (5)**
CCB + Diuretics + β blockers + RAS blockers	79 (73.8)
Centrally active drug + Other drug class	17 (15.9)
Vasodilator + Other drug class	6 (5.6)
2 RAS blockers + Other drug class	4 (3.7)
Five-drug strategies and more †	**11 (0.4)**
CCB + Diuretics + β blockers + RAS blockers + Centrally active drug	4 (40.0)
CCB + Diuretics + β blockers + RAS blockers + Vasodilator	4 (40.0)
CCB + Diuretics + RAS blockers + Centrally active drug + Vasodilator	1 (10.0)
Diuretics + β blockers + 2 RAS blockers + Centrally active drug	1 (10.0)

Legend: β blockers: Beta blockers, CCB: Calcium channel blockers, RAS blockers: Renin-Angiotensin System blockers

*Combination therapy recommended

† Patient with six-drug strategies were not presented

Supplemental Table 2: Treatments characteristics by country among treated patients

	Niger	Togo	Benin	Guinea	Mozambic	Dem. Rep of the Congo	Congo	Senega	Côte d'Ivoire	Cameroon	Mauritania	Gabon
N, (%)	71(3.")	104 (4.9)	246 (11.6)	170 (8.0)	148 (7.0)	255 (12.0)	177 (8.3)	142 (6.7)	292 (13.7)	354 (16.7)	84 (3.9)	80 (3.8)
Blood pressure control* (Uncontrolled vs controlled), N (%)	65 (84.4)	77 (72.6)	142 (57)	125 (73.5)	119 (80.4)	232 (89.2)	134 (75.3)	128 (80.5)	228 (77.8)	285 (76.6)	68 (81)	89 (100
NA	3	0	1	2	0	1	0	1	2	3	0	0
Therapeutic Strategies, N (%)												
Monotherapy	10 (14.1)	14 (13.5)	72 (29.3)	76 (44.7)	66 (44.6)	123 (48.2)	24 (13.6)	40 (28.2)	74 (25.3)	101 (28.5)	23 (27.4)	30 (37.5)
Two-drug strategies	31 (43.7)	44 (42.3)	120 (48.9)	89 (52.4)	47 (31.8)	88 (34.5)	80 (45.2)	60 (42.2)	140 (47.9)	153 (43.0)	39 (46.4)	36 (45.0)
Three and more drugs strategies	30 (42.3)	46 (44.2)	54 (22.0)	5 (2.9)	35 (23.6)	44 (17.3)	73 (41.2)	42 (29.6)	78 (26.7)	100 (28.2)	22 (26.2)	14 (17.5)

***** Uncontrolled hypertension was defined by a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) of ≥90 mmHg on either of office BP measures in the clinic

Supplemental Table 3: Linear regression coefficient of sociodemographic and treatments factors for severity of hypertension in univariate analysis

	N	Linear regression coefficients	CI 95%	P value
Age	1017	-0.0021	-0.006 – 0.002	0.32
Sex (Male versus Female)	1023	0.087	-0.012 – 0.186	0.08
Patient Wealth index:	1004			0.10
Low versus high		0.15	0.0012 – 0.305	
Middle versus high		0.009	-0.101 – 0.12	
Location : urban versus rural	1001	-0.011	-0.136 – 0.112	0.86
Therapeutic strategy:	1023			<0.01
Monotherapy versus two-drugs		-0.106	-0.22 – 0.007	
Three-drugs and more versus two-drugs		0.155	0.037 – 0.273	
Antihypertensive drug class:				
Calcium channel blockers	1023	0.107	0.008 – 0.207	0.03
Diuretics	1023	0.136	0.039 – 0.233	<0.01
RAS blockers : ACEI	1023	0.043	-0.057 – 0.144	0.39
RAS blockers : ARB	1023	0.090	-0.05 – 0.231	0.21
Beta blockers	1023	-0.015	-0.131 – 0.099	0.797
Prescription of generic drug	731	0.025	-0.099 – 0.147	0.68
Use of traditional medicine	976	0.168	0.045 – 0.291	<0.01

Legend: Linear regression coefficients derived from separated linear regression with a random effect on country

to account for inter-country variability

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional 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	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	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
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
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	7
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	7
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	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*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
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10-11
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	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*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	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	16

*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.