Original Article

Substandard drugs among five common antihypertensive generic medications: an analysis from 10 African countries

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Objective: Hypertension results in more deaths than any other risk factor and has been on the rise in sub-Saharan Africa over the past few decades. Generic drugs have helped improve accessibility and affordability of antihypertensive therapy in developing countries. However, assessment of quality standards of these products is important. We performed a quality assessment of five commonly used antihypertensive generic drugs in 10 sub-Saharan African countries and studied the impact of price on quality.

Methods: Drug samples were prospectively collected using standardized methods between 2012 and 2014. We developed a validated reversed-phase liquid chromatography with tandem mass spectrometry method to accurately quantify the active ingredient in a certified public laboratory. Quality was defined based on the percentage ratio of measured to expected dosage of active ingredient.

Results: A total of 1185 samples were assessed, of which 70.0% were generic ($n = 830$). Among the generic drugs, the percentage of poor-quality drugs was 24.3% ($n = 202/830$). The percentage ratio of measured to expected dosage of active ingredient ranged from 49.2 to 111.3%; the majority (81.7%) of the poor-quality samples had insufficient quantity of the active ingredient. Moreover, poor quality was not associated with purchase price of the drug.

Conclusion: In this study from 10 sub-Saharan African countries, nearly one-quarter of the available generic antihypertensive drugs were found to be of poor quality. Concerted measures to improve the quality of antihypertensive drugs could lead to major improvements in hypertension control with attendant reduction of its deleterious consequences in low-income and middle-income countries.

Keywords: antihypertensive agents, cardiology, developing countries, drug quality, hypertension, substandard drugs

INTRODUCTION

Hypertension results in more deaths than any other risk factor; 16.5% of deaths worldwide and 7.0% of global disability adjusted life years are attributed to high blood pressure (BP) [1]. Although traditionally considered a disease of the developed world, the burden of hypertension has been increasing in sub-Saharan Africa over the past few decades and has now emerged as critical health concern [2,3].

Multiple randomized control trials have demonstrated the efficacy of antihypertensive therapies, and international guidelines recommend their use to prevent cardiovascular

diseases [4]. It follows that effective use of proven medications can prevent a large number of these avoidable deaths. WHO's Global Action Plan has set a goal to increase the availability of genuine, affordable medicines in developing countries to improve the treatment of major noncommunicable diseases worldwide by 2025 [5].

Generic drugs provide the opportunity for major savings in healthcare expenditure as they are usually more affordable than brand name versions of drugs. Their use can help increase access to cardiovascular treatment in low-income and middle-income countries [6].

However, concerns exist about the manufacture of low-cost generic drugs at the expense of the quality of these products [7]. Scarce data exist as regards to the quality of generic medicines used in noncommunicable disease such as antihypertensive drugs.

The SEVEN study is the first large multinational study to describe quality of cardiovascular drugs in Africa [8]. In this article, we undertake further analysis of data from the SEVEN study focusing on antihypertensive generic drugs.

We therefore performed a quality assessment of five commonly used antihypertensive drugs (angiotensin-converting enzyme inhibitor, beta blocker, calcium channel blocker, two diuretics) in 10 countries of sub-Saharan Africa. We also studied the relationship between the purchase price of the drug and quality.

METHODS

We performed a post-hoc analysis of the SEVEN study, the first major study of cardiovascular drug quality from sub-Saharan Africa, using data from five antihypertensive drugs: furosemide, hydrochlorothiazide (diuretics), captopril (angiotensin-converting enzyme inhibitor), atenolol (beta blocker) and amlodipine (calcium channel blocker). Although furosemide is not formally recommended for the management of high BP [4], this drug is commonly used in Africa to treat hypertension.

Study design

The methodology/design of the SEVEN study has already been published elsewhere [8]. The SEVEN study was conceived and designed by a multidisciplinary collaborative team of epidemiologists, cardiologists and pharmacists from France and Africa. The study was registered with the French national drug agency (Agence Nationale Sécurité du Médicament ID_RCB:2014-A01275-42). This study was exclusively supported by a public grant to avoid any conflict of interest with the pharmaceutical industry. The team of SEVEN had extensive prior research experience and existing collaborations with a network of physician-scientists in Africa such as in the field of rheumatic heart disease [9,10] and sickle cell disease [11] which aided planning and launch of the current study.

The certified public laboratory of AGEPS (e.g. Agence Générale des Equipements et Produits de Santé, AP-HP, Paris, France) developed and performed the chemical analysis. This is an agency dedicated to the quality control of drugs as per good manufacturing practices (WHO) [12].

There are important differences with regard to public health services and drug supply chain between countries in the developing world. Ten African countries participated in the study with one local investigator responsible for sample collection in each country.

Sample collection

The sampling protocol was developed according to medicine quality assessment reporting guidelines (MEDQUARG) guidelines [13] that described how medicine quality surveys should be conducted.

Drug samples were prospectively collected between November 2012 and August 2014 in 10 countries: Benin, Burkina Faso, Congo, Democratic Republic of the Congo, Guinea, Côte d'Ivoire, Mauritania, Niger, Senegal and Togo.

There were no reliable estimates for the prevalence of poor-quality medicines or for the proportion of places of sale selling such medicines for any country. Samples were collected from licensed (pharmacy) sources selected randomly and unlicensed (street market) places of sale chosen as per the local investigator's convenience. Lists of licensed outlets were obtained from the Council of the Order of Pharmacists of each country which enabled random sampling; unlicensed markets were identified based on the local investigator's knowledge. If the study medications were not available in the first randomly selected pharmacy, investigators selected another one randomly and so on. Drug samples were purchased in the capital city and when possible in one city located close to the country's border. Medicines were obtained by the study investigator's staff who posed as customers. For each drug sample, investigators were asked to collect generic versions and brand name versions of the drug if available.

After purchase, all drugs were stored at ambient temperature, in a dry place avoiding direct sunlight.

Samples were sent via courier to the coordinating center in France. Quality assessment tests were completed within 40 days of sample collection.

The income level of each country was obtained from World Bank data [14].

Quality analysis

The packaging of each medication was systematically collected and examined. Version of drug (generic or branded), international nonproprietary names and pharmacological class, place of manufacture (indicated on the packaging or deduced by authors) and the form of the medication (capsule or tablet) were noted. Chemical analyses of samples were performed in a blinded fashion by the department of laboratories in Paris (AGEPS, AP-HP). A validated reversed-phase liquid chromatography with tandem mass spectrometry method was developed [15] to accurately quantify the content of active pharmaceutical ingredient in the sample. Reference standards of active pharmaceutical ingredient were purchased from INRESA Pharma (Bartenheim, France: amlodipine, atenolol, captopril, furosemide, hydrochlorothiazide). The analytical method was validated as per the International Conference on Harmonisation recommendations [16] with respect to specificity, linearity, accuracy, precision and limits of detection and quantification. Each drug was identified and then quantified. For every drug, 10 samples randomly chosen by place of sale and country were tested.

Definition of poor quality

There is no clear and uniformly accepted definition of poor-quality medicines encompassing both counterfeit and substandard drugs [17]. The WHO defines a counterfeit drug as one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient (inadequate) quantities of ingredient(s) or with fake packaging. On the other hand, substandard medicines are genuine medicines produced by manufacturers authorized by the National Medicines Regulatory Authority which do not meet quality specifications set for them by National standards [18]. For the purpose of this study, quality was defined based on percentage ratio of measured to expected dosage of active ingredient (good quality: 95–105%, poor quality: <95 or >105%).

Additional forensic testing of the medications to detect other potentially toxic compounds, to determine substandard vs. counterfeit drug was not performed in this study.

Price of purchase

Price of purchase is given per unit of the drug

Seven countries out of the 10 in this study [Benin, Burkina Faso, Congo (Brazzaville), Côte d'Ivoire, Niger, Senegal and Togo] have the same currency that is the West African Coopération Financière en Afrique (CFA) Franc. We converted the drug price of purchase of the other three countries (Mauritania, Guinea and Democratic Republic of the Congo) to the West African CFA Franc. To compare the drug price taking into account the standard of living of each country, we converted West African CFA Franc to international dollars (Int$) using purchasing power parity (PPP) conversion factor [19]. PPP conversion factor is the number of units of a country's currency required to buy the same amounts of goods and services in the domestic market as US dollar would buy in the United States. PPP rates provide a standard measure allowing comparison of real levels of expenditure between countries.

Statistical analysis

Categorical variables are summarized as counts and percentages, and quantitative variables as mean and SD. We performed univariate and multivariate logistic regression analyses to identify the determinants of quality (poor vs. good) of the antihypertensive medications. To account for intrabatch and interbatch variability (a batch consists of samples obtained from one drug, in one pharmaceutical presentation collected in one country and in one place of sale), generalized linear mixed models with random effect on the batch were used. All analyses were performed through scripts developed in the R software (Version 0.99.891 – 2009–2016; RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/). The level of significance was set at P less than 0.05.
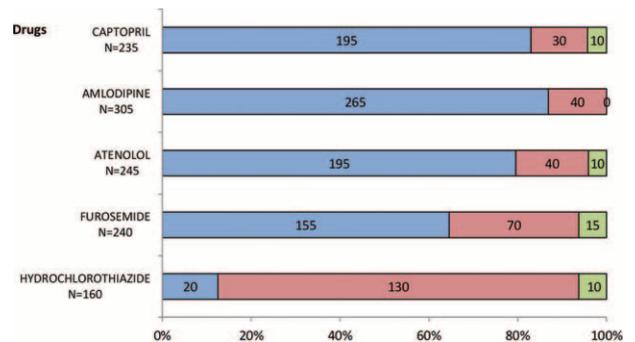

FIGURE 1 Number of the tested samples by drug and version (generic, branded name and unknown).

RESULTS

Sample characteristics

A total of 2719 samples were collected. All study medicines could be successfully obtained. According to the sampling protocol, 10 samples per drug, randomly chosen by place of sale and country, were analyzed. Consequently, the quality of 1185 samples was assessed. Among the tested samples, 70.0% were generic ($n = 830$), 26.2% brand-name ($n = 310$) and 3.8% ($n = 45$) unknown versions (repacked drugs). All drugs were available in brand name and generic version (Fig. 1). However, captopril, amlodipine, atenolol as well as furosemide (to a less extent) were mostly generics, unlike hydrochlorothiazide. Looking at these results by drug class, diuretics (furosemide and hydrochlorothiazide) were more often available in brand name version (50%, $n = 200$) as compared with generic (44%, $n = 175$).

As shown in Table 1, the proportion of generics varied according to purchase sites (income level of countries, city of purchase and outlet). Generic drugs were more likely to be found in low-income countries (81.4 vs. 63.6% in middle-income countries), border cities (92.3 vs. 70.3% in capital) and unlicensed places of sale (75.0 vs. 71.2% in pharmacies). However, none of the differences reached statistical significance.

Proportion of generic drugs compared with brand name differed according to their place of manufacture ($P < 0.001$). All drugs produced in Asia (100%) and substantial majority of those produced in Africa (91.7%) were available in generic version, whereas drugs produced in Europe were almost equally divided between generics (58.3%) and brand names (41.7%).

Among the 10 participating countries, the proportion of generic drugs ranged from 40.0% in Senegal to 87.5% in Niger. Only Senegal and Togo had a smaller proportion of generic drugs compared with brand name.

Quality assessment

Among the generic drugs, the percentage of poor-quality drugs reached 24.3% ($n = 202/830$) (Table 2). The ratio of measured to expected content of active ingredient ranged from 49.2 to 111.3%. Samples with insufficient quantities of active ingredient (percentage ratio <95%) accounted for 81.7% ($n = 165/202$) of the poor-quality samples.

TABLE 1. Characteristics of the tested samples according to drug version (generic vs. brand name)

	Global	Generic		
	n	*n*	%	*P* value[*]
n total	1140[a]	830	(72.8%)	
Purchase sites				
Income level of country, *n* (%)				0.52
Low	590	480	(81.4%)	
Lower middle	550	350	(63.6%)	
City of purchase, *n* (%)				0.28
Border city	130	120	(92.3%)	
Capital	1010	710	(70.3%)	
Seller/outlet, *n* (%)				0.24
Unlicensed (street market)	480	360	(75.0%)	
Licensed (pharmacy)	660	470	(71.2%)	
Manufacture and packaging				
Indicated place of manufacture, *n* (%)				<0.001
Asia	235	235	(100.0%)	
Africa	120	110	(91.7%)	
Unknown	90	80	(88.9%)	
Europe	695	405	(58.3%)	
Packaging, *n* (%)				0.22
Blisters in a package	970	740	75.9%	
Blisters	160	80	50.0%	
Repacked drugs	10	10	20.0%	
Pharmaceutical form, *n* (%)				0.77
Capsule	30	0	0.0%	
Tablet	1110	830	79.4%	

[a]*n* total does not include unknown version of drugs (*n* = 45).
[*]*P* value: univariate test using a random effect (generic vs. brand name).

Prevalence of poor quality was significantly different ($P < 0.001$) between generic (24.3%, $n = 202/830$) and brand name versions (3.5%, $n = 11/310$). Among unknown version of drugs, the percentage of poor quality was 8.9% ($n = 4/45$).

Also, prevalence of poor quality within generic drugs differed between drugs, being the lowest for hydrochlorothiazide (0%, $n = 0/20$) and highest for captopril (30.8%, $n = 60/195$) (Table 2). However, this difference did not reach statistical significance ($P = 0.15$). Although poor quality exceeded 30% in two generic drugs (captopril and amlodipine), on the other hand, two brand name drugs (captopril and furosemide) did not contain any poor-quality samples (Table 2).

There was wide variation in the prevalence of poor-quality generic drugs within the study countries, ranging from 0% in Senegal to 47.1% in Congo Brazzaville (Fig. 2). Poor quality exceeded 30% in three countries (Congo, Benin and Democratic Republic of the Congo) and was below 20% in four countries (Senegal, Guinea, Burkina Faso and Mauritania). However, the difference in prevalence of poor-quality generic drugs between countries was not statistically significant ($P = 0.106$).
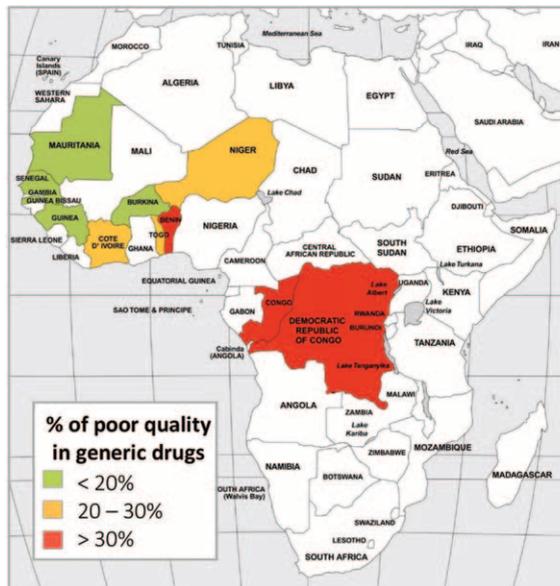
Drug price of purchase

The average price of generic drugs was 122.0 (95.5) CFA corresponding to 0.56 ($\pm$0.57) in Int\$ (Table 3). The mean price of generic drugs was not significantly different [122.0 CFA ($\pm$95.5), 0.56 ($\pm$0.57) Int\$] from that of brand name drugs [136.4 ($\pm$59.2) CFA, 0.62 ($\pm$0.42) Int\$] ($P = 0.8$).

Significant price differences were noted among generic drugs ($P < 0.001$). Atenolol was the most expensive [mean 161.0 ($\pm$119.5) CFA, 0.82 ($\pm$0.96) Int\$] and hydrochlorothiazide the cheapest [mean 7.5 ($\pm$0.01) CFA, 0.03 ($\pm$0.01) Int\$].

Drug price of purchase was also different between countries ($P < 0.01$) and ranged from 151.50 ($\pm$47.06)

TABLE 2. Percentage of poor quality by drugs and by version of drugs

Version of drugs				
	Generic, *n* = 830		Brand name, *n* = 310	
Drug name	*n*	% of poor quality	*n*	% of poor quality
Captopril	60/195	30.8	0/30	0.0
Amlodipine	80/265	30.2	7/40	17.5
Furosemide	30/155	19.4	0/70	0.0
Atenolol	32/195	16.4	1/40	2.5
Hydrochlorothiazide	0/20	0.0	3/130	2.3
Total	202/830	24.3	11/310	3.5

FIGURE 2 Percentage of poor quality in generic antihypertensive drugs according to the country of purchase.

Country of Purchase	Poor quality in generic drugs		
	N		%
Congo	33/70	🟥	47.1%
Benin	61/190	🟥	32.1%
Dem. Rep of Congo	19/60	🟥	31.7%
Côte d'Ivoire	42/160	🟧	26.3%
Niger	14/70	🟧	20.0%
Togo	8/40	🟧	20.0%
Mauritania	13/80	🟩	16.3%
Burkina Faso	10/90	🟩	11.1%
Guinea	2/30	🟩	6.7%
Senegal	0/40	🟩	0.0%
Total	**202/830**	🟧	**24.3%**

TABLE 3. Purchase price of drugs (per unit) by version of drugs

Drug price				
	Generic, $n = 830$		Brand name, $n = 310$	
Drug name, mean (SD)	CFA	Int$	CFA	Int$
Amlodipine	160.4 (87.6)	0.71 (0.34)	416.3 (54.4)	1.66 (0.36)
Atenolol	161.0 (119.5)	0.82 (0.98)	106.3 (31.8)	0.50 (0.5)
Captopril	83.3 (58.9)	0.36 (0.24)	259.2 (22.2)	1.49 (0.68)
Furosemide	66.0 (46.9)	0.28 (0.20)	65.8 (24.3)	0.28 (0.09)
Hydrochlorothiazide	7.5 (0)	0.03 (0)	39.2 (7.71)	0.17 (0.03)
Total	122.0 (95.5)	0.56 (0.57)	136.4 (136.8)	0.62 (0.65)

CFA stands for West African CFA Franc and Int$ for international dollar. CFA, Coopération Financière en Afrique.

CFA, 0.64 ($\pm$0.20) Int$ in Côte d'Ivoire to 95.00 ($\pm$57.68) CFA, 0.41 ($\pm$0.25) Int$ in Togo.

Poor-quality generic drugs were less expensive (mean 116.8 CFA, 0.48 Int$) compared with good-quality generic drugs (mean 123.8 CFA, 0.59 Int$), but this difference was NS ($P = 0.34$). Quality was not associated with drug price after adjusting for drug and country of purchase ($P = 0.38$) (Fig. 3).

DISCUSSION

Generic drugs are largely used in Africa as we observed in our study. In our study, we found a high prevalence of poor quality among generic antihypertensive medicines; nearly a quarter of the tested samples did not meet standards. The prevalence of poor quality was not associated with the drug price of purchase ($P = 0.34$). The percentage ratio of measured-to-expected dosage of active ingredient ranged from 49.2 to 111.3%; the majority (81.7%) of the poor-quality samples had insufficient quantities of active ingredient. However, we did not find samples with complete absence of the active ingredient unlike other studies assessing quality

of antimicrobial agents [20–22]. This suggests that we are more likely dealing with substandard drugs rather than falsified medicines. Indeed, substandard medicines are a far more serious and widespread problem than counterfeit medicines, but specific attention and resources devoted to tackle this problem are lacking [23]. In many cases, the lack of a uniform content of drug suggests poor manufacturing techniques. In low-income and middle-income countries, strict standards and controls ensuring the drug's effectiveness and safety have yet to be developed to detect substandard drug production. Our findings underline the inadequacy of drug regulatory control in those countries. Assuring the quality and safety of drugs is therefore essential to achieving effective implementation of national drug policies and pharmaceutical programs. To some extent, inadequate concentration of medication can also imply deleterious effects of tropical climate on drug formulations. Twagirumukiza et al. [24] showed that seven of 10 antihypertensive drugs were degraded (substandard in content) after 6 months of storage under accelerated testing conditions.

The WHO has set a goal to reach an availability and affordability rate of 80% among essential noncommunicable
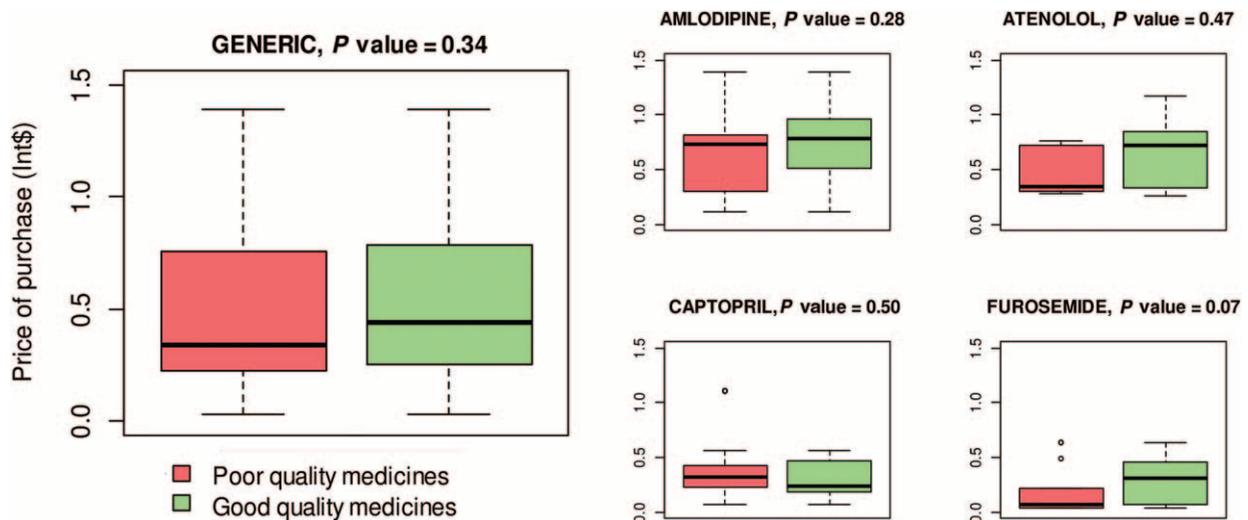
FIGURE 3 Drugs price of purchase (per unit) according to quality in antihypertensive generic drugs. Red and green boxplots represents, respectively, poor-quality generic drugs and good-quality generic drugs according to their price of purchase. No samples of poor quality were found in hydrochlorothiazide in their generic form, indeed hydrochlorothiazide is not represented on this figure. Int$ stands for international dollar.

disease medicines which should be of good quality, well tolerated and efficacious [5]. Scarce availability and low affordability of cardiovascular disease medicines have been reported in low-income and middle-income countries [25]. Based on the analysis of the PURE study data, Khatib *et al.* have shown that availability and affordability of cardiovascular disease medicines were not optimum in low-income countries, and this strongly impacts their use in those countries. Production of low-cost generic drugs contributes to the global effort to increase access to medications in low-income and middle-income countries, but assuring the quality of these products is a prerequisite to successful treatment.

Continuous use of poor-quality antihypertensive drugs might lead to treatment failure and variability of BP level and therefore be involved in the progression of organ damage and in triggering of vascular events [26–28]. Poor-quality medicine results in lack of therapeutic efficacy and a consequent loss of confidence in the healthcare system among patients and healthcare practitioners [29]. This problem might be even more enhanced in countries where traditional medicine cohabitate with modern medicine.

Important strengths of this prospective standardized study include the large number of drugs and samples collected, adherence to MEDQUARG guidelines in collection, the number of countries covered as well as the use of a validated fully quantitative method to assess active ingredient content by drug. However, we acknowledge some limitations. Only a small number of samples ($n = 20$) of hydrochlorothiazide in generic form were available; thus, the result about quality and price of this drug should be interpreted with caution. However, it reflects the poor availability of this drug in its generic version on the African market probably due to the very low price of hydrochlorothiazide. We also admit that the comparison of price within countries is sensitive because of different standards of living in each country. We used a standard measure (Int$ calculated with PPP rates), allowing comparison of real levels of expenditure between countries, as a way to get around this problem.

In conclusion, in this large prospective study of drug quality from 10 African countries, nearly a quarter of generic antihypertensives were found to be of low quality. Although low-cost generic drugs are the key to increase access to medications in low-income and middle-income countries, this should not be at the expense of the quality of these products. Substandard medicines represent a serious clinical and public health matter, and our findings highlight the urgent need to implement controls to assure quality and safety of generic medicines from production chain to the final use. Ensuring quality standards of antihypertensive drugs would be a major step forward in the effective control of hypertension and its consequences in low-income and middle-income countries.

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Conflicts of interest
There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

The most interesting finding of the manuscript is the rigorous evaluation of the quality of generic drugs in a area of the world where the treatment of hypertension is not very effective and should be supported by the administration of good antihypertensive drugs. The conclusion may also apply to the more industrialized countries where the quality of generic drugs strictly depend on their area of manufacturing that is not necessarily different from the one involving the Sub-Saharian territories.

The greatest limitation is the heterogeneity of the information that cannot be extended to any country where the same generic drugs are currently in the market.

Reviewer 2

The present study analyses the quality of five commonly used antihypertensive generic drugs distributed in ten Sub-Saharan African countries. The authors found one-quarter of the available generic antihypertensive drugs of poor quality. They rise a word of caution on the consequences on control rates and cardiovascular and renal risk protection in an emergent disease in these countries. This is one more barrier for BP control added to the difficulties in availability of drugs by healthcare structure and price of drugs. The study should be presented to the health authorities of these countries in order to take action on increase control of the quality of drugs released in the markets.