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BRIEF REPORT

Single-Pill, Triple Antihypertensive Therapy in Rural Sub-Saharan Africa: Preliminary Experience

Clara Stroppa · Isabella Hunjan · Alice Umulisa · Benitha Irebe · Gianfranco Parati · Mario G. Bianchetti · Bienvenu Muvunyi · Evariste Ntaganda · Vincent Sinabubaraga · Dragana Radovanovic · Sebastiano A. G. Lava · Franco Muggli

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ABSTRACT

Introduction: Worldwide, arterial hypertension is the foremost preventable and modifiable cardiovascular risk factor. In addition to lifestyle changes, recent international guidelines recommend single-pill, low-dose combinations as initial treatment strategy. We investigated whether this approach is feasible in a rural sub-Saharan Africa setting.

Methods: Diagnosis of hypertension was established over three sets of blood pressure measurements, performed according to the European Society of Hypertension recommendations by trained personnel, using a validated, automated, oscillometric device OMRON M7 IT-HEM-7322-E. In 98 individuals with arterial hypertension, a once-daily, single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide was prescribed at an appropriate dose. Patients were instructed on its administration and potential side effects and encouraged towards lifestyle modifications. The treatment regimen was adjusted, if needed, at each outpatient clinic

Clara Stroppa and Isabella Hunjan contributed equally to this work.

C. Stroppa · I. Hunjan · G. Parati
School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

C. Stroppa · I. Hunjan · M. G. Bianchetti · D. Radovanovic · F. Muggli
Family Medicine Institute, Faculty of Biomedical Sciences, Università Della Svizzera Italiana, Lugano, Switzerland

A. Umulisa · B. Irebe
Health Care Centre of Nyamyumba, Nyamyumba, District of Nyaruguru, Rwanda

G. Parati
Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano IRCCS, San Luca Hospital, Milan, Italy

B. Muvunyi
Medical Specialized Services, King Faisal Hospital, Kigali, Rwanda

E. Ntaganda
Cardiovascular Diseases Unit, Non-Communicable Diseases Division, Rwanda Biomedical Center, Kigali, Rwanda

V. Sinabubaraga
District Hospital, Munini, Rwanda

S. A. G. Lava (✉)
Pediatric Cardiology Unit, Department of Pediatrics, Centre Hospitalier Universitaire Vaudois, and University of Lausanne, 1011 Lausanne, Switzerland
e-mail: webmaster@sebastianolava.ch

S. A. G. Lava
Clinical Pharmacology & Therapeutics Group, University College London, London, UK

scheduled after 4, 8, 12, and 16 weeks.
Results: Seventy-nine patients (aged 61 [53–70] years; median and interquartile range) strictly adhered to the treatment schedule, while 19 individuals (70 [65–80] years) dropped out. Blood pressure was < 140/90 mmHg after 4 weeks in 44 (56%), after 8 weeks in 62 (78%), after 12 weeks in 69 (87%), and after 16 weeks in 74 (94%) participants. Excellent tolerance was reported.
Conclusions: These results provide real-life evidence that hypertension management with a once-daily, single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide as initial treatment is feasible and effective also in a rural sub-Saharan setting. Single-pill combinations should be made available also in rural and remote areas in low- and middle-income countries as a reliable first-line treatment strategy.

Keywords: Amlodipine; Arterial hypertension; Blood pressure; Hydrochlothiazide; Olmesartan; Polypill; Rural; Single-pill combination; Sub-Saharan Africa

Key Summary Points

Why carry out this study?

Once-daily, single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide is an effective and well-tolerated first-line treatment for arterial hypertension, and has recently been recommended.

We aimed to investigate whether this approach improves treatment adherence and hypertension control also in rural areas of sub-Saharan Africa.

What was learned from the study?

A program for diagnosis and management of hypertension showed that this treatment strategy is feasible and successful in a rural sub-Saharan Africa setting.

The implementation of antihypertensive single-pill combinations into national essential medicines lists and their availability on the market would represent a key step in promoting cardiovascular health in sub-Saharan Africa.

INTRODUCTION

Arterial hypertension is worldwide the most important preventable and modifiable risk factor for cardiovascular disease and its associated adverse outcomes, including cardiovascular events, disability, and death [1, 2]. Despite extensive knowledge on hypertension diagnosis, prevention, and treatment, its global incidence, prevalence, and associated cardiovascular complications remain alarmingly high, as recently documented in a dedicated World Health Organization report [3].

Abundant clinical data indicate that lowering blood pressure with antihypertensive drugs effectively reduces cardiovascular morbidity and mortality [2]. Following lifestyle modification, for the initial pharmacological treatment of hypertension, single-pill, low-dose combinations have recently been recommended because they allow achieving better treatment adherence and higher rates of hypertension control than usual care, and are generally well tolerated [2, 4].

Treatment with a single-pill combining the angiotensin II receptor antagonist olmesartan, the calcium channel blocker amlodipine, and the thiazide-type diuretic hydrochlorothiazide is associated with a higher blood pressure reduction rate compared with dual combination therapy or monotherapy [5]. Single-pill combination therapy is expected to improve treatment adherence and hypertension control

also in rural areas of low- and middle-income countries, where access to healthcare facilities is limited and people are often not inclined to adhere to pharmacological therapy with multiple drugs [1]. For these reasons, the above-mentioned triple drug combination was employed to control blood pressure in hypertensive individuals identified within the "Study for Better Blood Pressure and Cardiovascular Risk Control in a rural area of the District of Nyaruguru (Rwanda)" (Rwanda National Ethics Committee approval Nr. 752/RNEC/2019), which was endorsed by the World Hypertension League. In this report, we present preliminary data from this treatment experience.

METHODS

General Information

Between February and July 2020, a community-based, house-to-house blood pressure screening was carried out in 12 of the 16 villages of Mata Sector in the District of Nyaruguru, a remote, rural sub-Saharan region in the Southern province of Rwanda at an altitude of approximately 1900 m above sea level. The screening identified hypertensive blood pressure values in 12% of approximately 7000 participants [6]. After a pause due to the COVID-19 pandemic, between May and June 2022, individuals previously identified with elevated blood pressure values underwent a second identical screening. Among those confirmed with a diagnosis of arterial hypertension, a first cohort of 229 individuals was invited to enter the subsequent phase of the program.

This third phase was conducted by a committed team composed of two Italian near-graduate medical students, a local nurse with a bachelor's degree in general nursing, and one local assistant. They were supported by the principal investigators and study supervisor, from whom they received specific training. The project was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments. The project was approved by the Rwanda National Ethics Committee (RNEC) as "Study for better Blood Pressure and Cardiovascular Risk Control in a rural area of the District of Nyaruguru" (RNEC Approval Nr 752/RNEC/2019). Written and verbal informed consent in Kinyarwanda, the national spoken language, was obtained from all participants.

Study Design

This third phase was conducted between July and December 2022 at the hypertension outpatient clinic of the Health Care Center of Nyamyumba, one of Mata Sector's villages. Only adults on no previous antihypertensive treatment were eligible for inclusion. Collected data encompassed socio-demographic characteristics, medical history including self-reported previous diagnosis of diabetes mellitus (with or without treatment), and habits of tobacco smoking, alcohol consumption, and adding extra salt to food. Apart from diabetes mellitus, in order to be included, subjects needed to have no previously known comorbidity. Measurements included body anthropometrics, blood pressure, and resting heart rate. At the following outpatient clinics, i.e., after 4, 8, 12, and 16 weeks, only blood pressure and resting heart rate were recorded.

Weight was measured using a digital Tanita® platform scale (Tanita Corporation, Tokyo, Japan), height using a 220-cm Seca 206® roll-up wall-attached measuring tape (Seca GmbH & Co.KG., Hamburg, Germany). Waist circumference was measured at the narrowest point between the lower costal border and the top of the iliac crest in standing and outbreathing position (using a non-stretching tape measure). The waist-to-height ratio was calculated dividing waist circumference by height in centimeters.

Blood pressure was assessed following the European Society of Hypertension recommendations for blood pressure measurements in the office and at home [7], using a validated, automated, oscillometric OMRON M7 IT-HEM-7322-E blood pressure monitor with Intelli Wrap Cuff (HEM-FL31-E) technology (Omron Healthcare UK Ltd, Milton Keynes, UK) [8, 9]. Resting heart rate was recorded with the same device.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [7]. The diagnosis was established during the first outpatient clinic based on the mean of blood pressure readings recorded during the 2020 and 2022 house-to-house screening visits, and the office blood pressure measurements on that day. Arterial hypertension was classified as grade I (systolic 140–159 and/or diastolic 90–99 mmHg), grade II (systolic 160–179 and/or diastolic 100–109 mmHg), or grade III (systolic ≥ 180mmHg and/or diastolic ≥ 110 mmHg) [7]. After recommending appropriate lifestyle changes, as indicated in the recent ESH Guidelines [7], an antihypertensive, low-dose, single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide (OLM/AML/HCTZ) was prescribed to newly diagnosed patients. This medication was available in two fixed-dosage combinations (20/5/12.5 and 40/10/12.5 mg). A third dosage (10/2.5/6.2 mg) was obtained by halving the former with a pill-splitter. A hypertension specialist determined the dosage of the medication based on age, weight, and the degree of hypertension. Each patient received an envelope with reported medication name, dose, and regimen, containing 1-month therapy, plus some spare pills. Patients were recommended to take the prescribed treatment once daily, early in the morning. They were also provided with culturally adapted notions of health care education related to cardiovascular diseases and hypertension and informed about possible side effects of this therapy, such as dizziness, fatigue, headaches, palpitations, peripheral edema, musculoskeletal pain, nausea, diarrhea, or constipation. Medication tolerance was considered excellent in cases without any of the mentioned side effects.

For each patient, blood pressure and heart rate readings as well as the assigned therapy and the following appointment were recorded into a personal booklet to gather at each subsequent visit along with any remaining pill (drug reconciliation). Patients were received at the outpatient clinic after 4, 8, 12, and 16 weeks from the initial visit to perform a clinical examination, verify drug tolerance, and adjust, if needed, their treatment regimen. When needed, dose was increased in order to attain a target clinic blood pressure of < 140/90 mmHg.

Statistical Analysis

Nominal and dichotomous categorical variables are expressed as counts and were analyzed by means of the χ^2 test [10]. The normality D'Agostino-Pearson omnibus test [11] disclosed that age, weight, height, waist-to-height ratio, blood pressure, and resting heart rate did not follow a Gaussian distribution. Consequently, continuous data are presented as median and interquartile range and were analyzed using the non-parametric Mann–Whitney–Wilcoxon *U* test and the Friedman test with the Dunn post hoc multiple comparison [10]. Blood pressure and resting heart rate are presented also in box-and-whisker plots (the bottom and top of the box represent the 25th and 75th centile, the middle band the median, and the ends of the whiskers the 10th and the 90th centile) [12]. Two-sided P values of < 0.05 were considered significant. GraphPad Prism for Macintosh 10.0.3 (GraphPad Software, San Diego, CA, USA) was used for statistical comparisons.

RESULTS

Seventy-two of the cohort of 229 presumably hypertensive individuals invited to the hypertension outpatient clinic in Nyamyumba did not attend their appointment. Of the remaining 157 individuals, 59 were found with normal office blood pressure readings. Hence, the diagnosis of hypertension was made in 98 participants, who were enrolled in the treatment phase. Throughout this phase, 19 participant dropouts were recorded, while 79 individuals adhered to the prescribed schedule and treatment regimen (Fig. 1).

The characteristics of the 98 included patients with hypertension (71 females and 27 males, aged 65 [55–71] years) are presented in Table 1. Less than 5% of individuals had a previous diagnosis of diabetes mellitus (with or without treatment), and reported their habit of adding extra salt to food. By contrast, 19% showed a positive history of tobacco smoking

and 96% of alcohol consumption. Compared to dropouts, completers were significantly younger (by 9 years, $P = 0.0005$) and less frequently (11 vs. 53%) smokers ($P = 0.0002$). Furthermore, their systolic blood pressure was higher by 10 mmHg ($P = 0.0152$). Correspondingly, completers more frequently had grade II or III office blood pressure readings as compared to dropouts ($P = 0.0004$).

Blood pressure and resting heart rate values obtained before and during treatment with the single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide are presented in Table 2 and Fig. 2. In completers, medication decreased systolic, respectively diastolic, blood pressure by 30 [22 to 40] / 13 [5 to 18] mmHg at week 4. The subsequent changes were less striking: 10 [0 to 19] / 5 [– 2 to 11] mmHg between week 4 and 8, 3 [– 4 to 13] / 3 [– 3 to 7] mmHg between week 8 and 12, and 0 [– 11 to 10] / 0 [– 5 to 4] mmHg between week 12 and 16. Forty-four (56%) patients reached blood pressure values < 140/90 mmHg at week 4, 62 (78%) at week 8, 69 (87%) at week 12, and 74 (94%) at week 16. Moreover, 55 out of the 79 completers (70%) achieved a target blood pressure of < 130/80 mmHg. Resting heart rate decreased by 2 [– 6 to 8] beats/min at week 4, by 2 [– 6 to 10] beats/min between week 4 and 8, by 5 [– 1 to 11] beats/min between week 8 and 12, and by - 2 [– 9 to 4] beats/min between week 12 and 16. For simplicity, significant P values appear in Table 2, upper panel, and in Fig. 2. Similarly, dropouts also showed a clinically significant decrease in blood pressure and heart rate (Table 2, lower panel). Single-pill prescription was customized according to blood pressure values and clinical characteristics, and subsequently adjusted, if needed, at each outpatient clinic (Table 2 and Fig. 2). Medication tolerance was excellent in most of both completers and dropouts (Table 2).

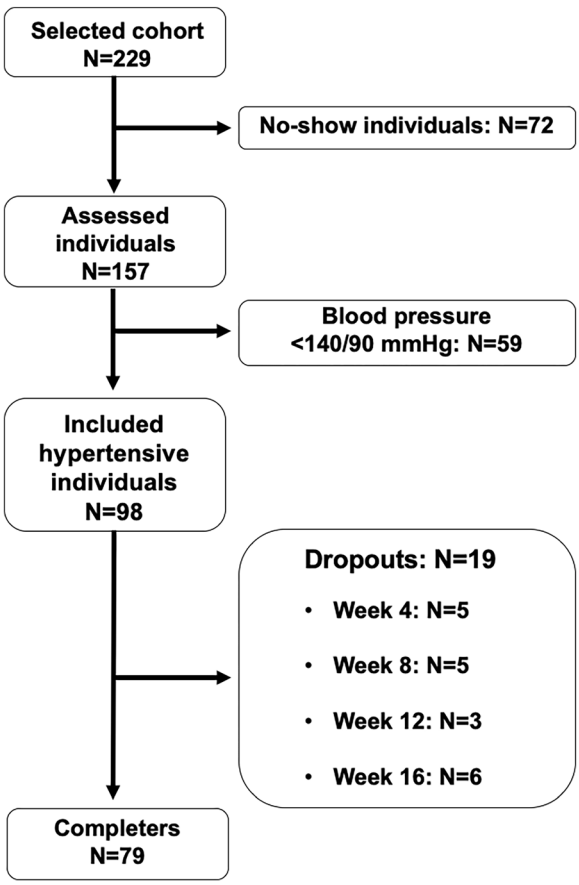


Fig. 1 Flowchart of study participants

DISCUSSION

The data presented in this report were collected in the District of Nyaruguru, a remote, rural sub-Saharan region in the Southern province of Rwanda. The results document that, in addition to recommended lifestyle changes, after 16 weeks of once-daily treatment with a single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide, blood pressure was reduced to < 140/90 mmHg in approximately 95% of patients. Comparable results were obtained with this combination in North America, Europe, and Asia [13].

The initial and early pharmacological management of hypertension with low-dose single-pill combinations is nowadays extensively supported and widely recommended [2]. Indeed, there is a strong consensus to replace traditional add-on drug treatment strategies with low-dose combinations as first-line therapy [14]. Single-pill combinations enhance treatment efficacy by simultaneously addressing various pathophysiological pathways involved in the development of hypertension [5, 15]. This increases the effectiveness of the initial medication and

Table 1 Characteristics of 98 included hypertensive individuals

	All	Dropouts	Completers	*P* value
N (%)	98	19 (19)	79 (81)	
Females: Males, *N* (%)	71 (72): 27 (28)	13 (13): 6 (6.1)	58 (59): 21 (21)	0.7757
Age, years	65 [55–71]	70 [65–80]	61 [53–70]	0.0005
Profession, *N* (%)				
Business	5 (5.1)	0	5 (6.3)	0.5265
Farming	38 (39)	8 (42)	30 (38)	
None	55 (56)	11 (58)	44 (56)	
Self-reported diabetes mellitus, *N* (%)	3 (3.1)	0	3 (4.0)	> 0.9999
Tobacco smoking, *N* (%)	19 (19)	10 (53)	9 (11)	0.0002
Alcohol consumption, *N* (%)	94 (96)	19 (100)	75 (95)	> 0.9999
Adding extra salt to food, *N* (%)	3 (3.1)	1 (5.3)	2 (2.5)	0.4801
Weight, kg	53 [46–60]	51 [47–59]	53 [46–60]	0.9626
Height, m	1.58 [1.55–1.66]	1.61 [1.57–1.70]	1.57 [1.54–1.64]	0.0550
Waist-to-height ratio	0.50 [0.47–0.54]	0.49 [0.47–0.52]	0.50 [0.47–0.54]	0.5871
Blood pressure				
Systolic, mmHg	162 [154–172]	154 [150–166]	164 [156–173]	0.0152
Diastolic, mmHg	95 [88–101]	93 [90–96]	96 [88–102]	0.4022
Grade I hypertension, *N* (%)	21 (22%)	10 (53%)	11 (14%)	0.0004
Grade II hypertension, *N* (%)	58 (59%)	9 (47%)	49 (62%)	
Grade III hypertension, *N* (%)	19 (19%)	0	19 (24%)	
Resting heart rate, beats/min	78 [68–87]	76 [58–87]	78 [69–87]	0.2208

Data are presented as frequency (with percentage) or as median (with interquartile range)

decreases the reluctance to escalate treatment when blood pressure remains uncontrolled [4, 16]. Furthermore, single once-daily therapy reduces pill burden and enhances medication adherence and persistence [4]. The antihypertensive action of low-dose combinations is additive, unlike their side effects [17]. Taken together, these features ultimately lead to better blood pressure control. Depending on regional circumstances, single-pill combinations may also be cost-effective.

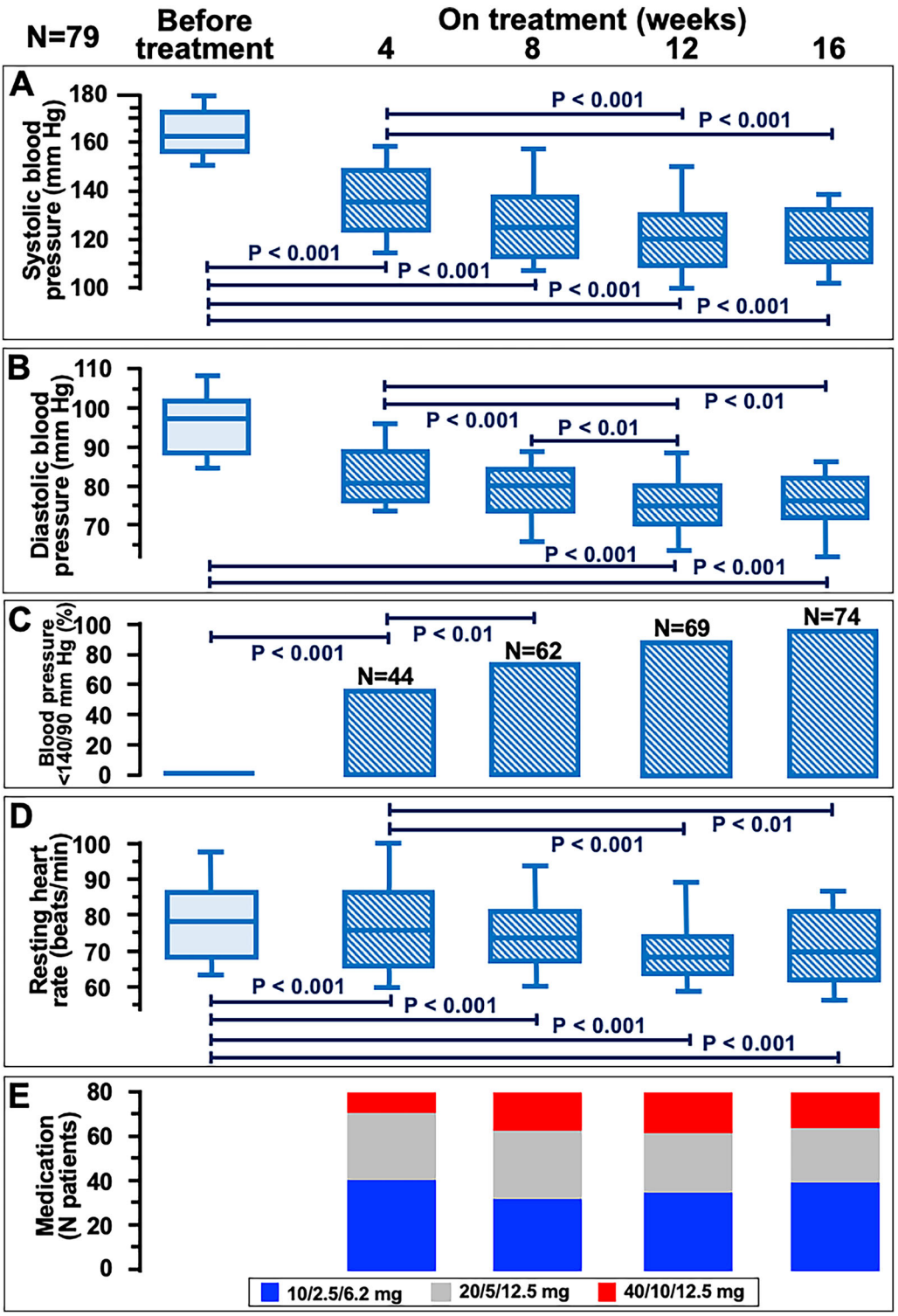
In the sub-Saharan setting, single-pill combinations are established as first-line treatment for tuberculosis [18], HIV [19], malaria [20], and hepatitis C [21]. However, antihypertensive single-pill combinations are still rather uncommon [22]. Their implementation into national essential medicines lists and national hypertension guidelines as well as availability on the market would represent key facilitators to promote this treatment strategy [23].

Resting heart rate slightly decreased on medication. These agents primarily target blood pressure and fluid balance rather than directly affecting heart rate. We speculate that this (somewhat unexpected) result on heart rate may be due to the indirect cross-effect between the renin–angiotensin–aldosterone system

Table 2 Blood pressure and resting heart rate of 79 completers (upper panel) and 19 dropouts (lower panel) before and during treatment with the single-pill combination olmesartan/amlodipine/hydrochlorothiazide (OLM/AML/HCTZ)

	Before treatment	Treatment (weeks)				*P* value
		4	8	12	16	
Completers (N = 79)						
Attenders, N	79	79	79	79	79	
Blood pressure, mmHg						
Systolic	164 [156–173]	135 [123–147]	124 [113–136]	120 [111–130]	120 [110–131]	< 0.0001
Diastolic	96 [88–102]	80 [80–88]	78 [73–84]	75 [70–80]	76 [71–82]	< 0.0001
Blood pressure < 140/90 mmHg, N (%)		44 (56)	62 (78)	69 (87)	74 (94)	< 0.0001
Resting heart rate, beats/min	78 [69–87]	76 [66–86]	73 [66–81]	67 [63–74]	70 [62–81]	< 0.0001
Medication (OLM/AML/HCTZ), mg						
10/2.5/6.2		40 (51)	33 (42)	36 (46)	39 (49)	
20/5/12.5		33 (42)	31 (39)	27 (34)	24 (30)	
40/10/12.5		6 (7)	15 (19)	16 (20)	16 (20)	
Excellent tolerance, N (%)		76 (96)	74 (94)	78 (99)	79 (100)	
Dropouts (N = 19)						
Attenders, N	19	14	9	6	0	
Blood pressure, mmHg						
Systolic	154 [150–166]	131 [122–138]	117 [110–121]	128 [117–137]		
Diastolic	90 [87–97]	80 [77–85]	72 [66–80]	81 [69–91]		
Blood pressure < 140/90 mmHg, N (%)		12 (86)	8 (89)	5 (83)		
Resting heart rate, beats/min	77 [67–85]	73 [66–82]	73 [62–85]	73 [67–79]		
Medication (OLM/AML/HCTZ), mg						
10/2.5/6.2		9 (64)	6 (66)	3 (50)		
20/5/12.5		5 (36)	2 (22)	2 (33)		
40/10/12.5		0	1 (11)	1 (17)		
Excellent tolerance, N (%)		14 (100)	8 (89)	6 (100)		

Data are presented as frequency (with percentage) or as median (with interquartile range)


N=79
Before treatment
On treatment (weeks)
4
8
12
16
A
Systolic blood pressure (mm Hg)
180
160
140
120
100
P < 0.001
P < 0.001
P < 0.001
P < 0.001
P < 0.001
P < 0.001
B
Diastolic blood pressure (mm Hg)
110
100
90
80
70
P < 0.01
P < 0.001
P < 0.01
P < 0.001
P < 0.001
C
Blood pressure <140/90 mm Hg (%)
100
80
60
40
20
0
P < 0.001
P < 0.01
N=44
N=62
N=69
N=74
D
Resting heart rate (beats/min)
100
90
80
70
60
P < 0.01
P < 0.001
P < 0.001
P < 0.001
P < 0.001
E
Medication (N patients)
80
60
40
20
0
10/2.5/6.2 mg
20/5/12.5 mg
40/10/12.5 mg

◀**Fig. 2** Systolic blood pressure (**A**), diastolic blood pressure (**B**), prevalence of blood pressure < 140/90 mm Hg (**C**), resting heart rate (**D**), and medication dosage (**E**) in 79 completers before (□) and during (▨) treatment with the single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide (OLM/AML/HCTZ) 10/2.5/6.2 mg (■), 20/5/12.5 mg (■), and 40/10/12.5 mg (■). Data contained in panels A, B, and D are presented as box-and-whisker plots (the bottom and top of the box represent the 25th and 75th centile, the middle band the median, and the whiskers' ends the 10th and the 90th centile, respectively)

inhibition and the sympathetic nervous system [24]. Furthermore, it might be postulated that, by improving cardiovascular function, these agents could indirectly lead to a reduced heart rate.

The dropout rate of about 20% observed in our study is consistent with that reported in the literature [25]. It is likely not related to a high prevalence of side effects, as evidenced by a high proportion of excellent tolerance also among dropouts (Table 2). Conversely, it is plausible that factors prior to attendance, such as age, distance from our clinic, difficulties in transportation, and lost productivity due to interruption of their work schedule, influenced patients' adherence to the study protocol [26].

This program has some noteworthy strengths. First, the diagnosis of hypertension was established over three sets of blood pressure measurements taken by trained healthcare personnel at three different visits on separate days, employing a clinically validated, automated, oscillometric device [8, 9] and carefully following international blood pressure measurement recommendations [7]. This resulted in an accurate estimate of blood pressure values in each participant. Second, we introduced an effective and manageable medication regimen whose titration was individually tailored at each outpatient clinic. Achieving a success rate of 94% is remarkable in Africa, considering the pretty modest results previously obtained, with control rates between 0.4% and 50% [1, 27, 28]. Very promisingly, the investigated approach allowed achieving the World Hypertension League's goal of 80% of treated patients with hypertension in Africa being controlled [1]. Third, we also promoted culturally adapted education and lifestyle modifications related to hypertension and cardiovascular risk factors. The positive results achieved also encourage forthcoming efforts to aim at achieving treated blood pressure values of < 130/80 mmHg [7].

However, we also acknowledge a few limitations of this study. Admittedly, cardiovascular risk factors, such as tobacco smoking, alcohol consumption, and adding extra salt to food, should have been better quantified. Furthermore, electrolyte levels and kidney function would have been reliable indicators of medication tolerability. Moreover, 24-h ambulatory blood pressure monitoring allows confirming and assessing hypertension, including identification of white-coat and masked hypertension, and characterization of nocturnal blood pressure phenotypes [7]. In this study in a remote, rural sub-Saharan region, this was unfortunately not possible. Nevertheless, the study design reflects everyday clinical life in low-income countries. Indeed, while ambulatory blood pressure monitoring is commonly employed in high-income countries, its expense prohibits its recommendation for use in sub-Saharan Africa [1]. Finally, we recognize that medication side effects should have been systematically explored in a more granular way. Future studies should gather this information.

CONCLUSIONS

The single-pill combination of olmesartan, amlodipine, and hydrochlorothiazide is an effective and practical initial treatment of hypertension also in rural sub-Saharan Africa.

This study represents real-life evidence in favor of extensive implementation of single-pill combination therapy also in low- and middle-income countries. Local healthcare authorities should include recommendation on their use in national guidelines and should also make them available in rural and remote areas at low or no cost, as reliable first-line treatment strategy in daily practice.

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Author Contributions. All authors have made substantive intellectual contributions to this project. Franco Muggli, Gianfranco Parati, and Alice Umulisa conceptualized the treatment phase of the project and developed the research tools and methodology. Franco Muggli acquired the funding. Franco Muggli, Bienvenu Muvunyi, Evariste Ntaganda, Vincent Sinabubaraga, Clara Stroppa, Isabella Hunjan, Alice Umulisa, and Benitha Irebe collected the data. Clara Stroppa, Isabella Hunjan, Mario G. Bianchetti, Sebastiano A. G. Lava, and Dragana Radovanovic conducted the formal data analysis. Clara Stroppa, Isabella Hunjan, and Mario G. Bianchetti wrote the original draft of the manuscript. All authors reviewed and edited the draft and agreed to submit the final manuscript for publication.

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Data Availability. Deidentified datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Clara Stroppa, Isabella Hunjan, Alice Umulisa, Benitha Irebe, Gianfranco Parati, Mario G. Bianchetti, Bienvenu Muvunyi, Evariste Ntaganda, Vincent Sinabubaraga, Dragana Radovanovic, and Franco Muggli have nothing to disclose. Sebastiano A.G. Lava is the current recipient of research grants from Fonds de perfectionnement, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; Fondation SICPA, Prilly, Switzerland; Fondazione Dr. Ettore Balli, Bellinzona, Switzerland; Fondazione per il bambino malato della Svizzera italiana, Bellinzona, Switzerland and Frieda Locher-Hofmann Stiftung, Zürich, Switzerland.

Ethical Approval. The project was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments. The project was approved by the Rwanda National Ethics Committee (RNEC) as "Study for better Blood Pressure and Cardiovascular Risk Control in a rural area of the District of Nyaruguru" (RNEC Approval Nr 752/RNEC/2019). Written and verbal informed consent in Kinyarwanda, the national spoken language, was obtained from all participants.

REFERENCES

1. Parati G, Lackland DT, Campbell NRC, et al. How to improve awareness, treatment, and control of

hypertension in Africa, and how to reduce its consequences: a call to action from the world hypertension league. Hypertension. 2022;79:1949–61.

2. Wang N, Rueter P, Atkins E, et al. Efficacy and safety of low-dose triple and quadruple combination pills vs monotherapy, usual care, or placebo for the initial management of hypertension: a systematic review and meta-analysis. JAMA Cardiol. 2023;8(6): 606–11.

3. Global report on hypertension: the race against a silent killer. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

4. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77(2):692–705.

5. Volpe M, Tocci G. Rationale for triple fixed-dose combination therapy with an angiotensin II receptor blocker, a calcium channel blocker, and a thiazide diuretic. Vasc Health Risk Manag. 2012;8: 371–80.

6. Muggli F, Parati G, Suter P, et al. Blood pressure in a population of a rural area of Rwanda: preliminary data. J Hypertens. 2021;39(Suppl 1): e400.

7. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens. 2023;41: 1874–2071.

8. Adler C, Ellert U, Neuhauser HK. Disagreement of the two oscillometric blood pressure measurement devices, Datascope accutorr plus and Omron HEM-705CP II, and bidirectional conversion of blood pressure values. Blood Press Monit. 2014;19:109–17.

9. Bilo G, Sala O, Perego C, et al. Impact of cuff positioning on blood pressure measurement accuracy: may a specially designed cuff make a difference? Hypertens Res. 2017;40:573–80.

10. Brown GW, Hayden GF. Nonparametric methods. Clinical applications. Clin Pediatr (Phila). 1985;24: 490–8.

11. Poitras G. More on the correct use of omnibus tests for normality. Econ Lett. 2006;90:304–9.

12. Bahna SL, McLarty JW. Data presentation. Ann Allergy Asthma Immunol. 2009;103:S15–21.

13. Burnier M, Redon J, Volpe M. Single-pill combination with three antihypertensive agents to improve blood pressure control in hypertension: focus on olmesartan-based combinations. High Blood Press Cardiovasc Prev. 2023;30:109–21.

14. Kjeldsen SE, Messerli FH, Chiang CE, Meredith PA, Liu L. Are fixed-dose combination antihypertensives suitable as first-line therapy? Curr Med Res Opin. 2012;28(10):1685–97.

15. Neutel JM, Smith DH. Hypertension management: rationale for triple therapy based on mechanisms of action. Cardiovasc Ther. 2013;31(5):251–8.

16. Rea F, Corrao G, Merlino L, Mancia G. Initial antihypertensive treatment strategies and therapeutic inertia. Hypertension. 2018;72(4):846–53.

17. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326(7404):1427.

18. Albanna AS, Smith BM, Cowan D, Menzies D. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. Eur Respir J. 2013;42(3):721–32.

19. Cutrell J, Bedimo R. Single-tablet regimens in the treatment of HIV-1 infection. Fed Pract. 2016;33(Suppl 3):24S-30S.

20. Alven S, Aderibigbe B. Combination therapy strategies for the treatment of malaria. Molecules. 2019;24(19):3601.

21 Sonderup MW, Afihene M, Ally R, et al. Gastroenterology and hepatology association of sub-Saharan Africa (GHASSA). Hepatitis C in sub-Saharan Africa: the current status and recommendations for achieving elimination by 2030. Lancet Gastroenterol Hepatol. 2017;2(12):910–9.

22. Ajayi AAL, Ajayi OE. Pathophysiologically based antihypertensive pharmacotherapeutics rationality, efficacy and safety in Sub Saharan African nations - a review. Int J Cardiol Cardiovasc Risk Prev. 2021;11: 200111.

23. Bruyn E, Nguyen L, Schutte AE, Murphy A, Perel P, Webster R. Implementing single-pill combination therapy for hypertension: a scoping review of key health system requirements in 30 low- and middle-income countries. Glob Heart. 2022;17(1):6.

24. Saxena PR. Interaction between the renin–angiotensin–aldosterone and sympathetic nervous systems. J Cardiovasc Pharmacol. 1992;19(Suppl 6): S80–8.

25 Choudhry NK, Kronish IM, Vongpatanasin W, et al. American Heart Association council on hypertension; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Medication adherence and blood pressure control: a scientific statement from the American Heart Association. Hypertension. 2022;79(1):e1–14.

26. Sibomana JP, McNamara RL, Walker TD. Patient, clinician and logistic barriers to blood pressure control among adult hypertensives in rural district hospitals in Rwanda: a cross-sectional study. BMC Cardiovasc Disord. 2019;19(1):231.

27. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-Saharan Africa: a systematic review and meta-analysis. Hypertension. 2015;65:291–8.

28. Turé R, Damasceno A, Djicó M, Lunet N. Prevalence, awareness, treatment, and control of hypertension in Bissau, Western Africa. J Clin Hypertens (Greenwich). 2022;24:358–61.