



Use of Perindopril Arginine/Indapamide/Amlodipine in the Management of Hypertension in Two Sub-Saharan African Island Countries of Madagascar and Mauritius

Armand Mbanya · Azarkhan Ackbarkhan · Mohammad Yaseen Mittoo ·

Haja Andriamiadanarivo Ramamonjisoa · Benja Ramilitiana ·

Eliane Mikkelsen Ranivoharisoa · Solohery Jean Noël Ratsimbazafy ·

Jean Claude Mbanya 

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ABSTRACT

Introduction: Most patients with hypertension in sub-Saharan Africa require two or more drugs to control their blood pressure. Triple fixed-dose combination therapy of perindopril arginine/indapamide/amlodipine is more effective in lowering blood pressure, offers better target organ protection and has increased adherence compared to monotherapy and free combination therapy, and is safe to use. This observational study evaluates the effectiveness of perindopril arginine/indapamide/amlodipine in controlling blood pressure at least 1 month after treatment initiation and assesses patient- and physician-

reported drug tolerance over a 3-month period in Madagascar and Mauritius.

Methods: A total of 198 patients with hypertension in ambulatory care who had been on fixed-dose combination of perindopril arginine, indapamide, and amlodipine for at least 4 weeks were included. The main outcome measures were changes in systolic and diastolic blood pressure, attainment of blood pressure control under 140/90 mmHg and 130/80 mmHg, self-reported drug tolerance by the patient, and perceived drug tolerance by the treating physician. Data was collected at 1 month and 3 months.

Results: Mean systolic blood pressure was significantly lower at the 1-month (-3.4 mmHg, $p = 0.002$) and 3-month (-8.5 mmHg, $p < 0.0001$) visits. Diastolic blood pressure also

A. Mbanya · J. C. Mbanya
Health of Population in Transition Research Group,
University of Yaoundé I, Yaoundé, Cameroon

A. Ackbarkhan
Cardiology Clinic, Port Louis, Mauritius

M. Y. Mittoo
General Practice Clinic, Curepipe, Mauritius

H. A. Ramamonjisoa
Department of Diabetology, AMADIA Diabetology
Clinic, Antananarivo, Madagascar

B. Ramilitiana
Department of Internal Medicine, University
Hospital Joseph Raseta Befelatanana, Antananarivo,
Madagascar

E. M. Ranivoharisoa
Department of Nephrology, University Hospital
Joseph Raseta Befelatanana, Antananarivo,
Madagascar

S. J. N. Ratsimbazafy
Department of Internal Medicine, University
Hospital Soavinandriana, Antananarivo,
Madagascar

J. C. Mbanya (✉)
Department of Internal Medicine and Specialties,
Faculty of Medicine and Biomedical Sciences,
University of Yaoundé I, Yaoundé, Cameroon
e-mail: jcmbanya3@gmail.com

decreased significantly (-2.4 mmHg at 1-month, $p = 0.017$ and -5.4 mmHg at the 3-month visits, $p < 0.0001$). At 3 months, 80.4% of the patients attained blood pressure targets less than 140/90 mmHg and 42.7% attained targets less than 130/80 mmHg on the basis of their baseline blood pressure. Excellent drug tolerance was reported by more than 90% of patients and physicians at the 1-month visit and by more than 95% at the 3-month visit.

Conclusion: Triple fixed-dose therapy of perindopril arginine/indapamide/amlodipine continues to show additional blood pressure-lowering capacity even months after initiating the treatment in patients with hypertension in Madagascar and Mauritius. It is also well tolerated by patients with hypertension and assessed as safe to use by physicians.

Keywords: Amlodipine; Antihypertensives; Blood pressure control; Hypertension; Indapamide; Perindopril arginine; Sub-Saharan Africa; Target blood pressure; Triple fixed-dose combination

Key Summary Points

There are few studies if any in African island nations evaluating the effectiveness and tolerance of triple fixed-dose therapy, months after treatment initiation.

This observational study assessed the additional changes in systolic and diastolic blood pressure and tolerance of triple fixed-dose therapy of perindopril arginine/indapamide/amlodipine 3 months after at least 4 weeks of initial treatment.

Even months after treatment initiation, triple fixed-dose therapy of perindopril arginine/indapamide/amlodipine continued to lower blood pressure while remaining safe.

These findings suggest that triple fixed-dose therapy can be used to improve blood pressure control to the lowest optimal targets in patients with hypertension in African island populations.

INTRODUCTION

Blood pressure control in patients with hypertension is crucial for clinical management and the prevention of cardiovascular, retinal, and renal complications [1, 2]. Evidence suggests that it is important to start treatment as soon as possible to achieve blood pressure goals in the shortest time possible to avoid target organ damage [1, 3]. In fact, fixed combination therapy as an initial therapy is often required to achieve blood pressure goals and long-term clinical benefits [4]. As a result, there has been a push for more aggressive blood pressure targets in patients with hypertension by several cardiovascular societies across the globe [5].

Consensus guidelines from the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology/European Society of Hypertension (ESC/ESH) recommend aggressive blood pressure targets in patients, with recommended blood pressure goal of less than 130/80 mmHg measured at each patient encounter [6, 7]. The ESC/ESH also recommends the use of combination therapy as initial therapy for patients with hypertension [5, 7]. This is supported by the fact that about 70% of patients with hypertension fail to achieve blood pressure targets of 140/90 mmHg with monotherapy; these numbers are even higher with the newer guidelines' recommendations of 130/80 mmHg [3, 8].

Long-term prospective studies have shown that patients with hypertension need an average of three antihypertensive drugs to adequately control their blood pressure [9]. Combination therapy provides better target organ protection compared to increasing the dose of monotherapy. This is because combination therapy of antihypertensive drugs works synergistically on several of the pathways causing increased blood pressure [3, 9] which may prove particularly useful in populations like in Mauritius and Madagascar where there is heterogeneity of patients from different ancestries. Many fixed-dose combination drugs for hypertension are available and should be considered if more than one agent is needed to

control blood pressure [10, 11], especially since patients are usually taking several other medications for common comorbidities such as diabetes and dyslipidemia. Moreover, fixed-dose combination therapies increase adherence by up to 24%, improve attainment of blood pressure targets, and are well tolerated [3, 12]. In fact, using triple fixed-dose combination anti-hypertensive drug as an initial treatment or an escalation from monotherapy or bi-therapy in patients with mild to moderate hypertension increases the number of patients who attain their blood pressure targets without compromising compliance [13].

The ESC/ESH recommends using combination therapies including angiotensin-converting enzyme (ACE) inhibitors in the management of hypertension [7]. This observational study assessed the efficacy and tolerability of a fixed-dose combination of perindopril arginine, indapamide, and amlodipine in lowering office blood pressure over a period of 3 months in patients who have been receiving this treatment for at least 1 month in ambulatory care in Madagascar and Mauritius.

METHODS

Study Design and Participants

This was a multicenter prospective observational study conducted in Madagascar and Mauritius from June 2019 to February 2021. Participating physicians consisting of cardiologists, diabetologists, neurologists, nephrologists, internists, and general practitioners included ambulatory patients with hypertension from selected sites within both countries. Physicians screened patients for inclusion criteria. Participants in this study were patients with hypertension with a diagnosis dating at least 3 months prior to inclusion, aged between 18 and 80 years who had been on fixed-dose combination of perindopril arginine, indapamide, and amlodipine for at least 4 weeks and had blood pressure levels not exceeding 150/95 mmHg. Exclusion criteria were any contraindication to any component of the medication, pregnancy and breastfeeding,

secondary hypertension, orthostatic hypotension, hospitalized patients, history of cardiovascular events in the last 3 months, already participating in a clinical trial, disabling diseases such as dementia or inability to cooperate, neoplastic diseases, type 1 diabetes, and clinical signs of ischemic heart disease.

Patients meeting the inclusion criteria were enrolled in the study. Dosage of perindopril arginine/indapamide/amlodipine ranged from 5/1.25/5 to 10/2.5/10 mg. Data were collected at baseline, 1 month, and 3 months (patients could have visits in between as needed).

The study protocol was approved by local ethics committee in Madagascar and Mauritius, and procedures were performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients provided informed consent to participate in the study. Patients could discontinue the study at any time and for any reason. Mauritius: Clinical Research Regulatory Council (Application N°63); Madagascar: Comité d’Ethique de la recherche Biomédicale auprès du Ministère de la Santé Publique (CERBM) (N°164MSANP/SG/AMM/CERBM).

Data Collection

Office blood pressure was measured at baseline, 1-month, and 3-month visits. Systolic and diastolic blood pressures were measured thrice in a seated position using a mercury or electronic sphygmomanometer with 2-min intervals and was repeated if there was a difference of more than 10 mmHg. The recorded office blood pressure was the average of the two last measurements. Heart rate was also measured simultaneously. Body mass index (BMI) was calculated by dividing the weight (in kilograms) by the height (in meters) squared, which were both measured at baseline. Patients were categorized into one of three age groups: 18–39 years, 40–59 years, 60–80 years.

Most recent laboratory measurements were collected for total cholesterol, HDL cholesterol, glycemia, serum potassium, serum sodium, serum creatinine, and creatinine clearance. These were compared only at baseline and the

3-month visit since these measurements are not done routinely every month.

Medication tolerance was measured on the basis of self-report from the patient and on evaluation from their physician at the 1-month and 3-month visits.

Statistical Analyses

Continuous variables were expressed as mean and standard deviation. Means at baseline and at the 3-month visits for total cholesterol, HDL cholesterol, blood glucose, serum creatinine, creatinine clearance, serum sodium, serum potassium, and heart rate were compared using paired *t* tests. For comparison of mean systolic and diastolic blood pressure across three visits (baseline, 1 month, and 3 months), we compared means using a one-way analysis of variance (ANOVA) with a Tukey post hoc test. Post hoc test results were reported as mean and standard error. We report numbers and percentages for categorical variables. All statistical analyses were performed using Stata (13.1, StataCorp LLC, College Station, TX). The null hypothesis was always rejected for $p < 0.05$.

RESULTS

A total of 198 patients [86 (43.4%) men and 112 (56.6%) women] were evaluated, of whom 14 (7.1%) were aged 18–39, 92 (46.5%) aged 40–59, and 92 (46.5%) aged 60–80 years. The mean duration of hypertension at the baseline was 6.7 ± 7.6 years. The average time between the baseline and 1-month visit was 5.2 ± 1.8 weeks and between the baseline and 3-month visit was 10.8 ± 2.1 weeks.

The cardiovascular risk factors and medical history of the patients are summarized in Table 1. The mean BMI was 27 ± 5.1 kg/m². More patients (39.6%) had a BMI ranging from 25 to 29.9 kg/m², followed by BMI ranging from 18.5 to 24.9 kg/m² (38.6%).

Of the 198 patients included in our study, 19.9% were smokers, 46.4% had a family history of diabetes, and 42.9% had a family history of cardiovascular disease. In addition, 6% had a

history of renal disease, 3.2% had a history of myocardial infarction, 4.3% had a history of congestive heart failure, 13.4% had a history of stroke, 7.5% had a history of angina, and 43.2% had a history of diabetes (Table 1).

Blood Pressure and Pressure Targets

Mean systolic blood pressure (132.8 ± 9.9 mmHg vs 129.4 ± 11 vs 124.3 ± 9.1 mmHg, $p < 0.0001$) and mean diastolic blood pressure (82.1 ± 8.2 vs 79.7 ± 8.9 vs 76.7 ± 9.4 mmHg, $p < 0.0001$) were lowered significantly between baseline, 1-month, and 3-month study visits (Fig. 1). Tukey post hoc tests (presented in mean \pm standard error) revealed that systolic blood pressure was significantly lower at the 1-month visit compared to baseline (-3.4 ± 1 mmHg, $p = 0.002$), at the 3-month visit compared to baseline (-8.5 ± 1 mmHg, $p < 0.0001$), and at the 3-month visit compared to the 1-month visit (-5.1 ± 1 mmHg, $p < 0.0001$). Diastolic blood pressure was significantly lower at the 1-month visit compared to baseline (-2.4 ± 0.9 mmHg, $p = 0.017$), at the 3-month visit compared to baseline (-5.4 ± 0.9 mmHg, $p < 0.0001$), and at the 3-month visit compared to the 1-month visit (-2.9 ± 0.9 mmHg, $p = 0.003$).

Of the 198 patients included in the study, 97 (49%) had blood pressure levels higher than 140/90 mmHg at baseline. At the 1-month visit, 62.9% of these patients achieved a blood pressure level less than 140/90 mmHg and 15.5% achieved blood pressure levels less than 130/80 mmHg (Fig. 2a). At the 3-month visit 80.4% of these patients (i.e., with blood pressure levels higher than 140/90 mmHg) achieved blood pressure levels less than 140/90 mmHg while 41.2% achieved blood pressure levels less than 130/80 mmHg (Fig. 2a).

At baseline, 178 (89.9%) patients had blood pressure levels higher than 130/80 mmHg. At the 1-month visit, 18.5% of these patients achieved a blood pressure level less than 130/80 mmHg and 42.7% achieved blood pressure levels less than 130/80 mmHg at the 3-month visit (Fig. 2b).

Table 1 Demographics, cardiovascular risk factors and comorbidities of patients at baseline

	Overall, <i>n</i>	Count, <i>n</i> (%)
Demographics		
Age (years)	198	
18–39		14 (7.1)
40–59		92 (46.5)
60–80		92 (46.5)
Sex	198	
Male		86 (43.4)
Female		112 (56.6)
Cardiovascular risk factors		
BMI (kg/m ²)	197	
< 18.5		1 (0.5)
18.5–24.9		76 (38.6)
25–29.9		78 (39.6)
30–39.9		36 (18.3)
> 40		6 (3.1)
Smokers	196	39 (19.9)
Family history of CVD	153	57 (42.9)
Family history of diabetes	196	91 (46.4)
Past history		
Diabetes	185	80 (43.2)
LVH	185	51 (27.6)
Renal disease	182	11 (6.0)
Myocardial infarction	185	6 (3.2)
Angina	187	14 (7.5)
CHF	187	8 (4.3)
Stroke	187	25 (13.4)

CVD cardiovascular disease, *LVH* left ventricular hypertrophy, *CHF* congestive heart failure

Clinical and Biological Characteristics

We observed a significant decrease in mean total cholesterol (5.4 ± 1.2 vs 5.1 ± 1.2 mmol/L, $p < 0.0001$), mean blood glucose (6.9 ± 1.9 vs 6 ± 1.3 mmol/L, $p < 0.0001$), and mean heart rate (80.4 ± 9.8 vs 75.5 ± 7.9 beats per minute, $p < 0.0001$) between the baseline and 3-month visit. There were no significant mean changes in serum sodium, serum potassium, serum creatinine, and creatinine clearance at the 3-month visit (Table 2).

Treatment Regimen

At baseline, 35.2% of patients took perindopril arginine/indapamide/amlodipine fixed-dose combination therapy at 5/1.25/5 mg, 13.5% at 5/1.25/10 mg, 9.8% at 10/2.5/5 mg, and 41.5% at 10/2.5/10 mg. At the 1-month visit, there were 13 documented modifications of dosage: seven patients had their dosage of perindopril arginine/indapamide/amlodipine decreased and six patients had their dosage increased. At the 3-month visit, two patients had their dosage increased.

There were 19 patients who were prescribed an additional antihypertensive drug to perindopril arginine/indapamide/amlodipine fixed-dose combination therapy at the 1-month visit consisting of beta-blockers (nebivolol, atenolol, carvedilol, and metoprolol), a centrally acting alpha-2 adrenergic agonist (methyldopa), a calcium channel blocker (amlodipine), and an aldosterone receptor antagonist (spironolactone). At the 3-month visit, 13 patients were prescribed an additional antihypertensive drug including beta-blockers (nebivolol, atenolol, carvedilol, and metoprolol), a centrally acting alpha-2 adrenergic agonist (methyldopa), and a calcium channel blocker (amlodipine). Of these 13, nine were taking perindopril arginine/indapamide/amlodipine fixed combination therapy at a dosage of 10/2.5/10 mg.

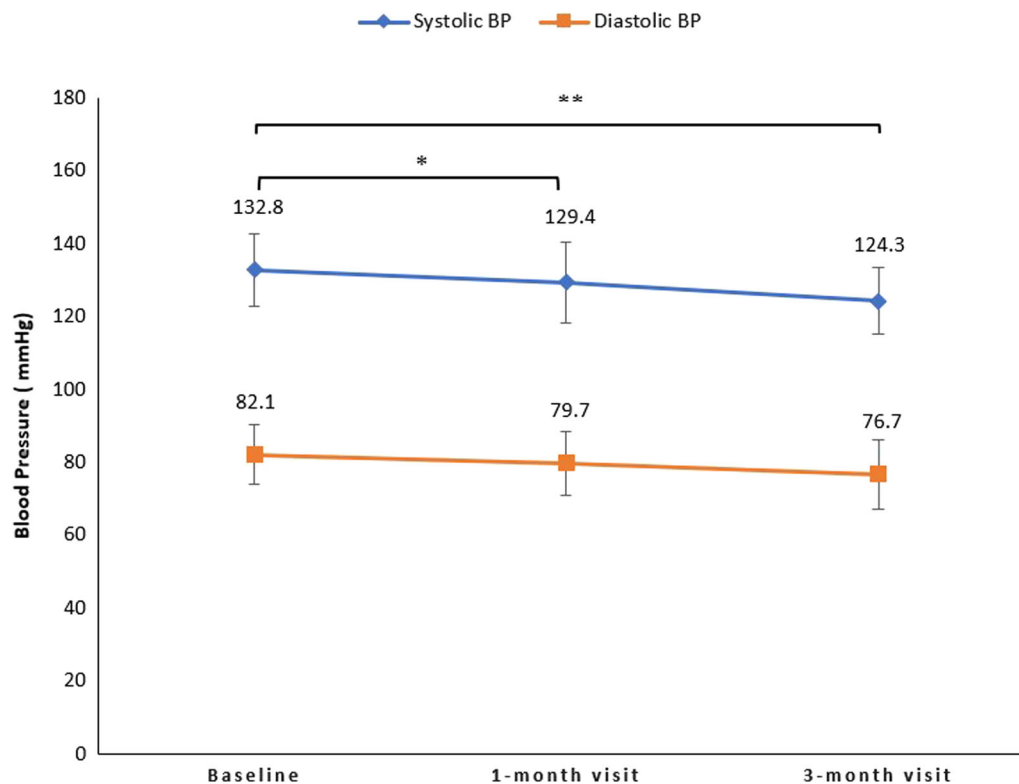


Fig. 1 Changes in systolic blood pressure and diastolic blood pressure between the baseline, 1-month, and 3-month study visit ($p < 0.05$, $**p < 0.0001$). The graph shows the mean (SD) systolic and diastolic blood pressure

readings at each study visit. The error bars represent the standard deviation. The p value denotes a significant difference in systolic and diastolic blood pressure means were compared across the three visits

Drug Tolerance

At the 1-month follow-up visit, data on self-reported tolerance from the patients were also collected and showed that 0.5% of patients described their tolerance as mediocre, 6.4% as average, and 93.1% as good to excellent. Physicians reported their patients’ drug tolerance as follows: 0.6% of patients described their tolerance as mediocre, 6.2% as average, and 93.3% as good to excellent (Fig. 3).

Self-reported tolerance from the patients at the 3-month visit revealed that 0.6% of patients described their tolerance as mediocre, 2.3% as average, and 97.1% as good to excellent. Physicians also assessed the tolerance of their patients at the 3-month visit and reported 0.5% as mediocre, 2.2% as average, and 97.3% as good to excellent (Fig. 3).

Of the 198 patients, 9 (4.5%) had mild side effects: hypotension (2), lower limb edema (1), cough (2), vertigo (1), electrolyte imbalance (1), elevated uric acid (1), and finally a patient presented with weakness (1) at the 1-month visit and tachycardia at their 3-month visit.

DISCUSSION

This observational study was performed in patients who had been receiving perindopril arginine/indapamide/amlodipine combination therapy for at least a month prior to the study and in ambulatory care for hypertension. There was a significant reduction in blood pressure in patients after 3 months of observation on perindopril arginine/indapamide/amlodipine at doses ranging from 5/1.25/5 to 10/2.5/10 mg. We found significantly lower blood pressure levels as early as 1 month of observation. In

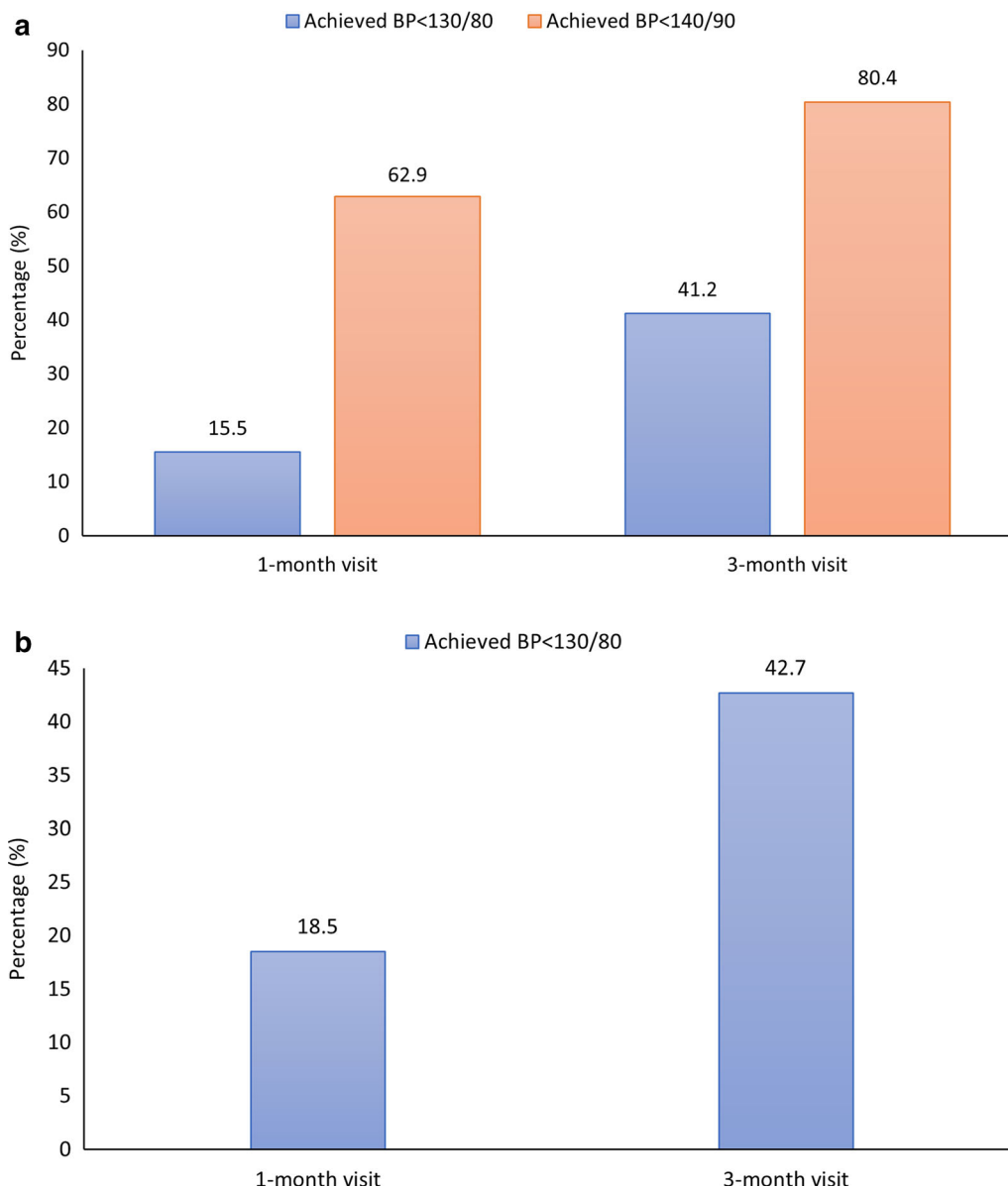


Fig. 2 a Percentage of patients who attained blood pressure (BP) targets of 140/90 mmHg and 130/80 mmHg across study visits when their baseline blood pressure was higher than 140/90 mmHg ($n = 97$).

b Percentage of patients who attained blood pressure (BP) targets of 130/80 mmHg across study visits when their baseline blood pressure was higher than 130/80 mmHg ($n = 178$)

addition, both patients and physicians reported good to excellent tolerance of triple fixed-dose combination therapy using perindopril arginine, indapamide, and amlodipine. This treatment was effective despite the fact that Mauritius and Madagascar have unique population characteristics of mixed African and

Asian descent, a population genotype being increasingly observed nowadays in populations in epidemiological transition.

This study showed that triple fixed-dose combination therapy of perindopril arginine/indapamide/amlodipine is an effective and safe long-term treatment option to decrease blood

Table 2 Clinical and laboratory measurements of patients at baseline and 3 months

Variable	Overall, <i>n</i> ^a	Baseline	3rd month	<i>p</i> value
Heart rate, bpm	152	80.4 ± 9.8	75.5 ± 7.9	0.0001
Total cholesterol (mmol/L)	118	5.4 ± 1.2	5.1 ± 1.2	0.0001
HDL cholesterol (mmol/L)	115	1.3 ± 0.5	1.2 ± 0.4	0.192
Blood glucose (mmol/L)	125	6.9 ± 1.9	6 ± 1.3	0.0001
Serum K ⁺ (mmol/L)	124	4.1 ± 0.5	4.1 ± 0.5	0.21
Serum Na ⁺ (mmol/L)	123	138.6 ± 5.2	137.7 ± 6.5	0.103
Serum creatinine (μmol/L)	111	93.2 ± 44.6	90.9 ± 30.7	0.122
Creatinine clearance (ml/min)	36	80.2 ± 26.6	78.9 ± 25.3	0.315

bpm beats per minute, *HDL* high density lipoprotein

^aShows the number of paired observations used in the comparison

pressure in patients with hypertension in Madagascar and Mauritius. This is particularly relevant because sub-Saharan African countries face unique challenges in the management of hypertension among their population [14, 15]. The contributing causes of lack of blood pressure control in sub-Saharan Africa are mainly poverty, as patients often cannot afford the cost of medications, and poor compliance to treatment [16]. Providing a fixed-dose combination pill has been shown to increase adherence and treatment persistence and can be cost-effective compared to free-combination therapies [12, 17].

Chronic exposure to high blood pressure levels leads to target organ damage and cardiovascular events therefore findings such as these have a significant clinical significance particularly in patients with hypertension in sub-Saharan Africa [2, 18]. Patients of African descent are known to have a higher frequency of resistant hypertension and target organ damage compared to other races [19, 20], which further highlights the importance of lowering blood pressure levels as quickly and safely as possible to attain recommended blood pressure targets in this population [20]. Notably, 80.4% of the patients in this study who were enrolled with blood pressure levels higher than 140/90 mmHg met the blood pressure target of less than 140/90 mmHg as recommended in 2020 by the

International Society of Hypertension (ISH) in Global Hypertension Practice Guidelines [21].

Furthermore, the AHA/ACC and the ESC/ESH recommend a more aggressive blood pressure target of less than 130/80 mmHg, which was achieved by 42.7% of the patients who had a baseline blood pressure measurement higher than 130/80 mmHg in this study [6, 7]. These rates are much higher compared to previous findings, showing that less than 20% of patients in sub-Saharan Africa treated for hypertension achieve blood pressure control [15]. As such, using combination therapy as initial treatment or for escalating monotherapy in a timely manner may be crucial to achieving recommended blood pressure control targets in these populations [16].

Adverse effects of medication in outpatient care are estimated to occur in about 25% of patients, with a study in Nigeria estimating them to be around 18% for antihypertensive medication [22, 23]. This is even more prevalent when high dose monotherapy is used to manage hypertension [3]; however, this study reported 9 (4.5%) patients with mild side effects, none of whom necessitated triple fixed-dose combination therapy to be stopped during the study period. The TRIUMPH study in Sri Lanka compared hypertension management strategy using a fixed low-dose triple combination pill therapy of telmisartan, amlodipine,

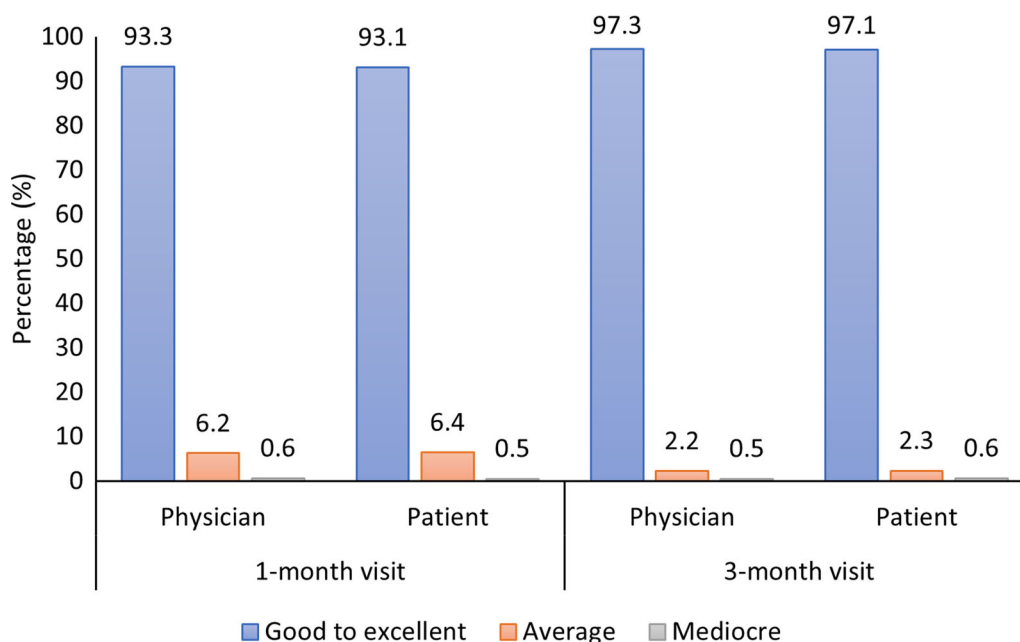


Fig. 3 Patient- and physician-reported drug tolerance at 1-month and 3-month visits. This graph represents the percentage of physicians and patients who reported their

tolerance to perindopril arginine/indapamide/amlodipine as mediocre, average, or good to excellent

and chlorthalidone in patients with mild to moderate hypertension compared with usual care over 6 months [13, 24]. The TRIUMPH study showed that using a triple fixed low-dose combination pill therapy improves blood pressure control; however, no reduction was observed in patient-reported adverse events (6.6% for triple fixed combination therapy) between the groups [13]. This difference in adverse events observed in the TRIUMPH study compared to this one may be attributable to the TRIUMPH study using a combination of telmisartan (20 mg), amlodipine (2.5 mg), and chlorthalidone (12.5 mg). Another large study with over 4700 high-risk patients with uncontrolled hypertension, the PIANIST study, found that triple fixed-dose combination of perindopril arginine/indapamide/amlodipine was not only effective in controlling blood pressure but it was also well tolerated [25]. The safety of the fixed combination therapy using perindopril/indapamide/amlodipine was highlighted in another trial by Mourad et al. [26] which compared triple fixed-dose combination therapy using perindopril arginine/indapamide/amlodipine over 4 months and showed that

uptitration was well tolerated and effective leading to over 80% of patients achieving blood pressure control. These studies highlight the safety of using triple fixed-dose combination therapy at higher doses and in some cases over longer periods of time (up to 6 months) to achieve and maintain blood pressure control in patients with hypertension [13, 25, 26].

Despite the need to understand effectiveness and tolerance of combination therapy in sub-Saharan African populations, few studies have assessed combination therapy in this setting [20]. The CREOLE study which enrolled 728 participants from six sub-Saharan countries compared three different drug combinations used in managing blood pressure: amlodipine plus hydrochlorothiazide, amlodipine plus perindopril, and perindopril plus hydrochlorothiazide [14]. The study authors reported that the amlodipine plus perindopril combination was the most effective in lowering blood pressure based on the mean change in the 24-h ambulatory systolic blood pressure between baseline and 6 months of treatment [14]. This suggests that combinations including amlodipine and perindopril may be effective in

managing blood pressure in patients with hypertension in sub-Saharan Africa.

A particular concern when using diuretics in hypertension management is diuretic therapy-induced hypokalemia [27, 28]. However, the co-administration of either an ACE inhibitor or an angiotensin II receptor antagonist with a diuretic corrects this electrolyte disturbance [27] which may explain why there was no observable significant change in serum potassium among patients in our study. Similarly to this study, the PAINT trial found a low incidence of adverse events potentially attributable to the mechanism of actions of perindopril and amlodipine and the metabolic neutrality of indapamide, which was the fixed-dosed combination therapy that they used [29]. These findings make a strong case for the safety of triple fixed-dosed combination therapy of perindopril arginine/indapamide/amlodipine in managing hypertension in sub-Saharan Africa.

Study Limitations

This was an observational study and therefore has the limitations associated with such studies. These include the non-standardization of all data collection, e.g., laboratory variables may have been measured using different techniques. Furthermore, biochemical measures are not routinely collected so we used the most recent values for this study. In addition, given the study design, we cannot account for the effect of patient education and lifestyle changes or the impact of concurrent non-blood pressure-lowering medications. Large-scale studies are needed in these populations to ascertain the blood pressure-lowering effect and tolerance of triple fixed-dose combination therapy using perindopril arginine/indapamide/amlodipine.

CONCLUSION

This observational study showed that triple fixed-dose combination therapy for hypertension management using perindopril arginine/indapamide/amlodipine is safe, well tolerated, and effective in lowering blood pressure in patients with hypertension in Madagascar and

Mauritius. Triple fixed-dose therapy of perindopril arginine/indapamide/amlodipine continues to show additional blood pressure-lowering capacity even months after initiating the treatment. This is particularly useful to improve blood pressure control to the lowest optimal targets in patients with hypertension in sub-Saharan African island populations.

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Disclosures. Armand Mbanya, Azarkhan Ackbarkhan, Mohammad Yaseen Mittoo, Haja Andriamiadanarivo Ramamonjisoa, Benja Ramilitiana, Eliane Mikkelsen Ranivoharisoa, and Solohery Jean Noël Ratsimbazafy have nothing to disclose. Jean Claude Mbanya is on the Advisory and Speaker Board of Servier.

Compliance with Ethics Guidelines. The study protocol was approved by local ethics committee in Madagascar and Mauritius, and procedures were performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients provided informed consent to participate in the study. Mauritius: Clinical Research Regulatory Council (Application N°63); Madagascar: Comité d'Ethique de la recherche Biomédicale auprès du Ministère de la

Santé Publique (CERBM) (N°164MSANP/SG/AMM/CERBM).

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

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