

Is a Low-Dose Triple-Drug Combination Pill Protocol the Answer for Hypertension Control in Sub-Saharan Africa?

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A sick man who eats many herbs does not know the one that made him well.

Variation on an African proverb

Hypertension, defined as a blood pressure of 140/90 mm Hg or higher, is the leading preventable risk factor for cardiovascular death and all-cause mortality worldwide.^{1,2} The World Health Organization (WHO) estimates that nearly 1.3 billion adults aged 30 to 79 years have hypertension, and only 1 in 5 have their blood pressure under control.³ The WHO also estimates that sub-Saharan Africa has the highest hypertension prevalence (27%).³ In a pooled analysis of 1201 population-representative studies with 104 million participants worldwide, sub-Saharan Africa had hypertension control rates of 13% in women and 9% in men in 2019.⁴ Most importantly, that study found little improvement in hypertension treatment and control rates in most countries in sub-Saharan Africa since 1990.⁴ Another study that pooled data from 33 surveys in sub-Saharan Africa involving more than 100 000 participants with a mean age of 40 years found a hypertension control rate of 7%.⁵ A recent cross-sectional study of 7 communities in East and West Africa showed a treatment rate of 30% among persons aware of their hypertension and a control rate of only 13%.⁶ Thus, concerted efforts to prevent, treat, and control hypertension in sub-Saharan Africa remain a major clinical and public health priority.

To address this important area of need, the Pan-African Society of Cardiology (PASCAR) convened a diverse, multidisciplinary team of physician and nonphysician experts on October 26-27, 2014, in Nairobi, Kenya, to undertake a situational analysis of hypertension treatment and control and identify the major roadblocks that hamper effective blood pressure control in Africa. This effort identified multiple roadblocks at the governmental, health systems, health care professional, and patient levels. Using findings from this effort and guidance from the World Heart Federation Roadmap template, PASCAR developed and published a road map customized to the local African context designed to help achieve a 25% hypertension control in Africa by the year 2025.⁷ The road map's treatment strategies take into account the level of blood pressure, existence of target-organ damage (defined to include hypertensive heart disease, stroke, or kidney disease), and the presence of diabetes.⁷ Both monotherapy and 2-drug combination therapy are recommended in the road map; however, there are no recommendations for 3-drug combination therapies.

Are 3-Drug Combination Pill Protocols Safe and Effective for Hypertension Treatment?

The superiority of 2-drug combination therapy over monotherapy as a first-line drug treatment strategy for hypertension control is well established, especially when blood pressure level exceeds 150/95 mm Hg or when diabetes or target organ damage is present.⁸⁻¹¹ Increasingly, there is also evidence for 3-drug combination therapy as a first-line treatment strategy. For example, a systematic review and meta-analysis of 7 randomized clinical trials that included a total of 1918 patients assessed the efficacy and safety of low-dose triple and quadruple combination pills compared with monotherapy, usual care, or placebo for the initial management of hypertension.¹² The analysis showed that low-dose combinations with 3 or 4 antihypertensive medications were effective and well tolerated.¹² None of the study participants were recruited from Africa, and with rare exceptions, most of the studies assessing the safety and efficacy of single-pill combinations of 3 or more antihypertensive medications have not been conducted in Africa despite the great need. So, the safety and effectiveness of a low-dose triple-pill protocol compared with standard care in Black African patients is unknown. This is the challenge Ojji and colleagues¹³ set out to address and now report on in this issue of *JAMA*.

In their randomized clinical trial conducted in Nigeria and including 300 adults with uncontrolled hypertension, Ojji et al¹³ used a novel single-pill combination of 3 drugs (telmisartan, amlodipine, and indapamide) in triple one-quarter dose, triple one-half dose, and standard doses as first-line treatment for hypertension. The comparator was standard care as recommended by the Nigeria hypertension treatment protocol, starting with amlodipine (5 mg). All study participants were recruited from 3 public hospital-based family medicine clinics. By the 6-month follow-up period, the primary effectiveness outcome (reduction in home mean systolic blood pressure) was significantly greater in the triple-pill protocol compared with the standard-care group (62% vs 28%; risk difference, 33% [95% CI, 22% to 44%]). The primary efficacy outcome (discontinuation of trial treatment due to adverse events) was equivalent in both study groups—no study participants discontinued trial medication because of adverse events.

These findings are important because they demonstrate that a low-dose, triple-drug combination pill protocol is safe and effective for hypertension control in Black African patients. While demonstrating safety and efficacy of a new pill and accompanying protocol at a 6-month follow-up is a crucial and important first step, much more is needed. Evidence of long-term safety and real-world effectiveness over a longer

period, especially in postmarket surveillance, would be reassuring to clinicians, payers, and patients. Additionally, obtaining regulatory approval to provide the assurance that the pill meets all necessary standards for use in the general population in the African context will be necessary. Equally importantly, demonstration of the pill's availability in the local African setting and its accessibility, affordability, and acceptability for sustained long-term use would be crucial. Economic analyses of costs and benefits from the perspectives of patients and their families as well as the perspectives of national and local government health programs, health insurers, and other health care payers would be crucial to demonstrate that the pill provides good value for the money compared with currently available therapies.

The Crucial Role of Implementation Science

The gap between the promise offered by this triple-pill protocol and achieving high hypertension control rates in real-world settings in sub-Saharan Africa is large. Effective dissemination and implementation research will be crucial in charting a path for success, beginning with the explicit use of validated implementation science theories, models, and frameworks to help gain insights into the barriers, facilitators, and mechanisms by which the use of this pill can

succeed in sub-Saharan Africa.¹⁴ In particular, future implementation trials and research studies will be necessary to explore specific factors external to the clinical care delivery setting that will be critical for successful and sustained uptake of this pill.¹⁵ Important among these factors are the local and national health policy environment, strategic partners and stakeholders in the public and private sectors, health communication channels, local cultural and linguistic factors, and the community of patients with hypertension, their families, and advocacy groups.

Ojji et al have the expertise to undertake these future studies in uncontrolled hypertension as they have done for diabetes and other chronic conditions in sub-Saharan Africa.^{16,17} The challenge is the capacity, political will, and availability of governmental and nongovernmental sources of funding to support this work. The greatest value from their study and others like it will come when the low-dose, triple-drug combination pill protocols become widely available and used sustainably in the long term by all who need it. As the old African proverb teaches, a sick man who eats many herbs may not know what made him well—but if the concoction is available, accessible, affordable, acceptable, safe, and effective, and if it brings him good health, he will gladly take it every time. So it will be for the low-dose combination pills for hypertension.

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