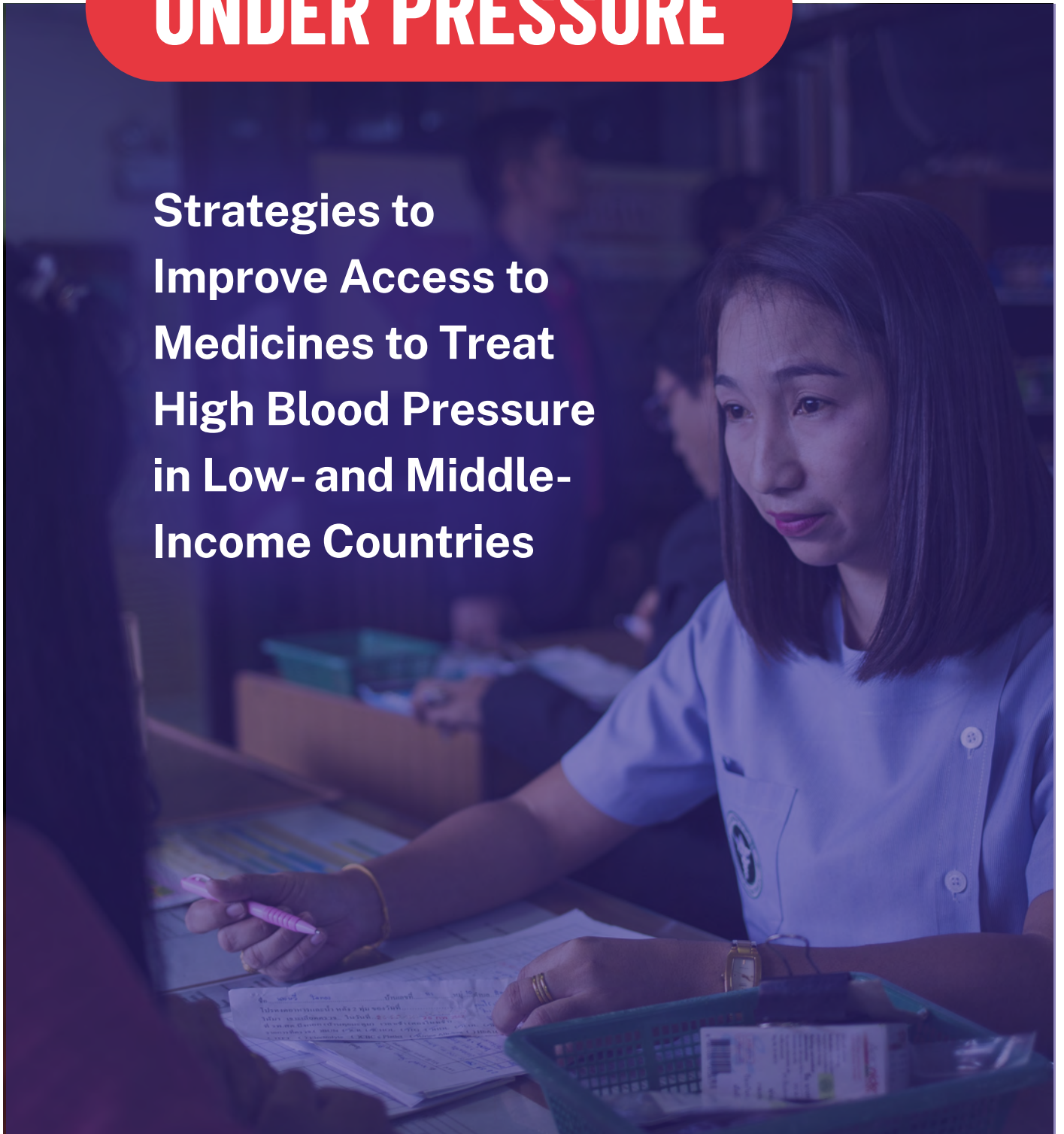


UNDER PRESSURE

**Strategies to
Improve Access to
Medicines to Treat
High Blood Pressure
in Low- and Middle-
Income Countries**



What the World Health Organization, national hypertension programs, civil society and manufacturers can do to **make antihypertensive medicines more available and affordable for people living with hypertension**





THE REPORT HAS THREE MAJOR FINDINGS:



Generic hypertension medicine prices vary substantially across LMICs, with medicines in some countries costing 40 times more than the estimated cost-based generic price.



Pills combining two or more medicines are recommended as the standard, but combination pills are often unavailable or unaffordable to patients.



Current prices put widespread treatment of high blood pressure out of reach of many people living in LMICs.



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EXECUTIVE SUMMARY

Hypertension — or high blood pressure — is the world’s single most important preventable risk factor for mortality and morbidity.

Almost three-quarters of people with hypertension live in low- and middle-income countries (LMICs).¹ Hypertension is treatable with standard medications, but currently, only about one in 10 hypertension patients in LMICs has their blood pressure controlled.² Global agencies and health stakeholders are striving to achieve hypertension control goals, but for most patients in LMICs, antihypertensive medications are unaffordable, inaccessible or not quality-assured. A major transformation in the global antihypertensive medicines market — to make quality-assured medicines affordable and available to patients at their primary care clinics and community pharmacies — will allow the world to meet the WHO target of reducing the prevalence of uncontrolled hypertension by 33% between 2010 and 2030 and save millions of lives in the decades to come.

This report identifies key challenges in the market and policy arenas that must be addressed to lower prices and make antihypertensive medicines more available to patients in LMICs. It provides recommendations for policymakers, pharmaceutical manufacturers and health advocates to promote a strong market of affordable antihypertensive medications for all patients who need them.

¹ NCD Risk Factor Collaboration. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021 Aug 24; 398 (10304): 957-980

² Geldsetzer P, Manne-Goehler J, Marchus M, Ebert C, Zhumadilov Z, Wesseh C et. al. The state of hypertension in 44 low-income and middle-income countries: a cross sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet*. 2019 Aug 24; 394(10199):452-662

Currently, only about **one in 10 hypertension patients in LMICs** has their blood pressure controlled.





STUDY FINDINGS AND KEY RECOMMENDATIONS

1 Alignment of national Essential Medicines Lists (EML) and clinical practice guidelines with WHO guidance for antihypertensive medicines

BACKGROUND: A prerequisite for making antihypertensive medicines more available in the public and private sectors is including them in clinical practice guidelines that inform country health care system design and health care provider behavior.

FINDING: National EMLs in the surveyed countries are mostly aligned with the 2021 World Health Organization (WHO) EML regarding the inclusion of antihypertensive medicine single agent pills (SAP; one medicine per pill), but most countries' EMLs and standard treatment protocols do not include single-pill combinations (SPCs; two or more medicines included in one pill).

RECOMMENDATION: National EMLs and standard hypertension treatment protocols should be updated to align with the latest WHO guidance.

2 Registration of antihypertensive medicines in LMICs

BACKGROUND: Registration of WHO-recommended antihypertensive drugs in LMICs is a critical requirement for making antihypertensive medicines more available in the public and private sectors in any country.

FINDING: Seven pharmaceutical manufacturers surveyed reported that less than 50% of selected antihypertensive formulations registered with a stringent regulatory authority (SRA) were also registered in at least one of 18 selected LMICs. Few SPCs were registered in the surveyed high-burden hypertension LMICs, limiting their availability in national markets.

RECOMMENDATION: Manufacturers should prioritize the submission of antihypertensive medicine regulatory dossiers, and national regulatory authorities (NRA) should deem these product registrations as public health priorities.



3

Availability of antihypertensive medicines, including SPCs, in selected LMICs

BACKGROUND: The latest WHO guidance, the 2021 [Guideline for the pharmacological treatment for hypertension in adults](#), and major national and regional guidelines recommend three specific medicine classes and initiating hypertension treatment with two drugs from these classes in combination. SPCs are preferred over SAPs, as they improve adherence, treatment efficiency and supply chain management.

FINDING: Generally, WHO-recommended antihypertensive SAPs were available in the five LMICs surveyed, though it is unknown whether the quantity of these drugs is sufficient to sustain full-scale national hypertension control programs. SPCs were less available than SAPs in the countries examined, especially in the public sector.

RECOMMENDATION: Ministries of health should increase the availability of antihypertensive medicines, particularly SPCs, in the public sector.

4

Antihypertensive medicine pricing in LMICs

BACKGROUND: There is a lack of evidence-based information on antihypertensive medicine pricing in the public and private sectors of LMICs.

FINDING: Antihypertensive medicine prices in the five LMICs surveyed were up to 41 times higher than the estimated cost-based generic prices for the same drugs. There are opportunities to reduce prices and increase affordability for WHO-recommended antihypertensive medicines in LMICs.

RECOMMENDATION: Procurement strategies should promote the transparency of antihypertensive medicine prices and incentivize medicine price benchmarking exercises and pooled procurement mechanisms for core antihypertensive medications.

5

Average per-patient costs of 2021 WHO-recommended hypertension treatment protocols using antihypertensive SAPs or SPCs

BACKGROUND: Medication regimen costing exercises can provide important information for country decision makers responsible for medicine purchasing and procurement.

FINDING: A costing exercise using WHO-recommended treatment protocols produced a wide range of per-patient costs for countries, suggesting that the average per-patient cost of SPC-based protocols is often equivalent to SAP-based protocols. However, in some settings, using the lowest prices available in the public sector, SAPs delivered the lowest cost per patient protocol.

RECOMMENDATION: Costing exercises using the highest and lowest available SPC and SAP prices within countries should be used to inform decision-making related to treatment protocol options, country medication procurement and budget allocation.



SUMMARY OF STAKEHOLDER-SPECIFIC RECOMMENDATIONS

WHO and technical partners

- Support countries to adopt the 2021 WHO hypertension treatment guideline and to update their national EML to align with the latest WHO Model List of Essential Medicines (WHO EML).
- Support the strengthening of national regulatory authorities until they reach WHO-Listed Authority (WLA) status.
- Support countries with surveys focused on antihypertensive medicine availability and prices using the WHO MedMon methodology for the private and public sectors.
- Support price transparency with comparability criteria in countries and across regions.
- Promote costing exercises to inform decision-making related to specific hypertension treatment protocol options.

Country governments/major procurers

- Integrate WHO guideline-recommended antihypertensive SAPs and SPCs into national EMLs.
- Adopt one of the two standard treatment protocol examples featured in the 2021 WHO hypertension treatment guideline.
- Include the chosen WHO-recommended SAPs and SPCs in the country reimbursement lists and health insurance plans.
- Prioritize registration of WHO-recommended antihypertensive medicines, including SPCs, through relevant NRAs.
 - Ensure that NRAs review antihypertensive drug dossiers submitted by manufacturers for registration in a timely manner. This is particularly important for quality-assured SPCs.
 - Negotiate framework agreements or long-term contracts with suppliers of quality-assured antihypertensive medicines. This includes medicines that are at least based on a Good Manufacturing Practices (GMP) certificate from an SRA for any solid oral formulations, and/or on WLA registration as of 2022 for local manufacturers compliant with WHO quality standards.
- Ensure that a basic set of antihypertensive medicines is available in the public sector to reduce out-of-pocket expenses and prevent poor health outcomes and catastrophic costs for patients and their families.
- Measure and regulate mark-ups along the national supply chain to avoid losing the benefits of adequate price negotiation with manufacturers, in terms of an affordability target for individual patients.



- Proceed to benchmark exercises during government tenders by comparing their domestic prices to estimated cost-based generic ones or those available through pooled procurement mechanisms or international suppliers with a quality assurance policy for medical procurement (e.g., the International Dispensary Association Foundation, IMRES, PAHO Strategic Fund, UNICEF and Medical Export Group).
- Seek to enter into regional or global multi-country pooled procurement agreements wherever this may increase access to more affordable antihypertensive medicines, or to purchase directly from international suppliers with quality-assured policies for medical procurement.
- Base forecasting and budgets on informed, protocol-specific costing exercises.
- Adopt medication quantification and forecasting tools that can integrate drug pricing options, so price negotiations are based on the anticipated need for specific drug classes and doses.
- Promote the implementation of facility-level monitoring and evaluation and quantification tools for hypertension cohorts to improve the accuracy of medication supply forecasting.
- Where possible, especially when distribution capacity from capital to districts is well-established, pool procurement of antihypertensive medicines across national administrative units. Facilitate central or regional procurement across countries to increase buying power.

Civil society/advocates

- Collect additional evidence on barriers hindering access to antihypertensive medicines to inform evidence-based advocacy messages.
- Demand affordable hypertension treatment; ideally without cost to patients, that is safe, reduces pill burden, maximizes the opportunity to achieve hypertension control and enables person-centered, community-based care models in accordance with the 2021 WHO hypertension treatment guideline.

Pharmaceutical manufacturers

- Register WHO-recommended antihypertensive medicines widely, first and foremost those aligned with the 2021 WHO hypertension treatment guideline, prioritizing high-burden hypertension countries.
- Consider contributing to pooled procurement mechanisms.





ABBREVIATIONS

ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin II receptor blocker
CCB	calcium channel blockers
CVD	cardiovascular disease
EML	essential medicines lists
GBT	global benchmarking tool
GMP	good manufacturing practices
LMICs	low-and middle-income countries
MSF	Médecins Sans Frontières
MoH	ministry of health
nEML	national essential medicines lists
NRA	national regulatory authorities
PAHO	Panamerican Health Organization
PIC/S	pharmaceutical inspection co-operation scheme
RTSL	Resolve to Save Lives
SAP	single agent pill
SRA	stringent regulatory authority
SPC	single-pill combination
WHO	World Health Organization
WLA	WHO-listed authority



INTRODUCTION

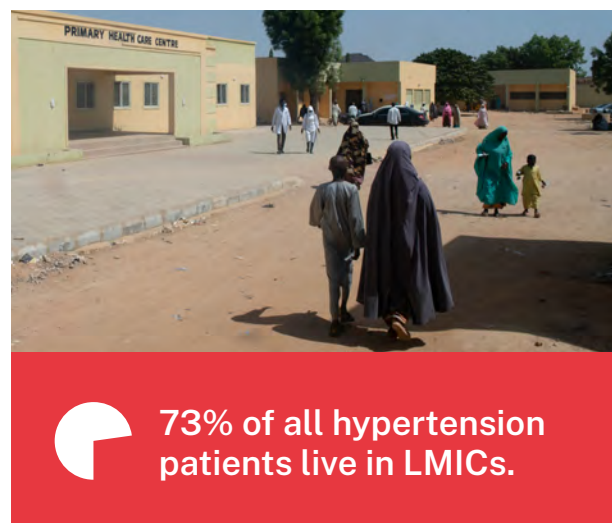
Rationale for an Antihypertensive Medicines Pricing Report

For the estimated 1.4 billion people living with hypertension worldwide, access to affordable, quality-assured medicines can mean the difference between a longer, healthier life and an early death.

But currently, access to these life-saving medicines can depend on where you live. Hypertension control has improved in many high-income countries during the past few decades, though even in these countries, the proportion of patients with controlled blood pressure (defined as <140/90 mmHg) remains less than 50%. The overwhelming majority of hypertension patients – about 73% – live in LMICs.³ In these countries, fewer than one in 10 people living with high blood pressure has it under control.⁴ This health crisis has spurred WHO to set ambitious targets for hypertension control, including reducing the prevalence of uncontrolled hypertension by 33% between 2010 and 2030.⁵

One of the biggest obstacles to achieving global hypertension control goals, and saving millions of lives, is poor access to affordable and quality-assured antihypertensive medicines.

While past comprehensive analyses of medicine prices and sourcing have contributed to making the HIV and tuberculosis medicine market more transparent, equivalent evidence is lacking for antihypertensive pharmaceuticals.^{6,7} This report examines the antihypertensive medicines access gap by surveying the current market and regulatory environment for antihypertensive medicines, including single pill combinations (SPCs), in a selection of LMICs. Its objective is to increase transparency regarding the current pricing, registration and availability of these medicines.



Under Pressure also aims to demonstrate the importance of analyzing the total costs of hypertension treatment to inform public health policies in the context of WHO-recommended standardized treatment algorithms, whether using SAPs or SPCs. Most importantly, it provides practical recommendations to WHO, ministries of health (MoHs), ministries of finance, clinicians, public health advocates and manufacturers about how to increase access to essential antihypertensive medicines.

3 NCD Risk Factor Collaboration. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021. Aug 24; 398 (10304): 957-980

4 Geldsetzer P, Manne-Goehler J, Marchus M, Ebert C, Zhumadilov Z, Wesseh C et. al. The state of hypertension in 44 low-income and middle-income countries: a cross sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet*. 2019 Aug 24; 394(10199):452-662

5 The World Health Organization [Internet] Hypertension–Key Facts; c2021[cited 2022 Nov 11]. Available from: <https://www.who.int/news-room/factsheets/detail/hypertension>

6 Médecins Sans Frontières. Untangling the Web: HIV Medicine Pricing & Access Issues. [cited 2022 Feb 25] Available from <https://msfaccess.org/untangling-web-hiv-medicine-pricing-access-issues-2020> 2020 Nov 30

7 Médecins Sans Frontières. DRTB drugs under the microscope: TB Medicine Pricing & Access Issues. [cited 2022 Feb 25] Available from <https://msfaccess.org/drtb-drugs-under-microscope>



Current Challenges to Access Affordable, Quality-Assured Treatment in LMICs

A number of practical barriers place hypertension treatment and blood pressure control out of reach for most patients living in LMICs.

Current hypertension treatment regimens are complex.

High blood pressure can be controlled, but it requires daily medication, typically over the long-term. Most patients require more than one type of medicine to reach their target blood pressure — and many countries have not yet prioritized SPCs as their first line of treatment. Having to take multiple pills daily to control blood pressure creates an adherence burden for hypertension patients.⁸

For health care providers, more than 10 types of blood pressure medication often crowd the formulary, and some of these medicines are not

within the three WHO-recommended classes. The WHO suggestion to initiate two-drug therapy in people with blood pressure $\geq 140/90$ mmHg has not been sufficiently translated into real-world practice, contributing to treatment failures.

The number of treatment options available, the complexity of treatment combinations and the high number of titration steps required to meet maximal therapy often lead to what is called “titration fatigue.” Combined with the challenges for patients taking multiple pills, these overly complicated practices mean that many cases of hypertension are left untreated or uncontrolled.⁹



8 Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011;378:1231–43. doi:10.1016/S0140-6736(11)61215 — Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *J Am Med Assoc* 2013;310:959–68. doi:10.1001/jama.2013.184182-Van der Linden EL, Agyemang C, van den Born BJH. Hypertension control in sub-Saharan Africa: Clinical inertia is another elephant in the room. *J Clin Hypertens* 2020;22:959–61. doi:10.1111/jch.13874

9 Huffman MD, Rao KD, Pichon-Riviere A, Zhao D, Harikrishnan S, Ramaiya K, et al. A cross-sectional study of the microeconomic impact of cardiovascular disease hospitalization



The cost of antihypertensive medicines can be prohibitive.

A wide range of antihypertensive medications from multiple drug classes being used across countries and prescribed by physicians within countries have created fragmented markets, with little opportunity for treatment protocol simplification and thus little opportunity for market-shaping. This situation undercuts governments’ and other payers’ power to negotiate lower prices for higher volumes of a narrow range of selected medicines. Past market research found that antihypertensive medicines can be prohibitively expensive to patients and are often unavailable in primary health care facilities, especially in the public sector.¹⁰ In settings without robust social security systems, many patients are unable to pay for antihypertensive medicines out of their own pockets due to the high costs of life-long treatment.

Over time, prohibitively high medication prices translate into widespread hypertension that goes untreated for years. Downstream, the missed opportunity to control blood pressure increases health risks for the patient and treatment costs for the system, as fatal or disabling cardiovascular disease (CVD) outcomes require medical interventions that are more costly and carry greater risk.¹¹

Another dangerous consequence of high antihypertensive medicine prices is the potential for shadow markets to emerge for substandard or falsified medicines with insufficient active ingredients and potentially toxic added ingredients.¹² Substandard or falsified medicines endanger patient health and erode the potential for a healthy market for quality-assured medicines.

SPCs are rarely available in LMICs, and particularly hard to find in the public sector.

Although most essential antihypertensive medicines have been available for years, information from Resolve to Save Lives (RTSL) and Médecins Sans Frontières (MSF) operations in LMICs suggests that access to recommended SPCs is lacking in many contexts.

The most expensive SAPs and SPCs were found in the private sector:

telmisartan 80mg:

Costs per tablet

\$0.03

Estimated cost-based generic price

\$0.84 33 X more expensive

Brazil private sector

telmisartan + amlodipine

40mg + 5mg:

Costs per tablet

\$0.02

Estimated cost-based generic price

\$0.81 41 X more expensive

Philippines private sector



10 Husain J, Datta B, Kostova D, Joseph K, Asma S, Richter P et. al. Access to cardiovascular disease and hypertension medicines in developing countries: An analysis of essential medicine lists, price availability and
 11 Huffman MD, Rao KD, Pichon-Riviere A, Zhao D, Harikrishnan S, Ramaiya K, et al. A cross-sectional study of the microeconomic impact of cardiovascular disease hospitalization
 12 Do N, Bellingham K, Newton P, Caillet C. The quality of medical products for cardiovascular diseases: a gap in global cardiac care. *BMJ Global Health.* 2021 Aug 19. 6:e006523. doi:10.1136/




The rational use of antihypertensive medicines in LMICs

Standard blood pressure-lowering medicines prevent cardiovascular deaths and disabling heart disease, strokes, heart failure and kidney damage.

Based on decades of clinical trial evidence and clinical experience, WHO's 2021 Guideline for the pharmacological treatment for hypertension in adults, as well as the WHO HEARTS technical implementation package¹³ and other international and national guidelines, strongly recommend three main therapeutic classes: renin-angiotensin-aldosterone system inhibitors [either angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB)], long-acting calcium channel blockers (CCB) or thiazide or thiazide-like diuretics.¹⁴ WHO recommends treating hypertension according to simple, standardized treatment protocols that specify recommended drugs and their doses.

Traditionally, hypertension treatment has been initiated with monotherapy – that is, starting with an SAP and intensifying treatment (increasing dose of the same medicine or adding a second medicine) based on blood pressure response. However, many patients require more than one medicine to control blood pressure, often resulting in a high pill burden and poor adherence.



Moving to single-pill combinations not only helps at the individual level, but also benefits health systems by reducing the number of patient visits and simplifying forecasting, procurement and supply chain management.

A shift from SAP to SPC antihypertensives

More recently, the 2021 WHO guideline and other national and regional hypertension treatment guidelines shifted to recommend initiating treatment with two-drug combinations, ideally in SPC formulations.¹⁵ SPCs have been shown to improve medication adherence, accelerate time to blood pressure control and have no greater risk of adverse events than the traditional SAP treatment approach.¹⁶ Because SPCs eliminate the need for higher doses of SAPs by combining two or more medicines, they avoid the higher side-effect risk expected with a high dose of any SAP taken alone. Moving to SPCs not only helps at the individual level, but also benefits health systems by reducing the number of patient visits and simplifying medicine forecasting, procurement and supply chain management.¹⁷

¹³ The World Health Organization, NCD Management-Screening, Diagnosis and Treatment. HEARTS technical package for cardiovascular disease management in primary health care: systems for monitoring. 2018. Jun 25 ISBN

¹⁴ The World Health Organization, Non communicable diseases. Guideline for the pharmacological treatment of hypertension in adults. 2021. Aug 24 ISBN: 9789240033993

¹⁵ The World Health Organization, Non communicable diseases. Guideline for the pharmacological treatment of hypertension in adults. 2021. Aug 24 ISBN: 9789240033993., JCH paper on this subject

¹⁶ Salam A, Huffman M, Kanukula R, Prasad E, Sharma A, Heller D. Two-drug fixed dose combinations of blood pressure-lowering drugs as WHO essential medicines: an overview of efficacy, safety and cost. *Journal of Clinical Hypertension*. 2020. Aug 20. 22 (10) 1769-1779

¹⁷ Salam A, Huffman M, Kanukula R, Prasad E, Sharma A, Heller D. Two-drug fixed dose combinations of blood pressure-lowering drugs as WHO essential medicines: an overview of efficacy, safety and cost. *Journal of Clinical Hypertension*. 2020. Aug 20. 22 (10) 1769-1779



The market for antihypertensive medicines

For diseases such as HIV/AIDS and tuberculosis, donor financing and international guidelines established a preference for a limited number of medicines, and thus promoted a consolidated market while retaining competition among suppliers.

However, this has not been the case for hypertension. The lack of dedicated programs to promote antihypertensive treatments in LMICS, based on limited human and financial resource investment despite high prevalence estimates, has led pharmaceutical manufacturers to channel their offerings to high-income countries where a larger proportion of people affected by hypertension are treated and social security systems allow steady revenues.

At the global level, the potential demand for antihypertensive medicines is vast.

Based on figures gathered by supply chain experts since 2016, more than 100 suppliers of finished pharmaceutical products exist for most antihypertensive medicines.¹⁸ Some have a global footprint and others focus on national and/or regional markets. Therefore, the capacity exists to manufacture the medications recommended by WHO to bridge current treatment gaps.

However, pharmaceutical companies are unlikely to enter new markets or lower prices unless they are convinced of the potential for large and steady demand. By updating their national policies according to the 2021 WHO hypertension treatment guideline and aligning the antihypertensive drug procurement in the public and private sectors to those recommendations, countries can bring greater visibility to suppliers on the potential demand for a preferred list of medicines.

As with any pharmaceuticals, the more countries that express a preference for significant volumes of quality-assured hypertensive medicines, the stronger the message will be to manufacturers regarding the size of the market upon which they can plan their manufacturing and marketing strategy. For generic markets, greater market size results in economies of scale that allow manufacturers to thrive, despite a thin profit margin.



Governments should bring greater visibility to suppliers on the potential demand for a preferred list of antihypertensive medicines.

18 The World Health Organization. Department for Noncommunicable diseases. From Maximising Purchasing and PricingPower: does pooled procurement work for NCD medicines. NCD Hard Talks 2021.



METHODS

Research supporting this report examined antihypertensive medicine availability, registration and pricing across the public and private sectors in selected LMICs from May to June 2021.

This was completed through a combination of desk research and pricing surveys in five high-burden hypertension LMICs:



Medicine selection

This report focuses only on long-acting, solid oral antihypertensive medicine formulations, which are the most-used products in primary health care facilities around the world.

Forty-three formulations of 16 antihypertensive medicines were included in the analysis (Table 1). Fifteen of the formulations are SAPs and 28 are SPCs. These medications were selected due to their inclusion in the 2021 WHO Essential Medicines List (WHO EML), the 2021 WHO hypertension treatment guideline and/or the WHO HEARTS technical package, or because they are relevant to one of the surveyed country analyses.





Table 1. Selected antihypertensive medicines analyzed for this report¹⁹

Single Agent Pill (SAP) Formulations				Single-Pill Combination (SPC) Formulations	
Calcium channel blocker (CCB)	Thiazide diuretic	Angiotensin converting enzyme inhibitor (ACEi)	Angiotensin II receptor blocker (ARB)	Dual-agent	Triple-agent
amlodipine • 5mg* • 10mg*	hydrochlorothiazide • 12.5mg • 25mg*	lisinopril • 20mg • 40mg	losartan • 25mg • 50mg* • 100mg*	lisinopril + amlodipine • 10mg + 5mg • 20mg + 5mg • 20mg + 10mg	losartan + amlodipine + hydrochlorothiazide • 50mg + 5mg + 12.5mg
-	-	-	telmisartan • 40mg* • 80mg*	lisinopril + hydrochlorothiazide • 10mg + 12.5mg • 20mg + 12.5mg • 20mg + 25mg	telmisartan + amlodipine + hydrochlorothiazide • 40mg + 5mg + 12.5mg • 80mg + 5mg + 12.5mg
-	-	-	valsartan • 40mg • 80mg* • 160mg* • 340mg	losartan + amlodipine • 50mg + 5mg* • 100mg + 5mg • 100mg + 10mg	valsartan + amlodipine + hydrochlorothiazide • 40mg + 5mg + 12.5mg
-	-	-	-	losartan + hydrochlorothiazide • 50mg + 12.5mg • 100mg + 12.5mg • 100mg + 25mg	-
-	-	-	-	telmisartan + amlodipine • 40mg + 5mg* • 80mg + 5mg • 80mg + 10mg	-
-	-	-	-	telmisartan + hydrochlorothiazide • 40 + 12.5mg • 40mg + 5mg • 80mg + 25mg	-
-	-	-	-	valsartan + amlodipine • 80mg + 5mg* • 160mg + 5mg • 160mg + 10mg	-

¹⁹ The medicines surveyed for availability and pricing in the Philippines differed from those listed in Table 1. They were chosen based on relevance to the local market, local hypertension treatment recommendations and the availability constraints in the private sector. Medicines indicated by * in Table 1 and enalapril 2.5 mg, enalapril 5 mg, telmisartan+hydrochlorothiazide 40mg+12.5mg and losartan+hydrochlorothiazide 50mg+12.5mg were included



Data from manufacturers

Nineteen manufacturers were asked to complete a standard questionnaire.

This is a sample of product innovators and generic manufacturers with wide registration and supply capacities globally. They produce antihypertensive medicines as part of a portfolio of solid oral formulations manufactured in sites that were either granted Good Manufacturing Practices (GMP) certificates by a stringent regulatory authority (SRA), or a national regulatory authority (NRA) from a country member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) or the WHO Prequalification Program. Questions about registration status of the antihypertensive medicines from Table 1 with SRAs and 18 LMICs with a high hypertension disease burden were included.²⁰



In-depth country landscape analysis

Five countries were selected for a more in-depth analysis: Brazil, Lebanon, Nigeria, the Philippines and South Africa.

They were chosen based on several criteria: high hypertension disease burden, geographical representation and/or ongoing RTSL or MSF operational activities.

The analysis collected prices of the antihypertensive medicines included in Table 1 across the public and/or the private sectors. The lowest and highest prices paid by hypertension patients in the public and/or the private sector were collected directly at pharmacies according to a simplified version of the WHO MedMon methodology for Nigeria and the Philippines, or by consulting online databases maintained by the local MoH for Brazil, Lebanon and South Africa.

The analysis also examined the inclusion of medicines on national EMLs, registration with NRAs and treatment algorithms in national clinical guidelines. Study investigators searched NRAs and health ministry medication databases and websites.

The average treatment cost per patient for one year was calculated for each country, assuming a hypothetical case of all countries using the same standard 2021 WHO-recommended protocols.²¹

²⁰ The World Health Organization [Internet]. List of Stringent Regulatory Authorities (SRAs). c2017 – [cited 2022 Feb 11] Available from: <https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs>

²¹ The World Health Organization, Non communicable diseases. Guideline for the pharmacological treatment of hypertension in adults. 2021. Aug 24 ISBN: 9789240033993



FINDINGS

1 Alignment of national EMLs and standard treatment guidelines with WHO guidance for antihypertensive medicines

FINDING 1

National EMLs in the surveyed countries are mostly aligned with the 2021 WHO EML regarding the inclusion of SAPs, but most countries' EMLs and standard treatment protocols do not include SPCs.

RECOMMENDATION 1

National EMLs and standard treatment protocols should be updated to align with the specific preferred-medicine and doses recommended in the latest WHO guidance.

The inclusion of antihypertensive medicines in national EMLs and countries' clinical practice guidelines sends an important signal to regulators, procurers and manufacturers that these medicines are a public health priority. In most countries, national EML inclusion is a prerequisite for purchasing or importation, alongside domestic registration (see Finding 2).

Updated every two years, the WHO EML includes medicines that are intended to meet priority health care needs. Countries adapt the WHO EML to meet the specific needs of their populations, publishing national EMLs that should align with clinical practice guidelines. Including SAPs and SPCs that align with the most recent WHO EML and other policy documents is critical to incentivizing access.

Detailed findings

Four out of five of the selected LMICs assessed in this report included WHO-recommended SAPs in their national EMLs (Figure 1). However, most countries (Nigeria, Lebanon, Brazil) did not include any SPCs in the same document. These results align with a recent global study where 57% (n=16) of LMICs analyzed (n=28) did not have SPCs included on their national EMLs.²²

In Nigeria, the standard hypertension treatment protocol, which has been endorsed by the Federal MoH, indicates a clear preference for SPCs of amlodipine plus losartan over SAPs. However,

SPCs are not included on the national EML. Three SPCs are included in the national EML for the Philippines. In South Africa's national EML for primary health care there is a clear statement encouraging the use of SPCs for control of hypertension, when available, as they promote greater adherence.

While no hypertension treatment protocols could be found for Lebanon or Brazil, hypertension protocols in the Philippines and South Africa are fully aligned with their respective national EMLs.



Figure 1.
Analysis of antihypertensive medicines included in national EMLs and treatment protocols

	Nigeria	Lebanon	Philippines	Brazil	South Africa
Alignment between WHO EML 2021 and nEML for SAPs					Hydralazine not listed, atenolol (same class as bisoprolol) is mentioned but not in the HTN section
At least one SPC included in nEML					nEML for PHC encourages the use of SPCs, when available
Medicines in national treatment protocol are included in nEML	In the national treatment protocol, SPC (amlodipine+ losartan) is preferred to free combination. However, no SPC is included in the nEML.	N/A No protocol found and HTN guidelines do not specify preferred medicines		N/A No updated guidelines or HTN treatment protocol found	

Although this was not within the scope of the analysis, it should be noted that the inclusion of antihypertensive medicines on national reimbursement lists also matters. This can guide the provision of free or subsidized medicines. Inclusion in national health insurance plans will help reduce out-of-pocket

Most national Essential Medicines Lists and clinical guidelines of the surveyed LMICs exclude WHO-recommended single-pill combinations (also known as fixed-dose combinations), which include two or more hypertension drugs in one pill. Single-pill combinations of multiple drugs at low or moderate doses improve patient adherence to medicines and reduce costs for pharmaceutical management.





Stakeholder-specific recommendations

WHO and technical partners:

- Support countries to adopt the 2021 WHO hypertension treatment guideline and update their national EML to align with the latest WHO EML.

Country governments/major procurers:

- Integrate WHO guideline-recommended antihypertensive SAPs and SPCs into national EMLs.
- Adopt one of the two hypertension standard treatment protocols featured in the 2021 WHO hypertension treatment guideline.
- Include the chosen WHO-recommended SAPs and SPCs within the country reimbursement lists and health insurance plans.



2 Registration of antihypertensive medicines in LMICs

FINDING 2

Seven pharmaceutical manufacturers reported that less than 50% of the selected antihypertensive formulations registered with an SRA were also registered in at least one of 18 selected LMICs. Few SPCs were registered in the surveyed high-burden hypertension LMICs, limiting their availability in national markets.

RECOMMENDATION 2

Manufacturers should prioritize the submission of antihypertensive medicine regulatory dossiers, and NRAs should deem reviewing and approving them public health priorities.

The registration of medicines by NRAs should guarantee their safety, efficacy and compliance with quality standards. Furthermore, according to most countries' laws, medicines must meet a number of prerequisites for purchasing or importation, which may also include their inclusion on the national EML (see Finding 1).

In 2019, WHO estimated that 74% of the regulatory authorities of the 194 WHO Member States did not have a stable and well-functioning regulatory system, all of which were in LMICs.²³

As a result, in many LMICs, national procurement may risk the purchase of substandard medicines, if their NRAs are unable to deliver the minimum regulatory package set by WHO. Regulatory system-strengthening strategies are ongoing across many LMICs, based on a WHO evaluation system and the Global Benchmarking Tool (GBT), with a move toward public designation as a WLA from 2022 and beyond.²⁴ The GBT assesses regulatory systems based on inputs, processes and outputs, and an NRA's designation as a WLA will mean that its regulatory outputs adhere to WHO standards, guidelines and good regulatory practice.

Essential medicines registered by a WLA, such as antihypertensive medicines, will be considered safe, efficacious and quality-assured.

²³The World Health Organization, Health Product Policy and Standards. WHO expert committee on specifications for pharmaceutical preparations. 2017. 14 June. ISBN: 978 92 4 121003 4

²⁴The World Health Organization. Delivering quality-assured medical products for all 2013-2023: WHO's five0year plan to help build effective and efficient regulatory systems. 2019 <https://apps.who.int/iris/handle/10665/332461>. License: CC BY-NC-SA 3.0 IGO



Detailed findings

Among the 19 manufacturers contacted (Annex B), seven had at least one of the selected antihypertensive medicines registered both with an SRA and within an LMIC.

Aurobindo, Lupin and Teva reported having more than 50% of the 43 selected antihypertensive formulations (SAP or SPC) registered with an SRA, with a higher percentage of SAPs registered than SPCs. Hetero has registered more than 50% of the selected SAP formulations with an SRA, but has not registered any SPCs. Macleods has registered half of the selected SAPs and a third of the SPCs with an SRA (Table 2).

All seven manufacturers reported that less than 50% of the 43 selected antihypertensive formulations registered with an SRA were also registered in at least one of the 18 LMICs (Table 2).



Table 2:
Registration statuses shared by manufacturers for the 43 selected antihypertensive formulations

Manufacturers	Number of HTN formulations registered by at least one SRA		Number of HTN formulations registered by at least one SRA and one of the 18 selected LMICs' NRA*	
	SAPs	SPCs	SAPs	SPCs
Aurobindo	14/15 (93%)	16/28 (57%)	7/15 (47%)	7/28 (25%)
Cipla	2/15 (13%)	3/28 (11%)	2/15 (13%)	3/28 (11%)
Glenmark	2/15 (13%)	3/28 (11%)	2/15 (13%)	3/28 (11%)
Hetero	11/15 (73%)	0/28 (0%)	11/15 (73%) <i>6 SAPs under regulatory assessment in 3 LMICs</i>	0/28 (0%)
Lupin	11/15 (73%)	18/28 (64%)	3/15 (20%)	2/28 (1%)
Macleods	7/15 (47%)	10/28 (36%)	0/15 (0%) <i>3 SAPs under regulatory assessment in 3 LMICs</i>	1/28 (1%) <i>10 SAPs under regulatory assessment in 3 LMICs</i>
Teva	15/15 (100%)	16/28 (57%)	0/15 (0%)	0/28 (0%)



When analyzing the proportion of SRA-approved antihypertensive formulations manufactured by each producer that are registered in LMICs, results varied. For example, all of the SRA-approved antihypertensives (both SAPs and SPCs) manufactured by Cipla and Glenmark were reported to be registered in at least one of the 18 selected LMICs. The same was true for Hetero's antihypertensive SAPs only. For Aurobindo, this was reported as around 50% for both SAPs and SPCs, and for Lupin this was <30% for both SAPs and SPCs.

Hetero and Macleods are in the process of applying for registration of several of their hypertension formulations for SRA approval in at least one selected LMIC.

Teva, one of the most important suppliers of antihypertensive medicines globally in terms of

volume, has not registered any of the selected SRA-approved hypertension formulations in any of the 18 selected LMICs.

There are multiple reasons why pharmaceutical manufacturers may have chosen not to prioritize registration of their anti-hypertension products in LMICs. One major factor is uncertainty about demand in those countries.

As the size of the market grows and demand becomes more clear, new opportunities will emerge for manufacturers in LMICs. By registering their quality-assured antihypertensive medicines, companies will be poised to take advantage of growing and more profitable markets, especially for SPCs. Country governments can take steps to express demand for antihypertensive medicines, recognizing that hypertension remains one of the leading causes of morbidity and mortality.

Stakeholder-specific recommendations

WHO and technical partners:

- Support the strengthening of NRAs until they achieve WLA status.

Country governments/major procurers:

- Prioritize registration of WHO-recommended antihypertensive medicines, including SPCs, through NRAs. Ensure that NRAs review the antihypertensive drug dossiers submitted by manufacturers for registration in a timely manner. This is particularly important for quality-assured SPCs.
- Negotiate framework agreements or long-term contracts with suppliers of quality-assured antihypertensive medicines. This includes medicines that are at least based on a GMP certificate from an SRA for any solid oral formulations, and/or on WLA registration as of 2022 for local manufacturers compliant with WHO quality standards.²⁵

Pharmaceutical Manufacturers:

- Register WHO-recommended antihypertensive medicines (including SPCs) widely, first and foremost those aligned with the 2021 WHO hypertension treatment guideline, prioritizing countries with a high hypertension disease burden.

²⁵Regulatory system strengthening strategies are ongoing across many LMICs based on a WHO evaluation system, the Global Benchmarking Tool (GBT), and from 2022 onwards will lead to the public designation of WHO-Listed Authorities (WLA). While the GBT serves to assess regulatory systems based on inputs, processes and outputs, the designation of a regulatory authority as a WLA will mean that its regulatory outputs are in adherence to WHO standards and guidelines as well as good regulatory practices



3 Availability of antihypertensive medicines, including SPCs, in selected LMICs

FINDING 3

Generally, antihypertensive SAPs were available in the five LMICs surveyed, though it is unknown whether this is sufficient to sustain national hypertension control programs. SPCs were less available than SAPs in the countries examined, especially in the public sector.

RECOMMENDATION 3

MoHs should increase the availability of antihypertensive medicines, particularly SPCs, in the public sector.

Making antihypertensive medicines — especially SPCs — more available in the public sector is key to addressing the poorly controlled hypertension burden in LMICs. The lack of availability at public-sector facilities forces many patients to pay for their medications out of pocket at private-sector pharmacies.

Detailed Findings

As shown in Table 3, the local registration rate of the selected SAPs ranges between 70% to 90% for Brazil, Lebanon, Nigeria and South Africa. For the selected SPCs, this figure falls to between 50% and 75%. While local registration of antihypertensive medicines is a crucial prerequisite to ensuring access, it does not necessarily translate into availability of WHO-recommended medicines in public- and private-sector primary health care facilities.

In the private market, more than 80% of the selected SAPs were available. It is unknown whether this availability reflects a quantity sufficient to treat all patients with hypertension in these countries. For SPCs, the availability rate dropped to 60% in Brazil and South Africa, and

less than 60% in Lebanon and Nigeria. SAPs were generally more available in the private sector than public. For SPCs, this disparity was even more pronounced, as already documented in the literature.²⁶ In South Africa, none of the SPCs were available in the public sector.

In order to implement the two recommended WHO protocols, at least one SAP formulation of the following three groups (ACEi/ARB, CCB, thiazide-like diuretic) was found available in the private sector of Brazil, Lebanon, Nigeria and South Africa. However, the lack of availability of SPCs in both the public and the private sectors, hinders the implementation of WHO protocols with preferred combination therapies.

26 Husain M, Datta B, Kostova D, Joseph K, Asma S, Richter P, et al. Access to Cardiovascular Disease and Hypertension Medicines in Developing Countries: an analysis of Essential Medicine Lists, Price, Availability and Affordability. J American Heart Association. 2020 Apr 25. 9(9) <https://www.ahajournals.org/doi/10.1161/JAHA.119.015302>



Table 3.
Registration status vs. availability of selected antihypertensive medicines in the private and public sectors of selected LMICs²⁷

Select LMICs	Formulations registered in the country by at least one manufacturer*				Formulations available in the private sector by at least one manufacturer**				Formulations available in the public sector by at least one manufacturer**			
	SAPs			SPCs	SAPs			SPCs	SAPs			SPCs
	ACEi / ARB	CCB	Thiazide diuretic†		ACEi / ARB	CCB	Thiazide diuretic†		ACEi / ARB	CCB	Thiazide diuretic†	
Brazil	10/11 (91%)	2/2 (100%)	1/2 (50%)	18/28 (64%)	10/11 (91%)	2/2 (100%)	1/2 (50%)	18/28 (64%)	-	-	-	-
Lebanon	9/11 (82%)	2/2 (100%)	1/2 (50%)	14/28 (50%)	9/11 (82%)	2/2 (100%)	1/2 (50%)	14/28 (50%)	9/11 (82%)	2/2 (100%)	1/2 (50%)	14/28 (50%)
Nigeria	9/11 (82%)	2/2 (100%)	1/2 (50%)	15/28 (54%)	10/11 (91%)	2/2 (100%)	2/2 (100%)	16/28 (57%)	9/11 (82%)	2/2 (100%)	1/2 (50%)	18/28 (64%)
South Africa	10/11 (91%)	2/2 (100%)	1/2 (50%)	21/28 (75%)	9/11 (82%)	2/2 (100%)	1/2 (50%)	19/28 (68%)	2/11 (18%)	2/2 (100%)	2/2 (100%)	0/28 (0%)

*Based on any manufacturers that have registered selected medicines in the country, irrespective of the manufacturer selection done for the report
 **Based on any manufacturers that have marketed selected in the country, irrespective of the manufacturer selection done for the report
 †Only hydrochlorothiazide was included in this analysis, as a thiazide diuretic regardless of any thiazide-like diuretic

Stakeholder-specific recommendations

WHO and technical partners:

- Support countries with surveys focused on antihypertensive medicine availability and pricing using the MedMon methodology for the private and public sectors.

Country governments/major procurers:

- Ensure that the recommended set of antihypertensive medicines is available in the public sector to reduce out-of-pocket expenses and prevent poor health outcomes and catastrophic costs for patients and their families.
- Promote the implementation of facility-level monitoring and evaluation and quantification tools for hypertension cohorts to improve the accuracy of supply forecasting.
- Where possible, especially when distribution capacities from capital to districts are well-established, pool the procurement of antihypertensive medicines across national administrative units. Facilitate central or regional procurement across countries to increase buying power.

Civil society/advocates:

- Collect additional evidence on pricing and availability, as well as other barriers hindering access to antihypertensive medicines to inform evidence-based advocacy messages.

²⁷ The medicine selection for the Philippines pricing survey differed from Table 1 medicines, therefore the Philippines was not included in this analysis



4 Antihypertensive medicine pricing in LMICs

FINDING 4

Numerous opportunities exist to reduce prices and increase affordability of WHO-recommended antihypertensive medicines in LMICs.

RECOMMENDATION 4

Procurement strategies should promote transparency of antihypertensive medicine prices and incentivize medicine price benchmarking exercises and pooled procurement mechanisms.

There is a lack of evidence-based information on antihypertensive medicine pricing in the public and private sectors of LMICs. Furthermore, few articles have been published comparing the prices of SPCs with the combined price of their component SAPs sold separately. This has hindered country efforts to assess whether the prices they are paying for these medicines are appropriate compared to the estimated cost based generic price of goods and what other countries might be paying. Lastly, given the limited engagement of pooled procurement mechanisms with the antihypertensive drug market so far, countries have not had the opportunity to look at the benefits they could gain by using such services.

Detailed Findings

Finding 4A.

Antihypertensive medicine prices in the countries analyzed were significantly higher than estimated cost-based generic prices for these drugs.

In 2016, researchers from Harvard University were commissioned by WHO to estimate cost-based generic prices for a broad range of essential medicines, including antihypertensive medicines amlodipine 5mg and hydrochlorothiazide 25 mg.^{28, 29}

Estimated cost-based generic prices provide objective arguments to drug purchasers at the country level, allowing them to negotiate better prices with manufacturers. They can also be an important tool for anticipating optimal target costs when assessing the cost-effectiveness of medicines and planning procurement for treatment programs. If medicine prices in a given

country are above the estimated cost-based generic prices, it is a signal that there is potential to negotiate lower prices with manufacturers.

In 2021, in collaboration with RTSL and MSF, the same researchers used the methodology developed in 2018 to calculate estimated cost-based generic prices for additional antihypertensive medicines (Annex A) included in the scope of the survey (Table 1).

In this analysis, the estimated cost-based generic prices of four SAPs — amlodipine 5mg, hydrochlorothiazide 25 mg, telmisartan 40mg and losartan 50mg — and two SPCs — telmisartan +

²⁸Hill A, Barber M, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. *BMJ Global Health*. 2018. Jan 29 8;3:e0005 <https://gh.bmj.com/content/3/1/e000571>

²⁹Cost-based generic prices are based on an estimation formula developed by reviewing published analyses of cost of production for medicines and assuming manufacture in India, which included costs of formulation, packaging, taxation and a 10% profit margin



amlodipine 40mg + 5mg and losartan + amlodipine 50mg + 5mg – were compared to the lowest prices found in five LMICs (Figure 2). The SAPs and SPCs examined are more expensive than estimated cost-based generic prices in both the private and public sectors of all the countries, except for amlodipine 5mg and hydrochlorothiazide 25mg in the public sector in South Africa³⁰ (Figure 2B). Moreover, SPCs are priced much higher than their estimated cost-based generic price compared to SAPs.

The most expensive SAPs were found in the private sector in Brazil (telmisartan 80mg, 33 times more expensive than the estimated cost-based generic

price) and in Lebanon (losartan 100mg, 18 times more expensive than the estimated cost-based generic price) (Annex A). The most expensive SPCs were found in the private sector in the Philippines (telmisartan + amlodipine 40mg + 5mg, 41 times more expensive than the estimated cost-based generic price) and in South Africa (losartan + amlodipine 50mg + 5mg, 27 times more expensive than the estimated cost-based generic price) (Figure 2A, Annex A). These findings suggest there is significant room for sustainable price decreases among the selected medicines.

Figure 2:
Estimated cost-based generic prices of antihypertensive medicines compared to lowest prices in selected LMICs



Estimated cost-based generic prices are useful benchmarking tools; countries can assess the efficiency of their national procurement mechanisms to negotiate affordable antihypertensive medicines in the public

³⁰ SPC pricing data could not be collected for the South Africa public sector and in Lebanon because of the lack of these formulations in the public sector. Public pricing was not collected for the Philippines and Brazil



and private sectors.

Finding 4B.

In the surveyed LMIC private markets, some SPCs were found to be less expensive than the combined price of their component SAPs sold separately.

To determine whether SPC pricing presents a barrier for implementing the 2021 WHO recommendations in LMICs, an analysis was performed, comparing the prices of selected SPCs to the combined prices of their related SAPs.³¹

Given the limited availability of SPCs in the public sector, the pricing data shown below are focused on the private sector.

Data collected from the limited selection of surveyed countries indicate that SPCs were often less expensive compared to the sum of their equivalent dose component SAPs in the private markets. For example, the average private-sector dual-drug SPC price was consistently lower than the corresponding two component SAPs sold separately in Brazil, South Africa and the Philippines (Figures 3A, 3B, 3C). These

observations are consistent with the results of the study of the Indian private pharmaceutical sector, which found several examples of SPC pricing lower than the equivalent component SAPs sold separately.³²

However, both in this study and in the Indian private-sector analysis, there are many SPCs that are priced higher than their equivalent SAPs sold separately in the private sector. For example, in Nigeria, SPCs tended to be more expensive than the sum of their related SAPs (Figure 3D). In Lebanon, the average private-sector dual-drug SPC price was also consistently higher than the corresponding two-component SAPs sold separately (Figure 3E).

Limited data on the public sector in Lebanon and Nigeria showed similar instances of lower average



³¹ Drug formulations shown in this analysis were chosen based on hypertension treatment protocols present in selected LMICs. Where treatment protocols were absent or if prices of national treatment protocol medications were not available, formulations recommended in the WHO 2021 hypertension guideline protocols were used

³² Negi S, Neupane D, Sahoo S, Mahajan T, Swaroop K, Moran A, Sharma B, et al. Prices of combination medicines and single-molecule antihypertensive medicines in India's private health care sector. *J Clin Hypertens (Greenwich)*. 2021 Apr 23 (4):738-743. doi:10.1111/jch.14143

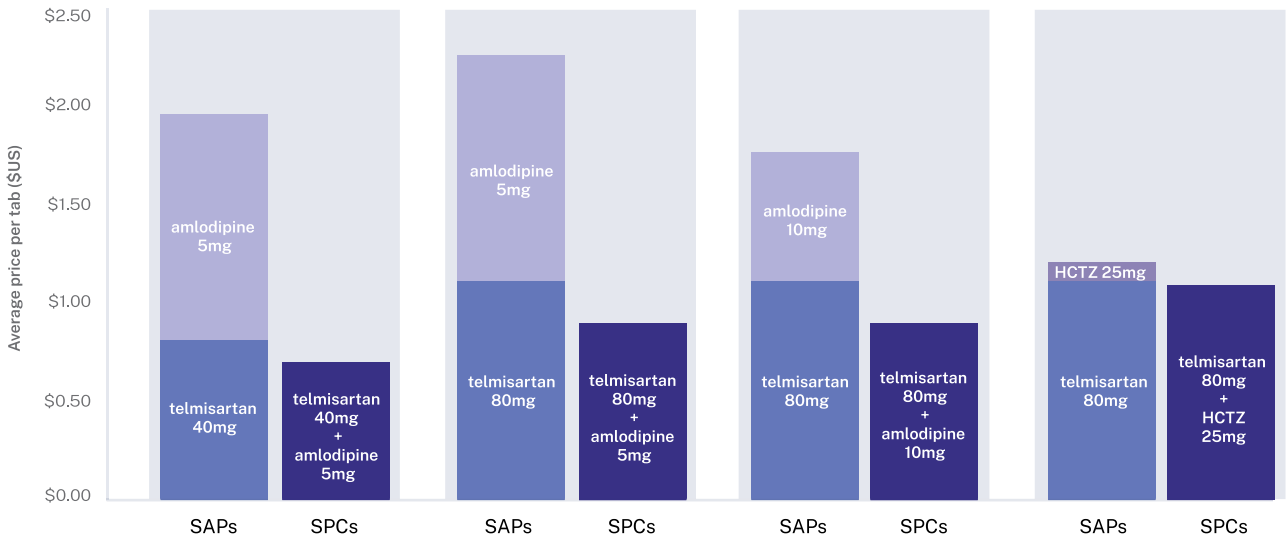


SPC prices compared to the sum of their related SAPs.

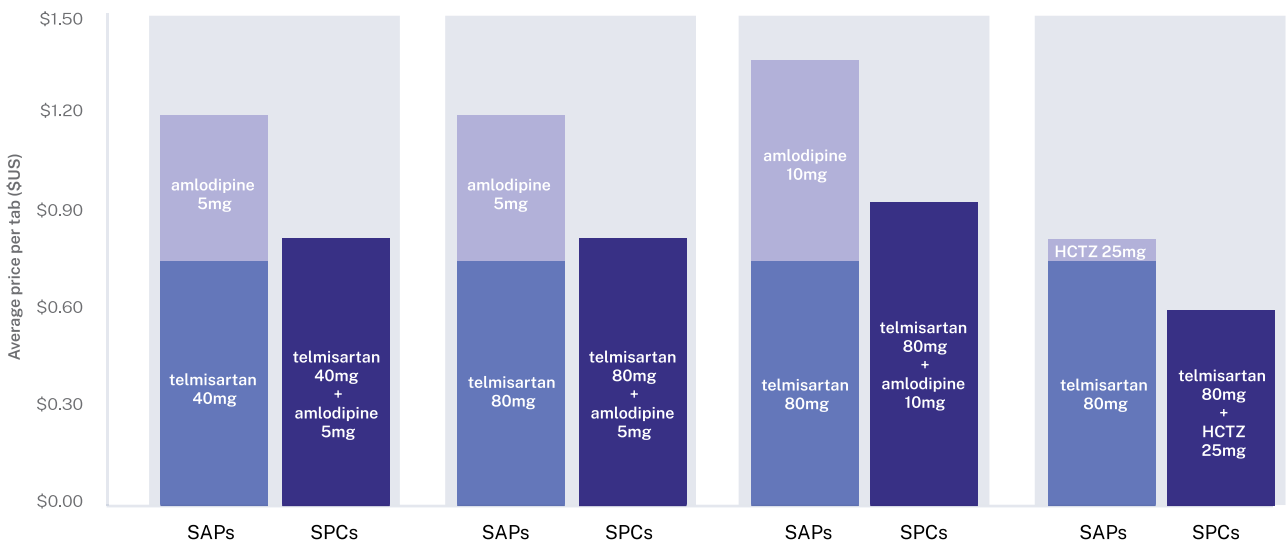
Figure 3:

Comparison of average prices (sum of SAPs versus corresponding SPCs) in the private sector of selected LMICs

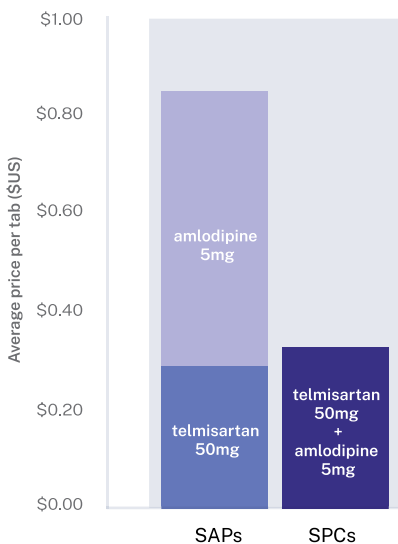
A) Brazil



B) South Africa

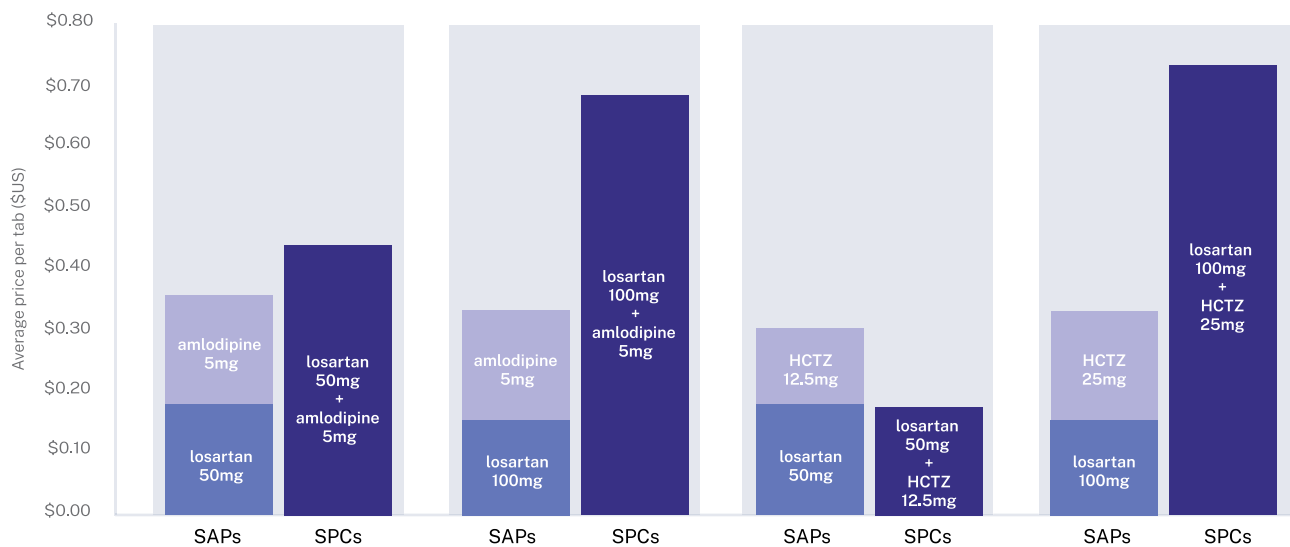


C) Philippines

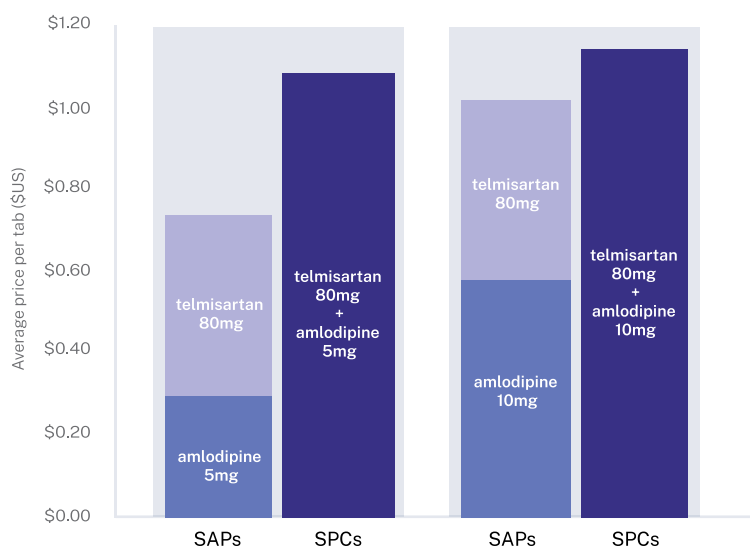




D) Nigeria



E) Lebanon





Finding 4C.

Prices of antihypertensive medicines that can be procured through the PAHO Strategic Fund vary from estimated cost-based generic prices.

International pooled procurement mechanisms can improve purchasers’ negotiating power by providing leverage in their procurement procedures based on high ordering volumes. Pooled procurement has been shown to be an important strategy for lowering prices in LMICs in other disease areas, such as HIV and tuberculosis, through vehicles, such as the Global Fund’s Pooled Procurement Mechanism and the Stop TB Partnership’s Global Drug Facility. In addition to making medicines more affordable for countries, some pooled procurement agencies offer other services, including technical assistance for forecasting, quantification and supply chain management.

The potential for pooling medicine procurement may be less evident in markets with a high number of manufacturers, such as hypertension. This procurement strategy may provide opportunities to increase access to affordable medicines while ensuring reasonable profit margins for manufacturers. However, pooling demand across countries and awarding tenders to a limited number of suppliers may reduce the number of manufacturers active in the market.

One example of a regional pooled procurement mechanism that includes antihypertensive medicines in its portfolio is the Pan-American Health Organization (PAHO) Strategic Fund, which serves member countries in the Latin America and Caribbean region. The PAHO Strategic Fund provides technical assistance and pools the procurement of essential medicines and strategic health supplies to countries in the Americas.³³

In the survey, four estimated cost-based generic SAP prices — amlodipine 5mg, hydrochlorothiazide 25mg, telmisartan 40mg, and losartan 50mg — and two SPCs — telmisartan + amlodipine 40mg + 5mg and telmisartan + amlodipine 80mg + 5mg — were compared with PAHO Strategic Fund prices (Figure 4). Only the amlodipine 5mg and hydrochlorothiazide 25mg prices from the PAHO Strategic Fund are lower compared to their corresponding estimated cost-based generic prices, and the price of losartan 50mg is comparable. While countries in the PAHO region can benefit from the competitive pricing of these three formulations, the PAHO Strategic Fund should seek to negotiate more affordable prices for telmisartan 40mg and the two SPCs.



These preliminary findings suggest that ordering amlodipine 5mg and hydrochlorothiazide 25mg through the PAHO Strategic Fund could lead to savings in countries of the Americas. Countries outside the PAHO region can consider leveraging other global or regional pooled procurement mechanisms to potentially achieve similar cost savings.

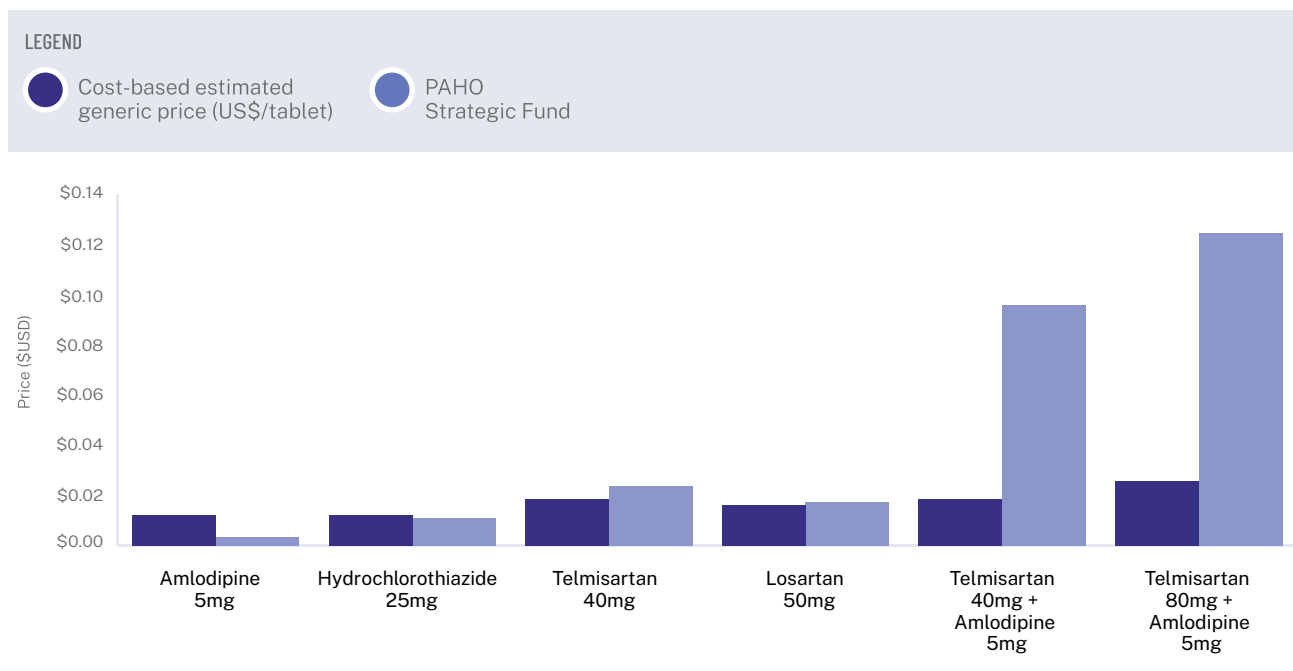
As a general principle, comparing drug prices in the public sector with prices negotiated by regional bodies, such as the PAHO Strategic Fund, is a useful benchmarking exercise for countries adopting the 2021 WHO hypertension treatment guideline approach and WHO-recommended antihypertensive drugs.

³³The Strategic Fund of the Pan American Health Organization [Internet]. c2021 [cited 2022 February 11]. Available from: <https://www.paho.org/en/paho-strategic-fund>



Figure 4:

Comparison of antihypertensive medicine prices from the PAHO Strategic Fund and estimated cost-based generic prices³⁴



Stakeholder-specific recommendations

WHO and technical partners:

- Support price transparency with comparability criteria in countries and across regions.

Country governments/major procurers:

- Measure and regulate mark-ups along the national supply chain to avoid losing the benefits of adequate price negotiation with manufacturers, in terms of an affordability target for individual patients.
- Proceed to benchmark exercises by comparing their domestic prices to estimated cost-based generic ones or those available through pooled procurement mechanisms or those at international suppliers with a quality assurance policy for medical procurement (e.g., the International Dispensary Association Foundation, IMRES and Medical Export Group).
- Seek to enter into regional or global multi-country pooled procurement agreements

wherever this may increase access to more affordable antihypertensive medicines, or to purchase directly from international suppliers with quality-assured policies for medical procurement.

Civil society/advocates:

- Collect additional evidence on barriers hindering access to antihypertensive medicines to inform evidence-based advocacy messages.
- Demand affordable hypertension treatment for patients that is safe, reduces pill burden, maximizes the opportunity to achieve hypertension control and enables person-centered, community-based care models in accordance with the 2021 WHO hypertension treatment guideline.

Manufacturers:

- Consider contributing to pooled procurement mechanisms.

³⁴ INCOTerms for PAHO Strategic Prices are Free On Board (FOB), meaning that they do not reflect price components existing at country level, such as VAT, transport costs



5

Average per-patient costs of 2021 WHO-recommended hypertension treatment protocols using antihypertensive SAPs or SPCs

FINDING 5

A costing exercise using WHO-recommended treatment protocols produced a wide range of per-patient costs for countries, suggesting that the average per-patient cost of SPC-based protocols is often equivalent to SAP-based protocols. However, in some settings, using the lowest prices available in the public sector SAPs delivered the lowest cost per patient protocol.

RECOMMENDATION 5

Costing exercises using the highest and lowest available SPC and SAP prices within countries should be used to inform decision-making related to treatment protocol options, country medication procurement and budget allocation.

Treatment protocol costing exercises can provide important information for country decisionmakers responsible for medicine purchasing and procurement. To support these exercises for antihypertensive medicines, RTSL developed a predictive tool for medication forecasting for hypertension control programs in LMICs. It allows a country government to quantify the financial implications of implementing an annual hypertension treatment protocol in a large public health care system.³⁵

The 2021 WHO hypertension treatment guideline includes two drug- and dose-specific hypertension treatment protocol examples (referred to as algorithms): a preferred protocol based on the initiation of treatment with a dual-drug

combination, and an alternative protocol that initiates treatment using a single drug (initial monotherapy). Using the RTSL forecasting tool, the weighted average cost per patient/year of the WHO-recommended treatment protocols was calculated using the highest and lowest prices of medicines collected from the study's five selected LMICs (Annex C). The first step of the WHO algorithm using the initial dual-drug combination can be practically administered using either a dual-drug SPC or two SAPs. Therefore, the cost of implementing the initial dual-drug combination protocol was calculated, starting with a dual-drug SPC and then two SAPs. The same exercise was repeated for the WHO protocol that uses initial monotherapy and SAPs throughout (Figure 5).³⁶

³⁵Cazabon D, Farrell M, Gupta R, Joseph L, Pathni A, Sahoo S et. al "A simple six-step guide to National-Scale hypertension control program implementation. J Hum Hypertens. 2021 Oct 26. <https://doi.org/10.1038/s41371-021-00612-6>

³⁶The WHO algorithm that uses initial monotherapy was not calculated using dual SPCs because the corresponding formulation (telmisartan+amlodipine 40+10mg) was not included in the pricing survey, therefore this pricing data was not available



For each of the three above-mentioned protocol combinations (initial dual-drug combination protocol using a dual-drug SPC, initial dual-drug combination protocol using two SAPs, and initial monotherapy protocol using SAPs throughout), a range of hypothetical annual weighted average per-patient costs was calculated. Estimates were weighted such that the price of the protocol Step 1 drug was weighted more heavily than the Step 2 drug because a proportion of all treated patients achieves blood pressure control at Step 1, and only the remainder require treatment according to Step 2 or beyond. Thus, the higher the protocol step, the lesser weight for that step's drug costs.

Among the three protocols, there is a wide range of weighted annual average costs per patient in each country. When comparing the two WHO regimens in the private sector of the five surveyed countries, the ranges of weighted average cost per patient treated overlapped between SPC and SAP-based protocols, suggesting that the weighted average cost of SPC-based regimens was often equivalent in price to SAP-based regimens. When all weighted-average cost per patient treated estimates from the five selected LMICs were pooled together, the median of these country weighted averages was slightly lower for initial SPC-based protocols (Figure 5). Each country's lowest-cost protocols would use SAPs.

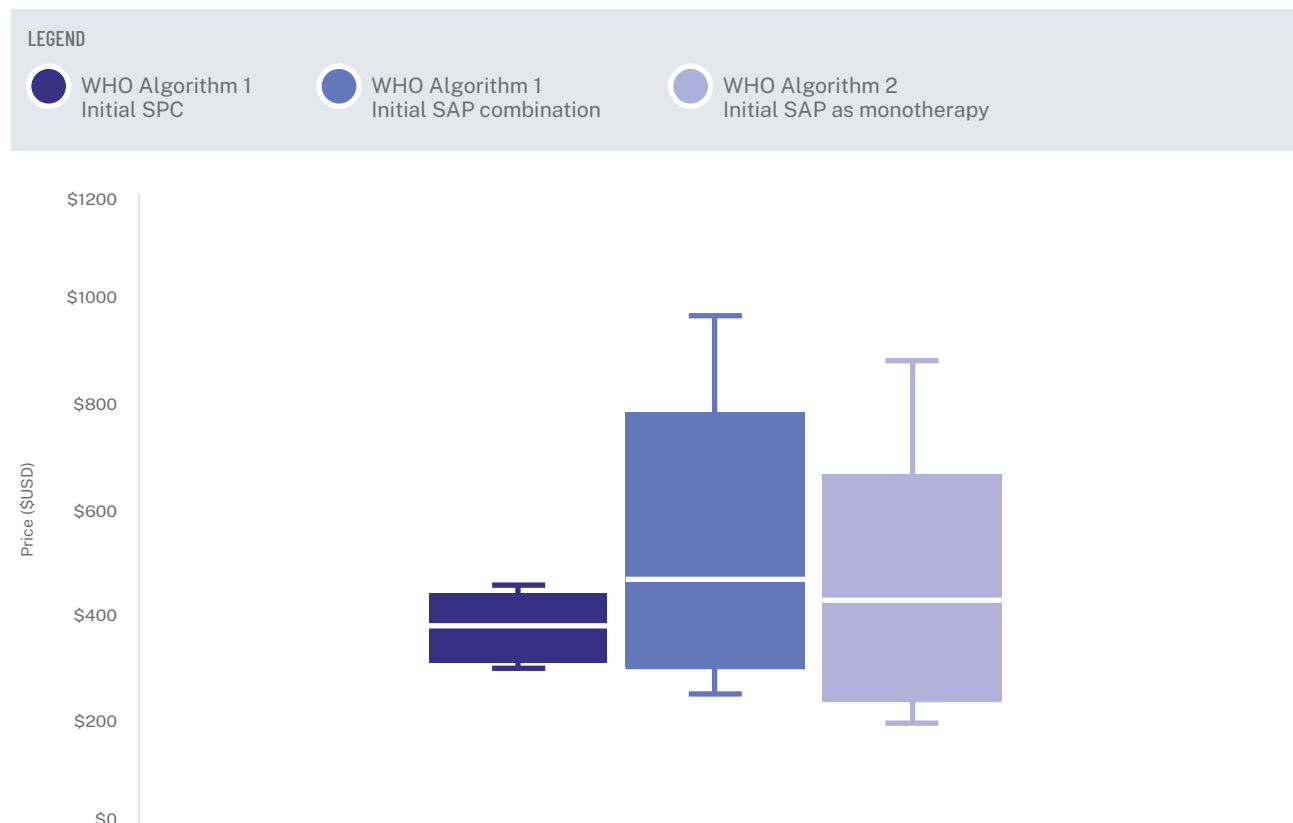
Comparing the weighted-average cost per patient using the highest and lowest SPC and SAP prices within a country is more informative for government decision makers than the mean-weighted average cost. For example, when calculating the average cost per patient treated at the highest-cost SPCs and SAPs in Brazil, the Philippines and South Africa, the WHO initial dual-drug combination protocol using SPC had a lower weighted average cost per patient than the WHO initial monotherapy protocol using SAPs. In Nigeria, at highest prices sampled, the WHO initial dual-drug combination protocol using SPC cost more per patient treated than initial monotherapy using SAPs. SPC pricing data was not available for Lebanon.

However, when the average price per treated patient per year was calculated using the lowest cost drugs in Brazil, Nigeria, South Africa and the Philippines, the WHO dual-drug combination using SPC was more expensive compared to the alternative WHO protocol using initial monotherapy with SAPs. The root cause of this trend could be the limited competition across manufacturers of SPCs compared to SAPs. The lowest available SPC prices may continue to be higher than the lowest available SAP prices until the demand rises for SPCs, allowing purchasers to gain leverage in their price negotiations with manufacturers.





Figure 5:
Range and medians of average annual hypertension treatment cost per patient with WHO initial dual drug combination (Algorithm 1) and WHO initial monotherapy (Algorithm 2) regimens across private sector markets of five selected LMICs.



Costs of each regimen were calculated using the lower strengths of each formulation (e.g., Amlodipine 5mg, Telmisartan 40mg)
 • Only one price available for the SPC telmisartan + amlodipine 40mg +5mg in Brazil
 • No data available for Lebanon for WHO SPC-initiated regimen due to the lack of telmisartan + amlodipine 40mg + 5mg on the market
 • Prices (\$USD) represent the median +/-range of weighted average costs per patient treated from five selected LMICs

The findings present only the costs of medicine within the protocol. They do not account for potential cost-saving from using SPCs related to shorter time to blood pressure control (reducing the burden on the health system and the number of visits for the patient) and supply chain efficiencies (reducing the total volumes of medicines that must be shipped, stored and transferred).

Stakeholder-specific recommendations

WHO and technical partners:

- Promote costing exercises to inform decision-making related to specific hypertension treatment protocol options.

Country governments/major procurers:


- Base forecasting and budgets on informed, protocol-specific costing exercises.
- Adopt medication quantification and forecasting tools that can integrate drug pricing options, so price negotiations are based on the anticipated need for specific drug classes and doses.



CONCLUSIONS

If global hypertension control goals are met, millions of people with hypertension will live longer, healthier lives in the coming decades.

However, these population health gains will not be achieved until quality-assured antihypertensive medicines are much more affordable and accessible to hypertension patients. The results of this report show that access to antihypertensive medicines can be improved through the inclusion of the WHO-recommended antihypertensive medications in national guidance, registration of recommended products, and reliable availability in primary health care facilities and lower prices in all LMICs. All stakeholders – WHO, technical partners, national program managers, civil society, health advocates and pharmaceutical manufacturers – have a role to play in ensuring that lifesaving medicines are available to everyone living with hypertension.



“Exorbitant drug pricing is forcing many people in lower- and middle-income countries to choose between food, shelter and life-saving medication. No one should have to make this choice. Leaders from governments, civil society and the pharmaceutical industry must make these medicines more affordable and accessible to millions of people living with high blood pressure.”

Dr. Tom Frieden,
President and CEO of
Resolve to Save Lives



ANNEX A:

Estimated cost-based generic prices of key antihypertensive medicines compared to the lowest prices of key antihypertensive medicines across five LMICs

Formulation (tablet)	Estimated cost-based generic price (US\$/tablet)	South Africa (public)	South Africa (Private)	Nigeria (public)	Nigeria (private)	Lebanon (private/public)	Phil* (private)	Brazil (private)
amlodipine 5mg	0.012	0.0082	0.112	0.017	0.026	0.2152	0.02	0.0717
amlodipine 10mg	0.0128	0.01184	0.168	0.024	0.03	0.3635	0.035	0.1363
hydrochlorothiazide 12.5mg	0.0118	0.010049	N/A	N/A	0.041	N/A	price not collected	N/A
hydrochlorothiazide 25mg	0.0124	0.0107	0.035	0.017	0.023	0.2296	0.071	0.033
losartan 25mg	0.0141	N/A	N/A	0.097	0.07	N/A	price not collected	0.1147
losartan 50mg	0.0169	0.01972	0.136	0.082	0.08	0.3194	0.06	0.0647
losartan 100mg	0.0225	0.04201	0.144	0.161	0.087	0.4385	0.06	0.2132
telmisartan 40mg	0.0184	N/A	0.31	0.073	0.146	0.393	0.16	0.3924
telmisartan 80mg	0.0256	N/A	0.31	0.091	0.138	0.4481	0.28	0.8431
losartan + amlodipine 50mg + 5mg	0.0176	N/A	0.481	0.231	0.195	N/A	0.079	0.0933
losartan + amlodipine 100mg + 5mg	0.0232	N/A	0.481	N/A	0.682	0.619	price not collected	0.6847
losartan + amlodipine 100mg + 10mg	0.024	N/A	N/A	N/A	N/A	0.6416**	price not collected	N/A
telmisartan + amlodipine 40mg + 5mg	0.0192	N/A	0.651	0.244	0.095	N/A	0.81	0.7005
telmisartan + amlodipine 80mg + 5mg	0.0263	N/A	0.651	0.696	0.287	0.9027	price not collected	0.8972
telmisartan + amlodipine 80mg + 10mg	0.0271	N/A	0.741	0.357	0.341	0.9513***	price not collected	0.8972

Cost-based generic prices are based on an estimation formula developed by reviewing published analyses of cost of production for medicines and assuming manufacture in India, which included costs of formulation, packaging, taxation and a 10% profit margin.
 N/A formulation not found in medications databases or through incountry pricing data collection
 * Philippines



ANNEX B:

Note on the pharmaceutical manufacturers included in the survey

Nineteen manufacturers were initially contacted, based on the fact that they were product innovators and generic manufacturers with wide registration and supply capacities globally, producing antihypertensive medicines as part of a portfolio of solid oral formulations manufactured in sites that were either granted GMP certificates by an SRA, or an NRA from a country member of the PIC/S or the WHO Prequalification Program.

Among the 19 manufacturers contacted, 10 provided regulatory status of the selected antihypertensive medicines.

- Seven manufacturers, whose answers are compiled in Table 2 of the report: Aurobindo, Cipla, Glenmark, Hetero, Lupin, Macleods and Teva, have manufacturing site(s) where selected antihypertensive medicines are granted a GMP certificate delivered by an SRA and are located in at least one of the selected LMICs.
- Three manufacturers only provided information on regulatory status in one or more of the LMICs, but not in SRAs (Aspen Pharmacare, Ipca, Strides Arcolab). Therefore, their answers were not integrated into Table 2.

No responses were received from Accord Healthcare (United Kingdom (UK)) - Intas Pharmaceuticals (India), Actavis (United States of America (USA)), AstraZeneca (UK), GSK (UK), Cadila (India) and Viatrix (USA/ India). Novartis-Sandoz (Switzerland) and Sunpharma-Ranbaxy (France/India) did not have data available and/or did not agree to publish the prices and registration status of their medicines.



ANNEX C:

Tool used to estimate country-specific average costs per patient per year for WHO-recommended hypertension treatment algorithms

A predictive tool for drug requirement forecasting for hypertension control programs in LMICs was developed by RTSL and partner entities. It allows for quantifying medicine requirements for a treatment protocol based on SAPs and/or SPCs.

For the sake of this report, the following data were uploaded into the predictive tool for each of the five select LMICs:

- Lowest and highest prices collected in the public and/or private sectors for SAPs and/or SPCs
- Selection of antihypertensive medicines from Table 1 recommended in the 2021 WHO guidelines algorithms

The predictive tool included assumptions for the proportion (%) of persons affected by hypertension who are controlled at each step of the corresponding treatment protocol. These assumptions were based on data available from the India Hypertension Control Initiative (IHCI)³⁷ and were applied across countries.

The 2021 WHO hypertension treatment guidelines include two drug and dose-specific protocol examples: one based on initiation of treatment with a SPC and the other on initiation of treatment using SAP (Figure X).

The table below shows the control assumptions used for the calculation of treatment costs for each of the 2021 WHO algorithms.³⁸ While control assumptions related to SAPs are based on evidence collected in India, those related to SPCs are hypothetical.

Initial SPC regimen*	Control assumption	Initial Monotherapy regimen*	Control assumption
Telmisartan + Amlodipine 40mg + 5mg**	65%	Amlodipine 5mg	40%
Increase to: Telmisartan + Amlodipine 80mg + 10mg**	25%	Increase to: Amlodipine 10mg	15%
Telmisartan + Amlodipine 80mg + 10mg** Add: Hydrochlorothiazide 25mg	5%	Amlodipine 10mg Add: Telmisartan 40mg	20%
Telmisartan + Amlodipine 80mg + 10mg** Increase to: Hydrochlorothiazide 50mg	5%	Increase to: Telmisartan 80mg Amlodipine 10mg	12%
		Telmisartan 80mg Amlodipine 10mg Add: Hydrochlorothiazide 25mg	8%
		Telmisartan 80mg Amlodipine 10mg Increase to: Hydrochlorothiazide 50mg	5%

* The medications mentioned serve as examples and can be replaced with any medication from any of the three drug classes (ACEis/ARBs, CCBs or thiazide/thiazide-like diuretics).
** This SPC can be replaced with other SPCs, depending on availability.

37 Kaur P, Kunwar A, Sharma M, et al. India Hypertension Control Initiative – Hypertension treatment and blood pressure control in a cohort in 24 sentinel site clinics, India. *J Clin Hypertens*. 2020;00:1–10. <https://doi.org/10.1111/jch.14141>

38 The World Health Organization, Non communicable diseases. Guideline for the pharmacological treatment of hypertension in adults. 2021. Aug 24 ISBN: 9789240033993

