Comparing scale up of status quo hypertension care against dual combination therapy as separate pills or single pill combinations: an economic evaluation in 24 low- and middle-income countries

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Summary

Background International hypertension treatment guidelines recommend initiating pharmacological treatment with combination therapy and using fixed dose single pill combinations (SPCs) to improve adherence. However, few countries have adopted combination therapy as a form of first-line treatment and SPC uptake in low- and middle-income countries is low due in part to cost and availability. Evidence on costs and cost-effectiveness is needed as health authorities consider incorporating new recommendations into national clinical practice guidelines.

Methods Over a 30-year time horizon, we used an Excel-based Markov cohort state-transition model to assess the financial costs (screening, treatment, program, and supply chain costs) and socio-economic outcomes (health outcomes, value of lives saved, productivity losses averted) of three antihypertensive treatment scenarios. A baseline scenario scaled treatment among adults age 30 plus while assuming continuation of the widespread practice of initiating treatment with monotherapy. Scenarios one and two scaled treatment while initiating patients on two antihypertensive medications, either as separate pills or as a SPC. Analysis inputs are informed by country-specific data, meta-analyses of the blood-pressure lowering of antihypertensive medications, and own-studies of medication costs. We compared costs, cost-effectiveness, and net-benefits across scenarios, and assessed uncertainty in a one-way sensitivity analysis.

Findings Using dual combination therapy (with or without SPCs) as first-line treatment would increase costs relative to current practices that largely use monotherapy. Required additional annual resources averaged as much as 3.6, 0.9, and 0.2 percent of government health expenditures in the analysis' low-, lower-middle, and upper-middle income countries. However, across 24 countries, over the next 30 years, combination therapy with separate pills could save 430,000 more lives and combination therapy with SPCs could save 564,000 more lives compared to baseline treatment practices. Administration of two or more medications using SPCs generated higher net benefits in most countries (16/24) compared to the baseline scenario.

Interpretation First line treatment employing SPCs is likely to generate higher net benefits compared to status quo treatment practices in countries with relatively higher incomes. To improve population health, national health systems would benefit from reducing structural and other barriers to the use of combination therapy and SPCs.

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Research in context

Evidence before this study

International hypertension treatment guidelines—e.g., WHO and European Society of Hypertension—recommend initiating pharmacological treatment with combination therapy and using fixed dose single pill combination (SPC) therapy to improve adherence.

There is scarce evidence on the cost-effectiveness of new guideline recommendations compared to status quo treatment practices, with the World Health Organization's *Guideline for the pharmacological treatment of hypertension in adults* stating: "Health economic analyses are needed to quantify cost-effectiveness and budget implications of implementing incremental initial combination therapy compared with initial monotherapy."

Added value of this study

This study helps to fill that evidence gap by assessing the financial costs (screening, treatment, program, and supply chain costs) and socio-economic outcomes (health outcomes, value of lives saved, productivity losses averted) of initiating antihypertensive treatment with combination therapy in adults aged 30 or above in 24 low- and middle-income countries—using either separate pills or SPCs—compared to the widespread practice of initiating treatment with monotherapy.

In scale up scenarios, using dual combination therapy (with or without SPCs) as first-line treatment would increase costs relative to current practices that largely use monotherapy. Required additional annual resources averaged as much as 3.6, 0.9, and 0.2 percent of government health expenditures in the analysis' low-, lower-middle, and upper-middle income countries. Across 24 countries, over the next 30 years, combination therapy with separate pills could save 430,000 more lives and combination therapy with SPCs could save 564,000 more lives compared to scale up of current treatment practices. Administration of two or more medications using SPCs generated higher net benefits in most countries (16/24) compared to the baseline scenario.

Implications of all the available evidence

First line treatment employing SPCs is likely to generate higher net benefits compared to status quo treatment practices in countries with relatively higher incomes. To improve population health, national health systems would benefit from reducing structural and other barriers to the use of combination therapy and SPCs. Especially for already over-burdened health systems, new or enhanced funding may be necessary given meaningful increases in costs to initiate treatment with combination therapy.

Introduction

Strengthening the hypertension care cascade by achieving high rates of screening, treatment, and control could save tens of millions of lives worldwide.[1] But antihypertensive treatment is well short of what is needed to meet global targets to reduce the prevalence of raised blood pressure by 25 percent between 2010 and 2025.[2]

Only 63 countries screen at least 50 percent of their population for hypertension, treat at least 50 percent of individuals who are identified with hypertension, *and* achieve control in at least 50 percent of the individuals who are treated.[3] Most (60 percent) of those countries are classified as "high income" by the World Bank. The end result is that nearly four in ten individuals with hypertension achieve control in high income countries, while only around one in ten do in low- and lower-middle income countries (LMICs).[3]

Low rates of hypertension control (generally defined as systolic blood pressure (SBP) <140 mm of mercury (mm Hg)) result from patient and provider barriers that exist along the care cascade, including individual-level barriers (e.g., skills, knowledge, beliefs, unfulfilled intentions) and health system-level barriers (i.e., the availability, affordability, and acceptability of care).[4] Many patients who initiate treatment do not achieve control,[3] suggesting that there is a need to address the quality and effectiveness of care among those who have already connected with the health system.

The 2021 World Health Organization (WHO) hypertension treatment guideline is based on a systematic review of randomized clinical trials and other evidence supporting hypertension treatment standard practices. One recommendation from the 2021 WHO guideline is to deploy combination therapy—the use of two or more medications—as the first-line initial treatment for hypertension.[5] Within those protocols, it is preferable to use fixed dose single pill combination (SPC) therapy—two or more medications in a single pill as opposed to two or more medications in separate pills.[5,6] The goal of the recommendations is twofold: 1) to increase the quality of treatment by cutting through therapeutic inertia—the "failure of a health provider to initiate or intensify therapy when therapeutic goals are not reached"[7]—and 2) to increase treatment adherence by reducing the pill burden for patients.

To date, however, few countries have adopted combination therapy as a form of first-line treatment.[8] In addition, SPC uptake in LMICs is low due in part to cost and availability.[9,10] Evidence is needed on the impact of potential changes as health authorities consider incorporating new recommendations into their national clinical practice guidelines.

The objective of this study was to assess the costs and consequences of initiating pharmacological treatment

on two medications (as opposed to monotherapy) and of using SPCs versus separate pills within those regimens. For each pathway, in 24 LMICs, we quantified the costs of scaling antihypertensive pharmacological treatment at the national level, and the expected health (i.e., avoided cardiovascular disease (CVD) events, deaths, disability-adjusted life years (DALYs)) and economic benefits (i.e., healthcare savings, monetized benefits of reduced mortality and morbidity).

Methods

We used an Excel-based Markov cohort state-transition model to conduct an economic evaluation of initiating antihypertensive treatment with combination therapy—using either separate pills or SPCs—compared to the widespread practice of initiating treatment with monotherapy. The model's structure, underlying data, costing methods, assumptions, and validity have been detailed elsewhere.[11] Updates to the model that are specific to this analysis are discussed below. Patients and clinicians were not engaged in the design of the study.

We conducted the analysis from a societal perspective that accounted for health and non-health outcomes in 24 LMICs that were chosen based on the availability of model input data from recent WHO STEPS surveys, population size, and representation of all WHO regions (Africa–Algeria, Kenya, Tanzania, Uganda. Americas—Argentina, Brazil, Colombia, Mexico. Eastern Mediterranean—Iraq, Libya, Morocco, Sudan. Europe–Azerbaijan, Belarus, Kyrgyzstan, Tajikistan. South-East Asia–Bangladesh, Myanmar, Nepal, Sri Lanka. Western Pacific–Cambodia, Lao, Mongolia, Vietnam). These represented two low-income countries, 14 lower-middle income countries, and eight upper-middle income countries. A 30-year time horizon was selected to assess outcomes in the medium term. Costs of the interventions and economic benefits are reported in 2020 USD, using a four percent discount rate recommended for economic evaluations of health programs in middle-income countries.[12]

We compared intervention costs to DALYs gained to assess cost-effectiveness using 1× gross domestic product (GDP) per capita and two other cost-effectiveness thresholds estimated by Ochalek et al—a country income-group-specific threshold and a country-specific health opportunity threshold.[13,14] The income-group specific thresholds are 0.18×, 0.15× and 0.55× GDP per capita for low-income, lower-middle-income and upper-middle-income group countries, respectively. The country-specific thresholds are Ochalek et al.'s 'DALY 3' estimates, which we updated by applying the cost per DALY averted as a per cent of GDP per capita to each country's 2020 GDP per capita.[13] Both threshold types from Ochalek et al. are opportunity costs, that is, they reflect the health benefits (in DALYs) that could be achieved from general investments in increasing health system expenditures as opposed to investments in specific interventions. We also compared intervention costs to monetized health benefits in the tradition of a benefit cost analysis.

Table 1 summarizes key model inputs, point estimates, and sources of data in the analysis. Appendix A contains a structured abstract and more information on the model and data (Tables S1.1–S1.9 and Fig. S1.1), medication costs underlying the analysis (Tables S2.1–S2.4). It also describes the guideline costs and SBP-lowering of relevant WHO evidence-based standardized treatment protocols (Fig. S3.1), reports detailed results of the main analysis (Tables S4.1–S4.5 and Figs. S4.1–S4.5) and those for a sub-analysis of different medications (Table S5.1–S5.3), and includes a sensitivity analysis (Figs. S6.1–S6.2). Appendix B is an Excel file containing the model. Our adherence to CHEERS guidelines is reported in Appendix C.

Model structure

The model simulated how mean SBP in the adult population age 30 plus—and consequent downstream health and economic outcomes—would change based on the hypertension care cascade and pharmacological treatment type and distribution (i.e., the percent of hypertension patients on 1-, 2-, or 3-medication regimens employing either separate pills or SPCs).

Comparing mean SBP in the adult population in the baseline and intervention scenarios, the model calculated the difference in two leading causes of hypertension-attributable ill-health—stroke and myocardial infarction.[90] Within the study, assessed health outcomes included differences in 1) acute CVD events, 2) CVD-attributable deaths, and 3) disability-adjusted life years (DALYs). Economic outcomes include the value of 1) averted healthcare expenditures and 2) reductions in fatal health outcomes, and 3) averted productivity losses due to hypertension-attributable CVD events (i.e., due to absenteeism, presenteeism, and labor force dropout).

Analyzed scenarios

In three distinct scenarios, we assessed strengthening countries' hypertension care cascades while following different hypertension treatment protocols. The three scenarios were chosen to assess how different treatment choices can affect the costs and socioeconomic benefits of antihypertensive treatment.

The differences across the three scenarios were in the anti-hypertensive treatment regimens deployed. In a *baseline scenario (S0)*, patients diagnosed with hypertension were initiated on the WHO evidence-based Angiotensin-converting enzyme inhibitors (ACE-I) or Angiotensin receptor blockers (ARB) pharmacological treatment protocol.[5,41] Within the protocol, patients initiate on monotherapy and—dependent on hypertension status—they can be titrated to combination therapy

Parameter	Point estimate[a]	Source(s)/Notes[b]
Epidemiology		
CVD incidence, prevalence, and death rates: acute myocardial infarction (AMI), ischemic stroke (IS), hemorrhagic stroke (HS) by sex and age	Country-specific	Institute for Health Metrics and Evaluation (IHME) Epi Visualizations database (modelled estimates)[15]—country- and sex-specific values in Appendix B, IHME EpiViz Data worksheet
Disability proportion (i.e., the percent of all persons who experience an acute CVD event who are "disabled" by the event.	Country invariant — AMI—7.1% IS—15.8% HS—28.0%	IHME Disability weights and Burstein et al. (2015)[16,17]—Table S1.7, note c.
Disability weights—(i.e., post CVD events, the disability weight of those with/without disability)	Country invariant — AMI—0.03/0.17 IS—0.03/0.38 HS—0.03/0.36	IHME Disability weights and Burstein et al. (2015)[16,17]—Table S1.7, note c.
Systolic blood pressure (SBP): mean SBP and hypertension (HTN) prevalence, adults age 30+ by severity level (e.g., 140–<150 mm Hg) and sex	Country-specific — Simple average mean SBP and HTN prevalence across countries—129.9 mm Hg; 25.2%	Country surveys[18–38]; NCD Risk Factor Collaboration (NCD-Risc)[39]—Table S1.3 and sex-specific values in Appendix B, Data worksheet
Treatment rates and strategies		
Effective coverage rate–status quo (i.e., rates of blood pressure screening, treatment, and control)	Country specific — Simple average among countries—13%	WHO STEPS surveys[18–38]; NCD-Risc (2021)[3] –Table S1.4
Effective coverage rate–intervention scenarios (Baseline, S1, S2)—(i.e., modelled rates of increase in screening, treatment, and control over 10 years, scaled linearly)	Country specific — Simple average among countries—41%	Analysis assumptions—Simulates ambitious progress in closing screening and treatment gaps (by 50% over 10 years), and scaling control rates to 60, 61, and 71% in LIC, LMIC, and UMICs respectively–levels that represent the highest achievements to date in those income levels.[3] Resulting effective coverage rates, averaging 41 percent across countries, generally fall within 51 percent effective control rates that have been advocated as targets for the hypertension care cascade[1]—Table S1.4
Rates of monotherapy–status quo (i.e., the percent of all patients who are receiving antihypertensive treatment who are on monotherapy) in low-, lower-middle, and upper-middle income countries (LIC, LMIC, UMIC)	Income-group specific — LIC—95% LMIC—62% UMIC—70%	Chow et al. (2013)[40]—Table S1.7, note b
Rates of monotherapy—Intervention scenarios	Country invariant — Baseline scenario–rates of monotherapy do not change from the status quo. In S1 and S2, 100% of patients take 2+ anti-hypertensives	Analysis assumptions–Table S1.7, note b
Antihypertensive medication treatment guidelines	Country invariant — HEARTS guideline–ACE-Inhibitors initiating with monotherapy (Baseline) or combination therapy (S1 & S2) as first-line treatment	WHO evidence-based treatment protocols[5,41]—Fig. S3.1
Chronic CVD treatment guidelines	Country invariant — HEARTS guideline–chronic CVD (ischemic heart disease and stroke)	WHO Evidence-based treatment protocols[5,41]—Appendix B, Treatment Regimens worksheet
Treatment Effect		
SBP-lowering (mmHg) of losartan (LST), telmisartan (T), amlodipine (AM), and hydrochlorothiazide (HCT) given as monotherapy in patients with baseline SBP ≈ 155 mmHg	Country invariant — LST 50 mg–10.7 mm Hg T 40 mg–12.8 mm Hg AM 5 mg–7.8 mm Hg HCT 25 mg–15.8 mm Hg	LST, AM, HCT–Paz et al. (2019)[42] T –The SBP-lowering effect is 2.1 mm Hg higher than LST based on a meta-analysis by Takagi et al. (2013)[43]—Table S1.7
Method for calculating the blood-pressure lowering of anti-hypertensive combination therapy (≥2 medications given in combination)	Country invariant — SBP reduction of multiple drugs is approximately additive, "allowing for the reduced effect of the added drug(s) due to the lower blood pressure achieved by the existing drug(s)"[44] p 292	Inputting drug-specific effects from Paz et al. (2019)[42] with equations from Wald et al. (2009)[44]—see worked example in Table S1.7, note d

(Table 1 continues on next page)

Parameter	Point estimate[a]	Source(s)/Notes[b]
(Continued from previous page)		
SBP-lowering of single pill combinations (SPC) compared to treatment with separate pills	Country invariant — −1.5 mm Hg	Kengne and colleagues (2023)–see their Fig. 5, random effects model[45]—Table S1.7
Relative risk: reductions in CVD complications (AMI, stroke) per 10 mm Hg decline in SBP	Country invariant — AMI–0.83 Stroke–0.73	Ettehad et al. (2016)[46]—Table S1.7
Costs of various forms of treatment		
Medication costs of anti-hypertensives–USD per pill losartan (LST), telmisartan (T), amlodipine (AM), hydrochlorothiazide (HCT)	Country invariant — LST 50 mg–0.046 LST 100 mg–0.085 T 40 mg–0.195 T 80 mg–0.316 AM 5 mg–0.022 AM 10 mg–0.041 HCT 25 mg–0.017	**Antihypertensive separate pills**–National databases,[47–59] WHO HAI database,[60] MSH International Products Guide,[61] personal correspondence,[62] and other sources[63,64] – Table S2.2
Costs of other medications used in micro-costing of treatment of chronic CVD—USD per pill acetylsalicylic acid (ASA), atenolol (A), enalapril (E), and simvastatin (S)—USD per pill	Country invariant — ASA 100 mg–0.034 A 50 mg–0.023 E 20 mg–0.054 S 20 mg–0.084	**Other separate pills**–National databases,[47–59] WHO HAI database,[60] MSH International Products Guide,[61] personal correspondence,[62] and other sources[63,64]—Table S2.2
Ratio of the purchasing price of LST/AM and T/AM combination pills compared to equivalent separate pills	Country invariant — LST/AM—0.95 T/AM—0.97	**SPCs**—Data from Resolve to Save Lives medication pricing report,[65] supplemented with data from sources described above for separate pills[47,48,53,57–59] and data from the PAHO Strategic Fund[66]—Tables S2.3 and S2.4
Primary care outpatient clinic visit to a facility with no beds (USD per visit)	Country specific — Simple average among countries – $8.5	WHO-CHOICE modelled country-specific estimates updated to 2020 USD[67]—Table S1.6, note b
Treatment costs for acute CVD events	Country specific — Simple average among countries – IHD $700; Stroke $1277	Using methods from Ding et al. (2016)[68] and data from the European Heart Network[69]—Table S1.6, note a
Supply chain on-cost (i.e., the percent on-cost to medication prices to distribute medications)	Country status (developed, less developed, post-conflict, failed) — Simple average among countries—19.9%	John Snow Inc. (2015)[70]—Table S1.6, note d
Annual programmatic costs (USD per capita, undiscounted)	Country specific — Simple average among countries—$0.03	WHO NCD Costing Tool[71]—Appendix B, Programmatic costs worksheet
Training costs to assist health providers to follow new protocols and to train on the administration of SPCs (USD per provider trained)	Country specific — Simple average among countries—$87	Calculated based on data and assumptions from[67,71–76]—Table S1.6, note e and Appendix B Data worksheet
Monetizing ill health (valuing socio-economic losses due to absenteeism, disability-induced labor exit, and HTN-attributable death)		
Adult employment rates without disability, by sex	Country specific — Simple average among countries (Males 76%; Females 49%)	ILO database[77,78]—Table S1.5
Adult employment rates with disability—relative reduction in employment rate from baseline level	Income group specific — LICs 21%; LMIC 53%, UMIC 42%	ILO database[77,78]—Table S1.5, note a
Earnings rates, annual (USD), by sex	Country specific — Simple average among countries (Males $3338; Females $2725)	ILO database[79] and ILO Global Wages Report[80]—Table S1.5, note b
Earnings growth rates	Region specific — Simple average among countries (2.6%)	ILO database[79] and ILO Global Wages Report[80]—Table S1.5, note c
Retirement age, by sex	Country specific — Simple average among countries (males 61; females 58)	United States Social Security Administration Program 'Social Security Programs Throughout the World[81]—Table S1.5

(Table 1 continues on next page)

Parameter	Point estimate[a]	Source(s)/Notes[b]
(Continued from previous page)		
Productivity loss due to absenteeism (i.e., excess days of work lost due to a specific condition)	Country invariant — AMI—39.5 Stroke—57.5 Chronic CVD—2.7	Anesetti-Rothermel et al. (2011); Gordois (2015)[82,83]—Table S1.7, note a
Value of a statistical life year (VSLY) (USD)	Country specific — Simple average among countries–$4303	Country VSLY extrapolated from 2020 U.S. estimate[84] following methods from Robinson et al. (2019)[85]—Table S1.5, note d
Other		
Annual survival rates, by age	Country specific population life tables	UN Population Division[86]—see Appendix B, Population data worksheet
Consumer price indices, purchasing power parity conversion rates, country income status, exchange rates, GDP per capita	Country specific — Simple average among countries—N/A	The World Bank database[87]
Discount rate (%)	Country invariant — 4.0%	Haacker et al. (2021)[12]—Table S1.7
Government health expenditures (GHE)—per capita and GHE as a percent of total health expenditures (THE)	Country specific — GHE per capita $125; GHE as % THE 46%	WHO Health Expenditures Database[88]—Table S1.2
Population age 30+, by sex	Country specific — Simple average among countries—23.2 million	UN Population Division[86]—Table S1.2
Real GDP Growth Rate (historical and projected)	Country specific — Simple average among countries—3.8%	International Monetary Fund World Economic Outlook[89]—Table S1.2

[a]For illustration of data input into the model, "Country specific" values are presented as the simple average across countries. The actual values used for each country may be found in Appendix A in tables specified in the Source/Notes column. Country-invariant values were used for all countries. [b]Tables with names beginning with "S" (e.g., Table S1.2) are found in Appendix A.

Table 1: **Summary of key model inputs, point estimates, and sources.**

employed using separate pills. The scenario reflects the gains that can be made if the care cascade strengthens following status quo treatment protocols—since in most LMICs monotherapy is the dominant form of treatment.

Two intervention scenarios were developed to investigate the health and economic gains that could occur should countries implement recommended changes to status quo treatment protocols, such as initiating patients on combination therapy using separate pills (S1) or initiating patients on combination therapy *that* employs single combination pills (S2). In both intervention scenarios, patients follow WHO evidence-based ACE-I or ARB + calcium channel blockers (CCB) protocols.[5,41] This protocol was selected because a) the medication–class combination is preferred based on its efficacy, tolerability, safety profile, and strong clinical trial evidence base[9]; and, b) for this study's purposes, the protocol's medications and dosages can be mirrored in single pill or combination form —suitable for analytical cost and efficacy comparisons.

We had sufficient data to investigate using losartan or telmisartan (both ARBs) as the ACE-I or ARB, amlodipine as the CCB, and hydrochlorothiazide as the diuretic. Within the main analysis we present results using losartan as the ARB. While less-efficacious than telmisartan, its lower cost may be more reflective of prices that LMICs can pay. In a sensitivity analysis, we explore, the extent to which results change if telmisartan, a more expensive but clinically preferred medication, is used.[9]

Compared to the baseline scenario, S1 isolates the costs and consequences of treating all patients with at least two antihypertensive medications instead of predominantly monotherapy. Compared to S1, S2 isolates treating all patients with SPCs versus separate pills.

Treatment protocols: medication costs, SBP-lowering, and patient distribution within protocol steps

The costs of treatment

We calculated the financial costs—those actually paid by the government–to scale and strengthen the care cascade, including costs to screen and treat with outpatient visits and medications; improve supply-chain availability; and provide hypertension education and train health providers on new treatment protocols. The methods and assumptions of that costing framework have been detailed elsewhere, including our previous research to capture private sector and public procurement prices of antihypertensive medications.[11]

For this study, the main costing adaptation required to build on the previously established costing framework was to assess purchasing prices of SPCs compared to their equivalent separate pills. Few published

comparisons have been made of the price of SPCs compared to their separate pill equivalents; however, Resolve to Save Lives shared data from a recent analysis comparing SPC and single agent pill prices in Brazil, Lebanon, Philippines, and South Africa and Nigeria.[91] In addition, we reviewed data from a similar study conducted in India,[92] and compiled data from our previous research detailing price comparisons in Argentina, Azerbaijan, Bangladesh, Brazil, Lebanon, Thailand, and within the Pan American Health Organization (PAHO) Strategic Fund.[47,48,53,57–59,66] A synthesis of the data is in Appendix A, Tables S2.3 and S2.4. Within the analysis, we used the average ratio across public and private sector prices: i.e., losartan/amlodipine and telmisartan/amlodipine combination pills are respectively about 95 percent and 97 percent of the total cost of their single pill equivalents.

SBP-lowering of antihypertensive treatment regimens

The SBP-lowering of separate pills in our analysis is from a meta-analysis of anti-hypertensive efficacy in over 94,000 patients across 208 clinical trials. In patients with starting SBP ≈ 155 mm Hg, Paz and colleagues (2019) found that respectively, 50 mg losartan, 5 mg amlodipine, and 25 mg hydrochlorothiazide reduced SBP by 10.7, 7.8, and 15.8 mm Hg. To estimate the effect of combination therapy, we followed methods from Wald and colleagues (2009), who found that multiple drugs produce an approximately additive effect, "allowing for the reduced effect of the added (drug(s) due to the lower blood pressure achieved by the existing drug[44] p 292 (see Appendix A Table S1.7's note D for worked examples).

To reflect the extent to which SPCs provide additional blood pressure-lowering compared to separate pills, we used evidence from Kengne and colleagues' (2023) meta-analysis synthesizing data from 12 studies (eight of which were randomized controlled trials). Those authors found that patients taking SPCs reduced their SBP by around 1.5 mm Hg more compared to patients taking either the same anti-hypertensive medications or different anti-hypertensive medications of the same drug class as separate pills.[45]

Patient distribution within protocol steps

Next, we needed to understand how many patients generally fall within each protocol step (i.e., the proportion that take one, two, or three medications by hypertension severity level). Since evidence on prescription behavior is published only in a small body of studies,[93] we leveraged data from the Prospective Urban Rural Epidemiology (PURE) study. It found that in 14 low-, lower-middle-, and upper-middle income countries spanning world regions, respectively, 95, 62, and 70 percent of treated patients with hypertension were administered monotherapy while the remainder in each setting took two or more medications.[40] In lieu of nationally-specific information, we used these income group averages for countries in our analysis.

We then considered how many medications a given patient with hypertension *should* take considering their level of pretreatment SBP. We compared the SBP-lowering impact of medications from Wald et al. (2009) and national-level data on mean SBP levels by hypertension severity level. We found that the SBP-lowering impacts of monotherapy reported by Wald and colleagues are generally sufficient to control hypertension for individuals in the SBP 140 to <150 mm Hg group, dual combination therapy is sufficient for adults in the SBP 150 to <160 group, and triple combination therapy is required to reduce those in the SBP 160+ group close to, but not below, the standard control threshold.[44]

As such, within our analysis we assumed that all persons treated for SBP 140 to <150 mm Hg received monotherapy. In Mexico, for example, this was 47 percent of all persons with hypertension. However, from the PURE study we knew that 70 percent of the treated population with hypertension in upper-middle income countries, like Mexico, receive monotherapy. We assumed that the remaining 23 percent of the population with hypertension that were receiving monotherapy all had SBP 150+.

Respectively 5, 38, and 30 percent of treated populations with hypertension in low-, lower-middle-, and upper-middle income countries receive combination therapy (the inverse of the PURE monotherapy data). We assumed that all treated individuals with SBP 150–160 mm Hg were given two medications—since dual combination therapy was generally sufficient for adults SBP 150 to <160 mm Hg to control SBP—and that treated individuals with SBP ≥160 mm Hg had an equal likelihood of receiving two or three medications.

Note b of Appendix Table S1.7 further describes methods and assumptions and provides worked examples to illustrate the status quo (i.e., baseline scenario) distribution of patients within protocol steps. In the intervention scenarios (S1 and S2), all patients who previously would have initiated treatment on monotherapy were shifted to initiate on two medications.

The economic value of improvements in health

Following the Reference Case Guidelines for Benefit-Cost Analysis in Global Health,[85] we valued reductions in *fatal* outcomes (i.e., years of life saved) using country-specific value of a statistical life year measures (VSLY) adjusted for expected real income growth year over year.

Nonfatal outcomes assessed in the analysis included averted healthcare expenditures (for acute and chronic cases of CVD) and averted indirect productivity losses due to ill-health. For healthcare expenditures, country-specific costs to treat acute cases of CVD were extrapolated from European country data following methods

developed by Ding et al. (2016),[68] and costs to treat chronic cases of CVD were estimated by applying medication costs and the cost of outpatient clinic visits from WHO CHOICE to Global Hearts treatment protocols.[67,94,95]

To estimate disability-induced labor-force dropout, we dispersed survivors of CVD events into disability states based on published estimates.[16,17] Using global data on employment rates with and without disability,[77,78] we then calculated the resulting labor force shortfall among CVD-event survivors. Among those who experience an acute CVD event or live with chronic CVD and remain in the workforce, we assessed the number of days of work due to their condition based on published literature.[82,83] Following recommendations in guidelines, we valued missed worker time based on worker earning rates.

Role of funding

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Results

Costs of alterations to status quo hypertension treatment strategies

In the baseline scenario, across all 24 countries, costs to scale hypertension care following status quo treatment practices that emphasize monotherapy are USD 35.6 billion. The incremental costs of moving from status quo treatment protocols to protocols initiating patients on dual combination therapy (S1) are about USD 5.9 billion across the 24 countries over the 30-year analysis time horizon. The incremental costs of moving from the baseline scenario to protocols initiating with dual combination therapy that employ SPCs (S2) is comparatively cost saving USD 1.5 billion. Fig. 1 shows that costs to supply and treat patients with anti-hypertensive medications drive costs to scale S1 and S2, since all patients treated for hypertension initiate treatment on at least two medications in the scenarios. Appendix A Fig. S4.3 reports costs by country and cost category.

Fig. 2 illustrates country financial costs in each scenario and the relative increase in government health expenditures (GHE) that would be required to implement scenarios. Respectively across low-, lower-middle, and upper-middle income countries in the analysis, simple averages of the increases in GHE required to fund the baseline scenario are 10.1, 5.1, and 1.4 percent, while S1 extended cost increases to 13.7, 5.9, and 1.6 percent of GHE.

Health benefits

Initiating hypertension patients on dual combination therapy using separate pills or SPCs (S1 and S2) had higher health benefits compared to treatment regimens in which monotherapy is the dominant form of treatment (baseline scenario).

Over 30 years, across countries, the baseline scenario would save more than 1.3 million lives, representing a nearly 7.5 percent reduction in deaths compared to if status quo effective coverage rates persisted. If all

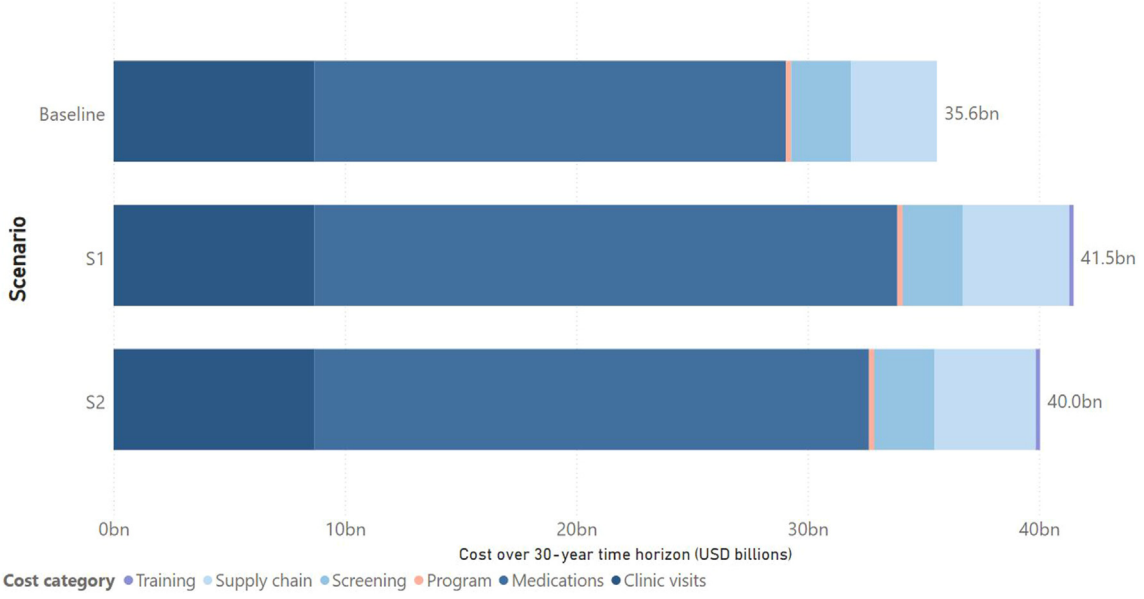
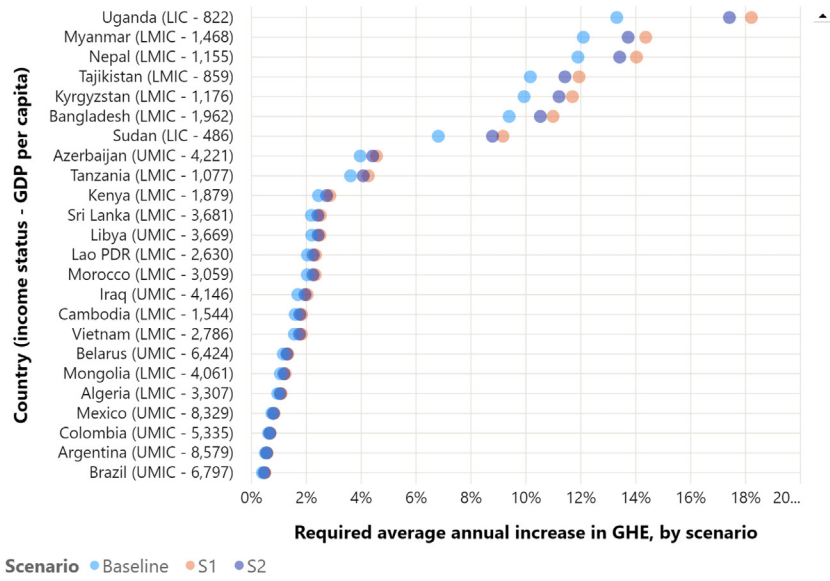


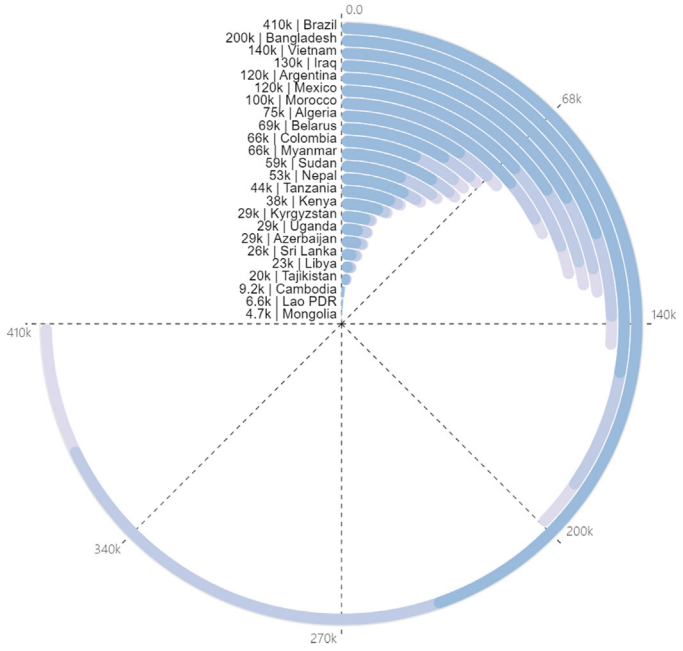
Fig. 1: **Total 30-year costs by scenario and cost sub-categories—screening, treatment (medications, clinic visits), supply chain, programmatic, and training.**



Country	Scenarios range - Required Annual increase in GHE	Scenarios range - Total 30-year costs (USD millions)
Uganda	13·31% - 18·21%	715 - 978
Myanmar	12·09% - 14·36%	1,352 - 1,606
Nepal	11·90% - 14·03%	995 - 1,174
Tajikistan	10·16% - 11·94%	392 - 461
Kyrgyzstan	9·93% - 11·69%	452 - 532
Bangladesh	9·39% - 10·99%	2,908 - 3,403
Sudan	6·81% - 9·16%	834 - 1,122
Azerbaijan	3·96% - 4·56%	472 - 543
Tanzania	3·61% - 4·26%	1,269 - 1,495
Kenya	2·45% - 2·86%	1,192 - 1,394
Sri Lanka	2·19% - 2·51%	672 - 772
Libya	2·20% - 2·50%	593 - 674
Lao PDR	2·04% - 2·34%	116 - 133
Morocco	2·04% - 2·32%	1,339 - 1,529
Iraq	1·69% - 2·03%	1,993 - 2,396
Cambodia	1·60% - 1·83%	175 - 200
Vietnam	1·57% - 1·82%	2,352 - 2,733
Belarus	1·16% - 1·33%	541 - 618
Mongolia	1·06% - 1·23%	72 - 84
Algeria	0·96% - 1·08%	1,420 - 1,604
Mexico	0·75% - 0·82%	5,071 - 5,586
Colombia	0·63% - 0·69%	2,315 - 2,535
Argentina	0·51% - 0·57%	2,691 - 3,003
Brazil	0·40% - 0·49%	5,652 - 6,916

Fig. 2: **Required percent increase in government health expenditures to fund scenario-based scale ups (figure), and range of total 30-year discounted costs (table), by country.**

individuals who would have been administered monotherapy in the baseline scenario instead were administered dual combination therapy employing separate pills (S1), 429,639 more lives could be saved. Additional blood-pressure lowering from using SPCs in place of separate pills in dual combination therapy regimens



Country	Baseline lives saved (% reduction)	S1 lives saved (% reduction)	S2 lives saved (% reduction)
Brazil	244,254 (7·5%)	126,300 (11·3%)	37,176 (12·5%)
Bangladesh	152,574 (7·2%)	37,005 (9·0%)	14,663 (9·7%)
Vietnam	108,291 (7·5%)	26,968 (9·3%)	8,994 (10·0%)
Iraq	93,792 (10·1%)	25,343 (12·8%)	7,942 (13·7%)
Argentina	88,064 (8·2%)	27,773 (10·8%)	8,249 (11·6%)
Mexico	74,835 (7·0%)	33,740 (10·1%)	10,609 (11·1%)
Morocco	78,128 (6·8%)	17,181 (8·3%)	6,352 (8·9%)
Algeria	54,585 (6·1%)	15,097 (7·8%)	5,758 (8·5%)
Belarus	50,226 (9·4%)	14,299 (12·1%)	4,103 (12·8%)
Colombia	38,625 (6·3%)	21,199 (9·8%)	6,269 (10·8%)
Myanmar	51,193 (7·8%)	11,060 (9·5%)	3,823 (10·1%)
Sudan	36,192 (6·1%)	19,609 (9·4%)	3,655 (10·0%)
Nepal	41,381 (8·6%)	8,687 (10·4%)	3,102 (11·0%)
Tanzania	35,810 (6·8%)	5,741 (7·9%)	2,034 (8·3%)
Kenya	30,610 (7·4%)	5,448 (8·7%)	1,934 (9·2%)
Kyrgyzstan	23,582 (9·2%)	4,219 (10·8%)	1,386 (11·4%)
Uganda	19,765 (5·8%)	7,923 (8·1%)	1,427 (8·5%)
Azerbaijan	21,289 (9·2%)	5,752 (11·8%)	1,641 (12·5%)
Sri Lanka	19,032 (7·8%)	5,382 (10·0%)	1,854 (10·7%)
Libya	17,365 (10·2%)	4,326 (12·7%)	1,224 (13·4%)
Tajikistan	15,888 (9·7%)	2,791 (11·4%)	1,008 (12·0%)
Cambodia	6,856 (6·1%)	1,739 (7·7%)	653 (8·3%)
Lao PDR	5,339 (8·0%)	902 (9·3%)	344 (9·8%)
Mongolia	3,154 (6·1%)	1,153 (8·3%)	413 (9·1%)
Total	1,310,830 (7·5%)	429,639 (10·0%)	134,615 (10·8%)

Fig. 3: **Number of lives saved over the 30-year time horizon, by country and scenario (% reduction in deaths).**[a] [a]The percent reduction in deaths compared to a status quo scenario in which there is no scale up of the effective coverage rates (e.g., in the status quo scenario, if effective coverage is 15 percent to begin the analysis there is no change through year 30).

Country	Income status, GDP per capita	Net benefits[a] (Baseline)	Net benefits (S1)	Net benefits (S2)	S2 only: CE ratio–CE status[b]
Argentina	UMIC, 8579	*3203*	*4810* ● [c]	*5449* ●	2.88–Y, Y, Y
Mexico	UMIC, 8329	*64*	*1992* ●	*2879* ●	1.64–N, Y, Y
Brazil	UMIC, 6797	*9192*	*16,097* ●	*18,795* ●	3.96–Y, Y, Y
Belarus	UMIC, 6424	*1601*	*2142* ●	*2335* ●	5.84–Y, Y, Y
Colombia	UMIC, 5335	*−277*	*667* ●	*1059* ●	1.28–N, Y, Y
Azerbaijan	UMIC, 4221	*183*	*290* ●	*357* ●	1.87–Y, N, Y
Iraq	UMIC, 4146	*1884*	*2545* ●	*2975* ●	2.01–Y, -, Y
Mongolia	LMIC, 4061	*83*	*129* ●	*152* ●	2.25–N, Y, Y
Sri Lanka	LMIC, 3681	*−149*	*−96* ●	*−17* ●	1.19–N, N, Y
Libya	UMIC, 3669	*1603*	*2071* ●	*2245* ●	1.14–N, -, Y
Algeria	LMIC, 3307	*−293*	*−151* ●	*25* ●	1.44–N, Y, Y
Morocco	LMIC, 3059	*206*	*360* ●	*542* ●	1.87–N, N, Y
Vietnam	LMIC, 2786	*1197*	*1707* ●	*2109* ●	1.34–N, Y, Y
Lao PDR	LMIC, 2630	*11*	*15* ●	*27* ●	1.13–N, -, Y
Bangladesh	LMIC, 1962	*506*	*840* ●	*1314* ●	1.04–N, N, Y
Kenya	LMIC, 1879	−774	−902	−818	0.43–N, N, N
Cambodia	LMIC, 1544	−82	−85	−69 ●	0.62–N, N, N
Myanmar	LMIC, 1468	−979	−1152	−1052	0.48–N, -, N
Kyrgyzstan	LMIC, 1176	−290	−341	−309	0.52–N, N, N
Nepal	LMIC, 1155	−698	−814	−741	0.42–N, N, N
Tanzania	LMIC, 1077	−993	−1176	−1095	0.24–N, N, N
Tajikistan	LMIC, 859	−290	−340	−314	0.29–N, N, N
Uganda	LIC, 822	−631	−860	−811	0.19–N, N, N
Sudan	LIC, 486	−765	−1016	−963	0.20–N, N, N

[a]Net benefits are total economic benefits minus total financial costs over the 30-year time horizon. Positive net benefits are indicated by italicized text. [b]Cost-effectiveness (CE) of Scenario 2. The ratio is the cost per DALY gained divided by GDP per capita. Letters designate the status, respectively, of whether treatment at the cut point is cost-effective using GDP per capita thresholds specific to World Bank income levels,[14] country-specific health opportunity thresholds,[13] and 1× GDP per capita. Y = Yes; N = No; = threshold not available. [c]The ● symbol indicates that the intervention scenario generates higher net benefits than the baseline scenario.

Table 2: **Net benefits and cost-effectiveness over the 30-year time horizon, by intervention scenario.**

(S2) saves an additional 134,615 thousand lives over S1. Altogether, treating patients with dual combination therapy and using SPCs within those regimens (S2) saves 43 percent more lives than adhering to status quo treatment practices (baseline scenario). Fig. 3 shows the number of lives saved in each scenario by country and scenario, and percent reduction in deaths compared to a status quo scenario. Appendix A Table S4.1 and Fig. S4.1 detail lives saved year-over-year, Table S4.1 details the absolute reduction in deaths in each scenario, Fig. S4.2 breaks down the ratio of lives saved by sex in the S2 scenario (47 percent female to 53 percent male) by country and Table S4.3 shows averted 30-year CVD incidence and DALYs by country.

Comparing the costs and benefits of treatment decisions

Table 2 displays net benefits and cost-effectiveness of each scenario by country, with countries ordered high to low by income status. Italicized text in cells indicates where net benefits are positive over the 30-year period. Filled black circles indicate that the intervention scenario produced higher net benefits than the baseline scenario. Appendix A Fig. S4.4 breaks down total socioeconomic benefits by country and benefit category.

In 12 out of 12 of the top-ranked countries by income, shifting to guidelines that ensure that all patients receive at least two medications (S1) generates higher net benefits, compared to only three out of the 12 bottom-ranked countries by income status. Shifting to guidelines that ensure that all patients receive at least two medications AND employing SPCs within those regimens (S2) results in higher net benefits in all but eight countries. Considering cost-effectiveness thresholds based on country income status, S2 was considered "cost-effective" in five countries; in eight countries considering country-specific income thresholds; and in 15 countries using a 1× GDP per capita threshold.

Discussion

Our analysis of 24 countries—spanning income levels and regions—demonstrated that adjusting treatment guidelines to administer two or more medications as *initial* therapy for patients with hypertension is likely to generate higher net benefits in relatively more developed countries, and that using SPCs within those guidelines generates higher net benefits in most (16/24) countries compared to baseline practices. While a

previous study by Borghi and colleagues (2021) modelled the health benefits (e.g., lives saved) of similar scenarios (see results comparison in Appendix A Table S4.2),[96] to our knowledge this is the first modelling study that has assessed the costs and health *and* socio-economic benefits of scaling combination treatment with and without SPCs. In doing so, our study answers the call to develop economic evaluations that assess the budgetary consequences and cost-effectiveness of combination versus monotherapy.[5] Results are supportive of recommendations in international hypertension treatment guidelines to administer combination therapy as first-line initial treatment using SPCs.[5,97,98] However, considering differing findings by income status, caution should be taken to consider economic circumstances and undertake country-specific analyses.

In laying the foundation for greater population coverage with standard antihypertensive treatment in general, and initial combination therapy and SPCs in particular, health systems can face barriers such as high procurement costs, low availability of hypertension medications (especially in SPC form), and other patient and provider barriers. Registration in national drug formularies and essential medicine lists is a first step toward improving access.[91] Among the 30 most populous LMICs worldwide, only 12 currently have SPCs registered on essential medicines lists.[99] Once SPCs are registered, clinical practice guidelines can be aligned. Currently, few LMIC national-level clinical practice guidelines and treatment protocols recommend treatment initiation with two or more medications.[8,91] Following international guidelines,[5,98] countries can revise them to elevate initial combination therapy and use of SPCs.

Updating treatment guidelines to reflect the evidence supporting initial combination therapy can help raise awareness of the benefits of combination therapy or SPCs, especially among health providers who may not yet view either as acceptable treatment options.[5] To support adoption among providers and patients, health systems could select SPCs that are supported by clinical trials, and allow for flexible dosing (i.e., tablets that can be split to support clinician titration).[9] Dedicated initiatives such as the WHO HEARTS program, with a framework to support roll out of standard simple treatment protocols and training of providers, are likely to improve adoption rates.[100] Most of the HEARTS countries in Latin America and the Caribbean[101] and Sri Lanka have all successfully implemented treatment protocols including initial dual drug combination therapy. Countries would benefit from explicitly considering cost-effectiveness criteria prior to issuing new clinical practice guidelines and treatment protocols. While evidence suggests many antihypertension medications are somewhat interchangeable in terms of effectiveness,[102] prices can differ significantly across drug classes and medications. Detailed results in Appendix A (see Table S5.1) describe how use of a higher higher-cost ARB—telmisartan—can materially lower cost-effectiveness ratios.

Efficient sourcing of medication is also essential to containing costs. Supra-national mechanisms, such as the PAHO Strategic Fund, can leverage national purchasing power to lower prices, though barriers—including issues with local product registration and entrenched procurement practices—persist among member countries sourcing antihypertensive medicines from the Strategic Fund. Success also requires a supply chain system that can follow through to make essential hypertension medications, including SPCs, available and accessible to all. Focusing national guidelines and procurement mechanisms on two to three medications can streamline the supply chain and pool demand to increase bargaining power, ultimately lowering medication prices.[100] Other supply chain strengthening strategies proven in low-resource settings include using best-practice forecasting methods to project consumption, establishing *multi-year* procurement contracts with *several* suppliers to ensure consistent availability, training pharmacists, and establishing protocols that maintain sufficient medication stocks relative to the number of registered patients.[103]

From the perspective of patients, uptake also depends on the affordability of medications. The burden of out-of-pocket costs is thus an essential consideration for health systems when planning for SPCs scale-up: especially in light of findings that around 33 percent of households in LMICs cannot affordably purchase two or more anti-hypertensive medications.[104] At the same time, it should be acknowledged that universal coverage of antihypertensive treatment can be a significant added cost for already burdened health systems, and initiating treatment with combination therapy requires even more resources. While health systems partially "recoup" this investment by averting treatment costs for hypertension-attributable complications (e.g., strokes)—within our analysis, averted treatment costs are equivalent to about six percent of the financial costs to implement and scale antihypertensive treatment (see Appendix A, Table S4.4)—new or enhanced funding may be necessary. Health taxes on products such as sugary-sweetened beverages, tobacco, and alcohol offer potential sources of revenue.[105]

Limitations of our model have been described elsewhere.[11] In this analysis, national-level data was not always available. One important example is on rates of administration of monotherapy versus combination therapy—a key datapoint for examining the shift in costs and benefits that results from moving from the baseline scenario to S1. We applied income-group averages from a cross-sectional study of adults in 14 LMICs, a few of which overlapped with countries featured in this

analysis (i.e., Argentina, Brazil, Colombia, Bangladesh). Better surveillance and reporting is needed on this important measure.

Data on the costs of SPCs compared to their single agent pill equivalents was also limited. We assumed slightly lower costs for SPCs based on own-study data and data from recent studies comparing SPCs to their single agent equivalents.[91,92] While plausible, the representativeness of that data across all countries is uncertain. Country-level analyses based on local data may be needed for country-specific decision-making.

The data that we used to inform the SBP-lowering of anti-hypertensive medications was derived from a meta-regression of over 208 published clinical trials,[42,106] in which 45 percent of participants were women and 17 percent were of African-American or African-Caribbean origin.[106] Similarly, our methods used to calculate the SBP-lowering effect of combination therapy versus monotherapy are from a meta-analysis of 42 trials, few of which included populations relevant to LMICs.[44] Finally, our analysis assumed an additional 1.5 mm Hg lowering from use of SPCs compared to single agent equivalents, based on data from a recent meta-analysis.[45] Effect sizes in the meta-analysis were derived from 12 studies, with three upper-middle income countries (Serbia, Turkey, and Russia) and no low- or lower-middle income countries represented. Each study individually compared the same medications or drug classes in separate pills to their SPC equivalents; however, the medications and classes that were examined in the studies were heterogeneous. As such, the effect size used in this analysis is a general estimate, rather than one specific to the medication combinations that formed the basis for our results (i.e., losartan/telmisartan, amlodipine, hydrochlorothiazide). While we use evidence from these studies as the best available data, our analysis would benefit significantly from more evidence on medications that are relevant to LMICs and from more research that includes LMIC populations.

Our study did not account for side effects and adverse outcomes of antihypertensive treatment. Combination therapy at low doses, and SPCs especially, are associated with fewer side effects compared to titrating initial agents to maximal doses.[5,9] However, if more patients are titrated upward from initial starting doses in combination therapy more adverse effects may occur, lowering the net-benefits of the S1 and S2 scenarios.

Despite limitations, our analysis provides evidence that can inform decision-making around treatment decisions for hypertension. First line treatment employing SPCs is likely to generate higher net benefits compared to status quo treatment practices in many countries. To improve population health, national health systems could benefit from reducing structural and other barriers to the use of combination therapy and SPCs.

Contributors

Conceptualization [DK, RN], formal analysis [BH], investigation [BH, RN], methodology [DK, RN, MJH, BH], project administration [BH], supervision [DK, RN], validation [DK, RN, MJH, BH], visualization [BH], writing—original draft [BH, DK, RN], and writing—review & editing [BH, DK, RN, MJH].

BH and DK accessed and verified the data and BH was responsible for the decision to submit the manuscript.

Data sharing statement

The model and underlying data are available as Supplemental Online Appendix B.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102778.

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