Application for the addition of triple drug fixed dose anti-hypertensive medicine combinations on the model list of essential medicines for treatment of essential hypertension in adults

Author	***Organization***
Gautam Satheesh	The George Institute for Global Health, India
Rupasvi Dhurjati	The George Institute for Global Health, India
Abdul Salam	The George Institute for Global Health, India
Andrew E Moran	Resolve to Save Lives, USA
Adrianna Murphy	London School of Hygiene and Tropical Medicine, UK
Pablo Perel	World Heart Federation, Switzerland
Thomas A Gaziano	World Heart Federation, Switzerland
Aletta E Schutte	University of New South Wales, Australia
Dorairaj Prabhakaran	Centre for Chronic Disease Control, India
Dike Ojji	University of Abuja, Nigeria
Asita De Silva	University of Kelaniya, Sri Lanka
Paul Whelton	World Hypertension League
Sohel Choudhury	National Heart Foundation, Bangladesh
Cai Jun	Beijing Anzhen Hospital, Beijing, China
Elija Ogola	Pan-African Society of Cardiology, Kenya
Ntobeko Ntusi	South African Medical Research Council (SAMRC)
Ana G. Munera Echeverri	InterAmerican Society of Cardiology, Colombia
Mark D Huffman	Washington University at St. Louis, USA
Anthony Rodgers	The George Institute for Global Health, Australia

Coordinated and submitted by:

The George Institute for Global Health

World Health Organization Contact:

Taskeen Khan (former lead, cardiovascular disease, WHO NCD branch)

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General items

Section 1: Summary statement of the proposal

Worldwide, 1.4 billion people have hypertension, defined as blood pressure (BP) ≥140/90 mmHg, but only one in five have BP controlled (<140/90 mmHg)(1). The World Health Organization (WHO) HEARTS package and 2021 WHO hypertension treatment guidelines recommend simple treatment protocols, and all HEARTS country protocols recommend three antihypertensive medicines if BP remains uncontrolled after the first two or three treatment steps. Further, the WHO 2021 and major regional and national guidelines recommend BP lowering to systolic BP <130 mmHg for high CVD risk patients, which typically requires three or more drug classes in most hypertensive patients (2, 3).

Fixed-dose combinations (FDCs) effectively lower BP by combining distinct antihypertensive drug classes acting on separate pathophysiological targets whilst avoiding adverse effects that are more frequent with high doses of any drug. FDCs also mitigate adverse effects by allowing one drug to counteract the adverse effects of another (4-8). FDCs used as initial or add-on therapy have superior efficacy compared with monotherapy and can facilitate reaching the WHO goal of >50% global population hypertension control (9).

In 2019, two-drug (dual) FDCs of antihypertensive medicines were added to the WHO-EML. While a proportion of treated patients achieve BP control with dual FDCs as second-line or first-line therapy, a substantial proportion of hypertension patients need triple drug combination therapy to achieve goal BP. The need for triple-drug treatment in some hypertension patients increases the relevance of affordable, effective and safe three-drug (triple) FDCs. Large cardiovascular outcomes trials that achieved SBP <130 mmHg utilized an average of 2-3 medicines per person in the intervention group (10-16). Current hypertension treatment protocols, including HEARTS simple hypertension treatment protocols recommended by WHO, also all recommend triple drug combination, usually as a third treatment step, and both HEARTS and the WHO 2021 guidelines recommend FDCs in preference to separate pills where possible to improve adherence (2, 3).

The efficacy of triple drug combinations compared to dual combinations has been established (17). Additionally, an updated systematic review of randomized double-blind trials of efficacy and safety of triple vs. dual combinations of antihypertensive medicines among patients with hypertension was completed for this application, including 19 trials with over 16,000 participants (Section 8, page 13). The results showed a clear improvement in efficacy with triple compared with dual combination, and with similar tolerability. The size of benefit was clinically important: an overall 5.4/3.2 mmHg (systolic/diastolic) additional reduction in BP and 16% additional improvement in BP control among patients receiving triple compared to dual combination therapy.

Superior efficacy of FDCs at low or standard doses compared with intensification of monotherapy to the maximally recommended dose is likely explained by the advantage of FDCs targeting multiple pathophysiological pathways causing hypertension. Adverse effects are the most frequent at maximal dose of the medicine. When all the component medicines in the FDC are at low doses (one quarter or one half of the maximal dose), not only does initial treatment with FDC lower BP more than initial monotherapy, the risk of adverse effects or serious adverse effects due to any of the component medicines is minimized. Triple FDCs also provide practical advantages for patients and healthcare programs, including simpler dose schedules and decreased pill burden resulting in improved patient medication adherence (improved persistence and execution), simplified medicine inventory, procurement, supply chain logistics, and fewer drug stock-outs, and greater ease of healthcare worker task sharing (18).

This application recommends the inclusion of triple FDCs of antihypertensive medicines to the WHO-EML, consisting of angiotensin converting enzyme inhibitor (ACEi) or angiotensin ii receptor blocker (ARB) plus calcium channel blocker (CCB) plus diuretic. Four indicative

examples are given, and two square box designations are proposed. The inclusion of a triple FDC would support the implementation of simplified hypertension treatment protocols that WHO and other organizations recommend and accelerate progress toward the global goal of ≥50% hypertension control by the year 2040 (9).

Section 2: Consultation with the WHO technical departments and focal point supporting the application (where relevant)

The following WHO staff were consulted on 19 June 2024 for technical advice on preparing the application:

- Lorenzo Moja, Department of Essential Health Standards and Products, WHO
- Bernadette Cappello, Department of Essential Health Standards and Products, WHO
- Taskeen Khan, Department of Non-Communicable Diseases, WHO

Section 3: Other organization(s) consulted and/or supporting the application

1. Resolve to Save Lives
2. World Hypertension League*
3. World Heart Federation
4. International Society of Hypertension
5. National Heart Foundation, Bangladesh
6. Centre for Chronic Disease Control, India*
7. Pan-African Society of Cardiology, Africa region*
8. Inter-American Society of Cardiology, Latin America & Caribbean region*
9. Beijing Institute for Heart, Lung, and Blood Vessel Diseases, China*
10. South African Medical Research Council

**Support letters are submitted as appendices*

Section 4: Key information summary for the proposed medicine(s)

International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine(s). Note that the first three combinations would be included in the same square box listing. The ICD code for all these combinations would be ICD-11 MMS: BA00, Essential Hypertension. Dosage forms, strengths and indications for current products are summarized in **Table 1** below.

Table 1: Proposed medicines for inclusion

INN	Amlodipine + Valsartan + Hydrochlorothiazide		
ATC code	C09DX01		
Indication	Essential hypertension		
ICD-11 code	BA00 Essential hypertension		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet or capsule	5 mg + 160 mg + 12.5 mg	Yes	No
	5 mg + 160 mg + 25 mg	Yes	No

	10 mg + 160 mg + 12.5 mg	Yes	No
	10 mg + 160 mg + 25 mg	Yes	No
	10 mg + 320 mg + 25 mg	Yes	No
INN	Amlodipine + Olmesartan + Hydrochlorothiazide		
ATC code	C09DX03		
Indication	Essential hypertension		
ICD-11 code	BA00 Essential hypertension		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet or capsule	5 mg + 20 mg + 12.5 mg	Yes	No
	5 mg + 40 mg + 12.5 mg	Yes	No
	5 mg + 40 mg + 25 mg	Yes	No
	10 mg + 40 mg + 12.5 mg	Yes	No
	10 mg + 40 mg + 25 mg	Yes	No
INN	Amlodipine + Telmisartan + Indapamide		
ATC code	Pending		
Indication	Essential hypertension		
ICD-11 code	BA00 Essential hypertension		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet or capsule	1.25 mg + 10 mg + 0.625 mg	Yes	No
	2.5 mg + 20 mg + 1.25 mg	Yes	No
	5 mg + 40 mg + 2.5 mg	Yes	No
INN	Amlodipine + Perindopril + Indapamide		
ATC code	C09BX01		
Indication	Essential hypertension		
ICD-11 code	BA00 Essential hypertension		
Dosage form	**Strength**	**EML**	**EMLc**
Tablet or capsule	5 mg + 5 mg + 1.25 mg	Yes	No
	10 mg + 5 mg + 1.25 mg	Yes	No
	5 mg + 10 mg + 2.5 mg	Yes	No
	10 mg + 10 mg + 2.5 mg	Yes	No

Among the few currently available triple drug FDCs, there are multiple dosage options per product. This variety of dose options within each FDC product addresses potential concerns about the need for choice and flexibility to lower BP to different degrees and address specific co-morbidities and adverse effects concerns. At the same time, not all possible dose combinations are recommended, to reduce complexity of purchase and supply for countries. Also, of relevance to this topic is that in 2014, the United States FDA mentioned that *"over the last decade, the Agency has actively discouraged antihypertensive monotherapy and combination doses with effects that were very close together, considering them a nuisance to physicians seeking to get patients to goal"* (19).

The safety and efficacy of the proposed FDCs have not been established in paediatrics, and the prevalence of hypertension is far lower than in adults; hence, their use in children is not recommended (20-24). The proposed medicines are therefore only recommended for treatment of hypertension in adults only. Therefore, the proposal is to add triple FDCs antihypertensive medicines to the WHO model list of essential medicines (EML) for adults but not the list for children (EMLc).

Section 5: Listing as an individual medicine or as representative of a pharmacological class.

The following main classes of anti-hypertensive medications are recommended as preferred by the WHO 2021 and other hypertension guideline: Angiotensin Converting Enzyme Inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB); long-acting dihydropyridine Calcium Channel Blocker (CCB); Thiazide or Thiazide-like Diuretic

Hence this application requests two sets of three-drug 'square box' inclusions, taken as representative of the classes comprising triple drug FDCs:

1. **Valsartan + Amlodipine + Hydrochlorothiazide:** C09CA Angiotensin II receptor blockers (ARBs), plain; C08CA dihydropyridine CCB derivatives; and diuretics that are thiazides (C03A eg. hydrochlorothiazide, chlorothiazide) or thiazide-like (C03BA eg. indapamide, chlorthalidone)

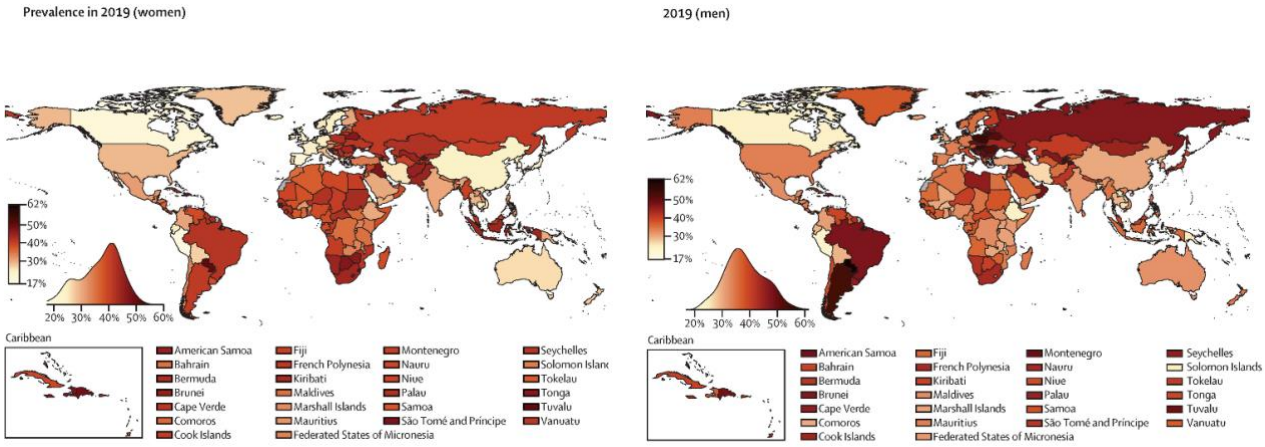
2. **Perindopril + Amlodipine + Indapamide:** C09AA ACEi, plain; C08CA dihydropyridine CCB derivatives; an d diuretics that are thiazides (C03A, hydrochlorothiazide, chlorothiazide) or thiazide-like (C03BA indapamide, chlorthalidone)

Please note that thiazide and thiazide-like diuretics are regarded by WHO as therapeutically equivalent, and so option 1 above should be regarded as ARB+CCB+thiazide/thiazide-like and option 2 should be regarded as ACEi+CCB+thiazide/thiazide-like

Section 6: Information supporting the public health relevance.

Epidemiological information on disease burden and treatment gaps

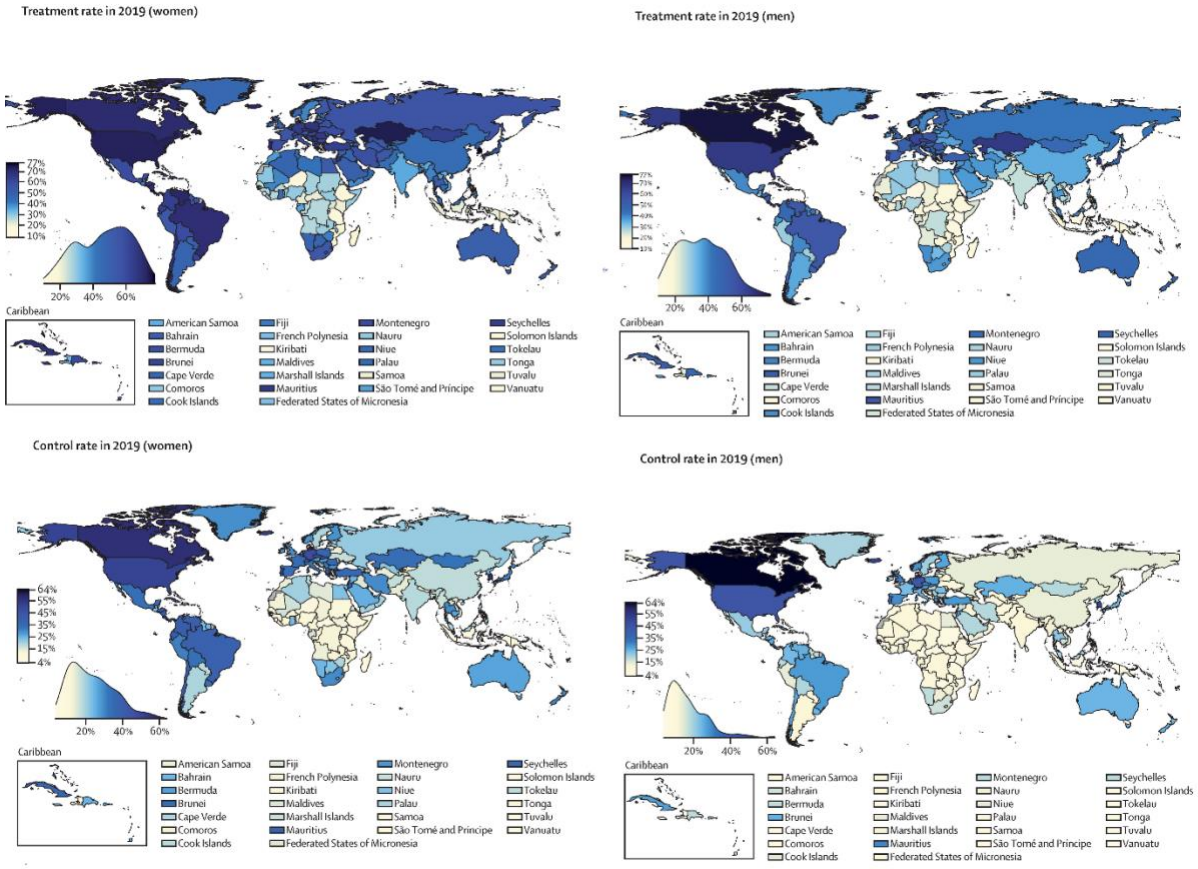
Figure 1: Worldwide levels of high blood pressure (1)



[1]NCD Risk Factor Collaboration (NCD-RisC). 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 Sep 11;398(10304):957-980

Globally, about one in every three adults (aged 30-79 years) lives with hypertension (9), and hypertension prevalence is above 25% in most of the world's countries, including LMICs (**Figure 1 and 2)**. The benefits of BP lowering in reducing cardiovascular (CV) events are well established (25), and there is clear evidence that greater BP reduction confers larger reduction in CV events (26-28). Overall, in all people living with hypertension, BP control (<140 and <90 mmHg) is reported at 21% globally and as low as 10% in LMICs (1, 29) **(Figure 2)**. There are substantial disparities among countries: high-income countries had almost double the proportions of awareness (66% versus 39%) and treatment (52% versus 30%) and three times the proportion of control among patients with hypertension (31% versus 10%) in comparison with low- and middle-income countries (29).

Figure 2*: *Gender-specific treatment and control rates among people with raised blood pressure [29].



Treatment is defined as self-reported antihypertensive medication use among those with hypertension. Control is defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg.

[28]NCD Risk Factor Collaboration (NCD-RisC). 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 Sep 11;398(10304):957-980

Importance of triple FDC therapy to achieve WHO recommended goals for treatment of hypertension

In WHO-HEARTS programs in LMICs, median facility-based hypertension control is 48% (30). This modest facility-based (i.e., only represents treated patients retained in care) control rate is in large part due to the fact that most treated patients only receive monotherapy, despite the 2021 WHO hypertension treatment guidelines recognizing that the many patients require a combination of two or more medicines to achieve BP control, especially when pre-treatment BP is 20 mmHg systolic or 10 mmHg diastolic from the treatment goal (31). Based on HEARTS program experience in India and other countries, about 35% of treated HTN patients are on two or more antihypertensive medicines, and approximately 10% are on three or more medicines.(18) Despite the advantage of dual combination therapy, there are several limitations. Even in randomized trials, dual combination therapy typically achieves BP control in <60% of the participants (17).

The importance of achieving and maintaining lower BP targets substantially increases the relevance of affordable, effective and safe triple SPCs, since such targets are rarely

possible with monotherapy and often not reached with dual therapy. Recent large outcome trials that have been successful in achieving intervention group targets (which in all cases involved SBP <130mmHg) all utilised an average of 2-3 drugs per person in the intervention group.(14, 15, 32-36) Modern hypertension treatment algorithms, such as those recommended by WHO,(37) also all include triple therapy, usually as a third treatment step, and all recommend FDCs in preference to separate pills, where possible, to improve adherence. The 2024 European Society of Cardiology Guidelines recommend initial low-dose dual followed by low-dose triple therapy for most patients.(38)

Target population(s)

Main Indications:

- For treatment of hypertension in patients with uncontrolled BP despite receiving dual antihypertensive drug therapy

- For treatment of hypertension in patients currently prescribed three antihypertensive medicines provided as separate pills, to reduce pill burden

Secondary indication (for low-dose triple drug FDCs):

- For treatment of hypertension in patients uncontrolled on antihypertensive drug monotherapy or for initial treatment in those with high absolute CVD risk and/or >20/10mmHg from target BP.

Likely impact of treatment on the disease

Inclusion of the proposed triple-drug FDC on the WHO-EML has the potential to significantly and efficiently improve BP control in many patients with hypertension and requiring three or more drug classes to reach control. Absolute impact measured as numbers of CVD events and deaths prevented is expected to be substantially higher in LMICs where most of the patients receive monotherapy and have uncontrolled BP.

Per numbers needed to treat calculations (39), with current projections, it is estimated that with any hypertension treatment, 1 in 125 would have prevented death, 1 in 67 would have prevented stroke and 1 in 100 prevented heart attack (fatal and non-fatal myocardial infarction and sudden/rapid cardiac death), compared to no BP-lowering treatment. Currently, there are no clinical trial meta-analyses comparing the efficacy of three-drug versus two drug BP lowering FDC treatment and using the clinical CVD or mortality outcomes necessary for calculating number needed to treat. From the updated systematic review that we completed as part of the application, using the surrogate outcome of BP control, compared with two-drug therapy, we estimate that one additional individual in every six individuals treated with the triple therapy will achieve BP control. The majority of the trials in the review only included patients with low to moderate risk, implying that patients at high CVD risk would require triple combinations to reach the WHO-recommended systolic blood pressure (SBP)<130 mmHg goal for this group.

Section 7: Treatment details (requirements for diagnosis, treatment and monitoring)

Diagnosis

Diagnosis of hypertension is consistently defined as per current guidelines (international or national). As per the 2021 WHO guidelines, hypertension diagnosis is confirmed when an individual has a clinic SBP of 140 mmHg or higher or a diastolic blood pressure (DBP) of 90 mmHg or higher, verified by at least two measurements taken on separate days. For

those with existing CVD or other risk factors like diabetes or chronic kidney disease, hypertension may be treated at lower BP thresholds, such as an SBP of 130-139 mmHg [2]. Before initiating treatment, it is recommended to conduct laboratory tests to screen for comorbidities and secondary causes of hypertension, if there is no delay in commencing treatment, to ensure a comprehensive understanding of the patient's health status.

General approach to hypertension treatment

The treatment of hypertension involves both lifestyle modifications and pharmacological interventions. Lifestyle changes include reducing salt intake, increasing the consumption of fruits and vegetables, engaging in regular physical activity, and limiting alcohol consumption. For pharmacological treatment, the WHO recommends starting with medicines from one or more of three classes of medications: thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-receptor blockers (ARBs), and long-acting calcium channel blockers (CCBs). In many cases, combination therapy using medicines from all three of the recommended classes is preferred, especially using FDCs, to improve adherence and efficacy. The choice of medication and treatment strategy should be tailored to the individual, considering their specific health conditions and risk factors.

Pharmacologic treatment decisions are guided by the local jurisdiction's simple treatment protocol and the patient's most recent BP. As stated above, the two main indications for triple drug FDC antihypertensive combinations are 1) treatment of uncontrolled BP among HTN patients taking two medication classes (step-up therapy) and 2) shift from separate pills to FDC as single pill for hypertension patients with BP controlled on three medication classes (replacement therapy). A secondary indication for triple drug FDCs is initial pharmacologic therapy or as step-up for patients with uncontrolled BP on one medication.

Monitoring of pharmacologic treatment

BP response to treatment and BP control status can be assessed using a standard BP measurement protocol in the clinic, home, or community setting. When initiating pharmacological therapy, laboratory tests should be performed prior to treatment to screen for comorbidities and secondary hypertension, provided that such testing does not delay or impede the start of treatment. When these tests are available, recommended tests include serum electrolytes and creatinine, lipid panel, thyroid stimulating hormone, HbA1C or fasting glucose, urine dipstick, and electrocardiogram (ECG). It is recommended to have monthly follow-up visits after starting or changing antihypertensive medications until the target BP is reached. Once BP is controlled, follow-up intervals can be extended to every 3-6 months.(39)

Treatment strategy with triple drug antihypertensive combinations

Treatment with an FDC requires considerations of recent BP lowering drug treatment and the magnitude of baseline BP elevation and therefore BP lowering required to reach the patient's goal BP. Adjustment of the existing BP lowering treatment may be needed. The FDC should be taken at about the same time every day as advised by the treating health care provider.

In patients receiving diuretic therapy electrolyte abnormalities, orthostatic hypotension or dizziness may occur following the initial dose of an FDC, particularly due to volume/salt depletion with diuretic therapy. In the elderly (age ≥75 years), although reported BP responses were like that in younger patients, it is recommended that the proposed FDC should be used after considering BP response and renal function. Dose should be selected cautiously, preferably starting with the low dose of FDC. Any dose versions of the proposed

FDC are not recommended in patients with severe renal impairment. In patients with mild-to-moderate renal impairment (eGFR 30-59 ml/min/1.73m^2) the FDC can be used after titration of the component medicines. FDCs are not indicated for the treatment of renovascular hypertension.

Whilst the WHO's 2021 hypertension treatment guidelines did not cover initial assessment of risk for serious adverse medication-related events, these risks and approach to assessing them are discussed in detail in American and European hypertension management guidelines (38). Nonetheless, the WHO 2021 guidelines mention "fewer side-effects" associated with combination therapy due to use of lower doses, and also mention that the treatment algorithms are contraindicated in pregnancy, given the fetal toxicity.

Section 8: Review of evidence for benefits and harms

In support of the application, we summarize below the evidence related to triple FDCs of antihypertensive medicines, in terms of efficacy and effectiveness in lowering BP or reducing cardiovascular events and comparative safety assessed.

Efficacy assessed in randomized clinical trials

Evidence supporting use of triple FDC in a single-pill combination compared with receiving triple-drug therapy as separate pills

Rigorous evidence supports the benefit of FDCs combined into a single, daily pill over the same medicines given as separate pills in terms of improved patient medication adherence (40). In a systematic review, nearly 80% of the studies showed significantly increased medication adherence among patients using FDCs, and 88% of the studies showed significant increase in medication persistence(40). Further, for the combinations of olmesartan/amlodipine/hydrochlorothiazide (41) and valsartan/amlodipine/hydrochlorothiazide, relatively better patient adherence to taking medicines conferred by a single pill FDC has been described (42). Improved medication-taking benefits arise for a range of reasons, including simplicity, ease of use and reduced co-pays, which can improve affordability from the patient perspective. This evidence base mirrors that established for FDCs used in other therapeutic areas.

Evidence supporting use of triple FDC among people uncontrolled on dual therapy

Systematic review of BP lowering efficacy of triple versus dual combinations

We conducted an updated systematic review of randomized trials that compared triple combination with dual combination BP lowering medicines. Through searching multiple databases and the United States FDA website until June 2024, we identified 19 randomized, double-blind trials involving 16,322 adult participants with hypertension, that compared triple versus dual combinations of BP lowering medicines over a minimum of 4 weeks and a maximum of 12 weeks. Meta-analyses were conducted using a random-effects model. Baseline BP averaged 162/99 mmHg in trials among people not on treatment, and 150/94 mmHg among people uncontrolled on dual therapy. See **Tables 2 and 3** below.

Table 2: Review of clinical trials assessing BP lowering efficacy of triple vs dual combinations

	Number of trials (participants)	**Effect size (95% CI)**	**P-value**	**I^2 (%)**	**Certainty of evidence (43)**
SBP reduction, mmHg	18 (14,372)	-5.4 (-4.7 to -6.2) mmHg	<0.001	52.73	⊕⊕⊕⊕ High
DBP reduction, mmHg	18 (14,372)	-3.2 (-2.6 to -3.7) mmHg	<0.001	63.61	⊕⊕⊕⊕ High
BP control, %	13 (11,274)	66.8% vs 50.2% (RR: 1.3 [1.2–1.4])	<0.001	69.43	⊕⊕⊕⊕ High

Table 3:Review of clinical trials assessing safety of triple vs dual combinations

	Number of trials (participants)	**Effect size (95% CI)**	**P-value**	**I^2 (%)**	**Certainty of evidence (43)**
Withdrawals due to adverse events (AEs)	16 (13,391)	4.0% vs 3.0% (RR: 1.4 [1.2–1.7])	<0.0001	0	⊕◯◯◯ Very low
Any AE	18 (13,989)	46.8% vs 36.4% (RR: 1.7 [1.5–2.0])	<0.0001	88	⊕⊕◯◯ Low
Treatment related AEs	17 (13,925)	20.7% vs 15.3% (RR: 1.7 [1.4–1.9])	<0.0001	64	⊕⊕◯◯ Low

Trial of triple drug combination versus dual-drug combination as the active control

The most recent randomized trial, and the first evaluating low-dose triple vs dual, published in 2024, enrolled 1385 hypertensive participants (mean age 59 years, ~half females) were recruited in clinical research units based in 7 countries (Australia, Czech Republic, New Zealand, Poland, Sri Lanka, United Kingdom, United States) (44). In a 4-week active run-in, existing medications were switched to a triple drug combination ½ dose (telmisartan 20mg/amlodipine 2.5mg/indapamide 1.25mg). Participants were then randomized in a 2:1:1:1 ratio to continued triple drug combination ½ dose or each possible dual combination of components at ½ doses (telmisartan 20mg/amlodipine 2.5mg, telmisartan 20mg/indapamide1.25mg, or amlodipine 2.5mg/indapamide 1.25mg). At week 6, doses of the assigned combinations were doubled in all groups, unless there was a clinical contraindication. The primary efficacy outcome was mean change in home SBP from baseline to week 12.

At week 12, home BP was lower with standard dose triple drug combination than standard doses of each of the dual combinations. Systolic BP/diastolic BP reductions for the triple drug combination compared to the dual drug (telmisartan 20mg/amlodipine 2.5mg, telmisartan 20mg/indapamide 1.25mg, or amlodipine 2.5mg/indapamide 1.25mg) groups were 2.5/2.1, 5.4/3.4 and 4.4/3.6 mmHg lower, respectively (all p<0.0001). For the same comparisons at week 12 the differences in clinic BP were 4.3/3.5, 5.6/3.7 and 6.3/4.5 mmHg, respectively. All measures of BP control were statistically significantly improved, including for all triple drug ½ dose vs dual ½ dose combination comparisons. Withdrawal

of treatment due to adverse events occurred in 2.0% of the triple drug combination participants and 1.4%, 1.1% and 1.4% of telmisartan/indapamide, telmistartan/amlodipine and amlodipine/indapamide groups, respectively, with none of the differences being statistically significant. The proportion of participants with a serious adverse event in the triple pill, telmisartan/indapamide, telmistartan/amlodipine and amlodipine/indapamide groups, respectively, was 3.1%, 2.5% 2.1% and 2.2%, and with symptomatic hypotension was 5.9%, 4.0%, 1.8%, and 1.4%. This active control efficacy trial demonstrated superior BP reduction and higher HTN control from triple drug combinations compared with dual drug combinations without an increase in risk of clinically significant adverse effects.

The results of this trial were included in the meta-analysis above (page 12).

Evidence supporting use of low-dose triple FDC for initial or early treatment

Trials of low-dose combinations vs usual care for the initial/early treatment of hypertension

We propose the inclusion of low-dose triple combination therapy due to its potential to confer larger BP reduction compared with full dose monotherapy and also lower risk of side effects than with full dose monotherapy.

For this application, we also performed an updated literature search in PubMed and Medline from the date of the last systematic review by Wang et al. in September 2022(45) until September 2024 to identify randomized controlled trials of hypertension low-dose combinations versus usual care and placebo. Trials were included if they compared FDCs of three or more antihypertensive medicines each at less than one standard dose (i.e., the most reported usual maintenance dose recorded by the British National Formulary, Martindale and Monthly Index of Medical Specialties, as defined by Bennett et al (46)), with usual care, defined as clinician choice of therapy with ability to choose multiple different medicines and doses according to treatment response. There were four trials totaling 1,648 participants that compared low dose FDC versus usual care **Table 4** (47-50).

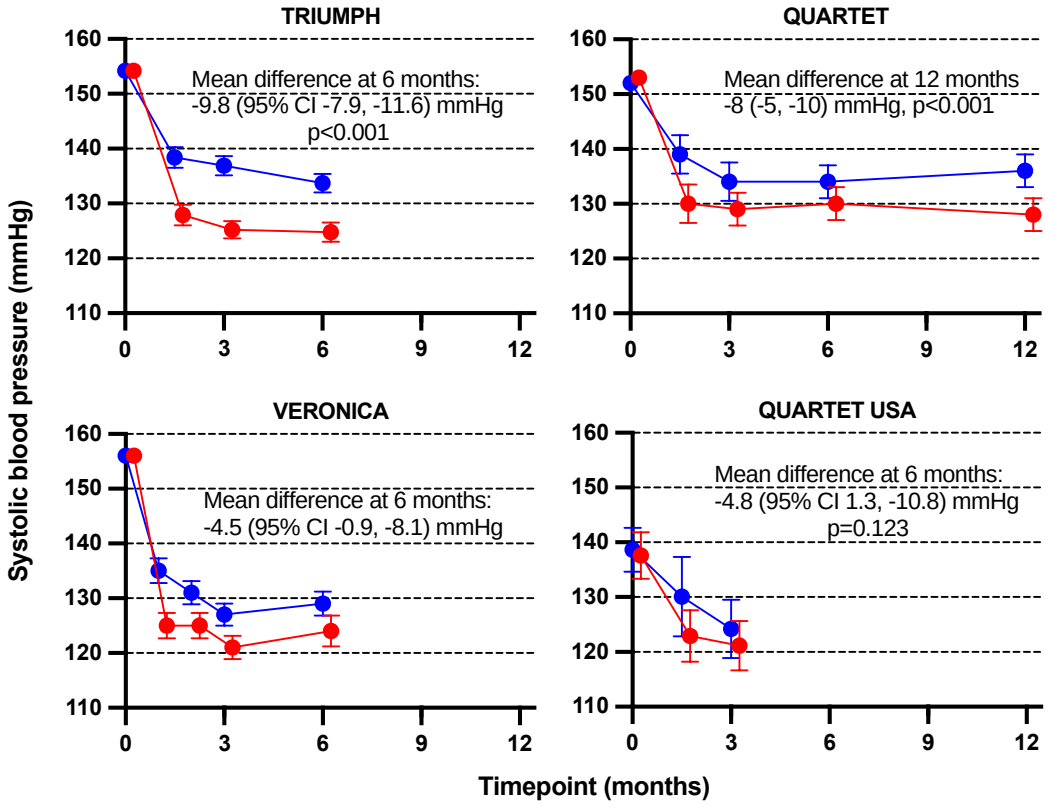
Table 4: Characteristics of previous trials of low dose triple combinations vs usual care

Trial name	No. pts	Mean age (years)	Female (%)	Proportion receiving monotherapy at baseline	Low dose combination components	Standard dose options for low dose combination	Comparator(s)	Baseline BP (mmHg)	Timepoint of first BP assessment	Timepoint of final BP assessment
TRIUMPH(49)	700	56	58	287 (41%)	Telmisartan + amlodipine + chlorthalidone	Triple half and standard	Usual care with 99% of patients receiving monotherapy between randomisation and first follow-up	154/90	6 weeks	26 weeks
QUARTET(47)	591	59	40	273 (46%)	Irbesartan + amlodipine + indapamide + bisoprolol	Quadruple quarter	Usual care comprising of Irbesartan 150mg as first treatment step	153/89	6 weeks	52 weeks
QUARTET USA(48)	62	52	45	52 (84%)	Candesartan + amlodipine + indapamide bisoprolol	Quadruple quarter	Candesartan 8mg at first follow-up with option to add amlodipine 5mg after 6 weeks	138/84	6 weeks	12 weeks

VERONICA(50)	276	51	54	115 (38%)	Telmisartan + Amlodipine + Indapamide	Triple quarter, half and standard	Usual care starting with amlodipine 5mg or amlodipine 5mg and losartan 50mg	156/97	4 weeks	26 weeks

Upfront use of low-dose combinations achieved significantly greater reductions in SBP at first follow-up visit, which remained superior to usual care at end of follow-up in all trials and was statistically significant in the three largest trials **(Figure 3**). Compared to usual care, low-dose FDC was associated with a greater mean (95% CI) difference in SBP and DBP at final follow-up of -7.2 (-5.2, -9.2) mmHg and -4.0 (-3.3, -4.8) mmHg, respectively. At final follow-up visit, BP control <140/90 mmHg was achieved in 534/668 (80%) patients randomized to low dose FDC compared to 438/670 (65%) patients randomized to usual care (RR 1.22, 95% CI 1.14-1.30).

Figure 3: Mean clinic systolic blood pressure levels with low dose combinations vs usual care with clinician guided treatment intensification.



Red lines represent low dose triple drug FDC therapy, blue represents usual care. Circles and error bars represent mean and 95% confidence intervals, respectively. Both treatment arms allowed for physician-directed treatment intensification based on follow-up BP measures and tolerability. P-values displayed for the comparison of mean SBP at final follow-up between LDC and usual care arms as reported in each trial.

In predefined subgroup analyses of the four trials that compared low-dose FDC and usual care, low-dose FDC was not associated with any significant increase in adverse events (**Table 5**).

Table 5: Adverse effects and tolerability for low dose combination compared to usual care

	low dose combination n/N (%)	**Usual care** n/N (%)	**Effect size** Risk ratio (95% CI)
Withdrawals due to adverse effects	27/831 (3%)	36/821 (4%)	1.03 (0.65, 1.62)
Serious adverse event	36/681 (5%)	24/672 (4%)	1.45 (0.88, 2.40)
Dizziness or symptomatic hypotension	112/799 (14%)	87/791 (11%)	1.27 (0.90, 1.80)
Headache	58/799 (7%)	56/791 (7%)	1.01 (0.71, 1.42)
Musculoskeletal pain	90/831 (11%)	93/821 (11%)	0.96 (0.74, 1.25)
Gastrointestinal discomfort	47/681 (7%)	42/672 (6%)	1.06 (0.72,1.57)
Peripheral oedema	27/649 (4%)	27/642 (4%)	0.97 (0.58, 1.63)

Further information is given below on the two trials conducted in LMICs with low-dose triple FDCs.

The Triple Pill vs Usual Care Management for Patients with Mild-to-Moderate Hypertension (TRIUMPH) pragmatic trial randomized Sri Lankan hypertension patients with uncontrolled hypertension to either once-daily fixed-dose triple combination pill (20 mg of telmisartan, 2.5 mg of amlodipine, and 12.5 mg of chlorthalidone) therapy (n = 349) or usual care hypertension management (n = 351) (49). Participants were recruited from 11 urban, hospital based primary care clinics in Sri Lanka. The primary outcome was proportion with controlled BP (<130/80 mm Hg in patients with diabetes or chronic kidney disease; <140/90 mm Hg in the remainder) at 6 months. Secondary outcomes included mean systolic/diastolic BP difference during follow-up and withdrawal of BP medications due to an adverse event. The triple combination pill increased the proportion achieving BP control vs usual care at 6 months (70% vs 55%, respectively; risk difference, 12.7% [95% CI, 3.2% to 22.0%]; P < .001). Mean systolic/diastolic BP at 6 months was 125/76 mm Hg for triple pill vs 134/81 mm Hg for usual care (adjusted difference in post-randomization BP over the entire follow-up: systolic BP, -9.8 [95% CI, -7.9 to -11.6] mmHg; diastolic BP, -5.0 [95% CI, -3.9 to -6.1] mm Hg; P < .001 for both comparisons, Error! Reference source not found.). There were no significant between-group differences in the proportion of patient withdrawal from BP lowering therapy due to adverse events (6.6% for triple combination pill vs 6.8% for usual care). TRIUMPH demonstrated superior BP lowering effect with triple drug FDC antihypertensive treatment compared with usual care in typical clinic settings of Sri Lanka, but without raising risk of medication-related adverse events.

Practical implications of TRIUMPH were limited due to having two dosing options (half or full doses of all three component medicines), and that neither the triple pill intervention arm nor the usual care arm used a WHO-HEARTS based simple treatment protocol. Lastly, the study design used relatively infrequent visits for medicine dose titration and therefore

did not allow the advantages of the triple medicine combination to be translated into an accelerated time to reach blood pressure control. All these limitations were addressed in the subsequent VERONICA trial.

The primary care practice-based VERONICA trial recruited 300 Nigerian participants with uncontrolled HTN and randomized 300 to a triple FDC protocol using a low dose triple FDC (telmisartan/amlodipine/indapamide 10/1.25/0.625, 20/2.5/1.25 and 40/5/2.5 i.e., triple ¼, ½, and standard doses), with accelerated uptitration (50). Of these 150 were randomized to a standard care protocol that followed the official Nigeria HEARTS hypertension management protocol, starting with standard dose monotherapy and following treatment steps at monthly intervals to achieve target BP <140/90 mmHg: amlodipine 5 mg, then FDC of amlodipine 5 mg + losartan 50 mg, then FDC of amlodipine 10 mg + losartan 100 mg, then FDC of amlodipine 10 mg + losartan 100 mg + hydrochlorothiazide 25 mg. About two-thirds of participants in both arms were treatment-naïve at baseline (54% female; mean age, 52 years; baseline mean home BP, 151/97 mm Hg; and clinic BP, 156/97 mm Hg); the other two-thirds had uncontrolled HTN on monotherapy. The primary effectiveness outcome was reduction in home mean SBP and the primary safety outcome was discontinuation of trial treatment due to adverse events, both from randomization to month six.

At six months' follow up, triple drug FDC protocol compared to standard care protocol achieved significantly greater home SBP reduction (adjusted difference, 5.8 mmHg; 95% confidence interval [CI], 3.6 to 8.0; P<0.001). Clinic SBP was also significantly lowered by triple drug FDC compared with usual care 6 months. (adjusted difference, 4.5 mmHg; 0.9 to 8.1, P <0.001; **Figure 3**)

The triple pill protocol led to >80% clinic-based HTN control by one month of follow up (compared with 55% in the standard protocol group); >80% controlled in the triple pill protocol was sustained up until month six. At final follow-up at month six, clinic BP control was 82% using triple protocol vs 72% in standard care (relative rate, 1.1 [95% CI 1.0, 1.3]) and home BP control (<130/80 mmHg) was 62% vs 28%. These data from the VERONICA trial demonstrated the superior effectiveness of initial low-dose triple drug combination compared with initial monotherapy in a typical primary care setting in Africa, while also demonstrating superior treatment efficiency in the triple pill arm (faster time to control, fewer pills, and fewer clinic visits).

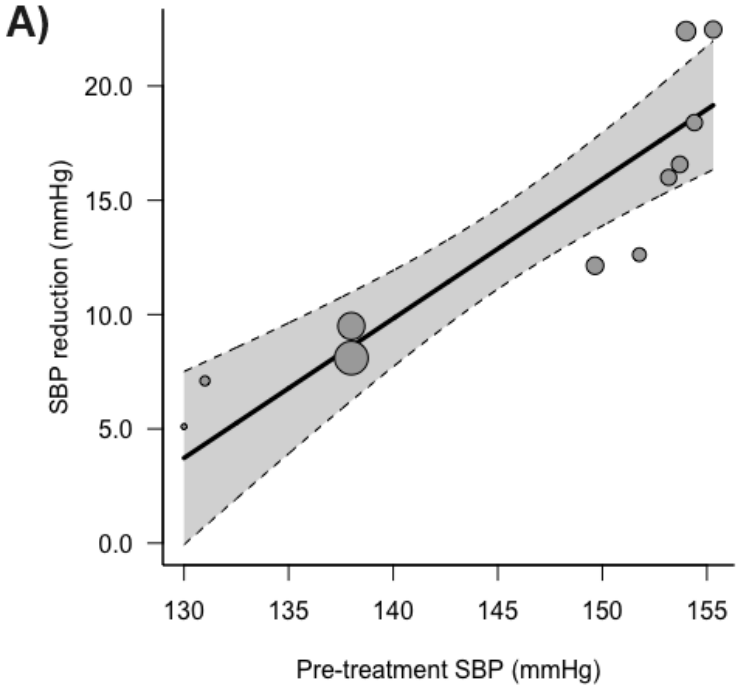
Trials of low-dose triple FDC versus placebo

A 2023 systematic review indicated that low-dose combinations conferred large BP reductions compared to placebo (mean SBP reduction, 18.0 mm Hg; 95% CI, 15.1-20.8) (45). A recent randomized trial of one of the products in the current proposal enrolled 295 hypertensive participants (mean age 51 years, just over half females) from Australia, Nigeria, Sri Lanka, the United States and the United Kingdom into a double-blind placebo-controlled trial of two low-dose triple combination pills [¼ dose (telmisartan 10 mg/amlodipine 1.25 mg/indapamide 0.625 mg) or ½ dose (telmisartan 20 mg/amlodipine 2.5 mg/indapamide 1.25 mg)] with a placebo control. Of all enrolled, 113 were randomized to triple ¼ dose, 119 to triple ½ dose, and 63 to placebo. Placebo-corrected least square mean differences (95% CI) in home SBP at Week 4 were -7.3 mmHg (-4.5, -10.8) for triple ¼ dose and -8.2 mmHg (-5.2, -11.3,) for triple ½ dose; and reductions for clinic BP were -8.0/-4.0 and -9.5/-4.9 mmHg. At week 4, clinic BP control (<140/90 mmHg) was 37%, 65%, and 70% for placebo, triple ¼ dose, and triple ½ dose, respectively (both p<0.001 vs placebo). No participant had a serum sodium

<130/>150mmol/l nor potassium <3.0/>6.0 mmol/l. Serious adverse events were reported by two participants in the placebo and tripe ½ groups and none in the triple ¼ group. The main relevant finding of this placebo-controlled trial was that ¼ and ½ dose triple drug combination pills were effective and safe compared with a placebo control.

Based on our updated systematic search (as described above), in total there are now 7 trials with 12 comparisons of low-dose combinations vs placebo, and **Figure 4** shows the extent of BP reduction is closely dependent on the level of pre-treatment BP. The difference in mean change in SBP reduction was -8.5 (-6.1, -11.0) mmHg for trials with pre-treatment SBP <140 mmHg compared to -17.7 (-15.4, -20.0) mmHg for trials with pre-treatment SBP ≥140 mmHg, with a significant interaction between the two subgroups (p<0.001) (**Appendix 5**). Meta-regression identified a strong relationship between pre-treatment SBP and placebo corrected SBP reduction, with an average 6 mmHg greater SBP reduction per 10 mmHg increase in pre-treatment SBP (R^2 = 1.0, p<0.001)

Figure 4: Low dose combinations vs placebo: meta-regression for blood pressure reduction according to pre-treatment systolic BP



Section 9: Summary of recommendations in current clinical guidelines

Consensus across guidelines for inclusion of triple therapy in treatment algorithms

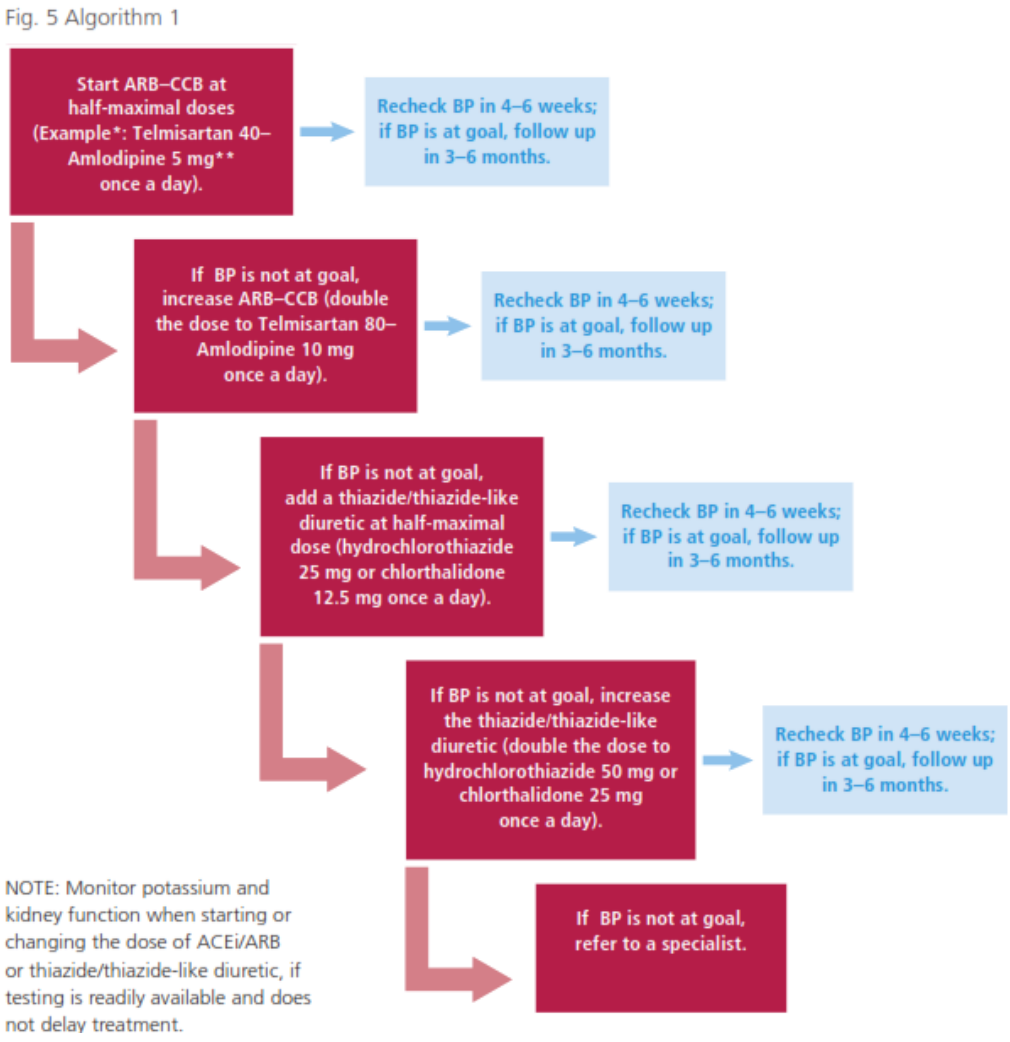
There is broad consensus across all international guidelines that triple therapy should be provided among those who do not achieve BP control with treatment with dual combinations. For example, the 2021 WHO Hypertension guideline recommends three BP-lowering medicines as the 3rd recommended treatment step in Algorithm 1 with initial dual therapy (**Figure 5**) and the 5th recommended step in Algorithm 2 with initial monotherapy. The 2021 WHO guideline recommended that antihypertensive medications used in combination therapy should be chosen from the following three drug classes: diuretics (thiazide or thiazide-like), angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-

receptor blockers (ARBs), and long-acting dihydropyridine calcium channel blockers (CCBs).

The WHO 2021 guideline recommendations and standard treatment algorithms align with the two main indications requested for triple drug antihypertensive FDC in this application, i.e., as "step up" therapy from dual therapy, or as "replacement" therapy for patients already taking three medicines as separate pills.

Based on recent clinical trial evidence regarding the comparative efficacy of low-dose triple medicine combination blood pressure lowering therapy, future guideline development groups may consider adding alternative hypertension treatment protocols starting with initial low-dose triple medicine combination therapy.

Figure 5: WHO 2021 guideline recommendation treatment algorithm (Algorithm 1), including use of triple therapy at the 3rd step



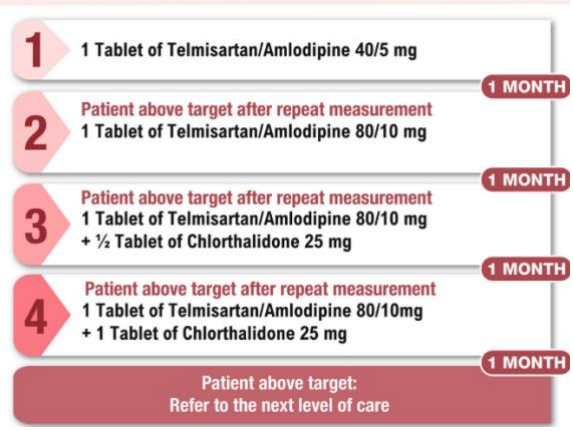
In addition to the 2021 WHO guidelines, all other major international guidelines recommend triple combination therapy for patients who do not achieve BP control with initial dual combination therapy (51) (52). This is increasingly early in treatment lines, given the consensus now that many or most patients should begin treatment with dual combinations. For example, triple therapy is recommended at step 3 and step 2 for the recommended algorithms for HEARTS in America and the 2024 European Society of Cardiology, respectively (Error! Reference source not found.**)**. In a review of 50 simple

standardized treatment protocols available globally, 6% recommend therapy with three medicines at Step 2, 40% at step 3, while 54% recommend it at step 4 or higher (53).

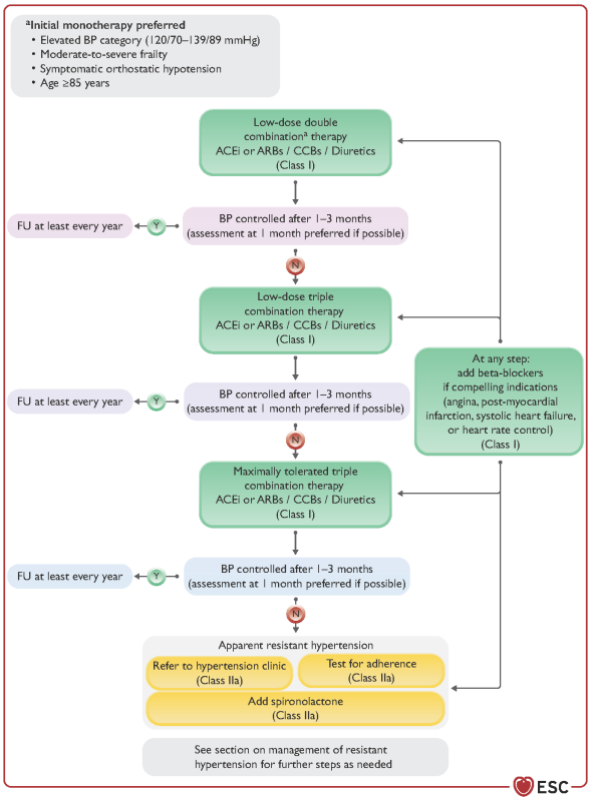
Other major national and regional hypertension management guideline recommendations and standard treatment algorithms align with the two main indications requested for triple drug antihypertensive FDC in this application, i.e., as "step up" therapy from dual therapy, or as "replacement" therapy for patients already taking three medicines as separate pills.

Figure 6: HEARTs in Americas and 2024 European Society of Cardiology Guideline recommendations, including use of triple therapy

HEARTS in Americas recommended algorithm, with triple therapy as 3rd step



2024 ESC Hypertension algorithm, with low-dose triple combination therapy as 2nd step



The 2021 WHO guideline additionally provided two implementation remarks: *"Combination medication therapy may be especially valuable when the baseline BP is ≥20/10 mmHg higher than the target blood pressure"* and *"Single-pill combination therapy improves medication-taking adherence and persistence and BP control."*

Further, the 2021 WHO guidelines also recommended a more intensive systolic BP treatment goal of <130 mmHg for high-risk hypertension patients (those with existing CVD, diabetes, chronic kidney disease, or high calculated ten-year CVD risk). Recent large clinical trials that achieved mean SBP <130mmHg in the intervention groups (12, 14-16, 32, 33, 35) all required an average of 2-3 drug classes per person to achieve this i.e. many or most participants received triple combination therapy. *The recommendation for more intensive medication therapy among high CVD risk patients supports the secondary indication proposed by this application, that is, single pill formulations of triple-drug for treatment of patients with high absolute CVD risk and/or >20/10mmHg from target BP.*

In summary, review of WHO guidelines, the WHO-HEARTS technical package, and standardized treatment protocols along with review of other national and regional guideline recommendations together demonstrates that in all hypertension control programs, a proportion of patients with hypertension require triple therapy to attain BP control. *Taken together, these normative guideline recommendations align with this application's proposed indications for triple drug antihypertensive FDCs.*

Consensus across global and regional guidelines for use of fixed dose combinations in preference to separate pills

The 2021 WHO hypertension treatment guidelines provided a conditional recommendation with moderate certainty evidence for combination therapy, preferably with a single pill combination (to improve adherence and persistence) for adults with hypertension requiring pharmacological treatment. This is consistent with other international guidelines that recommend single pill combinations over separate medicines where possible. For example, the 2024 ESC Guidelines state *"If combination BP lowering therapy is pursued, single-pill combinations are preferred"*.(52) Kenyan hypertension guidelines and Kenya 2023 national essential medicine list include two of the triple-drug FDCs proposed in this application: perindopril+amlodipine+indapamide (at two dose strengths) and telmisartan+amlodipine+hydrochlorothiazide (at one dose strength).

These WHO, regional, and national normative guidance support this application's second main indication for triple drug, single-pill FDC as "replacement therapy" for patients already prescribed three medicines given as separate pills.

Guideline recommendations for use of low-dose triple combinations in initial/early treatment of hypertension

The recommendation in the 2024 European Society of Cardiology for use of triple combination at a second step is noted above.(52) Guidelines have not as yet recommended low-dose triple therapy among those uncontrolled on monotherapy, or for initial treatment among those with high CV risk and/or particularly high BP. In large part this reflects the current absence of products with this approved indication, although noted above at least one product is planned to be available in 2025. There is also relatively recent availability of clinical trials evidence supporting initial triple FDC therapy – with two of the four available published in 2024.

This recent, accumulating evidence of the superior efficacy of low-dose triple-drug FDCs supports this application's secondary indication of triple-drug antihypertensive FDCs for treatment of hypertension in patients uncontrolled on antihypertensive drug monotherapy or for initial treatment in those with high absolute CVD risk and/or >20/10mmHg from target BP.

Section 10: Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

Data on comparative costs are outlined below, showing the triple FDCs can potentially be low-cost: in countries with large domestic manufacturing capacity and competition (the prototypic example being India), the prices of triple FDCs are often comparable to the sum of the prices of the components. However, in many countries triple FDCs are currently unaffordable, a factor potentially limiting widespread access. The theory of change is that

inclusion of triple FDCs in the 2025 WHO EML will act as a stimulus to improve affordability in more regions and countries, thereby increasing the demand and competition to lower prices and open access. One of the products proposed here has been developed with this in mind, and a commitment to provide at as low as possible cost in low-income countries.

Prices of fixed dose combinations versus single agent pills

A cost analysis of the India Hypertension Control Initiative showed that the procurement prices of FDCs are comparable to those of the individual pills in the public sector.(54) For the private sector, the Under Pressure report, developed by the Resolve to Save Lives in collaboration with the Médecins Sans Frontières Access Campaign to identify barriers to affordable antihypertensives in LMICs, found that FDCs were cheaper than the separate agent equivalents in the private sector in countries with larger domestic manufacturing capacity, i.e., Brazil, South Africa, and Philippines. However, the reverse was true for countries with smaller domestic pharmaceutical market, such as Nigeria and Lebanon (18).

Furthermore, FDCs can be more affordable than the same medications as separate pills. A 2020 comparison of FDCs (dual and triple drug combinations) and single agent pills (i.e., equivalent doses of the same medicines sold as separate pills) across different manufacturers in India showed that in the Indian private sector, the lowest prices of both FDCs and the sum of component single agent pills were nearly identical across different manufacturers. Although there were other instances where the triple pill combinations appeared to cost higher than the sum of individual pills, this could be attributed to the very limited number of manufacturers in 2020; the paper reports data from about 2 or 3 brands each for a total of 3 triple drug combinations (55). We report that the number of manufacturers for each triple pill combinations in India is much higher in 2024 (**Table 6**).

Retail prices of the proposed triple FDCs

We conducted a targeted search in India, Kenya, Nigeria, Sri Lanka, US, and China, using available drug databases and online pharmacies, for the retail prices of the proposed products available in the private sector. Median unit prices (in USD) and affordability are shown in Table 6. Cost of a month's supply was calculated assuming single daily dosing for each combination. Affordability was defined using the WHO/Health Action International standards, according to which a drug is "affordable" if the cost of one month's supply is lower than the lowest daily wage of a government worker in that area. Note that these prices do not include pharmacist dispensing fees. Due to combining three medicines in a single pill, pharmacist dispensing fees will be reduced with triple drug single pill combinations as dispensing fees are charged per medicine and increase with separate agent pills.

Table 6: Retail prices and affordability of proposed FDCs in private markets in selected countries

Country	FDC	Dose (mg)	No. Brands	Marketed by	Price/ tab (USD)	Cost for 1 month supply (USD)	Minimum Daily wage (USD)	Number of days' wages
India	Perindopril/ Amlodipine/ Indapamide	4 + 1.25 + 5	1	Servier India	0.23	6.88	3.6	1.9
	Olmesartan/ Amlodipine/ Hydrochlorothiazide	20 + 5 + 12.5	32		0.21	6.18	3.6	1.7
		40 + 5 + 6.25	32	(multiple)	0.21	6.22	3.6	1.7
	Valsartan/ Amlodipine/ Hydrochlorothiazide	80 + 5 + 12.5	1	Globela Pharma	0.47	14.18	3.6	4.0
		160 + 10 + 12.5	1	Torque Pharmaceutcals	0.12	3.61	3.6	1.0
Kenya		5 + 1.25 + 10	1	Servier	1.06	31.82	2.3	13.8

	Perindopril/ Amlodipine/ Indapamide	10 + 2.5 + 5	1	Servier	1.16	34.92	2.3	15.2
		10 + 2.5 + 10	1	Servier	1.25	37.44	2.3	16.3
	Valsartan/ Amlodipine /Hydrochlorothiazide	160 + 10 + 12.5	1	Novartis Pharmaceuticals	1.24	37.30	2.3	16.2
		160 + 5 + 12.5	1	Novartis Pharmaceuticals	0.93	28.04	2.3	12.2
Nigeria	Perindopril/ Indapamide/ Amlodipine	5 + 1.25 + 5	1	Servier	0.46	13.77	1.6	8.6
		10 + 2.5 + 5	1	Servier	0.62	18.56	1.6	11.5
		10 + 2.5 + 10	1	Servier	0.76	22.82	1.6	14.2
	Valsartan/ Amlodipine/ Hydrochlorothiazide	160 + 5 + 12.5	1	Novartis Farmaceutica S.A.	1.11	33.27	1.6	20.7
		160 + 5 + 25	1	Novartis Farmaceutica S.A.	1.11	33.27	1.6	20.7
		160 + 10 + 12.5	1	Novartis Farmaceutica S.A.	0.96	28.86	1.6	17.9
		160 + 10 + 25	2	Novartis Farmaceutica S.A.	0.54	16.13	1.6	10.0
		320 + 10 + 25	1	Novartis Farmaceutica S.A.	1.11	33.35	1.6	20.7
Philippines	Perindopril/ Indapamide/ Amlodipine	5 + 1.25 + 5	1	Servier	0.80	23.89	7.6	3.1
		5 + 1.25 + 10	1	Servier	0.89	26.70	7.6	3.5
		10 + 2.5 + 10	1	Servier	0.92	27.63	7.6	3.6
	Olmesartan/ Amlodipine/ Hydrochlorothiazide	20 + 5 + 12.5	1	Ajanta Pharma	0.33	9.88	7.6	1.3
		40 + 5 + 12.5	1	Ajanta Pharma	0.55	16.42	7.6	2.1
		40 + 10 + 12.5	1	Ajanta Pharma	0.56	16.68	7.6	2.2
	Valsartan + Amlodipine + Hydrochlorothiazide	160 + 5 + 12.5	1	Novartis	0.45	13.61	7.6	1.8
		160 + 5 + 25	1	Novartis	0.49	14.68	7.6	1.9
		160 + 10 + 12.5	1	Novartis	0.46	13.80	7.6	1.8
		160 + 10 + 25	1	Novartis	0.52	15.48	7.6	2.0
		320 + 10 + 25	1	Novartis	0.61	18.42	7.6	2.4

A 2024 cost-benefit analysis using the Pharmaceutical Benefits Scheme data in Australia, reported that single pill combinations always cost less than the same medicines sold separately. Single pill combinations resulted in cost savings of 30% on average for patients and up to 26% for the government. Further, the mean cost per mmHg SBP reduction was 27% lower when using single pill combinations compared to free-drug combinations. For triple drug combinations, there is a marginal cost increase of AUD 10.3 for the government, which is however accompanied by a substantial cost saving for out-of-pocket payment by the patient (AUD 17.9–26.7) (56).

Evergreening strategies and FDC price points

FDCs have in numerous instances been used as 'evergreening' strategies, in efforts to reduce price erosion once a molecule comes off patent. However, there are now many different dual combination medicines that are available at low cost. Once established on the market, there is potential for cost saving from use of triple combination therapy compared to the cost of separate products, both from direct medication costs and reduced script fees from a triple combination (56).

Cost and Cost-effectiveness

The retail drug prices need to be contextualized within the potential cost-savings from improved hypertension control due to improved compliance (57-59), faster time to BP

control leading to fewer total clinic follow up visits (60, 61), and a more streamlined procurement and supply chain process owing to fewer pills to move through the system.

In a meta-analysis (62) published in 2011, the annual total health care costs from 44,336 patients in all included observational studies (n = 7) were lower for patients treated with FDC compared to individual monotherapy for hypertension (mean pooled difference -1357.01 USD; 95% CI -1935.49 USD, -778.53 USD). An analysis using data from the 2004 Medical Expenditure Panel Survey in the United States demonstrated that total monthly prescription expenditures were lower for 23 of 27 FDC medications examined compared to equivalent doses of separate individual medicines (63) (mean decrease in monthly total costs $20.89, 95% CI $20.10, $21.68). Using pharmacy claims data in Japan, a study demonstrated transitioning to FDC therapy from separate medicines was associated with an annual saving of $112 for patients (64). The cost savings of FDC therapy for patients also translate to the larger health system. In Canada, 60-100% of patients receiving two separate medicines transitioning to FDC therapy would lead to an estimated yearly cost-saving of $27 to $45 million (65).

Numerous cost-effectiveness analyses have been conducted showing the cost-effectiveness of hypertension treatment overall and comparing and contrasting different options for targeting therapy. An accepted cost-effectiveness threshold is <3 times GDP per quality-adjusted life year (QALY), and therefore what is considered cost-effective in low-income countries is quite different to middle-income countries (66). In China, India and South Africa risk based approaches to BP lowering therapy have been shown to be cost-effective by targeting those who would benefit most (67-69). These strategies often require a greater number of BP lowering medicines than the treat-to-target approach (67-69). FDCs become the dominant strategy in two scenarios:

1. If they were less costly than purchasing the individual components for those people who require more than one drug (58).
2. By providing superior efficacy at equivalent cost to monotherapy, for those undertreated on monotherapy.

With approximately equal efficacy and safety of standard doses of monotherapy in the major BP lowering classes,(70) the most cost-effective choice will be the least-expensive option.(71) However, a combination that provides greater efficacy with similar safety and cost will be the preferred choice.

The economic evaluation of the TRIUMPH trial in Sri Lanka, showed that when a triple pill costs USD 0.16 per pill, the triple-pill strategy, compared with usual care, the cost was estimated at USD 7·9 (95% CI 6·6–11·8) per participant reaching BP targets at 6 months, and the incremental cost-effectiveness ratio was USD 2842·8 (-28·7–5714·2) per disability-adjusted life year (DALY) averted over a 10-year period incremental to usual care. Thus, using a conventional willingness-to-pay threshold, the triple-pill strategy was cost-effective for the initial or early treatment of patients with mild-to-moderate hypertension.(72)

Implications on cost of FDC for hypertension if added to WHO EML

In summary, triple drug combinations can potentially be cost effective from health system and patient perspectives through superior efficacy, equivalent safety, fewer healthcare visits to reach BP control, streamlined supply chains, and lower pharmacy dispensing fees.

Given the large and growing global burden of hypertension and the increasing and political attention to non-communicable diseases, addition of triple FDC for hypertension as a WHO essential medicine prompts other nations to follow, thereby reducing overall costs for patients and governments – while allowing more people to be treated.

In discussing implications of EML listing, Magrini et al (73) indicated that:
"*Previous expert committees have recognized the message that comes with identifying a medicine as essential. In some cases, medicines have been included in the core list to*

underscore their importance, for example, antiretrovirals in 2002.5 In other cases, the model list has been used to stimulate the entry of new manufacturers for products that are not widely available, such as with zinc sulfate in 2005 and rectal artesunate in 2009. Inclusion of effective but expensive medicines in the model list may also focus the attention of all stakeholders on the need to increase affordability and access to essential medicines."

The addition of FDC for hypertension to the WHO EML is an example, in our view, where reduced costs will be a consequence, not a precondition, to listing. As with most medicines, listing of triple FDC for hypertension in the WHO EML leads to more countries listing them in their national EMLs or formularies, and subsequently the FDCs come under price control and are included in the reimbursement mechanisms. Listing of triple FDCs could stimulate new manufacturers of products and sharpen attention on FDC costs, as seen for FDC for tuberculosis and HIV/AIDS (74).

Section 11: Regulatory status, market availability, and pharmacopeial standards

The market availability of the proposed FDCs is outlined in **Table 7** below. However, numerous countries do not have all the options listed, which supports the rationale for a square box listing for each FDC, since alternative acceptable options have similar dose intensity and are widely available. Amlodipine/Telmisartan/Indapamide is not yet available in any country. It is included in this application since it will be the first low-dose triple combination on the market, if approved by regulatory authorities, with an ongoing FDA review and submissions in multiple other countries including Nigeria, other countries in Africa and Sri Lanka planned in 2025 and onwards.

A sample of countries in which the products are currently available is given in the table below – this is not a comprehensive list, given the lack of a freely available data source that has a comprehensive list of marketed medicines by country.

Table 7: *Market Availability of proposed triple drug FDCs in the United States, Europe, Canada and other countries*

Combinations	**Country**
Amlodipine/Valsartan/HCTZ	United States of America
	Multiple countries in Europe (75)
	Australia
	Argentina
	India
	Sri Lanka
	Nigeria
	Kenya
	Philippines
Amlodipine/Perindopril/Indapamide	Multiple countries in Europe (76)
	Argentina
	Mexico
	India
	Nigeria

	Kenya
	Philippines
Amlodipine/Olmesartan/Hydrochlorothiazide	Multiple countries in Europe (77)
	Mexico
	Australia
	India
	Kenya
	Philippines

Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

All the components of the proposed FDCs (Amlodipine, HCTZ, indapamide, perindopril, olmesartan, telmisartan, valsartan) are available in the following pharmacopeia: British Pharmacopoeia, The United States Pharmacopoeia, The European Pharmacopoeia, Indian Pharmaceopoeia.

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***Appendix 1**: Global hypertension awareness, treatment, & control by sex and country (2019)*

	Hypertension (%)		Detection/ awareness (%)		Treatment (%)		Control (%)	
	Women	***Men***	***Women***	***Men***	***Women***	***Men***	***Women***	***Men***
Central and Eastern Europe								
Central Europe								
Albania	40.8 (32.7-48.9)	42.6 (33.8-51.7)	54.4 (41.1-67.0)	28.5 (17.9-40.7)	43.7 (29.7-57.7)	19.3 (10.7-30.2)	11.5 (4.6-21.9)	5.3 (1.9-10.8)
Bosnia and Herzegovina	41.3 (30.2-53.2)	46.9 (34.4-59.8)	64.5 (48.0-79.3)	48.2 (32.3-64.3)	56.7 (37.5-74.7)	42.0 (25.4-59.4)	21.5 (6.5-43.4)	11.7 (3.0-26.5)
Bulgaria	40.7 (26.9-55.6)	49.4 (33.0-66.0)	71.1 (48.2-89.3)	56.8 (32.3-79.6)	60.4 (31.7-84.4)	45.2 (20.0-71.8)	28.1 (6.7-59.7)	18.4 (3.7-43.8)
Croatia	45.3 (35.0-56.2)	51.4 (40.3-62.9)	78.9 (63.4-90.2)	70.3 (54.3-83.8)	62.1 (45.3-76.8)	46.2 (30.6-61.8)	24.7 (9.9-44.4)	14.6 (5.1-29.5)
Czechia	34.0 (27.3-41.2)	49.1 (41.4-56.9)	78.3 (68.7-86.5)	69.5 (59.3-79.1)	68.2 (56.1-78.5)	59.1 (47.8-69.9)	42.4 (27.4-58.2)	30.7 (18.8-44.4)
Hungary	40.9 (27.5-56.0)	55.9 (41.2-70.7)	71.2 (47.9-89.2)	51.9 (32.7-70.7)	60.2 (32.9-83.4)	46.0 (25.9-66.6)	28.3 (6.8-58.5)	18.2 (4.9-40.1)
Montenegro	40.8 (26.9-55.8)	49.5 (33.7-66.2)	71.3 (48.2-89.0)	56.9 (33.3-78.9)	60.4 (32.4-84.2)	45.0 (20.6-71.2)	28.5 (6.8-58.6)	18.2 (3.6-42.8)
North Macedonia	40.7 (27.4-55.7)	49.4 (33.6-65.5)	71.5 (47.5-89.1)	57.0 (32.5-78.6)	60.6 (32.4-84.3)	45.2 (19.6-71.8)	28.1 (6.7-59.7)	18.3 (3.5-43.4)
Poland	42.7 (35.5-50.1)	55.5 (46.9-64.2)	74.0 (64.0-82.7)	64.8 (54.4-74.7)	67.6 (56.4-77.4)	56.2 (44.7-67.5)	37.4 (23.0-52.9)	28.3 (16.9-41.5)
Romania	43.9 (35.1-52.8)	52.6 (43.1-62.4)	74.6 (61.8-85.4)	61.9 (48.8-74.3)	65.7 (50.8-78.9)	53.3 (39.4-66.7)	36.6 (20.3-55.0)	23.2 (11.9-38.0)
Serbia	42.1 (32.4-52.1)	49.9 (38.3-61.3)	74.5 (60.2-85.8)	58.6 (44.1-72.2)	67.7 (51.2-81.7)	49.7 (34.0-65.2)	31.3 (13.6-53.3)	19.5 (7.6-36.3)
Slovakia	38.0 (27.6-49.3)	47.4 (35.8-59.0)	78.1 (62.0-90.0)	67.6 (51.5-81.8)	69.9 (51.8-84.9)	58.5 (40.6-74.6)	40.6 (18.7-64.9)	30.0 (12.8-51.7)
Slovenia	40.7 (26.9-55.2)	49.6 (33.2-66.2)	71.1 (47.7-88.8)	57.0 (32.7-79.2)	60.2 (31.2-84.6)	45.4 (21.2-71.8)	28.4 (6.8-59.0)	18.3 (3.6-43.2)
Eastern Europe								
Belarus	46.6 (38.1-55.3)	51.6 (41.9-61.1)	75.3 (62.8-85.7)	60.6 (46.5-73.4)	56.6 (41.0-71.2)	37.6 (24.1-51.6)	13.7 (5.6-25.9)	6.6 (2.3-13.3)
Estonia	34.2 (23.6-46.2)	45.9 (32.9-59.2)	55.6 (36.7-73.3)	47.1 (30.6-63.7)	41.8 (23.4-62.1)	35.9 (19.4-54.1)	18.9 (5.6-39.3)	13.0 (3.4-28.9)
Latvia	38.9 (27.3-51.6)	48.9 (34.5-63.0)	72.8 (55.9-86.4)	63.1 (44.4-79.9)	57.3 (36.4-76.1)	44.5 (25.7-63.9)	19.9 (5.5-43.2)	14.8 (4.0-32.7)
Lithuania	42.0 (30.2-55.0)	54.0 (39.5-67.8)	74.1 (58.9-86.6)	64.7 (47.2-80.2)	52.9 (32.5-72.3)	37.3 (20.2-56.6)	15.8 (3.6-36.4)	9.9 (2.0-25.3)
Moldova	46.9 (35.4-58.6)	49.3 (37.1-61.5)	64.5 (46.7-79.8)	53.8 (37.2-69.2)	41.6 (24.5-59.8)	31.2 (17.3-47.8)	9.1 (2.2-22.1)	7.4 (1.9-17.2)
Russian Federation	41.2 (33.3-49.3)	47.3 (38.2-56.3)	80.9 (71.7-88.4)	67.0 (56.1-77.1)	57.0 (42.7-69.9)	42.6 (30.6-54.8)	21.4 (10.6-35.2)	14.1 (6.6-24.5)
Ukraine	41.6 (34.4-49.3)	44.5 (36.2-53.1)	73.1 (62.4-82.5)	54.0 (41.4-66.4)	58.9 (45.2-71.5)	36.0 (24.5-48.8)	17.3 (8.7-28.3)	10.1 (4.5-18.2)

Central Asia, Middle East and North Africa								
Central Asia								
Armenia	46.2 (36.9-55.5)	48.5 (38.0-58.9)	44.5 (29.9-59.0)	35.6 (22.7-48.8)	32.9 (19.7-47.5)	22.5 (11.9-35.0)	10.1 (3.3-20.7)	7.3 (2.3-15.6)
Azerbaijan	42.1 (33.4-51.3)	39.6 (30.6-48.8)	62.9 (48.6-75.8)	46.5 (33.6-59.6)	49.6 (34.6-64.4)	32.5 (20.5-45.9)	17.8 (7.8-30.9)	8.8 (3.5-17.2)
Georgia	42.3 (33.7-51.4)	46.5 (36.6-56.3)	68.4 (54.8-80.4)	60.1 (47.4-72.0)	54.0 (39.2-67.8)	41.0 (27.9-54.5)	20.5 (9.1-35.3)	13.1 (5.5-24.3)
Kazakhstan	42.5 (34.9-50.3)	40.9 (32.4-49.6)	86.4 (79.0-92.4)	80.3 (71.3-87.7)	74.3 (62.6-84.3)	65.7 (53.6-76.9)	34.5 (20.7-49.9)	25.4 (14.4-39.0)
Kyrgyzstan	43.2 (33.5-53.7)	38.1 (28.2-48.6)	61.1 (44.5-75.8)	45.8 (31.0-60.3)	49.0 (33.0-64.8)	30.8 (17.7-45.8)	11.3 (3.3-24.9)	8.7 (2.5-19.4)
Mongolia	40.7 (33.6-48.1)	45.0 (37.3-52.7)	76.8 (66.6-85.2)	63.9 (54.1-73.1)	63.8 (51.6-74.9)	45.7 (34.7-56.9)	32.7 (20.4-46.8)	18.7 (10.7-29.0)
Tajikistan	42.8 (35.3-50.4)	50.9 (40.8-61.6)	55.4 (42.0-67.9)	39.9 (26.6-53.9)	43.2 (30.2-56.5)	23.3 (12.6-36.6)	9.8 (4.2-18.4)	5.3 (1.5-12.0)
Turkmenistan	40.2 (32.9-47.7)	37.6 (30.1-45.6)	64.7 (53.0-74.9)	52.8 (41.4-63.9)	52.7 (40.3-65.1)	38.2 (26.8-50.8)	13.9 (6.5-24.4)	8.7 (3.7-16.0)
Uzbekistan	44.6 (37.3-52.2)	46.7 (38.6-55.1)	62.9 (51.5-73.5)	44.0 (33.4-54.9)	53.0 (40.1-65.5)	33.6 (23.3-44.8)	21.7 (12.7-33.0)	11.3 (5.8-18.8)
Middle East and North Africa								
Algeria	37.4 (29.6-45.7)	35.0 (26.6-44.2)	59.6 (46.3-72.3)	40.3 (28.6-52.9)	47.9 (34.1-61.6)	30.1 (19.2-42.0)	20.4 (9.8-34.4)	11.1 (4.6-20.5)
Bahrain	35.3 (23.5-49.2)	40.1 (26.4-55.2)	61.1 (38.1-81.8)	47.0 (24.9-69.6)	51.2 (24.8-76.8)	37.6 (16.0-62.6)	24.5 (5.5-52.6)	16.4 (3.4-39.5)
Egypt	40.7 (33.6-48.3)	35.6 (28.3-43.4)	61.4 (50.2-71.5)	43.8 (32.9-54.5)	52.2 (40.2-64.1)	34.6 (24.7-45.3)	22.9 (12.4-36.0)	14.2 (7.4-23.6)
Iran	25.8 (22.5-29.3)	26.6 (22.7-30.7)	69.2 (62.4-75.7)	49.0 (42.3-55.9)	57.9 (50.0-65.2)	37.6 (30.7-44.5)	29.8 (22.2-38.1)	18.6 (13.2-24.8)
Iraq	47.7 (37.3-58.2)	48.4 (37.7-59.4)	66.6 (51.1-79.9)	55.9 (41.2-69.9)	48.3 (31.6-64.4)	38.7 (24.7-54.3)	15.2 (5.5-28.7)	11.3 (4.2-22.2)
Jordan	35.7 (29.9-41.7)	39.6 (33.1-46.5)	71.7 (62.2-79.9)	58.8 (49.6-67.9)	66.0 (56.0-75.0)	51.5 (41.7-61.2)	35.9 (24.1-48.5)	28.7 (19.3-39.3)
Kuwait	35.2 (26.8-44.3)	43.5 (33.9-53.2)	73.4 (60.4-83.7)	57.9 (46.0-69.7)	66.7 (53.3-78.8)	51.2 (38.7-63.7)	38.6 (21.4-57.0)	27.2 (14.3-43.1)
Lebanon	34.2 (26.5-42.4)	42.1 (33.1-51.6)	61.3 (48.2-72.8)	48.9 (36.7-61.2)	54.6 (41.3-67.5)	43.6 (31.2-56.8)	31.8 (17.7-48.1)	23.0 (12.0-36.4)
Libya	39.4 (28.2-51.0)	45.9 (33.1-59.0)	56.6 (37.9-73.6)	39.5 (24.0-56.1)	43.1 (23.9-62.2)	28.1 (14.3-44.4)	15.1 (4.0-33.7)	7.6 (1.6-19.6)
Morocco	35.6 (27.7-44.2)	35.0 (26.5-44.3)	51.5 (37.5-65.6)	33.8 (21.7-47.2)	36.7 (23.1-51.6)	20.3 (11.2-31.5)	13.5 (5.8-24.6)	6.4 (2.2-13.0)
Occupied Palestinian Territory	37.4 (26.9-49.1)	40.7 (29.3-52.8)	53.2 (36.3-70.2)	49.6 (34.0-66.5)	50.7 (32.9-69.3)	47.1 (30.1-64.7)	20.7 (6.6-41.9)	17.7 (6.2-35.1)
Oman	38.8 (30.6-47.3)	48.3 (38.9-57.8)	50.7 (37.6-63.6)	35.9 (25.3-47.4)	44.9 (31.9-58.2)	30.4 (20.3-41.9)	19.9 (9.8-33.1)	11.3 (5.3-19.7)
Qatar	37.7 (28.0-48.3)	41.6 (30.5-53.0)	67.3 (52.0-80.7)	54.6 (39.6-69.1)	60.4 (44.0-75.7)	47.8 (31.6-63.6)	32.5 (14.5-54.7)	21.2 (8.2-39.1)
Saudi Arabia	30.2 (21.4-40.1)	36.3 (26.6-46.7)	60.1 (42.2-76.3)	46.8 (30.4-63.3)	49.5 (30.6-68.3)	37.0 (21.1-54.3)	25.6 (11.1-44.8)	19.0 (7.8-34.5)
Syrian Arab Republic	39.8 (27.7-53.2)	42.4 (29.0-56.5)	60.7 (36.3-81.3)	47.1 (25.2-70.1)	50.8 (24.3-76.5)	37.7 (15.9-63.7)	24.5 (5.6-53.5)	16.6 (3.5-39.3)
Tunisia	34.8 (25.6-45.0)	34.5 (24.7-45.5)	53.5 (39.2-67.5)	36.4 (23.9-50.5)	43.2 (27.4-59.7)	29.6 (17.6-43.4)	18.5 (6.5-36.2)	10.3 (3.4-21.2)
Turkey	34.4 (27.3-41.8)	30.8 (24.2-38.3)	69.4 (57.3-79.7)	53.1 (41.4-63.7)	63.8 (51.7-74.4)	50.6 (39.3-61.3)	35.9 (22.0-51.6)	28.2 (16.8-41.6)
United Arab Emirates	34.5 (26.9-42.4)	43.9 (35.3-52.9)	52.5 (39.6-65.2)	40.5 (29.3-52.2)	45.6 (32.4-59.0)	35.0 (24.3-46.5)	24.6 (13.2-38.6)	18.3 (9.9-29.2)

Yemen	29.6 (18.8-42.9)	29.1 (18.5-41.4)	49.3 (30.2-68.4)	40.6 (24.1-58.4)	39.3 (20.7-59.9)	33.6 (18.1-51.6)	19.8 (5.6-41.6)	13.1 (3.3-30.3)
East and Southeast Asia								
East Asia								
China	24.1 (18.4-30.4)	30.2 (23.4-37.2)	56.4 (44.7-67.2)	47.7 (37.4-57.8)	44.6 (32.1-56.6)	35.1 (25.1-45.1)	17.8 (9.2-29.0)	13.9 (7.3-22.7)
North Korea	25.2 (14.2-37.9)	28.1 (16.9-40.8)	56.8 (30.7-79.8)	50.4 (25.5-74.8)	46.9 (18.6-76.3)	39.3 (14.9-67.4)	24.8 (4.5-56.2)	20.4 (3.9-48.7)
Taiwan	20.8 (14.0-28.7)	27.3 (18.9-37.2)	67.6 (52.4-80.8)	61.7 (47.9-74.2)	66.0 (48.2-80.8)	56.6 (41.4-70.7)	46.2 (24.4-67.8)	37.1 (20.4-55.7)
Southeast Asia								
Brunei Darussalam	45.6 (36.4-55.0)	47.0 (36.8-57.5)	69.7 (55.4-82.0)	61.8 (48.6-74.0)	61.8 (46.1-75.9)	52.1 (38.7-65.5)	35.0 (18.9-53.2)	25.6 (13.2-40.5)
Cambodia	25.4 (15.2-37.5)	25.8 (15.3-37.7)	59.4 (39.9-77.9)	40.5 (24.2-58.1)	44.9 (24.0-66.0)	27.0 (12.5-44.5)	26.6 (8.5-50.9)	16.4 (4.7-35.1)
Indonesia	44.5 (36.8-52.6)	35.9 (28.5-43.8)	41.0 (29.3-52.8)	29.0 (20.3-38.7)	21.4 (12.9-31.1)	15.4 (9.1-23.1)	5.1 (2.1-9.8)	3.6 (1.5-6.9)
Lao PDR	31.4 (20.9-43.4)	25.6 (16.3-36.3)	49.3 (31.4-67.1)	40.2 (24.7-57.4)	35.6 (18.6-55.8)	27.3 (13.6-44.1)	15.5 (4.4-32.9)	12.8 (3.6-28.0)
Malaysia	41.0 (31.4-50.5)	40.5 (30.4-51.0)	52.3 (37.6-65.7)	46.6 (33.4-59.3)	45.5 (30.2-60.5)	40.3 (26.9-54.2)	19.1 (7.7-34.2)	19.6 (9.3-33.4)
Maldives	35.4 (24.0-48.2)	32.6 (20.7-45.9)	48.4 (28.5-68.5)	39.4 (22.7-57.8)	34.0 (15.6-55.4)	27.7 (12.9-46.2)	15.4 (3.5-35.4)	14.0 (3.3-31.9)
Myanmar	40.0 (29.8-50.9)	35.2 (25.4-45.5)	63.7 (48.5-77.5)	49.2 (35.9-62.2)	39.8 (24.4-55.9)	27.1 (15.6-39.8)	16.6 (6.4-31.8)	12.8 (4.8-25.0)
Philippines	32.8 (24.5-41.9)	34.7 (25.7-44.6)	59.1 (44.9-72.3)	45.7 (33.3-58.2)	42.2 (27.9-57.0)	28.7 (18.2-41.1)	20.8 (9.5-36.6)	13.4 (6.0-24.2)
Thailand	29.2 (18.8-41.0)	29.1 (18.4-41.3)	58.9 (42.9-74.3)	47.1 (31.9-62.5)	51.2 (31.5-70.5)	37.0 (20.9-54.2)	29.8 (10.7-54.2)	22.0 (7.5-41.8)
Timor-Leste	36.7 (25.5-49.1)	33.8 (23.2-45.4)	38.9 (22.8-57.1)	35.9 (21.6-51.4)	25.7 (12.2-42.4)	22.6 (10.9-36.9)	10.5 (2.9-23.1)	11.9 (3.6-25.0)
Viet Nam	26.4 (18.9-35.1)	32.9 (23.9-42.5)	52.9 (37.5-68.9)	42.3 (30.4-55.3)	34.2 (20.1-49.4)	26.1 (15.8-38.0)	15.0 (5.5-29.3)	10.7 (4.1-21.1)
High-income Asia Pacific								
Japan	22.5 (18.8-26.4)	40.3 (35.0-45.8)	68.8 (55.1-81.0)	65.8 (51.3-79.2)	51.2 (43.0-59.3)	45.9 (38.8-53.1)	30.3 (21.6-39.8)	24.1 (17.3-31.8)
Singapore	27.1 (21.7-32.9)	35.4 (28.9-42.3)	67.7 (57.2-77.6)	64.9 (55.1-74.3)	62.9 (51.7-73.3)	58.9 (48.8-68.5)	39.5 (26.1-53.9)	36.2 (24.6-49.5)
South Korea	21.2 (17.7-24.9)	32.0 (27.1-37.4)	77.5 (68.0-85.5)	40.3 (35.0-45.8)	77.5 (70.2-83.6)	67.2 (60.5-73.3)	57.3 (45.9-68.0)	49.8 (40.2-59.2)
High-income western								
High-income English-speaking countries								
Australia	26.3 (21.0-32.3)	32.3 (26.2-39.0)	61.3 (49.1-71.6)	57.7 (47.2-67.1)	49.5 (37.8-60.8)	46.7 (36.5-57.0)	27.0 (16.5-39.2)	24.9 (15.6-35.8)
Canada	19.9 (16.0-24.4)	24.3 (20.0-29.0)	75.1 (66.4-82.6)	80.1 (73.1-86.2)	70.6 (60.5-79.2)	75.8 (67.8-82.4)	56.9 (44.5-68.3)	64.0 (53.6-73.8)
Ireland	24.1 (17.3-31.8)	38.2 (26.5-50.6)	54.2 (36.5-71.7)	47.5 (31.8-64.4)	45.1 (27.5-63.8)	37.6 (22.3-54.6)	27.6 (10.4-50.1)	21.1 (7.7-40.8)
New Zealand	36.2 (24.6-49.5)	34.4 (27.4-42.0)	65.0 (53.9-75.3)	61.2 (51.2-70.8)	52.3 (40.6-63.8)	47.0 (36.5-57.4)	30.2 (18.1-44.1)	24.9 (15.2-36.2)
United Kingdom	49.8 (40.2-59.2)	29.9 (25.9-34.0)	58.4 (51.0-65.6)	59.5 (53.0-65.7)	47.9 (40.6-54.8)	47.4 (41.1-53.7)	29.2 (22.1-37.1)	30.6 (24.1-37.7)
United States of America	29.0 (23.6-34.7)	34.1 (28.0-40.4)	82.8 (75.6-88.7)	78.4 (70.8-85.0)	73.3 (64.0-81.5)	66.3 (56.8-74.7)	51.0 (38.2-63.8)	44.8 (33.2-56.9)
North Western Europe								

Austria	30.2 (19.3-42.8)	37.5 (24.7-51.5)	65.1 (40.6-85.0)	61.7 (37.8-82.6)	53.7 (31.0-76.5)	54.3 (33.0-75.2)	27.1 (7.7-57.0)	27.5 (8.9-54.1)
Belgium	26.1 (20.5-32.2)	33.8 (26.5-41.4)	73.4 (62.5-82.9)	62.0 (50.3-72.7)	65.0 (52.6-76.0)	55.2 (44.2-66.0)	42.3 (27.6-58.2)	34.7 (22.8-47.9)
Denmark	28.6 (21.7-36.0)	43.3 (34.3-52.2)	58.1 (43.7-72.1)	54.1 (41.4-66.8)	27.3 (17.5-38.4)	25.1 (17.5-33.8)	10.2 (4.3-19.1)	8.8 (4.0-15.8)
Finland	30.6 (24.1-37.4)	41.0 (33.0-49.5)	70.8 (59.7-80.6)	65.9 (55.6-75.4)	53.9 (40.4-67.0)	48.8 (38.4-58.8)	29.1 (16.2-43.7)	27.0 (15.9-39.2)
Germany	25.0 (17.0-34.2)	34.4 (24.5-45.0)	70.8 (57.0-83.4)	72.2 (58.8-83.9)	65.0 (48.6-79.8)	61.1 (46.5-74.5)	48.0 (25.3-70.7)	43.2 (23.1-63.8)
Greenland	28.4 (18.3-39.9)	37.9 (25.2-51.2)	59.0 (39.0-77.8)	50.3 (33.0-68.0)	46.3 (25.4-67.9)	38.4 (21.9-56.7)	29.3 (10.4-54.9)	19.7 (5.9-40.8)
Iceland	24.2 (16.7-32.8)	30.9 (22.3-40.6)	82.0 (69.4-91.2)	82.8 (72.2-91.1)	71.8 (55.3-85.6)	71.0 (56.8-82.8)	52.9 (30.3-75.2)	50.9 (29.3-71.4)
Luxembourg	24.2 (18.4-30.4)	36.6 (29.0-44.4)	59.6 (46.3-72.2)	58.8 (47.3-70.0)	51.3 (37.3-64.6)	51.1 (38.9-63.1)	33.7 (19.2-50.8)	26.8 (15.4-40.5)
Netherlands	24.8 (18.0-32.3)	36.2 (27.4-44.8)	55.0 (39.5-69.4)	48.8 (35.4-62.6)	46.5 (32.6-61.2)	39.6 (28.7-51.6)	26.5 (13.4-43.3)	20.5 (9.9-35.4)
Norway	25.5 (16.8-36.0)	35.3 (24.4-47.3)	66.4 (41.9-86.4)	62.4 (39.6-82.6)	45.6 (25.9-67.1)	47.8 (30.3-66.3)	28.7 (10.1-55.4)	28.8 (10.1-52.5)
Sweden	24.6 (18.5-31.4)	35.6 (27.1-44.1)	55.1 (42.4-67.1)	53.1 (40.8-65.5)	39.8 (27.1-53.0)	39.6 (28.2-52.2)	19.2 (8.7-33.1)	20.5 (9.9-33.9)
Switzerland	17.5 (11.9-24.2)	26.4 (19.3-34.5)	73.8 (61.0-84.7)	72.7 (61.4-82.9)	56.8 (40.7-72.0)	55.8 (42.3-68.9)	39.4 (21.6-59.5)	35.2 (19.3-52.9)
South Western Europe								
Andorra	26.2 (15.2-38.7)	35.7 (22.0-50.7)	68.5 (44.7-87.2)	61.9 (37.1-82.2)	58.8 (31.1-83.6)	52.3 (27.8-75.7)	37.5 (12.0-68.4)	29.8 (8.7-59.1)
Cyprus	26.0 (15.7-39.1)	35.7 (22.5-50.7)	68.4 (44.7-87.3)	61.8 (38.8-81.8)	58.7 (30.2-83.6)	52.1 (27.2-75.9)	37.6 (11.8-69.3)	30.0 (8.6-57.7)
France	24.4 (17.8-32.0)	34.1 (26.7-42.4)	68.3 (54.4-80.2)	62.2 (49.9-73.4)	55.7 (40.6-70.1)	49.9 (36.9-63.1)	34.6 (18.0-53.5)	23.4 (11.4-39.3)
Greece	26.2 (20.3-32.6)	36.5 (29.1-44.5)	70.3 (59.5-80.1)	59.3 (49.2-68.9)	67.1 (55.6-77.6)	55.4 (45.0-65.4)	39.7 (24.7-56.0)	28.4 (17.1-41.3)
Israel	25.3 (18.9-32.8)	33.0 (25.2-41.8)	66.3 (52.7-78.0)	60.5 (47.9-72.1)	56.6 (42.1-70.3)	49.6 (36.8-61.9)	31.0 (16.6-47.7)	24.1 (12.4-38.4)
Italy	28.6 (23.1-34.5)	39.1 (32.0-46.3)	65.3 (55.2-74.5)	59.3 (49.2-68.6)	58.0 (46.3-69.2)	51.0 (41.5-60.4)	32.9 (20.5-47.0)	24.6 (14.8-36.0)
Malta	24.8 (17.9-32.9)	34.1 (25.4-43.5)	73.8 (58.6-86.1)	69.5 (55.3-81.3)	68.6 (51.7-82.6)	65.1 (50.2-78.3)	48.0 (28.2-69.0)	42.9 (24.5-61.6)
Portugal	28.0 (20.7-36.2)	37.0 (28.0-46.8)	75.0 (62.1-86.1)	64.1 (50.3-76.6)	70.9 (55.8-83.7)	57.2 (42.1-71.4)	52.0 (31.8-70.9)	38.4 (21.5-57.4)
Spain	20.8 (15.7-26.5)	33.5 (26.2-41.4)	71.6 (60.6-80.7)	61.4 (50.9-71.4)	58.0 (45.1-70.6)	51.0 (40.3-61.9)	34.5 (20.0-50.5)	29.5 (17.5-43.6)
Latin America and Caribbean								
Andean Latin America								
Bolivia	27.2 (14.8-42.6)	29.4 (15.3-47.1)	70.7 (45.9-88.9)	51.0 (26.9-75.0)	59.8 (29.1-86.2)	39.3 (15.6-67.2)	33.7 (9.0-66.9)	19.3 (3.9-45.2)
Ecuador	25.1 (18.9-32.1)	29.2 (22.0-37.2)	74.5 (62.4-84.3)	50.7 (39.0-61.8)	63.0 (49.6-75.1)	37.2 (26.0-49.1)	40.0 (24.9-56.1)	18.2 (9.6-29.1)
Peru	18.4 (15.3-21.8)	22.8 (19.0-27.1)	60.0 (51.7-67.7)	35.5 (29.0-42.0)	53.7 (44.9-62.0)	28.9 (23.1-35.0)	31.1 (22.8-40.4)	14.1 (9.5-19.4)
Caribbean								
Antigua and Barbuda	43.2 (28.0-59.2)	41.9 (25.9-58.6)	71.8 (47.0-89.7)	53.3 (29.7-76.3)	57.7 (27.7-83.1)	39.7 (16.0-66.6)	27.4 (6.4-58.3)	18.1 (3.5-42.9)
Bahamas	43.6 (31.0-57.2)	45.5 (32.7-58.6)	73.3 (55.7-87.3)	57.2 (40.3-73.6)	62.9 (42.4-80.0)	42.3 (24.8-60.4)	27.5 (9.7-50.4)	16.9 (5.1-34.7)
Barbados	43.3 (31.9-56.1)	40.0 (28.7-52.7)	78.0 (61.7-90.0)	61.7 (44.5-77.3)	68.3 (48.1-84.5)	51.0 (33.0-69.3)	37.7 (16.0-63.1)	28.9 (11.6-50.9)

Belize	38.0 (24.5-53.2)	38.0 (24.1-53.7)	71.7 (50.8-88.0)	47.1 (28.3-66.9)	56.1 (31.6-78.1)	34.0 (16.2-55.5)	26.7 (7.2-54.7)	15.9 (3.4-35.3)
Bermuda	43.2 (28.3-58.9)	42.0 (26.0-59.6)	71.8 (47.1-90.2)	53.3 (29.3-76.6)	58.1 (29.7-84.0)	40.0 (16.9-68.0)	27.1 (6.1-58.5)	17.8 (3.4-41.8)
Cuba	39.5 (27.5-52.8)	40.3 (27.6-53.9)	76.9 (59.9-89.4)	63.3 (45.6-78.5)	68.6 (47.9-84.6)	52.5 (33.0-71.3)	38.0 (15.3-64.0)	27.6 (10.4-50.5)
Dominica	49.9 (35.4-64.9)	45.5 (31.1-60.3)	67.1 (45.9-84.9)	47.7 (29.0-67.1)	54.5 (31.1-76.1)	36.2 (17.8-57.2)	20.7 (5.0-46.0)	14.4 (3.2-33.6)
Dominican Republic	49.2 (36.5-62.4)	49.0 (35.5-62.2)	74.5 (58.4-86.8)	60.6 (43.8-75.9)	60.1 (40.3-78.0)	46.4 (28.2-64.7)	25.1 (8.0-48.9)	17.9 (5.5-36.5)
Grenada	45.6 (33.1-58.8)	47.6 (33.9-61.5)	73.3 (54.5-87.8)	53.0 (35.3-70.4)	59.7 (39.1-78.8)	35.3 (18.6-53.8)	23.8 (7.0-47.6)	14.7 (4.0-32.1)
Guyana	41.8 (31.8-51.9)	38.2 (28.3-48.7)	70.6 (55.1-83.2)	54.8 (39.2-69.5)	53.4 (35.9-70.2)	40.1 (24.7-56.5)	23.7 (10.0-41.7)	16.4 (6.7-29.6)
Haiti	47.8 (38.5-57.3)	37.6 (28.8-46.8)	66.0 (52.3-78.4)	43.0 (29.7-56.8)	33.1 (20.2-47.4)	21.4 (12.2-32.9)	8.6 (3.0-17.3)	7.5 (2.8-14.7)
Jamaica	47.8 (34.9-61.4)	44.5 (31.8-58.0)	76.8 (60.0-89.2)	51.0 (34.1-67.6)	63.7 (43.8-80.8)	37.3 (20.9-55.1)	23.6 (7.3-45.9)	14.0 (4.0-29.6)
Puerto Rico	43.2 (28.0-59.7)	41.8 (25.5-59.6)	71.7 (47.8-89.6)	53.4 (29.9-76.6)	58.0 (28.8-83.6)	39.6 (16.4-66.3)	27.0 (5.7-58.4)	17.8 (3.4-41.7)
Saint Kitts and Nevis	45.1 (30.7-59.7)	45.1 (29.9-60.6)	70.3 (49.9-86.3)	50.3 (31.6-69.4)	59.9 (35.7-80.4)	37.8 (18.9-59.1)	27.7 (7.0-55.7)	16.8 (3.9-38.1)
Saint Lucia	40.8 (29.5-53.0)	38.8 (26.4-51.9)	80.0 (64.3-91.5)	57.3 (40.3-73.7)	65.5 (44.4-82.3)	37.5 (20.8-56.2)	31.0 (11.6-55.2)	12.1 (3.1-26.5)
Saint Vincent and the Grenadines	41.5 (31.1-52.4)	37.2 (26.3-48.5)	73.0 (56.7-86.4)	49.1 (33.6-64.2)	56.7 (37.2-74.3)	33.3 (19.2-49.2)	25.4 (9.3-46.1)	15.3 (5.4-29.8)
Suriname	43.3 (31.2-56.3)	42.4 (29.7-55.8)	72.5 (55.0-86.5)	54.6 (37.9-70.7)	57.0 (35.8-76.7)	41.6 (23.7-60.5)	23.9 (7.8-45.7)	18.1 (5.7-35.2)
Trinidad and Tobago	41.6 (29.2-54.6)	43.2 (30.8-56.6)	67.6 (49.2-82.6)	52.3 (35.5-68.7)	53.9 (32.5-73.1)	39.5 (23.0-57.1)	24.5 (7.4-48.1)	17.3 (5.3-35.8)
Central Latin America								
Colombia	30.8 (21.8-40.6)	31.1 (21.4-41.9)	76.3 (62.4-87.4)	60.3 (46.3-73.4)	63.9 (46.6-79.3)	45.6 (30.9-61.6)	41.0 (20.5-64.0)	24.0 (9.9-43.1)
Costa Rica	39.4 (29.6-48.9)	36.0 (26.9-45.6)	81.7 (71.7-90.2)	71.8 (60.2-82.6)	76.1 (63.8-86.2)	63.5 (50.7-75.7)	53.5 (34.4-72.9)	45.4 (28.3-63.2)
El Salvador	33.6 (24.2-43.8)	31.4 (22.2-41.8)	81.6 (69.8-90.8)	61.2 (46.6-74.8)	71.0 (55.7-84.1)	50.6 (34.6-66.3)	48.3 (28.2-68.5)	26.6 (12.5-44.1)
Guatemala	32.6 (22.9-44.1)	31.5 (21.0-43.1)	62.7 (46.2-77.9)	48.5 (32.8-64.1)	40.4 (22.9-60.7)	30.3 (16.0-47.5)	22.7 (8.3-43.3)	14.7 (4.7-31.1)
Honduras	34.4 (22.2-48.5)	33.2 (20.1-48.2)	74.3 (54.9-89.5)	56.1 (34.3-76.9)	67.3 (43.2-86.8)	47.9 (24.6-70.9)	39.0 (13.5-69.1)	25.4 (7.2-52.1)
Mexico	31.4 (25.8-37.2)	32.8 (26.4-39.2)	67.5 (58.3-76.5)	46.9 (37.8-56.2)	59.7 (48.8-69.3)	39.3 (30.3-48.8)	33.7 (22.7-45.7)	21.2 (13.5-30.5)
Nicaragua	36.9 (23.3-52.1)	34.5 (21.1-50.6)	75.8 (55.1-90.5)	56.3 (33.8-77.1)	69.2 (44.9-88.6)	49.7 (25.4-73.5)	41.8 (15.1-71.5)	25.8 (7.2-52.2)
Panama	35.3 (23.8-48.2)	36.8 (23.8-51.3)	75.6 (58.1-89.2)	59.0 (41.5-75.7)	63.9 (41.8-82.7)	45.7 (26.7-66.2)	35.8 (13.9-62.0)	21.4 (6.8-43.4)
Venezuela	39.1 (30.5-48.5)	39.7 (30.1-50.0)	79.4 (67.5-89.0)	64.8 (51.5-77.5)	71.3 (57.5-83.2)	54.2 (40.5-67.8)	39.6 (22.4-58.2)	25.3 (12.9-41.4)
Southern Latin America								
Argentina	41.2 (33.7-49.3)	54.0 (45.1-62.9)	65.1 (52.9-76.1)	52.5 (41.0-63.6)	48.1 (35.0-60.5)	35.3 (24.9-46.4)	19.4 (10.1-31.6)	11.0 (5.4-18.7)
Brazil	42.1 (35.1-48.9)	47.9 (40.2-55.6)	73.4 (64.0-81.3)	61.8 (52.4-70.8)	69.8 (60.3-78.4)	54.4 (44.9-63.8)	38.9 (26.4-52.1)	28.1 (18.5-39.2)
Chile	33.1 (25.3-41.5)	39.0 (29.8-48.2)	79.7 (67.7-88.8)	63.7 (51.3-75.4)	68.2 (54.1-81.0)	49.9 (36.8-62.8)	41.8 (24.3-60.9)	26.7 (14.4-42.6)
Paraguay	50.9 (38.0-64.2)	61.6 (47.8-74.4)	67.9 (49.5-83.3)	44.0 (28.2-61.1)	48.9 (29.8-68.2)	28.4 (15.3-44.1)	17.9 (5.0-38.1)	8.4 (2.0-20.0)
Uruguay	38.9 (29.3-49.5)	46.0 (35.0-57.4)	72.7 (57.6-84.4)	61.0 (46.6-74.5)	62.6 (46.5-76.7)	47.3 (33.0-61.6)	33.4 (16.1-54.2)	24.9 (11.2-42.1)

Oceania								
Melanesia								
Fiji	40.5 (27.8-54.1)	36.5 (24.1-50.5)	60.9 (41.5-78.6)	45.3 (27.9-62.8)	40.9 (20.9-62.7)	27.7 (12.6-45.7)	15.6 (3.3-36.1)	9.1 (1.7-23.2)
Papua New Guinea	30.1 (17.2-45.5)	25.4 (14.0-40.3)	36.8 (17.3-60.3)	27.7 (11.8-47.4)	20.6 (6.0-42.4)	17.5 (5.4-35.5)	11.3 (1.6-31.8)	8.6 (1.2-24.6)
Solomon Islands	34.5 (24.8-45.1)	24.9 (16.4-35.0)	42.3 (25.8-60.5)	24.7 (13.3-38.0)	16.8 (7.0-30.9)	11.2 (4.2-21.5)	7.4 (1.7-18.3)	5.2 (1.1-13.2)
Vanuatu	41.8 (28.5-55.6)	37.4 (25.1-51.5)	35.8 (18.3-57.1)	23.9 (11.0-40.3)	16.0 (5.4-33.0)	11.0 (3.5-22.6)	6.1 (0.8-19.1)	3.6 (0.5-11.0)
Polynesia and Micronesia								
American Samoa	45.5 (31.2-59.6)	48.8 (33.5-63.9)	50.6 (32.4-68.6)	44.8 (26.2-63.1)	34.3 (15.4-56.3)	27.6 (11.5-46.7)	13.6 (2.6-33.7)	8.8 (1.5-23.8)
Cook Islands	41.1 (29.9-52.6)	44.6 (32.7-56.6)	59.4 (41.8-75.4)	54.0 (38.5-69.3)	44.6 (27.2-62.5)	38.7 (24.0-54.6)	18.3 (6.1-36.3)	14.9 (5.3-29.7)
Federated States of Micronesia	33.9 (24.1-44.4)	31.7 (21.9-42.0)	56.2 (39.8-71.9)	43.9 (30.1-58.1)	31.5 (17.2-48.6)	23.7 (12.3-37.4)	15.2 (5.2-31.2)	11.7 (3.8-24.8)
French Polynesia	41.5 (28.7-55.3)	43.7 (30.4-57.4)	46.7 (27.3-67.4)	39.2 (23.3-56.9)	32.0 (15.1-52.6)	29.0 (14.5-46.0)	12.8 (3.0-30.4)	11.6 (2.9-26.2)
Kiribati	43.8 (33.1-55.2)	40.4 (29.7-52.3)	35.8 (20.8-51.7)	31.0 (18.4-45.1)	15.0 (6.6-26.9)	15.6 (7.0-27.1)	7.7 (2.1-17.6)	5.3 (1.3-12.7)
Marshall Islands	32.9 (25.2-41.4)	30.8 (22.4-39.6)	49.1 (34.9-63.0)	41.9 (29.3-55.1)	34.0 (20.8-49.2)	26.5 (15.6-38.9)	17.0 (7.4-29.8)	12.3 (5.4-22.0)
Nauru	39.7 (29.4-50.7)	43.7 (32.5-55.6)	57.4 (41.3-72.7)	49.0 (33.2-64.2)	30.0 (15.3-47.4)	27.6 (15.0-42.5)	17.2 (5.9-34.1)	12.8 (4.3-26.4)
Niue	39.7 (27.3-53.1)	39.1 (26.5-52.8)	58.4 (39.5-76.4)	49.7 (32.3-68.5)	45.8 (26.0-66.2)	37.6 (20.7-56.6)	22.7 (7.0-45.8)	14.4 (3.9-31.8)
Palau	42.5 (33.0-51.9)	45.1 (35.2-55.4)	61.0 (45.8-75.2)	48.5 (34.6-62.2)	44.9 (30.4-60.3)	29.2 (18.4-41.9)	19.5 (8.5-35.2)	9.5 (3.7-18.9)
Samoa	37.9 (27.0-49.5)	38.6 (27.8-50.3)	40.2 (24.2-56.9)	30.2 (17.8-44.5)	20.6 (9.1-36.3)	20.3 (9.7-34.4)	10.0 (2.5-22.7)	9.9 (2.9-22.1)
Tokelau	37.5 (26.8-49.3)	41.3 (29.2-54.5)	53.8 (35.3-71.6)	41.8 (26.3-58.8)	42.8 (25.2-62.0)	24.3 (11.7-39.8)	17.8 (5.9-35.8)	7.5 (1.8-18.7)
Tonga	46.8 (37.9-55.9)	39.6 (30.6-49.4)	40.8 (28.0-54.5)	32.1 (20.9-44.1)	29.4 (18.1-42.0)	22.5 (13.0-33.7)	11.6 (4.8-21.2)	6.8 (2.6-13.5)
Tuvalu	50.8 (39.2-62.3)	49.2 (36.9-61.8)	35.8 (20.6-52.3)	29.8 (17.1-45.3)	20.9 (9.7-36.0)	18.9 (9.0-32.0)	6.3 (1.4-14.9)	5.8 (1.4-13.9)
South Asia								
Afghanistan	45.3 (35.5-55.1)	35.3 (26.5-45.0)	66.0 (52.0-78.5)	43.9 (30.7-57.6)	54.3 (39.1-69.4)	34.6 (21.7-49.0)	17.3 (7.9-30.2)	9.9 (4.1-18.3)
Bangladesh	34.2 (28.2-40.7)	23.5 (17.9-29.8)	53.5 (43.3-63.1)	44.8 (34.8-54.9)	41.5 (32.0-51.5)	34.1 (24.5-44.2)	15.1 (8.7-22.9)	14.0 (7.7-21.9)
Bhutan	43.0 (35.6-50.7)	43.6 (35.7-51.9)	52.4 (40.2-64.3)	40.7 (30.4-51.5)	31.4 (20.9-42.7)	21.1 (13.5-29.9)	10.7 (5.2-18.3)	6.9 (3.3-12.3)
India	30.5 (23.5-37.6)	31.6 (25.1-38.7)	41.7 (30.8-53.5)	31.7 (23.4-40.6)	35.1 (25.0-46.9)	25.1 (17.3-33.8)	18.5 (10.0-29.6)	11.3 (6.0-18.4)
Nepal	33.9 (28.4-39.8)	39.6 (33.6-45.9)	35.5 (26.5-45.1)	30.3 (22.8-38.6)	21.2 (15.0-28.3)	15.9 (11.0-21.4)	8.5 (4.7-13.4)	5.9 (3.3-9.5)
Pakistan	44.8 (32.4-57.7)	41.6 (29.4-54.3)	54.3 (37.8-70.1)	34.0 (20.5-49.1)	44.1 (26.3-62.5)	24.9 (12.4-39.9)	14.1 (4.2-29.6)	8.4 (2.1-19.5)
Sri Lanka	36.5 (26.7-47.5)	34.4 (24.5-45.0)	53.1 (36.1-68.8)	38.7 (24.5-53.6)	41.6 (25.9-57.9)	28.6 (16.6-42.1)	17.6 (6.6-33.1)	13.0 (4.7-25.1)
Sub-Saharan Africa								
Central Africa								
Angola	40.8 (27.2-56.1)	36.5 (22.4-51.7)	55.2 (33.6-76.2)	39.1 (20.3-60.8)	26.9 (10.0-49.8)	22.2 (8.5-41.2)	13.4 (2.8-33.2)	9.3 (1.7-24.4)

Central African Republic	42.8 (32.3-53.6)	39.5 (28.6-50.8)	40.1 (25.4-55.9)	25.0 (14.6-36.9)	20.9 (9.6-36.1)	14.1 (6.4-24.7)	6.2 (1.5-14.7)	4.9 (1.3-12.0)
Congo	41.5 (25.5-58.3)	38.0 (22.6-55.0)	45.2 (22.7-68.8)	30.9 (13.3-51.8)	25.9 (8.1-51.1)	21.6 (6.9-42.2)	11.2 (1.4-31.8)	7.6 (1.0-23.4)
DR Congo	35.7 (21.5-52.3)	32.7 (19.2-48.5)	43.9 (23.2-66.0)	34.7 (17.3-54.6)	26.5 (9.0-51.1)	25.4 (9.4-46.4)	12.4 (1.9-33.4)	10.7 (1.7-28.3)
Equatorial Guinea	39.9 (23.5-58.3)	36.6 (20.9-54.6)	48.5 (23.9-73.4)	34.2 (13.6-58.4)	30.1 (8.3-61.0)	22.6 (5.9-47.1)	13.3 (1.7-36.4)	9.6 (1.1-27.9)
Gabon	38.7 (24.4-54.3)	36.0 (22.0-51.2)	52.0 (30.2-72.5)	32.6 (17.1-50.9)	35.2 (15.0-59.8)	22.7 (8.7-41.4)	15.6 (2.9-37.6)	10.8 (2.0-27.7)
East Africa								
Burundi	35.6 (21.6-51.5)	32.5 (18.5-48.4)	47.5 (24.1-71.7)	32.7 (14.1-56.1)	29.3 (8.5-56.7)	20.1 (5.5-42.7)	13.3 (2.0-35.6)	9.2 (1.2-26.6)
Comoros	36.2 (24.7-49.2)	30.0 (19.1-42.1)	49.7 (31.4-68.6)	31.5 (17.6-47.9)	29.7 (13.6-49.0)	18.7 (7.8-33.7)	12.9 (3.1-29.3)	9.4 (2.3-22.5)
Djibouti	35.8 (21.4-51.6)	32.7 (18.6-49.0)	47.5 (23.4-71.9)	32.9 (13.8-56.0)	28.9 (8.5-55.9)	20.1 (5.3-42.3)	13.3 (2.1-35.0)	9.1 (1.2-26.4)
Eritrea	24.7 (14.8-36.6)	22.5 (12.9-33.9)	42.9 (24.9-62.7)	33.3 (18.5-50.0)	26.7 (11.8-45.8)	21.4 (9.3-37.7)	13.6 (3.2-31.2)	11.5 (3.0-25.8)
Ethiopia	30.1 (20.8-40.6)	24.5 (16.3-34.3)	37.4 (22.5-53.1)	30.1 (18.4-43.3)	15.6 (7.1-27.7)	15.6 (7.5-26.2)	6.6 (1.8-15.2)	5.6 (1.5-12.9)
Kenya	34.7 (25.8-44.3)	31.4 (22.6-41.0)	49.2 (33.1-65.5)	27.8 (16.8-40.3)	20.5 (10.0-33.9)	9.9 (4.1-18.4)	7.7 (2.2-16.6)	4.5 (1.2-10.4)
Madagascar	38.9 (24.9-54.2)	34.7 (21.1-49.9)	40.3 (21.3-61.7)	26.7 (12.8-44.8)	18.6 (6.0-37.2)	12.6 (3.8-26.7)	7.1 (1.0-21.3)	5.7 (0.8-16.6)
Malawi	31.6 (24.2-39.4)	26.8 (19.0-35.0)	45.3 (32.4-58.3)	26.7 (17.3-37.8)	28.9 (18.2-41.4)	16.6 (9.4-25.7)	13.9 (6.1-24.9)	6.4 (2.4-12.7)
Mauritius	32.0 (24.4-39.5)	34.2 (26.2-42.7)	72.2 (60.7-82.5)	61.2 (49.6-72.1)	66.2 (53.1-78.0)	54.4 (41.5-66.7)	38.7 (22.7-57.0)	30.5 (17.1-46.4)
Mozambique	41.9 (31.4-53.0)	34.3 (24.3-45.4)	35.7 (21.5-51.8)	22.2 (12.1-34.8)	18.9 (8.6-33.0)	10.1 (4.0-19.1)	9.2 (2.7-20.6)	4.9 (1.1-12.0)
Rwanda	30.9 (20.1-42.8)	28.5 (18.2-40.9)	28.6 (13.7-46.5)	17.7 (7.8-30.7)	11.4 (3.5-24.0)	9.7 (3.2-19.8)	5.8 (1.1-16.4)	5.9 (1.2-16.0)
Seychelles	42.3 (32.3-52.7)	45.8 (34.5-57.6)	74.3 (60.8-85.1)	58.6 (43.4-72.2)	64.5 (47.4-80.1)	47.1 (31.5-63.4)	35.8 (16.8-58.3)	18.5 (7.1-34.3)
Somalia	38.6 (26.5-51.8)	33.4 (21.0-47.9)	44.8 (26.0-64.7)	34.4 (17.9-53.8)	29.4 (13.2-49.7)	22.9 (9.3-40.4)	10.2 (2.1-24.4)	8.8 (1.8-22.0)
South Sudan	36.0 (22.2-51.5)	32.3 (18.0-48.6)	47.4 (23.8-71.8)	32.6 (13.0-56.6)	29.2 (8.8-56.8)	20.5 (5.7-43.2)	13.2 (1.9-35.6)	9.3 (1.3-26.1)
Sudan	43.5 (33.1-54.0)	38.0 (28.1-48.9)	39.8 (25.3-55.5)	24.8 (14.5-37.3)	28.2 (16.4-43.0)	16.3 (8.2-26.8)	9.7 (3.3-19.9)	6.4 (2.1-13.5)
Tanzania	35.4 (25.9-45.5)	30.9 (21.7-40.8)	40.4 (26.6-55.8)	25.5 (15.4-37.3)	16.6 (8.0-28.0)	13.7 (6.8-23.1)	8.0 (2.5-17.2)	6.0 (1.8-13.5)
Uganda	33.9 (23.6-45.3)	30.9 (20.8-41.9)	41.5 (26.2-58.3)	24.8 (14.1-37.7)	22.7 (11.0-38.0)	13.0 (5.5-23.0)	8.6 (2.4-19.5)	6.5 (1.7-15.5)
Zambia	33.8 (25.6-42.2)	30.3 (21.6-39.7)	52.1 (37.7-66.3)	34.1 (21.9-47.2)	28.7 (16.7-42.6)	17.8 (9.5-28.5)	11.9 (4.5-23.3)	6.6 (2.2-13.9)
Southern Africa								
Botswana	47.0 (35.0-59.4)	40.3 (29.1-52.2)	65.0 (48.4-80.0)	49.8 (34.4-65.0)	47.5 (30.2-65.3)	32.5 (18.9-47.9)	22.4 (8.8-41.6)	13.3 (4.4-27.0)
Eswatini	47.3 (35.8-58.8)	37.4 (26.2-49.1)	58.8 (42.0-75.1)	37.4 (23.8-53.0)	39.9 (23.5-57.3)	26.9 (14.7-41.7)	14.9 (4.6-30.7)	9.1 (2.6-19.8)
Lesotho	46.8 (35.8-57.7)	32.1 (22.5-42.5)	60.8 (43.5-76.4)	40.8 (27.0-55.3)	51.1 (34.5-67.8)	29.4 (16.6-43.8)	20.8 (7.9-38.9)	13.9 (4.9-27.4)
Namibia	44.8 (32.3-57.9)	42.6 (30.1-54.9)	57.3 (39.0-75.2)	45.6 (29.8-61.7)	48.1 (30.1-66.1)	38.9 (23.2-55.5)	24.5 (9.2-45.6)	17.7 (6.4-34.8)
South Africa	44.3 (36.8-51.7)	43.8 (36.6-51.2)	62.8 (51.8-73.2)	42.5 (33.5-51.8)	54.7 (43.7-65.5)	37.2 (28.2-46.5)	29.9 (18.4-42.6)	16.4 (9.7-24.2)
Zimbabwe	46.4 (30.6-63.1)	36.9 (22.0-53.3)	53.5 (27.6-78.1)	38.2 (16.0-62.4)	40.6 (14.1-70.2)	27.5 (8.3-52.9)	18.9 (3.3-47.4)	12.4 (1.9-32.9)

West Africa								
Benin	33.0 (26.1-40.4)	28.9 (22.1-36.1)	46.6 (33.5-59.9)	28.3 (19.6-38.2)	29.2 (18.8-41.5)	19.4 (12.1-28.1)	10.2 (4.4-18.7)	8.1 (3.8-14.4)
Burkina Faso	31.7 (20.9-43.2)	29.1 (19.0-40.2)	44.1 (26.6-62.7)	29.4 (16.4-44.7)	26.1 (12.3-43.2)	13.7 (5.4-26.0)	11.2 (3.0-25.6)	5.9 (1.3-15.0)
Cabo Verde	41.7 (34.4-49.2)	45.7 (37.0-54.4)	64.5 (51.7-76.0)	40.8 (29.3-52.9)	47.1 (34.0-60.4)	24.8 (15.9-35.4)	19.4 (9.9-31.6)	8.6 (3.8-15.1)
Cameroon	38.6 (27.7-50.6)	34.8 (23.9-46.6)	42.5 (26.9-59.2)	29.6 (17.4-43.9)	21.9 (9.9-37.1)	16.2 (7.1-28.5)	10.3 (2.7-23.3)	4.3 (0.7-11.6)
Chad	`40.7 (26.8-56.1)	35.1 (21.5-50.1)	45.9 (24.6-69.3)	33.3 (15.7-53.6)	27.9 (10.1-52.3)	20.3 (7.3-39.4)	12.8 (2.1-32.6)	9.1 (1.6-23.7)
Cote d'Ivoire	37.6 (23.6-53.1)	36.9 (23.5-51.5)	44.5 (24.9-65.6)	31.7 (16.1-50.5)	26.6 (10.5-48.0)	20.3 (7.6-38.7)	11.0 (1.9-29.2)	6.4 (1.0-18.0)
Gambia	40.2 (27.5-53.8)	34.7 (23.2-47.4)	53.1 (34.1-71.8)	35.6 (20.4-52.8)	32.6 (16.1-52.6)	22.0 (10.2-37.2)	10.9 (2.4-26.1)	8.0 (1.7-19.9)
Ghana	36.1 (26.6-46.3)	31.4 (22.0-41.2)	60.0 (45.5-73.7)	37.8 (26.2-51.2)	44.6 (30.1-60.2)	27.6 (16.5-40.7)	23.7 (10.7-40.7)	13.5 (5.2-25.6)
Guinea	42.5 (29.3-56.7)	38.3 (25.2-53.0)	53.2 (33.1-72.8)	31.0 (16.3-48.0)	26.5 (10.4-47.4)	16.6 (6.2-31.7)	8.2 (1.3-23.1)	5.7 (0.9-16.9)
Guinea Bissau	39.7 (25.0-56.2)	36.0 (20.9-52.7)	50.7 (26.1-75.9)	34.1 (14.5-58.1)	30.8 (9.6-57.9)	21.2 (5.8-44.3)	13.2 (1.9-36.0)	8.6 (1.1-25.2)
Liberia	41.3 (28.8-54.5)	37.4 (26.2-49.5)	47.0 (28.4-66.0)	35.6 (20.0-52.7)	28.6 (13.4-47.5)	23.7 (10.5-41.0)	8.8 (1.8-22.2)	7.9 (1.7-19.4)
Mali	38.3 (24.8-53.1)	30.5 (18.5-44.0)	59.7 (39.5-78.6)	43.0 (24.9-62.9)	39.7 (19.0-63.0)	29.6 (12.6-50.0)	16.4 (3.7-37.4)	11.8 (2.2-29.6)
Mauritania	39.7 (24.6-56.6)	35.9 (21.8-52.4)	50.9 (25.8-75.7)	33.7 (14.2-57.5)	30.5 (9.9-57.4)	21.1 (5.5-44.4)	13.1 (2.0-34.7)	8.6 (1.2-24.5)
Niger	42.6 (28.5-57.4)	40.4 (27.0-54.3)	33.3 (16.3-54.6)	19.1 (7.9-34.6)	14.9 (4.8-31.4)	11.7 (3.6-25.0)	8.0 (1.2-22.6)	4.0 (0.5-12.6)
Nigeria	39.0 (31.5-47.0)	33.0 (25.7-40.8)	50.6 (37.9-63.3)	41.7 (30.3-53.9)	29.6 (19.1-41.8)	27.4 (18.0-38.7)	10.8 (4.9-19.0)	11.4 (5.5-19.5)
Sao Tome and Principe	48.0 (39.8-56.6)	41.9 (33.2-50.9)	61.1 (48.1-73.4)	36.0 (24.8-48.1)	36.1 (23.8-49.5)	19.3 (11.1-29.6)	11.4 (5.0-20.7)	6.9 (2.8-13.3)
Senegal	42.9 (30.1-56.3)	37.3 (24.5-51.0)	44.5 (25.0-64.8)	30.1 (14.9-48.0)	25.0 (9.3-45.6)	15.5 (5.6-30.7)	11.1 (2.3-27.6)	7.2 (1.5-18.1)
Sierra Leone	43.4 (30.1-57.3)	38.0 (25.1-51.8)	44.6 (25.6-64.3)	29.7 (15.5-46.8)	24.2 (10.1-43.1)	15.5 (5.8-29.8)	10.5 (2.1-26.2)	6.2 (1.1-16.6)
Togo	37.5 (25.2-51.0)	34.3 (22.2-47.2)	52.3 (32.8-71.9)	30.0 (16.0-47.5)	26.1 (11.4-45.1)	13.7 (4.6-27.1)	13.0 (3.0-30.9)	5.2 (0.8-15.0)

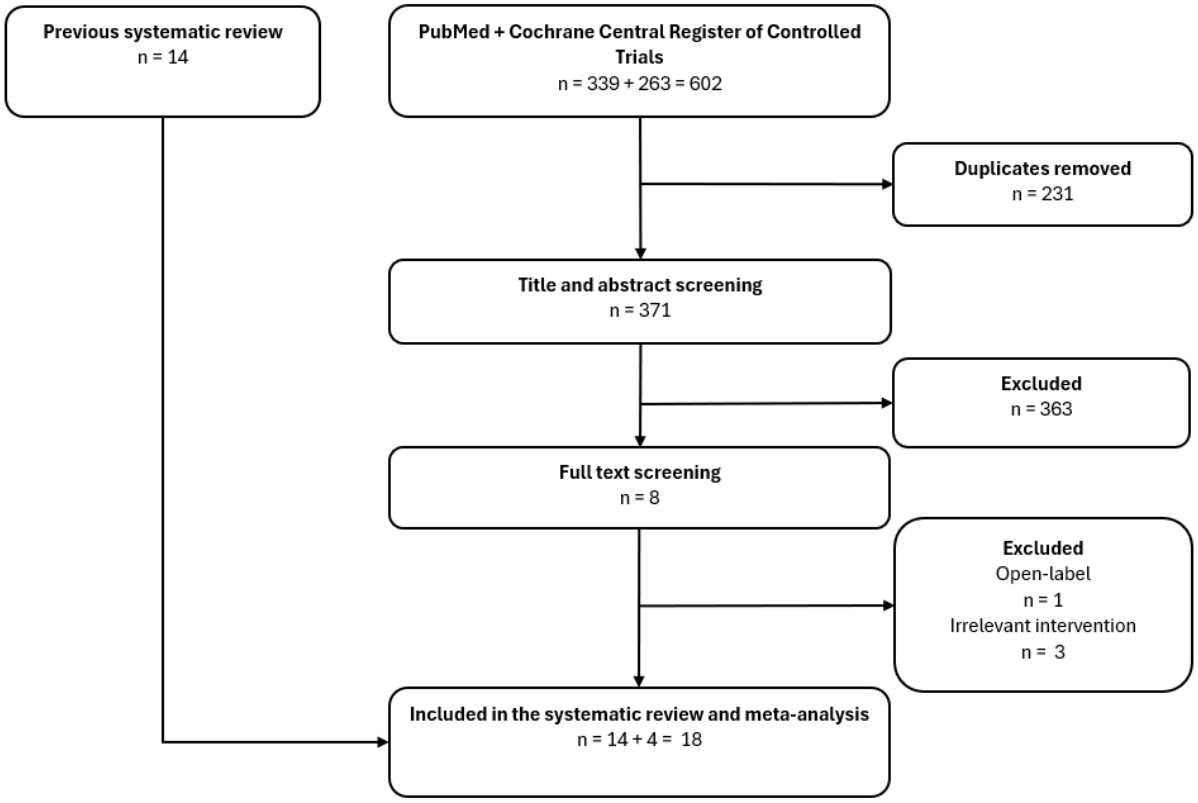
Appendix 2: Triple versus dual FDC trials search strategy, PRISMA and summary of characteristics of included trials

Last Search Date: Dec 2023

PubMed Search strategy:

#	Searches
1	exp Antihypertensive Agents/
2	antihypertensive*.mp.
3	or/1-2
4	exp Vascular Diseases/
5	hypertension.mp.
6	or/4-5
7	Triple.mp.
8	Quadruple.mp.
9	multidrug.mp.
10	Fixed dose*.mp.
11	Fixed combination.mp.
12	Polypill.mp.
13	Polycap.mp.
14	Single pill.mp.
15	*Drug Therapy, Combination/
16	polypharmacy/
17	or/7-16
18	exp Randomized Controlled Trial/
19	exp Random Allocation/
20	"random*".ab,kf,kw,ot,pt,ti.
21	or/18-20
22	3 and 6 and 17 and 21
23	limit 22 to humans

Appendix 3: Flow chart for triple versus dual FDC review



Appendix 4: Summary of characteristics of included trials for triple versus dual drug review

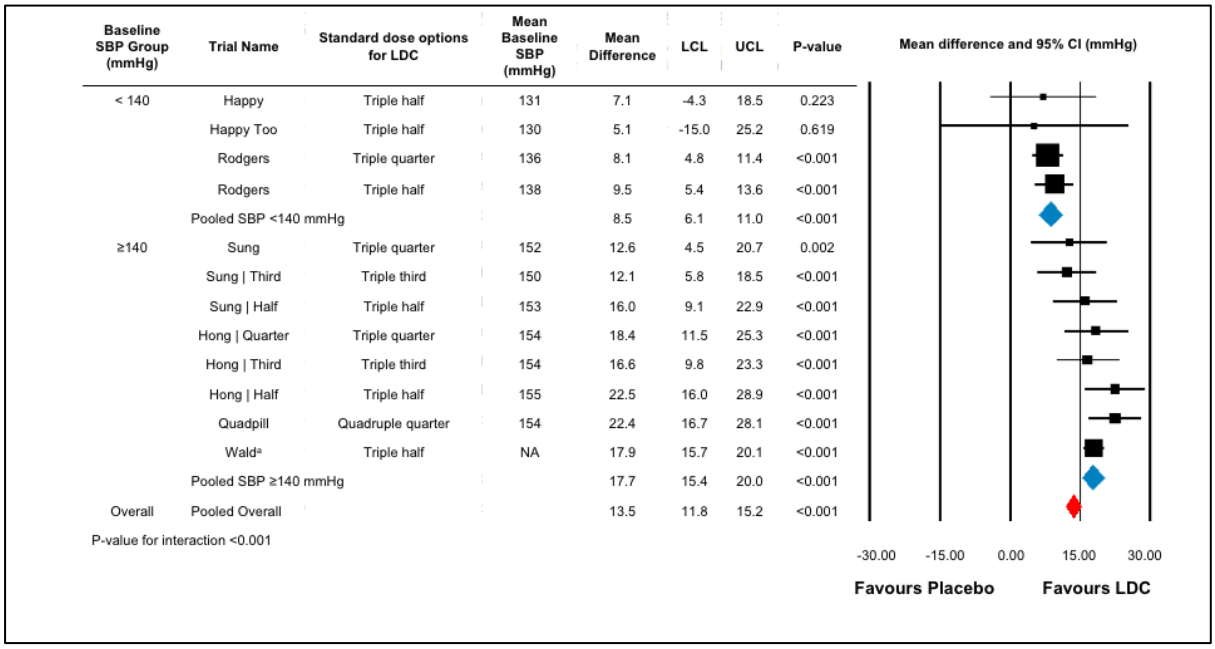
Author/Study, Year	Eligibility	Sample size	Concomitant conditions	Washout/ placebo run in weeks	BP measure	SBP, mmHg	DBP, mmHg	Regimen	Triple therapy	Dual therapy	Treatment duration, weeks	Add on therapy
Cho, 2023	SBP140-≤200, T2DM or CKD-SBP130-≤200 after 4 weeks on Telm40+Amlo5	374	T2DM-24% CKD- 14% Dyslipidemia-49%	No	NR	149.9	88.5	Forced uptitration	Telm80+Amlo5+Chlor25	Telm80+Amlo5	8	Yes
Sung , 2018	SBP 140-199 or 130-199 for DM/CKD after 4 weeks on Telm 40 + Amlo 5	310	DM 26% CKD 15%	No	seated, NR	153	89	Forced uptitration	Telm 80+Amlo 10+Hctz 25	Telm 80+Amlo 10	8	Yes
Higaki , 2017	DBP 90-114, SBP ≤200, after 6 weeks on Telm 80 + Hctz 12.5	132	NR	No	seated,trough	143	97	Fixed	Telm 80+Amlo 5+Hctz 12.5	Telm 80+Hctz 12.5	8	Yes
Hong , 2017	SBP 140-199 after 4 weeks on Amlo 5 + losa 50	340	DM 17%	No	seated, NR	151	92	Forced uptitration	Amlo 5+ losa 100+Chlo 25	Amlo 5+ losa 100	8	Yes
Mourad , 2017	SBP/DBP ≥150/95 after 1 month on peri 5 + inda 1.25	454	NR	No	seated,trough	160	101	Fixed	Peri 5+inda 1.25+ Amlo 5	Peri 5+inda 1.25	4	Yes
Higaki, 2016	DBP 90-114, SBP ≤200, after 6 weeks on Telm 80 + Amlo 5	309	NR	No	seated,trough	142	96	Fixed	Telm 80+Amlo 5+Hctz 12.5	Telm 80+Amlo 5	8	Yes
Sohn, 2016	SBP >140/90 or >130/80 for DM/CKD after 4 weeks on Olme 20 + Hctz 12.5	341	DM 20% CKD 11%	No	seated, NR	147	94	Fixed	Olme 20+Amlo 5+Hctz 12.5	Olme 20+Hctz 12.5	8	Yes

Rump , 2016	SBP≥140, DBP≥90 after 4 weeks on olme40+amlo10	808	DM 13% Obese 49% CVD 36% CKD 3%	No	Seated, NR	148.3	93.7	Fixed	olme40+amlo10+hctz12.5 olme40+amlo10+hctz25	olme40+amlo10	8	Yes
Rakugi , 2015-2	DBP 90-109 & SBP 140-199 after 8 weeks on Losa 50 + Amlo 5	327	DM 13%	No	seated,trough	150	96	Fixed	losa 50+Amlo 5+Hctz 12.5	Losa 50+Amlo 5	8	Yes
Rakugi , 2015-1	DBP 90-109 & SBP 140-199 after 8 weeks on Losa 50 + Hctz 12.5	286	DM 16%	No	seated,trough	152	96	Fixed	Losa 50+Amlo 5+Hctz 12.5	Losa 50+Hctz 12.5	8	Yes
CS8635-A-E303, 2010	SBP 140-200 & DBP 90-115 after 4 weeks on Olme 40 + Amlo 10	808	NR	No	seated,trough	148	94	Fixed	Olme 40+Amlo 10+Hctz 12.5 Olme 40+Amlo 10+Hctz 25	Olme 40+Amlo 10	8	Yes
Sung , 2023	SBP≥140-<180, DBP<110	245	DM 61%	4	Seated, trough	152.6	92.1	Fixed	amlo1.67+losa16.67+chlor4.17 amlo1.67+losa16.67+chlor4.17 amlo1.67+losa16.67+chlor4.17	amlo1.67+losa16.67 losa16.67+chlor4.17 amlo1.67+chlor4.17	8	No
Rakugi, 2017	SBP 150-179, DBP 95-109 after 4 weeks on placebo	209	NR	4	seated,trough	161	100	Forced uptitration	Azil 20+Amlo 5+Hctz 12.5 Azil 20+Amlo 5+Hctz 6.25	Azil 20+Amlo 5	10	No
Volpe , 2012	SBP 160-199 & DBP 100-114 after 3 weeks washout	2690	DM 15% CKD 2% CVD 29% Obese 51%	3	seated,trough	168	104	Forced uptitration	Olme 20+Amlo 5+Hctz 12.5 Olme 40+Amlo 5+Hctz 12.5 Olme 40+Amlo 5+Hctz 25 Olme 40+Amlo 10+Hctz 12.5 Olme 40+Amlo 10+Hctz 25	Olme 20+Amlo 5 Olme 40+Amlo 5 Olme 40+Amlo 10	8	No
Wright , 2011	SBP 160-199 after 1-2 weeks of washout	488	DM 20%	1 to 2	seated, NR	168	98	Forced uptitration	Vals 160+Amlo 5+Hctz 25	Losa 100+Hctz 25	6	No
Oparil , 2010	SBP≥140, DBP≥100 (untreated) or ≥160 & ≥90 (treated-off treatment)	2492	DM 16% CKD 4% CVD 9%	3	seated,trough	169	101	Forced uptitration	Olme 40+Amlo 10+Hctz 25	Olme 40+Amlo 10 Olme 40+Hctz 25 Amlo 10+Hctz 25	8	No

Calhoun, 2009	SBP 145-199 &DBP 100-119 after 1-4 weeks on placebo	2271	NR	1 to 4	seated,trough	170	106	Forced uptitration	Vals 320+Amlo 10+Hctz 25	Vals 320+Hctz 25 Vals 320+Amlo 10 Amlo 10+Hctz 25	8	No
Anthony, 2024	SBP 140-179 (no drugs), SBP 130-170 (1 drug), SBP 120-160 (2 drugs), SBP 110-150 (3 drugs)	1385	NR	No	Seated, trough	142	85	Forced uptitration	Telm40+Amlo5+Inda2.5	Amlo5+Inda2.5 Telm40+Inda2.5 Telm40+Amlo5	12	No

0 = placebo; Amlo = Amlodipine; Aten = Atenolol; Azil = Azilsartan; Chlo = Chlorthalidone; CKD = Chronic kidney disease; CVD = Cardiovascular disease; DBP = Diastolic blood pressure; DM = Diabetes Mellitus; Dysli- Dyslipidaemia; Hctz = Hydrochlorothiazide; Inda = Indapamide; Losa = Losartan; NR = not reported; Olme = Olmesartan; Peri = Perindopril; Rami = Ramipril; SBP = Systolic blood pressure; Telm = Telmisartan; Triam = Triamterene; Vals = Valsartan

Appendix 5: *Low dose combination vs placebo: Mean systolic blood pressure reduction at first follow-up visit*



Appendix 6: Retail prices and affordability of alternative products in selected countries

Country	Type	Dose (mg)	No. Brands	Marketed by	Price/ tab (USD)	Cost for 1 month supply (USD)	Minimum Daily wage (USD)	Number of days' wages
India	Telmisartan/ Amlodipine/ Chlorthalidone	20 + 5 + 12.5	1	Wonset Healthcare	0.12	3.53	3.6	1.0
		40 + 5 + 6.25	12	(multiple)	0.13	3.80	3.6	1.1
		40 + 5 + 12.5	32	(multiple)	0.14	4.12	3.6	1.1
		80 + 5 + 6.25	5	(multiple)	0.21	6.21	3.6	1.7
		80 + 5 + 12.5	11	(multiple)	0.21	6.21	3.6	1.7
	Telmisartan/ Amlodipine/ Hydrochlorothiazide	20 + 2.5 + 6.25	1	Dr Reddy's Laboratories	0.17	4.95	3.6	1.4
		40 + 5 + 12.5	46	(multiple)	0.14	4.11	3.6	1.1
		80 + 5 + 12.5	4	(multiple)	0.21	6.17	3.6	1.7
	Losartan/ Amlodipine/ Chlorthalidone	50 + 5 + 6.25	3	Torrent Pharmaceuticals	0.13	3.81	3.6	1.1
		50 + 5 + 12.5	4	(multiple)	0.09	2.82	3.6	0.8
	Losartan/ Amlodipine/ Hydrochlorothiazide	50 + 5 + 12.5	3	Zydus Cadilla, Sun Pharmaceutical Industries, Micro Labs	0.16	4.72	3.6	1.3
	Olmesartan/ Amlodipine/ Chlorthalidone	20 + 5 + 6.25	1	Torrent Pharmaceuticals	0.14	4.25	3.6	1.2
		20 + 5 + 12.5	43	(multiple)	0.20	5.94	3.6	1.7
		40 + 5 + 6.25	2	Torrent Pharmaceuticals	0.28	8.28	3.6	2.3
		40 + 5 + 12.5	40	(multiple)	0.21	6.26	3.6	1.7
Kenya	Amlodipine/Losartan/ Hydrochlorothiazide	5 + 50 + 12.5	2	Micro Labs	0.46	13.68	2.3	5.9
	Amlodipine/Telmisartan/ Hydrochlorothiazide	80 + 5 + 12.5	1	N/A	0.77	23.04	2.3	10.0

Appendix 7: Certainty of evidence assessment using GradePRO

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Triple	Dual	Relative (95% CI)	Absolute (95% CI)		
Reduction in SBP												
18	randomised trials	not serious	not serious	not serious	not serious	strong association dose response gradient	6341	7827	-	MD **5.4 mm Hg lower** (6.2 lower to 4.7 lower)	⨁⨁⨁⨁ High	CRITICAL
Reduction in DBP												
18	randomised trials	not serious	not serious	not serious	not serious	strong association	6341	7827	-	MD **3.2 mm Hg lower** (3.7 lower to 2.6 lower)	⨁⨁⨁⨁ High	CRITICAL
BP control												
13	randomised trials	not serious	not serious	not serious	not serious	none	3233/4840 (66.8%)	3107/6192 (50.2%)	**RR 1.3** (1.2 to 1.4)	**151 more per 1,000** (from 100 more to 201 more)	⨁⨁⨁⨁ High	CRITICAL
Any adverse event												
18	randomised trials	not serious	serious	not serious	serious	none	2629/5615 (46.8%)	2458/6745 (36.4%)	**RR 1.7** (1.5 to 2.0)	**255 more per 1,000** (from 182 more to 364 more)	⨁⨁◯◯ Low	IMPORTANT
Treatment-related adverse events												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Triple	Dual	Relative (95% CI)	Absolute (95% CI)		
17	randomised trials	not serious	serious	not serious	serious	none	1186/5736 (20.7%)	1090/7108 (15.3%)	**RR 1.7** (1.4 to 1.9)	**107 more per 1,000** (from 61 more to 138 more)	⨁⨁◯◯ Low	IMPORTANT
Withdrawal due to adverse events												
16	randomised trials	very serious	serious	not serious	serious	none	263/5949 (4.4%)	239/7442 (3.2%)	**RR 1.4** (1.2 to 1.7)	**13 more per 1,000** (from 6 more to 22 more)	⨁◯◯◯ Very low	CRITICAL
CI: confidence interval; **RR:** risk ratio; **MD**: mean difference												

Appendix 8: Letters of support

October 16, 2024

From:
Professor Paul Whelton
President, the World Hypertension League
Show Chwan Health System Endowed Chair in Global Public Health,
Tulane University, New Orleans, Louisiana, USA

To:
Expert Committee on Selection and Use of Essential Medicines
The World Health Organisation
Geneva, Switzerland

Re: Application to add triple-drug fixed-dose antihypertensive medicine combinations to the 2025 World Health Organisation (WHO) Model List of Essential Medicines

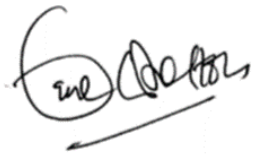
To the Expert Committee:

I am writing to you in my role as President of the World Hypertension League (WHL) and on behalf of the WHL Board of Directors (BOD). I am a clinician and investigator who has devoted his professional career to generation of rigorous evidence supporting the prevention and treatment of hypertension. The WHL has approximately 100 Council members, each of whom is a national or regional league or professional society dedicated to the prevention and treatment of high blood pressure. We are in official relations with the WHO and are strong supporters of the WHO guidelines for management of hypertension and implementation of the WHO HEARTS initiative. Our primary focus is at the population level in middle- and low-income countries. We assist our member organizations in their efforts to prevent and control hypertension across the globe.

I am writing to express my strongest support, and that of the WHL BOD, for the application to add single-pill triple-therapy fixed-dose combination antihypertensive medicines to the 2025 WHO Model List of Essential Medicines. The WHL previously supported the addition of dual-drug fixed dose antihypertensive medicines in 2019, which led to increased use of dual-drug combinations. I am especially familiar with the adoption of single-pill dual combination antihypertensive drug therapy in the Latin American & Caribbean regional HEARTS in the Americas program. Unfortunately, dual-drug combinations are not sufficient for successful treatment in many patients with hypertension. They require triple-drug therapy to reach their blood pressure control goal. This includes many adults at high risk for cardiovascular disease, for whom the WHO recommends a more intensive treatment goal of <130 mmHg systolic blood pressure.

There is no time to waste in terms of improving access to these essential triple drug combination medicines. Combination therapy simplifies and improves treatment outcomes for patients while concurrently streamlining procurement and supply chain processes for health system managers. On behalf of the WLD BOD, I strongly urge the Committee to include single-pill triple therapy antihypertensive drug combinations in the 2025 WHO EML.

Yours sincerely,



Paul K. Whelton, MB, MD, MSc
Show Chwan Chair in Global Public Health
Tulane University

President, World Hypertension League

cc: World Hypertension League Board of Directors

23 October 2024

From: Professor Elijah Ogola, President, the Pan-African Society of Cardiology (PASCAR)

To: Expert Committee on Selection and Use of Essential Medicines, The World Health Organization, Geneva, Switzerland

Re: Application to add triple-drug fixed-dose antihypertensive medicine combinations to the 2025 World Health Organization (WHO) Model List of Essential Medicines

To the Expert Committee:

On behalf of the Pan-African Society of Cardiology (PASCAR), I am writing to strongly support this application titled: **Application to add triple-drug fixed-dose antihypertensive medicine combinations to the 2025 World Health Organization (WHO) Model List of Essential.**

With recent evidence from high quality randomized trials of hypertension treatment interventions globally including in African populations, the need to add triple-drug fixed-dose antihypertensive medicine combinations to the World Health Organization (WHO) Model List of Essential Medicines cannot be over emphasized.

The need for such an addition is further strengthened by the result of the recently concluded VERONICA trial which was presented in Hotline II of the 2024 European Society of Cardiology Meeting in London and published simultaneously in the Journal of the American Medical Association. The trial demonstrated a 10-percentage point higher hypertension control and faster time to control with a triple-drug antihypertensive medicine combination compared to monotherapy and dual combinations, in Nigerian patients with hypertension, further strengthens the need for such an addition.

In addition, with more successes in the implementation of public health programmes on the African continent such as WHO-HEARTS, Healthy Hearts Africa, and the Hypertension Treatment in Nigeria Programme amongst others, the need for a more simplified treatment strategy hypertension and other cardiovascular diseases risk factors cannot be over-emphasized.

W www.pascar.org E info@pascar.org T +27 83 458 5954

Specifically, triple drug combinations have the advantage of providing practical advantages for patients and healthcare programs, including simpler dose schedules and decreased pill burden resulting in improved patient medication adherence, simplified medicine inventory, procurement, supply chain logistics, and fewer drug stock-outs, and greater ease of healthcare worker task sharing.

Based on the latest evidence and on the extraordinary unmet need to control hypertension in sub-Saharan Africa and globally, PASCAR strongly recommend adoption of the proposed triple drug fixed-dose combinations to the WHO EML.

Yours sincerely

Prof Elijah Ogola M.D., FACC, FESC
President Pan-African Society of Cardiology

W www.pascar.org E info@pascar.org T +27 83 458 5954

SIAC
SOCIEDAD INTERAMERICANA DE CARDIOLOGÍA

Our mission: to improve cardiovascular health in the Americas

October 25, 2024

Gautam Satheesh (The George Institute for Global Health)
Abdul Salam (The George Institute for Global Health)
Anthony Rodgers (The George Institute for Global Health)

Dear Dr. Satheesth, Dr. Salam and Dr. Rodgers:

On behalf of the Inter-American Society of Cardiology (SIAC), we support the application to add a triple-drug fixed dose anti-hypertensive medicine combination listed on the model list of essential medicines for treating essential hypertension in adults.

Based on scientific evidence, cost-benefit studies, the importance of the need for better control of blood pressure figures, and evidence indicating efficacy and safety for low-dose triple combinations among those uncontrolled on monotherapy or untreated.

From SIAC, we give our unreserved support to:

1) "Step up" therapy from dual drug combination;
2) Provide “Replacement" therapy, switching from three separate pills to a triple-drug combination pill;
3) Recommend initial/early therapy for those at high risk.

Thank you very much for the opportunity.

Sincerely,

Dra. Ana Múnera E.
President Elect

首都医科大学附属北京安贞医院

October 14, 2024

From:
Professor Cai Jun
President, Beijing Anzhen Hospital affiliated to Capital Medical University
President, Beijing Institute of Heart Lung and Blood Vessel Diseases
Beijing, China

To:
Expert Committee on Selection and Use of Essential Medicines
The World Health Organisation
Geneva, Switzerland

Re: Application to add triple-drug fixed-dose antihypertensive medicine combinations to the 2025 World Health Organisation (WHO) Model List of Essential Medicines

To the Expert Committee

As an expert in the science of hypertension and a clinical cardiologist dedicated to cardiovascular disease prevention in China, I am writing to express my strong support for the application to add triple drug fixed dose combination antihypertensive medicines to the WHO Model List of Essential Medicines List. Over 200 million Chinese adults are living with hypertension; only 16% of them have their blood pressure controlled below 140/90 mmHg.

In addition, recent Chinese guidelines recommend a more intensive blood pressure goal for hypertensive patients. The implication of these data is that too many Chinese adults living with hypertension are undertreated.

To reach national hypertension goals, more Chinese adults with hypertension will require three antihypertensive medicines to reach blood pressure control. Fixed-dose combinations are proven as superior to equivalent doses of separate pills in lowering blood pressure. Adding triple drug fixed dose antihypertensive medicines to the WHO EML is an important step toward ensuring access to these life-saving medicines.

Sincerely,

Cai Jun, MD

Centre for Chronic Disease Control
A World Health Organization (WHO) & Indian Council of Medical Research (ICMR) Collaborating Centre

October 17, 2024

To
Expert Committee on Selection and Use of Essential Medicines
The World Health Organization
Geneva, Switzerland

Re: Application to add triple-drug fixed-dose antihypertensive medicine combinations to the 2025 World Health Organization (WHO) Model List of Essential Medicines

To the Expert Committee,

Both as a Cardiologist and an Epidemiologist, I have devoted myself to the control of cardiovascular disease and other chronic non-communicable diseases in India and globally.
My research center, the Centre for Chronic Disease Control, has built strong evidence supporting a team-based, patient-centred approach to treating chronic conditions like hypertension.

I am writing the Committee to urge you to adopt triple-drug fixed dose combination antihypertensive medicines to the 2025 WHO Model List of Essential Medicines. Millions of people living with hypertension in India will have a very high blood pressure at the time of diagnosis (i.e., more than 20 mmHg systolic blood pressure higher than goal) and will require three medicines to reach that goal. As this application demonstrates, the most up-to-date evidence supports providing the three WHO-recommended antihypertensive medicine classes in a fixed-dose combination formulation.

Based on evidence and based on the extraordinary unmet need to control hypertension in India and globally, I recommend adoption of the proposed triple drug fixed-dose combinations.

Sincerely,

Prof Dorairaj Prabhakaran
M.D., DM (Cardiology), MSc, FRCP, FNASc, FNA, DSc (Honoris Causa)
Executive Director, Centre for Chronic Disease Control (CCDC)
Distinguished Professor, Public Health Foundation of India (PHFI)

C1/52, 2nd Floor, Safdarjung Development Area, New Delhi - 110016, India
+91-11-46082601, 41618456 ccdc@ccdcindia.org www.ccdcindia.org