Guideline for the pharmacological treatment of hypertension in adults

WEB ANNEX A

Summary of evidence



Guideline for the pharmacological treatment of hypertension in adults. Web Annex A. Summary of evidence ISBN 978-92-4-003399-3 (electronic version)

© World Health Organization 2021

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (http://www.wipo.int/amc/en/mediation/rules/).

Suggested citation. Guideline for the pharmacological treatment of hypertension in adults. Web Annex A. Summary of evidence. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, **rights and licensing**. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

This publication forms part of the WHO guideline entitled *Guideline for the pharmacological treatment of hypertension in adults*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014).

Contents

List o	f tables	3
PICO	question 1: At what level of blood pressure should pharmacological therapy be started to prevent cardiovascular events?	7
	Systematic review for desirable and undesirable effects	7
	Evidence to decision for PICO question 1	23
PICO	question 2: Is any laboratory testing necessary prior to initiation or during titration of pharmacological treatments?	25
	Systematic review for desirable and undesirable effects	25
	Evidence to decision for PICO question 2	27
PICO	question 3: Should cardiovascular risk assessment be used to guide initiation of antihypertensive medications?	29
	Systematic review for desirable and undesirable effects	29
	Evidence to decision for PICO question 3	32
PICO	question 4: In adults with hypertension requiring pharmacological treatment, which drugs should be used as first-line agen	
	Systematic review for desirable and undesirable effects	
PICO) question 5: In adults with hypertension requiring pharmacological treatment, which drugs (BB, CCB, diuretics, ACE, or AR BB, CCB, diuretics, ACE, or ARB in head-to-head studies) should be used as first-line agents?	
	Systematic review for desirable and undesirable effects	64
PICO	question 6: In adults with hypertension requiring pharmacological treatment, which drugs (monotherapy using BB, CCB, diuretics, ACE or ARB vs combination therapy using BB, CCB, diuretics, ACE or ARB) should be used as first-line agents'	? 113
	Systematic review for desirable and undesirable effects	113
PICO	Question 7: In adults with hypertension requiring pharmacological treatment, which combination therapy of two or more dru (BB, CCB, diuretics, ACE, or ARB) vs different combination therapy of two or more drugs (BB, CCB, diuretics, ACE, or AR should be used as first-line agents?	RB)
	Systematic review for desirable and undesirable effects	
	Evidence to decision for PICO questions 4–7	131
PICO	question 8: In adults with hypertension requiring pharmacological intervention, is the use of a single-pill combination of antihypertensive drugs associated with improved outcomes?	135
	Systematic review for desirable and undesirable effects	135
	Evidence to decision for PICO question 8	138
PICO) question 9: What target blood pressure should pharmacological treatment aim to achieve?	140
	Systematic review for desirable and undesirable effects	140
	Evidence to decision for PICO question 9	154
PICO	question 10: In adults with hypertension given pharmacological treatment, when should blood pressure be reassessed? Systematic review for desirable and undesirable effects	
	Evidence to decision for PICO question 10	160
PICO	on the provided by nonphysician care providers?	
	Systematic review for desirable and undesirable effects	
	Evidence to decision for PICO question 11	173
	AMSTAR table	
	References	

List of tables

Table 1 Components for PICO question 1	7
Table 2 Evidence profile 1a: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	8
Table 3 Evidence profile 1b: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	9
Table 4 Evidence profile 1c: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	9
Table 5 Evidence profile 1d: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 140-159 mmHg	
Table 6 Evidence profile 1e: Treatment compared to no treatment in patients with baseline BP 130–140 without CAD	
Table 7 Evidence profile 1f: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	14
Table 8 Evidence profile 1g: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure <140 mmHg and diabetes	
Table 9 Evidence profile 1h: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	17
Table 10 Evidence profile 1i: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	18
Table 11 Evidence profile 1j: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	19
Table 12 Evidence profile 1k: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood	20
Table 13 Evidence profile 1I: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 140-159 mmHg and a history of stroke or transient ischemic attack	21
Table 14 Evidence profile 1m: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure >160 mmHg and a history of stroke or transient ischemic attack	
	24
Table 16 Components for PICO question 2	
Table 17 Utilities per outcome for PICO question 2	28
	29
Table 19 Evidence Profile 3a: A formal cardiovascular risk estimation compared to no formal cardiovascular risk estimation in	
patients with hypertension without pre-identified cardiovascular disease who are starting antihypertensive medications	30
Table 20 Utilities per outcome for PICO question 3	33
Table 21 Components for PICO question 4	34
Table 22 Evidence profile 4a: Antihypertensive drug therapy (a mix of different class of antihypertensives) compared to placebo ir individuals with hypertension	
Table 23 Evidence profile 4b: Thiazide diuretics (low or high dose) compared to control in individuals with hypertension	
Table 24 Evidence profile 4c: Loop diuretics compared to placebo in individuals with hypertension	39
Table 25 Evidence profile 4d: Diuretic antihypertensive therapy compared to placebo in individuals with hypertension (mix of different diuretics – outcome of incident dementia and falls)	rent
Table 26 Evidence profile 4e: Beta-blocker (BB) compared to placebo in individuals with high BP	42
Table 27 Evidence profile 4f: Angiotensin converting enzyme inhibitor (ACEi) compared to placebo in treatment of hypertension	
Table 28 Evidence profile 4g: Angiotensin receptor blocker (ARB) compared to placebo in individuals with hypertension	46
Table 29 Evidence profile 4h: Calcium channel blocker (CCB) compared to placebo in individuals with hypertension	48
Table 30 Evidence profile 4i: Antihypertensive drug therapy compared to placebo or no therapy in individuals aged 18 to 59 years with hypertension	3
Table 31 Evidence profile 4j: Antihypertensive drug therapy compared to placebo or no active comparator therapy in individuals o 60 years with hypertension	ver
Table 32 Evidence profile 4k: Antihypertensive drug therapy compared to placebo or no treatment in individuals over 80 years with hypertension	54
Table 33 Evidence profile 4l: Dual alpha- and beta-blockers compared to placebo in individuals with hypertension	55
Table 34 Evidence profile 4m: Beta-1 selective beta-blocker compared to placebo in individuals with hypertension	
Table 35 Evidence profile4n: Angiotensin-converting enzyme inhibitor (ACEi) compared to placebo for non-dialysis chronic kidney disease stages 3–5	

Table 36 Evidence profile 4o Angiotensin II receptor blocker (ARB) compared to placebo for non-dialysis chronic kidney disease stages 3–5
Table 37 Evidence profile 4p: BP-lowering drugs compared to placebo or no treatment for patients with a history of stroke or transient ischaemic attack
Table 38 Evidence profile 4q: Antihypertensive drug therapy compared to placebo or no treatment in individuals with pre-
hypertensive levels of BP (systolic BP 120–139 mmHg and diastolic BP <90 mmHg)
Table 39 Components for PICO question 5
Table 40 Evidence profile 5a: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to calcium channel blocker (CCB)
for individuals with hypertension
Table 41 Evidence profile 5b: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to thiazide for individuals with
hypertension
Table 42 Evidence profile 5c: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to beta-blocker (BB) for individuals
with hypertension
Table 43 Evidence profile 5d: Angiotensin converting enzyme inhibitor (ACEi) compared to angiotensin receptor blocker (ARB) in
individuals with hypertension
Table 44 Evidence profile 5e: Beta-blocker (BB) compared to diuretic for individuals with hypertension
Table 45 Evidence profile 5f: Beta-blocker (BB) compared to calcium channel blocker (CCB) for individuals with hypertension75
Table 46 Evidence profile 5g: Beta-blocker (BB) compared to renin-angiotensin-aldosterone system inhibitor (RAASi) for individuals
with hypertension
Table 47 Evidence profile 5h: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to calcium channel blocker (CCB)
for hypertensive patients with type 2 diabetes mellitus
Table 48 Evidence profile 5i: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to beta-blocker (BB) for
hypertensive patients with type 2 diabetes mellitus
Table 49 Evidence profile 5j: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to diuretic for hypertensive patients
with type 2 diabetes mellitus
Table 50 Evidence profile 5k: Calcium channel blocker (CCB) use compared to non-calcium channel blocker use for elderly patients
with hypertension
Table 51 Evidence profile 5l: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to diuretic for black patients with
hypertension
Table 52 Evidence profile 5m: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to beta-blocker (BB) for black
patients with hypertension
Table 53 Evidence profile 5n: Renin-angiotensin-aldosterone-system inhibitor (RAASi) compared to calcium channel blocker (CCB)
for black patients with hypertension
Table 54 Evidence profile 5o: Calcium channel blocker (CCB) compared to non-calcium channel blocker antihypertensives for Asian
populations with hypertension
Table 55 Evidence profile 5p: Calcium channel blocker (CCB) compared to angiotensin receptor blocker (ARB) for Asian populations
with hypertension
Table 56 Evidence profile 5q: Angiotensin-converting enzyme inhibitor compared to angiotensin receptor blocker for hypertensive
patients with myocardial infarction or heart failure
Table 57 Evidence profile 5r: Angiotensin-converting enzyme inhibitors (ACEi) compared to diuretics for non-dialysis chronic kidney
disease stages 3–5
Table 58 Evidence profile 5s: Angiotensin-converting enzyme inhibitor (ACE) compared to calcium channel blocker (CCB) for non-
dialysis chronic kidney disease stages 3–597
Table 59 Evidence profile 5t: Angiotensin-converting enzyme inhibitor (ACE) compared to beta-blocker for non-dialysis chronic
kidney disease stages 3–599
Table 60 Evidence profile 5u: Angiotensin-converting enzyme inhibitor (ACE) compared to Angiotensin II receptor blocker (ARB) for
non-dialysis chronic kidney disease stages 3–5101
Table 61 Evidence profile 5v: Angiotensin II receptor blocker (ARB) compared to diuretics for non-dialysis chronic kidney disease
stages 3–5103
Table 62 Evidence profile 5w: Angiotensin II receptor blocker (ARB) compared to calcium channel blocker (CCB) for non-dialysis
chronic kidney disease stages 3–5105
Table 63 Evidence profile 5x: Angiotensin II receptor blocker (ARB) compared to beta-blocker (BB) for non-dialysis chronic kidney
disease stages 3–5107
Table 64 Evidence profile 5y: Beta-blocker (BB) compared to angiotensin receptor blocker (ARB) for individuals with hypertension
and non-dialysis chronic kidney disease 3-5108

Table 65 Evidence profile 5z: Calcium channel blocker (CCB) compared to non-calcium channel blocker for individuals with
hypertension and established cardiovascular disease (defined through patient history or investigations)
Table 66 Evidence profile 5aa: Calcium channel blocker (CCB) compared to non-calcium channel blocker for individuals with hypertension and previous stroke
Table 67 Components for PICO question 6
Table 68 Evidence profile 6a: Combination therapy compared to monotherapy for individuals with hypertension
Table 69 Evidence profile 6b: Dual agents (ACEi/ARB and CCB) compared to single agent (ACEi/ARB only) for patients with
hypertension and chronic kidney disease
Table 70 Evidence profile 6c: Calcium channel blocker (CCB) + angiotensin receptor blocker (ARB) at standard-dose compared to
high-dose calcium channel blocker (CCB) for individuals with hypertension
Table 71 Evidence profile 6d: Dual renin-angiotensin-aldosterone inhibitor (RAASi) compared to RAASi monotherapy for non-dialysis
chronic kidney disease stages 3–5
Table 72 Components for PICO question 7
Table 73 Evidence profile 7a: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to
RAASi + diuretic for individuals with hypertension
Table 74 Evidence profile 7b: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to CCB + diuretic for individuals with hypertension
Table 75 Evidence profile 7c: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to
CCB + beta-blocker (BB) for individuals with hypertension
Table 76 Evidence profile 7d: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to
beta-blocker (BB) + diuretic for individuals with hypertension
Table 77 Evidence profile 7e: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to
renin angiotensin system (RAASi) inhibitor + diuretics for individuals with hypertension
Table 78 Utilities per outcome for PICO questions 4–7
Table 79 Components for PICO question 8
Table 80 Evidence profile 8a: Single-pill combination compared to no single-pill combination in patients with hypertension
Table 81 Utilities per outcome for PICO question 8
Table 82 Components for PICO question 9
Table 83 Evidence profile 9a: A systolic blood pressure target <130 mm/Hg compared to a systolic blood pressure target <140
mm/Hg in patients with hypertension141
Table 84 Evidence Profile 9b: A systolic blood pressure target <120 mm/Hg compared to a systolic blood pressure target 130-139
mm/Hg in patients with hypertension who are >65 years old
Table 85 Evidence Profile 9c: A systolic blood pressure target <130 mm/Hg compared to a systolic blood pressure target 130-149
mm/Hg in patients with hypertension who are >65 years old
Table 86 Evidence profile 9d: A systolic blood pressure target <140 mm/Hg compared to a systolic blood pressure target 140–160
mm/Hg in patients with hypertension who are >65 years old
Table 87 Evidence profile 9e: A blood pressure target <140/90 mmHg compared to a blood pressure target <150 to 160/ 95 to 105
mm/Hg in patients with hypertension who are >65 years old
Table 88 Evidence profile 9f: A systolic blood pressure target <130 mm/Hg compared to a systolic blood pressure target <140
mm/Hg in patients with ischemic stroke, haemorrhagic stroke, or transient ischemic attack147
Table 89 Evidence profile 9g: A blood pressure target <135/85 mm/Hg compared to a blood pressure target <140 to 160/90 to 100
mm/Hg in patients with hypertension and cardiovascular disease
Table 90 Evidence profile 9h: A systolic blood pressure target < 120 (mmHg) compared to a systolic blood pressure target <140
(mmHg) for individuals with hypertension and chronic kidney disease and without diabetes
Table 91 Utilities per outcome for PICO question 10
Table 92 Components for PICO question 10
Table 93 Evidence profile 10a: A 3-month interval compared to a 6 month interval for reassessment of patients with hypertension
receiving pharmacological treatment
Table 94 Evidence profile 10b: An approximately 3-month interval compared to an approximately 1 month interval for reassessments
of patients with hypertension receiving pharmacological treatment
Table 95 Utilities per outcome for PICO question 10
Table 96 Components for PICO question 11
Table 97 Evidence profile 11a: Pharmacological management by a pharmacist compared to usual care in patients with hypertension
163
Table 98 Evidence profile 11b: Pharmacological management by a nurse compared to usual care in patients with hypertension165
Table 99 Evidence profile 11c: Self-management (self-monitoring) compared to usual care in patients with hypertension167

Table 100 Evidence profile 11d: Pharmacological management by a pharmacist compared to usual care in patients with	
hypertension in low- and middle-income countries	169
Table 101 Evidence profile 11e: Pharmacological management by a nurse compared to usual care in patients with hypertension in	١
low- and middle-income countries	170
Table 102 Evidence profile 11f: Pharmacological management by a dietitian compared to usual care in patients with hypertension	in
low- and middle-income countries	171
Table 103 Evidence profile 11g: Pharmacological management by a community health worker compared to usual care in patients	
with hypertension in low- and middle-income countries	172
Table 104 Utilities per outcome for PICO question 11	175

PICO question 1: At what level of blood pressure should pharmacological therapy be started to prevent cardiovascular events?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 1) to determine at what level of blood pressure pharmacological therapy should be started to prevent cardiovascular events (Tables 3–15).

Table 1 Components for PICO question 1

Population	Intervention	Comparison	Outcome	Subgroup
Adults suspected of or who have hypertension	Specific systolic and diastolic blood pressure thresholds*: - Systolic (mm Hg): - ≥120 - ≥130 - ≥140 - ≥150 - Diastolic (mm Hg): - ≥80 - ≥90	 placebo systolic or diastolic BP threshold that is higher than intervention thresholds 	 death (all-cause mortality) cardiovascular death (death from MI, sudden cardiac death or stroke) stroke myocardial infarction end-stage kidney disease cognitive impairment/ dementia heart failure events adverse effects 	 based on different effect modifiers such as: estimated cardiovascula risk (pre-existing cad) stroke diabetes age sex chronic kidney disease race/ethnicity



https://www.yunbaogao.cn/report/index/report?reportId=5_23648



