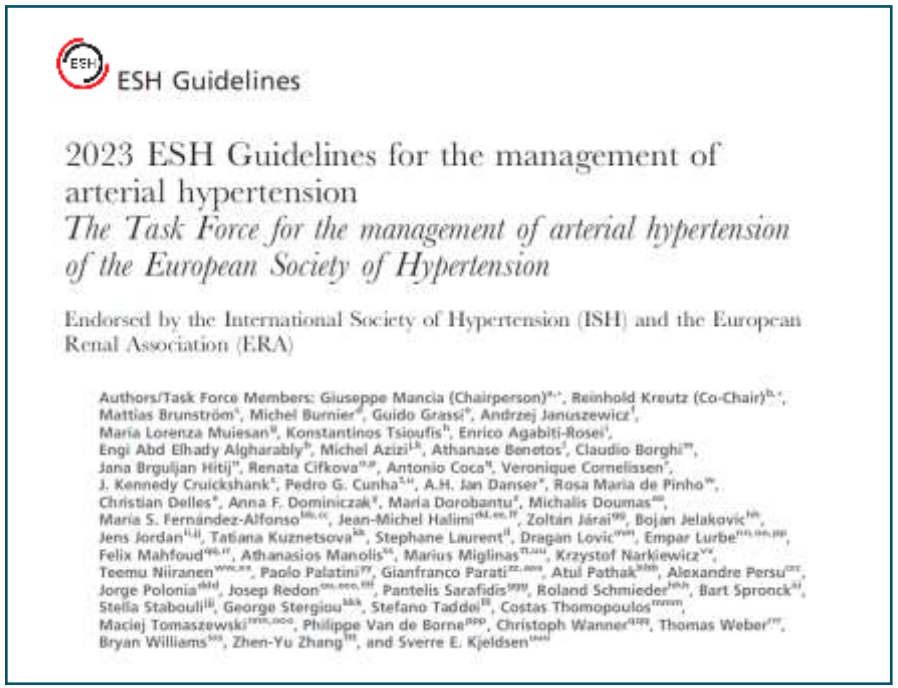
NEW HORIZONS FOR TREATMENT OF HYPERTENSION

- PROF.DR ERTUGRUL OKUYAN
- ISTANBUL



ESH Guidelines

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

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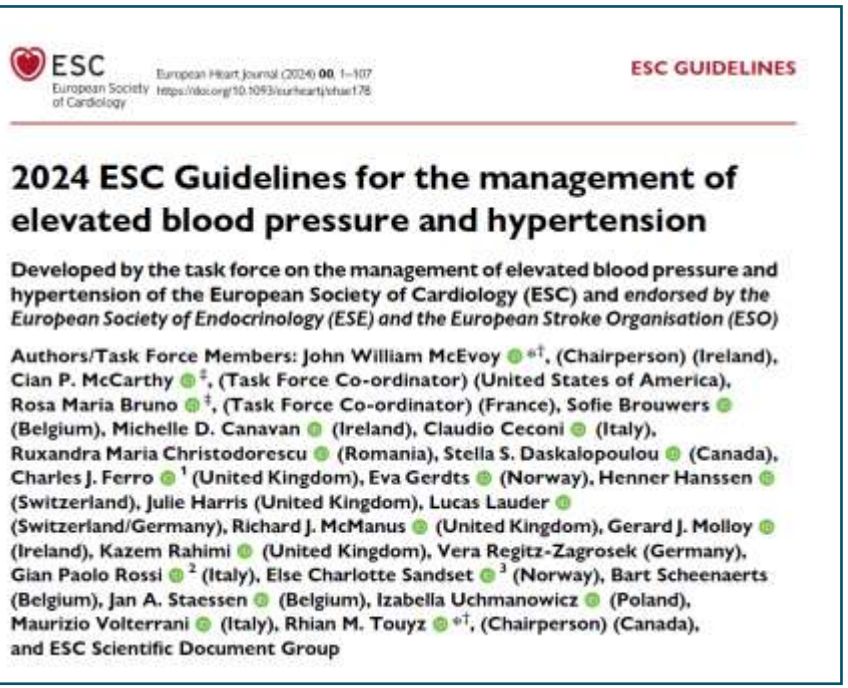

ESC European Society of Cardiology

European Heart Journal (2024) 00, 1–107 https://doi.org/10.1093/eurheartj/ehae178

ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and *endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)*

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Optimal BP	<120/80 mmHg	
Normal BP	120-129/80-84 mmHg	
High-normal BP	130-139/85-89 mmHg	
Hypertension	≥140/90 mmHg	Grade 1: 140-159/90-99 mmHg Grade 2: 160-179/100-109 mmHg Grade 3: ≥180/≥110 mmHg

Recommendations and statements	CoR	LoE
It is recommended that BP is classified as optimal, normal, high normal, or grade 1, 2 or 3 hypertension, according to office BP.	I	C
In addition to grades of hypertension, which are based on BP values, it is recommended to distinguish stage 1, 2, and 3 hypertension. **Stage 1:** Uncomplicated hypertension without HMOD, diabetes, CVD and without CKD ≥ stage 3. **Stage 2:** Presence of HMOD, diabetes, or CKD stage 3. **Stage 3:** Presence of CVD or CKD stage 4 or 5.	I	C

ESC

Non elevated BP	<120/70 mmHg
NEW **Elevated BP**	120-139/70-89 mmHg
Hypertension	≥140/90 mmHg

No hypertension grades defined NEW

BP: blood pressure. **CKD**: chronic kidney disease. **CVD**: cardiovascular disease. **HMOD**: hypertension-mediated organ damage.

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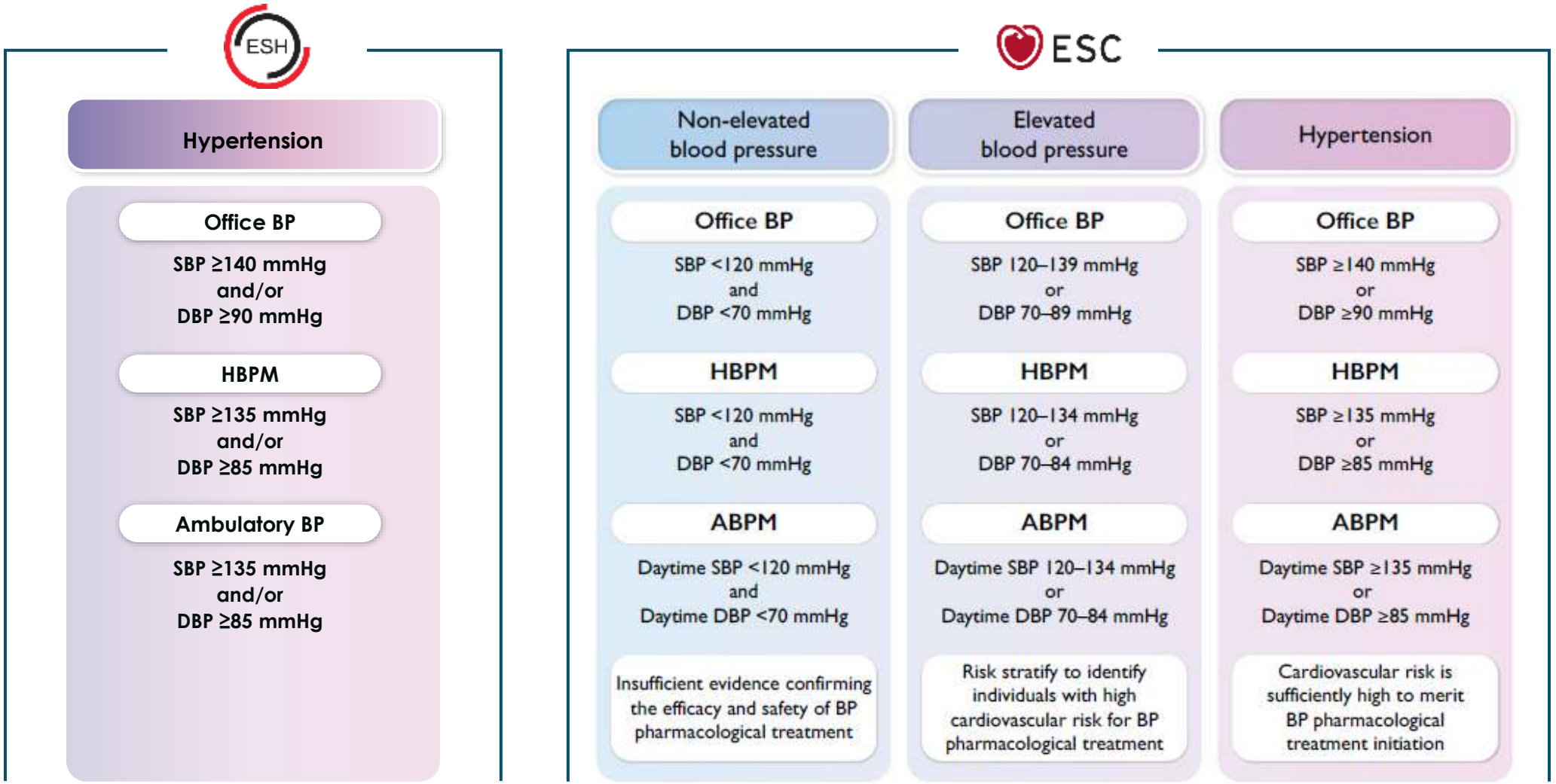

ABPM: ambulatory blood pressure measurement. **DBP/SBP**: diastolic/systolic blood pressure. **HBPM:** home blood pressure measurement.

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Estimation of total CV risk is recommended in each hypertensive patient **because of its relevance for hypertension management.**

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors[a]	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Moderate to high risk	High risk	High risk	Very high risk
Stage 3	Established CVD or CKD grade ≥4	Very high risk	Very high risk	Very high risk	Very high risk

Risk assessment in hypertension with SCORE2 and SCORE2-OP

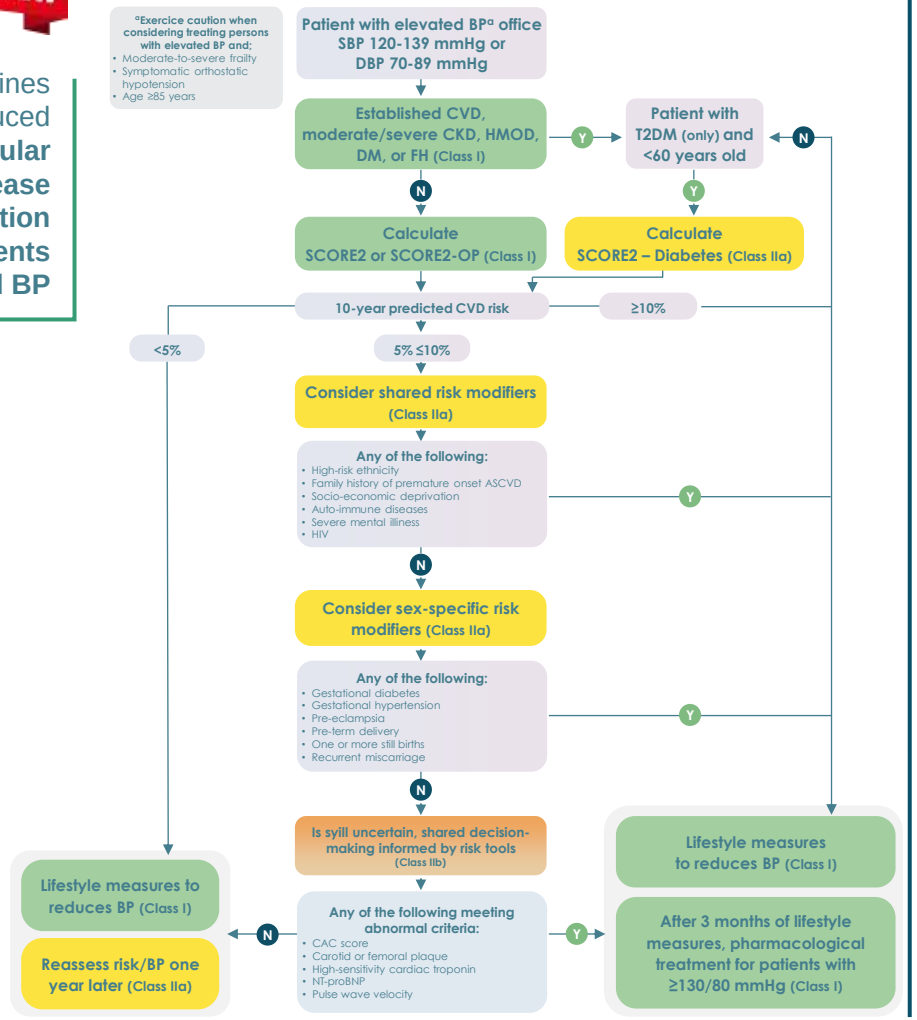
	<50 years	60–69 years	≥70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

Complementary risk estimation in Stage 1 with SCORE2/SCORE2-OP

Recommendations and statements	CoR	LoE
CV risk assessment with the SCORE2 and SCORE2-OP system is recommended for hypertensive **patients who are not already at high or very high risk** due to established CVD or CKD, long-lasting or complicated diabetes, severe HMOD (e.g. LVH) or a markedly elevated single risk factor (e.g. cholesterol, albuminuria).	I	B

ESC NEW

ESC 2024 guidelines introduced **Cardiovascular disease risk-stratification approach in patients with elevated BP**



ASCD: atherosclerotic cardiovascular disease. **BP:** blood pressure. **CAC:** coronary artery calcium. **CV:** cardiovascular. **CVD:** cardiovascular disease. **CKD:** chronic kidney disease. **DM:** diabetes mellitus. **HMOD:** hypertension mediated organ damage. **HIV:** human immunodeficiency virus. **NT-proBNP:** N-terminal pro-brain natriuretic peptide. **SCORE-2/2-OP:** Systematic COronary Risk Evaluation 2/Older Persons

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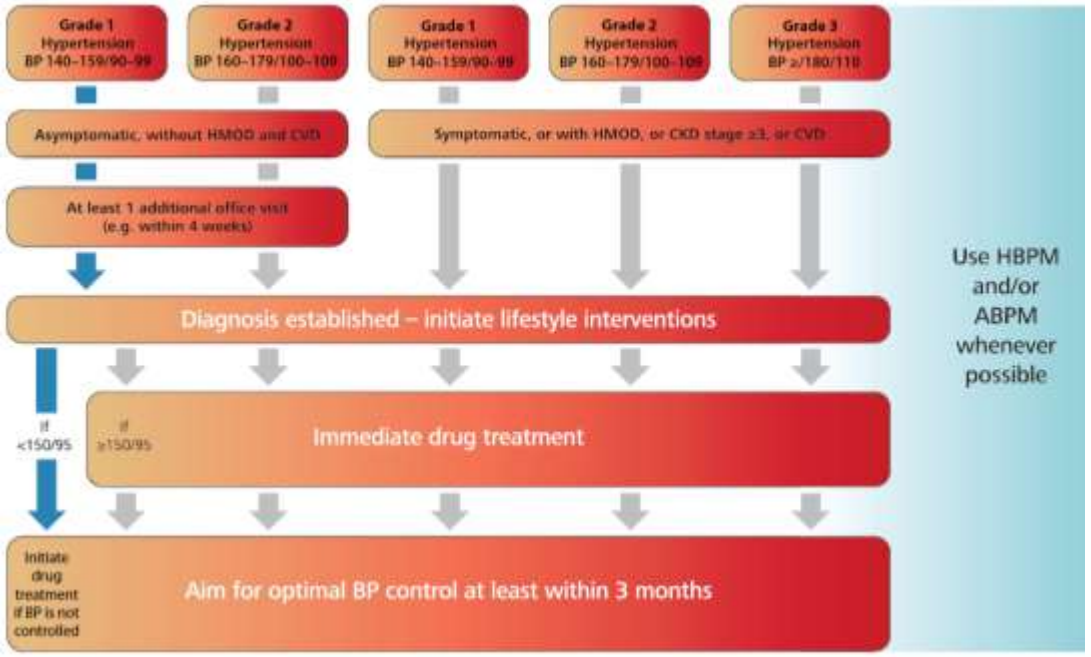
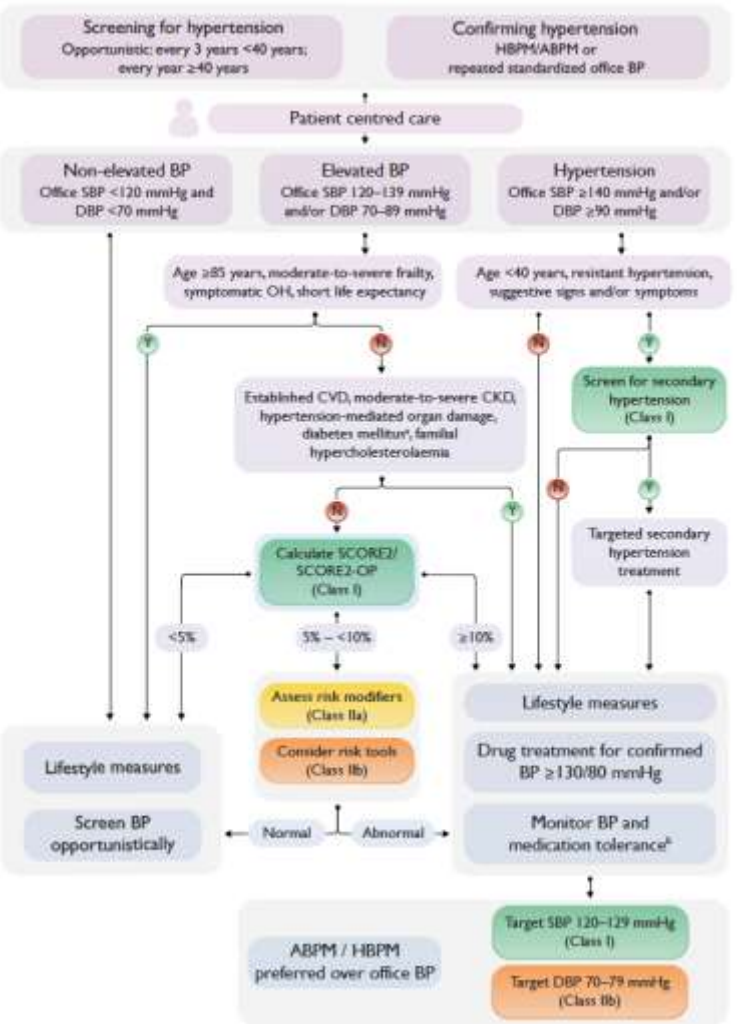
Treatment should be initiate according to BP value and CV risk



"The decision regarding treatment may be different ***in patients with a high-normal BP and a very high CV risk****.[…]* ***treating people with high-normal BP and established CVD, especially CAD, can be recommended because this has a protective effect, albeit limited to some BP-dependent outcomes and restricted to patients at very high CV risk****. It should be considered, however, that the* ***vast majority of these patients will probably already be under BP-lowering drugs****, administered in the context of GDMT (e.g. RAS inhibitors or BBs in patients with CAD)* ***for their direct CV protective properties****."*

CVD risk-stratification approach at the heart of the decision-making for BP treatment in adults with elevated BP



ABPM: ambulatory blood pressure measurement. **BB:** beta-blocker. **CAD:** coronary artery disease. **CKD:** chronic kidney disease. **CVD:** cardiovascular disease. **DBP/SBP:** diastolic/systolic blood pressure. **HBPM:** home blood pressure measurement. **HMOD:** hypertension-mediated organ damage. **SBP:** systolic blood pressure. **SCORE-2/2-OP:** Systematic COronary Risk Evaluation 2/Older Persons

ESH

In most patients 120-

Systolic BP target

Diastolic BP target

Recommendations	Class	Level
Patients 18 to 64 years old		
The goal is to lower office BP to <130/80mmHg.	I	A
Patients 65 to 79 years old		
The primary goal of treatment is to lower BP to <140/80mmHg.	I	A
However, lowering BP to below 130/80mmHg can be considered if treatment is well tolerated.	II	B
Patients 65 to 79 years old with ISH		
The primary goal of treatment is to lower SBP in the 140 to 150 mmHg range.	I	A
However, a reduction of office SBP in the 130 to 139 mmHg range should be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	I	B
Patients ≥80 years old		
Office SBP should be lowered to a SBP in the 140 to 150 mmHg range.	I	A
However, reduction of office SBP between 130 to 139 mmHg may be considered if well tolerated, albeit cautiously if DBP is already below 70 mmHg.	II	B

[a] Despite the smaller incremental benefit, an **effort should be made to reach a BP range of 120-129/70-79 mmHg in patients up to 79 years old**, but only if treatment is well tolerated. Evidence on the advantages of this lower BP target range is not available or unequivocal in a number of clinically important subgroups of patients (e.g. patients with LVH, CKD, or ISH). These issues are discussed in the sections on special conditions (see Sections 17 to 20).

[a] In patients **at least 80 years old who are not frail, the first objective** of antihypertensive treatment is **to lower BP below 150 mmHg**. However, a SBP target range between **130-139 mmHg may be considered, if well tolerated.**

[a] **In very frail patients, treatment targets should be individualized.**

ESC

In most patients SBP

Pre-treatment symptomatic orthostatic hypotension and/or age >85 years

Recommendations	Class	Level
To reduce CVD risk, it is recommended that treated systolic BP values in most adults be targeted to **120– 129 mmHg**, provided the treatment is well tolerated.	I	B
In cases where BP-lowering treatment is poorly tolerated and achieving a systolic of 120–129 mmHg is not possible, it is recommended **to target a systolic BP level that is 'as low as reasonably achievable'** (ALARA principle).	I	B
Because the CVD benefit of an on-treatment systolic BP target of 120–129 mmHg may not generalize to the following specific settings, personalized and more lenient BP targets (e.g. <140 mmHg) should be considered among patients meeting the following criteria: pre-treatment symptomatic orthostatic hypotension, and/or age ≥85 years.	IIa	C
Because the CVD benefit of an on-treatment systolic BP target of 120–129 mmHg may not generalize to the following specific settings, personalized and more lenient BP targets (e.g. <140/90 mmHg) may be considered among patients meeting the following criteria: clinically significant moderate-to-severe frailty at any age, and/or limited predicted lifespan (<3 years).	IIb	C
In cases where on-treatment systolic BP is at or below target (120–129 mmHg) but diastolic BP is not at target (≥80 mmHg), intensifying BP-lowering treatment **to achieve an on-treatment diastolic BP of 70–79 mmHg** may be considered to reduce CVD risk.	IIb	C

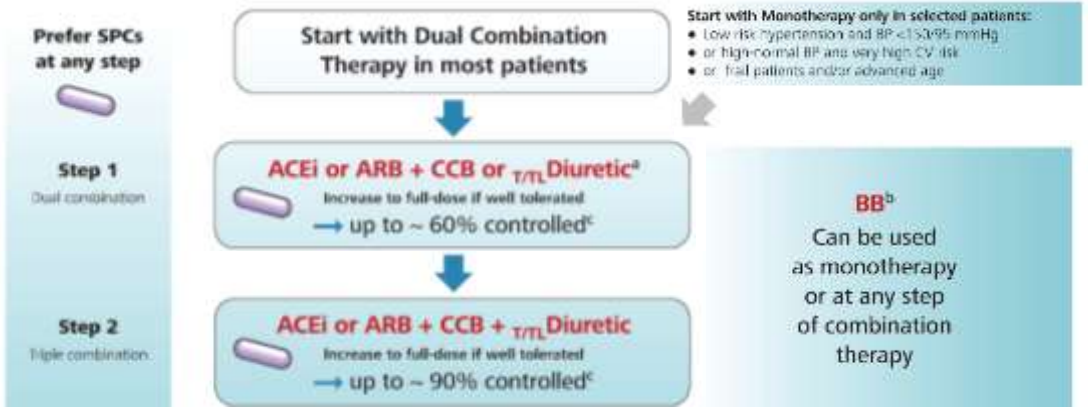
FIGURE 20: **Systolic blood pressure categories and treatment target range.**

BP: blood pressure. **CV:** cardiovascular. **DBP/SBP:** diastolic/systolic blood pressure; **ISH**, isolated systolic hypertension.

ESH 2023 & ESC 2024 guidelines

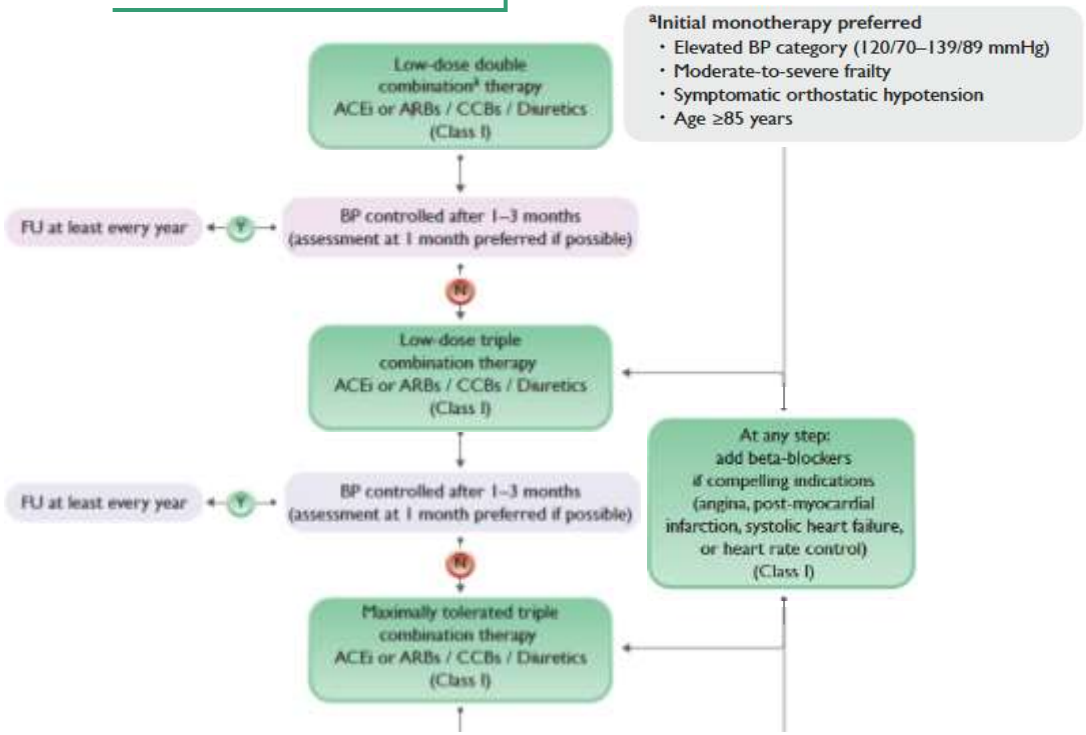
Full doses for dual & triple combinations

Uptitrate to the maximal tolerated doses of dual combination before adding a third drug



Earlier use of triple combination

Continue with triple low-dose combination rather than uptitrate dual combination



ACEi: angiotensin-converting enzyme inhibitor. **ARB:** angiotensin receptor blocker. **BB:** beta-blocker. **BP:** blood pressure.
CCB: calcium channel blocker. **CV:** cardiovascular. **eGFR:** estimated glomerular filtration rate. **FU:** follow-up. **SPC:** single-pill combination.
T/TL: thiazide/thiazide-like

ESH

Recommendations and statements	CoR	LoE
The use of single pill combinations (SPCs) should be **preferred at any treatment step**, i.e. during initiation of therapy with a two-drug combination and at any other step of treatment.	I	B

ESC NEW

Recommendations	Class	Level
In patients receiving **combination BP-lowering treatment, fixed-dose single-pill combination** treatment is recommended.	I	B
In BP is not controlled with a two-drug combination, increasing to a three-drug combination is recommended, usually a RAS blocker with a dihydropyridine CCB and thiazide/thiazide-like diuretic, and **preferably in a single-pill combination.**	I	B

BP: blood pressure. **CCB**: calcium channel blocker. **eGFR**: estimated glomerular filtration rate. **RAS**: renin-angiotensin system.

TABLE S7
Doses of first-line BP-lowering drugs

Drug class	Drug name	Low dose (mg/day)	Standard dose (mg/day)	High dose (mg/day)	Recommended dosing regimen
ACE inhibitors					
	Captopril	12.5	50	100	b.i.d.
	Enalapril	5	10	40	o.d.
	Perindopril	**2.5**	**5**	**10**	**o.d**
ARBs					
	Candesartan	4	8–16	32	o.d.
	Irbesartan	75	150	300	o.d.
	Losartan	25	50–100	100	o.d.
	Olmesartan	10	20	40	o.d.
	Telmisartan	40	40–80	80	o.d.
	Valsartan	80	16	320	o.d.
	Azilsartan	40	40–80	80	o.d.
Calcium channel blockers					
Dihydropyridines	**Amlodipine**	**5**	**5-10**	**10**	**o.d**
	Lercanidipine	10	10–20	20	o.d.
	Nifedipine	30	30–60	90	o.d.
	Manidipine	10	10–20	40	o.d.
Diuretics					
Thiazide and thiazide-like diuretics	Chlorthalidone	12.5	12.5–25	25	o.d.
	Indapamide	**1.25**	**2.5**	**2.5**	**o.d**
Potassium-sparing diuretics					
	Eplerenone	25	50	200	o.d. (b.i.d. may be needed)
	Spironolactone	12.5	25	100	o.d.
Beta-blockers[a]					
	Bisoprolol	**2.5**	**5**	**10-20**	**o.d**
	Labetalol[b]	100	200	400	b.i.d.
	Metoprolol succinate	25	50	100	o.d.
	Metoprolol tartrate	25	50	100–200	b.i.d.
	Nebivolol[b]	2.5	5	10	o.d.
	Propranolol	40	80	160	b.i.d.

NEW

Coversyl® - Hypertension

"The **recommended starting dose is 5mg** given once daily in the morning."

Starting dose of 2.5 mg is recommended for:

- Patients with a strongly activated RAAS
  (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension)
- In hypertensive patients in whom the diuretic cannot be discontinued
- In elderly patients

RAS: renin-angiotensin-aldosterone system

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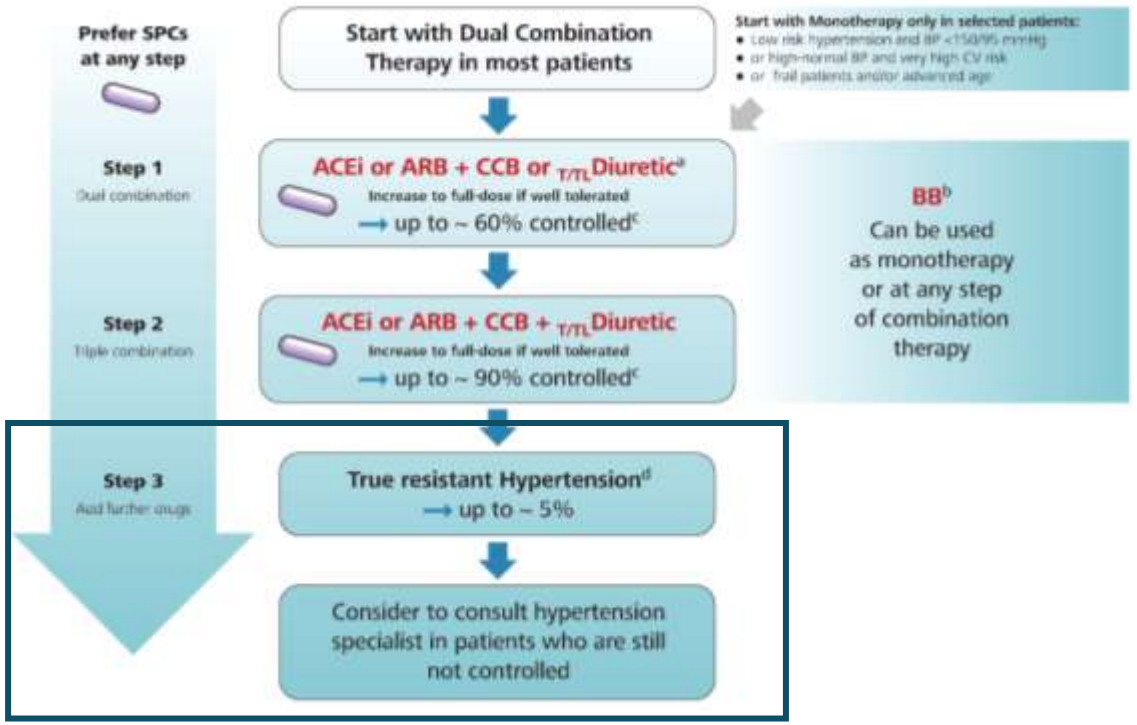
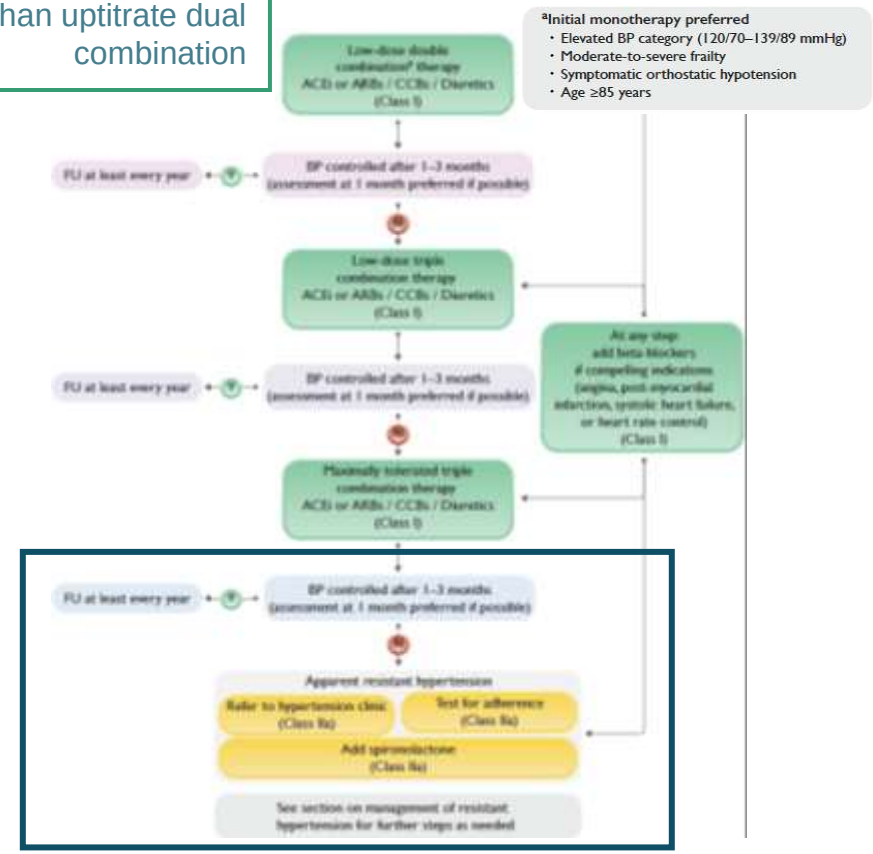
Full doses for dual & triple combinations

Uptitrate to the maximal tolerated doses of dual combination before adding a third drug



Earlier use of triple combination

Continue with triple low-dose combination rather than uptitrate dual combination



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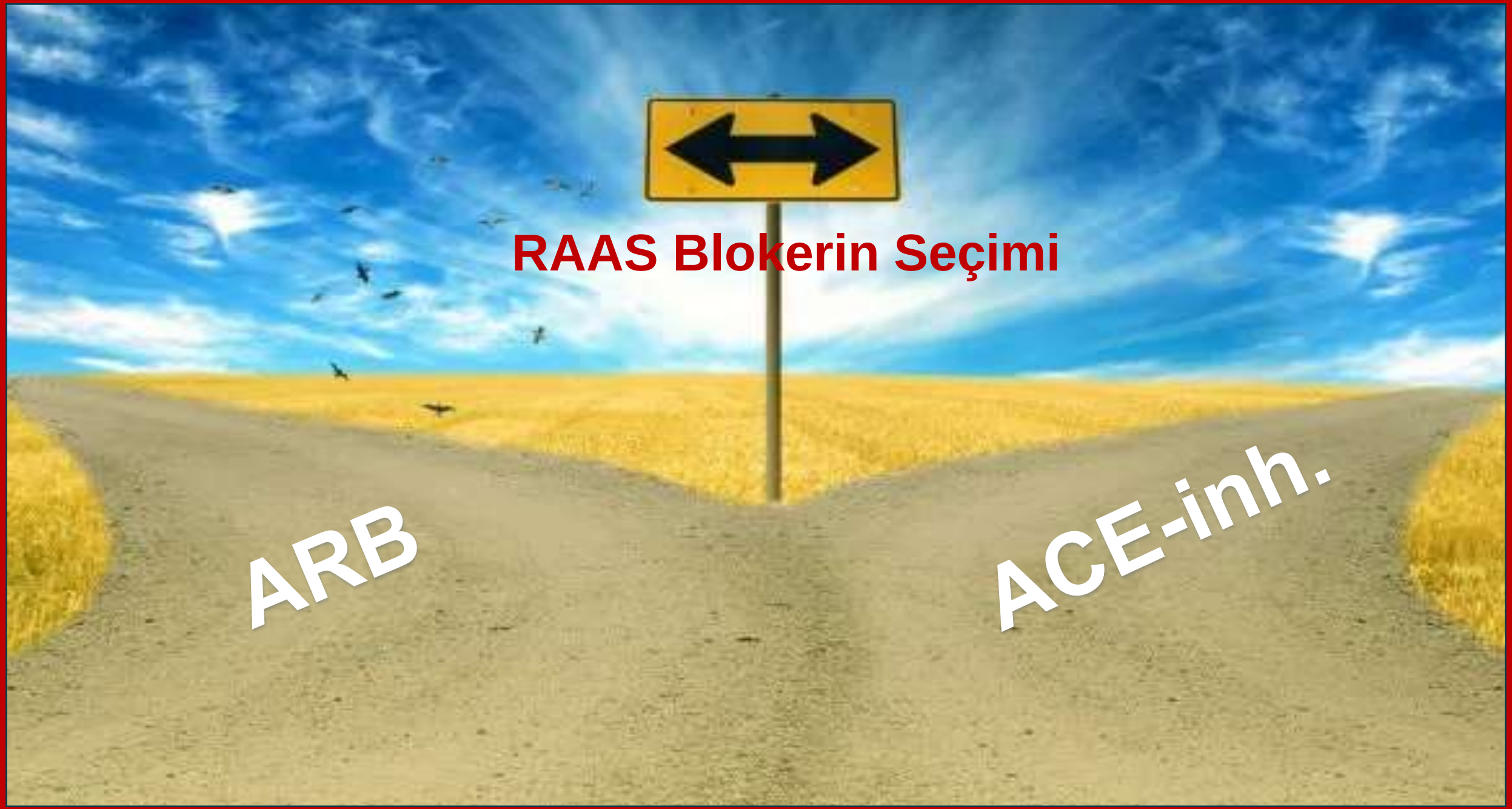

RAAS Blokerin Seçimi
ARB
ACE-inh.

Systematic Review and Meta-Analysis

Medicine®

13 trials

Comparison of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular outcomes in hypertensive patients with type 2 diabetes mellitus

A PRISMA-compliant systematic review and meta-analysis

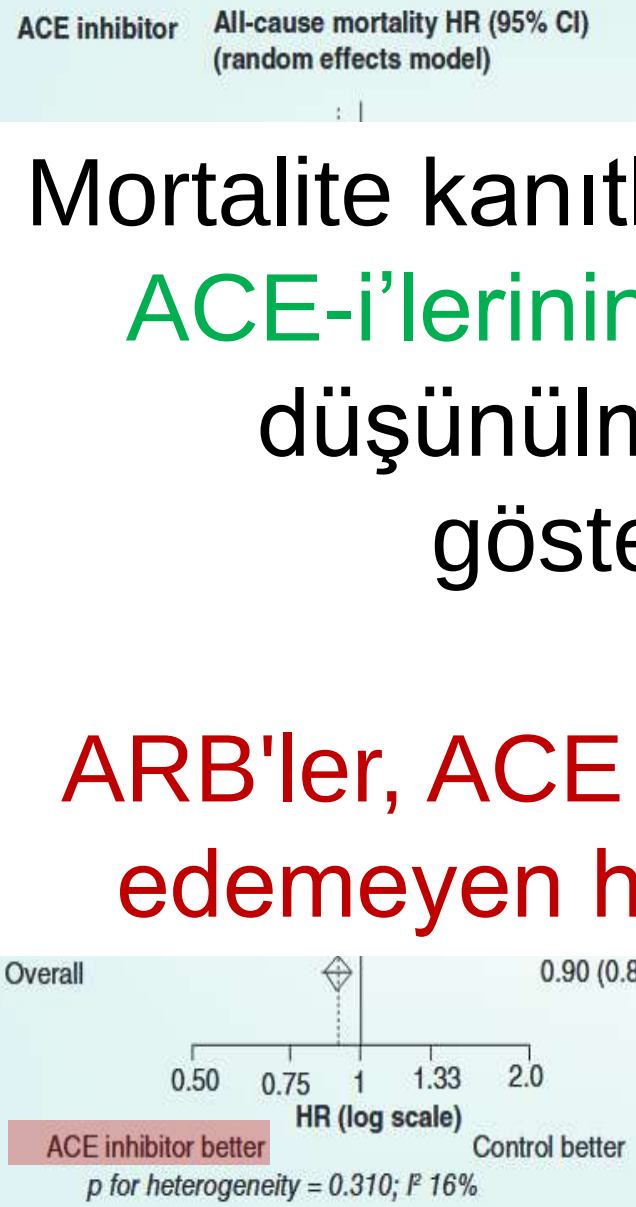
Treatment with ACEI showed a significant CV protection for all-cause mortality, CV death, and major CV events, whereas ARBs had no benefits.

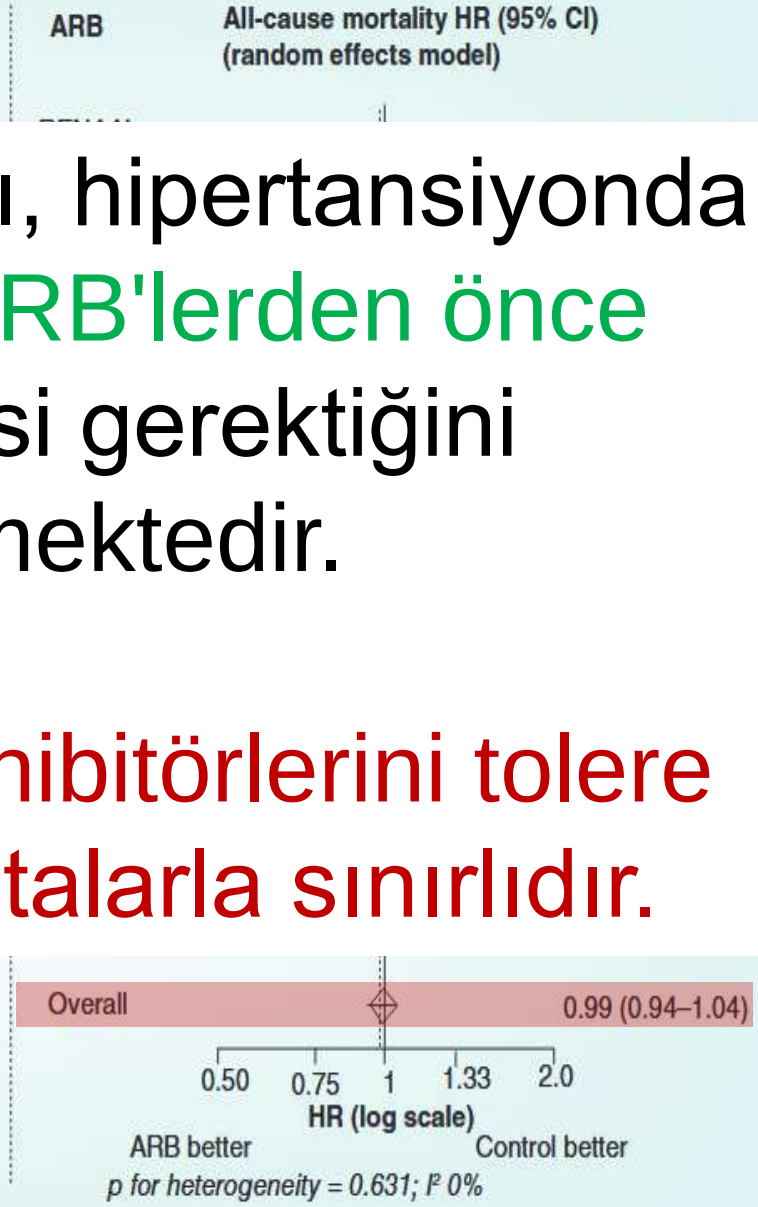
Medicine (Baltimore). 2018 Apr; 97(15): e0256

EXPERT REVIEWS

The impact of ACE inhibition on all-cause and cardiovascular mortality in contemporary hypertension trials: a review

Expert Rev. Cardiovasc. Ther. 11(6), 705–717 (2013)





Mortalite kanıtları, hipertansiyonda ACE-i'lerinin ARB'lerden önce düşünülmesi gerektiğini göstermektedir.

ARB'ler, ACE inhibitörlerini tolere edemeyen hastalarla sınırlıdır.

Figure 2. Angiotensin-Converting Enzyme Inhibitors (ACEIs) and All-Cause Mortality Stratified by Comparison Group (Placebo vs Active)

Study or Subgroup	ACEIs Events	ACEIs Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Weight, %
Placebo						
ADVANCE study,[34] 2007	408	5569	471	5571	0.87 (0.76-0.98)	21.1
Bauer et al,[41] 1992	1	18	0	15	2.53 (0.11-57.83)	0.1
DIABHYCAR study,[14] 2004	334	2443	324	2469	1.04 (0.90-1.20)	19.8
HOPE study,[30] 2000	196	1808	248	1769	0.77 (0.65-0.92)	17.1
Laffel et al,[42] 1995	1	70	0	73	3.13 (0.13-75.49)	0.1
Lewis et al,[25] 1993	8	207	14	202	0.56 (0.24-1.30)	1.7
Nankervis et al,[43] 1998	0	17	3	14	0.12 (0.01-2.13)	0.2
Parving et al,[44] 1989	1	15	1	17	1.13 (0.08-16.59)	0.2
PERSUADE substudy,[26] 2005	73	721	93	781	0.85 (0.64-1.14)	10.2
Ravid et al,[38] 1998	3	77	2	79	1.54 (0.26-8.96)	0.4
Sano et al,[45] 1994	1	31	0	31	3.00 (0.13-70.92)	0.1
Subtotal		**10976**		**11021**	**0.89 (0.79-0.99)**	**71.1**
Total Events	**1026**		**1156**			
Heterogeneity: $\tau^2=0.01$; $\chi^2=12.47$, $df=10$, $P=.25$; $I^2=20\%$						
Test for overall effect: $Z=2.13$, $P=.03$						
Active						
ABCD study,[33] 1998	13					
Bakris et al,[40] 1996	1					
CAPPP study,[29] 2001	20					
DETAIL study,[54] 2004	6					
FACET study,[31] 1998	4					
Fogari et al,[37] 2002	3					
JMIC-B study,[27] 2004	5					
STOP-2 substudy,[24] 2000	56					
UKPDS 39 study,[32] 1998	75					
Subtotal						
Total Events	**183**					
Heterogeneity: $\tau^2=0.06$; $\chi^2=13.26$, $df=8$, $P=.10$						
Test for overall effect: $Z=1.45$, $P=.15$						
Total		**12767**		**12777**	**0.87 (0.78-0.98)**	**100.0**
Total Events	**1209**		**1365**			
Heterogeneity: $\tau^2=0.01$; $\chi^2=25.79$, $df=19$, $P=.14$; $I^2=26\%$						
Test for overall effect: $Z=2.38$, $P=.02$						

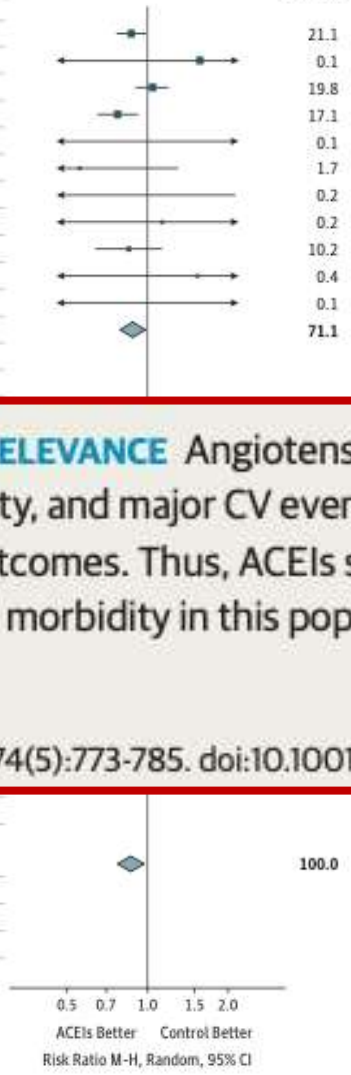
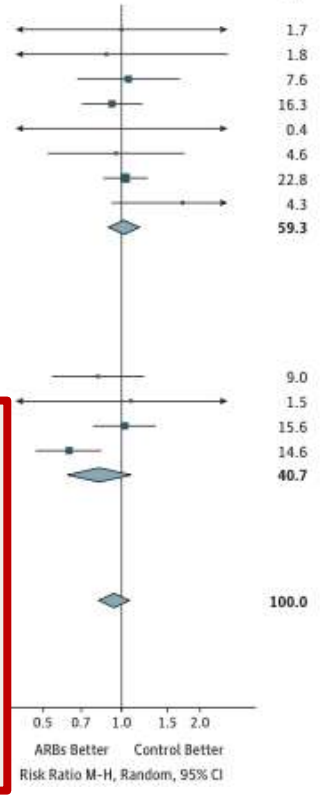


Figure 3. Angiotensin II Receptor Blockers (ARBs) and All-Cause Mortality Stratified by Comparison Group (Placebo vs Active)

Study or Subgroup	ARBs Events	ARBs Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Weight, %
Placebo						
DIRECT-Prevent 1 study,[49] 2009	7	710	7	710	1.00 (0.35-2.84)	1.7
DIRECT-Protect 1 study,[49] 2009	7	951	8	951	0.88 (0.32-2.40)	1.8
DIRECT-Protect 2 study,[50] 2008	37	949	35	953	1.06 (0.67-1.67)	7.6
IDNT (placebo) study,[12] 2001	87	579	93	569	0.92 (0.70-1.20)	16.3
IRMA study,[48] 2001	3	194	1	201	3.11 (0.33-29.62)	0.4
ORIENT study,[47] 2011	19	288	20	289	0.95 (0.52-1.75)	4.6
RENAAL study,[46] 2001	158	751	155	762	1.03 (0.85-1.26)	22.8
ROADMAP study,[15] 2011	26	2232	15	2215	1.72 (0.91-3.24)	4.3
Subtotal		**6654**		**6650**	**1.03 (0.89-1.18)**	**59.3**
Total Events	**344**		**334**			
Heterogeneity: $\tau^2=0.00$; $\chi^2=4.32$, $df=7$, $P=.74$; $I^2=0\%$						
Test for overall effect: $Z=0.36$, $P=.72$						
Active						
CASE-J study,[51] 2010	40	1011	49	1007	0.81 (0.54-1.22)	9.0
						1.5
						15.6
						14.6
						40.7
						100.0



CONCLUSIONS AND RELEVANCE Angiotensin-converting enzyme inhibitors reduced all-cause mortality, CV mortality, and major CV events in patients with DM, whereas ARBs had no benefits on these outcomes. Thus, ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population.

JAMA Intern Med. 2014;174(5):773-785. doi:10.1001/jamainternmed.2014.348

Original Investigation

Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus

A Meta-analysis

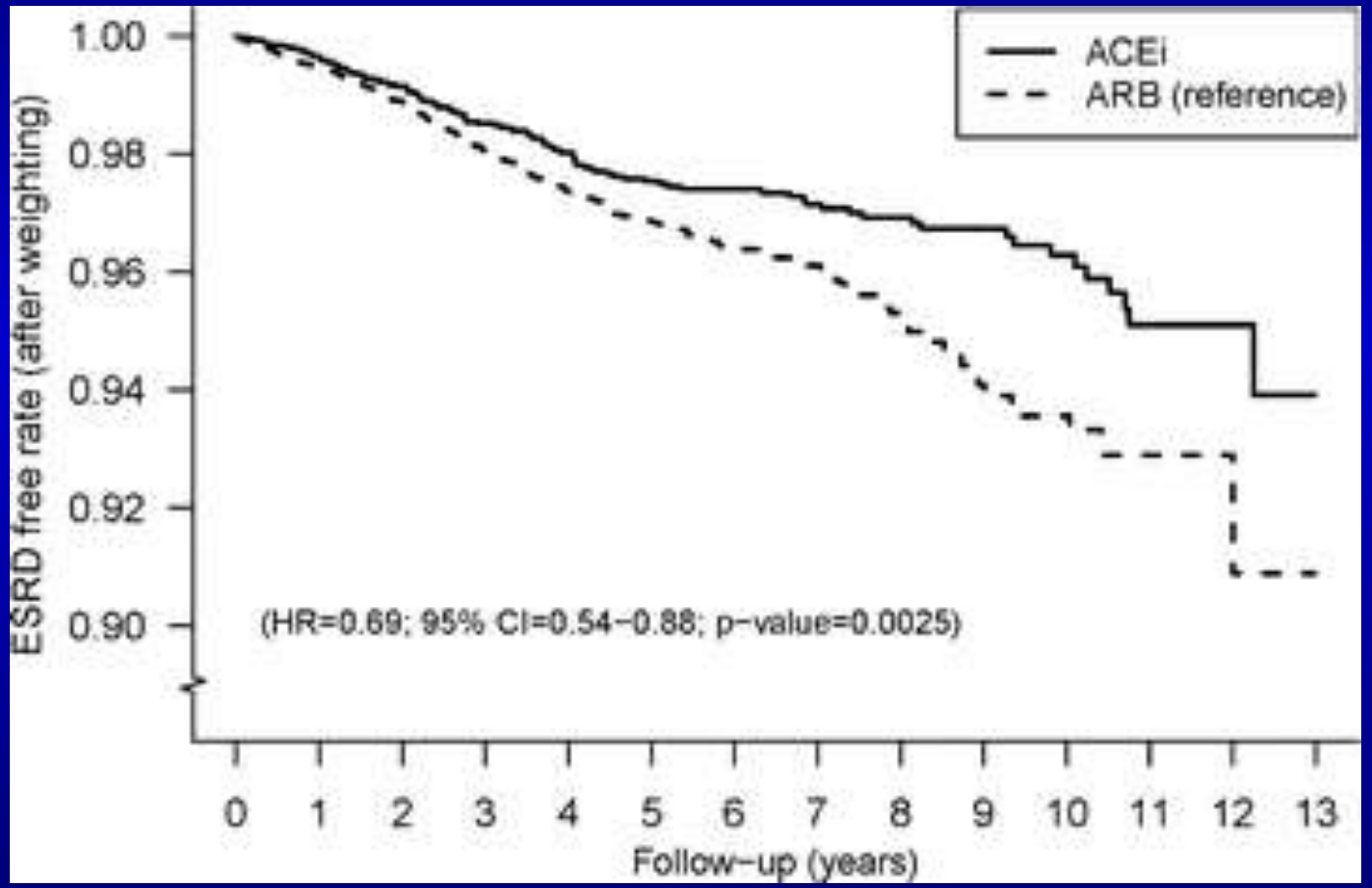
EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2012) **33**, 2088–2097
doi:10.1093/eurheartj/ehs075

CLINICAL RESEARCH
Hypertension

Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients

A comparison between angiotensin converting enzyme inhibitors and angiotensin receptor blockers on end stage renal disease



The risk of **ESRD** was **lower** in the **ACE-i group** than the ARB group [hazard ratio (HR: 0.69, P = 0.0025].

Cardiovasc Diabetol. 2016 Apr 2;15:56.

ACE inhibitors, a class widely recommended over ARBs in European guidelines.[1-5]

HYPERTENSION + CCS[1]

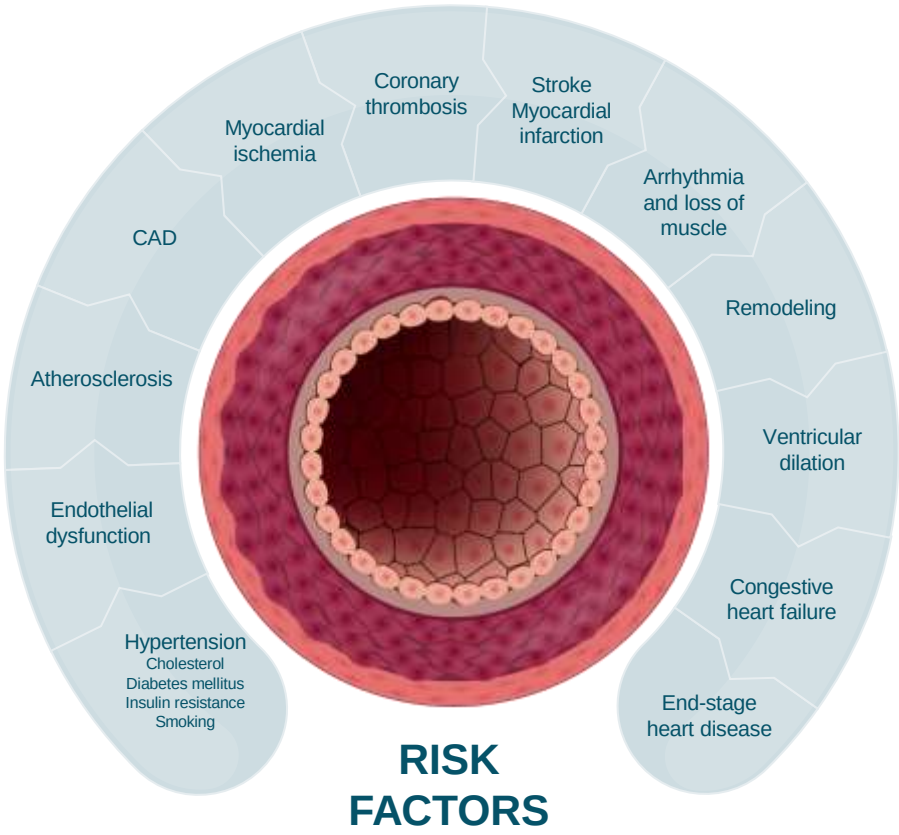
2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

ACEi ✓ ARBs ±

HYPERTENSION + DIABETES[2]

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

ACEi ✓ ARBs ±



HYPERTENSION + MI[3-4]

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

ACEi ✓ ARBs ±

HYPERTENSION + HF[5]

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

ACEi ✓ ARBs ±

ACE: angiotensin-converting enzyme; **ACEi**: angiotensin-converting enzyme inhibitor; **CAD**: coronary artery disease; **HF**: heart failure; **MI**: myocardial infarction.
RECOMMENDED IF ACE inhibitors NOT TOLERATED

1. Knuuti J et al. *Eur Heart J.* 2020;41:407-477. 2. Cosentino F et al. *Eur Heart J.* 2020;41:255-323 3. Ibanez B et al. *Eur Heart J.* 2018;39:119-177.4. Roffi M et al. *Eur Heart J.* 2016;37:267-315. 5. Ponikowski P et al. *Eur Heart J.* 2016;37:2129-2200.

- **Larger evidence (RCT) with ACEi** than with ARB, **particularly** in patients with **HF, CAD and at high CV risk**
- **ACEis (ARBs if not tolerated)** are recommended
  - → In patient with CAD
  - → In patients with HFrEF

- **ACEis (ARBs if not tolerated)** are recommended In patients with **symptomatic HFr(m)EF**

NEW

ACEis (ARBs if not tolerated)

NEW 2024 ESC Guidelines for the management of chronic coronary syndromes

2023 ESC Guidelines for the management of acute coronary syndromes

2021 ESC Guidelines for the diagnosis & treatment of acute & chronic heart failure

2023 AHA/ACC Guideline for the Management of Patients With Chronic Coronary Disease

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Dual combination with CCB and ACEi mentioned as effective in Black African patients

*"In **Black patients in sub-Saharan Africa**, **amlodipine plus** **either hydrochlorothiazide or perindopril** was more effective than perindopril plus hydrochlorothiazide at lowering BP"*

NEW

Dual combination with CCB and ACEi is now recommended in Black African patients

Recommendations	CoR	LoE
In black patients from Sub-Saharan Africa who require BP-lowering treatment, combination therapy including a CCB combined with either a thiazide diuretic or a RAS blocker should be considered.	IIa	B

ACC, American college of cardiology; **ACEi**, angiotensin-converting enzyme inhibitor; **AHA**, American heart association; **ARB**, angiotensin receptor blocker; **BP**, blood pressure; **CAD**, coronary artery diseasr; **CCB**, calcium channel blocker; **HF(m)rEF**, heart failure with (mildly) reduced ejection fraction; **RAS,** renin-angiotensin system; **RCT,** randomized control trial

"*The thiazide-like diuretics, chlorthalidone and indapamide, are* ***more potent and have a longer duration of action*** *compared with hydrochlorothiazide,*
but ***a greater incidence of side effects has been reported for chlortalidone in some studies***"

"*More recently, two case-control studies suggested that the use of* ***hydrochlorothiazide is associated with an increased risk of developing squamous cell carcinoma in the skin and lip***"

Chlorthalidone (12.5 to 25 mg once daily) can be used with or without a loop diuretic if eGFR is <30 ml/min/1.73m^2.	II	B

NEW

"***BP control may be improved by switching*** *hydrochlorothiazide* ***to long-acting thiazide-like diuretics****, such as chlorthalidone."*

"*Of note, the* ***risk of hypokalaemia was higher in the chlorthalidone*** *group than in the hydrochlorothiazide group."*

In patients with **chronic cerebrovascular disease and cognitive impairment**, It is recommended that the BP-lowering drug treatment strategy for preventing recurrent stroke should comprise a RAS blocker plus a CCB or a **thiazide-like diuretic.**	I	A

	Thiazide-like diuretics vs HCTZ		
	Longer duration of action & more potent	Greater evidence for CV protection	Preferred use of thiazide-like diuretics
	ADA 2023 American Diabetes Association Standards of Care in Diabetes		
	2020 International Society of Hypertension global hypertension practice guidelines		
	Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, & Treatment of Hypertension in Adults & Children		
NICE	2019 NICE Hypertension in adults: diagnosis and management (last update Nov 2023)		
	2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, & Management of High Blood Pressure in Adults		

BP: blood pressure. **CAD:** coronary artery disease. **CCB:** calcium channel blocker. **HF(m)rEF:** heart failure with (mildly) reduced ejection fraction. **RAS:** renin-angiotensin system. **RCT:** randomized control trial.

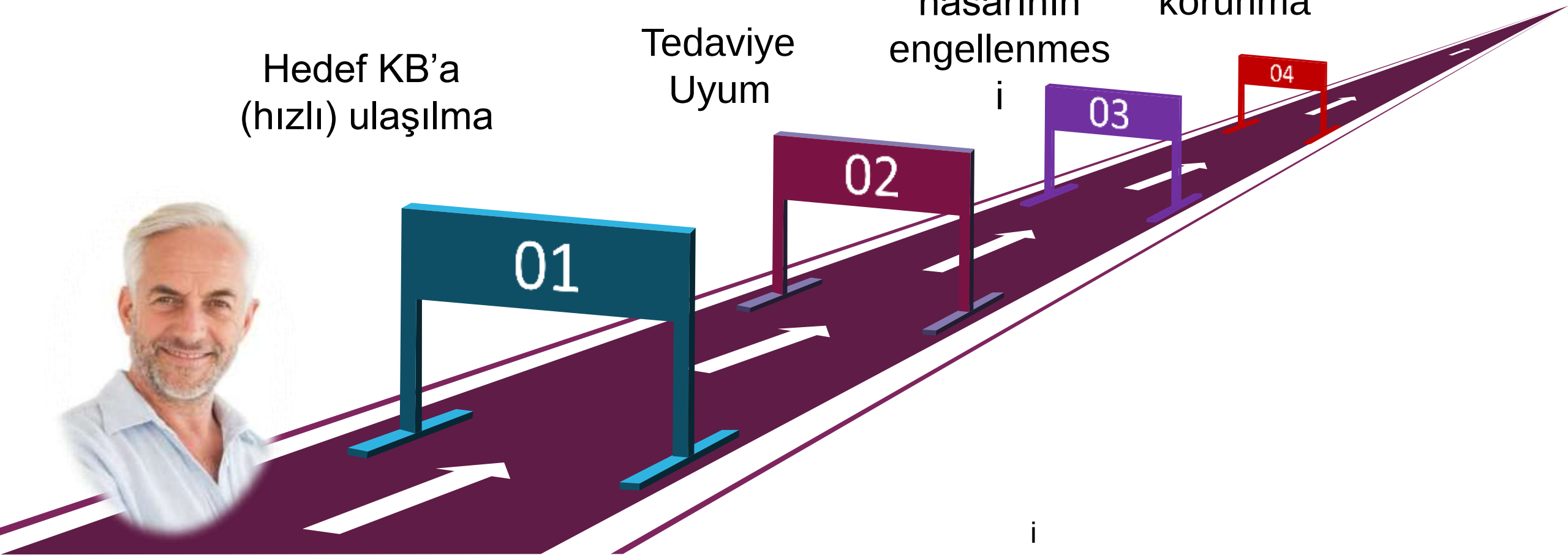
- Several common recommendations
- Patients at the center of both guidelines
- Need to adapt depending on the region/country/doctor

Hedef KB’a (hızlı) ulaşılma

Tedaviye Uyum

Hedef organ hasarının engellenmesi

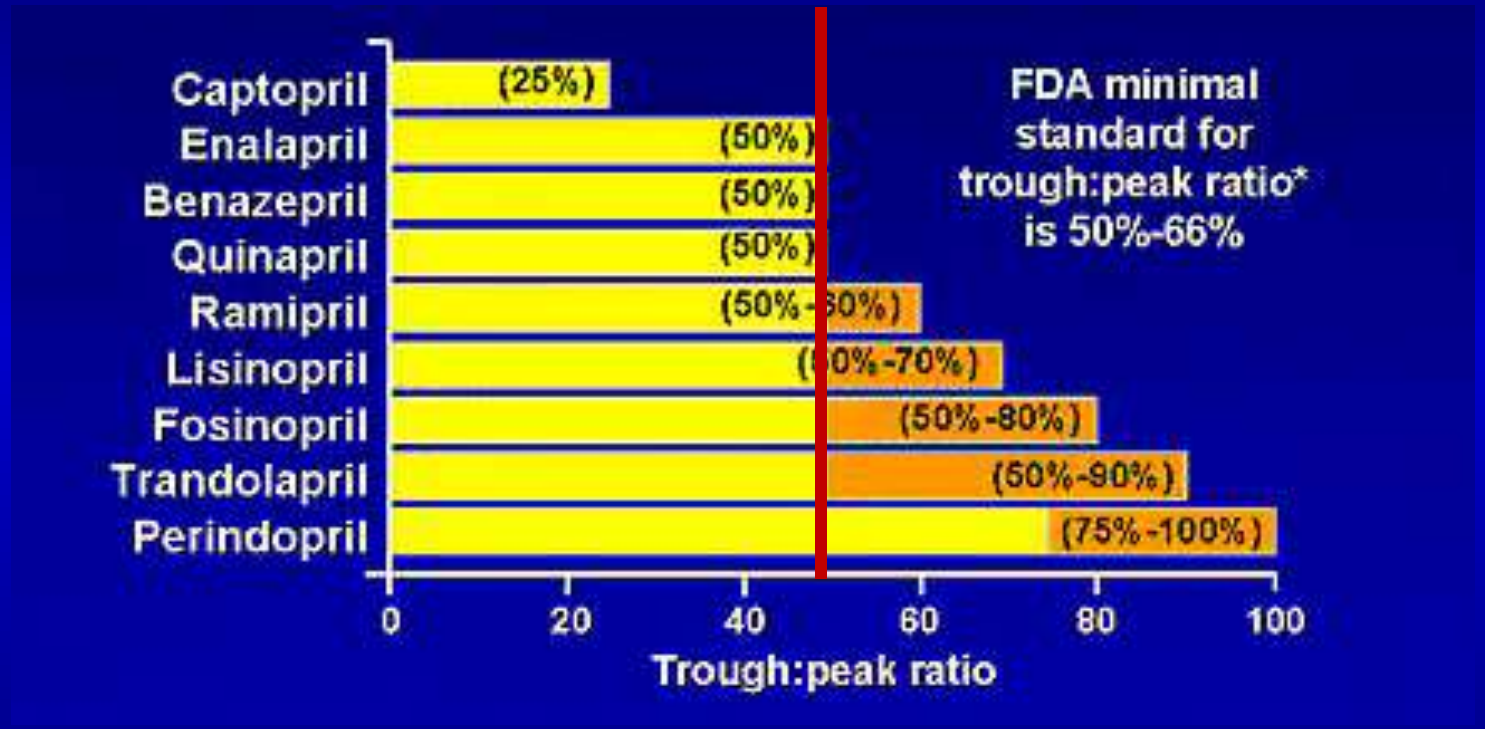
Etkin KV korunma



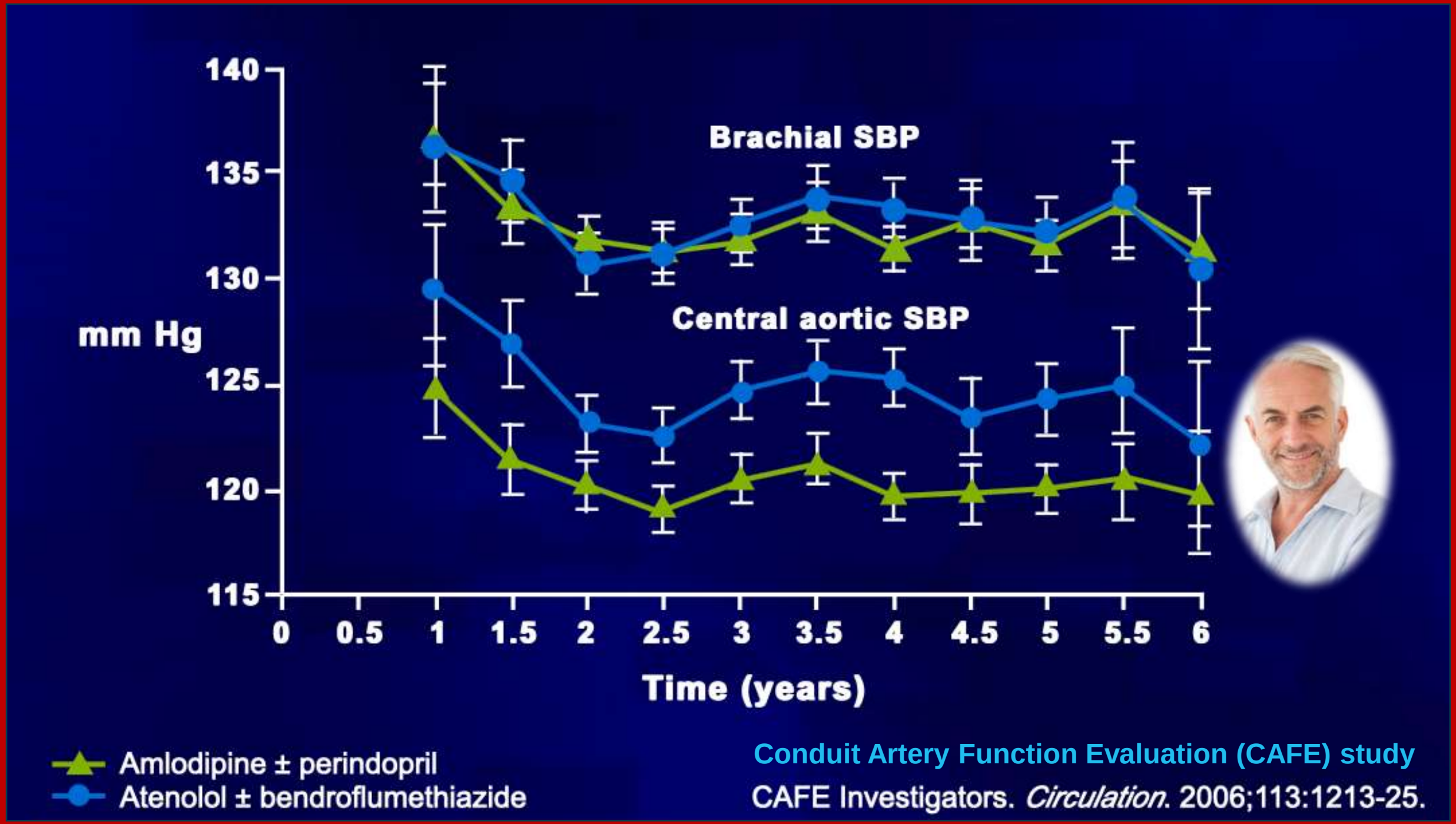

Hangi ACE-İnhibitörü
Lisinopril, Ramipril
Perindopril
Benazepril, Enalapril

Vadi Tepe Oranı

1



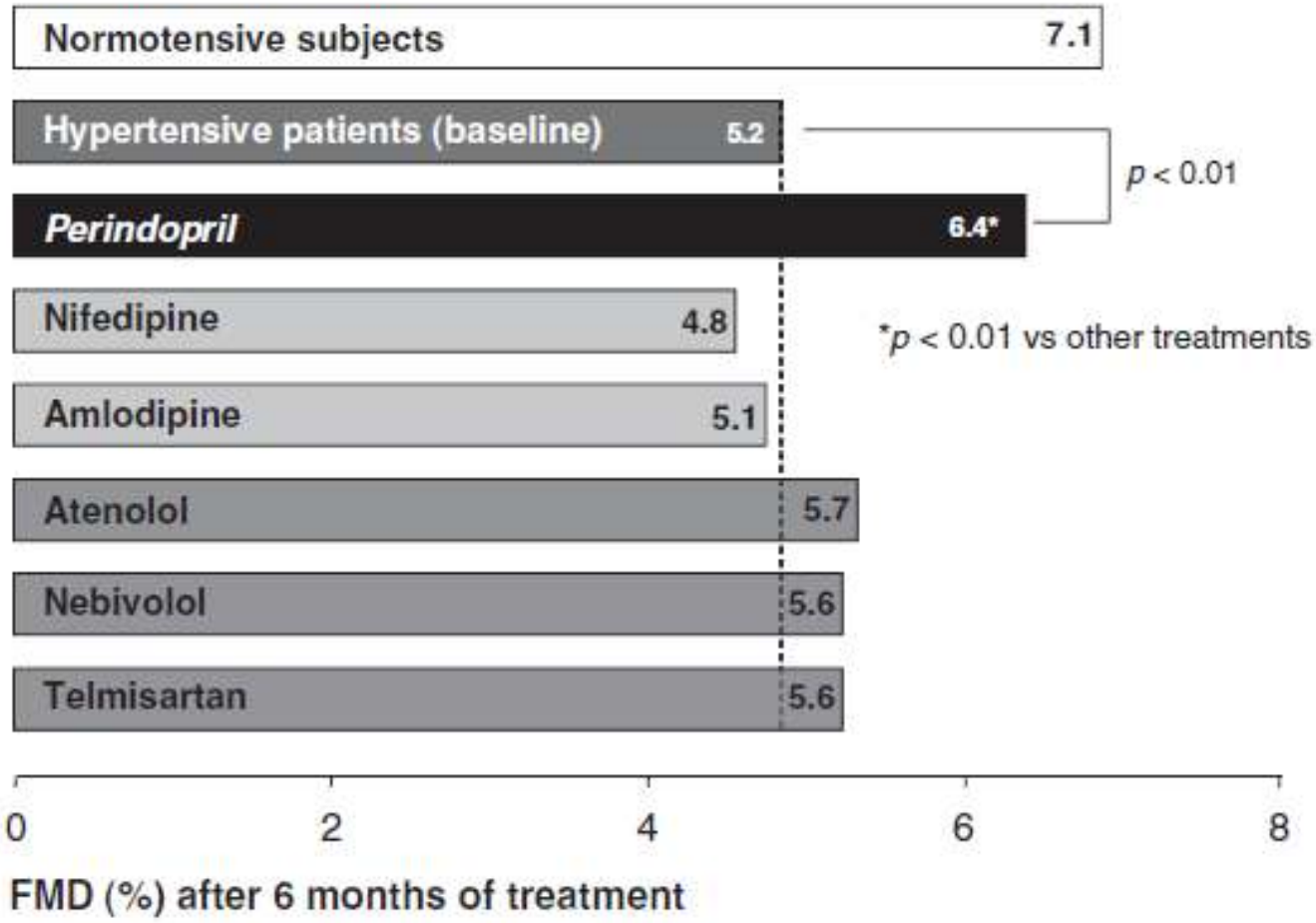
https://www.medscape.org/viewarticle/439193_4



Conduit Artery Function Evaluation (CAFE) study

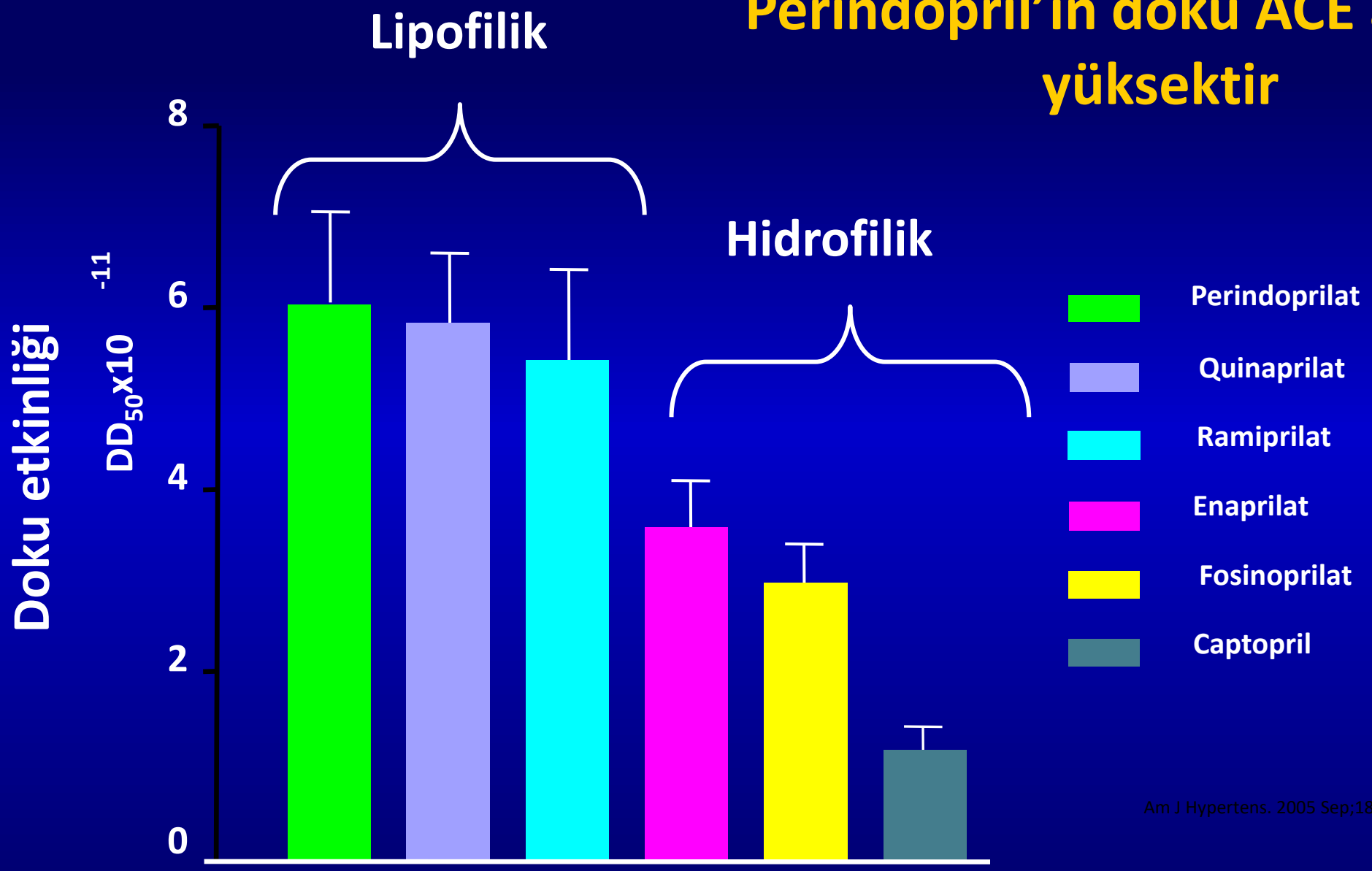
CAFE Investigators. *Circulation*. 2006;113:1213-25.

Perindopril,
Endotel Fonksiyonlarında En Fazla Düzelme Yapan Anti Hipertansiftir



Hypertension. 2003;41:1281–1286

Perindopril'in doku ACE afinitesi yüksektir



Am J Hypertens. 2005 Sep;18(9 Pt 2):142S-154S.

İndapamid Çift Yönlü Etki Göstermektedir

Renal Salüretik Etki

Arteriyel Na
yükünün azaltılması

Doğrudan Vasküler Etki

-Vasküler düz kaslara Ca^{++} girişinin düzenlenmesi

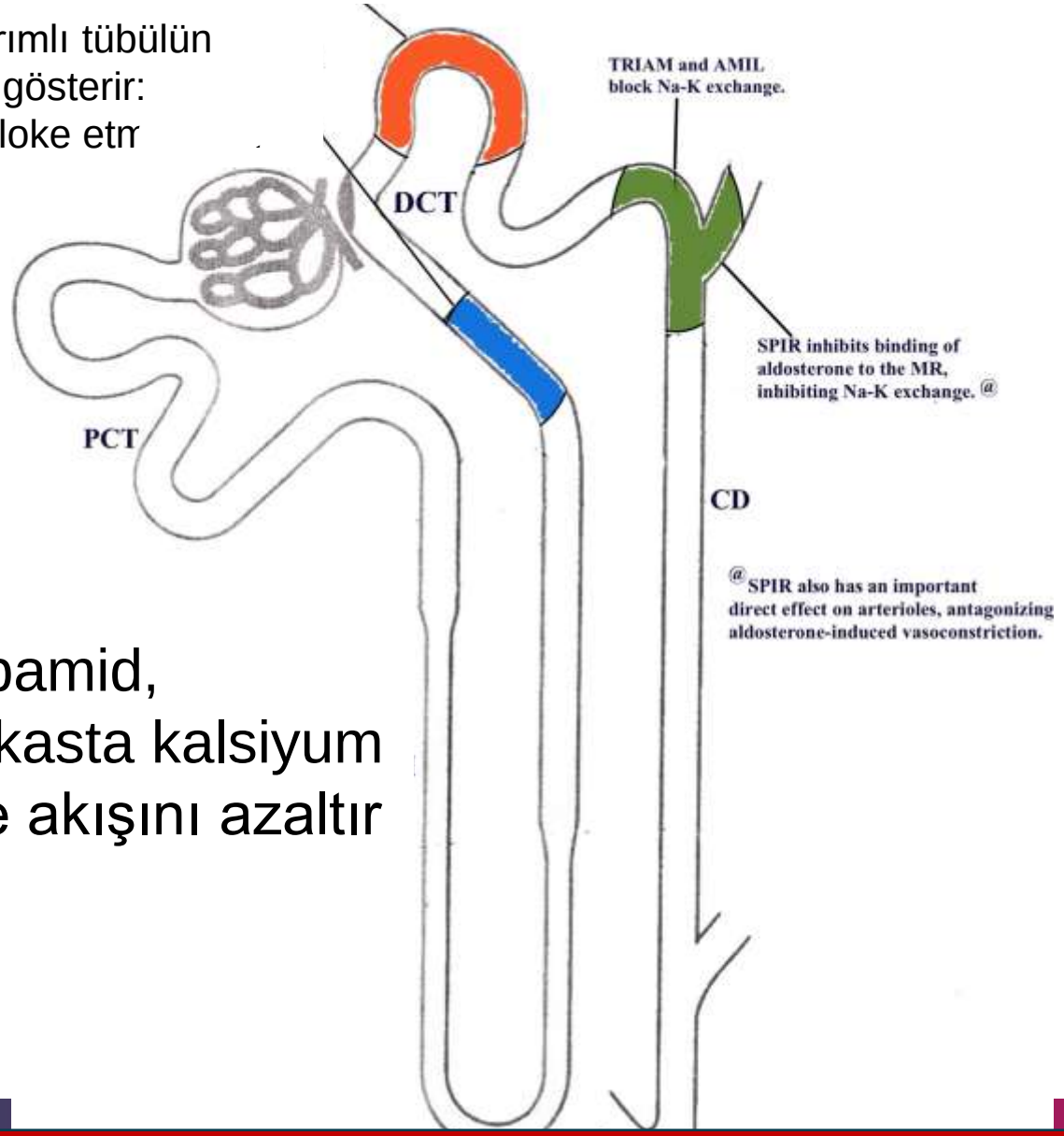
- PGE_2 ve PGI_2 sentezinin artması

- Epinefrin, Norepinefrin ve AT II' ye karşı damar yanıtında azalma

Curr Hypertens Rep (2015) 17:31

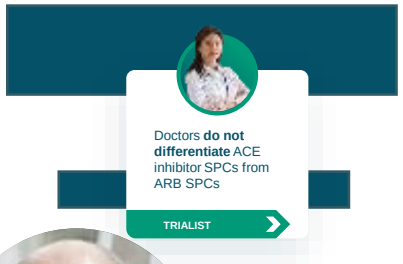
HCTZ, distal kıvrımlı tübül üzerinde etki gösterir: NaCL kotransporterini bloke etmek için

Indapamid, distal kıvrımlı tübülün prksimalinde etki gösterir: NaCL kotransporterini bloke etm



Indapamid,
vasküler düz kasta kalsiyum iyonlarının içe akışını azaltır

Curr Hypertens Rep (2015) 17:31



BP VARIABILITY IS AN INDEPENDENT RISK FACTOR FOR CV EVENTS AND DEATH.[1,2]

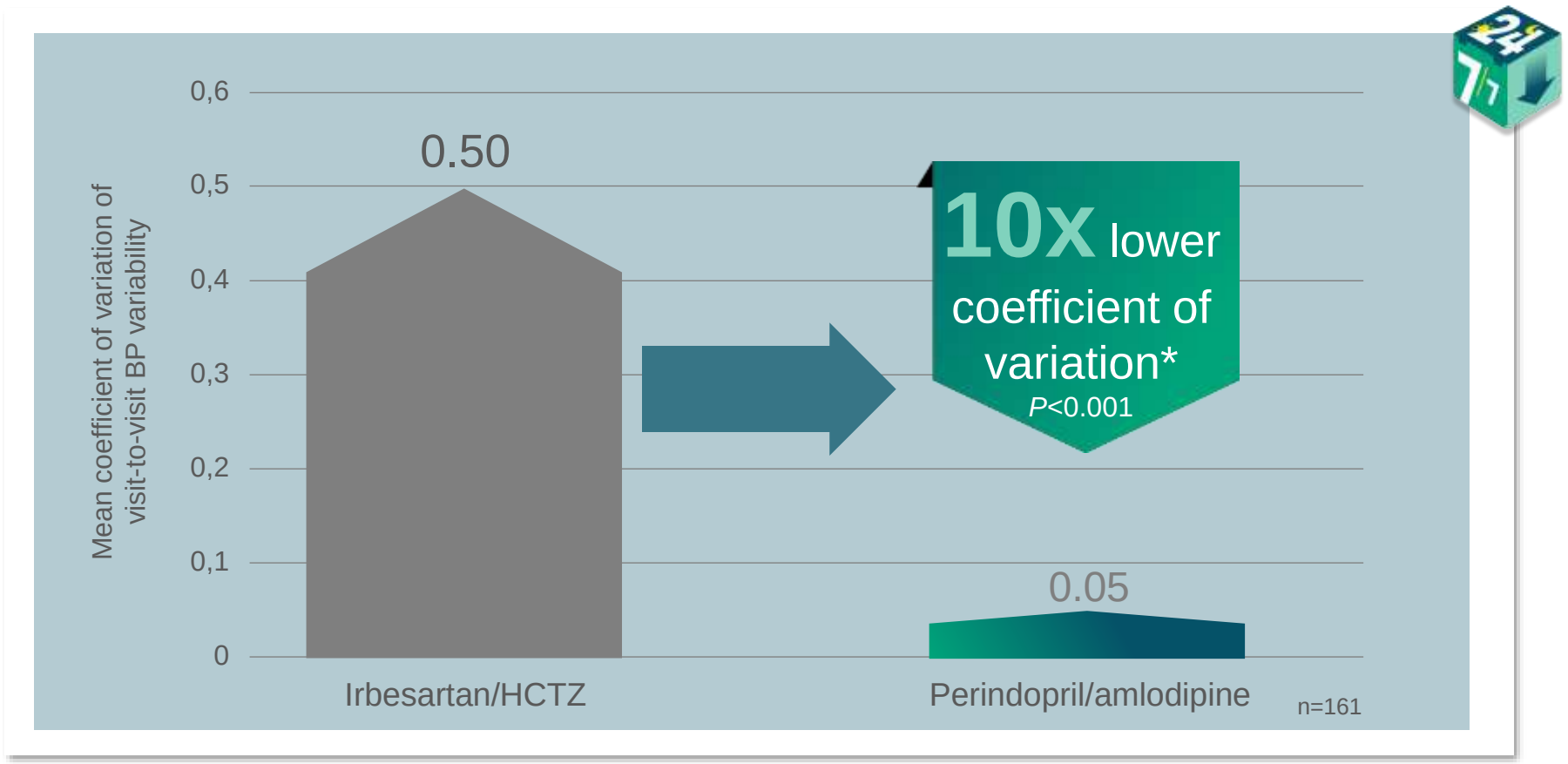
BP: blood pressure; **CV:** cardiovascular.

1. Stevens SL et al. *BMJ.* 2016;354:i4098. Systematically reviews studies quantifying the associations of long-term, mid-term, and short-term variability in blood pressure, independent of mean blood pressure, with cardiovascular disease events and mortality. Increased long-term variability in systolic blood pressure was associated with risk of all-cause mortality (hazard ratio 1.15, 95% confidence interval 1.09 to 1.22), cardiovascular disease mortality (1.18, 1.09 to 1.28). 2. Sheikh AB et al. *J Am Heart Assoc.* 2023;12(9):e029297.

PERINDOPRIL/AMLODIPINE IS THE SPC THAT SIGNIFICANTLY REDUCES BP VARIABILITY.[1]

Doctors **do not differentiate** ACE inhibitor SPCs from ARB SPCs

TRIALIST



BP: blood pressure; **CV**: cardiovascular; **MOA:** mechanism of action; **SPC:** single-pill combination.

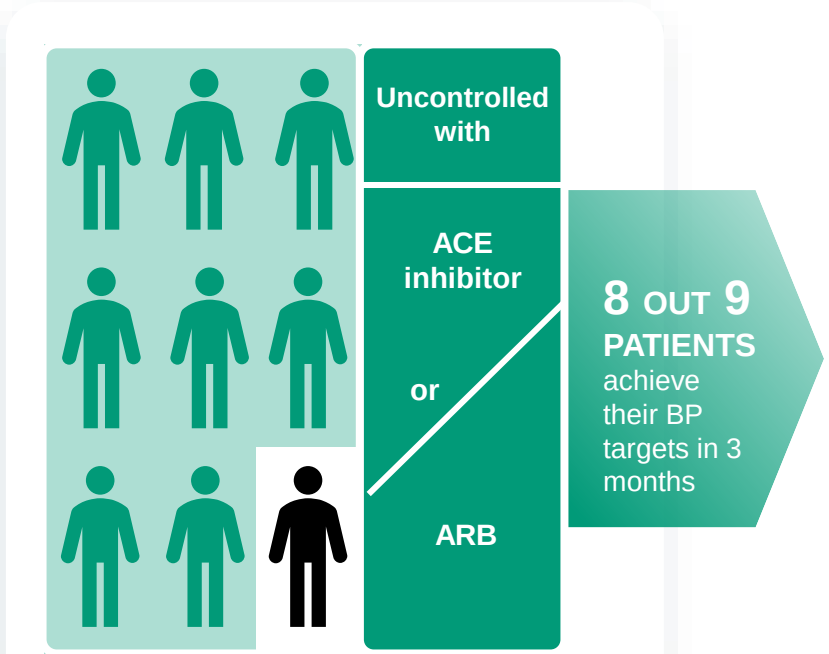
1. Poulter NR et al. *Am J Cardiovasc Drugs.* 2019;19(3):313-323. 4 dosages evaluated for perindopril/amlodipine treatment were 3.5/2.5, 7/5, 14/5, and 14/10 mg.

* The mean coefficients of variation in the two treatment groups were compared using a t test from a logarithmic transformation,as the distribution was skewed.

WITH PERINDOPRIL AND AMLODIPINE COMBINATION, 8 OUT OF 9 PATIENTS ACHIEVE THEIR BP TARGETS IN 3 MONTHS.*[1]

Doctors **do not differentiate** ACE inhibitor SPCs from ARB SPCs

TRIALIST



<130/80 mm Hg

SBP

REDUCTION OF **32 mm Hg**

DBP

REDUCTION OF **17 mm Hg**

*Not in line with Coveram® EU indication and must be approved by local RA -COVERAM is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

ACE: angiotensin-converting enzyme; **ARB:** angiotensin receptor blocker; **BP**: blood pressure; **DBP**: diastolic blood pressure; **SBP**: systolic blood pressure.

1. Kobalava ZD et al. *Ter Arkh*. 2015;87:66-70.

1 out of 4 patients require 3 drugs to achieve BP control.[1,2]

Triple SPCs have an important role in HT management[1]

Guidelines recommendation[2]

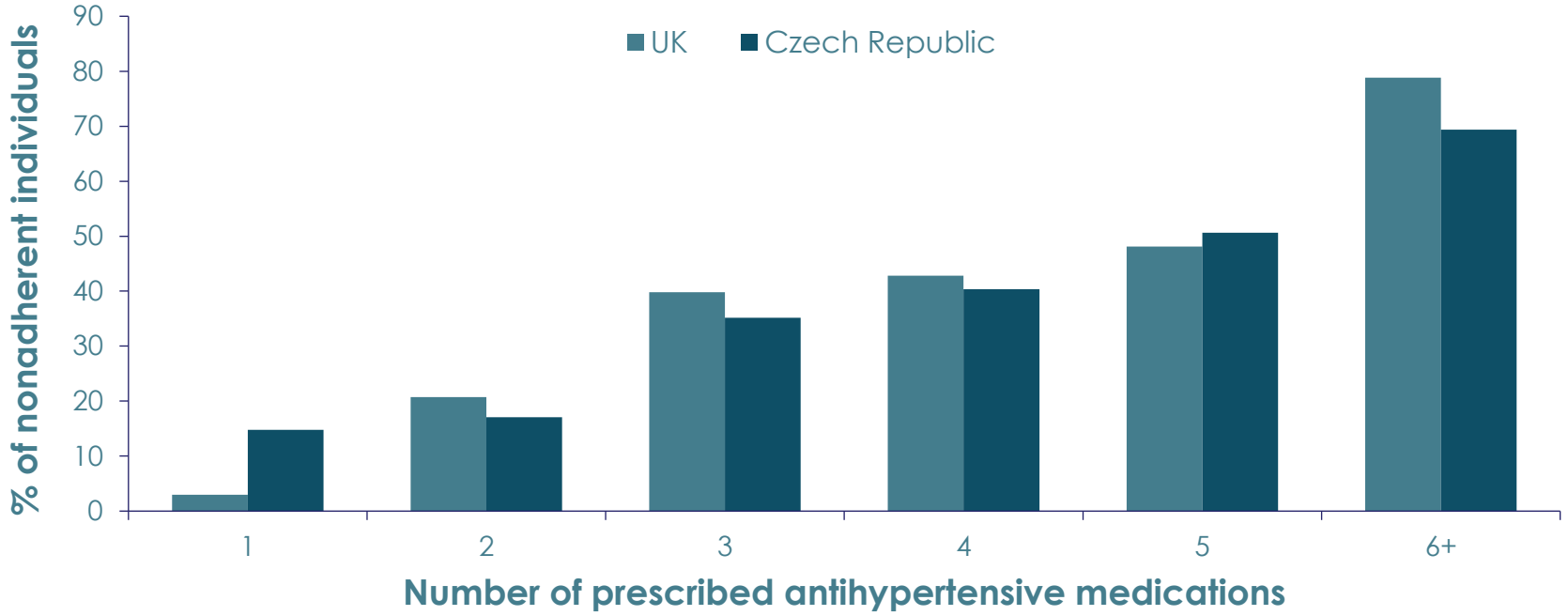
130/80
mm Hg

BP: blood pressure; **CCB:** calcium channel blocker; **RAAS:** renin-angiotensin aldosterone system; **SPCs:** single-pill combinations

1. Syed YY et. *Am J Cardiovasc Drugs*. 2022;22(2):219-230. 2. Unger T et al. *J Hypertens*. 2020;38:982-1004.
Triplixam® is indicated as substitution therapy in patients already controlled with perindopril/indapamide and amlodipine.

Risk of Nonadherence Increases with Number of Prescribed Blood-Pressure-Lowering Medications

Biochemically confirmed nonadherence in **1348 patients** with hypertension from the UK and Czech Republic[1]



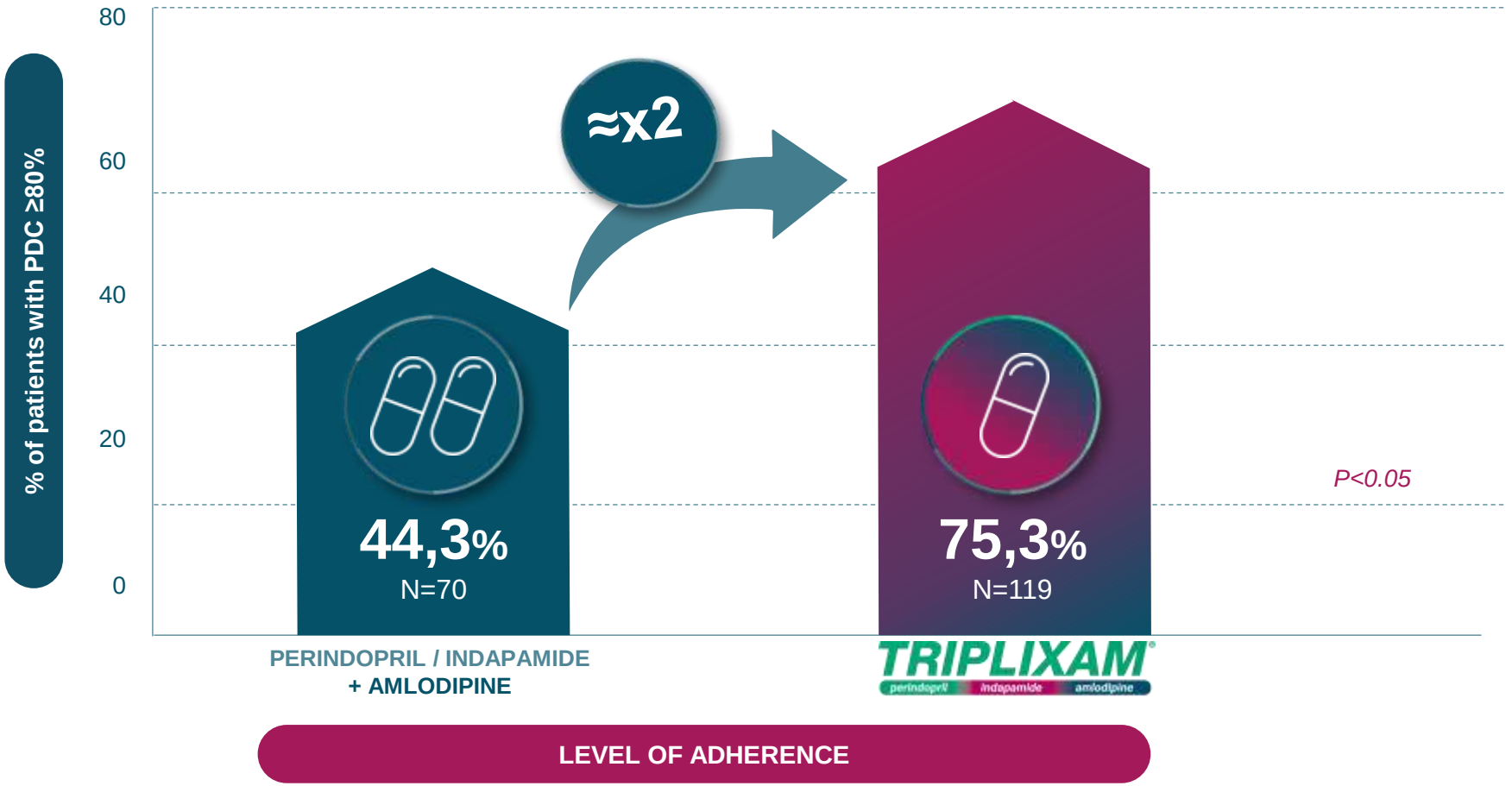
80% of UK patients prescribed ≥6 BP-lowering medications were nonadherent to antihypertensive treatment

BP, blood pressure; **UK**, United Kingdom

1. Gupta P et al. *Hypertension*. 2017;69:1113-1120

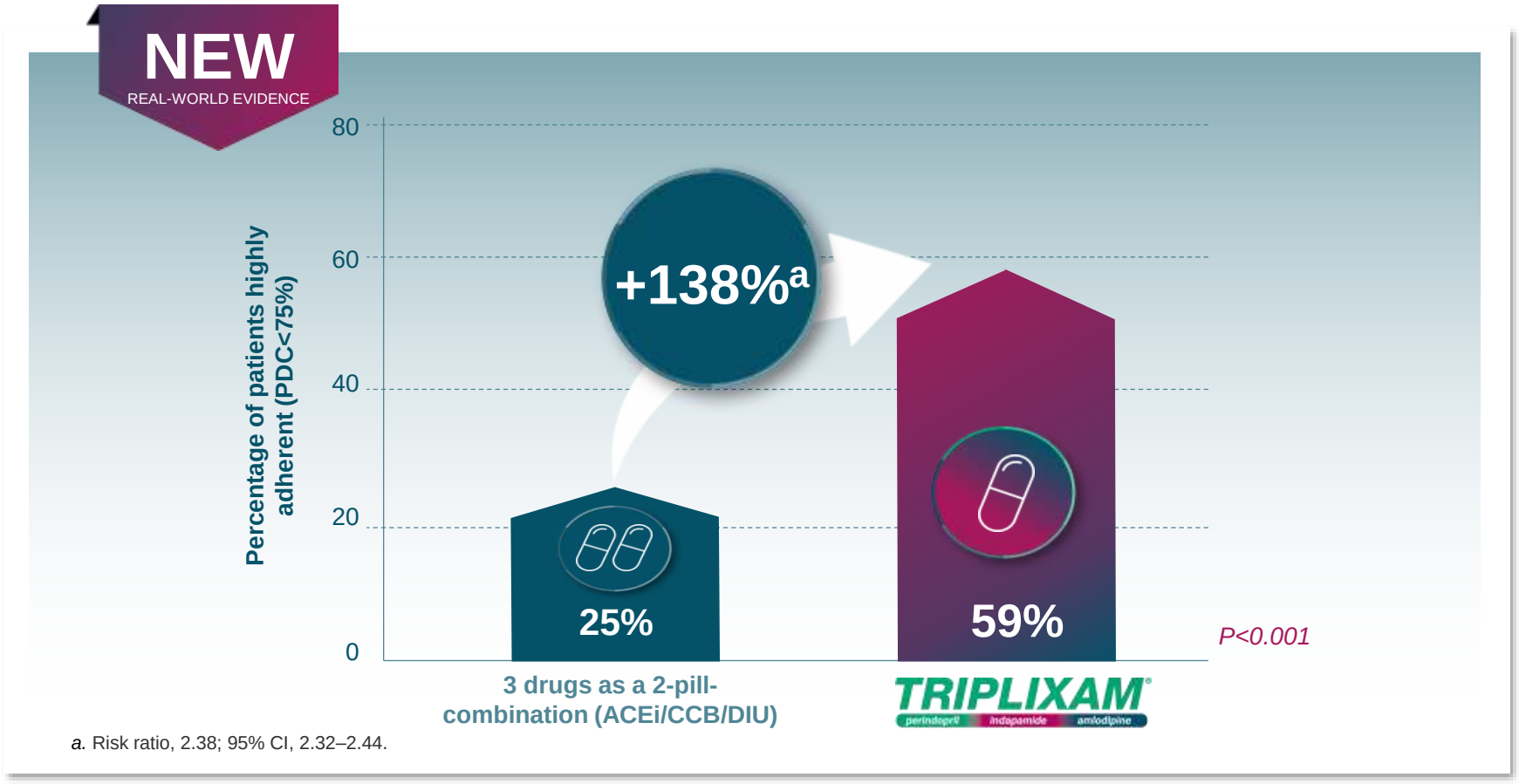
Triplixam®, one pill a day, increases significantly treatment adherence.[1]

NEW
REAL-WORLD-EVIDENCE



1. Borghi C. *Adv Ther*. 2023;40(4):1765-1772.
Adherence was calculated as the proportion of days covered (PDC). PDC <40%, nonadherent; PDC =40–79%, partially

TRIPLIXAM® PROVIDES A HIGHER CHANCE OF BEING HIGHLY ADHERENT THAN FREE COMBINATIONS..[1]

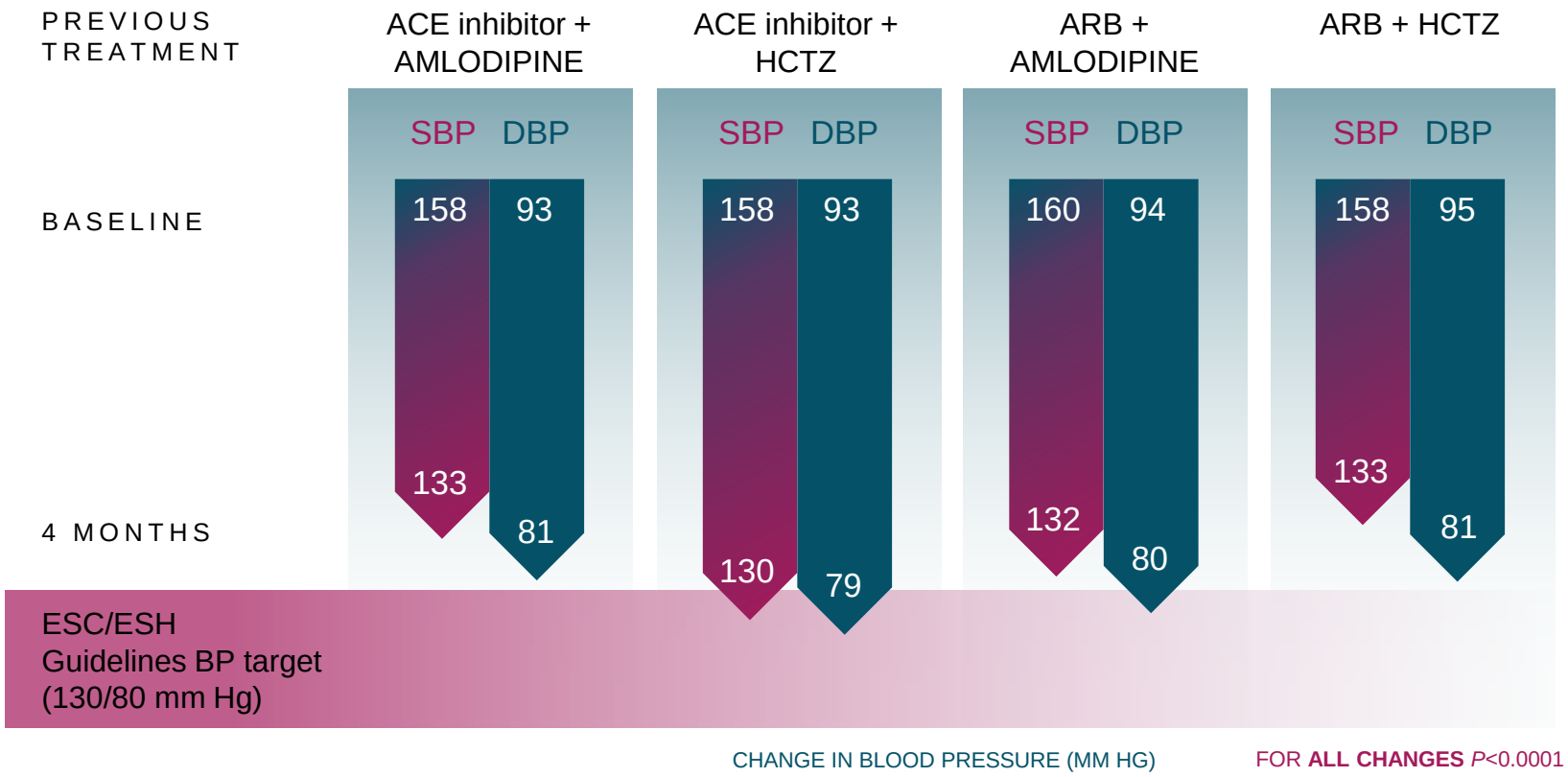


a. Risk ratio, 2.38; 95% CI, 2.32–2.44.

BP: blood pressure; CV, cardiovascular; PDC: proportion of days covered.

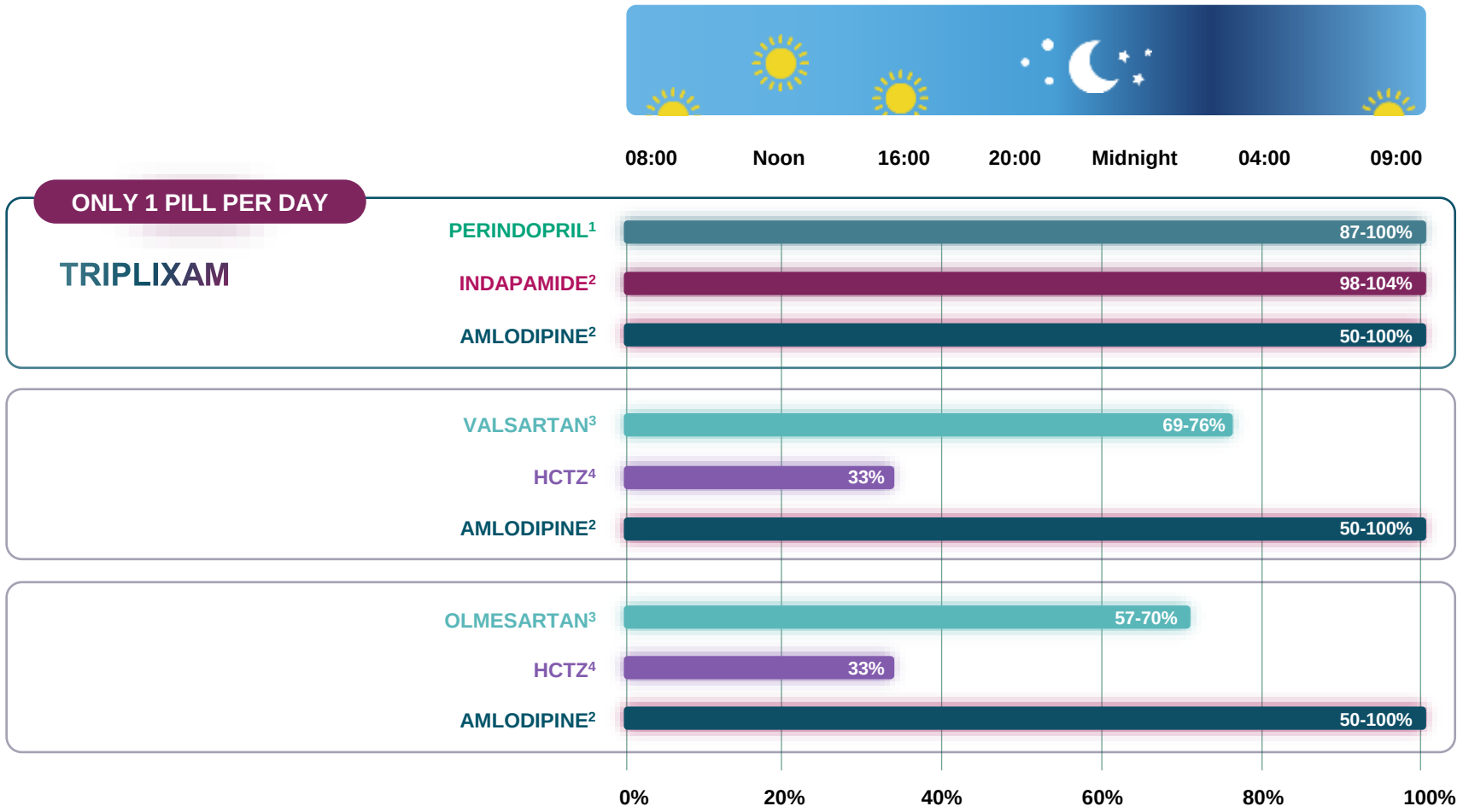
1. Rea F et al. *J Hypertens.* 2023;41(9):1466-1473. This study is not listed in the EU SmPC of Triplixam® and not in line with the approved indication. In the EU, Triplixam® is approved for substitution therapy only, according to the current SmPC (to be adapted and approved by local RA).

THE COMBINATION OF PERINDOPRIL, INDAPAMIDE AND AMLODIPINE ALLOWS PATIENTS TO ACHIEVE BP TARGETS* REGARDLESS OF PREVIOUS TREATMENT.[1]



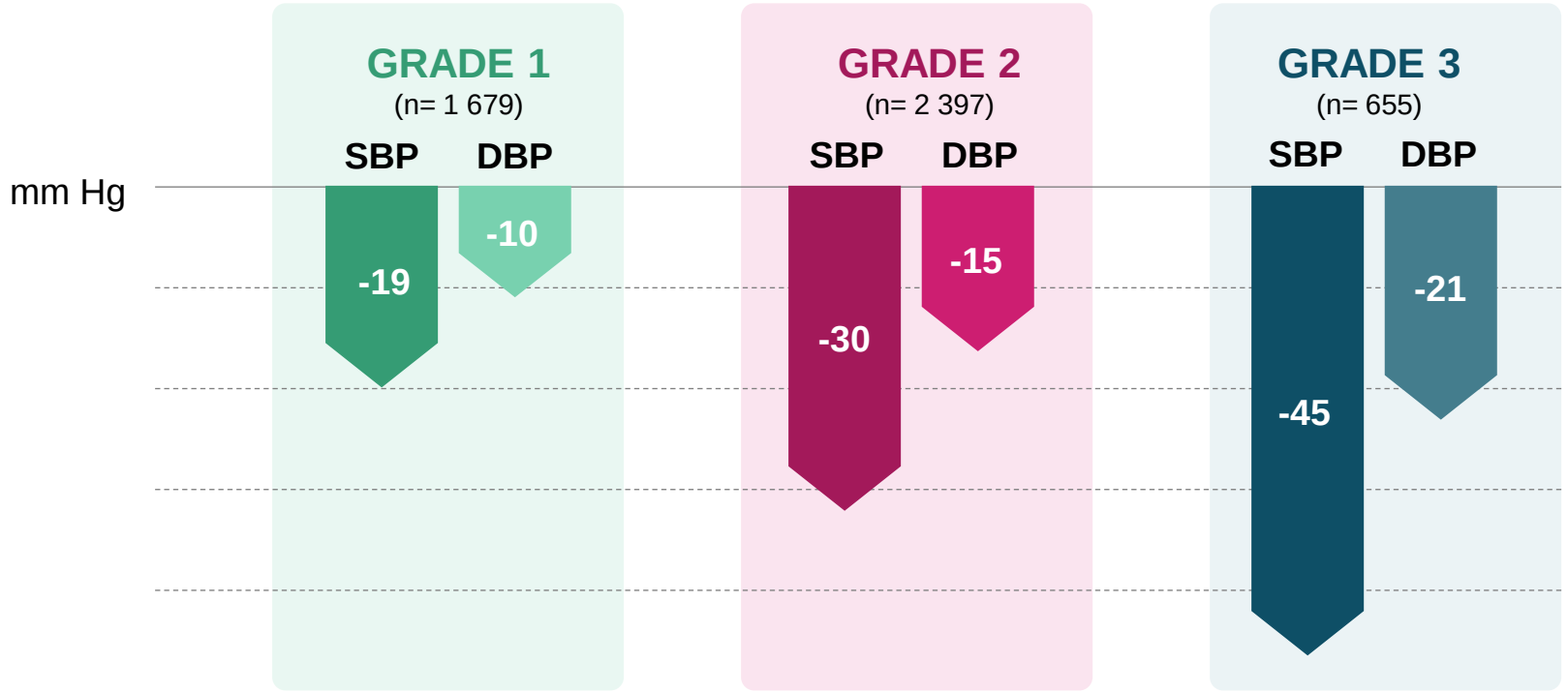
ACE: angiotensin-converting enzyme; **ARB:** angiotensin receptor blocker; **BP:** blood pressure; **DBP:** diastolic blood pressure; **HCTZ:** hydrochlorothiazide; **SBP:** systolic blood pressure. - 1.Tòth K *et al*; PIANIST Investigators. *Am J Cardiovasc Drugs*. 2014;14:137-145. *This study is not listed in the EU SmPC of Triplixam and not in line with the approved indication. In the EU, Triplixam® is approved for substitution therapy only, according to the current SmPC (to be adapted and approved by local RA).

DURABLE ACTION OVER 24 HOURS[1-4]



Perindopril/indapamide + amlodipine demonstrated adapted BP reduction.[1]

3D BP control



Multicenter, prospective, observational, noninterventional, 4-month, open-label clinical study. Patients at high or very high cardiovascular risk were enrolled if they had essential hypertension that was not properly controlled despite antihypertensive therapy. The primary end point was the decrease of office BP (OBP). After 4 months of therapy, OBP decreased by 28.3 ± 13.5/13.8 ± 9.4 to 132.2 ± 8.6/80.0 ± 6.6 mm Hg (P<0.0001). Patients who met study and treatment dose criteria (perindopril 10 mg/ indapamide 2.5 mg + amlodipine 5 or 10 mg) were included in the analysis (N = 4731).

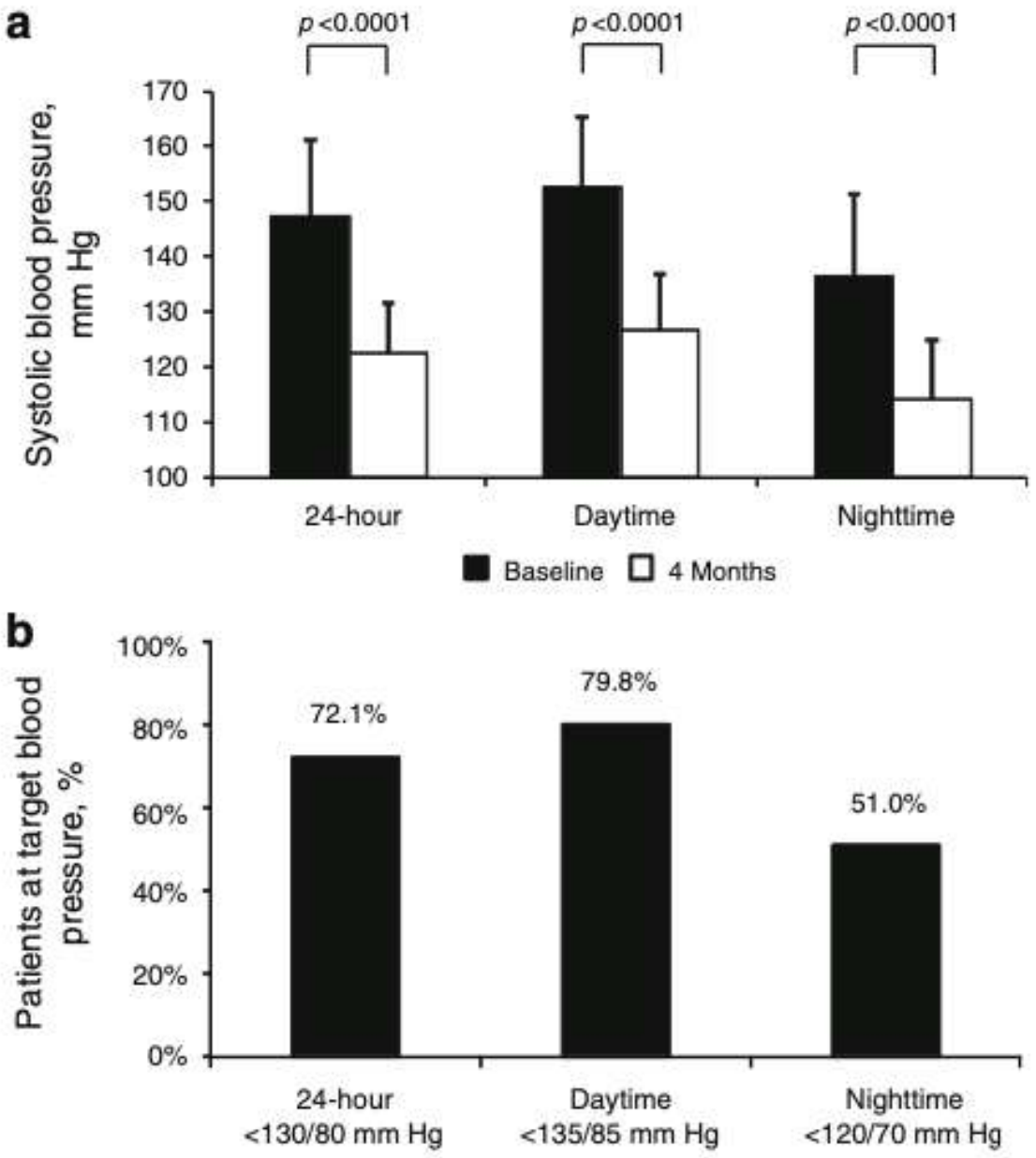
SBP: systolic blood pressure; DBP: diastolic blood pressure

1. Tòth K et al. *PIANIST Investigators. Am J Cardiovasc Drugs*. 2014;14:137–145. Study not described in the Reference Product information.

Triplixam® is indicated as substitution therapy in patients already controlled with perindopril/indapamide and amlodipine. To be approved by local RA.

Antihypertensive Efficacy of **Triple Combination Perindopril/ Indapamide Plus Amlodipine** in High-Risk Hypertensives: Results of the PIANIST Study

A total of 4,731 patients at high or very high cardiovascular risk with hypertension



Am J Cardiovasc Drugs (2014) 14:137–145

FIND OUT MORE ABOUT THE STUDY

Antihypertensive Efficacy of Triple Combination Perindopril/Indapamide Plus Amlodipine in High-Risk Hypertensives: results of the PIANIST study.

The Perindopril-Indapamide plus AmlodipiNe in high-rISk hyperTensive patients (PIANIST) trial was an observational, 4-month, open-label study which objective was to evaluate a triple-drug antihypertensive strategy for blood pressure control in patients with difficult-to-treat hypertension. A total of 4,731 patients at high or very high cardiovascular risk with hypertension that was not properly controlled despite antihypertensive therapy, and for whom study treatment (fixed-dose perindopril 10 mg/ indapamide 2.5 mg plus amlodipine 5 or 10 mg) was consistent with their existing therapeutic plan, were included.

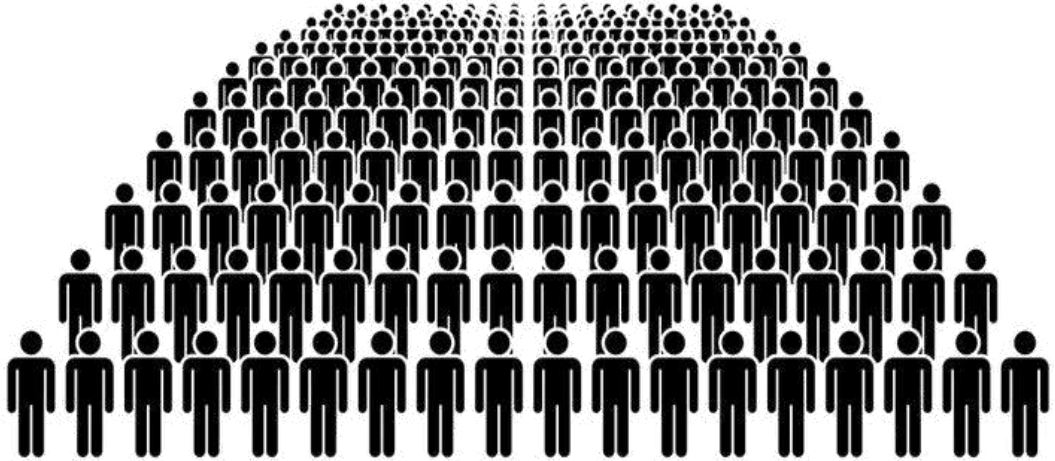
Mean baseline office blood pressure (OBP) was 160.5 ± 13.3/93.8 ± 8.7 mmHg. After 4 months of therapy, OBP decreased by 28.3 ± 13.5/13.8 ± 9.4 to 132.2 ± 8.6/80.0 ± 6.6 mmHg (*P*<0.0001). Blood pressure targets were reached by 72.0 %of patients and by 81 and 91 % of patients previously treated with an angiotensin-converting enzyme inhibitor/hydrochlorothiazide or an angiotensin receptor blocker/hydrochlorothiazide, respectively. Changes in OBP were 18.7 ± 8.3/9.7 ± 7.2 mmHg for grade 1 (n = 1,679), 30.4 ± 10.1/14.7 ± 8.6 mmHg for grade 2 (n = 2,397), and 45.4 ± 15.1/20.7 ± 12.1 mmHg for grade 3 patients (n = 655; all *P*<0.0001). In patients who underwent ambulatory blood pressure monitoring (n = 104), 24-h mean blood pressure decreased from 147.4 ± 13.8/82.1 ± 11.9 to 122.6 ± 9.1/72.8 ± 7.4 mmHg (*P*<0.0001). Ankle edema was infrequent (0.2 % of patients).

Conclusion:

Triple combination perindopril/indapamide/amlodipine was effectively and safely administered to a large population of high- and very high-risk hypertensive patients who had not reached target OBP values with previous treatment.

1. Tòth K *et al*; PIANIST Investigators. *Am J Cardiovasc Drugs.* 2014;14:137-145. *This study is not listed in the EU SmPC of Triplixam and not in line with the approved indication. In the EU, Triplixam® is approved for substitution therapy only, according to the current SmPC (to be adapted and approved by local RA).

The Antihypertensive Efficacy of the Triple Fixed Combination of Perindopril, Indapamide, and Amlodipine: The Results of the PETRA Study



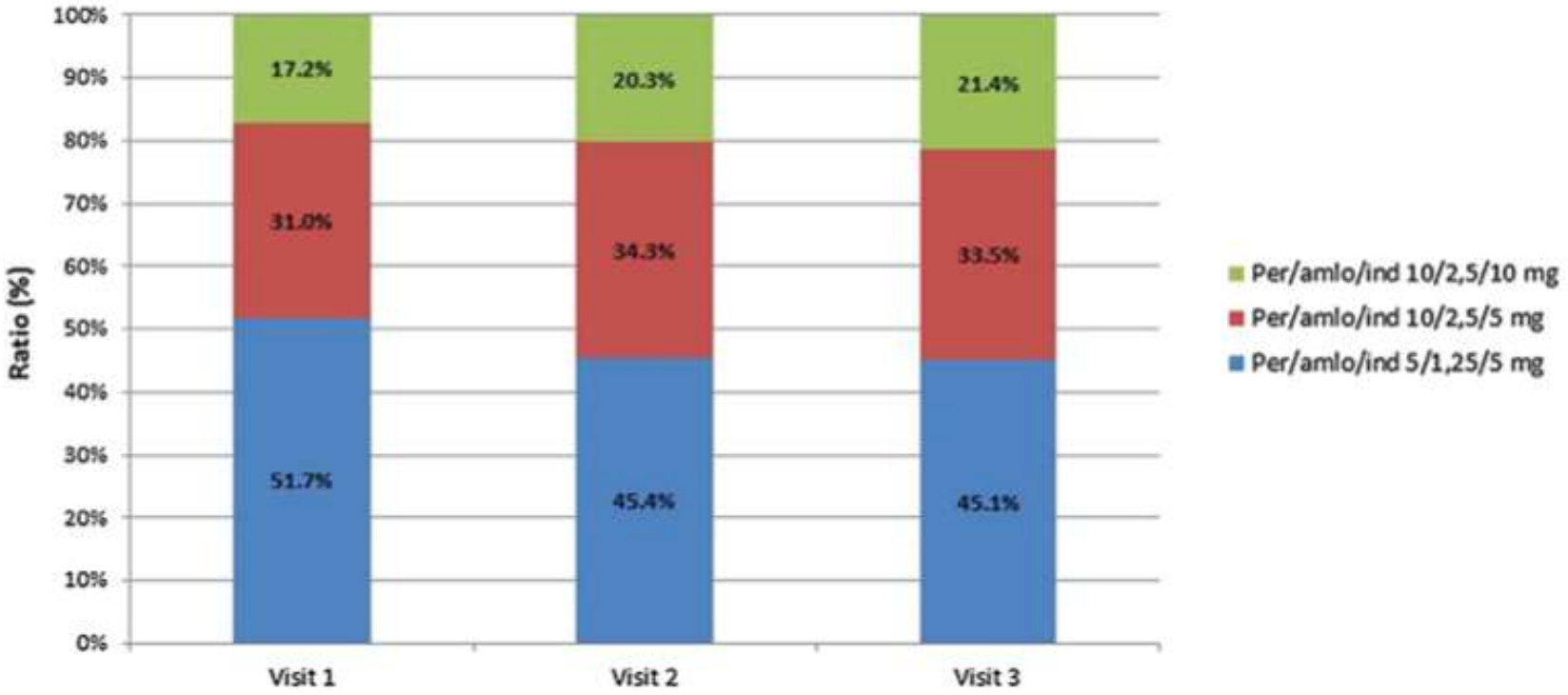
Hasta sayısı:11,209

Kadın: %47.6

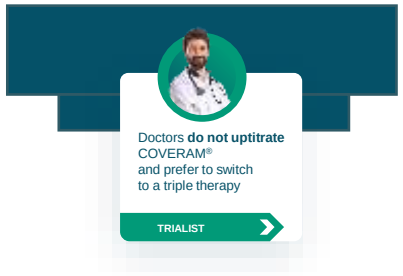
Hipotansiyon %0.02

Adv Ther. 2017 Jul;34(7):1753-1763.

The Antihypertensive Efficacy of the Triple Fixed Combination of Perindopril, Indapamide, and Amlodipine: The Results of the PETRA Study



Adv Ther. 2017 Jul;34(7):1753-1763.



INTENSIFICATION OF TREATMENT IN UNCONTROLLED HYPERTENSIVE PATIENTS PROVIDES CV BENEFITS.[1,2]

Hypertensive patients
(SBP ≥ 130 mm Hg)

+

At least one other CV disease[1,2]

-25% CV events.[2]

-27% overall risk of death[2]

Intensive BP control

No increase in adverse events.[2]

BP: blood pressure; **CV:** cardiovascular; **SBP:** systolic blood pressure; **SPC**: single-pill combination.

1. The SPRINT Research Group. *N Engl J Med.* 2015;373:2103-2116. 2. Kitagawa K et al. *Hypertens Res*. 2022;45(4):591-601.

AMLODIPINE +/- PERINDOPRIL PROVIDES CARDIO PROTECTION SUSTAINED OVER THE YEARS.*[1]

Doctors **do not differentiate** ACE inhibitor SPCs from ARB SPCs

TRIALIST

ANGLO-SCANDINAVIAN ASCOT CARDIAC OUTCOMES TRIAL

Anglo-Scandinavian ascot Cardiac Outcomes Trial

LEGACY

amlodipine +/- perindopril *vs* atenolol +/- thiazide

20-year
FOLLOW-UP

8580 patients

-8% *P*=0.024 CORONARY EVENTS[2]

-18% *P*=0.003 STROKE[2]

CV: cardiovascular.

*Not in line with Coveram® EU indication and must be approved by local RA. COVERAM® is indicated as substitution therapy for the treatment of essential hypertension and/or stable coronary artery disease. This study was not conducted with the single-pill combination of perindopril/amlodipine.

1. Gupta A et al. *J Hypertens*. 2021;39(e-suppl 1):e8. doi:10.1097/01.hjh.0000744436.51700.9f. Not in accordance with Coveram® EU indication, to be approved by local RA.