Goals beyond hypertension management in High-risk patients

"Cardiovascular & Renal Protection" (ACEIs/ARBs: Telmisartan)

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- What is/are the **potential Mechanisms/benefits** of **Renin-angiotensin system blockers** to reduce cardiovascular (CV) risk?

1- By only lower BP which is one of the most important CV risk factors.

2- By only Attenuate the atherosclerotic disease process directly

3- Or by both.

- Do you think that **all ARBs** **despite** **different pharmacology profile** (e.g. half-life, receptor-affinity, lipophilic, and PPAR-γ activation) have the **same CV prevention indications**?

  1- Yes
  2- No
  3- Not sure

Hypertension - Reasons for concern

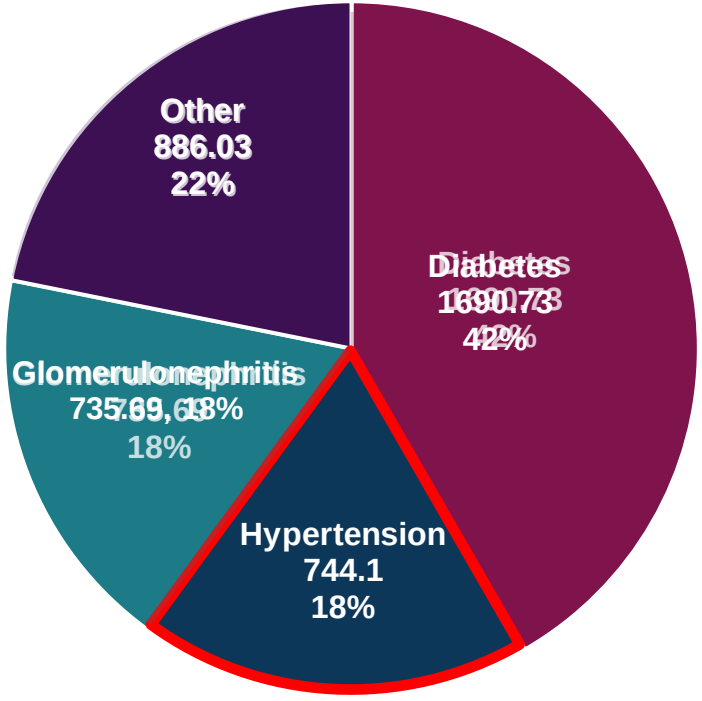
- **High prevalence** (~ 3 out of 10 Citizens of GCC **(30 %)** have hypertension*.
- Many (up to 35%) hypertensive patients are **unaware** of their condition.
- Many hypertensive patients with treatment have **not reached their goal BP goal < 130/80** (**ISH, ESC, and AHA/ACC)**.
- Major **CV risk factor** (**Stroke, CHD, and mortality**).
- Major **cause** of **CHF** and **CKD/ESRD,** which are significantly increasing.
- **Strong association** with **DM II**.

1.Bhagavathula AS, Shah SM, Aburawi EH. Prevalence, awareness, treatment, and control of hypertension in the United Arab Emirates: a systematic review and meta-analysis. International Journal of Environmental Research and Public Health. **2021** Dec 2;18(23):12693.

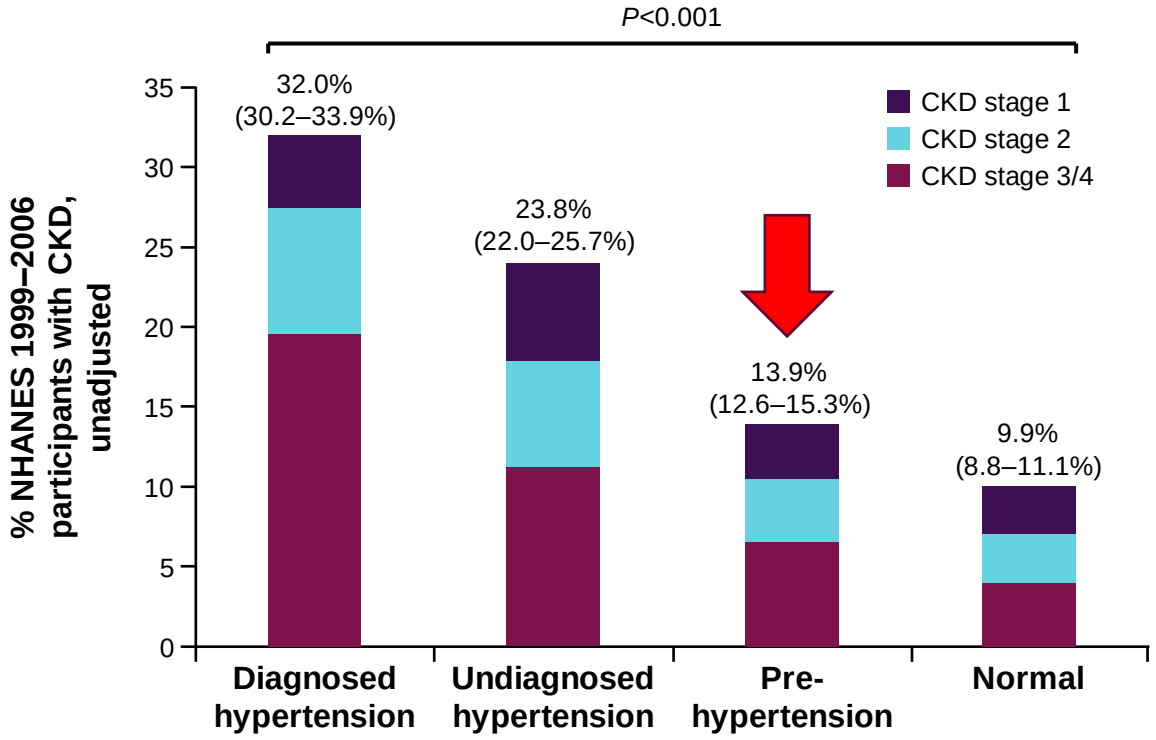
Hypertension is the 2nd most significant cause of CKD & ESRD

- Hypertension is the cause of CKD in approximately **24 million** patients globally[1]
- The rate of age-standardized CKD DALYs per 100,000 persons in hypertension is 98.19[2]

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016[2]



Prevalence of CKD according to hypertension status[3]



[a]Hypertension was prevalent in those with diabetes (92%) and those without diabetes (80%)

CKD, chronic kidney disease; DALY, disability-adjusted life year; NHANES, National Health and Nutrition Examination Survey

1. Global Burden of Disease Collaborators 2017. *Lancet* 2018,392:1789–1858; 2. Xie Y et al. *Kidney Int* 2018;94:567–581; 3. Crews DC, et al. *Hypertension* 2010;55:1102–1109

Benefits of Lowering BP

	Average Percent Reduction
Stroke incidence	35–40%
Myocardial infarction	20–25%
Heart failure	50%

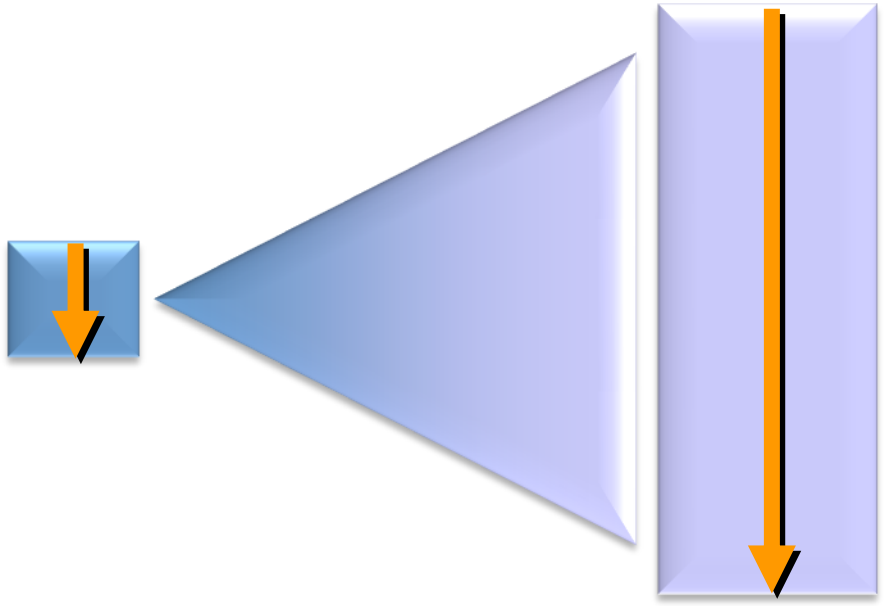
In stage 1 HTN and additional CVD risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will **prevent 1 death for every 11 patients treated**.

Lowering BP reduces cardiovascular risk

Small systolic BP (SBP) reductions yield significant benefit on a long-term basis

Meta-analysis of 61 prospective, observational studies One million adults, 12.7 million person-years[1]

2 mmHg decrease in mean SBP maintained over 10 years



7% reduction in risk of ischemic heart disease mortality

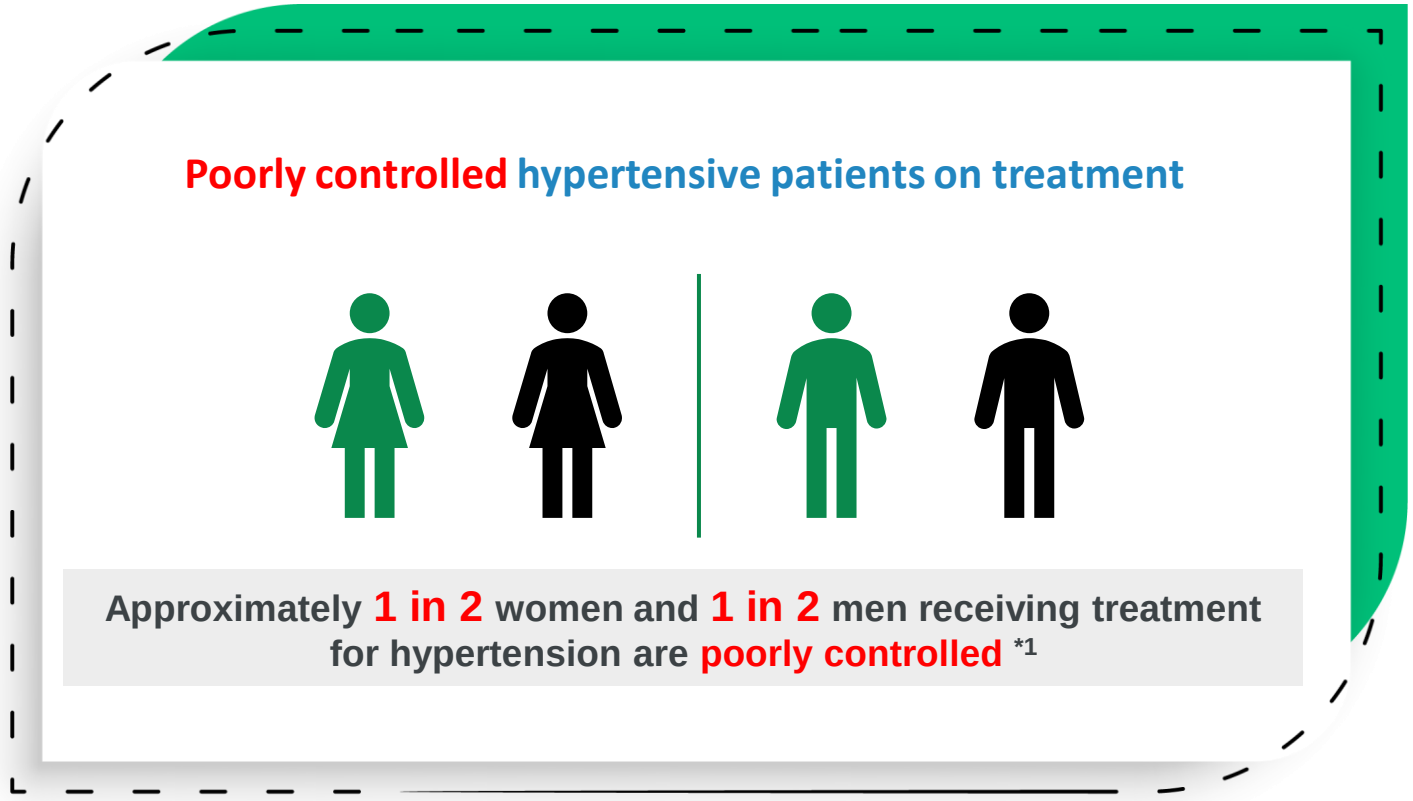
10% reduction in risk of stroke mortality

1. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913.

Tight Control of Hypertension With Treatment Is still a Major Unmet Need of Patients[1]

> than 280 million

uncontrolled hypertension patients worldwide although receiving a treatment *1



* A pooled analysis of 1201 population-representative studies with 104 million participants, data from 1990 to 2019 on people aged 30–79 years from population-representative studies.

1. Zhou, B., Carrillo-Larco, R.M., Danaei, G., Riley, L.M., Paciorek, C.J., Stevens, G.A., Gregg, E.W., Bennett, J.E., Solomon, B., Singleton, R.K. and Sophiea, M.K., 2021. 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. *The Lancet*, *398*(10304), pp.957-980.

The Reasons for the High Proportion of Patients Not Reaching BP Goals Although Receiving Treatment Are Varied, but Include:[1,2]

1. Adherence problems
2. Treatment doses that are too low
3. An absence of synergy between the treatments used
4. Clinical inertia

1. Hassanein, M., Akbar, M.A., et al. 2022. Management of Diabetes and Hypertension within the Gulf Region: Updates on Treatment Practices and Therapies. Diabetes Therapy, pp.1-28.
2. Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo Jr, J.L., Jones, D.W., Materson, B.J., Oparil, S., Wright Jr, J.T. and Roccella, E.J., 2003. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. hypertension, 42(6), pp.1206-1252.

Table 1

High risk conditions in hypertension*

Systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg
Diabetes mellitus
Metabolic syndrome
Three or more cardiovascular risk factors
One or more manifestations of subclinical organ damage, eg, left ventricular hypertrophy
Established coronary artery disease
Established cerebrovascular disease
Established peripheral vascular disease
Established chronic kidney disease

Note:

*Adapted from the 2007 European Society of Hypertension and the European Society of Cardiology guidelines for the treatment of arterial hypertension.[10]

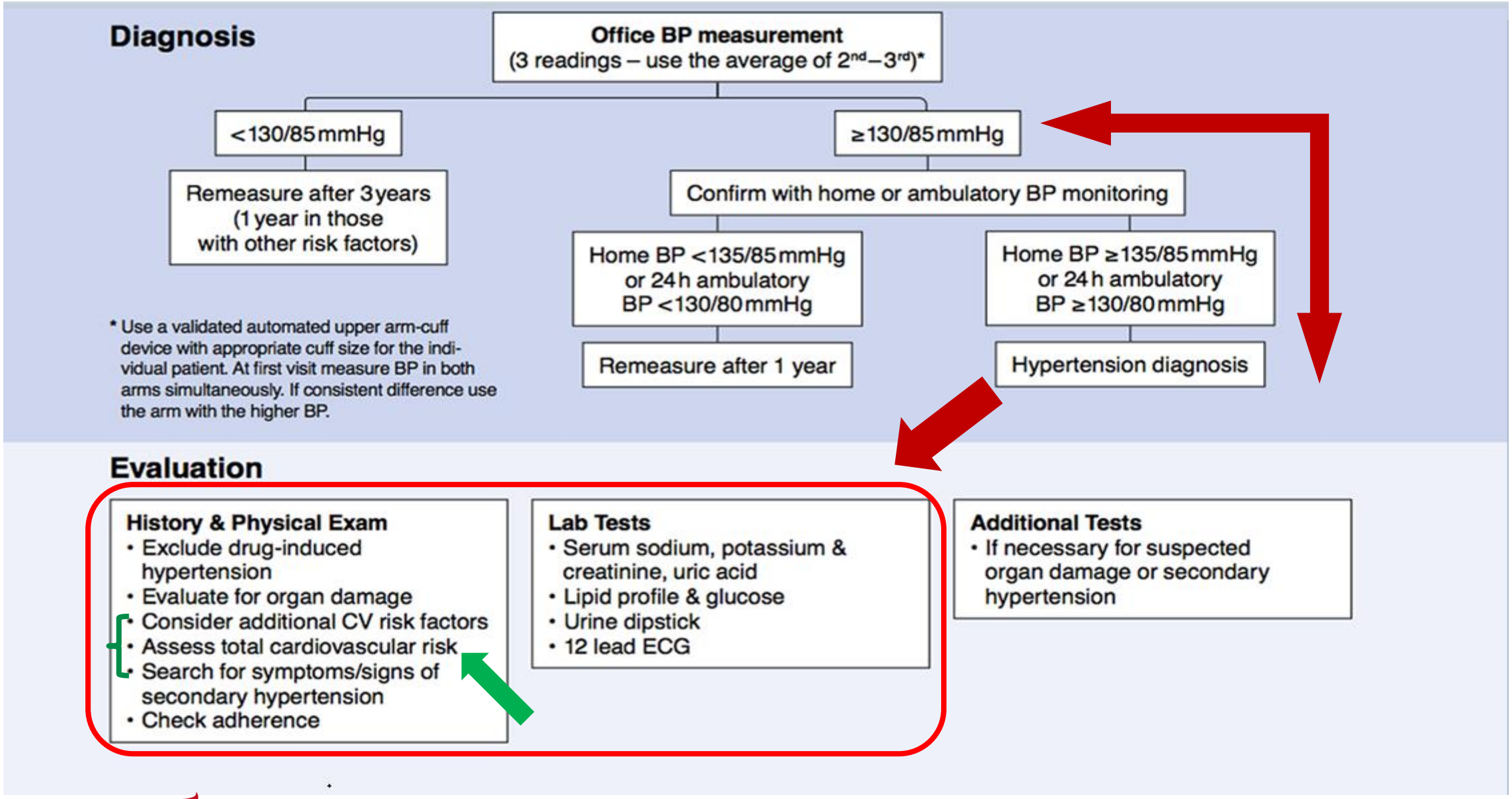
Identification of high-risk patients

The risk of a cardiovascular event increases dramatically when a hypertensive patient has vascular disease, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease.[1,4,6] In patients with diabetes mellitus, up to 65% of deaths are due to coronary artery disease and/or stroke, and diabetes mellitus has been considered as a coronary disease equivalent.[4,7] Clustering of risk factors increases the risk of cardiovascular events. The Multiple Risk Factor Intervention Trial demonstrated that cardiovascular mortality increases significantly when the number of risk factors accumulates.[8] The presence of left ventricular hypertrophy has also been shown to increase the risk of cardiovascular events in hypertension significantly.[9]

Total cardiovascular risk assessment is recommended during the initial evaluation of all hypertensive patients.[10] Factors influencing prognosis include blood pressure levels, other cardiovascular risk factors, diabetes mellitus or metabolic syndrome, subclinical organ damage, and established vascular or renal disease.[10] A summary of high-risk conditions is listed in Table 1.

8. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care.* 1993;**16**:434–444. [PubMed] [Google Scholar]

9. Chobanian AV, Bakris JL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA.* 2003;**289**:2560–2571. [PubMed] [Google Scholar]



Thomas Unger. Hypertension. 2020 International Society of Hypertension Global Hypertension Practice Guidelines, Volume: 75, Issue: 6, Pages: 1334-1357, DOI: (10.1161/HYPERTENSIONAHA.120.15026)

Some TOD markers

Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid intima-media thickness	+++	+++	++
Arterial stiffness (pulse wave velocity)	+++	+	++
Ankle-brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/white matter lesions	?	++	++++
eGFR	+++	++++	+
MAU	+++	++++	+

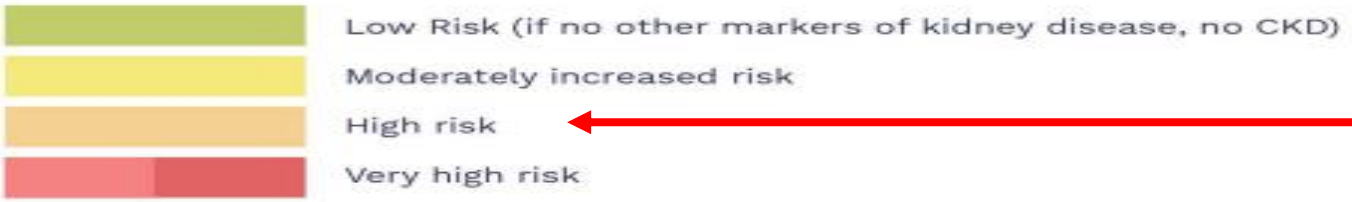
KDIGO Heat Map

Albuminuria manifests as the **earliest sign of kidney damage** in **43%** of Patients with **Hypertension**

Measuring eGFR alone do not always lead to CKD diagnosis

CKD is classified based on: *Cause (C) *GFR (G) *Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min per 1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15-29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

*Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring.



Clinical Case

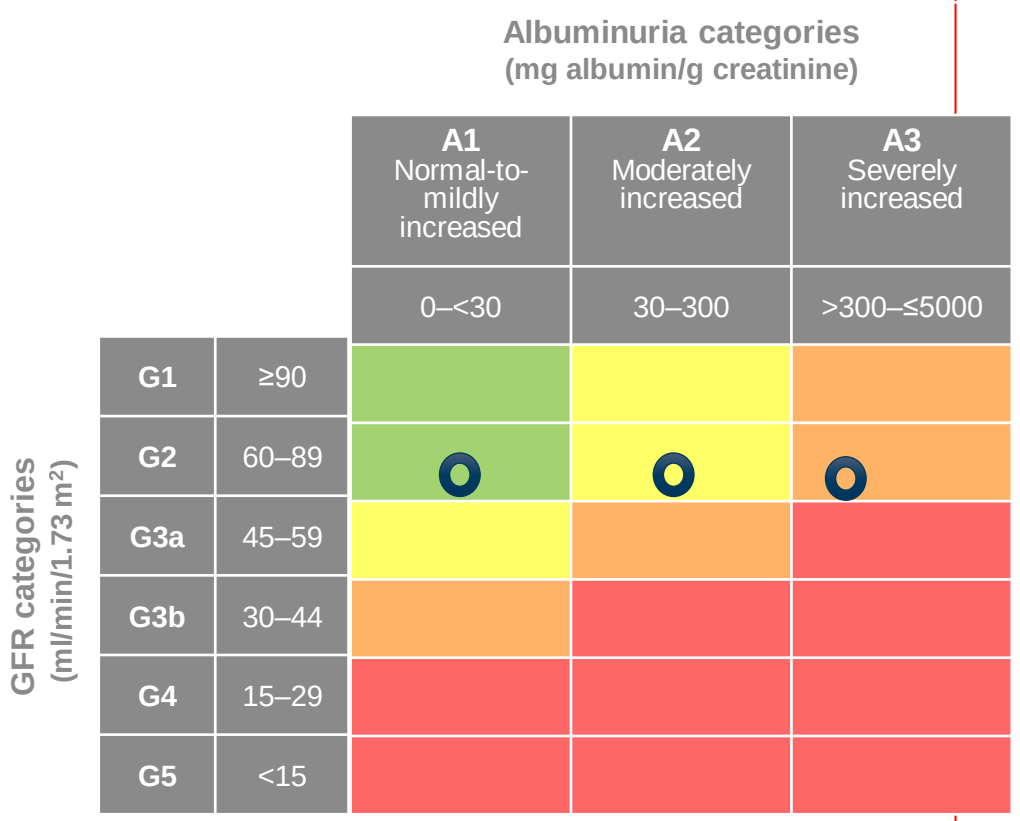
- **56-year-old** female was seen in the clinic as a new patient to follow up on her BP and medication refill.
- PMH: **HTN** for last 6-year, **TIA** last year, osteoarthritis of both knees, and hypothyroidism.
- F. Hx:
  - Father had **HTN and CAD** before the age of 50**.**
  - Older brother has **HTN**.
- Social Hx:
  - Teacher, **Sedentary lifestyle,** not very complaint with salt restriction and follow up visits, non-smoker.
- Medication at home:
  - Nifedipine XL 90 mg daily.
  - Levothyroxine 75 mcg daily.
  - Aspirin 100 mg daily & Atorvastatin 40 mg at bedtime.
  - Naproxen PRN.

Clinical Case

- BMI: **26.6** (weight 75 Kg, height 168 Cm)
- BP: **145/85** (average of last two reading of 3),
- pulse: 72 regular.
- Home BP**: 140-150 / 80-90**

- HbA1C: **5.5**, fasting BS **98**.
- Cr: 94 mmol/L (baseline CR 90, eGFR 70)
- UACR : **380 mg/g**
- eGFR: 67 ml/min/1.73m^2

- Echo: Normal except **LVH**, EF 55%.

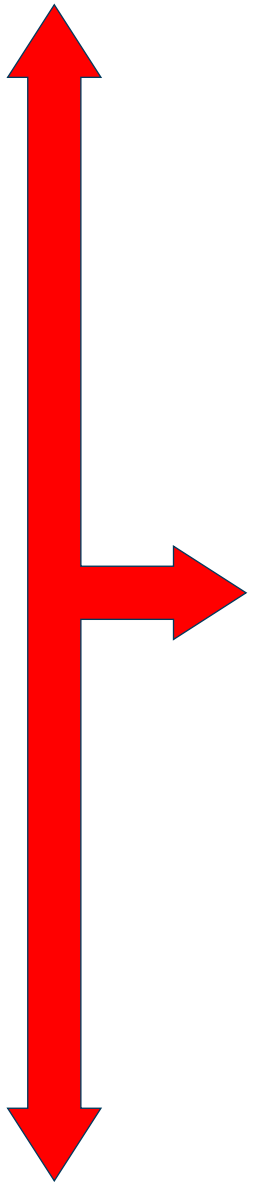


Clinical Case – Problem list

- BMI: **26.6**
- BP**: 145/85,** pulse: 72 regular.
- Home BP**: 140-150 / 80-90**

- Cr: 94 mmol/L (baseline 90)
- UACR : **380 mg/g**
- eGFR: 67 ml/min/1.73m^2

- HbA1C: **5.5**
- Echo: Normal except **LVH**, EF 55%.



- **Overweight**
- **Uncontrolled HTN with EOD: LVH, CKD, and TIA.**

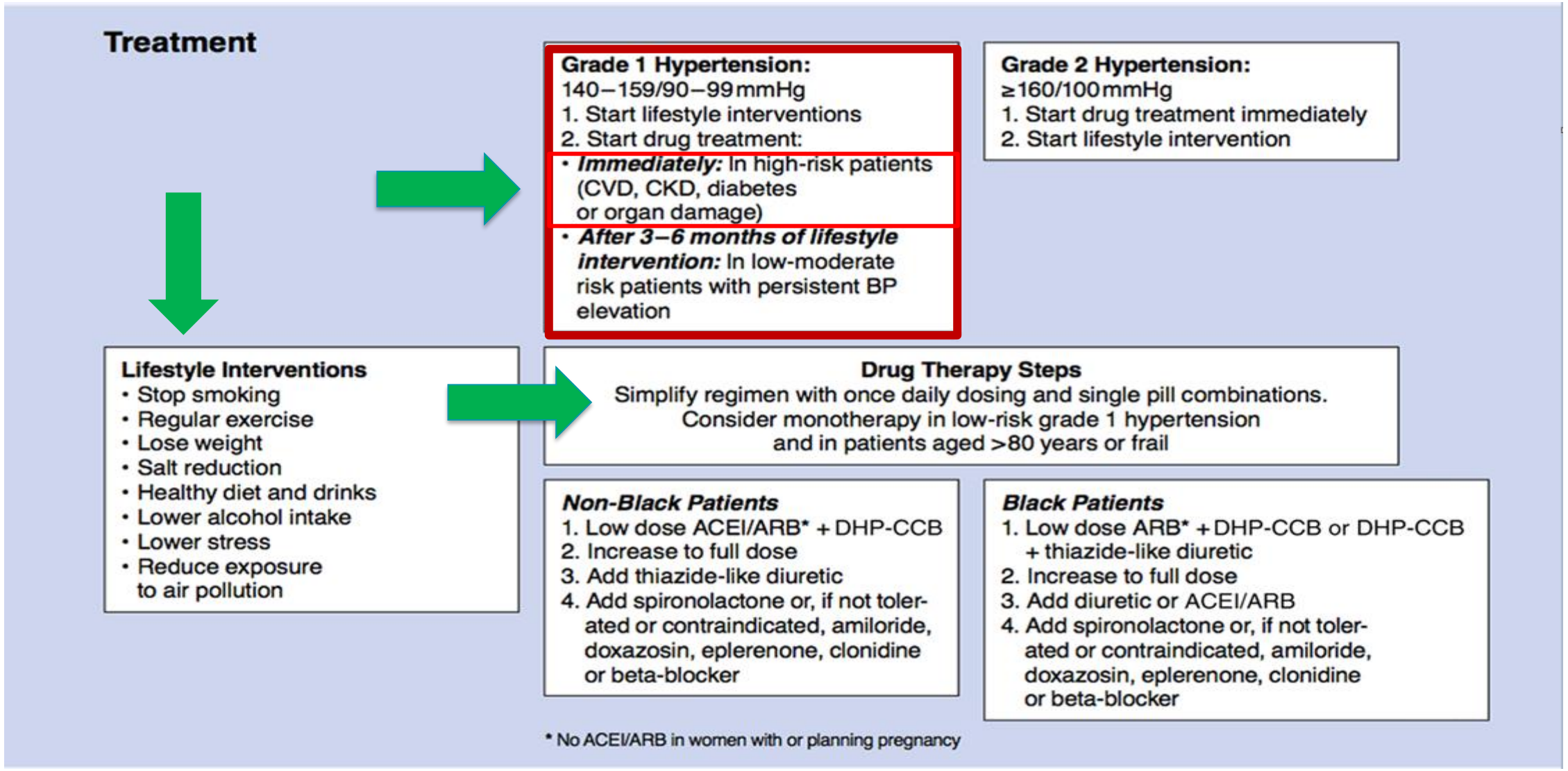
- CKD: Stage **G2** A3

Table 6. Simplified Classification of Hypertension Risk according to additional Risk Factors, Hypertension-Mediated Organ Damage (HMOD), and Previous Disease*

Other Risk Factors, HMOD, or Disease	High-Normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP ≥160 DBP ≥100
No other risk factors	Low	Low	Moderate / High
1 or 2 risk factors	Low	Moderate	High
≥3 risk factors	Low / Moderate	High	High
HMOD, CKD grade 3, diabetes mellitus, CVD	High	High	High

*Example based on a 60 year old male patient. Categories of risk will vary according to age and sex.

Hypertension adds to other CV risk factors



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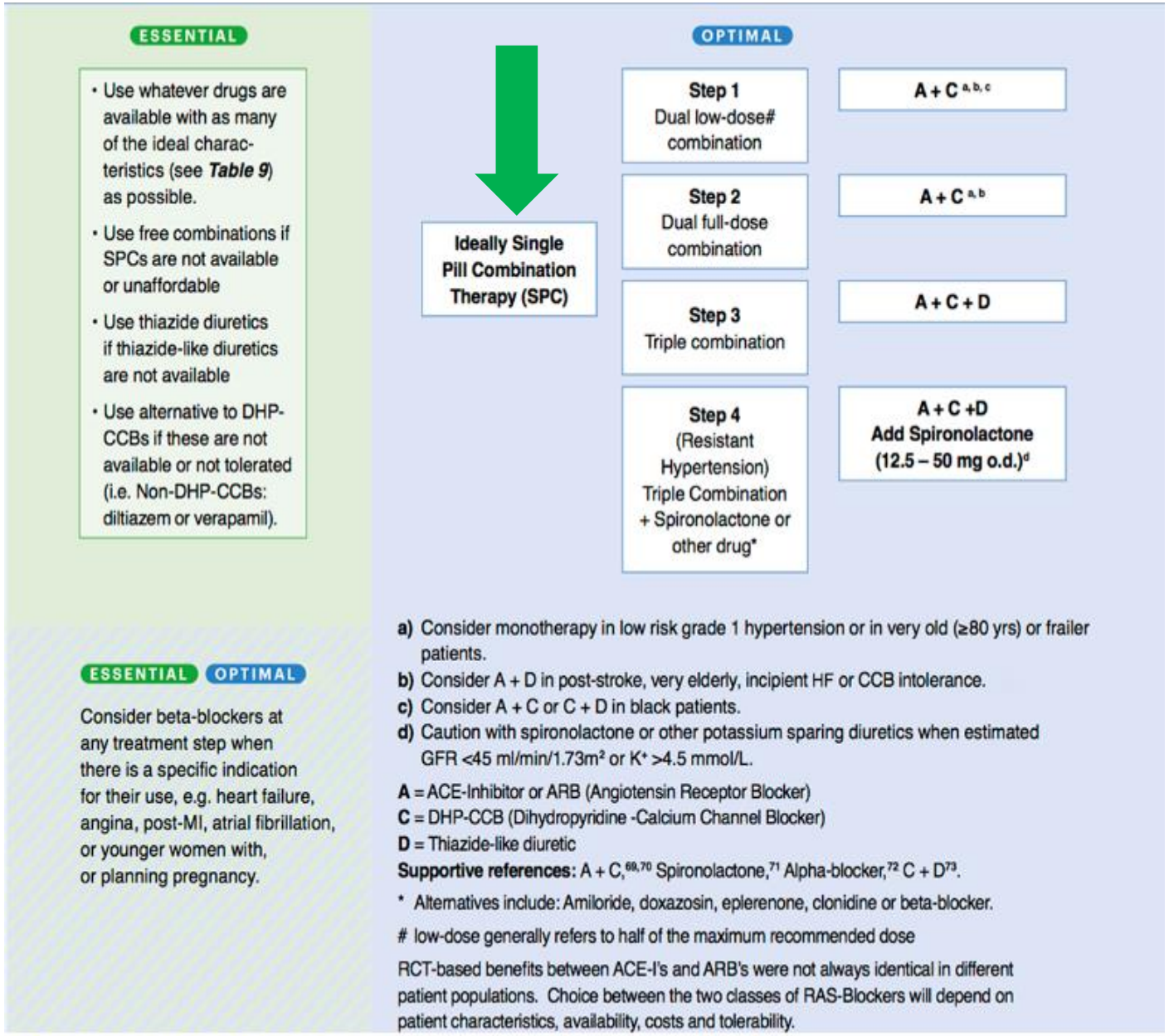

Table 9. Ideal Characteristics of Drug Treatment

1.	Treatments should be evidence-based in relation to morbidity/mortality prevention.
2.	Use a once-daily regimen which provides 24-hour blood pressure control.
3.	Treatment should be affordable and/or cost-effective relative to other agents.
4.	Treatments should be well-tolerated.
5.	Evidence of benefits of use of the medication in populations to which it is to be applied.

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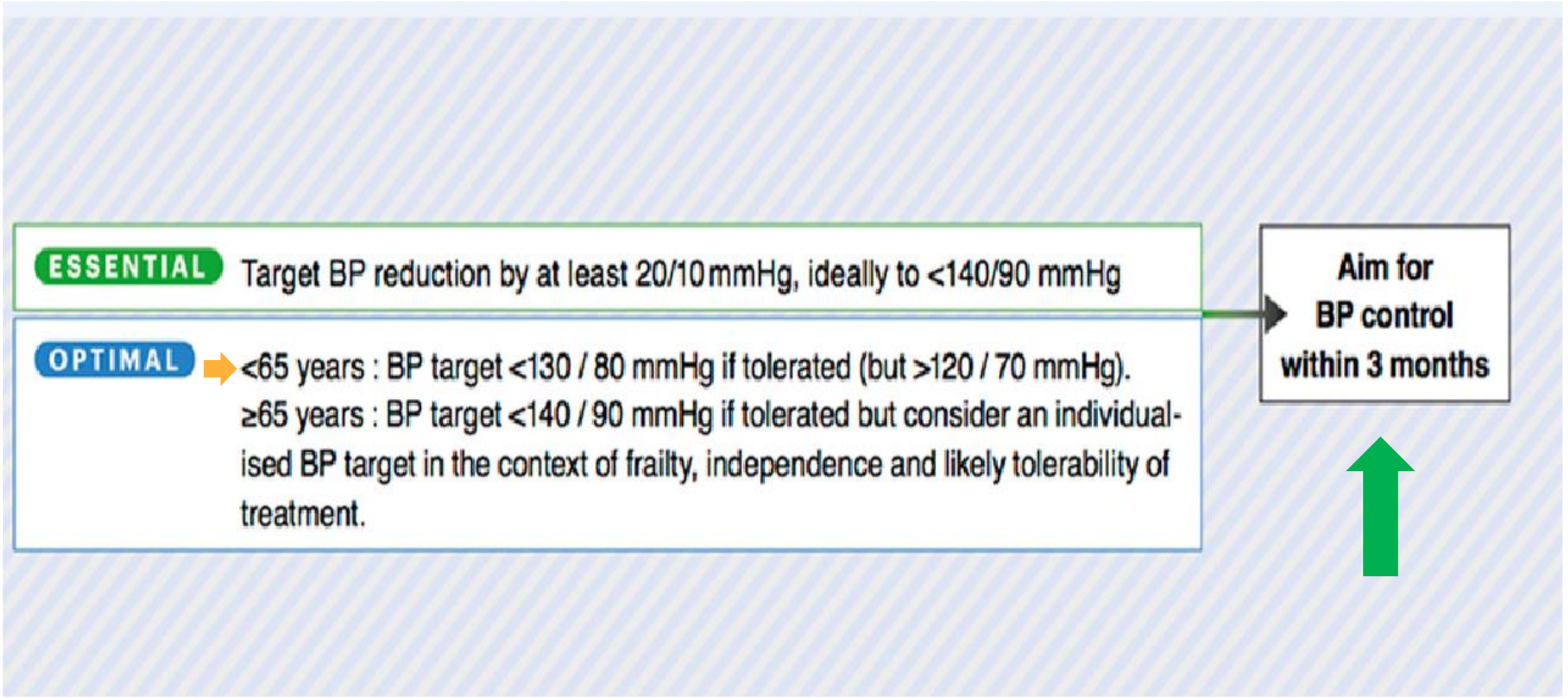

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The Latest ACC/AHA Hypertension Guidelines Recommends[1]

CVD/ASCVD Risk Assessment

ACC/AHA guidelines **recommends** **risk stratification** for **all adults with hypertension** but **especially important** for treatment decisions in **adults with Stage 1 hypertension** (confirmed systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg).[1]

CVD risk based on history of CVD or **10-year ASCVD risk ≥10% in adults 40–79 years of age***	
Higher-risk category	CVD or 10-year ASCVD risk **≥10%**
Lower-risk category	no CVD and 10-year ASCVD risk <10%

Lifetime risk assessment encouraged in younger adults.

Prescribing medication for stage I hypertension is recommended if:

- **Previous cardiovascular event such as a heart attack or stroke.**
- **High risk of heart attack or stroke based on age.**
- **Diabetes mellitus.**
- **Chronic kidney disease.**
- **10-year atherosclerotic CVD risk ≥10%.***

* Using the ACC/AHA Pooled Cohort Equations

1. Whelton, P.K., Carey, et. al., 2022. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines: Comparisons, Reflections, and Recommendations. *European heart journal*, *43*(35), pp.3302-3311.

The Latest ACC/AHA Hypertension Guidelines

Recommendations for Treatment Targets:

<130/80 mmHg target

Recommended for all adults with hypertension

SBP <130 mmHg

For older adults (≥65 years), who are noninstitutionalized, ambulatory, and community dwelling, the target is**, if tolerated.**

For older adults with a high burden of comorbidity and limited life expectancy, treatment decisions should be based on clinical judgment, patient preference, and a **team-based assessment of risk/benefit.**

1. Whelton, P.K., Carey, et. al., 2022. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines: Comparisons, Reflections, and Recommendations. *European heart journal*, *43*(35), pp.3302-3311.

Recommended office blood pressure target ranges

Age group	Office SBP treatment target ranges (mmHg)				
	Hypertension	+ DM	+ CKD	+ CAD	+ Stroke/TIA
18–69 years	120–130	120–130	<140–130	120–130	120–130
	Lower SBP acceptable if tolerated				
≥70 years	**<140 mmHg, down to 130 mmHg if tolerated** *Lower SBP acceptable if tolerated*				
DBP treatment target (mmHg)	<80 for all treated patients				

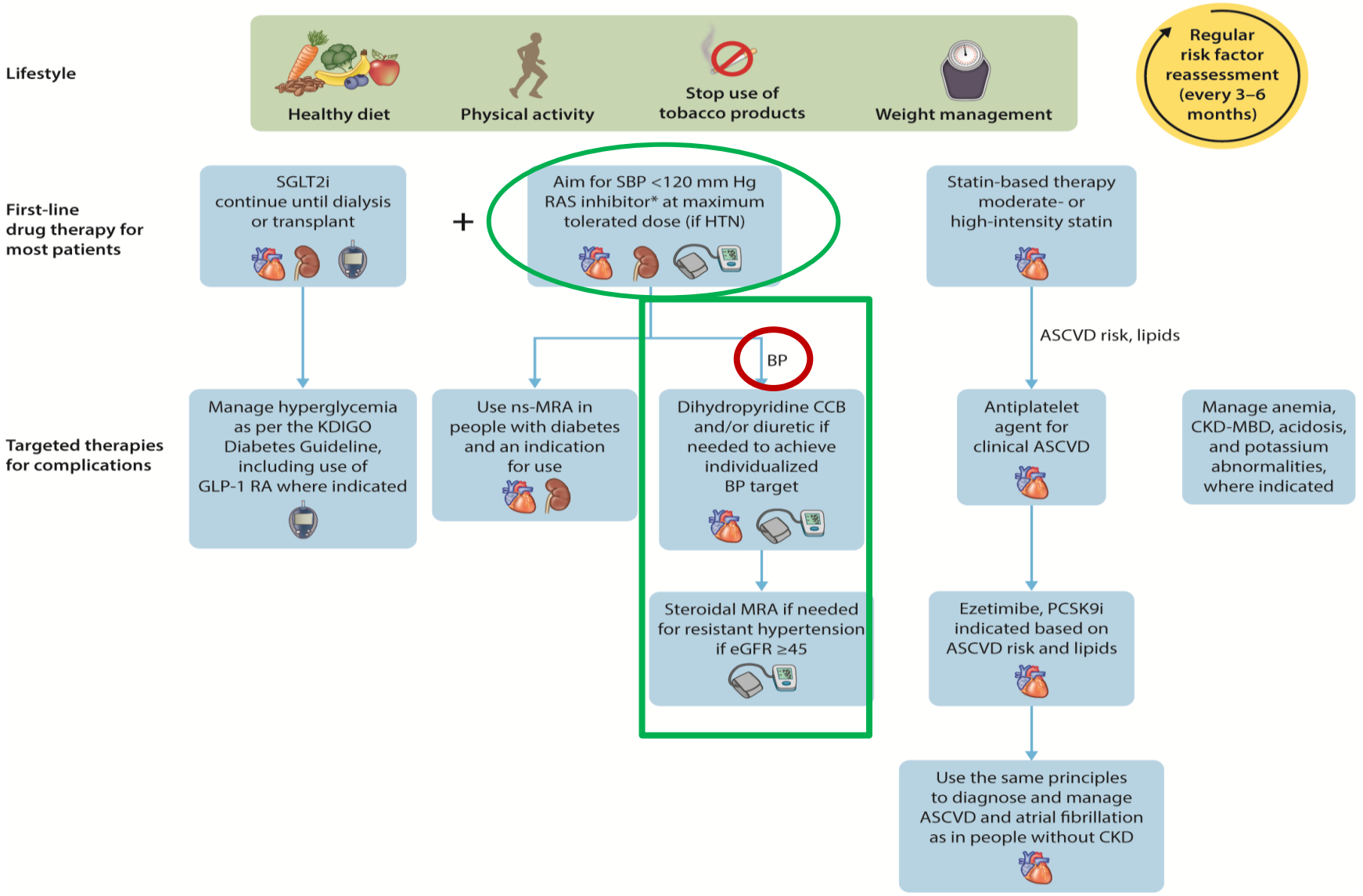
2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

This Patient Has CKD G2 A3

THE **KDIGO 2024** CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF **CKD**

KDIGO GUIDELINE CO-CHAIRS:
ADEERA LEVIN, MD, FRCPC
PAUL E. STEVENS, MB, FRCP

Management of People with or at Risk of CKD
Individualize BP Control



Individualize BP-lowering therapy and treatment targets in people with:
frailty, high risk of falls, very limited life expectancy, or symptomatic postural hypotension.

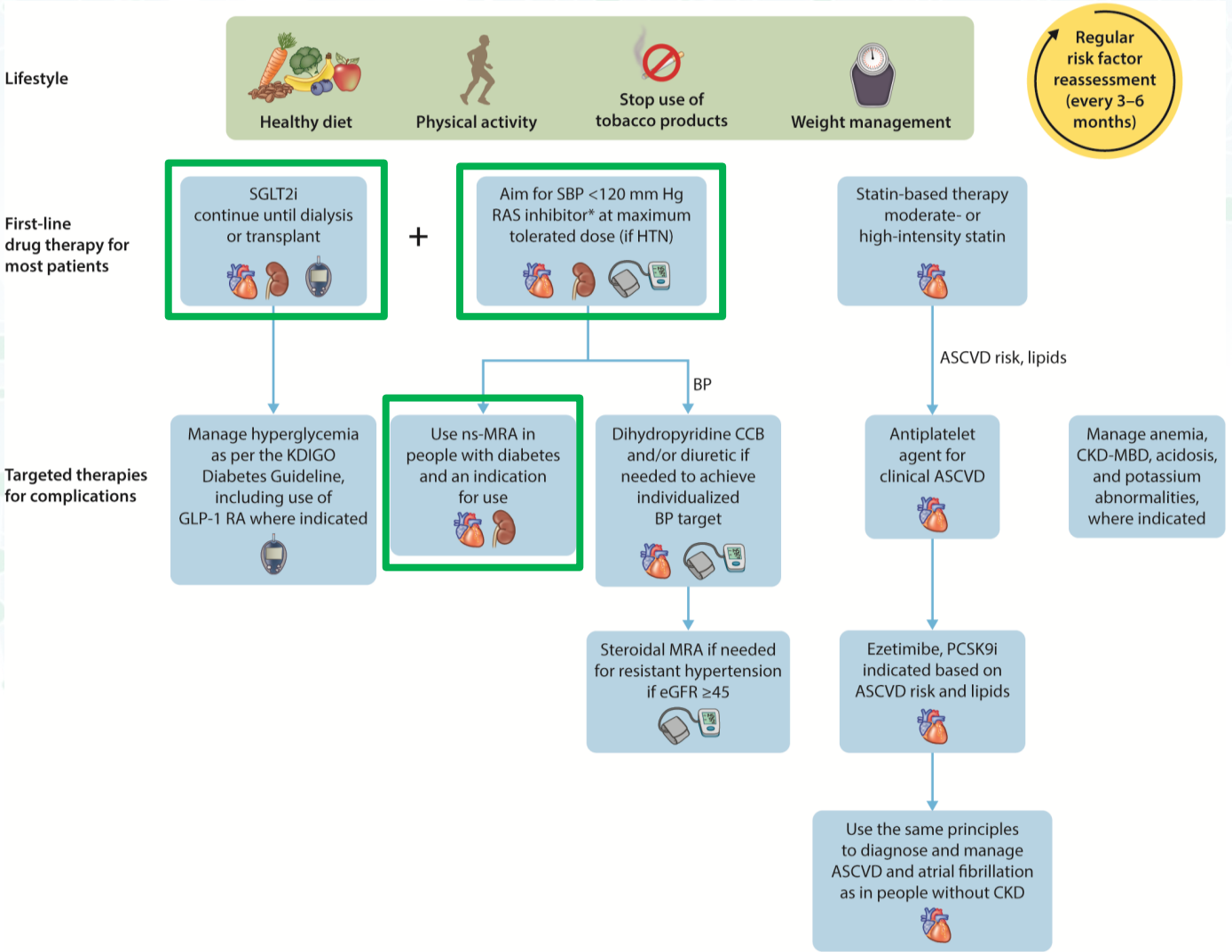
Key Renal Outcome Trials
SGLT2i & MRA

	SGLT-2i			MRA
	DAPA-CKD[1,2] N = 4304	**CREDENCE**[3] N = 4401 T2D	**EMPA-KIDNEY**[4-6] N = 6609	**FIDELIO-DKD**[7,8] N = 5734 T2D
Status	**Completed**	**Completed**	**Stopped Early**	**Completed**
Intervention	Dapagliflozin vs Placebo ≥4 weeks stable on ACEi or ARB	Canagliflozin vs Placebo ≥4 weeks stable on ACEi or ARB	Empagliflozin vs Placebo ≥8-12 weeks on ACEi or ARB	Finerenone vs Placebo ≥4 weeks on ACEi or ARB
Patient Population	• T2D and non-DM • eGFR ≥25 to ≤75 mL/min/1.73m^2 • UACR ≥200 to ≤5000 mg/g	• T2D • eGFR ≥30 to <90 mL/min/1.73m^2 • UACR >300 to ≤5000 mg/g	• T2D and non-DM • eGFR ≥20 to <45 mL/min/1.73m^2 **or** ≥45 to <90 mL/min/1.73m^2 and UACR ≥200 mg/g	• T2D • eGFR ≥25 to <60 mL/min/1.73m^2 and UACR ≥ 30 to <300 mg/g and presence of diabetic retinopathy **or** eGFR ≥25 to <75 mL/min/1.73m^2 and UACR ≥300 mg/g
Primary Endpoint	**Composite** • ≥50% sustained eGFR decline • ESKD • Renal or CV death	**Composite** • Doubling of serum creatinine • ESKD • Renal or CV death	**Composite** • Kidney disease progression • CV death	**Composite** • Kidney failure • ≥40% sustained eGFR decline • Renal death
Secondary Endpoints	• Renal composite • CV death or hHF • All-cause death	• CV death or hHF • CV death, MI, or stroke • hHF • Renal composite • CV death • All-cause death • Composite of CV death, MI, stroke, hHF or hospitalization for UA	• CV death or hHF • All-cause hospitalizations • All-cause death • Kidney disease progression • CV death • CV death or ESKD	• Stroke or hHF • All-cause death • All-cause hospitalizations • ≥57% sustained eGFR decline, kidney failure or renal death • UACR change from baseline

1. Study NCT03036150. ClinicalTrials.gov website; 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 3. Perkovic V et al. *N Engl J Med*. 2019;380:2295-2306; 4. Study NCT03594110. ClinicalTrials.gov website; 5. Boehringer Ingelheim press release. Published March 16, 2022; 6. EMPA-KIDNEY Collaborative Group. Online ahead of print. *Nephrol Dial Transplant*. 2022; 7. Study NCT02540993. ClinicalTrials.gov website; 8. Bakris GL et al. *Am J Nephrol*. 2019;50:333-344.

MANAGEMENT OF CKD – RASI AND SGLT2I

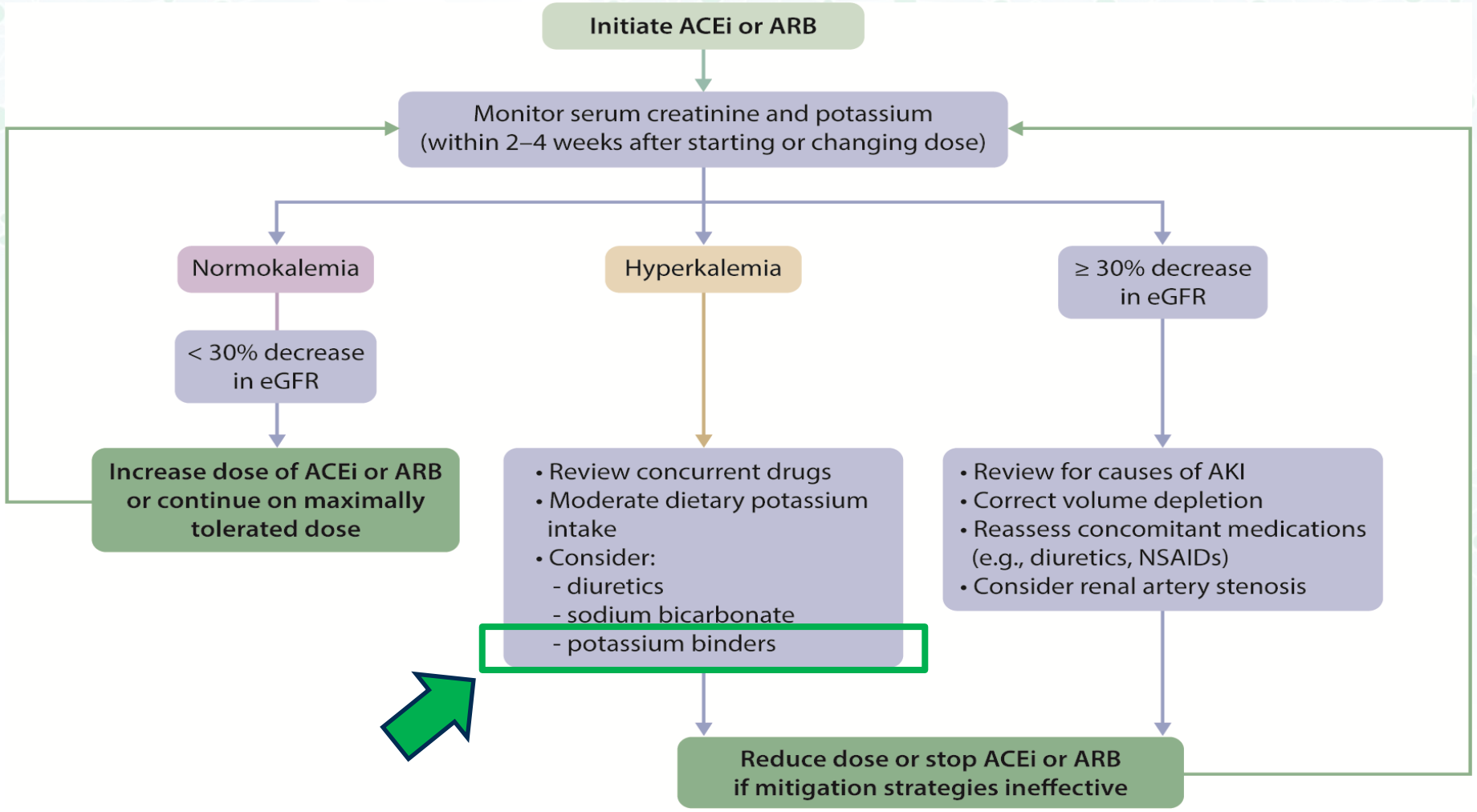
Treatments that delay progression of CKD with a strong evidence base include **RASi** and **SGLT2i**. In people with CKD and heart failure, SGLT2i confer benefits irrespective of albuminuria.



Initial dips in eGFR

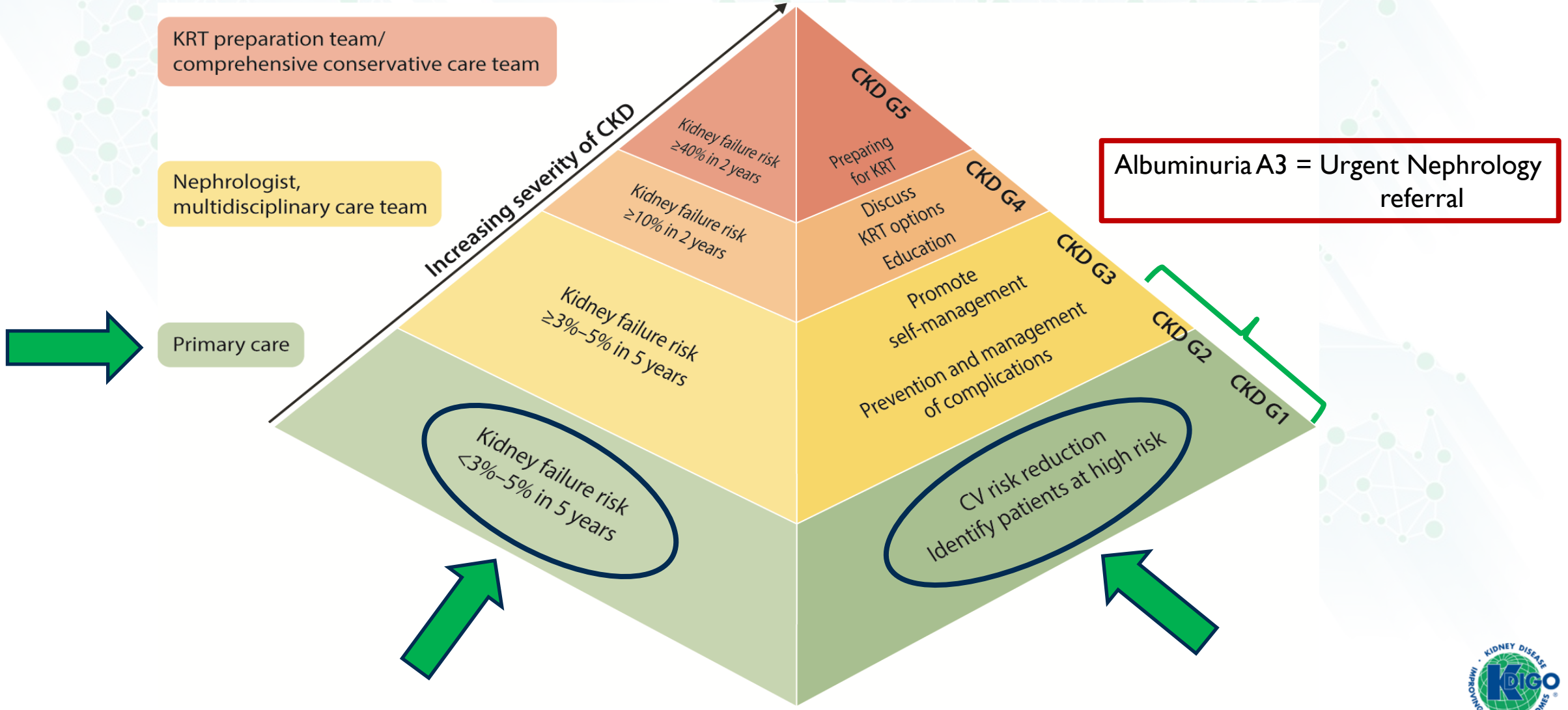
are expected following initiation of both RASi and SGLT2i

GFR reductions of ≥30% from baseline exceed the expected variability and warrant evaluation



MANAGEMENT OF CKD

"PRIMARY CARE ROLE"



Albuminuria A3 = Urgent Nephrology referral

Why do the ESC/ESH, AHA/ACC & ISH guidelines recommend starting with Single Pill Combination?

- **Better & faster BP** short & long-term **control = more patients reach target blood pressures**
- Less variability in response = **more patients respond to Rx.**
- **Better safety & tolerability** (reduces need for high doses)
- Fewer pills – **better adherence, more convenient**
- **Minimizes physician inertia** – failure to escalate therapy
- Beneficial in terms of **reduction in CV events**
- **Synergetic / complementary Mechanism of actions**

The Latest ACC/AHA Hypertension Guidelines

Initial monotherapy versus initial combination drug therapy[1,2]

Adults with **Stage 1** hypertension and BP goal <130/80 mmHg	Initiate a single antihypertensive drug	Dosage titration and sequential addition of other agents to achieve the BP target
Adults with **Stage 2** hypertension and BP >20/10 mmHg above their BP target	Initiate 2 first-line agents of different classes	Separate agents or in a fixed-dose combination

If there is no compelling clinical indication for selection of a BP-lowering medication, treat with ≥1 drugs from the following classes: Diuretics, CCBs, ACE inhibitors, or ARBs.[1,2]

Combination therapy is required in **most patients** and is specifically recommended:

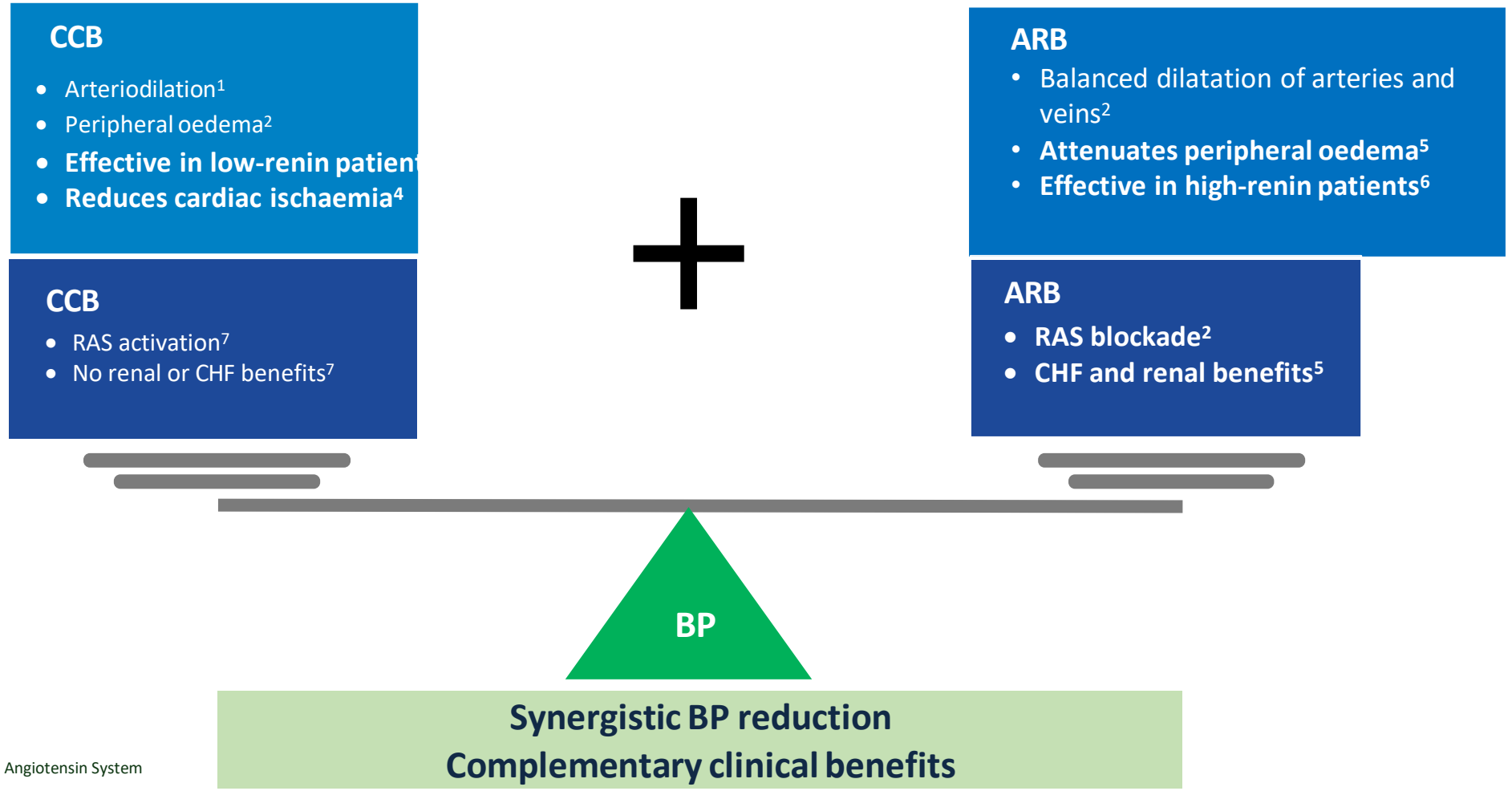
- **African Americans**
- **Adults with a starting SBP/DBP ≥20/10 mmHg above the BP treatment target.**

Dual- and triple-drug therapy should include agents with complementary mechanisms of action.[1,2]

1.Whelton, P.K., Carey, R.M., Aronow, W.S., et. al, E.J., 2018. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *71*(19), pp.e127-e248.

2. Whelton, P.K., Carey, et. al., 2022. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines: Comparisons, Reflections, and Recommendations. *European heart journal*, *43*(35), pp.3302-3311.

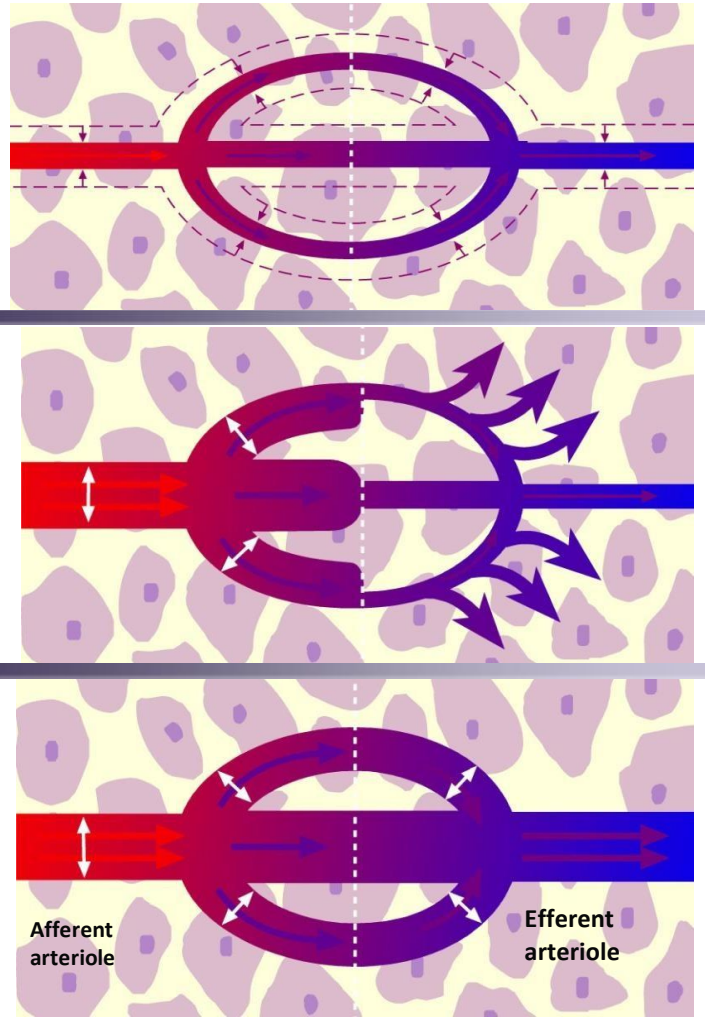
CCB + ARB: The Synergies of Counter-Regulation



CHF: Congestive Heart Failure; RAS : Renin- Angiotensin System

1. Lin Y, Ma L. Blood pressure lowering effect of calcium channel blockers on perioperative hypertension: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2018;97(48):e13152. **2.** Mistry NB, Westheim AS, Kjeldsen SE. The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother*. 2006;7(5):575-581. **3.** Bühler FR, Bolli P, Kiowski W, Erne P, Hulthén UL, Block LH. Renin profiling to select antihypertensive baseline drugs. Renin inhibitors for high-renin and calcium entry blockers for low-renin patients. *Am J Med*. 1984;77(2A):36-42. **4.** Sueta D, Tabata N, Hokimoto S. Clinical roles of calcium channel blockers in ischemic heart diseases. *Hypertens Res*. 2017;40(5):423-428. **5.** Oparil S, Weber M. Angiotensin receptor blocker and dihydropyridine calcium channel blocker combinations: an emerging strategy in hypertension therapy. *Postgrad Med*. 2009;121(2):25-39. **6.** Brown MJ. Renin: friend or foe?. *Heart*. 2007;93(9):1026-1033. **7.** Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. Drugs. 2002;62(3):443-462. doi:10.2165/00003495-200262030-00003.

Reduced Edema by Co-Administration of ARBs With CCB



Arterial hypertension

- Constricted blood vessels[1]

CCBs

- Calcium channel blockers dilate arteries to a greater extent than veins, thus increasing capillary pressure and causing fluid to collect in interstitial spaces[1]

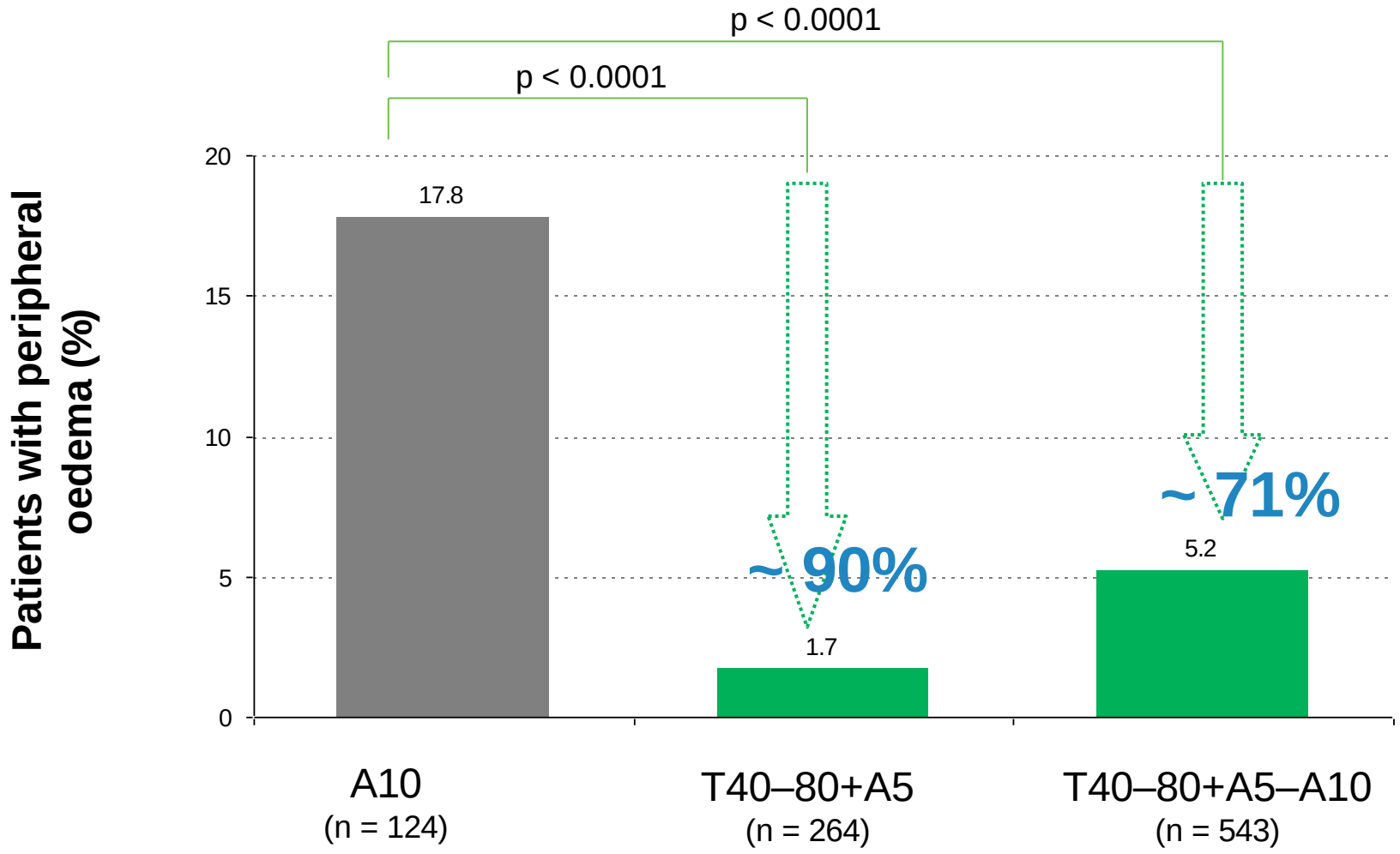
CCBs + RAS inhibitors*

- Normalized pressure gradient
- ARBs reduce the lower extremity edema induced by CCBs because they decrease fluid volume (via inhibition of the RAAS) and dilate both arterial and venous capillary beds[1]

CCB: Calcium Channel Blocker; RAAS: Renin- Angiotensin Aldosterone System; RAS : Renin- Angiotensin System

1. Oparil S, Weber M. Angiotensin receptor blocker and dihydropyridine calcium channel blocker combinations: an emerging strategy in hypertension therapy. *Postgrad Med*. 2009;121(2):25-39

(Single pill telmisartan + amlodipine) Is Associated With Less Peripheral Edema Compared With Amlodipine 10 mg[1]



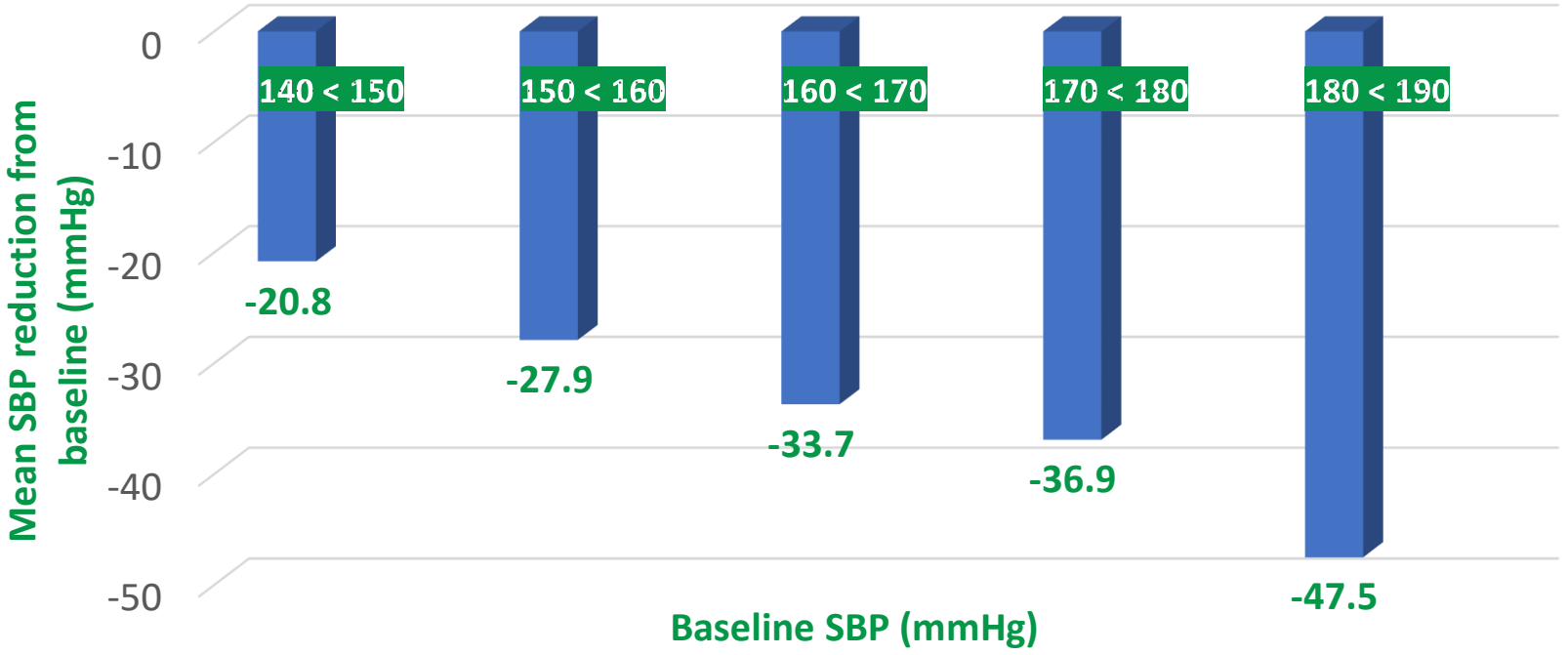
A: Amlodipine; T:Telmisartan.

1. Littlejohn TW 3rd, Majul CR, Olvera R, et al. Results of treatment with telmisartan- amlodipine in hypertensive patients. *J Clin Hypertens (Greenwich)*. 2009;11(4):207-213.

4. UNIQUE PROFILE OF MICARDIS®
(telmisartan)

Power of (telmisartan + amlodipine) in BP Reductions Needed to Get Hypertensive Patients to GOAL

Mean systolic BP reductions after 8 weeks of treatment with TWYNSTA® 80/10 mg



BP: Blood Pressure

Adapted from ref. 1

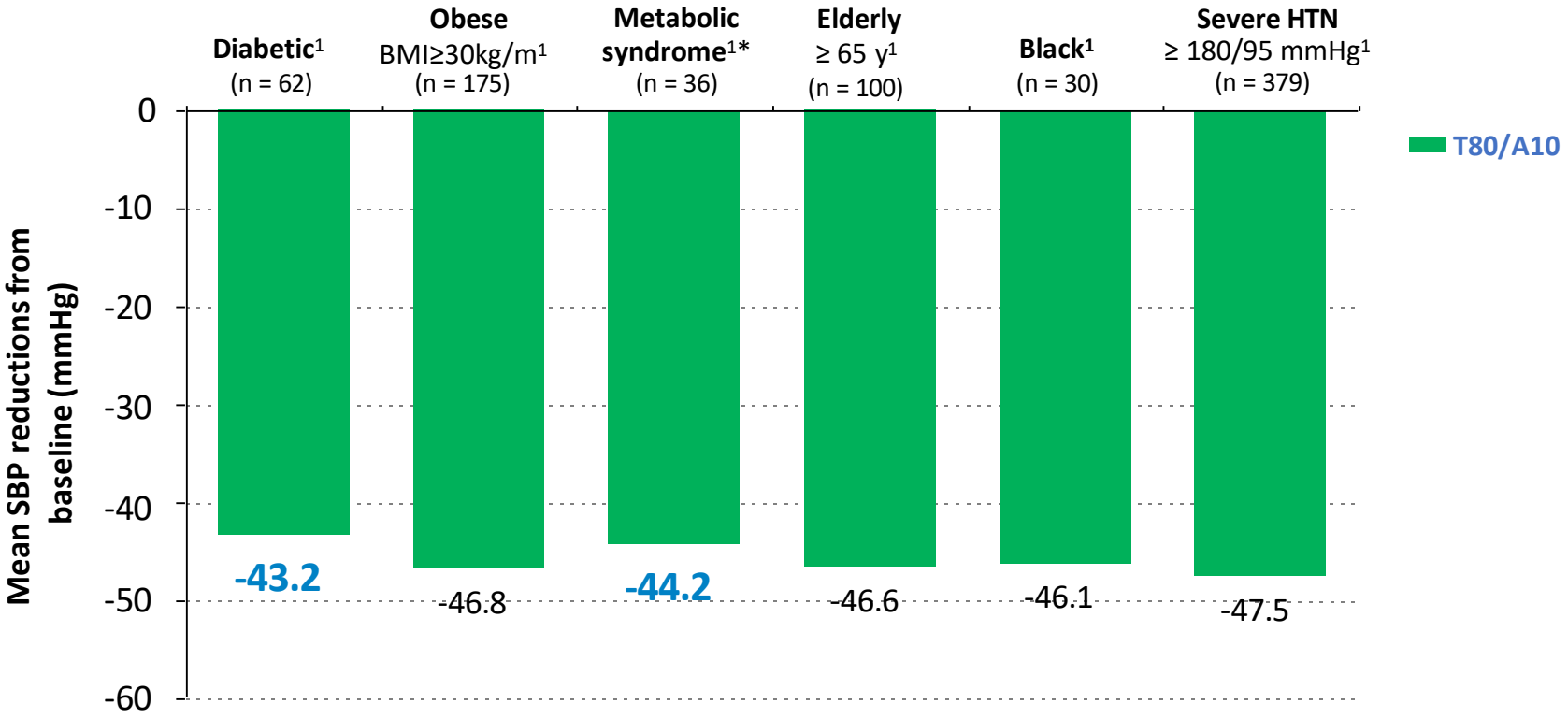
1. Suárez C. Single-pill telmisartan and amlodipine: a rational combination for the treatment of hypertension. *Drugs*. 2011;71(17):2295-2305. 2. Neutel JM, Mancia G, Black HR, et al. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. *J Clin Hypertens (Greenwich).* 2012;14(4):206-215

(telmisartan + amlodipine) Provides Consistently BP Reductions in Hypertensive at-Risk Patients[1]

Mean baseline BP = 185.4/103.2 mmHg

* Diabetes, obesity (BMI ≥ 30kg/m²), and HTN

TWYNSTA® reduce BP more than 40mmHg in all type risk of hypertension.[1]



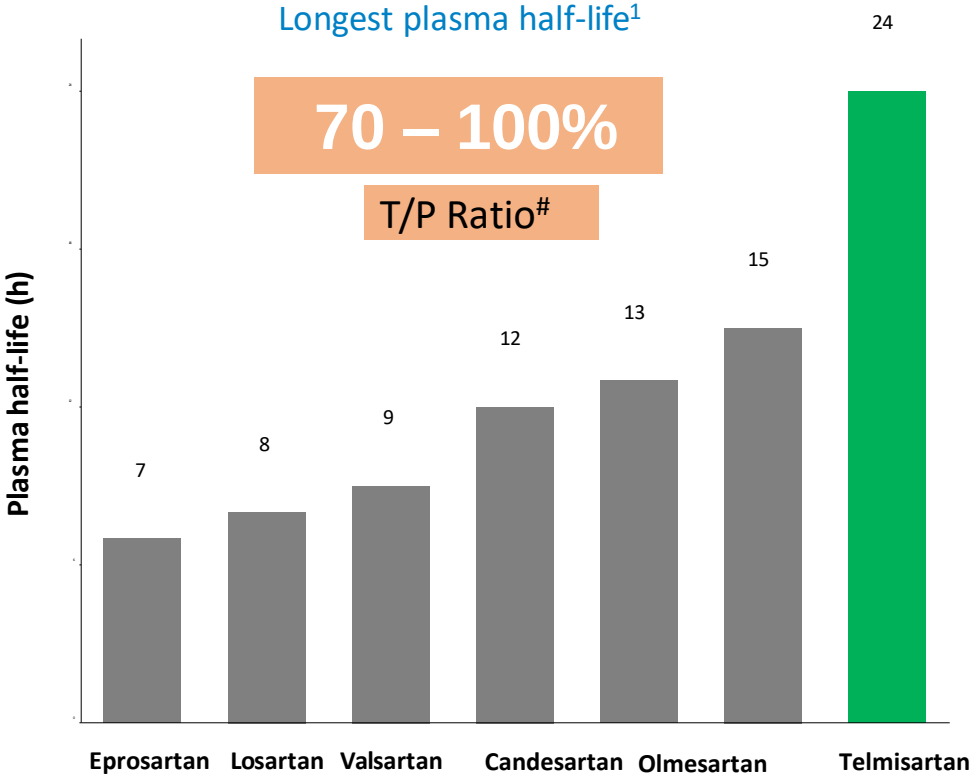
1. Neutel JM, Mancia G, Black HR, et al. Single-pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. *J Clin Hypertens (Greenwich).* 2012;14(4):206-215.

Telmisartan Unique Pharmacology Profile in Its Class (ARB)

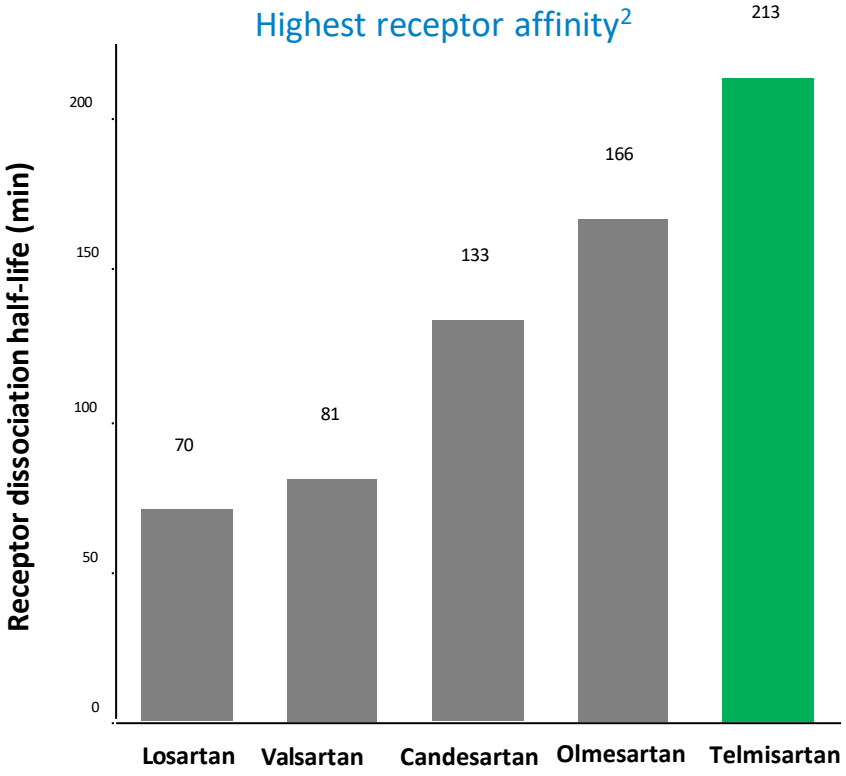
Longest plasma half-life[1]

70 – 100%

T/P Ratio#



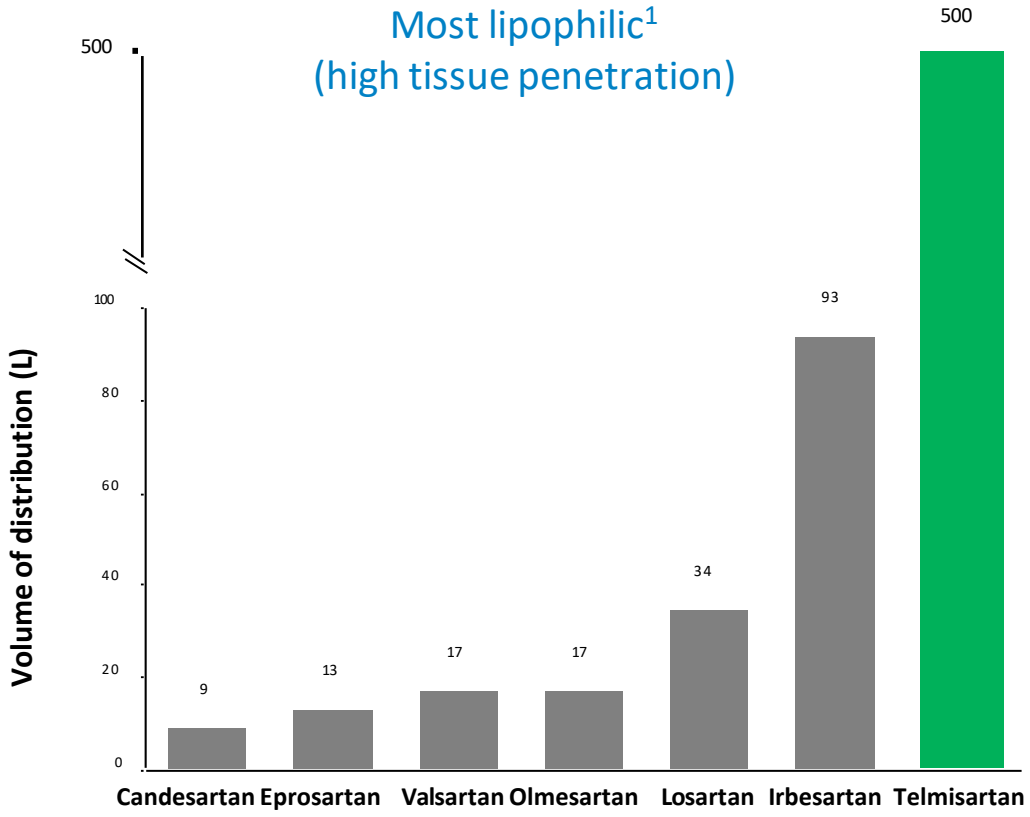
Highest receptor affinity[2]



1. Asmar R. Targeting effective blood pressure control with angiotensin receptor blockers. Int J Clin Pract. 2006;60(3):315-320. **2.** Kakuta H, Sudoh K, Sasamata M, Yamagishi S. Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers. *Int J Clin Pharmacol Res.* 2005;25(1):41-46.**3**. Benson SC, Pershadsingh HA, Ho CI, et al. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension*. 2004;43(5):993-1002.

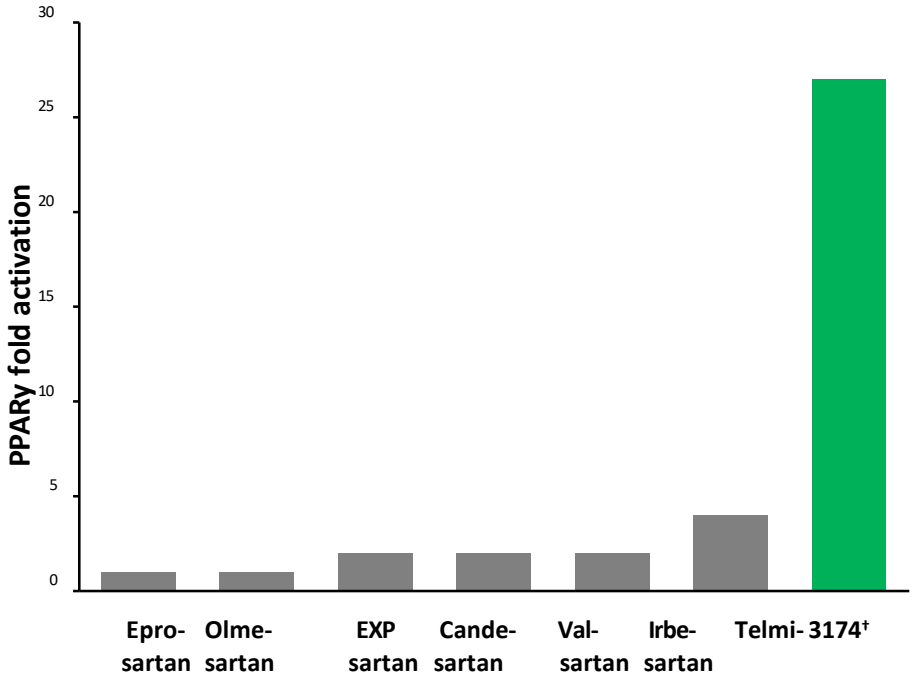
Telmisartan Unique Pharmacology Profile in Its Class (ARB)

Most lipophilic[1] (high tissue penetration)



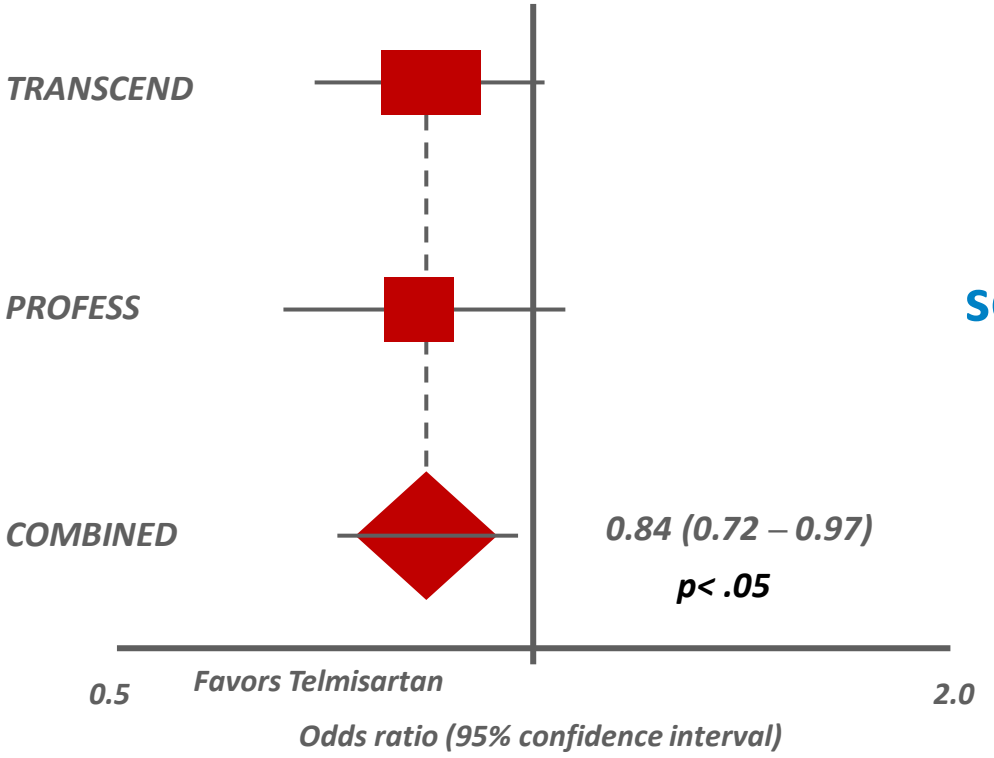
Highest selective PPAR-γ activation[3]

† Active metabolite of losartan



1. Asmar R. Targeting effective blood pressure control with angiotensin receptor blockers. Int J Clin Pract. 2006;60(3):315-320. **2.** Kakuta H, Sudoh K, Sasamata M, Yamagishi S. Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers. *Int J Clin Pharmacol Res.* 2005;25(1):41-46.**3**. Benson SC, Pershadsingh HA, Ho CI, et al. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension*. 2004;43(5):993-1002.

Meta-Analysis of the Effects of Telmisartan 80 mg on New Onset Diabetes in PRoFESS and TRANSCEND Trials (comparisons against placebo groups)



Telmisartan has Highest selective PPAR-γ activation

- Significant **anti-diabetic** effect of **Telmisartan** vs placebo
- ***16% risk reduction for diabetes***

TW Kurtz and U Klein, Hypertension Research, 2009

Cardiovascular Protection & Benefits Beyond BP control

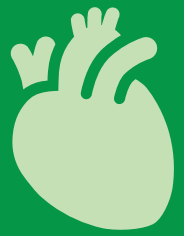


Table 9. Ideal Characteristics of Drug Treatment	
1.	Treatments should be evidence-based in relation to morbidity/mortality prevention.
2.	Use a once-daily regimen which provides 24-hour blood pressure control.
3.	Treatment should be affordable and/or cost-effective relative to other agents.
4.	Treatments should be well-tolerated.
5.	Evidence of benefits of use of the medication in populations to which it is to be applied.

Table 2

Major clinical trials on the treatment of hypertension for high-risk patients

Trial name	Patients randomized (n)	Characteristics of study population	Drugs	Duration (years)	Primary endpoint
Heart Outcomes Prevention Evaluation (HOPE)[11]	9541	Age ≥55 years with one high-risk condition	Ramipril Placebo	4.5	Ramipril 14.0% versus placebo 17.8% ($P < 0.001$)
Losartan Intervention For Endpoint reduction in hypertension (LIFE)[12]	9193	Hypertension and left ventricular hypertrophy	Losartan Atenolol	4.8	Losartan 11.0% versus atenolol 12.8% ($P = 0.021$)
Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) blood pressure-lowering arm[13]	19,257	Hypertension with ≥3 specified risk factors	Amlodipine ± perindopril Atenolol ± bendroflumethiazide-K	5.0	Amlodipine-based 4.5% versus atenolol-based 4.9% ($P = 0.105$)
Action in Diabetes and Vascular Disease: Preterax and Diamicron-Controlled Evaluation Trial (ADVANCE)[14]	11,140	Diabetes mellitus	Perindopril ± indapamide Placebo	4.3	Perindopril + indapamide 15.5% versus placebo 16.8% ($P = 0.04$)

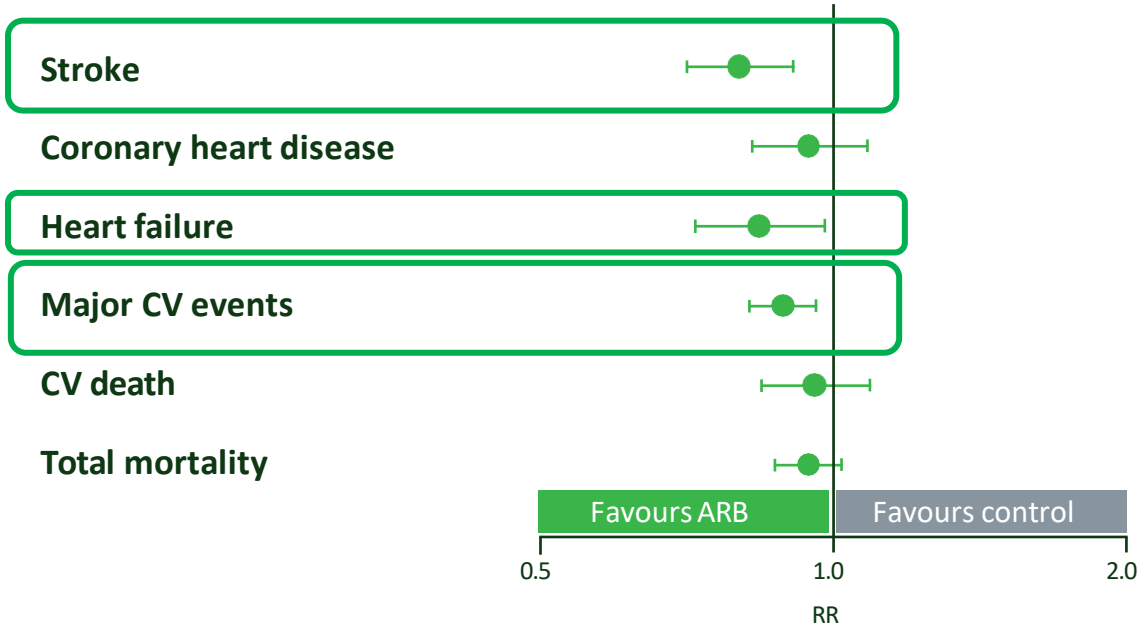
Table 2

Major clinical trials on the treatment of hypertension for high-risk patients

Trial name	Patients randomized (n)	Characteristics of study population	Drugs	Duration (years)	Primary endpoint
Ongoing Telmisartan alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)[15]	25,620	High-risk patients with coronary, peripheral arterial, or cerebrovascular disease, or diabetic patients with target organ damage	Ramipril Telmisartan Ramipril + telmisartan	4.7	Ramipril 16.5% versus telmisartan 16.7% versus ramipril + telmisartan 16.3%
Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND)[16]	6666	As ONTARGET study with angiotensin-converting enzyme inhibitor intolerance	Telmisartan Placebo	4.7	Telmisartan 15.7% versus placebo 17.0% ($P = 0.22$)
Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)[17]	11,506	High-risk hypertensive patients	Benazepril + amlodipine Benazepril + hydrochlorothiazide	3.0	Benazepril + amlodipine 9.6% versus benazepril + hydrochlorothiazide 11.6% ($P < 0.001$)

ARBs Provide CV Protection Beyond BP Reduction

Meta-analysis of 4 trials (n=16 791) comparing ARBs with control regimens[1]



	RR (95% CI)	P value
Stroke	0.79 (0.69–0.90)	0.46
Coronary heart disease	0.96 (0.85–1.09)	0.43
Heart failure	0.84 (0.72–0.97)	0.26
Major CV events	0.90 (0.83–0.96)	0.78
CV death	0.96 (0.85–1.08)	0.34
Total mortality	0.94 (0.86–1.02)	0.59

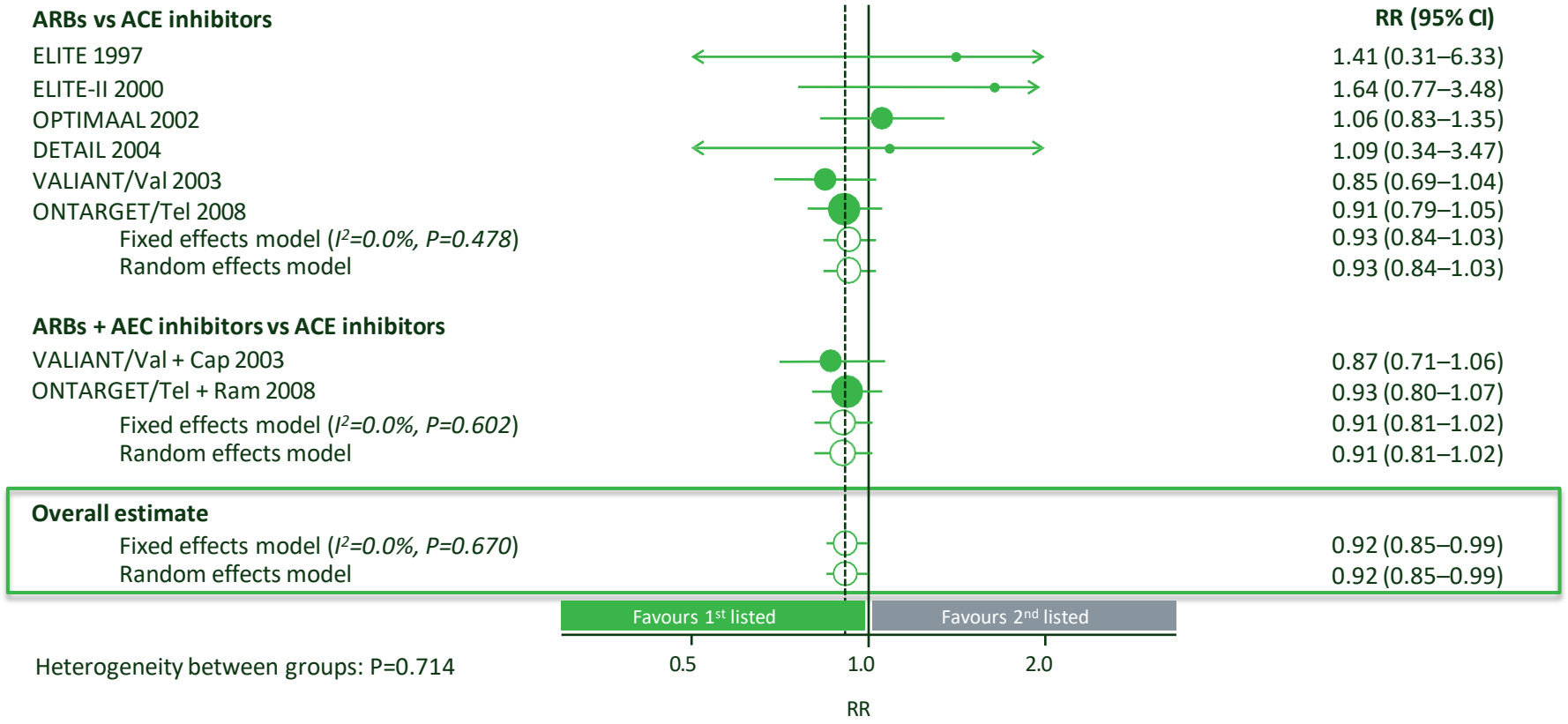
Risks of **stroke, heart failure, and major cardiovascular events** were lower with ARBs compared with control regimens.

ARB: Angiotensin Receptor Blocker; BP:, Blood Pressure; CV: Cardiovascular.

1.Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362(9395):1527-1535.

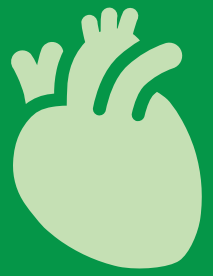
Meta-Analysis Demonstrated ARBs Reduced Stroke Risk by 8% vs ACE Inhibitors[1]

Meta-analysis of 6 trials comparing ARBs (n=31 632) with ACE inhibitors (n=18 292)[1]



ACE: Angiotensin Converting Enzyme; ARB: Angiotensin Receptor Blocker; BP: Blood Pressure.

1. Reboldi G, Angeli F, Cavallini C, Gentile G, Mancia G, Verdecchia P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. *J Hypertens.* 2008;26(7):1282-1289.

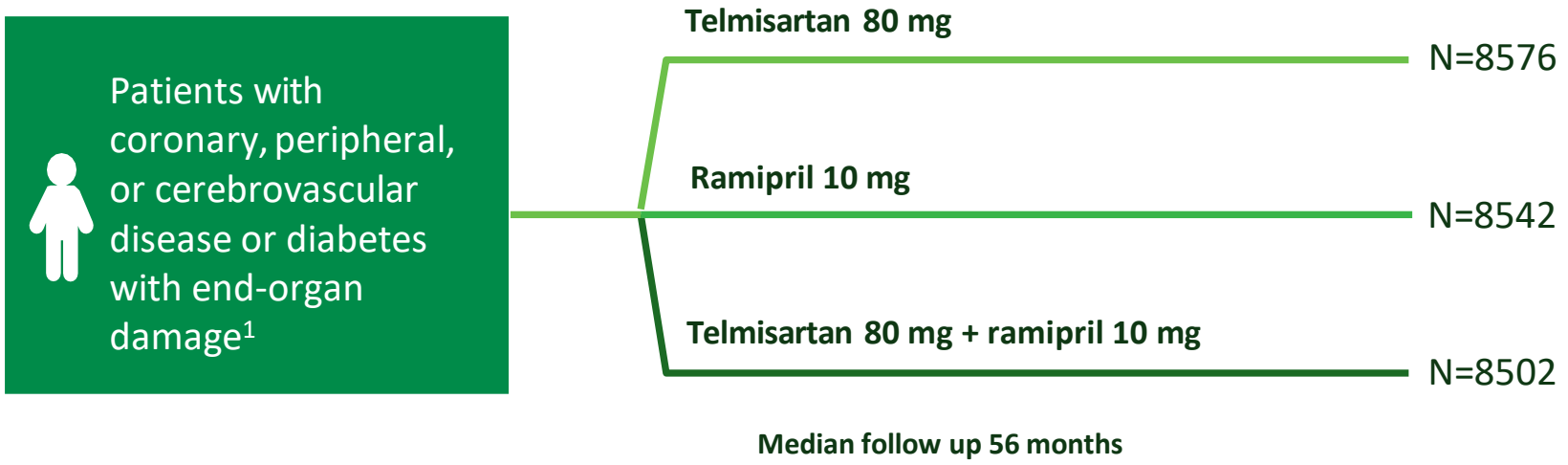


THE ONTARGET TRIAL
Cardiovascular Protection
telmisartan

ONTARGET Compared Clinical Outcomes for Telmisartan vs Ramipril in Patients at High Vascular Risk

ONTARGET

Ongoing telmisartan alone and in combination with ramipril global end-point trial



Primary endpoint: Composite of CV death, MI, stroke, or hospitalization for heart failure[1]

1. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.

The ONTARGET Trial Programme

Prospective RCT, Non-Inferior Study[1]

Outcomes

Primary composite cardiovascular endpoint:[1]

- Cardiovascular mortality
- Non-fatal myocardial infarction
- Hospitalisation for congestive heart failure
- Non-fatal stroke

Inclusion criteria

Age ≥55 years[1]

At high risk of developing a CVD event, with a history of:[1]

- Coronary artery disease
- Peripheral arterial occlusive disease (PAOD)
- Cerebrovascular event
- Diabetes mellitus with end-organ damage

Intolerant to ACE inhibitors (TRANSCEND only)[2]

1. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008;358(15):1547-1559. 2. Teo K, Yusuf S, Sleight P, et al. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J.* 2004;148(1):52-61.

The ONTARGET Trial Programme

Baseline Characteristics[1]

Medications (% of patients)	ONTARGET (n=25,620)	TRANSCEND (n=5,304*)
Demography		
Age (years)	66.4	67.0
Male (%)	73.3	57.5
Physical Exam		
BP at run-in (mmHg)	143\82	142\82
BP at randomisation (mmHg)	134\77	135\78
Body mass index	28.2	28.3
Waist–hip ratio	0.9	0.9
Medical history		
Hypertension	68.3	75.0
MI	48.7	46.3
Stable angina	34.8	36.5
Stroke/TIA	20.7	21.6
Claudication	11.8	10.2
Diabetes	37.3	35.0
Current smoker	12.5	9.5

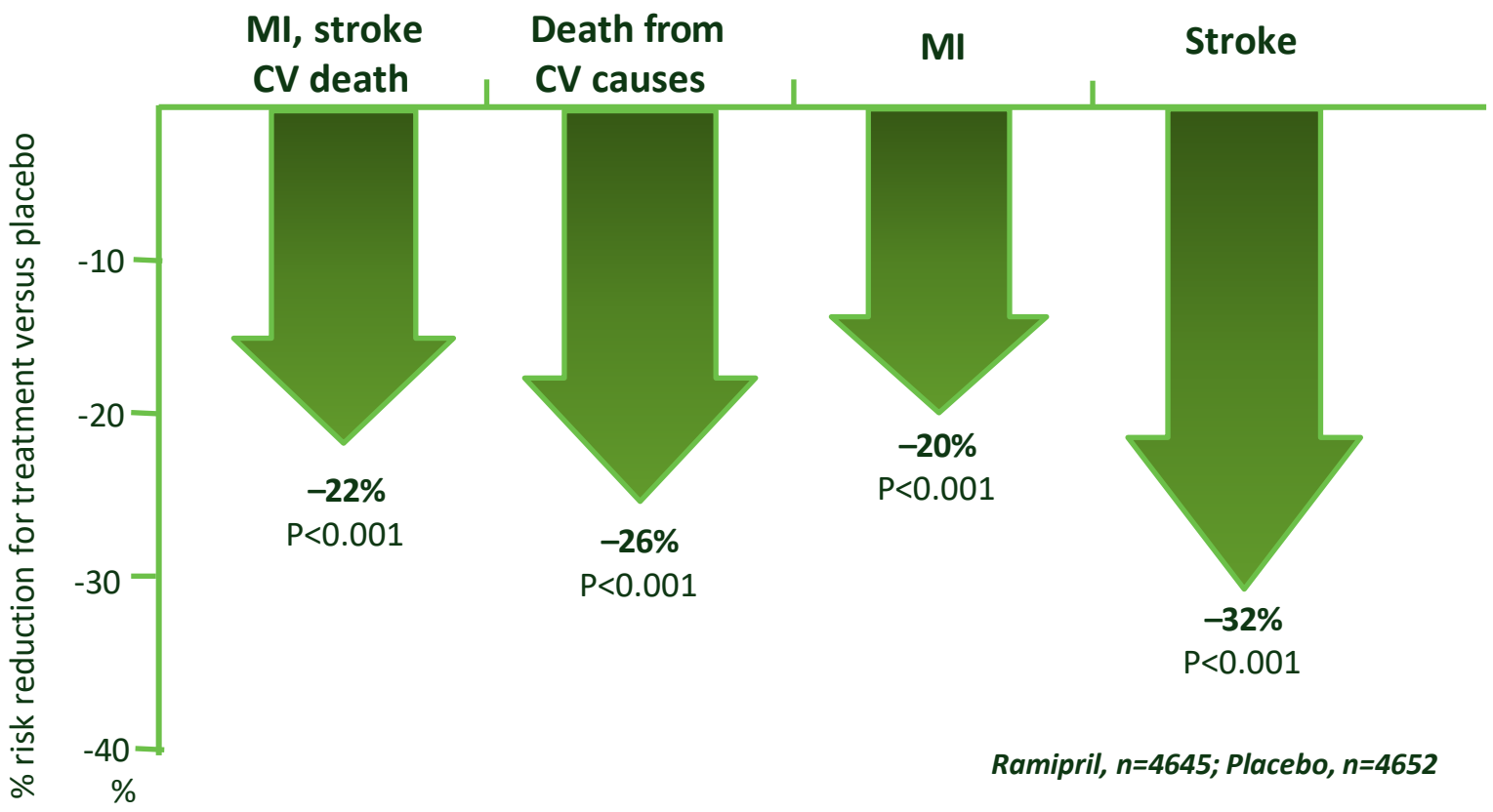
High risk patients

* TRANSCEND as of January 2004. Final TRANSCEND recruitment, n=5,926

1. Sleight P. The ONTARGET/TRANSCEND Trial Programme: baseline data. *Acta Diabetol*. 2005;42 Suppl 1:S50-S56.

Why Compared Telmisartan to Ramipril in ONTARGET Trial?

HOPE study Primary composite outcomes (CV death, MI or stroke)[1]

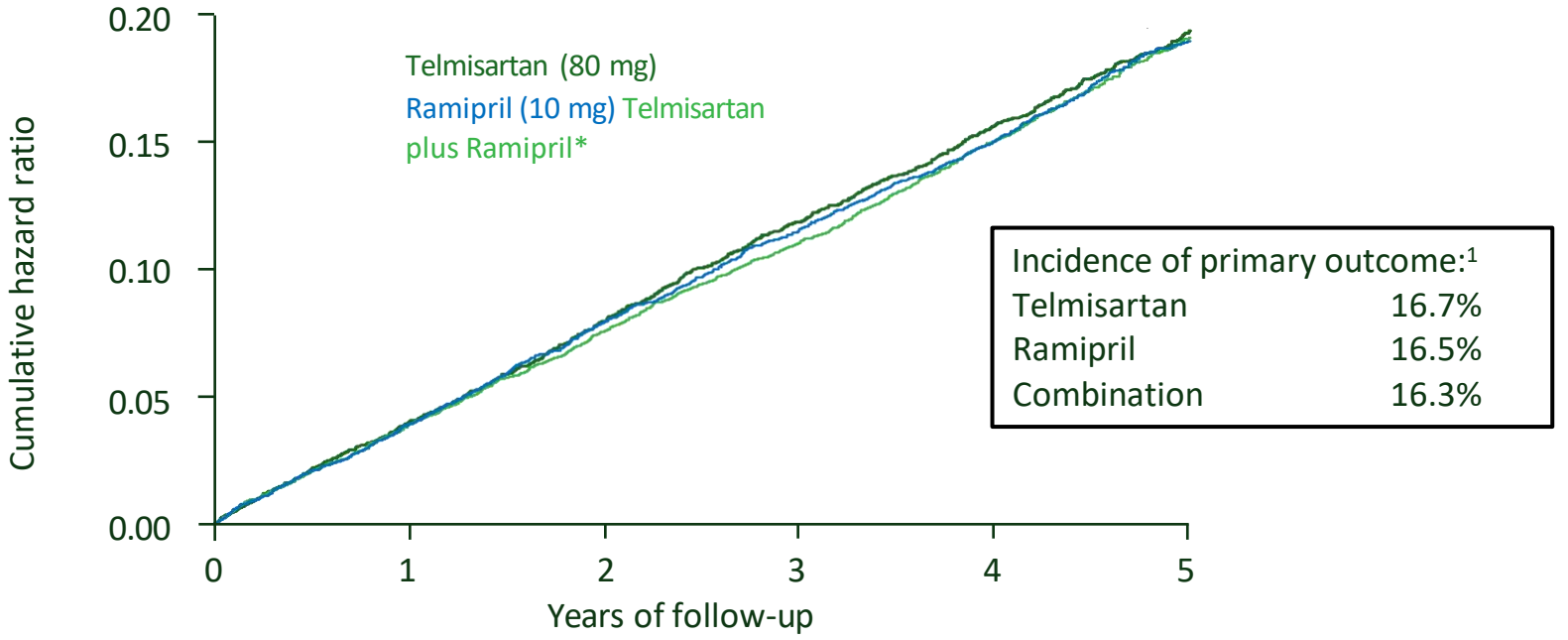


CV: Cardiovascular; MI: Myocardial Infraction.

1. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients [published correction appears in 2000 May 4;342(18):1376] [published correction appears in N Engl J Med 2000 Mar 9;342(10):748]. *N Engl J Med*. 2000;342(3):145-153

ONTARGET: The Risk of CV Events Was Similar for Patients Receiving telmisartan vs Ramipril

Composite of CV death, MI, stroke, or hospitalisation for heart failure[1]



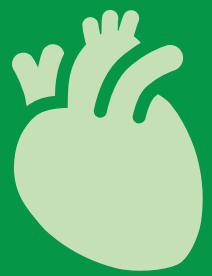
Incidence of primary outcome:[1]	
Telmisartan	16.7%
Ramipril	16.5%
Combination	16.3%

N at risk

Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

*Combination therapy (telmisartan plus ramipril) was associated with increased AEs; as a result, this combination is not recommended.
CV: Cardiovascular; MI: Myocardial Infraction.

1. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.

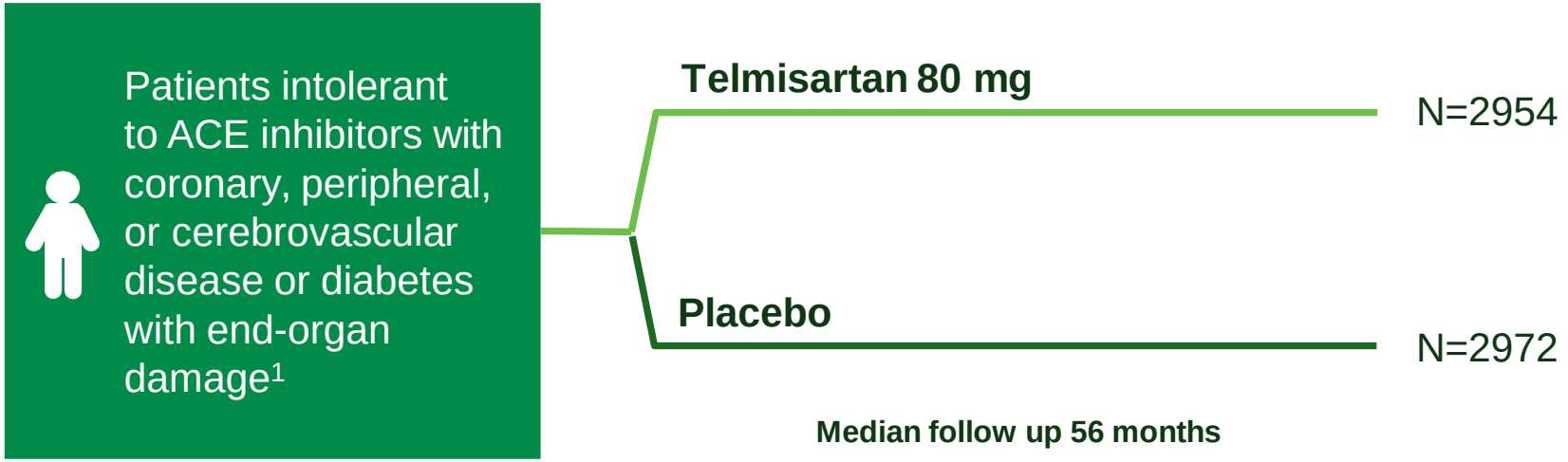


THE TRANSCEND TRIAL
Cardiovascular Protection

TRANSCEND Compared the CV Risk Reduction Profile of Telmisartan vs Placebo in Patients at High Vascular Risk Who Were Intolerant to ACE Inhibitors

TRANSCEND

Telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease[1]



Primary endpoint: Composite of CV death, MI, stroke, or hospitalisation for heart failure[1]

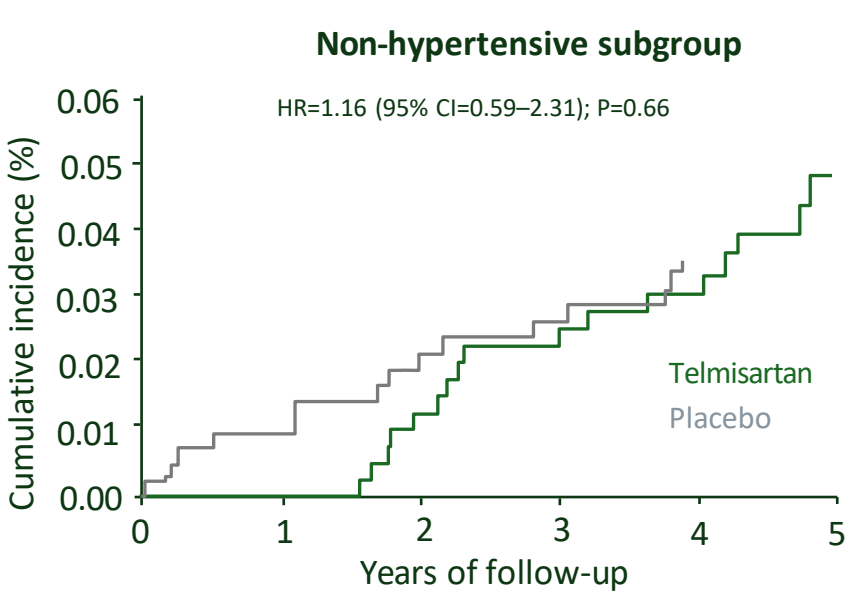
ACE: Angiotensin Converting Enzyme; CV: Cardiovascular; MI: Myocardial Infraction

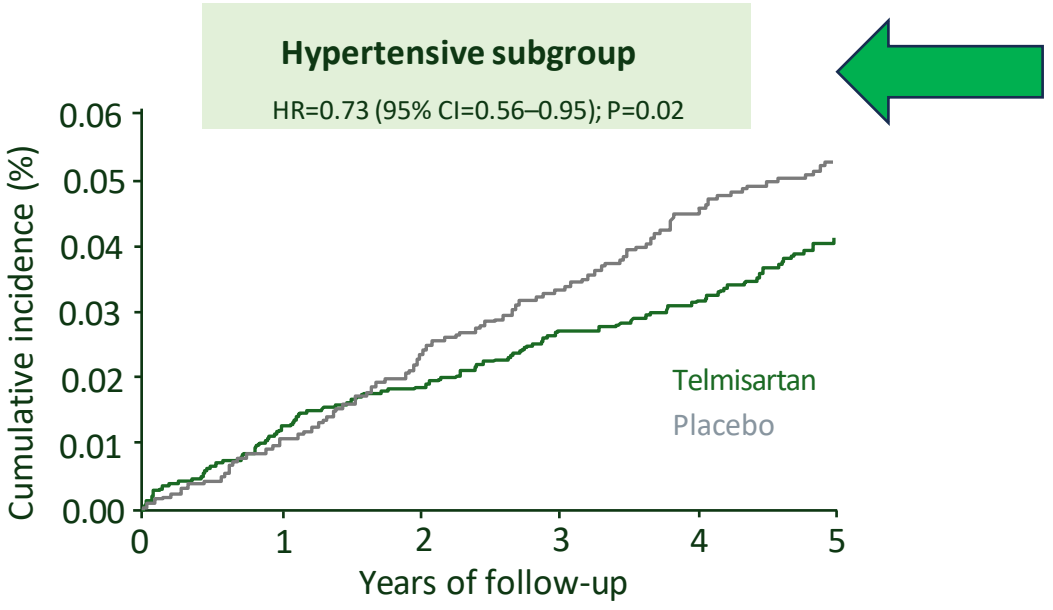
1. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial [published correction appears in Lancet. 2008 Oct 18;372(9647):1384]. Lancet. 2008;372(9644):1174-1183.

TRANSCEND: Telmisartan Reduced the Risk of MI in Hypertensive Patients[1]

In hypertensive patients, but not in nonhypertensive ones,

Telmisartan demonstrated a **27% risk reduction** in MI compared with placebo[1]





No difference in the effect of treatment between hypertensive and nonhypertensive patients for primary composite endpoint (CV death, MI, stroke, hospitalization for heart failure)[1]

CV: Cardiovascular; MI: Myocardial Infraction

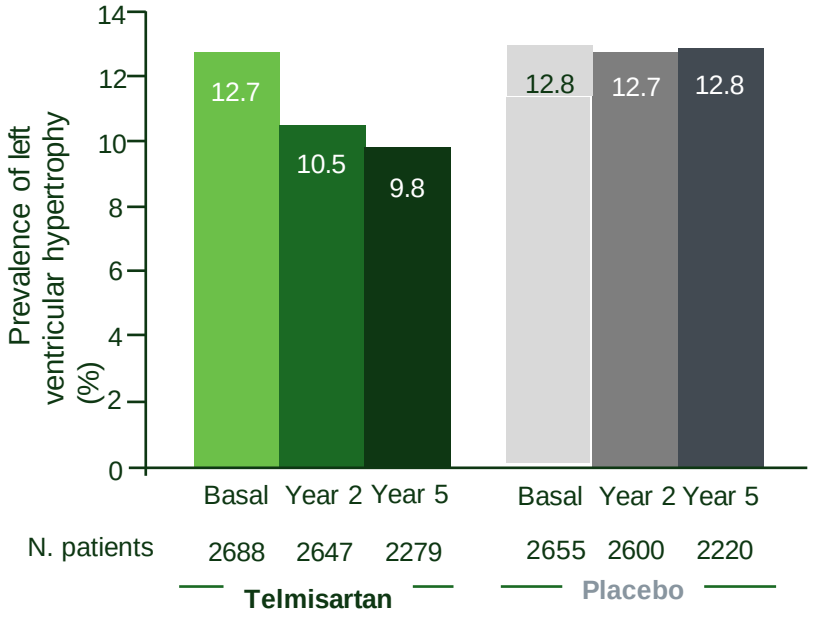
1. Foulquier S, Böhm M, Schmieder R, et al. Impact of telmisartan on cardiovascular outcome in hypertensive patients at high risk: a Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease subanalysis. J Hypertens. 2014;32(6):1334-1341.

TRANSCEND: Telmisartan vs Placebo in Prevalence and New Development of Left Ventricular Hypertrophy

Prevalence of LVH

at baseline and after 2 and 5 years

Overall OR=0.79 (95% CI=0.68–0.91); **P=0.0017**

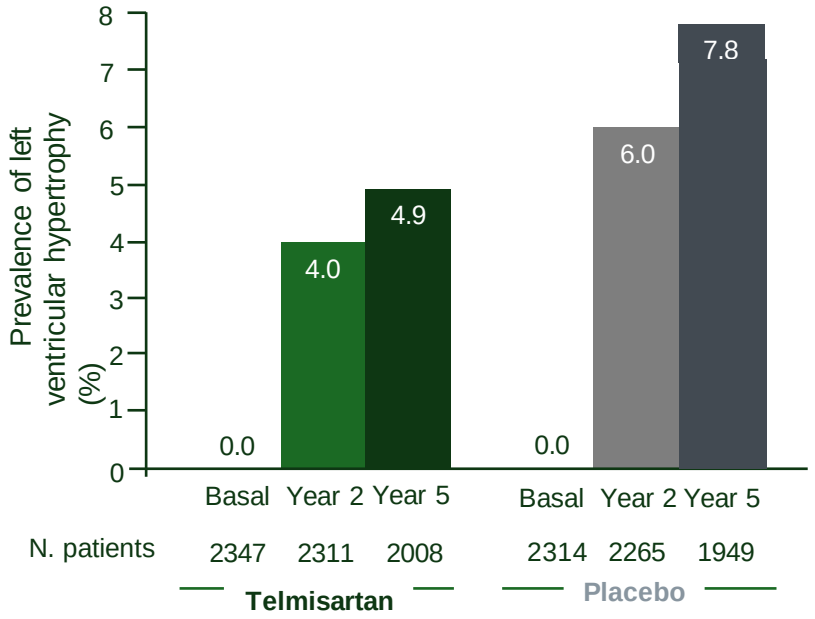


Overall **21% reduction** in LVH risk with Telmisartan vs placebo[1]

New development of LVH

at 2 and 5 years

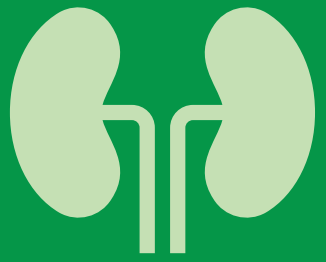
Overall OR=0.63 (95% CI=0.51–0.79); **P=0.001**



Overall **37% reduction** in LVH risk at follow up with Telmisartan vs placebo[1]

LVH: Left Ventricular Hypertrophy

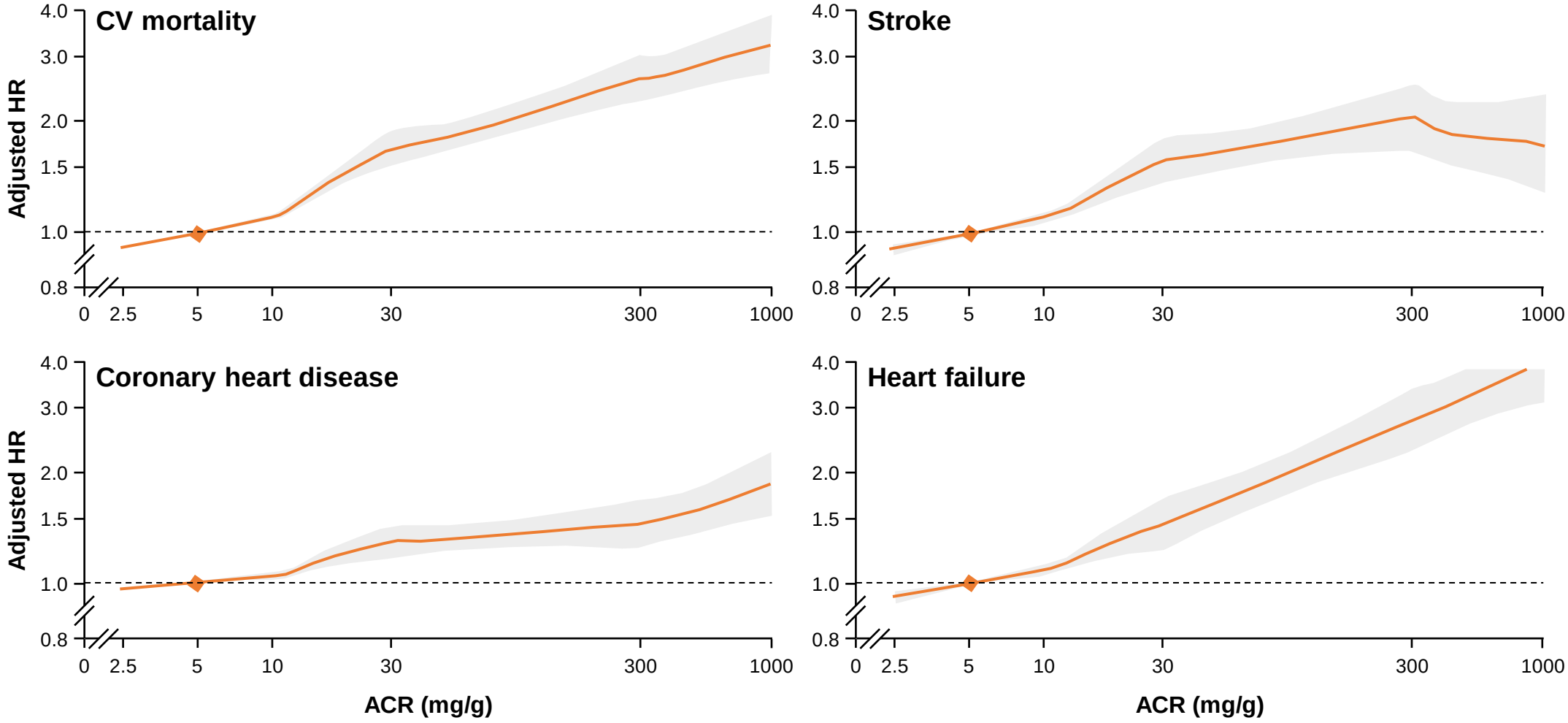
1. Verdecchia P, Sleight P, Mancia G, et al. Effects of telmisartan, ramipril, and their combination on left ventricular hypertrophy in individuals a high vascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease. Circulation. 2009;120(14):1380-1389.



Reno-Protection

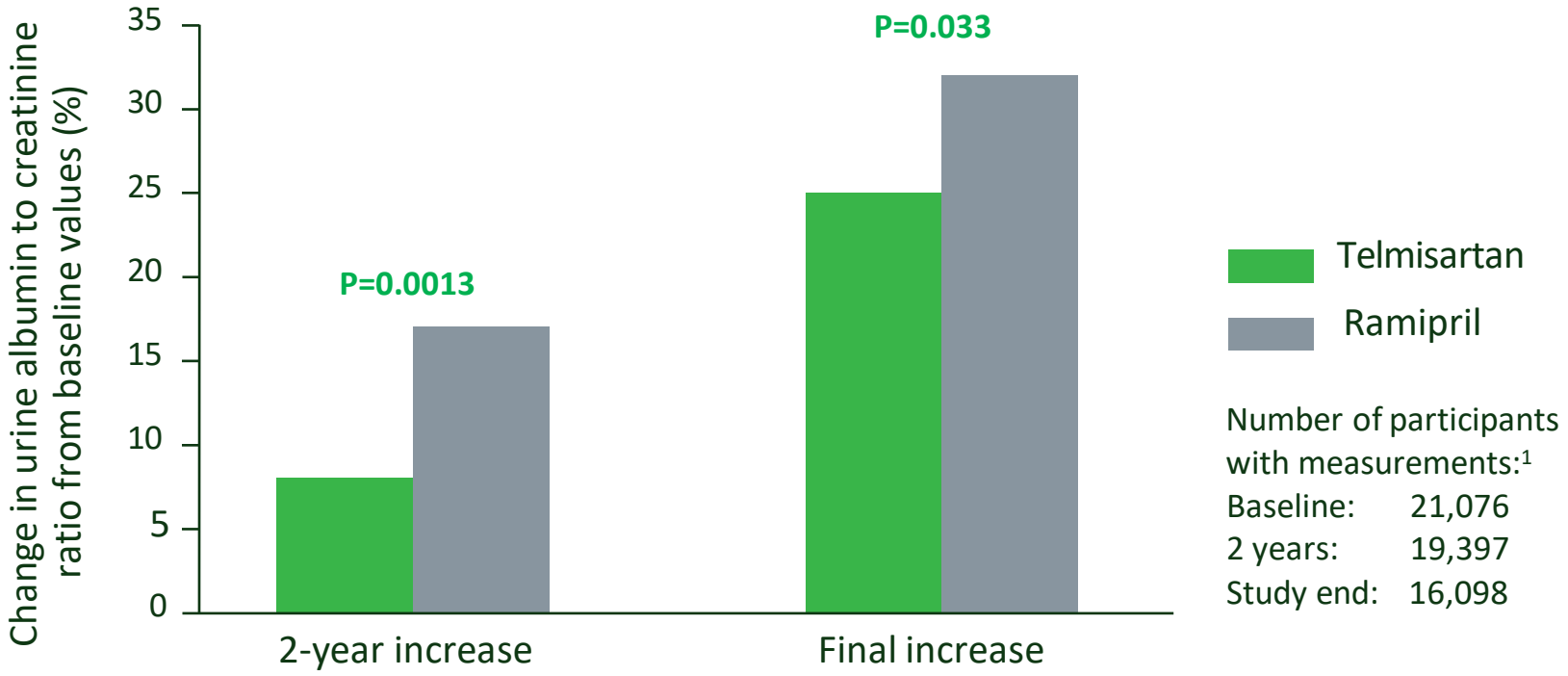
Proteinuria is a risk factor for CKD progression, CVD & CV mortality

Cardiovascular outcomes according to ACR[a]



[a]Reference value 5 mg/g (diamonds)
ACR, albumin:creatinine ratio; CV, cardiovascular; HR, hazard ratio
Matsushita K, et al. *Lancet Diabet Endocrinol* 2015;3:514–525

ONTARGET: Renal Outcomes of Telmisartan vs Ramipril in People at High Vascular Risk[1]



Urine albumin increased at 2 years and at study end to a lesser extent in participants assigned Telmisartan vs those assigned ramipril.[1]

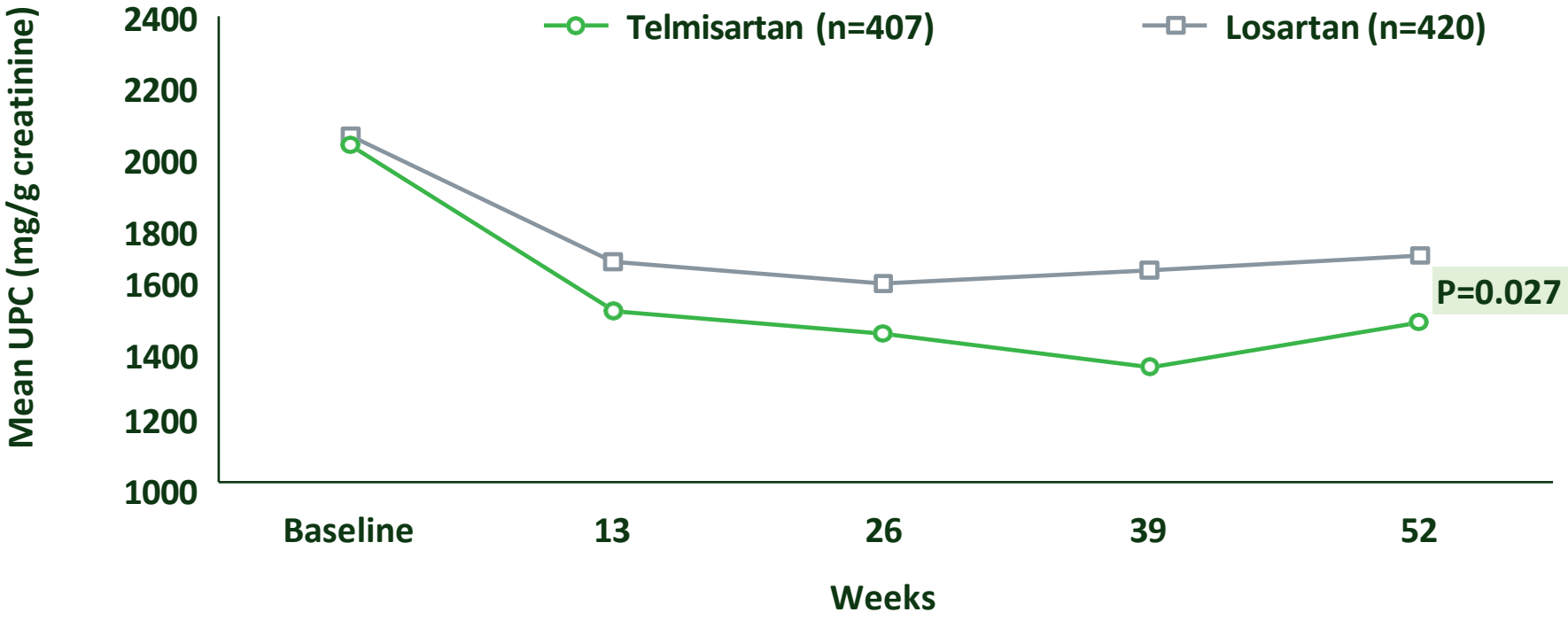
The geometric mean of urine albumin excretion at baseline ranged between 0·81 mg/mmol and 0·83 mg/mmol creatinine and was not different between the randomized groups.

1. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double- blind, controlled trial. Lancet. 2008;372(9638):547-553.

AMADEO Trial

Telmisartan Is More Effective Than Losartan at Reducing Proteinuria[1]

The reduction in UPC from baseline was greater for telmisartan vs losartan (P=0.03)[1]



Both Telmisartan (29.8%; P<0.0001) and losartan (21.4%; P<0.0001) significantly reduced mean UPC at 52 weeks[1]

UPC = Urinary Protein to Creatinine

1. Bakris G, Burgess E, Weir M, Davidai G, Koval S; AMADEO Study Investigators. Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney Int*. 2008;74(3):364-369.

- Which **ARB** has a **broader indication (broader range of patients at increased CV risk)** for **CV risk prevention** in patients with atherothrombotic disease or diabetes with end-organ damage?

    1- Olmesartan
    2- Telmisartan
    3- Candesartan
    4- Irbesartan
    5- Valsartan
    6- Losartan

Telmisartan Is the Only ARB Approved for CV Prevention

(Based on Evidence From the ONTARGET Trial Program)

	Hypertension			Cardiovascular Prevention				Heart failure or LVSD
	Hypertension	Renal disease in hypertension with T2DM	Reduction of stroke in hypertension with LVH	Diabetes with target organ damage	Coronary heart disease	Stroke	Peripheral Arterial disease	
Telmisartan[1]	✓			✓	✓	✓	✓	
Candesartan[2]	✓							✓
Valsartan[3]	✓							✓
Olmesartan[4]	✓							
Azilsartan[5]	✓							
Eprosartan[6]	✓							
Irbesartan[7]	✓	✓						
Losartan[8]	✓	✓	✓					✓

T2DM: Type 2 Diabetes Mellitus; LVH: Left Ventricular Hypertrophy; LVSD: Left Ventricular Systolic Dysfunction.

1. MICARDIS (Telmisartan) summary of product characteristics,EMA. 2. Atacand (candesartan cilexetil) Prescribing information, AstraZeneca, 2009. 3. Diovan (Valsartan) prescribing information, Novartis, 2011. 4. BENICAR (olmesartan medoxomil) prescribing information, Daiichi Sankyo, Inc, 2017. 5. EDARBI ((azilsartan medoxomil) Summary of product characteristics. 6. TEVETEN (eprosartan mesylate) prescribing information, Abbvie Inc., 2014. 7. Aprovel (Irbesartan), summary of product characteristics, 2020. 8. COZAAR (losartan potassium)prescribing information, Merck & Co., Inc., 2019.

Conclusion

- Patients with HTN are at **higher risk of cardiovascular events** if they have:
  - Stroke, established coronary artery disease, or a coronary artery disease equivalent.
  - Diabetes or metabolic syndrome.
  - Chronic kidney disease.
  - End organ damage, e.g., LVH.

- **Blood pressure-lowering therapy** has been shown to **reduce cardiovascular events** in these patients significantly.

- **Identification of high-risk patients** by global risk evaluation is **recommended for every hypertensive patient.**

- Treatment of hypertension in **high-risk patients** with an **ACEi or ARB**, **with or without addition of a dihydropyridine calcium channel antagonist**, is a recommended approach based on current clinical trials.

THANK YOU