Management of Hypertension in CKD Patients

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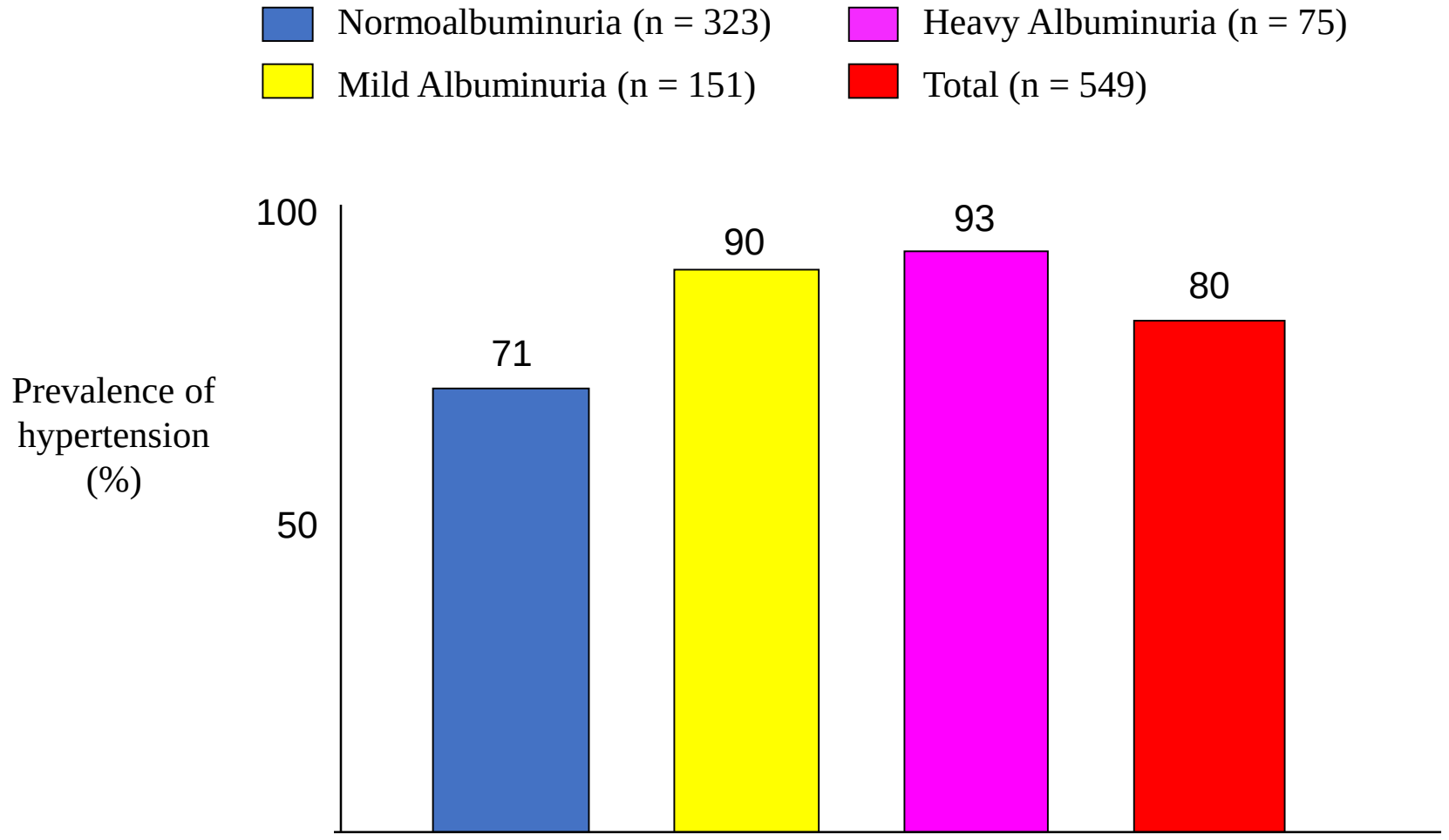
Key Facts on Hypertension. WHO, May 2024

- Hypertension is a serious medical condition that significantly increases the risks of heart, brain, kidney and other diseases.
- An estimated 1.4 billion adults aged 30-79 years worldwide have hypertension, most (two-thirds) are living in low- and middle-income countries.
- An estimated 46% of adults with hypertension are unaware that they have the condition.
- Less than half of adults (42%) with hypertension are diagnosed and treated.
- Approximately 1 in 5 adults (21%) with hypertension have it under control.

Key Facts on Hypertension. WHO, May 2024

- Hypertension affects about 40% of the industrialized populations and its prevalence is increasing. (48% of USA Population).
- Hypertension is associated with additional risk factors in over 80% of patients.
- Hypertension is a co-morbid condition in over 85% of cardiac patients.
- Globally, Hypertension is responsible for :
  - 10.8 million deaths each year (14.5% of total)
  - 6.3 millions of years of disability (9% of global disability-adjusted life years (DALYs)).

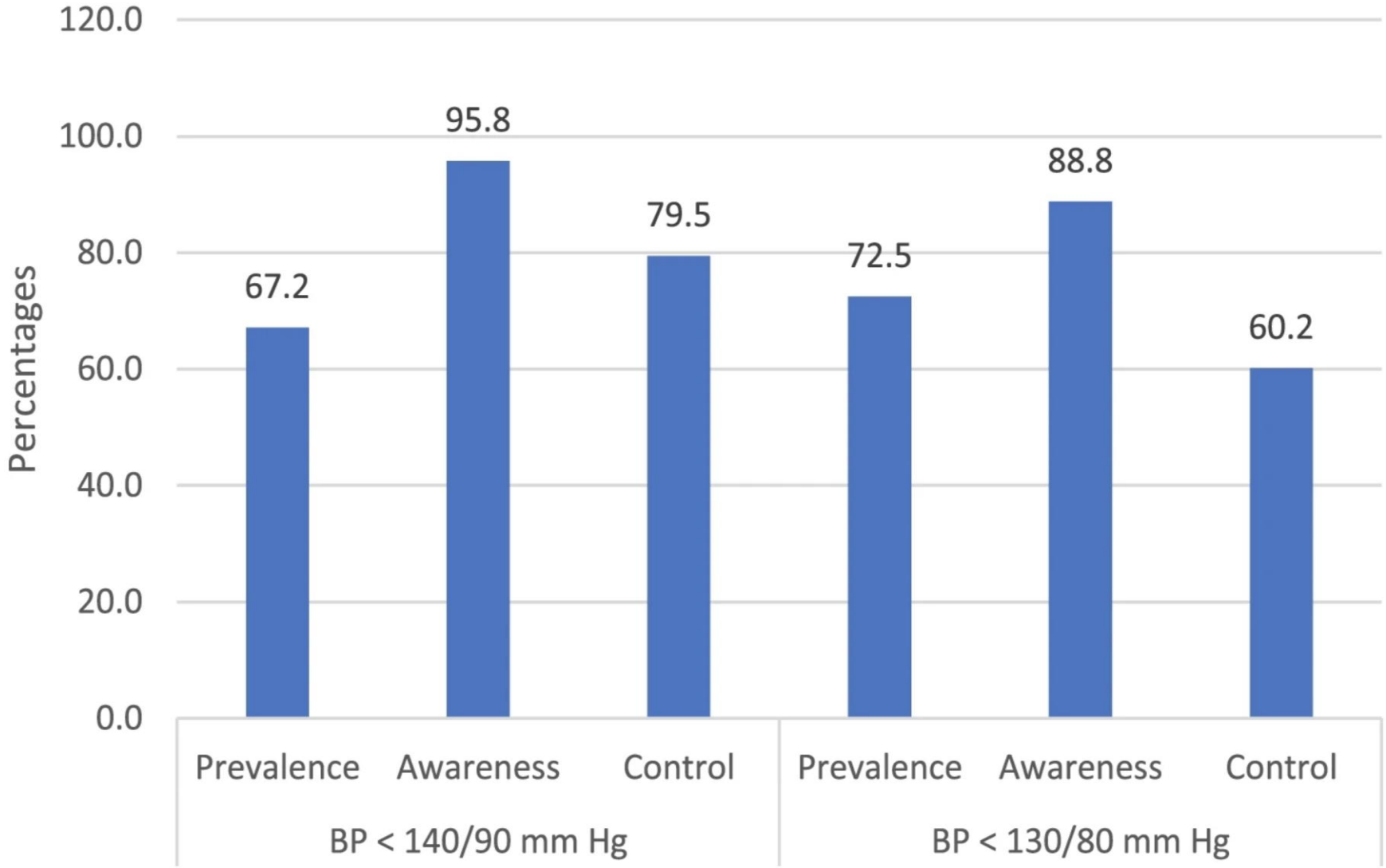
Prevalence of Hypertension in Type 2 Diabetes



Hypertension defined as [3]140/90 mm Hg.

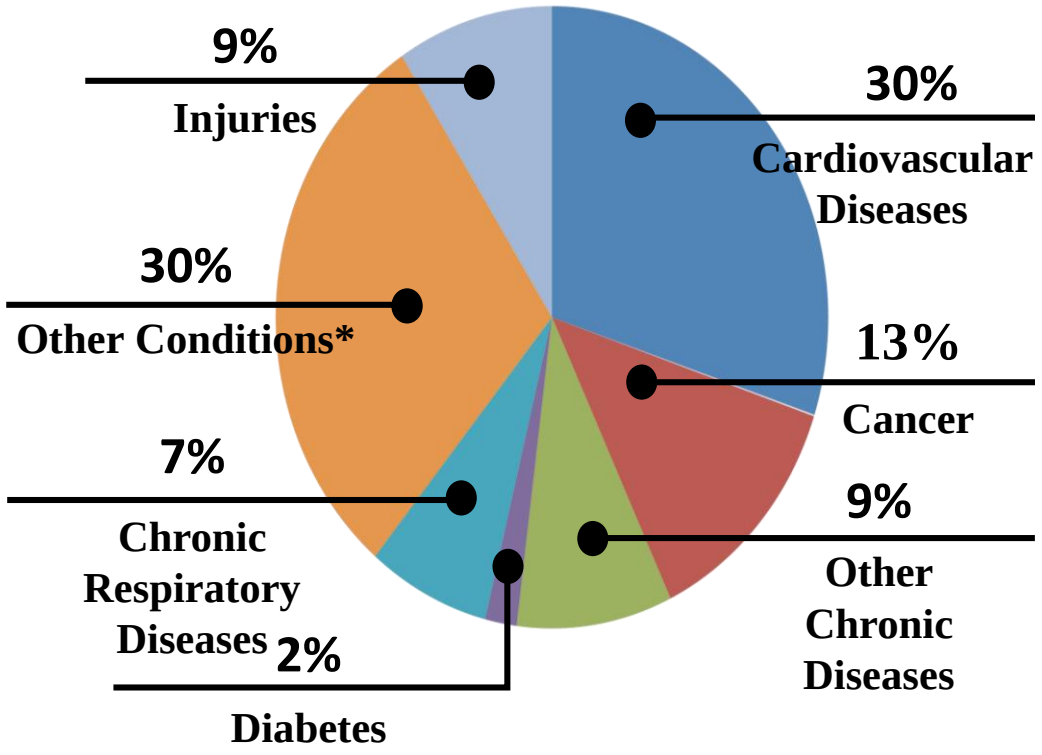
Tarnow L et al. *Diabetes Care* 1994;17:1247-1251

Prevalence of Hypertension in Type 2 DM 2022



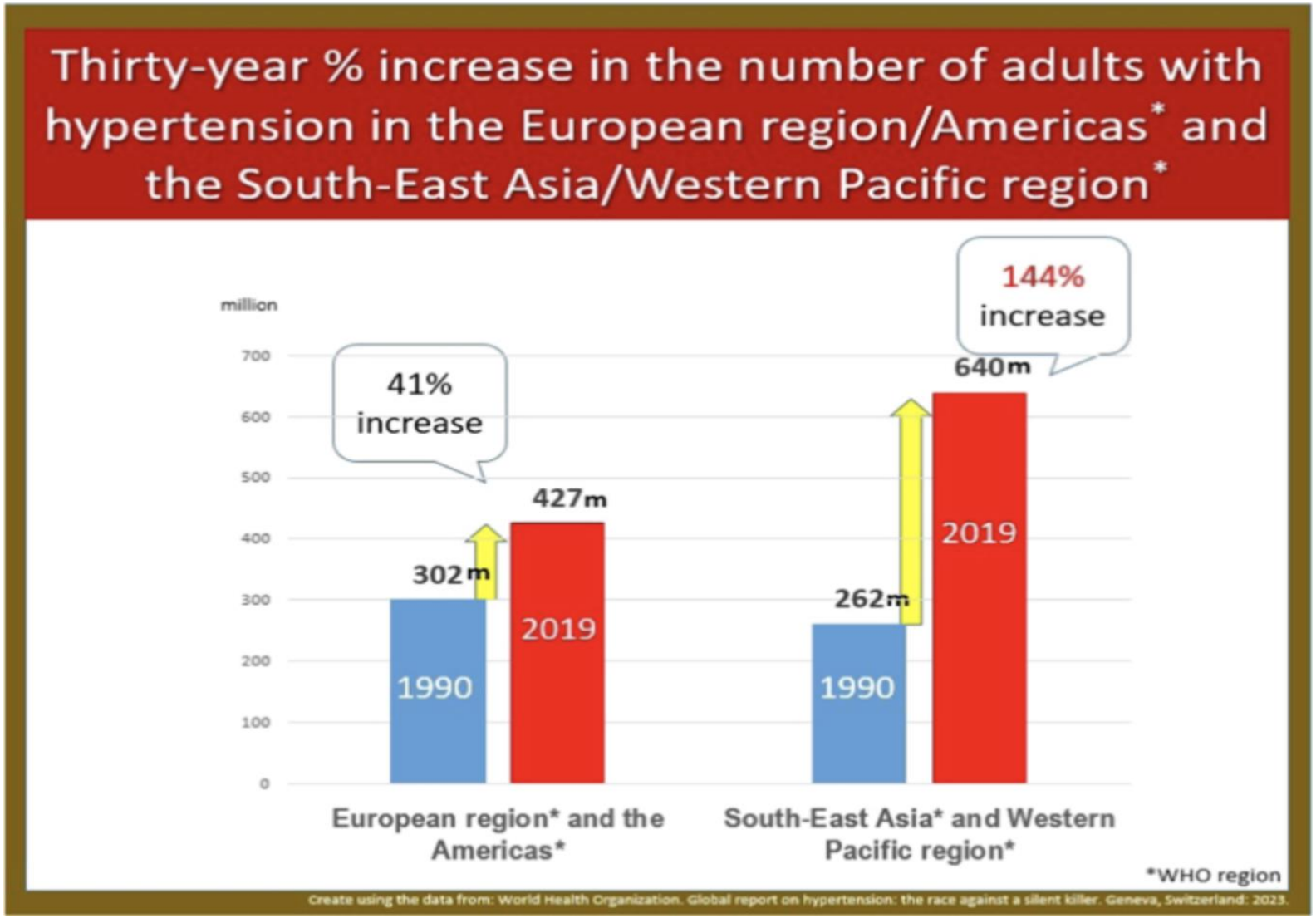
Hypertension awareness, prevalence and control among people with T2DM based on BP < 140/90 mmHg and < 130/80 mmHg. Note: Hypertension awareness: among all participants with hypertension; Hypertension control: among participants receiving hypertension treatment

Hypertension and Cardiovascular Risk WHO

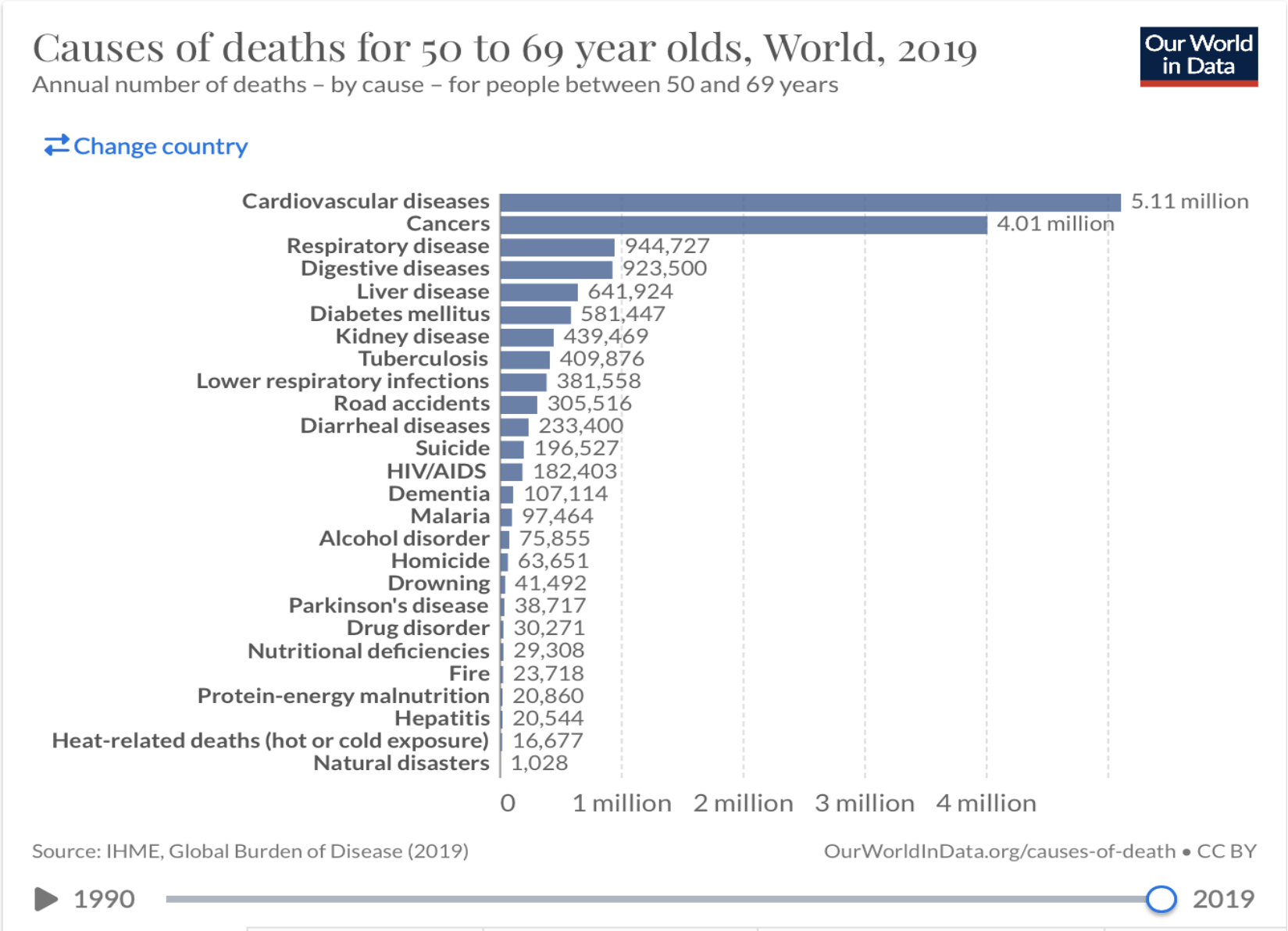


Non-communicable diseases (NCD) account for a total of 41 million deaths (71%) annually.
Cardiovascular Diseases Lead The Deaths In NCD, About 17.9 Million Per Year.
One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 30% between 2010 and 2025.

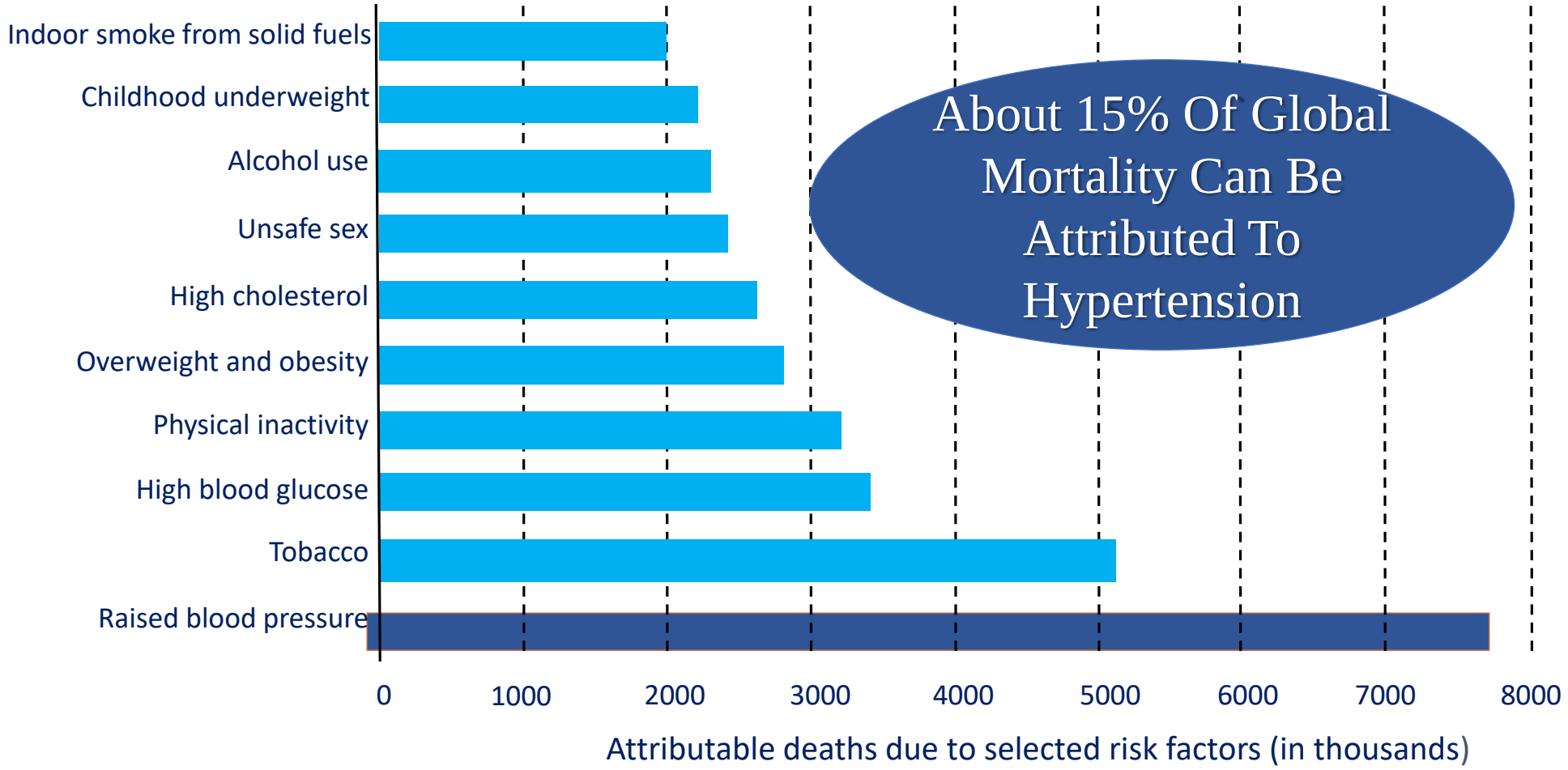
Unfortunately the Prevalence is Increasing



Causes of Death Between 50 and 69 years

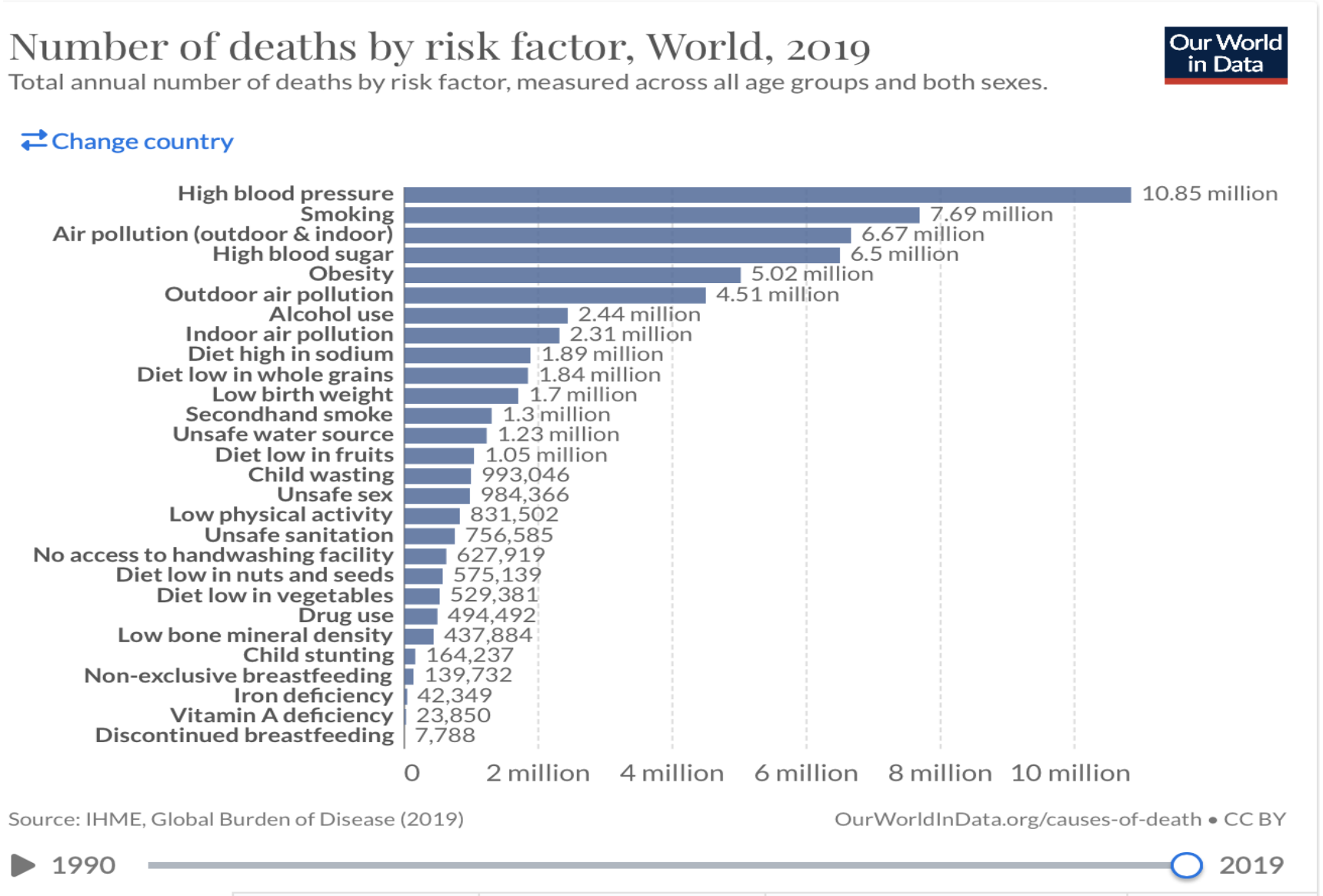


Hypertension is the Number One Risk Factor for Global Mortality



World Health Organisation. Global atlas on cardiovascular disease prevention and control. 2011. Available at: http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/index.html

Hypertension is the Number One Risk Factor for Global Mortality (All Ages)



Not Only Common BUT Morbid and Lethal!

Increases RR by 2.0-4.0 fold for:

CAD, Stroke, HF, PAD, AF, CKD
Dementia: vascular, Alzheimer
Mild cognitive deficits

Attributable Risk for HTN:

Stroke 54% HF 49% CKD 30%
Premature death 24% MI 25%

Aftermath:

Shortens lifespan 5y

14.5% of Deaths, 10.8 million deaths per year.
131 Billion USD/year.

Hypertension: Very Treatable

- Reducing Systolic BP/Diastolic BP by 10/5 mm Hg for 5y:

  (Meta-analysis: 68 RCTs, 245,885 Patients, 4.3y FU)

% Risk Reduction :

- Heart failure: 43%
- Stroke: 36%
- CVD events: 25%
- MI: 16%
- Mortality: 11%
- Dementia: ??

J Hypertension 2014; 32:2285

ESC Guidelines 2024

- The title has changed from ‘Guidelines on the management of arterial hypertension’ to **‘Guidelines on the management of elevated blood pressure and hypertension.**
- The 2024 Guidelines continue to define hypertension as office systolic BP of ≥140 mmHg or diastolic BP of ≥90 mmHg. However, a new BP category called ‘Elevated BP’ was introduced.
- Elevated BP is defined as an office systolic BP of 120–139 mmHg or diastolic BP of 70–89 mmHg.
- A major, evidence-based change in the 2024 Guidelines is the recommendation to pursue a target systolic BP of 120–129 mmHg among adults receiving BP-lowering medications.

ESC Guidelines 2024

Recommendations	Class[a]	Level[b]
5. Measuring blood pressure		
It is recommended to measure BP using a validated and calibrated device, to enforce the correct measurement technique, and to apply a consistent approach to BP measurement for each patient.	I	B
Out-of-office BP measurement is recommended for diagnostic purposes, particularly because it can detect both white-coat hypertension and masked hypertension. Where out-of-office measurements are not logistically and/or economically feasible, then it is recommended that the diagnosis be confirmed with a repeat office BP measurement using the correct standardized measurement technique.	I	B

ESC Guidelines 2024

6. Definition and classification of elevated blood pressure and hypertension, and cardiovascular disease risk assessment		
It is recommended to use a risk-based approach in the treatment of elevated BP, and individuals with moderate or severe CKD, established CVD, HMOD, diabetes mellitus, or familial hypercholesterolaemia are considered at increased risk for CVD events.	I	B
It is recommended that, irrespective of age, individuals with elevated BP and a SCORE2 or SCORE2-OP CVD risk of ≥10% be considered at increased risk for CVD for the purposes of risk-based management of their elevated BP.	I	B

ESC Guidelines 2024

8. Preventing and treating elevated blood pressure

It is recommended to take medications at the most convenient time of day for the patient, to establish a habitual pattern of medication taking to improve adherence.	I	B
In adults with elevated BP and low/medium CVD risk (<10% over 10 years), BP lowering with lifestyle measures is recommended and can reduce the risk of CVD.	I	B
In adults with elevated BP and sufficiently high CVD risk, after 3 months of lifestyle intervention, BP lowering with pharmacological treatment is recommended for those with confirmed BP ≥130/80 mmHg to reduce CVD risk.	I	A
It is recommended that in hypertensive patients with confirmed BP ≥140/90 mmHg, irrespective of CVD risk, lifestyle measures and pharmacological BP-lowering treatment is initiated promptly to reduce CVD risk.	I	A
It is recommended to maintain BP-lowering drug treatment lifelong, even beyond the age of 85 years, if well tolerated.	I	A

Hypertension in CKD Patients

Introduction

- Hypertension is the commonest comorbidity in CKD patients, it affects 80%–85% of individuals with CKD.
- The prevalence of hypertension progressively increases with advancing CKD stages, reaching 95% in individuals with CKD stage G4 or G5 before initiation of renal replacement therapy
- Hypertension is a strong and independent risk factor for development of CKD and progression to ESKD, and is by far the commonest modifiable factor for CKD progression.
- Treatment-resistant hypertension, elevated nighttime BP and masked hypertension are common in patients with CKD.

Introduction

- The first critical step in managing hypertension in CKD patients is the accurate measurement of office BP, the minimum requirement is the adoption of the **Research-Grade BP Measurement** methodology in our daily practices.
- The protocol of research grade BP measurement specified a 5-min seated rest period followed by three automated office BP (AOBP) recordings taken without the presence of an observer in a quiet room.

Ambulatory BP monitoring

- Ambulatory BP monitoring (ABPM) is considered as the reference standard for the diagnosis of hypertension .
- Typically performed over 24 h and BP is recorded every 15–20 min during daytime and every 30 min during nighttime.
- ABPM enables the diagnosis of nocturnal hypertension and abnormal diurnal variation of BP (i.e. non-dipping and reverse-dipping BP pattern) , which are frequently diagnosed in patients with CKD.

Home BP Monitoring

- BP measurements at home (two recordings in the morning and two recordings at bedtime) for at least 3 days, and preferably 7 days, using validated automated BP monitors .
- Cohort studies showed that 1-week averaged home BP is of superior predictive value as compared with office BP in patients with CKD.
- Home BP monitoring has the advantage of being more broadly available and can be repeatedly used to monitor the BP-lowering response to antihypertensive therapy over long-term periods of follow-up.

Initiation of Treatment

- The 2021 KDIGO Guidelines did not specify thresholds for initiating antihypertensive medication.
- The 2023 ESH Guidelines set specific BP thresholds, based on age and CV risk.

❖ It is recommended that in patients aged 18–79 years, the office threshold for initiation of drug treatment is 140 mmHg for SBP and/or 90 mmHg for DBP. Level 1A

❖ In adult patients with a history of CVD, predominantly coronary artery disease, drug treatment should be initiated in the high-normal BP range (SBP ≥130 or DBP ≥80 mmHg) Level IA

Treatment Targets

- 2021 KDIGO guidelines recommend SBP target of <120 mmHg for all patients with CKD based on SPRINT.
- 2023 ESH guidelines:

❖ It is recommended that:

In all CKD patients the primary goal is to lower office SBP to <140 mmHg and DBP <90 mmHg Level IA

In most CKD patients (young patients, patients with a urine ACR ≥300 mg/g, high CV risk patients) office BP may be lowered to <130/80 mmHg, if tolerated. Level IIB

Lifestyle Interventions

Recommended in all patients with hypertension, including those with CKD (KDIGO. ESH. ISH)

- Weight loss. Level IA
- Healthy dietary pattern. Level IA
- Exercise. Level IB
- Reduction of alcohol intake. Level IB
- Smoking cessation. Level IB
- Dietary salt restriction to <5 g (~2 g sodium) daily. Level IB
- Increased potassium consumption via dietary modification, is recommended for adults with elevated BP, except for patients with advanced CKD. Level IB

Sodium Restriction

- The 2021 KDIGO guidelines recommend that dietary sodium intake should be restricted to <90 mmol of sodium per day.
- An updated Cochrane meta-analysis showed that among patients with CKD, a mean reduction of 73.51 mmol/day in dietary sodium intake is associated with an average reduction of 6.91/3.91 mmHg in office BP and with a 36% reduction in albuminuria.
- *Post hoc* analyses of clinical trials showed that dietary sodium restriction enhances the albuminuria-lowering action of RAAS blockers in patients with albuminuric CKD.

Potassium-containing Salt Substitute

- Well established in the general population but not in CKD patients.
- Neal B et al (*N Engl J Med* 2021) concluded that the use of a potassium-containing salt substitute (75% NaCl and 25% KCl) compared to 100% NaCl lowered the risk of:

❖ Stroke by 14%

❖ Major adverse cardiovascular events by 13%

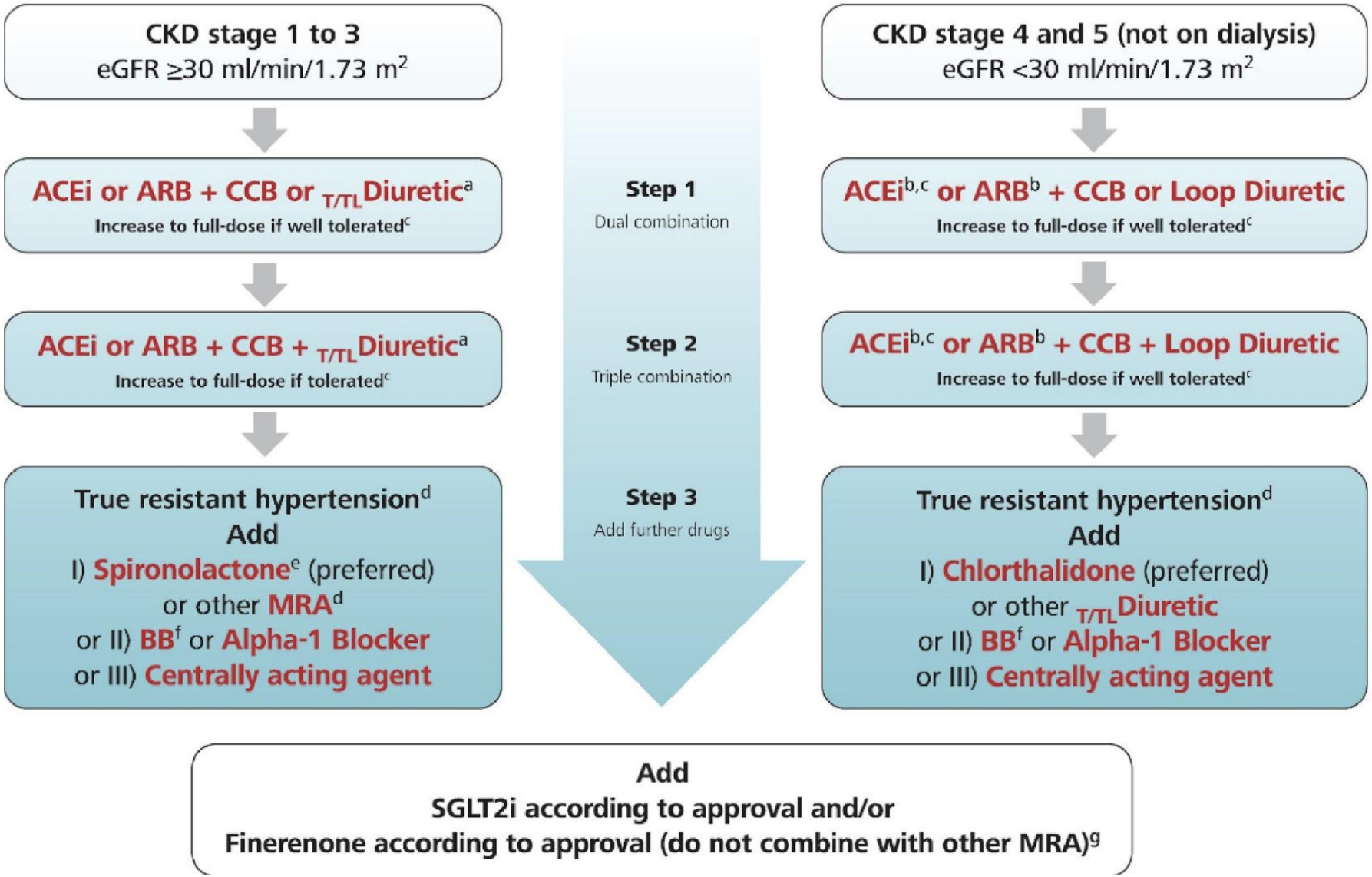
❖ All-cause mortality by 13%

Drug Therapy

Drug Therapy

Guideline/Year	BP target	Office BP measurement	First-line therapy	Second-line therapy	Third-line therapy	Fourth-line therapy
AHA/ACC 2017	<130/80 mmHg	Standardized	ACEI or ARB in those with very high albuminuria	CCB or diuretic	Diuretic or CCB	Spironolactone*
ESH/ESC 2018	Systolic <140 down to 130 mmHg, if tolerated	Standardized	Initial combination of an ACEI or an ARB + CCB or diuretic		Combination therapy with ACEI or ARB + CCB + diuretic	Spironolactone*
ISH 2020	<130/80 mmHg (<140/90 mmHg in elderly patients)	Standardized	ACEI or ARB	CCB or diuretic	Diuretic or CCB	Spironolactone*
ESC 2021	Systolic <140 down to 130 mmHg, if tolerated	Standardized	Initial combination of an ACEI or an ARB + CCB or diuretic		Combination therapy with ACEI or ARB + CCB + diuretic	Spironolactone*
KDIGO 2021	Systolic <120 mmHg, when tolerated	Standardized	ACEI or ARB in those with very high albuminuria			

Drug Therapy (ESH 2024)



RAAS Inhibitors

- For patients with high BP, CKD and very high albuminuria, the 2021 KDIGO guidelines provide a strong recommendation that RAAS Inhibitors should be the antihypertensive agent of first choice. (Level 1B)
- The use of RAS blockade as first-line therapy in albuminuric CKD is consistently supported by all major hypertension guidelines on the basis of robust clinical trial evidence (RENAAL , IDNT , AASK) .

Stopping or Continuing RAAS Inhibitors in Advanced CKD

- To continue or stop RAASI in patients with advanced CKD who are nearing the initiation of dialysis remains an area of controversy.
- **STOP-ACEi trial** (*Nephrol Dial Transplant 2016*) : 411 patients with advanced and progressive CKD were randomized either to stop or to continue RAS inhibitor therapy.
- Conclusions: Over 3 years of follow-up,

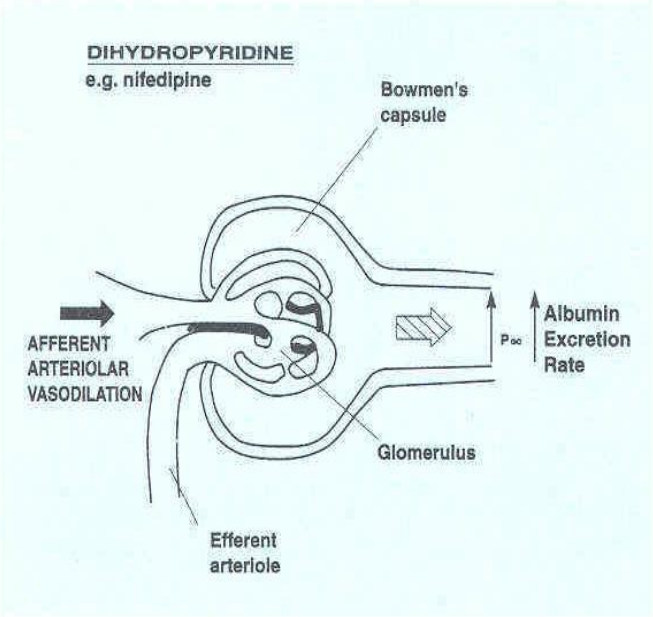
❖ There was no difference in the rate of eGFR decline between the discontinuation and continuation groups.

❖ There was a trend to worse outcome in those who discontinued RAS inhibitors.

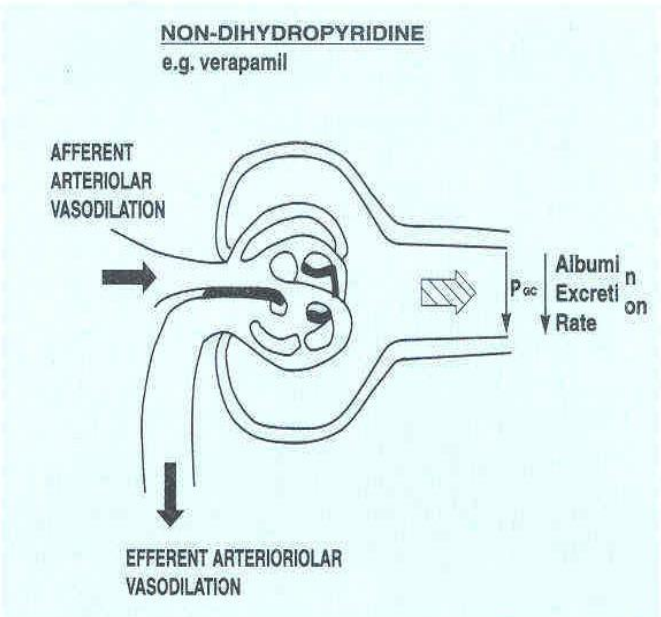
Drug Therapy

- Second-line therapy can include either a long-acting dihydropyridine calcium channel blocker (DHP-CCB), non-dihydropyridine calcium channel blocker (NDHP-CCB) or a diuretic.
- Third-line therapy in the algorithm completes the combination of a RAAS blocker, CCB and a diuretic.
- The use of single-pill combinations is preferable; reducing pill burden, improving treatment adherence and better BP control rates.

Intrarenal Effect OF DHP-CCBS Vs Non DHP-CCBS



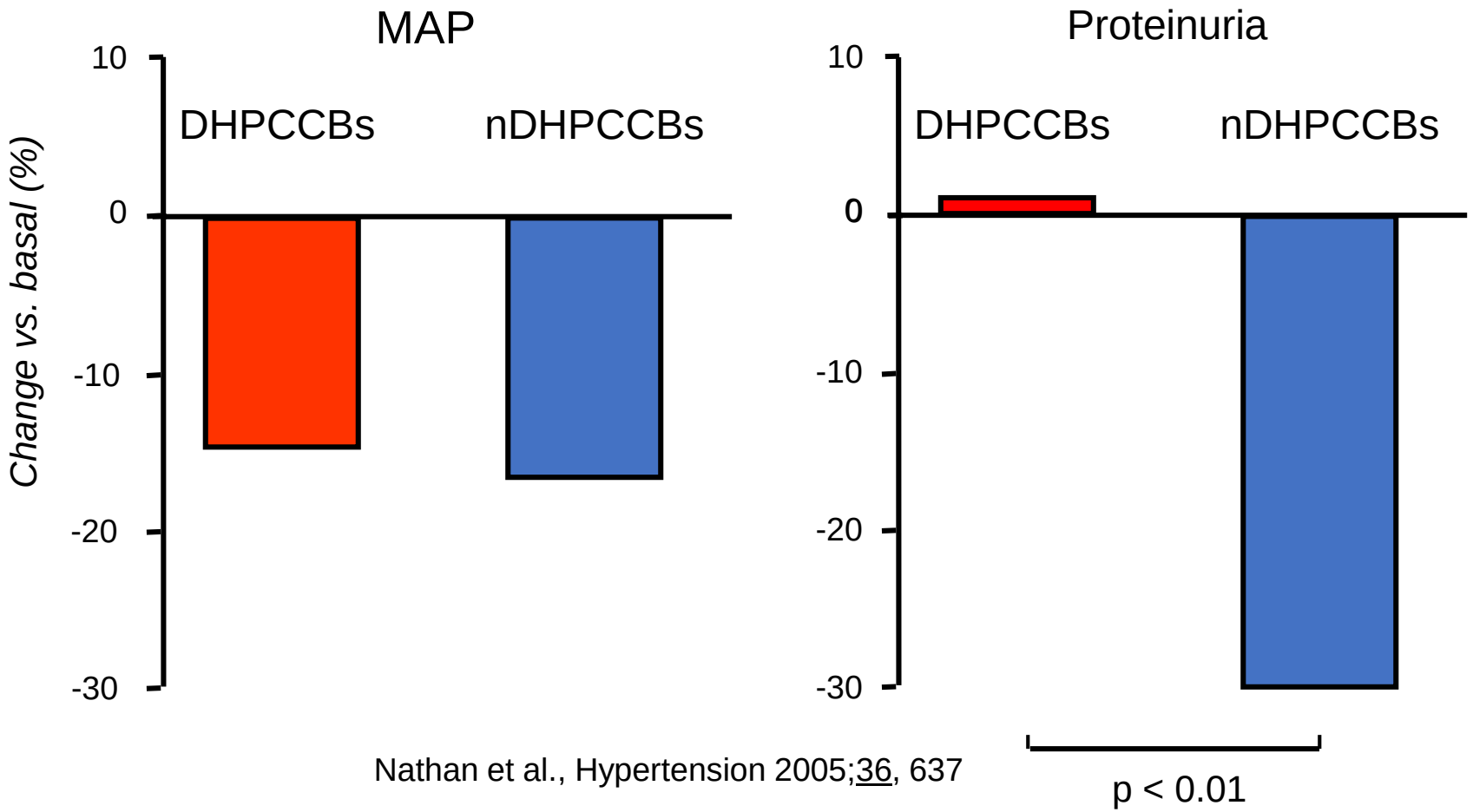
Afferent arteriolar vasodilation without efferent arteriolar vasodilation allows giomerular hyper-perfusion, increased intraglomerular pressure and albumin excretion rate



Dillation of afferant and efferent arteriolar pre-vents increased blood blow to the glomerlus. Normalisation of systemic blood pressure reduces intraglomerular pressure and albumin excretion rate

Effects of Calcium Antagonist Subclasses on Markers of Nephropathy Progression

A systematic review of randomized trials of DHPCCBs and nDHPCCBs in hypertensive adults with proteinuria



Nathan et al., Hypertension 2005;36, 637

The primary aim of the BErgamo NEphrologic DIabetic Complications Trial (BENEDICT) was to assess whether microalbuminuria can be prevented in people with hypertension, type 2 diabetes, and normal urinary albumin excretion

Ruggenenti P, *et al*. *N Engl J Med* 2004; 351: 1941-51.

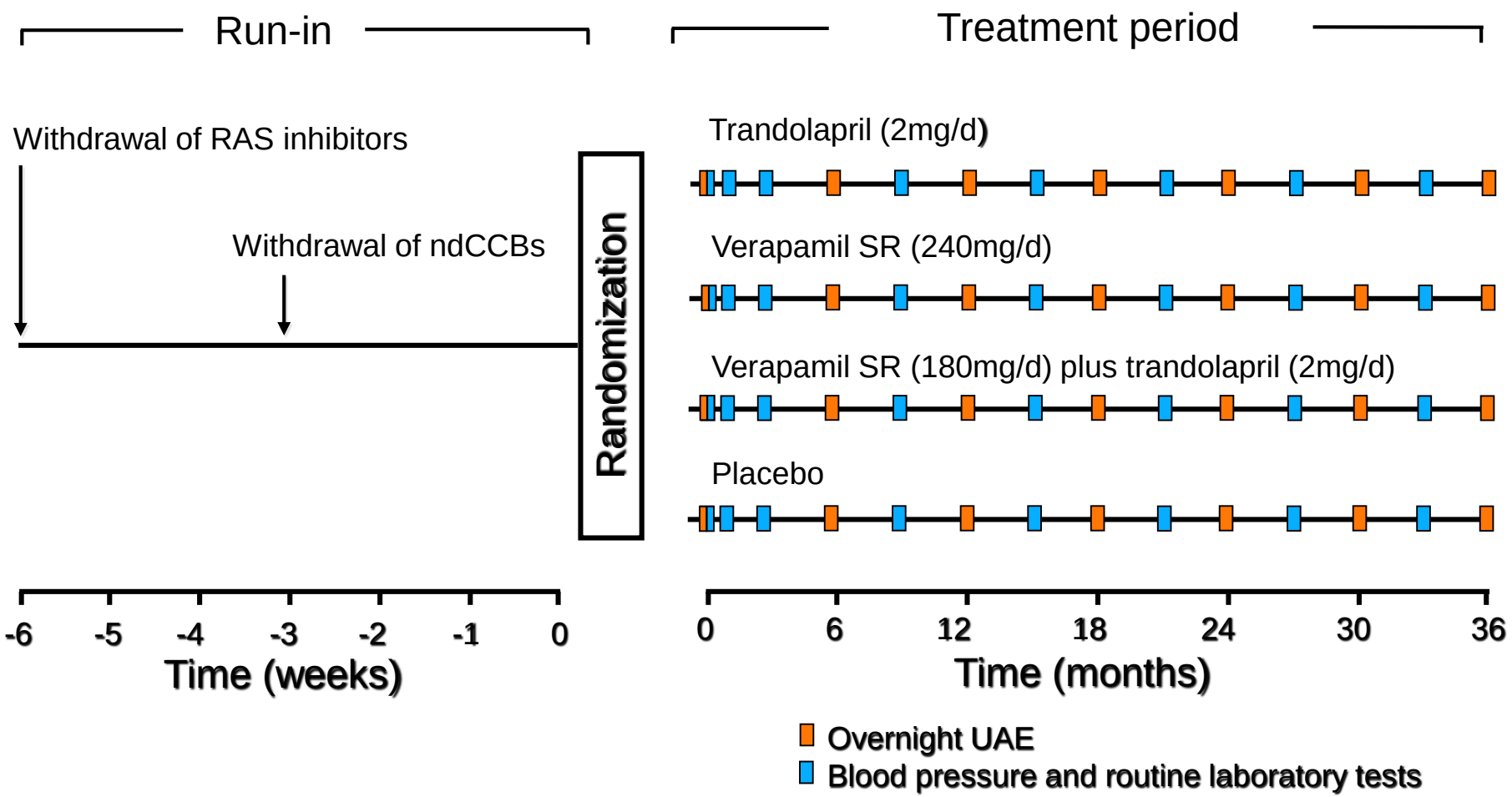
The BENEDICT trial

Patients	1204 normoalbuminuric patients with type 2 diabetes
Endpoint	Progression to microalbuminuria (incipient nephropathy)
Target metabolic control	HbA_{1c} <7.0%
Target BP control	≤120/80mmHg

Ruggenenti P, *et al*. *N Engl J Med* 2004; 351: 1941-51

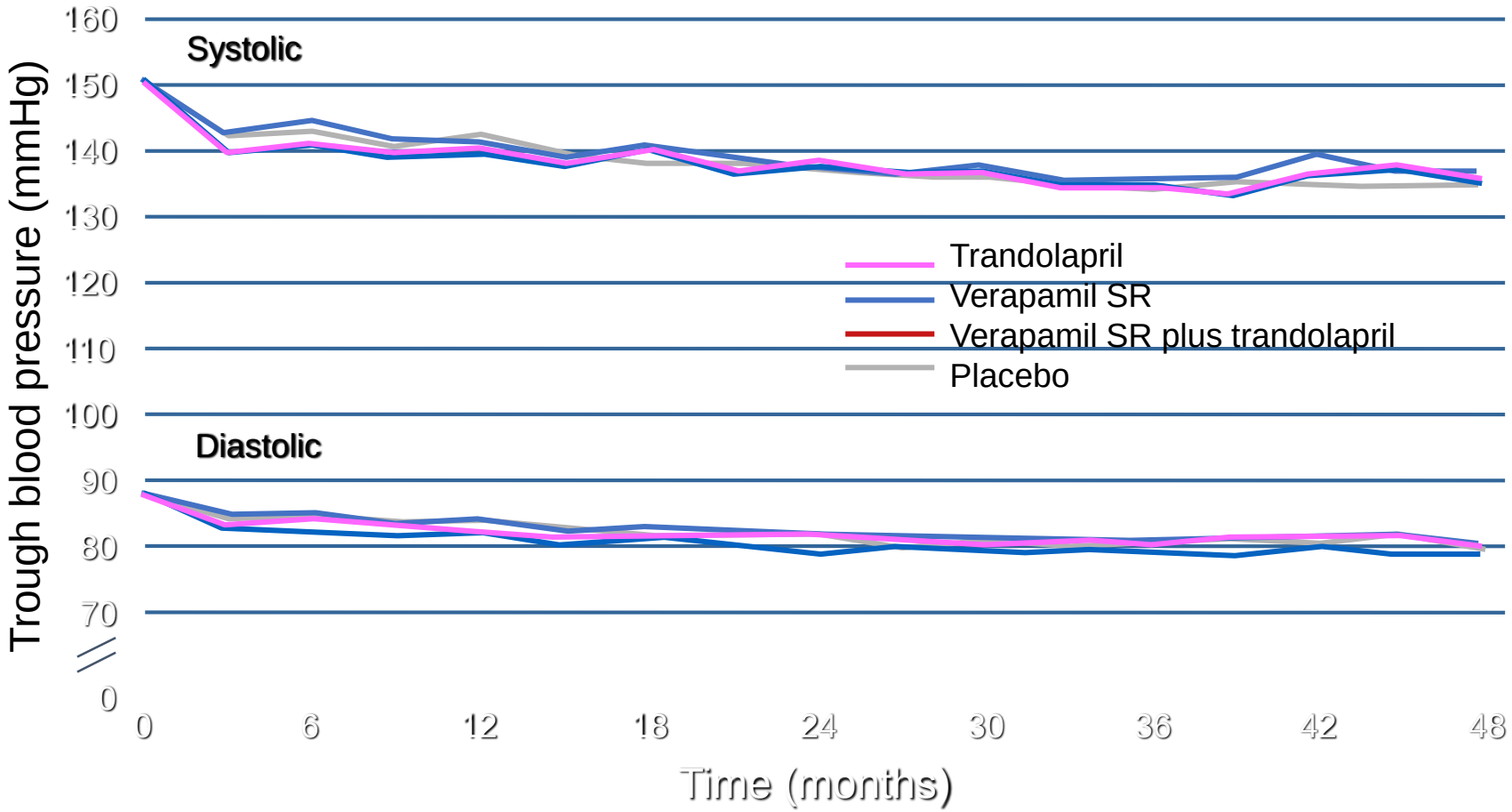
BENEDICT

The BENEDICT Design



Ruggenenti P, *et al*. *N Engl J Med* 2004; 351: 1941-51.

Blood Pressure Results

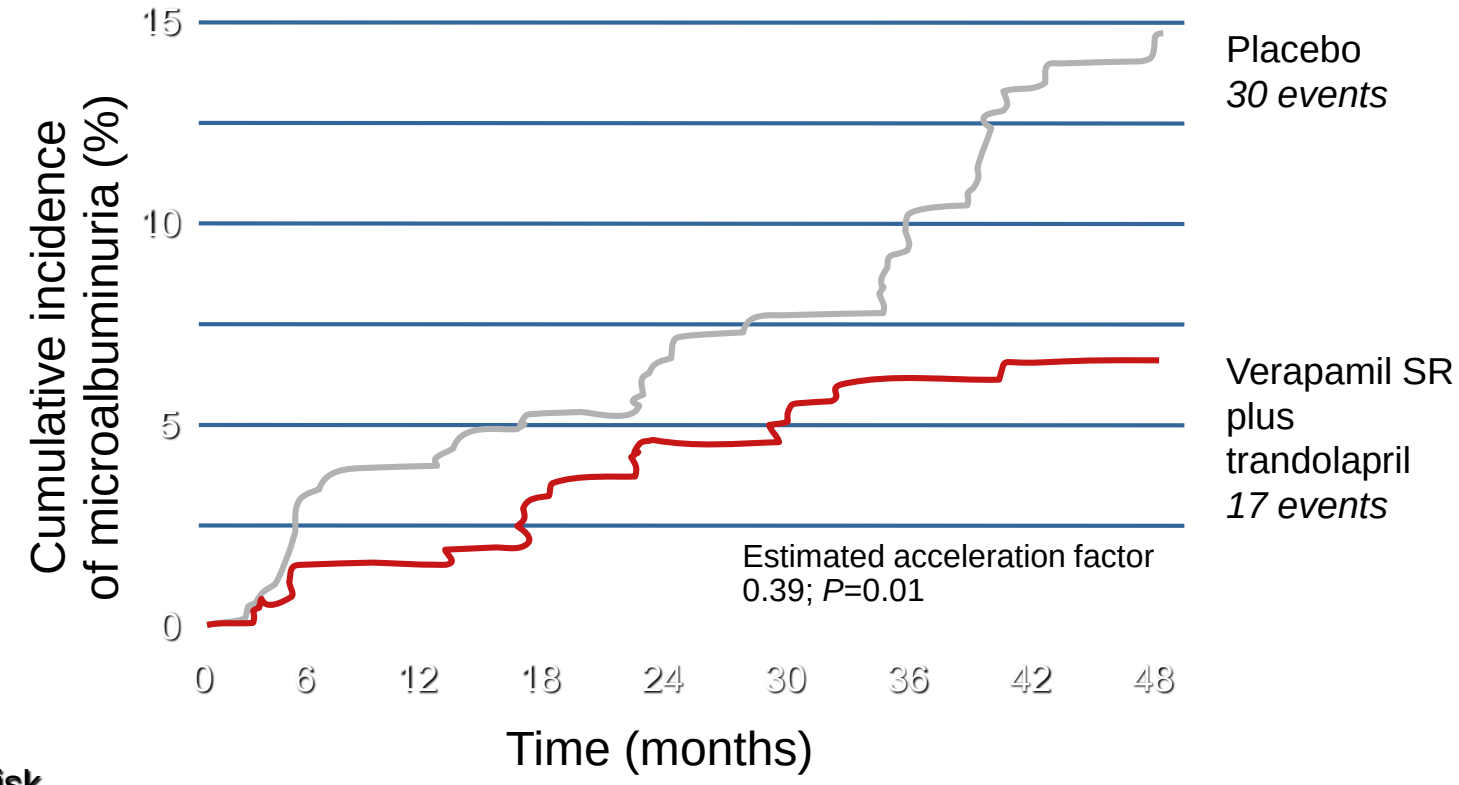


HbA_{1c} was comparable in all four groups

Ruggenenti P, *et al. N Engl J Med* 2004; 351: 1941-51.

BENEDICT

Incidence Of Microalbuminuria Over Time: Primary Endpoint



No. at risk									
Verapamil SR plus trandolapril	300	249	232	217	210	201	192	162	115
Placebo	300	229	214	203	187	176	164	136	89

Ruggenenti P, *et al. N Engl J Med* 2004; 351: 1941-51.

The BENEDICT trial: Conclusions

- Optimal blood pressure was achieved in these normoalbuminuric patients with type 2 diabetes
- Onset of microalbuminuria was significantly delayed with verapamil SR plus trandolapril compared with placebo (*P*=0.01)
- The delay in onset of microalbuminuria with verapamil SR plus trandolapril VS trandolapril alone exceeded expectations based on changes in blood pressure alone

Ruggenenti P, *et al*. *N Engl J Med* 2004; 351: 1941-51.

BENEDICT

Diuretic Therapy

- Most of guidelines released over the past years recommend the use of a loop diuretic when the eGFR is <30 mL/min/1.73 m^2
- Higher doses are typically necessary to achieve a therapeutic effect in patients with CKD.
- Of the loop diuretics, Torsemide may be preferable over furosemide, because it can be dosed once daily and its BP effect in people with CKD is similar to twice-daily furosemide.

Thiazide or Thiazide-like Diuretics

- Generally considered as ineffective in patients with advanced CKD.
- CLICK (Chlorthalidone in Chronic Kidney Disease) trial:
- 160 patients with stage 4 CKD and uncontrolled hypertension.
- Randomized to receive chlorthalidone (at a starting dose of 12.5 mg/day) or placebo for 12 weeks.

❖ Conclusions:

Chlorthalidone provoked a reduction of 10.5 mmHg in 24-h ambulatory SBP.

This potent BP-lowering effect was paralleled with a placebo-subtracted reduction of 50% in albuminuria, preliminary data supporting a potential cardiorenal protective action of chlorthalidone

Resistant Hypertension

- Uncontrolled BP despite adherence to **maximally tolerated doses** of a RAAS blocker, a CCB and a diuretic fulfill the diagnostic criteria of resistant hypertension.
- Spironolactone is recommended by guidelines as the fourth-line agent for the treatment of resistant hypertension.
- (PATHWAY-2) trial: spironolactone is superior to placebo as well as superior to doxazosin or bisoprolol in reducing home SBP over 12 weeks.
- Spironolactone is discouraged in patients with an eGFR <45 mL/min/1.73 m^2 and a serum potassium concentration of >4.5 mmol/L.

Spironolactone

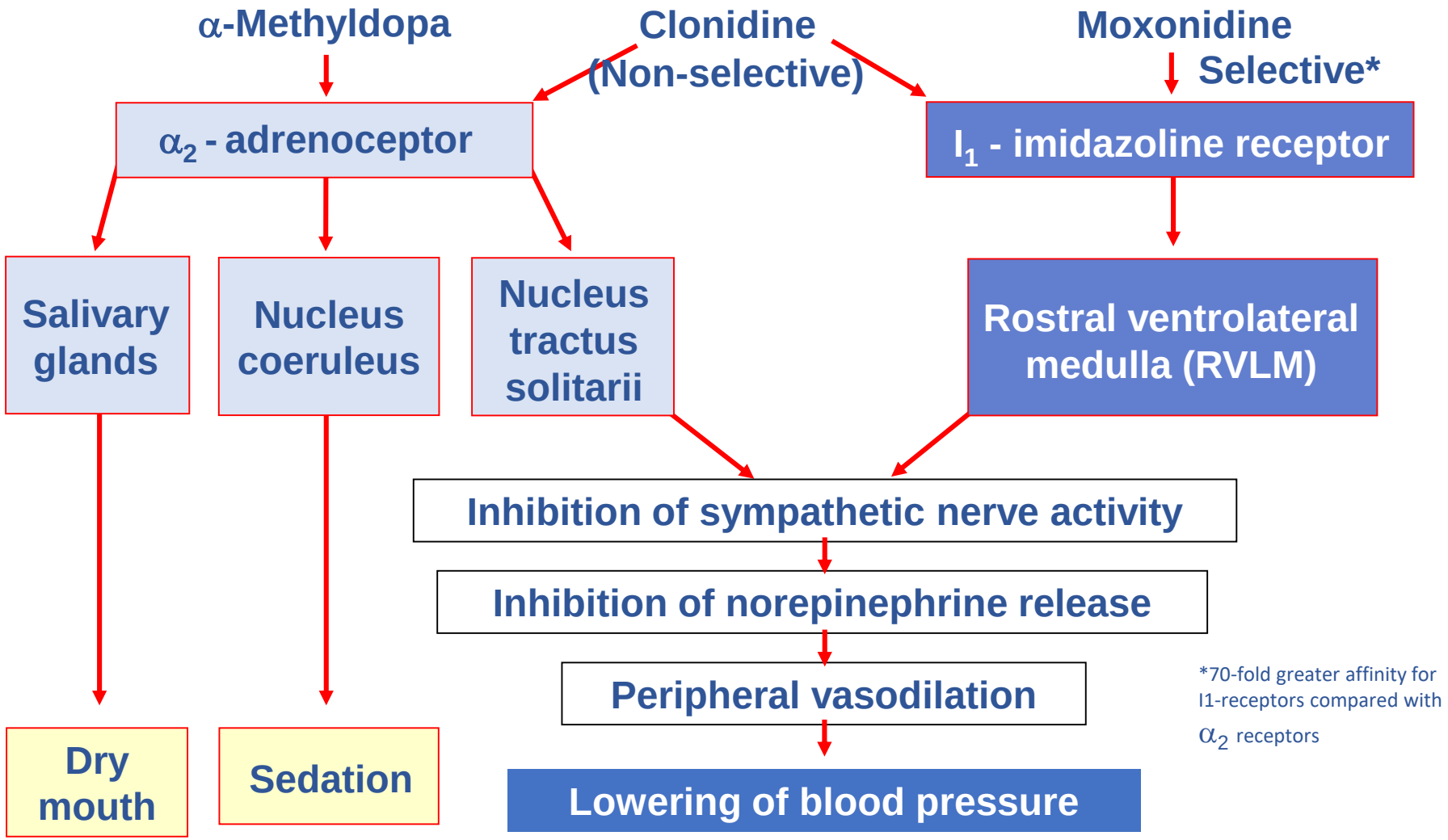
- Since hyperkalemia acts as a barrier and limits the broad utilization of spironolactone , adding a potassium-binding polymer to spironolactone may be an option.
- **AMBER** (Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease) trial.

✓ 295 patients with eGFR ranging from 25 to ≤45 mL/min/1.73 m^2 and uncontrolled resistant hypertension to receive spironolactone and Patiromer or with placebo .

✓ Patiromer enabled more patients to maintain on spironolactone treatment as compared with placebo.

Centrally Acting Antihypertensive Drugs
(Selective VS Non-Selective)

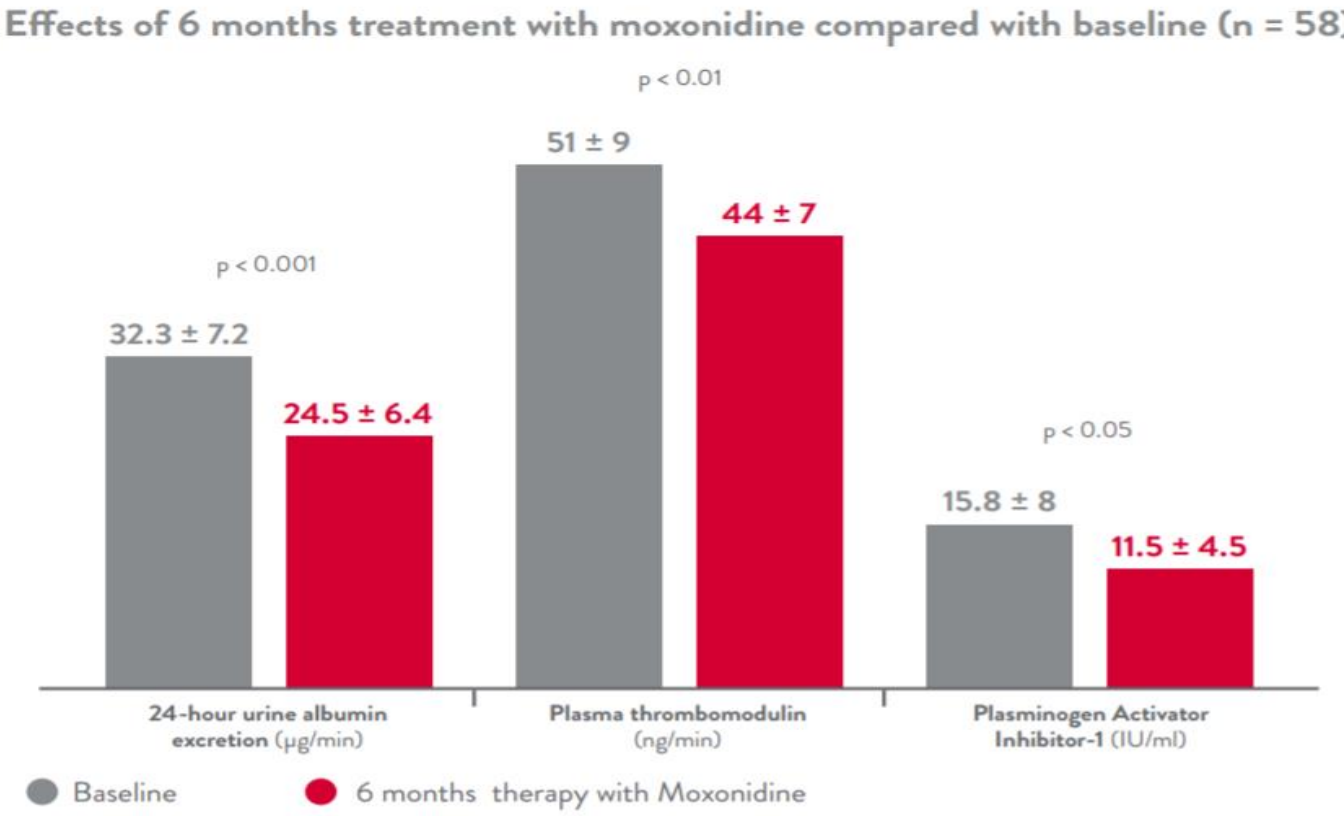
Mechanism of Action



van Zwieten. J Hypertens 1999;17(suppl 3):S15-S21

Moxonidine Had A Favorable Effect On Renal Function And Endothelial Homeostatic Mechanisms

Moxonidine significantly reduced urine albumin excretion, plasma thrombomodulin and plasma activator inhibitor-1 in Fifty-eight patients with essential hypertension and microalbuminuria

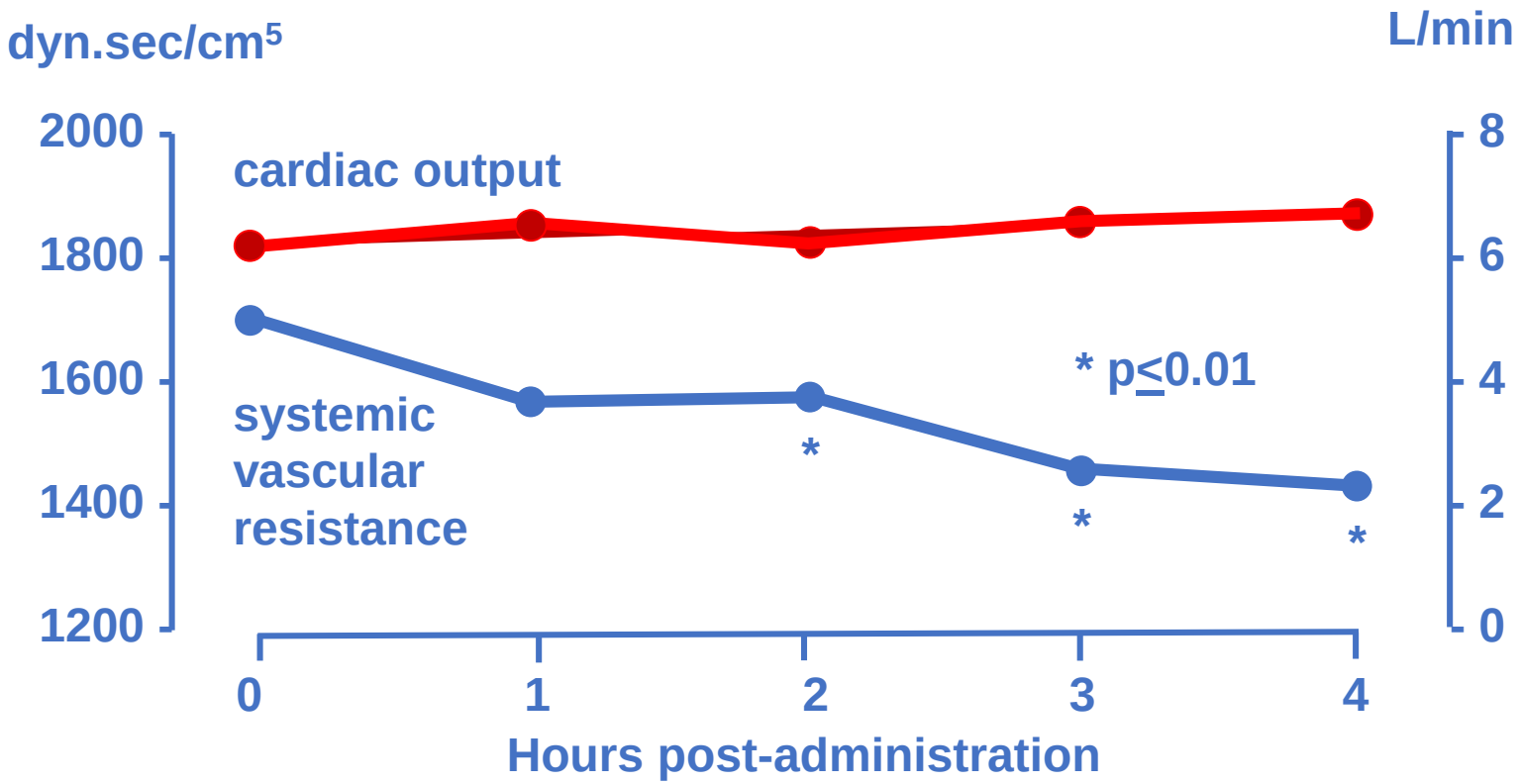


The aim of this study was to evaluate the effect of moxonidine, on microalbuminuria (urine albumin excretion, UAE), plasma thrombomodulin (TM), and tissue plasminogen activator inhibitor (PAI-1) in patients with mild to moderate essential hypertension associated with increased UAE. Fifty-eight patients with essential hypertension and microalbuminuria, with a mean age of 56.6 ± 8.2 years and body mass index of 23.8 ± 3.1 kg/m2 who responded to moxonidine therapy (0.3-0.4 mg daily) were studied before and after their blood pressure control. The 24-hour urine albumin excretion, as well as thrombomodulin and plasminogen activator-1 plasma levels, were determined before and 6 months after the initiation of treatment with moxonidine.

Krespi PG, Makris TK, Hatzizacharias AN. Moxonidine Effect on Microalbuminuria, Thrombomodulin, and Plasminogen Activator Inhibitor-1 Levels in Patients with Essential Hypertension. Cardiovascular Drugs and Therapy, 1998; 12: 463-467

Haemodynamic Effects Of Moxonidine

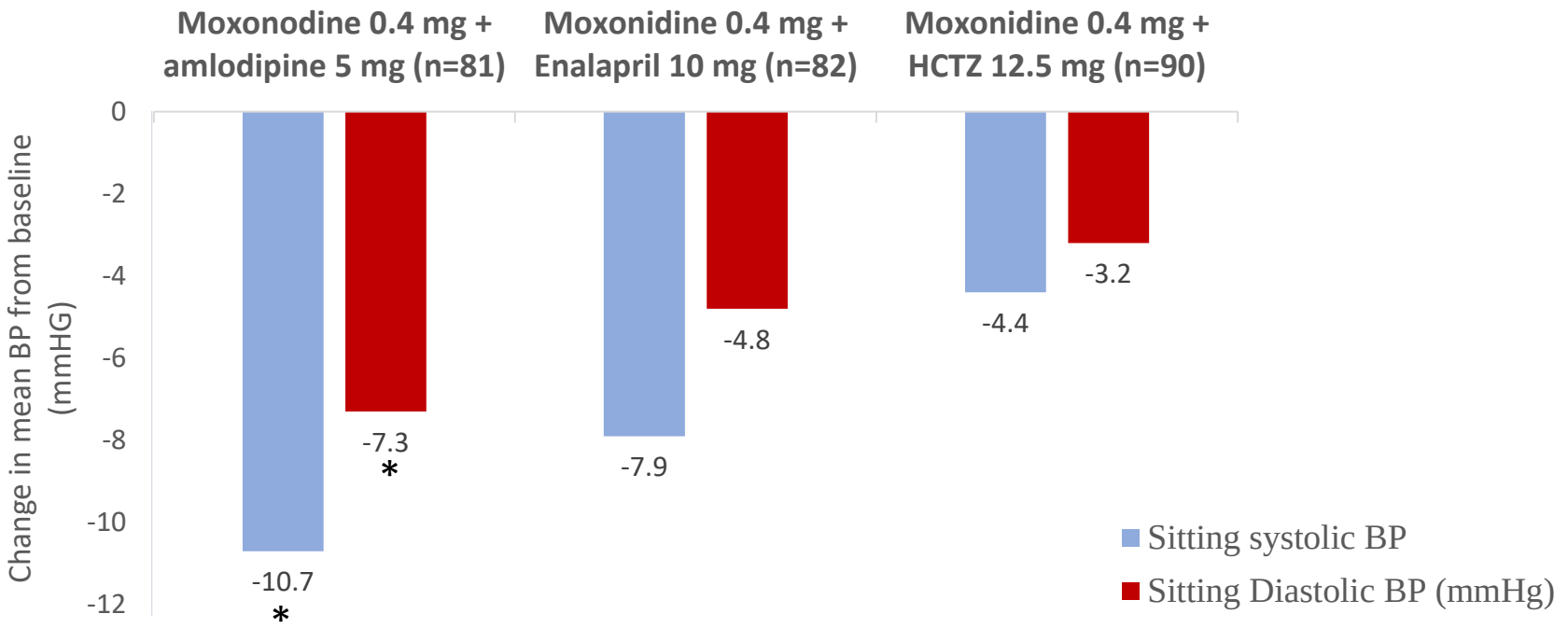
Moxonidine lowered blood pressure by reducing systemic vascular resistance while maintaining cardiac output and heart rate.



17. Mitrovic V et al. Cardiovasc Drugs Ther 1991;5:967-972

Moxonidine and Combination therapy

Moxonidine is effective when used either alone or in combination for the management of essential hypertension.



TOPIC study:

272 hypertensive patients randomized to 4 weeks double blind therapy during which they received the 3 combinations in 138 general practice centres in the UK, for 12 weeks

* $p<0.05$ versus the other combinations

Reduction in BP was seen in all 3 combinations, the combination Moxonidine amlodipine reduced BP to a greater extent than the other combinations

Waters J et al. J Clin Basic Cardiol 1999;2:219-224

A non-steroidal Mineralocorticoid Receptor Antagonist (MRA), Ocedurenone

- Formerly known as KBP-5074.
- 162 patients with stage 3b/4 CKD with uncontrolled hypertension in doses of 0.25 mg and 0.5 mg For 12 week.
- The primary endpoint was the change in systolic BP from baseline to Week 12.
- Compared with placebo, a 0.25-mg dose lowered systolic BP 7 mmHg.
- A 0.5-mg dose lowered systolic AOBP 10.2 mmHg.
- The incidence of mild hyperkalemia (serum potassium concentration ≥5.6 to <6.0 mmol/L) was low and comparable among groups.

Aldosterone Synthase Inhibitor, Baxdrostat

BrigHTN trial:

- 248 patients with resistant hypertension, in doses of 0.5, 1 and 2 mg . BP averaged 148/88 mmHg.
- Compared with placebo: a 1-mg dose lowered systolic BP 8.1 mmHg and a 2-mg dose lowered systolic AOBP 11 mmHg
- Treatment-induced elevations in serum potassium levels were observed in only two patients
- However, this trial excluded patients with CKD stage 3b or higher—eGFR was about 85 mL/min/1.73 m^2 at baseline—therefore, safety is difficult to establish in this 12-week study.

Dual Endothelin Antagonist, Aprocitentan

- **PRECISION trial** : phase 3 study.
- 730 patients with resistant hypertension at doses of 12.5 mg and 25 mg.
- The primary endpoint was the change in systolic AOBP from baseline to 4 weeks.
- Compared to placebo Aprocitentan 12.5-mg dose, lowered 24-h ambulatory SBP 4.2 mmHg and for the 25-mg dose by 5.9 mmHg.
- Subgroup analyses showed numerically greater reductions in standardized office SBP in patients who had very high albuminuria or stage 3–4 CKD

Renal Denervation

- Recent studies support the long-term antihypertensive efficacy, tolerability and safety of catheter-based renal denervation.
- Mahfoud F et. al (Lancet 2022) showed that renal denervation provoked a clinically meaningful reduction of 10/5.9 mmHg in 24-h ambulatory BP at 36 months of follow-up.
- Small uncontrolled interventional studies showed remarkable reductions in BP with renal denervation in patients with stage 3–4 CKD.

Hypertension in Kidney Transplant Recipients

- The ESH 2023 Guidelines: No RCTs in kidney transplant recipients (KTRs).
- BP targets for hypertension management in these individuals are extrapolated from data in CKD populations.
- Both 2023 ESH and 2021 KDIGO Guidelines use the same target for KTRs.
- A target BP of <130/80 mmHg is considered as a reasonable target for KTRs. Level IIB

Conclusions

- Research-grade BP measurement methodology must move from research to clinics.
- The diagnosis of hypertension can be improved using HBPM or ABPM.
- Dietary Na restriction is often overlooked, but effective strategy to manage poorly controlled hypertension.
- RAAS Inhibitors remain the first-line agents for treating hypertension in patients with CKD, particularly with very high albuminuria.

Conclusions

- Patients with uncontrolled BP despite adherence to triple therapy with maximally tolerated doses of a RAAS blocker, CCB and a diuretic have by definition **resistant hypertension**.
- In such patients, the addition of spironolactone to the baseline antihypertensive regimen is the pharmacological intervention of choice.

Conclusions

- Newer BP-lowering medications, such as the non-steroidal MRA Ocedurenone, the aldosterone synthase inhibitor Baxdrostat and the dual endothelin receptor antagonist Aprocitentan, are currently under investigation in clinical trials, offering hope for improved BP control .
- β-blockers are not recommended by guidelines as first-line therapies, but this drug category is useful for the treatment of hypertension is CKD patients with specific indications (i.e. heart failure with reduced ejection fraction or after an acute MI).


Thank you