Nefroprotezione: targets pressori, ACEi/ARB

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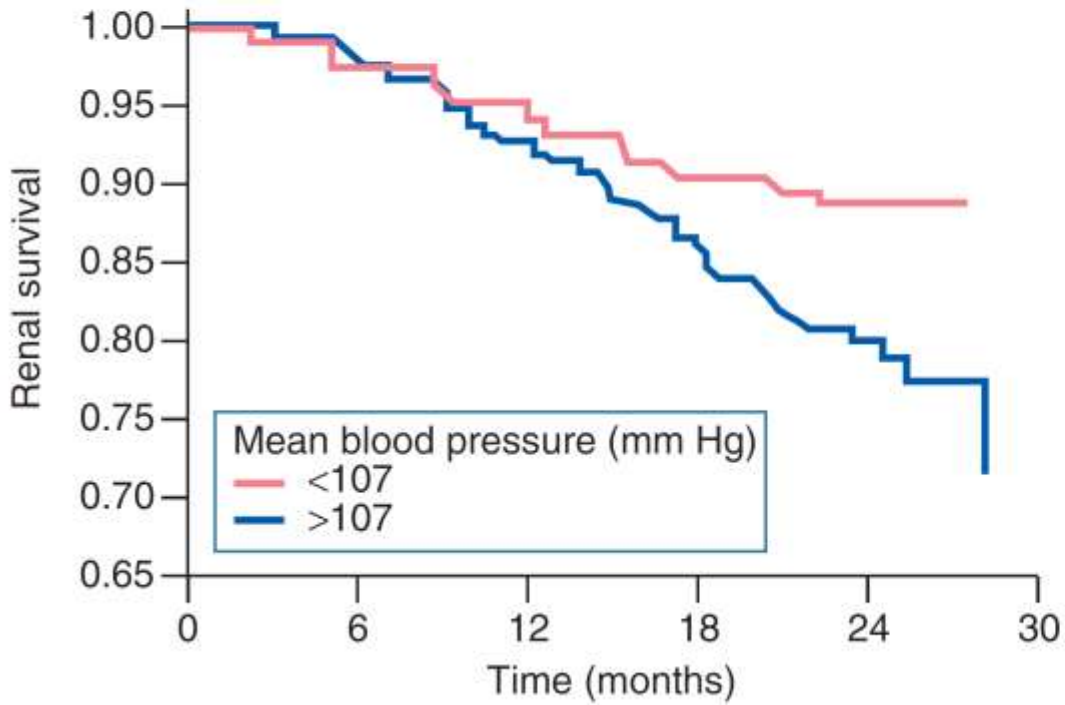
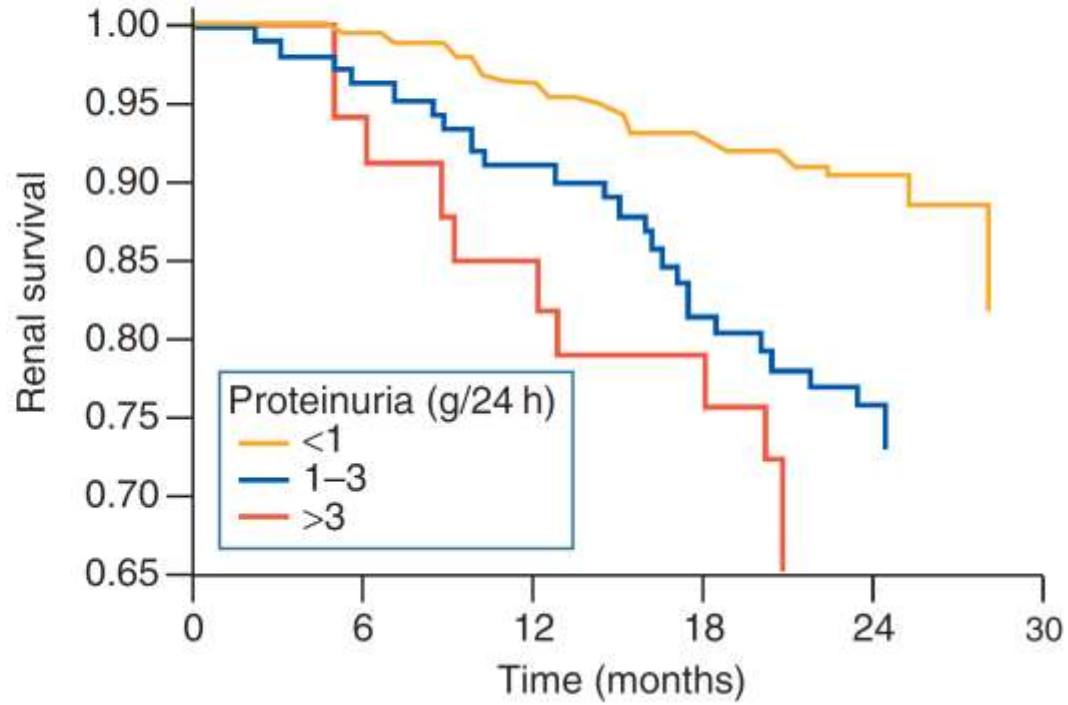
Renal Survival and Blood Pressure



Renal Survival and Level of Proteinuria



Frehally et al. Johnson's Comprehensive Clinical Nephrology. 2014 ed

Landmark RCTs on ACE-Is or ARBs in CKD

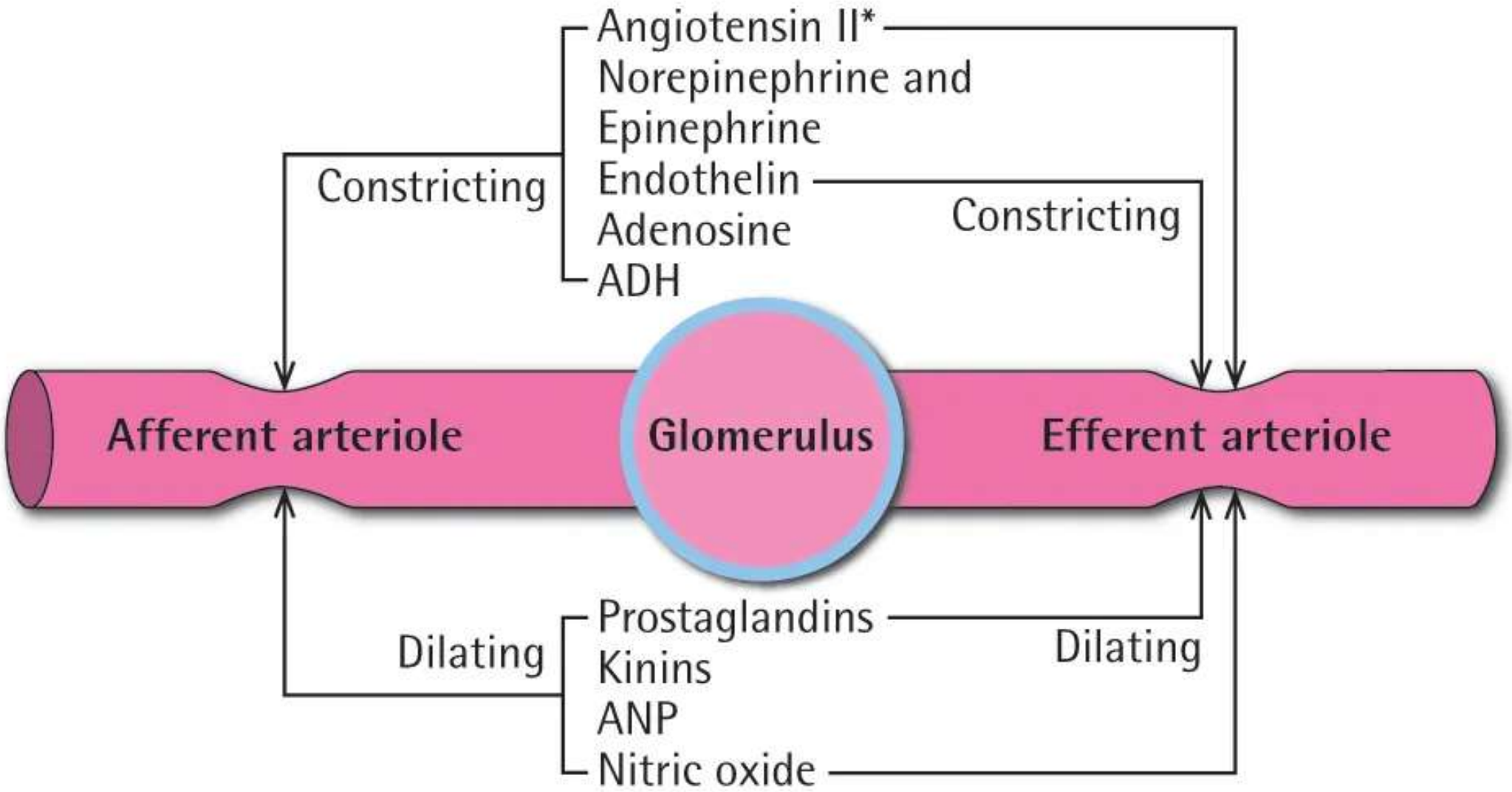
Parameter	276(n=166)	RENAAL77 (n=1513)	IDNT78 (n=1715)	AASK68 (n=1094)	(n=224)
Kidney related inclusion criteria	CrCl 20-70 mL/min/1.73 m^2 and protein excretion ≥3 g/day	SCr 1.3-3.0 mg/dL and ACR ≥300 mg/g or protein excretion ≥0.5 g/day	SCr 1.0-3.0 mg/dL in women and 1.2-3.0 mg/dL in men and protein excretion ≥900 mg/day	GFR 20-65 mL/min/1.73 m^2 and PCR ≤2.5 g/g	SCr 3.1-5.0 mg/dL and protein excretion >0.3 g/day
Drug Comparator(s)	Ramipril 1.25-5 mg daily Placebo	Losartan 50-100 mg daily Placebo	Irbesartan 300 mg daily Placebo; amlodipine 10 mg daily	Ramipril 2.5-10 mg daily Metoprolol 50-200 mg daily; amlodipine 5-10 mg daily	Benazepril 20 mg daily Placebo
Follow-up % with diabetes	Mean ~1.3 years 0% with insulin dependent diabetes	Mean 3.4 years 100%	Mean 2.6 years 100%	Median ~3-4 years 0%	Mean 3.4 years 0%
Baseline GFR, eGFR, or SCr	Mean GFR ~39 mL/min/1.73 m^2	Mean SCr ~1.9 mg/dL	Mean SCr ~1.7 mg/dL	Mean GFR 46 mL/min/1.73 m^2	Mean eGFR ~26 mL/min/1.73 m^2
Baseline PCR, ACR, protein or albumin excretion*	Mean protein excretion ~5.3 g/day	Median ACR 1261 mg/g for placebo group and 1237 mg/g for losartan group	Median protein excretion ~2.9 g/day and albumin excretion ~1.9 g/day	Median PCR 0.08 g/g	Mean protein excretion ~1.7 g/day
Primary outcome	Mean GFR decline† 0.53 (SE 0.08) mL/min per month for ramipril *v* 0.88 (0.13) for placebo (P=0.03)	Hazard ratio for composite of doubling SCr, ESKD, or death 0.84 (95% CI 0.72 to 0.98)	Relative risk for composite of doubling SCr, ESKD, or death 0.80 (95% CI 0.66 to 0.97) for irbesartan *v* placebo; 0.77 (0.63 to 0.93) for irbesartan *v* amlodipine	Mean difference for total GFR slope (mL/min/1.73 m^2 per year) 0.61 (SE 0.22) for ramipril *v* metoprolol (P=0.007); −0.34 (0.38) for ramipril *v* amlodipine (P=0.38)	Risk reduction for composite of doubling SCr, ESKD, or death 43% (P=0.005)

ACR=urine albumin-to-creatinine ratio; CI=confidence interval; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; GFR=glomerular filtration rate; IDNT=Irbesartan Diabetic Nephropathy Trial; AASK=African American Study of Kidney Disease and Hypertension; PCR=urine protein-to-creatinine ratio; SCr=serum creatinine; SE=standard error; REIN=Ramipril Efficacy In Nephropathy; RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

- * To convert ACR from mg/g to mg/mmol, multiply by 0.113.
- † n=117 with ≥3 GFR evaluations.

Chen TK et al. Advances in the management of chronic kidney disease. BMJ. 2023

Regulation of Glomerular Filtration Rate



*Angiotensin II has a greater effect on the efferent arteriole than on the afferent arteriole, so it will initially serve to maintain GFR at low BP.
ADH, antidiuretic hormone; *ANP*, atrial natriuretic peptide.

Evidence-based benefits in CKD

- A 2001 meta-analysis of 11 studies suggested that, for non-diabetic CKD, the use of angiotensin converting enzyme (ACE) inhibitors resulted in a 30% reduction in risk of KFRT or doubling of serum creatinine
- Clinical trials in populations with CKD and diabetes (for example, IDNT, RENAAL) have also shown benefit of angiotensin receptor blockers (ARB) in preventing CKD progression
- The Heart Outcomes Prevention Evaluation (HOPE) study showed that ACE inhibitors reduced the risks of myocardial infarction, stroke, and cardiovascular death in populations at high risk for cardiovascular disease, including those with diabetes and albuminuria.
- The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) showed that ACE inhibitors and ARB were generally equivalent in the prevention of cardiovascular events

Can RAAS inhibitors can be safely continued as GFR declines?

- The Benazepril in Advanced CKD study showed that benazepril reduced the risk of the primary composite kidney endpoint by 43% compared with placebo, thus suggesting that RAAS inhibitors are beneficial even in advanced CKD (baseline serum creatinine 3.1-5.0 mg/dL)
- A retrospective, propensity score matched study of patients with estimated GFR <30 mL/min/1.73 m2 showed higher risk of all cause mortality and major adverse cardiovascular events in those who stopped RAAS inhibitors compared with those who continued them, as did a Swedish trial emulation study.
- The risk of kidney replacement therapy associated with cessation of RAAS inhibitors was not statistically significant in the first study and lower in the second study. In an open label randomized trial, cessation of RAAS inhibitors did not show significant between group differences in long term decline in estimated GFR or initiation of kidney replacement therapy, providing reassurance that RAAS inhibitors can be safely continued as GFR declines.

Cosa dicono le linee guida ESH 2023

Topic	Recommendation
Instruments for BP measurement.	a) Validated electronic, upper-arm cuff devices recommended (I B). Hybrid manual auscultatory devices recommended only if automated devices are not available (I B). b) Consult www.stridebp.org for a listing of clinically validated devices (I C). c) Cuffless BP devices not recommended (III C).
Diagnosis of hypertension.	a) Office BP measurement recommended (I A). Definition of hypertension: Office BP ≥140 mmHg systolic or 90 mmHg diastolic. b) Diagnosis of hypertension based on three measurements, with average of the last two (IC) on at least 2 visits within 4 weeks (I C). BP readings at a single visit is sufficient to make diagnosis of hypertension if (a) BP is ≥180/110 mmHg; (b) there is evidence of organ damage, prior CV disease or 'hypertension related symptoms' (IC).
24-hour ambulatory BP monitoring.	a) Recommended in addition to office BP (II B), using BP measurement devices clinically validated according to an established protocol (I C). b) Frequency of measurements should be one every 20 min day and night (I C).
Unattended BP measuremment	a) Skepticism about unattended BP measurement.
Definition of hypertension according to home BP and 24-hour ambulatory BP.	a) Home BP ≥135/75 mmHg; b) 24-hour ambulatory BP ≥130/80 mmHg; c) Daytime ambulatory BP ≥135/85 mmHg; d) Nighttime ambulatory BP ≥120/70 mmHg
Preferential clinical indications for home and 24-hour ambulatory BP.	Specific conditions favoring the use of: a) **Home BP measurement**: long-term follow-up of treated individuals to improve adherence and hypertension control; patients unwilling to perform 24-hour ambulatory BP monitoring. b) **24-hour ambulatory BP monitoring**: assessment of nocturnal BP and dipping in specific conditions such as sleep apnea, chronic kidney disease, diabetes, endocrine hypertension, autonomic dysfunction.
Risk assessment.	SCORE2 and SCORE2-OP recommended in hypertensive patients not at high or very high CV risk (I B)

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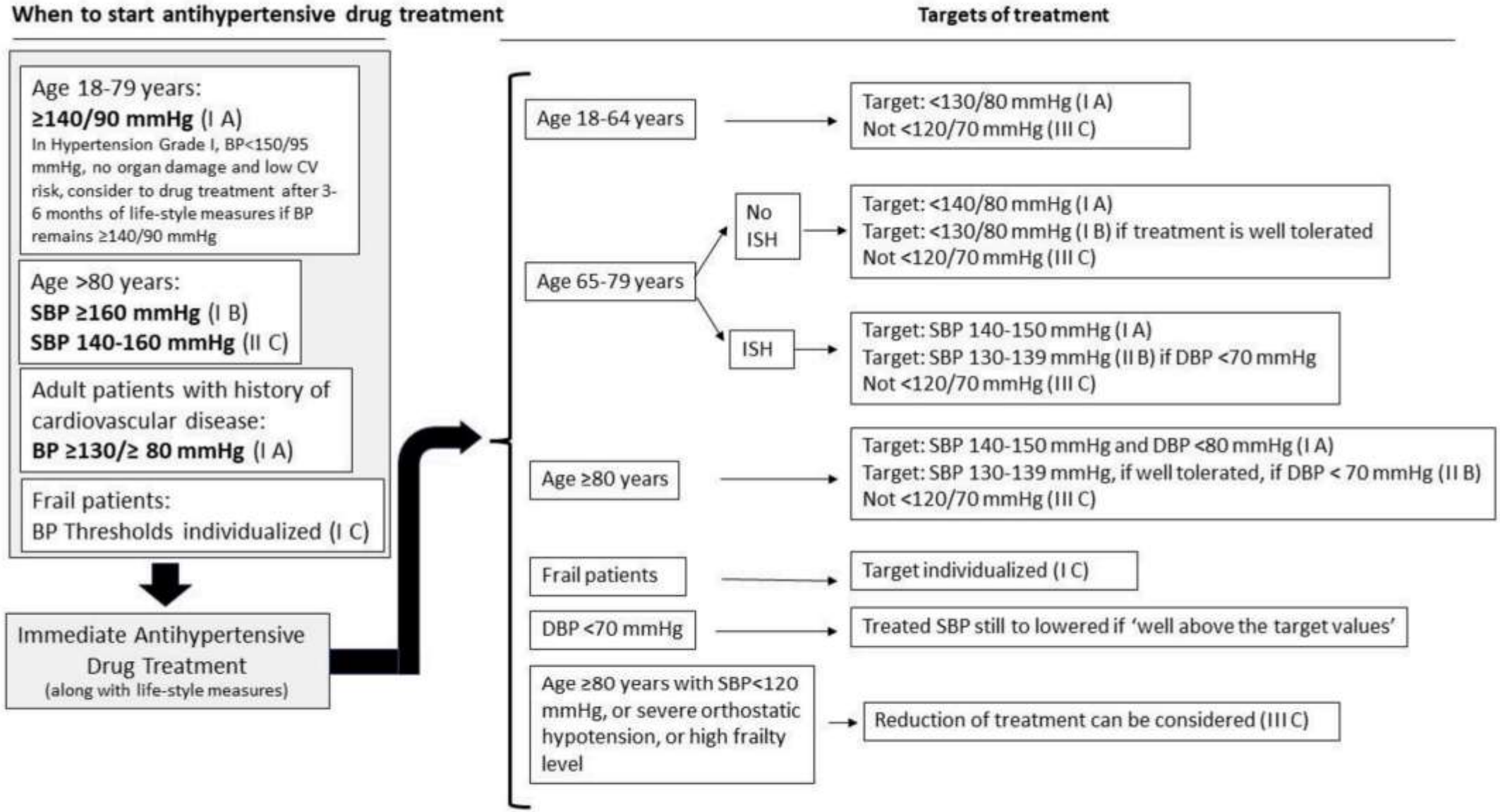

Fig. 1. When to start drug treatment and targets of treatment. Abbreviations: BP=Blood pressure; ISH=Isolated systolic hypertension; SBP=Systolic blood pressure; DBP=Diastolic blood pressure.

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Table 3
Drug treatment of hypertension.

Recommendation	CoR	LoE
The **benefits of antihypertensive treatment** originate from BP reduction, not from the specific drug used.	I	A
Five classes of antihypertensive drugs are recommended alone and in combinations: a) ACE-inhibitors (ACEIs) b) Angiotensin II Receptor Blockers (ARBs), c) β-blockers, d) Calcium channel blockers (CCBs), e) Thiazide-like diuretics (D) It is recommended to start treatment with a two-drug combination in most patients.Preferred combinations are ACEIs or ARBs combined with CCBs or D.	I	A
β-blockers should be used at initiation of therapy and at any step in the treatment of patients who have heart failure with reduced ejection fraction, chronic coronary syndromes, or atrial fibrillation needing heart rate control.	I	A
Single-pill combinations are preferred at any treatment step.	I	B
Initiation with monotherapy can be considered in: a) Grade 1 hypertension at low risk if BP is <150/95 mmHg; b) high-normal BP and very high cardiovascular risk; c) frailty and/or advanced age	I	C
If BP remains uncontrolled despite two-drug combination (at the highest recommended and tolerated doses), treatment should be increased to a three-drug combination, usually ACEIs or ARBs combined with CCBs and D. **If BP is still uncontrolled** despite a three-drug combination, it is recommended to extend treatment according to recommendations for resistant hypertension.	I	A
The combination of ACEIs and ARBs is not recommended due to increased risk of adverse events.	III	A

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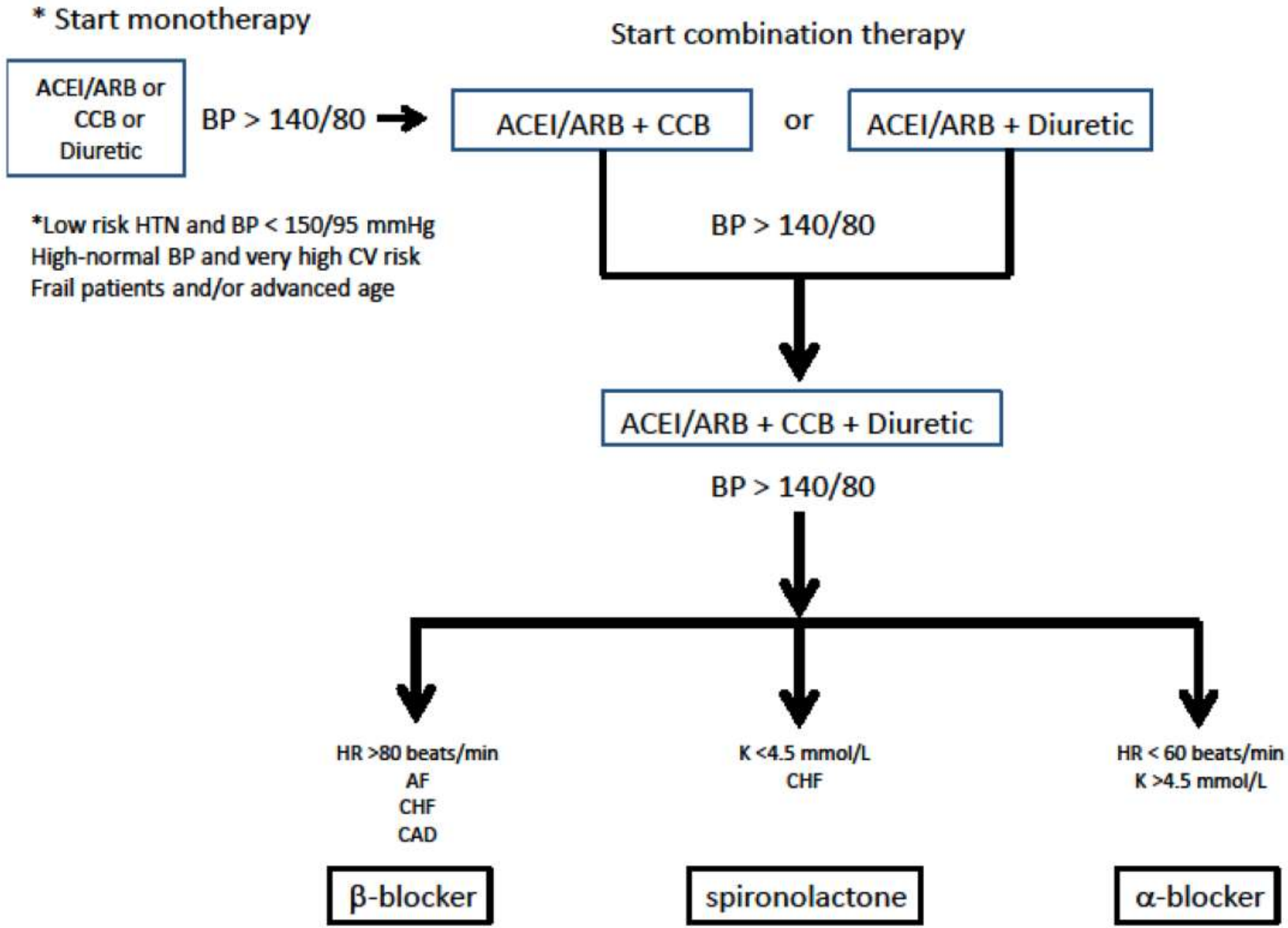

Fig. 2. Simplified algorithm on the choice of antihypertensive drug treatment according to the 2023 ESH Guidelines. Modified[6]. Abbreviations: ACEI=Angiotensin converting enzyme inhibitor; ARB=Angiotensin receptor blocker; BP=Blood pressure; CCB=Calcium channel blocker; HR=Heart rate; CHF=Congestive heart failure.

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Recommendations and statements	CoR	LoE
CV risk assessment with the SCORE2 and SCOR2-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

Mancia G. et al. 2023 J Hypertension

Top 10 Takeaways for Clinicians from the KDIGO 2021 Clinical Practice Guideline for Blood Pressure Management in CKD*

1 Standardized office BP measurement

Standardized BP measurement emphasizes the importance of appropriate preparations and the measurement technique, not the type of device. The relationship between routine office BP and standardized office BP is highly variable; therefore, it is not possible to apply a correction factor to translate a given routine BP value to a standardized BP value.

2 Home BP monitoring

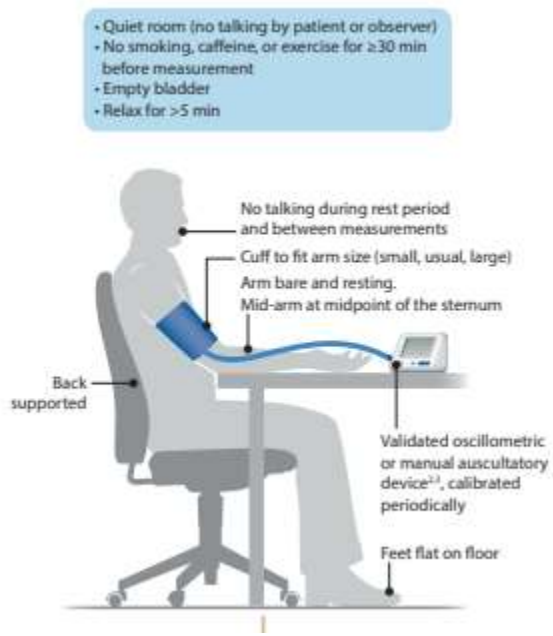
HBPM may be particularly important for the management of BP when a clinic visit is not practical, for example, during the coronavirus disease 2019 (COVID-19) pandemic. However, at present, HBPM should only be used to complement standardized office measurement and not guide treatment decisions, if standardized office BP is available.

3 BP target in CKD not treated with dialysis

Adults with high BP and CKD should be treated to a target SBP <120 mm Hg which must be measured using standardized office BP preparations and techniques. When measured under standardized conditions, targeting SBP <120 mm Hg reduces the risks of CV events and all-cause mortality in CKD; however, the effects on progression of kidney disease are uncertain.

4 BP target in CKD subgroups

The SBP target of <120 mm Hg also applies to the subgroups of older adults and those with increased albuminuria. The balance of benefits and harms is less certain in people with CKD G5 and in those with severely increased albuminuria (A3).



Incremento albuminuria
Normale-lieve: < 30 mg/g
Moderato: 30-300 mg/g
Severo: > 300 mg/g

5 BP target in patients with diabetes

The benefits of intensive BP lowering are less certain among patients with concomitant CKD and diabetes, compared to patients with CKD without diabetes.

6 Antihypertensive agents in CKD

RASi (ACEi or ARB) should be used in patients with CKD and increased albuminuria, with or without diabetes. The evidence for use of RASi in patients with moderately increased albuminuria is lower in quality than in severely increased albuminuria.

7 Lifestyle interventions

Low sodium intake (<2 g/day) and moderate-intensity physical activity (≥150 min/week) are suggested in accordance with recommendations for the general population.

8 BP target in KTR

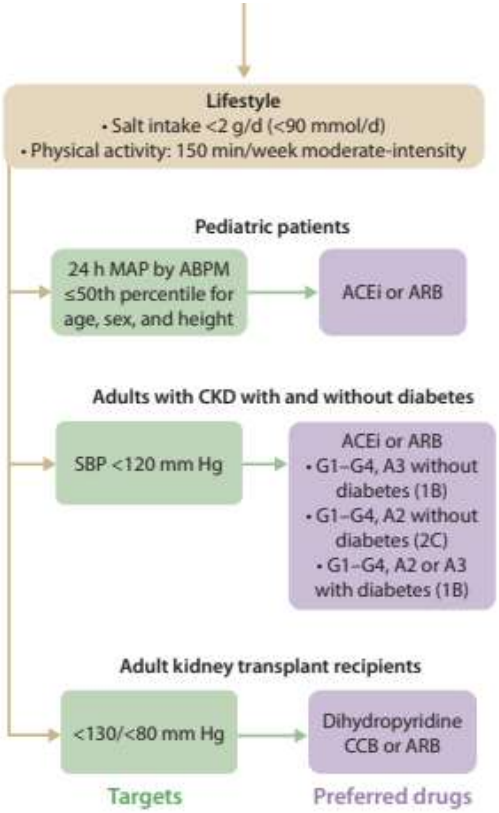
For adult kidney transplant recipients, a target of <130/<80 mm Hg, using standardized office measurement, is still a reasonable goal. A lower SBP goal (<120 mm Hg) for kidney transplant recipients would require additional data on the risks and benefits in this population.

9 Antihypertensive agents in KTR

Dihydropyridine CCB or ARB should be used as the first-line antihypertensive agent in adult kidney transplant recipients given their efficacy in and the importance of preventing graft loss.

10 BP management in children

BP target in children with high BP and CKD should be lowered to ≤50th percentile for age, sex, and height according to 24-hour MAP by ABPM. When ABPM is not available, standardized auscultatory office measurement should be used to target SBP <90th percentile.



*The KDIGO Guideline for the Management of BP is applicable to patients with CKD not receiving dialysis. ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; HBPM, home blood pressure monitoring; KTR, kidney transplant recipient(s); MAP, mean arterial pressure; RASi, renin-angiotensin system inhibitor; SBP, systolic blood pressure

Problema linee guida KDIGO

- Raccomandazioni prevalentemente basate su esito trial SPRINT, controverse
- Rischio di deterioramento della funzione renale con controllo intensivo di cui non si conosce l'impatto su outcome renale a medio-lungo termine
- Difficile/impossibile applicazione pratica della misurazione ambulatoriale «standardizzata»

Chapter 2: Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis

2.1. Sodium intake

Recommendation 2.1.1: We suggest targeting a sodium intake <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD *(2C)*.

Practice Point 2.1.1: Dietary sodium restriction is usually not appropriate for patients with sodium-wasting nephropathy.

Practice Point 2.1.2: The Dietary Approaches to Stop Hypertension (DASH)–type diet or use of salt substitutes that are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism or other causes of impaired potassium excretion because of the potential for hyperkalemia.

2.2. Physical activity

Recommendation 2.2.1: We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance *(2C)*.

Sono venti minuti di cyclette al giorno!

Thomson CRV et al. 2021 Annals of Internal Medicine

Practice Point 3.2.1: It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASi (ACEi or ARB).

Practice Point 3.2.2: RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 2-4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.

Practice Point 3.2.4: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.

Practice Point 3.2.5: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose.

Practice Point 3.2.6: Consider reducing the dose or discontinuing ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment, or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2).

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Recommendation 3.1.1: We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement (*2B*).

Practice Point 3.1.2: Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy or symptomatic postural hypotension.

Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 2–4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.

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Thomson CRV et al. 2021 Annals of Internal Medicine

Nella pratica clinica

- ACE-inibitore o sartano alla massima dose tollerata: avviare in ogni paziente con malattia renale cronica o con albuminuria > 300 mg/g senza diabete o con albuminuria 30-300 mg/g con diabete
- Dopo 2-4 settimane, dosare creatinina e potassio; se K+ > 4.8 mmol/L, associare chelante del potassio/valutare presenza di acidosi/associare diuretico; se creatinina incrementata > 30%, ridurre la dose del farmaco ed escludere stenosi arteria renale e ricontrollare a 2-4 settimane, sospendere se persistente/peggiorativo

Nella pratica clinica

- Iniziare sempre terapia combinata, preferendo associazione ACE-inibitore/sartano + calcio antagonista o ACE-inibitore/sartano più tiazidico
- L'edema da calcio antagonista non è un indicazione a cessare il farmaco: problema cosmetico, discutere col paziente se lo tollera; se non lo tollera, sostituirlo con tiazidico
- Il diuretico dell'ansa è da impiegare come anti-ipertensivo in sostituzione di un diuretico tiazidico SOLO in caso di GFR < 30 mL/min
- Non combinare mai diuretico dell'ansa e tiazidico

Nella pratica clinica

- Titolati i farmaci di prima linea (ACEi/ARB, CCB, diuretici), se ipertensione ancora non controllata introdurre anti-aldosteronico a bassa dose (ad es. canrenoato di potassio 25 mg die, eplerenone 50 mg die) e/o beta-bloccante
- Se ipertensione ancora non controllata, ricorrere ad alfa litici (doxazosina 4 mg da titolare fino a 16 mg die, in una-due somministrazioni giornaliere, preferendo la somministrazione serale)

Nella pratica clinica

- Dopo introduzione di ACE-inibitore/sartano, controllare sempre a 2-4 settimane creatinina e potassio
- Dopo introduzione di tiazidico, controllare sempre a 2-4 settimane creatinina, sodio, potassio
- Dopo introduzione di antagonista del recettore mineralcorticoide, controllare sempre a 2-4 settimane creatinina e potassio