IPERTENSIONE ARTERIOSA IN PAZIENTE CON EMATURIA

SIIA

AO AL Azienda Ospedaliera di ALESSANDRIA Santi Antonio e Biagio e Cesare Arrigo

PAZIENTE L.C. 72 ANNI

ANAMNESI

- Anemia sideropenica (EGDS negativa, colon polipi diminutivi asportati)
- Osteroporosi
- TEP sine causa (Apixaban)
- Bronchite cronica con quadro spirometrico misto
- Allergia alimentare ai crostacei

FATTORI DI RISCHIO CV

- Sovrappeso (BMI 26)

MOTIVO RICOVERO: DISPNEA

DIAGNOSI di INGRESSO: riacutizzazione BPCO

RICOVERO COMPLICATO DA: polmonite nosocomiale bilaterale

TERAPIA: piperacillina - tazobactam

Posizionato il CV e praticata terapia diuretica

Ecocardiografia :

VSX non dilatato-ipertrofico, FE 62%, MAPSE 19. Non alterazioni cinesi segmentaria. Alterato rilasciamento diastolico, normale E/E'. Atrio SN non dilatato. Lieve insufficienza mitralica. Valvola aortica tricuspide sclerocalcifica, continente. Sezioni DX non dilatate con funzione radiale, longitudinale conservate. PAPs non cifrabili, non segni di ipertensione polmonare. Non pletora cavale. Non versamento pericardico.

LA PAZIENTE MIGLIORA… MA…

DOPO CIRCA 7 GIORNI DALLA RIMOZIONE DEL CV

IPERTENSIONE (170/90)
MACROEMATURIA
EDEMI INGRAVESCENTI

↓

SINDROME NEFRITICA

WORK UP DIAGNOSTICO

- ESAME URINE: ematuria + leucocituria
- UROCOLTURA: negativa
- PROETEINURIA 24 H: non nefrosica (1,99 g/24 ore)
- TIPIZZAZIONE DELLA PROTEINURIA: proteinuria glomerulare non selettiva e presenza di proteinuria tubulare (INDICE di CAMERON 0,7)
- ALBUMINEMIA: ridotta (1,8 mg/dL)
- CREATININA: aumentata (0,4 mg/dL a 1,7 mg/dL)

GLOMERULONEFRITE

WORK UP DIAGNOSTICO

- C3- C4 → Nella norma
- ANA e anti-ds DNA → Negativi
- ANCA, anti fosfolipidi → Negativi
- HIV,HCV, HBV → Negativi
- Catene leggere sieriche → Assenti
- Immunofissazione sierica → Nella norma
- Legionella/pneumococco → Negativi
- Anti GBM e Anti PLA2R → Non eseguiti

WORK UP DIAGNOSTICO

- Crioglobuline → Negative
- Biopsia renale → Non eseguita
- Esclusione neoplasie occulte → TCTB, PET, citologia urinaria: negativo
- Ecocardiografia → Negativa per endocardite
- Farmaci/tossine → Esclusi
- HbA1c% e glicemia → Nella norma

INFEZIONI ASSOCIATE A GLOMERULONEFRITE

Bacterial
Mycobacterium leprae, M. tuberculosis
Treponema pallidum
Salmonella typhi, S. paratyphi, S. typhimurium
Streptococcus pneumoniae, S. virdans, S. pyogenes
Staphyloccoccus aureus, S. epidermidis, S. albus
Leptospira species[a]
Yersinia enterocolitica[a]
Neisseria meningitidis, Neisseria gonorrhoeae[a]
Corynebacterium diphtheriae[a]
Coxiella burnettii[a]
Brucella abortus[a]
Listeria monocytogenes[a]

Fungal
Histoplasma capsulatum[a]
Candida[a]
Coccidiodes immitis[a]

Protozoal
Plasmodium malariae, P. falciparum
Leishmania donovani
Toxoplasma gondii
Trypanosoma cruzi, T. bruci
Toxocara canis[a]
Strongyloides stercoralis[a]

Viral
Hepatitis B and C
Human immunodeficiency virus
Epstein-Barr virus
Coxsackie B
ECHO virus
Cytomegalovirus
Varicella zoster
Mumps
Rubella
Influenza

Helminthic
Schistosoma mansoni, S. japonicum, S. haematobium
Wuchereria bancrofti
Brugia malayi
Loa loa
Onchocerca volvulus
Trichinella spiralis[a]

ECHO, enteric cytopathic human orphan; GN, glomerulonephritis.
[a]Only case reports documented.

KDIGO guidelines 2012; SH Nasr et al.: Bacterial Infection-related glomerulonephritis in adults
Kidney international (2013) 83, 792-803

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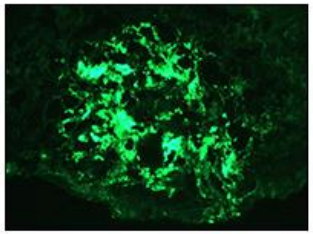
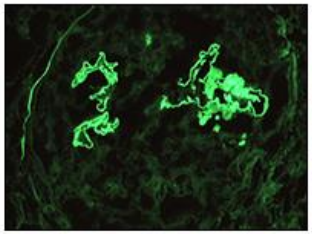
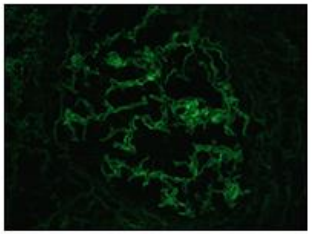
QUADRO ISTO-PATOLOGICO

Histologic appearance and clinical associations of the three major pathogenic types of glomerulonephritis

Immune complex GN	Anti-GBM disease	ANCA/small vessel vasculitis
Granular deposits	Linear deposits	Few or no deposits
		
▪ Infection related ▪ Autoimmune (eg, SLE) ▪ MPGN ▪ IgA nephropathy ▪ Membranous nephropathy (shown above)	▪ Renal limited disease ▪ Lung limited disease ▪ Renal and lung involvement (Goodpasture disease)	▪ Polyangiitis with granulomatosis (Wegener granulomatosis) ▪ Microscopic polyangiitis ▪ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

GN: glomerulonephritis; GBM: glomerular basement membrane; ANCA: antineutrophil cytoplasmic autoantibody; SLE: systemic lupus erythematosus; MPGN: membranoproliferative glomerulonephritis; IgA: immunoglobulin A.

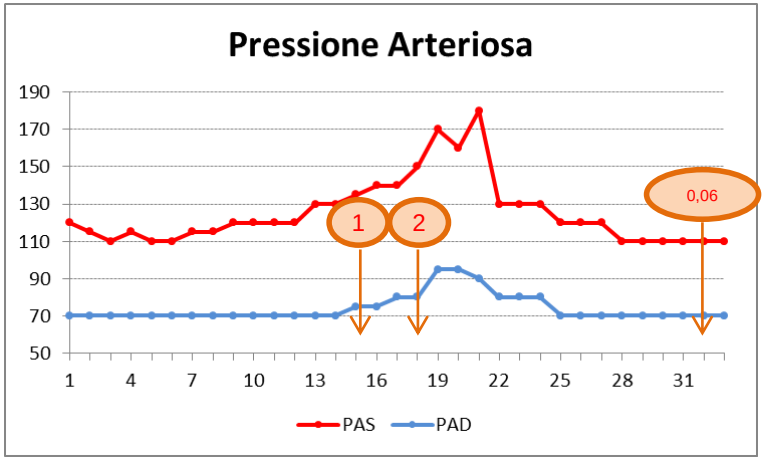
Courtesy of Jai Radhakrishnan, MD, MS. Images courtesy of M. Barry Stokes, MD.

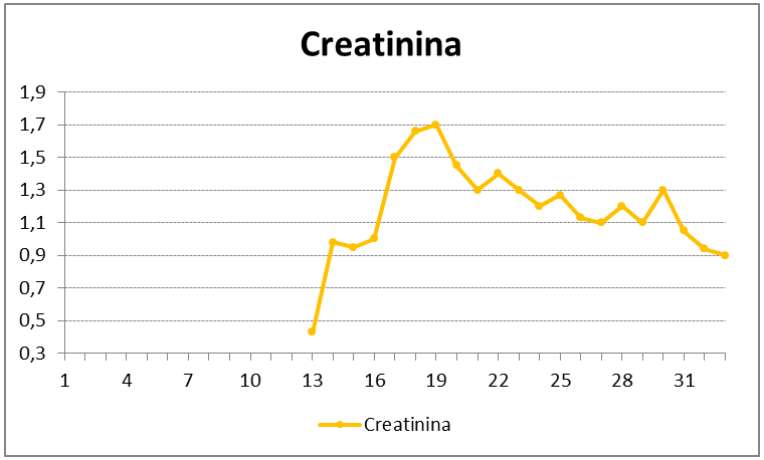
Glomerulosclerosi focale e segmentaria e la malattia a lesioni minime, tipiche della GN post-infettiva, in genere hanno remissione spontanea

TERAPIA: SUPPORTO

Profilassi antitrombotica/ Terapia anticoagulante	→	Enoxaparina 4000 UI/bid
Diuretico dell'ansa	→	Furosemide ev
Anti-ipertensivo	→	Ramipril 5 - 10 mg + Amlodipina 5 mg
Dieta/Iperlipidemia	→	↓ Sodio/Statina
Terapia antibiotica	→	Piperacillina/tazobactam (conclusa)

DECORSO





Proteinuria
g/24 ore

TERAPIA ANTI-IPERTENSIVA

- ACE INIBITORI – ARB a dose titolabile
- ACE INIBITORI – ARB possono ridurre la proteinuria fino al 40-50% con meccanismo dose-dipendente
- Indicato ottenere il controllo pressorio con terapia di associazione
- KDIGO 12: Target pressorio 130/80 mmHg.
- KDIGO 12: Dati limitati su target 125/75 mmHg in pazienti con proteinuria > 1 g/die
- KDIGO 21: Nuovo target pressorio per pz con CKD < 120

CONCLUSIONI

- La GN post-infettiva è una patologia che può colpire qualsiasi età della vita
- E' molto più frequente nell'anziano rispetto al giovane adulto
- Clinica: sindrome nefritica a 1-6 settimane dall'evento infettivo, talvolta contestuale
- L'ipertensione è quasi sempre presente nell'adulto, pressoché costante nella presentazione dell'anziano
- Altri segni laboratoristici: ematuria (micro/macro solo nel 20-50%); leucocituria (58-65%)
- Aumento della creatinina: variabile, più frequente nell'anziano specie se con comorbidità

CONCLUSIONI

- Ipocomplementemia C3-C4: adulto 35-80%; bambino 90%
- Biopsia renale: trova indicazione nei casi di rapido e progressivo declino della funzionalità renale; persistenza di proteinuria e/o di ipocomplementemia (> 3 mesi)
- Prognosi: spesso benigna autolimitante
- Terapia steroidea: boli di metilprednisolone in casi selezionati
- Sempre indicata la terapia di supporto; il caposaldo della terapia anti-ipertensiva rimane l'ACE inibitore


THANK YOU

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KDIGO executive conclusions

Chapter 1: Blood pressure measurement	
• **Recommendation 1.1**	We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (*1B*).
• **Recommendation 1.2**	We suggest that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP *(2B)*.
Chapter 2: Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis	
• **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)*.
• **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)*.
Chapter 3: Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis	
• **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)*.
• **Recommendation 3.2.1**	We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes *(1B)*.
• **Recommendation 3.2.2**	We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (*2C*).
• **Recommendation 3.2.3**	We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (*1B*).
• **Recommendation 3.3.1**	We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes *(1B)*.
Chapter 4: Blood pressure management in kidney transplant recipients (CKD G1T–G5T)	
• **Practice Point 4.1**	Treat adult kidney transplant recipients with high BP to a target BP of <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).
• **Recommendation 4.1**	We recommend that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (*1C*).

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Antihypertensive drugs. There is limited evidence on the use of specific antihypertensive agents to treat high BP in CKD. Many people with CKD and BP who are at least 20 mm Hg above the target will need combinations of 2 or more antihypertensive drugs. Starting combination therapy in such people is, therefore, suggested. There are, however, no randomized trials comparing different drug combinations in CKD, as there are no randomized trials on antihypertensive classes other than renin-angiotensin system inhibitors (RASi), β-blockers, and calcium-channel blockers (CCBs) compared to placebo or to each other. Any antihypertensive treatment algorithm in CKD, therefore, beyond monotherapy, is based on expert opinion, pathophysiologic or pharmacodynamic considerations, or extrapolation from findings in the general population or from surrogate outcomes. Figure 3 displays the algorithm for BP therapy used in SPRINT.[2]

A recent network meta-analysis by Xie *et al.*, including 119 randomized trials conducted in 64,768 patients with CKD with or without diabetes and albuminuria, examined the benefits of treating with RASi compared to other active therapies or placebo for kidney and cardiovascular outcomes.[20] Both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) reduced the risk of kidney failure and major cardiovascular events. However, ACEi, but not ARB, reduced the odds of all-cause death compared to active control.

In those with CKD without diabetes and severely increased albuminuria, 3 moderate quality trials (REIN Stratum-1, GISEN [REIN Stratum-2], Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency [AIPRI], and Hou *et al.*) suggest CV benefits of RASi versus placebo in addition to kidney benefits (Figure 4[21–24]). The results of AASK support the kidney benefit of RASi in CKD based on the analysis of the slope of glomerular filtration rate (GFR) over time.[10]

In those with concomitant diabetes and CKD with severely increased albuminuria, 2 studies demonstrated kidney benefits from RASi independent of BP control. These are the 3-arm Irbesartan Diabetic Nephropathy Trial (IDNT), in which ARB was compared with placebo and with CCB,[25] and the 2-arm Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL), in which ARB was compared to placebo.[26] In a meta-analysis performed by the guideline Evidence Review

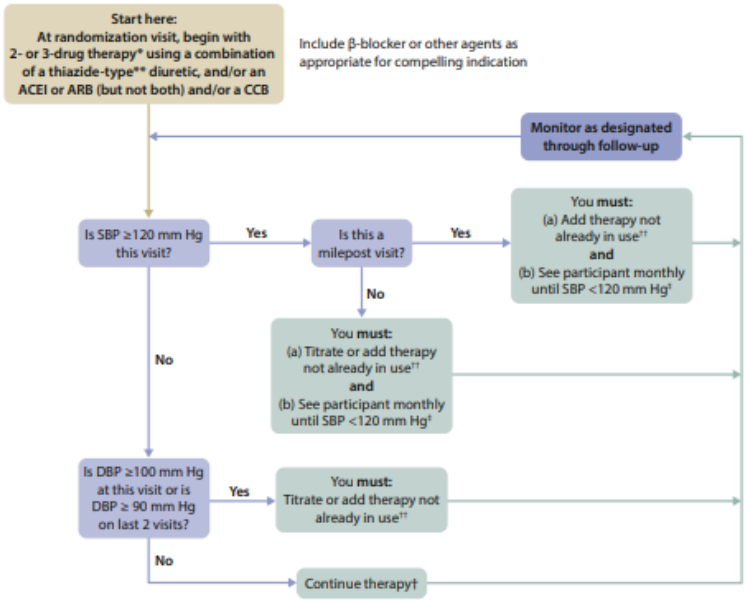

Figure 3 | Treatment algorithm for intensive SBP arm (target SBP <120 mm Hg) in SPRINT trial protocol. From *The New England Journal of Medicine*, the SPRINT Research Group, A Randomized Trial of Intensive Versus Standard Blood-Pressure Control, Volume 373, Pages 2103–2116, Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial. *May begin with a single agent for participants aged ≥75 years with SBP <140 mm Hg on 0–1 medications at study entry. A second medication should be added at the 1-month visit if participant is asymptomatic and SBP ≥130 mm Hg. **May use loop diuretic for participants with advanced CKD. †Unless side effects warrant change in therapy. ††Consider adding a fifth antihypertensive medication. ‡Or until clinical decision is made that therapy should not be increased further.

In those with concomitant diabetes and CKD with severely increased albuminuria, 2 studies demonstrated kidney benefits from RASi independent of BP control. These are the 3-arm Irbesartan Diabetic Nephropathy Trial (IDNT), in which ARB was compared with placebo and with CCB,[25] and the 2-arm Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL), in which ARB was compared to placebo.[26] In a meta-analysis performed by the guideline Evidence Review Team, ACEi did not reduce the risk of all-cause mortality in patients with diabetes with or without albuminuria compared to placebo or standard of care. The risk of doubling of serum creatinine was, however, reduced. The effect of ARBs was similar to those of ACEi (Guideline Supplementary Tables S21 and S22).

A summary of the strength of recommendations for the use of RASi in the presence or absence of diabetes and various albuminuric states is presented in Figures 1 and 5.

Diuretics are often used in CKD patients with high BP because many of them have fluid overload, but the literature on the effects of diuretics on major clinical outcomes in this population is limited. The mineralocorticoid receptor antagonist finerenone was examined for kidney and cardiovascular outcomes in CKD with diabetes in a randomized trial. In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study, finerenone showed kidney and cardiovascular protection with modest effects on SBP (2–3 mm Hg lower) but a higher incidence of hyperkalemia.[27] At the writing of this guideline, finerenone has not been approved for clinical use. The trial was published after the evidence review cutoff for the guideline but will be assessed in future updates.

An important future research topic calls for randomized trials examining various BP targets in advanced CKD, CKD with diabetes, and severely increased albuminuric CKD, with cardiovascular, cognitive, and survival outcomes.

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Table 1. Recommendations and Practice Points From the KDIGO 2021 Clinical Practice Guideline for the Management of BP in CKD

Chapter 1: BP measurement

Recommendation 1.1: We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (1B).

Practice Point 1.1: An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement; however, standardization emphasizes adequate preparations for BP measurement, not the type of equipment.

Practice Point 1.2: Automated office BP, either attended or unattended, may be the preferred method of standardized office BP measurement.

Practice Point 1.3: Oscillometric devices can be used to measure BP among patients with atrial fibrillation.

Recommendation 1.2: We suggest that out-of-office BP measurements with ABPM or HBPM be used to complement standardized office BP readings for the management of high BP (2B).

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

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 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.

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).

Practice Point 2.2.1: Consider the cardiorespiratory fitness status, physical limitations, cognitive function, and risk of falls when deciding on the implementation and intensity of physical activity interventions in individual patients.

Practice Point 2.2.2: The form and intensity of physical activity should be considered and modified as necessary in individual patients. There may still be important health benefits even if physical activity falls below targets proposed for the general population.

Chapter 3: BP management in patients with CKD, with or without diabetes, not receiving dialysis

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

Practice Point 3.1.1: It is potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a nonstandardized manner.

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.

Recommendation 3.2.1: We recommend starting RASI therapy (ACEI or ARB) for people with high BP, CKD, and severely increased albuminuria (CKD G1-G4; albuminuria category A3) without diabetes (1B).

Recommendation 3.2.2: We suggest starting RAS therapy (ACEI or ARB) for people with high BP, CKD, and moderately increased albuminuria (CKD G1-G4; albuminuria category A2) without diabetes (2C).

Recommendation 3.2.3: We recommend starting RASI therapy (ACEI or ARB) for people with high BP, CKD, and moderately to severely increased albuminuria (CKD G1-G4; albuminuria categories A2 and A3) with diabetes (1B).

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 (eGFR <15 mL/min/1.73 m^2).

Practice Point 3.2.7: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in kidney function, particularly among patients with low eGFR.

Recommendation 3.3.1: We recommend avoiding any combination of ACEI, ARB, and direct renin inhibitor therapy in patients with CKD, with or without diabetes (1B).

Chapter 4: BP management in kidney transplant recipients (CKD G1T-G5T)

Practice Point 4.1: Treat adult kidney transplant recipients with high BP to a target BP of <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).

Recommendation 4.1: We recommend that a dihydropyridine calcium-channel blocker or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (1C).

Chapter 5: BP management in children with CKD

Recommendation 5.1: We suggest that in children with CKD, 24-h mean arterial pressure by ABPM should be lowered to ≤50th percentile for age, sex, and height (2C).

Practice Point 5.1: We suggest monitoring BP on ≥ a year with ABPM, and monitoring every 3–6 mo with standardized auscultatory office BP in children with CKD.

Practice Point 5.2: In children with high BP and CKD, when ABPM is not available, normal auscultatory office BP obtained in a protocol-driven standardized setting targeting achieved SBP <90th percentile for age, sex, and height of normal children is a reasonable approach.

Practice Point 5.3: Use an ACEI or ARB as first line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated, but they carry risk for hyperkalemia and have adverse fetal risks for pregnant women.

ABPM = ambulatory BP monitoring; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; CKD = chronic kidney disease; DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic BP; eGFR = estimated GFR; GFR = glomerular filtration rate; HBPM = home BP monitoring; KDIGO = Kidney Disease: Improving Global Outcomes; RASI = renin-angiotensin system inhibitor; SBP = systolic BP.

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Appendix Table 5. Research Recommendations for BP Targets

Information is needed on how patient values and preferences influence decisions related to BP-lowering therapy. This would be an ideal topic for the SONG initiative.
Conduct adequately powered RCTs to examine the effects of intensive BP control among patients with CKD with concomitant diabetes, concomitant severely increased proteinuria (>1 g/d), or very low GFR (<30 mL/min/1.73 m^2). ACCORD included only small numbers of patients with CKD, most of whom qualified for the trial as a result of albuminuria, and is, therefore, uninformative for patients with CKD G3-G5*. On the other hand, SPRINT explicitly excluded patients with diabetes.
In some Asian countries, stroke is more common than cardiac diseases as the cause of CV deaths. Whether intensive SBP control has similar, greater, or less CV-protective effect in the CKD population is unclear and may require confirmation.
Although there is strong evidence that ambulatory or home BP measurements are better predictors of adverse outcomes than office BP, all large RCTs on BP targets in adults used standardized office BP. RCTs targeting home or ambulatory BP measurements are needed.
SGLT2 inhibitors have major CV, kidney, and survival benefits among patients with CKD. In addition to reducing BP, they cause an early, acute decrease in GFR, a pattern that is also seen in intensive SBP lowering. The effects of these drugs, in combination with intensive BP-lowering therapy, on CV outcomes, all-cause mortality, and cognition, as well as acute and chronic changes in kidney function, require further examination.

ACCORD = Action to Control Cardiovascular Risk in Diabetes; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; GFR = glomerular filtration rate; RCT = randomized controlled trial; SBP = systolic BP; SGLT2 = sodium-glucose cotransporter-2; SONG = Standardised Outcomes in Nephrology; SPRINT = Systolic Blood Pressure Intervention Trial.
* GFR <60 mL/min/1.73 m^2.