Hypertension management in chronic kidney disease

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- Chronic kidney disease (CKD) affects 10–15% of the population worldwide and its prevalence is increasing .
- CKD is defined as the presence of reduced kidney function (an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m2) or kidney damage (often indicated by the presence of proteinuria) for ≥ 3 months duration .
- Hypertension, defined by the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) as a blood pressure (BP) of ≥ 140/80 mmHg affects ~ 30% of the general adult population and up to 90% of those with CKD

- Hypertension is both a cause and effect of CKD and contributes to its progression . As eGFR declines, the incidence and severity of hypertension increase .
- hypertension and CKD are both independent risk factors for cardiovascular disease (CVD).
- lowering BP can slow eGFR decline, delay progression to ESRD, and reduce the incidence of CVD in this patient group

pathogenesis

1. Sodium and volume excess due to diminished sodium excretory capacity.
2. Activation of the renin-angiotensin-aldosterone system due to primary vascular disease or to regional ischemia induced by scarring.
3. Increased activity of the sympathetic nervous system.
4. An increase in endothelium-derived vasoconstrictors (such as endothelin)
5. A reduction in endothelium-derived vasodilators (such as nitric oxide).
6. The administration of erythropoietin (EPO).
7. An increase in intracellular calcium induced by PTH excess.
8. Calcification of the arterial tree (arterial stiffness).
9. Preexistent primary hypertension.

Measurement of blood presure

- For management of hypertension to be effective, accurate BP measurements are essential.
- clinic or office BP recordings may be inaccurate due to lack of repeat measurement, diurnal variation and white coat HT
- 24-Hour ambulatory BP monitoring (ABPM) provides a more accurate depiction of BP phenotype and is a better predictor of CVD events in those with CKD than clinic reading
- Home BP mointoring is an alternative strategy

Association of hypertension phenotype with all-cause mortality

BP Phenotype	Description	All-cause mortality hazard ratio (95% CI)
Normotension	Normal clinic BP, normal 24-h ABPM	Reference
White-coate hypertension	High clinic BP, normal 24-h ABPM	1.79 (1.38–2.32)
Sustained hypertension	High clinic BP, high 24-h ABPM	1.80 (1.41–2.31)
Masked hypertension	Normal clinic BP, high 24-h ABPM	2.83 (2.12–3.79)

Values represent patients on treatment and without chronic kidney disease

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *CI* confidence interval

[a]Normal clinic BP defined as < 140/90 mmHg. Normal 24-h BP defined as < 130/80 mmHg

Proteinuria

- Proteinuria is an important marker of renal damage and is incrementally and independently associated with CKD progression and incident CVD
- BP reduction reduces proteinuria, which slows eGFR decline and reduces CVD . More intense BP reduction (a target systolic BP < 120 mmHg) may offer greater renoprotection in those with significant proteinuria (> 1 g/day; PCR > 100 mg/mmol, ACR > 70 mg/mmol) than in those without proteinuria .

Goals of blood pressure

- Management of blood pressure in chronic kidney disease that goal blood pressure depends upon the degree of proteinuria:

- Proteinuric CKD, (500 mg/day or higher),

-the BP < 130/80 mmHg.

- Nonproteinuric CKD, (<500 mg/day),

-the BP < 140/90 mmHg

Achieving BP Targets

- Achieving BP targets is challenging.
- SPRINT demonstrated that, despite intensive input including monthly medication reviews, > 50% of those in the intensive treatment group failed to achieve the target systolic BP .
- Results in those with CKD suggest that it may be even more challenging to achieve BP goals than in the general hypertension population .
- Despite treatment with non-pharmacological interventions and multiple antihypertensive agents, the majority of CKD patients fail to reach target BP

Lifestyle Modification

1. Life style modification is the sheet anchor in the management Hypertension.
2. This surely reduces the number of drugs used and their dosage in controlling HTN.
3. Any drug treatment has value only when coupled with lifestyle meatures

Lifestyle Measures: KDIGO

- Weight:

  Achieve or maintain a normal weight (BMI 20-25 kg/m^2)

- Salt:

  < 2 g sodium (5 g salt) per day unless contraindicated

- Exercise:

  At least 30 minutes 5 times per week

- Alcohol:

  Limit to maximum of 2 standard drinks per day

- Smoking:

No direct effect on long-term BP but cessation reduces CV risk

Pharmacological Treatment

- direct BP-lowering effects,
- renoprotective action
- cardioprotective action

Renin–Angiotensin–Aldosterone System Blockade

- ACE inhibitors and angiotensin II receptor antagonists (blockers) (ARBs) have both cardioprotective and renoprotective properties and are therefore of particular value in patients with CKD .
- RAAS blockade can reduce systolic BP by ~ 20 mmHg in patients with hypertension and CKD
- these agents offer a BP-independent reduction in proteinuria in both diabetic and non-diabetic CKD and are therefore generally accepted as first-line management of hypertension in patients with proteinuric CKD

- In those with non-proteinuric CKD the superior renoprotective effect of RAAS blockade has recently been questioned.

RAAS Blockade

- although ACE inhibitors may be used as first-line agents in those with hypertension and non-proteinuric CKD, CCBs and thiazide or thiazide-like diuretics should also be considered as alternative first-line choices in this population
- ACEI: mainly renal excretion (except fosinopril, trandolapril), ARB mainly hepatic excretion
- Potential problems associated with RAAS blockade include hyperkalaemia and the development of AKI.

RAAS Blockade

- **Positive aspects**

  Improve Diastolic function, Systolic function
  Control Proteinuria, Very favorable in DM
  Improve Coronary Ischemia, Good on Lipids
  Reduce LVH, Morbidity & Mortality

- **Negative aspects**

  Bradykinin accumulation, Angio - edema
  ↑ Serum K , ↓ GFR

- **Don't use in**

  Pregnancy, ↑ K 5.0 meq/L
  Bilateral Renal Artery Stenosis, Angio - edema

Pharmacokinetic Properties of ACE inhibitors in ESRD

	T1/2(h) normal	T1/2(h) ESRD	Initial dose in HD	Maintenance dose in HD	Removal during HD
Captopril	2-3	20-30	12.5 q24h	25-50 q24h	Yes
Enalapril	11	prolonged	2.5 q24h or q48h	2.5-10 q24h or q48h	Yes
Fosinopril	12	prolonged	10 q24h	10-20 q24h	Yes
Lisinopril	13	54	2.5 q24h or q48h	2.5-10 q24h or q48h	Yes
Ramipril	11	prolonged	2.5-5q24h	2.5-10 q24h	yes

Pharmacokinetic Properties of ARB's in ESRD

	T1/2(h) normal	T1/2(h) ESRD	Initial dose in HD	Maintenance dose in HD	Removal during HD
Candesartan	9	?	4 q24h	8-32 q24h	No
Irbesartan	11-15	11-15	75-150 q24h	150-300 q24h	No
Losartan	2	4	50 q24h	50-100 q24h	No
Telmisartan	24	?	40 q24h	20-80 q24h	No
Valsartan	6	?	80 q24h	80-160 q24h	No

Diuretics

- Volume overload, often subclinical, affects up to 50% of people with CKD and is an independent risk factor for CVD .
- Diuretic therapy can reduce volume expansion and improve left ventricular mass index and arterial stiffness in those with CKD .
- Thus, diuretics are frequently used as part of combination drug therapy in CKD and offer antihypertensive and cardioprotective effect

- Treatment with a diuretic may also reverse the loss of physiological nocturnal dip in BP described in CKD
- Diuretics should generally be avoided in patients with polycystic kidney disease due to accelerated cyst growth and loss of excretory function associated with their use
- Mineralocorticoid receptor antagonists (blockers) (such as spironolactone) effectively reduce BP in CKD but run the risk of exacerbating hyperkalaemia
- The combination of a loop and thiazide diuretic is particularly powerful, and care should be taken to avoid fluid depletion.

- **Thiazide diuretics :e.g.Hydrochlorothiazide,Bendroflumethiazide**.
- **Thiazide-like diuretics**: e.g. Chlorthalidone, Indapamide.
- **Loop diuretics**: e.g. Furosemide, Torasemide, Bumetanide.
- Widely used as patients with CKD are characterised by sodium and water retention
- For antihypertensive therapy:
- GFR >50 mL/min: Thiazides alone or in combination with distal diuretics (e.g. spironolactone)
- GFR <30 mL/min: Loop diuretics. Avoid distal (potassium sparing) diuretics.

Diuretic

- **positve aspects**

  Fluid depletion, Na washout, Low cost
  Improve CHF, Systolic function, Ca saving
  Reduce LVH.

- **negative aspects**

  Potassium washout, ↑ in Uric acid, ↑ Ca
  Adverse on Lipids, Glucose control

- **Don't use in**

  Gout, Hypokalemia
  Dyslipidaemia, Uncontrolled DM

Calcium Channel Antagonists (Blockers)

- Both dihydropyridine and non-dihydropyridine CCBs are useful in the management of hypertension in CKD.
- Dihydropyridine CCBs (such as amlodipine) can be used as first-line therapy in non-proteinuric CKD, either alone or in combination.
- In proteinuric CKD their effect is inferior to RAAS blockade .
- ESC/ESH guidelines which advocate combination therapy with an ACE inhibitor and CCB as first-line therapy in proteinuric patients .
- Non-dihydropyridine CCBs (such as verapamil) have a superior effect on proteinuria reduction and are as effective as dihydropyridine CCBs in terms of BP control [84]
- Although generally well-tolerated, CCBs have the potential to worsen peripheral oedema, something that can be particularly troublesome for those with CKD .

- **Positive aspects**

  Vasodilatory, Suitable in elderly, Low cost

  Anti arrhythmic (Verapamil), ↑Coronary BF (Diltiazem) Neutral on lipidemia, Vasospastic Angina

- **Negative aspects**

  Fluid retention, Impair failing heart

  , Pedal edema .

- **Don't use in**

  Tachycardia, arrhythmias, CHF,

  Uncontrolled DM, Volume overload

Calcium Channel Blockers

	Class	Accumulate in renal failure	Increase CNI levels	Increase sirolimus levels
Amlodipine	D	N	Y	—
Diltiazem	B	N	Y	Y
Felodipine	D	N	—	—
Isradipine	D	N	—	—
Lercanidipine	D	N	—	—
Nicardipine	D	Y	Y	Y
Nifedipine	D	N	N	—
Nimodipine	—	Y	—	—
Nisoldipine	D	N	—	—
Verapamil	P	N	Y	Y

B, non-dihydropyridine benzothiazepine; CNI, calcineurin inhibitor; D, Dihydropyridine; N, No; P, phenylalkylamine; Y, Yes; —, no data.

β-Blockers

- β-Blockers effectively reduce BP in CKD due to their effect on the dysregulated sympathetic nervous system .
- The cardioprotective benefits of these drugs are well-established
- BB can be safely used in all degrees of renal impairment.
- Direct comparisons with ACE inhibitors have shown β-blockers to offer inferior renoprotection
- The AASK study did, however, demonstrate lower rates of ESRD and death in CKD patients treated with metoprolol versus amlodipine . β-Blockers should therefore be considered as useful additions in those with established RAAS blockade, particularly when overt CVD coexists.

B- blockers

- **Positive aspects**
  ↓Heart rate, ↓Force of contraction, ↓Conduction
  ↓Myocardial O2 demand, Improve Ischemia
  Useful in CHF, Migraine
- **Negative aspects**
  Constrict peripheral vessels, Bradycardia
  Unfavorable on Lipids, Glucose
- **Don't in**
  Bradycardia, Conduction defects, Caution in CHF
  Prinzmetal Angina, PVD, BA, COPD,
  Pheochromocytoma, Chronic smokers

Pharmacologic Properties of B-blockers in Chronic Dialysis Patients

	T1/2(h) normal	T1/2(h) ESRD	Initial dose in HD	Maintenance dose in HD	Removal during HD
Acebutolol	3.5	3.5	200 q24h	200-300 q24h	yes
Atenolol	6-9	<120	25 q48h	25-50 q48h	Yes
Carvedilol	4-7	4-7	5 q24h	5 q24h	no
Metoprolol	3-4	3-4	50 b.i.d.	50-100 b.i.d.	high
Propranolol	2-4	2-4	40 b.i.d.	40-80 b.i.d.	yes

α-Blockers

- Peripherally acting α-blockers (such as doxazosin) are commonly used as part of combination therapy for the management of hypertension in CKD.
- This may be due to a pharmacokinetic profile that is undisturbed by declining eGFR in addition to favourable effects on glycaemic control .
- α-Blockers should not, however, be considered for first-line therapy, as they are less effective than other agents for reducing the incidence of CVD

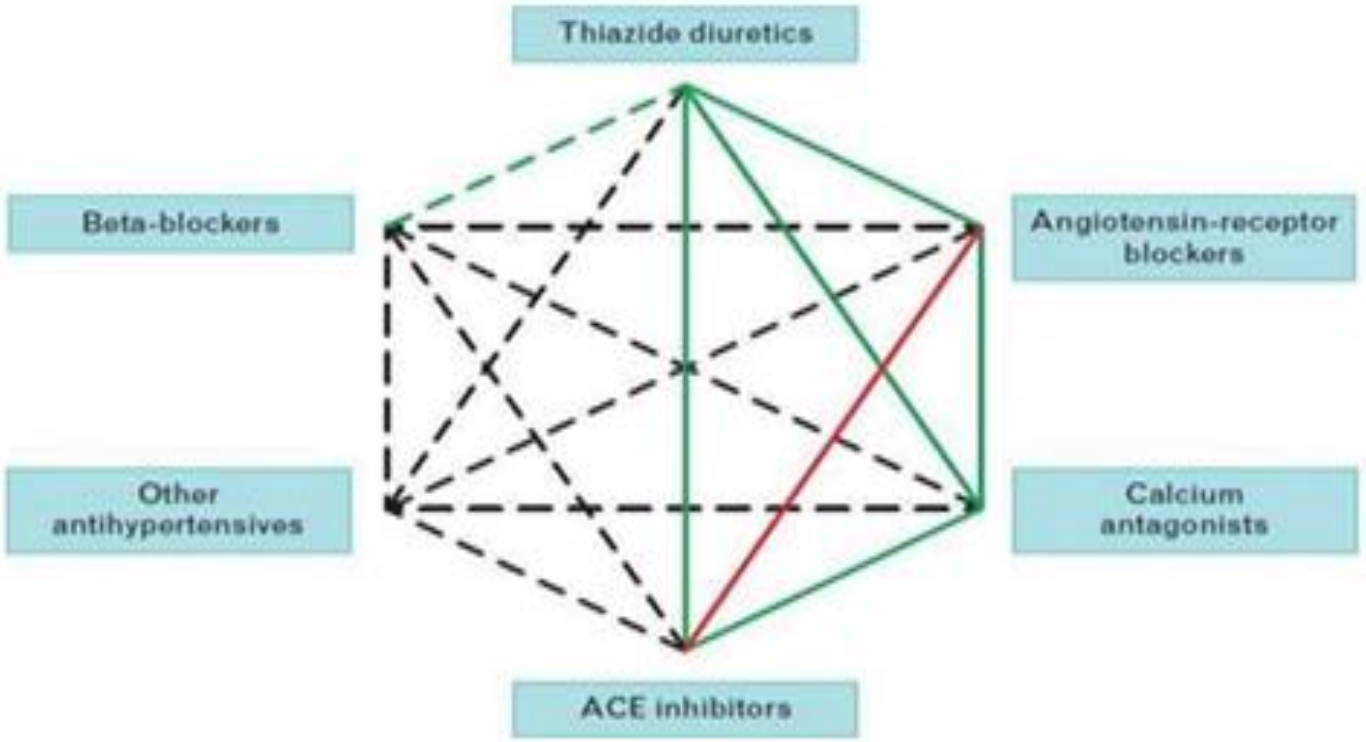
Chronotherapy

- As the diurnal variation of BP can be influenced by timing of antihypertensive medications, it has been hypothesised that evening dosing could reverse the non-dipping nocturnal BP seen in CKD. Chronotherapy would therefore seem to be one of the more straightforward methods of achieving improved outcomes for those with hypertension and CKD.

Adherence

Despite the risks of CKD progressing to ESRD and patients requiring dialysis and/or transplantation, adherence to therapy is no better in those with CKD than in those without . Antihypertensive regimens should therefore be simplified wherever possible, with consideration given to the quantity, timing and formulation of interventions. Continuity of care may also have an impact and, where possible, attempts should be made to allow patients to see the same clinician at each visit, something that has been demonstrated to improve outcomes

Often Combination Therapy will be Required



Keys point

- Controlling hypertension in those with CKD not only slows progression of renal damage but reduce the risk of CVD
- Achieving BP control in CKD may be difficult, often requiring a combination of antihyptensive medication as well as life style modification .
- One size does not fit all


Thank You.