

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined by a reduction in the glomerular filtration rate (GFR) and/or urinary abnormalities or structural abnormalities of the renal tract. The severity of CKD is classified from 1 to 5 depending upon the level of glomerular filtration rate (GFR).

Classification of chronic kidney disease:

This classification from National Kidney Foundation's Kidney Dialysis Outcomes & Quality Initiative is based on GFR and also accounts for structural evidence of kidney damage:

Stages of CKD	Glomerular filtration rate	Description
1	≥ 90 mL/min + proteinuria/haematuria or structural damage	Kidney damage with normal or increased GFR but other evidence of kidney damage
2	60–89 mL/min + proteinuria/haematuria or structural damage	Slight decrease in GFR with other evidence of kidney disease
3	30-59 mL/min	Moderate reduction in GFR With or without evidence of other kidney disease
4	13–29 mL/min	Severe reduction in GFR
5	<15 mL/min	Kidney failure, use suffix (D) if dialysis

Measurement of Renal function:

The scale of chronic kidney disease has only been recognized in recent years because detection is dependent upon an accurate estimation of the GFR. The GFR is defined as the volume of filtrate produced by the glomeruli of both kidneys each minute and is a reliable indicator of renal function.

➤ **Measurement using inulin:**

It is laborious and expensive to measure GFR by gold standard tests such as inulin or radiolabelled isotope clearance. These tests are only used when extremely accurate assessment of kidney function is required.

As a consequence, a number of equations have been validated for use in the routine clinical setting. These equations provide an estimate of glomerular filtration rate (eGFR) based on the combination of serum or plasma creatinine and a number of variables which add precision to the estimation of kidney function.

➤ **Measurement using Creatinine:**

- Is a by-product of normal muscle metabolism,
- Formed at rate proportional to muscle mass(20 gm muscle mass= 1 mg creatinine),
- Freely filtered by glomerulus, nearly all filtered creatinine appears in urine,
- Creatinine undergo significant tubular secretion which limits the value of measuring serum creatinine in advanced CKD (stage 4 & 5).

Measurement of Creatinine Clearance (CLcr):

- Requires accurate collection of 24 hour urine samples with a serum creatinine sample midway through this period.

$$CL_{Cr} = \frac{U \times V}{S}$$

U = urine creatinine concentration

V = urine flow rate

S = serum creatinine concentration

Cockcroft-Gault equation:

$$CL_{Cr} = \frac{F [140 \times \text{age in years}] \times \text{weight in Kg}}{S}$$

Serum creatinine ($\mu\text{mol/L}$)

F = 1.04 in case of females

= 1.23 in case of males

The commonest eGFR equation used in clinical practice is the four-variable **MDRD** (Modification of Diet in Renal Disease Study) equation:

$$\text{GFR} = 186 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{age})^{-0.203}$$

($\times 0.742$ for females)
($\times 1.210$ for blacks)

ETIOLOGY

SUSCEPTIBILITY FACTORS:

Susceptibility factors to Chronic kidney disease are advanced age, low income or education, and racial/ethnic minority status, as well as reduced kidney mass, low birth weight, and family history of Chronic kidney disease.

INITIATION FACTORS:

Initiation factors are conditions that directly result in kidney damage, and are modifiable by pharmacologic therapy.

1. **Diabetes Mellitus:** Individuals with type 1 diabetes mellitus have a 40% lifetime risk of developing chronic kidney disease of any stage, whereas individuals with type 2 diabetes mellitus have a 50% lifetime risk. Although not all individuals with diabetic nephropathy progress to stage 5 chronic kidney disease, the lifetime risk is considerable.

2. **Hypertension:** Hypertension also increases the risk of CKD prospective studies have shown that elevated blood pressure increases the risk for the development of CKD among subjects without initial kidney disease. Hypertension generally develops concomitantly with progressive kidney disease. For example, hypertension is present in 40% of individuals with a GFR of 90 mL/ min per 1.73 m²; in 55% of those with a GFR of 60 mL/min per 1.73 m²; and 75% of individuals with a GFR of 30 mL/min per 1.73 m.
3. **Glomerulonephritis:** Glomerular diseases are also considered initiation factors of CKD. Some conditions, such as Goodpasture's disease or Wegener's granulomatosis, may progress rapidly to stage 5 CKD.

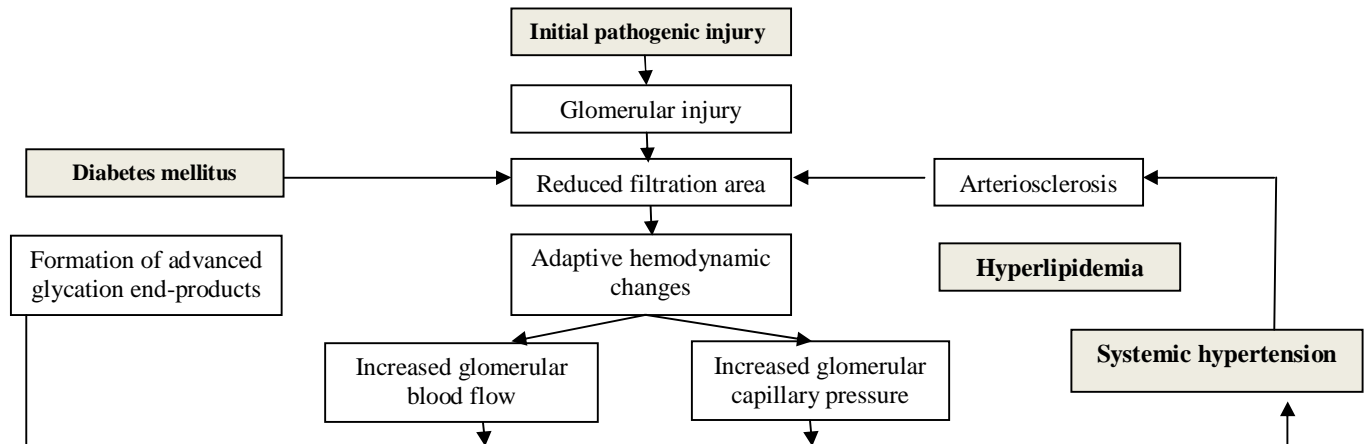
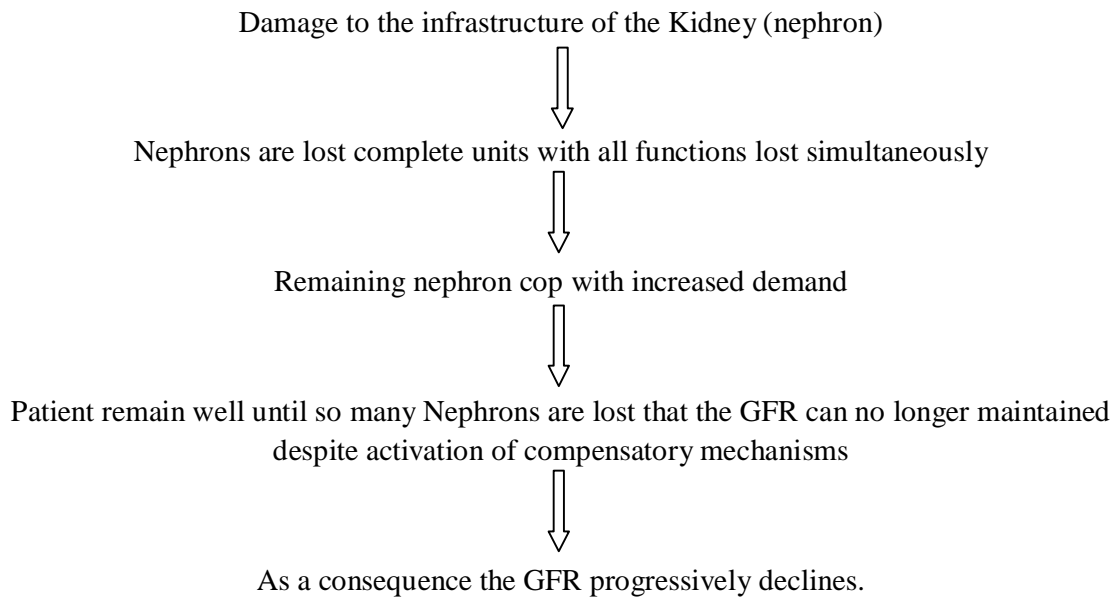
PROGRESSION FACTORS:

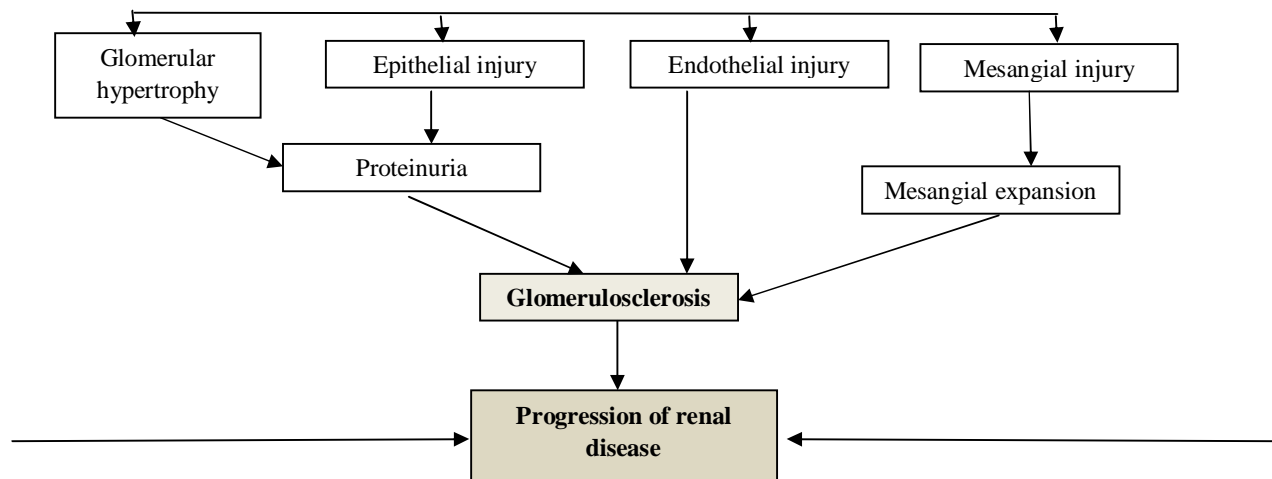
Progression risk factors are those associated with further kidney damage. This is generally evident as an increase in the rate of decline in kidney function in those who already have damaged kidneys.

1. **Proteinuria:** In diabetic kidney disease (types 1 and 2), an albumin excretion rate higher than 30 mg per 24 hours (micro albuminuria) strongly predicted the development of overt nephropathy (proteinuria) and subsequent loss of kidney function.
2. **Hypertension:** The early treatment of hypertension and the achievement of aggressive target values has been demonstrated to slow the rate of progression of CKD.
3. **Diabetes Mellitus:** Hyperglycemia is an initiation and progression risk factor for CKD. The presence of diabetes mellitus leads to diabetic nephropathy in CKD patients.
4. **Smoking:** Recent studies suggest that smoking may promote initiation and progression of CKD in subjects with type 1 and type 2 diabetes. Smoking has also been identified as a risk factor for progression in patients with IgA nephropathy, polycystic kidney disease, and systemic lupus erythematosus.

5. **Hyperlipidemia:** The prevalence of hyperlipidemia appears to increase as kidney function declines and hyperlipidemia is a characteristic of the nephrotic syndrome.
6. **Obesity:** Recent studies show an association of obesity with development of stage 5 CKD. A recent population-based study showed that a BMI ≥ 25 kg/m² at age 20 years is associated with a threefold increase in risk of CKD compared to a BMI lower than 25 kg/m².

PATHOPHYSIOLOGY





Proposed mechanisms for progression of renal disease

CLINICAL PRESENTATION

CKD development and progression is insidious. Patients with stage 1 or 2 CKD usually do not have symptoms or metabolic derangements seen with stages 3 to 5, such as anemia, secondary hyperparathyroidism, cardiovascular disease, malnutrition, and fluid and electrolyte abnormalities that are more common as kidney function deteriorates.

- **Uremic symptoms** (fatigue, weakness, shortness of breath, mental confusion, nausea, vomiting, bleeding, and anorexia) are generally absent in stages 1 and 2, minimal during stages 3 and 4, and common in patients with stage 5 CKD who may also experience itching, cold intolerance, weight gain, and peripheral neuropathies.
- **Polyuria and nocturia:** Polyuria, where the patient frequently voids high volumes of urine, is often seen in CKD and results from medullary damage and the osmotic effect of a high serum urea level.
- **Proteinuria:** A degree of proteinuria is common in CKD and the prevalence of proteinuria increases with the severity of CKD.
- **Haematuria:** Haematuria can be either macroscopic or microscopic; macroscopic haematuria is likely to result from lower urinary tract pathology (such as bladder lesions) and microscopic haematuria is most often of glomerular origin.

- **Hypertension and fluid overload:** Severe renal impairment leads to sodium retention, which in turn produces circulatory volume expansion with consequent hypertension.
- **Anemia:** Anaemia is a common consequence of CKD and affects most people with CKD stages 4 and 5. The principal cause results from damage of peritubular cells leading to inadequate secretion of erythropoietin
- **Bone disease (renal osteodystrophy):** Renal osteodystrophy describes the four types of bone disease associated with CKD:
 - Secondary hyperparathyroidism
 - Osteomalacia (reduced mineralisation)
 - Mixed renal osteodystrophy (both hyperparathyroidism and osteomalacia)
 - Adynamic bone disease (reduced bone formation and resorption).

TREATMENT: PROGRESSION-MODIFYING THERAPIES

DESIRED OUTCOME:

- Reverse or arrest the process causing renal damage (this may not be possible).
- Avoid conditions that might worsen renal failure.
- Treat secondary complications.
- Relieve symptoms

NONPHARMACOLOGICAL TREATMENT:

Dietary Protein Restriction: Patients with a GFR of less than 25 mL/min , a protein intake of 0.6 g/kg per day was significantly associated with a decreased rate of progressive renal disease.

Sodium restriction: Sodium intake can be reduced to a satisfactory level of 80 mmol/day by avoiding convenience foods and snacks or the addition of salt to food at the table.

Potassium restriction: Avoiding potassium-rich foods such as fruit and fruit drinks, vegetables, chocolate, beer, instant coffee and ice cream.

Many medicines have high potassium content, for example, potassium citrate mixture, some antibiotics and ispaghula husk sachets

PHARMACOLOGICAL TREATMENT:

Intensive insulin therapy (Diabetic Chronic Kidney Disease):

IIT was achieved by administration of three or more times daily insulin injections or by insulin pump infusion so as to attain pre-prandial and postprandial blood glucose levels of 70 to 120 mg/dL and <180 mg/dL, respectively.

Hypertension Control:

The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a goal blood pressure of <130/80 mm Hg for patients with CKD. To achieve adequate blood pressure goals, three or more different blood pressure medications are usually required.

1. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB):

The current evidence base supports the principle that all diabetic patients with micro/macroalbuminuria and CKD should be treated with ACE inhibitors or ARBs regardless of blood pressure.

ACEI clearance is reduced in CKD, therefore treatment should begin with the lowest possible dose followed by gradual titration to achieve target blood pressure.

ACE Inhibitors:

Mechanism of Action: Several mechanisms participate in the renal protection afforded by ACE inhibitors. Increased glomerular capillary pressure induces glomerular injury, and ACE inhibitors reduce this parameter both by decreasing arterial blood pressure and by dilating renal efferent arterioles. ACE inhibitors increase the permeability selectivity of the filtering membrane, thereby diminishing exposure of the mesangium to proteinaceous factors that may stimulate mesangial cell proliferation and matrix production, two processes that contribute to expansion of the mesangium in diabetic nephropathy.

Captopril: Captopril is a potent ACE inhibitor ($K_i \approx 1.7$ nM). Given orally, captopril is absorbed rapidly and has a bioavailability of $\approx 75\%$. Peak concentrations in plasma occur within an hour, and the drug is cleared with a $t_{1/2}$ of ≈ 2 hours. The oral dose 25 mg three times a day. Since food reduces the oral bioavailability of captopril by 25–30%, the drug should be given 1 hour before meals.

Enalapril: Enalapril maleate is a prodrug that is hydrolyzed by esterases in the liver to produce the active dicarboxylic acid, enalaprilat. Enalaprilat is a highly potent inhibitor of ACE. The oral dosage of enalapril is 10 mg once daily. Enalapril is absorbed rapidly when given orally and has an oral bioavailability of about 60% (not reduced by food). Enalapril has a $t_{1/2}$ of 1.3 hours; enalaprilat, because of tight binding to ACE, has a plasma $t_{1/2}$ of ≈ 11 hours.

Other: Lisinopril 10 mg once daily, Ramipril 10 mg once daily.

Adverse effects of ACE inhibitors:

Serious untoward reactions to ACE inhibitors are rare, and they generally are well tolerated. Most commonly encountered adverse effects are:

- Cough In 5–20% of patients, ACE inhibitors induce a dry cough,

- Acute Renal Failure By constricting the efferent arteriole
- Hypotension A steep fall in blood pressure may occur following the first dose of an ACE inhibitor
- Fetopathic Potential Administration of ACE inhibitors during the second and third trimesters can cause oligohydramnios, fetal calvarial hypoplasia, fetal pulmonary hypoplasia, fetal growth retardation, fetal death, neonatal anuria, and neonatal death.
- Angioedema In 0.1– 0.5% of patients, ACE inhibitors induce a rapid swelling in the nose, throat, mouth, glottis, larynx, lips, and/or tongue.
- Skin Rash

Angiotensin Receptor Blockers:

ARBs are renoprotective in type 2 diabetes mellitus and many experts now consider them the drugs of choice for renoprotection in diabetic patients. ARBs are superior to β_1 adrenergic receptor antagonists in reducing stroke in hypertensive patients with left ventricular hypertrophy.

Losartan: Approximately 14% of an oral dose of losartan is converted to the 5-carboxylic acid metabolite EXP 3174, which is more potent than losartan. Peak plasma levels of losartan and EXP 3174 occur \square 1–3 hours after oral administration, respectively, and the plasma half-lives are 2.5 and 6–9 hours, respectively. The plasma clearance of losartan and EXP 3174 is affected by hepatic but not renal insufficiency. Losartan should be administered orally 50 mg once daily.

Others: Telmisartan 40–80 mg once daily, Candesartan, once or twice daily for a total daily dosage of 4–32 mg.

ADVERSE EFFECTS: Unlike ACE inhibitors, ARBs do not cause cough, and the incidence of angioedema with ARBs is much less than with ACE inhibitors. ARBs have teratogenic potential and should be discontinued before the second trimester of pregnancy.

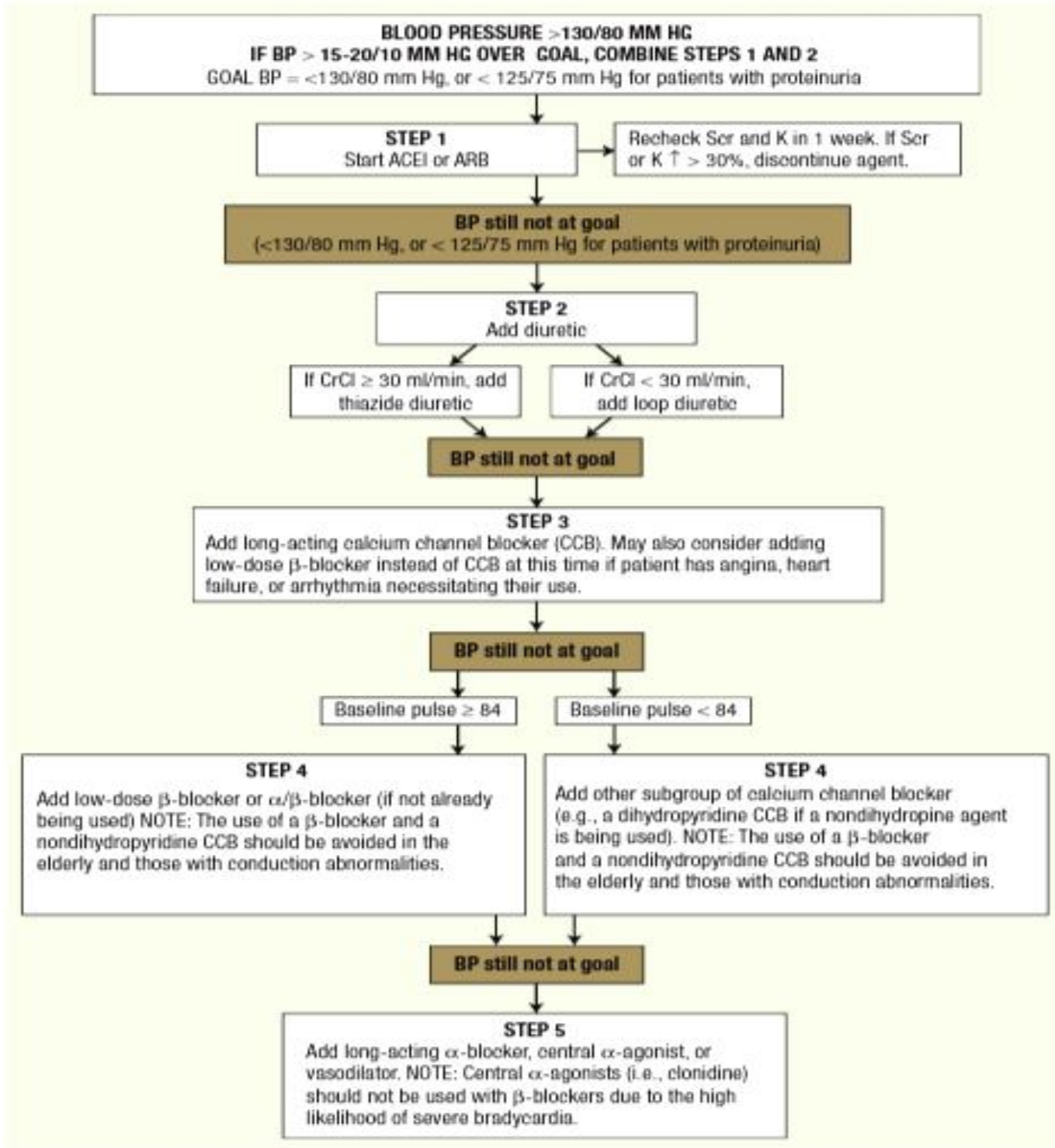
2. Diuretics:

Diuretics are of use in patients with salt and volume overload, usually indicated by the presence of oedema. The choice of agent is generally limited to a loop diuretic.

Furosemide: It is active even in patients with relatively severe renal failure. The major site of action is the thick AscLH (site II) where furosemide inhibits Na^{+} - K^{+} - 2Cl^{-} cotransport. Furosemide is rapidly absorbed orally but bioavailability is about 60%. Lipid-solubility is low, and it is highly bound to plasma proteins. mainly excreted unchanged by glomerular filtration as well as tubular secretion. Plasma $t_{1/2}$ averages 1–2 hour but is prolonged in patients with pulmonary edema, renal and hepatic insufficiency. Dose Usually 20–80 mg once daily in the morning. In renal insufficiency, upto 200 mg 6 hourly has been given by i.m./i.v. route.

3. β -Blockers:

- β -blockers have a particular role in the rational therapy of hypertension without fluid overload.
- β -blockers can reduce cardiac output, It is advisable to use the more cardioselective β -blockers atenolol or metoprolol.



Hypertension management algorithm for patients with chronic kidney disease

ANEMIA OF CKD:

- The normochromic, normocytic anaemia of CKD does not respond to iron or folic acid unless there is a coexisting deficiency. Erythropoiesis Stimulating Agents (ESAs) e.g. epoetin alfa and beta are used.
- Subcutaneous (SC) administration of epoetin alfa is preferred because IV access is not required, and the SC dose that maintains target indices is 15% to 50% lower than the IV dose.
- Darbepoetin alfa is a recombinant hyperglycosylated analogue of epoetin having terminal half-life in man is three times longer than that of epoetin. The starting dose is 0.45 mcg/kg IV or SC administered once weekly
- Iron supplementation is necessary to replete iron stores. Parenteral iron therapy improves response to erythropoietic therapy and reduces the dose required to achieve and maintain target indices. In contrast, oral therapy is often inadequate.

SECONDARY HYPERPARATHYROIDISM AND RENAL OSTEODYSTROPHY:

In CKD, starting in stage 3, vitamin D deficiency, low calcium, and elevated phosphate can all contribute to secondary hyperparathyroidism. The general goal of therapy is to suppress PTH toward normal while maintaining normal serum calcium and phosphate. This can be addressed in three steps:

- A. Repletion of vitamin D stores (25-OH vitamin D),
 - B. Control of dietary phosphate with binders and
 - C. Administration of active vitamin D (1,25-dihydroxyvitamin D or an analog).
- **Deficient stores (25-OH vitamin D, 30 ng/mL)** should be corrected with oral ergocalciferol 50,000 IU capsule weekly or every other week, or cholecalciferol 2,000 to 4,000 IU daily. The duration of treatment depends on severity of the deficiency, with levels, 5 ng/dL warranting at least 12 weeks of treatment. Once at goal, maintenance therapy can rely on either monthly ergocalciferol 50,000 IU or daily cholecalciferol 1,000 to 2,000 IU.

- **Phosphate control** can be difficult as GFR declines, even with appropriate dietary restriction. Phosphate binders inhibit gastrointestinal absorption. Calcium-based binders are effective when given with meals, as calcium carbonate (200 mg of elemental calcium per 500 mg tablet) or calcium acetate (169 mg of elemental calcium per 667 mg tablet). In general, the total daily elemental calcium administered should be ,1,500 mg. Lanthanum carbonate and sevelamer carbonate are non–calcium-based alternatives.
- **Active vitamin D (1,25-dihydroxyvitamin D)** and its synthetic analogs are potent suppressors of PTH, and can be administered if serum PTH remains elevated. Options include daily calcitriol (0.25 to 1 mcg), paricalcitol (1 to 5 mcg), or doxercalciferol (1 to 5 mcg). Calcium levels need to be monitored regularly and doses adjusted to avoid hypercalcemia.
- **Cinacalcet** is a calcimimetic that acts on the parathyroid gland to suppress PTH release. It should be used only in dialysis patients, and usually in conjunction with active vitamin D, as it may induce significant hypocalcemia and is relatively ineffective as monotherapy.

Metabolic acidosis:

As renal function deteriorates, the kidney is unable to appropriately excrete sufficient acid resulting in metabolic acidosis (mixed high and normal anion gap). To compensate, alkaline buffer is released from the skeleton but can ultimately worsen bone mineral disease.

- Treatment with **sodium bicarbonate** 650 to 1,300 mg thrice daily can help maintain the serum bicarbonate level at 22 mEq/L. Such therapy, however, can increase the sodium load and contribute to edema or hypertension.

Preparation for renal replacement therapy:

Patients should be counseled at an early stage to determine preferences for renal replacement therapies, including hemodialysis, peritoneal dialysis (PD), and eligibility for renal transplantation.

In stage 4 CKD, preparation for the creation of a permanent vascular access for hemodialysis should be initiated by protecting the nondominant forearm from intravenous catheters and blood draws. Timely referral for vein mapping and to an access surgeon can facilitate the creation and maturation of an arteriovenous (AV) access.