2019 VA/DoD Clinical Practice Guideline

Chronic Kidney Disease (CKD) Algorithms & Medication Management

Pharmacologic Management of CKD and Associated Conditions

Topic	Medication	Information
Diabetes	Metformin	First-line therapy for type 2 diabetes in stage 1 to 3 CKD to reduce all-cause mortality. *Dose adjustment if eGFR 30-45. Contraindicated if eGFR <30.*
	Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Option for add-on therapy for type 2 diabetes in stage 1 to 3 CKD to reduce CKD progression and the risk of cardiovascular events. *Contraindicated if eGFR <30.*
	Liraglutide or dulaglutide [glucagon-like peptide-1 (GLP-1) receptor agonists]	Option for add-on therapy for type 2 diabetes in patients with CKD to reduce CKD progression.

Pharmacologic Management of CKD and Associated Conditions

Topic	Medication	Information
Diabetes (continued)	Thiazolidine-diones (TZD) or Dipeptidyl peptidase-4 (DPP-4) inhibitors	Insufficient evidence to recommend for or against TZD or DPP-4 inhibitors in CKD and type 2 diabetes.
Hypertension	Suggest intensive blood pressure management (insufficient evidence to recommend a specific target) beyond a target of less than 140/90 mmHg to reduce mortality in patients with eGFR below 60 mL/minute/1.73 m^2.	
	Angiotensin-converting enzyme inhibitors (ACEI) or Angiotensin II receptor blockers (ARB)	Recommend ACEI to prevent CKD progression in patients with non-diabetic CKD, hypertension, and albuminuria. ARBs may be substituted for patients with an ACEI-induced cough.
		Recommend ACEIs or ARBs to slow CKD progression in patients with diabetes, hypertension, and albuminuria, unless there is documented intolerance.
		Recommend against combination renin-angiotensin-aldosterone system blockade (ACEIs with ARBs or ACEIs or ARBs with a direct renin inhibitor) in CKD.

Pharmacologic Management of CKD and Associated Conditions

Topic	Medication	Information
Contrast-Associated Kidney Injury (CA-AKI)	Isotonic Saline	Recommend volume expansion with intravenous isotonic saline prior to and following iodinated contrast administration for patients at increased risk for CA-AKI.
	N-acetylcysteine (NAC)	Recommend against NAC for prevention of CA-AKI.
	Recommend against renal replacement therapy for CA-AKI prophylaxis.	
Anemia	Oral iron	Suggest oral iron to support iron requirements in patients with CKD.
	Erythropoiesis-stimulating agents (ESA)	Recommend against ESAs in patients with CKD for the purpose of achieving a hemoglobin target above 11.5 g/dL due to increased risk of stroke and hypertension.
		Recommend against initiating ESAs at a hemoglobin greater than 10 g/dL.
Bone Health	Vitamin D analogs	Suggest against active Vitamin D analogs (e.g., calcitriol, paricalcitol) for hyperparathyroidism in stage 3 and 4 CKD.
	Calcimimetics	Suggest against calcimimetics for hyperparathyroidism in stage 3 and 4 CKD.
	Phosphate Binders	Insufficient evidence to recommend for or against phosphate binders to reduce mortality, CKD progression, or major cardiovascular outcomes in stage 2 to 5 CKD.
Other Medications to Slow CKD Progression	Sodium Bicarbonate	Suggest sodium bicarbonate supplementation in CKD patients with metabolic acidosis to slow CKD progression.
	Urate-lowering Therapy (ULT)	Insufficient evidence to recommend for or against ULT in patients with CKD and asymptomatic hyperuricemia for slowing progression of CKD.
	Tolvaptan	In patients at risk for rapidly progressing autosomal dominant polycystic kidney disease, suggest Tolvaptan, in consultation with nephrologist, to slow decline in eGFR.

Nephrotoxic Medications

Medication	Many commonly used medications may be nephrotoxic to patients with CKD to include:
Analgesics	NSAIDs (e.g., Aspirin, Celcoxib, Ibuprofen, Naproxen), Aspirin (high doses)
Antimicrobials	Acyclovir, Adefovir, Aminoglycosides, Amphotericin B, Beta-Lactamase Inhibitors, Cephalosporins, Cidofovir, Foscarnet, Ganciclovir, Penicillins, Pentamidine, Quinolones, Rifampin, Sulfonamides, Vancomycin
Antiretrovirals	Atazanavir, Indinavir, Tenofovir
Bisphosphonates	Pamidronate, Zoledronic Acid
Calcineurin inhibitors (CNI)	Cyclosporine, Tacrolimus
Chemotherapeutic agents	Alkylating Agents, Cisplatin, Methotrexate, Mitomycin, Interferon-Alpha, Proteasome Inhibitors, Vascular Endothelial Growth Factor (VEGF) Inhibitors, Checkpoint Inhibitors
Contrast dye	See Algorithm Module D
Diuretics	Loop Diuretics (e.g., Bumetanide, Ethacrynic acid, Furosemide, Torsemide), Triamterene
Proton pump inhibitors (PPI)	Dexlansoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole
Others	Allopurinol, Gold Sodium Thiomalate, Lithium, Quinine, Sodium Phosphate
Herbal products	Aristolochic Acid, Cats Claw, Licorice Root

Nephrotoxicity may result from various mechanisms and result in different manifestations. Drugs may alter intraglomerular hemodynamics, induce inflammation (glomerulonephritis or interstitial nephritis), or form crystals, which would manifest as renal dysfunction, hematuria or proteinuria. In addition, drugs may cause rhabdomyolysis and thrombotic microangiopathy, which may also cause renal injury. Direct tubular injury more commonly presents with electrolyte abnormalities, including Fanconi-like syndrome. Finally, some medications may induce or exacerbate hypertension. General recommendations include avoiding use of nephrotoxic medications or use of non-nephrotoxic alternatives whenever possible, adjusting medication dose based on kidney function, ensuring adequate hydration, and close monitoring of the patient for evidence of nephrotoxicity when high-risk medications are used.

*Information obtained from the 2019 VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease, Appendix K: Parts B Nephrotoxic Agents and Part C Medication Dose Adjustments in CKD (pg.132).

Medication Dose Adjustments in CKD

Dose adjustments are most often based on the patient's SCr, CrCl, or eGFR. The extent of dose reduction typically depends on the level of kidney function, and some medications may be contraindicated in those with severe renal dysfunction. The table below includes a select list of commonly used medications that may require dose adjustment based on kidney function or that warrant caution in patients with CKD. Information obtained from the 2019 VA/DoD CPG for the Management of Chronic Kidney Disease, App. K: Part C, Medication dose adjustments in CKD (pg.133).

	Medications
Antibiotics and antiviral agents	All antibiotics and antiviral agents with the exception of: macrolides, clindamycin, ceftriaxone, and metronidazole
CV agents	• Atenolol • Sotalol • Digoxin • Dofetilid Thiazide diuretics: Chlorthalidone, Hydrochlorothiazide, Indapamide • Potassium-sparing diuretics • Renin-angiotensin-aldosterone system (RAAS) blockers: ACEIs, ARBs, Aliskiren, Eplerenone, Spironolactone
Anticoagulants	• Direct oral anticoagulant (DOAC): Apixaban, Dabigatran, Edoxaban, Rivaroxaban • Low molecular weight heparins
Antilipemics	• Statins: fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin • Fibric acid derivatives: fenofibrate and gemfibrozil
Analgesics	• Codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol • NSAIDs, Cyclooxygenase-2 (COX-2) inhibitors (Appendix L)
Hypoglycemic agents	• Insulin, metformin, exenatide • Sulfonylureas: glyburide, glipizide, glimepiride, chlorpropamide • Alpha-glucosidase inhibitors: acarbose, miglitol • Meglitinides: nateglinide, repaglinide • DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin • SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
Gastrointestinal agents	• Histamine 2 blockers (H2) antagonists: cimetidine, famotidine, ranitidine • PPI: dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Antidepressants	Bupropion, citalopram, escitalopram, duloxetine, mirtazapine, paroxetine, venlafaxine
Agents for gout	Allopurinol, febuxostat, colchicine
Bisphosphonates	Alendronate, etidronate, ibandronate, pamidronate, risedronate, zoledronic acid
Antipsychotic or antimanic agents	Lithium, paliperidone, risperidone , brexpiprazole, cariprazine, clozapine, lurasidone, pimavanserin
Anticonvulsants	Gabapentin, pregabalin, levetiracetam, topiramate
Anti-cancer therapies	Cytotoxic drugs, targeted agents, biologics
Phosphodiesterase Type-5 (PDE-5) inhibitors	Sildenafil, tadalafil
Dementia medications	Memantine, galantamine

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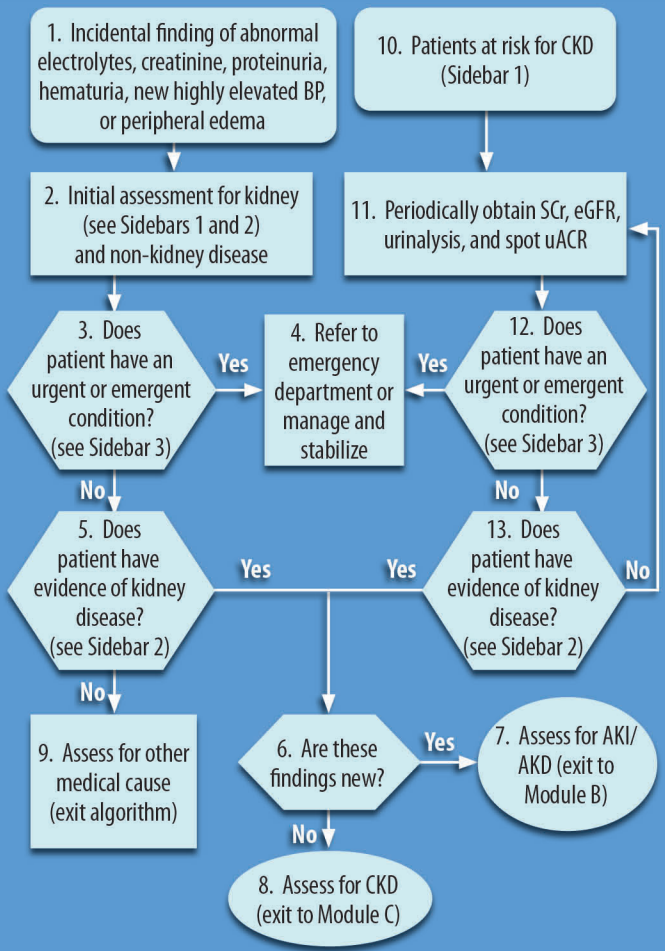
Chronic Kidney Disease (CKD) Algorithms & Medication Tables

Module A: Screening for CKD and Initial Assessment



Access to the full 2019 guideline and additional resources are available at https://www.healthquality.va.gov/guidelines/CD/CKD/

Sidebar 1: At-Risk Population

- DM, hypertension, cardiac disease/congestive heart failure, or vascular disease
- Systemic illness (e.g., HIV, systemic lupus erythematosus, multiple myeloma)
- Urinary tract abnormalities
- History of AKI, proteinuria, or other known kidney disease
- Family history of kidney disease (e.g., ADPKD)
- Patients age 60 and above
- Ethnicities associated with increased risk (e.g., African Americans, Hispanics, Native Americans)

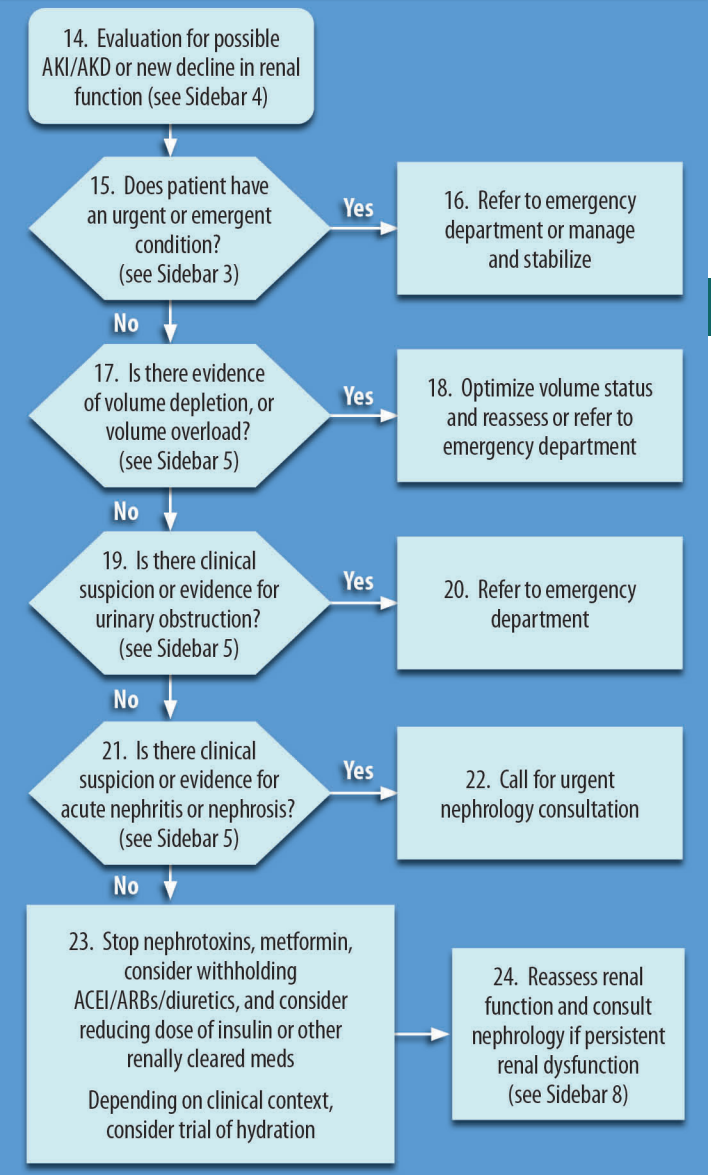
Sidebar 2: Assessment for Kidney Disease

- History:
  - Symptoms of volume depletion (lightheadedness, dizziness) or overload (pedal edema, dyspnea)
  - Cause of volume depletion (diarrhea, vomiting, decreased oral intake, heat exposure)
  - Medications and supplements (NSAIDs, diuretics, BP med changes)
  - Recent illnesses/infections (upper respiratory infection, osteomyelitis)
  - Urinary changes (hematuria, obstruction)
  - Rheumatologic symptoms
- Physical: vital signs, peripheral edema, volume status
- Labs: assess for abnormal labs (e.g., electrolytes, creatinine, hematuria, microalbuminuria/proteinuria) and lab trends then repeat labs (as clinically appropriate)

Sidebar 3: Urgent/Emergent Conditions

- Clinical signs:
  - Unstable vital signs
  - Decompensated heart failure/symptomatic volume overload
  - Signs or symptoms of uremia
  - Anuria
- Abnormal labs:
  - Significantly abnormal potassium (<2.5 mEq/L or ≥6 mEq/L)
  - Acute unexplained decline in kidney function
  - Severe acid-base disturbance

Module B: Evaluation for AKI or New Decline in Renal Function



Sidebar 4: Definition of AKI and AKD

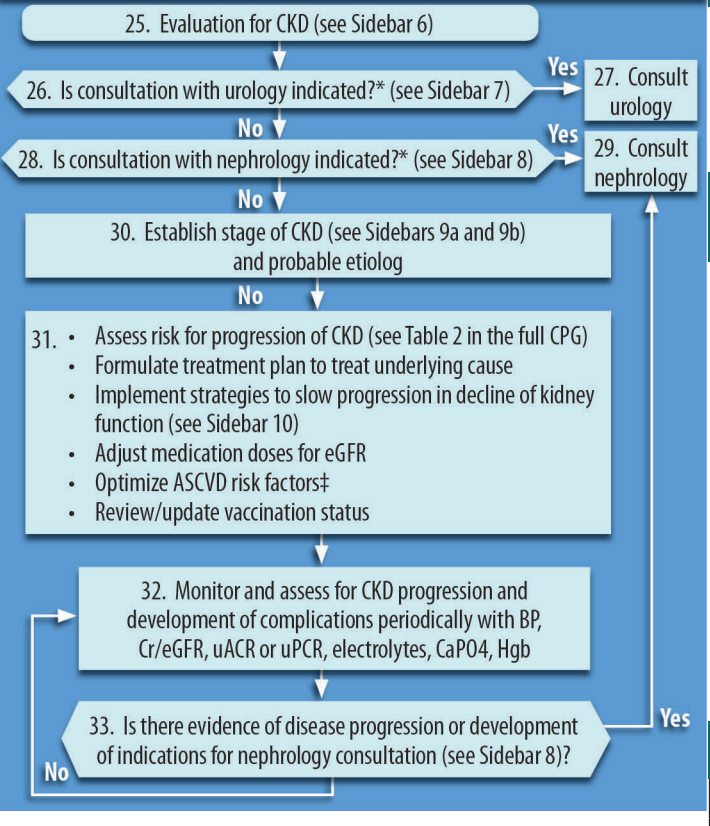
- Definition of AKI (presence of any of the following):
  - Increase in SCr of >0.3 mg/dL over not more than 48 hrs
  - Increase in SCr of >50% as compared to baseline, presumed to have occurred over not more than 7 days
  - Urine output of <0.5 mL/kg/hr over 6 hrs
- Definition of AKD (presence of any of the following):
  - GFR <60 mL/min/1.73 m for <3 months
  - Decrease in GFR by >35% or increase in SCr by >50% for <3 months
  - Kidney damage (structural) for <3 months

Sidebar 5: Assessment for AKD

- For volume depletion:
  - Lightheadedness or dizziness
  - Hypotension
  - Orthostasis
- For volume overload:
  - Shortness of breath
  - Rales
  - Edema
  - Jugular vein distension
- For urinary obstruction:
  - Symptoms of voiding dysfunction
  - Flank pain or hematuria
  - Elevated post-void bladder volume
  - Evidence of obstruction on kidney imaging (e.g., hydronephrosis)
- For suspicion of acute nephritis or nephrosis (hematuria, dysmorphic RBCs or RBC casts, new onset proteinuria) with:
  - Recent illness (e.g., infection)
  - Constitutional or rheumatologic symptoms
  - Rash
  - Edema
  - Hemoptysis

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ADPKD: auto- somal dominant polycystic kidney disease; AKD: acute kidney disorder; AKI: acute kidney injury; ARB: angiotensin receptor blocker; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; Ca: calcium; CKD: chronic kidney disease; CPG: clinical practice guideline; dL: deciliter; DM: diabetes mellitus; DoD: Department of Defense; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; hr: hour; HTN: hypertension; kg: kilogram; L: liter; m: meter; mEq: milliequivalent; mg: milligram; min: minute; mL: milliliter; NSAID: non-steroidal anti-inflammatory drug; PO4: phosphate; RBC: red blood cell; SCr: serum creatinine; SGLT2: sodium-glucose transport protein 2; STEMI: ST-segment elevation myocardial infarction; uACR: urine albumin-to-creatinine ratio; uPCR: urine protein-to-creatinine ratio; VA: Department of Veterans Affairs

Module C: Evaluation for CKD



*Referral should be made following shared decision making with patient that ensures the referral focus is consistent with the patient values and preferences
‡As appropriate, refer to the following VA/DoD Clinical Practice Guidelines: Chronic Heart Failure, Diabetes, Hypertension, Dyslipidemia, Overweight and Obesity, and Tobacco Cessation

Sidebar 6: Criteria for CKD

Sustained abnormality for ≥3 months of either:

- eGFR <60 mL/min/1.73 m^2

<u>or</u> any of the following:

- Albuminuria (uACR >30) or proteinuria (uPCR >0.2)
- Hematuria or abnormal urinalysis/microscopy
- Solitary or horseshoe kidney
- History of abnormal renal histology
- History of renal transplantation

Sidebar 7: Indications for Urology Consultation

- Isolated or gross hematuria
- Renal masses or complex renal cysts
- Symptomatic or obstructing nephrolithiasis
- Hydronephrosis or bladder abnormalities
- Urinary symptoms (e.g., nocturia, hesitancy, urgency, incontinence)

Sidebar 8: Potential Indications for Nephrology Consultation*

- eGFR <30 ml/min/1.73 m^2
- Rapid decline of eGFR (>5 mL/min/1.73 m2 per year)
- Non-diabetics with heavy proteinuria (24 hr urine protein >500 mg, uPCR >0.5, UACR >300)
- Diabetics with >3 g proteinuri (UPCR >3) or hematuria
- Unclear cause of CKD, hematuria, or proteinuria
- Complications of CKD (e.g., anemia, acidosis, hyperphosphatemia, hyperparathyroidism)
- ADPKD
- Renal transplant
- Metabolic management (prevention) of kidney stone disease
- Electrolyte abnormalities (e.g. hyperkalemia, hyponatremia)
- Patient's level of disease exceeds the comfort level of the primary care provider

Sidebar 9a: Stage of CKD* – GFR Categories

Stage	eGFR (mL/min/1.73 m^2)	Description
G1	≥90	Kidney damage with normal or in-creased eGFR
G2	60 – 89	Kidney damage with mildly de-creased eGFR
G3a	45 – 59	Mildly to moderately decreased eGFR
G3b	30 – 44	Moderately to severely decreased eGFR
G4	15 – 29	Severely decreased eGFR

Sidebar 9b: Stage of CKD* – Albuminuria Categories

A1	<30	Normal to mildly increased
A2	30 – <300	Moderately increased
A3	≥300	Severely increased

*Consider one-time cystatin C measurement to confirm CKD diagnosis and stage (see Recommendation 3 in the full CPG)

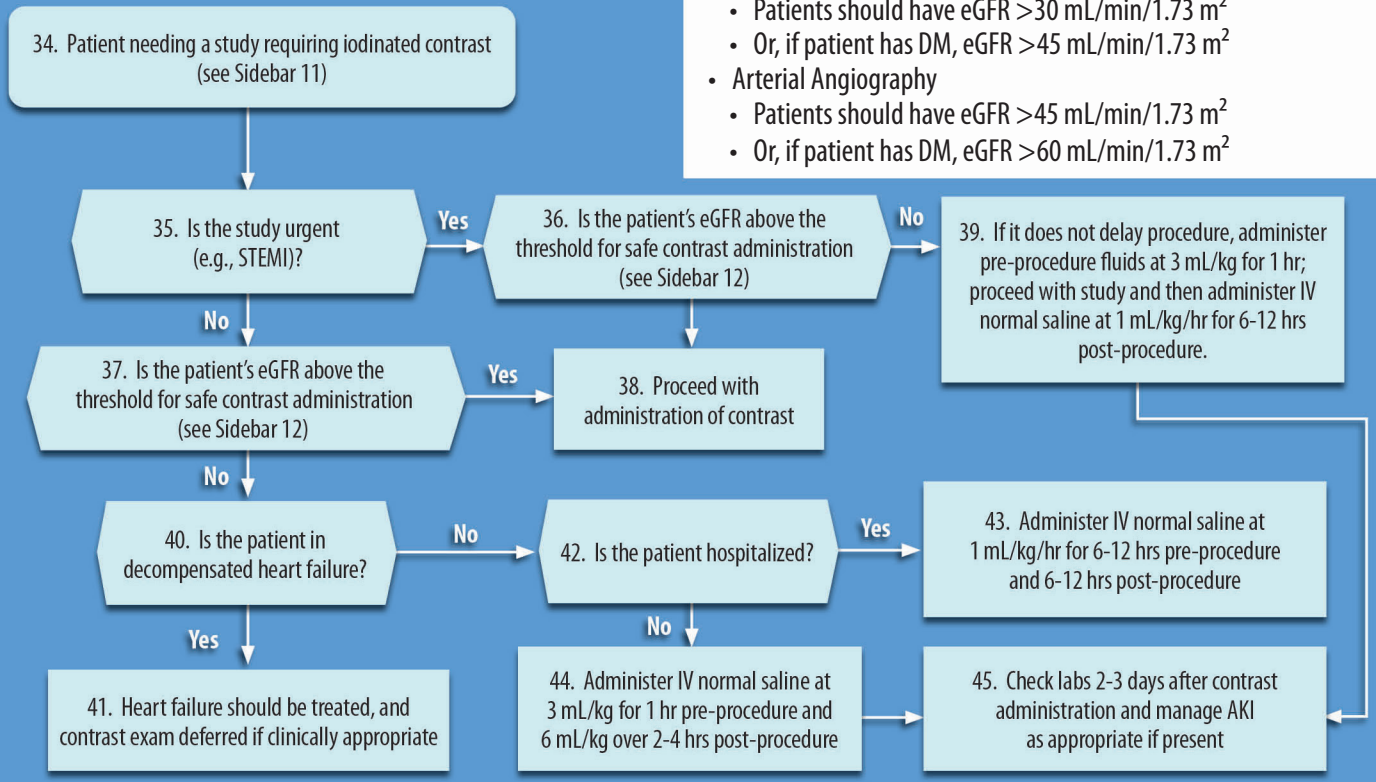
Sidebar 10: Strategies to Slow Progression of CKD

- Control of hypertension with preferential use of either ACEI or ARB in patients with albuminuria/proteinuria
- Individualized control of DM
- Use of SGLT2 inhibitors in patients with type 2 DM and an eGFR > 30 mL/min/1.73 m^2
- Eliminate/avoid nephrotoxic agents whenever possible (e.g., NSAIDs, iodinated contrast)
- Refer to dietitian for medical nutrition therapy (e.g., protein intake, sodium restriction, weight loss)

Sidebar 11: Considerations for When Studies Requiring Iodinated Contrast are Indicated

- Consider non-contrast studies as alternative
- Use minimum amount of contrast necessary for appropriate testing
- Consider holding metformin due to risk of lactic acidosis (see Recommendation 16 discussion section in the full CPG)
- Assess for risk factors for CA-AKI:
  - Decreased kidney function
  - DM
  - Proteinuria
  - Heart failure
  - Volume depletion
  - Para-proteinemia

Module D: Management of Patients with CKD Requiring Iodinated Contrast



Sidebar 12: eGFR Cutoffs for Contrast

- Venous Contrast:
  - Patients should have eGFR >30 mL/min/1.73 m^2
  - Or, if patient has DM, eGFR >45 mL/min/1.73 m^2
- Arterial Angiography
  - Patients should have eGFR >45 mL/min/1.73 m^2
  - Or, if patient has DM, eGFR >60 mL/min/1.73 m^2