

CARDIOVASCULAR DRUGS IN CHRONIC KIDNEY DISEASE

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Introduction

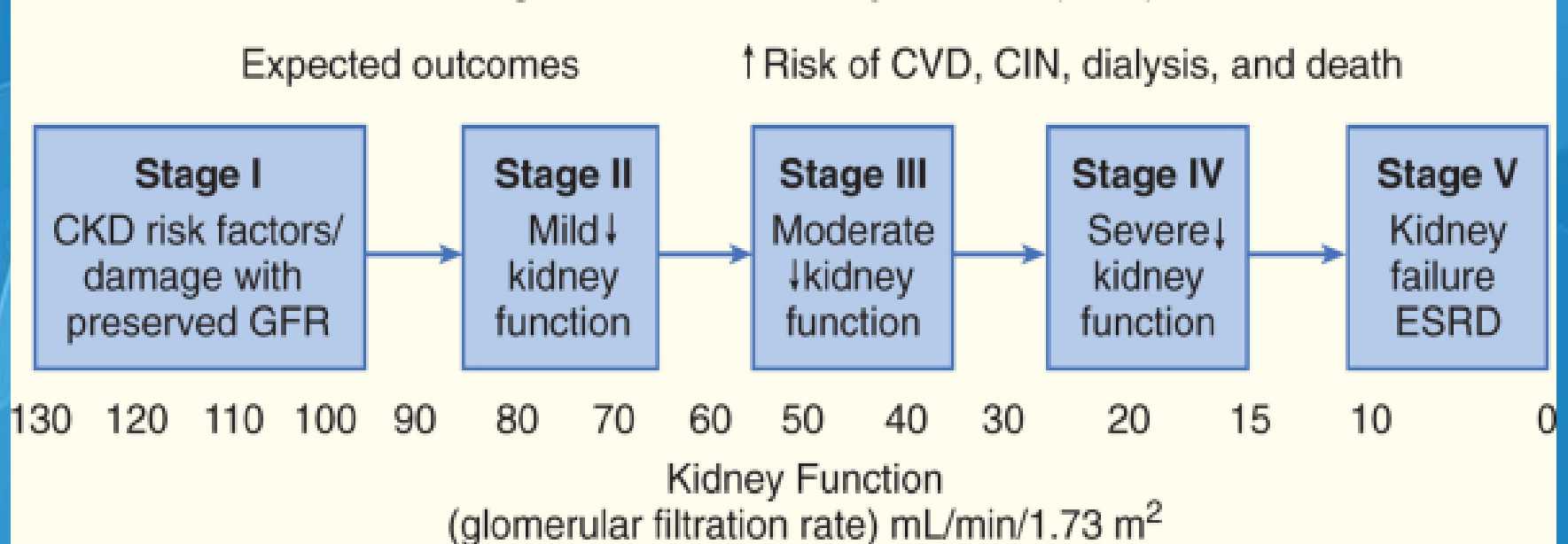
- ▣ Cardiovascular disease is a common comorbidity and a major cause of mortality in patients with chronic renal disease
- ▣ Drug regimens in patients with cardiovascular disease are frequently complex and can be significantly affected by alterations in renal function
- ▣ Several cardiovascular drugs directly affect renal function and the management of patients with renal disease

Diagnostic criteria for chronic kidney disease

1. Kidney damage for ≥ 3 months, as defined by structural and functional abnormalities of the kidney, with or without decreased GFR, manifest by either:
 - Pathological abnormalities; or
 - Markers of kidney damage, including abnormalities in the composition of the blood and urine, or abnormalities in imaging tests
2. eGFR < 60 ml/min/1.73m² for ≥ 3 months, with or without kidney damage

Diagnostic criteria for chronic kidney disease

Stages of Chronic Kidney Disease (CKD)



Impact of renal dysfunction on the pharmacokinetics of cardiovascular drugs

□ Distribution

Potential causes for V_d alterations in renal dysfunction patients

- # Changes in plasma protein concentrations which bind drugs
- # Accumulation of endogenous byproducts that compete for protein binding of drugs
- # Alterations in the binding characteristics caused by specific changes in the protein binding site

Impact of renal dysfunction on the pharmacokinetics of cardiovascular drugs

□ Distribution

Examples:

Renal dysfunction produces significant reduction in the Vd of digoxin

Produces an increase in the Vd of furosemide

Decreased Vd is clinically significant and require a reduction in loading dose of 30% to 50%

Impact of renal dysfunction on the pharmacokinetics of cardiovascular drugs

□ Metabolism

- # Renal tissue has approximately one-third of the enzyme activity of the liver and these enzymes can be impaired in experimental renal failure
- # Although these clearance alterations in renal insufficiency are statistically significant they do not appear clinically important

Impact of renal dysfunction on the pharmacokinetics of cardiovascular drugs

□ Excretion

➤ Route of excretion

Renal

Others: bile duct, lung, sweat, faeces

➤ Elimination half life ($t_{1/2}$): Time to decrease plasma level 50% of former level

Impact of renal dysfunction on the pharmacokinetics of cardiovascular drugs

□ Excretion

- Depending on the solubility, ionization, and protein binding of the compound
- Although most cardiovascular drugs are primarily eliminated via hepatic metabolism, many exhibit a large degree of renal clearance and are significantly affected by renal dysfunction

Dosing adjustments for cardiovascular drugs in dialysis

□ Pharmacokinetics

Protein binding

- # Any drug bound to plasma proteins cannot be filtered because of the size of the drug-protein complex
- # Drugs having a low degree of protein binding (<30%) would be more likely to have clinically significant removal by extracorporeal methods

Dosing adjustments for cardiovascular drugs in dialysis

□ Pharmacokinetics

Vd

- # Directly correlated with the amount of drug that is bound to tissue
- # Dialysis would significantly alter the clearance of drugs that have a small Vd and would have little effect on a drug with a large Vd

Dosing adjustments for cardiovascular drugs in dialysis

□ Pharmacokinetics

Drug molecular weight

- Conventional hemodialysis membrane: only allow the passage of drugs with a molecular weight of less than 500D
- High-flux membrane: can remove drugs in the molecular weight range of up to 5000 to 20000D
- The majority of cardiovascular drugs have a molecular weight less than 500D and therefore particle size is not a limiting factor
- digoxin: 780D. Because of its large volume of distribution, digoxin is not removed to a significant degree by dialysis with either conventional or high flux membranes

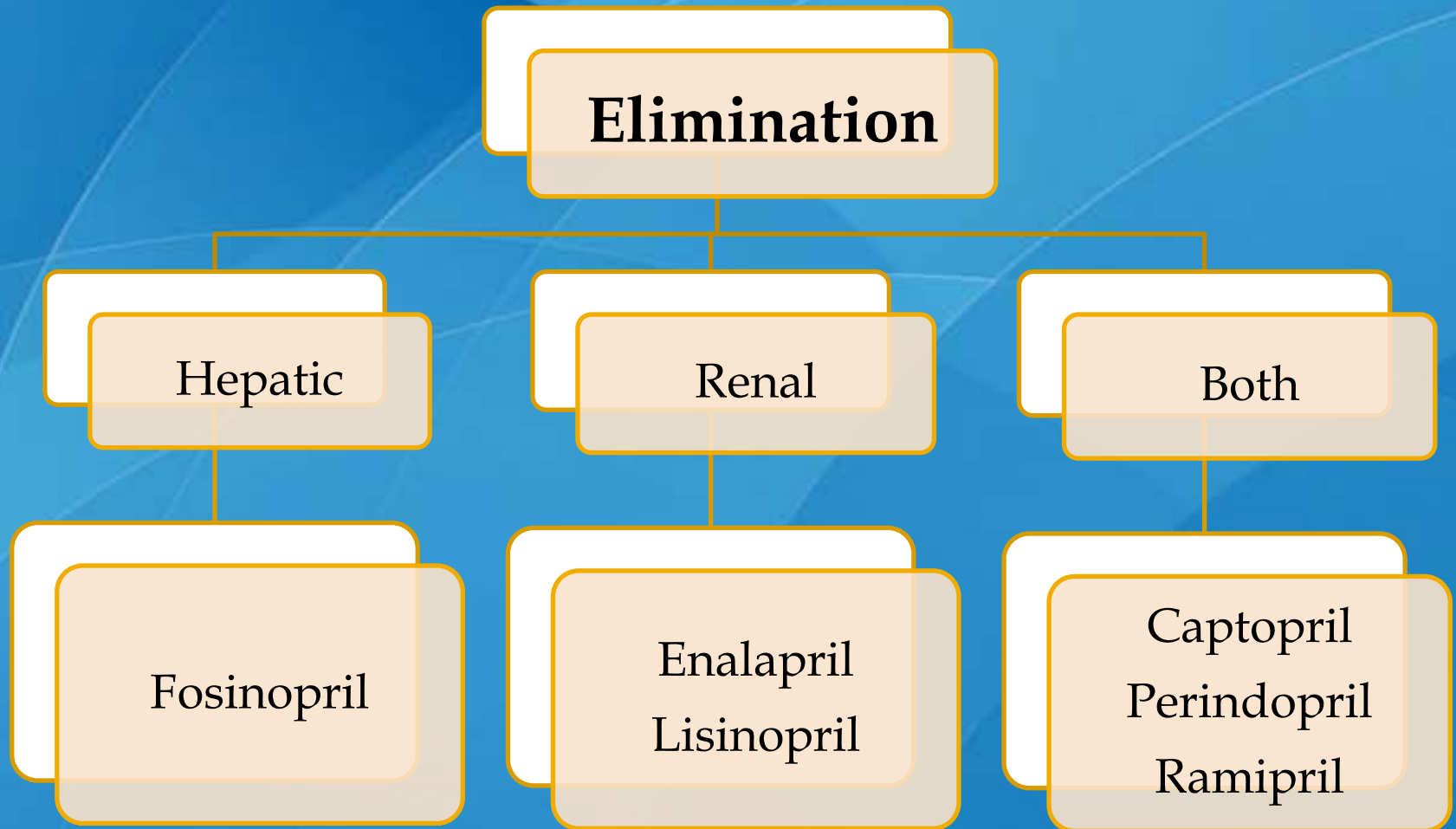
ACE inhibitors

- ▣ ACE inhibitors and ARBs are considered first-line therapy for hypertension, congestive heart failure, diabetes or chronic kidney disease
- ▣ Safe in patients with chronic kidney disease and reduced renal function
- ▣ Should be initiated at low doses and titrated upwards slowly with close monitoring of renal function and serum potassium.

ACE inhibitors

- ▣ To prevent hyperkalemia, potassium-sparing diuretics, potassium supplements and non-steroidal anti-inflammatory drugs should be used with caution in patients with reduced renal function who are treated with ACE inhibitors or ARBs
- ▣ Blockade of the renin-angiotensin system causes dilatation of the afferent arteriole supplying blood to the glomerulus, leading to a reduction in pressure within the glomerulus and thus lowering the GFR
- ▣ An initial rise in serum creatinine is associated with clinical response to treatment with ACE inhibitors or ARBs, and an increase in serum creatinine by as much as 30% should be acceptable in the first 2 months of therapy in closely monitored patients

ACE inhibitors



Captopril (Capoten)

Dose for normal renal function: 25-50 mg every 8h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	75%	50%

Supplement dose after hemodialysis: Yes

Enalapril (Enalapril)

Dose for normal renal function: 5-20 mg every 12-24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	50-100%	25%

Supplement dose after hemodialysis: Yes

Lisinopril (Zestril)

Dose for normal renal function: 5-20 mg every 24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	50-75%	25-50%

Supplement dose after hemodialysis: Yes

Perindopril (Coversyl)

Dose for normal renal function: 2-8 mg every 24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
2mg q24h	2mg q24-48h	2mg q48h

Supplement dose after hemodialysis: Yes

Ramipril (Tritace)

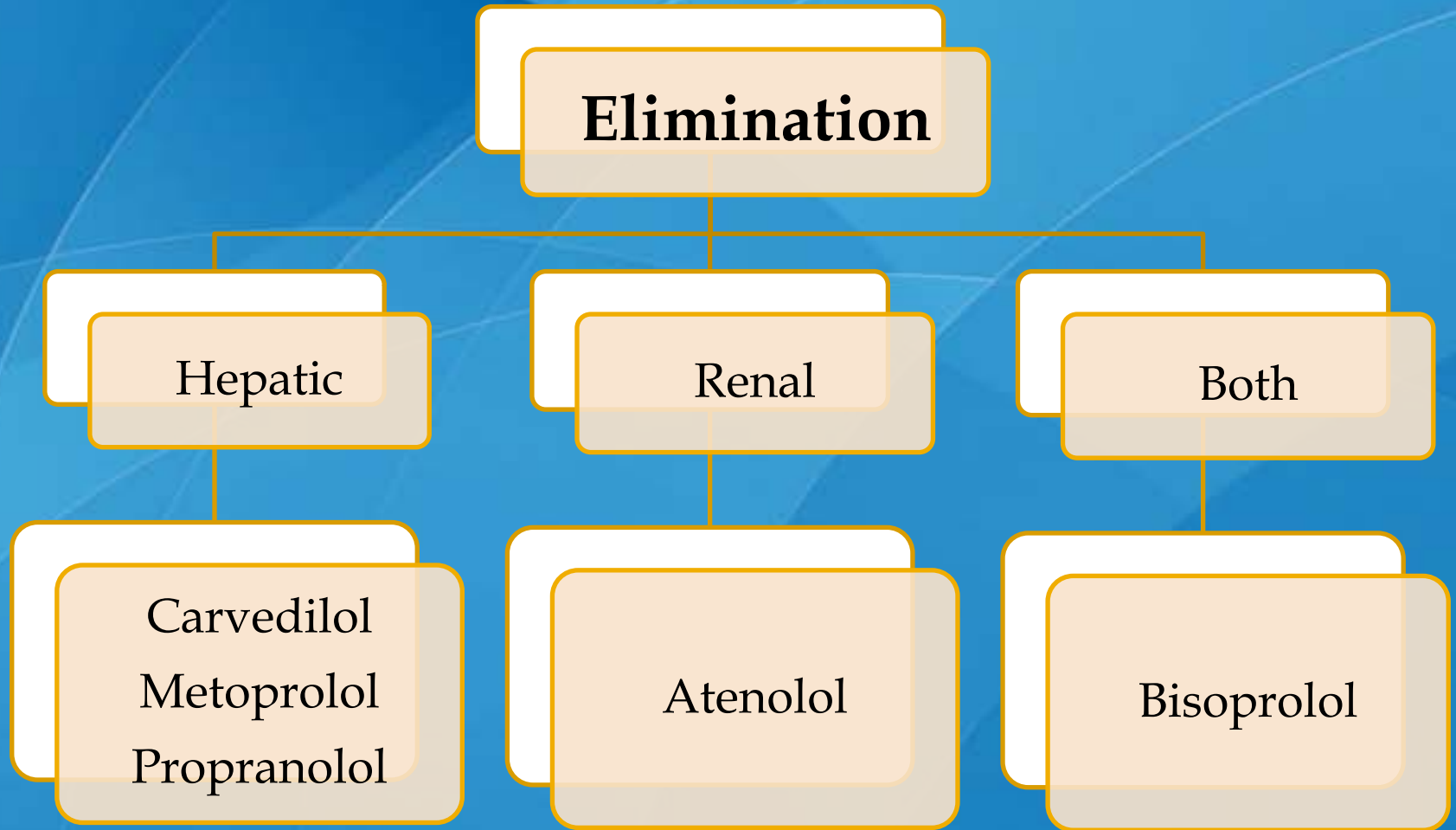
Dose for normal renal function: 2.5-10 mg every 24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	25-50%	25%

Supplement dose after hemodialysis: Yes

Being eliminated BY hepatic
metabolism, **FOSINOPRIL** is the
ONLY ACEI that DOES NOT NEED
DOSE ADJUSTMENT

Beta blockers



Beta blockers

No need of dose adjustment in:

- ▣ Carvedilol (Dilaterolol) 3.125-25 mg q12-24h
- ▣ Metoprolol (Betaloc) 50-400 mg q24h
- ▣ Propranolol (Inderal) 80-160 mg q6-12h

Atenolol (Tenormin)

Dose for normal renal function: 50-200 mg every 24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	50%	25%

Supplement dose after hemodialysis: Yes

Bisoprolol (Concor)

Dose for normal renal function: 2.5-20 mg every 24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	50%	25%

Supplement dose after hemodialysis: No

Diuretics

Therapeutic options in patients with renal dysfunction

- Crcl < 30 ml/min, thiazides will fail to provide effective diuresis
- Loop diuretics
 - # Retain some efficacy even at low Ccr
 - # Increase renal blood flow and solute excretion in ARF
 - # Initiated at conventional doses and then increased until a desirable effect is established

Diuretics

Diuretic resistance

- The effectiveness of loop diuretics will decrease as renal function declines because of the reduced ability of the diuretic to reach its site of pharmacologic activity
- Results in the need to administer larger than normal doses in order to produce an acceptable diuresis
- May require the use of combination therapy

Diuretics

Diuretic resistance

- Additive and/or synergistic diuretic activity has been shown between *loop diuretics* and *metolazone* and *furosemide* and *hydrochlorothiazide*
- When doses in the range of 400 to 600mg per day of furosemide(or equivalent doses of other loop diuretics) addition of metolazone 5 to 20 mg per day or hydrochlorothiazide 25 to 200mg per day

Diuretics

No need of dose adjustment in:

Loop diuretics

- ▣ Bumetanide (Burinex): 0.5-2 mg q24h
- ▣ Furosemide (Lasix): 20-500 mg q12-24h
- ▣ Toresmide (Examide): 10-20 mg q24h

Thiazides

- ▣ Hydrochlorothiazide (Hydratic): 6.25-200 mg q24h
- ▣ Indapamide (Natrlix SR): 2.5mg q24h
- ▣ Metolazone (Metenix): 5-20 mg q24h (No dose adjustment is needed)

Diuretics

Despite no dose adjustment is required in renal impairment, Hydrochlorothiazide and indapamide are ineffective when $GFR < 10\text{ml}/\text{min}$

Digitalis glycosides

Toxicity of digoxin in patients with renal dysfunction:

- Therapeutic range of digoxin is narrow
- Serum levels should be followed closely in patients with renal dysfunction

Digitalis glycosides

Toxicity of digoxin in patients with renal dysfunction:

- Hypokalemia and hypomagnesemia both increase the risk of digoxin cardiac toxicity
- Hyperkalemia increases the risk of AV nodal blockade with digoxin
- Digoxin toxicity has been associated with refractory hyperkalemia in patients with renal failure through inhibition of the Na-K ATPase pump

Digitalis glycosides

Toxicity of digoxin in patients with renal dysfunction:

- Despite withdrawal of the drug, patients with chronic renal failure are at prolonged risk of adverse events
- In patients with renal failure experiencing life-threatening digoxin toxicity, administration of digoxin specific antibody fragments(Fab) is indicated

Digoxin (Lanoxin)

- ▣ 75-85% excreted unchanged
- ▣ $t_{1/2}$: 36-44 h
- ▣ Plasma protein binding: 20-30%
- ▣ V_d : 5-8 L/kg

Digoxin (Lanoxin)

Dose for normal renal function: 0.25 mg every 24h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	25-75% q 36h	10-25% q 48h

Supplement dose after hemodialysis: No

Antiplatelets

- ▣ Commonly prescribed oral antiplatelet agents used in the management of coronary artery and cerebrovascular disease do not require specific dose adjustment for renal function
- ▣ All antiplatelet therapies have a degree of bleeding risk associated with them, and this feature should be closely monitored in elderly patients with severe renal impairment and resultant platelet dysfunction

Aspirin

- ▣ It appears that the cardiovascular benefits of low-dose aspirin therapy far outweigh the renal hazards
- ▣ Therefore, No good reason for changing the current practice of recommending low-dose aspirin to patients at risk for cardiovascular disease.

Aspirin

Dose for normal renal function: 650 mg/kg q4h
Excretion: hepatic and renal

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	4-6h	avoid

Antiplatelets

- ▣ Despite their documented efficacy in patients with reduced renal function, both eptifibatide and tirofiban are renally excreted and have been associated with increased bleeding in patients with renal insufficiency
- ▣ Abciximab is eliminated by platelet binding, and has not been associated with an increased relative risk of bleeding in patients with reduced renal function

Tirofiban (Aggrastat)

Dose for normal renal function: 0.4 mcg/kg/min for 30 min then 0.1 mcg/kg/min

Excretion: renal

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	50% if GFR <30	50%

Enoxaparin (Clexane)

- ▣ $t_{1/2}$: 2-10h
- ▣ Plasma protein binding: no data
- ▣ V_d : 0.06-0.13 L/kg

Enoxaparin (Clexane)

Dose for normal renal function: 1 mg/kg q12h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	No adjustment	50%

Supplement dose after hemodialysis: No

Fondaparinux (Arixtra)

Dose for normal renal function: 2.5 mg q24h
 $t_{1/2} = 17$ h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	Avoid if GFR less than 30 ml/min	Avoid

Supplement dose after hemodialysis: No

Statins

- ▣ Emphasis is increasing on aggressive lipid-lowering therapies in patients with known coronary artery disease or a coronary-artery-disease equivalent
- ▣ Statin therapy might also delay the progression of chronic kidney disease making this therapy an attractive option in patients with proteinuria or decreased renal function
- ▣ The recommended titration schedules are more conservative in patients with severely decreased renal function, but statins can be used safely in closely monitored patients

Statins

- ❑ If adjunctive therapy is necessary to reach target lipid levels, more intensive monitoring is recommended because of the synergistic risk of hepatotoxic effects and rhabdomyolysis
- ❑ The combination of a statin and fibrate must be used with caution in elderly patients with a GFR lower than 60 ml/min/ 1.73 m²
- ❑ Nevertheless, in patients with decreased renal function, the recommended fibrate is gemfibrozil, which does not require dose adjustment for renal function
- ❑ Doses of nicotinic acid should be reduced in elderly patients with decreased renal function

Statins

- ▣ Statins (except for Pravastatin and Simvastatin 50% dose reduction when GFR < 50ml/min) DON'T NEED DOSE ADJUSTMENT

Antiarrhythmic drugs

1. Class I:

Ia: Quinidine, Disopyramide, Procainamide

Ib: Lidocaine, Mexiletine

Ic: Propafenone, Flecainide

2. Class II: Beta blockers

3. Class III: Amiodarone, Sotalol

4. Class IV: CCB

Quinidine

- ▣ 20% excreted unchanged
- ▣ $t_{1/2}$: 4-8 h
- ▣ Plasma protein binding: 80-90%
- ▣ V_d : 1.5-4.0 L/kg

Quinidine

Dose for normal renal function: 300-600 mg q8-12h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	No adjustment	75%

Supplement dose after hemodialysis: Yes

Disopyramide

- ▣ 35-65% excreted unchanged
- ▣ $t_{1/2}$: 5-8 h
- ▣ Plasma protein binding: 50-80%
- ▣ Vd: 0.8-2.6 L/kg
- ▣ Excretion: renal and hepatic

Disopyramide

Dose for normal renal function: 100-200 mg q6h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	q 12-24h	q 24-48h

Supplement dose after hemodialysis: No

Sotalol (Betacor)

- ▣ 80-90% excreted unchanged
- ▣ $t_{1/2}$: 10-20h
- ▣ Plasma protein binding: <1%
- ▣ Vd: 1.2-2.4 L/kg

Sotalol (Betacor)

Dose for normal renal function: 80-160 mg q12h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	q 24-48h	q 48-72h

Supplement dose after hemodialysis: no

Hydralazine (Aprosoline)

Dose for normal renal function: 25-50 mg tid

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	No adjustment	q8-16h

Supplement dose after hemodialysis: yes

Nitroprusside (Nepride)

Dose for normal renal function: 0.25-10.0 g/kg/min

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	No adjustment	Avoid

Supplement dose after hemodialysis: Avoid

Alpha methyl dopa(Aldomet)

Dose for normal renal function: 250-500 mg q8h

> 50 ml/min (GFR)	10-50 ml/min (GFR)	< 10 ml/min (GFR)
No adjustment	q8-12h	q12-24h

Supplement dose after hemodialysis: yes

INOTROPES

- ▣ Dobutamine is metabolized peripherally
- ▣ Milrinone are renally excreted and should be started at the lowest recommended dose in patients with reduced renal function
- ▣ Dopamine and norepinephrine are metabolized peripherally

Cardiovascular drugs with no dose adjustment in renal impairment

- ▣ Nitrates
 - ▣ Calcium channels blockers
 - ▣ Loop diuretics
 - ▣ Thiazide diuretics
 - ▣ Dobutamine
 - ▣ Adenosine
 - ▣ Class Ib: lidocaine, mexiletine
 - ▣ Class Ic: Propafenone
 - ▣ Amiodarone
 - ▣ Thrombolytics
 - ▣ UFH
 - ▣ Warfarin
 - ▣ Aspirin
 - ▣ Clopidogrel
- ARBs (except for candesartan 50% dose reduction when $GFR < 50\text{ml/min}$)
 - Statins (except for Pravastatin and Simvastatin 50% dose reduction when $GFR < 50\text{ml/min}$)

THANK YOU