Renal impairment in cardiac patients how it changes your drug protocols and management strategies

CardioMilitary 19/1/2017
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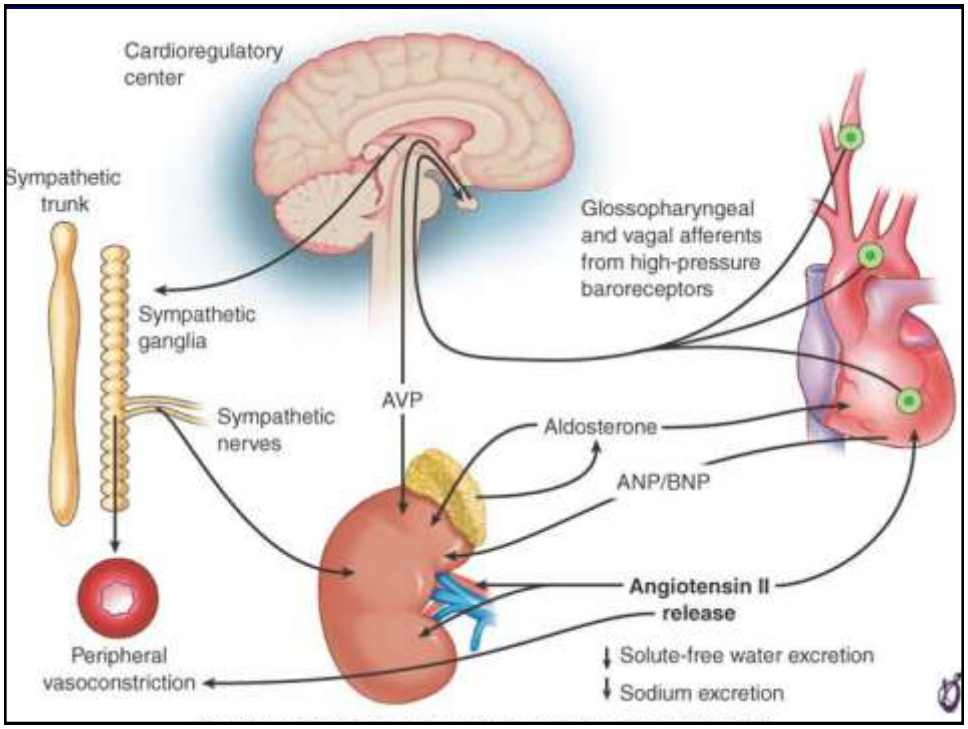
National Heart Institute

Renal blood flow

- Each kidney weights about 150 grs
- Blood flow is 400 ml /100gr /min (20-25 % of cardiac output) perfusing 1 million nephron



CARDIOVASCULAR DISEASE

- Renal hypoperfusion
- Prerenal azotemia
- Atheroembolism
- Septic embolism
- Immunologic phenomena
- Side effect of drugs

CHRONIC KIDNEY DISEASE

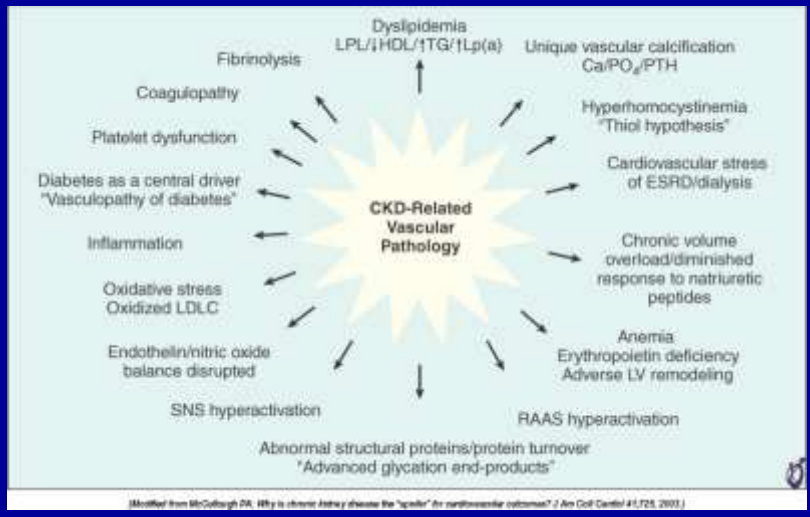
- Accelerates atherosclerosis
- Hypertension
- Heart failure
- Pericardial effusion
- Myocardial disease
- Valvular disease
- Cardiac arrhythmias
- Sudden death
- Dialysis related problems

CHRONIC KIDNEY DISEASE

- eGFR of less than 60 ml/min/1.73 m2 for more than 3 months
- serum creatinine (Cr) greater than 1.5 mg/dl
- presence of kidney damage
- microalbuminuria at any level of eGFR (random urine albumin-to-Cr ratio (ACR) of 30 to 300 mg/gm)

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			



Kidney dysfunction in HF (including chronic kidney disease, acute kidney injury, cardio-renal syndrome and prostatic obstruction) :

- HF and CKD frequently coexist, share many risk factors (diabetes, hypertension, hyperlipidaemia) and interact to worsen prognosis. Patients with severe renal dysfunction (eGFR <30 mL/min/1.73m2) have systematically been excluded from randomized clinical trials (lack of evidence-based therapies in these patients).

- A further deterioration in renal function, termed worsening renal function (WRF), is used to indicate an increase in serum creatinine, usually by <26.5 mmol/L (0.3 mg/dL) and/or a 25% increase or a 20% drop in GFR.

- Large increases in serum creatinine, termed acute kidney injury (AKI), are relatively rare in HF and are probably associated with the combination of diuretic therapy with other potentially nephrotoxic drugs such as some antibiotics (gentamicin and trimethoprim), contrast media, ACEIs, ARBs, NSAIDs, etc.

- In HF, WRF is relatively common, especially during initiation and uptitration of RAAS inhibitors. Despite the fact that RAAS blockers can frequently cause a decrease in GFR in patients with HF, this reduction is usually small and should not lead to treatment discontinuation unless there is a marked decrease, as the treatment benefit in these patients is probably largely maintained. When large increases in serum creatinine occur, care should be taken to evaluate the patient thoroughly and should include assessment of a possible renal artery stenosis, excessive hyper- or hypovolaemia,concomitant medication and hyperkalaemia, which frequently coincides with WRF

- Diuretics, especially thiazides, but also loop diuretics, may be less effective in patients with a very low GFR, and if used, should be dosed appropriately (higher doses to achieve similar effects).
- Renally excreted drugs (e.g. digoxin, insulin and low molecular weight heparin) may accumulate in patients with renal impairment andmay need dose adjustment
- Prostatic obstruction is common in older men and can interfere with renal function; it should therefore be ruled out in men with HF with deteriorating renal function. a-adrenoceptor blockers cause hypotension and sodium and water retention, and may not be safe in HFrEF. For these reasons, 5-a-reductase inhibitors are generally preferred in the medical treatment of prostatic obstruction in patients with HF.

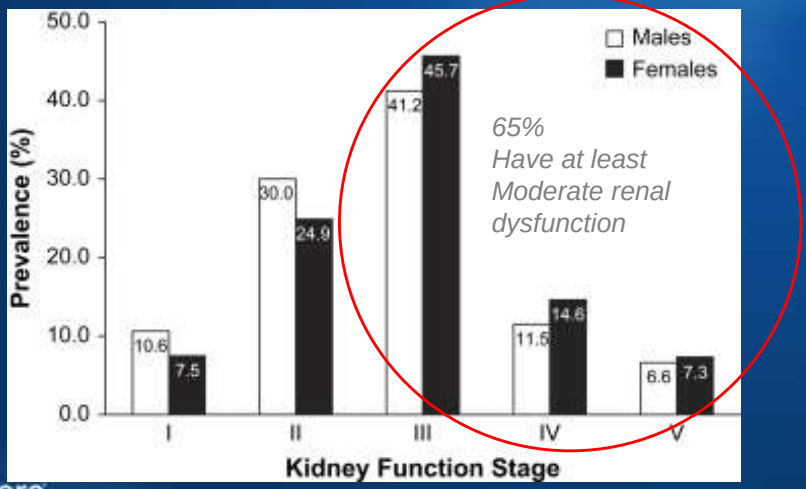
Cardiorenal syndromes CRS

Refers to disorders of the heart and Kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other

- Type I, acute CRS
- Type II, chronic CRS
- Type III, acute renocardiac syndrome
- Type IV, chronic renocardiac syndrome
- Type V, secondary CRS -- sepsis, amyloidosis

High Prevalence of Renal Dysfunction and Its Impact on Outcome in 118,465 Patients Hospitalized With Acute Decompensated Heart Failure: A Report From the ADHERE Database

J. Thomas Heywood MD et al J Card Failure Sept 2007



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Heart Failure

Estimated Glomerular Filtration Rate and Prognosis in Heart Failure

Value of the Modification of Diet in Renal Disease Study-4, Chronic Kidney Disease Epidemiology Collaboration and Cockroft-Gault Formulas

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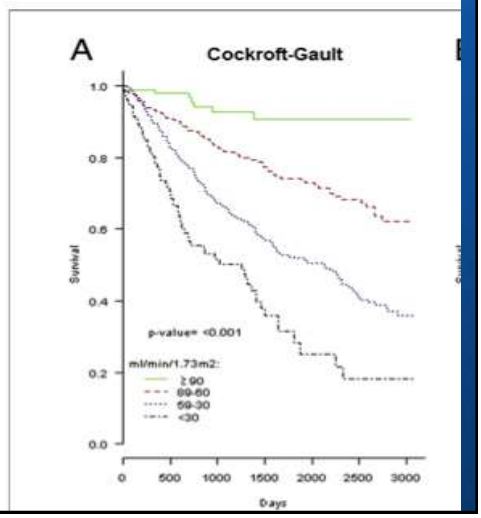


Treatment of the Cardiorenal Syndrome 5 important questions…

- What is the fluid status?
- Is the blood pressure adequate for renal perfusion?
- What is the cardiac output?
- Is there evidence of high central venous pressure?
- Is there intrinsic renal disease?

Hypovolemic Cardiorenal Syndrome

Too Dry!!!

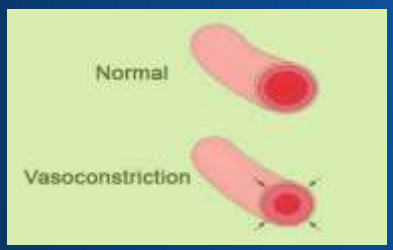
- Overdiuresed or intercurrent illness results in volume loss and renal dysfunction
- Give fluids, stop diuretics and IV vasodilators
- Often a reluctance to give fluids to HF patients but it may be critical in this situation and time is of the essence to avoid irreversible renal damage

CRS due to high central venous pressure

Too Wet!!!

- Poor renal perfusion due to high central venous pressure
- Usually CVP > 15-20 mm Hg coupled with reduced blood pressure
- Diuretics often held because of worsening renal function and misguided idea of " intravascular volume depletion"
- Continue diuretics to reduce central venous pressure
- Ultrafiltration

CRS with vasoconstriction

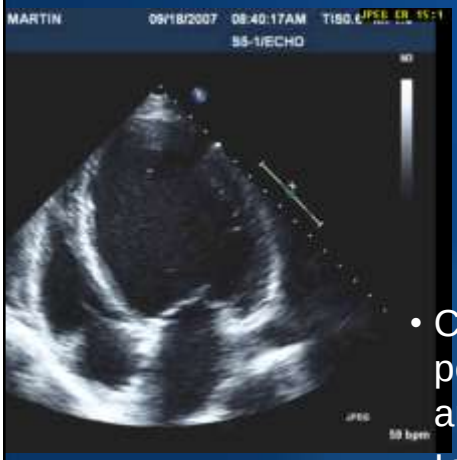


Clamped Down!!!

- Low CO and hence renal hypoperfusion due to HF mediated vasoconstriction (Ang II, endothelin induced increased afterload)
- CO is low and SVR high, often over 1800-2000
- ACEI and vasodilators very useful since CO can increase significantly if afterload normalized. Actual improvement in renal function may be seen
- May need temporary inotropic support if systolic BP <90 as vasodilators are added

Adhere

CRS with normal SVR but low CO or BP

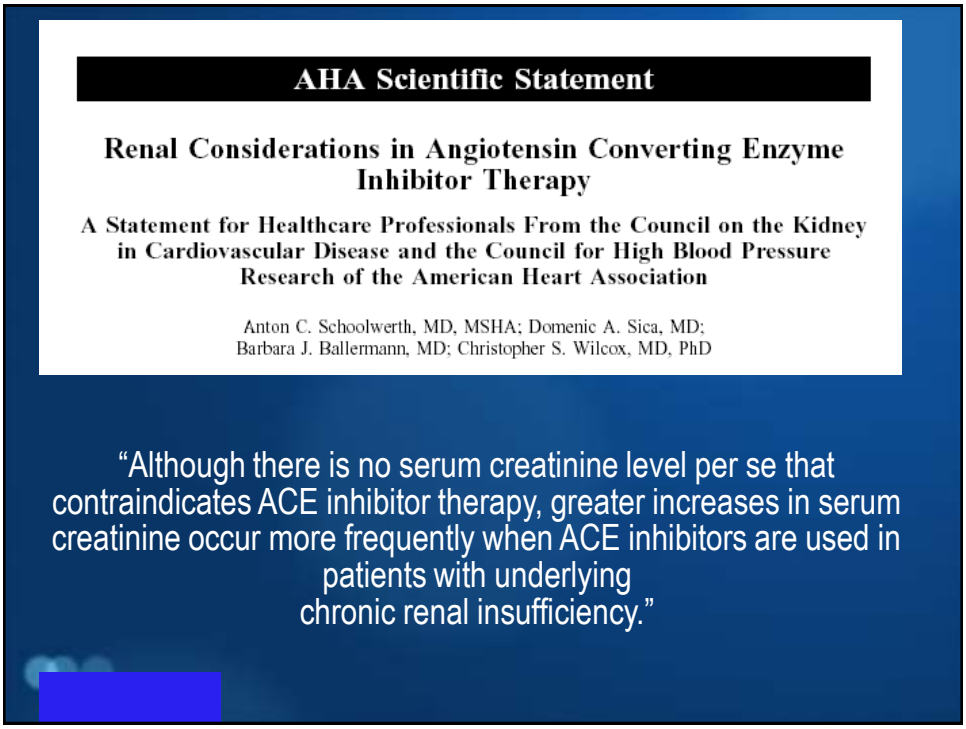


" No Pump!!!"

- CRS due to inadequate renal perfusion because of low CO and/or BP, Nml SVR!!!
- Inotropes, Pressors, Temporary circulatory support
- LVAD

ACEI play a complex role in renal function in HF

- May improve CO in some patient and hence increase effective renal perfusion
- ACEI may lower BP to the point where effective renal perfusion is impaired
- With chronic renal disease, there is hyperfiltration in the remaining nephrons. ACEI decreases efferent arteriole constriction and hence decreases glomerular capillary pressure which may preserve renal function longterm
- This may result in a 10-20% increase in creatinine, but over the long term renal function is preserved



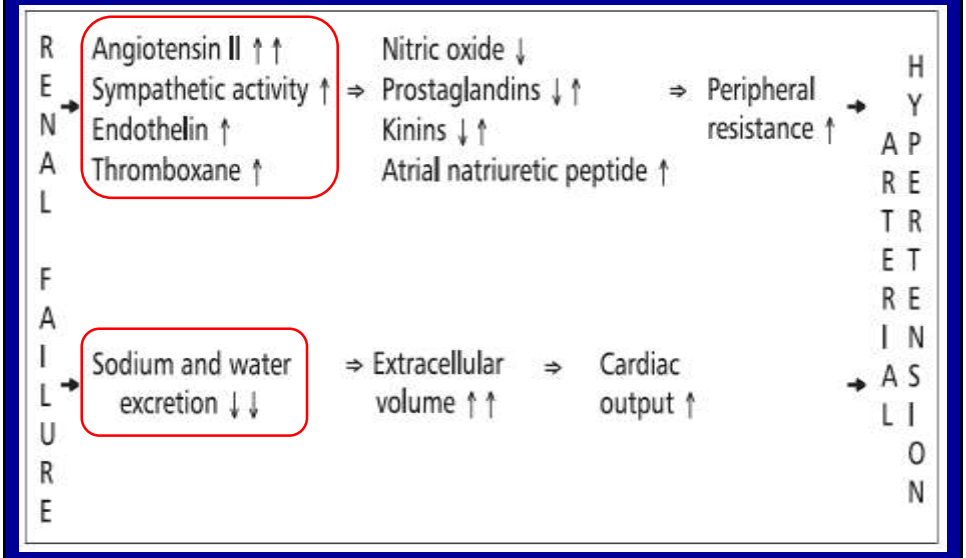
ACEI/ARB in *CKD*

- Use ACEI or ARB in patients down to an eGFR of 15 ml/min/1.73 m2
- Below this level, case reports suggest a high rate of hyperkalemia and the concern of accelerating the course to ESRD and dialysis .

ACEI/ARB in *CKD*

- CKD patients enjoy an improved survival and reduced rates of ESRD on ACEI/ARB agents even though the serum Cr is chronically elevated on these agents because of reductions in intraglomerular pressure.
- Discontinuation of ACEI/ARB drugs because of moderate, asymptomatic rises in Cr is a common management error.

Arterial Hypertension in Chronic Kidney Disease



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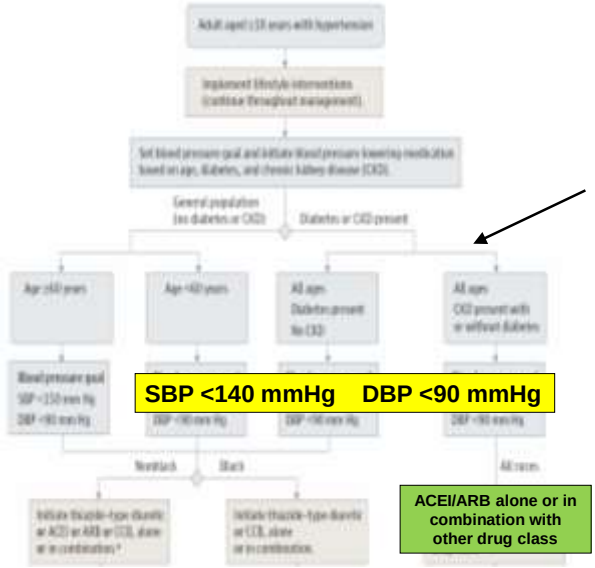
JNC 8



James PA et al. JAMA 2014

ESH/ESC

CKD

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs	• Lifestyle changes • BP drugs	• Lifestyle changes • Immediate BP drugs
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

SBP <140 mmHg DBP <90 mmHg

2013 ESH/ESC Guidelines. J Hypertens 2013

KDIGO

- **Non-diabetic adults with CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if micro or macroalbuminuric
- **Diabetic adults with non dialysis-dependent CKD:**
  ≤140 mmHg systolic and ≤90 mmHg diastolic if normoalbuminuric
  ≤130 mmHg systolic and ≤80 mmHg diastolic if micro or macroalbuminuric
- **Kidney transplant recipients:**
  ≤130 mmHg systolic and ≤80 mmHg diastolic
- **Elderly people with CKD:**
  probably ≤140 mmHg systolic and ≤90 mmHg diastolic, but set targets after consideration of co-morbidities

Aim for <130/80 mmHg if albuminuria is present

KDIGO Blood Pressure Work Group. Kidney Int Suppl 2012

RENAL DISEASE AND HYPERTENSION

- Pharmacological therapy : RAAS antagonist often in combination with a thiazide-type diuretic.
- Dihydropyridine **CCBs** alone, cause relative afferent arteriolar dilation, increase intraglomerular pressure and worsen glomerular injury and thus should be avoided as singular agents for BP control.

Diuretics

Thiazide diuretics: e.g. Hydrochlorothiazide, Bendroflumethiazide

Thiazide-like diuretics: e.g. Chlorthalidone, Indapamide

Loop diuretics: e.g. Furosemide, Torasemide

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.

Calcium Channel Blockers

Antihypertensive action.

Oedema and fluid retention.

Dihydropyridines predominantly dilate the afferent arteriole and thereby increase GFR but also the glomerular pressure.

Non-DHPs seem not to have this effect.

Beta-Blockers

Beta-blockers reduce increased sympathetic activity in CKD.

Indication in heart failure.

Often combined with diuretics in RCTs but no reason why not combine with others.

No robust evidence for superiority of certain beta-blockers.

Alpha-Blockers

Alpha-blockers have additional antiproliferative properties.

Hepatic excretion.

Beneficial in prostate hypertrophy.

ACUTE CORONARY SYNDROMES

- Renal dysfunction is a very important prognostic factor for long-term mortality
- Comorbidities, in particular DM and HF
- Included in many risk scores
- Therapeutic nihilism (underutilization of proven therapies such as antithrombotics, thrombolysis or primary angioplasty)
- Toxicity of therapies.
- Biological and pathophysiological factors in renal dysfunction

DIAGNOSIS OF ACUTE CORONARY SYNDROMES

- Patients with CKD presenting to the hospital with chest discomfort represent a high-risk group
- 40 % MACE rate at 30 days.
- Higher silent ischemia rates .
- Troponin I is the preferred biomarker.
- Skeletal myopathy of CKD can elevate creatine kinase, myoglobin, and some troponin T assays

ACUTE CORONARY SYNDROMES

- Excess thrombin generation and decreased platelet aggregation
- Increased rates of coronary thrombosis and increased bleeding

ACUTE CORONARY SYNDROMES

- Elevations in homocysteine
- Enhancing oxidation of LDL-C
- progression of atherosclerotic lesions
- High rate of plaque rupture &CVD events.
- Imbalance between ET and NO, may worsen HTN and may augment intravascular wall stress that could further contribute to CAD events.

TREATMENT OF ACUTE MYOCARDIAL INFARCTION

- Good benefit to risk ratio for ASA, beta blockers, ACEI, ARB, aldosterone receptor antagonists, and statins.
- dose adjustment for LMWH, bivalirudin, GP IIb/IIIa antagonists

Recommendations for the management of patients with chronic kidney disease and non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to assess kidney function by eGFR in all patients.	I	C	
It is recommended to administer the same first-line antithrombotic treatment as in patients with normal kidney function, with appropriate dose adjustment if indicated.	I	B	453, 454
Depending on the degree of renal dysfunction, it is recommended to switch parenteral anticoagulation to UFH or to adjust the doses of fondaparinux, enoxaparin and bivalirudin, as well as the dose of small molecule GPIIb/IIIa inhibitors.	I	B	453, 454

It is recommended to switch s.c. or i.v. anticoagulation to UFH infusion adjusted to the aPTT when eGFR is <30 mL/min/1.73 m^2 (for fondaparinux, when eGFR is <20 mL/min/1.73 m^2).	I	C
In patients undergoing an invasive strategy, hydration with isotonic saline and low- or iso-osmolar contrast media (at lowest possible volume) are recommended.	I	A
Coronary angiography and, if needed, revascularization are recommended after careful assessment of the risk–benefit ratio, in particular with respect to the severity of renal dysfunction.	I	B
In patients undergoing PCI, new-generation DESs are recommended over BMSs.	I	B
CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.	IIa	B

CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.	IIa	B
PCI should be considered over CABG in patients with multivessel CAD whose surgical risk profile is high or life expectancy is <1 year.	IIa	B

Chronic Kidney Disease

Recommendations	COR	LOE
CrCl should be estimated in patients with NSTE-ACS, and doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications.	I	B
Patients undergoing coronary and LV angiography should receive adequate hydration.	I	C
An invasive strategy is reasonable in patients with mild (stage 2) and moderate (stage 3) CKD.	IIa	B

Helping Cardiovascular Professionals Learn, Advance, Heal

American Heart Association.

While most anticoagulants may need dose adjustment in renal insufficiency, this is not the case for oral antiplatelet agents. Safety and efficacy data for the use of P2Y12 inhibitors in stage 5 CKD patients (i.e. eGFR <15 mL/min/1.73m2) are insuf-ficient. Therefore in this setting, P2Y12 inhibitors should be reserved for selected high-risk indications (i.e. coronary stent thrombosis prevention), with bleeding risk carefully weighed. In this context there is more safety experience with clopidogrel than ticagrelor or prasugrel.

In patients with stage 3 or 4 CKD (eGFR 15 – 59 mL/min/1.73m2), the clearance of eptifibatide is reduced by 50% and steady-state plasma levels are approximately double. The maintenance dose of eptifibatide should therefore be reduced from 2.0 to 1.0 ug/kg/min in patients with an eGFR<50 mL/min/1.73m2, eptifibatide is contraindicated in patients with severe renal impairment. In patients with stage 4 CKD (eGFR 15 –29 mL/min/1.73m2), the infusion rate of tirofiban should be adjusted from 0.1 to 0.05 ug/kg/min.

UFH does not require dose adjustment in patients with stage 4 or 5 CKD (eGFR ,29 mL/min/1.73m2). Conversely, enoxaparin is eliminated predominantly via the renal pathway. As a consequence, it is recommended to extend the dosing interval of the maintenance dose of enoxaparin (1.0 mg/kg) from 12 h to 24 h in patients with stage 4 CKD (eGFR 15 –29 mL/min/1.73m2). In the case of fondaparinux, no dose reduction is required for patients with stage 2 or 3 CKD (GFR 30– 89 mL/min/1.73m2), whereas it should be avoided in patients with an eGFR <20 mL/min/1.73m

The infusion dose of bivalirudin may need to be reduced in patients with advanced CKD. Dose adjustment from 1.75 to 1.0 or 0.25 mg/kg/h should be considered in patients with stage 4 or 5 CKD, respectively

- With regard to NOACs, it is advisable to assess renal function before starting therapy with dabigatran and to test it regularly in patients>75 years of age or with an eGFR<50 mL/min/1.73m2 . Since dabigatran is cleared primarily by the kidneys, leading to accumulation and hence potentially more bleeding complications, patients with CKD could theoretically benefit from a lower dose. A dose modification of rivaroxaban from 20 to 15 mg once daily is required in patients with an eGFR<50 mL/min/1.73m2 , whereas it is not recommended in patients with stage 5 CKD. With respect to apixaban, patients with severe renal impairment (eGFR 15 –29 mL/min/1.73m2) or 2 or more among serum creatinine ≥133 mmol/L (1.5 mg/dL), age ≥80 years or body weight ≤60 kg should receive apixaban at a lower dose of 2.5 mg twice daily. In patients with stage 5 CKD or undergoing dialysis, apixaban should not be administered.

Take Home Message

- Data that have become available in recent years generally reinforce the importance of CVD in determining quality of life and prognosis of CKD patients.
- Increasing evidence demonstrates that pathology, manifestations, and complications of CVD differ in the presence of CKD. Thus, the risk–benefit relationship of management strategies evaluated in the general population may differ significantly in patients with CKD
- The number of trials that specifically address CVD in CKD patients, or that enroll CKD patients, remains small