Cardio-Renal Syndrome

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Cardio-Renal Syndrome (CRS)

- It is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other.

Subtypes

- **I:** acute worsening of heart function (AHF-ACS) leading to kidney injury and/or dysfunction.
- **II:** chronic abnormalities in heart function (CHF-CHD) leading to kidney injury or dysfunction.
- **III:** acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction.
- **IV:** chronic kidney disease (CKD) leading to heart injury, disease and/or dysfunction.
- **V:** systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney.

Pathophysiological Mechanisms

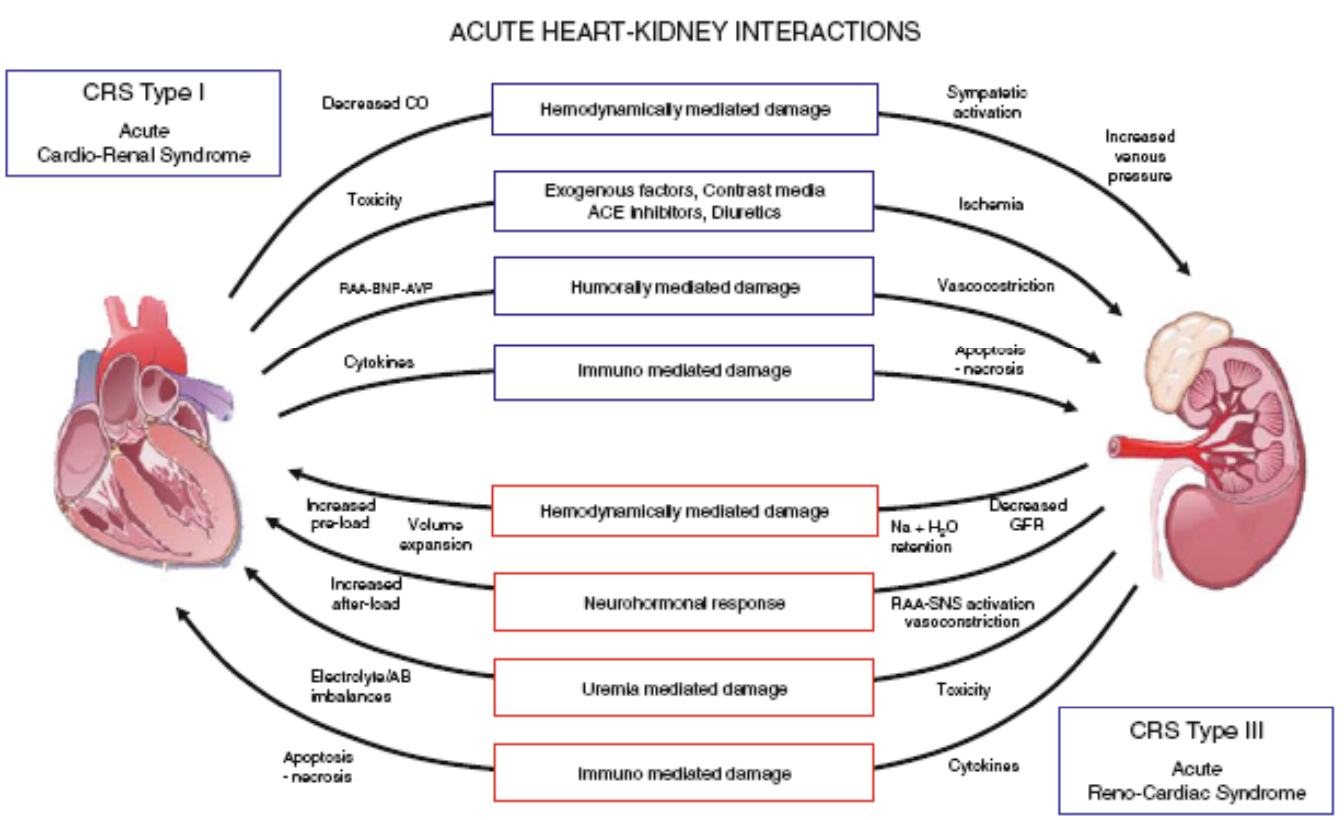

Fig. 1 Diagram illustrating and summarizing the major pathophysiological interactions between heart and kidney in types 1 and 3 cardio-renal syndromes (acute interactions)

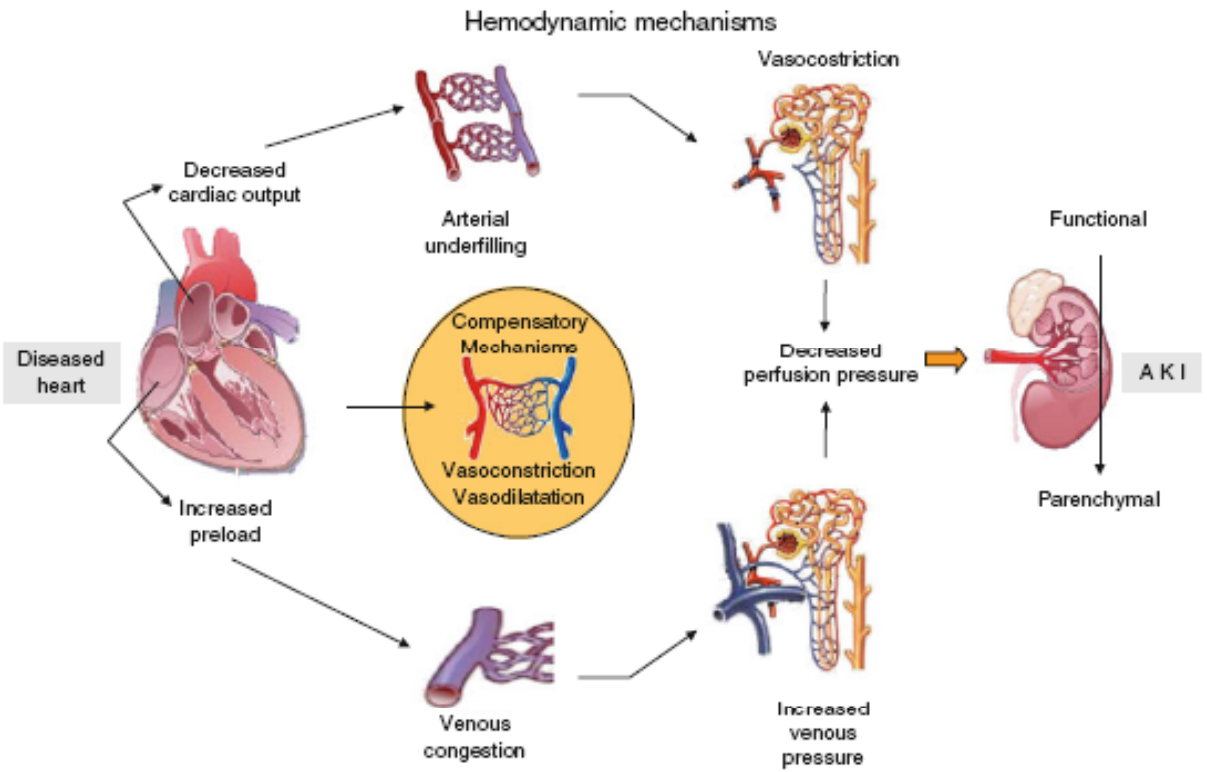

Fig.2 Diagram illustrating and summarizing the major mechanisms involved in renal hypoperfusion in CRS type I

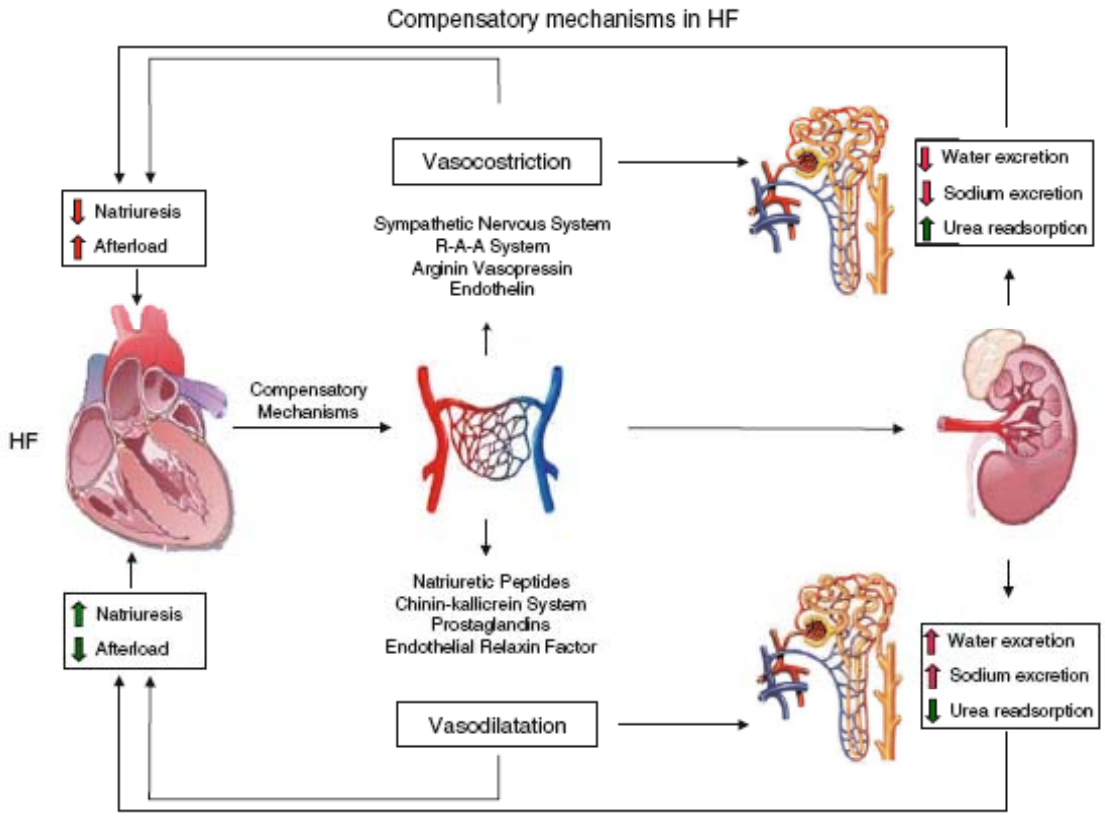

Fig.3 Diagram illustrating and summarizing the major compensateory mechanisms involved in CRS type I

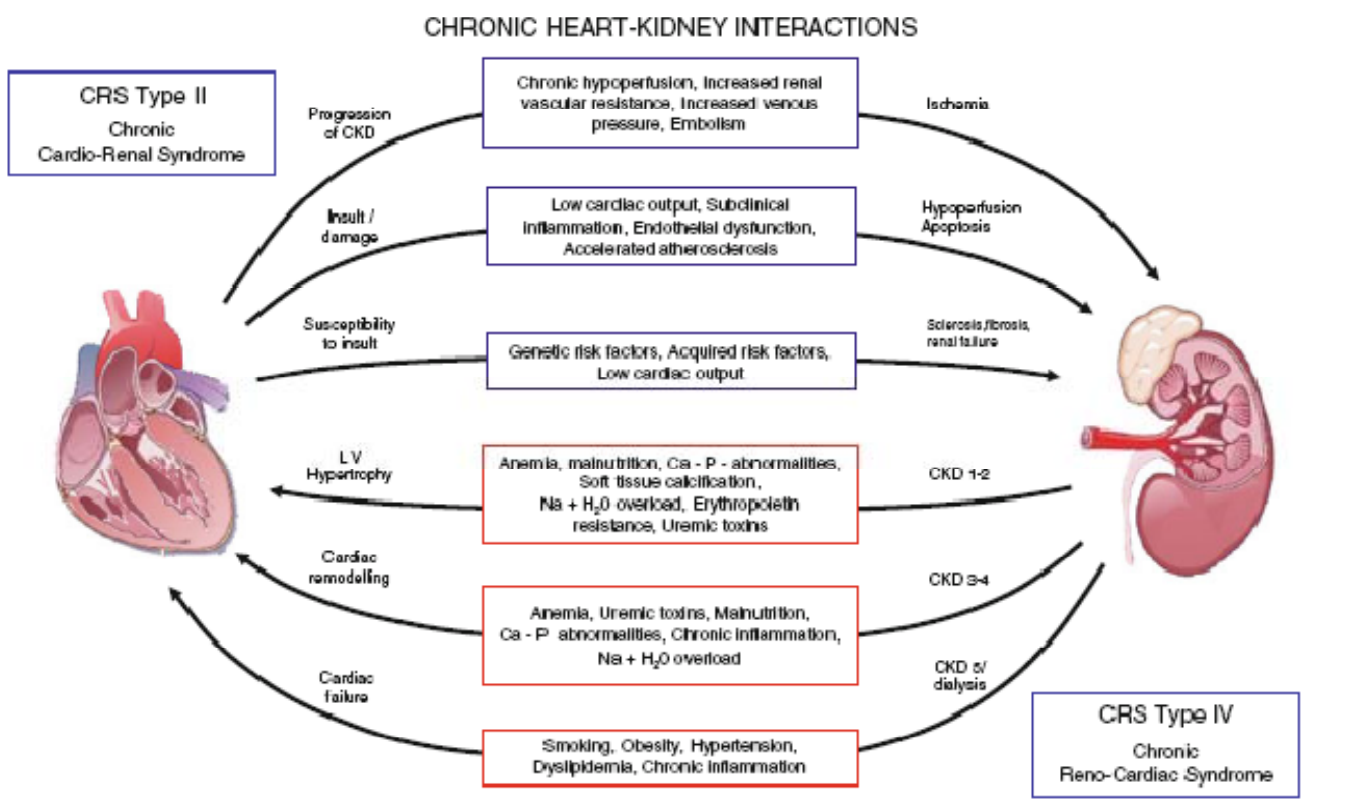

Fig.4 Diagram illustrating and summarizing major pathophysiological interactions between heart and kidney in type 2 and type 4 CRS (chronic interactions)

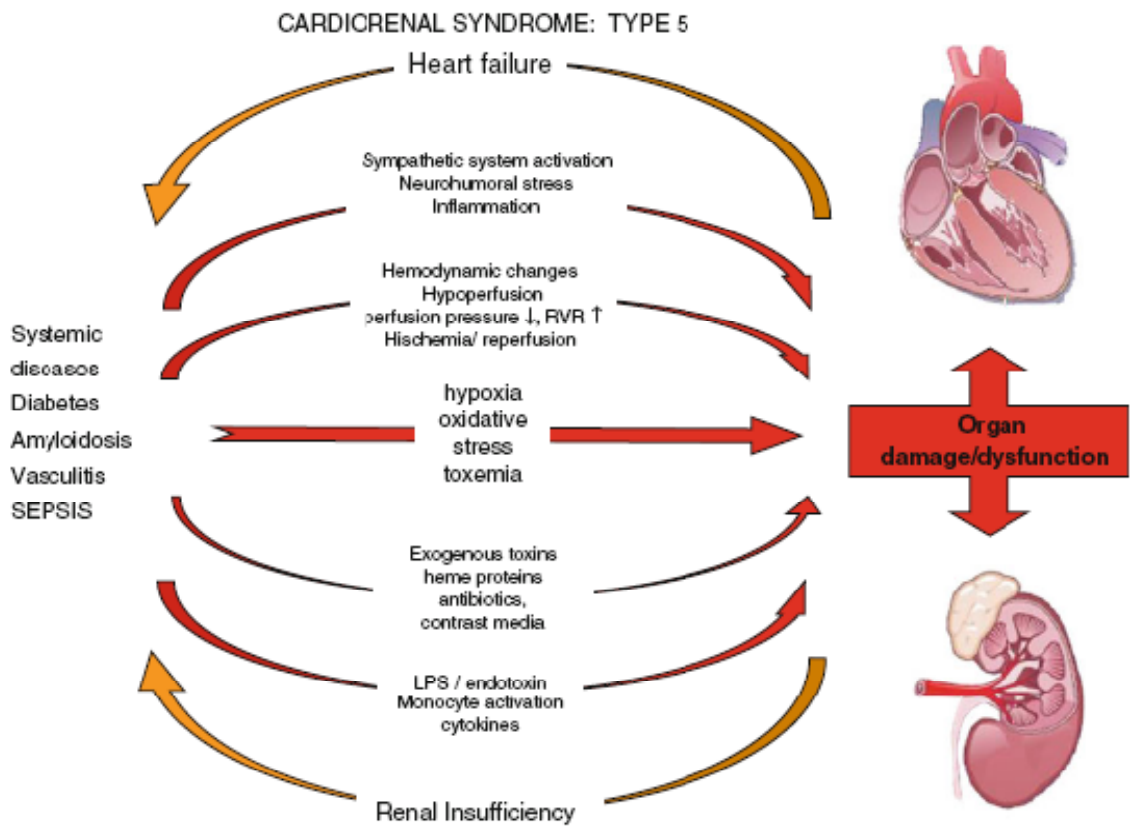

Fig.5 Diagram illustrating and summarizing the major pathophysiological interactions between heart and kidney in type 5 CRS

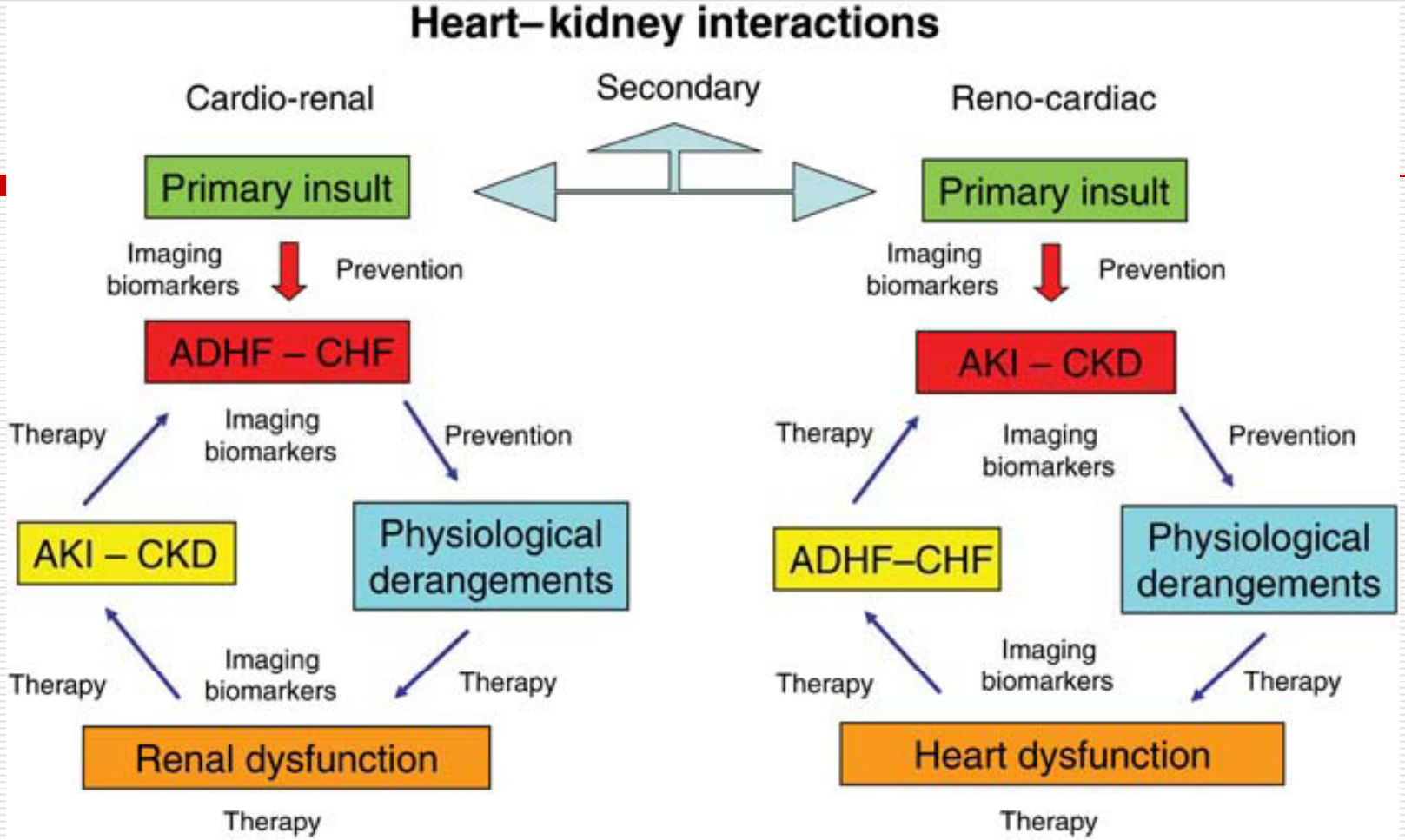

Fig.6 Heart and kidney interactions

Diagnosis and Biomarkers

Biomarkers of CRS

- To (early) identify and classify CRS?
- To risk-stratify patients with regard to reversibility?
- As targets for treatment?
- To monitor the effects of treatment?
- Can imaging of the heart and kidneys be combined effectively with biomarkers across the spectrum of diagnosis and treatment of CRS?

Natriuretic peptides and HF

- Natriuretic peptides (NPs) are elevated in patients with CRS (type 1) in which AKI occurs as a consequence of ADHF.
- They have shown prognostic utility in patients with various stages of renal insufficiency, demonstrating potential applications in CRS types 2 and 4.

Biomarkers of renal injury

Neutrophil gelatinase-associated lipocalin (NGAL)

- In a recent study, a single measurement of urinary NGAL was able to differentiate those with subsequent AKI, with a sensitivity and specificity of 90 and 99%.
- NGAL could be used as an earlier marker of impending WRF during the treatment of ADHF.

Cystatin C

- Cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with CKD.
- In AKI, urinary excretion of cystatin C has been shown to predict the requirement for RRT earlier than creatinine.

Kidney injury molecule-1 (KIM-1)

- KIM-1 is a protein detectable in the urine after ischaemic or nephrotoxic insults to proximal tubular cells.
- Urinary KIM-1 seems to be highly specific for ischaemic AKI and not for pre-renal azotemia, CKD, or contrast induced nephropathy.

N-acetyl-β-(D)glucosaminidase

- N-acetyl-β-(D) glucosaminidase has been shown to function as a marker of kidney injury, reflecting particularly the degree of tubular damage.
- It is not only found in elevated urinary concentrations in AKI and CKD, but also in diabetic patients, patients with essential hypertension, and HF.

Interleukin-18

- It displays good sensitivity and specificity for ischaemic AKI with an AUC $>$90% with increased levels 48 h prior to increases in serum creatinine.
- Urinary NGAL and IL-18 have been studied as joint biomarkers for delayed graft function following kidney transplantation.

Bioimpedance vector analysis

- This may be used in combination with NGAL and BNP to guide fluid management strategies.
- Patients will be kept within the narrow window of adequate hydration preventing worsening of both kidney and heart function.

Imaging

- Suspected CRS, to avoid the use of iodinated contrast media if not strictly necessary.
- The presence of coronary disease should be excluded by stress echo or stress myocardial perfusion (SPECT/PET) in types III, IV, and V CRS and in types I and II CRS when the primary cardiac disease is valvular, congenital, or myopathic.

Prevention

Type 1

- Blood pressure control
- Block the RAAS
- Beta adrenergic blockers (BB)
- Coronary artery disease risk factor modification
- Compliance with dietary and drug treatments.

Type 2

- ACE-I
- ARB
- BB
- Aldosterone receptor blockers, combination of nitrates and hydralazine, and cardiac re-synchronization therapy.

Type 3

- Avoidance of hypervolaemia should help prevent cardiac decompensation.
- Uremic changes, hyperkalaemia, and mediators of inflammation can have adverse cardiac consequences.

Type 4

- The core prevention concept beyond attention to usual risk factor modification is that the reduction in the rate of progression of CKD may lead to reduced rates of type 4 CRS.

Type 5

To treatment of the primary illness.

- diabetes mellitus
- Amyloidosis
- Sepsis
- Rhabdomyolysis
- haemorrhagic shock, etc.

Management strategies

Type 1

- Vasodilators and loop diuretics are widely recommended in cases of ADHF and in CRS type 1.
- Vasodilators (e.g. nesiritide) may also affect renal function and in some cases exacerbate renal injury.
- Vasopressin receptor 2 antagonists can improve hyponatraemia, but without any clear survival benefit. If congestion coincides with low blood pressure, inotropic agents should be considered.

Cardiogenic shock

- Dobutamine or dopamine
- Phosphodiesterase inhibitors, milrinone, and levosimendan.
- Extracorporeal ultrafiltration may be useful in ADHF associated with diuretic resistance.
- For systemic hypotension, norepinephrine , elective ventilation and/or intra-aortic balloon pumping, CABG.

Type 2

- ACEIs, β-blockers, ARBs, and aldosterone antagonists significantly reduce mortality and morbidity in CHF.
- The optimal approach is to combine ACE-I and β-blocker, titrate dosages, to which either an ARB or aldosterone antagonist is subsequently added depending on clinical condition and patient characteristics. In patients unable to tolerate these agents, hydralazine and nitrates may be an option.
- Digoxin and diuretics improve symptoms in CHF but have no effect on mortality.

- Cardiac re-synchronization therapy is now recommended for symptomatic CHF patients (NYHA III–IV) with poor left ventricular ejection fraction (LVEF) and QRS prolongation, as are implantable cardiac defibrillators for both survivors of cardiac arrest and/or sustained ventricular arrhythmias and also for symptomatic CHF patients with impaired LVEF.
- In selected patients who do not respond to treatment, mechanical assist devices and/or cardiac transplantation may be appropriate.

- More intensive diuretic treatment is needed.
- Thiazide diuretics may be less effective, and loop diuretics are preferred. To improve natriuresis, loop diuretic infusions are more potent, and combinations with amiloride, aldosterone antagonists, or metolazone may be considered, as increasing doses of loop diuretics are associated with worse outcomes.
- In refractory cases, RRT may be required.

- ACEI and ARB initiation may cause deterioration in renal function, which is frequently transient and reversible. Patients with CKD or renal artery stenosis are at a higher risk, and careful monitoring is recommended.
- If renal function declines, then other secondary causes such as excessive diuresis, persistent hypotension, prescription of nephrotoxic agents or underlying renovascular disease should be excluded.
- Hyperkalaemia occurs with these agents and dietary restriction may be required.

- Anaemia is often present in patients with type 2 CRS, and correction of anaemia may improve symptoms without increasing survival.
- Renal dysfunction is associated with altered drug clearances, and some drugs, e.g. digoxin and allopurinol, require dose adjustment, and the risk of spontaneous haemorrhage with warfarin is increased.

Type 3

- As previously discussed, type 3 CRS has only recently been recognized as a clinical entity, hence there is little known about the treatment of this complication.
- Since a typical clinical scenario would include AKI following contrast exposure, or following cardiovascular surgery (CSA-AKI), prevention likely affords a better chance to improve outcome than treating established disease.

- In terms of prevention of CSA-AKI, in a recent prospective, double-blind study of patients with left ventricular dysfunction undergoing cardiac surgery, nesiritide was associated with improved post-operative renal function compared with patients without nesiritide, thus suggesting a renoprotective property.

Type 4

- Despite cardioprotective strategies such as ACE-Is and/or β-blockers only a minority of dialysis patients are prescribed these drugs. Antihypertensives have been thought to increase intradialytic hypotension, but this has not been proven.
- Progressive CKD often leads to sodium retention due to reduced renal excretion, and similarly during haemodialysis due to dietary noncompliance, inappropriately high dialysate sodium and inability to achieve target or 'dry' weight.
- Besides preventing hypervolaemia and a positive sodium balance, the other key management strategies include correcting anaemia and minimizing vascular calcification.

Conclusions

- To facilitate better understanding of epidemiology
- To have opportunities for early diagnosis through biomarkers
- To develop the preventive strategies
- To apply evidence-based management strategies

Table 1. Acute kidney injury classification systems

Stage	Creatinine criteria	Urine output criteria
RIFLE system		
Risk	1.5-2 fold increase in serum creatinine concentration or 25% decrease in GFR	Urine output < 0.5 mL/kg/hr for 6 hr
Injury	2-3 fold increase in serum creatinine concentration or 50% decrease in GFR	Urine output < 0.5 mL/kg/hr for 12 hr
Failure	> 3 fold increase in serum creatinine concentration or 75% decrease in GFR or serum creatinine concentration > 4 mg/dL (350 µmol/L) with an acute elevation of > 0.5 mg/dL (44µmol/L)	Urine output < 0.3 mL/kg/hr for 24 hr or anuria for 12 hr
Loss	Complete loss of renal function (e.g. requirement for RRT) for more than 4 weeks	
End-stage kidney disease	Complete loss of renal function (e.g. requirement for RRT) for more than 3 months	
AKIN system		
1	1.5-2 fold increase in serum creatinine concentration or increase in serum creatinine concentration ≥ 0.3 mg/dL (27 µmol/L)	Urine output < 0.5 mL/kg/hr for 6 hr
2	2-3 fold increase in serum creatinine concentration	Urine output < 0.5 mL/kg/hr for 12 hr
3	> 3 fold increase in serum creatinine concentration or serum creatinine concentration ≥ 4 mg/dL (354 µmol/L) with an acute increase > 0.5 mg/dL (44 µmol/L)	Urine output < 0.3 mL/kg/hr for 24 hr or anuria for 12 hr

RRT, renal replacement therapy.

Thanks for your attentions

and

Meet with you next year!