Cardio-renal and reno-cardiac Challenges

May 31, 2018
Cardiorenal syndrome (CRS)

• **DEFINITION:**

Disorder of *heart and kidneys* where dysfunction in one organ leads to dysfunction in the other organ. This can be either acute or chronic.
Cardio-Renal Syndromes

- Term was first coined 63 years ago in 1951 to describe this clinical entity – relationship between heart and kidneys

- Since about 2000 there has been a renewed interest in better defining it – with a view to guiding research into the pathogenesis and treatment

- Recognition of the high risk of repeat hospital admissions and mortality of these patients
Cardio-renal Syndrome: Epidemiology

- **Cardiovascular disease (CVD):** an independent risk factor for worsening renal function (34%) and development of new kidney disease (6%)

  Atherosclerosis Risk in Communities (ARIC) & Cardiovascular Health Study (CHS)

- **Congenital heart disease adults:** 45% have CKD with 3 fold risk of mortality

  Circulation 2008 117:18 p 2320
Cardio-renal Syndrome: Epidemiology

- **Acute decompensated heart failure (ADHF):** 20 to 35% have AKI and of those patients, 50% have persistent kidney dysfunction and high rates of readmission.
- **6 month mortality reported as:**
  - 17% with no AKI
  - 20% with transient change in renal function
  - 46% with persistent change in renal function

Aronson J of Cardiac failure 2010 16:7 p541
IMPACT OF CARDIORENAL SYNDROME

- As many as 1 in 7 patients (15%) of hospital admissions to internal medicine have diagnosis of cardiorenal syndrome
- A GFR between 30 to 40 ml/min is associated with 1.5 times the risk of cardiovascular disease when compared with better kidney function
- Patients with congestive heart failure who develop kidney disease or dropping GFR have a significant increase in mortality
Chronic cardio-renal Syndrome

Decompensated Heart Failure

Chronic cardio-renal Syndrome

Acute cardio-renal syndrome (type 1): acute worsening of heart function leading to kidney injury and/or dysfunction

Chronic cardio-renal syndrome (type 2): chronic abnormalities in heart function leading to kidney injury or dysfunction

Acute reno-cardiac syndrome (type 3): acute worsening of kidney function leading to heart injury and/or dysfunction.

Chronic reno-cardiac syndrome (type 4): chronic kidney disease leading to heart injury, disease and/or dysfunction.

Secondary cardio-renal syndromes (type 5): systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney.
Mr. B

- 53 year old man with a dilated non-ischemic cardiomyopathy diagnosed in 2001 with LVEF 15-20%

- Comorbidities: atrial fibrillation, type 2 diabetes, obesity, hypertension, peripheral vascular disease

- Increasing symptoms by 2011: on cozaar, carvedilol, spironolactone, furosemide, lipitor, metformin, insulin

- Serum creatinine 130 to 150 umol/L (eGFR 40 ml/min)
Mr. B

- August 2012: decompensated HF with AKI diuresed for 8 Kg - Cozaar discontinued
- September 2012: CHF with AKI treated with inotropes (milronone) and IV furosemide and metolazone
- Hemodialysis (few runs) for AKI and volume removal – run of VT on hemodialysis terminated by his ICD
- November 2012: CHF (creatinine 200 umol/L) treated with IV furosemide and milronone
- Peritoneal dialysis catheter inserted complicated by bleeding at exit site
Mr. B

- January 2013 LVAD inserted with improvement – PD catheter was removed
- April 2013: decompensated again with AKI
- LVAD had cardiac output of 10 L
- Had several hemodialysis runs for ultrafiltration
- Eventually improved and discharged home off HD with creatinine of 160 umol\L
Mr B

- Heart transplant February 7, 2014 uneventful with MAP 70 to 80
- Preop creatinine 160 umol/l
- Postop AKI needing 2 hemodialysis runs for clearance and ultrafiltration and then recovered with creatinine now at 120 to 140 umol/l
Heart failure events and worsening renal function
Fig. 1 Mechanisms of cardiorenal syndrome. AVP Arginine vasopressin
Pathophysiology of cardiorenal syndrome

ACEI: angiotensin converting enzyme inhibitor; ARBs: angiotensin II receptor blockers; CO: cardiac output; CVP: central venous pressure; LVEDP: left ventricular end-diastolic pressure; ETs: endothelins; NO: nitric oxide; NP: natriuretic peptides; NSAIDs: nonsteroidal antiinflammatory drugs; RAAS: renal angiotensin aldosterone system; SNS: sympathetic nervous system; SV: stroke volume; GFR: glomerular filtration rate.
Cardio-renal Syndrome - ADHF

Pathophysiology:

**Decreased cardiac function leads to:**

- Decreased renal blood flow and perfusion
- Decreased GFR
- Acute ischemia and AKI and eventually renal fibrosis and CKD
- Right sided heart failure and venous congestion – also causing AKI and possibly CKD
Physiology of Circulation

Fig. 18.1

Mean Arterial Pressure (MAP)...

Diastolic + 1/3 pulse pressure

Fig. 19.6
Pathophysiology involves more than just poor forward flow

- Inotropic support to increase MAP helps some patients in short term, but not all

- ESCAPE trial (2005) (to assess benefit of PAC in ADHF) found no correlation between cardiac index and baseline renal function
Raised interstitial pressure
Renal oedema
- Local inflammation
- Venous congestion
- Tubular leakage

Increased venous pressure
Increased renal vascular resistance
Extrinsic pressure (intra-abdominal hypertension)

Increased venous pressure
Reduced ultrafiltration gradient
Raised tubular pressure
Increased renal vascular resistance
Cardio-renal Syndrome - ADHF

Pathophysiology:

Activation of sympathetic nervous system:
- Systemic and renal vasoconstriction
- Increased proximal tubule Na and H2O reabsorption
- Activates Renin-angiotensin-aldosterone system

Activation of RAAS:
- Systemic & renal vasoconstriction; release aldosterone
- More Na and H2O retention
- Further cardiac injury via fluid overload
Mr. B

Therapeutic Options:

- Beta-blockers
- RAAS inhibition
- Aldosterone antagonism
- Inotropic support
- Diuretics
- Ultrafiltration
- LVAD as bridge to cardiac transplantation
CRS: PREVENTING DECOMPENSATION

Involves interventions and expertise we already practice in our kidney care clinics

“BUT I ALREADY DO ALL THAT!”
CRS: preventing decompensation

- **Sodium** and fluid control
- **Blood pressure** control
- **Glycemic** control
- **Weight** reduction
- **Smoking** cessation
- **Anemia** management
- **AKI** prevention (medications, contrast)
- **Statin** use: not entirely clear for overall prognosis but have been shown to reduce hospitalizations for congestive heart failure (better with higher doses)
Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022

Placebo
Eze/simv
17 % reduction
SHARP Study

- Most of the risk reduction was in decreasing strokes and peripheral vascular disease with less impact on coronary events.

- No impact on overall mortality.

- Other studies however have shown that in those with heart failure statins reduce heart failure hospital admissions.
CRS: Preventing decompensation

- Appropriate use of diuretics for maintenance of euvolemia
- **Beta-blockers** for decreasing sympathetic activity
- Renin angiotensin aldosterone system (RAAS) inhibition increases cardiac survival even in patients with low GFR: ACE inhibitors
  - Angiotensin receptor blocker blockers
  - Aldosterone blockers
**Spironolactone** well tolerated in patients with serum creatinine less than 200 umol/l. Patients with worse renal function excluded from studies.

**Additional benefits in CKD:**
- Anti-fibrotic effects in kidneys
- Anti-proteinuric effects

*Randomized Aldactone Evaluation Study (RALES)*
NEJM 1999 341: 709
SGLT2 inhibitors in heart failure

Figure 1—Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy. P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.
Decreased hospitalizations for heart failure in empag group

Figure 6. The cumulative incidence of hospitalisation for heart failure in the empagliflozin group versus placebo in the EMPA-REG OUTCOME study.

Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.
Empagliflozin reduces nephropathy progression vs placebo.

- All patients had type 2 diabetes and eGFR ≥30 ml/min/1.73 kg²
- Consistent benefit seen across prespecified subgroups and empagliflozin 10- and 25-mg/d doses
- Benefit primarily driven by reduction in new-onset albuminuria

Incident or worsening nephropathy: 39% lower relative risk with empagliflozin

- HR = 0.61 (0.53, 0.70)  P < 0.001
- 18.8% (n=388)

- Empagliflozin (n=4,124)
- Placebo (n=2,061)

- 12.7% (n=525)

Assessment of renal outcomes was a prespecified component of the secondary microvascular outcome in EMPA-REG OUTCOME

REDUCTION IN CARDIOVASCULAR EVENTS WITH ALBUMINURIA REDUCTION
ENTRESTO = valsartan + sacubitril

Orly Vardeny et al. JCHF 2014;2:663-670
Figure 1: Kaplan–Meier curves for key study outcomes of PARADIGM-HF trial according to study group: probabilities of the primary composite endpoint (death from cardiovascular causes or first hospitalization for heart failure; A), death from cardiovascular causes (B), first hospitalization for heart failure (C), and death from any cause (D). PARADIGM-HF = Prospective Comparison of Angiotensin Receptor-neprilysin Inhibitor with Angiotensin Converting Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure.

ACUTE DECOMPENSATED HEART FAILURE (ADHF)

- Will require hospital admission
- Intravenous diuretics
- Inotropic support to increase cardiac output
- May require ultrafiltration with dialysis
- In appropriate patients, a left ventricular assist device (LVAD) may be needed as a bridge to transplantation
- At this point in Canada LVAD not usually used as destination therapy
PERITONEAL DIALYSIS

- Associated with longer preservation of residual renal function
- More stable volume status and hemodynamic status
- Peritoneal membrane is more biocompatible

➢ Provides more independence than hemodialysis
Left ventricular assist devices

Teaching old nephrology teams new tricks
(Patients can be fully mobile)

Left ventricular assist device (LVAD) connected to heart

Battery
A cable connects the external control unit and internal LVAD through a small hole in the abdomen

Control unit

LVAD pumps blood into the aorta (to the body)

Blood from the left ventricle enters the LVAD

LVAD Cable connecting to control unit

Heart is shown in cross-section
Continuous Flow LVAD
Non Pulsatile LVAD

- Studies have shown improved and preserved renal function as well as cognitive function
- Can generate blood flows of 3 to 8 liters per minute
- Levels of ANP, aldosterone, renin usually decreased
- Animal studies: renal arterial smooth muscle hyperplasia and interstitial nephritis in long term use
Renal challenges with LVAD

- Risk of AKI post implantation varies between 7 to 30 % depending on pre-operative hemodynamic stability

- AKI and need for CRRT is associated with higher mortality

- Those with AKI have higher risk of needing long-term hemodialysis (either from repeated ischemic injury or other intrinsic renal disease) and mortality in these patients is high
Long-term renal replacement challenges

- **Vascular access**: arterio-venous graft is preferred access. Lines carry high risk of infection. AV fistulas may be difficult – higher risk clotting.

- **Blood pressure** monitoring: impossible or unreliable.

- **Excessive ultrafiltration** could drop LVAD pump flow and therefore evaluation and monitoring of dry weight is potential challenge.

- **Peritoneal dialysis** is possible with new LVAD.
Reno-Cardiac Challenges

Chronic kidney disease increasing risk of cardiovascular disease
Mr. C

- 60 year old man with ESRF due to diabetic nephropathy starting dialysis in 2008
- Diabetes complicated by retinopathy, neuropathy and PVD
- Comorbidities: gout, sleep apnea, pneumonia
- 2010: ACS - angioplasty and RCA stent with immediate in stent thrombosis, RV infarct and cardiogenic shock
- 2013: ACS – CABG x 2 and aortic and mitral valve replacements complicated by sepsis and weakness
- LVEF on echo was 55%
Mr. C

- Sept 2013 (7 mons later) low BP on dialysis with MIBI showing LVEF of 33%, anterior wall ischemia with transient ischemic LV dilatation
- Angiogram showed his grafts were 70% occluded with ostial lesions too high risk for angioplasty
- November 2013: admitted with ischemic feet and intractable pain with no re-constructable disease on CT
- He chose to withdraw from dialysis and died comfortably with palliative care team support
Mr C.

CT Angiogram
November 2013
CRS – OMINOUS CO-EXISTENCE

2-year mortality and incidence of ESRD in a 5% sample of Medicare patients from the USA (1.1 million patients)

<table>
<thead>
<tr>
<th></th>
<th>2 Year mortality %</th>
<th>2 Year Incidence of ESRD%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Anaemia/ CHF/ CKI</td>
<td>7.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>16.6</td>
<td>0.1</td>
</tr>
<tr>
<td>CHF</td>
<td>26.1</td>
<td>0.2</td>
</tr>
<tr>
<td>CHF &amp; Anaemia</td>
<td>34.6</td>
<td>0.3</td>
</tr>
<tr>
<td>CKI</td>
<td>16.4</td>
<td>2.6</td>
</tr>
<tr>
<td>CKI &amp; Anaemia</td>
<td>27.3</td>
<td>5.4</td>
</tr>
<tr>
<td>CHF &amp; CKI</td>
<td>38.4</td>
<td>3.5</td>
</tr>
<tr>
<td>CHF, CKI &amp; Anaemia</td>
<td>45.6</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Causes of death in dialysis patients

- Acute MI: 19.6%
- Cardiac arrest: 16.9%
- Other cardiac: 16.1%
- Infection: 12.6%
- Stroke: 10.2%
- Cancer: 3.5%
- Other: 12.6%
- Unknown: 15.6%

USRDS 1996 Annual Data Report
Traditional and non-traditional risk factors for CVD in CKD patients

Types of Vascular Calcification in Chronic Kidney Disease

Atherosclerosis

Uremic arteriopathy
What is the role of elevated phosphorus levels in vascular calcification and CVD?

- Elegant in vitro and in vivo (mice) experiments showing that PO4 causes vascular calcification by increasing expression of *ostrix* – osteoblast specific transcription factor (by the vascular cell) JASN 2008 19(6): 1092

- But phosphate control in humans has proven disappointing in its impact on vascular calcification, CVD and mortality
In addition to phosphate there is a multitude of potential inflammatory mediators in CKD.
1. Control of DRY WEIGHT with salt intake control, fluid intake advice and diuretics as needed
2. Blood pressure control
3. RAAS inhibition
4. Beta-blockers
5. Use of statins
6. Glycemic control
7. Consider probable renal and cardiac benefits of SGLT2 inhibitors
8. Smoking cessation
9. Maintain activity
10. Phosphate and PTH control
Approach to primary and secondary prevention of CVD in CKD patients

- Even though our CKD patients have a higher risk of side effects from CHF and CVD medications (e.g. hyperkalemia), they should be treated in similar ways as non-renal patients (statins, beta-blockers, RAAS inhibition, aldosterone blockade)

- Even though they may have a higher risk of AKI, they should still be investigated with angiography and proceed with angioplasty or CABG as indicated by their coronary anatomy
Thank You

Questions ?
Conclusion

- Cardio-renal and reno-cardiac syndrome patients remain a big challenge to our multidisciplinary teams.

- We have come a long way in last 60 years in understanding the pathophysiology, clinical presentations and therapeutic options.

- There are many unanswered questions for interested young clinicians and researchers.
Acknowledgments:

- I am extremely grateful to my wonderful colleagues:
  - Doctors:
    Monica Beaulieu
    Myriam Farah
    John Gill
    Jagbir Gill
    Abeed Jamal
    Beverley Jung
    Mercedeh Kiaii
    David Landsberg
    Adeera Levin
    Gary Nussbaumer
    David Prchal
    Paul Taylor
  - Nurse Practitioner:
    Stan Marchuk

- For all our wonderful nursing and allied staff

- And for our amazing fellows, medical residents and students whose contributions to our professional satisfaction, integrity and education are immeasurable!
**Acute cardiorenal syndrome (type 1)**
Acute worsening of heart function leading to kidney injury and/or dysfunction

**Chronic cardiorenal syndrome (type 2)**
Chronic abnormalities in heart function leading to kidney injury or dysfunction

**Acute reno-cardiac syndrome (type 3)**
Acute worsening of kidney function leading to heart injury and/or dysfunction

**Chronic reno-cardiac syndrome (type 4)**
Chronic kidney disease leading to heart injury, disease and/or dysfunction

**Secondary cardiorenal syndromes (type 5)**
Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney

Antiapoptotic effects of STAT3 mediated by: iNOS; MnSOD; MT1, MT2; Bcl-xL; mitochondrial stabilization
Renin Angiotensin System Activation

- Decreased renal artery perfusion
- Increased renal venous pressure
- Decreased distal nephron sodium delivery
- Activation of the sympathetic nervous system

All of these occur in ADHF
Diuretic Mechanisms

Proposed positive and negative effects of loop diuretics as well as sites of action for thiazide diuretics and natriuretic doses of aldosterone antagonists. CHF = congestive heart failure; LV = left ventricular; MR = mitral regurgitation; RAAS = renin-angiotensin-aldosterone system.
Cardiac output \[\rightarrow\] perfusion \[\rightarrow\] RAAS, SNS \[\rightarrow\] Venous pressure.

Nitrous Oxide

Cytokines secretion \[\rightarrow\] NGAL, Urinary KIM-1, IL-18, NAC
Serum Creatinine and Cystatin C

Renal hypoperfusion
Tubular cell toxicity
Decrease GFR

Troponin, CK-MB, BNP, NT-proBNP, MPO andIMA.

Acute heart failure.
Acute coronary syndrome.
Cardiogenic Shock.

Myocyte Apoptosis, Neutrophil Infiltration

Acute kidney injury.
Glomerulonephritis

Pulmonary edema \[\leftarrow\] Fluid overload
Arrhythmias \[\leftarrow\] Hyperkalemia
Contractility \[\leftarrow\] MDS \[\leftarrow\] Uremia
Pulmonary VC \[\leftarrow\] Acidemia
Figure Legend:

Freedom From Heart Failure Rehospitalization
Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration (red line) and standard care (blue line) groups.
Figure Legend:

Schematic of Dose–Response Curve of Loop Diuretics in Heart Failure Patients Compared With Normal Controls

In heart failure patients, higher doses are required to achieve a given diuretic effect and the maximal effect is blunted.
HEMODIALYSIS - over time leads to loss of residual renal function

Intra-dialytic hypotension

Release of cytokines due to exposure of blood to Membrane

Platelet - platelet and platelet - leukocyte aggregation
Collateral Damage from Excess FGF23

- **FGF23**
- **Phosphaturia**
- **PTH**
- **1,25D**

**Collateral Damage**
- CKD progression
- Left ventricular hypertrophy
- Endothelial dysfunction
- Vascular stiffness
- Death

Wolf M JASN 2010;21:1427-1435
Fig. 1. A mutant model mouse is useful for studies of aging. The *klotho* phenotype (premature aging) is caused by a disruption of the single gene, *klotho*. 
Renal and extrarenal functions of FGF23.

Martin A et al. Physiol Rev 2012;92:131-155

©2012 by American Physiological Society
FGF23 Induces Left Ventricular Hypertrophy

- Induces hypertrophy of isolated cardiomyocytes in vitro
- Mice develop LVH with injection of FGF23
- Ascending quartiles of FGF23 associated with significantly increased LV mass index
# SHARP: Major Atherosclerotic Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any revascularization</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>16.5% SE 5.4 reduction (p=0.0022)</td>
<td></td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>162 (3.5%)</td>
<td>182 (3.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>45 (1.0%)</td>
<td>37 (0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other major vascular events</td>
<td>207 (4.5%)</td>
<td>218 (4.7%)</td>
<td>5.4% SE 9.4 reduction (p=0.57)</td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td>701 (15.1%)</td>
<td>814 (17.6%)</td>
<td>15.3% SE 4.7 reduction (p=0.0012)</td>
<td></td>
</tr>
</tbody>
</table>

www.SHARPInfo.org
## SHARP: Cause-specific mortality

<table>
<thead>
<tr>
<th>Event</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary</strong></td>
<td>91 (2.0%)</td>
<td>90 (1.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other cardiac</strong></td>
<td>162 (3.5%)</td>
<td>182 (3.9%)</td>
<td></td>
</tr>
<tr>
<td>Subtotal: Any cardiac</td>
<td>253 (5.4%)</td>
<td>272 (5.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>68 (1.5%)</td>
<td>78 (1.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other vascular</strong></td>
<td>40 (0.9%)</td>
<td>38 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Subtotal: Any vascular</td>
<td>361 (7.8%)</td>
<td>388 (8.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>150 (3.2%)</td>
<td>128 (2.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>164 (3.5%)</td>
<td>173 (3.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other non-vascular</strong></td>
<td>354 (7.6%)</td>
<td>311 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Subtotal: Any non-vascular</td>
<td>668 (14.4%)</td>
<td>612 (13.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unknown cause</strong></td>
<td>113 (2.4%)</td>
<td>115 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Total: Any death</td>
<td>1142 (24.6%)</td>
<td>1115 (24.1%)</td>
<td></td>
</tr>
</tbody>
</table>

- **Coronary**: 7.4% SE 8.4 reduction (p=0.38)
- **Stroke**: 7.3% SE 7.0 reduction (p=0.30)
- **Cancer**: 8.6% SE 5.8 increase (p=0.14)
- **Unknown cause**: 1.9% SE 4.2 increase (p=0.65)

[www.SHARPIInfo.org](http://www.SHARPIInfo.org)
SHARP: Major Atherosclerotic Events by renal status at randomization

<table>
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<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>16.5% SE 5.4 reduction (p=0.0022)</td>
</tr>
</tbody>
</table>

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

Eze/simv better  Placebo better

www.SHARPIInfo.org
Objectives

1. To better understand the relationship between cardiac and renal disease and the pathophysiological mechanisms involved
2. To review benefits and challenges of therapies
Renal blood flow and GFR decrease significantly when MAP falls below 60
Figure 3. Distribution of central venous pressure (CVP) and the relationship between CVP and estimated GFR in 2557 patients.
Figure 2. The relationship between changes in IAP with diuresis and the change in serum creatinine.
All-cause (A) and CV mortality (B) of ESRD patients as a function of their arterial calcification status.


ERA–EDTA 2003; all rights reserved
Association of Baseline Ca*P Levels With Incidence of New Cardiovascular Events

RR of new event or cause-specific death

- **Ca*P <55 (Ref.)**
- **Ca*P 55-70**
- **Ca*P >70**

**MI**
- 1.00
- 1.14*
- 1.05

**CHF**
- 1.00
- 1.10*
- 1.22*

**Stroke**
- 1.00
- 1.17
- 1.35*

**PVD**
- 1.00
- 1.25*
- 1.45*

*p-value <0.03; adjusted for age, sex, race, years on dialysis, hemoglobin, albumin, Ca*P, and 14 comorbid conditions; stratified by region (US, Japan, Europe/Australia-New Zealand/Canada)*
Mortality increases as GFR declines

Go et al. NEJM 2004; 351:1296-305

Age-standardized rate of death from any cause (per 100 person-yr)

Estimated GFR (ml/min/1.73m²)

No. of events 25,803 11,669 7802 4408 1842

Go et al. NEJM 2004; 351:1296-305
Our patients with LVAD’s

- Patients like Mr B whose renal function stabilized
- Patients who have been on hemodialysis, went on to have heart transplant and then later a kidney transplant
- Mrs S who was on hemodialysis and has now changed to peritoneal dialysis
- Mr N. who was on dialysis in remote community unit and recently had a combined heart kidney transplant
Mean arterial pressure

\[
\text{MAP} = P_{\text{diastolic}} + \frac{1}{3} \text{pulse pressure} \quad (P_{\text{systolic}} - P_{\text{diastolic}})
\]

\[
\text{MAP} = P_{\text{systolic}} + \frac{2}{3} (P_{\text{diastolic}})
\]
Cardio-renal syndrome pathophysiology

CKD-Associated myocardial changes
- Myocyte hypertrophy
- Myocyte dysfunction
- ↑Interstitial Fibrosis
- ↓Capillary density
- ↑TLV Mass
- Elevated serum troponin levels

CKD-Associated vascular changes
- Accelerated atherosclerosis
- ↑Vascular stiffness
- ↓Smooth muscle density
- Osteoblastic VSMC transformation
- Intracellular-and extracellular calcification

Acute on chronic cardiac disease
- Chronic neurohormonal
  - ↑SNS, RAS, Aldosterone
  - ↓Vitamin D
  - ↑PTH
  - ↑PO4
  - Hypotestosteronism
  - ↓EPO
  - ↓Fe utilization
  - ↓Na-K ATPase

Inciting events
- ↓Medical compliance
- ↑Sodium intake
- Ischemia
- Arrhythmias (AF)
- OSAS

Added insults
- NSAIDS, TZDs

LV Failure Mechanisms
- Pressure overload
- Volume overload
- CKD-related non-hemodynamic factors

Precipitators
- Diuretics
- Vasodilators
- Procedures

Acute neurohormonal activation
- SNS+RAS+Aldosterone + Endothelin+ADH+, renal vasoconstriction (adenosine)+prostaglandin dysregulation

Natriuretic peptides
- ANP/BNP

Blocked natriuresis

Humoral signaling
- IL-1, TNF-α

Monocyte activation
- Endothelial dysfunction

Cytokine secretion
- ↓Tubulo-glomerular function

Anemia/Relative ↓Epo/Fe transport blocked

Adhesion molecules, ↑Enzymatic activation, ↑Oxidative stress

McCullough PA, Diez J, KDIGO 2010 workshop, adapted, courtesy ronco, C 2009
Epidemiology of cardiovascular disease in haemodialysis patients

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Annual mortality (%)</th>
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<tbody>
<tr>
<td>25-34</td>
<td>0.01</td>
</tr>
<tr>
<td>35-44</td>
<td>0.1</td>
</tr>
<tr>
<td>45-54</td>
<td>10</td>
</tr>
<tr>
<td>55-64</td>
<td>100</td>
</tr>
<tr>
<td>65-74</td>
<td>25-34 35-44 45-54 55-64 65-74 75-84 &gt;85</td>
</tr>
</tbody>
</table>

Foley et al. AJKD 1998; 32:S112-9
Fibroblast Growth Factor 23
FGF23

- Phosphate regulating hormone synthesized by osteoclasts and osteoblasts in bone

- Phosphate, 1,25 \((\text{OH})_2\text{D}\) and PTH all activate the promoter of the gene and cause an increase circulating levels of FGF23
Fibroblast Growth Factor 23

FGF23

- Promotes phosphate excretion by the kidney and therefore links bone phosphate flux to kidney handling of phosphate

- Has important biological roles: e.g. Congenital excess (gene mutation) is linked to autosomal dominant hypophosphatemic rickets
Temporal aspects of disordered phosphorus metabolism in progressive CKD and after kidney transplantation.

Wolf M JASN 2010;21:1427-1435

©2010 by American Society of Nephrology
Functions of Klotho

- Cofactor in FGF23 signalling (membrane)
- Enzymatic activity modulating calcium transporters in the kidney promoting reabsorption of Ca (shed or soluble forms)
- Has direct effects to inhibit the NaPi cotransporter causing phosphaturia
- Protective effect against oxidative stress by increasing the expression of superoxide desmutase
Total cholesterol and CV mortality among 350,000 men: MRFIT prospective study

Total cholesterol and all-cause mortality among 12,000 haemodialysis patients

![Graph showing the relative risk of death associated with different cholesterol levels.

Large-scale statin studies enrolling CKD patients

- **ALERT**
  - 2100 renal transplant patients
  - Fluvastatin vs. placebo; mean FU 5.1 years
  - Results published Lancet June 2003

- **4D**
  - 1300 diabetic haemodialysis patients
  - Atorvastatin vs. placebo
  - Results published NEJM June 2005

- **AURORA**
  - 2700 haemodialysis patients
  - Rosuvastatin vs. placebo
  - Results published in NEJM April 2009.

- **SHARP**
  - Pre-dialysis 6247 patients: dialysis 3023
  - Ezetimibe 10 mg/simvastatin 20 mg vs. placebo
  - Lancet 2011 vol 377
LVAD can be used as:

- Bridge to recovery
- Bridge to heart transplant
- Destination therapy
FGF-23 in CKD

Kidney Inter Suppl 2011;1:130-135
Klotho

Wall in Berlin Cemetery
Outline: cardio-renal challenges

- Review epidemiology and **basic** pathophysiology cardio-renal syndrome – primarily addressing acute decompensated heart failure (ADHF)

- Present the case of a patient who underwent most of the available treatments for ADHF

- A review of some of those treatments especially the ones which involve the nephrology team
Outline: reno-cardiac challenges

- Case presentation of dialysis patient with extensive cardiac disease and vascular disease

- Review of the pathophysiology of vascular disease in patients with CKD and ESRF

- Review of some of the therapeutic options
Decreased forward flow

Venous congestion
NFP = Net filtration pressure
  = outward pressures – inward pressures
  = \( HP_{gc} \) – \( HP_{cs} + OP_{gc} \)
  = (55) – (15 + 30)
  = 10 mm Hg
Interlobular artery

Afferent arteriole

Efferent arteriole

Oxygen supply

Interlobular artery
Angiotensin II Direct Inflammatory Effects
Aquadex Flex Flow (Gambro)

- Fluid removal rate usually 200ml/hour (max 500)
- Blood flow rate 40ml/min
- Can be used with 2 large peripheral lines
- Central line often required
Aldosterone Direct Inflammatory Effects

T cells
- MR
- Aldo
- CD4 cell
- T cells
- IL-6
- TGFβ
- IL-17

Endothelial cell
- Corticosterone
- 11βHSD-2
- ICAM
- P-selectin
- IL-18 release
- vWF release
- Aldo
- Aldo
- Cort

Macrophage
- Cort
- Aldo
- MR
- GR
- TNF
- CTGF
- TGFβ
- PAI-1
- COL III
- ADM
- HTRA
- Ym1
- F13A1
- HTRA1
- SERPINE2

Cardiomycocyte
- Aldo
- Cort
- MR
- NOX2
- p22phox
- CCR5
- Inflammatory cells (late)
- TGFβ, PAI-1 (early)
- MMP2/MMP9

↑ ROS
↓ Inflammation
↓ Adhesion
↓ Fibrosis
UNLOAD
Costanzo et al. J Am Coll Cardiol 2007 49: 675-83

- 200 patients multicenter randomized to UF or diuretics (either IV or bolus at physician discretion)
- Diuretics were at about 2 times the oral dose prior to admission
- 48 hour treatment

**Results:**
- Higher weight loss in UF group
- No symptomatic difference
- Trend towards creatinine rise with UF
ICODEXTRIN:
• Cornstarch-like
• Absorbed very slowly from peritoneum therefore UF continues for over 12 hours
Fibroblast growth factor - FGF-23

Annu. Rev. Physiol. 75:503–33
Gene is activated by PO$_4$, PTH & 1,25 (OH)$_2$D

<table>
<thead>
<tr>
<th>Receptor complex</th>
<th>FGFR</th>
<th>FGFR4</th>
<th>FGFR1c</th>
<th>FGFR1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotho</td>
<td></td>
<td>βKlotho</td>
<td></td>
<td></td>
</tr>
<tr>
<td>αKlotho</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bioactivity**

- **Postprandial:**
  - Bile acid synthesis
  - Glycogen and protein synthesis
  - Gluconeogenesis
- **Postprandial:**
  - Relaxation and filling
- **Fasting:**
  - Fatty acid oxidation
  - Torpor

**Phosphate homeostasis**

- Urinary P$_i$ excretion
- PTH

---

Annu. Rev. Physiol. 75:503–33
In kidney FGF-23 needs Klotho to bind
Chronic Kidney Disease and FGF23

- FGF23 increases very early in CKD before serum PO₄ levels are elevated.

- Helps to maintain serum PO₄ at normal level and early on is probably helpful in preventing phosphate induced vascular calcification.
Chronic Kidney Disease and FGF23

- With decreased renal mass FGF23 loses its effectiveness as a phosphaturic hormone but serum levels still continue to rise.

- In dialysis patients FGF23 levels can be increased 1000 fold and at that point are correlated with mortality. Directly harmful or just a marker??
In vitro FGF-23 induces hypertrophy of isolated cardiomyocytes

Mice injected with FGF-23 develop LVH
- Decreased re-hospitalization in UF group
- Secondary end-point in a subset of patients
1997 **Kuro-o** describes a mouse with short life-span, osteoporosis, emphysema, arteriosclerosis, skin atrophy, hyperphosphatemia and ectopic calcifications.

He identified the gene for **Klotho**, which when over-expressed causes mice to live longer.
The Moirai – The Fates

Daughters of Zeus (the god of fate) and Themis
Klotho - spinner
Lakhesis - measures
Atropos - cuts thread of life
The thread of life
Functions of Klotho

- Involved in endothelial integrity and endothelial dependent vasodilation
- Protective against oxidative stress
- Inhibits TGF-B signaling and suppresses interstitial fibrosis in animal models
- Expressed in the sino-atrial node and decreased expression leads to SA node malfunction and premature death

- *Circulating levels of Klotho are decreased in CKD*
Decreased circulating Klotho and increased FGF-23
FGF-23 and Klotho plasma levels with progressive renal failure

Annu. Rev. Physiol. 75:503–33
CKD $\rightarrow$ Inflammation

$\downarrow$ Klotho

FGF23 "resistance" ($\uparrow$ FGF23 levels)

$\downarrow$ phosphaturia $\uparrow$ phosphorus in serum

Transformation VSMC to Osteo/chondrocytic cells

Endothelial dysfunction

Vascular calcification

CV disease
FGF-23 and Klotho in CKD and Vascular Disease

- Intriguing and generating significant research interest

- But at this point the research has not led to any potential therapies in humans
DryWt = PreWt – UF

UF = Fluid Retention

Interdialytic weight gain (fluid retention) over ~44 hrs
Intradialytic ultrafiltration (UF) over ~4 hrs
Predialysis weight (PreWt)
Postdialysis or dry weight (DryWt)

0 → 12 → 24 → 36 → 48 hrs → 72 hrs → 96 hrs
Monday  Tuesday  Wednesday  Thursday  Friday

Circulation 2009; 119:671-679
34,000 patients  Prospective cohort, multicenter
Circulation 2009; 119:671-679
34,000 patients  Prospective cohort, multicenter
How Can We Help

BLOOD PRESSURE STABILITY
Blood Pressure Challenges on Dialysis

Intradialytic Hypotension
- Recurrent Myocardial Stunning
  - Myocardial Fibrosis
    - Systolic Dysfunction
      - Cardiovascular Death

Interdialytic Hypertension
- Endothelial Cell Dysfunction
  - Atherosclerosis
    - Ischemic Heart Disease
      - Left Ventricular Hypertrophy
    - Arteriosclerosis
      - Cardiovascular Death

Inrig, J. KI 2013 84, 641-644
Pathophysiology
Cardio-renal syndrome - ADHF
Other contributors to cardiac and renal injury

- Treatment related worsening of renal function: diuretics, RAAS inhibition, aldosterone receptor antagonists

- Contrast mediated renal injury during investigations
How Can We Help

BETA BLOCKERS
114 hemodialysis patients with dilated cardiomyopathy; max dose 25mg BID

log-rank: 8.58; p<0.005
How Can We Help

LIPID CONTROL
AURORA: Primary endpoint
Kaplan-Meier estimate of time-first major CV event

Normal renal tubules

Mr B. Acute tubular necrosis with dilatation flattened epithelium and vacuoles
Normal glomerulus

- Mr B. * Acute tubular injury
  * Chronic tubular atrophy, interstitial fibrosis
  * Mild to moderate mesangial expansion from diabetes
  * Arteriolar hyalinosis (arrows)
Use of Ultrafiltration in Decompensated Heart Failure
188 patients randomized to ultrafiltration at rate of 200ml per hour or to Intravenous diuretics titrated to achieve urine output of 3 to 5 liters per day

Treatment period was about 4 days and follow-up was 60 days

Small improvement in symptoms was similar in both groups
Both groups had average 5.5 kg weight loss after 4 days
Increased creatinine in UF group
Higher risk of bleeding, bacteremia and cellulitis in UF group
Mr B. needed both isolated ultrafiltration and hemodialysis for worsening renal function.

Sometimes with prolonged UF/HD there is loss of residual kidney function and HD dependency due to:

- Hypotension
- Cytokine activation (blood-filter contact)
- platelet- leukocyte aggregation
Cardio-renal syndrome pathophysiology

- **CKD-Associated myocardial changes**
  - Myocyte hypertrophy
  - Myocyte dysfunction
  - ↑↑Interstitial Fibrosis
  - ↓Capillary density
  - ↑↑TLV Mass
  - Elevated serum troponin levels

- **CKD-Associated vascular changes**
  - Accelerated atherosclerosis
  - ↑Vascular stiffness
  - ↓Smooth muscle density
  - Osteoblastic VSMC transformation
  - Intracellular-and extracellular calcification

- **Acute on chronic cardiac disease**

- **Chronic neurohormonal**
  - ↑SNS, RAS, Aldosterone
  - ↑Vitamin D
  - ↑PTH
  - ↑PO4
  - Hypotestosteronism
  - ↓EPO
  - ↓Fe utilization
  - ↓Na-K ATPase

- **Inciting events**
  - ↓Medical compliance
  - ↑Sodium intake
  - Ischemia
  - Arrhythmias (AF)
  - OSAS

- **Added Insults**
  - NSAIDS, TZDs

**LV Failure Mechanisms**
- Pressure overload
- Volume overload
- CKD-related non-hemodynamic factors

**Precipitators**
- Diuretics
- Vasodilators
- Procedures

**Acute neurohormonal activation**
SNS+RAS+Aldosterone+Endothelin+ADH+, renal vasoconstriction (adenosine)+prostaglandin dysregulation

**Precipitating factors**
- Decreased perfusion
- Increased venous pressure
- Renal congestion
- Toxicity vasoconstriction

**Biomarkers**
- ↑BNP/NT-proBNP
- ↑N-GAL
- ↑KIM-1
- ↑IL-18
- Catalytic iron
- ↑Cystatin-C
- ↑Creatinine
- Urine albumin
- Many others

**McCullough PA, Diez J, KDIGO 2010 workshopt, adapted, courtesy ronco, C 2009**
Proposed pathophysiology of renal venous hypertension, congestion, and dysfunction
Most studies exclude patients with significant renal failure.

Concerns include worsening of renal function and hyperkalemia.

Patients unable to tolerate RAAS Inhibition have higher mortality: is this a marker of poor prognosis or are we stopping these medications too soon?
Questions about diuretics in ADHF

- Dose required
- Diuretic resistance
- Rebound fluid retention with short action of furosemide
- Is continuous infusion better than bolus administration
Diuretic Strategies in Patients with ADHF (DOSE trial) NEJM 2011 364:9

- 308 randomized patients treated for 72 hours
- 60 days of follow-up

Low dose = total home oral dose per day
High dose = 2.5 times oral dose

Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients’ previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).
DOSE Trial

- Trend towards higher creatinine with high dose: no difference at 60 days
- No significant differences in patients’ global assessment of symptoms

Use what works for each patient
What should we do?

- Stepped up pharmacologic therapy to ensure adequate diuresis (e.g. addition of metolazone)
- IV bolus or continuous infusion – whichever works
- If BP or cardiac output low – defer to our cardiology colleagues to decide what’s next (e.g. ? Inotropes)
- If all fails, consider ultrafiltration or dialysis as needed
British Columbia Data

Patient Survival Rate on Dialysis

Year: (1yr surv.; 95% C.I.) (Mean Age; % DM)
07/08: (0.84; 0.81-0.87) (66; 45%)
08/09: (0.85; 0.82-0.88) (66; 51%)
09/10: (0.83; 0.80-0.86) (66; 50%)
10/11: (0.83; 0.80-0.86) (66; 53%)
11/12: (0.85; 0.82-0.88) (66; 54%)

Probability of Survival

Months from Dialysis Initiation

Test for adjusted HR* for Year of Dialysis Initiation: Chi-sq=2.3960, p=0.0634
*Adjusted for age, gender, diabetes, initial modality, HA at dialysis initiation, CHD follow-up
Renal blood flow and GFR decrease significantly when MAP falls below 60