NO CONFLICT OF INTEREST TO DECLARE
End-stage renal disease and other arrhythmias: what relationships and clinical implications?

Dr Charlie Ferro
Queen Elizabeth Hospital Birmingham, UK
“Birmingham has more miles of canals than Venice and more trees than Paris. But, unfortunately for the canals and trees, they are in Birmingham and not Venice or Paris. This makes them all quite sad.”
Cardiologists and nephrologists

Palmer et al AJKD 2011
Quality as well as quantity
Plan

• Haemodialysis?
• Overview of Arrhythmias in ESKD
• Sudden Cardiac Death
• Causes
• Potential therapeutic options
• The Future
Haemodialysis

- 3 x weekly for 4 hours ie intermittent...
- BUT week = 7 days
- Gives a creatinine clearance of approx 10 ml/min
- Does not replace all the other kidney functions:
  - Ca/Phos/Vit D axis
  - Erythropoietin synthesis
  - Middle/large molecule clearance?
  - Etc, etc
Dialysis has not changed much: patients have!
How co-morbid are dialysis patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>89%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>66%</td>
</tr>
<tr>
<td>PVD</td>
<td>30%</td>
</tr>
<tr>
<td>CHF</td>
<td>39%</td>
</tr>
<tr>
<td>MI</td>
<td>16%</td>
</tr>
<tr>
<td>Angina</td>
<td>5%</td>
</tr>
<tr>
<td>COPD</td>
<td>19%</td>
</tr>
<tr>
<td>Cancer</td>
<td>19%</td>
</tr>
<tr>
<td>Rh arthritis</td>
<td>7%</td>
</tr>
</tbody>
</table>

Salter et al BMC Geriatrics 2015
Arrhythmias are common in dialysis patients
Monitoring in Dialysis (MID) Study

- 50 haemodialysis patients – 6 months
- Reveal XT™ Implantable Cardiac Monitoring
- Quantify clinically significant arrhythmias
  - VT ≥ 130 bpm for ≥ 30 seconds
  - Asystole ≥ 3 seconds
  - Bradycardia ≤ 40 bpm for ≥ 6 seconds
  - Symptomatic arrhythmias

Preliminary results published in abstract form
Arrhythmias Confirmed by ECG Review

<table>
<thead>
<tr>
<th>Review Confirmed Arrhythmic episodes</th>
<th>Atrial</th>
<th>Brady</th>
<th>Asystole</th>
<th>Ventricular</th>
<th>Sinus Tach</th>
<th>Patient Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events (% of total)</td>
<td>7801</td>
<td>4478</td>
<td>1197</td>
<td>28</td>
<td>706</td>
<td>3165</td>
</tr>
<tr>
<td>Subjects with events (% of implanted)</td>
<td>50 (100%)</td>
<td>46 (92%)</td>
<td>13 (26%)</td>
<td>6 (12%)</td>
<td>38 (76%)</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>Expected events per patient month (95% CI)</td>
<td>29.7 (19.2-46.0)</td>
<td>16.4 (10.2-26.5)</td>
<td>5.2 (1.3-20.0)</td>
<td>0.1 (0-0.3)</td>
<td>2.7 (1.6-4.5)</td>
<td>11.9 (7.0-20.3)</td>
</tr>
</tbody>
</table>

Preliminary results published in abstract form.
Timing of Arrhythmias

Preliminary results published in abstract form
Sudden Cardiac Death
Sudden Cardiac Death is the Leading Cause of Death in Dialysis Patients

Prevalent dialysis patients 2009-2011

- Non-cardiovascular: 58%
- Arrhythmia/cardiac arrest: 27%
- AMI: 5%
- CHF: 5%
- CVA: 3%
- Other cardiac: 2%
- Nongcardiovascular: 58%
Risk of SCD in Haemodialysis Patients is 20x Greater than in General Population

Events per 1000 patient years (n=19,440)

- Gen pop: 1.9
- CVD: 4.2
- CKD 3-4: 7.3
- CKD 5 ND: 12.5
- ESRD HD: 24.1

Pun et al Kidney Int 2009
Sudden cardiac death and arrhythmias are more common after the long dialysis break

Foley et al. NEJM 2011

Rate per 100 patient years

32,000 US HD patients

Arrhythmia Hosp.
Cardiac Death
Infectious Death
Why?

• Misclassification?
  – Unlikely rates consistent across observational cohorts, registries, interventional trials etc

• Same disease as in general population, only worse?
  – Ischaemic heart disease, diabetes, heart failure

• New disease, novel risk factors?
Sudden Cardiac Death in CKD/ESKD

Unique CKD/Dialysis Related Factors
- Uraemia
- CKD-MBD
- Anaemia
- MIA syndrome
- Autonomic instability
- Electrolyte shifts
- Fluid Shifts

Conventional Risk Factors
- Hypertension
- Atheroma
- Electrolytes
- Arterial stiffness
- Diabetes mellitus

CARDIOMYOPATHY

Malignant arrhythmias

ARRHYTHMOGENESIS

SCD
Increased LV Mass and Myocardial Fibrosis

Edwards et al JACC Imaging 2015
Cardiac fibrosis associated with increased mortality ESRD patients.
Serum phosphate is associated with LVM in CKD

Phosphate is a Mediator of Cardiovascular Disease

Increased Cardiovascular Risk

FGF-23
LV Mass Increases with Increasing Aortic Calcification and Decreasing Bone Density

Chue et al Plos One 2013
Pre-dialysis Sudden Cardiac Arrest and Serum Potassium

Pun et al. Kidney Int 2011
Low dialysate potassium associated with worse outcomes

Pun et al. Kidney Int 2011
Low calcium dialysate associated with increased risk of SCD

Pun et al cJASN 2013
Potential “Conventional” Treatments

• Beta-blockers
• RAAS Inhibition
• Implantable Cardioverter Defibrillators
Double-blind RCT of Carvedilol in Dialysis Patients with Dilated Cardiomyopathy

N=114

log-rank: 8.58; p<0.005

Cice et al JACC 2003
Aldosterone: a pro-inflammatory and pro-fibrotic stimulus in the heart and vasculature

Brown NJ. Hypertension 2008
Aldosterone and Myocardial Necrosis

Representative myocardial necrotic lesions induced by L-NAME/Ang II/NaCl treatment.

Myocardium of an animal receiving L-NAME/Ang II/NaCl treatment in the presence of eplerenone showing no necrotic lesions.

Rocha et al. Endocrinology 2000; 141: 3871-8
Addition of low dose spironolactone lowers LV Mass independently of blood pressure in optimally managed patients with CKD

Data are mean ± SD
† p<0.05 †† p<0.01

Edwards et al JACC 2009
Spironolactone Reduces Cardiovascular and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients (n=309)

CV death or CV hospitalization

All-cause Mortality

Matsumoto et al. JACC 2014
Implantable Cardioverter Defibrillators in Dialysis Patients

• No dialysis patients included in any RCT
• In secondary prevention:
Observational analyses found survival advantage in cardiac arrest survivors fitted with ICD
  – Confounded by indication

Genovesi, S et al IJC 2015
Charytan et al AJKD 2011
Herzog et al Kidney Int 2005
ICD for primary prevention in dialysis patients: a matched cohort study

Pun et al NDT 2015
Reduced Kidney Function Associated with less benefit from ICD in primary prevention trials: a patient level meta-analysis

N=2,867

Pun et al AJKD 2014
Why Might ICDs Not work in ESKD?

• Increased defibrillation thresholds
• Events might not be “shockable”
  (38% of dialysis patients with an ICD still have a sudden death)
• Competing risks
  – High death rate
  – Bacteraemia/endocarditis
  – Associated vascular access problems
Longer or more frequent dialysis associated with less SCD/Arrhythmias?

• Studies relatively small (52 – 245 patients)
• BUT
  – Lower blood pressure
  – Reduce interdialytic weight gain
  – Reduced LV mass
  – Improved blood results – potassium, calcium, phosphate, PTH

All of which theoretically should lower risk (?)

Culleton et al JAMA 2007
Chertow et al NEJM 2010
Current therapeutic options

• Prevent/treat cardiomyopathy
  – Beta-blockers in dilated cardiomyopathy
  – Treat elements of CKD MBD

• Avoid precipitating factors
  – Avoid low potassium and calcium dialysates
  – Reduce IDWG/large fluid shifts
  – Adjust dialysis prescription – daily dialysis?
Cardiotonic Steroids?
**Arterial Wall Inhibition/signaling**

- \( \alpha_1, \alpha_2, \alpha_3 \) Na/K ATPase

**Short term:**
- Vasoconstriction

**Long term adaptation:**
- Arterial hypertension
- Muscle hypertrophy

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**Brain**

- High NaCl

- Ouabain

**Short term:**
- Inotropy

**Long term adaptation:**
- Hypertrophy
- Fibrosis
- Diastolic dysfunction
- Arrhythmogenesis

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**Kidney NKA Inhibition/signalling**

- \( \alpha_1, \alpha_2, \alpha_3 \) Na/K ATPase

**Short term:**
- Natriuresis

**Long term adaptation:**
- Hypertrophy
- Glomerulosclerosis

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**Cardiac NKA Inhibition/signalling**

- \( \alpha_1, \alpha_2, \alpha_3 \) Na/K ATPase

**Short term:**
- Vasoconstriction

**Long term adaptation:**
- Arterial hypertension
- Muscle hypertrophy

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*Pavlović D. Nephron 2014*
EDITORIAL

Randomised-controlled trials in chronic kidney disease – a call to arms!

Misery acquaints a man with strange bedfellows.
Trinculo, The Tempest by William Shakespeare

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