HEART FAILURE IN CHRONIC KIDNEY DISEASE

Angela Yee-Moon WANG
Department of Medicine
Queen Mary Hospital
University of Hong Kong
Hong Kong
For Congress:

Registration opens: 9 Sept 2019
Abstract submission Opened: 20 July 2019

http://enweb.ckd-cn.org/
http://www.renal-nutrition.org/
DISCLOSURES

• No relevant disclosures.
Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Andrew A. House\textsuperscript{1}, Christoph Wanner\textsuperscript{2}, Mark J. Sarnak\textsuperscript{3}, Ileana L. Piña\textsuperscript{4}, Christopher W. McIntyre\textsuperscript{5}, Paul Komenda\textsuperscript{6,7,8}, Bertram L. Kasiske\textsuperscript{9}, Anita Deswal\textsuperscript{10,11}, Christopher R. deFilippi\textsuperscript{12}, John G.F. Cleland\textsuperscript{13,14}, Stefan D. Anker\textsuperscript{15,16,17}, Charles A. Herzog\textsuperscript{18,19}, Michael Cheung\textsuperscript{20}, David C. Wheeler\textsuperscript{21}, Wolfgang C. Winkelmayer\textsuperscript{22} and Peter A. McCullough\textsuperscript{23,24}; for Conference Participants\textsuperscript{25}
• High-quality data are lacking on all aspects of HF
  • pathophysiology, epidemiology, diagnosis, prevention, and treatment of HF
  • specific to the population of patients with advanced non-dialysis CKD as well as dialysis and transplant patients

• Breakout Group Discussions
I. Heart failure with preserved ejection fraction (EF≥50%) (HFpEF) and non-dialysis CKD
II. Heart failure with reduced ejection fraction (EF< 40%)(HFrEF) and non-dialysis CKD
III. HFpEF and dialysis-dependent CKD
IV. HFrEF and dialysis-dependent CKD
V. HF in kidney transplant patients.
Objectives

- To review the medical management options for patients with both advancing CKD and HF
- At the end of this talk, the audience will have a greater understanding of the limitations of current knowledge, and areas for future study
What is the scope of this Global Problem?

Between 45-65% of HF patients will have or develop CKD

500 million

40 million

Chronic Kidney Disease

Heart Failure
CUMULATIVE PROBABILITY OF HEART FAILURE IN CKD, DIALYSIS AND KIDNEY TRANSPLANT POPULATIONS

CKD: Incident general Medicare CKD patients, age 66 & older, 2001–2003 combined
ESKD: Incident ESKD patients, age 20 & older
Patients with CHF at baseline excluded. Probabilities unadjusted

Excerpts from USRDS 2007 Annual Data Report. AJKD 2008
Reduced Kidney Function as a Risk Factor for Incident Heart Failure and Heart Failure Increased Risk of eGFR Decline

Percentage change in eGFR between study visits 2 and 4 in individuals who developed HF versus those who did not.

Relative hazard (RH) of incident HF across the range of GFR before and after accounting for measurement error in eGFR.

Prognostic Impact of CKD in HF with Preserved, Mid-Range, and Reduced Ejection Fraction

Swedish HF Registry


Lofman I, et al. EJHF 2017
PATHOPHYSIOLOGY OF HEART FAILURE IN CKD PROGRESSING TO ESKD

Myocyte/Capillary Mismatch in the Heart of Uremic Patients

KERSTIN AMANN,* MICHAEL BREITBACH,‡ EBERHARD RITZ,† and GERHARD MALL‡
Departments of *Pathology and ‡Nephrology, University of Heidelberg, Heidelberg, Germany; and †Department of Pathology, Darmstadt, Germany.

- Arteriolar wall thickening with hypertrophy of VSMCs
- Perivascular interstitial tissue expansion
- Collagen deposition, Interstitial fibrosis
- Capillary rarefaction, decreased ischemic tolerant
Clinical Outcomes of PD Patients Having Heart Failure with Preserved or Reduced Ejection Fraction

P<0.0001

Diagnosis

• No accepted definitions or criteria for HF diagnosis in CKD
• Intravascular and extravascular volume overload can occur in the absence of structural heart disease, especially in patients with dialysis-dependent CKD.
• Echocardiography can support the diagnosis of HF (by providing info on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function and filling pressures) and are fundamental in managing ESKD.
• Imaging should be done when patients on dialysis are close to dry weight (eg. on non-dialysis day for HD patients).
• In addition to reduced LV EF, indicators for LV dysfunction included: LV diastolic volume index > 86ml/m² or LV systolic volume index of > 37ml/m².
• Newly discovered HFrEF in patients undergoing dialysis should prompt full risk stratification for an ischemic versus non-ischemic etiology.
• Revascularization in patients with HFrEF in the general population was supported by 10-year outcome data but no such data exist in dialysis population.
Diagnosis

• HFpEF – assessment using the American Society of Echocardiography grade of diastolic function (grades 1 – 4)
• Other Investigations:
  • Biomarkers such as natriuretic peptides, cardiac troponins, etc may provide additional prognostic values.
  • Chest radiograph – screen for other causes of dyspnoea.
  • Electrocardiograph – detect rhythm disturbances or evidence of myocardial damage or pericardial disease.
• Cardiac MRI
• Whole body bioimpedance
• Extended cardiac rhythm monitoring through wearable and implantable monitors
Prevention of Incident HF

• Hypertension – Tight BP control, defined as targeting systolic BP to < 120mmHg, reduces incident HF with LV Ejection fraction $\geq$ 35% even in the presence of CKD.

• Glycemic control
Prevention of Incident HF - Effect of Intensive BP Treatment on HF Events in the Systolic Blood Pressure Reduction Intervention Trial (SPRINT)

SPRINT ADHF Outcome by treatment group

Subgroup analysis

Upadhya B, et al. Circ Heart Failure 2017

Hazards Ratio: 0.63 (95% CI: 0.46–0.85)
Meta-regression analyses: Relative Risk Reductions for major cardiovascular disease events and HF proportional to the magnitude of BP Reduction achieved

# Standardised Effects of a 10 mmHg Reduction in Systolic Blood Pressure on Major Outcomes

<table>
<thead>
<tr>
<th>Studies</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95% CI) per 10 mm Hg reduction in systolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Participants</td>
<td>Events</td>
<td>Participants</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>---------</td>
<td>--------------</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>55</td>
<td>13209</td>
<td>137319</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>56</td>
<td>4862</td>
<td>136986</td>
</tr>
<tr>
<td>Stroke</td>
<td>54</td>
<td>4635</td>
<td>136682</td>
</tr>
<tr>
<td>Heart failure</td>
<td>43</td>
<td>3284</td>
<td>115411</td>
</tr>
<tr>
<td>Renal failure</td>
<td>16</td>
<td>890</td>
<td>39888</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>57</td>
<td>9775</td>
<td>138298</td>
</tr>
</tbody>
</table>

### Phase 3/4 RCTs of Sodium Glucose Co-transporter-2 Inhibitors

| Drug                        | EMPA-REG OUTCOME | CANVAS Program | DECLARE-TIMI 58 |
|-----------------------------|------------------|----------------|----------------
| Doses analysed             | Empagliflozin    | Canagliflozin  | Dapagliflozin  |
|                             | 10 mg, 25 mg (once daily) | 100 mg, 300 mg (once daily) | 10 mg (once daily) |
| Median follow-up time, years| 3.1              | 2.4            | 4.2            |
| Trial participants          | 7020             | 10142          | 17160          |
| Age, mean                   | 63.1             | 63.3           | 63.9           |
| Women                       | 2004 (28.5%)     | 3633 (35.8%)   | 6422 (37.4%)   |
| Patients with established atherosclerotic cardiovascular disease | 7020 (100%) | 6656 (65.6%) | 6974 (40.6%) |
| Patients with a history of heart failure | 706 (10.1%) | 1461 (14.4%) | 1724 (10.0%) |
| Patients with eGFR < 60 mL/min per 1.73 m² | 1819 (25.9%) | 2039 (20.1%) | 1265 (7.4%) |

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

### Population (prevention)

<table>
<thead>
<tr>
<th>100% Secondary</th>
<th>30% Primary 70% Secondary</th>
<th>60% Primary 40% Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>14% ↓</td>
<td>14% ↓</td>
</tr>
</tbody>
</table>

KDIGO
# Meta-analysis of SGLT-2i Trials on Hospitalization for Heart Failure and Cardiovascular Death Stratified by Presence of Established ASCVD

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>463</td>
<td>19.7</td>
<td>30.9</td>
<td>0.66</td>
<td>(0.55-0.79)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>524</td>
<td>21.0</td>
<td>27.4</td>
<td>0.77</td>
<td>(0.65-0.92)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>597</td>
<td>19.9</td>
<td>23.9</td>
<td>0.83</td>
<td>(0.71-0.98)</td>
</tr>
<tr>
<td>Fixed effects model for atherosclerotic cardiovascular disease (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
<td>(0.69-0.84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Treatment (n)</th>
<th>Placebo (n)</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>128</td>
<td>8.9</td>
<td>9.8</td>
<td>0.83</td>
<td>(0.58-1.19)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>316</td>
<td>7.0</td>
<td>8.4</td>
<td>0.84</td>
<td>(0.67-1.04)</td>
</tr>
<tr>
<td>Fixed effects model for multiple risk factors (p=0.0634)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.84</td>
<td>(0.69-1.01)</td>
</tr>
</tbody>
</table>

Meta-analysis of SGLT2i trials on Hospitalisation for Heart Failure and Cardiovascular Death

Stratified by history of heart failure

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Patients with history of heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>462</td>
<td>244</td>
<td>124</td>
<td>63.6</td>
<td>85.5</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>803</td>
<td>658</td>
<td>203</td>
<td>35.4</td>
<td>56.8</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>852</td>
<td>872</td>
<td>314</td>
<td>45.1</td>
<td>55.5</td>
</tr>
<tr>
<td>Fixed effects model for history of heart failure (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with no history of heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4225</td>
<td>2089</td>
<td>339</td>
<td>15.5</td>
<td>24.9</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>4992</td>
<td>3689</td>
<td>449</td>
<td>13.6</td>
<td>15.2</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>7730</td>
<td>7706</td>
<td>599</td>
<td>8.9</td>
<td>10.5</td>
</tr>
<tr>
<td>Fixed effects model for no history of heart failure (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Composite of worsening of renal function, end-stage renal disease, or renal death

Hospitalisation for Heart Failure and Cardiovascular Death

Meta-analysis of SGLT2i trials on the Different Outcomes Stratified by eGFR Levels

The goal of HF treatment is to improve symptoms, function, Quality of Life (QOL) and decrease hospitalizations and mortality.

Class I recommendations for ACEi and beta blockers first line (substitute ARB where appropriate).

Mineralocorticoid receptor antagonist (MRA) for those who remain symptomatic.

Diuretics used for symptoms or signs of volume overload and congestion.
Treatment of HF in CKD

• Unfortunately, most clinical trials of RAS blockade have systematically excluded patients with advanced CKD (i.e. <30 mL/min/1.73m²)
• Stage 3 CKD (eGFR 30-59) much better represented in pivotal trials
• Small numbers of stage 4 CKD patients did get entered in trials (e.g. SAVE trial of captopril included ~10% of patients with eGFR <45)
• Beta blocker trials have tended to include more advanced CKD patients.
• No proven treatment for HFpEF including in the setting of CKD as trials were done in HFrEF and benefits cannot be assumed to be the same for HFpEF.
<table>
<thead>
<tr>
<th>Study, yr</th>
<th>BB</th>
<th>Pts</th>
<th>Dur</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-HF, 2009</td>
<td>Metoprolol Max 200mg/d</td>
<td>EF &lt; 40%, NYHA II–IV (n=3991), eGFR: 67 ± 20 (mean ± SD)</td>
<td>Mean: 1 yr</td>
<td>All-cause mortality (1° endpoint): HR 0.41 (95% CI 0.25 to 0.68; P &lt;0.001) for CKD subgroup GFR &lt; 45 compared to HR, 0.71 (95% CI, 0.54 to 0.95; P &lt;0.021) for those with eGFR &gt; 60</td>
</tr>
<tr>
<td>CIBIS-II, 2010</td>
<td>Bisoprolol Max 10mg/d</td>
<td>EF ≤ 35%, NYHA III-IV (N=2622), Scr &lt;300umol/L</td>
<td>Mean: 1.3 yr</td>
<td>All-cause mortality (1° endpoint): HR 0.66 (95% CI 0.54–0.81, p &lt;0.0001). SCD: HR 0.56 (0.39–0.80, p=0.0011). Hazard for all-cause mortality, composite of all-cause mortality or HF-hospitalization and HF-hospitalization alone consistently &lt; 1.0 across all eGFR categories. Rate of bisoprolol discontinuation higher with eGFR &lt; 45. Absolute benefit of bisoprolol was greater with CKD versus those without</td>
</tr>
<tr>
<td>Cice, et al. 2003</td>
<td>Carvedilol Max 25mg BD</td>
<td>EF ≤ 35%, NYHA II-III, dialysis (HD pts) (n=114)</td>
<td>24 m</td>
<td>All-cause mortality (1° endpoint): AHR, 0.51 (0.32 - 0.82) All CV mortality: AHR, 0.32 (0.18 - 0.57) All-cause hospitalizations: AHR, 0.44 (0.25 - 0.77) Non-fatal MIs: AHR, 0.81 (0.61 - 1.34) Combined endpoint: 0.76 (0.47 - 1.22) Hospital admission for worsening heart failure: AHR, 0.19 (0.09 – 0.41)</td>
</tr>
</tbody>
</table>
### Point Estimates for Hazard Ratios in the 3 eGFR subgroups

<table>
<thead>
<tr>
<th>No. of events (rate)</th>
<th>Favors Meto CR/XL</th>
<th>Favors Placebo</th>
<th>HR(95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR&lt;45</td>
<td>44(21.7)/24(9.1)</td>
<td></td>
<td>0.41(0.25-0.68)</td>
<td>p=0.095</td>
</tr>
<tr>
<td>eGFR≥45≤60</td>
<td>61(12.2)/39(8.3)</td>
<td></td>
<td>0.68(0.45-1.02)</td>
<td></td>
</tr>
<tr>
<td>eGFR&gt;60</td>
<td>112(8.9)/80(6.4)</td>
<td></td>
<td>0.71(0.54-0.95)</td>
<td></td>
</tr>
<tr>
<td>All randomized</td>
<td>217(11.0)/145(7.2)</td>
<td></td>
<td>0.66(0.53-0.81)</td>
<td></td>
</tr>
</tbody>
</table>

| All-cause mort./all-cause hosp. |                   |                |                  |                     |
| eGFR<45              | 135(98.4)/112(54.8)|                | 0.58(0.45-0.75)  | p=0.046             |
| eGFR≥45≤60           | 213(54.6)/176(47.6)|                | 0.87(0.71-1.06)  |                     |
| eGFR>60              | 417(39.2)/348(32.7)|                | 0.83(0.72-0.95)  |                     |
| All randomized       | 767(48.0)/641(38.8)|                | 0.82(0.73-0.91)  |                     |

| All-cause mort./HF hosp. |                   |                |                  |                     |
| eGFR<45              | 81(45.5)/50(20.2) |                | 0.44(0.31-0.63)  | p=0.011             |
| eGFR≥45≤60           | 133(29.2)/86(19.8)|                | 0.68(0.52-0.89)  |                     |
| eGFR>60              | 224(18.8)/172(14.5)|                | 0.75(0.62-0.92)  |                     |
| All randomized       | 439(23.9)/311(16.5)|                | 0.69(0.60-0.80)  |                     |

Renal Excretion and Dialyzability of Beta-blockers

• Caution with beta-blockers that have significant renal excretion as it may result in over-exposure such as atenolol, nadolol or sotalol.

• Atenolol may be used thrice weekly in HD for BP control and coronary disease.

• Considerations should be given to the potential for dialyzability of certain beta-blockers, as a 1.4 fold high mortality risk was observed in the group treated with highly dialyzable beta-blockers such as metoprolol (Weir MA, JASN 2015).
Evidence for ACEi/ARB in CKD

- Survival and Ventricular Enlargement (SAVE) study of captopril versus placebo post MI
  - >2,200 patients with HFrEF and serum creatinine ≤ 2.5 mg/dL (220 umol/L)
  - ~1/3 had eGFR < 60 mL/min/1.73 m²
  - ~1/10 had eGFR < 45 mL/min/1.73 m²
- CKD patients did worse, but superiority of captopril was maintained in patients irrespective of CKD
  - Tokmakova et al, Circulation 2004

- Other trials of ACEi/ARBs reported similar positive results in patients with CKD G3a and HFrEF.
Worsening kidney function with ACEi/ARB

• Increase in creatinine, or decrease in GFR, is an expected “side effect” of ACEi or ARB

• HF studies that examine kidney outcomes generally show early decline in GFR with stabilization over time

• This does not equate to renal damage \textit{per se}, as it is generally reversible upon reduction or withdrawal

• Studies in patients with renal disease show acute increases up to 30\% that stabilize are strongly associated with renal protection
Role of aldosterone in CRS

### Mineralocorticoid Receptor Antagonist Studies – CKD subgroup analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Primary Outcome</th>
<th>LVEF</th>
<th>NYHA</th>
<th>Renal Function Exclusion; Creatinine, mg/dl (µmol/l)</th>
<th>Baseline Renal Function (eGFR or sCr)</th>
<th>Concomitant Therapy</th>
<th>Renal Subgroup Analysis</th>
<th>Relative Risk (Primary Outcome Study) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>1,663</td>
<td>Spirolactone vs. Placebo</td>
<td>ACM</td>
<td>25</td>
<td>69% III</td>
<td>&gt;2.5 (221)</td>
<td>1.2 mg/dl</td>
<td>48</td>
<td>94</td>
<td>10</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>6,632</td>
<td>Eplerenone vs. Placebo</td>
<td>ACM</td>
<td>33</td>
<td>NA</td>
<td>&gt;2.5 (221)</td>
<td>79 ml/min/1.73 m²</td>
<td>33</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>EMPHASIS</td>
<td>2,737</td>
<td>Eplerenone vs. Placebo</td>
<td>CV mortality or HF hosp</td>
<td>26</td>
<td>100% II</td>
<td>eGFR &lt; 30 ml/min/1.73 m²</td>
<td>71 ml/min/1.73 m²</td>
<td>33</td>
<td>93</td>
<td>87</td>
</tr>
</tbody>
</table>
Influence of Baseline and Worsening Renal Function on Efficacy of Spironolactone in Patients With Severe HF: Insights from RALES Study

Vardeny O, et al. JACC 2012
Primary outcome - a composite of death from CCV events or hospitalization for CCV events
Secondary outcome - death from any cause

N=309 oligoanuric HD pts, 3 years
Angiotensin Receptor Neprilysin Inhibitors (ARNI)

• Valsartan combined with sacubitril (NI) recommended in the ESC guidelines as a replacement for ACE inhibitor (or ARB)
  • symptomatic HFrEF with $\text{LVEF} \leq 35\%$, NYHA II - IV
  • symptomatic despite maximum-tolerated evidence-based doses of ACE inhibitors (or ARBs), β-blockers, and MRAs
  • with a systolic blood pressure of $\geq 100$ mmHg and
  • eGFR $\geq 30$ mL/min/1.73 m$^2$ and
  • potassium $\leq 5.2$ mmol/L

Based on data from PARADIGM-HF trial
PARADIGM-HF Trial
Enalapril vs ARNI

• ~8,400 patients with HFrEF
• stopped early due to an overwhelming benefit in overall mortality, CV mortality, hospitalizations, and HF symptoms in favor of angiotensin receptor neprilysin inhibitor (ARNI)
• Fewer ARNI patients experienced worsening kidney function or serious hyperkalemia

• Important exclusions:
  • baseline eGFR < 30 mL/min/1.73 m²
  • During run-in eGFR falling to <30 mL/min/1.73 m² or >35% decrease in eGFR
  • During run-in K ≥ 5.5 mEq/L

Hyperkalemia

• With combinations of ACEi or ARBs, MRAs, ARNIs - diabetes, CKD and elderly are at risk for hyperkalemia

• New agents (patiromer and ZS-9) which bind potassium showed promising results in controlling hyperkalemia and maintaining normokalemia among subjects with CRS at risk of hyperkalemia

• May allow better implementation of guidelines-mandated use of RAASi, especially MRAs among patients with symptomatic HFrEF and CKD and enable maximal dose of these drugs to be used.

• Need randomized trials.
PHARMACOTHERAPY FOR PREVENTION AND TREATMENT OF HFREF IN CKD PROGRESSION TO ESKD

Other considerations

Avoid AKI (e.g., radiocontrast, NSAIDs, aminoglycosides, vancomycin, lithium)
Treat iron-deficiency anemia
Treat vitamin B and thiamine deficiencies
Optimize CKD-MBD measures
ICD/CRT—as feasible and appropriate

Kidney transplantation

- Nocturnal home hemodialysis
- Peritoneal dialysis
- In-center 3x/week dialysis

ACUTE CRRT

- i.v. thiazides
- i.v. loop diuretics
- Oral metolazone
- Oral loop diuretics
- Oral thiazides

Digoxin
AF control

- H-ISDN
  - If RAASI/ARNI intolerant
  - African American

Lidocaine
- On maximum tolerated β-blocker
- Normal sinus rhythm heart rate > 70

Mineralocorticoid antagonist
- If potassium is acceptable or manageable

- β-Adrenergic blocker
  - Carvedilol/metoprolol tartrate/bisoprolol

ACEi
ARB if ACEi-intolerant
ARNI
Positioning of HF Therapies according to LV EF and Renal Filtration Function
What are the general considerations and limitations of the data?

**General considerations**
- RAS blockade is of primary importance; may need to be reduced or withheld with worsening renal function
- Aldosterone antagonists should be considered and cautiously monitored
- Beta-blockers are important adjuncts in congestive heart failure and/or ischemic heart disease
- ARNiS for symptomatic patients despite maximal tolerated doses of above agents
- Concomitant iron deficiency may worsen symptoms and outcomes

**Caveats/opportunities**
- Most studies exclude patients with significant kidney disease; increase in Creat > 30% or K > 5.0 mmol/L cause for concern
- Creat > 2.5 mg/dL (> 220 µmol/L) or K > 5.0 mmol/L were exclusions in clinical trials
- Some agents (atenolol, nadolol, sotalol) have altered PK; carvedilol, bisoprolol and metoprolol are evidence based
- eGFR <30 or decrease > 35% or K > 5.0 mmol/L all exclusions in PARADIGM
- Parenteral iron improves symptoms, HF hospitalizations and mortality as well as renal function
What other considerations in the CKD population?

**General considerations**

- Multifaceted, with traditional and non-traditional risk factors; graded risk based on degree of CKD
- Anemia closely related to poor outcomes; current guidelines recommend ESA for Hgb < 100 g/L and targeting 100–120 g/L
- Management of CKD-MBD; phosphate binders, vitamin D analogs, controlling PTH
- Lipid lowering with statins

**Caveats/opportunities**

- Lifestyle modification (smoking, weight control, activity, and nutrition) of probable benefit
- Studies show increased harm from higher targets; concerns have been raised about stroke risk, and risk in patients with cancer
- Efficacy largely limited to putative surrogate endpoints; trials with hard CV endpoints discouraging
- Efficacy in dialysis-dependent patients is questioned; in lesser degrees of CKD risk reduction is clearly established
Key Conclusions

• A multidisciplinary approach is vital for improving the understanding of mechanistic and clinical data concerning HF in CKD.

• The interpretation of azotemia ‘Changes in creatinine’ as representing “kidney damage” versus transient worsening kidney function is a great challenge facing clinicians
  
  • Call for a strong mandate for using serum biomarkers beyond creatinine and urea, with improved imaging and refined definitions

• Urgent need for cardiologists and nephrologists to partner and conduct clinical trials esp. in stage 4,5 CKD and that trials be integrative as possible.

• Important to avoid medication toxicity and complications with cardiovascular or renal procedures in the setting of HF and CKD

• Better define role of potassium-lowering medications in HF and CKD

• Important to determine optimal timing, mode, frequency of renal replacement therapy in patients with HF

• Important to include patient-oriented outcomes as well as end-of-life preferences when evaluating therapeutic strategies, particularly in patients who are dialysis-dependent.