Heart Failure in Chronic Kidney Disease

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KDIGO Conference

- In May 2017, in Athens, Controversies Conference on Heart Failure in CKD
- High-quality data are lacking
  - 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

Some Key Conclusions

- Improve understanding of pathophysiology of HF in CKD
- Changes in creatinine as representing “kidney damage” versus transient dynamic functional change is a great challenge
  - Biomarkers, improved imaging, refined definitions
- Urgent need for cardiologists and nephrologists to carry out clinical trials esp. in stage 4,5 CKD
- Determine optimal timing, mode, frequency of renal replacement therapy in patients with HF
- Better define role of potassium-lowering medications

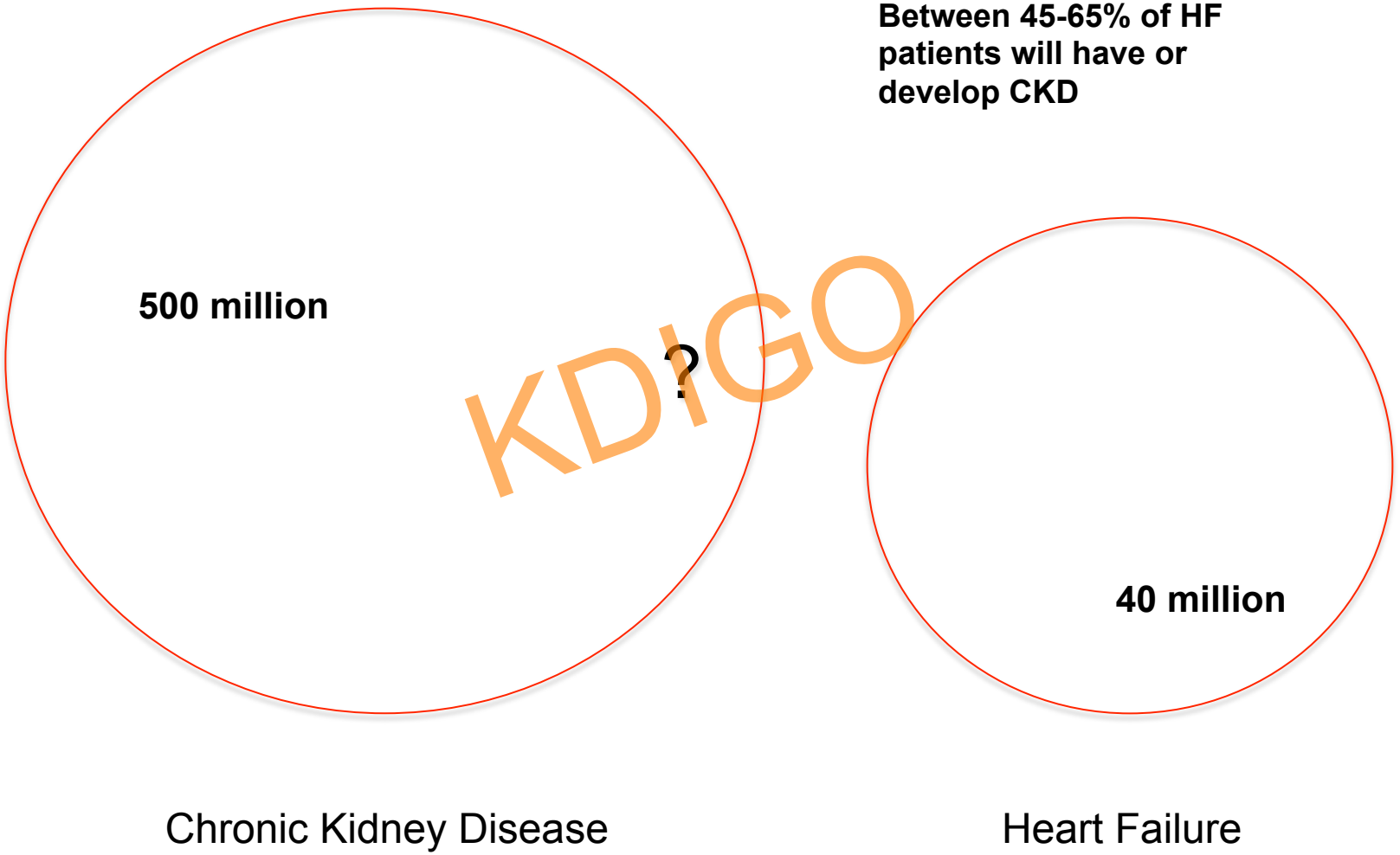
Objectives

- 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
- As there is currently no evidence for *any* treatment of HF with preserved ejection fraction (HFpEF), irrespective of CKD, this talk focuses on HF with reduced EF (HFrEF)

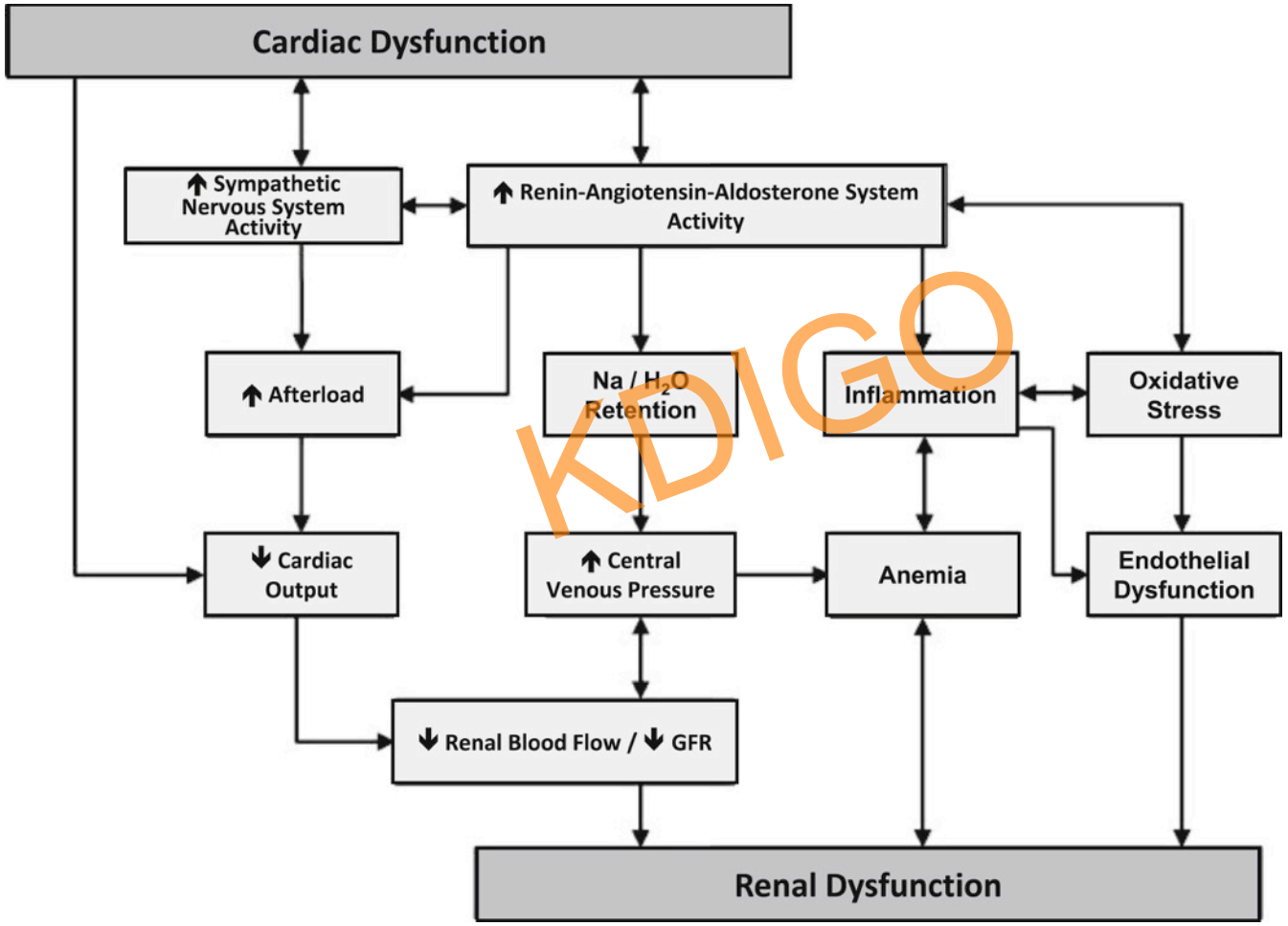
Case presentation

- 82 year old man, long-standing HTN, remote MI, HF with reduced EF of 38%
- ASA 81 mg, Bisoprolol 2.5 mg, Furosemide 40 mg, Candesartan 8 mg, Atorvastatin 40 mg
- ACEi gives intolerable cough
- Symptoms under good control
- BP 118/72, HR 64, mild edema and few crackles
- eGFR between 27 and 30 mL/min/1.73m2, potassium always < 5.0 mmol/L

What is the scope of this? Global Problem



Cardio-Renal Pathophysiology



House AA. *Am J Kidney Dis* 2018

ESC Guidelines for CHF

- The goal of CHF treatment is to improve symptoms, function, QOL and decrease hospitalizations and mortality
- Class I recommendations for ACEi and beta blockers first line (substitute ARB where appropriate)
- MRA for those who remains symptomatic
- Diuretics used for symptoms or signs of volume overload and congestion

ESC Guidelines add-ons

- Select groups may also qualify for:
  - Angiotensin receptor neprilysin inhibitor (ARNI)
  - Cardiac resynchronization therapy (CRT)
  - Implantable cardioverter defibrillator (ICD)
  - Ivabradine
  - Digoxin
  - Hydralazine-isosorbide dinitrate (H-ISDN)
  - Mechanical support or transplant

Guidelines and CKD

- Unfortunately, most clinical trials of RAS blockade have systematically excluded patients with advanced CKD (i.e. <30 mL/min/1.73m^2)
- 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

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 m^2
- ~1/10 had eGFR < 45 mL/min/1.73 m^2
- CKD patients did worse, but superiority of captopril was maintained in patients irrespective of CKD

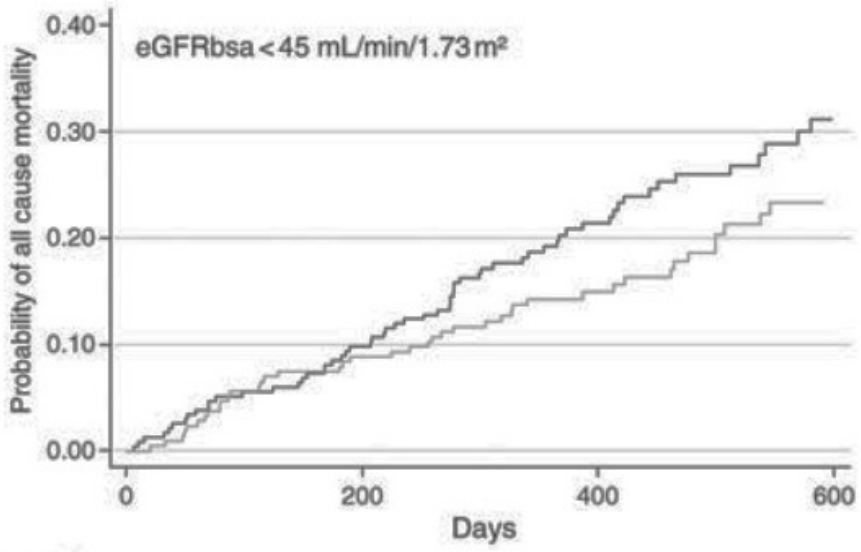
Tokmakova et al, Circulation 2004

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 *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

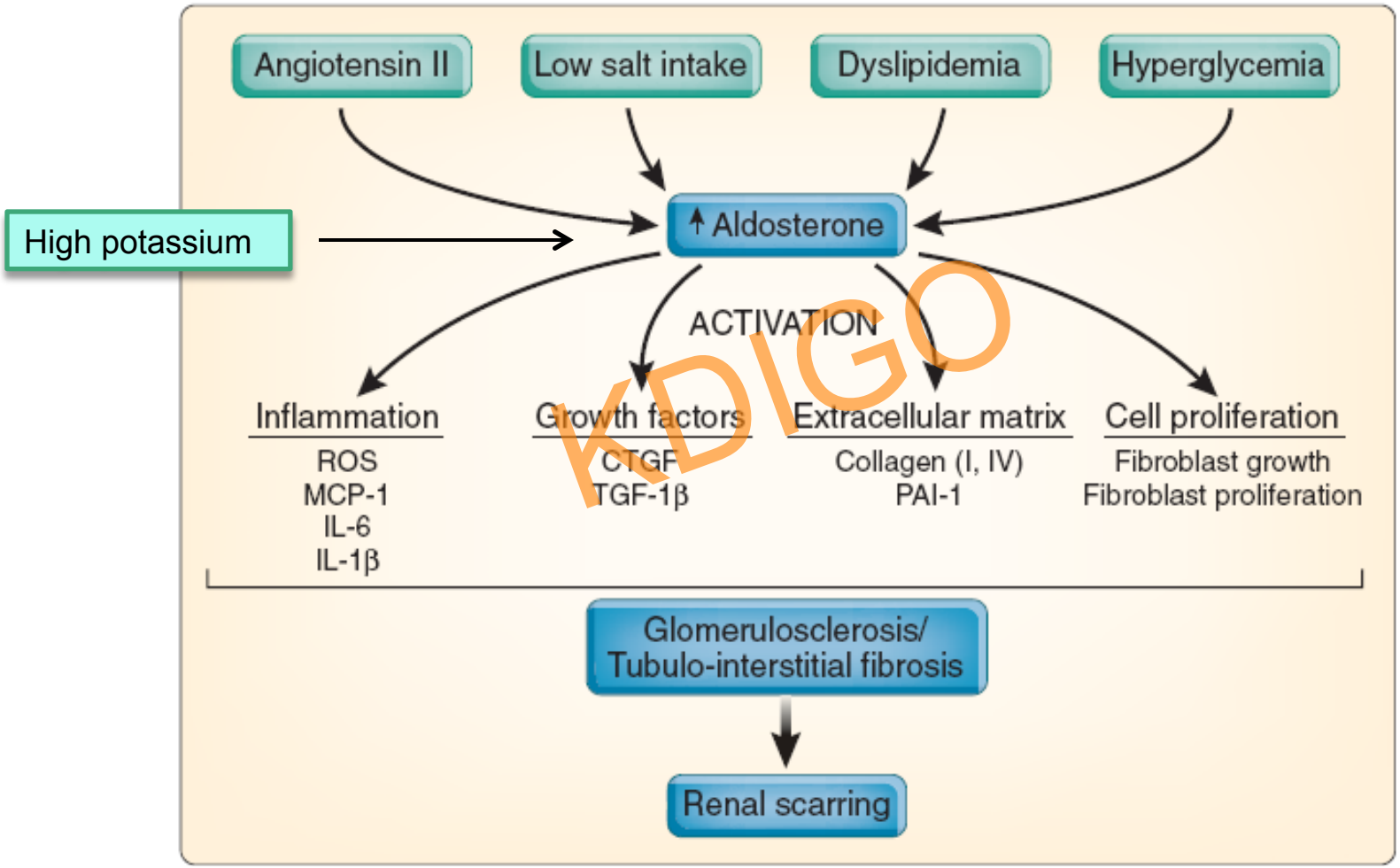
β-blockers in HF and CKD

- Metoprolol CR/XL (MERIT-HF) ~ 4,000 patients
  - ~500 patients with eGFR < 45 mL/min/1.73m^2
- HR for total mortality was 0.41 in favor of metoprolol for the CKD subgroup (as good or better than other subgroups)
- Bisoprolol (CIBIS II) ~ 2,600 patients
  - Included serum creat up to 300 µmol/L (3.4 mg/dL)
  - HR for death 0.66 (0.54-0.81)
- No decrease in the benefits of bisoprolol with worsening kidney function



Ghali JK et al. J Card Fail 2009
Castagno D et al. Eur J Heart Fail 2010

Role of aldosterone in CRS



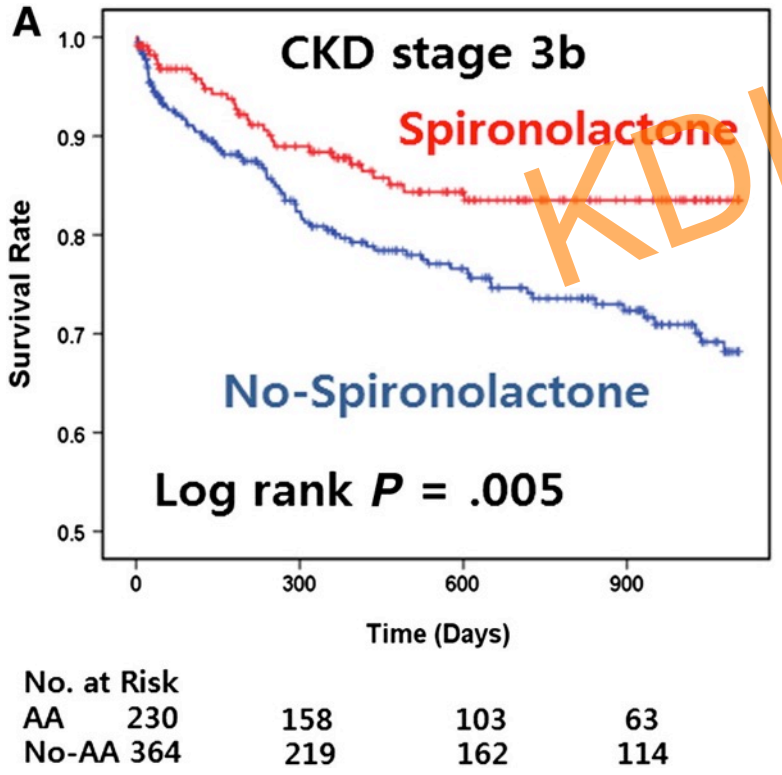
Remuzzi *et al:* J Am Soc Nephrol (2008) 19, 1459–1462

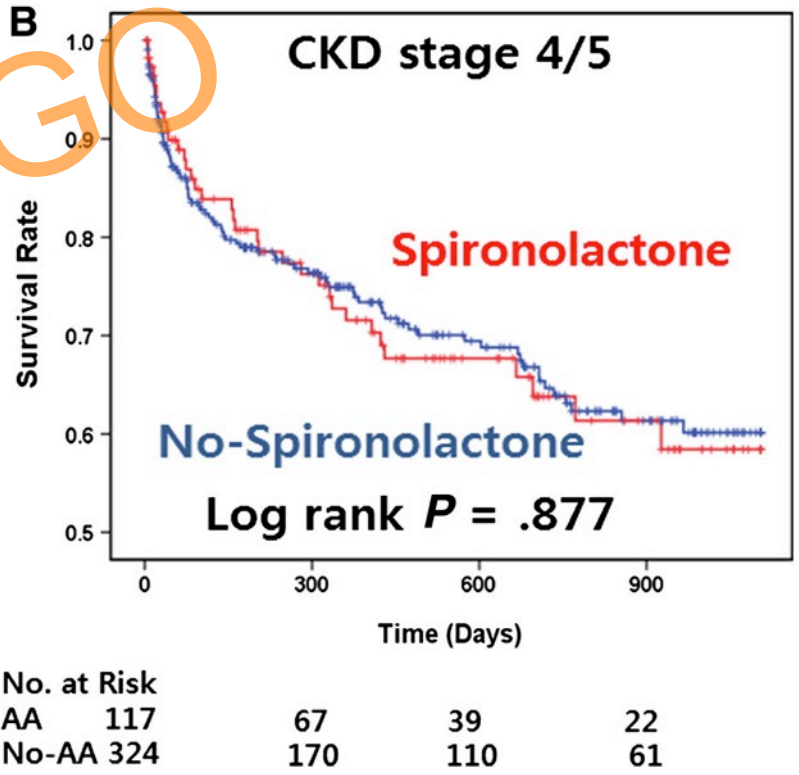
MRA / Aldosterone Blockade

- Pivotal trials of MRA (RALES and EPHESUS) showed benefits on treatment of advanced HF
- Looked at changes in creatinine over time, but as with RAS blockade, difficult to tease out the effect of initial changes in GFR due to ECFV contraction
- No examination of important long-term renal outcomes (doubling of Creat, renal death), nor any renal injury biomarkers
- Significant CKD and/or hyperkalemia were exclusions

MRA and severe CKD
Korean HF Registry

- ~1000 pts hospitalized for HF with eGFR < 45 mL/min
- Use of spironolactone assoc. with decreased mortality in univariate, but not multivariate analysis





Oh J et al. Am Heart J, 2015

Case

- Do guidelines apply to the patient in our case?
- Pretty borderline with eGFR between 27 and 30 mL/min
- ARB with good BP control, stable renal function, normal potassium so reasonable to leave it
- Beta blockers have a bit more evidence at levels below 30 mL/min
- MRA might be a consideration but high risk for hyperkalemia

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 LVEF ≤ 35%
  - symptomatic despite maximum-tolerated evidence-based doses of ACE inhibitors (or ARBs), β-blockers, and MRAs

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 favour of ARNI
- Fewer ARNI patients experienced worsening kidney function or serious hyperkalemia
- Important exclusions:
  - baseline eGFR < 30 mL/min/1.73 m^2
  - During run-in eGFR falling to <30 mL/min/1.73 m^2 or >35% decrease in eGFR
  - During run-in K ≥ 5.5 mEq/L

McMurray JJ et al. *N Engl J Med.* 2014

Hyperkalemia

- With combinations of ACEi or ARBs, MRAs, ARNIs, diabetes, CKD all are risks for hyperkalemia
- New agents (patiromer and ZS-9) which bind potassium are showing promise in allowing use of these agents in this population
- Cost, availability, limited post-marketing surveillance, potential for drug interactions / binding are potential limitations

Case continues

- During a severe bout of pneumonia, patient develops AKI, hyperkalemia, worsening CHF symptoms
- ARB and furosemide stopped
- At discharge he has more edema, eGFR is well below 20 mL/min and potassium is 5.2
- We reintroduce furosemide, then carefully resume ARB. Creatinine rises over 50% and potassium up to 5.6. Now what?

What to do for the truly ACEi/ARB intolerant patient?

- Hydralazine-isosorbide dinitrate (H-ISDN)
  - Opinion-based (mine) versus evidence-based
  - Fixed dose combination H-ISDN was used in African-American Heart Failure Trial (A-HeFT) added to standard therapy
    - ~40% reduction in mortality and hospitalization
    - Included 17% of patients with CKD
  - Very old trials V-HeFT I and II showed H-ISDN to be better than placebo for mortality
    - Incomplete data on kidney function

Taylor AL et al. *Circulation.* 2007

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

Case conclusion (?)

- Uptitrated H-ISDN to maximum tolerated dose of 200 mg / 120 mg daily in four divided doses
- Flexible diuretic regimen to maintain target weight
- Followed in multidisciplinary CKD clinic with information on dialysis and conservative care
- Intermittent parenteral iron
- His symptoms, functional status and renal function stabilize
- Just celebrated his 90th birthday!!

Summary

- Worldwide rates of CKD are steadily increasing
  - Steady improvement in prevention and treatment of infectious disease, cancers and CVD
  - Aging population
  - High rates of diabetes and HTN
- Increased prevalence of patients suffering both CKD and HF
  - Shared risk factors between CKD and heart disease
  - Important contributions of CKD to HF and vice versa
- Significant gaps in the literature with more advanced CKD

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