New advances in Hyperkalaemia management in Diabetic Kidney Disease and beyond

Dr Kieran McCafferty
Disclosures

AstraZeneca:
Grant holder from company
Honoraria: Advisory boards, presentations at meetings, Congress attendance

Vifor Fresenius
Honoraria: Advisory boards, presentations at meetings, Congress attendance
Overview

Hyperkalaemia: prevalence and associations
3 decades of RAASi therapy for the Heart and Kidney
Hyperkalaemia: a barrier to guideline-recommended RAASi therapy
Current treatment options for Hyperkalaemia have limitations
Current/future Potassium binders
Summary
Hyperkalaemia† is often associated with cardio-renal disease and patients typically suffer from multiple comorbidities

†defined as serum potassium > 5.0 mmol/L

Up to 40-50% of patients with advanced CKD experience hyperkalaemia, occurring more commonly in those with diabetes.¹

Up to ~40% of patients with HF experience hyperkalaemia over a mean 2.2 year period.²

†defined as serum potassium > 5.0 mmol/L

Up to 16% of patients with diabetes develop with hyperkalaemia over a 4-year period.³

†defined as serum potassium > 5.0 mmol/L

CKD, Chronic Kidney Disease; HF, Heart Failure; HK, hyperkalaemia

Higher serum K⁺ levels and comorbidities increase the mortality risk associated with HK.

Risk of all-cause mortality by serum K⁺ level and comorbidities (N=911,698)*

Adapted from: Collins AJ, et al. (2017)

* Retrospective analysis of medical records from a geographically diverse population in the US. ** Control group comprised of individuals without known HF, CKD, DM, CVD, or HTN.

CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HK, Hyperkalaemia; HTN, hypertension

CKD patients with hyperkalaemia have significantly increased 24-h mortality

Higher serum potassium levels are associated with an increased risk of mortality in haemodialysis patients.

K⁺ concentrations and survival in haemodialysis patients (n=74,219)

Kovesdy cJASN 2007
Many patients with CKD have recurrent episodes of hyperkalaemia, with successively shorter time between episodes.

Population-based cohort study linking individual data from mandatory hospital, prescription, and laboratory databases in Northern Denmark (population 1.8 million) during 2000–2012 (N=157,766)

CKD, chronic kidney disease; HK, hyperkalaemia

From the source population of all individuals living in northern Denmark between 2000 and 2012, a cohort of patients were identified with an incident CKD diagnosis, defined as the first occurrence of one of the following: (i) a second creatinine measurement >90 days following a prior measurement, corresponding to a second estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²; (ii) an incident hospitalisation with a diagnosis of CKD or (iii) hospital-based codes for renal dialysis. The severity of CKD was further classified according to CKD stage, based on the lowest eGFR recorded (or presence of dialysis) up to the date of meeting the CKD definition (the index date), as follows: Stages 1 and 2: eGFR 60 mL/min/1.73m²; Stage 3A: eGFR 45–59; Stage 3B: eGFR 30–44; Stage 4: eGFR 15–29; Stage 5: eGFR <15 or dialysis

25 years of RAASi therapy in renoprotection
THE EFFECT OF ANGIOTENSIN-CONVERTING-ENZYME INHIBITION ON DIABETIC NEPHROPATHY

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D.,
AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*

400 patients with Type 1 DM and Cr <221
Received Captopril versus placebo
The Collaborative Study Group

Risk reduction: 48% (16, 69)  
\[ P = 0.007 \]

Risk reduction: 50% (18, 70)  
\[ P = 0.006 \]

EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

N=590, hypertensive, type 2 DM and microalbuminuria

RENOProtective effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes

IDNT study N=1715
33% reduction in doubling serum creatinine
23% reduction in development of ESRD

3 decades of HFrEF Studies in 1 slide…

Favours treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARNI + BB + MRA</td>
<td>0.37 (0.19, 0.65)</td>
</tr>
<tr>
<td>ACEi + BB + MRA</td>
<td>0.44 (0.26, 0.66)</td>
</tr>
<tr>
<td>ACEi + ARB + BB</td>
<td>0.52 (0.31, 0.80)</td>
</tr>
<tr>
<td>ACEi + MRA</td>
<td>0.57 (0.35, 0.91)</td>
</tr>
<tr>
<td>ARB + BB</td>
<td>0.47 (0.23, 0.86)</td>
</tr>
<tr>
<td>ACEi + ARB</td>
<td>0.83 (0.51, 1.24)</td>
</tr>
<tr>
<td>ACEi + BB</td>
<td>0.57 (0.41, 0.72)</td>
</tr>
<tr>
<td>BB</td>
<td>0.57 (0.33, 0.94)</td>
</tr>
<tr>
<td>ARB</td>
<td>0.88 (0.61, 1.26)</td>
</tr>
<tr>
<td>ACEi</td>
<td>0.83 (0.66, 1.01)</td>
</tr>
</tbody>
</table>

Favours placebo

Burnett H et al. 2017 Circ Heart Fail,
However, due to RAASi-induced hyperkalaemia, guidelines also recommend discontinuation of RAASi therapy.

Serum Potassium treatment threshold (mmol/L)

<table>
<thead>
<tr>
<th>Threshold</th>
<th>NICE</th>
<th>KDOQI</th>
<th>TK/RA/BSHF</th>
<th>ESC–HF 2016</th>
<th>ESC 2018</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.0</td>
<td>Do not initiate RAASi therapy.¹</td>
<td>Down-titrate RAASi therapy by 50%.⁶</td>
<td>Down-titrate RAASi therapy by 50%.³</td>
<td>short term cessation RAASi.²</td>
<td>Initiate potassium-lowering agent.⁵</td>
<td>Treatment with insulin dextrose ± salbutamol; discontinue RAASi.⁴</td>
</tr>
<tr>
<td>&gt;5.5</td>
<td></td>
<td>Use RAASi therapy with caution.⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of Patients Who Had Adverse Outcomesa, or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stages 3-4 (N = 31,546)</td>
<td>CKD Stages 3-4 (N = 31,546)</td>
</tr>
<tr>
<td>Total patients across dose categories</td>
<td>Maximum Dose 50.1%</td>
</tr>
<tr>
<td>Heart Failure (N = 13,602)</td>
<td>Heart Failure (N = 13,602)</td>
</tr>
<tr>
<td>Total patients across dose categories</td>
<td>Maximum Dose 57.7%</td>
</tr>
<tr>
<td>Diabetes (N = 37,693)</td>
<td>Diabetes (N = 37,693)</td>
</tr>
<tr>
<td>Total patients across dose categories</td>
<td>Maximum Dose 45.3%</td>
</tr>
<tr>
<td>Total Populationb (N = 90,898)</td>
<td>Total Populationb (N = 90,898)</td>
</tr>
<tr>
<td>Total patients across dose categories</td>
<td>Maximum Dose 48.6%</td>
</tr>
</tbody>
</table>

---

a% of patients with at least one adverse outcome event (prespecified or otherwise).
bTotal population includes all patients who had at least one AEs event from any source or indication during the study period.
In 2013 over 70,000 ED visits due to hyperkalaemia.
>50% admitted to hospital. Mean stay of 3.1 days. Mean inpatient cost of $27,802
Barriers to ACEi/ARB use and optimization

- Retrospective observational study
- Identified all patients with Type 2 diabetes as a cause of their CKD and excluded those on dialysis/renal transplant.
- Examined those patients for maximum ACE/ARB, and the barriers to this.
A total 259 (62.9%) were on suboptimal doses of ACE/ARB or not on these agents at all.
Reasons for ACEi/ARB suboptimal dosing

Chong et al. ASN 2017 (poster)
### Current treatment options for managing hyperkalaemia

#### Temporising agents
- iv insulin dextrose ± salbutamol
- **Pros:**
  - Temporising agent only (i.e. shifts potassium into the cells).
  - Significant risk of hypoglycaemia.
  - May require >1 dose.
  - Occasions of suboptimal management, highlighted by an NHS Improvement Safety Alert in 2018.
- **Cons:**
  - There are few studies demonstrating evidence of efficacy.
  - Gastric irritation, anorexia, nausea, vomiting, constipation and occasionally diarrhoea may occur.
  - Potential non-compliance due to GI tolerability.
  - Concerns of bowel necrosis and poor tolerability may limit chronic use.

#### Other pharmacological interventions
- Calcium resonium

#### Diet
- Low potassium diets
- **Pros:**
  - Low potassium diet falls outside what is generally recommended as a healthy diet.
  - Dietary restrictions are difficult to adhere to.
  - However, it can offer a level of empowerment to patients to control their health condition.
  - A low potassium intake may increase blood pressure.
- **Cons:**
  - See next slide

#### Modification of current therapies
- Down-titration / discontinuation of RAASi

### A&E / inpatient setting vs. Outpatient setting
Insulin Dextrose

• Is not a benign therapy…

• Large retrospective cohort of general medical admissions with insulin dextrose:
  – 9% became hypoglycaemic <4
  – Almost 3% had blood sugars 2.2 or below¹

• In non diabetic dialysis patients: 10U of Insulin and 50ml of 50% Dextrose, led to hypoglycaemia (glucose<3) in 75% of patients at 1h²

---

Are we optimally managing patients with HK?

HK, hyperkalaemia; RAASi, renin–angiotensin–aldosterone system inhibitor
Novel Potassium binders

- Patiromer/Veltassa
- Lokelma/SZC
OPAL-HK Phase 3 Patients With CKD on RAASi

Part A: Treatment Phase (Single-Blind)
- Subjects with CKD* on RAASi (N=243)
  - Mild hyperkalemia: Baseline serum K⁺ 5.1–<5.5 mEq/L; 4.2 g BID starting dose (n=92)
  - Moderate to severe hyperkalemia: Baseline serum K⁺ 5.5–6.5 mEq/L; 8.4 g BID starting dose (n=151)

Part B: Randomized Withdrawal Phase (Single-Blind)
- Subjects with Part A baseline K⁺ ≥5.5 mEq/L who completed Part A and
  - Serum K⁺ 3.8–<5.1 mEq/L at Part A, week 4
    - Still on patiromer
    - Still on RAASi (n=107)
- Patiromer, continued RAASi (n=55)
- Placebo, continued RAASi (n=52)

Baseline Part A
Week 4 Part A Primary Endpoint
Baseline Part B
Week 4 Part B Primary Endpoint
Week 8 Part B Sec. Endpoints

Primary and Secondary Efficacy Endpoints

Secondary Efficacy Endpoint: 76% of subjects had serum K⁺ in the target range (3.8 to <5.1 mEq/L) at week 4.

Primary efficacy endpoint: mean change from baseline to Week 4 (all subjects)

- Mild HK
  - Change: -0.65 (95% CI -0.74, -0.55)
- Mod/Severe HK
  - Change: -1.23 (95% CI -1.31, -1.16)
- All subjects
  - Change: -1.01 (95% CI -1.07, -0.95)

*p < 0.001

Exploratory end point: effect of Patiromer on the proportion of patients discontinuing RAASi therapy

**AMETHYST-DN: Study Design**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Run-in</th>
<th>Randomization</th>
<th>Treatment Phase</th>
<th>Daily, Long-term Maintenance Phase</th>
<th>4-Wk Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 days</td>
<td>≤4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 1:</strong> Discontinue RAASi and start losartan 100 mg/d (add spiro after wk 2 for BP control if needed)</td>
<td>Mild HK (K⁺ &gt;5.0 – 5.5 mEq/L)</td>
<td>4.2 g patiomer BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 2:</strong> Continue current RAASi and add spiro 25 mg/d</td>
<td>Moderate HK (K⁺ &gt;5.5–&lt;6.0 mEq/L)</td>
<td>8.4 g patiomer BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 3:</strong> All above criteria minus ACR requirement</td>
<td>Skip run-in, maintain current RAASi</td>
<td>12.6 g patiomer BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.8 g patiomer BID</td>
<td>Patiomer dose titrations in all groups, as needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- RAASi: renin-angiotensin-aldosterone system inhibitor, spiro: spironolactone.
- eGFR 15-60 mL/min/1.73 m².

**Study visit, wk**

- **Baseline**
- 1
- 4
- 8
- 12
- 16
- 20
- 24
- 28
- 32
- 36
- 40
- 44
- 48
- 52
- 2
- 4

**Serum potassium (mEq/L)**

- **Mild**
- **Moderate**

**No. of patients**

- **Hyperkalemia**
  - Mild: 218, 204, 199, 192, 175, 168, 161, 161, 163, 158, 156, 151, 148, 149, 145, 131, 126

**Follow-up**

- Day 3

---

*All serum $K^+$ analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum $K^+$ value at baseline and therefore are not included in the analysis at this timepoint. At all timepoints, $P<0.001$ (2-sided t-test) for least-squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study).*

Novel Potassium binders

- Patiromer/Veltassa
- Lokelma/SZC
HARMONIZE (004): Study design

Primary efficacy endpoint

The primary endpoint is the comparison of mean potassium levels between placebo and each treatment arm during days 8 through to 29 of randomised phase. Population: 258 patients with hyperkalaemia (K⁺ ≥ 5.1 mmol/L, baseline average 5.6 mmol/L).
SZC: Reduction of serum potassium levels

In the 48 hour open label phase of the study, one dose (10g) of SZC significantly reduced the mean serum K\(^+\) level after 1 hour.\(^1,2\)

-0.2 mmol/L compared to baseline. 95% CI: -0.3 to -0.2.\(^2\)

In an emergency situation, standard of care should be used in line with local or national guidelines.

Results of open label induction phase (absolute change in K\(^+\) and proportion of patients achieving normokalaemia) are secondary endpoints.

88% of patients achieved normokalaemia at 48 hours.\(^1\)

Adapted from Kosiborod et al., 2014\(^2\)
HARMONIZE (004): Open-label extension

Primary efficacy endpoint

The primary endpoint is the comparison of mean potassium levels between placebo and each treatment arm during days 8 through to 29 of randomised phase. Population: 258 patients with hyperkalaemia (K+ ≥5.1mmol/L, baseline average 5.6mmol/L).¹

---

**Open-label phase**

- n=258
- THREE TIMES DAILY
- SZC 10g
- Patients who achieved normokalaemia a

**28-DAY RANDOMISED¹**

- n=237
- ONCE DAILY
- Placebo
- SZC 5g
- SZC 10g
- SZC 15g

**11-MONTH EXTENSION²**

- n=123 c
- ONCE DAILY
- SZC 10g

SZC dose was increased or decreased in increments/decrements of 5g OD to maximum of 15g OD or minimum of 5g every other day if Abbott i-STAT™ potassium values increased to >5.5 mmol/L or decreased to between 3.0 and 3.4 mmol/L, respectively.²

Please note that the 15g dose is not approved for use.²
SZC: Sustained serum $K^+\$ control for up to 1 year when used as maintenance therapy.

- Once-daily maintenance dosing of SZC sustains normokalaemia (3.5 – 5.0 mmol/L) for up to one year.$^{1,2}$
- 88% of patients in the Extension Phase receiving SZC maintained an average serum $K^+$ of <5.1 mmol/L over 11 months.$^{1,2}$
- No dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations.$^{1,2}$
SZC: consistent serum K⁺ reduction in all studied patient groups.

Subgroup analysis performed on data from the open label induction phase showed:

- **SZC consistently reduced serum K⁺, regardless of comorbidities*, use of RAASi therapy, or baseline K⁺ level.**²
- Greater reductions in serum K⁺ were observed in patients with higher baseline serum K⁺ levels.²

Statistical analysis of differences between baseline and 48 hours was not reported in Kosiborod et al (2014).²
Drug-drug interactions.

- As SZC is not absorbed or metabolised by the body, and does not meaningfully bind other medicinal products
- SZC can transiently increase gastric pH by absorbing hydrogen ions and can lead to changes in solubility and absorption kinetics for co-administered medicinal products with pH-dependent bioavailability.

However, SZC should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability. Examples of medicinal products that should be administered 2 hours before or after SZC to avoid possible raised gastric pH drug interaction are:

- **azole antifungals** (ketoconazole, itraconazole and posaconazole),
- **anti-HIV drugs** (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir and rilpivirine) and
- **tyrosine kinase inhibitors** (erlotinib, dasatinib and nilotinib).
SZC dosage and methods of administration
Recommended dosing of SZC to achieve and sustain normokalaemia

**Correction phase**

Recommended starting dose: 10g three times daily for up to 48 hours until normokalaemia is achieved.*

In an emergency situation, standard of care should be used in line with national or local guidelines.

**Maintenance phase**

Recommended starting dose: 10g three times daily for up to 48 hours until normokalaemia is achieved.*

To establish minimum effective dose, SZC may be titrated:
• Up to 10g once daily or
• Down to 5g once every other day

No more than 10g once daily should be used for maintenance therapy.

1×/day**

5g for up to 1 year

Mix SZC with 3 tablespoons (45 mL) of water for oral administration.

- Tasteless and odourless
- May be taken with most other medication
- May be taken with or without food
- No special conditions for storage

In a correction phase, standard of care should be used in line with national or local guidelines.
NICE approval 4th September 2019

- Sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults only if used:
- In emergency care for acute life-threatening hyperkalaemia alongside standard care or
- In outpatient care for people with persistent hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure, if they:
  - have a confirmed serum potassium level of at least 6.0 mmol/litre
  - are not taking an optimised dosage of renin-angiotensin-aldosterone system (RAAS) inhibitor because of hyperkalaemia and
  - are not on dialysis.

In outpatient care, stop sodium zirconium cyclosilicate if RAAS inhibitors are no longer suitable.
Comparison of novel K binders
<table>
<thead>
<tr>
<th><strong>Lokelma</strong></th>
<th><strong>Patiromer</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inorganic crystalline zirconium silicate compound, swapping Na for K</td>
<td>Cation exchange polymer containing a calcium-sorbitol complex as a counterion</td>
</tr>
<tr>
<td>Dose: 5g-10g</td>
<td>Dose 8.4g-25.2g</td>
</tr>
<tr>
<td>Cost: £7.12 for 5g</td>
<td>Cost: £10 for 8.4g</td>
</tr>
<tr>
<td>Onset of Action: 1 hour</td>
<td>Onset of action: 4-7 hours</td>
</tr>
<tr>
<td>Data on safety and effectiveness out to 1 year</td>
<td>Data on safety and effectiveness out to 1 year</td>
</tr>
<tr>
<td>No effect on Ca/Mg</td>
<td>May lower calcium/magnesium by a small amount</td>
</tr>
<tr>
<td>Interactions: avoid administration within 2h of drugs affected by gastric pH bioavailability: some azole antifungals, anti-HIV drugs and tyrosine kinase inhibitors.</td>
<td>Interactions: Concomitant administration of Patiromer showed reduced bioavailability of ciprofloxacin, levothyroxine and metformin.</td>
</tr>
<tr>
<td>Can be taken with food</td>
<td>Avoid food/other medications within 3h</td>
</tr>
<tr>
<td>Most frequent adverse reactions reported from trials oedema related events (5.7%), constipation (2.9%), nausea (1.6%) diarrhoea (0.9%), abdominal pain/distension (0.5%), and vomiting (0.5%)</td>
<td>Most frequent adverse reactions reported from trials constipation (6.2%), diarrhoea (3%), abdominal pain (2.9%), flatulence (1.8%) and hypomagnesaemia (5.3%)</td>
</tr>
<tr>
<td>Chronic treatment fall in around 0.8-1.2mmol K</td>
<td>Chronic treatment fall in around 0.8-1.2mmol K</td>
</tr>
<tr>
<td>NICE approved</td>
<td>Not currently NICE approved</td>
</tr>
</tbody>
</table>
Summary

- Hyperkalaemia is common in patients with CKD, HF, diabetes, and hypertension, and is associated with clinical burden and increased healthcare costs.
- Hyperkalaemia treatment options may be associated with limitations:
  - Low-potassium diets, diuretics, lowering RAASi dosing, older potassium binders.
- Novel K binders represent a leap forward in hyperkalaemia management: both appear safe and effective in the short and long term (up to 1 year).