The clinical landscape of managing patients with CKD: Where are we now and what can we expect?

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The Clinical Landscape of Managing CKD: Where Are We Now and What Can We Expect

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Speaker disclosure

Relationships with commercial entities:

• Consulting / honoraria: Boehringer Ingelheim, Lilly, Janssen, Merck, AstraZeneca, Mitsubishi-Tanabe, Sanofi,

• Clinical trials: CREDENCE, TRANSLATE, BETWEEN, DIAMOND, DAPA-CKD, SCORED, EMPA-CKD, INDORSE, ERADICATE-HF
Objectives

• Hemodynamic effects of sodium glucose cotransport-2 (SGLT2) inhibitors
• Effects of SGLT2 inhibitors in non-diabetic CKD
• Future trials
SGLT2 inhibition

SGLT2, sodium–glucose co-transporter 2
The “Tubular Hypothesis”: Normal Physiology

The “Tubular Hypothesis”: Diabetes and Hyperfiltration

The “Tubular Hypothesis”: Diabetes and SGLT2 Inhibition

SNGFR and the afferent arteriole

Kidokoro et al. ADA (abstract) 2018
In vivo imaging of A.A. change before and after empagliflozin

Before medication

Efferent A.

Afferent A.

G

2hrs after medication

Efferent A.

Afferent A.

G

Red: BSA-Alexa594

Courtesy: Kidokoro//Kashihara. American Diabetes Association Meeting – Saturday June 23, 2018
SGLT2 inhibition and the role of adenosine

Kidokoro et al. ADA (abstract) 2018
The alteration of SNGFR by empagliflozin under A1aR antagonist

Before medication

SNGFR (nl/min)

Control
Control
/A1aR-a
/Ins2+/Akita
/Ins2+/Akita
Empa
/A1aR-a

30 min after medication

Red: BSA-Alexa594

*p = 0.01

*p = 0.0011

*p = 0.01

p = 0.99

Courtesy: Kidokoro//Kashihara. American Diabetes Association Meeting – Saturday June 23, 2018
Pharmacological actions:

**SGLT2 inhibition**
- Afferent constriction

**RAAS blockade**
- Efferent dilation

**SGLT2 inhibition and RAAS blockade**
- Afferent constriction and Efferent dilation

Haemodynamic effects and clinical implications:

- **A**
  - Decreased intraglomerular pressure due to increased afferent resistance in T1D-H patients
  - Decreased hyperfiltration

- **B**
  - Decreased intraglomerular pressure due to decreased efferent resistance
  - Decreased hyperfiltration
  - Proven renal protection in clinical trials

- **C**
  - Normalisation of intraglomerular pressure due to increased afferent and decreased efferent resistance?
  - Potential for additive intraglomerular pressure reduction?
  - Potential for long-term renal protection?
SGLT2 inhibition

Neil et al. NEJM June 12, 2017
SGLT2 Inhibitors – Non-Diabetic Conditions

Overweight otherwise healthy\(^1\)

- \(\sim 8\% \text{ measured GFR} \)

\[ \Delta 8 \text{ ml/min/1.73 m}^2 \]

- Baseline
- Day 3

- \(* p < 0.05 \text{ vs baseline} \)

Pre-diabetes or obesity\(^2\)

- \(\sim 12\% \text{ creatinine clearance} \)

\[ \Delta 16 \text{ ml/min/1.73 m}^2 \]

- Baseline
- Acute

\(+p=NS \text{ vs baseline} \)

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Renal protection in *non-diabetic* kidney disease? Pilot data in patients with FSGS

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.2±9.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female Sex - n (%)</td>
<td>4 (40)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>30.0±8.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FSGS duration, years</td>
<td>5.6±5.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GFR</td>
<td>93.9±18.2</td>
<td>85.9±16.9</td>
<td>NS</td>
</tr>
<tr>
<td>Renal plasma flow</td>
<td>513.5±161.2</td>
<td>496.6±152.0</td>
<td>NS</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.19±0.035</td>
<td>0.18±0.039</td>
<td>NS</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>881.7±287.1</td>
<td>853.0±245.6</td>
<td>NS</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>0.11±0.03</td>
<td>0.11±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>24 hour urine protein</td>
<td>2.6±1.9</td>
<td>2.4±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>112.7±8.5</td>
<td>112.8±11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>71.8±6.5</td>
<td>69.6±8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight</td>
<td>88.2±25.1</td>
<td>87.0±25.4</td>
<td>NS</td>
</tr>
<tr>
<td>24h urine glucose (g/day)</td>
<td>0.2±0.2</td>
<td>37.5±23.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.5±0.5</td>
<td>5.5±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.40±0.054</td>
<td>0.42±0.049</td>
<td>0.023</td>
</tr>
</tbody>
</table>
Renal function, structure: subtotally nephrectomized (SNx) Sprague-Dawley rats

- No effect: $\text{GFR}_{\text{inulin}}$, $\text{ERPF}_{\text{PAH}}$, proteinuria
CREDENCE Trial
- Focus on T2D/DKD
- Only completed DKD trial (terminated early due to efficacy)
  - eGFR ≥30 to <90 ml/min/1.73 m² and >300 mg/g UACR

DKD, eGFR 30-75 ml/min/1.73m² and >300 mg/g UACR

EMPAA-KIDNEY Trial
- Patients with T1D
- DKD + non-DKD etiologies
- Lowest eGFR level (20 ml/min/1.73m²)
- Patients with/without albuminuria for eGFR 20-45 ml/min/1.73m²
- With eGFR >45 ml/min/1.73m² must have >200 mg/g UACR

T2D
- eGFR 45-75 ml/min/1.73m² + UACR >300 mg/g
- Primary composite includes renal and CV endpoints
- Excludes PCKD, immunosuppression

DKD + non-DKD etiologies eGFR 25-75 ml/min/1.73m² and >200 mg/g UACR

DAPA-CKD Trial
DKD+non-DKD etiologies eGFR 25-75 ml/min/1.73m² and >200 mg/g UACR
**EMPA-KIDNEY** is an phase III, randomised, double-blind, placebo-controlled outcome trial

*Single RAS inhibition in clinical appropriate dose and management of CV risk factors and other existing comorbidities incl. hypertension and diabetes

ClinicalTrials.gov NCT03594110 (all accessed July 2018)
Both CVOTs and dedicated renal outcomes trials with SGLT2 inhibitors will generate data on renal endpoints

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient cohorts</th>
<th>N</th>
<th>Endpoints</th>
</tr>
</thead>
</table>
| DELIGHT¹      | Dapagliflozin / dapagliflozin + saxagliptin / placebo 1:1:1 | 460 | **Primary:** Percentage change in HbA1c, UACR  
**Secondary:** Proportion of patients achieving 30% reduction in UACR, body weight, FPG, seated SBP |
| DECLARE²      | Dapagliflozin / placebo 1:1                             | 17,150 | **Primary:** MACE non-inferiority and then superiority of co-primary endpoints of MACE and hospitalisation for heart failure or CV death  
**Secondary:** all-cause mortality; renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m² and/or ESRD and/or renal or CV death) |
| CREDENCE³     | Canagliflozin / placebo 1:1                            | 4200 | **Primary:** Composite renal and CV endpoint (ESRD, doubling of serum creatinine, renal or CV death)  
**Secondary:** 5P-MACE (CV death, non-fatal MI or non-fatal stroke, hospitalisation for CHF, hospitalization for unstable angina), renal composite endpoint (ESRD, doubling of serum creatinine, renal death), all-cause mortality |
| DAPA-HF⁴ (HFrEF) | Dapagliflozin / placebo 1:1                           | 4500 | **Primary:** Composite CV endpoint (CV death, hospitalization for HF or urgent HF visit)  
**Secondary:** CV death or hospitalization for HF, total HF hospitalizations and CV death events, KCCQ, renal composite (≥50% sustained decline in eGFR, ESRD, renal death), all-cause mortality |
| DAPA-CKD⁵ (CKD) | Dapagliflozin / placebo 1:1                           | 4000 | **Primary:** Composite renal endpoint (≥50% sustained decline in eGFR, ESRD, CV or renal death)  
**Secondary:** Renal composite (≥50% sustained decline in eGFR, ESRD, renal death), CV death or hospitalization for HF, all-cause mortality |

Conclusions and key messages

• SGLT2i: ↓intraglomerular hypertension
  – eGFR dip: occurs in CKD stages 3a, 3b, CKD
  – ↓eGFR slope, albuminuria, effects in large CV trials
  – CREDENCE study: stopped early due to efficacy
  – DAPA-CKD and empagliflozin studies

• Effects relatively independent of HbA1c lowering

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium–glucose co-transporter 2 inhibitor; TGFβ, tubuloglomerular feedback; UACR, urinary albumin:creatinine ratio
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