Unlocking the Potential of SGLT2 Inhibitors in Renal Protection

Narges sadat Zahed
Nephrologist
Aug 2021
Outlines

• Epidemiology
• Guidelines overview
• Reno-protective mechanism of sodium-glucose cotransporter-2 (SGLT2) inhibitors
• Clinical trials
Epidemiology: Diabetes and CKD
Key Facts

• The overall prevalence of chronic kidney disease (CKD) in the general population is approximately 14 percent.

• High blood pressure and diabetes are the main causes of CKD.

• Almost half of individuals with CKD also have diabetes and/or self-reported cardiovascular disease (CVD).

National Institute of Diabetes and Digestive and Kidney Diseases, November 2020
Diabetes: The Leading Cause of ESRD

- Diabetes: 51%
- Hypertension: 18%
- All other causes: 31%

A Review on Guidelines
KDIGO 2020 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE

Diabetes with CKD
Kidney–heart risk factor management

Treatment algorithm in T2D and CKD

- Lifestyle therapy
- Physical activity
  - Nutrition
  - Weight loss
- First-line therapy
  - Metformin
    - eGFR < 45: Reduce dose
    - eGFR < 30: Discontinue
  - Dialysis: Discontinue
- SGLT2 inhibitor
  - eGFR < 30: Do not initiate
  - Dialysis: Discontinue

- GLP-1 receptor agonist (preferred)
- DPP-4 inhibitor
- Sulfonylurea
-TZD
- Alpha-glucosidase inhibitor

- Additional drug therapy as needed for glycemic control

- Guided by patient preferences, comorbidities, eGFR, and cost
- Includes patients with eGFR < 30 ml/min per 1.73 m² or treated with dialysis
- See Figure 20

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KDIGO Practice Points

• Most patients with **T2D**, **CKD**, and **eGFR ≥30** ml/min per 1.73 m² would benefit from treatment with both **metformin** and an **SGLT2i**

• An **SGLT2i** can be added to other antihyperglycemic medications for patients whose glycemic targets are not currently met or who are meeting **glycemic targets** but can safely attain a lower target.

• For patients in whom additional glucose-lowering may increase risk for **hypoglycemia** (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate **addition of an SGLT2i**.

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KDIGO Practice Points

• The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

• A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

• Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 30 ml/min per 1.73 m² unless it is not tolerated or kidney replacement therapy is initiated.

References:

Renoprotective Mechanism of SGLT2i
Renoprotective Mechanism of SGLT2i

• It has been well demonstrated that SGLT2i protect kidneys by anti-inflammatory effects via reducing serum levels of leptin and IL-6, increasing adiponectin concentrations, mitigating systemic inflammation through decreasing CRP (C-reactive protein) level, and inhibition the IL-1β secretion by macrophages via the ROS-NLRP3-caspase-1 pathway.

• It seems that the anti-inflammatory effects of SGLT2i as well as some other mechanisms such as lowering serum uric acid levels, blood pressure, and glomerular hyperfiltration are independent of their glucose-lowering properties.

Clinical Trials
Class effects of SGLT2 inhibitors on cardiorenal outcomes

Aaron Y. Kluger\textsuperscript{1,2,*}, Kristen M. Tecson\textsuperscript{1,2,3}, Andy Y. Lee\textsuperscript{4,5}, Edgar V. Lerma\textsuperscript{6}, Janani Rangaswami\textsuperscript{7,8}, Norman E. Lepor\textsuperscript{9,10}, Michael E. Cobble\textsuperscript{11} and Peter A. McCullough\textsuperscript{1,3,4,5}
Composite Renal Outcomes of SGLT2i

Composite Renal Outcomes of SGLT2i

Conclusion
Cardiorenal Outcomes of SGLT2i

• Dapaglifozin, empaglifozin, and canaglifozin have internally and externally consistent and biologically plausible class effects on cardiorenal outcomes.

• Baseline renal filtration function and degree of albuminuria are the most significant indicators of risk for both CV and renal events. Thus, these two factors also anticipate the greatest clinical benefit for SGLT2i.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Maximilian von Eynatten, M.D.,
Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D.,
Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D.,
for the EMPA-REG OUTCOME Investigators*
Prespecified Renal Outcomes

- Incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease)

- Post hoc renal composite outcome (a doubling of the serum creatinine level, the initiation of renal replacement therapy, or death from renal disease)

Key Renal Outcomes

A. Incident or Worsening Nephropathy

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

Cumulative Probability of Event (%)

Month

Placebo
Empagliflozin

No. at Risk
Empagliflozin 4124 3994 3848 3669 3171 2279 1887 1219 290
Placebo 2061 1946 1836 1703 1433 1016 833 521 106

B. Post Hoc Renal Composite Outcome

Hazard ratio, 0.54 (95% CI, 0.40–0.75)
P<0.001

Cumulative Probability of Event (%)

Month

Placebo
Empagliflozin

No. at Risk
Empagliflozin 4645 4500 4377 4241 3729 2715 2280 1496 360
Placebo 2323 2229 2146 2047 1771 1289 1079 680 144

Change in eGFR over 192 Weeks

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

A  ESKD

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Overall

$P^2=0.0\%$; $I^2_{het}=0.41$  

B  Substantial loss of kidney function, ESKD, or death due to kidney disease

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Overall

$P^2=0.0\%$; $I^2_{het}=0.49$  

C  Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease

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Overall

$P^2=60.3\%$; $I^2_{het}=0.056$  

Overall

$P^2=0.0\%$; $I^2_{het}=0.41$  

Overall

$P^2=0.0\%$; $I^2_{het}=0.49$  

Overall

$P^2=60.3\%$; $I^2_{het}=0.056$  

Overall

$P^2=0.0\%$; $I^2_{het}=0.41$  

Overall

$P^2=0.0\%$; $I^2_{het}=0.49$  

Overall

$P^2=60.3\%$; $I^2_{het}=0.056$  

Overall

$P^2=0.0\%$; $I^2_{het}=0.41$  

Overall

$P^2=0.0\%$; $I^2_{het}=0.49$  

Overall

$P^2=60.3\%$; $I^2_{het}=0.056$
Effect of SGLT2i on Acute Kidney Injury

## SGLT2i Effect on Major Kidney Outcomes

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<td>Dialysis, transplantation, or death due to kidney disease</td>
<td>252</td>
<td>38723</td>
<td>0.67 (0.52–0.86)</td>
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<td>ESKD</td>
<td>335</td>
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<td>0.65 (0.53–0.81)</td>
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<td>Substantial loss of kidney function, ESKD, or death due to kidney disease</td>
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<td>38671</td>
<td>0.58 (0.51–0.66)</td>
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<td>Substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease</td>
<td>2323</td>
<td>38676</td>
<td>0.71 (0.63–0.82)</td>
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<td>Acute kidney injury</td>
<td>943</td>
<td>38684</td>
<td>0.75 (0.66–0.85)</td>
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EMPA-KIDNEY is enrolling a broad CKD population

*If no other markers of kidney disease, no CKD.
Conclusion

• SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease in individuals with type 2 diabetes and provided protection against acute kidney injury.

• These data provide substantive evidence supporting the use of SGLT2 inhibitors to prevent major kidney outcomes in people with type 2 diabetes.
Thanks for your attention