New insights and guidelines in managing patients with CKD and diabetes: What are the challenges?

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Diabetic kidney disease:

3 gigantic risks: (1) premature death, (2) kidney failure, (3) CV disease: What helps?

- Insulin (ORIGIN)
- SUs (CAROLINA)
- DPP-4i (CARMELINA)
- SGLT-2i (CREDENCE, DAPA_CKD)
- GLP-1 RA (FLOW)
- other
**Figure 18. Treatment Algorithm for Selecting Antihyperglycemic Drugs for Patients with T2D and CKD**

- **Lifestyle therapy**
- **First-line therapy**
  - **Metformin**
    - eGFR < 45
      - Reduce dose
    - eGFR < 30
      - Discontinue
    - Dialysis
      - Discontinue
  - **SGLT2 inhibitor**
    - eGFR < 30
      - Do not initiate
    - Dialysis
      - Discontinue
- **Physical activity**
  - Nutrition
  - Weight loss
- **Additional drug therapy as needed for glycemic control**
  - GLP-1 receptor agonist (preferred)
    - Directed by patient preferences, comorbidities, eGFR, and cost
    - Includes patients with eGFR < 30 ml/min per 1.73 m^2 or treated with dialysis
    - See Figure 20
  - DPP-4 inhibitor
  - Insulin
  - Sulfonylurea
  - TZD
  - Alpha-glucosidase inhibitor
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**Additional drug therapy as needed for glycemic control**
- **GLP-1 receptor agonist (preferred)**
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**Physical activity**
- Nutrition
- Weight loss

- **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**
Evidence supporting use of GLP-1 RAs
CV and renal outcomes

**Renal outcomes with GLP-1 RA trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER 1</td>
<td>0.78</td>
<td>(0.61; 0.99)</td>
</tr>
<tr>
<td>LEADER 4</td>
<td>0.80</td>
<td>(0.67; 0.95)</td>
</tr>
<tr>
<td>SUSTAIN-6 2</td>
<td>0.64</td>
<td>(0.46; 0.88)</td>
</tr>
<tr>
<td>SUSTAIN 6 2</td>
<td>0.74</td>
<td>(0.58; 0.95)</td>
</tr>
<tr>
<td>REWIND 3</td>
<td>0.88</td>
<td>(0.79; 0.99)</td>
</tr>
<tr>
<td>REWIND 5</td>
<td>0.85</td>
<td>(0.77; 0.93)</td>
</tr>
</tbody>
</table>

*CV death, non-fatal MI or non-fatal stroke; *development of new-onset macroalbuminuria, decline in estimated glomerular filtration rate (or increase in creatinine), progression to end-stage kidney disease, or death attributable to kidney causes.

CV, cardiovascular; GLP-1 RA, glucagon like peptide 1 receptor agonist; MACE, major adverse cardiovascular events


LEADER and SUSTAIN 6
NEW OR WORSENING NEPHROTYPATHY

**LEADER**

Macroalbuminuria, doubling of serum creatinine*, ESRD or renal death

HR: 0.78 (95% CI: 0.67; 0.92)  
P = 0.003

**SUSTAIN 6**

Macroalbuminuria, doubling of serum creatinine† or ESRD

HR: 0.64 (95% CI: 0.46; 0.88)  
P = 0.005

*Persistent doubling of the serum creatinine level and an eGFR of ≤45 mL/min/1.73 m² of body-surface area. † Persistent doubling of the serum creatinine level and an eGFR of <45 mL/min/1.73 m² of body-surface area.

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio

Annual eGFR loss is less with semaglutide vs placebo: eGFR subgroups (SUSTAIN 6 and PIONEER 6)

**p < 0.01; **p < 0.001; ***p < 0.0001. Full analysis set. Data are mean ± 95% CI. Renal function is based on eGFR mL/min/1.73 m² per Chronic Kidney Disease-Epidemiology Collaboration formula.

CI, confidence interval; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference.

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GLP-1 Receptor Agonist Efpeglenatid reduces CV & kidney outcomes (AMPLITUDE-O)

Kidney composite
ESKD or eGFR loss >40% : 
N= 76 / 121

New Macroalbuminuria 
N= 244 / 348

Gerstein HC et al. NEJM 2021;385:896
GLP-1 Receptor Agonist Efpeglenatid reduces CV & kidney outcomes (AMPLITUDE-O) +- SGLT-2i

Gerstein HC et al. NEJM 2021;385:896-907

Lam et al. Circulation 2022;145:565-574