KDIGO 2020 Clinical Practice Guideline on Diabetes Management in CKD Speaker’s Guide

KDIGO Guideline Co-Chairs:
Ian de Boer, MD, MS
Peter Rossing, MD, DMSc
## Table of Contents

- **Introduction**

- **Guideline Development Process:**
  - Evidence Review
  - Guideline Format

- **Guideline Statements and Rationale from:**
  - Chapter 1. Comprehensive Care in Patients with Diabetes and CKD
  - Chapter 2. Glycemic Monitoring and Targets in Patients with Diabetes and CKD
  - Chapter 3. Lifestyle Interventions in Patients with Diabetes and CKD
  - Chapter 4. Antihyperglycemic Therapies in Patients with Diabetes and CKD
  - Chapter 5. Approaches to Management of Patients with Diabetes and CKD

- **Question and Answer**
KDIGO PROGRAMS

Guidelines
• KDIGO’s core mission. KDIGO is the only organization developing global guidelines in nephrology.

Controversies Conferences
• International Conferences that examine significant topics in nephrology and related disciplines that are not fully resolved. Results in a published paper, usually in Kidney International. Often a Controversies Conference will prompt development of a guideline or a guideline update.

Implementation Activities
• Dissemination and Implementation of KDIGO Guidelines
• Controversies Conference Reports and Observations
• Live Clinical Practice Conferences – usually with a nephrology society to bring global KDIGO’s work to local audiences, using case studies
• Implementation Summits bring local experts together to discuss local or regional barriers and opportunities
• Core Implementation Kits – educational materials including Speaker’s Guides, Reference Tools, and Case Studies to assist with implementation of all KDIGO publications
KDIGO CONTROVERSIES CONFERENCE: DIABETES & CKD

• February, 2015 (Vancouver, BC)

• Topics:
  • Lifestyle measures
  • Glycemic control
  • Cardiovascular & other outcomes
  • Paths forward for new therapies


• Led to initiation of new clinical practice guideline

Management of patients with diabetes and CKD: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference

Vladimir Perkovic, Raji Agarwal, Paola Fioretto, Brenda R. Hemmelgarn, Adeera Levin, Merin C. Thomas, Christoph Wanner, Bertram L. Kasiske, David C. Wanner, and Per Henrik Groop, for Conference Participants

The prevalence of diabetes around the world has reached epidemic proportions and is projected to increase to 442 million people by 2040. Diabetes is already the leading cause of end-stage kidney disease (ESKD) in most developed countries, and the growth in the number of people with ESKD around the world parallels the increase in diabetes. The presence of kidney disease is associated with a markedly elevated risk of cardiovascular disease and death in people with diabetes. Several new therapies and novel investigational agents targeting chronic kidney disease patients with diabetes are now under development. This conference was convened to assess our current state of knowledge regarding optimal glycemic control, current antidiabetic agents and their safety, and new therapies being developed to improve kidney function and cardiovascular outcomes for this vulnerable population.

Correspondence: Vladimir Perkovic, The George Institute for Global Health, Building 301, Level 1, Sydney, NSW 2006, Australia; e-mail: vlaper@thegeorge.org.au, or Per Henrik Groop, Kidney Research Centre, University of Stockholm and University Hospital, S-171 76 Stockholm, Sweden; e-mail: per.henrik.groop@ki.se

*See Appendix for list of other conference participants.

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The prevalence of diabetes around the world is expected to reach 442 million people by 2040. About 40% of people with diabetes will develop chronic kidney disease (CKD), including a significant number who will develop end-stage kidney disease (ESKD). Diabetes is the leading cause of ESKD in most developed countries, and has driven growth in ESKD globally over recent decades. There is a strong economic and health imperative to improve outcomes for people with diabetes and kidney disease.

The identification of renin-angiotensin system (RAS) blockade as an effective strategy for the prevention of ESKD in diabetes was a major step forward, but subsequent research has had limited success in building upon these gains. A number of promising treatments have been found to be ineffective or harmful, many of which have now been abandoned in this population. One common feature of these failures has been the emergence of severe and sometimes fatal adverse events, highlighting the importance of safety considerations in future trials and in view of what is known about the safety of existing treatments in this patient population.

With a number of new agents under development targeting newly identified mechanistic pathways underlying
Proposed Scope of Work for KDIGO Clinical Practice Guideline on the Management of Diabetes and Chronic Kidney Disease
SCOPE OF THE CLINICAL PRACTICE GUIDELINE

Include:
- Types 1 and 2 diabetes
- All stages of CKD
  - Kidney transplant recipients
  - Dialysis
- Interventions addressed with rigorous data (RCTs)
  - Lifestyle
  - Pharmacotherapy
  - Systems

Exclude:
- Interventions covered elsewhere
  - Blood pressure
  - Lipids
- Prevention & screening
- Topics with insufficient data
  - Diagnosis
  - Emerging & pipeline therapies
GUIDELINE GOALS

• Generate a useful resource for clinicians and patients
  • Address relevant questions with actionable recommendations
  • Take on controversial topics when sufficient evidence
  • Communicate clearly: highlight figures and tables

• Stay true to evidence

• Target audience: broad, primarily clinicians treating diabetes & CKD

• Be mindful of implications for policy and payment

• Propose research questions
**WORK GROUP**

- Diverse expertise
- Worldwide scope
- Deep experience
- Patients
- Evidence Review Team

**WORK GROUP CO-CHAIRS**

Ian H. de Boer, MD, MS  
Kidney Research Institute  
University of Washington  
Seattle, WA, USA  

Wasiu A. Ololruwa, MBBS, FCMPaed  
Obafemi Awolowo University  
Teaching Hospitals Complex  
Ile-Ife, Osun State, Nigeria  

**WORK GROUP**

M. Luiza Caramori, MD, PhD, MSc  
University of Minnesota  
Minneapolis, MN, USA  

Wasim Salahuddin, MBBS, FRCPath  
University of Manchester  
Medical School  
Manchester, United Kingdom  

Juliana C.N. Chan, MBChB, MD, FHKCP, FHKAM, FRCP  
The Chinese University of Hong Kong  
Hong Kong, China  

Tami Sadusky, MBA  
Patient Representative  
Seattle, WA, USA  

Hiddo J.L. Heerspink, PhD, PharmD  
University of Groningen  
Groningen, The Netherlands  

Nikhil Tandon, MBBS, MD, PhD  
All India Institute of Medical Sciences  
New Delhi, India  

Clint Hurst, BS  
Patient Representative  
Houston, TX, USA  

Katherine R. Tuttle, MD, FASN, FACP, FNKF  
University of Washington  
Spokane, WA, USA  

Kamlesh Khunti, MD, PhD, FRCP, FRCGP, FMedSci  
University of Leicester  
Leicester, United Kingdom  

Christoph Wanner, MD  
University Hospital of Würzburg  
Würzburg, Germany  

Adrian Liew, MBBS, MRCP (UK), FAMS, FRCP (Edin), FASN, MClinEpid  
Mount Elizabeth Novena Hospital  
Singapore  

Katy G. Wilkens, MS, RD  
Northwest Kidney Centers  
Seattle, WA, USA  

Erin D. Michos, MD, MHS, FAHA, FACC, FASE, FASPC  
Johns Hopkins University School of Medicine  
Baltimore, MD, USA  

Sophia Zoungas, MBBS, FRACP, PhD  
Monash University  
Melbourne, Australia  

Sankar D. Navaneethan, MD, MS, MPH  
Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center  
Houston, TX, USA  

**Cochrane Kidney and Transplant, Sydney, Australia**

Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Evidence Review Team Director  
Martin Howell, PhD, Assistant Project Director  
David J. Turniciliffe, PhD, Evidence Review Project Team Leader and Project Manager
WORK GROUP CO-CHAIRS

Ian H. de Boer, MD, MS
Kidney Research Institute
University of Washington
Seattle, WA, USA

Peter Rossing, MD, DMSc
Steno Diabetes Center Copenhagen
University of Copenhagen
Copenhagen, Denmark

M. Luiza Caramori, MD, PhD, MSc
University of Minnesota
Minneapolis, MN, USA

M. Luiza Caramori, MD, PhD, MSc
University of Minnesota
Minneapolis, MN, USA

Juliana C.N. Chan, MBChB, MD, FHKCP, FHKAM, FRCP
The Chinese University of Hong Kong
Hong Kong, China

Wasiu A. Olowu, MBBS, FMCPaed
Obafemi Awolowo University
Teaching Hospitals Complex
Ile-Ife, Osun State, Nigeria

Hiddo J.L. Heerspink, PhD, PharmD
University of Groningen
Groningen, The Netherlands

Taimi Sadusky, MBA
Patient Representative
Seattle, WA, USA

Clint Hurst, BS
Patient Representative
Houston, TX, USA

Nikhil Tandon, MBBS, MD, PhD
All India Institute of Medical Sciences
New Delhi, India

Kanmlesh Khunti, MD, PhD, FRCP, FRCGP, FMedSci
University of Leicester
Leicester, United Kingdom

Katherine R. Tuttle, MD, FASN, FACP, FNKF
University of Washington
Spokane, WA, USA

Adrian Liew, MBBS, MRCP (UK), FAMS, FRCP (Edin), FASN, MClinEpil
Mount Elizabeth Novena Hospital
Singapore

Christoph Wanner, MD
University Hospital of Würzburg
Würzburg, Germany

Erin D. Michos, MD, MHS, FAHA, FACC, FASE, FASPC
Johns Hopkins University School of Medicine
Baltimore, MD, USA

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Sankar D. Navaneethan, MD, MS, MPH
Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center
Houston, TX, USA

Sophia Zourougas, MBBS, FRACP, PhD Monash University
Melbourne, Australia
Michel Jadoul, MD
KDIGO Co-Chair

Wolfgang C. Winkelmayer, MD, MPH, ScD
KDIGO Co-Chair

**METHODS CHAIR**
Marcello A. Tonelli, MD, SM, MSc, FRCPC

**EVIDENCE REVIEW TEAM**

Cochrane Kidney and Transplant, Sydney, Australia

Jonathan C. Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD, Evidence Review Team Director
Stefania C. Palmer, MBChB, FRACP, PhD, Evidence Review Team Co-Director
Giovanni F.M. Strippoli, MD, MPH, M Med (Clin Epi), PhD, Evidence Review Team Co-Director
Martin Howell, PhD, Assistant Project Director
David J. Tunnicliffe, PhD, Evidence Review Project Team Leader and Project Manager
Fiona Russell, PhD, Cochrane Kidney and Transplant, Managing Editor
Gail Y. Higgins, BA, Grad Ed, Grad Dip LibSc, Information Specialist
Tess E. Cooper, MPH, MSc (Evidence-based Health Care), Research Associate
Nicole Evangelidis, MPH, MPhil, Research Associate
Brydie Cashmore, MPH, Research Associate
Rubia Khalid, MND, Research Associate
Claris Teng, BPysch (Hons), Research Associate
Patrizia Natale, MSc (ClinEpi), Research Associate
Marina Russo, PhD, MSc (ClinEpi), Research Associate
Valeria Saglimbene, PhD, Research Associate
Min Jun, PhD, Research Associate
Challenges to the Guideline

• What to do when evidence is lacking?
  • Balance providing guidance with rigor

• How to address clinically relevant groups of patients?
  • Type 1 and Type 2 diabetes
  • CKD stages
  • Kidney failure/ESKD
  • Transplant recipients
## Evidence Review

- ERT - Cochrane Kidney Transplant
- PICO questions developed
- Clinical and important outcomes identified

<table>
<thead>
<tr>
<th>Critical outcomes</th>
<th>Important outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Albuminuria progression</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>3-point and 4-point MACE</td>
<td>Falls</td>
</tr>
<tr>
<td>Kidney failure (ESKD)</td>
<td>Harms (fatigue, amputations, fractures, etc.)</td>
</tr>
<tr>
<td>Cardiovascular outcomes - myocardial infarction, stroke, heart failure</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Doubling serum creatinine</td>
<td>Quality of life</td>
</tr>
<tr>
<td>Hypoglycemia requiring 3rd party assistance</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Body weight, body mass index (BMI)</td>
</tr>
</tbody>
</table>
### Evidence Review

- **ERT - Cochrane Kidney Transplant**
  - Existing PICO questions and new PICO questions developed
  - Clinical and important outcomes identified

<table>
<thead>
<tr>
<th>Critical outcomes</th>
<th>Important outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Albuminuria progression - (onset of albuminuria, micro to macroalbuminuria)</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular outcomes - MACE, myocardial infarction, stroke, heart failure</td>
<td></td>
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<tr>
<td>Doubling serum creatinine</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia requiring 3rd party assistance</td>
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<tr>
<td>HbA1c</td>
<td></td>
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</tbody>
</table>
## PICO QUESTIONS

- Focus on RCTs - mapped to existing Cochrane Systematic reviews
  - New systematic reviews undertaken as required
  - Some focused observational studies reviews
  - General diabetes population - Existing systematic reviews

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comprehensive care</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Antihypertensive – <strong>RAS</strong>, <strong>aldosterone antagonists</strong>, <strong>direct renin inhibitors</strong></td>
<td>Placebo / standard of care</td>
<td>Critical and important outcomes, hyperkalemia, AKI</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Other – <strong>potassium binders</strong>, <strong>antiplatelet</strong> therapy, <strong>bariatric surgery</strong>, <strong>weight loss</strong> therapy, <strong>smoking cessation</strong></td>
<td>Placebo / standard of care</td>
<td>Critical and important outcomes, hyperkalemia, AKI, QoL, BP, BMI, weight fatigue</td>
</tr>
</tbody>
</table>
### Glycemic monitoring and targets

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Patients with CKD and diabetes | • **Continuous** glucose monitoring  
• **Self-monitoring** blood glucose | • Measured blood glucose/ HbA1c | • Diagnosis – sensitivity, specificity  
• Correlation |
| General diabetes population | • Alternative biomarkers (glycated albumin, fructosamine, carbamylates albumin) | • Measured blood glucose/ HbA1c | • Diagnosis – sensitivity, specificity  
• Correlation |
| Patients with CKD and diabetes | • **Tight glycemic** control (HbA1c targets - ≤7.0%, ≤6.5%, ≤6.0%) | • Standard glycemic control | • Critical and important outcomes |
| General diabetes population | | | |

### Lifestyle interventions

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Dietary interventions (protein, salt, potassium, dietary patterns – DASH diet)</td>
<td>Usual diet</td>
<td>Critical and important outcomes, QoL, BP, BMI, weight, fatigue</td>
</tr>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Exercise interventions</td>
<td>Standard of care</td>
<td>Critical and important outcomes, QoL, BP, BMI, weight, fatigue</td>
</tr>
<tr>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
</tr>
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<tr>
<td><strong>Antihyperglycemic therapies</strong></td>
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</tr>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Older – metformin, sulfonylureas, thiazolidinediones, insulins</td>
<td>Standard of care vs other therapies</td>
<td>• Critical and important outcomes, BMI, weight</td>
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<tr>
<td></td>
<td>Newer – SGLT2 inhibitors, GLP1 agonists, DPP-4 inhibitors</td>
<td></td>
<td>• Harms - Hypoglycemia, lactic acidosis, amputations</td>
</tr>
<tr>
<td><strong>Approaches to management</strong></td>
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</tr>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Education and self-management programs</td>
<td>Standard of care</td>
<td>Critical and important outcomes, QoL, fatigue</td>
</tr>
<tr>
<td>General diabetes population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with CKD and diabetes</td>
<td>Models of care</td>
<td>Standard of care</td>
<td>Critical and important outcomes, QoL, fatigue</td>
</tr>
<tr>
<td>General diabetes population</td>
<td></td>
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</tbody>
</table>
**Literature Search**

**October 2018; Updated in February 2020**

**Randomized controlled trials**
- Search 18th October 2018: Cochrane Kidney and Transplant Registry of studies
  - 2628 studies retrieved
- Updated search February 2020: Cochrane Kidney and Transplant Registry of studies
  - 3039 citations retrieved
- Antihypertensive therapy: 86 RCTs
  - Potassium binders: 1 RCT
  - Antiplatelet therapy: 2 RCTs
  - Smoking cessation: 1 RCT
  - Bariatric surgery: 0 RCTs
  - Weight loss therapies: 0 RCTs
  - Exercise interventions: 47 RCTs
  - Dietary interventions: 28 RCTs
- Alternative biomarkers and glucose monitoring: 0 RCTs
- Glycemic targets: 14 RCTs
- Glycemic therapies: 58 RCTs
- Education: 4 RCTs
- Models of care: 3 RCTs

**Observational studies**
- Alternative biomarkers and glucose monitoring correlation search: February 2019 and updated search February 2020
  - 1373 citations retrieved
  - 56 duplicates removed
  - 1241 citations excluded
  - 45 citations excluded
  - Full-text screening
  - Included studies
    - 244 RCTs (n = 150,000)
    - 31 observational studies
    - 50 reviews

**Reviews**
- Search October 2018 and updated search February 2020
  - 2311 citations retrieved
  - 66 duplicates removed
  - 2148 citations excluded
  - Full-text screening
EVIDENCE SYNTHESIS

• Standard Cochrane methods – Two independent reviewers
  • Data abstraction
  • Critical appraisal – using validated tools

• Data-analysis
  • Random effects meta-analysis and generic inverse variance
  • Relative risk for dichotomous outcomes
  • Mean difference for continuous outcomes
  • Heterogeneity assessed using the I² statistic

Risk of bias graph example

Forest plot example – SGLT2 inhibitors – 3-point MACE

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Experimental</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
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<td>CANTOS (2015)</td>
<td>-0.18</td>
<td>0.03</td>
<td>237</td>
<td>228</td>
<td>232</td>
<td>0.96</td>
<td>0.83 (0.70, 1.00)</td>
<td>0.96 (0.82, 1.12)</td>
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<tr>
<td>DECLARE (2017)</td>
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<td>0.03</td>
<td>234</td>
<td>236</td>
<td>235</td>
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<td>Total (95% CI)</td>
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<td>0.97 (0.85, 1.10)</td>
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GRADING RECOMMENDATIONS

• GRADE methodology
  • The quality of the evidence – Level A, B, C, D
    • Study limitations
    • Inconsistency
    • Indirectness
    • Imprecision
    • Publication bias

• Strength of the recommendation – “We recommend” or “We suggest”
  • Two face-to-face meetings – New Orleans Jan 2019, Barcelona Sept 2019
    • Balance of benefits and harms
    • Quality of the evidence
    • Patient values and preferences – Two patients on the workgroup
    • Resources and other considerations
KDIGO guidelines continue to use the GRADE methodology, but we have strengthened the link between the recommendation statements and underlying evidence base.

Guidelines now include a mix of recommendations and “practice points” to help clinicians better evaluate and implement the guidance from the expert Work Group.

All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

Practice points are a new addition to KDIGO guidance, and may be formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Guidelines will be published in print form and simultaneously posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Below is an FAQ outlining the rationale for this shift along with an example recommendation in the new format.
GUIDELINE FORMAT

How should I use practice points when caring for my patients?

- As noted, practice points are consensus statements about a specific aspect of care, and supplement recommendations for which a larger quantity of evidence was identified.
- Note that practice points represent the expert judgment of the guideline Work Group, but may also be based on limited evidence.
- Unlike recommendations, practice points are not graded for strength of recommendation or quality of evidence.
- Users should consider the practice point as expert guidance, and use it as they see fit to inform the care of patients.

New guideline disseminated → Start with recommendations → Consider relevant practice points
MAGICapp — Evidence to Recommendation

- Summary of findings tables presented in MAGICapp
- Tables are linked directly to recommendations - transparency
MAGICapp – Evidence to Recommendation

• Studies and references linked directly to tables
• Easy updating – new studies added easily
DIABETES & CKD GUIDELINE CONTENTS

• Chapter 1. Comprehensive care in patients with diabetes and CKD
  • Comprehensive diabetes and CKD management
  • RAS blockade
  • Smoking cessation

• Chapter 2. Glycemic monitoring and targets in patients with diabetes and CKD
  • Glycemic monitoring
  • Glycemic targets

• Chapter 3. Lifestyle interventions in patients with diabetes and CKD
  • Nutrition intake
  • Physical activity

• Chapter 4. Antihyperglycemic therapies in patients with diabetes and CKD
  • Overall approach
  • Metformin
  • SGLT-2 inhibitors
  • GLP-1 receptor agonists

• Chapter 5. Approaches to management of patients with diabetes and CKD
  • Self-management education programs
  • Team-based integrated care
COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figure 2).
Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).
COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2-4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

Practice Point 1.2.3: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose (Figure 4).

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.
**Figure 4. Monitoring of Serum Creatinine and Potassium during ACEi or ARB Treatment - Dose Adjustment and Monitoring of Side Effects**

1. **Initiate ACEi or ARB**
2. **Monitor serum creatinine and potassium** (within 2–4 weeks after starting or changing dose)
   - **Normokalemia**
     - **< 30% increase in creatinine**
       - **Increase dose of ACEi or ARB or continue on maximally tolerated dose**
   - **Hyperkalemia**
     - **> 30% increase in creatinine**
       - **Review concurrent drugs**
         - Moderate potassium intake
           - Consider:
             - diuretics
             - sodium bicarbonate
             - GI cation exchangers
       - **Review for causes of AKI**
         - Correct volume depletion
         - Reassess concomitant medications (e.g., diuretics, NSAIDs)
         - Consider renal artery stenosis
   - **Reduce dose or stop ACEi or ARB as last resort**
COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping ACEi or ARB immediately (Figure 4).

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite medical treatment outlined in Practice Point 1.2.5., or to reduce uremic symptoms while treating kidney failure (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m²).

Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

Practice Point 1.2.8: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low eGFR.
Drugs causing hyperkalemia

Angiotensin-converting enzyme inhibitors

Angiotensin I → Angiotensin II

Direct renin inhibitor

Impaired release of renin
NSAIDs
Beta blockers
Cyclosporine, tacrolimus
Diabetes
Elderly

Renin

Angiotensin receptor blockers

Adrenal gland

Impaired aldosterone mechanism
Adrenal disease
Heparin
Ketoconazole

Juxtaglomerular cells

Afferent arteriole

Sodium channel blockers
Amiloride
Triamterene
Trimethoprim
Pentamidine

Lumen (-)

Collecting duct (principal cell)

Na⁺ → Na⁺

K⁺ ← K⁺

Aldosterone receptor blockers
Spironolactone
Eplerenone
Drospirenone
Recommendation 1.3.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (1D).

Practice Point 1.3.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.
**Glycemic Monitoring and Targets in Patients with Diabetes and CKD**

**Recommendation 2.1.1:** We recommend hemoglobin A1c (HbA1c) to monitor glycemic control in patients with diabetes and CKD (1C).

Practice Point 2.1.1: Monitoring long-term glycemic control by HbA1c twice per year is reasonable for patients with diabetes. HbA1c may be measured as often as 4 times per year if the glycemic target is not met or after a change in antihyperglycemic therapy.

Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4-G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability.
**GLYCEMIC MONITORING AND TARGETS IN PATIENTS WITH DIABETES AND CKD**

Practice Point 2.1.3: A glucose management indicator (GMI) derived from continuous glucose monitoring (CGM) data can be used to index glycemia for individuals in whom HbA1c is not concordant with directly measured blood glucose levels or clinical symptoms.

Practice Point 2.1.4: Daily glycemic monitoring with CGM or self-monitoring of blood glucose (SMBG) may help to prevent hypoglycemia and improve glycemic control when antihyperglycemic therapies associated with risk of hypoglycemia are used.

Practice Point 2.1.5: For patients with type 2 diabetes (T2D) and CKD who choose not to do daily glycemic monitoring by CGM or SMBG, antihyperglycemic agents that pose a lower risk of hypoglycemia are preferred and should be administered in doses that are appropriate for the level of eGFR.

Practice Point 2.1.6: CGM devices are rapidly evolving with multiple functionalities (e.g., real-time and intermittently scanned CGM). Newer CGM devices may offer advantages for certain patients, depending on their values, goals, and preferences.
**Figure 6. Frequency of HbA1c Measurement and Use of GMI in CKD**

<table>
<thead>
<tr>
<th>Population</th>
<th>Measure</th>
<th>Frequency</th>
<th>Reliability</th>
<th>GMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD G1–G3b</td>
<td>Yes</td>
<td>• Twice per year</td>
<td>High</td>
<td>Occasionally useful</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Up to 4 times per year if not achieving target or change in therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD G4–G5 including treatment by dialysis</td>
<td>Yes</td>
<td>• Twice per year</td>
<td>Low</td>
<td>Likely useful</td>
</tr>
<tr>
<td>or kidney transplant</td>
<td></td>
<td>• Up to 4 times per year if not achieving target or change in therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 7. Glossary of glucose-monitoring terms**

**Self-monitoring of blood glucose (SMBG)**
Self-sampling of blood via fingerstick for capillary glucose measurement using glucometers. Since sampling is performed intermittently, episodes of hypoglycemia or hyperglycemia are often harder to detect.

**Continuous glucose monitoring (CGM)**
Minimally invasive subcutaneous sensors which sample interstitial glucose at regular intervals (e.g., every 5–15 min). There are three categories of CGMs:

(a) **Retrospective CGM**
Glucose levels are not visible while the device is worn. Instead, a report is generated for evaluation after the CGM is removed.

(b) **Real-time CGM (rtCGM)**
Refers to sensors transmitting and/or displaying the data automatically throughout the day, so that the patient can review glucose levels and adjust treatment as needed.

(c) **Intermittently scanned CGM**
Also known as ‘flash’ CGM or FGM for short. Glucose levels can be seen while the device is worn when the device is queried.

**Glucose management indicator (GMI)**
Provides a measure of average blood glucose levels calculated from CGM readings, expressed in units of A1C (%), that can be used to gauge whether clinical A1C levels are falsely high or low.

**Time in range (TIR)**
This is a metric of glycemic control that assesses the percentage of CGM readings within a certain range.

Commonly accepted ranges are 70–180 mg/dl (3.9–10.0 mmol/l) at >70% of readings; time per day.

*Adapted from Battelino T, *et al.*
GLYCEMIC MONITORING AND TARGETS IN PATIENTS WITH DIABETES AND CKD

Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) (1C).
GLYCEMIC MONITORING AND TARGETS IN PATIENTS WITH DIABETES AND CKD

Practice Point 2.2.1: Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by CGM or SMBG and by selection of antihyperglycemic agents that are not associated with hypoglycemia.

Practice Point 2.2.2: CGM metrics, such as time in range and time in hypoglycemia, may be considered as alternatives to HbA1c for defining glycemic targets in some patients.
Practice Point 3.1.1: Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages.
Recommendation 3.1.1: We suggest maintaining a protein intake of 0.8 g of protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis (2C).

Practice Point 3.1.2: Patients treated with hemodialysis, and particularly peritoneal dialysis should consume between 1.0 and 1.2 g protein/kg (weight)/d.

**Animal proteins**
- Meat, poultry, fish, seafood, eggs:
  - 28 g (1 oz) = 6–8 g protein
  - 1 egg = 6–8 g protein
- Dairy, milk, yogurt, cheese:
  - 250 ml (8 oz) = 8–10 g protein
  - 28 g (1 oz) cheese = 6–8 g protein

**Plant proteins**
- Legumes, dried beans, nuts, seeds:
  - 100 g (0.5 cup) cooked = 7–10 g protein
- Whole grains, cereals:
  - 100 g (0.5 cup) cooked = 3–6 g protein
- Starchy vegetables, breads:
  - 2–4 g protein
Recommendation 3.1.2: We suggest that sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD (2C).
**Figure 14. Ten ways to cut out salt**

1. **Use salt-free spices and fresh herbs to add flavor**
2. **Buy fresh foods and cook at home**
3. **Avoid foods with more than 400 mg sodium per serving**
4. **Avoid salty processed meats. Use fresh meat, poultry and eggs or plant proteins instead**
5. **Read labels: choose lower salt brands when possible. The goal is less than 2 g of sodium per day**
6. **Use sweet, sour, bitter and spicy or hot flavors to season food instead of salt**
7. **Keep healthy unsalted snacks on hand, including fresh fruit**
8. **Use unsalted butter, unsalted margarine, cooking oil or other unsalted fats when possible**
9. **When eating out in restaurants, order sauces, dressings and gravies in a separate dish and use less**
10. **Cut salty sauces like soy sauce (e.g., replace with pineapple juice or unseasoned rice vinegar)**
Lifestyle Interventions in Patients with Diabetes and CKD

Practice Point 3.1.3: Shared decision-making should be a cornerstone of patient-centered nutrition management in patients with diabetes and CKD.

Practice Point 3.1.4: Accredited nutrition providers, registered dietitians and diabetes educators, community health workers, peer counselors, or other health workers should be engaged in the multidisciplinary nutrition care of patients with diabetes and CKD.

Practice Point 3.1.5: Health care providers should consider cultural differences, food intolerances, variations in food resources, cooking skills, comorbidities, and cost when recommending dietary options to patients and their families.
LIFESTYLE INTERVENTIONS IN PATIENTS WITH DIABETES AND CKD

Recommendation 3.2.1. We recommend that patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (1D).

<table>
<thead>
<tr>
<th>Intensity of physical activity</th>
<th>METs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>&lt;1.5</td>
<td>Sitting, watching television, reclining</td>
</tr>
<tr>
<td>Light</td>
<td>1.6–2.9</td>
<td>Slow walking, household work such as cooking, cleaning</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0–5.9</td>
<td>Brisk walking, biking, yoga, swimming</td>
</tr>
<tr>
<td>Vigorous</td>
<td>&gt;6</td>
<td>Running, biking, swimming, lifting heavy weights</td>
</tr>
</tbody>
</table>
**Lifestyle Interventions in Patients with Diabetes and CKD**

Practice Point 3.2.1: Recommendations for physical activity should consider age, ethnic background, presence of other comorbidities, and access to resources.

Practice Point 3.2.2: Patients should be advised to avoid sedentary behavior.

Practice Point 3.2.3: For patients at higher risk of falls, health care providers should provide advice on the intensity of physical activity (low, moderate, or vigorous) and type of exercises (aerobic vs. resistance, or both).

Practice Point 3.2.4: Physicians should consider advising/encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR ≥30 ml/min per 1.73 m².
**Figure 17. Suggested Approach to Address Physical Inactivity and Sedentary Behavior in CKD**

1. **Assess baseline physical activity level**
   - **Sedentary**
     - Assess fall risk and comorbidity burden
       - **Low risk**
         - Recommend low-intensity activity and increase intensity as tolerated
       - **High risk**
         - Referral to exercise specialists
   - **Physically active for < 150 min/wk**
     - Recommend to increase physical activity level to achieve > 150 min/wk
     - **Unable to increase activity level due to comorbid conditions**
       - Continue current level
     - **Achieves recommended physical activity level**
   - **Physically active for > 150 min/wk**
     - Assess and recommend muscle-strengthening activities
CLINICAL TRIALS OF NEW DIABETES DRUGS

Cefalu W et al, Diabetes Care 2018
# Summary of the Benefits and Harms of SGLT2 Inhibitors, GLP-1 Receptor Agonists, and DPP-4 Inhibitors, by Class, as Observed in Large, Placebo-Controlled Clinical Outcomes Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>HbA1c lowering</th>
<th>Major atherosclerotic cardiovascular events</th>
<th>Heart failure</th>
<th>Albuminuria or albuminuria-containing composite outcome</th>
<th>GFR loss*</th>
<th>Notable adverse effects</th>
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</thead>
<tbody>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genital mycotic infections, diabetic ketoacidosis, possibly amputations (canagliflozin)</td>
</tr>
<tr>
<td>(CKD G1–G2)</td>
<td>0.6–0.9%</td>
<td>I/−</td>
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<tr>
<td>(CKD G3a)</td>
<td>0.3–0.5%</td>
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<td>−</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(CKD G3b–G4)</td>
<td></td>
<td></td>
<td>−</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA (CKD G5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gastrointestinal, primarily nausea and vomiting</td>
</tr>
<tr>
<td>(CKD G3a–4)</td>
<td>1.0–1.2%</td>
<td>I/−</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>DPP-4 inhibitors</strong></td>
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<td></td>
<td></td>
<td></td>
<td>Possibly heart failure (saxagliptin)</td>
</tr>
<tr>
<td>(CKD G3a–4)</td>
<td>0.5–0.7%</td>
<td>−</td>
<td>−/†</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control (Figure 18).

Practice Point 4.2: Most patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m² would benefit from treatment with both metformin and an SGLT2i.

Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonists (GLP-1 RA) generally preferred (Figure 20).
Figure 18. Treatment algorithm for selecting antihyperglycemic drugs for patients with 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

Additional drug therapy as needed for glycemic control:
- GLP-1 receptor agonist (preferred)
- DPP-4 inhibitor
- Insulin
- Sulfonylurea
- TZD
- Alpha-glucosidase inhibitor

- 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
**Figure 20. Patient factors influencing selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD**
ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m² with metformin (1B).

Practice Point 4.1.1: Treat kidney transplant recipients with T2D and eGFR ≥30 ml/min per 1.73 m² with metformin according to recommendations for patients with T2D and CKD.

Practice Point 4.1.2: Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when eGFR is <60 ml/min per 1.73 m² (Figure 22).
**Figure 22. Suggested approach in dosing metformin based on the level of kidney function**

- **eGFR < 30**
  - Yes: Stop metformin; do not initiate metformin
  - No: eGFR ≥ 60
    - Immediate release:
      - Initial 500 mg or 850 mg once daily
      - Titrate upwards by 500 mg/d or 850 mg/d every 7 days until maximum dose
    - OR
      - Extended release:
        - If GI side effects from immediate release
          - Initial 500 mg daily
          - Titrate upwards by 500 mg/d every 7 days until maximum dose

- **eGFR 45–59**
  - Initiate at half the dose and titrate upwards to half of maximum recommended dose

- **eGFR 30–44**
  - Annually if on metformin for more than 4 years or at risk of vitamin B12 deficiency

- **Dose initiation**
  - Monitor vitamin B12
  - Monitor kidney function

- **Subsequent dose adjustment**
  - eGFR ≥ 60
    - Continue same dose
  - eGFR 45–59
    - Continue same dose. Consider dose reduction in certain conditions (see text)
  - eGFR 30–44
    - Halve the dose
ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Practice Point 4.1.3: Adjust the dose of metformin when eGFR is <45 ml/min per 1.73 m², and for some patients when eGFR is 45-59 ml/min per 1.73 m² (Figure 22).

Practice Point 4.1.4: Monitor patients for vitamin B12 deficiency when they are treated with metformin for more than 4 years.
Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m² with an SGLT2i (1A).

Practice Point 4.2.1: 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 (Figure 24).
**Figure 24. Algorithm for Initiation of SGLT2i Therapy for Patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 m², Who Are Already Being Treated with Antihyperglycemic Medications**

Meeting individualized glycemic target?

- Yes → Can lower glycemic target be safely achieved by adding an SGLT2 inhibitor?
  - Yes → Add SGLT2 inhibitor
  - No → Discontinue or decrease dose of a current antihyperglycemic medication (other than metformin)

- No → Educate on potential adverse effects
  - Follow up on glycemia
  - Monitor for adverse effects
**CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy**

<table>
<thead>
<tr>
<th>Study design and participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>4401 patients with T2DM &amp; UACR &gt;300 mg/g</td>
<td>Stable on maximum dose tolerated ACEi or ARB for 4 weeks</td>
<td>Primary outcome (Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)</td>
</tr>
</tbody>
</table>

- Canagliflozin
- Placebo

**Outcomes**

- **Primary outcome**
  - HR 0.70 (95% CI 0.59-0.82)
  - NNT 21

- **End-stage kidney disease**
  - HR 0.68 (95% CI 0.54-0.86)
  - NNT 42

**Conclusion**

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events.

- **No increased risk of:**
  - Amputations: HR 1.10 (95% CI 0.79-1.56)
  - Fractures: HR 0.98 (95% CI 0.70-1.37)
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

**WHO WAS TESTED**
Type 2 DM. Prior history of CV disease

N = 7,020

- Age 63.1
- A1c 8.1%
- Diabetic nephropathy (>300 mg/g) 11%
- Blood pressure 135/77
- ACEi or ARB in 81%
- Statins in 77%

**WHAT WAS DONE**

- Empagliflozin 25 mg (N = 2,342)
- Empagliflozin 10 mg (N = 2,345)
- Placebo (N = 2,333)

2.6 years on treatment (3.1 years for outcomes)

**WHAT THEY FOUND**

The primary outcome was a composite of CV death, nonfatal MI, nonfatal stroke

- **Primary Outcome**
  - Empagliflozin: 10.5%
  - Placebo: 12.1%
  - Hazard Ratio: 0.86 (P < 0.001)

- **CV death**
  - Empagliflozin: 3.7%
  - Placebo: 5.9%
  - Hazard Ratio: 0.62 (P < 0.001)

- **Total mortality**
  - Empagliflozin: 5.7%
  - Placebo: 8.3%
  - Hazard Ratio: 0.68 (P < 0.001)

**Actual reductions at 12 weeks and 94 weeks**

- Hgb A1c
  - Empagliflozin 10 mg: 0.54% (25 mg: 0.60%)
  - Placebo: 0.42% (0.47%)

- Systolic BP
  - Reduction: 5 mmHg
Canagliflozin (SGLT2i) for type 2 DM: cardiovascular outcomes

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.

**N=4,330**

**CANVAS**

- Age 63.3 ± 8.3
- A1c 8.2%
- Hx of CVD 65%
- GFR 76
- Albuminuria 12 mg/g Cr

**10,142**

**CANVAS-R**

- N=5,812

**PRINCIPAL OUTCOME**

- Composite: CV death, nonfatal MI, nonfatal stroke

**CANAQLIFLOZIN**

- 29% drop out
- 188 Weeks (3.6 years)

**PLACEBO**

- 30% drop out

**AMPUTATIONS**

- Non-traumatic amputations of toes, feet, or legs

**PRIMARY OUTCOME**

- 26.9 per 1,000 patient years

**DECREASE of 4.6 events/1000 patient years**

**AMPUTATIONS**

- 6.3 per 1,000 patient years

**INCREASE of 2.9 events/1000 patient years**

**Additional benefits from canagliflozin**

- Hgb A1c 0.58%
- 1.6 kg

95% CI, 0.75 to 0.97
P<0.001 for noninferiority,
P=0.02 for superiority

**3.9** per 1,000 patient years

95% CI, 1.41 to 2.75
Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program


CANVAS Program
N= 10,142

- Canagliflozin
- Placebo

For every 1000 patients with CKD treated for 5 years

- ↓65 fewer cases of CV death/nonfatal MI/nonfatal stroke
- ↓18 fewer cases of ESKD/renal death/40% ↓ in eGFR
- ↓47 fewer cases of hospitalization for heart failure
- ↑25 more cases of amputation (15 minor, 10 major)

CKD (eGFR <60)
N= 2,039

68 years  BP 137/76  HbA1c 8.3%  eGFR 49

Albuminuria 22 mg/g

Canagliflozin consistently prevents CV and renal outcomes across different levels of kidney function
**Impact of Canagliflozin on Renal Outcomes in Type 2 DM**

A prespecified exploratory analysis of the CANVAS and CANVAS – R trials

**Cohort**

- n = 10,142
- 667 centres

**Composite Outcome**

- 2X Creatinine
- ESKD
- Renal Cause Mortality
- eGFR Decline
- New Onset Albuminuria
- Renal Adverse Events

**Canagliflozin**

- n = 5,795
- 1.5 per 1000 pt. yr
- 1.8 mL/min/yr
- 100.4 per 1000 pt. yr
- 2.5 per 1000 pt. yr

- HR 0.53
- CI 0.33–0.84
- Mean diff 2 mL/min
- CI 1.5–2.6
- HR 0.80
- CI 0.73–0.88
- NS

**Placebo**

- n = 4,347
- 2.8 per 1000 pt. yr
- 3.9 mL/min/yr
- 130.8 per 1000 pt. yr
- 3.3 per 1000 pt. yr

**Conclusion:** Treatment with Canagliflozin reduced the risk of sustained loss of kidney function, attenuated eGFR decline, and a reduction in albuminuria. This supports its possible renoprotective effect type 2 DM.

@divyaa24 for #LastmonthinNephrology

Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis

Toyama & Neuen et al. Diabetes, Obesity and Metabolism doi: 10.1111/dom.13648 @brendonneuen

- 27 included studies
- Up to 7,363 participants
- eGFR <60mL/min/1.73m²

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, nonfatal stroke</td>
<td>0.81</td>
<td>0.70-0.94</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.61</td>
<td>0.48-0.78</td>
</tr>
<tr>
<td>eGFR slope</td>
<td>1.35mL/min/1.73m²/year</td>
<td>0.78-1.93</td>
</tr>
<tr>
<td>Renal composite outcome</td>
<td>0.71</td>
<td>0.53-0.95</td>
</tr>
</tbody>
</table>

Overall effect estimate: 0.41, 0.68, 0.11, 0.93

P-heterogeneity for differences between individual agents: 0.41, 0.68, 0.11, 0.93

Conclusion: SGLT2 inhibitors reduce the risk of cardio-renal outcomes in patients with T2DM and CKD, without clear evidence of additional safety concerns beyond those already known for the class.
### SGLT2 Inhibitors and CKD Progression

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio / Risk Ratio)</th>
<th>SE</th>
<th>Experimental Total</th>
<th>Control Total</th>
<th>Hazard Ratio / Risk Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio / Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.7.1 Stage 1–2 CKD</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CANVAS Proram (CANVAS / CANVAS-R) 2017</td>
<td>-0.5447 0.177</td>
<td>2813</td>
<td>2811</td>
<td>11.0%</td>
<td>0.58 [0.41, 0.82]</td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>-0.2614 0.1273</td>
<td>3838</td>
<td>3894</td>
<td>21.4%</td>
<td>0.77 [0.60, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>6651</td>
<td>6705</td>
<td>32.4%</td>
<td>0.69 [0.52, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.02; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 2.71 (P = 0.007)</td>
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</tr>
<tr>
<td><strong>1.7.2 Stage 3–5 CKD</strong></td>
<td></td>
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</tr>
<tr>
<td>EMPA-REG OUTCOME 2013</td>
<td>-0.416 0.245</td>
<td>1196</td>
<td>605</td>
<td>5.8%</td>
<td>0.66 [0.41, 1.07]</td>
<td></td>
</tr>
<tr>
<td>CANVAS Proram (CANVAS / CANVAS-R) 2017</td>
<td>-0.4943 0.1552</td>
<td>1110</td>
<td>929</td>
<td>14.4%</td>
<td>0.61 [0.45, 0.83]</td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>-0.5903 0.1322</td>
<td>4444</td>
<td>4553</td>
<td>19.8%</td>
<td>0.55 [0.43, 0.72]</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>6750</td>
<td>6087</td>
<td>39.9%</td>
<td>0.39 [0.49, 0.71]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 5.70 (P &lt; 0.00001)</td>
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</tr>
<tr>
<td><strong>1.7.3 All stage CKD</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CREDENCE 2019</td>
<td>-0.4155 0.1119</td>
<td>2202</td>
<td>2199</td>
<td>27.6%</td>
<td>0.66 [0.53, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>2202</td>
<td>2199</td>
<td>27.6%</td>
<td>0.66 [0.53, 0.82]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 3.71 (P = 0.0002)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 5 (P = 0.58); I² = 0%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 7.53 (P &lt; 0.00001)</td>
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</tr>
<tr>
<td>Test for subgroup differences: Chi² = 1.09, df = 2 (P = 0.58), I² = 0%</td>
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</tbody>
</table>
## SGLT2 Inhibitors and 3-Point Major Cardiovascular Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Experimental Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Stage 1-2 CKD</strong></td>
<td></td>
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</tr>
<tr>
<td>CANVAS Program (CANVAS / CANVAS-R) 2017</td>
<td>-0.0513</td>
<td>0.0877</td>
<td>2813</td>
<td>2811</td>
<td>16.1%</td>
<td>0.95 [0.80, 1.13]</td>
<td></td>
</tr>
<tr>
<td>DECLARE--TIMI 58</td>
<td>-0.0513</td>
<td>0.0689</td>
<td>3838</td>
<td>3894</td>
<td>23.0%</td>
<td>0.95 [0.83, 1.09]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>6651</td>
<td>6705</td>
<td>39.1%</td>
<td>0.95 [0.85, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.00, df = 1 (P = 1.00); I^2 = 0%</td>
<td>Test for overall effect: Z = 0.95 (P = 0.34)</td>
<td></td>
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</tr>
<tr>
<td><strong>1.1.2 Stage 3-5 CKD</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EMPA--REG RENAL 2014</td>
<td>-0.91</td>
<td>0.725</td>
<td>334</td>
<td>224</td>
<td>0.3%</td>
<td>0.40 [0.10, 1.67]</td>
<td></td>
</tr>
<tr>
<td>DIA3004 2013</td>
<td>-0.282</td>
<td>0.632</td>
<td>179</td>
<td>90</td>
<td>0.4%</td>
<td>0.75 [0.22, 2.60]</td>
<td></td>
</tr>
<tr>
<td>MB102029 2014</td>
<td>-0.693</td>
<td>0.562</td>
<td>168</td>
<td>84</td>
<td>0.5%</td>
<td>0.50 [0.17, 1.50]</td>
<td></td>
</tr>
<tr>
<td>CANVAS Program (CANVAS / CANVAS-R) 2017</td>
<td>-0.3567</td>
<td>0.126</td>
<td>1110</td>
<td>929</td>
<td>8.8%</td>
<td>0.70 [0.55, 0.90]</td>
<td></td>
</tr>
<tr>
<td>EMPA--REG OUTCOME 2013</td>
<td>-0.128</td>
<td>0.126</td>
<td>1212</td>
<td>607</td>
<td>8.8%</td>
<td>0.88 [0.69, 1.13]</td>
<td></td>
</tr>
<tr>
<td>DECLARE--TIMI 58</td>
<td>-0.0646</td>
<td>0.0616</td>
<td>4444</td>
<td>4553</td>
<td>26.6%</td>
<td>0.94 [0.83, 1.06]</td>
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</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td></td>
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<td></td>
<td>7447</td>
<td>6487</td>
<td>45.5%</td>
<td>0.84 [0.73, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.01; Chi^2 = 6.58, df = 5 (P = 0.25); I^2 = 24%</td>
<td>Test for overall effect: Z = 2.29 (P = 0.02)</td>
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<tr>
<td><strong>1.1.3 All stages of CKD</strong></td>
<td></td>
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</tr>
<tr>
<td>CREDENCE 2019</td>
<td>-0.2231</td>
<td>0.0905</td>
<td>2202</td>
<td>2199</td>
<td>15.4%</td>
<td>0.80 [0.67, 0.96]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2202</td>
<td>2199</td>
<td>15.4%</td>
<td>0.80 [0.67, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Z = 2.47 (P = 0.01)</td>
<td></td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>16300</td>
<td>15391</td>
<td>100.0%</td>
<td>0.89 [0.82, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 9.49, df = 8 (P = 0.30); I^2 = 16%</td>
<td>Test for overall effect: Z = 3.05 (P = 0.002)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 3.38, df = 2 (P = 0.18), I^2 = 40.8%</td>
<td></td>
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</tr>
</tbody>
</table>

Less with SGLT2i | Less with placebo

[Graph showing the comparison between less with SGLT2i and less with placebo]

SGLT-2 INHIBITION AND GLOMERULAR HEMODYNAMICS IN DIABETES
THE KIDNEY-HEART CONNECTION FOR ORGAN PROTECTION

Scheen AJ; Circ Res 2018;122:1439-1459


ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Practice Point 4.2.2: 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.

Practice Point 4.2.3: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 4.2.4: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 4.2.5: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.
**Anti-hyperglycemic Therapies in Patients with Diabetes and CKD**

Practice Point 4.2.6: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 4.2.7: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if eGFR falls below 30 ml/min per 1.73 m², unless it is not tolerated or kidney replacement therapy is initiated.

Practice Point 4.2.8: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i treatment does not apply to kidney transplant recipients. (see Recommendation 4.2.1)
Recommendation 4.3.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).

3-point Major Cardiovascular Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>GLP-1 agonists Total</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Stage 1–2 CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harmony Outcomes 2018</td>
<td>-0.3711</td>
<td>0.1065</td>
<td>2208</td>
<td>2209</td>
<td>13.5%</td>
<td>0.69 [0.56, 0.85]</td>
<td></td>
</tr>
<tr>
<td>LEADER 2017</td>
<td>-0.0305</td>
<td>0.0983</td>
<td>1932</td>
<td>1937</td>
<td>14.5%</td>
<td>0.97 [0.80, 1.18]</td>
<td></td>
</tr>
<tr>
<td>EXSCEL 2017</td>
<td>-0.1278</td>
<td>0.055</td>
<td>5769</td>
<td>5745</td>
<td>21.0%</td>
<td>0.88 [0.79, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>9909</td>
<td>9891</td>
<td>49.0%</td>
<td>0.85 [0.72, 1.00]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.01; Chi² = 5.95, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 1.97 (P = 0.05)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>GLP-1 agonists Total</th>
<th>Placebo Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.2 Stage 3–5 CKD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PIONEER 6</td>
<td>-0.3011</td>
<td>0.3013</td>
<td>463</td>
<td>435</td>
<td>3.1%</td>
<td>0.74 [0.41, 1.34]</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN–6 2016</td>
<td>-0.174</td>
<td>0.2</td>
<td>469</td>
<td>470</td>
<td>6.1%</td>
<td>0.84 [0.57, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Harmony Outcomes 2018</td>
<td>-0.073</td>
<td>0.127</td>
<td>1098</td>
<td>1124</td>
<td>11.2%</td>
<td>0.93 [0.72, 1.19]</td>
<td></td>
</tr>
<tr>
<td>LEADER 2017</td>
<td>-0.371</td>
<td>0.102</td>
<td>1116</td>
<td>1042</td>
<td>14.1%</td>
<td>0.69 [0.57, 0.84]</td>
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</tr>
<tr>
<td>EXSCEL 2017</td>
<td>0.012</td>
<td>0.083</td>
<td>1565</td>
<td>1626</td>
<td>16.7%</td>
<td>1.01 [0.86, 1.19]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>4711</td>
<td>4697</td>
<td>51.0%</td>
<td>0.85 [0.71, 1.02]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 9.07, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 1.72 (P = 0.09)

Total (95% CI)
Heterogeneity: Tau² = 0.01; Chi² = 15.06, df = 7 (P = 0.04); I² = 54%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%
All-cause Mortality with GLP-1 Receptor Agonists in Patients with T2D

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log(Hazard Ratio)</th>
<th>SE</th>
<th>Experimental Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8.1 Albuminuria</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LEADER 2017</td>
<td>-0.2231</td>
<td>0.0982</td>
<td>0</td>
<td>0</td>
<td>52.7%</td>
<td>0.80 [0.66, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.27 (P = 0.02)</td>
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</tr>
<tr>
<td>3.8.2 Stage 3–5</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AWARD-7 2017</td>
<td>0.0198</td>
<td>0.4905</td>
<td>382</td>
<td>194</td>
<td>2.1%</td>
<td>1.02 [0.39, 2.67]</td>
<td></td>
</tr>
<tr>
<td>Idorn 2013</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>10</td>
<td>44.4%</td>
<td>0.74 [0.60, 0.91]</td>
</tr>
<tr>
<td>LEADER 2017</td>
<td>-0.3011</td>
<td>0.107</td>
<td>1116</td>
<td>1046</td>
<td>44.4%</td>
<td>0.74 [0.60, 0.91]</td>
<td></td>
</tr>
<tr>
<td>LIRA–RENAI 2016</td>
<td>1.3635</td>
<td>1.1146</td>
<td>140</td>
<td>137</td>
<td>0.4%</td>
<td>3.91 [0.44, 34.75]</td>
<td></td>
</tr>
<tr>
<td>PIONEER 5</td>
<td>-0.7133</td>
<td>1.1645</td>
<td>163</td>
<td>161</td>
<td>0.4%</td>
<td>0.49 [0.05, 4.80]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1815</td>
<td>1548</td>
<td>47.3%</td>
<td>0.76 [0.62, 0.93]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.72, df = 3 (P = 0.44); I^2 = 0%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.66 (P = 0.008)</td>
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<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1815</td>
<td>1548</td>
<td>100.0%</td>
<td>0.78 [0.68, 0.90]</td>
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<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.86, df = 4 (P = 0.58); I^2 = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.48 (P = 0.0005)</td>
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<tr>
<td>Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.71), I^2 = 0%</td>
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</tbody>
</table>
GLP-1 Receptor Agonists in Discovery and Pre-Clinical Science

- GLP-1 receptors in the kidney.
  - Endothelial cells
  - Macrophages
  - Proximal tubular cells

- Mediators for effects of GLP-1 receptor agonists.
  - Signaling – PKC beta inhibition
  - Oxidative Stress – increased cAMP and PKA, NAD(P)H oxidase inhibition
  - Inflammation – inhibition of ICAM-1 expression, macrophage infiltration

- GLP-1 receptor agonists in experimental models.
  - Reduce albuminuria
  - Decrease mesangial expansion and GBM thickness
  - Endothelial protection
  - Restore podocytes

ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

Practice Point 4.3.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Practice Point 4.3.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly (Figure 27).

Practice Point 4.3.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

Practice Point 4.3.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA are used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.
### Figure 27. Dosing for available GLP-1 RA agents and dose modification for CKD

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Dose</th>
<th>CKD adjustment</th>
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</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>0.75 mg and 1.5 mg once weekly</td>
<td>No dosage adjustment Use with eGFR &gt;15 ml/min per 1.73 m²</td>
</tr>
<tr>
<td>Exenatide</td>
<td>10 µg twice daily</td>
<td>Use with CrCl &gt;30 ml/min</td>
</tr>
<tr>
<td>Exenatide extended-release</td>
<td>2 mg once weekly</td>
<td>Use with CrCl &gt;30 ml/min</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6 mg, 1.2 mg, and 1.8 mg once daily</td>
<td>No dosage adjustment Limited data for severe CKD</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>10 µg and 20 µg once daily</td>
<td>No dosage adjustment Limited data for severe CKD</td>
</tr>
<tr>
<td>Semaglutide (injection)</td>
<td>0.5 mg and 1 mg once weekly</td>
<td>No dosage adjustment Limited data for severe CKD</td>
</tr>
<tr>
<td>Semaglutide (oral)</td>
<td>3 mg, 7 mg, or 14 mg daily</td>
<td>No dosage adjustment Limited data for severe CKD</td>
</tr>
</tbody>
</table>
ONGOING AND UPCOMING KIDNEY OUTCOME TRIALS

EMPA-KIDNEY
The study of heart and kidney protection with empagliflozin

FLOW
semaglutide renal outcomes trial

DAPA-CKD

FIDELIO-DKD
RCT Protocol

Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD)
Rationale and trial protocol

Interventions

- Dapagliflozin 10 mg
- Placebo

Follow-up

- ~ 45 months
- Event-driven (681 events)

Primary outcome

Composite renal endpoint
- ≥ 50% decline in eGFR

End-stage kidney disease

Renal or cardiovascular death

Heerspink HJL et al. NDT (2019)
@NDTSocial
Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D.,
Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D.,
Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D.,
Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D.,
Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D.,
for the DAPA-CKD Trial Committees and Investigators*

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P=0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.
Does Finerenone Help Reduce Kidney Failure and Progression in Diabetic Kidney Disease?

**FIDELIO-DKD**
Randomized Double-blind Placebo-controlled
- 47 countries
- 5.5 years
- eGFR ≥ 25 to < 75 ml/min/1.73m²
- Urine Alb/Crea ≥ 30 to ≤ 500 mg/g
- n = 5,734

**Primary Efficacy Endpoint**
Time to first occurrence of the composite onset of:
- Kidney failure
- Sustained decrease of eGFR ≥ 40% from baseline over at least 4 weeks
- Renal death

To assess whether finerenone reduces cardiorenal morbidity and mortality in patients with Type 2 DM and CKD when used in addition to standard of care.

At least 90% power to detect a 20% reduction in the risk of primary outcome.

Conclusion: FIDELIO-DKD will determine whether an optimally treated cohort of T2D patients with CKD at high risk of renal and CV events will experience cardiorenal benefits with the addition of finerenone to their treatment regimen.


Visual Abstract by Edgar Lerma @edgarlermamd
Outcome trials have dramatically improved our knowledge on the non-HbA$_{1c}$ effects of GLP-1 receptor agonists, DPP4 inhibitors and SGLT2 inhibitors.

The CV benefit of GLP-1 receptor agonists and SGLT2 inhibitors has been well-proven and use of these drugs have been implemented in guidelines.

The kidney benefit of new glucose lowering medications are being extensively investigated.
APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

Recommendation 5.1.1: We recommend that a structured self-management educational program be implemented for care of people with diabetes and CKD (Figure 28) (1C).

Practice Point 5.1.1: Health care systems should consider implementing a structured self-management program for patients with diabetes and CKD, taking into consideration local context, cultures, and availability of resources.

Key objectives are to:

- Improve diabetes-related knowledge, beliefs, and skills
- Improve self-management and self-motivation
- Encourage adoption and maintenance of healthy lifestyles
- Improve vascular risk factors
- Increase engagement with medication, glucose monitoring, and complication screening programs
- Reduce risk to prevent (or better manage) diabetes-related complications
- Improve emotional and mental well-being, treatment satisfaction, and quality of life
APPROACHES TO MANAGEMENT OF PATIENTS WITH DIABETES AND CKD

Recommendation 5.2.1: We suggest that policymakers and institutional decision-makers should implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD (2B).
Approaches to Management of Patients with Diabetes and CKD

Practice Point 5.2.1: Team-based integrated care, supported by decision-makers, should be delivered by physicians and nonphysician personnel (e.g., trained nurses and dieticians, pharmacists, health care assistants, community workers, peer supporters) preferably with knowledge of CKD (Figure 33).
OVERALL SUMMARY

• First KDIGO guideline on Diabetes and CKD now available
• Provide recommendations and practice points on:
  • Comprehensive care
  • Glycemic monitoring and targets
  • Lifestyle interventions
  • Antihyperglycemic therapies
  • Approaches to management of patients

• Patient-centered decision-making and support; and consistent efforts at improving diet and exercise remain the foundation of all glycemic management
• Control of risk factors including RAS blockade remains part of standard of care
• Glycemia is monitored with HbA1c and blood glucose
• Glycemic targets should be individualized with focus on increased risk for hypoglycemia with declining kidney function
• Initial use of both metformin and SGLT2i is recommended
• Health care organizations should support a coordinated effort.
QUESTION AND ANSWER