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
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

Vlad Perkovic, Rajagopal Ayyavu, Paola Fiozzo, Brenda H. Herrmann, Adeera Levin, Melvin C. Thomas, Christoph Wanner, Bertram L. Kasiske, David C. Wheeler, and Per Henrich, for Conference Participants

KDIGO Conference for Global Health, University of Sydney, Sydney, NSW, Australia; Angel North Shore Hospital, Sydney, New South Wales, Australia; Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana, USA; Takeda Development Laboratories, Inc., Kibbutz El Hanets, and Diabetes Institute, Melbourne, Victoria, Australia; Department of Medicine, Mie University, Mie, Japan; Department of Medicine, University of Calgary, Calgary, Alberta, Canada; The Yorkshire Institute for Health, Research and Education, St. George’s Hospital, London, UK; Diabetes Institute, University of Helsinki, Helsinki, Finland; Department of Kidney Disease Research Center, Helsinki, Finland; and Department of Medicine, Diabetes & Obesity Research Program, Research Programs Unit, University of Helsinki, Helsinki, Finland. The authors are co-authors of the Kidney International elsewhere, and have been found to be financially or otherwise, in any capacity, as part of their work for this conference.

The prevalence of diabetes around the world has reached epidemic proportions and is projected to increase to 642 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 in patients with diabetes are now under development. This conference was convened to assess our current state of knowledge regarding optimal glycemic control, current antihypertensive agents and their safety, and new therapies. The conference included presentations of new data on kidney function and cardiovascular outcomes for the vulnerable population. The conference also featured discussions of emerging data on new therapies for the prevention of ESKD.

Correspondence: Vlad Perkovic, The George Institute for Global Health, 323 Kent Street, Sydney NSW 2000, Australia; mail@georgeinstitute.org.au; or Per Henrich, Medizinisches Zentrum Muenchen, University of Munich and Klinikum der Ludwig-Maximilians-Universitat Muenchen, Lichtenbergstrasse 4, 81377 Munich, Germany; med@klinikum-muenchen.de

Received 5 August 2016; revised 16 September 2016; accepted 30 September 2016

www.kidneyinternational.org

Copyright © 2016, International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND 4.0 license.
The Beginning

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
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

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

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

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

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, M Clin Epid
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 Zongas, 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. Tunnillcliffe, 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

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

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

Tami Sadusky, MBA
Patient Representative
Seattle, WA, USA

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

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

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

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

Clint Hurst, BS
Patient Representative
Houston, TX, USA

Christoph Wanner, MD
University Hospital of Würzburg
Würzburg, Germany

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

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

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

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

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

Sankar D. Navaneethan, MD, MS, MPH
Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center
Houston, TX, USA
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
Svetanita 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 J. 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
Bryde Cashmore, MPH, Research Associate
Rubia Khalid, MND, Research Associate
Clarise Teng, BPsych (Hons), Research Associate
Patrizia Natale, MSc (ClinEpi), Research Associate
Marinella Ruospo, 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
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
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
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**

- **Initiate ACEi or ARB**
  - 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 for causes of AKI
        - Correct volume depletion
        - Reassess concomitant medications (e.g., diuretics, NSAIDs)
        - Consider renal artery stenosis
      - • Review concurrent drugs
        - Moderate potassium intake
          • Consider:
            - diuretics
            - sodium bicarbonate
            - GI cation exchangers
  - 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.
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.
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>HbA1c</th>
<th>Reliability</th>
<th>GMI</th>
</tr>
</thead>
</table>
| CKD G1–G3b                                      | Yes                          | • Twice per year  
• Up to 4 times per year if not achieving target or change in therapy | High       | Occasionally useful |
| CKD G4–G5 including treatment by dialysis or kidney transplant | Yes                          | • Twice per year  
• Up to 4 times per year if not achieving target or change in therapy | Low        | Likely useful      |
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 they are 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).

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>CKD G1</th>
<th>Absent/minor</th>
<th>Few</th>
<th>Long</th>
<th>Present</th>
<th>Available</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6.5%</td>
<td>Severity of CKD</td>
<td>Macrovacular complications</td>
<td>Comorbidities</td>
<td>Life expectancy</td>
<td>Hypoglycemia awareness</td>
<td>Resources for hypoglycemia management</td>
<td>Propensity of treatment to cause hypoglycemia</td>
</tr>
<tr>
<td>HbA1c</td>
<td>CKD G5</td>
<td>Present/severe</td>
<td>Many</td>
<td>Short</td>
<td>Impaired</td>
<td>Scarce</td>
<td>High</td>
</tr>
</tbody>
</table>
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.
Lifestyle Interventions in Patients with Diabetes and CKD

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
LIFESTYLE INTERVENTIONS IN PATIENTS WITH DIABETES AND CKD

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. Keep healthy unsalted snacks on hand, including fresh fruit.
7. Use sweet, sour, bitter and spicy or hot flavors to season food instead of salt.
8. Use unsalted butter, unsalted margarine, cooking oil or other unsalted fats when possible.
9. Cut salty sauces like soy sauce (e.g., replace with pineapple juice or unseasoned rice vinegar).
10. When eating out in restaurants, order sauces, dressings and gravies in a separate dish and use less.
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**

- **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>HbA$_1c$ lowering</th>
<th>Cardiovascular effects</th>
<th>Kidney effects</th>
<th>GFR loss*</th>
<th>Notable adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td></td>
<td>Major atherosclerotic cardiovascular events</td>
<td>Heart failure</td>
<td>Albuminuria or albuminuria-containing composite outcome</td>
<td>1 1/2 1/2</td>
</tr>
<tr>
<td>(CKD G1–G2)</td>
<td></td>
<td>0.6–0.9% (CKD G1–G2)</td>
<td>1/2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>(CKD G3a)</td>
<td></td>
<td>0.3–0.5% (CKD G3a)</td>
<td>1/2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>(CKD G3b–G4)</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>(NA (CKD G5)</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonists</strong></td>
<td>1.0–1.2% (CKD G3a–4)</td>
<td>1/2</td>
<td>1/2</td>
<td>1</td>
<td>Gastrointestinal, primarily nausea and vomiting</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>0.5–0.7% (CKD G3a–4)</td>
<td>1/2</td>
<td>1/2</td>
<td>1</td>
<td>Possibly heart failure (saxagliptin)</td>
</tr>
</tbody>
</table>
ANTHIHYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

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**
- **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
  - Alpha-glucosidase inhibitor

- **Additional drug therapy as needed for glycemic control**

- **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**
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

- **Dose initiation**
  - 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

- **Monitor vitamin B12**
  - At least annually
    - 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

- **Monitor kidney function**
  - At least every 3–6 months
    - 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

- **Subsequent dose adjustment**
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.
ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD

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
      - Educate on potential adverse effects
      - Follow up on glycemia
      - Monitor for adverse effects
    - No: Discontinue or decrease dose of a current antihyperglycemic medication (other than metformin)
  - No: (No further action indicated)

- Discontinue or decrease dose of a current antihyperglycemic medication (other than metformin)
  - (No further action indicated)
**CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy**

### Study design and participants
- 4401 patients with T2DM & UACR >300 mg/g
- 62 years
- eGFR 57
- UACR 927 mg/g

### Intervention
- Stable on maximum dose tolerated ACEi or ARB for 4 weeks

### Outcomes
#### Primary outcome
- (Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)
- 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

#### No increased risk of:
- Amputations
  - HR 1.10
  - (95% CI 0.79-1.56)
- Fractures
  - HR 0.98
  - (95% CI 0.70-1.37)

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

CV death
Empagliflozin 3.7%
Placebo 5.9%

Total mortality
Empagliflozin 5.7%
Placebo 8.3%

Hazard Ratio
Empagliflozin vs Placebo
Hgb A1c
10 mg
25 mg
12 weeks
0.54%
0.60%
94 weeks
0.42%
0.47%
Systolic BP
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

29% drop out

188 Weeks (3.6 years)

CANAGLIFLOZIN

PLACEBO 30% drop out

PRIMARY OUTCOME
Composite: CV death, nonfatal MI, nonfatal stroke

26.9 per 1,000 patient years

DECREASE of 4.6 events/1000 patient years

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

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
3.9
1.4
Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program


CANVAS Program
N= 10,142

Canagliflozin
Placebo

CKD (eGFR <60)
N= 2,039

68 years  BP 137/76  HbA1c 8.3%  eGFR 49

Albuminuria 22 mg/g

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)

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

\[ HbA_1c \text{ 7.0-10.5 \%} \]

AND

\[ 30\text{yr} + \text{Symptomatic Atherosclerosis} \]

OR

\[ 50\text{yr} + \geq 2 \text{ CV Risk Factors} \]

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

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

**CV death, nonfatal MI, nonfatal stroke**

- RR 0.81 (95% CI 0.70-0.94)
- 𝑃- heterogeneity for differences between individual agents: 0.41

**Hospitalization for heart failure**

- RR 0.61 (95% CI 0.48-0.78)
- 1.35mL/min/1.73m²/year (95% CI 0.78-1.93)
- 0.68

**eGFR slope**

- 0.11

**Renal composite outcome**

- RR 0.71 (95% CI 0.53-0.95)
- 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.

The George Institute for Global Health
### 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>Weight</th>
<th>Hazard Ratio / Risk Ratio</th>
<th>Hazard Ratio / Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.7.1 Stage 1–2 CKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Proram (CANVAS / CANVAS–R) 2017</td>
<td>-0.5447</td>
<td>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</td>
<td>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><strong>Subtotal (95% CI)</strong></td>
<td></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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.71 (P = 0.007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.7.2 Stage 3–5 CKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA–REG OUTCOME 2013</td>
<td>0.416</td>
<td>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</td>
<td>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</td>
<td>0.1322</td>
<td>4444</td>
<td>4553</td>
<td>19.8%</td>
<td>0.55 [0.43, 0.72]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.70 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.7.3 All stage CKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDENCE 2019</td>
<td>-0.1555</td>
<td>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><strong>Subtotal (95% CI)</strong></td>
<td></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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.71 (P = 0.0002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 5 (P = 0.58); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.53 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 1.09, df = 2 (P = 0.58), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# SGLT2 Inhibitors and 3-Point Major Cardiovascular Events

**Study or Subgroup**

<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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANDAS Proram (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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95 [0.85, 1.06]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.95 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.2 Stage 3-5 CKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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 Proram (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>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.84 [0.73, 0.98]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01; Chi² = 6.58, df = 5 (P = 0.25); I² = 24%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.29 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.1.3 All stages of CKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.80 [0.67, 0.96]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.47 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.89 [0.82, 0.96]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 9.49, df = 8 (P = 0.30); I² = 16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.05 (P = 0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 3.38, df = 2 (P = 0.18), I² = 40.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SGLT-2 Inhibition and Glomerular Hemodynamics in Diabetes

Alicic RZ, Johnson EJ, Tuttle KR.
Am J Kidney Dis 2018;72:267-277
THE KIDNEY-HEART CONNECTION FOR ORGAN PROTECTION

Scheen AJ; Circ Res 2018;122:1439-1459
Antihyperglycemic 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)
Anti-Hyperglycemic Therapies in Patients with Diabetes and CKD

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) SE</th>
<th>GLP-1 agonists Total</th>
<th>Placebo Total</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>
</tr>
<tr>
<td>Harmony Outcomes 2018</td>
<td>-0.3711 0.1065</td>
<td>2208</td>
<td>2209</td>
<td>0.69 [0.56, 0.85]</td>
</tr>
<tr>
<td>LEADER 2017</td>
<td>-0.0305 0.0983</td>
<td>1932</td>
<td>1937</td>
<td>0.97 [0.80, 1.18]</td>
</tr>
<tr>
<td>EXSCEL 2017</td>
<td>-0.1278 0.055</td>
<td>5769</td>
<td>5745</td>
<td>0.88 [0.79, 0.98]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>9909</td>
<td>9891</td>
<td>0.85 [0.72, 1.00]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01; Chi² = 5.95, df = 2 (P = 0.05); I² = 66%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.97 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 3.1.2 Stage 3–5 CKD     |                     |                      |               |                                 |
| PIONEER 6               | -0.3011 0.3013      | 463                  | 435           | 0.74 [0.41, 1.34]               |
| SUSTAIN–6 2016          | -0.174 0.2          | 469                  | 470           | 0.84 [0.57, 1.24]               |
| Harmony Outcomes 2018   | -0.073 0.127        | 1098                 | 1124          | 0.93 [0.72, 1.19]               |
| LEADER 2017             | -0.371 0.102        | 1116                 | 1042          | 0.69 [0.57, 0.84]               |
| EXSCEL 2017             | 0.012 0.083         | 1565                 | 1626          | 1.01 [0.86, 1.19]               |
| Subtotal (95% CI)       |                     | 4711                 | 4697          | 0.85 [0.71, 1.02]               |
| 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)

14620 14588 100.0% 0.85 [0.76, 0.95]

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>
<td></td>
<td></td>
<td></td>
<td></td>
<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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.27 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.8.2 Stage 3–5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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>10</td>
<td>44.4%</td>
<td>0.74 [0.60, 0.91]</td>
<td></td>
</tr>
<tr>
<td>LEADER 2017</td>
<td>-0.3011</td>
<td>0.107</td>
<td>1116</td>
<td>1046</td>
<td>4.4%</td>
<td>3.91 [0.44, 34.75]</td>
<td></td>
</tr>
<tr>
<td>LIRA-RENAL 2016</td>
<td>1.3635</td>
<td>1.1146</td>
<td>140</td>
<td>137</td>
<td>0.4%</td>
<td>0.49 [0.05, 4.80]</td>
<td></td>
</tr>
<tr>
<td>PIONEER 5</td>
<td>-0.7133</td>
<td>1.1645</td>
<td>163</td>
<td>161</td>
<td>47.3%</td>
<td>0.76 [0.62, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1815</td>
<td>1548</td>
<td></td>
<td></td>
<td>47.3%</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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.66 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1815</td>
<td>1548</td>
<td>100.0%</td>
<td></td>
<td>0.78 [0.68, 0.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.86, df = 4 (P = 0.58); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.48 (P = 0.0005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.71), I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</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>
</tr>
</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

- **Multicentre ~ 400**
- **Target n = 4300**
- **Patients with and without type 2 diabetes**

- **≥ 18 years**
- **25–75 ml/min/1.73 m²**
- **uACR ≥ 200 mg/g**

- **Polycystic kidney disease**
- **Lupus nephritis**
- **ANCA vasculitis**
- **Type 1 diabetes**

**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.

DOI: 10.1056/NEJMoa2024816
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 @edgarvlerma.md
Impact of Outcome Trials on Treatment Guidelines

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).
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.
**Central Illustration**

**Comprehensive management of patients with diabetes and CKD**
- BP control: use maximal ACEI or ARB dose in patients with hypertension, diabetes, and albuminuria as directed. Avoid RAS dual blockade and use of DRI with RASI
- Lipid control
- Glycemic control
- Use antiplatelet therapies where appropriate

**Goals**
- It's not just about glucose!
  1. Treat multiple targets (glycemia, BP, lipids)
  2. Use organ-protective therapies
  3. Promote self-management and team-based integrated care

**Glycemic monitoring and targets**
- Use HbA1c to monitor glycemic control
- Individualize HbA1c targets (< 5.5% to < 8.0%) based on patient comorbidities, hypoglycemia risk, resources and preferences
- Use CGM or SMBG when treatment associated with risk of hypoglycemia or when HbA1c is not concordant with blood glucose

**Antihyperglycemic therapies for T2D**
- First-line therapy
  - Metformin: eGFR < 45, reduce dose, eGFR < 30, discontinue
  - SGLT2 inhibitor
    - Do not initiate, discontinue
  - GLP-1 receptor agonist (preferred)
  - DPP-4 inhibitor
  - Insulin
  - SGLT2 inhibitor
  - TZD
  - Alpha-glucosidase inhibitor

**Lifestyle interventions**
- Consume diet high in vegetables, fruits, whole grains, plant-based proteins
- For patients not on dialysis, aim for 0.8 g protein/kg weight per day
- For patients on dialysis, aim for 1.0–1.2 g protein/kg weight per day
- Limit sodium intake < 2 g/day (< 5 g NaCl)
- Exercise for at least 150 min per week
- Stop tobacco use

**Coordinated care**
QUESTION AND ANSWER