



KDIGO Controversies Conference on Maintaining Kidney Health and Preventing CKD

November 30 – December 3, 2023

Rome, Italy

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of people with kidney disease worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences to review the state-of-the-art on a focused subject pertaining to kidney disease and set priorities for improving patient care and outcomes. In addition to highlighting areas for which additional research is needed, sometimes the conferences can lead to KDIGO guideline development efforts.

CONFERENCE BACKGROUND AND RELEVANCE

The main focus of chronic kidney disease (CKD) care has been on managing disease progression and treating kidney failure by dialysis or transplant. Maintaining or restoring kidney health has received scant attention by nephrology, primary care, or related specialties such as endocrinology and cardiology. While CKD prevention has been previously considered,^{1,2} progress has been hampered by lack of evidence or interest. Even the most recent consensus report by KDIGO and the American Diabetes Association (ADA) addressed CKD care in diabetes only after disease onset, defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m² or albuminuria categories A2 or A3.³ Yet recent data show that interventions can maintain kidney health if applied before disease onset or at early stages of CKD.⁴⁻⁷

A Lifespan Approach to Improving Kidney Health and Preventing CKD

CKD prevention has historically relied on interventions such as healthy lifestyles, treatment of risk factors, e.g., glycemic control in diabetes and blood pressure control in hypertension, and avoiding kidney injuries, e.g., toxins and adverse intrauterine conditions. Nevertheless, the number of individuals with CKD has steadily grown and now exceeds 850 million worldwide.⁸ CKD is estimated to rise to the fifth leading cause of death by 2040.⁹ In contrast, the burden of disability and death from cardiovascular diseases (CVDs) including stroke and ischemic heart disease has progressively decreased⁹ after several decades of emphasis on prevention.¹⁰

Strategies to Prevent, Delay, or Reverse CKD

Post-hoc analyses of the cardiovascular outcomes trials (CVOTs) EMPA-REG Outcome (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and DECLARE-TIMI-58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) showed that treatment with a sodium-glucose co-transporter 2 (SGLT2) inhibitor may prevent, delay, or reverse CKD.^{11 12} In a subset of EMPA-REG Outcome participants without CKD, SGLT2 inhibitor treatment reduced the rate of annual decline in eGFR.¹¹ In subsets with A2 or A3 albuminuria categories at baseline, along with slowing eGFR decline, albuminuria remitted on empagliflozin treatment with sustained reductions of 22-29% after treatment withdrawal at median follow-up times of 34-35 days.¹¹ Treatment of participants without CKD was also associated with decreased risks for all-cause mortality and for reaching a composite endpoint of progression to albuminuria category A3, doubling of serum creatinine accompanied by eGFR of <45 ml/min per 1.73 m², initiation of kidney replacement therapy, or death from kidney disease.⁴ Similar kidney protection was observed for a subset of DECLARE-TIMI-58 participants without CKD at baseline.¹² Interestingly, in both trials, participants without CKD at baseline had the lowest residual risk of adverse kidney outcomes while on SGLT2 inhibitors, at 0.6% to 0.8%, which was 11- to 12-fold lower than for patients with advanced CKD.

Glucagon-like peptide 1 (GLP-1) receptor agonists and a dual incretin GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist were originally developed for hyperglycemia and obesity, and like the SGLT2 inhibitors, were also studied in CVOTs.¹³⁻¹⁸ As in the CVOTs, trials of glycemic lowering with these agents found

reductions in kidney disease events as major secondary outcomes. GLP-1 receptor agonists (e.g., liraglutide, semaglutide, lixisenatide, dulaglutide) and a dual GIP/GLP-1 receptor agonist (tirzepatide) reduced albuminuria and slowed eGFR decline in patients with type 2 diabetes, most of whom did not have CKD.¹⁹⁻²⁴ In studies of obese people with or without type 2 diabetes, semaglutide also reduced albuminuria and increased the number who remitted from albuminuria categories A2 or A3 to lower levels, including A1.²⁵ Meta-analyses of the GLP-1 receptor agonists studied in CVOTs also found lower risk of a composite kidney disease outcome (A3 albuminuria, serum creatinine doubling, $\geq 40\%$ eGFR decline, kidney failure, death due to kidney disease) with a hazard ratio of 0.77 (95% confidence interval 0.79-0.87).⁷ In SURPASS 4, a CVOT of the dual GLP-1/GIP receptor agonist tirzepatide, the rate of eGFR decline was significantly slower, and albuminuria onset or progression were prevented across strata of eGFR and albuminuria, including those without CKD at baseline.⁵ In a mediation analysis of kidney disease outcomes (A3 albuminuria, doubling of serum creatinine, eGFR < 45 mL/min per 1.73 m², kidney failure) from CVOTs of liraglutide and semaglutide in type 2 diabetes, lower glycemia or blood pressure only moderately mediated (10-25%) these benefits, pointing to direct actions on the kidney by GLP-1 receptor agonists.²⁶

Anti-inflammatory therapies may also prevent CKD, although data examining CKD prevention are limited, and most studies explored CKD treatment. In a clinical trial of participants with atherosclerotic cardiovascular disease and diabetes or metabolic syndrome with eGFR > 40 ml/min/ 1.73 m², those who received low-dose methotrexate had less eGFR decline over a median follow-up time of nearly two years compared with placebo, irrespective of baseline kidney function, although this trial did not assess albuminuria.²⁷ In patients with type 2 diabetes and albuminuria, a Janus kinase 1/2 inhibitor (baricitinib) studied in a 6-month, phase 2, placebo-controlled trial reduced albuminuria in a dose-related manner with a sustained effect after a 4-week washout period, inferring persistence of albuminuria remission.^{28, 29} Similarly, non-steroidal mineralocorticoid antagonists such as finerenone are believed to provide kidney protection by anti-inflammatory actions of blocking aldosterone in kidney cells.³⁰ However, only data evaluating CKD treatment in people with type 2 diabetes are available to date.³¹⁻³³ Assessing the potential of anti-inflammatory strategies for CKD prevention or remission requires additional studies.



In sum, studies of SGLT2 inhibitors, incretins, and anti-inflammatory therapies have provided evidence that it may be possible to identify persons at risk of CKD onset or progression who could benefit from interventions to prevent, delay, or reverse disease. Potential novel therapies for specific forms of kidney diseases such as IgA nephropathy, lupus nephritis, focal segmental glomerulosclerosis, etc. that target underlying causal pathomechanisms have also shown promises in preventing kidney manifestations, nephron loss, or regression/reversal of the kidney disease process itself (e.g., proteinuria reduction, GFR improvement, reduction of total kidney volume).

CONFERENCE OVERVIEW

This KDIGO conference will gather a global panel of multidisciplinary clinical and scientific expertise (primary care, pediatrics, geriatrics, nephrology, cardiology, endocrinology, pharmacology) as well as patient experts. The objective is to assess the current state of knowledge related to CKD prevention across the lifespan. Primary prevention will refer to pharmacologic and non-pharmacologic approaches to prevent CKD or delay disease onset in persons who are at risk. Primordial prevention of CKD is understood as preventing the risk factors for CKD. Although a main focus of the conference will be on primary prevention, the potential for secondary prevention to arrest CKD progression or stimulate regression, especially in those with early CKD (e.g., CKD G3a, low-level albuminuria), will also be included as part of the conference remit. Discussion of CKD prevention will extend beyond traditional risk factors (e.g., diabetes or hypertension) to include novel risk factors (e.g., genetic risk scores) and newer treatment strategies (e.g., anti-inflammatory agents³⁴).

Four breakout groups will work to:

- a) Define CKD prevention, consider its integration within a wider prevention ecosystem, and identify endpoints to assess the impact of prevention strategies and interventions
- b) Define high-risk populations in different settings (e.g., throughout the lifespan, in the presence of different comorbidities or geographical locations) that may benefit from interventions for preventing or the reversing/regression of CKD



c) Assess available evidence on prevention or the reversing/regression of CKD by medical and non-medical means and define a research agenda to evaluate the clinical effectiveness of novel interventions

d) Identify optimal, cost-effective means for implementing a lifespan approach to kidney health

Drs. Alberto Ortiz (Fundación Jiménez Díaz, Spain) and Katherine R. Tuttle (University of Washington, USA) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. This highly interactive conference will invite key thought leaders and relevant stakeholders, including patients, in nephrology and other related specialties who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research.

APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: The Case for Kidney Health

Goal: Define CKD prevention, consider its integration within a wider prevention ecosystem, and identify endpoints to assess the impact of prevention strategies and interventions

- **CKD current definition and shortcomings**
 1. Do treatable pathogenic events pre-date the current eGFR or albumin-creatinine ratio (ACR) threshold values used to diagnose CKD?
 2. How can we define the syndromic nature of obesity, metabolic syndrome, diabetes, and cardiovascular-kidney disease to promote early diagnosis for prevention and treatment?
 3. Are there studies showing outcomes by CKD assessment, i.e., one-time eGFR versus repeat measures within 90 days, spot-urine ACR versus persistent, eGFR or ACR only?"

- **Definition of primary prevention of CKD**
 1. What are the most accurate ways and nomenclature to describe prevention of CKD and the possibility of CKD reversal?
 2. Do we need a nomenclature that clearly identifies CKD prevention as conceptually different from CVD prevention?
 3. How do we differentiate primary prevention of CKD from secondary prevention of CVD for research and implementation?
 4. How do we conceptually integrate primary prevention into a wider prevention ecosystem of primordial and secondary prevention of CKD?
 5. How should lifestyle interventions be implemented in primordial CKD prevention? What research is needed? What population would benefit most?

- **Assessing the success of a primary prevention intervention**
 1. Can we use ACR maintained in A1/A2 and GFR categories 1/2 with stable eGFR decline <1 ml/min per 1.73^2 within a certain time frame as a definition of prevention or remission of CKD (similar to remission of diabetes)?



2. Are there biomarkers besides cystatin C that improve the predictive value of ACR, serum creatinine, and cystatin?
3. How can standardization of biomarkers move forward faster?
4. Why is cystatin C not used routinely as a replacement for (or in addition to) serum creatinine?
5. Can we use major adverse kidney events (MAKE)? If so, which ones? 40 or 50% decrease in eGFR? Doubling of serum creatinine or kidney failure or kidney death?
6. Given that kidney failure is a rare outcome early in the disease process, should risk models for CVD also be used to assess CKD prevention (i.e., CVD outcomes as CKD complications)?
7. Since proteinuria/albuminuria reduction has been used as a surrogate measure for trials in glomerular disease, can these surrogate endpoints and others (e.g., total kidney volume) be more broadly used for ascertaining CKD prevention or regression? If so, what is the appropriate rate of decline? Are there biomarkers (laboratory or histological measures) that can potentially be used to assess CKD prevention (e.g., nephron loss?)

Breakout Group 2: Identifying and Stratifying Individuals for CKD Prevention and Lifestyle Interventions

Goal: Define high-risk populations in different settings (e.g., throughout the lifespan, in the presence of different comorbidities or geographical locations) that may benefit from interventions for preventing CKD

- **Identifying and stratifying individuals for CKD prevention**
 1. Should CKD screening be performed in the general population, or should CKD screening be focused on at-risk populations?
 2. If screening is focused on at-risk populations, what factors determine CKD risk now or in the future, e.g., comorbidities, family history, BMI, birthweight, genetic risk scores, hyperfiltration, or others?
 3. Can tools that predict CKD risk efficiently stratify individuals with high CKD risk who should be screened? Are there any novel diagnostic point-of-care instruments or incident CKD risk estimation tools?
 4. What factors should be included in tools that predict CKD risk to stratify CKD screening, especially environmental and occupational factors, in low-resource settings?
 - a. What is the utility of using lifecourse events as primordial factors to identify vulnerable individuals, such as those with family history, suboptimal perinatal development (e.g., preterm birth, low birth weight), major childhood illnesses, or other kidney events (e.g., gouty arthritis, use of NSAIDs)?
 - b. Can we use family history, obesity, and risk scores to identify people who have the highest lifetime risk for developing CKD for regular monitoring and targeted treatment?
 - c. Are there risk scores to predict onset of CKD, and what is their performance and feasibility for implementation?
 5. What level of predicted CKD risk in which timeline should lead to CKD screening recommendations? For example, is a 5% risk in 10 years an indicator for testing?
 6. If screening is focused on at-risk populations, how will clinicians determine CKD risk?
 7. Should CKD risk screening have age limits?



8. Should CKD risk screening address non-GFR kidney function, e.g., tubular function?
 9. What populations should have follow-up or routine annual CKD or CKD risk screening? For example, following nephrectomy, certain types of chemotherapy, heart failure, others?
- **Lifestyle interventions**
 1. What is the evidence on the association of lifestyle factors (e.g., diet with high content of red meat/processed foods, sugar-sweetened beverages, foods with high glycemic indexes) and onset of CKD? What are considerations or benefits for protective lifestyles (e.g., plant-based diets, exercise)?
 2. What lifestyle interventions should be recommended to reduce CKD risk?
 3. What research is needed to identify lifestyle interventions to lower CKD risk?
 4. What recommendations should be made regarding environmental causes of CKD (e.g., unknown CKD) to lower population risk for CKD?

Breakout Group 3: Medical Interventions for CKD Prevention

Goal: Assess available evidence on prevention of CKD by medical and non-medical means and define a research agenda to evaluate the clinical effectiveness of novel interventions

- **Pharmacological interventions**
 1. What is the existing evidence on effective pharmaceutical interventions for CKD prevention?
 - a. What is the evidence for using metformin and renin-angiotensin system inhibitors (RASi) as highly affordable medications in the primary prevention of CKD?
 - b. What is the evidence for using other novel medications in the primary prevention of CKD?
 2. What outstanding research is still needed to establish standardized interventions for CKD prevention?
 3. Which healthcare professionals are responsible for medication stewardship, particularly regarding avoidance of nephrotoxic agents such as NSAIDs, herbal remedies, and other toxic agents that may negatively impact the kidney?
 4. What trial designs (e.g., pragmatic RCT, length of follow-up, outcomes such as GFR thresholds, rates of decline, CKD onset) should be employed to assess the effectiveness of an intervention for CKD prevention/regression?
- **Procedural interventions (e.g., bariatric, renal denervation) to reduce CKD-related risk factors**
 1. What is the existing evidence to support the effectiveness of procedural interventions to reduce CKD-related risk factors?
 2. What research is still needed to address effectiveness of existing procedural interventions to reduce CKD-related risk factors?
- **Other interventions and devices in treatment-resistant hypertension**
 1. What is the existing evidence to support carotid baroreceptor stimulation?
 2. What is the existing evidence to support renal denervation strategies?



- **Who are the main stakeholders?**
 1. Especially in settings where nephrologists may not be readily available, how can we better engage primary care providers and other allied health partners (e.g., community workers and clinical educators) as primary stakeholders for CKD prevention and regression?
 2. Who are other relevant stakeholders that can assist (e.g., nurses, social workers, pharmacists)?
 3. What do payers need to get involved in an agenda for preventing CKD?



Breakout Group 4: Implementing a Lifespan Approach to Kidney Health

Goal: Identify optimal, cost-effective means for implementing a lifespan approach to kidney health

- **Dissemination and education**
 1. Who are the appropriate audiences for implementing a lifespan approach to kidney health?
 2. What is the appropriate timing, cadence, and content for disseminating information to these audiences?
 3. Should primary care doctors be certified to highlight their interest and competency in implementing cardiovascular-kidney disease detection, prevention, and treatment programs? How can we better incentivize them?
 4. Could CKD-cardiovascular disease competencies or fellowships be used for encouraging the use of multidisciplinary approaches?
 5. Can we develop simple tools (similar to diabetes risk scores) to help primary care providers, teachers, and the public to enhance patient activation (i.e., promote self-assessment and self-management)?
 6. How can we encourage electronic health record vendors (e.g., Epic, Cerner) to create standardized, non-proprietary CKD care tools (e.g., incident CKD estimation, Tangri kidney failure prognostication, ASCVD 10-yr risk score) that do not require extensive customizations?
 7. How can governments or payers (e.g., insurance) be informed to use policies and system approaches to detect and prevent CKD?

- **Implementation strategies**
 1. What key principles should guide the implementation of a lifespan approach?
 2. What are the available levers to implement a lifespan approach to kidney health? These might include but are not limited to:
 - a. Public policy, including subsidies
 - b. Government and commercial payers
 - c. Employers and self-insured health plans
 - d. Professional medical societies
 - e. Business sector and industry

- f. Patient organizations
 - g. Local or regional government agencies
 - h. Philanthropic sources
 - i. Political interest groups
 - j. Social media and other societal influence channels
3. Are there any technological or motivational instruments to facilitate behavioral change?
 4. What incentives can be taken to boost adoption of urinary ACR measurements for early intervention?
 - a. What are the barriers and facilitators for measuring urinary ACR?
 - b. Can we bundle the annual measurement of blood pressure, blood glucose, eGFR, and ACR along with BMI and waist to identify high-risk subjects (may add TG/HDL-C), especially in those with primordial risk factors?
 5. How can we implement a strategy of intensified control of multiple risk factors (e.g., J-DOIT3) to prevent onset of CKD?
 6. What new cost-effectiveness studies are needed to justify early detection of CKD?
- **Implementation of measurements and benchmarks for recommendations:**
 - What are the targets?**
 1. What are the critical early life and socioeconomic determinants that contribute to the development of kidney diseases later in life?
 - a. How can we identify and address these changing determinants to improve kidney health in the long term?
 2. Which criteria exist to determine appropriate metrics for evaluating effectiveness of a lifestyle approach to kidney health?
 - a. What are the most effective lifestyle modifications and behavioral interventions for optimizing kidney health across the lifespan?
 3. Which potential metrics are available now, and which are needed? This might include but are not limited to:
 - a. Process and adherence to recommended interventions
 - b. Patient reported outcome measures (PROMs)
 - c. Hard and soft clinical endpoints



- d. Government and economic (e.g., employment, spending, healthcare price indexes, etc.)
 - e. Payer financial and quality metrics (e.g., per patient per month, HEDIS, NQF, etc.)
4. What data collection/access/infrastructure and privacy concerns must be addressed to establish benchmarks and track performance in these metrics?
- **Obtaining resources for implementation and showing cost effectiveness**
 1. Which audiences are interested in the cost effectiveness of a lifespan approach to kidney health, and for what reason(s)?
 2. How should cost-effectiveness data be used with these audiences to gain resources and support for implementation?
 3. What are the policy implications of adopting a lifespan approach to optimizing kidney health and diagnosing and managing kidney diseases?
 - **Lessons and approaches gleaned from programs implementing CVD primary prevention: Emulating success and sidestepping failures**
 1. What are the opportunities for knowledge exchange and learning from other disciplines?
 2. Are there any examples of system-level primary prevention that have been implemented at scale that could be used to inform kidney health lifespan approaches?
 - **How are we going to do it?**
 1. What are the key challenges and opportunities in coordinating care within a lifespan approach?
 - a. How can health systems be optimized to support this approach and ensure equitable access to care?
 2. What strategies can be employed to optimize care for individuals with multiple chronic conditions?
 - a. How can we tailor screening approaches to account for the lifespan perspective?
 - b. What are the potential benefits and challenges of implementing personalized strategies?



3. What minimum financial resources, system structure, and local market conditions are necessary to implement a lifespan approach to kidney health?

References

1. Kelly JT, Su G, Zhang L, *et al.* Modifiable lifestyle factors for primary prevention of CKD: A systematic review and meta-analysis. *J Am Soc Nephrol* 2021; **32**: 239-253.
2. Levey AS, Schoolwerth AC, Burrows NR, *et al.* Comprehensive public health strategies for preventing the development, progression, and complications of CKD: report of an expert panel convened by the Centers for Disease Control and Prevention. *Am J Kidney Dis* 2009; **53**: 522-535.
3. de Boer IH, Khunti K, Sadusky T, *et al.* Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022; **102**: 974-989.
4. Levin A, Perkovic V, Wheeler DC, *et al.* Empagliflozin and cardiovascular and kidney outcomes across KDIGO risk categories: Post hoc analysis of a randomized, double-blind, placebo-controlled, multinational trial. *Clin J Am Soc Nephrol* 2020; **15**: 1433-1444.
5. Tuttle KR, Wong L, St Peter W, *et al.* Moving from evidence to implementation of breakthrough therapies for diabetic kidney disease. *Clin J Am Soc Nephrol* 2022; **17**: 1092-1103.
6. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: Collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022; **400**: 1788-1801.
7. Sattar N, Lee MMY, Kristensen SL, *et al.* Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021; **9**: 653-662.
8. Jager KJ, Kovesdy C, Langham R, *et al.* A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Kidney Int* 2019; **96**: 1048-1050.

9. Foreman KJ, Marquez N, Dolgert A, *et al.* Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: Reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018; **392**: 2052-2090.
10. Dalen JE, Alpert JS, Goldberg RJ, *et al.* The epidemic of the 20(th) century: Coronary heart disease. *Am J Med* 2014; **127**: 807-812.
11. Cherney DZI, Zinman B, Inzucchi SE, *et al.* Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: An exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017; **5**: 610-621.
12. Mosenzon O, Raz I, Wiviott SD, *et al.* Dapagliflozin and prevention of kidney disease among patients with type 2 diabetes: Post hoc analyses from the DECLARE-TIMI 58 Trial. *Diabetes Care* 2022; **45**: 2350-2359.
13. Marso SP, Daniels GH, Brown-Frandsen K, *et al.* Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**: 311-322.
14. Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**: 1834-1844.
15. Holman RR, Bethel MA, Mentz RJ, *et al.* Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017; **377**: 1228-1239.
16. Gerstein HC, Colhoun HM, Dagenais GR, *et al.* Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. *Lancet* 2019; **394**: 121-130.
17. Husain M, Birkenfeld AL, Donsmark M, *et al.* Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019; **381**: 841-851.
18. Del Prato S, Kahn SE, Pavo I, *et al.* Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): A randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* 2021; **398**: 1811-1824.
19. Tuttle KR, Lakshmanan MC, Rayner B, *et al.* Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease

- (AWARD-7): A multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; **6**: 605-617.
20. Mann JFE, Ørsted DD, Brown-Frandsen K, *et al.* Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; **377**: 839-848.
 21. Muskiet MHA, Tonneijck L, Huang Y, *et al.* Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: An exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018; **6**: 859-869.
 22. Shaman AM, Bain SC, Bakris GL, *et al.* Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: Pooled analysis of SUSTAIN 6 and LEADER. *Circulation* 2022; **145**: 575-585.
 23. Heerspink HJL, Sattar N, Pavo I, *et al.* Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: Post-hoc analysis of an open-label, randomised, phase 3 trial. *Lancet Diabetes Endocrinol* 2022; **10**: 774-785.
 24. Tuttle KR, Bosch-Traberg H, Cherney DZI, *et al.* Post hoc analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo. *Kidney Int* 2023; **103**: 772-781.
 25. Heerspink HJL, Apperloo E, Davies M, *et al.* Effects of semaglutide on albuminuria and kidney function in people with overweight or obesity with or without type 2 diabetes: Exploratory analysis from the STEP 1, 2, and 3 Trials. *Diabetes Care* 2023; **46**: 801-810.
 26. Mann JFE, Buse JB, Idorn T, *et al.* Potential kidney protection with liraglutide and semaglutide: Exploratory mediation analysis. *Diabetes Obes Metab* 2021; **23**: 2058-2066.
 27. Sparks JA, Vanni KMM, Sparks MA, *et al.* Effect of low-dose methotrexate on eGFR and kidney adverse events: A randomized clinical trial. *J Am Soc Nephrol* 2021; **32**: 3197-3207.



28. Tuttle KR, Brosius FC, 3rd, Adler SG, *et al.* JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: Results from a Phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant* 2018; **33**: 1950-1959.
29. Alicic RZ, Johnson EJ, Tuttle KR. Inflammatory mechanisms as new biomarkers and therapeutic targets for diabetic kidney disease. *Adv Chronic Kidney Dis* 2018; **25**: 181-191.
30. Tuttle KR, Agarwal R, Alpers CE, *et al.* Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney Int* 2022; **102**: 248-260.
31. Bakris GL, Ruilope LM, Anker SD, *et al.* A prespecified exploratory analysis from FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes. *Kidney Int* 2023; **103**: 196-206.
32. Pitt B, Filippatos G, Agarwal R, *et al.* Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021; **385**: 2252-2263.
33. Agarwal R, Filippatos G, Pitt B, *et al.* Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: The FIDELITY pooled analysis. *Eur Heart J* 2022; **43**: 474-484.
34. Ruiz-Ortega M, Lamas S, Ortiz A. Antifibrotic agents for the management of CKD: A review. *Am J Kidney Dis* 2022; **80**: 251-263.