# KDIGO 2020 Guidelines on CKD and Hypertension in Patients with Diabetes

Matthew R. Weir, MD
Professor and Director
Division of Nephrology
University of Maryland School of Medicine

# DISCLOSURES

**Scientific Advisor: Janssen, Astra, BI, MSD, Akebia, Relypsa, Boston Scientific, Lexicon, Bayer, Vifor, CareDx**

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# Overview

- KDIGO Guidelines
- Treatment of Hypertension
- Treatment of Diabetes in CKD Patients
- Conclusions

# GUIDELINE GOALS

- Generate a useful resource for clinicians and patients
  - Address relevant questions with actionable recommendations
  - Take on controversial topics when sufficient evidence
  - Communicate clearly: highlight figures and tables
- Stay true to evidence
- Target audience: broad, primarily clinicians treating diabetes & CKD
- Be mindful of implications for policy and payment
- Propose research questions

# 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

# Blood Pressure Measurement

- Recommendation 1.1: We recommend standardized office BP in preference to routine office BP for the management of high BP in adults.
- Practice Point 1.1: An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement; however, standardization emphasizes the adequate preparations for BP measurement, not the type of equipment.
- Practice Point 1.2: Automated office BP (AOBP), either attended or unattended, may be the preferred method of standardized office BP measurement.
- Practice Point 1.3: Oscillometric devices can be used to measure BP among patients with atrial fibrillation.

# Blood Pressure Measurement

Recommendation 1.2: We suggest that out-of-office BP measurements be used with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to complement standardized office BP readings for the management of high BP.

# Blood Pressure targets

- Recommendation 3.1.1: We suggest that adults with CKD and high BP be treated with a target systolic blood pressure (SBP) of less than 120 mmHg, when tolerated, using standardized office BP measurement.
- Practice Point 3.1.1: It is potentially hazardous to apply the recommended SBP target of <120 mmHg to BP measurements obtained in a non-standardized manner.
- Practice Point 3.1.2: Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy of symptomatic postural hypotension.

# Treatment with antihypertensive drugs, including RAS inhibitors (RASi)

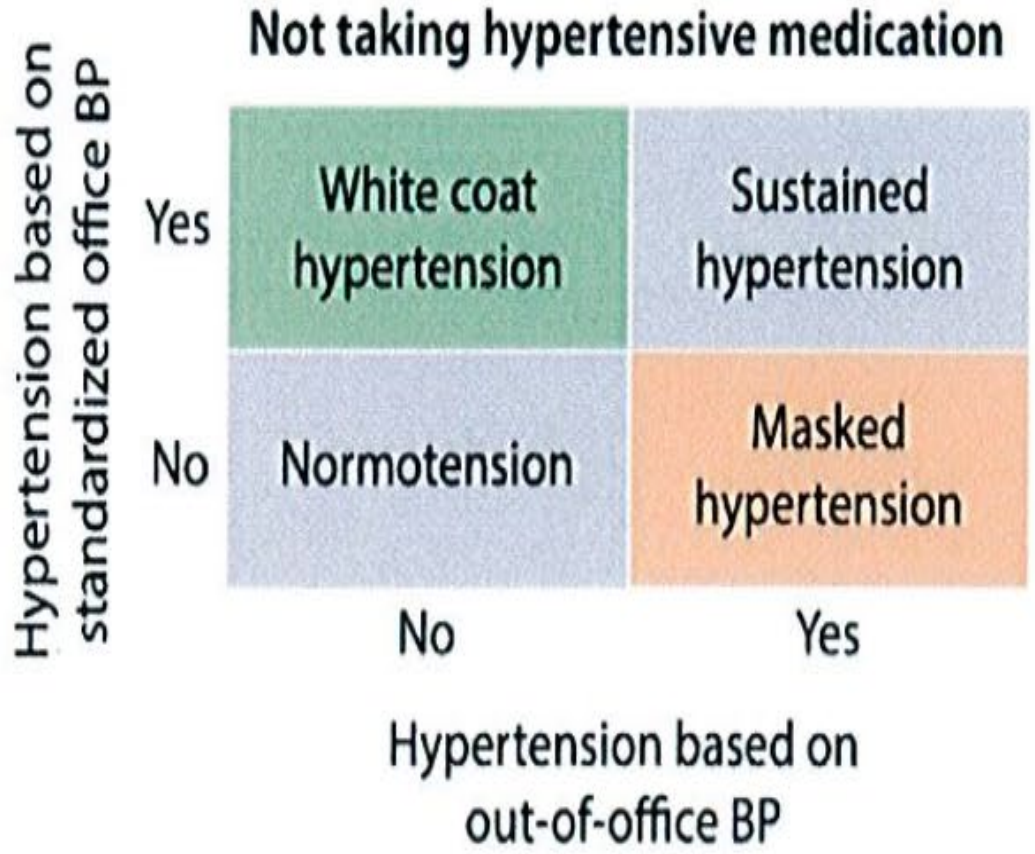
- Recommendation 3.2.1: We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and severely increased albuminuria (G1-G4, A3) without diabetes.
- Recommendation 3.2.2: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1-G4, A2) without diabetes.
- Recommendation 3.2.3: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and increased albuminuria (G1 to G4, A2 and A#) with diabetes.

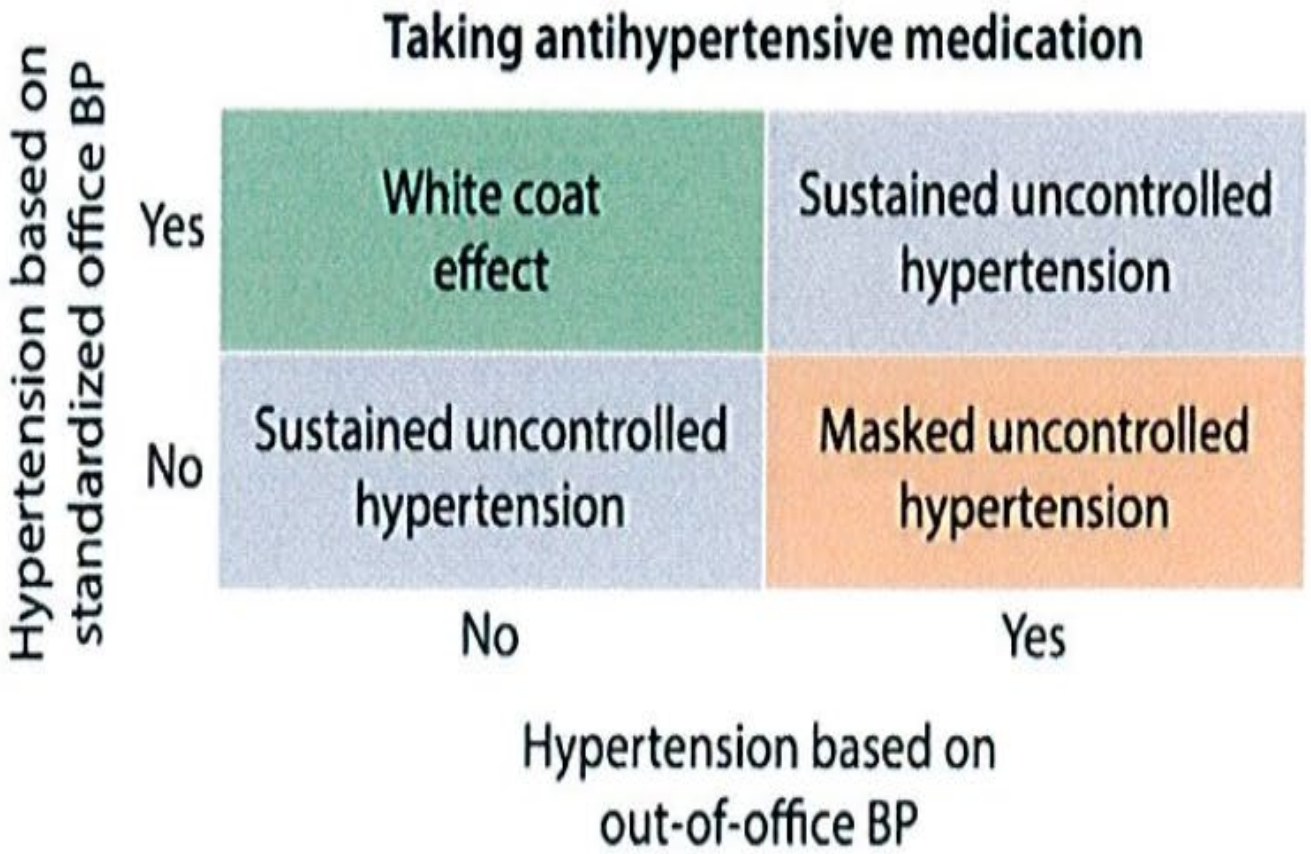
# TREATMENT WITH ANTIHYPERTENSIVE DRUGS, INCLUDING RAS INHIBITORS (RASI)

- Practice Point 3.2.1: It may be reasonable to treat people with high BP, CKD, no albuminuria with or without diabetes with RASi (ACEi or ARB)
- Practice Point 3.2.2: RASi (ACEi or ARB) should be administered using maximally recommended doses to achieve the benefits described because the proven benefits were achieved in trials using these doses.
- Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 1-4 weeks of initiation or increased in the dose of RASi, depending on the current GFR and serum potassium.
- Practice Point 3.2.4: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the potassium level rather than decreasing the dose or stopping RASi

- Practice Point 3.2.5: Continuation or RASi can be considered unless serum creatinine rise by >30% within 4 weeks of initiation or upon dose increase.
- Practice Point 3.2.6: Consider reducing the dose or discontinuing ACEi or ARB in the setting of uncontrolled hyperkalemia despite medical treatment and reduce uremic symptoms while treating kidney failure.
- Practice Point 3.2.7: Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause a decline in kidney function or hyperkalemia, particularly among patients with low eGFR.

# BLOOD PRESSURE PATTERNS INFORMED BY OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENTS IN ADDITION TO STANDARDIZED OFFICE BLOOD PRESSURE MEASUREMENT



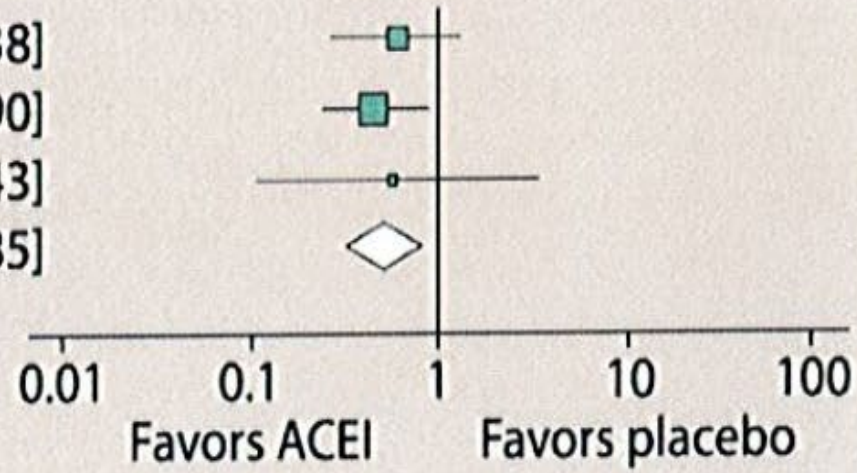



# CARDIOVASCULAR EVENTS IN PATIENTS WITH CKD G3 TO G4, A3 WITHOUT DIABETES

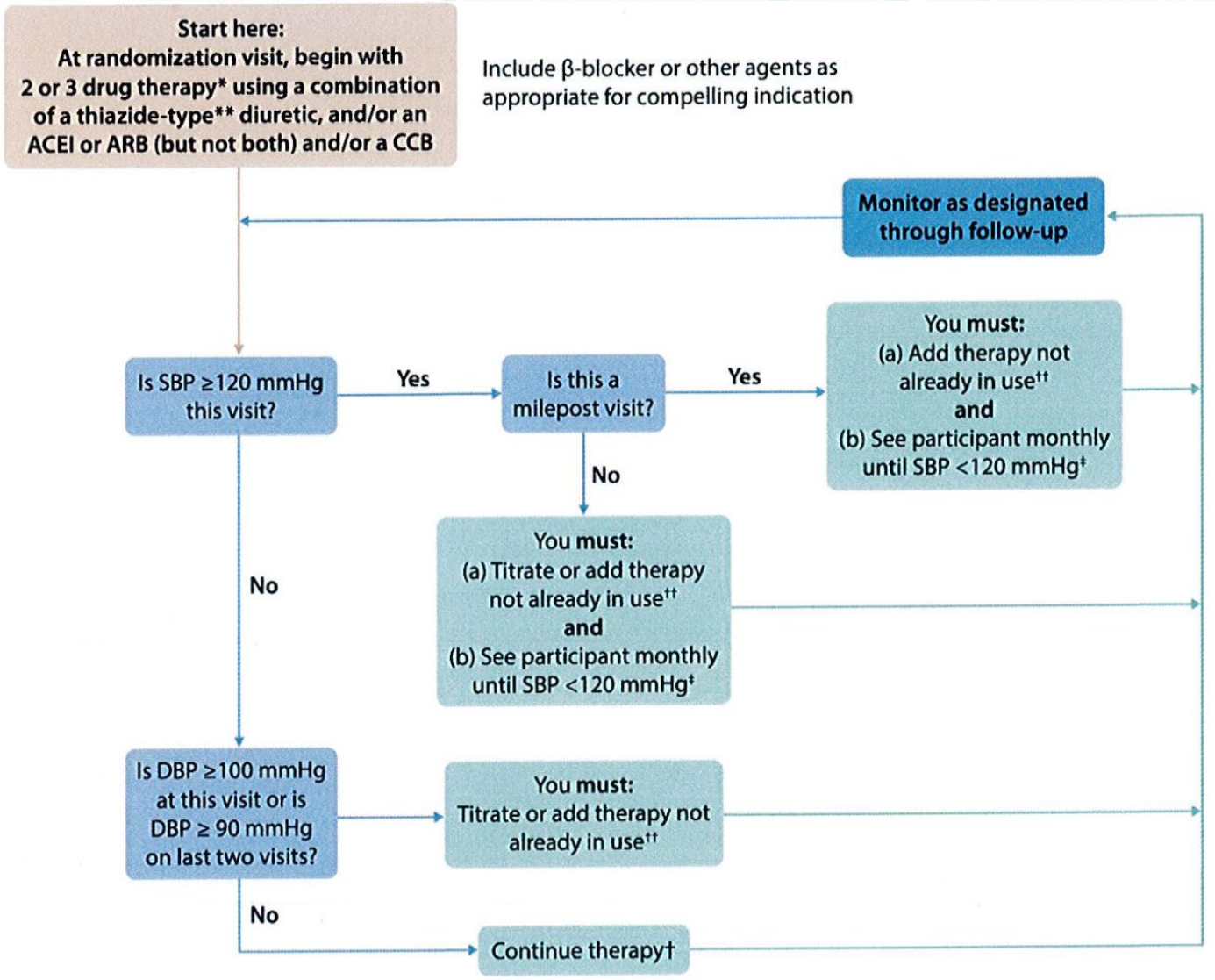
| Study or subgroup | ACEI Events | ACEI Total | Placebo/ no treatment Events | Placebo/ no treatment Total | Weight | Risk ratio M–H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.10.1 Albuminuria/proteinuria** | | | | | | |
| AIPRI 1996 | 9 | 300 | 14 | 286 | 33.9% | 0.61 [0.27, 1.38] |
| Hou 2006 | 14 | 216 | 16 | 112 | 49.5% | 0.45 [0.23, 0.90] |
| REIN–1 Stratum 1999 | 2 | 99 | 3 | 87 | 7.3% | 0.59 [0.10, 3.43] |
| Subtotal (95% CI) | | 615 | | 482 | 90.8% | 0.52 [0.31, 0.85] |
| **Total events** | **25** | | **33** | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.31$, $df = 2$ ($P = 0.86$); $I^2 = 0\%$

Test for overall effect: $Z = 2.58$ ($P = 0.010$)



# SPRINT RESEARCH TREATMENT ALGORITHM FOR THE INTENSIVE GROUP (GOAL SBP< 120 MMHG)

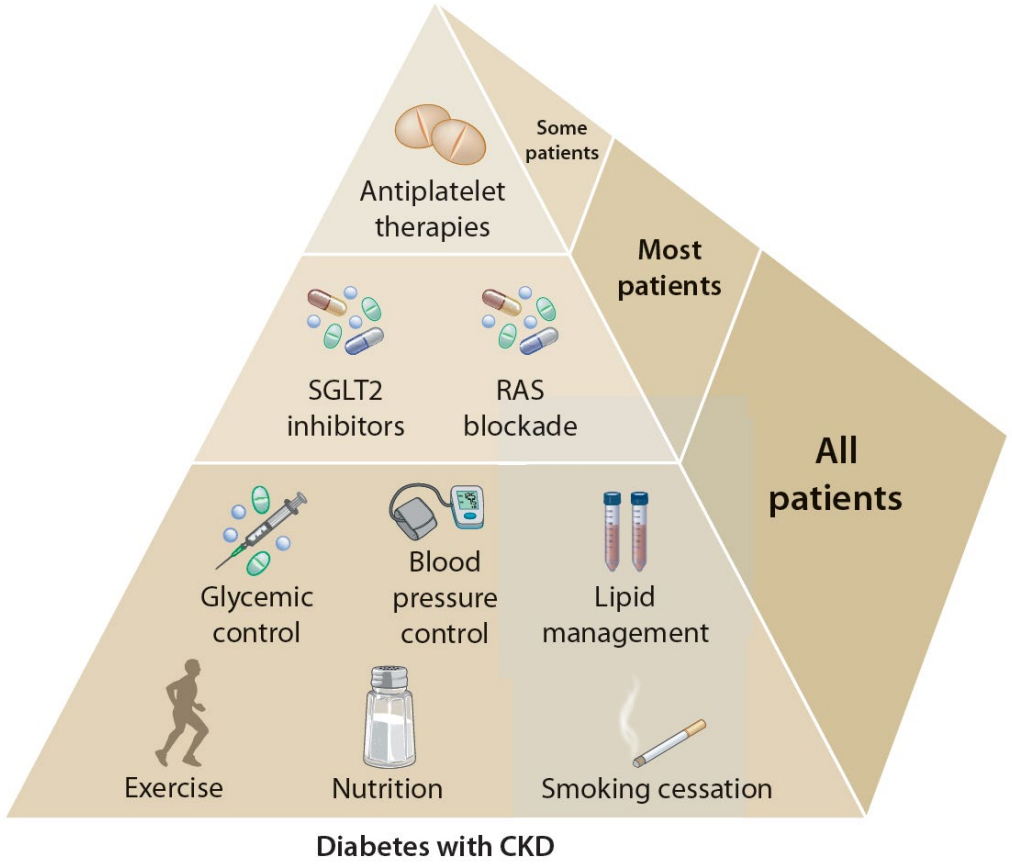


# Diabetes & CKD Guideline Contents

- Chapter 1. Comprehensive care in patients with diabetes and CKD
  - Comprehensive diabetes and CKD management
  - RAS blockade
  - Smoking cessation
- Chapter 2. Glycemic monitoring and targets in patients with diabetes and CKD
  - Glycemic monitoring
  - Glycemic targets
- Chapter 3. Lifestyle interventions in patients with diabetes and CKD
  - Nutrition intake
  - Physical activity
- Chapter 4. Antihyperglycemic therapies in patients with diabetes and CKD
  - Overall approach
  - Metformin
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
- Chapter 5. Approaches to management of patients with diabetes and CKD
  - Self-management education programs
  - Team-based integrated care

# Comprehensive Care in Patients with Diabetes and CKD

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figure 2).



# Comprehensive Care in Patients with Diabetes and CKD

**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.

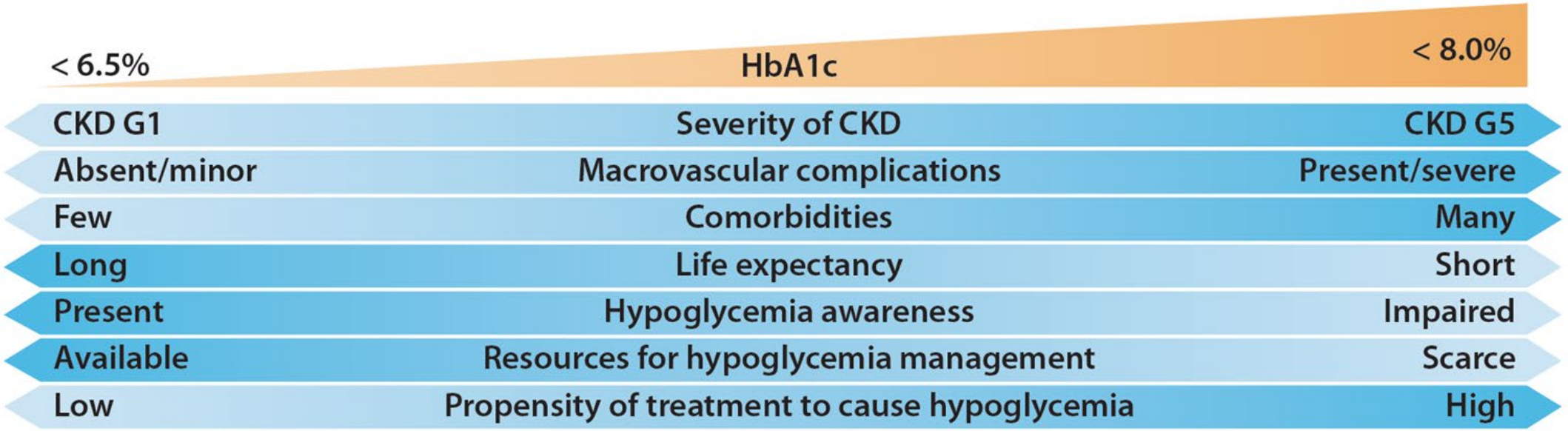
Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2-4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

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.

# Glycemic Monitoring and Targets in Patients with Diabetes and CKD

**Recommendation 2.2.1. We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) *(1C)*.**



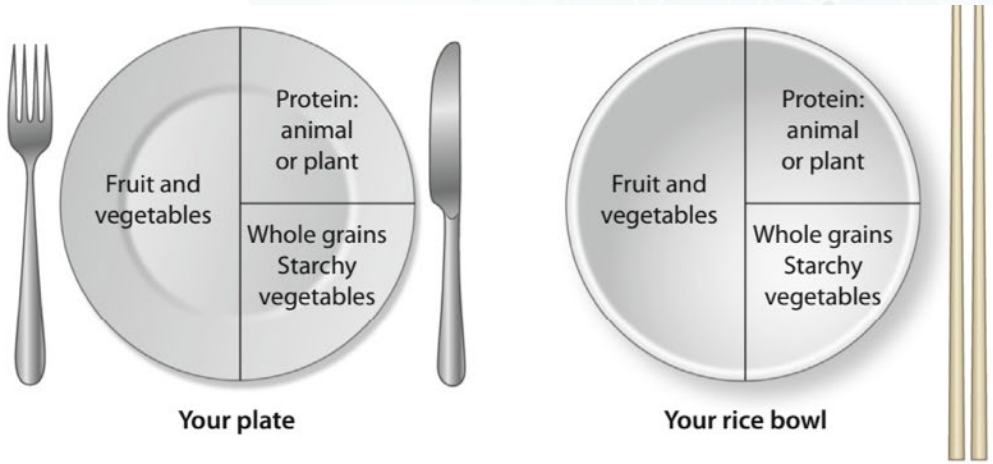
# Glycemic Monitoring and Targets in Patients with Diabetes and CKD

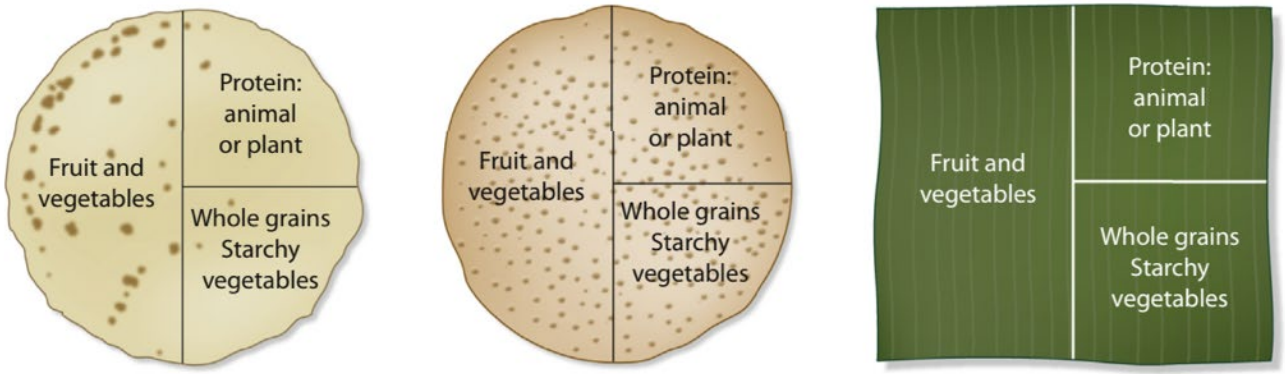
Practice Point 2.2.1: Safe achievement of lower HbA1c targets (e.g., <6.5% or <7.0%) may be facilitated by CGM or SMBG and by selection of antihyperglycemic agents that are not associated with hypoglycemia.

Practice Point 2.2.2: CGM metrics, such as time in range and time in hypoglycemia, may be considered as alternatives to HbA1c for defining glycemic targets in some patients.

# Lifestyle Interventions in Patients with Diabetes and CKD

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.



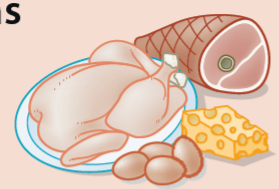



# Lifestyle Interventions in Patients with Diabetes and CKD

**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

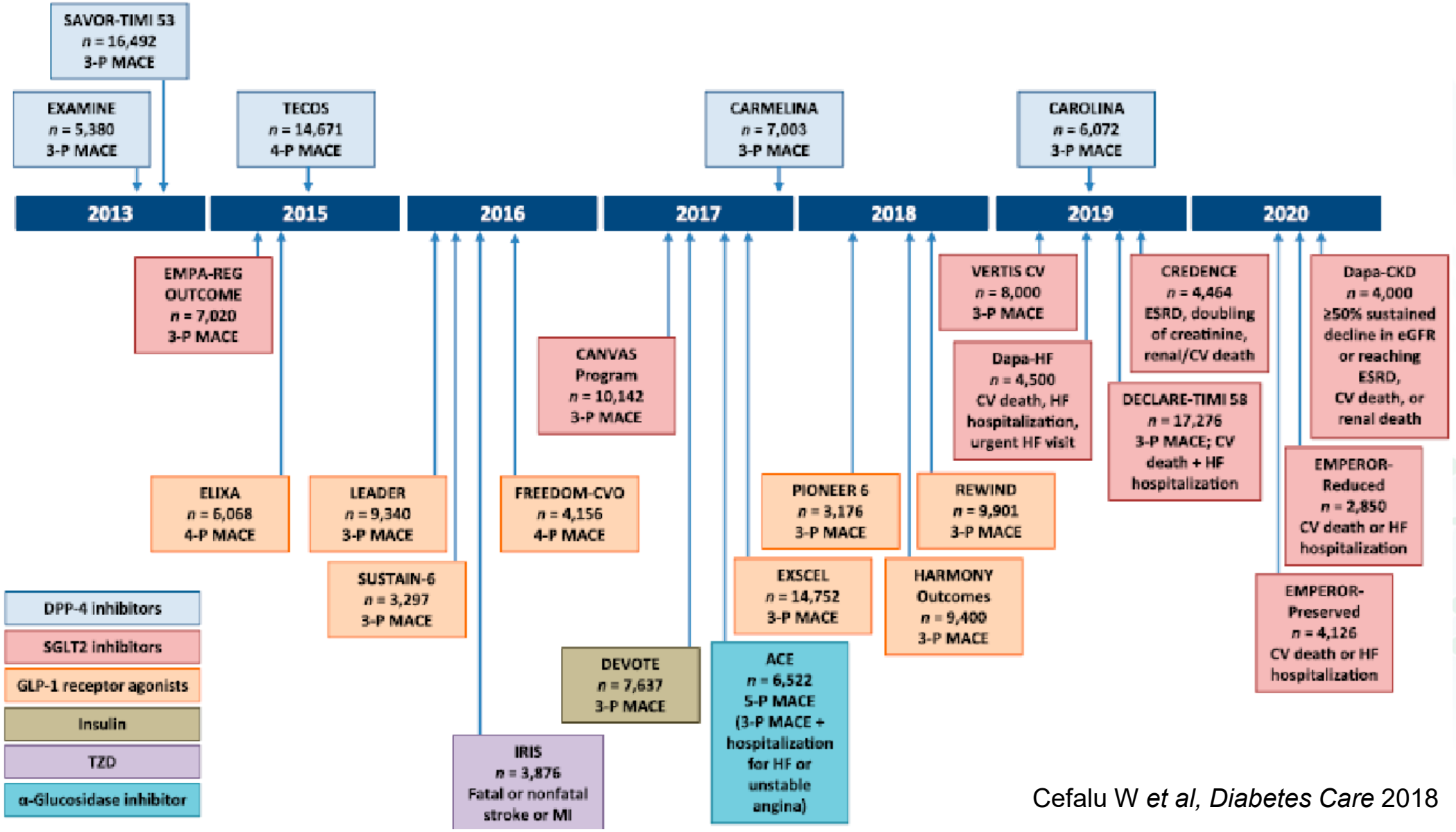
**Plant proteins**

**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

# 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

| | | Cardiovascular effects | | Kidney effects | | |
|---|---|---|---|---|---|---|
| **Drug** | **$HbA_{1c}$ lowering** | **Major atherosclerotic cardiovascular events** | **Heart failure** | **Albuminuria or albuminuria-containing composite outcome** | **GFR loss*** | **Notable adverse effects** |
| **SGLT2 inhibitors** | ↓ 0.6–0.9% (CKD G1–G2)<br>↓ 0.3–0.5% (CKD G3a)<br>↔<br>(CKD G3b–G4)<br>NA<br>(CKD G5) | ↓/– | ↓↓ | ↓↓ | ↓↓ | Genital mycotic infections, diabetic ketoacidosis, possibly amputations (canagliflozin) |
| **GLP-1 receptor agonists** | ↓ 1.0–1.2% (CKD G3a–4) | ↓/– | – | ↓ | ↓/– | Gastrointestinal, primarily nausea and vomiting |
| **DPP-4 inhibitors** | ↓ 0.5–0.7% (CKD G3a–4) | – | –/↑ | ↓ | – | Possibly heart failure (saxagliptin) |

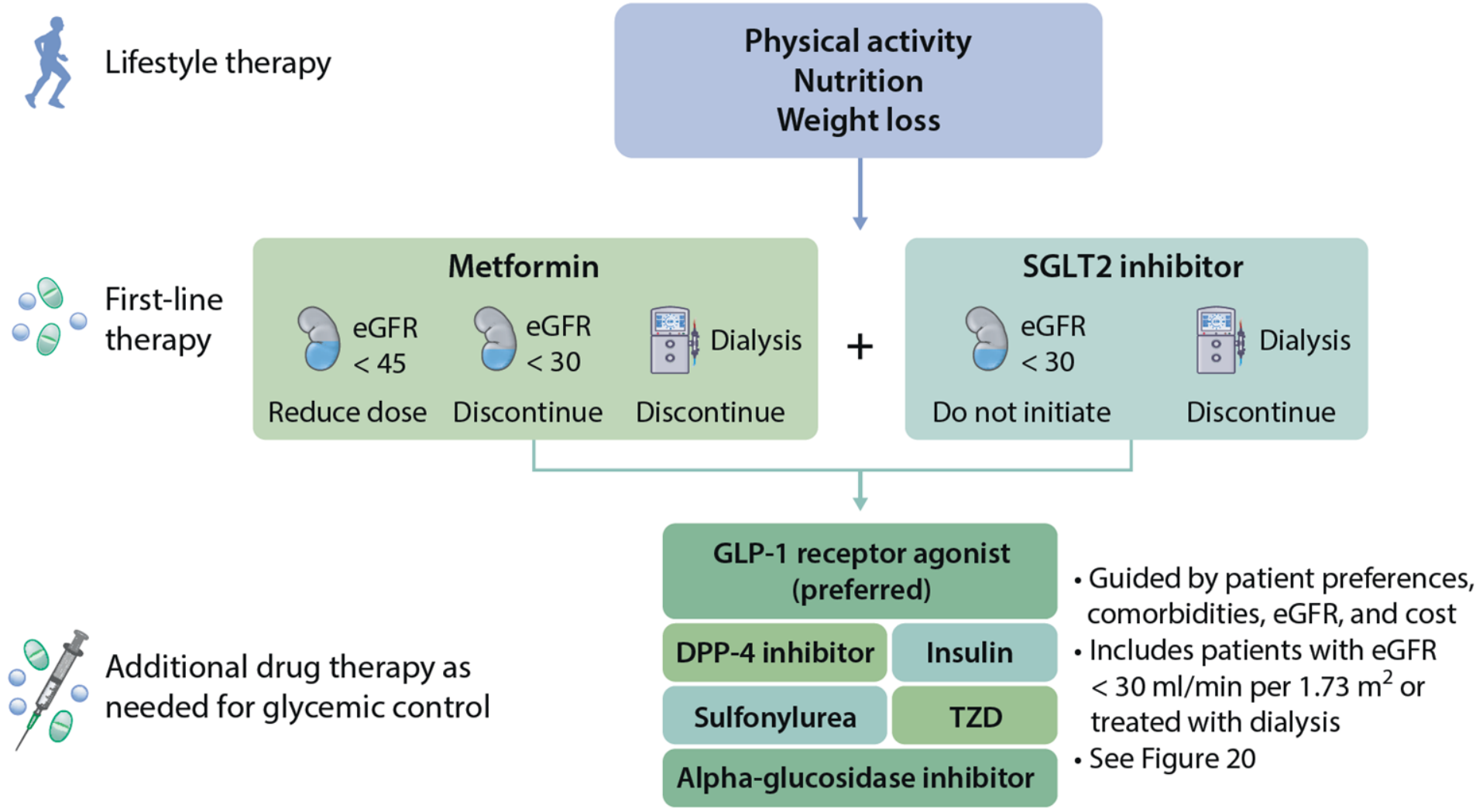
# Anti-hyperglycemic Therapies in Patients with Diabetes and CKD

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).

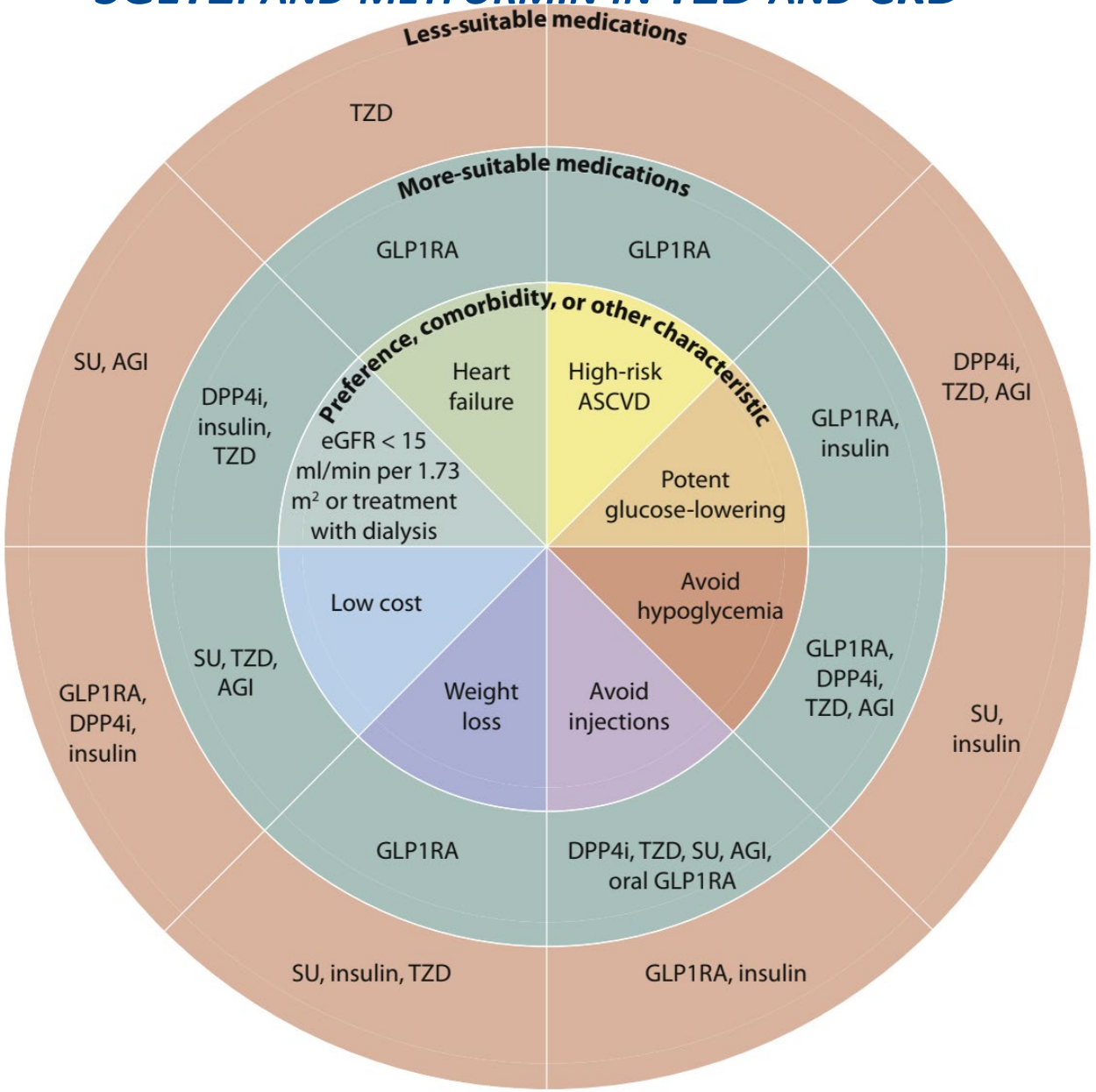
Practice Point 4.2: Most patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 $m^2$ would benefit from treatment with both metformin and an SGLT2i.

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



# FIGURE 20. PATIENT FACTORS INFLUENCING SELECTION OF GLUCOSE-LOWERING DRUGS OTHER THAN SGLT2I AND METFORMIN IN T2D AND CKD



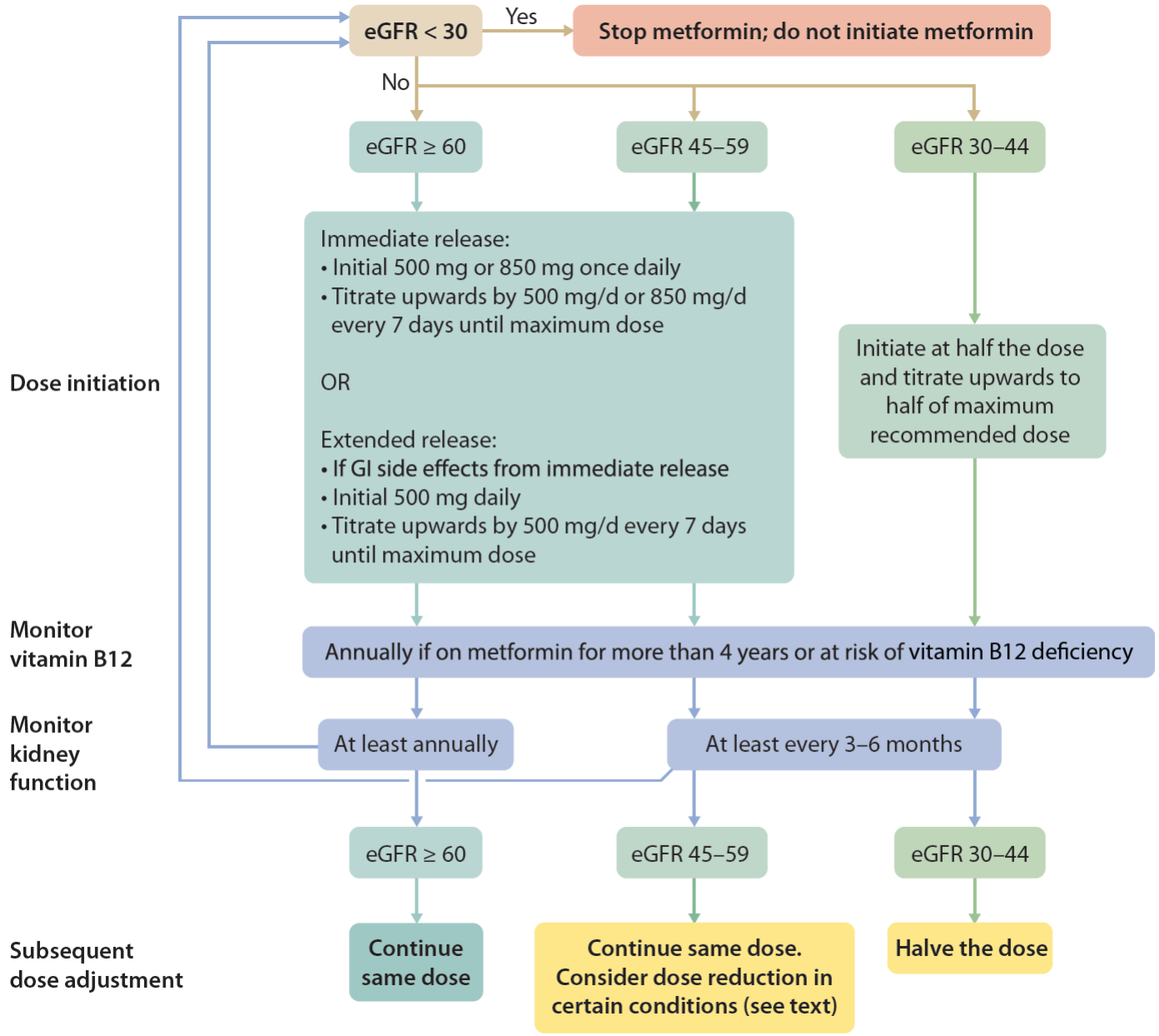
# Anti-hyperglycemic Therapies in Patients with Diabetes and CKD

**Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 $m^2$ with metformin *(1B)*.**

Practice Point 4.1.1: Treat kidney transplant recipients with T2D and eGFR ≥30 ml/min per 1.73 $m^2$ 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 $m^2$ (Figure 22).

# FIGURE 22. SUGGESTED APPROACH IN DOSING METFORMIN BASED ON THE LEVEL OF KIDNEY FUNCTION

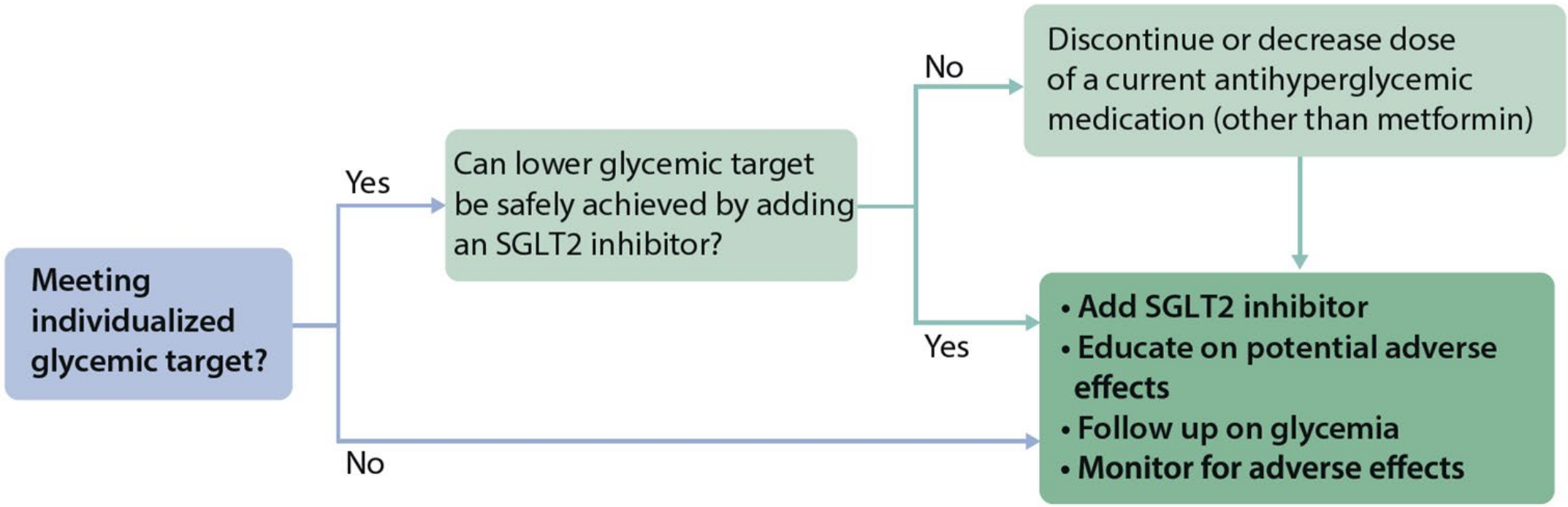


# Anti-hyperglycemic Therapies in Patients with Diabetes and CKD

**Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and eGFR ≥30 ml/min per 1.73 $m^2$ 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 $M^2$, WHO ARE ALREADY BEING TREATED WITH ANTIHYPERGLYCEMIC MEDICATIONS



# CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

## Study design and participants

**4401 patients with T2DM & UACR >300 mg/g**

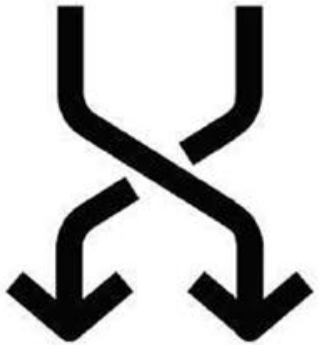
**62 years**

**eGFR 57**

**UACR 927 mg/g**

## Intervention

**Stable on maximum dose tolerated ACEi or ARB for 4 weeks**

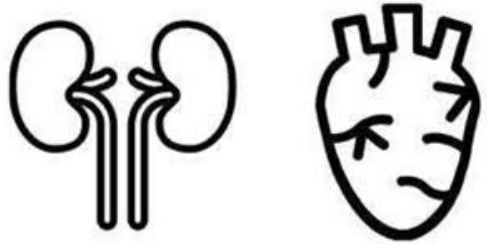


**Canagliflozin** **Placebo**

## 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**

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

Toyama & Neuen et al.

Diabetes, Obesity and Metabolism doi: 10.1111/dom.13648

@brendonneuen

27 included studies

Up to 7,363 participants

eGFR <60mL/min/1.73m$^2$

Overall effect estimate

*P*-heterogeneity for differences between individual agents

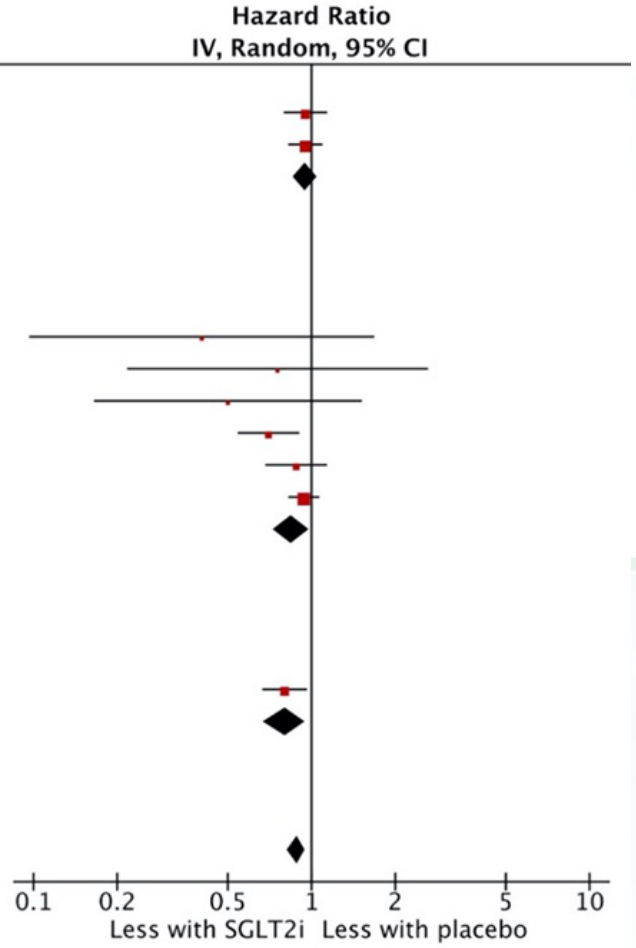
| CV death, nonfatal MI, nonfatal stroke | Hospitalization for heart failure | eGFR slope | Renal composite outcome |
|---|---|---|---|
| **RR 0.81 (95% CI 0.70-0.94)** | **RR 0.61 (95% CI 0.48-0.78)** | **1.35mL/min/1.73m$^2$/year (95% CI 0.78-1.93)** | **RR 0.71 (95% CI 0.53-0.95)** |
| 0.41 | 0.68 | 0.11 | 0.93 |

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

The George Institute for Global Health

# SGLT2 INHIBITORS AND 3-POINT MAJOR CARDIOVASCULAR EVENTS

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



# SGLT2 INHIBITORS AND KIDNEY OUTCOMES

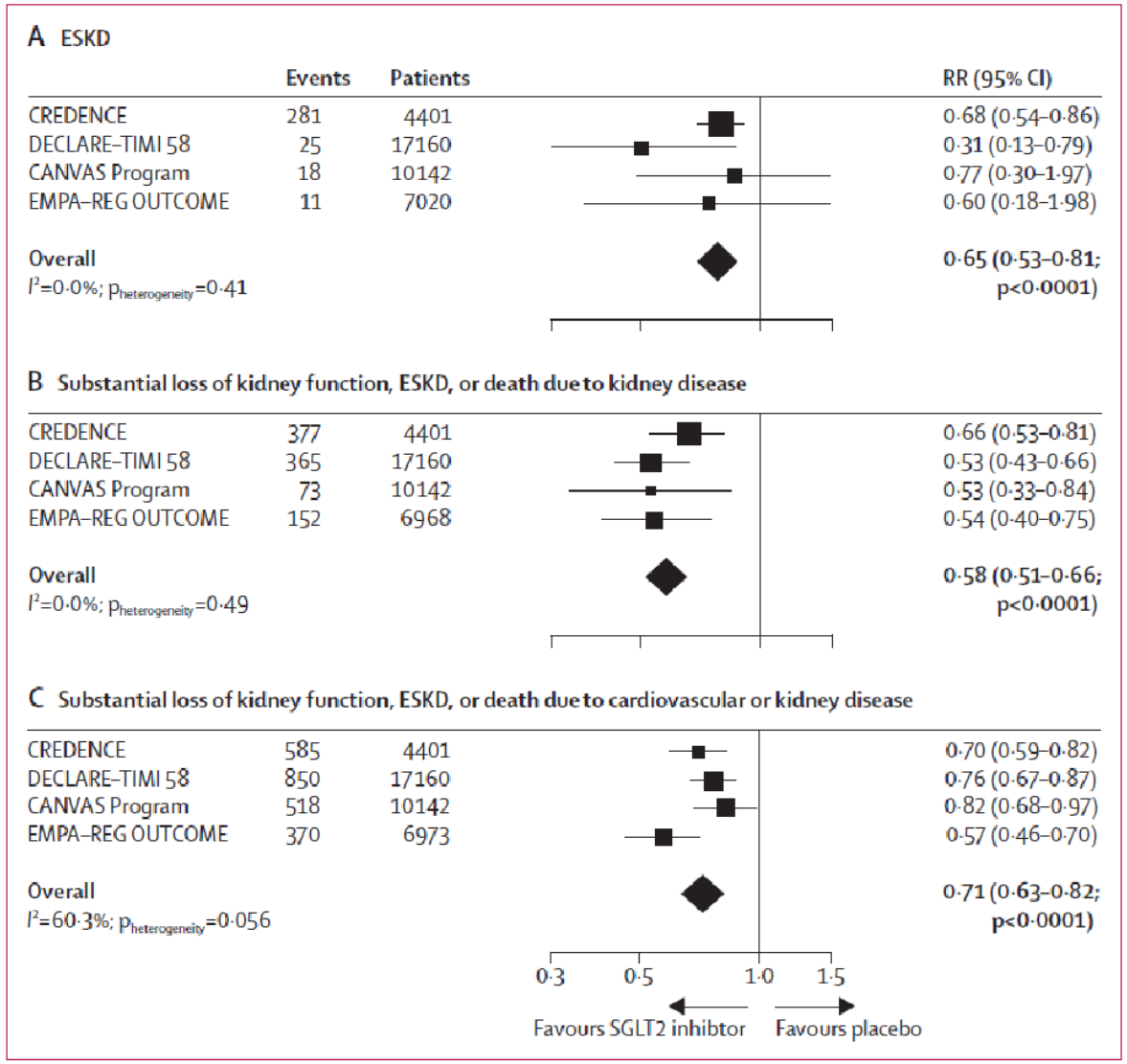
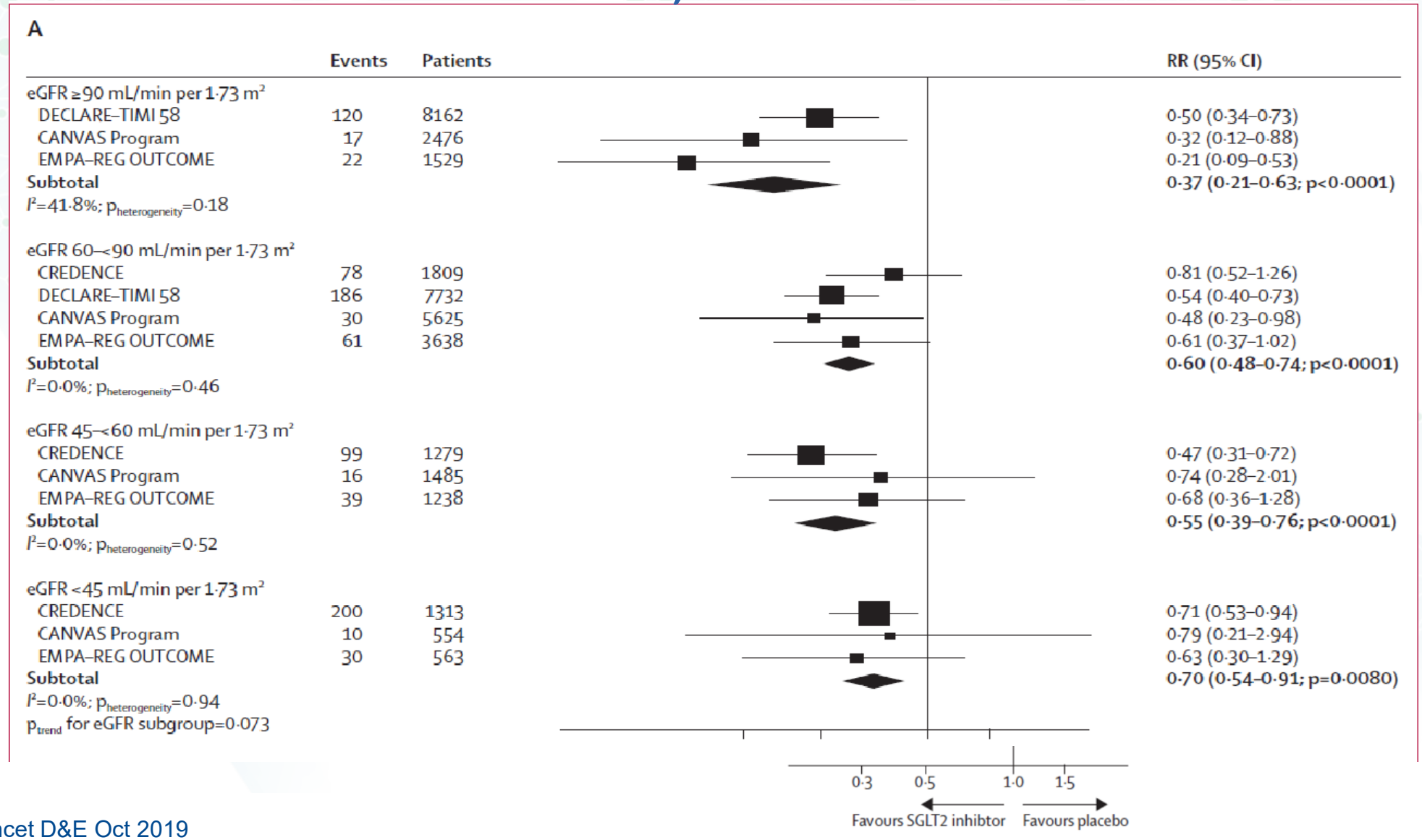



*Figure 2:* Effect of SGLT2 inhibitors on ESKD (A), substantial loss of kidney function, ESKD, or death due to kidney disease (B), and substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease (C)

B Neuen et al The Lancet D&E Oct 2019

# EFFECT OF SGLT2I ON SUBSTANTIAL LOSS OF KIDNEY FUNCTION, ESKD, OR DEATH DUE TO KIDNEY DISEASE, STRATIFIED BY BASELINE EGFR

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# Anti-hyperglycemic Therapies in Patients with Diabetes and CKD

Practice Point 4.2.2: For patients in whom additional glucose-lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.

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

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

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

# Anti-hyperglycemic Therapies in Patients with Diabetes and CKD

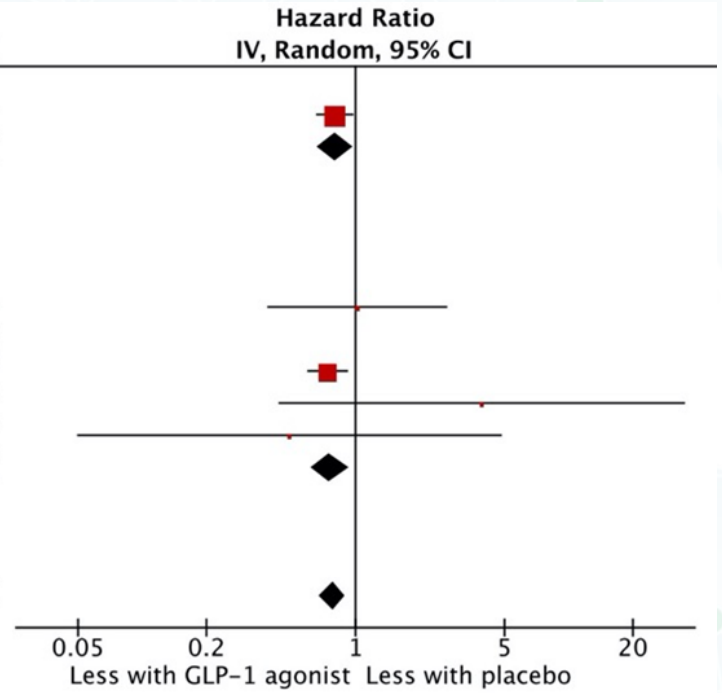
Practice Point 4.2.6: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 4.2.7: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if eGFR falls below 30 ml/min per 1.73 $m^2$, 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)

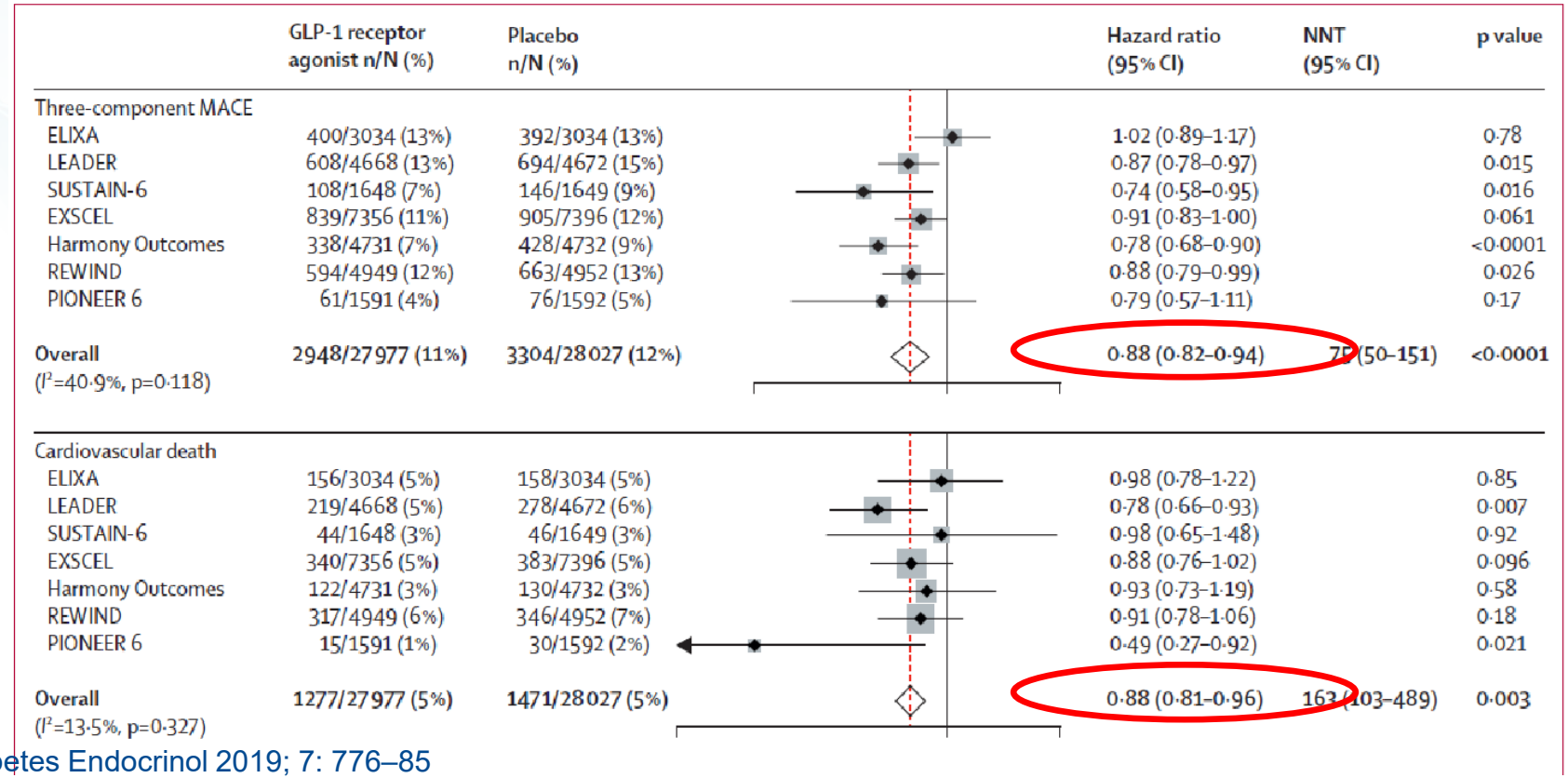
# ALL-CAUSE MORTALITY WITH GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH T2D

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



# 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, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.**



| | GLP-1 receptor agonist n/N (%) | Placebo n/N (%) | Hazard ratio (95% CI) | NNT (95% CI) | p value |
|---|---|---|---|---|---|
| Three-component MACE | | | | | |
| ELIXA | 400/3034 (13%) | 392/3034 (13%) | 1·02 (0·89–1·17) | | 0·78 |
| LEADER | 608/4668 (13%) | 694/4672 (15%) | 0·87 (0·78–0·97) | | 0·015 |
| SUSTAIN-6 | 108/1648 (7%) | 146/1649 (9%) | 0·74 (0·58–0·95) | | 0·016 |
| EXSCEL | 839/7356 (11%) | 905/7396 (12%) | 0·91 (0·83–1·00) | | 0·061 |
| Harmony Outcomes | 338/4731 (7%) | 428/4732 (9%) | 0·78 (0·68–0·90) | | <0·0001 |
| REWIND | 594/4949 (12%) | 663/4952 (13%) | 0·88 (0·79–0·99) | | 0·026 |
| PIONEER 6 | 61/1591 (4%) | 76/1592 (5%) | 0·79 (0·57–1·11) | | 0·17 |
| **Overall** ($I^2$=40·9%, p=0·118) | **2948/27977 (11%)** | **3304/28027 (12%)** | 0·88 (0·82–0·94) | 75 (50–151) | <0·0001 |
| Cardiovascular death | | | | | |
| ELIXA | 156/3034 (5%) | 158/3034 (5%) | 0·98 (0·78–1·22) | | 0·85 |
| LEADER | 219/4668 (5%) | 278/4672 (6%) | 0·78 (0·66–0·93) | | 0·007 |
| SUSTAIN-6 | 44/1648 (3%) | 46/1649 (3%) | 0·98 (0·65–1·48) | | 0·92 |
| EXSCEL | 340/7356 (5%) | 383/7396 (5%) | 0·88 (0·76–1·02) | | 0·096 |
| Harmony Outcomes | 122/4731 (3%) | 130/4732 (3%) | 0·93 (0·73–1·19) | | 0·58 |
| REWIND | 317/4949 (6%) | 346/4952 (7%) | 0·91 (0·78–1·06) | | 0·18 |
| PIONEER 6 | 15/1591 (1%) | 30/1592 (2%) | 0·49 (0·27–0·92) | | 0·021 |
| **Overall** ($I^2$=13·5%, p=0·327) | **1277/27977 (5%)** | **1471/28027 (5%)** | 0·88 (0·81–0·96) | 163 (103–489) | 0·003 |

SL Kristensen et al Lancet Diabetes Endocrinol 2019; 7: 776–85

# 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.

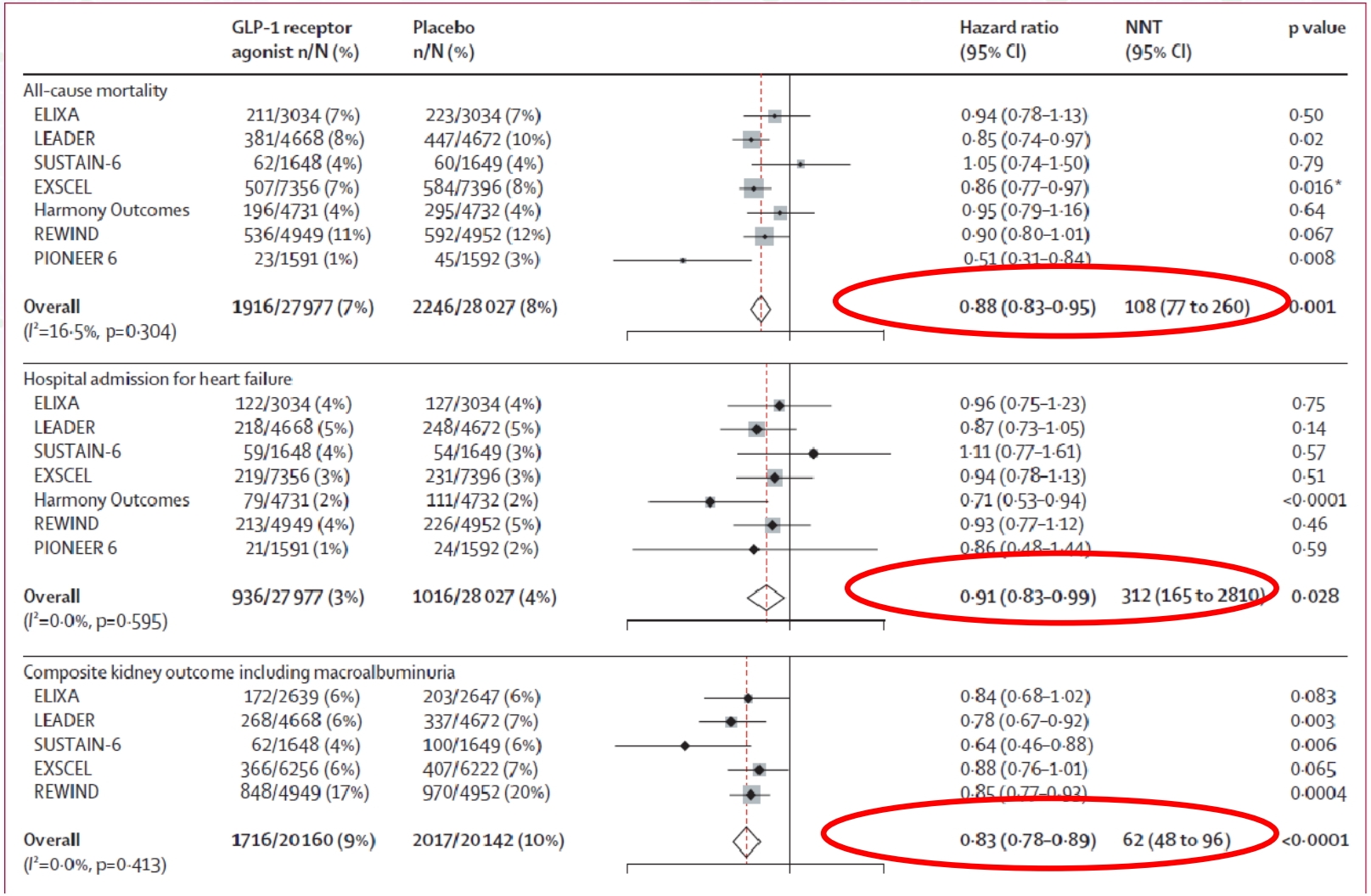
Practice Point 4.3.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA are used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

# FIGURE 27. DOSING FOR AVAILABLE GLP-1 RA AGENTS AND DOSE MODIFICATION FOR CKD

| GLP-1 RA | Dose | CKD adjustment |
|---|---|---|
| **Dulaglutide** | 0.75 mg and 1.5 mg once weekly | No dosage adjustment<br>Use with eGFR >15 ml/min per 1.73 $m^2$ |
| **Exenatide** | 10 µg twice daily | Use with CrCl >30 ml/min |
| **Exenatide extended-release** | 2 mg once weekly | Use with CrCl >30 ml/min |
| **Liraglutide** | 0.6 mg, 1.2 mg, and 1.8 mg once daily | No dosage adjustment<br>Limited data for severe CKD |
| **Lixisenatide** | 10 µg and 20 µg once daily | No dosage adjustment<br>Limited data for severe CKD |
| **Semaglutide (injection)** | 0.5 mg and 1 mg once weekly | No dosage adjustment<br>Limited data for severe CKD |
| **Semaglutide (oral)** | 3 mg, 7 mg, or 14 mg daily | No dosage adjustment<br>Limited data for severe CKD |

# Cardiovascular mortality and kidney outcomes with GLP-1 receptor agonists in patients with T2D: A systematic review and meta-analysis of CVOTs

## Mortality, hospitalization for heart failure and composite kidney outcomes



| | GLP-1 receptor agonist n/N (%) | Placebo n/N (%) | Hazard ratio (95% CI) | NNT (95% CI) | p value |
|---|---|---|---|---|---|
| **All-cause mortality** | | | | | |
| ELIXA | 211/3034 (7%) | 223/3034 (7%) | 0·94 (0·78–1·13) | | 0·50 |
| LEADER | 381/4668 (8%) | 447/4672 (10%) | 0·85 (0·74–0·97) | | 0·02 |
| SUSTAIN-6 | 62/1648 (4%) | 60/1649 (4%) | 1·05 (0·74–1·50) | | 0·79 |
| EXSCEL | 507/7356 (7%) | 584/7396 (8%) | 0·86 (0·77–0·97) | | 0·016* |
| Harmony Outcomes | 196/4731 (4%) | 295/4732 (4%) | 0·95 (0·79–1·16) | | 0·64 |
| REWIND | 536/4949 (11%) | 592/4952 (12%) | 0·90 (0·80–1·01) | | 0·067 |
| PIONEER 6 | 23/1591 (1%) | 45/1592 (3%) | 0·51 (0·31–0·84) | | 0·008 |
| **Overall** ($I^2$=16·5%, p=0·304) | **1916/27977 (7%)** | **2246/28027 (8%)** | **0·88 (0·83–0·95)** | **108 (77 to 260)** | **0·001** |
| **Hospital admission for heart failure** | | | | | |
| ELIXA | 122/3034 (4%) | 127/3034 (4%) | 0·96 (0·75–1·23) | | 0·75 |
| LEADER | 218/4668 (5%) | 248/4672 (5%) | 0·87 (0·73–1·05) | | 0·14 |
| SUSTAIN-6 | 59/1648 (4%) | 54/1649 (3%) | 1·11 (0·77–1·61) | | 0·57 |
| EXSCEL | 219/7356 (3%) | 231/7396 (3%) | 0·94 (0·78–1·13) | | 0·51 |
| Harmony Outcomes | 79/4731 (2%) | 111/4732 (2%) | 0·71 (0·53–0·94) | | <0·0001 |
| REWIND | 213/4949 (4%) | 226/4952 (5%) | 0·93 (0·77–1·12) | | 0·46 |
| PIONEER 6 | 21/1591 (1%) | 24/1592 (2%) | 0·86 (0·48–1·44) | | 0·59 |
| **Overall** ($I^2$=0·0%, p=0·595) | **936/27977 (3%)** | **1016/28027 (4%)** | **0·91 (0·83–0·99)** | **312 (165 to 2810)** | **0·028** |
| **Composite kidney outcome including macroalbuminuria** | | | | | |
| ELIXA | 172/2639 (6%) | 203/2647 (6%) | 0·84 (0·68–1·02) | | 0·083 |
| LEADER | 268/4668 (6%) | 337/4672 (7%) | 0·78 (0·67–0·92) | | 0·003 |
| SUSTAIN-6 | 62/1648 (4%) | 100/1649 (6%) | 0·64 (0·46–0·88) | | 0·006 |
| EXSCEL | 366/6256 (6%) | 407/6222 (7%) | 0·88 (0·76–1·01) | | 0·065 |
| REWIND | 848/4949 (17%) | 970/4952 (20%) | 0·85 (0·77–0·93) | | 0·0004 |
| **Overall** ($I^2$=0·0%, p=0·413) | **1716/20160 (9%)** | **2017/20142 (10%)** | **0·83 (0·78–0·89)** | **62 (48 to 96)** | **<0·0001** |

SL Kristensen et al Lancet Diabetes Endocrinol 2019; 7: 776–85

# Does Finerenone Help Reduce Kidney Failure and Progression in Diabetic Kidney Disease ?

American Journal of Nephrology

**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**

**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**

## 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**

**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.

Bakris G, Agarwal R, Anker S, Pitt B, Ruliope L, Nowack C, Kolkhof P, Ferreira A, Schloemer P, Filippatos G: Design and Baseline Characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial .
Am J Nephrol DOI: 10.1159/000503916

Visual Abstract by Edgar Lerma @edgarvlermamd

# 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 |

# 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.