Anti-Glycemic Agents in 2019: Beyond Glucose Control

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The Diabetic Epidemic
Diabetic Kidney Disease: Asia leads the way…

Percent of patients

- Malaysia: 67%
- Singapore: 66%
- Jalisco (Mexico): 65%
- Rep. of Korea: 50%
- Israel: 50%
- Hong Kong: 49%
- New Zealand: 48%
- Chile: 48%
- Indonesia: 48%
- United States: 47%
- Taiwan: 46%
- Kuwait: 45%
- Qatar: 44%
- Japan: 43%
- Jordan: 42%
- Thailand: 41%
- Hungary: 40%
- Uruguay: 40%
- Slovakia: 40%
- Brazil: 40%
by the FDA in 2013. Vildagliptin has been approved for use in Europe but is not available in the United States.

These compounds are associated with an A1C reduction of ~0.8%. They are weight neutral and do not tend to cause hypoglycemia. However, pancreatitis has been reported in patients treated with DPP-4 inhibitors.

**Amylin Agonists**

Amylin, the endogenous neuroendocrine hormone, was discovered in 1987. Amylin is co-secreted with insulin by the β-cells in equimolar amounts. Patients with type 2 diabetes have reduced amounts of amylin, whereas patients with type 1 diabetes have essentially no amylin.

The only amylin analog currently on the market is pramlintide, which was approved by the FDA in 2005. Its physiological effect includes weight loss, delayed gastric emptying, and a reduction in both postprandial glucose and glucagon. The primary side effect is nausea.

Pramlintide has a modest effect on A1C reduction of ~0.5%. This compound is usually reserved for use in patients with type 1 diabetes treated with intensive insulin therapy. It reduces postprandial glucose excursions via the mechanisms mentioned above.

**Bromocriptine**

Bromocriptine is a dopamine agonist that was approved for use in the United States as an antihyperglycemic medication in 2009. Its mechanism is not certain but may be related to its dopaminergic activity in the brain and the subsequent inhibition of sympathetic tone. Its impact on glycemia is modest, with A1C reductions of up to 0.7%.

**Colesevelam**

Colesevelam is an interesting compound that has a dual effect of lowering LDL cholesterol and reducing blood glucose levels. This drug was specifically developed for its ability to bind bile acids, effectively removing them from circulation and resulting in reductions in LDL cholesterol. The mechanism of action of the glucose lowering observed with this compound is not known. The drug was approved by the FDA for use in patients with type 2 diabetes in 2008.

Colesevelam is typically associated with an A1C reduction of ~0.5% and LDL cholesterol reduction of 13%. Its side effects are similar to those encountered with AGIs and are primarily gastrointestinal. Also, it should be noted that colesevelam may cause a slight increase in triglycerides.

**Sodium Glucose Co-Transporter 2 Inhibitors**

The sodium glucose co-transporter 2 (SGLT-2) inhibitors are a novel group of compounds that antagonize a high-capacity, low-affinity glucose transporter found primarily in the kidney. This transporter is responsible for ~90% of glucose reabsorption in the kidney. When this transporter is antagonized, excess glucose in the renal tubules is not reabsorbed, and glucose is excreted in the urine. This results in a net loss of glucose and a reduction in hyperglycemia.

A recent meta-analysis of placebo-controlled studies evaluating SGLT-2 inhibitors reported A1C reductions of 0.5–0.6% in patients treated with these agents. In addition to reducing hyperglycemia, SGLT-2 inhibitors have also been associated with slight reductions in weight and BMI.

The primary side effect of SGLT-2 inhibition is an increase in urinary or genital infections. These infections are much more common than in placebo-treated patients (about four times as many) but are usually mild.

Canagliflozin was the first SGLT-2 inhibitor to be approved by the FDA, in March 2013. Dapagliflozin was approved in the United States in early 2014. Empagliflozin and other SGLT-2 inhibitors are under development.

**Conclusion**

There are now 11 different categories of medications directed at the management of hyperglycemia in patients with diabetes. These compounds have been developed during the past 90 years (Figure 1), and among these categories, myriad subtypes exist.
Diabetic Medications: More to come...

Bailey CJ et al.
Diabetic Treatment: The Era of Personalized Medicine

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY). IF HbA₁c ABOVE TARGET PROCEED AS BELOW

ESTABLISHED ASCVD OR CKD

IF HbA₁c above target

- GLP-1 RA with proven CV benefit
- If further intensification is required or patient is now unable to tolerate GLP-1 RA or SGLT2i, choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1 RA or SGLT2i) with proven CV benefit
  - DPP-4i if not on GLP-1 RA
  - Basal insulin
  - TZD
  - SU

Without ESTABLISHED ASCVD OR CKD

IF HbA₁c above target

- Avoid TZD in the setting of HF
  - Consider adding the other class with proven CV benefit
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin
  - SU

- SGLT2i OR TZD

HF OR CKD PREDOMINATES

- PREFERABLY SGLT2i with evidence of reducing HF and/or CV progression in CVOTs if eGFR adequate
- OR If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CV benefit
- If HbA₁c above target

- GLP-1 RA
- SGLT2i
- TZD

COMPPELLING NEED TO MINIMISE HYPOGLYCAEMIA

- If HbA₁c above target

- GLP-1 RA
- SGLT2i
- TZD

- OR DPP-4i

- OR GLP-1 RA

COMPPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

- If HbA₁c above target

- GLP-1 RA with good efficacy for weight loss
- SGLT2i
- TZD

COST IS A MAJOR ISSUE

- If HbA₁c above target

- GLP-1 RA with good efficacy for weight loss
- SGLT2i
- TZD

- SU
- TZD

- SU

Consider the addition of SU or basal insulin:
- Choose latter generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia

If HbA₁c above target

- Continue with addition of other agents as outlined above

Metformin
The Reliable Agent of Old
Metformin: First Indication of Benefits beyond Glucose Control

UKPDS-34 Study:
Amongst patients allocated to intensive blood-glucose control, Metformin compared to Chlorpropamide, glibenclamide or insulin:
- Greater effect for any diabetes-related endpoint (p=0.0034)
- All-cause mortality (p=0.021)
- Stroke (p=0.032)
### Metformin: Purported Benefits

- Effective HbA1c reduction
- Lower risk for severe hypoglycemia
- Beneficial effect on body weight reduction
- Reduce risk of cardiovascular events and death
- Safe and inexpensive
- Widely available even in low resource settings

### Table 1. Effects of Metformin Compared With Sulfonylurea Monotherapy on Long-Term All-Cause Mortality and Cardiovascular Mortality and Morbidity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Range in RR From RCTs</th>
<th>Range in RD From RCTs</th>
<th>Adjusted HR From Observational Studies</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.5 to 1.0 (2 studies [15, 16])</td>
<td>-5.0% to -0.1% (2 studies [15, 16])</td>
<td>0.5 to 0.8 (7 studies* [17-23])</td>
<td>Low</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>0.6 to 0.7 (2 studies [15, 16])</td>
<td>-2.9% to -0.1% (2 studies [15, 16])</td>
<td>0.6 to 0.9 (3 studies [19, 21, 24])</td>
<td>Moderate</td>
</tr>
<tr>
<td>CVD morbidity</td>
<td>0.7 to 1.6 (2 studies [15, 16])</td>
<td>-0.4% to 10.1% (2 studies [15, 16])</td>
<td>0.3 to 0.9 (5 studies† [19, 20, 22, 25, 26])</td>
<td>Low</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; HR = hazard ratio; RCT = randomized, controlled trial; RD = risk difference; RR = relative risk.

* One additional retrospective cohort study reported an odds ratio of 0.9 (27).
† One additional case-control study reported an odds ratio of 0.8 (28).
Consensus recommendation

Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes.
KDIGO

The New Wonder Kid on the Block

SGLT2 Inhibitors
in comparison with the sulfonylurea, there was a substantial mean 4.5-kg reduction in body weight and a 90% lower risk of hypoglycemia with the SGLT2 inhibitor.16 Similar results were observed for canagliflozin, 17 whereas a longer 208-week study of dapagliflozin confirmed this metabolic benefit (HbA1c lowering was 0.3% lower than the active comparator glipizide), with substantial benefits in terms of blood pressure (BP)–lowering and eGFR preservation.18 Placebo-controlled studies of SGLT2 inhibition in patients on complex insulin regimens similarly revealed further HbA1c reduction, lower insulin dose requirement, and greater weight loss, each observed without additional hypoglycemia.19–21 This extensive clinical trial record emphasizes the series of metabolic benefits observed when an SGLT2 inhibitor is used particularly in place of an insulin-providing agent such as a sulfonylurea, or when used to attenuate total daily insulin doses.

**SUMMARY OF ADVERSE EFFECTS OF SGLT2 INHIBITION**

There is a series of well-recognized and suspected adverse events associated with augmenting the presence of glucose and sodium in urine. Although a mild-to-modest increase in the incidence of urinary tract infections has been observed in some studies,10 but not other large-scale studies,22 the strong causal relationship with mycotic genital infections, usually with *Candida* species, is indisputably the most common adverse event associated with SGLT2 inhibition.10 The magnitude of the absolute risk increment ranges between ≈3% in the placebo versus ≈9% to 18% with the active comparators in women,20 and about half those rates have been reported in men.22

The risk of volume depletion arising from the osmotic diuresis of glucose, and from natriuresis, represents an infrequent but clear causal adverse event from SGLT2 inhibition, more common in older adults, among those who use higher doses of the SGLT2 inhibitors, use loop diuretics, and have kidney dysfunction.20,23 However, such an increase was not observed in EMPA-REG OUTCOME, which was a large-scale controlled clinical trial involving patients with established cardiovascular disease, as discussed below.22 Earlier concerns for a numerically higher case finding of bladder cancer, particularly in the dapagliflozin development program, and of breast cancer, have not been consistent, and the totality of evidence does not suggest a causal relationship.10,24 Rather, one potential speculation is that of a differential surveillance bias induced by SGLT2 inhibition. For example, any increase in urinary symptoms, such as urinary tract or genital infections, may increase the likelihood of investigations that identify bladder cancer, and a loss in weight may increase the likelihood of identifying breast lesions.

Although small mean changes in electrolytes have been described in a controlled trial of canagliflozin,25 such changes have not been observed in a large-scale study in which plasma levels of sodium, potassium, calcium, magnesium, and phosphate did not differ in >2300 participants exposed to each of placebo and low- and high-dose empagliflozin.22 However, hyperkalemia may be seen among those who develop kidney dysfunction and who are concomitantly exposed to antihypertensive medications that may elevate potassium levels, independent of SGLT2 inhibitor use.26 Early reports of minor elevations in serum phosphate26 raised concerns of an exaggerated phosphate resorption induced by distal sodium delivery, which could explain an increase in parathyroid hormone and its consequent effect on bone turnover, density, and fracture risk. However, observations, made primarily in the canagliflozin trial program, have been inconsistent and inconclusive regarding a risk of bone loss, and the small loss in bone mineral density that was observed with empagliflozin in EMPA-REG OUTCOME was associated with a lower rate of clinical fractures.27

**Figure 1.** The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule. Modified from Bakris et al4 with permission of the publisher. Copyright © 2009, Elsevier.
The effect of combining the SGLT2 inhibitor canagliflozin with a thiazide, nor does the combination produce a greater natriuretic effect in comparison with either drug alone. Similar to this report using canagliflozin, the addition of a thiazide diuretic to dapagliflozin does not yield additional antihypertensive effect, whereas β-blocker and calcium channel blocker combinations with dapagliflozin did accentuate the degree of BP lowering. Similarly, the addition of dapagliflozin to a background of a renin-angiotensin-aldosterone system (RAAS) inhibitor in patients with T2D lowers systolic BP by an additional 3 to 4 mm Hg, an effect that has been supported by results from animal studies. Whether this apparent synergy is on the basis of plasma volume contraction leading to RAAS activation, which is then inhibited pharmacologically by angiotensin-converting enzyme (ACE) inhibition or an angiotensin receptor blocker, resulting in enhanced BP lowering is not known. Alternatively, angiotensin II increases SGLT2 mRNA expression and proximal tubular sodium uptake, perhaps promoting volume expansion and worsening hypertension. It is therefore conceivable that the greater BP-lowering effect observed with the combination of an SGLT2 inhibitor with a RAAS-blocking agent versus either agent alone could represent suppressed proximal tubular sodium reabsorption and volume contraction.

**Mechanisms for SGLT2i Protective Effects**

- Glycosuria
- Natriuresis
- Blood pressure
- Tubuloglomerular feedback
- Plasma volume
- Myocardial stretch
- Ventricular arrhythmias
- Activation of ACE2 – Ang1/7
- No sympathetic nervous system activation

**Figure 2. Physiologic mechanisms implicated in the cardiovascular and renal protection with SGLT2 inhibition.**

- HbA1c indicates hemoglobin A1c; and SGLT2, sodium-glucose cotransporter-2.
SGLT2 Inhibitors: RCTs beyond Glucose Control

**Empagliflozin**

**EMPA-REG OUTCOME Trial**
(n=7,020)


**Primary Outcome:**
1. Composite of Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke (EMPA-REG OUTCOME and CANVAS Trials)
2. MACE and a composite of cardiovascular death or hospitalization for heart failure. (DECLARE-TIMI Trial)

**Canagliflozin**

**CANVAS Trial**
(n=10,142)


**Dapagliflozin**

**DECLARE-TIMI Trial**
(n=10,186)


**CREDENCE Trial - Canagliflozin**

**Primary Outcome:**
1. Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR < 15 ml/min/1.73m²), doubling of serum creatinine, or death from renal or cardiovascular causes.
Efficacy of SGLT2 Inhibitors: CANVAS Study

**Glycated Hemoglobin**
- **Placebo**
- **Canagliflozin**

**Body Weight**
- **Placebo**
- **Canagliflozin**

**Systolic Blood Pressure**
- **Placebo**
- **Canagliflozin**

**Diastolic Blood Pressure**
- **Placebo**
- **Canagliflozin**

Cardiovascular Protection with SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS Program</th>
<th>DECLARE-TIMI 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses analysed</td>
<td>10 mg, 25 mg (once daily)</td>
<td>100 mg, 300 mg (once daily)</td>
<td>10 mg (once daily)</td>
</tr>
<tr>
<td>Median follow-up time, years</td>
<td>3.1</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Trial participants</td>
<td>7020</td>
<td>10 142</td>
<td>17 160</td>
</tr>
<tr>
<td>Age, mean</td>
<td>63.1</td>
<td>63.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Women</td>
<td>2004 (28.5%)</td>
<td>3633 (35.8%)</td>
<td>6422 (37.4%)</td>
</tr>
<tr>
<td>Patients with established atherosclerotic cardiovascular disease</td>
<td>7020 (100%)</td>
<td>6656 (65.6%)</td>
<td>6974 (40.6%)</td>
</tr>
<tr>
<td>Patients with a history of heart failure</td>
<td>706 (10.1%)</td>
<td>1461 (14.4%)</td>
<td>1724 (10.0%)</td>
</tr>
<tr>
<td>Patients with eGFR &lt;60 mL/min per 1.73 m²</td>
<td>1819 (25.9%)</td>
<td>2039 (20.1%)</td>
<td>1265 (7.4%)</td>
</tr>
</tbody>
</table>

Meta-analysis of SGLT2i trials on the composite of MI, Stroke and CV death (MACE)

**Cardiovascular Protection with SGLT2 Inhibitors**

**Meta-analysis of SGLT2i trials on hospitalization for heart failure and CV death, stratified by atherosclerotic cardiovascular diseases and history of heart failure.**

ADA Consensus Recommendations

Consensus recommendation
Among patients with type 2 diabetes who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycaemic management (Figs 2 and 3).

Consensus recommendation
Among patients with ASCVD in whom HF coexists or is of special concern, SGLT2 inhibitors are recommended (Figs 2 and 3).

SGLT2i Trials: The Surprisingly Impressive Suggestion of Renoprotection

The Next Best Thing After RAAS Blockade for Diabetic Kidney Disease

**CREDENCE Trial - Canagliflozin**

**Primary Outcome:**
1. Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR < 15 ml/min/1.73m²), doubling of serum creatinine, or death from renal or cardiovascular causes.

- CREDENCE began before any CV outcomes trials had reported

- Renal effects were not the primary focus of the CV outcomes trials


CREDENCE enrollment  EMPA-REG OUTCOME  CANVAS Program  DECLARE

KDIGO
CREDENCE: SGLT2i and Renoprotection

STUDY DESIGN

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m²
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K⁺ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

2-week placebo run-in

Double-blind randomization (1:1)

Follow-up at Weeks 3, 13, and 26 (F2F)
then every 13 weeks (alternating phone/F2F)

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

12,900 screened
8499 excluded
4401 randomized

2199 placebo
25 (1.1%) did not complete
11 (0.5%) withdrew consent
2197 (99.9%) vital status known
2174 (98.9%) completed study

2202 canagliflozin
15 (0.7%) did not complete
5 (0.2%) withdrew consent
2198 (99.8%) vital status known
2187 (99.3%) completed study

CREDENDE: SGLT2i and Renoprotection

**HbA1c**
- Baseline (%): Canagliflozin 8.3, Placebo 8.3
- Mean difference over study: –0.25% (95% CI: –0.31, –0.20)

**Blood Pressure**
- Baseline (mmHg): Canagliflozin 139.8, Placebo 140.2
- Mean difference over study: –3.30 mmHg (95% CI: –3.87, –2.73)

**Body Weight**
- Baseline (kg): Canagliflozin 87.3, Placebo 86.9
- Mean difference over study: –0.80 kg (95% CI: –0.92, –0.69)

**Albuminuria**
- Median baseline (mg/g): Canagliflozin 914, Placebo 918
- Mean % difference over study: –32% (95% CI: –36, –28)

Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death

Hazard ratio, 0.70 (95% CI, 0.59–0.82)  
$P = 0.00001$

**CREDENCE: SGLT2i and Renoprotection**

*ESKD, Doubling of Serum Creatinine, or Renal Death*

- Hazard ratio, 0.66 (95% CI, 0.53–0.81)
- $P < 0.001$

**Participants with an event (%)**

- **Placebo**
- **Canagliflozin**

**Months since randomization**

- 224 participants (Placebo)
- 153 participants (Canagliflozin)

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CREDENCE: SGLT2i and Renoprotection

**Effects on eGFR**

**Baseline**
- Canagliflozin: 56.4
- Placebo: 56.0

**Acute eGFR slope (3 weeks)**
- Difference: -3.17 (95% CI, -3.87, -2.47)

**Chronic eGFR slope**
- Difference: 2.74/year (95% CI, 2.37–3.11)

**LS mean change (±SE) in eGFR (mL/min/1.73 m²)**

**No. of Participants**
- Placebo: 2178, 2084, 1985, 1882, 1720, 1536, 1006, 583, 210
- Canagliflozin: 2179, 2074, 2005, 1919, 1782, 1648, 1116, 652, 241

CREDENCE: Where does it all fit in?

Sustained RRT Events

<table>
<thead>
<tr>
<th>Program</th>
<th>DECLARE</th>
<th>CANVAS Program</th>
<th>EMPA-REG OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained RRT Events</td>
<td>Not reported</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>

Mean eGFR (mL/min/1.73 m²) | Median UACR (mg/g)
---|---
DECLARE               | 85 | 13 |
CANVAS Program        | 76 | 12 |
EMPA-REG OUTCOME      | 74 | 18 |
**CREDENCE: Putting it in Perspective**

### Hazard ratio (95% CI) for Interaction P value

<table>
<thead>
<tr>
<th>Screening eGFR</th>
<th>Hazard ratio</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to &lt;45 mL/min/1.73 m²</td>
<td>0.75 (0.59–0.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>45 to &lt;60 mL/min/1.73 m²</td>
<td>0.52 (0.38–0.72)</td>
<td></td>
</tr>
<tr>
<td>60 to &lt;90 mL/min/1.73 m²</td>
<td>0.82 (0.60–1.12)</td>
<td></td>
</tr>
</tbody>
</table>

**NNT in patients with eGFR 30 to <45 mL/min/1.73 m²**

16
Should SGLT2 Inhibitors be initiated in all patients with Type 2 diabetes mellitus and albuminuria, with eGFR > 30 ml/min/1.73m²?
KDIGO

The Middle Child

GLP-1 Receptor Agonists
Actions of GLP-1

Insulinotropic

Glucagonostatic

GLP-1RA and Renal Hemodynamics

LEADER Trial: Liraglutide vs Placebo

Randomized 9,340 patients with high cardiovascular risks
Median Follow-up of 3.84 years

Primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

LEADER Trial: Liraglutide vs Placebo

Pre-specified secondary renal outcomes which was a composite of new-onset persistent albuminuria, doubling of serum creatinine, ESRD or death to renal causes

LEADER Trial: Liraglutide

Estimated GFR

Mean Estimated GFR (ml/min/1.73 m²)

Estimated trial-group ratio at 36 mo, 1.02 (95% CI, 1.00–1.03) P=0.01

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Months since Randomization</th>
<th>Placebo</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>4672</td>
<td>4668</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4356</td>
<td>4349</td>
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<td>12</td>
<td>4237</td>
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<td>3911</td>
<td>4031</td>
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<tr>
<td>48</td>
<td></td>
<td>755</td>
<td>812</td>
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</table>

LEADER Trial: Liraglutide

### Table

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>9340</td>
<td>0.78 (0.67–0.92)</td>
<td>—</td>
</tr>
<tr>
<td>Estimated GFR</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 ml/min/1.73 m²</td>
<td>2158</td>
<td>0.84 (0.67–1.05)</td>
<td>0.20</td>
</tr>
<tr>
<td>≥60 ml/min/1.73 m²</td>
<td>7182</td>
<td>0.68 (0.54–0.86)</td>
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</tr>
<tr>
<td>Microalbuminuria or macroalbuminuria</td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Yes</td>
<td>3422</td>
<td>0.81 (0.68–0.96)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5918</td>
<td>0.69 (0.46–1.04)</td>
<td></td>
</tr>
<tr>
<td>Combined estimated GFR and albuminuria status</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Estimated GFR &lt;60 ml/min/1.73 m² and microalbuminuria or macroalbuminuria</td>
<td>1130</td>
<td>0.81 (0.64–1.03)</td>
<td></td>
</tr>
<tr>
<td>Estimated GFR ≥60 ml/min/1.73 m² or no microalbuminuria or macroalbuminuria</td>
<td>8210</td>
<td>0.70 (0.56–0.87)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Composite Renal Outcome, According to Baseline Renal Risk.

The estimated glomerular filtration rate (GFR) was calculated with the use of the Modification of Diet in Renal Disease formula. Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with interaction between trial group and renal risk at baseline. The composite renal outcome consisted of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and an estimated GFR of 45 ml or less per minute per 1.73 m², the need for continuous renal-replacement therapy (end-stage renal disease), or death due to renal disease.
The Final of the CV Trio

DPP-4 Inhibitors
0.2–0.3% reduction in HbA1c obtained with saxagliptin compared with placebo throughout the trial (23). However, it must be made clear that preliminary data demonstrate that GLP-1RA have stronger efficacy in terms of correction of the major risk factors for CVD (including blood pressure and lipids) (135); indeed SAVOR, EXAMINE, and other smaller studies did not show any significant effect on both blood pressure and lipids. If these purported protective effects of DPP4-I translate into better outcomes in people with diabetes, they should be verified by the several ongoing clinical trials. Indeed, caution should be paid when trying to translate findings obtained in animal models and small clinical studies to the heterogeneous population of diabetic patients, as long as results from specifically designed randomized controlled trials are not available. In addition to the aforementioned aspects, the effect of DPP4-I on BM stem cells is also promising to achieve microvascular protection at distant sites. Ultimately, reducing the burden of microangiopathy may translate into better outcomes in people with diabetes.
Linagliptin and Diabetic Kidney Disease

**Diagram**

- **Pooled population**
  - \( n = 2,472 \)
  - 30 < baseline UACR ≤ 3,000 mg/g Cr and baseline eGFR ≥ 30 mL/min/1.73 m²
  - \( n = 564 \)

- **Excluded (n = 1,908)***
  - Baseline UACR ≤ 30 mg/g Cr (n = 1,756)
  - Baseline UACR > 3,000 mg/g Cr (n = 7)
  - Baseline eGFR < 30 mL/min/1.73 m² (n = 1)
  - Missing UACR value (n = 145)

- **Excluded (n = 347)**
  - No ACEI/ARB therapy at baseline (n = 249)†
  - Unstable ACEI/ARB therapy# (n = 98)

- **Pooled analysis set with stable ACEI/ARB therapy**
  - \( n = 217 \)

- **Linagliptin**
  - \( n = 162 \)

- **Placebo**
  - \( n = 55 \)

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Linagliptin and Diabetic Kidney Disease

Urine ACR at week 24 was reduced by 32% with Linagliptin compared with 6% with placebo, between-group difference of 28%.

Albuminuria lowering effect of Linagliptin was not influenced by race or HbA1c and systolic blood pressure values at baseline or after treatment.

KDIGO

Summary
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Wide range of anti-glycemic agents, where benefits have gone beyond just glucose control and HbA1c reduction.

Metformin remains the most widely recommended drug for initial monotherapy, for benefits on weight reduction and CV protection.

SGLT2 inhibitors are going to be game changers for the management of patients with Type 2 diabetes mellitus, with impressive results on cardio- and renal protective benefits.

Long-acting GLP-1 Receptor Agonist, Liraglutide, could be an alternative in patients who are not able to tolerate SGLT2 inhibitors.

DPP-4 inhibitors may be added in patients with diabetic kidney disease, who has poor glucose control after metformin and SGLT2 inhibitors/GLP-1 receptor agonist.