Endocrine Intelligence

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Clinical question

Best SGLT-2

Answer

There Is No Single "Best" SGLT-2 Inhibitor – Selection Is Context-Dependent

The current evidence base does not identify one SGLT-2 inhibitor as universally superior to the others. What it does establish is that **the class, combined with metformin, is the most clinically effective antidiabetic strategy** across multiple high-risk populations, and that three agents—**canagliflozin, dapagliflozin, and empagliflozin**—carry the strongest and most consistent outcome-trial evidence for cardiovascular and renal protection. The "best" choice for an individual patient depends on the dominant comorbidity, renal function, and local formulary.

Class-Level Recommendation

NICE NG28 (2026) states that network and pairwise meta-analyses show metformin plus an SGLT-2 inhibitor is more clinically effective at reducing HbA1c, weight, and cardiovascular events (cardiovascular mortality, myocardial infarction, non-fatal stroke, hospitalisation for heart failure) than any other metformin-plus-one-other-medicine combination or metformin alone. The committee recommends this combination as the **standard initial treatment** for adults with type 2 diabetes who have:

- Atherosclerotic cardiovascular disease (ASCVD)
- Heart failure
- Obesity

This is reinforced by the ADA/EASD 2022 consensus, which places greater emphasis on cardiorenal protection and weight management, with SGLT-2 inhibitor outcome-trial data informing broader treatment recommendations.

Agents With the Strongest Outcome-Trial Evidence

The KDIGO 2022 guideline identifies three SGLT-2 inhibitors with proven cardiovascular and kidney benefits, supported by large cardiovascular outcome trials:

Agent	Key CVOT	Additional renal-specific trial
Empagliflozin	EMPA-REG OUTCOME	EMPA-KIDNEY (results pending at time of guideline)
Canagliflozin	CANVAS	CREDENCE
Dapagliflozin	DECLARE-TIMI 58	DAPA-CKD

Ertugliflozin (VERTIS CV) demonstrated cardiovascular non-inferiority, including in CKD subgroups, but the evidence base for hard renal endpoints is less extensive than for the three agents above. KDIGO's practical provider guide lists **canagliflozin 100 mg, dapagliflozin 10 mg, and empagliflozin 10 mg** as the SGLT-2 inhibitors with proven benefits for patients with type 2 diabetes and CKD (eGFR ≥ 20 ml/min/1.73 m²).

NICE specifically notes that **canagliflozin and dapagliflozin** reduced the risk of end-stage renal failure in the evidence reviewed. For the eGFR 20–30 ml/min/1.73 m² band (where metformin is contraindicated), NICE recommends **dapagliflozin or empagliflozin** because these are the two SGLT-2 inhibitors licensed for use in that population.

How to Choose Among the Three

- **ASCVD-dominant phenotype:** All three (empagliflozin, canagliflozin, dapagliflozin) have CVOT-level evidence. NICE does not differentiate among them for ASCVD; the recommendation is to the class. Empagliflozin and dapagliflozin additionally have dedicated heart-failure trials (EMPEROR-Reduced/Preserved, DAPA-HF), which is relevant if there is any degree of reduced ejection fraction.

- **Heart failure (HFrEF or HFpEF):** Dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced, EMPEROR-Preserved) have dedicated heart-failure outcome trials enrolling patients with and without diabetes. Canagliflozin's heart-failure evidence is less direct. If heart failure is the dominant comorbidity, dapagliflozin or empagliflozin are the better-supported choices.

- **CKD / diabetic kidney disease:** All three have renal-outcome data. KDIGO gives a **strong recommendation** for an SGLT-2 inhibitor for kidney and cardiovascular protection in T2D with CKD, citing EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, and SCORED. The choice among the three is less about efficacy differences and more about which is licensed at the patient's eGFR and available on the local formulary. For eGFR 20–30, NICE limits the choice to dapagliflozin or empagliflozin.

- **Obesity / weight management:** NICE recommends metformin + SGLT-2 inhibitor as standard initial treatment for adults living with obesity, noting SGLT-2 inhibitors are cost-effective in this group. The class effect on weight (modest loss of 2–3 kg) is broadly similar across agents; no single agent is singled out as superior for weight.

- **eGFR < 30 ml/min/1.73 m²:** Metformin is contraindicated. NICE recommends dapagliflozin or empagliflozin (the two licensed agents in this band) to reduce end-stage renal and cardiovascular events. KDIGO's practical guide sets the eligibility threshold at eGFR ≥ 20 ml/min/1.73 m².

Practical Considerations

- **Dosing:** The standard starting doses in the outcome trials are canagliflozin 100 mg, dapagliflozin 10 mg, and empagliflozin 10 mg. KDIGO's provider guide uses these as the reference doses.
- **Safety monitoring:** KDIGO flags potential contraindications/cautions including genital mycotic infection risk, euglycaemic diabetic ketoacidosis, volume depletion, and foot ulcers. A sick-day protocol and perioperative care plan should be provided at initiation.
- **Health equity:** NICE notes that people in the most deprived areas experience the greatest absolute health benefit from SGLT-2 inhibitors and recommends ensuring universal access.

- **Combination with other agents:** SGLT-2 inhibitors are additive to metformin, GLP-1 receptor agonists, and RAAS inhibitors. They do not replace RAAS blockade in albuminuric CKD but complement it.

Bottom Line

For most adults with type 2 diabetes and a relevant comorbidity (ASCVD, heart failure, CKD, or obesity), **any of canagliflozin, dapagliflozin, or empagliflozin is an evidence-based first-line partner to metformin**. The selection narrows when:

1. **Heart failure** is present → favour dapagliflozin or empagliflozin (dedicated HF trials).
2. **eGFR is 20–30** → dapagliflozin or empagliflozin (licensing).
3. **Local formulary or cost** constrains the choice.

There is no head-to-head trial demonstrating that one of the three is superior to the others for the primary outcomes of interest. The class effect is the dominant signal, and the individual agent choice is driven by the specific comorbidity profile, renal function, and practical access rather than a proven efficacy hierarchy.

Evidence and citations

[1] Type 2 diabetes in adults: management
National Institute for Health and Care Excellence
https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493

Supporting passage supplied to the model

> Overall, network and pairwise meta-analyses comparing antidiabetic therapies showed that therapy combining metformin with an SGLT-2 inhibitor was more clinically effective at reducing HbA1c, weight and cardiovascular events than: • any other therapy combining metformin with 1 other medicine, and • metformin alone. Cardiovascular events covered included cardiovascular mortality, myocardial infarction, non-fatal stroke and hospitalisation for heart failure. Evidence showed that canagliflozin and dapagliflozin reduced the risk of end-stage renal failure. The committee agreed that therapy combining metformin with an SGLT-2 inhibitor is the most clinically effective option for people with atherosclerotic cardiovascular disease and recommended this as the standard initial treatment. Data on health inequalities showed that people living in the most deprived areas experience the greatest benefits for their health from SGLT-2 inhibitors. The committee believe this is an important reason for ensuring universal access to SGLT-2 inhibitors.

[2] Type 2 diabetes in adults: management
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> 131 Type 2 diabetes in adults: management (NG28) Why the committee made these recommendations Metformin and SGLT-2 inhibitors There is a significant body of evidence showing that type 2 diabetes management should aim at holistic health improvements (in particular, cardiovascular and renal protection), rather than just HbA1c targets. Overall, network and pairwise meta-analyses comparing antidiabetic therapies showed that therapy combining metformin with an SGLT-2 inhibitor was more clinically effective at reducing HbA1c, weight and cardiovascular events than: • any other therapy combining metformin with 1 other medicine, and • metformin alone. Cardiovascular events covered included cardiovascular mortality, myocardial infarction, non-fatal stroke and hospitalisation for heart failure. Evidence showed that canagliflozin and dapagliflozin also reduced the risk of end-stage renal failure. The committee agreed that therapy combining metformin with an SGLT-2 inhibitor is the most clinically effective option for people with heart failure and recommended this as the standard initial treatment. There was limited evidence for people with type 2 diabetes and heart failure.

[4] Type 2 diabetes in adults: management
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> For the wider population, therapy with metformin and an SGLT-2 inhibitor was more clinically effective at reducing HbA1c, weight and cardiovascular events than: • any other therapy combining metformin with 1 other medicine, and • metformin alone. Cardiovascular events covered included cardiovascular mortality, myocardial infarction, non-fatal stroke and hospitalisation for heart failure. Evidence showed that canagliflozin and dapagliflozin reduced the risk of end-stage renal failure. The committee agreed that therapy combining metformin with an SGLT-2 inhibitor is the most clinically effective option for people living with obesity and recommended this as the standard initial treatment. SGLT-2 inhibitors were cost effective for people living with obesity. Data on health inequalities also showed that people living in the most deprived areas experience the greatest benefits for their health from SGLT-2 inhibitors. The committee believe this is an important reason for ensuring universal access to SGLT-2 inhibitors. © NICE 2026. All rights reserved. Subject to Notice of rights (https://www. nice. org. uk/terms-and- Page 59 of conditions#notice-of-rights).

[5] Type 2 diabetes in adults: management
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[7] kdigo.org
kdigo.org
https://kdigo.org/wp-content/uploads/2022/10/KDIGO-2022-Clinical-Practice-Guideline-for-Diabetes-Management-in-CKD.pdf

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> 3. 1 for more details). Kidney International (2022) 102 (Suppl 5S), S1–S127 chapter 1 www. kidney-international. org Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD Assessment Intervention Eligible patients: • eGFR ≥20 ml/min/1. 73 m 2 Patient selection High priority features: • ACR ≥200 mg/g [≥20 mg/mmol] • Heart failure Potential contraindications: • Genital infection risk • Diabetic ketoacidosis • Foot ulcers • Immunosuppression SGLT2 inhibitor with proven benefits: • Canagliflozin 100 mg • Dapagliflozin 10 mg • Empagliflozin 10 mg Education: • Sick day protocol* • Perioperative care† • Foot care Glycemia Hypoglycemia risk? • Insulin or sulfonylurea • History of severe hypoglycemia • HbA1c at or below goal If high Volume Volume depletion risk?

[8] KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease
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> There is substantial evidence confirming that SGLT2i confer significant kidney and heart protective effects in these patients. This was demonstrated in: (i) Three large RCTs reporting on efficacy for primary cardiovascular outcomes and secondary kidney outcomes among patients with T2D: the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) trial, the CANagliflozin cardioVascular Assessment Study (CANVAS), and the Dapagliflozin Effect on S37 chapter 1 CardiovascuLAR Events [DECLARE-TIMI 58] trial. 87–90 Subsequently, there was an additional RCT of patients with T2D and ASCVD that found non-inferiority for cardiovascular outcomes with an SGLT2i, including among CKD subgroups (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial [VERTIS CV]91). (ii) A meta-analysis of these 3 cardiovascular outcome trials (EMPA-REG, CANVAS, DECLARE-TIMI 58) that was stratified by CKD subgroups92; this analysis was conducted before VERTIS CV was published.

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> 73 m2, the current KDIGO guideline recommends using an SGLT2i for the purposes of kidney and cardiovascular protection, whereas metformin is still used for glucose control among patients with an eGFR $30 ml/min per 1. 73 m2. The recommendation is strong due to the known kidney and/or cardiovascular protective effects in patients with T2D and CKD as shown in high-quality trials, such as EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, SCORED, DAPA-HF, SOLOIST, EMPEROR-Reduced and EMPEROR-Preserved. VERTIS CV showed cardiovascular non-inferiority, as well as safety. In the judgment of the Work Group, nearly all well-informed patients would prefer to receive this treatment over the risks of developing diabetic ketoacidosis, mycotic infections, and foot complications. As mentioned above, the EMPA-KIDNEY trial will report results by the end of 2022. Once the full trial data are published, KDIGO will incorporate the new data into metaanalyses to provide updated summary estimates of SGLT2i benefits and risks.

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[12] Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

Europe PMC

https://pubmed.ncbi.nlm.nih.gov/36151309/

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> The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the previous consensus statements on the management of hyperglycaemia in type 2 diabetes in adults, published since 2006 and last updated in 2019. The target audience is the full spectrum of the professional healthcare team providing diabetes care in the USA and Europe. A systematic examination of publications since 2018 informed new recommendations. These include additional focus on social determinants of health, the healthcare system and physical activity behaviours including sleep. There is a greater emphasis on weight management as part of the holistic approach to diabetes management. The results of cardiovascular and kidney outcomes trials involving sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, including assessment of subgroups, inform broader recommendations for cardiorenal protection in people with diabetes at high risk of cardiorenal disease. After a summary listing of consensus recommendations, practical tips for implementation are provided.

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[14] kdigo.org

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Prepared by Endocrine Intelligence for clinician review. This record preserves the complete model-authored answer and its cited evidence.