Treat-to-target protocols for type 2 diabetes: when to use empagliflozin

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Clinical question
Metformin remains the first-line treatment for type 2 diabetes. In patients with existing atherosclerotic cardiovascular disease (ASCVD), what should we add next?

Recommendations

Type 1 diabetes

Note: Empagliflozin should not be used in type 1 diabetes due to an increased risk of diabetic ketoacidosis.

Type 2 diabetes

After metformin, we have a variety of options for second-line treatment in patients with type 2 diabetes. Historically, we have lacked cardiovascular data to support the use of one strategy over another. More recent data, however, shows evidence of cardiovascular and mortality benefit with the addition of empagliflozin, an SGLT-2 inhibitor, in type 2 diabetic patients with a history of ASCVD.

Empagliflozin:

- Works by decreasing the renal threshold for glucose reabsorption. This leads to increased urinary glucose loss and lower blood glucose levels.
- Leads to a relatively mild average HbA1c reduction of 0.6–0.9%.
- Should not be used if GFR is under 45 mL/min.
- Can lower blood pressure due to its diuretic effect. Patients should be encouraged to drink plenty of fluid to maintain good hydration status. Other diuretics and anti-hypertensive agents may need to be adjusted.
- Has as its most common adverse effect an increase in genitourinary mycotic (yeast) infections related to increased glucose in the urine. (Up to 15% of women in studies of SGLT-2 inhibitors experience this adverse effect.)
- Can be added to metformin, insulins, sulfonylurea, or GLP-1 agonists (exenatide [Bydureon]).
- Comes in two doses: 10 mg and 25 mg. Studies show no difference in benefit between the two doses, so we prescribe ½ x 25 mg tablet (12.5 mg) once daily as a cost-containment strategy.

Prior authorization criteria for empagliflozin (Jardiance)
Type 2 diabetes patients who:

- Are currently on metformin or contraindication/intolerance to metformin with a history of clinical atherosclerotic cardiovascular disease (ASCVD) OR
- Have failure, contraindication, or intolerance of maximum tolerated dose of metformin, a sulfonylurea, and rapid plus basal insulin combination.

Quantity limit: 30-day supply
How could this change my practice?

- If a patient has type 2 diabetes and ASCVD (CAD, MI, stroke, PAD), empagliflozin should be considered as second-line therapy after metformin.
- If you have a patient with type 2 diabetes and ASCVD who has already achieved goal HbA1c (about 7.5% for this group) on metformin plus other agent, consider lowering or stopping the other agent and replacing it with empagliflozin.

Why did we choose this topic?

- Cardiovascular disease remains the leading cause of death in patients with type 2 diabetes [1], so medications that mitigate this risk should be prioritized.
- We have learned from previous data [2] that lowering HbA1c in itself does not always lead to improved outcomes. The type of therapy we choose may be more important than simply lowering blood glucose values.
- Treat-to-target protocols can be individualized based on a patient's comorbid conditions.
- Despite the increased cost of adding a newer and more expensive therapy, empagliflozin use in appropriate patients will provide significant medical cost savings by preventing cardiovascular events.

Evidence summary

In the 2015 Empa-Reg Study [3], more than 7,000 participants with high cardiovascular risk (existing ASCVD) were randomized to receive empagliflozin 10 mg once daily, empagliflozin 25 mg once daily, or placebo, in addition to standard care. Standard care included known cardioprotective medications such as statins, ACE inhibitors, and aspirin. Median follow-up was 3.1 years. Participants randomized to empagliflozin demonstrated a greater than 30% reduction in cardiovascular death and death from any cause. There was no significant difference in outcomes between the groups receiving 10 mg and 25 mg doses of empagliflozin. The number needed to treat (NNT) over 3.1 years to avoid one cardiovascular event in this trial was 45.

References


Resources

KPWA Type 2 Diabetes Guideline