

Intervention

Empagliflozin 10mg once daily by mouth for up to 28 days (stopped at discharge if sooner)

Summary of information on empagliflozin in COVID-19

Sodium glucose co-transporter 2 inhibitors (SGLT-2i), such as empagliflozin, are routinely used in the treatment of type 2 diabetes and have also been shown to have rapid effects in other diseases, such as heart failure¹. In COVID-19, they may be beneficial through multiple mechanisms including their impacts on energy metabolism^{2,3}, endothelial function⁴, oxidative stress⁴, inflammation⁵ and haemodynamic decongestion⁶. The DARE-19 trial compared the SGLT-2i dapagliflozin with placebo for 30 days among 1250 hospitalised COVID-19 patients with mild hypoxia and at least one co-morbid disease risk factor⁷. The treatment was well-tolerated. The hazard ratio for the composite primary outcome of organ failure or death was 0.80 (95% confidence interval 0.58-1.10)⁸; although this was not statistically significant the trial lacked power and the results support the rationale for a larger trial.

Potential harm

Common side effects include genital candidiasis and hypoglycaemia when used in combination with insulin or insulin secretagogues (eg, sulphonylureas). Rare, but important, side effects include ketoacidosis (particularly in type 1 diabetes mellitus). Mitigating measures are described below and in the study protocol.

SGLT-2i are not considered to be safe in pregnancy and breastfeeding so these women will be excluded from the comparison.

Based on the mode of action, there are no theoretical grounds to modify the dose in elderly patients or those with hepatic impairment. We do not recommend a dose modification in renal impairment as outlined below.

Frequently asked questions

1. What are the contraindications to empagliflozin?

- Type 1 diabetes mellitus or post-pancreatectomy diabetes
- History of ketoacidosis
- Pregnancy and breast-feeding
- Current blood ketones ≥ 1.5 mmol/L or urine ketones $\geq 2+$

2. Is empagliflozin contraindicated in renal impairment?

No.

Although the SmPC advises against initiation in patients with an $eGFR < 60 \text{ mL/min/1.73m}^2$, SGLT-2i have been tested across a broad range of kidney function in large trials (such as DAPA-CKD and EMPA-KIDNEY) and treatment is continued to up to after the initiation of renal replacement therapy with no specific safety concerns identified. We therefore do not exclude or suggest a dose modification for patients with renal impairment in the trial.

3. Is there a risk of hypoglycaemia?

Empagliflozin does not cause hypoglycaemia in isolation but may do so in patients also taking insulin or sulphonylureas. Blood sugar levels should be monitored regularly and other diabetic medications may require dose modifications.

The occurrence of severe hypoglycaemia (reduced conscious level requiring the assistance of another person to recover) will be recorded on the study follow-up case report form.

4. Can we include patients already taking an SGLT-2i in RECOVERY?

Patients already on an SGLT-2i (empa-, dapa- or cana-gliflozin) should not participate in the empagliflozin comparison, but they can participate in any other suitable comparisons in the trial.

5. What should we do about the risk of ketoacidosis?

Empagliflozin can cause ketoacidosis, especially in patients with type 1 diabetes mellitus. It is rare in patients with type 2 diabetes mellitus but clinicians should be aware and the following mitigating measures are recommended:

- Patients with type 1 diabetes mellitus, post-pancreatectomy diabetes and history of ketoacidosis should be excluded from this comparison
- Participants with diabetes mellitus should have regular checks of ketones
 - Twice daily blood ketones (or daily urine ketones if blood ketone testing not available)
 - If ketosis (blood ketones ≥ 1.5 mmol/L or urine ketones $\geq 2+$) develops then action is required:
 - Ensure adequate fluid and calorific intake
 - Involve local diabetes team (if available) and follow local protocols for ketosis
 - Consider increasing insulin if patient receives it
 - Consider withholding empagliflozin whilst ketotic
- Study staff should be aware of and have a low threshold for considering a diagnosis of “euglycaemic” ketoacidosis (ie, ketoacidosis with a relatively low blood glucose), which may occur with empagliflozin. Ketones (ideally blood) should be checked if this is suspected (e.g. unexplained metabolic acidosis).

The occurrence of ketoacidosis (defined as combination of ketosis (blood ketones ≥ 1.5 mmol/L or urine ketones $\geq 2+$) and metabolic acidosis (bicarbonate < 15 mmol/L)) will be recorded on the study follow-up case report form (in addition to usual suspected serious adverse reaction reporting).

6. Is there a risk of dehydration?

Empagliflozin causes an osmotic diuresis and may cause volume depletion. All patients with COVID-19 require careful fluid balance assessment.

Although acute kidney injury was initially thought to be an adverse effect of SGLT-2i, all the large trials have demonstrated that SGLT-2i actually reduce the risk of acute kidney injury.

Peak creatinine during admission will be recorded on the study follow-up case report form.

7. Is there a risk of urinary tract or genital infections?

Fungal genital infections, such as candidiasis, can occur. These are less likely with short-term use in RECOVERY than for long-term licensed indications. If they do occur, they can easily be treated with topical antifungals and may not require interruption of treatment.

Urinary tract infections have been reported with SGLT-2i but the large trials show there is no excess risk compared to placebo.

It is unclear whether it increases the risk of Fournier's gangrene (a rare, invasive genital infection) but clinicians should be aware.

8. Are there any important drug interactions?

Co-administration of empagliflozin with insulin and insulin secretagogues (eg, sulphonylureas) can increase the risk of hypoglycaemia. Please see above.

Co-administration of empagliflozin with diuretics, vasodilators and anti-hypertensives can increase the risk of hypotension through volume depletion. Please see above.

References

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7. Kosiborod M, Berwanger O, Koch GG, et al. Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: Design and rationale for the DARE-19 study. *Diabetes Obes Metab* 2021; **23**(4): 886-96.
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