Empagliflozin (Jardiance®) for the treatment of type 2 diabetes mellitus, the EMPA REG OUTCOME study

POSITION STATEMENT: Clinicians should continue to follow MHRA advice and NICE technology appraisal guidance for empagliflozin for use as a monotherapy/combination therapy for the treatment of type 2 diabetes mellitus – **Empagliflozin LMMG RAG status "Green" as monotherapy/combination therapy**.

There are limitations with the EMPA REG OUTCOME study therefore the superiority of empagliflozin in reducing cardiovascular mortality/morbidity based on this one study is not fully substantiated.

Further confirmatory trials are required before the position of empagliflozin in the treatment pathway for type 2 diabetes mellitus may be reviewed.

Summary

The EMPA REG OUTCOME study for empagliflozin has been published, reporting data indicating long term cardiovascular morbidity and mortality benefits for empagliflozin.

There are limitations with the EMPA REG OUTCOME study therefore the superiority of empagliflozin in reducing cardiovascular mortality/morbidity based on this one study is not fully substantiated.

Further confirmatory trials are required before the position of empagliflozin in the treatment pathway for type 2 diabetes may be reviewed.

- The trial was intended to demonstrate the cardiovascular safety of empagliflozin in patients at high risk of cardiovascular events and was not designed to show a benefit. Applicability to the wider population of patients is unknown.
- Silent MI was not included in the primary composite endpoint despite being included in the original primary composite endpoint protocol. Only approximately half the patients were screened for silent MI. When including this in the primary analysis the primary endpoint still demonstrates non-inferiority but no longer shows superiority.
- Significant differences in the primary composite endpoint were chiefly due to differences in cardiovascular death between treatment arms. Results for stroke and myocardial infarction, two of the composite components, did not demonstrate superiority for empagliflozin when compared with placebo.
- Empagliflozin demonstrates a reduction in all-cause mortality but many of the deaths (n=124) were categorized as "non-assessable" and adjudicated as presumed CV deaths (71 versus 53 for empagliflozin versus placebo). Deaths that were "non-assessable" but presumed to be CV-deaths comprised 40% of CV deaths, and 27% of overall deaths in the trial. In a sensitivity analysis that removes all "non-assessable" deaths from the primary endpoint, empagliflozin was no longer demonstrated to be superior to placebo.

NHS Midlands and Lancashire CSU
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Background

Empagliflozin is an orally administered selective sodium-glucose cotransporter-2 (SGLT-2) inhibitor, which lowers blood glucose in people with type 2 diabetes by blocking the reabsorption of glucose in the kidneys and promoting excretion of excess glucose in the urine. Empagliflozin has been recommended by NICE for the management of type 2 diabetes mellitus in two technology appraisals and SGLT-2 inhibitors as a class are incorporated in the clinical guideline for the management of type 2 diabetes mellitus in adults. As the drug has been approved by NICE, a full review was not necessary for it to be listed as a Green drug on the LMMG web site. The relevant NICE guideline and guidance are as follows:

1. **NICE Technology Appraisal Guidance TA390 (Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes) states:**

   Empagliflozin is recommended as monotherapy for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

   - a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
   - a sulfonylurea or pioglitazone is not appropriate. [1]

2. **NICE Technology Appraisal Guidance TA336 (Empagliflozin in combination therapy for treating type 2 diabetes) states:**

   Empagliflozin in a dual therapy regimen in combination with metformin is an option for the treatment of type 2 diabetes, only if:

   - a sulfonylurea is contraindicated or not tolerated, or
   - the patient is at significant risk of hypoglycaemia or its consequences.

   Empagliflozin in a triple therapy regimen is an option for the treatment of type 2 diabetes in combination with:

   - metformin and a sulfonylurea or
   - metformin and a thiazolidinedione.

   Empagliflozin in combination with insulin with or without other antidiabetic drugs is an option for the treatment of type 2 diabetes. [2]

3. **NICE Clinical Guideline NG28 (Type 2 diabetes in adults: management) states:**

   SGLT-2 inhibitors may be used at First Intensification of Drug Treatment:

   Treatment with 2 non‑insulin blood glucose lowering therapies in combination (dual therapy) Consider:

   - Metformin plus DPP4-inhibitor
   - Metformin plus pioglitazone
   - Metformin plus sulfonylurea
   - Metformin plus SGLT-2 inhibitor

   SGLT-2 inhibitors may be used at Second Intensification of Drug Treatment:

   Consider triple therapy with:

   - Metformin plus DPP4-inhibitor plus a sulfonylurea

- Metformin plus pioglitazone plus a sulfonylurea
- Metformin plus pioglitazone or a sulfonylurea plus an SGLT-2 inhibitor

NB – SGLT-2 inhibitors are only recommended when metformin is co-prescribed, they are not listed as options when metformin is contraindicated or not tolerated. NG28 also allows treatment with SGLT-2 inhibitors when insulin is prescribed. [3]

Diabetes and Cardiovascular Risk

Cardiovascular disease is a major cause of death and disability in people with diabetes, accounting for 52% of deaths in people with type 2 diabetes. There is a 138.8% increased risk of angina, a 94.2% increased risk of myocardial infarction, a 126.2% increased risk of heart failure and a 62.5% increased risk of stroke among people with both types of diabetes. People with type 2 diabetes have a two-fold increased risk of stroke within the first five years of diagnosis compared with the general population. Around one fifth of hospital admissions for heart failure, heart attack and stroke are in people with diabetes. [5] The last decade has seen a significant increase in the number of medicines used for treating type 2 diabetes. Whilst all have demonstrable effects on lowering glucose few have shown genuine cardiovascular benefits. Of the available blood glucose-lowering drugs, metformin appears to be the safest, and has shown benefits in preventing cardiovascular morbidity and mortality. [6] There have been longstanding concerns about the cardiovascular effects of glitazones, and possibly sulfonylureas. [7]

EMPA REG OUTCOME study

Since the NICE TAs were published, the cardiovascular risk study EMPA REG OUTCOME has been published, providing additional data regarding empagliflozin's impact on long term cardiovascular morbidity and mortality. [4] The EMPA REG OUTCOME study was a randomised, double-blind, placebo-controlled trial of 7020 high risk cardiovascular patients comparing the effect of placebo, empagliflozin 10mg and empagliflozin 25mg on a composite primary outcome of cardiovascular death and nonfatal myocardial infarction or nonfatal stroke. Over the duration of the study (median observation time, 3.1 years) the primary endpoint occurred in 490 of 4687 patients (10.5%) in the combined 10mg and 25mg empagliflozin groups compared with 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the pooled empagliflozin group, 0.86; [CI95% 0.74; 0.99, P = 0.04 for superiority]). [4]

Data from the EMPA-REG outcome trial was reviewed by the EMEA, leading to an update of the prescribing information of empagliflozin on 15 December 2016, highlighting the drug's effect on cardiovascular events. [8]

Interpretation of the evidence from the EMPA REG OUTCOME study

The FDA published a briefing document which explored the findings of the EMPA REG OUTCOME trial and assessed the robustness of this evidence in supporting its long term use. [9] The main conclusions drawn in this report are summarised as follows:

- The study was intended as a safety study to prove that empagliflozin does not increase long term cardiovascular risk; subsequently the design of the trial was not typical of an efficacy trial to show positive cardiovascular outcomes.
- Given that the study was designed to measure mortality/morbidity in patients at high risk of cardiovascular events, the relevance of the results of the EMPA REG OUTCOME study to the wider population of patients with diabetes is uncertain.
- The protocol of the study was amended a number of times which may have influenced the overall conclusions of the trial. The study originally proposed to continue until 691 deaths were reached but the trial continued to 772 deaths.

- Silent MI was not included in the primary composite endpoint despite being included in the original primary composite endpoint protocol**.** Only approximately half the patients were screened for silent MI. When including this in the primary analysis the primary endpoint still demonstrates non-inferiority but no longer shows superiority.
- Significant differences in the primary composite endpoint were chiefly due to differences in cardiovascular death between treatment arms. Results for stroke and myocardial infarction, two of the composite components, did not demonstrate superiority for empagliflozin when compared with placebo.
- Hazard ratio (HR) estimates for cardiovascular death and all-cause death show results favouring the pooled empagliflozin arm compared to the placebo arm. Results were similar when looking at the individual doses with both the 10mg and the 25mg arm when compared to the placebo arm.
- The superiority of empagliflozin in terms of primary composite endpoint is driven by results from the South American study centres. Evidence from European centres did not show superiority of empagliflozin for the primary composite endpoint and actually demonstrated statistically significant risk of non-fatal stroke in this subset of patients.
- Empagliflozin demonstrates a reduction in all-cause mortality but many of the deaths (n=124) were categorized as "non-assessable" and adjudicated as presumed CV deaths (71 versus 53 for empagliflozin versus placebo). Deaths that were "non-assessable" but presumed to be CV-deaths comprised 40% of CV deaths, and 27% of overall deaths in the trial. In a sensitivity analysis that removes all "non-assessable" deaths from the primary endpoint, empagliflozin was no longer demonstrated to be superior to placebo.

RECOMMENDATION

There are limitations with the EMPA REG OUTCOME trial therefore the superiority of empagliflozin in reducing cardiovascular mortality/morbidity based on this one study is not fully substantiated. It is important to await further confirmatory trials before altering the position of empagliflozin in the treatment pathway for type 2 diabetes.

References

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