INTRODUCTION

• Canagliflozin is a new insulin-independent oral glucose-lowering agent that is complementary to other anti-hyperglycaemic 26-week, 300 mg insulin. As an inhibitor of sodium glucose co-transporter-2 (SGLT-2), canagliflozin causes urinary glucose excretion, which results in lowering of blood glucose levels and in weight reduction [1].

• A systematic literature review and network meta-analysis (NMA) were conducted as part of the assessment of canagliflozin for the treatment of type 2 diabetes (T2DM) in patients inadequately controlled on metformin and sulfonylurea.

OBJECTIVES

• To assess the relative efficacy and safety of canagliflozin, as add-on to metformin and sulfonylurea, compared to GLP-1 agonists (exenatide and liraglutide), DPP-4 inhibitors (sitagliptin and linagliptin) and insulin (biphasic insulin and long-acting insulin) over 26 weeks.

METHODS

• Bayesian NMAs were conducted based on a systematic literature review described elsewhere [2]. Methods were in line with NICE guidelines [3-4].

• Outcomes of interest included HbA1c change from baseline, weight change from baseline and incidence of hypoglycaemic events at 26 weeks.

• Networks were based on treatment- and dose-specific nodes where possible. The following insulin were used: long-acting insulin (glargine, detemir) and biphasic/pre-mixed insulin. These classes were defined in line with the NICE guidelines for the management of type 2 diabetes [5].

• Due to missing data, canagliflozin was not compared to liraglutide 1.8mg for the incidence of hypoglycaemic events.

• Non-informative prior distributions were used to produce results driven by the data. The selection of using a fixed or random effects model was based on the Deviance Information Criterion (DIC), which measures the relative goodness of fit between models [6]. Sensitivity analyses were performed to assess the impact of prior distribution on random effects models.

• An analysis based on a reduced network that excluded studies causing heterogeneity identity [2]. Methods were in line with NICE guidelines [3-4].

RESULTS

Figure 1: Network of evidence

- The systematic literature review led to the inclusion of 10 trials reporting results after 26 weeks (4 weeks).

- Two trials assessed canagliflozin 100mg and/or 300mg at 26 weeks [1,9].

- The trial by Harthmann [2] assessing pegglipozon versus NPH insulin was disconnected from the network [10].

- On the basis of the DIC, a random effects model was selected for the analysis of HbA1c and weight based on the full network. A fixed effects model was selected for the analysis of hypoglycaemic events and for HbA1c and weight based on the reduced network.

HbA1c change from baseline

• HbA1c-reduction (x) for canagliflozin 300mg was comparable to GLP-1 agonists (x=0.08, CrI95%: [0.240.40] and x=0.01, CrI95%: [-0.27.20.23] versus liraglutide 1.8mg and exenatide 10µg) and biphasic insulin (x=0.03, CrI95%: [0.32.0.40]) and was higher than DPP-4 inhibitors (x=0.21, CrI95%: [0.03.1.10] and x=0.09 CrI95%: [0.05.0.19] versus sitagliptin and linagliptin respectively).

• HbA1c-reduction for canagliflozin 100mg was comparable to DPP-4 inhibitors (x=0.04, CrI95%: [-0.17.28] versus sitagliptin and linagliptin respectively).

• Consistency was suspected within the loop placebo/long-acting insulin/biphasic insulin/exenatide 10µg (p-value for the comparison of direct and indirect evidence 0.0016).

- The trial by Bergental [9] assessing exenatide 10µg versus biphasic insulin included patients with a higher mean HbA1c at baseline (higher than 10%) compared to other trials. HbA1c at baseline is an important treatment modifier[12] and could explain the inconsistency within this loop. Analysis excluding Bergental [9] was conducted (Figure 1) - which demonstrated the study’s influence on estimates of the treatment effect for canagliflozin compared to long-acting insulin and biphasic insulin. Credibility intervals were narrower compared to the full network analysis, as a fixed effects model was selected in this analysis.

DISCUSSION

• Sensitivity analysis indicated that results were robust to the change of prior distributions for heterogeneity parameters in random effects models. [Data not shown]

• The analysis investigating the inconsistency for HbA1c had minor impact on all estimates except for the effect of canagliflozin versus long-acting and biphasic insulin. Point estimates from the full network analysis were conservative for canagliflozin.

CONCLUSION

• The NMA of add on therapies to metformin plus sulphonylurea suggests that canagliflozin 300mg is associated with increased HbA1c-reduction versus DPP-4 inhibitors while canagliflozin 100mg provides at least similar effects. Canagliflozin 300mg was found to be comparable to biphasic and long-acting insulin and to GLP-1 agonists.

• Weight reduction associated with canagliflozin 100mg and 300mg was comparable to GLP-1 agonists and substantially higher than all other classes.

• All classes showed significantly less risk of hypoglycaemic events compared to insulin.

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