RQ 1.2: Subsequent pharmacological therapy for the management of type 2 diabetes

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Additional analysis for people with chronic kidney disease (CKD)

An additional study was identified for inclusion in the review during rerun searches (Perkovic 2024). This study reported results for subcutaneous semaglutide compared to placebo for people with type 2 diabetes and chronic kidney disease including 3,533 participants.

Network meta-analysis was repeated for change in HbA1c and change in body weight as there were loops in the networks that the addition of the new study would influence. Network meta-analysis was not repeated for other outcomes reported in the study.

Subpopulation with CKD: Change in HbA1c - additional treatment

This analysis included 25 studies of 18 treatments (Figure 1. Network of evidence for change in HbA1c in the subpopulation with CKD.

). NMA using a fixed effects treatment model was appropriate based on model fit statistics (Table 2).

The treatment effects were compared against the results from the previous analysis. There were minimal differences between the two. The results for semaglutide (subcutaneous) showed greater certainty in the result, with the credible intervals narrowing substantially. This is expected given the sample size of the node increased from 54 participants up to 1821 participants. The addition of the study provided a direct estimate for semaglutide (subcutaneous) compared to placebo which was previously estimated using an indirect estimate. This direct estimate became the dominant factor in the analysis and ultimately became the final posterior median and credible interval values (value reported in Perkovic 2024 MD 95% CI -0.81, -0.9 to -0.72).

The results for dapagliflozin with saxagliptin and glimepiride changed marginally, with the results for dapagliflozin with saxagliptin showing a greater reduction in HbA1c while the results for glimepiride having less of a reduction. Dapagliflozin and saxagliptin is a small node (151 participants). Providing greater certainty to the estimate of semaglutide (subcutaneous) and placebo may have altered the result for dapagliflozin + saxagliptin due to the uncertainty in the direct estimate as small changes in the indirect estimate can have greater effects on the overall estimate. This could also be true for glimepiride, where the size of the node is even smaller (29 participants).

There is evidence supporting reduction in % HbA1c compared to placebo for pioglitazone, glimepiride and all represented members of the SGLT2-inhibitor class. There was clear evidence supporting a reduction in % HbA1c for dulaglutide, semaglutide by both routes and liraglutide (GLP1-receptor agonists) and linagliptin and saxagliptin (DPP4 inhibitors) (Figure 2). The evidence for a reduction in % HbA1c relative to placebo was weaker for insulin, exenatide, vildagliptin and sitagliptin, where there was greater uncertainty around the effect of treatment.

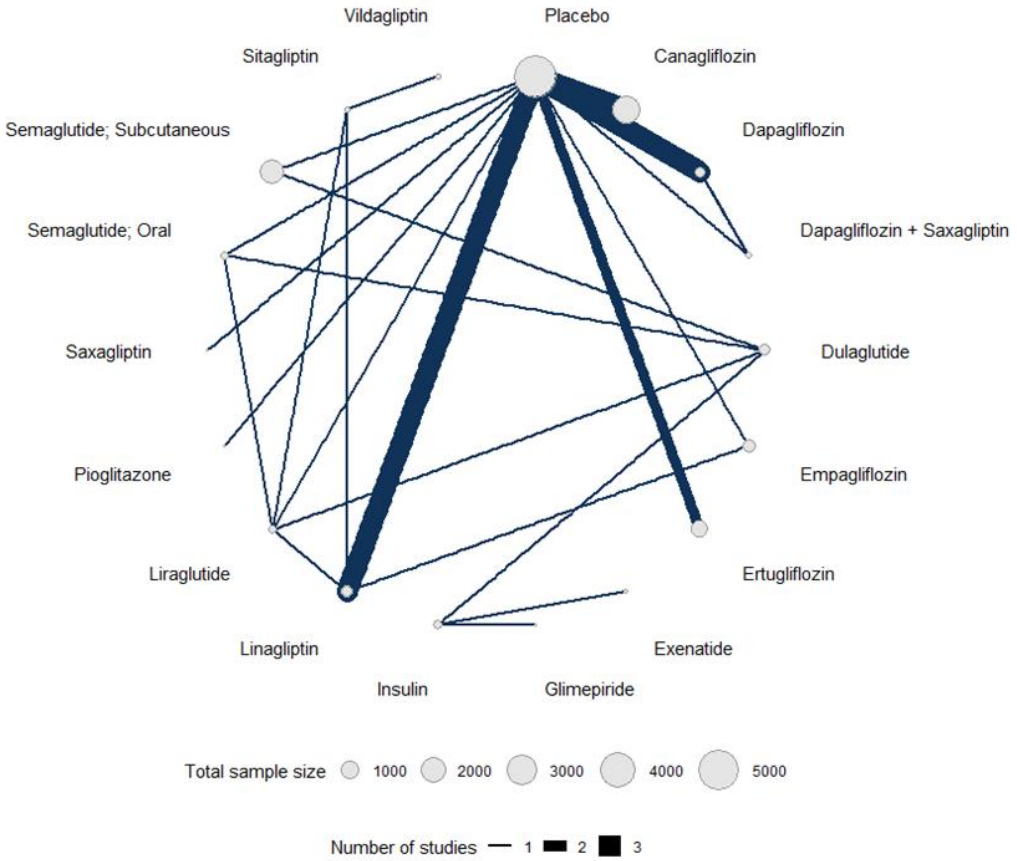

Figure 1. Network of evidence for change in HbA1c in the subpopulation with CKD.

Table 1. Change in HbA1c relative to placebo for all 17 active treatments in the network, with fixed-effects structure on treatment effects. The results before adding Perkovic 2024 (previous analysis) are compared with those after (new analysis) and major changes are bolded.

Class	Treatment	Previous analysis Change in HbA1c Posterior median (95%CrI)	New analysis Change in HbA1c Posterior median (95%CrI)
DPP-4i	Linagliptin	-0.54 (-0.66, -0.41)	-0.54 (-0.67, -0.41)
	Saxagliptin	-0.63 (-1.24, -0.02)	-0.63 (-1.24, -0.01)
	Sitagliptin	-0.21 (-0.58, 0.15)	-0.22 (-0.56, 0.14)
	Vildagliptin	-0.19 (-0.70, 0.31)	-0.20 (-0.68, 0.3)
GLP-1RA	Dulaglutide	-0.42 (-0.72, -0.12)	-0.41 (-0.61, -0.22)
	Exenatide	-0.09 (-0.85, 0.66)	-0.10 (-0.79, 0.61)
	Liraglutide	-0.54 (-0.71, -0.37)	-0.55 (-0.72, -0.38)
	Semaglutide (Oral)	-0.92 (-1.15, -0.70)	-0.92 (-1.13, -0.72)
	Semaglutide (Subcutaneous)	**-0.82 (-1.19, -0.44)**	**-0.81 (-0.9, -0.72)**
Insulin	Insulin	-0.32 (-0.71, 0.06)	-0.31 (-0.62, -0.01)
SGLT2 with DPP-4i	Dapagliflozin with Saxagliptin	**-0.58 (-0.79, -0.36)**	**-0.63 (-0.82, -0.42)**

SGLT-2i	Canagliflozin	-0.20 (-0.32, -0.08)	-0.20 (-0.32, -0.08)
	Dapagliflozin	-0.23 (-0.39, -0.06)	-0.23 (-0.39, -0.06)
	Empagliflozin	-0.51 (-0.63, -0.39)	-0.50 (-0.62, -0.37)
	Ertugliflozin	-0.10 (-0.22, 0.02)	-0.10 (-0.22, 0.02)
Sulfonylurea	Glimepiride	**-0.92 (-1.70, -0.13)**	**-0.81 (-1.6, -0.02)**
TZD	Pioglitazone	-0.81 (-1.47, -0.16)	-0.80 (-1.45, -0.16)

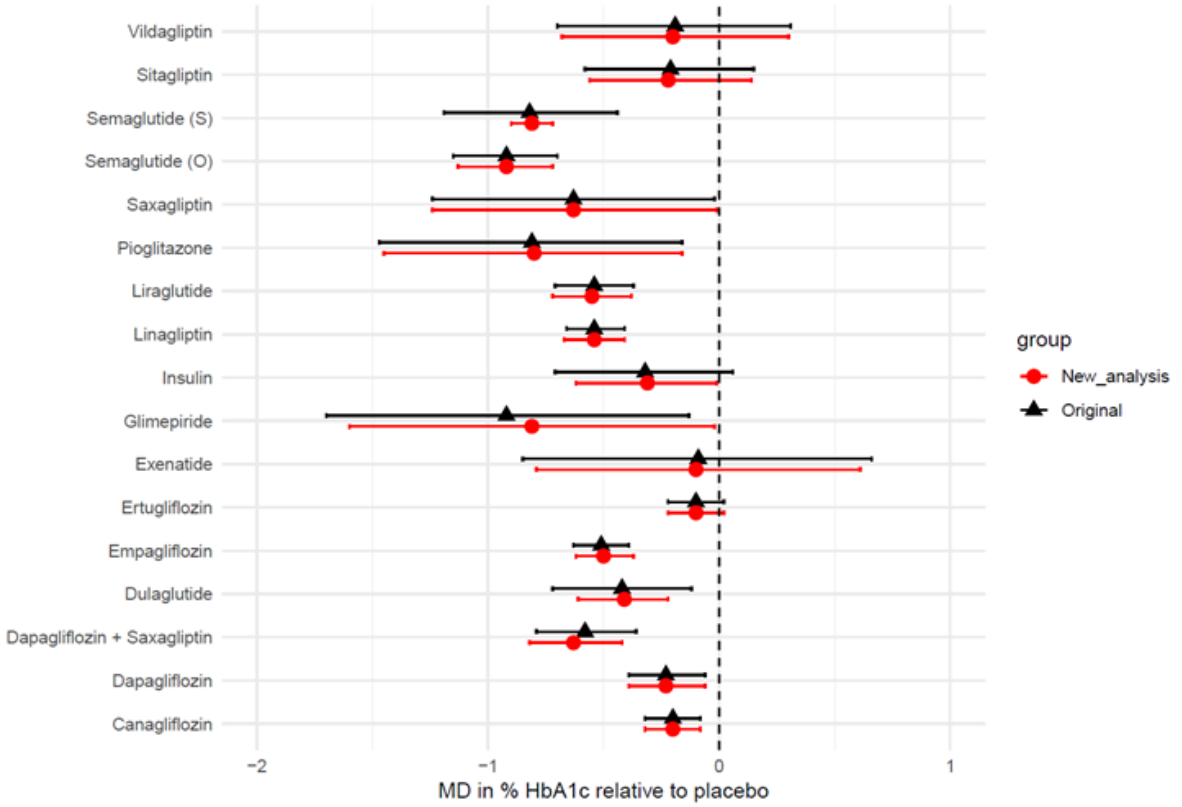

Figure 2. Mean difference (MD) in % HbA1c relative to placebo in the subpopulation with diabetes and CKD. Mean treatment effects (with 95% CrI) are given for original analysis (black triangles) and for the new analysis (red circles).

Tables of model fit

Total residual deviance and DIC values were calculated within RStudio version 2023.09.0 Build 463, R version 4.3.3, (2024-02-29 ucrt) using the multinma package version 0.6.1.9003, using TSD standard code to estimate the total residual deviance, which is equivalent to the number of data points in a well-fitting model, and the DIC function to calculate pD and DIC, which is a measure of model fit penalised for complexity: i.e., the sum of posterior mean residual deviance (D-bar) and the number of effective parameters (pD).

Subpopulation with diabetes and CKD

Table 2. Model fit statistics for network meta-analysis (NMA) and unrelated mean-effects (UME) models of change in % HbA1c in the subpopulation with diabetes and CKD. [1]Lower values for model fit and DIC preferred.

Model	NMA effect structure	Number of data points	Model fit (total residual deviance[1])	pD (number of effective parameters)	DIC (penalised deviance[1])	Between-study SD median, (95% CrI)
NMA	Fixed	51	54.7	35.3	90.0	-
	Random	51	51.4	39.0	90.4	0.06 (0.00 – 0.2)
UME	Fixed	51	50.2	39.0	89.2	-

References

Balk EM, Earley A, Patel K, Trikalinos TA, Dahabreh IJ. Empirical assessment of within-arm correlation imputation in trials of continuous outcomes. Rockville: Agency for Healthcare Research and Quality; 2012.

Daly C, Welton, S.J., Dias, S., Anwer, S., Ades, A.E. Meta-Analysis of Continuous Outcomes. Guideline Methodology Document 2: NICE Guidelines Technical Support Unit 2021.

Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from https://www.sheffield.ac.uk/nice-dsu/tsds

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials. Medical Decision Making 2013 33:641-656

R code

```
md.net <- set_agd_contrast(md.df,
                    study=parent_study_name,
                    trt=trt,
                    y=md,
                    se=se,
                    sample_size=n)

print(md.net)
plot(md.net, weight_nodes=TRUE, nudge=0.2) +
  ggplot2::theme(legend.position = "bottom",
            legend.box = "vertical")

# ARM DATA (y)
# set_agd_arm = set aggregate arm data
y.net <- set_agd_arm(y.df,
                  study=parent_study_name,
                  trt=trt,
                  y=y,
                  se=se,
                  sample_size=n)

print(y.net)
plot(y.net, weight_nodes=TRUE, nudge=0.2) +
  ggplot2::theme(legend.position = "bottom",
            legend.box = "vertical")

# COMBINE CONTRAST AND ARM DATA
comb.net <- combine_network(md.net, y.net,
                      trt_ref="Placebo")

```

```
print(comb.net)
plot(comb.net, weight_nodes=TRUE, nudge=0.2) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

######################## Run NMA ######################
nma.fe <- nma(comb.net, trt_effects="fixed")
nma.fe
dic.fe <- dic(nma.fe)

nma.re <- nma(comb.net, trt_effects = "random")
nma.re
dic.re <- dic(nma.re)

######################## Run UME ######################
nma.Ufe <- nma(comb.net,
               trt_effects="fixed",
               consistency="ume")
nma.Ufe
dic.Ufe <- dic(nma.Ufe)

nma.Ure <- nma(comb.net,
               trt_effects = "random",
               consistency = "ume",
               adapt_delta=0.99)
nma.Ure
dic.Ure <- dic(nma.Ure)

dic.fe
dic.re
dic.Ufe
```

1 dic.Ure