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

September 2025

Sarah Dwyer, Lina Manounah, Sarah Matthews, Emily Terrazas-Cruz, George Wood, NICE

Additional analysis for people with heart failure (HF)

An additional study was identified for inclusion in the review (Kosiborod, 2024). This study reported results for subcutaneous semaglutide compared to placebo for people with type 2 diabetes and heart failure including 616 participants.

Network meta-analysis was repeated for the adverse events of hospitalisation for heart failure and cardiovascular mortality, as the addition of the new study would create novel direct estimates for semaglutide (subcutaneous) for both adverse events. Network meta-analysis was not repeated for other outcomes reported in the study.

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 HF: hospitalisation for heart failure

This analysis included 11 studies of 11 treatments (*Figure 1*). Ten studies reported hazard ratios, with eight of these reporting both hazard ratios and the number of hospitalisations. Hospitalisation for heart failure affected between 6% and 13% of the participant populations of the studies where the number of events was reported.

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. The addition of the study which included 616 participants with heart failure and T2DM resulted in a novel direct estimate for semaglutide (subcutaneous) compared to placebo which

showed clear evidence for a decreased hazard of hospitalisation for heart failure. The data for the remaining treatments remained largely the same with minimal differences between the original and the updated NMA (*Table 1* and *Figure 2*).

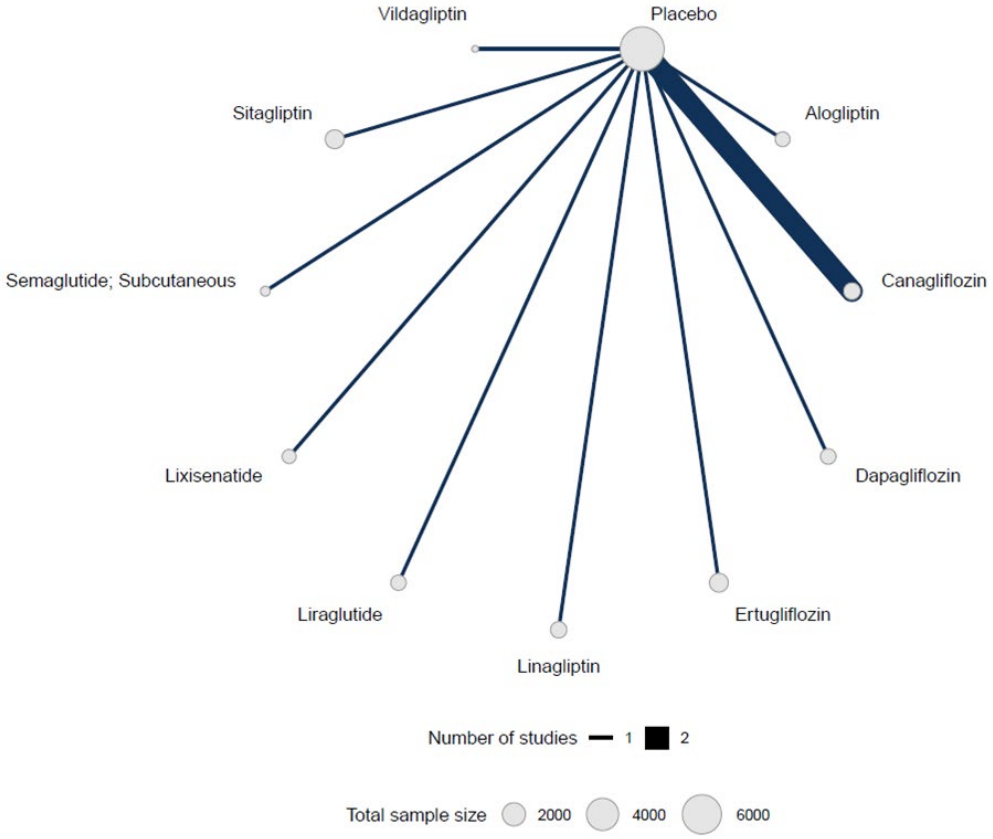

Figure 1. Network of evidence for hospitalisation for heart failure in the subpopulation with HF

Table 1. Hazard ratios and posterior median rank with 95% CrI for hospitalisation for heart failure in the subpopulation with diabetes and HF, relative to placebo.

Class	Treatment	Previous analysis		New analysis	
		Hazard ratio median (95%CrI)	Rank Median (95% CrI)	Hazard ratio median (95%CrI)	Rank Median (95% CrI)
DPP-4i	Alogliptin	1.00 (0.71, 1.41)	7 (3, 10)	1.00 (0.71, 1.43)	8 (4, 11)
	Linagliptin	0.88 (0.68, 1.14)	5 (2, 9)	0.88 (0.68, 1.13)	6 (3, 10)
	Sitagliptin	1.05 (0.79, 1.39)	8 (4, 10)	1.05 (0.80, 1.39)	9 (5, 11)

	Vildagliptin	1.32 (0.58, 3.10)	10 (2, 10)	1.29 (0.58, 3.10)	11 (2, 11)
GLP-1RA	Liraglutide	0.98 (0.75, 1.28)	7 (3, 10)	0.98 (0.75, 1.27)	8 (4, 11)
	Lixisenatide	0.93 (0.66, 1.31)	6 (2, 10)	0.93 (0.66, 1.31)	7 (3, 11)
	Semaglutide (Subcutaneous)	**NA**	**NA**	**0.41 (0.16, 1.02)**	[illegible]
SGLT2	Canagliflozin	0.61 (0.45, 0.84)	2 (1, 4)	0.61 (0.45, 0.83)	2 (1, 5)
	Dapagliflozin	0.73 (0.55, 0.96)	3 (1, 6)	0.73 (0.55, 0.96)	4 (2, 7)
	Ertugliflozin	0.63 (0.44, 0.90)	2 (1, 5)	0.63 (0.44, 0.89)	3 (1, 6)

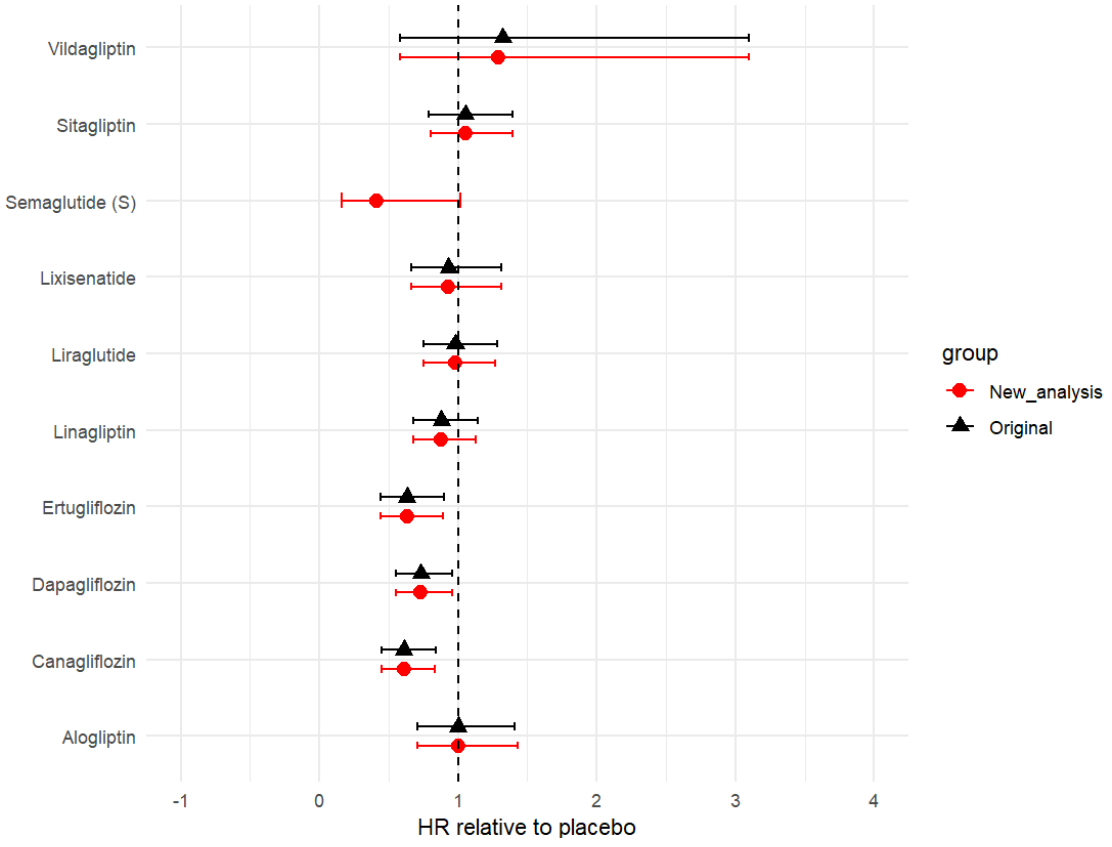

Figure 2. Hazard ratio for hospitalisation for HR, relative to placebo with T2D and HF.

Table 2. Model fit statistics for network meta-analysis (NMA) models of change in hospitalisation for heart failure in the subpopulation with diabetes and HF. [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	12	12.4	10.8	23.2	-
	Random	12	11.9	11.6	23.5	0.34 (0.02 – 1.30)

Subpopulation with HF: cardiovascular mortality

This analysis included seven studies of eight treatments (*Figure 3*). Five studies reported the hazard ratio, with three also reporting the number of events and two reporting the number of events alone. Between 4% and 10% of participants experienced CV mortality in those studies where the number of events was reported.

NMA using a fixed effects treatment model was appropriate based on model fit statistics (*Table 3*).

The treatment effects were compared against the results from the previous analysis. The addition of the study which included 616 participants with heart failure and T2DM resulted in a novel direct estimate for semaglutide (subcutaneous) compared to placebo which showed evidence for a decreased hazard of cardiovascular mortality but with wide credible intervals. The data for the remaining treatments remained largely the same with minimal differences between the original and the updated NMA (

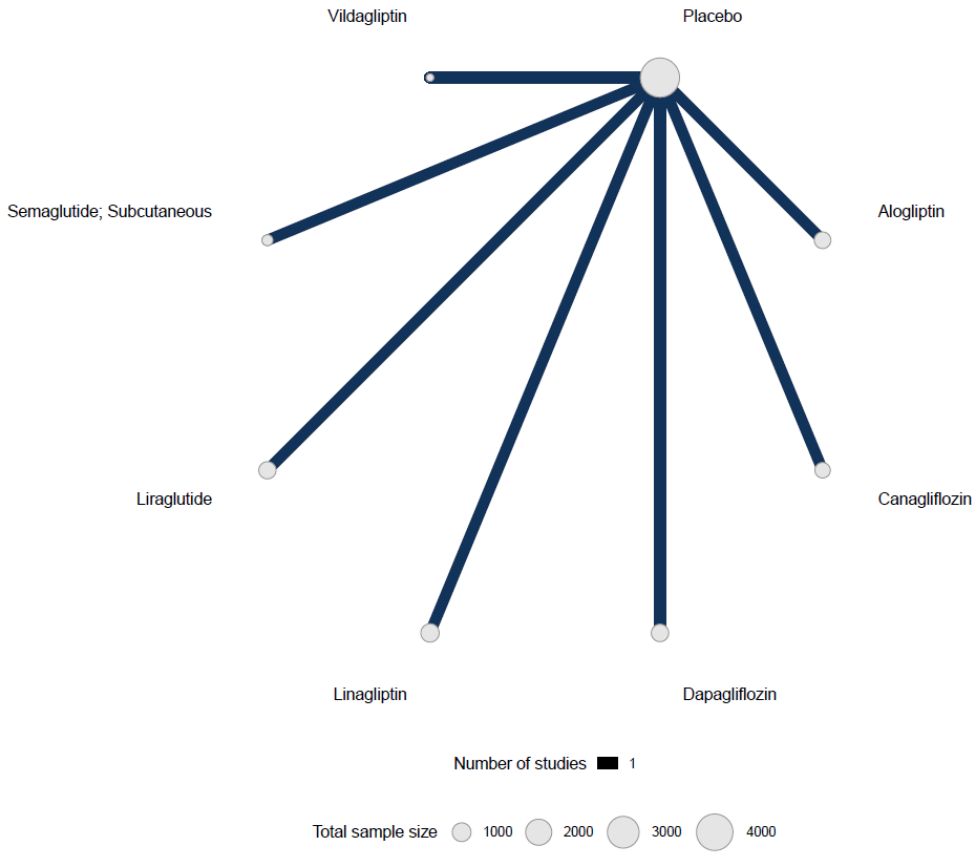

Figure 3 Network of evidence for cardiovascular mortality in the subpopulation with HF

Table 3 Hazard ratios and posterior median rank with 95% CrI for cardiovascular mortality in the subpopulation with diabetes and HF, relative to placebo.

Class	Treatment	Previous analysis		New analysis	
		Hazard ratio median (95%CrI)	Rank Median (95% CrI)	Hazard ratio median (95%CrI)	Rank Median (95% CrI)
DPP-4i	Alogliptin	0.77 (0.54, 1.09)	2 (1, 6)	0.77 (0.55, 1.11)	3 (1, 7)
	Linagliptin	0.96 (0.76, 1.26)	4 (2, 7)	0.96 (0.72, 1.27)	5 (2, 8)
	Vildagliptin	1.80 (0.54, 7.15)	7 (1, 7)	1.76 (0.52, 6.77)	8 (2, 8)
GLP-1RA	Liraglutide	0.85 (0.63, 1.15)	3 (1, 6)	0.85 (0.62, 1.16)	4 (2, 7)
	Semaglutide (Subcutaneous)	**NA**	**NA**	**0.25 (0.02, 1.62)**	**1 (1, 8)**

SGLT2	Canagliflozin	0.72 (0.51, 1.02)	2 (1, 5)	0.72 (0.51, 1.02)	2 (1, 6)
	Dapagliflozin	1.01 (0.73, 1.39)	5 (2, 7)	1.01 (0.73, 1.38)	6 (2, 8)

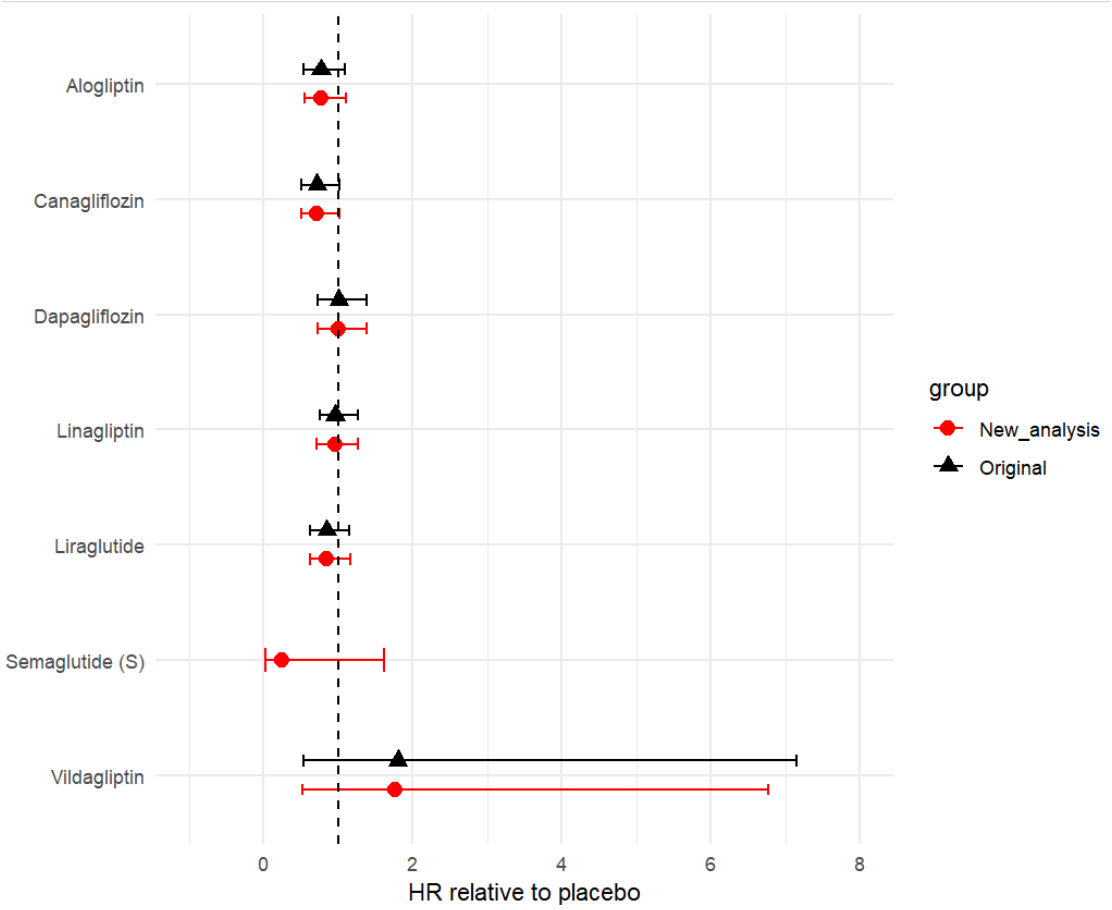

Figure 4 Hazard ratio for cardiovascular mortality, relative to placebo with T2D and HF.

Table 4 Model fit statistics for network meta-analysis (NMA) models of change in cardiovascular mortality in the subpopulation with diabetes and HF. [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	9	9	9	18	-
	Random	9	8.9	8.9	17.7	0.84 (0.04 – 3.32)

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

Phillippo DM (2024). multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data. doi:10.5281/zenodo.3904454 <https://doi.org/10.5281/zenodo.3904454>, R package version 0.7.2, https://dmphillippo.github.io/multinma/

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)
```