MULTIVARIATE NETWORK META-ANALYSIS: AN EXAMPLE IN TYPE 2 DIABETES FOR THE ANALYSIS OF GLYCAEMIC CONTROL

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Introduction & Objectives

• Network meta-analyses are commonly conducted within a Bayesian framework to enable the ranking of interventions, based on the probability of each treatment to be associated with the best efficacy.
• Multivariate models have been developed to deal with correlation between outcomes as they allow to account for the within-study correlation between endpoints.
• Moreover, the multivariate models allow to use data from studies reporting only one outcome to inform the analysis of other outcomes based on correlations observed in studies reporting several. This is an important advantage as some publications may report an endpoint but not the other.
• The objective of this study was to conduct a Bayesian multivariate network meta-analysis (NMA) to take into account the correlation between three outcome measures assessing glycaemic control for the monotherapy treatments of type 2 diabetes mellitus (T2DM).

Methods

• A systematic literature review was conducted to identify relevant randomised clinical trials [1].
• The efficacy of T2DM treatments on glycaemic control was assessed using the change in HbA1c from baseline, the change in fasting plasma glucose (FPG) from baseline and the proportion of patients reaching HbA1c < 7%.
• A Bayesian multivariate NMA [2] accounting for the correlation between these outcomes was conducted to model these three glycaemic control outcomes simultaneously and results were compared to the estimates from the three univariate NMAs.
• This multivariate NMA was divided in two stages: the first stage in which the within-study and between-study correlations were estimated using information from the outcomes and studies (Pearson correlation coefficients estimated based on aggregate data [3]). In the second stage the effect estimates of each outcome were predicted using the assumption that treatment effects are exchangeable between outcomes [2].
• Relative efficacy was evaluated based on differences between treatments (A) or odds-ratios (OR) and corresponding credible intervals [4].
• Vague prior distributions were used to produce results driven by the data.
• The analysis of between-study correlation was conducted with SAS 9.4® and the Bayesian multivariate NMA with Winbugs 1.4.
• For the methodological purpose of this analysis, it was decided to focus on results for dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin and vildagliptin) and sulphonylureas (glibenclamide, gliclizide, glipizide and glibizide) versus placebo.

Results

• The systematic literature review resulted in the identification of 40 trials that were suitable for inclusion in the analysis at 26 weeks (44 weeks, Figure 1). All of them reported results in terms of HbA1c change from baseline, 36 trials reported results for FPG and 22 for the proportion of patients reaching HbA1c < 7%.

Figure 1. Network of evidence

Results (continued)

• Results for the multivariate NMA and the three univariate NMAs are reported in Figure 2 to Figure 4 for the 3 glycaemic control endpoints for DPP-4 inhibitors and sulphonylureas versus placebo.
• Results for the analysis of glycaemic control from the multivariate NMA were overall consistent with the three univariate NMAs and point estimates were comparable.
• There was no data available for the proportion of patients reaching HbA1c < 7% for sulphonylureas in the publications assessing these treatments therefore the univariate NMA could not assess these treatments for this endpoint. The multivariate NMA estimated the proportion of patients reaching HbA1c < 7% for sulphonylureas even though no data were published for this outcome.
• For the analysis of the change in FPG the credible intervals were narrower in the multivariate NMA and for the mean change in HbA1c, the 95% credible intervals were of similar range. For the analysis of the proportion of patients reaching HbA1c < 7% the results for the sulphonylureas were associated with broad intervals as they were obtained through the multivariate NMA using results from the other outcomes.

Discussion

• One of the main limitation of this multivariate NMA was the estimation of the correlation between the outcomes. Ideally the correlation between outcomes would be estimated based on the patient level data. However, in the context of NMA, patients level data are rarely available, therefore the correlation has to be assessed based on aggregate data from publication reporting several outcomes of interest.

Conclusions

• This multivariate network meta-analysis of treatments in T2DM provided more precise estimates than separate univariate NMAs on glycaemic control. It enabled estimations of treatment effect for all comparators on all endpoints of interest including the ones for which data were not directly available.

REFERENCES