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A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2 diabetes mellitus

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ABSTRACT

Objectives: To develop a longitudinal statistical model to indirectly estimate the comparative efficacies of two drugs, using model-based meta-analysis (MBMA). Comparison of two oral dipeptidyl peptidase (DPP)-4 inhibitors, sitagliptin and linagliptin, for type 2 diabetes mellitus (T2DM) treatment was used as an example.

Design: Systematic review with MBMA.

Data sources: MEDLINE, EMBASE, http://www.ClinicalTrials.gov, Cochrane review of DPP-4 inhibitors for T2DM, sitagliptin trials on Food and Drug Administration website to December 2011 and linagliptin data from the manufacturer.

Eligibility criteria for selecting studies: Double-blind, randomised controlled clinical trials, ≥12 weeks' duration, that analysed sitagliptin or linagliptin efficacies as changes in glycated haemoglobin (HbA1c) levels, in adults with T2DM and HbA1c >7%, irrespective of background medication.

Model development and application: A Bayesian model was fitted (Markov Chain Monte Carlo method). The final model described HbA1c levels as function of time, dose, baseline HbA1c, washout status/duration and ethnicity. Other covariates showed no major impact on model parameters and were not included. For the indirect comparison, a population of 1000 patients was simulated from the model with a racial composition reflecting the average racial distribution of the linagliptin trials, and baseline HbA1c of 8%.

Results: The model was developed using longitudinal data from 11 234 patients (10 linagliptin, 15 sitagliptin trials), and assessed by internal evaluation techniques, demonstrating that the model adequately described the observations. Simulations showed both linagliptin 5 mg and sitagliptin 100 mg reduced HbA1c by 0.81% (placebo-adjusted) at week 24. Credible intervals for participants without washout were −0.88 to −0.75 (linagliptin) and −0.89 to −0.73 (sitagliptin), and for those with washout, −0.91 to −0.76 (linagliptin) and −0.91 to −0.75 (sitagliptin).

Conclusions: This study demonstrates the use of longitudinal MBMA in the field of diabetes treatment. Based on an example evaluating HbA1c reduction with linagliptin versus sitagliptin, the model used seems a valid approach for indirect drug comparisons.

ARTICLE SUMMARY

Article focus

- In the absence of evidence from head-to-head trials, indirect and mixed treatment comparisons can be used for drug comparisons.
- The aim of this study was to develop an approach, using Bayesian methodology (Markov Chain Monte Carlo method) to indirectly estimate the comparative efficacy of two compounds, incorporating longitudinal dose–response data.

Key messages

- A longitudinal statistical model was developed for the indirect comparison of two pharmaceutical compounds (oral DPP-4 inhibitors linagliptin and sitagliptin), with respect to changes in glycated haemoglobin (HbA1c) levels in patients with type 2 diabetes mellitus (T2DM).
- The model was evaluated by comparing model predictions with observed values.
- The model demonstrated that both linagliptin and sitagliptin reduced HbA1c levels by 0.8% (placebo-adjusted) when administered to patients with T2DM for 24 weeks, irrespective of background medication.

INTRODUCTION

Ideally, head-to-head, randomised controlled trials should be conducted to estimate the

ARTICLE SUMMARY

Strengths and limitations of this study

- This study represents a novel use of longitudinal model-based meta-analysis in the field of diabetes treatment, being the only instance to date that adequately accounts for longitudinal correlations in each treatment arm, which is a prerequisite to the correct characterisation of uncertainty in estimation of drug effects.
- When relevant head-to-head comparisons are not available, the model described in this study could have an important role in treatment decision-making.
- Although the analysis included a large sample of 11 234 patients with T2DM, its applicability to the general population of patients with T2DM might be limited by the relatively selected patient populations in the included trials. Additionally, while our analysis adjusts for key differences in study designs, there remains the possibility of bias attributable to covariate effects that could not be estimated with the available data.

comparative efficacy of different treatments. However, it is not always feasible to conduct direct comparisons among all available treatment options. Network meta-analysis (mixed treatment comparisons) has been used to estimate relative efficacy when there are no direct comparative data, to provide the best available evidence to facilitate decision-making by physicians and other stakeholders, such as payers. However, these approaches have certain limitations, including the risk of bias arising from inherent differences in the designs of the included studies, and the difficulties of finding appropriate summary statistics to compare the findings of individual trials.[1 2] In particular, endpoint-based approaches cannot be sensibly applied when the studies involved in the review vary substantially with respect to treatment duration.

An approach, recently described as model-based meta-analysis (MBMA), has been developed and used to estimate the comparative efficacy of two medications. MBMA can be used to provide a mechanism for integrating information from heterogeneously designed trials and thus to evaluate outcomes with different drugs that have not been compared directly.[3] MBMA is distinguished from the methodology of conventional meta-analysis by the manner in which it incorporates longitudinal and/or dose–response data. By modelling the response as a parametric function of time, MBMA allows the integration of information from trials of different durations and with different sampling time-points. This enables the use of less restrictive inclusion/exclusion criteria for study selection, and more efficient use of data from the studies that are selected, thereby resulting in a particularly comprehensive summary of all relevant data.[3]

In response to the growing worldwide epidemic of diabetes mellitus, new antihyperglycaemic agents are continuously being developed. The dipeptidyl peptidase (DPP)-4 inhibitors are a relatively new class of oral antihyperglycaemic drugs developed for the treatment of type 2 diabetes mellitus (T2DM) that are increasingly being used in clinical practice because of their clinically meaningful efficacy, promising tolerability, safety and convenience—in particular, a virtually absent risk of hypoglycaemia or weight gain.[4] Although several DPP-4 inhibitors are already available in many countries, to date, only one published trial has been conducted to directly compare individual drugs within this class.[5] Therefore, further research is needed to understand the comparative effects of the drugs within this class.

The model developed in this study incorporates Bayesian methodology and aims to provide a valid approach to estimate the comparative efficacy of different compounds. Bayesian approaches are acknowledged by the Cochrane collaboration to have a role in meta-analysis, particularly in the setting of indirect comparison.[1]

This approach to drug comparison employs a mathematical model to describe the timecourse of glycated haemoglobin (HbA1c) levels, and is being increasingly used to characterise longitudinal data. The general meta-analytic methodology of Ahn and French[3] has previously been used to successfully describe longitudinal metadata from clinical trials in Alzheimer's disease,[6 7] rheumatoid arthritis,[8] lipid disorders,[9] glaucoma[10] and chronic obstructive pulmonary disease.[11] Similar approaches have been used to perform dose–response meta-analyses in a range of therapeutic areas, including migraine,[12] postoperative anticoagulant therapy[13] and rheumatoid arthritis.[14] This analytical approach has also been used in the field of diabetes in a recent study by Gibbs *et al*,[15] which evaluated the relationship between DPP-4 inhibition and HbA1c reduction using data obtained from clinical trials of four drugs in this class.

Objective

To use an MBMA approach to develop a longitudinal statistical model for the comparison of the efficacy of two oral DPP-4 inhibitors, shown by changes in HbA1c levels, in patients with T2DM who had started treatment with one of two DPP-4 inhibitors, regardless of background medication. The two drugs evaluated were linagliptin, which has recently been approved for clinical use in several jurisdictions, and sitagliptin, the most commonly used DPP-4 inhibitor.

METHODS

Data sources

Sitagliptin studies were identified from a systematic search in MEDLINE, EMBASE, studies listed on http://www.ClinicalTrials.gov that included a reference to publication, the latest-date Cochrane review of DPP-4 inhibitors for T2DM[16] and details of sitagliptin trials on the Food and Drug Administration website, to December 2011.[17] Details of the search strategy used are provided in the appendix (see online supplementary table S1).

Results of the relevant studies for linagliptin were obtained from the manufacturer's database, several of

which have been subsequently published as full papers[18–21] or abstracts.[22–24]

Study selection

Included studies were double-blind, randomised controlled trials of ≥12 weeks' duration that analysed the efficacy of sitagliptin or linagliptin in the reduction of HbA1c levels in adults with T2DM and HbA1c >7%, irrespective of background medication. Excluded studies were: open-label studies (and data from open-label extensions to double-blind studies) and extension studies that used patient response in the initial study to determine eligibility in the extension phase of the study (eg, if the extension phase included only those who did not require rescue medication during the initial study). Other excluded study types were special population studies (eg, studies in patients with declining renal function) and phase IV studies or study arms in which patients were randomly assigned to initial combination therapies.

Two independent reviewers extracted aggregated data from all selected studies, according to treatment arm (sitagliptin, linagliptin or placebo). We extracted data on: the first author's name, year of publication of the trial, comparator, dose(s) of sitagliptin or linagliptin evaluated, trial duration, number of participants and their gender, ethnicity, duration of T2DM, mean age, baseline HbA1c (%), HbA1c at evaluated time-points, baseline body mass index (BMI, kg/m^2), fraction of patients on previous antihyperglycaemic therapy, and the presence and duration of washout and concomitant medication. A common data template was defined. The main outcome of interest was HbA1c, the primary endpoint of all included studies. Intention-to-treat populations were included whenever possible and group means, as reported, were used or were calculated, using the last observation carried forward approach. The analyses were conducted using the maximum licensed dose of sitagliptin (100 mg) and the licensed dose of linagliptin (5 mg). However, when data at other dose levels were available, they were included in the analysis, and appropriate adjustments were made via the dose–response terms in the model.

Data selection process

For the linagliptin studies, the dataset was built from the original Boehringer Ingelheim database using SAS scripting. The quality of the dataset was assured by an independent script review. For the sitagliptin studies, the dataset was built manually by collecting information given in the different source publications. If the results were available as numbers in the publications, these numbers were included in the dataset. Where the results were only available as graphics, the corresponding data were collected using GetData Graph Digitilizer, V.2.24 software (http://www.getdata-graph-digitizer.com). The quality of the manually built sitagliptin dataset was assured by an independent second reviewer. The initial dataset consisted of HbA1c data, presented as either the change from baseline and/or the actual HbA1c measurements, depending on the information provided in the publication. R scripting (R V.2.10.1, The R Foundation for Statistical Computing, Vienna, Austria) was then used to obtain an analysis-ready dataset with consistent encoding of information (eg, baseline values were added to changes from baseline in order to obtain actual HbA1c measurements for all records).[25]

Statistical analysis

Model development

The statistical models that were considered represent a particular class of non-linear mixed-effects models in which model precision terms are scaled according to sample sizes. Sample size adjustments are carried out in a manner that approximately estimates and adjusts for longitudinal correlations, following an approach described elsewhere.[3]

Initial exploratory data analyses were used to derive a suitable parametric (algebraic) description of the average HbA1c trends as a function of time, dose, washout status/duration and ethnic origin. Qualitative prior information was also used to guide the initial selection of parametric forms. The following assumptions were made: (1) given the known properties of measured HbA1c, it was assumed that in the absence of additional interventions, HbA1c levels for patients washing out prior antidiabetes medication (during the study washout/run-in phase) would rise for some time until achieving a plateau, and (2) the incremental (placebo-adjusted) effect of DPP-4 inhibitors on HbA1c was expected to approach a plateau during the time frame of interest (24 weeks). Bayesian prior distributions for parameters describing the magnitude and onset of drug effects were specified separately and independently for linagliptin and sitagliptin. Magnitudes of drug effect were parameterised as fractional reductions from baseline and were assigned uniform prior distributions between zero and one, implying that both drugs have some beneficial effects (a defensible assumption for marketed drugs) and that neither can reduce HbA1c levels below zero (patently true), and assigning equal likelihood to all possibilities between these two extremes.

The model was fitted using Bayesian Markov Chain Monte Carlo methodology. The computations were carried out using OpenBUGS V.3.2.1 (2010) software (Free Software Foundation, Boston, Massachusetts, USA). Final inferences were based on 1000 approximately independent draws from the posterior (after discarding burn-in samples and thinning to de-correlate samples[26]). The model was adjusted for baseline HbA1c and washout status/duration. Other covariates considered were: standard covariates including demographics, such as ethnicity, age, BMI and gender, antihyperglycaemic background medication, duration of T2DM and the fraction of patients who underwent washout of previous antihyperglycaemic therapy. The OpenBUGS code is available from the authors on request.

Model selection and evaluation

Following a 'full model estimation approach',[27 28] initial preference was given to a full model, meaning one that includes all terms of potential interest. In order to achieve stable parameter estimation, selective simplifications were applied, guided by exploratory data analysis, to the full model until we obtained satisfactory convergence diagnostics. Covariates were excluded from the model for the purpose of achieving stable parameter estimation; however, each excluded covariate was evaluated graphically to ensure that it was not associated with model residuals (differences between the observed values and those predicted by the model). A graphic representation of the final model, for patients with or without a prerandomisation washout period, is shown in figure 1A,B.

The final model was evaluated using posterior predictive check methodology[26] in order to assess whether the observed data were consistent with the range of expectation implied by the model. This model inherently adjusted for baseline HbA1c and washout status/duration. The other covariates (see previous page), with the exception of ethnicity, showed no major impact on the model parameters and were therefore not included in the final model. Further details of the mathematical and statistical specifications of the final model are presented in the online supplementary technical appendix.

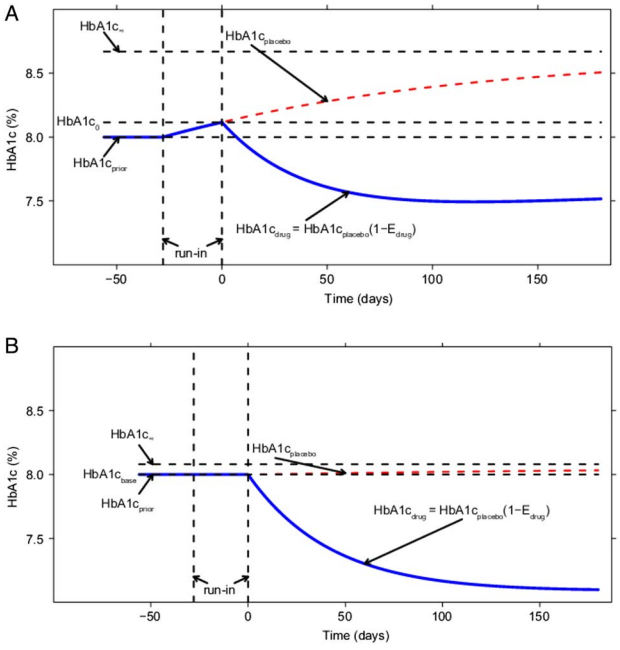

Figure 1 (A) Graphic representation of the components of the final model, for study arms that included patients washing out their prior antihyperglycaemic medication in the run-in period. (B) Graphic representation of the components of the final model, for study arms that included patients who were treatment-naïve or had completely washed out their prior antihyperglycaemic medication before enrolment.

Model summary and inference

Since the mean predicted values are not directly available as model parameters, these were estimated by taking averages of values that were simulated from the fitted model. In the same way that variances can be appropriately scaled according to sample size during model fitting, variances were scaled during simulation to simulate trial arms of different sizes. This included scaling simulation variances to correspond to n=1, which we conceptualised as the simulation of an individual patient.

In order to assess the efficacy of the two DPP-4 inhibitors in comparable patients under similar conditions, a population of 1000 patients was simulated from the model under reference conditions and the average HbA1c level was computed at each time-point for this simulated population. Data for each patient were simulated as if arising from an individual trial, so that the resulting inference represents an average over the expected range of intertrial variation. The simulation of this population average was then repeated for each of the 1000 different parameter configurations represented in the posterior sample (the entire posterior simulation therefore involved a total of 10^6 simulated patients), resulting in inferences that reflect posterior parameter uncertainty as well as intertrial and interpatient variation. The reference racial composition for this simulated population was 61.5% White, 1.5% Black and 37% Asian, reflecting the average enrolled distribution in linagliptin trials. The median simulated baseline HbA1c (%) in this population was 8 Results are expressed as mean differences, with 95% credible intervals (the Bayesian equivalent of CIs).

RESULTS

A total of 31 sitagliptin studies were assessed for eligibility for inclusion in the analysis, and 16 were excluded on the basis of the study design that did not meet our inclusion criteria (see online supplementary table S2). A further 10 linagliptin studies were included.

The included studies were between 12 and 26 weeks' duration, with one exception (the study by Seck *et al*[29] lasted 104 weeks; table 1).

Data from a total of 11 234 participants were included in the analysis, arising from 25 randomised trials (10 linagliptin and 15 sitagliptin). The mean age at baseline of all study participants was 56.5 years, with reported means for treatment arms of the included studies ranging from 50.9 to 62 years; the proportion of women across all study participants was 45.5%, with reported proportions for study groups ranging from 22.8% to 64%; and the mean BMI was 29.7 kg/m^2, with reported means for treatment arms ranging from 24.1 to 32.7 kg/m^2. Mean baseline HbA1c was 8%, with reported means for treatment arms ranging from 7.49% to 8.87%. The most commonly used background medication was metformin monotherapy. Metformin was also used in combination with glimepiride or pioglitazone, and one study[40] included patients receiving initial monotherapy with pioglitazone.

Table 1 Summary of design and demographics of studies in the analysis dataset

Study	Drug	Dose (mg/day)	Treatment duration (weeks)	Patients (n)	Baseline age (years)	Female (%)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Washout duration (weeks)	Concomitant medications
Aschner *et al*[30]	Placebo	NA	24	244	54.3	48.6	8.03	30.8	14	NA
	Sitagliptin	100	24	229	53.4	42.9	8.01	30.3	14	NA
		200	24	238	54.9	53.2	8.08	30.3	14	NA
Bergenstal *et al*[31]	Sitagliptin	100	26	166	52.0	48.0	8.50	32.0	0	Metformin
Charbonnel *et al*[32]	Placebo	NA	24	224	54.7	40.5	8.03	31.5	18	Metformin
	Sitagliptin	100	24	453	54.4	44.2	7.96	30.9	18	Metformin
Goldstein *et al*[33]	Placebo	NA	24	165	53.3	47.2	8.68	32.5	14	NA
	Sitagliptin	100	24	175	53.6	48.0	8.87	31.2	14	NA
Hanefeld *et al*[34]	Placebo	NA	12	107	55.9	36.9	7.59	31.4	8	NA
	Sitagliptin	25	12	107	55.1	48.6	7.71	31.9	8	NA
		50	12	107	55.3	54.5	7.60	31.6	8	NA
		50	12	108	55.2	55.9	7.79	32.7	8	NA
		100	12	106	56	44.5	7.78	31.6	8	NA
Hermansen *et al*[35]	Placebo	NA	24	106	55.2	45.3	8.43	30.7	16	Glimepiride
	Sitagliptin	100	24	106	54.4	47.2	8.42	31.0	16	Glimepiride
	Placebo	NA	24	113	57.7	47.8	8.26	30.7	16	Glimepiride +metformin
	Sitagliptin	100	24	116	56.6	47.4	8.27	31.3	16	Glimepiride +metformin
Iwamoto *et al*[36]	Placebo	NA	12	73	60.2	31.5	7.74	24.1	8	NA
	Sitagliptin	25	12	80	59.9	36.3	7.49	25.0	8	NA
		50	12	72	60.2	34.7	7.57	24.5	8	NA
		100	12	70	58.3	48.6	7.56	24.2	8	NA
		200	12	68	60.6	41.2	7.65	24.4	8	NA
Mohan *et al*[37]	Placebo	NA	18	169	50.9	40.0	8.70	24.9	8	NA
	Sitagliptin	100	18	339	50.9	43.0	8.70	25.1	8	NA
Nonaka *et al*[38]	Placebo	NA	12	75	55.0	34.0	7.69	25.1	8	NA
	Sitagliptin	10	12	75	55.6	40.0	7.54	25.2	8	NA
Raz *et al*[39]	Placebo	NA	18	103	55.5	37.3	8.05	32.5	14	NA
	Sitagliptin	100	18	193	54.5	46.3	8.04	31.8	14	NA
		200	18	199	55.4	49.5	8.14	32.0	14	NA
Rosenstock *et al*[40]	Placebo	NA	24	174	56.9	46.9	8.00	31.0	18	Pioglitazone
	Sitagliptin	100	24	163	55.6	42.1	8.05	32.0	18	Pioglitazone
Scheen *et al*[5]	Saxagliptin	5	18	334	58.8	52.9	7.68	31.1	0	
	Sitagliptin	100	18	343	58.1	49.2	7.69	30.9	0	Metformin
Seck *et al*[29]	Sitagliptin	100	104	576	56.8	42.9	7.69	31.2	0	Metformin
Scott *et al*[41]	Placebo	NA	12	121	55.3	37.6	7.88	31.6	10	Metformin
	Sitagliptin	10	12	122	55.1	50.4	7.89	30.8	8	NA
		25	12	122	56.2	52	7.85	30.5	8	NA
		50	12	120	55.6	42.3	7.89	31.4	8	NA

Continued

Table 1 Continued

Study	Drug	Dose (mg/day)	Treatment duration (weeks)	Patients (n)	Baseline age (years)	Female (%)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Washout duration (weeks)	Concomitant medications
		100	12	121	55.1	47.6	7.96	30.4	8	NA
Scott *et al* [42]	Placebo	NA	18	88	55.3	41.0	7.68	30.0	8	NA
	Sitagliptin	100	18	91	55.2	45.0	7.75	30.3	0	NA
Boehringer Ingelheim	Placebo	NA	12	63	59.0	49.2	8.27	30.9	0	NA
Study 1218.5[43]	Linagliptin	0.5	12	57	58.0	22.8	8.24	31.0	6	NA
		2.5	12	55	60.0	52.7	8.38	31.5	6	NA
		5	12	54	56.0	42.6	8.38	31.2	6	NA
Forst *et al* [19]	Placebo	NA	12	70	60.0	38.6	8.37	32.2	6	NA
	Linagliptin	1	12	64	59.0	43.8	8.24	32.2	6	Metformin
		5	12	62	60.0	46.8	8.46	31.6	6	Metformin
		10	12	66	62.0	47.0	8.35	31.7	6	Metformin
Del Prato *et al* [18]	Placebo	NA	24	163	55.0	54.0	8.00	29.2	6	Metformin
	Linagliptin	5	24	333	56.0	51.4	8.00	29.0	6	NA
Taskinen *et al* [21]	Placebo	NA	24	175	57.0	42.3	8.02	30.1	6	NA
	Linagliptin	5	24	513	57.0	46.8	8.09	29.8	6	Metformin
Owens *et al* [20]	Placebo	NA	24	262	58.0	53.2	8.14	28.2	6	Metformin
	Linagliptin	5	24	778	58.0	51.5	8.15	28.4	0	Metformin+SU
Gallwitz *et al*[22]	Linagliptin	5	52	776	60.0	40.7	7.69	30.2	0	Metformin+SU
Araki *et al*[44]	Placebo	NA	12	80	60.0	28.6	7.95	24.3	8	Metformin
	Linagliptin	5	12	159	60.0	30.2	8.07	24.6	4	NA
		10	12	160	61.0	30.0	7.98	25.0	4	NA
Lewin *et al*[45]	Placebo	NA	18	82	56.0	39.0	8.60	28.1	4	NA
	Linagliptin	5	18	158	57.0	52.5	8.61	28.3	6	SU
Patel *et al*[23]	Placebo	NA	18	73	56.0	57.5	8.06	30.0	6	SU
	Linagliptin	5	18	147	57.0	64.0	8.11	29.0	6	NA
Rafeiro *et al*[24]	Placebo	NA	12	43	59.0	51.2	7.92	28.6	6	NA
	Linagliptin	5	12	435	58.0	42.3	7.97	29.7	6	Metformin

BMI, body mass index; HbA1c, glycated haemoglobin; NA, not applicable; SU, sulfonylurea.

Figure 2A,B depict the application of the statistical model to each individual study, demonstrating that the observed data from the studies fall mostly within the 90% prediction interval (between 5% and 95% prediction bounds), with no overall systematic overprediction or underprediction. Both change from baseline and placebo-corrected change from baseline HbA1c percentage points are presented to demonstrate longitudinal model performance for each therapy. Similarly, figure 3A–D show the 90% credible intervals at the endpoint for the linagliptin and sitagliptin change from baseline and placebo-corrected change from baseline, demonstrating accurate prediction of the effect, on average.

The simulations performed using the model show that both linagliptin 5 mg and sitagliptin 100 mg reduce HbA1c levels by 0.81% (placebo-adjusted), at week 24, when administered to patients with T2DM for 24 weeks (figure 4A,B). Credible intervals for participants without washout were −0.88 to −0.75 (linagliptin) and −0.89 to −0.73 (sitagliptin). For those who underwent washout of previous antihyperglycaemic therapy, the credible intervals were −0.91 to −0.76 (linagliptin) and −0.91 to −0.75 (sitagliptin). Figure 5 shows simulated differences in the true effect at 24 weeks between linagliptin 5 mg and sitagliptin 100 mg with no washout, demonstrating that the model predicted difference lies almost entirely within 0.2 percentage points, less than the previously suggested margins for non-inferiority of 0.3–0.4 percentage points.[46 47]

As a post hoc assessment, a t test was used to compare the HbA1c difference from placebo residuals (unexplained variations after fitting of the model) for linagliptin and sitagliptin. A p value of 0.14 was generated, suggesting no evidence of a systematic bias in favour of linagliptin by conventional thresholds ($p<0.05$).

DISCUSSION

The model developed in this study incorporates Bayesian methodology and provides a tangible approach to indirectly estimating the comparative efficacy of two compounds. The findings presented suggest that the model developed in this study provides a valid alternative approach to indirect drug comparisons. The findings of this MBMA show that linagliptin is as effective as sitagliptin in the reduction of HbA1c levels, both showing a mean, placebo-adjusted reduction of approximately 0.81% after 24-weeks' treatment of patients with T2DM. In this study, evidence was gathered from the results of randomised, double-blind trials of sitagliptin and linagliptin. The sensitivity analyses performed in this study, using various prior distributions, support the robustness of the model. Although the use of MBMA is relatively new in the field of diabetes therapy, this method is nonetheless being increasingly recognised as an important tool in the evaluation of pharmaceutical therapies.[48 49]

There might be some limitations in applying the findings of the present analysis to the general population of patients with T2DM because of the relatively selected patient populations in the included trials, which included mostly white, middle-aged patients with mean baseline HbA1c <9%. The participants in the analysed trials would have been further restricted during pretrial run-in periods, which would exclude those with poor treatment adherence. Furthermore, the analysis was performed

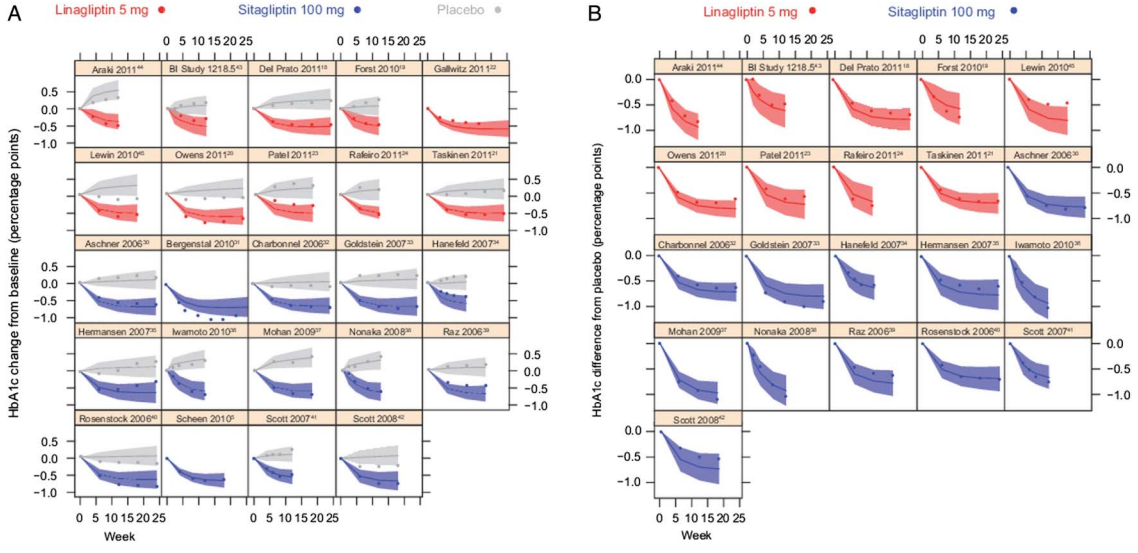

Figure 2 Drug effects (as glycated haemoglobin (HbA1c) percentage points) of the studies with relevant treatment arms (ie, studies with linagliptin 5 mg, or sitagliptin 100 mg and placebo arms) over time: (A) comparison of observed and predicted HbA1c change from baseline and (B) difference from placebo. For visual clarity, Hermansen *et al*[35] represented only for the arms that excluded metformin background; both sets of arms are shown in figure 3. The study by Seck *et al*[29] is omitted from figure 2A because of long treatment duration. Filled dots represent observed data, the shaded regions show the unconditional 90% prediction intervals, and the central line represents the median prediction.

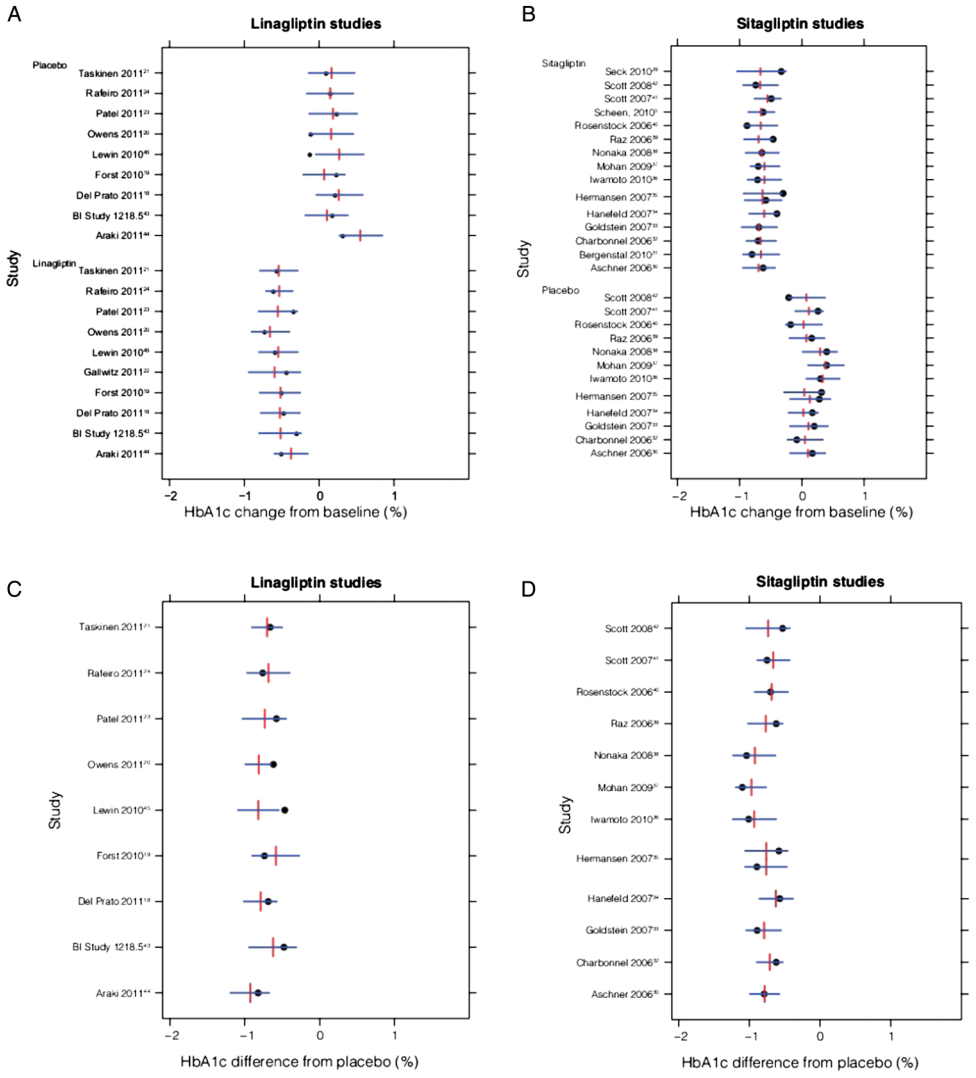

Figure 3 Drug effects (as glycated haemoglobin (HbA1c) percentage points) of the relevant studies at their respective endpoints. Filled dots represent observed data; horizontal lines show the 90% unconditional prediction intervals and also represent the median predicted value. (A) Linagliptin change from baseline. (B) Sitagliptin change from baseline. (C) Linagliptin difference from placebo. (D) Sitagliptin difference from placebo.

retrospectively, using data from different trials. As with all meta-analyses based on published data, there is a potential for publication bias. In the context of the present analysis, this potential bias pertains only to our estimates of the effects of sitagliptin, as our linagliptin data sources were not subject to publication selection. However, this is unlikely to have a substantial impact on the findings for sitagliptin, as current practice in clinical research mandates that all clinical trials are published regardless of their results and several sources were searched, including trial registries and documents used in the regulatory process.

The model includes the assumption that HbA1c levels are maintained after the full effect of treatment has been reached. This is based on observations in previous 24-week trials, where HbA1c levels have been shown to be maintained for this period,[19–21 50] and the known pharmacological properties of DPP-4 inhibitors.[4 51 52] The final model was adjusted for baseline HbA1c, ethnic origin and washout duration. Other covariates (concurrent medications, fraction of patients on previous oral antidiabetic drugs, BMI, age, gender, duration of T2DM) were not included in the final model because they did not show significant impact on the model parameters. Reasons for this might be either that only mean covariate values were available, or that some covariates are confounded (eg, BMI was shown to vary as a function of ethnic origin, making it difficult to isolate the independent effects of these covariates). It is important to recognise that these covariates might be of clinical importance, and their exclusion from the model could simply reflect an inability to reliably estimate the independent effect of these factors with the data available.

To date, four standard meta-analyses of the DPP-4 inhibitor class have been published, none of which has provided any results on the comparative efficacies of linagliptin and sitagliptin.[16 53–55] These analyses confirm

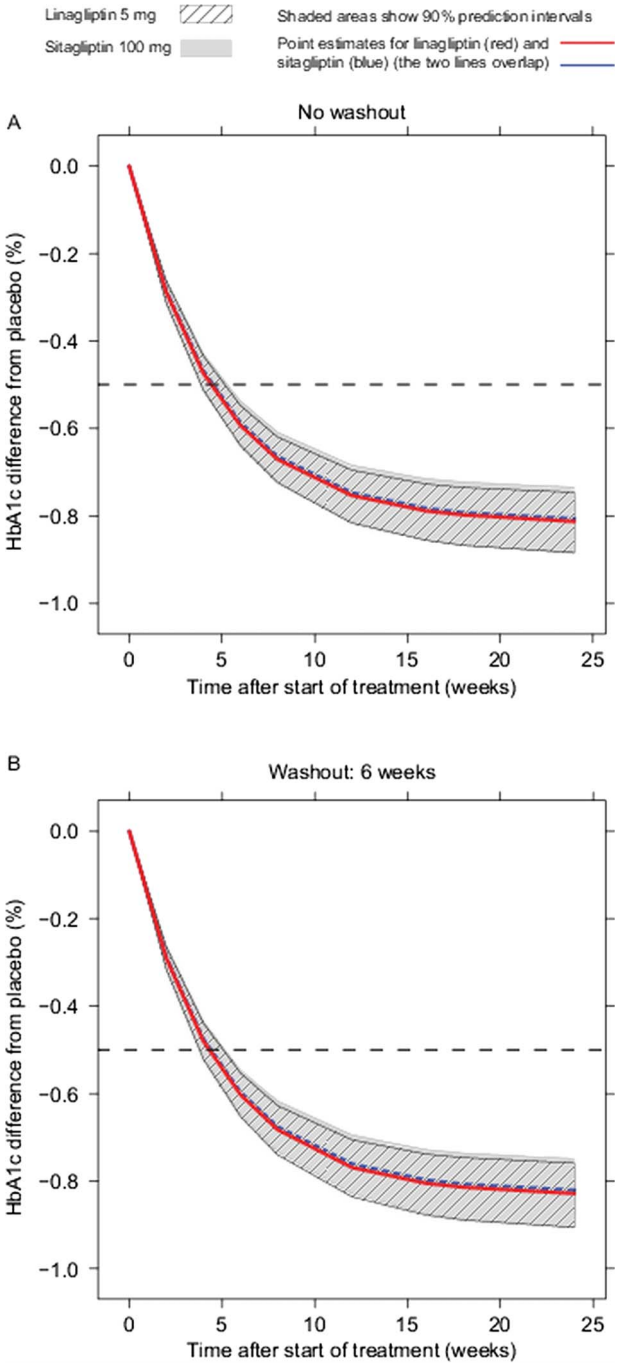

Figure 4 (A) Estimated drug effects on glycated haemoglobin (HbA1c) for reference population, with no pretreatment washout, over 24 weeks (difference from placebo). (B) Estimated drug effects on HbA1c for reference population, with 4-week washout plus 2-week placebo run-in period, over 24 weeks (difference from placebo). Reference population of 1000 participants, baseline HbA1c: 8%, racial composition: 61.5% White, 1.5% Black, 37% Asian.

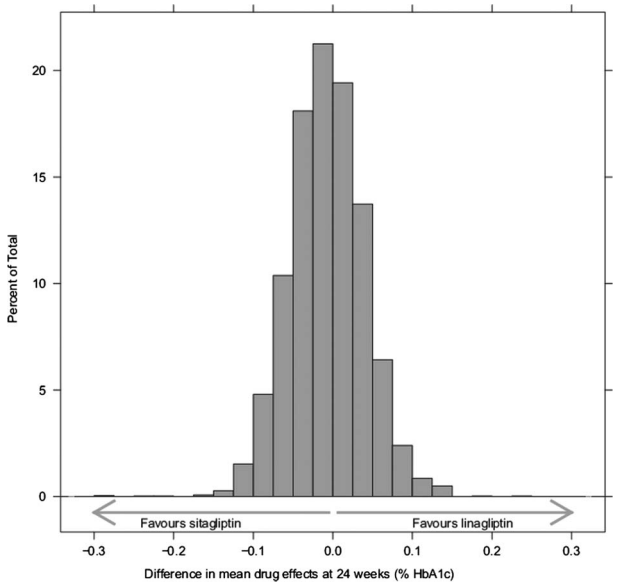

Figure 5 Posterior distribution for the difference in effect estimates between linaglitpin (5 mg) and sitagliptin (100 mg) at 24 weeks. Reference population of 1000 participants (therefore involving 10^6 simulated patients), baseline glycated haemoglobin (HbA1c): 8%, racial composition: 61.5% White, 1.5% Black, 37% Asian.

the efficacy of DPP-4 inhibitors, in terms of HbA1c reduction, and their tolerability, in particular resulting from the absence of weight gain and low risk of hypoglycaemia associated with monotherapy. The findings also indicate that therapy with DPP-4 inhibitors reduces HbA1c reductions to a similar extent to comparator drugs.[53] Several of the limitations associated with traditional meta-analysis arise from the fact that only study end-point data are used in these analyses. For example, difficulties in selecting an appropriate summary statistic are often encountered because the treatment effect of interest varies as a function of the duration of treatment. Similarly, it might be difficult to appropriately adjust for the effect of covariates on treatment response when response is assessed at different time-points in different studies. To address the limitations of traditional meta-analysis, a general methodology has recently been proposed for the statistically valid use of MBMA.[3] The advantage of this approach, also used in the present study, is that it enabled the synthesis of longitudinal data from multiple studies with different durations and different sampling schedules, resulting in analyses that are both more comprehensive (including a greater number of studies) and more efficient (incorporating more of the relevant data within each study) than previous methods. The unique MBMA approach in the current study also allows adjustment for covariates (eg, differences in the use of washout or racial composition in individual trials) to allow comparison of treatment response in comparable patients under similar conditions. One limitation of the study by Gibbs *et al*[15] was that the MBMA used did not account for correlations across time points within treatment arms, which could lead to an overestimation of the intertrial variability in drug effect. In contrast, our approach takes account of longitudinal correlations, in accordance with previously published methods,[3] which is a prerequisite to the correct characterisation of uncertainty in the estimation of drug effects.

As the clinical use of DPP-4 inhibitors increases, patients, prescribers and payers will require information on the relative benefits of the individual drugs within this class. Based on the model developed in this study, it is apparent that the efficacy of the two DPP-4 inhibitors, sitagliptin and linagliptin, is virtually indistinguishable, in terms of changes in mean HbA1c levels, in patients with T2DM treated with a range of background antihyperglycaemic therapies. Both linagliptin and sitagliptin act by inhibiting the DPP-4 enzyme that rapidly inactivates the intestinal hormone, glucagon-like peptide (GLP)-1. GLP-1 stimulates insulin secretion in a glucose-dependent manner. Sitagliptin is largely excreted via the kidneys, with the major portion of the oral dose (87%) being excreted in the urine.[56] Unlike sitagliptin and other DPP-4 inhibitors, linagliptin has a largely non-renal route of excretion (only ~5% excreted renally), with the majority being eliminated via the bile and gut[57 58]; it therefore does not require dose adjustment in patients with declining renal function.[59] In view of the similar efficacy of these two drugs, treatment choices might, therefore, be made on the basis of other differences between the drugs and consideration of patient clinical characteristics, such as the patient's renal function.

Broadening the use of MBMA has the potential to improve the comparison of individual drug therapies, compared with older statistical methods, and could provide a new way of generating results for populations that have not yet been studied.

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Contributors All authors were fully responsible for all content and editorial decisions. They were involved at all stages of manuscript development, including reviewing and revising the manuscript for scientific content, and have approved the final version. In addition: JG contributed to the data analysis and interpretation of the findings. JR, DP and WG shared primary responsibilities for developing the statistical analysis plan, executed all statistical analyses (including model development, model selection and model summary) and interpreted the findings. SP monitored data collection, and contributed to data selection, the statistical analysis plan and interpretation of the results. CF contributed to the analysis concept, the statistical analysis plan and interpretation of the findings. BM contributed to data collection and the statistical analysis plan, and interpreted the findings. YG contributed to the interpretation of the findings. AS contributed to the analysis strategy, the statistical analysis plan and interpretation of the results. SR contributed to analysis strategy, the statistical analysis plan, data collection and interpretation of the results.

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