

# A Model-Based Meta-Analysis of 24 Antihyperglycemic Drugs for Type 2 Diabetes: Comparison of Treatment Effects at Therapeutic Doses

Alan Maloney<sup>1</sup>, Julio Rosenstock<sup>2</sup> and Vivian Fonseca<sup>3</sup>

Model-based meta-analysis was used to compare glycemic control, weight changes, and hypoglycemia risk across 24 antihyperglycemic drugs used to treat type 2 diabetes. Electronic searches identified 229 randomized controlled studies comprising 121,914 patients. To ensure fair and unbiased treatment comparisons, the analyses adjusted for important differences between studies, including duration of treatment, baseline glycated hemoglobin, and drug dosages. At the approved doses, glycemic control was typically greatest with glucagon-like peptide 1 receptor agonists (GLP-1RAs), and least with dipeptidyl peptidase-4 (DPP-4) inhibitors. Weight loss was highly variable across GLP-1RAs but was similar across sodium-glucose cotransporter 2 (SGLT2) inhibitors. Large weight increases were observed with sulfonylureas and thiazolidinediones. Hypoglycemia risk was highest with sulfonylureas, although gliclazide was notably lower. Hypoglycemia risk for DPP-4 inhibitors, SGLT2 inhibitors, and thiazolidinediones was generally very low but increased slightly for both GLP-1RAs and metformin. In summary, important differences between and within drug classes were identified.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Glycemic control, weight changes, and hypoglycemia risk are important factors in the choice of an antihyperglycemic drug in type 2 diabetes, but differences between studies (e.g., baseline glycated hemoglobin (HbA1c), duration of treatment, and drug dosages), along with limited head-to-head direct comparisons, severely limit the ability of conventional network meta-analysis methods to accurately compare the different antihyperglycemic drugs.

### WHAT QUESTION DID THIS STUDY ADDRESS?

☑ A model-based meta-analysis (MBMA) approach was used to accurately compare 24 antihyperglycemic drugs from six

drug classes in terms of glycemic control, weight changes, and hypoglycemia risk.

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This is the first, comprehensive, MBMA across three key endpoints in type 2 diabetes. The results identified important differences between drug regimens both across and within each drug class; it is the drug and dose and not simply drug class that matters.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This work provides a platform to facilitate the benchmarking of new antihyperglycemic drugs to a wide range of approved antihyperglycemic drugs.

In 2015, the number of people aged 20–79 years with diabetes has been estimated at 415 million, with ~90% having type 2 diabetes.<sup>1</sup> The importance of glycemic control has been clearly shown to reduce the risk of microvascular complications and may contribute to lessen the risk of major cardiovascular events.<sup>2–5</sup> The American Diabetes Association (ADA) recommends a patient-centered approach to guide the choice of antihyperglycemic drug, considering “efficacy, hypoglycemia risk, impact on weight, potential side

effects, cost, and patient preferences”<sup>6,7</sup> but no systematic analysis has compared the composite impact of these effects on all drugs currently available. To enable patients and physicians to make informed choices between the numerous antihyperglycemic drugs available, our objective was to accurately compare glycemic control, weight changes, and hypoglycemia risk across 24 drugs from 6 drug classes (dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1RAs), sodium-glucose

<sup>1</sup>Equation AB, Halmstad, Sweden; <sup>2</sup>Dallas Diabetes Research Center at Medical City, Dallas, Texas, USA; <sup>3</sup>Tulane University Health Sciences Center, New Orleans, Louisiana, USA. Correspondence: Alan Maloney (alanmaloney123@gmail.com)

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cotransporter 2 (SGLT2) inhibitors, thiazolidinediones (TZDs), sulfonylureas (SUs), and the biguanide metformin). These six drug classes represent all therapies recommended by the ADA as either first-, second-, or third-line therapies<sup>6</sup> (excluding insulin-based regimens).

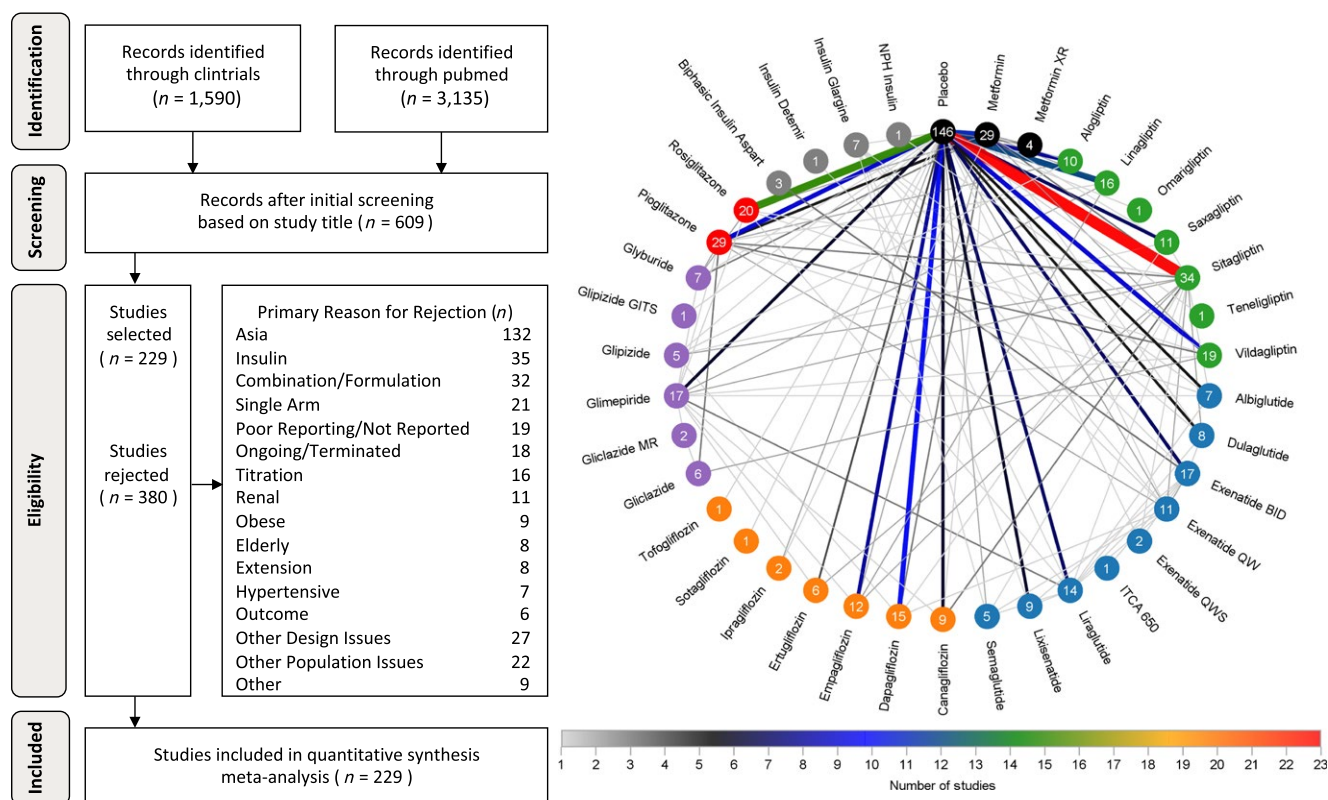
The choice of meta-analysis method is critical to ensure fair and unbiased treatment comparisons, because the studies will differ (be heterogeneous) in many important ways. For example, changes in glycated hemoglobin (HbA1c) would be expected to be larger for a study with a higher HbA1c baseline mean (e.g., 9.0% (75 mmol/mol)) compared with a similar study with a lower HbA1c baseline mean (e.g., 8.0% (64 mmol/mol)).<sup>8</sup> Similarly, changes in HbA1c in a 26-week study may be expected to be larger than in a 12-week study, so it is important to capture how the treatment effects change over time. Dosage, in addition to the type of drug, is a key driver of the treatment effect observed, and it is rational to expect the treatment effect for pioglitazone 30 mg to be somewhere between the effects seen at 15 and 45 mg (although not necessarily in the middle).

A number of extensive meta-analyses have used standard network meta-analysis techniques comparing HbA1c, weight, and hypoglycemia risk across multiple drug classes.<sup>9,10</sup> In these analyses, however, different drugs and dose levels were pooled based on drug class, therefore assuming an identical treatment effect across all drugs and doses within a drug class. This is a major weakness

for such meta-analyses because real differences do exist between doses and drugs within a given drug class, as observed in the results of both head-to-head studies<sup>11,12</sup> and meta-analyses investigating individual drug classes.<sup>13–16</sup> In a meta-analysis that did investigate treatment effects by drug and dose,<sup>17</sup> failure to incorporate baseline HbA1c compromised the interpretation of certain results; a treatment effect of  $-0.90\%$  (9.8 mmol/mol) for pioglitazone 15 mg from a baseline HbA1c of 9.9% (85 mmol/mol) and a treatment effect of  $-0.70\%$  (7.7 mmol/mol) for pioglitazone 45 mg from a baseline HbA1c of 7.5% (58 mmol/mol) would suggest no additional benefit in HbA1c lowering with higher pioglitazone doses, which is contrary to that seen in numerous dose-finding studies with pioglitazone.<sup>17–22</sup> Clearly, adjusting for the influence of baseline HbA1c on the resulting treatment effects is essential if we wish to ensure unbiased treatment comparisons.<sup>23</sup>

Meta-analyses that considered studies of 12 weeks duration or longer<sup>10</sup> did not seem to make any adjustment for the fact that the full treatment effect on HbA1c or weight would not have been reached by week 12. The pooling of studies across regions in meta-analyses has also been criticized.<sup>24</sup> The above reasons may explain why it is common that standard network meta-analyses identify statistical heterogeneity between studies, thus weakening the conclusions that can be drawn.

Model-based meta-analysis (MBMA)<sup>25,26</sup> is an advanced technique that has been successfully used in type 2 diabetes to model



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection (left) and a circular network graph overview of the data (right). The width of the lines is proportional to the number of studies comparing each pair of treatments, and each node shows the number of unique studies for each drug. Color is used to identify the drug class: dipeptidyl peptidase-4 inhibitors (green), glucagon-like peptide 1 receptor agonists (blue), sodium glucose transporter-2 inhibitors (orange), sulfonylureas (purple), thiazolidinediones (red), and insulins (gray), along with metformin and placebo (black).

the relationship between HbA1c and fasting plasma glucose<sup>27</sup> to predict long-term efficacy<sup>28</sup> and describe an individual drug class.<sup>29</sup> This technique can appropriately adjust for baseline HbA1c and treatment duration, and the use of dose-response models allows data from all doses to be included in the analysis. Using dose-response models can also increase the precision of the estimated treatment effects because it uses the totality of the information learned from all doses. In addition to being able to incorporate all studies and dose levels, predictions can be made for all regimens of interest for an identical study design.

Our objective was to use a MBMA approach to accurately quantify the similarities and differences across 24 antihyperglycemic drugs for 3 important end points.

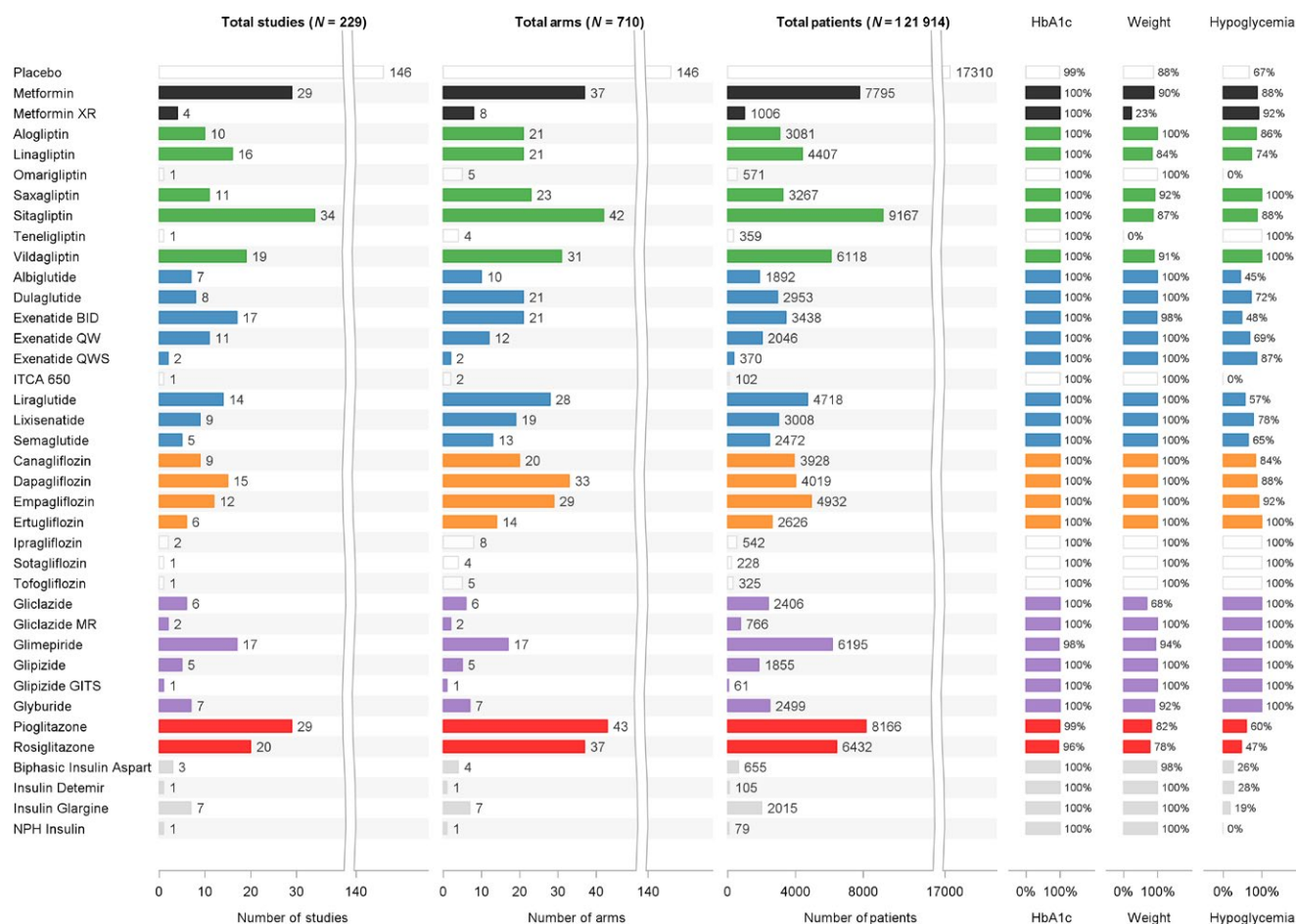
## RESULTS

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the search methods, along with a complete list of exclusions, is shown in **Figure 1a**. Data from 229 studies were collated, representing 710 individual treatment arms and 121,914 total patients. A circular network graph is

shown in **Figure 1b**, and a detailed overview of the data is shown in **Figure 2**. Placebo was used in 146 studies with sitagliptin (34 studies), metformin (29 studies), and pioglitazone (29 studies) being the three most studied drugs. Patients were drug-naïve in 35% (80/229) of studies, on stable background therapy (mainly metformin) in 59% (135/229) of studies, with the remaining 6% (14/229) of studies recruiting both types of patients.

Overall, study data was reported and usable for 99% (227/229 studies (703 unique arms)), 90% (207/229 studies (637 unique arms)), and 87% (170/195 studies (520 unique arms)) for the HbA1c, weight, and hypoglycemia analyses, respectively. A total of 34 studies were excluded from the hypoglycemia analysis because all patients were on background SU treatment, or some patients were on background SU treatment and data were not reported separately for the subset of patients not on background SU treatment.

The final models could describe the observed data, with excellent agreement between the observed and predicted changes from baseline for HbA1c and weight, and the observed and predicted rate for hypoglycemia (**Figures S1–S3**). Individual studies were also well described, with individual study level predictions looking



**Figure 2** Overview of the analysis database, with completeness reported by end point as the percentage of patients in each analysis relative to the total patient numbers. Color is used to identify the drug class: the biguanide metformin (black), dipeptidyl peptidase-4 inhibitors (green), glucagon-like peptide 1 receptor agonists (blue), sodium glucose transporter-2 inhibitors (orange), sulfonylureas (purple), thiazolidinediones (red), and insulin-based therapies (gray). The six drugs used in the model qualification are shown without color (i.e., omarigliptin, teneligliptin, ITCA 650, ipragliflozin, sotagliflozin, and tofogliflozin).

sensible and reflecting the observed data (e.g., **Figure S4** shows the observed HbA1c data and predictions for all 34 studies with a sitagliptin treatment arm).

The drug effect parameters (the maximum effect ( $E_{max}$ ) and the dose required to give 50% of the maximum effect ( $ED_{50}$ )) are shown in **Table 1** for HbA1c and weight, and examples of the estimated dose-response relationships are shown in **Figure 3** for HbA1c (top panels) and weight (bottom panels) for five drugs (metformin, sitagliptin, liraglutide, empagliflozin, and pioglitazone). For the SUs, it was not possible to estimate clear dose-response relationships. For these drugs, a simple fixed-effect or log-linear dose-response model was used. No dose-response relationships could be determined in the hypoglycemia analysis. Individual graphs for all drugs in which a dose-response was estimated are provided for HbA1c (**Figure S5**) and weight (**Figure S6**). **Figure 4** illustrates

the estimated delay (effect of treatment duration) and scalar (effect of baseline) for HbA1c and weight. Of note, the drug effects scaled supraproportionally with baseline HbA1c, with drug effects being 30% smaller for a baseline HbA1c of 7.5% compared with a baseline HbA1c of 8.5%.

**Figure 5** shows the estimated treatment effects vs. placebo at 6 months for each end point at reference/approved doses. For HbA1c, the greatest reductions were seen with GLP-1RAs, although there were considerable differences within this class, with the maximum reduction of 1.77% (19.3 mmol/mol) (1.67%, 1.87%) with semaglutide 1.0 mg. The reductions in HbA1c were smallest with DPP-4 inhibitors, with estimated reductions ranging from 0.58% (6.3 mmol/mol) with alogliptin 12.5 mg to 0.72% (7.9 mmol/mol) with sitagliptin 100 mg. Studies in patients on background therapy yielded treatment effects that were 13% (9%,

**Table 1** Estimated dose-response model parameters for HbA1c and weight

Drug	HbA1c		Weight	
	$ED_{50}$ (mg)	$E_{max}$ (%)	$ED_{50}$ (mg)	$E_{max}$ (kg)
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Metformin	1,070 (751, 1,580)	-1.77 (-2.12, -1.47)	1,960 (236, 4,424)	-0.9 (-1.4, -0.5)
Alogliptin	4.37 (1.95, 9.33)	-0.97 (-1.20, -0.86)	761 (87, 14,892) <sup>a</sup>	4.9 (1.5, 12.5) <sup>a</sup>
Linagliptin	1.59 (0.90, 2.88)	-0.97 (-1.20, -0.86)	348 (35, 67,518) <sup>a</sup>	4.9 (1.5, 12.5) <sup>a</sup>
Saxagliptin	1.56 (0.83, 2.96)	-0.97 (-1.20, -0.86)	94 (15, 319) <sup>a</sup>	4.9 (1.5, 12.5) <sup>a</sup>
Sitagliptin	8.24 (2.95, 17.7)	-0.97 (-1.20, -0.86)	1,221 (219, 3,450) <sup>a</sup>	4.9 (1.5, 12.5) <sup>a</sup>
Vildagliptin	13.8 (5.57, 26.4)	-0.97 (-1.20, -0.86)	446 (56, 1,051) <sup>a</sup>	4.9 (1.5, 12.5) <sup>a</sup>
Albiglutide	33.2 (25.5, 64.1)	-1.86 (-2.43, -1.63)	17,935 (872, 336,843)	-10.0 (-39.2, -5.7)
Dulaglutide	0.27 (0.17, 0.53)	-1.86 (-2.43, -1.63)	8.3 (3.6, 50.1)	-10.0 (-39.2, -5.7)
Exenatide BID	9.69 (3.82, 50.8) <sup>b</sup>	-1.49 (-3.03, -1.14)	99.1 (44.4, 595) <sup>b</sup>	-10.0 (-39.2, -5.7)
Exenatide QW	0.75 (0.52, 1.38)	-1.86 (-2.43, -1.63)	11.2 (4.8, 69.7)	-10.0 (-39.2, -5.7)
Exenatide QWS	0.83 (0.32, 1.80)	-1.86 (-2.43, -1.63)	58.5 (9.8, 727)	-10.0 (-39.2, -5.7)
Liraglutide	0.49 (0.35, 0.91)	-1.86 (-2.43, -1.63)	7.3 (3.4, 42.9)	-10.0 (-39.2, -5.7)
Lixisenatide	18.3 (9.61, 91.1) <sup>b</sup>	-1.49 (-3.03, -1.14)	162 (67.1, 996) <sup>b</sup>	-10.0 (-39.2, -5.7)
Semaglutide	0.31 (0.21, 0.82)	-2.71 (-3.90, -2.32)	1.5 (0.7, 9.1)	-10.0 (-39.2, -5.7)
Canagliflozin	36.5 (16.4, 100)	-1.62 (-2.10, -1.38)	38.3 (15.5, 95.6)	-2.9 (-3.6, -2.4)
Dapagliflozin	1.20 (0.55, 2.34)	-1.15 (-1.37, -1.02)	3.1 (1.5, 7.8)	-2.9 (-3.6, -2.4)
Empagliflozin	1.66 (0.69, 3.36)	-1.15 (-1.37, -1.02)	1.9 (0.6, 5.6)	-2.9 (-3.6, -2.4)
Ertugliflozin	0.55 (0.09, 1.54)	-1.15 (-1.37, -1.02)	2.5 (1.1, 7.0)	-2.9 (-3.6, -2.4)
Pioglitazone	20.0 (11.4, 112)	-1.68 (-3.22, -1.27)	23.1 (13.0, 116)	4.9 (3.6, 10.1)
Rosiglitazone	4.50 (2.70, 24.7)	-1.68 (-3.22, -1.27)	5.60 (3.20, 27.7)	4.9 (3.6, 10.1)
	Fixed	Slope	Fixed	Slope
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Gliclazide	-1.04 (-1.14, -0.95)	<sup>c</sup>	2.4 (2.1, 2.8)	<sup>c</sup>
Glimepiride	-0.97 (-1.03, -0.91)	-0.20 (-0.32, -0.09)	2.4 (2.2, 2.6)	<sup>c</sup>
Glipizide	-0.86 (-0.95, -0.76)	-0.27 (-0.47, -0.07)	2.3 (2.0, 2.6)	0.6 (0.1, 1.0)
Glyburide	-1.17 (-1.23, -1.10)	-0.16 (-0.40, 0.08)	2.8 (2.5, 3.0)	0.9 (0.1, 1.6)

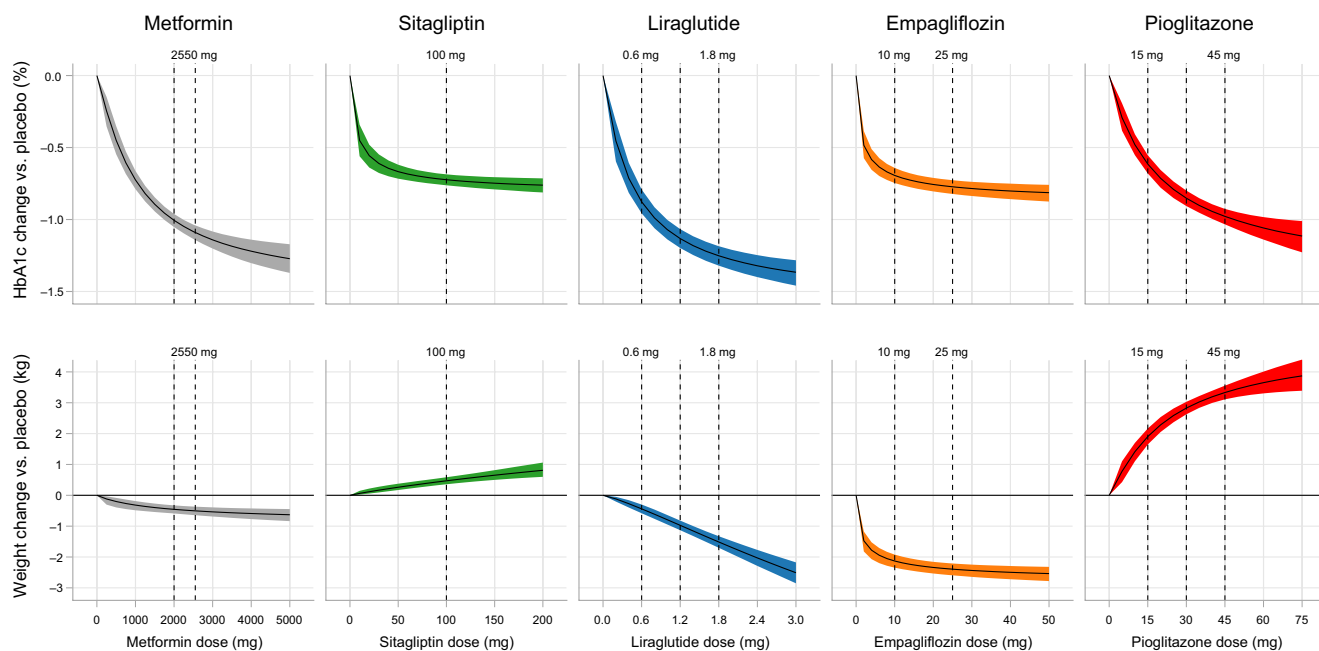
CI, credible interval;  $ED_{50}$ , the dose required to give 50% of the maximum effect;  $E_{max}$ , maximum effect; HbA1c, glycated hemoglobin.

<sup>a</sup>The  $E_{max}$  and  $ED_{50}$  for the dipeptidyl peptidase-4 class should be interpreted very cautiously, as the dose levels studied were much lower than the  $ED_{50}$  estimated. The data simply support the notion that the small treatment effects observed at, say, vildagliptin 50 mg ( $\approx$ 0.6 kg) tended to increase with increasing dose (vildagliptin 100 mg ( $\approx$ 1.0 kg)). However, extrapolation beyond these doses is highly speculative, as observed by the very wide credible interval for the  $E_{max}$  parameter.

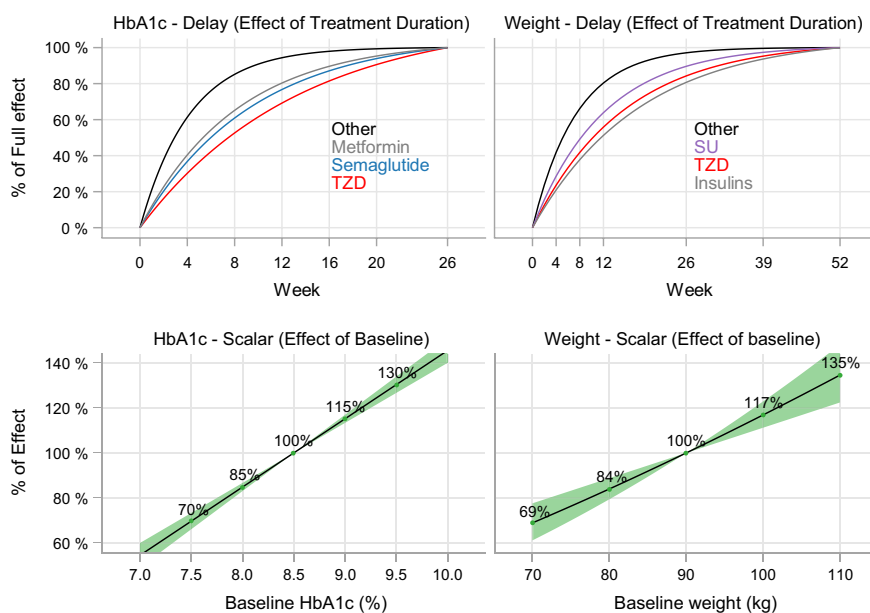
<sup>b</sup>The  $ED_{50}$  for exenatide BID and lixisenatide are in microgram units.

<sup>c</sup>Not estimated.





**Figure 3** Examples of the estimated dose-response relationships (+95% credible intervals) for glycated hemoglobin (HbA1c; top panels) and weight (bottom panels) for five drugs (metformin, sitagliptin, liraglutide, empagliflozin, and pioglitazone). Reference/approved doses are shown as dashed vertical lines. These results are for a drug-naive population with a baseline HbA1c of 8.0%, a baseline weight of 90 kg, after 26 weeks of treatment.

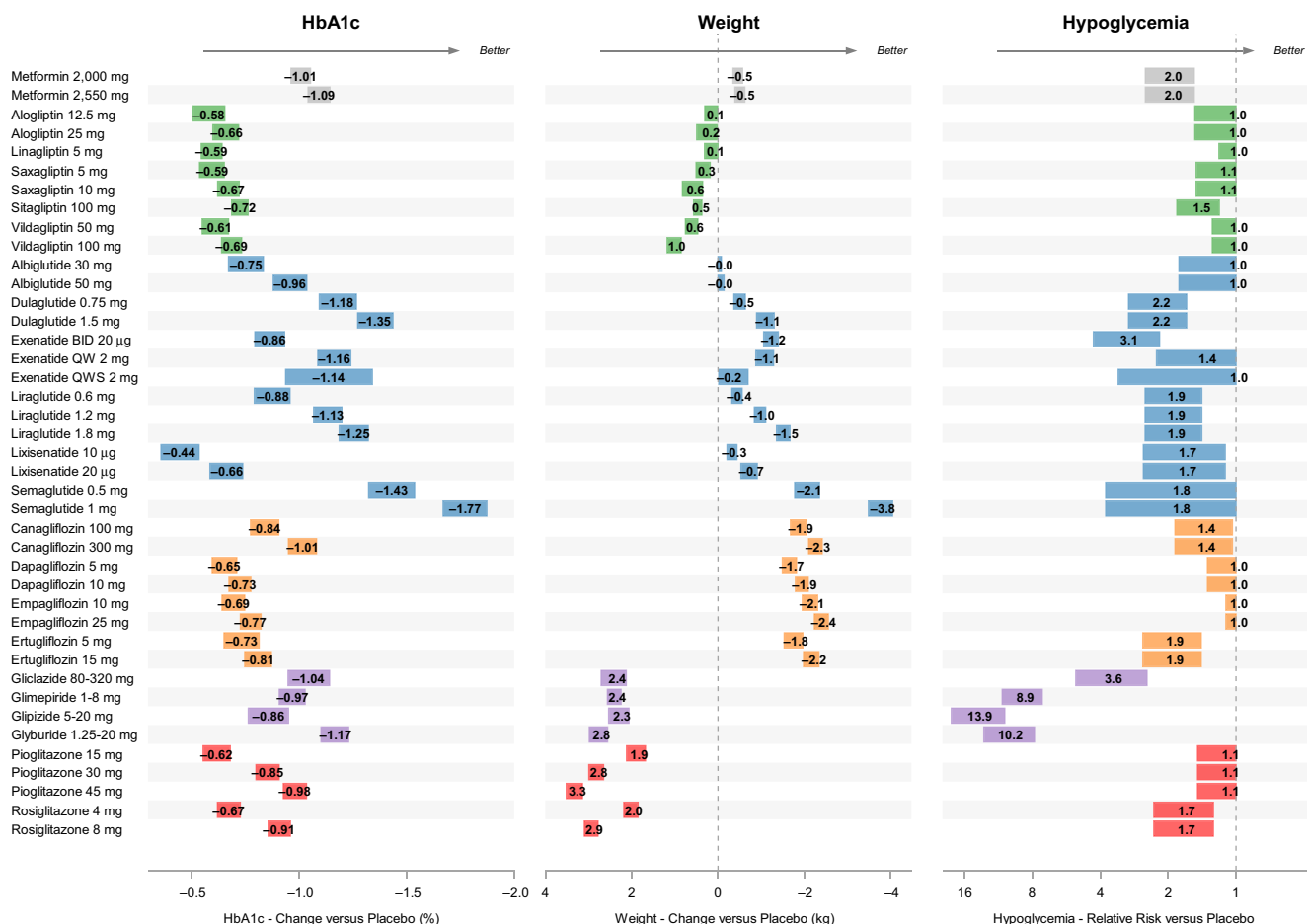


**Figure 4** Illustration of the estimated delay (effect of treatment duration) for glycated hemoglobin (HbA1c; top left) and weight (top right). All drugs used the same delay function except for the drugs/classes highlighted. The effect of Scalar (effect of baseline) on the magnitude of the treatment effects is shown for HbA1c (bottom left) and weight (bottom right) along with the 95% credible intervals (shaded regions). SU, sulfonylurea; TZD, thiazolidinedione.

16%) smaller than those observed in comparable studies in a drug-naive study population.

For body weight, consistent reductions were seen with SGLT2 inhibitors, with estimated reductions within this class ranging from 1.7 kg (1.5 kg, 1.9 kg) with dapagliflozin 5 mg to 2.4 kg

(2.2 kg, 2.6 kg) with empagliflozin 25 mg. GLP-1RAs, with the exception of albiglutide, also reduced body weight, ranging from 0.4 kg (0.3 kg, 0.6 kg) with liraglutide 0.6 mg to 3.8 kg (3.4 kg, 4.1 kg) with semaglutide 1.0 mg. Metformin resulted in a small weight loss ( $\approx 0.5$  kg), whereas DPP-4 inhibitors typically yielded



**Figure 5** Treatment estimates and 95% credible intervals (bars) vs. placebo for a drug-naive population with a baseline glycated hemoglobin (HbA1c) of 8.0%, a baseline weight of 90 kg, after 26 weeks of treatment. The absolute hypoglycemia risk (95% credible interval) for placebo was 0.9% (0.6–1.3%). Color is used to identify the drug class: the biguanide metformin (gray), dipeptidyl peptidase-4 inhibitors (green), glucagon-like peptide 1 receptor agonists (blue), sodium glucose transporter-2 inhibitors inhibitors (orange), sulfonylureas (purple), and thiazolidinediones (red).

small weight increases. Larger body weight increases were observed with SUs and TZDs, typically in the order of 2–3 kg.

Interestingly, as background reference, the risk of documented hypoglycemia for placebo over 6 months was estimated at 0.9% (0.6%, 1.3%). The relative hypoglycemia risk increase vs. placebo was highest with SUs, although gliclazide 3.6 (2.5, 5.1) was notably lower than glimepiride (8.9 (7.3, 10.9)), glyburide (10.2 (7.9, 13.2)), and glipizide (13.9 (10.6, 18.4)). The hypoglycemia risk for DPP-4 inhibitors, SGLT2 inhibitors, and TZDs was generally very low but increased slightly for both GLP-IRAs and metformin.

Finally, it is worth noting that in the HbA1c analysis, SUs were associated with a 23% (16%, 29%) yearly reduction in effect (from a nadir at week 16), although these results should be interpreted cautiously, as only two studies<sup>30,31</sup> had a primary end point analysis longer than week 56 (both week 104).

**DISCUSSION**

In this comprehensive MBMA, data from 229 studies for HbA1c, body weight, and hypoglycemia risk were successfully used to

accurately determine the composite treatment effects for 24 antihyperglycemic drugs. To ensure fair comparisons, the extensive analysis appropriately adjusted for important factors, including the duration of treatment, baseline HbA1c, baseline weight, background treatment (drug-naive or metformin), and dose regimen.

Our results may be used by practicing physicians to make valid comparisons between drugs at a glance for the decision-making process when choosing treatment. For example, **Figure 5** clearly demonstrates that the HbA1c lowering of semaglutide is the greatest among all drugs and that the HbA1c lowering potential is lowest with pioglitazone 15 mg and DPP-4 inhibitors. On the other hand, the latter drugs may be selected for other clinical reasons. Similarly, hypoglycemia is greatest with glipizide and least with DPP-4 inhibitors; whereas body weight loss is most with semaglutide and weight gain highest with pioglitazone 45 mg. Although these facts may be known from individual papers, this is the first attempt to comprehensively evaluate and report all drugs simultaneously.

As all antihyperglycemic drugs reduce systemic glucose levels, they all have the potential to increase the risk of hypoglycemia. Clearly, the mechanism by which they reduce glucose levels is very

important, and we see that SUs are associated with the highest risk. However, the magnitude of this risk is likely to be a complex integration of pharmacological differences between the drugs (e.g., in pharmacokinetics and pharmacodynamics) combined with multiple physiological, biological, and behavioral (e.g., compliance, exercise, and diet) patient-level factors and, most importantly, the interpatient and inpatient variability in all of these factors. Our results showed that the relative risk with gliclazide (3.6) is more similar to metformin (2.0) than other SUs, such as glipizide (13.9). Thus, although class is important, drugs within the same class may exhibit real and important differences in hypoglycemia risk.

The HbA1c analysis used data from 99% (227/229) of studies, with body weight (90% (207/229)) and hypoglycemia (87% (170/195)) only using studies in which results were reported. If the missingness is considered random,<sup>32,33</sup> all results would be considered unbiased. Although it is impossible to exclude the possibility that the unreported studies may be different to the studies analyzed, the treatment effects in this subset of studies would need to be substantially different to change the treatment effects markedly.

These results are naturally reflective of the (insulin-naïve) type 2 diabetes populations recruited into the studies we considered. The exclusion of important patient populations (e.g., Asian studies, elderly, obese, etc.) does limit the generalizability of these results. The future inclusion of these studies, along with an accurate quantification of the similarities and differences between populations, would significantly strengthen the value of these results. Furthermore, although 6 months is sufficient time for the full effects on HbA1c to be reached, clearly, these results only represent the initial differences between treatments that will be used to manage a chronic condition, and, hence, may not fully reflect the durability of these effects with longer-term use. Our observation that glycemic control reduced over time with SUs vs. other regimens is consistent with observed results seen in the ADOPT<sup>34</sup> and Del Prato studies.<sup>35</sup>

The hypoglycemia analysis could clearly identify differences between drugs in the risk of hypoglycemia, but the data were not powerful enough to clearly identify dose-response relationships across doses within each drug (supporting the notion that within-drug differences are much smaller than between drug differences). In addition, the analysis did not focus on severe hypoglycemia, because these events are very rare in (insulin-naïve) type 2 diabetes studies. Thus, whether the treatment differences determined would directly translate to similar differences in the risk of severe hypoglycemia risk is unknown. The definition of documented hypoglycemia was also not identical across studies, and, hence, our estimated risk (95% credible interval) of documented hypoglycemia for placebo over 6 months of 0.9% (0.6%, 1.3%) represents a “typical” study (and, hence, a “typical” definition of documented hypoglycemia). We believe the future use and consistent reporting of hypoglycemia in accordance with ADA guidelines will significantly enable an improved comparison of hypoglycemia risks for both current and future antihyperglycemic drugs.

The choice of antihyperglycemic drug will always depend on the unique patient characteristics and benefit-risk profile of each drug, and may incorporate recent findings in major adverse cardiovascular event outcome studies.<sup>36–40</sup> However, it is hoped that our

results will enable patients and physicians to better understand the similarities and differences across 24 antihyperglycemic drugs for 3 important clinical end points.

## METHODS

### Data sources and searches

The PRISMA guidelines for network meta-analysis<sup>41</sup> were used to collate data for the following 24 drugs: the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin, the GLP-1RAs albiglutide, dulaglutide, exenatide BID (Byetta), exenatide QW (Bydureon), exenatide QWS (Bydureon BCise), liraglutide, lixisenatide, and semaglutide, the SGLT2 inhibitors canagliflozin, dapagliflozin, empagliflozin and ertugliflozin, the SUs gliclazide, glipizide, glimepiride, and glyburide (glibenclamide), the TZDs pioglitazone and rosiglitazone, and the biguanide metformin. Additional drug classes (e.g., alpha glucosidase inhibitors and meglitinides) were not considered at this time.

The following sources of data were investigated: Medline (via PubMed), ClinicalTrials.gov (<http://www.clinicaltrials.gov>), the US Food and Drug Administration summary basis of approval documents and drug labels, and sponsor websites.

Searches were conducted simultaneously using the generic, code, and trade names for each drug (e.g., “exenatide OR AC 2993 OR Byetta OR Bydureon OR ITCA 650”). PubMed searches were restricted to “clinical studies/human,” and ClinicalTrials.gov searches were restricted to “Intervention/phase 2–4.” Studies older than 1996 and non-English language reports were not considered.

It is worth noting that the US Food and Drug Administration summary basis of approval documents provide lists of all studies that are conducted/ongoing at the time of submission, and, hence, provided an additional check of the completeness of the included studies.

In addition to the phase II–IV study data from the 24 drugs of primary interest, phase II study data from 6 additional drugs (omarigliptin, teneligliptin, ITCA 650, ipragliflozin, sotagliflozin, and tofogliflozin) were included. The ability of the models to describe this additional data would provide a useful “internal qualification” of the generalizability of the dose-response models beyond the primary 24 drugs.

The models were developed using data up November 15, 2017.

### Study selection

The goal was to ensure fair and unbiased treatment comparisons. Hence, all randomized type 2 diabetes studies were included with the following planned exceptions: studies run primarily in Asia, studies in special type 2 diabetic populations (e.g., hypertensive, obese, renally impaired, high cardiovascular risk, elderly, and pediatric), studies with insulin background treatment, studies with SU background treatment (for hypoglycemia analysis only), single arm studies, combination treatment arms, and phase I studies.

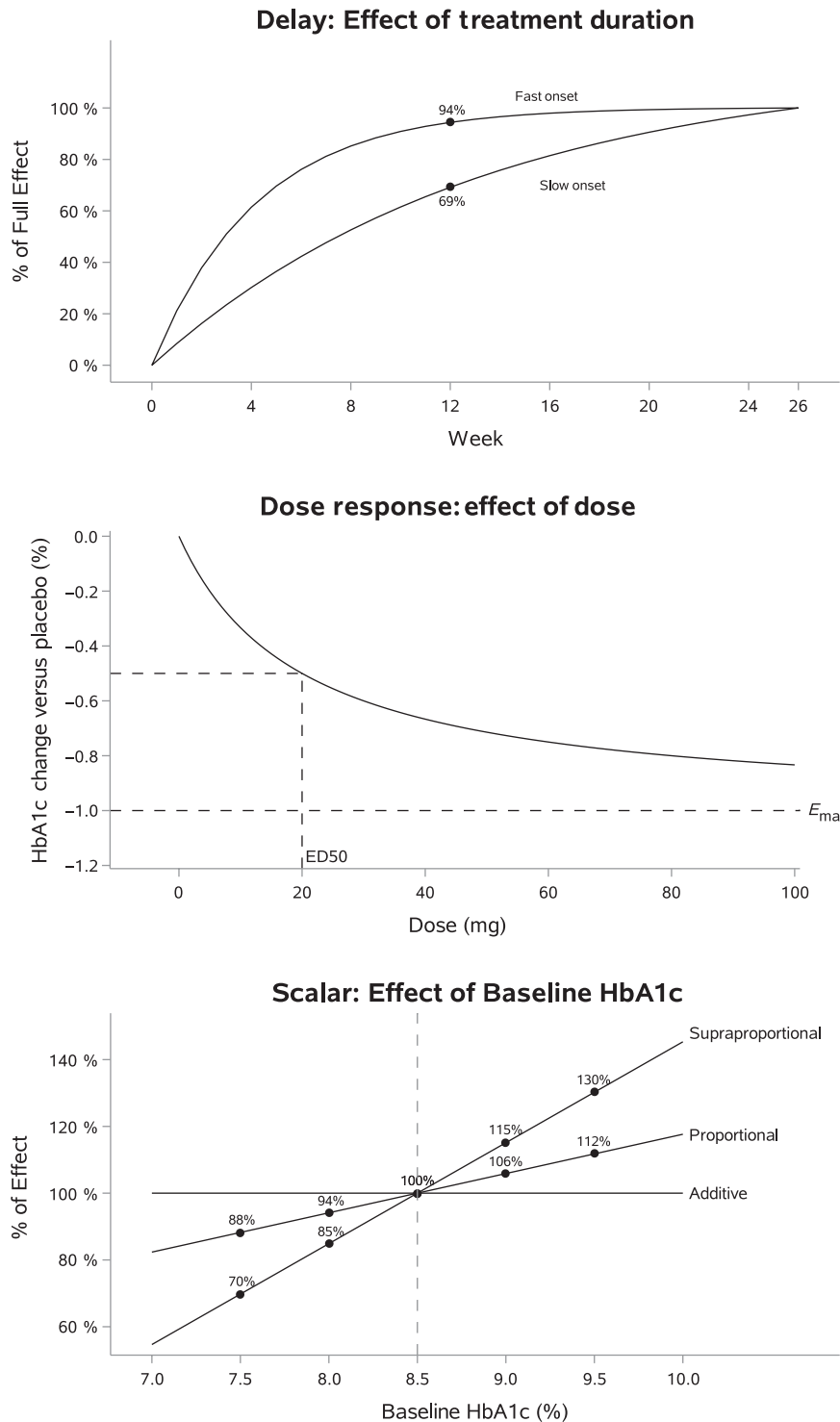
The rationale for excluding these different patient populations was to ensure the final comparisons were not compromised by imbalances between drugs with respect to these potentially confounding factors. For example, as well as having different baseline characteristics (e.g., weight), Japanese patients may be expected to have, on average, higher concentrations for a given dose compared with patients in a typical “Western” population, and, hence, treatment effects can differ between populations for a given dose. The rationale for excluding studies with insulin as background treatment was again to avoid potential bias. This is because it is not uncommon that patients modify their insulin dose dependent on the efficacy of their randomized treatment, with more efficacious treatments resulting in less insulin use.<sup>42,43</sup> Thus, final comparisons between treatments in these studies are confounded with differential insulin usage (a similar analysis of insulin combination studies is being conducted separately). Similarly, for the hypoglycemia analysis, data were only included for studies with patients with no background SU or if data were presented for that proportion of patients who were not taking

background SU. The exclusion of any study was based of the review of the study characteristics alone and not on any review or judgment of the results from that study.

**Data extraction and quality assessment**

To facilitate this landmark type MBMA,<sup>44</sup> the following key data variables were collected for each arm/study using the study week as

defined for the primary end point analysis: drug, dose, regimen, mean baseline, mean change from baseline and standard error, sample size, analysis method (last observation carried forward or mixed-model repeated-measures), week and percentage of patients by background therapy at baseline (e.g., drug naïve, metformin, etc.). For hypoglycemia, the rate was recorded (number of patients with at least one event/sample size), along with the end point definition. This was either as an



**Figure 6** Illustration of how model-based meta-analysis can incorporate the effect of treatment duration (top), the dose-response of each drug (middle), and the effect of baseline glycated hemoglobin (HbA1c) on the magnitude of the drug effect (bottom).



“adverse event” (typically older studies) or using the ADA hypoglycemia definitions<sup>45</sup> (i.e., document, asymptomatic, probable, severe, or a combination thereof (if a definition of “symptomatic” was stated, this was recoded to “documented + probable” in the analysis)).

For SUs, treatment regimens were typically titrated (e.g., glimepiride titrated over 1–8 mg q.d. as needed). In this case, both the maximum dose and the mean dose at end point were recorded (e.g., 4.0 mg). Four additional insulin-based therapies (biphasic insulin aspart, insulin detemir, insulin glargine, and isophane insulin) were used as comparators in some studies. These were included in the analysis, although no predictions are presented for these regimens (see **Supplementary Material S1**- Insulin-based therapies for further details).

### Statistical analysis

Brief descriptions of the key features of the MBMA for HbA<sub>1c</sub> are shown below, including the significant advantages compared with a standard network analysis. A more technical exposition is available in the Statistical analysis section of **Supplementary Material S1**.

In a standard network meta-analysis model for HbA<sub>1c</sub>, treatment effects could be simply described as:

$$\text{Change from Baseline in HbA}_{1c} = \text{Placebo} + \text{Drug}$$

where “Placebo” represents the typical change from baseline for placebo (e.g., 0.1% (1.1 mmol/mol)) and “Drug” represents the unique effect of each drug (e.g., –1.0% (10.9 mmol/mol)). This approach implicitly assumes the “Drug” effect is identical across all studies, and, hence, does not take into account key factors (e.g., study duration, drug dose, and baseline HbA<sub>1c</sub>) that are known to influence the magnitude of the drug effect observed. MBMA can be viewed as extending the simple “Drug” effect to incorporate these important factors. Thus:

$$\text{Change from Baseline in HbA}_{1c} = \text{Placebo} + \text{Delay} \cdot \text{Dose Response} \cdot \text{Scalar}$$

The three additional factors (Delay, Dose Response, and Scalar) are described below, and illustrated in **Figure 6**.

Delay describes the change in drug effect as a function of study duration, increasing (nonlinearly) from 0% at week 0 to 100% (full effect) at week 26. Each drug class could have its own “delay” for HbA<sub>1c</sub>, essentially reflecting differences in the mechanism of action between the different drug classes. **Figure 6a** shows this “delay” for two hypothetical drug classes, one with a faster onset of drug effect and one with a slower onset of drug effect. The graph shows that studies of 12-week duration for the drug class with the faster onset yielded 94% of the (full) drug effect observed in studies of 26 weeks duration, compared with 69% for the slower onset drug class.

Dose response describes the change in drug effect as a function of the dose (**Figure 6b**). The sigmoidal  $E_{\max}$  model is a widely used dose-response model<sup>46</sup> and describes the effect of drug  $i$ , class  $j$ , and dose  $D$  as:

$$\text{Drug}_{i,\text{Dose } D} = \frac{E_{\max,j} \cdot D^{\gamma_j}}{ED_{50,i}^{\gamma_j} + D^{\gamma_j}}$$

where  $E_{\max,j}$  is the (theoretical) maximal drug effect for class  $j$ ,  $ED_{50,i}$  is the dose required to give 50% of the maximal response for drug  $i$ , and  $\gamma_j$  is the Hill coefficient for class  $j$  (i.e., the steepness of the dose-response curve). This approach allows all doses to be included in the modeling and unique predictions for each dose level to be made. **Figure 6b** shows the dose-response for a hypothetical drug with an  $E_{\max}$  of –1%, an  $ED_{50}$  of 20 mg, and a Hill coefficient of 1.

Scalar describes the change in drug effect as a function of the baseline HbA<sub>1c</sub>, allowing higher HbA<sub>1c</sub> baselines to have larger treatment effects,

and lower HbA<sub>1c</sub> baselines to have smaller treatment effects (**Figure 6c**). We used the following formula to describe this:

$$\text{Scalar}_{\text{baseline HbA}_{1c}} = \left( \frac{\text{HbA}_{1c}(\%) - \text{Threshold}}{8.5\% - \text{Threshold}} \right)$$

The parameter threshold is estimated from the data and is the same for all drug classes. It can be considered a system property that is independent of drug. An estimated threshold parameter of zero would suggest that the drug effects scale proportionally with baseline HbA<sub>1c</sub>, whereas an estimated threshold parameter of 5.2% (33 mmol/mol) would suggest that the drug effects are supraproportional (or, stated equally, are proportional to the amount the HbA<sub>1c</sub> baseline is above 5.2% (33 mmol/mol)). The value of Scalar is 100% for an HbA<sub>1c</sub> baseline of 8.5% (69 mmol/mol). **Figure 6c** shows how Scalar changes for three different scenarios: proportional, supraproportional, and additive (i.e., where the drug effects are not dependent on baseline HbA<sub>1c</sub>).

The background therapy of the study population (e.g., drug-naïve or stable background therapy) could also potentially influence the magnitude of the treatment effects. Therefore, the percentage change in the treatment effects was estimated for studies in patients on background therapy relative to a drug-naïve study population (the reference population).

Unlike a standard network meta-analysis, the predictions for each study arm depend on multiple factors (e.g., study duration, drug dose, and baseline HbA<sub>1c</sub>), and, therefore, standard plots (e.g., forest plots) are not appropriate. However, checking that the model predictions are consistent with the observed data is an integral component of MBMA. This included comparing the predicted effect for each treatment arm with the observed estimate and 95% confidence interval. The differences between the observed change from baselines and the predicted change from baselines were also checked to ensure there were no systematic under- or overprediction with respect to drug class, drug, dose, study duration, baseline HbA<sub>1c</sub> and body weight, background therapy, and sample size.

Following a full Bayesian analysis, estimates for the change from placebo were determined for all regimens for a baseline HbA<sub>1c</sub> of 8.0% (64 mmol/mol), a baseline body weight of 90 kg, and 26 weeks of treatment. For the hypoglycemia analysis (a binary response), the relative risk vs. placebo (i.e., predicted rate drug/prediction rate placebo) was calculated using the hypoglycemia category “documented” as the reference category. All drug regimens are displayed with the total daily dose, implicitly assuming standard treatment regimens (e.g., the label “metformin 2,550 mg” would be “metformin 850 mg t.i.d.”). As SU regimens were often titrated, results using typical drug regimen ranges were used and displayed.

All estimates are presented with the associated 95% credible interval (the interval within which there is 95% probability that the true effect is located). All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

### SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website ([www.cpt-journal.com](http://www.cpt-journal.com)).

**Figure S1.** Observed (+95% CI) vs. predicted change from baseline in HbA<sub>1c</sub> by drug. Predictions that fall outside the observed 95% CI are highlighted in red. Ideally most of the 703 individual treatment arms should be close to the line of identity (i.e., the diagonal line, where the observed and predicted values are identical).

**Figure S2.** Observed (+95% CI) vs. predicted change from baseline in weight by drug. Predictions that fall outside the observed 95% CI are highlighted in red. Ideally most of the 637 individual treatment arms should be close to the line of identity (i.e., the diagonal line, where the observed and predicted values are identical).

**Figure S3.** Observed (+95% CI) vs. predicted hypoglycemia rate by drug. Predictions that fall outside the observed 95% CI are highlighted in red. Ideally most of the 520 individual treatment arms should be close to the line of identity (i.e., the diagonal line, where the observed and predicted values are identical).

**Figure S4.** Change from baseline in HbA1c. Predictions (left figure in bold) compared to the observed results (+95% CI (right figures)) for all 34 studies with at least one sitagliptin arm. Predictions outside the observed 95% CI are highlighted in red.

**Figure S5.** Estimated dose-response relationships for HbA1c.

**Figure S6.** Estimated dose-response relationships for weight.

**Supplementary Material S1.** Additional supporting text, figures, and tables.

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## CONFLICT OF INTEREST

A.M. has received consulting fees from AstraZeneca. J.R. has served on scientific advisory boards and received honoraria or consulting fees from Eli Lilly, Novo Nordisk, Sanofi, Janssen, Boehringer Ingelheim, and Intarcia and has received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, AstraZeneca, Janssen, Genentech, Boehringer Ingelheim, Intarcia, and Lexicon. V.F. has served as a paid consultant to Eli Lilly, Takeda, Novo Nordisk, Sanofi-Aventis, AstraZeneca, Abbott, Boehringer Ingelheim, and Tulane University Endocrinology has also received grants and Research Support from Novo Nordisk, Asahi, Abbott, Sanofi, and Bayer.

## AUTHOR CONTRIBUTIONS

A.M., J.R., and V.F. wrote the manuscript. A.M., J.R., and V.F. designed the research. A.M. performed the research. A.M. analyzed the data.

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- Ogurtsova, K. *et al.* IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res. Clin. Pract.* **128**, 40–50 (2017).
- Turnbull, F.M. *et al.* Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* **52**, 2288–2298 (2009).
- Zhang, C.-Y. *et al.* Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: a meta-analysis. *Ann. Med.* **42**, 305–315 (2010).
- Ismail-Beigi, F. *et al.* Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes. An analysis of the ACCORD randomised trial. *Lancet* **376**, 419–430 (2010).
- Zoungas, S. *et al.* Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes. A meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol.* **5**, 431–437 (2017).
- Pharmacologic approaches to glycemic treatment. *Diabetes Care* **40** (suppl. 1), S64–S74 (2017).
- Inzucchi, S.E. *et al.* Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* **58**, 429–442 (2015).
- DeFronzo, R.A., Stonehouse, A.H., Han, J. & Wintle, M.E. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet. Med.* **27**, 309–317 (2010).
- Palmer, S.C. *et al.* Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* **316**, 313–324 (2016).
- Phung, O.J., Scholle, J.M., Talwar, M. & Coleman, C.I. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* **303**, 1410–1418 (2010).
- Wysham, C. *et al.* Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* **37**, 2159–2167 (2014).
- Ahmann, A.J. *et al.* Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (sustain 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* **41**, 258–266 (2018).
- Zaccardi, F., Webb, D.R., Htike, Z.Z., Youssef, D., Khunti, K. & Davies, M.J. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes. Metab.* **18**, 783–794 (2016).
- Singh, S. *et al.* Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes. Metab.* **19**, 228–238 (2017).
- Zaccardi, F., Htike, Z.Z., Webb, D.R., Khunti, K. & Davies, M.J. Benefits and harms of once-weekly glucagon-like peptide-1 receptor agonist treatments: a systematic review and network meta-analysis. *Ann. Intern. Med.* **164**, 102–113 (2016).
- El Aziz, A., Mirna, S., Kahle, M., Meier, J.J. & Nauck, M.A. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes. Metab.* **19**, 216–227 (2017).
- Sherifali, D., Nerenberg, K., Pullenayegum, E., Cheng, J.E. & Gerstein, H.C. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care* **33**, 1859–1864 (2010).
- Kipnes, M.S., Krosnick, A., Rendell, M.S., Egan, J.W., Mathisen, A.L. & Schneider, R.L. Pioglitazone hydrochloride in combination with sulfonyleurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am. J. Med.* **111**, 10–17 (2001).
- Herz, M. *et al.* A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. *Clin. Ther.* **25**, 1074–1095 (2003).
- Aronoff, S., Rosenblatt, S., Braithwaite, S., Egan, J.W., Mathisen, A.L. & Schneider, R.L. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. *Diabetes Care* **23**, 1605–1611 (2000).
- DeFronzo, R.A., Burant, C.F., Fleck, P., Wilson, C., Mekki, Q. & Pratley, R.E. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **97**, 1615–1622 (2012).
- Nauck, M.A., Di Domenico, M., Patel, S., Kobe, M., Toorawa, R. & Woerle, H.-J. Linagliptin and pioglitazone combination therapy versus monotherapy with linagliptin or pioglitazone: a randomised, double-blind, parallel-group, multinational clinical trial. *Diab. Vasc. Dis. Res.* **13**, 286–298 (2016).
- Home, P.D. Validity of meta-analysis in diabetes: we need to be aware of its limitations. *Diabetes Care* **36**, 3361–3367 (2013).
- Home, P. Comment on Abd El Aziz *et al.*, a meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. *Diabetes Obes. Metab.* **19**, 304–305 (2017).
- Mould, D.R. Model-based meta-analysis: an important tool for making quantitative decisions during drug development. *Clin. Pharmacol. Ther.* **92**, 283–286 (2012).
- Mandema, J.W., Gibbs, M., Boyd, R.A., Wada, D.R. & Pfister, M. Model-based meta-analysis for comparative efficacy and safety: application in drug development and beyond. *Clin. Pharmacol. Ther.* **90**, 766–769 (2011).
- Vaddady, P. *et al.* A comprehensive model-based meta-analysis (MBMA) of diabetes studies in type 2 diabetes mellitus patients

- to quantify the relationship between HbA1c and fasting plasma glucose. <[www.page-meeting.org/?abstract=7301](http://www.page-meeting.org/?abstract=7301)> (2017). Abstract 7301.
28. Liu, J. et al. Prediction of long-term efficacy of antidiabetic drugs on HbA1c using longitudinal model-based meta-analysis (MBMA) of literature data (abstract). American Society for Clinical Pharmacology and Therapeutics. *Clin. Pharmacol. Ther.* **99**, S5–S107 (2016).
  29. Maloney, A. et al. (2005) An application of modelling and simulation to type 2 diabetes: development of a general drug-disease model based on a meta analysis of over 40 studies investigating 5 PPAR drugs. <[www.page-meeting.org/?abstract=776](http://www.page-meeting.org/?abstract=776)>.
  30. Foley, J.E. & Sreenan, S. Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulfonylurea gliclazide after two years of monotherapy in drug-naïve patients with type 2 diabetes. *Horm. Metab. Res.* **41**, 905–909 (2009).
  31. Ahrén, B. et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care* **37**, 2141–2148 (2014).
  32. Little, R.J.A. & Rubin, D.B.. *Statistical Analysis with Missing Data*. 2nd ed. (Wiley, Hoboken, NJ, 2002).
  33. Sterne, J.A.C. et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* **338**, b2393 (2009).
  34. Kahn, S.E. et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* **355**, 2427–2443 (2006).
  35. Del Prato, S. et al. Long-term glycemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. *Diabetes Obes. Metab.* **17**, 581–590 (2015).
  36. Zinman, B. et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **373**, 2117–2128 (2015).
  37. Neal, B. et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N. Engl. J. Med.* **377**, 644–657 (2017).
  38. Marso, S.P. et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **375**, 311–322 (2016).
  39. Holman, R.R. et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **377**, 1228–1239 (2017).
  40. Marso, S.P. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **375**, 1834–1844 (2016).
  41. Hutton, B. et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann. Intern. Med.* **162**, 777–784 (2015).
  42. Riddle, M.C. et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care* **36**, 2489–2496 (2013).
  43. Ahmann, A. et al. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes. Metab.* **17**, 1056–1064 (2015).
  44. Boucher, M. & Bennetts, M. The many flavors of model-based meta-analysis: part I - introduction and landmark data. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 54–64 (2016).
  45. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* **28**, 1245–1249 (2005).
  46. Holford, N.H.G. & Sheiner, L.B. Understanding the dose-effect relationship. *Clin. Pharmacokinet.* **6**, 429–453 (1981).