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Effectiveness of sitagliptin compared to sulfonylureas for type 2 diabetes mellitus inadequately controlled on metformin: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the effectiveness of sitagliptin compared to sulfonylureas as add-on to metformin in adults with type 2 diabetes mellitus from both randomised controlled trials (RCTs) and 'real-world' non-randomised studies.

Methods and analyses We conducted a systematic review of EMBASE, MEDLINE, CENTRAL and grey literature for RCTs and non-randomised studies. We reported outcomes relating to change in HbA1c, fasting glucose, weight, blood pressure and lipids from baseline and need for treatment change. No study investigating macrovascular and microvascular diabetes complications was found. Meta-analysis was used where studies were sufficiently homogenous.

Results Seven RCTs and five non-randomised studies were eligible for inclusion from 1335 articles retrieved. Meta-analysis of three homogenous RCTs revealed a statistically significant decrease in weight with sitagliptin when compared to sulfonylureas (weighted mean difference (WMD) −2.05 kg; 95% CI −2.38 to −1.71); however, a similar change from baseline in HbA1c (WMD 0.05; 95% CI −0.03 to 0.12), fasting glucose (WMD 0.11; 95% CI −0.08 to −0.29), blood pressure, lipids and the proportion achieving HbA1c <7% by study end (OR 0.98; 95% CI 0.85 to 1.13) was observed. Non-randomised studies identified consisted of four prospective and one retrospective cohort study. Three of these five studies were of moderate/high quality, and results though less precise suggested similar real-world comparative glycaemic and weight effectiveness for both treatments. Data from two cohort studies suggested that treatment change (HR 0.65; 95% CI 0.57 to 0.73) and insulin initiation (HR 0.76; 95% CI 0.65 to 0.90) were less likely among those prescribed sitagliptin; however, inadequate reporting of HbA1c at time of treatment change made interpreting results challenging.

Conclusion Sitagliptin users experienced modest weight loss compared to gain with sulfonylureas; however, this difference was around 2 kg, which may not be of major clinical significance for most individuals. Similar change was observed across most other effectiveness outcomes reported. Further studies are needed to address longer-term effectiveness outcomes for sitagliptin compared to sulfonylureas as add-on to metformin.

PROSPERO registration number CRD42016033983.

Strengths and limitations of this study

- We provide a comprehensive overview examining a wide range of effectiveness outcomes for sitagliptin versus sulfonylureas as add-on to metformin.
- We assess and report evidence from both randomised clinical trials and 'real-world' non-randomised studies.
- We have undertaken and presented meta-analysis where methodologically appropriate.
- We have focused on effectiveness issues only in this review as safety has been evaluated in depth elsewhere; however, we have summarised the safety literature in our introduction.
- We have focused on sitagliptin only as this is the most widely prescribed dipeptidyl-peptidase-4 inhibitor in the UK.

INTRODUCTION

Management of patients with type 2 diabetes mellitus (T2DM) is complex and often requires multiple pharmacological treatments to achieve adequate control of the disease.[1 2] Most clinical guidelines recommend metformin as initial monotherapy; however, there is no consensus on second-line treatment.[1–4] This is further complicated by the increasing number of pharmacological treatments options now available. Dipeptidyl-peptidase-4 (DPP-4) inhibitors and sulfonylureas represent two of the largest classes of therapy prescribed worldwide.[5 6] Sitagliptin has been the most extensively prescribed DPP-4 inhibitor in the UK and USA,[7] while alongside metformin, sulfonylureas such as gliclazide are the most widely prescribed oral antidiabetic agent for T2DM.[5] Sitagliptin slows the inactivation of incretin hormones (glucagon-like-peptide-1 and glucose insulinotropic peptides), which in turn increase insulin synthesis and release and suppress

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glucagon release.[8] Sulfonylureas, however, work solely through increasing insulin secretion via direct stimulation of β-cells in the pancreas.[8] Clinicians often have to choose between prescribing sitagliptin or a sulfonylurea as potential options to add-on in patients with T2DM inadequately controlled on metformin.[5]

Clinical guidance from the American Association of Clinical Endocrinologists now recommends sitagliptin usage over sulfonylureas for second-line treatment[9]; however, most other major international guidelines such as those from the UK National Institute of Heath and Care Excellence, American Diabetes Association, European Association for study of Diabetes and International Diabetes Federation do not significantly discriminate between treatments and advocate that either may be selected as potential options to add-on, having accounted for patient preferences and medication safety.[1–4] Medication safety takes priority across Asian clinical guidelines as well, which tend to be individualised across most countries[10]; however, studies have shown increasing usage of both treatments particularly in Eastern Asian countries as well.[6]

From a safety perspective, both sulfonylureas and sitagliptin have been studied in considerable depth. To summarise, a several-fold higher risk of hypoglycaemia has been well established with sulfonylureas across adult and several vulnerable population groups such as older individuals.[11–14] An increased risk of pancreatitis with sitagliptin has also been reported,[15] though absolute risk appears low, while conflicting evidence regarding a worsening of heart failure in patients prescribed sitagliptin has been signalled.[8 16]

Though safety of both treatments has been well evaluated, less has been characterised about the comparative effectiveness of sitagliptin compared to sulfonylureas from both randomised controlled trials (RCTs) and non-randomised studies using 'real-world' data.

Several randomised placebo controlled trials have been conducted on both sitagliptin and sulfonylureas[17–20]; however, these do not facilitate direct comparison between the two. We carried out a systematic review to collate and analyse evidence from both RCTs and non-randomised studies to ascertain the effectiveness of sitagliptin compared to sulfonylureas in patients inadequately controlled on metformin. We examined a wide range of clinical effectiveness outcomes for which data have been reported.

METHODS

We conducted this systematic review in accordance with a prespecified published protocol.[21] We have reported our findings in order to comply with both the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement and MOOSE (Meta-Analyses and Systematic Reviews of Observational Studies) reporting guidelines.[22 23]

Eligibility criteria

A study was eligible if it was an RCT or non-randomised study conducted postmarketing authorisation comparing sitagliptin with sulfonylureas (gliclazide, glipizide, glibenclamide, tolbutamide, chlorpropamide, glimepiride) in adults with T2DM inadequately controlled on metformin. We required that all studies have a minimum of 1-month patient follow-up after initiation with sitagliptin or sulfonylurea for outcomes (however, a minimum of 3 months was required for reported changes in HbA1c).

Search strategy and study selection

Eligible studies written in English were identified using electronic searches for RCTs, non-randomised observational studies and conference abstracts using MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 1 June 2016 and EMBASE (1 January 1980 to 1 June 2016). Search strategies were developed for individual databases and reviewed by an information specialist to ensure rigour (online supplementary methods 1a–2c). Additional studies and grey literature were retrieved by screening references of retrieved studies and by searching International Pharmacy Abstracts, conference proceedings on Scopus and the WHO international clinical trial registry. We also contacted authors and manufacturers directly in cases where data were not available in the public domain; however, no additional data were made available.

One reviewer (MS) performed the full search strategy, removed duplicates and selected the articles. A second reviewer (NB) independently analysed these selections for eligibility of inclusion. Studies were screened based on title and abstract initially, following which full texts were obtained and assessed for inclusion. All records identified in searches were managed and stored in a reference management software (EndNote X7, Thomson Reuters, New York, USA).

Data extraction

All data were independently extracted by two reviewers (MS and NB) into standardised electronic forms. Data extracted included study details, participant details and intervention details (drug name, dose, frequency). Reported intention-to-treat analysis results were used where possible. Outcomes examined compared sitagliptin and sulfonylurea for change from baseline in HbA1c (%), fasting plasma glucose (mmol/l), weight (kg), body mass index (BMI) (kg/m^2), systolic and diastolic blood pressure (mm Hg), total cholesterol (mmol/mol) and triglycerides (mmol/mol) and the number of individuals achieving HbA1C at study end of <7% and <6.5%. In addition, all data on longer-term outcomes involving over 2 years of patient follow-up where reported were also extracted. This included data examining the risk of needing treatment change or insulin initiation after commencement of sitagliptin compared to sulfonylureas. We also proposed to extract data on longer-term outcomes examining risk of macrovascular and microvascular

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complications of diabetes; however, no such data were retrieved. All disagreements between reviewers were resolved by consensus or discussion with a third (IN) and fourth reviewer (IP) where needed.

Quality assessment

The Cochrane Collaborations Risk of Bias Tool was used to assess heterogeneity and quality for the RCTs. All six domains in the risk of bias tool were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each domain was graded as (a) low bias, (b) unclear bias or (c) high bias.[24]

The methodological quality of non-randomised studies included was assessed using the Newcastle-Ottawa Quality Assessment Scale.[25] This scale consists of a 'star-rating system' in which a study is judged on three broad domains: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.[25]

All study assessments were carried out independently by two reviewers and checked for agreement. Differences were resolved through consensus or in consultation with a third (IN) and fourth reviewer (IP).

Data analysis

Mean differences (MDs) were calculated for continuous outcomes and ORs or HRs for dichotomous outcomes where possible. Adjusted data (adjusted OR or HR with 95% CI) from non-randomised studies were used where available. We planned to conduct meta-analysis if included articles were sufficiently homogenous and of high quality. However, given the wide range of research methods identified, significant variation in duration of follow-up across studies and overlapping patient populations in some studies, a meta-analysis across all studies was not deemed appropriate. Nonetheless, forest plots were constructed for comparison and an overall descriptive analysis was undertaken examining each outcome across the studies where reported with a comprehensive account of study quality.

We did undertake meta-analysis for outcomes where two or more studies were available of a sufficiently homogenous standard. Data synthesis was undertaken using a fixed-effects model (Mantel-Haenszel method) unless our assessment of study qualities determined that a fixed-effects model was unsuitable or significant heterogeneity was evident.[26] Heterogeneity was assessed using the I^2 statistic, with an I^2 statistic greater than 50% considered indicative of significant heterogeneity and necessitating use of a random-effects model (Dersimonian-Laird method) for meta-analysis.[24 27]

Sensitivity analysis undertaken to explore impact of duration of follow-up on meta-analysis results did not alter findings. All analysis was undertaken using STATA statistical software package (version 13).

RESULTS

Search results and study characteristics

In total, 12 studies were eligible for inclusion (figure 1) with a list of excluded studies following full text review in the online supplementary table S1. Included studies consisted of seven RCTs[28–34] and five non-randomised (table 1).[35–39] Among the RCTs, four studies used glimepiride exclusively as the sulfonylurea comparator,[28–30 34] two studies exclusively used glipizide,[32 33] while one study used glibenclamide.[31] Among the non-randomised studies, use of various sulfonylureas were permitted. Duration of patient follow-up in the RCT studies ranged from 1 month for the shortest[30] to 24 months for the longest studies.[28 33] Duration of patient follow-up was, in general, longer in the non-randomised studies ranging from 3 months in the shortest prospective cohort study[38] to 72 months in the longest.[36] Four of the seven RCT studies required patients to be on metformin at a dose of ≥1500 mg at baseline,[28 29 32 33] while this was not required for any of the non-randomised studies. Further details on study exclusion criteria can be found in online supplementary table S2.

The characteristics of participants across the studies are summarised in table 2. The study population ranged from 34 individuals in the smallest RCT[30] to 1172 in the largest.[33] Non-randomised study sizes ranged from 69 participants to 20 529 individuals in the largest cohort study.[36 37] The mean age of participants ranged from 54.3 years to 59.6 years in the RCTs and 46.9 years to 64.2 years in the non-randomised studies. The mean baseline HbA1c ranged from 7.0% to 8.3% in the RCT, while it ranged from 7.5% to 8.7% across the non-randomised studies. Mean weight at baseline ranged from 80.6 kg to 91.8 kg in the RCTs, while it ranged from 63.8 kg to 74.5 kg in the non-randomised studies; however, it was often poorly reported.

Quality assessment

Risk of bias assessment for RCTs

Out of seven RCTs, three studies were judged to be at high risk of bias in one of the seven domains examined as shown in online supplementary table S3. A lack of blinding of participants and personnel put both Srivastava *et al* and Koren *et al* at high risk of bias.[31 34] Additionally, Koren *et al* was also deemed to be at high risk of selection bias due to the absence of adequate randomisation of participants.[31] Kim *et al* was at high risk of reporting bias as all outcomes, for example, change in HbA1c were reported in absolute terms without adjustment (despite imbalance in gender and baseline fasting plasma glucose after randomisation) and no comparative analysis examining both treatments was undertaken.[30] In Kim *et al*, it was unclear whether sequence generation for randomisation was inadequate or baseline imbalances were simply due to the small sample size for the study of 34. However, this lack of adjustment in analysis meant any results presented in Kim *et al* could not be used for our comparative analysis. Risk of other bias was also high for

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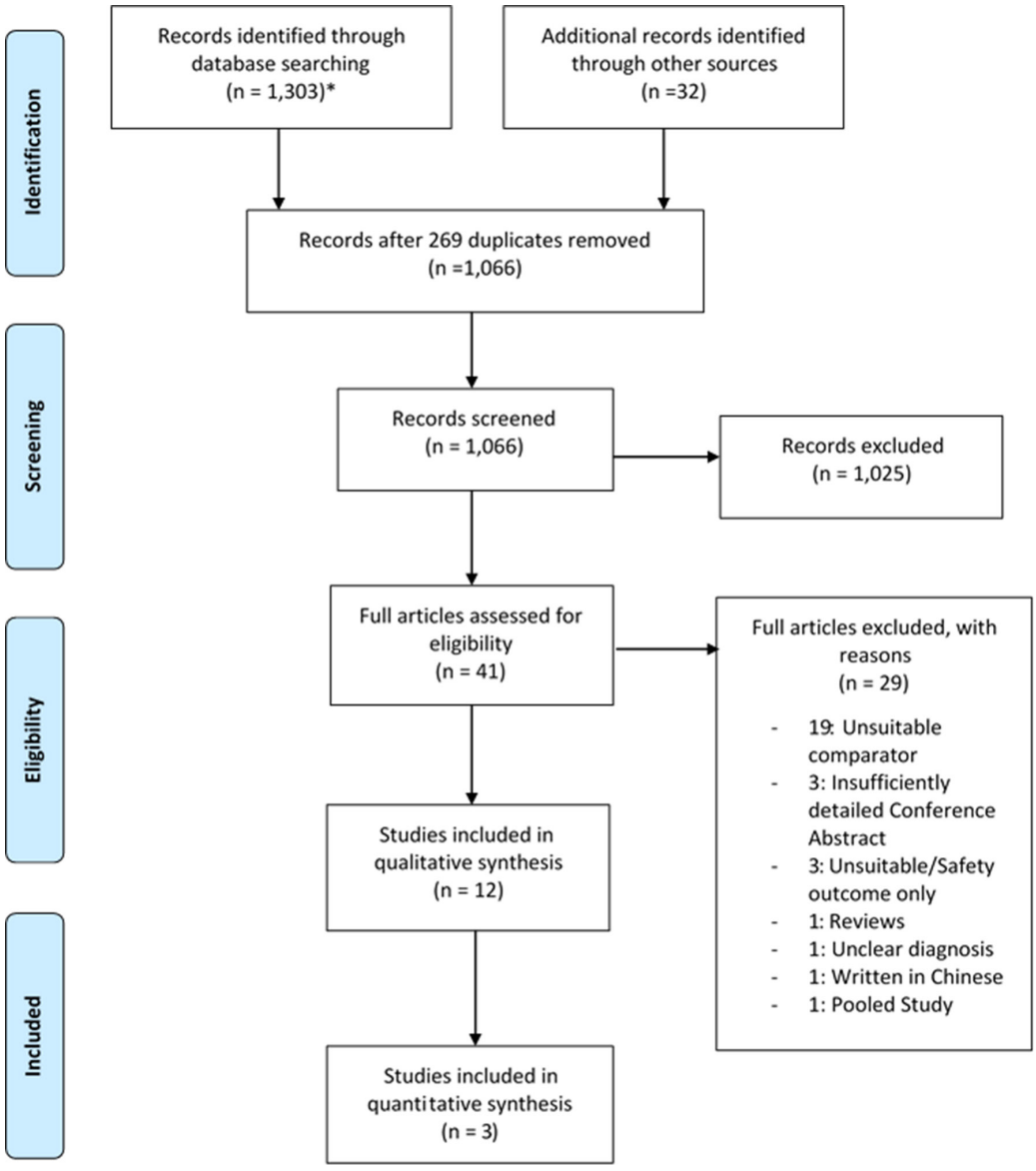

Figure 1 PRISMA flow diagram: study identification, selection and exclusions. *Monthly automated alerts from 01/11/15 to 01/06/16 consisting of updates to the search strategy identified additional articles in Embase, Medline and CENTRAL that have been included in the flow diagram above. However, no eligible studies for inclusion were obtained through these updates

Srivastava *et al* due to a lack of information on baseline characteristics of study participants, which made the final study results challenging to interpret.[34]

Assessment of study quality of non-randomised observational studies using Newcastle-Ottawa Scale

Based on use of the Newcastle-Ottawa Scale described earlier, two of the five non-randomised studies were deemed to be of low quality as shown in online supplementary table S4. Suraj *et al* achieved a low-quality rating as it did not meet the standard expected for cohort comparability mainly due to a failure to adjust for important confounders such as age, sex, baseline HbA1c, weight and metformin dose in the final analysis.[38] Derosa *et al* achieved a low-quality rating as they had a strict cohort study exclusion criteria excluding more ill diabetic patients, and though they matched for age, sex and diabetes duration, they failed to adjust for other potential relevant confounders such as socioeconomic status, comorbidities, among others. Derosa *et al* also had significant loss to follow-up and failed to describe it with sufficient clarity or evaluate whether this may have biased results.[35] Further details on methodological approaches used to control confounding in each of the five non-randomised studies are provided in online supplementary table S5.

Outcomes

Glycaemic change

Seven studies in total reported glycaemic change (figure 2A). We performed meta-analysis for three of these RCTs because they were of high quality and exceeded 6 months in duration. A fourth study, led by Nauck *et al*, could not be included for meta-analysis, as

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Table 1 Characteristics of the included studies

Study	Type	Sita dose	Sulf dose	Duration*	Inclusion criteria	Primary outcome
Ahrén *et al*†[28]	RCT	100 mg	Glim 2–4 mg	24	Aged ≥18 years and T2DM and baseline HbA1c ≥7.0% and ≤10.0% and prescribed metformin ≥1500 mg or maximum tolerated dose, BMI 20–45 kg/m^2; creatinine clearance >60 mL/min; normal thyroid-stimulating hormone concentration or clinically euthyroid	Change in HbA1C from baseline
Arechavaleta *et al*[29]	RCT	100 mg	Glim 1–6 mg	7.5	Aged ≥18 years with T2DM and baseline HbA1c ≥6.5% and ≤9.0% and prescribed metformin ≥1500 mg/day	Change in HbA1C from baseline
Kim *et al*[30]	RCT	100 mg	Glim 2 mg	1	Aged 18–80 years and T2DM for <10 years baseline HbA1c ≥7.0% and ≤10.0% prescribed metformin and BMI 20–30 kg/m^2	Change in HbA1C from baseline
Koren *et al*[31]	RCT	100 mg	Glib 5 mg	3	Aged 18–75 years and T2DM with baseline HbA1c ≥7.0% and prescribed metformin	Change in arterial stiffness from baseline
Nauck *et al*[32]	RCT	100 mg	Glip 5–20 mg	12	Aged 18–78 years and T2DM and baseline HbA1c ≥6.5% and ≤10.0% and prescribed metformin ≥1500 mg/day	Change in HbA1C from baseline
Seck *et al*‡[33]	RCT	100 mg	Glip 5–20 mg	24	Aged 18–78 years and T2DM and baseline HbA1c ≥6.5% and ≤10.0% and prescribed metformin ≥1500 mg/day	Change in HbA1C from baseline
Srivastava *et al*[34]	RCT	50–200 mg	Glim 1–4 mg	4.5	Aged ≥18 years with T2DM and baseline HbA1c ≥7.0% and ≤10.0% and prescribed metformin	Change in HbA1C from baseline
Derosa *et al*[35]	Prosp. Cohort	100 mg	Var§	60	Aged >18 years with T2DM and baseline HbA1c ≥8.0%, prescribed metformin and BMI 25–30 kg/m^2).	Change in HbA1C from baseline
Inzucchi *et al*[36]	Retro. Cohort	Var	Var§	72	Aged ≥18 years, initiated therapy with metformin in the 12 months preceding the index date on which sitagliptin/sulfonylurea initiated	Risk of insulin initiation
Lee *et al*[37]	Prosp. Cohort	100 mg	Var§	6	Aged ≥18 years with T2DM with a baseline HbA1c level ≥7.5% and prescribed metformin	Change in HbA1C from baseline
Suraj *et al*[38]	Prosp. Cohort	100 mg	Var§	3	Aged 18–70 years with T2DM and a baseline HbA1c ≥7.0% and prescribed metformin	Change in HbA1C from baseline
Valensi *et al*[39]	Prosp. Cohort	100 mg	Var§	36	Aged ≥18 years and prescribed metformin with inadequately controlled T2DM as determined by physician judgement	Risk of need for treatment change

*Duration reported in months.
†Only sitagliptin and sulfonylurea RCT arms considered.
‡Seck *et al* is an extended follow-up study of Nauck *et al*; only Seck *et al* was included for meta-analysis.
§Use of any sulfonylurea drug was permitted. In Suraj *et al*, 5 mg glibenclamide, 1 mg glimepiride or 60 mg gliclazide were permitted only.
BMI, body mass index; Glib, glibenclamide; Glim, glimepiride; Glip, glipizide; HbA1c, haemoglobin A1c; Prosp, prospective; RCT, randomised controlled trial; Retro, retrospective; Sita, sitagliptin; Sulf, sulfonylureas; T2DM, type 2 diabetes mellitus.

Table 2 Patient characteristics across the included studies

Study	Participants		Age (SD)		Male (n) (%)		Diabetes duration (years) (SD)		HbA1c (%) (SD) (mmol/mol, SD)		FPG (mmol/l) (SD)		Weight (kg) (SD)	
	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf
Ahrén *et al*[28]	302	307	54.3 (9.8)	54.4 (10.0)	139 (46.0)	158 (51.5)	5.8 (4.8)	6.0 (4.8)	8.1 (0.8) (65, 8.7)	8.1 (0.8) (65, 8.7)	9.2 (2.6)	9.3 (2.5)	90.3 (19.1)	91.8 (20.4)
Arechavaleta *et al*[29]	516	519	56.3 (9.7)	56.2 (10.1)	284 (55.0)	279 (53.8)	6.8 (4.6)	6.7 (4.8)	7.5 (0.7) (58, 7.7)	7.5 (0.8) (58, 8.7)	8.0 (1.8)	8.1 (19)	80.6 (15.2)	82.0 (16.7)
Kim *et al*[30]	17	17	59.6 (6.7)	55.8 (6.6)	12 (75.0)	7 (41.2)	4.8 (5.2)	5.9 (4.2)	7.0 (0.5) (53, 5.5)	7.3 (0.4) (56, 4.4)	7.3 (0.5)	8.7 (0.7)	NR	NR
Koren *et al[31]**	40	40	59.0 (10.0)	59.0 (10.0)	25 (62.5)	25 (62.5)	7.8 (5.0)	7.8 (5.0)	8.3 (1.1) (67, 12)	8.3 (1.1) (67, 12)	9.4 (0.7)	9.4 (0.7)	NR	NR
Nauck *et al*[32]	588	584	56.8 (9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	6.5 (6.1)	6.2 (5.4)	7.7 (0.9) (61, 9.8)	7.6 (0.9) (60, 9.8)	9.2 (2.3)	9.1 (2.3)	89.5 (17.4)	89.7 (17.5)
Seck *et al*§[33]	588	584	56.8 (9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	6.5 (6.1)	6.2 (5.4)	7.7 (0.9) (61, 9.8)	7.6 (0.9) (60, 9.8)	9.2 (2.3)	9.1 (2.3)	89.5 (17.4)	89.7 (17.5)
Srivastava *et al*[34]	25	25	NR	NR	NR	NR	NR	NR	8.3 (0.4) (67, 4.4)	8.2 (0.6) (66, 6.6)	10.2 (0.6)	9.9 (0.7)	NR	NR
Derosa *et al*[35]	216	NR†	NR	NR	NR	NR	NR	NR	8.3 (0.3) (67, 3.3)	8.5 (0.5) (69, 5.5)	8.1 (0.8)	8.3 (0.9)	NR	NR
Inzucchi *et al*[36]	6104	14 425	57.4 (11.8)	58.0 (12.5)	3074 (50.4)	7504 (52.0)	NR	NR	7.9 (1.6) (63, 17.5)	8.4 (2.0) (68, 21.9)	NR	NR	NR	NR
Lee *et al*[37]	38	31	50.2 (13.7)	54.8 (11.6)	24 (63.2)	16 (51.6)	1 (0.6)‡	1 (0, 12)‡	9.4 (7.9, 11.1) ‡ (79 (63, 98))	8.9 (8.2, 10.2) ‡ (74 (66, 88))	9.6 (7.5, 11.3)‡	9.3 (7.7, 10.8)‡	74.5 (11.6)	69.9 (15.4)
Suraj *et al*[38]	50	50	46.9 (9.6)	48.9 (9.3)	34 (68.0)	19 (38.0)	3.4 (3.5)	2.8 (3.0)	8.2 (1.0) (66, 10.9)	8.7 (1.4) (72, 15.3)	10.2 (3.2)	10.8 (3.4)	65 (12.2)	63.8 (9.7)
Valensi *et al*[39]	1874	733	62.4 (10.8)	64.2 (11.5)	1108 (59.4)	422 (57.6)	6.4 (5.9)	7.0 (5.6)	7.5 (1.0) (58, 10.9)	7.6 (1.0) (60, 10.9)	8.6 (2.1)	8.5 (2.2)	NR	NR

*Crossover trial; hence, characteristics are the same in both arms.
†In Derosa *et al*, the authors compared several groups of patients prescribed with metformin (metformin and sulfonylurea, metformin and pioglitazone) and did not detail how many were in the metformin and sulfonylurea group specifically.
‡Median and IQR reported (not mean).
§Seck *et al* is an extended follow-up study of Nauck *et al*; only Seck *et al* was included for meta-analysis.
hbA1c, haemoglobin A1c, FPG, fasting plasma glucose; NR, not reported; SD, standard deviation; Sita, sitagliptin; Sulf, sulfonylureas.

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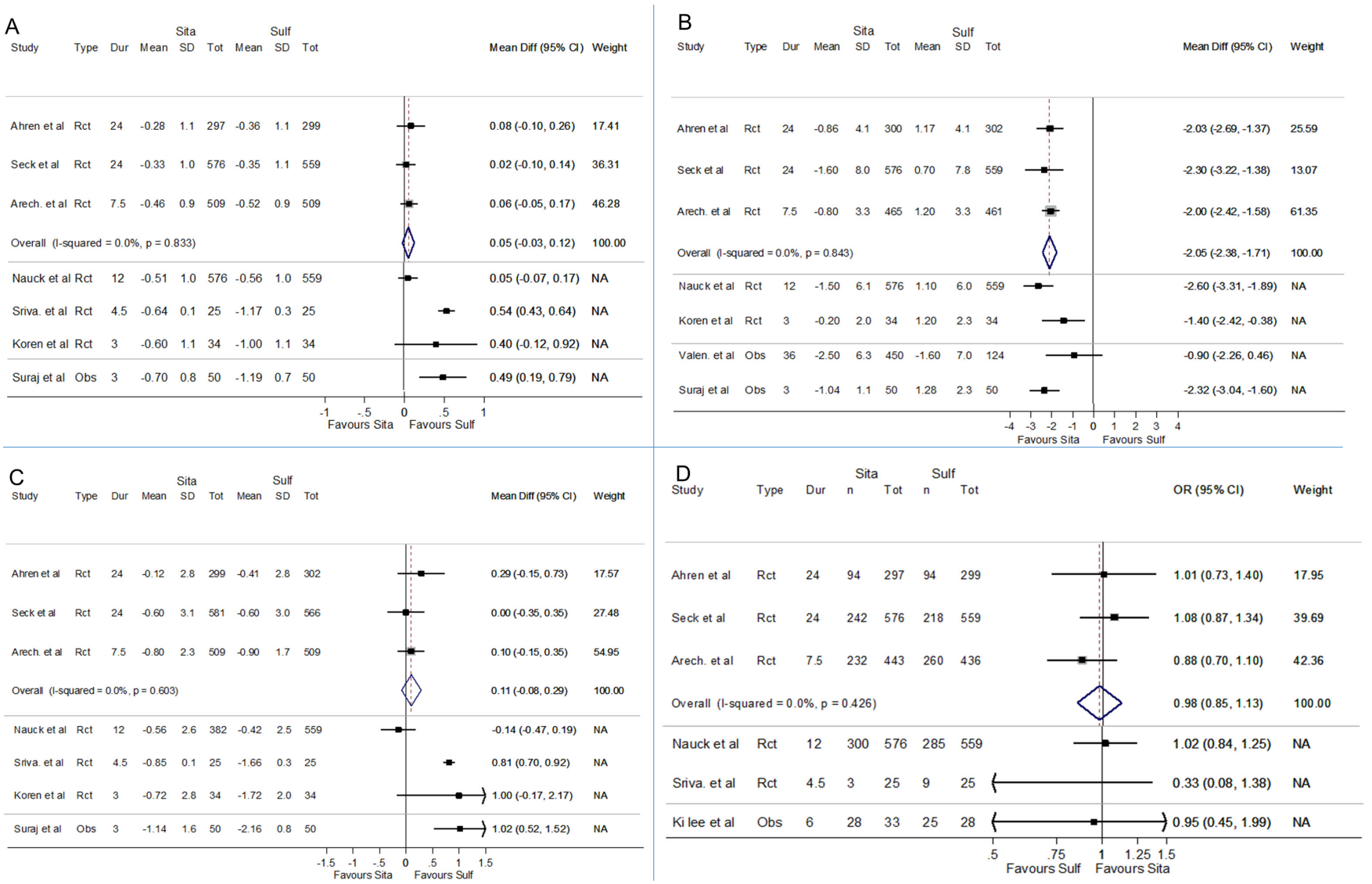

Figure 2 Forest plots comparing sitagliptin and sulfonylureas for change from baseline in hbA1c (%) (A), weight (kg) (B), fasting plasma glucose (mmol/mol) (C) and for proportions achieving a hbA1c <7% (53 mmol/mol) at end of study (D). Dur, duration in months; Mean Diff, mean difference; NA, not applicable; Obs, Non-randomized Observational study; OR, Odds ratio; Rct, Randomized controlled trial; SD, Standard deviation; Sita, sitagliptin; Sulf, sulfonylureas; Tot, total participants. Note: Weights where present are from Fixed effects meta-analysis though Random-effects estimates were identical. Tau^2=0% for all meta-analyses

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Seck *et al* was an extended follow-up of this study and this would have led to double counting of patients. Meta-analysis showed that, compared to sulfonylureas, treatment with sitagliptin produced a similar glycaemic change, as measured by reductions in HbA1c from baseline: (weighted mean difference (WMD) in HbA1c 0.05%; 95% CI −0.03% to 0.12%; I^2=0%)) (graph in HbA1c units of mmol/mol is included in online supplementary figure S1). The odds of achieving a HbA1c of <7% by study end was also meta-analysed across these three RCTs, and no significant difference was observed between sitagliptin and sulfonylureas (OR 0.98 95%; CI 0.85 to 1.13, I^2=0%) (figure 2D). Only in the shorter 4.5-month RCT study led by Srivastava, not included in meta-analysis, were sulfonylureas shown to be superior (mean difference (MD) in HbA1c 0.54%; 95% CI 0.43% to 0.64%).

Glycaemic change was also reported in the observational study led by Suraj *et al* (MD 0.49%; 95% CI 0.19% to 0.79%) where a significantly greater reduction in HbA1c was observed with sulfonylureas (figure 2A). Derosa *et al* reported change from baseline in HbA1c after 5 years in a prospective cohort study; however, they did not undertake any formal analysis to adjust for relevant confounders, which made results difficult to interpret, and we have not presented them.

Weight change

Meta-analysis of the three RCTs that could be pooled showed statistically significant reduction in weight with sitagliptin from baseline compared to sulfonylureas (WMD −2.05 kg; 95% CI −2.38 to −1.71 kg; I^2=0%) (figure 2B). This equated to a modest weight increase of approximately 1 kg with sulfonylureas and loss of 1 kg with sitagliptin. Treatment with sitagliptin also showed significant reduction in weight in the remaining RCTs as shown in figure 2B. The greatest comparative weight reduction was observed in the 12-month RCT led by Nauck *et al* (MD −2.60 kg; 95% CI −3.31 to −1.89 kg).

The prospective cohort study led by Suraj *et al* also revealed a similar weight reduction as the RCTs[38]; however, the cohort study led by Valensi *et al* did not find this reduction to be significant with a longer 36-month follow-up (figure 2B).[39]

Changes in body mass index were also reported in a small number of studies, and as results, necessarily, mirror weight change, they have been included in appendix for reference (online supplementary figure S2).

Fasting plasma glucose

Meta-analysis of the three RCTs showed that, compared to sulfonylureas, treatment with sitagliptin produced similar change in fasting plasma glucose (mmol/l) from baseline (WMD 0.11 mmol/L 95%; CI −0.08 to 0.29 mmol/L; I^2=0%) (figure 2C). Of the remaining RCTs, only the shorter 4.5-month RCT study led by Srivastava *et al* demonstrated a more significant reduction in fasting plasma glucose with sulfonylureas (MD 0.81 mmol/l %; 95% CI 0.70 to 0.92 mmol/L).

The observational study led by Suraj *et al* also demonstrated a more significant reduction in fasting plasma glucose with sulfonylureas compared to sitagliptin (MD 1.02 mmol/L; 95% CI 0.52 to 1.52 mmol/L).[38]

Blood pressure and lipid changes

Two RCTs reported no significant difference between sitagliptin and sulfonylureas for change in systolic and diastolic blood pressure, level of triglycerides and cholesterol between study end and baseline (figure 3A–D).

In the RCT led by Ahren *et al*, a clinically insignificant but statistically significant reduction in total cholesterol was observed with sitagliptin compared to sulfonylureas (MD −0.16 mmol/mol; 95% CI −0.29 to −0.03 mmol/mol).[28]

Longer-term outcomes

Two non-randomised studies reported outcomes from longer follow-up of patients not reported in any RCTs retrieved. The 36-month cohort study led by Valensi *et al* explored the risk of needing treatment change after add-on of sitagliptin compared to sulfonylureas (figure 3E).[39] They found that the adjusted risk of needing treatment change was lower with sitagliptin (HR 0.65; 95% CI 0.57 to 0.73).

The 72-month cohort study led by Inzucchi *et al* demonstrated that individuals prescribed sitagliptin had a lower risk for initiating insulin during follow-up after relevant adjustment (HR 0.76; 95% CI 0.65 to 0.90) (figure 3F).[36]

DISCUSSION

In this systematic review, the meta-analysis conducted using three RCTs in which follow-up was greater than 6 months demonstrated similar glycaemic improvement after add-on of sitagliptin compared to sulfonylureas in individuals inadequately controlled on metformin. Statistically significant reduction in weight of approximately 2 kg was observed with sitagliptin when compared to sulfonylureas driven by modest weight increase with sulfonylureas and modest decrease with sitagliptin. This may not be of clinical significance for most individuals other than those at more extremes of weight, for example, frail elderly patients or those struggling to lose weight. Outcome reporting for change in blood pressure and lipids from baseline was low, and meta-analysis was not possible, although data from two RCTs did not show any clinically meaningful difference between both add-on treatments. Two cohort studies reported longer-term outcomes, relating to time before a treatment change or insulin initiation was needed. In both of these high-quality non-randomised studies, results suggested that fewer individuals prescribed sitagliptin than sulfonylureas needed treatment change at 36-month and 72-month follow-ups, respectively.

Meta-analysis of high-quality homogenous RCTs represents the highest source of evidence,[40] and we identified three homogenous RCTs for meta-analysis. However,

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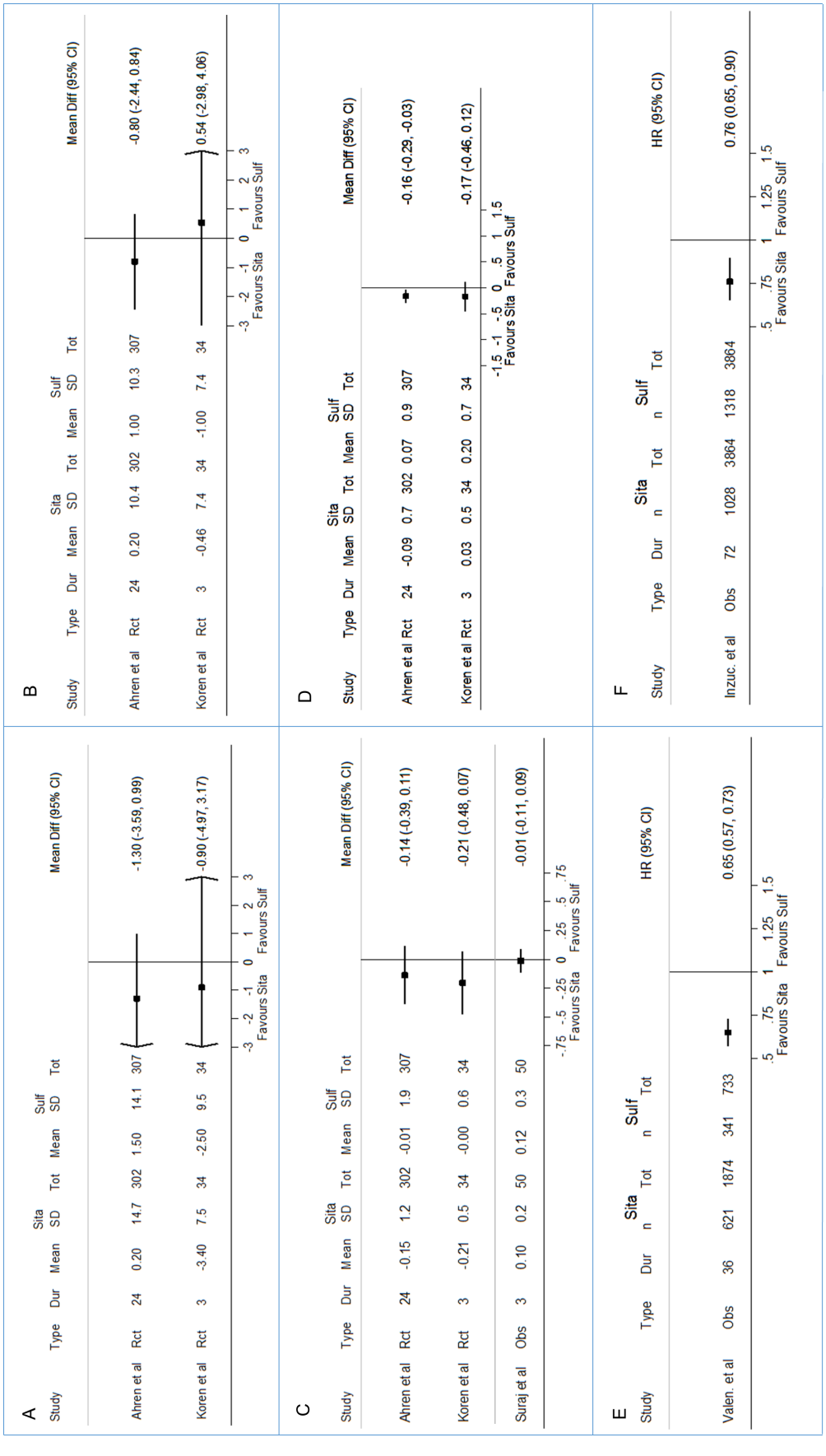

Figure 3 Forest plots comparing sitagliptin and sulfonylureas for change from baseline for systolic blood pressure (mmHg) (A), diastolic blood pressure (mmHg) (B), triglycerides (mmol/l) (C), total cholesterol (mmol/mol) (D), risk of needing treatment change (E) and risk of initiating insulin (F). Dur, duration in months; HR, hazard ratio; Mean Diff, mean difference; Obs, non-randomised observational study; Rct, randomised controlled trial; SD, standard deviation; Sita, sitagliptin; Sulf, sulfonylureas.

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the RCT inclusion criterias may have led to exclusion of important population subgroups frequently seen in clinical practice decreasing external validity of the findings from the meta-analysis alone. For example, Arechavaleta *et al* excluded individuals with a baseline HbA1c >9%,[29] and Seck *et al* excluded individuals >78 years of age.[33] Drug utilisation studies have shown that such criteria alone can exclude close to 50% of individuals seen in real-world clinical practice.[41] Therefore, by assessing and reporting on the quality of the remaining clinical trials that could not be meta-analysed (some of which had more pragmatic inclusion criteria[31]) and including non-randomised studies that provide insight into effectiveness in actual clinical practice and longer-term outcomes, we believe this study was made more informative.

Glycaemic control achieved with sitagliptin or sulfonylureas in patients inadequately controlled on metformin was similar in our meta-analysis. Synergistic improvement in glycaemic effectiveness has been reported when sitagliptin and metformin are used together; however,[42] our study has shown that the glycaemic reduction results are similar to that achieved when metformin and sulfonylureas are used together. One RCT[34] and cohort study reported significant reductions in HbA1c and fasting glucose with sulfonylureas compared to sitagliptin; however, these were both of 4.5 months in duration only.[38] This peak in sulfonylurea glycaemic efficacy within the first 6 months of treatment has been previously described.[43 44] For all studies of greater than 6-month duration, we found that glycaemic benefit with sitagliptin and sulfonylurea was comparable in line with guidance from major international bodies.[1–4 9]

Statistically significant weight loss with sitagliptin compared to sulfonylurea of approximately 2 kg was evident in our meta-analysis and also across all RCTs and non-randomised studies reported up to 2 years in duration. This difference was driven by modest weight decrease with sitagliptin and increase with sulfonylureas. Sitagliptin is often described as having only a weight neutral effect[45–47]; however, when compared directly with sulfonylureas, a small reduction in weight is evident. This comparative reduction is unlikely to be clinically significant for most individuals other than those at more extremes of weight or those struggling to lose weight.

Longer-term outcomes with follow-up greater than 2 years were reported in two cohort studies only.[36 39] The risk of requiring a change in treatment or initiating insulin was found to be lower with sitagliptin, suggesting that sitagliptin patients are less likely to need treatment change over longer follow-up. However, decisions to change treatment or initiate insulin are based on clinician decisions, which can be subjective and hence vary. Furthermore, treatment inertia is a well-established problem in care of individuals with type 2 diabetes.[48] Without data on glycaemic control at the time of treatment change, we cannot fully assess whether clinicians changed treatment appropriately, making this finding challenging to interpret.

Only 2 RCTs reported data on markers of cardiovascular disease and these did not show any clinically significant change being achieved in blood pressure or lipids through being prescribed sitagliptin or sulfonylureas as add-on to metformin. Cardiovascular outcome studies comparing sitagliptin to placebo have also been conducted recently[49]; however, direct comparisons between a DPP-4 inhibitor and sulfonylurea will not emerge until 2019 on completion of the CAROLINA study.[50] This study will focus on use of linagliptin rather than sitagliptin, which raises a challenge as recent RCT results for different DPP-4 inhibitors were conflicting, raising the possibility that different DPP-4 inhibitors may exhibit different cardiovascular risks.[49 51 52] Equally, the effect of sulfonylureas on cardiovascular disease is still poorly understood despite many years of usage.[53 54] Studies have reported increased mortality from cardiovascular disease with use of sulfonylureas particularly tolbutamide and chlorpropamide[43 55]; however, results from more recent RCTs with newer sulfonylureas like gliclazide are more reassuring.[43 56] Further research is needed.

No RCTs or non-randomised studies reported longer-term data on the risk of complications of diabetes such as retinopathy, neuropathy and nephropathy despite these being well established as consequences of poor longer-term glycaemic control.[22] A comparative effectiveness pragmatic clinical trial, the Glycemia Reduction Approaches in Diabetes, is underway that will compare sitagliptin with sulfonylureas in individuals with T2DM inadequately controlled on metformin for longer-term complications.[57] However, the results of this trial are not expected until 2020, and this evidence is needed urgently. Mounting observational data could help investigate these outcomes.

Strengths and limitations

Our study has some important strengths. This is the first systematic review, to our knowledge, to assess effectiveness from both RCTs and non-randomised studies comparing sitagliptin with sulfonylureas as add-on to metformin. Secondly, we have reported data across a wide range of outcomes, and thirdly, we have undertaken meta-analysis only where methodologically appropriate in accordance with our prespecified protocol.[21]

There are also some limitations to acknowledge. Firstly, we have focused entirely on effectiveness in this review because safety has been evaluated in-depth elsewhere as summarised earlier.[8 11 12 15 58] Secondly, we have presented intention-to-treat results (where available) from each study reported. Though this can bias results towards equivalence if there are high dropout rates or considerable switching in studies, this was not the case across studies included. Moreover, our goal was to shed further light on the effectiveness of sitagliptin compared to sulfonylureas with a focus on the initial prescribing decision, and this was the most informative approach to achieve this. Thirdly, our analysis has focused on sitagliptin only as it has been the most extensively prescribed DPP-4 inhibitor

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in the UK and USA.[7] Different sulfonylureas do exhibit different pharmacokinetic behaviour, particularly with regards to duration of action; however, they have been grouped together because included studies used mainly newer generation sulfonylureas, which from a pharmacodynamic effectiveness point of view, behave similarly.[43] Finally, despite high prevalence of type 2 diabetes in Asia, no study based solely within an Asian country qualified for the meta-analysis. This omission is of significance as evidence is emerging that suggests that glycaemic effectiveness of DPP-4 inhibitors like sitagliptin may in fact be greater in East Asians. This may be due to phenotypic variation in diabetes and highlights why further research may be needed to identify Asian ethnic subgroups who may need different therapeutic approaches.[59]

CONCLUSIONS

In summary, the absence of data on effectiveness comparing sitagliptin with sulfonylureas among individuals with T2DM inadequately controlled on metformin for reducing longer-term complications of T2DM means treatments decisions for effectiveness (once safety has been considered) must be based on short-term to medium-term outcome data available. In this respect, we have shown that glycaemic control with both treatments was similar. Statistically significant weight reduction of close to 2 kg was observed with use of sitagliptin when compared to sulfonylureas in both RCTs and non-randomised studies, though this may not be of major clinical importance for most individuals. Non-randomised studies also reported that there was a lower likelihood of treatment change after initiation of sitagliptin compared to sulfonylureas. However, it was difficult to interpret if this was necessarily a positive finding due to lack of glycaemic data at time of treatment change. Further comparative effectiveness research work is needed from RCTs or non-randomised studies to address evidence gaps relating to risks of longer-term macrovascular and microvascular complications of T2DM.

Contributors MS, IN and IP collectively planned the study. MS drafted both the systematic review protocol and manuscript. MS and NB assessed eligibility of included articles, extracted data and assessed quality of the studies. IN and IP served as adjudicators for disagreements. MS performed the analysis and with NB, IN and IP interpreted the results. MS, NB, IN and IP all reviewed the manuscript for intellectual content and approved the final version.

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Disclaimer I, Manuj Sharma, lead author, confirm that this manuscript is an honest, accurate and transparent account of the studies being reported; that no important aspects of the studies have been omitted; and that any discrepancies from this study as planned from our protocol have been explained.

Competing interests All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf. MS, IN and IP report grants from Novo Nordisk A/S, during the conduct of the study. The authors (MS, NB, IN and IP) do not declare any conflicts of interest relevant to this manuscript.

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Data sharing statement All data included for this systematic review have been provided in either the main manuscript or supplementary appendix. There are no further unpublished data available relating to this manuscript.

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