RESEARCH PAPER

AGE AND AGEING

COMPARATIVE EFFECTIVENESS OF SITAGLIPTIN VS SULPHONYLUREAS IN OLDER PEOPLE

Short title: Effectiveness of Sitagliptin vs Sulphonylureas in Older People

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ABSTRACT

Background: Two common anti-diabetic treatments used are sitagliptin and sulphonylureas however evidence examining their comparative effectiveness in older people is limited

Objective: To evaluate effectiveness of sitagliptin vs sulphonylureas when added to metformin in older (aged ≥75) vs younger people (18-75)

Design: Retrospective Cohort Study

Setting: UK Primary Care

Subjects: 2,904 individuals prescribed sitagliptin (223 aged≥75) and 13,683 prescribed sulphonylureas (1,725 aged≥75)

Methods: Multivariable regression to analyse difference in HbA1c and weight, 12 months after add-on initiation and proportion achieving different glycaemic targets.

Results: After multivariate adjustment to remove baseline differences, the HbA1c after 12 months of treatment was on average 1 mmol/mol (95%CI -0.7-2.8) higher with sitagliptin vs sulphonylureas in older people though this was not statistically significant. The weight however, was significantly lower -1.4kg (95%CI -2.1 to -0.7) with sitagliptin vs sulphonylureas. A lower proportion prescribed sitagliptin vs sulphonylureas recorded HbA1c <48mmol/mol by study end: Odds Ratio 0.63 (95%CI 0.42-0.95). In younger people, similar HbA1c reductions were also observed with both treatments, however weight after 12 months was even lower with sitagliptin vs sulphonylureas: -2.3kg (95%CI -2.5 to -2.0).

Conclusions: Similar HbA1c reduction was observed when sitagliptin or sulphonylureas were added to metformin in older and younger age-groups. Sitagliptin use led to modest comparative weight loss. There may be greater risk of over-treatment with sulphonylureas evidenced by greater proportion recording HbA1c <48mmol/mol by study end. This evidence supporting use of sitagliptin when add-on therapy is selected in older adults should be considered alongside the wider evidence-base and patient-preference.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) increases with age with recent estimates suggesting a prevalence of over 15% in the UK, in those aged ≥75 years.[1] Maintaining adequate glycaemic control in older adults often requires pharmacotherapy, with treatment choice more challenging due to greater risk of hypoglycaemia.[2] Most treatments remain less well studied in older people as they are often excluded from clinical trials, due to comorbidities and recruitment challenges.[2] Yet, treatment effectiveness in older adults can vary due to these comorbidities, as well as polypharmacy and altered drug handling.[3] In older people without significant renal impairment, metformin is recommended first-line treatment by NICE.[4] Once metformin has failed, prescribing become more challenging and guidelines advise that prescribing decisions account for patient preferences.[4,5] Drug-utilisation work has shown that the DPP-4 inhibitor, sitagliptin and sulphonylureas remain two commonly prescribed add-on therapies in older people, hence we focused on this comparison in this study.[1,2] This prescribing pattern, is despite emergence of newer therapies such as SGLT-2 inhibitors and further DPP-4 inhibitors like linagliptin in recent years.[5] There exists strong evidence to support a several-fold higher risk of hypoglycaemia with sulphonylureas while a small increased risk of pancreatitis may exist with sitagliptin[6,7] However, few studies have examined “real world” comparative effectiveness of these treatments in those aged ≥75 years as in this study. We will conduct an evaluation of the effectiveness of sitagliptin versus sulphonylureas as add-on to metformin on glycaemic control and weight change in older people (aged ≥75 years), framing our results in the context of younger people (aged 18-75 years). This is to help prescribers making clinical decisions of effectiveness in older adults when choosing between these two treatments, once safety concerns and patient preferences have been considered.

METHODS

Data Source

The Health Improvement Network (THIN) is a UK primary care database containing anonymised healthcare records with information collected during routine patient consultations in GP on demographic, diagnosis, prescribing and clinical examination and testing. THIN contains records from over 587 UK general practices (with around 12 million individuals contributing data)[8] and has been

shown to be broadly representative of the UK population.[9,10]. Scientific approval to undertake this study was obtained from IQVIA Committee in August 2016. (Reference-Number:16-072).

Study Population

All individuals with Type 2 Diabetes Mellitus (T2DM) in THIN between 2007-2014 (identified using a algorithm previously described[11] and detailed in Supplementary Methods S1), aged ≥75 years and aged 18-75 years prescribed sitagliptin or a sulphonylurea as add-on to metformin were included in this study. The date on which the first prescription for either sitagliptin or sulphonylurea was added-on was defined as the index date. We excluded anyone prescribed any antidiabetic other than metformin in the 12 months prior to add-on initiation. We included all individuals who were issued at least one metformin prescription within 60 days after the index date, to ensure our sample included those on dual therapy and not after a treatment switch. We also required that all individuals had a recorded HbA1c and weight at both baseline and between 9-18 months after add-on initiation to evaluate change. All individuals were followed up for a minimum of 9 and a maximum of 18 months. We excluded people who did not have at least 9 months of data after baseline (for example if they died before then, if they left their general practice or data stopped being collected from that respective general practice)

Statistical Analysis

We first examined absolute mean change in HbA1c and weight with each treatment separately to identify the change in HbA1c/weight observed. To actually compare both treatments, we then examined the mean difference in HbA1c and weight at 12 months between those initiated on sitagliptin compared to those initiated on sulphonylureas as add-on to metformin using multivariable linear regression analysis to adjust for baseline differences (confounders). We used multivariable logistic regression to compare odds for achieving a HbA1c below different glycaemic thresholds (<64mmol/mol, <58mmol/mol and <48 mmol/mol) by study end across treatment groups. Our analysis was undertaken in both age-groups (≥75 and 18-75 years) for comparison.

We adjusted for several covariates which were a subset of variables selected *a priori* (detailed in Table 1) that were shown to be statistically associated with both treatment choice and outcome. We undertook sensitivity analysis within a subgroup of those individuals who were deemed “adherent” to treatment. This “adherent” subgroup referred to those issued prescriptions of metformin and the

sitagliptin/sulphonylurea for 18 months with no more than a 60 days gap between successive prescriptions. This term “adherent” is used with a caveat that using issue of continuous prescriptions is only a surrogate measure for true adherence. Additionally, in accordance with recommended epidemiological practice, we explored impact of missing data in those with and without missing data for relevant covariates at baseline and for duration of follow-up to investigate if differences in characteristics may bias analysis.[12]

RESULTS

Baseline Characteristics

A total of 2,904 individuals prescribed sitagliptin (223 individuals aged ≥75 and 2,681 aged 18-75 years) and 13,683 prescribed sulphonylureas (1,725 individuals aged ≥75 and 11,958 aged 18-75) were included (Supplementary Figure S1).

Apart from differences observed in baseline weight and HbA1c, sitagliptin and sulphonylurea groups were reasonably well balanced for most comorbidities and concomitantly prescribed treatments in both age-groups.

The older group had a lower mean baseline HbA1c compared to the younger population (65.8mmol/mol vs 70.8mmol/mol for sitagliptin and 69.6mmol/mol vs 74.8mmol/mol for sulphonylureas respectively) (Table 1). Mean weight was also lower (84.6kg vs 100.9kg mmol/mol for sitagliptin and 80.5kg mmol/mol vs 93.1kg for sulphonylureas respectively). The percentage of individuals with evidence of renal impairment and diabetes complications such as cardiovascular disease (52.5% vs 23.1% for sitagliptin and 48.5% vs 27.1% for sulphonylureas) and retinopathy (24.7% vs 16.4% for sitagliptin and 16.5% vs 14.8% for sulphonylureas) was higher in the older population as was the prevalence of most comorbidities (Table 1).

Table 1 Baseline Characteristics

	Aged ≥ 75 years		**Aged 18-75 years**	
	Sita	**Sulf**	**Sita**	**Sulf**
Total (N)	**223**	**1725**	**2681**	**11958**
Baseline HbA1c mmol/mol, mean (SD)	65.8 (11.7)	69.6 (17.1)	70.8 (14.8)	74.8 (18.8)

	Aged ≥ 75 years		Aged 18-75 years	
	Sita	**Sulf**	**Sita**	**Sulf**
Age at index date years, mean (SD)	79.3 (3.8)	79.6 (3.7)	57.1 (9.7)	58.8 (9.9)
Sex				
Male	128 (57.4)	919 (53.3)	1597 (59.6)	7446 (62.3)
Female	95 (42.6)	806 (46.7)	1084 (40.4)	4512 (37.7)
Baseline weight kg, mean (SD)	84.6 (16.1)	80.5 (15)	100.9 (21.7)	93.1 (19.6)
Year Entry, n(%)				
2007	3 (1.3)	205 (11.9)	3 (1.3)	206 (11.7)
2008	3 (1.3)	246 (14.3)	3 (1.3)	251 (14.3)
2009	26 (11.7)	311 (18)	28 (12)	318 (18.1)
2010	53 (23.8)	315 (18.3)	54 (23.2)	321 (18.3)
2011	57 (25.6)	239 (13.9)	61 (26.2)	244 (13.9)
2012	41 (18.4)	206 (11.9)	43 (18.5)	209 (11.9)
2013	37 (16.6)	190 (11)	38 (16.3)	194 (11)
2014	3 (1.3)	13 (0.8)	3 (1.3)	13 (0.7)
F2FC*, mean (SD)	8.4 (5.1)	8.5 (5.3)	7.2 (5)	7.3 (4.9)
Townsend Quintile, n(%)				
1 (least deprived)	63 (28.3)	412 (23.9)	634 (23.6)	2469 (20.6)
2	61 (27.4)	436 (25.3)	527 (19.7)	2532 (21.2)
3	40 (17.9)	353 (20.5)	569 (21.2)	2575 (20.6)
4	32 (14.3)	316 (18.3)	541 (20.2)	2441 (20.4)
5 (most deprived)	27 (12.1)	208 (12.1)	410 (15.3)	1941 (16.2)
Smoking Status, n(%)				
Non	114 (51.1)	880 (51)	1234 (46)	5403 (45.2)
Ex	83 (37.2)	647 (37.5)	820 (30.6)	3609 (30.2)
Current	26 (11.7)	198 (11.5)	627 (23.4)	2946 (24.6)
Renal Impairment, n(%)				
(CrCl>60 ml/min)	124 (55.6)	757 (43.9)	2470 (92.1)	10506 (87.9)
(CrCl 30-59 ml/min)	98 (43.9)	937 (54.3)	211 (7.9)	1450 (12.1)
(CrCl<30 ml/min)	1 (0.4)	31 (1.8)	0 (0)	2 (0)
Metformin Dose at Baseline, n(%)				
<1500mg	167 (74.9)	1197 (69.4)	2115 (78.9)	9382 (78.5)
≥1500mg	56 (25.1)	528 (30.6)	566 (21.1)	2576 (21.5)
Sulphonylurea Type, n(%)				
Gliclazide	-	1574 (91.2)	-	10937 (91.5)
Glipizide	-	61 (3.5)	-	377 (3.2)
Glibenclamide	-	6 (0.3)	-	79 (0.7)
Tolbutamide	-	34 (2)	-	44 (0.4)
Glimepiride	-	122 (7.1)	-	970 (8.1)
Chlorpropamide	-	0 (0)	-	0 (0)
Other	-	0 (0)	-	0 (0)
Binary Comorbidity Indicator Variables, n(%)				
History of excess alcohol Intake**	22 (9.9)	121 (7)	426 (15.9)	1810 (15.1)
History of Hypoglycaemia	2 (0.9)	14 (0.8)	18 (0.7)	114 (1)
Neuropathy	13 (5.8)	112 (6.5)	83 (3.1)	441 (3.7)
Retinopathy	55 (24.7)	285 (16.5)	439 (16.4)	1651 (13.8)

	Aged ≥ 75 years		Aged 18-75 years	
	Sita	**Sulf**	**Sita**	**Sulf**
Cardiovascular disease	117 (52.5)	836 (48.5)	620 (23.1)	3242 (27.1)
Heart failure	67 (30)	441 (25.6)	236 (8.8)	1113 (9.3)
Anaemias	32 (14.3)	202 (11.7)	225 (8.4)	956 (8)
Dementia	7 (3.1)	33 (1.9)	10 (0.4)	32 (0.3)
Liver disease	3 (1.3)	34 (2)	91 (3.4)	460 (3.8)
Arrythmias	50 (22.4)	308 (17.9)	146 (5.4)	744 (6.2)
Cancer	51 (22.9)	459 (26.6)	322 (12)	1491 (12.5)
Hypothyroidism	25 (11.2)	200 (11.6)	204 (7.6)	941 (7.9)
Hyperthyroid	1 (0.4)	40 (2.3)	33 (1.2)	158 (1.3)
Pancreatitis	1 (0.4)	21 (1.2)	28 (1)	157 (1.3)
Binary Treatment Indicator Variables¥, n(%)				
Anti-hypertensive	184 (82.5)	1457 (84.5)	1850 (69)	8109 (67.8)
Antiplatelets	105 (47.1)	889 (51.5)	831 (31)	4603 (38.5)
Anticoagulants	35 (15.7)	186 (10.8)	99 (3.7)	444 (3.7)
Anti-arrythmic	2 (0.9)	21 (1.2)	13 (0.5)	75 (0.6)
Diuretics	98 (43.9)	768 (44.5)	680 (25.4)	3023 (25.3)
Statins	182 (81.6)	1381 (80.1)	2133 (79.6)	9361 (78.3)
Other lipid lowering drugs	16 (7.2)	73 (4.2)	147 (5.5)	664 (5.6)
Antidepressants	28 (12.6)	219 (12.7)	487 (18.2)	2127 (17.8)
Antipsychotics	1 (0.4)	16 (0.9)	58 (2.2)	255 (2.1)
Antiobesity	0 (0)	1 (0.1)	87 (3.2)	189 (1.6)
Steroids –oral/intravenous	20 (9)	150 (8.7)	88 (3.3)	553 (4.6)
Thyroxine	26 (11.7)	203 (11.8)	191 (7.1)	916 (7.7)
Anti-thyroid drugs	0 (0)	4 (0.2)	3 (0.1)	15 (0.1)
Anxiolytics	12 (5.4)	96 (5.6)	115 (4.3)	570 (4.8)

*Mean Face to Face Consultation Frequency per year
**Defined as recording of an intake of >35 units of alcohol a week for males or > 28 units for females
¥Concomitantly prescribed within 3 months prior to index date
CrCl=Creatinine Clearance estimated in ml/min, SD=Standard Deviation
Full covariate definitions can be found in Supplementary Methods S2

Outcomes

Change in HbA1c

The unadjusted absolute mean HbA1c reduction in the older group treated with sitagliptin after 12 months was 9.0 mmol/mol (95% CI 7.1-10.8) and with sulphonylurea was 13.5mmol/mol (95% CI 12.6-14.4). The corresponding reductions for the younger group was 9.6mmol/mol (95% CI 9.0-10.2) with sitagliptin and 14.1mmol/mol (95% CI 13.7-14.4) with sulphonylureas.

Though evidence of HbA1c reduction with both groups, to allow us to compare reduction between treatments, we examined mean difference in HbA1c at 12 months between both groups, after fully adjusting for baseline differences (i.e. HbA1c, sex, age and other confounders as detailed in Figure 1).

After full adjustment, the HbA1c 12 months after initiation was on average 1mmol/mol [Mean difference in HbA1c 1.0mmol/mol (95% CI -0.7 to 2.8)] (Figure 1 and Supplementary Appendix Table S1) higher with sitagliptin compared to sulphonylureas in the older group, though this was not statistically significant. A small statistical difference was observed in the younger group though this was not clinically significant; [Mean difference in HbA1c 0.8mmol/mol (95% CI 0.2-1.4)] (Figure 1).

Sensitivity analysis undertaken using the subgroup of deemed "adherent" defined earlier, produced similar results (Supplementary Appendix Table S1). Investigations of differences among those with and without missing data did not reveal any characteristics that may bias analysis.

Change in Weight

The unadjusted absolute mean weight reduction in the older group treated with sitagliptin after 12 months was -1.6kg (95% CI -2.2 to -1.1) while no significant change in weight was observed with sulphonylurea; 0.1kg (95% CI -0.2 to 0.3). The corresponding changes for the younger group was a weight reduction of -1.3kg (95% CI -1.5 to -1.1) with sitagliptin and weight gain of 1.4kg (95% CI 1.3-1.5) with sulphonylurea.

However, to compare treatments we adjusted for baseline weight, sex, age and other confounders. After adjustment, the weight 12 months after initiation was on average 1.4 kg lower in the older group for those prescribed sitagliptin compared to sulphonylureas [Mean difference in weight -1.4kg (95% CI -2.1 to -0.7)] (Figure 1 and Supplementary Appendix Table S2). After similar adjustment in the younger group, the weight 12 months after the index date was even lower: [Mean difference in weight -2.3kg (95% CI -2.5 to -2.0)] for those prescribed sitagliptin compared to sulphonylureas.

Sensitivity analysis undertaken included in the appendix produced similar results (Supplementary Appendix Table S2). Investigations of differences among those with and without missing data did not reveal any differences in characteristics that may bias analysis.

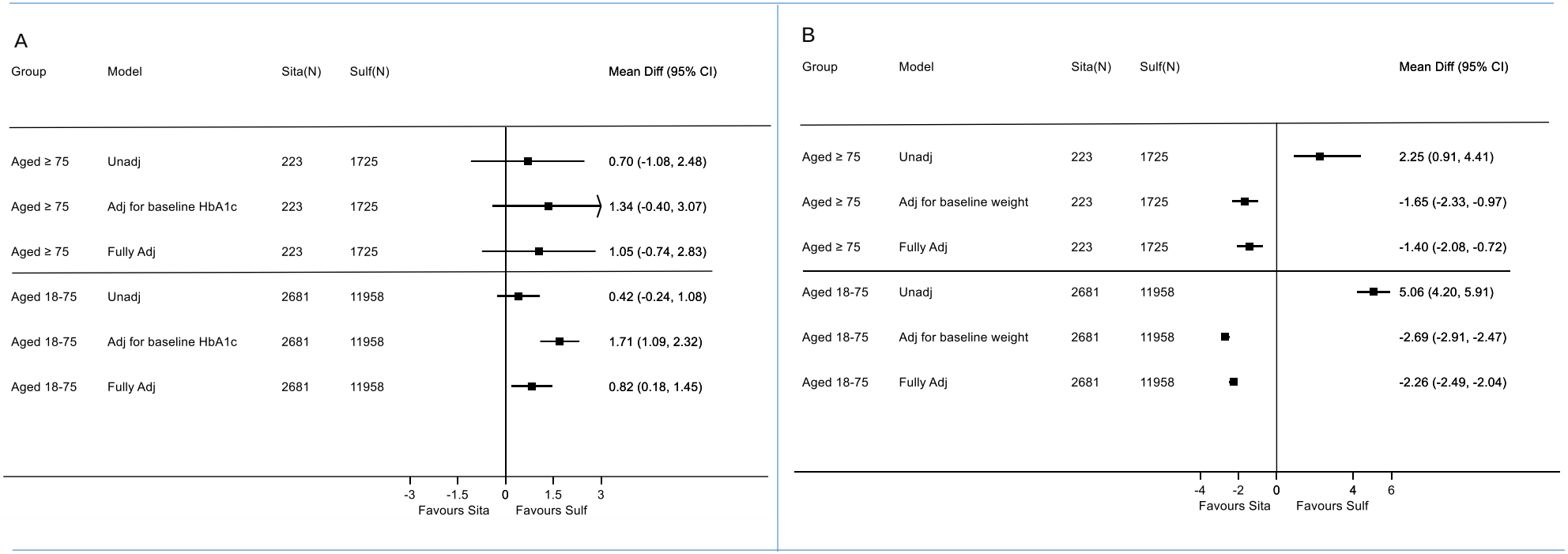

Figure 1 Forest plot comparing sitagliptin and sulphonylureas for mean difference in HbA1c, mmol/mol (A) and weight, kg (B) 12 months after baseline in those aged ≥ 75 years and those aged 18-75 years

Unadj=Unadjusted, Adj=Adjusted, Mean Diff=mean difference, Sita(N)=Number of individuals in Sitagliptin group, Sulf(N)=Number of individuals in sulphonylurea group, CI=confidence interval, .

Note: (1)Fully adjusted model examining mean difference in HbA1c (A) is adjusted for baseline HbA1c, baseline weight, age, year entry, F2FC (Average Face to Face consultation frequency per year), sex, Townsend deprivation quintile, smoking status, metformin dose, history of excessive alcohol intake, hypoglycaemia, neuropathy, heart failure, anaemias, liver disease and having a prescription within 3 months prior to the index date (date of initiation of add-on treatment) for diuretics, statins, antidepressants and oral or intravenous steroid medication.

(2) Fully adjusted model examining mean difference in weight (B) is adjusted for baseline weight, baseline HbA1c, age, year entry, F2FC, sex, Townsend deprivation quintile, smoking status, metformin dose, history of excessive alcohol intake, hypoglycaemia, neuropathy, heart failure, anaemias, liver disease and having a prescription within 3 months prior to the index date (date of initiation of add-on treatment) for diuretics, statins, antidepressants and oral/intravenous steroid medication.

Proportion recording a HbA1c <64mmol/mol (8.0%), <58mmol/mol (7.5%) and <48 mmol/mol (6.5%)

In the older group, the proportion recording a HbA1C level <64mmol/mol by study end was 82.5% of those prescribed sitagliptin and 81.9% of those prescribed sulphonylurea. (Table 2). A smaller proportion recorded a HbA1c <58mmol/mol, 65.9% and 65.6% respectively while least recorded a HbA1c <48mmol/mol, 13.9% and 21.5% for sitagliptin and sulphonylurea respectively. The corresponding proportions with a record of a HbA1c below each of these three thresholds was slightly lower in the younger group for both treatments (Table 2).

After adjustment, the odds were significantly lower only for recording a HbA1c <48mmol/mol by the end of the study in older people who were prescribed sitagliptin compared to sulphonylureas; Odds Ratio 0.63 (95%CI 0.42-0.95). A similar Odds Ratio was observed in the younger group as well [0.75 (95%CI 0.66-0.86)].

Table 2 Proportions recording a HbA1c below thresholds of 64 mmol/mol, 58 mmol/mol and 48 mmol/mol

	Aged ≥ 75 years			**Aged 18-75 years**		
	Sita, n(%)	**Sulf, n(%)**	**Adjusted OR¥, 95% CI**	**Sita, n(%)**	**Sulf, n(%)**	**Adjusted OR¥, 95% CI**
Proportion achieving HbA1c **< 64** mmol/mol	184 (82.5)	1413 (81.9)	0.98 (0.67-1.45)	1808 (67.4)	8065 (67.4)	0.98 (0.89-1.08)
Proportion achieving HbA1c **< 58** mmol/mol	147 (65.9)	1131 (65.6)	1.00(0.73-1.37)	1364(50.9)	6139 (51.3)	0.98 (0.89-1.07)
Proportion achieving HbA1c **< 48** mmol/mol	31 (13.9)	371 (21.5)	0.63 (0.42-0.95)	365 (13.6)	2123(17.8)	0.75 (0.66-0.86)

¥Mutually adjusted for baseline HbA1c, baseline weight, age, year entry, F2FC (Average Face to Face consultation frequency per year), sex, Townsend quintile, smoking status, metformin dose, history of excessive alcohol intake, hypoglycaemia, neuropathy, heart failure, anaemias, liver disease and having a prescription within 3 months prior to the index date (date of initiation of add-on treatment) for diuretics, statins, antidepressants and oral or
intravenous steroid medication.
OR= Odds Ratio, CI=confidence interval.
Note: Individuals prescribed sulphonylureas are the reference population in all estimates above.

DISCUSSION

After adjusting for important baseline differences (such as baseline HbA1c , weight, and other comorbidities etc), no clinically significant difference was observed in HbA1c lowering effects between sitagliptin or sulphonylurea when they were added to metformin after 12 months in people aged ≥75 years; 1.0mmol/mol (95% CI -0.7 to 2.8) and people aged 18-75 years; 0.8mmol/mol (95% CI 0.2-1.4). A significant comparative reduction in weight was observed at 12 months with sitagliptin compared to sulphonylureas of -1.4kg (95% CI -2.1 to -0.7) in the older group. This was driven by modest weight loss with sitagliptin and no observed weight gain with sulphonylureas. The larger comparative weight change observed in the younger group: -2.3kg (95% CI -2.5 to -2.0) was driven by additional weight gain with sulphonylureas.

The proportion of individuals recording a HbA1c of <64mmol/mol and <58mmol/mol by study end was similar in both age-groups in those prescribed sitagliptin and sulphonylurea. However, a greater proportion of those prescribed sulphonylureas recorded a HbA1c <48mmol/mol in both older group: Odds Ratio 0.63 (0.42-0.95) and younger group 0.75 (95%CI 0.66-0.86) by study end. Though, the former two targets are desirable for HbA1c control, the latter target can represent too low a value in older people and may place them at higher risk of hypoglycaemia, especially with sulphonylureas.[13]

To our knowledge, this is the first study examining effectiveness of sitagliptin vs sulphonylureas as add-on to metformin in older people aged ≥75. An RCT conducted in Japan by Terauchi et al in 2017, showed similar glycaemic change with sitagliptin compared to sulphonylureas in 272 individuals aged ≥60 years, 12 months after initiation (1.2mmol/mol, 95% CI -0.2 to 2.6).[14] The mean age of the 272 individuals was 70.5 (Standard Deviation 5.5), hence most were younger than our cohort.[14] Despite this difference, results obtained by Terauchi et al were comparable to ours. Terauchi et al also reported similar findings with a decrease in weight of approximately 1kg with sitagliptin and no weight gain with sulphonylureas as in our study.[14]

The greater risk of hypoglycaemia with sulphonylurea compared to sitagliptin has been repeatedly demonstrated in clinical studies and is known to be even greater in older people.[6,15] Our finding

that a greater proportion of individuals prescribed sulphonylureas were being treated to a HbA1c <48mmol/mol was therefore of concern. Though being treated to a HbA1c <48mmol/mol, is not a direct predictor of hypoglycaemic risk or indeed severity of hypoglycaemia, it can raise hypoglycaemic risk as well as that of associated complications and is unnecessary in this older age-group.[13,16] Clinical inertia relating to a failure to intensify treatment has been a long-standing problem in the management of T2DM,[17] but paradoxically in these older people, there appears to be a risk in UK clinical practice of overtreatment. Our findings support those from the GUIDANCE study, which included 4,459 individuals aged ≥ 65 years from several European countries including the UK and also provided evidence of over-treatment with sulphonylureas.[18]

Some clinical studies have previously suggested a greater glycaemic reduction is observed with sulphonylureas than sitagliptin.[19,20] However our study adds to a growing evidence base that indicates glycaemic reduction is similar with both once adjustment is complete for baseline differences. Sitagliptin is generally accepted as being weight neutral but some modest weight lost is still observed with its usage. Given these findings, the established lower risk of hypoglycaemia with sitagliptin and our observed overtreatment of T2DM in clinical practice with sulphonylureas, there is evidence that sitagliptin could be prescribed in preference to sulphonylureas in older people where improved glycaemic control is desired after metformin. This preference for a Dipeptidyl-peptidase-4 inhibitor over a sulphonylurea for add-on treatment is in line with position statement of the American Association of Clinical Endocrinologists (AACE/ACE).[5] NICE and the American Diabetes Association however, do not discriminate based on effectiveness here with guidelines advocating a patient-centred approach.[4,21]

There are several strengths to this study. We have evaluated treatment effectiveness using data from actual clinical practice in a population of older people that have been excluded from previous clinical studies. We compared head-to-head effectiveness of two widely prescribed treatments as add-on to metformin making findings relevant for practice. We have also compared effectiveness across older and younger groups and demonstrated good comparability of findings in this latter group to existing trials and literature.[22] This helps demonstrate credibility of our overall study design and analytical approach. We also provide a useful template for undertaking future treatment

effectiveness work in older people. Sensitivity analysis undertaken using the “adherent” cohort demonstrated a consistency in findings which adds a further degree of robustness to results. There are limitations. We have focused on effectiveness rather than safety relating to recording of hypoglycaemia as the latter has been evaluated in depth and we have summarised that literature.[6,7,15] We have focused on use of sitagliptin rather than the DPP-4 inhibitor class as it was the most extensively prescribed DPP-4 inhibitor in the UK and US during our study period accounting for over 75% of DPP-4 inhibitors prescribed, leaving us with insufficient power to examine any other medicines in this class.[23] There are several new antidiabetics now licensed on the market such as SGLT-2 inhibitors hence our findings should be considered in the wider clinical context.

CONCLUSION

Sitagliptin produced a similar improvement to sulphonylureas in glycaemic control when added to metformin in the treatment of T2DM. Sitagliptin also led to some comparative weight loss in both those aged ≥75 and 18-75 years. There was evidence of a greater risk of over-treatment with sulphonylureas as evidenced by a greater proportion recording a HbA1c <48mmol/mol by study end. This is of concern, especially in the older group as it is unnecessary and can potentially increase risk of hypoglycaemia. We therefore present evidence in support of sitagliptin when add-on therapy is being selected in older populations that should be considered alongside the wider evidence-base and patient preference.

SUMMARY POINTS

- Evidence examining comparative effectiveness of sitagliptin vs sulphonylureas in “real world” clinical practice as add-on to metformin is limited especially in older adults aged ≥75 years
- We undertook a retrospective cohort study using data from UK primary care and compared treatment effectiveness across adults aged ≥75 years versus those aged 18-75 years for change in HbA1c, weight and the proportion recording a HbA1c below different glycaemic thresholds
- A similar Hba1c reduction was seen with both treatments across both age-groups, sitagliptin use led to modest weight reduction while individuals prescribed sulphonylureas were more likely to record a HbA1c < 48mmol/mol by study end which is unnecessary and might place older adults in particular, at greater risk of hypoglycaemia
- We present evidence of a similar glucose-lowering effect and lower risk of over-treatment with sitagliptin compared to sulphonylureaas in older adults in this manuscript, which when combined with the well-established lower risk of hypoglycaemia with sitagliptin supports its use in older adults

FIGURE LEGENDS

Figure 1 Forest plot comparing sitagliptin and sulphonylureas for mean difference in HbA1c, mmol/mol (A) and weight, kg (B) 12 months after baseline in those aged ≥ 75 years and those aged 18-75 years

TABLE LEGENDS

Table 1 Baseline characteristics

Table 2 Proportions recording a HbA1c below thresholds of 64 mmol/mol, 58 mmol/mol and 48 mmol/mol

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CONTRIBUTORSHIP STATEMENT

MS, IN and IP collectively planned the study. MS performed any analysis and wrote the manuscript.

MS, IN and IP all reviewed the manuscript for intellectual content and approved the final version.

CONFLICT OF INTERESTS DECLARATION

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TRANSPARENCY DECLARATION

I, MS, 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 prot