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Changing the approach to type 2 diabetes treatment: A comparison of glucagon-like peptide-1 receptor agonists and sulphonylureas across the continuum of care

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Abstract

Despite the importance of individualised strategies for patients with type 2 diabetes mellitus (T2DM) and the availability of alternative treatments, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sulphonylureas are still widely used in practice. Clinical evidence shows that GLP-1 RAs may provide better and more durable glycaemic control than sulphonylureas, with lower risk of hypoglycaemia. Other reported benefits of GLP-1 RAs include weight loss rather than weight gain (as observed with sulphonylureas), blood pressure reduction and improvement in lipid profiles. In general, the main adverse events with GLP-1 RAs are gastrointestinal in nature. The respective modes of action of GLP-1 RAs and sulphonylureas contribute to differences in the durability of glycaemic control (related to effects on beta-cells) and effects on body weight. Moreover, the glucose-dependent mode of action of GLP-1 RAs, which favours a low incidence of hypoglycaemia, contrasts with the glucose-independent mode of action of sulphonylureas. Evidence from cardiovascular outcomes trials indicates a consistent finding of cardiovascular safety across the GLP-1 RAs and suggests a class benefit for the long-acting GLP-1 RAs in reducing three-point major adverse cardiovascular events, cardiovascular mortality and all-cause mortality. In contrast, potential concerns relating to an increased incidence of adverse cardiovascular events with sulphonylureas have yet to be fully resolved. Recent updates to management guidelines recommend that treatment selection for patients with T2DM should consider clinical trial evidence of cardiovascular safety. Available evidence suggests that this selection should give preference to GLP-1 RAs over sulphonylureas, especially for patients at high cardiovascular risk.

KEYWORDS
cardiovascular safety, durability, GLP-1 RAs, glycaemic control, hypoglycaemia, sulphonylureas

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have a well-established efficacy and safety profile and, as a class, represent an increasingly important option for the treatment of patients with type 2 diabetes mellitus (T2DM).[1] Clinical studies in patients with T2DM show that GLP-1 RAs provide good glycaemic control, promote weight loss, and are typically associated with lipid and blood pressure reductions.[1–5]

In clinical practice, many patients with T2DM eventually require a combination of interventions to maintain glycaemic control and reduce the risk of long-term complications.[6] Most current practice guidelines recommend lifestyle and dietary modification as an initial step to maintain glycaemic control, usually followed by metformin monotherapy, and then by a combination of metformin with other therapies, including oral and injectable medications.[1,6–10] As options for combination therapy, guidelines typically recommend consideration of either a sulphonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose co-transporter-2 (SGLT-2) inhibitor, GLP-1 RA or basal insulin, if glycated haemoglobin (HbA1c) targets are not met after approximately 3–6 months. Importantly, the most recently issued updates to management guidelines recommend that treatment selection should be based on clinical trial evidence of reductions in adverse cardiovascular events and/or cardiovascular mortality in patients with T2DM and established cardiovascular disease[6,7,9–11] and that sulphonylureas should be used as third-line therapy only, especially where hypoglycaemia or weight gain is a concern.[10,11]

Among the currently available treatment options, the sulphonylureas (a class that includes gliclazide, glimepiride, glibenclamide and glipizide) can achieve glycaemic control but are associated with weight gain and increased risk of hypoglycaemia.[1,6,8,12] Over recent years, potential concerns have also arisen regarding the cardiovascular safety of the sulphonylurea class in comparison with other treatments for diabetes.[1,6,13–18] As these concerns are not yet fully resolved, more recent guideline updates do not recommend sulphonylureas in patients who have experienced prior cardiovascular events.[10,11] Furthermore, some guidelines recommend that sulphonylureas should be used with caution because of the risk of hypoglycaemia, especially in older patients.[6,10]

Despite the disadvantages of sulphonylureas and the availability of options that are not associated with the known drawbacks of this class, the use of sulphonylureas in clinical practice continues to be high overall in some countries (e.g., Canada,[19] England and Wales,[20] and the United States[21,22]) and higher than that of GLP-1 RAs in others (e.g., Italy[23,24] and Denmark[25]).

It is possible that the continued widespread use of sulphonylureas reflects an aspect of clinical inertia—the failure to switch or discontinue therapy when targets are not achieved[26]—and the relatively low acquisition cost of sulphonylureas (World Health Organization guidelines for treatment intensification in low-resource settings recommend these drugs for second-line use after metformin).[27] An additional reason may be a lack of familiarity among physicians with the newer therapies, such as GLP-1 RAs. None of the recent reviews summarising the effects of GLP-1 RAs and sulphonylureas compare directly the overall evidence available for these two classes. The aim of this narrative review was to contrast the mode of action, clinical efficacy and safety of GLP-1 RAs with those of sulphonylureas. Available data for GLP-1 RAs and sulphonylureas as individual classes have been extensively reviewed.[2,4,5,12,28–33] Consequently, in this review, differences in clinical efficacy and safety between the two drug classes were examined by focussing primarily on important information from recent network meta-analyses, clinical studies involving head-to-head comparisons of GLP-1 RAs and sulphonylureas, and studies of cardiovascular outcomes.

2 | MODE OF ACTION

Some of the most important clinical differences between GLP-1 RAs and sulphonylureas could be related to the mechanisms that lead to reductions in blood glucose, as summarised briefly below. In particular, the glucose-dependent effects of GLP-1 RAs may present distinct physiological advantages when considered alongside the pharmacological effects of sulphonylureas in stimulating insulin secretion.

2.1 | Glucagon-like peptide-1 receptor agonists

GLP-1 RAs activate GLP-1 receptors on pancreatic beta-cells, potentiating glucose-stimulated insulin secretion through several mechanisms, including the closure of ATP-sensitive potassium (K_{ATP}) channels and the potentiation of voltage-dependent calcium channels.[34] These agents can be categorised as either short-acting (exenatide twice daily and lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide once weekly, liraglutide and semaglutide), depending on the duration of their action at GLP-1 receptors.[35] Through effects on the incretin pathway, GLP-1 RAs target pathophysiological processes that seem to be fundamental to the progression of T2DM.[36] GLP-1 RAs appear to reduce fasting hyperglycaemia and enhance postprandial glucose control predominantly through a delaying effect on gastric emptying (short-acting molecules) and by enhancing glucose-dependent pancreatic beta-cell insulin production and secretion (long-acting agents); furthermore, a reduction in the production of glucagon is observed.[35,37,38] Since GLP-1 RAs have little or no effect on insulin secretion in the absence of hyperglycaemia, the risk of GLP-1 RA-induced hypoglycaemia is minimal.[38]

2.2 | Sulphonylureas

By contrast, the mode of action of sulphonylureas is not glucose dependent, and drugs of this class promote insulin secretion directly by binding to receptors on pancreatic beta-cells and closing K_{ATP}

channels.[39] Variability in glucose-independent receptor selectivity and consequent differential tissue effects seen with sulphonylurea receptors may contribute to the increased incidence of hypoglycaemia that is observed with these agents.[28]

2.3 | Mode of action and effects on durability of glycaemic control and bodyweight

The differences between GLP-1 RAs and sulphonylureas in mode of action at the pancreatic beta-cell may contribute to other important differences between these two classes of drug, particularly in terms of durability of glycaemic control and effects on body weight.

Compared with those receiving GLP-1 RAs, patients who receive long-term treatment with sulphonylureas may progress more rapidly to pancreatic beta-cell failure,[40,41] potentially accelerating the need for insulin treatment. These undesirable long-term effects of sulphonylureas on beta-cells may restrict options for dose escalation.[36,42] For example, a post-hoc analysis of the GENERATION trial assessed whether baseline beta-cell function was a potential risk factor for hyperglycaemia by comparing glimepiride with the DPP-4 inhibitor, saxagliptin (another type of incretin-based therapy) as add-on to metformin in older patients. The results indicated that the addition of glimepiride to metformin was associated with an increased risk of hypoglycaemia in patients with lower compared with higher beta-cell function, suggesting that sulphonylureas should be used with caution in patients with poor beta-cell function.[43]

In contrast, GLP-1 RAs have been associated with improvements in beta-cell function.[39,44–48] Evidence suggests that GLP-1 RAs can modulate insulin secretion by directly stimulating beta-cells or indirectly through weight loss and enhanced insulin sensitivity.[49]

In addition to hypoglycaemia (discussed above), another consequence of the glucose-independent promotion of insulin secretion by sulphonylureas is weight gain.[39,50] In contrast, GLP-1 RAs reduce body weight in patients with T2DM, acting through GLP-1 receptors in the central nervous system to suppress appetite and increase satiety.[35,51]

3 | CLINICAL EFFECTS AND SAFETY/TOLERABILITY OF GLP-1 RAS AND SULPHONYLUREAS

3.1 | Summary of efficacy and safety

3.1.1 | GLP-1 RAs

As a class, GLP-1 RAs demonstrate good glycaemic efficacy and are characterised by their ability to reduce body weight in patients with T2DM. Other reported benefits of GLP-1 RAs include blood pressure reductions and improvements in lipid profiles.[2,4,12,30,33,52–54]

The network meta-analysis by Orme et al.[2] assessed the comparative effectiveness of liraglutide, albiglutide, dulaglutide and exenatide twice daily and once weekly, with a focus on glycaemic control (HbA1c target <7%) at approximately 6 months. All GLP-1 RAs resulted in statistically significantly lower HbA1c at follow-up compared with placebo. With dulaglutide, exenatide once weekly and liraglutide, the absolute reductions in HbA1c at 6 months ranged from 0.9% to 1.4% and were significantly greater than that with exenatide twice daily.

The network meta-analysis by Liu et al.[53] described differences between GLP-1 RAs, sulphonylureas and other classes of glucose-lowering drugs (with the exception of SGLT-2 inhibitors, which were not available at the time of the analysis). GLP-1 RAs, biphasic insulin and basal insulin were ranked the top three drug classes in terms of glycaemic control. Weight loss was seen for GLP-1 RAs and alpha-glucosidase inhibitors, compared with weight gain for the other treatment classes. Hypoglycaemia risk was higher for sulphonylureas, glinides, biphasic insulin and basal insulin than for placebo.

In general, the main adverse events with GLP-1 RAs are gastrointestinal in nature, and are mainly related to nausea. Other common adverse effects include injection-site reactions (with variable incidence for the different molecules in the class), headache and nasopharyngitis, but these effects do not usually result in treatment discontinuation.[55]

Concerns have been expressed regarding the effects of GLP-1 RAs on pancreatic and thyroid tissue, since animal studies and analyses of drug databases seem to indicate an association with pancreatitis, pancreatic cancer and thyroid cancer. Prescribing information in the United States for long-acting GLP-1 RAs contains warnings about the risk of medullary thyroid cancer, and these products are contraindicated in patients with a personal or family history of thyroid tumours.[56–60] However, meta-analyses, as well as information collected from cardiovascular outcomes trials (CVOTs) involving the long-term follow-up of thousands of patients, have found insufficient evidence to support an increased risk of acute pancreatitis or cancer associated with GLP-1 RAs.[55,61–64] One recent meta-analysis did, however, report increased risk of cholelithiasis with these drugs.[64]

3.1.2 | Sulphonylureas

Data from randomised controlled trials have established that although treatment with sulphonylureas can be effective in achieving glycaemic control initially; this lacks durability.[1] Other well-documented drawbacks of sulphonylurea use in clinical practice include the increased risk of hypoglycaemia and weight gain.[1,6,65]

Network meta-analyses have shown that gliclazide is associated with the lowest risk of hypoglycaemia among the newer-generation sulphonylureas, including glibenclamide, glimepiride and glipizide.[28,32] In a recent population-based, propensity-matched cohort study, glimepride was found to be associated with a non-significant trend towards a higher incidence of severe hypoglycaemia compared with other second-generation sulphonylureas
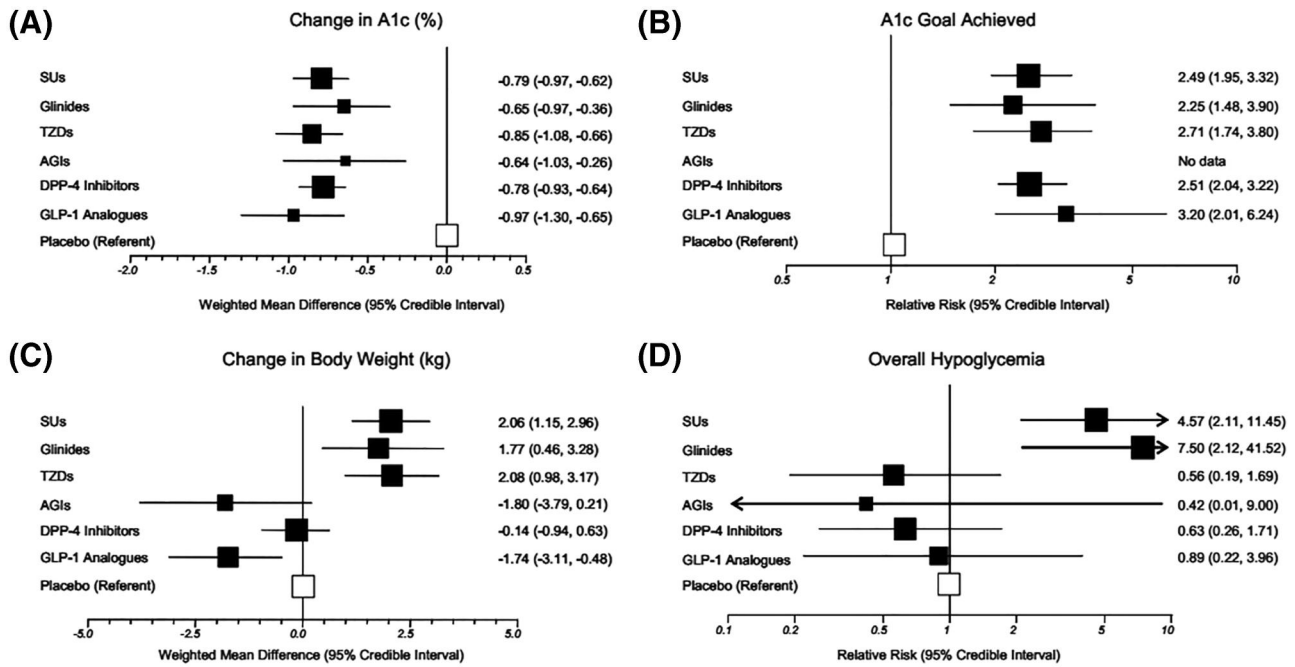
FIGURE 1 Results for a mixed-treatment comparison meta-analysis for sulphonylureas, glucagon-like peptide-1 receptor agonists and other non-insulin glucose-lowering drugs. Reproduced with permission from Phung et al.[12] HbA1c goal <7% (53 mmol/mol). The squares represent the pooled effect size for each class of oral glucose-lowering drug. Error bars represent 95% credible intervals. The number of trials included in each mixed-treatment comparison analysis is as follows: A = 26 trials, B = 13 trials, C = 15 trials and D = 24 trials. AGI, alpha-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; SU, sulphonylurea; TZD, thiazolidinediones. To convert changes in HbA1c % values to mmol/mol: HbA1c value/0.09148.[67]

(glibenclamide, gliclazide, glipizide, gliquidone, glibornuride and glymidine).[66]

The relative cardiovascular safety of GLP-1 RAs and sulphonylureas is described in more detail in a later section of the manuscript.

3.2 | Network meta-analyses including GLP-1 RAs and sulphonylureas

Using a mixed-treatment comparison meta-analysis, Phung et al.[12] demonstrated that sulphonylureas were associated with greater increases in body weight gain and a higher incidence of hypoglycaemia than GLP-1 RAs in patients with T2DM not controlled by metformin alone (Figure 1). Their overall findings have been confirmed in other network meta-analyses or indirect comparisons.[2,5,12,29,68]

3.3 | Comparative data from prospective clinical trials

Prospective, randomised controlled trials have compared albiglutide, dulaglutide, exenatide twice daily, liraglutide or lixisenatide with sulphonylureas.[42,45–47,69–77] The main findings from these studies are summarised in Table 1.

3.3.1 | Glycaemic control, weight change and safety of GLP-1 RAs, and sulphonylureas in head-to-head studies

Albiglutide
The 104-week HARMONY 3 study compared the efficacy and safety of weekly albiglutide 30–50 mg with daily sitagliptin 100 mg, daily glimepiride 2–4 mg and placebo, all added to metformin in patients with T2DM. This demonstrated that albiglutide produced superior reductions in HbA1c at 104 weeks compared with placebo, sitagliptin or glimepiride and resulted in weight loss compared with glimepiride.[71] The incidence of hypoglycaemia with albiglutide was comparable to that seen with placebo and less frequent than that seen with glimepiride.

Dulaglutide
In a 26-week, phase III, double-blind, randomized study in oral glucose-lowering drug-naïve East-Asian patients with T2DM, Chen et al.[74] compared the efficacy and safety of weekly dulaglutide 0.75 and 1.5 mg with daily glimepiride 1–3 mg as monotherapy. Both dulaglutide doses produced significantly greater reductions from baseline in HbA1c and bodyweight at 26 weeks (all $p < 0.001$) than glimepiride. The incidence of hypoglycaemia was significantly higher ($p < 0.001$) in the glimepiride arm than with either dulaglutide 0.75 or 1.5 mg.

TABLE 1 Difference in mean glycated haemoglobin, change in body weight, incidence of hypoglycaemia and summary of adverse events in patients treated with glucagon-like peptide-1 receptor agonists or sulphonylureas reported in prospective, randomised trials

Study	Duration	Concomitant therapy	Comparative treatments and doses	Mean change in HbA1c (%)	Patients achieving HbA1c target <7.0%	Incidence of hypoglycaemia	Mean changes in body weight (kg)	Summary of adverse events
Albiglutide								
HARMONY 3[71]	104 weeks	Metformin	Albiglutide 30–50 mg QW (n = 302)	−0.63	38.6%	3.0%[a]	−1.21	Diarrhoea (albiglutide 12.9%, other groups 8.6–10.9%) and nausea (albiglutide 10.3%, other groups 6.2%–10.9%) were generally the most frequently reported gastrointestinal events
			Sitagliptin 100 mg/day (n = 302)	−0.28	31.6%	1.7%[a]	−0.86	
			Glimepiride 2–4 mg/day (n = 307)	−0.36	31.4%	17.9%[a]	+1.17	
			Placebo (n = 101)	+0.27	15.5%	4.0%[a]	−1.0	
Dulaglutide								
Chen et al.[74]	26 weeks	Monotherapy	Dulaglutide 0.75 mg QW (n = 244)	−1.22	63.6	3.6%	−0.77	Incidence of treatment-emergent dulaglutide ADAs: 5.1% drug-related hypersensitivity reactions: five patients (dulaglutide 1.5 mg, n = 1; dulaglutide 0.75 mg, n = 3; glimepiride, n = 1)
			Dulaglutide 1.5 mg QW (n = 248)	−1.48	74.1	5.7%	−1.46	
			Glimepiride 1–3 mg (n = 245)	−0.90	57.4	15.6%	+0.89	

(Continues)

TABLE 1 (Continued)

Study	Duration	Concomitant therapy	Comparative treatments and doses	Mean change in HbA1c (%)	Patients achieving HbA1c target <7.0%	Incidence of hypoglycaemia	Mean changes in body weight (kg)	Summary of adverse events
Li et al.[73]	26 weeks	OAM allowed (not GLP-1 RA, DDP-4 inhibitor, thiazolidinedione or insulin)	Dulaglutide 0.75 mg QW (n = 8)/1.5 mg QW (n = 5)	−1.7	NR	NR	−0.23	Abdominal distension: 3 patients receiving dulaglutide; loss of appetite: 1 patient receiving glimepiride
			Glimepiride starting at 1 mg/day and titrated based on patient's glucose levels (n = 10)	−1.24	NR	NR	+1.2	
Exenatide twice daily								
Derosa et al.[45]	12 months	Metformin	Exenatide 5–10 mcg bid (n = 57)	−1.2	NR	NR	−5.1	NR
			Glimepiride 1–2 mg tid (n = 54)	−1.4	NR	NR	−0.9	
EUREXA[42]	Study period of 2–3 years. Primary outcome was time to inadequate glycaemic control and need for alternative treatment (defined as HbA1c >9% after 3 months or HbA1c >7% at two consecutive visits 3 months apart	Metformin	Exenatide 5–10 mcg bid (n = 490)	−0.89	44%	20%[a]	−3.32	More patients on exenatide bid had adverse events, predominantly gastrointestinal effects such as nausea and diarrhoea, and discontinued therapy. Most adverse events occurred within the first 6 months of treatment
			Glimepiride starting at 1 mg and titrated to maximum tolerated dose (n = 487)	−0.79 Changes reported at time of treatment failure or other study endpoint	31%	47%[a]	+1.15	

TABLE 1 (Continued)

Study	Duration	Concomitant therapy	Comparative treatments and doses	Mean change in HbA1c (%)	Patients achieving HbA1c target <7.0%	Incidence of hypoglycaemia	Mean changes in body weight (kg)	Summary of adverse events
Liraglutide								
LEAD-2[47]	26 weeks	Metformin	Liraglutide 0.6 mg/day (n = 242)	−0.7	28.0%	~3%[b]	−1.8	Nausea: 11%–19% liraglutide groups; 3%–4% glimepiride and placebo groups
			Liraglutide 1.2 mg/day (n = 240)	−1.0	35.3%	~3%[b]	−2.6	
			Liraglutide 1.8 mg/day (n = 242)	−1.0	42.4%	~3%[b]	−2.8	
			Glimepiride 4 mg/day (n = 242)	−1.0	36.3%	17%[b]	+1.0	
			Placebo (n = 121)	+0.1	10.8%	~3%[b]	−1.5	
LEAD-2 extension[69]	24 months (data shown for ITT population)	Metformin	Liraglutide 0.6 mg/day (n = 242)	−0.4	19.7%	5.0%[b]	−2.1	Liraglutide was well-tolerated overall: gastrointestinal events were more common than with glimepiride or metformin monotherapy, but occurrence decreased with time
			Liraglutide 1.2 mg/day (n = 240)	−0.6	29.9%	4.2%[b]	−3.0	
			Liraglutide 1.8 mg/day (n = 242)	−0.6	31.1%	4.1%[b]	−2.9	
			Glimepiride 4 mg/day (n = 242)	−0.5	23.5%	24.0%[b]	+0.7	
			Metformin monotherapy (n = 121)	+0.3	10.8%	2.5%[b]	−1.8	

(Continues)

TABLE 1 (Continued)

Study	Duration	Concomitant therapy	Comparative treatments and doses	Mean change in HbA1c (%)	Patients achieving HbA1c target <7.0%	Incidence of hypoglycaemia	Mean changes in body weight (kg)	Summary of adverse events
LEAD-3 Mono[46]	52 weeks	Monotherapy	Liraglutide 1.2 mg/day (n = 251)	−0.84	7.5%	12%[b]	Weight loss (~2.0 kg)	Five patients in the liraglutide 1.2 mg group and one in the liraglutide 1.8 mg group discontinued treatment due to vomiting versus none in the glimepiride group
			Liraglutide 1.8 mg/day (n = 247)	−1.14	7.2%	8%[b]	Weight loss (~2.2 kg)	
			Glimepiride 8 mg/day (n = 248)	−0.51	7.8%	24%[b]	Weight gain (~1.0 kg)	
LEAD-3 Mono extension[70]	104 weeks (data shown for ITT population)	Monotherapy	Liraglutide 1.2 mg/day (n = 251)	−0.6	36.9%	12%[b]	−1.89	With liraglutide, nausea was most frequently reported early in the trial and remained >5% throughout the extension. No participants withdrew from the extension because of nausea
			Liraglutide 1.8 mg/day (n = 246)	−0.9	44.4%	10%[b]	−2.7	
			Glimepiride 8 mg/day (n = 248)	−0.3	23.2%	26%[b]	+0.95	
Feng et al.[75]	24 weeks	Monotherapy	Liraglutide 1.8 mg/day (n = 30)	−3.01	NR	NR	−5.6	Liraglutide/metformin/gliclazide (n): Appetite suppression: 22/6/0; Nausea: 3/4/0; Diarrhoea: 4/10/0; Abdominal distension: 3/5/0; Injection-site rash: 1/0/0; Mild hypoglycaemic reaction: 0/2/2
			Gliclazide 120 mg/day (n = 32)	−2.6	NR	NR	−0.59	

TABLE 1 (Continued)

Study	Duration	Concomitant therapy	Comparative treatments and doses	Mean change in HbA1c (%)	Patients achieving HbA1c target <7.0%	Incidence of hypoglycaemia	Mean changes in body weight (kg)	Summary of adverse events
			Metformin 1000 mg bid (n = 31)	−3.33	NR	NR	−3.6	
LIRA-Ramadan[76,d]	33 weeks	Metformin	Liraglutide 1.8 mg/day (n = 171)	−1.25/−1.24	57.1/50.7	8.6%/17.0%[a]	−5.5/−5.1	TEAEs: liraglutide 23.7%/76.6%; SU 20.9%/57.1%. SAEs: liraglutide 1.3/2.9%; SU 0/1.2%
			Pretrial SU at maximum tolerated dose (n = 170)	−0.60/−0.55	26.4/25.7	17.8%/32.4%[a]	−1.4/−0.1	
Lixisenatide								
LixiRam[77,d]	22 weeks	Basal insulin ±Metformin	Lixisenatide 20 mcg/day (n = 92)	Baseline to post-Ramadan visit: −0.4	NR	4.3%/5.4%[c]	Baseline to post-Ramadan visit: −2.1	TEAEs: Lixisenatide 17.4%/45.7%; SU 16.3%/22.8%
			SU (dose as per pre-trial) (n = 92)	−0.5	NR	17.4%/26.1%[c]	−1.4	

Note. To convert changes in HbA1c % values to mmol/mol: HbA1c value/0.09148; to convert actual HbA1c values to mmol/mol: [HbA1c value - 2.142]/0.09148.

Abbreviations: ADA, antidrug antibodies; bid, twice daily; ITT, intent-to-treat; NR, not reported; OAM, oral antidiabetes medication; QW, once weekly; SAE, severe adverse events; SU, sulphonylurea; TEAE, treatment-emergent adverse event; tid, three times daily

[a]Hypoglycaemia defined as plasma glucose <3.1 mmol/L (56 mg/dL)

[b]Hypoglycaemia defined as plasma glucose <3.9 mmol/L (<70 mg/dL)

[c]Hypoglycaemia defined as plasma glucose ≤3.9 mmol/L (≤70 mg/dL)

[d]Change from baseline to end of Ramadan period/whole treatment period, unless otherwise mentioned.

In a small study by Li et al.,[73] weekly dulaglutide 0.75 or 1.5 mg (results combined) demonstrated superior reductions from baseline in HbA1c and bodyweight compared with glimepiride in Chinese patients with T2DM.

In both of the above studies, which compared dulaglutide with glimipiride, patients receiving glimepiride experienced weight gain, compared with weight loss in those receiving dulaglutide.

Exenatide twice daily

A small study by Derosa et al.[45] compared the effects of exenatide twice daily and glimepiride on glycaemic control, body weight and insulin resistance in patients with T2DM taking metformin. The two treatments produced a similar improvement in glycaemic control, but only exenatide twice daily decreased body mass index and markers of insulin resistance and inflammation.

Liraglutide

The majority of head-to-head studies that have compared a GLP-1RA with a sulphonylurea have involved liraglutide. The LEAD-2 (Liraglutide Effect and Action in Diabetes-2) trial compared the efficacy and safety of adding liraglutide 0.6, 1.2 or 1.8 mg/day, placebo or glimepiride 4 mg once daily to metformin in patients previously treated with oral glucose-lowering drugs.[47] Over 26 weeks, HbA1c was significantly reduced in all liraglutide groups and with glimepiride versus placebo. Body weight decreased in the liraglutide groups and increased in the glimepiride group ($p < 0.0001$). The incidence of hypoglycaemia with liraglutide was comparable to that seen with placebo but less frequent than with glimepiride ($p < 0.001$). The incidence of nausea was notably higher in liraglutide-treated individuals than in those receiving placebo or glimepiride.

Patients completing the 26-week double-blind phase of LEAD-2 could enter an 18-month open-label extension.[69] In the intent-to-treat (ITT) population, after 2 years, HbA1c had decreased non-significantly with liraglutide and with glimepiride. Groups treated with liraglutide 0.6, 1.2 and 1.8 mg exhibited significant weight loss compared with weight gain with glimepiride ($p < 0.0001$). The occurrence of minor hypoglycaemia was <5.0% in all liraglutide groups, significantly less than with glimepiride ($p < 0.0001$). Gastrointestinal events were more common with liraglutide than with glimepiride, but their occurrence decreased with time. Post-hoc analysis revealed that a composite endpoint of HbA1c <7.0%, with no weight gain or hypoglycaemia, was achieved by 13.2%, 23.3% and 25.6% of patients in the groups receiving liraglutide 0.6, 1.2 and 1.8 mg, respectively, by 6.6% of patients receiving glimepiride and by 8.3% of patients receiving metformin alone.

The LEAD-3 study compared monotherapy with liraglutide 1.2 or 1.8 mg/day and glimepiride 8 mg/day for 52 weeks and showed that liraglutide produced greater reductions in HbA1c, weight, hypoglycaemia and blood pressure than glimepiride.[46] Patients completing the study could continue with open-label treatment for a further year.[70] This extension study showed that, in both the ITT population

and in patients completing 2 years of treatment, liraglutide was more effective in reducing HbA1c and weight, with lower rates of minor hypoglycaemia than glimepiride.

In a recent small study, conducted in Chinese patients with both T2DM and non-alcoholic fatty liver disease, Feng et al.[75] compared the effect of daily liraglutide, glimepiride or metformin monotherapy on body composition. All treatments produced significant improvements from baseline in HbA1c levels at week 24 ($p < 0.01$), but reductions were greater in the liraglutide and metformin arms than in the gliclazide arm ($p < 0.05$ for both comparisons). Body weight decreased significantly from baseline ($p < 0.01$) only in the liraglutide and metformin arms, with little change in the gliclazide arm ($p < 0.01$ vs. liraglutide and metformin). Liraglutide and metformin were associated with lower rates of hypoglycaemia than glimepiride.

Azar et al.[76] sought to compare the effects of daily liraglutide or sulphonylurea, both plus metformin, on change in glycaemic control during Ramadan fasting in patients with T2DM. In LIRA-Ramadan, patients were randomised to either continue with their pre-trial sulphonylurea (at the already established maximum tolerated dose) or switch to liraglutide (dose escalated from 0.6 to 1.8 mg/day). From baseline to end of treatment, which included the 4-week Ramadan period, glycaemic control improved and bodyweight decreased significantly with liraglutide versus sulphonylurea ($p < 0.0001$). Liraglutide was associated with notably lower rates of hypoglycaemia than glimepiride throughout the study.

Lixisenatide

Hassanein et al.[77] compared the efficacy and safety of daily lixisenatide or sulphonylurea, both added to basal insulin ± metformin in patients with T2DM who fasted during Ramadan. In this phase 4, international, multicentre, open-label, parallel-group clinical trial (LixiRam), patients were randomised to continue on their pre-trial dose of sulphonylurea or to subcutaneous lixisenatide 20 mcg/day. Similar, small reductions in HbA1c from baseline to the post-Ramadan period were reported in both the lixisenatide and sulphonylurea arms. Reductions in body weight were also similar in both treatment arms; however, lixisenatide was associated with a notably lower incidence of hypoglycaemia than sulphonylurea therapy over the entire study period.

3.3.2 | Durability of glycaemic control

Albiglutide

In the HARMONY 3 study, in which albiglutide, sitagliptin, glimepiride or placebo were added to metformin for a period of 104 weeks, albiglutide had a more durable effect on glycaemic control than the other three drugs.[71]

Exenatide twice daily

The EUREXA (European Exenatide) study was an open-label, randomised, controlled trial comparing exenatide twice daily with

glimepiride as add-on to metformin in patients with T2DM who had not achieved glycaemic control with metformin alone. The study found that exenatide twice daily achieved significantly longer durability of glycaemic control than glimepiride.[42] The primary outcome was the time to inadequate glycaemic control and the need for alternative treatment (defined as an HbA1c >9% after 3 months or >7% at two consecutive visits 3 months apart). In total, 203 of 490 patients (41%) receiving exenatide twice daily versus 262 of 487 (54%) receiving glimepiride experienced treatment failure (risk difference 12.4; 95% confidence interval [CI] 6.2–18.6; hazard ratio [HR] 0.748 [95% CI 0.623–0.899], $p = 0.002$). Significantly more patients receiving exenatide twice daily achieved an HbA1c <7% (44% vs. 31%, $p < 0.0001$) or <6.5% (29% vs. 18%, $p = 0.0001$). Patients receiving exenatide twice daily also experienced a significantly greater decrease in body weight compared with those receiving glimepiride ($p < 0.0001$). Significantly fewer patients in the exenatide twice daily group than in the glimepiride group reported hypoglycaemia. More patients receiving exenatide twice daily had adverse events, predominantly gastrointestinal effects such as nausea and diarrhoea, and discontinued therapy. Most adverse events occurred within the first 6 months of treatment.

Data on cardiovascular risk markers were also collected throughout the EUREXA trial as secondary endpoints.[72] Over 36 months, differences were significantly in favour of exenatide twice daily versus glimepiride for body weight, waist circumference and blood pressure. Fewer patients randomised to exenatide twice daily versus glimepiride required the addition of antihypertensive or lipid-lowering medication.

Liraglutide

The extensions to the LEAD-2 and LEAD-3 studies demonstrated that 2 years of treatment with liraglutide, either in combination with metformin or as monotherapy, provided sustained improvements in glycaemic control and body weight compared with glimepiride, with a lower risk of hypoglycaemia.[69,70]

The ongoing GRADE study is investigating the effects of four drug classes (sulphonylureas [glimepiride], DPP-4 inhibitors [sitagliptin], GLP-1 RAs [liraglutide] and basal insulins [insulin glargine]), when added to metformin therapy, on durability of glycaemic control, diabetic complications and cardiovascular risk factors.[78] The anticipated mean observation period of just under 5 years will provide information on the long-term effects of these medications.

4 | CARDIOVASCULAR SAFETY

Over recent decades, morbidity and mortality have improved for patients with T2DM because of improvements in research and treatment, greater emphasis on the achievement of strict glycaemic control and improvements in other cardiometabolic risk factors.[79,80]

4.1 | GLP-1 RAs

GLP-1 RAs have a number of direct and indirect benefits. These include moderate blood pressure lowering, changes in lipid profiles, and effects on cardiac output, ischaemic conditioning, inflammatory processes and endothelial function that may decrease cardiovascular risk.[62,81] Since 2008, regulatory authorities have required that the cardiovascular safety of drugs in development for T2DM be studied, and the outcomes of the resultant CVOTs have been reviewed extensively.[62,63,79,82–84] Individual CVOT outcomes with GLP-1 RAs have been heterogeneous, possibly reflecting differences in study designs, treatment persistence and study populations.[79]

Fully published GLP-1 RA CVOTs include those for albiglutide (HARMONY Outcomes trial),[85] dulaglutide (REWIND[86] [Researching Cardiovascular Events with a Weekly Incretin in Diabetes]), exenatide once-weekly (EXSCEL[87] [EXenatide Study of Cardiovascular Event Lowering]), liraglutide (LEADER[88] [Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results]), lixisenatide (ELIXA[89] [Evaluation of Lixisenatide in Acute Coronary Syndrome]), and semaglutide (SUSTAIN-6[90] [Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes] and PIONEER 6[91] [Trial Investigating the Safety of Oral Semaglutide in Subjects With Type 2 Diabetes]).

To date, most of the fully published GLP-1 RA CVOTs (the HARMONY Outcomes trial, LEADER, ELIXA, SUSTAIN-6 and PIONEER 6) have tested the cardiovascular safety of GLP-1 RAs to be non-inferior to placebo, based on the primary three-point MACE (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke).

The recently published REWIND[86] trial prospectively tested whether dulaglutide was superior to placebo with regard to cardiovascular outcomes. In this study, dulaglutide was found to meet the primary efficacy objective, with significant reductions in the primary three-point MACE in a broad population of patients with T2DM, only 32% of whom had established cardiovascular disease.

Additionally, the LEADER, SUSTAIN-6 and HARMONY Outcomes trials showed significant reductions compared with placebo in the primary three-point MACE.[85,88,90] The ELIXA study reported no cardiovascular benefit with lixisenatide versus placebo in patients with a recent history of acute coronary syndrome using a four-point MACE outcome that included hospital admission for unstable angina in addition to the three-point MACE components.[89] Although not yet published in full, the pre-approval FREEDOM-CVO cardiovascular safety trial found that a formulation of exenatide that offers continuous subcutaneous delivery demonstrated non-inferiority to placebo with respect to major cardiovascular events.[92]

Whether these differences in cardiovascular outcomes are related to the differential properties of individual GLP-1 RAs remains to be determined.[63] To examine this, meta-analyses have recently been published on the outcomes of published studies (Table 2).[62,63,84] While acknowledging the potential for differences among drugs, and considering factors such as study design, duration of treatment exposure and the cardiovascular risk of study populations at baseline,

TABLE 2 Cardiovascular and mortality outcomes from fully published cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists. Adapted from Giugliano et al.[84]

	HR (95% CI)	p-Value
Three-point MACE		
Overall	**0.87 (0.80–0.96)**	**<0.011**
ELIXA	1.02 (0.89–1.17)	
LEADER	0.87 (0.78–0.97)	
SUSTAIN 6	0.74 (0.58–0.95)	
EXSCEL	0.91 (0.83–1.00)	
HARMONY	0.78 (0.68–0.90)	
REWIND	0.88 [0.79–0.99]	
PIONEER 6	0.79 [0.57–1.10]	
Test for heterogeneity: $p = 0.12$, $I^2 = 46.6$		
Cardiovascular mortality		
Overall	**0.88 (0.78–0.98)**	**<0.030**
Test for heterogeneity: $p = 0.330$, $I^2 = 13\%$		
All-cause mortality		
Overall	**0.89 (0.79–0.99)**	**<0.034**
Test for heterogeneity: $p = 0.304$, $I^2 = 42.1\%$		

Note. Three-point MACE is a composite of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. Three-point MACE, CV mortality, All-cause mortality and Overall. Unbolded rows show results for different aspects of these outcomes.

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular events.

the evidence to date suggests a class benefit for the long-acting GLP-1 RAs in reducing three-point MACE, cardiovascular mortality and all-cause mortality.[62,84,93]

4.2 | Sulphonylureas

Sulphonylureas exert their insulinogenic effects by closing K_{ATP} channels on pancreatic beta-cells. However, K_{ATP} channels function in a number of tissues other than the pancreas, including cardiac, skeletal and smooth muscle, with different sulphonylureas displaying different tissue receptor selectivity.[94] Effects mediated via cardiac or vascular receptors may inhibit ischaemic preconditioning (an endogenous protective mechanism in which brief periods of ischaemia followed by reperfusion may increase the resilience of cardiac tissue to periods of more profound, potentially harmful, ischaemia) and some sulphonylureas may therefore affect cardiovascular risk.[39,94]
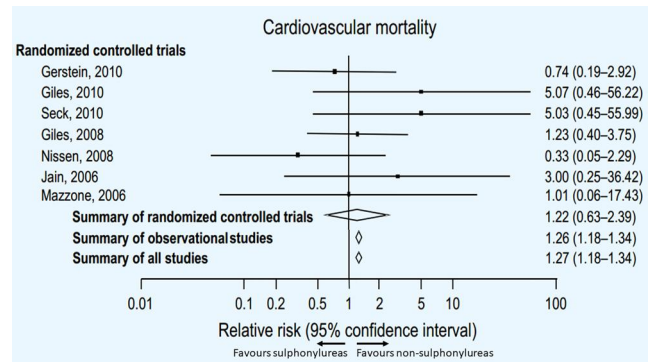

FIGURE 2 Sulphonylureas were associated with a significantly increased risk of cardiovascular mortality.[103–109] Adapted with permission from Phung et al.[101]

Controversy surrounding the cardiovascular safety of sulphonylureas dates back to the University Group Diabetes Program conducted in the 1960s,[95] which reported significantly increased risk of all-cause and cardiovascular mortality in patients receiving tolbutamide when compared with placebo. However, this study was not powered to test for cardiovascular safety and has since been criticised because the data were not corrected for baseline differences in cardiovascular risk.[96]

An important landmark was represented by data from 10-year post-trial follow-up in the UK Prospective Diabetes Study, which suggested that tight glycaemic control with either sulphonylurea or insulin therapy was associated with risk reductions for myocardial infarction and all-cause mortality.[97] However, over subsequent years, data concerning the safety of sulphonylureas have been conflicting in terms of mortality and cardiovascular outcomes, and have been reviewed extensively.[13,16,17,98–102]

As discussed above, tissue selectivity may nullify the beneficial effects of ischaemic preconditioning, and the risk of hypoglycaemia may differ among sulphonylureas. These factors led Simpson et al.[100] to conduct a systematic review and network meta-analysis to assess whether mortality and risk of cardiovascular events also varies. They found that gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular-related mortality than glibenclamide. The relative risk of death (using glibenclamide as a reference) was 0.65 for gliclazide (95% credible interval [CrI] 0.53–0.79), 0.83 for glimepiride (95% CrI 0.68–1.00) and 0.98 for glipizide (95% CrI 0.80–1.19). The relative risk of death was higher for the first-generation sulphonylureas, tolbutamide (1.13; 95% CrI 0.90–1.42) and chlorpropamide (1.34; 95% CrI 0.98–1.86), than for glibenclamide.[100] Additionally, a recent population-based, propensity-matched cohort study found glimepride to be associated with a lower incidence of all-cause mortality (HR 0.77, 95% CI 0.67–0.89) and a similar but non-significant trend for cardiovascular death (HR 0.83, 95% 0.65–1.05] than other second-generation sulphonylureas (glibenclamide, gliclazide, glipizide, gliquidone, glibornuride and glymidine).[66]

In a systematic review and meta-analysis, Phung et al.[101] compared the cardiovascular risk associated with sulphonylureas with that of other non-sulphonylurea glucose-lowering drugs, and included 33 randomised clinical or observational studies reporting data from over 1.3 million patients, with a follow-up of up to 10.4 years. Considering all studies, use of sulphonylureas was associated with significantly increased risk of cardiovascular death compared with non-sulphonylureas (relative risk 1.27; 95% CI 1.18–1.34) (see Figure 2). Relative risk of a composite endpoint of cardiovascular events (myocardial infarction, stroke, cardiovascular-related hospitalisation or cardiovascular death) was also increased with sulphonylurea use compared with use of any non-sulphonylurea drug (relative risk 1.10; 95% CI 1.04–1.16).[101]

Meta-analyses of randomised controlled trials have yielded conflicting results. Phung et al.[101] and Rosenstock et al.[16] found no significant association between use of sulphonylureas and cardiovascular mortality and cardiovascular events, respectively. Rosenstock et al.[16] also commented on an absence of adequately designed head-to-head CVOTs. In contrast, a meta-analysis of randomized controlled trials by Liu et al.[110] reported that sulphonylurea treatment in patients with T2DM was associated with an increased risk of stroke versus other antidiabetic drugs, potentially via inhibition of the neuroprotective effects of K_{ATP} channels, and suggested that sulphonylureas should be used with caution in the long-term management of T2DM.

In 2017, a meta-regression analysis of 19 observational studies found that sulphonylureas were associated with an increased risk of cardiovascular events and death, especially in studies with no major design-related biases.[17] This report also highlights the need to recognise and minimise bias when assessing the safety of glucose-lowering drugs considered for treatment intensification.

In 2019, the CAROLINA study, designed to establish the non-inferiority of linagliptin relative to glimepiride in the incidence of three-point MACE, found no increase in the risk of cardiovascular events with glimepiride compared with linagliptin (incidence of three-point MACE, 12.0% vs. 11.8% for glimepiride and linagliptin, respectively).[111] However, given that the findings of a number of previous comparative studies have highlighted differences in cardiovascular outcomes between sulphonylureas,[66,100] whether this neutral cardiovascular effect for glimepiride relative to linagliptin can be extended to other sulphonylureas, and to the sulphonylurea class as a whole, remains to be determined.

The TOSCA.IT study, conducted in 57 diabetes clinics in Italy, compared pioglitazone (a thiazolidinedione) and sulphonylurea (each added to metformin) and reported a similar incidence of cardiovascular events in the two treatment arms.[112] Subsequent commentary on the outcomes of this study has expressed concern that sulphonylureas may increase the risk of heart failure and its complications in patients with T2DM, a risk that may be overlooked by physicians in their treatment selections.[113]

Evidence also indicates that hypoglycaemia may be associated with increased risk of cardiovascular events. For example, long-term follow-up of patients in the ADVANCE study showed that severe hypoglycaemia was associated with a significantly higher risk of major macrovascular events, major microvascular events and cardiovascular mortality.[114] Zhao et al.[115] reported on a study involving over 44,000 patients with T2DM in a real-practice setting that demonstrated an increased risk for cardiovascular events and microvascular complications associated with episodes of hypoglycaemia. The combination of metformin with a sulphonylurea has also been associated with increased risk of severe hypoglycaemia, cardiovascular events and all-cause mortality compared with metformin in combination with a DPP-4 inhibitor.[18]

Given the incidence of hypoglycaemia associated with sulphonylureas, the possibility of an association between hypoglycaemia and cardiovascular events is of relevance in treatment selection.[2,5,12]

5 | CONCLUSIONS

Clinical evidence shows that GLP-1 RAs may provide better and more durable glycaemic control than sulphonylureas. Furthermore, GLP-1 RAs are associated with a lower risk of hypoglycaemia and result in weight loss rather than the weight gain observed with sulphonylureas. Such differences in the clinical effects of GLP-1 RAs and sulphonylureas can have an important influence on the likelihood of patients with T2DM achieving and maintaining glycaemic targets, which in turn can affect the longer-term risk of complications.[93,97,116] Adverse effects such as weight gain and hypoglycaemia may also affect treatment persistence and patient adherence.[117]

Considering all these aspects from an economic point of view, and given the increased cardiovascular risk observed for sulphonylureas and the increased need for blood glucose monitoring, the annual cost per patient associated with use of GLP-1 RAs compared with sulphonylureas may be less pronounced than expected. A cost-utility analysis comparing the economic impact of the GLP-1 RA dulaglutide and the sulphonylurea gliclazide (both plus metformin) from the perspective of the Italian National Healthcare System indicated that dulaglutide was associated with lower direct costs associated with glycaemic self-monitoring, hypoglycaemia and cardiovascular complications than gliclazide over a one-year time horizon.[118]

It is well-known that many patients with T2DM do not achieve glycaemic control promptly after diagnosis or with ongoing treatment, a phenomenon that has been described as 'clinical inertia'.[119–121] This is important as it can lead to patients being exposed to long-term elevations in HbA1c, which negatively impacts their prognosis.[97,116]

The importance of individualised treatment strategies for T2DM, with careful consideration of patient needs, is reflected in practice guidelines.[8] Recent updates to guidelines recommend that treatment selection includes consideration of cardiovascular safety, especially in patients with established cardiovascular disease.[6,7,9–11] Available evidence, therefore, suggests that preference should be given to GLP-1 RAs over sulphonylureas, especially for patients at high cardiovascular risk. The most recently updated treatment algorithms

also include sulphonylureas as third-line rather than second-line therapies.[10,11] The range of GLP-1 RAs available allows selection of an option to address clinical need based on efficacy, tolerability and cardiovascular safety while considering the preferences of individual patients for factors affecting adherence, including convenience, frequency of administration, ease of use and cost. Consequently, GLP-1 RAs present a compelling alternative to sulphonylureas across the continuum of care for patients with T2DM.

CONFLICT OF INTERESTS

In the last three years, Stefano Genovese has received speaking and/ or consulting fees and research grants from: Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Bruno Farmaceutici, Eli Lilly, Hikma Pharmaceuticals, Janssen, Johnson & Johnson, Menarini, Merck Sharp & Dohme, Molteni Farmaceutici, Mundipharma, Novartis, Novo Nordisk, Sanofi, Takeda. Marco Orsini Federici and Antonella Corcos are employees of Eli Lilly and Company. Raffaella Gentilella is an employee of Jazz Pharmaceuticals - Jazz Healthcare Italy s.r.l., and a minor shareholder of Eli Lilly. Enrico Torre has received fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi.

ETHICS STATEMENT

A statement describing explicitly the ethical background to this study and any institutional or national ethical committee approval has been included in the manuscript.

AUTHOR CONTRIBUTION

Marco Orsini Federici was involved in the conception, design of the work and interpretation of data. Marco Orsini Federici was also involved in drafting the work as well as providing critical revisions of content. Raffaella Gentilella, Antonella Corcos and Enrico Torre were involved in the conception, design and interpretation of data for the work, and provided critical revisions to the content. Stefano Genovese was involved in the conception and acquisition of data for the work, as well as critical revisions of the content.

All authors give their approval of the final manuscript, and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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