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Combination Therapy with Metformin plus Gliclazide in Patients with Type 2 Diabetes

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Abstract

Type 2 diabetes is a chronic, degenerative disease, which requires management of the symptoms via lifestyle modification and anti-diabetic pharmacotherapies. If glycaemic targets are not maintained, patients can often require the addition of a second drug to help achieve glycaemic control. Polypharmacy represents a substantial problem in some patient groups, reducing adherence and potentially impacting on clinical outcomes. Patients with type 2 diabetes may be taking a number of concomitant medications. For this reason, a single-tablet, combined therapy is an attractive prospect for achieving and maintaining glycaemic targets, reducing complexity and burden on patients, while promoting adherence. Metformin is widely used as a monotherapy, acting to improve insulin sensitivity, reducing glucose production and increasing uptake and utilisation of glucose in tissues. Gliclazide, a second generation sulfonylurea, stimulates the production of insulin. Combination of metformin and gliclazide is an appealing dual therapy option due to their complementary modes of action. The efficacy and safety of a range of combination therapies have been investigated in a number of clinical trials. In patients with inadequate glycaemic control, combination of metformin and gliclazide has consistently demonstrated favourable efficacy in clinical trials, reducing glycated haemoglobin, fasting blood glucose and post-prandial glucose. Both therapies are well-tolerated and show comparable, if not favourable safety profiles, including hypoglycaemia, weight loss, cardiovascular measures, and some evidence of benefits to oxidative status. In this review, we evaluate the efficacy and safety evidence supporting combined metformin and gliclazide therapy for the treatment of type 2 diabetes and consider the wider benefits of combining these drugs as a single tablet.

Introduction

Diabetes is a chronic degenerative disease that can result in long-term complications affecting the heart and blood vessels, eyes, kidneys, and peripheral and autonomic nervous systems [1]. Diabetes is associated with an increased risk of heart disease and stroke, and cardiovascular disease is the major cause of death in people with type 2 diabetes [2]. Neuropathy and reduced blood flow in the feet increase the chance of ulcers and infection, and, in developed countries, lower-limb amputations are ≥10-times more common in people with diabetes than those without the disease [3]. Diabetic retinopathy is responsible for 1% of all-cause blindness worldwide, [4] and diabetes is among the leading causes of kidney failure in both developed and developing countries [3]. Diabetes is also associated with an increased risk of overall and site-specific cancers, including pancreatic, liver, colorectal, endometrial, and breast [5].

Over 380 million people are estimated to have diabetes mellitus, with type 2 diabetes, characterised by insulin resistance and/or relative insulin deficiency, accounting for at least 85–95% of cases [6]. In recent estimates, 6–16% of all-cause deaths worldwide are due to diabetes [6,7]. In addition, diabetes care and management is associated with significant costs, and accounted for an estimated 12% of global healthcare expenditure in 2010 [8].

For many patients, monotherapy is insufficient to achieve glycaemic targets, and therefore, additional therapies are advised [9]. However, the burden of increasing polypharmacy, especially in vulnerable patient groups, can negatively affect adherence. By combining treatments in a single tablet, the polypharmacy and complex daily-dosing regimens endured by many individuals with type 2 diabetes can be alleviated. By lessening the burden of polypharmacy, combination treatment can have a positive impact on adherence, which in turn may give rise to improved treatment outcomes.

This review examines the efficacy and safety/tolerability of combination therapy with metformin plus gliclazide in people with type 2 diabetes. In addition, the benefits of combining metformin and gliclazide in a single fixed-dose treatment will be explored.

Management of Type 2 Diabetes

Current international guidelines for the management of type 2 diabetes support initial lifestyle modification (diet and exercise), with metformin being preferred and recommended as first–line anti-diabetic pharmacotherapy for patients without contraindications to this agent [10,11]. Following the initiation of metformin monotherapy, glycaemic targets should be reviewed at around 3–6 months. If at that stage, the patients' diabetes is suboptimally controlled (target glycated haemoglobin [HbA_{1c}] <7.0% [53 mmol/mol] or <6.5% [48 mmol/mol]), then dual combination therapy with a second oral agent, preferably a sulfonylurea, is advised [12,13]. Other guidelines such as those of the Sociedade Brasiliera de Diabetes or the American Association of Clinical Endocrinologists and American College of Endocrinology consensus statement recommend starting with a combination therapy in type 2 diabetic patients presenting with a more severe glycaemia (fasting plasma glucose [FPG] of 200 to 300 mg/dL or HbA_{1c} >7.5%) [14,15]. Following the initiation of dual combination therapy, or any other subsequent changes to diabetes therapy, glycaemic targets should be reviewed at around 3 months, and regularly thereafter, in order to determine whether treatment goals are being achieved and whether therapy is required to be intensified further [10].

Combination therapy is often necessary to achieve target glycaemic control in patients with diabetes

Initially, oral metformin monotherapy plus lifestyle interventions may be successful in controlling the symptoms of type 2 diabetes, but 5-10% of patients per year subsequently fail to maintain target HbA_{1c} levels [16]. In a prospective study of patients with newly diagnosed type 2 diabetes (N=4075), randomised to lifestyle modification alone or lifestyle modification plus either a sulfonylurea, metformin or insulin therapy, 50% of patients receiving monotherapy required the addition of a second drug after 3 years; and by 9 years, 75% needed multiple therapies to achieve target HbA_{1c} levels [9]. A meta-analysis of 15 randomised clinical trials evaluated the benefit of combination treatment in type 2 diabetes involving almost 7,000 patients [17]. In this analysis, mean age range was 48.4–62.7 years, mean baseline HbA_{1c} was 7.2–9.9%, and mean diabetes duration was 1.6–4.1 years. The drugs combined with metformin in these trials included thiazolidinediones (TZDs), insulin secretagogues, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose transporterase (SGLT-2) inhibitors. Combination therapy with metformin showed significant reductions in HbA_{1c} (weighted mean difference [WMD]: -0.43%; 95% confidence interval [CI]: -0.56 to -0.30) compared to metformin monotherapy. Combination therapy increased HbA_{1c} goal level attainment (HbA_{1c} <7%) (risk ratio [RR]: 1.40; 95% CI: 1.33 to 1.48) and reduced FPG (WMD: –14.30 mg/dL; 95% CI: –16.09 to –12.51) [17].

Evidence Supporting Metformin plus Gliclazide Combination Therapy

Metformin is a biguanide oral anti-hyperglycaemic agent that improves insulin sensitivity, reduces basal liver glucose production, and increases insulin-stimulated uptake and utilisation of glucose by peripheral tissues in patients with type 2 diabetes [18]. A meta-analysis of 35 trials in type 2 diabetes indicated that metformin monotherapy lowered HbA_{1c} by an average of 1.12% (12 mmol/mol) compared with placebo in individuals previously being treated by lifestyle modification alone, by 0.95% (11 mmol/mol) versus placebo when added as a combination therapy to another oral anti-diabetic drug (OAD) and by 0.6% (6 mmol/mol) versus placebo when added to insulin therapy [19]. Gastrointestinal events (including diarrhoea, nausea, vomiting, flatulence and abdominal pain) are the most common adverse events reported with metformin, but are generally mild to moderate and temporary [19].

Metformin is widely viewed as the most appropriate option for monotherapy due to the extensive clinical experience with the drug, the positive hypoglycaemia profile, the lack of weight gain or weight loss associated with therapy, the low cost of treatment and the fact that metformin treatment was associated with a reduced risk of cardiovascular disease compared to conventional treatment (primarily diet) in the UK Prospective Diabetes Study (UKPDS) [10,20]. One factor limiting the use of metformin, particularly in the United States, are the criteria specified by the Food and Drug Administration contraindicating metformin in people with renal disease or dysfunction (serum creatinine ≥1.5 mg/dL in men and ≥1.4 mg/dL in women) [21]. Metformin is also contraindicated in Europe for those with moderate (stage 3b) or severe renal failure or dysfunction (estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m^2) [22]. There is some evidence, however, that these contraindications may be too restrictive and that metformin could be used in patients with mild-to-moderate chronic kidney disease (eGFR 30–60 mL/min/1.73 m^2) with suitable dose reductions and monitoring of kidney function [10,21].

Gliclazide is a second-generation sulfonylurea oral anti-hyperglycaemic agent that improves defective insulin secretion [23]. The immediate-release (IR) formulation of gliclazide requires twice-daily dosing, but a modified-release (MR) version has been developed that is therapeutically equivalent to gliclazide IR, but allows for once-daily dosing [24].

The 2015 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) guidelines note a number of advantages for sulfonylureas, including extensive clinical experience, the association of sulfonylurea treatment with a reduction in macrovascular risk in UKPDS and the fact that they are a low-cost option [10,24]. Gliclazide may also provide improved beta cell outcomes compared to other sulfonylureas, as indicated by an increased time to insulin treatment when comparing gliclazide treatment to glibenclamide (mean duration from onset of diabetes for gliclazide: 27.7 years; 95% CI: 24.7–30.7; mean duration for glibenclamide: 21.4 years; 95% CI: 18.7–24.2; p<0.001) [25]. Potential disadvantages of sulfonylureas include an increased risk of hypoglycaemia, body-weight gain and a potentially increased risk of secondary failure compared with other OADs [13,14].

Given that metformin acts by improving insulin sensitivity and reducing basal liver glucose production and that gliclazide acts by stimulating insulin production, there is a medical rationale for combination therapy given their complementary mechanisms of action. The clinical evidence that supports combination treatment with gliclazide and metformin will be reviewed in the next section.

Efficacy and Safety/Tolerability of Metformin plus Gliclazide Combination Therapy in Patients with Type 2 Diabetes

There are a wide range of trials examining the efficacy and safety of combination therapy with gliclazide and metformin in individuals with type 2 diabetes insufficiently controlled with metformin, or other OAD monotherapy; [26-35] with combination OAD therapy [29] or with lifestyle modification alone (Table 1) [36-38].

Efficacy

Type 2 diabetes insufficiently controlled by metformin monotherapy

The metformin plus gliclazide combination is effective at improving glycaemic control in patients with type 2 diabetes insufficiently controlled by first-line monotherapy (Table 1) [26-35]. The addition of gliclazide to metformin monotherapy was associated with reductions in HbA_{1c} of between 0.27% [28] and 1.7% [29] (equivalent to 3.3 to 18.6 mmol/mol) (Table 1). Reported HbA_{1c} reductions with gliclazide were comparable with those observed with nateglinide, [27,28] pioglitazone, [30,32] and rosiglitazone (Table 1) [31]. FPG reductions ranging between the equivalent of 12.43 (calculated from data in Ristic et al, 2007) [28] to 67.08 mg/dL [26] (corresponding to 0.69 to 3.73 mmol/L) were reported following the addition of gliclazide to metformin monotherapy (Table 1). In the more limited number of trials that reported post-prandial glucose (PPG) results, reductions were in the range of 40.0 (calculated from data in Galeone et al. [39] to 96.03 mg/dL [26] (corresponding to 2.23 to 5.34 mmol/L) (Table 1). Following the addition of gliclazide to metformin monotherapy, between 37% and 47% of participants across trials achieved HbA_{1c} ≤7% (equivalent to 53 mmol/mol) (Table 1). HbA_{1c} reductions of ≥0.5% (5.5 mmol/mol) were observed in 49.2% of participants at 24 weeks, [27] and in 24.2% of participants at 52 weeks (6-month extension) after the initiation of gliclazide and metformin combination therapy [28].

Type 2 diabetes insufficiently controlled by other OAD monotherapy or combination therapy

In a trial of patients inadequately controlled with either metformin or α-glucosidase inhibitor monotherapy, the addition of gliclazide or glimepiride resulted in HbA_{1c} reductions of approximately 1% (10.0 mmol/mol) and FPG reductions of 1.3% to 1.4% [34]. A retrospective analysis examined the combination of either gliclazide or rosiglitazone with metformin in individuals with type 2 diabetes treated with prior

Reference	Population	Study design	Treatment	Main efficacy outcomes			Main safety outcomes
				Outcome	Baseline	Follow-up	
Pareek et al. [26]	T2D (n=115) uncontrolled with oral monotherapy	12-week, prospective, open-label, multicentre study	GLI (80 to 320 mg OD) MET (500 to 2000 mg OD)	HbA_{1c}, % ΔHbA_{1c} ≥0.5%, % HbA_{1c} <7%, % FPG, mg/dL PPG, mg/dL	8.51 ± 0.77 N/R N/R 178.34 ± 37.64 261.68 ± 66.77	Δ –1.16 ± 1.02* 84.35 37.39 Δ –67.08 ± 36.18* Δ –96.03 ± 64.03*	AEs: 22/124 (17.7%); 20 mild, 2 moderate 16 AEs possible hypos
Ristic et al. [27]	T2D (n=247) uncontrolled with MET monotherapy (≥1000 mg)	24-week, double-blind, double-dummy, parallel group, randomised, multicentre study	GLI (80 to 240 mg OD) (n=118)	HbA_{1c}, % (SE) ΔHbA_{1c} ≥0.5%, % HbA_{1c} <7%, % FPG, mmol/L (SE)	7.57 ± 0.57 N/R EC HbA_{1c} 6.8–9% 8.65 ± 1.49	Δ −0.57* (0.08) 49.2 46.6 Δ −0.82* (0.18)	Drug-related AEs: 7.1% Confirmed hypo: 22.2% Weight: +<0.5 kg (n=126)
			NAT (60 to 180 mg TID) (n=129)	HbA_{1c}, % ΔHbA_{1c} ≥0.5%, % HbA_{1c} <7%, % FPG, mmol/L	7.66 ± 0.59 N/R EC HbA_{1c} 6.8–9% 8.49 ± 1.49	Δ −0.41 ± 0.08* 48.8 34.9 Δ −0.63 ± 0.17*	Drug-related AEs: 6.9% Confirmed hypo: 21.5% Weight: +<0.5 kg (n=130)
Ristic et al. [28]	T2D (n=213) uncontrolled with MET monotherapy (>1000 mg)	52-week, (6-month trial and 6-month extension) double-blind, double-dummy, multicentre study	GLI (80 to 240 mg OD) (n=101)	HbA_{1c}, % ΔHbA_{1c} ≥1.0%, % HbA_{1c} <7%, % FPG, mmol/L (SE)	7.55 ± 0.57 N/R EC HbA_{1c} 6.8–9% 8.51 ± 1.44	Δ −0.27 ^{LS} 24.2 47.5 Δ –0.69 (0.23)^{LS}	Confirmed hypo: 14.9% Weight: +0.91 kg
			NAT 60 to 180 mg TID (n=112)	HbA_{1c}, % ΔHbA_{1c} ≥ 1.0%, % HbA_{1c} ≤7%, % FPG, mmol/L (SE)	7.65±0.60 N/R EC HbA_{1c} 6.8–9% 8.98 ± 1.52	Δ −0.14 20.0 40.0 Δ –0.20 (0.22)	Confirmed hypo: 15.2% Weight: +0.42 kg (NS vs GLI group)
Vilar et al. [29]	T2D (n=250), monotherapy or combination therapy	Retrospective study	GLI (60 to 90 mg/d) + MET (850 to 1000 mg BID) (n=65)	HbA_{1c}, % HbA_{1c} <7%, % FPG, mg/dL PPG, mg/dL	9.3±0.6 EC HbA_{1c} >7% 195.1 ± 10.7 205.2 ± 19.4	Δ –1.7±0.2 41.5 –58.2±5.3% −50.6±4.2%	Symptomatic hypo: 7.7% Weight: +2.2 kg
			ROSI (4 mg BID) + MET (850 to 1000 BID (n=30)	HbA_{1c}, % HbA_{1c} <7%, % FPG, mg/dL PPG, mg/dL	9.2 ± 0.8 EC HbA_{1c} >7% 192.9 ± 7.7 204.1 ± 20.5	Δ –1.2±0.4** 28‡ –46.2 ± 4.7%** –42.1 ± 5.3%**	Symptomatic hypo: 3.3% Weight: +2.1 kg
			GLI (60 to 90 mg/d) + ROSI (4 mg BID) (n=30)	HbA_{1c}, % HbA_{1c} <7%, % FPG, mg/dL PPG, mg/dL	9.2 ± 0.5 EC HbA_{1c} >7% 193.8 ± 8.8 206.5 ± 19.6	Δ –1.6 ± 0.3 40 −55.4 ± 7.8% −48.2 ± 6.6%	Symptomatic hypo: 10.0% Weight: +5.5 kg**
Betteridge and Verges [30]	T2D (n=630) uncontrolled with MET monotherapy	2-year, randomised, double-blind, double-dummy trials	GLI (80 to 320 mg/d) + MET (n=313)	HbA_{1c}, %	N/R	Δ –0.77	N/R
			PIO (15 to 45 mg/d) + MET (n=317)	HbA_{1c}, %	N/R	Δ –0.89	N/R
Hamann et al. [31]	T2D (n=596) uncontrolled with MET monotherapy	52-week, randomised, double-blind, parallel-group study	GLI (80 to 320 mg/d) or GLIB (5 to 15 mg/d) + MET (2000 mg/d) (n=302)	HbA_{1c}, % FPG, mmol/L	8.0 ± 1.0 10.2 ± 2.9	Δ –0.86 ± 0.06 Δ −2.25 ± 0.16	AEs: 58% ≥ 1 hypo event: 30%** Confirmed hypo: 7.0% Weight: +1.6 kg
			ROSI (4 to 8 mg/d) + MET 2000 mg/d (n=294)	HbA_{1c}, % FPG, mmol/L	8.0 ± 0.9 10.5 ± 2.8	Δ –0.78 ± 0.06 Δ −2.29 ± 0.16	AEs: 56% ≥ 1 hypo event: 6% Confirmed hypo: <1.0% Weight: 2.7 kg#

Matthews et al. [32]	T2D (n=630) uncontrolled with MET monotherapy	52-week, randomised, double-blind, parallel-group, double-dummy study	GLI (80 to 320 mg/d) + MET (500-3000 mg/d) (n=313)	HbA_{1c}, % FPG, mmol/L	8.53 ± 0.89 11.3 ± 2.6	Δ –1.01 Δ–1.6	AEs: 58.1% Hypo event: 11.2% Weight: +1.4 kg
			PIO (15 to 45 mg OD) + MET (500-3000 mg/d) (n=317)	HbA_{1c}, % FPG, mmol/L	8.71 ± 1.00 11.8 ± 3.1	Δ –0.99 Δ –2.1	AEs: 55.5% Hypo event: 1.3% Weight: +1.5 kg
Onuchin et al. [37]	Uncontrolled T2D in women aged >55 years (n=182)	1-year, open-label prospective study	Group 1: MET (2500 to 5000 mg/d)	HbA_{1c}, %	10.4 ± 1.6	7.1 ± 0.6	Safety: N/R
			Group 2: MET (1500 to 2500 mg/d) + GLI (30 to 90) mg/d)	HbA_{1c}, %	10.6 ± 1.8	6.7 ± 0.5	N/R
Galeone et al. [39]	Uncontrolled T2D with maximum dose of GLI (240 mg/d, n=57)	3-month, prospective, uncontrolled study	GLI (120 mg/d divided into 3 daily doses) + MET (1500 mg/d divided into 3 daily doses)	HbA_{1c}, % FPG, g/L PPG (lunch), g/L PPG (dinner), g/L	9.9 ± 1.1 1.94 ± 0.30 2.29 ± 0.41 2.08 ± 0.19	8.4 ± 1.0¶ 1.48 ± 0.30¶ 1.74 ± 0.27 1.68 ± 0.16	No severe hypos or lactic acidosis Weight: No significant change
Lee et al. [38]	Uncontrolled T2D (drug-naïve) (n=116)	24-week, prospective, nonrandomised, open-label study	Group 1: GLI (30 to 60 mg), or GLIM (2.5 to 4.0 mg) + MET (1000 mg/d) (n=31)	HbA_{1c}, median %, (range) HbA_{1c} ≤7%, % FPG, median mg/dL (range) PPG, median mg/dL (range)	8.9 (8.2 to 10.3) EC HbA_{1c}>7% 166.5 (139.0 to 195.0) 226.5 (192.5 to 312.0)	6.4* (6.0 to 6.7) 89.3 103.5* (89.0 to 112.0) 157.0* (124.0 to 219.5)	No major hypos
			Group 2: PIO (15 m/d) + MET (1000-1700 mg/d) (n=30)	HbA_{1c}, median %, (range) HbA_{1c} ≤7%, % FPG, median mg/dL (range) PPG, median mg/dL (range)	9.0 (8.4 to 11.2) EC HbA_{1c}>7% 174.0 (145.0 to 223.0) 238.0 (195.5 to 324.0)	6.6* (6.1 to 6.9) 81.5 111.0* (101.5 to 120.0) 157.0* (133.5 to 196.5)	No major hypos
			(Group 3, n=38) SITA (100 mg/d) + MET (1000-1700 mg/d)	HbA_{1c}, median %, (range) HbA_{1c} ≤7%, % FPG, median mg/dL (range) PPG, median mg/dL (range)	9.3 (7.8 to 10.4) EC HbA_{1c}>7% 173.0 (135.0 to 204.0) 251.0 (196.0 to 306.0)	6.3* (6.0 to 6.7) 84.8 105.0* (100.0 to 124.0) 148.0* (115.0 to 172.0)	No major hypos
Schernthaner et al. [34]	T2D (n=845) treated with diet or MET or α-GLUi monotherapy	27-week, randomised, double-blind, parallel-group	GLI MR (30 to 120 mg/d) + MET, or α-GLUi (pre-study dose; n=405)	HbA_{1c}, % HbA_{1c} ≤7%, % FPG, mmol/L	8.4±1.1 EC HbA_{1c} 6.9–11.5% 10.2 ± 2.6	Δ −1.1±1.1* ~50 Δ–1.4	Confirmed hypo: 3.7%‡ Other AEs: 40.9% Weight: +0.5 kg
			GLIM (1 to 6 mg/d) + MET, or α-GLUi (pre-study dose; n=440)	HbA_{1c}, % HbA_{1c}<7%, % FPG, mmol/L	8.2 ± 1.0 EC HbA_{1c} 6.9–11.5% 10.1 ± 2.6	Δ −1.0 ± 1.1* ~50 Δ–1.3	Confirmed hypo: 8.9% Other AEs: 40.1% Weight: +0.6 kg
Filozof et al. [35]	Uncontrolled T2D with MET (n=1007)	52-week, randomised, double-blind, active-controlled, multicentre	GLI (80 to 320 mg/d) + MET (1500 mg/d) (n=494)	HbA_{1c}, % (SE) HbA_{1c} ≤7%, % FPG, mmol/L	8.5 ± 1.0 EC HbA_{1c} 7.5–11% 10.6 ± 2.8	Δ –0.85 (0.06) 31.9 Δ 1.52 (0.14)	AEs: 61.3% Hypos: 11 events Withdrawal due to AE: 4.7% Weight: +1.36 kg

			VILDA (50 mg BID) + MET (1500 mg/d (n=513)	HbA_{1c}, % HbA_{1c} <7%, % FPG, mmol/L	8.5 ± 1.0 EC HbA_{1c} 7.5–11% 10.8 ± 2.8	Δ –0.81 ± 0.06 29.6 Δ 1.31 ± 0.14	AEs: 61.8% Hypos: 6 events Withdrawal due to AE: 6.7% Weight: +0.08 kg**

Table 1: Summary of key studies involving metformin and gliclazide combination therapy in patients with type 2 diabetes
†p<0.05; ‡p<0.05 vs comparator; ¶p<0.01; #p=0.002 vs comparator; *p<0.001 vs baseline; **p<0.001 vs comparator groups.
AEs: Adverse Events; BID: Twice Daily; EC: Entry Criteria; FPG: Fasting-Plasma Glucose; GLI: Gliclazide; GLIB: Glibenclamide; GLIM: Glimepiride; HbA_{1c}: Glycated Haemoglobin; Hypo: Hypoglycaemia; LS: Least Square; MET: Metformin; N/A: Not Applicable; NAT: Nateglinide; N/R: Not Reported; NS: Not Significant; OD: Once Daily; PIO: Pioglitazone; PPG: Post-Prandial Glucose; ROSI: Rosiglitazone; SITA: Sitagliptin; TID: Three-Times Daily; T2D: Type 2 Diabetes; VILDA: Vildagliptin; α-GLUi: α-Glucosidase Inhibitor; Δ: Change
All data are means ± SD unless otherwise stated

OAD monotherapy or combination therapy [29]. In this population, patients treated with gliclazide and metformin had significantly greater HbA_{1c}, FPG and PPG reductions compared with rosiglitazone plus metformin (Table 1).

Type 2 diabetes inadequately controlled by lifestyle modification

A trial investigated the initiation of gliclazide or glimepiride in combination with metformin compared to combination treatment with pioglitazone or sitagliptin and metformin in previously drug-naïve individuals with type 2 diabetes [38]. Gliclazide or glimepiride plus metformin significantly reduced HbA_{1c} from 8.9% (74 mmol/mol) at baseline to 6.4% (46 mmol/mol), FPG from 9.25 mmol/L to 5.75 mmol/L and PPG from 12.56 mmol/L to 8.72 mmol/L from baseline to follow-up at 24 weeks [38]. These reductions observed with gliclazide or glimepiride and metformin were comparable with reductions observed with pioglitazone or sitagliptin in combination with metformin (Table 1) [38].

A meta-analysis that compared efficacy outcomes from nine clinical studies with gliclazide versus other oral insulinotropic agents (sulfonylureas, dipeptidyl peptidase-4 inhibitors and glinides) concluded that HbA_{1c} reductions were greater with gliclazide than with the other oral insulinotropic agents (WMD: −0.11%; 95% CI: −0.19 to −0.03%; p=0.008), and similar to other sulfonylureas (WMD: −0.12%; 95% CI: −0.25 to 0.01%; p=0.07) [40]. These findings were supported by a second meta-analysis of 19 studies, which concluded that gliclazide was comparable to other oral therapies, excluding metformin, in terms of HbA_{1c} reduction (treatment difference: −0.13%; 95% CI: −0.25 to −0.02) [41].

Safety/tolerability

Both metformin and gliclazide have been licensed for many years and have proven favourable tolerability and safety in monotherapy and in free combination. No major safety findings differing from the established overall safety profile of metformin have been noted during the most recent periodic safety update reports, and no specific safety concerns have arisen in relation to metformin application in mild and moderate renal insufficiency.

Gliclazide is generally well tolerated by the majority of patients, with mild gastrointestinal, skin and central nervous system effects being the most commonly reported adverse events [23]. The most frequent types of treatment-related adverse events observed with combined metformin and gliclazide therapy in the studies reviewed here were headache, giddiness, hypertension, and diarrhoeas [26,28,35]. The majority of adverse events reported with gliclazide and metformin were mild-to-moderate in severity and withdrawals due to adverse events were uncommon (4.7% reported in one study) (Table 1) [26,35].

Hypoglycaemia

Gliclazide not cause clinically relevant hypoglycaemia [42,43]. A meta-analysis of nine clinical trials identified that the risk of hypoglycaemia with gliclazide was significantly lower compared with other sulfonylureas (RR: 0.47; 95% CI: 0.27 to 0.79; p=0.004) and was similar to other insulinotropic agents (RR: 0.85; 95% CI: 0.66 to 1.09; p=0.20) [40]. In a second meta-analysis of 19 trials, severe hypoglycaemia was reported in a similar proportion (1/2387 [0.04%]) of those treated with gliclazide and in the comparator group treated with other OADs (1/2430 [0.04%]) [41]. Symptomatic hypoglycaemia was reported in 7/19 studies and was observed in 25/1152 (2.2%) of the gliclazide group and 22/1162 (1.8%) of the comparator group (RR: 1.09; 95% CI: 0.20 to 5.78) [41].

Weight-gain: In a meta-analysis of 19 trials, gliclazide treatment was comparable to other sulfonylureas and meglitinides in terms of body-weight effects; however, the meta-analysis showed gliclazide was associated with increased weight gain versus metformin (1.37 kg; 95% CI: 0.15 to 2.60). None of the studies included in the meta-analysis were designed to evaluate cardiovascular outcomes [41]. Weight loss associated with metformin therapy is well-established [44]. The body-weight results reported in the meta-analysis are comparable with those reported in the studies reviewed here of combination therapy of metformin plus gliclazide versus metformin plus pioglitazone, [27,28] rosiglitazone, [29] or glimepiride [34]. However, in a study of metformin plus either gliclazide or vildagliptin, body weight was stable with vildagliptin (+0.08 kg) and increased slightly with gliclazide (+1.36 kg; p<0.001) [35].

Other safety-related endpoints: In a 16-week study in patients with type 2 diabetes (N=47) randomised to metformin monotherapy or metformin plus gliclazide, the early use of combination therapy increased the number and function of circulating endothelial progenitor cells (EPCs) compared with metformin monotherapy [45]. These circulating EPCs are thought to slow the development and progression of diabetic vascular complications; however, in individuals with type 2 diabetes the numbers of EPCs are reduced and their function (proliferation, adhesion and migration) is impaired [45]. Therefore, this study provides initial indications, albeit in a small cohort, that early use of metformin plus gliclazide combination therapy may have a beneficial impact on vascular health. Potential cardiovascular benefits of metformin and gliclazide have also been reported in a study of women aged >55 years with a history of type 2 diabetes who were randomised to either metformin (n=46), metformin plus gliclazide MR (n=47), metformin plus insulin (n=44), or insulin (n=45) [37]. After 12 months, patients taking metformin alone or in combination with gliclazide showed a reduced risk of developing cardiovascular complications (risk of ischemic heart disease [IHD], risk of death from IHD, risk of acute cerebrovascular event [ACVE] and risk of death from ACVE), decreased arterial hypertension, and reduced diastolic dysfunction compared with participants receiving insulin monotherapy [37]. While these small studies have indicated possible cardiovascular

benefits of metformin and gliclazide combination therapy, these benefits need to be confirmed by larger clinical trials.

The metabolic and vascular effects of gliclazide were compared to glimepiride in metformin-treated individuals with type 2 diabetes [33]. Glycaemic responses at 4 weeks, measured by serum fructosamine levels, were similar with both gliclazide (315 mmol/L) and glimepiride (329 mmol/L). Macrovascular function, measured by arterial stiffness and vascular pressor responsiveness, were similar with both treatments [33]. Microvascular vasodilator responses were also similar with gliclazide (peak acetylcholine response 68 ± 36 perfusion units) and glimepiride (63 ± 34 perfusion units) [33]. The study concluded that there was no evidence that gliclazide (an SUR1-specific sulfonylurea) and glimepiride (a non-specific sulfonylurea that also acts on SUR2) had differential effects on macrovascular or microvascular endpoints [33].

A randomised, open-label trial compared gliclazide and metformin with respect to glycemic control and effects on lipid peroxidation markers in 36 adult patients with type 2 diabetes [46]. Both agents significantly decreased HbA1c ($p<0.05$), fructosamine ($p<0.05$), and the glucose-excursion curve during the oral glucose tolerance test ($p<0.01$). There was no change in the standard lipid profile; however, both agents increased serum vitamin E (gliclazide: $p<0.01$; metformin: $p<0.05$) and decreased the level of lipid peroxidation markers in low-density lipoprotein and high-density lipoprotein particles ($p<0.05$). The authors concluded that gliclazide and metformin contributed to an improved antioxidant/lipid peroxidation status [46].

A fixed-dose combination may improve patient adherence to anti-diabetic therapy

Polypharmacy places an additional burden on patients, potentially reducing treatment adherence, which could adversely impact clinical outcomes. A study of 154 people with type 2 diabetes identified that individuals took on average 8.4 different drugs daily, and in one case 16 different drugs daily, to treat their diabetes and other co-morbidities/health issues [47]. This entailed individuals administering an average of 8.6 tablets and 2.6 injections daily. The majority (97%) of these prescriptions was in accordance with guideline recommendations, indicating that the drugs prescribed were appropriate and necessary [47]. However, the burden of taking so many different medications on a daily basis is considerable, particularly in more vulnerable patient populations, such as the elderly.

Polypharmacy is inconvenient and may cause confusion, with patients mixing up the timing of doses [48]. In a single-centre study of 240 patients with type 2 diabetes, which assessed compliance using a questionnaire; 83% of patients taking five medications daily were treatment adherent, whereas, only 27% of patients were adherent when they had to administer eight different medications daily [49]. This study also identified a higher rate of non- adherence among retired patients (70%) compared with others (41%), [49] suggesting that elderly patients may have more trouble coping with polypharmacy compared with younger patients.

Given the issue of polypharmacy in people with type 2 diabetes, single-tablet, fixed-dose combinations of two OADs can reduce treatment complexity, and can significantly improve adherence over separate dual-combination therapy [50,51]. For example, a meta-analysis examining fixed-dose combination drugs and free-drug regimens in diseases such as tuberculosis (2 studies), hypertension (4 studies), HIV (1 study) and diabetes (2 studies) identified a 26% decrease in non-adherence with fixed-dose combinations *vs* free drugs (RR: 0.74; 95% CI: 0.69 to 0.80; $p<0.0001$) [50]. In a study of patients receiving anti-diabetic monotherapy, free-combination therapy or fixed-dose combination therapy that included metformin (N=6502), adherence rates were significantly lower (54%; 95% CI: 0.52 to 0.55) in patients switched to free-combination therapy versus those receiving fixed-dose combination therapy (77%; 95% CI: 0.72 to 0.82). Similarly, adherence was also significantly improved in patients who switched from free- to fixed-dose combination therapy (71% vs 87%; $p<0.001$) [52]. Taken together these data suggest that fixed-dose combinations such as metformin plus gliclazide can help alleviate the key issue of polypharmacy in people with type 2 diabetes and improve treatment adherence.

Summary

In summary, studies indicate that a combined, single-tablet metformin and gliclazide treatment option for patients with type 2 diabetes would be a safe and effective therapeutic strategy. For some patients with type 2 diabetes, the management of symptoms and maintenance of glycaemic control necessitates a number of therapeutic interventions. With the problems that arise from the burden of polypharmacy, reducing the number of tablets a patient needs to take, would provide the benefits of improved glycaemic control, while improving patient adherence to their therapeutic regimens. With this in mind, a fixed-dose combination of metformin and gliclazide is an attractive prospect for improving clinical outcomes for such patients.

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