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## Efficacy, effectiveness and safety of sulphonylurea–metformin combination therapy in patients with type 2 diabetes

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Sulphonylureas and biguanides have been employed in the treatment of type 2 diabetes for almost half a century, both alone and in combination. The antihyperglycaemic efficacy of either type of agent has been established in a large number of studies [1,2]. However, clinical trials on outcome in terms of morbidity or mortality are few and contradictory. The much-debated study of the University Group Diabetes Program (UGDP) indicated that treatment with either a sulphonylurea (tolbutamide) or a biguanide (phenformin) had little, if any, clinical benefit and that they might even increase cardiovascular mortality [3,4]. On the other hand, the more recent, larger and longer United Kingdom Prospective Diabetes Study (UKPDS) indicated that treatment with either a sulphonylurea (chlorpropamide, glibenclamide or glipizide) or insulin reduced microvascular complications and did not increase cardiovascular mortality [5]. Moreover, in overweight patients, metformin treatment reduced both micro- and macrovascular complications and even reduced mortality [6]. Therefore, the prevailing view is that sulphonylureas and metformin are beneficial rather than harmful.

Sulphonylurea and metformin have different mechanisms of action, allowing additive or even synergistic antihyperglycaemic effects. Accordingly, it would seem rational to combine these agents in the treatment of type 2 diabetes patients whose glucose control is not satisfactory on either agent. Indeed, combination therapy

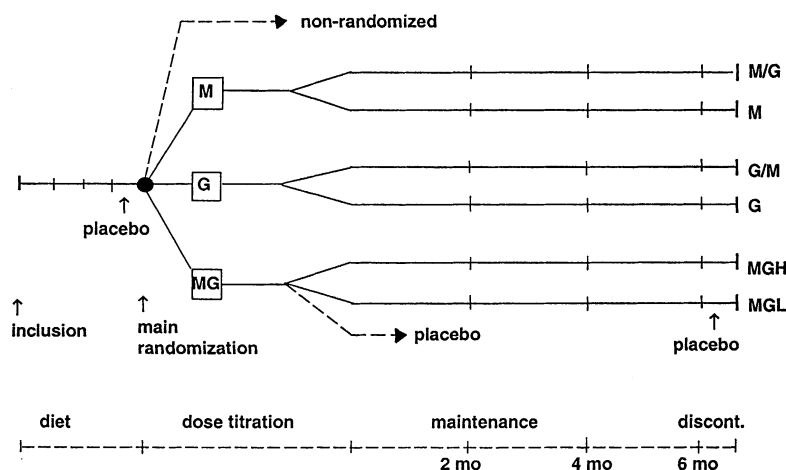
by adding metformin to sulphonylurea in patients with secondary sulphonylurea failure has been highly effective in short-term studies on glucose control [2,7]. However, there is, as yet, no evidence that such therapy reduces morbidity or mortality. Instead, a UKPDS sub-study indicated that addition of metformin to sulphonylurea treatment was associated with higher mortality than seen without such addition [6]. The effect of adding sulphonylurea to metformin in subjects insufficiently treated with metformin as first-line drug has not been investigated systematically but was included in the randomized study summarized below [8,9]. This study also assessed addition of metformin to sulphonylurea but focused on primary combination therapy with both drugs as initial pharmacotherapy after diet failure. This approach seems rational as both basic defects in type 2 diabetes, i.e. impaired insulin secretion and insulin resistance, are targeted simultaneously at the outset of the disease. Recently, large randomized studies have been performed in the US with the combination of glibenclamide and metformin as first-line, as well as second-line, treatment, using a new fixed combination tablet. The results of these trials, available from abstracts, are promising. The present review comprises a number of studies addressing the efficacy, effectiveness and safety of sulphonylurea–metformin combination treatment, although excluding studies reported only as abstracts.

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**Fig. 1** Design of the study by Hermann *et al.* 1994 [8,9]. Inclusion: 165 obese and non-obese patients. Diet period: 8 weeks (including 2 weeks placebo run-in). Randomization: three parallel groups: M = metformin; G = glibenclamide; MG = primary combination. Dose titration: 2–12 weeks, six dose levels, i.e. M 1.0–3.0 g, G 3.5–14.0 mg and combinations. Maintenance: 6 months on M (n = 19), G (n = 19) and combination (n = 86), i.e. G added to M (M/G, n = 12), M added to G (G/M, n = 11) and primary combination in low (MGL, n = 46) and high (MGH, n = 17) dose. Discontinuation: 2 weeks placebo. Patients with dose reduction from dose 1 in the MG group were on placebo. Non-randomized patients achieved the blood glucose target with diet alone.

### Randomized, Dose-titrated, Double-blind, Double-dummy, Placebo-controlled Trial on Metabolic Parameters in Non-selected Patients

So far, only one controlled study [8,9] has been published that has compared single-drug treatment with combination treatment, without restricting selection of patients to those with ongoing sulphonylurea therapy and poor glucose control. In addition, only this study used a design including (a) randomization of patients to (i) sulphonylurea (glibenclamide) alone; (ii) metformin alone or (iii) glibenclamide plus metformin from the study start, (b) double-blind and double-dummy technique, and (c) parallel three-level dose titration towards a pre-set goal of  $<6.7$  mmol/l in each group. Moreover, in those not reaching this goal, another parallel three-level dose titration towards the same goal was introduced by (d) adding metformin to those on glibenclamide alone, (e) adding glibenclamide to those on metformin alone, and (f) further dose increase of both agents in those on combination therapy from the study start.

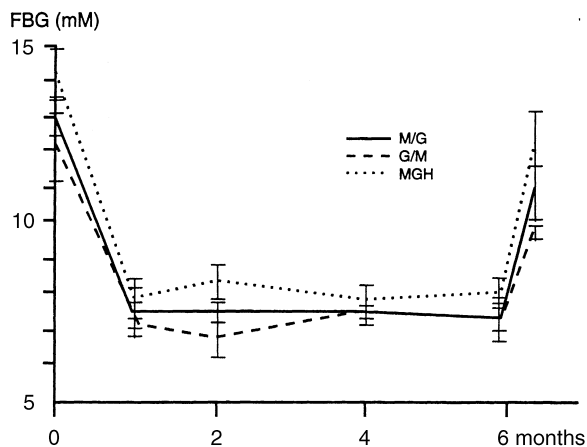
This complex design was used in an effort to combine the scientific demands of the randomized, balanced, double-blind, placebo-controlled clinical trial with clinical practice in the form of individually optimized dosage of either agent, and of the combination as well. Both obese and non-obese patients were included (n = 165), and the randomization was stratified by body mass index (b.m.i.). The study recruited equal proportions of type 2 diabetes patients who were either newly

diagnosed, previously treated by diet alone or had been treated with oral antihyperglycaemic agents (withdrawn 2–3 weeks before inclusion). The design is shown in figure 1, and the results are summarized below.

The single-drug treatments reduced hyperglycaemia to the same extent. Low-dose combination therapy promoted a higher short-term success rate and equivalent long-term efficacy. The mean HbA<sub>1c</sub> change ( $\pm$ s.e.) in the latter, after 6 months of maintenance therapy, was  $-1.2 \pm 0.1\%$  (from baseline  $6.8 \pm 0.1\%$ ; n = 46). Patients who by protocol needed combination therapy and were maintained on various high-dose combinations (n = 40) had mean HbA<sub>1c</sub> reductions of 2.0–2.3% (from baseline 7.8–8.4%) and correspondingly large reductions of fasting blood glucose concentrations (from a mean of 13.3–7.8 mmol/l (figure 2). Meal-stimulated glucose concentrations (AUC) also decreased considerably. Discontinuation of active therapy by placebo substitution led to rapid deterioration of glucose control (figure 2).

Combination therapy averted the weight gain observed after glibenclamide monotherapy (figure 3). It was also associated with less increase of insulin levels [8]. Changes in lipid levels were small and did not differ significantly among groups. Lactate levels were unaltered. Side-effects were not more frequent on combination therapy than on monotherapy.

Other clinical trials on combination therapy have been restricted to patients with secondary sulphonylurea failure [2,7]. Placebo-controlled studies of this kind [10–16]



**Fig. 2** Efficacy of high-dose combination therapy in the study by Hermann *et al.* 1994 [8,9]. Mean (s.e.) fasting blood glucose (FBG) at baseline, at completed dose titration, after maintenance therapy for 2, 4 and 6 months, and 2 weeks after discontinuation of active therapy. M/G = glibenclamide added to metformin; G/M = metformin added to glibenclamide; MGH = primary combination therapy (high dose). See also figure 1.

are summarized in table 1 and comparisons with reference therapies [17–23] in table 2.

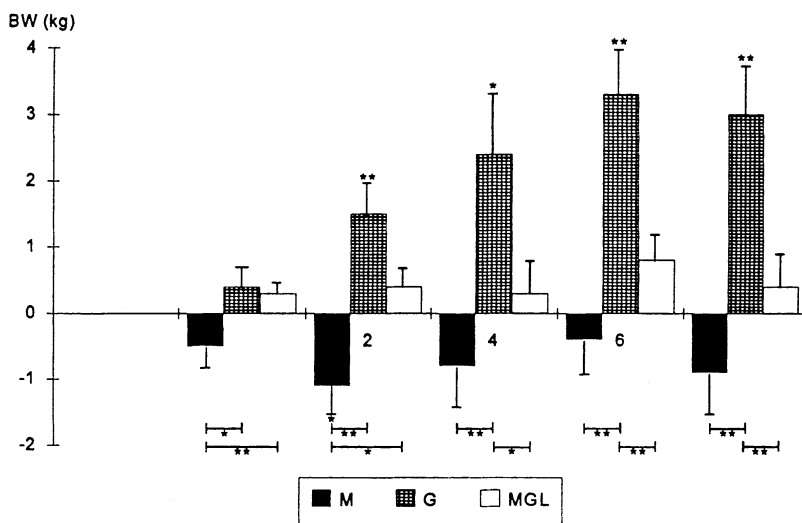
**Randomized, Double-blind, Placebo-controlled Trials on Metabolic Parameters in Patients with Secondary Sulphonylurea Failure**

One study that was pivotal for the approval of metformin in the US was a randomized, double-blind, parallel-group trial comparing glibenclamide plus metformin

(n = 213) with glibenclamide plus placebo (n = 209) and metformin plus placebo (n = 210) in obese patients with sulphonylurea failure [14]. Glibenclamide was maintained at constant and maximum dose (20 mg daily) whereas metformin dosage was titrated by weekly increments of 500 mg daily during 5 weeks, most patients reaching the maximum dose of 2.5 g daily. This was then maintained for 24 weeks. The mean change ( $\pm$ s.e.) in glycosylated haemoglobin at week 29 was  $-1.7 \pm 0.1\%$  in the combination group vs.  $+0.2 \pm 0.1\%$  in those on glibenclamide alone and  $-0.4 \pm 0.1\%$  in those on metformin alone. Lipid levels were improved in those receiving metformin either alone or in combination. Body weight and fasting lactate were unchanged after combination therapy. Mild, single episodes of hypoglycaemic symptoms, not documented biochemically, occurred more frequently during combination therapy.

The placebo-controlled studies (table 1) confirm the complementary antihyperglycaemic effect of metformin. This could be attributed to decreased hepatic glucose production [11,13,15] and increased insulin-mediated glucose disposal [13]. The role of adipose tissue and reduced levels of free fatty acids (FFA) as a basis for increased basal glucose clearance rate was highlighted in another study [16].

Recently, the non-sulphonylurea insulin secretagogue, repaglinide, has been introduced for prandial glucose regulation. A randomized, double-blind, placebo-controlled study of repaglinide added to metformin showed synergy between these two drugs [24]. A similar drug, nateglinide, has also been successfully combined with metformin [25].



**Fig. 3** Weight changes in the study by Hermann *et al.* 1994 [8,9]. Mean changes (s.e.) from baseline in body weight (BW) at completed dose titration, after maintenance therapy for 2, 4 and 6 months, and 2 weeks after discontinuation of active therapy. MM = metformin monotherapy; GG = glibenclamide monotherapy; MGL = primary combination therapy (low dose). See also figure 1.

**Table 1** Placebo-controlled studies of sulphonylurea + metformin (SU + M) combination therapy in patients with secondary SU failure

First author (year) ref.	n (T/M)	ob	Design	Time	Groups	Glycaemia			Other results (in combination group)
						Initial	Final	% Change	
Higginbotham (1979) <sup>10</sup>	17/17	+ / 0	r, db, x	2 months	G + M	12.4	9.9	20	
					G + P	12.4	13.8†		
Jackson (1987) <sup>11</sup>	10/9	0	r, sb, x	5 months	G + M	9.5	5.7	40	HGP↓
					Placebo	M			Glucose disposal 0
Gregorio (1990) <sup>12</sup>	30/20	+ / 0	≠	5 weeks	SU + M	10.5	7.2	31	Diurnal profiles of intermediary metabolites 0
					SU + P	No change			
Marena (1994) <sup>13</sup>	10/10	0	r, db, x	6 weeks	G + M	6.4	6.1	5	HGP↓
						i9.5	8.7	8.4	Glucose disposal ↑
					G + P	6.4	6.4		TG↓
DeFronzo (1995) <sup>14</sup>	632/213	+	r, db, ≠	29 weeks	G + M	13.9	10.4	25	TG, CH, LDL↓
						i8.8	7.1	19	HDL↑
					G + P	13.7	14.5		
						i8.5	8.7		
Cusi (1996) <sup>15</sup>	20/7	+	r, db, ≠	15 weeks	SU + M	10.8	8.4	22	HGP↓
						i12.5	9.2	26	Glucose disposal 0
					SU + P	10.7	11.2		TG, CH, LDL↓
						i11.8	12.2		HDL 0
Abbasi (1997) <sup>16</sup>	16/8	+	r, db, ≠	8 weeks	GZ + M	12.3	8.5†	31	HGP 0
						Mean hourly glucose:			Basal glucose disposal 0
					GZ + P	15.4	11.5	25	FFA↓
					12.2	12.0†			

Percentage reduction of mean fasting plasma glucose and glycosylated haemoglobin, GHb (i), values in mmol/l and per cent (%) respectively ([10], fasting blood glucose). GHb = HbA<sub>1c</sub> in [13], but = HbA<sub>1</sub> in [15]. Normal range for GHb in [14], 3.3–6.8%. Body weight was unchanged after combination therapy (except for a slight increase in [14]). Insulin and lactate levels were unchanged.

n = number of patients included (T = total, M = metformin added to SU); ob = obese;

r = randomized; db = double-blind; sb = single-blind; x = crossover; ≠ = parallel groups;

time = duration of combination therapy; SU = sulphonylurea; G = glibenclamide; GZ = glipizide; M = metformin; P = placebo, HGP = hepatic glucose production, TG = triglycerides, CH-LDL-HDL = total-, LDL- and HDL-cholesterol,

FFA = free fatty acids; 0 = no change, ↑ = increase, ↓ = decrease.

† = estimated from figure.

### Open Trials on Metabolic Parameters in Patients with Secondary Sulphonylurea Failure

A number of open, randomized studies have used reference therapies, for example insulin (table 2). In addition, a non-randomized, parallel-group study compared sulphonylurea plus metformin both with insulin and with sulphonylurea plus acarbose [23]. Also, a fixed combination of glibenclamide and metformin has been compared with glibenclamide alone in a non-randomized, parallel-group study [26] and in a randomized, double-blind, crossover study using different strengths of fixed combination tablets [27]. These trials showed better effect of the combination therapy. The use of fixed

combination tablets with sulphonylurea and metformin is attractive from a practical point of view, as combination therapy is necessary to attain good glucose control in the majority of patients with type 2 diabetes [28].

Open studies of sulphonylurea–metformin combination therapy vs. reference therapies are summarized in table 2. Mostly, it appears that this combination was antihyperglycaemic as the rather simple insulin regimens used. Insulin may be stopped in type 2 diabetes and successfully replaced by sulphonylurea–metformin combination therapy [29]. The combination has also been compared with sulphonylurea plus acarbose, giving similar [30] or better [23] effect. One of the comparative studies with twice-daily insulin as reference therapy

**Table 2** Controlled studies of sulphonylurea + metformin (SU + M) combination therapy vs. reference therapies in patients with secondary SU failure

First author (year) ref.	n (T/M)	ob	Design	Time	Groups	Glycaemia			BW	Other results (in SU + M group)
						Initial	Final	% Change		
Peacock (1984) <sup>17</sup>	58/33	+/0	r, x	6 months	G + M	11.0 i11.2	11.2 10.3		(↓)	G + M better than INS in 19 patients
					INS	11.0 i11.2	10.6 10.2		↑	INS better than G + M in 18 patients
Holman (1987) <sup>18</sup>	15/14	+/0	r, x	2 months	SU + M	8.9† i11.8†	7.3 10.7	18 9	0	Lipids 0 Insulin 0
					SU + INS	8.9† i11.8†	~5.0 ~9.8		↑	
					SU	10.9 i11.7	8.9† 11.8†			
Groop (1989) <sup>19</sup>	24/12	0	r, ≠	6 months	G + M	13.1 i10.1†	10.1 9.0†	23 11	0	HGP (↓) Glucose disposal ↑
					INS	13.2 i10.7†	9.1 8.6†	31 19	↑	Lipids 0 Insulin 0
Klein (1991) <sup>20</sup>	50/25	+/0	r, ≠	1 year	G + M	11.2 i12.0	10.0 8.4	11 30	(↓)	Lipids 0 Insulin 0 ↓
					G + INS	12.0 i12.8	9.4 8.0	22 37.5	(↑)	
Trischitta (1992) <sup>21</sup>	20/16	+/0	r, x	2 months	G + M	13.5 i9.5	9.7 8.0	28 16	0	Lipids 0
					G + INS	14.1 i9.6	9.5 7.8	32 19	↑	
Trischitta (1998) <sup>22#</sup>	50/50	+/0	r, x	2 months	G + M	13.1 i8.6	10.0 7.6	24 12	(↑)	CH (↓) Postprandial glucose:
					G + INS	13.7 i8.7	8.4 7.6	38 13	↑	G + M ↓33% G + INS ↓25%
Calle-Pascual (1995) <sup>23</sup>	36/12	+/0	≠	6 months	SU + M	i9.2	7.5	18	0	HDL ↑
					SU + A	i9.5	8.6	9	0	BP ↓
					INS	i9.1	7.3	20	0	

(HbA1c values)

Percentage reduction of mean fasting plasma glucose and glycosylated haemoglobin, GHb (i), values in mmol/l and per cent respectively ([17], fasting blood glucose). GHb = HbA<sub>1c</sub> in [22,23] but = HbA<sub>1</sub> in [17–21].

Symbols and abbreviations as in table 1, except INS = insulin; A = acarbose; BW = body weight.

# = it is not stated in the paper if patients in Trischitta (1992)<sup>21</sup> are included in this study.

used the euglycaemic clamp technique for the estimation of glucose disposal and isotope dilution technique for measuring hepatic glucose production [19]. In this 6-month study, metformin was added to glibenclamide in non-obese patients with sulphonylurea failure and diabetes of long duration. Both treatments improved glucose control to the same extent. Glucose disposal was increased by the addition of metformin, whereas insulin reduced hyperglycaemia solely by reducing basal hepatic glucose production. Similar antihyperglycaemic efficacy of metformin and insulin when either agent

was coadministered with glibenclamide has also been reported [20–22].

It should be noted that good glucose control was only rarely reached in the studies in which metformin was added to patients with secondary sulphonylurea failure. Only two (placebo-controlled) trials [10,12] showed reduced fasting blood glucose from the unacceptable to the acceptable range. Patients with high baseline glucose levels appeared to have low success rates [18] whereas patients with well preserved  $\beta$ -cell function (as judged from C-peptide levels) may respond better [21]. However,

the response seems difficult to predict [22]. Patients with secondary sulphonylurea failure probably represent a negative selection for sulphonylurea–metformin combination therapy; apparently, such treatment should be introduced earlier in the disease [9]. Nevertheless, even late introduction may have some benefit and may obviate the need for insulin.

Other open studies have shown improved glucose control after addition of metformin to sulphonylurea, and sometimes other benefits as well, both in large patient groups [31], during long-term treatment [32] and in the elderly [33]. The feasibility of adding metformin to sulphonylurea in elderly patients with type 2 diabetes has been confirmed recently in a randomized, long-term study comparing high-dose sulphonylurea with low-dose combination therapy [34]. The combination promoted reduced hyperglycaemia and additional improvements of other cardiovascular risk factors. Lactate concentrations were unchanged, and no serious side-effects were observed. A non-controlled study employing the clamp technique investigated the addition of metformin to glipizide in obese patients [35]. Glucose disposal increased, hepatic glucose production decreased, lipids improved, and insulin and FFA levels declined.

### Conclusions from Studies on Metabolic Parameters

Although the above-mentioned studies have differed greatly in design, dosage, severity and duration of diabetes, and in metabolic control, all of them indicate that treatment with sulphonylurea and metformin in combination promotes better glucose control than single-drug treatment. In addition, dyslipidaemia may be reduced and weight increase counteracted. This makes it likely, but does not prove, that even clinical outcome in terms of morbidity and mortality would be improved by combination therapy. Moreover, insulin treatment may be postponed.

### Randomized Clinical Trial on Clinical Outcome

There is only one randomized trial on the clinical outcome of sulphonylurea–metformin combination therapy, the UKPDS [6]. However, the primary aim of the UKPDS was not to assess combination therapy but to compare and assess conventional (mainly dietary regulation) vs. intensive treatment (addition of sulphonylurea or insulin) with regard to morbidity and mortality from diabetic complications. Metformin could be used in overweight patients.

A second protocol was introduced 13 years after the start of the main study in the first 15 centres. With

euglycaemia as a target, addition of metformin to sulphonylurea was allowed in a subgroup of obese and non-obese patients originally allocated to glibenclamide or chlorpropamide, who had fasting plasma glucose concentrations of 6.1–15.0 mmol/l, but no symptoms, on maximum sulphonylurea dosage [6]. This second randomization occurred 7.1 years (median) after the primary randomization. The analysis comprised 268 patients who had metformin added to sulphonylurea and 269 patients who continued on sulphonylurea alone. The median follow-up time was 6.6 years.

The addition of metformin reduced hyperglycaemia by 15% [6], and  $\beta$ -cell function seemed to improve [36]. Surprisingly, mortality was higher in the group assigned combination therapy [6]. The relative risk for diabetes-related death was increased by 96% (95% CI 1.02–3.75,  $p = 0.039$ ) and for all-cause mortality by 60% (1.02–2.52,  $p = 0.041$ ).

In contrast, no mortality increase was seen among patients on combination therapy in an epidemiological analysis comprising 457 other UKPDS patients on such treatment (107 initially allocated to diet, 257 to sulphonylurea or metformin and 93 who refused insulin). Compared with all other treatments, combination treatment was associated with a non-significant mortality reduction of 5%. Likewise, a meta-analysis of all patients allocated to metformin in the main study and in the substudy showed a non-significant mortality reduction, as well as a significant ( $p = 0.033$ ) 19% reduction for any diabetes-related end-point and a non-significant 24% reduction of myocardial infarction.

It has been suggested that the apparent mortality increase in patients randomized to combination therapy was a result of spuriously low mortality in the group on sulphonylurea alone [37]. Ironically, the same kind of argument was used to explain the apparent mortality increase in the sulphonylurea group of the UGDP study [3]; mortality in the placebo group was alleged to be spuriously low [38]. The end-point numbers in the UKPDS substudy were indeed small (26 diabetes-related deaths in the combination group, 14 in the sulphonylurea group). The latter figure would signify only 8.6 diabetes-related deaths per 1000 patient-years [6] vs. 11 diabetes-related deaths per 1000 patient-years in the main UKPDS cohort of sulphonylurea-treated patients [5]. It should also be emphasized that the substudy showed no difference between groups in non-fatal events (myocardial infarction and strokes). The low mortality in the substudy sulphonylurea group compared with that of the entire UKPDS sulphonylurea cohort is particularly confusing, as the substudy patients were older, more hyperglycaemic and had more abnormal lipid patterns.

### Observational Studies on Clinical Outcome

Two observational studies have been carried out to compare mortality in type 2 diabetes patients using sulphonylurea alone and in combination with metformin. In a Swedish study [39], all type 2 diabetes patients living in two neighbour municipalities during an 11-year period were identified. A total of 169 patients were on combination therapy and 741 were on sulphonylurea alone. They were followed from the first day they were on either therapy, according to available patient records. Regularly, patients on combination therapy had started on sulphonylurea alone. However, they were not evaluated during this treatment.

At the start of follow-up, patients on combination therapy were 3.6 years younger, had 3.2 years longer diabetes duration and 1.3 mmol/l higher fasting blood glucose than those using sulphonylurea alone. Mean (range) follow-up time was 6.1 (0.1–13.0) years. A total of 88 patients on combination therapy and 467 on sulphonylurea alone died during follow-up. The odds ratio for all-cause mortality in patients on combination therapy, with those on sulphonylurea alone as reference, adjusted for age, sex, duration of diabetes, study area, year of inclusion and fasting blood glucose at inclusion was 1.63 (95% CI 1.27–2.09). Adjusted odds ratios for ischaemic heart disease mortality and stroke mortality were 1.73 (95% CI 1.17–2.55) and 2.33 (95% CI 1.17–4.63) respectively.

An Israeli study [40] examined the 5-year survival of 2395 patients with type 2 diabetes and ischaemic heart disease being treated with diet alone ( $n = 990$ ), sulphonylurea ( $n = 1041$ ), metformin ( $n = 78$ ) and sulphonylurea and metformin in combination ( $n = 266$ ). In addition, 9045 non-diabetic subjects were followed as a reference group. The four groups of diabetic patients were similar with respect to age, gender, hypertension, smoking, heart failure, angina and prior myocardial infarction. However, the mean fasting glucose levels at baseline differed significantly, being 8.7 (diet alone), 10.2 (sulphonylurea alone), 10.6 (metformin alone) and 12.1 mmol/l (combination therapy). The crude mortality rate was higher among the diabetics than among the non-diabetics (21.8% vs. 11.2%,  $p < 0.001$ ). Among the diabetics, crude mortality rates were 18.5% (diet alone), 22.5% (sulphonylurea), 25.6% (metformin) and 31.6% (sulphonylurea and metformin combined).

After adjustment for age differences, the lowest mortality was found among those on diet alone and the highest among those on metformin (alone or in combination with sulphonylurea). After adjustment for variables connected with long-term prognosis, use of metformin (including those on combination with sulphonylurea) was associated with an increased relative risk (RR)

for all-cause mortality of 1.42 (95% CI 1.10–1.85) but use of sulphonylurea alone was not (RR 1.11, 95% CI 0.90–1.36). It should be noted that the authors did not adjust for duration of diabetes or exposure to hyperglycaemia [cf 41]. The authors also emphasize that caution is necessary in interpreting their findings. Recently, 7.7-year follow-up data from this study have been published, showing a time-related increased mortality on combination therapy [42].

A third observational study was based on an Italian population [43] and compared outcomes among patients treated with diet alone (reference group), sulphonylurea alone, sulphonylurea + biguanide and insulin, respectively. Mortality – all-cause, cardiovascular, ischaemic heart disease and cerebrovascular – increased with treatment in the presented order. However, only mortality increments in the insulin-treated group were significant.

### Conclusions from Outcome Studies

Both the randomized UKPDS substudy and the two (but not a third) observational studies on mortality in patients with type 2 diabetes infer that the combination of sulphonylurea and metformin may be harmful. On the other hand, all studies on metabolic control have shown beneficial effects. It is possible that the UKPDS finding was because of spuriously low mortality in the control group of patients on sulphonylurea alone, and it is probable that the higher mortality associated with combination therapy in the observational studies was because of more severe diabetes rather than treatment *per se*. However, it is also judicious to emphasize that there is, as yet, no evidence that combination therapy actually *reduces* morbidity or mortality. Accordingly, there is an urgent need for new, long-term studies addressing the pros and cons of combination therapy with sulphonylurea and metformin. Such studies should not be restricted to patients with secondary sulphonylurea failure.

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