

Metformin for Type 2 Diabetes Mellitus. Systematic Review and Meta-Analysis

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Objective. To evaluate the efficacy of metformin against placebo, diet, oral anti-diabetics, or insulin in type 2 diabetes mellitus.

Design. Systematic review.

Data sources. MEDLINE (1966-2003), EMBASE (1974-2003), LILACS (1986-2003), Cochrane library (Issue 3, 2003).

Selection of studies. 29 randomized clinical trials of metformin in monotherapy, with results on mortality, morbidity, and biochemistry.

Extraction of data. RevMan 4 computer program. Two reviewers extracted the data and evaluated the quality. *Main variables:* any clinical event related to diabetes (mortality, coronary disease, stroke, arterial disease, and retinopathy). *Secondary variables:* weight and biochemistry.

Results. 29 clinical studies with 37 comparisons of metformin were analyzed (13 with sulphonylureas, 12 with placebo, 3 with diet, 3 with thiazolidinediones, 2 with α -glucosidase inhibitors, 2 with insulin, and 2 with meglitinides). Metformin was more beneficial than the sulphonylureas or insulin for any clinical event associated with diabetes (relative risk [RR]=0.78; 95% confidence interval [CI], 0.65-0.94) and than diet (RR=0.74; 95% CI, 0.60-0.90). Metformin decreased glycosylated hemoglobin A_{1c} (weighted mean difference, -1.21%; 95% CI, -1.48 to -0.94), low density lipoprotein cholesterol (weighted mean difference, -0.24; 95% CI, -0.40 to -0.09), and weight (standardized mean difference, -0.11; 95% CI, -0.18 to -0.04). Metformin was more beneficial than the placebo, diet or the thiazolidinediones on glycosylated hemoglobin A_{1c}, and than the sulphonylureas or insulin on weight.

Conclusions. In the long term metformin reduces the risks of clinical events associated with diabetes. There are no long term clinical trials which compare α -glucosidase inhibitors, meglitinides, and thiazolidinediones with metformin, in primary results. The different treatments compared with metformin did not obtain more benefit for the secondary results evaluated.

Key words: Metformin. Biguanides. Type 2 diabetes mellitus. Systematic review. Meta-analyses.

METFORMINA PARA LA DIABETES MELLITUS TIPO 2. REVISIÓN SISTEMÁTICA Y METAANÁLISIS

Objetivo. Evaluar la eficacia de la metformina frente a placebo, dieta, antidiabéticos orales o insulina en la diabetes mellitus tipo 2.

Diseño. Revisión sistemática.

Fuentes de datos. MEDLINE (1966-2003), EMBASE (1974-2003), LILACS (1986-2003), Cochrane library (Issue 3, 2003).

Selección de estudios. Se seleccionaron 29 ensayos clínicos aleatorizados de metformina en monoterapia, con resultados sobre mortalidad, morbilidad y bioquímica.

Extracción de datos. Programa informático RevMan 4. Dos revisores extrajeron los datos y evaluaron la calidad. *Variables principales:* cualquier acontecimiento clínico relacionado con la diabetes (mortalidad, coronariopatía, ictus, nefropatía, arteriopatía y retinopatía). *Variables secundarias:* peso y bioquímica.

Resultados. Se analizaron 29 ensayos clínicos con 37 comparaciones de metformina (13 con sulfonilureas, 12 con placebo, 3 con dieta, 3 con tiazolidindionas, 2 con inhibidores de la α -glucosidasa, 2 con insulina y 2 con meglitinidas). La metformina mostró mayor beneficio que las sulfonilureas o la insulina para cualquier acontecimiento clínico relacionado con la diabetes (riesgo relativo = 0,78; intervalo de confianza [IC] del 95%, 0,65 a 0,94) y que la dieta (riesgo relativo = 0,74; IC del 95%, 0,60 a 0,90). La metformina disminuyó la hemoglobina A_{1c} glucosilada (diferencia media ponderada: -1,21%; IC del 95%, -1,48 a -0,94), colesterol unido a lipoproteínas de baja densidad (diferencia media ponderada: -0,24; IC del 95%, -0,40 a -0,09) y peso (diferencia media estandarizada: -0,11; IC del 95%, -0,18 a -0,04). La metformina presentó mayor beneficio que el placebo, la dieta o las tiazolidindionas en la hemoglobina A_{1c} glucosilada, y que las sulfonilureas o la insulina en el peso.

Conclusiones. A largo plazo la metformina disminuye el riesgo de acontecimientos clínicos relacionados con la diabetes. No existen ensayos clínicos a largo plazo que comparen con metformina los inhibidores de la α -glucosidasa, meglitinidas y tiazolidindionas, en resultados primarios. Las diferentes intervenciones comparadas con metformina no obtuvieron más beneficio para los resultados secundarios evaluados.

Palabras clave: Metformina. Biguanidas. Diabetes mellitus tipo 2. Revisión sistemática. Metaanálisis.

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A commentary follow
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Farma Roche obtained the complete texts of the potentially relevant reference for us.

The Laín Entralgo Agency of the Autonomous Community of Madrid carried out an updated bibliographic search for us.

The Cochrane Iberoamerican Collaboration helped us with the statistical study.

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Introduction

Type 2 diabetes mellitus is a chronic disease with significant morbidity and mortality, and a growing incidence in developed countries. All the patients require medical advice and the majority need medication. Although many therapeutic agents exist, it is not clear which of them, and which patient sub-groups, produces more benefit in primary results, such as mortality, coronary disease, stroke, nephrotic disease, arterial disease retinopathy.¹

Metformin is a biguanide which increases the peripheral and hepatic sensitivity to insulin, improves the fasting and post-prandial glycemic profile,² and lacks significant risk in producing lactic acidosis, which has been reported previously with another biguanide.³

There are 2 published meta-analyses of metformin compared to sulphonylureas^{4,5} and to diet,⁵ which present secondary results (changes in weight, glycemia, and lipids), but do not report primary results.⁶

This review has as its aim, to answer 2 questions: if the use of metformin in monotherapy, compared with any other treatment, in type 2 diabetics is associated with beneficial changes in primary and secondary results and if there is any sub-group of patients with type 2 diabetes who might benefit more from treatment with metformin.

Patients and Methods

The inclusion criteria have been: randomized clinical trials, open, simple or double blind, published or unpublished, in any language, on metformin in monotherapy (with metformin as primary treatment option, or changing to it from a different treatment used previously), compared with placebo, diet, α -glucosidase inhibitors, meglitinides, sulphonylureas, thiazolidinediones, or insulin, in the type 2 diabetic population, recruited in general medical or diabetic clinics, with pharmacological treatment for a minimum of 3 months, and which reported primary or secondary results.

As primary results any event associated with diabetes has been searched for (death, myocardial infarction, angina, stroke, nephrotic disease, peripheral arterial disease, vitreous hemorrhage, retinopathy, and cataracts), mortality associated with diabetes, total mortality and microvascular disease. Secondary results included: glycosylated hemoglobin A_{1c} (HbA_{1c}), fasting glucose, weight or body mass index (BMI), lipids, C peptide, insulinemia, systolic and diastolic blood pressure, microalbuminemia, and adverse reactions.

A search has been carried out on MEDLINE (1966 to 2003), EMBASE (1974 to 2003), LILACS (1986 to 2003), and the Cochrane Library (part 3, 2003), using the terms: "metformin," "biguanide," "type 2 diabetes," "non-insulin dependent diabetes," "random," and "clinical trial." The lists of references of the relevant studies obtained have been analyzed. Two reviewers (A.S.C. and I.F.E.), independently, evaluated each title and summary. If the reference appeared to comply with the inclusion criteria, a complete copy of the article was obtained. Contact was made

with the manufacturers of the medicine to obtain additional references (although no new reference was added), and with some authors to resolve doubts. Duplications were eliminated. Two reviewers (A.S.C. and I.F.E.), independently, extracted the data and scored the quality.^{7,8} The studies were divided into 2 quality groups: high and medium-low. The quality was considered high when the study obtained 4 or 5 points on the Jadad scale⁷ and it has mentioned that reasonable allocation concealment had been attempted.⁸ To incorporate the evaluations of the validity of the studies a sensitivity analysis was used, using the inclusion and exclusion of the studies of medium-low quality, and a meta-regression including the quality as a co-variable.¹ The origin and authorship of the studies were not concealed from the reviewers. Discrepancies were resolved by consensus. The inter-observer agreement was analyzed using the kappa⁹ statistic, which was 0.85, which indicated substantial agreement.

For the calculations RevMan version 4.2 and Stata version 5 were used. The weighted mean differences (WMD) have been calculated for data on the same scale and the standardized mean differences (SMD) for different scales. Whenever possible the mean of the change \pm its standard deviation was used,¹⁰⁻¹⁶ and the final results for the rest,¹⁷⁻³⁷ carrying out an intention to treat analysis. The dichotomic data were included as number of events and relative risk (RR). We have summarized the data in a total combined result using the random effects model due to the heterogeneity detected. We carried out an analysis of sensitivity based on: double blind trials, high quality trials, and trials with concealed allocation. To calculate the presence of bias of publication we used the Begg³⁸ correlation test and the Egger graph.³⁹ We have evaluated heterogeneity using the Z marker, the χ^2 statistic and the I² statistic (values of I² greater than 50% were considered excessive),⁴⁰ with meta-regression.

Analysis of subgroups was carried out to examine the influence of cardiovascular risk factors on the size of the effect and also if any sub-group could benefit from treatment with metformin to a greater extent. These sub-groups were: obesity (BMI > 30 kg/m² or weight greater than 85 kg), hypertension, low density lipoprotein cholesterol (LDL-C > 3.99 mmol/L), fibrinogenemia, platelet function, and over 65 years.

Results

In the search 1306 different references were identified and 215 considered relevant. 179 were excluded for not complying with the inclusion criteria and 7 crossed studies for not offering data at the first cross. They included 29 randomized clinical trials¹⁰⁻³⁷ (with 37 treatment groups and 5259 participants) which compared metformin (29 trials and 2007 participants) with sulphonylureas (13 studies and 1167 participants),^{10-13,18-25} placebo (12 studies and 702 participants),^{12,14,15,17,26-33} diet (3 studies and 493 participants),^{18,24,34} thiazolidinediones (3 trials and 132 participants),^{16,30,36} insulin (2 trials and 439 participants),^{31,35} meglitinides (2 studies and 208 participants),^{31,35} and α -glucosidase inhibitors (2 trials and 111 participants).^{14,15} Metformin was used in doses up to 3 g (range, 1-3 g). A clinical trial was obtained before publication.¹⁷ The mean age of the patients was 56 years (range, 35-73), the majority were white race and 50% were women. The mean duration of the trials was 5 months

TABLE 1

Characteristics of the Studies Include. Clinical Trials of Metformin Compared With Other Treatments, With Random Assignment*

Trial	Comparison	Metformin N/ N Comparison	Weeks	Data Available for Analysis of Sub-Groups					Design	Quality
				Obese	HBP	Hyperlipemia	>65 years	Fibrinogen		
UKPDS (a) ¹⁸	Chlorpropamide	342/265	10.7 years	Yes	No	No	No	No	OS	B
Amador et al ²³	Glibenclamide	28/23	12	No	No	No	No	No	OS	B
Támez et al (a) ²⁴	Glibenclamide	29/29	12	Yes	No	Yes	No	No	OS	B
UKPDS (b) ¹⁸	Glibenclamide	342/277	10.7 years	Yes	No	No	No	No	OS	B
Collier et al ¹⁹	Gliclazide	12/12	24	No	No	No	No	Yes	OS	B
Noury and Nandeuil ²⁰	Gliclazide	30/27	12	No	No	No	No	No	SB	B
Tessier et al ²¹	Gliclazide	18/18	24	No	No	No	No	No	OS	B
Charpentier et al ¹⁰	Glimepiride	75/150	20	No	No	No	No	No	DB	A, OAA
Campbell et al ²²	Glipizide	24/24	52	Yes	No	No	No	No	OS	B
Goldstein et al ¹¹	Glipizide	76/84	18	Yes	No	No	No	No	DB	A
DeFronzo and Goodman (a) ¹²	Glyburide	210/209	29	No	No	No	No	No	DB	B
Hermann et al ¹³	Glyburide	38/34	24	Yes	Yes	No	No	No	DB	A, OAA
Dalzell et al ²⁵	Tolbutamide	18/15	52	No	No	No	No	No	OS	B
Chiasson and Nadtich (a) ¹⁵	Placebo	81/82	36	Yes	No	No	No	No	DB	B
Damsbo et al ²⁶	Placebo	9/9	12	Yes	No	No	No	No	DB	A
DeFronzo and Goodman (b) ¹²	Placebo	143/146	29	No	No	No	No	No	DB	A
Del Prato et al ²⁷	Placebo	284/144	26	Yes	No	No	No	No	DB	A
Dornan et al ²⁸	Placebo	30/30	32	Yes	No	No	No	No	DB	B
Grant ²⁹	Placebo	52/23	24	No	No	No	No	No	DB	B
Hallsten et al (a) ³⁰	Placebo	13/14	26	Yes	No	No	No	No	DB	B
Hoffmann and Spengler (a) ¹⁴	Placebo	31/32	24	No	No	No	No	No	SB	B
Horton et al (a) ³¹	Placebo	178/172	24	No	No	No	No	No	DB	A, OAA
Lee y Morley ³²	Placebo	24/24	24	Yes	No	No	No	No	DB	A
Mather et al ³³	Placebo	29/15	12	Yes	No	No	No	No	OS	A, OAA
Uehara ¹⁷	Placebo	11/11	12	Yes	Yes	No	No	No	DB	B
Támez et al (b) ²⁴	Diet	29/32	12	Yes	No	No	No	No	OS	B
Teupe y Bergis ³⁴	Diet	50/50	120	Yes	Yes	No	No	No	OS	B
UKPDS (c) ¹⁸	Diet	342/411	10.7 years	Yes	No	No	No	No	OS	B
Pavo et al ¹⁶	Pioglitazone	100/105	32	Yes	Yes	No	No	No	DB	A
Hallsten et al (b) ³⁰	Rosiglitazone	13/14	26	No	No	No	No	No	DB	B
Inzucchi et al ³⁶	Troglitazone	15/13	12	Yes	No	No	No	No	OS	B
Fanghanel et al ³⁷	Insulin	30/30	12	No	No	No	No	No	OS	B
UKPDS (d) ¹⁸	Insulin	342/409	10.7 years	Yes	No	No	No	No	OS	B
Horton et al (b) ³¹	Nateglinide	178/179	24	No	No	No	No	No	DB	A, OAA
Moses et al ³⁵	Repaglinide	27/29	12	Yes	No	No	No	No	DB	B
Hoffmann and Spengler (b) ¹⁴	Acarbose	31/31	24	No	No	No	No	No	SB	B
Chiasson and Nadtich (b) ¹⁵	Miglitol	81/80	36	Yes	No	No	No	No	DB	B

*UKPDS indicates United Kingdom Prospective Diabetes Study; N, number of participants at start; A, high quality; B, medium-low quality; ACA, adequate allocation concealment; DB, double blind; SB, simple blind; OT, open trial; HBP, high blood pressure (systolic >140 and/or diastolic >90 mm Hg); hyperlipemia, low density lipoprotein cholesterol >160 mg/dL or 3.99 mmol/L; fibrin: studies with changes in the fibrinogen concentrations.

(range, 3–24), and 10.7 years for the UK Prospective Diabetes Study (UKPDS).¹⁸ Ten studies were considered high quality. Four had adequate concealed allocation (Table 1). The Begg and Egger tests indicated that there had been

no publication biases.^{38,39} With the exception of obesity, which was recorded in 17 studies, data in the anticipated subgroups could not be combined. Only 4 studies included hypertensive patients and 2 hyperlipemic ones. One trial

studied platelet function¹⁹ and none offered data specific to over 65 years.

Primary Results (Table 2)

Five studies reported primary results^{12,18,30,31,34} and another 4 specifically reported they did not have them.^{14,16,35,36} In the UKPDS, in overweight patients,¹⁸ metformin in monotherapy (n=342) showed a greater benefit than chlorpropamide, glibenclamide, or insulin (n=951); in all of them intensive glycemic control was attempted (fasting glucose <106 mg/dL) for any event associated with diabetes (98 vs 350; RR=0.78; 95% confidence interval (CI), 0.65-0.94), and for total mortality (50 vs 190; RR=0.73; 95% CI, 0.55-0.97). Metformin was compared with non-intensive conventional treatment (fasting glucose <270 mg/dL; n=411 patients) and showed a greater benefit for any event associated with diabetes (98 vs 190; RR=0.74; 95% CI, 0.60-0.90), death associated with diabetes (28 vs 55; RR=0.61; 95% CI, 0.40-0.94), total mortality (50 vs 89; RR=0.68; 95% CI, 0.49-0.93) and myocardial infarction (39 vs 73; RR=0.64, 95% CI, 0.45-0.92). In the other 4 clinical trials they reported 4 myocardial infarctions, 2 of them fatal, and all the events were registered in the patients in the metformin group (4 vs 0; RR=3.58; 95% CI, 0.73-17.52).

Primary results were not reported in clinical trials with hyperlipemic patients, nor were any data offered from patients over 65 years old. A small trial recorded, non significant changes in fibrinogen.

As regards the secondary results (Figures 1-4), in the comparison before and after metformin (Figure 1) the patients on metformin showed a significant reduction in HbA_{1c} (WMD=-1.21%; 95% CI, -1.48 to -0.94), glycemia (WMD=-2.31 mmol/L; 95% CI, -2.97 to -1.64), cholesterol (WMD=-0.19 mmol/L; 95% CI, -0.34 to -0.04), LDL cholesterol (WMD=-0.24 mmol/L; 95% CI, -0.40 to -0.09), triglycerides (WMD=-0.25 mmol/L; 95% CI, -0.42 to -0.09), insulin (WMD=-20 mU/ml; 95% CI, -33 to -6), diastolic pressure (WMD=-4.64 mm Hg; 95% CI, -8.39 to -0.90), and weight (SMD=-0.11 kg; 95% CI, -0.18 to -0.04).

In comparison with patients on treatment with sulphonylureas, patients on metformin showed a greater benefit for glycemia (WMD=-0.31 mmol/L; 95% CI, -0.57 to -0.05), LDL cholesterol (WMD=-0.22 mmol/L; 95% CI, -0.35 to -0.10), triglycerides (WMD=-0.24 mmol/L; 95% CI, -0.46 to -0.02), and weight (BMI) (SMD=-0.45 kg/m²; 95% CI, -0.80 to -0.10). A small clinical trial²³ showed a benefit of metformin for microalbuminuria (WMD=-53 mg/day; 95% CI, -86 to -19). The meta-regression analysis did not show any significant explained variable of heterogeneity. These results were consistent with the sensitivity analysis of double blind trials. In the sub-group of overweight patients, metformin had a greater benefit on weight (BMI) (SMD=-0.58 kg/m²; 95%

CI, -1.00 to -0.16), cholesterol (WMD=-0.38 mmol/L; 95% CI, -0.55 to -0.20) and LDL cholesterol (WMD=-0.27 mmol/L; 95% CI, -0.40 to -0.14). There were more cases of hypoglycemia in the patients who received sulphonylureas (*P*=.004) and more diarrhea with metformin (*P*=.02).

In comparison with the placebo, metformin showed a greater benefit for HbA_{1c} (WMD=-1.06%; 95% CI, -1.38 to -0.73) and glycemia (WMD=-1.84 mmol/L; 95% CI, -2.38 to -1.30). The meta-regression indicated metformin had a greater effect on obesity (*P*=.001) and in studies where a diet was not enforced (*P*=.001). The results were consistent with the sensitivity analysis in double blind trials on obesity, of high quality and with adequate concealed assignment. There were more cases of diarrhea with metformin (*P*=.005).

In comparison with diet, metformin showed greater benefit for HbA_{1c} (WMD=-1.44%; 95% CI, -2.62 to -0.26), cholesterol (WMD=-0.61 mmol/L; 95% CI, -0.93 to -0.29), insulin (WMD=-60 mU/mL; 95% CI, -79 to -40), and C peptide (WMD=-0.61 nmol/L; 95% CI, -0.89 to -0.33). There was more hypoglycemia with diet (*P*=.01).

Compared with thiazolidinediones, showed a greater benefit for HbA_{1c} (WMD=-0.24%; 95% CI, -0.46 to -0.02).

Metformin improved weight compared to insulin (SMD=-0.91 kg; 95% CI, -1.44 to -0.37), cholesterol (WMD=-0.42 mmol/L; 95% CI, -0.69 to -0.15), LDL cholesterol (WMD=-0.47 mmol/L; 95% CI, -0.75 to -0.19), the systolic pressure (WMD=-9.50 mm Hg; 95% CI, -15.15 to -3.85), and the diastolic (WMD=-7.00 mm Hg; 95% CI, -9.41 to -4.59).

Compared with the meglitinides, metformin showed greater benefit for glycemia (WMD=-0.73 mmol/L; 95% CI, -1.18 to -0.28). There were no differences in the rest of the comparisons. There were more cases of diarrhea in the metformin group (*P*=.0002).

On comparing metformin with α -glucosidase inhibitors, the cholesterol levels improved in the patients on acarbose (WMD=1.92 mmol/L; 95% CI, 1.20-2.64). There were more digestive problems in the metformin group (*P*=.002).

There were no cases of lactic acidosis in the 29 clinical trials.

Discussion

The UKPDS¹⁸ prospective study continues to be the longest study to date (median of 10.7 years and 4075 participants). In overweight patients, attempting intensive glycemic control, metformin in monotherapy was beneficial compared with intensive control with chlorpropamide, glibenclamide or insulin, thus reducing the incidence of any event associated with diabetes and total mortality. It was

**TABLE
2**

**Primary
Results***

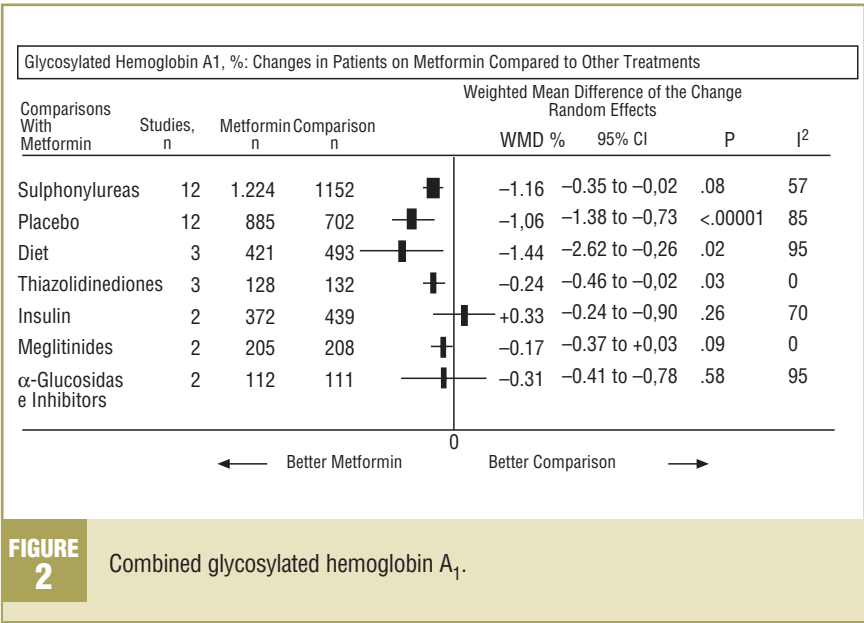
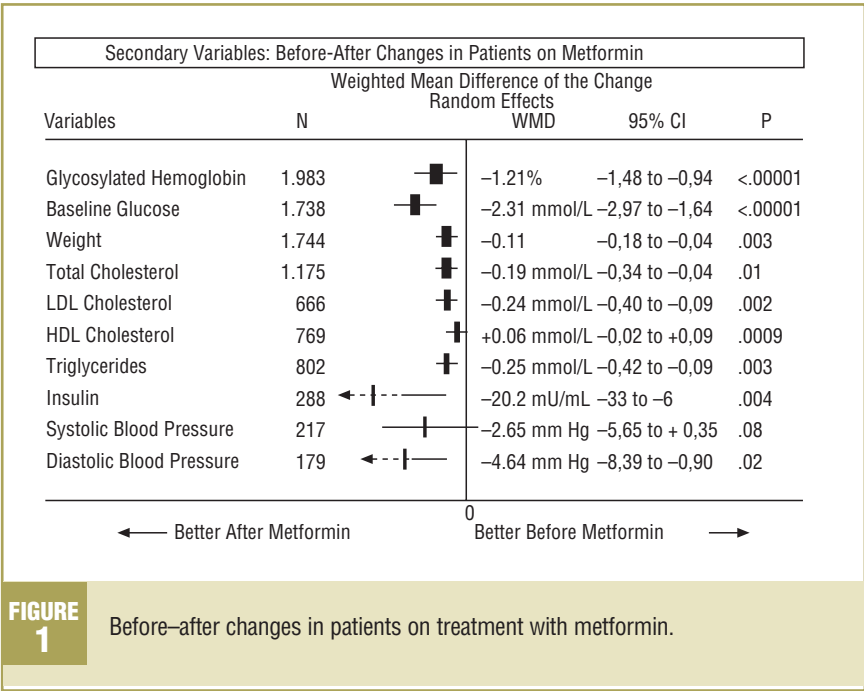
	UKPDS ¹⁸ Metformin (n=342) Versus Sulphonylureas or Insuline (n=951)	UKPDS ¹⁸ Metformin (n=342) Versus Conventional (n=411)	DeFronzo and Goodman (a) ¹² Metformin (n=210) Versus Glyburide (n=209)	Hallsten et al ³⁰ Metformin (n=13) Versus Placebo (n=14) Versus Rosiglitazone (n=14)	Horton et al ³¹ Metformin (n=178) Versus Placebo (n=172) Versus Nateglinide (n=179)	Teupe and Bergis ³⁴ Metformin (n=50) Versus Diet (n=50)
<i>Any event associated with diabetes</i>						
No. of events	98 versus 350	98 versus 160	1 versus 0	1 versus 0 versus 0	1 versus 0 versus 0	1 versus 0
RR (95% CI)	0.78 (0.6-0.9)	0.74 (0.6-0.9)	2.99 (0.12-72.88)	3.21† (0.14-72.55)	2.92† (0.12-72.6)	3.0 (0.13-71.92)
RRR (95% CI)	22% (6-35)	26% (9.5-40.1)				
NNT (95% CI)	12 (7-40)	10 (6-28)			3.02 (0.12-73.56)	
P	.009	.004	NS	NS	NS	NS
<i>Death associated with diabetes</i>						
No. of events	28 versus 103	28 versus 55	1 versus 0	0 versus 0 versus 0	1 versus 0 versus 0	0 versus 0
RR (95% CI)	0.76 (0.51-1.13)	0.61 (0.40-0.94)	2.99 (0.12-72.88)	NE	2.92‡ (0.12-72.6)	NE
RRR (95% CI)	NS	39% (5.8-60.3)				
NNT (95% CI)	NS	19 (10-124)			3.02 (0.12-73.56)	
P	NS	0.003	NS	NS		
<i>Mortality by all causes</i>						
No. of events	50 versus 190	50 versus 89	1 versus 0	0 versus 0 versus 0	1 versus 0 versus 0	0 versus 0
RR (95% CI)	0.73 (0.55-0.97)	0.68 (0.49-0.93)	2.99 (0.12-72.88)	NE	2.92‡ (0.12-72.6)	NE
RRR (95% CI)	27% (2.6-45.0)	32% (7.5-50.7)				
NNT (95% CI)	19 (10-119)	14 (8-64)			3.02\$ (0.12-73.56)	
P	0.003	0.01	NS	NS		
<i>Myocardial infarction</i>						
No. of events	39 versus 139	39 versus 73	1 versus 0	1 versus 0 versus 0	1 versus 0 versus 0	1 versus 0
RR (95% CI)	0.78 (0.56-1.09)	0.64 (0.45-0.92)	2.99 (0.12-72.88)		2.92‡ (0.12-72.6)	
RRR (95% CI)	NS	36% (7.8-55.3)				
NNT (95% CI)	NS	16 (9-73)			3.02\$ (0.12-73.56)	
P	NS	.02	MS	NS	NS	
<i>Stroke</i>						
No. of events	12 versus 60	12 versus 23	ND	ND	ND	ND
RR (95% CI)	0.56 (0.30-1.02)	0.63 (0.32-1.24)				
RRR (95% CI)	NS	NS				
NNT (95% CI)	NS	NS				
P	NS	NS				
<i>Microvascular complications</i>						
No. of events	24 versus 74	24 versus 38	ND	ND	ND	ND
RR (95% CI)	0.90 (0.48-1.41)	0.71 (0.43-1.19)				
RRR (95% CI)	NS	NS				
NNT (95% CI)	NS	NS				
P	NS	NS				

*CI indicates confidence interval; n, sample size; ND, no data; NE, not estimable; NNT, number necessary to treat; NS, not significant; P, statistical significance; RR, relative risk; RRR, relative risk reduction.

†Comparison with placebo and rosiglitazone.

‡Comparison with placebo.

\$Comparison with nateglinide.



the same when compared with a conventional treatment (mainly diet), since it reduced the incidence of any event associated with diabetes, mortality and myocardial infarction. These results confirm the findings of the UKPDS, although we have not found the benefit reported for stroke (RR=0.56; 95% CI, 0.30-1.02), probably because we did not have access to individual data.¹⁸ The study of the effect of the addition of metformin to other medications has not been the objective of this review,

but it has to be mentioned that in the UKPDS the benefit in the primary results were not able to demonstrate this on adding it to a sulphonylurea. It reported an increase in mortality in the metformin-sulphonylurea treatment without overweight group compared to sulphonylurea only, although as an explanation baseline differences between patients were adjusted.¹⁸ Despite the doubts created, the recent clinical trials of metformin combined with other treatments have yet to report primary results, in combination with sulphonylureas⁴¹ as well as with insulin.⁴² No clinical study lasting longer than 8 months has been found which compares new oral agents (new sulphonylureas, α-glucosidase inhibitors, meglitinides, or thiazolidinediones) with metformin to be able to make a comparison of primary results, which it makes it difficult to recommend new drugs instead of metformin as the first therapeutic option, since the moderate benefits in isolated secondary results have still to show benefit in primary results. In fact, the UKPDS has demonstrated that there is a benefit in morbimortality with intensive glyce-mic control, but given similar control in all groups, the possible benefit of metformin could not be due only to its glyce-mic control and other possible effects on platelet aggregation and thrombolysis have been put forward as a hypothesis.⁴³ It must not be forgotten that diabetes added to other cardiovascular risk factors increases the risk of coronary disease and stroke, and that in a sub-study of the UKPDS the cardiovascular benefit from controlling hypertension was better than that of hyperglycemia.⁴⁴ However, with the exception of a greater benefit with metformin in overweight patients, this review has not found and has not been able to combine results specific to diabetic sub-groups such as in hypertensives, hyperlipemics, with fibrinolysis disturbances or over 65 years. For this reason it would be advisable that future investigators make an effort in recruiting these populations to better apply their results to our usual patients.

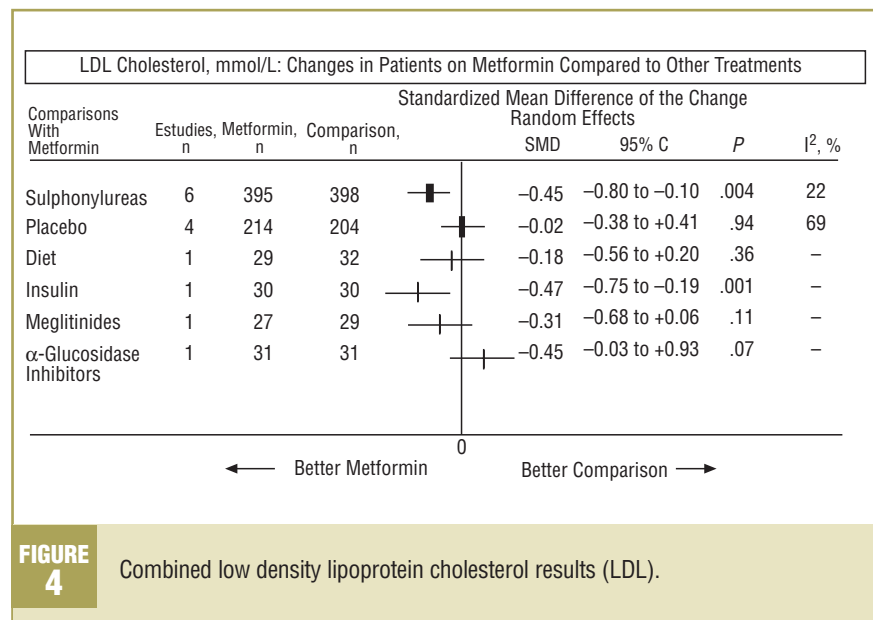
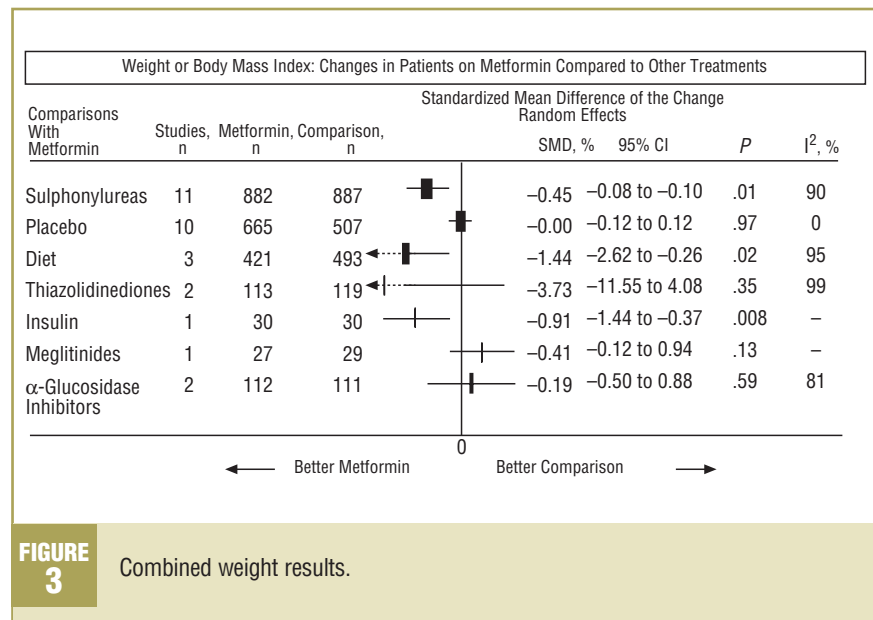
In the combined result of the 29 studies, patients on metformin had considerably improved glycemic control (HbA_{1C} by -1.21% and glucose by -2.31 mmol/L) and a modest decrease in weight, lipid values, and diastolic pressure. Patients on metformin also achieved a greater benefit in glycemic control than those assigned to a placebo, diet or thiazolidinediones, and a greater benefit in weight control and LDL cholesterol than those assigned to sulphonylureas or insulin. On the other hand, the more modern agents such as the thiazolidinediones and meglitinides did not provide any greater benefit in glycaemia, lipid values, weight, or blood pressure than metformin.

In this review, which includes 2007 patients assigned to treatment with metformin a minor reversible adverse effect was found (diarrhea), but no cases of lactic acidosis, which confirms the safety evidence of metformin, which has been published in a systematic review.³

One limitation of this review is the low number of existing double blind clinical trials, lack of data on the allocation concealment and the heterogeneity. The latter has been studied by meta-regression and 2 variables have been found which can explain it. One is the greater benefit of metformin in the overweight population and the other the attempt to enforce the diet by protocol, which could be an independent factor in the improvement of glycaemia. It is probable that in establishing these protocols in this type of clinical study biases in fulfillment are avoided.

There were also some noteworthy points: the combined effects were consistent in the sensitivity analysis, no publication biases were found and there was no significant disagreement between trials, despite their differences in design and quality. The secondary results are concordant with the 2 systematic reviews carried out previously, although the contribution of this review is the widening of the study to all anti-diabetic medications used in this disease, including insulin and diet, as well as recording the primary results, which are of most interest to the patients.^{4,5}

To sum up, in the long term metformin, in single intensive treatment in overweight patients with type 2 diabetes,



compared with intensive treatment with glibenclamide, chlorpropamide, or insulin and with conventional treatment shows greater benefits in primary results. No other anti-diabetic has been analyzed in comparison with metformin, thus this review supports the usefulness of this as a primary therapeutic option in type 2 diabetes mellitus, where it plays an important role in the prevention of vascular complications.

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Discussion
Key points

What Is Known About the Subject

- Metformin is a first option therapy in the management of type 2 diabetes mellitus, especially in overweight patients, and can prevent vascular complications.
- Two meta-analyses have been published comparing metformin with sulphonylureas, but without reporting the primary results.

What This Study Contributes

- Metformin continues to be the first therapeutic option in type 2 diabetes mellitus patients with overweight and obesity, and can prevent vascular complications.
- There are no clinical studies with sub-groups of type 2 diabetics with hyperlipemia, hypertension, hyper-coagulability or over 65 years which allows predicting who will benefit most from the use of metformin.
- The lack of long term clinical trials with primary results prevents recommending the new sulphonylureas, the α -glucosidase inhibitors, the meglitinides or the thiazolidinediones as opposed to metformin as a primary therapeutic option.
- Metformin produces significant beneficial changes in glycemia, and moderate ones in weight, lipids, insulinemia, and diastolic blood pressure.
- Metformin has more benefit in glycemia than placebo, diet or the thiazolidinediones, and on the weight than the sulphonylureas or insulin.

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COMMENTARY

The rehabilitation of metformin

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Diabetes mellitus is a metabolic problem caused by a defect in insulin secretion, in its action or in both. In type 2 diabetes mellitus the defect in the action generally predominates (insulin resistance) in obese patients, and the secretory defect in those of normal weight or slim. Diabetes mellitus 2 associated with obesity is most common in our area. In recent years the choice of drugs for the treatment of diabetes mellitus 2 is a pertinent and current issue, which has acquired great relevance due to several factors: the increase in pharmacological options that have appeared and the pressure of the pharmaceutical industry of these new drugs. Among the options available for glycemic control in diabetes mellitus 2, metformin is the only one which, up to now, has been shown to reduce the risk of morbidity and total mortality in the first long-term clinical trial (10.7 years), with primary results, the UK Prospective Diabetes Study (UKPDS). Metformin has been on the Spanish market for more than 40 years, but its use has not been as high and is still not as high as it should be. On the other hand, its low cost means it is not commercially promoted.

The UKPDS^{1,2} shows that in obese patients with diabetes mellitus 2, the choice of metformin as a first line drug due to the failure of treatment by diet, provides more benefits than risks, when it is compared with conventional treatment, as well as intensive treatment with other drugs (sulphonylureas or insulin). It not only reduces the risk of microvascular complications but also macrovascular ones and mortality. This study is the first proof which demonstrates the reduction in the risk of cardiovascular disease in the pharmacological treatment of patients with diabetes mellitus 2. The number of patients which is required to treat during 10 years to prevent one event more than makes up for the problems found. The patients included are newly diagnosed obese patients with type 2 diabetes mellitus, not controlled by diet treatment, with characteristics similar to those who attend our clinics. Although the study is carried out in the hospital environment, similar results can be obtained in primary care, since it does not require superhuman efforts: the patients are seen every month for the first 3 months and then every 3 months, or more often if control objectives need to be obtained.

Fasting glucose is used in each visit to adjust the treatment and glycosylated haemoglobin A1 each year to evaluate the level of control. Self testing of glucose is only

Key Points

- Metformin is regarded as a drug of choice for the start of monotherapy treatment in the patient with type 2 diabetes mellitus 2 and obesity.
- There is no justification for not using the combined treatment metformin plus sulphonylureas in obese patients with diabetes mellitus 2, although there is some doubt over its use in non-obese patients which will have to be clarified in subsequent studies.

used in those patients to whom insulin has to be added to achieve the required control.

The systematic review and meta-analysis published in this issue, after an exhaustive review of the literature, updates the subject, adding new studies which point in the same direction as regards the benefits gained. Thus, it confirms that metformin is a first choice drug in patients with diabetes and overweight or obese. It also adds studies where they compare with other drugs for secondary results, the new drugs not surpassing metformin as regards these results, although they may not yet have had time to show more beneficial results as regards primary results or safety profile.

Likewise it confirms that published in a recent systematic review of the virtually zero risk of lactic acidosis.^{3,4} The fear of lactic acidosis has always been taken into account when taking decisions. We actually do not know the real incidence of lactic acidosis, fatal or non-fatal, associated with the use of metformin in patients with type 2 diabetes mellitus. In population studies rates of 2 to 9 cases of lactic acidosis per 100 000/year have been reported among patients treated with metformin, most of them occurring in patients with serious acute problems, such as renal failure, which in itself can cause lactic acidosis.

The risk attributable to metformin is answered if we know that 9 cases per 100 000/persons/year have been reported in patients with type 2 diabetes not treated with metformin. The results of this systematic review confirm that previously reported in descriptive studies: no cases of lactic acidosis are seen.

It is a superb review which greatly exceeds the quality criteria of the QUOROM checklist. They should have ended perfectly with a last paragraph which pointed out the questions still requiring answers which will direct the necessary lines of investigation required, although in the text some of them are hinted at. Basically they are:

1. The effectiveness of metformin in non-overweight patients.
2. Comparison of primary results as regards the new drugs.
3. The combination of metformin due to the failure of other drugs.
4. An interesting aspect which remains outside this review is the promising treatment combined with insulin⁵. It is not uncommon to find patients with diabetes mellitus 2 on treatment with insulin where it is difficult to achieve acceptable glycemic control and frequently enter a vicious circle: insulin causes greater weight gain, increases insulin resistance, does not improve control, leading to increasing the insulin dose, the patient continues gaining weight and control does not improve. The use of a drug directed against insulin resistance, metformin, could be useful in these patients. The lack of studies directed to evaluating this aspect of treatment, which hypothetically seems promising, of the patient with diabetes mellitus 2 is striking. There are a few localized studies, which are of different quality, short duration and with a small sample size, although all show the usefulness of adding metformin. It is one of the typical cases where lack of interest of the usual sponsors of clinical trials leads to a lack of scientific proof on a potentially useful and efficient treatment. We think studies are necessary which might confirm these benefits in large populations and in the long term, studies which possibly may have to have several financial backers from the industry. In the 7 trials they studied only 232

patients and a maximum follow up time of 6 months, but it is worth mentioning that in all of them the results point in the same direction of benefit, therefore we think that, while other proof is gathered, the addition of metformin to the treatment of patients with diabetes mellitus 2 insufficiently controlled with insulin is a useful alternative, especially if overweight, and if there are no contraindications for its use.

5. Its behaviour in age sub-groups, dyslipemic, hypertensive and metabolic syndrome patients in the prevention of diabetes.

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