Locator web
Article 81.980

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

A. Sáenz Calvo,[a] I. Fernández Esteban,[b] A. Mataix Sanjuán,[b] M. Ausejo Segura,[c] M. Roqué,[d] and D. Moher[e]

Objective. To evaluate the efficacy of metformin against placebo, diet, oral antidiabetics, 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, morbility, 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_1 (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_1, 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_1 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_1 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.

Spanish version available at
www.atencionprimaria.com/81.980

A commentary follow this article (pág. 000)

[a]Centro de Salud Pozuelo 1, Área 6, Instituto Madrileño de la Salud, Pozuelo de Alarcón, Madrid, Spain.

[b]Área 11, Instituto Madrileño de la Salud, Madrid, Spain.

[c]Servicio de Evaluación del Gasto Farmacéutico, Dirección General de Farmacia, Consejería de Sanidad y Consumo, Madrid, Spain.

[d]Centro Cochrane Iberoamericano, Servicio de Epidemiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

[e]Director del Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ontario, Canada.

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.

In 2002 Dr Sáenz received an award for the investigation financed by Novartis.

The complete review was published in the Cochrane Collaboration (Issue 3).

Correspondence: Antonio Sáenz. Pintura, 14. 28224 Pozuelo de Alarcón. Madrid. España.
E-mail: antoniosaenz@ya.com

Manuscript received July 21, 2004.

Manuscript accepted for publication January 19, 2005.

Introduction

Type 2 diabetes mellitus is a chronic disease with significant morbility 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_1 (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 scale[7] 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 kappa[9] 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 ± 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 Begg[38] correlation test and the Egger graph.[39] We have evaluated heterogeneity using the Z marker, the χ^2 statistic and the I^2 statistic (values of I^2 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/m^2 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 trials[10-37] (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 function[19] 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=−0.31mmol/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/M^2; 95% CI, −0.80 to −0.10). A small clinical trial 23 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/m^2; 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 assignation. 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 UKPDS[18] 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 Nateglidine (n=179)	Teupe and Bergis[34] Metformin (n=50) Versus Diet (n=50)
Any event associated with diabetes						
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
Death associated with diabetes						
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		
Mortality by all causes						
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		
Myocardial infarction						
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	
Stroke						
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				
Microvascular complications						
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.

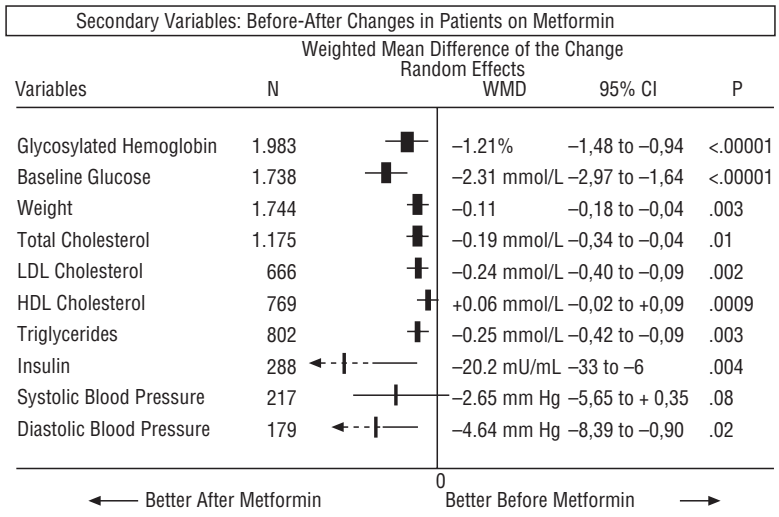

FIGURE 1 Before–after changes in patients on treatment with metformin.

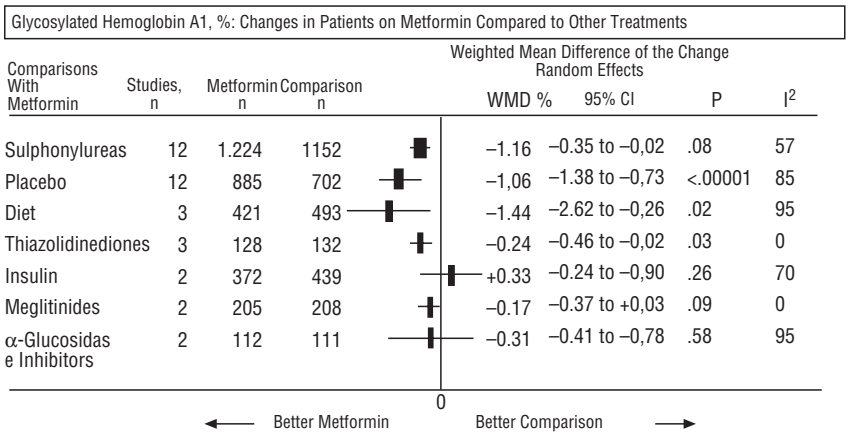

FIGURE 2 Combined glycosylated hemoglobin A_1.

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 sulphonylureas[41] 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 glycemic control, but given similar control in all groups, the possible benefit of metformin could not be due only to its glycemic 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 glycemia, lipid values, weight, or blood pressure than metformin.

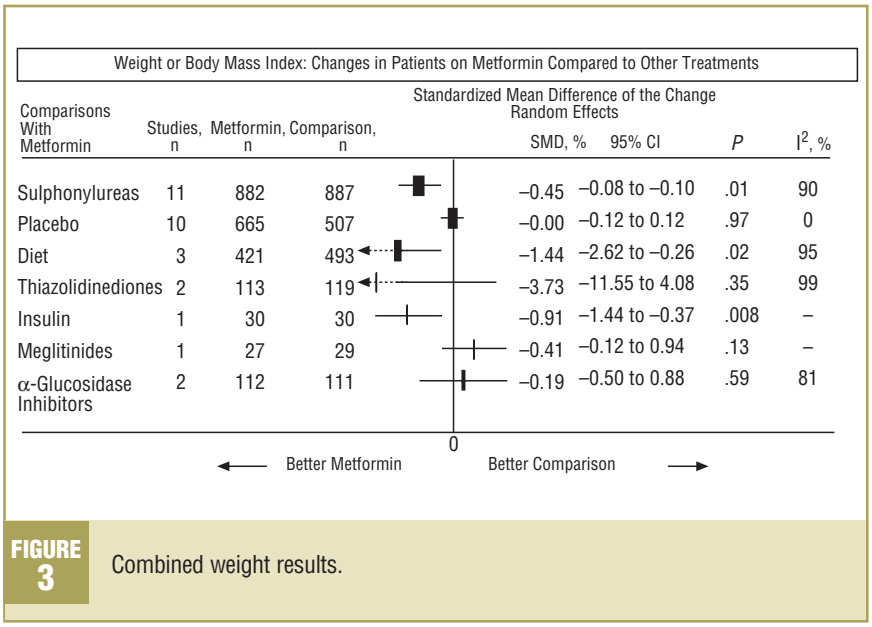

FIGURE 3 Combined weight results.

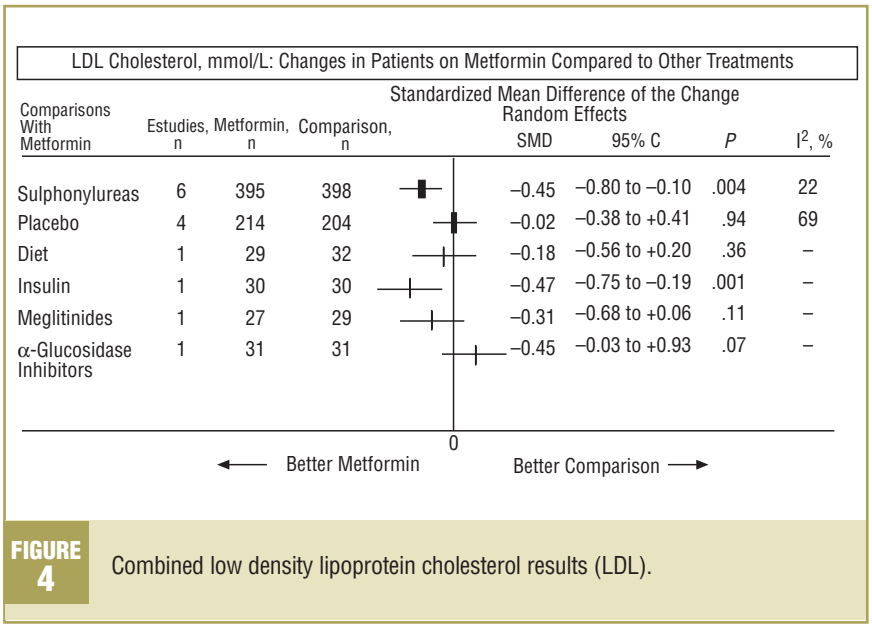

FIGURE 4 Combined low density lipoprotein cholesterol results (LDL).

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 glycemia. It is probable that in establishing these protocols in this type of clinical study biases in fulfillment are avoided.

There were also some noteworthy pints: 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.

Acknowledgements

To Aureli Tobías, for help in the statistical methods of publication biases, and to Dr Miguel Brito, for his critical reading of the manuscript.

Discussion
Key points

What Is Known About the Subjec

- 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.

References

1. Richter B, Berger M, Bergerhoff K, Clar C, de Leiva A, Manning P et al. Cochrane Metabolic and Endocrine Disorders Group. In: Cochrane Library, Issue 3. Oxford: Update Software; 2001.
2. Bailey CJ, Turner RC. Drug therapy: metformin. N Engl J Med. 1996;334:574-9.
3. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus (Cochrane Review). In: Cochrane Library, Issue 4.Oxford: Update Software; 2003.
4. Campbell IW, Howlett HCS .Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. Diabetes Metab Rev. 1995;11 Suppl 1:57-62.
5. Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta-analysis. Diabetes Care. 1999;22:33-7.
6. Shaughnessy AF, Slawson DC. What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes. BMJ. 2003;327:266-9.
7. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds JM, Gavaghan DJ, et al. Assessing the quality of reports of randomised clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12.
8. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995;273:408-12.
9. Fleiss JL. Statistical methods for rates and proportions. 2nd edition. New York: Wiley; 1981. p. 217-34.
10. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med. 2001;18:828-34.
11. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. Clin Ther. 2003;25:890-903.
12. deFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995;333:541-9.
13. Hermann LF, Schersten B, Bitzen PO, Kjellstrom T, Lindgärde F, Melander A. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care. 1994;17:1100-9.
14. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. Am J Med. 1997;103:483-90.
15. Chiasson JL Nadtich L, for the Miglitol Canadian University Investigator Group. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. Diabetes Care. 2001;24:989-94.
16. Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab. 2003;88:1637-45.
17. Uehara MH. Metabolic and haemodynamic effects of metformin in patients with type 2 diabetes mellitus and hypertension. Diabetes Obes Metab. 2001;3:319-25.
18. Turner RC, Holman RR, Stratton IM, Cull CA, Matthews DR, Manley SE, et al, for the UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
19. Collier A, Watson HH, Patrick AW, Ludlam CA, Clarke BF. Effect of glycaemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non-insulin- dependent) diabetic patients. Diabete Metab. 1989;15:420-25.
20. Noury J, Nandeuil A. Comparative three-month study of the efficacies of metformin and gliclazide in the treatment of NIDD. Diabete Metab. 1991;17(1 Pt 2):209-12.
21. Tessier D, Maheux P, Khalil A, Fulop T. Effects of gliclazide versus metformin on the clinical profile and lipid peroxidation markers in type 2 diabetes. Metabolism. 1999;48:897-903.
22. Campbell IW, Menzis DG, Chalmers J, McBain AM, Brown IRF. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. Diabete Metab. 1994;20:394-400.

23. Amador-Licona N, Guizar-Mendoza J, Vargas E, Sánchez-Camargo G, Zamora-Mata L. The short-term effect of a switch from glibenclamide to metformin on blood pressure and microalbuminuria in patients with type 2 diabetes mellitus. Arch Med Res. 2000;31:571-5.
24. Támez Pérez HE, Gómez de Ossio MD, Ibarra Martínez IB. Normoglucemia en diabetes mellitus no dependiente de insulina de reciente diagnóstico. Tratamiento no farmacológico vs. tratamiento farmacológico. Med Int Mex. 1997;13:272-5.
25. Dalzell GW, Hadden DR, Atkinson AB, Kennedy L, Weavwe JA. A randomized trial tolbutamide and metformin for persistent severe hyperglycaemia in non insulin dependent diabetes mellitus (NIDDM). Irish J Med Sci. 1986;155:341-2.
26. Damsbo P, Hermann LS, Vaag A, Hother-Nielsen O, Beck-Nielsen H. Irreversibility of the defect in glycogen synthase activity in skeletal muscle from obese patients with NIDDM treated with diet and metformin. Diabetes Care. 1998;21:1489-94.
27. del Prato S, Erkelens DW, Leutenegger M. Six-month efficacy of benfluorex vs. placebo or metformin in diet-failed type 2 diabetic patients. Acta Diabetol. 2003;40:20-7.
28. Dornan TL, Heller SR, Peck GM, Tattersall RB. Double-blind evaluation of efficacy and tolerability of metformin in NIDDM. Diabetes Care. 1991;14:342-4.
29. Grant PJ. The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. Diabetes Care. 1996;19:64-6.
30. Hallsten K, Virtanen KA, Lonnqvist F, Sipila H, Oksanen A, Viljanen T, et al. Rosiglitazone but not metformin enhances insulin-and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes. 2002;51:3479-85.
31. Horton ES, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care. 2000;23:1660-5.
32. Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. Obes Res. 1998;6:47-53.
33. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001;37:1344-50.
34. Teupe B, Bergis K. Prospective randomized two-years clinical study comparing additional metformin treatment with reducing diet in type 2 diabetes. Diabetes Metab. 1991;17:213-7.
35. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 1999;22:119-24.
36. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS,Walton V, et al. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med. 1998;338:867-72.
37. Fanghanel G, Sánchez-Reyes L, Trujillo C, Sotres D, Espinosa-Campos J. Metformin´s effects on glucose and lipid metabolism in patients with secondary failure to sulphonylureas. Diabetes Care. 1996;19:1185-9.
38. Begg CB, Mazundar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088-101.
39. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.
40. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. BMJ. 2003;327:557-60.
41. Tosi F, Muggeo M, Brun E, et al. Combination treatment with metformin and glibenclamide versus single-drug therapies in type 2 diabetes mellitus: a randomized double-blind, comparative study. Metabolism. 2003;52:862-7.
42. Buse J. Combining insulin and oral agents. Am J Med. 2000;108 Suppl 6A:23-32.
43. Mamputu JC, Wiernsperger NF, Renier G. Anti-atherogenic properties of metformin: the experimental evidence. Diabetes Metab. 2003;29(4 Pt 2):6S71-6.
44. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317:703-13.

COMMENTARY

The rehabilitation of metformin

I. Fernández Fernández
Aljarafe Health District, Sevilla, Spain.

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

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.

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 insulin[5].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.

References

1. UKPDS 34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet. 1998;352:854-65.
2. Fernández Fernández I, Ríos Bonnin, C, Villafuerte Fernández I. La metformina reduce el riesgo de complicaciones en el paciente con diabetes tipo 2 y obesidad. E4 Unidad docente. 2000;2:21-5.
3. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 dia betes mellitus. Systematic review and meta-analysis. Arch Intern Med. 2003;163:2594-602.
4. Fernández Fernández I. El tratamiento con metformina reduce el riesgo de acidosis láctica en la diabetes tipo 2. FMC. 2004;11:355.
5. Fernández Fernández I. Pregunta clínica: en el paciente con diabetes mellitus tipo 2 con mal control bajo tratamiento insulínico; ¿el tratamiento combinado con metformina mejora el control glucémico? Atención primaria basada en la Evidencia. FMC.2001;8:7-8.
6. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, for the QUOROM Group. Improving the quality of randomised controlled trials; the QUOROM statement. Lancet. 1999;354:1896-900.