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ORIGINAL ARTICLE

Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials

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Aim: Some studies suggested that metformin could reduce cardiovascular risk to a greater extent than that determined by glucose reduction. Aim of the present meta-analysis is to assess the effects of metformin on the incidence of cardiovascular events and mortality.
Methods: An extensive search of Medline, EMBASE and the Cochrane Library (any date up to 31 October 2009) was performed for all trials containing the word 'metformin'. Randomized trials with a duration ≥52 weeks were included. A meta-regression analysis was also performed to identify factors associated with cardiovascular morbidity and mortality in metformin-treated patients.
Results: A total of 35 clinical trials were selected including 7171 and 11 301 participants treated with metformin and comparator, respectively, who had 451 and 775 cardiovascular (CV) events, respectively. Overall, metformin was not associated with significant harm or benefit on cardiovascular events (MH-OR 0.94[0.82–1.07], p = 0.34). A significant benefit was observed in trials versus placebo/no therapy (MH-OR 0.79[0.64–0.98], p = 0.031), but not in active-comparator trials (MH-OR 1.03[0.72–1.77], p = 0.89). Meta-regression showed a significant correlation of the effect of metformin on cardiovascular events with trial duration and with minimum and maximum age for inclusion, meaning that the drug appeared to be more beneficial in longer trials enrolling younger patients. It is likely that metformin monotherapy is associated with improved survival (MH-OR: 0.801[0.625–1.024], p = 0.076). However, concomitant use with sulphonylureas was associated with reduced survival (MH-OR: 1.432[1.068–1.918], p = 0.016).
Conclusion: Available evidence seems to exclude any overall harmful effect of metformin on cardiovascular risk, suggesting a possible benefit versus placebo/no treatment. The observed detrimental effect of the combination with sulphonylureas deserves further investigation.
Keywords: cardiovascular events, meta-analysis, metformin, mortality, type 2 diabetes

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Introduction

Metformin is recommended as the first-line drug for type 2 diabetes by most International guidelines [1–5]. The preference for metformin over other available drugs is based on its efficacy on blood glucose control, tolerability, safety and low cost [1–5]. Furthermore, metformin has a favourable action on several risk factors, including lipids, body weight and blood pressure [6,7]. Experimental studies have also shown that this drug could have beneficial effects on fibrinolysis and platelet aggregation [8,9]. The UK Prospective Diabetes Study (UKPDS) reported that long-term treatment with metformin could reduce cardiovascular morbidity and mortality in type 2 diabetes to a greater extent than other agents with similar glucose-lowering effect [10], suggesting that the cardiovascular protection conferred by metformin could go beyond that determined by the improvement of glucose control.

The heterogeneity of results of clinical trials assessing the cardiovascular effects of metformin could be due, at least partly, to their inadequate size for this specific endpoint; in fact, no trial specifically designed for the assessment of the effects of metformin on cardiovascular events has ever been performed so far. As a result, patients enrolled in metformin trials often have a lower cardiovascular risk, leading to the observation of a limited number of events.

When several underpowered and discordant studies are available, a meta-analysis can add relevant information. The two available meta-analyses of trials with metformin providing information on cardiovascular events [11,12] failed to detect any effect of the drug on cardiovascular morbidity and mortality. Both analyses were restricted to trials performed on type 2 diabetic patients, which is the only approved indication of metformin, and they did not include some recent trials, such as RECORD [13]. One of the two meta-analysis included also studies of short duration, which could have diluted the cardiovascular effects of the drug [11]. The other meta-analysis [12] assessed the effects of metformin only in monotherapy, excluding trials in which the dug was associated with other glucose-lowering agents; this eliminates the possible interference of co-treatment, but it restricts the applicability of results, considering that the large majority of metformin-treated patients are also receiving other glucose-lowering therapies [14].

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The aim of the present meta-analysis is to assess the effects of metformin on the incidence of cardiovascular events and mortality.

Methods

The meta-analysis was reported following the PRISMA checklist ([15], Table S1).

Data Sources

An extensive search of Medline, EMBASE and the Cochrane Library (any date up to 31 October 2009, restricted to randomized clinical trials, published in English) was performed for all trials containing in any field the word 'metformin'. No attempt was made at identifying and retrieving unpublished studies.

Study Selection

All trials comparing metformin with placebo, active glucose-lowering therapies, or no therapy, were included, provided that their duration was $\geq$52 weeks and that concurrent therapies were not different in metformin and comparator arms. The database included trials in which cardiovascular events were a pre-defined endpoint, together with trials designed for other (mainly metabolic) endpoints.

Data Extraction

Data were retrieved from the paper reporting the main results of each trial; missing information was searched for in other publications on the same trial. Data for analysis were extracted independently by two observers (C. L. and M. M.) and potential conflicts were resolved by a senior investigator (E. M.). Cardiovascular events were defined as either fatal or non-fatal cases of myocardial infarction, stroke and peripheral artery disease or other cardiovascular death. Results on all-cause and incidence of heart failure (as serious adverse event) were also retrieved.

Data Synthesis and Analysis

The quality of trials was assessed using some of the parameters proposed by Jadad et al. [16]. The score was not used as a criterion for the selection of trials, whereas some items were used only for descriptive purposes (Table S2). Heterogeneity was assessed using Q statistics; if no heterogeneity was detected, we applied both a random-effects and a fixed-effects model. We report here the results of the random-effects model, because the validity of tests of heterogeneity can be limited with a small number of component studies [17]. Publication bias was assessed by a visual inspection of the Begg's funnel plot; the Egger's test was used to provide statistical evidence of funnel plot symmetry. These tests are based on the unproven hypothesis that smaller studies have a greater publication bias, whereas large-scale trials are unlikely to escape public knowledge. A Begg's Funnel plot was drawn for the assessment of publication bias, explored using the Egger's test. Mantel–Henzel Odds Ratio (MH-OR) was calculated for cardiovascular events, using a random-effects model. Separate analyses were performed for trials with different comparators or exploring the effects of metformin as add-on to different therapies and for those including either diabetic or non-diabetic patients. Separate analyses were also performed for trials including patients aged <30 or >65 years. A meta-regression was performed to identify moderators of the effects of metformin on cardiovascular morbidity. Baseline characteristics possibly associated with cardiovascular morbidity and mortality included metformin dose, duration of trial, minimum and maximum age, HbA1c and BMI for inclusion, as well as mean age, BMI, lipid profile, HbA1c and fasting blood glucose of patients at enrolment and proportion of women enrolled. All these analyses were performed using Comprehensive Meta-Analysis, version 2.2.046 (NJ, USA). Power calculation for each endpoint was performed on the basis of observed proportion of incident cases in control groups, using Lenth's Piface version 1.72, and calculating the minimum risk reduction in the metformin group to obtain a 90% power for a $p < 0.05$, considering the sample sizes actually available.

Results

The process of trial retrieval and selection is summarized in figure 1. A total of 35 clinical trials were selected including 7171 and 11 301 participants treated with metformin and comparator, respectively, who had 451 and 775 CV events, respectively. The median duration of trials was 112 weeks (range: 52–343 weeks) with a total follow-up was 71 123 patient $\times$ years (Table 1). The number of events reported in each trial is summarized in Table 2. Of the trials retrieved, eight did not describe major cardiovascular events. Those trials

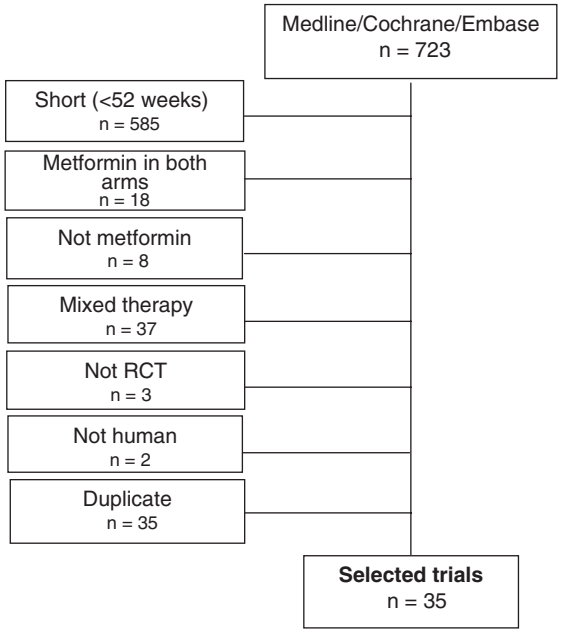

Figure 1. Trial flow diagram. RCT, randomized clinical trial.

Table 1. Characteristics of included randomized clinical trials.

Study (Reference)* In type 2 diabetes	Follow-up (weeks)	Comparator	Metformin dosage (mg/day)	Sample size number (Met/C)	Add-on to	Mean age† (years)	Male† (%)	Mean HbA1c† (%)
Hermann [32]	52	Placebo	1.700	16/19	None	57.5	54.2	8.9
Yki—Yarvinen [33]	52	Glibenclamide	2.000	19/22	Insulin	59.0	58.5	9.8
	52	Insulin	2.000	19/24	Gliben	59.0	58.5	9.8
Campbell [34]	52	Glipizide	1.000	24/24	None	57.0	33.3	11.6
Klein [35]	52	Insulin	2.550	25/25	SU	67.0	24.0	12.4
Vahatalo [36]	52	None	2.500	26/11	Insulin	62.0	67.3	9.9
	52	Glipizide/	2.500-	26/15	Insulin	62.0	67.3	9.9
Yamanouchi [37]	52	Glimepiride	750	39/37	None	54.9	50.0	9.9
	52	Pioglitazone	750	39/38	None	54.9	50.0	10.1
Douek [38]	52	Placebo	2.000	92/91	None/SU	58.0	65.0	9.8
Schweizer [39]	52	Vildagliptin	2.000	254/526	None	53.2	54.3	8.7
Shernthaner [40]	52	Pioglitazone	2.000	597/597	None	56.5	55.2	8.7
Derosa [41]	64	Pioglitazone	3.000	67/69	None	54.5	48.6	9.1
Gregorio [42]	76	Placebo	1.700	89/85	SU	74.5	47.1	10.3
Teupe [43]	104	Placebo	1.700	50/50	None	53.7	40.0	9.0
Charbonnel [44]	104	Pioglitazone	2.550	320/319	SU	60.0	54.0	8.8
Barnett [45]	128	Insulin	NR	211/235	SU	57.8	NR	9.8
Maji [46]	156	None	500	48/90	None	NR	40.1	7.4
	156	Rosiglitazone	500	48/48	None	NR	40.1	7.4
	156	Acarbose	500	48/48	None	NR	40.1	7.4
Kahn (ADOPT) [47]	208	Glibenclamide	2.000	1454/1441	None	57.0	56.9	7.3
	208	Rosiglitazone	2.000	1454/1456	None	57.0	56.9	7.3
Kooy [48]	220	Placebo	2.000	196/194	None	61.5	45.6	7.9
Home (RECORD) [12]	260	Rosiglitazone	2.550	1122/1103	SU	59.7	49.8	8.0
UKPDS 34‡ [10]	556	SU/Insulin	2.550	342/951	None	58	60.0	7.5
	556	None	2.550	342/411	None	58	60.0	7.5
UKPDS 34‡ bis [10]	343	None	2.550	268/269	SU	59	60.0	7.5
Palomba [49]	52	Placebo	1.700	15/15	PCOS	24.5	0.0	NR
Ibanez [50]	52	Placebo	850	12/12	PCOS	12.4	0.0	NR
Harborne [51]	52	Placebo	1.500	26/26	PCOS	31.5	0.0	NR
Tomazic [52]	52	Rosiglitazone	1.000	30/30	HIV	42.3	NR	NR
Li [53]	52	Placebo	2.000	33/37	IGT	49.5	71.4	7.3
Martinez [54]	52	Placebo	1.700	35/73	HIV	41.6	25.0	NR
Gambineri [55]	52	Placebo	1.700	40/40	PCOS	26.5	0.0	NR
Lund [56]	52	Placebo	2.000	49/51	DM1§	45.5	64.0	9.5
Charles (BIGPRO, [57])	52	Placebo	1.700	164/160	IGT	49.0	33.0	NR
Zhang [58]	76	None	750	49/45	NGT	53.5	43.5	NR
Stakos [59]	104	Glipizide	500	59/25	NGT	40.7	25.0	NR
	104	Placebo	500	59/97	NGT	40.7	25.0	NR
Shuster [60]	104	Placebo	500	45/81	NGT	NR	NR	NR
Ramachandran [61]	156	None	500	262/269	IGT	45.0	79.2	6.2
Knowler (DPP, [11])	156	Placebo	1.700	1073/1082	IGT	50.3	32.4	5.9
Ibanez [62]	208	Placebo	425	19/19	EPG	8.4	0.0	NR

Met/C, metformin versus comparators; Gliben., glibenclamide; SU, sulphonylureas; Charact., characteristics; DM1, type 1 diabetes mellitus; PCOS, polycystic ovary syndrome; NR, not reported; IGT, impaired glucose tolerance; HIV, HIV infected patients; EPG, early puberty in girls.
*See Appendix S1 for references [32–62].
†Mean value between metformin- and comparator group.
‡The UKPDS 34 was divided into two separate studies.
§Add-on to insulin.

were excluded from the analysis, along with studies with no events (n = 15). The meta-analysis on cardiovascular events was therefore performed on 12 trials (5455 and 8996 patients on metformin and comparators, respectively), 2 and 10 of which were performed in non-diabetic and diabetic patients, respectively. All trials on diabetic patients included in the meta-analysis were performed in type 2 diabetes, within the approved indications of the drug. The total number of events was 451 and 775 in metformin and comparator groups, respectively. The shape of the Begg's funnel plot (figure 2) did not reveal any evidence of obvious asymmetry and the results of Egger's test did not suggest any evidence of publication bias ($p = 0.46$). The trials included in the meta-analysis had a $Q = 10.08$ ($p = 0.46$), suggesting the lack of relevant heterogeneity.

Table 2. Outcome variables in individual studies included in the meta-analysis.

Study (Reference)* In type 2 diabetes	CVD morbidity (Met/C)	Myocardial Infarction (Met/C)	Stroke (mg/day)	Chronic heart failure (Met/C)	All-cause mortality (Met/C)	CVD mortality (Met/C)
Hermann [32]	1/0	1/0	0/0	0/0	0/0	0/0
Yki—Yarvinen [33]	0/0	0/0	0/0	0/0	1/0	0/0
	0/0	0/0	0/0	0/0	1/0	0/0
Campbell [34]	0/0	0/0	0/0	0/0	0/0	0/0
Klein [35]	2/0	1/0	1/0	0/0	0/0	0/0
Vahatalo [36]	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Yamanouchi [37]	0/0	0/0	0/0	0/0	0/0	0/0
	0/0	0/0	0/0	0/0	0/0	0/0
Douek [38]	NR/NR	NR/NR	NR/NR	NR/NR	0/0	0/0
Schweizer [39]	NR/NR†	2/0	NR/NR	NR/NR	0/0	0/0
Shernthaner [40]	23/22	NR/NR	NR/NR	NR/NR	2/3	NR/NR
Derosa [41]	0/0	0/0	0/0	0/0	0/0	0/0
Gregorio [42]	0/0	0/0	0/0	0/0	0/0	0/0
Teupe [43]	1/0	1/0	0/0	0/0	0/0	0/0
Charbonnel [44]	NR/NR	NR/NR	NR/NR	NR/NR	0/0	0/0
Barnett [45]	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Maji [46]	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Kahn (ADOPT, [47])	58/41	23/18	19/17	19/9	31/31	NR/NR
	58/62	23/27	19/16	19/22	31/34	NR/NR
Kooy [48]	46/45	28/25	9/9	3/4	9/6	3/1
Home (RECORD, [12])	169/163	NR/NR	NR/NR	NR/NR	72/54	NR/NR
UKPDS 34‡ [10]	57/211	39/139	12/60	11/NR	50/190	25/NR
	57/105	39/73	12/23	11/17	50/89	25/53
UKPDS 34‡ bis [10]	71/73	31/33	15/13	9/6	46/30	25/13
In other conditions						
Palomba [49]	0/0	0/0	0/0	0/0	0/0	0/0
Ibanez [50]	0/0	0/0	0/0	0/0	0/0	0/0
Harborne [51]	0/0	0/0	0/0	0/0	0/0	0/0
Tomazic [52]	0/0	0/0	0/0	0/0	0/0	0/0
Li [53]	0/0	0/0	0/0	0/0	0/0	0/0
Martinez [54]	0/0	0/0	0/0	0/0	0/0	0/0
Gambineri [55]	0/0	0/0	0/0	0/0	0/0	0/0
Lund [56]	2/5	NR/NR	NR/NR	NR/NR	0/0	0/0
Charles (BIGPRO, [57])	0/0	0/0	0/0	0/0	1/0	0/0
Zhang [58]	0/0	0/0	0/0	0/0	0/0	0/0
Stakos [59]	0/0	0/0	0/0	0/0	0/0	0/0
	0/0	0/0	0/0	0/0	0/0	0/0
Shuster [60]	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Ramachandran [61]	5/6	NR/NR	NR/NR	NR/NR	1/2	0/1
Knowler (DPP, [11])	16/42	NR/NR	NR/NR	NR/NR	NR/NR	1/6
Ibanez [62]	0/0	0/0	0/0	0/0	0/0	0/0

CVD, cardiovascular disease; Met/C, metformin versus comparators; NR, not reported.
*See Appendix S1 for references [32–62].
†There are further serious adverse events but they are not specified (with the exception of myocardial infarction).
‡The UKPDS 34 was divided into two separate studies.

Overall, metformin treatment did not produce any significant effect on cardiovascular events (figure 3). Separate analyses provided similar results for diabetic and non-diabetic patients, and for trials in which metformin was used as add-on to different therapies. Metformin was associated with a significant reduction of cardiovascular events in comparisons with placebo or no therapy, whereas no such effect was observed in active-comparator trials (figure 4). In direct comparisons with rosiglitazone (n = 2), the OR for major cardiovascular events in patients treated with metformin was 1.06[0.87–1.28] (p = 0.57). The drug reduced cardiovascular morbidity only in trials with protocols which allowed the enrolment of patients aged <30 years, and in those which excluded patients aged >65 years (figure 4). No significant effect of metformin was observed on the incidence of myocardial infarction, stroke or heart failure (MH-OR 0.90[0.71–1.14], 0.92[0.65–1.29], 1.12[0.25–9.04]

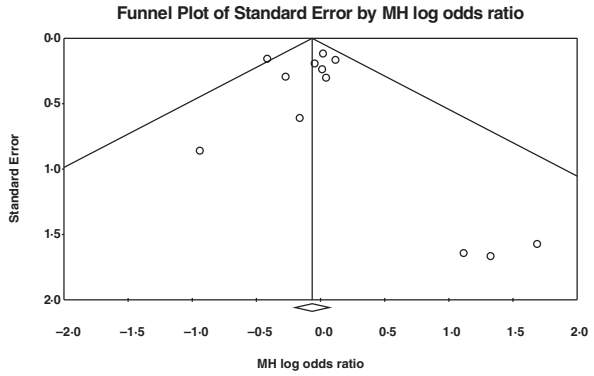

Figure 2. Funnel plot of standard error by standardized difference in means (cardiovascular events).

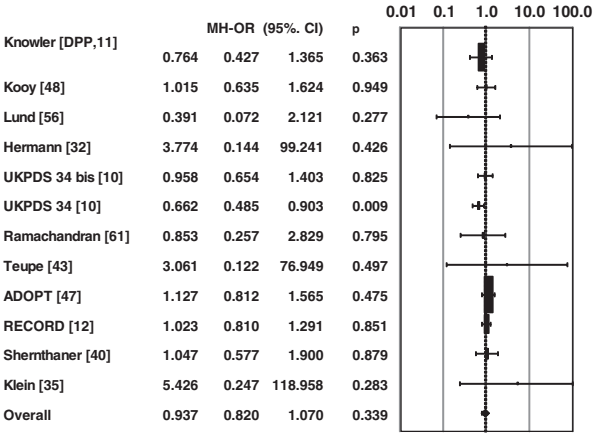

Figure 3. Effect of metformin on cardiovascular events across all randomized clinical trials included in the analysis. The size of the data markers represents the relative weight of the trial according to patient-years. MH-OR, Mantel–Henzel odds ratio; CI, confidential intervals. See Appendix S1 for references [32–62].

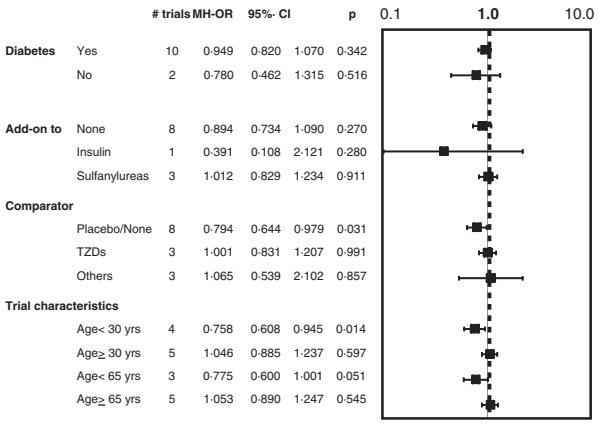

Figure 4. Separate analyses to explore the differential effects of metformin on cardiovascular events. TZDs, Thiazolidinediones; yrs, years; MH-OR, Mantel–Henzel odds ratio; CI, confidential intervals.

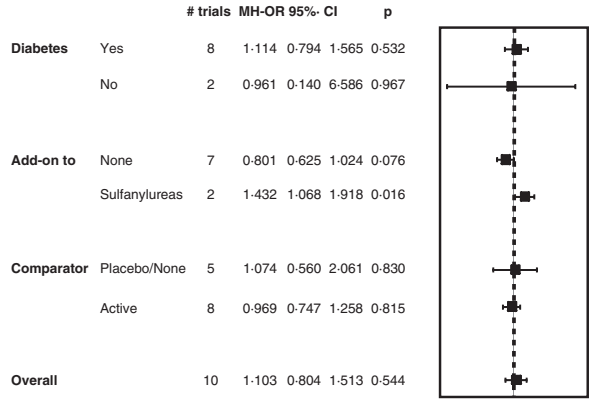

Figure 5. Separate analyses to explore the differential effects of metformin on all-cause mortality. MH-OR, Mantel–Henzel odds ratio; CI, confidential intervals.

in eight, five and six trials with at least one event, respectively; all $p > 0.35$). At meta-regression, the effect of metformin on cardiovascular events appeared to be greater in trials of duration, and in those with lower minimum and maximum age for inclusion, meaning that the drug appeared to be more beneficial in longer trials enrolling younger patients (Table 3).

All-cause and cardiovascular mortality could be analysed in ten and five trials with at least one event, respectively (Table 2). Metformin did not appear to have any effect on all-cause mortality, both in diabetic or non-diabetic patients, and in trials comparing metformin either with placebo/no therapy or with active comparators. A significant increase of mortality was detected in the two trials in which metformin was added to sulphonylureas, whereas a trend toward improved survival was observed in studies on metformin monotherapy, although it did not quite reach full statistical significance (figure 5). Similar results were obtained for cardiovascular mortality: the MH-OR in the five available trials was 0.923[0.361–2.320] ($p = 0.86$); when the four trials on metformin monotherapy were analysed separately, a significant reduction of mortality was observed (MH-OR 0.554[0.356–0.890], $p = 0.014$). At meta-regression, the drug appeared to have a more beneficial effect on all-cause mortality in trials of longer duration (Intercept: 0.612[0.138–1.087]; Slope: −0.002[−0.003 to −0.00004], $p = 0.008$), and in those enrolling a higher proportion of women (Intercept: 2.237[0.184–4.290]; Slope: −0.039[−0.076 to −0.003], $p = 0.034$).

The total sample size of trials included in the meta-analysis has a 90% power to detect a reduction of risk in the metformin group, in comparison with controls, of 18, 29, 42 and 59% for all cardiovascular events, myocardial infarction, stroke and heart failure, respectively; the corresponding figures for all-cause and cardiovascular mortality are 23 and 55%, respectively.

Discussion

Despite the efforts at controlling blood glucose and associated risk factors, cardiovascular morbidity and mortality remain higher in diabetic patients than in the rest of the population [18]. The accurate treatment of hyperglycaemia is considered one of the tools for preventing cardiovascular disease, in type 1 as well as in type 2 diabetic patients [19,20]. Many

Table 3. Moderators of the effect of metformin treatment on cardiovascular events.

	Cardiovascular events		
Moderator	Intercept	Slope	p
Trial duration (weeks)	0.24 [−0.06 to 0.055]	−0.001 [−0.002 to − 0.0001]	0.02
Age (years)	−1.540 [−4.121 to 1.042]	0.02 [−0.02 to 0.07]	0.26
Sex (male)	0.325 [−0.621 to 1.266]	−0.007 [−0.021 to 0.019]	0.41
Duration of diabetes (years)	−0.143 [−0.490 to 0.203]	0.011 [−0.032 to 0.054]	0.79
HbA1c at baseline (%)	−1.012 [−2.670 to 0.633]	0.121 [−0.094 to 0.349]	0.26
BMI at baseline (kg/m^2)	−1.721 [−4.629 to 1.177]	0.051 [−0.038 to 0.151]	0.26
FPG (mg/dl)	−0.421 [−1.456 to 1.0.617]	0.040 [−0.078 to 0.151]	0.50
Metformin dosage (mg/day)	0.154 [−0.749 to 1.055]	−0.001 [−0.0001 to 0.001]	0.63
Minimum age* (years)	−0.651 [−1.319 to 0.021]	0.021 [0.009−0.041]	0.049
Maximum age* (years)	−1.791 [−3.592 to 0.081]	0.022 [0.001−0.054]	0.050

FPG, Fasting Plasma Glucose.
*Min/Max, minimum and maximum age for inclusion in the trial.

classes of drugs have been shown to be effective as glucose-lowering agents, at least in the short and medium term; it has been suggested that some of these molecules, including metformin, could confer a cardiovascular protection beyond the beneficial effect of the improvement of glucose control [6–9], because of the reduction of total and LDL cholesterol, triglyceride body weight and blood pressure [6,7]. Furthermore, treatment with metformin is associated with enhanced fibrinolysis and reduced platelet hyperaggregation [8,9]. It has also been suggested that the reduction of hyperinsulinemia, in insulin-resistant type 2 diabetic subjects, could have beneficial effects on cardiovascular risk [8].

We show here that, despite all these interesting properties, metformin does not appear to have any relevant additional effect on cardiovascular events, apart from that determined by its glucose-lowering action. Although individual studies may lack the statistical power to detect differences between treatments, the meta-analytical approach overcomes this difficulty, at least for the composite endpoint of all major cardiovascular events. In fact, power calculations showed that the overall sample would have been sufficient to detect a between-group difference in the incidence of cardiovascular events as small as 18%. Our results confirm those reported in a previous meta-analysis which did not include some of the most recent trials (26 trials, including RECORD [13]). Interestingly, metformin was associated with a reduction of cardiovascular risk when compared with placebo or no therapy, whereas its effect disappeared when including active-comparator trials. It can be speculated that the cardiovascular protection conferred by metformin is largely because of the improvement of blood glucose control; this would explain the lack of additional effects in comparison with other agents, similarly effective as glucose-lowering treatments, in active-comparator trials [13]. In fact, no beneficial action of metformin on cardiovascular events has ever been reported in trials performed in non-diabetic individuals [21].

Metformin appeared to be associated with a reduction of cardiovascular events in trials of longer duration. This suggests that the drug could have a beneficial effect, which becomes evident only after several years of treatment. Furthermore, the limited statistical power to detect a protective effect of metformin on single endpoints, such as myocardial infarction, stroke or heart failure, could have prevented the observation of some beneficial action. It should also be considered that the significant result in studies versus placebo/no therapy is largely driven by one trial, the UKPDS [10], the results of which are discordant from most of other available evidence. The UKPDS was performed much earlier than most large-scale trials assessing the effects of metformin on cardiovascular events [13,21]; the greater accuracy in the treatment of extra-glycaemic cardiovascular risk factors in recent years, which reduced the overall incidence of myocardial infarction and stroke in diabetic patients, could have limited the possibility of further, drug-induced beneficial effects on cardiovascular events.

Differences in the characteristics of the patients enrolled could theoretically provide an explanation for the discrepancies in results of clinical trials. The meta-regression approach was used to investigate this hypothesis, showing that lower age limits for inclusion are associated with a greater cardiovascular benefit of metformin. This result parallels the progressive reduction of the efficacy of other treatments on cardiovascular morbidity and mortality with increasing age [22]. It should also be considered that prevention of cardiovascular events usually requires long-term treatment of risk factors; it is possible that the effect of metformin on this outcome could have been blunted by the inclusion of some shorter-term trials.

A trend toward a reduction in mortality was observed in patients on metformin monotherapy, in comparison with placebo or no treatment, but this difference did not reach full statistical significance. Considering that the number of deaths in clinical trials is obviously smaller than that of all (fatal and non-fatal) major cardiovascular events, the negative result could be because of an insufficient sample size, particularly for cardiovascular mortality. Furthermore, all-cause mortality includes deaths determined by causes on which metformin is very unlikely to produce any effect (infections, accidents, etc.). Interestingly, all-cause mortality was actually increased in the two trials with events in which metformin was added to a pre-existing therapy with sulphonylureas. A significantly higher mortality with metformin plus sulphonylurea in comparison with sulphonylurea alone, observed in the UKPDS combination study had been dismissed by the authors as

a casual finding, because of the small sample size [10]; a similar, although non-significant, result was obtained in the comparison of sulphonylurea/metformin combination with rosiglitazone/metformin in the RECORD trial [13]. If studies in which metformin is added to a sulphonylurea are excluded from the analysis, a significant reduction of cardiovascular mortality, and a non-significant trend toward a reduction of all-cause mortality, is observed. Although those results are far from conclusive, the possibility of an increased mortality associated with combination therapy of metformin with sulphonylureas, which is also suggested by several epidemiological studies [23,24], deserves further investigation. If such a negative interaction exists, this could lead to an underestimation of the actual effects of metformin, per se, on all-cause and cardiovascular mortality. The mechanisms underlying the potential interaction between metformin and sulphonylureas are presently unknown. Interestingly, in epidemiological studies, the increase of mortality associated with metformin/sulpfonylurea combinations is more evident among patients with known coronary artery disease [25]; furthermore, the combination of metformin with glyburide is associated with higher mortality rates in comparison with other drugs of the same class with lower myocardial affinity [26]. On the basis of these data, it can be speculated that metformin potentiates the unfavourable effect of sulphonylureas on the ischaemic myocardium.

Ideally, the cardiovascular effect of a pharmacological treatment should be verified through randomized trials with major cardiovascular events as the primary endpoint. However, additional information can be obtained from the analysis of serious adverse events recorded in trials with other, non-cardiovascular, endpoints. Recently, the Food and Drug Administration has recommended to use such approach with phase III trials, to assess the cardiovascular safety of drugs for diabetes prior to registration (www.fda.gov). Interestingly, metformin, unlike most older drugs, would comply with FDA requirements (i.e. OR < 1 with upper confidence limit <1.3 for major cardiovascular events).

The prevention of cardiovascular disease in type 2 diabetic patients requires an accurate glycaemic control [1–5]. Considering that the reduction of HbA1c is effective in the prevention of myocardial infarction [27–29], blood glucose should be maintained as close to normal as possible. An aggressive approach to hyperglycaemia in type 2 diabetes is limited by the side effects of pharmacological treatments, such as weight increase and hypoglycaemia [30], which could have a detrimental effect on cardiovascular mortality [27]. Metformin, which provides sustained glucose control with low hypoglycaemic risk, is a very interesting approach for cardiovascular protection. Although this drug does not appear to have additional beneficial actions on cardiovascular events beyond those determined by the improvement of glucose control, the present meta-analysis excludes any adverse effect of metformin on cardiovascular morbidity and mortality. Considering its safety, low cost and possible effects on other, non-cardiovascular endpoints, such as malignancies [31], the use of metformin as first-line agent in type 2 diabetes appears to be completely justified.

Conflict of Interest

The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. C. L. has received consultancy fees from Eli Lilly, research grants from Eli Lilly, and speaking fees from Eli Lilly, Novo Nordisk and Sanofi-Aventis. M. M. has received speaking fees from Eli Lilly MSD, Guidotti and Sanofi-Aventis. N. M. has received speaking fees from Eli Lilly, Novo Nordisk and Sanofi-Aventis, and research grants from Eli Lilly, Novo Nordisk and Sanofi-Aventis. E. M. has received consultancy fees from Eli Lilly and Novo Nordisk, speaking fees from Eli Lilly, MSD, Guidotti, Novartis, Astra Zeneca, Novo Nordisk and Sanofi-Aventis, and research grants from Eli Lilly, Novo Nordisk and Sanofi-Aventis. M. M. and E. M. designed the study and did analysis. C. L., M. M. and E. M. did data collection. C. L., M. M., N. M. and E. M. wrote the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Checklist of items to include when reporting a systematic review or meta-analysis.

Table S2. Characteristics of included randomized clinical trials.

Appendix S1. List of references.

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