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ANALYSIS

Metformin as firstline treatment for type 2 diabetes: are we sure?

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Abstract

Rémy Boussageon and colleagues ask whether metformin is bringing practical benefit to patients and question the focus on surrogate measures

Metformin is recommended as the first glucose lowering treatment for people with type 2 diabetes.[1] The recommendation is based on the supposedly conclusive results of the UK Prospective Diabetes Study (UKPDS 34) published in 1998.[2] The study found a reduction in 10 year mortality from any cause (relative risk 0.64, 95% confidence interval 0.45 to 0.91), and myocardial infarction (0.61, 95% CI 0.41 to 0.89). The number needed to treat to avoid one death was 14 and the absolute risk reduction was 0.07. However, these impressive results were obtained in a randomised subgroup of obese patients (342 patients in the metformin group and 411 in the conventional group) and have never been reproduced.[3] From a scientific point of view, the reproducibility of results is an essential validity criterion. Meta-analyses of randomised controlled trials evaluating the effectiveness of metformin in patients with type 2 diabetes found that metformin did not significantly modify clinically relevant outcomes (table 1⇓).[4 5] The analysis of all types of trial shows no efficacy of metformin at all.

Risk of bias in UKPDS

Methodological shortcomings in UKPDS could have led to bias in the metformin result (table 2⇓).[6 7] The diabetologist David Nathan noted in an editorial published to accompany the study that the "finding should be accepted cautiously."[7] Indeed, UKPDS 34 found a significant 60% higher death rate in patients given metformin plus sulfonylurea compared with those given sulfonylurea alone (1.60, 1.02 to 2.52). This surprising result was attributed to chance,[2] raising the question why positive results for metformin have been given credence and cited so copiously by the medical community while the increased risk of death observed for sulfonylurea plus metformin has been widely overlooked. It may be an example of the biased knowledge created by excessively citing a positive result.[8] Both our meta-analysis and that by Lamanna and colleagues found an additional risk when metformin was added to sulfonylureas (table 3⇓).[4 9]

There are several reasons why bias might have occurred. The study was not double blinded, and no placebo was administered to the control group. This could result in problems such as differing approaches to treatment, concomitantly administered treatments, and divergent outcome assessments. It is known that studies without double blinding have a general tendency to overestimate the efficacy of study treatments.[10] This may have been exacerbated by the fact that concealment of allocation was not guaranteed. When a randomisation sequence does not remain secret, the results can be overestimated by as much as 40%.[11]

The concluding publication[12] indicates that a significance threshold of 1% was initially chosen (P< 0.01). This was changed after the 1987 analysis to 5% (P<0.05) for the three main composite criteria. The positive results achieved with metformin for total mortality and myocardial infarction in UKPDS 34[2] are above the initial threshold (P=0.017 and P=0.011, respectively). Changing the significance values during the study increases the probability that the results are due to chance alone. Multiple analyses and alpha risk inflation are also a problem that was not taken into account at the outset of the study.[13] With UKPDS 33 and 34, there were more than 100 statistical analyses.[2 12] As chance alone will give a positive result in 5/100 tests at 5% significance and 1/100 at 1% significance, the possibility of the metformin result being down to chance cannot be ruled out.

Lastly, given the long follow-up, it would have been important to make sure that comparability between the two groups was maintained throughout the open label study. Identical management of cardiovascular factors, such as antihypertensive treatment and aspirin is especially important because there is evidence that these treatments reduce diabetic complications (such as myocardial infarction).[14] For example in UKPDS 33, at six year follow-up, the mean blood pressure in the chlorpropamide treated group was much higher than in other

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groups (143/82 mm Hg *v* 138/80 mm Hg, P<0.001).[12] The authors emphasised that 43% were getting antihypertensive treatment in the chlorpropamide group compared with 34%, 36%, and 38% in other groups (lifestyle and diet, glibenclamide, and insulin, respectively, P=0.022). Details on concomitant treatments received by the study participants in UKPDS have not been published despite the need for this information being highlighted.[15 16] We therefore cannot be sure that the results are not related to concomitant treatments rather than intensive glycaemic control.[14]

Is UKPDS 10 year follow-up report reliable?

Ten years after the main publication, a follow-up report of UKPDS patients was published.[17] This reported a significant beneficial effect in all groups (sulfonylureas, insulin, or metformin) for total mortality and cardiovascular mortality, leading the medical community to use the terms "glycaemic memory" or "legacy effect." Glycaemic memory refers to the putative long term effect of intensive early glucose control and highlights the need to prescribe suitable drugs as soon as type 2 diabetes is diagnosed. However, this report is subject to attrition bias (1525 (36%) of the 4209 randomised patients were analysed[17]) in addition to the biases described above and should be interpreted with caution. The level of evidence is similar to that for an observational study, and the results need to be confirmed.

What are we to think of these data?

It is not possible to draw a definitive conclusion regarding the efficacy of metformin on clinically important outcomes because of the lack of adequately designed randomised clinical trials. An insufficient statistical power to identify a significant effect is one possible explanation, but inefficacy of metformin is another possibility deserving examination.

Metformin belongs to the biguanide class. The first molecule of this class, phenformin, was shown to increased cardiovascular risk in a double blind randomised controlled trial against placebo.[18] Pharmacologically, there are few differences between metformin and phenformin and they might therefore be expected to have similar cardiovascular effects.[19]

If the main aim of treating type 2 diabetes is glycaemic control, then metformin has probably the best benefit:risk ratio because of its favourable safety profile even in the presence of renal disease.[20-24] The frequency of lactic acidosis in patients taking metformin, for example, is very low, estimated at 2.3/100 000 patient years.[23] However, if metformin is ineffective in reducing clinically important outcomes these adverse effects should be taken into account because patients could be subject to unnecessary harm. We need rigorous assessment of all antidiabetic medications using patient relevant outcomes rather than the surrogate markers such as glycated haemoglobin concentrations. Simply showing non-inferiority compared with placebo, as observed in I-DPP4 evaluation,[25] is not sufficient or ethically acceptable, given the absence of proof of clinical efficacy of antidiabetic drugs.[26] The significant results for total mortality and cardiovascular mortality observed in the recent EMPAREG study,[27] which compared empagliflozin with placebo, open new perspectives. The box outlines a suggested trial that would provide better evidence on glucose lowering drugs. Although the safety profile of metformin is good, given its widespread use in type 2 diabetes, we should have unambiguous proof that it is more clinically effective than managing cardiovascular risk with angiotensin converting enzyme inhibitors and statins.

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Contributors and sources: This article is the result of joint discussions conducted by three authors on the effectiveness of antidiabetic drugs in type 2 diabetes. RM is experienced in meta-analysis, especially in glucose lowering drugs. FG is experienced in pharmacology and evidence based medicine and has done several meta-analyses. CC is an endocrinologist and is experienced in meta-analysis. She is a former member of a health authority working group on glucose lowering drugs in type 2 diabetes. All authors contributed to study conceptualisation and design, data collection, and analysis. RM drafted the manuscript, which was revised by FG and CC. All authors approved the final manuscript.

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A big and beautiful trial for glucose lowering drugs in type 2 diabetes

Clinically relevant research questions—Is a drug strategy better than no drug at all, in addition to diet and exercise and appropriate cardiovascular risk management with angiotensin converting enzyme (ACE-1) inhibitors and statins? Is one drug class better than the others as initial treatment?

Adequate management of cardiovascular risk factors—Treatment with ACE-I and statins (high level of evidence)

Clinically relevant outcomes—A composite of cardiovascular death, myocardial infarction, stroke, heart failure, and symptoms affecting quality of life such as peripheral neuropathy requiring analgesics, significant vision alteration, renal death

Double blind design—With appropriate measures such as central biological follow-up to prevent follow-up and assessment biases

Adequate follow-up duration—The event rate in this population could be expected to be 10-15% after five years

Adequate statistical power—Between 5000 and 10 000 participants needed to show a 15% relative risk reduction for one comparison

Key messages

Metformin has been considered the best firstline drug for type 2 diabetes since 1998

The UKPDS 34 study, on which the recommendation is based, had some methodological flaws

No placebo controlled trial has unambiguously shown that metformin reduces microvascular and macrovascular complications

Better clinical evidence is needed to guide use of metformin and other antidiabetic drugs

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Tables

Table 1| **Table 1 Results of meta-analysis of randomised trials of metformin in type 2 diabetes**[6]

Outcome of interest	No in each group		Relative risk (95% CI)
	Metformin	Control	
Total mortality	252/9338	211/3502	0.99 (0.75 to 1.31)
Cardiovascular mortality	163/9167	215/3268	1.05 (0.67 to 1.64)
Myocardial infarction	193/8701	176/2854	0.90 (0.74 to 1.09)
Stroke	57/8033	47/2379	0.76 (0.51 to 1.14)
Heart failure	74/8033	36/2379	1.03 (0.67 to 1.59)
Peripheral vascular disease	15/806	18/874	0.90 (0.46 to 1.78)
Leg amputation	10/806	11/874	1.04 (0.44 to 2.44)
Microvascular complications	54/806	71/873	0.83 (0.59 to 1.17)

Table 2| **Table 2 Cochrane risk of bias assessment for UKPDS study**

Bias	Risk
Random sequence generation (selection bias)	Low
Allocation concealment (selection bias)	Unclear
Blinding of participants and personnel (performance bias)	High
Blinding of outcome assessment (detection bias)	High
Incomplete outcome data (attrition bias)	Low
Selective reporting (reporting bias)	Unclear
Other bias	High

Table 3| **Table 3 Risk ratio of treatment of type 2 diabetes with metformin and sulfonylureas versus sulfonylureas alone**

Meta-analysis	No of included studies	No of participants (metformin + sulfonylurea *v* sulfonylurea)	Total mortality (95% CI)	Cardiovascular mortality (95% CI)
Boussageon et al[4]	3	974 *v* 793	RR=1.53 (1.02 to 2.31)	RR=2.20 (1.20 to 4.03)
Lamanna et al[9]	2	Not reported	MH OR=1.43 (1.07 to 1.92)	Not reported

RR=relative risk, MH OR=Mantel-Haenszel odds ratio.