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Editorial

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Metformin in type 2 diabetes: where is the evidence?

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Taking into consideration the main evidence available in 2015, Boussageon contest the status of metformin as the first -line treatment for DT2 patients. He contends that as regards macrovascular and microvascular complications, its efficacy has never been proven in a double-blind RCT. This observation leads to a more general interrogation on how anti-diabetes medication is to be assessed.

Key messages

Ever since the results of the UK Prospective Diabetes Study (UKPDS) 34 were published in 1998, metformin has been considered as the first-line pharmacological treatment for type 2 diabetes.

However, from several standpoints the UKPDS was methodologically questionable. The effectiveness of metformin with regard to microvascular and macrovascular complications has never been proven in a randomized double-blind placebo-controlled clinical trial.

And upon analysis of published randomized clinical trials taken as a whole, it becomes increasingly apparent that the effectiveness of metformin has not been proven, even when microvascular complications are involved.

This observation leads to a more general interrogation on the fact that assessment of the clinical benefits of antidiabetic medication in general is presently lacking.

Has the effectiveness of metformin actually been proven?

Metformin is an oral antidiabetic drug (OAD) in the biguanide class [1]. It is the recommended first-line treatment for type 2 diabetes (DT2) patients [2]. Its efficacy was supposedly conclusively demonstrated in the UKPDS 34 study published in 1998 (reduction in mortality: RR=0.64; CI 95% (0.45 to 0.91) and in myocardial infarction: RR=0.61; CI 95% (0.41 to 0.89) [3]. However, these rather impressive results regarding total 10 year mortality (ARR=0.07; NNT=14) in a small subgroup of obese type 2 diabetes patients (342 in the metformin group vs. 411 patients in the conventional group) have never been reproduced [4]. For instance, the home study [5] evaluated the efficacy of metformin versus placebo (in addition to insulin). After four years of follow-up, no statistically significant difference was found for total mortality: RR=1.48; CI 95% (0.54 to 4.09) or for IDM: RR=0.99; CI 95% (0.25 to 3.90). Taking into account all the other randomized clinical trials (RCTs) having evaluated the specific effectiveness of metformin in DT2 patients [6], it becomes evident that metformin has not significantly modified total mortality: RR=0.99; CI 95% (0.75 to 1.31), cardiovascular mortality: RR = 1.05; CI 95% (0.67 to 1.64), IDM occurrence: RR=0.90; CI95% (0.74 to 1.09), cerebrovascular accidents: RR=0.76; CI95% (0.51 to 1.14), cardiac insufficiency: RR=1.03; CI 95% (0.67 to 1.59), peripheral vascular events: RR=0.90; CI 95% (0.46 to 1.78), lower limb amputations: RR=1.04; CI 95% (0.44 to 2.44) or microvascular complications: RR=0.83; CI95% (0.59 to 1.17). Once an analysis without selection bias has been carried out, it becomes apparent that on the basis of clinical criteria, the efficacy of metformin has not been proven; in science, the reproducibility of results remains an essential validity criterion.

The dark side of UKPDS

In point of fact, the benefit imputed to metformin is quite possibly related to biases in the UKPDS, which is not without methodological shortcomings [7-9]. As it was written by the diabetologist David M Nathan in an editorial with regard to publication of the results of the UKPDS pertaining to metformin, "This finding should be accepted cautiously" [9]. Indeed, in the same study an abnormally high death rate was found in the metformin plus hypoglycemic sulfamides association vs. sulfamides alone: RR=1.60; CI 95% (1.02 to 2.52). In the final analysis, however, this

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astonishing result was attributed to chance, prompting the following questions: Why have only the positive results in favor of metformin been given credence and so copiously cited by the medical community, while the elevated risk of death observed in conjunction with the sulfamides-metformin association has been widely overlooked? If the favorable UKPDS34 results are deemed valid, then why are the unfavorable results considered as coincidental? It may be an example of the biased knowledge created by excessively citing a positive result [10]. It should be noted that in both our meta-analysis [6] and in the meta-analysis authored by Lamanna et al., this additional risk has been found to exist [11].

Here are some of the methodological problems presented in the UKPDS: (i) Firstly, the study was not double-blinded, and no placebo was administered to the control group. Its objective did not consist in assessing the efficacy specific to metformin. As a result, the study was not exempted from the biases that might occur subsequent to randomization such as differing approaches to treatment, concomitantly administered treatments, divergent assessments. It is well-known when double blinding is not applied, there is a general tendency to overestimate the efficacy of treatments under evaluation [12]; (ii) Secondly, the randomization procedure was inadequately described. Given the lack of double-blind testing, randomization is the one and only procedure likely to avoid selection bias and to guarantee the initial comparability of the groups. When a randomization sequence does not remain secret, the results can be overestimated by as much as 40% [13]; (iii) Thirdly, according to a text published in 1984 [14], the study was scheduled for completion in 1992. In 1987, 10 years after the beginning of the study, there existed no statistical difference between the intensive treatment and conventional treatment of the initial subjects with a 1% alpha risk [15]. Interim analysis led to inclusion of a larger number of patients (inclusion of 826 supplementary subjects) so as to increase the statistical power of the study. It should be pointed out that their inclusion was not envisioned in the protocol, and that it was decided upon due to the just-mentioned absence of significant difference between the two groups [15]; (iv) Fourthly, in the concluding publication [15] we learn that while a threshold of 1% was initially chosen, subsequent to the 1987 analysis it was heightened to 5% for the 3 main composite criteria. As a result, the positive results achieved with metformin for total mortality and myocardial infarction in the UKPDS 34 [3] are significant only at the threshold of 5%, and not at the threshold of 1% (respectively $p=0.017$ and $p=0.011$); (v) Another major problem pertains to the multiple analyses and particularly to alpha risk inflation, which was not taken into account at the outset of the study [16]. With UKPDS 33 [15] and 34 [3], there were more than 100 statistical studies. As chance alone can entail on the average 5 significant tests at 5% and 1 significant test at 1% out of every 100 tests performed, couldn't chance likewise explain the favorable results ascribed to metformin? (vi) Lastly, given the protracted duration of follow-up, it would have been important to make sure that comparability between the two groups had been maintained throughout the study, which, rather importantly, was an open study. Was the dietary regimen identically respected [17]? Did management of cardiovascular factors remain identical, particularly with regard to antihypertensive treatment and statin administration, which can be effective in the event of diabetic complications [18]? Details on concomitant treatments received by the study participants in the UKPDS have not been published. The authors of the UKPDS ten year follow-up did not provide any explanations [19]. Might the results observed in the UKPDS 33 and 34 be related to more possible concomitant treatments than to the intensive glycemic control strategy [18]?

Is the UKPDS [20] follow-up report reliable?

Ten years after the main publication, a follow-up report of UKPDS patients was published [20]. A beneficial effect was reported in all groups on significant outcome measures such as total mortality and cardiovascular mortality. These results impelled the medical community to employ the term "glycemic memory" or "legacy effect", which represents the long-term effect of intensive early glucose control and underscores the need to prescribe suitable drugs as soon as T2D is diagnosed. These results need to be confirmed since they do not have a high level of evidence, similar to what is observed in an observational study. Considering the methodological flaws of the UKPDS (only 1525 of the 4209 randomized patients, that is to say 36% of those initially included in the study were analyzed, lack of blinding, multiple outcome measures added during the study), caution is indeed called for.

What are we to think of these data?

Obviously enough, the limited number of presently available randomized clinical trials (RCTs) does not allow us to draw any definitive conclusion in the actual effects of metformin. While a lack of statistical power likely to highlight a significant effect is one possible explanation, the actual inefficacy of metformin is another possibility deserving examination. Metformin belongs to the biguanide class of drugs. The first molecule of this class, phenformin, induced increased cardiovascular risk in the UGDP study, which was a double-blind, randomised controlled trial versus placebo. And pharmacologically speaking, there are few differences between metformin and phenformin [1]. Phenformin is monosubstituated by a longer side chain than metformin, thereby conferring it with lipophilic characteristics, a greater affinity for the mitochondrial membranes and an inhibitory effect on the functioning of the mitochondrial respiratory chain. While these small molecular differences may explain a decreased risk of lactic acidosis with metformin [1], do they suffice to explain the only favourable results observed in the UKPDS34 subgroup?

If metformin were to be lacking in effectiveness, this would be extremely detrimental for all the type 2 diabetes patients to whom it has been administered as the first-line pharmacological treatment [2]. It could be responsible for serious adverse reactions such as lactic acidosis, especially in the event of acute renal insufficiency [21] and vitamin B12 deficiency, as was clearly shown in the HOME study [22].

Moreover, glycemic control has little effect on cardiovascular events [23]. On the other hand, it is of

recognized effectiveness with regard to microvascular complications. But in that case, why favor metformin as first-line treatment, as it not brought about reduction of these events or complications, either in the UKPDS 34 [3] or in méta-analysis [6]?

To conclude, if the level of evidence concerning the efficacy of metformin is poor, and given the fact that it is proposed as first-line treatment, what are we to think of the other antidiabetic medicines? If metformin is no longer the treatment of reference, then it is pharmacological treatment of DT2, taken as a whole, that needs to be reevaluated. Indeed, it is high time to rigorously reassess antidiabetic medication on the basis not of the so-called surrogate HbA1c, but rather according to patient-relevant outcomes. Is demonstration of cardiovascular safety (and of "non-inferiority to the placebo"!), as is observed in I-DPP4 evaluation [24], sufficient and ethically acceptable, given the absence of proof of the clinical efficacy of antidiabetic medication [25]?

Conflicts of interest

Author declares no conflicts of interest.

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