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Review

Effects of pharmacological treatments on micro- and macrovascular complications of type 2 diabetes: What is the level of evidence?

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Abstract

Antidiabetic drugs for type 2 diabetes receive marketing authorization if they show efficacy in reducing levels of HbA_{1c}. However, efficacy on this biological criterion does not necessarily reflect clinical benefit to patients. Several randomized clinical trials have shown that antidiabetic drugs reduce HbA_{1c} without a corresponding reduction in clinical events. This suggests a need to focus on the clinical effectiveness (morbimortality criteria) of our available antidiabetic drugs. In this non-extensive review of the literature, it was found that none of the current antidiabetic drugs have clearly proven their superiority over placebo in the gold standard double-blind randomized clinical trials. Thus, in 2013, the level of evidence for the clinical efficacy of antidiabetic drugs is disappointing and does not support the millions of prescriptions being written for them.

Keywords: Antidiabetic drugs; Type 2 diabetes; Clinical efficacy; Level of evidence

1. Introduction

The treatment of type 2 diabetes (T2D) is based on a seemingly simple principle. Observational studies have shown that hyperglycemia is a risk factor for excess mortality, cardiovascular events and microvascular complications [1]. It therefore appears logical that T2D patients would benefit from any treatment reducing hyperglycemia, and any drug with proven efficacy on the intermediate outcome of lowering HbA_{1c} may be considered efficacious at preventing the clinical complications of T2D. Indeed, the US Food and Drug Administration (FDA) now approves marketing authorizations for new antidiabetic drugs if they reduce HbA_{1c} and show an excess relative risk of cardiovascular events that is clearly < 80% (upper limit of the confidence interval, or CI) [2]. On this basis, several new antidiabetic drugs have received marketing authorization, such as the dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide (GLP)-1 analogues, and even new insulins and insulin analogues.

HbA_{1c} has, until now, been considered a reliable surrogate outcome despite the lack of any formal demonstration in randomized controlled trials (RCTs) using relevant clinical outcomes (such as morbimortality criteria). However, this should probably now be questioned. Several randomized trials with a high level of evidence have disproved the idea that reducing HbA_{1c} is beneficial for patients with T2D [3–5]. There was an increased all-cause and cardiovascular mortality (which led to premature termination of the study) in patients receiving intensified treatment in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [3] trial, even though their HbA_{1c} levels were lowered by 1.1% on average. In the Veterans Affairs Diabetes Trial (VADT) [4], there was a difference of 1.5% in HbA_{1c} values between the two groups throughout the follow-up (6.9% vs 8.4%), yet no differences were observed in total mortality [risk ratio (RR) = 1.08; 95% CI: 0.83–1.41], cardiovascular mortality (RR = 1.22; 95% CI: 0.78–1.92) and non-fatal myocardial infarctions (RR = 0.78; 95% CI: 0.55–1.11). Benfluorex, rosiglitazone and pioglitazone were recently removed from the French marketplace, even though they reduce HbA_{1c}. The reason was that no convincing reduction in morbimortality factors was seen with these drugs. Also, whenever serious

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side effects were reported, their benefit/risk ratios were likely to become negative.

In the present brief review, our primary focus was on RCTs and meta-analyses evaluating the efficacy of the main antidiabetic drugs currently available in France on the basis of clinically relevant criteria.

2. Metformin

Metformin, an oral antidiabetic drug (OAD) of the biguanide class, is considered a first-line intervention for patients with T2D [6]. The efficacy of metformin vs diet showed statistical significance for all-cause mortality (RR = 0.64, 95% CI: 0.45–0.91) and prevention of myocardial infarction (RR = 0.61, 95% CI: 0.41–0.89) in the United Kingdom Prospective Diabetes Study (UKPDS) 34 published in 1998 [7]. However, even though this trial was randomized, it did not compare metformin with placebo and it was not double blind; moreover, the aim of UKPDS 34 was not to assess the efficacy of metformin. As diabetologist David M. Nathan wrote in the editorial on publishing the results of UKPDS 34 on metformin [8], "These findings should be accepted cautiously".

In fact, the positive results of UKPDS 34 are considered factual and have been cited many times, yet they have never been reproduced. Another study, "Hyperinsulinemia: the outcome of its metabolic effects (HOME) [9] trial", assessed the efficacy of metformin vs placebo (on top of insulin). After 4 years of follow-up, no statistically significant difference was observed for either all-cause mortality (RR = 1.48, 95% CI: 0.54–4.09) or myocardial infarction (RR = 0.99, 95% CI: 0.25–3.90). The HOME trial differed from the UKPDS by many ways but, in science, it is the reproducibility of results that is the major criterion of validation. Moreover, the UKPDS 34 observed excess mortality with the combination of metformin plus sulphonylurea vs sulphonylurea alone (RR = 1.60, 95% CI: 1.02–2.52). In the absence of pharmacological interaction, this result could only have been due to the specific effect of metformin. Yet, it was considered an artifact and removed from the collective conscience—indeed, the combination is even recommended in guidelines [6].

If the results of UKPDS 34 are valid, how is it that the negative results of the combination of metformin and sulphonylurea are considered due to chance? A recent systematic review and meta-analysis of RCTs assessed the efficacy of metformin in patients with T2D, and included 13 RCTs (two of which were designed to assess the safety of metformin) with 15 comparisons and a total of 13,110 patients [10]. Of these patients, 9560 received metformin while 3550 received other conventional treatments. Metformin failed to significantly influence several important patient outcomes:

- all-cause mortality (RR = 0.99, 95% CI: 0.75–1.31);
- cardiovascular mortality (RR = 1.05, 95% CI: 0.67–1.64);
- all myocardial infarctions (RR = 0.90, 95% CI: 0.74–1.09);
- all strokes (RR = 0.76, 95% CI: 0.51–1.14);
- heart failure (RR = 1.03, 95% CI: 0.67–1.59);
- peripheral vascular events (RR = 0.90, 95% CI: 0.46–1.78);
- amputations of a lower extremity (RR = 1.04, 95% CI: 0.44–2.44);
- microvascular complications (RR = 0.83, 95% CI: 0.59–1.17).

Significant heterogeneity was observed in a meta-analysis for all-cause mortality and cardiovascular mortality ($P = 0.10$, $I^2 = 41\%$ and $P = 0.02$, $I^2 = 59\%$, respectively). This was mainly due to the inclusion of two subgroups from UKPDS 34 (metformin vs diet alone and the metformin–sulphonylurea combination vs sulphonylurea alone). The meta-analysis also confirmed the excess risk associated with the combination of sulphonylurea and metformin vs sulphonylurea on its own (all-cause mortality: RR = 1.55, 95% CI: 1.03–2.33), which was consistent with the results of another meta-analysis by Lamanna et al. [11] [all-cause mortality: Mantel–Haenszel odds ratio (MH OR) = 1.432, 95% CI: 1.068–1.918; $P = 0.016$].

The Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus With Coronary Artery Disease (SPREADDIMCAD) [12], a recent RCT that included 304 patients with T2D and coronary artery disease in secondary prevention, showed a reduction in the main composite outcome (all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke and arterial revascularization) on comparing metformin with glipizide [hazard ratio (HR) = 0.54, 95% CI: 0.30–0.90; $P = 0.02$] after a 5-year follow-up. This was the first study designed to compare metformin with sulphonylurea as regards cardiovascular outcomes, but its results failed to demonstrate that metformin is efficacious. Its data are reported from the end of the 5-year follow-up period—in other words, 2 years after stopping the intervention. However, no protocol for the trial is available to allow clarification of whether the decision not to report results at the end of the interventional period was predefined, nor is this information reported on the clinicaltrials.gov website.

The ADOPT (A Diabetes Outcome Progression Trial) [13] included 1400 patients divided into three treatment groups, and the primary outcome was intervention failure. After 4 years of follow-up, there was no significant difference, according to clinical criteria, between the patient groups treated with metformin and with glyburide. Although fewer serious cardiovascular disease (CVD) events were observed in the glyburide than in the metformin arm (RR = 0.57, 95% CI: 0.35–0.92; $P = 0.02$), the number of CVD events was similar for metformin and rosiglitazone [13].

This indicates that, thus far, the clinical efficacy of metformin has not been formally established.

3. Sulphonylurea

Patient-relevant outcomes with sulphonylurea have been evaluated in two trials: the University Group Diabetes Program (UGDP) [14] and UKPDS 33 [15]. The UGDP showed excess mortality in patients treated with tolbutamide compared with a placebo [14]. This was the first hypoglycemic sulphonylurea prescribed for patients with T2D, but it turned