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 HbA1c. However, efficacy on this biological criterion does not necessarily reflect clinical benefit to patients. Several randomized clinical trials have shown that antidiabetic drugs reduce HbA1c, 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. © 2014 Elsevier Masson SAS. All rights reserved.

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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 HbA1c 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 HbA1c 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.

HbA1c 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 HbA1c 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 HbA1c levels were lowered by 1.1% on average. In the Veterans Affairs Diabetes Trial (VADT) [4], there was a difference of 1.5% in HbA1c 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 HbA1c. The reason was that no convincing reduction in morbimortality factors was seen with these drugs. Also, whenever serious
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, I²=41% and P = 0.02, I²=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 intervention 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 tobutamide compared with a placebo [14]. This was the first hypoglycemic sulphonylurea prescribed for patients with T2D, but it turned
out to be more harmful than beneficial. The UKPDS 33 [15] initiated in 1978, the main results of which were published in 1998, was an open trial evaluating the effect of a therapeutic pharmaceutical strategy (sulphonylurea, insulin and metformin) targeting fasting glycaemia <6 mmol/L compared with lifestyle changes targeting fasting glycaemia <15 mmol/L. In 1987, after 10 years of follow-up, no difference between the two groups was observed, so the researchers decided to continue the study after including more patients. Also, another outcome measure—retinal photocoagulation—was added in 1991 [16]. For normal-weight patients when the results in subgroups treated with chlorpropamide and glibenclamide were compared with health-related and dietary changes, the sulphonylureas had reduced no mortality or diabetes-related complications except for retinal photocoagulation, with a risk reduction of 37% (RR = 0.63, 99% CI: 0.40–1.00 with glibenclamide). However, the risk of hypoglycaemia was doubled by glibenclamide (1.4% vs 0.7% per year with lifestyle changes).

Two recent meta-analyses of sulphonylurea in randomized trials also showed no clinical efficacy [17,18], and one of the studies even suggested cardiovascular toxicity [18]. The conclusion by the authors of the Cochrane meta-analysis [17] was clear: “There is insufficient evidence from RCTs to support the decision as to whether to initiate sulphonylurea monotherapy. Data on patient-important outcomes are lacking. Therefore, large-scale and long-term randomized clinical trials with low risk of bias, focusing on patient-important outcomes, are required”. Thus, the benefit/risk ratio with sulphonylureas is still not clear in terms of the prevention of micro- and macrovascular complications of T2D.

4. Insulin therapy

The efficacy of insulin was only evaluated using relevant clinical criteria in the UKPDS 33 [15]. After a 10-year (on average) follow-up and compared with lifestyle changes, insulin therapy failed to reduce either mortality or diabetes-related complications except for retinal photocoagulation, with a decreased risk of 33% (RR = 0.67, 99% CI: 0.45–0.99). In comparison, the risk of insulin-induced hypoglycaemia (1.8% vs 0.7% per year with lifestyle changes) was increased by 130%.

Thus, in 2013, there is still no strong evidence that insulin reduces mortality or any other clinically relevant criteria in patients with T2D [19]. Three recent mega-trials—the ACCORD [3], VADT [4] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [5]—showed that insulin use frequently achieved glycemic targets. However, none of these studies found any effect on patient-relevant outcomes, whereas excess mortality was observed in the ACCORD trial [3]. In fact, the efficacy of insulin was based on the reduction in the number of retinal photocoagulations in UKPDS 33 [15], a criterion that was added during the study 4 years after an inconclusive intermediary analysis [16], and in an open study.

5. Ten-year follow-up of the UKPDS

Ten years after the main report was published, a follow-up report of the UKPDS patients was published [20]. A beneficial effect was found in all groups for significant outcome measures such as total and cardiovascular mortality. These results pushed the medical community towards the concept of “glycemic memory”, or the “legacy effect”—the effect of anti-diabetic treatments over the long term and, thus, the need to prescribe them as soon as T2D is diagnosed. However, these results still need to be confirmed, as they do not have a high level of evidence, but are similar to those found in an observational study. Given the methodological flaws of the UKPDS (its huge attrition bias, with only 78% of the patients initially included being analyzed; the absence of blinding; and multiple outcome measures added during the study), its findings should be considered only with caution [8,16,21].

6. Alpha-glucosidase inhibitors

The efficacy of these agents was evaluated in 2006 in a Cochrane meta-analysis of patients with T2D [22] that included the UKPDS 44 [23], a large double-blind placebo-controlled trial of nearly 1000 patients. After a 3-year follow-up, the alpha-glucosidase inhibitors were not superior to acarbose and, therefore, the Cochrane authors concluded that there was no evidence of clinical efficacy with these inhibitors [22]. On the other hand, earlier meta-analysis had shown a strikingly marked effect of acarbose especially in reducing the risk of myocardial infarction (HR = 0.36, 95% CI: 0.16–0.89) [24]. However, that systematic review involved limited bibliographical research and a vague methodology, and did not specify its inclusion methods and criteria. It included only seven RCTs and excluded the UKPDS 44 study [23]. The results were mainly derived from the Study to Prevent NIDDM (STOP-NIDDM) [25], which included patients with glucose intolerance. As a consequence, the efficacy of acarbose was not properly demonstrated. The Acarbose Cardiovascular Evaluation (ACE) trial [26] is currently being conducted in Asia and is expected to lead to a final conclusion. The results on the clinical efficacy of acarbose should be available in 2014, nearly 10 years after it was first marketed—and widely prescribed.

7. Incretins

7.1. Dipeptidyl peptidase-4 inhibitors (DPP4-I)

The results of two large RCTs—the SAVOR-TIMI 53 [27] (for saxagliptin) and the Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) [28]—were published in September 2013. Before that, three meta-analyses of RCTs had reported on the efficacy of DPP4-I vs placebo based on clinical criteria [29–31]. The first showed no greater cardiovascular risk with these drugs [29]—“Risk of adverse CV events with DPP4 inhibitor therapy was not significantly different compared to placebo (RR = 1.05, 95% CI 0.39 to 2.82, P = 0.92)—whereas
the second [30] and third studies [31], carried out by the same team, found a reduction in the risk of major adverse cardiovascular events (MACEs; MH OR = 0.689, 95% CI: 0.528–0.899; $P = 0.006$) and a reduction in total mortality (MH OR = 0.60, 95% CI: 0.41–0.88) [31]. However, the results of the SAVOR-TIMI 53 [27] and EXAMINE [28] trials refute these findings from meta-analyses of small trials, again providing proof that large-scale well-conducted clinical trials are needed to properly evaluate the efficacy of treatments.

The SAVOR-TIMI 53 trial [27] assessed the effect of saxagliptin in 16,492 patients with T2D over an average of 10 years (initial HbA1c: 8%). A total of 8280 patients took saxagliptin vs 8212 who took a placebo. This study evaluated both the non-inferiority of saxagliptin vs placebo (as requested by the US FDA) and its superiority given the size of the study. After 2 years of follow-up, there was no evidence of clinical efficacy with saxagliptin according to the main endpoints (cardiovascular death, myocardial infarction or stroke: RR = 1.00, 95% CI: 0.89–1.12). Furthermore, saxagliptin failed to reduce total mortality (RR = 1.11, 95% CI: 0.96–1.27) or any other important criterion such as myocardial infarction or stroke. However, the risk of hospitalization for congestive heart failure rose unexpectedly (RR = 1.27, 95% CI: 1.07–1.51). There was also a statistically significant 14% increase in the risk of hypoglycemia in patients taking saxagliptin. Although these were secondary criteria, given the lack of proof of efficacy for other clinical criteria, the benefit/risk ratio of saxagliptin appears to be unfavorable at this time. There was, however, no increased risk of developing cardiovascular disorders, cancer or pancreatitis. Saxagliptin appeared to work for one biological criterion (microalbuminuria), but this did not constitute effectiveness according to ‘hard’ composite renal criteria (doubled creatinine, dialysis initiation, kidney transplantation, serum creatinine > 530 umol/L: RR = 1.08, 95% CI: 0.88–1.32).

The EXAMINE [28] evaluated alogliptin in 2701 patients with T2D for an average of 7 years (initial HbA1c: 8%) and

**Fig. 1.** Update of the Monami et al. [31] meta-analysis of randomized controlled trials (vs placebo): (A) all-cause mortality; (B) cardiovascular mortality; (C) all myocardial infarction; and (D) all stroke.
acute coronary syndrome over the previous 90 days vs patients taking a placebo (n = 2679). After an average follow-up of 18 months, this study showed that alogliptin had no better clinical efficacy on the main endpoint or on any other criteria, although the results for “hospitalization for heart failure” and microvascular criteria (retinopathy and neuropathy) were not mentioned, and any effect on nephropathy was not shown. However, hypoglycemia did not often arise in the group treated with alogliptin.
No significant difference was found as regards serious adverse effects.

Thus, these two major trials failed to demonstrate the clinical efficacy of DPP4-Is in the short term (1.5–2 years of follow-up), while an update of the Monami et al. [31] meta-analysis of RCTs vs placebo (SAVOR TIMI 53 [27] and EXAMINE [28], including >30,000 patients) showed no greater efficacy on major clinical cardiovascular criteria (Fig. 1A–D). Indeed, even a 10% reduction of total mortality can be excluded. This suggests that the benefit/risk ratio for DPP4-Is is still unfavorable until proven otherwise. Moreover, this type of “non-inferiority over placebo” trial does not allow any possible serious adverse effects to be measured over the long term.

7.2. Glucagon-like peptide analogues: exenatide and liraglutide

The effect of GLP-1 analogues on clinical criteria (major cardiovascular events) has also been reported in a meta-analysis [32], but failed to demonstrate either positive or negative effects: “The MH-OR for all GLP-1 receptor agonists was 0.74 (0.50–1.08), P = .12 (0.85 [0.50–1.45], P = .55, and 0.69 [0.40–1.22], P = .20, for exenatide and liraglutide, resp.).” But these results need to be interpreted with caution due to the lack of studies on long-term efficacy, with most lasting <26 weeks. This means that, at this time, no conclusions can be drawn on the clinical efficacy of GLP-1 analogues. However, considering the potential excess risk for developing acute pancreatitis [33] and pancreatic cancer [34], the benefit/risk ratio with GLP-1 analogues must be uncertain.

8. Conclusion

In 2013, the level of evidence for the clinical efficacy of OADs and insulin in patients with T2D is low. As double-blind RCTs using relevant (patient-centered) clinical criteria remain the gold standard, such efficacy has yet to be clearly demonstrated. Any benefit is currently hypothetical and relies on extrapolations from observational and pathophysiological data. Despite this, marketing authorizations are still being issued on the basis that they decrease levels of HbA1c. Yet, the hypothesis that HbA1c is an adequate surrogate marker for clinical outcomes in T2D should probably be questioned [35–37]. A good surrogate marker changes in parallel with the clinical outcome and predicts clinical benefit [38]. This situation is in contrast to other therapeutic domains wherein large-scale double-blind RCTs demonstrate efficacy on morbimortality criteria with proven links to the surrogate. As an example, blood pressure has been shown to predict to some extent the risk reduction of stroke, myocardial infarction and cardiovascular mortality through meta-regression of aggregate data [39], thereby explaining a significant part of stroke reduction due to treatment in models using individual patient data [40]. No such data can be produced for HbA1c, for which meta-regression proposes no relationship whatsoever (personal data).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data (French summary) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.12.010.

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