Review
Treatment of type 2 diabetes: New clinical studies and effects of GLP-1 on macrovascular complications

Traitement du diabète de type 2 : nouvelles études cliniques et effets du GLP-1 sur les complications macrovasculaires

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Résumé
Les publications de 2009 montrent que le traitement des patients ayant un diabète de type 2 (DT2) avec complications macrovasculaires est encore sujet à controverse, que ce soit pour l’utilisation des glitazones, ou pour la meilleure stratégie de prise en charge du patient DT2 coronarien stable ou pour l’utilisation des incrétino-mimétiques chez les patients atteints de pathologies cardiaques. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) a comparé la morbi-mortalité cardiovasculaire sous rosiglitazone en association à la metformine ou à un sulfamide hypoglycémiant versus metformine plus sulfamide hypoglycémiant. Les résultats de cette étude indiquent que la rosiglitazone n’est pas inférieure à l’association metformine-sulfamide en termes de mortalité et d’hospitalisation cardiovasculaire, mais l’interprétation de ces données doit être prudente dans le contexte d’une étude où le taux d’événements a été faible. Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) est un essai de morbi-mortalité cardiovasculaire dont le but était de déterminer la meilleure stratégie de contrôle glycémique et de revascularisation chez des patients DT2 avec coronaropathie stable. Les résultats suggèrent que la revascularisation précoce n’est pas clairement bénéfique, sauf dans un sous-groupe de patients relevant a priori d’une revascularisation chirurgicale. L’utilisation des analogues du Glucagon-Like Peptide-1 (GLP-1) à la phase aiguë, d’une ischémie myocardique sur des modèles animaux a donné des résultats prometteurs. Des études cliniques suggèrent également une amélioration des facteurs de risque cardiovasculaire avec ces traitements. Il faut attendre les résultats d’études de morbi-mortalité pour mieux juger de l’efficacité à long terme de ces nouvelles molécules.

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Mots clés : Diabète de type 2 ; Complications macrovasculaires ; BARI 2D ; RECORD ; GLP-1

Abstract
Various publications in 2009 showed that the treatment of type 2 diabetic (T2D) patients with macrovascular complications is still a controversial subject, whether with regard to the use of glitazones, to the best management strategy for T2D patients with stable coronary artery disease or to the use of incretin mimetic drugs in patients with heart disease. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes study (RECORD) compared cardiovascular morbidity-mortality outcomes in patients taking rosiglitazone in combination with metformin or sulfonylurea versus metformin with sulfonylurea. The results showed that rosiglitazone was not inferior to the metformin-sulfonylurea combination in terms of mortality and cardiovascular hospitalization, but caution must be used when interpreting the results, as the event rate was low. The BARI 2D study (Bypass Angioplasty Revascularization Investigation 2 Diabetes) is a cardiovascular morbidity-mortality trial with the goal of determining the best strategy for blood glucose control and revascularization in T2D patients with stable coronary artery disease. The results of this trial showed that early revascularization is not clearly beneficial, except in a subgroup of patients in whom surgical
revascularization is indicated. The use of GLP-1 analogs (Glucagon-Like Peptide-1) in the acute phase of myocardial ischemia in animal models provided promising results. Some clinical studies also suggest an improvement in cardiovascular risk factors with these treatments. Results from morbidity-mortality studies are needed to better assess the long-term efficiency of these new drugs.

Keywords: Type 2 diabetes; Macrovascular complications; BARI 2D; RECORD; GLP-1

1. Introduction

This article focuses on the macrovascular complications of type 2 diabetes data presented at the scientific session of the American Diabetes Association (ADA), held in New Orleans in June 2009. It reports on the results of the two morbidity-mortality studies, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D), as well as on the experimental and clinical data of the incretin mimetic class of antidiabetic drugs.

After the 2008 publication of the results of the large cardiovascular morbidity-mortality studies of Action in Diabetes and Vascular Disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) [1], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [2] and Veteran Administration Diabetes Trial (VADT) [3], two studies presented at the 2009 ADA scientific session and published shortly afterwards [4,5] received widespread attention. Diabetics are patients with high cardiovascular risk that require multifactorial management, for which the best strategy of blood glucose control is still being debated. The RECORD study [4] was highly awaited by endocrinologists regarding the safety of rosiglitazone, especially after the 2007 publication of the meta-analysis by Nissen and Wolski [6]. The BARI 2D study [5] attempted to respond to a question asked by both endocrinologists and cardiologists about the best treatment strategy for diabetic patients with stable coronary artery disease. In fact, as a cause of mortality in 65 to 80% of cases, cardiovascular complications are the main prognosis determinants of diabetes [7].

Moreover, the dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs may also have positive effects on cardiovascular status, in addition to their now well-documented beneficial effects on blood glucose control.

2. RECORD, a very anticipated study

2.1. 2007: the controversy over rosiglitazone

The thiazolidinediones, a group of drugs currently used in the treatment of type 2 diabetes, have stirred up a lot of attention since their marketing authorization in 2000. These drugs demonstrated their effectiveness on glycemic control but with significant side effects, such as heart failure. The two PPAR-gamma agonists, pioglitazone and rosiglitazone, are different essentially in their impact on lipid metabolism. Pioglitazone increases the level of HDL cholesterol and decreases the level of triglycerides, without modifying the total and LDL cholesterol levels, while rosiglitazone slightly increases LDL and total cholesterol levels without any effect on triglycerides [8].

With regard to the use of pioglitazone, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) secondary prevention morbidity-mortality trial [9], which was inconclusive for its primary composite cardiovascular endpoints, showed a reduction in the risk of death, myocardial infarction (MI) and stroke in the pioglitazone group. This was not the same with the use of rosiglitazone following the publication of the meta-analysis by Nissen and Wolski in 2007 [6]. This study, which considered 42 randomized trials, including the A Diabetes Outcome Progression Trial (ADOPT) [10] and Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) [11] studies, showed an increased risk of MI, with an odd ratio of 1.43 ($P = 0.03$), as well as a non-significant increase of cardiovascular mortality in the group of rosiglitazone-treated patients. However these trials, using very different protocols, were not designed to study cardiovascular morbidity-mortality, and recorded relatively low rate of events. Another meta-analysis, published in 2007, including four trials (three of which were versus an active comparator with a study duration longer than one year and with a majority of events that were adjudicated) also found an increased incidence of MI, with an odd ratio of 1.42 ($P = 0.02$) but without increased cardiovascular mortality in the group of patients receiving rosiglitazone [12].

2.2. 2009: RECORD: procedure and results

The results of the RECORD study were therefore highly anticipated at the ADA scientific session. This study, which began in 2001, compared the cardiovascular morbidity-mortality outcomes in patients treated with rosiglitazone in combination with metformin or sulfonylurea (rosiglitazone group) versus patients receiving metformin plus sulfonylurea (control group). The American and European health authorities required that to address the question of heart failure risk. This study involved 4,447 T2D patients, aged of 45 to 75 years, with a BMI higher than 25 kg/m², a HbA1c level between 7 and 9%, and no history of heart failure or cardiovascular events through the three months prior to inclusion. It was a randomized open-label, non-inferiority, intention-to-treat study with a composite primary endpoint associating hospitalization or death from cardiovascular causes (these events being adjudicated by an independent committee).

In the context of the 2007 Nissen and Wolski meta-analysis, an unplanned interim analysis was performed after only 3.75 years of follow-up, and did not show increased risk of MI or cardiovascular mortality in the rosiglitazone group, although caution is needed because of limited statistical power.
The final analysis after 5.5 years of follow-up confirmed the interim analysis data with a hazard ratio of 0.99 (confidence interval 0.85–1.16) for the primary endpoint. As the confidence limit was less than 1.20, the study showed that rosiglitazone added on metformin or a sulfonylurea was not inferior to the metformin-sulfonylurea combination for death from cardiovascular causes and hospitalizations for cardiovascular events (primary endpoint), or for the incidence of MI (hazard ratio 1.14, confidence interval 0.80–1.97). However, history of a coronary artery event tended to increase the risk of MI for rosiglitazone compared to the metformin-sulfonylurea combination. This study also showed that the blood glucose control and the lipid profile parameters were better in the rosiglitazone group.

2.3. RECORD or the safety of rosiglitazone?

The RECORD population (mean age of 57 years, mean diabetes duration of 6 years) did not have cardiovascular risk as important as that of the three large trials published in 2008, and only 15% of the patients had a history of coronary artery events. Moreover, the study had less statistical power than initially planned since the final cardiovascular event rate was only 2.8% over 5.5 years versus an expected event rate of 11% per year over 6 years. In addition, use of statins and loop diuretics was greater in the rosiglitazone group than in the control group (+8% and +5% respectively), which was considered as a bias since it might have reduced the cardiovascular risk in the relevant group. This also means that the management of cardiovascular risk factors was better than it was in the past few years. Another potential bias is the lost-to-follow-up rate of 13.2%, which was particularly high in the rosiglitazone group (1.4%) after 2007 following the Nissen and Wolski meta-analysis. Lastly, the RECORD study confirms the known side effects of glitazones, especially with a two-fold increased risk of heart failure, which has already been described in the PROactive trial and in the Nissen and Wolski report, as well as weight gain (+3 kg on average) and increased incidence of fractures in women.

In light of all of these data, it seems reasonable to maintain using rosiglitazone, as long as the formal contra-indication is respected in patients with heart failure and caution is applied in women at high risk of fractures.

3. BARI 2D: better management of diabetic patients with stable coronary artery disease

3.1. BARI: the rationale behind BARI 2D

The BARI 2D study attempted to respond to two questions that were raised following the Bypass Angioplasty Revascularization Investigation (BARI) trial [13], the goal of which was to compare angioplasty and coronary bypass with regard to survival and MI in patients that had undergone revascularization between 1988 and 1991. The incidence of angioplasty and bypass were equivalent after 7 years [14] and then 10 years [15] of follow-up, nevertheless the authors demonstrated a benefit of bypass in the sub-group of diabetic patients. The procedures have improved since 1988, both with regard to surgery and angioplasty techniques. At the same time, both medical treatment and management of cardiovascular risk factors have been intensified and new oral antidiabetic drugs appeared on the market. The aim of BARI 2D was to evaluate two strategies:

- the pertinence of early revascularization compared to intensive medical treatment alone in T2D patients with stable coronary artery disease;
- and the modalities of blood glucose control, either with a treatment directed at insulin secretion deficiency using insulin or sulfonylurea (IS), or with a treatment directed at insulin resistance using metformin or any thiazolidinedione (IR).

3.2. BARI: protocol and results

A population of 2,238 patients, with a mean age of 62 years and a mean duration of diabetes of 10.4 years was randomized according to a somewhat complex factorial procedure (Fig. 1). The eligible patients were required to have more than 50% stenosis on the coronarography with a positive stress test, or else more than 70% stenosis on a major epicardial coronary artery with classic angina. Patients were asymptomatic in 82.1% of cases. The first randomization directed the patient either towards early revascularization via angioplasty or bypass (the technique was chosen by the cardiologist according to the coronarography findings), or towards intensive medical therapy alone. The second randomization determined the type of treatment, IS or IR, for the control of blood glucose to achieve a target glycated hemoglobin level of less than 7.0%. The primary endpoint was mortality from any cause and the secondary endpoint was a combination of cardiovascular death, MI and stroke.

After five years of follow-up, there was no difference with regard to rates of death and cardiovascular events between the two revascularization strategies and the two strategies of blood glucose control. The event rate however of deaths/MI/stroke was lower in the early revascularization with bypass sub-group, especially those patients on IR treatment.

3.3. Practical consequences of the BARI 2D results

These results suggest that coronary bypass revascularization has an advantage over optimal medical treatment with regard to rates of cardiovascular events but no beneficial effect on mortality when surgical revascularization is indicated in diabetic patients with stable coronary artery disease. They are consistent with the results of the initial BARI trial. Therefore, there is probably a subgroup of high-risk diabetic patients with multiple arterial involvement in whom bypass must not be delayed. On the other hand, in patients in whom bypass was not indicated based on coronaryography findings, medical treatment was just as beneficial as early revascularization, even though only 42% of those patients who initially received medical therapy required revascularization during the subsequent 5 years of follow-up and 58% didn’t need one. These results confirm those of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study [16], which were positive.
for first-line intensive medical treatment of patients, including 32% of diabetics with stable coronary artery insufficiency. In the BARI 2D study, the angioplasty procedure used drug-eluting stents in one-third of cases; but this probably did not significantly affect the trial results since use of drug-eluting stents do not reduce rates of death and cardiovascular events in patients with stable coronary artery disease [17].

The BARI 2D study thus suggests that early revascularization is probably beneficial in the sub-group of patients with stable coronary artery disease in whom revascularization by coronary bypass is indicated but not in the other patients strata.

In addition, in patients for whom surgery has been indicated, treatment that acts primarily on insulin resistance is associated with a reduction of cardiovascular events. As rosiglitazone treatment was administered to 55% of patients from the IR group without increased mortality, these data tend to confirm the safety results of this drug in the RECORD study.

4. GLP-1: benefit for patients with cardiac disease

The GLP-1 analogs and the DPP-4 inhibitors, now currently used to improve blood glucose control of T2D patients, could also be beneficial in the field of cardiovascular complications since GLP-1 receptors have been identified on cardiomyocytes, endocardium, coronary epithelium and vascular smooth muscle cells [18]. GLP-1 analogs could thus exert a cardioprotective effect in different diseases such as dilated cardiomyopathy or myocardial ischemia [19].

4.1. GLP-1 and myocardial ischemia

There are some experimental data on the use of GLP-1 during an MI. In dogs undergoing a brief (10 minutes) occlusion of the circumflex coronary artery followed by reperfusion, Nikolaidis et al. showed attenuation of the myocardial stunning (reversible contractile dysfunction in the territories presenting with acute ischemia) in animals under GLP-1 infusion compared to controls. The improvement of left ventricular contractile performance occurred earlier and was more complete in dogs, which were infused with GLP-1 [20]. GLP-1 could interfere in the myocardial stunning phenomenon by increasing glucose uptake during myocardial ischemia. Indeed, metabolic interventions which increase glucose uptake during myocardial ischemia have improved cardiac function [21,22]. GLP-1 may therefore interfere through this indirect mechanism. On isolated rat heart preparations undergoing transient ischemia, GLP-1 infusion was associated with an increase of glucose uptake [23].
GLP-1 analogs may also have a beneficial effect on the post-ischemia myocardium. On a cardiac ischemia-reperfusion rodent model, administration of exenatide limited the extent of induced hypoxic lesions [24,25]. In an induced ischemia-reperfusion porcine model, the administration of exenatide also decreased the infarct size and improved systolic and diastolic cardiac function [26]. Liraglutide, administered to rodents seven days before induced ischemia, also had positive effects on myocardial ischemia through action on the antiapoptotic routes of the myocytes [25].

A clinical study has been done on this topic [27], using a GLP-1 infusion over 72 hours in the acute phase of an MI in 10 diabetic or non diabetic patients with decreased left ventricular ejection fraction (LVEF < 40%), who received intensive medical treatment and angioplasty. Compared to the control subjects, the LEVF was significantly improved after GLP-1 administration, both in diabetic and non diabetic individuals.

These effects, seemingly very promising, must be interpreted with caution since a recent study delivering liraglutide in a porcine model did not demonstrate any significant influence on the infarct size [28].

4.2. GLP-1 and cardiac failure

GLP-1 may also improve cardiac function in non-ischemic dilated cardiomyopathy. In dogs presenting severe dilated cardiopathy, infusion of 1.5 pmol/kg of GLP-1 over 48 hours improved the LEVF compared to an infusion of isotonic solution [29]. Infusion of GLP-1 in 21 obese patients with cardiac insufficiency (LEVF<40%), was followed by an improvement of clinical, echographic and quality-of-life parameters compared to a control group [30].

4.3. GLP-1 and cardiovascular risk factors

An improvement of cardiovascular risk factors was observed with GLP-1 analogs in several clinical studies [31]. In a retrospective study of 1444 diabetic subjects treated with exenatide for 3.5 years, the lipid parameters were significantly improved, with reduction of LDL cholesterol level, increase of HDL cholesterol levels [32], and where as both systolic and diastolic blood pressure decreases. In an open-label study of 120 T2D patients, with a mean age of 56 years and a mean BMI of 35.2 kg/m², pressure decreases. In an open-label study of 120 T2D patients, the lipid parameters were significantly improved, increase of HDL cholesterol level, and reduction of LDL cholesterol level, increase of HDL cholesterol levels [33,34]. The meta-analysis of the Liraglutide Effect and Action in Diabetes (LEAD) program, including six phase-3 studies, also demonstrated a significant reduction of systolic blood pressure in patients treated with liraglutide compared to those receiving a placebo [35]. These beneficial modifications of the risk factors may be explained, at least in part, by a weight loss relative to the GLP-1 analogs, since the same was not observed after DPP4 inhibitors administration which has no effect on body weight. However, those beneficial effects on blood pressure and lipid profile appeared before weight loss, suggesting a direct effect of the GLP-1 analogs on these parameters.

These clinical results on cardiovascular risk factors are promising, but they must be confirmed by morbidity-mortality studies.

5. Conclusion

The year 2009 offered us new data for the management of diabetic patients with cardiac disease. For diabetologists, the RECORD study supports the continued use of rosiglitazone, as long as the formal contraindications are observed. The BARI 2D study provided useful insights for management of diabetic patients with coronary artery disease and supported the RECORD results with regard to the safety of rosiglitazone. All of these trials, some of which have controversial points, agree on the fact that the rate of cardiovascular events is declining, which probably means that patients are being treated better overall. There are still unanswered questions however, especially in patients with the highest cardiovascular risk. Greater improvement in this management should consider each patient individually according to his/her risk factors and use a multidisciplinary approach. There is not one treatment for diabetes but several therapeutic classes that may be applied to different patient profiles.

The new treatments with GLP-1 analogs that are currently available on the market have positive effects on the cardiovascular risk factors associated with diabetes and could have protective effects on the myocardium. Morbidity-mortality studies are necessary to confirm this hypothesis. However, considering the reduction in the rate of cardiovascular events observed over the last several years, these morbidity-mortality studies will be increasingly difficult and lengthy to implement from a methodological standpoint.

Conflict of interest

The authors have not declared any conflict of interest.

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