Elsevier Editorial System(tm) for Diabetes & Metabolism
Manuscript Draft

Manuscript Number:

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Article Type: For debate / Pour debat

Keywords: Cardiovascular disease; Evidence-based medicine; Microangiopathy; Outcome; Type 2 diabetes

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Manuscript Region of Origin: BELGIUM

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To be submitted to Diabetes & Metabolism

For debate

Effects of glucose-lowering agents on vascular outcomes in type 2 diabetes : a critical reappraisal

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Running title : Controversial efficacy of antidiabetic agents

Word count :

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ABSTRACT

Type 2 diabetes mellitus is strongly associated with cardiovascular complications, especially coronary artery disease. Numerous epidemiological studies showed a close relationship between major cardiovascular events and glycaemia and several pathophysiological mechanisms have been described that explain how hyperglycaemia induces vascular damages. However, randomized controlled trials that investigated either an intensive glucose lowering strategy versus standard care or the addition of a new glucose-lowering agent versus a placebo largely failed to demonstrate any clinical benefits in terms of cardiovascular morbidity or mortality. This lack of evidence led some people to contest the clinical efficacy of lowering blood glucose in patients with type 2 diabetes, despite its positive effects on microvascular complications. In this article, we analyze the various reasons that may explain such discrepancies. There are still strong arguments in favour of targeting hyperglycaemia, but avoiding other counterproductive effects, such as hypoglycaemia and weight gain, and integrating the glucose-lowering approach within a global multirisk strategy to reduce the burden of cardiovascular disease in type 2 diabetes.

Key-words : Cardiovascular disease – Evidence-based medicine – Microangiopathy – Outcome – Type 2 diabetes

Effets des médicaments anti-hyperglycémiants sur les événements cardiovasculaires dans le diabète de type 2 : une réévaluation critique

RESUME

Le diabète de type 2 est fortement associé à des complications cardiovasculaires, en particulier la maladie coronaire. De nombreuses études épidémiologiques ont montré une relation étroite entre la survenue d'événements cardiovasculaires majeurs et le niveau de glycémie et divers mécanismes physiopathologiques ont été décrits expliquant comment l'hyperglycémie induit des dommages vasculaires. Cependant, les essais cliniques contrôlés qui ont évalué soit les effets d'une stratégie hypoglycémiante intensive versus un traitement standard, soit ceux de l'ajout d'un nouveau médicament anti-hyperglycémiant versus un placebo ont assez largement échoué dans la démonstration de bénéfices cliniques en termes de morbidité et mortalité cardiovasculaires. Cette absence de preuves a conduit certaines personnes à contester l'intérêt de corriger l'hyperglycémie chez les patients diabétiques de type 2, malgré les effets positifs sur les complications microvasculaires. Dans cet article, nous analysons les raisons qui peuvent expliquer ces discordances. Il existe des arguments forts en faveur de la correction de l'hyperglycémie, mais en évitant des effets contre-productifs, comme la survenue d'hypoglycémie et de prise pondérale, et en intégrant la thérapie anti-hyperglycémiante dans une stratégie multi-risques de façon à réduire l'important impact délétère des maladies cardiovasculaires dans le diabète de type 2.

Mots-clé : Critère de jugement – Diabète de type 2 – Maladies cardiovasculaires – Médecine factuelle – Microangiopathie

Acronyms of clinical trials

ACCORD : Action to Control Cardiovascular Risk in Diabetes

ADVANCE : Action in Diabetes and Vascular disease : preterAx and diamicroN-MR Controlled Evaluation

BARI-2D : Bypass Angioplasty Revascularization Investigation 2 Diabetes

DCCT : Diabetes Control and Complications Trial

EDIC : Epidemiology of Diabetes Interventions and Complications

EXAMINE : EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome

Look AHEAD : Action for Health in Diabetes

ORIGIN : Outcome Reduction with an Initial Glargine Intervention

PROactive : PROspective pioglitAzone Clinical Trial In macroVascular Events

RECORD : Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes

SAVOR-TIMI 53 : Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis In Myocardial Infarction

SOS : Swedish Obese Subjects study

TECOS : Trial Evaluating Cardiovascular Outcomes with Sitagliptin

UKPDS : United Kingdom Prospective Diabetes Study

VADT : Veterans Affairs Diabetes Trial

4S : Scandinavian Simvastatin Survival Study

Introduction

Vascular complications are a major concern in the natural history of diabetes mellitus and their prevention is a big challenge for all physicians. Both type 1 (T1DM) [1] and type 2 (T2DM) [2] diabetes mellitus are associated with endothelial dysfunction and vascular damage. Classically T1DM, which is an almost "pure hyperglycaemic disease", is more commonly associated with microangiopathy (retinopathy, nephropathy). In contrast, T2DM, because of its strong relationship with other vascular risk factors (segregated in the so-called metabolic syndrome), is more commonly associated with macroangiopathy (coronary artery disease, cerebrovascular disease, peripheral arteriopathy) [3]. Nevertheless, both types of complications may occur in the two forms of diabetes and represent a burden for diabetic persons in terms of quality of life and for the society because of the associated high overall cost, especially in T2DM [4].

If hyperglycaemia is associated with diabetic complications, reducing chronic hyperglycaemia should be a key target in the management of diabetes [5, 6] and, if the hypothesis is true, should result in a significant reduction in vascular complications [7]. The UKPDS showed a significant reduction in microangiopathy complications but no significant reduction in macroangiopathy complications when comparing intensive arm (insulin/sulphonylureas) with the conventional arm [8]. Nowadays, two sets of clinical trials are available in the literature : either a treat-to-target strategy comparing intensive treatment versus standard therapy and trying to test the hypothesis "the lower, the better" as in ACCORD [9], ADVANCE [10] and VADT [11], or a classical add-on treatment strategy investing the effect of adding a glucose-lowering medication to existing background therapy as in PROactive [12], SAVOR-TIMI 53 [13] or EXAMINE [14]. However, whatever the strategy used, the results of clinical trials aiming to demonstrate such positive impact of lowering blood glucose levels on hard cardiovascular outcomes were rather disappointing. In this issue of Diabetes and Metabolism, Boussageon and colleagues emphasized the low level of evidence of clinical efficacy of both oral antidiabetic and insulin for the prevention of cardiovascular diseases and even questioned their use for T2DM patients [15]. Even if we can agree with some of the arguments raised by these Authors, based upon the principles of evidence-based medicine, we believe that a critical reappraisal of this conclusion about a possible absence of clinical efficacy of glucose-lowering agents on vascular outcomes in T2DM is mandatory.

Reasons of failure to demonstrate a clinical benefit on cardiovascular outcomes

There are several reasons why it is difficult to demonstrate a beneficial effect of glucose-lowering agents on vascular complications of T2DM patients in randomized controlled trials as requested by the evidence-based medicine. We will briefly discussed reasons related to the pathophysiology of T2DM, the pharmacological properties of the medications used, the characteristics of the populations recruited in clinical trials and the particularities of the study protocols (Table 1).

1) Reasons related to disease pathophysiology

a) Hyperglycaemia : a risk marker rather than a risk factor ?

Numerous epidemiological observations have reported a strong association between glucosuria and degenerative diabetic complications [5], fasting glucose and mortality [16] or cardiovascular disease [17], post-challenge hyperglycaemia and macrovascular complications and premature mortality [18], and fasting glucose, postprandial glucose or glycated haemoglobin (HbA1c) and coronary heart disease [19].

However, these studies do not allow decide whether hyperglycaemia is a risk factor or only a risk marker [2]. Indeed, hyperglycaemia in patients with T2DM is commonly associated with other well known cardiovascular risk factors such as hypertension, atherogenic dyslipidaemia, abdominal obesity, and metabolic syndrome [20]. Especially, insulin resistance associated with hyperinsulinaemia has been considered as a major cardiovascular risk factor [21]. Thereby, hyperglycaemia in T2DM might be considered only as a risk marker rather than a true risk factor. Nevertheless, two arguments may be given in favour of a pathogenic role of hyperglycaemia in the development of vascular complications. First, T1DM, a pure hyperglycaemic disease without associated metabolic syndrome and other comorbidities may be associated with a higher risk of cardiovascular complications [1]. The Diabetes Control and Complications Trial (DCCT)- Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that reduction of hyperglycaemia leads to a significant reduction of cardiovascular complications in patients with T1DM [22, 23], even despite the fact that intensive insulin therapy is associated with some weight gain and secondary increase in other vascular risk factors (elevated blood pressure, disturbances of

lipid profile)[24, 25] . Second, numerous pathophysiological mechanisms, reviewed elsewhere, have been demonstrated to support a strong link between high blood glucose concentrations and endothelial dysfunction and arterial damage [2, 26].

b) Hyperglycaemia : minor role in a complex pathophysiology of vascular disease

The accelerated atherosclerosis and cardiovascular disease commonly observed in diabetes are likely to be multifactorial : besides hyperglycaemia, diabetic dyslipidaemia (high triglycerides, low HDL cholesterol , increased proportion of small dense LDL), elevated arterial blood pressure (hypertension is common in patients with T2DM) and silent inflammation (including that in adipose tissue) play a role in the acceleration of vascular injury [26]. Thereby, even if hyperglycaemia plays the role of a risk factor, its specific contribution may be only limited within the constellation of multiple risk factors. In a overview of the impact of reducing risk factor in T2DM, Ray showed that the benefit from a 0.9 % reduction in HbA1c is much more modest than is that from a per 1 mmol/L reduction in LDL cholesterol or from a 4 mm Hg lower blood pressure [7]. Consequently, targeting specifically hyperglycaemia as unique risk factor may be insufficient to improve the overall vascular prognosis of T2DM patients. Alternatively, the demonstration of a beneficial effect of reducing hyperglycaemia, in absence of other interventions, would require a study of long duration in a very large population, a study that is hardly feasible [27].

2) Reasons related to pharmacological properties of the commonly available anti-diabetic agents

a) Agents acting only on a risk marker and not a risk factor

Glucose-lowering agents are specifically designed to reduce blood glucose levels. Their mode of action differs between compounds. They may increase the circulating insulin concentrations by stimulating insulin secretion (sulphonylureas, glinides) or replacing insufficient insulin secretion by exogenous insulin injection, reduce insulin resistance (insulin sensitizers as thiazolidinediones - TZDs) or inhibit hepatic glucose production (metformin, with only a modest effect on insulin sensitivity). Whether the mode of action may impact on cardiovascular prognosis remains hypothetical although some data suggest a more favourable

effect of drugs that improve insulin action rather than increase plasma insulin concentrations. In the UKPDS, metformin (although evaluated only in a small subgroup, as pointed out by Boussageon and colleagues) was more effective in reducing coronary heart disease complications than insulin therapy or sulphonylureas [28]. In the more recent BARI-2D study, the reduction in myocardial infarction and cardiac death/myocardial infarction was significant only in an insulin sensitization subgroup and not in the insulin provision group [29]. The respective roles of hyperglycaemia and hyperinsulinaemia (an indirect marker of insulin resistance) probably deserve further consideration [21].

If hyperglycaemia is only a risk marker or a risk factor that plays a limited role amongst numerous other risk factors, it is easily conceivable that the demonstration of a beneficial effect of reducing hyperglycaemia on vascular complications would remain a big challenge for pharmacological interventions targeting glucose control only. Furthermore, the occurrence of vascular complications in the natural history of diabetes is a rather late event, suggesting that chronic hyperglycaemia must be sustained to exert its deleterious effects. Conversely, reducing hyperglycaemia during a few years only may be not sufficient to demonstrate a favourable impact of pharmacological compounds on vascular complications, especially in a late stage of the disease (see below).

b) **Counterproductive effects of drug-induced adverse events**

Another possible explanation may be that the positive effect of lowering hyperglycaemia is counterbalanced by adverse events that may increase the risk of cardiovascular complications. Various side effects have been reported with several glucose-lowering agents such as hypoglycaemia with sulphonylureas and insulin, weight gain with sulfonylureas, TZDs and insulin or fluid retention sometimes complicated by congestive heart failure with TZDs.

Hypoglycaemia is probably the confounding factor that raised most interest. In a post-hoc analysis of ADVANCE, severe hypoglycaemia was strongly associated with increased risks of a range of adverse clinical outcomes (adjusted risks of major macrovascular events, major microvascular events, death from a cardiovascular cause, and death from any cause). However, it is not possible to decide whether severe hypoglycaemia contributes to adverse outcomes as a causal factor or is just a marker of vulnerability of patients to present such events [30]. In the ACCORD study, symptomatic, severe hypoglycaemia was associated with

an increased risk of death within each study arm, either the intensive group or the standard glucose control group [31]. Furthermore, in the intensive group of the ACCORD study, a small but statistically significant inverse relationship, of uncertain clinical importance however, was identified between the number of recognized and unrecognized hypoglycaemic episodes (not classified as severe hypoglycaemia) and the risk of death among participants [32]. A similar relationship between severe hypoglycaemia and the risk of death was shown in both arms (glargine and standard care) of the ORIGIN study evaluating patients with prediabetes or mild T2DM [33]. A systematic review indicates that hypoglycaemia mechanistically contributes to cardiovascular risk by increasing thrombotic tendency, causing abnormal cardiac repolarization, inducing inflammation, and contributing to the development of atherosclerosis and to severe events such as unstable angina, non-fatal and fatal myocardial infarction, sudden death, and stroke in patients with diabetes [34].

Weight gain is another counterproductive effect of some glucose-lowering agents. In type 1 diabetes, excess weight gain in the intensive therapy group of DCCT was associated with sustained increases in central obesity, insulin resistance, dyslipidaemia and blood pressure [24], as well as more extensive atherosclerosis during the EDIC follow up [25]. The burden of weight excess and weight gain is even more prominent in T2DM [35] and may contribute to a higher cardiovascular risk [36]. Weight gain in ACCORD was greater with intensive than with standard treatment and generally associated with reduction of HbA1c from elevated baseline values. Initiation of a TZD and/or insulin therapy was the most important medication-related factor associated with weight gain [37]. However, the association between weight gain and cardiovascular events was not reported in ACCORD study. Nevertheless, in another observational (thus not interventional) study, increased body mass index within the first 18 months of T2DM diagnosis was associated with an increased long-term risk of cardiovascular mortality in a large cohort of primary care patients [38].

Fluid retention is specific for TZD therapy in T2DM patients [39]. However, although the incidence of serious heart failure was increased with pioglitazone versus placebo in the total PROactive population of patients with T2DM and macrovascular disease, subsequent mortality or morbidity was not increased in patients with serious heart failure [40]. Overall, the cardiovascular benefits seen with pioglitazone appear to outweigh the cardiovascular risks [41, 42]. The available data with rosiglitazone are more controversial, especially after the suspicion of an increased risk of myocardial infarction and cardiovascular mortality raised in the meta-analysis by Nissen and Wolski [43]. In the RECORD cardiovascular outcome trial,

although the data are inconclusive about any possible effect on myocardial infarction, rosiglitazone did not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs [44]. Among patients with T2DM and coronary artery disease in the BARI 2D trial, neither on-treatment nor propensity-matched analysis supported an association of rosiglitazone treatment with an increase in major ischemic cardiovascular events [45].

3) Reasons related to study populations

a) **Patients at rather low risk or at a late stage of the disease**

Even if diabetes (especially T2DM) is associated with a significantly increased risk of cardiovascular complications, most initial studies included patients with rather low risk of cardiovascular events, at least in a rather short term. This was the case in the DCCT that randomized rather young patients with T1DM [46]; this may explain why the difference between the two arms was only observed almost 10 years after the end of the trial itself, in the observational follow up period EDIC [22]. Similarly, in the UKPDS, patients with recently diagnosed T2DM were included in the trial so that rather few cardiovascular events were collected at the end of the controlled trial [8]. Again, a statistically significant reduction in cardiovascular events in the intensive (insulin or sulphonylureas) arm compared to the conventional (diet and exercise) arm was only observed 10 years after the end of the study (UKPDS), which emphasizes the importance of a long-duration follow up [47].

T2DM patients included in more recent trials, such as ACCORD [9], ADVANCE [10] or VADT [11], had a longer duration of the disease and thereby a higher theoretical risk of cardiovascular disease. However, because of an advanced disease, it is plausible that the impact of any type of intervention trying to improve blood glucose control might be almost impossible to be demonstrated, at least on a rather short term basis. Furthermore, most of these T2DM patients were receiving numerous other pharmacological agents aiming protect them against cardiovascular events. Finally, a majority of patients included in the ORIGIN trial had only mild dysglycaemia but antecedents of cardiovascular complications. This suggests that the role of hyperglycaemia in their cardiovascular disease was rather limited and may explain the neutral effects of a treatment with insulin glargine even after a mean follow-up of 6.2 years [27].

b) **Patients already receiving protective poly-pharmacotherapy**

According to the guidelines [3], most T2DM patients are currently treated with lipid-lowering compounds (statins), antiplatelet agents (aspirin), blockers of the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists) or various cardioprotective medications (among which beta-blockers). This situation not only reduces the overall cardiovascular risk of the population, but also diminishes the potential to demonstrate a beneficial effect of adding a new drug, i.e. an antihyperglycaemic medication. In their provocative analysis suggesting that aspirin prevents 32% of ischaemic heart disease events when used alone but prevents only an additional 5% of the original number of expected events when added to the other components in the combination [48]. In the PROactive trial [12], pioglitazone or placebo was added to any glucose-lowering therapy in T2DM patients with a history of cardiovascular disease who, for most of them, already received a protective polytherapy at inclusion : lipid-lowering agents (53% of patients), antiplatelet medications (85%), renin-agiotensin system blockers (70%) and beta-blockers (55%). Adding pioglitazone to this background therapy led to a non significant reduction of 10 % of the large primary composite endpoint (HR=0.90, 95% CI 0.80–1.02, p=0.095) and a significant reduction of 24 % of the more focused so-called principal secondary endpoint (composite of all-cause mortality, non-fatal myocardial infarction, and stroke : HR =0.84, 0.72–0.98, p=0.027). Although these results were highly debated and considered as not clinically relevant by most trialists (as Boussageon and colleagues), they should be interpreted in the light of the data reported by Wald and Law [48]. In more recent cardiovascular outcome studies as SAVOR-TIMI 53 [13] or EXAMINE [14] , the background therapy with cardioprotective agents was even more intensive (> 80-90 % use of antiplatelet therapy, statins and beta-blockers), which may at least partly explained the absence of difference in cardiovascular events between placebo and the DPP-4 inhibitor.

4) Reasons related to study protocol

a) **Short duration of follow up**

In recently diagnosed T1DM patients, the effect of intensive diabetes therapy on the risk of cardiovascular disease could not be observed at the end of the DCCT but only in the

long term during the 10-year EDIC observational follow up [22]. Similar results were shown in the main UKPDS [8] and UKPDS follow-up [47] studies.

Recently the results of two large prospective trials were reported in patients with T2DM : SAVOR-TIMI 53 comparing saxagliptin and placebo in persons with stable cardiovascular disease or at high risk of cardiovascular disease [13] and EXAMINE comparing alogliptin and placebo in patients with recent acute coronary syndrome [14]. The two trials did not find any significant differences between the DPP-4 inhibitor and placebo in the incidence of major cardiovascular events, a finding that may be considered as disappointing and pointed out by Boussageon and colleagues in their paper [15]. However, the duration of these two trials was rather short with a median follow up of only 2.1 years (SAVOR-TIMI 53) or 1.5 years (EXAMINE). Most statin trials lasted 4-6 years to demonstrate efficacy. For instance, in the landmark Scandinavian Simvastatin Survival Study (4S), almost no difference was observed between the two curves during the first two years in patients with high cardiovascular risk whereas the two curves diverge afterwards with a statistically significant difference in total mortality after a median follow up of 5.4 years favouring simvastatin versus placebo [49]. This reduction in overall mortality persisted over 10 years of follow-up, a difference largely attributable to lower coronary mortality in the simvastatin group [50]. Even with aggressive interventions time is required to observe a significant reduction in cardiovascular events. For instance, in the STENO-2 trial, which compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in T2DM patients with microalbuminuria, the mean follow-up was 7.8 years when an significant effect on a composite cardiovascular endpoint (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation) was reported [51]. In the Swedish Obese Subjects (SOS) study, compared with usual care, bariatric surgery was associated with reduced number of cardiovascular deaths and lower incidence of non fatal cardiovascular events in obese adults (with and without diabetes) after a median follow-up of 14.7 years [52]. The results of longer-term trials with DPP-4 inhibitors are waited with interest such as those of TECOS (follow up > 4 years but perhaps also too short ?) that should be presented at the end of 2014 [53]. Regulators should consider the potential advantages of offering extended patent protection in order to encourage companies to conduct long-term trials in diabetes [54].

b) **Non-inferiority trials**

The potential for some agents to increase the risk of cardiovascular events has led to substantial changes in regulatory requirements for new anti-diabetic therapies. In 2008, the Food and Drug Administration (FDA) edited a new guidance for evaluating cardiovascular risk of new antidiabetic therapies to treat T2DM [55]: " If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3". These requirements, while key to ensuring the cardiovascular safety of new agents, fail to emphasize the need to show clinical benefits, especially as far as hard vascular outcomes are concerned. Consequently, the primary objective of recently published trials with DPP-4 inhibitors, SAVOR-TIMI 53 [13] and EXAMINE [14], and further ongoing trials (TECOS, …)[53], is to demonstrate safety first [56]. Therefore, such trials were primarily designed to show non-inferiority compared to placebo. Possible superiority is tested in a second hierarchical step only. Therefore, even if SAVOR-TIMI 53 and EXAMINE trials showed a comparable incidence of major cardiovascular events between a gliptin and placebo, and thus were considered as negative trials by Boussageon and colleagues [15], in reality they succeeded by their primary objective that was to demonstrate no increased cardiovascular risk of the glucose-lowering agent as recommended by the FDA [55, 56]. Moreover, it must be emphasized that, in these trials, what was evaluated was a specific beneficial or deleterious effect of a given agent rather than reducing blood glucose with this agent since anti-diabetic treatments had to be intensified and were intensified (more insulin in SAVOR, more insulin, metformin and sulphonylureas in EXAMINE) more in the so-called placebo arm resulting, by design of these studies, in a rather small difference in HbA1c between the 2 arms (only 0.3% between the DPP-4 inhibitor and placebo). The same remark may be raised concerning the PROactive trial with a mean difference in HbA1c of 0.5 % between pioglitazone and placebo [12]. Cooperative efforts among regulators, sponsors, clinical trialists and physicians are needed to address unresolved issues including re-definition of therapeutic targets that are meaningful to patients with T2DM and consideration of the ethical and operational challenges of non-inferiority designs [54].

Impact of glucose-lowering agents on microvascular complications

Besides macrovascular complications, microangiopathy represents a major burden and seems more strongly linked to chronic hyperglycaemia than macroangiopathy, both in T1DM [57] andT2DM [6]. It has a major impact on the quality of life but also reduces life expectancy, especially when diabetic nephropathy is present [58]. All diabetic retinopathy end points (including proliferative retinopathy, macular edema, and vision-threatening retinopathy) increases with diabetes duration and poor glucose control (assessed by high HbA1c), although their prevalence is higher in people with T1DM compared with T2DM [59]. Diabetic nephropathy remains a major clinical burden [60]. During the last decade, end-stage renal disease (ESRD) incidence decreased significantly over time for patients with T1DM, but increased significantly for patients with T2DM [61]. Therefore, besides targeting macrovascular disease, avoiding the occurrence of microvascular damage or limiting its progression is a major goal in the management of T2DM. Despite the title of Boussageon's article suggests a low level of evidence of the effects of glucose-lowering pharmacotherapy on microvascular complications of T2DM, this conclusion is poorly documented in their review and deserves further consideration [15].

Tight blood sugar control reduces the risk of developing microvascular diabetes complications, especially retinopathy, in both T1DM (DCCT) [57] and T2DM (UKPDS) [62]. The evidence of benefit appears stronger in younger patients at early stages of the disease whereas the effects of tight blood sugar control seem to become weaker once complications have been manifested [57]. In a recent Cochrane Database Systematic Review, targeting intensive versus conventional glycaemic control reduced the risk of developing a composite outcome of microvascular diseases (RR 0.88, 95% CI 0.82 to 0.95; P=0.0008; 25,927 participants, 6 trials), nephropathy (RR 0.75, 95% CI 0.59 to 0.95; P=0.02; 28,096 participants, 11 trials), retinopathy (RR 0.79, 95% CI 0.68 to 0.92; P=0.002; 10,300 participants, 9 trials), and the risk of retinal photocoagulation (RR 0.77, 95% CI 0.61 to 0.97; P=0.03; 11,212 participants, 8 trials) [62]. Although we can agree that there is few evidence-based data regarding the positive impact of glucose-lowering therapies on hard microvascular outcomes such as the risk of dialysis, blindness or nephropathy-associated mortality [63], data on surrogate endpoints such as albuminuria are clinically relevant considering the natural history of diabetic nephropathy. Indeed, albuminuria is the predominant renal risk marker of nephropathy in patients with T2DM, the higher the albuminuria, the greater the renal risk. Conversely, reduction in albuminuria is associated with a proportional effect on renal protection, the greater the reduction, the greater the renal protection. Thus, albuminuria

should be considered a validated risk marker for progressive loss of renal function in T2DM with nephropathy, as well as a target for therapy [64].

In ACCORD, intensive therapy did not reduce the risk of advanced measures of microvascular outcomes, but delayed the onset of albuminuria and some measures of eye complications and neuropathy. Seven secondary measures at study end favoured intensive therapy with significant differences versus standard therapy [65]. In a systematic review focusing on the role of intensive glucose control in development of renal end points in T2DM patients, intensive glucose control reduces the risk for microalbuminuria and macroalbuminuria, but evidence is lacking that intensive glycaemic control reduces the risk for significant clinical renal outcomes, such as doubling of the serum creatinine level, ESRD, or death from renal disease during the years of follow-up of the trials [63]. Nevertheless, in a recent analysis of the ADVANCE trial, intensive glucose control significantly reduced the risk of ESRD by 65%, microalbuminuria by 9%, and macroalbuminuria by 30%. The number of participants needed to treat over 5 years to prevent one ESRD event ranged from 410 in the overall study to 41 participants with macroalbuminuria at baseline. Thus, improved glucose control could improve major kidney outcomes, at least in some patients with T2DM [66].

As for macrovascular disease, a multifactorial approach, including long-term renin-angiotensin inhibition, is recommended for diabetic nephropathy in T2DM [60], and has proven its efficacy on overall prognosis [67]. Nevertheless, laboratory studies and clinical observations show that adequate glucose control plays a key role in renal protection in diabetes [68]. However, benefits need to be weighed against risks including severe hypoglycaemia, and patient training is an important aspect in practice [57].

Discussion

Evidence-based medicine requires the demonstration of efficacy and safety of addressing a risk factor/marker or using a specific drug in randomized controlled trials (RCTs). These trials are generally performed by academic bodies for the risk factors (UKPDS, ACCORD, …) and by pharmaceutical companies for the drugs (PROactive, SAVOR TIMI 53, EXAMINE). A major driven force for planning such trials is the commercialization of novel drugs and their implantation in clinical practice. This strategy was very successful in the field of hypertension, a disease for which several pharmacological therapies were successively developed for the last 40 years (beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin AT1 receptor blockers). In

the field of lipidology, the arrival of statins led to a remarkable clinical development programme, starting with 4S [49], with numerous controlled trials that demonstrated the efficacy of such lipid-lowering therapy targeting LDL cholesterol in both primary and secondary prevention approaches. In the field of T2DM, the development of oral glucose-lowering therapy consisted in two phases separated by a big gap of several decades. Old oral therapies have been available in the form of biguanides (metformin) and sulphonylureas for over 50 years. This predates by most of that time the successful deployment of large RCTs of individual therapies, with the result that the cardiovascular evidence base for glucose-lowering agents remains weak and therefore open to divergent interpretation [69]. Diabetologists had to wait until the begin of the current century to acknowledge the arrival of new pharmacological approaches developed to treat T2DM, with the successive launch of TZDs (glitazones), DPP-4 inhibitors (gliptins) and, very recently, SGLT2 inhibitors (gliflozins). The commercialization of TZDs initiated two clinical trials with cardiovascular outcomes, only one for each TZD : PROactive with pioglitazone [12] and RECORD with rosiglitazone [44]. As already discussed, these two trials led to controversial results. It was only recently, in fact driven by the new guidance of the FDA [55] and the development of incretin-based therapies, that numerous clinical trials started that were specifically designed to investigate cardiovascular outcomes with novel glucose-lowering therapies. Within a limited number of years the evidence base for newer agents (such as the DPP-4 inhibitors, GLP-1 receptor agonists or SGLT-2 inhibitors) will exceed that of much longer-used therapies such as metformin and sulphonylureas. However, because the request of the FDA following the rosiglitazone story, clinical trials have been designed to prove safety and thus primarily tested a non-inferiority hypothesis for oral glucose-lowering agents compared to placebo [69].

In contrast with hypertension and hypercholesterolaemia, T2DM is a more rapidly evolving disease due to a progressive decline of B-cell function and insulin secretion. Therefore, despite the initiation of pharmacological therapies, the improvement of glucose control may be only transient as shown by the landmark UKPDS [8]. This progressive metabolic deterioration results in difficulties to maintain a sustained improvement in glucose control, without intensifying glucose-lowering therapies, especially if the study is of rather long duration as again shown in the UKPDS [8]. In addition, correcting hyperglycaemia with intensive sulphonylureas/insulin therapy may lead to hypoglycaemia, a condition that stimulates the sympathetic system and may result in cardiovascular adverse events [70]. Finally, T2DM, besides being an evolving complex disease, is also associated with other

comorbidities, such as dyslipidaemia and hypertension, which also require appropriate management and may represent confounding factors, especially if many other cardioprotective medications are prescribed, as already discussed. Most T2DM patients have lipid and blood pressure abnormalities which are intensively treated in the recent "diabetes" studies. As a result, these studies addressed blood glucose reduction or a specific anti-diabetic agent within a multifactorial intervention, more than in the previous "blood pressure" or "statin" trials, which may dilute a possible beneficial effect. The overall consequences of these particularities are that it is more difficult to provide evidence of a positive impact of glucose-lowering therapies on vascular outcomes in patients with T2DM than it was for the management of hypertension or hypercholesterolaemia. Interestingly enough, this challenge does not only concern pharmacological approaches but also lifestyle intervention in T2DM patients as reported in the Look AHEAD cardiovascular outcome trial that was recently stopped prematurely because of futility [71].

Glycaemic control might be an inadequate surrogate marker of cardiovascular event reduction in patients with T2DM. Indeed, clinical trials to date have been unsuccessful in identifying a therapeutic approach that addresses the underlying problem in diabetes (glycaemic control) and reduces cardiovascular risk, as pointed out by Boussageon and colleagues [15]. However, there are simple explanations for this absence of evidence. Ideally, glucose control should start early in the natural history of T2DM [27] but in those patients at lower risk of cardiovascular disease the low incidence of events hinders the demonstration of any clinical benefit, except if the study is of very long duration and recruits a large population. This is hardly feasible, especially in front of an evolving disease that requires progressive therapy intensification as shown by the difficulties encountered in the landmark UKPDS [8]. Thus, the alternative may be a later intervention in patients at higher risk of cardiovascular disease and thereby exposed to more cardiovascular events. However, in this case, we have to face a too advanced disease with severe vascular damages that are only poorly reversible or even completely irreversible, at least in a rather short-term. This may explain the absence of positive effects first in ACCORD [9] and VADT [11], and later on in SAVOR-TIMI 53 [13] and EXAMINE [14]. Consequently, in both scenarios, failure of the glucose-lowering intervention on cardiovascular outcomes is not so astonishing and could rather be a logical consequence of the natural history of the disease.

In a meta-analysis performed by the Control Group (a total of 27,049 participants and 2,370 major vascular events) the allocation to more-intensive, compared with less-intensive,

glucose control reduced the risk of major cardiovascular events by 9% (HR 0.91, 95% CI 0.84-0.99), primarily because of a 15% reduced risk of myocardial infarction (HR 0.85, 95% CI 0.76-0.94) [72]. However, mortality was not decreased, with non-significant HRs of 1.04 for all-cause mortality (95% CI 0.90-1.20) and 1.10 for cardiovascular death (95% CI 0.84-1.42). These results, especially the absence of reduction in mortality, were confirmed in further meta-analyses [62, 73, 74] and emphasized in the paper published by Boussageon and colleagues in this issue of Diabetes & Metabolism [15]. Most probably, the demonstration of a significant reduction in mortality would require a long follow-up in a large population.

The fact that the demonstration of a positive impact of glucose-lowering intervention is not shown in available RCTs does not mean that a favourable effect does not exist. All efficacious interventions could not be tested in RCTs as previously discussed in a paper using the provocative comparison with the parachute protection, which has never been tested in a RCT [75, 76] ! Observational studies and common clinical experience have extensively shown improved prognosis of diabetic patients during the last decades, with a marked reduction or postponing (i.e. occurring at a later age) of cardiovascular complications and cardiovascular mortality [77-79].

Thus, glycaemic control remains an important component of treatment for T2DM and contrasting results from several trials that aimed at intensifying glucose-lowering therapies control should not discourage physicians from controlling blood glucose levels [80]. However, to reduce cardiovascular mortality and total mortality in T2DM, glucose control should be integrated within a global risk management [3], opening the door to a so-called polypill strategy [81]

Many of the traditional agents used for treating T2DM, such as insulin and sulphonylureas (“insulin providers”), do not improve cardiovascular prognosis despite improving hyperglycaemia. However, drugs that reduce postprandial glucose and improve insulin resistance without predisposing patients to hypoglycemia appear to both control hyperglycaemia and improve cardiovascular prognosis [82]. Treating patients who have early signs of hyperglycaemia, including elevated postprandial glucose level, with intensive glucose control that does not lead to weight gain, and ideally may be associated with weight reduction, may be vital to preventing or reducing later cardiovascular morbidity and mortality [83]. Alternatively, the challenge will be to demonstrate the protective effect of glucose-lowering agents that do not have counterproductive effects (weight gain, hypoglycaemia) in a

controlled-study of long duration enough recruiting a large number of patients at CV risk but already receiving other cardiovascular protective medications [84].

Conclusions

As pointed out by Boussageon and colleagues, most RCTs failed to demonstrate the efficacy of glucose-lowering agents in reducing cardiovascular complications in patients with T2DM. Because of the natural history and the complexity of the disease, such demonstration in RCTs would be very difficult to obtain. However, subgroup analysis has provided evidence suggesting that the potential beneficial effect largely depends on patients' characteristics, including age, diabetes duration, previous glucose control, presence of cardiovascular disease, and risk of hypoglycaemia. Furthermore, correction of chronic hyperglycaemia results in a significant reduction in microvascular complications. Glycaemic control remains an important component of treatment for T2DM and the overall negative conclusions of review articles like that published by Boussageon and colleagues in the current issue of Diabetes and Metabolism should not discourage physicians from controlling blood glucose levels. The goal for managing patients with type 2 DM is to lower the blood glucose level as much as possible for as long as possible without causing hypoglycaemia or weight gain and, if possible, with promoting weight reduction and reducing other cardiovascular risk factors.

Funding and conflict of interest

No sources of funding were used to assist in the preparation of this manuscript. No conflicts of interest are directly relevant to the content of this manuscript.

A.J. Scheen has received lecture/advisor fees from Abbott, AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, NovoNordisk, Sanofi-Aventis and Takeda.

B. Charbonnel has received fees for consultancy, speaking, travel or accommodation from: Merck-Serono,Takeda, GlaxoSmithKline, Merck Sharpe & Dohme, AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Novo-Nordisk, Lilly, Janssen, Sanofi, Novartis.

Table 1 : Proposed explanations of failure to demonstrate a protective effect of glucose-lowering agents on vascular complications in clinical trials.

Possible reasons of failure	**Proposed explanation**
Pathophysiology of the disease	- Hyperglycaemia as risk marker versus risk factor - Complex pathophysiology of vascular damage in T2DM, combining many risk factors - Long time for hyperglycaemia-linked vascular damage to be reverted
Pharmacology of the antidiabetic medications	- Insulin providers less protective than insulin sensitizers - Counterproductive effects of drug-induced adverse events - Dilution effects due to therapy adjustment in the placebo group
Study population	- Patients with too low risk and delayed cardiovascular events - Patients with too advanced (poorly reversible) disease - Patients already receiving numerous cardioprotective drugs
Study protocol	- Too short follow-up for a chronic disease - Too small HbA1c difference versus placebo arm - Non-inferiority trial designed to demonstrate safety rather than efficacy

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Effets des médicaments anti-hyperglycémiants sur les événements cardiovasculaires dans le diabète de type 2 : une réévaluation critique

RESUME

Le diabète de type 2 est fortement associé à des complications cardiovasculaires, en particulier la maladie coronaire. De nombreuses études épidémiologiques ont montré une relation étroite entre la survenue d'événements cardiovasculaires majeurs et le niveau de glycémie et divers mécanismes physiopathologiques ont été décrits expliquant comment l'hyperglycémie induit des dommages vasculaires. Cependant, les essais cliniques contrôlés qui ont évalué soit les effets d'une stratégie hypoglycémiante intensive versus un traitement standard, soit ceux de l'ajout d'un nouveau médicament anti-hyperglycémiant versus un placebo ont assez largement échoué dans la démonstration de bénéfices cliniques en termes de morbidité et mortalité cardiovasculaires. Cette absence de preuves a conduit certaines personnes à contester l'intérêt de corriger l'hyperglycémie chez les patients diabétiques de type 2, malgré les effets positifs sur les complications microvasculaires. Dans cet article, nous analysons les raisons qui peuvent expliquer ces discordances. Il existe des arguments forts en faveur de la correction de l'hyperglycémie, mais en évitant des effets contre-productifs, comme la survenue d'hypoglycémie et de prise pondérale, et en intégrant la thérapie anti-hyperglycémiante dans une stratégie multi-risques de façon à réduire l'important impact délétère des maladies cardiovasculaires dans le diabète de type 2.

Mots-clé : Critère de jugement – Diabète de type 2 – Maladies cardiovasculaires – Médecine factuelle – Microangiopathie