For debate

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

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Abstract

Type 2 diabetes mellitus (T2DM) is strongly associated with cardiovascular complications, especially coronary artery disease. Numerous epidemiological studies have shown a close relationship between major cardiovascular events and glycaemia, and several pathophysiological mechanisms have been described that explain how hyperglycaemia induces vascular damage. However, randomized controlled trials investigating either an intensive glucose-lowering strategy vs standard care or the addition of a new glucose-lowering agent vs a placebo have largely failed to demonstrate any clinical benefits in terms of cardiovascular morbidity or mortality. This lack of evidence has led some people to contest the clinical efficacy of lowering blood glucose in patients with T2DM, despite its positive effects on microvascular complications. This article analyzes the various reasons that might explain such discrepancies. There are still strong arguments in favour of targeting hyperglycaemia while avoiding other counterproductive effects, such as hypoglycaemia and weight gain, and of integrating the glucose-lowering approach within a global multi-risk strategy to reduce the burden of cardiovascular disease in T2DM.

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

1. 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

2. 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 [1] and type 2 [2] diabetes mellitus (T1DM and T2DM, respectively) 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 within 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 people in terms of quality of life and for society because of the associated high overall costs, especially with T2DM [4].

If hyperglycaemia is associated with diabetic complications, then reducing chronic hyperglycaemia should be a key target in the management of diabetes [5,6]; and if this hypothesis is true, it should then 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 the intensive treatment arm (insulin/sulphonylureas) with the conventional arm [8]. Nowadays, two sets of clinical trials are available in the literature: a treat-to-target strategy comparing intensive treatment with standard therapy in an attempt to test the hypothesis “the lower, the better”, as in the ACCORD [9], ADVANCE [10] and VADT [11]; and a classical add-on treatment strategy investigating the effect of adding a glucose-lowering medication to the existing background therapy, as in PROactive [12], SAVOR-TIMI 53 [13] and EXAMINE [14]. However, whatever the strategy used, the results of clinical trials aiming to demonstrate the positive impact of lowering blood glucose levels on hard cardiovascular outcomes have been rather disappointing. In this issue of Diabetes & Metabolism, Boussageon et al. [15] have emphasized the low level of evidence of clinical efficacy for both oral antidiabetics and insulin for the prevention of cardiovascular diseases, and have even questioned their use for T2DM patients. Even if we can agree with some of the arguments raised by those authors, based on the principles of evidence-based medicine, we believe that a critical reappraisal of this conclusion regarding the possible lack of clinical efficacy with glucose-lowering agents on vascular outcomes in T2DM is mandatory.

3. Reasons for failure to demonstrate 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 required by evidence-based medicine. What follows is a brief discussion of the reasons related to the pathophysiology of T2DM, the pharmacological properties of the medications used, the characteristics of the populations recruited into clinical trials and the particularities of the study protocols (Table 1).

### Table 1

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#### T2DM: type 2 diabetes mellitus.

3.1. Reasons related to disease pathophysiology

3.1.1. Hyperglycaemia: a risk marker rather than 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 determine whether hyperglycaemia is a risk factor or merely 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 the metabolic syndrome [20]. In particular, insulin resistance associated with hyperinsulinaemia has been considered a major cardiovascular risk factor [21]. This suggests that hyperglycaemia in T2DM might be considered only a risk marker and not a true risk factor. Nevertheless, two arguments may be made in favour of a pathogenic role of hyperglycaemia in the development of vascular complications. First, T1DM, a purely hyperglycaemic disease with no associated metabolic syndrome or other comorbidities, may be associated with a higher risk of cardiovascular complications [1]. The DCCT and EDIC study showed that reduction of hyperglycaemia leads to a significant reduction of cardiovascular complications in patients with T1DM [22,23], despite the fact that intensive insulin therapy is associated with weight gain and a 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].

3.1.2. Hyperglycaemia: a minor role in the 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 high-density lipoprotein (HDL) cholesterol, increased proportion of small dense low-density lipoprotein (LDL)], elevated arterial blood pressure (hypertension is common in patients with T2DM) and silent inflammation (including in adipose tissue) play a role in the acceleration of vascular injury [26]. Thus, even if hyperglycaemia plays the role of a risk factor, its specific contribution may be limited to only a constellation of multiple risk factors. In an overview of the impact of reducing risk factors in T2DM, Ray et al. [7] showed that the benefit from a 0.9% reduction in HbA1c is much more modest than from a 1-mmol/L reduction in LDL cholesterol or a 4-mmHg lower blood pressure. Consequently, targeting hyperglycaemia specifically as a unique risk factor may be insufficient to improve the overall vascular prognosis of T2DM patients. In fact, demonstration of a beneficial effect of reducing hyperglycaemia in the absence of other interventions would require a study of long duration in a very large population, making such a study hardly feasible [27].

3.2. Reasons related to pharmacological properties of the commonly available antidiabetic agents

3.2.1. Agents acting only on risk markers and not risk factors

Glucose-lowering agents are specifically designed to reduce blood glucose levels. Their mode of action differs across compounds. They may increase circulating insulin concentrations by stimulating insulin secretion (sulphonylureas, glinides) or replacing insufficient insulin secretion by exogenous insulin injection, reduce insulin resistance [insulin sensitizers, such as thiazolidinediones (TZDs)] or inhibit hepatic glucose production (metformin, with only a modest effect on insulin sensitivity). Whether the mode of action has an 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 (albeit evaluated in only a small subgroup, as pointed out by Boussageon et al.) was more effective in reducing coronary heart disease complications than either insulin or sulphonylurea therapy [28]. In the more recent BARI 2D study, the reduction in myocardial infarction and cardiac death/myocardial infarction was significant only in the insulin-sensitized subgroup and not the insulin-provision group [29]. The respective roles of hyperglycaemia and hyperinsulinaemia (an indirect marker of insulin resistance) probably merit further consideration [21].

If hyperglycaemia is only a risk marker or a risk factor that plays only a limited role among numerous other risk factors, it is easily conceivable that demonstration of a beneficial effect on vascular complications by reducing hyperglycaemia would remain a major challenge for pharmacological interventions targeting only glucose control. 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 for only a few years may not be sufficient to demonstrate a favourable impact of pharmacological compounds on vascular complications, especially in late-stage disease (see below).

3.2.2. Counterproductive effects of drug-induced adverse events

Another possible explanation may be that the positive effect of lowering hyperglycaemia is counteracted by adverse events that 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 sulphonylureas, TZDs and insulin, and fluid retention sometimes complicated by congestive heart failure with TZDs.

Hypoglycaemia is probably the confounding factor that has raised the most interest. In a post-hoc analysis of ADVANCE, severe hypoglycaemia was strongly associated with an increased risk 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 determine whether severe hypoglycaemia contributes to adverse outcomes as a causal factor or is simply a marker of the likelihood of patients to present with such events [30]. In the ACCORD study, symptomatic, severe hypoglycaemia was associated with an increased risk of death within each study arm, comprising an intensive treatment group and a standard glucose control group [31]. Furthermore, in the intensive group of the ACCORD, a small but statistically significant inverse relationship of uncertain clinical importance 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 either prediabetes or mild T2DM [33]. A systematic review indicated 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 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 T1DM, excess weight gain in the intensive therapy group of the 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...
3.3.1. Patients at lower risk or with late-stage disease

Although 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 the relatively short term. This was the case in the DCCT, which randomized comparatively young patients with T1DM [46], and may explain why any difference between the two arms was only observed nearly 10 years after the end of the trial, during the EDIC observational follow-up period [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 with the conventional (diet and exercise) arm was only observed 10 years after the end of the study (UKPDS), thus, emphasizing the importance of a long duration follow-up [47].

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

3.3.2. Patients already receiving protective polypharmacotherapy

As per the guidelines [3], most T2DM patients are currently treated with lipid-lowering compounds (statins), antiplatelet agents (aspirin), renin–angiotensin system blockers (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists) and various cardioprotective medications (including beta-blockers). This situation not only reduces the overall cardiovascular risk of the population, but also diminishes the potential to demonstrate any beneficial effect of adding a new drug, for example, an antihyperglycaemic medication. In their provocative analysis suggesting that a polypill might reduce cardiovascular disease by more than 80%, Wald and Law [48] reported 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. In the PROactive trial [12], either pioglitazone or a placebo was added to the glucose-lowering therapy of T2DM patients with a history of cardiovascular disease who were, in most cases, already receiving protective polytherapy at baseline, including lipid-lowering agents (53% of patients), antiplatelet medications (85%), renin–angiotensin system blockers (70%) and beta-blockers (55%). Adding pioglitazone to this background therapy led to a non-significant 10% reduction of the broader primary composite endpoint (HR: 0.90, 95% CI: 0.80–1.02; P = 0.095), but a significant 24% reduction of the more focused so-called principal secondary endpoint (composite of all-cause mortality, non-fatal myocardial infarction and stroke: HR: 0.84, 95% CI: 0.72–0.98; P = 0.027). Although these results were highly debated and considered not clinically relevant by most trialists (such as Bous sageon et al.), they should be interpreted in the light of the data reported by Wald and Law [48]. In the more recent cardiovascular outcome studies, such as SAVOR-TIMI 53 [13] and 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 explain the lack of differences in cardiovascular events between placebo and the dipeptidyl peptidase (DPP)-4 inhibitor.

3.4. Reasons related to study protocol

3.4.1. Short duration of follow-up

In the recently diagnosed T1DM patients in the DCCT, the effect of intensive diabetes therapy on the risk of cardiovascular disease could not be observed at the end of the study,
but only during the long-term, 10-year, EDIC observational follow-up [22]. Similar results were found with the main UKPDS [8] and UKPDS follow-up [47].

Recently, the results of two large-scale prospective trials were reported in patients with T2DM: SAVOR-TIMI 53 compared saxagliptin and placebo in patients with either stable cardiovascular disease or at high risk of cardiovascular disease [13]; and EXAMINE compared alogliptin and placebo in patients with recent acute coronary syndrome [14]. The two trials could find no significant differences between the DPP-4 inhibitor and placebo in the incidence of major cardiovascular events, a finding that could be considered disappointing, as pointed out by Boussageon et al. 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) and 1.5 years (EXAMINE). Most statin trials have lasted for 4 to 6 years to demonstrate efficacy. For instance, in the landmark 4S, almost no differences were observed between the two curves during the first 2 years in patients with high cardiovascular risk, whereas the two curves diverged thereafter, with a statistically significant difference in total mortality after a median follow-up of 5.4 years favouring simvastatin vs 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]. Thus, even with aggressive interventions, time is needed to observe significant reductions in cardiovascular events.

In the Steno-2 trial, which compared the effect of a targetted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in T2DM patients with microalbuminuria, the mean follow-up duration was 7.8 years before a significant effect on the composite cardiovascular endpoint (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, revascularization and amputation) could be reported [51]. In the SOS study, bariatric surgery compared with the usual care was associated with a reduced number of cardiovascular deaths and a lower incidence of non-fatal cardiovascular events in obese adults (with or without diabetes) after a median follow-up of 14.7 years [52]. The results of longer-term trials of DPP-4 inhibitors, such as TECOS (follow-up >4 years, which may perhaps still be too short?) are awaited with interest and should be ready early 2015 [53]. Regulators should consider the potential advantages of offering extended patent protection to encourage companies to conduct longer-term trials in diabetes [54].

3.4.2. Non-inferiority trials

The potential of some agents to increase the risk of cardiovascular events has led to substantial changes in regulatory requirements for new antidiabetic therapies. In 2008, the US Food and Drug Administration (FDA) published new guidelines for evaluating the 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 risk ratio is between 1.3 and 1.8, and the overall risk–benefit analysis supports approval, a post-marketing 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, however, while key to ensuring the cardiovascular safety of new agents, fail to emphasize the need to show clinical benefit, especially as far as hard vascular outcomes are concerned. As a consequence, the primary objective of recently published trials with DPP-4 inhibitors, such as SAVOR-TIMI 53 [13] and EXAMINE [14], and of other ongoing trials (such as TECOS) [53] is to demonstrate safety first [56]. This means that such trials were primarily designed to show non-inferiority compared with placebo, with possible superiority tested only as a second hierarchical step. Therefore, even if the SAVOR-TIMI 53 and EXAMINE trials showed a comparable incidence of major cardiovascular events between a glititin and placebo – and thus are considered negative trials by Boussageon et al. [15] – in reality, they succeeded according to their primary objective, which was to demonstrate no increased cardiovascular risk with the glucose-lowering agent as recommended by the FDA [55,56]. It must also be emphasized that, in these trials, what was evaluated was a specific beneficial or deleterious effect of a given agent rather than the reduction of blood glucose with this agent, indeed antidiabetic treatments were intensified (more insulin in SAVOR, and more insulin, metformin and sulphonylureas in EXAMINE) more in the so-called placebo arm, which resulted, by design, in a small difference in HbA1c between the two study arms (only 0.3% between the DPP-4 inhibitor and placebo). The same may be said for PROActive, which found 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 such unresolved issues, including redefinition of therapeutic targets that are meaningful to patients with T2DM, and greater consideration of the ethical and operational challenges of non-inferiority study designs [54].

4. Impact of glucose-lowering agents on microvascular complications

Besides macrovascular complications, microangiopathy represents a major burden that may be more strongly linked to chronic hyperglycaemia than macroangiopathy in both T1DM [57] and T2DM [6] patients. It has a major impact on quality of life, and it also reduces life expectancy, especially when diabetic nephropathy is present [58]. All diabetic retinopathy end points (including proliferative retinopathy, macular oedema and vision-threatening retinopathy) increase with diabetes duration and poor glucose control (as assessed by high HbA1c), although their prevalence is greater in those with T1DM compared with T2DM [59]. Diabetic nephropathy remains a major clinical burden [60]. During the last decade, the incidence of end-stage renal disease (ESRD) has decreased significantly over time for patients with T1DM, but increased significantly for patients with T2DM [61]. Therefore, besides targeting macrovascular disease, the avoidance of microvascular damage or limiting its progression is a major goal in the management of T2DM. Although the title of the Boussageon et al. [15] 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.

Tight blood sugar control reduces the risk of microvascular diabetes complications, especially retinopathy, in both T1DM (DCCT) [57] and T2DM (UKPDS) [62] patients. The evidence of benefit appears to be stronger in younger patients at early stages of the disease, whereas the effects of tight blood sugar control seem weaker once complications have manifested [57]. In a recent Cochrane Database Systematic Review, targeting intensive vs conventional glycaemic control reduced the risk of developing a composite outcome of microvascular disease (RR: 0.88, 95% CI: 0.82–0.95; P = 0.0008; 25,927 participants, six trials), nephropathy (RR: 0.75, 95% CI: 0.59–0.95; P = 0.02; 28,096 participants, 11 trials) and retinopathy (RR: 0.79, 95% CI: 0.68–0.92; P = 0.002; 10,300 participants, nine trials), and the risk of retinal photocoagulation (RR: 0.77, 95% CI: 0.61–0.97; P = 0.03; 11,212 participants, eight trials) [62]. Although we agree that there are few evidence-based data for the positive impact of glucose-lowering therapies on hard microvascular outcomes, such as the risk of dialysis, blindness and nephropathy-associated mortality [63], data for 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, and the higher the albuminuria, the greater the renal risk. Conversely, albuminuria reduction is associated with a proportional renal-protective effect, and 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 cases with nephropathy as well as a target for therapy [64].

In the ACCORD, intensive therapy did not reduce the risk of advanced measures of microvascular outcomes, although it delayed the onset of albuminuria and some measures of eye complications and neuropathy. Seven secondary measures at the study end favoured intensive therapy with significant differences vs standard therapy [65]. In a systematic review focused on the role of intensive glucose control in the development of renal end points in T2DM patients, intensive glucose control reduced the risks of microalbuminuria and macroalbuminuria, but there was no evidence that intensive glycaemic control reduced the risk of significant clinical renal outcomes, such as doubling of serum creatinine levels, ESRD and death from renal disease, during the years of follow-up of the trials [63]. Nevertheless, in a recent analysis of ADVANCE, 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 for 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 can 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 in terms of overall prognosis [67]. 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].

5. Discussion

Evidence-based medicine requires demonstration of the 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 risk factors (UKPDS, ACCORD) and by pharmaceutical companies for drugs (PROactive, SAVOR–TIMI 53, EXAMINE). A major driving force behind the planning of such trials is the commercialization of novel drugs and their implementation in clinical practice. This strategy was very successful in the field of hypertension, a disease for which several pharmacological therapies have successively been developed over the past 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 the 4S [49] and followed by numerous controlled trials that demonstrated the efficacy of such lipid-lowering therapy targeting LDL cholesterol in both primary and secondary preventative approaches. In the field of T2DM, the development of oral glucose-lowering therapy consisted of two phases separated by a wide gap of several decades. Old oral therapies have been available in the form of biguanides (metformin) and sulphonylureas for more than 50 years. Most of that time predates the successful deployment of large RCTs of individual therapies, with the result that the cardiovascular evidence base for glucose-lowering agents remains weak and thus opens to divergent interpretation [69]. Diabetologists had to wait until the beginning of the current century to see the arrival of new pharmacological approaches developed to treat T2DM with the successive launching of TZDs (glitazones), DPP-4 inhibitors (gliptins) and, very recently, sodium-glucose co-transporter (SGLT)-2 inhibitors (gliplozins). The commercialization of TZDs initiated two clinical trials with cardiovascular outcomes, albeit 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—and, in fact, driven by new guidelines from the FDA [55] and the development of incretin-based therapies—that numerous clinical trials were started that were specifically designed to investigate cardiovascular outcomes with novel glucose-lowering therapies. Within a small number of years, the evidence base for these newer agents [such as DPP-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists and SGLT-2 inhibitors] is expected to exceed that of the much longer-used therapies, such as metformin and sulphonylureas. However, because of the FDA’s request following the rosiglitazone story, clinical trials have been essentially designed to prove safety and, thus, have primarily tested a non-inferiority hypothesis for oral glucose-lowering agents compared with placebo [69].

In contrast to hypertension and hypercholesterolaemia, T2DM is a more rapidly evolving disease due to the progressive
decline of beta-cell function and insulin secretion. Therefore, despite the initiation of pharmacological therapies, improvement of glucose control may only be transient, as shown by the landmark UKPDS [8]. Such progressive metabolic deterioration results in difficulty in maintaining sustained improvements in glucose control without intensifying the glucose-lowering therapy, especially when the study is of relatively long duration, again as shown by the UKPDS [8]. In addition, correcting hyperglycaemia with intensive sulphonylurea/insulin therapy may lead to hypoglycaemia, a condition that stimulates the sympathetic nervous system and may result in cardiovascular adverse events [70]. As well as being an evolving complex disease, T2DM is also associated with other comorbidities, such as dyslipidaemia and hypertension which, in turn, require appropriate management and may represent confounding factors, especially if other cardioprotective medications are prescribed, as already discussed. Most T2DM patients have lipid and blood pressure abnormalities that were intensively treated in the recent “diabetes” studies. As a result, those studies addressed blood glucose reduction or a specific antidiabetic agent within a multifactorial intervention more than in the previous “blood pressure” or “statin” trials, which may have diluted any possible beneficial effects. The overall consequence of these particularities is 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 concerns not only pharmacological approaches, but also lifestyle interventions in T2DM patients, as reported by the Look AHEAD cardiovascular outcomes trial, recently stopped prematurely for reasons 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 both addresses the underlying problem in diabetes (glycaemic control) and reduces cardiovascular risk, as pointed out by Boussageon et al. [15]. However, there are simple explanations for this lack 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 demonstration of any clinical benefit unless the study is of very long duration and recruits a very large population. This is hardly feasible, especially in the face of an evolving disease that requires progressive therapy intensification, as shown by the difficulties encountered in the landmark UKPDS [8]. Therefore, the alternative may be later intervention in patients at higher risk of cardiovascular disease and thus more vulnerable to cardiovascular events. In this case, however, it is possible that we are then faced with too advanced disease with severe vascular damage that is only poorly reversible or even completely irreversible, at least in the short-term. This may explain the absence of positive effects first in ACCORD [9] and VADT [11], and later in SAVOR-TIMI 53 [13] and EXAMINE [14]. Consequently, in both scenarios, the failure of the glucose-lowering intervention on cardiovascular outcomes is not so astonishing and may instead be the logical consequence of the natural history of the disease.

In a meta-analysis by the control group (involving a total of 27,049 participants and 2370 major vascular events), allocation to more intensive rather than 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, and especially the absence of reduction in mortality, were confirmed by further meta-analyses [62,73,74] and emphasized in the report by Boussageon et al. [15]. Most probably, demonstration of a significant reduction in mortality would require a long follow-up in a large population.

The fact that no positive impact of glucose-lowering interventions was demonstrated in the available RCTs does not mean that favourable effects do not exist. All efficacious interventions could not be tested in RCTs, as previously discussed in a paper using the provocative comparison with parachute protection, which has never been tested in an RCT [75,76]! Observational studies and common clinical experience have extensively shown an improved prognosis for diabetic patients over the past decades, with marked reductions or postponements (occurring at a later age) of cardiovascular complications and cardiovascular mortality [77–79].

Glycaemic control remains an important component of treatment for T2DM, and the conflicting results of several trials aiming to intensify glucose-lowering therapy should not discourage physicians from attempting to control blood glucose levels [80]. However, to reduce both cardiovascular and total mortality in T2DM, glucose control should be integrated within a global risk-management approach [3], thus, 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. Nevertheless, drugs that reduce postprandial glucose and improve insulin resistance without predisposing patients to hypoglycaemia appear to both control hyperglycaemia and improve cardiovascular prognosis [82]. Treating patients who have early signs of hyperglycaemia, including elevated postprandial glucose levels, with intensive glucose control that does not lead to weight gain, but ideally may be associated with weight reduction, may be vital for preventing or reducing later cardiovascular morbidity and mortality [83]. Ultimately, the challenge may be to demonstrate the protective effects of glucose-lowering agents without counterproductive effects (weight gain, hypoglycaemia) in a controlled study of sufficiently long duration and including a large number of patients at cardiovascular risk despite already taking other cardiovascular protective medications [84].

6. Conclusion

As pointed out by Boussageon et al., most RCTs have failed to demonstrate the efficacy of glucose-lowering agents in reducing cardiovascular complications in patients with T2DM. Given the
natural history and complexity of the disease, such a demonstration in RCTs would be difficult to obtain. However, subgroup analysis has provided evidence suggesting that the potential beneficial effect may largely depend on patients’ characteristics, including age, diabetes duration, previous glucose control, presence of cardiovascular disease and risk of hypoglycaemia. In addition, correction of chronic hyperglycaemia results in a significant reduction in microvascular complications. Thus, glycaemic control remains an important component of treatment for T2DM, and the overall negative conclusions of reviews, such as the one by Boussageon et al. in the current issue of this journal, should not discourage physicians from controlling blood glucose levels. The goal in managing patients with T2DM is to lower blood glucose as much as possible for as long as possible without causing hypoglycaemia or weight gain, and, if possible, with the promotion of weight loss and the reduction of other cardiovascular risk factors, too.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2014.03.004.

References


