Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en
Diabetes & Metabolism 40 (2014) 176–185

For debate

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

A.J. Scheen [a,*], B. Charbonnel [b]

[a] *Division of Diabetes, Nutrition and Metabolic Disorders, Division of Clinical Pharmacology, CHU de Liège, University of Liège, Liège, Belgium*
[b] *Endocrinology Department, University of Nantes, Nantes, France*

Received 18 March 2014; accepted 22 March 2014
Available online 30 April 2014

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

* Corresponding author. Department of Medicine, CHU Sart Tilman (B35), 4000 Liège 1, Belgium. Tel.: +32 4 3667238; fax: +32 4 3667068.
E-mail address: andre.scheen@chu.ulg.ac.be (A.J. Scheen).

http://dx.doi.org/10.1016/j.diabet.2014.03.004
1262-3636/

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
Proposed reasons for failure to demonstrate any protective effects with glucose-lowering agents on vascular complications in clinical trials.

Possible reasons for failure	Proposed explanations
Pathophysiology of diabetes	Hyperglycaemia as a risk marker vs risk factor
	Complex pathophysiology of vascular damage in T2DM that combines many risk factors
	Long time required for hyperglycaemia-linked vascular damage to be reversed
Pharmacology of antidiabetic medications	Insulin providers less protective than insulin sensitizers
	Counterproductive effects of drug-induced adverse events
	Dilution effects due to therapy adjustment in 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 HbA_{1c} difference vs placebo arm
	Non-inferiority trial designed to demonstrate safety rather than efficacy

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 (HbA_{1c}) 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