Nutrition, Metabolism & Cardiovascular Diseases (2015) **25**, 697–705

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

VIEWPOINT

Oral hypoglycemic agents and the heart failure conundrum: Lessons from and for outcome trials

B.A. Kappel [a,c], N. Marx [c], M. Federici [a,b,*]

[a] Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[b] Center for Atherosclerosis, Policlinico Tor Vergata, Rome, Italy
[c] Department of Internal Medicine I, University Hospital Aachen, Germany

Received 21 April 2015; received in revised form 13 June 2015; accepted 13 June 2015
Available online 18 June 2015

KEYWORDS
Oral antidiabetic agents;
Heart failure;
Cardiovascular disease;
Cardiovascular safety;
TECOS

Abstract *Aim:* Type 2 diabetes is not only an independent risk factor for cardiovascular (CV) disease but is also associated with a greater incidence of heart failure (HF). The aim of this review is to examine the effects of oral antidiabetic drugs on CV disease and HF.
Data synthesis: Trials of anti-diabetic agents are now designed to assess CV safety, but frequently HF is not included as a primary endpoint. However, HF in patients with diabetes is more frequent than other CV events and seems to be underestimated. A burning question is therefore if the most used trial design to monitor CV safety, i.e. non-inferiority, allows clinical translation of trial findings. Available data further suggest that the CV effects of anti-diabetic drugs may be rather class-specific and are only partly due to their glucose-lowering actions. Metformin, recommended as first line in most guidelines, shows positive CV effects while other classes like thiazolidinediones may precipitate HF. Experimental results on the relatively novel dipeptidyl peptidase IV (DPP IV) inhibitors imply CV protective effects, but the non-inferiority trials published to date show an overall neutral CV outcome and a potential increase in HF by saxagliptin. However, results on sitagliptin of the recently released TECOS indicate that HF is not a class-dependent effect of DPP IV inhibitors.
Conclusion: Further basic research and long-term outcome studies to clarify the effects of antidiabetic agents on CV and HF are required so that we can select the optimal antidiabetic therapy for our patients.

Introduction

The number of patients with type 2 diabetes mellitus (T2DM) is increasing at an alarming rate – nearly 400 million people worldwide have the condition and there were an estimated 4.9 million deaths in 2014, most of which were as a result of cardiovascular (CV) disease [1,2]. After adjustment for other common risk factors, the chance of developing CV disease is nearly doubled in patients with T2DM and life expectancy is more than 6 years less for a 40-year-old patient with diabetes compared to someone without diabetes [2]. T2DM is not only an independent risk factor for CV disease but is also associated with a higher incidence of heart failure (HF) in both women (5-fold increase) and men (2.4-fold increase) [2–4]. It is therefore vital that healthcare professionals worldwide implement effective treatment strategies not only to improve outcomes and the quality of life of

* Corresponding author. Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, 00133 Rome, Italy. Tel.: +39 0620902085; fax: +39 0672596890.
E-mail address: federicm@uniroma2.it (M. Federici).

http://dx.doi.org/10.1016/j.numecd.2015.06.006
0939-4753/

patients with T2DM but also to reduce the ever-increasing costs to public healthcare systems.

Levels of hemoglobin A1c (HbA1c), a widely accepted marker for glycemic control in T2DM, correlate not only with micro- and macrovascular complications but also with new-onset HF, leading to the long-held assumption that reducing HbA1c with glucose-lowering drugs also reduces CV events and HF [5,6]. More recently this hypothesis has been questioned and the beneficial CV effects of antidiabetic drugs seem to be class-specific rather than caused by their glucose lowering effects. Moreover, some antidiabetic agents have been suspected to have detrimental CV effects, such increased risk of HF.

Is HF underestimated in T2DM?

HF in patients with T2DM is a serious condition resulting in high morbidity and mortality and as such should not be underestimated. Bertoni and colleagues showed an almost 10-times greater mortality per 100 person-years in patients with T2DM with HF, compared to patients without HF (32.7 vs. 3.7 per 100 person-years) [7]. Moreover, it is worth noting that in most diabetes trials such as Look AHEAD [8], RENAAL [9], PROactive [10] and ALTITUDE trial [11], the incidence of HF is even more common than that of other CV events such as stroke and myocardial infarction (MI). Only the UK Prospective Diabetes Study (UKPDS) showed a smaller incidence of HF compared to MI (3 vs. 15%) [17,18] perhaps due to the fact that only patients with newly diagnosed diabetes were recruited. The incidence of HF increases with age and disease progression and, as most studies exclude elderly and patients with history of HF, the risk of developing HF might be even greater than that reflected in most studies. An important issue is the lack of randomized trials evaluating the effect of antidiabetic drugs on HF prognosis. A systematic review by Gitt and colleagues revealed that existing evidence is mainly based on retrospective studies and subgroup analyses of larger trials, whereas randomized trials addressing this issue are only available for thiazolidinediones and sulfonylureas [12].

An additional challenge is the heterogeneity of HF with respect to its pathogenesis, clinical presentation and link to diabetes. As an example, studies generally include patients with post-ischemic HF and reduced systolic ejection fraction, while trials that specifically include patients with diastolic dysfunction – HF with preserved ejection fraction that is common in patients with T2DM – are rare [12]. Clearly, a better identification of HF subtypes in T2DM subjects would lead to define patients who could be included in safety trials and diabetic treatments that may negatively or positively affect the course of HF independently from the hypoglycemic effect.

Antidiabetic agents and cardiovascular safety concerns

A meta-analysis by Nissen and colleagues published in 2007 suggested that rosiglitazone slightly increases risk of MI [13]. This finding raised the question of the CV safety of antidiabetic drugs and changed the entire landscape of subsequent diabetic trials. In 2008 the US Food and Drug Administration (FDA) revised the approval process for new antidiabetic agents to ensure CV safety of novel drugs [14]. At present, if clinical data of a new antidiabetic drug before approval reveal an upper boundary of the two-sided 95% CI for increased CV risk between 1.3 and 1.8, a subsequent study is required for approval of the drug to show that the upper boundary of the 95% CI is below 1.3. As a consequence, greater numbers of patients as well as patients with more advanced stages of disease have to be included to reach the more stringent test of below 1.3 [15]. These new requirements were welcomed, because more T2DM cardiovascular outcome trials are enrolled and more valid CV safety data regarding antidiabetic drugs are acquired. However, most studies are designed to satisfy safety requirements in the shortest time possible and as a result adverse events of antidiabetic drugs in the long-term might not be recorded. Another major issue is that, in general, only major adverse CV events (MACE) (normally defined as CV death, MI, or stroke) are required as primary outcomes to demonstrate CV safety. Consequently, many large randomized trials did not include HF as primary endpoint and some not even as secondary [16]. Interestingly, although regulatory agencies advocate that pharmaceutical companies produce clinical evidence that antidiabetic drugs do not cause MACE, so far no glucose-lowering drug has clearly been associated to increased incidence of MACE in a randomized trial, whereas some antidiabetic drugs have shown an association to increased HF risk [16].

Effects of intensive glucose lowering

The UKPDS, published in 1998 was the first trial to address the effects of Hb1Ac lowering on CV outcomes [17,18]. In this large-scale, landmark trial, patients with newly diagnosed T2DM were randomized to receive either a conventional glucose-lowering strategy (diet intervention, secondary randomization to glucose-lowering treatment if fasting glucose $>$ 15 mmol/l) or intensive treatment with insulin, sulfonylurea or metformin (obese patients). While microvascular complications were significantly reduced in the intensive treatment group (25% relative risk reduction, $p = 0.0099$), the relative risk reduction for MI was only close to significant (15%, $p = 0.052$). Only the metformin group had a significant reduction in CV events [17,18]. While the effects of intensive blood glucose lowering on microvascular complications are undisputed, the fact that changes in macrovascular events only reached borderline significance has been intensively debated. The 10-year UKPDS follow-up published in 2008, did provide expected results – a significant risk reduction for MI (15%, $p = 0.01$) as well as all-cause mortality (13%, $p = 0.007$) in the former intensive treatment group with greater results in the metformin subgroup [19], although glycemic differences between the two groups were lost one year after the study end. The authors interpreted those findings as being caused by a 'legacy effect' of former treatment.