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REVIEW

DPP-4 inhibitors and cardiovascular disease in type 2 diabetes mellitus. Expectations, observations and perspectives

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Abstract *Aims:* Cardiovascular disease (CVD) is the greatest burden of type 2 diabetes mellitus (T2DM) in terms of morbility, mortality and costs for individuals and societies. Therefore, its prevention is a major goal in diabetes care. Optimal treatment of hyperglycemia is certainly instrumental to CVD prevention. Optimal treatment means both establishing the most appropriate glycemic target for the given individual and selecting the medication(s) with the most favourable benefit/safety ratio. CVD safety, if not a clear CVD benefit, is certainly required for all antidiabetic agents.

Dipeptidyl-peptidase-4 (DPP-4) inhibitors are among the classes of antidiabetic agents most recently made available for diabetes care. A major question to be addressed is the effect of these compounds on CVD. Expectations were high for their mechanism of action, which targets also post-prandial glucose and minimize hypoglycemia risk, thereby providing a sort of global glucose control, and for some potentially beneficial extra-glycemic effects. This article reviews the existing literature on this issue.

Data synthesis: Data published so far document that DPP-4 inhibitors have a wide spectrum of glycemic and extra-glycemic effects potentially reducing the risk of CVD as well as favourable effects on intermediate or surrogate CVD endpoints. These data heralded a better CVD outcome. Accordingly, pooling CVD safety data from phase 3 and 4 studies conducted with DPP-4 inhibitors suggested that their use might translate into a better CVD outcome. Data from three CVD outcome RCTs with alogliptin, saxagliptin and sitagliptin documented no harm but did not show any benefit on major CVD events. A modest but significant increased risk of hospitalization for heart failure was observed with saxagliptin and with alogliptin (only in subjects with no history of heart failure before randomization) but not with sitagliptin. A study currently in progress with linagliptin will provide further insights in the issue of CVD safety and benefit.

Conclusions: It should be considered that most alternative oral antidiabetic agents generally do not possess a better CVD risk profile than DPP-4 inhibitors and that some of them, indeed, should be used with caution because of potentially adverse effects on heart and vasculature. Overall, the selection of antidiabetic agent(s) with the most favourable CVD profile is mandatory but still challenging in diabetes care.

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Cardiovascular disease in type 2 diabetes

Type 2 diabetes mellitus (T2DM) incidence and prevalence are steadily increasing worldwide due to several reasons, including aging of the population, earlier development of the disease, longer survival of people affected, spreading of sedentariness and physical inactivity with consequent greater occurrence of overweight and obesity [1,2]. The endless expansion of T2DM population results in costs which are continuously raising and hard to be borne by individuals, families and societies. Nowadays, diabetes-related costs already exceed 10% of overall health providing expense in affluent countries [3]. Remarkably, diagnosis, monitoring and care of chronic complications represent the largest fraction of diabetes-related costs [4].

Among chronic complications, cardiovascular diseases (CVD), although not-diabetes specific as retinopathy, are certainly the most prevalent and money-consuming. As many as 80% of hospitalizations from diabetes complications are due to cardiovascular disease [5]. Myocardial infarction, stroke and other varieties of CVD (e.g., aortic aneurisms or peripheral arteriopathy) are by far the leading cause of death in diabetes [6,7] and the main cause of decreased life expectancy in diabetic persons [8,9]. Also non fatal CVD events are more common in diabetic vs. nondiabetic persons, with relative risk being 2 (coronary or cerebrovascular) to 10-fold (leg amputations) higher [10,11]. Interestingly the relative risk of CVD was higher in women than in men with diabetes as compared to their nondiabetic counterparts [12]. These figures clearly point out the need to identify the most effective intervention strategies and the best clinical practices to prevent, delay or arrest the progression of CVD in T2DM. Among them, it is obvious to consider optimal glycemic control, although optimal might not be equivalent to intensive in all individuals with T2DM. In this context it is noteworthy mentioning that the relationship between HbA1c and CVD hospitalization and all-cause mortality is J-shaped or U-shaped in observational studies [13].

Glycemic control and cardiovascular disease in diabetes

Fasting, 2-h OGTT and HbA1c levels are directly correlated to CVD morbidity and mortality in observational studies carried out in samples from the general population [14–16]. The same was found in observational studies focusing on people with T2DM [17–19].

Although the main target remains HbA1c, the modern vision of diabetes care is that a quintet of markers of glycemic homeostasis should be carefully monitored and considered when addressing CVD prevention: HbA1c, fasting glucose, post-prandial glucose, glucose variability and hypoglycemia. These markers are indeed pathogenetic factors responsible for fatal events: collectively they could be defined as a “deadly glycemic quintet”. In fact, although fasting and interprandial glucose levels are the main determinants of HbA1c, post-prandial peaks, which are very common in T2DM, also contribute to HbA1c [20,21] and have been associated to a greater CVD risk [22]. Yet, glycemic variability has been associated to greater CVD mortality [23]. As to hypoglycemia, many observational and intervention studies documented that it is a predictor of future CVD events [24–26].

Experimental studies provided biological plausibility to the concept that high glucose is harmful for arteries [27,28] and strengthened the idea that increased risk of CVD in diabetes can be attributed, at least partially, to higher than normal glucose levels. Other experimental studies pointed out the detrimental vascular effects of glucose peaks [29,30], glucose fluctuations [31,32], and hypoglycemia [33,34].

Many of the criteria supporting a cause–effect relationship between glycemia and CVD have been satisfied by epidemiological and experimental studies but the most important ones have not been satisfied or have been fulfilled in a conflicting way. Intervention trials in which subjects with different HbA1c targets were compared, in fact, provided controversial or inconclusive results. In these trials, however, the beneficial effect of lowering glucose could be intertwined with the effects, perhaps not always favorable, of the medications used to lower blood glucose. This concept is somewhat neglected.

In the UGDP study, an increased CVD mortality was observed in patients treated with sulphonylureas, and similar CVD mortality rates were recorded in less intensively vs. more intensively insulin-treated patients, despite the lower glucose levels achieved in the latter [35]. In the UKPDS the incidence of myocardial infarction was not significantly reduced in subjects more intensively treated with sulphonylureas or insulin and only the use of metformin resulted in a better CVD outcome in intensively-treated subjects [36,37]. In the UKPDS, however, a significant CVD benefit of intensive treatment with sulphonylureas or insulin could be detected in the post-trial observation extended for further 10 years [38]. In the ACCORD study the effect of a very aggressive glucose-lowering treatment (HbA1c goal $<6\%$) vs. standard treatment was unfavorable, with an increased all-cause and CVD death rate, despite a lower incidence of non-fatal CVD events [39]. Only in certain subgroups of ACCORD study (e.g., subjects without prior CVD) intensive treatment of diabetes yielded a better CVD outcome. Also in the ADVANCE study a more intensive (HbA1c $\leq$ 6.5%) vs. a standard glucose control was unable to improve CVD outcome [40]. The same negative result was found in the VADT, another study where patients at high CVD risk and long standing T2DM were treated with a more vs. less aggressive glucose control (difference in HbA1c of about 2% in the two arms) [41], although some benefit was observed in an extended observation [42]. Yet, the ORIGIN trial, mainly focusing on subjects with pre-diabetes but including also several patients with diabetes and high CVD risk, failed to demonstrate an advantage of a very strict vs. less stringent glucose control achieved with basal insulin [43]. Although several meta-analyses support the conclusion that intensive glucose control can prevent CVD in diabetes [44–46], the concept was developed, then consolidated in current guidelines [47] and recently