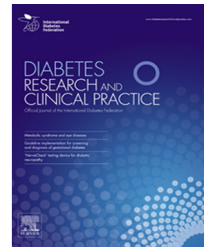




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# Implications of the recent CVOTs in type 2 diabetes: The right place for DPP-IV inhibitors today

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The use of small molecule inhibitors of the enzyme dipeptidyl peptidase IV (DPP4i) was proposed in 1998 as an approach to the management of diabetes, acting by reducing glucagon-like peptide 1 (GLP-1) degradation and hence potentiating its insulinotropic effect [1]. By 2005, effects of the DPP4i vildagliptin [2] and sitagliptin [3] were reported in human trials, leading to the development of a class of drugs whose use among US Medicare beneficiaries alone accounted for expenditure of \$1.5 billion in 2012, increasing to \$3.9 billion in 2017 [4]. During these two decades, there have been tremendous changes in our understanding of the outcomes of treatment of type 2 diabetes (T2D), with questions raised about potential harms of rosiglitazone by some authors [5], although debated [6], leading to an administrative decision by the US FDA that all treatments for T2D are required to undergo clinical trials to determine whether they are safe in persons with cardiovascular disease (CVD), considerably increasing the cost of developing such treatment [7].

Trials of DPP4i have suggested no overall CVD harm for saxagliptin [8], alogliptin [9], sitagliptin [10], and linagliptin [11]. The trial with saxagliptin showed, however, a significant increase in hospitalization for heart failure (8), and the point estimate and 95% confidence limits did not exclude such an adverse effect with alogliptin (9). No such effect was seen either for sitagliptin or for linagliptin [12]. At the same time, trials of GLP-1 receptor activators (GLP-1 RA) demonstrated CVD outcome benefit, and trials of the sodium glucose transporter (SGLT)-2 inhibitors suggested CVD benefit, particularly in persons with T2D at risk of heart failure and mortality, the latter agents as well showing improvement in renal disease outcome [13], and both the GLP-1 RA and DPP4i associated with reduction in albuminuria [14].

Does this allow us to, at best, only say that “DPP4 inhibitors are a safe choice within the glucose-lowering stepped algorithm” (13)? Certainly, the DPP4i are effective glucose-lowering agents. In a 5-year study of nearly 2000 persons with

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T2D selected early after diagnosis, compared with initial use of metformin alone, the combination of vildagliptin with metformin led to nearly 50% less treatment failure (defined by HbA1c exceeding 7%) [15]. In the CARMELINA CV outcome trial, patients randomized to linagliptin had HbA1c 0.3–0.6% lower than those receiving matching placebo, despite investigators being encouraged “to monitor and use additional medication for glycemic control” for the latter group (11). Furthermore, the DPP4i are safer than sulfonylureas in terms of hypoglycemia and weight gain. In the CAROLINA CV outcome trial comparing linagliptin with the sulfonylurea (SU) glimepiride, glycemic control was comparable, and CV outcomes were similar, but glimepiride led to 4.8x more hypoglycemia than linagliptin, 11.1 vs 2.3 events per 100 participant years, with severe hypoglycemia occurring at rates of 0.45 vs 0.07 per 100 patient-years and hospitalization for hypoglycemia at rates of 0.18 vs 0.01 per 100 participant-years; glimepiride was also associated with a 1.54 kg greater final weight than linagliptin [16]. Observational studies affirm the CVD safety of the DPP4i [17], with a suggestion of CVD benefit in one metaanalysis [18], while a number of observational studies have led to the suggestion that, compared with other agents, including DPP4i, the SU may be associated with adverse CVD outcome [19–22].

The use of DPP4i in combination with other agents should be discussed. It may particularly be the case that DPP4i lead to lower mortality than SU when given in combination with metformin ([23]). Although the trial comparing metformin alone with metformin plus vildagliptin was not powered to assess differences in CVD outcomes, 2.4% of those receiving the combination but 3.3% of those randomized to metformin alone had adjudicated macrovascular events (15). DPP4i are useful components of glucose-lowering treatment in combination with insulin [24], a setting in which concomitant treatment with SU often is discontinued [25]. The use of DPP4i in combination with SGLT2i may have important effect in not only further improving glycemia but also in leading to further reduction in albuminuria [26], potentially increasing renal outcome benefit.

An emerging concept is that the DPP4i may improve CVD outcome when given early in the course of T2D. Although the GLP-1RA are more potent glucose-lowering agents than the DPP4i in clinical trials, because of their gastrointestinal side effects the observation has been made that, in clinical practice the two groups are of similar efficacy, suggesting that treatment adherence may be greater with the DPP4i [27]. It is increasingly recognized that there are numerous barriers to T2D patient adherence [28], and, over the long term, the DPP4i may have important advantages in this regard. Furthermore, it has been speculated that, given before development of atherosclerosis, DPP4i may exert benefit by GLP-1-dependent mechanisms on endothelial and myocardial function [29], while in addition acting to increase stromal derived factor (SDF)-1 $\alpha$  [30]. SDF-1 $\alpha$  may exert cardioprotective effects early, prior to the development of clinical CVD, by increasing angiogenesis, while, later, SDF-1 $\alpha$  may already be present to the extent that further elevation may have profibrotic effects, acting by increasing mesenchymal precursors (12), possibly explaining the evidence of increasing heart failure risk in diabetic persons with existing CVD discussed above. In animal

models of stress-induced vascular aging, DPP4i improved molecular and morphological vascular characteristics [31].

Thus, there remain important roles for the DPP4i today. They are in widespread use, well-tolerated, not causing hypoglycemia or weight gain, and lacking the gastrointestinal side effects of the GLP-1RA and the genitourinary side effects of the SGLT2i. Although not having the evidence of CVD outcome benefit seen in trials of the GLP-1RA and SGLT2i in persons with T2D selected as being at high CVD risk, there has been interesting speculation that they may have such benefit when given over longer time periods beginning earlier in the course of T2D [32,33].

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## Declaration of Competing Interest

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