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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)-1α [30]. SDF-1α may exert cardioprotective effects early, prior to the development of clinical CVD, by increasing angiogenesis, while, later, SDF-1α 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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REFERENCES

[1] Deacon CF, Hughes TE, Holst JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. Diabetes 1998;47:764–9.
[2] Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, et al. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. J Clin Endocrinol Metab 2005;90:4888–94.
[3] Herman GA, Stevens C, Van Dyck K, Bergman A, Yi B, De Smet M, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clin Pharmacol Ther 2005;78:675–88.
[4] Sumarsono A, Everett BM, McGuire DK, Fonarow GC, Butler J, Pandey A, et al. Trends in aggregate use and associated expenditures of antihyperglycemic therapies among US medicare beneficiaries between 2012 and 2017. JAMA Intern Med 2019. https://doi.org/10.1001/jamainternmed.2019.3884.
[5] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
[6] Bloomgarden ZT. The Avandia debate. Diabetes Care 2007;30:2401–8.
[7] McGuire DK, Marx N, Johansen OE, Inzucchi SE, Rosenstock J, George JT. FDA guidance on antihyperglyacemic therapies for type 2 diabetes: one decade later. Diabetes Obes Metab 2019;21:1073–8.
[8] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317–26.
[9] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 Oct 3;369 (14):1327–35.

[10] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of Sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015 Jul 16;373(3):232–42.
[11] Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2019;321(1):69–79.
[12] Bell DSH, Goncalves E. Heart failure in the patient with diabetes: Epidemiology, aetiology, prognosis, therapy and the effect of glucose-lowering medications. Diabetes Obes Metab 2019 Jun;21(6):1277–90.
[13] Home P. Cardiovascular outcome trials of glucose-lowering medications: an update. Diabetologia 2019 Mar;62(3):357–69.
[14] Bloomgarden Z. The kidney and cardiovascular outcome trials. J Diabetes 2018;10:88–9.
[15] Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet. 2019 Sep 17. pii: S0140-6736(19)32131-2. doi: 10.1016/S0140-6736(19)32131-2.
[16] Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019 Sep 19. doi: 10.1001/jama.2019.13772.
[17] Liu D, Jin B, Chen W, Yun P. Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. BMC Pharmacol Toxicol 2019 Mar 4;20(1):15. https://doi.org/10.1186/s40360-019-0293-y.
[18] Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. Curr Med Res Opin 2011;27(Suppl 3):57–64.
[19] Bain S, Druyts E, Balijepalli C, Baxter CA, Currie CJ, Das R, et al. Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: a Bayesian meta-analysis of survival data. Diabetes Obes Metab 2017 Mar;19(3):329–35.
[20] Raghavan S, Liu WG, Saxon DR, Grunwald GK, Maddox TM, Reusch JEB, et al. Oral diabetes medication monotherapy and short-term mortality in individuals with type 2 diabetes and coronary artery disease. BMJ Open Diabetes Res Care 2018 Jun 15;6(1) e000516.
[21] Prentice JC, Conlin PR, Gellad WF, Edelman D, Lee TA, Pizer SD. Capitalizing on prescribing pattern variation to compare medications for type 2 diabetes. Value Health 2014 Dec;17 (8):854–62.
[22] Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Association between first-line monotherapy with sulphonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. Diabetes Obes Metab 2014 Oct;16 (10):957–62.
[23] Crowley MJ, Gokhale M, Pate V, Stürmer T, Buse JB. Impact of metformin use on the cardiovascular effects of dipeptidyl peptidase-4 inhibitors: an analysis of Medicare claims data from 2007 to 2015. Diabetes Obes Metab 2019;21:854–65.
[24] Roussel R, Duran-García S, Zhang Y, Shah S, Darmiento C, Shankar RR, et al. Double-blind, randomized clinical trial comparing the efficacy and safety of continuing or discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin when initiating insulin glargine therapy in patients with type 2 diabetes: the CompoSIT-I Study. Diabetes Obes Metab 2018 Nov 4. https://doi.org/10.1111/dom.13574.
[25] Xu Y, Pilla SJ, Alexander GC, Murimi IB. Use of non-insulin diabetes medicines after insulin initiation: a retrospective cohort study. PLoS ONE 2019;14 e0211820.
[26] Pollock C, Stefánsson B, Reyner D, Rossing P, Sjöström CD, Wheeler DC, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2019;7:429–41.
[27] Carls GS, Tuttle E, Tan RD, Huynh J, Yee J, Edelman SV, et al. Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. Diabetes Care 2017 Nov;40(11):1469–78.
[28] Larkin AT, Hoffman C, Stevens A, Douglas A, Bloomgarden Z. Determinants of adherence to diabetes treatment. J Diabetes 2015 Nov;7(6):864–71.
[29] Dicembrini I, Monami M, Mannucci E. Dypeptidylpeptidase-4 inhibitors and the cardiovascular system: How to manage the fil rouge. Nutr Metab Cardiovasc Dis 2019;29:215–9.
[30] Gilbert RE. Potential for cardiac protection with dipeptidyl peptidase-4 inhibitors: the stromal cell-derived factor-1α hypothesis. J Diabetes 2013;5:258–60.
[31] Xin M, Jin X, Cui X, Jin C, Piao L, Wan Y, et al. Dipeptidyl peptidase-4 inhibition prevents vascular aging in mice under chronic stress: modulation of oxidative stress and inflammation. Chem Biol Interact 2019 Oct;2. https://doi.org/10.1016/j.cbi.2019.108842 108842.
[32] Bloomgarden Z. Dipeptidyl peptidase-4 inhibitor approaches. J Diabetes 2017 Jan;9(1):5–7.
[33] Scheen AJ. Cardiovascular safety of DPP-4 inhibitors compared with sulphonylureas: results of randomized controlled trials and observational studies. Diabetes Metab 2018;44:386–92.