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Commentary

Why not adding a glucose-lowering agent with proven cardioprotection in high-risk patients with type 2 diabetes at HbA1c target on metformin?

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The American Diabetes Association (ADA) – European Association for the Study of Diabetes (EASD) consensus report 2018 provides an updated view of the management of hyperglycaemia in patients with type 2 diabetes [1]. It emphasizes the crucial role of a personalized approach and places in the foreground the presence of cardiovascular disease as a key element to guide the selection of a second glucose-lowering agent to be added to metformin. The addition of a sodium-glucose cotransporter type 2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended in patients with atherosclerotic cardiovascular disease if glycated haemoglobin (HbA1c) is above the target. This consensus report undoubtedly will help physicians in the selection of a second glucose-lowering agent after failure of metformin monotherapy.

However, this opens a crucial question for clinical practice. Indeed, there is a discrepancy between the target of HbA1c that is recommended in patients at high cardiovascular risk ("less aggressive targets"; i.e. around 8% [64 mmol/mol] instead of <7% [53 mmol/mol]) [2] and the recommended strategy in the consensus report, i.e. adding a glucose-lowering agent with proven cardiovascular benefit if HbA1c is above the target. As a consequence, if physicians strictly follow the proposal, a SGLT2 inhibitor or a GLP-1 receptor agonist will only be added to metformin if HbA1c is above the target, thus in patients with atherosclerotic cardiovascular disease around or above 8% % [64 mmol/mol]. Furthermore, patients with heart failure considered to be at HbA1c target also may be deprived of the benefit by a SGLT2 inhibitor despite the positive effects consistently reported with the pharmacological class that appear independent of glucose control [3,4].

Caution to reduce HbA1c levels to low levels in patients at high risk of cardiovascular disease was driven by the results of the ACCORD (« Action to Control Cardiovascular Risk in Diabetes ») trial that reported a higher risk of cardiovascular mortality (but a lower risk of myocardial infarction) in patients randomized to the group with intensive glucose control [5,6]. However, this restriction is highly debatable and deserves careful reconsideration. First, ACCORD was performed at a time when SGLT2 inhibitors and GLP-1 receptor agonists were not available and intensification of glucose-lowering therapy at that time was mainly based upon insulin, sulphonylureas and glitazones, drugs that may increase the risk of hypoglycaemia and/or heart failure [5]. Furthermore, cardiovascular mortality in the intensified group was observed mainly in patients who did not succeed in reaching HbA1c targets despite the intensification of glucose-lowering therapy rather than in those with low HbA1c [7]. This was confirmed in another post-hoc analysis of ACCORD: intensive treatment was associated with a reduction in a composite of cardiovascular events (primary outcomes) in the low and moderate haemoglobin glycation index subgroups but not in the high haemoglobin glycation index subgroup [8]. Second, all recently published cardiovascular outcome trials that reported a cardiovascular protection, either with SGLT2 inhibitors (empagliflozin in EMPA-REG OUTCOME [9], canagliflozin in CANVAS [10]) or GLP-1 receptor agonists (liraglutide in LEADER [11], semaglutide in SUSTAIN 6 [12], exenatide extended release in EXSCEL [13] and albiglutide in HARMONY

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Table 1 – Subgroup analyses of the primary outcome (triple MACE : major cardiovascular events) according to HbA1c at baseline in cardiovascular outcome trials with SGLT2 inhibitors or GLP-1 receptor agonists. Results are expressed as hazard ratio versus placebo (with 95% confidence interval).

Trials	HbA1c (%) Inclusion criteria	HbA1c (%) (mean ± SD)	Patients "at target"		Patients "not at target"		P for interaction
			HbA1c threshold %	HR (95% CI)	HbA1c threshold %	HR (95% CI)	
EMPA-REG OUTCOME [9]	≥7–≤9	8.07 ± 0.85	<8.5	0.76 (0.64–0.90)	≥8.5	1.14 (0.86–1.50)	0.01
CANVAS [10]	≥7–≤10.5	8.2 ± 0.9	<8.0	0.94 (0.77–1.15)	≥8.0	0.80 (0.68–0.94)	0.29
LEADER [11]	≥7	8.7 ± 1.6	≤8.3	0.89 (0.76–1.05)	>8.3	0.84 (0.72–0.98)	0.58
SUSTAIN-6 [12]	≥7	8.7 ± 1.5	≤8.5	0.72 (0.50–1.03)	>8.5	0.74 (0.52–1.04)	0.94
EXSCEL [13]	6.5–10.0	Median 8.0 (interquartile range : 7.3–8.9)	<8.0	0.91 (0.80–1.05)	≥8.0	0.91 (0.80–1.04)	0.97
HARMONY [14]	≥7	8.76 ± 1.5	<8.0	0.94 (0.73–1.22)	≥8.0–<9.0 ≥9.0	0.68 (0.52-0.89) 0.73 (0.58–0.91)	0.187

HbA1c: glycated haemoglobin. HR: hazard ratio. IC: confidence interval. SD: standard deviation.

[14]) recruited type 2 diabetes patients with baseline HbA1c ≥ 6.5–7.0% (48–53 mmol/mol) as inclusion criterion (Table 1). No significant interaction was observed regarding the reduction in primary outcome (triple major cardiovascular events, i.e. cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke) when the diabetic population was divided according to the baseline HbA1c level: <8–8.5% (weighted mean ± SD hazard ratio or HR 0.87 ± 0.08) versus > 8.0–8.5% (HR 0.84 ± 0.12); mean difference 0.04, NS. No heterogeneity was observed between SGLT2is and GLP-1 receptor agonists [15], but yet across trials ($p < 0.0001$), mainly due to the results of EMPA-REG OUTCOME. This trial that compared empagliflozin with placebo in patients with type 2 diabetes and established cardiovascular disease is the only one that showed a significant between-subgroup interaction ($p = 0.01$), with a better (not worse) protection by empagliflozin in patients with HbA1c < 8.5% [HR 0.76 (95% CI 0.64–0.90)] compared with patients with HbA1c ≥ 8.5% [HR 1.14 (95% CI 0.86–1.50)] at baseline [9]. Third, both SGLT2 inhibitors and GLP-1 receptor agonists are not associated with a higher risk of hypoglycaemia, except when they are added to sulphonylureas or insulin therapy, so there is no obvious risk to prescribe these agents even in metformin-treated patients with rather well controlled type 2 diabetes. Fourth, there are an increasing amount of arguments suggesting that the cardioprotection by either SGLT2 inhibitors [16,17] or GLP-1 receptor agonists [18,19] occurs independently of improvement of glucose control [6,15]. Fifth, the favourable effects of SGLT2 inhibitors on cardiovascular outcomes, heart failure and total mortality were confirmed in large observational studies like CVD-REAL, suggesting that the data from randomized clinical trials with SGLT2 inhibitors to a large extent may be extrapolated to real life clinical practice [4].

Thus, a key unresolved question for clinical practice is how to manage patients with established cardiovascular disease who have HbA1c < 8.0–8.5% [64–69 mmol/mol] on metformin monotherapy. When analysing the available data from clinical trials, there is no reason not to prescribe a SGLT2 inhibitor or a GLP-1 receptor agonist with proven cardiovascular benefit in this population even if HbA1c is between 7% [53 mmol/mol] and 8% [64 mmol/mol]. Despite the enormous effort of the expert panel to provide a helpful document [1], there remains an open question whether a SGLT2 inhibitor or a GLP-1 receptor agonist should or should not be used in type 2 diabetes patients with atherosclerotic cardiovascular disease or heart failure who are still considered to be at target for HbA1c.

Conflict of interest disclosure

No conflicts of interest are directly relevant to the content of this letter.

A.J. Scheen has received lecturer/advisor fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, NovoNordisk, Sanofi and Servier. He worked as clinical investigator in the TECOS, LEADER, EMPA-REG OUTCOME, CANVAS-R and HARMONY-OUTCOMES trials.

REFERENCES

[1] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European association for the study of diabetes (EASD). Diabetologia 2018;61:2461–98.

[2] American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2018. Diabetes Care. 2018;41:S55–S64.

[3] Butler J, Hamo CE, Filippatos G, Pocock SJ, Bernstein RA, Brueckmann M, et al. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. Eur J Heart Fail 2017;19:1390–400.

[4] Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. Circ Res 2018;122:1439–59.

[5] Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff Jr DC, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–28.

[6] Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a Diabetes Care Editors' Expert Forum. Diabetes Care 2018;41:14–31.

[7] Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Byington RP, Cohen RM, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983–90.

[8] Hempe JM, Liu S, Myers L, McCarter RJ, Buse JB, Fonseca V. The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Diabetes Care 2015;38:1067–74.

[9] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.

[10] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.

[11] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.

[12] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.

[13] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–39.

[14] Hernandez AF, Green JB, Janmohamed S, D'Agostino Sr RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–29.

[15] Scheen AJ. Cardiovascular outcome studies in type 2 diabetes: comparison between SGLT2 inhibitors and GLP-1 receptor agonists. Diabetes Res Clin Pract. 2018;143:88–100.

[16] van Baar MJB, van Ruiten CC, Muskiet MHA, van Bloemendaal L, RG IJ, van Raalte DH. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018;41:1543–56.

[17] Kuo S, Ye W, Duong J, Herman WH. Are the favorable cardiovascular outcomes of empagliflozin treatment explained by its effects on multiple cardiometabolic risk factors? A simulation of the results of the EMPA-REG OUTCOME trial. Diabetes Res Clin Pract 2018;141:181–9.

[18] Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation 2017;136:849–70.

[19] Wang Q, Liu L, Gao L, Li Q. Cardiovascular safety of GLP-1 receptor agonists for diabetes patients with high cardiovascular risk: A meta-analysis of cardiovascular outcomes trials. Diabetes Res Clin Pract 2018;143:34–42.