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Commentaries

Commentary: Glucose control: Not just a bystander in GLP-1RA-mediated cardiovascular protection

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Cardiovascular (CV) disease prevention in type 2 diabetes (T2D) demands multifactorial interventions including treatment of dyslipidemia, hypertension, hypercoagulability, and certainly hyperglycemia [1]. However, randomized controlled trials specifically addressing the impact of intensive glucose control (IGC) on CV outcomes yielded ambiguous results [2], while real-life evidence from a Swedish nationwide registry showed hyperglycemia as the strongest predictor of myocardial infarction (MI) and stroke [3]. Although CV outcome trials (CVOT) with GLP-1 receptor agonists (GLP-1RA) were designed to achieve glycemic equipoise, all showed a greater HbA1c reduction in the intervention arm [4–10], allowing to consider the potential effect of different degrees of glucose-lowering on their results.

A recent meta-regression analysis suggested a significant association between mean HbA1c reduction at the end of the trial and MACE HR in CVOT with DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1RA [11]. This association would seem to be restricted only to non-fatal stroke and to CVOT with GLP-1RA [12]. We have confirmed this association with MACE HR considering the between-arm HbA1c difference throughout GLP-1RA CVOT ($R^2 = 0.69$, $p < 0.05$) (Fig. 1, A). Similarly, a mediation analysis of the LEADER trial suggested HbA1c reduction as the most significant mediator of the liraglutide beneficial effects on MACE [13]. The meta-analysis by Kristensen et al. indicated that GLP-1RA CV protection was driven by reductions of stroke and CV death compared to MI [14], while the benefit of IGC in the historical trials was mainly due to MI reduction with little effect on stroke [2]. Interestingly, though, we have performed a univariate regression analysis of GLP-1RA CVOT showing that the association of between-arm difference in HbA1c and MACE HR appears to be driven by reduction of stroke ($R^2 = 0.89$, $p < 0.01$; Fig. 1, B) rather than CV mortality or MI HR (Fig. 1, C–D). Despite its limitations due to a relatively low number of studies vs. high number of variables tested, a step-wise multiple regression analysis reinforces this association, which is maintained after adjustment for sample size, mean diabetes duration, and CV risk of the population (expressed as stroke events/100 patient-year in the control arm of each trial) ($R^2 = 0.99$, $p < 0.05$). Accordingly, a mediation analysis of the REWIND trial recently estimated that HbA1c reduction accounted for approximately 50% of the known salutary effect of dulaglutide on stroke [15]. The beneficial effect of dulaglutide might be limited to ischemic stroke, which was also the most frequently reported type of cerebrovascular event in REWIND [6,15], with negligible effects on hemorrhagic stroke (HR 0.75, 95% CI 0.59–0.94 vs. HR 1.05, 95% CI 0.55–1.99) [15]. Of note, the risk of stroke in the REWIND population was one of the lowest among GLP-1RA CVOT, albeit the number of patients experiencing this type of event was one of the largest (Table 1).

The REWIND trial stood out from the other GLP-1RA CVOT as it enrolled a lower-risk population with better baseline glycemic control (median HbA1c 7.2%) and had the longest follow-up [9]. Also, patients in the intervention arm exhibited a 0.61% lower least square mean (LSM) HbA1c, indicating that most of them achieved and maintained glycemic targets throughout the trial [9], differently than in the other CVOT [14]. Until REWIND, CV benefit from GLP-1RA was demonstrated only in the presence of established CV disease [16]. The hypothesis that tighter glucose control might have contributed to dulaglutide showing MACE reduction in a population at lower CV risk (2.7 vs. 3.7–6.3 CV events/100 patient/year in placebo arm of REWIND vs. other GLP-1RA CVOT, respectively) [17] is tempting. Indeed, IGC previously showed a benefit largely in patients without a history of CV events [2].

Of note, the LSM HbA1c difference in REWIND echoed that seen in ADVANCE [18], one of the three IGC trials: −0.61% vs. −0.67%, respectively. These two trials also share similar participants' age (66 years), median baseline HbA1c (7.2%), mean duration of diabetes (10 years vs. 8 years), and history of CV disease (31.5% vs. 32.2%), as well as median duration of follow-up (5.4 vs. 5.0 years) (Table 2) [9,18]. Nonetheless, ADVANCE failed to show the superiority of IGC on MACE reduction both at the end of the trial (HR 0.94, 95% CI 0.84–1.06, $p = 0.32$) [18] and after 6 years of follow-up (HR 1.00, 95% 0.92–1.08) [19], in contrast to REWIND [9]. The underwhelming results of ADVANCE and the other IGC trials were explained on the basis of using “flawed” drugs, frequently causing hypoglycemia and weight gain, in the “wrong” patients, as a high proportion of them had established CV disease (32–40%) [20]. Not only did dulaglutide lack such adverse events, but evidence accrued so far also showed that GLP-1RA may exert direct CV protection through mechanisms independent of their glucose-lowering effect [17,21], likely explaining the remaining 50% of dulaglutide-mediated cerebrovascular protection [15]. GLP-1RA are widely known to hamper the progression of atherosclerosis modulating systemic inflammation, oxidative stress and endothelial function [21–23]. Furthermore, in vivo animal studies showed that

Abbreviations: CV, cardiovascular; T2D, type 2 diabetes; CVOT, cardiovascular outcome trials; GLP-1RA, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular events; HR, hazard ratio; IGC, intensive glucose control; MI, myocardial infarction; DPP-4, dipeptidyl peptidase-4; SGLT-2, Sodium-glucose costransporter-2; LSM, least square mean.

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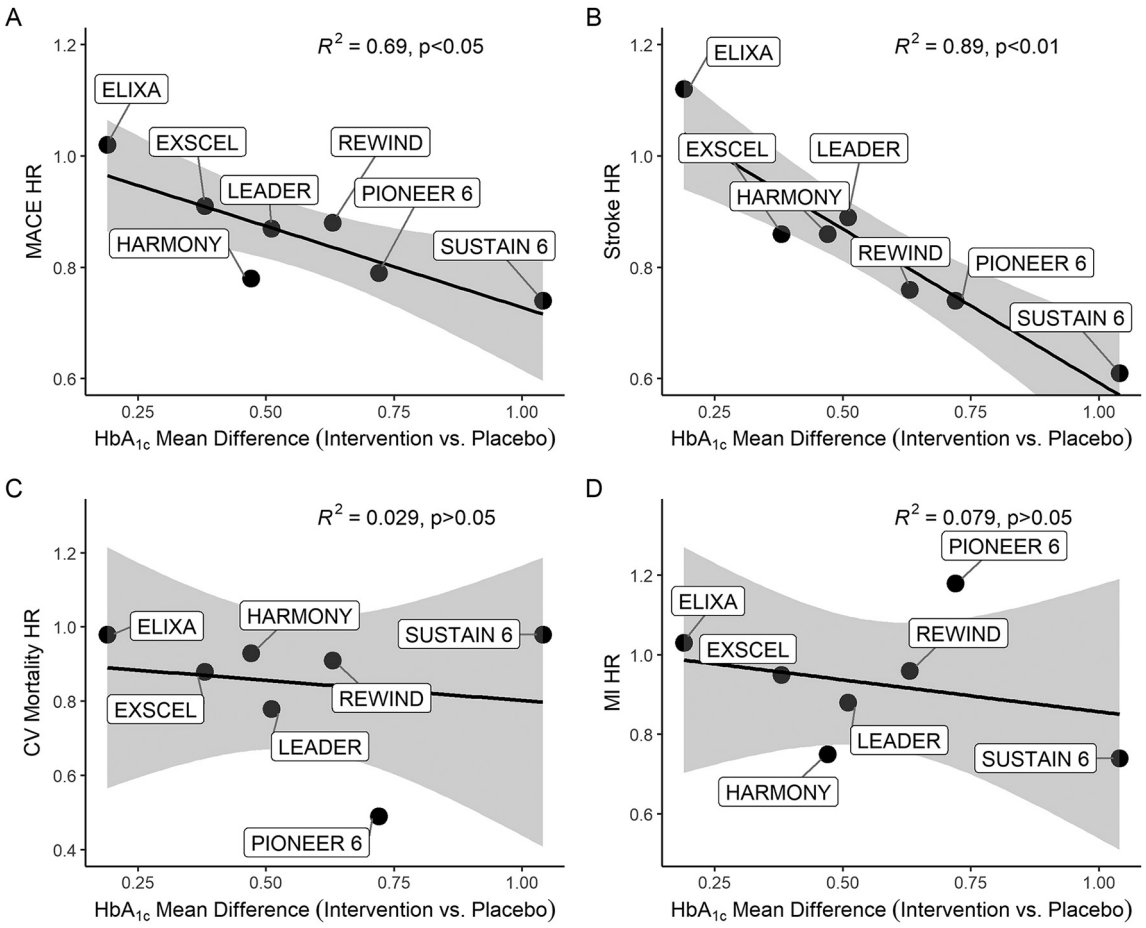

Fig. 1. Association of mean between-arm HbA1c difference and MACE HR. The association of mean between-arm HbA1c difference and MACE HR (A) ($R^2 = 0.69$, $p < 0.05$) is largely driven by reduction of stroke (B) rather than CV mortality (C) or MI (D) HR. The between-arm HbA1c difference was diversely reported in each GLP-1RA CVOTs. To obtain a homogeneous measure, the graphs in each GLP-1RA CVOT were considered, and mean between-arm HbA1c difference was calculated using an Excel Macro specifically developed to measure the areas of irregular polygons, corresponding to the area between the lines describing the HbA1c change over time in the control and intervention arms, respectively. These polygons were traced and measured with reference to the axis scales in each graph, their area representing the integral of %HbA1c over the trial period. Finally, the mean HbA1c difference throughout each trial was calculated by dividing each value per the respective trial duration.

GLP-1RA administration pre- and post-experimental stroke reduced local inflammation, excitotoxicity, blood-brain barrier leakage, oxidative stress and apoptosis [24]; finally, these drugs might even play a beneficial role in neurodegenerative diseases [25,26].

All in all, while IGC alone could hinder the development of atherosclerosis at its early stages but is not as relevant in the presence of overt vascular damage due to the legacy effect [27], the anti-atherosclerotic properties of GLP-1RA might be exploitable in T2D patients with both subclinical and full-blown CV disease [8,9,17]. Hence, the comparison between ADVANCE and REWIND trials fuels the hypothesis that it is the combination of the GLP-1RA safety, anti-atherosclerotic effects and sustained glucose-lowering in the context of a favorable baseline metabolic profile that may bring to light the CV superiority of dulaglutide, especially as pertains to cerebrovascular protection. Interestingly, applying the novel BRAVO risk engine onto the population of CVOT with SGLT-2 inhibitors confirmed the relevant role of glycemic control in CV benefit, mainly on angina and MI, but inaccurately predicted a decrease in stroke that actually did not happen in any of these trials [28]. This suggests that achieving glycemic control per se, while useful, may not be sufficient to confer a cerebrovascular benefit unless it is being achieved with GLP-1RA.

Where IGC strategies [2] and most antidiabetic medications failed to reduce the incidence of stroke and pioglitazone exhibited cerebrovascular protection in patients with a history of stroke and either diabetes or insulin resistance yet increasing risk of fractures, weight gain and heart failure [29,30], GLP-1RA hold the promise of combining overall safety and cerebrovascular efficacy. Indeed, GLP-1RA CVOT were heterogeneous due to baseline characteristics of the population, study design, drugs added in the control arm, adherence and exposure time to GLP-1RA, and changes occurred in CV risk factors, including the level of glycemic control [17]; glycemic efficacy undoubtedly reflected the relative potency of each GLP-1RA, the dose to be used in clinical practice identified following the phase II program, and adherence/exposure to

Table 1
Incidence rate of stroke and number of patients presenting a first event of stroke in the GLP-1RA CVOT.

	Incidence rate of stroke (events/100 patient-year)		Patients with stroke (n.)	
	Control arm	Intervention arm	Control arm	Intervention arm
ELIXA	0.90	1.00	60	67
LEADER	1.10	1.00	199	173
SUSTAIN-6[a]	1.31	0.80	44	27
EXSCEL	0.90	0.80	218	187
HARMONY	1.45	1.25	108	94
Outcomes				
REWIND	0.81	0.61	205	158
PIONEER 6[a]	0.80	0.60	16	12

[a] In SUSTAIN-6 and PIONEER 6, these figures refer only to non-fatal stroke.

Table 2
Key features of the ADVANCE and REWIND trials.

	ADVANCE	REWIND	
Mean age (years)	66	66	*Population*
Female sex (%)	42	46	
Mean diabetes duration (years)	8	10	
CV disease history (%)	32	31	
Median baseline HbA1c (%)	7.2	7.2	
Trial design	Gliclazide MR + other drugs required to achieve HbA1c <6.5% vs. standard treatment	Dulaglutide + SOC vs. placebo +SOC	*Methods*
Median follow-up (years)	5	5.4	
MACE HR	0.94 (95% CI, 0.84–1.06)	0.88 (95% CI, 0.79–0.99)	*Outcomes*
MI HR	0.92 (95% CI, 0.79–1.07)	0.96 (95% CI, 0.79–1.15)	
Stroke HR	0.97 (95% CI, 0.81–1.16)	0.76 (95% CI, 0.62–0.94)	
CV death HR	0.88 (95% CI, 0.74–1.04)	0.91 (95% CI, 0.78–1.06)	
Death from any cause HR	0.93 (95% CI, 0.83–1.06)	0.90 (95% CI, 0.80–1.01)	
Renal outcomes[a] HR	0.79 (95% CI, 0.66–0.93)	0.85 (95% CI, 0.77–0.93)	

CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; MR, modified release; SOC, standard of care.
[a] Defined as new or worsening nephropathy in the ADVANCE trial and as development of a urinary albumintocreatinine ratio >33.9 mg/mmol in those with a lower baseline concentration, a sustained 30% or greater decline in eGFR or chronic renal replacement therapy in the REWIND trial.

the medication – a key factor to the GLP-1RA CV benefit [17]. Moreover, the GLP-1RA CVOT differed in regard to stroke incidence and number of patients with such events (Table 1). Despite the limitations of this analysis and acknowledging GLP-1RA CVOT were not powered to investigate the individual components of the primary endpoint, it could be hypothesized that achieving glucose control specifically with GLP-1RA might convey a distinct cerebrovascular benefit.

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Declaration of competing interest

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