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Editorial

Sodium Glucose Cotransporter 2 Inhibitors, Glucagon-Like Peptide 1 Agonists and Cardiovascular Outcomes – A Lot to Like, A Lot we Still Need to Know

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Editorial

The Federal Drug Administration's (FDA) requirement of cardiovascular safety data for new diabetes agents to be approved in the United States (US) has resulted in several promising clinical studies in the last few years suggesting some diabetes agents may not only be safe and pose no increased cardiovascular risk but may actually provide a cardiovascular benefit in certain patients. What second-line agent to add to initial metformin monotherapy regimen is usually dependent on cost, efficacy, side effect profile (including hypoglycemia risk), and effects on weight [1]. Given the tremendous burden cardiovascular disease has in contributing to diabetes-related complications, an agent to treat hyperglycemia when added to metformin that may also provide a reduction in cardiovascular outcomes would appear quite attractive in our treatment of type 2 diabetes. Such benefit would also then contribute, in addition to the above parameters, in the consideration of a second-line agent to metformin.

Studies to date in assessing the cardiovascular safety of dipeptidyl peptidase-4 inhibitors suggest, outside of a small increased risk for heart failure admissions with the use of saxagliptin, that this class of agent does not increase cardiovascular risk but also do not provide any potential cardiovascular benefit either [2-4]. However, published clinical trials evaluating the cardiovascular safety of Sodium Glucose cotransporter 2 inhibitors (SGLT2i) (Table 1) and Gucagon-Like Peptide 1 (GLP1) agonists (Table 2) in the last two years have provided us with a collection of both promising and not so promising results. There is much to like about these intriguing new trials but there remains a lot we simply do not understand as well. What's to like? With the exception of lixisenatide [5], each of the GLP1 agonists evaluated [6,7] and both of the SGLT2i assessed to date [8,9] have shown a statistically significant decrease in their primary outcome of cardiovascular morbidity and mortality. What secondary outcomes drove these changes in the composite primary outcome varies between study and agent evaluated. Despite identical inclusion criteria, the once-daily GLP1 agonist liraglutide showed a significant reduction in both all-cause and cardiovascular mortality but no effect on cardiovascular morbidity [6] while the once-weekly administered semaglutide did not show a mortality benefit but a reduced risk for stroke and revascularization [7]. With respect to the studied SGLT2is, empagliflozin showed a significant reduction in both cardiovascular mortality and heart failure admissions with no effect on other cardiovascular outcomes [8] while canagliflozin showed only a reduction in heart failure admissions, no mortality benefit, and an increased risk for amputation [9]. The mortality benefits observed with empagliflozin and liraglutide have led to FDA-approved label changes stating in addition to improvements in hyperglycemia the agents may also reduce the risk for cardiovascular death. These are the first ever approved claims for a diabetes medication in this capacity. The results have also led to updates in the American Diabetes Association (ADA) guidelines to now consider the use of either agent in patients with type 2 diabetes whose dysglycemia is not controlled and have established cardiovascular disease [10]. Several of the agents evaluated have also showed a reduced risk for kidney-related outcomes as well [9,11,12]. That's a lot to like.

However, just as promising as these results are, there are issues we simply do not know or can understand at this point in time. First, why the difference in outcomes between the different agents currently evaluated? One possible explanation is the differences in inclusion criteria and hence overall baseline cardiovascular risk. In the canagliflozin study the investigators included patients with established cardiovascular disease (65%) but also included those at high-risk for such (35%) while the empagliflozin study only included those with a history of cardiovascular disease. Subgroup analysis of the canagliflozin trial shows a much higher rate (over two-fold) of the primary outcome in those with established disease than those simply at high risk for such [9]. The higher baseline risk may explain some of the differences in outcomes between these two agents. This issue, however, does not explain why liraglutide and semaglutide, but not lixisenatide, showed improved outcomes as inclusion requirements in the assessment of lixisenatide required an acute coronary syndrome within 180 days of inclusion into the trial while the former agents included a mix of both primary and secondary prevention subjects. Perhaps it is the relatively shorter study duration in the lixisenatide study that explains the differences between agents in this class or conceivably, though doubtful, there is some intrinsic property of liraglutide and semaglutide that explain the differences. One must also remember the cardiovascular safety studies are powered to be non inferior, not superior, to placebo and as such are likely not adequately designed to detect a difference in the secondary outcomes evaluated. As such for the agents that did not show a positive cardiovascular outcome, we can say these agents appear safe from a cardiovascular standpoint however the trials are not adequately designed to assess cardiovascular benefit.

Second, the true mechanism(s) behind the reduced cardiovascular outcomes remain unknown and there does not appear to be a

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Table 1: SGLT-2 Inhibitor CVD Clinical Trial Data.

Study Name	Drug (dose)	Main Inclusion Criteria	Baseline Age (years)	Number of Subjects	Study Duration (years)	Primary Outcome (Relative % Change, p-value)	Key Secondary Outcomes (Relative % Change, p-value)
EMPA-REG OUTCOME [8]	Empagliflozin (10 or 25 mg daily) *vs* placebo	Established CVD	63	7020	3.1	Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (-14%, 0.04)	• Death from any cause (-32%,<0.001) • Death from CV cause (-38%, <0.001) • HF hospitalization (-35%, 0.002) • Fatal or nonfatal MI (-13%, NS) • Fatal or nonfatal stroke (+18%, NS)
CANVAS [9]	Canagliflozin (100 or 300 mg daily) *vs* placebo	Established CVD (65% of patients) or 50 years of age with 2+ CVD risk factors*	63	10,142	3.6	Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (-14%, 0.02)	• Death from any cause (-13%, NS) • Death from CV cause (-13%, NS) • HF hospitalization (-33%, SS, p value not provided) • Fatal or nonfatal MI (-11%, NS) • Fatal or nonfatal stroke (-13%, NS) • Amputation (+97%, SS, p value not provided?

MI: myocardial infarction; CVD: cardiovascular disease; HF: heart failure; NS: non-significant; SS: statistically significant. *CVD risk factors included: 10 year or more history of type 2 diabetes, systolic blood pressure 140+ mm Hg and receiving blood pressure medication, current smoker, microalbuminuria, or macroalbuminuria, or high-density lipoprotein cholesterol < 38.7mg/dl.

Table 2: GLP 1 Agonist CVD Clinical Trial Data.

Study Name	Drug (dose)	Main Inclusion Criteria	Baseline Age (years)	Number of Subjects	Study Duration (years)	Primary Outcome (Relative % Change, p-value)	Key Secondary Outcomes (Relative % Change, p-value)
ELIXA [5]	Lixisenatide (20 mcg once daily)	History of ACS within the last 180 days	60	6068	1.1	Death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (+2%, NS)	• Death from any cause (-6%, NS) • Death from CV causes (-2%, NS) • Fatal or non-fatal MI (+3%, NS) • Fatal or non-fatal Stroke (+12%, NS) • HF Hospitalization (-4%, NS)
LEADER [6]	Liraglutide (1.8 mg once daily)	50 years of age with CVD (81% of patients) or 60 years of age at 1+ factor*	64	9340	3.8	Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (-13%, 0.01)	• Death from any cause (-15%, 0.02) • Death from CV causes (-22%, 0.007) • Fatal or non-fatal MI (-14%, NS) • Fatal or non-fatal Stroke (-14%, NS) • HF Hospitalization (-13%, NS)
SUSTAIN 6 [7]	Semaglutide (0.5-1.0 mg once weekly)	50 years of age with CVD (83% of patients) or 60 years of age at 1+ factor*	64	3297	2.1	Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (-26%, 0.02)	• Death from any cause (+5%, NS) • Death from CV causes (-2%, NS) • Non-fatal MI (-26%, NS) • Non-fatal Stroke (-39%, 0.04) • HF Hospitalization (+11%, NS) • Revascularization (-35%, 0.003)

ACS: acute coronary syndrome; MI: myocardial infarction; CVD: cardiovascular disease; HF: heart failure; NS: non-significant. *CVD risk factors included: increased urine albumin excretion, hypertension with left ventricular hypertrophy, systolic or diastolic dysfunction, or peripheral artery disease.

consensus on the matter but rather speculation as to the real cause [13,14]. That discussion is beyond the scope of this editorial. However, given both classes of medication have benefits not only in improving hyperglycemia, but reduce blood pressure and weight, and have some favorable effects on lipids as well, these likely contribute to the improved cardiovascular outcomes seen in the clinical trials.

Third, are these agents cost-effective? Cost-effectiveness data would be very helpful. None of these agents are inexpensive or likely going to be in the near future. Is the number of patients to treat to prevent one cardiovascular event sufficient to warrant the cost of these newer agents?

What do we need in the future to help in our interpretation of the existing results? Cardiovascular data is still pending on the other US approved SGLT2i, dapagliflozin, and the other once weekly GLP1 agonists, dulaglutide, albiglutide, and exenatide. Hopefully results from ongoing studies in the near future will shed additional light on the subject and help guide clinical practice. If true cardiovascular benefit is to be evident, placebo controlled studies need to be sufficiently powered to do such else we can simply state they are non-inferior to placebo in cardiovascular safety when no obvious outcome is found to be significant. Likewise comparative studies within and between diabetes drug classes would also help in distinguishing one agent or class over another agent in cardiovascular outcomes. To date, the agents have only been compared to placebo. Head to head data in the same patient population, though unlikely to occur due to cost and potential risk to a manufacturer for not seeing a clinical difference, would go a long way in agent selection.

For now, clinicians need to be judicious in clinical decisions in making sure we are selecting the right agent for the right type of patient. At this time if selecting one of these agents to improve both hyperglycemia and cardiovascular outcomes, particularly mortality, the agent selection should be consistent with the ADA recommendations and the recent label changes for some of the agents, i.e. empagliflozin and liraglutide, in that the reduction in cardiovascular events is more profound in those with existing cardiovascular disease. When discussing potential benefit to patients, the information should be consistent with agent selected and its clinical outcomes data. Should new trial data suggest these agents may also play a role in primary cardiovascular prevention, provide additional information on who the idea candidates for therapy may be, and is cost effective, then one could make a strong argument to consider some of these agents a great second-line therapy to add to metformin. Until that time, should it actually arrive, clinicians should stick with what the existing trial data tells us.

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