The Antidiabetic Armamentarium: Reducing the Residual Cardiovascular Risk with HbA_{1c(v)}-Lowering Medications

Editorial to: “GLP-1 Receptor Agonists and Cardiovascular Disease: A Meta-Analysis of Recent Cardiac Outcome Trials” by Jia X, Alam M, Ye Y et al.

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The cardiovascular (CV) safety of pharmacologic therapies to treat patients with type 2 diabetes mellitus (T2DM) has been a concern in the recent past [1–4]. After a series of diabetes medications were observed to be potentially harmful, a guidance document heralded a change in regulatory requirements for any new antidiabetic agent seeking approval after 2008 [5]. Specifically, the guidance document [5] pragmatically identified patient populations at high CV risk that should be included in pre-marketing clinical trials, as they are likely to be treated with glucose-lowering agents (e.g., elderly patients, patients with renal impairment, those with advanced diabetes). Fortuitously, through larger studies aiming to prove CV safety, CV risk reduction has since been reported with two classes of antihyperglycemics—glucagon-like peptide-1 receptor agonist(s) (GLP-1 RA) [6] and sodium-glucose cotransporter-2 inhibitors (SGLT2i) [7, 8].

Three out of four CV-outcome randomized controlled trial(s) (RCT) with GLP-1 RA have reported non-inferiority findings [9–11] and one agent, liraglutide, was found to be superior to placebo [6]. In this issue of *Cardiovascular Drugs and Therapy*, Jia and colleagues conducted a meta-analysis of 33,457 subjects

from these placebo-controlled studies (i.e., LEADER [6] [liraglutide], SUSTAIN-6 [9] [subcutaneous semaglutide], EXSCEL [10] [exenatide extended-release {ER}] and ELIXA [11] [lixisenatide]). Their findings suggest there was not a significant class reduction in the composite of major adverse CV events (MACE) with GLP-1 RA (relative risk [RR] 0.91; 95% confidence interval [CI] 0.81 to 1.02) [12]. However, they did demonstrate that there was a significant reduction in both all-cause mortality (11% relative risk reduction; 95% CI 0.82 to 0.96) and CV mortality (12% relative risk reduction; 0.80 to 0.97). Favorable findings were also found with GLP-1 RA use on diabetic nephropathy (RR 0.73, 95% CI 0.58 to 0.92), but there was increased risk for acute gallstone disease (RR 1.27; 95% CI 1.03 to 1.57). No additional safety concerns were reported, such as severe hypoglycemia and retinopathy, and lingering safety concerns (e.g., acute pancreatitis, medullary thyroid carcinoma) were not significantly increased with the use of this class. The significant reduction in both the patient-centered outcomes of all-cause and CV mortality for this class holds promise. Although significance was not found for the composite MACE endpoint, slightly heterogeneous MACE definitions may be attributable to this finding (e.g., ELIXA [11] included the soft endpoint, hospitalization for unstable angina).

Although the absolute risk reduction (ARR) observed in this meta-analysis may appear small (all-cause mortality ARR 0.89%; CV mortality ARR 0.62%), one should consider that the clinical focus is reducing a patient's residual CV risk. In other words, the vast majority of subjects enrolled in these outcome studies were on standard-of-care medications for CV risk reduction (e.g., statin, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker, etc.), and therefore, the potential incremental benefit is not surprisingly small above and beyond contemporary optimal medical therapy (OMT) [13–15].

The results from this meta-analysis of over 30,000 subjects suggest a positive class effect with GLP-1 RA in patients with

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T2DM with respect to all-cause and CV mortality, in addition to a potential renal benefit. However, given the lack of superiority findings with three of the four outcome studies and differences in patient populations, one has to consider the applicability of these findings to the class as a whole.

The discrepant findings may be attributable, at least in part, to the heterogeneity of the subjects studied. As the authors identify, the ELIXA study [11] (lixisenatide) included high-risk subjects whom had experienced an acute coronary syndrome (ACS) within the past 180 days. All other outcome studies enrolled a combination of both high-risk primary and secondary prevention subjects. One would anticipate a significant clinical benefit in an exclusively secondary prevention population of higher-risk subjects that had recently experienced an ACS. For example, a major RCT with an SGLT2i found significant benefit in a secondary prevention population [7]. The absence of such a benefit in ELIXA raises reasonable questions about their efficacy. Perhaps, the clinical CV benefit relates back to the chemical structure of the GLP-1 RA, with increasing homology to endogenous GLP-1 yielding significant benefit. Or, the CV benefit may relate to the duration of action for a GLP-1 RA; as Jia et al. illustrate, MACE was significantly reduced with long-acting agents (i.e., exenatide ER, liraglutide, semaglutide) [RR 0.88; 95% CI 0.81 to 0.97], but a significant finding was not observed with the shorter-acting agent, lixisenatide (1.02, 95% CI 0.89 to 1.16) [12].

Mechanistically, some may attribute the CV benefit to the glucose-lowering effects with this class and the tighter glycemic control achieved in the treatment arm. However, multiple large outcome studies in subjects with T2DM have failed to demonstrate a reduction in macrovascular findings with intensive glycemic control (i.e., ACCORD [16], ADVANCE [17], United Kingdom Prospective Diabetes Study [UKPDS, initial study] [18] and VADT [19]); arguably, in the UKPDS 10-year follow-up study [20], myocardial infarction decreased significantly in the intensive glycemic control arm. Therefore, the lingering question is whether the findings are medication- and/or class-specific. Jia et al. describe many plausible mechanisms that may explain the observed benefit [12]; however, can one attribute a glucose-independent benefit to a medication and/or class when glycemic equipoise was not achieved? In other words, despite the opportunity to optimize glycemic control with non-incretin-based therapies, the placebo arm in all studies failed to achieve a similar HbA_{1c}. Interestingly, in EXSCCEL [10], a large CV RCT with exenatide ER, dipeptidyl peptidase-4 inhibitors (DPP4i) [i.e., alogliptin, linagliptin, saxagliptin, sitagliptin] were permitted (new DPP4i usage: exenatide ER 7.5%; placebo: 10.6%), which may have blunted the incretin benefit with exenatide ER. Initiation of an SGLT2i during follow-up was also higher in the placebo arm (exenatide ER 6.5%; placebo 9.4%), which is the

only other antihyperglycemic class demonstrating CV benefit [7, 8]. The imbalance in DPP4i and SGLT2i usage, may in part, explain why exenatide ER failed to demonstrate superiority to placebo.

In addition to the disparity in both DPP4i and SGLT2i use, the lack of a superiority finding may be a function of the high discontinuation rate observed in EXSCCEL [10], as identified by Jia and colleagues [12]. Premature permanent discontinuation of treatment was about 44% in both the treatment arm and placebo arm; the main cited reason for discontinuation related to subject decision and individuals not wanting to administer injections. Surprisingly, gastrointestinal events were not the main reason for stopping therapy, which is a well-recognized, early-onset side effect with this class. Clinically, it is important to recognize that the formulation for study drug administration used in this trial was the vials, not the prefilled pens that patients often prefer. Therefore, an inconvenient study drug formulation may have been a burden to subjects, resulting in the highest discontinuation rate across all GLP-1 RA CV RCT.

In summary, Jia et al.'s meta-analysis establishes the efficacy of the GLP-1 RA class in significantly reducing patient-centered outcomes (i.e., all-cause and CV mortality) [12]. The data also reinforce the overall safety profile for this class. In light of parallel findings of CV benefit for two SGLT2i inhibitors [7, 8] a new cadre of clinical questions has arisen, including whether the combination of these two classes would yield an additive CV benefit. It is even more remarkable that we have come to this point as a consequence of unanticipated findings in trials aiming to disprove harm. When considering add-on therapies for patients with T2DM, the nucleus of efficacy has always been an agent's HbA_{1c}-lowering abilities to reduce microvascular outcomes. The development of medications that can also improve CV outcomes, a long-awaited goal, is likely to substantially rework the management of this disease.

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