GLP-1 Receptor Agonists for Cardiovascular Protection: A Matter of Time

Irene Caruso, Angelo Cignarelli, Luigi Laviola, and Francesco Giorgino[a]

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Efpeglenatide is a newly developed exendin-derived long-acting glucagon-like peptide 1 receptor agonist (GLP-1RA). It is characterized by a single-amino-acid modification of the original primary structure to elude dipeptidyl peptidase 4 degradation and conjugation through a flexible linker to the fragment crystallizable region of human IgG4 using the innovative long-acting protein/peptide technology to decrease renal clearance and prevent antidrug antibody development (1). Preclinical studies showed that efpeglenatide may behave as a superagonist, exhibiting lower binding affinity to the GLP-1 receptor (GLP-1R) and inducing reduced GLP-1R internalization and cell desensitization compared with liraglutide and dulaglutide (2). Due to its chemical structure, efpeglenatide is administered once weekly and even once monthly, with glucometabolic effects comparable to those of liraglutide (1).

In the recent AMPLITUDE-O trial, the cardiovascular (CV) safety of efpeglenatide was investigated in patients with baseline features similar to those of other previous CV outcome trials (CVOTs), mostly White (87%) males (67%) in their sixties with longstanding (15.4 years) uncontrolled (HbA_{1c} 8.9%) type 2 diabetes and, in the majority, a history of CV disease (90.5%) (3,4). Distinctive characteristics of the AMPLITUDE-O population compared with other CVOTs with GLP-1RAs were a slightly higher proportion of patients with chronic kidney disease (estimated glomerular filtration rate of <60 mL/min/1.73 m^2 in 32% vs. 21.7–28.5%) and higher use of sodium–glucose cotransporter 2 inhibitors (15.2% vs. 0.2–9.6%); however, it should be noted that the extent of sodium–glucose cotransporter 2 inhibitor drop-in at the end of the trial was similar to that of previous CVOTs (2.3% vs. 2.1–6.5% and 6% vs. 2.8–9.4% in the intervention and control arm, respectively) (3,4). Once-weekly efpeglenatide significantly reduced incident major adverse CV events (MACE) in AMPLITUDE-O, including nonfatal myocardial infarction, nonfatal stroke, or death from CV or undetermined causes, compared with the placebo (hazard ratio [HR] 0.73, 95% CI 0.58–0.92, $P = 0.007$ for superiority) (4). Notably, AMPLITUDE-O is the first CVOT to show the CV superiority of an exendin-derived GLP-1RA.

Percentage of time of exposure to the investigational GLP-1RA throughout the trial was different in the individual CVOTs and could be a relevant contributor to the heterogeneity of results when assessing superiority versus placebo in MACE reduction (3). In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, despite a high reported time of exposure to lixisenatide (88%), one should consider the relatively short half-life ($\sim$3 h) of this particular GLP-1RA, suggesting an estimated actual GLP-1R engagement of only 60% throughout the 24-h period; clinical studies comparing the effect of lixisenatide and liraglutide on heart rate changes corroborated this consideration (3). In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, despite the long pharmacokinetics of exenatide long-acting release (LAR), the unwieldy injection device and other factors related to the pragmatic study design possibly caused a lower time of exposure to this investigational drug throughout the trial (76% vs. 80–90% in other GLP-1RA CVOTs) (3). Of note, lixisenatide and exenatide LAR did not show the superiority of these exendin-derived GLP-1RAs versus the placebo on MACE in ELIXA and EXSCEL, respectively, possibly due to the lower time of exposure to these GLP-1RAs in these trials compared with that of the other GLP-1RA CVOTs. Indeed, a significant positive correlation can be shown between the time of exposure to the investigational GLP-1RA and the MACE absolute risk reduction (ARR) as well as a negative correlation with the MACE HR, as we have recently suggested (3). However, other authors have attributed the lack of CV protection with lixisenatide and exenatide LAR to their exendin-derived structure possibly exerting different biological effects (5). Nevertheless, different biological effects between exendin- and human GLP-1-derived GLP-1RAs have yet to be shown by experimental studies.

During the AMPLITUDE-O trial, adherence to the study treatment regimen was high, as participants were exposed to efpeglenatide and placebo for 88.9% and 91.1% of their maximum follow-up time, respectively (4). Following inclusion of data from AMPLITUDE-O in our previous analysis (3), the positive correlation between percentage of time of exposure to the investigational GLP-1RA

Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy

Corresponding author: Francesco Giorgino, francesco.giorgino@uniba.it

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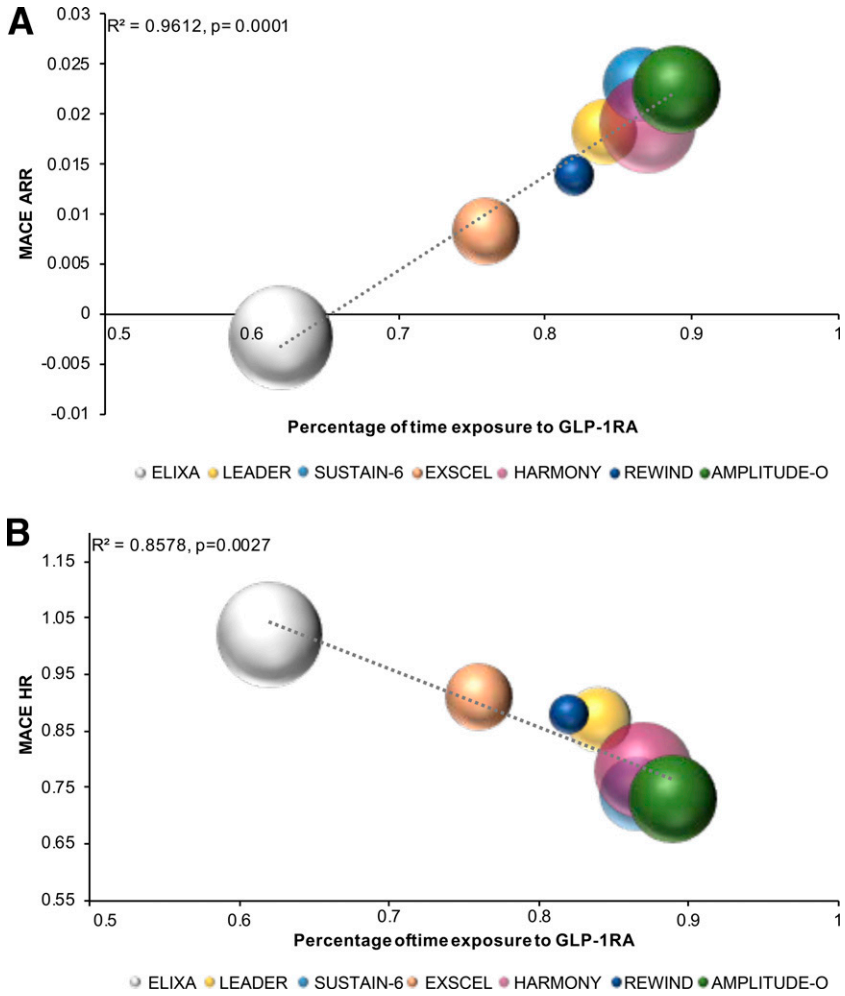

Figure 1–Correlation between percentage of time of exposure to GLP-1RA and the risk of MACE in CVOTs. MACE ARR (*A*) and HR (*B*) are plotted as a function of percentage of time of exposure to GLP-1RA throughout each trial. Sphere size represents the CV risk of the study population expressed as MACE rate in the control arm (number of events per 100 patient-years). The percentage of time of exposure to lixisenatide was reduced from 88% to 55%, accounting for its short half-life and leading to its complete elimination in 15 h, and 60% 24-h exposure compared with 100% 24-h exposure of other GLP-1RAs. Exposure time to oral semaglutide in the Peptide Innovation for Early Diabetes Treatment 6 (PIONEER 6) trial was not disclosed; thus, it was not included in this analysis. LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; HARMONY, Harmony Outcomes trial; REWIND, Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes.

throughout each of the CVOTs and MACE ARR (R^2 = 0.96, $P < 0.001$) and the negative correlation between percentage of time of exposure to the investigational GLP-1RA and MACE HR (R^2 = 0.86, $P < 0.01$) were even strengthened (Fig. 1*A* and *B*). Instead, MACE incident rate in the control arm, a proxy of the study population CV risk, was not significantly correlated with MACE ARR or HR (Fig. 1*A* and *B*). Thus, regardless of their chemical structure, whether derived from human GLP-1 or exendin-4, GLP-1RAs appear to exert CV protection by reducing the MACE incidence as long as patients are exposed to the individual GLP-1RA for a sufficiently long amount of time throughout the study, possibly close to 90%. Consequently, CV protection should be held as a class effect of all GLP-1RAs.

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