Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL)

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Background EXSCEL is a randomized, double-blind, placebo-controlled trial examining the effect of exenatide once-weekly (EQW) versus placebo on time to the primary composite outcome (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) in patients with type 2 diabetes mellitus (DM) and a wide range of cardiovascular (CV) risk.

Methods Patients were enrolled at 688 sites in 35 countries. We describe their baseline characteristics according to prior CV event status and compare patients with those enrolled in prior glucagon-like peptide-1 receptor agonist (GLP-1RA) outcomes trials.

Results Of a total of 14,752 participants randomized between June 2010 and September 2015, 6,788 (46.0%) patients were enrolled in Europe; 3,708 (25.1%), North America; 2,727 (18.5%), Latin America; and 1,529 (10.4%), Asia Pacific. Overall, 73% had at least one prior CV event (70% coronary artery disease, 24% peripheral arterial disease, 22% cerebrovascular disease). The median (IQR) age was 63 years (56, 69), 38% were female, median baseline HbA1c was 8.0% (7.3, 8.9) and 16% had a prior history of heart failure. Those without a prior CV event were younger with a shorter duration of diabetes and better renal function than those with at least one prior CV event. Compared with prior GLP-1RA trials, EXSCEL has a larger percentage of patients without a prior CV event and a notable percentage who were taking a dipeptidyl peptidase-4 inhibitor at baseline (15%).

Conclusions EXSCEL is one of the largest global GLP-1RA trials, evaluating the safety and efficacy of EQW with a broad patient population that may extend generalizability compared to prior GLP-1RA trials (ClinicalTrials.gov number, NCT01144338). (Am Heart J 2017;187:1-9.)

Incretin-based medications including glucagon-like peptide-1 receptor agonists (GLP-1RAs) are routinely used for the treatment of type 2 diabetes mellitus (T2DM).[1] These medications effectively regulate glucose metabolism and have favorable effects on the myocardium and vascular system.[2] GLP-1RAs may also have additional cardioprotective effects such as weight loss.[3] Evidence from randomized clinical trials supports the cardiovascular safety of GLP-1RAs[4] and recent clinical trial data with GLP-1RAs have shown an improvement in major adverse cardiac events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke.[5,6] However, a prior GLP-1RA trial was neutral with respect to MACE[4] suggesting the lack of a class effect and highlighting the need for empiric evaluation of different agents in this class.

The EXSCEL trial is an academically led, placebo-controlled randomized trial of the GLP-1RA exenatide-once-weekly (EQW) in patients with T2DM[7] that has recently completed enrollment. This is a pragmatic trial[8] designed to assess the intervention in a real-world setting with broad entry criteria and streamlined trial conduct (eg, study visits every 6 months, laboratory evaluations as part of routine care) to enhance generalizability. The primary objective of EXSCEL is

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to evaluate the effect of EQW, used in addition to the current usual care for glycemic control and other CV risk factors, on major macrovascular events when administered to patients with T2DM. The study includes both a primary safety hypothesis, that EQW is non-inferior to usual care for MACE, and a primary efficacy hypothesis, that EQW is superior to usual care for MACE.

EXSCEL is unique in that it enrolled patients with a broad range of cardiovascular risk (including those without a prior cardiovascular event) and was not enriched for older people or other specific cardiovascular risk factors, allowed dual usage of incretin therapies [GLP-1 agonist investigational product and dipeptidyl peptidase-4 (DPP-4) inhibitor use] and did not include a run-in period often included to select more compliant patients than in routine practice. Additionally, there are both primary safety and efficacy hypotheses in EXSCEL in contrast to many other large T2DM cardiovascular outcomes trials with only a primary hypothesis of non-inferiority.[4,5] In the present manuscript, we describe the baseline characteristics of EXSCEL participants according to their baseline prior cardiovascular event status and enrolling region and compare patients with those enrolled in prior large GLP-1RA trials.

Methods

The EXSCEL trial is an ongoing, multinational, double-blind, placebo-controlled, randomized trial of the once-weekly GLP-1RA exenatide (EQW) at a dose of 2 mg in addition to usual care for T2DM. The study background and design has been previously published.[7] In brief, the trial enrolled participants with a broad range of cardiovascular risk, from 688 sites in 35 countries from North America, Latin America, Europe, and Asia Pacific. Randomization targeted approximately 70% with a history of a cardiovascular event and 30% without known cardiovascular disease as detailed in the design manuscript.[7] In brief, a prior cardiovascular event was defined as at least one of the following: a major clinical manifestation of coronary artery disease (CAD), ischemic cerebrovascular disease or atherosclerotic peripheral arterial disease (PAD). The trial has completed recruitment and is currently in the follow-up phase until the target event number of 1360 subjects with a confirmed primary composite outcome, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, has accrued.

In the present manuscript, baseline characteristics are presented in a blinded manner for the entire trial population according to prior cardiovascular event status at enrollment and by region. Regions were defined a priori (see Supplemental Table I for countries within each region) and broadly conform to regions defined in other studies in this field to facilitate comparison. We also compare EXSCEL patients with those enrolled in prior large GLP-1RA trials.[4-6]

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Results

Overall, 14,752 participants were randomized between June 2010 and September 2015. The baseline characteristics of the full population are presented in Table I. The majority of patients enrolled in EXSCEL were white (75.8%) with inclusion of 9.8% Asian and 6.0% Black. With regard to ethnicity, 3028 patients (20.5%) reported being Hispanic or Latino. The median (IQR) age was 63 years (56, 69), 38% were female, and 16% had a prior history of heart failure (HF). The median (IQR) HbA1c, diabetes duration, and body mass index (BMI) were 8.0% (7.3, 8.9), 12 (7, 18) years, and 32 (28, 36) kg/m^2, respectively. The most common anti-diabetic medication was metformin (76.5%) followed by insulin (46.2%) and sulfonylureas (36.6%), and DPP-4 inhibitors (14.9%). The baseline use of thiazolidinediones and SGLT-2 Inhibitors was low at 3.9% and 0.9%, respectively.

In terms of World region, 6,788 (46.0%) patients were enrolled in Europe; 3,708 (25.1%), North America; 2,727 (18.5%), Latin America; and 1529 (10.4%), Asia Pacific. Figure 1 shows the enrollment by regions in EXSCEL. Supplemental Table I presents the number of sites and patients enrolled in each country. Table I presents baseline characteristics by World region. Patients from North America tended to be older with a longer duration of DM, a higher BMI and more CAD compared to other regions. Nearly half of the patients from Latin America were women and PAD was more prevalent in Latin America than other regions, yet statin and anti-platelet use was the lowest. Patients from Asia Pacific had the lowest BMI and had less usage of angiotensin converting enzyme (ACE)-inhibitors and angiotensin receptor blockers (ARBs) compared to other regions. In Europe, patients had the highest baseline blood pressure and nearly a quarter of patients had a prior history of HF.

With regard to baseline cardiovascular disease, 73% had at least one prior cardiovascular event (70% CAD, 24% PAD, 22% cerebrovascular disease). Table II presents characteristics by baseline cardiovascular event status. The patients with a prior cardiovascular event tended to be older men with a longer duration of T2DM and worse renal function, but lower BMI and low-density lipoprotein (LDL) cholesterol, and similar blood pressure and HbA1c compared to those without known prior cardiovascular events at baseline. Compared to patients without a prior cardiovascular event, patients with a prior cardiovascular event had similar usage of DPP-4 inhibitors, less metformin and sulfonylurea use, and more insulin therapy. Evidence-based medications to address cardiovascular risk (eg, anti-hypertensive therapy, aspirin,