Neutral Results Obtained in the ELIXA Trial

Written by Muriel Cunningham

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of mortality after experiencing an acute coronary syndrome (ACS) event, so reducing cardiovascular (CV) risk in this population is an ongoing research effort. Eldrin F. Lewis, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented results from the event-driven ELIXA trial. The rationale, design, and baseline characteristics of this study have been previously published [Bentley-Lewis R et al. *Am Heart J*. 2015].

This was a large double-blind placebo-controlled trial in patients with T2DM who had experienced an ACS event within the previous 180 days. Key exclusion criteria were age <30 years, type 1 diabetes mellitus, HbA_{1c} <5.5% or >11.0%, the use of incretin-based agents, planned revascularization within the next 90 days, percutaneous coronary intervention within 15 days, estimated glomerular filtration rate <30 mL/min/1.73m^2, HbA_{1c} <10 g/dL, pancreatitis, amylase/lipase >3 times the upper limit of normal, and calcitonin >20 pg/mL.

Patients were randomly assigned 1:1 to lixisenatide or matching placebo at an initial dose of 10 µg/d with dose adjustments allowed (maximum of 20 µg/d). Glucose control was managed by each investigator. The primary end point was a composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for unstable angina.

A total of 6068 patients were enrolled: 3034 in the placebo arm and 3034 in the lixisenatide arm. Demographic characteristics were similar between the 2 groups. The mean age was approximately 60 years; 30% were women; 75% were white; 11% were current smokers; and 76% had a history of hypertension. The mean duration of T2DM was 9 years, with a mean fasting glucose of 148±51 mg/dL and a mean HbA_{1c} of 7.6%. Eighty-two percent of patients had an MI as their qualifying ACS event, with a mean time of 72 days from the ACS event to randomization. Cholesterol and blood pressure were well controlled. Twenty-two percent had an MI before the index ACS event; 22% had heart failure (HF) prior to randomization; and 70% had undergone revascularization.

In the primary end point analysis, lixisenatide was noninferior to placebo (HR, 1.02; 95% CI, 0.89 to 1.17). The study had a 96% power to detect noninferiority, with an upper bound <1.3 for the 95% CI. Of 434 deaths, 76 (18%) occurred after hospitalization for HF. Compared with patients not hospitalized for HF, patients who were hospitalized for HF had a higher risk of all-cause mortality (HR, 9.3; 95% CI, 7.2 to 11.9), suggesting that HF hospitalization is a meaningful end point.

Table 1. ELIXA End Point Results

End Point	HR (95% CI)
Primary outcome (CV death, myocardial infarction, stroke hospitalization for unstable angina)	1.02 (0.89 to 1.17)
Mortality following HF hospitalization	9.3 (7.2 to 11.9)
Primary + HF hospitalization	0.97 (0.85 to 1.10)
HF hospitalization	0.96 (0.75 to 1.23)
Primary + HF hospitalization + coronary revascularization	1.00 (0.90 to 1.11)
All-cause death	0.94 (0.78 to 1.13)
HF hospitalization by history of HF	
With history of HF	0.93 (0.66 to 1.30)
No history of HF	0.97 (0.67 to 1.40)
CV death + HF hospitalization by history of HF	
With history of HF	0.97 (0.75 to 1.24)
No history of HF	0.96 (0.75 to 1.23)

CV, cardiovascular; HF, heart failure.

Significant changes were seen in the following biomarkers when lixisenatide was compared with placebo: HbA_{1c} (absolute value) was 0.27% lower (with similar hypoglycemia events); weight change was 0.7 kg less (with more frequent discontinuations due to gastrointestinal complaints; 4.9% vs 1.2%); systolic blood pressure was 0.8 mm Hg less; albuminuria increased less (24% vs 34%); and heart rate was increased by 0.4 beats per minute (all P<.05). Other end points are summarized in Table 1.

In summary, while the results of the ELIXA trial demonstrated the safety of lixisenatide as defined by FDA guidance, it was not superior to placebo in reducing CV events.

Composite Analysis of Home-Based Intervention Studies in Cardiac Disease

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Determining the optimal disease management strategies for patients with cardiovascular (CV) disease is an ongoing area of research. Several studies comparing a nurse-led home-based intervention (HBI) with standard care (SC) in patients with chronic heart disease have recently been completed. Simon Stewart, MD, PhD, Australian Catholic