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

Written by Muriel Cunningham

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

University, Melbourne, Australia, presented the results of a composite analysis of 3 randomized trials: the WHICH? trial [Stewart S et al. *Int J Cardiol*. 2014], the SAFETY trial [Stewart S et al. *Lancet*. 2015], and the NIL-CHF study [Stewart S et al. *Eur J Heart Fail*. 2015]. The hypothesis was that HBI would be superior to high levels of SC in the prevention of repeated hospitalizations and premature mortality and that the effectiveness of HBI would increase as the complexity of the clinical cases increased.

The 3 trials enrolled patients across the spectrum of cardiac disease. The WHICH? trial enrolled patients with heart failure (HF) with reduced ejection fraction and preserved ejection fraction, the SAFETY trial enrolled patients with chronic atrial fibrillation without HF, and the NIL-CHF study enrolled cardiac patients, most with acute coronary syndrome, without HF. In all of the studies, patients were recruited during acute hospitalization before returning home. All 3 trials were compliant with the Consolidated Standards of Reporting Trials, had independent data management and statistical analysis, and had blinded end point acquisition and adjudication. Follow-up ranged from 2 years (SAFETY) to 3 years (WHICH? and NIL-CHF).

A total of 1226 patients were analyzed, of which 612 received HBI and 614 received SC. The demographics of the study cohort were well matched across interventions. Patients were older (approximately 70 years), had multiple comorbidities and high clinical complexity, and had received appropriate levels of treatment. Thirty percent of patients were women.

Several aspects of recurrent hospital stays significantly favored HBI, including the median length of stay per patient in unplanned admission days ($P=.011$), CV admission days ($P=.039$), and all admissions (days in the hospital; $P=.017$). Further, all-cause mortality was lower with HBI vs SC (15.4% vs 20.2%; adjusted HR, 0.56; 95% CI, 0.41 to 0.78; $P=.001$). Patients in the HBI group also achieved a mean of 1210±463 days alive and out of the hospital (90.1%; 95% CI, 88.2 to 92.0) compared with 1184±494 days event free in the SC group (87.2%; 95% CI, 85.1 to 89.3; $P=.02$).

HBI was associated with worse event-free survival in lower clinical complexity cases, and Dr Stewart noted that HBI worked best when the clinical complexity was increased. Accordingly, to reduce the chance for harm, HBI should be reserved for cases that are more clinically complex.

Limitations of this study include that it was a post hoc analysis of studies in which the participants were not blinded. The mechanisms through which HBI increases events at low clinical complexity and benefits cases of high clinical complexity need to be further explored.

TECOS Finds Sitagliptin Does Not Increase Heart Failure Risk

Written by Muriel Cunningham

The TECOS study [Green JB et al. *New Eng J Med*. 2015] was a large randomized placebo-controlled trial conducted in patients with type 2 diabetes mellitus (T2DM) and prevalent cardiovascular (CV) disease. Frans Van de Werf, MD, PhD, University of Leuven, Leuven, Belgium, presented the results of a prespecified secondary analysis from this trial.

The objective of the TECOS study was to evaluate CV risk with sitagliptin added to usual care. For the primary composite end point of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina, sitagliptin was noninferior to placebo for CV risk (HR, 0.98; 95% CI, 0.88 to 1.09; $P<.001$).

Patients with T2DM and atherosclerosis are at an increased risk of hospitalization for heart failure (HF). Two large clinical trials have suggested that dipeptidyl peptidase-44 inhibitors could increase HF hospitalizations: saxagliptin in the SAVOR-TIMI 53 trial [Scirica BM et al. *New Eng J Med*. 2013] and alogliptin in the EXAMINE trial [White WB et al. *New Eng J Med*. 2013]. A prespecified secondary analysis of TECOS investigated the potential effects of sitagliptin on hospitalization for HF and associated outcomes in the study population and selected subgroups.

Of the 14671 patients enrolled in TECOS, 457 (3.1%) had a hospitalization for HF during the study. Baseline characteristics for these 2 groups are presented in Table 1. There

Table 1. Baseline Characteristics by Hospitalization for HF

Characteristic	With Hospitalization for HF (n = 457)	No Hospitalization for HF (n = 14 214)
Age, y	68.5 ± 7.6	65.4 ± 8.0
Women	25.2	29.4
Duration of diabetes, y	12.3 ± 8.7	11.6 ± 8.1
Percentage HbA_{1c}	7.3 ± 0.5	7.2 ± 0.5
eGFR, mL/min/1.73 m^2	66.5 ± 20.9	75.2 ± 21.1
Prior vascular disease		
Coronary artery disease	85.3	73.7
Cerebrovascular disease	29.1	24.3
Peripheral artery disease	17.3	16.6
Prior myocardial infarction	58.2	42.1
Prior HF	41.8	17.3

Values are presented as mean ± SD or percentage.
eGFR, estimate glomerular filtration rate; HF, heart failure.
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