At a mean follow-up of 2.3 years, the cumulative risk of stroke or systemic embolism was 1.46%/year with 150 mg dabigatran versus 1.60%/year with dabigatran 110 mg (HR, 0.91; 95% CI, 0.69 to 1.20). Other endpoint results at 2.3 years were stroke,1.24%/year with dabigatran 150 mg versus 1.38%/year with dabigatran 110 mg (HR, 0.89; 95% CI, 0.66 to 1.21); ischemic stroke, 1.15%/year versus 1.24%/year (HR, 0.92; 95% CI, 0.67 to 1.27); hemorrhagic stroke, 0.13%/year versus 0.14%/year (HR, 0.89; 95% CI, 0.34 to 2.30); MI, 0.69%/year versus 0.72%/year (HR, 0.96; 95% CI, 0.63 to 1.45); and pulmonary embolism, 0.13%/year versus 0.11%/year (HR, 1.14; 95% CI, 0.41 to 3.15).

Table 1. RELY-ABLE and RE-LY Efficacy Outcomes for Dabigatran 110 and 150 mg.

Endpoint	RELY-ABLE 110 mg (%/Year)	RELY-ABLE 150 mg (%/Year)	RE-LY 110 mg (%/Year)	RE-LYLY 150 mg (%/Year)
Stroke or systemic embolism	1.60	1.46	1.53	1.11
SAll stroke	1.38	1.24	1.44	1.01
Ischemic stroke	1.24	1.15	1.34	0.92
Hemorrhagic stroke	0.14	0.13	0.12	0.10
Myocardial infarction	0.72	0.69	0.72	0.74
Pulmonary embolism	0.11	0.13	0.12	0.15

Adapted from Connolly SJ et al. Dabigatran Versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2009; 361:1139-51.

Stroke and systemic embolism results for patients in the RELY-ABLE study who received 150 mg versus 110 mg dabigatran at a mean follow-up of 4.25 years (were 0.89%/year versus 1.05%/year at a mean follow-up of 4.25 years,) and 1.25%/year versus 1.54%/year in all dabigatran patients (RE-LY and RELY-ABLE) at a mean follow-up of 3 years. (1.25%/year vs 1.54%/year).

Patients treated with dabigatran 150 mg had higher rates of major bleeding (3.74%/year) compared with dabigatran 110 mg (2.99%/year) at 2.3 years in the RELY-ABLE extension study. Life-threatening, intracranial, and extracranial bleeding were higher with 150 mg versus 110 mg dabigatran, whereas GI and fatal bleeding were similar in both groups. Total mortality in the RELY-ABLE study at 2.3 years follow up with 150 mg versus 110 mg dabigatran was 3.02%/year and 3.10%/year.

Patients in both dabigatran dose groups had very low rates of hemorrhagic stroke over more than 4 years. Patients who continued in RELY-ABLE treated with 150 mg compared with 110 mg of dabigatran had low ischemic stroke/systemic emboli rates (1.46%/year and 1.60%/year, respectively) but higher major bleeding rates (3.74%/year and 2.99%/year, respectively). These two doses of dabigatran were associated with similar mortality rates. Whether the trade-off between the yearly risk of stroke/embolism protection and major bleeding changes over time, and whether a break-even point exists when that trade-off becomes equivalent or even unfavorable, deserves further study.

Impact of LX4211 on Cardiovascular Risk Factors in Type 2 Diabetes

Written by ***Phil Vinall***

LX4211, a dual inhibitor of sodium glucose transporters 1 and 2 (SGLT1/2), demonstrated a clear dose reduction in plasma glucose concentration (HbA1C) in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin monotherapy in the Safety and Efficacy of LX4211 with Metformin in T2DM Patients with Inadequate Glycemic Control on Metformin study. SGLT1 is primarily responsible for gastrointestinal (GI) glucose absorption, while SGLT2 is primarily responsible for renal glucose reabsorption, leading to reductions in blood glucose levels and weight loss. Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center, Dallas, Texas, USA, who presented this study believes that LX4211 has the potential to address multiple cardiovascular disease risk factors in diabetic patients.

The study was designed to evaluate the dose-range efficacy and safety of LX4211 versus placebo from baseline to Week 12 in patients with T2DM inadequately controlled on metformin monotherapy. Additional eligibility criteria included being aged 18 to 75 years with a body mass index ≤45 kg/m^2, and HbA1C ≥7% to ≤10.5%. After 2 weeks of screening, subjects were randomly assigned to treatment with placebo or 1 of 4 LX4211 dosages (75 mg QD, 200 mg QD, 200 mg BID, or 400 mg QD) for 12 weeks and followed for an additional 2 weeks. The primary study endpoint was the change in HbA1C from baseline to Week 12. Secondary outcomes included percentage of patients reaching target HbA1C of ≤7% at Week 12, fasting plasma glucose change from baseline to Week 12, body weight change, blood pressure (BP) change, urinary glucose change, and safety.

Randomized patients (n=299) were mean age 56 years,

42% female, and had a BMI of 32 to 34 kg/m^2, and HbA1C of 7.9% to 8.3 %. Patients had normal blood pressure (BP) and lipid levels. All doses of LX411 significantly reduced HbA1C compared with baseline, with dose related changes from 0.4% to 0.9%. Baseline characteristics were balanced between randomization groups.

Relative to placebo after 12 weeks of treatment; LX411 reduced HbA1C beginning at Week 1 and continuing out to Week 12 ($p<0.001$ for the 200-mg BID and 400-mg QD doses; $p<0.05$ for 75-mg and 200-mg QD doses;). Maximum effect on urinary glucose excretion was achieved with 200 mg QD at Weeks 4, 8, and 12. No further glucose excretion was achieved with the 200-mg BID or 400-mg QD doses. However, further reductions in HbA1C were evident with the higher doses of LX411, which probably indicates further inhibition of SGLT1. Weight loss was achieved with all doses except for the 75-mg dose, up to 2.5 kg at Week 12 with 200 mg BID ($p<0.001$). Compared with placebo, systolic BP was significantly ($p<0.05$) reduced with the 200-mg BID and 400-mg QD doses over the 12-week period. Diastolic BP was not significantly changed. No clinically meaningful changes in high- or low-density lipoprotein cholesterol levels over baseline or compared with placebo were evident.

Adverse events (AEs) were well balanced across the treatment arms and similar in frequency to those seen with placebo. Common AEs associated with LX4211 were vaginal infections (3% to 5%), GI disorders, and headaches. There were no dose-related differences in drug discontinuation due to AEs.

In poorly controlled patients with T2DM on metformin, dual SGLT 1 and 2 inhibition with LX2411 improved glucose control and was associated with consistent reductions in systolic BP and body weight without an increase in hypoglycemia. Dr. Rosenstock concluded that, because of its insulin-independent effects, LX4211 can potentially address multiple cardiovascular risk factors in patients with T2DM and it warrants further study.

All novel oral glycemic agents are now required to undergo Phase 3 study evaluations to determine whether they affect clinical cardiovascular endpoints, including heart failure and ischemic events. In addition, these Phase 3 trials are often longer than the initial studies investigating glucose control and are helpful to evaluate, serious AEs, such as hypoglycemia, hypotension, or off-target effects. With this particular class of diabetic agents, an increase in genitourinary infections may be plausible since glycosuria is increased with this therapy.

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