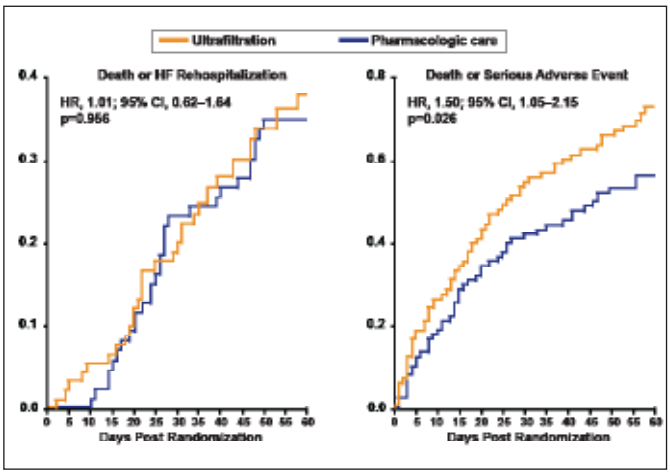
the index admission for heart failure (HF) were eligible for inclusion. Additional inclusion criteria included at least 2 of the following conditions at the time of randomization: at least 2+ peripheral edema, jugular venous pressure greater than 10 cm of water, or pulmonary edema or pleural effusion on chest radiography.

In total, 188 patients were randomized to a strategy of stepped pharmacologic therapy (n=94) or ultrafiltration (n=94). The primary endpoint was a composite of change from baseline in serum creatinine level and body weight at 96 hours. Clinical outcomes were assessed at 60 days.

Results showed that ultrafiltration was inferior to pharmacologic therapy with respect to the primary endpoint of changes in serum creatinine and body weight at 96 hours (p=0.003); this was due primarily to an increase in creatinine levels in the ultrafiltration group.

The mean change in the creatinine level at 96 days was –0.04±0.53 mg/dL in the pharmacologic therapy group compared with +0.23±0.70 mg/dL in the ultrafiltration group (p=0.003). There was no significant difference in weight loss between patients in the pharmacologic therapy group and those in the ultrafiltration group 96 hours after enrollment (a loss of 5.5±5.1 kg and 5.7±3.9 kg, respectively; p=0.58). At 60 days, there was no difference in death (17% vs 14%; p=0.55) or HF hospitalization (26% vs 26%; p=0.97), but serious adverse events (AEs) were more frequent with ultrafiltration (p=0.03) and there was a significant increase in the rate of death or serious AE with ultrafiltration compared with pharmacologic therapy (HR, 1.50; 95% CI, 1.05 to 2.15; p=0.026; Figure 1).

Figure 1. 60-Day Outcomes Post-Randomization.



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Dr. Bart concluded that, compared with pharmacologic therapy, ultrafiltration as administered in this study was associated with deterioration in renal function and worse clinical outcomes, and should not be used routinely in clinical practice. Whether or not ultrafiltration could be useful using slower rates of volume removal or as guided by hemodynamics is unknown. He said, "Treatment of these patients with ADHF, worsened renal function, and persistent congestion remains a challenging clinical problem in need of better therapy."

Long-Term Dabigatran Extension Study for Stroke Prevention in Treatment for Atrial Fibrillation

Written by ***Toni Rizzo***

Previously, the Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY] trial evaluated two doses of dabigatran (110 and 150 mg BID; open dabigatran but blinded dose) versus warfarin (open-label) in patients with nonvalvular atrial fibrillation and at least 1 risk factor for stroke [Flaker et al. *J Am Coll Cardiol* 2012]. The goal of the RELY-ABLE extension study [NCT00808067] presented by Stuart J. Connolly, MD, McMaster University, Hamilton, Ontario, Canada, was to describe the long-term efficacy and safety of ongoing dabigatran therapy after the RE-LY trial.

Patients who had been randomized to dabigatran and were still taking it at then end of the the blinded dose of dabigatran taken in RE-LY trial were eligible for the was continued in the RELY-ABLE extension study. Patients continued on the same dose of dabigatran (the dose of dabigatran remained blinded) trial for a mean of 2.3 years. In the RE-LY trial, patients were randomized to dabigatran 110 mg (n=6015) or dabigatran 150 mg (n=6076) in a blinded fashion, or open-label warfarin (n=6022). Among these, 4492 (75%) in the 110-mg arm and 4519 (75%) in the 150-mg arm completed RE-LY and were still receiving dabigatran. Of these, 3395 (76%) in the 110-mg arm and 3397 (75%) in the 150-mg arm were beeing followed at a site participating in RELY-ABLE.

A total of 2914 patients receiving dabigatran 110 mg and 2937 patients receiving dabigatran 150 mg were enrolled in RELY-ABLE, and 2511 and 2508 patients, respectively, completed the study, representing 86% and 85% of the patients.

During 2.3 years of additional dabigatran treatment after RE-LY (total mean follow up of 4.3 years), rates of stroke and major bleeding remained low and comparisons of the 2 doses were consistent with those observed during the main RE-LY trial. The rates of stroke and myocardial infarction (MI) from the RELY-ABLE and RELY trials are compared in Table 1.

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,