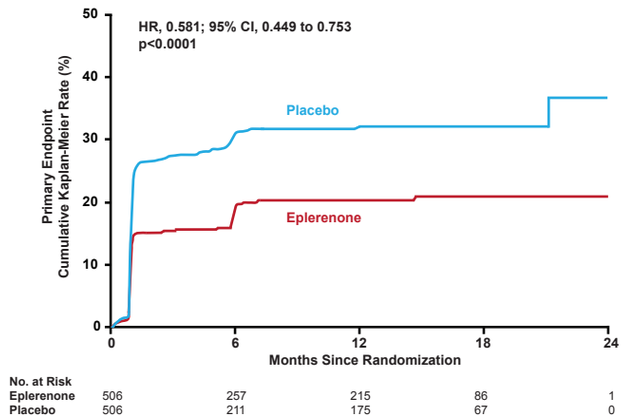
primary composite endpoint was the biochemical endpoint of elevated BNP/NT-proBNP (16.0% with eplerenone vs 25.9% with placebo; HR, 0.58; 95% CI, 0.44 to 0.77; p=0.0002).

Figure 1. Primary Composite Endpoint for Eplerenone Versus Placebo



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Consistent with the primary endpoint were trends towards reductions in individual clinical events including CV mortality (HR, 0.52; 95% CI, 0.05 to 5.99; p=0.60) and HF rehospitalization or extended stay (HR, 0.56; 95% CI, 0.20 to 1.54; p=0.26). In addition, the trial was originally designed with an expected placebo-group primary event rate of 42%. Despite extending the sample size to accommodate for an observed lower than expected blinded aggregate event rate (21% at 6 months), the trial remained underpowered for the primary analysis.

Adverse events were balanced between groups with the exception of hyperkalemia (>5.5 mmol/L), which was more frequent with eplerenone (5.6% vs 3.2%; p=0.09).

REMINDER is the first study to demonstrate benefit and safety of early eplerenone treatment in patients presenting with STEMI in the absence of HF. The benefit was largely driven by biochemical improvements (BNP and NT-proBNP) but with consistent numerical reductions in clinical endpoints. Additional well-powered trials studying clinical outcomes would confirm these benefits.

Ranolazine Provides Benefit Over Placebo for T2DM Patients With Angina

Written by Larry Hand

In a trial focused on the treatment of stable angina in patients with type 2 diabetes (T2DM), ranolazine significantly reduced the frequency of angina episodes compared with placebo. Mikhail Kosiborod, MD, St. Luke's Mid America Heart Institute, Kansas City, Missouri, USA, presented the results of the Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina study [TERISA; Kosiborod M et al. *J Am Coll Cardiol* 2013].

The primary objective of the randomized double-blind TERISA study was to evaluate the efficacy of ranolazine versus placebo on angina frequency in T2DM patients with coronary artery disease and chronic stable angina who were also taking 1 or 2 antianginal medications (eg, β-blockers). The primary endpoint was the average weekly number of angina episodes from Week 2 to Week 8 of treatment, while secondary endpoints included the average weekly number of sublingual nitroglycerin (SL NTG) doses from Week 2 to Week 8.

The trial enrolled 949 patients at 104 sites in Europe, Asia, and North America. Following a 4-week single-blind baseline-setting placebo period, patients (mean age 64 years) were randomized to receive ranolazine 1000 mg BID (n=473) or placebo (n=476) for 8 weeks. Eleven patients in each arm that either initiated or discontinued the study drug during the first 2 weeks were excluded from the final analysis. Researchers received daily data transmissions from patients who recorded angina episodes and SL NTG use in handheld electronic device diaries (98% compliance). Researchers followed-up with a phone call 2 weeks after the end of the 8-week period. Randomized patients were mostly male (61%) and had a mean diabetes duration of 7.5 years and a mean baseline HbA1C of 7.3%.

For the primary endpoint, patients in the ranolazine group experienced significantly fewer average weekly angina episodes from Week 2 to Week 8 than patients in the placebo group (3.8 vs 4.3,; p=0.008; Figure 1). Furthermore, patients in the ranolazine group took fewer average weekly SL NTG doses from Week 2 to Week 8 than those in the placebo group (1.7 vs 2.1, respectively; p=0.003; Figure 2). There were few serious adverse events, with no significant difference between the 2 groups.

Figure 1. Angina Frequency With Ranolazine Versus Placebo

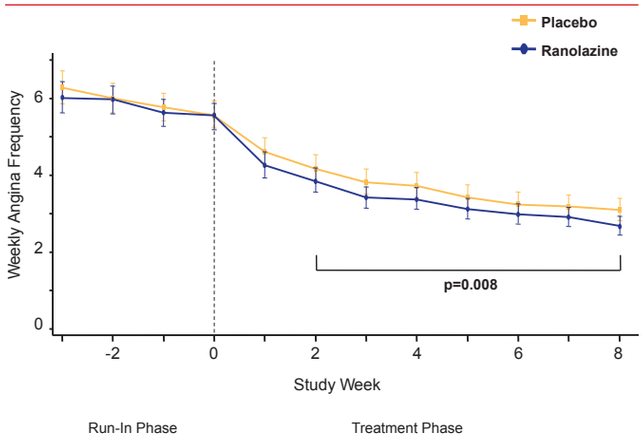

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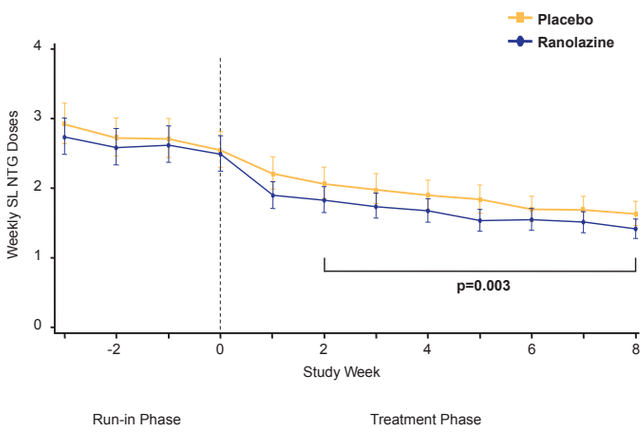
Figure 2. Average SL NTG Doses With Ranolazine Versus Placebo



SL NTG=sublingual nitroglycerin.

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It should be noted that generalizability of these results may be limited due to the lack of racial diversity of the study population. In addition, the short follow-up limits conclusions about the durability of therapy. Significant geographic heterogeneity was seen in treatment effect (p for interaction=0.016) with an apparent attenuation of benefit in selected Eastern European countries. Dr. Kosiborod said that an investigation is currently ongoing to determine the reason for this lack of an effect in these patients. In another subgroup analysis, the overall benefit with ranolazine versus placebo was more pronounced in patients with higher baseline HbA1C levels (p for interaction=0.027); however, measurement was not taken on follow-up for possible comparison.

In conclusion, TERISA showed that ranolazine was more effective than placebo in reducing angina frequency in T2DM patients with coronary artery disease and chronic stable angina. Future studies may shed light on potential dual effects of ranolazine on angina and glucose control in T2DM patients.

Digoxin Reduces 30-Day Hospital Admission in Older Ambulatory Patients With Heart Failure

Written by **Rita Buckley**

A post hoc subanalysis of the Digitalis Investigation Group trial found that digoxin reduces all-cause hospital admission at 30 days in older ambulatory patients with chronic systolic heart failure (HF) [Bourge RC. *Am J Med* 2013]. Reduction in hospital readmissions is of particular interest in the United States due to related financial penalties levied by the Center for Medicare and Medicaid Services (CMS) from October 2012 for older patients with HF.

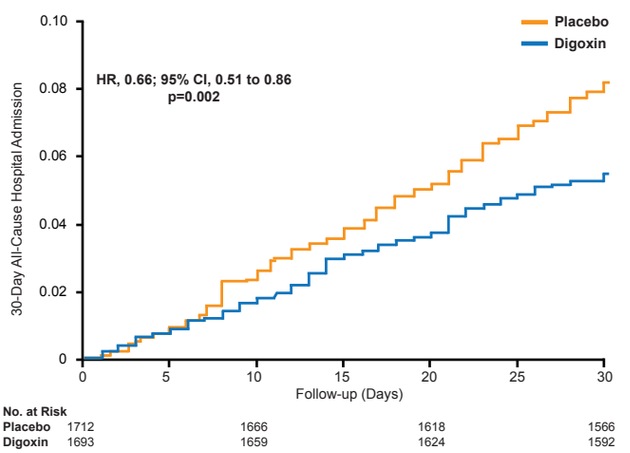
The objective of the post hoc analysis by Ali Ahmed, MD, MPH, University of Alabama, Birmingham, Alabama, USA, and colleagues, was to examine the effect of digoxin on 30-day all-cause hospital admission in a subgroup of older, potentially Medicare-eligible, adults with HF and reduced ejection fraction from the main DIG trial which randomized 6800 ambulatory patients with chronic HF to either digoxin or placebo on a background of standard therapy from 1991 through 1993 [DIG Investigators. *N Engl J Med* 1997].

The presented analysis included a subset of 3405 patients aged ≥65 years with chronic HF (ejection fraction ≤45%) in normal sinus rhythm from the United States and Canada. They had a mean age of 72 (±5) years, 25% were women, 76% had a primary etiology of ischemic heart failure, 61% had chronic kidney disease, and 11% were nonwhite. Angiotensin-converting enzyme inhibitors were used at baseline in 94% and diuretics were used in 82%. The proportion on β-blockers was not collected.

In the subgroup of interest, 1712 were randomized to digoxin and 1693 to placebo. Overall, baseline characteristics between groups were similar except for a slightly lower body mass index among those assigned to digoxin (p=0.04).

In the 30 days after randomization, the all-cause hospital admission rate was significantly lower in the digoxin- versus placebo-treated group (5.4% vs 8.1%, respectively; HR, 0.66; 95% CI, 0.51 to 0.86; p=0.002; Figure 1). Over the same time period, digoxin reduced both the absolute (-2.7%) and relative (-34%) risks of all-cause hospital admission.

Figure 1. 30-Day All-Cause Hospital Admissions With Digoxin Versus Placebo



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