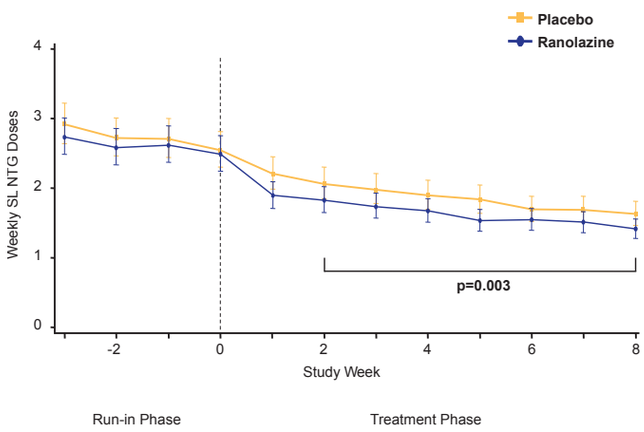
Figure 2. Average SL NTG Doses With Ranolazine Versus Placebo



SL NTG=sublingual nitroglycerin.

Reproduced from Kosiborod M et al. Evaluation of Ranolazine in Patients with Type 2 Diabetes Mellitus and Chronic Stable Angina. Results from the TERISA randomized clinical trial. *Journal of the American College of Cardiology* Jan 2013; 10.1016/J.JACC.2013.02.011. With permission from Elsevier.

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.

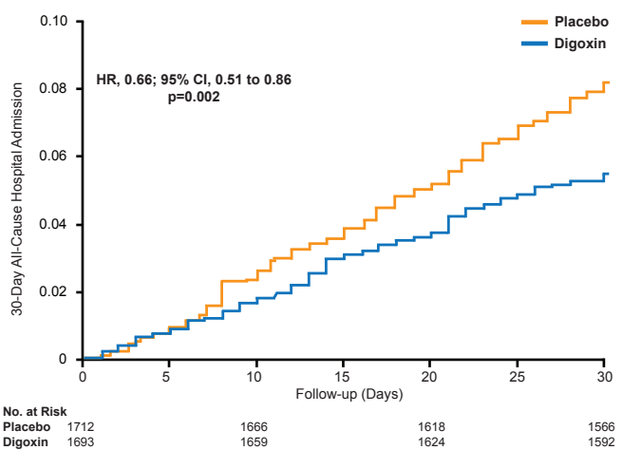
The objective of the post hoc analysis by Ali Ahmed, MD, MPH, University of Alabama, Birmingham, Alabama, USA, and colleagues, was to examine the effect of digoxin on 30-day all-cause hospital admission in a subgroup of older, potentially Medicare-eligible, adults with HF and reduced ejection fraction 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



Reproduced with permission from A Ahmed, MD, MPH.

The reduction in all-cause hospital admissions with digoxin persisted through 60 days (HR, 0.76; 95% CI, 0.63 to 0.91; p=0.003) and 90 days (HR, 0.75; 95% CI, 0.63 to 0.88; p<0.001) post randomization. This suggests that the early benefit of digoxin was not achieved at the cost of harm at a later time.

In the 30 days following randomization, digoxin significantly reduced the risk of hospital admission due to cardiovascular causes by 47% (HR, 0.53; 95% CI, 0.38 to 0.72; p<0.001) and due to worsening HF by 60% (HR, 0.40; 95% CI, 0.26 to 0.62; p<0.001). Differences between 30-day mortality outcomes for all-cause and cardiovascular mortality were not significant between the digoxin and placebo groups. A favorable trend toward less frequent progression of HF (HR, 0.22; 95% CI, 0.05 to 1.04; p=0.056) was observed with digoxin.

Since these results were derived from post hoc subgroup analyses, the findings should be considered hypothesis-generating that require confirmation in prospective studies. Clinicians should be cautious about generalizing these results to patients in clinical practice, in part because the study was conducted in the early 1990s when current background therapies were either not standard-of-care (eg, β-blockers, spironolactone) or unavailable (eg, angiotensin receptor blockers).

If these findings can be replicated in current older HF patients on guideline recommended background therapy, digoxin may be a low-cost option to reduce 30-day all-cause readmissions and avoid penalties imposed by CMS.

Early Fibrinolysis as Effective as Primary PCI When Reperfusion Delay Is Long

Written by **Wayne Kuznar**

Fibrinolytic therapy coupled with timely coronary angiography results in effective reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) who cannot undergo primary percutaneous coronary intervention (PCI) within 1 hour of presentation, said Frans Van de Werf, MD, PhD, University of Leuven, Leuven, Belgium, who presented the results of the Strategic Reperfusion (With Tenecteplase and Antithrombotic Treatment) Early After Myocardial Infarction trial [STREAM; Armstrong PW et al. *N Engl J Med* 2013].

Although prompt delivery of primary PCI is the preferred strategy to treat patients with acute STEMI, delays in performing PCI are common when patients present to emergency medical services or hospitals without the capability for catheterization. The delay in reperfusion that results from long transfer to a hospital for primary PCI increases the rates of morbidity and mortality.

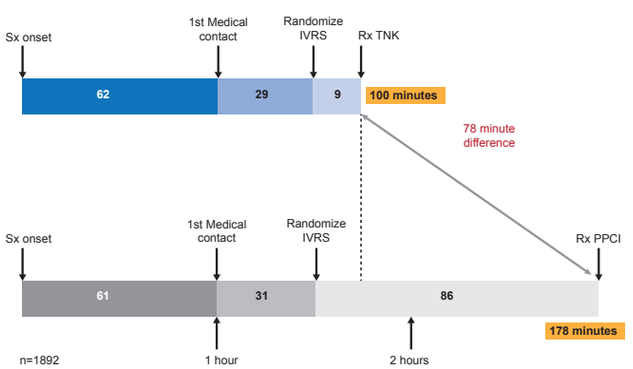
In STREAM, patients with STEMI (≥2 mm ST elevation in 2 contiguous leads) who presented within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact were randomized to 1 of 2 strategies: 1) early fibrinolysis followed by coronary angiography in 6 to 24 hours or rescue PCI, if needed, or 2) standard primary PCI. Patients from 99 sites in 15 countries were included in this trial.

In the early fibrinolysis group, patients received a weight-based bolus of tenecteplase along with aspirin, clopidogrel, and enoxaparin in the ambulance or emergency department. Rescue intervention was performed if there was <50% ST-segment resolution in the single lead of an electrocardiogram or clinical evidence of failed reperfusion within 90 minutes after fibrinolytic therapy. In the primary PCI group patients received antiplatelet and antithrombin treatment according to local guidelines, and underwent standard primary PCI.

The trial was designed as a proof-of-concept study where all statistical tests were of an exploratory nature. The primary endpoint was a composite of death, shock, congestive heart failure, or reinfarction at 30 days [Armstrong PW et al. *N Engl J Med* 2013].

After 20% of the planned recruitment into the study, the bolus dose of tenecteplase was halved in patients aged ≥75 years to reduce the risk of intracranial bleeding. A total of 1892 patients were randomized. The median time from symptom onset to the start of reperfusion therapy was 100 minutes in patients randomized to the early fibrinolysis group versus 178 minutes in the primary PCI group (Figure 1).

Figure 1. Median Time to Treatment: Early Fibrinolysis Versus Primary PCI



IVRS=interactive voice response system; PPCI=primary percutaneous coronary intervention; TNK=tenecteplase.

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