Of the 544 patients randomized, the efficacy analysis included 322 patients who received study medication, underwent PCI and had biomarkers assayed at all timepoints.

The duration of PCI and rates of drug-eluting and bare-metal stent deployment were similar between the 3 arms, as were use of concomitant medications.

The mean percent change in Tn-I was −22.4% at 16 hours (p=0.07) and −24.4% (p=0.05) for patients receiving inclacumab 20 mg/kg relative to those receiving placebo. Peak Tn-I was numerically reduced by 23.8% with this dose (p=0.05). There was no significant difference in Tn-I concentration observed with inclacumab 5 mg/kg at either timepoint.

The percent change in Tn-I at 24 hours with inclacumab 20 mg/kg versus placebo was similar in patients with or without diabetes (–33.2% and vs –31.6% respectively; p=0.03 in patients without diabetes; Table 1).

Table 1. Change in Troponin I at 24 Hours

Troponin I (Tn-I)	Placebo n=115	Inclacumab 5 mg/kg n=95	Inclacumab 20 mg/kg n=112
Baseline geometric mean IQR	1.03 0.24-4.69	0.71 0.17-3.44	0.82 0.19-3.73
24 hours post-PCI	1.76	1.21	0.99
Change from baseline[1]	57.7%	55.5%	19.1%
Placebo-adjusted change[2] 95% CI; p value	-- --	-1.4% (-26.7, 32.7) 0.93	-24.4% (-43.1, 0.4) 0.05

PCI=percutaneous coronary intervention; IQR=interquartile range.

[1] Adjusted geometric mean percent change (based on repeated ANCOVA model).

[2] Placebo-adjusted geometric mean percent change obtained by exponentiating the delta adjusted mean from repeated ANCOVA, then subtracting 1 and X100.

The change in creatine kinase-myocardial band (CK-MB) was similar to the findings for troponin with a borderline significant result in favor of high-dose inclacumab (–17.4% vs placebo; p=0.06). The incidence of CK-MB increases more than 3 times the upper limit of normal was 18.3% in the placebo group and 8.9% in the inclacumab 20 mg/kg group (p=0.05).

Safety data were collected at 120 days, at which time there was no increase in the rates of infection or bleeding with inclacumab. Of note, there were higher numbers of deaths (6 vs 0) and nonfatal MI (11 vs 2) in patients randomized to inclacumab versus placebo but the study was not adequately powered to detect differences in clinical endpoints.

While these findings show a favorable pattern in biomarker concentration with high-dose inclacumab in the setting of PCI for NSTEMI, the clinical relevance of these findings is not clear from this Phase 2 study. Further clinical investigation is required to determine the clinical impact of inclacumab administration in patients presenting with MI.

Eplerenone Post Myocardial Infarction Plus Standard Treatment May Prevent Adverse Cardiovascular Outcomes

Written By Rita Buckley

Early administration of eplerenone added to standard treatment in postmyocardial infarction (MI) patients appears to reduce the risk of adverse cardiovascular (CV) outcomes and heart failure (HF), according to results from the Impact of Eplerenone on Cardiovascular Outcomes in Patients Post-Myocardial Infarction trial [REMINDER; NCT01176968].

The randomized double-blind REMINDER trial included 1102 patients with ST-segment elevation myocardial infarction (STEMI) in the absence of HF. The lead investigator for the study, Gilles Montalescot, MD, PhD, Pitié-Salpétrière Hospital, Paris, France, reported that the provision of a mineralocorticoid receptor antagonist early in the acute phase of MI suggests a potential long-term CV benefit.

Eligible patients were identified following emergency room or ambulance evaluation and diagnosis of acute STEMI without HF. Key exclusion criteria were a known left ventricular ejection fraction (LVEF) <40%, any previous known history of HF, uncontrolled hypotension (systolic blood pressure <90 mm Hg), and known renal insufficiency (eGFR ≤30 mL/min/1.73m^2). Patients were randomized to eplerenone (25 to 50 mg QD; n=506) or placebo (n=506), with the first dose of the study drug administered within 24 hours of symptom onset, and if possible, within 12 hours. All patients otherwise were to receive standard medical therapy.

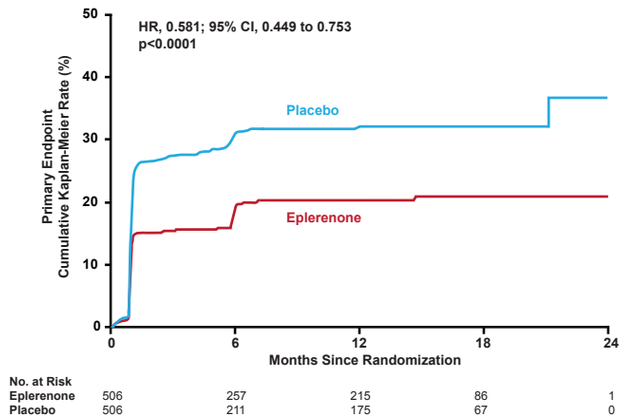
The primary endpoint was a composite of CV mortality, rehospitalization or extended initial hospital stay due to HF, sustained ventricular tachycardia or ventricular fibrillation, LVEF ≤40% after 1 month post randomization, or elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) at 1 month post randomization.

Baseline characteristics were well balanced between the 2 treatment arms; the mean age of participants was 58 years, 17% were female, and 35% had anterior STEMI on presentation. Patient background medical therapy was representative of guideline-recommended practice (approximately 98% received aspirin, 98% P2Y12 antagonist, 79% heparins or fondaparinux, 29% a GPIIb/IIIa inhibitor); approximately 85% received primary percutaneous coronary intervention.

After a mean follow-up of 10.5 months, the primary composite endpoint was significantly lower in the eplerenone (18.4%) versus placebo group (29.6%; HR, 0.58; 95% CI, 0.45 to 0.75; p<0.0001; Figure 1). However, the main driver and only statistically significant component of the

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

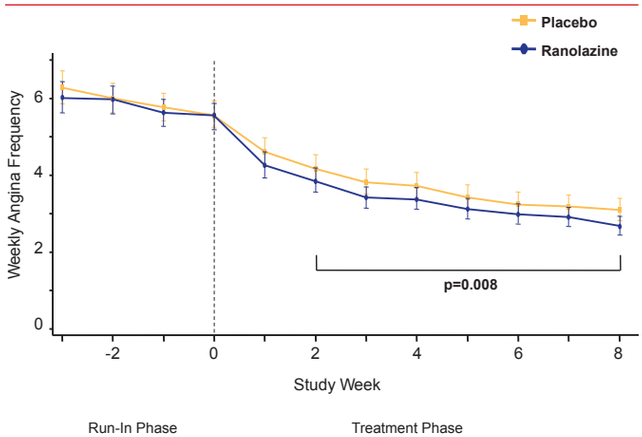
In a trial focused on the treatment of stable angina in patients with type 2 diabetes (T2DM), ranolazine significantly reduced the frequency of angina episodes compared with placebo. Mikhail Kosiborod, MD, St. Luke's Mid America Heart Institute, Kansas City, Missouri, USA, presented the results of the 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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