assess acute efficacy of ranolazine in acute coronary syndrome (ACS) by determining the potential for a decrease in major cardiovascular events, 2) to assess chronic efficacy of the drug for secondary prevention and relief of angina and 3) to evaluate the safety of the compound in the acute and chronic setting.

The trial included patients hospitalized with non-ST-elevation ACS with ischemic symptoms at rest and at least one of four features indicating moderate to high risk: 1) an increase in troponin (myocardial infarction limit) or creatinine kinase -MB (upper limit of normal); 2) ST-depression ≥0.1mV; 3) diabetes mellitus, or; 4) a TIMI risk score for unstable angina/non-ST-elevation myocardial infarction ≥3.

A total of 6,550 patients were randomly assigned in a 1:1 ratio to one of two treatment groups: 1) ranolazine IV 200 mg over one hour, followed by 80 mg/hour infusion for up to 96 hours, followed by ranolazine 1000 mg/day PO or; 2) IV and oral placebo given in an identical fashion. Patients were monitored by continuous Holter for one week. The primary endpoint was a composite of cardiovascular death, new/recurrent myocardial infarction (MI), and recurrent ischemia. The primary endpoints were adjudicated by a blinded cardiovascular events committee.

The baseline demographic characteristics were well balanced between the ranolazine (n=3,279) and the placebo group (n=3,281). Primary endpoint analyses indicated no statistically significant difference in the composite of cardiovascular death, MI, or recurrent ischemia between the two groups (p=0.11; Figure 1). In an analysis of the components of the primary endpoint, ranolazine had no effect on cardiovascular death or MI. However, ranolazine was significantly better than placebo in reducing recurrent ischemia (p=0.03; Figure 2).

Figure 1. Primary Endpoint.

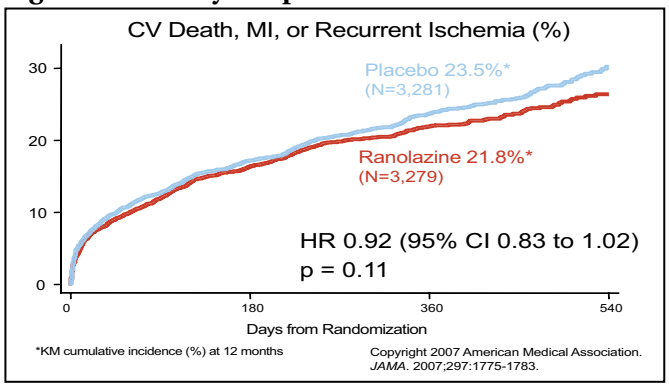
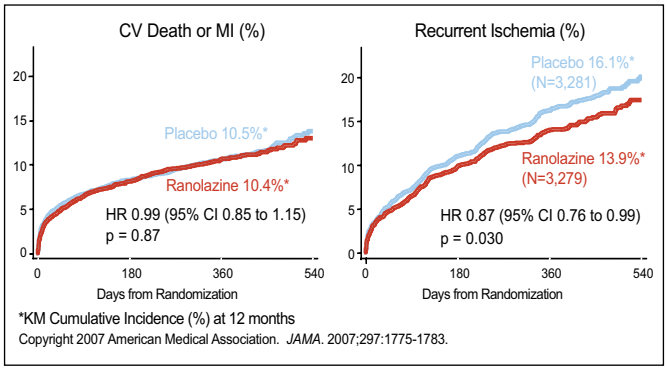


Figure 2. Components of Primary Endpoint.



The safety findings indicated no significant differences in death from any cause, sudden cardiac death, death or cardiovascular hospitalization, or symptomatic documented arrhythmia. Significantly more placebo-treated patients experienced a pre-specified set of arrhythmias on Holter (83.1% vs 73.7%, respectively; p<0.001). Dr. Morrow concluded by saying that ranolazine does not add to standard therapy for acute management of ACS. Ranolazine did not reduce cardiovascular death or MI, but was effective as an anti-anginal, with overall safety findings that were reassuring, including potential anti-arrhythmic effects that deserve further study.

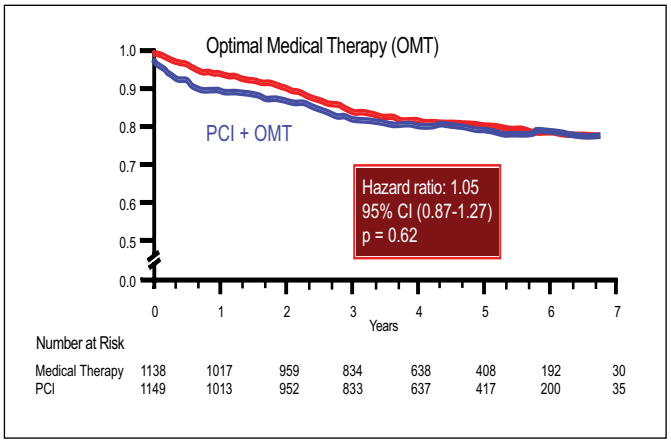
The COURAGE Trial: Optimal Medical Therapy Equivalent to PCI

Percutaneous coronary intervention (PCI) is a widely used method of restoring normal blood flow to the myocardium and is lifesaving during acute coronary events. There are little long-term clinical outcome data, however, on the benefits of PCI in patients who have stable coronary artery disease (CAD). William E. Boden, MD, of the Western New York Veterans Affairs Healthcare Network presented the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation (COURAGE) study (*N Engl J Med*. 2007; 356:1503-1516). The objective of this study was to determine if PCI combined with optimal medical therapy (OMT) was more beneficial than optimal medical therapy alone in patients with stable coronary artery disease. The primary endpoint was death from any cause or nonfatal myocardial infarction (MI) during a median follow-up period of 4.6 years.

The study was conducted from 1999 to 2004 at 50 sites in the United States and Canada. Patients with myocardial ischemia and significant CAD were randomly assigned to either PCI with OMT (n=1,149) or OMT alone (n=1,138). OMT was defined as the best pharmacological treatment possible including medications such as aspirin, beta-blockers, statins (target LDL-C of 60 to 85 mg/dL), HDL-C raising therapies if required, and ACE inhibitors plus therapeutic lifestyle changes such as weight loss, improved diet, exercise, and smoking cessation. PCI was attempted in 1,007 patients; 1,006 received at least one stent. It is important to note that this study evaluated bare metal stents, as drug-coated stents were not yet available.

During follow-up, no differences were observed in the primary endpoint (HR=1.05; 95% CI, 0.87 to 1.27). Results were virtually identical for the secondary endpoint death, MI, and stroke (HR=1.05; 95% CI, 0.87 to 1.27; Figure 1). Additional analyses also indicated no differences in acute coronary syndrome hospitalizations (hazard ratio=1.07; 95% CI, 0.84 to 1.37) or MI (HR=1.13; 95% CI, 0.89 to 1.43). A similar number of patients required subsequent coronary artery bypass grafts (77 in the PCI group; 81 in the OMT group). Subgroup analyses did not reveal any interactions between the treatment effect and defined variables such as age, sex, or diabetes.

Figure 1. Survival Free of Death from Any Cause and Myocardial Infarction.



William S. Weintraub, MD, of the Christiana Healthcare System, Wilmington, Delaware gave a brief overview of the health status and economic outcomes data from the COURAGE study. Quality of life data was gathered by administering surveys including the Seattle Angina Questionnaire, the Rand 36, and the Utility by Gamble, at baseline, 1, 3, 6, and 12 months after randomization, and annually thereafter. The investigators found that angina improved in both treatment arms although the PCI group had a slight but significant incremental benefit compared to OMT. However, PCI was a more expensive choice for patients with stable CAD.

The authors concluded that the results of this study confirm the current American College of Cardiology/ American Heart Association clinical practice guidelines that state that PCI may be deferred in stable patients as long as OMT is initiated.

Succinobucol Treatment Leads to Mixed Signals

Succinobucol (AGI-1067) is a novel compound believed to reduce inflammation in blood vessel walls. Jean-Claude Tardif, MD, of the Montreal Heart Institute gave an overview of the findings from the Phase 3 randomized, double-blind Aggressive Reduction of Inflammation Stops Events (ARISE) study. This study, conducted at 261 sites in the United States, Canada, South Africa, and the United Kingdom, compared succinobucol to placebo in 6,144 patients with acute coronary syndrome (ACS). Eligible patients had been hospitalized 14 to 365 days prior to study entry with an acute myocardial infarction (MI) or unstable angina. The primary endpoint of the study was a composite of cardiovascular (CV) death, resuscitated cardiac arrest, MI, stroke, unstable angina, or coronary revascularization.

There were no significant differences between the succinobucol 300 mg/day group (n=3,078) and the placebo group (n=3,066) in terms of baseline demographic variables. The study failed to meet its primary endpoint and the survival curves of the two treatment groups were virtually identical.

"The two Kaplan-Meier curves are almost super-imposed and in fact there was an almost identical