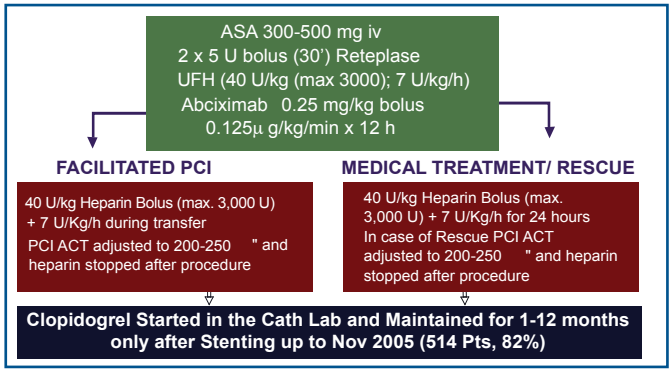
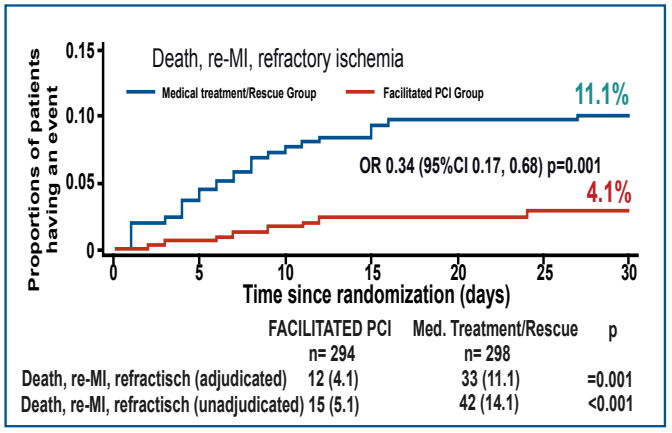
STEMI who presented less than 12 hours after symptom onset were randomly assigned to either facilitated PCI or medical treatment/rescue after fibrinolysis with half-dose reteplase and abciximab (Figure 1). The primary outcome was the composite of all-cause mortality, reinfarction, or refractory ischemia at 30 days. Of the patients in the medical treatment/rescue group, 36% were subsequently referred for PCI.

Figure 1. CARESS Treatment Summary.



Prof. Di Mario reported that facilitated PCI (with half-dose reteplase + abciximab) led to a 67% reduction in the incidence of the composite endpoint (Figure 2) compared to medical treatment with half-dose reteplase + abciximab followed by rescue PCI as needed. When the components of the primary endpoint were assessed individually, refractory ischemia was significantly less frequent in the facilitated PCI group (0.7% vs 5.0%; p<0.002). The incidences of death and reinfarction were also lower in the facilitated PCI group, but these differences did not reach statistical significance (3.1% vs 4.4%, p=0.403, and 0.3% vs 1.7%, p=0.104, respectively). Severe bleeding was rare in both groups, and Prof. Di Mario suggested that this was because the study excluded older patients and patients at high risk for bleeding.

Figure 2. Primary Outcome at 30 Days.



"In our view," concluded Prof. Di Mario, "this trial confirms and expands the indication of the current ESC guidelines to perform early angioplasty, within 24 hours after lysis, and suggests that high-risk STEMI patients should be immediately transferred for angiography after lysis."

Professor Freek Verheugt, Nijmegen University, the Netherlands, who discussed the study, noted that the results of CARESS confirmed the findings of other studies that have indicated the benefit of immediate PCI. He said that one of the remaining questions is how the results would have differed if all patients had been given clopidogrel. In addition, he noted that an important factor to determine is the optimal time interval between fibrinolysis and PCI. This interval has ranged from 2.3-17 hours in trials showing benefit of facilitated PCI.

One of the limitations of the CARESS trial was the absence of a standard strategy (eg, full-dose fibrinolytic or primary PCI without preceding fibrinolysis) as the comparator. Without such an "anchor" to serve as the gold-standard, it is possible that neither of the strategies tested in CARESS would be superior to currently recommended reperfusion strategies. Such a scenario would be consistent with the findings of the GUSTO-V (half-dose rPA + abciximab was not superior to full-dose rPA) and FINESSE (half-dose rPA + abciximab prior to PCI was less beneficial than primary PCI with abciximab in the catheterization laboratory) studies, thus emphasizing the importance of including existing standard treatments in trials that are evaluating novel therapies.

Study Supports Anti-Arrhythmic Effects of Ranolazine in Patients with Acute Coronary Syndrome

Ranolazine, an anti-ischemic agent approved for use in the treatment of chronic angina, has also been shown to have anti-arrhythmic effects in experimental models. The MERLIN-TIMI 36 trial was the first study in which the anti-arrhythmic effects of ranolazine were evaluated in humans.

MERLIN-TIMI 36 involved 6,560 patients with unstable angina/non-ST-elevation acute coronary syndrome who were randomly assigned to receive ranolazine or placebo in addition to standard therapy. The primary results of the study were recently published [Morrow DA et al.

JAMA 2007]. In a major trial substudy, continuous 3-lead electrocardiography recordings were obtained for 6,351 patients during the first 7 days after randomization.

Benjamin Scirica, MD, Brigham and Women's Hospital, Boston, Massachusetts, reported the findings of the arrhythmia endpoints analysis within MERLIN-TIMI 36. Dr. Scirica reviewed the novel mechanism of action of ranolazine, an inhibition of the late phase of the sodium current, one consequence of which is a reduction of the detrimental electrophysiologic effects associated with intracellular sodium and calcium overload in the myocardium [Antzelevitch C et al. *Circulation* 2004]. Because ranolazine is known to cause a slight prolongation of the QT interval, there was concern that ranolazine might have pro-arrhythmic effects such as had been observed with other drugs that prolong the QT interval such as some class IC anti-arrhythmic, fluoroquinolone antibiotics, and anti-histamines.

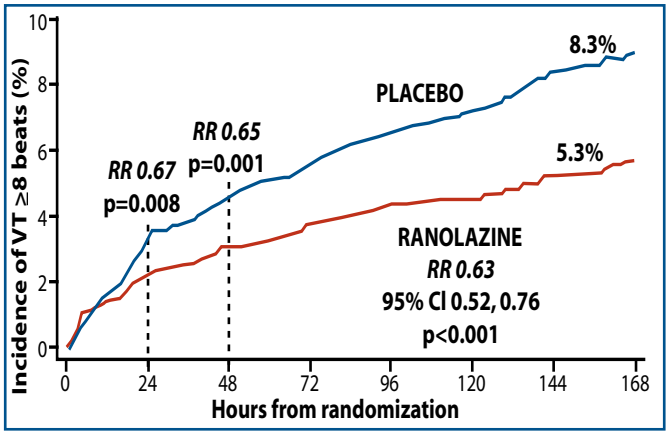
Dr. Scirica reported that evaluation of the electrocardiography recordings for a prespecified set of arrhythmias demonstrated that ranolazine resulted in significantly fewer episodes of ventricular tachycardia, supraventricular tachycardia, and bradyarrhythmias (Table 1).

Table 1. Comparison of Arrhythmia Endpoints Associated with Ranolazine and Placebo in MERLIN-TIMI 36.

Arrhythmias	Ranolazine (%)	Placebo (%)	P value
Ventricular tachycardia			
≥3 beats	52.0	60.6	<0.001
≥8 beats	5.3	8.3	<0.001
Supraventricular events			
Supraventricular tachycardia ≥4 beats	44.7	55.0	<0.001
New-onset atrial fibrillation	1.7	2.4	0.08
Bradycardic events			
Rate <45 bpm, complete heart block, or pause ≥2.5 sec	39.8	46.6	<0.001
Pauses ≥3 sec	3.1	4.3	0.01

Ranolazine led to a 37% decrease in the risk of ventricular tachycardia of 8 beats or more (Figure 1). This significant effect occurred early, within 24 hours after treatment with ranolazine began, and persisted throughout the 7 days of monitoring. He added that the significant reduction in ventricular tachycardia persisted when the defined duration was extended to 10, 15, and 20 or more beats.

Figure 1. First Occurrence of Ventricular Tachycardia Lasting ≥ 8 Beats.



The positive effect of ranolazine was consistent across several high-risk subgroups based on ejection fraction, corrected QT interval, TIMI risk score, history of heart failure, and the presence or absence of ischemia on electrocardiography. In addition, there was no evidence of a significant excess risk in either life-threatening arrhythmias, such as polymorphic ventricular tachycardia, or sudden cardiac death in patients treated with ranolazine.

The most "impressive and noteworthy" finding according to A. John Camm, MD, St. George's Hospital Medical School, London, UK, who discussed the study, was the significant decrease in the incidence of ventricular tachycardia of 8 beats or more among patients with an ejection fraction of less than 40 (16.6% vs 8.8%; p=0.001). Dr. Camm further commented, "This trial suggests that ranolazine is anti-arrhythmic rather than pro-arrhythmic. It is very impressive and seriously adds to the convincing safety database ranolazine."

The full study report was published online on 5 September 2007 (*Circulation*. 2007;116:000-000) and is available at and is available at: http://circ.ahajournals.org/

Subgroup Analysis of BENEFiT Trial to Evaluate Effect of Bosentan for Patients with CTEPH

Irene Lang, MD, Medical University of Vienna, Austria, presented the results of a pre-defined subgroup analysis from the bosentan for inoperable chronic thromboembolic pulmonary hypertension (BENEFiT)