high-risk group, early management reduced this risk by 35% compared with delayed management (14.1% vs 21.6%; HR, 0.65; 95% CI, 0.48 to 0.88; p=0.005; Figure 2).

Figure 1. Primary Outcome of Death, MI, or Stroke at 180 Days.

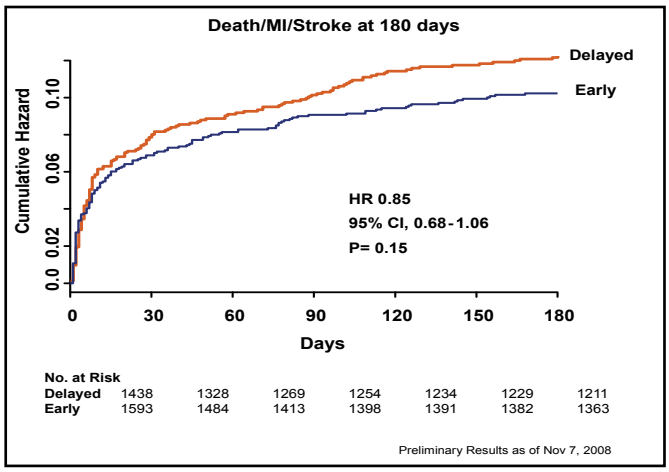
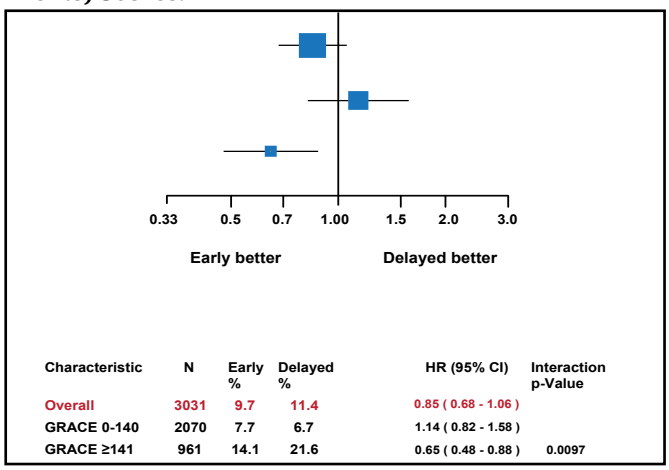


Figure 2. GRACE (Global Registry of Acute Coronary Events) Scores.



"Most patients with acute coronary syndromes can be managed safely with either an early or a delayed invasive strategy," said Shamir R. Mehta, MD, MSc, McMaster University, Hamilton, Ontario, Canada, who reported the TIMACS findings. However, early intervention appears to be superior for high-risk patients, who should be considered for early heart catheterization, he said.

"In all other patients with acute coronary syndrome, the decision regarding timing of intervention can depend on other factors, such as catheterization laboratory availability, health care system, convenience and economic considerations," Dr. Mehta concluded.

Tailored Clopidogrel Dosing Reduces Adverse Events in Patients With Clopidogrel Resistance Undergoing PCI

For patients who undergo nonemergent percutaneous coronary intervention (PCI), tailoring the loading dose of clopidogrel according to platelet reactivity reduced the rate of early stent thrombosis, according to findings from a new trial. Individualized dosing also reduced the incidence of major adverse cardiovascular events (MACE) without increasing bleeding events.

Franck Paganelli, MD, Hôpital Université Nord, Marseilles, France, reported findings from the Tailored Clopidogrel Loading Dose According to Platelet Reactivity Monitoring to Prevent Stent Thrombosis study at the American Heart Association Scientific Sessions meeting in New Orleans.

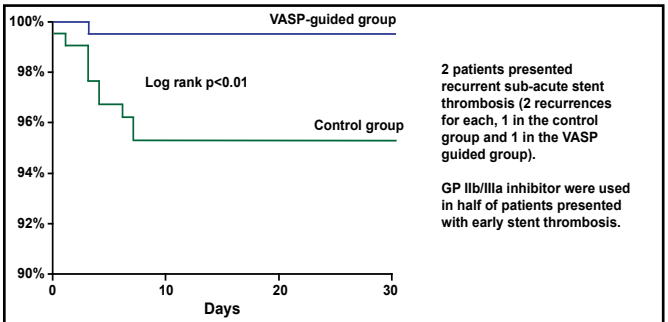
Clopidogrel resistance has been linked to increased adverse events in patients who are undergoing PCI. Dr. Paganelli and colleagues have been exploring the role of the vasodilator-stimulated phosphoprotein (VASP) index, a measure of platelet reactivity that is specific to the $P2Y_{12}$ receptor, to guide clopidogrel dosing. The present study examines whether additional loading doses of clopidogrel, based on the VASP index, can overcome problems that are related to clopidogrel resistance, including stent thrombosis and MACE, which have been shown to occur more frequently in patients with elevated platelet reactivity (elevated VASP index).

The trial included 429 "low responders" to clopidogrel, whose VASP index remained ≥50% (elevated platelet reactivity) after an initial loading dose of clopidogrel 600 mg. These patients were randomly assigned to additional VASP-guided clopidogrel dosing, with the goal of achieving a VASP index <50% (low platelet reactivity) prior to PCI (n=214), or PCI without additional clopidogrel dosing (n=215). In the VASP-guided arm, up to 3 additional loading doses of 600 mg of clopidogrel (maximum clopidogrel dose 2400 mg) were administered before PCI.

After the second clopidogrel dose in the VASP-guided group, 132 patients (61%) had a low VASP index of <50% and proceeded to PCI. Of the remaining patients, 83 (38%) required third doses and 40 (18%) required fourth doses of clopidogrel prior to intervention. The latter group included 17 patients (8%) whose VASP index remained elevated (>50%) despite a total of 2400 mg of clopidogrel. The primary endpoint was the rate of early definite stent thrombosis.

During the first 30 days after PCI, 1 patient in the VASP-guided group and 10 patients in the control group experienced stent thrombosis (p<0.01). All thrombotic events occurred within the first 7 days of the 30-day observational period (Figure 1).

Figure 1. Early Definite Stent Thrombosis During 1-Month Follow-Up.



Endpoint n, (%)	Control group (n= 214)	VASP-guided group (n= 215)	p
Acute stent thrombosis	2 (0.9)	0	0.25
Sub-acute stent thrombosis	8 (3.7)	1 (0.5)	0.02
Early DST	10 (4.7)	1 (0.5)	0.01

Tailored clopidogrel dosing also reduced the secondary endpoint of MACE in the VASP-guided group (0.5%) compared with the control group (8.9%; p<0.001). These results included a reduction in myocardial infarction (0.5% vs 4.8%; p=0.01), trends toward fewer cardiovascular deaths (0% vs 1.8%; p=0.06), and urgent revascularizations (0% vs 2.3%; p=0.06).

Increasing clopidogrel dosing up to 2400 mg prior to PCI did not appear to increase bleeding risk. No differences were observed between the VASP-guided and control groups in all TIMI bleeding (3.7% vs 2.8%; p=0.8), major bleeding (0.9% vs 0.9%; p=1.0), or minor bleeding (2.8% vs 1.9%; p=0.8; Figure 2).

Figure 2. Secondary Endpoint: TIMI Bleeding.

	Control (n= 214)	VASP-guided (n= 215)	p value
Major bleeding	2 (0.9)	2 (0.9)	1
Minor bleeding	4 (1.9)	6 (2.8)	0.8
All	6 (2.8)	8 (3.7)	0.8

No difference in bleeding complication between the 2 groups

No intra-cerebral bleeding, no fatal bleeding

Majority of patients had PCI through the radial access (55.6%)

"Trying to identify the optimal loading dose using a laboratory test is a very creative idea," said Elliott Antman, MD, Brigham and Women's Hospital, Boston, MA. Dr. Antman cautioned that giving iterative loading doses of clopidogrel based on VASP index results takes time, up to 3 days in patients who require third and fourth clopidogrel loading doses. "You need time for the loading dose to exhibit its effect, and then you need time for the laboratory result to come back," because bedside testing currently is not available, he said.

Future alternatives to clopidogrel therapy, such as prasugrel, AZD 6140, and cangrelor, may provide simpler dosing that is not susceptible to wide variations in treatment response, Dr. Antman said.

I-PRESERVE Trial Fails to Find Clinical Benefit of Irbesartan in Patients With Heart Failure and Preserved Ejection Fraction

Approximately 50% of heart failure (HF) patients have a left ventricular ejection fraction (EF) ≥45%. The majority of them are women and older patients. Unlike low ejection fraction HF, the primary underlying condition in heart failure with preserved ejection fraction (HFPEF) is hypertension. There currently are no evidence-based treatments to improve outcomes in patients with HFPEF.

Peter E. Carson, MD, Georgetown University and Washington DC Veterans Affairs Medical Center, Washington, DC, presented the results of the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE; NCT00095238) at the American Heart Association Scientific Sessions meeting in New Orleans.

I-PRESERVE was a multicenter, multinational, randomized, placebo-controlled, phase 3 trial. The objective was to determine whether treatment with the angiotensin-receptor blocker irbesartan reduces all-cause mortality and hospitalizations in patients with HFPEF. A secondary objective was to better define the characteristics, natural history, and prognosis of HF in this population. The primary study endpoint was a composite of all-cause mortality or hospitalization for a cardiovascular (CV) cause. Secondary endpoints were the individual components of the primary outcome; sudden death or death or hospitalization that was related to HF; change in quality of life at 6 months (as assessed by the Minnesota Living with Heart Failure score);