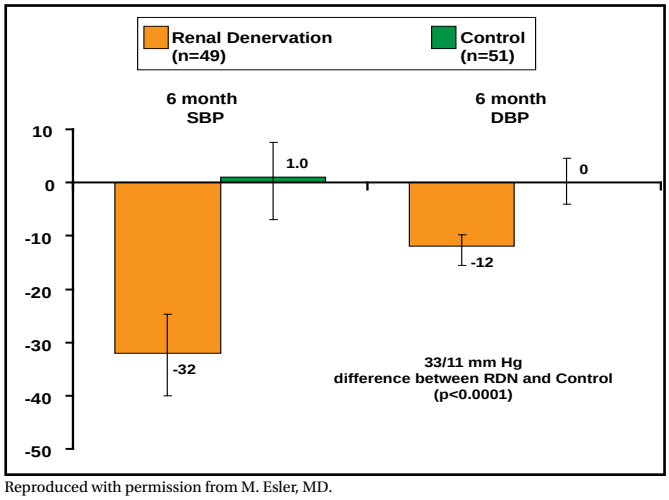
continuing medical therapy (n=52) or continuing medical therapy only (n=54). Interestingly, 19% of the screened failures were patients who did not meet the SBP threshold after 2 weeks of documented medication compliance. Another 16% of screened failures were due to ineligible anatomy (eg, multiple renal arteries). Study participants had a mean age of 58 years, mean baseline SPB of 178 mm Hg, and average BMI 31 kg/m^2 and were taking 5.3 antihypertensive medications on average. More than 75% of study participants had been taking antihypertensive medications for more than 5 years. Almost all participants were taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Other drug classes included calcium channel blockers (79% of RDN patients vs 83% of control patients), beta-blockers (83% vs 69%), and diuretics (89% vs 91%). Mean eGFR was 77 ml/min/1.73 m^2 in the denervation group versus 86 ml/min/1.73 m^2 in the control group (p=0.013)

Bilateral RDN was performed successfully in all 52 patients who were assigned to this study arm. At 6 months, patients in the RDN-treated group demonstrated significant decreases in SBP and DBP (33/11 mm Hg; p<0.0001) relative to control (Figure 1), with 84% of patients who were undergoing RDN experiencing a ≥10-mm Hg decrease in SBP (vs 35% of controls; p<0·0001). Similar decreases were noted for home and 24-hour ambulatory BP. BP reductions were progressive over the observation period, indicating the possibility of greater benefits over time. Use of antihypertensive medications declined in 20% of patients who were assigned to RDN versus 6% of control patients (p=0.04).

Figure 1. Primary Endpoint.



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There were no serious device- or procedure-related complications. No acute renal artery damage or radiofrequency dosing-related abnormalities were detected in the 6-month follow-up period.

This treatment appears promising for hypertensive patients whose blood pressure does not achieve the treatment goal using currently available therapies and affirms the crucial relevance of renal nerves in the persistence of elevated BP. "This procedure provides a revolutionary, nondrug method for controlling high blood pressure in patients who are unresponsive to multiple antihypertensive drugs," Dr. Esler said.

A randomized US-based trial is in development, while the future application of the technique in patients with less severe essential hypertension is also under consideration.

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High-Dose Clopidogrel in Patients With High Residual Reactivity: Results from the GRAVITAS Trial

Doubling the dose of clopidogrel in patients with high residual platelet activity after percutaneous intervention (PCI) has no significant effect on cardiovascular (CV) outcomes. The neutral results of the Gauging Responsiveness with A VerifyNow Assay—Impact on Thrombosis And Safety (GRAVITAS; NCT00645918) trial were presented by Matthew Price, MD, Scripps Clinic, La Jolla, California, USA.

The trial was designed to test the hypothesis that high-dose clopidogrel for 6 months would be superior to standard-dose clopidogrel in preventing adverse CV events in patients with high residual platelet reactivity after PCI. At least 7 studies, involving more than 3000 patients, have found that high residual (on-clopidogrel) platelet reactivity, as measured by the VerifyNow P2Y12 test, is associated with poor clinical outcomes after PCI [Price MJ et al. *Eur Heart J* 2008; Campo G et al. *J Am Coll Cardiol* 2010; Marcucci R et al. *Circulation* 2009; Mangiacapra F et al. *J Am Coll Cardiol Intv* 2010; Patti G et al. *J Am Coll Cardiol* 2008; Migliorini A et al. *Circulation* 2009; Bonello L et al. *J Am Coll Cardiol* 2010].

While some clinicians have already begun to treat patients with residual platelet reactivity with higher doses (>300-mg load, >75-mg daily maintenance) of clopidogrel, this was the first large, randomized, clinical trial to test a treatment strategy in such a patient population.

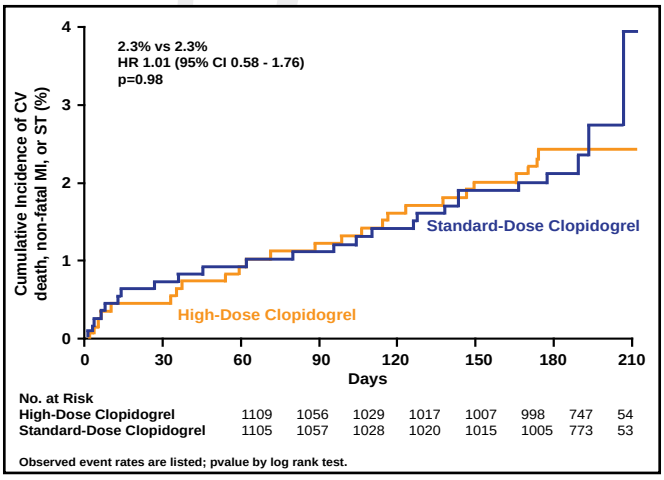
The trial involved 5429 subjects who received the standard clopidogrel regimen around the time of the PCI procedure. Their platelet function was evaluated with the VerifyNow P2Y12 test 12 to 24 hours after PCI. Of them, 2214 (41%)

had high residual platelet reactivity (platelet reactivity units [PRU] >230) and were randomized to continue on the 75-mg standard clopidogrel dose or to receive another 600-mg loading dose and a higher maintenance dose of 150 mg daily. Follow-up VerifyNow assays, the results of which were not available to the treating physician, were performed at 30 days and 6 months to assess the effect of the intervention on platelet reactivity. All participants also received daily low-dose aspirin.

The primary efficacy endpoint was CV death, nonfatal myocardial infarction (MI), or stent thrombosis at 6 months. The key safety endpoint was moderate or severe bleeding at 6 months.

Most enrolled patients were at relatively low risk at baseline, with 84% having stable coronary artery disease or low-risk unstable angina. Results showed no significant differences between the 6-month rate of CV death, MI, or stent thrombosis, which was 2.3% for both groups (HR, 1.01; 95% CI, 0.58 to 1.76; p=0.98; Figure 1). Rates of bleeding, whether moderate or severe, were also similar in both groups (1.4% vs 2.3%, high dose and standard dose respectively; p=0.10).

Figure 1. Primary Endpoint: CV Death, MI, Stent Thrombosis.



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Persistently high PRU levels (> 230) were significantly more common in the standard-dose group at 30 days (62% vs 40%; p<0.001), although achieving a lower PRU with higher-dose clopidogrel did not translate into improved clinical outcomes. One possible explanation is that the magnitude of the effect on platelet reactivity was not sufficient to demonstrate a clinically significant difference between these two dosing strategies of clopidogrel.

Dr. Price noted that high-dose clopidogrel was safe and that future trials should investigate more potent antiplatelet agents, focus on different populations, and test different treatment strategies—eg, treating to a specific PRU target rather than basing treatment upon a single post-PCI assessment of platelet function.

Results From the ASCEND-HF Trial

Results from a large, prospective clinical trial that was designed to assess the safety and efficacy of nesiritide that was added to standard care in patients with acute decompensated heart failure (ADHF) showed that nesiritide is safe but offers no significant benefit in terms of mortality or HF rehospitalization rates. There was a modest improvement in dyspnea. Renal function was not compromised.

Nesiritide is a recombinant intravenous (IV) formulation of human B-type natriuretic peptide that is known to reduce dyspnea and intracardiac filling pressures within 3 hours of administration in patients with ADHF. It was approved in 2001 to reduce pulmonary capillary wedge pressure and improve dyspnea and was widely used until 2005, when the results of two meta-analyses questioned its safety, noting a higher mortality rate [Sackner-Bernstein JD et al. *JAMA* 2005] and increased risk of kidney injury [Sackner-Bernstein JD et al. *Circulation* 2005]. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF; NCT00475852) was designed as the result of an independent safety and efficacy review of nesiritide data in an attempt to assess the concerns that were raised by the 2005 reports more fully.

ASCEND-HF was a prospective, double-blind, randomized trial in 7141 patients (median age 67 years; ~34% women) with ADHF, dyspnea at rest or with minimal activity, and one clinical sign and one objective measure of HF. Within 24 hours of hospitalization, subjects were randomly assigned to receive either IV nesiritide (n=3496; initial IV bolus of 2 µg/kg at the discretion of the investigator, followed by continuous IV infusion of 0.01 µg/kg) or matching placebo (n=3511) for up to 7 days, along with usual care. The duration of treatment was based on the investigator's assessment of clinical improvement.

The two coprimary endpoints were rehospitalization for HF/all-cause mortality within 30 days and dyspnea at 6 or 24 hours (p-value for significance prespecified at ≤0.005 for both assessments or ≤0.0025 for either assessment). Improvement in dyspnea was self-reported using a 7-point Likert scale: markedly worse, moderately worse, minimally worse, no change, minimally better, moderately better, and markedly better. Safety endpoints included impact on renal function (25% decrease in eGFR through Day 30) and hypotension.