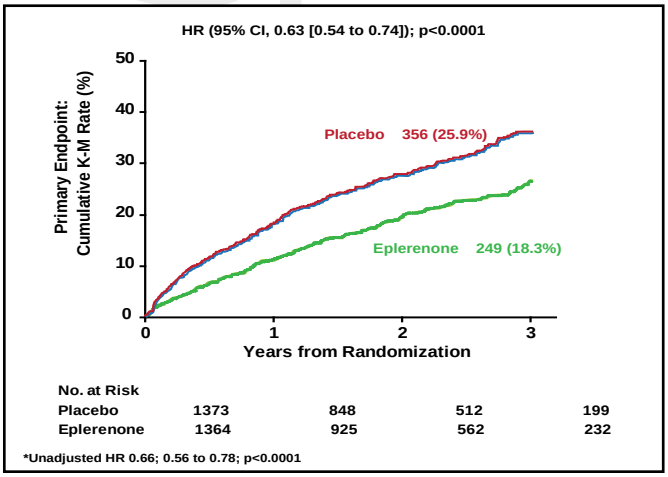
chronic systolic HF. The study comprised 2737 subjects (mean age 68 years; more than 75% men) with an ejection fraction ≤30% and an eGFR <30 ml/min/1.73 m^2. Subjects were randomly assigned to receive either eplerenone (n=1364) or placebo (n=1373) in addition to standard HF therapy and were followed for a median of 21 months. The dose of eplerenone was adjusted from 25 mg every day to 50 mg daily, depending on serum potassium, which, along with renal function, was monitored every 4 months. The primary endpoint was a composite of time to cardiovascular (CV) death or first hospital admission for worsening HF, whichever occurred first.

Due to the overwhelming benefit in the eplerenone arm, the trial was stopped early. Incidence of the primary outcome of of CV death or hospitalization occurred in 18.3% of patients treated with eplerenone versus 25.9% who received placebo (HR, 0.63; 95% CI, 0.54 to 0.74; p<0.0001; Figure 1). The number that was needed to treat to prevent one patient from experiencing the primary endpoint per year of follow-up was 19. The effect of eplerenone on the primary outcome was consistent across all prespecified subgroups.

Figure 1. Primary Endpoint CV Death or Hospitalization for HF.



Mortality from any cause was reduced by 24% with eplerenone (12.5%) versus placebo (15.5%; p=0.0081). CV death and death from worsening HF were significantly (p=0.01 and p=0.05, respectively) reduced with the addition of eplerenone. In addition, eplerenone reduced the rate of hospitalization from any cause by 30% (p<0.001) and the rate of hospitalization for HF by 12% (p<0.001).

Hyperkalemia is a known side effect of aldosterone antagonists, whose use requires routine potassium and renal function assessments. Patients who were treated with eplerenone had significantly (8.0% vs 3.7%; p<0.001) higher rates of hyperkalemia but lower (p=0.05) incidence of hypokalemia. There were no significant differences regarding drug withdrawal due to adverse events, hospitalization for worsening renal failure, or hyperkalemia between the eplerenone and placebo treatment groups.

Findings from the EMPHASIS-HF trial in patients with class II HF expanded the results of the EPHESUS trial, which showed a benefit of eplerenone over placebo in post-MI patients with NYHA class III/IV symptoms and significant LV dysfunction. "We believe that the robustness of these findings, in conjunction with the consistent results from the earlier RALES and EPHESUS trials, provides compelling evidence to change medical practice," concluded Prof. Zannad. Studies to examine the impact of eplerenone in high-risk, untargeted patients are planned.

This study was published simultaneously in the New England Journal of Medicine. *Zannad F et al. N Engl J Med 2010.*

Results From Symplicity HTN-2

The role of the sympathetic nervous system in hypertension has been known for some time, but its potential as a therapeutic avenue has been overshadowed by drug therapy. Murray D. Esler, MD, Baker IDI Heart and Diabetes Institute, Melbourne, Australia, presented the results of the first human randomized controlled trial of sympathetic renal denervation as a treatment for treatment-resistant hypertension, which showed substantial reductions in systolic blood pressure (SBP).

The International, Multicenter, Prospective, Randomized, Controlled Trial of Endovascular Selective Renal Sympathetic Denervation for the Treatment of Hypertension (Symplicity HTN-2; NCT00888433) was conducted in 24 centers in Europe, Australia, and New Zealand. The primary study endpoint was change in office-based automated SBP between baseline and 6 months. Secondary endpoints included acute and chronic procedural safety issues and home/ambulatory BP reductions.

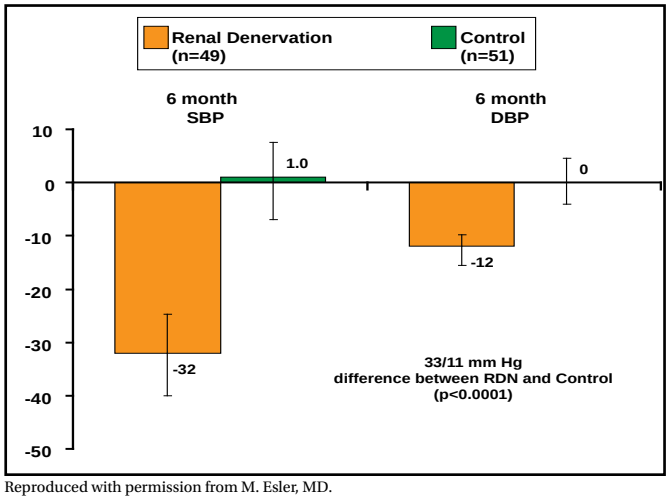
Patients aged between 18 and 85 years with an office SBP ≥160 mm Hg (≥150 mm Hg in individuals with type 2 diabetes) and a bilateral single main renal artery >20 mm long and 4 mm in diameter who were taking at least 3 antihypertensive medications were eligible for this trial. Patients with renal artery duplication or stenosis, eGFR <45 mL/min, type 1 diabetes, or unstable angina/recent cerebrovascular accidents were excluded.

A total of 190 patients were screened, and 106 were randomly assigned to renal denervation (RDN) plus

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.

This article was published simultaneously in *The Lancet.* Symplicity HTN-2 Investigators. *Lancet* 2010.

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%)