SYMPLICITY HTN-3 Trial: No Blood Pressure Reduction in Patients With Resistant Hypertension Treated With Renal Denervation

Written by Muriel Cunningham

Previous research suggests that catheter-based renal artery denervation (RDN) reduces blood pressure (BP) in patients with resistant hypertension. Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the results of the Renal Denervation in Patients With Uncontrolled Hypertension trial [SYMPLICITY HTN-3; Bhatt DL et al. *N Engl J Med* 2014]. This was a large, prospective, randomized, blinded sham-controlled study conducted to assess the safety and efficacy of percutaneous RDN in patients with resistant hypertension.

The study was conducted at 88 sites in the United States. Patients were eligible if they were aged 18 to 80 years at the time of randomization, were on a stable regimen of ≥3 antihypertensive medications of different classes (including a diuretic) with no changes in the previous 2 weeks and no expected changes in the next 6 months, and had a mean office systolic BP (SBP) ≥160 mm Hg. Patients with any of the following were excluded: an ambulatory BP monitor (ABPM) 24-hour average SBP <135 mm Hg, an estimated glomerular filtration rate of <45 mL/min/1.73 m^2, main renal arteries <4 mm diameter or <20 mm treatable length, multiple renal arteries, renal artery stenosis >50%, an aneurysm in either renal artery, or a history of prior renal artery intervention.

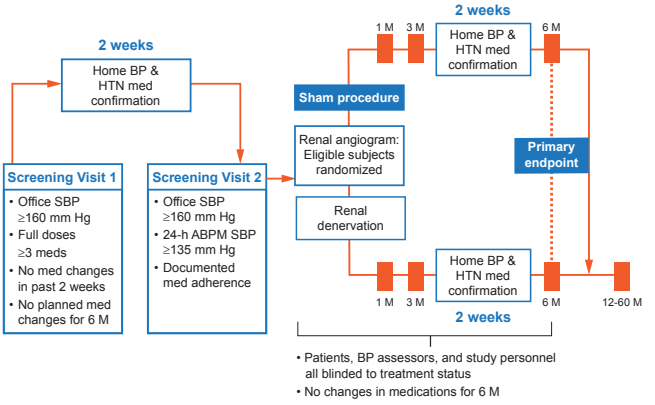
The study design is illustrated in Figure 1. Patients were randomized to either RDN or a sham procedure (renal angiogram). The primary endpoint was the change in SBP (office, superiority margin 5 mm Hg) at 6 months with the change in mean 24-hour ambulatory SBP as a secondary endpoint. The primary safety endpoint was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis at 6 months.

A total of 535 patients were randomized to RDN (n=364) and to the sham procedure (n=171). The mean age was 57 years, ~62% were male, ~70% were white, and patients were taking a mean of five antihypertensive agents. The mean baseline office SBP was 180 mm Hg, and the mean baseline ABPM was 160 mm Hg.

SBP in the two groups at 6 months was similar (difference of –2.39 mm Hg; 95% CI, –6.89 to 2.12; p=0.26) and SBP in both arms decreased from baseline to 6 months –14.1 mm Hg for the RDN group and –11.7 mm Hg for the sham group.

There was no difference in the major adverse event rate for RDN (1.4%) versus the sham arm (0.6%; p=0.67). The secondary efficacy analysis of the change in 24-hour mean systolic ABPM was also nonsignificant: –1.96 mm Hg (95% CI, –4.97 to 1.06).

Figure 1. Study Schematic



ABPM=ambulatory blood pressure monitor; BP=blood pressure; HTN=hypertension; M=months; SBP=systolic blood pressure.

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When presenting these results Dr. Bhatt concluded, "Further study in rigorously designed clinical trials will be necessary to confirm previously reported benefits of renal denervation in patients with resistant hypertension or to validate alternate methods of renal denervation."

Darapladib Without Significant CV Benefit in Stable Coronary Heart Disease (STABILITY)

Written by Wayne Kuznar

An investigational, selective, orally active inhibitor of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) failed to significantly reduce the risk for cardiovascular (CV) death, myocardial infarction (MI), or stroke in stable coronary heart disease (CHD) patients on optimal medical therapy.

The design and results of the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial [STABILITY; The STABILITY Investigators. *N Engl J Med* 2014] were presented by Harvey D. White, DSc, Auckland City Hospital, Auckland, New Zealand.

Elevated plasma levels of Lp-PLA_2 are associated with an increased risk of coronary events. The enzyme is secreted by T cells and macrophages and circulates largely bound to low-density lipoproteins [Zalewski A, Macphee C. *Arterioscler Thromb Vasc Biol* 2005]. Within atheromatous plaque, it hydrolyzes oxidatively modified polyunsaturated

fatty acids producing lysophosphatidylcholine and oxidized nonesterified fatty acids, explained Prof. White. "Unstable" plaques are characterized by a higher content of Lp-PLA_2 and other markers of inflammation [Corson MA et al. *Am J Cardiol* 2008].

Darapladib decreases Lp-PLA_2 levels by ~60% [Serruys PW et al. *Circulation* 2008]. In preclinical investigations, it reduced Lp-PLA_2 levels and necrotic core area within atherosclerotic plaque [Wilensky RL et al. *Nat Med* 2008]. In humans, treatment with darapladib was shown to halt progression of coronary artery necrotic plaque core volume in patients with CHD, but not atheroma volume [Serruys PW et al. *Circulation* 2008].

STABILITY compared darapladib at a dosage of 160 mg/day with placebo in a double-blind, randomized, global trial of 15,828 patients with chronic CHD receiving standard of care. The median patient age was 65 years, ~80% were white, and ~80% were male. Fifty-nine percent had a qualifying diagnosis of MI for more than 1 month prior to randomization and 75% had undergone prior coronary revascularization. Fifteen percent had multivessel CHD at baseline. Very high rates of evidence-based background therapies were used at baseline and throughout the duration of the study (>90% use of aspirin; >95% use of statins; ~80% use of β-blockers; and ~50% use of angiotensin-converting enzyme inhibitors).

At a median follow-up of 3.7 years, the primary endpoint—a composite of CV death, MI, and stroke—occurred in 819 patients randomized to placebo (10.4%) compared with 769 patients randomized to darapladib (9.7%), corresponding to a hazard ratio of 0.94 (95% CI, 0.85 to 1.03) that did not achieve significance (p=0.20). Results for the components of the primary endpoint are shown in Table 1. There were no significant differences between darapladib and placebo on any of the individual components of the primary endpoint or all-cause mortality.

Coronary-specific endpoints suggested benefit to darapladib. Darapladib was associated with a reduction in the rate of the prespecified secondary endpoints of major coronary events (10.3% vs 9.3%; HR, 0.90; p=0.045) and total coronary events (16.1% vs 14.6%; HR, 0.91; p=0.019; Table 1). These findings should be considered exploratory in light of the lack of effect on the primary endpoint, said Prof. White.

Serious adverse events occurred at a similar frequency in the darapladib and placebo arms, 42.6% and 43.7%. Adverse events leading to study drug discontinuation occurred in 19.8% and 13.5% in the darapladib and placebo arms, respectively. Side effects that led to darapladib discontinuation included diarrhea, abnormal feces, abnormal skin odor, and abnormal urine odor.

Table 1. Cardiovascular and Mortality Endpoints

	Placebo	Darapladib	HR (95% CI)	p Value
CV death	4.7%	4.5%	0.96 (0.83, 1.11)	0.59
MI	5.1%	4.6%	0.89 (0.77, 1.03)	0.11
Stroke	1.9%	1.9%	1.01 (0.81, 1.27)	0.92
All-cause mortality, MI, stroke	12.2%	11.7%	0.96 (0.88, 1.05)	0.40
All-cause mortality	7.3%	7.3%	1.01 (0.90, 1.13)	0.87
Major coronary events (CHD death, MI, urgent coronary revascularization)	10.3%	9.3%	0.90 (0.82, 1.00)	0.045
Total coronary events (CHD death, MI, any coronary revascularization, hospitalization for unstable angina)	16.1%	14.6%	0.91 (0.84, 0.98)	0.019

CHD=coronary heart disease; CV=cardiovascular; MI=myocardial infarction.

In STABILITY, subgroup analyses based on biomarkers and genetics will further explore the potential utility of darapladib in specific high-risk patient subsets. The SOLID TIMI-52 trial [NCT010007277] which is testing darapladib in ~13,000 post-ACS patients is expected to report results in 2014.

Monoclonal Antibody Reduces LDL-C in Presence of Statin (LAPLACE-2)

Written by **Wayne Kuznar**

A fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), when added to background statin therapy, reduces levels of low-density lipoprotein cholesterol (LDL-C) in patients with hypercholesterolemia and mixed dyslipidemia.

The monoclonal antibody evolocumab (previously AMG 145), which inhibits PCSK9, dramatically lowered levels of LDL-C in Phase 2 clinical trials when administered alone or in combination with a statin, including among patients intolerant of statin therapy, those with familial hypercholesterolemia, and in those treated in a 52-week study [Koren MJ et al. *Circulation* 2013; Giugliano RP et al. *Lancet* 2012; Koren MJ et al. *Lancet* 2012; Raal F et al. *Circulation* 2012; Sullivan D et al. *JAMA* 2012]. These observations led to the randomized, multicenter, placebo-controlled, double-blind Phase 3 LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2 study [LAPLACE-2; NCT01763866], the results of which were presented by Jennifer G. Robinson, MD, MPH, University of Iowa, Iowa City, Iowa, USA.