on renal function. The mean glomerular filtration rate (GFR) was 79 mL/min/1.73m^2 prior to the procedure and 83 mL/min/1.73m^2 6 months following renal denervation.

Percutaneous renal sympathetic denervation represents a simple and effective approach to the management of hypertension in patients who are refractory to conventional pharmacologic therapy, Dr. Krum concluded. Future trials will define the long-term efficacy of renal denervation in resistant hypertension and other disorders, he said.

Activation of the Carotid Baroreflex

An implantable device that activates the baroreceptors of the carotid sinus significantly reduces blood pressure in patients with refractory hypertension, according to results from a small phase 2 feasibility study.

In hypertensive patients, blood pressure receptors within the carotid sinus do not detect elevated intravascular blood pressure, leading to an inadequate autonomic response. The Rheos® hypertension system consists of a pulse generator, implanted near the collarbone, and carotid sinus leads. The device electrically stimulates the carotid sinus to activate blood pressure reflexes that lower heart rate, dilate blood vessels, and induce diuresis.

The phase 2 trial included 61 patients with systolic blood pressure ≥160 mm Hg who were resistant to 3 or more antihypertensive medications, including diuretics. After the Rheos device was surgically implanted and activated, blood pressure levels were measured at 1 year, 2 years, and 3 years. Marcos Rothstein, MD, Washington University School of Medicine, St. Louis, MO, presented findings in a late-breaking clinical trials session.

Mean blood pressure at baseline was 183/105 mm Hg despite treatment with a mean of 5.1 antihypertensive medications. On average, systolic blood pressure dropped by 25 mm Hg after 1 year, 22 mm Hg after 2 years, and 31 mm Hg after 3 years ($p<0.001$ at all time points). Diastolic blood pressure dropped by 15 mm Hg at 1 and 2 years and by 21 mm Hg by 3 years ($p<0.001$ at all time points).

Mean heart rate also fell by 7 bpm at 1 year ($p<0.005$), 8 bpm at 2 years ($p<0.005$), and 5 bpm at 3 years ($p=0.15$). Dr. Rothstein also observed a significant improvement in cardiac structure and function at 1 year, as measured by a decrease in left ventricular mass ($p<0.05$), left atrial dimension ($p<0.05$), and mitral A-wave velocity ($p<0.05$).

Based on promising early-phase results, the Rheos hypertension system is currently under evaluation in a phase 2 prospective, randomized, double-blind, placebo-controlled, multicenter trial with a target enrollment of 300 patients.

Clopidogrel Added to Aspirin Reduces Stroke Risk in Atrial Fibrillation Patients Unsuitable for Vitamin K Antagonist Therapy

For high-risk atrial fibrillation (AF) patients who are unsuitable for Vitamin K antagonist (eg, warfarin) therapy, dual antiplatelet therapy with clopidogrel and aspirin reduces the risk of major vascular events compared with aspirin alone, according to findings from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-A trial (NCT000249873).

Stuart Connolly, MD, McMaster University, Hamilton, ON, Canada, reported findings from ACTIVE-A, which was designed to evaluate the addition of clopidogrel to aspirin in high-risk AF patients who were unsuitable for oral anticoagulation. A vitamin K antagonist, such as warfarin, is the treatment of choice for the prevention of stroke in high-risk patients with AF. However, due to increased bleeding risk, patient preference, or other medical contraindications, fewer than 50% of high-risk patients are suitable candidates for oral anticoagulation therapy.

ACTIVE-A included 7554 patients with documented AF, at least one risk factor for stroke, and no major risk factors for bleeding. All patients were treated with aspirin 75 to 100 mg/day, and were randomly assigned to additional treatment with clopidogrel 75 mg/day (n=3772) or placebo (n=3782). The primary outcome was a composite of major vascular events including stroke, myocardial infarction (MI), non-central nervous system (CNS) systemic embolism, or vascular death.

After a median follow-up of 3.6 years, dual antiplatelet therapy reduced the risk of the primary outcome by 11% compared with aspirin alone, from an annual rate of 7.6% to 6.8% (HR, 0.89; 95% CI, 0.81 to 0.98; p=0.01).

According to an analysis of the components of the primary endpoint, the benefit of clopidogrel was mainly in the reduction of stroke risk from 3.3% per year with aspirin alone to 2.4% per year with clopidogrel and aspirin

(HR, 0.72; 95% CI, 0.62 to 0.83; p<0.001). Moreover, the risk reduction was particularly related to the annual risk of non-hemorrhagic stroke in the aspirin alone (3.2%) and clopidogrel plus aspirin (2.1%) groups (RR, 0.68; 95% CI, 0.59 to 0.80; p<0.001). The annual risk of hemorrhagic stroke was 0.2% in both treatment groups (RR, 1.37; 95% CI, 0.79 to 2.37; p=0.27).

There was also a nonsignificant trend toward a reduction in the risk of MI from 0.9% with aspirin alone to 0.7% with dual antiplatelet therapy (HR, 0.78; 95% CI, 0.59 to 1.03; p=0.08). However, there were no differences between treatment groups in the risk of vascular death (4.7% per year in both groups; p=0.97) or non-CNS systemic embolism (0.4% per year in both groups; p=0.84).

Clopidogrel increased the risk of bleeding in patients on long-term aspirin therapy. Compared with patients taking aspirin alone, those taking clopidogrel and aspirin had a higher rate of major bleeding (1.3% vs 2.0% per year; RR, 1.57; 95% CI, 1.29 to 1.92; p<0.001), including severe bleeding (1.0% vs 1.5% per year; p<0.001), with a trend toward increased fatal bleeding (0.2% vs 0.3% per year; p=0.07). The excess risk of major bleeding included both intracranial bleeding (0.2% vs 0.4% per year; p=0.006) and extracranial bleeding (1.1% vs 1.6%; p<0.001).

Overall, adding clopidogrel to aspirin therapy for 3 years in 1000 patients with atrial fibrillation unsuitable for anticoagulation will prevent 28 strokes, including 17 fatal or disabling strokes, and 6 MIs. This strategy will also cause 20 major bleeds, including 3 fatal bleeds, which is an acceptable balance of clinical benefits and hemorrhagic risks, Dr. Connolly concluded.

Findings from the ACTIVE-A trial were simultaneously published online in the *New England Journal of Medicine.*

Adding Cardiac Resynchronization Therapy (CRT) May Prevent Disease Progression In Asymptomatic and Mildly Symptomatic Heart Failure (HF) Patients Already on OMT

The 24-month results of the European cohort of the Resynchronization Reverses Remodeling in Systolic left ventricular dysfunction (REVERSE; NCT00271154) trial showed that CRT that is combined with optimal medical therapy (OMT) produces improved clinical outcomes, as well as improved ventricular structure and function in persons with NYHA Class I-II HF patients. Jean-Claude Daubert, MD, Centre Hospitalier Universitaire, Rennes, France, suggested that CRT may prevent disease progression in these patients.

The 1-year results from REVERSE failed to show that adding CRT to OMT significantly influenced the primary endpoint, which was percentage of worsening. This subset analysis (from the European dataset) included 261 patients with HF that was associated with a QRS duration ≥120 ms, an LVEF ≤40%, and left ventricular end diastolic diameter (LVEDD) ≥55 mm who received a CRT device with or without a defibrillator. Patients in REVERSE were randomly assigned to an active CRT group (CRT on; 180 patients) or a control group (CRT off; 82 patients) for 24 months, while OMT for HF was maintained. The primary endpoint was the HF clinical composite response (including all-cause mortality, HF hospitalizations, crossover due to worsening HF, NYHA class, and the patient global assessment), which compared the proportion of improved, unchanged, or worsened patients in the CRT-off versus CRT-on groups. The prospectively powered secondary endpoint was LV end-systolic volume index (LVESVi).

After 24 months, the clinical composite response was significantly (p=0.01) worsened in more patients in the CRT-off (34%) versus the CRT-on group (p=0.0006). Significant differences were noted at 6 months and remained for the duration of the study. Worsening was attributed to death or HF hospitalization in 69% of patients in the CRT-off group. Compared with patients in the CRT-off group, CRT-on patients experienced a significant reduction in LVESVi (p<0.0001) and other measures of LV remodeling. Time to first HF hospitalization or any death was significantly delayed in CRT on compared with CRT off (HR, 0.38; 95% CI, 0.20 to 0.73; p=0.003). Minnesota living with HF score, 6-minute Hall Walk score, and NYHA class score were not significantly different between the CRT-on and CRT-off groups.

Most of the results of this study concur with the earlier 12-month North American/Canadian arm of the REVERSE study [Linde C et al. *J Am Coll Cardiol* 2008], except in that analysis, the HF clinical composite response endpoint was not significantly different between patients who worsened in the CRT-on (16%) group compared with those in the CRT-off (21%) group (p=0.10). When questioned about this disparity, Dr. Daubert responded, "It was probably due to differences in study length."