



European Society of Cardiology Congress 2012

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This year's premier European Society of Cardiology (ESC) conference in Munich, Germany, from August 25 to 29, welcomed nearly 28,000 participants from 140 countries. Key sessions on antiplatelet therapies, renal denervation (a non-drug therapy that is being adopted rapidly in Europe), contrast-induced nephropathy, "e-cigarettes," and an online resource on treatment-resistant hypertension are discussed.

Cardiologists Gather for Research Findings: From Antiplatelets to 'E-Cigarettes' To Online Help for Hypertension

Prasugrel and Clopidogrel for Acute Coronary Syndromes: The TRILOGY ACS Trial

- Magnus Ohman, MB, ChB, Professor of Medicine, Duke Clinical Research Institute, Durham, N.C.
- Spencer King, MD, President, Heart and Vascular Institute, St. Joseph's Hospital, Atlanta, Ga.

TRILOGY ACS (TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes) was the largest trial to date of acute coronary syndrome (ACS) patients who were treated with medication without revascularization.¹ The trial included 7,243 patients younger than 75 years of age and 2,083 patients 75 years of age and older with unstable angina or non-ST segment myocardial infarction (NSTEMI). All patients were randomly assigned to receive prasugrel (Effient, Daiichi Sankyo/Eli Lilly), 5 mg daily for those weighing less than 60 kg or for those 75 years of age or older or 10 mg daily, or clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi) 75 mg daily. Patients were observed for 2.5 years.

Prasugrel is a newer, more potent thienopyridine than clopidogrel. In preclinical studies, prasugrel was found to have about 10-fold the platelet inhibitory effects of clopidogrel. In TRILOGY ACS, the minimum treatment duration was 6 months and the maximum was 30 months. All patients were receiving aspirin; a low dose of less than 100 mg was recommended. The primary efficacy endpoint was cardiovascular death, myocardial infarction (MI), or stroke.

After 30 months, the primary efficacy endpoint in the primary cohort of patients who were 75 years of age or younger was reported at a rate of 16.0% for clopidogrel and 13.9% for prasugrel (hazard ratio [HR] = 0.91; 95% confidence interval [CI], 0.54–0.97; $P = 0.21$).

The rates for the individual components (clopidogrel/prasugrel) were 6.8%/6.6% for cardiovascular death (HR = 0.93;

95% CI, 0.75–1.15); 10.5%/8.3% for all MIs (HR = 0.89; 95% CI, 0.74–1.07)]; and 2.2%/1.5% for all strokes (HR = 0.67; 95% CI, 0.42–1.06)].

The primary efficacy endpoint in the overall population through 30 months occurred in 20.3% of patients receiving clopidogrel and in 18.7% of patients receiving prasugrel (HR = 0.96; 95% CI, 0.86–1.07; $P = 0.45$).

There was a trend in the period after 1 year, Dr. Ohman pointed out, for a time-dependent benefit for prasugrel for each of the primary endpoint components and a significant interaction with treatment and time for the primary combined endpoint (HR = 0.64, 95% CI, 0.48–0.86; $P = 0.02$).

Although major or minor bleeding was significantly higher with prasugrel than with clopidogrel (1.9% vs. 1.3%, respectively; $P = 0.02$), rates of major, life-threatening, or fatal bleeding or intracranial hemorrhage did not differ between groups in the 75-and-younger age group. In the overall population, Thrombosis in Myocardial Infarction (TIMI) major bleeding was reported at a rate of 2.5% for prasugrel and 1.8% for clopidogrel.

For the prespecified endpoint of all ischemic events over time in patients younger than 75 years of age, there was a lower risk of multiple recurrent ischemic events with prasugrel therapy (HR = 0.85, 95% CI, 0.72–1.00; $P = 0.04$). Two or more events were reported among 95 patients receiving prasugrel and among 134 patients receiving clopidogrel. Rates of non-benign neoplasm occurrence were similar between treatment groups.

Dr. King commented in an interview:

The message for cardiologists who might be attempting to treat all their ACS patients with the more powerful agent is that the trial couldn't show any advantage. On the other hand, for those physicians who want to treat their patients with the more powerful agent but are worried that there would be more bleeding—that turned out not to be true either.

Renal Sympathetic Denervation In Resistant Hypertension: The SYMPLICITY Trial, 18-Month Results

- Murray Esler, MBBS, PhD, Professor of Medicine, Monash University, and Senior Director, Baker International Diabetes Institute/Heart and Diabetes Institute, Melbourne, Australia
- Horst Sievert, MD, Professor, Cardiovascular Center, Frankfurt, Germany

Treatment-resistant hypertension is defined by a failure to achieve blood pressure (BP) goals despite the use of three or more antihypertensive medications (with lifestyle measures included in the treatment plan) or the achievement of BP goals in patients needing four or more antihypertensive drugs. Goals are a systolic BP below 140 mm Hg and a diastolic BP below 90 mm Hg (and lower if the patient has other complications).

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Approximately 15% of patients treated for hypertension meet these criteria.

Renal denervation in SYMPLICITY HTN-2 was achieved through radiofrequency (RF) ablation of the nerves in the wall of the renal artery. The investigators used a RF generator (Ardian/Medtronic) to power the delivery of a catheter through the femoral artery to the renal arteries.

“The twofold logical basis for this strategy,” Dr. Esler said, “lies in the fact that patients with hypertension often have high renal sympathetic tone, and in experimental animals, surgical denervation often prevents or delays the development of hypertension.”

Dr. Esler reported 18-month findings in 43 patients who had undergone the procedure and 31 who had crossed over to renal denervation per protocol at 6 months. The included population had systolic BPs of 160 mm Hg or higher (150 mm Hg or higher with type-2 diabetes mellitus) despite stable drug regimens of three or more antihypertensive medications. Patients’ ages ranged from 18 to 85 years. Results were as follows:

- In the active-treatment group, systolic BP was 178 mm Hg at baseline and 147 mm Hg 6 months after the procedure.
- In the control group (n = 49), mean systolic BP was 183 mm Hg at baseline and 191 mm Hg 6 months after the procedure.
- In the initial renal denervation group, systolic and diastolic BP had dropped (18 months after the procedure) by 32 and 12 mm Hg, respectively, from baseline values.
- In the crossover group, systolic and diastolic BP reductions (12 months after the procedure) were 28 and 11 mm Hg, respectively.

All of these reductions were significant ($P < 0.01$), compared with pre-procedure values for each group.

Compared with baseline measures, pulse pressure decreases of about 20 mm Hg were sustained in the renal denervation group from 6 to 18 months after the procedure ($P < 0.01$). Pulse pressures fell in the crossover group as well (by 17.6 mm Hg). At 18 months, heart rates were 68 beats/minute for the renal denervation and crossover groups; at baseline, these rates had been 75 and 72 beats/minute, respectively. Reliance on antihypertensive medications tended to diminish over time. Three patients had hypertensive crises, and one patient required hospitalization. One case of mild transient acute renal failure resolved, and two deaths were unrelated to the procedure or to therapy.

No significant changes in renal function were noted, as assessed by the estimated glomerular filtration rate (eGFR), compared with pre-procedure values. No renal vascular events were experienced between the 12- and 18-month evaluations.

“In this study at [the] 18-month follow-up in both arms, we have good safety and good efficacy of the procedure,” Dr. Esler concluded.

Dr. Sievert noted in an interview that renal denervation, while currently available for patients with resistant hypertension in Europe, is also being tested in patients with less severe disease.

“We are publishing the data on borderline resistant hypertension—with the SYMPLICITY device in patients between 140 and 160 mm Hg. It is effective there. We don’t know if it is effective in very mild hypertension patients. That has to be studied,” he said.

Contrast-Induced Nephropathy: Prospective Study, 3 Years of Follow-up

- Miguel Pighi, MD, University of Verona, Verona, Italy

“In general, people have thought that contrast media cause acute events, but not long-term kidney injury,” Dr. Pighi said in an interview. He also noted that contrast-induced nephropathy (CIN) has been associated with increased morbidity and mortality, and although cardiologists have suggested a direct relationship between acute and long-term injury, data have been insufficient to establish a causal link.

To address this problem, Dr. Pighi and colleagues conducted a prospective pilot study during which all 216 patients received low-osmolar or iso-osmolar contrast medium and preventive hydration with isotonic saline before and after the procedure, except those patients who were treated emergently because of acute MI. All patients were undergoing coronary angiography, interventions, or both, and were considered to be at risk for CIN. CIN was defined as an acute impairment of renal function, expressed as a relative increase in serum creatinine of at least 25% of baseline values or an absolute increase in serum creatinine of at least 0.5 mg/dL (44.2 μmol/L) in the absence of other related causes.

CIN occurred in nearly 21% of patients, but no significant correlation was found between CIN and in-hospital and major adverse events (defined as death, MI, or need for permanent dialysis at 1 and 3 years of follow-up). Strong correlations were reported, however, between morbidity and mortality at 3 years and in-hospital reductions from baseline measures of GFR and increments of serum creatinine values after the procedure. Event-free survival was $92.1\% \pm 2.7\%$ for patients with a GFR of 60 mL/minute or higher and $77.6\% \pm 4.2\%$ for those with a GFR of less than 60 mL/minute ($P = 0.006$).

“Acute damage to the kidney’s tubular system leads to persistent damage,” Dr. Pighi said. “If you have a normal GFR before the procedure, but after the procedure at 12 hours or 48 hours you have a GFR decrease, you will probably develop a persistent kidney injury.”

He added that patients who developed CIN 30 days after the procedure showed a persistent impairment of renal function manifesting through significant serum creatinine increments at 1 and 3 years compared with baseline values.

Dr. Pighi concluded, “Reductions in GFR in response to use of iodine contrast media during cardiovascular invasive procedures predict long-term kidney injury.”

He recommended a prophylactic strategy consisting of the use of small quantities of contrast medium with plenty of hydration before and after the procedure to dilute the contrast material and speed excretion.

A follow-up study enrolling 1,000 patients is planned.

Regular and Electronic Cigarettes: Effects on Myocardial Function

- Konstantin Farsalinos, MD, Cardiologist, Onassis Cardiac Surgery Center, Athens, Greece

Electronic cigarettes are used by millions of individuals, including 2.5 million in the U.S. E-cigarettes, in addition to

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addressing psychological addiction through their similarity in form to regular cigarettes, do deliver nicotine, but they are less toxic. Although tobacco smoke has been shown to contain more than 4,000 chemicals, e-cigarettes deliver only a few of these. The World Health Organization has called for clinical studies of the electronic devices, and, Dr. Farsalinos said, it is clear that they should be regulated.

E-cigarettes are generally battery-powered. They incorporate a cartridge containing nicotine dissolved in propylene glycol and a microprocessor controlling a heater that vaporizes the liquid without combustion. Most have a light-emitting diode that activates when the patient draws on the e-cigarette.

Dr. Farsalinos launched the first study of the effects of e-cigarettes on cardiac function. The study enrolled 22 e-cigarette users as controls (all of whom had quit smoking more than 1 month before entering the study) and 20 current heavy smokers (with a 5-year history or more of smoking 15 or more cigarettes per day).

All of the patients were assessed via echocardiography (GE Vivid 7, EchoPac). The e-cigarette used in the study (Nobacco, USA Mix) contained liquid with nicotine at a concentration of 11 mg/mL. The regular cigarettes contained 1 mg of nicotine, 10 mg of tar, and 10 mg of carbon monoxide. Hemodynamic measurements and an echocardiogram were performed at baseline and after the smoking of one regular cigarette among controls and after 7 minutes of e-cigarette use.

In the group smoking regular cigarettes, BP rose significantly (systolic BP by 8% and diastolic BP by 6%) as did heart rate (by 10%). Users of e-cigarettes had nonsignificant increases of 4% in diastolic BP only.

Although diastolic function was not impaired in these participants, regular cigarette users showed acute impairment in several measures of cardiac function (e.g., mitral annulus velocity, myocardial performance index, and isovolumic relaxation time).

Asked about the mechanisms behind the e-cigarette benefits at an ESC press conference, Dr. Farsalino speculated that less nicotine is absorbed at the lower temperatures produced in the e-cigarette (at 200°C in contrast to 800°C for regular cigarettes).²

Also, with the e-cigarette's absence of combustion and simpler chemical composition, fewer toxic chemicals are created and absorbed than with regular cigarettes.

"Electronic cigarettes may be a safer alternative to tobacco cigarettes, and substituting them may be beneficial to health," Dr. Farsalino concluded.

He emphasized that e-cigarettes are marketed as aids for smoking reduction and cessation, not as a substitute for regular cigarettes.

"They are a product for a tobacco harm-reduction strategy," he said.

PowerOverPressure.com

Digital Help for Refractory Hypertension

- Suzanne Oparil, MD, Professor of Medicine, Physiology and Biophysics, and Director, Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, University of Alabama at Birmingham

The launch of *PowerOverPressure.com*, the first worldwide online resource on treatment-resistant hypertension for physicians, pharmacists, patients, and caregivers, was announced at ESC Congress 2012. The American Society of Hypertension and the European Society of Hypertension have both endorsed the program.

Dr. Oparil, co-chair of the *PowerOverPressure.com* steering committee, noted that treatment-resistant hypertension (defined as persistently high BP despite treatment with adequate doses of three or more antihypertensive medications, preferably a diuretic among them) affects 120 million people worldwide. Even with the advent of multiple new pharmacotherapies, the percentage of patients with refractory hypertension (approximately 15% of those treated) increased by 62% over the previous two decades.

Speaking in an interview, Dr. Oparil suggested that multiple factors, among them the growing elderly population, high rates of obesity, sedentary lifestyles, and increased levels of dietary salt are conspiring to make the problem worse. In addition, she said, few individuals she sees in her clinic are at their ideal body weight, and many patients have comorbidities, including insulin resistance or diabetes, impaired kidney function, and obstructive sleep apnea, which is associated with neural stimulation and increased aldosterone levels.

"While most resistant hypertension can be controlled through optimization of medication choices and doses, and careful attention to adherence along with lifestyle modification," she said, "a valid part of the picture is that many are genuinely intolerant of many of the drug classes."

The intention of *PowerOverPressure.com*, Dr. Oparil explained, is to increase awareness that BP management is actually a difficult challenge, one demanding intensified awareness, monitoring, and adherence to therapy. Referral to a hypertension specialist or a hypertension clinic may increase the likelihood of successful treatment.

The *PowerOverPressure.com* Web site provides information on accurate diagnosis of treatment-resistant hypertension and on the multidrug and combination treatment strategies of current approaches. Mention is made, as well, of investigational device-based therapeutic approaches targeting the sympathetic nervous system (i.e., renal denervation and baroreceptor stimulation).

The Web site also offers a downloadable reference tool; slide kits; and links to hypertension guidelines, clinical trials, and medical societies focused on advancing hypertension prevention and treatment and on conducting research that will further those goals in cardiology, nephrology, and endocrinology.

PowerOverPressure.com is funded by Medtronic, which manufactures an investigational renal denervation device (described on page 592) that is now in phase 3 clinical trials. The company is also conducting research on baroreceptor stimulation.

REFERENCES

1. Roe MT, Armstrong MD, Fox K, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*, August 26, 2012 (online).
2. Bullen C, McRobbie H, Thornley S, et al. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences, and nicotine delivery: Randomised cross-over trial. *Tob Control* 2010;19:98-103. ■