PAH Therapies Slashed Admissions and Deaths

BY BRUCE JANCIN

BARCELONA — Targeted therapies for pulmonary arterial hypertension collectively reduced all-cause mortality by 43% compared with placebo, in a meta-analysis of the randomized, placebo-controlled, clinical trials conducted during the last 18 years.

Moreover, treatment reduced by 61% the hospitalization rate for pulmonary arterial hypertension (PAH), an end point with major economic and quality of life consequences, Dr. Nazzareno Galiè noted at the annual congress of the European Society of Cardiology.

These findings, while highly significant both statistically and clinically, probably underestimate the true magnitude of treatment benefit in clinical practice because the meta-analysis included negative trials of drugs subsequently denied marketing approval due to lack of efficacy, such as beraprost and terbogrel, as well as studies of approved drugs in non-approved, suboptimal doses.

"This is a very, very conservative approach," said Dr. Galiè, professor of cardiology and head of the pulmonary hypertension center at the University of Bologna (Italy).

The meta-analysis offers a rebuttal to critics who claim current therapies for PAH provide only marginal clinical benefit. The critics have trumpeted another meta-analysis that concluded the treatments produced "limited benefits in clinical end points" and failed to support a significant survival advantage (Am. Heart J. 2007;153:1037-47). But this was a seriously flawed meta-analysis that missed six randomized trials available at the time, according to Dr. Galiè.

The 21 randomized placebo-controlled trials included in the meta-analysis involved 3,140 PAH patients followed during an average of 14.3 weeks of treatment. The trials involved endothelin-receptor antagonists, thromboxane synthase inhibitors, prostanoids, and phosphodiesterase type-5 inhibitors.

"Interestingly enough, there are four times more commentaries and editorials than there are randomized studies," the cardiologist noted.

All-cause mortality occurred in 1.5% of patients in the active treatment arms, compared with 3.8% of placebo-treated controls. That translated into a need to treat 61.2 patients for 14.3 weeks to prevent one death. The PAH hospitalization rate was 3.2% in the active treatment groups and 8.0% in controls, for a number needed to treat of 19.9.

Treatment reduced by 61% the hospitalization rate for pulmonary arterial hypertension.

DR. GALIÈ

The database was not of sufficient size to show any significant differences in efficacy for the various drug classes, according to Dr. Galiè.

Six-minute walk distance improved with active treatment by a mean of 11% over baseline, or just under 36 m, in the 19 randomized trials reporting this end point.

Small to moderate improvements in various hemodynamic parameters with active treatments were also identified via right heart catheterization. Among these were a 1.84 mm Hg weighted mean reduction in right atrial pressure.

"This is the first time a statistically significant decrease in right atrial pressure has been shown. It is not all that much, but there is no single randomized controlled study with a significant reduction in right atrial pressure," Dr. Galiè said.

Although this meta-analysis refutes the argument that current treatments for PAH bring little clinical benefit, Dr. Galiè was nonetheless quick to point out he considers these therapies inadequate. Mortality over the intermediate and long term remains high, and many patients have extensive hemodynamic and functional impairments despite treatment.

Another avenue worth pursuing is the use of combined-drug regimens for initial treatment, he said. But regulatory agencies have frowned upon proposals for randomized trials taking this approach, and pharmaceutical companies with competing agents for PAH have been reluctant to participate.

The meta-analysis was funded by the University of Bologna. Dr. Galiè disclosed having served on advisory boards for several pharmaceutical companies. ■

Variation in Mortality Risk Related To Type of Metabolic Syndrome

BY MITCHEL L. ZOLER

BARCELONA — Some metabolic syndrome types are substantially deadlier than others, according to an analysis of 3,000 people followed in the Framingham Offspring Study.

People who first developed metabolic syndrome because of abdominal obesity, hypertension, and hyperglycemia had a greater than twofold increased risk for a later cardiovascular disease event, and a threefold increased risk of death, compared with people with metabolic syndrome first diagnosed because of other risk-factor combinations, Dr. Oscar H. Franco said at the annual congress of the European Society of Cardiology.

Deaths were threefold more common in those with the obesity, hypertension, hyperglycemia triad.

DR. FRANCO

The data came from 5,124 Framingham, Mass., residents who entered the Offspring Study in 1971-1975 and were children of the first Framingham Heart Study cohort. Dr. Franco and his associates focused on 3,078 who underwent their fourth, fifth, and sixth serial examinations, in 1987-1991, 1991-1995, and 1995-1998. Data from these visits established whether each participant had metabolic syndrome. Follow-up tracked the incidence of new cardiovascular disease events and deaths during the 10 years following 1998, said Dr. Franco, a public health researcher at the University of Warwick in Coventry, England.

Metabolic syndrome was defined in 2004 as the concurrence of at least three of these five cardiovascular disease risk factors: abdominal obesity, defined by waist circumference; low serum HDL cholesterol level; elevated triglyceride level; systolic or diastolic hypertension or on an antihypertensive drug; and elevated fasting blood glucose level (Circulation 2004;109:433-8).

The prevalence of metabolic syndrome among the people studied jumped during the decade of the three exams, from a 23% rate during the first exam to a 41% rate at the third exam. The biggest jumps in risk factors came for abdominal obesity, which rose from a 25% prevalence to 51% from the first exam to the third, and hyperglycemia, which spiked from 18% in exam one to 43% in exam three. By the third exam, the most common risk factor was hypertension, in 77%.

The most common triad of risk factors for metabolic syndrome was obesity, hypertension, and hyperglycemia, in 29% of the people included. The least common triad was low HDL, hyperglycemia, and high triglycerides, in 15%.

During 10 years of follow-up after the last examination, events were 2.3-fold more common in people who had the obesity, hypertension, and hyperglycemia triad, compared with all other people with a metabolic syndrome triad. People with low HDL, hypertension, and high triglycerides had a 90% higher risk for a cardiovascular event, compared with those with other triads. All the other triads had event rates that were close to the reference rate of one, and some triads had relative risks of less than one.

Deaths were slightly more than threefold more common among those with the obesity, hypertension, hyperglycemia triad, and 70% more common in those with low HDL, hypertension, and high triglycerides, Dr. Franco said. ■

Interval Workouts Excel In Curbing Hypertension

BY BRUCE JANCIN

BARCELONA — Aerobic interval exercise training is a more effective treatment for hypertension than is moderate-intensity continuous exercise, according to a Norwegian study.

In the study, 89 patients with grade 1 or 2 hypertension who were not on medication were randomized to one of three exercise training regimens carried out three times per week for 12 weeks. The three study arms consisted of supervised aerobic interval exercise with a target intensity of 90%-95% of maximum heart rate, supervised isocaloric continuous exercise at 70% of maximum, or, as a control, standard medical advice about the importance of physical activity but no supervised training.

After 12 weeks, mean 24-hour blood pressures in the aerobic interval training group had improved from a baseline of 154/94 mm Hg to 141/87 mm Hg. Moreover, their maximal oxygen uptake (VO_{2max}) increased by about 15%, from 36.3 to 41.7 mL/kg per minute. Those were significantly greater improvements than noted in the moderate-intensity exercise group, which in turn did better than the unsupervised controls, Dr. Harrald E. Moelmen-Hansen reported at the annual congress of the European Society of Cardiology.

Mean 24-hour blood pressures in the moderate-intensity continuous exercise group, for example, went from 151/92 to 147/88 mm Hg, while VO_{2max} improved from 34.0 to 35.8 mL/kg per minute.

Mean heart rate decreased significantly in the aerobic interval group, from 73 to 69 bpm, but remained unchanged over time in the others. Similarly, nighttime blood pressures improved significantly, from 140/84 to 129/79 mm Hg, with interval training but were unchanged in the other two patient groups, according to Dr. Moelmen-Hansen of the Norwegian University of Science and Technology, Trondheim.

Endothelial function measured as flow-mediated dilation of the brachial artery increased from 6.12% to 10.07% in the high-intensity exercise group but was unaffected in the others.

HDL cholesterol increased from 54.5 to 57.2 mg/dL with aerobic interval training, and from 57.6 to 58.6 mg/dL in the continuous exercise group. It was unchanged in the unsupervised controls, Dr. Moelmen-Hansen said. ■