Elevated Fibrinogen Predicts PVD Before Age 60

BY MARK S. LESNEY
Senior Editor

Coronary artery disease and elevated serum fibrinogen were stronger predictors of peripheral vascular disease in subjects younger than 60 years than in older subjects, according to a study that used the results of the National Health and Nutrition Examination Survey 1999-2002 to evaluate a variety of possible risk factors.

Chronic renal insufficiency was more highly predictive of peripheral vascular disease (PVD) in subjects aged 60 years and over, according to Dr. Louis M. Messina and colleagues at the University of California, San Francisco. Their analysis was presented at the annual meeting of the Western Vascular Society, Deer Valley, Utah. The investigators used the NHANES data to determine the prevalence of premature PVD in the U.S. population, and they used presumptive risk factors as covariates to model the occurrence of the condition.

PVD in patients under age 60 years is considered premature, according to the researchers. Premature PVD is associated with an extremely poor prognosis, including high rates of cardiovascular morbidity, limb loss, and premature death. Previous studies have been small, have dealt only with a limited number of risk factors, and focused on coronary vascular disease as the outcome of interest, according to the researchers.

Based on the hypothesis that there was an interaction between risk factors and age, the investigators analyzed the data to compare the population aged less than 60 years (mean age 49) with those 60 years and older (mean age 70).

NHANES began to provide data in 1999 from detailed lower extremity examinations, including measurement of the ankle-brachial index (ABI). An ABI of less than 0.9 was considered indicative of lower peripheral vascular disease, according to the researchers, and was correlated with the other variables collected in the sampled population. Previous research has shown that a low ABI is one of the strongest predictors of cardiovascular morbidity and all-cause mortality.

Although this result was not sufficient to support wide-scale screening, it did suggest that testing may have clinical relevance for secondary intervention.

The investigators compared data from 2,498 patients under age 60 with those from 2,585 patients aged 60 years and older. Peripheral vascular disease rates were approximately 2% in the younger group and 12% in the older group.

A history of coronary artery disease appeared to be highly predictive of PVD in the population under age 60. The odds ratio was 2.9 for this younger group, compared with approximately 1.3 for the older population.

In an analysis of the other possible risk factors, the researchers found that a 10-mg/dL increase in fibrinogen was associated with a 7% increase in odds in subjects under age 60, compared with a 3% increase in patients 60 years and older.

Although the authors did not believe this result was sufficient to indicate wide-scale screening of high fibrinogen levels to detect PVD, they did suggest that it may have clinical relevance for secondary intervention, since fibrates and niacin can lower fibrinogen levels.

In contrast, a decreased creatinine clearance was significantly associated with PVD in individuals aged 60 and older, with a 10-unit decrease in clearance affording a 16% increase in the PVD odds ratio. There was no significant correlation in the younger age group, the researchers reported.

Strong risk factors that are independently associated with PVD regardless of age category include smoking and hypertension. Metaanalysis of plasma homocysteine levels showed only a weak association with the development of PVD.

Although there was no difference found in risk associated with gender between the age groups, being male was a significant overall predictor (odds ratio slightly greater than 2.0).

"That premature peripheral vascular disease is associated with elevated fibrinogen suggests what many had suspected but not proven, that premature PVD is associated with a 'hypercoagulable state.' It was important to confirm this in a large population-based study. The other important risk factor was the presence of coronary artery disease. That coronary artery disease correlated more closely with premature peripheral vascular disease in those less than 60 years of age is equally surprising," Dr. Messina added. ■

Information on NHANES and its data sets is available at www.cdc.gov/nchs/nhanes.htm.

Pharmacy Service Helps PAD Patients Achieve Lipid Control

BY MARK S. LESNEY
Senior Editor

Patients with peripheral arterial disease often are undertreated with regard to atherosclerotic risk factor modification.

Such patients can benefit from the use of a clinical pharmacy service in conjunction with physician recommendations for lipid control, according to Dr. Thomas F. Rehring and colleagues from the Kaiser Permanente Colorado Region and the University of Colorado Health Sciences Center in Denver.

In a cohort of 691 outpatients with peripheral arterial disease (PAD) validated by noninvasive arterial study, 90 patients were enrolled into a pharmacist-managed, physician-monitored algorithmic approach for the management of lipids, and 601 were given standard care, according to Dr. Rehring, of the vascular surgery department at Kaiser Permanente, and his colleagues. They presented the results of their research at the annual meeting of the Western Vascular Society in Deer Valley, Utah.

Low-density lipoprotein cholesterol (LDL-C) control goals were achieved by a greater percentage of the pharmacist-managed group (79%) than the standard treatment group (54%). And a significant difference in the patients with LDL-C values over 130 mg/dL was noted between the treatment (1.2%) and control (14%) groups. In the control group, nearly 52% of patients used statins, compared with 84% of the pharmacist-managed group, a statistically significant difference.

All patients in the study were members of a not-for-profit managed care system serving approximately 405,000 patients. Outpatient records of medical, pharmacy, laboratory, and radiology information were stored electronically, allowing for "current and comprehensive analysis," the researchers reported.

Mean follow-up was slightly more than 17 months. Fasting lipid profiles were screened in 95% (86/90) of the patients in the algorithmic group and nearly 67% (402/601) of the standard care group.

All patients accepting enrollment in the algorithmic approach interacted regularly with a pharmacist-manager who collected data, monitored medication and laboratory compliance while making treatment plan adjustments, and kept the responsible primary care physician notified. ■

Novel Postmarketing Surveillance System Confirms Bosentan's Safety

BY BRUCE JANCIN
Denver Bureau

STOCKHOLM — An Internet-based postmarketing surveillance program has provided reassurance regarding the long-term safety of bosentan (Tracleer) in routine clinical practice for treating various subgroups of pulmonary arterial hypertension.

The experience with this novel Internet-based data collection system has been so favorable that the system deserves broader consideration as a possible new model for widespread postmarketing surveillance—and not just for orphan drugs such as bosentan, the nonselective dual endothelin receptor antagonist that is the only approved oral treatment for pulmonary arterial hypertension (PAH), Dr. Jørn Carlsen said at the annual congress of the European Society of Cardiology.

The program, known as the Tracleer Excellence Post Marketing Surveillance (TRAX PMS), was set up by Actelion Pharmaceuticals in cooperation with the European Agency for the Evaluation of Medicinal Products.

Liver abnormalities were a particular focus of attention in the surveillance program. That's because in the clinical trials that led to bosentan's marketing approval, 12.7% of treated patients developed elevated liver enzyme levels.

Although regulators approved bosentan on the grounds that its demonstrated clinical benefits trumped the safety concerns as they were understood at the time, they also sought additional data about the drug's long-term liver effects.

The Internet-based system has been so effective it should be considered for widespread use.

DR. CARLSEN

In less than 2.5 years, the TRAX PMS program enrolled nearly 5,000 patients treated with bosentan in 18 European countries. Mean exposure time was 39 weeks, for a total of more than 3,400 patient-years of follow-up on bosentan. To put the resultant accrued wealth of safety data in context, Dr. Carlson, of the Rigshospitalet, Copenhagen, noted the pivotal trial that led to bosentan's marketing approval featured just 59 patient-years of follow-up. The interactive surveillance program provided prescribing physicians with treatment and safety-monitoring algorithms. The program also collected what Dr. Carlsen termed "safety signals"—data on adverse events, hospitalizations, deaths, and reasons for drug discontinuation.

In the total group of nearly 5,000 treated patients, 7.7% developed liver enzyme levels in excess of three times the upper limit of normal. In the overall PAH population, the risk was greatest during the first 3 months of therapy and declined with time. Half of the affected patients required permanent discontinuation of treatment. Roughly 30 continued to have elevated enzymes after discontinuation; however, there were no cases of fatal or permanent clinical hepatic injury.

Dr. Carlsen presented additional data on liver enzyme elevation rates in three subgroups of patients in TRAX PMS: 5.5% in the 470 patients with chronic thromboembolic pulmonary hypertension (CTEPH); 2.8% in 579 patients with PAH associated with congenital heart disease; and 8.4% in 1,583 with idiopathic PAH.

The mean time on bosentan before liver enzyme abnormalities occurred was 127 days in the CTEPH group. That was longer than in patients with idiopathic or congenital heart disease–associated PAH. ■