Inflammation Drives Up Risk of PAD in Women

BY BRUCE JANCIN
Denver Bureau

New Orleans — Women with metabolic syndrome have an increased risk of developing symptomatic peripheral artery disease, mediated mainly by the syndrome's associated inflammation and endothelial activation, according to a prospective study of more than 27,000 women.

"The bottom line is if you account for the inflammation associated with the metabolic syndrome, there is no residual risk associated with the syndrome itself," Dr. Aruna D. Pradhan said at the annual scientific sessions of the American Heart Association.

She reported on 27,111 middle-aged female health professionals free of known cardiovascular disease when they enrolled in the Women's Health Study. At entry, one-quarter met criteria for the metabolic syndrome. At that time 28% of those with metabolic syndrome had diabetes, as did 1.8% of the others.

During a median 13.3 years of prospective follow-up, 114 women developed symptomatic peripheral artery disease (PAD). In an unadjusted first-pass analysis, women with metabolic syndrome at baseline were 62% more likely to develop the disease. And for each additional metabolic syndrome– defining risk factor beyond the requisite minimum three out of five, the risk of the disease was increased by 26%.

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However, women with metabolic syndrome also were slightly older, less likely to exercise, more likely to smoke, and had a higher body mass index in addition to their greater prevalence of diabetes. Upon adjustment for these factors in a Cox multivariate proportional hazards analysis, the presence of the metabolic syndrome remained a significant risk factor for PAD. Women with metabolic syndrome had an adjusted 48% greater likelihood of PAD, and this risk rose by another 21% for each additional metabolic syndrome–defining trait present, said Dr. Pradhan of Brigham and Women's Hospital, Boston.

But the nearly 7,000 women with metabolic syndrome also differed from the others in another important way: They had markedly higher levels of biomarkers of systemic inflammation.

The median plasma level of high-sensitivity C-reactive protein (hsCRP) in participants with metabolic syndrome at baseline was 3.98 mg/L, compared with 1.53 mg/L in those without metabolic syndrome. Levels of soluble intercellular adhesion molecule-1 (ICAM-1) averaged 374 ng/mL in the metabolic syndrome group and 333 ng/mL in the comparison arm. As the number of metabolic syndrome elements present increased from zero to five, median CRP increased from 1.0 to 5.9 mg/L and median ICAM-1 rose from 321 to 413 ng/mL.

When hsCRP and ICAM-1 levels were folded into the multivariate adjustment model, metabolic syndrome was no longer associated with a significantly increased risk of PAD, suggesting that systemic inflammation is the driving force in the development of PAD, not the high triglycerides, low HDL, or other components of the metabolic syndrome.

Session cochair Dr. William R. Hiatt, professor of medicine at the University of Colorado, Denver, said it's speculative as to whether these findings apply to men, or to the development of asymptomatic PAD, which is far more prevalent than symptomatic disease. Men have a higher incidence of symptomatic PAD than do women, at least in clinical trials, he noted. ■

CVD Linked to Diabetes, Impaired Glucose Tolerance in Older Adults

BY MITCHEL L. ZOLER
Philadelphia Bureau

New Orleans — Nearly a quarter of people aged 50 years or older with cardiovascular disease or aged 55 or older with at least one cardiovascular-disease risk factor had diabetes in a study that screened over 35,000 people.

Another 28% of the people in this screened group were found to have impaired glucose tolerance, Dr. M. Angelyn Bethel, an endocrinologist at Duke University, Durham, N.C., and her associates reported in a poster at the annual scientific sessions of the American Heart Association.

In addition, a risk assessment based on history, physical-examination findings, and common blood measures such as lipids and fasting glucose was able to identify three-quarters of the people diagnosed with diabetes using an oral glucose tolerance test. In contrast, identifying people as having metabolic syndrome based on the current U.S. definition was a relatively poor method for predicting who would be diagnosed with diabetes, the researchers reported.

They used data collected in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, a study that began in 2002 and is planned to end next August. The study, sponsored by Novartis, which markets nateglinide (Starlix) and valsartan (Diovan), enrolled about 9,300 people with impaired glucose tolerance. They were aged 50 or older and diagnosed with cardiovascular disease or were aged 55 or older and had at least one cardiovascular disease risk factor such as hypertension, hypercholesterolemia, or current smoking.

The study's primary end point is prevention of diabetes and cardiovascular events.

To find participants for the study, Dr. Bethel and her associates screened more than 42,000 people who met the age and cardiovascular-disease history requirements in 39 countries. Their average age was 62 years, about half were women, and their average body mass index was about 29 kg/m^2. Their average blood pressure was 140/82 mm Hg.

They screened these people with an oral glucose tolerance test, with valid results available for 35,744 people.

Of those screened, 22% had outright diabetes; 28% had impaired glucose tolerance, defined as a fasting glucose level of less than 126 mg/dL and a blood glucose level 2 hours following oral challenge of 140-199 mg/dL; 30% had impaired fasting glucose, meaning their fasting glucose level was 100-126 mg/dL but their glucose level 2 hours after oral challenge was less than 140 mg/dL; and the remaining 20% had normal glucose tolerance, with a fasting level of less than 100 mg/dL and a 2-hour level following challenge of less than 140 mg/dL.

These statistics showed the high prevalence of both diabetes and impaired glucose tolerance in the type of people eligible for screening in the study, said the reseachers.

Their next goal was to find factors that could identify people with the type of history used by the study who had an especially high risk for diabetes. It would be impractical to use an oral glucose tolerance test on everyone with this history because of cost and inconvenience, they said.

The presence of metabolic syndrome, defined using the criteria of the Adult Treatment Panel III guidelines of the U.S. National Cholesterol Education Program, was only slightly better than flipping a coin, identifying 58% of those with diabetes. In contrast, an assessment taking into account several risk factors including sex, age, blood pressure, triglyceride level, LDL cholesterol level, fasting glucose level, and a history of cardiovascular disease events accurately identified 75% of those who had diabetes when they were assessed with an oral glucose challenge.

Middle-aged or older people with such a risk profile are good candidates for an oral glucose tolerance test that would provide an early diagnosis of diabetes, they said. ■

Rosiglitazone Risks Outpace Pioglitazone's in the Elderly

BY MARY ANN MOON
Contributing Writer

Elderly patients who started taking rosiglitazone had higher rates of all-cause mortality and hospitalization for heart failure during the following year than did those who started taking pioglitazone, in a study of nearly 30,000 subjects.

Previous research has suggested that rosiglitazone carries greater cardiovascular risks than pioglitazone, but "to date, only sparse information has become available from head-to-head comparisons between these two drugs," said Dr. Wolfgang C. Winkelmayer and his associates at Brigham and Women's Hospital, Boston.

They conducted such a comparison in a large cohort of elderly patients with recent-onset type 2 diabetes. "To our knowledge, this is the first study specifically aimed at detecting any differences in relative cardiovascular safety between these two thiazolidinediones in typical elderly patients initiating such therapy."

The study participants were identified using medical claims data that included comprehensive prescription drug coverage for elderly patients throughout New Jersey and Pennsylvania. The 28,361 patients were older than 65 years when they filled their first prescriptions for pioglitazone (50.3%) or rosiglitazone (49.7%) between 2000 and 2005.

The median time of exposure to the drugs was about 1 year. During that time 1,869 people died.

Rosiglitazone users had significantly higher rates of all-cause mortality. Crude, unadjusted event rates per 1,000 person-years were 60 for pioglitazone and 69 for rosiglitazone initiators, which yielded an unadjusted incident rate ratio of 1.17. After adjustment for patient characteristics, a Cox regression showed a 15% greater mortality rate in patients initiated with rosiglitazone compared those who took pioglitazone.

Use of rosiglitazone also was associated with a 13% greater risk of heart failure, Dr. Winkelmayer and his colleagues reported (Arch. Intern. Med. 2008;168:2368-75).

This association remained robust when the data were analyzed in different statistical models, and it was consistent across important subgroups of patients, such as those who had already begun insulin therapy.

The study was limited in that patients were not randomly assigned to the two drugs, but were given them at the discretion of their treating physicians.

In addition, the study didn't include information on cause of death, so although the findings suggested a higher cardiovascular case fatality rate for rosiglitazone, "we cannot formally examine this possibility," the authors wrote.

Nevertheless, the results "confirm the safety concerns that have been raised for rosiglitazone, compared with pioglitazone," they added.

Dr. Winkelmayer has participated, without receiving an honorarium, in the advisory boards of Amgen, Roche, Genzyme, and Fresenius Medical Care. This study was supported by the American Heart Association, Satellite Healthcare Inc., and investigator-initiated grants from Amgen, Fresenius, and GlaxoSmithKline. ■