

Autopsy Study Elucidates Coronary Disease in RA

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — Coronary artery disease in patients with rheumatoid arthritis is characterized by less extensive atherosclerosis but more inflammation and unstable atherosclerotic plaques than is coronary artery disease in arthritis-free matched controls, according to a first-of-its-kind autopsy study.

"We see less garden-variety CAD, with less multiple-vessel disease and a lower overall grade of stenosis," Dr. Sherine E. Gabriel said at a symposium sponsored by the American College of Rheumatology.

Rheumatoid arthritis (RA) patients are known to have an increased risk of ischemic heart disease, compared with the general population. This elevated risk is present early in the course of RA. By the time patients meet ACR criteria for a diagnosis of RA, they already have a several-fold



greater prevalence of prior hospitalization for acute myocardial infarction and electrocardiogram evidence of silent MI than do matched controls, noted Dr. Gabriel, the William J. and Charles H. Mayo Professor of Medicine and Epidemiology at the Mayo Clinic, Rochester, Minn.

The study by Dr. Gabriel and colleagues in the Rochester Epidemiology Project included 41 RA patients who died at a mean age of 79 years, 25 with known cardiovascular disease, who were matched by age, gender, and cardiovascular disease history to 82 non-RA controls.

Among subjects with cardiovascular disease, only 32% of RA patients were found at autopsy to have multivessel disease, vs. 61% of controls. Stenoses of 51% or greater were present in the left main arteries of only 7% of RA patients, vs. 54% of non-RA controls; there were similar trends in the left anterior descending and right coronary arteries. Coronary atherosclerosis was less extensive in the RA group, with only

32% having a score greater than 2 on a 4-point scale, vs. 61% of controls. However, unstable plaques were found in the left anterior descending arteries of 48% of RA patients with cardiovascular disease, but in only 22% of controls. In addition, medial inflammation of the left circumflex artery was detected in 30% of RA subjects, compared with 9% of controls. Inflammation was also significantly more common in the adventitia of the left anterior descending artery of the RA patients than it was in controls (J. Rheumatol. 2007;34:937-42).

Similar trends (more evidence of inflammation but less extensive and severe atherosclerosis in the RA group) were noted in the subgroup of 18 RA subjects and 34 controls with a history of heart failure, Dr. Gabriel added.

In the RA patients, atherosclerosis was less extensive but there was more inflammation.

DR. GABRIEL

She also presented highlights of a Rochester Epidemiology Project study showing the increased risk of ischemic heart disease in patients with RA precedes a diagnosis of the rheumatologic disease. The retrospective study involved 603 patients diagnosed with RA by the relatively strict ACR criteria at a mean age of 58 years, and 603 matched non-RA controls. A comprehensive analysis of all in- and outpatient medical records from age 18 years on showed that the RA group already had a threefold greater history of acute MI by the time their rheumatologic disease was diagnosed. Coronary disease in the RA group tended to present atypically, with less angina pectoris.

During a mean of 15 years follow-up post RA diagnosis, the rate of sudden cardiac death was 35 cases per 10,000 person-years in the RA group and 18 per 10,000 in controls. The rate of silent MI was also greater in the RA group, but cumulative incidence of angina remained less than in controls (Arthritis Rheum. 2005; 52:402-11).

Seven other population-based studies published in the last 5 years have shown a roughly twofold increased risk of ischemic heart disease in RA, Dr. Gabriel noted. ■

Can Tight Control Prevent Heart Disease in RA Patients?

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — The time is right to consider organizing large randomized clinical trials looking at whether tight pharmacologic control of systemic inflammation will lower the high cardiovascular morbidity and mortality associated with rheumatoid arthritis, Dr. Sherine E. Gabriel declared at a symposium sponsored by the American College of Rheumatology.

"The only way we're going to be able to figure out how to approach cardiovascular risk reduction in RA patients is the way the diabetologists did when they conducted very large trials of tight metabolic control and looked at its effect on long-term cardiovascular outcomes. We're getting pretty close to the limit of what our observational data can tell us," said Dr. Gabriel, the William J. and Charles H. Mayo Professor of Medicine and Epidemiology at the Mayo Clinic, Rochester, Minn.

The large observational studies that have tried to examine the impact of RA drugs on cardiovascular end points are fraught with potential confounders. This may explain the conflicting results. For example, last November's annual meeting of the ACR saw presentation of two large observational studies on the impact of tumor necrosis factor inhibitors on cardiovascular outcomes—with very different conclusions.

In a nested case-control study involving roughly 20,000 RA patients in the MediCal database, investigators at Stanford (Calif.) University concluded that those treated with a TNF inhibitor plus methotrexate had an adjusted 80% reduction in acute MI risk compared with those on methotrexate alone.

But in a cohort study involving nearly 6,000 Medicare patients with RA in two states, physicians at Brigham and Women's Hospital, Boston, determined that those with no baseline history of heart failure had an adjusted 3.1-fold greater risk of a first hospitalization for heart failure after being placed on a TNF inhibitor compared with those who got

methotrexate. And among the 1,033 patients with a baseline history of heart failure, the adjusted risk of an exacerbation requiring hospitalization was 50% greater in those on a TNF inhibitor than with methotrexate.

"It's very tough to tease out what's going on with these drugs," Dr. Gabriel commented. "I'm still not clear on their role."

She and her coinvestigators in the Rochester Epidemiology Project have shown that the mortality gap between RA patients and the general population has been growing for decades, largely because of excess cardiovascular deaths in the RA population. Yet people with RA don't have a greater prevalence or severity of the traditional cardiovascular risk factors—and that has important implications for efforts to reduce the mortality gap in RA.

"Effective, even optimal control of the traditional cardiovascular risk factors in people with RA is important, but it's not going to be enough by itself," said Dr. Gabriel.

That point was brought home in a recent report by Dr. Gabriel and her Mayo colleagues. They analyzed the relative impact of traditional cardiovascular risk factors in 603 patients followed for a mean of 15 years after diagnosis of RA and in 603 non-RA controls. While many of the risk factors imparted similar risk in the two groups, three of them—smoking, male gender, and personal cardiac history—imparted significantly less risk in the RA patients (Ann. Rheum. Dis. 2008;67:64-9).

The weaker impact of these traditional cardiovascular risk factors in the RA group suggests the existence of additional competing cardiovascular disease-promoting mechanisms present only in the RA group.

There is strong evidence to suggest that the systemic inflammation of RA may be the key factor, which is why it's time for randomized trials of the impact on cardiovascular events of TNF inhibitors, methotrexate, and other systemic inflammation-reducing drugs, Dr. Gabriel said. ■

Subintimal Angioplasty Bests Bypass for Severe Limb Ischemia

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

WASHINGTON — For patients with severe critical limb ischemia and medical comorbidities, subintimal angioplasty is a safer and less expensive alternative to bypass surgery, and is just as effective at preventing amputation, according to the results of a randomized, single-surgeon study.

"These findings have caused a paradigm shift in the way we manage critical limb ischemia in these patients," Dr. Niamh Hynes said at a symposium sponsored by the Cardiovascular Research Institute at Washington Hospital Center.

The 5-year, randomized controlled trial compared subintimal angioplasty with bypass surgery in 309 patients with severe critical limb ischemia. The average age was 72 years, and all patients had severe lesions (level C and D according to the Transatlantic InterSociety Consensus [TASC] Classification system). Diabetes was present in 22%; all patients had a high medical comorbidity score.

Subintimal angioplasty was performed in 190 patients; 119 underwent bypass surgery, according to Dr. Hynes of University College Hospital, Galway, Ireland. The procedures were performed by a single surgeon, Dr. Sherif Sultan, at the hospital from 2002 to 2007.

At 5 years, primary patency rates were greater, but not significantly so, in the angioplasty group (73% vs. 65%). Neither the use of a stent nor the number of stents employed significantly affected patency rates. No blood marker (homocysteine, glucose level, C-reactive protein, or fibrinogen levels) was associated with patency rates.

Angioplasty also was associated with better primary assisted patency and secondary patency rates at 5 years, although these differences were not statistically significant.

Both interventions were effective at maintaining amputation-free survival (angioplasty 73%, bypass 71%) and all-cause survival (77% and 80%) at 5 years. At 5 years,

68% of angioplasty patients were free from major adverse events, compared with 57% of bypass patients, a significant difference.

When short-term results were considered, angioplasty appeared at least as successful as bypass surgery. All-cause 30-day mortality was half that seen with bypass, although the difference was not significant (1.6% vs. 3%). Length of hospital stay was significantly shorter (14 vs. 24 days).

Angioplasty was significantly less expensive than bypass surgery (€11,650 vs. €18,700). When cost was broken down by quality-adjusted life-year, angioplasty also was significantly less expensive (cost per QALY €5,660 vs. €9,170). ■