Stage of Kidney Disease Affects Heart Failure Risk

BY DOUG BRUNK

SAN DIEGO — The more advanced the stage of chronic kidney disease, the greater the risk of developing heart failure and subsequent risk of death, results from a large analysis of Medicare patients showed.

"Even a modest degree of chronic kidney disease is a very strong predictor of having cardiovascular morbidity and mortality," Dr. Charles A. Herzog said in an interview at the annual meeting of the American Society of Nephrology.

"Chronic kidney disease is something that primary care physicians can easily detect, because it's very easy to do a serum creatinine in an office setting," said Dr. Herzog, director of the Minneapolis–based cardiovascular special studies center of the U.S. Renal Data System Coordinating Center.

He identified just over 1 million patients aged at least 66 years from the general Medicare database and followed them during 2006-2007. Patients with heart failure and end-stage renal disease at baseline were excluded from the analysis.

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DR. HERZOG

The researchers used a Cox proportional hazard model to assess the patients' risk of developing incident heart failure, adjusting for demographics, comorbidities, and stage of chronic kidney disease. They used the Kaplan-Meier method to estimate the age-adjusted survival of patients after the development of incident heart failure.

At baseline, 59% of the patients were women and 88% were white. Most (95.8%) had no chronic kidney disease, 0.4% had stage I-II disease, 1.4% had stage III-IV disease, and the remainder (2.4%) had an unknown stage of disease.

After 1 year, heart failure occurred in 5.3% of patients with no chronic kidney disease at baseline, 12.7% of those with stage I-II disease, 15% of those with stage III-IV disease, and 12.3% of those whose disease stage was unknown.

Independent predictors of heart failure were age 70-74 years (hazard ratio 1.30); age 75-79 years (HR 1.75); age 80-84 years (HR 2.42); and age 85 years and older (HR 3.82). Other independent predictors included black race (HR 1.21); stage I-II chronic kidney disease (HR 1.45); stage III-IV disease (HR 1.68), and unknown stage of chronic kidney disease (HR 1.27).

Dr. Herzog also found that the the following comorbid conditions predicted heart failure: anemia (HR 1.22), diabetes (HR 1.57), ischemic heart disease (HR 1.67), and dysrhythmia (HR 1.94).

Over the 1-year period, 83% of patients with no chronic kidney disease survived, compared with 77% of those with stage I-II disease, 75% of those with stage II-IV disease, and 67% of those whose disease stage was unknown.

Dr. Herzog acknowledged that a limitation of the study was its reliance on Medicare claims data.

Dr. Herzog is a consultant for Amgen Inc., a scientific adviser for CorMedix Inc., and a trustee of the Roche Foundation for Anemia Research. ■

NYHA Class Improvement Seen

Iron Repletion *from page 1*

aside from an expected, modest increase in gastrointestinal disorders. Dr. Anker also expressed eagerness to test this strategy in patients with diastolic dysfunction: heart failure with preserved left ventricular function.

About 20%-30% of heart failure patients likely have iron deficiency, said Dr. Anker, professor in the Center for Cardiovascular Research at Charité University in Berlin. Dr. Cleland said this estimate probably underestimates the actual prevalence. Iron deficiency is probably prevalent in many heart failure patients because of a combination of poor diet and poor gastrointestinal absorption, and because of increased bleeding linked with aspirin use, Dr. Cleland said.

Poor diet, poor GI absorption, and aspirin-related bleeding contribute to iron deficiency in heart failure patients.

DR. ANKER

The Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial enrolled patients during June 2007–December 2008 at 75 sites in 11 countries. Dr. Anker and his associates screened more than 950 patients to find the 459 who fulfilled the study's criteria for heart failure and serum ferritin level. Eligible patients had either New York Heart Association class III heart failure and a left ventricular ejection fraction of 45% or less, or class II heart failure and an ejection fraction of 40% or less. Their hemoglobin at enrollment could be 95-135 g/L, and so the study included nearly equal numbers of patients with anemia (hemoglobin of 120 g/L or less) and those without (more than 120 g/L). Their average age was 68, and 82% had class III heart failure.

The researchers randomized patients on a two-to-one basis to receive an intravenous, bolus injection of ferric carboxymaltose equivalent to 200 mg iron weekly or placebo. Once iron repletion occurred, after 8 or 12 weeks, the iron dosage scaled back to one injection every 4 weeks.

The study was sponsored by Vifor Pharma, a Swiss company that markets a formulation of ferric carboxymaltose (Ferinject) in Europe but which does not have U.S. approval.

After 24 weeks, the self-reported Patient Global Assessment was at least moderately improved in 50% of the 304 patients receiving iron and in 28% of the 155 patients on placebo, a statistically significant difference for this primary end point. New York Heart Association heart failure class improved in 47% of the patients on iron and in 30% of the control patients, also a significant difference in the second primary end point. The results appeared in an article published online (N. Engl. J. Med. 2009 Nov. 17 [doi:10.1056/NEJMoa0908355]) concurrently with Dr. Anker's presentation.

Improvement in a nonspecific, global score "is very hard to achieve. I wanted to set a high bar" for efficacy, Dr. Anker said. The improvement in both primary end points was similar and statistically significant compared with placebo in both the patients who entered the study with anemia and those who did not.

Dr. Anker said the fast action may relate to his hypothesis to explain how iron supplementation exerts a benefit that is apparently independent of a hemoglobin effect.

"Iron is needed for the proper function of mitochondria to generate energy in both the heart and in peripheral muscles. Many of the [heart failure] outcome measures are measures of the physical ability to perform. I think intravenous iron is a powerful intervention; it's a legal way to do doping," Dr. Anker said.

During the study, mortality rates were 3% in the iron group and 6% in the control patients, a nonsignificant difference. Hospitalization for any cardiovascular reason occurred in 10% of the iron patients and 20% of the controls, a difference that came close to, but did not reach, statistical significance. Cardiac disorders of any type were significantly more common in the control patients, 50%, than in those on iron, 28%. The most notable adverse event more common in the iron patients was gastrointestinal disorder, in 17% of the iron patients and 7% of the controls, a difference that just missed statistical significance.

The apparent safety of ferric carboxymaltose in this study contrasts with the drug's performance in studies done in women with iron-deficiency anemia secondary to heavy uterine bleeding or post partum in data presented to the Food and Drug Administration in early 2008. These studies used a different formulation of intravenous ferric carboxymaltose, Injectafer, made by Luitpold Pharmaceuticals. An FDA advisory panel voted against immediate approval primarily out of concern about a mortality imbalance in the cumulative clinical data that raised a question about the iron drug's safety.

Dr. Anker noted that his new findings show no suggestion of a safety concern, but he conceded that the current experience is limited and the drug needs testing in more patients. Vifor Pharma is currently discussing what further steps it will take in studying its ferric carboxymaltose formulation in patients with heart failure, said Dr. David R. Ebsworth, Vifor's chief executive officer. ■

VITALS

Major Findings: At 24 weeks, Patient Global Assessment scores improved in 50% of heart failure patients receiving intravenous iron and in 28% of placebo patients, a statistically significant difference.

Source of Data: FAIR-HF, placebo-controlled phase III study of 459 patients, from 75 sites in 11 countries, randomized to iron or placebo.

Disclosures: Dr. Anker has received fees from Vifor, for consulting, lecturing, and serving on the study's executive committee; Roche; and Amgen. Dr. Jessup disclosed that she is a speaker for, or consultant to, Boston Scientific, Medtronic, Ventracor, and ACORN. Dr. Cleland received research support from several drug and cardiac device companies.

MY TAKE

Iron Therapy's Rapid Response

DR. PACKER

This is a remarkable result. I am especially impressed that the separation in the primary end points between the patients receiving iron and those on placebo began to be statistically significant after the first 4 weeks on treatment and then continued to separate further.

The effect occurs so quickly. This is probably the fastest separation we've seen in a clinical trial in heart failure.

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