Early Dialysis Linked to Greater 1-Year Mortality

BY MARY ANN MOON

FROM THE ARCHIVES OF INTERNAL MEDICINE

Although the use of early hemodialysis in relatively young and healthy end-stage renal disease patients has more than doubled since 1996, that practice may have increased their 1-year mortality risk, new research suggests.

The findings, together with those of several other studies of the issue, indicate that early hemodialysis – begun when the estimated glomerular filtration rate (eGFR) is still 10 mL/minute per 1.73 m^2 or greater – is harmful, regardless of any potential benefit, said Dr. Steven J. Rosansky of William Jennings Bryan Dorn Veterans Hospital, Columbia, S.C., and his associates (Arch. Intern. Med. 2010 [doi: 10.1001/archinternmed.2010.415]).

According to U.S. Renal Data System (USRDS) records, the proportion of patients initiating hemodialysis early rose from 20% to 52% between 1996 and 2008, even though there is no evidence of substantial benefit with the practice. In fact, nine recent studies have reported a survival disadvantage with early hemodialysis.

Critics of those studies say that earlier hemodialysis makes intuitive sense, and that the high rates of comorbidities and older age in most study subjects confounded the results. To "reduce or eliminate much of the selection biases and lessen the need for multiple adjustments for comorbid conditions that confounded earlier studies," Dr. Rosansky and his colleagues undertook a large observational study restricted to the Medicare records of 81,176 relatively young ESRD patients (aged 20-64 years) who had no comorbidities other than hypertension.

In that healthy cohort, mortality in the first year after the start of hemodialysis was 9.4%, compared with an average 24% 1-year mortality in the entire USRDS population.

The investigators said that 1-year mortality was 20.1% in patients who started hemodialysis early, compared with 6.8% in those who started later.

Patients with the lowest albumin levels (less than 2.5 g/dL) were five times as likely to die in the first year of hemodialysis as were patients with the highest albumin levels (at least 3.5 g/dL), at 21% vs. 4.7%, respectively.

Among the healthiest group (albumin level at least 3.5 g/dL), those patients with an eGFR of at least 15 were 3.5 times as likely to die as were those with an eGFR of less than 5 (1-year mortality rates of 12.5% vs. 3.6%, respectively).

It is possible that the poorer survival might be related to fewer competing factors for mortality in those young and relatively healthy patients, the researchers noted.

Alternatively, relatively healthy patients with a higher eGFR at the start of hemodialysis "might have been more susceptible to potential harm from the hemodialysis procedure," the investigators said.

The authors replicated their analyses using serum creatinine values rather than eGFR as a measure of kidney function, "and the results were the same; ostensibly, better kidney function … was associated with higher mortality," they added.

A potential limitation of the study was the fact that it was based on registry data. Approximately one-third of the subjects in the study who were listed as having no comorbidities were missing one or more laboratory values corroborating that classification. However, separate analysis excluding that group produced the same result as with the entire study cohort.

The mechanism by which earlier hemodialysis may raise 1-year mortality is not yet known. "Possible mechanisms might include recurrent episodes of myocardial ischemia and 'stunning,' and eventual functional and structural changes with fixed systolic dysfunction induced by conventional thrice-weekly hemodialysis," Dr. Rosansky and his associates said.

In addition, research has shown that endogenous renal function provides a survival benefit over hemodialytic clearance, and more than half of endogenous renal function can be lost during the first months of hemodialysis therapy, they noted.

The results of the study, together with those of other studies, "provide evidence questioning the trend to early start of hemodialysis," the investigators said. "Initiation of hemodialysis should not be based on an arbitrary level of eGFR or serum creatinine level unless this measure is accompanied by definitive end-stage renal failure-related indications for hemodialysis."

One of Dr. Rosansky's associates reported ties to numerous industry sources. ■

VIEW ON THE NEWS

Weigh Symptoms, Quality of Life

The findings of this study, like those of the randomized controlled Initiating Dialysis Early and Late (IDEAL) clinical trial, do not support the widespread practice of beginning hemodialysis based on numerical criteria alone, said Dr. Kirsten L. Johansen.

"Rather, we need to reexamine what we consider to be uremic symptoms worthy of dialysis initiation. The bar for these symptoms has been dramatically lowered in recent years, with no data to support a benefit to patients," she said.

Early hemodialysis in the study not only failed to improve survival, it also failed to improve quality of life.

"I am suggesting that (in the absence of uremic indications) we shift our paradigm to consider starting dialysis when the symptoms are worse than the anticipated lifestyle burden and effects of dialysis, which are considerable and include a substantial time commitment, frequent fatigue, and infections, among other things," Dr. Johansen noted.

That approach of carefully weighing clinical factors and quality-of-life issues "will require close follow-up and ongoing discussion with our patients," she added.

KIRSTEN L. JOHANSEN, M.D., *is at the San Francisco VA Medical Center and the University of California, San Francisco. She reported no financial disclosures. The comments are taken from her editorial accompanying Dr. Rosansky's report (Arch. Intern. Med. 2010 [doi:10.1001/archinternmed. 2010.413]).*

Vytorin Lowered Cardiac Risk in Chronic Kidney Disease

BY M. ALEXANDER OTTO

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF NEPHROLOGY

DENVER – A once-daily combination of ezetimibe 10 mg and simvastatin 20 mg reduced the risk of major atherosclerotic events in patients with chronic kidney disease by 16.5%, according to a randomized, placebo-controlled trial funded by the drug's maker, Merck.

However, the combination (trade name Vytorin) did not slow progression to end-stage renal disease in the trial or significantly impact mortality.

The "trial results provide clear evidence that lowering cholesterol with [Vytorin] reduces the risk of major atherosclerotic events," in patients with chronic kidney disease, said Dr. Colin Baigent, Oxford University professor of epidemiology, and the lead investigator of the Study of Heart and Renal Protection (SHARP) trial. He presented the study results at the meeting.

Merck will seek Food and Drug Administration approval for Vytorin use in CKD patients based on the SHARP trial results, the company said.

In SHARP, 4,650 patients with chronic kidney disease were randomized to Vytorin, and 4,620 to placebo. The median duration of therapy was 4.9 years. The mean age at baseline was 62 years, and patients had no revascularization or myocardial infarction histories. A total of 23% had diabetes, and 15% had vascular disease.

About a third of the patients started the clinical trial on dialysis; the remainder had a baseline average estimated glomerular filtration rate of 26.5 mL/minute per 1.73 m^2.

The average LDL cholesterol at enrollment was 108 mg/dL. Midway through the trial, Vytorin lowered LDL cholesterol by an average of 32 mg/dL.

Major atherosclerotic events – coronary death, myocardial infarction, nonhemorrhagic stroke, or revascularization – occurred in 11.3% (526) of patients in the Vytorin group, and in 13.4% (619) of patients in the placebo group.

That translated to a significant 16.5% risk reduction among Vytorin users, results similar to previous statin studies in other populations, noted Dr. Baigent.

The rate of treatment compliance was about two-thirds among patients in both the placebo and Vytorin arms of the trial. "With full compliance, we would be likely to reduce the risk of vascular events by about a quarter," he predicted.

However, lowering patients' LDL did not affect progression to end-stage renal disease, which developed in about a third of patients in each arm: 33.9% of the treatment group, and 34.6% of the control group.

Cancer was also on the minds of investigators during the trial, due to reports about possible carcinogenicity associated with use of ezetimibe (trade name Zetia).

The Food and Drug Administration concluded in December 2009 that "it is unlikely that Vytorin or Zetia increases the risk of cancer or cancer-related death," and the SHARP results supported the assertion.

There were 438 cancers diagnosed and 150 cancer deaths in the Vytorin group, compared with 439 cancers diagnosed and 128 cancer deaths in the placebo group. The mortality difference was not significant.

Overall, cardiac, renal, and vascular-related deaths were less frequent in Vytorin users, but nonvascular deaths were more frequent.

As with cancer deaths, however, the differences between the groups were small and not significant.

Similarly, there were no significant differences in myopathy, rhabdomyolysis, liver dysfunction, pancreatitis, or gallstone complications between the two groups.

Dr. Baigent said he has no conflicts of interest. He added that the trial was run independently of Merck, and that he and his colleagues do not accept payments from the pharmaceutical industry, other than the costs of attending scientific meetings. ■