

## Stroke in ESRD: The Other Cardiovascular Disease

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**I**n 1998, the National Kidney Foundation convened a Task Force on Cardiovascular Disease in Chronic Renal Disease. The task force members reviewed the considerable evidence linking chronic kidney disease (CKD), especially in dialysis patients, with cardiac diseases, including heart failure, coronary disease, and cardiovascular mortality. However, in their review of cerebrovascular disease, the investigators were unable to draw any conclusions, noting:

... cerebrovascular disease ... [is] ... of importance in patients with [CKD], and some recommendations of the Task Force may apply to them, however, [cerebrovascular disease] was not considered because the literature is scant.<sup>1</sup>

In the more than 10 years since this report was issued, the link between CKD and cerebrovascular disease has become strikingly apparent, and the large evidence gap cited by the task force members has been slowly but gradually narrowed. This is especially true in the study of cerebrovascular disease in dialysis patients, for which studies in Japan<sup>2</sup> and the United States<sup>3</sup> suggested a 5- to 10-fold greater risk of acute stroke compared with the general population. Vascular imaging studies have documented a markedly greater burden of carotid artery atherosclerosis<sup>4,5</sup> in dialysis patients compared with controls with normal kidney function, consistent with the well-established association between kidney failure and generalized atherosclerotic vascular disease. Furthermore, concern has been raised about the acute effects of hemodialysis treatment on stroke risk, with 20% to 35% of all strokes in hemodialysis patients occurring during dialysis or within 30 minutes after a dialysis session in a Japanese cohort<sup>6</sup> and acute decreases in cerebral blood flow occurring after hemodialysis, even in patients without frank hypotension.<sup>7</sup> More recently, a nearly 5-fold greater frequency of subclinical or silent stroke has been recognized in imaging studies of dialysis patients.<sup>8</sup>

In this issue of the *American Journal of Kidney Diseases*, Sozio et al<sup>9</sup> examine in greater detail the patterns and outcomes of acute stroke in an incident hemodialysis and peritoneal dialy-

sis population by using data from the prospective multicenter Choices for Healthy Outcomes in Caring for ESRD (CHOICE) cohort study. In more than 1,000 patients (including 17% with prevalent cerebrovascular disease) followed up for a median of 2.7 years, the total cerebrovascular event rate (encompassing fatal and nonfatal stroke and carotid endarterectomy) was nearly 5 events/100 person-years. This is an extraordinarily high event rate that is nearly 10 times the rate in individuals in the general population of similar age.<sup>10</sup> In the first 2 years after initiating dialysis therapy, stroke rates were especially striking at approximately 20 events/100 person-years. Equally striking, outcomes after stroke were very poor, with a 35% case fatality rate and only 56% of cases discharged to home or for acute rehabilitation. In contrast to the Japanese cohort study described, the onset of stroke symptoms was not significantly more common in the peridialysis period compared with the interdialytic period.

A major strength of this study is the characterization of stroke subtype through review of stroke case records by using established consensus criteria; unfortunately, such records were available for less than two-thirds of cases. Nevertheless, the distribution of ischemic stroke subtypes (cardioembolic, 28%; large artery, 11%; small vessel, 20%) is approximately consistent with the relative frequency of these subtypes in the general population in the United States and Europe.<sup>11,12</sup> This suggests similarities in the pathophysiological processes leading to acute stroke in dialysis patients and the general population, although the relative influence of specific risk factors on vascular disease of the brain in dialysis patients versus the general population is unclear.

Overall, this study provides important new information regarding stroke incidence, subtypes, and outcomes in a maintenance dialysis

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population. In the context of the prior studies described, there is now overwhelming evidence that cerebrovascular disease, and stroke in particular, is a major source of morbidity and mortality in maintenance dialysis patients. This problem clearly warrants the type of expansive investigation that has occurred for cardiac disease in kidney disease populations. Although the rate of acute stroke in dialysis patients is relatively well defined, future investigations should focus on potential factors that account for the increased risk and potential interventions to reduce risk.

Unfortunately, with regard to pharmacotherapy, we cannot assume that standard therapies for primary and secondary prevention of stroke, proved effective in studies in the general population, are equally effective in dialysis patients. A striking example of this differential effect of stroke prevention was shown in Die Deutsche Diabetes Dialyse Studie (4D study) of atorvastatin in patients with diabetes on hemodialysis therapy. There was no benefit of atorvastatin on risk of all strokes (HR = 1.04) and even a doubling of risk of fatal strokes (including fatal ischemic strokes; HR = 2.04),<sup>13</sup> whereas the same drug in patients with diabetes without advanced kidney disease reduced the rate of stroke by nearly 50%.<sup>14</sup> Likewise, the effect of revascularization, carotid endarterectomy, and stenting procedures in stroke prevention in dialysis patients is unknown. In the general population, such revascularization is effective at reducing stroke risk, but only in selected patients with an acceptable perioperative risk. In patients with CKD, this risk is increased considerably, such that the risk-benefit trade-off is unclear. Clearly, additional study is needed of the effects of established and novel stroke preventions in dialysis patients. Ideally, such studies would take the form of randomized controlled trials, but there also is a role for well-designed observational studies with appropriate control for confounding by indication.

Given the current state of the evidence, what can nephrologists and allied health care providers do to improve cerebrovascular outcomes in dialysis patients? First and foremost, we need a high index of suspicion when our patients develop acute or even sub-acute neurological signs and symptoms. In the CHOICE study, the median time from symptom onset to clinical presentation was more than 8 hours, considerably longer

than the 4 to 6 hours reported in most general population studies. This suggests lack of recognition of acute stroke symptoms by maintenance dialysis patients and even by dialysis staff and health care providers. Although lack of recognition and knowledge about stroke symptoms is not limited to dialysis patients,<sup>15,16</sup> given the exceedingly high stroke rates and poor associated outcomes in this population, educational initiatives to improve stroke symptom recognition and knowledge clearly are warranted. Overall, there are significant opportunities to improve stroke outcomes in dialysis patients and advance the clinical investigation of renal-cerebrovascular interactions; collaborations between nephrologists and neurologists are essential to address these challenges.

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