
See related article, “TGF-α Mediates Genetic Susceptibility to Chronic Kidney Disease,” on pages 327–335.

Atrial Fibrillation in Dialysis Patients: A Neglected Comorbidity

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Atrial fibrillation is the most common and potentially difficult to treat cardiac arrhythmia encountered in clinical practice. It is classified according to its temporal pattern as paroxysmal (self-limiting), persistent (amenable to cardioversion), or permanent. 1 Although the frequency of each type depends on the population studied, it is estimated that paroxysmal fibrillation accounts for 35% to 66% of all cases of atrial fibrillation. 2–4 The prevalence of this disorder increases with age, rising above 5% in people older than 65 years of age. 5

Independent risk factors for fibrillation, from long-term follow-up data of the Framingham study, include male sex, hypertension, diabetes, heart failure, and valvular heart disease. 6 Because of its high prevalence, hypertension accounts for most cases of fibrillation in the population compared with all other risk factors. Among chronic kidney disease patients starting dialysis, 36% have heart failure, and an additional 7% develop heart failure while receiving dialysis. 7 Consequently, it is not unexpected that those patients on renal replacement therapy are at a particularly increased risk for the development of atrial fibrillation compared with the general population.

The prevalence of atrial fibrillation in dialysis patients is also driven by the changing age distribution of this population. Thirty years ago, approximately 27% of new end-stage kidney disease patients in the United States who began chronic renal replacement therapy were ≥65 years of age. In 2005, the total number of patients who started renal replacement therapy in the United States was 106,912, of which 52,434 (49%) were >65 years of age. 8 Although the incidence rates between 2000 and 2005 have been relatively stable for most age groups (changing <3.0%), the incidence rate has grown 10% from 1570 to 1725 per million for patients ≥75 years of age.

In the general population, atrial fibrillation may affect longevity because it is associated with approximately doubling all-cause and cardiovascular mortality rates. 9,10 Mortality, as expected in this setting, is driven by cerebrovascular events, progressive ventricular dysfunction, and increased coronary mortality. In addition, age-adjusted incidence of stroke in the Framingham study after 34 years of follow-up was nearly fivefold higher when nonrheumatic atrial fibrillation was present compared with those without atrial fibrillation. 11

The mechanism that triggers most atrial premature beats that initiate frequent paroxysms of fibrillation originates in the pulmonary veins, which has generated interest in ablative therapy of this region in selected patients. 12 Despite its important clinical relevance and potential effect on morbidity and mortality, there have been very limited data studying this comorbidity in dialysis patients in the United States and only a few worldwide published reports in this population. 13–16

In this issue, Winkelmayer et al. examine the epidemiology (including prevalence, risk factors, and mortality) of atrial fibrillation in patients on maintenance dialysis in the United States over a period of 15 years (1992 to 2006) using the U.S. Renal Data System annual cohorts. The overall prevalence of atrial fibrillation in this patient population exceeded 10% in 2006. In older patients, the prevalence was 13.2% in patients aged 65 to 75 years, 19.2% in those aged 75 to 85 years, and 22.5% in those >85 years of age. More importantly, atrial fibrillation was associated with considerable excess mortality in
this population (crude 1-year mortality of 38.8% versus 18.6%), although the odds ratio was attenuated in the fully adjusted model.

This study presents the first comprehensive evaluation of atrial fibrillation in patients on maintenance dialysis in the United States. It provides a contemporary estimate of the prevalence of fibrillation in this population with an impressive overall higher prevalence compared with the general population (8% versus 1%). The results also reflect the growing proportion of elderly individuals on maintenance dialysis. As indicated by the authors, the study is limited by its cross-sectional nature and reliance on medical claims data, which could be potentially incomplete. Another issue is the temporal trend in atrial fibrillation prevalence, in which the number of affected patients increased more than sixfold during the study period.

Can secular trends in the diagnosis and aggressive coding of atrial fibrillation favor increased detection of this arrhythmia in more recent years and can it explain this phenomenon? As the authors suggest, aggressive coding may explain the significant increase in atrial fibrillation rates in recent years (as shown in Figure 3 of Winkelmayer et al., approximately 50% increase in the adjusted relative prevalence in 2006 versus 1992). Nonetheless, these results are consistent with the temporal trend observed in the general population, in which fibrillation is also becoming more prevalent with time, even after adjustment for age and structural heart disease. The difference in atrial fibrillation risk among races is also similar to what has been observed in the general population, in which prevalence of atrial fibrillation was higher in whites than in blacks in the Anticoagulation and Risk Factors in Atrial Fibrillation study (2.2% versus 1.5%; \( P < 0.001 \)). Although the authors attempted to capture those with recurrent paroxysmal, persistent, or permanent atrial fibrillation, the relative prevalence of each type was not reported. It is also quite possible that paroxysmal fibrillation, particularly those triggered by dialysis treatment itself, were not accurately captured.

Determining the pattern of atrial fibrillation in dialysis has significant clinical and therapeutic implications for this particular patient population. Do dialysis patients have an increased risk for permanent atrial fibrillation, which may require chronic anticoagulation or antiarrhythmic therapy? If further studies can define the independent effect of atrial fibrillation on morbidity and mortality in the dialysis population, it will directly inform the aggressiveness with which we ought to pursue its clinical modification, recognizing the real risk of stroke in treating these patients.

Despite its limitations, Winkelmayer’s study is important and lays the groundwork for future studies designed to explore specific patterns of atrial fibrillation in this population, potential preventive measures, and treatment options such as anti-coagulation. Defining the dividends realized from identification and treatment of atrial fibrillation in the dialysis population will be of enormous clinical consequence for our patients.

DISCLOSURES
None.

REFERENCES


Mortality Risk in Dialysis Patients with Naturally Higher Hemoglobins

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Pioneering studies by Eshbach1 demonstrated the effectiveness of treating the anemia of ESRD with erythropoietin-stimulating agents (ESAs). These results led to more aggressive treatment of anemia in an effort to improve quality of life and survival for dialysis and predialysis patients. Unfortunately, clinical trials do not confirm the benefits of an aggressive correction and rather suggest that it may be harmful,2–5 leading to calls to rethink the goals for ESA treatment of renal anemia.6–8

The Normal Hematocrit Trial studied 1233 hemodialysis patients with heart disease.2 Participants were randomly assigned to target hematocrit values of 42 and 30%. The primary end point was time to death or first nonfatal myocardial infarction. The study was stopped after 29 months, when the numbers of deaths and first nonfatal myocardial infarctions were higher in the normal hematocrit arm. Although the difference in event-free survival between groups did not reach the pre-specified boundary for stopping the trial, the difference in mortality made it unlikely that continuing would reveal a benefit for the normal hematocrit arm. The mean dosage of epoetin was threefold higher in the normal hematocrit arm. These results suggested that using high doses of epoetin to target a normal hematocrit may have adverse effects. However, within each arm was an inverse relationship between achieved hematocrit and mortality. The excess of prespecified events in the normal hematocrit arm may have occurred largely in resistant patients who received high epoetin dosages but failed to achieve the target hematocrit.

Three recent randomized clinical trials of patients with CKD also failed to demonstrate a benefit associated with targeting a normal hemoglobin concentration.9–13 The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study randomly assigned 1432 patients to receive epoetin alpha therapy to achieve a hemoglobin level of 13.5 versus 11.3 g/dl.5 The primary outcome was a composite of cardiovascular events. There were more composite events in the group targeted to achieve a hemoglobin level of 13.5 versus 11.3 g/dl. There was no difference in quality of life between the arms.

The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study explored the hypothesis that targeting hemoglobin levels of 13.0 to 15.0 g/dl versus 10.5 to 11.5 g/dl would reduce cardiovascular events in 603 patients with CKD and mild to moderate anemia (11.0 to 12.5 g/dl).3 The primary end point was a composite of cardiovascular events. The median weekly epoetin beta dosage was 5000 and 2000 IU in the arms targeted to full and partial correction of anemia, respectively. The trial was stopped after the second interim analysis because the conditional power for demonstrating a benefit in the normal hemoglobin group was <5%. However, neither the efficacy nor the futility boundaries had been crossed, but the risk for cardiovascular events favored the arm with the lower hemoglobin target. There was significant improvement in quality of life but an increased risk for ESRD in the normal hemoglobin arm.

The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) randomly assigned 4038 patients with CKD, type 2 diabetes, and mild anemia to treatment with darbepoetin alpha versus placebo to target a hemoglobin level of 13 versus 9 g/dl.4 There were no significant differences in the occurrence of either of the composite end points—death and cardiovascular events or death and ESRD—between the arms. However, fatal and nonfatal strokes were increased significantly in the normal hemoglobin arm.

Only limited data are available from the preceding studies on the relationship of ESA dosage to cardiovascular events and all-cause mortality. Therefore, it is difficult to tease out the relative contributions of achieved hemoglobin and ESA dosage to the selected primary and secondary outcomes. It is possible that high