The atrial fibrillation conundrum in dialysis patients

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Abstract The burden of atrial fibrillation (AF) and the risk of stroke are high in dialysis patients. The decision to use anticoagulation rests heavily on effective risk stratification. Because both the pathophysiology of the disease and the response to therapy differ in dialysis, data from the general population cannot be extrapolated. The effect of vitamin K antagonists (VKAs) on the risk of stroke in dialysis patients with AF has not been studied in randomized trials. The available observational data provide contradictory results, reflecting differences in the degree of residual confounding, quality of international normalized ratio control, and stroke characterization. Dialysis patients have a high baseline bleeding risk. It remains unclear to what extent VKAs affect the overall bleeding propensity, but they may significantly increase the risk of intracerebral hemorrhage. Vascular calcifications are extremely prevalent in dialysis patients and independently associated with an adverse outcome. Vitamin K antagonists inhibit the activity of key anticalcifying proteins and may thus compound the risk of vascular calcification progression in dialysis. In the absence of evidence-based guidelines for anticoagulation in dialysis patients with AF, we provide recommendations to assist clinicians in individualized risk stratification. We further propose that new oral anticoagulants may have a better benefit-risk profile in dialysis patients than VKA, provided appropriate dose reductions are made. New oral anticoagulant may yield more on-target anticoagulation, reduce the risk of intracerebral bleeding, and not interfere with vascular calcification biology. Clinical trials with new oral anticoagulant in dialysis patients are eagerly awaited, to reveal whether these assumptions can be confirmed. (Am Heart J 2016;174:111-119.)

Atrial fibrillation (AF) is very common in dialysis patients and its prevalence has risen substantially over the past few decades,[1] mainly reflecting the increasing age and comorbid conditions of the dialysis population. In accordance with recent guidelines,[2] a sizable proportion of these patients are treated with vitamin K antagonists (VKAs), with the intention to reduce the risk of stroke and systemic embolism. However, evidence is mounting that the benefit-risk ratio of VKA and patient risk stratification tools applicable to the general population may not be extrapolated to patients with end-stage renal disease (ESRD). Concerns about the use of VKA in dialysis patients have been mainly ventilated in the nephrology literature, although VKAs are preferentially prescribed by cardiologists. The present in-depth review intends to give a balanced account of the risks and benefits of VKA specifically in the dialysis population, highlighting 3 main aspects: protection against stroke, risk of major bleeding and in particular intracerebral hemorrhage, and progression of vascular calcifications.

Epidemiology and pathophysiology of AF in dialysis patients

A systematic review including 25 studies in patients with ESRD reported an average prevalence of 11.6% (range 5.4%-27%) and incidence of 2.7/100 patient-years (range 0.97-5.9/100 patient-years) of AF.[3] This wide scatter is undoubtedly related to the variability in age distribution and racial composition of the study population and to the AF identification strategies. Because two-thirds of AF in dialysis may be paroxysmal[3] and several studies only reported symptomatic episodes, the true incidence of AF in this population may be largely underestimated.

Age is one of the most important risk factors for development of AF, with an increase in odds of 25% per 5-year increments.[4] However, the occurrence of AF in dialysis patients markedly exceeds that in the general population for each age category,[4] in large part due to the high burden of comorbid conditions known to be associated with AF. For instance, patients 67 years or older when initiating dialysis had an incidence of AF of 14.8/100 patient-years,[1] as compared with 2.8/100

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patient-years in the general Medicare population in the same age range.[5] Blacks, Asians, Native Americans, and Hispanics are at substantially lower risk for incident AF compared with whites,[1] somewhat counterintuitively in view of the less favorable cardiovascular risk profiles of black and Hispanic patients, suggesting a role for genetic or epigenetic factors in the genesis of AF in dialysis.

Although chronic kidney disease (CKD) is a well-known risk factor for AF, incident AF is independently associated with a 67% higher rate of subsequent ESRD.[6] These observations highlight a bidirectional relationship between AF and CKD, fueled by inflammatory and profibrotic factors, neurohumoral activation, and altered hemodymamics. Finally, the hemodialysis procedure itself, with its periodic swings in fluid and electrolyte status, may be a risk factor for the onset of AF. Registration of the exact time of onset of AF, by continuous implantable cardioverter defibrillator monitoring, demonstrated that most episodes occurred during dialysis, especially toward the end of the procedure.[7] The occurrence of AF was associated with higher ultrafiltration rates and lower diastolic pressure after dialysis, suggesting a role of intravascular volume depletion.[7] In addition, dialysis induces a prolongation of the P-wave duration, a measure of intra-atrial conduction velocity, closely linked to the reduction of serum potassium concentration during the procedure.[8]

Epidemiology and pathophysiology of stroke in dialysis patients

Based on an overview of 20 studies in dialysis populations, the incidence of stroke can be estimated to be between 3.1 and 9.5/100 patient-years, and 71% to 87% of strokes can be characterized as ischemic.[9] Studies reporting on an exclusively Japanese population found a lower incidence, with a relatively higher proportion of hemorrhagic strokes.[9] The increased risk of stroke (up to 10 times higher than in the general population) obviously reflects the high burden of traditional stroke risk factors in the dialysis population, although emerging evidence reveals that CKD-specific risk factors, including mineral and bone disorders, chronic inflammation, and uremic toxins, may also play a role.[9] A particularly relevant question is whether in the dialysis population, AF poses a true risk of ischemic stroke and, as a consequence, whether (any form of) anticoagulation is warranted in these patients. It has been suggested that uremic platelet dysfunction and thrice-weekly systemic anticoagulation during dialysis protect against ischemic stroke in dialysis patients with AF. In addition, strokes are more likely to be hemorrhagic than in the general population. Although the association between stroke and AF appeared to be less apparent in some studies,[10] a meta-analysis of 13 studies reported an event rate of 5.2/100 patient-years in dialysis patients with AF vs 1.9/100 patient-years in those without AF.[3] Atrial fibrillation patients on renal replacement therapy not receiving VKA have a higher risk of stroke compared with AF patients without CKD, ranging from 5.5-fold in the low-risk to 1.6-fold in the high-risk CHA_2DS_2-VASc strata.[11] It would appear therefore that AF indeed causes ischemic stroke in dialysis patients, perhaps with a lower attributable risk than in the general population, which leads to the important question of risk stratification. Are the $CHADS_2$ and the CHA_2DS_2-VASc scores useful to stratify stroke risk in dialysis patients with AF and guide the decision to initiate anticoagulation? Although neither score has been formally validated in populations with CKD, both the $CHADS_2$[4,12] and the CHA_2DS_2-VASc score[13] were reported to adequately predict stroke risk in patients undergoing dialysis. However, a closer look at the data reveals a significant problem in applying these scores to ESRD patients. In a population of 10,999 Asian dialysis patients with AF perceived by physicians as being at low risk of stroke, less than 4% had a CHA_2DS_2-VASc score lower than 2.[13] Similarly, less than 10% of 12,284 US dialysis patients with newly diagnosed AF had a CHA_2DS_2-VASc score lower than 2.[14] In essence, the components of the CHA_2DS_2-VASc score (congestive heart failure, hypertension, advanced age, diabetes, previous stroke, vascular disease) are so prevalent in dialysis patients with AF, that most who would qualify for oral anticoagulation were the guidelines for the general population be extrapolated to ESRD. In our opinion, the current application of the CHA_2DS_2-VASc score does not adequately discriminate between dialysis patients deriving a net benefit and those suffering a net harm from anticoagulation. Perhaps the threshold for anticoagulation should be set higher than 2, the weight of certain components of the CHA_2DS_2-VASc score should be modified, and other more dialysis-specific factors should be taken into account.

Vitamin K antagonist and the risk of stroke in dialysis patients

In the general population with AF, VKAs are an extremely effective treatment, preventing nearly two-thirds of strokes with an acceptable risk of major bleeding.[15] In high-risk AF patients with stage 3 CKD, VKA have a similar efficacy for prevention of ischemic stroke with a low rate of major hemorrhage.[16] Such clear evidence derived from randomized controlled trials (RCTs) is absent in patients with ESRD. Observational studies[4,11,14,17–23] have yielded conflicting results (Table I) and generated clinical equipoise. A meta-analysis of 6 observational studies reported no benefit of VKA in ESRD,[24] but did not include a number of recent large studies.[11,14,18,22]

Observational studies inevitably suffer from confounding by indication. Patients at the highest risk for stroke receive anticoagulation; therefore, patients on VKA appear to have higher stroke rates. This was very nicely illustrated in the