Mapping Progress in Reducing Cardiovascular Risk with Kidney Disease

Atrial Fibrillation

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Introduction

Atrial fibrillation is the most common sustained arrhythmia, and it contributes to adverse outcomes in affected patients, including morbidity, mortality, and higher health care resource utilization. Patients with kidney disease are particularly prone to developing atrial fibrillation, with both lower eGFR and increased proteinuria associated with higher incidence of atrial fibrillation (1). In addition, CKD and atrial fibrillation share a number of traditional and nontraditional risk factors (2). Therefore, it is not surprising that atrial fibrillation is particularly common among patients with irreversible kidney failure (ESKD), especially among those undergoing maintenance dialysis. Although insurance claims and registry studies have pinned the prevalence of atrial fibrillation at 10% or higher in unselected dialysis populations (2), more careful investigations using electrocardiograms or newer loop rhythm recorders have found that atrial fibrillation may be as common as one quarter or even one third of patients on hemodialysis (3,4).

The most apparent risk from atrial fibrillation has long been recognized as various thromboembolic events, in particular ischemic stroke, a potentially devastating event that also occurs more commonly in patients with irreversible kidney failure with or without atrial fibrillation. Oral anticoagulation using vitamin K antagonists has long been established as an efficacious and effective intervention toward preventing ischemic stroke in patients predominantly free from advanced CKD. Despite causing increased bleeding risk, the benefits outweigh these risks, and as a result, guidelines have recommend using vitamin K antagonists toward a target international normalized ratio of two to three in most patients with atrial fibrillation who possess certain risk factor constellations as calculated in risk scores that may incorporate older age, heart failure, hypertension, diabetes, prior stroke or thromboembolism, and other factors (5).

Although considerable progress has been made over the past decade in defining the epidemiology of atrial fibrillation in advanced kidney disease and ESKD, including its prevalence, affected patients' phenotypes, their prognosis, and associated practice patterns (detailed summary tables are in a recent report from a Kidney Disease: Improving Global Outcomes [KDIGO] Controversies Conference on CKD and Arrhythmias [2]), therapeutic advances in these patient populations have been elusive. As is so often the case, patients with advanced kidney disease were excluded from the trials establishing oral anticoagulation in atrial fibrillation, and especially for patients with ESKD on dialysis, special considerations pertain. These include increased risks of major and minor bleeding (*e.g.*, gastrointestinal, intracranial, and dialysis access related) as well as concerns that use of warfarin may interfere with the vitamin K–dependent γ-glutamyl carboxylase enzyme. This enzyme is required for the activation of matrix G1a protein, which inhibits vascular calcification, and several studies have shown that vascular or valvular calcification accelerates when matrix G1a protein, activity is impaired (6). Furthermore, observational studies evaluating warfarin effectiveness and safety have produced widely varying results, perhaps owing to important differences in study design. As a result, only a small proportion of patients with ESKD on dialysis and atrial fibrillation receive oral anticoagulation (typically $\leq$30% [3]).

Recent Therapeutic Advances

An important innovation became available with the approval of the first target-specific, direct oral anticoagulant in late 2010. The direct thrombin inhibitor dabigatran and the subsequently introduced factor X antagonists rivaroxaban, apixaban, and edoxaban satisfied an important medical need that stemmed from some of the limitations of vitamin K antagonist treatment, including it being target unspecific and narrow ranged and requiring bridging and international normalized ratio monitoring as well as having numerous food-drug and drug-drug interactions. All of these medications were found to be noninferior (even superior in some comparisons) regarding their ability to both prevent thromboembolic stroke and prevent the ensuing risk for major bleeding compared with active vitamin K antagonist control. Subgroup analyses of these trials focusing on patients with

relatively diminished kidney function (usually considered present if the creatinine clearance was <50 ml/min) found similar results, which support the use of target-specific oral anticoagulants in these patients with moderate kidney disease (7). Despite their high cost, these medications have swiftly garnered market share in the general population, because many patients (were) switched to target-specific oral anticoagulants from warfarin or initiated *de novo* oral anticoagulation using these drugs.

Clinical Implications of Recent Advances

Unfortunately, patients with advanced CKD, including patients with ESKD on dialysis, were excluded from the pivotal trials of these new medications, and the labels approved by the US Food and Drug Administration restricted indication to patients with creatinine clearances >15 ml/min (2). Specifically, the labeled indications of these target-specific oral anticoagulants excluded patients with creatinine clearance <15 ml/min or those with ESKD. Although some off-label use of dabigatran and rivaroxaban was observed in patients with ESKD on dialysis, it certainly did not reflect any mainstream move into this therapeutic class (8). The situation differed for apixaban, which received relatively greater adoption in patients with ESKD early on after its approval. Also, in January 2014, the Food and Drug Administration approved modification of the apixaban label, with a specific dosing recommendation pertaining to patients with ESKD on hemodialysis (essentially apixaban 5 mg twice daily; one half of that dose if age ≥80 years old or weight ≤60 kg). The evidence supporting this dosing recommendation was shallow (to say the least), but it nevertheless seems to have provided additional encouragement and led to further acceleration of apixaban use (9). More recently, a limited repeat dosing study over 8 days in five patients on maintenance hemodialysis suggested that apixaban 5 mg twice daily may lead to excess drug concentrations (10). However, an observational comparative effectiveness study suggested reduced thromboembolism rates with 5 mg twice daily compared with 2.5 mg twice daily, with comparable rates of major or gastrointestinal bleeding, albeit with rather wide confidence intervals (11). Rivaroxaban also received a label update in August 2016 for a reduced dose of 15 mg daily in patients with ESKD maintained on intermittent hemodialysis. It is not yet known how this updated label may have affected utilization of rivaroxaban in the ESKD population.

High-Priority Areas for Research

Despite these therapeutic advances for oral anticoagulation in the general population, several key questions for their use in patients with ESKD on dialysis remain and should be addressed at the highest priority. (*1*) Is oral anticoagulation in general efficacious and net beneficial in patients with ESKD on dialysis? (*2*) Do the benefits and risks differ between vitamin K antagonist and target-specific oral anticoagulants (as well as among target-specific oral anticoagulants)? (*3*) How do we interpret findings from longer-term electrocardiograms (especially loop recorders) that detect relatively low-burden atrial fibrillation episodes in otherwise asymptomatic patients? When and in what particular circumstances do we initiate oral anticoagulation?

Several additional high-priority research questions have recently been compiled by international experts convened by KDIGO and were cataloged in a report from their KDIGO Controversies Conference on CKD and Arrhythmias (2).

Currently, the Study of the Benefit / Risk Ratio of Oral Anticoagulation in Hemodialysis Patients With Atrial Fibrillation (AVKDIAL) is enrolling patients into a randomized, open label comparison of anticoagulation using a vitamin K antagonist versus a nonanticoagulation strategy. This French trial plans to enroll 855 participants with a follow-up of 2 years. Interestingly and encouragingly, at least two trials are currently enrolling patients into randomized comparisons between apixaban and international normalized ratio-targeted oral anticoagulation using a vitamin K antagonist (to international normalized ratio target range of two to three). The United States-based randomized, controlled Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation (RENAL-AF) Trial (NCT02942407) plans to enroll 762 patients with ESKD on dialysis to warfarin or apixaban 5 mg twice daily (with dose reduction per stated criteria in the label). Also, the German multicenter A Safety Study Assessing Oral Anticoagulation With Apixaban Versus Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease on Chronic Hemodialysis Treatment (AXADIA) Trial (NCT02933697) aims to enroll 222 patients with ESKD and atrial fibrillation with open label randomization to either phenprocoumon or apixaban 2.5 mg twice daily. Both trials focus primarily on the comparison of safety events (bleeding), with secondary outcomes including evaluations of thromboembolic stroke, and they have pharmacodynamics substudies that will establish additional evidence toward appropriate longer-term dosing of apixaban in the ESKD population. Neither study is adequately powered to establish reasonable noninferiority (or superiority) for thromboembolic outcomes.

It cannot be emphasized enough how unusual it is to have randomized trials specifically conducted in the distinct population of patients with ESKD on dialysis. The AVKDIAL Study, the RENAL-AF Trial, and the AXADIA Trial provide rare opportunities to establish the highest-level evidence in this population for a common problem where currently no conclusive evidence exists and where opinion-based treatment or "renalism" reigns. It is our shared responsibility to do the best that we can to overcome the difficulties of enrolling patients undergoing maintenance hemodialysis in prospective trials and elevate our practice to a more solid evidence base.

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