



Oral Anticoagulants to Prevent Stroke in Nonvalvular Atrial Fibrillation in Patients With CKD Stage 5D: An NKF-KDOQI Controversies Report

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Stroke risk may be more than 3-fold higher among patients with chronic kidney disease stage 5D (CKD-5D) compared to the general population, with the highest stroke rates noted among those 85 years and older. Atrial fibrillation (AF), a strong risk factor for stroke, is the most common arrhythmia and affects >7% of the population with CKD-5D. Warfarin use is widely acknowledged as an important intervention for stroke prevention with nonvalvular AF in the general population. However, use of oral anticoagulants for stroke prevention in patients with CKD-5D and nonvalvular AF continues to be debated by the nephrology community. In this National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) controversies report, we discuss the existing observational studies that examine warfarin use and associated stroke and bleeding risks in adults with CKD-5D and AF. Non–vitamin K–dependent oral anticoagulants and their potential use for stroke prevention in patients with CKD-5D and nonvalvular AF are also discussed. Data from randomized clinical trials are urgently needed to determine the benefits and risks of oral anticoagulant use for stroke prevention in the setting of AF among patients with CKD-5D.

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Introduction

The National Kidney Foundation–Kidney Dialysis Outcome Quality Initiative (NKF-KDOQI) was launched to develop guidelines for treating patients with end-stage renal disease treated by dialysis (ie, those with chronic kidney disease stage 5D [CKD-5D]). The first guideline, published by NKF-KDOQI in 1997, addressed dialysis adequacy and did not discuss cardiovascular disease (CVD) management.¹ It was not until 2005 that clinical guidelines for the diagnosis, prevention, and treatment of CVD, including stroke, were published.² These recommendations were based on observational studies or the clinical experience of the writing group

because most major CVD trials excluded patients with advanced kidney disease. Today, CVD remains a major cause of mortality for patients with CKD-5D,³ yet level I evidence from well-designed clinical trials is lacking for most clinical decisions regarding CVD, including stroke prevention in the setting of nonvalvular atrial fibrillation (AF). To date, no randomized trials have examined the efficacy and safety of warfarin or any of the non–vitamin K oral anticoagulants (NOACs) in adults with CKD-5D and nonvalvular AF. The lack of clinical trial data is especially alarming because rates of hospitalized ischemic strokes may be at least 2-fold higher among adults with CKD-5D compared to the general

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population,⁴ whereas nonvalvular AF, a strong risk factor for stroke and mortality,⁵ affects at least 1 of every 10 adults with CKD-5D.^{6,7}

NKF-KDOQI publishes a series of reports addressing controversial questions in nephrology care for which evidence is lacking or contradicting, thus preventing clinical practice guidance. These topics are selected based on responses to surveys posted on the KDOQI website (www.kidney.org/professionals/guidelines). In a 2016 survey administered by the NKF on the KDOQI website asking "Should warfarin be used in dialysis patients with non-valvular atrial fibrillation?," 45.1% of 5,063 respondents answered "No," while 54.9% responded "Yes." In this NKF-KDOQI controversy report, we discuss controversies regarding the benefits and risk of anticoagulant use for stroke prevention in adults with AF and CKD-5D. We also outline areas of research for which evidence is urgently needed to guide clinical decision making regarding stroke prevention for patients with CKD-5D. Because nephrology continues to lag behind all other medical subspecialties in total funding for and number of clinical trials, the overall goal of the KDOQI controversy reports is to bring attention to key clinical questions in nephrology for which evidence is lacking and urgently needed.

Epidemiology of AF in CKD-5D

In CKD-5D, the prevalence of AF ranges from 7% to 27%,^{3,7-13} depending on methods of ascertainment, with the highest AF prevalence noted with Holter monitoring. Based on diagnosis codes, AF affects at least 1 of every 10 adults with CKD-5D.^{6,7} However, the optimal method for identifying AF in the CKD-5D population remains poorly evaluated. Risk factors for incident AF in the CKD-5D population generally reflect risk factors noted in the general population, such as hypertension, diabetes, heart failure, and ischemic heart disease.^{7,10,14} Volume overload frequently accompanies CKD-5D and may lead to left atrial dilatation and subsequent atrial remodeling, heightening the risk for AF.^{11,13,15-19} The dialysis procedure itself may trigger AF because AF is most likely to occur on dialysis days and during a dialysis session.^{16,19,20} Dialysis-specific risk factors for AF include high dialysate calcium and low dialysate potassium concentrations.^{10,12} However, to date, few studies have examined risk factors for AF unique to the CKD-5D population and whether modifying these risk factors reduces AF incidence.

Link Between AF and Stroke in CKD-5D

In the setting of CKD-5D, AF is associated with an approximately 4-fold increased risk for stroke and

2-fold increased risk for death.^{6,7,10,11,14,21} Although the proportion of strokes associated with AF in the CKD-5D population remains poorly quantified, ~20% of all ischemic strokes are attributed to AF in the general population.²² Regardless of the population, strokes in the setting of AF are associated with higher morbidity and mortality.²¹⁻²⁵ Stroke-associated mortality may be increased by 50% when strokes occur in the setting of AF.²⁵ Age-adjusted stroke rates as determined by stroke-related hospitalizations are overall approximately 3- to 9-fold higher in the CKD-5D population compared to the general population, with the highest hazard rates for stroke associated with CKD-5D noted among white women.²⁶ The overall risk for strokes among adults with CKD-5D increases upon dialysis therapy initiation²⁷ and may be >5% during the first 2 years after dialysis therapy initiation. Risk factors for stroke include advanced age, diabetes, and white race.²⁸

In the CKD-5D population, at least 75% of strokes are ischemic in nature, while up to 25% are hemorrhagic.²⁷⁻³⁰ Silent strokes are common and existing data suggest that the prevalence of silent strokes may be up to 5-fold higher in the CKD-5D population versus the general population.^{27,29,30} Most strokes in patients with CKD-5D are lacunar infarcts, and brain white matter lesions are common in this population.³⁰⁻³² Overall prognosis is poor for an adult with CKD-5D who experiences a stroke. Approximately one-third of all strokes among adults with CKD-5D are fatal events and most who survive a stroke will die within 1 year.²⁸

Information on how to best predict stroke risk in the CKD-5D population remains scant and precludes the ability to identify the patients at high risk for stroke. In the general population, several prediction scores may be used to estimate stroke risk based on established risk factors. The most commonly used prediction scores are CHADS₂,³³ CHA₂DS₂-VASc,³⁴ ATRIA,³⁵ and the R₂CHADS₂.³⁶ The CHADS₂ score includes age (65-74 years, 1 point; ≥75 years, 2 points), female sex (1 point), congestive heart failure (1 point), hypertension (1 point), anemia (1 point), diabetes mellitus (1 point), and previous stroke, transient ischemic attack, or thromboembolism (2 points).³⁷ The CHA₂DS₂-VASc adds vascular disease (1 point) to the CHADS₂ score and may be used to further delineate bleeding risk.³⁴ Scores of 2 points or higher indicate a ≥4% risk for stroke during the next year. The ATRIA and R₂CHADS₂ scores include the presence of CKD as a risk factor for stroke, whereas all other prediction scores do not.^{35,38,39}

No stroke risk prediction scores have been specifically developed for patients with CKD-5D with AF. The existing stroke risk prediction scores show good

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