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Anticoagulation for atrial fibrillation in patients on dialysis: are the benefits worth the risks?

Jenny I. Shen^a, Mintu P. Turakhia^{b,c}, and Wolfgang C. Winkelmayer^a

^aDivision of Nephrology, Stanford University School of Medicine and Veterans Affairs Palo Alto Healthcare System, Palo Alto, California, USA

^bDivision of Cardiovascular Medicine, Stanford University School of Medicine and Veterans Affairs Palo Alto Healthcare System, Palo Alto, California, USA

^cDepartment of Medicine, Stanford University School of Medicine and Veterans Affairs Palo Alto Healthcare System, Palo Alto, California, USA

Abstract

Purpose of review—Atrial fibrillation is common among patients with end-stage renal disease undergoing hemodialysis. Although oral anticoagulation is recommended for stroke prevention in most patients with atrial fibrillation, limited evidence is available to guide treatment in hemodialysis patients with this arrhythmia. We summarize the available evidence on the epidemiology of atrial fibrillation in dialysis patients and review the data on the effectiveness of oral anticoagulation in this population.

Recent findings—Atrial fibrillation is increasingly common in patients undergoing chronic hemodialysis, especially among older patients wherein one in six patients is diagnosed with this arrhythmia. Patients with atrial fibrillation experience double the mortality of otherwise similar patients without it. Few hemodialysis patients with atrial fibrillation receive oral anticoagulation, which is consistently associated with excess risks of hemorrhagic stroke. Observational studies did not detect a beneficial association of oral anticoagulation with the risk of ischemic stroke, with some studies describing higher risks of ischemic stroke among warfarin users. New therapeutic options including one oral direct thrombin inhibitor and two oral factor Xa inhibitors have become available, but were not tested in patients with advanced kidney disease.

Summary—Atrial fibrillation is increasingly common in patients undergoing hemodialysis, yet little is known about the optimal management of these patients. The current evidence does not support net benefits from oral anticoagulation in the dialysis population.

Keywords

atrial fibrillation; end-stage renal disease; hemorrhage; mortality; stroke

INTRODUCTION

Atrial fibrillation is the most common arrhythmia encountered in clinical practice, affecting an estimated 2.7 million individuals in the United States and 5.6 million by 2050 [1]. Among Medicare beneficiaries aged 67 or older, the prevalence of atrial fibrillation has sharply increased from 6.7% in 1998 to 8.6% in 2007 [2]. Among these patients, one in four will die within one year after diagnosis. The most dreaded consequence of atrial fibrillation is stroke, which is associated with 15% of the 700 000 ischemic strokes per year. The proportion of strokes attributable to atrial fibrillation increases steeply from 1.5% at 50–59 years of age to 23.5% at 80–89 years of age [3,4].

Oral anticoagulation has been shown to substantially reduce the risk of ischemic stroke by up to 60% [5], but at the expense of an increase in risk of bleeding, including major intestinal bleeding and intracranial hemorrhage, which may be disabling or fatal. Among patients at low risk for major bleeding, the benefits of anticoagulation generally outweigh the risks, and oral anticoagulation is recommended for patients with atrial fibrillation and one or two accompanying risk factors for stroke [6–8].

Kidney function is strongly associated with the risk of atrial fibrillation [9,10], but patients with advanced kidney disease including those requiring dialysis were not adequately represented in or excluded from the trials establishing efficacy for anticoagulation strategies. Therefore, there is uncertainty and controversy regarding the risks and benefits of anticoagulation in patients with atrial fibrillation on hemodialysis. The objective of this review is to dissect the available evidence on the burden of atrial fibrillation in the hemodialysis population, weigh the considerations for and against the use of oral anticoagulation, and also examine the sparse evidence on the effectiveness and safety of this treatment strategy in patients undergoing hemodialysis.

BURDEN OF ATRIAL FIBRILLATION IN THE HEMODIALYSIS POPULATION

Patients undergoing chronic dialysis have a particularly high risk for atrial fibrillation. In a cross-section of point-prevalent US hemodialysis patients on 31 December 2006, who had fee-for-service Medicare as their primary health insurance, 10.5% had been diagnosed with atrial fibrillation at least twice in the year before and affected patients experienced double the mortality of otherwise similar patients without atrial fibrillation [11]. In a recent study focusing on the ‘dually eligible’ population, of both Medicare and Medicaid, Wetmore *et al.* [12] found 7% of prevalent hemodialysis patients in 2004–2005 to have been diagnosed with atrial fibrillation. Using different methodology (questionnaire rather than evidence from billing claims) and a representative population sample, the Dialysis Outcomes and Practice Patterns Study (DOPPS) estimated an atrial fibrillation prevalence of 12.5% in the United States [13]. Interestingly, an international comparison showed considerable heterogeneity, with prevalence estimates ranging from 5.6% (Japan) to 24.7% (Belgium) [13]. Many patients appear to have atrial fibrillation even prior to starting dialysis. In patients initiating dialysis in 2003 or 2004 at a large national dialysis provider in the United States, 4.5% had been diagnosed and documented with atrial fibrillation by the time of their first treatment [14]. In older patients (> 67 years) initiating dialysis in the United States between 1995 and 2008, 34% had been diagnosed with atrial fibrillation in the two years

preceding their dialysis initiation [15]. Older age and white race as well as several cardiovascular and other comorbidities were associated with increased risk of atrial fibrillation. From the studies that specifically investigated trends over time, it is also apparent that both the incidence and the prevalence of atrial fibrillation in US hemo-dialysis patients have been increasing [11,15].

UTILIZATION PATTERNS OF ORAL ANTICOAGULATION IN HEMODIALYSIS PATIENTS WITH ATRIAL FIBRILLATION

In general, warfarin use has been found to be rather low in hemodialysis patients with atrial fibrillation. In a study of older hemodialysis patients with atrial fibrillation in two eastern states, only one quarter had filled a prescription of warfarin in the previous 45 days [16]. In the DOPPS, 26% of prevalent US hemodialysis patients with atrial fibrillation were reported to be taking warfarin [13]. Neither of these studies was able to determine the specific indication for warfarin use (atrial fibrillation or other, e.g., vascular access patency) or the level of anticoagulation achieved. Of 1671 patients who had preexisting atrial fibrillation and initiated hemodialysis with a large national dialysis provider in 2003/2004, 45% were reported to have received warfarin at dialysis initiation [14]. International normalized ratios (INRs) were unavailable in 204/747 patients; of the remainder, 10% had an INR less than 1.5, 29% an INR between 1.5 and 1.9, 60% between 2 and 3 (the recommended target range) [8], and 11% were above target range with an INR more than 3 at the time of dialysis initiation.

The slightly higher rate of warfarin use in the latter study can be partly explained by selection factors (eligible patients had to survive and remain on hemodialysis for 3 months after initiation) and the fact that only incident patients were studied. It is possible that warfarin is discontinued in a significant number of patients initiating hemodialysis who had used it prior to starting maintenance hemodialysis. These data indicate that the utilization of anticoagulation in hemodialysis patients is much lower than has been shown in the general population [17–20].

CONSIDERATIONS ABOUT THE INDICATION OF ORAL ANTICOAGULATION IN HEMODIALYSIS PATIENTS WITH ATRIAL FIBRILLATION

The rather low use of warfarin in hemodialysis patients with atrial fibrillation in the studies discussed in the previous section appears to reflect skepticism about the net benefits of warfarin anticoagulation. Indeed, the studies that established the efficacy of warfarin did not include patients with advanced kidney disease and it is possible that the evidence from populations without hemodialysis cannot be extrapolated to patients who are dependent on it. There are several reasons that the relation between risks and benefits may be shifted toward reduced net benefit or even harm in patients undergoing dialysis.

RISK OF STROKE

On the one hand, the risk of thromboembolic events in the dialysis population is high [21,22], which could possibly enhance benefits from oral anticoagulation. Compared to the general population, dialysis patients have four to 10 times the risk of being hospitalized with an ischemic stroke, dependent on their race and sex (white men: adjusted rate ratio, aRR =

6.1; white women: aRR = 10.1; African American men: aRR = 4.3; African American women: aRR = 6.5) [21,23]. Compared to the rate in the general population, dialysis patients over age 65 had more than 400 excess ischemic stroke events per 10 000 person-years in men and more than 600 in women [21]. Focusing solely on the US dialysis population, the crude rate of ischemic stroke was 33 per 1000 person-years [22]. However, due to the high burden of atherosclerotic disease, hemodialysis patients may present with atherothrombotic stroke (rather than embolic stroke), which could also explain the reduced treatment benefit with warfarin.

RISK OF BLEEDING

On the other hand, dialysis patients are also at a high risk of bleeding events, making oral anticoagulation potentially more risky. The age-adjusted rate ratios of hospitalization for hemorrhagic stroke in dialysis patients compared to the general population were 5.9 for white men, 6.7 for white women, 4.1 for African American men, and 4.0 for African American women [21]. Dialysis patients are also at particular risk of another type of bleeding event: upper gastrointestinal bleeding [24]. In a recent study of US dialysis patients whose primary insurance was Medicare fee-for-service, the rate of nonvariceal upper gastrointestinal bleeding was estimated to be 57 episodes per 1000 person-years using a stringent definition or 328 episodes per 1000 person-years using a more lenient definition [25]. These rates were up to two orders of magnitude higher than those reported in the general population, and 30-day mortality following such an event was high, exceeding 10% [25]. In addition to hemorrhagic stroke and upper gastrointestinal bleed, hemodialysis patients are also at risk of minor bleeding, specifically from their vascular access puncture sites [26]. These high bleeding risks may also be augmented by the relatively widespread use of other medications affecting coagulation and thrombostasis other than warfarin, including aspirin, clopidogrel, and heparin in this population [14,27,28].

Finally, there has been concern and controversy about warfarin-associated risk of accelerated vascular calcification in patients undergoing maintenance hemodialysis [29,30]. Although the argument is mostly built on theoretical grounds and in-vitro findings, there are clinical data weakly linking warfarin use and its duration to aortic valve calcification in dialysis patients [31]. In addition, warfarin use has long been identified as a risk factor for calcific uremic arteriolopathy ('calciophylaxis') [32], although it is clearly a component cause and not sufficient cause for the development of this often life-threatening condition.

DIRECT EVIDENCE ON THE EFFECTIVENESS AND SAFETY OF WARFARIN ANTICOAGULATION IN PATIENTS UNDERGOING HEMODIALYSIS

To date, no randomized trials have tested the efficacy of warfarin anticoagulation in patients undergoing dialysis and studies in the general or other specific populations (e.g., heart failure) have systematically excluded patients with end-stage renal disease (ESRD). Only a few studies have examined the outcomes associated with warfarin anticoagulation in dialysis patients [13,14,33–36,37■■■]. Herein we examine the three most recent and largest studies (Table 1).

Chan *et al.* [14] used the clinical database of a large US dialysis provider and identified from all patients initiating hemodialysis in 2003 and 2004 those who had a diagnosis of atrial fibrillation documented in the electronic medical record at the time of their first outpatient dialysis. To be included in the study, patients had to have begun dialysis within 30 days and were required to survive 90 days. Warfarin use within 90 days of initiation of hemo-dialysis was ascertained from medical records. The identified 1671 patients were then followed for the event of stroke (any; ischemic; hemorrhagic), also derived from electronic medical records, or death. In multivariable adjusted as well as in propensity score-matched analyses, the risk of any stroke was double in patients with baseline warfarin use compared to those who had no warfarin use recorded. When examining ischemic and hemorrhagic stroke events separately, both were found to be associated with baseline warfarin use: users had 1.81 times the rates of ischemic stroke and 2.22 times the rates of hemorrhagic stroke (Table 1).

Wizemann *et al.* [13] used data from the DOPPS and identified patients who had been reported to have had atrial fibrillation at enrollment into DOPPS. Presumably, warfarin use was also queried at the same time. All 3245 patients with atrial fibrillation at baseline were then followed for the event of stroke (hospitalized or listed as cause of death) and associations with baseline warfarin use were then estimated. Age appeared to have modified the association, with warfarin users over age 75 years experiencing 2.17 times higher stroke rates than otherwise similar patients who were not reported to have used warfarin at baseline. The associations were not significant, though also in the direction of harm, in the two younger age strata. Specific type of stroke (ischemic versus hemorrhagic) was not ascertained in this study.

Winkelmayer *et al.* [37■■] used insurance data from Medicare and several state-sponsored prescription drug benefit programs for the elderly in Pennsylvania and New Jersey. They assembled a cohort of older patients who initiated dialysis without any evidence of diagnosed atrial fibrillation in insurance claims preceding ESRD incidence. These patients were then followed for a first hospitalization in which atrial fibrillation was diagnosed and coded in billings submitted to Medicare. Patients were then required to not have received warfarin prior to this hospitalization and had to survive 30 days after discharge. During this 30-day window, initiation of warfarin treatment was ascertained from filled prescriptions for this drug. Patients were then followed for the appearance of healthcare claims containing diagnosis codes for ischemic or hemorrhagic stroke. In a propensity-matched cohort of warfarin users and nonusers, initiators of warfarin after their first hospitalization when atrial fibrillation was recorded had 2.38 times the risk of hemorrhagic stroke compared with otherwise similar patients who did not initiate warfarin within 30 days of discharge. The association between warfarin use and the risk of ischemic stroke, however, was null, though with confidence limits that included the potential for sizeable benefit (a 39% risk reduction) and harm (a 37% risk increase).

Mortality from any cause was not associated with warfarin use in the two studies that reported this association [14,37■■]. None of the three studies found any associations between warfarin use and gastrointestinal bleeding [37■■] and hospitalizations for bleeding [13,14].

One potential explanation for increased bleeding events on warfarin may be the quality of anticoagulation or INR control in hemodialysis patients. Time in therapeutic range (TTR; INR between 2.0 and 3.0) has been repeatedly demonstrated to be a potent predictor of warfarin effectiveness and safety [38]. However, comorbidities are associated with decreased TTR in randomized trials and observational studies [39]. Chronic kidney disease decreases TTR [40] and patients on hemodialysis have the most significant declines in risk-adjusted TTR [41].

For the clinician, it is challenging to make sense of these disparate findings and to synthesize a recommendation from these studies [42]. Although the finding that warfarin use (and anticoagulation intensity [14]) associates with increased risks of hemorrhagic stroke is plausible, it is the difference in the reported associations with ischemic (and any) stroke that baffle the consumer of this research. Clearly, the three studies differ quite a bit in their setting, the way data are collected, and in their study design and analytical approach. It is possible that studies that focus on patients with preexisting atrial fibrillation and existing users of warfarin induce biases by not focusing on the moment of decision-making, the time when atrial fibrillation was first diagnosed, and the time when the decision whether to prescribe warfarin or not was made. A detailed discussion on inception cohorts and new user designs is available elsewhere [37■] and does not need to be repeated here. But all studies have in common that treatment was assigned based on clinical information and not by the flip of a coin as would occur in a clinical trial. Therefore, the evidence from all these studies needs to be consumed with caution.

POTENTIAL OF EMERGING ANTICOAGULANTS IN PATIENTS ON HEMODIALYSIS

Because the excess bleeding risk in dialysis patients may be, at least in part, due to poor INR control with warfarin, anticoagulants without this variability in potency could be effective. Over the last several years, one oral direct thrombin inhibitor (dabigatran) and two oral factor Xa inhibitors (rivaroxaban and apixaban) have been studied against warfarin in three large pivotal phase III randomized trials [43–45]. Unfortunately, patients with severe chronic kidney disease (estimated glomerular filtration rate <25 or 30 ml/min/ 1.73 m²) were excluded from all three trials. Still, the US Food and Drug Administration (FDA) approved half-dose (75 mg twice daily) dabigatran in patients with creatinine clearance of 15–30 ml/min, even in the absence of randomized trial data. Unfortunately, postmarketing surveillance reports of fatal bleeding events in patients treated with dabigatran have been reported worldwide [46–48]. Many of these bleeding events appear to occur in elderly patients with chronic kidney disease, which may reflect the increased tendency of drug accumulation as 80% is eliminated by the kidney [49].

Therefore, in contrast to the FDA, the European Medicines Agency now recommends that dabigatran not be prescribed if creatinine clearance is less than 30 ml/min [50]. The FDA is analyzing post-marketing reports of adverse events for evidence of inappropriate dosing and other clinical factors that may be associated with bleeding events. In a subgroup analysis of atrial fibrillation patients with moderate kidney disease (creatinine clearance 30–49 ml/min) randomized to rivaroxaban versus warfarin, there were comparable risk reductions with rivaroxaban, although overall event rates were higher in the moderate chronic kidney disease

group. However to this day, there are no published comparative data on safety events for any of the new oral anticoagulants in patients on hemodialysis.

CONCLUSION

Given the limited evidence available, how should the clinician then manage dialysis patients with atrial fibrillation? Specifically how should (s)he weigh the risks and benefits of warfarin treatment in these patients? A recent decision analysis has used the limited information available at the time and suggested that use of warfarin was cost-effective in hemodialysis patients with atrial fibrillation, but the authors warned that considerable uncertainty was present in their study [51]. Since then, additional data have been published that cast doubt on some of the assumptions made in this model. We feel that the current evidence does not support general use of oral anticoagulation for all hemodialysis patients with atrial fibrillation. Although risk scoring algorithms such as the CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or transient ischemic attack) score have been shown to predict risk of ischemic stroke in the hemodialysis population [14], knowing a patient's risk score does not inform the relation of risks to benefits in these patients, which makes individualization of treatment decisions difficult. Thus, we do not believe that all hemodialysis patients with atrial fibrillation should receive anticoagulation based on current risk stratification criteria (CHADS₂), but it may be reasonable, though of uncertain benefit, in situations of particularly high-stroke risk. In light of ambiguity of evidence and resulting clinical equipoise, conducting randomized clinical trials of anticoagulation in patients with ESRD, especially those undergoing hemodialysis, not only is ethical, but also should be a high research and funding priority.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 663–664).

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention – the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001; 285:2370–2375. [PubMed: 11343485]
2. ■ Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. *Circ Cardiovasc Qual Outcomes* 2012. 5:85–93. [Landmark study describing the epidemiology and trends of diagnosed atrial fibrillation in older US adults.]

3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991; 22:983–988. [PubMed: 1866765]
4. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003; 290:1049–1056. [PubMed: 12941677]
5. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of anti-thrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994; 154:1449–1457. [PubMed: 8018000]
6. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001; 285:2864–2870. [PubMed: 11401607]
7. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009; 151:297–305. [PubMed: 19721017]
8. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006. 114:e257–e354.
9. Baber U, Howard VJ, Halperin JL, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol*. 2011; 4:26–32. [PubMed: 21076159]
10. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2011; 123:2946–2953. [PubMed: 21646496] [First study to describe the association of chronic kidney disease with incident atrial fibrillation in a prospective cohort study.]
11. Winkelmayer WC, Patrick AR, Liu J, et al. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol*. 2011; 22:349–357. [PubMed: 21233416] [Landmark study describing the trends in the population prevalence of atrial fibrillation and associated mortality in the US hemodialysis population.]
12. Wetmore JB, Mahnken JD, Rigler SK, et al. The prevalence of and factors associated with chronic atrial fibrillation in Medicare/Medicaid-eligible dialysis patients. *Kidney Int*. 2012; 81:469–476. [PubMed: 22189842] [This study describes the epidemiology of atrial fibrillation in the dually eligible population.]
13. Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int*. 2010; 77:1098–1106. [PubMed: 20054291]
14. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol*. 2009; 20:2223–2233. [PubMed: 19713308]
15. Goldstein, BA.; Turakhia, M.; Arce, CM.; Winkelmayer, WC. Trends in the incidence of atrial fibrillation in older patients initiating dialysis in the United States.. 49th European Renal Association-European Dialysis and Transplant Association Congress; Paris, France. 2012;
16. Winkelmayer WC, Liu J, Patrick AR, et al. Prevalence of atrial fibrillation and warfarin use in older patients receiving hemodialysis. *J Nephrol*. 2012; 25:341–353. [PubMed: 22180223]
17. Glazer NL, Dublin S, Smith NL, et al. Newly detected atrial fibrillation and compliance with antithrombotic guidelines. *Arch Intern Med*. 2007; 167:246–252. [PubMed: 17296879]
18. Reynolds MR, Shah J, Essebag V, et al. Patterns and predictors of warfarin use in patients with new-onset atrial fibrillation from the FRACTAL Registry. *Am J Cardiol*. 2006; 97:538–543. [PubMed: 16461052]
19. Darkow T, Vanderplas AM, Lew KH, et al. Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. *Curr Med Res Opin*. 2005; 21:1583–1594. [PubMed: 16238898]

20. Herzog CA, Solid CA. Atrial fibrillation and stroke in the general Medicare population: a fifteen year perspective (1992–2007) [abstract]. *Circulation* 2011; 124:A8293.
21. Seliger SL, Gillen DL, Longstreth WT Jr, et al. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int.* 2003; 64:603–609. [PubMed: 12846756]
22. Seliger SL, Gillen DL, Tirschwell D, et al. Risk factors for incident stroke among patients with end-stage renal disease. *J Am Soc Nephrol.* 2003; 14:2623–2631. [PubMed: 14514741]
23. Vazquez E, Sanchez-Perales C, Garcia-Garcia F, et al. Atrial fibrillation in incident dialysis patients. *Kidney Int.* 2009; 76:324–330. [PubMed: 19494800]
24. Boyle JM, Johnston B. Acute upper gastrointestinal hemorrhage in patients with chronic renal disease. *Am J Med.* 1983; 75:409–412. [PubMed: 6604455]
25. Yang JY, Lee TC, Montez-Rath ME, et al. Trends in acute nonvariceal upper gastrointestinal bleeding in dialysis patients. *J Am Soc Nephrol.* 2012; 23:495–506. [PubMed: 22266666]
26. Elseviers MM, Van Waeleghem JP. Identifying vascular access complications among ESRD patients in Europe. A prospective, multicenter study. *Nephrol News Issues.* 2003; 17:61–64. 66–68, 99. [PubMed: 12882114]
27. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. *J Am Soc Nephrol.* 2009; 20:872–881. [PubMed: 19297555]
28. Shen JI, Winkelmayer WC. Use and safety of unfractionated heparin for anticoagulation during maintenance hemodialysis. *Am J Kidney Dis.* 2012; 60:473–486. [PubMed: 22560830]
29. Bennett WM. Should dialysis patients ever receive warfarin and for what reasons? *Clin J Am Soc Nephrol.* 2006; 1:1357–1359. [PubMed: 17699369]
30. Horl WH. Coumarin use in dialysis patients with atrial [corrected] fibrillation: yes, after individual risk stratification. *Nephrol Dial Transplant.* 2009; 24:3285–3287. [PubMed: 19666666]
31. Holden RM, Sanfilippo AS, Hopman WM, et al. Warfarin and aortic valve calcification in hemodialysis patients. *J Nephrol.* 2007; 20:417–422. [PubMed: 17879207]
32. Coates T, Kirkland GS, Dymock RB, et al. Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis.* 1998; 32:384–391. [PubMed: 9740153]
33. Wiesholzer M, Harm F, Tomasec G, et al. Incidence of stroke among chronic hemodialysis patients with nonrheumatic atrial fibrillation. *Am J Nephrol.* 2001; 21:35–39. [PubMed: 11275630]
34. Abbott KC, Trespalacios FC, Taylor AJ, Agodoa LY. Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality. *BMC Nephrol.* 2003; 4:1. [PubMed: 12546711]
35. Genovesi S, Pogliani D, Faini A, et al. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. *Am J Kidney Dis.* 2005; 46:897–902. [PubMed: 16253730]
36. Lai HM, Aronow WS, Kalen P, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. *Int J Nephrol Renovasc Dis.* 2009; 2:33–37. [PubMed: 21694919]
37. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol.* 2011; 6:2662–2668. [PubMed: 21959598] [This study uses an inception cohort of older patients with new atrial fibrillation and compares new use of warfarin with nonuse of this drug. Whereas warfarin was associated with increased risk of hemorrhagic stroke, no association was found with ischemic stroke risk.]
38. Veeger NJ, Piersma-Wichers M, Tijssen JG, et al. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. *Br J Haematol.* 2005; 128:513–519. [PubMed: 15686461]
39. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet.* 2010; 376:975–983. [PubMed: 20801496]

40. Rose AJ, Hylek EM, Ozonoff A, et al. Patient characteristics associated with oral anticoagulation control: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *J Thromb Haemost*: JTH. 2010; 8:2182–2191.
41. Yang F, Xu X, Winkelmayer WC, et al. Warfarin use and bleeding risk in veterans with incident atrial fibrillation and severe chronic kidney disease: the TREAT-AF Study [abstract]. *Heart Rhythm*. 2012; 9:S2922012.
42. Turakhia MP. Quality of stroke prevention care in atrial fibrillation: many moving targets. *Circ Cardiovasc Qual Outcomes*. 2011; 4:5–8. [PubMed: 21245458]
43. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009; 361:1139–1151. [PubMed: 19717844]
44. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365:883–891. [PubMed: 21830957]
45. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011; 365:981–992. [PubMed: 21870978]
46. [6 December 2011] European Medicines Agency Updates on Safety of Pradaxa (Press Release). http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117818.pdf.
47. Australian Government Department of Health and Ageing Therapeutic Goods Administration. [7 December 2011] Dabigatran (Pradaxa): risk of bleeding relating to use. <http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm>.
48. Australian Government Department of Health and Ageing Therapeutic Goods Administration. [7 December 2011] Dabigatran (Pradaxa) & the risk of bleeding: new recommendations for monitoring kidney function. <http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111103.htm>.
49. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet*. 2008; 47:285–295. [PubMed: 18399711]
50. Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011; 32:2387–2394. [PubMed: 21873708]
51. Quinn RR, Naimark DM, Oliver MJ, Bayoumi AM. Should hemodialysis patients with atrial fibrillation undergo systemic anticoagulation? A cost-utility analysis. *Am J Kidney Dis*. 2007; 50:421–432. [PubMed: 17720521]

KEY POINTS

- Atrial fibrillation is common in patients undergoing chronic hemodialysis, but few of these patients receive oral anticoagulation with warfarin.
- No randomized trials have studied the efficacy and safety of oral anticoagulation in hemodialysis patients with atrial fibrillation.
- Few observational studies have studied this clinical question and none have found net benefits from oral anticoagulation using warfarin.
- Large efficacy trials of several newer anticoagulants did not include any dialysis patients.
- No general recommendations in favor of oral anticoagulation in hemodialysis patients with atrial fibrillation can be made at this point.

Table 1

Features and findings from three recent cohort studies testing the effectiveness of warfarin in hemodialysis patients with atrial fibrillation

Study	Population	Atrial fibrillation	Warfarin	Ischemic stroke	Hemorrhagic stroke	Any stroke	Mortality
Chan <i>et al.</i> [14]	Patients newly admitted to an outpatient clinic of a large US dialysis provider in 2003-2004 and who had initiated HD within 30 days.	Prevalent ('preexisting'), documented in electronic medical record of dialysis provider prior to start of HD in their facility. $N = 1671$ (all); $N = 1400$ (PS)	Any recorded use within 90 days from HD initiation; additional analyses among warfarin users by INR levels.	All patients: HR = 1.81 (1.12-2.92)	All patients: HR = 2.22 (1.01-4.91)	All patients: HR = 1.93 (1.29-2.90); PS-matched: HR = 2.00 (1.32-3.04); higher INR levels were associated with higher risk of any stroke.	All patients: HR = 1.10 (0.94-1.30); PS-matched: HR = 1.10 (0.93-1.30); no difference in risk of hospitalized bleeding.
Wizemann <i>et al.</i> [13]	Representative samples of HD patients in the participating countries of the Dialysis Outcomes and Practice Patterns Study; DOPPS I (1996-2001) and II (2002-2004).	Patients with previously reported ('preexisting') atrial fibrillation ('yes' or 'suspected' checked on the medical questionnaire). $N = 3245$ (all)	Not specified in methods section. Appears to be prevalent use.	NA (type of stroke was not ascertained)	NA (type of stroke was not ascertained)	All patients, by age stratum: age <65 years: HR = 1.29 (0.45-3.68); age 65-75 years: HR = 1.35 (0.69-2.63); age >75 years: HR = 2.17 (1.04-4.53)	Not reported. No difference in risk of hospitalized bleeding.
Winkelmayr <i>et al.</i> [37**]	Patients over age 66 years who initiated HD treatment in NJ or PA in 1994-2006 who had state-sponsored prescription drug coverage. Patients with diagnosed AF were removed.	First hospital claim with diagnosed AF. Patients with prior warfarin prescriptions were excluded. Patients had to survive >30 days from discharge. $N = 2313$ (all); $N = 1185$ (PS)	New warfarin prescription filled within 30 days from discharge.	PS-matched: HR = 0.92 (0.61-1.37)	PS-matched: HR = 2.38 (1.15-4.96)	PS-matched: HR = 1.38 (1.15-4.96)	PS-matched: HR = 1.06 (0.90-1.24); no difference in risk of gastrointestinal bleed

AF, atrial fibrillation; DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, hemodialysis; HR, hazard ratio (warfarin non-use was the referent in all analyses); INR, international normalized ratio; PS, propensity score. Reported HRs were from multivariable-adjusted ('all patients') or propensity score-matched Cox models.