Use of Oral Anticoagulation in the Management of Atrial Fibrillation in Patients with ESRD: Con

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Abstract

Among patients with atrial fibrillation, prophylaxis for stroke prevention with the use of anticoagulation is well established in the general population. A number of randomized controlled trials and evidence-based risk prediction tools clearly delineate the benefit and risks of therapy. Despite the high incidence of atrial fibrillation in the late stage CKD and ESRD populations, little high quality evidence exists in these populations. Is it appropriate then to extrapolate findings from the general population to those with CKD/ESRD? In our view, too much uncertainty exists regarding proof of efficacy with clear signals of harm. Routine anticoagulation for stroke prevention in atrial fibrillation is not recommended for the majority of CKD and ESRD patients.

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Introduction

Clinicians are faced with a difficult conundrum when deciding whether to prescribe anticoagulants for stroke prevention in kidney disease patients with atrial fibrillation. In the general population, the use of anticoagulants is well established by multiple, large randomized controlled trials. Furthermore, validated predictive scores exist that aid in identifying patients who will benefit the most (congestive heart failure, hypertension, anemia, diabetes mellitus and stroke [CHADS2], CHA2DS2-VASc) and who is at the highest risk of hemorrhagic complications (ORBI, HEMMORHAGE) (Table 1). This allows for informed decision-making regarding the risks and benefits of therapy. However, should the clinician extrapolate these data to patients with CKD/ESRD? Although reasonable, the nephrology literature contains numerous studies of therapies in the general population that did not work in CKD/ESRD (for example, renin angiotensin-aldosterone system blockade in dialysis patients to prevent cardiovascular outcomes). We argue that extrapolating the role of anticoagulation for stroke prevention in kidney disease patients with atrial fibrillation is currently not warranted. This review will discuss the following: (*1*) the unclear evidence for efficacy and significant limitations of the literature, (*2*) the large risk of complications related to therapy, (*3*) the inability to predict who should receive therapy, (*4*) the uncertainty of physicians, and (*5*) alternatives to warfarin. The discussion will be primarily focused on dialysis patients; however, summaries of studies in late stage CKD (stage 4/5) will be presented.

Is Warfarin Effective in Preventing Ischemic Strokes?

To date, randomized controlled trials assessing the efficacy and safety of warfarin in atrial fibrillation have systematically excluded patients with late stage CKD and those requiring RRT (1). As such, the entire evidence is based on observational studies; a few of which are small prospective studies and the majority retrospective administrative database studies. A selection of studies are summarized in Tables 2 and 3 (2–10).

Overall, the outcomes for dialysis patients on anticoagulants for stroke prophylaxis in atrial fibrillation seem conflicting. Chan *et al.* (7) retrospectively examined 1671 incident hemodialysis patients with atrial fibrillation, and found an increased risk of stroke (hazard ratio [HR], 1.93; 95% confidence interval [95% CI], 1.29 to 2.90) associated with warfarin use compared with nonuse. Similar results were reported by other investigators (3,4,6). In contrast to these negative studies, Olesen *et al.* (5) reported in patients taking warfarin the HR for stroke or systemic thromboembolism was 0.44 (95% CI, 0.26 to 0.74). The majority of studies to date have focused on hemodialysis patients, with a few including peritoneal dialysis patients (3,5,11). A recent systematic review and meta-analysis of observational studies of warfarin and atrial fibrillation in CKD/ESRD included 13 publications from 11 cohorts (six retrospective and five prospective) including >48,500 total patients with >11,600 warfarin users (12). In patients with atrial fibrillation and ESRD, warfarin did not decrease the risk of stroke (HR, 1.12; 95% CI, 0.69 to 1.82; $P=0.65$) or that of death (HR, 0.96; 95% CI, 0.81 to 1.13; $P=0.60$) but was associated with a higher risk of major bleeding (HR, 1.30; 95% CI, 1.08 to 1.56; $P=0.01$).

These findings seem to differ from those with late stage CKD where warfarin use appears to reduce stroke risk. In incident atrial fibrillation patients, Banerjee *et al.* (9) noted a 50% relative risk reduction for the composite of stroke/thromboembolism/all-cause mortality with vitamin K antagonist use across eGFR categories. Similar findings were reported by Carrero *et al.* (8) in CKD patients with atrial fibrillation postmyocardial infarction and by Olesen *et al.* (5). As the risk of stroke,

Table 1. Atrial fibrillation stroke risk score and bleeding risk score acronyms

Stroke Risk Scores

$CHADS_2$
- Congestive heart failure
- Hypertension
- Age ≥75 years
- Diabetes mellitus
- Stroke or transient ischemic attack

$CHADS_2$-VASc
- Congestive heart failure
- Hypertension
- Age ≥75 years
- Diabetes mellitus
- Stroke or transient ischemic attack
- Vascular disease
- Age 65-74 years
- Sex category

R_2CHADS_2
- Renal dysfunction
- Congestive heart failure
- Hypertension
- Age ≥75 years
- Diabetes mellitus
- Stroke or transient ischemic attack

Bleeding Risk Scores

OBRI
(Outpatient Bleeding Risk Index)
- Age≥65
- History of stroke
- History of gastrointestinal bleeding
- One or more of the following
  - Recent myocardial infarction
  - Hematocrit <30%
  - Serum creatinine >1.5 mg/dL
  - Diabetes mellitus

$HEMORR_2HAGES$
- Hepatic or renal disease
- Ethanol abuse
- Malignancy
- Older age (>75 years)
- Reduced platelet count or function
- Rebleeding risk (history of prior bleed)
- Hypertension
- Anemia
- Genetic factors
- Excessive fall risk
- Stroke

HAS-BLED
- Hypertension
- Abnormal renal and/or hepatic function
- Stroke
- Bleeding tendency/predisposition
- Labile INR on warfarin
- Elderly (age >65 years)
- Drugs (aspirin or NSAIDs) and/or alcohol

hemorrhage, and atrial fibrillation differ substantially between CKD and dialysis patients, we must be cautious in extrapolating findings between the groups.

Several limitations of these studies render the interpretation of the results problematic. Administrative data has considerable issues related to data quality and accuracy (13). Studies that define CKD by International Classification of Diseases 9/10 codes are prone to misclassification as validation studies have reported positive predictive values consistently <50% (5,11,14). Further misclassification of AKI as CKD may occur in studies that used a single serum creatinine to define CKD (11,12,15). Issues regarding outcome ascertainment exist for ischemic stroke as International Classification of Diseases codes have a variable positive predictive value for ischemic strokes (range 46%–94%) (16). Furthermore, the timing of ischemic stroke events may be uncertain. A body of evidence is now emerging demonstrating up to 50% of dialysis patients experience silent cerebral infarcts with no clinical stroke history (17). Imaging may detect the presence of these silently accruing cerebral infarcts and they may erroneously be attributed to a lack of anticoagulation. Numerous studies are subject to an incident/prevalent bias (3,5,6,11). Many studies define the onset of atrial fibrillation during a hospital admission thereby missing the possible "true" onset and disease diagnosis that may have occurred as an outpatient. The timing matters as anticoagulants may have been prescribed and possible outcomes (transient ischemic attack/hemorrhage) already have taken place. No studies account for compliance with warfarin use and maintenance of therapeutic range international normalized ratio (INR). Other important confounders are often missing including the effect of proteinuria, vascular access, and receipt of heparin with hemodialysis. Lastly, warfarin therapy was not randomly allocated. Patients prescribed warfarin are selectively healthier than those with atrial fibrillation not treated with warfarin. For example, in the study by Carrero *et al.* mortality occurred in 17.5% (n=924) patients treated with warfarin compared with 23.3% (n=4434) not treated with warfarin (8). At first glance, this seems explainable by the prevention of ischemic strokes in the treatment group, thereby leading to a decrease in mortality. However, the mortality reduction is much larger than the number of strokes prevented, suggesting a selection bias in the treatment allocation where healthier patients receive warfarin. A similar observation is clear in the study by Banerjee *et al.* (9).

Taken together, the evidence for the efficacy of anticoagulation therapy is prone to considerable bias. Nonrandom allocation of warfarin, misclassification, nonvalidated data definitions, and lack of important confounders render the results difficult to interpret and not suitable for clinical decision and application.

What Are the Risks?

Risk of Bleeding

A growing body of evidence suggests the risk of bleeding is higher in CKD/ESRD (summarized in Tables 4 and 5). In a recent administrative data study of >500,000 adults with CKD, the risk of major hemorrhage increased in a

Table 2. Efficacy of warfarin in preventing ischemic strokes in CKD patients with atrial fibrillation

Study	Country	Design	*N*	Adjusted HR for Ischemic Stroke (95% CI)	Comments
Banerjee *et al.*, 2014 (9)	France	Retrospective	5912 (2982 with eGFR<60 ml/min per 1.73 m^2 and 1550 on warfarin)	0.79 (0.44 to 1.42)[a]	1) Proteinuria data not available. 2) Small number of patients with eGFR≤30 ml/min per 1.73 m^2.
Carrero *et al.*, 2014 (8)	Sweden	Prospective	24317 (5292 on warfarin)	eGFR>30–60 ml/min per 1.73 m^2: 0.73 (0.66 to 0.80); eGFR>15–30 ml/min per 1.73 m^2: 0.84 (0.70 to 1.02); eGFR≤15 ml/min per 1.73 m^2: 0.57 (0.37 to 0.86)	1) Postmyocardial infarct cohort so results may not be generalizable. 2) GFR was determined by only one creatinine value. Potential for misclassification. 3) No INR data. 4) No data on duration of warfarin therapy or discontinuation rate. 5) Short follow-up 1 yr.
Lai *et al.*, 2009 (10)	United States	Retrospective	399 (232 on warfarin)	0.71 (0.43 to 1.16)[a]	1) Unclear if incident atrial fibrillation population was studied. 2) Hemodialysis patients were grouped together with other CKD stages.
Olesen *et al.*, 2012 (5)	Denmark	Retrospective	3587 (609 on warfarin)	0.84 (0.69 to 1.01)	1) CKD identified by ICD code. 2) GFR was determined by only one creatinine value. Potential for misclassification. 3) No INR data. 4) Unable to differentiate CKD stages.

HR, hazard ratio; 95% CI, 95 % confidence interval; INR, international normalized ratio; ICD, International Classification of Diseases.
[a]Hazard ratio taken from reference Dahal *et al*. (12).

Table 3. Efficacy of warfarin in preventing ischemic strokes in ESRD patients with atrial fibrillation

Study	Country	Design	*N*	Adjusted HR for Ischemic Stroke (95% CI)	Comments
Shen *et al.*, 2015 (2)	United States	Retrospective	12284 (1838 warfarin users)	0.73 (0.44 to 1.20)	1) Incident atrial fibrillation. 2) INR achieved was not reported. 3) 69.7% of users were off drug 1 yr after initiation.
Shah *et al.*, 2014 (3)	Canada	Retrospective	1626 (756 warfarin users)	1.14 (0.78 to 1.67)	1) Unclear if nonvalvular AF was excluded. 2) Included patients >65 yr.
Genovesi *et al.*, 2014 (4)	Italy	Prospective	290 (134 on warfarin)	0.12 (0.00 to 3.59)	1) INR variability included. 2) Small number of patients.
Olesen *et al.*, 2012 (5)	Denmark	Retrospective	901 at baseline, 1378 during the study period (178 on warfarin)	0.44 (0.26 to 0.74)	1) Studied incident atrial fibrillation. 2) No INR data.
Winkelmayer *et al.*, 2011 (6)	United States	Retrospective	2313 (warfarin in 249)	0.92 (0.61 to 1.37)	1) Studied incident atrial fibrillation in patients 66 yrs and older. 2) Warfarin users were less frail.
Chan *et al.*, 2009 (7)	United States	Retrospective	1671 (508 on warfarin)	1.93 (1.29 to 2.90)	1) Studied incident hemodialysis patients with preexisting atrial fibrillation. Used propensity score matching and time-varying analysis.

HR, hazard ratio; 95% CI, 95 % confidence interval; INR, international normalized ratio; AF, atrial fibrillation.

graded fashion with declining eGFR and increasing albuminuria. The 3-year cumulative incidence of hemorrhage increased 20-fold across declining eGFR and increasing urine albumin to creatinine ratio groupings (18). In contrast, a few authors found no increased hemorrhage risk (11,12). Inconsistency in the CKD evidence is likely based on variable definitions of hemorrhage, short durations of follow-up, and intention-to-treat as opposed to as-treated analysis.

The risk of hemorrhage in ESRD is more clear and consistent. Overall, roughly one in seven incident hemodialysis patients has a major hemorrhagic event requiring hospitalization within the first 3 years of dialysis initiation (19). Among warfarin users with atrial fibrillation, Olesen *et al.* reported an HR of major hemorrhage on warfarin of 2.70 (95% CI, 2.38 to 3.07) (5) with similar findings by other investigators (2–4,6). Of particular concern is the increased risk of intracranial hemorrhage, which confers an especially poor prognosis. Both Winkelmayer *et al.* (6) and Shen *et al.* (2) report >2.5-fold increase in the risk of intracranial hemorrhage with warfarin usage (2,6).

The risk of major hemorrhage after warfarin initiation is heterogeneous with an increased risk in the initial few weeks after starting therapy (20). In a population-based study, the risk of major bleeding in the first 30 days after warfarin initiation had an adjusted incidence rate ratio of 10.3 (95% CI, 2.3 to 45.5) for eGFR<15 ml/min per 1.73 m^2 compared with eGFR>90 ml/min per 1.73 m^2 (20). The majority of studies define incident atrial fibrillation upon hospitalization, thereby possibly missing bleeding events for patients initiated on anticoagulants in the outpatient setting and significantly underestimating the risk.

An emerging cause of hemorrhage in the CKD/ESRD population is vitamin K deficiency and INR variability (4,21). Malnutrition, frequent antibiotic exposure, and chronic illness are proposed mechanisms of vitamin K deficiency in CKD/ESRD (21,22). This has led to poorer anticoagulation control as assessed by the proportion of out-of-range INRs (22,23). Limdi *et al.* examined patients with CKD stage 4/5 and found they required significantly lower warfarin dosages (P=0.001), spent less time with their INR within the target range (P=0.05), and were at a higher risk for over-anticoagulation (INR>4; P=0.05), compared with patients with no, mild, or moderate CKD (22).

An interesting entity termed anticoagulant-related nephropathy has recently been described with warfarin use. Excessive anticoagulation coexists with AKI secondary to glomerular hemorrhage and tubular obstruction directly related to red blood cells. The presumed diagnosis of warfarin-related nephropathy is more common in CKD, is associated with higher mortality, and may accelerate ESRD (24,25).

Vascular Calcification and Calcific Uremic Arteriopathy

Calcific uremic arteriopathy, or calciphylaxis, is a rare disorder characterized by medial calcifications of arteries leading to painful, ulcerative skin lesions and is associated with warfarin therapy (26–30). The arrest of progression of lesions has been reported after switching from warfarin to heparin (26). Matrix GLA protein is an inhibitor of calcification in the arterial wall whose activity is inhibited by warfarin (31,32) This confers "biologic plausibility" for the hypothesis (33,34).

Can We Accurately Predict in CKD/ESRD Benefit and Harm from Warfarin Prophylaxis?

To date, numerous risk prediction scores for stroke and bleeding have been developed in the general population but few have been evaluated in CKD/ESRD (Table 6). The original CHADS2 score had excellent discrimination in predicting those who will go on to develop stroke from those who will not (c-statistic 0.82) (35). However, they are much less accurate in predicting stroke among those with CKD and ESRD, with c-statistics of 0.64 and 0.61–0.68, respectively (36–39). A modified risk formula, the R2CHADS2, which includes creatinine clearance, also is relatively poor at discrimination (c-statistic 0.63–0.67) (38,39). The problem lies in the factors included in the risk scores themselves. For example, applying the CHA2DS2-VASc score to a dialysis patient would require an accurate definition of congestive heart failure (How to distinguish from volume overload?), hypertension (Pre-, during or postdialysis? Forty-four-hour measure?), and anemia (optimal targets unknown). As these "risk factors" are ubiquitous but ill-defined in CKD/ESRD patients, almost all patients are categorized as high risk. In the study by Bonde *et al.* (9), over 90% and 80% of CKD and hemodialysis patients

Table 4. Major bleeding risk in atrial fibrillation patients with ESRD treated with warfarin

Study	Country	Design	*N*	Adjusted HR Major Bleeding (95% CI)
Shen *et al.*, 2015 (2)	United States	Retrospective	12,284 (1838 warfarin users)	GI bleeding: 1.36 (0.89 to 2.07) Hemorrhagic stroke: 1.92 (0.82 to 4.48)
Shah *et al.*, 2014 (3)	Canada	Retrospective	1626 (756 warfarin users)	1.44 (1.13 to 1.85)
Genovesi *et al.*, 2014 (4)	Italy	Prospective	290 (134 on warfarin)	3.96 (1.15 to 13.68)
Olesen *et al.*, 2012 (5)	Denmark	Retrospective	901 (178 on warfarin)	2.70 (2.38 to 3.07)
Winkelmayer *et al.*, 2011 (6)	United States	Retrospective	2313 (warfarin in 249)	GI bleeding: 0.90 (0.60 to 1.35) Hemorrhagic stroke: 2.63 (1.01 to 6.88)

HR, hazard ratio; 95% CI, 95 % confidence interval; GI, gastrointestinal.

Table 5. Major bleeding risk in atrial fibrillation in patients with CKD treated with warfarin

Study	Country	Design	*N*	Adjusted HR Major Bleeding (95% CI)
Banerjee *et al.*, 2014 (9)	France	Retrospective	5912 (2982 with eGFR<60 ml/min per 1.73 m^2 and 1550 on warfarin)	0.96 (0.55 to 1.67)
Carrero *et al.*, 2014 (8)	Sweden	Prospective	24317 (5292 on warfarin)	eGFR>30–60 ml/min per 1.73 m^2: 1.08 (0.89 to 1.32) eGFR>15–30 ml/min per 1.73 m^2: 0.93 (0.60 to 1.44)
Olesen *et al.*, 2012 (5)	Denmark	Retrospective	3587 (609 on warfarin)	2.24 (2.10 to 2.38)

HR, hazard ratio; 95% CI, 95 % confidence interval.

were deemed high risk (score of 2 or greater) with a recommendation to initiate anticoagulation. Figure 1 shows receiver operating characteristic curves of CHADS2 and CHA2DS2-VASc scores in predicting ischemic stroke in the ESRD population. Conversely, current bleeding risk scores seem to underestimate the risk of bleeding when applied to CKD/ESRD. The HAS-BLED score places only 28% of CKD and 20% of hemodialysis patients at high risk (3 or greater), compared with 18% of the general population (11).

Unclear What to Do? You Are Not Alone

The lack of clarity in the existing evidence has led to considerable uncertainty among physicians. A survey of Canadian nephrologists found >70% of respondents agree with clinical equipoise regarding warfarin use and a similar proportion would be willing to enroll patients in a clinical trial of warfarin versus placebo (40). Few nephrologists would prescribe warfarin when a patient presented with both a high stroke risk and a high bleeding risk (CHAD S2=5, CHA2DS2VASc=8) and a risk for falls (42). Also, that most respondents would discontinue warfarin use in this scenario highlighted the complexity of decision-making and uncertainty (40). The most recent guidelines from the Canadian Cardiovascular Society suggested patients with ESRD (eGFR<15 ml/min per 1.73 m^2) not routinely receive anticoagulation or acetylsalicyclic acid for stroke prevention in atrial fibrillation (41). This is consistent with the KDIGO recommendation against the use of routine anticoagulation of dialysis patients with atrial fibrillation for primary prevention of stroke (42).

What Are the Alternatives to Warfarin?

The newer oral anticoagulants (NOACs) dabigatran, apixaban, rivaroxaban, and edoxaban are excreted renally to a variable extent. Randomized controlled trials that have examined their efficacy and safety in atrial fibrillation have excluded patients with advanced CKD. Analysis of data from the trials that included patients with CKD shows that the risk of stroke or systemic embolism in patients with creatinine clearance 30–49 ml/min is significantly lower with NOACs than conventional agents (3.9% versus 5.3%; odds ratio, 0.72; 95% CI, 0.57 to 0.92; absolute risk reduction, 1.4%; number needed to treat, 71) (43). In a recent meta-analysis of nine trials, Raccah *et al.* observed that NOACs were associated with a significantly decreased risk of major bleeding in patients with estimated creatinine clearance 50–80 ml/min (risk ratio, 0.84; 95% CI, 0.78 to 0.91), and a nonsignificant decrease in the risk of major bleeding in patients with estimated creatinine clearance <50 ml/min (risk ratio, 0.80; 95% CI, 0.63 to 1.01) when compared with use of warfarin (44). They have been used erroneously in the dialysis population with poor outcomes (45). In summary, although they may be a safer alternative to warfarin in patients with milder CKD, the safety and efficacy of NOACs in late stage CKD and dialysis patients remain unknown.

Table 6. Risk prediction scores for stroke in patients with CKD

Study	Score	Population Studied	c-Statistic
Banerjee *et al.*, (38)	CHADS2	CKD	0.64 (0.61–0.67)
Banerjee *et al.*, (38)	CHA2DS2-VASc	CKD	0.64 (0.62–0.67)
Chao *et al.*, (39)	CHADS2	ESRD undergoing RRT	0.608
Chao *et al.*, (39)	CHA2DS2-VASc	ESRD undergoing RRT	0.682
Piccini *et al.*, (36)	R2CHADS2	CKD, creatinine clearance >30 ml/min	0.672 (0.651–0.692)
Bautista *et al.*, (36)	R2CHADS2	CKD, eGFR<30 ml/min per 1.73 m^2	0.631

Values given are 95% confidence interval. C-statistic with 95% confidence interval, if available.
CHADS2, congestive heart failure, hypertension, anemia, diabetes mellitus and stroke.

Conclusions

Stroke prevention in atrial fibrillation is going to be a more commonly encountered issue as the incidence of both atrial fibrillation and CKD are on the rise. The current evidence for CKD and ESRD is based on a few observational studies with methodologic limitations. The efficacy of anticoagulation for stroke prevention, despite the use of sophisticated analytic techniques and large cohorts, is currently inconclusive. Concurrently there are clear risks of harm with anticoagulation. Application of risk scores developed in the general population is inaccurate and inappropriate among those with CKD/ESRD. Lastly, the uncertainty regarding treatment decisions is widespread among fellow nephrologists and cardiologists.

At present, there is a pressing need for a randomized controlled trial(s) in this area. We feel that, with the considerable uncertainties and risk for harm, a trial of warfarin (or NOACs after an improved understanding of their actions with an eGFR<30 ml/min per 1.73 m^2) versus placebo is warranted. Another promising therapy is left atrial appendage closure, which in early observational studies demonstrates a significant reduction in stroke and/or hemorrhage in CKD patients (46).

A conservative approach without the use of anticoagulants is warranted. The use of antiplatelet agents may represent a compromise (although untested) as they may partially mitigate the risk of stroke with a more reasonable hemorrhagic profile. If anticoagulation is to be initiated (for example on the basis of patient preferences or previous thromboembolic stroke), hemorrhagic reduction strategies such as discontinuation of antiplatelet agents, reduction in heparin use with dialysis, prophylactic proton pump inhibitor use, and the use of citrate locks for dialysis catheters should be considered. It is often in the caregivers psyche to treat or prescribe, as sitting idle is akin to doing nothing. However, in the scenario where treatment confers harm without clear benefit, often sitting idle is the most prudent therapeutic option.

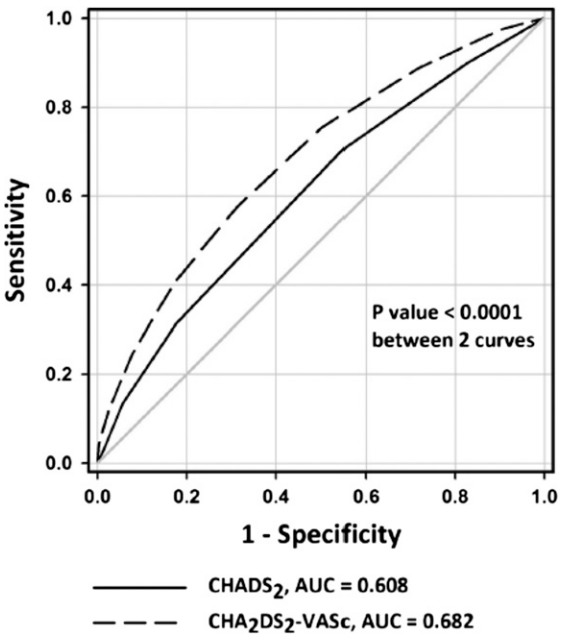

Figure 1. | **Receiver operating characteristic curves of CHADS2 and CHA2DS2-VASc scores in predicting ischemic stroke in patients with ESRD**. (Modified from Chao *et al.* reference 39, with permission). CHADS2, congestive heart failure, hypertension, anemia, diabetes mellitus and stroke.

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Disclosures

None.

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