Effect of anticoagulation therapy in older patients with chronic kidney disease and atrial fibrillation

A meta-analysis

Wenfeng He, MD, Hao Zhang, MS, Wengen Zhu, MD, Zhengbiao Xue, MS

Abstract

Background: The role of anticoagulation therapy for stroke prevention in older atrial fibrillation (AF) patients with chronic kidney disease (CKD) remains unclear. Therefore, we conducted a meta-analysis to explore the efficacy and safety of anticoagulation therapy in this population.

Methods: The Cochrane Library, PubMed, and Embase databases were systematically searched for studies reporting the effect of anticoagulation therapy in older patients with AF and CKD. The risk ratios (RRs) and 95% confidence intervals (CIs) were regarded as the risk estimates. A random-effects model selected was to evaluate the treatment outcomes. The presentations were based on the Preferred Reporting Items for reporting systematic reviews and meta-analyses statement.

Results: A total of 7 studies with 24,794 older patients with AF and CKD were included. The follow-up of the included studies ranged from 0.9 to 9.0 years. In older patients with no dialysis, compared with nonanticoagulants, anticoagulants reduced the risk of all-cause death (RR 0.66, 95% CI 0.54–0.79), but had comparable risks of ischemic stroke/transient ischemic attack (TIA, RR 0.91, 95% CI 0.46–1.79) and bleeding (RR 1.17, 95% CI 0.86–1.60). In older patients with dialysis, compared with nonanticoagulants, anticoagulants increased the risk of bleeding (RR 1.37, 95% CI 1.09–1.74), but had similar risks of ischemic stroke/TIA (RR 1.18, 95% CI 0.89–1.58) and death (RR 0.87, 95% CI 0.60–1.27).

Conclusion: Compared with nonanticoagulation, anticoagulation therapy is associated with a reduced risk of death in older AF patients with nondialysis, but an increased risk of bleeding in older patients with dialysis.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, NOAC = nonvitamin K antagonist oral anticoagulant, NOS = Newcastle–Ottawa Scale, RR = risk ratio, TIA = transient ischemic attack, VKA = vitamin K antagonist.

Keywords: anticoagulation therapy, atrial fibrillation, chronic kidney disease, dialysis, older

1. Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) are increasingly common conditions, affecting millions of people worldwide and leading to substantial morbidity and health-care expenditure.[1,2] The prevalence of AF is high in patients with CKD: approximately 18% to 20% in CKD with nondialysis[3,4] and 15% to 40% in patients with dialysis.[5,6] AF and CKD often coexist, cause, and exacerbate each other.[7,8] CKD patients with concomitant AF suffer from a worse prognosis.[9,10] In addition, a meta-analysis has shown that AF with increased mortality, allograft loss, and stroke after kidney transplantation.[11] Among patients with coexisting AF and CKD, the rates of stroke and bleeding events increase when the kidney function decreases.[12,13] A previous study[14] has shown that patients with AF and nonend-stage CKD had a 49% increased risk of stroke or systemic thromboembolism compared with AF patients without CKD; and the highest risk was observed in AF patients with end-stage CKD on dialysis. Moreover, AF patients on dialysis need routine heparin anticoagulant therapy during dialysis, which may increase the risk of bleeding. Hence, balancing the risks of thromboembolic and bleeding is a key consideration in AF patients with CKD. Recently, several studies have found that warfarin shows benefits in patients with AF and CKD.[14–16]

Older patients (aged ≥65 years) with CKD are at a high risk of AF.[15] The proportion of older patients accounts for 60% to 80% of the entire patients with AF and CKD.[14] The incidence of stroke and bleeding may increase with age in AF patients.[17,18]
However, whether anticoagulation therapy is effective and safe in patients with coexisting AF and CKD is still unclear. More recently, several studies have investigated the efficacy and safety of anticoagulation therapy in patients with AF and CKD, but these studies yield conflicting results. Therefore, we performed a meta-analysis to elucidate the efficacy and safety of anticoagulation therapy in patients with AF and CKD.

2. Methods
In this meta-analysis, the presentations were based on the Preferred Reporting Items for reporting systematic reviews and meta-analyses statement. There was no need to provide the ethical approval because this meta-analysis was performed based on the published studies.

2.1. Literature search
Using electronic retrieval methods, we systematically searched the Cochrane Library, PubMed, and Embase databases until April 2019 for studies reporting the anticoagulation therapy in older patients with AF and CKD. No language restrictions were imposed during the searches. Non-English articles were translated into English using Google’s automatic-translation software. To identify studies involving relevant participants, we performed the search with the following terms: atrial fibrillation, chronic kidney disease, renal insufficiency, renal failure, end-stage renal disease, renal replacement therapy, dialysis, hemodialysis, and peritoneal dialysis. To identify studies involving intervention, we performed the search with the following terms: oral anticoagulation, anticoagulation, warfarin, phenprocoumon, low molecular weight heparin, unfractionated weight heparin, dabigatran, rivaroxaban, apixaban, edoxaban, darexaban, betrixaban, ximelagatran, otamixaban, and argatroban. These 2 items were combined using the Boolean operator “and.” The electronic search strategy is provided in Supplementary Table 1, http://links.lww.com/MD/D293. In addition, we screened the reference lists of the review articles to identify the additional reports.

2.2. Inclusion and exclusion criteria
Studies satisfying the following criteria were included: study type, observational studies (prospective or retrospective); study subjects, older patients (≥65 years) with concomitant AF and CKD; comparisons, anticoagulation therapy (nonvitamin K antagonist oral anticoagulants [NOACs], vitamin K antagonists [VKAs], and unfractionated or low molecular weight heparin) versus nonanticoagulation therapy; and the efficacy outcomes included all-cause death and ischemic stroke/transient ischemic attack (TIA), and the safety outcome was total bleeding. Studies that enrolled patients with renal transplant or certain complications (e.g., reviews, editorials, letters, and animal studies) were excluded in this meta-analysis.

2.3. Quality assessment
The quality of the included studies was appraised using the Newcastle–Ottawa Scale (NOS) by 3 reviewers (H-WF, ZB-X, and H-Z) independently. Three reviewers (H-WF, ZB-X, and H-Z) scored the bias risk of the cohort studies in 3 domains including selection of cohorts, comparability of cohorts, and assessments of outcome. We defined studies with an NOS score ≥6 stars as moderate-to-high quality and studies with an NOS score <6 stars as low-quality.

2.4. Data extraction
The retrieved studies were screened by 2 reviewers (ZB-X and H-Z) independently. The first phase of screening was performed by reading titles and/or abstracts. The second phase of screening was to review the full text. ZB-X and H-Z reviewed the eligibility of the retrieved articles. Disagreements were settled by discussion with a third author (H-WF). Ultimately, articles meeting the eligibility criteria were included.

For each study, the extracted information included the following characteristics: name of the first author, year of publication, study design, inclusion criteria, age, proportion of male patients, total number of patients, duration of follow-up, and endpoints.

2.5. Statistical analysis
For each study, the effect measurements estimate chosen were the risk ratios (RRs) and the corresponding 95% confidence intervals (CIs). We selected a random-effects model to evaluate the treatment outcomes, which accounts for variability both within studies and between studies. The heterogeneity across the included studies was measured with an I² statistical test, where values of 25%, 50%, and 75% represent low, intermediate, and high inconsistency, respectively. In the sensitivity analysis, we excluded the included studies one by one. We performed the subgroup analysis based on dialysis versus nondialysis.

All the statistical analyses were performed using the Review Manager Version 5.3 software (Cochrane Collaboration, Copenhagen, Denmark).

3. Results
The search steps are illustrated in Figure 1. A total of 1187 potential articles (935 through PubMed, 221 through Embase, and 31 through the Cochrane Library) were identified. After duplicates were removed, 1142 records remained. Based on the screenings of the titles and/or abstracts, 1114 records were excluded, and 28 articles remained for the full-text review. Twenty-one articles were subsequently excluded because 4 studies compared the outcomes of NOACs with VKAs, 1 study did not report the outcomes of interest, and 16 studies did not report the outcomes in older AF patients with CKD. Finally, a total of 7 retrospective studies involving 24,794 participants were included in this meta-analysis.

3.1. Characteristics of included studies
The baseline characteristics of the 7 included studies are shown in Table 1. Three studies enrolled AF patients with nondialysis CKD, while 4 studies included AF patients with dialysis. Among AF patients with CKD, 9994 (40.3%) patients used anticoagulants, and 14,800 (59.7%) patients were the nonusers. The anticoagulants used were VKAs (9184, 91.9%), NOACs (726, 7.3%), and unfractionated or low molecular weight heparin (84, 0.8%). The follow-up time of the included studies ranged from 0.9 to 9.0 years. Most of the included studies were conducted in the Europe and North
America. In addition, the quality of the included studies was generally good, with an NOS score of 7 to 9 (Table 2).

3.2. Efficacy and safety of anticoagulants versus nonanticoagulants

3.2.1. Ischemic stroke/TIA. Data for ischemic stroke/TIA were available in 7 studies. As shown in Figure 2, compared with nonanticoagulation, anticoagulation therapy had a comparable risk of ischemic stroke/TIA (RR 1.06, 95% CI 0.76–1.50) in older patients with AF and CKD (Fig. 2). In view of a significant heterogeneity across the included studies ($I^2 = 88\%$), we performed the subgroup analysis based on dialysis versus nondialysis. The pooled results still showed a similar risk of ischemic stroke/TIA between anticoagulation and nonanticoagulation in patients with dialysis (RR 1.18, 95% CI 0.88–1.58) or without dialysis (RR 0.91, 95% CI 0.46–1.79).

3.2.2. All-cause death. Five studies reported the all-cause death in AF patients with CKD. As presented in Figure 3, compared with nonanticoagulation, anticoagulation therapy significantly reduced the risk of all-cause death by 38% (RR 0.72, 95% CI 0.61–0.84). In the subgroup analysis, compared with nonanticoagulation, the use of anticoagulation therapy was associated with a decreased risk of all-cause death in patients with nondialysis (RR 0.66, 95% CI 0.54–0.79), but did not reduce the risk of all-cause death in patients with dialysis (RR 0.87, 95% CI 0.60–1.27).

3.2.3. Bleeding. Compared with nonanticoagulation, anticoagulation significantly increased the risk of bleeding by 26% (RR 0.72, 95% CI 1.03–1.54; Fig. 4). In the subgroup analysis, anticoagulants increased the risk of bleeding in patients with dialysis (RR 1.37, 95% CI 1.09–1.74), but did not increase the risk of bleeding in patients with nondialysis (RR 1.17, 95% CI 0.86–1.60).

3.3. Sensitivity analysis

The aforementioned results were stable in the sensitivity analysis by excluding the included studies one by one.

4. Discussion

Anticoagulation therapy is recommended for AF patients with CKD and patients on dialysis by guidelines.[29,30] However, the role of anticoagulation therapy in older patients with AF and CKD is still ill-defined. In the current meta-analysis, we first evaluated the efficacy and safety of anticoagulation therapy in the older patients with AF and CKD. On the basis of the predefined inclusion criteria, a total of 7 studies with 24,794 participants were selected and assessed in the final analysis. Our results suggested that anticoagulation therapy reduced the risk of all-cause death in older patients with CKD and AF, but increased the bleeding risk in older AF patients with dialysis.

AF is the most common arrhythmia in CKD patients. AF and CKD coincide in many patients, as these conditions have a common pathophysiology and a number of similar risk factors. Elderly is associated with the increased risks of thromboembolism and bleeding; and therefore, elderly is included in the CHA2DS2-VASc score[31] and HAS-BLED score.[32] Moreover, older patients with CKD are easy to discontinue the use of anticoagulants because of safety concerns.[13] The benefit-risk profiles of anticoagulation therapy remain unclear in the older patients with AF and CKD.

Our results showed that compared with nonanticoagulation therapy, anticoagulation therapy had a comparable risk of ischemic stroke/TIA in older patients with AF and CKD regardless of dialysis. Among older patients with AF and CKD, the risks of thromboembolic events would increase. Furthermore, the risk of thromboembolism increases with the progression of renal function deterioration. The anticoagulant
Table 1
Clinical characteristics of the 7 included studies.

| Study design       | Renal function | Country       | User | Nonuser |
|--------------------|----------------|---------------|------|---------|
| Wizemann, 2010     | Retrospective  | International | 363  | 1881    |
| Winkelmayer, 2011  | Dialysis       | US            | 188  | 1651    |
| Shah, 2014         | Dialysis       | Canada        | 237  | 948     |
| Jun, 2017          | eGFR < 60 mL/min/1.73 m² | Canada | 756 | 3146 |
| Keskar, 2017       | Dialysis       | Canada        | 2424 | 1417    |
| Tan, 2019          | eGFR < 45 mL/min/1.73 m² | Japan | 2424 | 1651 |
| Kumar, 2018        | Dialysis       | United States | 3146 | 3146    |

- **Hypertension**
  - NA (n = 363) NA (n = 1881)
  - 82.7% (n = 237) 82.1% (n = 948)
  - 77.0% (n = 756) 75.3% (n = 3146)

- **Diabetes**
  - NA (n = 363) NA (n = 1881)
  - 60.3% (n = 237) 59.7% (n = 948)
  - 43.7% (n = 756) 45.9% (n = 3146)

- **CAD**
  - NA (n = 363) NA (n = 1881)
  - 46.8% (n = 237) 47.2% (n = 948)
  - 62.2% (n = 756) 64.5% (n = 3146)

- **Prior stroke/TIA**
  - NA (n = 363) NA (n = 1881)
  - 23.3% (n = 237) 23.0% (n = 948)
  - 8.1% (n = 756) 4.7% (n = 3146)

- **CHADS2**
  - NA (n = 363) NA (n = 1881)
  - 23.3% (n = 237) 23.0% (n = 948)

- **CHADS2VaSc**
  - NA (n = 363) NA (n = 1881)
  - 4.3% (n = 237) 4.3% (n = 948)

- **Follow-up, y**
  - 8.0 (n = 237) 8.0 (n = 948)

5. Limitations
Several limitations might affect the validity of this meta-analysis.
First, although most of the included studies adjusted for a series of confounding variables, we still could not exclude the effects of residual confounding due to the nature of observational studies. Second, the majority of patients received warfarin in our included analysis. There were no studies reporting the bleeding rates of NOAC users. Therefore, we could not compare the effects of NOACs with warfarin in older patients with AF and CKD. Third, our current analyses were limited to some outcomes including ischemic stroke/TIA, all-cause death, and bleeding. We did not assessed other outcomes such as osteoporosis (VKAs could increase the risk of osteoporotic fracture[39]). Fourth, the significant heterogeneity existed across the included studies in some comparisons. As such, we should draw a relatively conservative conclusion based on the results of the random-effects model. Further studies are still needed to confirm our results. Fifth, the protocol of this meta-analysis was not registered in PROSPERO. Nevertheless, we found no relevant protocol of this topic in PROSPERO. Finally, the time within therapeutic range of warfarin users was not considered due to the limiting data.

6. Conclusions
Based on current published studies, compared with nonanticoagulation, anticoagulation therapy is associated with a reduced risk of death in older AF patients with nondialysis, but an
Table 2
Quality assessment of the included studies.

| Study         | Selection | Outcome |
|---------------|-----------|---------|
|               | Exposure  | Nonexposed | Ascertainment | Outcome of interest | Comparability | Assessment of Outcome | Length of Follow-up | Adequacy of Follow-up | Total |
| Wizemann, 2010| ++        | +          | +             | +                 | *             | *                    | *                    | *                    | 8     |
| Winkelmayer, 2011| ++       | +          | +             | +                 | *             | *                    | *                    | *                    | 8     |
| Shah, 2014    | ++        | +          | +             | +                 | *             | *                    | *                    | *                    | 8     |
| Jun, 2017     | ++        | +          | +             | +                 | *             | *                    | *                    | *                    | 7     |
| Keskar, 2017  | ++        | +          | +             | +                 | *             | *                    | *                    | *                    | 8     |
| Tan, 2019     | ++        | +          | +             | +                 | *             | *                    | *                    | *                    | 8     |
| Kumar, 2018   | ++        | +          | +             | +                 | *             | *                    | *                    | *                    | 8     |

Asterisks represent stars used in the Newcastle–Ottawa Scale.

Figure 2. Forest plot for the outcome of ischemic stroke/TIA between anticoagulants and nonanticoagulants in older AF patients with CKD. AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, IV = inverse of the variance, SE = standard error, TIA = transient ischemic attack.

Figure 3. Forest plot for the outcome of all-cause death between anticoagulants and nonanticoagulants in older AF patients with CKD. AF = atrial fibrillation, CI = confidence interval, CKD = chronic kidney disease, IV = inverse of the variance, SE = standard error.
increased risk of bleeding in older patients with dialysis. Further high-quality prospective studies are needed to confirm our findings.

Author contributions

Data curation: Wenfeng He, Hao Zhang, Zhengbiao Xue.
Formal analysis: Hao Zhang, Zhengbiao Xue.
Investigation: Wenfeng He, Wengen Zhu, Zhengbiao Xue.
Methodology: Wenfeng He, Wengen Zhu, Zhengbiao Xue.
Software: Wenfeng He, Hao Zhang, Zhengbiao Xue.
Supervision: Zhengbiao Xue.
Validation: Wenfeng He, Wengen Zhu.
Writing – original draft: Hao Zhang, Zhengbiao Xue.
Writing – review & editing: Wenfeng He, Zhengbiao Xue.

References

[1] Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;137:e67–492.
[2] Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (Lond, Engl) 2017;390:1211–59.
[3] Soliman EZ, Prince RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). Am Heart J 2010;159:1102–7.
[4] Ananthapanyasut W, Napan S, Rudolph EH, et al. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. Clin J Am Soc Nephrol 2010;5:173–81.
[5] Goldstein BA, Arce CM, Hlatky MA, et al. Trends in the incidence of atrial fibrillation in older patients initiating dialysis in the United States. Circulation 2012;126:2293–301.
[6] Turakhia MP, Blankstein PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Eur Heart J 2018;39:2314–25.
[7] Bansal N, Xie D, Tao K, et al. Atrial fibrillation and risk of ESRD in adults with CKD. Clin J Am Soc Nephrol 2016;11:1189–96.
[8] Watanabe H, Watanabe T, Sasaki S, et al. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J 2009;158:629–36.
[9] Hwang HS, Park MW, Yoon HE, et al. Clinical significance of chronic kidney disease and atrial fibrillation on morbidity and mortality in patients with acute myocardial infarction. Am J Nephrol 2014;40:345–52.
[10] Bansal N, Fan D, Hsu CY, et al. Incident atrial fibrillation and risk of death in adults with chronic kidney disease. J Am Heart Assoc 2014;3:592.
[11] Thongprayoon C, Chokesuwattansuk R, Bathini T, et al. Epidemiology and prognostic importance of atrial fibrillation in kidney transplant recipients: a meta-analysis. J Clin Med 2018;7.
[12] 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;123:2946–53.
[13] Molnar AO, Bota SE, Garg AX, et al. The risk of major hemorrhage with CKD. J Am Soc Nephrol 2016;27:2825–32.
[14] Olesen JB, Lip GY, Kampfer AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. New Engl J Med 2012;367:625–33.
[15] Bonde AN, Lip GY, Kamper AL, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. J Am Coll Cardiol 2014;64:2471–82.
[16] Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. JAMA 2014;311:1919–28.
[17] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
[18] Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689–96.
[19] Wizemann V, Tong L, Satayathum S, et al. Atrial fibrillation in hemo dialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int 2010;77:1098–106.
[20] Winkelmayer WC, Liu J, Setoguchi S, et al. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. Clin J Am Soc Nephrol 2011;6:2662–8.
[21] Shah M, Avgil Tasdok M, Jackevicuus CA, et al. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129:1196–203.
[22] Jun M, James MT, Ma Z, et al. Warfarin initiation, atrial fibrillation, and kidney function: comparative effectiveness and safety of warfarin in older adults with newly diagnosed atrial fibrillation. Am J Kidney Dis 2017;69:734–43.
[23] Kestkar V, McArthur E, Wald R, et al. The association of anticoagulation, ischemic stroke, and hemorrhage in elderly adults with chronic kidney disease and atrial fibrillation. Kidney Int 2017;91:928–36.
[24] Tan J, Bae S, Segal JB, et al. Warfarin use and the risk of stroke, bleeding, and mortality in older adults on dialysis with incident atrial fibrillation. Nephrology (Carlton, Vic) 2019;24:234–44.
Kumar S, de Lusignan S, McGovern A, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. BMJ (Clin Res Ed) 2018;360:k342.

Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clin Res Ed) 2009;339:b2700.

Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.

Zhu W, Wan R, Liu F, et al. Relation of body mass index with adverse outcomes among patients with atrial fibrillation: a meta-analysis and systematic review. J Am Heart Assoc 2016;5:e4006.

January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:2071–104.

Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.

Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263–72.

Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093–100.

Winkelmayr WC, Turakhia MP. Warfarin treatment in patients with atrial fibrillation and advanced chronic kidney disease: sins of omission or commission? JAMA 2014;311:913–5.

van Gorp RH, Schurgers LJ. New insights into the pros and cons of the clinical use of vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs). Nutrients 2015;7:9538–57.

Sozio SM, Armstrong PA, Coresh J, et al. Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. Am J Kidney Dis 2009;54:468–77.

Banerjee A, Fauchier L, Vourc'h P, et al. A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest 2014;145:1370–82.

Huang MJ, Wei RB, Wang Y, et al. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. BMJ Open 2017;7:e014294.

Ng KP, Edwards NC, Lip GY, et al. Atrial fibrillation in CKD: balancing the risks and benefits of anticoagulation. Am J Kidney Dis 2013;62:615–32.

Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. J Am Coll Cardiol 2011;57:1339–48.

Gage BF, Birman-Deych E, Radford MJ, et al. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med 2006;166:241–6.