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Original Article



ORIGINAL ARTICLE

# Anticoagulation in patients with end-stage kidney disease and atrial fibrillation: a national population-based study

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## ABSTRACT

**Background.** The prevalence of atrial fibrillation (AF) in patients with end-stage kidney disease (ESKD) is high and increasing. However, evidence regarding oral anticoagulant (OAC) use in these patients is insufficient and conflicting.
**Methods.** This retrospective cohort study included patients in the Korea National Health Insurance System diagnosed with AF after ESKD onset from January 2007 to December 2017. The primary outcome was all-cause death. Secondary outcomes were ischaemic stroke, hospitalization for major bleeding and major adverse cardiovascular events (MACE). Outcomes were compared between OAC users and non-users using 6-month landmark analysis and 1:3 propensity score matching (PSM).
**Results.** Among patients with ESKD and AF, the number of prescribed OACs increased 2.3-fold from 2012 ($n = 3579$) to 2018 ($n = 8341$) and the proportion of direct OACs prescribed increased steadily from 0% in 2012 to 51.4% in 2018. After PSM, OAC users had a lower risk of all-cause death {hazard ratio [HR] 0.67 [95% confidence interval (CI) 0.55–0.81]}, ischaemic stroke [HR 0.61 (95% CI 0.41–0.89)] and MACE [HR 0.70 (95% CI 0.55–0.90)] and no increased risk of hospitalization for major bleeding [HR 0.99 (95% CI 0.72–1.35)] compared with non-users. Unlike warfarin, direct OACs were associated with a reduced risk of all-cause death and hospitalization for major bleeding.
**Conclusions.** In patients with ESKD and AF, OACs were associated with reduced all-cause death, ischaemic stroke and MACE.

**Keywords:** anticoagulation, atrial fibrillation, bleeding, death, stroke

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## KEY LEARNING POINTS

**What was known:**

- There is insufficient evidence to support recommending warfarin or direct oral anticoagulants for stroke prevention in patients with end-stage kidney disease (ESKD) and atrial fibrillation (AF).

**This study adds:**

- For patients with ESKD and AF who had a $CHA_2DS_2$-VASc score ≥1 (men) or ≥2 (women), the use of oral anticoagulants was associated with a lower risk of all-cause death, ischaemic stroke and major adverse cardiovascular events, without an increased risk of hospitalization for major bleeding.

**Potential impact:**

- Anticoagulation may be beneficial for patients with ESKD and AF who had a $CHA_2DS_2$-VASc score ≥1 (men) or ≥2 (women).

## INTRODUCTION

The prevalence of atrial fibrillation (AF) in patients with end-stage kidney disease (ESKD) has been increasing, with a 3-fold increase from 3.5% in 1992 to 10.7% in 2006 in patients receiving haemodialysis (HD) [1, 2]. Furthermore, patients with ESKD have an elevated risk of bleeding and thromboembolic events [3, 4]. Although the $CHA_2DS_2$-VASc score [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischaemic attack (doubled), vascular disease, age 65–74, female] has not been validated in patients with ESKD, current guidelines recommend oral anticoagulants (OACs) for stroke prevention based on this score [5–8].

Recent meta-analyses have shown no definite benefits of preventive warfarin therapy in patients with ESKD who have AF [9–11]. Thus the Kidney Disease: Improving Global Outcomes (KDIGO) 2018 conference concluded that there is insufficient high-quality evidence to recommend warfarin or direct OACs (DOACs) for stroke prevention in this patient population [5]. However, based on observational studies and the consensus statement, the rate of warfarin anticoagulation in patients with ESKD and AF gradually decreased from 2007 to 2013 [12].

DOACs are partially eliminated by the kidneys, with renal clearance accounting for 80, 27, 50 and 35% of the elimination of dabigatran, apixaban, edoxaban and rivaroxaban, respectively [13]. These medications may therefore accumulate in patients with ESKD, potentially increasing the risk of bleeding. Nevertheless, the proportion of DOAC prescriptions among all OAC prescriptions has gradually increased in patients with ESKD and AF. In 2018, the number of patients prescribed DOACs surpassed those treated with warfarin [14, 15]. A few retrospective cohort studies based on US Renal Data System data and a single-centre study from Korea showed that OAC use in patients with ESKD and AF was associated with a lower mortality rate, compared with no anticoagulation, although selection bias was a potential limitation of these studies [16, 17].

We investigated the hypothesis that OACs may reduce the risk of mortality and ischaemic stroke without increasing the likelihood of major bleeding in patients with ESKD and AF. To accomplish this, we used nationwide claims-based cohort data that included all patients who underwent renal replacement therapy in South Korea during the study period.

## MATERIALS AND METHODS

### Data source and study population

In this study we analysed data from the National Health Insurance Service (NHIS) of Korea database. The NHIS is a mandatory national health insurance system provided by the Korean government covering almost the entire population (97%) of the Republic of Korea. This data source has been widely validated and used in many other studies. The NHIS provides data with approval (NHIS-2020-1-467) through the Korean National Health Insurance Sharing Service (http://nhiss.nhis.or.kr). Details of the codes used to define each diagnosis, procedure and drug in this study are shown in Supplementary Tables S1 and S2.

Figure 1 depicts a flowchart describing the study population. We identified 21 468 patients in the NHIS database with a diagnosis of AF after initiating renal replacement therapy between 1 January 2007 and 31 December 2017. We first excluded 12 485 patients for the following reasons: contraindication to OAC therapy (e.g. mitral valve stenosis), OAC prescribed for a non-AF cause (e.g. systemic embolism, deep vein thrombosis, cancer, post-arthroplasty surgery) or a low risk of stroke ($CHA_2DS_2$-VASc score of 0 in men or 0–1 in women). As shown in Supplementary Fig. S1, among patients with ESKD who were diagnosed with AF after initiating renal replacement therapy, OAC therapy was initiated >6 months after the AF diagnosis in almost 40% of patients with ESKD who were prescribed an OAC after being diagnosed with AF. A prolonged time between AF diagnosis and initiation of anticoagulation increases the likelihood that the OAC was prescribed for a non-AF indication. Therefore, we used 6-month landmark analysis to overcome selection bias. We also excluded 2671 patients who developed an outcome (died or were diagnosed with an ischaemic stroke) between the cohort entry and landmark dates, were not consistently receiving an OAC [medication possession ratio (MPR) <80%] or were consistently prescribed an OAC beginning >6 months after being diagnosed with AF. The MPR was calculated as follows: MPR = 100 × {[number of days a prescribed medication was obtained (i.e. possessed) during the treatment period]/[total number of days in the treatment period]}.

The final OAC user group consisted of 562 patients who were prescribed an OAC after being diagnosed with AF. Specifically, this group included patients who were prescribed more than two prescriptions for OACs or an OAC prescribed for a total of >30 days) within 6 months of the AF diagnosis and whose MPR was ≥80%. The initial OAC non-user group included 5750 patients with AF who were not prescribed an OAC (they either received no prescription or were prescribed an OAC less than two times or for a total of <30 days). Patients in this group were then subjected to propensity score matching (PSM) analysis (as described below) to establish the final matched OAC non-user group ($n = 1636$) (Fig. 1).

The Institutional Review Board (IRB) of the Yonsei University Wonju College of Medicine (Wonju, Korea) approved this study

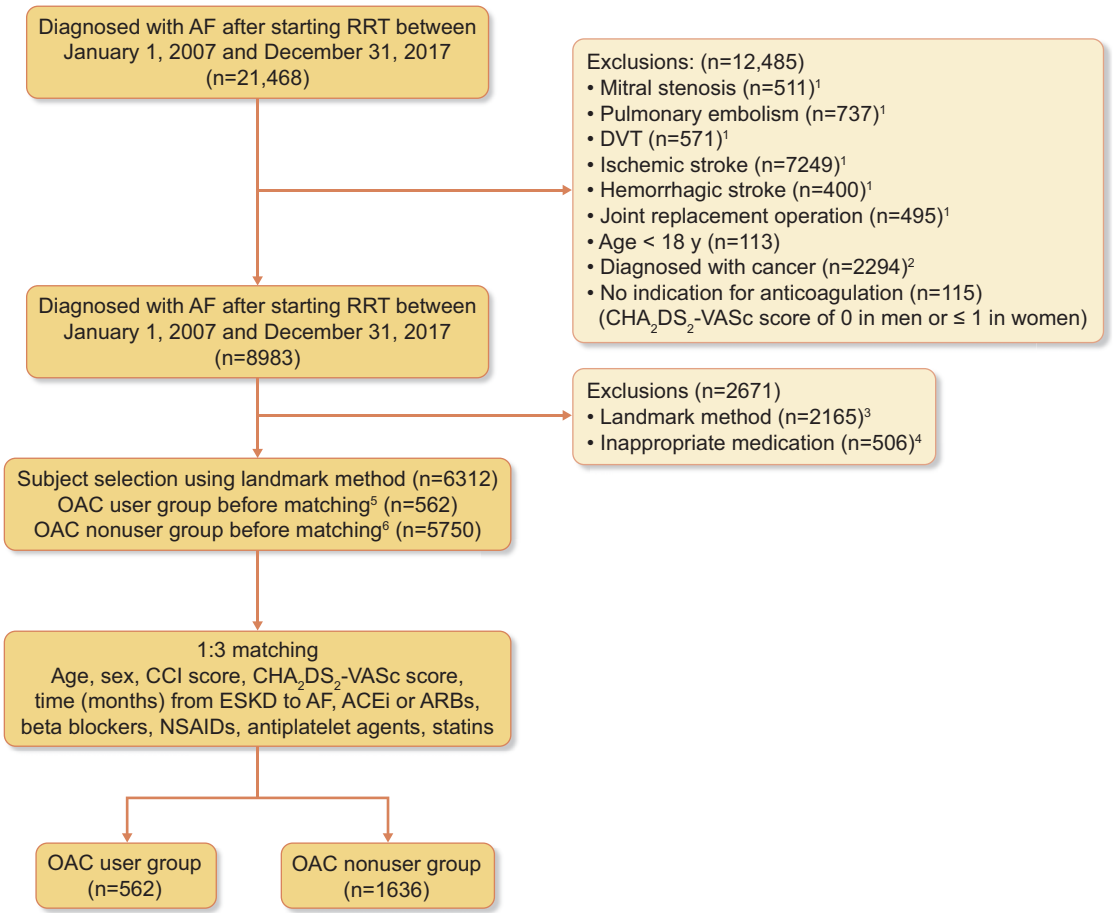


**Figure 1:** Flow diagram showing selection of the study population. 1. Diagnosed within 1 year before AF diagnosis. 2. Diagnosed within 5 years before AF diagnosis. 3. Patients who died or were diagnosed with ischaemic stroke between cohort entry and landmark dates ($n = 2165$; Supplementary Fig. S2). 4. MPR <80% ($n = 119$) or prescription of OAC started >6 months after AF diagnosis ($n = 389$). 5. Prescribed OAC (>2 prescriptions or total number of prescription days >30) after AF diagnosis. 6. Not prescribed any OAC or prescribed only a short-duration OAC (<2 prescriptions or total number of prescription days <30). The MPR was calculated as follows: MPR = {[number of days a prescribed medication was obtained (i.e. possessed) during the treatment period]/[total number of days in the treatment period]}. Among the 562 patients in the final OAC users group, 337 (60%) were prescribed warfarin, 53 (9.4%) were prescribed apixaban, 98 (17.4%) were prescribed other direct OACs and 74 (13.2%) changed OACs during the follow-up period. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; DVT: deep vein thrombosis; NSAID: non-steroidal anti-inflammatory drug; RRT: renal replacement therapy.

(CR319352) and informed consent was waived because anonymous and de-identified information was used for the analyses.

## PSM

We performed PSM in a 1:3 ratio using greedy (nearest neighbour) matching techniques with a calliper of 0.1 standard deviation (SD) to match the OAC user group and OAC non-user group. Age, sex, Charlson Comorbidity Index (CCI) score, $CHA_2DS_2$-VASc score, time from ESKD diagnosis to AF diagnosis and medications were used to generate propensity scores (Fig. 1). After PSM, the covariate balance was evaluated by calculating the standardized mean difference of covariates between groups [18]. These differences were <0.1 for all covariates, indicative of adequate balance between the matched OAC user and OAC non-user groups (Supplementary Fig. S2).

## Data collection and study outcomes

For each patient, we recorded all underlying conditions based on diagnoses reported within 1 year before AF and used these data to calculate the CCI score [19]. Non-OAC medications that may affect thromboembolic or cardiovascular events were recorded based on prescription information within 3 months before AF diagnosis.

The primary study outcome was all-cause death. The secondary outcomes were the occurrence of ischaemic stroke, hospitalization for major bleeding or major adverse cardiovascular events (MACE). Hospitalization for major bleeding was defined as a diagnosis of gastrointestinal bleeding or haemorrhagic stroke requiring hospital admission [20–22]. MACE was defined as cardiovascular mortality, non-fatal myocardial infarction or stroke (ischaemic or haemorrhagic). The study population was followed until death, 5 years after AF diagnosis or 31 December 2018, whichever occurred first.

## Statistical analysis

Baseline characteristics were compared between the OAC user and non-user groups both before and after PSM using the *t*-test or chi-squared test, as appropriate. Categorical and continuous variables are expressed as numbers and percentage and

**Table 1: Baseline patient characteristics.**

| Characteristics | Before matching | | | After matching | |
|---|---|---|---|---|---|
| | OAC users ($n = 562$) | OAC non-users ($n = 5750$) | *P*-value | OAC non-users ($n = 1686$) | *P*-value |
| Age (years), mean ± SD | 69.3 ± 12.5 | 65.7 ± 13.9 | <.001 | 69.4 ± 12.7 | .898 |
| Male, *n* (%) | 323 (57.5) | 3385 (58.9) | .521 | 981 (58.2) | .767 |
| $CHA_2DS_2$-VASc score, mean ± SD | 3.9 ± 1.7 | 3.7 ± 1.7 | .073 | 3.8 ± 1.7 | .650 |
| Diabetes mellitus | 335 (59.6) | 3839 (66.8) | .001 | 1033 (61.3) | .485 |
| Hypertension | 508 (90.4) | 5165 (89.8) | .672 | 1505 (89.3) | .450 |
| Age 65–75 years | 191 (34.0) | 1701 (29.6) | .030 | 508 (30.1) | .087 |
| Age >75 years | 199 (35.4) | 1544 (26.9) | <.001 | 605 (35.9) | .839 |
| Stroke/TIA/thromboembolism | 14 (2.5) | 173 (3.0) | .490 | 53 (3.1) | .431 |
| Vascular disease | 211 (37.5) | 2367 (41.2) | .096 | 642 (38.1) | .821 |
| Year of ESKD diagnosis[a], *n* (%) | | | <.001 | | .807 |
| 2007–2011 | 255 (45.4) | 3343 (58.1) | | 755 (44.8) | |
| 2012–2017 | 307 (54.6) | 2407 (41.9) | | 931 (55.2) | |
| Year of AF diagnosis, *n* (%) | | | <.001 | | .692 |
| 2007–2011 | 71 (12.6) | 1675 (29.1) | | 224 (13.3) | |
| 2012–2017 | 491 (87.4) | 4075 (70.9) | | 1462 (86.7) | |
| Time from ESKD to AF (days), mean ± SD | 921.9 ± 988.3 | 767.2 ± 877.6 | <.001 | 890.6 ± 949.3 | .504 |
| CCI score, *n* (%) | | | | | |
| Mean ± SD | 4.8 ± 2.3 | 5.1 ± 2.3 | <.001 | 4.6 ± 2.3 | .283 |
| Congestive heart failure | 234 (41.6) | 2042 (35.5) | .004 | 568 (33.7) | .001 |
| Dementia | 32 (5.7) | 345 (6.0) | .770 | 121 (7.2) | .227 |
| Chronic pulmonary disease | 209 (37.2) | 2157 (37.5) | .880 | 629 (37.3) | .960 |
| Rheumatologic disease | 35 (6.2) | 230 (4.0) | .012 | 60 (3.6) | .007 |
| Peptic ulcer disease | 160 (28.5) | 1659 (28.9) | .849 | 467 (27.7) | .724 |
| Mild liver disease | 170 (30.3) | 1802 (31.3) | .595 | 490 (29.1) | .593 |
| Hemiplegia or paraplegia | 18 (3.2) | 74 (1.3) | .000 | 19 (1.1) | .001 |
| Renal disease | 562 (100.0) | 5750 (100.0) | 1.000 | 1686 (100.0) | 1.000 |
| Any malignancy, including leukaemia and lymphoma | 30 (5.3) | 300 (5.2) | .902 | 77 (4.6) | .457 |
| Moderate or severe liver disease | 6 (1.1) | 119 (2.1) | .104 | 30 (1.8) | .244 |
| Metastatic solid tumour | 5 (0.9) | 38 (0.7) | .529 | 8 (0.5) | .261 |
| AIDS | 1 (0.0) | 3 (0.0) | .311 | 2 (0.0) | .739 |
| Medications, *n* (%) | | | | | |
| ACEis or ARBs | 393 (69.9) | 4096 (71.2) | .514 | 1180 (70.0) | .979 |
| Beta-blockers | 260 (46.3) | 2824 (49.1) | .197 | 768 (45.6) | .769 |
| Calcium channel blockers | 389 (69.2) | 4034 (70.2) | .643 | 1159 (68.7) | .833 |
| NSAIDs | 407 (72.4) | 3602 (62.6) | <.001 | 1219 (72.3) | .957 |
| SSRIs | 32 (5.7) | 418 (7.3) | .166 | 143 (8.5) | .033 |
| Antiplatelet agents | 307 (54.6) | 3384 (58.9) | .052 | 933 (55.3) | .769 |
| Heparin or nafamostat | 59 (10.5) | 616 (10.7) | .875 | 212 (12.6) | .191 |
| H2 blockers | 402 (71.5) | 3700 (64.4) | .001 | 1138 (67.5) | .075 |
| Statins | 254 (45.2) | 2716 (47.2) | .355 | 745 (44.2) | .677 |
| Glucocorticoids | 34(6.1) | 268 (4.7) | .141 | 87 (5.2) | .418 |

ACEis: angiotensin-converting enzyme inhibitors; AIDS: acquired immune deficiency syndrome; ARBs: angiotensin receptor blocker; H2: histamine 2; NSAID: non-steroidal anti-inflammatory drug; SSRI: selective serotonin reuptake inhibitor; TIA: transient ischaemic attack.
[a]Year of initial ESKD diagnosis, based on dialysis-specific codes or International Classification of Diseases, 10th Revision codes.

mean ± SD, respectively. Analysis using the landmark approach was performed to reduce immortal time bias. This approach was used to compare the effects of OACs (Supplementary Fig. S3). Kaplan–Meier survival curves and the logrank test were used to compare the cumulative incidence of outcomes between PSM groups. For each outcome, hazard ratios (HRs) were determined after PSM, as well as using multivariate Cox regression models adjusting for baseline characteristics that were statistically different between groups before PSM. HRs determined after PSM were additionally adjusted by variables that remained significantly different between the two groups after matching. For all outcomes except all-cause death, other causes of mortality were considered competing risks, and regression analyses were performed using Fine and Gray's model. All *P*-values were two-sided and those <.05 were considered statistically significant. The statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R version 3.63 for Windows (http://cran.r-progect.org/).

## RESULTS

### Oral anticoagulant use trends and patient baseline characteristics

A total of 290 428 patients were diagnosed with ESKD in South Korea between 1 January 2002 and 31 December 2017. Of those, 51 004 (17.6%) were diagnosed with AF (Supplementary Fig. S4). The number of patients with AF undergoing dialysis

**Table 2: Cumulative incidences and hrs for each outcome in oral anticoagulant users versus non-users after PSM.**

| Outcomes | Group | Cumulative incidence (%) | | | Unadjusted HR (95% CI) | Adjusted HR (95% CI)[a] | P-value[b] |
|---|---|---|---|---|---|---|---|
| | | 1 year | 3 years | 5 years | | | |
| All-cause mortality | OAC non-users | 14.7 | 32.4 | 44.5 | 1.00 (reference) | 1.00 (reference) | |
| | OAC users | 9.6 | 25.0 | 35.6 | 0.70 (0.58–0.85) | 0.67 (0.55–81) | <.001 |
| Ischaemic stroke | OAC non-users | 4.2 | 11.1 | 19.4 | 1.00 (reference) | 1.00 (reference) | |
| | OAC users | 2.4 | 7.8 | 12.0 | 0.62 (0.43–0.91) | 0.61 (0.41–89) | .014 |
| Hospitalization for major bleeding | OAC non-users | 4.8 | 12.4 | 15.6 | 1.00 (reference) | 1.00 (reference) | |
| | OAC users | 4.6 | 11.9 | 18.8 | 1.03 (0.76–1.39) | 0.99 (0.72–1.35) | .954 |
| MACE[c,d] | OAC non-users | 8.9 | 20.1 | 33.1 | 1.00 (reference) | 1.00 (reference) | |
| | OAC users | 5.9 | 17.3 | 28.8 | 0.76 (0.59–0.97) | 0.70 (0.55–0.90) | .006 |

[a]Adjusted for congestive heart failure, rheumatologic disease, hemiplegia or paraplegia and SSRIs that remained significantly different between the two populations after PSM.
[b]P-value for 5-year outcomes.
[c]Composite outcome of cardiovascular death, non-fatal acute myocardial infarction or stroke (haemorrhagic or ischaemic).
[d]For MACE, causes of mortality other than cardiovascular disease and loss to follow-up were considered competing risks.
SSRI: selective serotonin receptor inhibitor.

who were prescribed OACs increased gradually from 2002 to 2012. Among patients with ESKD and AF, the number of OAC prescriptions increased 2.3-fold from 2012 ($n = 3579$) to 2018 ($n = 8341$). After the introduction of DOACs in Korea in 2012, their use increased progressively and eventually exceeded warfarin use by 2018 (when DOACs accounted for 51.4% of OAC prescriptions) (Supplementary Fig. S5). After applying the study exclusion criteria, OACs were prescribed to only 562 (8.9%) of the 6312 patients with ESKD and AF who had a $CHA_2DS_2$-VASc score ≥1 (men) or ≥2 (women) during the study period (2007–2017).

Baseline characteristics of the study population are shown in Table 1. After PSM, all variables were similar between the OAC user group ($n = 562$) and OAC non-user group ($n = 1686$). The mean age was 69.3 ± 12.5 years in the OAC user group and 69.4 ± 12.7 years in the OAC non-user group ($P = .898$). Men were more prevalent in both groups (57.5% in OAC users versus 58.2% in OAC non-users, $P = .767$). The use of bleeding-related drugs, such as antiplatelet agents, heparin and non-steroidal anti-inflammatory drugs, was also similar between groups. Baseline characteristics of the OACs (warfarin and DOACs) are shown in Supplementary Table S3.

### Clinical outcomes

During a mean follow-up of 2.65 ± 2.13 years (2.75 ± 2.11 years in OAC users and 2.61 ± 2.13 years in OAC non-users), 137 (24.4%) patients in the OAC user group and 548 (32.5%) patients in the OAC non-user group died ($P < .001$). In both groups, cardiovascular disease was the most common cause of death [$n = 85$ (62.0%) in users and $n = 291$ (53.1%) in non-users]. Other causes of death are shown in Supplementary Fig. S6.

In Kaplan–Meier curve analysis, the OAC user group had a significantly lower all-cause mortality than that in the OAC non-user group ($P < .001$). The cumulative incidences of all-cause death at 1, 3 and 5 years were 9.6%, 25% and 35.6% in the OAC user group and 14.7%, 32.4% and 44.5% in the OAC non-user group, respectively. The HR for all-cause death in OAC users (compared with non-users) was 0.67 [95% confidence interval (CI) 0.55–0.81, $P < .001$] (Table 2). The risk of ischaemic stroke and MACE were also significantly lower in the OAC user group than in the OAC non-user group, with HRs of 0.61 (95% CI 0.41–0.89, $P = .014$) and 0.70 (95% CI 0.55–0.90, $P = .006$), respectively (Fig. 2).

The risk of hospitalization for major bleeding was not significantly different between OAC users and non-users [HR 0.99 (95% CI 0.72–1.35, $P = .954$]. Similar results were observed for all outcomes in a multivariate adjusted Cox regression analysis of OAC users versus non-users before PSM (Supplementary Table S4).

### Subgroup analysis

In the subgroup analysis, compared with non-use, OAC use was associated with a mortality benefit in patients receiving HD, older patients (age >65 years) and patients with a $CHA_2DS_2$-VASc score ≥2 (men) or ≥3 (women). OAC use was also associated with protective effects for ischaemic stroke and MACE in patients receiving HD, age ≤80 years and individuals with a $CHA_2DS_2$-VASc score ≥2 (men) or ≥3 (women) (Supplementary Table S5).

In subgroup analysis according to the type of OAC, warfarin was marginally associated with an increased risk of hospitalization for major bleeding [HR 1.38 (95% CI 0.99–1.91)] but showed no reduction in the risk of mortality, ischaemic stroke or MACE. In contrast, DOACs were associated with a reduced risk of death [HR 0.54 (95% CI 0.34–0.86)] and hospitalization for major bleeding [HR 0.29 (95% CI 0.09–0.90)], but showed no reduction in the risk of ischaemic stroke or MACE (Fig. 3).

## DISCUSSION

This real-world nationwide cohort study showed that, compared with no anticoagulant therapy, appropriate OAC therapy was associated with reduced rates of all-cause death, ischaemic stroke and MACE, while no increase was noted in the risk of hospitalization for major bleeding. No significant difference was observed in the incidence of stroke between patients taking warfarin and those taking DOACs. However, the latter had a lower risk of hospitalization due to a major bleeding event compared with those taking warfarin.

Data on the risk:benefit ratio of OAC in patients with ESKD and AF is conflicting. Reported data from the US Medicare program showed no association between OACs and the risk of mortality or stroke [12]. However, several differences were observed compared with our data. First, the US study did not evaluate medications that affect patients' mortality or bleeding risk (angiotensin-converting enzyme inhibitors or angiotensin

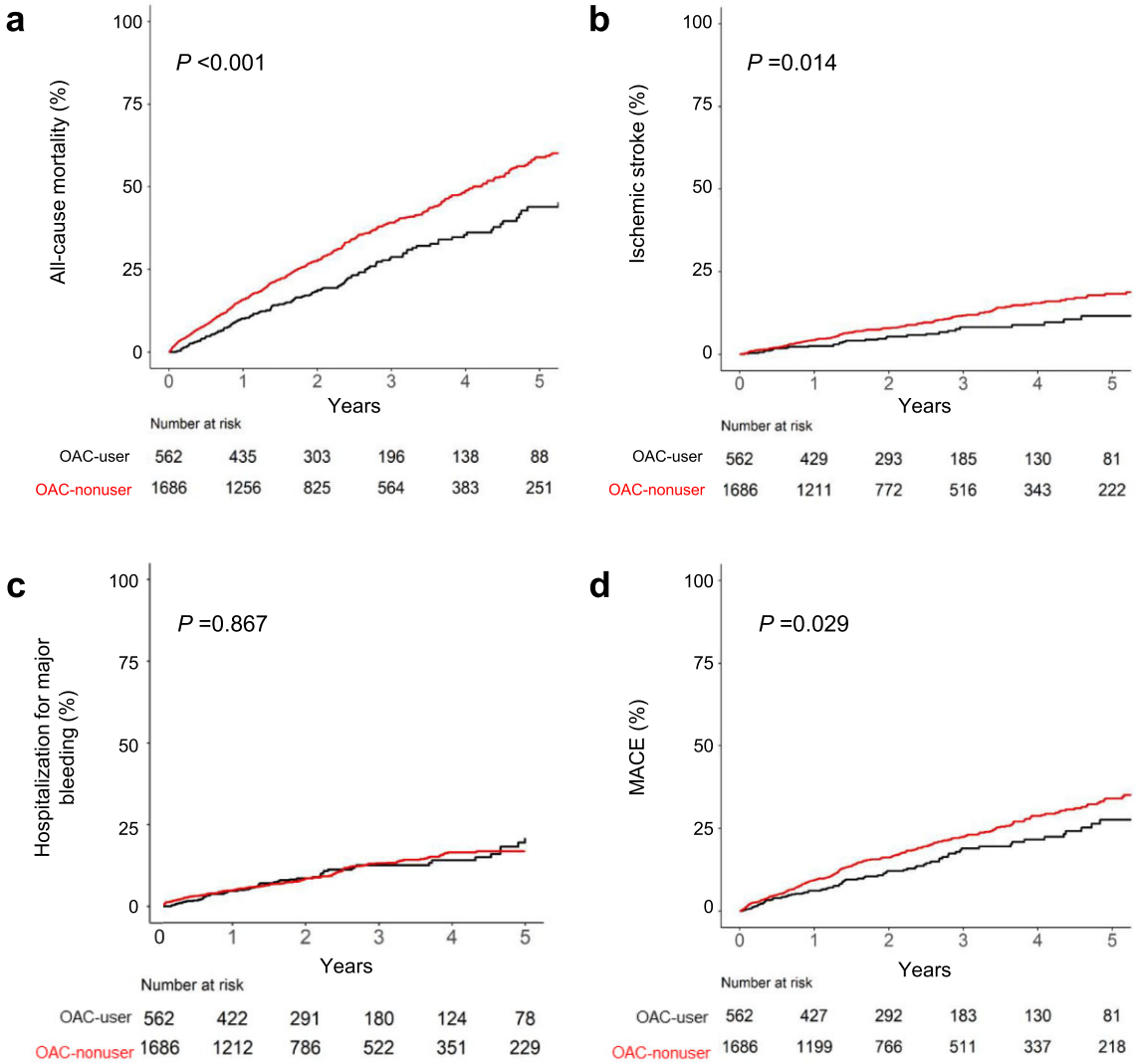


**Figure 2:** Kaplan–Meier curves for each outcome: **(a)** all-cause mortality, **(b)** ischaemic stroke, **(c)** hospitalization for major bleeding and **(d)** MACE (composite outcome of cardiovascular mortality, non-fatal acute myocardial infarction or stroke)..

receptor blockers, beta-blockers and antiplatelet agents). Second, in our study, patients with indications for anticoagulation therapy other than AF (history of thromboembolism, joint replacement surgery or cancer) were included. Third, our study was mainly conducted in an Asian population. Additionally, the inclusion criteria for the $CHA_2DS_2$-VASc score are different [our criteria were ≥1 (men) or ≥2 (women)].

Furthermore, Kuno *et al.* [23] reported no survival benefit from warfarin. A study from The Netherlands reported that warfarin increased the risk of all-cause death compared with no anticoagulation therapy; however, 26.4% of patients in that study had a $CHA_2DS_2$-VASc score <2 [24]. A nationwide Danish registry study showed that warfarin was associated with a lower risk of death in patients with ESKD and AF who had a $CHA_2DS_2$-VASc score ≥2 [25]. Despite extensive experience with warfarin in patients with ESKD, the effectiveness of warfarin hinges on maintaining the international normalized ratio (INR) within the target therapeutic range. However, the percentage of time in which the INR remains in the target range is low, even in clinical research settings. In a retrospective study, the INR was within the therapeutic range in only 21% of patients with AF and ESKD treated with warfarin [26–28].

Our study revealed no differences in the efficacy of warfarin and DOACs in terms of stroke incidence. However, DOACs offer a safety advantage by reducing the incidence of hospitalization for major bleeding events. Several studies reported no difference in the efficacy of warfarin and DOACs on the incidence of stroke [14, 15, 28–31, 34]. A Taiwanese nationwide retrospective cohort study showed no significant disparity in the risk of developing ischaemic stroke, systemic embolism or major bleeding between DOACs and warfarin [29]. Retrospective cohort studies from the US Renal Data System indicate that for patients with ESKD and non-valvular AF, apixaban was associated with a lower risk of major bleeding, with no significant difference in the risk of systemic embolism or stroke compared with warfarin [14, 23, 30]. Conversely, in patients with ESKD and non-valvular AF, dabigatran was associated with an increased risk of major bleeding, with no difference in the risk of stroke or systemic embolism compared with warfarin [15, 23]. Some studies in this patient population demonstrated that rivaroxaban is associated with

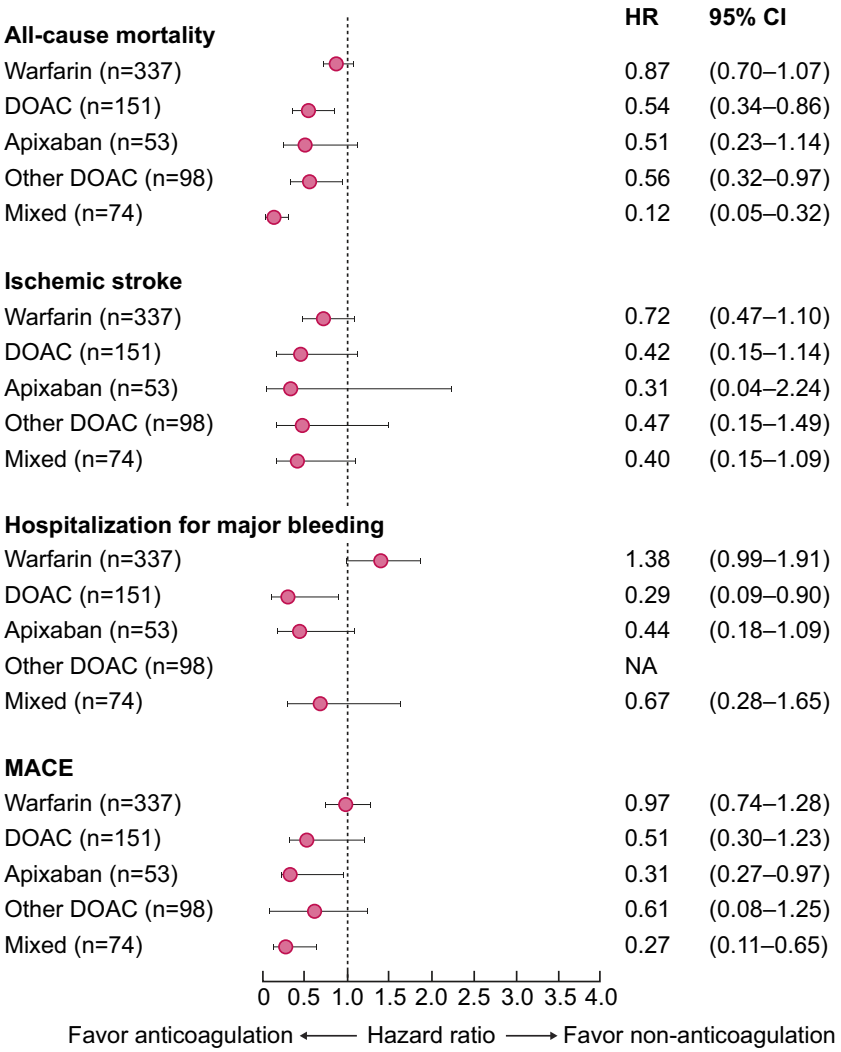


**Figure 3:** Subgroup analyses for **(a)** all-cause mortality and **(b)** MACE (composite outcome of cardiovascular death, non-fatal AMI or stroke). All results were adjusted for congestive heart failure, rheumatologic disease, hemiplegia or paraplegia and SSRIs, which remained significantly different between the two population after PSM. Mixed: patients who changed oral anticoagulants during follow-up periods. AMI: acute myocardial infarction; CABG: coronary artery bypass graft; KT: kidney transplantation; PCI: percutaneous coronary intervention; SSRIs: selective serotonin receptor inhibitors.

a similar or lower risk of major bleeding or thromboembolism than warfarin [31, 32]. However, in multicentre randomized controlled trials (RCTs), rivaroxaban conferred reduced rates of cardiovascular events and major bleeding compared with warfarin [33].

In terms of safety, DOACs have the advantage of reducing the incidence of major bleeding events compared with warfarin, although safety profiles may vary among different DOACs [14, 23, 29, 30, 34]. As all four DOACs are primarily eliminated by the kidneys, with rates of renal elimination ranging from 27% for apixaban to 80% for dabigatran, the risk of bleeding may increase in patients with ESKD due to the accumulation of these medications [6]. Our results showed that anticoagulation therapy is associated with a reduced risk of all-cause death driven by the reduced incidence of ischaemic stroke. Initiating appropriate and individualized anticoagulation therapy to prevent ischaemic stroke may ultimately improve survival in patients with ESKD and AF. Kuno *et al.* [23] reported that administration of 5 mg of apixaban twice on dialysis was associated with lower mortality compared with no anticoagulation therapy [23]. However, further research conducted through RCTs is required to confirm these findings.

Nevertheless, conducting comparative studies can be challenging due to variability in comorbidities within ESKD patients. A recent RCT failed to recruit a sufficient number of patients [28]. In our nationwide study, only 2198 of 299 084 patients with ESKD met the inclusion criteria. In contrast to other retrospective cohort studies, our study used several strategies to overcome inherent bias. In addition to landmark analysis and PSM, including only patients diagnosed with AF after an established diagnosis of ESKD could set the date of the first AF diagnosis as the index date, thereby reducing lead time bias due to AF duration [35]. In contrast to most studies, we used the most recently updated $CHA_2DS_2$-VASc score in the inclusion criteria and the sex-specific cut-off values for recommended OAC use [7, 8]. We observed that the beneficial effects of OAC use were greater in patients with higher $CHA_2DS_2$-VASc scores, consistent with the results of the Danish study [25].

Our study has some limitations. The information included in the claims database was limited, therefore we could not assess data such as laboratory results or OAC dosage. We could not completely eliminate selection bias related to these parameters. As this study was based on nationwide data, obtaining INR values was not possible, making it difficult to determine whether the INR fell within the target range for patients taking warfarin. Additionally, the diagnosis of cardiovascular and cerebrovascular disease was established through operational definitions, which may have led to misdiagnosis.

In conclusion, this nationwide observational cohort study showed that in patients with non-valvular AF and ESKD, OAC therapy was associated with a decreased risk of death, MACE and ischaemic stroke. Although patients with ESKD receiving anticoagulation may be particularly susceptible to bleeding, we did not observe an increased risk of hospitalization for major bleeding in these patients. Thus OACs appear to be beneficial in patients with ESKD and AF. Nevertheless, individualized anticoagulant therapy should be considered to reduce the likelihood of major bleeding.

## SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

## CONFLICT OF INTEREST STATEMENT

None declared.

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