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a systematic review and meta-analysis

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Correct dosing, adherence and persistence of DOACs in atrial fibrillation and chronic kidney disease: a systematic review and meta-analysis

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ABSTRACT

Background Chronic kidney disease (CKD) and atrial fibrillation (AF) are increasing in prevalence globally and share common risk factors.

Our aim was to characterise real-world evidence on direct oral anticoagulant (DOAC) prescribing for people with AF and CKD, in terms of adherence, persistence and renal dose titration.

Methods PubMed, EMBASE and CINAHL were searched from inception to June 2022. Our search terms included a combination of Medical Subject Headings (MeSH) terms and keywords including 'atrial fibrillation', 'chronic kidney disease', 'adherence', 'persistence', 'direct oral anticoagulants' and 'dosing'. Data extraction and quality assessment were undertaken by two reviewers independently. Meta-analyses for pooled estimates were performed using DerSimonian and Laird random-effects models. Age, sex, diabetes, hypertension and heart failure were chosen as variables of interest.

Results From 19 studies, a total of 252 117 patients were included with CKD and AF. Meta-analysis was only possible in seven studies with 128 406 patients, five on DOAC dose titration and two on adherence. There were insufficient studies on persistence. Our meta-analysis of dosing showed that 68% of patients with CKD and AF had correct dosing. There was no evidence to show any association between correct DOAC dosing and variables of interest. Overall, 67% of patients were DOAC adherent.

Conclusion Adherence and correct dosing of DOACs were suboptimal compared with other medications in the pooled studies with respect to CKD and AF. Thus, further research is required as the lack of generalisation of findings is a rate-limiting factor for improved DOAC management in AF and CKD.

PROSPERO registration number CRD;42022344491.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Guidelines recommend using direct-acting oral anticoagulants (DOACs) for atrial fibrillation (AF) as first-line anticoagulants in those without moderate to severe mitral stenosis or prosthetic valves. DOAC dosage is adjusted in renal impairment. Patients with AF and chronic kidney disease (CKD) have a higher risk of stroke, cardiovascular morbidity and all-cause mortality compared with patients who have either condition alone. DOACs reduce these risks if managed correctly. The improvement in outcomes with DOACs in patients with AF is dependent on adherence to the correct dose. Hence, the aim of this research is to explore these fundamental factors and to evaluate associations between them and their determinants.

WHAT THIS STUDY ADDS

⇒ We found that there is a prescribing gap in appropriate dose reduction of DOACs in patients who have AF and CKD and that adherence to DOAC therapy is poor in this group. Little was found about DOAC persistence in this group of patients or the determinants of DOAC correct prescribing, adherence and persistence in CKD and AF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research is needed in primary care, since these clinicians are routinely involved in and responsible for DOAC management, including correct DOAC dosing, adherence, and persistence.

INTRODUCTION

Direct oral anticoagulants (DOACs) changed the landscape of atrial fibrillation (AF) treatment since their introduction in 2010. DOAC prescribing has significantly increased while vitamin K antagonist (VKA) prescribing has declined in the USA and Europe, including the UK.[1] Clinical trials have shown that DOACs are at least non-inferior to VKA for the prevention of stroke and systemic embolism, and all have consistently superior safety profiles, particularly with reduced risk of intracranial bleeding.[2–5] Therefore, among patients with AF who are suitable for DOAC treatment, the current UK NICE guidance, European Society of Cardiology guidelines and joint American cardiac societies guidelines all advocate DOACs over VKAs as a preferable anticoagulation approach.[5–7]

There are more than 800 million people on the globe who suffer from chronic kidney disease (CKD), affecting over 10% of the population.[8] AF is the the most common arrhythmia worldwide.[9] The global prevalence of AF was estimated to be 59.7 million worldwide with nearly five million new cases occurring every year.[9] The prevalence of each condition increases with age, and patients with both conditions have a higher risk of stroke, cardiovascular morbidity and all-cause mortality compared with those with either AF or CKD alone.[8 10 11]

DOACs do not require therapeutic monitoring of anticoagulant effect, unlike VKAs.[11 12] However, this does not obviate the need for regular clinical review and dose titration in CKD.[13 14] One may speculate that, in comparison to people receiving VKAs, a reduced frequency of interaction with healthcare professionals might lead to reduced treatment adherence in people on DOACs. Thus, we undertook a comprehensive systematic review and meta-analysis of DOAC monitoring, adherence and persistence in CKD.[15]

METHODS

Study design

This study was designed in accordance with the Meta-analysis Of Observational Studies in Epidemiology.[16] The protocol was peer-reviewed and registered (CRD42022344491) with the International Prospective Register of Systematic Reviews, PROSPERO.

Eligibility criteria

We included studies that assessed DOAC correct dosing, adherence and persistence among patients with AF and CKD with a participant age of 18 years and over. All studies with participants under the age of 18 years and any patient that did not have CKD and AF were excluded. Studies reporting participants on DOACs for reasons other than AF, such as deep venous thrombosis, pulmonary embolism, moderate or severe mitral stenosis, and mechanical valves were excluded.

Dialysis patients and those with CKD stage 5 were excluded from the systematic review as current guidelines state that DOACs should not be routinely prescribed to patients with a creatinine clearance <15 mL/min.[6 7 16]

We excluded case reports/series, systematic literature reviews and conference posters. Studies that were not published in English language, or that used subjective adherence measures, such as the Morisky Medication Adherence Scale, or medication event monitoring systems were also excluded.[17]

Search strategy

We searched the PubMed, EMBASE and CINAHL databases from 30 June 2008 to 30 June 2022 (online supplemental table 1) with snowballing effect. We did not apply any language restrictions during our initial search, and our search terms included a combination of Medical Subject Headings (MeSH) terms and keywords including 'atrial fibrillation', 'chronic kidney disease', 'adherence', 'persistence', 'direct oral anticoagulants (DOAC)'.

Data extraction and screening

Information extracted included study design, population characteristics, sample size, definition and measure for the outcome measure. Multiple reports from the same studies were grouped during the data collection process and any duplicates were removed. In addition, we contacted authors of studies to request additional data that were not reported in the manuscript.

We conducted a two-stage screening process to improve the quality of the final dataset. In the first stage, two reviewers independently mapped abstracts against the inclusion criteria. Studies were retained if they met all criteria. Rejection of studies was on agreement between both reviewers. Any instances of disagreement were retained for full-text screening. In the second stage of screening, the full-text articles of each study retained from stage 1 were independently reviewed by both reviewers. Studies were retained or rejected according to consensus between the two reviewers as shown in the PRISMA diagram below. Any disagreements between the reviewers were resolved by discussion. We additionally searched the references of included studies to identify any further articles for screening and analysis.

Outcomes assessed

We extracted three primary variables: (1) fidelity of prescribing to recommended doses in CKD, (2) adherence to prescribed dose and (3) persistence of treatment. We assessed the fidelity of prescribing against manufacturers' recommendations on dose titration in CKD (table 1).

We assessed adherence using the proportion of days covered (PDC) over the year following the index date, according to the following formula, with good adherence defined as PDC>80%, in line with other studies.[18 19]

$$\text{PDC} = \frac{\text{number of days covered with drug } (\leq 365)}{\text{Number of days between first and last prescription } (+30 \text{ days}) \text{ or } 365 \text{ days}*}$$

*Whichever is shorter.

We assessed persistence as the proportion of patients without any gaps longer than 90 days between prescriptions in the year following the index date.[20 21]

Study quality assessment

All studies were observational studies. As such, it was important to assess the risk of bias, reliability of the analysis and validity of the evaluation conducted. The Newcastle-Ottawa Scale (NOS) was used to conduct this assessment.[22] NOS allows 9 points of risk bias associated with the study group, comparability within the groups based on outcomes as well as exposure and outcomes. A risk of bias table has been made available as online supplemental table 2. Studies were ranked according to low risk (7–9 stars), high risk (4–6 stars) or very high risk (1–3 stars) of bias.[23]

Table 1 Dosing criteria according to renal guidelines

Dosing criteria for AF	Edoxaban	Apixaban	Dabigatran	Rivaroxaban
Normal dosing regime	60 mg once per day	5 mg two times per day	150 mg two times per day	20 mg once per day
Reduced dosing regime	30 mg once per day	2.5 mg two times per day	110 mg two times per day	15 mg once per day
Renal criteria for dose reduction	CrCl 15–50 mL/min	CrCl 15–30 mL/min or ≥2 of: Age>80 years, body weight ≤60 kg, creatinine ≥133 umol/L	CrCl 30–50 mL/min	CrCl 15–50 mL/min
Contraindication (renal)	CrCl ≤15 mL/min	CrCl ≤15 mL/min	CrCl ≤30 mL/min	CrCl ≤15 mL/min

CrCl, creatinine clearance.

Statistical analysis plan

A systematic synthesis was performed along with a meta-analysis. For the statistical synthesis, we grouped two or more studies that shared comparable outcome data (eg, ORs) and pooled these data in meta-analysis. Pairwise meta-analysis was performed using random effects model[24] to account for variation in how the outcome measure was assessed. We reported the pooled estimates of effect with 95% CI.

Heterogeneity among the studies was determined using the Q-test; a p value<0.1 implies heterogeneity between the studies. A tau-squared value and I^2 statistic with 95% CI were also reported, where an I^2 value of <30%, 30%–59%, 60%–90% and more than 90% inferred low, moderate, substantial and considerable heterogeneity, respectively. To assess the risk of publication bias, we used funnel plots and performed Egger's test to determine asymmetry. Data synthesis was performed in RStudio software, V.1.3.959, using the package metafor.[25–27]

RESULTS

Study selection

A total of 837 studies were explored initially where 732 were retained following removal of duplicates. Following title and abstract review, 538 articles were excluded and 194 articles underwent full-text review. Studies were limited to those in the English language, and those published after 2008, the year DOACs were first licensed. We also excluded systematic reviews, clinical trials, conference abstracts, letters and case reports. Following this, 147 were excluded, leaving 19 eligible studies[28–47] for systematic literature review. After assessing studies that used the same data sources, and therefore, with overlapping populations, we included seven studies[28–34] in the meta-analysis, of which two dealt with medication adherence[33 34] and five[28–32] dealt with fidelity of prescribing to recommended doses (figure 1).

Study characteristics

Of the 19 studies,[28–46] all were observational (table 2).

The studies included a total of 661 855 patients with AF taking DOACs of which 19.3% (n=128 406) had CKD. Ten studies[28–32 37 38 44–46] reported monitoring, six[33 34 39–43] reported adherence and three[33 35 36] reported persistence. Information required for meta-analysis was only found in seven studies with 252 117 patients, five on correct dosing[28–32] and two on adherence.[33 34] Within these studies, only 3.5% (9800) of the patients had CKD. Four of the studies were from USA,[28–30 32 34] one from Asia[31] and one from Europe.[33] The earliest data was collected from 2010, and the latest from 2019, with the publications ranging from 2014 to 2021. Five studies were from primary or community care alone,[32–34 40] four were from a combination of primary and secondary care,[28 35 44 46] and the remainder were from hospital outpatients. There were only two studies which were CKD-specific[29 30] but these were relatively small, with 207 and 1134 patients only; the data from others was a subanalysis of AF studies with DOACs not specific to CKD. Most compared the findings to VKA.

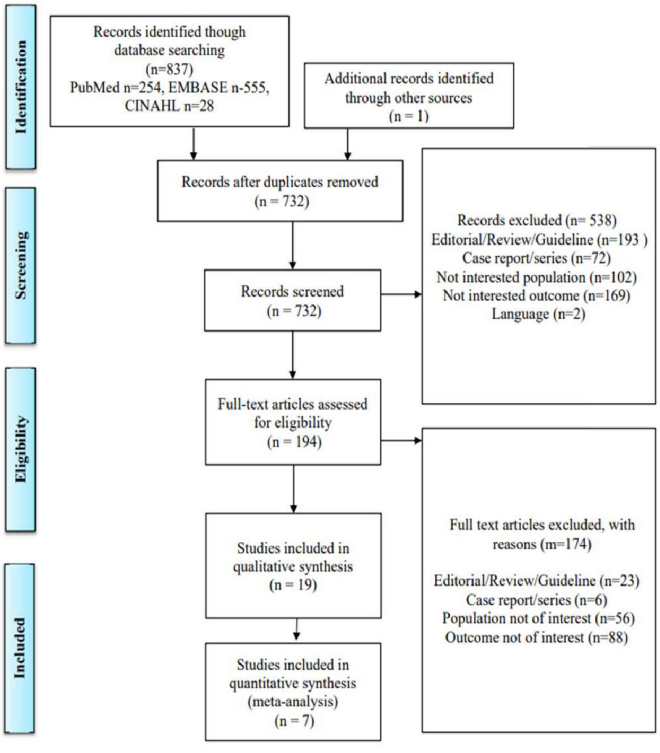

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of studies identified by searches, screened and included in final analysis.

Table 2 Studies in qualitative analysis

Study name	Renal function (CrCl, eGFR or not specified)	Poss CKD specific/CKD criteria	Study type	Country	Length of study	DOAC and if comparator	Total sample size /CKD sample size	Outcome CKD DOAC dosing /adherence/ persistence	Primary care/ community/ hospital
1. Briasoulis *et al*[82]	CKD dose for 15–30 mL/min	AF specific/not CKD specific	Retrospective cohort	USA	2010–2016 5 years	Dabigatran rivaroxaban	Total 14 863 9221 CKD	Correct dosing 52.74%	Primary care
2. Leef *et al*[28]	CKD defined by eGFR into CKD 3–5	AF/not CKD specific	Retrospective cohort	USA	2003–2015	Dabigatran rivaroxaban	230 762 1312 CKD	Correct dosing 83.23%	Hospital and primary care
3. Ting *et al*[29]	CrCl<50 mL/min	CKD-specific -moderate/severe renal impairment including haemodialysis patients	Retrospective cohort	USA	June 2015–Dec 2018 Median follow-up 20 months	Dabigatran edoxaban rivaroxaban apixaban	207 CKD patients total	Correct dosing 70.5%	Hospital
4. Erdogan *et al*[81]	CKD defined as eGFR<50	AF/not CKD specific	Cohort (25.2% retrospective/ remaining prospectively)	Turkey	April 2017–May 2018	Rivaroxaban apixaban dabigatran	302 overall 105 CKD	Correct dosing 60.95%	Hospital outpatients
5. Jackson *et al*[80]	CrCl 30—50 mL/ min	CKD specific -Moderate renal impairment CrCl 30–50 mL/min	Retrospective cohort	USA	20 Feb 2013 and 12 July 2016 2-year follow-up	Rivaroxaban apixaban dabigatran edoxaban	1134 CKD patients	65.5% correct DOAC dosing	Hospital outpatients
6. Banerjee *et al*[83]	CrCl/eGFR not discussed but assumed CKD 3–5.	Not CKD Specific	Retrospective cohort	UK	2011–2016 5 years	Dabigatran edoxaban apixaban rivaroxaban	36 652, of which 18 731 had CKD	Adherence (A)—overall 70.4%. Also, persistence 67.7%	Primary care
7. Shore *et al*[84]	CKD not defined	Not CKD Specific	Retrospective cohort	USA	October 2010–September 2012	Dabigatran	5372 of which 652 had CKD	71.4% adherence	Primary care
8. Choi *et al*[44]	CKD not defined. CrCl not defined	Not CKD Specific	Retrospective cohort	Korea	1 July 2015–31 December 2016 15 months follow-up	Dabigatran, rivaroxaban, apixaban	56 504 of which 2566 had CKD	Mention that patients with CKD were underdosed. No statistical analysis given	Hospital and primary care
9. Xing *et al*[46]	CKD not defined. No CrCl defined	Not CKD specific	Retrospective cohort	Denmark	2011–2017	Dabigatran, rivaroxaban, apixaban	24 489 of which 892 had CKD	CKD dosing. Dose reduction seen in CKD. No analysis	Hospital and primary care

Continued

Table 2 Continued

Study name	Renal function (CrCl, eGFR or not specified)	Poss CKD specific/CKD criteria	Study type	Country	Length of study	DOAC and if comparator	Total sample size /CKD sample size	Outcome CKD DOAC dosing /adherence/ persistence	Primary care/ community/ hospital
10. Akao *et al*[38]	Dosing acc to CrCl 15 >100 mL/min	Not CKD specific	Retrospective cohort	Japan	Jan 2012–Jan 2019	Dabigatran, rivaroxaban, apixaban and edoxaban	32,713, of which 6325 CKD	Appropriate dosing/ warfarin therapy associated with CKD/ no analysis in CKD	Hospital
11. Beshir *et al*[36]	CKD not defined	Not CKD specific	Retrospective cohort	Malaysia	2010–2015	Dabigatran	Total 192 of which 9 patients CKD	Persistence	Hospital
12. Guo *et al*[45]	CKD classified. Used eGFR than CrCl	Not CKD specific	Retrospective cohort	China	October 2014–Dec 2018	Rivaroxaban dabigatran	5742 of which 698 CKD	DOAC dosing. Incorrect dosing associated with CKD. Not enough analysis	Hospital
13. Pagès *et al*[43]	Definitions of CKD as stage 3,4,5	Not CKD Specific	Retrospective cohort	France	Sept 2016–August 2017	Dabigatran, rivaroxaban and apixaban grouped together.	405 of which 111	Adherence	Hospital
14. Dhamane *et al*[35]	eGFR/CrCl not discussed	Not CKD specific	Retrospective cohort	USA	Jan 2012–June 2019	Dabigatran, rivaroxaban, apixaban. Edoxaban excluded	362 823 of which 58 804	Persistence	Hospital and primary care
15. Charlton *et al*[40]	No CrCl given	Not CKD specific	Retrospective cohort	Spain	Jan 2009–Dec 2015	Apixaban dabigatran rivaroxaban	12 257 of which 1790 CKD	Adherence. Not enough data for CKD	Primary care
16. Piccini *et al*[39]	eGFR rate<60	Not CKD specific	Retrospective cohort	USA	Jan 2013–September 2017	Apixaban rivaroxaban dabigatran edoxaban	33 235 of which 10 707 CKD	Correct dosing. Not enough data for CKD	Hospital
17. Sato *et al*[37]	CrCl <50 mL/min	Not CKD Specific	Retrospective cohort	Japan	Sept 2011–Jan 2016	Dabigatran, rivaroxaban, apixaban and edoxaban	2272 CKD 1460	Correct dosing. Not enough data for CKD	Hospital
18. Yeo *et al*[42]	No CrCl given	Not CKD specific	Retrospective cohort	Singapore	2010–2014	No specific DOAC	2299, of which 1139 CKD	Adherence. Grouped with clopidogrel and other anticoagulants	Hospital
19. Maura *et al*[41]	No CrCl	Not CKD Specific	Retrospective observational	France	2012–2013	Rivaroxaban/ dabigatran	22 267 571 CKD	Adherence. CKD looked at; no specific data given	Hospital outpatients

AF, atrial fibrillation; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate.

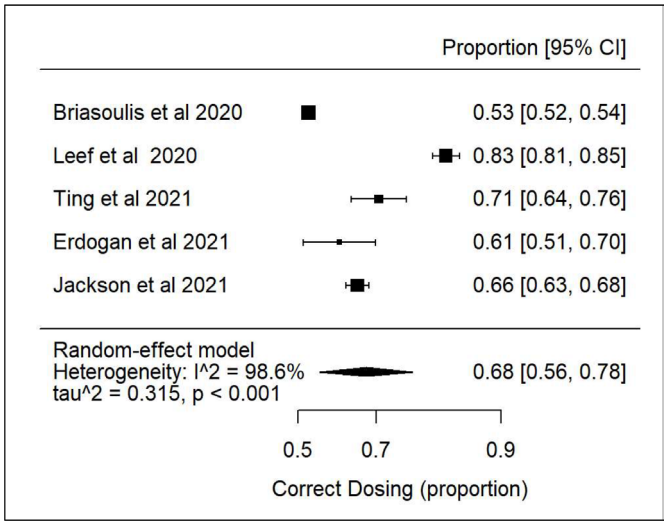

Figure 2 Forest plot: correct direct oral anticoagulant dosing according to creatinine clearance.

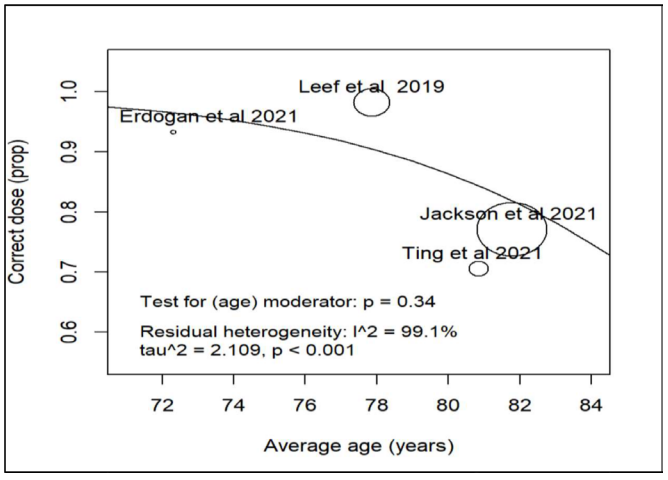

Figure 4 Subanalysis correct direct oral anticoagulant dosing and age.

Study quality

The quality of the studies was generally good. The mean quality score of the studies using the Newcastle-Ottawa Quality Assessment Scale was 7.2 (median=7). All studies scored 7 to 9 for the quality assessment and, hence, had a low risk of bias (online supplemental table 2). However, the majority of the studies did not provide details relating to the loss of individuals during the follow-up period.

Correct dosing

Our meta-analysis on correct dosing of the five studies[28–32] showed that there was high heterogeneity and that 68% of patients with CKD and AF had correct dosing (figure 2).

Sub-analysis

We did further subanalysis on various demographics to see if there was any association between specific determinants and correct dosing. There was only sufficient data to evaluate age, sex, diabetes, hypertension and heart failure. All showed high heterogeneity and hence any association was inconclusive (figures 3–7).

Adherence

Again, there was high heterogeneity[33 34] (figure 8) with 67% of patients' adherent to DOACs. Subanalysis of the two papers[33 34] with reference to adherence was not possible as there were not sufficient data.

Persistence

Only three papers.[33 35 36] looked at DOAC persistence in CKD and AF. However, as CKD was not part of their original primary outcome this was not evaluated, and their definitions of persistence differed.

It was difficult to make any combined analysis. Banerjee *et al*[33] found that 67.7% of patients persisted on anticoagulants for a full year after the index prescription, corresponding to 61.8% of patients on dabigatran, 74.7% on rivaroxaban and 81.6% apixaban compared with 63.6% of VKA patients. However, sample size was not reported for each specific DOAC, but only for the overall CKD

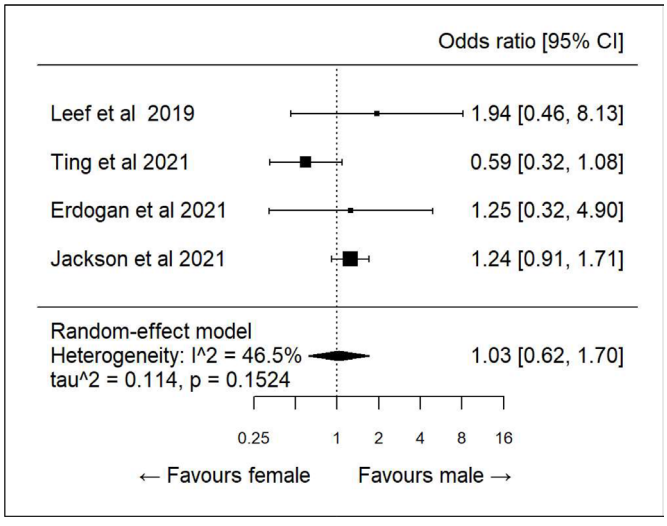

Figure 3 Subanalysis correct direct oral anticoagulant dosing and sex.

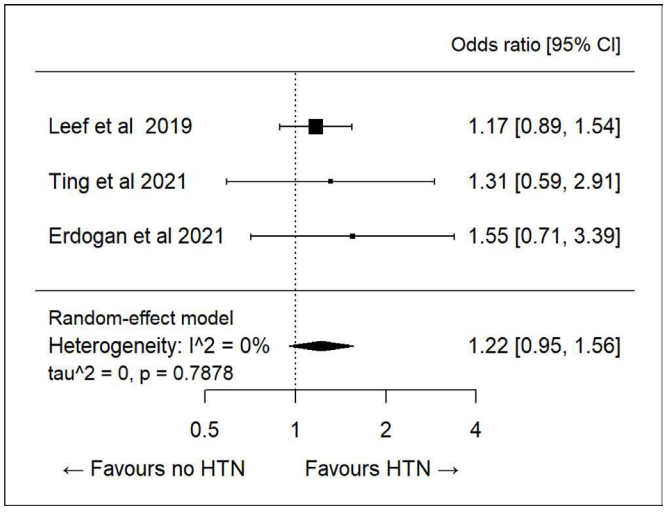

Figure 5 Subanalysis: correct direct oral anticoagulant dosing and hypertension (HTN).

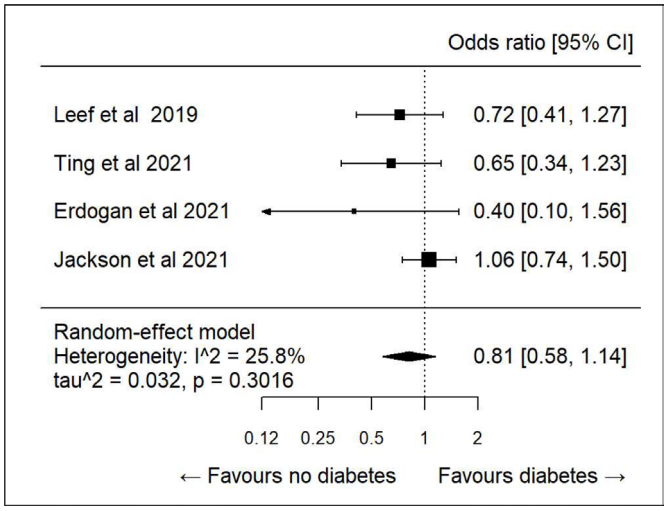

Figure 6 Subanalysis: correct direct oral anticoagulant dosing and diabetes.

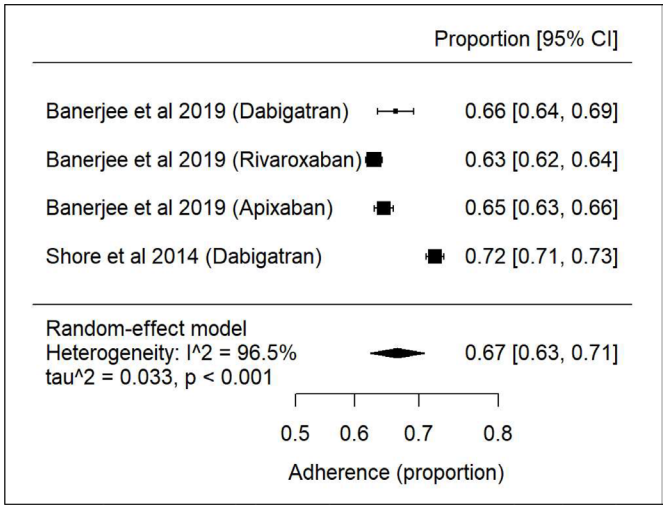

Figure 8 Forest plot showing adherence of direct oral anticoagulants in chronic kidney disease and atrial fibrillation.

cohort. Beshir *et al*[36] had a small sample size of 195 and overall persistence in AF was 86.5% at 1 year and 83.4% at 2 years. This was relatively better than VKA (warfarin) which was 83.4%. However, only 9 AF patients had CKD and out of this 55.5% (n=5) had good persistence.

In Dhamane *et al*,[35] 66 826 patients had CKD. Of these, 55.6% were on apixaban, 21.0% were on rivaroxaban and 3.9% were on dabigatran. CKD was associated with non-persistence with HR 1.02 but no other details on sample sizes were found in the study.

Publication bias

The funnel plot for correct dosing showed some asymmetry on visual inspection (online supplemental figure 1). However, Egger's test for a regression intercept found a p value of 0.9042 which implies a low probability of publication bias. As the number of studies in the meta-analysis was small, no sensitivity analysis was done.

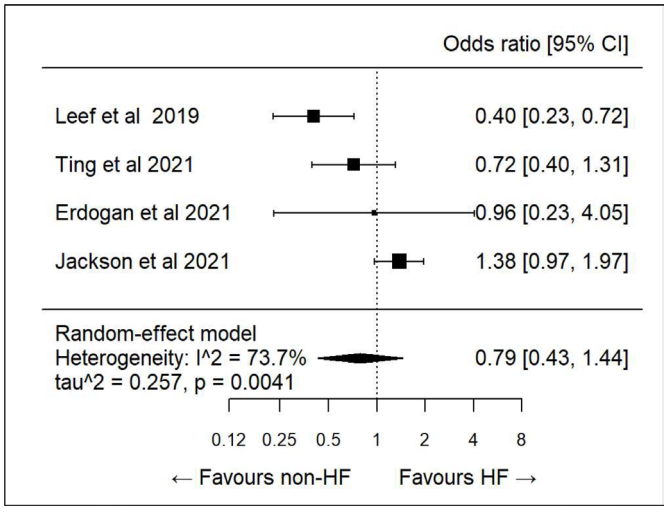

Figure 7 Subanalysis: correct dosing and heart failure (HF).

DISCUSSION

This systematic review found that seven papers were suitable for meta-analysis with most addressing correct DOAC dosing and the remainder focusing on DOAC adherence. There were no papers to compare persistence. Despite an abundance of publications on the use of DOACs in AF, there is a lack of data currently available in the context of AF and CKD.

Correct DOAC dosing

Our analysis shows that 68% of patients with correct DOAC dosing is in line with other studies for overall correct DOAC dosing in AF.[37 48] This has increased since the DOACs was initially introduced. Most systematic literature reviews in this area have focused on risk of bleeding and stroke[38–40] on the assumption that real-world DOAC dosing mirrors the adherence and persistence typical of clinical trials. This is the first systematic literature review and meta-analysis which is specific to DOAC monitoring in CKD and AF. It was not possible to do subanalysis of the various dosing structures of standard and low doses of each DOAC as the studies did not divide it according to CKD groups 3–4 which covers the overarching grouping of CKD for which DOACs are licensed; the lower doses will generally be in those with CKD; some may be in those without CKD if they are older or have low body weights as in the case of apixaban according to guidelines. There were too few studies available to assess correct dosing by individual drug.

Adherence

The DOAC adherence was suboptimal but similar to other studies with AF overall.[33 41 49] However, this is much lower than other chronic disease medications.[50] Very few studies had adherence at CKD level and hence limited data is available. However, the findings of Shore *et al*[34] showed good adherence to dabigatran.[34] This was done very early on in 2014 when DOACs had recently been introduced, and hence patients may have been seen more often which

increased adherence. In addition, the numbers of patients involved on dabigatran with CKD are much less due to stringent guidelines with respect to creatinine clearance. Eighty per cent to 85% of dabigatran is excreted by the kidneys via glomerular filtration, and hence it can only be used in moderate renal impairment unlike the factor Xa inhibitors (apixaban, rivaroxaban and edoxaban). There were no adequate studies on adherence in CKD and AF as we only had two studies to show a link between non-adherence and worsening kidney disease.

Adherence with two times per day dosing regimens is assumed to be lower than with once per day regimens in real-world settings and in patients with a high pill burden. Conversely, two times per day dosing is expected to deliver a more stable anticoagulant effect over the course of 24 hours. A meta-analysis of the four key efficacy RCTs of DOAC in AF revealed that two times per day dosing provided a better benefit–risk equation than once per day dosing. The economic impact of non-adherence is well documented with significantly higher annual adjusted per-patient medical costs (inpatient and outpatient).[43]

We found no associations between adherence and any determinants. Although it has been shown in other studies that increasing comorbidity (by CHA_2DS_2VASc) was associated with decreased likelihood of non-adherence.[33 41] Age ≥75 years, diabetes, female gender and anaemia were also associated with reduced risk of non-adherence, while hypertension and vascular disease were associated with increased risk. Adherence was non-linearly associated with time since the introduction of DOACs, increasing for approximately 2 years (to early 2013) before starting to decrease, returning to its original level by early 2015 and then dropping below its original level.

Persistence

Beshir *et al*[36] and Banerjee *et al*[33] differed on the documentation of what persistence was with the former deeming individuals to be persistent if no gaps of >90 days appear in the prescription history in the year following the index date while the latter felt it was >60 days following the index date. Thus, only qualitative analysis was possible. The limited findings in both studies were consistent with those of other studies in AF overall that showed persistence in DOACs to be better than VKAs.[30 32]

Dhamane *et al*[35] also deemed patients persistent with no gaps >60 days and said non-persistence was affected by CKD with HR 1.02 but no further details were given.[35]

Further analysis at drug level was not possible overall for comparison but Banerjee *et al*[33] reported a higher risk of non-persistence among dabigatran users than rivaroxaban and warfarin users. The two times per day dosing of dabigatran was thought to be a possible explanation for these observations. However, patients receiving apixaban, which also has a two times per day dosing regimen, had a lower risk of non-persistence than those receiving rivaroxaban and warfarin. This suggests that factors other than the dosing regimen play a major role in the lower persistence associated with dabigatran.

No studies have shown the determinants of persistence in CKD and AF. However, in just AF, heart failure, vascular disease, CKD, prior bleeding and alcohol misuse were associated with increased risk of non-persistence, while hypertension and age >65 years were associated with reduced risk.[33 41] Although the persistence rate of DOACs was higher than VKA, suboptimal persistence with DOAC therapy remains a great concern for patients with AF and CKD.

Limitations and strengths

Our study has several strengths. There is a high level of congruence between our findings and those reported in the existing literature. This is a timely systematic review that synthesises the evidence on extent of poor adherence to oral anticoagulants, its determinants, and clinical and economic outcomes, among patients with AF and CKD. We focused on mainly observational studies to evaluate the evidence on patients' real-world medication-taking behaviour. We considered all oral anticoagulants, including the newer drugs (apixaban, rivaroxaban, dabigatran and edoxaban), and aimed to generate pooled adherence at the individual drug level.

Our study also had some limitations. First and foremost, there were very few studies specifically on combined CKD, AF and DOAC. Second, there was heterogeneity of the included studies, possibly due to variations in definitions of adherence, small numbers, as well as follow-up durations. We tried to conduct subgroup analyses to pool the same definitions, however, residual heterogeneity persisted. Third, there was no universal tool available to assess the risk of bias for systematic reviews of observational studies. We used the Newcastle-Ottawa Scale, a commonly used tool, however, due to the similar methodology for our included studies; this tool did not differentiate between study quality and rated all included studies at the level of good quality. Finally, the included studies used scripts prescribed than dispensed, which does not necessarily mean they were taken. It is therefore possible that adherence and persistence rates are even lower than from the papers.

CONCLUSION

Adherence and correct dosing to DOACs were suboptimal in the pooled studies with respect to CKD and AF. Future research is needed as the lack of statistically significant sample sizes prevents the generalisability of findings. This is a rate-limiting factor for improved clinical and patient-reported outcomes. Insufficient data was available on persistence in CKD and AF to make any conclusions. As the ageing population increases with the identification of AF and CKD, there is greater importance of clinician awareness to DOAC adherence, persistence and appropriate dosing and its association to sex, age, ethnicity,

presence or absence of comorbidities and CHA_2DS_2-VASc scores.

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