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Comparative Efficacy of Direct Oral Anticoagulants vs. Warfarin in Atrial Fibrillation

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ABSTRACT
In patients with advanced kidney disease (AKD) and atrial fibrillation (AF), the safety and efficacy of direct oral anticoagulants (DOACs) have not yet been thoroughly proven. Goals to ascertain the safety and efficacy of combined or targeted DOACs in relation to warfarin in patients with AKD and AF. Techniques Retrospective identification was conducted in a Hospital for patients with AF and AKD (estimated glomerular filtration rate < 30mL/min) who were treated with warfarin or DOAC between June 2013 and December 2022. Major bleeding and hospitalizations for stroke/systemic embolism were the main consequences. Any bleeding and any ischaemia were considered secondary outcomes. Previously, prescriptions for dabigatran, rivaroxaban, apixaban and edoxaban were written in 2012, 2013, 2015 and 2017, respectively. Following the introduction of DOACs, the proportion of patients using warfarin dropped significantly over time (100% in 2011 and 20% in 2020). Similarly, following a sharp increase to a peak of 30.2% in 2013 and 35.4% in 2015, respectively, a downward tendency is seen with dabigatran and rivaroxaban. DOACs were associated with a decreased risk of ischaemic events in individuals with AF and AKD, while apixaban was associated with a lower risk of both ischaemia and bleeding overall compared to warfarin.

INTRODUCTION

Moreover, the presence of CKD is linked with an additional risk of thromboembolism and bleeding in patients with AF and vice versa[1]. As a result, it is crucial to pursue the most adequate oral anticoagulant (OAC) to strike the balance between preventing ischemic stroke and mitigating bleeding events in AF patients with CKD.

Warfarin has been the mainstay of treatment in patients with AF and renal impairment for decades. However, war- farin has several limitations, including a narrow therapeu- tic window for safety, constant monitoring requirements, numerous diet and drug-drug interactions[2]. Direct oral anticoagulants (DOACs) are relatively new agents, including dabigatran, rivaroxaban, apixaban and edoxaban, which have been demonstrated to be superior or not inferior to warfarin in AF for efficiency and safety[3-7]. Furthermore, DOACs have fixed dosing regimens, which enhance the compliance and persistence with oral anticoagulant therapy. As a result, with the availability of DOACs, the prescription volumes of warfarin have decreased globally[8-12].

However, few randomized controlled trials of oral antico- agulants comprised patients with advanced kidney disease (AKD), estimated glomerular filtration rate (eGFR) <30 mL/min. Although several regulatory agencies have authorized DOACs (except dabigatran) for patients with an eGFR above 15 mL/min on the basis of pharmacokinetic data and a meta-analysis has validated the efficacy and safety of DOACs in this population[13], the evidence of efficacy and safety between DOACs and warfarin remains low, par- ticularly in comparisons between different DOACs. The disparities in efficacy and safety among DOACs in patients with AKD patients may be influenced by differences in their pharmacokinetic profiles. Existing studies mostly contrasted single DOAC (e.g., rivaroxaban, apixaban)[14-16] or pooled DOACs[17,18] with warfarin, with less data on edoxaban or simultaneous comparison of the four DOACs individually with warfarin in AF patients with AKD.

The COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) database contains individual patient data from the 4 pivotal trials of DOACs versus warfarin in patients with AF[19]. We used data from the COMBINE AF database to perform network meta-analyses, aimed at assessing the overall safety and efficacy of DOACs versus warfarin, including 2 different DOAC treatment strategies (standard dose and lower dose). In these network meta-analyses, we aimed to leverage the strengths of individual patient data and estimate treatment effects by standardizing followup duration for time-to-event outcomes and study population across trials and to assess effect modification with a Cox regression model as well as across the spectrum of age as a continuous covariate.

MATERIALS AND METHODS

We recruited outpatients who were over 20 years old and who had been prescribed any kind of oral anticoagulant between June 2013 and December 2022. The date of treatment beginning was defined as the cohort entry date and the index date was the combination of the OAC prescription date and eGFR < 30mL/min. Cockcroft-Gault formula was used to measure CrCl. Those who had (1) no visits or only one visit with a diagnosis of AF within a year prior to the OAC prescription., (2) eGFR ≥30 mL/min during the study period or unknown., (3) evidence of an anticoagulant prescription., (4) a history of valve surgery, mitral stenosis, or kidney transplant within six months prior to the cohort entry date (i.e., the washout period) and (5) any other condition (see Table S1-S4 for codes).

The study began on the day following the index date and continued until the outcomes were disclosed. This included switching to different study medications, stopping anticoagulation prescriptions or waiting more than 30 days between new prescriptions, having no or recovering renal function (eGFR ≥30 mL/min) for more than 6 months, withdrawing from valve surgery, kidney transplantation, or mitral stenosis, dying, or the study ending on December 31, 2020, whichever came first (see Figure S1 for more information).

Statistical Analysis: We present the patterns in the research population's prescriptions for oral anticoagulants. To balance the differences in baseline characteristics between treatment groups, we used the inverse probability of treatment weighting (IPTW) technique for analysis. A multi variate logistic regression model was utilized to anticipate the likelihood of obtaining DOACs as opposed to warfarin, taking into account all factors. We multiplied the weights by the total number of patients in the treatment groups to stabilize them after we had weighted the patients using the inverse of this likelihood[20].

Before and after implementing IPTW, we used descriptive statistics to analyse the study population, and an absolute standardised difference (ASD) of ≥0.1 was considered to indicate a potentially significant imbalance[21]. In the weighted DOAC and warfarin cohorts, survival free of an incident was quantified using log-rank testing and Kaplan-Meier curves. The adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were determined using multivariate Cox proportional hazard regression models weighted with IPTW. The multivariate model included significant (ASD ≥0.1) variables as well as clinically relevant confounders (age, sex, CHA2DS2-VASc/HAS-BLED

score, smoking status, previous bleeding, cerebrovascular disease, myocardial infarction, peripheral vascular disease, venous thromboembolism, antiplatelets and non-steroidal anti-inflammatory drugs). In order to conduct a sub-analysis, we divided the group of DOACs included in the main analysis into four cohorts: those treated with dabigatran, rivaroxaban, apixaban and edoxaban and compared each cohort with warfarin.

RESULTS AND DISCUSSIONS

Dabigatran, rivaroxaban, apixaban and edoxaban were previously prescribed in 2012, 2013, 2015 and 2017, respectively. After the development of DOACs, the percentage of warfarin decreased markedly over the period (100% in 2011 and 20% in 2020). Similarly, a down- ward tendency can be observed in dabigatran and rivaroxa- ban, after a rapid elevation to a peak of 30.2% in 2013 and 35.4% in 2015, respectively. In contrast, the percentage of apixaban gradually increased and apixaban use (31.7%) exceeded warfarin use (23.4%) in 2017. By 2020, apixaban use was still prevalent (44.2%). The percentage of edoxaban was constant at around 21.1% between 2017 and 2020.

The incidence rates and aHRs of outcomes are expressed in (Table 2) and Kaplan-Meier survival curves of outcomes after integrating IPTW are depicted. The incidence rate of stroke/SE was 3.21 and 7.52 per 110 patient-years for the DOACs and warfarin groups with a considerably lower risk of stroke/SE between the groups (log-rank P=0.0440). In multi variate Cox regression analysis after IPTW, the aHR for DOACs versus warfarin was 0.30 (95% CI, 0.08-0.98., P=0.0440) for stroke/SE. No substantial difference between the two groups was found for major bleeding (5.31 and 3.72 per 110 patient-years for DOACs and warfarin, respectively) with a non-significant association estimate (aHR, 0.98., 95% CI, 0.35-3.91., P=0.9853). Furthermore, DOACs were linked to a significantly lower risk of any ischemia (aHR, 0.43., 95% CI, 0.23-0.80., P=0.0068). Finally, there was a non-significant trend toward less bleeding in the DOACs group (aHR, 0.75., 95% CI, 0.51-2.08., P=0.1237).

DOACs substantially decreased the risk of stroke/SE and any ischemia in patients with AF and AKD compared with warfarin. In the sub-anal- ysis of each DOAC, apixaban was linked to a significant reduction in the risk of any ischemia and any bleeding com- pared with warfarin. In the current study, we observed that the percentage of DOAC use in patients with AF and AKD has consistently increased in the last decade, with a corresponding decline in warfarin. A similar trend was found in the other stud- ies of AF patients with chronic renal disease[22-25], We discovered that rivaroxaban and apixaban were the two most prevalently prescribed DOACs, which is coherent with prior studies in AF patients[26,27]. The increasing use of DOACs highlights the importance of their use in AKD populations to assess efficacy and safety, necessitating the need for additional evidence.

Based on our findings, DOACs seem to be more efficient than warfarin in preventing ischemic stroke/systemic embolism and any ischemia events among patients with AF patients with AKD. A multi center retrospective cohort study, also undertaken in Taiwan, revealed similar results[28]. A systematic review and meta-analysis merging data from various observational studies of this population dis- covered similar outcomes[16]. In the present study, we observed a significant disparity in the distribution of individuals with end-stage renal disease (ESRD, eGFR <15mL/min with or without dialysis) between DOACs and warfarin (DOACs 3.7% versus warfarin 33.2%). This finding aligns with the results reported by Betra *et al*., indicating that warfarin remains the preferred OAC choice for patients with ESRD[29]. Previous meta- analyses comparing DOACs with warfarin in the ESRD population, primarily focusing on dialysis patients, have yielded inconsistent outcomes. See *et al.* reported no signifi- cant difference in effectiveness and safety outcomes between DOACs and warfarin in AF patients on dialysis[30]. In con- trast, Elfar *et al.* demonstrated that DOACs were associated with higher rates of systemic embolization, minor bleeding, and death compared to warfarin[31]. Conversely, Li *et al.* found that DOACs were associated with a reduced risk of gastrointestinal bleeding[32]. Furthermore, none of the studies have specifically examined ESRD patients without dialysis. Therefore, further studies are needed to validate OAC selection for the AF patients with ESRD.

We identified evidence of interaction favoring standard-dose DOACs over warfarin with respect to the major bleeding outcome for the subgroup of patients with low baseline body weight. Interaction testing from 3 of the 4 individual trials have shown no statistically significant interaction for major bleeding by baseline body weight[33-35], whereas 1 of the 4 individual trials showed findings similar to those from our meta-analyses with respect to a treatment interaction favoring DOACs in lower body weight[36]. The interaction may relate to the finding that the incidence of major bleeding was higher among patients with lower body weight, which in turn is related to other factors such as older age and worse kidney function, both of which are associated with higher risk for major bleeding and tendency for greater safety with DOACs. Dedicated analyses from COMBINE AF analyzing body weight as a continuous variable are forthcoming. We identified evidence of interaction favoring standard-dose DOACs over warfarin with respect to the stroke or systemic embolism outcome for the subgroup of patients with low baseline creatinine

Table 1: Baseline Characteristics of the Study Population Before and After Inverse Probability of Treatment Weighting

Variables	Before Weighting			After Weighting		
	DOACs (N=819)	Warfarin (N=212)	Absolute standard - ized difference	DOACs (N=513)	Warfarin (N=518)	Absolute standard - ized difference
Demographics						
Age, mean (SD), y	85.3 (8.2)	79.1 (11.4)	**0.67**	84.3 (7.4)	83.4 (13.5)	0.08
Female sex, (%)	43.8	43.7	0.01	43.9	44.8	0.03
Weight, mean (SD), kg	59.1 (12.3)	61.6 (13.4)	**0.24**	59.4 (9.6)	59.5 (18.3)	0.03
eGFR, No. (%)			0.83			0.03
15-29mL/min	97.1	67.7		92.1	91.6	
<15mL/min, including dialysisa	4.8	34.1		9.5	8.3	
Comorbidities, No. (%)						
CHA_2DS_2-VASc score, mean (SD)	5.6 (2.3)	5.6 (2.5)	0.05	5.3 (2.3)	6.8 (3.1)	0.03
HAS-BLED score, mean (SD)	4.2 (2.4)	4.5 (2.1)	**0.26**	4.1 (2.0)	4.6 (2.6)	0.03
Quan-Charlson Comorbidity Index, mean (SD)	3.8 (3.1)	4.0 (3.2)	**0.15**	3.6 (2.7)	3.4 (4.1)	0.01
Anemia	14.2	18.7	**0.13**	14.5	12.3	0.08
Asthma	7.4	4.3	0.06	7.1	4.2	0.05
Cancers	20.7	15.3	**0.16**	20.2	20.6	0.03
Cerebrovascular disease	34.5	32.9	0.05	33.5	36.8	0.07
Congestive heart failure	49.2	48.1	0.04	49.7)	49.2	0.00
Myocardial infarction	5.3	8.7	**0.24**	5.6	6.0	0.01
Peripheral vascular disease	5.1	9.2	**0.18**	5.6	4.5	0.05
Chronic obstructive pulmonary disorder	19.1	18.7	0.01	20.4	16.3	**0.11**
Diabetes	34.7	44.3	**0.20**	37.3	40.5	0.08
Gastrointestinal ulcer	17.5	17.2	0.01	18.3)	14.2	**0.12**
Hypertension	78.7	81.4	0.07	79.5	81.6	0.05
Hyperlipidemia	27.4	35.1	**0.18**	29.5)	31.2	0.04
Liver disease	9.1	11.6	**0.11**	9.2	9.6	0.03
Prior bleeding[b]	26.3	22.7	0.09	25.2	23.2	0.06
Smoking			**0.13**			0.08
Current non-smoker	94.6	95.2		95.3	96.3	
Current smoker	3.2	4.1		3.1	2.7	
Unknown	5.4	3.1		4.6	3.7	
Thyroid Disease	8.7	9.7	0.05	9.4	11.2	0.07
Venous thromboembolism	3.4	2.7)	0.05	3.3	4.7	0.08
Medication use, No. (%)						
Antianxiety agents	28.1	33.4	**0.12**	29.1	26.9	0.07
Antiarrhythmic agents	28.3	33.1	**0.12**	28.7	29.3	0.01
Anti-depressants	12.7	11.8	0.04	13.5	14.3	0.05
Antiplatelets	36.5	44.9	**0.18**	37.5	37.1	0.01
Anti-hyperlipidemics	32.4	39.4	**0.17**	34.7	39.3	0.08
ACEi / ARB	58.3	66.7	**0.19**	60.3	61.2	0.03
ß-Blockers	55.4	58.3	0.07	55.7	57.2	0.03
Calcium channel blockers	68.4	71.2	0.07	67.7	70.1	0.05
Diuretics	64.2	66.3	0.05	65.8	70.2	0.11
Other anti-hypertensive	13.8	23.1	**0.26**	14.2	13.2	0.05
Insulin	8.6	20.1	**0.28**	12.3	12.7	0.01
Antidiabetics	25.6	32.8	**0.17**	27.1	31.8	0.11
NSAIDs	25.4	20.7	**0.12**	25.2	27.1	0.05
Proton pump inhibitors	18.1	24.4	**0.17**	19.2	20.1	0.04

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors., ARBs, angiotensin II receptor antagonists., DOACs, direct oral anticoagu- lants,. eGFR, estimated glomerular filtration rate., NSAIDs, non-steroidal anti-Inflammatory drugs.

[a] Three (0.6%) patients in the DOACs group and 13 (2.6%) patients in the warfarin group received hematolysis.

[b] Prior bleeding included gastrointestinal bleeding, intra cranial hemorrhage and other major bleeding, e.g., hematuria, epistaxis and hemop-

Table 2: Incidence Rates and Hazard Ratios of Outcomes After Inverse Probability of Treatment Weighting

Outcome	DOACs group (n=513)			Warfarin group (n=518)			
	Events	PY	Rate (95%CI)[a]	Events	PY	Rate (95%CI)[a]	Adjusted HR (95% CI)[b]
Stroke/SE	10	218	3.21 (0.92-6.52)	22	269	7.53 (4.06-10.53)	0.30 (0.08-0.98)
Major bleeding	14	218	5.31 (3.24-9.31)	12	267	3.72 (1.31-5.74)	0.98 (0.35-3.91)
Any ischemia	22	212	9.28 (6.11-14.31)	40	258	15.11 (11.9-20.71)	0.43 (0.23-0.80)
Any bleeding	60	104	29.31 (22.81-37.94)	70	212	33.30 (26.32-42.21)	0.75 (0.51-3.08)

clearance. Previous study-level meta-analyses have similarly suggested a greater benefit of standard-dose DOACs over warfarin in patients with lower baseline creatinine clearance[37], but these analyses have been limited by the use of categorical creatinine clearance cutoffs that restrict the generalizability of the results. Dedicated analyses from Combine AF analyzing creatinine clearance as a continuous variable are forthcoming. An important strength of these analyses is the ability to assess effect modification using continuous baseline variables. We demonstrate consistent benefits of standard-dose DOACs versus warfarin for stroke or systemic embolism across the continuous spectrum of age. For the major bleeding outcome, younger patients experienced a greater reduction in bleeding with standard-dose DOACs versus warfarin, perhaps because of a lower prevalence of competing comorbidities such as

previous gastrointestinal bleeding or kidney dysfunction. Previous reports assessing treatment interaction by age are limited by the use of categorical data, with a typical age cut point of < or ≥75 years. There is generally more information in a continuous variable when assessed as such. Moreover, data derived from categorical cut points are challenging to interpret because within each category exists a wide spectrum of competing comorbidities, some of which are factors influencing DOAC dose reduction for 3 of the 4 individual trials. Although there was little or no between-trial heterogeneity detected in these analyses for the examined efficacy outcomes, moderate between-trial heterogeneity with respect to bleeding outcomes was detected, thus aggregate findings for bleeding outcomes must be interpreted with caution.

CONCLUSION

When compared to warfarin, the use of DOACs was associated with a decreased risk of ischaemic events in individuals with AF and AKD. When compared to warfarin, apixaban among DOACs was associated with a significant decrease in the risk of any ischaemia and any bleeding.

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