의학박사 학위논문

중등도 이상의 삼첨 판막 역류증 이 동반된 심방세동 환자에서 Direct-acting Oral Anticoagulant 사용의 유용성

Use of Direct-acting Oral Anticoagulants in Patients with Atrial Fibrillation and Significant Tricuspid Regurgitation

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양 유 진

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이 논문을 의학박사 학위 논문으로 제출함

2023 년 8 월

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2023 년 08 월

국문요약

배경

비판막성 심방세동 환자에서 Direct-oral anticoagulant (DOAC) 은 항응고제 치료의 표준치료로 자리 잡았다. 하지만, 중등도 이상의 삼첨판 역류증에서, DOAC 의 효능과 안정성에 대한 연구는 제한적이다. 중등도 이상의 삼첨판 역류증은 장 간정맥의 울혈을 유발하며 간, 소장, 신장의 기능장애를 일으킬 수 있다. 이로 인해, 이런 환자에서 Prothrombin time 의 연장이나 DOAC 의 생체 이용률 감소가 보일 수 있다. 따라서, 우리는 중등도 이상의 삼첨판 역류와 심방세동을 가진 환자에서, 항응고제 중 와파린과 DOAC 의 효과와 안정성에 대해 비교하였다.

방법

서울아산병원에서 2010 년 1 월부터 2020 년 12 월에 심초음파상 중등도 이상의 삼첨판 역류증과 비판막성 심방세동이 동반된 환자를 후향적으로 검토하였고, 1215 명 (와파린 491, DOAC 724 명) 이 최종 분석에 포함되었다. 일차 평가 변수는 허혈성 뇌졸중과 전신 색전증 그리고 주요 출혈로 정하였다. 이차 평가 변수는 뇌출혈, 소화기 출혈, 모든 사망, 복합 지표 (허혈성 뇌졸중과 전신 색전증, 주요 출혈로 인한 입원, 모든 사망) 로 정하였다. 통계적으로 inverse probability treatment weighting (IPTW)을 이용하여 두 군을 조정하여 비교하였다.

결과

이번 분석의 추적 관찰 기간 중앙값은 2.4 년이다. IPTW 보정한 군에서, DOAC 은 허혈성 뇌졸중과 전신 색전증 (adjusted hazard ratio[aHR]:0.95, 95% confidence interval

[CI]:0.67-1.36, p =0.79), 주요 출혈 (aHR:0.78, 95% CI:0.57-1.06; p=0.11)에서 비슷한 위험도를 보였다. 2 차 평가 지표로는 DOAC 이 뇌출혈 (aHR:0.27 ,95% CI: 0.14-0.54, p=0.0002), 복합지표 (aHR:0.81, 95% CI:0.67-0.99, p=0.04)에서는 낮은 위험도를 보였다. 그 외에 소화기 출혈 (aHR: 1.15, 95% CI:0.78-1.71; p=0.47), 모든 사망(aHR:0.89, 95% CI:0.65-1.21, p=0.44)은 비슷한 위험도를 보였다. 중증의 독립적 삼천 판막 역류증 환자에서는, DOAC 은 일차, 이차 평가 지표에서 비슷한 위험도를 보였다. DOAC 복용군중, 허용사항 용량군과 허용 사항 외 저용량을 와파린과 비교할 때 두 용량 군 모두 와파린에 비해 유의미하게 뇌출혈 위험은 낮았다. (aHR: 0.16, 95% CI:0.06-0.40; p<0.001) (aHR: 0.45, 95% CI:0.24-0.85; p=0.01). 허용 사항 용량군과 허용 사항 외 저용량 군을 비교했을 때 뇌출혈이 허용사항 용량군이 낮게 나오는 경향을 보였으나 유의미하지는 않았다. 하위 군 분석에서는 몸무게가 60kg 미만인 경우에 허혈성 뇌졸중과 전신 색전증에서 DOAC 군이 더 낮은 위험도를 보였다. 그리고 주요 출혈은, 하대정맥 울혈이 없는 군, 삼첨판 막 역류가 중등도인 군, 몸무게가 60kg 미만인 경우에서 DOAC 이 더 유리한 결과를 보여주었다.

결론

이 후향적 연구에서 비판막성 심방세동과 중등도 이상의 삼첨판 역류 증 환자에서, DOAC 은 허혈성 뇌졸중 및 전신 색전증, 주요출혈에 대해 비슷한 효능을 보였고, 뇌출혈에 대해서는 더 낮은 위험을 보였다. DOAC 은 특히 몸무게 60kg 미만 환자에서 효과적이고 안전하며, 중등도 삼첨판 군과 역류 하대정맥 울혈이 없는 군에서 안전한 경향을 보였다. 이 논문은 중등도 이상의 삼첨판 막 역류 증 환자에서도 DOAC 의 효용성과 안정성을 뒷받침하는 근거를 제공할 수 있다.

Contents

ABBREVIATION LIST

AF: atrial fibrillation

aHR: adjusted hazard ratio

CI: confidence interval

DOAC: direct-oral anticoagulant

GI: gastrointestinal

ICH: intracranial hemorrhage

IPTW: inverse probability treatment weighting

LV: left ventricular

RCT: randomized controlled trials

SMD: standardized mean difference

IS/SE: ischemic stroke and systemic embolic event

TR: tricuspid regurgitation

INTRODUCTION

The prevalence of significant (moderate or greater) tricuspid regurgitation (TR) is 0.55%, which increases with age; its prevalence is estimated at 5% in the population over 75 years of age.[1] The majority of cases of significant TR are secondary to causes that dilate the right atrium and right ventricle, including left-sided valvular disease, left ventricular dysfunction, and chronic atrial fibrillation (AF).[2] Although secondary TR is caused by a dilated right atrium or right ventricle, a vicious cycle occurs as TR exacerbates right ventricle remodeling. The late stages of severe TR manifest as right heart failure, with fatigue, peripheral edema, and hepatomegaly.[2] Additionally, significant TR can contribute to renal and hepatic dysfunction by elevation of central venous pressure and splanchnic congestion.[3, 4]

AF is a major cause of secondary TR and in these patients' anticoagulation is essential to prevent strokes. The safety and efficacy of direct-oral anticoagulants (DOACs) in patients with AF were well established by four landmark randomized controlled trials (RCTs),[5-8] and DOACs became the main anticoagulant therapy in patients with nonvalvular AF. In patients with non-valvular AF and significant valvular heart disease, DOACs also showed consistent efficacy and safety in the subgroup analyses of four RCTs [9-12]. In these subgroup studies, DOACs showed comparable or superior efficacy and comparable safety outcomes. However, most of the significant valvular heart disease in these subgroup studies was mitral regurgitation. There is limited data on

DOAC use in patients with significant TR with AF, especially in cases with hepatic or renal dysfunction due to elevated central venous pressure caused by significant TR. Therefore, in the present study, we focused on significant TR with AF and compared the efficacy and safety of DOACs and warfarin in these patients.

METHODS

Study design and population

This retrospective study was conducted at Asan Medical Center. We included patients with significant (moderate or severe) TR with non-valvular AF seen from Jan 2010 to Dec 2020. The exclusion criteria were: 1) rheumatic mitral stenosis, 2) percutaneous mitral balloon valvuloplasty or valve surgery, 3) congenital heart disease, 4) percutaneous left atrial appendage closure device, 5) moderate to severe aortic or mitral valvular heart disease, 6) constrictive pericarditis, 7) cardiac amyloidosis, 8) idiopathic pulmonary hypertension, 9) other diseases requiring anticoagulation, such as pulmonary thromboembolism, 10) prescription of oral anticoagulants for less than 1 month, 11) end stage renal disease, and 12) chronic obstructive pulmonary disease. The study population flow chart is shown in **Figure 1**. The study was approved by the Asan Medical Center Institutional Review Board (IRB no; 2020-1872).

Clinical and laboratory data

The baseline clinical covariates were age; sex; weight; body mass index; and comorbidities, including hypertension, diabetes mellitus, heart failure, cancer, history of stroke, history of coronary intervention, history of percutaneous transluminal angioplasty, history of intracranial hemorrhage (ICH), history of gastrointestinal (GI) bleeding, history of major bleeding, and the presence of a permanent pacemaker. CHA2DS2-VASc scores were also calculated; congestive heart failure, hypertension, diabetes, vascular disease, age of 65-74 years, and female sex were each assigned one point, and an age of 75 years or older and a prior stroke or transient ischemic attack was assigned two points.[13] Anti-platelet medication (aspirin, clopidogrel, prasugrel, or ticagrelor) during the follow up period was evaluated. Laboratory data, including hemoglobin

levels, platelet counts, creatinine clearance (Cockcroft–Gault), total cholesterol, liver function test results (aspartate aminotransferase, alanine transaminase, total bilirubin, alkaline phosphatase, r-glutamyl transferase), and B-type natriuretic peptide were also included.

Echocardiographic data

Baseline echocardiographic parameters at the time of TR diagnosis were included: left ventricular dimension in diastole/systole, left ventricular posterior wall thickness, interventricular septal thickness in diastole, left ventricular mass index, left atrium, ejection fraction, TR grade, tricuspid valve peak velocity, and the presence of inferior vena cava (IVC) plethora. The left ventricular dimension in diastole, left ventricular posterior wall thickness, interventricular septal thickness in diastole, and the left atrium were measured in the parasternal long-axis view. Using these values, the left ventricular (LV) mass was calculated using the linear method cube formula and was divided by the body surface area to calculate the LV mass index.[14] The LV ejection fraction was measured using the biplane Simpson volumetric method, combining apical 4- and 2-chamber views.[14] Moderate to severe TR was graded by the echocardiographic criteria of the 2017 European Society of Cardiology.[15] A group with a peak TR velocity of 3.4 m/s or higher is considered to have a high probability of pulmonary hypertension according to the 2015 European Society of Cardiology review article.[16] IVC plethora is defined as a less than 50% decrease in IVC diameter after deep inspiration.[17]

Clinical outcomes and follow up.

The primary efficacy and safety outcomes were clinical outcomes to compare the effectiveness and safety of DOACs versus warfarin: ischemic stroke and systemic embolic event (IS/SE), and hospitalization for major bleeding. A major bleeding event was defined as fatal bleeding, symptomatic bleeding in a critical organ, and bleeding either causing a fall in hemoglobin

levels of more than 2 g/dL or leading to the transfusion of two or more units of whole blood or red cells, as defined by the International Society on Thrombosis and Haemostasias.[18] Secondary efficacy outcomes were all-cause mortality and a composite outcome (IS/SE + hospitalization for major bleeding + all-cause mortality). Secondary safety outcomes were ICH and GI bleeding. ICH was defined as any bleeding within the intracranial vault, including bleeding into the brain parenchyma and surrounding meningeal spaces. [19] The index date was the date of initial warfarin or DOAC prescription. Patients were censored at the time of the outcome event, valve surgery, or last follow up period (September 2021). In cases with anti-coagulant change, if we ensured the separation of the data for each anti-coagulant period, patients were included twice, once for each treatment period.

Statistical analysis

The propensity score method was used for comparisons between the warfarin and DOAC treatment groups. The propensity score of being in the warfarin or the DOAC group was assessed by a logistic regression model, which included the following baseline characteristics: age, weight, diastolic blood pressure, CHA2DS2-VASc score, creatinine clearance, hemoglobin, total cholesterol, low density lipoprotein, total bilirubin, albumin, left atrial diameter, left ventricular mass index, ejection fraction, and peak TR velocity as continuous variables and sex, anti-platelet medication, heart failure, hypertension, diabetes mellitus, history of stroke, history of coronary intervention, history of percutaneous transluminal angioplasty, history of major bleeding, cancer, presence of pacemaker, TR grade (moderate or severe), and presence of IVC plethora as categorical variables. Variables related to IS/SEs and major bleeding with clinical relevance or a *P*-value <0.1 in univariable analysis were included. Based on the calculated propensity score, inverse probability treatment weighting (IPTW) was used to balance covariates between the two treatment groups in the total study population and

the severe TR group. [20] C-statistics for the propensity score models of the total population and patients with severe TR were 0.68 and 0.71. The balance of covariates between the two treatment groups was assessed by standardized mean differences (SMDs). An SMD ≤ 0.1 is considered a good balance between the two treatment groups.[21] The balance of the baseline covariates before and after weighting in the total population are presented (Supplementary Table 1). A weighted Cox proportional hazard regression model was used for clinical outcome analysis. The proportional hazards assumption of the Cox proportional hazard model was confirmed by examination of the log (-log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no significant violations were found. The hazard ratios of the DOACs group for clinical outcomes were calculated using the warfarin group as a reference.

In a subgroup of patients with severe TR, the warfarin and DOAC groups were also evaluated using the propensity score method (Supplementary Table 2).

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R software version 4.0.5. (R Foundation for Statistical Computing, Vienna, Austria). *P* values <0.05 were considered to indicate statistical significance.

Subgroup analysis

To compare efficacy and safety within the DOAC group, we divided patients by dose regimen, as on-label dose and off-label underdose groups. Individuals on full dose DOAC therapy (5 mg apixaban, 20 mg rivaroxaban, 60 mg edoxaban, or 150 mg dabigatran) or apixaban 2.5 mg if patients fulfilled two of three criteria: age ≥80 year, weight ≤ 60kg, and serum creatinine ≥1.5mg/dL; rivaroxaban15 mg if creatinine clearance was ≤ 50 ml/min; edoxaban 30 mg if weight was ≤ 60 kg or creatinine clearance was ≤50 ml/min; and dabigatran 110 mg if age was

≥80 and creatinine clearance ≥ 30ml/min, were classified as on-label dose users. [22] Individuals taking reduced dose without fulfilling the above criteria are classified as off-label underdose users. Each treatment group was also rebalanced using IPTW by the calculated propensity score (Supplementary Table 3). Analysis according to multiple groups, including warfarin and DOAC types (dabigatran, rivaroxaban, apixaban, and edoxaban) could not be done because of imbalances after the use of the IPTW method. In the total study population, subgroup analysis was performed according to presence of IVC plethora, TR grade, age strata (<65, 65 to 74, and ≥75 years), sex, body weight (<60 kg and ≥60 kg), liver function (total bilirubin <2 mg/dL and ≥2 mg/dL) and renal function (creatinine clearance <50 ml/min and ≥50 ml/min). Subgroup analysis was performed using weighted Cox proportional hazard models in a well-balanced total population cohort and *P* for interaction was also calculated.

RESULTS

Baseline characteristics

A total of 1215 patients with moderate to severe TR and non-valvular AF, who were prescribed warfarin (n = 491) and DOACs (n=724), were included. Among the patients on DOACs, 9.7% were prescribed dabigatran (n=70), 30.8% rivaroxaban (n=223), 33.4% apixaban (n=242), and 26.1% edoxaban (n=189). Among the patients on DOACs, 34.4% were prescribed off-label underdoses (n=249). Time in the therapeutic range by the traditional method of the warfarin group was 57.5%.

Before propensity score weighting, DOAC users were older and had less history of heart failure. For echocardiographic data, DOAC users tended to have a less severe TR grade, lower left ventricular mass index, smaller left atrial diameter, higher ejection fraction, and less IVC

plethora. For laboratory data, DOAC users had a lower total bilirubin (**Table 1**). After propensity score weighting, the two treatment groups were well-balanced in terms of the baseline covariates (Supplementary Table 1).

Clinical outcomes in patients with moderate to severe tricuspid regurgitation

The median duration of follow-up was 2.4 years (interquartile range; 1.0 to 4.1 years) The incidence rate of all the clinical outcomes is shown in **Table 2**. Nine cases of major bleeding events, other than ICH and GI bleeding, were reported; they included four cases of muscle hematoma, one of hemarthrosis, one of hemoptysis, one of hematuria, one of vaginal bleeding, and one of chest tube bleeding. Six cases of systemic embolic events were reported; they included two renal infarctions, three acute limb events, one superior mesenteric infarction, and one splenic infarction. Compared to warfarin (reference), DOACs had comparable risk for IS/SE (adjusted hazard ratio [aHR]: 0.95, 95% confidence interval [CI]: 0.67-1.36; *P*=0.79) and major bleeding (aHR: 0.78, 95% CI: 0.57-1.06; *P*=0.11). For the secondary outcomes, DOACs had lower risk for ICH (aHR: 0.27, 95% CI: 0.14-0.54; *P*<0.001) and the composite outcome (aHR: 0.81, 95% CI: 0.67-0.99; *P*=0.04) compared to warfarin. DOACs showed similar risks for GI bleeding (aHR: 1.15, 95% CI: 0.78-1.71; *P*=0.47) and all-cause mortality (aHR: 0.89, 95% CI: 0.65-1.21; *P*=0.44) (**Table 2**). The weighted incidence curves of the primary and secondary outcomes in the moderate to severe TR group are shown in **Figures 2 and 3**.

Clinical outcomes in patients with severe TR

In the total study population, 18% of patients (n=256) were classified as severe TR; of these, 53% (n=136) were on warfarin and 47% (n=120) on DOACs. Before IPTW, the DOAC users tended to be older, have higher CHA2DS2 VAS scores, less heart failure, more diabetes

mellitus, more hypertension, more history of ICH, less IVC plethora, and a lower total bilirubin level (Supplementary Table 2).

The distribution of patients with severe TR before and after IPTW is presented in Supplementary Table 2. After IPTW analysis, the key baseline covariates were well balanced. There was one systemic embolic event, which was a renal infarction, and three bleeding events (two muscle hematomas and one hemarthrosis) in the severe TR group. The incidence rates and hazard ratios of the clinical outcomes are shown in **Table 3**. In the severe TR group, DOAC users had a comparable risk with warfarin for primary and secondary outcomes: IS/SE (aHR: 1.20, 95% confidence interval [CI]: 0.65-2.24; *P*=0.56), major bleeding (aHR: 1.03, 95% CI: 0.55-1.92; *P*=0.92), ICH (aHR : 0.79, 95% CI: 0.18-3.43; *P*=0.76), GI bleeding (aHR: 1.11, 95% CI: 0.50-2.46; *P*=0.80), all-cause mortality (aHR: 0.67, 95% CI: 0.34-1.34; *P*=0.26), and the composite outcome (aHR: 0.90, 95% CI: 0.62-1.32; *P*=0.60). The weighted incidence curves of the primary outcomes in the severe TR group are shown in Supplementary Figure 1.

Subgroup analysis: DOAC doses

Among DOAC users (n=724), 34% were prescribed off-label underdoses (n=252) and 66% on-label doses (n=478). Baseline characteristics and echocardiographic data according to DOAC dose, off-label underdose, and on-label dose, are presented in Supplementary Table 3. After weighting, key baseline covariates were relatively well balanced with SMD although some variables were slightly higher than 0.1 (Supplementary Table 3). The incidence rate of the clinical outcomes according to DOAC dose, off-label underdose, and on-label dose, are shown in Supplementary Table 4. Both the on-label dose DOAC and off-label underdose DOAC showed lower risk for ICH compared to warfarin (aHR: 0.16, 95% CI: 0.06-0.40; *P*<0.001) and (aHR: 0.45, 95% CI: 0.24-0.85; *P*=0.01), respectively. On-label dose DOACs

had a better composite outcome than warfarin (aHR: 0.72, 95% CI: 0.58-0.90; *P*=0.003) (**Table 4**). On-label dose DOAC and off-label underdose DOAC showed similar risks for the primary and secondary outcomes. The weighted incidence curves of the primary outcomes in the total group, according to DOAC dose and warfarin, are shown in Supplementary Figure 2.

Subgroup analyses stratified by inferior vena cava plethora, tricuspid regurgitation grade, age, sex, body weight, total bilirubin, and creatinine clearance.

The crude incidences of the clinical outcomes, according to treatment by DOACs or warfarin in various subgroups, are presented in Supplementary Table 5.

The adjusted hazard ratios for the primary outcomes, according to several groups, are shown in **Table 5.** Interaction with treatment was significant for IVC plethora (major bleeding), TR grade (major bleeding), and body weight (stroke and embolic events, major bleeding). DOACs tended to be more effective in patients under 60 kg (aHR: 0.53, 95% CI: 0.31-0.91; *P* for interaction=0.01) and safer in groups with weights under 60 kg (aHR: 0.53, 95% CI: 0.33-0.85; *P* for interaction=0.02), groups with no IVC plethora (aHR: 0.62, 95% CI: 0.43-0.89; *P* for interaction=0.03) and groups with moderate TR grades (aHR: 0.67, 95% CI: 0.47-0.95; *P* for interaction=0.04) (**Figures 4 and 5**) The adjusted hazard ratios for secondary outcomes, according to several groups, are shown in Supplementary Table 6.

DISCUSSION

We used this retrospective, single center study of patients with moderate to severe TR and non-valvular AF on anticoagulants to compare the efficacy and safety of DOACs and warfarin. The main findings were as follows: (1) DOACs had similar risks for IS/SE and major bleeding as warfarin, (2) For secondary outcomes, DOACs had a lower risk for ICH and the composite outcome compared to warfarin, (3) In the group with severe TR, DOACs had a comparable

risk for primary and secondary outcomes, (4) On-label dose DOACs and off-label underdose DOACs both showed reduced risk for ICH compared to warfarin. On-label dose DOACs and off-label dose DOACs had a similar risk for the primary and secondary outcomes. (4) In subgroup analysis, DOACs tended to be safer in the group with weight under 60 kg, the group with no IVC plethora, and groups with moderate TR.

There are several meta-analysis and subgroup studies that evaluated the efficacy and safety of DOACs in patients with valvular heart disease.[9-12, 23] The sub-group studies of RCTs [9-12] included patients with moderate valvular heart disease, at minimum, most of which was mitral regurgitation. The sub studies of the ROCKET AF and ENGAGE AF-TIMI 48 trials did not include TR.[9, 12] These four sub studies showed consistent results, in that patients with valvular heart disease had an increased risk for major bleeding and a comparable risk for IS/SE compared to patients without valvular heart disease. For treatment and valvular heart disease interaction, dabigatran, apixaban, and edoxaban showed no significant interactions, demonstrating consistent efficacy and safety in valvular heart disease.[9-11] However, rivaroxaban tended to have a high bleeding risk, mostly GI bleeding, in patients with valvular heart disease.[12] It is unclear whether this effect of rivaroxaban on major bleeding is a real drug effect or just a post RCT analysis issue. The study population of these sub studies included heterogenous significant valvular disease, including aortic and mitral valve disease. Additionally, two studies did not include TR. Therefore, these results have limitations in their applicability to patients with significant TR.

In this study, the study population was limited to patients with moderate to severe TR with non-valvular AF and excluded other significant valvular heart disease. The incidence rates of the clinical outcomes were comparable with those of four previous landmark RCTs.[5-8] For treatment outcomes, DOACs had comparable IS/SE and major bleeding risks, but a

significantly lower risk for ICH. Other than the lower risk for IS/SE with apixaban and dabigatran 150 mg in two RCT sub-studies, [10, 11] this study result is similar to that of previous sub-studies. [9-12] In the severe TR group, DOACs had comparable IS/SE, major bleeding, and secondary outcomes, including ICH. It is uncertain why DOAC's favorable risk profile was not observed in the severe TR group. This could be because of the small sample number or a real result for the severe TR group. The comparable risk profile of DOACs and warfarin can be attributed to renal and hepatic dysfunction due to prolonged splanchnic congestion in severe TR. Further studies with large sample sizes are needed for severe TR.

In subgroup analysis, in the low weight group (under 60 kg), DOACs tended to have a reduced risk for IS/SE and major bleeding compared to warfarin. Although there is a study on the negative association between dabigatran and body weight and trough concentration,[24] the association between weight and drug trough concentration for other DOACs is not considered significant. The interaction between the type of anticoagulant and clinical outcomes according to body weight was not clear.[25] Therefore, this result should be interpreted with caution as DOACs were also effective and safe in the low body weight group. There was significant interaction between treatment and major bleeding events according to the TR grade and the presence of IVC plethora. DOAC's favorable safety profile for major bleeding was not evident in the group with severe TR or IVC plethora. It can be assumed that right volume overload can increase hepatic venous pressure, which can cause perisinusoidal edema. This can affect hepatic drug clearance and drug metabolism.[26, 27] This result suggests that there is an increased risk of major bleeding in the group with severe TR or IVC plethora, compared to those with moderate TR or without IVC plethora, especially in patients taking DOACs.

The prevalence of moderate to severe TR is estimated at 5% in the population over the age of 75. [1] Considering that most TR is secondary to AF, the incidence of TR will increase. There is

limited data on DOAC efficacy and safety in these patients. This study suggests that DOACs are also effective and safe in patients with moderate to severe TR.

This study has several limitations. First, it is a retrospective study, therefore confounding variables that were not considered may have influenced the findings. Therefore, our findings should be considered as hypothesis-generating only. Second, the study population was relatively small so propensity score matching could not be applied among the DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban). Previous studies have shown different risks for clinical outcomes among the DOACs, such as rivaroxaban's high bleeding risk tendency in valvular heart disease. Because balance among these groups could not be achieved, we could not compare efficacy and safety among the DOACs. Further large sample studies or analyses of patients with significant TR would help identify the different profiles of the DOACs. Third, this study did not include a control group of AF patients without significant TR on anticoagulation. Due to the lack of a control group, it was difficult to compare the effect of significant TR on patients with AF directly. However, there are many previous studies, with patients with AF and without significant TR, that can be referenced. Despite these limitations, our study is the first to evaluate the efficacy and safety of DOACs in patients with significant TR. This study could provide evidence that DOACs have comparable efficacy and safety in patients with significant TR.

CONCLUSION

In this retrospective study, in patients with significant TR and non-valvular AF, DOACs had comparable risks for IS/SE and major bleeding. In severe TR, DOACs had a similar risk for IS/SE and major bleeding. Between on-label dose DOACs and off-label underdose DOACs, there was no significant difference in risk for clinical outcomes. In subgroup analyses, in the

low weight group, DOACs tended to be more effective and safer than warfarin. Additionally, in moderate grade TR or in the no IVC plethora group, DOACs tended to be safer than warfarin.

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Table 1. Baseline characteristics of patients on warfarin or direct oral anticoagulants

		Unadjusted	
Characteristics	**Warfarin**	**DOACs**	**SMD**
(Total=1215)	**(N=491)**	**(N=724)**	
Male	245 (49.9)	334 (46.1)	0.075
Age, years	71.5±10.0	74.1±9.4	0.269
Anti-platelet drugs	80 (16.3)	104 (14.4)	0.054
Severe TR	136 (27.7)	120 (16.6)	0.289
CHA2DS2_VAS score	3.0±1.5	3.2±1.5	0.163
Heart failure	108 (22.0)	102 (14.1)	0.207
Hypertension	304 (61.9)	482 (66.6)	0.097
Diabetes mellitus	105 (21.4)	175 (24.2)	0.066
History of stroke	121 (24.6)	154 (21.3)	0.08
History of PCI/CBGA	51 (10.4)	94 (13.0)	0.08
History of PTA	11 (2.2)	11 (1.5)	0.053
History of ICH	7 (1.4)	17 (2.3)	0.068
History of GI bleeding	10 (2.0)	15 (2.1)	0.002
History of other bleeding	2 (0.4)	3 (0.4)	0.001
History of major bleeding	18 (3.7)	35 (4.8)	0.058
Cancer			0.052
Active	15 (3.1)	29 (4.0)	
Passive	48 (9.8)	70 (9.7)	
PPM	25 (5.1)	26 (3.6)	0.074
SBP, mmHg	128±55	126±19	0.035
DBP, mmHg	73±11	75±13	0.153
Weight, kg	62.4±10.8	63.4±11.4	0.089
BMI, kg/m^2	24.3±3.6	24.7±3.5	0.103

Echocardiographic data			
LVID, diastolic, mm	49.6±6.06	49.0±5.7	0.107
LVID, systolic, mm	33.8±7.2	32.8±6.3	0.146
LVMI, g/m^2	102.9±22.8	97.6±23.4	0.231
IVS, diastolic, mm	9.6±1.8	9.4±1.6	0.131
LVPW, diastolic, mm	9.5±1.3	9.3±2.2	0.121
Left atrium, mm	49.6±6.7	48.6±6.7	0.154
EF, %	54.5±11.1	56.6±9.8	0.200
EF less than 45%	84 (17.1)	74 (10.2)	0.202
TR Vmax, m/s	2.9±0.4	2.9±0.4	0.07
TR Vmax ≥3.4	57 (11.6)	75 (10.4)	0.04
IVC plethora	146 (29.8)	149 (20.6)	0.212
Laboratory data			
Hemoglobin, g/L	12.8±2.1	12.8±2.1	0.007
Platelets, $10^3/\mu g$	197±68	196±67	0.018
Creatinine clearance, mg/dL	62±24	63±24	0.037
Total Cholesterol, mg/dL	150.6±35.8	147.6±36.2	0.082
LDL, mg/dL	96±29	97±31	0.019
Albumin, g/dL	3.7±0.6	3.7±0.5	0.014
AST, IU/L	32±25	39±183	0.057
ALT, IU/L	24±25	30±112	0.072
ALP, IU/L	81±33	80±53	0.023
r_GTP, IU/L	59±71	56±87	0.034
Total bilirubin, mg/dL	1.1±0.8	0.9±0.6	0.224
BNP (log)	5.5±1.0	5.5±1.0	0.022

Data are presented as means±SD or number (%).

Abbreviations: TR, tricuspid regurgitation; DOAC, direct oral anticoagulant; IPTW, inverse propensity treatment weighting; SMD, standard mean difference; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; ICH, intracranial hemorrhage; GI, gastrointestinal; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVID, left ventricular internal dimension; LVMI, left ventricular mass index; IVS, interventricular septum thickness; LVPW, left ventricular posterior wall thickness; EF, ejection fraction; IVC, inferior vena cava; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, Alkaline phosphatase; r-GTP, gamma-glutamyl transferase; BNP, B type natriuretic peptide

Table 2. Incidence rates and hazard ratios for clinical outcomes with warfarin versus direct oral anticoagulants in the total study population

Clinical outcomes	**Warfarin**	**DOACs**	**Unadjusted**			**IPTW adjusted**		
(Total=1215)	**(N=491)**	**(N=724)**	**HR**	**95% CI**	***P* Value**	**HR†**	**95% CI**	***P* Value**
Stroke and systemic embolism	31 (2.10%)	31 (1.64%)	0.76	0.46-1.25	0.28	0.95	0.67-1.36	0.79
Major bleeding	39 (2.66%)	43 (2.31%)	0.87	0.56-1.35	0.54	0.78	0.57-1.06	0.11
Intracranial hemorrhage	16 (1.06%)	7 (0.37%)	0.33	0.13-0.81	0.02	0.27	0.14-0.54	<0.001
Gastrointestinal bleeding	19 (1.28%)	32(1.70%)	1.33	0.74-2.38	0.34	1.15	0.78-1.71	0.47
All-cause mortality	41 (2.70%)	42 (2.18%)	0.81	0.52-1.26	0.35	0.89	0.65-1.21	0.44
Composite outcome‡	99 (6.29%)	102 (8.45%)	0.77	0.58-1.02	0.06	0.81	0.67-0.99	0.04

The incidence rate is presented as the number of total events (events/100 patients*years)

‡Composite=all-cause mortality + stroke and systemic embolism + major bleeding

Abbreviations: DOAC, direct oral anticoagulant; IPTW, inverse probability treatment weighting; HR, hazard ratio

Table 3. Incidence rates and hazard ratios for clinical outcomes with warfarin versus direct oral anticoagulants in severe tricuspid regurgitation

Clinical outcomes	**Warfarin**	**DOAC**	**Unadjusted**			**IPTW adjusted**		
(Total=256)	**(N=136)**	**(N=120)**	**HR**	**95% CI**	***P* Value**	**HR†**	**95% CI**	***P* Value**
Stroke and systemic embolism	11 (2.50%)	7 (2.63%)	1.05	0.40-2.77	0.92	1.20	0.65-2.24	0.56
Major bleeding	10 (2.22%)	10 (4.01%)	1.7	0.68-4.26	0.26	1.03	0.55-1.92	0.92
Intracranial hemorrhage	3 (0.64%)	2 (0.74%)	1.26	0.18-9.05	0.82	0.79	0.18-3.43	0.76
Gastrointestinal bleeding	6 (1.31%)	7 (2.72%)	1.83	0.60-5.56	0.29	1.11	0.50-2.46	0.80
All-cause mortality	15 (3.18%)	7 (2.55%)	0.8	0.31-2.04	0.64	0.67	0.34-1.34	0.26
Composite outcome‡	32 (7.50%)	21 (8.45%)	1.05	0.60-1.85	0.87	0.90	0.62-1.32	0.60

The incidence rate is presented as the number of total events (events/100 patients*years)

‡Composite = all-cause mortality + stroke and systemic embolism + major bleeding

Abbreviations: DOAC, direct oral anticoagulant; IPTW, inverse probability treatment weighting' HR, hazard ratio

Table 4. Hazard ratios for clinical outcomes by on-label dose and off-label underdose direct oral anticoagulants versus warfarin in the total study population

	On-label dose vs. warfarin				Off-label underdose vs. warfarin				On-label dose vs. off-label underdose			
Clinical outcomes	**Unadjusted**		**IPTW adjusted**		**Unadjusted**		**IPTW adjusted**		**Unadjusted**		**IPTW adjusted**	
(Total=1215)	**HR (95% CI)**	***P* Value**	**HR† (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR† (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR† (95% CI)**	***P* Value**
IS/SE	0.70 (0.39-1.27)	0.24	0.81 (0.54-1.21)	0.30	0.84 (0.44-1.62)	0.61	0.81 (0.55-1.20)	0.29	0.84 (0.41-1.71)	0.62	1.00 (0.66-1.53)	1.00
Intracranial hemorrhage	0.22 (0.06-0.76)	0.02	0.16 (0.06-0.40)	<.0001	0.52 (0.17-1.56)	0.24	0.45 (0.45-0.24)	0.01	0.42 (0.10-1.90)	0.26	0.35 (0.13-0.95)	0.05
Gastrointestinal bleeding	1.12 (0.58-2.18)	0.74	1.02 (0.66-1.58)	0.93	1.68 (0.85-3.32)	0.14	1.31 (0.87-1.98)	0.20	0.67 (0.33-1.34)	0.26	0.78 (0.51-1.18)	0.24
Major bleeding	0.73 (0.43-1.24)	0.25	0.72 (0.51-1.01)	0.06	1.10 (0.64-1.89)	0.74	0.95 (0.69-1.30)	0.73	0.67 (0.37-1.22)	0.19	0.76 (0.53-1.08)	0.12

All-cause mortality	0.76 (0.46-1.27)	0.29	0.80 (0.56-1.14)	0.22	0.89 (0.50-1.58)	0.69	0.89 (0.63-1.26)	0.50	0.86 (0.46-1.58)	0.62	0.90 (0.62-1.30)	0.58
Composite outcome‡	0.71 (0.52-0.99)	0.04	0.72 (0.58-0.90)	0.00	0.86 (0.60-1.23)	0.41	0.82 (0.66-1.02)	0.07	0.83 (0.56-1.23)	0.35	0.88 (0.69-1.11)	0.26

‡Composite = all-cause mortality + stroke and systemic embolism + major bleeding

Abbreviations: IS/SE, ischemic stroke and systemic embolic event; ICH, intracranial hemorrhage; GI, gastrointestinal; IPTW, inverse probability treatment weighting; HR, hazard ratio

Table 5. Hazard ratios for primary outcomes with direct oral anticoagulants versus warfarin by subgroup

	IS/SE		Major bleeding	
Subgroups	**aHR (95% CI)**	***P* ***	**aHR (95% CI)**	***P* ***
IVC plethora		0.67		0.03
No	1.00 (0.64-1.58)		0.62 (0.43-0.89)	
Yes	0.85 (0.48-1.50)		1.40 (0.77-2.53)	
TR grade		0.09		0.04
Moderate	0.80 (0.52-1.22)		0.67 (0.47-0.95)	
Severe	1.61 (0.85-3.06)		1.38 (0.72-2.64)	
Age (years)		0.46		0.10
<65	1.38 (0.50-3.83)		1.55 (0.54-4.47)	
65-74	1.23 (0.55-1.93)		0.89 (0.52-1.53)	
≥75	0.7 8(0.48-1.25)		0.59 (0.40-0.88)	
Sex		0.53		0.35
Male	1.13 (0.56-2.29)		0.76 (0.48-1.19)	
Female	0.82 (0.55-1.25)		0.72 (0.47-1.08)	
Body weight		0.01		0.02
<60 kg	0.53 (0.31-0.91)		0.53 (0.33-0.85)	
≥60 kg	1.47 (0.91-2.38)		0.98 (0.66-1.47)	
Total bilirubin		0.13		0.25
<2 mg/dL	0.84 (0.57-1.22)		0.76 (0.56-1.05)	
≥2 mg/dL	2.81 (0.78-10.1)		2.41 (0.32-18.2)	
CrCL		0.94		0.65
<50 mg/dL	0.91 (0.53-1.56)		0.95 (0.60-1.51)	
≥50 mg/dL	0.99 (0.62-1.59)		0.70 (0.46-1.06)	

*P**=*P* for interaction

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; IVC, inferior vena cava; IS/SE, ischemic stroke and systemic embolic event; TR, tricuspid regurgitation; TB, total bilirubin; CrCL, creatinine clearance

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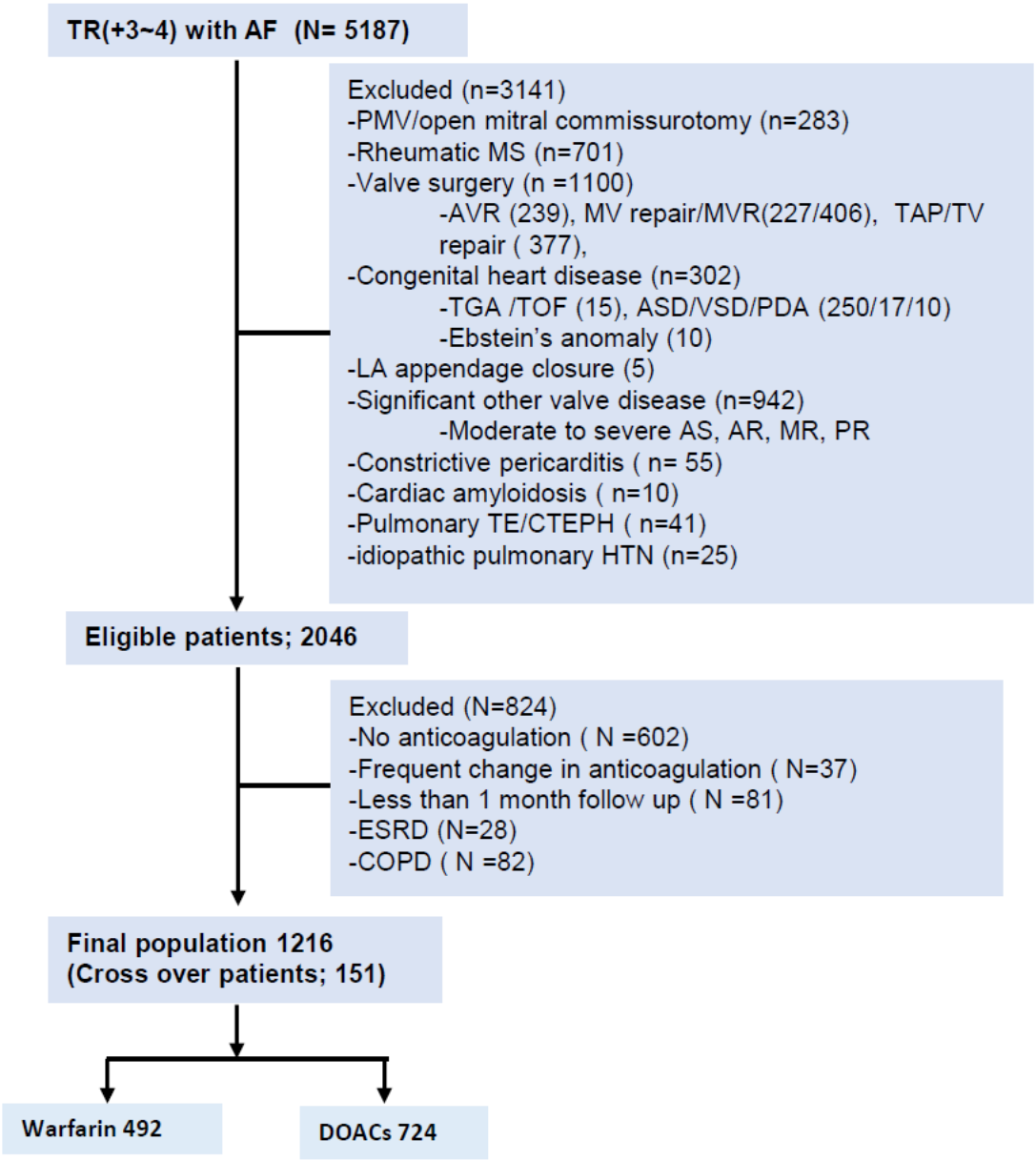


Figure 1. Study population flow diagram

Abbreviations: TR, tricuspid regurgitation; AF, atrial fibrillation; PMV, percutaneous mitral valvotomy; MS, mitral stenosis; AVR, aortic valve replacement; MV, mitral valve; MVR, mitral valve replacement; TAP, tricuspid annuloplasty; TV, tricuspid valve; TGA, transposition of great arteries; TOF, tetralogy of Fallot; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; LA, left atrial; AS, aortic stenosis;

AR, aortic regurgitation; MR, mitral regurgitation; PR, pulmonic regurgitation; TE, thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; HTN, hypertension; ESRD, end stage renal disease; COPD, chronic obstructive pulmonary disease

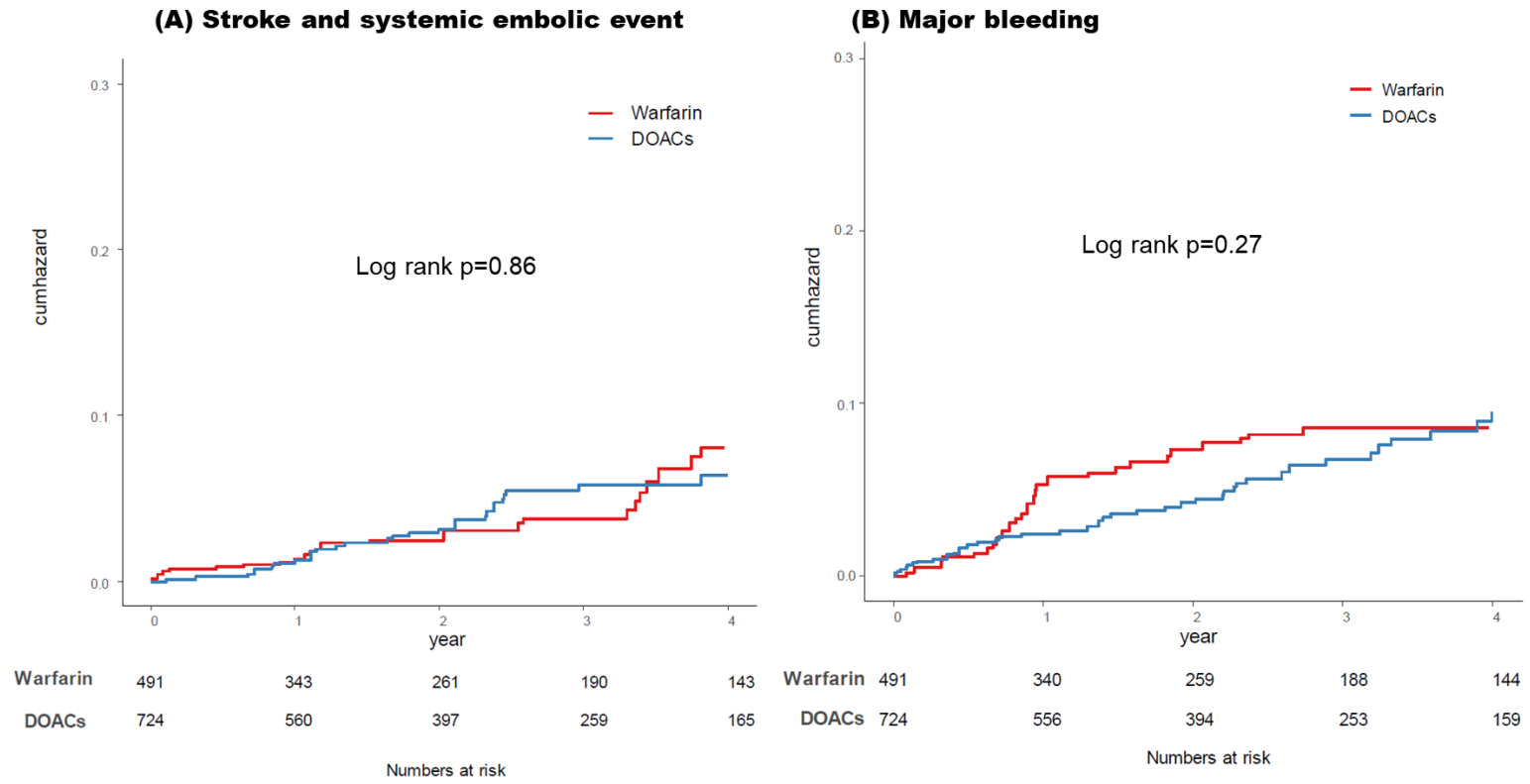


Figure 2. Weighted cumulative incidence curves of primary outcomes for the DOAC and warfarin groups in moderate to severe TR. (A) Stroke and systemic embolism. (B) Major bleeding

Abbreviations: DOAC, direct oral anticoagulant; TR, tricuspid regurgitation

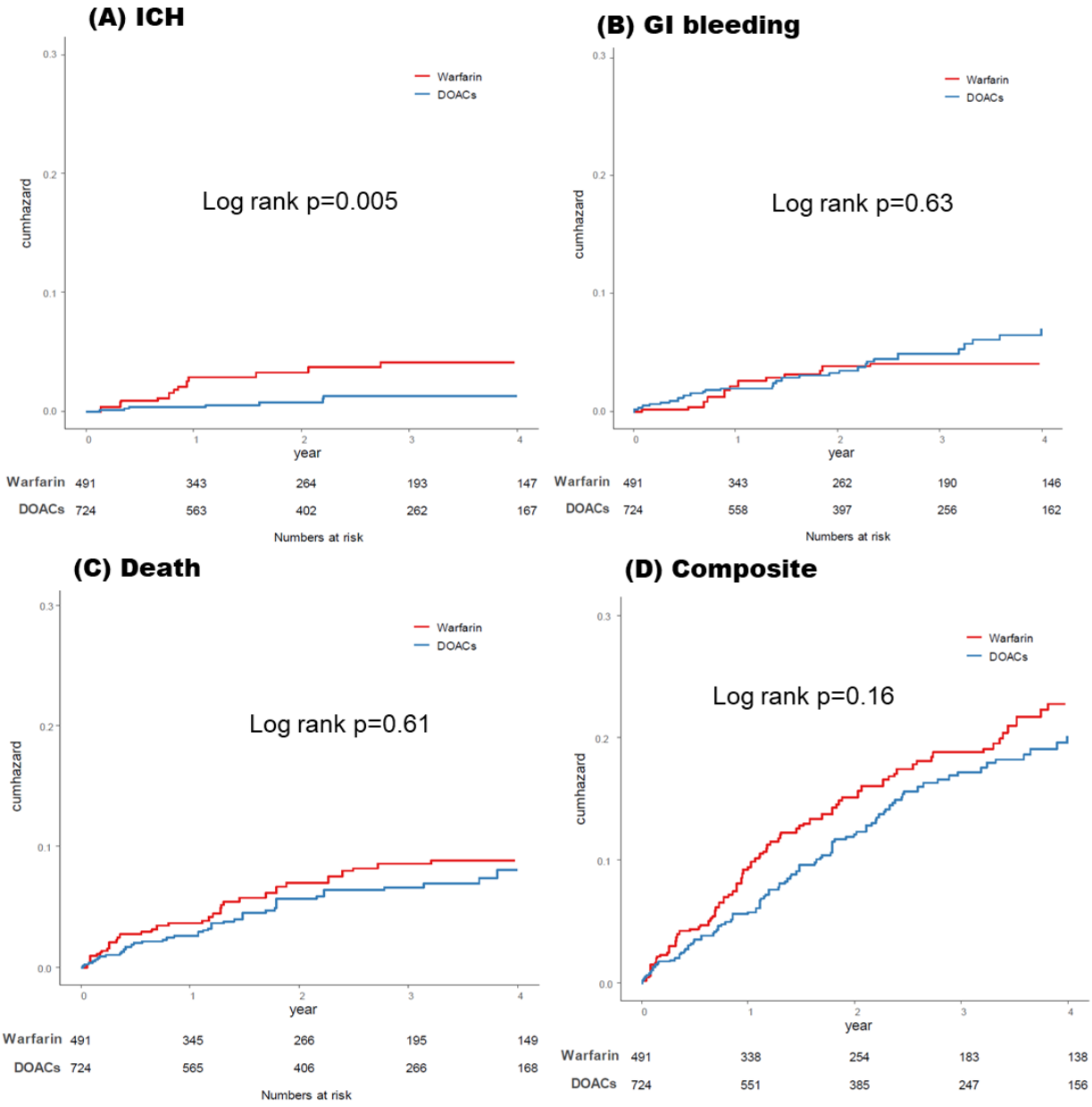


Figure 3. Weighted cumulative incidence curves of secondary outcomes for the DOAC and warfarin groups in moderate to severe TR. (A) Intracranial hemorrhage. (B) Gastrointestinal bleeding. (C) Death. (D) Composite outcome

Abbreviations: DOAC, direct oral anticoagulant; TR, tricuspid regurgitation

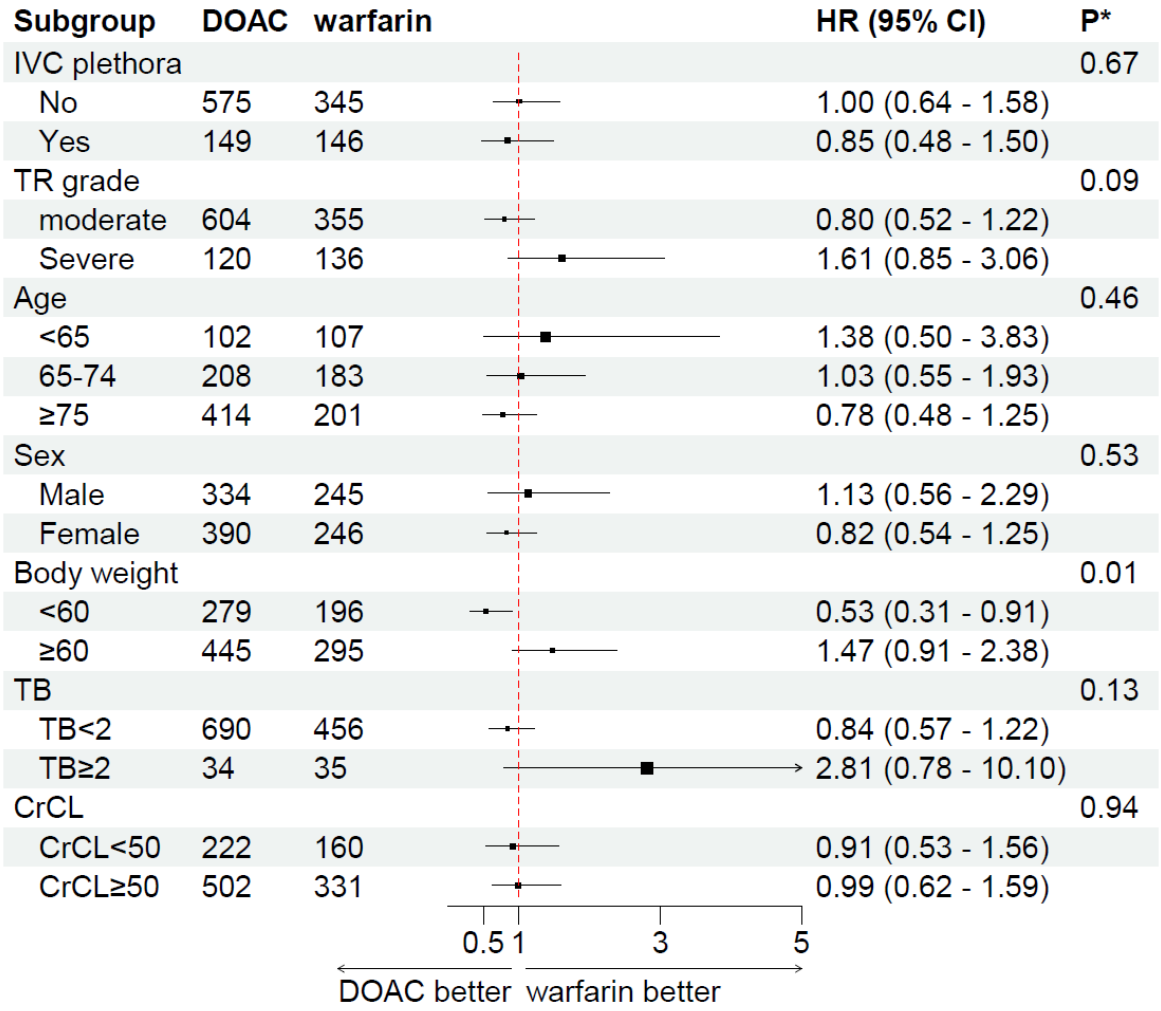


Figure 4. Hazard ratio of ischemic stroke and systemic embolic events according to subgroups.

*P**; *P* for interaction

Abbreviations: DOAC, direct oral anticoagulant; HR, hazard ratio; CI, confidence interval; IVC, inferior vena cava; TR, tricuspid regurgitation; TB, total bilirubin; CrCL, creatinine clearance

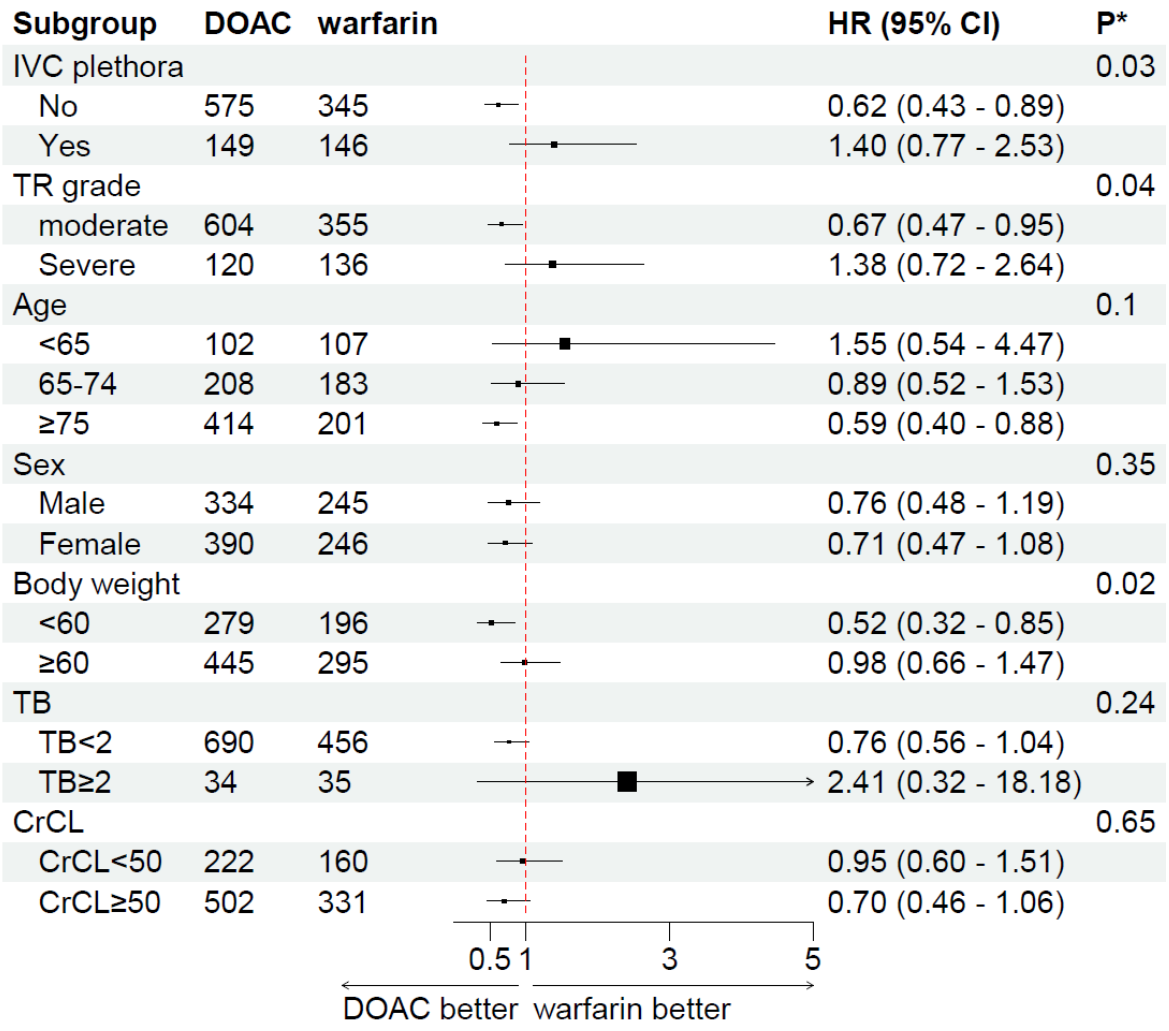


Figure 5. Hazard ratio of major bleeding according to subgroups.

*P**; *P* for interaction

Abbreviations: DOAC, direct oral anticoagulant; HR, hazard ratio; CI, confidence interval; IVC, inferior vena cava; TR, tricuspid regurgitation; TB, total bilirubin; CrCL, creatinine clearance

Supplementary Content

Yujin Yang et al, “Use of Direct-acting Oral Anticoagulant in Patients with Atrial Fibrillation and Significant Tricuspid Regurgitation.”

Supplementary Table 1. Standardized mean differences in the variables included in the inverse propensity score weighting before and after adjustment in the total population.

Supplementary Table 2. Standardized mean differences in the variables included in the inverse propensity score weighting before and after adjustment in severe tricuspid regurgitation.

Supplementary Table 3. Standardized mean differences in the variables included in the inverse propensity score weighting before and after adjustment by warfarin versus on-label dose and off-label underdose direct oral anticoagulants in the total population.

Supplementary Table 4. Incidence rate for clinical outcomes with on-label dose and off-label underdose direct oral anticoagulants versus warfarin in the total population

Supplementary Table 5. Incidence rate for clinical outcomes with direct oral anticoagulants versus warfarin in subgroups

Supplementary Table 6. Hazard ratios for secondary outcomes by subgroups among direct oral anticoagulants versus warfarin

Ⅱ. Supplementary Figures

Supplementary Figure 1. Weighted cumulative incidence curves of the primary outcome for the DOAC and warfarin groups in severe TR. (A) Stroke and systemic embolism. (B) Major bleeding

Supplementary Figure 2. Weighted cumulative incidence curves of the primary outcome for on-label dose DOAC, off-label underdose DOAC, and warfarin in moderate to severe TR. (A) Stroke and systemic embolism. (B) Major bleeding

Supplementary Table 1. Standardized mean differences in the variables included in the inverse propensity score weighting before and after adjustment in the total population.

Characteristics	**Warfarin**	**DOACs**	**SMD before weighting**	**SMD after weighting**
(N=1215)	**(N=491)**	**(N=724)**		
Male	245 (49.9)	334 (46.1)	0.075	0.015
Age, years	71.53±9.96	74.13±9.43	0.269	-0.012
Anti-platelet drugs	80 (16.3)	104 (14.4)	0.054	0.002
Severe TR	136 (27.7)	120 (16.6)	0.289	-0.002
CHA2DS2_VAS score	2.99±1.49	3.23±1.49	0.163	-0.003
Heart failure	108 (22.0)	102 (14.1)	0.207	0.001
Hypertension	304 (61.9)	482 (66.6)	0.097	0.006
Diabetes mellitus	105 (21.4)	175 (24.2)	0.066	0.001
History of stroke	121 (24.6)	154 (21.3)	0.080	-0.005
History of PCI/CBGA	51 (10.4)	94 (13.0)	0.080	-0.007
History of PTA	11 (2.2)	11 (1.5)	0.053	0.002
History of ICH	7 (1.4)	17 (2.3)	0.068	0.010
History of major bleeding	18 (3.7)	35 (4.8)	0.058	-0.002
Cancer			0.052	0.034
active	15 (3.1)	29 (4.0)		
passive	48 (9.8)	70 (9.7)		
PPM	25 (5.1)	26 (3.6)	0.074	0.007
DBP, mmHg	72.71±11.42	74.58±13.04	0.153	0.009
Weight, kg	62.44±10.75	63.42±11.43	0.089	-0.011
Echocardiographic data				
Left atrium, mm	49.6±6.7	48.6±6.7	0.154	0.043
LVMI, g/m^2	102.9±22.8	97.6±23.4	0.231	0.006
EF, %	54.5±11.1	56.6±9.8	0.200	-0.006
TR Vmax, m/s	2.9±0.4	2.9±0.4	0.070	-0.017
IVC plethora	146 (29.8)	149 (20.6)	0.212	0.002

Laboratory data				
Hemoglobin, g/L	12.8±2.1	12.8±2.1	0.007	0.007
Creatinine clearance, mg/dL	61.7±24.3	62.6±23.8	0.037	-0.021
Total cholesterol, mg/dL	151±36	148±36	0.082	0.002
LDL, mg/dL	96±29	97±31	0.019	-0.00
Albumin, g/dL	3.7±0.6	3.7±0.5	0.014	0.018
Total bilirubin, mg/dL	1.1±0.8	0.9±0.6	0.224	-0.002

Data are presented as mean±SD or number (%).

Abbreviations: TR, tricuspid regurgitation; DOAC, direct oral anticoagulant; SMD, standard mean difference; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; DBP, diastolic blood pressure; LVMI, left ventricular mass index; EF, ejection fraction; IVC, inferior vena cava; LDL, low density lipoprotein; BNP, B type natriuretic peptide

Supplementary Table 2. Standardized mean differences in variables included in the inverse propensity score weighting before and after adjustment in severe tricuspid regurgitation.

Characteristics	**Warfarin**	**DOAC**	**SMD before weighting**	**SMD after weighting**
(Total=256)	**(N=136)**	**(N=120)**		
Male	58 (42.6)	44 (36.7)	0.122	-0.062
Age, years	71.27±10.26	74.50±9.77	0.322	0.062
Anti-platelet drugs	18 (13.2)	15 (12.5)	0.022	-0.018
CHA2DS2_VAS score	2.78±1.56	3.23±1.63	0.285	0.053
Heart failure	28 (20.6)	15 (12.5)	0.219	0.088
Hypertension	71 (52.2)	86 (71.7)	0.409	0.007
Diabetes mellitus	30 (22.1)	37 (30.8)	0.2	0.0180
History of stroke	28 (20.6)	25 (20.8)	0.006	0.010
History of PCI/CBGA	10 (7.4)	9 (7.5)	0.006	-0.007
History of PTA	6 (4.4)	3 (2.5)	0.105	-0.048
History of ICH	2 (1.5)	5 (4.2)	0.163	0.073
History of GI bleeding	3 (2.2)	3 (2.5)	0.019	-0.049
Cancer			0.113	0.0342
Active	5 (3.7)	7 (5.8)		
Passive	16 (11.8)	12 (10.0)		
PPM	6 (4.4)	4 (3.3)	0.056	-0.030
DBP, mmHg	73.07±12.07	76.85±16.06	0.266	0.020
Weight, kg	61.25±10.66	62.42±12.53	0.101	-0.029
Echocardiographic data				
Left atrium, mm	50.9±7.3	50.0±6.8	0.115	0.043
LVMI, g/m^2	99.73±24.79	97.52±24.98	0.089	0.032
EF, %	55.56±10.32	56.75±9.82	0.118	-0.016
TR Vmax, m/s	2.94±0.54	2.97±0.51	0.057	0.021
TR Vmax ≥3.4	20 (14.7)	24 (20.0)	0.14	0.118
IVC plethora	72 (52.9)	49 (40.8)	0.244	0.032

Laboratory data				
Hemoglobin, g/L	12.5±2.1	12.3±2.3	0.093	0.004
Creatinine clearance, mg/dL	60.5±25.2	61.6±26.2	0.042	-0.015
Total cholesterol, mg/dL	143±37	142±34	0.015	0.051
LDL, mg/dL	91±29	91±31	0.007	0.021
Albumin, g/dL	3.7±0.6	3.7±0.5	0.021	0.034
Total bilirubin, mg/dL	1.18±0.77	0.89±0.47	0.452	0.028

Data are presented as mean±SD or number (%).

Abbreviations: TR, tricuspid regurgitation; DOAC, direct oral anticoagulant; SMD, standard mean difference; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; DBP, diastolic blood pressure; LVMI, left ventricular mass index; EF, ejection fraction; IVC, inferior vena cava; LDL, low density lipoprotein; BNP, B type natriuretic peptide

Supplementary Table 3. Standardized mean differences in variables included in the inverse propensity score weighting before and after adjustment by warfarin versus on-label dose and off-label underdose direct oral anticoagulants in the total population.

	Warfarin	**DOAC**		**SMD before weighting**	**SMD after weighting**
Characteristics		**On-label dose**	**Off-label underdose**		
(Total =1215)	**(N=491)**	**(N=475)**	**(N=249)**		
Male	245 (49.9)	120 (48.2)	214 (45.1)	0.065	0.094
Age, years	71.53±9.96	74.99±8.65	73.69±9.79	0.244	0.079
Anti-platelet drugs	80 (16.3)	45 (18.1)	59 (12.4)	0.105	0.108
Severe TR	136 (27.7)	40 (16.1)	80 (16.8)	0.232	0.146
CHA2DS2_VAS score	2.99±1.49	3.32±1.32	3.18±1.57	0.154	0.066
Heart failure	108 (22.0)	36 (14.5)	66 (13.9)	0.142	0.121
Hypertension	304 (61.9)	177 (71.1)	305 (64.2)	0.13	0.128
Diabetes mellitus	105 (21.4)	68 (27.3)	107 (22.5)	0.092	0.066
History of stroke	121 (24.6)	43 (17.3)	111 (23.4)	0.121	0.161
History of PCI/CBGA	51 (10.4)	43 (17.3)	51 (10.7)	0.134	0.110
History of PTA	11 (2.2)	2 (0.8)	9 (1.9)	0.079	0.112
History of ICH	7 (1.4)	7 (2.8)	10 (2.1)	0.065	0.034
History of major bleeding	18 (3.7)	16 (6.4)	19 (4.0)	0.084	0.080

Cancer				0.095	0.073
Active	15 (3.1)	14 (5.6)	15 (3.2)		
Passive	48 (9.8)	21 (8.4)	49 (10.3)		
PPM	25 (5.1)	10 (4.0)	16 (3.4)	0.057	0.064
DBP, mmHg	73±11	75±13	74±13	0.125	0.090
Weight, kg	62±11	65±10	63±12	0.148	0.049
Echocardiographic data					
Left atrium, mm	50.0±6.7	49.5±6.5	48.1±6.7	0.153	0.006
LVMI, g/m^2	102.9±22.8	98.8±21.1	97.0±24.5	0.173	0.124
EF, %	54.5±11.1	56.5±9.8	56.7±9.8	0.139	0.089
TR Vmax, m/s	2.89±0.44	2.90±0.39	2.84±0.41	0.097	0.063
IVC plethora	146 (29.8)	55 (22.3)	94 (19.8)	0.155	0.095
Laboratory data					
Hemoglobin, g/L	12.80±2.06	12.74±1.83	12.81±2.15	0.027	0.018
Creatinine clearance, mg/dL	61.7±24.3	64.0±20.0	61.8±25.5	0.069	0.055
Total cholesterol, mg/dL	151±36	146±36	148±36	0.078	0.065
LDL, mg/dL	96±29	94±31	98±31	0.091	0.057
Albumin, g/dL	3.7±0.6	3.7±0.5	3.7±0.5	0.011	0.050

Total bilirubin, mg/dL	1.1±0.8	1.0±0.7	0.9±0.6	0.170	0.123

Data are presented as mean±SD or number (%).

Abbreviations: TR, tricuspid regurgitation; DOAC, direct oral anticoagulant; SMD, standard mean difference; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty; DBP, diastolic blood pressure; LVMI, left ventricular mass index; EF, ejection fraction; IVC, inferior vena cava; LDL, low density lipoprotein; BNP, B type natriuretic peptide

Supplementary Table 4. Incidence rate of clinical outcomes with on-label dose and off-label underdose direct oral anticoagulants versus warfarin in the total population

Clinical outcomes	**Warfarin**	**DOAC**	
		On-label dose	**Off-label underdose**
(N=1215)	**(N=491)**	**(N=478)**	**(N=252)**
Stroke and systemic embolism	31 (2.1%)	18 (1.53%)	13 (1.84%)
Intracranial hemorrhage	16 (1.06%)	3 (0.25%)	4 (0.56%)
Gastrointestinal bleeding	19 (1.28%)	17 (1.44%)	15 (2.14%)
Major bleeding	39 (2.66%)	23 (1.96%)	20 (2.89%)
All-cause mortality	41 (2.70%)	25 (2.09%)	17 (2.37%)
Composite outcome‡	99 (6.91%)	60 (5.20%)	42 (6.15%)

The incidence rate is presented as the number of total events (events/100 patients*years)

‡Composite = all-cause mortality + stroke and systemic embolism + major bleeding

Abbreviations: DOAC, direct oral anticoagulant; IPTW, inverse probability treatment weighting; HR, hazard ratio

Supplementary Table 5. Incidence rate for clinical outcomes with direct oral anticoagulants versus warfarin in subgroups

Subgroups	Treatment	Number	IS/SE	Major bleeding	ICH	GI bleeding	Death	Composite outcome
			Events (IR/100 PY)	Events (IR/100PY)	Events (IR/100PY)	Events (IR/100 PY)	Events (IR/100 PY)	Events (IR/100 PY)
IVC plethora								
No	Warfarin	345	16 (1.52)	29 (2.78)	13 (1.21)	14 (1.33)	21 (1.95)	61 (5.97)
	DOACs	575	21 (1.42)	30 (2.03)	5 (0.33)	23 (1.55)	28 (1.86)	70 (4.82)
Yes	Warfarin	146	15 (3.51)	10 (2.37)	3 (0.69)	5 (1.17)	20 (4.52)	38 (9.34)
	DOACs	149	10 (2.48)	13 (3.37)	2 (0.50)	9 (2.29)	14 (3.45)	32 (8.36)
TR grade								
Moderate	Warfarin	355	20 (1.94)	29 (2.85)	13 (1.25)	13 (1.27)	26 (2.48)	67 (6.69)
	DOACs	604	24 (1.48)	33 (2.05)	5 (0.31)	25 (1.54)	35 (2.13)	81 (5.10)
Severe	Warfarin	136	11 (2.46)	10 (2.22)	3 (0.64)	6 (1.32)	15 (3.18)	32 (7.50)
	DOACs	120	7 (2.63)	10 (4.01)	2 (0.76)	7 (2.73)	7 (2.62)	21 (8.46)
Age (years)								
<65	Warfarin	107	5 (1.19)	3 (0.73)	1 (0.24)	2 (0.48)	5 (1.19)	11 (2.68)

	DOACs	102	3 (1.07)	5 (1.81)	0 (0.00)	3 (1.08)	3 (1.06)	10 (3.64)
65-74	Warfarin	183	12 (2.04)	15 (2.60)	8 (1.35)	4 (0.69)	17 (2.85)	41 (7.23)
	DOACs	208	9 (1.54)	12 (2.03)	1 (0.17)	8 (1.35)	9 (1.50)	26 (4.51)
≥75	Warfarin	201	14 (2.96)	21 (4.39)	7 (1.43)	13 (2.6)	19 (3.80)	47 (10.40)
	DOACs	414	19 (1.86)	26 (2.61)	6 (0.59)	21 (2.09)	30 (2.91)	66 (6.70)
Sex								
Male	Warfarin	245	22 (3.30)	20 (2.97)	9 (1.31)	9 (1.33)	18 (2.61)	53 (8.14)
	DOACs	334	24 (2.29)	24 (2.31)	3 (0.28)	18 (1.72)	23 (2.15)	63 (6.19)
Female	Warfarin	246	9 (1.11)	19 (2.40)	7 (0.85)	10 (1.25)	23 (2.78)	46 (5.92)
	DOACs	390	7 (0.84)	19 (2.31)	4 (0.48)	14 (1.68)	19 (2.26)	39 (4.76)
Body weight								
<60 kg	Warfarin	196	18 (3.61)	20 (3.98)	9 (1.76)	8 (1.58)	19 (3.70)	51 (10.46)
	DOACs	279	11 (1.52)	16 (2.24)	2 (0.27)	11 (1.53)	18 (2.46)	43 (6.08)
≥60 kg	Warfarin	295	13 (1.33)	19 (1.97)	7 (0.70)	11 (1.13)	22 (2.19)	48 (5.10)
	DOACs	445	20 (1.72)	27 (2.36)	5 (0.43)	21 (1.82)	24 (2.03)	59 (5.23)
Total bilirubin								
<2 mg/dL	Warfarin	456	29 (2.11)	38 (2.79)	16 (1.14)	19 (1.3)	37 (2.62)	93 (7.03)
	DOACs	690	28 (1.56)	41 (2.32)	7 (0.39)	31 (1.74)	37 (2.04)	93 (5.34)

≥2 mg/dL	Warfarin	35	2 (1.90)	1 (0.94)	0 (0.00)	0 (0.00)	4 (3.74)	6 (5.71)
	DOACs	34	3 (3.20)	2 (2.13)	0 (0.00)	1 (1.06)	5 (5.30)	9 (9.64)
CrCL								
<50 mg/dL	Warfarin	160	14 (3.65)	21 (5.27)	8 (1.97)	11 (2.73)	17 (4.13)	44 (11.86)
	DOACs	222	13 (2.64)	20 (4.30)	5 (1.03)	16 (3.38)	20 (4.02)	47 (10.20)
≥50 mg/dL	Warfarin	331	17 (1.55)	18 (1.68)	8 (0.73)	8 (0.74)	24 (2.17)	55 (5.20)
	DOACs	502	18 (1.29)	23 (1.65)	2 (0.14)	16 (1.14)	22 (1.56)	55 (4.00)

‡Composite = all-cause mortality + stroke and systemic embolism + major bleeding

Abbreviations: DOAC, direct oral anticoagulant; IVC, inferior vena cava; IS/SE, ischemic stroke and systemic embolic event; TR, tricuspid regurgitation; TB, total bilirubin; CrCL, creatinine clearance; ICH, intracranial hemorrhage; GI, gastrointestinal; IR, incidence rate; PY, person-years

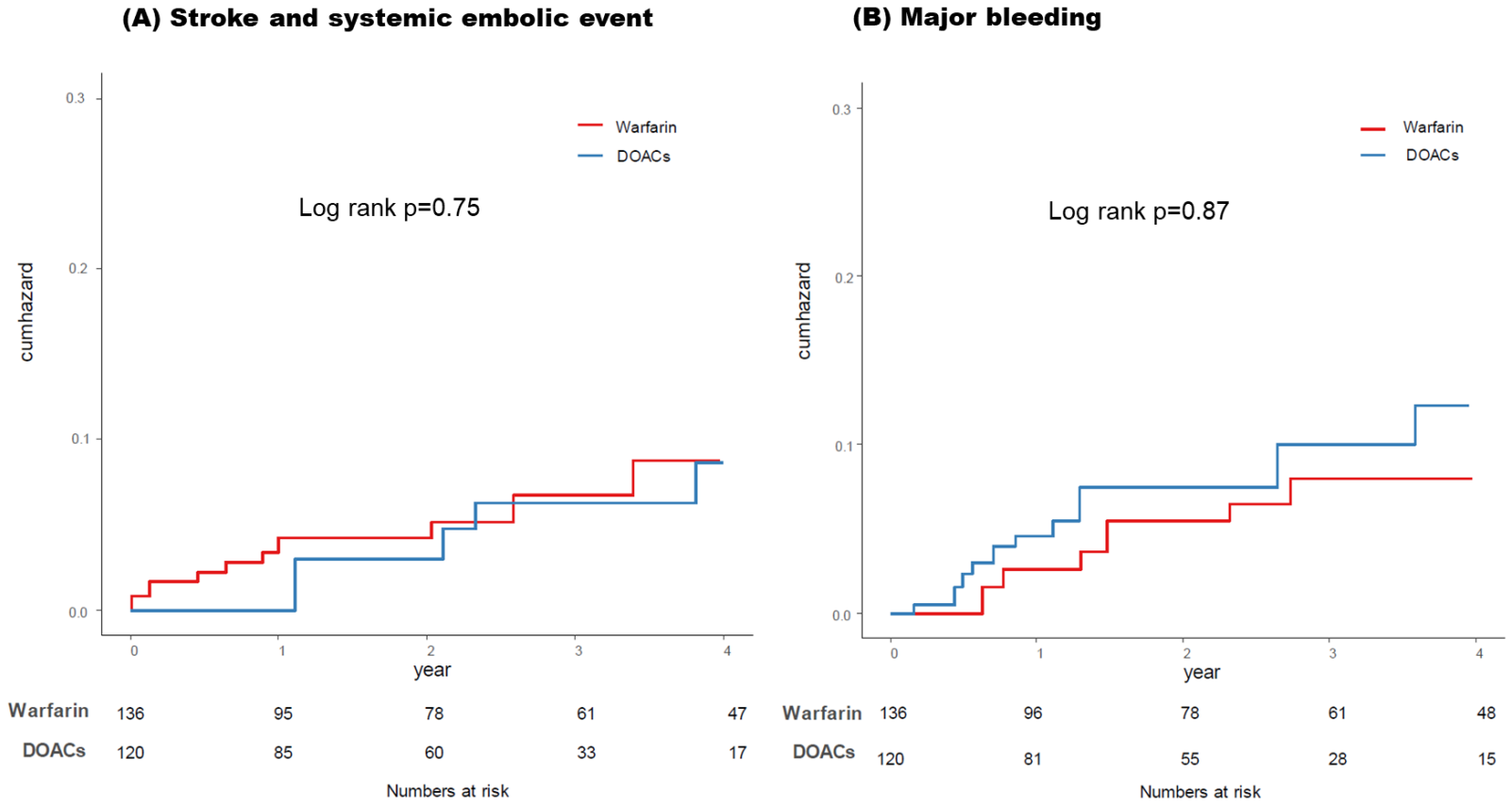
Supplementary Table 6. Hazard ratio for secondary outcomes by subgroups among direct oral anticoagulants versus warfarin

	ICH		GI bleeding		Death		Composite	
Subgroups	**aHR (95% CI)**	***P* ***	**aHR (95% CI)**	***P* ***	**aHR (95% CI)**	***P* ***	**aHR (95% CI)**	***P* ***
IVC plethora		0.34		0.10		0.78		0.26
No	0.22(0.10-0.50)		0.95(0.61-1.50)		0.87(0.59-1.29)		0.74(0.58-0.94)	
Yes	0.50(0.14-1.76)		1.99(0.89-4.47)		0.92(0.55-1.55)		0.97(0.69-1.36)	
TR grade		0.06		0.34		0.71		0.08
Moderate	0.20(0.09-0.44)		1.07(0.68-1.66)		0.91(0.64-1.29)		0.74(0.59-0.93)	
Severe	1.13(0.26-4.85)		1.51(0.68-3.40)		0.86(0.45-1.65)		1.15(0.78-1.69)	
Age (years)		0.31		0.04		0.97		0.12
<65	-		1.82(0.44-7.58)		0.79(0.24-2.57)		1.35(0.70-2.60)	
65-74	0.08(0.02-0.48)		2.63(1.12-6.18)		0.80(0.47-1.37)		0.79(0.57-1.12)	
≥75	0.44(0.20-0.99)		0.74(0.47-1.19)		0.88(0.59-1.32)		0.70(0.54-0.91)	
Sex		0.26		0.73		0.67		0.53
Male	0.34(0.14-0.85)		1.07(0.61-1.89)		0.83(0.54-1.28)		0.80(0.59-1.08)	
Female	0.21(0.08-0.57)		1.10(0.65-1.89)		0.90(0.58-1.41)		0.77(0.60-1.00)	
Body weight		0.10		0.07		0.35		0.01
<60 kg	0.14(0.04-0.51)		0.70(0.37-1.32)		0.75(0.48-1.18)		0.60(0.45-0.80)	

≥60 kg	0.38(0.17-0.87)		1.54(0.94-2.55)		0.98(0.64-1.50)		1.00(0.76-1.30)	
Total bilirubin		-		0.07		0.11		0.008
<2 mg/dL	0.28(0.14-0.55)		1.13(0.76-1.67)		0.81(0.58-1.13)		0.74(0.61-0.91)	
≥2 mg/dL	-		-		1.52(0.57-4.04)		2.18(1.01-4.70)	
Creatinine clearance		0.17		0.63		0.17		0.19
<50 mg/dL	0.50(0.21-1.24)		1.36(0.78-2.38)		1.30(0.80-2.12)		1.00(0.74-1.35)	
≥50 mg/dL	0.15(0.05-0.46)		1.03(0.59-1.80)		0.69(0.46-1.05)		0.72(0.55-0.93)	

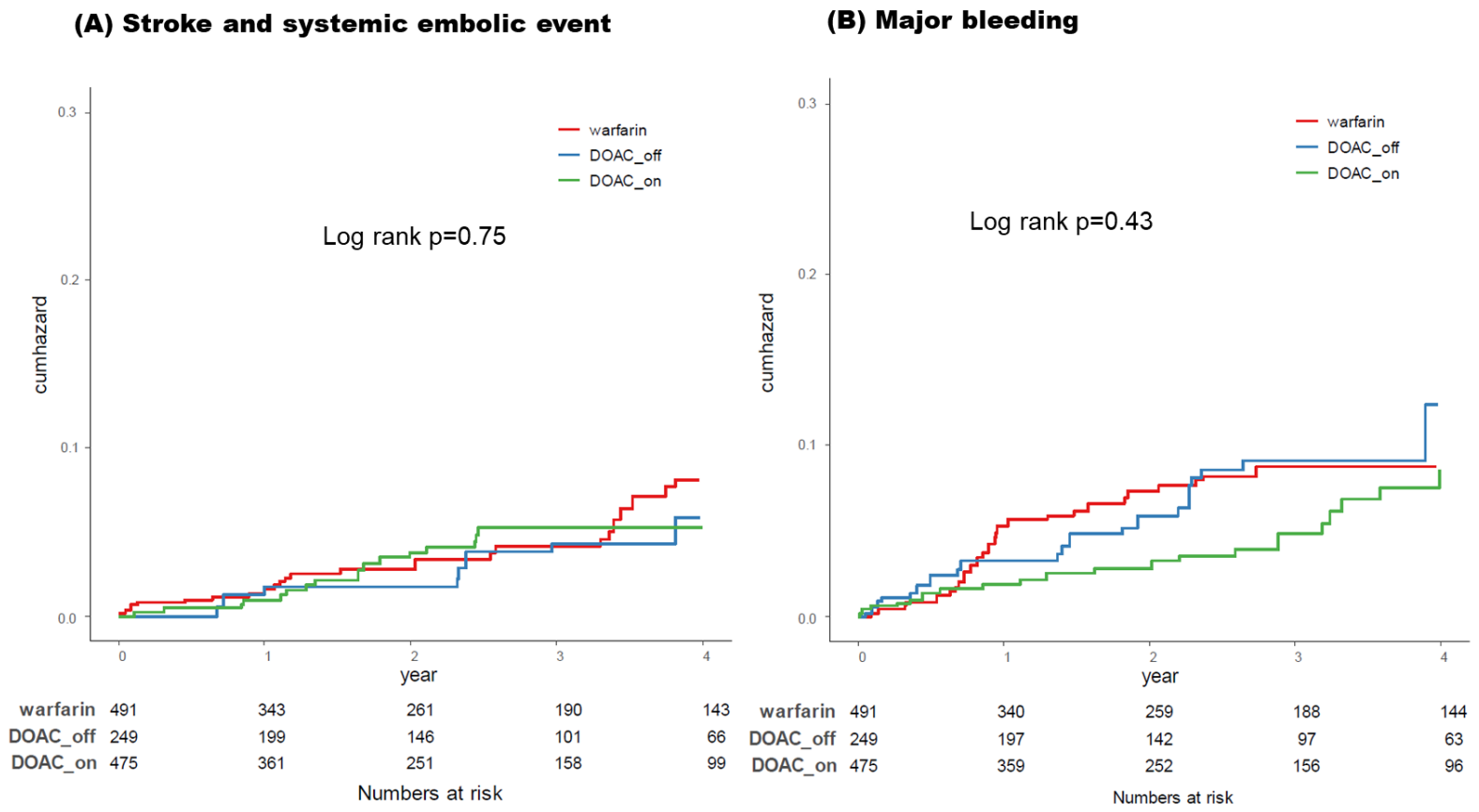
*P**=*P* for interaction

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; IVC, inferior vena cava; ICH: intracranial hemorrhage; GI, gastrointestinal; TR, tricuspid regurgitation; TB, total bilirubin; CrCL, creatinine clearance



Supplementary Figure 1. Weighted cumulative incidence curves of the primary outcome for the DOAC and warfarin groups in severe TR. (A) Stroke and systemic embolism. (B) Major bleeding

Abbreviations: DOAC, direct oral anti-coagulant; TR, tricuspid regurgitation



Supplementary Figure 2. Weighted cumulative incidence curves of the primary outcome for on-label dose DOAC, off-label underdose DOAC, and warfarin in moderate to severe TR. (A) Stroke and systemic embolism. (B) Major bleeding

Abbreviations: DOAC, direct oral anti-coagulant; TR, tricuspid regurgitation

ABSTRACT

BACKGROUND

Direct-oral anticoagulants (DOACs) became standard anticoagulant therapy in patients with non-valvular atrial fibrillation (AF). However, there is limited data on the efficacy and safety of DOACs in patients with significant tricuspid regurgitation (TR) and AF. Significant TR can cause splanchnic and hepatic congestion, resulting in hepatic dysfunction and intestinal malabsorption. Accordingly, patients with significant TR can be at risk for prolongation of prothrombin time or a decrease in the oral bioavailability of DOACs. We sought to compare the efficacy and safety of DOACs and warfarin in patients with atrial fibrillation (AF) and significant TR.

METHODS

The data of patients with AF and significant (moderate or greater) TR treated with oral anticoagulants from Jan 2010 to Dec 2020 were retrospectively reviewed, and 1215 patients (491 on warfarin and 724 on DOACs) were finally included in the analysis. The primary outcomes were ischemic stroke and systemic embolic events (IS/SE) and hospitalization for major bleeding. The secondary outcomes were intracranial hemorrhage (ICH), hospitalization for gastrointestinal (GI) bleeding, all-cause mortality, and the composite outcome (IS/SE + hospitalization for major bleeding + all-cause mortality). All endpoints were compared after adjustment using inverse probability treatment weighting (IPTW).

RESULTS

The median follow-up duration was 2.4 years. In the IPTW adjusted cohort, DOACs had a similar risk for IS/SE (adjusted hazard ratio [aHR]: 0.95, 95% confidence interval [CI]: 0.67-

1.36, *P* =0.79) and major bleeding (aHR: 0.78, 95% CI: 0.57-1.06; *P*=0.11) compared to warfarin. For the secondary outcomes, DOACs had a lower risk for ICH (aHR: 0.27, 95% CI: 0.14-0.54, *P*=0.002) and the composite outcome (aHR: 0.81, 95% CI: 0.67-0.99, *P*=0.04). DOACs had a comparable risk for GI bleeding (aHR: 1.15, 95% CI: 0.78-1.71; *P*=0.47) and all-cause mortality (aHR:0.89, 95% CI: 0.65-1.21, *P*=0.44). In patients with severe TR (N=256), DOACs had a comparable risk for the primary and secondary clinical outcomes. Among three groups on label dose DOAC, off- label underdose DOAC, and warfarin, both the DOAC dose groups had a lower risk for ICH (aHR: 0.16, 95% CI: 0.06-0.40; *P*<0.001), (aHR: 0.45, 95% CI: 0.24-0.85; *P*=0.01), respectively. On-label dose DOAC and off-label underdose DOAC had similar risks for the primary and secondary outcomes. In subgroup analysis, the lower weight group (under 60 kg) tended to have a lower risk for IS/SE and major bleeding. (*P* for interaction [IS/SE] = 0.007, *P* for interaction [major bleeding] = 0.02). In the group without inferior vena cava plethora, and the moderate TR group, DOACs tended to have a lower risk for major bleeding. (*P* for interaction [inferior vena cava plethora] = 0.03, *P* for interaction [TR grade] = 0.04).

CONCLUSION

In this retrospective study, in patients with significant TR and AF, DOACs showed comparable efficacy for IS/SE and major bleeding, with lower risk for ICH. DOACs tended to be effective and safer in the low weight group (under 60 kg) and safer in the moderate TR group and the group without inferior vena cava plethora. This study suggests that DOACs are also effective and safe in patients with significant TR and AF.