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Safety and effectiveness of direct oral anticoagulants in fragile patients with venous thromboembolism: a retrospective cohort observational study

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Purpose: The use of direct oral anticoagulants (DOACs) is challenging in fragile patients, including those with cancer, chronic kidney disease (CKD), and old age. We aimed to compare the safety of DOACs in terms of bleeding complications in these patients.
Methods: Using hospital data from 2013 to 2019, we compared the risk of bleeding and major bleeding, including intracranial bleeding, any bleeding requiring transfusion, and all-cause bleeding, in patients with venous thromboembolism (VTE) who were naïve to DOAC (n = 12,369) and warfarin (n = 4,123). Hazard ratios (HRs) for the clinical outcomes were analyzed using Cox regression analysis, with warfarin as a reference.
Results: The study included 4,078 eligible patients, predominantly female (54.1%), with a mean age of 62.5 years. DOACs were the primary treatment in 74.1% of the patients. DOAC treatment was associated with lower all-cause mortality compared to warfarin (HR, 0.799; 95% confidence interval [CI], 0.707–0.904). Although rates of recurrent VTE or major bleeding did not significantly differ between the groups, DOAC-treated patients had lower bleeding risk (HR, 0.562; 95% CI, 0.393–0.805; P = 0.002). The individual DOAC drugs did not differ significantly in terms of composite outcomes, recurrence, or bleeding events.
Conclusion: DOAC showed comparable outcomes with warfarin in the fragile patient population.
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Key Words: Direct oral anticoagulants, Cancer-associated thrombosis, Chronic kidney disease, Venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious and life-threatening condition requiring immediate medical attention. Heparin, low-molecular-weight heparin (LMWH), and warfarin are the traditional standard treatments for VTE. The development of direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, has revolutionized VTE treatment.

Randomized clinical trials have demonstrated that DOACs are as effective as traditional standard anticoagulation therapy for reducing recurrent VTE, with similar or reduced rates of major bleeding. However, VTE is more common in patients with multiple comorbidities, and cancer or aging is regarded as one of its strongest and most prevalent risk factors [1-3]. In these patients, polypharmacy and altered pharmacokinetics, often predisposing to major bleeding, render the use of

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anticoagulants challenging [4,5].

Only a small fraction of the patient population has been included in randomized controlled trials as well as real-world prospective studies that investigated the potential of DOACs in the management of the condition. Several studies have demonstrated the efficacy and safety of DOACs in patients with atrial fibrillation [6,7]. However, the results cannot be generalized to VTE patients due to the differences in drug dosages. Therefore, the objective of the present study was to evaluate the efficacy and safety of DOACs in fragile populations, including patients with chronic kidney disease (CKD), cancer, or old age, in a real-world setting.

METHODS

Ethics statement

The Institutional Review Board of Asan Medical Center approved this cohort study (No. 2020-1923) and waived the need for informed consent in this study because of its retrospective nature.

Study design and cohort definition

This retrospective observational study used data from a single-center clinical data warehouse (CDW). This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines. A cohort of 4,078 patients with VTE was identified between January 1, 2013 and December 31, 2019, using ICD-10 codes: I80.1-3, 8-9, I82.2, I82.9, and I26.

Patients with VTE aged ≥18 years were included. Patients with the following conditions were excluded: pregnancy-related VTE; previous warfarin or DOACs prescription before January 2013 (to analyze data of only those who were first-time oral anticoagulants [OAC] users); and a potential alternative indication for OAC treatment, such as atrial fibrillation or mechanical valve replacement. Decisions regarding warfarin or DOACs were made based on physicians' risk/benefit analysis.

Baseline covariates

Patients' baseline characteristics, including age, sex, comorbidities (hypertension, diabetes mellitus, cancer, and dialysis), laboratory tests including hemoglobin, estimated glomerular filtration rate (eGFR), creatinine, and liver function tests, were obtained.

Active cancer was defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer that is not in complete remission [8]. The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to estimate eGFR [9]. Stages of eGFR were defined as follows: stage 1 (eGFR, >90 mL/min/1.73 m^2), stage 2 (eGFR, 60–90 mL/min/1.73 m^2), stage 3 (eGFR, 30–59 mL/min/1.73 m^2), stage 4 (eGFR, 15–29 mL/min/1.73 m^2), and stage 5 (eGFR, <15 mL/min/1.73 m^2). Old age was defined as ages >75 years.

Clinical outcomes and follow-up

Older patients, patients with active cancer, those with lower body weight, and those undergoing regular dialysis were categorized as fragile. The primary outcome was a composite endpoint of effectiveness and safety. The effectiveness outcome objectively confirmed the recurrent VTE during the study period. The safety outcome was the major or clinically relevant nonmajor bleeding [10]. The index date was defined as the date of the first DOAC or warfarin administration during the study period.

Statistics

Baseline characteristics are presented descriptively. Categorical variables are presented as frequencies or percentages. Continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]) after performing the normality test (Kolmogorov-Smirnov test). Univariate analysis was performed using the Fisher exact test to analyze the associations between categorical variables and underlying risk factors. We calculated the incidence rates of recurrence, odds ratios, and 95% confidence intervals (CIs) by comparing the DOAC group with the warfarin group. Crude incidence rates of recurrence are presented as the number of events per 100 person-years (PY). The risk of clinical outcomes over time for DOACs compared to warfarin was analyzed using survival analysis, with the Kaplan-Meier method and log-rank test for univariate analysis. Then, Cox proportional hazard models were used to estimate hazard ratios (HRs) for clinical outcomes. Given that the assumption of proportional hazards was not met, a time-varying Cox model was employed. Anticoagulant use (DOAC or warfarin) was modeled as a time-dependent covariate to account for variations in treatment duration and ensure proper adjustment for changes in exposure over time. Because there was a noticeable difference in baseline characteristics between the DOAC and warfarin groups, the warfarin group was matched to the DOAC group in a 1:1 ratio by closely aligning age, sex, creatinine levels, and the presence of active cancer. Bleeding, recurrent VTE, and composite outcomes were then analyzed using Kaplan-Meier survival analysis.

The P-values were two-sided and deemed statistically significant at $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Corp.) and R software ver. 4.1.2 (The R Foundation).

Subgroup analyses

Subgroup analyses were performed to compare the HR of

composite outcomes of recurrence and bleeding between DOACs and warfarin, which included patients' age (i.e., ≤80 or >80 years), active cancer, body weight (i.e., ≤60 kg or >60 kg), and renal function (i.e., CKD patients undergoing regular dialysis or not).

RESULTS

Characteristics of patients

A total of 4,078 patients were eligible for the study. The baseline characteristics of the participants are summarized in Table 1. Out of these patients, 2,208 (54.1%) were female, and the mean age at the index date was 62.5 ± 15.1years. The median follow-up duration was 24.0 months (IQR, 7–48

Table 1. Baseline characteristics

Characteristic	DOAC group	Warfarin group	P-value
No. of patients	3,020	1,058	
Age (yr)	63.1 ± 14.9	61.0 ± 15.6	<0.001
18–50	576 ± 19.1	253 ± 23.9	
51–65	980 ± 32.5	337 ± 31.9	
66–80	1,184 ± 39.2	384 ± 36.3	
>80	280 ± 9.3	84 ± 7.9	
Male sex (%)	1,324 (43.8)	546 (51.6)	<0.001
Body mass index (kg/m^2)	24.1 ± 4.1	24.0 ± 4.4	0.410
Weight (kg)	62.6 ± 13.8	62.7 ± 14.0	0.796
Weight <60 kg	1,678 (55.5)	608 (55.4)	0.972
DOAC type			
Rivaroxaban	2,117 (70.1)		
Apixaban	615 (20.4)		
Edoxaban	147 (4.9)		
Dabigatran	141 (4.7)		
Hypertension	1,049 (34.7)	404 (38.2)	0.197
Diabetes mellitus	452 (15.0)	190 (18.0)	0.024
Chronic viral hepatitis	76 (2.5)	54 (5.1)	<0.001
AST (U/L)	30.1 ± 29.4	35.4 ± 84.2	0.044
ALT (U/L)	26.3 ± 35.8	30.7 ± 63.1	0.095
Total bilirubin (mg/dL)	0.6 ± 0.6	0.9 ± 1.7	<0.001
Creatinine	0.8 ± 0.4	1.1 ± 1.2	<0.001
CKD stage			
1	1,571 (52.0)	434 (41.0)	<0.001
2	1,139 (37.7)	410 (38.8)	
3	295 (9.8)	133 (12.6)	
4	11 (0.4)	41 (3.9)	
5	4 (0.1)	40 (3.8)	
Dialysis	74 (2.5)	107 (10.1)	<0.001
Antiplatelet	183 (6.1)	75 (7.1)	0.241
Cancer	1,605 (53.1)	494 (46.7)	<0.001
Gastrointestinal tract	295 (18.4)	89 (18.0)	
Hepatobiliary pancreas	209 (13.0)	99 (20.0)	
Lung	289 (18.0)	76 (15.4)	
Breast	68 (4.2)	16 (3.2)	
Female genital organs	178 (11.1)	42 (8.5)	
Male genital organs	66 (4.1)	13 (2.6)	
Urinary tract	127 (7.9)	34 (6.9)	
Hematologic	157 (9.8)	51 (10.3)	
Endocrine	43 (2.7)	20 (4.0)	
Others	173 (10.8)	54 (10.9)	
Intravenous chemotherapy	1,003 (60.8)	277 (53.3)	0.003
Metastasis	550 (18.2)	175 (16.5)	0.225

DOAC, direct oral anticoagulant; CKD, chronic kidney disease.

months). Among the patients, 3,020 (74.1%) received treatment with a DOAC, while 1,058 patients (25.9%) were treated with warfarin. The number of patients with DVT with or without PE was 2,083, and 1,995 had only PE. Overall, 2,099 patients (51.5%) had cancer, with the most common types being gastrointestinal (GI) cancer (384 patients, 18.3%) and lung cancer (365 patients, 17.4%); 725 patients (34.5%) had metastasis. Among those receiving DOACs, 2,117 (70.1%) were prescribed rivaroxaban; 615, apixaban (20.4%); 147, edoxaban (4.9%); and 141, dabigatran (4.7%). A reduced dose of DOAC was used in less than 1% (n = 16) of the participants. The mean medication duration was 483.8 ± 285.4 days for warfarin and 230.6 ± 285.4 days for DOACs (P < 0.001).

Patients treated with DOACs, compared to those receiving warfarin, had a higher mean age at the index date (63.1 ± 14.9 years *vs.* 61.0 ± 15.6 years) and were more likely to have cancer (1,605 patients [53.1%] *vs.* 494 patients [46.7%]). Patients treated with warfarin included more males rather than females (546 patients [51.6%] *vs.* 1,324 patients [43.8%]) and were more likely to have diabetes, chronic viral hepatitis, and advanced CKD (all P < 0.05). No significant intergroup differences were observed in body weight, body mass index, or hypertension.

During the study period, 1,199 patients (29.1%) died, with 1,046 deaths (25.4%) being cancer-related. The mean overall patient survival was 71.5 months (95% CI, 68.4–74.5 months) in the warfarin group and 77.3 months (95% CI, 75.3–79.2 months) in the DOAC group (P = 0.001).

Effectiveness and safety outcomes

Clinical outcomes, including all-cause mortality, effectiveness, and safety, are presented in Table 2. Patients treated with DOACs had significantly lower all-cause mortality rates than those treated with warfarin (HR, 0.799; 95% CI, 0.707–0.904). The cumulative incidences of effectiveness and safety outcomes are shown in Fig. 1. Recurrent VTE or major bleeding occurred in 168 patients (5.6%) treated with DOACs and 70 patients (6.6%) treated with warfarin (HR, 1.000; 95% CI, 0.997–1.003; P = 0.984). There were 96 patients in the DOAC group (3.2%) and 23 patients in the warfarin group (2.2%) who met the effectiveness outcome of recurrent VTE with an increased risk (HR, 1.017; 95% CI, 1.003–1.032; P = 0.015). The incidence rate per 1,000 PY of recurrence was 7.5 in the DOAC group and 7.4 in the warfarin group. There were 74 patients in the DOAC group (2.5%) and 52 patients in the warfarin group (4.9%) who had nonmajor and major bleeding events, with a significantly lower risk in the DOAC group (HR, 0.990; 95% CI, 0.980–0.999; P = 0.037). The most common bleeding site was the GI tract in both groups (38 patients [51.4%] in the DOAC group and 29 patients [55.8%] in the warfarin group). There was 1 death in the warfarin group, whereas no deaths occurred in the DOAC group. Patients taking concurrent antiplatelet drugs did not show a significantly different risk of bleeding compared to those not taking the drugs in either the warfarin group (HR, 0.765; 95% CI, 0.839–1.138; P = 0.490) or DOAC group (HR, 0.957; 95% CI, 0.745–1.228; P = 0.729).

After performing propensity score matching, we obtained 1,058 patients from each group (Supplementary Fig. 1). There was no significant difference in the composite outcome (HR, 1.001; 95% CI, 0.988–1.014, P = 0.878). However, the incidence of recurrent VTE was higher in the DOAC group (HR, 1.019; 95% CI, 1.003–1.035, P = 0.017), while the bleeding risk was lower in the DOAC group (HR, 0.973; 95% CI, 0.957–0.990, P = 0.002).

Table 2. Clinical outcomes including all-cause mortality, effectiveness, and safety

Variable	DOAC group (n = 3,020)	Warfarin group (n = 1,058)	HR (95% CI)	P-value
All-cause mortality, n (%)	821 (27.2)	368 (34.8)	0.799 (0.707–0.904)	<0.001
Composite outcome[a], n (%)	168 (5.6)	70 (6.6)	0.964 (0.728–1.277)	0.799
Recurrent VTE, n (%)	96 (3.2)	23 (2.2)	1.776 (1.123–2.808)	0.014
Incidence of recurrent VTE (/1,000 PY)	7.5	7.4		
Rivaroxaban (/PY)	13.6 (69/5,087.0)			
Apixaban (/PY)	12.3 (16/1,302.4)			
Edoxaban (/PY)	18.0 (5/278.3)			
Dabigatran (/PY)	14.7 (6/408.8)			
Bleeding, n (%)	74 (2.5)	52 (4.9)	0.562 (0.393–0.805)	0.002
Gastrointestinal bleeding	38 (51.4)	29 (55.8)		0.077
Intracranial bleeding	5 (6.8)	0 (0)		
Other sites	31 (41.9)	23 (44.2)		
Major bleeding, n (%)	42 (1.4)	32 (3.0)	0.509 (0.320–0.809)	0.004
Death from bleeding, n (%)	0 (0)	1 (0.1)		

DOAC, direct oral anticoagulant; HR, hazard ratio; CI, confidence interval; VTE, venous thromboembolism; PY, person-years.
[a]Composite outcomes included both recurrence and bleeding.

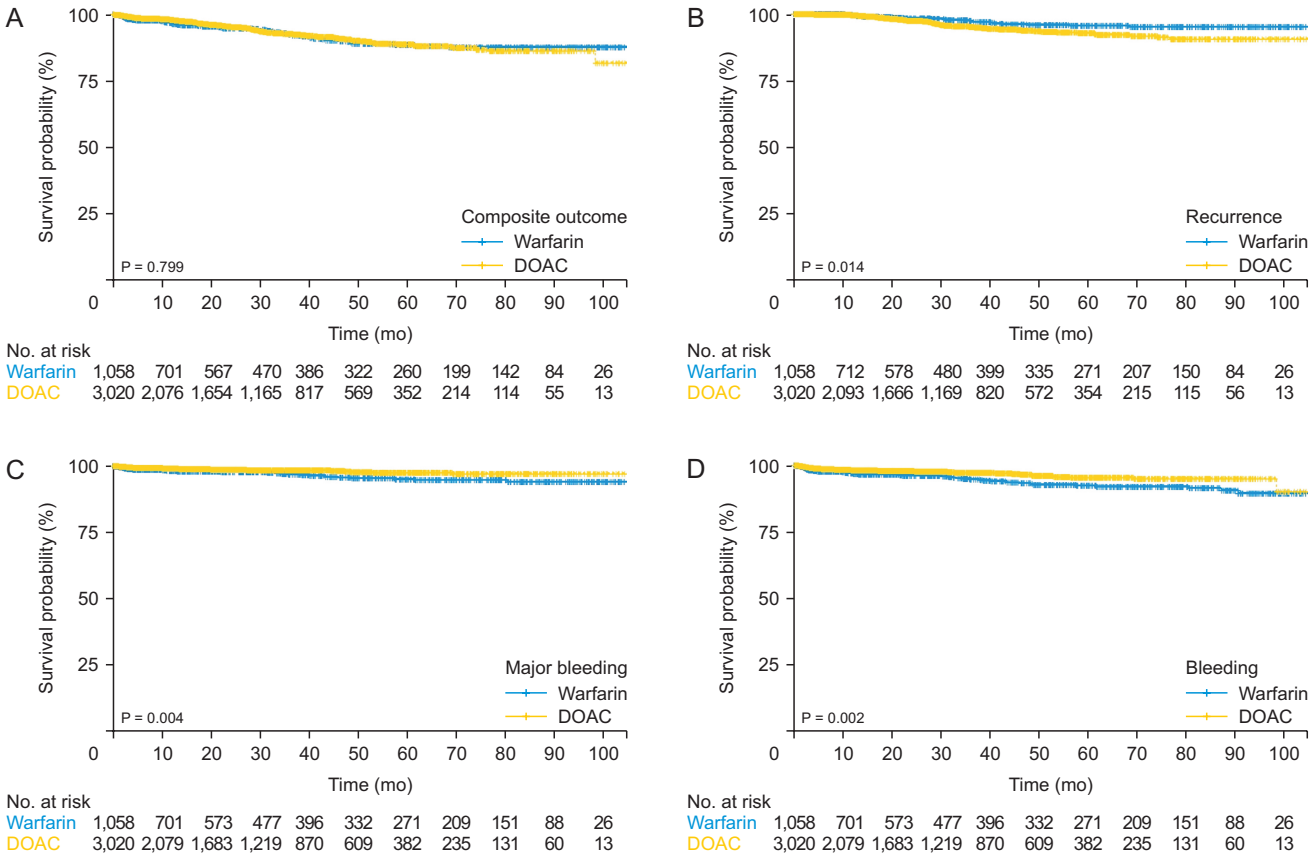

Fig. 1. Cumulative incidence of effectiveness and safety outcomes. (A) Composite outcome, (B) recurrence, (C) major bleeding, and (D) any bleeding. DOAC, direct oral anticoagulant.

Subgroup analyses

The risks for combined recurrent VTE and bleeding were not significantly different among all subgroups, regardless of whether they had cancer or were on dialysis, or age (Fig. 2A). The recurrence risk was not significantly different in fragile patients, whereas in patients aged <80 years without cancer or undergoing dialysis, those treated with DOACs had a higher risk of recurrent VTE (Fig. 2B). Bleeding risk was significantly lower in patients treated with DOACs when they were under the age of 80 years or had a body weight >60 kg (Fig. 2C). Regardless of the presence of cancer, the risk of bleeding was lower in patients treated with DOACs (Fig. 2C). In patients older than 80 years or those with combined risk factors, DOAC showed no significant differences in bleeding and recurrent VTE (Supplementary Table 1).

The bleeding risk was not significantly different when comparing each drug in cancer patients (Fig. 3A, $P > 0.05$) or in GI cancer (Fig. 3B, $P > 0.05$). When comparing individual DOAC types, composite outcomes occurred with rivaroxaban in 117 cases (5.5%), apixaban in 33 cases (5.4%), dabigatran in 7 cases (5.0%), and edoxaban in 11 cases (7.5%) ($P > 0.05$). Recurrence occurred with rivaroxaban in 69 cases (3.3%), apixaban in 16 cases (2.6%), dabigatran in 6 cases (4.3%), and edoxaban in 5 cases (3.4%) ($P > 0.05$). Bleeding events occurred with rivaroxaban in 49 cases (2.3%), apixaban in 17 cases (2.8%), dabigatran in 1 case (0.7%), and edoxaban in 7 cases (4.8%) ($P > 0.05$). Major bleeding occurred with rivaroxaban in 29 cases (1.4%), apixaban in 9 cases (1.5%), dabigatran in 1 case (0.7%), and edoxaban in 3 cases (2.0%) ($P > 0.05$).

DISCUSSION

As studies have demonstrated the non-inferiority of DOACs to warfarin, the use of DOACs has surged. Nonetheless, the efficacy of DOAC in conditions requiring special attention, such as old age and CKD, remains uncertain. Despite this uncertainty, the established efficacy and safety of DOACs in the general population, coupled with the convenience of not necessitating continuous monitoring, have led to a gradual increase in their use among these patient groups, pending further definitive evidence [11]. This study compared the safety and effectiveness of DOACs and warfarin specifically in fragile patients, defined as those with advanced age, reduced renal function, or low body weight. The term 'fragile patients,' while less commonly used in the literature compared to 'frail' or 'sarcopenic,' has been applied in studies to describe populations

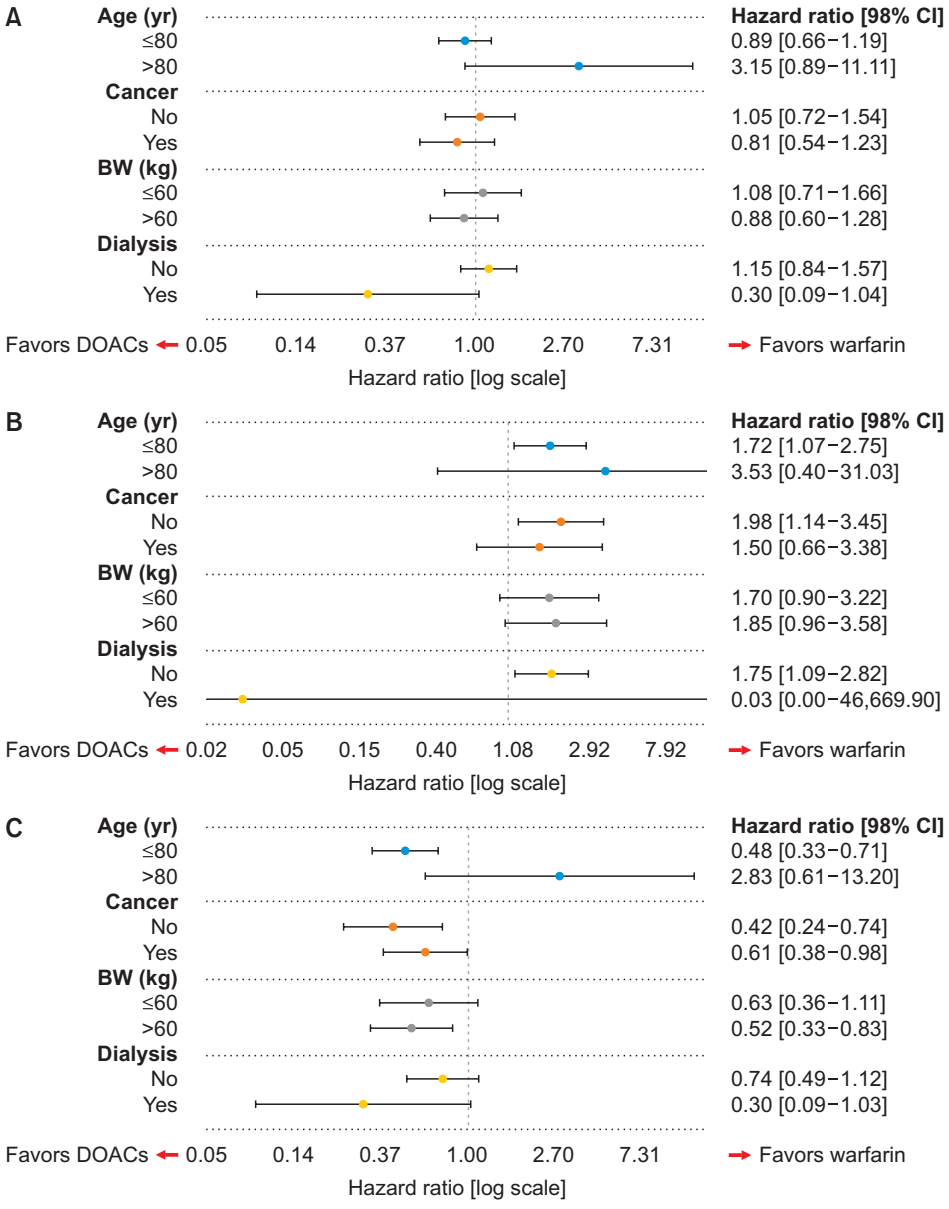

Fig. 2. Clinical outcomes, including composite outcomes (A), recurrence (B), and bleeding (C) by subgroup. CI, confidence interval; BW, body weight.

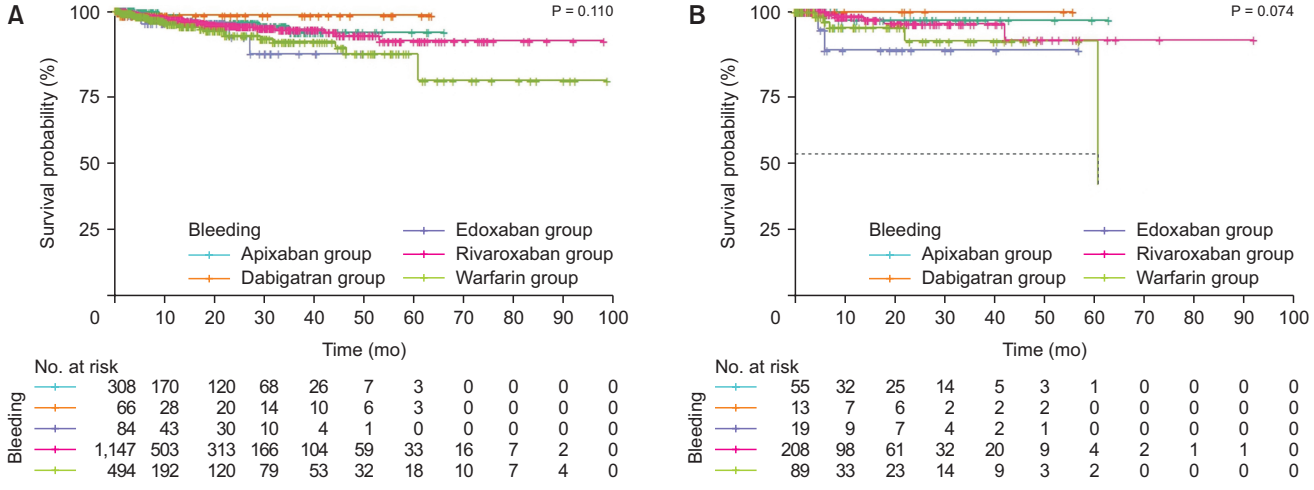

Fig. 3. Cumulative incidence of bleeding outcomes. (A) Cancer patients and (B) gastrointestinal cancer patients.

with advanced age, reduced renal function, or low body weight, particularly in the context of anticoagulation therapy [12,13]. This categorization reflects overlapping vulnerabilities relevant to anticoagulant use, as supported by prior studies [12,13]. Although the term is less frequently used, its inclusion here aims to comprehensively represent a subgroup defined by established clinical risk factors.

Older patients often experience a decline in muscle mass, renal function, and stomach pH, which affect medication clearance and absorption. They are at a heightened risk of bleeding, particularly female, who face a 20%–25% higher risk than male. However, they are frequently underrepresented in clinical trials, leading to a dearth of evidence on the optimal anticoagulants for this demographic [14]. Research on DOACs in the older population suggests similar efficacy and safety compared to warfarin in treating VTE, particularly in patients aged ≥75 years; this is supported by meta-analyses which indicate that DOACs offer similar efficacy to warfarin with significantly lower major bleeding risk [14-17]. Our study found no significant differences in recurrence and bleeding risk between older patients treated with DOACs and those treated with warfarin, which is consistent with previous reports [15-17]. However, the data on the safety and effectiveness of each DOAC are inconsistent. Further research is needed to determine whether there are differences between these drugs in terms of safety and effectiveness or if dosage adjustments are necessary.

The annual incidence of VTE in cancer patients varies widely depending on cancer type, ranging from approximately 0.5% to 20% [18,19]. Among cancer patients with VTE, mortality was 3 times higher than in those without VTE [20]. LMWH is the preferred treatment for VTE in patients with cancer; however, early clinical trials with DOACs prompted further investigation in this population. DOACs offer advantages over warfarin in patients with cancer because of their shorter onset time, half-life, and fewer drug interactions. These characteristics suggest that DOACs may be more advantageous when maintaining the appropriate dosage of warfarin becomes difficult due to cancer treatments such as chemotherapy, biopsy, or surgery [21]. Meta-analyses that included subsequent trials such as Hokusai VTE Cancer, SELECT-D, ADAM VTE, and Caravaggio, comparing DOACs with LMWH, found that DOACs significantly reduced the risk of recurrent VTE, despite an increased risk of clinically relevant nonmajor bleeding with DOACs [22,23]. Based on these findings, the current guidelines support DOACs' efficacy and safety in cancer-associated VTE, suggesting that they are acceptable alternatives, with caution in GI and genitourinary malignancies, owing to bleeding risk [24,25]. Our study compared OACs with a focus on safety and efficacy in a specific patient population; therefore, LMWH was not included as a comparator. In patients with VTE and cancer undergoing OAC treatment, DOACs were a better option, with a lower risk of bleeding and a comparable risk of recurrence in our study. In cancer patients with multiple risk factors, DOAC showed a similar risk of bleeding and recurrent VTE.

The use of DOACs in patients with CKD, especially in those with a creatinine clearance <30 mL/min, has not been extensively studied in previous randomized trials. Owing to the increased baseline bleeding risk associated with uremia-induced platelet dysfunction and renal elimination of DOACs, patients with advanced CKD were often excluded from previous DOAC-related studies [26]. However, recent studies have shed more light on this population. Population-based cohort and retrospective studies comparing DOACs with warfarin have shown similar rates of major bleeding across different CKD stages [27,28]. In particular, apixaban has demonstrated promising results in reducing recurrent VTE and major bleeding in patients with CKD [29,30]. Notably, in patients with VTE undergoing dialysis, apixaban has shown a lower risk of bleeding than warfarin, although caution is advised due to its accumulation in dialysis patients [31]. Apixaban, due to its high plasma protein binding, is minimally removed by hemodialysis, leading to its accumulation in the serum in patients undergoing dialysis. Therefore, a reduced dose of apixaban may be a viable option for patients on hemodialysis [32,33]. In our study, DOAC showed similar rates of bleeding or recurrent VTE to the standard dose in most patients. Further research is warranted to validate these findings or to determine safe dosages in larger cohorts of patients with CKD.

This study had several limitations. Its retrospective study design introduced a selection bias owing to physicians' preferences for certain drugs, which may not accurately provide a fair comparison. Additionally, a comparison was not made between patients with different stages of cancer who differ in bleeding risks. Furthermore, in our study, the warfarin treatment group included more patients with advanced CKD than the DOAC group. This could be due to a preference for warfarin treatment over DOACs, owing to the potential risks associated with DOAC use; this may have introduced a selection bias. Moreover, while our study found no differences in efficacy and safety among the different DOACs, the relatively lower inclusion of edoxaban and dabigatran compared to rivaroxaban and apixaban may have resulted in an unequal comparison. Further research comparing different DOACs among fragile patients is required. Furthermore, we were unable to obtain precise DOAC dosage data or information on international normalized ratio (INR) titration for warfarin. This limitation restricted our ability to assess the potential impact of dosage variations and INR adjustments on clinical outcomes. Consequently, the findings should be interpreted with caution, as individualized dosing factors may influence treatment efficacy and safety.

The strength of this study is that it compared a relatively

large number of patients using hospital CDW data and provided meaningful results based on anticoagulant treatment in an unselected real-world setting. Our study provides insights into the efficacy and safety of DOACs in fragile patients.

In conclusion, when compared with warfarin, DOACs did not differ significantly in terms of the clinical outcomes of recurrent VTE or bleeding in fragile patients with cancer, CKD, or old age.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 and Supplementary Fig. 1 can be found via https://doi.org/10.4174/astr.2025.108.3.168.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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