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Comparison of Direct Oral Anticoagulants and Low-Molecular-Weight Heparins in Cancer Patients with Nonvalvular Atrial Fibrillation: Insights from a Single-Center Experience

ABSTRACT

Background: Atrial fibrillation (AF) is frequently encountered in patients with cancer and poses challenges for anticoagulant management. The present study was conducted to compare clinical outcomes associated with direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH) in individuals with active malignancy and nonvalvular AF (NVAF).

Methods: Data from patients with active cancer who received LMWH or DOACs for NVAF were retrospectively screened. Efficacy, safety, and survival outcomes were analyzed.

Results: The study enrolled 222 patients, of whom 25.7% received LMWH and 74.3% received DOACs. Cancer stage, type, and treatment were comparable between groups. The DOAC group had higher CHA_2DS_2-VA (3.13 ± 1.21 vs. 2.42 ± 1.33; $P < .001$) and HAS-BLED scores (2.13 ± 0.83 vs. 1.84 ± 0.79; $P = .022$). The primary composite endpoint occurred more frequently in the LMWH group (17.5% vs. 12.1%; log-rank $P = .036$). Myocardial infarction was significantly higher in the LMWH group (8.8% vs. 1.8%; log-rank $P = .003$), while rates of ischemic stroke (3.5% vs. 6.7%; log-rank $P = .927$) and venous thromboembolism (5.3% vs. 4.8%; $P = .537$) were similar. Any bleeding (17.5% vs. 13.3%; log-rank $P = .039$) and major bleeding (7.0% vs. 1.8%; log-rank $P = .010$) were more frequent with LMWH, whereas clinically relevant non-major bleeding was comparable (10.5% vs. 11.5%; log-rank $P = .359$). All-cause mortality was significantly higher in the LMWH group (75.4% vs. 49.1%; log-rank $P < .001$), and LMWH use independently predicted mortality (hazard ratio = 2.14, $P < .001$, 95%CI: 1.45-3.17).

Conclusion: Although unmeasured confounders such as drug adherence and selection bias cannot be excluded due to the retrospective design, DOACs appear to be more effective and safer than LMWH in cancer patients with AF.

Keywords: Atrial fibrillation, cancer, cardio-oncology, direct oral anticoagulants, low-molecular-weight heparin

INTRODUCTION

As a highly prevalent cardiac arrhythmia, atrial fibrillation (AF) confers nearly a fivefold increased risk of both systemic embolism and ischemic stroke.[1] The prevalence of AF among cancer patients can be as high as 15%-19%.[2,3] Cancer itself promotes a prothrombotic state, while anticancer therapies further elevate thromboembolic risk and, paradoxically, predispose to bleeding.[4,5] Consequently, patients with both cancer and AF face a 4- to 7-fold higher risk of venous thromboembolism (VTE) and a 2-fold higher bleeding risk compared to those with AF alone.[6] Thus, optimizing anticoagulation in this high-risk group is critical.

In individuals with nonvalvular AF (NVAF), direct oral anticoagulants (DOACs) have been shown to effectively reduce the risk of stroke,[1] yet cancer patients were largely excluded from randomized trials, leaving limited evidence.[7] Vitamin K antagonists (VKAs) pose challenges due to dietary interactions, narrow therapeutic windows, and the need for frequent blood monitoring.[1] Randomized trials and meta-analyses indicate DOACs provide efficacy and safety comparable to VKAs in cancer patients with NVAF.[5-8] In oncology settings, VKAs are restricted to

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those with moderate-to-severe mitral stenosis or prosthetic valves.[5-8] The efficacy of low-molecular-weight heparin (LMWH) in stroke prevention is uncertain; it is mainly used short term, supported by data from VTE management.[8,9] Current guidelines recommend LMWH when oral anticoagulants are not possible or when DOACs cannot be used, such as in inoperable gastrointestinal system (GIS)/genitourinary system (GUS) cancers, severe renal failure, drug interactions, or platelet counts <50 000/μL, while DOACs or LMWH can otherwise be chosen individually in other cases.[8,9]

Despite these recommendations, anticoagulation management in cancer patients remains complex due to patient heterogeneity and the delicate thromboembolic–bleeding balance.[10] Malignancy is an independent predictor of oral anticoagulant nonuse, with nearly half of cancer patients with AF being untreated.[10,11] In practice, concerns about drug interactions and bleeding often lead physicians to prefer LMWH.[9,12] While multiple studies comparing LMWH and DOACs in cancer-associated VTE favor DOACs, data in NVAF are scarce.[13-15] Moreover, there are studies conducted in the country evaluating AF and no national data specifically address anticoagulant use in cancer patients with AF.[16-18] Therefore, the study aimed to assess and compare the clinical outcomes associated with the use of LMWH and DOACs—the agents most commonly employed in daily clinical practice—with active malignancy and NVAF. It is hypothesized that the findings of this study would provide valuable insights to guide clinical practice, support clinical decision-making, and promote timely initiation of anticoagulant therapy.

HIGHLIGHTS

- Atrial fibrillation (AF) is prevalent among cancer patients, presenting challenges in anticoagulation management due to an increased risk of both thrombosis and bleeding.
- Direct oral anticoagulants (DOACs) demonstrated lower rates of major bleeding, any bleeding, myocardial infarction, and major adverse cardiovascular events compared with low-molecular-weight heparin (LMWH) in patients with active cancer and nonvalvular AF.
- Ischemic stroke, venous thromboembolism, and clinically relevant non-major bleeding were similar between the 2 anticoagulant treatment strategies.
- Despite higher baseline CHA_2DS_2-VA and HAS-BLED scores, patients treated with DOACs had more favorable safety and efficacy outcomes.
- The LMWH therapy was associated with an increased risk of all-cause mortality, likely multifactorial, reflecting underlying patient characteristics rather than a direct drug effect.
- Comprehensive prospective trials are needed to clarify the comparative efficacy and safety of anticoagulation strategies in cancer patients with AF.

METHODS

Study Design and Patients

This study was designed as a retrospective analysis. Patients diagnosed with NVAF (except those with moderate-to-severe mitral stenosis or prosthetic valve) who were treated for active cancer in the medical oncology outpatient clinic between January 2018 and June 2024 and referred to the cardiology outpatient clinic through consultation were included. The majority of patients were managed in the outpatient setting. Accordingly, anticoagulant therapies, including LMWH and DOACs, were mainly initiated and maintained in this setting. In routine clinical practice at the center, the selection of anticoagulant therapy (LMWH or DOAC) was not based on a strict institutional Standard Operating Procedure but rather on an individualized clinical decision-making process. Treatment decisions were guided by current guideline recommendations, physician preference, and patient-specific factors, including comorbidities, bleeding risk, potential drug–drug interactions, and overall clinical status. In most cases, this choice was made through a multidisciplinary approach involving both cardiologists and oncologists during outpatient evaluation. To avoid bias in anticoagulant selection and comparison of results, patients with a life expectancy of <1 year, patients for whom LMWH should be preferred according to guideline recommendations (unoperated GIS/GUS cancers, severe renal dysfunction with glomerular filtration rate (GFR) <15 mL/min/1.73 m^2, platelet <50 000/μL, drug interactions with DOACs), or patients with a high bleeding risk (active bleeding or major bleeding within the last month, platelet <25 000/μL) who are not suitable for anticoagulation were excluded from the study.[6,8] Patients with hematological malignancies were also excluded from the study because their clinical course was not recorded in the hospital information system. Other cancer patients whose medical records were not accessible and patients who were on multiple anticoagulants for varying durations were also excluded from the study. Figure 1 illustrates the number and characteristics of patients who were excluded according to the study design.

Data Collection

After identifying the individuals, they were stratified into 2 groups according to the anticoagulant they were using before admission or had recently started during cardiological evaluation: group 1: those receiving LMWH; group 2: those receiving DOACs (dabigatran, rivaroxaban, edoxaban, and apixaban).

All patients' sociodemographic characteristics, additional comorbidities, smoking and alcohol habits, laboratory tests, transthoracic echocardiography findings, medical treatments, cancer type and stage, chemotherapy protocols, whether or not they received radiotherapy, clinical follow-up, and mortality data were collected through electronic medical record systems.

Definitions and Outcomes

Nonvalvular atrial fibrillation was primarily diagnosed using 12-lead electrocardiography and 24-hour Holter monitoring

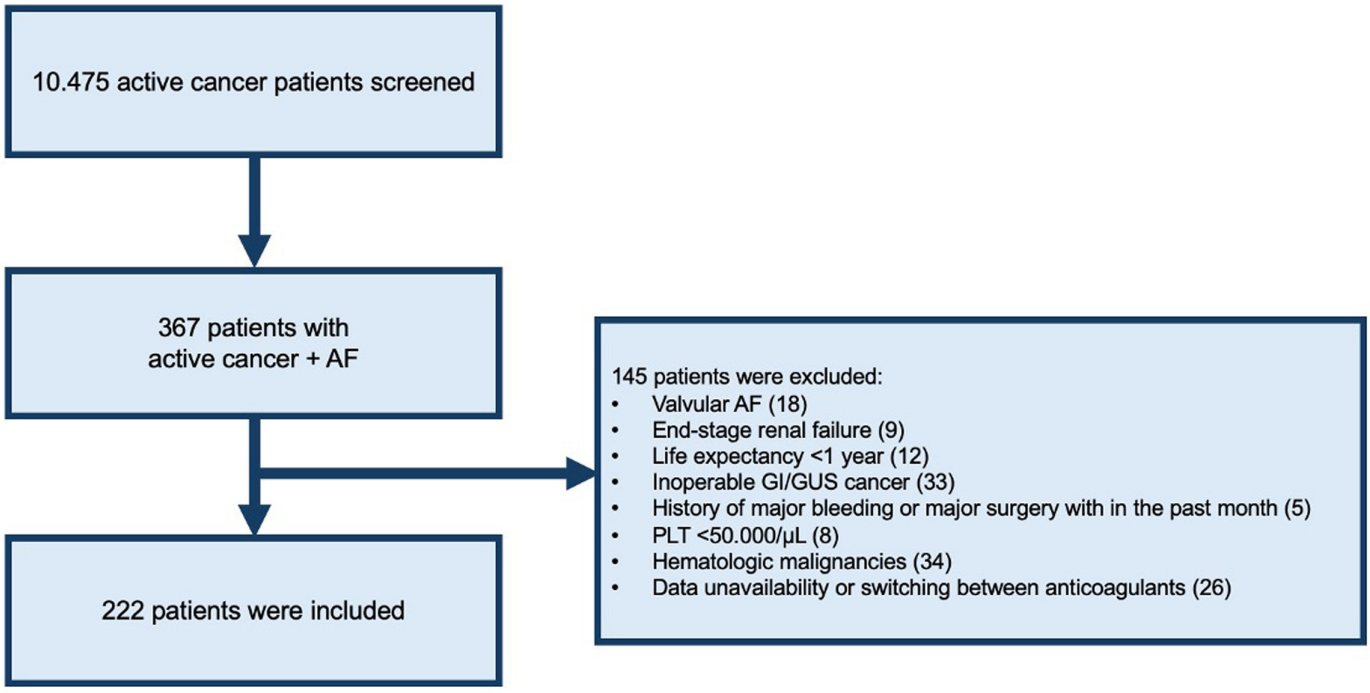

Figure 1. The number and characteristics of the excluded participants.

when clinically indicated. Active cancer was defined as a malignancy that has been diagnosed within the past 6 months, represents recurrent, regionally advanced, or metastatic disease, or has required treatment such as systemic therapy, radiation, or surgery within the preceding 6 months.[19] The primary efficacy endpoint consisted of a composite of major adverse cardiovascular events (MACE), encompassing ischemic stroke, myocardial infarction, and VTE events. The safety endpoint was any bleeding, which encompassed all bleeding-related events and was classified as major bleeding or clinically relevant non-major bleeding (CRNMB). Additionally, survival and predictors of mortality were evaluated. Major bleeding was classified as any lethal bleeding event or symptomatic hemorrhage occurring in a critical organ or anatomical site. The definition also encompassed cases involving a hemoglobin decrease of ≥2 g/dL or those necessitating 2 or more units of blood transfusion. Clinically relevant non-major bleeding referred to bleeding that necessitated medical evaluation or treatment by healthcare professionals but did not fulfill the criteria for major bleeding.[20] Venous thromboembolism encompasses deep vein thrombosis (DVT) together with pulmonary embolism.

Ethical Approval

This research adhered to national ethical requirements and the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval Number: 2024-07/93, Date: July 11, 2024). Artificial intelligence tools—such as large language models, chatbots, or image-generation software—were not employed at any point during the study.

Statistical Analysis

For categorical characteristics, results were described in terms of counts and proportions, while continuous measurements were presented either as mean ± standard deviation or as median accompanied by the minimum–maximum interval. The chi-square test was used for comparisons involving categorical variables, whereas Fisher's exact test was conducted when over 25% of the expected counts fell below the threshold of 5. The Kaplan–Meier method was applied for both cumulative incidence function and survival analyses, while survival differences across groups were examined using the log-rank test. Independent factors associated with mortality were explored using Cox proportional hazards regression analysis. Factors reaching a significance threshold of $P < .20$ on univariate analysis were carried forward for inclusion in the multiple regression model. Effect estimates were presented in the form of hazard ratios (HRs), accompanied by 95% CIs. Statistical significance across all tests was set at a threshold of $P < .05$. Data were analyzed with IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). Plots were generated using the SRplot online analysis platform.[21]

RESULTS

Baseline Characteristics

For the study, data from 10 475 active cancer patients were screened, and 367 patients with active cancer and NVAF were examined. Of these, 145 were excluded due to exclusion criteria. In total, 222 patients were enrolled in the study (Figure 1). Of these patients, 57 (25.7%) were using LMWH and 165 (74.3%) were using DOACs. When the groups were examined in terms of demographic variables, male sex

Table 1. Baseline Characteristics of the Study Population

Variables	All Cases (n = 222)	LMWH Group (n = 57)	DOACs Group (n = 165)	*P*
Age, years	71.24 ± 8.85	69.11± 10.84	71.98± 7.98	.070
Male sex, n %	111 (50.0)	36 (63.2)	75 (45.5)	.021*
Body mass index, kg/m^2	27.80 ± 4.33	27.26 ± 3.26	27.99 ± 4.65	.277
Smoking status, n (%)	107 (48.2)	28 (49.1)	79 (47.9)	.871
Alcohol use, n(%)	17 (7.7)	3 (5.3)	14 (8.5)	.430
CHA2DS2-VA score	2.96 ± 1.25	2.42 ± 1.33	3.13 ± 1.21	<.001*
HAS-BLED score	2.06 ± 0.82	1.84 ± 0.79	2.13 ± 0.83	.022
AF, paroxysmal, n(%)	46 (20.7)	15 (26.3)	31 (18.8)	.227
Comorbidities, n (%)				
Hypertension	189 (85.1)	44 (77.2)	145 (87.9)	.051
Diabetes	76 (34.2)	14 (24.6)	62 (37.6)	.074
Heart failure	55 (24.8)	14 (24.6)	41 (24.8)	.965
Coronary artery disease	83 (37.4)	13 (22.8)	70 (42.4)	.008*
Peripheral artery disease	12 (5.4)	3 (5.3)	9 (5.5)	.956
Cancer characteristics, n (%)				
Stage, n (%)				
• Stage I-II	22 (9.9)	3 (5.3)	19 (11.5)	.153
• Stage III	86 (38.7)	19 (33.3)	67 (40.6)	
• Stage IV	114 (51.4)	35 (61.4)	79 (47.9)	
ECOG category, n(%)				
• ECOG 0	42 (18.9)	9 (15.8)	33 (20)	.603
• ECOG I	110 (49.5)	26 (45.6)	84 (50.9)	
• ECOG II	57 (25.7)	18 (31.6)	39 (23.6)	
• ECOG III	13 (5.9)	4 (7)	9 (5.5)	
Region of the cancer, n (%)				
• Breast	56 (25.2)	11 (19.3)	45 (27.3)	.218
• Lung	41 (18.5)	13 (22.8)	28 (17.0)	
• Gastrointestinal	60 (27.0)	19 (33.3)	41 (24.8)	
• Genitourinary	28 (12.6)	3 (5.3)	25 (15.2)	
• Others	37(16.7)	11 (19.3)	26 (15.8)	
Cancer treatment, n(%)				
• Anthracyclines	22 (9.9)	5 (8.8)	17 (10.3)	.769
• HER2-targeted therapy	8 (3.6)	2 (3.5)	6 (3.6)	.964
• Taxanes	54 (24.3)	13 (22.8)	41 (24.8)	.757
• Alkylating agents	3 (1.4)	1 (1.8)	2 (1.2)	.766
• Tyrosine kinase inhibitors	11 (5.0)	4 (7)	7 (4.2)	.422
• Targeted therapy	7 (3.2)	1 (1.8)	6 (3.6)	.457
• Hormonotherapy	44 (19.8)	8 (14)	36 (21.8)	.191
• Radiotherapy	38 (17.1)	10 (17.5)	28 (17)	.740
• Immunotherapy	40 (18.0)	11 (19.3)	29 (17.6)	.771
Medications (cardiovascular), n (%)				
Antiplatelet treatment	24 (10.8)	6 (10.5)	18 (10.9)	.936
Beta-blockers	162 (73.0)	38 (66.7)	124 (75.2)	.214
RAS inhibitors	89 (40.1)	13 (22.8)	76 (46.1)	.002*
MRA	2 (0.9)	0 (0)	2 (1.2)	.275
SGLT-2 inhibitors	5 (2.3)	0 (0)	5 (3)	.032*
Digoxin	42 (18.9)	17 (29.8)	25 (15.2)	.015*
CCB (dihydropyridin)	28 (12.6)	11 (19.3)	17 (10.3)	.078
Amiodarone	9 (4.1)	4 (7)	5 (3)	.240

(*Continued*)

Table 1. Baseline Characteristics of the Study Population (*Continued*)

Variables	All Cases (n = 222)	LMWH Group (n = 57)	DOACs Group (n = 165)	*P*
Echocardiographic measurements				
LVEF, %	57.3 ± 5.72	57.39 ± 5.93	57.24 ± 6.56	.150
LA diameter, mm	41.7 ± 5.92	40.91 ± 6.42	41.95 ± 5.74	.255
Laboratory parameters				
Hemoglobin,g/dL	11.3 ± 2.21	10.75 ± 2.53	11.49 ± 1.96	.048*
Platelet, 10^3/μL	242.11 ± 118.42	242.43 ± 140.07	241.92 ± 110.51	.978
GFR, mL/dak/1, $73m^2$	71.1 ± 26.21	75.56 ±33.70	69.70± 23.87	.230

AF, atrial fibrillation; CCB, calcium channel blocker; DOAC, direct oral anticoagulants; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; HER 2, human epidermal growth factor receptor-2; LA, left atrium; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RAS, renin angiotensin system; SGLT-2, sodium-glucose co-transporter 2. **P* values < .05 indicate statistical significance.

(*P* = .021) was more prevalent in the DOAC group. Coronary artery disease was significantly more prevalent in the DOAC group (42.4% vs. 22.8%; *P* = .008), while hypertension showed a trend toward higher prevalence (87.9% vs. 77.2%; *P* = .051) in the same group. No significant differences were found between cancer stage, types, and treatments used. CHA_2DS_2-VA score (3.13 ± 1.21, 2.42 ± 1.33, *P* < .001) and HAS-BLED score (2.13 ± 0.83, 1.84 ± 0.79, *P* = .022) were higher in the DOAC group. Additionally, antiplatelet use was similar between the 2 anticoagulant treatments (*P* = .936). Baseline characteristics were presented in Table 1.

Primary Efficacy Endpoint—Thromboembolic Events and Myocardial Infarction

The primary composite endpoint was observed in 30 (13.5%) patients during a median 11.3 months of follow-up. Ischemic stroke occurred in a total of 13 (5.9%) patients. Two (0.9%) patients experienced DVT, 9 (4.0%) patients experienced pulmonary embolism, and 8 (3.6%) patients experienced myocardial infarction. Cumulative incidence function analyses revealed that the primary efficacy endpoint, the incidence of MACE, was significantly higher in the LMWH group compared to the DOAC group (17.5% vs. 12.1%; log-rank *P* = .036) (Table 2). Notably, the incidence of myocardial infarction was significantly higher in the LMWH group (8.8% vs. 1.8%; log-rank *P* = .003), while no significant differences were observed between the groups in the incidence of ischemic stroke (3.5% vs. 6.7%; log-rank *P* = .927) or VTE (5.3% vs. 4.8%; log-rank *P* = .537) (Figure 2).

Bleeding

Any bleeding-related events occurred in 32 (14.4%) patients while 7 (3.1%) of the cases were major bleeding. Five of these had major gastrointestinal bleeding, 1 had major intracranial bleeding, and 1 had major genitourinary bleeding. Cumulative incidence function analyses revealed that the incidence of CRNMB was similar between the LMWH and DOAC groups (10.5% vs. 11.5%; log-rank *P* = .359). In contrast, major bleeding events were significantly more frequent in the LMWH group compared with the DOAC group (7.0% vs. 1.8%; log-rank *P* = .010). Consistently, the overall occurrence of any bleeding, encompassing both major bleeding and CRNMB events, was higher in patients receiving LMWH than in those treated with DOACs (17.5% vs. 13.3%; log-rank *P* = .039) (Figure 3).

All-Cause Mortality

During follow-up, 124 patients experienced all-cause mortality (55.9%). Mortality rates were significantly higher in the LMWH group than in the DOAC group (75.4% vs. 49.1%, respectively, *P* = .001) and overall survival was significantly

Table 2. Clinical Outcomes of LMWH and DOAC Groups

Clinical Outcomes (n) %	All Patients (n = 222)	LMWH Group (n = 57)	DOAC Group (n = 165)	*P*
Efficacy endpoints				
Primary composite efficacy endpoint (Ischemic stroke + MI + VTE)	30 (13.5)	10 (17.5)	20 (12.1)	.036*
Ischemic stroke	13 (5.9)	2 (3.5)	11 (6.7)	.927
VTE	11 (5.0)	3 (5.3)	8 (4.8)	.537
MI	8 (3.6)	5 (8.8)	3 (1.8)	.003*
Safety endpoints, n (%)				
Any bleeding	32 (14.4)	10 (17.5)	22 (13.3)	.039*
Major bleeding	7 (3.2)	4 (7.0)	3 (1.8)	.010*
CRNMB	25 (11.3)	6 (10.5)	19 (11.5)	.359
Mortality				
All-cause mortality	124 (55.9)	43 (75.4)	81 (49.1)	<.001*

CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulants; LMWH, low molecular weight heparin; MI, Myocardial infarction; VTE, venous thromboembolism. **P* values < .05 indicate statistical significance. *P* values derived from log-rank tests were reported in the event analyses.

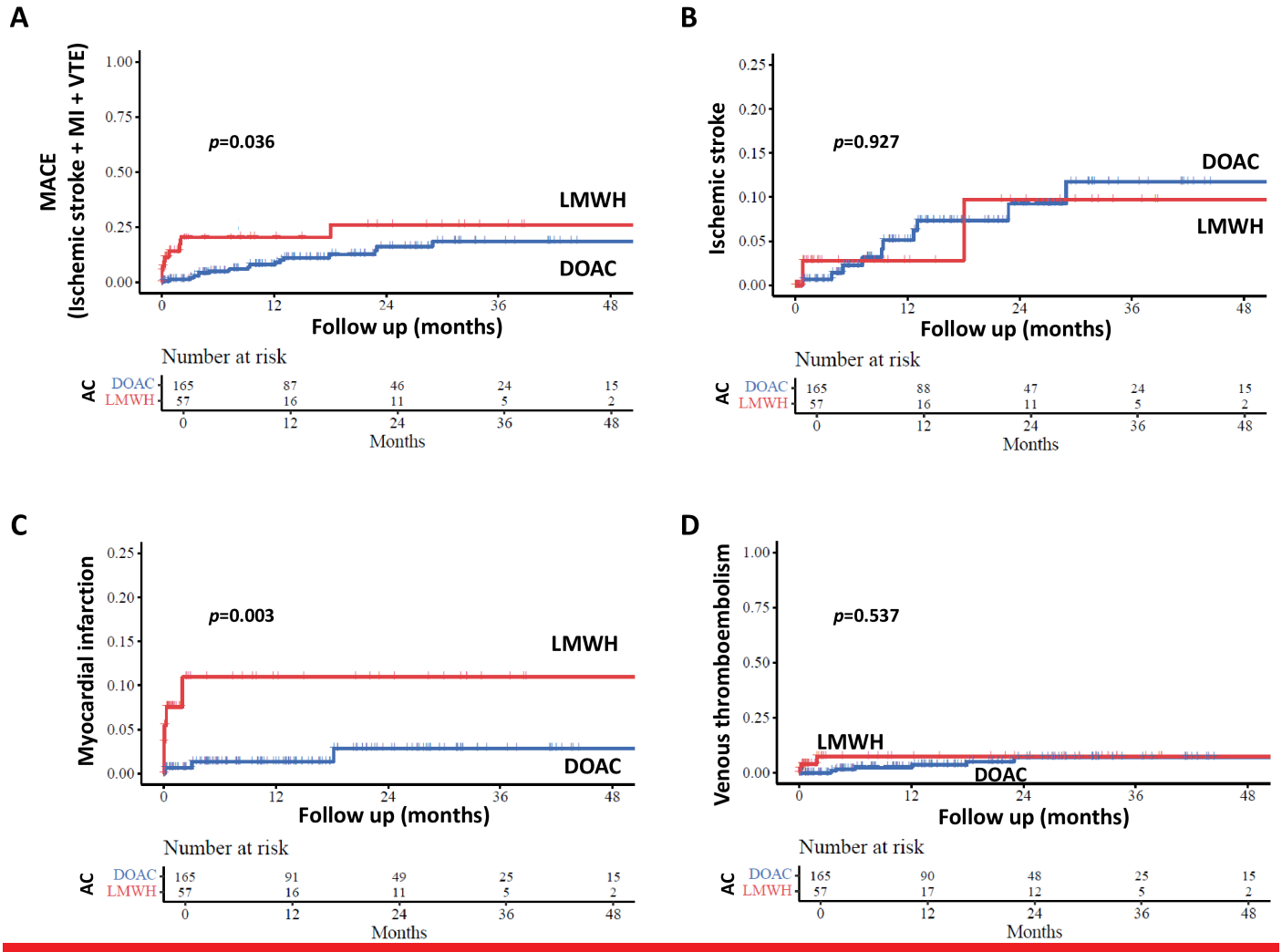

Figure 2. Cumulative incidence of thromboembolic events in patients receiving LMWH or DOAC therapy. A: major adverse cardiovascular events, B: ischemic stroke, C: myocardial infarction, D: venöz thromboembolism. DOAC, direct oral anticoagulants; LMWH, low-molecular-weight heparin.

lower in the LMWH group compared with the DOAC group (log-rank $P < .001$) (Figure 4).

When factors associated with mortality were examined, LMWH use (HR = 2.14, $P < .001$, 95% CI: 1.45-3.17), male sex (HR = 1.64, $P = .015$, 95% CI: 1.10-2.46), and advanced tumor stage, stage III-IV vs. lower stages; (HR = 1.76, $P = .01$, 95% CI: 1.26-2.46), Eastern Cooperative Oncology Group (ECOG) score (HR = 1.46, $P = .02$, 95% CI: 1.14-1.86), albumin (HR = 0.98, $P = .023$, 95% CI: 0.96-0.99) were found to be independent risk factors for mortality (Table 3).

Regarding AF subtype, a total of 46 patients (20.7%) had paroxysmal AF. When stratified according to both AF subtype

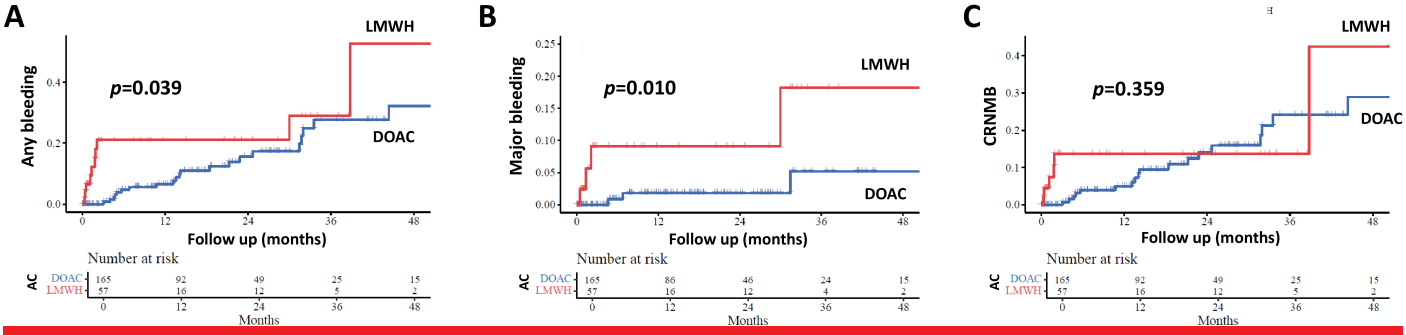

Figure 3. Cumulative incidence of bleeding events in patients receiving LMWH or DOAC therapy. A: Any bleeding, B: Major bleeding, C: clinically relevant non-major bleeding. DOAC, direct oral anticoagulants; LMWH, low-molecular-weight heparin.

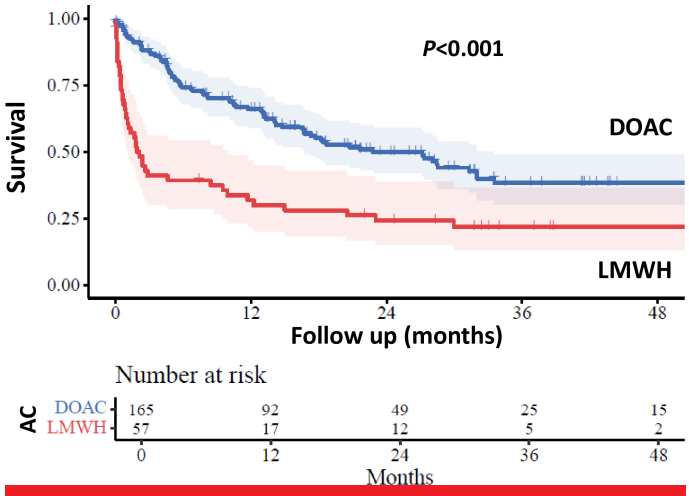

Figure 4. Overall survival in patients receiving LMWH or DOAC therapy. DOAC, direct oral anticoagulants; LMWH, low-molecular-weight heparin.

and anticoagulant strategy, the highest mortality rate was observed in patients with persistent AF receiving LMWH (80.9%), whereas the lowest mortality rate was observed in patients with paroxysmal AF treated with DOACs (19.3%) (*P* = .001). However, no statistically significant differences were observed between the groups with regard to embolic and bleeding events (all *P* > .05) (Supplementary Table S1).

DISCUSSION

This study evaluated patients with active cancer who received LMWH or DOAC therapy for NVAF and observed that: (i) both the composite MACE endpoint and major bleeding were more frequent among patients treated with LMWH, while the incidences of CRNMB, ischemic stroke, and VTE were comparable between groups; (ii) all-cause mortality was higher among patients treated with LMWH; and LMWH use, male sex, advanced cancer stage, ECOG score, and albumin were identified as independent predictors of overall mortality in this population.

Table 3. Univariable and Multiple Cox Regression Analysis for the Predictors of All-Casue Death in the Study Cohort (n = 222)

	Univariable Analysis		Multiple Analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (per year)	1.01 (0.99-1.03)	.099	1.00 (0.98-1.02)	.694
Sex, male	2.59 (1.78-3.76)	<.001	1.64 (1.10-2.46)	.015*
Cancer stage	2.13 (1.53-2.94)	<.001	1.76 (1.26-2.46)	.001*
ECOG score	1.53 (1.24-1.90)	<.001	1.46 (1.14-1.86)	.002*
Type of AC (LMWH vs. DOAC)	2.38 (1.64-3.45)	<.001	2.14 (1.45-3.17)	<.001*
Use of RAS inhibitor	0.69 (0.48-1.00)	.052	0.69 (0.47-1.01)	.057
Creatinine, mg/dL	1.26 (0.97-1.64)	.076	1.02 (0.81-1.28)	.835
Albumin, g/dL	0.98 (0.97-0.99)	.010	0.98 (0.96-0.99)	.023*

AC, anticoagulant; DOAC, direct oral anticoagulants; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LMWH, low molecular weight heparin; RAS, renin angiotensin system. **P* values < .05 indicate statistical significance.

Management of AF in patients with active cancer is a challenging process that requires balancing both cancer treatment and cardiovascular risks.[8,9] Atrial fibrillation is present in approximately 5% of cancer patients at diagnosis or during the first months of treatment.[22] Long-term anticoagulation is recommended in adult patients with a CHA_2DS_2-VA score ≥2 and should also be considered when the score is 1.[1] The same approach may be recommended for patients with cancer and AF, considering that the risk score likely underestimates their thromboembolic risk.[8] According to current data, approximately 80% of cancer patients with AF have indications for chronic anticoagulation.[23] Another study demonstrated that anticoagulant treatment is often insufficient in patients with AF and active cancer; 25% of patients did not receive any anticoagulant therapy, and 33% were administered prophylactic, subtherapeutic doses of LMWH.[24] Another study indicated that following cancer diagnosis, patients starting anticoagulant treatment were more frequently prescribed LMWH or unfractionated heparin (UFH) rather than VKA or DOACs.[12] In this study, approximately one-quarter of patients were receiving LMWH, while three-quarters were treated with DOACs. This increased trend toward DOAC use may be due to the fact that the study included patient records from the period after the publication of the European Society of Cardiology 2022 cardio-oncology guidelines, and the study excluded a patient group in whom LMWH should be the primary choice. Nevertheless, these results are promising for adherence to current guidelines in clinical practice and the adoption of individualized anticoagulant therapy approaches in patient management.

Cancer is linked to a higher bleeding risk due to factors such as thrombocytopenia, metastatic spread, renal and hepatic damage, vascular injury from tumor invasion of vessel walls, invasive interventions, and radiation therapy.[12,25,26] All these factors increase the risk of bleeding related to anticoagulants in these patients.[12] Another significant challenge in administering anticoagulants to cancer patients is the drug interactions with chemotherapy and supportive agents.[12] In a retrospective cohort study, trends in anticoagulant prescribing and the safety and efficacy profile of DOACs were examined using real-life data in follow-up cancer patients. A total of 214 cancer patients were included in the study; 71 (33%) of these patients used DOACs. Fewer bleeding events and/or drug discontinuations were observed in patients using DOACs compared to the LMWH group. However, no significant difference was found in terms of major or minor bleeding when DOACs were compared with LMWH or VKAs.[27] In another prospective multicenter study, the safety and efficacy of DOACs versus LMWH were assessed in 302 patients with NVAF undergoing active cancer treatment. Among these, 192 patients (63.5%) received DOACs, while 110 were treated with LMWH. The annual rates of major bleeding were 4.1% in the DOAC group and 6.5% in the LMWH group, with no statistically significant difference observed between the groups.[28] In the study, while the incidence of CRNMB was

similar between the LMWH and DOAC groups, the rates of major bleeding and the overall occurrence of any bleeding, encompassing both major bleeding and CRNMB events, were significantly higher in the LMWH group. This finding contrasts slightly with previous reports. The higher bleeding rates observed with LMWH in the cohort may be explained by several factors, including differences in patient selection across studies and the inherent heterogeneity of cancer patients. Variations in comorbidities, concomitant medications, and cancer type or stage could have contributed to the increased susceptibility to bleeding.

On the other hand, thromboembolic complications are frequently observed in patients with active cancer and are complex due to multiple factors, including inflammation, pathophysiological changes related to malignancy, treatment-related side effects, and surgical interventions.[29,30] Antithrombotic therapy, a current priority in cardio-oncology, is gaining increasing importance due to the increasing frequency of both venous and arterial thromboembolism in this patient group.[15,31,32] In particular, arterial complications have been linked to increased mortality, and patients with advanced malignancies carry a significantly elevated risk of stroke and myocardial infarction.[33,34] In the study, ischemic stroke occurred in 14 patients, VTE in 12 patients, and myocardial infarction in 13 patients during follow-up. Survival analyses demonstrated no significant differences between the LMWH and DOAC groups with respect to the incidence of ischemic stroke or VTE; however, the rates of MACE and myocardial infarction were significantly higher in the LMWH group. A study including cancer patients with NVAF compared those receiving DOACs and LMWH; stroke and systemic embolism rates were found to be significantly higher in the LMWH group.[28] Conversely, another study including active cancer patients receiving anticoagulant therapy for AF or VTE compared DOACs and LMWH groups and, unlike the findings, found no significant difference in thromboembolic events.[27] The observed difference may partly be explained by the older mean age of patients in the LMWH group in the cohort compared with the other study (69 vs. 61 years). In addition, the possibility of non-therapeutic LMWH dosing or reduced adherence related to subcutaneous administration may also have contributed to this finding.

Finally, the coexistence of AF and cancer may lead to an increased risk of major bleeding, thromboembolic events, and higher mortality compared to cancer patients without concomitant AF.[35,36] The study evaluated the effects of anticoagulant therapy choices on all-cause mortality and found that mortality was significantly higher in the LMWH group. In the present analysis, LMWH use was identified as an independent predictor of all-cause mortality. However, given the lack of clear data showing that most deaths were due to bleeding or embolic complications and the potential for residual confounding inherent to the retrospective design, this association should be interpreted with caution. Although baseline characteristics, including cancer stage, were broadly comparable between groups, unmeasured factors such as disease severity, performance status, and overall clinical condition may have influenced both treatment selection and outcomes. Moreover, the findings are consistent with similar studies in the literature. In a multicenter study conducted by Chai-Adisaksopha et al,[12] all-cause mortality was found to be significantly higher in patients using LMWH/UFH compared to DOAC and VKA users (14.3 vs. 5.4 and 4.0 events/100 patient-years). Patients receiving LMWH/UFH exhibited a significantly higher mortality risk than those treated with VKA ($P < .001$). On the other hand, another study found no significant association between anticoagulant therapy and mortality; instead, mortality was more strongly associated with cancer type and overall patient condition. In the present analysis, although no statistically significant differences were observed between the 2 groups with respect to patient and cancer-related characteristics, the higher proportion of patients with ECOG II-III scores in the LMWH group may, at least in part, be explained by a numerically higher proportion of stage IV cancer in this group. This may indicate a trend toward poorer overall clinical condition. Nevertheless, the increased mortality in the LMWH group may have been attributable to an increased incidence of MACE, myocardial infarction, any bleeding, and major bleeding in this group. From a clinical perspective, in light of the findings, closer clinical follow-up of patients receiving LMWH may be particularly important. Careful reassessment of anticoagulant strategy throughout the course of treatment, optimization of modifiable cardiovascular and bleeding risk factors, may help reduce adverse outcomes. In addition, thorough review of concomitant therapies and avoidance of unnecessary use of nonsteroidal anti-inflammatory drugs or antiplatelet agents may contribute to minimizing the risk of bleeding events, thereby improving patient outcomes. Overall, these findings suggest that the observed association between LMWH use and increased mortality is likely multifactorial rather than indicative of a direct causal relationship. Therefore, these results should be interpreted cautiously, and further prospective studies incorporating detailed clinical variables are warranted to better clarify the impact of anticoagulant selection on survival in this complex patient population.

Strengths and Limitations

The study has several limitations. Patients using combined anticoagulants or those who received no anticoagulant therapy were not included in the analysis. The retrospective design of the study is another limitation. Furthermore, because patients with hematological malignancies and those with a life expectancy of less than 1 year were excluded, the generalizability of the findings to all cancer patients is limited. Moreover, potential overlooked confounders such as patient frailty, which may have influenced clinicians' treatment selection, could have introduced bias. Since the analysis is an intention to treat analysis, the data do not provide sufficient information regarding treatment adherence and temporary treatment interruptions. No subgroup analyses for DOACs or stratification based on dose appropriateness were performed. Additionally, due to the retrospective design of ther study, detailed data regarding LMWH dosing, including dose adjustments, and potential deviations from

therapeutic dosing, were not consistently available in the medical records. Therefore, the potential impact of non-therapeutic dosing on clinical outcomes could not be fully assessed.

Despite these limitations, to the best of knowledge, this study is the first in the country to evaluate anticoagulant therapy in patients with NVAF and active cancer. It is valuable because it presents the experience of an oncology center with high patient data accuracy and optimal follow-up and recording. The balanced clinical characteristics of the patient groups compared enhance the reliability of the results. Furthermore, the study evaluated numerous outcome events, and cancer characteristics were collected in detail. Scores that have prognostic importance in the evaluation of patients could be calculated accurately and completely. In all these aspects, the study provides important data on anticoagulant treatment preferences, contributes to the understanding of clinical practices in this field, and has the potential to shed light on more comprehensive, prospective studies to be conducted in the future.

CONCLUSION

This study compared the clinical outcomes of DOACs and LMWH in patients with active cancer and NVAF. The findings demonstrate that, although patients receiving DOACs exhibited higher baseline thromboembolic and bleeding risk scores, the incidence of thromboembolic and bleeding complications was significantly higher in the LMWH group. Importantly, LMWH use was associated with higher all-cause mortality; however, this finding may reflect underlying differences in patient characteristics and unmeasured confounding factors rather than a direct causal effect. Taken together, these findings suggest that, although unmeasured confounders such as drug adherence and selection bias—given the potential preferential use of LMWH in frail patients—cannot be ruled out due to the retrospective nature of the study, DOACs appear to offer greater efficacy and safety than LMWH in cancer patients with AF. Future prospective randomized controlled trials are warranted to elucidate the comparative efficacy and safety of various anticoagulation strategies in cancer patients with AF.

Ethics Committee Approval: This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No: 2024-07/93, Date: July 11, 2024)

Informed Consent: Due to the nature of the retrospective study, informed consent from participants was omitted.

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REFERENCES

1. Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45(36):3314-3414. [CrossRef]
2. Kattelus H, Kesäniemi YA, Huikuri H, Ukkola O. Cancer increases the risk of atrial fibrillation during long-term follow-up (OPERA study). *PLoS One*. 2018 October 5;13(10):e0205454. [CrossRef]
3. O'Neal WT, Lakoski SG, Qureshi W, et al. Relation between cancer and atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke Study). *Am J Cardiol*. 2015 April 15;115(8):1090-1094. [CrossRef]
4. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol*. 2014;63(10):945-953. [CrossRef]
5. Chen Y, Mao M, Chang J, et al. Safety and efficacy of new oral anticoagulants compared to those of warfarin in AF patients with cancer: a meta-analysis of randomized clinical trials and observational studies. *Eur J Clin Pharmacol*. 2021 June;77(6):849-857. [CrossRef]
6. Truong B, Hornsby L, Fox B, Chou C, Zheng J, Qian J. Effectiveness and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation and cancer: a target trial emulation from SEER-medicare database. *Cardiovasc Drugs Ther*. 2025 August;39(4):823-835. [CrossRef]
7. Chan YH, Chao TF, Lee HF, et al. Clinical outcomes in atrial fibrillation patients with a history of cancer treated with non-vitamin K antagonist oral anticoagulants: a nationwide cohort study. *Stroke*. 2021 October;52(10):3132-3141. [CrossRef]
8. Lyon AR, López-Fernández T, Couch LS, et al . 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361. [CrossRef]
9. Undas A, Drabik L. Non-vitamin K antagonist oral anticoagulants (NOACs) in cancer patients with atrial fibrillation. *Anatol J Cardiol*. 2020 January;23(1):10-18. [CrossRef]
10. Fradley MG, Ellenberg K, Alomar M, et al. Patterns of Anticoagulation Use in PatientsWith Cancer with atrial fibrillation and/or Atrial Flutter. *JACC CardioOncol*. 2020;2(5):747-754. [CrossRef]
11. Maciorowska M, Uziębło-Życzkowska B, Gorczyca-Głowacka I, et al. Oral anticoagulation therapy in atrial fibrillation patients at high risk of bleeding: clinical characteristics and treatment strategies based on data from the Polish multicenter register of atrial fibrillation (POL-AF). *Kardiol Pol*. 2024;82(1):37-45. [CrossRef]
12. Chai-Adisaksopha C, Watanabe AH, Dilokthornsakul P, Navaravong L, Witt DM, Chaiyakunapruk N. Impact of type of anticoagulant on clinical outcomes in cancer patients who had atrial fibrillation. *Sci Rep*. 2023 July 6;13(1):10937. [CrossRef]
13. Douros A, Filliter C, Azoulay L, Tagalakis V. Effectiveness and safety of direct oral anticoagulants in patients with cancer associated venous thromboembolism. *Thromb Res*. 2021 June;202:128-133. [CrossRef]

14. Di Nisio M, Lee AY. Direct oral anticoagulants: the new standard of care for cancer associated thrombosis. *Eur J Intern Med*. 2024 May;123:60-62. [CrossRef]
15. Gervaso L, Dave H, Khorana AA. Venous and arterial thromboembolism in patients with cancer: *JACC: CardioOncology* state-of-the-art review. *JACC CardioOncol*. 2021 April 20;3(2):173-190. [CrossRef]
16. Badak Ö, Özkaramanlı Gür D, Kaya Ç, et al. Assessment of non-vitamin K antagonist oral anticoagulant dosing patterns in Turkish patients with non-valvular atrial fibrillation: a multicenter, cross-sectional study with insights from the ASPECT-NOAC study. *Turk Kardiyol Dern Ars*. 2024 December;52(8): 574-580. [CrossRef]
17. Kocabaş U, Ergin I, Yavuz V, et al. Real-world evaluation of anticoagulant treatment patterns in patients with atrial fibrillation: data from multicenter ROTA study. *Turk Kardiyol Dern Ars*. 2023 March;51(2):88-96. [CrossRef].
18. Gedikli Ö, Altay S, Ünlü S, et al. Real-life data of major and minor bleeding events with direct oral anticoagulants in the one-year follow-up period: the NOAC-TURK study. *Anatol J Cardiol*. 2021;25(3):196-204. [CrossRef]
19. Frere C, Crichi B, Lejeune M, Spano JP, Janus N. Are patients with active cancer and those with history of cancer carrying the same risks of recurrent VTE and bleeding while on anticoagulants? *Cancers (Basel)*. 2020;12(4):917. [CrossRef]
20. Pacholczak-Madej R, Bazan-Socha S, Zaręba L, Undas A, Dropiński J. Direct oral anticoagulants in the prevention of stroke in breast cancer patients with atrial fibrillation during adjuvant endocrine therapy: a cohort study. *Int J Cardiol*. 2021 February 1;324:78-83. [CrossRef]
21. Tang D, Chen M, Huang X, et al . SRplot: A free online platform for data visualization and graphing. *PLOS One*. 2023 November 9;18(11):e0294236. [CrossRef]
22. Sanz AP, Gómez JLZ. AF in cancer patients: A different need for anticoagulation? *Eur Cardiol*. 2019 April;14(1):65-67. [CrossRef]
23. Chao CH, Wang HY, Kao CH. Occult cancer and thromboembolism: current epidemiology and its practical implications. *Pol Arch Intern Med*. 2018 September 28;128(9):539-544. [CrossRef]
24. Malavasi VL, Fantecchi E, Gianolio L, et al . Atrial fibrillation in patients with active malignancy and use of anticoagulants: under-prescription but no adverse impact on all-cause mortality. *Eur J Intern Med*. 2019 January;59:27-33. [CrossRef]
25. Undas A, Drabik L, Potpara T. Bleeding in anticoagulated patients with atrial fibrillation: practical considerations. *Kardiol Pol*. 2020 February 25;78(2):105-116. [CrossRef]
26. Steffel J, Verhamme P, Potpara TS, et al . The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Kardiol Pol*. 2018;76(9):1283-1298. [CrossRef]
27. Xiang E, Ahuja T, Raco V, Cirrone F, Green D, Papadopoulos J. Anticoagulation prescribing patterns in patients with cancer. *J Thromb Thrombolysis*. 2018 January;45(1):89-98. [CrossRef]
28. Olivera PE, Velasquez CA,Campoy D, et al. Effectiveness and safety of direct oral anticoagulants vs. low molecular weight heparin as anticoagulant therapy in patients with active cancer therapy and non valvular atrial fibrillation. *Blood*. 2019;134(suppl 1):3661. [CrossRef]
29. Pastori D, Marang A, Bisson A, et al. Thromboembolism, mortality, and bleeding in 2,435,541 atrial fibrillation patients with and without cancer: a nationwide cohort study. *Cancer*. 2021 June 15;127(12):2122-2129. [CrossRef]
30. Wright JC, Sharma S, Potter AS. Arrhythmia challenges in cardio-oncology: high-risk therapies, management, and anticoagulation. *Cardiol Clin*. 2025 February;43(1):43-56. [CrossRef]
31. Lenihan DJ, Fradley MG, Dent S, et al. Proceedings From the Global Cardio-Oncology Summit: the Top 10 Priorities to Actualize for CardioOncology. *JACC CardioOncol*. 2019 December 17;1(2):256-272.
32. Breccia M, Carver JR, Szmit S, Jurczak W, Salvatorelli E, Minotti G. Mechanisms and clinical course of cardiovascular toxicity of cancer treatment II. Hematology☆. *Semin Oncol*. 2019 December;46(6):403-407. [CrossRef]
33. Mulder FI, Horváth-Puhó E, van Es N, et al. Arterial thromboembolism in cancer patients: A Danish population-based cohort study. *JACC CardioOncol*. 2021 April 20;3(2):205-218. [CrossRef]
34. Navi BB, Reiner AS, Kamel H, et al . Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017 August 22;70(8):926-938. [CrossRef]
35. Li M, Huang B, Lam SHM, et al . Long-term risks and benefits of oral anticoagulation in atrial fibrillation patients with cancer: a report from the GLORIA-AF registry. *Eur J Clin Invest*. 2025 February;55(2):e14347. [CrossRef]
36. Murtaza M, Baig MMA, Ahmed J, Serbanoiu LI, Busnatu SS. Higher mortality associated with new-onset atrial fibrillation in cancer patients: A systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:867002. [CrossRef]

Supplementary Table 1. Comparison of clinical outcomes according to AF subtype and anticoagulant therapy

Clinical outcomes (n) %	Paroxysmal AF + LMWH (n=15)	Paroxysmal AF + DOAC (n=31)	Persistent AF + LMWH (n=42)	Persistent AF + DOAC (n=134)	*P*
Mortality†	9 (60%)	6 (19.3%)	34 (80.9%)	75 (55.9%)	0.001*
Ischemic stroke**	0 (0%)	3 (9.7%)	2 (4.8%)	8 (5.9%)	0.946
Major bleeding**	2 (13.3%)	1 (3.2%)	2 (4.8%)	2 (1.5%)	0.142
CRNMB **	0 (0%)	2 (6.5%)	6 (14.3%)	17 (12.7%)	0.096

**Fisher exact test,†Chi-square test ; AF,atrial fibrillation; LMWH, low molecular weight heparin ;DOAC, direct oral anticoagulants; CRNMB, clinically relevant non-major bleeding; **P*-values<0.05 indicate statistical significance.