



Effectiveness and Safety of DOACs vs. VKAs in AF Patients With Cancer: Evidence From Randomized Clinical Trials and Observational Studies

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Liu F, Xu Z, Luo J, Yu P, Ma J, Yuan P and Zhu W (2021) Effectiveness and Safety of DOACs vs. VKAs in AF Patients With Cancer: Evidence From Randomized Clinical Trials and Observational Studies. Front. Cardiovasc. Med. 8:766377. doi: 10.3389/fcvm.2021.766377 **Background:** The use of direct oral anticoagulants (DOACs) is recommended as the preferred treatment drug in patients with nonvalvular atrial fibrillation (AF). However, the effectiveness and safety of DOACs compared with vitamin K antagonists (VKAs) in patients with cancer and AF are still controversial. Therefore, we performed a meta-analysis regarding the effectiveness and safety of DOACs vs. VKAs in AF patients with cancer.

Methods: A search of the Pubmed and EMBASE databases until August 2021 was performed. Adjusted risk ratios (RRs) and 95% confidence intervals (CIs) were pooled using a random-effects model with an inverse variance method.

Results: Thirteen studies were deemed to meet the criteria. For the effectiveness outcomes, the use of DOACs compared with VKAs use was significantly associated with decreased risks of stroke or systemic embolism (RR = 0.66, 95% CI: 0.54–0.80) and venous thromboembolism (RR = 0.40, 95% CI: 0.26–0.61), but not ischemic stroke (RR = 0.79, 95% CI: 0.56–1.11), myocardial infarction (RR = 0.78, 95% CI: 0.56–1.11), cardiovascular death (RR = 0.76, 95% CI: 0.53–1.09), and all-cause death (RR = 0.82, 95% CI: 0.43–1.56). For the safety outcomes, compared with VKAs use, the use of DOACs was associated with reduced risks of intracranial bleeding (RR = 0.60, 95% CI: 0.50–0.71) and gastrointestinal bleeding (RR = 0.87, 95% CI: 0.80–0.95). There were no significant differences in major bleeding (RR = 0.87, 95% CI: 0.74–1.04), major or nonmajor clinically relevant bleeding (RR = 0.87, 95% CI: 0.74–1.01), and any bleeding (RR = 0.88, 95% CI: 0.76–1.03).

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Conclusion: Compared with VKAs, DOACs appeared to have significant reductions in stroke or systemic embolism, venous thromboembolism, intracranial bleeding, and gastrointestinal bleeding, but comparable risks of ischemic stroke, myocardial infarction, cardiovascular death, all-cause death, major bleeding, major or nonmajor clinically relevant bleeding, and any bleeding in patients with AF and cancer.

Keywords: atrial fibrillation, cancer, direct oral anticoagulants, vitamin K antagonists, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in adults. The currently estimated prevalence of AF in adults is between 2 and 4%, and a 2.3-fold rise is expected, due to the longevity in the general population and the increased screenings of patients with undiagnosed AF (1). Increasing age is a foremost risk factor, but the increasing burdens of other comorbidities (e.g., hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease) are also important. Several other modifiable risk factors are potential contributors to AF development and progression (1). AF increases the risks of cardiovascular and cerebrovascular complications including a 5-fold risk of stroke (2). AF-related thromboembolic events are the main reasons for the increased rates of morbidity and mortality (3, 4).

A published research report involving more than 24,000 patients diagnosed with cancer showed that the prevalence of AF combined at the time of cancer diagnosis was about 2.4%, and the incidence of AF after cancer diagnosis was 1.8% (5). AF and cancer may interact with each other on pathophysiological grounds. AF in cancer patients may be caused by inflammation, age, comorbidities, surgery or medical cancer treatment, or direct tumor effects. However, cancer patients are at higher risks of thromboembolism and bleeding complications, because cancer interacts with the coagulation system, which is related to a hypercoagulable state (2). AF and cancer have independently increased risks of arterial and venous thrombosis compared with a single disease. Anticoagulation therapy for patients with AF and cancer is challenging because of the increased risk of thromboembolism and bleeding in this special population.

The current international guidelines recommend the use of direct oral anticoagulants (DOACs) as replacement therapy for vitamin K antagonists (VKAs) in patients with nonvalvular AF. DOACs also have advantages in the elderly, or AF patients with specific diseases such as acute coronary syndrome and chronic kidney disease (6). However, whether these recommendations apply to patients with cancer and AF needs further evidence. So far, most of the data on anticoagulant therapy for cancer patients is mainly for the treatment and prevention of venous thromboembolism (VTE). International guidelines recommend low molecular weight heparin (LMWH) (rather than VKAs or DOACs) for the prevention and treatment of VTE in cancer patients (7). Although DOACs have non-inferiority compared with VKAs in patients with AF, these drugs are not recommended in the guidelines for cancer patients. The effectiveness and

safety of anticoagulation therapy in patients with AF and cancer are unclear.

Previous DOAC-related randomized controlled trials (RCTs) in the AF population only include a small number of cancer patients or even exclude some cancer patients (8–11). Current data of *post-hoc* analyses of RCTs (12–15) and observational cohort studies (3, 16–19) regarding the effectiveness and safety of DOACs compared with VKAs in patients with AF and cancer have been published. Therefore, this meta-analysis aimed to evaluate the effect of DOACs vs. VKAs in AF and cancer patients.

METHODS

Literature Retrieval

The two common databases of PubMed and Embase were systematically searched until August 2021 for available studies using the following search terms: (1) atrial fibrillation, (2) cancer OR tumor OR malignancy, (3) non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban, and (4) vitamin K antagonists OR warfarin. The detailed searching strategies are shown in **Supplementary Table 1**. In this meta-analysis, we included publications in English.

Inclusion and Exclusion Criteria

We included the *post-hoc* analyses of RCTs or observational cohort studies focusing on the effectiveness and/or safety of DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) compared with VKAs in AF patients with cancer. The effectiveness outcomes included stroke or systemic embolism (SSE), ischemic stroke, myocardial infarction (MI), VTE, all-cause death, cardiovascular death; whereas the safety outcomes included major bleeding, major or nonmajor clinically relevant (NMCR) bleeding, intracranial bleeding, gastrointestinal bleeding, and any bleeding. The follow-up time was not restricted. We excluded certain publication types such as reviews, case reports, case series, editorials, and meeting abstracts because they had no sufficient data. Studies with overlapping data were also excluded.

Study Screenings and Data Extraction

Two authors (FW-L and ZX-X) independently did the process of data extraction. We first screened the titles and abstracts of the searched records to select potential studies, and the full text of which was screened in the subsequent phase. Disagreements were resolved through discussion, or consultation with the third researcher (WG-Z). If two or more studies were from the same data source, the study that was more designed to meet the predefined criteria was included. If two studies met the inclusion criteria, we would include the newly published study, or the study with the longest follow-up or highest sample size.

Two authors independently collected the following characteristics from each included study, mainly included the first author and publication year, location, data source, study design, inclusion period, patient age and sex, types of DOACs, follow-up time, effectiveness and safety outcomes, type of cancers, the sample size and number of events in the VKA- or DOAC- groups, and adjusted risk ratios (RRs) and 95% confidence intervals (CIs).

Study Quality Assessment

Two authors (FW-L and ZX-X) used the Newcastle-Ottawa Scale (NOS) to perform the quality assessment for the included studies independently. The NOS tool had three domains with a total of nine points including the selection of cohorts (0–4 points), the comparability of cohorts (0–2 points), and the assessment of the outcomes (0–3 points). In this study, we defined studies with the NOS of <6 points as low quality (20).

Statistical Analysis

We assessed the consistency across the included studies using the Cochrane Q-test and I^2 statistic. A P < 0.1 for the Q statistic, or $I^2 \ge 50\%$ indicated substantial heterogeneity. We first collected the sample size and number of events in the VKA- or DOAC-groups and calculated their corresponding crude rates of effectiveness and safety outcomes. The comparison results between the VKA- or DOAC-groups were expressed as odds ratios (ORs) and 95% CIs. Second, we assessed the effectiveness and safety of DOACs vs. VKAs in AF patients with cancer using the adjusted RRs. The adjusted RRs and 95% CIs were converted to the natural logarithms and standard errors, which were pooled by a random-effects model using an inverse variance method. The publication bias for the reported effect estimates was assessed using the funnel plots.

All the statistical analyses were conducted using the Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark; https:// community.cochrane.org/). The statistical significance threshold was set at a P < 0.05.

RESULTS

The process of the literature retrieval is presented in **Supplementary Figure 1**. A total of 1,116 studies were identified through the electronic searches in the PubMed and Embase databases. According to the predefined criteria, we finally included 13 studies (four *post-hoc* analyses of RCTs and nine observational cohorts) in this meta-analysis (3, 4, 12–17, 19, 21–24). **Table 1** shows the baseline patient characteristics of the included studies. All of these included

studies had a moderate-to-high quality with the NOS score of ≥ 6 points.

Crude Event Rates Between DOACs vs. VKAs

A total of nine included studies reported the crude rates of effectiveness or safety outcomes between DOACs vs. VKAs (3, 4, 12–17, 19). For the effectiveness outcomes shown in **Figure 1**, compared with VKA-users, DOAC-users had lower event rates of SSE (3.10 vs. 5.36%, OR = 0.55, 95% CI: 0.30–0.99), ischemic stroke (9.83 vs. 12.2%, OR = 0.60, 95% CI: 0.41–0.90), VTE (2.26 vs. 7.63%, OR = 0.40, 95% CI: 0.18–0.88), and MI (1.46 vs. 1.67%, OR = 0.64, 95% CI: 0.44–0.91), but there were comparable rates of cardiovascular death (4.79 vs. 6.63%, OR = 0.74, 95% CI: 0.49–1.12) and all-cause death (25.7 vs. 44.6%, OR = 0.69, 95% CI: 0.41–1.14).

The safety outcomes of DOACs vs. VKA are presented in **Figure 2**. The pooled results showed that DOAC-users had lower event rates of major bleeding (7.15 vs. 9.17%, OR = 0.61, 95% CI: 0.39–0.94) and intracranial bleeding (0.14 vs. 1.67%, OR = 0.13, 95% CI: 0.04–0.44) than VKA-users. However, there were no significant differences in major or NMCR bleeding (26.5 vs. 25.0%, OR = 0.88, 95% CI: 0.72–1.09), gastrointestinal bleeding (3.79 vs. 2.34%, OR = 0.75, 95% CI: 0.37–1.22) between the two studied groups.

Adjusted Data of Outcomes Between DOACs vs. VKAs

A total of nine included studies reported the adjusted data of effectiveness or safety outcomes between DOACs vs. VKAs (3, 12–14, 17, 21–24). Adjusted confounders of the included studies are presented in **Supplementary Table 2**. As shown in **Figure 3**, for the effectiveness outcomes, the use of DOACs compared with VKA use was significantly associated with decreased risks of SSE (RR = 0.66, 95% CI: 0.54–0.80) and VTE (RR = 0.40, 95% CI: 0.26–0.61), but not ischemic stroke (RR = 0.79, 95% CI: 0.56–1.11), MI (RR = 0.78, 95% CI: 0.56–1.11), cardiovascular death (RR = 0.76, 95% CI: 0.53–1.09), and all-cause death (RR = 0.82, 95% CI: 0.43–1.56).

For the safety outcomes shown in **Figure 4**, compared with VKA use, the use of DOACs was significantly associated with reduced risks of intracranial bleeding (RR = 0.60, 95% CI: 0.50–0.71) and gastrointestinal bleeding (RR = 0.87, 95% CI: 0.80–0.95). There were no significant differences in major bleeding (RR = 0.87, 95% CI: 0.74–1.04), major or NMCR bleeding (RR = 0.87, 95% CI: 0.74–1.01), and any bleeding (RR = 0.88, 95% CI: 0.76–1.03).

Publication Bias

As shown in **Supplementary Figures 2**, **3**, no obvious publication biases were observed when assessed by using the funnel plots. Also, it was noted that the publication bias should not be evaluated for some reported outcomes when fewer than 10 included studies were included.

TABLE 1 | Baseline characteristics of the included studies.

Included studies	Study design	Data source	Sample size	Age (mean, y)/Sex	DOACs	VKAs	Efficacy outcomes	Safety outcomes	Follow- up (years)	Types of cancers
Chen et al. (12)	<i>Post-hoc</i> analysis of RCT	ROCKET AF; multicenter	640	77/both	Rivaroxaban	Warfarin	SSE, ischemic stroke, VTE, MI, cardiovascular death, and all-cause death	Major bleeding, major or NMCR bleeding, intracranial bleeding, and any bleeding	1.9	Prostate (28.6%), breast (14.7%), gastrointestinal (3.0%), lung (3.1%), head and neck (3.9%), colorectal (16.1%), melanoma (5.9%), leukemia or lymphoma (5.2%), gynecologic (6.6%), genitourinary (12.2%), thyroid (2.5%), brain (0.3%), unspecified (3.9%), and others (3.0%)
Fanola et al. (13)	Post-hoc analysis of RCT	ENGAGE AF-TIMI 48; multicenter	1,153	75/both	Edoxaban	Warfarin	SSE, ischemic stroke, MI, cardiovascular death, and all-cause death	Major bleeding, major or NMCR bleeding, and any bleeding	2.8	Prostate (13.7%), breast (6.5%), bladder (7.5%), gastrointestinal (20.5%), lung or pleura (11.0%), skin (5.9%), liver, gallbladder, or bile ducts (3.8%), pancreatic (3.8%), esophageal (2.5%), renal (2.5%), uterine (2.1%), oropharyngeal (2.6%), brain (2.1%), genital (1.3%), thyroid (1.1%), leukemia (2.8%), lymphoma (2.2%), others (1.3%), and unspecified (1.5%)
Melloni et al. (14)	<i>Post-hoc</i> analysis of RCT	ARISTOTLE; multicenter	1,236	–/both	Apixaban	Warfarin	SSE, ischemic stroke, VTE, MI, and all-cause death	Major bleeding, major or NMCR bleeding, intracranial bleeding, and any bleeding	1.8	Prostate (29%), breast (16%), bladder (7%), colon (11%), gastric (2%), ovarian/uterus (6%), lung (3%), melanoma (6%), rectal (3%), renal cell carcinoma (4%), Hodgkin's lymphoma (1%), non-Hodgkin's lymphoma (1%), leukemia (<1%), lymphoma (1%), and others (10%)
Flack et al. (15)	Observational cohort	RE-LY; multicenter	546	–/both	dabigatran	Warfarin	-	Gastrointestinal bleeding	2.2	Gastrointestinal
Ording et al. (16)	Observational cohort	Danish population-based medical databases	11,855	77/both	Not available	Unspecified	Ischemic stroke, VTE, and MI	Gastrointestinal bleeding	1.0	Urological (15%), breast cancer (12%), gastrointestinal (12%), lung (4%), hematological (3%), intracranial (0.1%), and others (54%)
Ording et al. (22)	Observational cohort	Danish nationwide cohort study	1,476	78/both	Dabigatran, rivaroxaban, apixaban, and edoxaban	Unspecified	-	Intracranial bleeding, gastrointestinal bleeding, and any bleeding	1.0	Gastrointestinal
Shah et al. (3)	Observational cohort	Market Scan databases, the United States	16,096	74/both	Dabigatran, rivaroxaban, and apixaban	Warfarin	lschemic stroke, VTE	Any bleeding	1.0	Breast (19.2%), gastrointestinal (12.7%), lung (12.3%), Genitourinary (29.2%), gyneco-oncological (2.4%), hematological (9.8%), and others (14.4%)

(Continued)

DOACs in AF and Cancer

Included studies	Study design	Data source	Sample size	Age (mean, y)/Sex	DOACs	VKAs	Efficacy outcomes	Safety outcomes	Follow- up (years)	Types of cancers
Kim et al. (4)	Observational cohort	Severance Cardiovascular Hospital, Seoul, Korea	1,651	70/both	Dabigatran, rivaroxaban, and apixaban	Warfarin	SSE, all-cause death	Major bleeding, intracranial bleeding, and gastrointestinal bleeding	1.8	Prostate (9.3%), gastrointestinal (20.6%), breast (2.4%), colorectal (14.9%), thyroid (10.8%), lung (12.2%), melanoma (5.9%), biliary tract (5.4%), urinary tract (6.1%), genitourinary (12.2%), head and neck (4.1%), hepatocellular carcinoma (3.0%), ovary and endometrial (2.6%), renal cell carcinoma (3.1%), hematologic malignancy (2.2%), and others (3.2%)
Pardo Sanz et al. (23)	Observational cohort	AMBER-AF registry, Oncology and Cardiology Departments, Spain	637	75.4/Fema	e Not available	Unspecified	SSE	Major bleeding	2.8	Breast
Sawant et al. (17)	Observational cohort	The national VA Healthcare data	196,521	76/both	dabigatran, rivaroxaban, apixaban	Warfarin	lschemic stroke, all-cause death	NA	1.0	Not available
Yasui et al. (19)	Observational cohort	Osaka International Cancer Institute, Japan	224	72.7/both	Dabigatran, rivaroxaban, apixaban, and edoxaban	Warfarin	SSE, ischemic stroke	Major bleeding, intracranial bleeding, gastrointestinal bleeding	1.0	Gastrointestinal (44.2%), Lung (24.1%), genitourinary (11.2%), head and neck (9.8%), breast (4.0%), hematological (3.1%), and others (3.6%)
Atterman et al. (24)	Observational cohort	Swedish Patient register	8228	75.1/both	NA	Warfarin	-	Major or NMCR bleeding, intracranial bleeding, and gastrointestinal bleeding	1.0	Prostate (27.2%), gastrointestinal (19.1%), pancreatic (1.0%), lung (6.8%), breast (9.1%), gynecological (4.9%), urological (35.6%), intracranial (1.3%), hematological (10.7%), metastasized (9.2%), and others (14.4%)
Chan et al. (21)	Observational cohort	Taiwan National Health Insurance Research Database	7955	77/both	dabigatran, rivaroxaban, apixaban, and edoxaban	Warfarin	SSE, VTE, and MI	Major bleeding, intracranial bleeding, and gastrointestinal bleeding	1.45	Not available

AF, atrial fibrillation; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; RCT, randomized controlled trial; SSE, stroke or systemic embolism; MI, myocardial infarction; VTE, venous thromboembolism; NMCR, non-major clinically relevant bleeding.

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Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 SSE							
Chen_2018	8	307	16	329	19.5%	0.52 [0.22, 1.24]	_ _ +
Fanola-2018	33	758	24	395	26 1%	0 70 [0 41 1 21]	
Kim-2018	9	388	40	388	22.0%	0.21 [0.10, 0.43]	_ _
Melloni-2017	15	615	14	621	22.0%	1 08 [0 52 2 27]	
Vasui-2019	3	127	4	97	10.4%	0.56 [0.12, 2.57]	
Subtotal (95% CI)	-	2195		1830	100.0%	0.55 [0.30, 0.99]	
Total events	68		98				•
Heterogeneity: Tau ² =	= 0 27·Ch	$i^{2} = 10$	94 df =	4 (P = 0.0)	$(3) \cdot ^2 = 6$	3%	
Test for overall effect	Z = 2.01	P = 0.0	04)	- (1 - 0.0	57,1 = 0	370	
1.1.2 Ischemic strok	e						
Chen_2018	4	307	12	329	7 4%	0 35 [0 11 1 09]	
Fanola_2018	28	758	21	395	13 7%	0.68 [0.38 1.22]	
Kim_2018	20	798	30	388	11 6%	0.00 [0.30, 1.22]	
Melloni_2017	14	615	0	621	10.3%	1 58 [0 68 3 60]	
Ordina_2017	14	1800	302	10046	16.0%		
Sawant-2010	4421	26240	21610	160177	10.3%	0.75 [0.52, 1.02]	
Samani-2013	121	607F	51013	1001//	17 10/	0.09 [0.00, 0.92]	_ 1
Shari-2010	40	127	204	10021	2 00/	1 15 [0.27, 0.31]	
Subtotal (95% CI)	3	46410	2	182074	100.0%	0.60 [0.19, 7.02]	
Total avente	4565	10413	22200	1020/4	100.070	0.00 [0.71, 0.50]	▼
Hotorogancing Tay.2	4303	1 ² _ 40	12 45	7 /0 - 0 0	00011. 12	- 96%	
Test for overall effect	- 0.22; Ch : Z = 2.48	I = 49. 3 (P = 0.1	15, af = 01)	/ (r < 0.0	(0001); F	- 0070	
1.1.2.475							
1.1.3 VIE							Ĺ
cnen-2018	4	307	4	329	17.3%	1.07 [0.27, 4.33]	
Melloni-2017	3	615	4	621	16.0%	0.76 [0.17, 3.39]	
Ording-2017	12	1809	162	10046	30.6%	0.41 [0.23, 0.73]	
Shah-2018	180	6075	1433	10021	36.2%	0.18 [0.16, 0.21]	
Subtotal (95% CI)		8806		21017	100.0%	0.40 [0.18, 0.88]	
1 1 4 MI		, u = 0.0	,				
Chen-2018	7	307	8	329	12 3%	0.94 [0 34 2 61]	
Fanola-2018	19	758	16	395	28 2%	0.61 [0 31 1 20]	_ _
Melloni-2017	12	615	12	621	19.8%	1 01 [0 45 2 27]	
	13	1809	154	10046	39.7%	0 46 [0 26 0 82]	_
Ording_2017		1005	134	11391	100.0%	0.64 [0.44, 0.91]	•
Ording-2017 Subtotal (95% Cl)	15	3489					
Ording-2017 Subtotal (95% Cl) Total events	51	3489	190				
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	51 = 0.00; Ch	3489 1i ² = 3.0	190 3, df = 3	(P = 0.39); I ² = 1%		
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	51 = 0.00; Ch : Z = 2.44	3489 1i ² = 3.0 (P = 0.0	190 3, df = 3 01)	(P = 0.39)); ² = 1%		
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular	51 = 0.00; Ch : Z = 2.44 • death	3489 1i ² = 3.0 ↓ (P = 0.0	190 3, df = 3 01)	(P = 0.39)); ² = 1%		
Ording-2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018	51 = 0.00; Ch : Z = 2.44 • death 17	3489 1i ² = 3.0 1 (P = 0.0 307	190 3, df = 3 01) 25	(P = 0.39 329	9); ² = 1% 42.2%	0.71 [0.38, 1.35]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018	51 = 0.00; Ch : Z = 2.44 • death 17 34	3489 1i ² = 3.0 1 (P = 0.0 307 758	190 3, df = 3 01) 25 23	(P = 0.39 329 395	9); ² = 1% 42.2% 57.8%	0.71 [0.38, 1.35] 0.76 [0.44, 1.31]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI)	51 = 0.00; Ch : Z = 2.44 • death 17 34	3489 Ii ² = 3.0 I (P = 0.0 307 758 1 065	190 3, df = 3 01) 25 23	(P = 0.39 329 395 724	9); ² = 1% 42.2% 57.8% 100.0%	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events	51 = 0.00; Ch : Z = 2.44 • death 17 34 51	3489 Ii ² = 3.0 I (P = 0.0 307 758 1 065	190 3, df = 3 01) 25 23 48	(P = 0.39 329 395 724)); ² = 1% 42.2% 57.8% 100.0%	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12]	
Ording-2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% Cl) Total events Heterogeneity: Tau ² =	51 = 0.00; Ch : Z = 2.44 • death 17 34 51 = 0.00; Ch	3489 11 ² = 3.0 1 (P = 0.0 307 758 1065 11 ² = 0.0	190 3, df = 3 01) 25 23 48 2, df = 1	(P = 0.39 329 395 724 (P = 0.88	(i); $i^2 = 1\%$ 42.2% 57.8% 100.0% (i): $i^2 = 0\%$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1 .12]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	51 = 0.00; Ch : Z = 2.44 • death 17 34 51 = 0.00; Ch : Z = 1.43	3489 $ii^{2} = 3.0$ $i (P = 0.0)$ 307 758 1065 $ii^{2} = 0.0$ $i (P = 0.1)$	190 3, df = 3 01) 25 23 48 2, df = 1 15)	(P = 0.39 329 395 724 (P = 0.88	9); I ² = 1% 42.2% 57.8% 100.0% 8); I ² = 0%	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	51 = 0.00; Ch : Z = 2.44 • death 17 34 51 = 0.00; Ch : Z = 1.43 h	3489 $i^{2} = 3.0$ $i (P = 0.0)$ 307 758 1065 $ii^{2} = 0.0$ $i (P = 0.1)$	190 3, df = 3 01) 25 23 48 2, df = 1 15)	(P = 0.39 329 395 724 (P = 0.88	9); l ² = 1% 42.2% 57.8% 100.0% 8); l ² = 0%	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat	51 = 0.00; Ch : Z = 2.44 • death 17 34 51 = 0.00; Ch : Z = 1.43 h	3489 $1i^{2} = 3.0$ $i (P = 0.1$ 307 758 1065 $ii^{2} = 0.0$ $i (P = 0.1$ 207	190 3, df = 3 01) 25 23 48 2, df = 1 15)	(P = 0.39 329 395 724 (P = 0.88	9); I ² = 1% 42.2% 57.8% 100.0% 8); I ² = 0%	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Enacle 2012	51 = 0.00; Ch : Z = 2.44 • death 17 34 = 0.00; Ch : Z = 1.43 h 32	3489 $i^{2} = 3.0$ $i (P = 0.1$ 307 758 1065 $ii^{2} = 0.0$ $i (P = 0.1$ 307 758	190 3, df = 3 01) 25 23 48 2, df = 1 15) 48	(P = 0.39 329 395 724 (P = 0.88 329	$\begin{array}{l} \mathbf{(}); \ \mathbf{(}^2 = 1\%)\\ 42.2\%\\ 57.8\%\\ 100.0\%\\ \mathbf{(}); \ \mathbf{(}^2 = 0\%)\\ 18.5\%\\ 20.2\%\end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Fanola-2018	51 = 0.00; Ch : Z = 2.44 • death 17 34 = 0.00; Ch : Z = 1.43 h 32 241	3489 $i^{2} = 3.0$ $i (P = 0.1$ 307 758 1065 $i^{2} = 0.0$ $i (P = 0.3$ 307 758 307	190 3, df = 3 01) 25 23 48 2, df = 1 15) 48 120	(P = 0.39 329 395 724 (P = 0.88 329 395	$\begin{array}{l} \text{(); } ^2 = 1\% \\ & 42.2\% \\ & 57.8\% \\ & 100.0\% \\ \text{(); } ^2 = 0\% \\ & 18.5\% \\ & 20.8\% \\ & 10.4\% \end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10] 1.07 [0.82, 1.39]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Kim-2018 Kim-2018	51 = 0.00; Ch : Z = 2.44 • death 17 34 51 = 0.00; Ch : Z = 1.43 h 32 241 41	3489 $i ^{2} = 3.0$ $i (P = 0.1)$ 307 758 1065 $i ^{2} = 0.0$ $i (P = 0.2)$ 307 758 388 627	190 3, df = 3 21) 25 23 48 2, df = 1 15) 48 120 93 93	(P = 0.39 329 395 724 (P = 0.88 329 395 388	$\begin{array}{l} \text{(); } ^2 = 1\% \\ & 42.2\% \\ & 57.8\% \\ \textbf{100.0\%} \\ \textbf{100.0\%} \\ \text{(); } ^2 = 0\% \\ & 18.5\% \\ & 20.8\% \\ & 19.4\% \\ & 1.6\% \end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Fanola-2018 Kim-2018 Melloni-2017 Sevent 2012	51 = 0.00; Ch : Z = 2.44 • death 17 34 • 51 = 0.00; Ch : Z = 1.43 h 32 241 41 54	3489 $i ^{2} = 3.0$ $i (P = 0.1$ 307 758 1065 $i ^{2} = 0.0$ $i (P = 0.2$ 307 758 388 615 26240	190 3, df = 3 21) 25 23 48 2, df = 1 15) 48 120 93 42 71010	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621	$\begin{array}{l} \text{(1)}; \ ^2 = 1\%\\ & 42.2\%\\ & 57.8\%\\ \textbf{100.0\%}\\ \text{(3)}; \ ^2 = 0\%\\ & 18.5\%\\ & 20.8\%\\ & 19.4\%\\ & 19.2\%\\ & 20.2\%\\ \end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI)	51 = 0.00; Ch : Z = 2.44 • death 17 34 • 17 34 51 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488	3489 $1 ^{2} = 3.0$ $4 (P = 0.1)$ 307 758 1065 $1 ^{2} = 0.0$ $4 (P = 0.1)$ $(P = 0.1)$ $(P = 0.1)$ 307 758 388 615 36340 3840	190 3, df = 3 21) 25 23 48 2, df = 1 15) 48 120 93 42 71919	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177	$\begin{array}{l} 42.2\%\\ 57.8\%\\ 100.0\%\\ 10; \ l^2=0\%\\ 18.5\%\\ 20.8\%\\ 19.4\%\\ 19.2\%\\ 22.1\%\\ 100.0\%\end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.74 [0.49, 1.12] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI) Total events Chen-2018	51 = 0.00; Ch : Z = 2.44 • death 17 34 • 51 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488	3489 hi ² = 3.0 k (P = 0.4 1065 hi ² = 0.0 k (P = 0.2 k (P = 0.2) k (P = 0.2) 307 758 388 615 36340 38408	190 3, df = 3 21) 25 23 48 2, df = 1 15) 48 120 93 42 71919 70000	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177 161910	$\begin{array}{l} 42.2\%\\ 57.8\%\\ 100.0\%\\ 1);\ l^2=0\%\\ 18.5\%\\ 20.8\%\\ 19.4\%\\ 19.2\%\\ 22.1\%\\ 100.0\%\end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.74 [0.49, 1.12] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44] 0.69 [0.41, 1.14]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI) Total events	51 = 0.00; Ch : Z = 2.44 • death 17 34 • 51 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488 9856	3489 $i ^{2} = 3.0$ $4 (P = 0.1)$ 1065 1065 $i ^{2} = 0.0$ $(P = 0.2)$ 307 758 307 758 3840 38408 $i^{2} =$	190 3, df = 3 25 23 48 2, df = 1 15) 48 120 93 42 71919 72222	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177 161910	$\begin{array}{l} 42.2\%\\ 57.8\%\\ 100.0\%\\ 30; \ 1^2 = 0\%\\ 18.5\%\\ 20.8\%\\ 19.4\%\\ 19.2\%\\ 22.1\%\\ 100.0\%\\ \end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44] 0.69 [0.41, 1.14]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	51 = 0.00; Ch : Z = 2.44 • death 17 34 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488 9856 = 0.31; Ch	3489 $i ^{2} = 3.0$ $i (P = 0.1)$ 307 758 1065 $i ^{2} = 0.0$ $i (P = 0.1)$ 307 758 388 615 36340 38408 $ i ^{2} = 75.$	190 3, df = 3 21) 25 23 48 2, df = 1 15) 48 120 93 42 71919 72222 27, df =	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177 161910 4 (P < 0.0	$\begin{array}{l} \text{(1)}; \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.74 [0.49, 1.12] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44] 0.69 [0.41, 1.14]	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Fest for overall effect	51 = 0.00; Ch : Z = 2.44 • death 17 34 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488 9856 = 0.31; Ch : Z = 1.46	3489 $i ^{2} = 3.0$ $i (P = 0.1)$ 1065 $i ^{2} = 0.0$ $i (P = 0.2)$ $i (P = 0.2)$ 307 758 363 8615 36340 38408 $i ^{2} = 75.2$ $i (P = 0.2)$	190 3, df = 3 25 23 48 2, df = 1 15) 48 120 93 42 71919 72222 27, df = 15)	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177 161910 4 (P < 0.0	$\begin{array}{l} 42.2\%\\ 57.8\%\\ 100.0\%\\ 100.0\%\\ 10; \ l^2 = 0\%\\ 18.5\%\\ 20.8\%\\ 19.4\%\\ 19.2\%\\ 22.1\%\\ 100.0\%\\ 00001); \ l^2\end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44] 0.69 [0.41, 1.14] = 95%	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	51 = 0.00; Ch : Z = 2.44 • death 17 34 • 51 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488 9856 = 0.31; Ch : Z = 1.46	3489 $ii^{2} = 3.0$ $i (P = 0.1)$ 1065 $ii^{2} = 0.0$ $i (P = 0.1)$ $(P = 0.1)$ 307 758 307 758 363 615 36340 38408 $ii^{2} = 75.1$ $i (P = 0.1)$	190 3, df = 3 21) 25 23 48 2, df = 1 15) 48 120 93 42 71919 72222 27, df = 15)	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177 161910 4 (P < 0.0	$\begin{array}{l} 42.2\%\\ 57.8\%\\ 100.0\%\\ 1);\ l^2 = 0\%\\ 18.5\%\\ 20.8\%\\ 19.4\%\\ 19.2\%\\ 22.1\%\\ 100.0\%\\ 00001);\ l^2\end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.74 [0.49, 1.12] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44] 0.69 [0.41, 1.14] = 95%	
Ording-2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.5 Cardiovascular Chen-2018 Fanola-2018 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.1.6 All-cause deat Chen-2018 Fanola-2018 Kim-2018 Melloni-2017 Sawant-2019 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	51 = 0.00; Ch : Z = 2.44 • death 17 34 • 51 = 0.00; Ch : Z = 1.43 h 32 241 41 54 9488 9856 = 0.31; Ch : Z = 1.46	3489 $i ^{2} = 3.0$ $i (P = 0.1)$ 1065 1065 $i ^{2} = 0.0$ $i (P = 0.2)$ 307 758 384 8615 36340 38408 $i ^{2} = 75.2$ $i (P = 0.2)$	190 3, df = 3 25 23 48 2, df = 1 15) 48 120 93 42 71919 72222 27, df = 15)	(P = 0.39 329 395 724 (P = 0.88 329 395 388 621 160177 161910 4 (P < 0.0	$\begin{array}{l} 42.2\%\\ 57.8\%\\ 100.0\%\\ 10; \ l^2 = 0\%\\ 18.5\%\\ 20.8\%\\ 19.4\%\\ 19.2\%\\ 22.1\%\\ 100.0\%\\ 00001); \ l^2\end{array}$	0.71 [0.38, 1.35] 0.76 [0.44, 1.31] 0.74 [0.49, 1.12] 0.68 [0.42, 1.10] 1.07 [0.82, 1.39] 0.37 [0.25, 0.56] 1.33 [0.87, 2.02] 0.43 [0.42, 0.44] 0.69 [0.41, 1.14] = 95%	0.01 0.1 DOACS VKAS

	DOA	Cs	VK/	As		Odds Ratio		Od	ds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Ra	ndom, 95%	, CI	
1.2.1 Major bleeding											
Chen-2018	23	309	33	331	22.8%	0.73 [0.42, 1.27]		_	•		
Fanola-2018	98	758	63	395	29.8%	0.78 [0.56, 1.10]			•		
Kim-2018	8	388	36	388	16.7%	0.21 [0.09, 0.45]		_			
Melloni-2017	4	127	4	97	7.5%	0.76 [0.18, 3.10]			•		
Yasui-2019	24	615	32	621	23.3%	0.75 [0.43, 1.28]					
Subtotal (95% CI)		2197		1832	100.0%	0.61 [0.39, 0.94]					
Total events Heterogeneity: Tau ² = Test for overall effect:	157 0.13; Cl Z = 2.20	hi ² = 9. 6 (P = (168 95, df =).02)	4 (P = 0	.04); I ² =	60%					
1.2.2 Major or NMCR	bleedin	g									
Chen-2018	97	309	96	331	29.6%	1.12 [0.80, 1.57]			+		
Fanola-2018	296	758	174	395	45.7%	0.81 [0.64, 1.04]			-		
Melloni-2017	53	615	67	621	24.7%	0.78 [0.53, 1.14]		-	-		
Subtotal (95% CI)		1682		1347	100.0%	0.88 [0.72, 1.09]			•		
Total events	446		337								
Heterogeneity: Tau ² =	0.01; C	hi ² = 2.	.74, df =	2 (P = 0	.25); I ² =	27%					
Test for overall effect:	Z = 1.13	3 (P = ().26)								
1.2.3 Intracranial blee	ding										
Chen-2018	1	309	6	331	33.0%	0.18 [0.02, 1.47]		-	+		
Kim-2018	1	388	8	388	34.2%	0.12 [0.02, 0.99]		-	_		
Melloni-2017	0	615	9	621	18.4%	0.05 [0.00, 0.90]	←		-		
Yasui-2019	0	127	1	97	14.4%	0.25 [0.01, 6.26]		-		_	
Subtotal (95% CI)		1439		1437	100.0%	0.13 [0.04, 0.44]					
Total events	2		24								
Heterogeneity: Tau ² =	0.00; C	$hi^2 = 0.$.67, df =	3 (P = 0)	.88); I ² =	0%					
Test for overall effect:	Z = 3.22	7 (P = ().001)								
1.2.4 Gastrointestinal	bleedir	ng									
Fanola-2018	61	758	38	395	29.9%	0.82 [0.54, 1.26]					
Flack-2017	34	398	10	148	18.4%	1.29 [0.62, 2.68]					
Kim-2018	7	388	25	388	15.3%	0.27 [0.11, 0.62]			-		
Ording-2017	27	1809	184	10046	30.7%	0.81 [0.54, 1.22]		-			
Yasui-2019	3	127	3	97	5.6%	0.76 [0.15, 3.84]			-		
Subtotal (95% CI)		3480		11074	100.0%	0.75 [0.49, 1.13]		•	\bullet		
Total events	132		260								
Heterogeneity: Tau ² =	0.10; C	hi² = 8.	.04, df =	4 (P = 0	.09); I ² =	50%					
Test for overall effect:	Z = 1.40	0 (P = 0)).16)								
1.2.5 Any bleeding											
Chen-2018	152	309	152	331	24.3%	1.14 [0.84, 1.56]			-		
Fanola-2018	322	758	195	395	25.0%	0.76 [0.59, 0.97]					
Melloni-2017	204	615	245	621	25.1%	0.76 [0.60, 0.96]			-		
Shah-2018	247	6075	1149	10021	25.7%	0.33 [0.28, 0.38]					
Subtotal (95% CI)		7757		11368	100.0%	0.68 [0.37, 1.22]					
Total events	925		1741								
Heterogeneity: $Tau^2 =$	0.35; Cl	hi ² = 8	5.94, df =	= 3 (P <	0.00001)	; l ² = 97%					
rest for overall effect:	z = 1.30	U (P = ().19)								
							L				- 10
							0.01	n 1	-	112	

DISCUSSION

The main findings of our current study were as follows: (1) DOACs use resulted in lower rates of SSE and VTE as compared to VKAs use; (2) DOACs were associated with safer profiles (lower intracranial or gastrointestinal bleeding) than VKAs; (3) In comparison to VKAs, DOACs were non-inferior regarding

the outcomes of ischemic stroke, MI, cardiovascular death, allcause death, major bleeding, major or NMCR bleeding, and any bleeding.

Considering that malignant tumors have unique clinical risk characteristics, the optimal anticoagulant treatment for patients with AF and cancer is still controversial. On the one hand, cancer is a pro-thrombotic state, and further increases the

Annaly and Company and	laulpi-la part i		M/+ ! - ! -	Risk Ratio	Risk Ratio
	iog[KISK Ratio]	SE	weight	iv, kandom, 95% Cl	IV, Random, 95% Cl
					_
han-2021	-0.528	0.125	62.6%	0.59 [0.46, 0.75]	
hen-2018	-0.654	0.435	5.2%	0.52 [0.22, 1.22]	
anola-2018[high dose]	-0.511	0.334	8.8%	0.60 [0.31, 1.15]	
anola-2018[low dose]	-0.139	0.311	10.1%	0.87 [0.47, 1.60]	
/lelloni-2017	0.086	0.37	7.1%	1.09 [0.53, 2.25]	
ardo Sanz-2019	-0.094	0.397	6.2%	0.91 [0.42, 1.98]	
ubtotal (95% CI)			100.0%	0.66 [0.54, 0.80]	•
leterogeneity: Tau ² = 0.0 fest for overall effect: Z =	00; Chi ² = 4.47, df = 4.28 (P < 0.0001)	= 5 (P)	= 0.48); l ^a	2 = 0%	
.1.2 Ischemic stroke					
hen-2018	-1.05	0.585	7.9%	0.35 [0.11, 1.10]	
anola-2018[high dose]	-0.545	0.358	17.9%	0.58 [0.29, 1.17]	
anola-2018[low dose]	-0.174	0.338	19.5%	0.84 [0.43, 1.63]	— — —
Aelloni-2017	0.464	0.426	13.6%	1.59 [0.69. 3.67]	-+
hah-2018	-0.198	0.181	41.1%	0.82 [0.58, 1.17]	
ubtotal (95% CI)			100.0%	0.79 [0.56, 1.11]	\bullet
leterogeneity: Tau ² = 0.0 Test for overall effect: Z =	04; Chi² = 5.45, df = 1.34 (P = 0.18)	= 4 (P	= 0.24); l ²	2 = 27%	
.1.3 VTE					
han-2021	-0.994	0.249	48.2%	0.37 [0.23. 0.60]	
Chen-2018	0.086	0.71	8.6%	1.09 [0.27. 4.38]	
Aelloni-2017	-0.274	0.765	7.5%	0.76 [0.17, 3.41]	_
hah-2018	-1 204	0.31	35.6%	0.30 [0 16 0 55]	_
ubtotal (95% CI)	-1.204	0.51	100.0%	0.40 [0.26. 0.61]	→
leterogeneity: Tau ² = 0.0 Test for overall effect: Z =	03; Chi ² = 3.61, df = 4.27 (P < 0.0001	= 3 (P)	= 0.31); l ²	2 = 17%	
.1.4 MI					
han-2021	-0.211	0.3	34.1%	0.81 [0.45, 1.46]	— — —
Chen-2018	-0.163	0.518	11.4%	0.85 [0.31, 2.34]	
anola-2018[high dose]	-0.777	0.453	15.0%	0.46 [0.19, 1.12]	_ _
anola-2018[low dose]	-0.186	0.383	20.9%	0.83 [0.39, 1.76]	_
Aelloni–2017	0.02	0.407	18.5%	1.02 [0.46, 2.27]	_
ubtotal (95% CI)	0.02		100.0%	0.78 [0.56, 1.11]	•
leterogeneity: $Tau^2 = 0.0$	00: Chi ² = 1.86. df	= 4 (P	= 0.76); l ²	$^{2} = 0\%$	•
		. (.			
est for overall effect: Z =	= 1.38 (P = 0.17)				
est for overall effect: Z = 1.5 Cardiovascular dea	= 1.38 (P = 0.17) ath				
est for overall effect: Z = . .1.5 Cardiovascular de a Chen-2018	= 1.38 (P = 0.17) ath -0.386	0.315	33.9%	0.68 [0.37, 1.26]	
est for overall effect: Z = . 1.5 Cardiovascular de: :hen-2018 anola-2018[high dose]	= 1.38 (P = 0.17) ath -0.386 -0.301	0.315 0.326	33.9% 31.7%	0.68 [0.37, 1.26] 0.74 [0.39, 1.40]	
est for overall effect: Z = .1.5 Cardiovascular de Chen–2018 [anola–2018[high dose] [anola–2018[low dose]	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128	0.315 0.326 0.313	33.9% 31.7% 34.4%	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62]	
est for overall effect: Z = .1.5 Cardiovascular de Chen–2018 anola–2018[high dose] anola–2018[low dose] ubtotal (95% CI)	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128	0.315 0.326 0.313	33.9% 31.7% 34.4% 100.0%	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09]	
est for overall effect: Z = .1.5 Cardiovascular dea Chen-2018 anola-2018[high dose] anola-2018[low dose] ubtotal (95% Cl) leterogeneity: Tau ² = 0.0 est for overall effect: Z =	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14)	0.315 0.326 0.313 = 2 (P	33.9% 31.7% 34.4% 100.0% = 0.84); I ²	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0%	
est for overall effect: Z = .1.5 Cardiovascular des Chen-2018 anola-2018[high dose] anola-2018[low dose] ubtotal (95% CI) leterogeneity: Tau ² = 0.0 est for overall effect: Z = .1.6 All-cause death	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14)	0.315 0.326 0.313 = 2 (P	33.9% 31.7% 34.4% 100.0% = 0.84); I ²	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0%	
Test for overall effect: Z = 1.1.5 Cardiovascular des Chen-2018 anola-2018[high dose] anola-2018[low dose] bubtotal (95% CI) leterogeneity: Tau ² = 0.(Test for overall effect: Z = 1.6 All-cause death Chen-2018	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 D0; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416	0.315 0.326 0.313 = 2 (P	33.9% 31.7% 34.4% 100.0% = 0.84); 1 ²	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0%	
Test for overall effect: Z = .1.5 Cardiovascular de Chen-2018 [anola-2018[high dose] [anola-2018[low dose] [ubtotal (95% Cl) leterogeneity: Tau ² = 0.6 Test for overall effect: Z = 1.6 All-cause death Chen-2018 [anola-2018[high docs]	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 D0; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.095	0.315 0.326 0.313 = 2 (P 0.231	33.9% 31.7% 34.4% 100.0% = 0.84); 1 ² 19.0%	$\begin{array}{c} 0.68 \ [0.37, \ 1.26] \\ 0.74 \ [0.39, \ 1.40] \\ 0.88 \ [0.48, \ 1.62] \\ 0.76 \ [0.53, \ 1.09] \end{array}$	
est for overall effect: Z = .1.5 Cardiovascular dea Chen-2018 anola-2018[high dose] anola-2018[low dose] iubtotal (95% Cl) leterogeneity: Tau ² = 0.6 est for overall effect: Z = .1.6 All-cause death Chen-2018 anola-2018[high dose] anola-2018[low dose]	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.066	0.315 0.326 0.313 = 2 (P 0.231 0.129	33.9% 31.7% 34.4% 100.0% = 0.84); 1 ² 19.0% 20.3%	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0% 0.66 [0.42, 1.04] 1.09 [0.85, 1.40]	
est for overall effect: Z = 1.5 Cardiovascular dea Chen-2018 anola-2018[high dose] anola-2018[low dose] ubtotal (95% CI) leterogeneity: Tau ² = 0.0 fest for overall effect: Z = 1.6 All-cause death Chen-2018 anola-2018[high dose] anola-2018[low dose] Alloni -2017	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.272	0.315 0.326 0.313 = 2 (P 0.231 0.129 0.13 0.205	33.9% 31.7% 34.4% 100.0% = 0.84); 1 ⁻ 19.0% 20.3% 20.3%	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0% 0.66 [0.42, 1.04] 1.09 [0.85, 1.40] 1.07 [0.83, 1.38]	
est for overall effect: Z = .1.5 Cardiovascular dea Chen-2018 anola-2018[high dose] anola-2018[low dose] ubtotal (95% CI) leterogeneity: Tau ² = 0.0 est for overall effect: Z = 1.6 All-cause death Chen-2018 anola-2018[high dose] anola-2018[low dose] Melloni-2017 Number 2010	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.278 0.272	0.315 0.326 0.313 = 2 (P 0.231 0.129 0.13 0.202	33.9% 31.7% 34.4% 100.0% = 0.84); 1 19.0% 20.3% 20.3% 19.4%	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0% 0.66 [0.42, 1.04] 1.09 [0.85, 1.40] 1.07 [0.83, 1.38] 1.32 [0.88, 1.98] 0.38 [0.26 0.42]	
Test for overall effect: Z = 1.1.5 Cardiovascular des Chen-2018 Chen-2018[high dose] Canola-2018[low dose] Subtotal (95% Cl) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.1.6 All-cause death Chen-2018 Chen-2018[high dose] Canola-2018[low dose] Aelloni-2017 awant-2019 Subtotal (95% Cl)	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.278 -0.978	0.315 0.326 0.313 = 2 (P 0.231 0.129 0.13 0.206 0.029	33.9% 31.7% 34.4% 100.0% = 0.84); 1 19.0% 20.3% 20.3% 19.4% 21.0%	$\begin{array}{c} 0.68 \; [0.37, 1.26] \\ 0.74 \; [0.39, 1.40] \\ 0.88 \; [0.48, 1.62] \\ 0.76 \; [0.53, 1.09] \end{array}$ $^{2} = 0\%$ $\begin{array}{c} 0.66 \; [0.42, 1.04] \\ 1.09 \; [0.85, 1.40] \\ 1.07 \; [0.83, 1.38] \\ 1.32 \; [0.88, 1.98] \\ 0.38 \; [0.36, 0.40] \\ 0.82 \; [0.42 \; 1.55] \end{array}$	
Test for overall effect: Z = 1.1.5 Cardiovascular des Chen-2018 Chen-2018[high dose] Canola-2018[low dose] Subtotal (95% CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.1.6 All-cause death Chen-2018 Chen-2018[high dose] Canola-2018[low dose] Aelloni-2017 awant-2019 Subtotal (95% CI) Letarogeneity: Tau ² = 0.0	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.278 -0.978 51: Chi ² = 155.47	0.315 0.326 0.313 = 2 (P 0.231 0.129 0.13 0.206 0.029	33.9% 31.7% 34.4% 100.0% = 0.84); 1 19.0% 20.3% 20.3% 19.4% 21.0% 100.0%	$\begin{array}{c} 0.68 \; [0.37, 1.26] \\ 0.74 \; [0.39, 1.40] \\ 0.88 \; [0.48, 1.62] \\ 0.76 \; [0.53, 1.09] \end{array}$ $^{2} = 0\%$ $\begin{array}{c} 0.66 \; [0.42, 1.04] \\ 1.09 \; [0.85, 1.40] \\ 1.07 \; [0.83, 1.38] \\ 1.32 \; [0.88, 1.98] \\ 0.38 \; [0.36, 0.40] \\ 0.82 \; [0.43, 1.56] \end{array}$	
Test for overall effect: Z = 1.1.5 Cardiovascular des Chen-2018 Canola-2018[high dose] Canola-2018[low dose] Subtotal (95% CI) Test for overall effect: Z = 1.1.6 All-cause death Chen-2018 Canola-2018[high dose] Canola-2018[low dose] Canola-2	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.278 -0.978 51; Chi ² = 155.47, = 0.61 (P = 0.54)	0.315 0.326 0.313 = 2 (P 0.231 0.12 0.13 0.206 0.029 df = 4	33.9% 31.7% 34.4% 100.0% = 0.84); I ² 19.0% 20.3% 20.3% 19.4% 21.0% 100.0% (P < 0.000	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0% 0.66 [0.42, 1.04] 1.09 [0.85, 1.40] 1.07 [0.83, 1.38] 1.32 [0.88, 1.98] 0.38 [0.36, 0.40] 0.82 [0.43, 1.56] 001); l ² = 97%	
Test for overall effect: Z = 1.1.5 Cardiovascular des Chen-2018 Canola-2018[high dose] Canola-2018[low dose] Subtotal (95% CI) Test for overall effect: Z = 1.1.6 All-cause death Chen-2018 Canola-2018[high dose] Canola-2018[low dose] Aelloni-2017 Cawant-2019 Subtotal (95% CI) Test for overall effect: Z = Subtotal (95% CI) Subtotal effect: Z = Subtotal eff	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.278 -0.978 51; Chi ² = 155.47, = 0.61 (P = 0.54)	0.315 0.326 0.313 = 2 (P 0.231 0.129 0.13 0.206 0.029 df = 4	33.9% 31.7% 34.4% 100.0% = 0.84); 1 19.0% 20.3% 20.3% 19.4% 21.0% 100.0% (P < 0.00)	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0% 0.66 [0.42, 1.04] 1.09 [0.85, 1.40] 1.07 [0.83, 1.38] 1.32 [0.88, 1.98] 0.38 [0.36, 0.40] 0.82 [0.43, 1.56] 001); I ² = 97%	
Test for overall effect: Z = 1.1.5 Cardiovascular des Chen-2018 Canola-2018[high dose] Canola-2018[low dose] Subtotal (95% CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 1.1.6 All-cause death Chen-2018 Canola-2018[high dose] Canola-2018[low dose] Aelloni-2017 Sawant-2019 Subtotal (95% CI) Heterogeneity: Tau ² = 0.9 Test for overall effect: Z =	= 1.38 (P = 0.17) ath -0.386 -0.301 -0.128 00; Chi ² = 0.35, df = 1.47 (P = 0.14) -0.416 0.086 0.068 0.278 -0.978 51; Chi ² = 155.47, = 0.61 (P = 0.54)	0.315 0.326 0.313 = 2 (P 0.231 0.129 0.13 0.206 0.029 df = 4	33.9% 31.7% 34.4% 100.0% = 0.84); 1 ² 19.0% 20.3% 20.3% 19.4% 21.0% 100.0% (P < 0.00)	0.68 [0.37, 1.26] 0.74 [0.39, 1.40] 0.88 [0.48, 1.62] 0.76 [0.53, 1.09] ² = 0% 0.66 [0.42, 1.04] 1.09 [0.85, 1.40] 1.07 [0.83, 1.38] 1.32 [0.88, 1.98] 0.38 [0.36, 0.40] 0.82 [0.43, 1.56] 001); ² = 97%	

FIGURE 3 | Adjusted effectiveness data of direct oral anticoagulants compared with vitamin K antagonists among atrial fibrillation patients with cancer.

Study or Subarcon	log[Dick Deti-1	er.	Weishe	Risk Ratio	Risk Ratio
Tudy or Subgroup	IOG[RISK RATIO]	SE	weight	IV, Kandom, 95% CI	IV, Kandom, 95% Cl
L.Z.1 Major bleeding	0.245	0 1 2 2	22 69/	0 70 10 50 0 051	_
Lnan-2021	-0.315	0.132	23.6%	0.73 [0.56, 0.95]	
Lnen-2018	-0.342	0.27	8.8%	0.71 [0.42, 1.21]	
-anola-2018[nign dose]	-0.02	0.184	15.8%	0.98 [0.68, 1.41]	
Fanola-2018[low dose]	-0.315	0.251	9.9%	0.73 [0.45, 1.19]	
Melloni-2017	-0.274	0.269	8.9%	0.76 [0.45, 1.29]	
Oraing-2021 Davida Sama 2010	0.104	0.243	10.4%	1.11 [0.69, 1.79]	
Pardo Sanz-2019	0.425	0.255	9.770	1.33 [0.93, 2.32]	
Subtotal (95% CI)	-0.174	0.211	100.0%	0.84 [0.56, 1.27]	
Heterogeneity: $Tau^2 = 0.0$	2° Chi ² = 9.40. df	= 7 (P	= 0.23)-1	$^{2} = 26\%$	•
Test for overall effect: Z =	= 1.51 (P = 0.13)		01207,1	-0/0	
1.2.2 Major or NMCR ble	eding				
Atterman-2021	-0.248	0.023	32.8%	0.78 [0.75, 0.82]	•
Chen-2018	0.086	0.144	15.7%	1.09 [0.82, 1.45]	+
Fanola-2018[high dose]	0.039	0.109	20.3%	1.04 [0.84, 1.29]	+
Fanola-2018[low dose]	-0.301	0.116	19.3%	0.74 [0.59, 0.93]	
Melloni-2017	-0.223	0.181	11.9%	0.80 [0.56, 1.14]	
Subtotal (95% CI)	D. CL 17	c	100.0%	0.87 [0.74, 1.01]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	= 1.86 (P = 0.06)	r = 4 (F	² = 0.02);	i ⁻ = 66%	
1.2.3 Intracranial bleedir	ng				
Atterman-2021	-0.478	0.062	84.8%	0.62 [0.55, 0.70]	
Chan-2021	-0.58	0.254	11.4%	0.56 [0.34, 0.92]	
Chen-2018	-1.772	1.086	0.7%	0.17 [0.02, 1.43]	
Ording-2021 Subtotal (95% CI)	-1.139	0.502	3.1% 100.0%	0.32 [0.12, 0.86]	
Heterogeneity: $Tau^2 = 0.0$	01; Chi ² = 3.21, df	= 3 (P	= 0.36);	$^{2} = 7\%$	•
Test for overall effect: Z =	= 5.80 (P < 0.0000)	1)			
1.2.4 Gastrointestinal bl	eeding				\perp
Atterman-2021	-0.128	0.047	83.0%	0.88 [0.80, 0.96]	
Chan-2021	-0.261	0.163	6.9%	0.77 [0.56, 1.06]	
Fanola-2018[high dose]	-0.02	0.238	3.2%	0.98 [0.61, 1.56]	+
Fanola-2018[low dose]	-0.248	0.254	2.8%	0.78 [0.47, 1.28]	
Ording-2021	-0.051	0.213	4.0%	0.95 [0.63, 1.44]	
Subtotal (95% CI)	0.01.7		100.0%	0.87 [0.80, 0.95]	•
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	$00; Chi^2 = 1.21, df = 3.13 (P = 0.002)$	= 4 (P	= 0.88);	~ = 0%	
1.2.5 Any bleeding					
Chen-2018	0.14	0.114	17.0%	1.15 [0.92, 1.44]	
Fanola-2018[high dose]	0	0.103	1 8.2%	1.00 [0.82, 1.22]	+
Fanola-2018[low dose]	-0.371	0.109	17.6%	0.69 [0.56, 0.85]	+
Melloni-2017	-0.186	0.092	19.5%	0.83 [0.69, 0.99]	-
Ording-2021	-0.051	0.156	13.0%	0.95 [0.70, 1.29]	+
Shah-2018	-0.274	0.136	14.8%	0.76 [0.58, 0.99]	
Subtotal (95% Cl)	2. Chi2 _ 13 03 -	6 - F /F	100.0%	0.88 [0.76, 1.03]	•
Heterogeneity: Tau* = 0.0 Test for overall effect: Z =	1.59 (P = 0.11)	r = 5 (F	r = 0.02);	i⁻ = 04%	

risk of thromboembolism in patients with AF and cancer (25). tumor On the other hand, cancer patients have a higher incidence of while

VTE and arterial thrombosis due to inflammatory cytokines,

tumor vascular invasion, and vascular toxicity cancer treatments, while cancer-related thrombocytopenia and chemotherapyrelated bone marrow suppression can increase bleeding complications (26–28). Not only that, some malignancies (e.g. primary or metastatic intracranial tumors and hematological malignancies) itself increase the risk of hemorrhage, potentially constituting contraindications to anticoagulation therapy or requiring thorough clinical surveillance even in patients at high thromboembolic risk. Therefore, concerns about bleeding complications and paucity of evidence-based data may result in the underuse of DOACs in cancer patients with AF.

Due to the extremely limited data, there are still no specific recommendations on the use of DOACs for cancer patients in the AF guidelines. Current RCTs involving antithrombotic therapy for cancer patients to prevent VTE have been published, the guidelines prefer LMWH over VKAs or DOACs in the prevention and treatment of VTE (5). Mounting evidence is demonstrating that DOACs could represent a valid choice in patients with cancer. Prior trials have shown that rivaroxaban and edoxaban are not inferior to LMWH in the treatment of cancer-related VTE (29, 30). Therefore, DOACs (rivaroxaban and edoxaban) are currently recommended for the treatment of VTE as an alternative treatment for LMWH in cancer patients (16, 31, 32). However, due to the different pathophysiology and risk characteristics between cancer and AF, these recommendations cannot be generalized to patients with cancer and AF.

Compared with DOACs, VKAs have several limitations, such as frequent international normalized ratio (INR) control, frequent dose adjustments, and diet or drug interactions. These deficiencies may be amplified in cancer and AF patients. In particular, chemotherapy drugs and warfarin have a strong pharmacological interaction, and cancer patients often have liver dysfunction, mucositis, or diarrhea, which lead to fluctuations in vitamin K absorption and increase the risk of anticoagulation therapy (33). Only about 12% of cancer patients receiving warfarin can obtain a stable INR therapeutic range (34). In addition, the anticoagulant activity of VKAs depends on TTR (time in therapeutic range). As such, it is difficult for cancer patients to receive cancer treatment to obtain the best INR range, and the prevalence of active cancer patients with TTR > 60%during the follow-up is only 10% (35). Moreover, DOACs are still more effective and safer than VKAs in AF patients with the best TTR (4).

The effectiveness and safety of DOACs compared with VKAs in AF and cancer patients have been explored in several recent studies. A prior systematic review by Russo et al. (36) supported that the effectiveness and safety profiles of NOACs in AF patients with malignancy appeared to be similar to those of VKA treatment. Unfortunately, they could not conduct a meta-analysis with the quantitative method to draw further conclusions due to the small number of included studies (36). Although the effectiveness and safety of DOACs and VKAs in AF patients with cancer are controversial, the conclusions seem to be more clear due to the emergence of several *posthoc* analyses of RCTs and observational studies. Casula et al. (37) performed a meta-analysis by including three *post-hoc* analyses of RCTs (12–14), suggesting that direct oral Xa inhibitors (rivaroxaban, apixaban, edoxaban) had similar effects but were

safer compared with warfarin in patients with cancer and AF. In addition to post-hoc analyses of RCTs, the meta-analyses by Chen et al. (38) and Mariani et al. (39) also included the different number of observational studies. By comparison, the largest number of studies (four post-hoc analyses of RCTs and nine observational cohorts) were included in our current meta-analysis. In addition, we assessed both crude event rates and adjusted data of outcomes between DOACs vs. VKAs in AF patients with cancer. Overall, in comparison to VKAs, DOACs appeared to have significant reductions in SSE, venous thromboembolism, intracranial bleeding, and gastrointestinal bleeding, but showed comparable rates of ischemic stroke, MI, cardiovascular death, all-cause death, major bleeding, major or NMCR bleeding, and any bleeding. Our meta-analysis was the largest and latest study comparing the effectiveness and safety outcomes of DOACs vs. VKAs in patients with nonvalvular AF and cancer, potentially suggesting that DOACs might be considered suitable anticoagulant agents in this special population. Further prospective trials evaluating the effectiveness and safety of DOACs vs. VKAs in patients with AF combined with cancer could confirm our findings.

Limitations

Our research still had some limitations. First, the clinical characteristics of patients in different included studies were heterogeneous, such as cancer type, cancer stage, cancer diagnosis time, anti-tumor drug use, or chemotherapy response. The incidence of thrombotic events varied with cancer types, stages, and patient-related or treatment-related factors. Second, all types of DOACs were analyzed together as one group despite their different pharmacological properties and differences in clinical effectiveness and safety in the different indications. Due to limited data, we did not conduct a subgroup analysis based on the specific types of DOACs and VKAs between patients with active cancer and those with a history of cancer. Finally, data of RCTs and observational studies should be assessed separately in future studies.

CONCLUSION

Current pooled data from the published studies suggested that in comparison to VKAs, DOACs appeared to have significant reductions in SSE, venous thromboembolism, intracranial bleeding, and gastrointestinal bleeding, but showed comparable rates of ischemic stroke, MI, cardiovascular death, all-cause death, major bleeding, major or NMCR bleeding, and any bleeding in patients with AF and cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm. 2021.766377/full#supplementary-material

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