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Real-world evidence of direct oral anticoagulants in patients with atrial fibrillation and cancer: A *meta*-analysis

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ABSTRACT

Background: Several observational cohort studies have been conducted to investigate the effectiveness and safety of direct oral anticoagulants (DOACs) compared with vitamin K antagonists (VKAs) in patients who have both atrial fibrillation (AF) and cancer. Herein, we conducted a *meta*-analysis to present a comprehensive overview of the real-world evidence on DOACs in patients with AF and cancer.

Methods: A comprehensive search strategy was performed in PubMed and Embase until February 2024 for studies that enrolled AF patients with cancer who received DOACs or VKAs. The adjusted risk ratios (RRs) and 95% confidence intervals (CIs) of each outcome were extracted and pooled by a random-effects model.

Results: Seven observational cohort studies were eligible for data extraction. The random-effects model analysis indicated that compared with VKA use, the use of DOACs was significantly associated with reduced risks of stroke or systemic embolism (RR=0.79, 95 % CI 0.64—0.97), major bleeding (RR=0.84, 95 % CI 0.71—0.99), intracranial bleeding (RR=0.61, 95 % CI 0.54—0.69), and gastrointestinal bleeding (RR=0.87, 95 % CI 0.80—0.95) in AF patients with concurrent cancer.

Conclusions: Compared with VKAs, the use of DOACs was associated with decreased risks of thrombotic and bleeding events in AF patients with cancer. Data from real-world scenarios support the use of DOACs as a favorable treatment option for this specific patient population.

1. Introduction

AF is one of the leading causes of cardiovascular diseases and related morbidity [1]. AF patients are at a nearly fivefold higher risk of stroke-related death than non-AF patients [2]. Besides, cancer and cancer-related treatments are associated with an elevated risk of thrombotic and hemorrhagic complications. Several risk factors are associated with AF, such as aging, genetic susceptibility, smoking, alcohol, obesity or overweight, diabetes, and coronary artery disease[3–5]. Also, coronary artery disease has emerged as a relevant risk factor for cancers given that inflammation is the common theme[6]. Accordingly, inflammation is the common theme among AF, coronary artery disease, and cancer. Among patients with AF and cancer, the risk of stroke or cerebrovascular death is increased, emphasizing the importance of early anticoagulant therapy to reduce stroke risk and mortality.

Vitamin K antagonists (VKAs), such as warfarin, have historically been extensively used in clinical practice for anticoagulation in patients with AF. However, the use of warfarin is limited by the narrow therapeutic window. Due to the advantages of not requiring routine monitoring and being less affected by other medications, direct oral anticoagulants (DOACs) have been demonstrated as a favorable treatment option compared to warfarin [7]. DOACs are recommended as the first-line anticoagulant drug in non-valvular AF patients [8].

However, it is still essential to conduct further research to examine the effectiveness and safety of DOACs in patients with both AF and cancer currently. Previous *meta*-analyses have been conducted on this matter, but these analyses included both randomized controlled trials (RCTs) and observational cohort studies. The decision to include RCTs in these studies could potentially limit the representativeness of the population under investigation and make it difficult to generalize the results to real-world scenarios. To address these limitations, we conducted a *meta*-analysis that encompassed recently published observational cohort studies to assess the real-world evidence on DOACs versus VKAs in patients with AF and cancer.

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2. Methods

We aimed to conduct this *meta*-analysis according to the guidance from the Cochrane Handbook for Systematic Reviews and presented the findings according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklists.

2.1. Inclusion and exclusion criteria

We included studies that met the following inclusion criteria: 1) study design: observational cohort studies reporting adjusted risk ratios (RRs) and 95 % confidence intervals (CIs); 2) population: patients with AF and cancer; 3) comparison: DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) versus VKAs; 4) outcomes: the effectiveness outcomes included stroke or systemic embolism (SSE), whereas the safety outcomes included major bleeding, intracranial bleeding, and gastrointestinal bleeding. RCTs and post hoc analyses of RCTs were not included. Certain publication types (e.g., reviews, preprint, case series, case reports, editorials) with no sufficient data for analysis were also excluded. We also excluded studies with no adjusted data.

2.2. Literature retrieval

Two authors (XY-L and RK-L) independently and systematically searched the two common databases (PubMed and Embase) until February 2024 for studies reporting the observational data of DOACs compared with VKAs in patients with AF and cancer. The following keywords were applied in the literature searches: (1) "atrial fibrillation", (2) "cancer" OR "malignancy" OR "tumor", (3) "non-vitamin K antagonist oral anticoagulants" OR "direct oral anticoagulants" OR "DOACs" OR "DOACs" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban", and (4) "vitamin K antagonists" OR "warfarin" OR "coumadin" OR "acenocoumarol" OR "phenprocoumon". Supplemental Table 1 shows the search strategies of this *meta*-analysis. In this study, we applied no linguistic restrictions in the literature searches.

2.3. Study selection and data extraction

Two authors (XY-L and RK-L) first screened the titles and abstracts of the searched records using the search strategies mentioned above, and then picked up the relevant studies. Second, the full texts of potential studies found in the first phase were screened to select the final studies of this *meta*-analysis. If facing disagreements, we could resolve these issues via consultation with the corresponding authors (WG-Z and DX-W). After that, the following characteristics were mainly collected: first author, publication year, data source, study period, study design, age and sex, type or dose of DOACs, VKA type, follow-up period, and outcome data.

2.4. Study quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality assessment of observational cohort studies. The NOS contained three domains with a total of 9 points, namely the selection of cohorts (4 points), the comparability of cohorts (2 points), and the assessment of the outcome (3 points). According to the previous publications[9,10], a NOS of < 6 points was regarded as low quality in this *meta*-analysis.

2.5. Statistical analyses

All the statistical analyses of this study were performed using the Review Manager version 5.4 software (the Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark). The consistency among the included studies was examined using the Cochrane Q test and I^2 statistic. We defined a P-value < 0.1 for the Q statistic, or $I^2 \geq 50$ % as substantial heterogeneity. In the pooled analysis, the adjusted RRs and 95 %CIs were converted to the natural logarithms (Ln[RR]) and standard errors, which were pooled by a random-effects model with an inverse variance method. In addition, we performed the subgroup analysis based on the DOAC type (dabigatran, rivaroxaban, and apixaban). Edoxaban was not included in the subgroup analysis due to the limited data. We assessed the publication bias for the reported effect estimates using the funnel plots.

3. Results

3.1. Study selection

As shown in Supplemental Figure 1, a total of 880 studies were identified in the electronic databases of PubMed and Embase. We first screened the titles and abstracts of these records and eliminated 852 studies that did not meet our inclusion criteria. Among the remaining 28 studies, we proceeded to review the full texts. By carefully comparing the content of each study to our predetermined criteria for inclusion and exclusion, we finally included 7 studies [11–17].

The baseline patient characteristics of these included studies are presented in Table 1. This table presents baseline data, such as demographics, DOAC types, and cancer types, allowing for a comprehensive comparison across the included studies. Furthermore, in order to assess the quality of the included studies, we used the NOS tool. All 7 observational cohort studies obtained scores of 6 points or higher, indicating their acceptable quality.

3.2. Effectiveness outcomes between DOACs and VKAs

As shown in Fig. 1, a total of 5 included studies reported the effectiveness outcomes between DOACs and VKAs in patients with AF and cancer. Deitelzweig et al and Shah et al reported the data of apixaban, dabigatran, and rivaroxaban, respectively. Chan et al, Mehta et al, and Pardo San et al reported a mixed of DOACs compared with VKAs. Therefore, a total of 9 effect estimates were included in the pooled analysis. The random-effects model analysis indicated that compared with VKA use, the use of DOACs was significantly associated with a reduced risk of SSE (RR=0.79, 95 % CI 0.64——0.97; $I^2 = 52$ %) (Fig. 1).

3.3. Safety outcomes between DOACs and VKAs

A total of 6, 3, and 3 studies were included for major bleeding, intracranial bleeding, and gastrointestinal bleeding, respectively. In the pooled analysis, compared with VKA use, the use of DOACs was significantly associated with decreased risks of major bleeding (RR=0.84, 95 % CI 0.71——0.99; $I^2 = 78$ %), intracranial bleeding (RR=0.61, 95 % CI 0.54——0.69; $I^2 = 0$ %), and gastrointestinal bleeding (RR=0.87, 95 % CI 0.80——0.95; $I^2 = 0$ %) in patients with AF and cancer (Fig. 2).

3.4. Subgroup analysis

We further performed the subgroup analysis based on the DOAC types. As results, dabigatran (RR=0.93, 95 % CI 0.68——1.26; $I^2 = 0$ %), rivaroxaban (RR=0.86, 95 % CI 0.68——1.08; $I^2 = 0$ %), or apixaban (RR=0.77, 95 % CI 0.45——1.31; $I^2 = 54$ %) and VKAs had a similar risk of SSE ($P_{interaction} = 0.82$) (Fig. 3). For the safety outcomes (Fig. 4), dabigatran (RR=0.80, 95 % CI 0.68——0.94; $I^2 = 1$ %) and apixaban (RR=0.58, 95 % CI 0.50——0.66; $I^2 = 0$ %) compared with VKAs were associated with a lower risk of major bleeding. However, the use of rivaroxaban did not show a significant reduction in major bleeding risk compared to VKAs.

3.5. Publication bias

In order to evaluate the possible presence of publication bias, we conducted an assessment using funnel plots (Supplemental Figures 2 and

Table 1
Baseline characteristics of the included studies of this *meta*-analysis.

Studies	Study type	Data source	Study period	Sample size (N)	Age (years)	Female sex (%)	DOAC type and dose	VKA type	TTR for VKA users	Follow-up time (years)	Cancer types	NOS tool (points)
Ording-2021	Observational cohort	Danish National Patient Registry	NA	1476	78	41.6 %	DA, API, RIV, EDO; standard dose DOAC (59 %) and reduced dose (41 %)	NA	NA	1.0	Gastrointestinal	7
Shah-2018	Observational cohort	Market Scan databases,the United States	January 2010-December 2014	16,096	74	40 %	DA, API, RIV	Warfarin	NA	1.0	Breast (19.2 %), Gastrointestinal (12.7 %), Lung (12.3 %), Genitourinary (29.2 %), Gyneco-oncological (2.4 %), Hematological (9.8 %), Others (14.4 %)	8
Pardo Sanz-2019	Observational cohort	AMBER-AF registry,Oncology and Cardiology Departments, Spain	NA	637	75.4	100 %	NA	NA	NA	2.8	Breast	7
Atterman-2021	Observational cohort	Swedish Patient register	January 2006 and December 2017	8228	75.1	36.5 %	NA	Warfarin	NA	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 %), Others(14.4 %)	7
Chan-2021	Observational cohort	Taiwan (NHIRD and CGMH)	June 2012-December 2017	7955 [NHIRD]; 2153 [CGMH]	77.0 [NHIRD]	41.9 % [NHIRD]	DA, API, RIV, EDO; 71 %, 91 %, 71 %, and 95 % users taking low-dose API (2.5 mgBID) , DA (110 mg BID), EDO (30 mg QD), and RIV (15/10 mg QD)	Warfarin	23.9 % [CGMH]	DOACs:1.45, Warfarin: 1.73	NA	8
Deitelzweiget-2021	Observational cohort	U.S. (Multi-center)	January 2013-September 2015	40,271	NA	NA	DA, API, RIV; API, DA,and RIV users (73 %, 81 %, and 69 %) on standard dose	Warfarin	NA	Warfarin: 0.63, API: 0.5, DA: 0.61, RIV: 0.59	Breast (17 %), Genitourinary(14 %), lung (13 %), and Gastrointestinal (13 %)	8
Mehta-2022	Observational cohort	SEER-Medicare	2010–2016	7675	76.6	48.1 %	DA, API, RIV, EDO	Warfarin		0.64	Prostate (22.2 %), Breast (19.6 %), Lung (19.3 %), Colorectal (14.5 %), Others	7

AF=atrial fibrillation; DOACs = direct oral anticoagulants; VKAs = vitamin K antagonists; TTR=time in therapeutic range; API=Apixaban; DA=Dabigatran; RIV=Rivaroxaban; EDO=edoxaban; NOS=Newcastle-Ottawa Scale; CGMH=Chang Gung Memorial Hospital; NHIRD=Taiwan National Health Insurance Research Database; SEER=Surveillance Epidemiology and End Results; NA=not available.

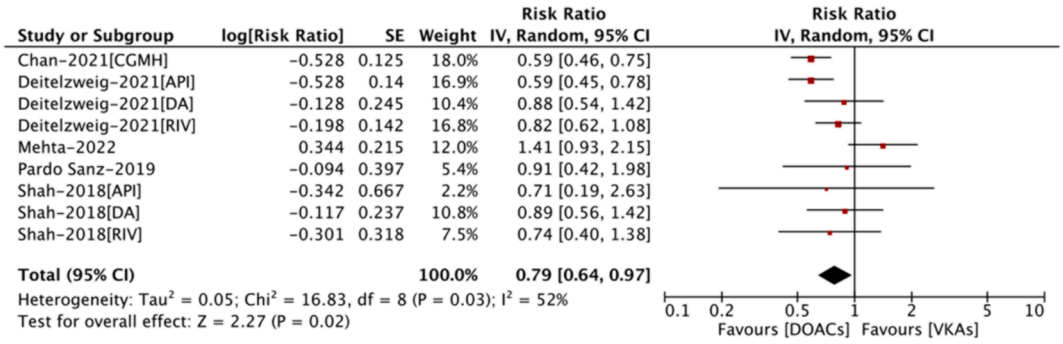

Fig. 1. Stroke or systemic embolism of DOACs versus VKAs in atrial fibrillation patients with cancer DOACs = direct oral anticoagulants; VKAs = vitamin K antagonists; RR=risk ratio; CI=confidence interval; API=Apixaban; DA=Dabigatran; RIV=Rivaroxaban; CGMH=Chang Gung Memorial Hospital.

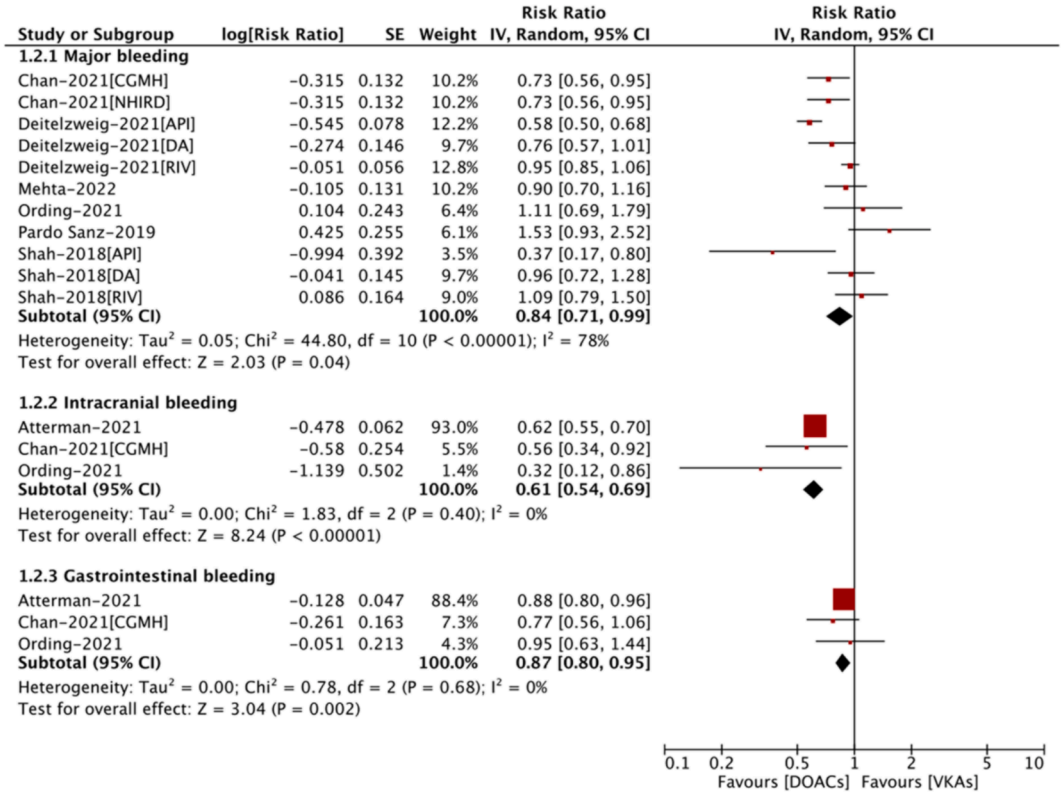

Fig. 2. Safety outcomes of DOACs versus VKAs in atrial fibrillation patients with cancer DOACs = direct oral anticoagulants; VKAs = vitamin K antagonists; RR=risk ratio; CI=confidence interval; API=Apixaban; DA=Dabigatran; RIV=Rivaroxaban; CGMH=Chang Gung Memorial Hospital; NHIRD=Taiwan National Health Insurance Research Database.

3**).** These funnel plots provide a visual representation of the distribution of effect sizes observed in different included studies.

4. Discussion

The findings from our *meta*-analysis suggested that, when compared with VKAs, the use of DOACs was associated with a lower risk of SEE in patients with both AF and cancer. Additionally, it was also found that DOACs were associated with a reduced risk of bleeding events compared to VKAs. Overall, the current real-world evidence supports the use of DOACs as a favorable treatment option for AF patients with concurrent cancer.

In AF patients, the presence of cancer was associated with increased risks of ischemic and bleeding events. Fauchier et al found that cancer can be a powerful predictor of mortality in AF patients[18]. AF is already a high-risk factor for thromboembolism due to the tendency to form atrial thrombi. When AF is combined with malignant diseases, the risk of thromboembolism becomes even higher [19]. Malignant diseases create a high hypercoagulable state in the body, meaning the blood is more prone to clotting. This, in combination with the already increased risk of clot formation due to AF, further enhances the likelihood of a thromboembolic event. Additionally, certain cancer treatments, particularly novel angiogenesis inhibitors, can exacerbate the risk of both thromboembolism and bleeding during anticoagulant therapy for AF.

The use of DOACs in AF patients with concomitant cancer is still not well established. Several studies have examined the effectiveness and safety of DOACs compared with VKAs in patients who have both AF and cancer [20,21]. A prior *meta*-analysis conducted by Barbarawi et al, including 3 post hoc analyses of RCTs and 8 retrospective cohorts, found that DOACs reduced the incidence of SSE and major bleeding events compared with warfarin in patients with both AF and cancer [20]. In another *meta*-analysis including 3 post hoc analyses of RCTs and 5

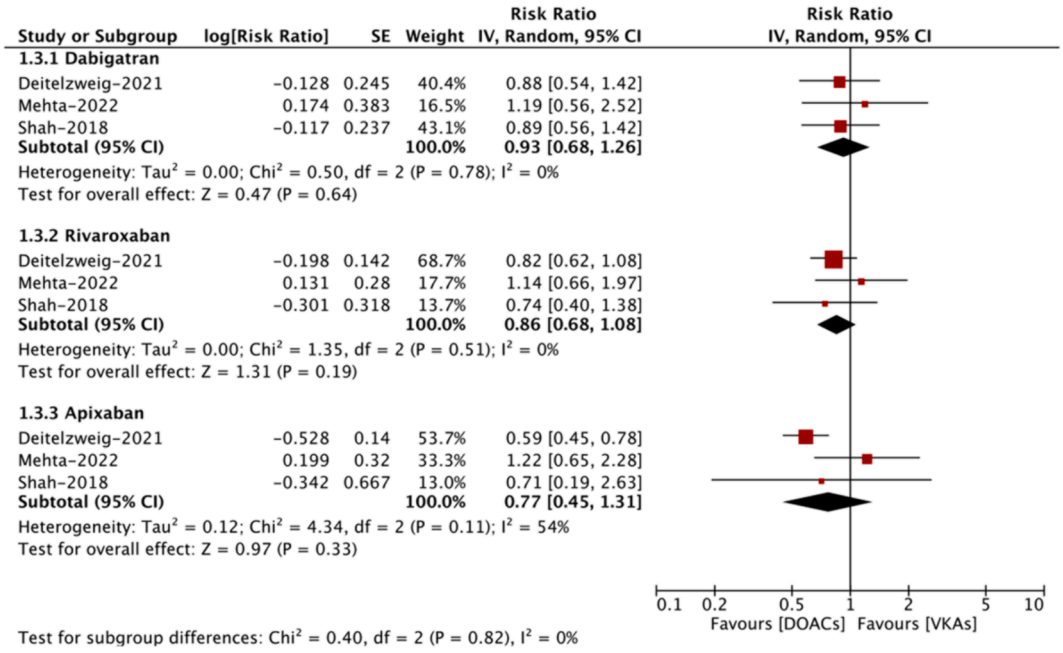

Fig. 3. Subgroup analysis of effectiveness outcomes for different DOACs versus VKAs in atrial fibrillation patients with cancer DOACs = direct oral anticoagulants; VKAs = vitamin K antagonists; RR=risk ratio; CI=confidence interval.

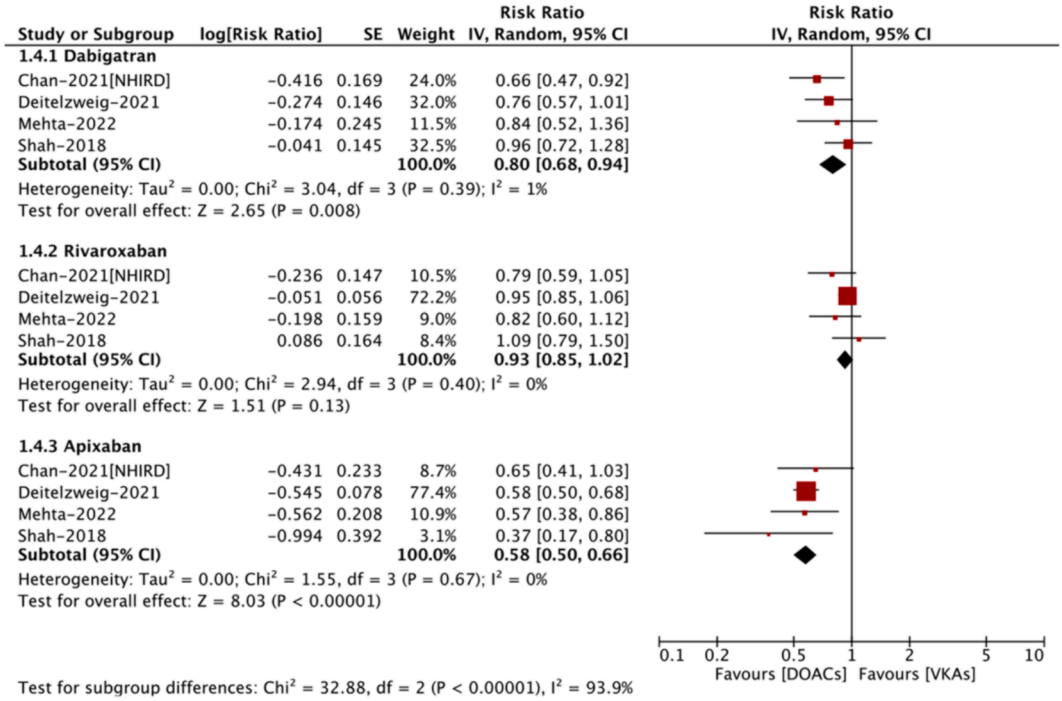

Fig. 4. Subgroup analysis of safety outcomes for different DOACs versus VKAs in atrial fibrillation patients with cancer DOACs = direct oral anticoagulants; VKAs = vitamin K antagonists; RR=risk ratio; CI=confidence interval; NHIRD=Taiwan National Health Insurance Research Database.

retrospective cohort studies, there was no significant difference in SSE and major bleeding between the DOAC and VKA groups [21].

The stringent enrollment and exclusion criteria in RCT studies effectively reduce the impact of confounding factors on the estimation of treatment effectiveness and safety, enhancing the reliability of the findings in a restricted and well-defined population cohort [22]. However, due to the stringent criteria, the study population may not always fully represent the comprehensive characteristics of the target population. Particularly, when considering the population with concomitant cancer and AF, this issue becomes even more pronounced. Due to the variations in tumor types and stages among different patients, as well as the presence of multiple comorbidities and diverse medication regimens in this patient population, standardizing anticoagulation treatment interventions becomes challenging, resulting in a high degree of heterogeneity within cohorts. The strict inclusion criteria of RCTs often result in the enrollment of only a small proportion of patients, limiting the generalizability of the study population to real-world settings.

In observational cohort studies, researchers have the freedom to

include a broader range of patients with varying characteristics and conditions, replicating the diversity seen in real-world clinical practice. Observational cohort studies can capture a more realistic representation of how medications work in different patient populations[23]. Considering the substantial heterogeneity in both the study population and anticoagulation strategies, observational cohort studies may provide a more realistic representation of drug safety and effectiveness in the real-world settings.

Although our *meta*-analysis intentionally excluded post hoc analyses of RCTs to focus on real-world observational data, it needs further discussion regarding the differences between findings from RCTs and observational studies. Our current study reported a reduced risk of gastrointestinal bleeding associated with DOACs compared to VKAs, which contrasts with the findings of post hoc analyses of RCTs. This discrepancy may be attributed to confounding factors inherent in observational studies, particularly confounding by indication and patient selection biases. In real-world settings, physicians may preferentially prescribe DOACs to patients perceived to have a lower risk of bleeding, thus leading to a more favorable safety profile for DOACs in these studies. These factors likely contributed to our findings of a lower risk of gastrointestinal bleeding with DOACs. Future research could conduct well-designed prospective studies with larger sample sizes to further clarify the effectiveness and safety of DOACs versus VKAs in patients with both AF and cancer.

4.1. Limitations

There were several limitations that should be considered in this *meta*-analysis. First, all the studies included in this analysis were observational cohort studies. While the studies have been evaluated using the NOS and have achieved scores of at least six points, there may still be the presence of selection bias and uncontrolled confounding factors due to the inherent limitations of this study design. Second, there was clinical heterogeneity among the different studies. This heterogeneity arises from variations in factors such as the type and dosage of DOACs, international normalized ratio levels during VKA use, the specific types of tumors, tumor staging, and the different treatments that patients received for their tumors. Third, it was important to consider the follow-up time of the included studies. In some cases, the follow-up period was relatively short, limiting the ability to comprehensively assess the long-term effects of anticoagulation. Lastly, due to the lack of consistent data on specific cancer types in the included studies, we were unable to perform a subgroup analysis stratified by cancer type. Future studies should address this limitation by exploring the differential effects of anticoagulants in various malignancies.

4.2. Future direction

The available research data comparing edoxaban with VKAs are limited, and we therefore did not perform the corresponding subgroup analysis. Therefore, the conclusions drawn regarding edoxaban's superiority should be interpreted with caution. Although we conducted the subgroup analysis based on the DOAC types regarding SSE and major bleeding events, due to the limited number of studies available for analysis, it was not feasible to conduct a subgroup analysis to examine the specific bleeding types associated with intracranial and gastrointestinal bleeding or other adverse outcomes. In addition, the number of included studies in each DOAC group was also limited. To further elucidate the results and develop more appropriate anticoagulation treatment strategies for AF patients with cancer, well-designed clinical studies with larger sample sizes are needed. Moreover, several factors such as tumor types, tumor staging, and different treatments for tumors should be considered in the further studies.

5. Conclusions

Compared with VKAs, the use of DOACs was associated with decreased risks of thrombotic and bleeding events in AF patients with cancer. Data from real-world scenarios support the use of DOACs as a favorable treatment option for this specific patient population.

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Authors' contributions: Wengen Zhu and Dexi Wu contributed to the study conception and design. Data search was performed by Xiuying Li and Runkai Li. Study selection and data extraction were performed by and Runkai Li. Data analyses and visualization were performed by Xiuying Li. The first draft of the manuscript was written by Xiuying Li and Runkai Li, and edited by Dexi Wu and Wengen Zhu.

CRediT authorship contribution statement

Xiuying Li: Writing – original draft. **Runkai Li:** Writing – original draft. **Wengen Zhu:** Writing – review & editing, Data curation, Conceptualization. **Dexi Wu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101512.

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