Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Cancer and Atrial Fibrillation: A Systematic Review and Meta-Analysis

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***Background*—**Several studies have investigated the effect of non–vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients with cancer, but the results remain controversial. Therefore, we conducted a meta-analysis to compare the efficacy and safety of NOACs versus warfarin in this population.

***Methods and Results*—**We systematically searched the PubMed and Embase databases until February 16, 2019 for studies comparing the effect of NOACs with warfarin in AF patients with cancer. Risk ratios (RRs) with 95% CIs were extracted and pooled by a random-effects model. Five studies involving 8908 NOACs and 12 440 warfarin users were included. There were no significant associations between cancer status and risks of stroke or systemic embolism, major bleeding, or death in AF patients. Compared with warfarin, NOACs were associated with decreased risks of stroke or systemic embolism (RR, 0.52; 95% CI, 0.28–0.99), venous thromboembolism (RR, 0.37, 95% CI, 0.22–0.63), and intracranial or gastrointestinal bleeding (RR, 0.65; 95% CI, 0.42–0.98) and with borderline significant reductions in ischemic stroke (RR, 0.63; 95% CI, 0.40–1.00) and major bleeding (RR, 0.73; 95% CI, 0.53–1.00). In addition, risks of efficacy and safety outcomes of NOACs versus warfarin were similar between AF patients with and without cancer.

***Conclusions*—**In patients with AF and cancer, compared with warfarin, NOACs had lower or similar rates of thromboembolic and bleeding events and posed a reduced risk of venous thromboembolism. **(*J Am Heart Assoc*. 2019;8:e012540. DOI: 10.1161/JAHA.119.012540.)**

Key Words: atrial fibrillation • cancer • efficacy • non–vitamin K antagonist oral anticoagulants • safety • warfarin

Atrial fibrillation (AF) is the most common serious abnormal heart rhythm, affecting >30 million people.[1–3] AF-associated thromboembolic events are the leading cause of substantial morbidity and mortality,[4,5] and thus high-risk AF patients often require anticoagulation therapy.[6] Vitamin K antagonists (VKAs), such as warfarin, are the most commonly used anticoagulants for stroke prevention in patients with AF. However, VKAs have many disadvantages that limit their use, including marked inter- and intraindividual variations in medication dosage, a narrow therapeutic window, frequent monitoring of anticoagulant activity, and various drug-drug or drug-food interactions.[7,8] Instead, non–vitamin K antagonist oral anticoagulants (NOACs) could overcome these shortcomings and have been recommended as the first-line anticoagulants in recent AF guidelines.[6,9] The efficacy and safety of NOACs (1 direct thrombin inhibitor [dabigatran] and 3 direct Xa inhibitors [rivaroxaban, apixaban, and edoxaban]) have been validated in 4 hallmark randomized clinical trials (RCTs).[10–13] In patients with AF, NOACs are at least as effective as VKAs for stroke prevention and even have a better safety profile.[10–13]

Emerging evidence suggests that cancer is associated with increased thromboembolic and bleeding risks, making anticoagulation management challenging in cancer patients for any indication.[14,15] AF and cancer often coexist,[16] which may result in elevated thromboembolic and bleeding complications. Although there is a noninferiority of NOACs compared

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Accompanying Tables S1 through S4 and Figures S1 through S10 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012540

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Clinical Perspective

What Is New?

- No significant associations between cancer status and risks of stroke or systemic embolism, major bleeding, and death were observed.
- Non–vitamin K antagonist oral anticoagulants had lower or similar rates of thromboembolic and bleeding events and a reduced risk of venous thromboembolism compared with warfarin.
- Similar rates of efficacy and safety outcomes (non–vitamin K antagonist oral anticoagulants versus warfarin) were observed between AF patients with and without cancer.

What Are the Clinical Implications?

- Our study indicates that the use of non–vitamin K antagonist oral anticoagulants is at least noninferior to warfarin for stroke prevention in atrial fibrillation patients with concomitant cancer.

with warfarin in AF patients, these agents are not recommended in AF guidelines for cancer patients because of the dearth of data. Previous RCTs of NOACs only included a small proportion of patients with cancer or potentially excluded some patients with cancer.[10–13] Thus far, evidence supporting the use of NOACs in patients with AF and cancer is extremely scarce. Although no head-to-head RCTs have been performed for the use of NOACs in this population, several post hoc analyses of RCTs or observational studies have explored the use of NOACs compared with warfarin in AF patients with a history of cancer.[17–21] Some studies have shown that patients with AF and cancer who took NOACs (compared with warfarin) had similar rates of stroke and bleeding risks,[17,19,21] but had a lower risk of venous thromboembolism (VTE).[18] In contrast, Kim et al[20] indicated lower risks of thromboembolic and bleeding events as well as all-cause death in patients with NOACs than in patients taking warfarin. Although a previous systematic review including 6 studies[21–26] performed a descriptive analysis on the efficacy and safety of NOACs in this population,[27] 3 studies did not regard warfarin as controls[24–26] and 2 studies did not report the adjusted effect estimates.[22,23] Therefore, we first conducted a meta-analysis to compare the efficacy and safety of NOACs with warfarin in nonvalvular AF patients with concomitant cancer.

Methods

This article does not contain any studies with human participants or animals performed by any of the authors.

The data, methods, and materials will be available to others for purposes of reproducing the results or replicating procedures by contacting the corresponding author. This meta-analysis was performed according to Cochrane methodological standards, and the presentations were based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[28] Ethical approval was not provided because no patients were involved in setting the research question, outcome measures, design, or implementation of the study; no patients were asked for advice on the interpretation or writing of the results; and there were no plans to involve patients in the dissemination of the article.

Literature Search

We systematically searched the PubMed and Embase databases until February 16, 2019 for studies that compared the efficacy and/or safety of any NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) with that of warfarin in patients with AF and cancer. The following 4 types of search terms were combined by using the Boolean operator "and": (1) "atrial fibrillation" OR "non-valvular atrial fibrillation"; (2) "neoplasia" OR "neoplasm" OR "tumor" OR "cancer" OR "malignancy"; (3) "non-vitamin K antagonists" OR "new oral anticoagulants" OR "novel oral anticoagulants" OR "direct oral anticoagulants" OR "oral thrombin inhibitors" OR "oral factor Xa inhibitors" OR "dabigatran" OR "rivaroxaban" OR "apixaban" OR "edoxaban"; and (4) "vitamin K antagonists" OR "warfarin." In addition, we further searched the reference lists of a previous systematic review[27] to identify additional studies of interest. We applied no restrictions on the language of publication, and the search strategies are shown in Table S1.

Inclusion and Exclusion Criteria

Studies were included if they satisfied the following criteria: (1) design of the study: post hoc analyses of RCTs; and prospective or retrospective cohorts; (2) study population: nonvalvular AF patients with cancer; (3) comparisons: any NOAC (dabigatran, rivaroxaban, edoxaban, or apixaban; any dose) versus warfarin; and (4) efficacy and/or safety outcomes measured: thromboembolic events, death, and bleeding.

Studies that evaluated AF patients undergoing cardioversion or ablation were excluded. Certain publication types (eg, reviews, case reports, meta-analyses, editorials, letters, and abstracts) or studies with insufficient data were also excluded. If the study population had a substantial overlap among different studies, we included the study with the longest follow-up or largest sample size.

Clinical Outcomes

To assess the efficacy and safety of NOACs versus warfarin in patients with AF and cancer, we included the following

outcomes: (1) thromboembolic events, including stroke or systemic embolism (SSE), ischemic stroke, myocardial infarction, and VTE; (2) major bleeding, nonmajor clinically relevant bleeding, intracranial or gastrointestinal bleeding, any bleeding (including major bleeding, nonmajor clinically relevant bleeding, and minor bleeding); and (3) all-cause death and cardiovascular death.

Objectives

The aims of this meta-analysis were to (1) compare the risks of thromboembolic events, death, and bleeding in AF patients with and without cancer; (2) assess the efficacy and safety outcomes of NOACs versus warfarin in AF patients with cancer; and (3) assess the effects of NOACs versus warfarin in AF patients with and without cancer.

Data Extraction and Quality Assessment

To ascertain accuracy, all of the studies retrieved by the search strategy were screened by 2 independent researchers (Y.Q.-D. and Y.F.-T.). The first phase of screening was performed by reading the titles and abstracts, whereas the second phase of screening was to review the full text. In situations of disagreement, issues were resolved through discussion with each other or through consultation with a third reviewer (H.-C.). Two studies required a discussion to reach a consensus because they included cancer patients with AF or VTE.[29,30] Ultimately, studies meeting the eligibility criteria were included. For each study, the following basic characteristics were collected: the first author and publication year, study design, number of NOACs/warfarin users, type of NOACs, follow-up time, efficacy and safety outcomes, and propensity-score–matched risk ratios (RRs) or adjusted RRs and their corresponding 95% CIs. If 2 dosages of NOAC were reported in 1 study, we only abstracted the RRs from the higher dose NOAC.

Newcastle–Ottawa Scale items, with a total score of 9 points, were used to evaluate the quality of cohort studies.[31] Post hoc analyses of RCTs were treated as cohorts to perform the quality assessment.[32] Each study was awarded a maximum of 1 point for each numbered item within the selection of cohorts (4 points), comparability of cohorts (2 points), and assessment of the outcome (3 points). A Newcastle–Ottawa Scale score of ≥6 points indicated a moderate-to-high quality, whereas a Newcastle–Ottawa Scale score of <6 points indicated a low quality.

Statistical Analysis

Statistical analysis was performed using Review Manager (Version 5.3; the Nordic Cochrane Center, Rigshospitalet, Denmark; http://ims.cochrane.org/revman). We evaluated the consistency across the included studies by using the Cochrane Q test and I^2 statistic. For the Q statistic, substantial heterogeneity was defined as a $P<0.1$. For the I^2 statistic, ≤25%, 50%, and ≥75% indicated low, moderate, and high heterogeneity, respectively. For each study, the effect estimates chosen were the RRs and their corresponding 95% CIs, which were converted to their corresponding natural logarithms and standard errors. Statistical heterogeneity (Cochrane Q test and I^2 statistic) should not be used to determine whether fixed-effects analysis is appropriate.[33] However, clinical heterogeneity (eg, types of cancer, types or dosages of NOACs, indication for treatment, and duration of treatment) could not be neglected. As such, we draw a relatively conservative conclusion based on the results of the random-effects model.[34] The sensitivity analysis was performed to examine the influence of each study on the pooled results. According to the Cochrane handbook, it was unsuitable to perform the publication bias for the reported effect estimates when the number of included studies was <10.[35] The statistical significance threshold was set at $P<0.05$.

Results

Study Selection

The literature retrieval process is shown in Figure 1. We initially identified 406 studies through electronic searches (PubMed, n=92; Embase, n=314), 57 of which were duplicate publications and removed. We found no additional studies through searching the reference lists of a previous systematic review.[27] Based on title and abstract screenings, 332 studies were excluded because they were certain publication types (eg, reviews, meta-analyses, editorials, letters, and abstracts) or other irrelevant studies. Subsequently, the 16 remaining studies were reviewed in more detail, and 11 studies did not meet with the inclusion criteria: (1) case reports (n=2)[36,37]; (2) studies not regarding warfarin as the reference (n=5)[24–26,38,39]; (3) cancer patients with both AF and VTE (n=2)[29,30]; and (4) studies not reporting the propensity-score–matched RRs or adjusted RRs (n=2).[22,23] Finally, a total of 5 studies (3 post hoc analyses from the ROCKET AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation],[17] ENGAGE AF-TIMI 48 [Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48],[19] and ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation][21] trials and 2 retrospective, population-based cohorts[18,20]) involving 8908 NOACs and 12 440 warfarin users were included in this meta-analysis.[17–21]

Study Characteristics and Quality

The detailed characteristics of the 5 included studies are presented in Table 1. The 3 post hoc analyses from the ROCKET AF,[17] ENGAGE AF-TIMI 48,[19] and ARISTOTLE[21] trials reported safety and efficacy of rivaroxaban, edoxaban, and apixaban, respectively. In the study by Shah et al,[18] safety and efficacy of dabigatran, rivaroxaban, and apixaban in patients with AF and cancer were separately reported. Kim et al[20] examined 3 types of NOACs, including dabigatran, rivaroxaban, and apixaban, but did not separately report the corresponding data. All 5 included studies had a Newcastle–Ottawa Scale score of ≥6 points (Table 1), indicating a moderate-to-high quality.

Association Between Cancer Status and Outcomes in AF Patients

Three post hoc analyses of RCTs, but not the 2 cohort studies, reported the associations between cancer status and outcomes in AF patients (Table S2). Pooling data from these 3 post hoc analyses showed that there were no differences in the rates of SSE (RR=0.99; 95% CI, 0.82–1.21; *P*=0.95), ischemic stroke (RR=0.90; 95% CI, 0.63–1.28; *P*=0.56), myocardial infarction (RR=1.21; 95% CI, 0.81–1.81; *P*=0.35), all-cause death (RR=1.58; 95% CI, 0.72–3.46; *P*=0.26), major bleeding (RR=1.32; 95% CI, 0.64–2.70; *P*=0.45), major or nonmajor clinically relevant bleeding (RR=1.09; 95% CI, 0.86–1.38; *P*=0.46), and intracranial bleeding (RR=0.75; 95% CI, 0.42–1.34; *P*=0.33) between patients with and without cancer

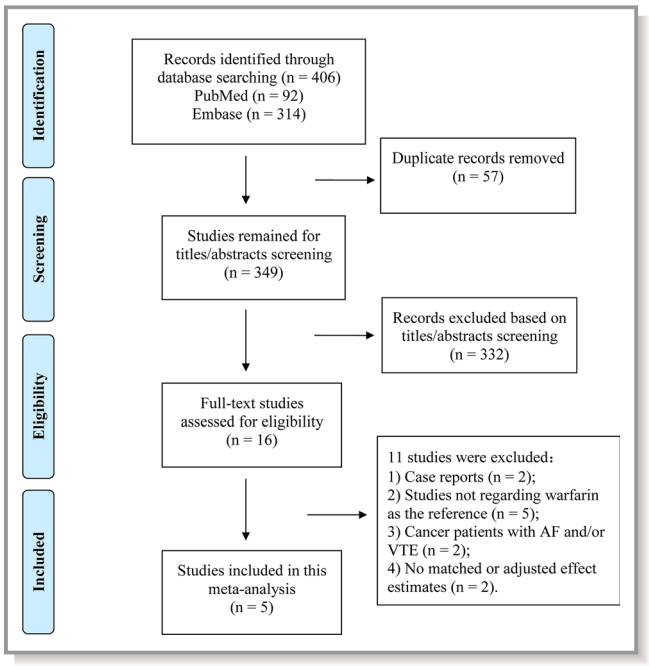

Figure 1. Overview of the research strategy. AF indicates atrial fibrillation; VTE, venous thromboembolism.

(Figure 2). Rates of some outcomes, such as all-cause death and major bleeding, had quite wide CIs, which might be largely attributed to the limited sample size and small number of events.

Efficacy and Safety of NOACs Versus Warfarin in AF Patients With Cancer

Within the 5 included studies, Chen et al[17] reported the outcomes of ischemic stroke/systemic embolism and hemorrhagic stroke separately, and we thus used these data to calculate the combined adjusted RR for SSE. Fanola et al[19] reported the outcomes of severe bleeding (intracranial or gastrointestinal) and other types of bleeding separately, and thus these data were used to calculate the combined adjusted RR for any bleeding.

The efficacy of NOACs versus warfarin

As shown in Figure 3, compared with the use of warfarin, the use of NOACs was significantly associated with reduced risks of SSE (RR=0.52; 95% CI, 0.28–0.99; *P*=0.04) and VTE (RR=0.37; 95% CI, 0.22–0.63; *P*<0.0001). There was a strong trend toward a reduction in the rate of ischemic stroke (RR=0.63; 95% CI, 0.40–1.00; *P*=0.05) with NOACs compared with warfarin. In contrast, NOACs versus warfarin yielded nonsignificantly different risks for myocardial infarction (RR=0.75; 95% CI, 0.45–1.25; *P*=0.26), all-cause death (RR=0.81; 95% CI, 0.49–1.32; *P*=0.39), and cardiovascular death (RR=0.71; 95% CI, 0.45–1.10; *P*=0.13).

The safety of NOACs versus warfarin

As presented in Figure 4, compared with warfarin use, the use of NOACs was associated with a decreased risk of intracranial or gastrointestinal bleeding (RR=0.65; 95% CI, 0.42–0.98; *P*=0.04). There was a strong tendency toward statistical significance for a reduced risk of major bleeding in patients with NOACs compared with warfarin (RR=0.73; 95% CI, 0.53–1.00; *P*=0.05). In contrast, risks of major or nonmajor clinically relevant bleeding (RR=1.00; 95% CI, 0.86–1.17; *P*=0.96) and any bleeding (RR=0.93; 95% CI, 0.78–1.10; *P*=0.39) of NOACs compared with warfarin were not significantly different.

Sensitivity analysis

After exclusion of 1 study at a time, the corresponding RR values were not changed substantially. We also reperformed the aforementioned analyses with a fixed-effects model. As shown in Table 2, NOACs versus warfarin yielded statistically significant differences in risks of SSE, ischemic stroke, and VTE. In addition, we also performed a subgroup analysis based on the design of the study. Similar rates of all the efficacy and safety outcomes were observed between patients taking

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Table 1. Clinical Characteristics of the 5 Included Studies

Study (First Author-Year)	Study Type	NOACs Presented	No. of NOACs/ Warfarin Users	Efficacy Outcomes	Safety Outcomes	Follow-up Time (y)	Type of Cancer	NOS Points
Chen-2019[17]	Post hoc analysis from ROCKET AF trial	RIV	Efficacy: 307/329 Safety: 309/331	SSE, ischemic stroke, hemorrhagic stroke, MI, VTE, all-cause death, cardiovascular death	Major bleeding (ISTH criteria), intracranial bleeding, NMCR bleeding, any bleeding*	1.9	Prostate (28.6%), breast (14.7%), colorectal (16.1%), gastrointestinal (3%), lung (3.1%), melanoma (5.9%), leukemia or lymphoma (5.2%), gynecological (6.6%), genitourinary (12.2%), head and neck (3.9%), thyroid (2.5%), brain (0.3%), others (3%), unspecified cancer type (3.9%)	8
Shah-2018[18]	Retrospective population-based cohort study	DA, RIV, API	6084/10 021	Ischemic stroke, VTE	Severe bleeding (intracranial or gastrointestinal), other bleeding	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
Fanola-2018[19]	Post hoc analysis from ENGAGE AF-TIMI 48 trial	EDO	395/750	SSE, ischemic stroke, MI, all-cause death, cardiovascular death	Major bleeding (ISTH criteria), gastrointestinal bleeding, NMCR bleeding, any bleeding*	2.8	Prostate (13.7%), breast (6.5%), bladder (7.5%), gastrointestinal (20.5%), lung or pleura (11%), skin (5.9%), pancreatic (3.8%), liver, gallbladder, or bile ducts (3.8%), esophageal (2.5%), oropharyngeal (2.6%), renal (2.5%), uterine (2.1%), brain (2.1%), genital (1.3%), thyroid (1.1%), leukemia (2.8%), lymphoma (2.2%), others (1.3%), unspecified cancer type (1.5%)	9
Kim-2018[20]	Retrospective population-based cohort study	DA, RIV, API	388/388	SSE, ischemic stroke, all-cause death	Major bleeding (ISTH criteria), gastrointestinal bleeding, intracranial bleeding, other bleeding	1.8	Stomach (20.6%), colorectal (14.9%), thyroid (10.8%), prostate (9.3%), 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%), breast (2.4%), ovary and endometrial (2.6%), renal cell carcinoma (3.1%),	7

Continued

Table 1. Continued

Study (First Author-Year)	Study Type	NOACs Presented	No. of NOACs/ Warfarin Users	Efficacy Outcomes	Safety Outcomes	Follow-up Time (y)	Type of Cancer	NOS Points
							hematologic malignancy (2.2%), others (3.2%)	
Melloni-2017[21]	Post hoc analysis from ARISTOTLE trial	API	615/621	SSE, MI, all-cause death	Major bleeding (ISTH criteria), NMCR bleeding, any bleeding*	1.8	Bladder (7%), breast (16%), colon (11%), gastric (2%), lung (3%), melanoma (6%), others (10%), ovarian/uterus (6%), prostate (29%), rectal (3%), renal cell carcinoma (4%), Hodgkin's lymphoma (1%), leukemia (<1%), lymphoma (1%), Non-Hodgkin's lymphoma (1%)	9

AF indicates atrial fibrillation; API, apixaban; DA, dabigatran; EDO, edoxaban; MI, myocardial infarction; NMCR, nonmajor clinically relevant bleeding; NOACs, non–vitamin K antagonist oral anticoagulants; NOS, Newcastle–Ottawa Scale; RIV, rivaroxaban; SSE, stroke or systemic embolism; VTE, venous thromboembolism.
*Any bleeding indicates major, NMCR, and minor bleeding.

NOACs and those taking warfarin after pooling the 3 post hoc analyses,[17,19,21] whereas there were significantly reduced risks of SSE, VTE, and all-cause death between NOACs and warfarin after pooling the 2 cohort studies.[18,20]

Effects of NOACs Versus Warfarin in AF Patients With and Without Cancer

Three post hoc analyses from the ROCKET AF,[17] ENGAGE AF-TIMI 48,[19] and ARISTOTLE[21] trials reported the effects of NOACs versus warfarin in AF patients with and without cancer (Table S3). Pooling results from these 3 trials showed similar rates of all the efficacy and safety outcomes (NOACs versus warfarin) between patients with and without cancer (all $P>0.05$; Table 3 and Figures S1 through S10).

Discussion

In comparison with the previous systematic review,[27] we first conducted a meta-analysis to compare the effect of NOACs versus warfarin in AF patients with cancer (Table S4). With the use of data from 5 included studies, our present meta-analysis suggested that (1) no significant associations between cancer status and the risks of SSE, major bleeding, and death were observed; (2) compared with warfarin, NOACs had lower or similar rates of thromboembolic and bleeding events as well as a reduced risk of VTE; and (3) similar rates of efficacy and safety outcomes (NOACs versus warfarin) were observed between AF patients with and without cancer.

Cancer is commonly associated with increased risks for thromboembolic and bleeding events. Nevertheless, after pooling the data from 3 post hoc analyses of RCTs, we observed similar rates of SSE, major bleeding, and death between AF patients with and without cancer. Similarly, Ording et al[23] also found that cancer was neither associated with an increased risk of thromboembolism nor bleeding in AF patients who received VKAs or NOACs. In AF patients with active cancer, the safety and efficacy of rivaroxaban was comparable to the results of the ROCKET-AF trial[12] in the general population.[26] This finding may be explained by the fact that AF patients with cancer would have a higher frequency of healthcare utilization than those without cancer. Additionally, Melloni et al[21] detected no significant differences in thromboembolic or bleeding events between AF patients with active cancer and those with remote cancer.

Current scoring systems (CHADS2, CHA2DS2-VASc, and HAS-BLED)[40,41] for thromboembolic and bleeding risk prediction have not been completely validated in patients with AF and cancer.[42–45] As such, the decision to initiate therapeutic anticoagulation in this high-risk population could be challenging, and current anticoagulant management still relies on a

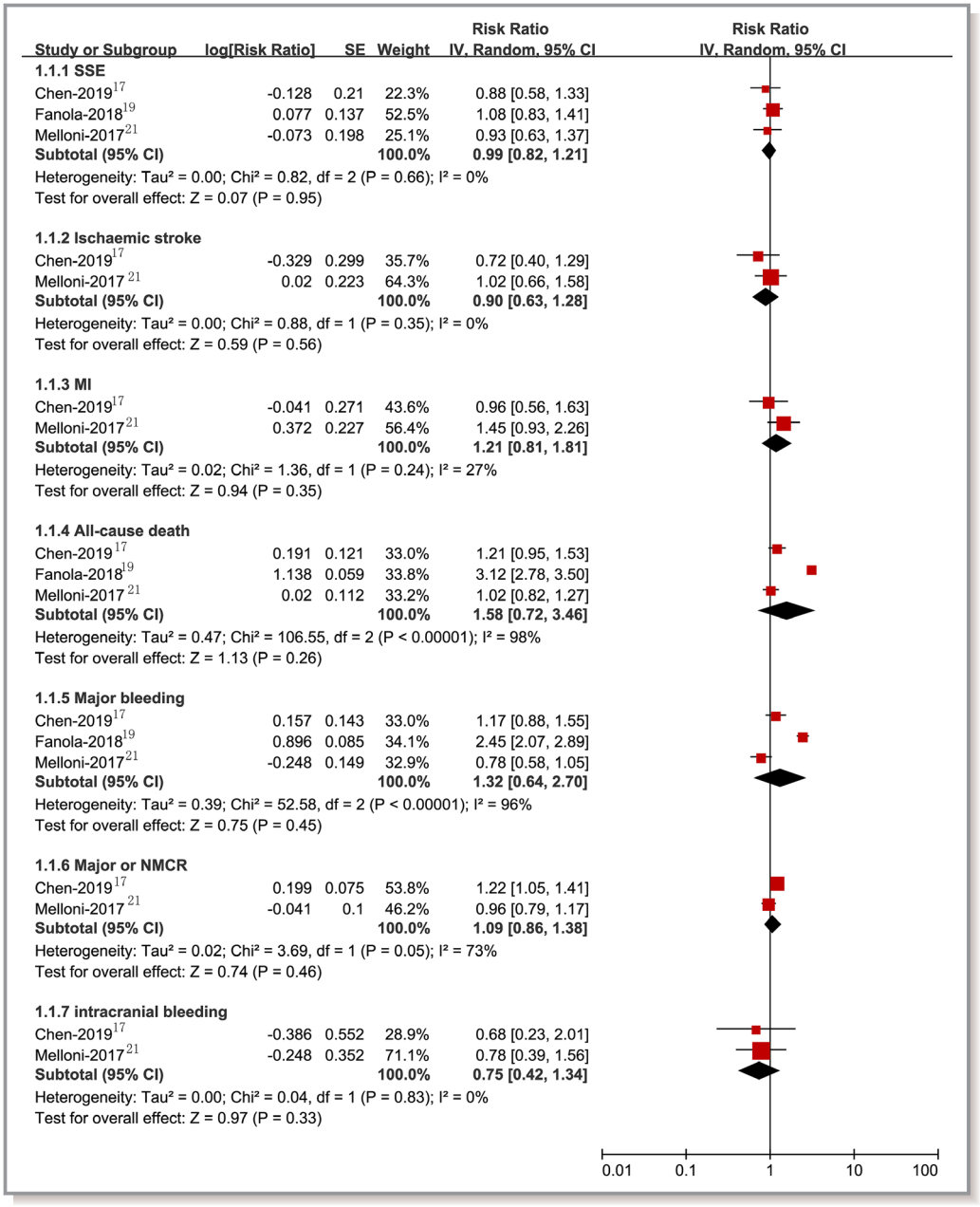

Figure 2. Forest plot for associations between cancer status and outcomes in AF patients. AF indicates atrial fibrillation; IV, inverse of the variance; MI, myocardial infarction; NOACs, non–vitamin K antagonist oral anticoagulants; SSE, stroke or systemic embolism.

highly individualized approach. The landmark RCTs indicate that NOACs offer an effective alternative to warfarin in AF patients.[10–13] However, there are still no specific recommendations for NOACs in patients with cancer in the AF guidelines because of extremely limited data. Current RCTs involving the selection of antithrombotic therapy for cancer patients with VTE are available, and the guidelines prefer low-molecular-weight heparins over VKAs or NOACs in the prophylaxis and treatment of VTE.[46] However, these data should not be generalized to cancer patients with AF because of the different pathophysiological and risk profiles between VTE and AF settings. In our meta-analysis, NOACs yielded lower or similar rates of thromboembolic and bleeding events, suggesting that the use of NOACs is at least noninferior to warfarin use in cancer patients with regard to the management of AF. Similarly, in the study by Ording et al,[23] compared with VKAs, NOACs seemingly had a lower risk of stroke, but a comparable rate of bleeding. In cancer patients with VTE and/or AF, there were no differences in thromboembolic or bleeding events when comparing NOACs with warfarin.[30] Importantly, we detected a reduced risk of VTE in patients taking NOACs compared with those taking warfarin. VTE

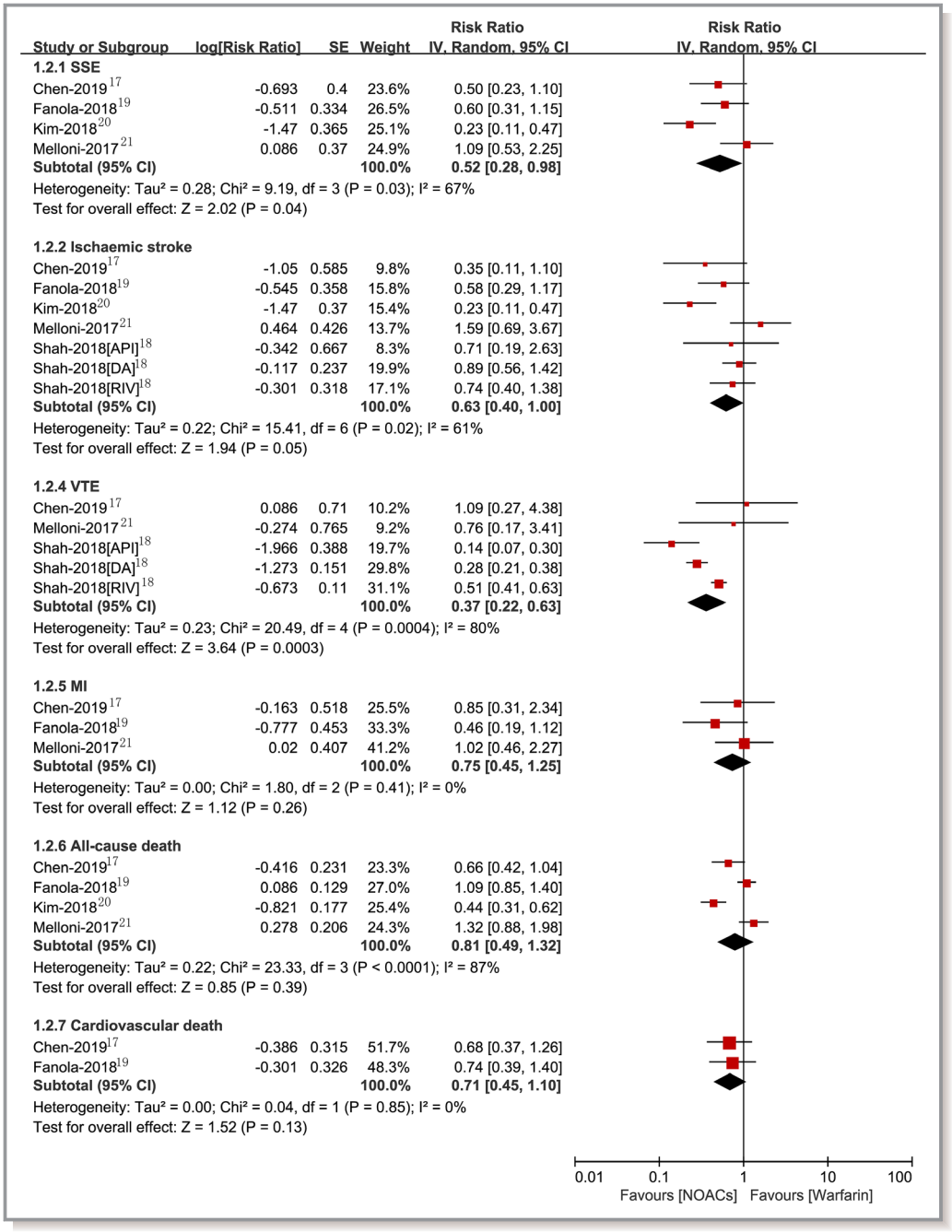

Figure 3. Forest plot for comparing the efficacy outcomes of NOACs with warfarin in patients with AF and cancer. AF indicates atrial fibrillation; API, apixaban; DA, dabigatran; IV, inverse of the variance; MI, myocardial infarction; NOACs, non–vitamin K antagonist oral anticoagulants; RIV, rivaroxaban; SSE, stroke or systemic embolism; VTE, venous thromboembolism.

events often account for a clinically significant increased risk of morbidity and mortality in cancer patients, but these risks occur less frequently after the administration of NOACs.[18] In addition, we also found that the benefits of NOACs in comparison with those of warfarin were consistent between AF patients with and without cancer. Therefore, NOACs may represent an alternative to warfarin in patients with AF and cancer. Of particular note, the pooled results between post-hoc analyses of RCTs and cohort studies are not completely consistent. Understandably, clinical trial populations are generally selected with strict inclusion and exclusion criteria under careful protocol-based follow-up, and participants in RCTs do not always reflect the broad range of patients in real-world daily practice. Effectiveness and safety of NOACs versus warfarin may differ between real-life patients with AF and those with cancer. Therefore, there is an increased need

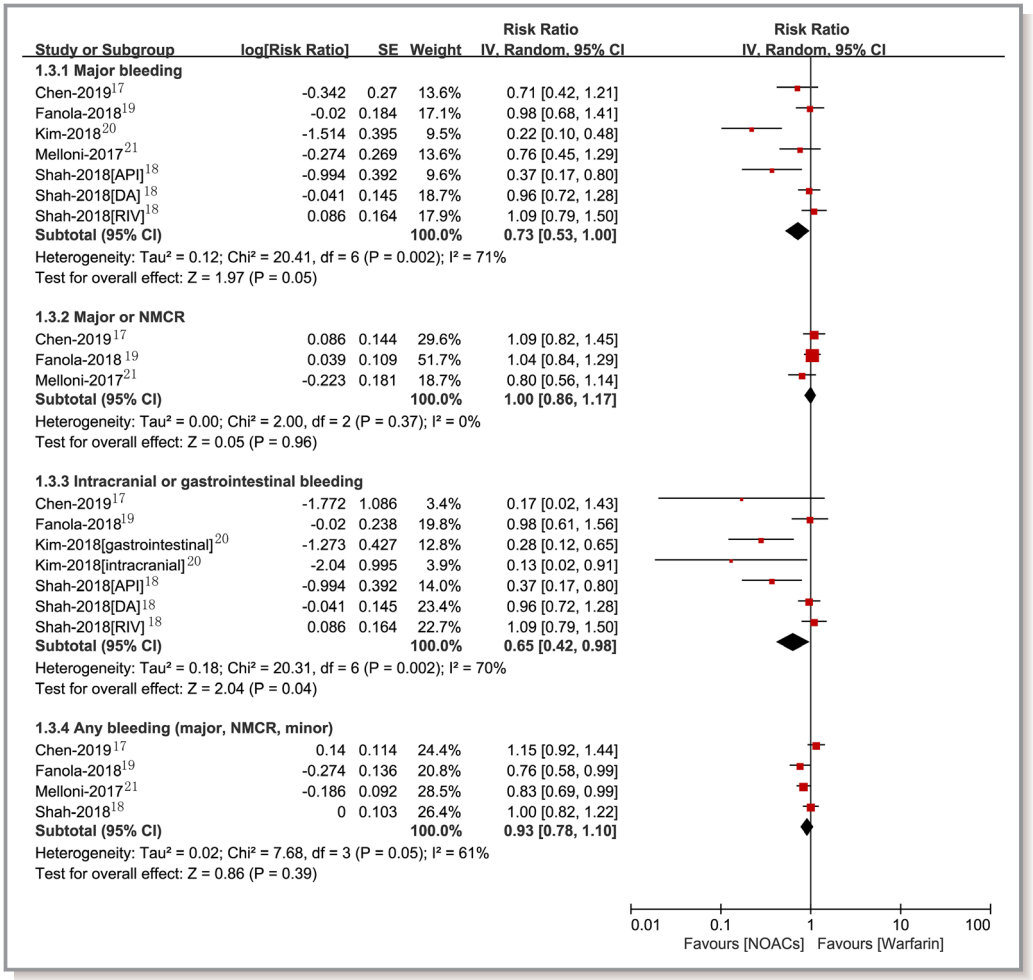

Figure 4. Forest plot for comparing the safety outcomes of NOACs with warfarin in patients with AF and cancer. AF indicates atrial fibrillation; API, apixaban; DA, dabigatran; IV, inverse of the variance; NMCR, nonmajor clinically relevant bleeding; NOACs, non–vitamin K antagonist oral anticoagulants; RIV, rivaroxaban.

for further large-scale observational studies validating the efficacy and safety of NOACs in AF patients with cancer.[17–21]

The cancer population in this meta-analysis was heterogeneous because there are limited data on the type of cancer, cancer staging, timing of cancer diagnosis, antineoplastic drugs, or chemotherapeutic response. This fact may contribute to certain uncontrolled confounding factors because the effect of NOACs versus warfarin may vary across different cancer conditions. For example, in patients with cancer, thromboembolic risks may vary based on cancer subtypes, where the risk of arterial thromboembolism seems to be highest in incidental cancer patients and generally attenuates over time.[47] In AF patients with cancer, NOACs yielded lower or similar rates of thromboembolic and bleeding events compared with those of warfarin, and these results were consistent across cancers at different sites.[18] In addition, apixaban versus warfarin seems to pose a greater benefit for ischemic composite outcomes in AF patients with active cancer versus no cancer, but not in patients with remote cancer versus no cancer. Furthermore, studies included in this meta-analysis provided limited data about staging for the majority of the cancers, which might have led to uncontrolled confounding if the type of anticoagulants (NOACs versus warfarin) varied by cancer staging. It would be important to take the heterogeneity of cancer patients into consideration in future investigations of the optimal anticoagulation strategies in patients with AF and cancer. In addition, there may be a dichotomy in thromboembolic risks between AF patients (taking NOACs) with active and remote cancer.[38] However, Melloni et al[21] showed that active and remote cancer patients with AF (taking NOACs or warfarin) had similar risks of thromboembolic and bleeding events, whereas active cancer patients appeared to have a higher risk of all-cause death. Given the limited sample size and small number of events, further studies could be performed to explore whether there is a risk of channeling more-severe cancer patients to either NOACs or warfarin.

Table 2. Efficacy and Safety of NOACs Versus Warfarin in Patients With AF and Cancer

	Random-Effects Model		Fixed-Effects Model		Post hoc Analyses*		Retrospective Cohorts*	
	RR and 95% CI	*P* Value	RR and 95% CI	*P* value	RR and 95% CI	*P* Value	RR and 95% CI	*P* Value
Efficacy								
SSE	0.52 (0.28–0.99)	0.04	0.53 (0.37–0.75)	0.0004	0.69 (0.44–1.08)	0.11	0.23 (0.11–0.47)	<0.0001
Ischemic stroke	0.63 (0.40–1.00)	0.05	0.67 (0.51–0.88)	0.004	0.72 (0.32–1.65)	0.44	0.58 (0.31–1.10)	0.09
VTE	0.37 (0.22–0.63)	0.0003	0.40 (0.34–0.47)	<0.00001	0.92 (0.33–2.56)	0.88	0.30 (0.16–0.54)	<0.0001
MI	0.75 (0.45–1.25)	0.26	0.75 (0.45–1.25)	0.26	0.75 (0.45–1.25)	0.26	NA	NA
All-cause death	0.81 (0.49–1.32)	0.39	0.85 (0.72–1.00)	0.05	1.01 (0.71–1.42)	0.97	0.44 (0.31–0.62)	<0.0001
Cardiovascular death	0.71 (0.45–1.10)	0.13	0.71 (0.45–1.10)	0.13	0.71 (0.45–1.10)	0.13	NA	NA
Safety								
Major bleeding	0.73 (0.53–1.00)	0.05	0.86 (0.73–1.00)	0.05	0.85 (0.66–1.11)	0.23	0.61 (0.34–1.08)	0.09
Major or NMCR	1.00 (0.86–1.17)	0.96	1.00 (0.86–1.17)	0.96	1.00 (0.86–1.17)	0.96	NA	NA
Intracranial or gastrointestinal bleeding	0.65 (0.42–0.98)	0.04	0.87 (0.73–1.04)	0.13	0.56 (0.11–2.78)	0.48	0.59 (0.35–1.01)	0.05
Any bleeding	0.93 (0.78–1.10)	0.39	0.93 (0.83–1.03)	0.16	0.90 (0.71–1.14)	0.39	1.00 (0.82–1.22)	1.00

AF indicates atrial fibrillation; MI, myocardial infarction; NA, not available; NMCR, nonmajor clinically relevant bleeding; NOACs, non–vitamin K antagonist oral anticoagulants; RR, risk ratio; SSE, stroke or systemic embolism; VTE, venous thromboembolism.
*The natural logarithms and standard errors were pooled by the random-effects model.

The findings in the present meta-analysis were driven by combining different NOACs. Because of the limited data, we did not perform a subgroup analysis based on the type or dosage of NOACs. Shah et al[18] found that compared with warfarin, apixaban showed a lower bleeding risk, but dabigatran or rivaroxaban showed similar bleeding risks, in AF and cancer patients; however, all 3 drugs had a reduced risk of VTE. The anticoagulant effects were different between any 2 types of NOACs. For example, dabigatran had a lower rate of VTE than rivaroxaban, and apixaban showed lower rates of VTE and severe bleeding than rivaroxaban.[18] However, Kim et al[20] reported no significant differences in the clinical

Table 3. Effects of NOACs Versus Warfarin in AF Patients With and Without Cancer*

	Cancer	No Cancer	*P* Value
Efficacy			
SSE	0.69 (0.44–1.08)	0.83 (0.74–0.93)	0.44
Ischemic stroke	0.72 (0.32–1.65)	0.99 (0.88–1.11)	0.45
VTE	0.92 (0.33–2.56)	0.81 (0.58–1.13)	0.81
MI	0.75 (0.45–1.25)	0.94 (0.81–1.09)	0.40
All-cause death	1.01 (0.71–1.42)	0.90 (0.84–0.96)	0.53
Cardiovascular death	0.71 (0.45–1.10)	0.91 (0.82–1.00)	0.29
Safety			
Major bleeding	0.85 (0.66–1.11)	0.85 (0.62–1.15)	0.97
Major or NMCR	1.00 (0.86–1.17)	0.85 (0.67–1.06)	0.22
Intracranial or gastrointestinal bleeding	0.56 (0.11–2.78)	0.98 (0.54–1.77)	0.52
Any bleeding	0.90 (0.71–1.14)	0.86 (0.64–1.15)	0.80

MI indicates myocardial infarction; NMCR, nonmajor clinically relevant bleeding; NOACs, non–vitamin K antagonist oral anticoagulants; SSE, stroke or systemic embolism; VTE, venous thromboembolism.
*Relative risks and 95% CI from 3 post hoc analyses (ROCKET AF, ENGAGE AF-TIMI 48, and ARISTOTLE) were pooled by the random-effects model.

outcomes according to the dosage and type of NOACs. Understandably, NOAC therapy may interact with several classes of chemotherapeutic agents through common metabolic pathways, such as cytochrome P450 3A4, and different NOACs may have different inhibitory effects. As the use of direct-acting oral anticoagulants becomes more widespread, further studies should consider the dosage and type of NOACs.

Until the results from RCTs specifically designed to focus on the safety and efficacy of NOACs are available with respect to patients with AF and cancer, our meta-analysis provides certain evidence that could give some confidence to clinicians when selecting NOACs for this population of patients who need anticoagulation. Our data supported that the use of NOACs is at least noninferior to warfarin use in this population. In addition, NOACs offer an effective anticoagulant choice that does not need monitoring. If the prescription of NOACs in AF patients with cancer does truly reduce the VTE or bleeding risks compared with the use of warfarin, more-widespread use of NOACs would significantly attenuate morbidity and mortality in cancer patients.

Limitations

Although we first suggest that NOACs might be at least as effective and safe as warfarin in patients with AF and cancer, these findings in this meta-analysis are still exploratory. Several limitations would be acknowledged, and further studies should take more information into consideration. First, the cancer population across the included studies was heterogeneous, which might result in uncontrolled confounding. In addition, some included studies might have had patient selection bias. For example, post hoc analysis from the ROCKET-AF trial potentially precluded some patients with advanced cancer. Second, given the nature of observational data, residual confounders might exist, although we only included propensity-score–matched or multivariate adjusted RRs. Third, in warfarin users, the time in the therapeutic range was not considered because only 1 included study[20] compared the NOACs versus warfarin with a time in the therapeutic range ≥60%. Finally, because of the limited data, the subgroup analysis based on the type or dosage of NOACs could not be clarified.

Conclusions

Based on previously published studies, there were no significant associations between cancer status and outcomes in AF patients. Compared with warfarin, NOACs showed a reduced risk of VTE, but yielded lower or similar rates of thromboembolic and bleeding events in patients with cancer and AF. Safety and efficacy of NOACs versus warfarin seem to be preserved between AF patients with and without cancer. Further data from randomized trials will be needed to clarify whether there is an advantage of NOACs over warfarin in this population.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. PubMed Search strategy determined on February 16, 2019.

Search	Query	
PubMed		
#1	'atrial fibrillation' OR 'non-valvular atrial fibrillation'	74512
#2	'neoplasia' OR 'neoplasm' OR 'tumor' OR 'cancer' OR 'malignancy'	4240813
#3	'non-Vitamin K antagonists' OR 'new oral anticoagulants' OR 'novel oral anticoagulants' OR 'direct oral anticoagulants' OR 'oral thrombin inhibitors' OR 'oral factor Xa inhibitors' OR 'dabigatran' OR 'rivaroxaban' OR 'apixaban'OR 'edoxaban'	15057
#4	'vitamin k antagonists' OR 'warfarin' OR 'coumadin' OR 'acenocoumarol'	34296
#5	#1 and #2 and #3 and #4	92
EMBASE		
#1	'atrial fibrillation' OR 'non-valvular atrial fibrillation'	149,152
#2	'neoplasia' OR 'neoplasm' OR 'tumor' OR 'cancer' OR 'malignancy'	23,424
#3	'non-Vitamin K antagonists' OR 'new oral anticoagulants' OR 'novel oral anticoagulants' OR 'direct oral anticoagulants' OR 'oral thrombin inhibitors' OR 'oral factor Xa inhibitors' OR 'dabigatran' OR 'rivaroxaban' OR 'apixaban'OR 'edoxaban'	97,644
#4	'vitamin k antagonists' OR 'warfarin' OR 'coumadin' OR 'acenocoumarol'	1,245,536
#5	#1 and #2 and #3 and #4	1,826

Table S2. Efficacy and safety outcomes in AF patients with and without cancer.

	Melloni-2017[1] (Total events)		Fanola-2018[2] (Total events)		Chen-2019[3] (Total events)		Total (Total events[rate%])	
	Cancer	**No cancer**	**Cancer**	**No cancer**	**Cancer**	**No cancer**	**Cancer**	**No cancer**
Efficacy	N=1236	N=1236	N=763	N=13,307	N=636	N=13507	N=2635	N=43761
SSE	29	447	57	959	24	549	110 (0.81)	1955 (4.47)
Ischemic stroke	23	313	49	755	16	397	88 (0.65)	1465 (3.35)
MI	24	168	35	408	15	257	74 (0.55)	833 (1.90)
All-cause death	96	1174	361	1988	80	1132	537 (3.98)	4294 (9.81)
Safety	N=1236	N=1236	N=763	N=13,307	N=640	N=13596	N=2639	N=43850
Major bleeding	56	733	161	1132	56	725	273 (10.34)	2590 (5.91)
Major or NMCR	120	1370	470	4150	193	2731	783 (29.67)	8251 (18.2)
Intracranial bleeding	9	165	99	480	7	132	115 (4.36)	777 (1.77)

AF = atrial fibrillation; SSE = stroke or systemic embolism; MI = myocardial infarction; VTE = venous thromboembolism; NMCR = non-major clinically relevant bleeding.

Table S3. Effects of NOACs versus warfarin in AF patients with and without cancer.

	Melloni-2017[1] (Total events)				Fanola-2018[2] (Total events)				Chen-2019[3] (Total events)				Shah-2018[4] (Total events)		Kim-2018[5] (Total events)	
	Cancer		No cancer		Cancer		No cancer		Cancer		No cancer		Cancer		Cancer	
	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin	NOACs	Warfarin
Efficacy	N=615	N=621	N=8493	N=8454	N=758	N=395	N=13311	N=6641	N=307	N=329	N=6754	N=6753	N=6073	N=16787	N=388	N=388
SSE	15	14	196	251	33	24	646	313	8	16	259	290	-	-	9	40
Ischemic stroke	14	9	147	166	28	21	541	214	4	12	201	196	46	204	9	39
VTE	3	4	27	33	-	-	-	-	4	4	35	43	180	1433	-	-
MI	12	12	78	90	19	16	283	125	7	8	123	134	-	-	-	-
All-cause death	54	42	548	626	241	120	1269	719	32	48	548	584	-	-	41	93
Cardiovascular death	-	-	-	-	34	23	1023	588	17	25	357	376	-	-	-	-
Safety	N=615	N=621	N=8493	N=8454	N=758	N=395	N=13311	N=6641	N=309	N=331	N=6802	N=6794	N=6073	N=16787	N=388	N=388
Major bleeding	24	32	303	430	98	63	638	494	23	33	372	353	-	-	8	36
Major or NMCR	53	67	560	810	296	174	2514	1636	97	96	1378	1353	-	-	-	-
Intracranial or gastrointestinal	0	9	52	113	61	38	320	160	1	6	54	78	148	594	8	33

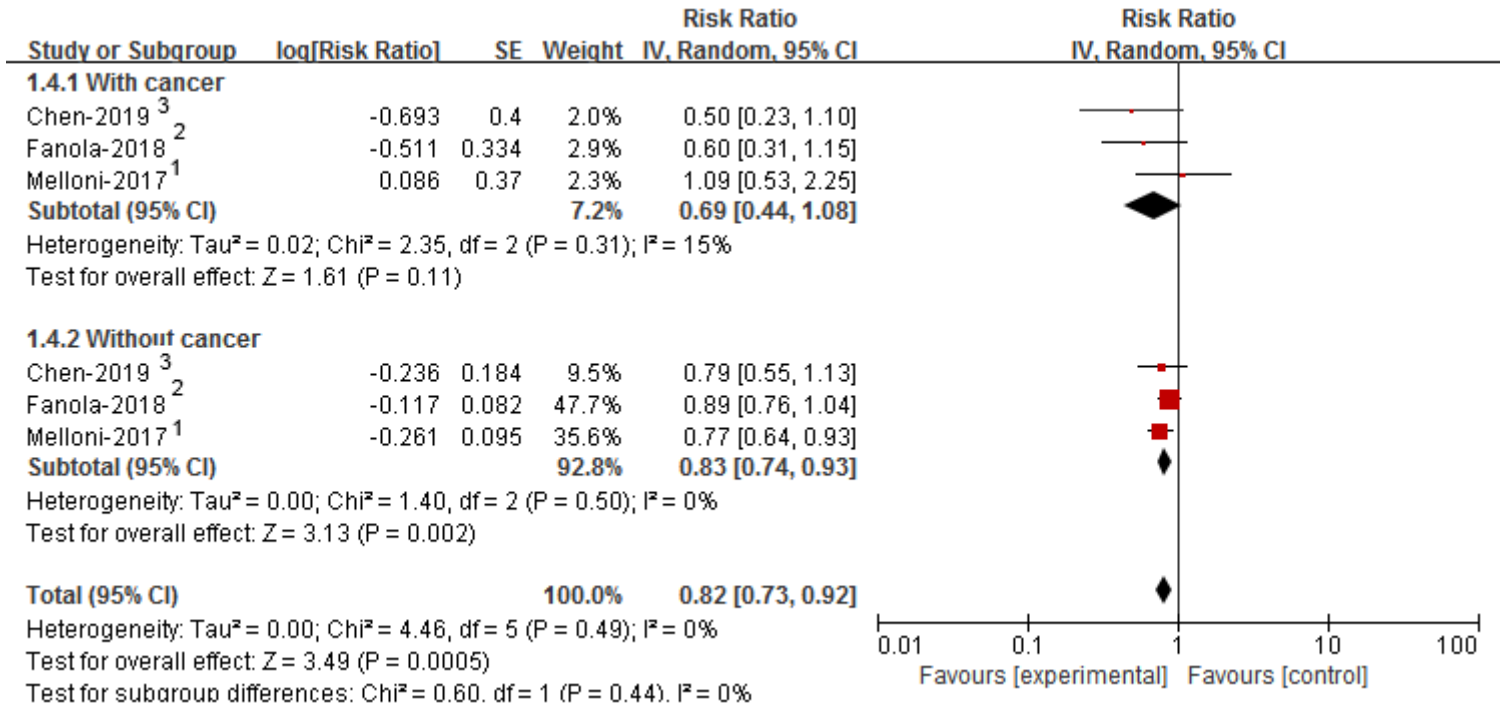
bleeding																
Any bleeding	204	245	2149	2815	322	195	3161	1969	152	152	2152	2132	-	-	-	-

AF = atrial fibrillation; SSE = stroke or systemic embolism; MI = myocardial infarction; VTE = venous thromboembolism; NMCR = non-major clinically relevant bleeding.

Table S4. Comparing the characteristics of our meta-analysis with previous systematic review.

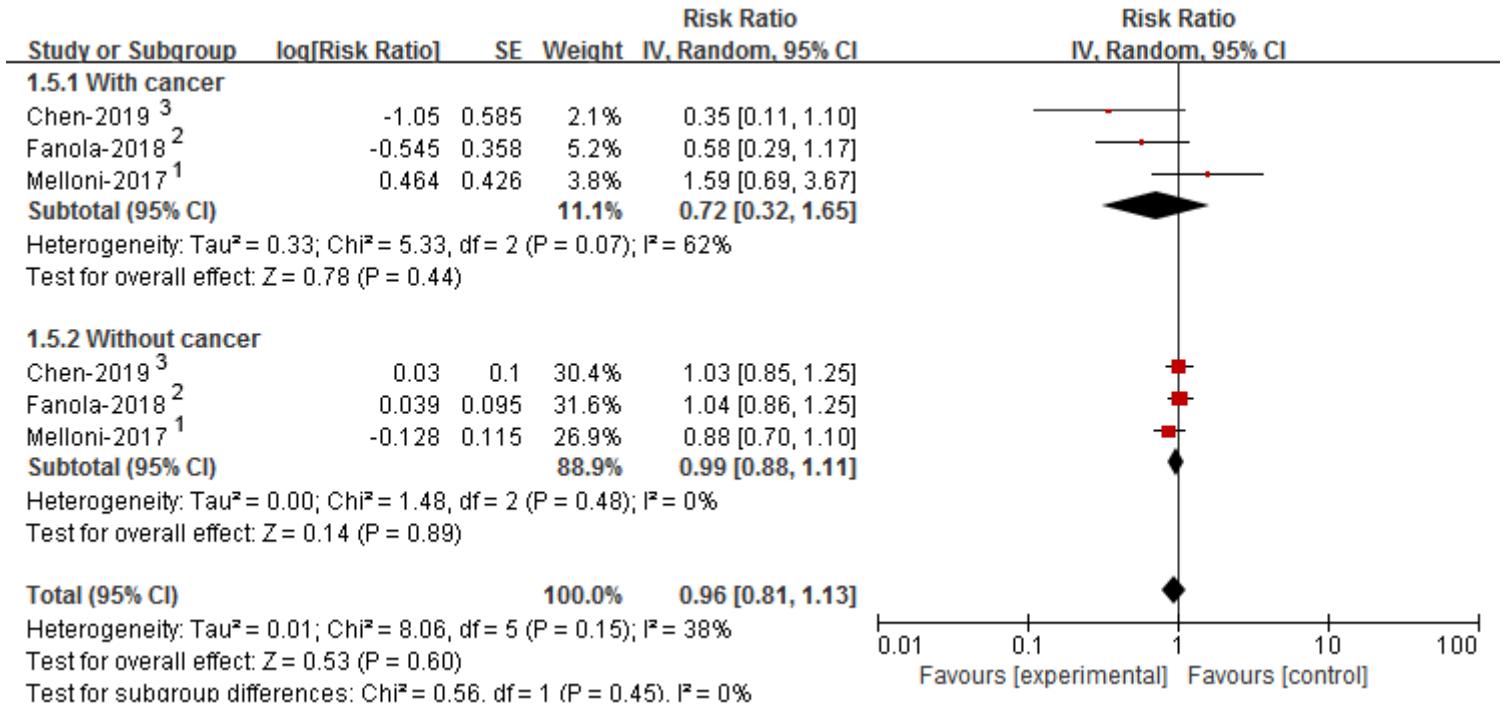
	Our meta-analysis	**Russo et al.**[6]
Type	Pooled analysis	Narrative analysis
Study population	AF patients with cancer	AF patients with cancer
Study design	Post hoc analyses of RCTs; prospective or retrospective cohorts	Post hoc analyses of RCTs; prospective or retrospective cohorts; case-control studies
Comparsions	NOACs (dabigatran, rivaroxaban, edoxaban or apixaban) vs. warfarin	NOACs (dabigatran, rivaroxaban, edoxaban or apixaban) vs. other antithrombotic therapies such as warfarin and aspirin
Outcomes	Thromboembolic events, death and bleeding	Thromboembolic events, death and bleeding
Included studies	1.European Heart Journal - Quality of Care and Clinical Outcomes. 2019;5(2):145-152. 2.Blood Advances. 2018;2(3):200-209. 3.J AM HEART ASSOC. 2018;7(16). 4.KOREAN CIRC J. 2018;48(5):406. 5.The American Journal of Medicine. 2017;130(12):1440-1448.	1.Cancer Med. 2017;6(6):1165-1172. 2.CLIN GASTROENTEROL H. 2017;15(5):682-690. 3.Am J Cardiol 2017;120(02):213-217 4.Semin Thromb Hemost 2018;44(04):370–376. 5.Int J Hematol 2017;106(04):517-521. 6.The American Journal of Medicine. 2017;130(12):1440-1448.
Effect estimates	Propensity score-matched or adjusted data	Adjusted or unadjusted data

Figure S1. Comparing the stroke or systemic embolism of NOACs versus warfarin between AF patients with and without cancer.



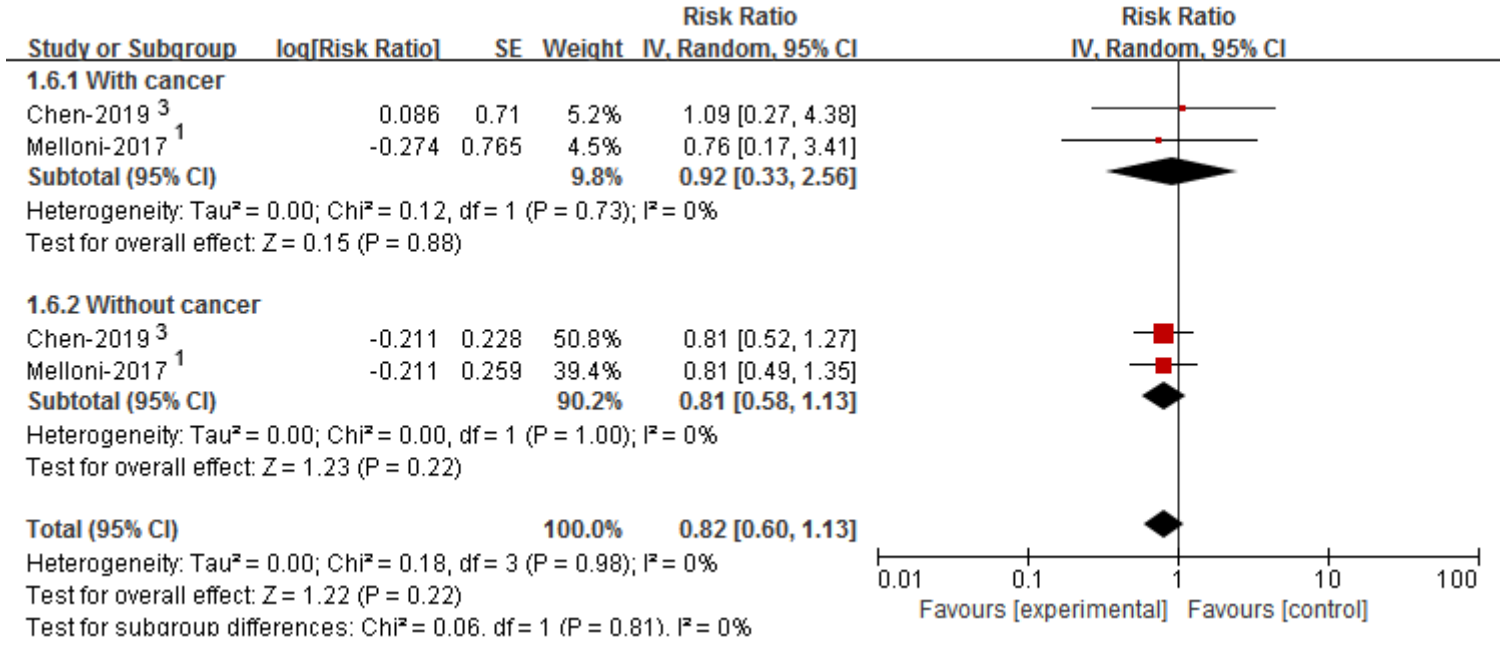
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S2. Comparing the ischemic stroke of NOACs versus warfarin between AF patients with and without cancer.



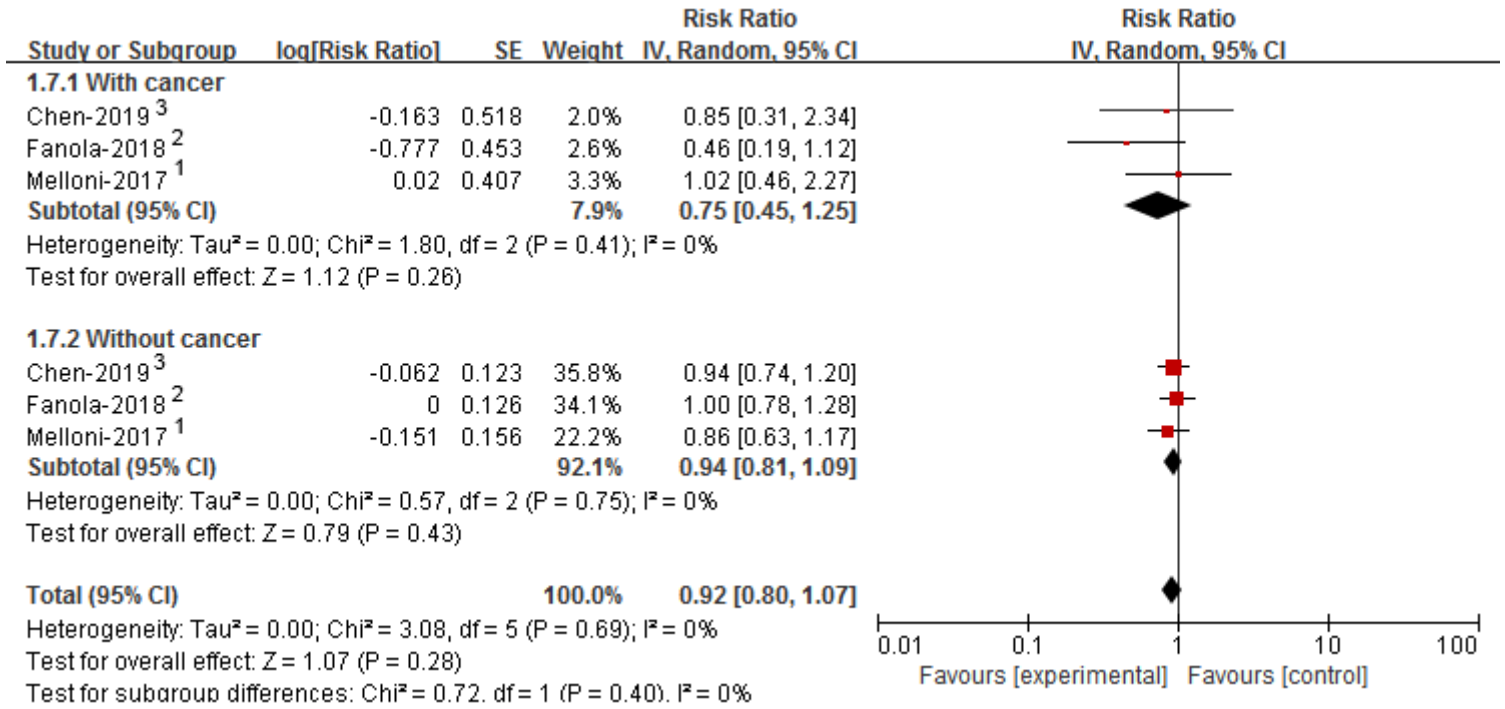
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure 3. Comparing the venous thromboembolism of NOACs versus warfarin between AF patients with and without cancer.



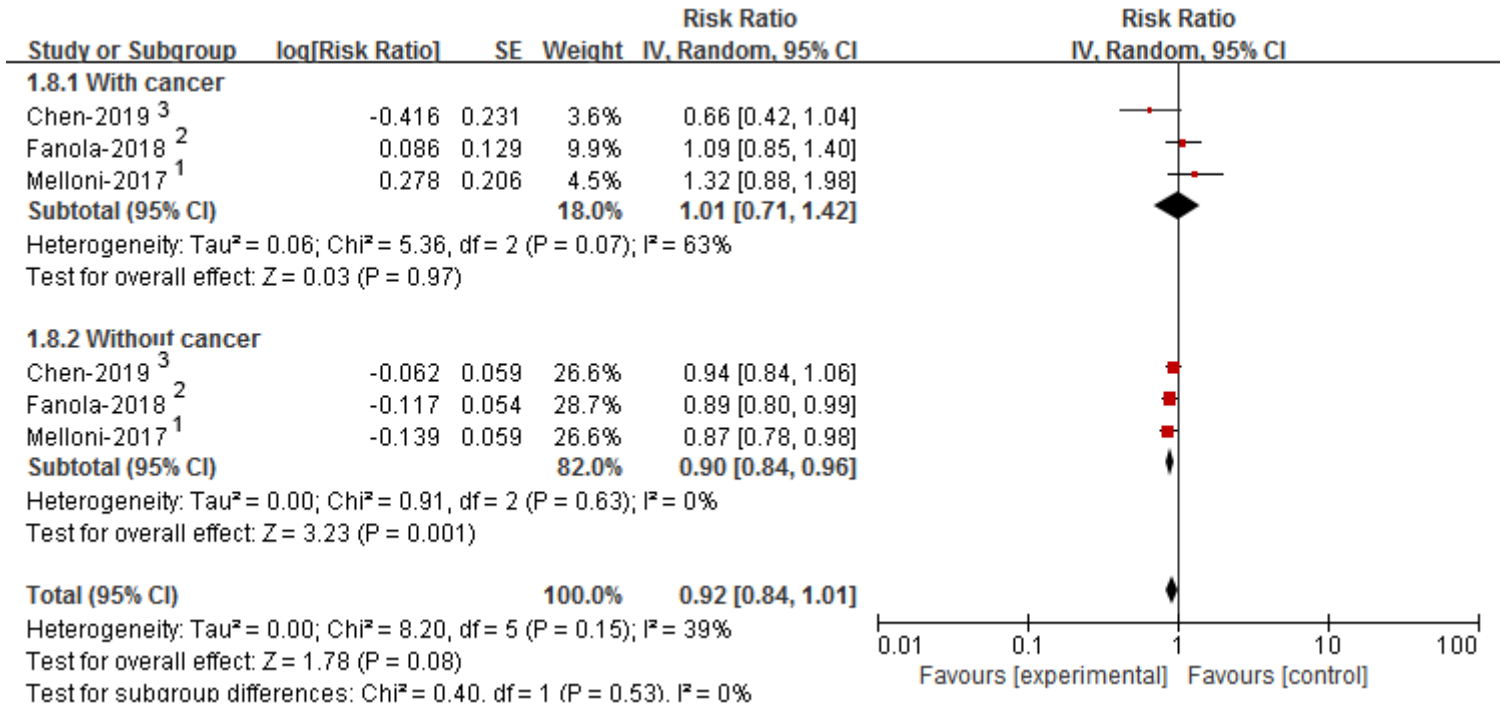
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S4. Comparing the myocardial infarction of NOACs versus warfarin between AF patients with and without cancer .



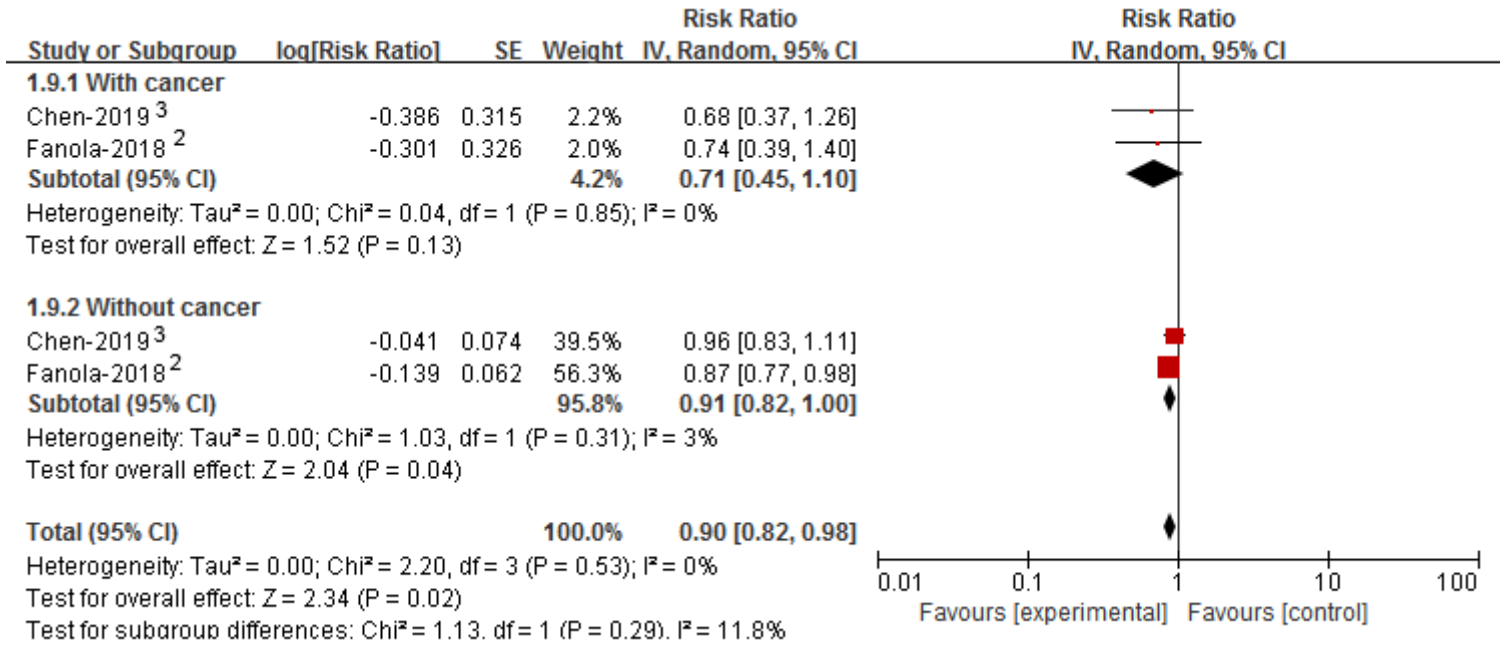
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure 5. Comparing the all-cause death of NOACs versus warfarin between AF patients with and without cancer.



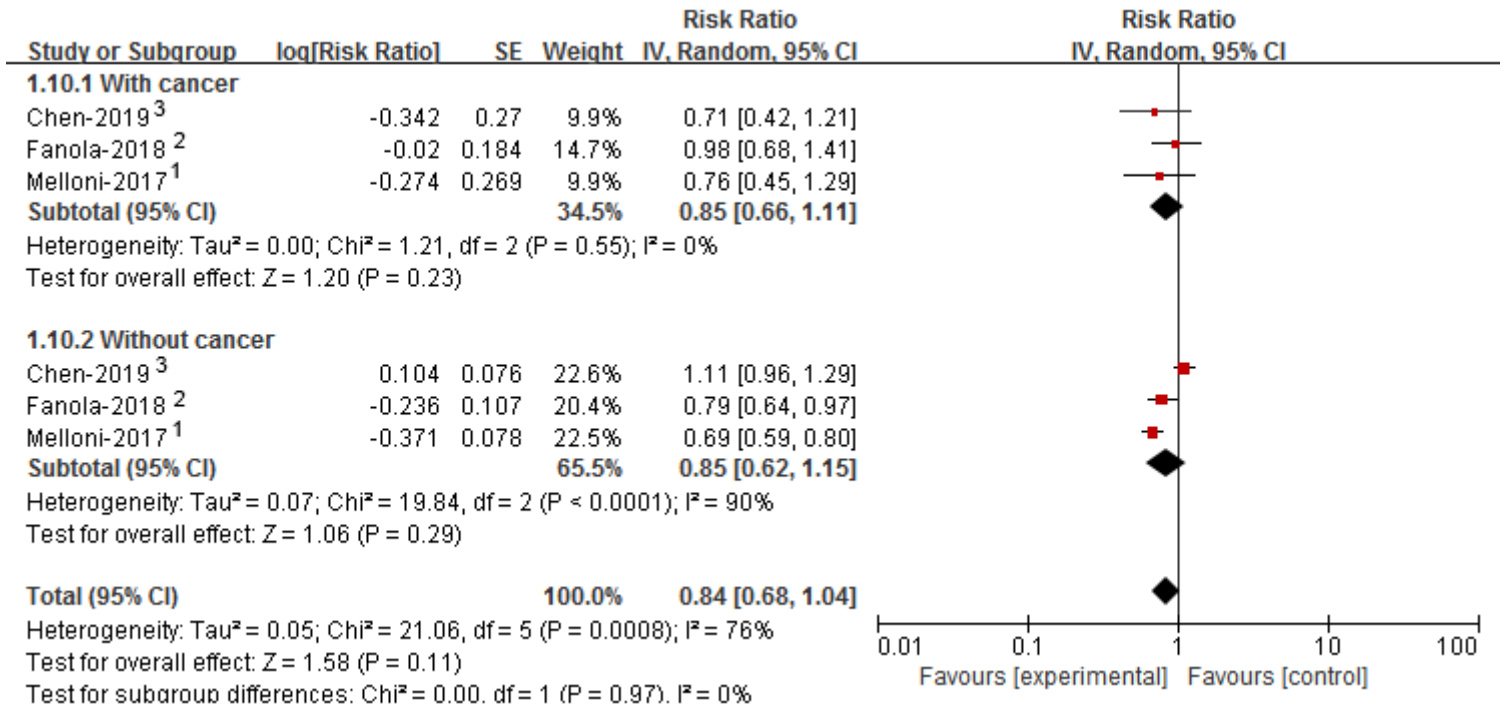
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S6. Comparing the cardiovascular death of NOACs versus warfarin between AF patients with and without cancer.



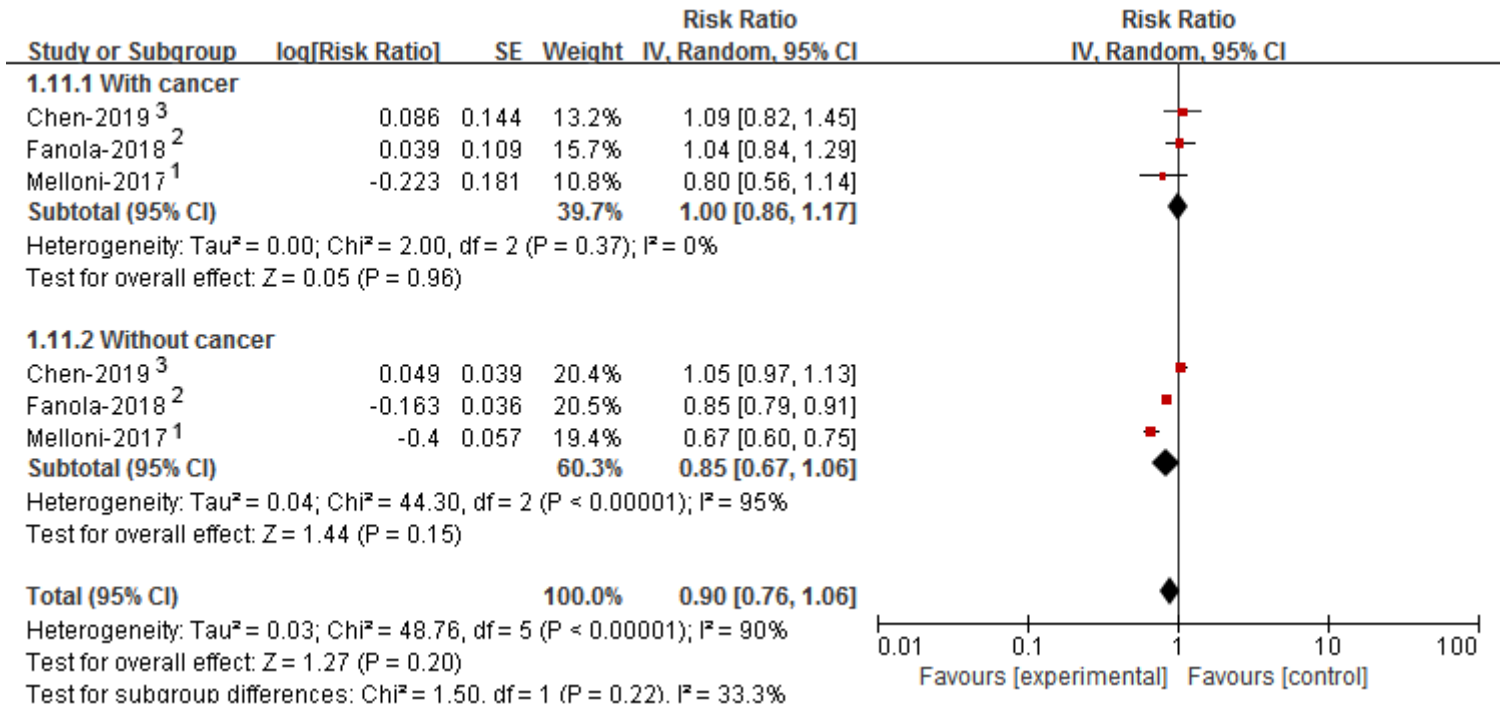
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S7. Comparing the major bleeding of NOACs versus warfarin between AF patients with and without cancer.



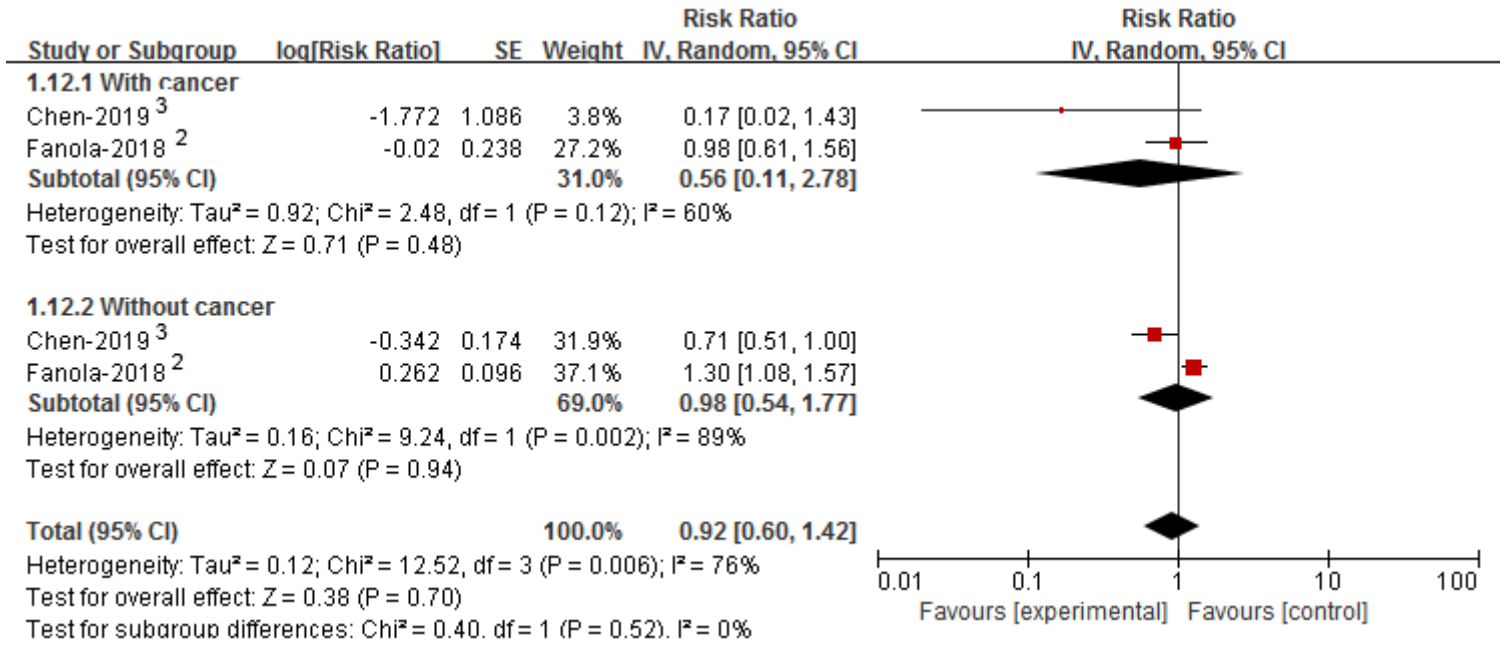
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S8. Comparing the major or NMCR bleeding of NOACs versus warfarin between AF patients with and without cancer.



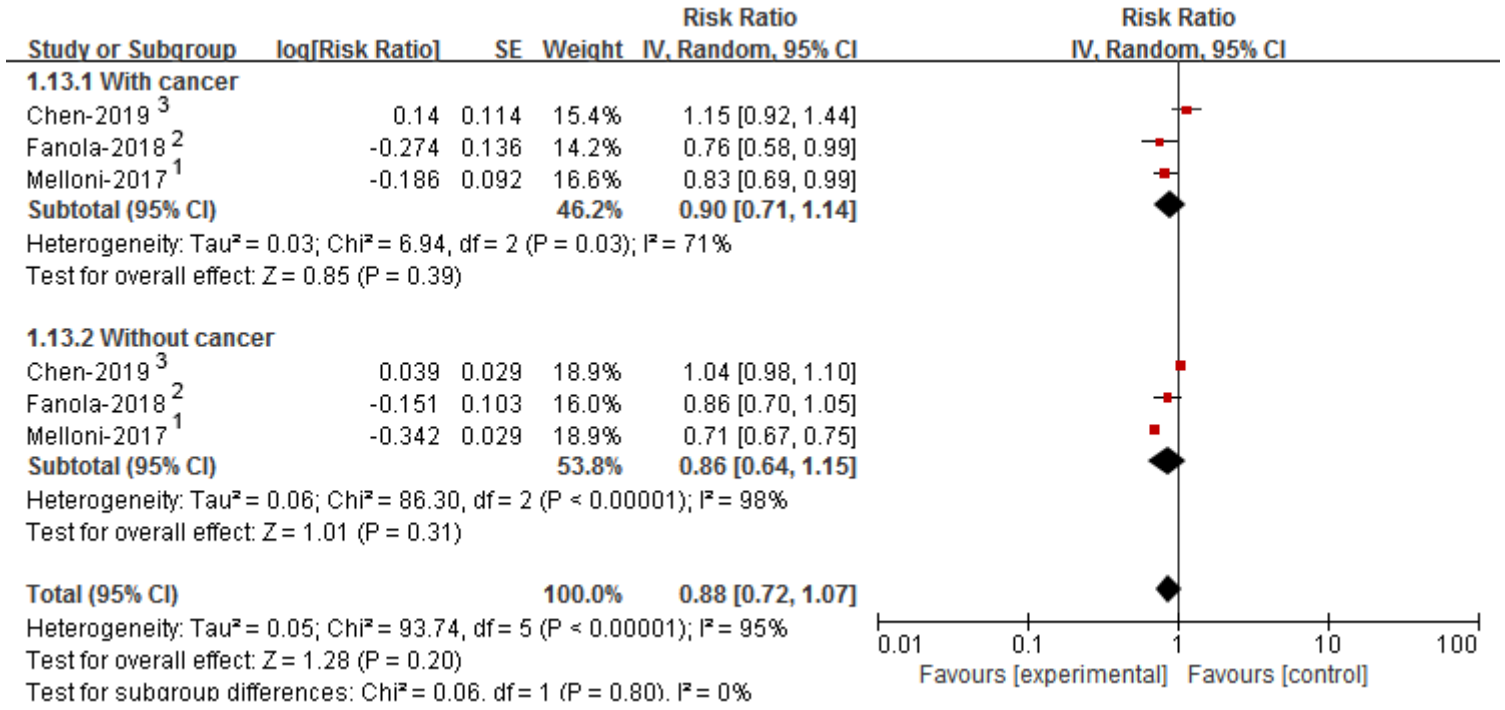
AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; NMCR = non-major clinically relevant bleeding; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S9. Comparing the gastrointestinal or intracranial bleeding of NOACs versus warfarin between AF patients with and without cancer.



AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Figure S10. Comparing the any bleeding of NOACs versus warfarin between AF patients with and without cancer.



AF = atrial fibrillation; NOACs = non-Vitamin K antagonist oral anticoagulants; CI = confidence interval; SE = standard error; IV = inverse of the variance.

Supplemental References:

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