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Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation and Cancer in Real World: Meta-Analysis of Retrospective Observational Studies

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Abstract: Background: Evidence on the safety and effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients with cancer is rather limited, so we performed this meta-analysis to compare the efficacy and safety of NOACs with vitamin K antagonists (VKAs) in real-world patients with AF and cancer. Methods: The PubMed and Embase databases were searched up to June 2020 for eligible studies. Outputs were presented as risk ratios (RRs) and corresponding 95% confidence intervals (CIs) using a random-effects model. Results: A total of five observational studies involving 232,234 cancer patients with AF were included. Compared with VKAs, use of NOACs was associated with decreased risks of stroke or systemic embolism (RR, 0.79; 95% CI 0.69-0.90), is chaemic stroke (RR, 0.82; 95% CI, 0.72-0.93), venous thromboembolism (VTE) (RR, 0.28; 95% CI 0.14-0.53), all-cause death (RR, 0.57; 95% CI 0.50-0.64), major bleeding (RR, 0.60; 95% CI 0.51-0.72) and intracranial or gastrointestinal bleeding (RR, 0.61; 95% CI, 0.51-0.73). Conclusions: In this combined analysis of real-world observational studies, NOACs showed lower risks of stroke or systemic embolism, ischaemic stroke, VTE, all-cause death and reduced rates of major bleeding and intracranial or gastrointestinal bleeding compared to VKAs in patients with AF and cancer.

1. Introduction

Atrial fibrillation (AF), inducing a five-fold increase in thromboembolic risk[1], is the most common cardiac arrhythmia. AF commonly occurs in cancer patients due to a hypercoagulable state, anticancer drugs or chest surgery[2]. Cancer patients are at high risk of morbidity and mortality due to thrombosis and bleeding[3]. The risks of both thromboembolic and bleeding incidents are higher

in AF patients with cancer compared to those free of cancer[4]. Therefore, the optimization of anticoagulation therapy is particularly important in reducing the risk of both thrombotic and bleeding complications in AF patients with cancer.

Warfarin is the most commonly prescribed anticoagulant in prevention of thrombosis among AF patients. However, warfarin therapy remains challenging in AF patients with caner because of the metabolic interactions with chemotherapy, chemotherapy-induced thrombocytopenia, and the frequent need for surgical or invasive procedures. Non-vitamin K antagonist oral anticoagulants (NOACs)are an alternative approach for stroke prevention in non-valvular AF (NVAF) patients. There are currently four NOACs available: factor Xa inhibitors (edoxaban, apixaban, and rivaroxaban) and direct thrombin inhibitor (dabigatran),which are considered as effective and safe as VKAs[5].

There were three meta-analyses assessing the performance of NOACs versus warfarin with the post hoc analysis data of RCTs and observational studies[6-8]. However, clinical trial populations are selected due to overly restrictive eligibility criteria and do not reflect all demographic features. Therefore, it's imperative to assess the efficacy and safety profiles of NOACs in real-world settings from observational studies. In this context, we performed an up-dated meta-analysis in observational studies of real-world representative populations to compare the efficacy and safety of NOACs with VKAs in NVAF patients with cancer.

2. Methods

The current analysis was performed according to the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE)[9].

2.1 Database and Search

We performed a systematic search in PubMed and Embase electronic database until June 2020 for relevant studies comparing the effect of any NOAC (apixaban, dabigatran, edoxaban or rivaroxaban) versus VKA in AF patients with cancer. The searching strategy was conducted by combining four kinds of search terms -1)"Atrial fibrillation" or "AF"AND 2) "cancer" or "carcinoma" AND 3) vitamin K antagonists OR warfarin AND 4) "new oral anticoagulants" or "non vitamin k antagonist oral anticoagulants" or "rivaroxaban" or "apixaban" or "edoxaban" or "dabigatran" or oral factor "Ⅹa inhibitors" or " oral factor Ⅱa inhibitors".

2.2 Selection and Criteria

Studies were considered to be eligible meeting the following criteria:1) Study design: observational studies; 2)Study population: AF patients with cancer; 3) Interventions: any NOAC(apixaban, dabigatran, edoxaban or rivaroxaban) compared to vitamin K antagonists or warfarin; 4) Outcomes: studies reported at least one of the efficacy or safety outcomes.

2.3 Efficacy and Safety Outcomes

To assess the efficacy and safety of NOACs versus VKA, we included the following clinical outcomes: 1) efficacy outcomes, including stroke or systemic embolism (SSE), ischaemic stroke (IS), venous thromboembolism(VTE) and all-cause death; 2) safety outcomes, including major bleeding, according to the definition of original research (e.g., International Society on Thrombosis and Hemostasis criteria) ,and and intracranial or gastrointestinal bleeding.

2.4 Data Extraction and Quality Assessment

All of the retrieved articles were assessed by two reviewers (Bo Cao and Xiaobo Hu) independently. The final selection of studies was performed by consensus. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included observational studies, which includes three components: selection(0-4 points), comparability(0-2 points) and the assessment of the outcome(0-3 points).

2.5 Statistical Analysis

All of the statistical analyses were performed by using the Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark) and Stata software (version 14.0, Stata Corp LP, College Station, TX). The risk ratio (RR) with 95% confidence interval (CI) was calculated for each included study, and then pooled by a random-effects model using the Mantel-Haenszel method. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1 Description of Included Studies

Database search generated 127 related articles and 5 studies[10-14]were identified for analysis after exclusion according to the eligibility criteria. All studies were retrospective and included a total of 232,234 patients, 44,739 were treated with NOACs and the remaining 187,495 with VKAs. All included studies had an acceptable quality with an (NOS score $\geqslant$ 6).

3.2 The Efficacy of Noacs Versus Vkas

As presented in Fig. 1, the rates of stroke or systemic embolism were 10.7% in patients treated with NOACs versus 12.9% in those on VKAs, showing the decreased risk of SSE for NOACs users compared with VKAs (RR, 0.79; 95% CI, 0.69-0.90; I^2=86%). The incidence of ischaemic stroke was significantly different between NOACs and VKAs (10.1% vs 11.82%; RR, 0.82; 95% CI, 0.72-0.93; I^2=85%). In two studies reporting venous thromboembolism, the use of NOACs was associated with reduced risk of VTE (2.4% vs 5.9%, RR, 0.28; 95% CI, 0.14-0.53; I^2=92%) compared with VKAs. All-cause death was reported in two studies, and the incidence was significantly reduced in the NOACs group (25.9% vs 44.8% in the VKAs group; RR, 0.57; 95% CI, 0.50-0.64; I^2=95%).

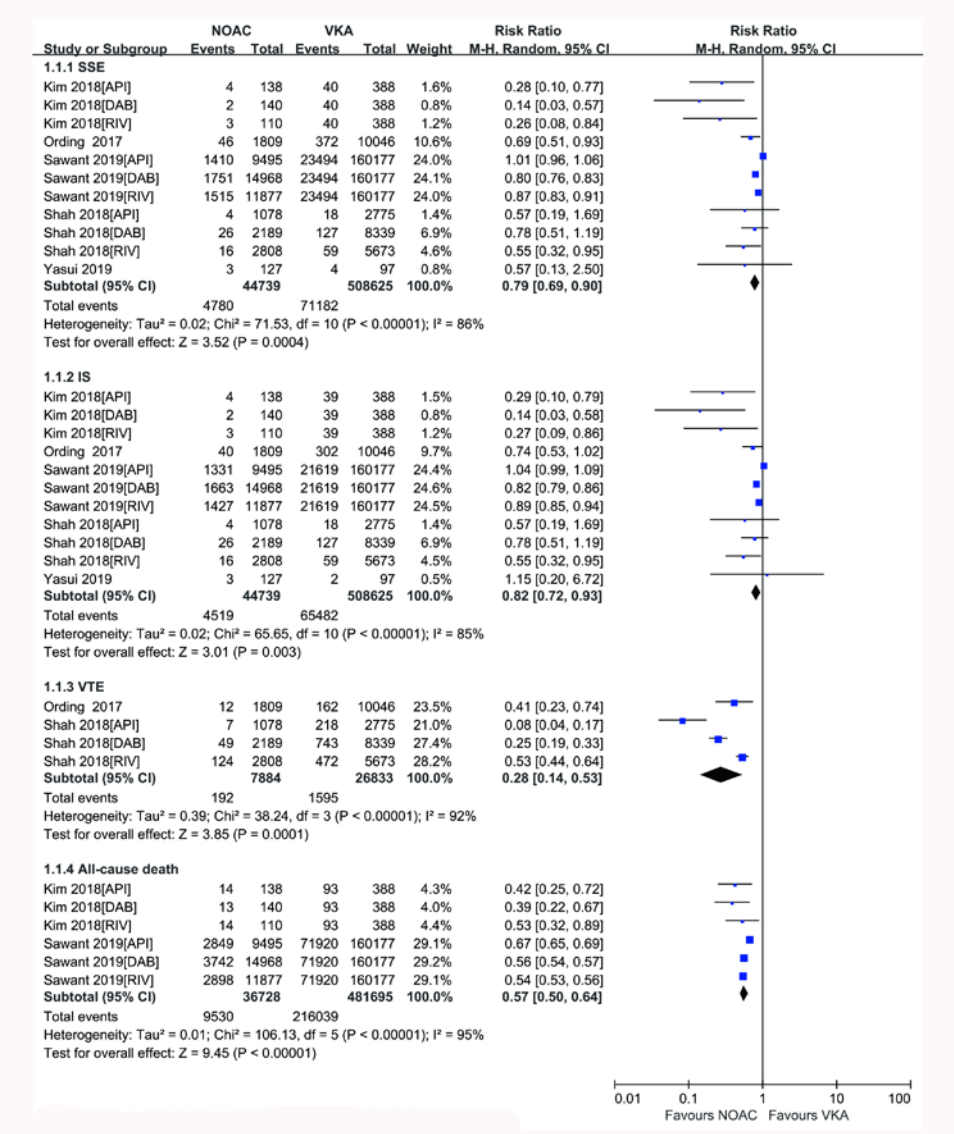

Fig. 1 Forest plot comparing NOACs vs VKAs regarding the efficacy outcomes in real-world patients with AF and cancer. AF, atrial fibrillation; SSE, stroke or systemic embolism; IS, ischaemic stroke; VTE, venous thromboembolism; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; API, apixaban; RIV, rivaroxaban; DAB, dabigatran.

3.3 The Safety of Noacs Versus Vkas

Major bleeding was reported in all included studies as shown in Fig. 2, the rate of major bleeding was significant lower in people treated with NOACs compared to VKAs (1.06% vs 1.61%, RR, 0.60; 95% CI, 0.51-0.72; I^2=59%). Intracranial or gastrointestinal bleeding occurred in 1.0% of patients receiving NOACs and in 1.46% of those on VKAs (RR, 0.61; 95% CI, 0.51-0.73; I^2=59%).

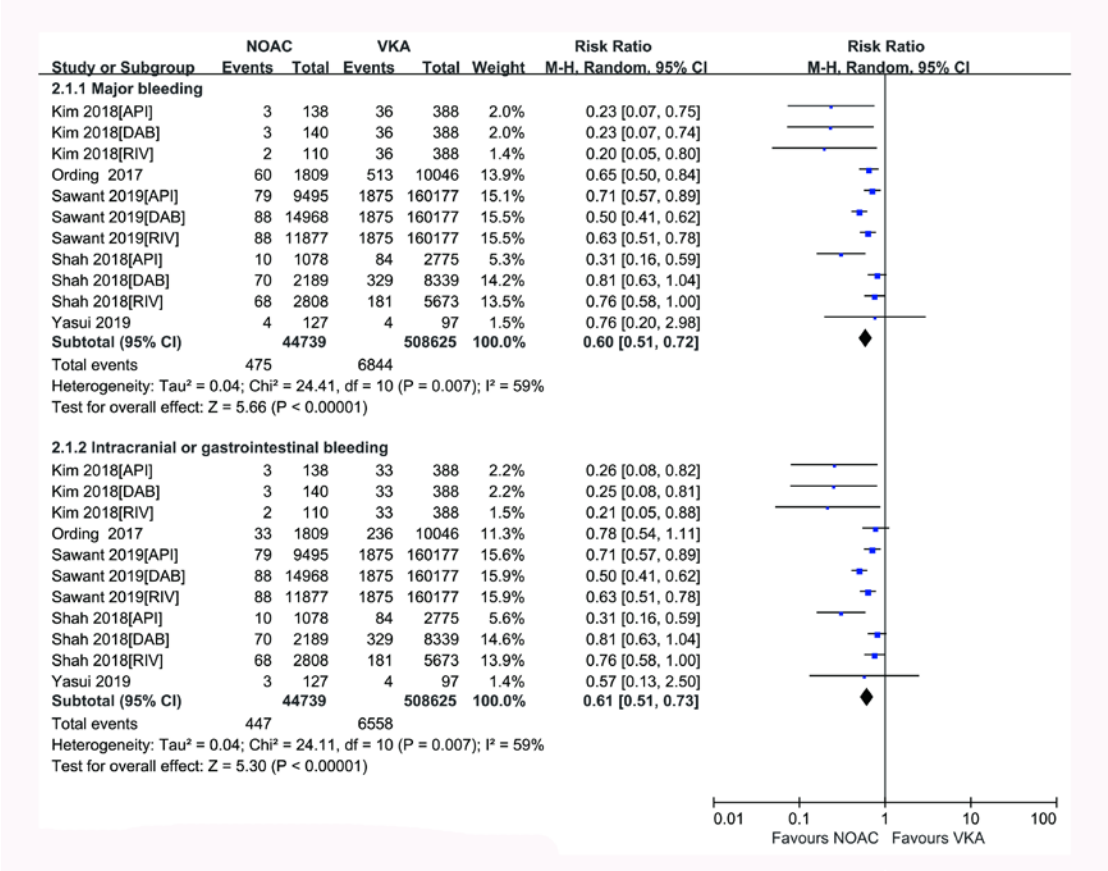

Fig. 2 Forest plot comparing NOACs vs VKAs regarding the safety outcomes in real-world patients with AF and cancer. AF, atrial fibrillation; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; API, apixaban; RIV, rivaroxaban; DAB, dabigatran.

3.4 Sensitivity Analysis

The sensitivity analysis was performed in analyzing the risk of stroke or systemic and major bleeding in NOACs versus VKAs, and the pooled effect results did not change when any individual included study was deleted at a time, which indicated a reliable results.

4. Discussion

In this meta-analysis of real-world observational studies, use of NOACs was associated with significant lower risks of stroke or systemic embolism, ischaemic stroke, VTE, all-cause death, major bleeding and intracranial or gastrointestinal bleeding compared to VKAs in AF patients with cancer.

The results are discordant from previous meta-analyses[6-8],which showed similar or lower rates of thromboembolic and bleeding events for NOACs users versus VKAs in AF patients with cancer. The results of Deng[8] showed the noninferior efficacy and safety of NOACs compared with VKAs but with wide confidence intervals and only borderline significant reductions in ischaemic stroke and major bleeding. Moreover, in Cavallari's meta-analysis[7], there were no significant reductions in thromboembolic events or major bleeding. However, participants in randomized clinical trials do not always represent the patients in real-world settings. Therefore, in our meta-analysis, only the real-world observational studies were included and we have extended the research period to June 2020, with much larger number of patients (232,234) in real-life settings.

5. Conclusions

Based on published real-world studies, NOACs showed lower risks of stroke or systemic embolism, ischaemic stroke, VTE, all-cause death and reduced rates of major bleeding and intracranial or gastrointestinal bleeding compared to VKAs irrespective of NOAC type in patients with AF and cancer.

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