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Non-vitamin K antagonist oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation: a systematic review and meta-analysis

Yunguo Zhou[1] · Wenfeng He[2] · Yue Zhou[3] · Wengen Zhu[4]

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Abstract

Several studies have explored the use of NOACs compared with vitamin K antagonists (VKAs) in patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF); and therefore, we aimed to compare the efficacy and safety outcomes of NOACs with VKAs in this population. We systematically searched the PubMed and Embase databases until August 5, 2019 for studies that compared the effect of NOACs with VKAs in patients with HCM and AF. The risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model. A total of four observational studies were included in this meta-analysis. Overall, compared with VKAs use, the use of NOACs was associated with reduced risks of ischemic stroke (RR 0.49, 95% CI 0.34–0.69), all-cause death (RR 0.44, 95% CI 0.35–0.55), and intracranial hemorrhage (RR 0.43, 95% CI 0.24–0.77). There were no differences in the risks of stroke or systemic embolism, major or clinically relevant bleeding, and gastrointestinal bleeding in patients with NOACs versus VKAs. Re-analyses with a fixed-effects model produced the similar results as the main analyses. For the efficacy and safety outcomes, comparisons of NOACs versus warfarin produced the similar results as those of NOACs versus VKAs. Based on current data from observational studies, compared with VKAs, NOACs had similar or lower risks of thromboembolic and bleeding events in patients with HCM and AF.

Keywords Atrial fibrillation · Hypertrophic cardiomyopathy · Anticoagulants · Efficacy · Safety

Co-authors: Yunguo Zhou, Wenfeng He, and Yue Zhou.

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✉ Yunguo Zhou
zhouyunguo839@163.com

✉ Wengen Zhu
18170044224@163.com

[1] Pediatric Heart Disease Treatment Center, Jiangxi Provincial Children's Hospital, The Affiliated Children's Hospital of Nanchang University, Nanchang of Jiangxi 330006, China

[2] Jiangxi Key Laboratory of Molecular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang of Jiangxi 330006, China

[3] Department of Children's Ophthalmology, The Second Affiliated Hospital of Nanchang University, Nanchang of Jiangxi 330006, China

[4] Department of Cardiology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou of Guangdong 510080, China

Highlights

- Compared with VKAs, NOACs had similar or lower risks of thromboembolic and bleeding events in patients with HCM and AF.
- The use of NOACs was at least non-inferior to VKAs for stroke prevention in patients with HCM and AF.

Introduction

Hypertrophic cardiomyopathy (HCM) is a common non-ischaemic primary myocardial disease, resulting in increased risks of stroke and death. Atrial fibrillation (AF) is the most common cardiac arrhythmia, which may greatly increase the mortality and morbidity, and result in a lot of unnecessary medical wastes and additional costs of care [1]. AF is commonly observed in patients with HCM and associated with elevated risks of thromboembolic events [2, 3]. The stroke-scoring systems such as the CHA2DS2-VASc tool

for stroke prediction have not completely been validated in HCM patients with AF [4, 5]. Due to the increased thromboembolic and bleeding risks, current guidelines recommend the lifelong oral anticoagulant therapy in HCM patients who develop AF without contraindications, regardless of the stroke-scoring systems [6]. The use of vitamin K antagonists (VKAs) is effective in this population [7], but have several shortcomings including variations in medication dosage, narrow therapeutic window, frequent international normalized ratio monitoring, and interactions with other foods or drugs.

Several randomized clinical trials (RCTs) have demonstrated that non-vitamin K antagonist oral anticoagulants (NOACs) are at least as effective as VKAs for stroke prevention, and even have a better safety profile in AF patients [8–11]. However, HCM patients are not included in these landmark RCTs. Data on the use of NOACs in AF patients could not be extrapolated to patients with AF and HCM directly because different forms of structural abnormalities in the heart may lead to different responses to anticoagulant therapy. The assumed role of NOACs in HCM patients with AF remains unknown because of the extremely limited data. Despite these, the results from the observational studies would provide some lights into the use of NOACs compared with VKAs in patients with HCM and AF [12–15], which may have great clinical significance in guiding the use of anticoagulants in this population. Therefore, we performed a meta-analysis to compare the efficacy and safety outcomes of NOACs with VKAs in patients with HCM and AF.

Methods

In this meta-analysis, the whole process was established according to the Cochrane handbook for systematic reviews [16]. The protocol and reporting of the results adhere to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [17]. Only the published studies were included in this meta-analysis; and therefore, the ethical approval was not warranted.

Eligibility criteria

We included studies if they met the following criteria: (1) study population-patients with HCM and AF. (2) Interventions: any NOAC (dabigatran, rivaroxaban, edoxaban or apixaban; any dose) versus VKAs (warfarin, coumadin, acenocoumarol, or phenprocoumon). (3) Outcomes: studies reported at least one of the efficacy or safety outcomes. Efficacy outcomes included stroke or systemic embolism (SSE), ischemic stroke (IS), and all-cause death; and safety outcomes included major or clinically relevant bleeding, intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeding. We adopted the definitions of outcomes from the original studies. (4) Study design-observational studies. (5) Effect estimates of the study: propensity score-matched or adjusted risk ratios (RRs) and 95% confidence intervals (CIs).

Studies reporting AF patients undergoing radiofrequency ablation, cardioversion, or left-atrial appendage closure were excluded. Studies with no relevant data such as reviews, case reports, case series, editorials, letters, guidelines, and meeting abstracts were also excluded. If study participants had a substantial overlap, the study with the longest follow-up or largest sample size could be included.

Literature search

We systematically searched two computer-based databases (PubMed and Embase) from inception to August 5, 2019 for studies that evaluated the effect of any NOAC with VKAs in patients with HCM and AF. The following four types of search terms (and their similar terms) were combined by using the Boolean operator "and": *hypertrophic cardiomyopathy*, *atrial fibrillation*, *non-vitamin K antagonist oral anticoagulants*, and *vitamin K antagonists*. The literature search strategy is shown in Supplemental Table 1. In additional, we performed further searches using the reference lists of the retrieved studies for additional studies. No language restrictions for publication were applied in the search.

Study selection and data abstraction

All of the retrieved studies were screened by three researchers (Yunguo Zhou, Wenfeng He, and Yue Zhou) independently. According to the pre-defined inclusion criteria, we first read the titles and abstracts to screen out the potentially available studies, and then reviewed the full texts of these studies in more detail. Discrepancies were resolved by consensus, or resolved by another researcher (Wengen zhu). For each study, we abstracted the following characteristics: the first author and publication year, study design, number of NOACs/warfarin users, and type of NOACs, follow-up time, and the efficacy and safety outcomes. We presented the definitions of AF or HCM in the Supplementary Table 2.

Quality assessment

For the observational studies, the study quality was assessed by using the Newcastle–Ottawa score (NOS), which involved the selection of cohorts, the comparability of cohorts, and the assessment of the outcome [18]. In this meta-analysis, the modified NOS tool was applied to evaluate the study quality (Supplemental Table 3). An NOS score of <6 indicated a low-quality as previously described [19].

Statistical analysis

The Cochrane Q test and I^2 statistic were used to evaluate heterogeneity, where $P < 0.1$ and $I^2 > 50\%$ indicated a substantial heterogeneity, respectively. The RRs and 95% CIs were regarded as the risk estimates. For each study, we calculated the natural logarithm of the RR (Ln[RR]) and its corresponding standard error ($SE_{Ln[RR]}$). To estimate the pooled results more conservative, Ln[RR] and $SE_{Ln[RR]}$ were pooled by a random-effects model weighted by the inverse-variance method. Two sensitivity analyses were performed as follows: (1) re-analyses with a fixed-effects model were used; and (2) the efficacy and safety outcomes of NOACs versus warfarin were analyzed solely. The subgroup analysis was not performed because of the limited data. 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 less than 10.

All statistical analyses were performed by using Review Manager version 5.30 software (the Cochrane Collaboration, Copenhagen, Denmark).

Results

Study selection

The steps of literature retrieval are shown in Supplemental Fig. 1. A total of 60 studies were initially identified through the electronic searches. No additional articles were found through the search of the reference lists. Finally, 4 observational studies were included in this meta-analysis [12–15].

The baseline characteristics of these included studies were presented in Table 1. Two studies were from Korea [12, 15], 1 study from America [14], and 1 study from Spain [13]. Only the study of Dominguez et al. [13] used acenocoumarol as the reference, whereas warfarin was regarded as controls in other included studies [12, 14, 15]. The follow-up time of the included studies ranged from 0.6 to 5.3 years. All of the included studies had an acceptable quality with an NOS score of ≥ 6.

Efficacy and safety of NOACs versus VKAs

Efficacy

As shown in Fig. 1, compared with VKAs use, the use of NOACs was significantly associated with a reduced risk of IS (RR 0.49, 95% CI 0.34–0.69; $P < 0.0001$) and all-cause death (RR 0.44, 95% CI 0.35–0.55; $P < 0.00001$). We observed no difference in the rate of SSE (RR 0.94, 95% CI 0.73–1.21; $P = 0.63$) in patients with NOACs versus VKAs. In this part, no evidence of heterogeneity was found across the included studies (all $I^2 = 0\%$).

Safety

As presented in Fig. 2, compared with VKAs use, the use of NOACs was significantly associated with a decreased risk of ICH (RR 0.43, 95% CI 0.24–0.77; $P = 0.004$; $I^2 = 2\%$). There were no differences in the risks of major or clinically relevant bleeding (RR 0.76, 95% CI 0.46–1.26; $P = 0.29$; $I^2 = 57\%$) and GI bleeding (RR 0.82, 95% CI 0.58–1.10; $P = 0.17$; $I^2 = 23\%$) in patients with NOACs versus VKAs.

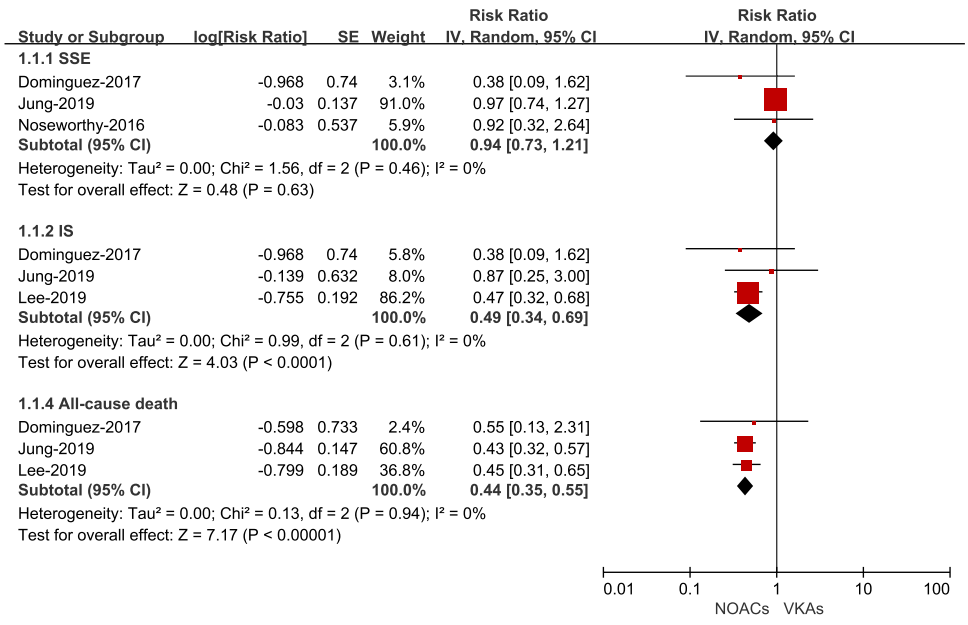

Fig. 1 Random-effects model for comparing the efficacy outcomes of NOACs with VKAs in patients with AF and HCM. *AF* atrial fibrillation, *HCM* hypertrophic cardiomyopathy, *NOACs* non-Vitamin K antagonist oral anticoagulants, *VKAs* vitamin K antagonists, *SSE* stroke or systemic embolism, *IS* ischemic stroke, *CI* confidence interval, *SE* standard error, *IV* inverse of the variance

Sensitivity analysis

For the efficacy outcomes of NOACs versus VKAs, re-analyses with a fixed-effects model produced similar results as the main analyses (Supplemental Fig. 2). For the safety outcomes, the use of NOACs versus VKAs reduced the risks of major or clinically relevant bleeding (RR 0.75, 95% CI 0.59–0.96; $P=0.02$) and ICH (RR 0.43, 95% CI 0.24–0.76; $P=0.004$), but not GI bleeding (RR 0.81, 95% CI 0.62–1.06; $P=0.12$) (Supplemental Fig. 3). We compared the efficacy and safety outcomes of NOACs with warfarin solely. As shown in Figs. 3 and 4, the pooled results did not change after we excluded the study of Dominguez et al. [13].

Discussion

In the present study, we first conducted a meta-analysis to compare the effect of NOACs versus VKAs in patients with HCM and AF. Our pooled data indicated that compared with VKAs use, the use of NOACs was associated with the reduced risks of IS, all-cause death, and ICH. There were no differences in the risks of SSE, major or clinically relevant bleeding, and GI bleeding in patients with NOACs versus VKAs. Re-analyses with a fixed-effects model produced the similar results as the main analyses. For the efficacy and safety outcomes, comparisons of NOACs versus warfarin produced the similar results as those of NOACs versus VKAs. Overall, in patients with HCM and AF, compared with VKAs, NOACs had similar or lower risks of thromboembolic and bleeding events and posed a reduced risk of all-cause death. Based on the published real-world studies, the use of NOACs was at least non-inferior to VKAs for stroke prevention in patients with HCM and AF.

Prior studies have indicated that VKAs such as warfarin, are the effective anticoagulants for reducing thromboembolic and bleeding events in patients with HCM and AF [7]. At present, there still have no RCTs to assess the role of NOACs in this high-risk population. Based on results from the previous studies taken together with our findings, the use of NOACs was associated with a lower risk of all-cause death compared with VKAs, especially for reducing the composite of fatal cardiovascular events [12]. NOACs might be effective and safe for stroke prevention in patients with HCM and AF. Jung et al. [12] reported that NOACs had a lower rate of all-cause death than VKAs in patients with HCM and AF irrespective of the NOAC type and dose. In addition, although the quality of life was similar, NOACs users had a higher treatment satisfaction than VKAs users [13]. In the post hoc analysis of RE-LY trial, dabigatran is superior to warfarin in reducing the efficacy outcomes in AF patients with left ventricle hypertrophy assessed by electrocardiogram [20]. Although this study did not examine the role of NOACs in AF patients with HCM directly, data

Table 1 Baseline characteristics of the included studies

Study (first author-year)	Source of participants	Age (years)	Sex (%males)	No. of NOACs/VKAs users	Type of NOACs (%)	Type of VKAs (%)	Follow-up time (years)	NOS
Lee (2019)	Korean Health Insurance Review and Assessment Service database, 2013–2016	Mean 66.9	41.1	Before PS matching: 1405/922; After PS matching: 1398/1001	DA (21.6%), RIV (38%), API (26.6%), EDO (13.8%); both standard and reduced dose	Warfarin	1.6	7
Jung (2019)	Korean National Health Insurance Service database, 01/2011–12/2016	Mean 69.6	55.7	Before PS matching: 2302/1188; After PS matching: 1504/955	DA (30.6%), RIV (38.7%), API (25.4%), EDO (5.3%); both standard and reduced dose	Warfarin	1.3	8
Dominguez (2017)	Spanish Inherited Cardiac Disease Units, 01/2011–02/2016	Mean 61	59.4	99/433	DA (29.3%), RIV (47.5%), API (23.2%); both standard and reduced dose	Acenocoumarol	5.3	7
Noseworthy (2016)	U.S. commercial insurance database, 10/2010–04/2015	Median 67	65.4	568/859	DA (NA), RIV (NA), API (NA); both standard and reduced dose	Warfarin	0.6	7

AF atrial fibrillation, *NOACs* non-Vitamin K antagonist oral anticoagulants, *DA* dabigatran, *RIV* rivaroxaban; *API* apixaban, *EDO* edoxaban, *VKAs* vitamin K antagonists, *SSE* stroke or systemic embolism, *TIA* transient ischaemic attack, *MI* myocardial infarction, *PS* propensity score, *NOS* Newcastle–Ottawa Scale, *NA* not available

*Any event that led to death within 1 month of its occurrence was considered a fatal event

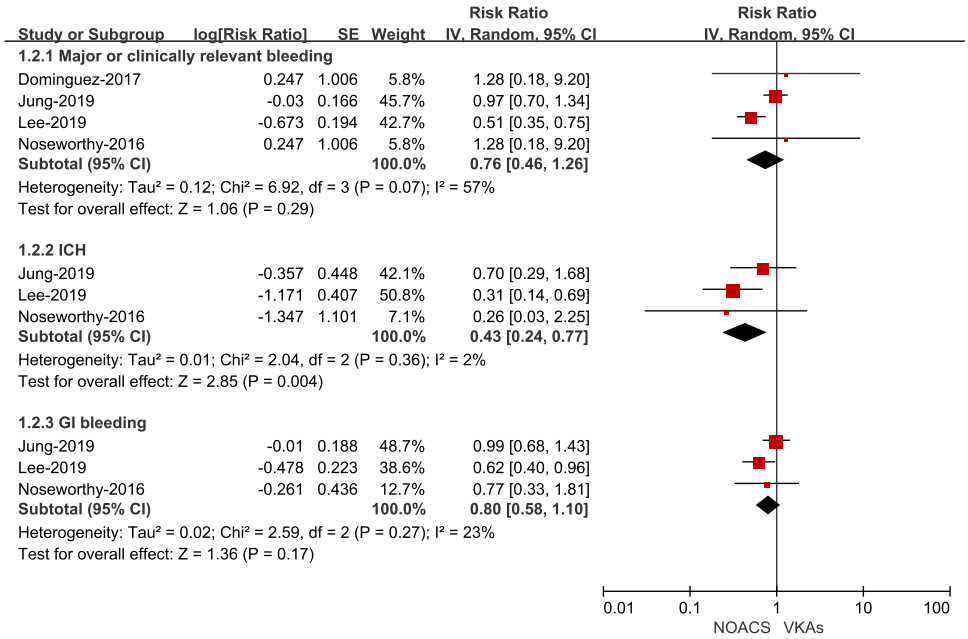

Fig. 2 Random-effects model for comparing the safety outcomes of NOACs with VKAs in patients with AF and HCM. *AF* atrial fibrillation, *HCM* hypertrophic cardiomyopathy, *NOACs* non-Vitamin K antagonist oral anticoagulants, *VKAs* vitamin K antagonists, *ICH* intracranial hemorrhage, *GI* gastrointestinal, *CI* confidence interval, *SE* standard error, *IV* inverse of the variance

from this study still suggested that AF patients with HCM might benefit from the treatment of NOACs [20].

All guidelines from different organizations including the American College of Cardiology, American College Of Cardiology Foundation, American Heart Association, European Society Of Cardiology, and Heart Rhythm Society uniformly recommend the lifelong oral anticoagulant therapy in HCM patients with AF [6, 21–25]. However, the recommendations for NOACs in HCM patients with AF remain unaligned. In 2011 American College Of Cardiology Foundation/American Heart Association guidelines, direct thrombin inhibitors (i.e., dabigatran) could be considered; however, evidence is unavailable [25]. The 2014 European Society Of Cardiology HCM guidelines proposed that NOACs could be recommended as the second-line drugs in patients with HCM and AF; [6] and the 2016 European Society Of Cardiology AF guidelines discuss the use of either VKAs or NOACs [26]. Since current recommendation for warfarin in patients with AF and HCM arises from observational data [7], our meta-analysis could give some confidences to clinicians when selecting the NOACs in this population. At least, the use of NOACs is a convenient anticoagulant choice that do not need the monitoring, and appears to be superior to VKAs in reducing the risk of death. As the use of NOACs becomes more widespread,

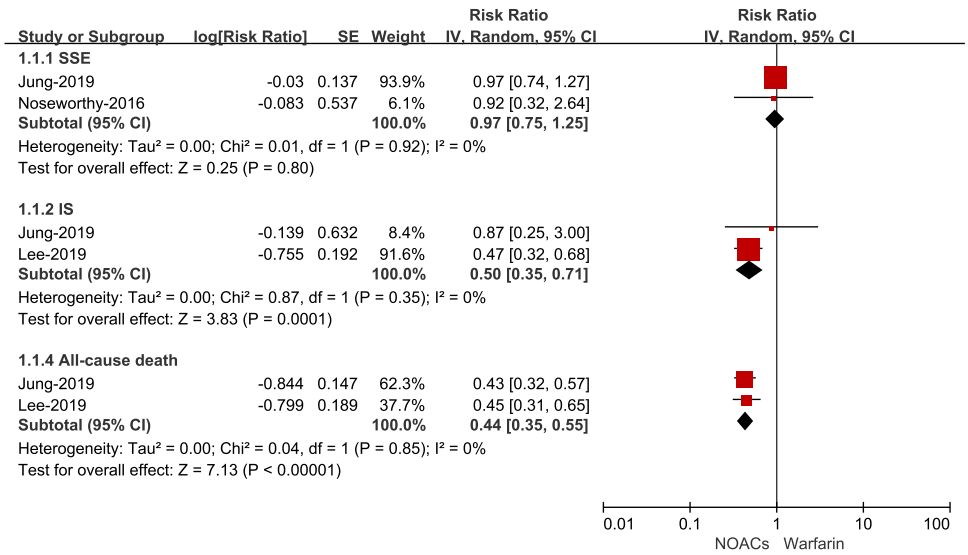

Fig. 3 Random-effects model for comparing the efficacy outcomes of NOACs with warfarin in patients with AF and HCM. *AF* atrial fibrillation, *HCM* hypertrophic cardiomyopathy, *NOACs* non-Vitamin K antagonist oral anticoagulants, *SSE* stroke or systemic embolism, *IS* ischemic stroke, *CI* confidence interval, *SE* standard error, *IV* inverse of the variance

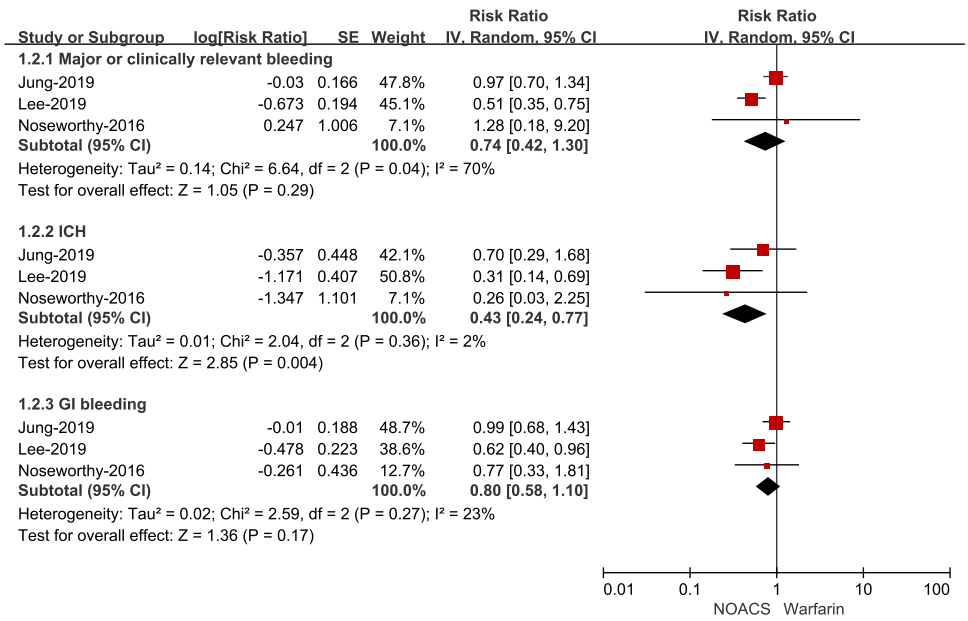

Fig. 4 Random-effects model for comparing the safety outcomes of NOACs with warfarin in patients with AF and HCM. *AF* atrial fibrillation, *HCM* hypertrophic cardiomyopathy, *NOACs* non-Vitamin K antagonist oral anticoagulants, *ICH* intracranial hemorrhage, *GI* gastrointestinal, *CI* confidence interval, *SE* standard error, *IV* inverse of the variance

further studies should take more factors into consideration to confirm our findings before arriving at a definitive conclusion.

Limitations

We acknowledged several limitations in this meta-analysis. First, some comparisons between NOACs versus warfarin were probably underpowered in terms of the limited sample size and small number of events. Second, we did not perform the subgroup analysis based on the type or dosage of NOACs due to the limited data. Third, the time in the therapeutic range of warfarin users was not considered. Fourth, due to the real-world data, the residual confounders should be considered when interpretation of our current results. Finally, HCM is a complex, genetic disease with a wide variety of phenotypes, ranging form apical variants to HCM with or without an outflow tract gradient, end-stage dilated cardiomyopathy and isolated apical aneurysms. The attendant risks of cardioembolic events may differ widely according to the phenotypes. Further study should address this in their analyses. Based on these limitations, we should interpret these findings cautiously, and these findings can not be completely generalizable to all HCM patients in clinical practice.

Conclusions

Based on current data from observational studies, compared with VKAs, NOACs had similar or lower rates of thromboembolic and bleeding events in patients with HCM and AF. NOACs might be reasonable alternatives to VKAs in patients with HCM and AF. These findings should be confirmed by including more prospective studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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