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Clinical outcomes in patients with atrial fibrillation receiving amiodarone on NOACs vs. warfarin

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Abstract

Purpose Amiodarone is a potent inhibitor of the CYP450:3A4 and inhibitor of the P-glycoprotein, both of which metabolize new oral anticoagulants (NOACs). Patients who are on NOACs and are concomitantly treated with amiodarone may have a higher risk of major bleeding according to recent retrospective trials. Whether this increased risk outweighs the benefits of NOACs compared to warfarin is unknown. We aimed to compare clinical outcomes between NOACs and warfarin in patients with atrial fibrillation (AF) being treated with amiodarone.

Methods We performed a systematic review of MEDLINE, Cochrane, and Embase for randomized controlled trials that compared NOACs to warfarin for prophylaxis of ischemic stroke/thromboembolic events (TEs) in patients with AF and reported outcomes on TE, major bleeding, and intracranial bleeding (ICB). Risk ratio (RR) and 95% confidence intervals were measured using the Mantel-Haenszel method. Fixed effects model was used, and if heterogeneity (I2) was > 25%, effects were analyzed using a random model.

Results A total of four studies comparing NOACs to warfarin were included in the analysis. The total number of patients on amiodarone was 6197. Mean follow up was 23 ± 5 months. No statistically significant difference for TE prevention (RR, 0.73; 95% CI 0.50–1.07), major bleeding (RR, 1.02; 95% CI 0.68–1.53), or ICB outcomes (RR, 0.58; 95% CI 0.22–1.51) between patients on NOACs + amiodarone when compared to patients on warfarin + amiodarone.

Conclusion Among patients with AF taking amiodarone, there is no increased risk of stroke, major bleeding, or ICB with NOACs compared to warfarin.

Keywords Atrial fibrillation · New oral anticoagulants · Vitamin K antagonists · Amiodarone · Clinical outcomes

Abbreviations

AF	atrial fibrillation
ARISTOTLE	apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial
CYP384	cytochrome p-450 3A4
ENGAGE AF-TIMI 48	effective anticoagulation with factor Xa next generation in atrial fibrillation trial
ICB	intracranial bleeding
INR	internationalized normalized ratio
LSPAF	long-standing persistent atrial fibrillation
NVAF	non-valvular atrial fibrillation
NOAC	new oral anticoagulant
OAC	oral anticoagulation
P-gp	P-glycoprotein
RE-LY	randomized evaluation of long-term anticoagulation therapy trial
ROCKET AF	the rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin k antagonism for prevention of

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	stroke and embolism trial in atrial fibrillation
TE	ischemic stroke/thromboembolic events
VKA	vitamin K antagonist

1 Introduction

The prevalence of atrial fibrillation (AF) in the United States is projected to exceed 10 million by 2050 [1]. Early pivotal trials demonstrated the efficacy of vitamin K antagonists (VKAs) for prevention of thromboembolic events (TEs) in patients with non-valvular AF (NVAF) and were mainstay treatment until the advent of the new oral anticoagulants (NOACs): dabigatran, rivaroxaban, apixaban, and edoxaban. The main drawback associated with VKAs is the need for constant monitoring due to their multiple drug-drug interactions and unpredictable pharmacokinetic and pharmacodynamic properties, which has often been attributed to the main cause of medication non-adherence [2]. On the other hand, the NOAC's predictable pharmacologic properties allow fixed-dose administration without the need of routine monitoring, thus improving adherence and quality of life in patients with NVAF [3, 4]. Additionally, NOACs have demonstrated to be at least non-inferior to VKAs in stroke prevention, with a reduced risk of bleeding, such as intracranial hemorrhage [5–8].

Amiodarone is the most commonly used antiarrhythmic in patients with AF, and up to 11% of patients treated with NOACs are also receiving amiodarone [9–11]. Importantly, amiodarone is a potent CYP450-3A4 and P-glycoprotein inhibitor, both of which metabolize NOACs [12]. Although no significant impact of amiodarone on the efficacy of NOAC has been established, a recently published study reported a higher risk of major bleeding and intracranial bleeding in patients who are concomitantly treated with amiodarone and NOACs as compared to patients on NOACs alone [13]. Nonetheless, there is no evidence from prospectively randomized trial supporting this finding. Additionally, it is currently unknown whether or not this increased risk of bleeding surpasses the risk of bleeding associated with concomitant use of amiodarone and warfarin use, in which case concurrent use of amiodarone and NOACs would result in a net clinical hazard.

In this meta-analysis, we aimed to compare clinical outcomes between NOACs and the vitamin K antagonist warfarin in patients with AF being treated with amiodarone.

2 Methods

2.1 Search strategy

We searched PubMed, Embase, and Cochrane Central Register of Clinical Trials using the terms *Atrial Fibrillation AND (Bleeding OR Stroke OR embolism OR thrombosis) AND (Dabigatran OR Rivaroxaban OR Edoxaban OR Apixaban) AND (Warfarin OR Vitamin K antagonist)* under clinical trials. Our search was limited to humans in peer-reviewed journals from 1990 to September 2017. No language restriction was applied. The reference lists of identified articles were also reviewed (Fig. 1).

2.2 Selection criteria

Studies had to fulfill the following criteria to be included in the analysis: (1) the study was designed in a randomized controlled fashion; (2) the population was composed of patients with non-valvular AF who were assigned to receive NOACs or VKAs; (3) information about the concurrent use of amiodarone was readily available; (4) trials included efficacy and safety outcomes as part of their respective analyses; (5) the study provided enough data to calculate risk ratios (RR). The PRISMA statement for reporting systematic reviews and meta-analyses was applied to the methods of this study.

3 Data extraction and quality assessment

Two authors (R.A and J.R) searched the studies and extracted the data independently and in duplicate. Data was extracted using standardized protocol and reporting forms. Disagreements were resolved by consensus. We extracted characteristics of each study including methodology and baseline patient demographics, comorbidities, use of amiodarone, warfarin and NOACs, acute complications, long-term stroke rate, major bleeding, and intracranial bleeding. If this information was not readily available in the written article, the principal investigator of the study was contacted to provide pertinent information. The quality of reporting of the studies was assessed using standard criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions [14]. This validated instrument for appraising randomized trials measures risk of bias in seven categories: (1) adequate random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Each trial is described as having a high, low, or unclear risk of bias in each of the seven domains [14].

4 Primary and secondary outcomes

The primary outcomes were risk of thromboembolic events (TEs), major bleeding, and intracranial bleeding (ICB) in patients with atrial fibrillation (AF) being treated with amiodarone taking NOACs or VKAs.

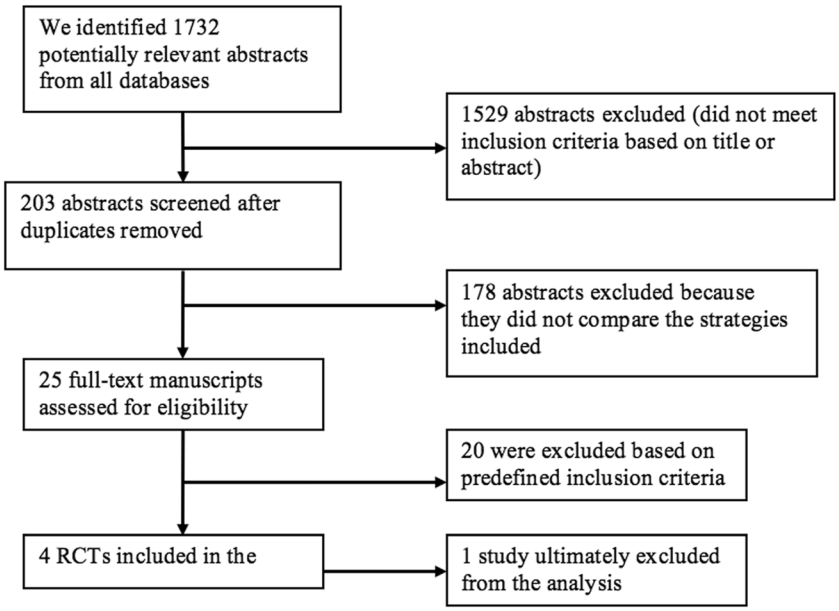

Fig. 1 Selection of studies

5 Statistical analysis

Descriptive statistics are presented as means and standard deviations (SDs) for continuous variables and number of cases (*n*) and percentages (%) for dichotomous and categorical variables. Statistical analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using Review Manager (RevMan), version 5.3, the Cochrane Collaboration, 2014. Heterogeneity was assessed using the I^2 statistics, which is the proportion of total variation observed among the studies attributable to differences between studies rather than sampling error (chance). Data were summarized across treatment arms using the Mantel-Haenszel risk ratio (RR) random-effects model. We considered I^2 less than 25% as low and I^2 greater than 75% as high. We used fixed effects models for analyses with low heterogeneity, whereas random-effects model of DerSimonian and Laird was used if $I^2 > 25\%$.

6 Sensitivity analysis

All analyses were performed using the intention-to-treat principle. Publication bias was estimated visually by funnel plots. If any bias was observed, further bias quantification was measured using the Begg–Mazumdar test, Egger test, and the Duval and Tweediés trim and fill test. Furthermore, the "left-out method" was used in order to assess specific impact of each study in the analysis.

7 Results

7.1 Study selection

A total of 1732 articles were identified, out of which 1529 did not meet inclusion criteria based on article and abstract evaluation (including 100 duplicate abstracts). After evaluation of the 203 abstracts, a total of 178 abstracts were excluded because they did not compare the strategies included in the present study. Twenty-five full-text manuscripts were assessed for eligibility, out of which 20 were excluded based on predefined inclusion criteria. One study was ultimately excluded from the final analysis since it did not include amiodarone use data [15]. Finally, 4 studies enrolling a total of 71,683 patients were included in the present analysis. Given that two doses of dabigatran and edoxaban were included in randomized evaluation of long-term anticoagulation therapy therapy (RE-LY) and effective anticoagulation with factor Xa next generation in atrial fibrillation trial (ENGAGE AF-TIMI 48), only patients receiving the current recommended doses of these medications (i.e., edoxaban 60 mg daily and dabigatran 150 mg bid) were included, yielding a total of 6197 receiving either NOACs or VKAs and amiodarone [5–8]. All of the included studies used warfarin as the selected VKA, and analysis in this trial was based on the results for this VKA. Post hoc analysis data missing from the original manuscript was used in patients with NVAF for the rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF), apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial (ARISTOTLE), and ENGAGE AF-TIMI 48

Fig. 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study, according Cochrane Handbook for Systematic Reviews of Interventions

trial with the purpose of analyzing the effect of amiodarone on the specified clinical endpoints (Fig. 1) [9–11].

8 Quality assessment and publication bias

Three of the studies included in this meta-analysis had a "low risk" for bias due to their randomized double-blind design, with the RE-LY trial considered to be at "unclear risk" for detection and performance bias due to its open-label design. Overall, all studies showed low risk of bias (Figs. 2 and 3). Funnel plots did not suggest publication bias.

9 Baseline characteristics data analysis

The safety and efficacy in clinical outcomes between NOACs and warfarin in patients with AF being treated with amiodarone were analyzed from four RCTs that enrolled a total of 71,683 patients (mean age 72 ± 8 years; male 62%). Mean follow up was 23 ± 5 months. A total of 3212 patients were concomitantly on NOAC and amiodarone, with 3085 patients concomitantly on warfarin and amiodarone.

Time in therapeutic range (TTR) for patients receiving warfarin was > 50% in all included studies, with lower TTR in patients receiving amiodarone compared to patients without amiodarone or on other antiarrhythmic drugs. No statistical difference was reported for the baseline variables in the four included studies.

10 Primary outcome

The total number of patients on amiodarone was 6197. There was no statistical difference for TE prevention (RR, 0.73; 95% CI 0.50–1.07), major bleeding (RR, 1.02; 95% CI 0.68–1.53), and ICB (RR, 0.58; 95% CI 0.22–1.51) between patients on NOACs when compared to patients on warfarin in patients with AF being treated with amiodarone (Fig. 4).

11 Sensitivity analysis

We examined every baseline characteristic (Table 1), and none of them was associated with a significant impact on the results of this meta-analysis. Analysis assessing exclusively factor Xa inhibitors did not demonstrate difference in the efficacy and safety outcomes (Figs. 1 and 2 in the Supplementary Data).

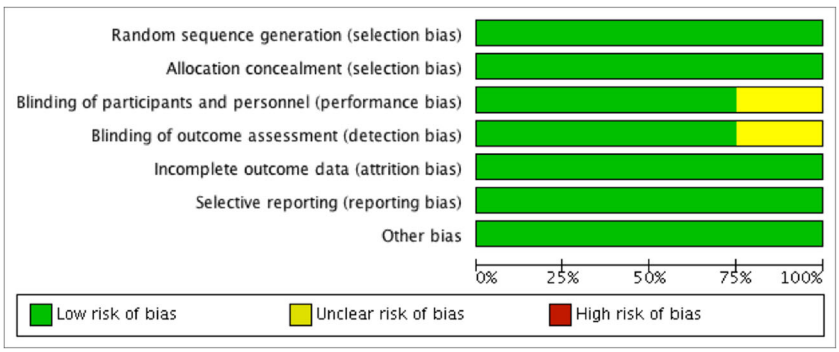

Fig. 3 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies, according Cochrane Handbook for Systematic Reviews of Interventions

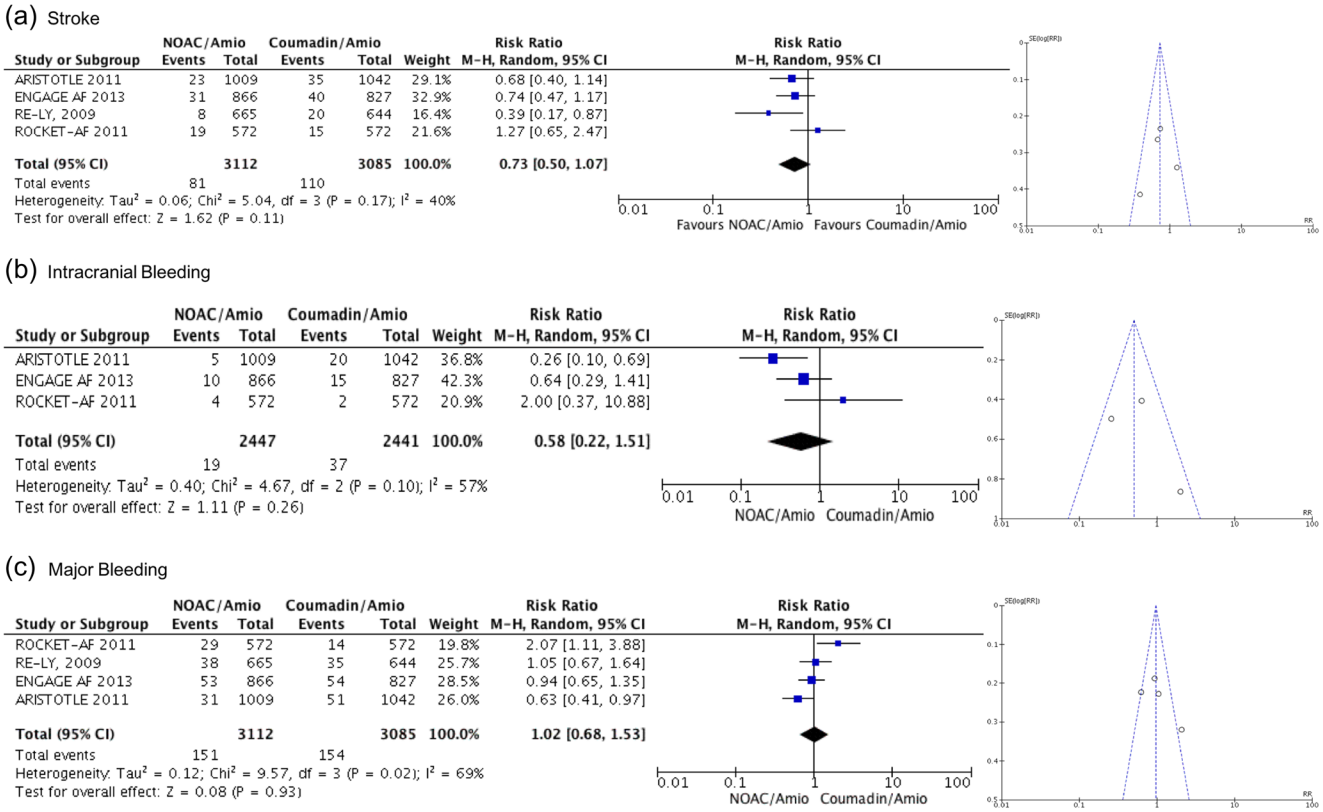

Fig. 4 Forrest plots and funnel plots for the comparative analyses of clinical outcomes in patients concomitantly using NOAC and amiodarone vs Coumadin and amiodarone. **a** Stroke. **b** Major bleeding, **c** Intracranial bleeding

12 Discussion

Currently available data demonstrate that NOACs are at least non-inferior (with a slight superiority for the entire NOAC group) when compared to warfarin for the prevention of stroke or systemic embolism, with a significant reduction in intracranial hemorrhage, total mortality, and major bleeding as compared to warfarin. Nonetheless, drug interactions could possibly have an impact on these positive results; particularly, amiodarone is known to interfere with hepatic metabolism of both NOACs and amiodarone. Although post hoc analyses of the ENGAGE AF, ARISTOTLE, and ROCKET AF trial have been published [9–11], to the best of our knowledge, this is the first meta-analysis including data for all four currently available NOACs. Importantly, we included 4 randomized studies, with a large number of patients and a mean follow up of 23 months. The pertinent findings of this study were as follows:

1. No statistically significant difference for TE prevention (RR, 0.73; 95% CI 0.50–1.07) was found in patients receiving NOACs + amiodarone vs. patients receiving warfarin + amiodarone.
2. The combination of NOACs + amiodarone demonstrated a similar safety profile to the combination of warfarin + amiodarone, demonstrated by no significant differences in major bleeding (RR, 1.02; 95% CI 0.68–1.53) or ICB (RR, 0.58; 95% CI 0.22–1.51) events (Fig. 4).

Amiodarone, a potent inhibitor of the P-gp transporter and moderate inhibitor of CYP3A4-mediated metabolism, significantly affects metabolism of both warfarin and NOAC, which could have significant impact in clinical outcomes. Amiodarone reduces time in therapeutic range (TTR) among patients taking warfarin [9–11], a measure that effectively predicts proper anticoagulation. As such, higher TTR is predictive of lower risk of stroke and major hemorrhages [16]. Warfarin non-adherence is considered to be the most common cause of explainable aberrant INRs in patients under this medication [17]. However, concurrent amiodarone use is associated with an increased risk of stroke in patients treated with warfarin, probably associated with a lower TTR (mostly below accepted therapeutic range) in this group of patients [9–11]. Our study demonstrated no difference between warfarin and NOACs in the rates of major bleeding, TE, or ICB in a large population of patients with similar characteristics receiving amiodarone (Fig. 4). Nonetheless, NOACs use only (without concurrent amiodarone use) had been previously demonstrated to be associated with a lower risk of these outcomes when compared to warfarin alone [5–8]. This lack of benefit seen with the combination of NOACs and amiodarone could be explained by an increase in the anticoagulant effect of NOACs caused by

Table 1 Baseline characteristics

Clinical trial, year (ref)	RE-LY, 2009		ROCKET-AF, 2011		ARISTOTLE, 2011		ENGAGE AF-TIMI 48, 2013	
AC therapy	Dabigatran 150 mg BID	Warfarin	Rivaroxaban 20 mg daily	Warfarin	Apixaban 5 mg BID	Warfarin	Edoxaban 60 mg BID	Warfarin
Trial design	Open label		Double blinded		Double blinded		Double blinded	
Characteristics								
Patients—no.	6076	6022	7131	7133	9120	9081	7035	7036
Mean follow up—year	2	2	1.9	1.9	1.8	1.8	2.8	2.8
Age—year	71 ± 9	72 ± 9	73 ± 8	73 ± 8	70 ± 7	70 ± 7	72 ± 7	72 ± 7
Male—no. (%)	3840 (63)	3809 (63)	4300 (60)	4301 (60)	5886 (64)	5899 (65)	4366 (62)	4395 (62)
Type of AF—no. (%)								
Paroxysmal	1978 (33)	2036 (34)	1254 (18)	1269 (18)	1371 (15)	1412(16)	1753 (25)	1778 (25)
Persistent/permanent	4097 (67)	3985 (66)	5786 (82)	5762 (82)	7744 (85)	7668 (84)	5282 (75)	5258 (75)
$CHADS_2$ score	2.2 ± 1.2	2.1 ± 1.1	3.5 ± 0.9	3.5 ± 0.9	2.1 ± 1.1	2.1 ± 1.1	2.8 ± 1.0	2.8 ± 1.0
Coexisting condition—no. (%)								
Previous IA/stroke	1233 (21)	1195 (20)	3916 (525)	3895 (55)	1748 (19)	1790 (29)	1976 (28)	1991 (28)
Prior MI	1029 (17)	968 (16)	1182 (17)	1286 (18)	1319 (14)	1266 (14)	844 (12)	774 (11)
Hypertension	4795 (79)	4750 (79)	6436 (91)	6474 (91)	7962 (87)	7954 (88)	6591 (94)	6588 (94)
Diabetes mellitus	1402 (23)	1410 (23)	2878 (40)	2817 (39)	2284 (25)	2263 (25)	2559 (36)	2521 (36)
Heart failure	1934 (32)	1922 (32)	4467 (63)	4441 (62)	3235 (36)	3216 (35)	4097 (58)	4048 (58)
Amiodarone (%)	665 (11)	644 (11)	572 (50)	572 (50)	1009 (11)	1042 (12)	866 (12)	827 (12)
Individual median TTR	–	67 (54–78)	–	58 (43–71)	–	66 (57–77)	–	68 (57–77)

AF atrial fibrillation, *MI* myocardial infarction, *CHADS2* congestive heart failure, hypertension, age > 75, diabetes mellitus and prior stroke or transient ischemic attack, *TTR* time in therapeutic range

amiodarone. Furthermore, Lupercio et al. described no difference in the rate of stroke, major bleeding, and ICB in a meta-analysis of randomized clinical trials when NOACs where used vs concomitant use of amiodarone [18]. Although this result could be interpreted as a major drawback for concurrent NOAC and amiodarone use, this combination is at least as safe as the combination of warfarin and amiodarone, with the added benefit of ease of use, reduced food and drug interactions, and lack of need for monitoring, all of which have a positive impact on patient satisfaction [19]. In turn, patient satisfaction is a strong predictor of adherence to anticoagulant treatment [20]. Furthermore, Briceno et al. showed that stroke prevention with NOACs is superior than warfarin for stroke prevention in patients with non-valvular atrial fibrillation, as evidenced by the results of their meta-analysis as there was a significant difference favoring NOACs for systemic embolism (OR, 0.84; 95% CI, 0.72–0.97; $P = 0.01$), all-cause mortality (OR, 0.89; 95% CI, 0.84–0.94; $P < 0.001$), and safety outcomes (OR, 0.79; 95% CI, 0.65–0.97; $P = 0.026$) compared with warfarin [21]. Therefore, we believe that even though no clinical benefit is seen with the combination of NOACs + amiodarone vs warfarin + amiodarone in our meta-analysis, NOACs should still be the drug of choice in patients with AF receiving amiodarone to increase patient satisfaction and adherence. Most patients receiving amiodarone have paroxysmal AF and have a lower prevalence of structural heart disease [9, 11]. Therefore, physicians should consider antiarrhythmic drugs other than amiodarone in such patients when treated with anticoagulants in order to avoid drug interactions.

13 Limitations

This study has several limitations, many of them common to meta-analyses. First, heterogeneous populations were enrolled across the included studies in this meta-analysis, since different study protocols were used. Nonetheless, due to the high methodological quality of the included studies, we believe our results provide strong evidence on the safety and effectiveness of NOACs in patients with concurrent amiodarone use. Additionally, sensitivity analysis did not reveal any difference among methodologies (Supplementary Figs. 1–2). Second, given that studies were randomized for receiving NOACs or warfarin, but not for amiodarone, a possible selection bias is introduced. Nonetheless, since amiodarone was not the primary medication to be evaluated in the studies and patients were randomized to one of two treatments, no significant differences between patients receiving NOACs and warfarin was found. Although the effect of the addition of amiodarone to NOACs could only be established by a randomized trial (in which patients with need of anticoagulant treatment and antiarrhythmic therapy were randomized to amiodarone vs other antiarrhythmics stratified according to anticoagulant treatment), we believe our results are reassuring both for patients and physicians who deal with concurrent amiodarone and NOACs use. Lastly, in view of the lack of current available data evaluating pharmacokinetic/pharmacodynamic properties, dose of amiodarone/time on amiodarone/BMI, and/or head to head comparison within the NOACs group, the study evaluated NOACs as a group and therefore we believe that they should be treated equally; future studies addressing this important topic might give further information to help the analysis of this group of medications.

14 Conclusions

In this meta-analysis of randomized trials, the concomitant use of amiodarone and NOACs in patients with NVAF appears to be safe and effective as compared with warfarin, as it does not negatively impact clinical outcomes such as TE, major bleeding, and ICB. Although physicians should consider alternative antiarrhythmic drugs in patients treated with anticoagulants for stroke prevention in NVAF, our results are reassuring about the safety and efficacy of this combination.

Author Contributions RA, J.R, and L.D.B designed the original research idea. R.A and J.R searched studies and extracted data independently. J.R., R.A., F.L., J.C.D., R.Q., A.G., A.N., M.J.G., A.K.K, and L.D.B drafted and approved the present manuscript.

Compliance with ethical standards

Conflict of interest Dr. Di Biase is a consultant for Biosense Webster, Boston Scientific, and St. Jude Medical, and has received speaker honoraria/travel from Medtronic, St. Jude Medical, Atricure, EPiEP, and Biotronik. The other authors have no pertinent conflicts of interest to report.

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