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ORIGINAL RESEARCH

Efficacy and Safety of Novel Oral Anticoagulants for Atrial Fibrillation Ablation: An Updated Meta-Analysis

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ABSTRACT

Introduction: Novel oral anticoagulants (NOACs) have been approved for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). A large number of patients are on NOACs when they present for AF ablation. We intended to evaluate the safety and efficacy of NOACs for AF ablation during the periprocedural period by

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performing a meta-analysis of trials comparing NOACs with warfarin.

Methods: Studies comparing NOACs (dabigatran and rivaroxaban) with warfarin as periprocedural anticoagulants for AF ablation were identified using an electronic search. Primary outcomes were: (1) a composite endpoint of stroke, transient ischemic attack (TIA), peripheral arterial embolism, or silent cerebral lesions on magnetic resonance imaging (MRI) and (2) major bleeding complications. A random effects model was used to pool the safety and efficacy data across all included trials.

Results: When compared to warfarin, there was an increased risk of the composite endpoint of stroke, TIA, peripheral arterial embolism, or silent cerebral lesions on MRI with NOACs as periprocedural anticoagulants for AF ablation [odds ratio (OR): 1.69, 95% confidence interval (CI): 1.06–2.68]. Sub-group analysis revealed a higher risk of composite endpoint with dabigatran as a periprocedural anticoagulant for AF ablation (OR: 2.01, 95% CI: 1.19–3.39) whereas the risk was similar with rivaroxaban (OR: 0.90, 95% CI: 0.34–2.41). Sensitivity analysis after excluding silent cerebral lesions on MRI showed there was no increased risk of

thromboembolic events with either dabigatran (OR: 1.69, 95% CI: 0.81–3.51) or rivaroxaban (OR: 0.70, 95% CI: 0.12–4.04). Risk of bleeding with NOACs was similar to warfarin (OR: 0.91, 95% CI: 0.62–1.34).

Conclusion: NOACs are comparable to warfarin in terms of bleeding complications. However, dabigatran therapy is potentially associated with a higher risk of silent cerebral lesions on MRI. The results of this study should be considered as hypothesis-generating and assessed further in prospective randomized clinical studies.

Keywords: Ablation; Atrial fibrillation; Bleeding; Complications; Meta-analysis; Novel oral anticoagulants (NOACs); Thromboembolism

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with an increased risk of mortality, heart failure, and thromboembolic events [1–3]. Warfarin reduces the risk of stroke in moderate to high-risk AF patients [4]. Novel oral anticoagulants (NOACs) have been approved for prevention of stroke and systemic embolism in patients with non-valvular AF (NVAF) [5–8]. Prevention of AF recurrence by radiofrequency ablation (RFA) is a well accepted therapeutic strategy in patients with symptomatic AF [9]. Given the increasing use of NOACs for stroke prevention in AF over the past few years, a large number of patients are already on NOACs when they present for AF ablation [10]. Few studies reported pooled data of safety and efficacy of NOACs as periprocedural anticoagulants for AF ablation [11–13]. To our knowledge, there is no pooled analysis addressing the risk of cerebral microthromboembolism with these procedures.

We performed a meta-analysis of trials comparing the safety and efficacy of NOACs with warfarin in patients undergoing AF ablation.

METHODS

We conducted a systematic review of published literature comparing NOACs with warfarin for AF ablation during the periprocedural period using Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [14]. We searched PubMed, the Cochrane library and Embase for studies comparing NOACs (dabigatran, apixaban, and rivaroxaban) with warfarin as periprocedural anticoagulants for RFA. The searches were extended from January 2009 to May 2014.

We used search terms "dabigatran" AND "ablation", "rivaroxaban" AND "ablation", "apixaban" AND "ablation". Meeting abstracts were searched in Embase. In the Cochrane database, search terms were limited by the term clinical trial. Limiting the search parameters to the English language was applied subsequently. Citations were screened at the title and abstract level and retrieved if they were either presented at conference or published as full reports, compared NOACs with warfarin, and provided information on the outcomes. The full texts of all potential articles were reviewed in detail. The bibliography of retained studies was used to seek additional relevant studies. All observational studies without a control group, case reports, editorials, pilot series, and reviews were excluded.

Inclusion Criteria

We included only studies that involved adult patients undergoing RFA alone and compared the outcomes with periprocedural anticoagulation with warfarin therapy (with or

without heparin bridging) and NOACs. When two similar studies were reported from the same institution or author, the most recent publication was included in the analysis. Inclusion was not limited to prospective studies but was extended to all observational studies including retrospective studies.

Exclusion Criteria

We excluded studies if outcomes of interest were not clearly reported or were impossible to extract or calculate from the published results.

Data Extraction

Data from included studies was extracted onto a pre-formed data extraction paper by two authors (AV, MM) independently. Data was then entered into Review Manager 5.2 for analysis. Data collected included first author, year and journal of publication, study design, inclusion/exclusion criteria, definition of primary and secondary end points, number of subjects included, study population demographics, anticoagulation agent used, type of procedure, and primary outcomes. Disagreement between the reviewers was resolved by discussion.

Study End Points

Primary outcomes were:
1. A composite endpoint of stroke, transient ischemic attack (TIA), peripheral arterial embolism, or silent cerebral lesions on magnetic resonance imaging (MRI)
2. Major bleeding:
   1. Bleeding requiring intervention/hospitalization
   2. Significant pericardial effusion

Statistical Analysis

We performed meta-analysis of primary outcomes using a random effects model of the Mantel–Haenszel method. Odds ratio (OR) estimates and 95% confidence intervals (CI) were used to calculate the overall effect size of both outcomes. Statistical significance for OR was set at $P < 0.05$ (two-tailed) provided the CI did not cross. Heterogeneity was assessed by a χ^2 and I^2 test. Significant heterogeneity was considered present for P values <0.10 and an $I^2 \geq 50\%$. Sensitivity analysis was performed by using a (1) fixed effects and random effects analysis (2) conducting a subgroup analysis (dabigatran vs. warfarin alone, rivaroxaban vs. warfarin) and (3) further subgroup analysis evaluating symptomatic thromboembolic events. Data analysis was performed using RevMan version 5.2.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Using the search key words, we identified 637 papers, of which 29 studies (dabigatran 23, rivaroxaban 6) were selected for the meta-analysis [15–41]. One study which compared NOACs with warfarin for both cardioversion and AF ablation was not included in the pooled analysis [42]. All studies included in the analysis were published between 2011 and 2014 (Fig. 1). Pooled analysis included 7671 patients, of whom 3220 (dabigatran 2629, rivaroxaban 591) were on

NOACs and 4451 were on warfarin. The study characteristics and overall patient demographics are presented in Table 1.

Composite Endpoint

There was no significant heterogeneity among studies when assessed by χ^2 and I^2 tests ($\chi^2 = 11.91$; $P = 0.94$; $I^2 = 0\%$; Fig. 2). Pooled analysis showed that there was an increased risk of the composite endpoint of stroke, TIA, peripheral arterial embolism, or silent cerebral lesions on MRI with NOACs compared to warfarin when used for AF ablation (OR: 1.69, 95% CI: 1.06–2.68, $P = 0.03$; Fig. 3).

Subgroup analysis of studies comparing dabigatran with warfarin for AF ablation showed that dabigatran increased the risk of the composite endpoint (OR: 2.01, 95% CI: 1.19–3.39, $P = 0.009$). Conversely, there was no difference in incidence of the composite endpoints between rivaroxaban and warfarin
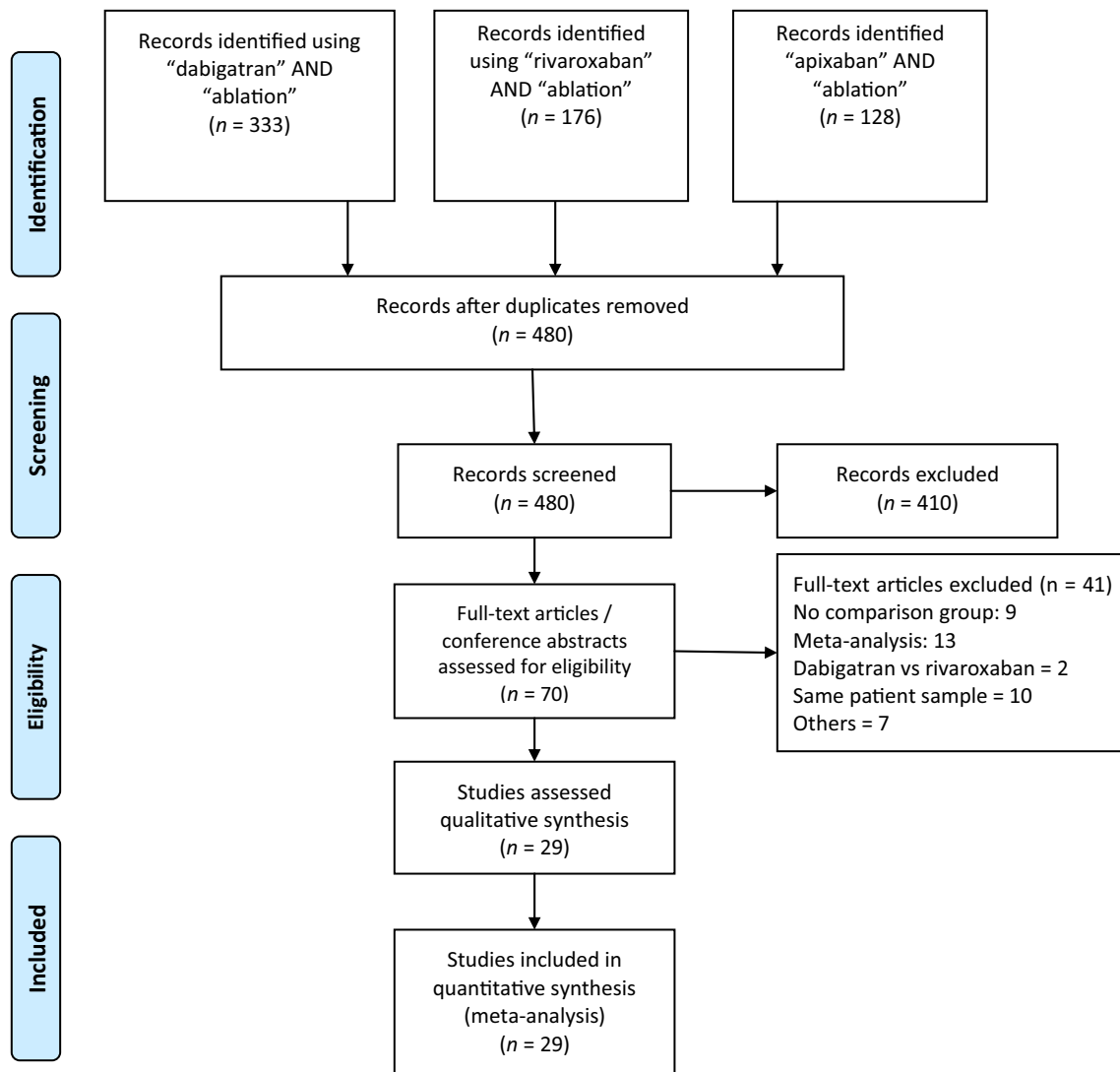
Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow sheet

Table 1 Characteristics of included studies

Study	Year	Publication/meeting	Sample size (NOACs, W)	Mean age [years; (NOACs, W)]	Females,% (NOACs, W)	PAF (%; NOACs, W)	Type of procedure	CHADS2 score (NOACs, W)	HAS-BLED score (NOACs, W)	NOACs: drug, dose (mg)	NOACs held	Warfarin
Arshad [15]	2013	HRS	298, 153	60.7 ± 10	28	67[a]	Abl.	1.3 ± 1.0	2.8 ± 1.0	D 150	Held 12 h pre-procedure and resumed on post-procedure night	Uninterrupted
Bassiouny [16]	2013	Circ EP	376, 623	59, 63	25, 27	57, 55	Abl.	–	–	D 150	1–2 doses held before procedure resumed at conclusion of the procedure	Uninterrupted
Bernard [17]	2013	ACC	(155, 75)[b], 44	(63, 63)[b], 67	–	(46, 57)[b], 50	Abl.	–	–	D 150, R	Held within 24 h pre-procedure and restarted within 24 h post-procedure	Uninterrupted
Ellis [18]	2012	HRS	61, 110	–	–	–	Abl.	1.2 ± 0.2	–	D 150, R	Held 12–48 h pre-procedure, resumed within 4–24 h after sheath pull	Subtherapeutic INR bridged with heparin
Gadiyaram [19]	2013	HRS	54, 128	62.7	24, 24	–	Abl.	–	–	R	Held 2 days before ablation, one dose of lovenox 6 h after hemostasis was achieved and R was resumed the next day	Uninterrupted
Haines [20]	2013	JICE	202, 202	60.2, 59.7	26, 31	55, 50	Abl.	1.6 ± 1.3, 1.9 ± 1.4[c]	–	D 150 (1 patient received D 110)	17% received D within 12 h before the procedure, D resumed within 24 h	Therapeutic pre-procedure INR in 80%, remaining bridged with lovenox
Ichiki [21]	2013	PACE	30, 180	57, 60	17, 22	70, 30	Abl.	1.1 ± 1.1, 1.0 ± 1.0	–	D 110–13 patients, D 150–17	Discontinued only on the morning of the procedure, resumed from the evening	Uninterrupted
Imamura [22]	2013	JICE	101, 126	61, 62	25, 30	44, 51	Abl.	0.9 ± 0.9, 1.1 ± 1.0	0.7 ± 0.8, 1.0 ± 0.9	D 110/D 150 depending on patient's condition	Held 12–24 h before and restarted 3 h after the procedure	Warfarin was stopped 3 days before the procedure and unfractionated heparin was administered
Kaiser [23]	2013	JICE	122, 135	58, 64	36, 32	69, 47	LAA abl.	1.2 ± 1, 1.6 ± 1	–	D 150	Held 24–30 h pre-procedure and restarted 4–6 h after hemostasis was achieved	Uninterrupted
Kaseno [24]	2012	Circulation Journal	110, 101	–	–	–	Abl.	–	–	D 110	Held on the morning of the procedure, and resumed on the next morning	Uninterrupted
Khan [25]	2013	ACC	50, 66	56.3, -	39	–	Abl.	1.06, -	–	D 150	Last dose held 24 h prior to the procedure and restarted 6 h after sheath removal	Uninterrupted

Table 1 continued

Study	Year	Publication/ meeting	Sample size (NOACs, W)	Mean age [years; (NOACs, W)]	Females,% (NOACs, W)	PAF (%; NOACs, W)	Type of procedure	CHADS2 score (NOACs, W)	HAS-BLED score (NOACs, W)	NOACs: drug, dose (mg)	NOACs held	Warfarin
Kim [26]	2013	Heart Rhythm	191, 572	61, 61	20, 26	53, 48	Abl.	1.0 ± 0.9, 1.1 ± 1.0	1.0 ± 0.9, 1.1 ± 1.0	D 150	Held after the morning dose on the day before the procedure and resumed 4 h after hemostasis was achieved	Uninterrupted
Konduru [37]	2012	JICE	24, 52	56.6, 60.9	21, 33	21, 44	Abl.	–	–	D 150	Continued without interruption (first 11 patients) or held 2 doses immediately prior to the procedure (last 13 patients). D was continued the evening following the procedure	Uninterrupted
Lakkireddy [27]	2013	JACC	145, 145	60.4, 60.3	21, 21	57, 57	Abl.	1.6 ± 1.4, 1.5 ± 1.3^c	1.2 ± 0.9, 1.1 ± 0.9	D 150	Held on the morning of the procedure, resumed within 3 h after hemostasis	Uninterrupted
Lakkireddy [38]	2014	JACC	321, 321	63, 63	31, 31	49, 49	Abl.	1.16 ± 1.0, 1.18 ± 1.0	1.47 ± 0.9, 1.70 ± 1.0	R 15, 20	Uninterrupted	Uninterrupted
Maddox [28]	2013	JCE	212, 251	62.3, 62.5	24, 33	63, 57	Abl.	0.92 ± 0.88, 0.92 ± 0.85	–	D 150	Morning dose on the day of the ablation procedure; post-procedural dabigatran was administered on the evening of the procedure	Uninterrupted
Mendoza [29]	2012	HRS	60, 58	62.9, 64.0	10, 12		Abl.	1.32, 1.29	1.47, 1.63	D 150	Held only the morning of the procedure and resumed immediately after sheath removal	Uninterrupted
Mohajer [30]	2013	Canadian Journal of Cardiology	43, 95	60, 63	–	69.8, 41.1	Abl.	0.6 ± 0.7, 0.9 ± 0.9	–	D 150 (D 110 in 3 patients)	Held 24 h prior to procedure	Uninterrupted
Nin [31]	2013	PACE	45, 45	61, 61	16, 20	34, 32	Abl.	–	–	D 110	Held on morning of the procedure and resumed 4 h after hemostasis	Uninterrupted
Pavaci [39]	2012	ESC	27, 27	–	–	–	Abl.	–	–	–	–	–
Rowley [40]	2012	HRS	113, 169	63	–	–	Abl.	1.3 ± 1	–	–	Last dose the day before AF ablation and typically restarted the day following ablation	Bridged with enoxaparin
Snipelisky [32]	2012	JICE	31, 125	60.6, 64.6	19.4, 25.6	68, 46	Abl.	0.84, 1.22	–	D 150	Held the dose on the morning of the procedure	Uninterrupted
Snipelisky [41]	2014	HRS	56, 25, 48	–	–	–	Abl.	–	–	D, R	–	–

Table 1 continued

Study	Year	Publication/ meeting	Sample size (NOACs, W)	Mean age [years; (NOACs, W)]	Females,% (NOACs, W)	PAF (%; NOACs, W)	Type of procedure	CHADS2 score (NOACs, W)	HAS-BLED score (NOACs, W)	NOACs: drug, dose (mg)	NOACs held	Warfarin
Stepanyan [33]	2014	JICE	89, 98, 114	59, 60, 62.9	42, 34, 33	70, 81, 64	Abl.	–	–	D, R	The last dose of D was given the morning 1 day prior to the procedure, and the last dose of R was given the evening 2 days prior. Bridged with heparin NOAC was resumed at 8:00 a.m. on the morning after the procedure	Uninterrupted
Tao [34]	2014	HRS	70, 70	66	30	73	Abl.	–	–	R 10, 15	Uninterrupted	Uninterrupted
Ueno [35]	2014	HRS	79, 15, 45	61	25	–	Abl.	–	–	D, R	–	–
Yamaji [36]	2013	Clinical Drug Inv.	106, 106	60, 61	25, 24	65, 64	Abl.	1.8 ± 1.6, 1.7 ± 1.6	–	D 110 (36), D 150 (70)	Held on the day of procedure, resumed 3 h after the completion	Uninterrupted

Abl. ablation, *ACC* American College of Cardiology, *D* dabigatran, *ESC* European Society of Cardiology, *HRS* Heart Rhythm Society, *INR* international normalized ratio, *NOACs* novel oral anticoagulants, *PAF* paroxysmal atrial fibrillation, *R* rivaroxaban, *W* warfarin

[a] Total PAF in study cohort

[b] NOACs (dabigatran, rivaroxaban)
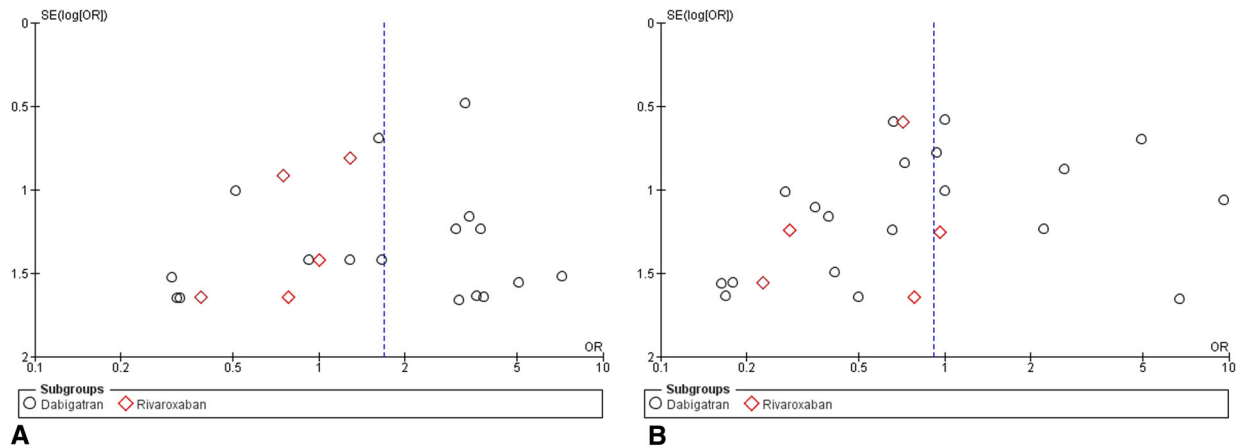
[c] CHADS2-Vasc score

Fig. 2 Funnel plot to assess publication bias for **a** the composite endpoint of stroke, TIA, peripheral arterial embolism, or silent cerebral lesions on MRI **b** major bleeding

for AF ablation (OR: 0.90, 95% CI: 0.34–2.41, $P = 0.84$). Sensitivity analysis was performed by using a fixed effects analysis method. Effect size did not change with fixed effects analysis.

To assess whether the time of holding NOAC affected the composite endpoint, exclusion sensitivity analysis was performed by including only those studies in which an NOAC was held on the day of AF ablation. This analysis showed that dabigatran was associated with increased risk of the composite endpoint (OR: 2.40, 95% CI: 1.10–5.22, $P = 0.03$). On the other hand, use of rivaroxaban did not increase the risk of thromboembolic complications (OR: 1.1, 95% CI 0.30–4.79, $P = 0.79$).

In four studies [18, 20, 22, 40], heparin was used for bridging during the periprocedural period for anticoagulation. To assess whether uninterrupted warfarin affected the composite endpoint, sensitivity analysis was conducted by omitting studies in which heparin bridging was used. Pooled analysis of the remaining studies revealed that dabigatran was associated with increased risk of the composite endpoint (OR: 1.81, 95% CI: 1.02–3.19, $P = 0.04$) whereas rivaroxaban therapy did not increase the risk of thromboembolic complications (OR: 0.90, 95% CI: 0.34–2.41, $P = 0.84$).

Exclusion sensitivity analysis including only symptomatic thromboembolic complications (stroke, TIA, and peripheral arterial embolism) was performed after omitting studies reporting silent cerebral lesions on MRI. Sensitivity analysis did not reveal any difference between NOACs and warfarin (OR: 1.48, 95% CI: 0.75–2.91, $P = 0.25$; Fig. 4). Subgroup analysis did not show any increased risk with either dabigatran or rivaroxaban for AF ablation (OR: 1.69, 95% CI: 0.81–3.51, $P = 0.16$ and OR: 0.70, 95% CI: 0.12–4.04, $P = 0.69$, respectively; Fig. 4).

Major Bleeding

There was no significant heterogeneity across the studies ($\chi^2 = 23$, degrees of freedom = 23; $P = 0.46$; $I^2 = 0\%$). Major bleeding events were similar with NOACs and warfarin for AF ablation (OR: 0.91, 95% CI: 0.62–1.34, $P = 0.63$; Fig. 5). Pooled analysis of studies in which uninterrupted warfarin was utilized for periprocedural anticoagulation did not show any significant difference in major bleeding between NOACs and warfarin (OR: 0.93, 95% CI: 0.58–1.50, $P = 0.77$).
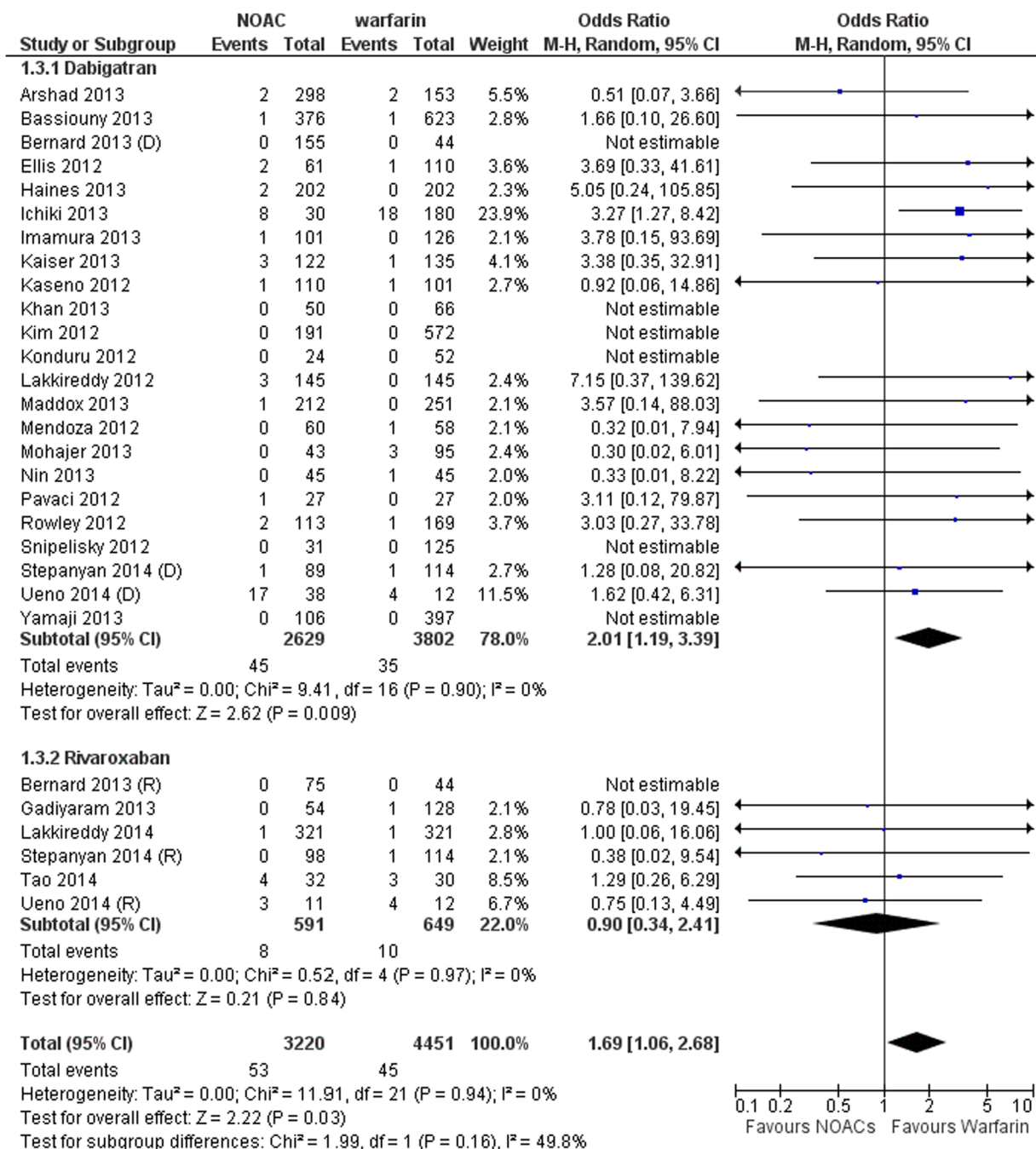
Fig. 3 Forest plot showing sub group analysis of the composite endpoint of stroke, TIA, peripheral arterial embolism, or silent cerebral lesions on MRI based on type of new oral anticoagulants

Major Bleeding-Type of NOACs

Subgroup analysis, based on the type of NOAC, revealed similar major bleeding with dabigatran and warfarin when used for AF ablation (OR: 0.99, 95% CI: 0.62–1.57, $P = 0.96$). There was no significance difference in major bleeding between rivaroxaban and warfarin (OR: 0.60, 95% CI: 0.25–1.45, $P = 0.25$).
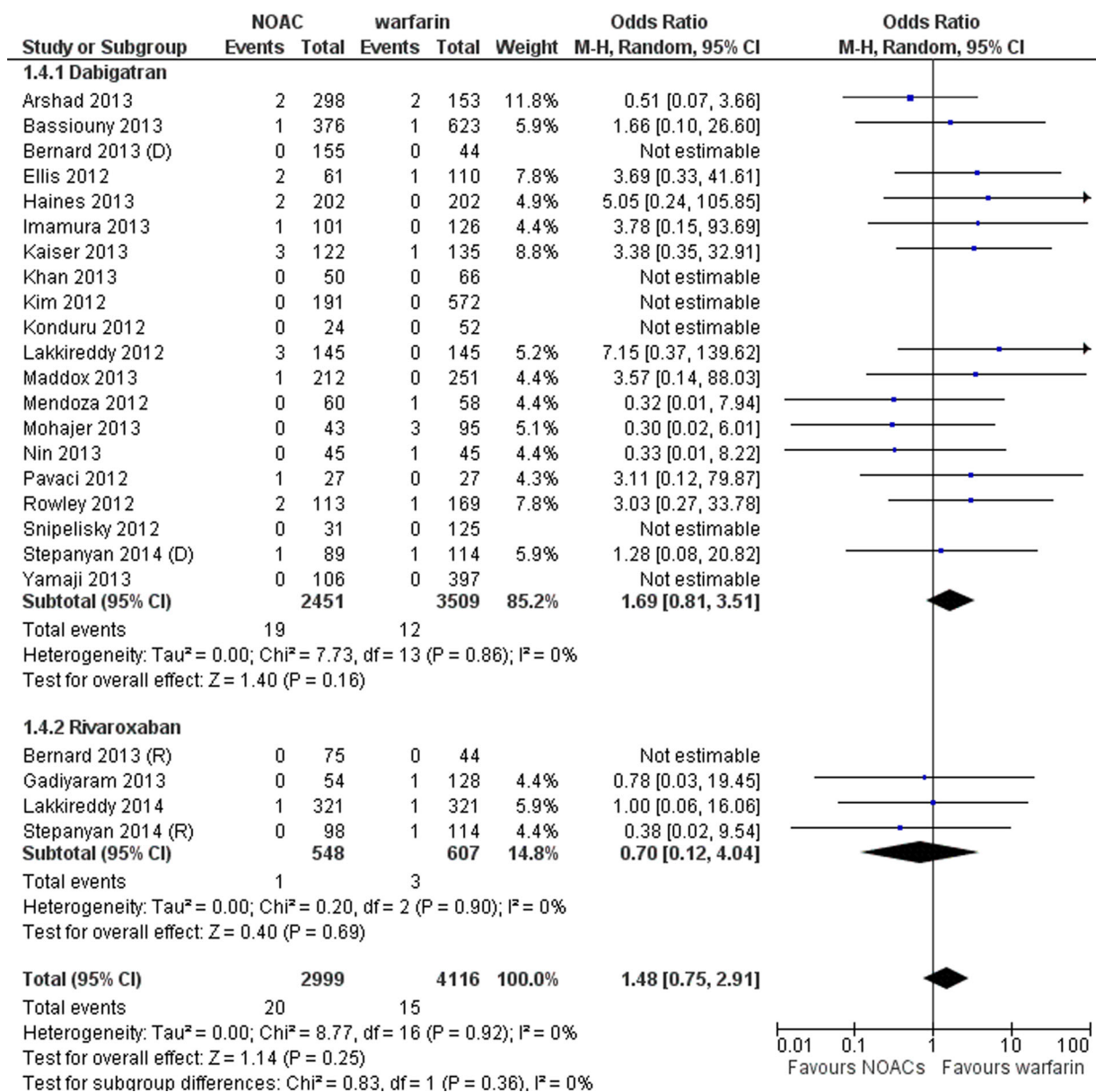
Fig. 4 Forest plot showing sub group analysis of symptomatic thromboembolic events (stroke, TIA, and peripheral arterial embolism) based on type of new oral anticoagulants

DISCUSSION

There are three major findings of this study. First, the use of dabigatran for periprocedural anticoagulation for AF ablation is associated with an increased risk of the composite endpoint of stroke, TIA, peripheral arterial embolism, or silent cerebral lesions on MRI compared to warfarin. However, the risk of symptomatic thromboembolic events with dabigatran therapy is similar to anticoagulation with warfarin. Second, rivaroxaban is not associated with increased risk of the composite endpoint when compared
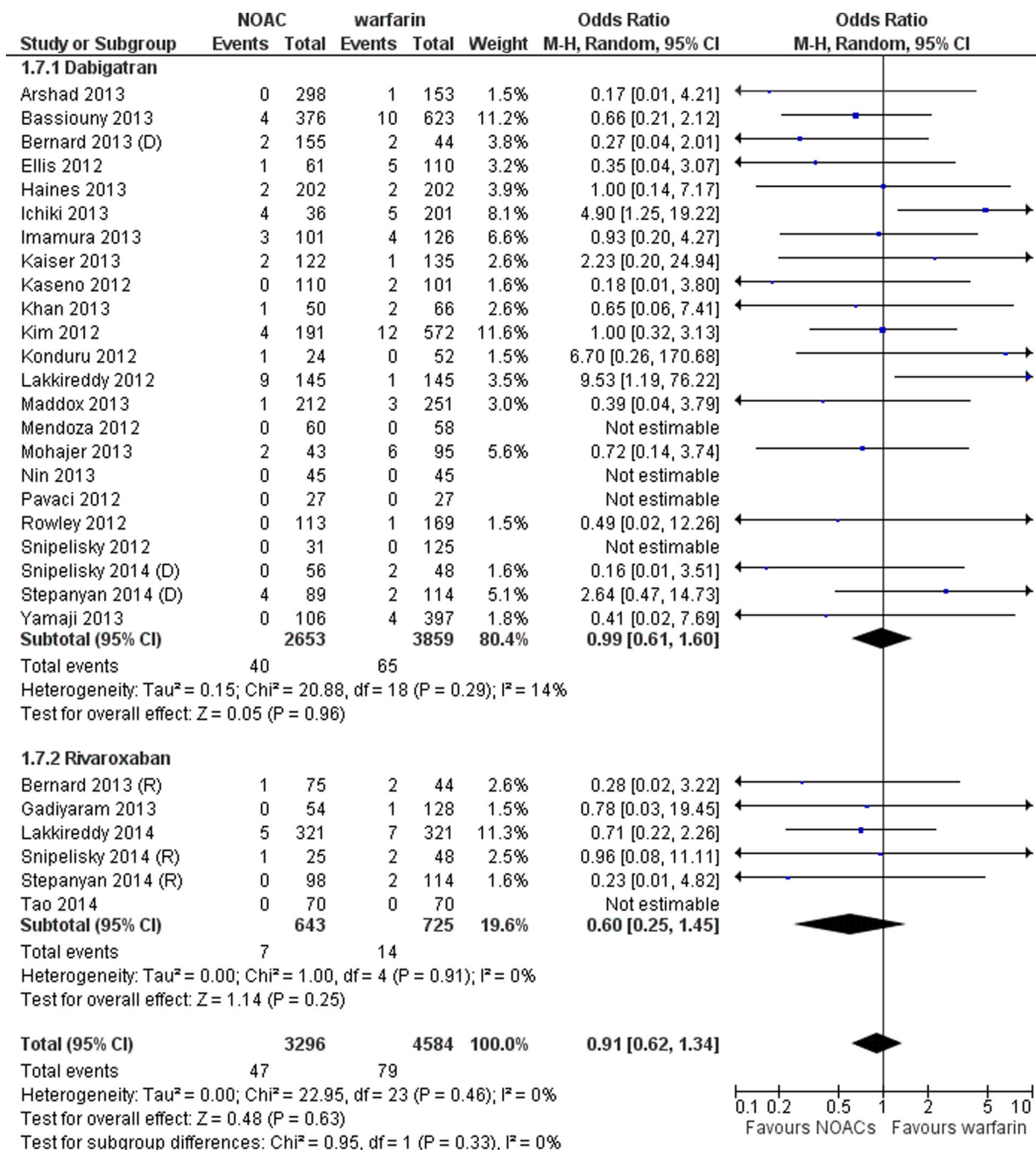
Study or Subgroup	NOAC Events	Total	warfarin Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 Dabigatran						
Arshad 2013	0	298	1	153	1.5%	0.17 [0.01, 4.21]
Bassiouny 2013	4	376	10	623	11.2%	0.66 [0.21, 2.12]
Bernard 2013 (D)	2	155	2	44	3.8%	0.27 [0.04, 2.01]
Ellis 2012	1	61	5	110	3.2%	0.35 [0.04, 3.07]
Haines 2013	2	202	2	202	3.9%	1.00 [0.14, 7.17]
Ichiki 2013	4	36	5	201	8.1%	4.90 [1.25, 19.22]
Imamura 2013	3	101	4	126	6.6%	0.93 [0.20, 4.27]
Kaiser 2013	2	122	1	135	2.6%	2.23 [0.20, 24.94]
Kaseno 2012	0	110	2	101	1.6%	0.18 [0.01, 3.80]
Khan 2013	1	50	2	66	2.6%	0.65 [0.06, 7.41]
Kim 2012	4	191	12	572	11.6%	1.00 [0.32, 3.13]
Konduru 2012	1	24	0	52	1.5%	6.70 [0.26, 170.68]
Lakkireddy 2012	9	145	1	145	3.5%	9.53 [1.19, 76.22]
Maddox 2013	1	212	3	251	3.0%	0.39 [0.04, 3.79]
Mendoza 2012	0	60	0	58		Not estimable
Mohajer 2013	2	43	6	95	5.6%	0.72 [0.14, 3.74]
Nin 2013	0	45	0	45		Not estimable
Pavaci 2012	0	27	0	27		Not estimable
Rowley 2012	0	113	1	169	1.5%	0.49 [0.02, 12.26]
Snipelisky 2012	0	31	0	125		Not estimable
Snipelisky 2014 (D)	0	56	2	48	1.6%	0.16 [0.01, 3.51]
Stepanyan 2014 (D)	4	89	2	114	5.1%	2.64 [0.47, 14.73]
Yamaji 2013	0	106	4	397	1.8%	0.41 [0.02, 7.69]
Subtotal (95% CI)		2653		3859	80.4%	0.99 [0.61, 1.60]
Total events	40		65			

Heterogeneity: Tau² = 0.15; Chi² = 20.88, df = 18 (P = 0.29); I² = 14%
Test for overall effect: Z = 0.05 (P = 0.96)

Study or Subgroup	NOAC Events	Total	warfarin Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.2 Rivaroxaban						
Bernard 2013 (R)	1	75	2	44	2.6%	0.28 [0.02, 3.22]
Gadiyaram 2013	0	54	1	128	1.5%	0.78 [0.03, 19.45]
Lakkireddy 2014	5	321	7	321	11.3%	0.71 [0.22, 2.26]
Snipelisky 2014 (R)	1	25	2	48	2.5%	0.96 [0.08, 11.11]
Stepanyan 2014 (R)	0	98	2	114	1.6%	0.23 [0.01, 4.82]
Tao 2014	0	70	0	70		Not estimable
Subtotal (95% CI)		643		725	19.6%	0.60 [0.25, 1.45]
Total events	7		14			

Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 4 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.25)

Total (95% CI)		3296		4584	100.0%	0.91 [0.62, 1.34]
Total events	47		79			

Heterogeneity: Tau² = 0.00; Chi² = 22.95, df = 23 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%

0.1 0.2 0.5 1 2 5 10
Favours NOACs   Favours warfarin

Fig. 5 Forest plot showing sub group analysis of bleeding events based on type of new oral anticoagulants

to warfarin. Third, dabigatran and rivaroxaban are comparable to warfarin in terms of bleeding complications.

Current American Heart Association (AHA)/ American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines recommend anticoagulation in patients with AF with high risk for thromboembolic events identified by the CHA2DS2-VASc score [43]. Recent meta-analyses presented mixed data regarding

the role of dabigatran therapy for periprocedural anticoagulation for AF ablation [11–13, 44]. Our study suggests dabigatran therapy for AF ablation may be associated with increased thromboembolic risk. Shurrab et al. [12] and Bin Abdulhak et al. [44] reported no significant difference in thromboembolic events between dabigatran and warfarin therapy. Sardar et al. [11] and Steinberg et al. [13] observed that periprocedural dabigatran use may be associated with increased risk of neurological events. In these meta-analyses, silent cerebral lesions on MRI were not included as one of the primary outcomes. Our study is the first pooled analysis to include and evaluate the incidence of silent cerebral lesions on MRI. Gaita et al. [45] reported an incidence of cerebral microthromboembolism of 14% with warfarin therapy for AF ablation and increased risk of cerebrovascular events was related to use of cardioversion. Our pooled analysis included silent cerebral lesions on MRI as one of the primary outcomes and it revealed that dabigatran therapy is potentially associated with a higher risk of silent cerebral lesions on MRI. Exclusion sensitivity analysis after omitting studies reporting silent cerebral lesions on MRI did not show any significant difference in thromboembolic events between dabigatran and warfarin therapy for AF ablation. Ueno et al. [46] showed that during AF ablation, pro-thrombotic factors are activated more with dabigatran than warfarin. Ichiki et al. [21] observed an increased risk of asymptomatic cerebral thromboembolic events with dabigatran therapy for AF ablation. Conversely, Kaseno et al. [24] reported similar cerebral microthromboembolism with dabigatran. Our analysis did not show any difference in the composite endpoints between rivaroxaban and warfarin therapy for AF ablation. This analysis may be limited by small

sample size of the rivaroxaban subgroup (548 vs. 2451 in the dabigatran subgroup).

Silent cerebral infarcts may be associated with neurocognitive impairment and/or gait abnormality [47]. A recent retrospective study evaluating the incidence of silent cerebral lesions with different NOACs including edoxaban suggested an increased risk of silent cerebral lesions with dabigatran [48]. This is consistent with the findings of our study, which showed potentially higher risk of silent cerebral lesions with dabigatran. The majority (91.8%) of the cerebral lesions noted on initial MRI were not seen on following MRI suggesting that only a few lesions develop into chronic cerebral lesions [48]. This study was limited by the retrospective and non-randomized nature of the study. Prospective randomized clinical studies are needed to evaluate the incidence of cerebral microthromboembolism with NOACs and to determine clinical characteristics which increase the likelihood of cerebral microthromboembolism.

Our study is consistent with other meta-analyses which revealed NOACs are associated with similar bleeding risk when compared to warfarin [11–13, 44]. Subgroup analysis based on type of anticoagulant did not show any difference between the NOACs.

Limitations

The studies included in the meta-analysis had differences in their study protocol. We could not study the risk of thromboembolic and bleeding events based on the dose of NOACs (110, 150 mg of dabigatran; 10, 15, 20 mg of rivaroxaban). There was significant heterogeneity in different protocols in terms of number of doses of NOACs held prior to the ablation, bridging therapy with heparin, and timing of resumption of NOACs after the

procedure. Definitions for safety and efficacy outcomes, and baseline characteristics of the patients varied across the studies. The majority of the studies were observational studies without any randomization or propensity matching. Apixaban is being increasingly used in clinical practice for AF ablation. Studies evaluating the safety and efficacy of periprocedural anticoagulation with apixaban and edoxaban for AF ablation were not included in the pooled analysis [48–50] as these studies were published after the completion of the literature search in May 2014.

CONCLUSIONS

Dabigatran and rivaroxaban are comparable to warfarin in terms of bleeding complications. However, dabigatran therapy is potentially associated with a higher risk of cerebral lesions on MRI. The results of study should be considered as hypothesis-generating and assessed further in prospective randomized clinical studies.

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