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

Ajay Vallakati · Abhishek Sharma · Mohammed Madmani · Madhu Reddy · Arun Kanmanthareddy · Sampath Gunda · Dhanunjaya Lakkireddy · William R. Lewis

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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 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 \( \chi^2 \) 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 $\chi^2$ 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](image-url)
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 |
|---------|------|---------------------|------------------------|------------------------------|----------------------|------------------|-------------------|----------------------|------------------------|------------------------|-------------|----------|
| Ashad [15] | 2013 | HRS                | 298, 153               | 60.7 ± 10                    | 28                   | 67⁷                | 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 | –                      | 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 ± 1.6 ± 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 |
| 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 |
| Lakireddy [27] | 2013 | JACC                | 145, 145               | 60.4, 60.3                 | 21, 21               | 57, 57           | Abl.             | 1.6 ± 1.4, 1.5 ± 1.3 | 1.2 ± 0.9, 1.1 ± 0.9      | D 150                    | Held on the morning of the procedure, resumed within 3 h after hemostasis | Uninterrupted |
| Lakireddy [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 | 1.27 ± 0.9, 1.30 ± 1.0    | D 150                    | Uninterrupted | 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) | Uninterrupted | Held 24 h prior to procedure |
| 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                     | –                  |
| 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   | 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

* Total PAF in study cohort
b NOACs (dabigatran, rivaroxaban)

\(^c\) CHADS2-Vasc score
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. 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
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, \( P = 0.25 \)).
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...
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 bleeding complications among NOACs and warfarin.

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

| Study or Subgroup | NOAC Events | Warfarin Events | Odds Ratio | Odds Ratio |
|------------------|-------------|-----------------|------------|------------|
|                  | Total | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| 1.7.1 Dabigatran |        |        |        |                      |                      |
| Arshad 2013      | 0 298 | 1 153 | 1.5%  | 0.17 [0.01, 4.21]    |                      |
| Bassiouy 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]    |                      |
| Ichik 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]  |                      |
| Lakkereddy 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
Heterogeneity: Tau² = 0.15; Chi² = 20.88, df = 18 (P = 0.29); I² = 14%
Test for overall effect: Z = 0.05 (P = 0.96)

1.7.2 Rivaroxaban

| Study or Subgroup | NOAC Events | Warfarin Events | Odds Ratio | Odds Ratio |
|------------------|-------------|-----------------|------------|------------|
|                  | Total | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Bernard 2013 (R) | 1 75  | 2 44  | 2.6%  | 0.28 [0.02, 3.22]    |                      |
| Gadyaram 2013    | 0 54  | 1 128 | 1.5%  | 0.78 [0.03, 19.45]   |                      |
| Lakkereddy 2014  | 5 321 | 7 321 | 11.3% | 0.71 [0.22, 2.26]    |                      |
| Snipelisky 2014 (R) | 5 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
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

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%
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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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.

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