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**Meta-Analysis of Effectiveness and Safety of Oral Anticoagulants in Atrial Fibrillation With Focus on Apixaban**

**Running Title:    Apixaban for anticoagulation in AF**

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**Abstract**

We performed a meta-analysis of data on the effectiveness and safety of apixaban compared with other oral anticoagulants (OACs, warfarin or rivaroxaban or dabigatran or edoxaban) for stroke prevention in atrial fibrillation (AF) in different settings of randomized controlled trials (RCTs), real-world studies, and radiofrequency ablation (RFA).   30 studies were searched in PubMed, the Cochrane Library and Clinicaltrials.gov databases reporting comparative effectiveness and safety of apixaban with warfarin (n=23), rivaroxaban (n=12) or dabigatran (n=13) or edoxaban (2) for stroke prevention in AF. In real-world estimates, apixaban was similar to warfarin for the prevention of stroke or systematic thromboembolism (Stroke/TE) (HR: 0.93, 95% CI: 0.71-1.14, $I^2$=82.9%, N=7), and safer than warfarin in the risks of major bleeding, (HR: 0.62, 95% CI: 0.54-0.70, $I^2$=18.7%, N=9) in AF patients.   The risk of stroke/TE with apixaban was similar to rivaroxaban, dabigatran and edoxaban in the settings of real-world studies and RFA.   Major bleeding with apixaban was generally lower than rivaroxaban(RR: 0.45, 95% CI: 0.38-0.53, $I^2$=0%, N=5) and similar to dabigatran in real-world studies (RR: 1.44, 95% CI: 0.33-6.30, $I^2$=97.7%, N=5), but similar to rivaroxaban, dabigatran and edoxaban in RFA. In conclusion, our meta-analysis provides a comprehensive estimate of the effectiveness and safety of apixaban compared with other OACs (warfarin, rivaroxaban, dabigatran, and edoxaban) in AF patients in different settings of RCT, real-world studies, and RFA.

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**Introduction**

In recent years, the development of non-vitamin-K antagonist oral anticoagulants (NOACs), including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) have increased therapeutic options for anticoagulation and could potentially overcome many drawbacks of warfarin.[1] Indeed, the NOACs provide a more convenient, and even more effective and safer alternative approach to warfarin in clinical practice [2,3] Further direct comparison assessments are therefore warranted for NOACs, especially apixaban, which became available much later than rivaroxaban and dabigatran. This meta-analysis was performed to focus on the oral Factor Xa inhibitor apixaban, with direct comparison data on the effectiveness and safety of the NOACs compared with warfarin, rivaroxaban, dabigatran or edoxaban for stroke prevention in AF in different settings such as RCTs, real-world studies, and radiofrequency ablation (RFA).

**Methods**

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and the reporting Meta-analyses of Observational Studies in Epidemiology (MOOSE) when performing this meta-analysis.[4,5]

A comprehensive search of PubMed, the Cochrane Library and Clinicaltrials.gov databases were performed by 2 independent reviewers (Y. B. and X-B. S.) using the following items "atrial fibrillation" OR "AF" AND "apixaban" OR "rivaroxaban" OR "dabigatran" OR "edoxaban" OR "warfarin" OR "NOAC" OR"DOAC" AND "human" on 20th July, 2016, and updated on 17th April, 2017. Any discrepancies were resolved by re-evaluation to reach

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consensus.

Studies that investigated the comparison between apixaban and the other OACs (warfarin, rivaroxaban or dabigatran or edoxaban) were included in the meta-analysis. Other inclusion criteria are as follows: (i) OACs used for stroke prevention in AF patients; (ii).Clearly defined outcomes of effectiveness or safety; and (iii). Studies published in English. We defined the effectiveness and safety outcomes based on the original papers. Outcomes of effectiveness included IS and Stroke/TE. Outcomes of safety were defined as major bleeding, intracranial hemorrhage (ICH) and gastrointestinal bleeding (GIB). For studies that did not report combined stroke and TE, separate IS, stroke or TE was used instead for meta-analysis. No restrictions on study size were defined in our analysis. Abstracts, editorials, case-reports, reviews and case series were also excluded. Studies using duplicate data were excluded unless additional information was provided.

The analysis was conducted using STATA, version 12.0 (Stata Corp.). Relative risks (RR) with 95% confidence intervals (95% CI) were mainly used to measure the effect sizes in our study, but we used adjusted hazard ratios for the comparisons of apixaban and warfarin in real-world studies. First, we used a fixed model, and then a random effects model if there was heterogeneity according to $I^2$ index .[6] Values of ≤ 25%, 25% to 50%, and ≥50% were defined as low, moderate and high degrees of heterogeneity, respectively. Begg's correlation test and Egger's regression test were used to assess publication bias and Begg's correlation was used where study numbers were < 3.[7,8] P<0.05 was taken as statistically significant.

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**Results**

A total of 1936 studies were initially identified. After screening titles and abstracts, we excluded 1863 papers and 73 remained for detailed evaluation. Of these, 42 were excluded as they did not meet the inclusion criteria (7 reviews and meta-analysis; 7 papers without outcomes of OACs; 9 papers without separate information on apixaban or rivaroxaban or dabigatran or edoxaban; 12 studies with duplicate data, 1 on the setting of direct current cardioversion and 7 with mixed diseases except for AF). Finally, 30 studies were included,[9-39] 11 of which were studies on specific settings of RFA [9,11-20]. The selection process is shown in **Supplementary Figure I**.

Baseline characteristics categorized by different settings are summarized in **Table 1, 2 and 3**. Extracted data of risk of stroke and TE, and major bleeding comparing apixaban with warfarin, rivaroxaban, dabigatran and edoxaban are shown in **Supplementary Tables I- VIII**.

When compared to warfarin, we found similar effectiveness of apixaban in stroke/TE prevention in the settings of real-world studies (HR: 0.93, 0.71-1.14, $I^2$=82.9%, N=7) **(Figure 1a),** and RFA (RR: 1.26, 0.75-2.11, $I^2$=0.0%, N=9), but superiority in RCTs (RR: 0.78, 95% CI: 0.65-0.93, $I^2$=19.6%, N=2) **(Figure 2a).**

Compared to warfarin, apixaban was associated with similar risk of major bleeding in the setting of RFA (RR: 1.12, 0.52-2.42, $I^2$=0.0%, N=10) **(Figure 2b)**, but lower risks in the settings of real-world studies (HR: 0.62, 0.54-0.70, $I^2$=66.9%, N=9) **(Figure 1b)** and RCTs (RR: 0.70, 0.61-0.81, $I^2$=0.0%, N=2). **(Figure 2b).**

We performed subgroup analyses on IS, ICH and GIB in real-world studies using adjusted HRs. Apixaban had a similar risk of IS compared with warfarin in AF patients (HR:   0.95, 95%

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CI: 0.73-1.17, $I^2$=80.3%, N=7), but was associated with reduced risk of ICH (HR: 0.51, 0.42-0.60, $I^2$=51.4%, N=7) and GIB (HR: 0.60, 0.54-0.67, $I^2$=32.8%, N=4) compared with warfarin **(Supplementary Figure II)**.

Apixaban had similar effectiveness for stroke/TE prevention when compared to rivaroxaban (RR: 1.46, 0.90-2.36, $I^2$=0.0%, N=5) or dabigatran (RR: 0.89, 0.51-1.57, $I^2$=0.0%, N=3) or edoxaban   (RR: 0.92, 0.44-1.91, $I^2$=0.0%, N=2)   in the settings of RFA **(Figure 3a, Supplementary Figure III a and Figure IV a)**, or compared to rivaroxaban (HR:1.16, 0.84-1.60, N=1) and dabigatran in the real-world studies **(Supplementary Figure III a)** (HR: 0.42, 0.04-5.02, $I^2$=66.9%, N=2)**.**   A lower risk of major bleeding was seen in real-world studies when apixaban was compared to rivaroxaban (RR: 0.45, 0.38-0.53, $I^2$=0.0%, N=5), but non-significantly different in the real-world studies when apixaban was compared to dabigatran (RR: 1.44, 0.33-6.30, $I^2$=97.7%, N=5) **(Figure 3b and Supplementary Figure III b)** or in RFA when compared to rivaroxaban , dabigatran or edoxaban **(Figure 3b, Supplementary Figure III b and Supplementary Figure IV b)**.

Apixaban was associated with similar risk of IS, ICH, and GIB compared with rivaroxaban or dabigatran in AF patients, when analyses were performed in real-world studies **(Supplementary Figure V)**.

No apparent publication bias was seen for all the meta-analyses performed **(Supplementary Table IX)**.


**Discussion**

In this meta-analysis, our principal findings are as follows: (i) apixaban was associated

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with similar effectiveness of Stroke/TE prevention compared with warfarin, dabigatran, rivaroxaban and edoxaban in real-world studies, and RFA; (ii) apixaban had similar safety to warfarin, rivaroxaban ,dabigatran and edoxaban for major bleeding in the setting of RFA, but was safer than warfarin in RCTs and real-world studies; (iii) apixaban was safer than rivaroxaban in real-world studies, and had similar safety compared to dabigatran; and (iv). apixaban had similar risk of ischemic stroke prevention compared to other OACs (warfarin, rivaroxaban and dabiagatran), but lower risk of ICH and GIB compared with warfarin in real-world studies.

This meta-analysis mainly focuses on the effectiveness and safety of apixaban, when compared with warfarin and other NOACs in AF patients based on different settings, including real-world studies, and RFA. The results are partially discordant from meta-analysis of the RCTs comparing apixaban with warfarin for the risk of stroke/TE in AF patients, which found the rate of Stroke/TE being 22% lower in apixaban compared with warfarin.[2,3] Confounding by indication is a known limitation in observational studies, and could partly explain why a similar risk of Stroke/TE with apixaban vs. warfarin was seen in most real-world studies.[27] Also, different diagnosis codes between the observational studies and RCTs may partially explain some of the discordant findings.

Hemorrhagic stroke was part of the composite of (all) stroke/TE in RCTs,[21] but not included in some observational studies in which ischemic stroke solely was evaluated based on cerebral infarction.[24,25] This assumption is supported by the subgroup analyses showing similar risk of ischemic stroke in comparisons of apixaban with warfarin in real-world studies **(Supplementary Figure II).**

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The effectiveness of Stroke/TE prevention in apixaban was similar to rivaroxaban or dabigatran or edoxaban in the settings of real-world studies, and RFA, consistent with previous indirect comparisons.[40] However, apixaban was superior to rivaroxaban in real-world studies, but similar to dabigatran in terms of safety, that is, major bleeding. No significant differences were evident between apixaban and other NOACs (rivaroxaban or dabigatran) with respect to other outcomes in everyday clinical practice. This might reflect the smaller number of events due to relatively fewer studies focused on the apixaban comparisons.

Consistent with previous meta-analysis of NOACs for RFA,[41,42] apixaban showed comparative effectiveness and safety with warfarin. Apixaban was non-inferior to rivaroxaban, dabigatran, and edoxaban when studies were performed on the terms of stroke/TE and major bleeding within NOACs in patients receiving RFA treatment. Further studies with larger populations and more high-quality follow-up are needed, and 1 prospective RCT is ongoing.[43]

This analysis should be interpreted with caution due to various limitations, some of which were inherent with any meta-analysis. Owing to the small sample size, there may be lower power in some included studies, hence the difficulty in drawing any firm conclusions on the safety outcomes of GIB and ICB of apixaban compared to other NOACs (rivaroxaban and dabigatran). Second, as apixaban was a relatively new NOAC and the follow-up period was usually shorter than other OACs, hence the 'peak' of adverse effects may not be reached in some observational studies.[23,30] Third, some events were crudely estimated because of no access to the original data, but we estimated the results using the adjusted HR for comparison of apixaban vs. warfarin in real-world studies. The lack of publication bias

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increases the reliability of the pooled estimate. Despite these limitations, this meta-analysis includes all relevant studies providing head-to-head comparisons of apixaban with other OACs.

Our meta-analysis provides a comprehensive estimate of the effectiveness and safety of apixaban compared with other OACs (warfarin, rivaroxaban, dabigatran and edoxaban) in AF patients.

**Disclosures:**

CSM has received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer Ingelheim (BI), and Bayer for giving lectures.

GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

Other authors: None declared

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**Figure 1**.Risk of Stroke/TE (a) and major bleeding (b) in comparison of Apixaban versus Warfarin in AF patients in real-world studies; AF, atrial fibrillation; IS, ischemic stroke; TE, systematic thromboembolism.

**Figure 2.** Risk of Stroke/TE (a) and major bleeding (b) in comparison of Apixaban versus Warfarin in AF patients with different settings; PAE, peripheral arterial embolism; RCT, randomized controlled trials; RFA, radiofrequency ablation; TIA, transient ischemic attack. a, Outcome refers to stroke/TE if not stated; b, Outcome refers to major bleeding if not stated. Other abbreviations see Figure 1.

**Figure 3.** Risk of Stroke/TE (a) and major bleeding (b) in comparison of Apixaban versus Rivaroxaban in AF patients with different settings; PE, pulmonary embolism; a, Outcome refers to stroke/TE if not stated; b, Outcome refers to major bleeding if not stated. Other abbreviations see Figure 1 and 2.

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**Table 1**.    Baseline characteristics of studies comparing apixaban versus warfarin

| Author, year | Region | Period | Study design | Cohort (Number) | | Low Dose (%) | Follow-up |
|---|---|---|---|---|---|---|---|
| | | | | Apixaban | Warfarin | Apixaban | |
| Coleman,2017[35] | Germany | 2013- 2014 | Retrospective | 937 | 7040 | 33.2 | 1 y |
| Hohnloser,2017[36] | Germany | 2013- 2015 | Retrospective | 3,633 | 16,179 | 39 | 0.6-0.8 y |
| Lamberts,2017[37] | Denmark | - 2015 | Registry | 7,963 | 24,230 | – | 1.1 y |
| Li,2017[38] | US | 2013- 2015 | Retrospective | 38,470 | 38,470 | 17.1 | 0.5y |
| Nielsen,2017[39] | Denmark | 2011- 2016 | Cohort | 4,400 | 38,893 | 100 | 1 y |
| Lip,2016[23] | US | 2013- 2014 | Retrospective | 7,438 | 15,461 | 13.5 | 0.4 y |
| Larsen, 2016[25] | Denmark | 2011- 2015 | Cohort | 6,349 | 35,436 | 0 | 1.9y |
| Coleman,2016[24] | US | 2012- 2014 | Retrospective | 18,591 | 26,083 | 15.5 | – |
| Halvorsen,2016[26] | Norway | 2013- 2015 | Registry | 6,506 | 11,427 | 29.2 | 0.4 y |
| Yao,2016[28] | US | 2010- 2015 | Retrospective | 7,698 | 85,869 | 18.1 | 0.5y; |
| Staerk,2016[27] | Denmark | 2011-2015 | Registry | 6,899 | 18,094 | 36.9 | 2y |

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| Granger,2011[21] | Multi-center | 2006- 2010 | RCT | 9120 | 9081 | 4.6 | 1.8y |
| Ogawa,2011[22] | Japan | – | RCT | 148 | 74 | 50 | 0.25y |

RCT, randomized controlled trials; NOACs, non-vitamin-K antagonist anticoagulants ; –,Not available.

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**Table 2**.    Baseline characteristics of studies comparing apixaban versus dabigatran or apixaban versus rivaroxaban

| Author, year | Region | Period | Study design | Cohort (Number) | | | Low dose (%) | | | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Apixaban n | Dabigatran n | Rivaroxaban n | Apixaban n | Dabigatran n | Rivaroxaban n | |
| Lip,2016[23] | US | 2013-2014 | Retrospective | 7,438 | 4,661 | 17,801 | 13.5 | 10.6 | 19.6 | 0.37-0.5y |
| Al-Khalili,2016[30] | Sweden | 2011-2014 | Retrospective | 251 | 233 | 282 | 16.0 | 36.0 | 18.0 | 0.95-1.18y |
| Noseworthy,2016[29] | US | 2010-2015 | Retrospective | 6,542 | 6,542 | – | 18.1 | 13.0 | – | – |
| Noseworthy,2016[29] | US | 2010-2015 | Retrospective | 6,565 | – | 6,565 | 18.3 | – | 28.7 | – |
| Deitelzweig,2016[34] | US | 2012-2014 | Retrospective | 4,138 | 32,838 | 37,754 | – | – | – | 0.08y |

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| Khan,2016[31] | US | 2011-2013 | Retrospective | 14 | 52 | 76 | – | – | – | 2.56 y |
| Pasca,2016[33] | Italy | 2013-2015 | Prospective | 66 | 23 | 54 | 62.1 | 69.6 | 44.5 | 0.8y |
| Lee,2015[32] | UK | 2013-2014 | Retrospective | 53 | 53 | 127 | – | – | – | 0.92y |

*Prospective cohort study, others Retrospective cohort studies. –,Not available.

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**Table 3.** Baseline characteristics of studies on oral anticoagulants used in radiofrequency ablation

| Author, year | Region | Period | Study design | Cohort (Number) | | | | Periprocedural Oral Anticogulants | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Apixaban n | Warfarin n | Rivaroxaban n | Dabigatran n | Uninterrupted | Interrupted |
| Yoshimura,2016[20] | Japan | 2013-2014 | prospective | 50 | 69 | 55 | – | warfarin, rivaroxaban | apixaban |
| *Nakamura,2016[17] | Japan | 2014-2015 | Retrospective | 87 | 46 | 89 | 47 | warfarin | NOAC |
| *Okishige,2016[18] | Japan | – | Retrospective | 30 | 19 | 81 | 66 | warfarin | NOACs |
| Hansen,2016[12] | Sweden | 2011-2014 | Prospective | 25 | – | 38 | 171 | – | NOACs |
| Koektuerk,2016[14] | Germany | 2012-2015 | Retrospective | 18 | 150 | 193 | 48 | – | NOACs |

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| Kuwahara,2016[15] | Japan | – | RCT | 100 | 100 | – | – | warfarin ,apixaban | – |
|---|---|---|---|---|---|---|---|---|---|
| Di Biase,2015[11] | US, Europe | 2013-2014 | Prospective | 200 | 200 | – | – | warfarin, apixaban | – |
| Rillig,2015[19] | Germany | 2013-2014 | – | 80 | 120 | 193 | 51 | warfarin | – |
| Nagao,2014[16] | Japan | 2013-2014 | Retrospective | 105 | 237 | – | – | warfarin, apixaban | – |
| Kaess,2014[13] | Germany | - 2014 | Matched | 105 | 210 | – | – | warfarin , apixaban | – |
| Armbruster,2014[9] | US | 2012-2013 | Retrospective | 17 | 173 | 61 | 123 | warfarin | – |

RCT, randomized controlled trials; NOACs, non-vitamin-K antagonist anticoagulants;

*The numbers of edoxaban are 17 and 61 in Nakamura,2016[17] and Okishige,2016[18], separately.

–, Not available.