“Real-World” Use of Apixaban for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and Purpose: The use of oral anticoagulant (OAC) therapy for stroke prevention in atrial fibrillation (AF) has been transformed by the availability of the non-vitamin K antagonist oral anticoagulants (NOACs). Real-world studies (RWS) on the use of NOACs would help elucidate their effectiveness and safety in daily clinical practice. Apixaban was the 3rd NOAC introduced to clinical practice, and increasing RWS have been published. Our aim was to summarize current evidence about RWS on apixaban for stroke prevention in AF.

Methods: We performed a systematic review and meta-analysis of all observational RWS comparing apixaban with other available OAC drugs.

Results: From the original 9680 results retrieved, 16 studies have been included in the final meta-analysis. Compared to warfarin, apixaban regular dose was more effective in reducing any thromboembolic event (odds ratio [OR]: 0.77, 95% confidence interval [CI]: 0.64-0.93), but no significant difference was found for stroke risk. Apixaban was as effective as dabigatran and rivaroxaban in reducing thromboembolic events and stroke. The risk of major bleeding was significantly lower for apixaban compared to warfarin, dabigatran and rivaroxaban (RRR 38 %, 35% and 46%, respectively). Similarly, the risk for intracranial hemorrhage (ICH) was significantly lower for apixaban than warfarin and rivaroxaban (46% and 54%, respectively), but not dabigatran. The risk of gastrointestinal bleeding was lower with apixaban when compared to all OAC agents (p<0.00001 for all comparisons).

Conclusions: Use of apixaban in real-life is associated with an overall similar effectiveness in reducing stroke and any thromboembolic events when compared to warfarin. A better safety profile was found with apixaban compared to warfarin, dabigatran and rivaroxaban.
The use of oral anticoagulant (OAC) therapy for stroke prevention in atrial fibrillation (AF) has been transformed by the availability of the non-vitamin K antagonist oral anticoagulants (NOACs) which show relative efficacy, safety and convenient alternatives to the vitamin K antagonists (VKA, e.g. warfarin)\(^1,2\). Currently four NOACs are available for clinical use, namely the direct thrombin inhibitor, dabigatran; and the oral Factor Xa inhibitors, rivaroxaban, apixaban and edoxaban. The numbers of post-marketing observational real-world studies (RWS) have largely reflected the sequence these drugs have been introduced to the market\(^3\). Compared to clinical trials, the RWS have less selected cohorts, helping to understand the effect of NOACs in specific clinical scenarios or conditions\(^3\). Prior RWS have analysed and been pooled together for dabigatran and rivaroxaban, broadly confirming the results from their respective phase III clinical trials\(^4,5\).

Our aim was to perform a systematic review and meta-analysis of all observational RWS comparing apixaban with other available OAC drugs (warfarin, dabigatran, rivaroxaban and edoxaban).
1 METHODS

In order to perform this systematic review and meta-analysis, the following criteria for studies selection were considered: i) observational studies focusing on patients with established AF; ii) studies reporting data on AF patients prescribed with OAC, comparing data about patients treated with apixaban and warfarin, dabigatran, rivaroxaban or edoxaban and their impact on major adverse events on follow-up observation; iii) At least 100 patients, with 50 patients taking apixaban or a relevant subgroup of apixaban treated patients; iv) At least 3 months of follow-up. Exclusion criteria were: i) conference abstracts, letters, comments, case reports, and editorials; ii) studies not published in English. No explicit protocol was drafted to perform the systematic review. The systematic review and meta-regression was performed according to PRISMA recommendations (http://www.prisma-statement.org/).

14 Search Strategy

A comprehensive literature search was performed using PubMed and Scopus databases up to 6th of March 2017. Search terms included “atrial fibrillation”, “apixaban”, “dabigatran”, “rivaroxaban”, “edoxaban”. The electronic search was carried out for peer-reviewed journals and, if applicable, some further additional references were gathered from searches through bibliographies of identified papers and from authors' personal knowledge.

All details about studies selection, data extraction, outcomes definition, as well as on bias assessment and statistical analysis have been reported in Web-only supplementary materials. All statistical analyses were undertaken using Review
1Manager (RevMan) version 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark).
RESULTS

The original literature search retrieved a total of 9680 results from Pubmed and Scopus databases [Figure 1]. After the selection process [Figure 1], a total of 173 studies underwent full-text assessment. Following the exclusion of 158 papers and the following addition of 2 papers, based on authors knowledge, a total of 16 studies were included in the systematic review and the final meta-analysis (Table 1).

Study Characteristics

Overall, a total of 170,814 patients treated with apixaban were included in the 16 studies. Of these, two studies were published in 2015, seven studies were published in 2016 and seven studies were published in 2017. Three out of 16 studies were single centre cohort studies, six studies were retrieved from insurance databases, one study was a regional database and six studies were taken from nationwide registries. Eight studies were based in Europe, while six studies were based in USA, 1 study was based in the Middle-East and 1 study in Japan.

Mean/median age was consistent among most of the studies, ranging from 70 to 76 years; one study enrolled slightly younger patients, mean (SD) age 68.5 (12.4) years, while another study enrolled significantly older patients, mean (SD) age 83.9 (8.2) years. Four studies enrolling patients with a very high thromboembolic risk (CHA2DS2-VASc score ≥4) compared apixaban with warfarin, dabigatran and rivaroxaban; four studies compared apixaban directly only with warfarin and four studies compared apixaban with both dabigatran...
1and rivaroxaban\textsuperscript{10,14,17,18}. No studies were retrieved comparing apixaban with edoxaban.

Data about use of reduced dose were available for 10 out of 16 studies\textsuperscript{7,9,11,13–16,19–21}. The lowest proportion of the reduced dose was 13.5\%\textsuperscript{13}, while the highest proportion reported was 37.8\%\textsuperscript{20}; of note, 5 out of 10 studies reported a proportion of reduced dose of >25\%.\textsuperscript{7,9,15,19,20} One study comprised only patients prescribed with NOACs reduced dose\textsuperscript{22}.

Studies Results

In the most studies comparing apixaban with warfarin, apixaban was associated with a lower risk for stroke and systemic embolic (SE) events, as well as for major bleeding, particularly ICH\textsuperscript{11,16,21}. Only in the study by Forslund et al, no difference was found between apixaban and warfarin\textsuperscript{7}.

Overall, the studies that compared apixaban with dabigatran and rivaroxaban found that apixaban was broadly comparable with dabigatran in terms of stroke/SE events with unclear differences compared with rivaroxaban\textsuperscript{10,14,18}. Conversely, apixaban demonstrated a significant lower risk for major bleeding events\textsuperscript{10,14,17,18}. In the study by Abraham and colleagues, the lower risk of GIB with apixaban was independent of age strata\textsuperscript{17}.

Risk of Bias Evaluation

A bias evaluation was performed (Table I in the online-only Supplementary Materials). Overall, most studies reported a low risk of bias (11 studies), while 3 studies\textsuperscript{10,12,22} had a moderate risk of bias and 2 studies\textsuperscript{8,18} had a high risk of bias. We
did not find significant publication bias in the main primary outcomes, for comparisons between apixaban, warfarin and dabigatran [Figures I-II in the online-only Supplementary Materials], while a small effect could be detected for rivaroxaban, particularly for the ‘any thromboembolic event’ outcome [Figure III in the online-only Supplementary Materials] and similarly for dabigatran, particularly for the ‘major bleeding event’ outcome [Figure IIb in the online-only Supplementary Materials].

Meta-Analysis of Selected Studies

a) Apixaban vs. Warfarin

When comparing apixaban and warfarin, there was overall no significant difference in any thromboembolic events (odds ratio [OR]: 0.92, 95% confidence interval [CI]: 0.71-1.17) [Figure 2, Panel A]. In the regular dose group, there was a significant reduction in risk of any thromboembolic event (OR: 0.77, 95% CI: 0.64-0.93); conversely, the reduced dose subgroup had a significant 27% relative risk increase in any thromboembolic event (p<0.0001 for subgroup differences).

For stroke, no significant difference was found between apixaban and warfarin, both in the regular and reduced dose subgroups [Figure 2, Panel B]. Conversely, hemorrhagic stroke risk was significantly reduced in apixaban treated patients (36% relative risk reduction [RRR], p=0.0003), especially for the regular dose group [Figure IV in the online-only Supplementary Materials].

Compared to warfarin, major bleeding risk was significantly lower for patients treated with apixaban (OR: 0.62, 95% CI: 0.51-0.75), with consistency for regular and low
1dose subgroups [Figure 2, Panel C]. Risk reduction with apixaban was even greater when considering ICH (46% RRR, p<0.00001) or GIB (OR: 0.63, 95% CI: 0.57-0.70; 3p<0.00001) compared to warfarin [Figure V in the online-only Supplementary Materials]. The risk for any bleeding was also lower in apixaban patients (p=0.009) [Figure VI in the online-only Supplementary Materials].

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7Given the extremely high level of heterogeneity, we did not perform the meta-analysis for occurrence of all-cause death. Currently, only a limited number of RWS reported about all-cause death risk comparing apixaban and warfarin [Figure VII in the online-only Supplementary Materials]. These studies reported controversial results with one study suggesting a significant protection for apixaban, one study suggesting no difference and one study indicating an higher risk for apixaban, even though it compared warfarin with apixaban reduced dose.

14

15Number of events for Forslund et al. were retrieved from Hazard Ratios (see Supplementary Methods in the online-only Supplementary Materials). A sensitivity analysis excluding that study showed superimposable results (data not shown).

18

b) Apixaban vs. Dabigatran

20Overall, there were non-significant differences between apixaban and dabigatran in risk of any thromboembolic event (p=0.30), although a lower risk was found in apixaban patients prescribed with the reduced dose (OR: 0.86, 95% CI: 0.75-0.99) [Figure 3, Panel A]. No difference was seen for stroke risk [Figure 3, Panel B].
Major bleeding risk was significantly lower in apixaban patients compared to dabigatran ones (35% RRR, p<0.00001), even though only one study was included in the reduced dose subgroup [Figure 3, Panel C]. While no difference was found for ICH [Figure 3, Panel D], patients prescribed apixaban had a significantly lower risk for GIB (57% RRR, p<0.00001) and any bleeding (31% RRR, p<0.00001) [Figures VIII-IX in the online-only Supplementary Materials]. No difference was found in all-cause death between apixaban and dabigatran [Figure X in the online-only Supplementary Materials].

Number of events for Noseworthy et al.14 were retrieved from Hazard Ratios (see Supplementary Methods in the online-only Supplementary Materials). A sensitivity analysis excluding that study showed superimposable results (data not shown).

c) Apixaban vs. Rivaroxaban

Compared to apixaban, there was a significant superiority for rivaroxaban for any thromboembolic event (OR: 1.27, 95% CI: 1.13-1.43) and stroke (OR: 1.31, 95% CI: 1.15-1.50, mainly driven by the treatment effect found in the reduced dose subgroup [Figure 4, Panel A and B]. No difference was found for hemorrhagic stroke occurrence, although few studies were available for evaluation [Figure XI in the online-only Supplementary Materials].

The risk of major bleeding was significantly lower in patients treated with apixaban compared to rivaroxaban (46% RRR, p<0.00001), consistent with doses subgroups [Figure 4, Panel C]. There was a significant risk reduction in ICH (OR: 0.46, 95% CI: 0.25-0.85) [Figure 4, Panel D] and GIB for apixaban compared to rivaroxaban (64%
1RRR, p<0.00001) [Figure XII in the online-only Supplementary Materials]; as well as
2for any bleeding (OR: 0.56, 95% CI: 0.50-0.61) [Figure XIII in the online-only
3Supplementary Materials]. There was a significant reduction for all-cause death with
4apixaban compared to rivaroxaban with the regular dose subgroup (50% RRR,
5p<0.00001) [Figure XIV in the online-only Supplementary Materials].

Number of events for Noseworthy et al.\textsuperscript{14} were retrieved from Hazard Ratios (see
8Supplementary Methods in the online-only Supplementary Materials). A sensitivity
9analysis excluding that study showed superimposable results (data not shown).

10

11\textbf{d) Bias-Stratified Sensitivity Analysis}

12A sensitivity analysis was performed, grouping studies according to risk of bias
13verifying all the outcomes for which a significant treatment effect was found, either
14for apixaban or any of the comparators. No significant differences were found for
15most of the outcomes analysed (data not shown). For the comparison of apixaban
16vs. warfarin for any thromboembolic event, bias stratified analysis found a 25% RRR
17(p<0.00001) when considering only low risk of bias studies [Figure XV in the online-only
18Supplementary Materials]. The risk reduction for any thromboembolic event
19occurrence with rivaroxaban was driven by the moderate/high risk of bias studies
20(OR: 1.38, 95% CI: 1.19-1.59), while no significant difference was found for the low
21risk of bias subgroup (OR: 1.10, 95% CI: 0.89-1.35) [Figure XVI in the online-only
22Supplementary Materials]. Similar findings were seen for stroke occurrence [Figure
23XVII in the online-only Supplementary Materials].

24

25
Absolute Risk Reductions and Number-Needed to Treat Compared to Warfarin

To assess the effectiveness of apixaban compared to warfarin in RWS, we estimated absolute risk reduction (ARR) and number-needed to treat (NNT). Compared to warfarin, apixaban resulted in a similar effect reducing any thromboembolic event (ARR: 0.23%), with a slightly better effectiveness in reducing risk of stroke (ARR: 0.48%). Comparing RWS data with the ARISTOTLE trial\textsuperscript{23}, apixaban allowed a consistently higher NNT for any thromboembolic event, while a similar clinical effectiveness was found for stroke event [Figure 5].

For major bleeding events, an ARR of 1.41% resulting in a NNT of 71, similar to ARISTOTLE. For ICH, a 2.7-fold increase in NNT was seen compared to ARISTOTLE (345 vs. 128), due to an ARR of 0.29% [Figure 5]. Similarly, with an ARR of 0.57% for GIB, a 1.8-fold increase in NNT was observed in RWS compared to ARISTOTLE. Despite an ARR of 1.67% in all-cause death, the NNT was lower in RWS than in the ARISTOTLE trial.
DISCUSSION

Our systematic review and meta-analysis shows that use of apixaban in real-life is associated with an overall non-significant difference in stroke and any thromboembolic events when compared to warfarin. A better safety profile was demonstrated when comparing apixaban use to warfarin, dabigatran or rivaroxaban.

Compared to the Phase III ARISTOTLE trial, RWS data showed that apixaban appears to have a similar effectiveness than warfarin in reducing any thromboembolic event occurrence, as seen in the randomized clinical trial context, with a slightly better effect for stroke event occurrence. Moreover, apixaban was as effective as dabigatran and rivaroxaban in reducing the risk of thromboembolic events. More importantly, apixaban was found to be strongly safer than warfarin in reducing major bleeding and particularly ICH and GIB. Also, apixaban was found to be safer than both dabigatran and rivaroxaban in reducing bleeding events. Data on mortality reduction were inconclusive in our analysis.

Since their introduction in daily practice, NOACs have been increasingly used, contributing to the increases in OAC uptake seen in several studies, even though treatment gaps still remain. NOACs are currently recommended over VKA in most of the international guidelines. Nevertheless, many patients eligible for use of NOACs are treated with a reduced dose, outwith the label recommendations for this reduced dose treatment. In an analysis from the “Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II” (ORBIT-AF II), 9.4% of patients were undertreated with reduced dose NOACs, with up to 11.8% of apixaban users prescribed with reduced dose, with reduced dose associated with increased rate of
major adverse outcomes. Our data showed that even greater proportion of patients are treated with the reduced dose, and our results suggest that treating patients with apixaban reduced dose is associated with worse outcomes. The finding that reduced dose apixaban was found more effective than dabigatran was unexpected. There is relatively limited evidence on direct or indirect comparisons of various reduced dose NOACs, so these data have to be cautiously interpreted. Indeed, we should consider the real-world observational nature of reported studies, where residual confounding may still be evident. Also, patients prescribed ‘low or reduced dose’ in RWS may be older, more fragile due to multiple comorbidities (or at least, perceived to be so).

Thus far, many RWS papers have been released about the use and comparisons of either NOACs versus warfarin, or one NOAC vs other NOAC. Carmo et al. performed a meta-analysis of dabigatran vs. warfarin in RWS, and found that dabigatran was associated with a lower risk of stroke and major bleeding. While a lower ICH risk was seen, an increased risk for GIB was reported for dabigatran 150mg. In another meta-analysis of RWS focused on rivaroxaban, Bai and colleagues reported that rivaroxaban compared with warfarin was associated with a significant reduction in thromboembolic events, but with a similar risk for major bleeding and GIB. Rivaroxaban was found to be as effective as dabigatran for prevention of thromboembolic events, but was associated with an increased risk of major bleeding.

Our paper extends prior meta-analyses in understanding the impact of apixaban in real-life clinical practice. Compared to warfarin, regular dose apixaban was associated with a marginally improved effectiveness in reducing thromboembolic
1events, even though overall the difference was non-significant and NNT indicated a
2higher number of subjects to be treated in order to avoid one thromboembolic event
3and a similar NNT for stroke prevention; however, a better safety profile, consistent
4with other RWS with other NOACs was evident. Additionally, apixaban had a similar
5effectiveness but a substantially better safety profile than dabigatran and
6rivaroxaban. Reassuring data about NOACs as a valid alternative to VKA from RWS
7have also been reported recently for secondary stroke prevention.\textsuperscript{32}
8
9Thus far, all NOACs are broadly similar in effectiveness, with some possible safety
10differences. Our data, even though based on RWS and indirect comparisons should
11be interpreted cautiously, but in the context of currently available RWS evidence,
12apixaban could possibly represent the best alternative balancing effectiveness and
13safety for many AF patients.
14
15Limitations
16Our study has various limitations. First, we could not account for quality of
17anticoagulation control, for the studies comparing apixaban with warfarin, nor
18adherence and/or persistence to NOACs. Indeed, these aspects are highly relevant
19in determining clinical outcomes.\textsuperscript{33–35} Another limitation is the relatively shorter follow-
20up of apixaban treated patients compared to other NOACs, and differences in length
21of exposure need to be considered with such comparisons.\textsuperscript{36} Additionally, several
22meta-analyses are based on studies with high-heterogeneity, as testified by large \( I^2 \)
23values. Also, the reduced number of studies included in some of the secondary
24comparisons has to be taken in consideration when interpreting the overall results.
Finally, being based on RWS, the presence of unaccountable confounders has to be taken under consideration when interpreting our results.

**SUMMARY**

In this systematic review and meta-analysis, the use of apixaban in real-life is associated with an overall similar effectiveness in reducing stroke and any thromboembolic events when compared to warfarin. A better safety profile was found with apixaban compared to warfarin, dabigatran and rivaroxaban.
1 FUNDING

No funding has been involved in the development of this project.

4 DISCLOSURES OF INTEREST

MP: Small consulting fee from Boehringer Ingelheim.

GYHL: 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. All other authors have no disclosures to declare.
REFERENCES


FIGURE LEGENDS

Figure 1: Flow-Chart of Studies’ Selection

Figure 2: Efficacy and Safety of Apixaban vs. Warfarin
Legend: A) Any Thromboembolic Events; B) Stroke; C) Major Bleeding; D) Intracranial Hemorrhage.

Figure 3: Efficacy and Safety of Apixaban vs. Dabigatran
Legend: A) Any Thromboembolic Events; B) Stroke; C) Major Bleeding; D) Intracranial Hemorrhage.

Figure 4: Efficacy and Safety of Apixaban vs. Rivaroxaban
Legend: A) Any Thromboembolic Events; B) Stroke; C) Major Bleeding; D) Intracranial Hemorrhage.

Figure 5: Number Needed-to-Treat Comparison between Real-World Studies and ARISTOTLE Trial
Legend: GIB= Gastrointestinal Bleeding; ICH= Intracranial Hemorrhage; TE= Thromboembolic Events; RWS= Real-World Studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Cohort</th>
<th>Location</th>
<th>N*</th>
<th>Reduced Dose</th>
<th>Age (Mean)</th>
<th>CHA₂DS₂-VASc (Mean)</th>
<th>Comparator(s)</th>
<th>Main Outcomes</th>
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<tr>
<td>Lee et al.⁸</td>
<td>2015</td>
<td>Single Centre Cohort</td>
<td>UK</td>
<td>53</td>
<td>NA</td>
<td>74 (Mean)</td>
<td>3</td>
<td>Warfarin, Dabigatran, Rivaroxaban</td>
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<td>Shiga et al.⁹</td>
<td>2015</td>
<td>Single Centre Cohort</td>
<td>Japan</td>
<td>102</td>
<td>36 (35.3%)</td>
<td>70 (Median)</td>
<td>NA</td>
<td>Warfarin, Dabigatran, Rivaroxaban</td>
<td>Discontinuation, TE, Major Bleeding</td>
<td>1.83-2 years</td>
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<tr>
<td>Al-Khalili et al.¹⁰</td>
<td>2016</td>
<td>Single Centre Cohort</td>
<td>Sweden</td>
<td>251</td>
<td>NA</td>
<td>73 (Median)</td>
<td>3</td>
<td>Dabigatran, Rivaroxaban</td>
<td>Any Bleeding, Discontinuation, All-Cause Death</td>
<td>0.95-1.18 years</td>
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<td>Coleman et al.¹¹</td>
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<td>Insurance Cohort</td>
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<td>4332</td>
<td>671 (15.5%)</td>
<td>71 (Median)</td>
<td>3.47</td>
<td>Warfarin</td>
<td>ICH, Ischemic Stroke</td>
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<td>2016</td>
<td>Nationwide Registries</td>
<td>Denmark</td>
<td>6349</td>
<td>0 (13.5%)</td>
<td>71.3 (Median)</td>
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<td>Warfarin, Dabigatran, Rivaroxaban</td>
<td>Stroke/SE, Ischemic Stroke, All-Cause Death</td>
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<td>Lip et al.¹³</td>
<td>2016</td>
<td>Insurance Database</td>
<td>USA</td>
<td>7438</td>
<td>1002 (18.3%)</td>
<td>68.5 (Median)</td>
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<td>2016</td>
<td>Insurance Database</td>
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<td>6565</td>
<td>1201 (18.3%)</td>
<td>73 (Median)</td>
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<td>(PSM Comparison) Dabigatran, Rivaroxaban</td>
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<td>2547 (36.9%)</td>
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<td>1393 (18.1%)</td>
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<td>2017</td>
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<td>Rivaroxaban (PSM Comparison)</td>
<td>Dabigatran, TE, Any Bleeding</td>
<td>0.9 year</td>
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<td>1126</td>
<td>Rivaroxaban</td>
<td>Warfarin, Any Stroke/IS/TIA, Major</td>
<td>1.07-1.61 years</td>
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<td>Halvorsen et al. [19]</td>
<td>2017</td>
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<td>Norway</td>
<td>6506</td>
<td>1901</td>
<td>Warfarin, Dabigatran, 0.9 year</td>
<td>Rivaroxaban, Major/CRNM Bleeding</td>
<td>0.39-0.58 years</td>
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<td>Halvorsen et al. [19]</td>
<td>2017</td>
<td>Nationwide</td>
<td>Norway</td>
<td>6506</td>
<td>1901</td>
<td>Warfarin, Dabigatran, 0.9 year</td>
<td>Rivaroxaban, Major/CRNM Bleeding</td>
<td>0.39-0.58 years</td>
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<tr>
<td>Lamberts et al. [20]</td>
<td>2017</td>
<td>Nationwide</td>
<td>Denmark</td>
<td>7963</td>
<td>3010</td>
<td>Warfarin, Dabigatran, 0.9 year</td>
<td>Warfarin, Major/CRNM Bleeding</td>
<td>0.73-1.4 year</td>
<td></td>
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</tr>
<tr>
<td>Lamberts et al. [20]</td>
<td>2017</td>
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<td>Denmark</td>
<td>7963</td>
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<td>0.73-1.4 year</td>
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<tr>
<td>Li et al. [21]</td>
<td>2017</td>
<td>Nationwide</td>
<td>Denmark</td>
<td>4400</td>
<td>100%</td>
<td>Warfarin</td>
<td>Stroke/SE, Major Bleeding</td>
<td>0.55 year</td>
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<tr>
<td>Nielsen et al. [22]</td>
<td>2017</td>
<td>Nationwide</td>
<td>Denmark</td>
<td>4400</td>
<td>100%</td>
<td>Warfarin</td>
<td>Stroke/SE, IS, Hemorrhagic Bleeding</td>
<td>2.3 years</td>
<td></td>
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</table>

**Legend:**
- *number of patients is referred to number of patients treated with apixaban; CRNM= Clinically-Relevant Non-Major; CVE= Cerebrovascular Events; FU= Follow-Up; GI= Gastrointestinal; ICH= Intracranial Hemorrhage; IS= Ischemic Stroke; NA= Not Available; OAC= Oral Anticoagulant; SE= Systemic Embolism; TE= Thromboembolic Events; TIA= Transient Ischemic Attach.*

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