Original Contribution

Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation

A Systematic Review and Meta-Analysis

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Background and Purpose—The use of oral anticoagulant therapy for stroke prevention in atrial fibrillation has been transformed by the availability of the nonvitamin K antagonist oral anticoagulants. Real-world studies on the use of nonvitamin K antagonist oral anticoagulants would help elucidate their effectiveness and safety in daily clinical practice. Apixaban was the third nonvitamin K antagonist oral anticoagulants introduced to clinical practice, and increasing real-world studies have been published. Our aim was to summarize current evidence about real-world studies on apixaban for stroke prevention in atrial fibrillation.

Methods—We performed a systematic review and meta-analysis of all observational real-world studies comparing apixaban with other available oral anticoagulant drugs.

Results—From the original 9680 results retrieved, 16 studies have been included in the final meta-analysis. Compared with warfarin, apixaban regular dose was more effective in reducing any thromboembolic event (odds ratio: 0.77; 95% confidence interval: 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 with warfarin, dabigatran, and rivaroxaban (relative risk reduction, 38%, 35%, and 46%, respectively). Similarly, the risk for intracranial hemorrhage 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 with all oral anticoagulant 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 with warfarin. A better safety profile was found with apixaban compared with warfarin, dabigatran, and rivaroxaban. **(*Stroke*. 2017;49:00-00. DOI: 10.1161/STROKEAHA.117.018395.)**

Key Words: apixaban ■ atrial fibrillation ■ major bleeding ■ stroke ■ warfarin

The use of oral anticoagulant (OAC) therapy for stroke prevention in atrial fibrillation (AF) has been transformed by the availability of the nonvitamin K antagonist oral anticoagulants (NOACs) which show relative efficacy, safety, and convenient alternatives to the vitamin K antagonists (eg, warfarin).[1,2] Currently, 4 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 postmarketing observational real-world studies (RWS) have largely reflected the sequence these drugs have been introduced to the market.[3] Compared with 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 analyzed 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).

Methods

To perform this systematic review and meta-analysis, the following criteria for studies selection were considered: (1) observational studies focusing on patients with established AF; (2) studies reporting data on patients with AF prescribed with OAC, comparing data about patients treated with apixaban and warfarin, dabigatran, rivaroxaban,

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or edoxaban and their impact on major adverse events on follow-up observation; (3) At least 100 patients, with 50 patients taking apixaban or a relevant subgroup of apixaban treated patients; (4) At least 3 months of follow-up. Exclusion criteria were as follows: (1) conference abstracts, letters, comments, case reports, and editorials; (2) studies not published in English. No explicit protocol was drafted to perform the systematic review. The systematic review and meta-analysis were performed according to PRISMA recommendations (http://www.prisma-statement.org/). The data that support the findings of this study are available from the corresponding author on reasonable request.

Search Strategy

A comprehensive literature search was performed using PubMed and Scopus databases up to 6 March, 2017. Search terms included atrial fibrillation, apixaban, dabigatran, rivaroxaban, and edoxaban. The electronic search was performed 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,[6] and statistical analysis have been reported in the online-only Data Supplement. All statistical analyses were undertaken using Review Manager (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. After the exclusion of 158 papers and the after addition of 2 papers, based on authors knowledge, a total of 16 studies[7–22] were included in the systematic review and the final meta-analysis (Table).

Study Characteristics

Overall, a total of 170814 patients treated with apixaban were included in the 16 studies. Of these, 2 studies were published in 2015,[8,9] 7 studies were published in 2016,[10–16] and 7 studies were published in 2017.[7,17–22] Three of 16 studies were single-center cohort studies,[8–10] 6 studies were retrieved from insurance databases, 1 study was a regional database,[7] and 6 studies were taken from nationwide registries.[12,15,18–20,22] Eight studies were based in Europe while 6 studies were based in United States, 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; 1 study enrolled slightly younger patients, mean (SD) age 68.5 (12.4) years[13] while another study enrolled significantly older patients, mean (SD) age 83.9 (8.2) years.[22] Four studies enrolling patients with a high thromboembolic risk (CHA_2DS_2-VASc score ≥4 [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category]).[14,16,17,22] Eight studies compared apixaban with warfarin, dabigatran, and rivaroxaban[8,9,12,13,15,19,20,22]; 4 studies compared

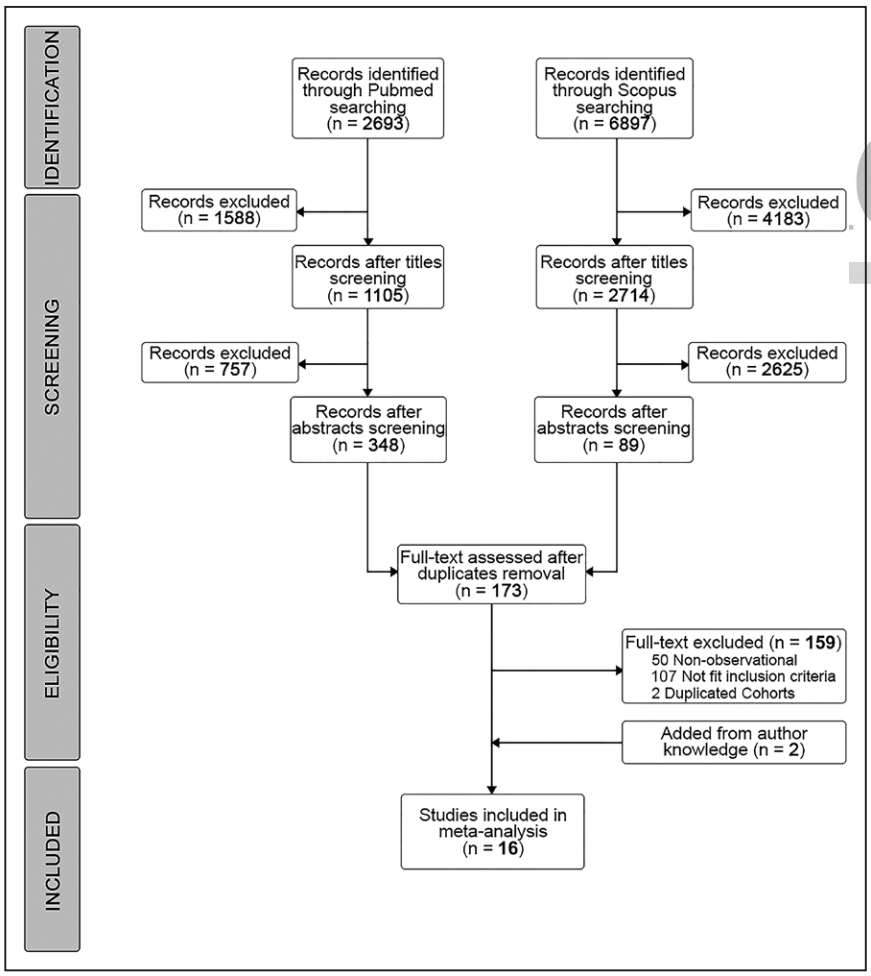

Figure 1. Flow-chart of studies' selection process.

Table. Selected Studies for Systematic Review and Meta-Analysis

Study	Year	Study Cohort	Location	n*	Reduced Dose	Age (Mean)	CHA_2DS_2-VASc (Mean)	Comparator(s)	Main Outcomes	FU (Mean)
Lee et al[8]	2015	Single-center cohort	United Kingdom	53	NA	74	3 (median)	Warfarin, dabigatran, rivaroxaban	CVE, any bleeding, all-cause death, OAC switching	0.92 y
Shiga et al[9]	2015	Single-center cohort	Japan	102	36 (35.3%)	70	NA	Warfarin, dabigatran, rivaroxaban	Discontinuation, TE, major bleeding	1.83–2 y
Al-Khalili et al[10]	2016	Single-center cohort	Sweden	251	NA	73	3 (median)	Dabigatran, rivaroxaban	Any bleeding, discontinuation, TE, all-cause death	0.95–1.18 y
Coleman et al[11]	2016	Insurance database	United States	4332	671 (15.5%)	71	3.47	Warfarin	ICH, ischemic stroke	0.48–0.52 y
Larsen et al[12]	2016	Nationwide registries	Denmark	6349	0	71.3	2.8	Warfarin, dabigatran, rivaroxaban	Stroke/SE, ischemic stroke, all-cause death	1.9 y
Lip et al[13]	2016	Insurance database	United States	7438	1002 (13.5%)	68.5	2.8	Warfarin, dabigatran, rivaroxaban (PSM comparison)	Major bleeding	0.40–0.48 y
Noseworthy et al[14]	2016	Insurance database	United States	6565	1201 (18.3%)	73 (median)	4 (median)	Dabigatran, rivaroxaban (PSM comparison)	Stroke/SE, major bleeding	NA
Staerk et al[15]	2016	Nationwide registries	Denmark	6899	2547 (36.9%)	76 (median)	3.11	Warfarin, dabigatran, rivaroxaban	Stroke/SE, ICH	0.56–1.06 y
Yao et al[16]	2016	Insurance database	United States	7698	1393 (18.1%)	73 (median)	4 (median)	Warfarin	Stroke/SE, major bleeding	0.50 y
Abraham et al[17]	2017	Insurance database	United States	6576	NA	72.3	4.0	Dabigatran, rivaroxaban (PSM comparison)	GI bleed	NA
Altay et al[18]	2017	Nationwide registry	Turkey	625	NA	70.3	NA	Dabigatran, rivaroxaban	TE, any bleeding	0.9 y
Forslund et al[7]	2017	Regional registry	Sweden	3587	1126 (31.4%)	75	3.69	Warfarin	Any stroke/IS/TIA, major bleeding, all-cause death	1.07–1.61 y
Halvorsen et al[19]	2017	Nationwide registries	Norway	6506	1901 (29.2%)	74.5	2.93	Warfarin, dabigatran, rivaroxaban	Major/CRNM bleeding	0.39–0.58 y
Lamberts et al[20]	2017	Nationwide registries	Denmark	7963	3010 (37.8%)	75.4	3 (median)	Warfarin, Dabigatran, rivaroxaban	Major bleeding, persistence	0.73–1.4 y
Li et al[21]	2017	Insurance database	United States	38 470	6568 (17.1%)	70.9	3.2	Warfarin (PSM comparison)	Stroke/SE, major bleeding	0.55 y
Nielsen et al[22]	2017	Nationwide registries	Denmark	4400	100%	83.9	4.3	Warfarin, dabigatran, rivaroxaban	Stroke/SE, IS, hemorrhagic stroke, major bleeding, GI bleeding, any bleeding	2.3 y

CRNM indicates clinically relevant nonmajor; CVE, cerebrovascular events; FU, follow-up; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; NA, not available; OAC, oral anticoagulant; PSM, propensity score matching; SE, systemic embolism; TE, thromboembolic events; and TIA, transient ischemic attach.

*Number of patients is referred to number of patients treated with apixaban.

apixaban directly only with warfarin[7,11,16,21]; and 4 studies compared apixaban with both dabigatran and rivaroxaban.[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.[7,9,11,13–16,19–21] The lowest proportion of the reduced dose was 13.5%[13] whereas the highest proportion reported was 37.8%[20]; of note, 5 of 10 studies reported a proportion of reduced dose of >25%.[7,9,15,19,20] One study comprised only patients prescribed with NOACs reduced dose.[22]

Study Results

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

Overall, the studies that compared apixaban with dabigatran and rivaroxaban found that apixaban was broadly comparable with dabigatran in terms of stroke/systemic embolic events with unclear differences compared with rivaroxaban.[10,14,18] Conversely, apixaban demonstrated a significant lower risk for major bleeding events.[10,14,17,18] In the study by Abraham et al,[17] the lower risk of gastrointestinal bleeding (GIB) with apixaban was independent of age strata.

Risk of Bias Evaluation

A bias evaluation was performed (Table I in the online-only Data Supplement). Overall, most studies reported a low risk of bias (11 studies) while 3 studies[10,12,22] had a moderate risk of bias and 2 studies[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 and II in the online-only Data Supplement) while a small effect could be detected for rivaroxaban, particularly for the any thromboembolic event outcome (Figure III in the online-only Data Supplement) and similarly for dabigatran, particularly for the major bleeding outcome (Figure IIB in the online-only Data Supplement).

Meta-Analysis of Selected Studies

Apixaban Versus 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 2A). 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 2B). 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 Data Supplement).

Compared with 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 dose subgroups (Figure 2C). 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; P<0.00001) compared with warfarin (Figure V in the online-only Data Supplement). The risk for any bleeding was also lower in apixaban patients (P=0.009; Figure VI in the online-only Data Supplement).

Given the extremely high level of heterogeneity, we did not perform meta-analysis for occurrence of all-cause death. Currently, only a limited number of RWS reported on all-cause death risks comparing apixaban and warfarin (Figure

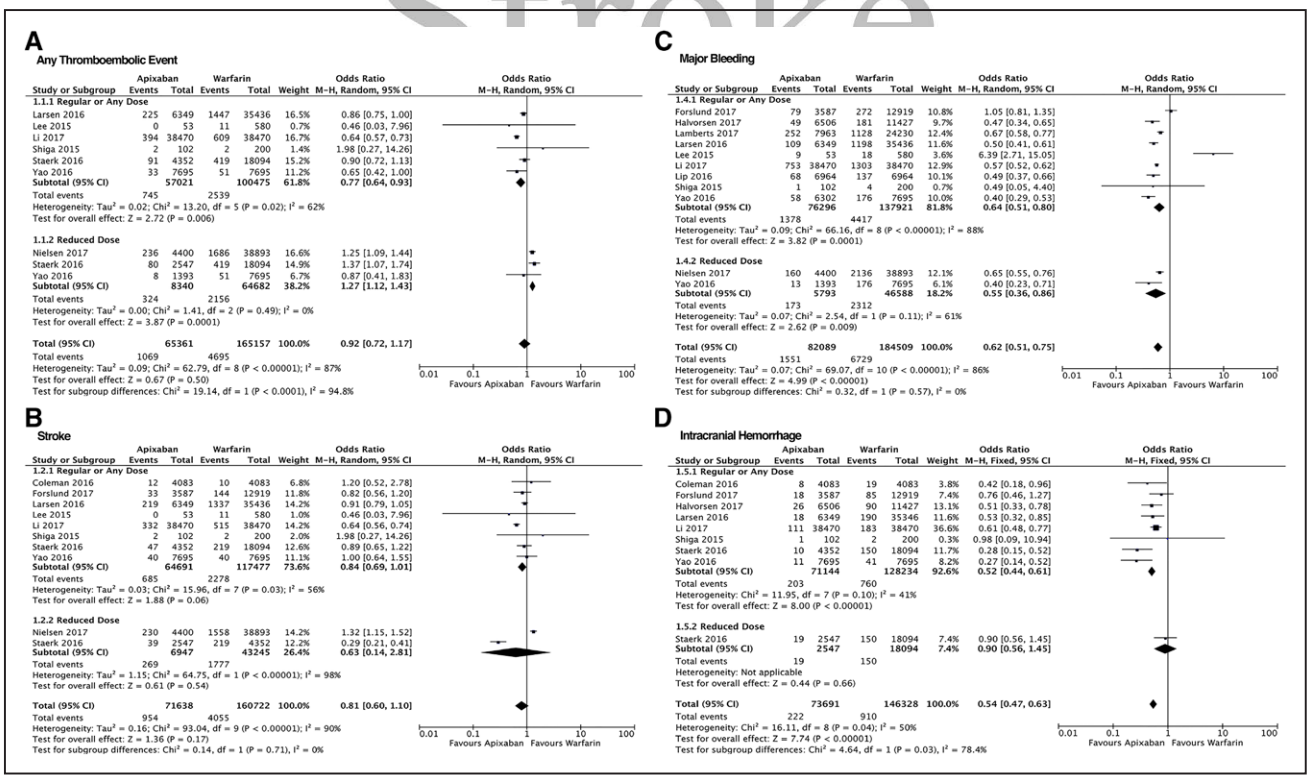

Figure 2. Efficacy and safety of apixaban vs warfarin. **A**, Any thromboembolic events; (**B**) stroke; (**C**) major bleeding; and (**D**) intracranial hemorrhage. CI indicates confidence interval.

VII in the online-only Data Supplement). These studies reported varying results with 1 study suggesting a significant protection for apixaban, 1 study suggesting no difference, and 1 study indicating a higher risk for apixaban even though it compared warfarin with apixaban reduced dose.

Number of events for Forslund et al[7] were retrieved from hazard ratios (see Methods in the online-only Data Supplement). A sensitivity analysis excluding that study showed superimposable results (data not shown).

Apixaban Versus Dabigatran

Overall, there were nonsignificant 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 3A). No difference was seen for stroke risk (Figure 3B).

Major bleeding risk was significantly lower in apixaban patients compared with dabigatran ones (35% RRR; P<0.00001) even though only 1 study was included in the reduced dose subgroup (Figure 3C). Although no difference was found for ICH (Figure 3D), 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 and IX in the online-only Data Supplement). No difference was found in all-cause death between apixaban and dabigatran (Figure X in the online-only Data Supplement).

Number of events for Noseworthy et al[14] were retrieved from hazard ratios (see Methods in the online-only Data Supplement). A sensitivity analysis excluding that study showed superimposable results (data not shown).

Apixaban Versus Rivaroxaban

Compared with 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 4A and 4B). No difference was found for hemorrhagic stroke occurrence although few studies were available for evaluation (Figure XI in the online-only Data Supplement).

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

Number of events for Noseworthy et al[14] were retrieved from hazard ratios (see Methods in the online-only Data Supplement). A sensitivity analysis excluding that study showed superimposable results (data not shown).

Bias-Stratified Sensitivity Analysis

A sensitivity analysis was performed, grouping studies according to risk of bias verifying all the outcomes for which a significant treatment effect was found, either for apixaban or any of the comparators. No significant differences were found for

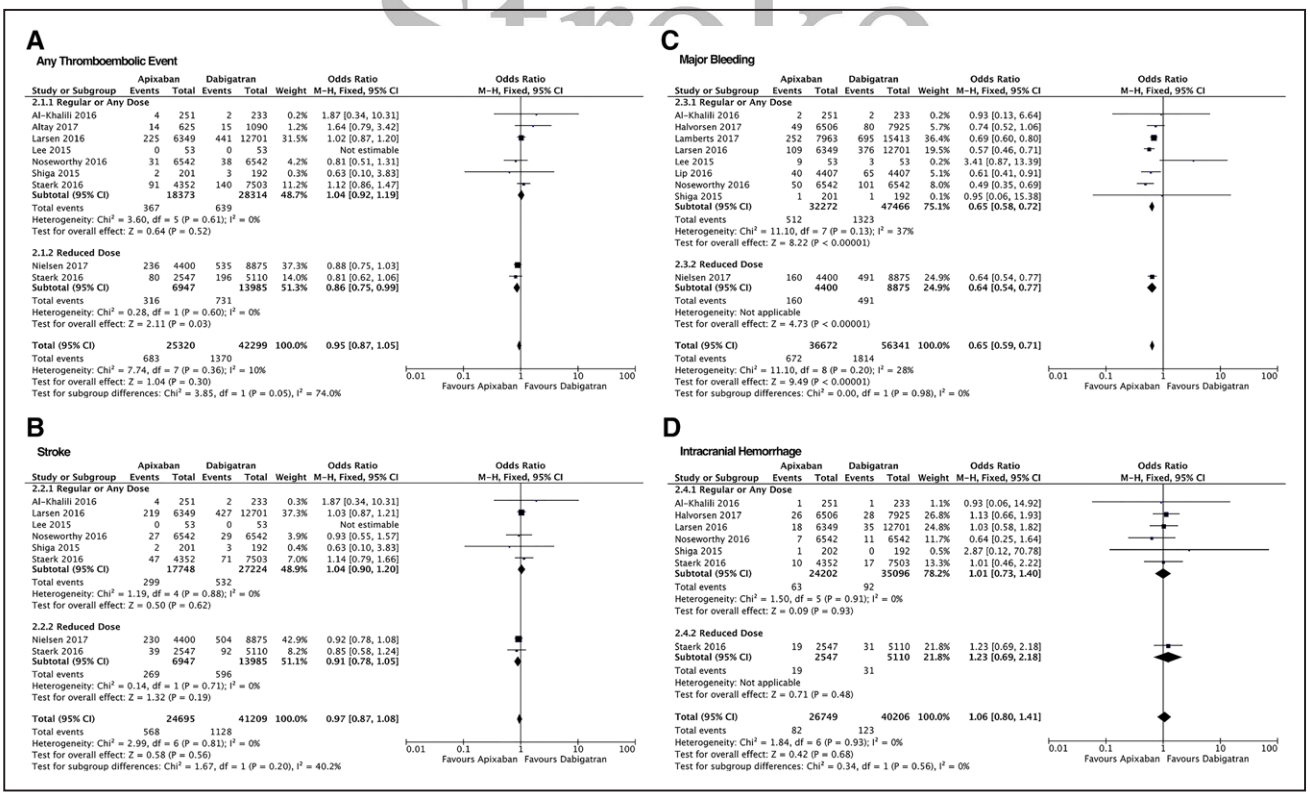

Figure 3. Efficacy and safety of apixaban vs dabigatran. **A**, Any thromboembolic events; (**B**) stroke; (**C**) major bleeding; and (**D**) intracranial hemorrhage. CI indicates confidence interval.

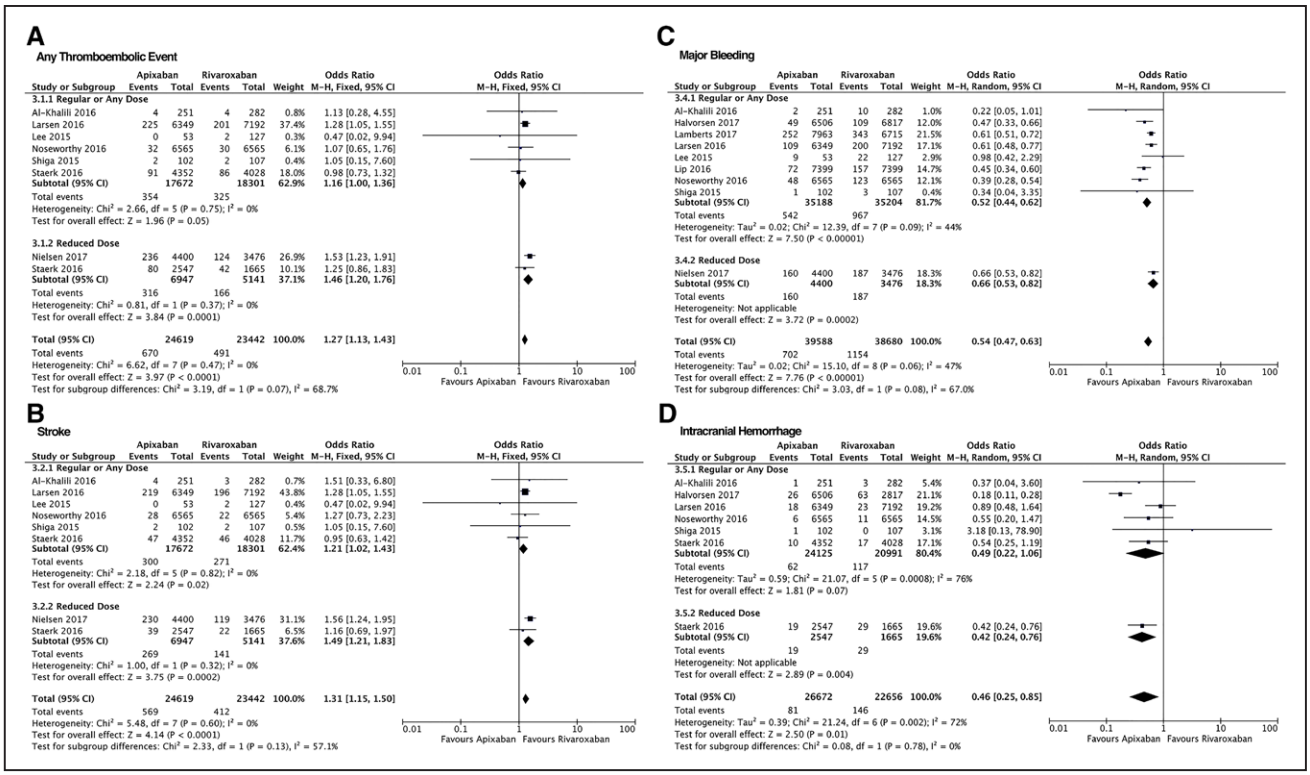

Figure 4. Efficacy and safety of apixaban vs rivaroxaban. **A**, Any thromboembolic events; (**B**) stroke; (**C**) major bleeding; and (**D**) intracranial hemorrhage. CI indicates confidence interval.

most of the outcomes analyzed (data not shown). For the comparison of apixaban versus warfarin for any thromboembolic event, bias-stratified analysis found a 25% RRR ($P<0.00001$) when considering only low risk of bias studies (Figure XV in the online-only Data Supplement). The risk reduction for any thromboembolic event occurrence with rivaroxaban was driven by the moderate/high risk of bias studies (OR, 1.38; 95% CI, 1.19–1.59) while no significant difference was found for the low risk of bias subgroup (OR, 1.10; 95% CI, 0.89–1.35; Figure XVI in the online-only Data Supplement). Similar findings were seen for stroke occurrence (Figure XVII in the online-only Data Supplement).

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

To assess the effectiveness of apixaban compared with warfarin in RWS, we estimated absolute risk reduction (ARR) and number-needed to treat (NNT). Compared with 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 (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation),[23] apixaban allowed a consistently higher NNT for any thromboembolic event while a similar clinical effectiveness was found for stroke events (Figure 5).

For major bleeding events, an ARR of 1.41% resulting in an NNT of 71, similar to ARISTOTLE. For ICH, a 2.7-fold increase in NNT was seen compared with ARISTOTLE (345 versus 128) because of 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 with 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 show that use of apixaban in real-life is associated with an overall nonsignificant difference in stroke and any thromboembolic events when compared with warfarin. A better safety profile was demonstrated when comparing apixaban use to warfarin, dabigatran, or rivaroxaban.

Compared with the phase III ARISTOTLE trial,[23] RWS data showed that apixaban seems 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. Importantly, apixaban was found to be safer than warfarin in reducing major bleeding, particularly ICH and GIB. Also, apixaban was 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 increase in OAC uptake seen in several studies,[24–26] even though treatment gaps still remain.[27] NOACs are currently recommended over vitamin K antagonists in most of the international guidelines.[28–30] Nevertheless, many patients eligible for use of NOACs are treated with a reduced dose, outwith the label

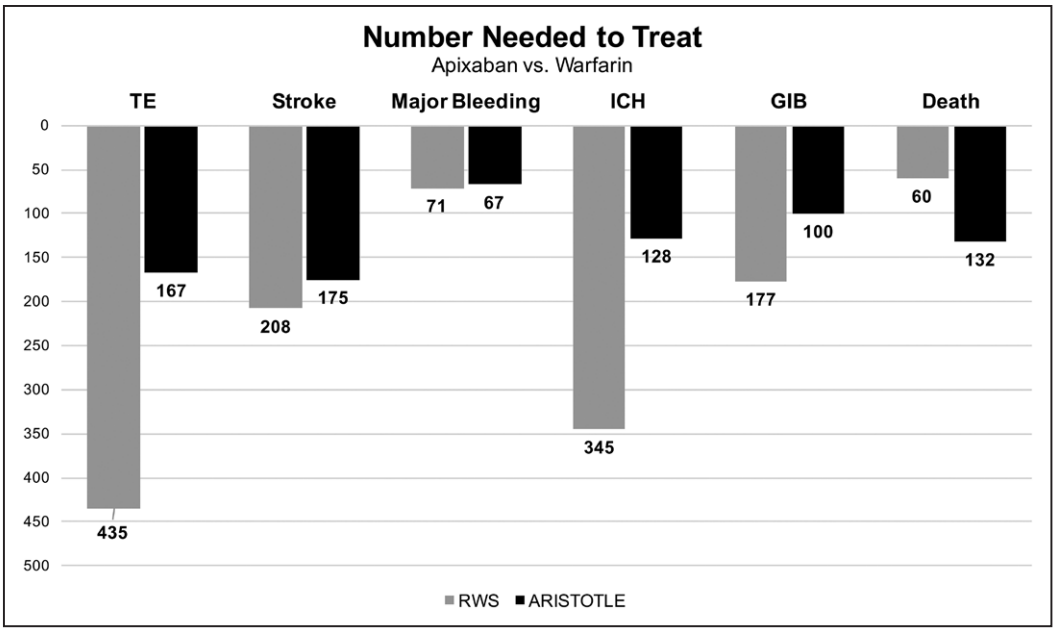

Figure 5. Number needed-to-treat comparison between real-world studies and ARISTOTLE trial. GIB indicates gastrointestinal bleeding; ICH, intracranial hemorrhage; RWS, real-world studies; and TE, thromboembolic events.

recommendations for this reduced dose treatment.[31] In an analysis from the ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase 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.[31] 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 and more fragile because of 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 1 NOAC versus other NOAC.[4,5] Carmo et al[4] performed a meta-analysis of dabigatran versus warfarin in RWS and found that dabigatran was associated with a lower risk of stroke and major bleeding. Although a lower ICH risk was seen, an increased risk for GIB was reported for dabigatran 150 mg.[4] In another meta-analysis of RWS focused on rivaroxaban, Bai et al[5] 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.[5]

Our article extends prior meta-analyses in understanding the impact of apixaban in real-life clinical practice. Compared with warfarin, regular dose apixaban was associated with a marginally improved effectiveness in reducing thromboembolic events even though overall the difference was nonsignificant and NNT indicated a higher number of subjects to be treated to avoid 1 thromboembolic event and a similar NNT for stroke prevention; however, a better safety profile, consistent with other RWS with other NOACs, was evident. In addition, apixaban had a similar effectiveness but a substantially better safety profile than dabigatran and rivaroxaban. Reassuring data about NOACs as a valid alternative to vitamin K antagonists from RWS have also been reported recently for secondary stroke prevention.[32]

Thus far, all NOACs have been considered broadly similar in effectiveness, with some possible differences in safety. Our data, even though based on indirect comparisons, and therefore to be interpreted cautiously, suggest that in the context of currently available RWS evidence apixaban could possibly represent the best alternative for OAC therapy, balancing effectiveness and safety for many patients with AF.

Limitations

Our study has various limitations. First, we could not account for quality of anticoagulation control, for the studies comparing apixaban with warfarin, nor adherence or persistence to NOACs. Indeed, these aspects are highly relevant in determining clinical outcomes.[33–35] Another limitation is the relatively shorter follow-up of apixaban-treated patients compared with other NOACs and differences in length of exposure need to be considered for such comparisons.[36] In addition, several meta-analyses are based on studies with high heterogeneity as testified by large I^2 values. Also, the reduced number of studies included in some of the secondary comparisons 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 with warfarin. A better safety profile was found for apixaban when compared with warfarin, dabigatran, and rivaroxaban.

Disclosures

Dr Proietti is a consultant for Boehringer Ingelheim. Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors report no conflicts.

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

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SUPPLEMENTAL MATERIAL

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

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SUPPLEMENTARY METHODS

Bias Assessment

All studies have been evaluated to assess the risk of bias, independently by two of the co-authors (MP and IR) according to recommendations of Agency for Healthcare Research and Quality (AHRQ)[1]. Evaluation was performed for the following bias categories: selection, performance, attrition, detection and reporting bias. Finally, an overall evaluation was performed. All studies have been categorised as low, moderate or high risk of bias. Publication bias was analysed for the main primary outcomes.

Studies Selection and Data Extraction

After search, all results have been screened by two co-authors independently (IR and GFR), with disagreement resolved by collegial discussion with a third co-author (MP). All articles retrieved from the search were evaluated according to titles, abstract and full-text evaluation, sequentially. Studies for which it was possible to clearly ascertain a relevant overlap of cohorts were evaluated according to time of data collection and/or year of publication. Accordingly, studies collected and/or published more recently were included in the analysis.

Data were extracted independently by two of the co-authors (MP and IR) using a shared electronic data sheet. All data on sample size of apixaban and any comparator subgroups, number of major adverse events, incidence rates or measures of effect were collected. Study characteristics, age and thromboembolic risk were also collected when available. Where available, data on use of reduced dose for every NOAC were extracted. Stratified analyses were performed according to the dose used when the study provided outcomes accordingly. Doses were defined as "regular or any dose" when regular dose was explicitly reported or when was not possible to establish which dose was used; "reduced dose" was used when explicitly reported for apixaban 2.5 mg bid, dabigatran 110 mg bid and rivaroxaban 15 mg od.

Outcomes Definition

Primary outcomes considered were stroke and/or any thromboembolic event, major bleeding and intracranial hemorrhage (ICH). Secondary outcomes considered where available were hemorrhagic stroke, gastrointestinal bleeding (GIB), any bleeding and all-cause death.

Outcomes were defined according to the definition and categorisation used in the original studies. Specifically, stroke outcome was used for all ischemic or undefined stroke, based on the original data. All central and/or peripheral embolic events were considered as 'any thromboembolic event'. Major bleeding, ICH, hemorrhagic stroke and GIB were defined only when they were unequivocally and undoubtedly defined as per the original study. ICH and hemorrhagic stroke were not considered as interchangeable and assigned according to the original study report and endpoint distinction. Otherwise, bleeding events were defined as "any bleeding".

Statistical Analysis

All statistical analyses were undertaken using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark). Outcomes from each study were pooled and compared using a fixed-

effect or random-effect model according to the heterogeneity between all included studies. Treatment effect was reported as odds ratio (OR) and 95% confidence interval (CI). We decided to report OR instead of RR for comparability with other references and for consistency: we have repeatedly stratified our results and used different outcomes, and OR tend to vary less over strata than risk ratios.
The I^2-statistic was quantified to measure heterogeneity. When an I^2 of >70% was observed, the DerSimonian and Laird random-effects model was used; while Mantel-Haenszel summaries were used otherwise. When there were no events in one group a pseudo-count of 0.5 was added to each cell. A sensitivity analysis, according to evaluated risk of bias, was performed for all the outcomes that reported a significant treatment effect. When necessary, the expected number of events was calculated using event rates, sample size and follow-up duration or by using subgroups sample size, hazard ratios (HR) and 95% CI. The latter was necessary for two studies which reported only HR, and given hazard rates were generally low we assumed RR and HR corresponded for that studies. Additionally, a sensitivity analysis removing those two studies led to the same conclusions reported. Absolute risk reduction (ARR) and the number-needed to treat (NNT) were calculated after pooling effect sizes for comparison between apixaban and warfarin. A p-value <0.05 was considered statistically significant.

SUPPLEMENTARY TABLES

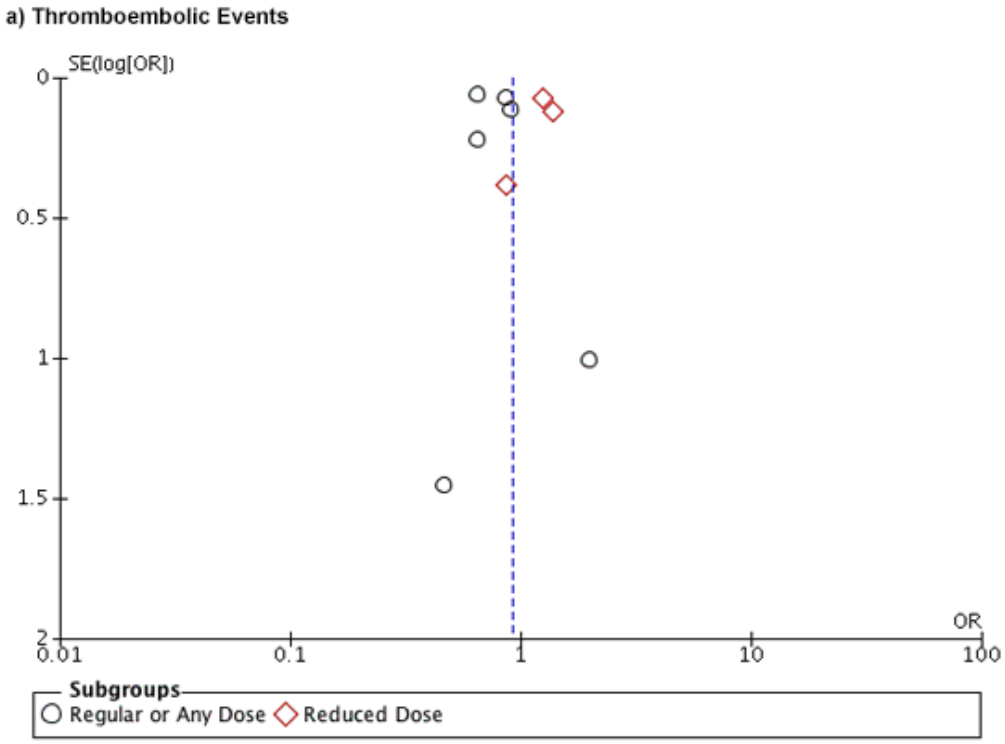
Table I: Risk of Bias Evaluation for Included Studies

STUDY	SELECTION BIAS	PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL BIAS
Lee	Moderate	High	Low	Low	High	**High**
Shiga	Low	Low	Low	Low	Low	**Low**
Al-Khalili	High	Low	Low	Low	Low	**Moderate**
Coleman	Low	Low	Low	Low	Low	**Low**
Larsen	High	Low	Low	Low	Low	**Moderate**
Lip	Low	Low	Low	Low	Low	**Low**
Noseworthy	Low	Low	Low	Low	Low	**Low**
Staerk	Low	Low	Low	Low	Low	**Low**
Yao	Moderate	Low	Low	Low	Low	**Low**
Abraham	Low	Low	Low	Low	Low	**Low**
Altay	High	High	High	Low	Moderate	**High**
Forslund	Low	Low	Low	Low	Low	**Low**
Halvorsen	Low	Low	Low	Low	Low	**Low**
Lamberts	Low	Low	Low	Low	Low	**Low**
Li	Low	Low	Low	Low	Low	**Low**
Nielsen	High	Moderate	Low	Low	Low	**Moderate**

SUPPLEMENTARY FIGURES

Figure I: Publication Bias in Main Primary Outcomes for Comparison between Apixaban and Warfarin

Legend: OR= odds ratio; SE= size effect.



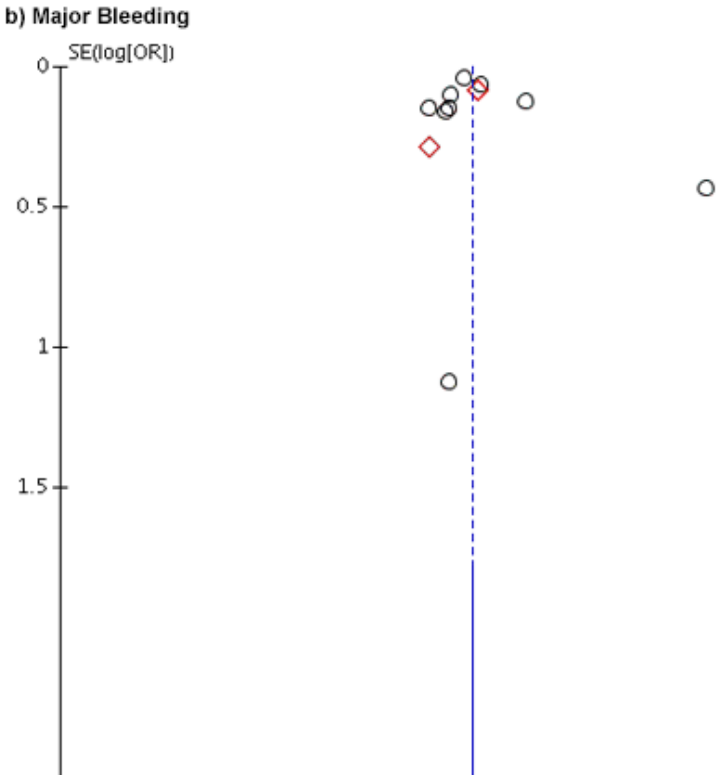


Figure II: Publication Bias in Main Primary Outcomes for Comparison between Apixaban and Dabigatran
Legend: OR= odds ratio; SE= size effect.

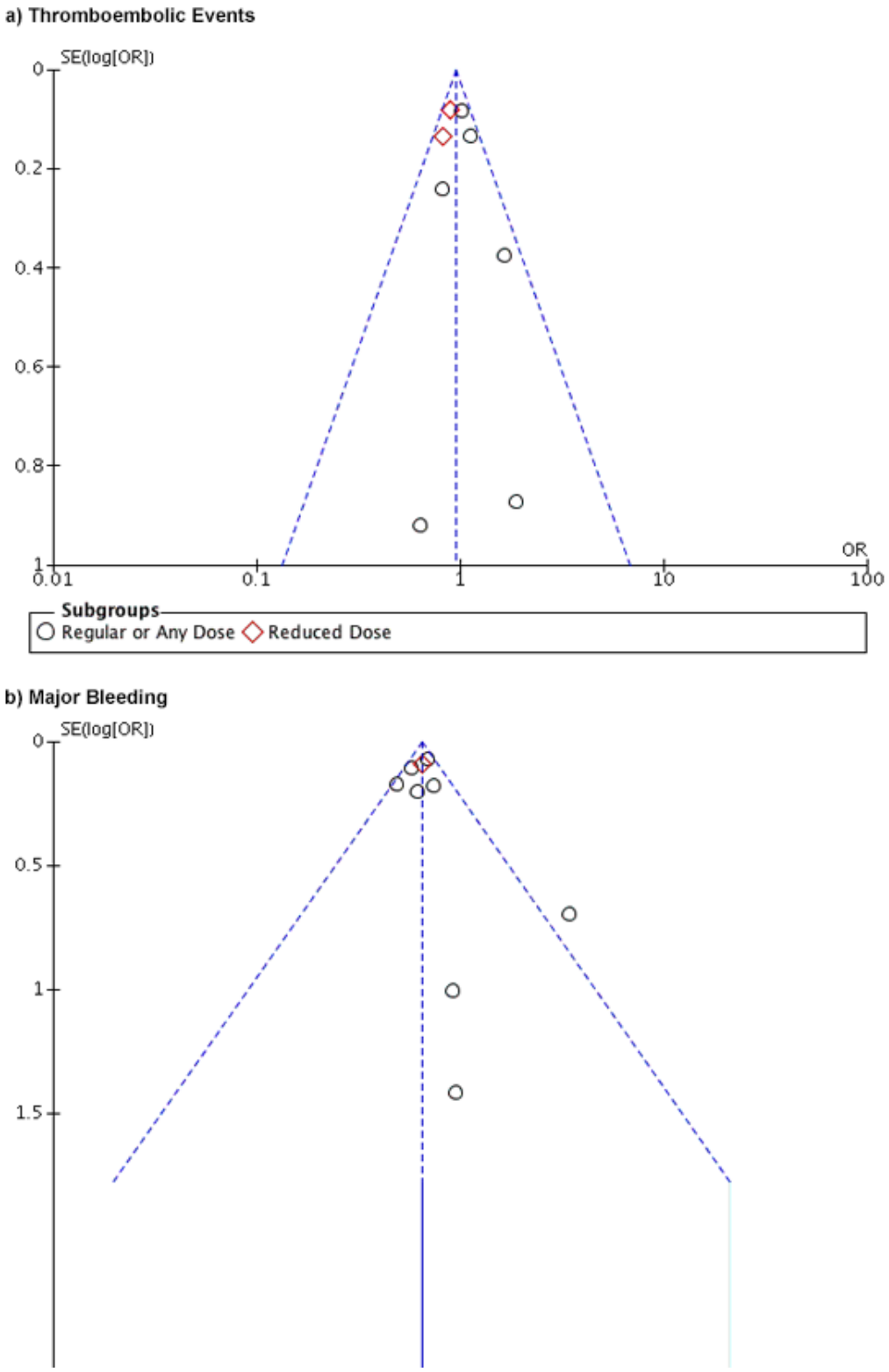
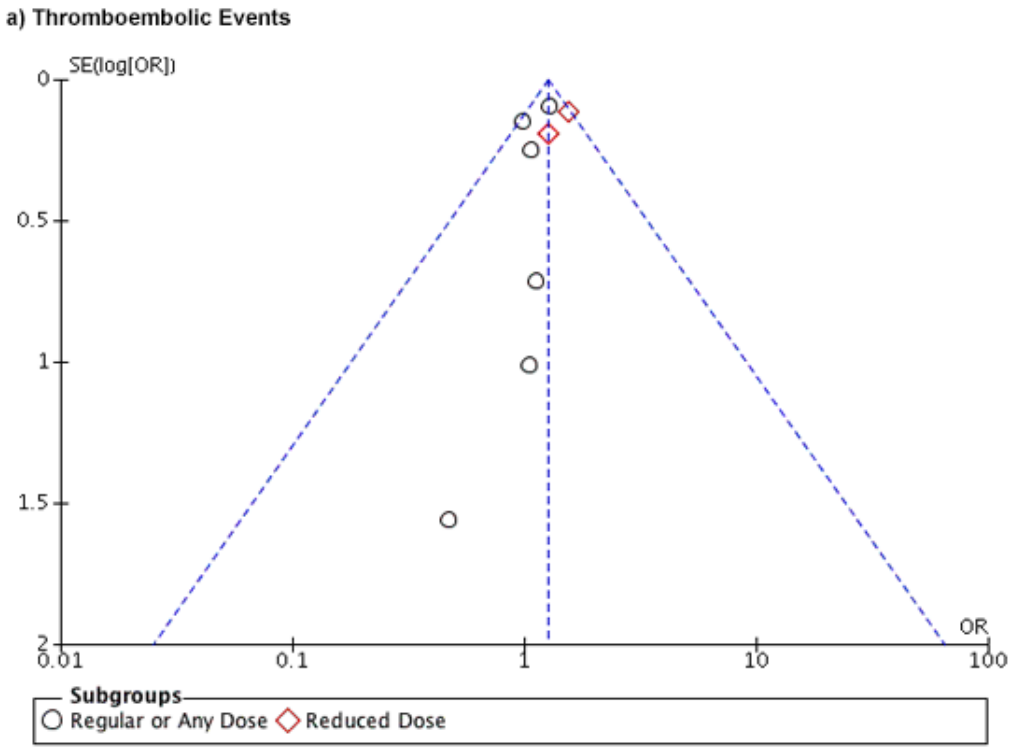


Figure III: Publication Bias in Main Primary Outcomes for Comparison between Apixaban and Rivaroxaban
Legend: OR= odds ratio; SE= size effect.



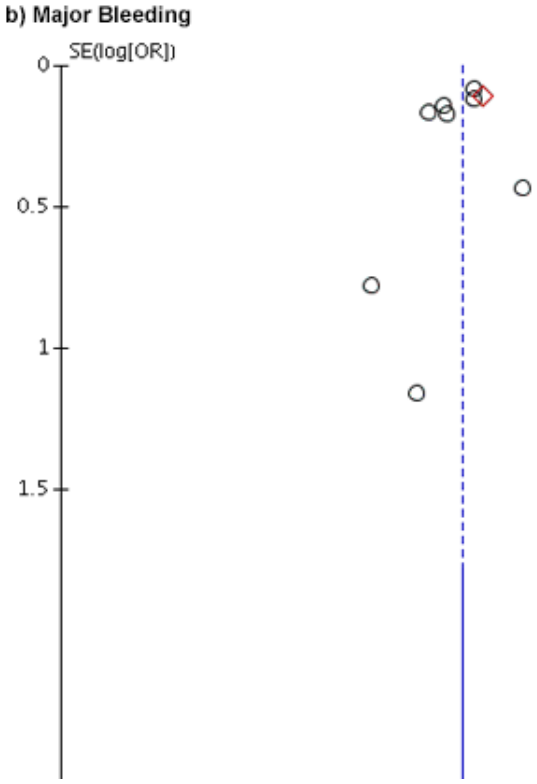


Figure IV: Comparison of Apixaban versus Warfarin in Hemorrhagic Stroke Occurrence
Legend: CI= confidence interval.

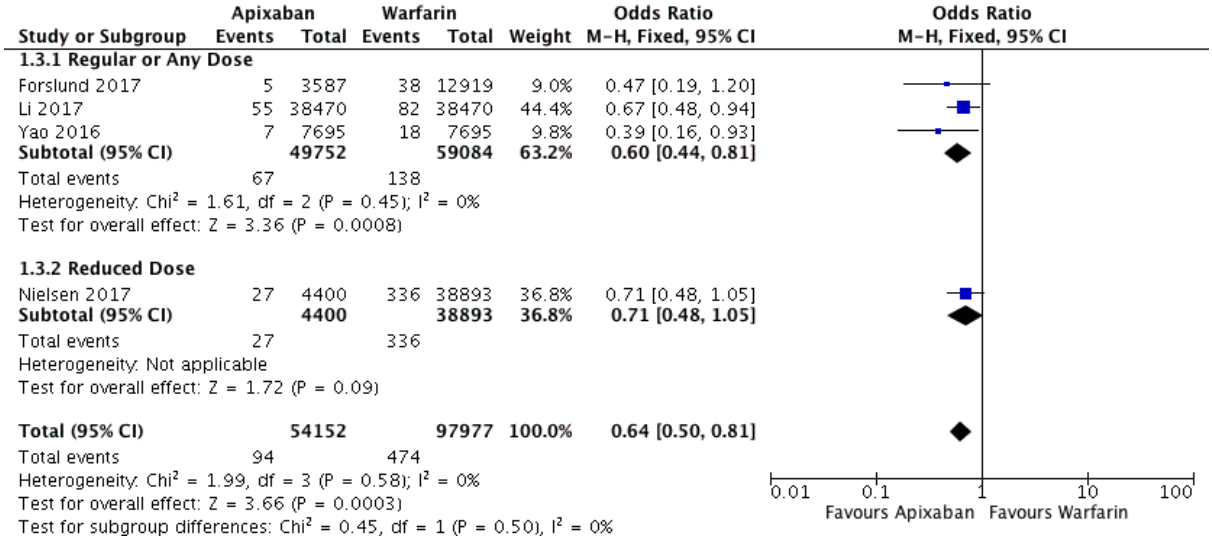


Figure V: Comparison of Apixaban versus Warfarin in Gastrointestinal Bleeding Occurrence
Legend: CI= confidence interval.

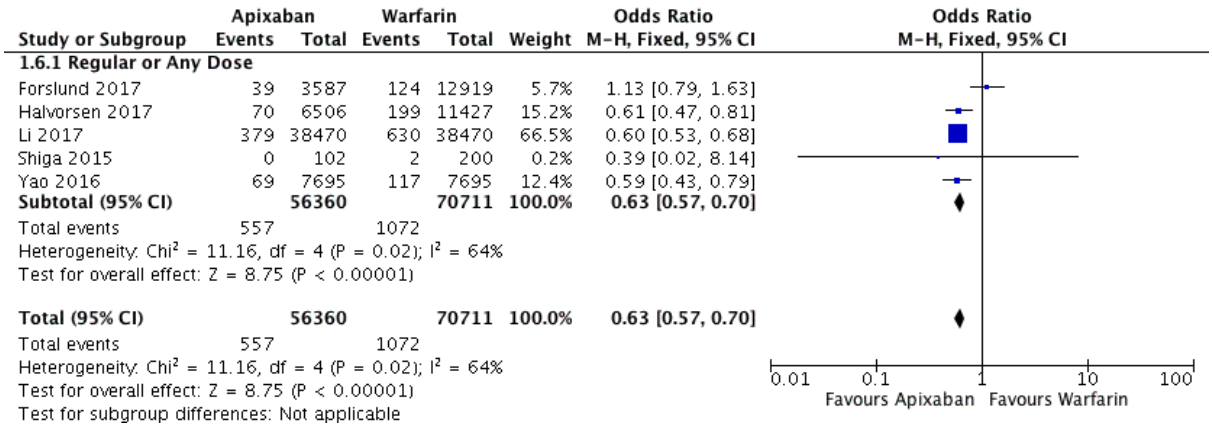
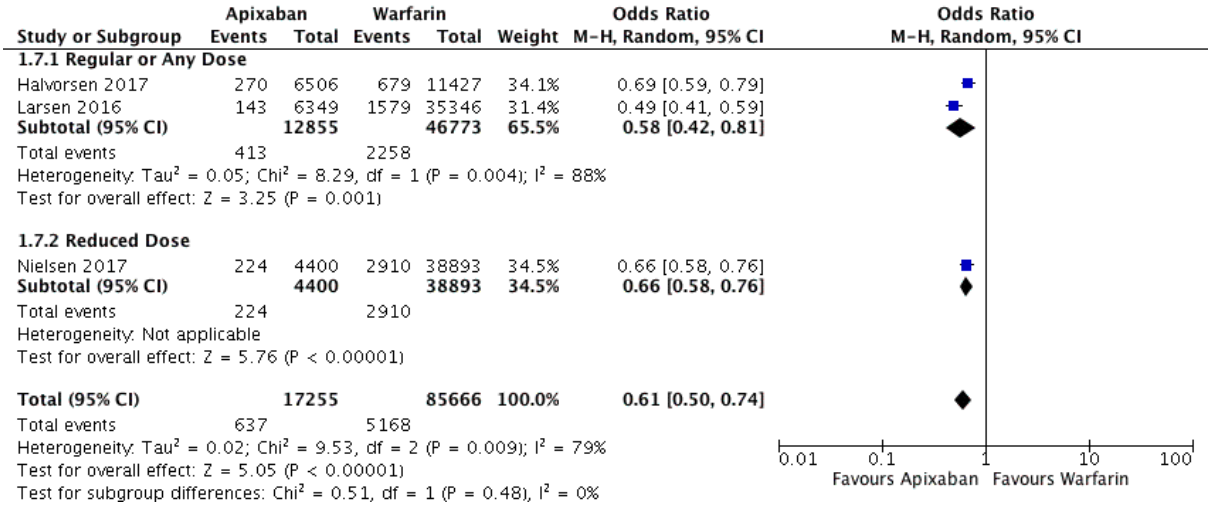


Figure VI: Comparison of Apixaban versus Warfarin in Any Bleeding Occurrence



Legend: CI= confidence interval.

Figure VII: Comparison of Apixaban versus Warfarin in All-Cause Death Occurrence
Legend: CI= confidence interval.

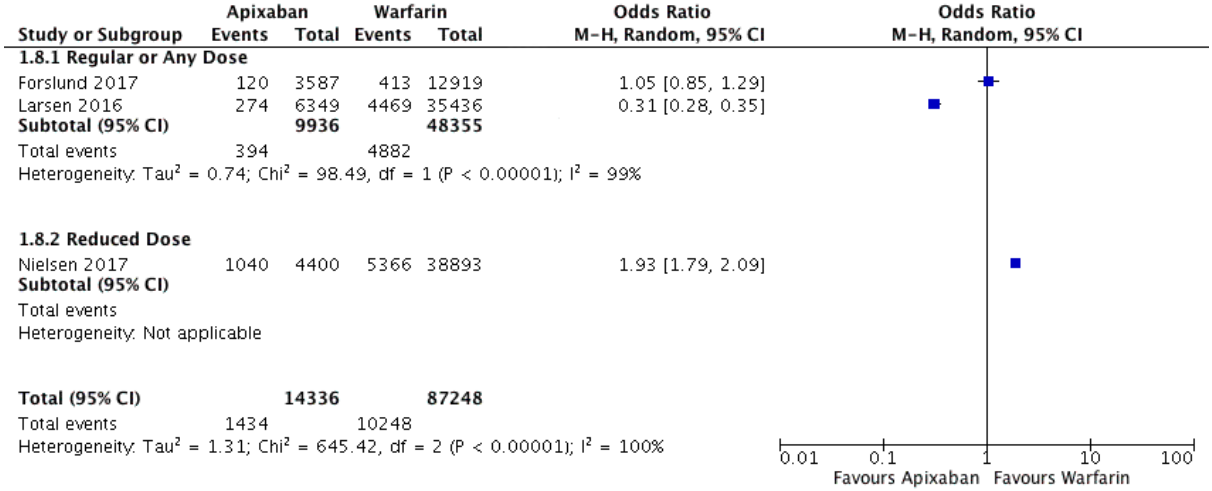


Figure VIII: Comparison of Apixaban versus Dabigatran in Gastrointestinal Bleeding Occurrence
Legend: CI= confidence interval.

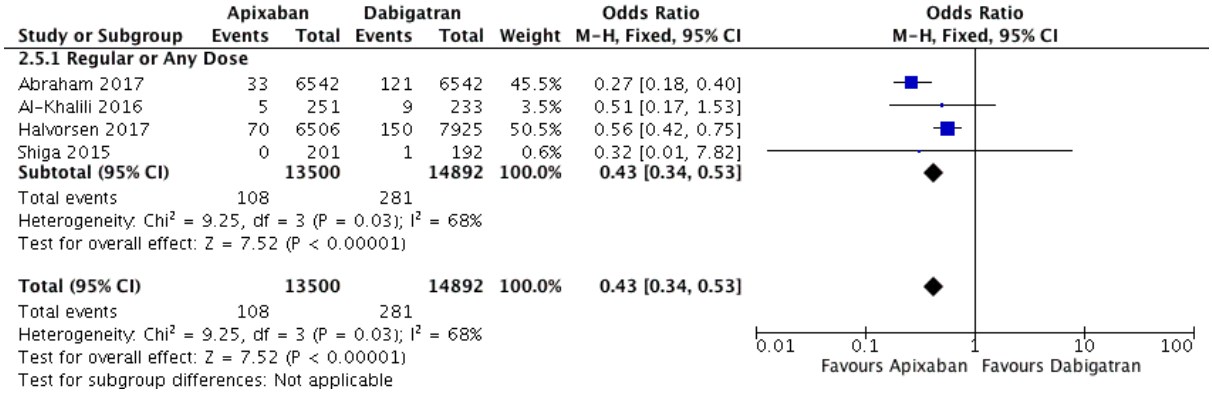


Figure IX: Comparison of Apixaban versus Dabigatran in Any Bleeding Occurrence
Legend: CI= confidence interval.

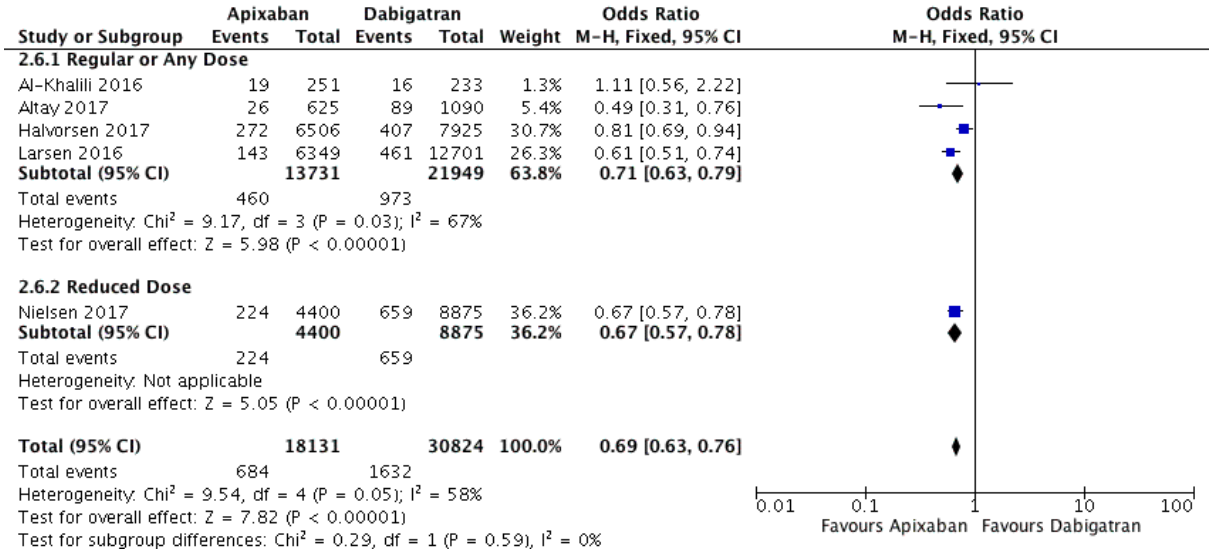


Figure X: Comparison of Apixaban versus Dabigatran in All-Cause Death Occurrence
Legend: CI= confidence interval.

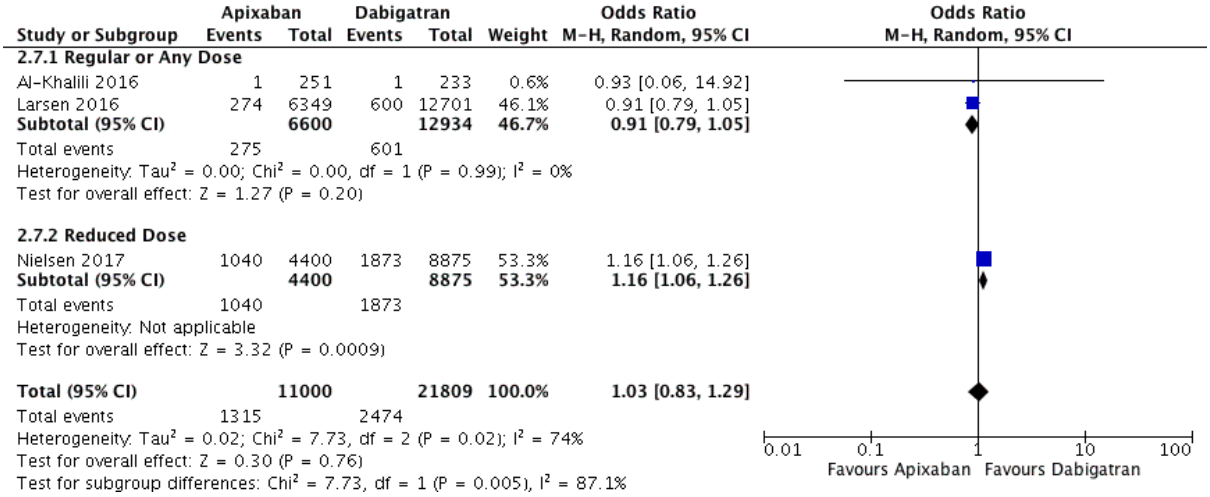


Figure XI: Comparison of Apixaban versus Rivaroxaban in Hemorrhagic Stroke Occurrence
Legend: CI= confidence interval.

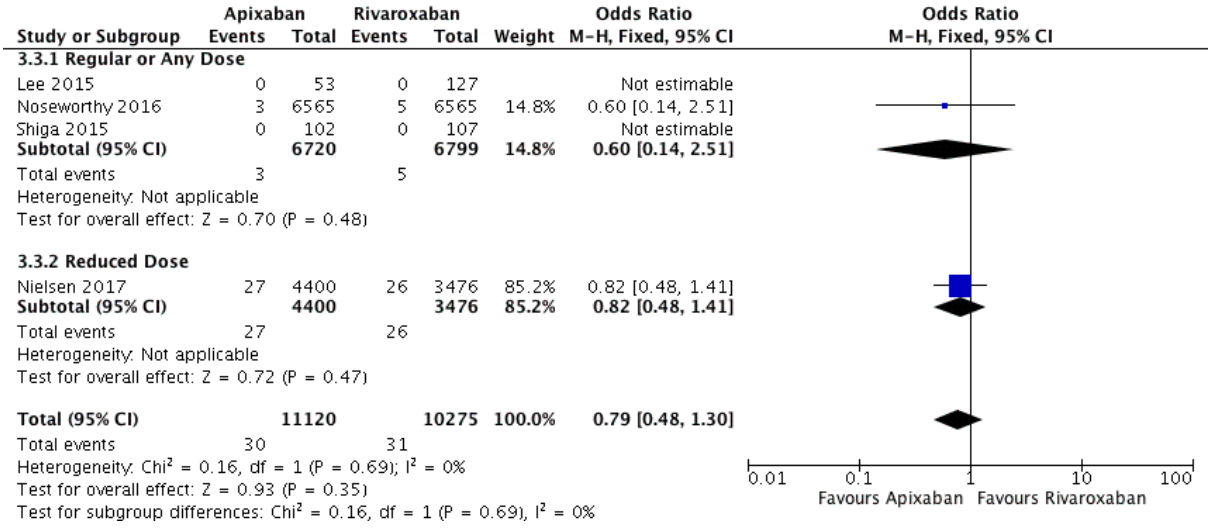


Figure XII: Comparison of Apixaban versus Rivaroxaban in Gastrointestinal Bleeding Occurrence
Legend: CI= confidence interval.

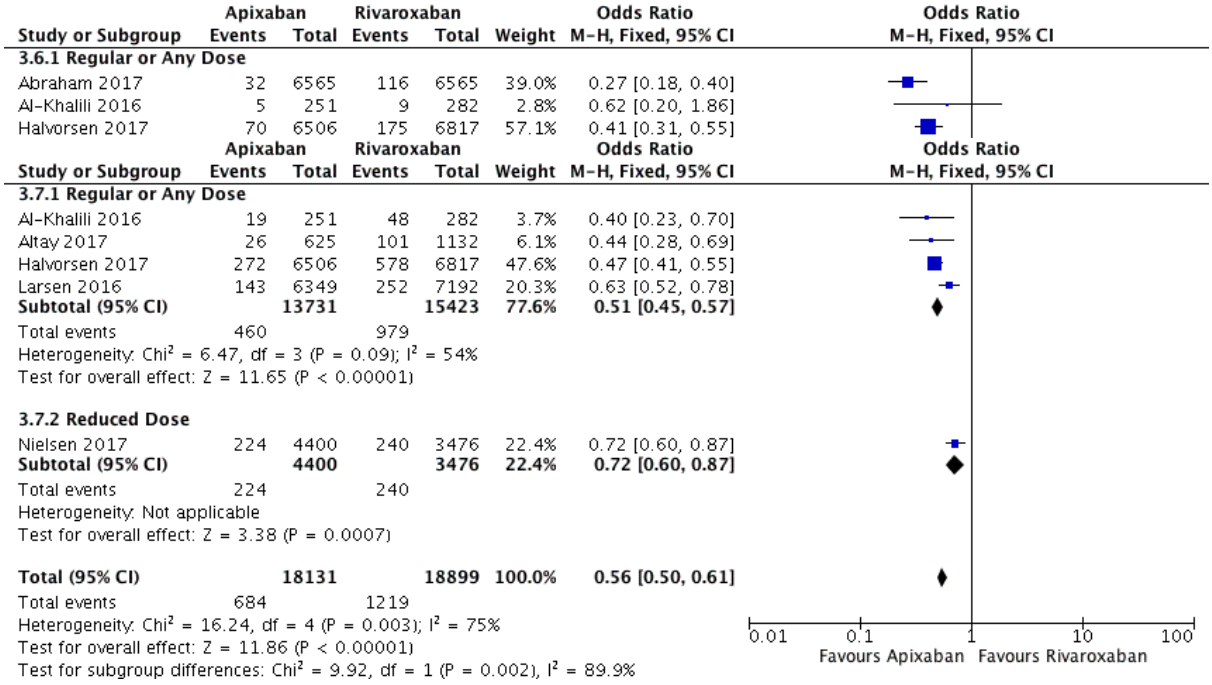


Figure XIII: Comparison of Apixaban versus Rivaroxaban in Any Bleeding Occurrence
Legend: CI= confidence interval.

Figure XIV: Comparison of Apixaban versus Rivaroxaban in All-Cause Death Occurrence
Legend: CI= confidence interval.

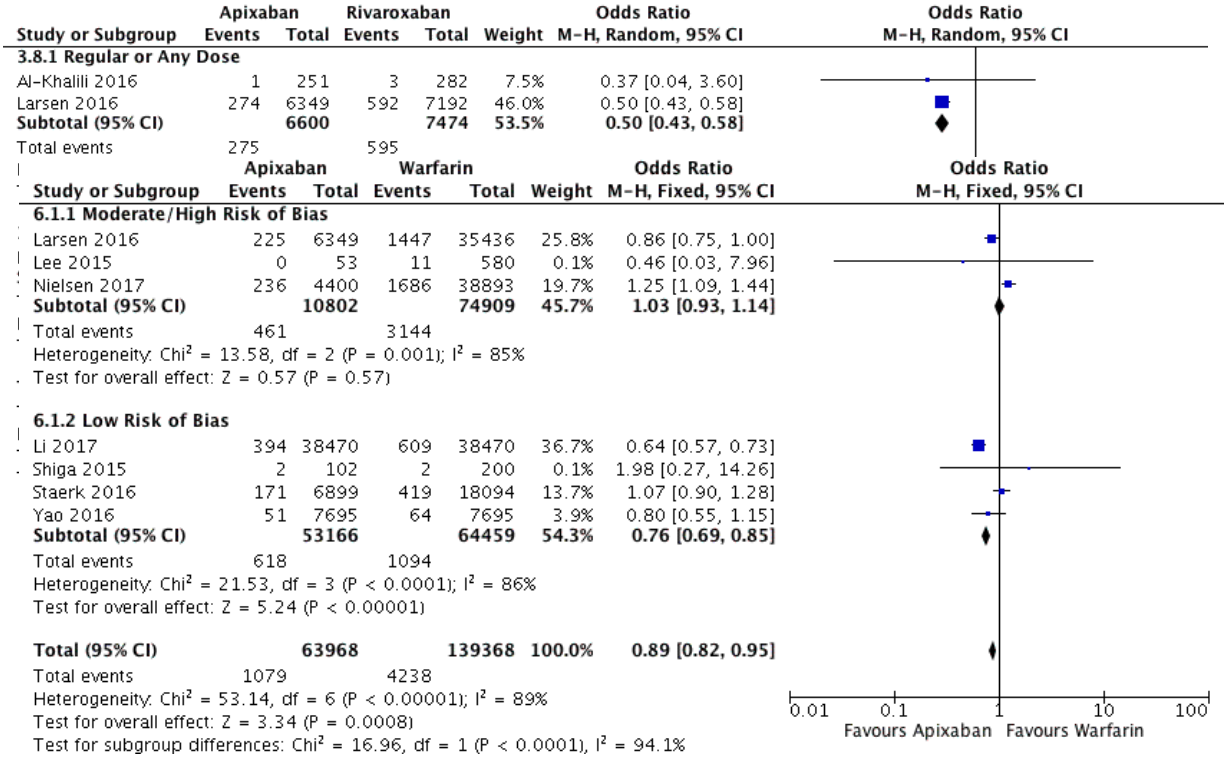


Figure XV: Comparison of Apixaban versus Warfarin in Any Thromboembolic Event Occurrence Stratified According Risk of Bias
Legend: CI= confidence interval.

Figure XVI: Comparison of Apixaban versus Rivaroxaban in Any Thromboembolic Event Occurrence Stratified According Risk of Bias
Legend: CI= confidence interval.

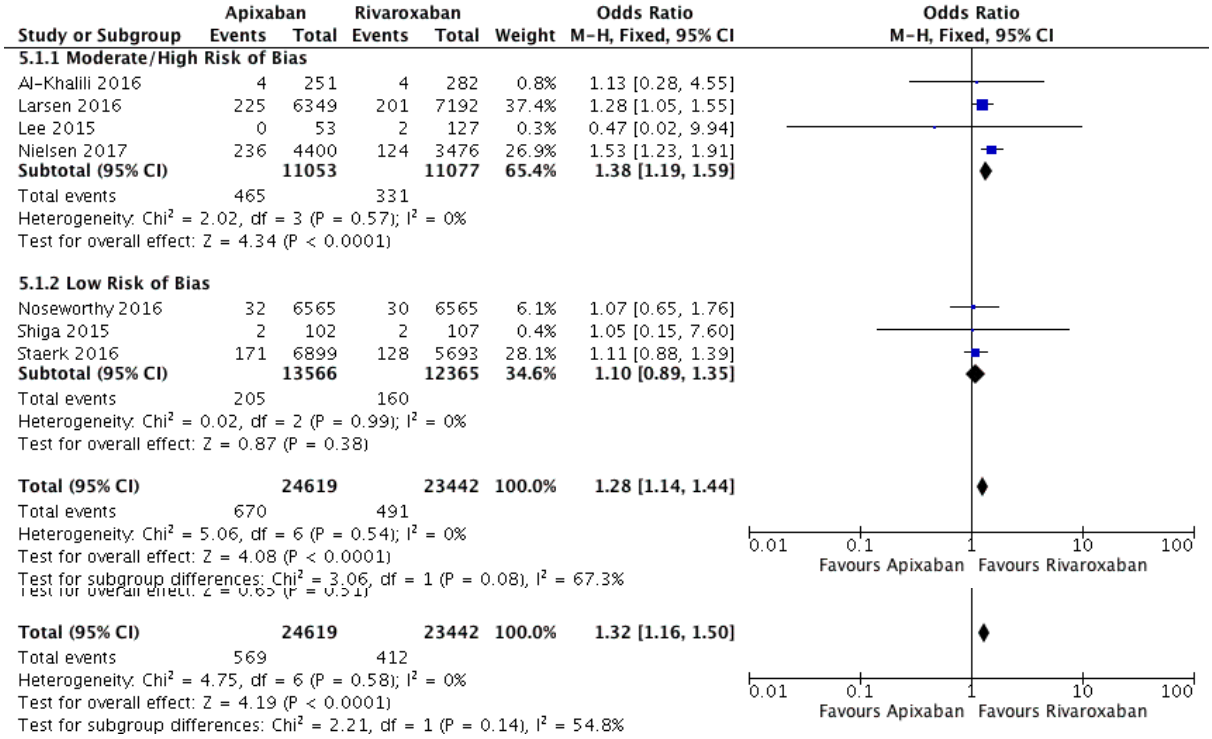


Figure XVII: Comparison of Apixaban versus Rivaroxaban in Stroke Occurrence Stratified According Risk of Bias
Legend: CI= confidence interval.

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