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## **Twice- or Once-Daily Dosing of Direct Oral Anticoagulants, a systematic review and meta-analysis**

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## ABSTRACT

**Aim.** The direct oral anticoagulants (DOAC) have similar half-lives, but the dosing regimen varies between once daily (QD) or twice daily (BID). For some prescribers, the QD regimen improves compliance. Others prefer BID regimens to promote better stability of plasma concentrations, particularly in the event of missed doses. Limited level of evidence provides guidance about the best treatment strategy. The purpose of this study was to compare the treatment effect of QD vs. BID administration of DOACs in major orthopedic surgery (MOS), non-valvular atrial fibrillation (NVAF), venous thromboembolism (VTE), and acute coronary syndrome (ACS).

**Methods.** We conducted a systematic review up to April 2020. We included phase II clinical trials comparing DOAC QD vs BID with same daily dose. We extracted data for the occurrence of major thrombosis (proximal deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke) and major hemorrhage (ISTH criteria and recommendations of the European Medicines Agency for surgical patients). Relative risks (RR) were combined using a fixed and random effects weighted meta-analysis.

**Results.** Twelve randomized, controlled, phase II trials were included (10,716 patients), representing 24 dosing regimen comparisons of apixaban, darexaban, edoxaban, rivaroxaban, letaxaban, and dabigatran. There was no difference for major thrombotic event ( $RR_{BID/QD}=1.06$ , 95%IC 0.86 – 1.30) nor for major bleeding ( $RR_{BID/QD}=1.02$ , 95%IC 0.84 – 1.23) between the BID vs QD regimens, without heterogeneity ( $I^2=0\%$ ).

**Conclusion.** Our study does not support a global difference in term of efficacy and safety of the BID and QD regimens of DOAC in MOS, NVAF, VTE and ACS.

**KEYWORDS**

Meta-analysis, direct oral anticoagulant, dosing regimen, major bleeding, risk of thrombosis

## INTRODUCTION

The direct oral anticoagulants (DOAC) inhibiting thrombin or factor Xa are now recommended for the prevention of systemic embolism in non-valvular atrial fibrillation (NVAf), the prevention of venous thromboembolism (VTE) in major orthopedic surgery (MOS) and the treatment of acute VTE and to a lesser extent, in the prevention of atherothrombotic events after acute coronary syndrome (ACS) [1,2]. Results of large phase III clinical trials have led to the approval of several DOAC by the Federal and Drug Administration and the European Medicines Agency thanks to an acceptable efficacy and a better safety profile in terms of reduction of major bleeding (MB) complications compared to vitamin K antagonist (VKA) or low molecular weight heparin (LWMH) [3–6] .

The dosing regimens in phase III clinical trials were based on the pharmacokinetics of the compound as well the effects of variable dosing fractionation on clinical outcomes in phase II trials. Therefore, according to the molecule and the indication chosen, the recommended dosing regimen varies between once daily (QD) or twice daily (BID). In pharmacokinetic models, while the QD regimen may improve compliance, the BID regimen may promote better stability of plasma concentrations, particularly in the event of missed doses, but the clinical impact of QD versus BID regimens remains unclear [7]. However, phase II clinical trials were underpowered to detect a statistical difference in outcomes between the QD and BID regimens. Consistently, a previous meta-analysis [8] suggested a superiority of BID versus QD in preventing thrombotic events, although these estimates may have been flawed by inconsistency due to the indirect comparison approach[9]. Moreover, the authors compounded several drugs depending on whether they were taken once or twice a day and restricted their analysis to atrial fibrillation, one specific indication of DOAC. The numerous randomized phase II clinical trials assessing variable DOAC dosing regimens allow the precise

estimation of the treatment effect of BID versus QD regimens on thrombotic and hemorrhagic events using head to head comparisons of multi-arms trials.

The main objective of this study is therefore to synthesize available evidence from direct comparison between twice- versus once-daily doses of DOAC for enrolled patients in phase II clinical trials comparing DOAC to active comparators or placebo.

## **METHODS**

The methods of this meta-analysis are in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. This report was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [10]. The protocol of the present study was submitted to PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>, registration CRD42020156371).

**Literature search strategy.** We searched Medline (PubMed), Embase, The Cochrane Library and ClinicalTrials.gov up to April 2020, using sensitive methods and employing the keywords: dabigatran (BIBR1048), rivaroxaban (BAY 59-7339), apixaban, betrixaban, edoxaban (DU-176b), ximelagatran, AVE5026, AZD0837, LY517717, eribaxaban (PD 0348292), RB006, SR123781A, darexaban (YM150), latexaban (TAK-442), TTP889, GW813893, RO-14, AS1927819-00, TB 402, AS1932804-00 and warfarin. Search terms included combinations of free text and medical subject headings (MeSH). The complete search strategies may be found in Appendix S1. We also reviewed the citations of the retrieved studies, reviews and meta-analyses obtained by searches of PubMed and Embase. No restriction with regard to language or population size was applied.

**Outcomes.** The efficacy outcome was major thrombotic events defined as, depending of the indication, proximal deep vein thrombosis or pulmonary embolism, stroke or myocardial

infarction, or severe recurrent ischemia. The main safety outcome was major bleeding defined by the International Society on Thrombosis and Haemostasis [11] or, the Bleeding Academy Research Consortium [12] for acute coronary syndromes or the Guidelines of European Medicines Agency for surgical patients [13], as reported in the individual trials.

**Study selection.** A single reviewer (SM) screened titles and abstracts. Then, two reviewers (SM, JCL) independently screened the full-text articles. Studies were included if the following criteria were fulfilled: randomized, controlled, phase II trials conducted in patients with ACS, NVAf, VTE, and MOS (including total knee and hip arthroplasties) thromboprophylaxis comparing the QD and BID regimen with the same daily dose of oral factor Xa or thrombin inhibitors. Patients in the control group had to receive an active referenced control or a placebo. Studies were excluded if they were cohort, cross-over or case-control studies. In case of conflict, consensus was reached through discussion.

**Data extraction and quality assessment.** Data from the included studies were independently extracted by two authors (SM, JCL). For each included study, we extracted the name of the study, first author's name, year of publication, indication (ACS, NVAf, VTE or MOS), follow-up period, number of participants, patient characteristics (mean age, male proportion), intervention drug and used doses, control drug and used dose and number of thrombotic and major bleeding events. The studies quality was assessed using the revised Cochrane tool for randomized trials [14]

**Statistical analyses.** Included studies were randomized controlled trials, therefore the risk ratio (RR) was calculated, using QD as reference, using the inverse variance weighting for pooling. The heterogeneity between studies was assessed using  $I^2$  test. Random-effects model was used if heterogeneity was detected ( $I^2 > 50\%$ ); otherwise, fixed-effect model was used. Subgroup and meta-regression analyses were planned to further investigate between-

study sources of significant heterogeneity. Four subgroups were defined for categorical variables: DOAC mechanism of action (direct reversible thrombin inhibitor or direct reversible Xa inhibitors), indication of DOAC (MOS, NVAf, VTE and ACS), the specific DOAC tested, and the DOAC approved vs. not approved. The continuous variable selected in the meta-regression was half-life of DOAC. Results were presented graphically (forest plots), including the RR and corresponding 95% confidence intervals (95% CI). The presence of publication bias was evaluated with funnel plots. The statistical significance was reached when the p-value of association was  $<0.05$ . Analyses were performed using R 3.1.2 (function metabin, package meta; R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

**Study selection.** Among the 1,025 records identified, 12 studies (10,716 patients) evaluating DOAC for MOS (k=4) [15–18], NVAf (k=2) [19,20], VTE (k=2) [21,22], and ACS (k=4) [23–26] were included in the quantitative meta-analysis, representing 24 dosing regimen comparisons. The reasons for excluding studies are provided in Figure 1. Details about the 32 phase II trials screened but not included because of the lack of comparison of the two regimens (QD or BID) for a same daily dose are available in Table S1. All included studies were randomized, controlled, phase II trials sponsored by pharmaceutical industries. Patients and study characteristics are shown in Table 1. Pharmacokinetic properties of the 5 factor Xa inhibitors (apixaban, k=3 [15,21,23]; darexaban, k=3 [17,19,26]; edoxaban, k=1 [20]; rivaroxaban, k=2 [22,24]; and letaxaban, k=2 [18,25]) and 1 direct thrombin inhibitors (dabigatran, k=1 [16]) evaluated are summarized in Table 2. The risk of bias assessment is provided in Table 3. Four of the 12 studies were considered as high risk of bias, mostly



because intention-to-treat analysis was not correctly applied or missing data for which it was not known how they were managed.

**Major thrombotic and bleeding events.** Major thrombotic events were reported in 188/4825 patients treated with DOAC BID, and in 177/4809 patients treated with DOAC QD ( $RR_{BID/QD}=1.06$ , 95%IC 0.86-1.30,  $I^2=0\%$ ; Figure 2A). Similarly, major bleeding events were reported in 204/5306 patients treated with DOAC BID and in 198/5314 patients treated with DOAC QD ( $RR_{BID/QD}=1.02$ , 95%IC 0.84-1.23,  $I^2=0\%$ ; Figure 2B). The visual inspection of the funnel plots did not suggest publication bias for thrombotic major bleeding events (Figure 3).

**Subgroup analyses.** In the subgroup analyses, there was no difference according to the DOAC mechanism of action (Figure S1), DOAC indication (Figure S2), specific DOAC evaluated (Figure S3), or approved vs. not approved DOAC (Figure S4) for thrombosis or major bleeding. Consistently, there was no association between DOAC half-life and RR of major thrombotic event ( $\beta=0.044$ , 95%IC -0.030 – 0.12,  $p=0.25$ ) and major bleeding ( $\beta=0.034$ , 95%IC -0.049 – 0.12,  $p=0.42$ ) in meta-regression. When excluding the studies at high risk of bias, thrombotic events ( $RR_{BID/QD}=0.96$ , 95%IC 0.76-1.20,  $I^2=0\%$ ) and major bleeding ( $RR_{BID/QD}=1.02$ , 95%IC 0.82-1.25,  $I^2=0\%$ ) remained non-significantly different between BID and QD (Figure S5).

## DISCUSSION

The present meta-analysis documented, using direct comparison from head to head phase II randomized controlled trials totalizing more than 10,000 patients, that BID or QD DOAC dosing regimens are associated with similar risk of thrombosis and major bleeding events when used in the context of ACS, NVAf, VTE, and MOS thromboprophylaxis. These results were also consistent across clinically relevant subgroups, including the primary indication for

DOAC, its mechanism of action or specific DOAC evaluated, supporting current dosing regimens for DOAC.

Direct oral anticoagulants differ in their mechanism of action with two classes: direct reversible thrombin (dabigatran) or factors Xa inhibitors (apixaban, darexaban, edoxaban, letaxaban, rivaroxaban). Few of them are prodrugs (dabigatran and darexaban). Oral availability largely differs between DOAC, ranging from 6% for dabigatran to 80-100% for rivaroxaban [2,27], whereas half-life estimates range 5 from 18 hours [2,27–29]. The regimen tested in the phase III trials were chosen based on various considerations [30]. For dabigatran, the QD dosing regimen was associated with a larger peak-trough difference compared to BID, even if efficacy and bleeding rate were almost identical [16]. Dabigatran QD was selected for VTE prevention to minimize the risk of bleeding [31,32], whereas dabigatran BID was selected for VTE treatment due to the high risk of recurrent thrombosis during the acute phase of VTE [33]. Similarly, only BID regimen was tested in phase II for dabigatran in NVAf [34]. For rivaroxaban, a robust database of phase II data supported by a pharmacological modeling and a population analysis of phase II clinical data confirmed that QD dosing does not expose patients to a greater risk of bleeding or thrombus progression in VTE [35]. The same dose was used by inference in NVAf. Conversely, a BID rivaroxaban dosing regimen was chosen for phase III ACS study, based on its pharmacokinetic and pharmacodynamic profile and a non-significant increase in clinically significant bleeding and thrombotic events with QD regimen in phase II ACS trials [24]. A population pharmacokinetic analysis of the exposure-response associated with a regression analysis on the dose response was performed to select the BID regimen for apixaban in NVAf [36], whereas the Apixaban 2.5mg BID was choosen based on the APROPOS trial reporting a non-significant decrease in the primary outcome (including VTE events and death from any cause) with BID regimen

compared to QD [15]. BID edoxaban was associated with more bleeding than QD in a NVAF phase II trial [20], and the QD dose was therefore chosen for phase III trials in all indications tested [37,38].

These results thus challenged the usual pharmacokinetic considerations [39]. A BID regimen should theoretically minimize daily fluctuations in plasma concentrations minimizing the bleeding risk due to supratherapeutic peak plasma concentrations ( $C_{\max}$ ) and maintaining sufficient trough concentrations ( $C_{\text{trough}}$ ) to prevent the development of thrombus, but the impact on clinical outcome remains to be proven [7]. In the real world, the efficacy/safety evaluation is also influenced by patient adherence to therapy. It is well admitted that QD dose regimen is usually better for patient adherence, as the percentage of doses taken is generally higher with less frequent dosing regimen [40,41]. Nevertheless, simulation of the consequences of non-adherence indicates that BID DOAC could be beneficial for maintaining continuity of drug action when there is variable drug exposure [7]. More importantly, current treatment regimens were most determined using exposure-response regression analysis or data from phase II clinical trials that were generally underpowered to detect slight although relevant differences in thrombotic and major bleeding events. Accordingly, the dosing regimen, QD or BID, remains debated.

In that context, meta-analysis may provide a more precise estimate of the effect of the dosing regimens on the thrombotic and major bleeding events than any individual study contributing to the pooled analysis. Two previous meta-analyses thus explored the QD versus BID regimens [8,42]. Importantly, both used an indirect comparison approach between single arms from phase III DOAC trials. Clemens *et al.* [8] first documented BID regimen to have better risk-benefit balance in NVAF. With 71,683 patients included, this powerful meta-analysis suffers from high heterogeneity, and common estimates are lacking especially

concerning bleeding risk. BID regimens are composed with apixaban and dabigatran, whereas QD included rivaroxaban and edoxaban. The conclusion of the paper is supported by two significant HR, respectively dabigatran vs rivaroxaban and edoxaban in stroke and systemic embolism (HR 0.75 95%CI 0.58-0.96), and dabigatran and apixaban vs rivaroxaban in intracranial hemorrhage (HR 0.57 95%CI 0.37-0.88). Other HR remain non-significant. Wang *et al.*[42] focused on 6,496 Asian patients. No significant difference in thrombotic risk and major bleeding was reported. Their results are comforted by a network analysis. However, as DOAC are used in several indications with a large diversity of patient's characteristics, indirect comparisons are at high risk of inconsistency related to confounders for comparing BID and QD regimens. The present meta-analysis included phase II studies and direct comparisons were available, limiting the inconsistency. Interestingly, the same question – BID vs. QD – arose with low molecular weight heparins in the management of venous thromboembolism. Several meta-analyses on the subject have been published [43,44], using direct or indirect comparisons, and none of them showed any significant difference in terms of thrombotic recurrence and bleeding event.

We acknowledge some limitations in this study. First, we pooled thrombotic and major bleeding events from trials evaluating DOAC for numerous indications, including VTE prophylaxis after MOS, stroke reduction related to NVAf, treatment of VTE, and ACS. The major efficacy outcome included therefore VTE, stroke and myocardial infarction. However, beyond the discrepancies of the patients' characteristics, the weight of outcomes should be considered as similar irrespective of anticoagulant indications, confirmed by the absence of significant heterogeneity amongst trials and the subgroup analyses. Second, not all drugs were evaluated in every indication for BID vs. QD regimens, which could mean that only the safest regimens were tested. On the other part, we also included drugs that were not

approved after phase II trials, to maximize the number of patients included and increase the power. Third, more than a third of the trials had a high risk of bias. Nevertheless, sensitivity analyses carried out after removing these studies found overlapping results. Four, despite the inclusion of more than 10,000 patients in the meta-analysis, we could not exclude a lack of power to detect a difference between dosing regimens. However, it is important to note that in our meta-analysis without substantial heterogeneity the bound of confidence interval did not exceed 30% of risk augmentation neither for thrombosis nor bleeding. The 30% increase in risk is less than most often chosen as a limit in non-inferiority studies comparing DOAC and warfarin [45,46]. At last, the included studies contain little information on drug adherence, even if this issue is central to the management of anticoagulants and can have an impact on outcomes. Of the included studies, only three (ODIXa-DVT, ONYX-3, Botticelli DVT) addressed treatment compliance. In one study, results were not reported. In the other two, compliance was above 80%.

## **CONCLUSION**

Our meta-analysis using direct comparison from head to head phase II randomized controlled trials suggest similar safety and efficacy for DOAC prescribed OD and BID for the various specific DOAC and indications evaluated to date. These results thus question the appropriateness of some currently approved dosing regimens. However, they are not applicable in real-life population, because providing from not recommended regimens. Moreover, patients from RCT are specific, with high compliance, and potential selection bias. To answer the question, a large real-life study comparing different dosing regimen should provide the strongest evidence.

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## **TABLES**

**Table 1** - Characteristics of included studies

**Table 2** - Pharmacokinetic properties of direct oral anticoagulants analyzed in the present meta-analysis

**Table 3** - Assessment of risk of bias according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB2)

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**Figure 1** - PRISMA flow diagram showing the selection process of trials for meta-analysis

**Figure 2** - Forest plot of major thrombotic events (A) and major bleeding events (B). A relative risk (RR) > 1 mean that direct oral anticoagulants (DOAC) twice daily (BID) was associated with more thrombotic event (A) or more bleeding (B) that DOAC once daily (QD). Studies are classified according to the half-life of DOAC (from shortest to longest)

**Figure 3** - Funnel plot of thrombotic events (A) and major bleeding (B)

**Table 1** - Characteristics of included studies

Study, year	Indication	Intervention drug	Comparator drug	Patients characteristics		Statistical analysis	Mean follow-up (months)	Randomization method
				Mean age (years)	Men (%)			
<b>APROPOS, 2007</b> [15]	Major orthopedic surgery	Apixaban 2.5 mg BID (n=153) / 5 mg QD (n=157) 5 mg BID (n=157) / 10 mg QD (n=156) 10 mg BID (n=154) / 20 mg QD (n=156)	Enoxaparin 30 mg BID (n=152) and warfarin, INR 1.8-3 (n=153)	66.7	36.7	Efficacy: ITT Safety: PP	1	Computer-generated allocation
<b>Botticelli DVT, 2008</b> [21]	Venous thrombo-embolism	Apixaban 10 mg BID (n=134) / 20 mg QD (n=128)	LMWH/VKA, INR 2-3 (n=128)	59	62	Efficacy: mITT Safety: PP	2.8	IVRS
<b>APPRAISE, 2009</b> [23]	Acute coronary syndrome	Apixaban 10 mg BID (n=248) / 20 mg QD (n=221)	Placebo (n=611)	60.5	75.9	Efficacy: ITT Safety: PP	6	IVRS
<b>RUBY-1, 2011</b> [26]	Acute coronary syndrome	Darexaban 5 mg BID (n=160) / 10 mg QD (n=163) 15 mg BID (n=161) / 30 mg QD (n=158) 30 mg BID (n=158) / 60 mg QD (n=155)	Placebo (n=324)	56.9	79.6	mITT	6	IVRS
<b>ONYX-3, 2014</b> [17]	Major orthopedic surgery	Darexaban 15 mg BID (n=374) / 30 mg QD (n=383) 30 mg BID (n=387) / 60 mg QD (n=385)	Enoxaparin 40 mg QD (n=393)	60	48.4	Efficacy: mITT Safety: PP	1	Computer-generated randomisation schedule prepared by the study sponsor
<b>OPAL-2, 2014</b> [19]	Non-valvular atrial fibrillation	Darexaban 15 mg BID (n=162) / 30 mg QD (n=161) 30 mg BID (n=162) / 60 mg QD (n=163) 60 mg BID (n=162) / 120 mg OD (n=163)	Warfarin, INR 2-3 (n=324)	65.2	68.7	PP	NR	Computer-generated randomisation schedule

Study, year	Indication	Intervention drug	Comparator drug	Patients characteristics		Statistical analysis	Mean follow-up (months)	Randomization method
				Mean age (years)	Men (%)			
<b>Weitz JTH, 2010</b> [20]	Non-valvular atrial fibrillation	Edoxaban 30 mg BID (n=245) / 60 mg QD (n=235)	Warfarin, INR 2-3 (n=251)	65	62.1	PP	NR	Central, interactive, automated telephone system
<b>Weitz, 2010</b> [18]	Major orthopedic surgery	Letaxaban 20 mg BID (n=129) / 40 mg QD (n=163) 40 mg BID (n=163) / 80 mg QD (n=163)	Enoxaparin 30 mg BID (n=163)	64.8	37.1	PP	1	IVRS
<b>Goldstein, 2014</b> [25]	Acute coronary syndrome	Letaxaban 20 mg BID (n=250) / 40 mg QD (n=250) 40 mg BID (n=253) / 80 mg QD (n=252) 80 mg BID (n=253) / 160 mg QD (n=251)	Placebo (n=745)	57	75	Efficacy: ITT Safety: PP	6	IVRS
<b>ODIXa-DVT, 2007</b> [22]	Venous thrombo-embolism	Rivaroxaban 20 mg BID (n=117) / 40 mg QD (n=121)	LMWH/VKA, INR 2-3 (n=126)	59.1	60.8	PP	1	By central computer
<b>ATLAS ACS-TIMI 46, 2009</b> [24]	Acute coronary syndrome	Rivaroxaban 2.5 mg BID (n=153) / 5 mg QD (n=155) 5 mg BID (n=527) / 10 mg QD (n=529) 10 mg BID (n=307) / 20 mg QD (n=304)	Placebo (n=1160)	57.4	77.2	Efficacy: ITT Safety: PP	6	NR
<b>BISTRO II, 2005</b> [16]	Major orthopedic surgery	Dabigatran 150 mg BID (n=390) / 300 mg QD (n=385)	Enoxaparin 40 mg QD (n=392)	66	39	Efficacy: ITT Safety: PP	1	Computer-generated scheme

BID: twice daily; ITT: intention-to-treat analysis; IVRS: interactive voice-response system; mITT: modified intention-to-treat analysis; PP: Per Protocol analysis; QD: once daily.

**Table 2** - Pharmacokinetic properties of direct oral anticoagulants analyzed in the present meta-analysis

	Apixaban	Dabigatran	Darexaban	Edoxaban	Letaxaban	Rivaroxaban
<b>Mechanism of action</b>	Direct Factor Xa inhibitor	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
<b>Prodrug</b>	No	Yes	Yes	No	No	No
<b>Oral bioavailability (%)</b>	~66	6.5		~50	50	80–100
<b>Fraction unbound in plasma (%)</b>	13	~65–70		~41–60		~5–10
<b>t<sub>max</sub> (h)</b>	1.0–3.0	1.25–3.0	1–1.5	1.0–2.0	1–2	2.0–4.0
<b>t<sub>1/2</sub> (h)</b>	8–15	12–14	14–18	6–11	9–13	5–13
<b>Elimination</b>	~25% renal; ~75% hepatobiliary	80% renal; 20% hepatobiliary	Equally via fecal and renal routes	~35–39% renal; ~61–65% hepatobiliary	30% renal	36% unchanged via active renal secretion; 30% renal excretion of inactive metabolites; 34% hepatobiliary (7% unchanged)
<b>Metabolism</b>	CYP3A4; P-gp substrate	P-gp substrate	Minimal food interactions and no reported drug–drug interaction	CYP3A4; P-gp substrate	NR	CYP3A4, CYP2J2 and CYP-independent mechanisms; P-gp substrate
<b>Dose in</b>						
- <b>VTE prevention</b>	2.5 mg BID	220 OD or 150 mg QD	Not approved		Not approved	10 mg QD
- <b>VTE treatment</b>	5 mg BID	150 mg BID		60 mg QD		15 mg BID 21d, then 20 mg QD
- <b>NVAF</b>	5 mg BID or 2.5 mg BID for risk categories	110 mg BID or 150 mg BID		60 mg QD (30 mg for risk categories) or 30 mg OD (15 mg for risk categories)		20 mg QD (15 mg QD if CrCl30–49)
- <b>ACS</b>						2.5 mg BID

ACS: acute coronary syndrome; BID: twice a day; CrCl: creatinine clearance, CYP: cytochrome P450; NVAF: non valvular atrial fibrillation; P-gp: P-glycoprotein; t<sub>1/2</sub>: half-life; QD: once a day; t<sub>max</sub>: time to maximum concentration; VTE: venous thrombo-embolism

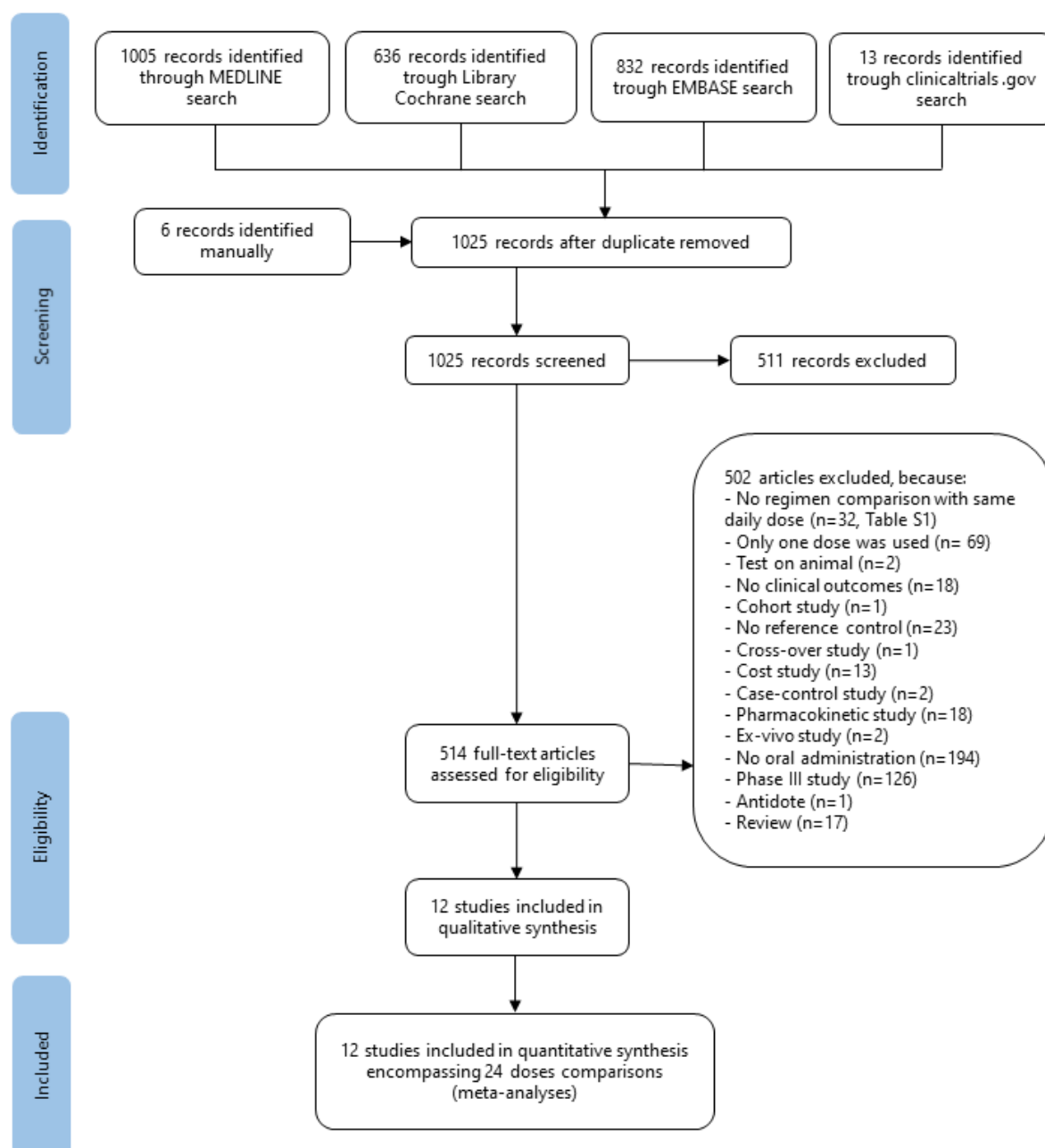
**Table 3** - Assessment of risk of bias according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB2)

Study ID	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
APPRAISE (2009)	Apixaban	Placebo	+	+	+	+	+	+
APROPOS (2007)	Apixaban	VKA/LMWH	+	—	?	+	+	—
Botticelli DVT (2008)	Apixaban	VKA/LMWH	+	?	?	+	+	—
BISTRO II (2010)	Dabigatran	LMWH	+	—	?	+	+	—
ONYX-3 (2014)	Darexaban	LMWH	+	—	+	+	+	—
OPAL-2 (2015)	Darexaban	VKA	+	+	+	+	+	+
RUBY-1 (2011)	Darexaban	Placebo	+	+	+	+	+	+
Weitz JTH (2010)	Edoxaban	VKA	+	?	?	+	+	?
Goldstein (2014)	Letaxaban	Placebo	+	?	+	+	+	?
Weitz (2010)	Letaxaban	LMWH	+	—	?	+	+	—
ATLAS ACS-TIMI 46 (2009)	Rivaroxaban	Placebo	?	+	+	+	+	?
ODIXa-DVT (2007)	Rivaroxaban	VKA/LMWH	+	?	?	+	+	?

+ Low risk  
 ? Some concerns  
 — High risk

## FIGURES

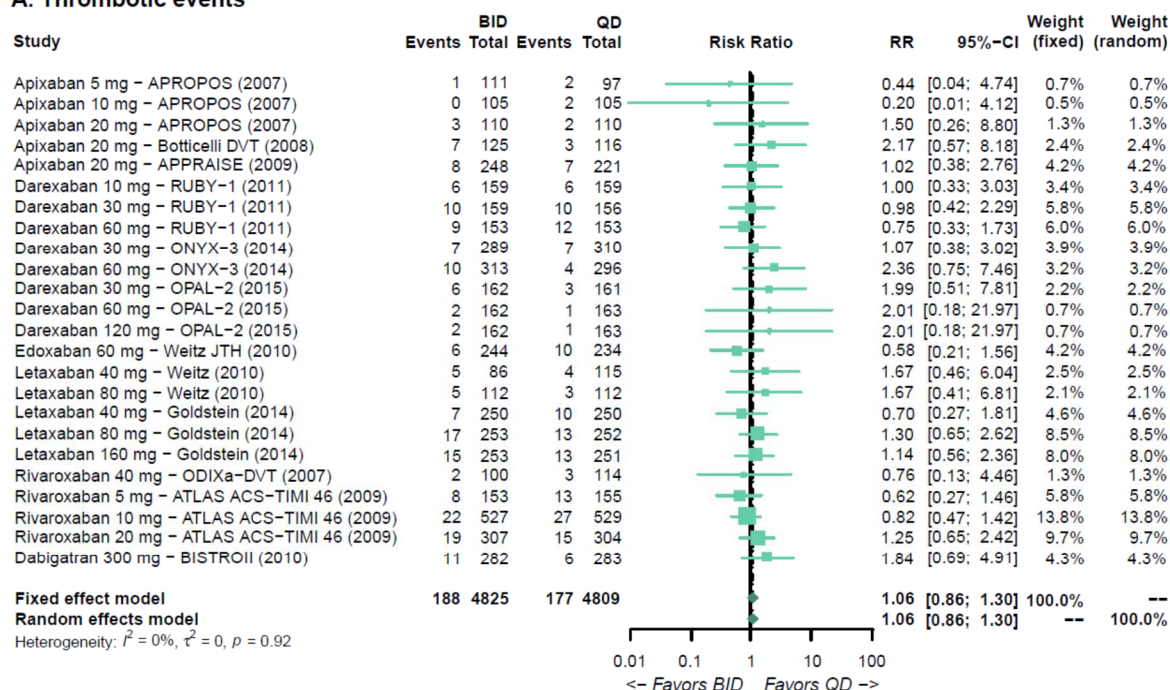
**Figure 1** - PRISMA flow diagram showing the selection process of trials for meta-analysis



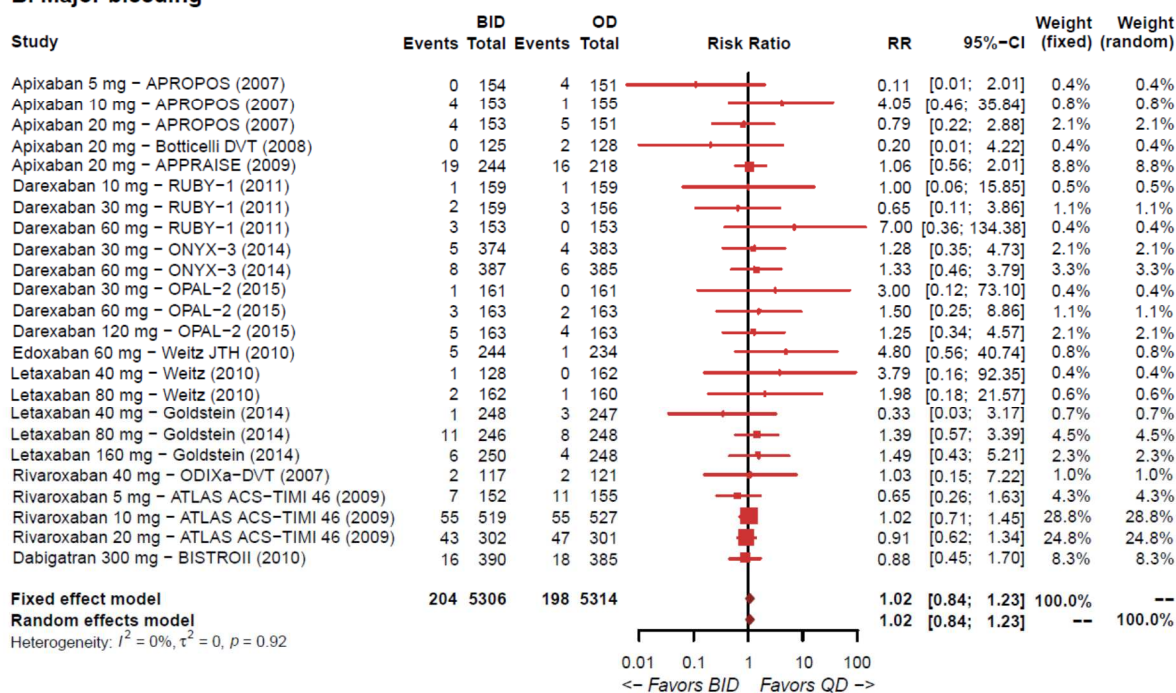


**Figure 2** - Forest plot of major thrombotic events (A) and major bleeding events (B). A relative risk (RR) > 1 mean that direct oral anticoagulants (DOAC) twice daily (BID) was associated with more thrombotic event (A) or more bleeding (B) than DOAC once daily (QD). Studies are classified according to the half-life of DOAC (from shortest to longest)

### A. Thrombotic events



### B. Major bleeding



**Figure 3** - Funnel plot of thrombotic events (A) and major bleeding (B)

