Direct-acting oral anticoagulants versus warfarin in relation to risk of gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials.

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Direct-acting oral anticoagulants versus warfarin in relation to risk of gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Direct-acting oral anticoagulants (DOACs) are increasingly used, with studies showing a lower risk of gastrointestinal bleeding (GIB), but overall data for GIB risk remains debatable. The objective was to assess non-fatal and fatal GIB risk in patients on DOACs compared with warfarin from randomized clinical trials (RCTs).

Methods RCTs comparing warfarin and DOACs for various indications (atrial fibrillation, thromboembolism, insertion of mechanical heart valves) were included. The primary endpoint was any GIB event. Other clinical events, such as fatal GIB, and effects of age (≤60 years or older), time in therapeutic range for warfarin, and choice of individual DOACs on GIB risk, were also assessed.

Results 14 RCTs were included, comprising 87,407 participants (DOACs n=46,223, warfarin control n=41,184). The risk of GIB with DOACs was similar to that of warfarin (relative risk [RR] 1.04, 95% confidence interval [CI] 0.85-1.27). Compared with warfarin, rivaroxaban (RR 1.23, 95%CI 1.03-1.48) and dabigatran (RR 1.38, 95%CI 1.12-1.71) had a higher risk of any GIB, whereas fatal GIB risk was lower in the DOACs group (RR 0.36, 95%CI 0.15-0.82). The risk of DOAC-related fatal GIB was lower in patients aged ≤60 years and in those with poor coagulation control (RR 0.39, 95%CI 0.15-0.98).

Conclusions DOACs compared with warfarin have a lower risk of fatal GIB, especially in those aged <60 years and those with poor coagulation control. However, the risk of GIB was comparable with warfarin and DOACs, except for rivaroxaban and dabigatran.

Keywords Direct-acting oral anticoagulant, DOACs, warfarin, coumadin, gastrointestinal bleeding

Introduction

The use of vitamin K antagonists (mainly warfarin) is characterized by frequent visits to the clinic for monitoring the international normalized ratio (INR) to assess therapeutic efficacy, in addition to concurrent heparin use for bridging, and the disadvantage of drug-drug and drug-food interactions requiring dose adjustments. Given these drawbacks, the use of warfarin is cumbersome and can lead to low adherence [1]. Direct-acting oral anticoagulants (DOACs) have the distinct advantage of fixed dosing and do not require continuous laboratory monitoring. These features, combined with the availability of FDA-approved reversal agents, have made them desirable anticoagulants [2,3].

Several studies have shown equivalent therapeutic efficacy of DOACs compared with warfarin in atrial fibrillation and venous thromboembolism (VTE) [4-6]. However, there are few specific guidelines available to guide physicians about the individualized use of a particular DOAC for patients. Most choices rely on
healthcare providers’ preference, the patient’s risk status, and the cost of the drugs, through a shared decision-making process.

In this meta-analysis, we aimed to evaluate the overall safety profile of DOACs, emphasizing overall risk of gastrointestinal bleeding (GIB) and, more specifically, risk of fatal GIB. In addition, we compared individual DOACs to warfarin regarding the risk of GIB and safety in light of the variability of INR controls, i.e. the time in therapeutic range (TTR).

Materials and methods

Protocol, eligibility, and data extraction

The meta-analysis was performed in compliance with PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [7]. Randomized controlled trials (RCTs) published from January 2009 to December 2019 comparing DOACs with warfarin were included in this study (Fig. 1A). Studies published in languages other than English, unpublished studies, observational and cohort studies were excluded. Studies that used another anticoagulant or antiplatelet agent in one or both study arms or did not report GIB events were also excluded. PubMed, Google Scholar, Cochrane and EMBASE search engines were used for the literature search. A detailed methodology of the broad search strategy and key terms used is outlined in Supplementary Table 1. RCTs were included that: 1) used DOACs for non-valvular atrial fibrillation, VTE, prevention of VTE, or mechanical valve thromboprophylaxis; and 2) reported outcomes of interest at minimum follow up lasting the total duration of the study, in addition to at least 12 months following study completion. Details of exclusion criteria and data extraction are provided in Fig. 1A. Two authors (MB and BM) independently participated in screening the studies for eligibility and obtaining full texts. There were no discrepancies as strict criteria for eligibility were applied.

Risk of publication bias and quality assessment

The risk of publication bias across studies was assessed using the funnel plot (Fig. 1B), and all included studies fell within the symmetric inverted funnel, indicating no publication bias with a 95% confidence interval (CI). The risk of bias of individual studies was assessed using the Cochrane method for random sequence generation, random allocation, blinding of participants and outcomes, incomplete outcome, and selective reporting outcome. It was graded as no risk (full data reported), questionable risk (partial data reported), and high risk (no data reported) (Supplementary Fig. 1).

Data synthesis and statistical analysis

We used the standard $F$ test for heterogeneity. An $F$ value >50 was considered to indicate the presence of some heterogeneity. Sensitivity analyses were performed by excluding one study at a time and estimating the impact of each such exclusion on the overall meta-analysis.

Outcomes

The primary safety outcomes included overall GIB and fatal GIB. Secondary subgroup analysis was performed for individual DOAC (apixaban, dabigatran, edoxaban, and rivaroxaban), age (younger than or equal to 60 vs. older than 60 years), and warfarin dose maintenance of INR (in the therapeutic range of 2-3, TTR higher than 60% vs. less than 60% of the time).

Results

Characteristics of the included studies

A broad search strategy through 4 search engines (PubMed, Google Scholar, Cochrane and EMBASE) using the keywords DOAC, warfarin, and human studies yielded 2304 citations. A total of 14 RCTs were finally included (Fig. 1A). The included studies comprised 87,407 participants (DOACs n=46,223, warfarin control n=41,184). Males comprised 64.4% of the study participants. The median age was 67.5 years (interquartile range [IQR] 57.4-71.4 years). The median follow up was 40 (IQR 21-103.25) weeks. Indications were atrial fibrillation (n=9), VTE (n=2), pulmonary embolism (PE) (n=1), VTE/PE (n=1), mechanical valve thromboprophylaxis (n=1). A detailed table of the characteristics of the included studies is available (Table 1).

Risk of publication bias and quality assessment of the included studies

Any GIB

Compared to warfarin use, overall DOAC use was associated with similar GIB events (RR 1.04, 95%CI 0.85-1.27; $P=0.0002$; $F=68\%$). All studies reported bleeding events (Fig. 2A). Results were predominately driven by 6 studies (AMPLIFY, ARISTOTLE, EINSTEIN, RE-ALIGN, RE-COVER, RE-LY). The dataset was considered heterogeneous, with a $\chi^2$ of 36.95 and $F$ of 68%. The Egger’s regression analysis of all the included studies showed no evidence of significant publication bias ($P=0.4069$).
Table 1: Detailed differences between study design, indications, demographics, study size and events

| Study trial (YR) [Ref.] | Design | Blinding | Mean age | Males % | Indication for trial | Mean CHADS2 | Study group (sub groups) | (n) | Warfarin (n) | Bridging | Median use of study agents (weeks) | Median duration follow up (weeks) | Total intracranial bleed (NOAC, VKA) | Fatal intracranial bleed (NOAC, VKA) | Total GI bleed (NOAC, VKA) | Fatal bleed-GI bleed (NOAC, VKA) |
|------------------------|--------|----------|----------|---------|----------------------|-------------|------------------------|-----|-------------|----------|-----------------------------------|-------------------------------|--------------------------------|-----------------------------------|-----------------------------|-------------------------------|
| ARISTOTLE (Granger 2011) [23] | RCT | Double blinded | 70 | 64.7 | AF | 2.1 | APIXIBAN | 9120 | 9081 | No | 120 | 120 | 52,122 | 42,67 | 105,119 | NR* (reported as combined with other non-ICB as 1.14% vs. 1.22%) |
| ARISTOTLE (Ogawa 2011) [24] | RCT | Partially blinded | 70 | 62 | AF | 1.9 | APIXIBAN (2.5, 5mg bid) | 74,74 | 74 | No | 12 | 16 | 0.0 | 0.0 | 24 | 0.0 |
| RELY (Connolly 2009) [25] | RCT | Double blinded | 71.5 | 63.8 | AF | 2.1 | DABIGATRAN (110, 150 mg qd) | 6015, 6076 | 6022 | No | 104 | 104 | 27,36,87 | NR | 133, 182,120 | NR |
| ROCKET AF (Patel 2011) [26] | RCT | Double blinded | 73 | 60.3 | AF | 3.47 | RIVAROXABAN | 7131 | 7133 | No | 84 | 101 | 55,84 | NR | 190,138 | 1.5 |
| ROCKET AF-J (Hori 2012) [27] | RCT | Double blinded | 71.1 | 80.6 | AF | 3.25 | RIVAROXABAN | 530 | 500 | No | 120 | 121 | 5,10 | NR | 6,12 | 1,3 |
| AMPLIFY (Agnelli 2013) [28] | RCT | Double blinded | 57.2 | 56.7 | VTE | NA | APIXIBAN | 2691 | 2704 | Yes | 24 | 28 | 3.6 | 1.2 | 7,18 | 0.0 |
| EINSTEIN-PE (Buller 2012) [29] | ROL | Randomized Open Label | 57.9 | 57.5 | PE | NA | RIVAROXABAN | 2419 | 2413 | Yes | 52 | 52 | 3.13 | 2.2 | 1,2 | 0.0 |
| ENGAGE-AF TIMI (Giugliano 2013) [30] | RCT | Double blinded | 72 | 72 | AF | 2 | EDOXABAN | 11406 | 7036 | No | 145 | 145 | 102,132 | 53,59 | 368,192 | 5,7 |
| HOKUSAI-VTE (Buller 2013) [31] | RCT | Double blinded | 55.7 | 57.2 | VTE/PE | NA | EDOXABAN | 4112 | 4118 | Yes | 12 | 60 | 5,12 | 0.6 | 298,368 | 1,2 |

*(Contd..)*
| Study trial (YR) [Ref.] | Design | Blinding | Mean age | Males % | Indication for trial | Mean CHADS2 | Study group (sub groups) | (n) | Warfarin (n) | Bridging | Median use of study agents (weeks) | Median duration follow up (weeks) | Total intracranial bleed (NOAC, VKA) | Fatal intracranial bleed (NOAC, VKA) | Total GI bleed (NOAC, VKA) | Fatal bleed-GI bleed (NOAC, VKA) |
|------------------------|--------|----------|----------|---------|----------------------|-------------|------------------------|-----|----------------|----------|----------------------------------|-------------------------------|--------------------------------|-------------------------------|---------------------------------|-------------------------------|
| RE-COVER (Schulman 2009) [11] | RCT | Double blinded | 55 | 58 | VTE | NA | DABIGATRAN | 1273 | 1266 | Yes | 24 | 28 | 0,3 | 0,3 | 53,35 | NR |
| Explore-Xa (Connolly 2013) [32] | RCT | Double blinded | 72 | 62 | AF (Post Cardioversion) | 2.2 | BETRIXIBAN | 127 | 127 | No | 21 | 21 | 1,1 | 1,1 | 0,0 | 0,0 |
| RE-ALIGN (Eikelboom 2013) [16] | ROL | Randomized Open Label | 56 | 65 | MV | NA | DABIGATRAN | 168 | 84 | No | 21 | 21 | 9,0 | NR | 1,0 | 0,0 |
| VENTURE (Cappato 2015) [33] | ROL | Randomized Open Label | 60 | 70 | AF (Post Ablation) | 1.6 | RIVAROXaban | 124 | 124 | No | 8 | 8 | 0,1 | 0,0 | 2,1 | 0,0 |
| Xa-Vert (Cappato 2014) [33] | ROL | Randomized Open Label | 65 | 72 | AF (Post Ablation) | RIVAROXaban | 1002 | 502 | No | 14 | 14 | 2,0 | 2,0 | 3,1 | 0,1 |

RCT, randomized controlled trial; ROL, randomized open label; NA, not applicable; NR, not reported; AF, atrial fibrillation; VTE, venous thromboembolism; PE, pulmonary embolism; MV, mechanical valve.
Apixaban. Any risk of GIB with Apixaban was included in 2 studies (AMPLIFY, ARISTOTLE) with a total of 15,240 patients on apixaban vs. 15,177 on warfarin. GIB events were again similar (RR 1.04, 95%CI 0.72-1.51; P=0.83; I² =66%). All studies reported bleeding events (Fig. 2B). The dataset was considered heterogeneous, with a χ² of 5.85 and I² of 66%.

Dabigatran. Any risk of GIB with dabigatran was included in 3 studies (RE-AGIGN, RE-COVER, RE-LY) with a total of 16,791 patients on dabigatran vs. 12,420 on warfarin. Similar numbers of GIB events were observed (RR 1.09, 95%CI 0.79-1.62; P=0.62; I² =87%). The dataset was considered heterogeneous, with a χ² of 15.04 and I² of 87%. Sensitivity
Figure 2 (A) Any gastrointestinal bleeding (GIB); (B) apixaban any GIB; (C) dabigatran any GIB (after sensitivity analysis); (D) edoxaban any GIB; (E) rivaroxaban any GIB

DOAC, direct-acting oral anticoagulant; CI, confidence interval

analysis reduced heterogeneity, reducing $I^2$ from 87% to 9% after the exclusion of RE-COVER, and also changed the results favoring warfarin for risk for any GIB (Fig. 2C).

**Edoxaban.** Any risk of GIB with edoxaban was included in only 2 studies (ENGAGE AF TIMI, HOKUSAI VTE) with a total of 2949 patients on edoxaban vs. 2913 on
warfarin. GIB events were less common on edoxaban (RR 0.48, 95% CI 0.19-1.17; P=0.11; I²=0%) (Fig. 2D). The dataset was considered non-heterogeneous, with a χ² of 0% and F of 0%.

**Rivaroxaban.** Any risk of GIB with rivaroxaban was included in 4 studies (EINSTEIN PE, ROCKET-AF, VENTURE, Xe-VERT) with a total of 8552 patients on rivaroxaban vs. 7970 on warfarin. GIB events were more common on rivaroxaban (RR 1.38, 95% CI 1.12-1.71; P=0.003; I²=0%) (Fig. 2E). The dataset was considered non-heterogeneous, with a χ² of 10% and F of 0%.

**Any GIB with age and DOAC use.** Risk of any GIB with use of DOACs was comparable with warfarin and did not differ in participants younger than 60 years compared with those older than 60 years (Supplementary Fig. 2A, B).

**Fatal GIB.** Meta-analysis of 11 studies that reported fatal GIB demonstrated that DOACs use was associated with a lower risk of fatal GIB when compared with warfarin (RR 0.36, 95% CI 0.15-0.82) (Supplementary Fig. 3A).

### Fatal GIB

The risk of fatal GIB with use of DOACs in participants younger than 60 years was assessed in a total of 25,068 patients on DOACs vs. 20,700 on warfarin. The DOAC groups showed fewer fatal GIB events (RR 0.39, 95% CI 0.15-0.98; P=0.05; I²=0%) (Supplementary Fig. 3B), compared with participants older than 60 years (Supplementary Fig. 3C).

**Dabigatran.** The risk of fatal GIB with dabigatran was included in 2 studies (RE-ALIGN and RE-COVER) with a total of 15,510 patients on dabigatran vs. 11,154 on warfarin. Fatal GIB events were less common on dabigatran (RR 0.45, 95% CI 0.16-1.27; P=0.13; I²=0%) (Supplementary Fig. 4). The dataset was considered non-heterogeneous, with a χ² of 1% and F of 0%.

**Rivaroxaban.** The risk of fatal GIB with rivaroxaban was included in 5 studies (EINSTEIN PE, ROCKET-AF, ROCKET-AF-J, VENTURE, Xe-VERT) with a total of 8552 patients on rivaroxaban vs. 7970 on warfarin. Fatal GIB events were less common on rivaroxaban (RR 0.19, 95% CI 0.03-1.12; P=0.07; I²=0%) (Supplementary Fig. 5). The dataset was considered non-heterogeneous, with a χ² of 1% and F of 0%.

**DOACs and patients with poor INR control.** Any GIB risk was equivalent between DOAC and warfarin groups, regardless of TTR (Supplementary Fig. 6A, B). However, TTR <60% was an adverse determinant of fatal GIB with warfarin and conferred a risk reduction advantage of DOAC use over warfarin by an RR of 0.39 (95% CI 0.15-0.98; Supplementary Fig. 7A). Good INR control, TTR >60%, was not an adverse determinant of fatal GIB with warfarin than DOACs, implying if INR was in the therapeutic range for more than 60% of the time, GIB risk associated with warfarin or DOAC was similar (Supplementary Fig. 7B).

### Study quality

All included studies had minimal or no risk of bias. Although 3 studies (RE-ALIGN, VENTURE, Xe-VERT) had a high risk of allocation and blinding bias, these studies had no bias in randomization or outcome reporting. Heterogeneity variance F in most analyses was low, indicating that homogenous study populations were compared. In a few analyses, where F was higher than desired, a robust sensitivity analysis was performed to eliminate the effect of heterogeneity, thereby preserving the quality of the meta-analysis results.

### Discussion

This meta-analysis shows that DOACs have GIB safety profiles comparable to that of warfarin. However, the risk of fatal GIB was lower with DOACs. These findings are in concordance with previous studies that showed a lower risk of major or fatal bleeding episodes [4-6,9]. However, those studies included patients from case-control and retrospective studies, not performed in a controlled environment, and the results cannot confer certainty given the presence of multiple confounding factors. Assessment of bleeding risk is crucial when we evaluate the safety of these agents, as well as the patients’ perception of the value of these agents [10]. Compared to warfarin use, overall DOAC use was associated with similar GIB events (RR 1.04, 95% CI 0.85-1.27; P=0.0002). Previous studies showed that fixed-dose dabigatran is as effective as warfarin in the treatment of acute VTE, with a safety profile similar to that of warfarin [11,12]. The risk of any bleeding (both major and minor) was lower with dabigatran. However, a trend towards increased GIB was noted in these studies with higher doses of dabigatran (150 mg b.i.d. associated with higher GIB compared to 110 mg b.i.d.) [11,12]. Dabigatran compound is mixed with an acid core (tartaric acid) to increase its absorption; this could affect the stomach lining, contributing to an increased risk of GIB [13]. A higher risk of GIB with warfarin could be due to a variable risk for bleeding in individuals with cardiovascular disease and VTE, as well as dosing changes [14]. Sensitivity testing changed the bleeding risk in favor of warfarin after the elimination of the RE-COVER data, compared with RE-LY and RE-ALIGN [11,15-17]. RE-LY was the main driver of the study results for dabigatran, because of its large sample size [11,15-17]. Heterogeneity was mainly contributed by RE-COVER, because dabigatran was not given in the group with chronic kidney disease, whereas in RE-LY 20% of those patients received dabigatran. A higher dabigatran dose of 150 mg was consistently used in RE-COVER, compared with 110 mg and 150 mg doses in RE-LY [11,15-17], similar to other meta-analyses [11,15]. One of the major limitations of other meta-analyses is the lack of data on fatal GIB, and the use of major bleeding (defined as Hb drop >2 g/dL or requiring transfusion of at least 2 units.
of packed red blood cells) as a surrogate marker for fatal GIB, as defined by the International Society of Thrombosis and Hemostasis. Such definitions are not universally followed in clinical trials and do not reflect real mortality data [18]. Our meta-analysis focused on actual fatal GIB, a rigorous and clinically meaningful endpoint, and showed that the risk of fatal GIB with DOAC was significantly lower than with conventional warfarin (RR 0.36, 95%CI 0.15-0.82). The bleeding risk of DOACs is dose-dependent and is partially attributed to their higher dwell time in the gastrointestinal tract [19]. Head-to-head comparison of DOACs is rare, especially when comparing bleeding risks. In our meta-analysis, both rivaroxaban and dabigatran showed a higher risk of any GIB compared with warfarin (rivaroxaban RR 1.23, 95%CI 1.03-1.48, dabigatran RR 1.38, 95%CI 1.12-1.71). Head-to-head comparison showed that dabigatran and rivaroxaban were not associated with a higher risk of GIB after 40 days of usage (dabigatran 5.3% vs. rivaroxaban 4.8%; P=0.8) [20]. Our findings suggest that poor INR control (TTR <60%) was a determinant of fatal GIB in the warfarin group. DOACs conferred a risk reduction (RR 0.39, 95%CI 0.15-0.98). Previous studies have used different INR targets for the therapeutic range. For example, the Hokusai-VTE trial had an INR target of 2.0-3.0, while other studies used a lower threshold target of INR 1.5-2.5 [21]. Japanese guidelines use a target INR of 1.5-2.5 instead of the conventional 2-3 [22].

The main strength of our study is the selection criteria, which were rigorous, with exclusion of concomitant antiplatelet agent use, to discern the specific effects on GIB of DOACs vs. warfarin. The risk of bias at every stage of each trial was analyzed in depth (risk-of-bias chart), and all studies had no or minimal bias. Another significant strength of this study is its emphasis on any GIB and fatal GIB, along with comparing individual DOACs with warfarin. Further, the analysis of the effects of age (above or below 60 years) and the TTR variable lend depth to the DOAC use analysis.

Despite strict inclusion and exclusion criteria, the trials analyzed here might not be inherently similar. For example, the ROCKET-AF trial required participants to have a CHADS score of 2 or higher, whereas ARISTOTLE and RE-LY included participants with scores 0 and 1. Other limitations were our inability to differentiate upper from lower GIB, and the unclear time to event (as these data were not consistently apparent in the included studies).

This meta-analysis provides a comprehensive assessment from published clinical trials of the risks of any GIB and fatal GIB associated with the use of FDA-approved DOACs compared with warfarin, and adds further essential information to the existing literature about the safety profile of DOACs. The risk of any GIB is similar with DOACs (except dabigatran and rivaroxaban) to warfarin. However, the risk of fatal GIB is significantly lower with all DOACs. The availability of data on adverse events such as GIB helps inform clinicians in a shared decision-making process with patients on the choice of DOACs vs. warfarin.

Summary Box

What is already known:

- Gastrointestinal bleeding (GIB) related to anticoagulant use is comparable between direct-acting oral anticoagulants (DOACs) and warfarin, according to cohort and observational studies; however, many of these studies and meta-analyses are confounded by the concomitant use of other anticoagulants or antiplatelet agents
- DOACs are increasingly favored over warfarin for their ease of dosing and fewer drug or food interactions
- The risk of fatal GIB from DOAC vs. warfarin use is largely unknown from meta-analyses of well constructed clinical trials

What the new findings are:

- This is the first systematic review and meta-analysis of randomized clinical trials comparing DOACs vs. warfarin, to study the risk of any GIB and fatal GIB
- DOAC use was associated with a lower risk of any GIB compared with warfarin
- DOACs compared with warfarin have a lower risk of fatal GIB, especially in patients aged ≤60 years
- A time in therapeutic range <60% for warfarin rendered warfarin inferior to DOACs

References

1. Connolly SJ, Pogue J, Eikelboom J, et al: ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029-2037.
2. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-520.
3. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373:2413-2424.
4. Senoo K, Kondo Y, Miyazawa K, Isogai T, Chun YH, Kobayashi Y. Safety and efficacy of direct oral anticoagulants over warfarin in Japanese patients with acute venous thromboembolism: A meta-analysis. J Cardiol 2017;69:763-768.
5. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huismann MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12:320-328.
6. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc 2016;5:e003725.
7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses:
8. Higgins JP, Altman DG, Gotzsche PC, et al; Cochrane Statistical Methods Group. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
9. Caldeira D, Costa J, Ferreira JJ, Lip GY, Pinto FJ. Non-vitamin K antagonist oral anticoagulants in the cardioversion of patients with atrial fibrillation: systematic review and meta-analysis. Clin Res Cardiol 2015;104:582-590.
10. Lancaster TR, Singer DE, Sheehan MA, et al. The impact of long-term warfarin therapy on quality of life. Evidence from a randomized trial. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. Arch Intern Med 1991;151:1944-1949.
11. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-2352.
12. Chan YH, See LC, Tu HT, et al. Efficacy and safety of apixaban, dabigatran, rivaroxaban, and warfarin in Asians with nonvalvular atrial fibrillation. J Am Heart Assoc 2018;7:e008150.
13. Blommel ML, Blommel AL. Dabigatran etexilate: A novel oral direct thrombin inhibitor. Am J Health Syst Pharm 2011;68:1506-1519.
14. Holster IL, Valkhoff VE, Kuipers EJ, Tywa ETTL. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 2013;145:105-112.
15. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363-2372.
16. Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206-1214.
17. Schulman S, Goldhaber SZ, Kearon C, et al. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. Thromb Haemost 2015;114:150-157.
18. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-694.
19. Desai J, Granger CB, Weite JL, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. Gastrointest Endosc 2013;78:227-239.
20. Sherid M, Sifuentes H, Sulaiman S, et al. Risk of gastrointestinal bleeding with dabigatran: a head-to-head comparative study with rivaroxaban. Digestion 2014;90:137-146.
21. Raskob GE, van Es N, Verhamme P, et al; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-624.
22. JCS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). Circ J 2011;75:1258-1281.
23. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.
24. Ogawa S, Shinohara Y, Kannuku M. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study. Circ J 2011;75:1852-1859.
25. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151.
26. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-891.
27. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J 2012;76:2104-2111.
28. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
29. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-1297.
30. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-2104.
31. Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-1415.
32. Connolly SJ, Eikelboom J, Dorian P, et al. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). Eur Heart J 2013;34:1498-1505.
33. Cappato R, Marchlinski FE, Hohnloser SH, et al. Uninterrupted rivaroxaban vs. interrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. Eur Heart J 2015;36:1805-1811.
34. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J 2014;35:3346-3355.
**Supplementary material**

**Supplementary Table 1 Cochrane search strategy and keywords used for the search PICO**

| PICO Strategy | Participants | Intervention | Comparator | Outcome |
|---------------|--------------|--------------|------------|---------|
| Study Focus   | Adult patients who require anticoagulation in the setting of a clinical trial | Direct-acting oral anticoagulant | Warfarin | Gastrointestinal bleeding’ |
| Free text and MeSH terms (BOOLEAN operators to maximize yield) | Deep vein (venous) thrombosis (OR) Pulmonary embolism (OR) Thromboembolism (OR) Atrial fibrillation (OR) Prosthetic valve (AND) Clinical Trial | (AND) Apixaban (OR) Rivaroxaban (OR) Dabigatran (OR) Edoxaban (OR) Betrixaban (OR) Oral anticoagulation (OR) Direct factor Xa Inhibitor (AND) Clinical Trial | (AND) Warfarin (OR) Coumadin (OR) Acenocoumarol (OR) Vitamin K antagonists (AND) Clinical Trial | (AND) ’Outcome was not included to keep the search criteria broad-based on the assumption that gastrointestinal bleeding as a complication does not always get included in the title or abstract |

Participants = adult patients who require anticoagulation in the setting of a clinical trial

Intervention = Direct-acting oral anticoagulant

Comparator = Warfarin

Outcome = Gastrointestinal bleeding

Search strategy
**Supplementary Figure 1** Cochrane method for analysis of study quality

**Supplementary Figure 2**

(A) GI bleed < 60y; (B) GI bleed > 60y

DOAC, direct-acting oral anticoagulant; CL, confidence interval
| Study or Subgroup | DOAC | WARFARIN | Risk Ratio | Risk Ratio |
|-------------------|------|----------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| ARISTOTLE (Granger et al. 2011) [23] | 74 | 0 | 74 | 0 | | | |
| EINSTEIN PE (Buller et al. 2012) [29] | 1 | 7131 | 5 | 7133 | 15.0% | 0.20 [0.02, 1.71] | | |
| EINSTEIN AF TIMI (Guigliane et al. 2013) [30] | 1 | 530 | 5 | 500 | 13.6% | 0.31 [0.03, 3.01] | | |
| EXPLORER Xa (Buller et al. 2013) [31] | 0 | 2691 | 0 | 2704 | | Not estimable | | |
| HOKUSAI VTE (Buller et al. 2013) [32] | 0 | 2419 | 0 | 2413 | | Not estimable | | |
| RE-ALIGN (Eikelboom et al 2013) [16] | 5 | 11406 | 7 | 7036 | 52.6% | 0.44 [0.14, 1.39] | | |
| RE-COVER (Schulman et al 2009) [23] | 1 | 4112 | 2 | 4118 | 12.0% | 0.50 [0.05, 5.52] | | |
| ROCKET AF (Patel et al. 2011) [29] | 0 | 127 | 0 | 127 | | Not estimable | | |
| ROCKET AF-J (Horii et al 2012) [27] | 0 | 168 | 0 | 84 | | Not estimable | | |
| VENTURE (Capraro et al 2015) [33] | 0 | 124 | 0 | 124 | | Not estimable | | |
| XEVERT (Capraro et al 2014) [34] | 0 | 1002 | 1 | 502 | 6.8% | 0.17 [0.01, 4.01] | | |

Total (95% CI) 22984 24815 100.0% 0.36 [0.15, 0.82]

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.72, df = 4 (P = 0.95); I^2 = 0%
Test for overall effect: Z = 2.64 (P = 0.01)

Supplementary Figure 4 Dabigatran fatal GI bleed

| Study or Subgroup | DOAC | WARFARIN | Risk Ratio | Risk Ratio |
|-------------------|------|----------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| ARISTOTLE (Granger et al. 2011) [23] | 74 | 0 | 74 | 0 | | | |
| EINSTEIN PE (Buller et al. 2012) [29] | 1 | 7131 | 5 | 7133 | 18.9% | 0.20 [0.02, 1.71] | | |
| EINSTEIN AF TIMI (Guigliane et al. 2013) [30] | 1 | 530 | 3 | 500 | 66.7% | 0.31 [0.03, 3.01] | | |
| EXPLORER Xa (Buller et al. 2013) [31] | 0 | 2691 | 0 | 2704 | | Not estimable | | |
| HOKUSAI VTE (Buller et al. 2013) [32] | 0 | 2419 | 0 | 2413 | | Not estimable | | |
| RE-ALIGN (Eikelboom et al 2013) [16] | 5 | 11406 | 7 | 7036 | 66.0% | 0.44 [0.14, 1.39] | | |
| RE-COVER (Schulman et al 2009) [23] | 1 | 4112 | 2 | 4118 | 15.1% | 0.50 [0.05, 5.52] | | |
| ROCKET AF (Patel et al. 2011) [29] | 0 | 127 | 0 | 127 | | Not estimable | | |
| ROCKET AF-J (Horii et al 2012) [27] | 0 | 168 | 0 | 84 | | Not estimable | | |
| VENTURE (Capraro et al 2015) [33] | 0 | 124 | 0 | 124 | | Not estimable | | |
| XEVERT (Capraro et al 2014) [34] | 0 | 1002 | 1 | 502 | 6.8% | 0.17 [0.01, 4.01] | | |

Total (95% CI) 25068 20700 100.0% 0.39 [0.15, 0.98]

Heterogeneity: Taur^2 = 0.00; Chi^2 = 0.26, df = 2 (P = 0.79); I^2 = 0%
Test for overall effect: Z = 2.00 (P = 0.05)

Supplementary Figure 5 Rivaroxaban fatal GI bleed

| Study or Subgroup | DOAC | WARFARIN | Risk Ratio | Risk Ratio |
|-------------------|------|----------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| RE-ALIGN (Eikelboom et al 2013) [16] | 5 | 11406 | 7 | 7036 | 81.2% | 0.44 [0.14, 1.39] | | |
| RE-COVER (Schulman et al 2009) [23] | 1 | 4112 | 2 | 4118 | 18.8% | 0.50 [0.05, 5.52] | | |

Total (95% CI) 15518 11154 100.0% 0.45 [0.16, 1.27]

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 = 0%
Test for overall effect: Z = 1.50 (P = 0.13)

Supplementary Figure 3 (A) Any fatal GI bleed, (B) Fatal GI bleed <60y, (C) Fatal GI bleed > 60y

DOAC, direct-acting oral anticoagulant; CI, confidence interval; GI, gastrointestinal
| Study or Subgroup | DOAC | | WARFARIN | | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| ARISTOTLE (Granger et al 2011) [23] | 2 | 74 | 0 | 74 | 3.2% | 0.50 [0.09, 2.65] | 0.50 [0.09, 2.65] |
| EINSTEIN PE (Buller et al 2012) [29] | 190 | 7131 | 138 | 7133 | 30.8% | 1.38 [1.11, 1.71] | 1.38 [1.11, 1.71] |
| RE-ALIGN (Eikelboom et al 2013) [16] | 368 | 11406 | 192 | 7036 | 32.6% | 1.18 [1.00, 1.40] | 1.18 [1.00, 1.40] |
| RE-COVER (Schulman et al 2009) [11] | 298 | 4112 | 368 | 4118 | 33.3% | 0.81 [0.70, 0.94] | 0.81 [0.70, 0.94] |
| ROCKET AF (Patel et al 2011) [20] | 0 | 127 | 0 | 127 | Not estimable | Not estimable | Not estimable |
| Total (95% CI) | 22850 | 18488 | 100.0% | 1.06 [0.78, 1.45] | 1.06 [0.78, 1.45] |

Total events: 858. Heterogeneity: Tau^2 = 0.07; Chi^2 = 20.34, df = 3 (P = 0.0001); I^2 = 85%
Test for overall effect: Z = 0.38 (P = 0.70)

Supplementary Figure 6 (A) Any GI bleed (INR<60% target therapeutic range) (B) Any GI bleed (INR>60% target therapeutic range)
DOAC, direct-acting oral anticoagulant; CI, confidence interval; GI, gastrointestinal; INR, international normalized ratio

| Study or Subgroup | DOAC | | WARFARIN | | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|---|
| | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| AMPLIFY (Aperts et al 2013) [28] | 105 | 9120 | 119 | 9081 | 27.2% | 0.88 [0.68, 1.14] | 0.88 [0.68, 1.14] |
| ARISTOTLE (Ogawa et al 2011) [24] | 158 | 6046 | 120 | 6022 | 28.1% | 1.31 [1.04, 1.66] | 1.31 [1.04, 1.66] |
| ENGAGE AF-TIMI (Gargiulano et al 2013) [20] | 6 | 530 | 12 | 500 | 8.6% | 0.47 [0.18, 1.25] | 0.47 [0.18, 1.25] |
| EXPLORE Xa (Buller et al 2013) [31] | 7 | 2691 | 18 | 2704 | 10.0% | 0.39 [0.16, 0.93] | 0.39 [0.16, 0.93] |
| HOKUSAI VTE (Buller et al 2013) [31] | 1 | 2419 | 2 | 2413 | 1.8% | 0.50 [0.05, 5.50] | 0.50 [0.05, 5.50] |
| RE-LY (Cannatelli et al 2009) [25] | 53 | 1273 | 35 | 1266 | 21.4% | 1.51 [0.99, 2.29] | 1.51 [0.99, 2.29] |
| ROCKET AF-J (Hori et al 2012) [27] | 1 | 168 | 0 | 84 | 1.0% | 1.51 [0.06, 36.65] | 1.51 [0.06, 36.65] |
| VENTURE (Cappato et al 2015) [33] | 2 | 124 | 1 | 124 | 1.8% | 2.00 [0.18, 21.77] | 2.00 [0.18, 21.77] |
| Total (95% CI) | 22371 | 22194 | 100.0% | 0.97 [0.70, 1.36] | 0.97 [0.70, 1.36] |

Total events: 333. Heterogeneity: Tau^2 = 0.09; Chi^2 = 16.17, df = 7 (P = 0.02); I^2 = 57%
Test for overall effect: Z = 0.15 (P = 0.88)

Supplementary Figure 7 (A) Fatal GI bleed (INR < 60% target therapeutic range) (B) Fatal GI bleed (INR > 60% target therapeutic range)
DOAC, direct-acting oral anticoagulant; CI, confidence interval; GI, gastrointestinal; INR, international normalized ratio