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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

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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

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Conflict of Interest: None

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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 I^2 test for heterogeneity. An I^2 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. Review Manager (Rev Man) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, was the statistical package used for the synthesis of the meta-analysis. The summary measure of each analysis was computed as relative risk (RR) with a 95%CI. The random-effects (rather than fixed-effects) model was chosen as the appropriate test, based on its better performance in the presence of heterogeneity with a smaller number of events, especially in the subgroup analysis [8].

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 years 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; I^2=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 χ^2 of 36.95 and I^2 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	2,4	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...)

Table 1 *(Continued)*

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
Xe-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
											24	40				

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

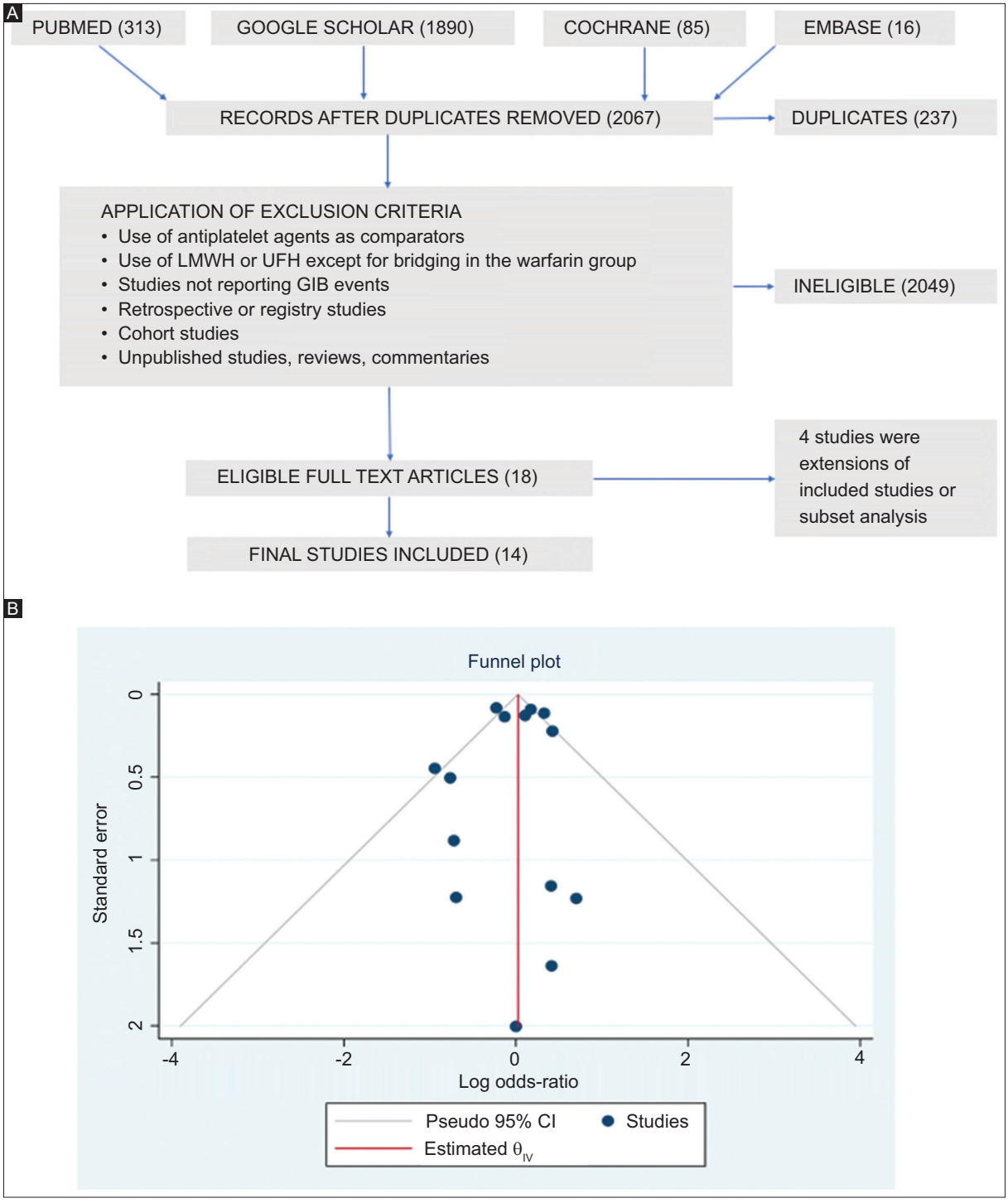

Figure 1 (A) results of literature search. (B) funnel plot of the included studies for publication bias
LMWH, low molecular weight heparin; UFH, unfractionated heparin; GIB, gastrointestinal bleeding; CI, confidence interval

Apixaban. Any risk of GIB with Apixaban was included in 2 studies (AMPLIFY, ARISTOTLE) with a total of 15,240 patients on apixaban vs. 15177 on warfarin. GIB events were again similar (RR 1.04, 95%CI 0.72-1.51; P=0.83; I^2=66%). All studies reported bleeding events (Fig. 2B). The dataset was considered heterogeneous, with a χ^2 of 5.85 and I^2 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 0.79-1.62-1.48; P=0.62; I^2=87%). The dataset was considered heterogeneous, with a χ^2 of 15.04 and I^2 of 87%. Sensitivity

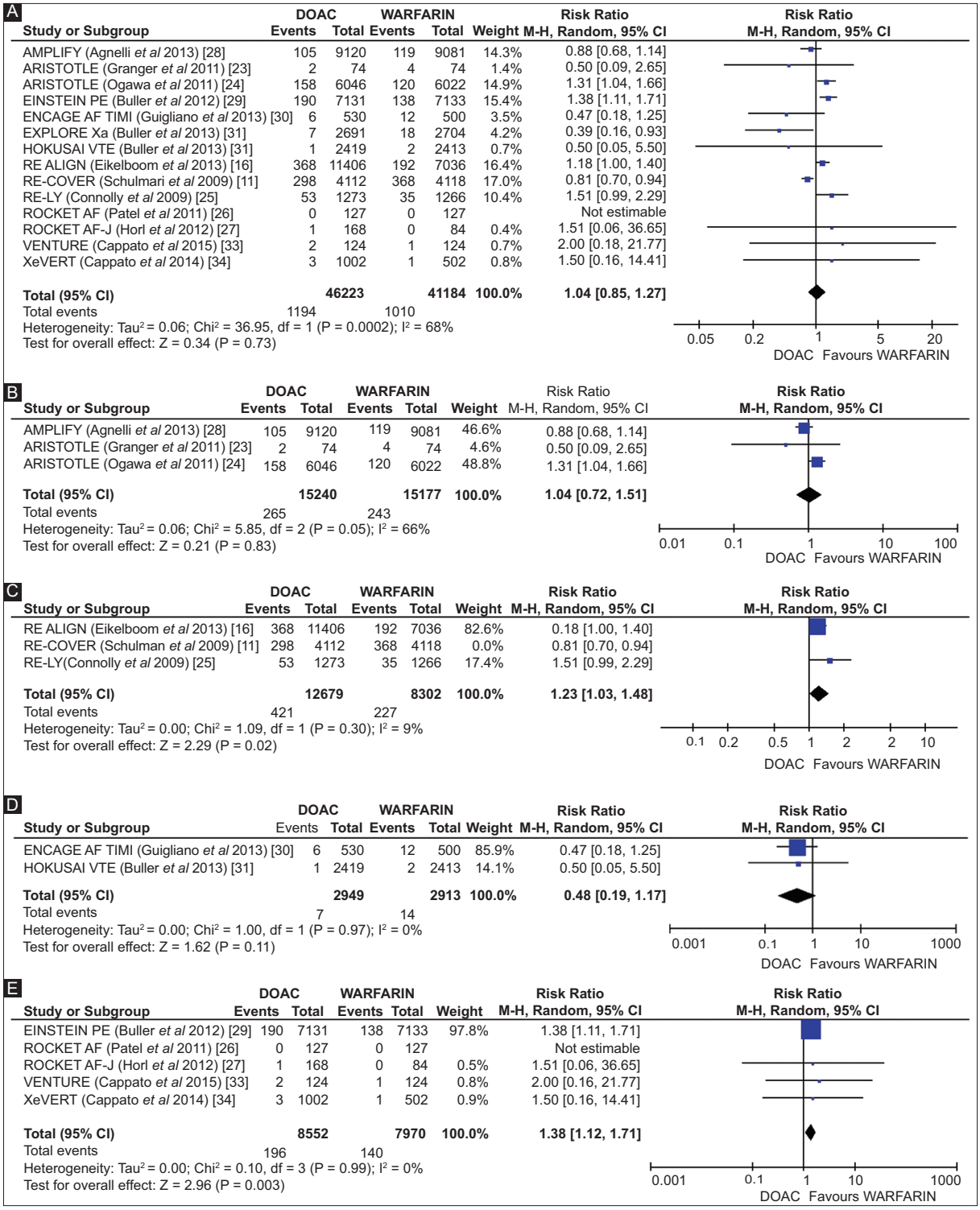

Figure 2 (A) Any gastrointestinal bleeding (GIB); (B) apixaban any GIB; (C) dabigatran any GIB (after sensitivity analysis); (D) edoxaban any GIB; (E) rivaroxaban any GIB
DOAC, direct-acting oral anticoagulant; CI, confidence interval

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 TM 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; I^2=0%) (Fig. 2D). The dataset was considered non-heterogeneous, with a χ^2 of 0% and I^2 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; I^2=0%) (Fig. 2E). The dataset was considered non-heterogeneous, with a χ^2 of 10% and I^2 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; I^2=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 DOACs (RR 0.45, 95%CI 0.16-1.27; P=0.13; I^2=0%) (Supplementary Fig. 4). The dataset was considered non-heterogeneous, with a χ^2 of 1% and I^2 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; I^2=0%) (Supplementary Fig. 5). The dataset was considered non-heterogeneous, with a χ^2 of 1% and I^2 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 I^2 in most analyses was low, indicating that homogenous study populations were compared. In a few analyses, where I^2 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 $CHADS_2$ 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

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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

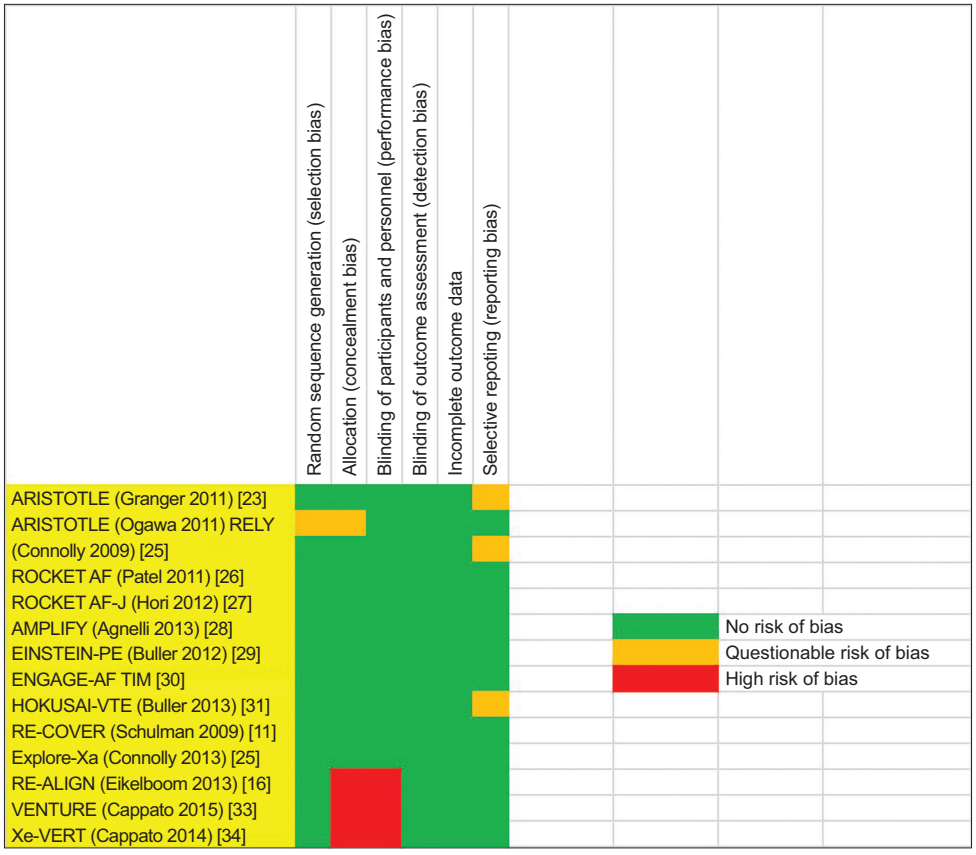
Participants = adult patients who require anticoagulation in the setting of a clinical trial

Intervention = Direct acting oral anticoagulant

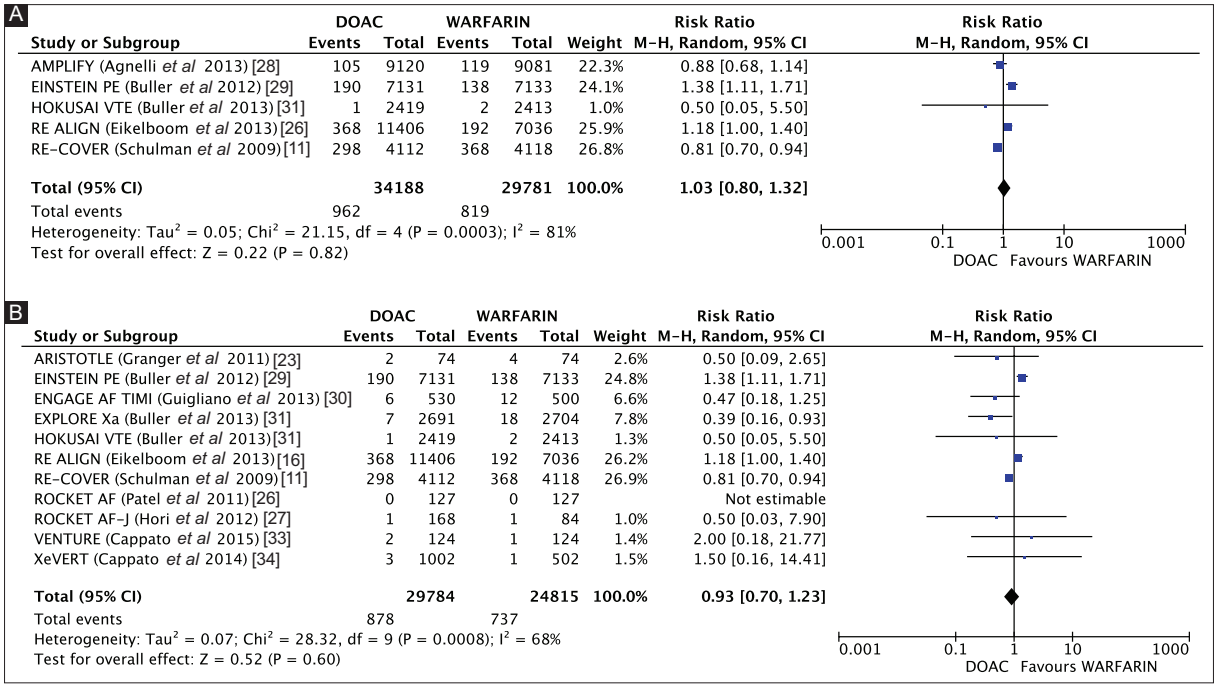
Comparator = Warfarin

Outcome = Gastrointestinal bleeding

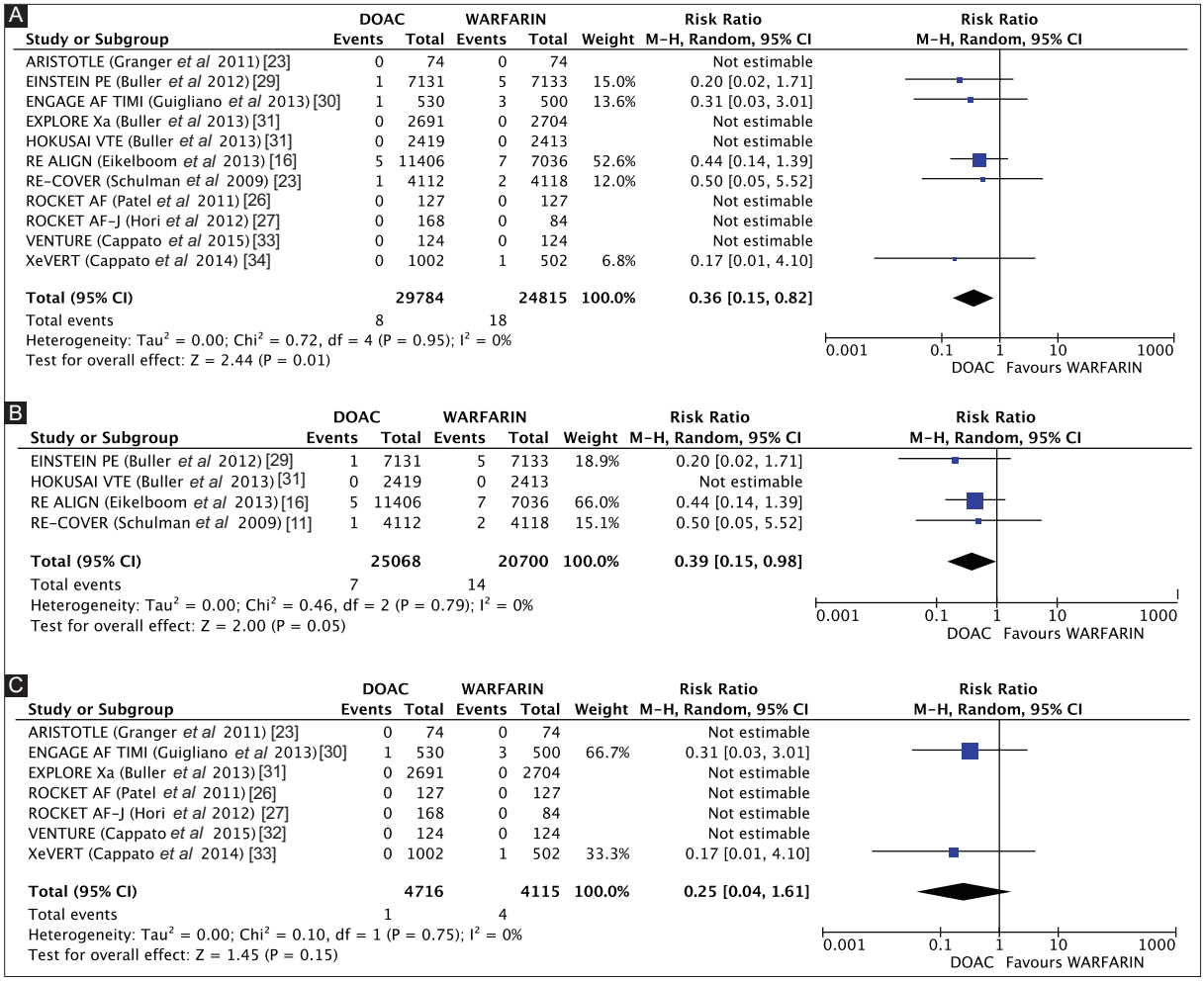
Search strategy



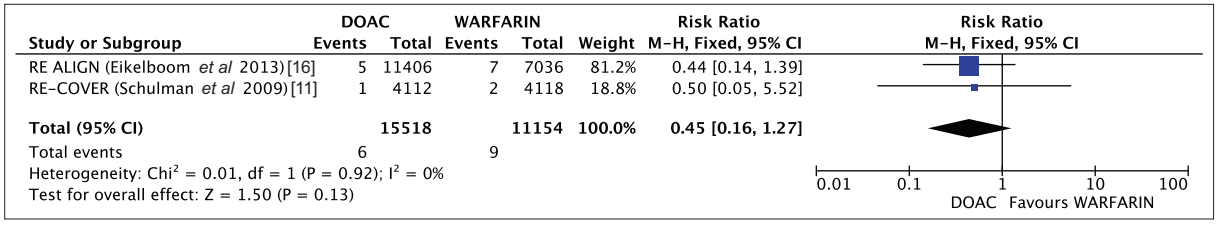
Supplementary Figure 1 Cochrane method for analysis of study quality



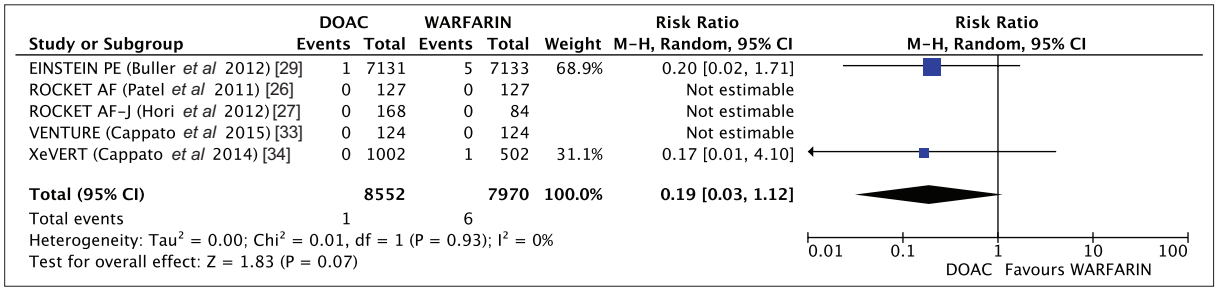
Supplementary Figure 2 (A) GI bleed < 60y; (B). GI bleed > 60y
DOAC, direct-acting oral anticoagulant; CI, confidence interval



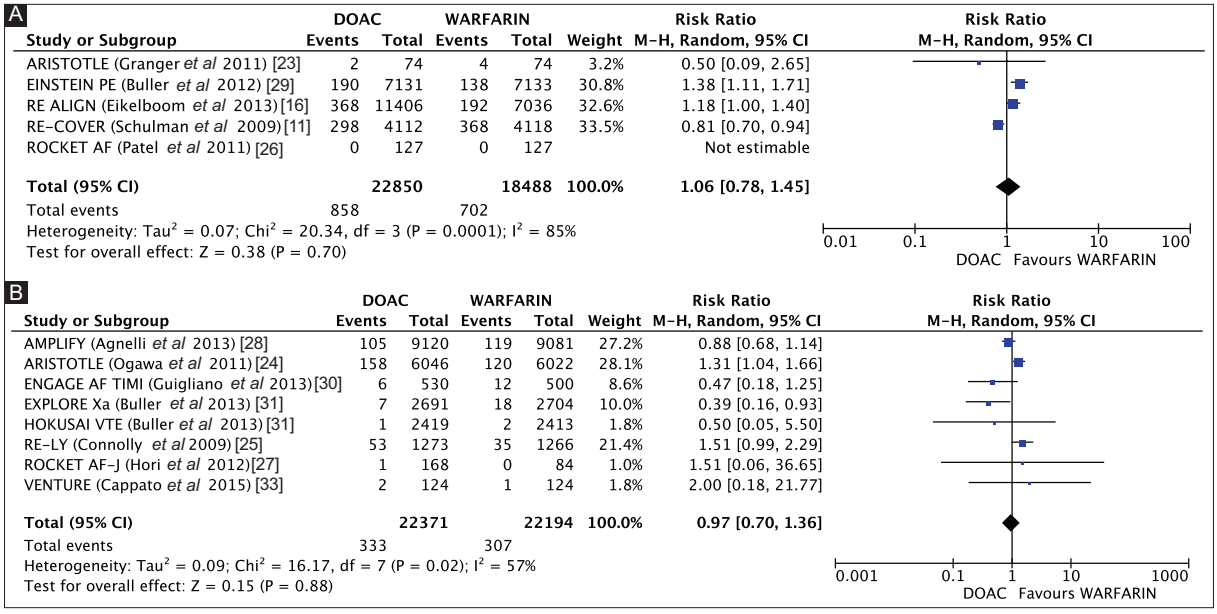
Supplementary Figure 3 (A) Any fatal GI bleed, (B) Fatal GI bleed <60y, (C) Fatal GI bleed > 60y
DOAC, direct-acting oral anticoagulant; CI, confidence interval; GI, gastrointestinal



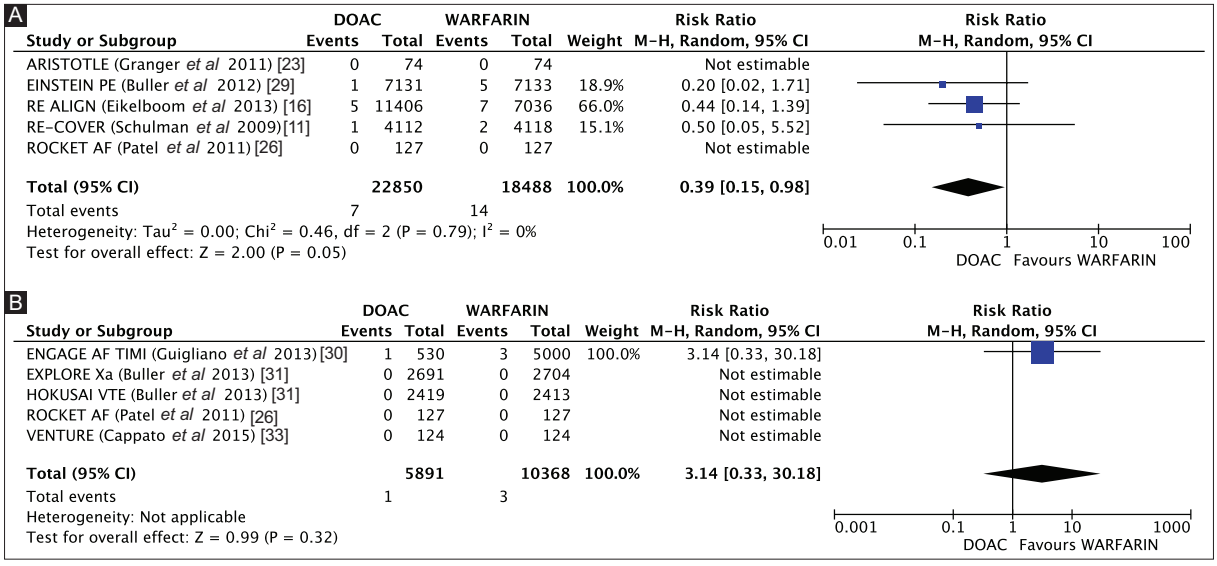
Supplementary Figure 4 Dabigatran fatal GI bleed
DOAC, direct-acting oral anticoagulant; CI, confidence interval



Supplementary Figure 5 Rivaroxaban fatal GI bleed
DOAC, direct-acting oral anticoagulant; CI, confidence interval; GI, gastrointestinal



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



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