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 Ann Gastroenterol 2021; 34 (5): 651-659

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Conflict of Interest: None

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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 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; 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 χ^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).

	Fatal bleed-GI bleed (NOAC, VKA)	NR* (reported as combined with other non- ICB as 1.14% vs . 1.22%)	0,0	NR	1,5	1,3	0,0	0,0	5,7	1,2
	Total GI bleed 1 (NOAC, 1 VKA) (105, 119	2,4	133, 182, 120	190,138	6,12	7,18	1,2	368, 192	298,368
	Fatal intracranial bleed (NOAC, VKA)	42,67	0,0	NR	NR	NR	1,2	2,2	53,59	0,6
	Total intracranial bleed (NOAC, VKA)	52,122	0,0	27, 36, 87	55,84	5,10	3,6	3,13	102,132	5,12
	Median duration follow up (weeks)	120	16	104	101	121	28	52	145	60
	Median use of study agents (weeks)	120	12	104	84	120	24	52	145	12
	Bridging	°Z	No	No	No	No	Yes	Yes	No	Yes
	Warfarin (n)	9081	74	6022	7133	500	2704	2413	7036	4118
	(n)	9120	74,74	6015, 6076	7131	530	2691	2419	11406	4112
lemographics, study size and events	Study group (sub groups)	APIXIBAN	APIXIBAN (2.5, 5mg bid)	DABIGATRAN (110, 150 mg qd)	RIVAROXABAN	RIVAROXABAN	APIXIBAN	RIVAROXABAN	EDOXABAN	EDOXABAN
ohics, study	Mean CHADS2	2.1	1.9	2.1	3.47	3.25	NA	NA	0	NA
ications, demograf	indication for trial	AF	AF	AF	AF	AF	VTE	PE	AF	VTE/PE
gn, indi	Males %	64.7	62	63.8	60.3	80.6	56.7	57.5	72	57.2
udy desi	Mean age	20	70	71.5	73	71.1	57.2	57.9	72	55.7
ices between st	Blinding	Double blinded	Partially blinded	Double blinded	Double blinded	Double blinded	Double blinded	Randomized Open Label	Double blinded	Double blinded
differen	Design	RCT	RCT	RCT	RCT	RCT	RCT	ROL	RCT	RCT
Table 1 Detailed differences between study design, indications, d	Study trial (YR) [Ref.]	ARISTOTLE (Granger 2011) [23]	ARISTOTLE (Ogawa 2011) [24]	RELY (Connolly 2009) [25]	ROCKET AF (Patel 2011) [26]	ROCKET AF-J (Hori 2012) [27]	AMPLIFY (Agnelli 2013) [28]	EINSTEIN- PE (Buller 2012) [29]	ENGAGE- AF TIMI (Giugliano 2013) [30]	HOKUSAI- VTE (Buller 2013) [31]

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oup (n) Warfarin Bridging Median Median Total Fatal Total GI Fatal ups) (n) Warfarin Bridging Median Median Total Eatal Total GI Fatal use of duration intracranial intracranial bleed bleed-GI study follow bleed bleed (NOAC, bleed agents up (NOAC, (NOAC, VKA) (NOAC,	1273 1266 Yes 24 28 0,3 0,3 53,35	IBAN 127 127 No 21 21 1,1 1,1 0,0 0,0	VTRAN 168 84 No 21 21 9,0 NR 1,0 0,0	XABAN 124 124 No 8 8 0,1 0,0 2,1 0,0	XABAN 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
	1266				502	i: VTE, venous thron
Study group (n) (sub groups)	DABIGATRAN 1273	BETRIXIBAN 127	DABIGATRAN 168	RIVAROXABAN 124	RIVAROXABAN 1002	d: AF. atrial fibrillation
Mean CHADS2	NA DAI	2.2	NA DAI	1.6 RIV	RIV	able: NR, not report
Mean Males Indication for age % trial	VTE	AF (Post Cardioversion)	MV	AF (Post Ablation)	AF (Post Ablation)	bel: NA. not applic
dean Male age %	55 58	72 62	56 65	60 70	72	zed open la
Design Blinding Me	Double 5 blinded	Double 7 blinded	Randomized 5 Open Label	Randomized 6 Open Label	Randomized 65 Open Label	I trial: ROL. randomi
Design	RCT	RCT	ROL	ROL	ROL	d controlled
Study trial Des (YR) [Ref.]	RE-COVER (Schulman 2009) [11]	Explore-Xa (Connolly 2013) [32]	RE-ALIGN (Eikelboom 2013) [16]	VENTURE (Cappato 2015) [33]	Xe-VERT (Cappato 2014) [33]	RCT. randomize

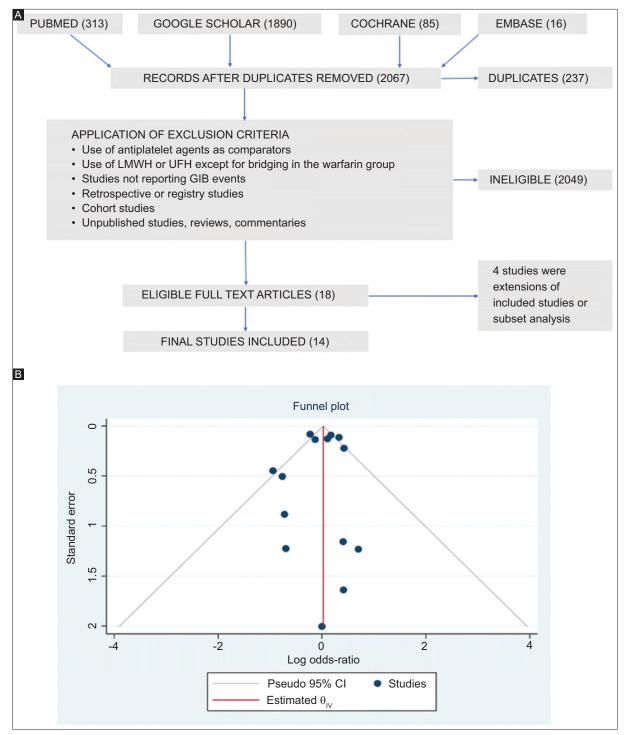


Figure 1 (A) results of literature search. (B) funnel plot of the included studies for publication bias *LMWH*, *low molecular weight heparin; UFH, unfractionated heparin; GIB, gastrointestinal bleeding; CI, confidence interval*

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 F 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 F of 87%. Sensitivity

Study on Subman		OAC	WARFA		Risk Ratio	Risk Ratio
Study or Subgroup	Event				M-H, Random, 95% CI	
AMPLIFY (Agnelli et al 2013) [28]	10		119	9081 14.3%		
ARISTOTLE (Granger et al 2011) [23]		2 74	4	74 1.4%		
ARISTOTLE (Ogawa et al 2011) [24]	15		120	6022 14.9%		
EINSTEIN PE (Buller et al 2012) [29]	19		138	7133 15.4%		
ENCAGE AF TIMI (Guigliano et al 2012)			12	500 3.5%		
EXPLORE Xa (Buller et al 2013) [31] HOKUSAI VTE (Buller et al 2013) [31]		7 2691 1 2419	18 2	2704 4.2% 2413 0.7%		
RE ALIGN (Eikelboom <i>et al</i> 2013) [31]	36		192	7036 16.4%		
RE-COVER (Schulmari et al 2009) [11]			368	4118 17.0%		
RE-LY (Connolly et al 2009) [25]	j 25 5		35	1266 10.4%		
ROCKET AF (Patel <i>et al</i> 2011) [26]		0 127	0	127	Not estimable	
ROCKET AF-J (Horl <i>et al</i> 2012) [27]		1 168	Ō	84 0.4%		
VENTURE (Cappato et al 2015) [33]		2 124	1	124 0.7%	2.00 [0.18, 21.77]	
XeVERT (Cappato et al 2014) [34]		3 1002	1	502 0.8%	1.50 [0.16, 14.41]	
Total (95% CI)		46223		41184 100.0%	1.04 [0.85, 1.27]	↓ ↓
Total events Heterogeneity: Tau² = 0.06; Chi² = 36.	119 95 df = 1		1010 02): l ² = 6	8%		
Test for overall effect: $Z = 0.34$ (P = 0.		1 (1 = 0.00	02), 1 = 0	0 /0		0.05 0.2 1 5 20
						DOAC Favours WARFARIN
	DOAC	W	RFARIN		Risk Ratio	Risk Ratio
					I-H, Random, 95% CI	M-H, Random, 95% Cl
AMPLIFY (Agnelli <i>et al</i> 2013) [28]		0.20	19 908		0.88 [0.68, 1.14]	T
ARISTOTLE (Granger et al 2011) [23]	2	74		4 4.6%	0.50 [0.09, 2.65]	
ARISTOTLE (Ogawa et al 2011) [24]	158 6	6046 1	20 602	48.8%	1.31 [1.04, 1.66]	
Total (95% CI)		5240		7 100.0%	1.04 [0.72, 1.51]	•
Total events	265		43			
Heterogeneity: Tau ² = 0.06; Chi ² = 5.8 Test for overall effect: Z = 0.21 (P = 0.		(P = 0.05);	$l^2 = 66\%$		F	0.01 0.1 1 10 10
Study or Subgroup E	DOAC	: W. Total Eve	ARFARIN		Risk Ratio I-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
RE ALIGN (Eikelboom <i>et al</i> 2013) [16]			192 703		0.18 [1.00, 1.40]	
RE-COVER (Schulman <i>et al</i> 2009) [11			368 411		0.81 [0.70, 0.94]	
RE-LY(Connolly <i>et al</i> 2009) [25]	53	1273	35 126		1.51 [0.99, 2.29]	
	00	1210	00 120		1.01 [0.00, 2.20]	
Total (95% CI)	1	12679	830	2 100.0%	1.23 [1.03, 1.48]	◆
Total events	421		227			
Heterogeneity: Tau ² = 0.00; Chi ² = 1.0	9, df = 1	(P = 0.30)	l ² = 9%		-	-+ + + + + + +
Test for overall effect: Z = 2.29 (P = 0.	02)					0.1 0.2 0.5 1 2 2 10
						DOAC Favours WARFARIN
		~ ~ ~				
Study or Subgroup		OAC ts Total E	WARFA Events		Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
	Even					
ENCAGE AF TIMI (Guigliano et al 201	Event 3) [30]	ts Total E	Events 12	Total Weight	M-H, Random, 95% CI	
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31]	Event 3) [30]	ts Total E 6 530 1 2419	12 2	Fotal Weight 500 85.9% 2413 14.1%	M-H, Random, 95% Cl 0.47 [0.18, 1.25] 0.50 [0.05, 5.50]	M-H, Random, 95% Cl
Study or Subgroup ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31] Total (95% CI) Total events	Event 3) [30]	ts Total E 6 530 1 2419 2949	Events 12 2	Total Weight 500 85.9%	M-H, Random, 95% Cl 0.47 [0.18, 1.25] 0.50 [0.05, 5.50]	M-H, Random, 95% Cl
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31] Total (95% CI) Total events	Event 3) [30]	ts Total E 6 530 1 2419 2949 7	Events 12 2 2 14	Fotal Weight 500 85.9% 2413 14.1%	M-H, Random, 95% Cl 0.47 [0.18, 1.25] 0.50 [0.05, 5.50]	M-H, Random, 95% Cl
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31] Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 1.0	Event 3) [30] 0, df = 1	ts Total E 6 530 1 2419 2949 7	Events 12 2 2 14	Fotal Weight 500 85.9% 2413 14.1%	M-H, Random, 95% Cl 0.47 [0.18, 1.25] 0.50 [0.05, 5.50]	M-H, Random, 95% Cl
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31]	Event 3) [30] 0, df = 1	ts Total E 6 530 1 2419 2949 7	Events 12 2 2 14	Fotal Weight 500 85.9% 2413 14.1%	M-H, Random, 95% Cl 0.47 [0.18, 1.25] 0.50 [0.05, 5.50]	M-H, Random, 95% Cl
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31] Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 1.0	Event 3) [30] 0, df = 1 11)	ts Total E 6 530 1 2419 2949 7 (P = 0.97);	Events 12 2 14 ² = 0%	Fotal Weight 500 85.9% 2413 14.1%	M-H, Random, 95% CI 0.47 [0.18, 1.25] 0.50 [0.05, 5.50] 0.48 [0.19, 1.17]	M-H, Random, 95% Cl
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31] Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 1.0 Test for overall effect: Z = 1.62 (P = 0.	Event 3) [30] 0, df = 1	ts Total E 6 530 1 2419 2949 7 (P = 0.97); WAR	Events 12 12 2 14 12 12 3 5 5 14 12 12 5 5 5 12 3 14 12 12 5 13 5 14 12 12 5 13 5 14 12 14 12 15 5 16 5 17 5 18 5 19 5 19 5 12 5 13 5 14 5 15 5 16 5 17 5 18 5 19 5 19 5 19 5 19 5 <tr tr=""> 19 5</tr>	Fotal Weight 500 85.9% 2413 14.1% 2913 100.0%	M-H, Random, 95% Cl 0.47 [0.18, 1.25] 0.50 [0.05, 5.50]	M-H, Random, 95% Cl
ENCAGE AF TIMI (Guigliano <i>et al</i> 201 HOKUSAI VTE (Buller <i>et al</i> 2013) [31] Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 1.0 Test for overall effect: Z = 1.62 (P = 0. Study or Subgroup	Event 3) [30] 0, df = 1 11) DOAC ents Tot	ts Total E 6 530 1 2419 2949 7 (P = 0.97); WAR tal Event	12 2 14 1 ² = 0%	Fotal Weight 500 85.9% 2413 14.1% 2913 100.0% Weight M-H	M-H, Random, 95% CI 0.47 [0.18, 1.25] 0.50 [0.05, 5.50] 0.48 [0.19, 1.17] Risk Ratio H, Random, 95% CI	M-H, Random, 95% Cl
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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; P=0%) (Supplementary Fig. 4). The dataset was considered non-heterogeneous, with a χ^2 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; 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 CHADS₂ 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 FDAapproved 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.

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Summary Box

What is already known:

- Gastrointestinal bleeding (GIB) related to anticoagulant use is comparable between directacting 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 metaanalysis 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

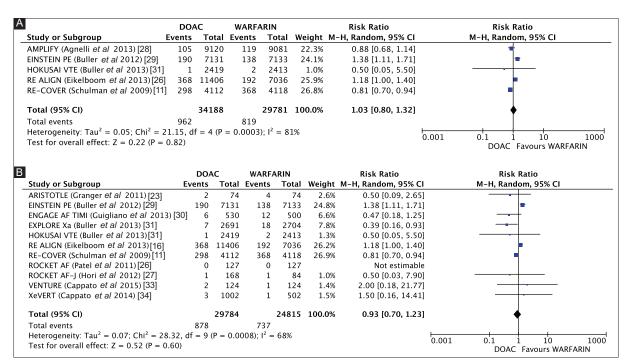
Comparator = Warfarin

Outcome = Gastrointestinal bleeding

Search strategy

	Random sequence generation (selection bias)	Allocation (concealment bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data	Selective repoting (reporting bias)		
ARISTOTLE (Granger 2011) [23] ARISTOTLE (Ogawa 2011) RELY								
(Connolly 2009) [25]								
ROCKET AF (Patel 2011) [26]								
ROCKET AF-J (Hori 2012) [27]								
AMPLIFY (Agnelli 2013) [28]							No risk of bias	
EINSTEIN-PE (Buller 2012) [29]							Questionable risk of I	bias
ENGAGE-AF TIM [30] HOKUSAI-VTE (Buller 2013) [31]							High risk of bias	
RE-COVER (Schulman 2009) [11]								
Explore-Xa (Connolly 2013) [25]								
RE-ALIGN (Eikelboom 2013) [16]								
VENTURE (Cappato 2015) [33]								
Xe-VERT (Cappato 2014) [34]				_				

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

Eve	nts	Total								
		TOLA	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ranc	lom, 95% Cl	
	0	74	0	74		Not estimable				
	1	7131	5	7133	15.0%	0.20 [0.02, 1.71]			+	
[30]	1	530	3	500	13.6%	0.31 [0.03, 3.01]				
	0	2691	0	2704		Not estimable				
	0	2419	0	2413		Not estimable				
	5	11406	7	7036	52.6%	0.44 [0.14, 1.39]			-	
	1	4112	2	4118	12.0%	0.50 [0.05, 5.52]				
	0	127	0	127		Not estimable				
	0	168	0	84		Not estimable				
	0	124	0	124		Not estimable				
	0	1002	1	502	6.8%	0.17 [0.01, 4.10]				
		29784		24815	100.0%	0.36 [0.15, 0.82]		•		
	4 (P	= 0.95)	; $I^2 = 0\%$				0.001	0.1	1 10	100
01)								DOAC	Favours WARF	ARIN
									-	
								M-H, Rand	om, 95% CI	
					18.9%	. , .			-	
5	11	406	7	7036	66.0%	0.44 [0.14, 1.39]			-	
] 1	4	112	2	4118	15.1%	0.50 [0.05, 5.52]				
	25	068	2	0700 1	100.0%	0.39 [0.15, 0.98]		•		
			14							
	= 2	(P = 0.1)	79); I ² =	0%			0.001	0.1	1 10	10
0.05)								DOAC	Favours WARF	ARIN
	DO/	AC	WARF	ARIN		Risk Ratio		Risk	Ratio	
Ev	ents	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% Cl	
3)[30]					66.7%				 	
,[00]			-		00.770	• / •				
	-		-							
	-		-							
			1	502	33.3%	0.17 [0.01, 4.10]			<u> </u>	
		4716		4115	100.0%	0 25 [0 04 1 61]				
	1	., 10	4		20010/0	0120 [010 1, 1101]				
10 df	1 /		-12 0	0/						
,	= т (r = 0.7	$(0, 1^{-} = 0)$	70			0.001	0.1	i 10	100
	'2, df = 01) DO Events 1 0 1 5] 1 7 7,46, df 0.05) Ev 33][30]	$\begin{array}{c} & 0 \\ & 0 \\ & 0 \\ & 0 \\ & 1 \\ & 0 \\$	$\begin{array}{c} 0 & 2691 \\ 0 & 2419 \\ 5 & 11406 \\ 1 & 4112 \\ 0 & 127 \\ 0 & 168 \\ 0 & 124 \\ 0 & 1002 \end{array}$ $\begin{array}{c} 29784 \\ 8 \\ 7 \\ 2, df = 4 (P = 0.95) \\ 01 \end{array}$ $\begin{array}{c} 0 & 2419 \\ 1 & 7131 \\ 0 & 2419 \\ 1 & 7131 \\ 0 & 2419 \\ 1 & 5 & 11406 \\ 1 & 4112 \end{array}$ $\begin{array}{c} 25068 \\ 7 \\ 1 & 4112 \\ 25068 \\ 7 \\ 1 & 4112 \\ 25068 \\ 7 \\ 0 & 2691 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 127 \\ 0 & 168 \\ 0 & 124 \\ 0 & 1002 \\ \end{array}$	$\begin{array}{c} 0 & 2691 \\ 0 & 2419 \\ 0 & 5 & 11406 \\ 7 & 1 & 4112 \\ 2 \\ 0 & 127 \\ 0 & 0 & 168 \\ 0 & 0 & 124 \\ 0 & 0 & 1002 \\ 1 \\ \hline \end{array}$ $\begin{array}{c} 29784 \\ r^2, df = 4 (P = 0.95); I^2 = 0\% \\ 01 \\ \hline \end{array}$ $\begin{array}{c} 29784 \\ r^2, df = 4 (P = 0.95); I^2 = 0\% \\ 01 \\ \hline \end{array}$ $\begin{array}{c} 29784 \\ r^2 & 1412 \\ 1 & 7131 \\ 5 \\ 0 & 2419 \\ 0 \\ 1 & 4112 \\ 2 \\ \hline \end{array}$ $\begin{array}{c} 25068 \\ 20 \\ 7 \\ 1 & 4112 \\ 2 \\ \hline \end{array}$ $\begin{array}{c} 25068 \\ 20 \\ 7 \\ 1 & 4112 \\ 2 \\ \hline \end{array}$ $\begin{array}{c} 25068 \\ 20 \\ 7 \\ 1 & 4112 \\ 2 \\ \hline \end{array}$ $\begin{array}{c} 25068 \\ 20 \\ 7 \\ 1 & 4112 \\ 2 \\ \hline \end{array}$ $\begin{array}{c} 25068 \\ 20 \\ 7 \\ 1 & 4112 \\ 2 \\ \hline \end{array}$ $\begin{array}{c} 25068 \\ 20 \\ 7 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0 2691 0 2704 Not estimable 0 2419 0 2413 Not estimable 5 11406 7 7036 52.6% 0.44 [0.14, 1.39] 1 4112 2 4118 12.0% 0.50 [0.05, 5.52] 0 127 0 127 Not estimable 0 168 0 84 Not estimable 0 1002 1 502 6.8% 0.17 [0.01, 4.10] 29784 24815 100.0% 0.36 [0.15, 0.82] 8 18 18 0.20 [0.02, 1.71] 0.26 [0.02, 1.71] 0 2419 0 2413 Not estimable 0 2419 0 2413 Not estimable 1 7131 5 7133 18.9% 0.20 [0.02, 1.71] 0 2419 0 2413 Not estimable 1 7131 5 7133 18.9% 0.20 [0.02, 5.52] 25068 20700 100.0% 0.39 [0.15, 0.98] 7 1 4112	D 2691 0 2704 Not estimable 0 2419 0 2413 Not estimable 5 11406 7 7036 52.6% 0.44 [0.14, 1.39] 1 4112 2 4118 12.0% 0.50 [0.05, 5.52] 0 127 0 127 Not estimable 0 168 0 84 Not estimable 0 1002 1 502 6.8% 0.17 [0.01, 4.10] 29784 24815 100.0% 0.36 [0.15, 0.82] 8 8 18 18 0.1002 0.001 0.001 29784 24815 100.0% 0.36 [0.15, 0.82] 8 8 18 18 0.001 0.001 0.001 101 1 7131 5 7133 18.9% 0.20 [0.02, 1.71] 0.2010 0 2419 0 2413 Not estimable 0.001 0.001 1 5 11406 7 7036 66.0% 0.44 [0.14, 1.39] 0.001 1 <td< td=""><td>$\begin{array}{c c c c c c c c c c c c c c c c c c c$</td><td>$\begin{array}{c c c c c c c c c c c c c c c c c c c$</td></td<>	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

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

	DOA	١C	WARFA	RIN		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M–H, Fixed, 95% Cl
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)[11] 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]	
Total events	6		9				
Heterogeneity: $Chi^2 = 0.01$, $df = 1$ (H	P = 0.92); $I^2 = 0$ %	6				0.01 0.1 1 10 100
Test for overall effect: Z = 1.50 (P =	0.13)						DOAC Favours WARFARIN

Supplementary Figure 4 Dabigatran fatal GI bleed

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

	DOA	C	WARFA	RIN		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		М-	H, Rand	om, 95%	CI	
EINSTEIN PE (Buller et al 2012) [29	9] 1	7131	5	7133	68.9%	0.20 [0.02, 1.71]				<u> </u>		
ROCKET AF (Patel et al 2011) [26]	0	127	0	127		Not estimable						
ROCKET AF-J (Hori et al 2012) [27	7] 0	168	0	84		Not estimable						
VENTURE (Cappato et al 2015) [33	3] 0	124	0	124		Not estimable						
XeVERT (Cappato et al 2014) [34]	0	1002	1	502	31.1%	0.17 [0.01, 4.10]	•			<u> </u>		
Total (95% CI)		8552		7970	100.0%	0.19 [0.03, 1.12]	-			+		
Total events	1		6									
Heterogeneity: $Tau^2 = 0.00$; Chi^2	= 0.01,	df = 1	(P = 0.93)	(); $I^2 = 0$	0%			01		1	10	1.00
Test for overall effect: $Z = 1.83$ (P	P = 0.07))					0.01	0.1	DOAC	I Favours	WARFARI	10 N

Supplementary Figure 5 Rivaroxaban fatal GI bleed

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

	DOA	۱C	WARFA	ARIN		Risk Ratio	Risk Ratio
Study or Subgroup Ev	vents	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
ARISTOTLE (Granger et al 2011) [23]	2	74	4	74	3.2%	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]	*
RE ALIGN (Eikelboom <i>et al</i> 2013)[16]	368	11406	192	7036	32.6%	1.18 [1.00, 1.40]	-
RE-COVER (Schulman et al 2009)[11]	298	4112	368	4118	33.5%	0.81 [0.70, 0.94]	=
ROCKET AF (Patel <i>et al</i> 2011) [26]	0	127	0	127		Not estimable	
Total (95% CI)		22850		18488	100.0%	1.06 [0.78, 1.45]	•
Total events	858		702				
	I	DOAC	WAI	RFARIN		Risk Ratio	Risk Ratio
Study or Subgroup	E	т.					
study of Subgroup	Evei	ונג וס	tal Even	τς ιοτ	ai weign	t M-H, Random, 95% CI	M-H, Random, 95% CI
AMPLIFY (Agnelli <i>et al</i> 2013) [28]			20 11				
AMPLIFY (Agnelli <i>et al</i> 2013) [28]	1		20 11		31 27.2	% 0.88 [0.68, 1.14]	+
	1	.05 91 .58 60	20 11 46 12	19 908	81 27.29 22 28.19	0.88 [0.68, 1.14] 1.31 [1.04, 1.66]	•
AMPLIFY (Agnelli <i>et al</i> 2013) [28] ARISTOTLE (Ogawa <i>et al</i> 2011) [24]	1	05 91 58 60 6 5	20 11 46 12 30 1	19 908 20 602	31 27.29 22 28.19 00 8.69	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25]	
AMPLIFY (Agnelli <i>et al</i> 2013) [28] ARISTOTLE (Ogawa <i>et al</i> 2011) [24] ENGAGE AF TIMI (Guigliano <i>et al</i> 2013)[1	05 91 58 60 6 5 7 26	20 11 46 12 30 1 91 1	19 908 20 602 12 50	31 27.29 22 28.19 00 8.69 04 10.09	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93]	
AMPLIFY (Agnelli <i>et a</i> l 2013) [28] ARISTOTLE (Ogawa <i>et a</i> l 2011) [24] SNGACE AF TIMI (Guigliano <i>et a</i> l 2013) EXPLORE Xa (Buller <i>et a</i> l 2013) [31] OKUSAI VTE (Buller <i>et a</i> l 2013) [31] RE-LY (Connolly <i>et a</i> l 2009) [25]	1 1 30]	05 91 58 60 6 5 7 26 1 24	20 11 46 12 30 1 91 1 19	19 908 20 602 12 50 18 270	31 27.29 22 28.19 00 8.69 04 10.09 .3 1.89	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93] % 0.50 [0.05, 5.50]	
AMPLIFY (Agnelli <i>et a</i> l 2013) [28] ARISTOTLE (Ogawa <i>et a</i> l 2011) [24] ENGAGE AF TIMI (Guigliano <i>et a</i> l 2013) [27]LORE Xa (Buller <i>et a</i> l 2013) [31] HOKUSAI VTE (Buller <i>et a</i> l 2013) [31]	1 1 30]	05 91 58 60 6 5 7 26 1 24 53 12	20 11 46 12 30 1 91 1 19 73	19 908 20 602 12 50 18 270 2 241 35 126	31 27.2 22 28.1 00 8.6 04 10.0 .3 1.8	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93] % 0.50 [0.05, 5.50] % 1.51 [0.99, 2.29]	
AMPLIFY (Agnelli <i>et a</i> l 2013) [28] ARISTOTLE (Ogawa <i>et a</i> l 2011) [24] SNGACE AF TIMI (Guigliano <i>et a</i> l 2013) EXPLORE Xa (Buller <i>et a</i> l 2013) [31] OKUSAI VTE (Buller <i>et a</i> l 2013) [31] RE-LY (Connolly <i>et a</i> l 2009) [25]	1 1 30]	05 91 58 60 6 5 7 26 1 24 53 12 1 1	20 11 46 12 30 1 91 1 19 73	19 908 20 602 12 50 18 270 2 241 35 126	31 27.29 22 28.19 00 8.69 04 10.09 .3 1.89 56 21.49 34 1.09	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93] % 0.50 [0.05, 5.50] % 1.51 [0.99, 2.29] % 1.51 [0.06, 36.65]	
AMPLIFY (Agnelli <i>et a</i> l 2013) [28] ARISTOTLE (Ogawa <i>et a</i> l 2011) [24] ENGAGE AF TIMI (Guigliano <i>et a</i> l 2013) [EXPLORE Xa (Buller <i>et a</i> l 2013) [31] OKUSAI VTE (Buller <i>et a</i> l 2013) [31] RE-LY (Connolly <i>et a</i> l 2009) [25] ROCKET AF-J (Hori <i>et a</i> l 2012)[27]	1 1 30]	05 91 58 60 6 5 7 26 1 24 53 12 1 1	20 11 46 12 30 1 91 1 19 1 73 3 68 24	19 908 20 602 12 50 18 270 2 241 35 126 0 8 1 12	31 27.29 22 28.19 00 8.69 04 10.09 .3 1.89 56 21.49 34 1.09	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93] % 0.50 [0.05, 5.50] % 1.51 [0.99, 2.29] % 1.51 [0.06, 36.65] % 2.00 [0.18, 21.77]	
AMPLIFY (Agnelli et al 2013) [28] ARISTOTLE (Ogawa et al 2011) [24] ENGAGE AF TIMI (Guigliano et al 2013) EXPLORE Xa (Buller et al 2013) [31] OKUSAI VTE (Buller et al 2013) [31] RE-LY (Connolly et al 2009) [25] ROCKET AF-J (Hori et al 2012) [27] VENTURE (Cappato et al 2015) [33] Fotal (95% CI) Total events	1 [30] 3	05 91 58 60 6 5 7 26 1 24 53 12 1 1 2 1 223 33	20 11 46 12 30 1 91 1 73 3 68 24 71 30	19 908 20 602 12 50 18 270 2 241 35 126 0 8 1 12 2219 27	31 27.29 22 28.19 00 8.69 04 10.09 .3 1.88 66 21.49 34 1.09 24 1.89	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93] % 0.50 [0.05, 5.50] % 1.51 [0.99, 2.29] % 0.51 [0.06, 36.65] % 2.00 [0.18, 21.77]	
AMPLIFY (Agnelli <i>et al</i> 2013) [28] ARISTOTLE (Ogawa <i>et al</i> 2011) [24] ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) EXPLORE Xa (Buller <i>et al</i> 2013) [31] OKUSAI VTE (Buller <i>et al</i> 2013) [31] RE-LY (Connolly <i>et al</i> 2009) [25] ROCKET AF-J (Hori <i>et al</i> 2012) [27] VENTURE (Cappato <i>et al</i> 2015) [33] Total (95% CI)	1 30] 37, df =	05 91 58 60 6 5 7 26 1 24 53 12 1 1 2 1 223 33	20 11 46 12 30 1 91 1 73 3 68 24 71 30	19 908 20 602 12 50 18 270 2 241 35 126 0 8 1 12 2219 27	31 27.29 22 28.19 00 8.69 04 10.09 .3 1.88 66 21.49 34 1.09 24 1.89	% 0.88 [0.68, 1.14] % 1.31 [1.04, 1.66] % 0.47 [0.18, 1.25] % 0.39 [0.16, 0.93] % 0.50 [0.05, 5.50] % 1.51 [0.99, 2.29] % 0.51 [0.06, 36.65] % 2.00 [0.18, 21.77]	

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

	DOA	С	WARF	ARIN		Risk Ratio		Risk	Ratio	
Study or Subgroup Eve	ents	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ranc	lom, 95% Cl	
ARISTOTLE (Granger <i>et al</i> 2011) [23]	0	74	0	74		Not estimable				
EINSTEIN PE (Buller et al 2012) [29]	1	7131	5	7133	18.9%	0.20 [0.02, 1.71]			+	
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)[11]	1	4112	2	4118	15.1%	0.50 [0.05, 5.52]			+	
ROCKET AF (Patel et al 2011) [26]	0	127	0	127		Not estimable				
Total (95% CI)	;	22850		18488	100.0%	0.39 [0.15, 0.98]			-	
Total events	7		14							
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$ Test for overall effect: $Z = 2.00$ ($P = 0.0$		- 2 (1 -	011 57, 1	0,0			0.01 0	D.1 DOAC	1 10 Favours WARFARI	
	5)					Risk Ratio	0.01 0	DOAC	Favours WARFARI	
	5) D	OAC		RFARIN	al Weigh	Risk Ratio t M-H, Random, 95% Cl		DOAC Risl		
Test for overall effect: $Z = 2.00 (P = 0.0)$	5) D Ever	OAC nts Tot	WA	RFARIN ts To	al Weigh	t M-H, Random, 95% Cl		DOAC Risl	Favours WARFARI	
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup	5) D Ever	OAC nts Tot	WA al Even	RFARIN ts To	0 100.09	t M-H, Random, 95% Cl	I	DOAC Risl	Favours WARFARI	
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) [3	5) D Ever	DOAC nts Tot 1 53	WA al Even 30 91	RFARIN ts To 3 50	00 100.09 04	t M-H, Random, 95% Cl 3.14 [0.33, 30.18]	 	DOAC Risl	Favours WARFARI	
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) [3 EXPLORE Xa (Buller <i>et al</i> 2013) [31]	5) D Ever	DOAC nts Tot 1 53 0 269 0 243	WA al Even 30 91	RFARIN ts To 3 50 0 27 0 24	00 100.09 04	t M-H, Random, 95% Cl % 3.14 [0.33, 30.18] Not estimable	 !	DOAC Risl	Favours WARFARI	10 IN
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) [3 EVPLORE Xa (Buller <i>et al</i> 2013) [31] HOKUSAI VTE (Buller <i>et al</i> 2013) [31]	5) D Ever	DOAC 1 53 0 269 0 243 0 13	WA al Even 30 91 19	RFARIN ts To 3 50 0 27 0 24 0 1	00 100.09 04 13	t M-H, Random, 95% Cl 3.14 [0.33, 30.18] Not estimable Not estimable	 2 2	DOAC Risl	Favours WARFARI	
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) [3 EXPLORE Xa (Buller <i>et al</i> 2013) [31] HOKUSAI VTE (Buller <i>et al</i> 2013) [31] ROCKET AF (Patel <i>et al</i> 2011) [26]	5) D Ever	DOAC 1 53 0 269 0 243 0 13	WA al Even 30 91 19 27 24	RFARIN <u>ts</u> <u>To</u> 3 50 0 27 0 24 0 1 0 1	00 100.09 04 13 27	t M-H, Random, 95% Cl 3.14 [0.33, 30.18] Not estimable Not estimable Not estimable Not estimable		DOAC Risl	Favours WARFARI	
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) [3 EXPLORE Xa (Buller <i>et al</i> 2013) [31] HOKUSAI VTE (Buller <i>et al</i> 2013) [31] ROCKET AF (Patel <i>et al</i> 2011) [26] VENTURE (Cappato <i>et al</i> 2015) [33]	5) D Ever	DOAC <u>nts</u> Tot 1 53 0 269 0 24 0 12 0 12	WA al Even 30 91 19 27 24	RFARIN <u>ts</u> <u>To</u> 3 50 0 27 0 24 0 1 0 1	00 100.09 04 13 27 24	t M-H, Random, 95% Cl 3.14 [0.33, 30.18] Not estimable Not estimable Not estimable Not estimable		DOAC Risl	Favours WARFARI	
Test for overall effect: Z = 2.00 (P = 0.0 Study or Subgroup ENGAGE AF TIMI (Guigliano <i>et al</i> 2013) [3 ENPLORE Xa (Buller <i>et al</i> 2013) [31] HOKUSAI VTE (Buller <i>et al</i> 2013) [31] ROCKET AF (Patel <i>et al</i> 2011) [26] VENTURE (Cappato <i>et al</i> 2015) [33] Total (95% CI)	5) D Ever	DOAC <u>nts</u> Tot 1 53 0 269 0 24 0 12 0 12 589	WA al Even 30 91 19 27 24	RFARIN ts To 3 50 0 27 0 24 0 1 0 1 103	00 100.09 04 13 27 24	t M-H, Random, 95% Cl 3.14 [0.33, 30.18] Not estimable Not estimable Not estimable Not estimable		DOAC Risl	Favours WARFARI	

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