Effectiveness and Safety of Non–vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses

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ABSTRACT

Purpose: The findings from the observational studies comparing the effectiveness and safety of non–vitamin K antagonist oral anticoagulants (NOACs) versus vitamin K antagonists (VKAs) for atrial fibrillation (AF) and venous thromboembolism (VTE) are inconsistent. We conducted separate meta-analyses examining the efficacy/effectiveness and safety of NOACs versus VKAs by disease (AF vs VTE), study design (randomized controlled trials [RCTs] vs observational studies), and NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban).

Methods: The main data sources included PubMed/MEDLINE, EMBASE, Web of Science, CINAHL, and Scopus from January 1, 2005, to February 15, 2016. We searched for Phase III RCTs and observational studies comparing NOACs versus VKAs. The primary outcomes were stroke/systemic embolism (SE) for AF; recurrent VTE/fatal pulmonary embolism (PE) for VTE; and major bleeding for both conditions. Secondary outcomes included stroke and myocardial infarction (MI) for AF, recurrent deep vein thrombosis (DVT)/PE for VTE, and mortality, intracranial hemorrhage (ICH), and gastrointestinal bleeding for both conditions. Pooled hazard ratios (HRs) were reported by using inverse variance–weighted random effects models.

Findings: A total of 13 RCTs and 27 observational studies (AF, n = 32; VTE, n = 8) were included. For AF, dabigatran and VKAs were comparable for stroke/SE risk in 1 RCT (HR, 0.77 [95% CI, 0.57–1.03]) and 6 observational studies (HR, 1.03 [95% CI, 0.83–1.27]). Rivaroxaban had a 20% decreased risk of stroke/SE in 3 RCTs (HR, 0.80 [95% CI, 0.67–0.95]) compared with VKA, but the effect was nonsignificant in 3 observational studies (HR, 0.78 [95% CI, 0.59–1.04]). Apixaban decreased stroke/systemic embolism risk (HR, 0.79 [95% CI, 0.66–0.95]) compared with VKA in 1 RCT, but edoxaban was comparable to VKA (HR, 0.99 [95% CI, 0.77–1.28]) in 1 RCT (no observational studies available for apixaban/edoxaban). Dabigatran, apixaban, and edoxaban decreased the risk of hemorrhagic stroke, mortality, major bleeding, and ICH by 10% to 71% compared with VKAs but not rivaroxaban. For VTE, NOACs and VKAs were comparable for recurrent VTE/fatal PE/DVT/PE risk in 7 RCTs and 1 observational study. The 7 RCTs demonstrated a 32% to 69% decreased risk of major bleeding for dabigatran, rivaroxaban, and apixaban compared with VKAs. No difference was shown in 1 rivaroxaban observational study (HR, 0.77 [95% CI, 0.40–1.49]) and 1 edoxaban RCT (HR, 0.84 [95% CI, 0.59–1.20]). Except for dabigatran, the NOACs had a 61% to 86% decreased risk of ICH and gastrointestinal bleeding.

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Implications: Overall, NOACs were comparable or superior to VKAs. Although no observational studies are currently available for apixaban/edoxaban, a few notable inconsistencies exist for dabigatran (ischemic stroke, MI) and rivaroxaban (stroke/SE, major bleeding in VTE) between RCTs and observational studies. Individualizing NOAC/VKA therapy based on benefit/safety profiles and patient characteristics is suggested. (*Clin Ther*. 2017;39:1456–1478) Published by Elsevier HS Journals, Inc.

Key words: atrial fibrillation, bleeding, meta-analysis, non–vitamin K antagonist oral anticoagulants, venous thromboembolism, warfarin.

INTRODUCTION

Nonvalvular atrial fibrillation (AF) and acute venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), are associated with substantial morbidity and mortality.[1,2] Since the 1950s, warfarin and other vitamin K antagonists (VKAs) have been the cornerstone of therapy for patients with AF and VTE. Although VKAs are inexpensive, they have a narrow therapeutic window, require frequent monitoring, have many interactions with food and drugs, and can result in poor adherence.[3,4]

Alternatively, there are now 4 non–vitamin K antagonist oral anticoagulants (NOACs) that have been approved by the US Food and Drug Administration (FDA) for use in AF and VTE: dabigatran, rivaroxaban, apixaban, and edoxaban. By the end of 2015, NOACs accounted for one third of the market share of oral anticoagulant prescriptions, and their use has increased substantially.[5] NOACs do not require laboratory monitoring and have fewer food–drug interactions. However, major concerns about NOACs include poor adherence in the absence of monitoring, cost ($\geq$3 times more expensive than warfarin even when including laboratory monitoring), bleeding risk, and current absence of a specific antidote (except idarucizumab for dabigatran).[6]

Several meta-analyses of the preapproval randomized controlled trials (RCTs) showed similar or superior efficacy and safety of NOACs compared with warfarin.[2,7–23] However, the results from these meta-analyses may lack broad generalizability to patients treated in clinical settings due to the presence of highly selective patients in the included RCTs.[24] Furthermore, several serious flaws in the RCTs comparing NOACs with VKAs raised concerns about superiority claims for the NOACs.[5] For example, the risk reduction in mortality for apixaban is not supported if the results from a clinical site in China are excluded (after an FDA inspection disclosed fabricated data).[25] Furthermore, the effectiveness and safety of NOACs may be influenced by actual adherence patterns, patient baseline risks, and other real-world differences that may not be predicted by RCT results. Given these concerns about RCTs and inconsistent findings from observational studies of NOACs,[26–52] rigorous meta-analyses of both RCTs and observational studies may offer a good basis for evidence-based decision-making in clinical care.

In the present study, we performed a systematic review and separate meta-analyses to examine the efficacy/effectiveness and safety of NOACs compared with VKAs according to condition (AF vs VTE), study design (RCTs vs observational studies), and each NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban).

MATERIALS AND METHODS

Data Source and Searches

The research methods and manuscript were prepared based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines, and it was registered with PROSPERO (CRD42015026897).[53,54] We searched for all articles from the National Library of Medicine PubMed/MEDLINE, Elsevier EMBASE, Thomson Reuters Web of Science, Science Citation Index Expanded, Social Sciences Citation Index and Arts & Humanities Citation Index, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Ebsco Academic Search Complete, Wiley Cochrane Libraries, Elsevier Scopus, clinical trial registries (clinicaltrials.gov, EU Clinical Trials, Nederland's Trial Register, the Australian New Zealand Clinical Trials Registry, and the ISRCTN Registry), and ProQuest's Dissertations and Theses from January 1, 2005, to February 15, 2016. Additional unpublished and gray literature was identified by manually searching bibliographies from the

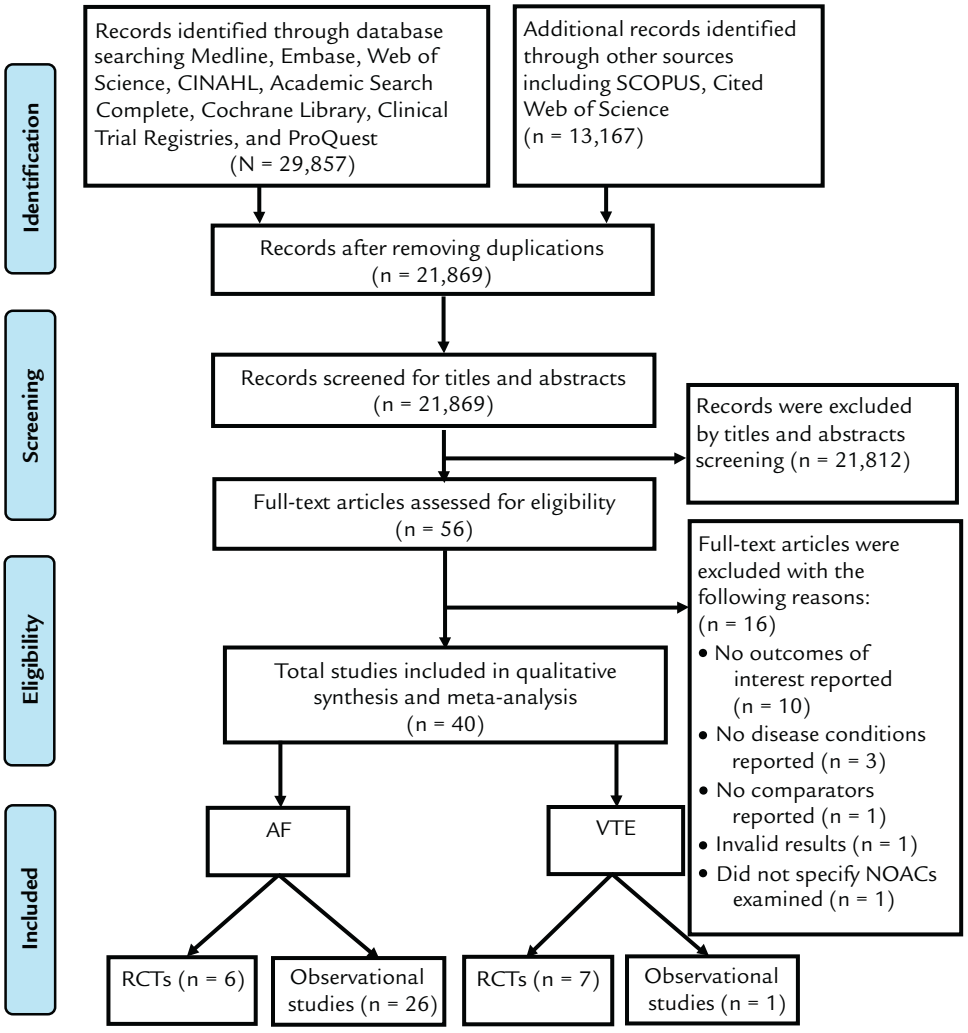

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram: literature search, study identification, selection, and exclusion. AF = atrial fibrillation; CINAHL = Cumulative Index to Nursing and Allied Health Literature; RCT = randomized controlled trial; VTE = venous thromboembolism.

retrieved studies/articles. The search strategy included a combination of terms, including text words and controlled vocabulary (details are given in **Supplemental Table I** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358).

Study Selection

Phase III RCTs and observational studies comparing NOACs (ie, dabigatran, rivaroxaban, apixaban, edoxaban) versus VKAs were identified. Non-English articles, editorials, commentary letters, reviews, case reports/series, economic or modeling studies, extensions of previously completed studies, and studies with invalid results were excluded (**Figure 1**). In addition, studies using NOACs for short-term anticoagulation (ie, cardioversion, catheter ablation, hip/knee arthroplasty) were excluded. Two investigators (A.R.A. and J.R.M.) performed the comprehensive literature search, removed duplicates, and selected articles based on the title and abstract. Two independent reviewers (A.R.A. and L.Z.) screened these selections for inclusion eligibility based on the full text and extracted

study data using a standardized Microsoft Excel form (Microsoft Corporation, Redmond, Washington). Any disagreement during the study process was resolved by consensus and/or consultation with a third reviewer (W.L.).

Data Extraction and Quality Assessment

Information was collected regarding study details (eg, country), participant characteristics (eg, demographic characteristics, $CHADS_2$ [congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke/transient ischemic attack (double risk weight)] score, CHA_2DS_2-VASc [congestive heart failure, hypertension, age $\geq$75 years (double risk weight), diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism (double risk weight), vascular disease, age 65–74 years, (female) sex category] score, HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly] score), intervention/exposure and outcome details, and adjusted confounders. We used the findings from an intention-to-treat analysis for RCTs and adjusted results for observational studies if data were available. Two reviewers (A.R.A. and L.Z.) independently assessed studies for potential bias (low, moderate, high, or unclear) using the Cochrane Collaboration's risk of bias assessment.[55,56]

The primary efficacy/effectiveness outcome was stroke and/or systemic embolism for AF and recurrent VTE and/or fatal PE for VTE. The primary safety outcome was major bleeding, based on the International Society on Thrombosis and Haemostasis (ISTH) definition (ie, fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin level $\geq$20 g/L, or leading to transfusion of $\geq$2 units of whole blood or red blood cells),[57] and any bleeding that required emergency department visits and/or hospitalizations that were commonly used in observational studies.

The secondary efficacy/effectiveness outcomes included stroke, ischemic stroke, hemorrhagic stroke, myocardial infarction (MI), and all-cause mortality for AF, and recurrent DVT, recurrent nonfatal PE, and all-cause mortality for VTE. The secondary safety outcomes included intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeding.

Data Synthesis and Analysis

The NOAC treatment effects compared with VKAs were estimated by performing a meta-analysis for each NOAC and each outcome separately. We synthesized the data according to their measure of relative risk, hazard ratio (HR), or odds ratio (OR). The pooled HRs were selected as the primary measure of treatment effects because they were used most frequently in the included studies and because HRs account for censoring due to loss of follow-up or deaths and are thus the preferred measure of relative risk for observational data.[58] The pooled ORs were used for a small number of studies (n = 3) reporting ORs. For studies with multiple dosage arms of NOACs and only reporting stratification results (eg, dabigatran 150 vs 110 mg), we first estimated the overall treatment effect of NOACs compared with VKAs by using a fixed effect meta-analysis based on previous literature given that the same studies were designed to estimate the same (common) treatment effect of NOACs with different dosage.[59] When the evidence of high variability existed for different regimens in the same study from the fixed effect models (I^2 $\geq$75%, $P_{heterogeneity} < 0.05$ in χ^2 test), a random effect model was used to pool average treatment effects.[59] We then obtained the pooled estimates with 95% CIs comparing NOACs and VKAs by using a random effects meta-analysis with inverse variance weighting in Stata 14 (Stata Corp, College Station, Texas).

An I^2 statistic was used to estimate the percentage of variability across studies that was attributable to heterogeneity. When high heterogeneity (I^2 >75%) was evident, we conducted additional stratification analyses according to dose regimen and/or naive status to NOACs/VKAs, or using different definitions of major bleeding (ISTH vs a broader definition) to examine differences among subgroups.[60] These stratified factors were chosen based on the major differences across the RCTs and observational studies. In addition, methods used in previous meta-analyses were considered.[10,11,13,14,17,18,23] For example, given that different dosing regimens were used across RCTs and observational studies included in our project, and some of the studies did not specify their dosing regimens, the groups used in our stratified analyses were based on 2 previous meta-analyses.[8,16] We assessed publication bias using both asymmetric distributions from the funnel plot and the Duval and

Tweedie nonparametric "trim and fill" model (if the number of studies was ≥10).[60]

RESULTS

The meta-analyses included 40 articles (n = 910,293 patients) (Figure 1). Thirty-two studies were for AF (6 RCTs [n = 73,251][61–66]; 26 observational studies [n = 802,485][26–51]), and 8 were for VTE (7 RCTs [n = 29,789][67–73]; 1 observational study [n = 4768][52]).

Study and Patient Characteristics

As listed in Table I, the follow-up duration ranged widely (3–48 months). One third (n = 12) were multinational studies. Among the total of 910,293 patients, 41.2% were women, and 33.7% were treated with NOACs. Among the 27 observational studies, 9 studies included only NOAC/VKA-naive patients. In 285,947 patients with AF treated with NOACs, dabigatran was used most often (84.4%), followed by rivaroxaban (7.5%), edoxaban (4.9%), and apixaban (3.2%). For AF studies (n = 32), the median age of patients ranged from 70 to 75 years and 61 to 83 years in RCTs and observational studies, respectively. Twenty-two studies reported mean $CHADS_2$ scores (RCTs, 2.1–3.5; observational studies, 0.9–4.2), and 15 observational studies used CHA_2DS_2-VASc scores (mean, 1.9–5.4). The majority of AF observational studies (70%) reported HAS-BLED scores (mean, 1.4–3.8). For VTE studies, mean patient age ranged from 54 to 58 years in the RCTs. Almost 40% of the VTE patients treated with NOACs used rivaroxaban, followed by edoxaban (23.6%) and dabigatran (22.8%).

Risk of Bias Assessment

The overall risk of bias for the 13 RCTs and 27 observational studies was low to moderate (see Supplemental Figures 1A and 1B in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358). However, 3 RCTs were open-label trials and were at high risk of bias due to a lack of blinding of participants and personnel.[61,69,70] The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study using rivaroxaban omitted 93 patients from analysis due to protocol violation and was at high risk of bias for having incomplete outcomes.[62] Mao et al[66] studied rivaroxaban and had a high risk of selection bias due to lack of random sequence generation and allocation concealment. In Supplemental Figure 1B (see the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), 4 observational studies of dabigatran are shown as having a high risk of bias due to a lack of adjustment for any covariates[34,41,43,51] and 3 studies of dabigatran due to a lack of adjustment for disproportionate non-adherence rates between treatment groups.[41,43,50] No publication bias was detected for dabigatran in the outcomes of major bleeding, ICH, GI bleeding, and MI.

Outcomes

Tables II and III summarize the pooled results of various outcomes according to NOAC and study type. For AF (Table II), NOACs seemed superior to VKAs in protection against hemorrhagic stroke, all-cause mortality, and ICH, with the best evidence from dabigatran, apixaban, and edoxaban. For VTE (Table III), NOACs were generally comparable in efficacy/effectiveness and exhibited some safety advantages (except dabigatran), primarily related to major bleeding and ICH. The findings for all meta-analyses are discussed in more detail in the following sections.

Primary Efficacy/Effectiveness Outcomes for AF: Stroke/Systemic Embolism

As shown in Figure 2, dabigatran and VKAs were no different in the risk of stroke/systemic embolism (RCT [n = 1]: HR, 0.77 [95% CI, 0.57–1.03]; I^2 = 75.2%; observational studies [n = 6]: HR, 1.03 [95% CI, 0.83–1.27]; I^2 = 56.7%). Although rivaroxaban had a 20% lower risk of stroke/systemic embolism compared with VKAs in the 3 RCTs (HR, 0.80 [95% CI, 0.67–0.95]), the decreased risk was not significantly different in 3 observational studies (HR, 0.78 [95% CI, 0.59–1.04]). Only single RCTs were available for apixaban and edoxaban. Apixaban had a 21% risk reduction in stroke/systemic embolism compared with warfarin from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (HR, 0.79 [95% CI, 0.66–0.95]), but the decreased risk was not found for edoxaban (HR, 0.99 [95% CI, 0.77–1.28]).

Table I. Characteristics of included studies for non-vitamin K oral anticoagulants (NOACs) in atrial fibrillation and venous thromboembolism (VTE).

Study, Year	Country	Follow-up Duration, mo	NOAC Dosage, mg	% Naive Patients	Patients, n		Mean Age, y		% Female		Mean $CHADS_2$		Mean CHA_2DS_2-VASc		Mean HAS-BLED		Adjusted Covariates
					NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	
Atrial fibrillation																	
Randomized controlled trials																	
ENGAGE AF-TIMI 48, 2013[64]	Multi-nation	34*	E: 30	NS	7034	7036	72*	72*	38.8	37.5	1.1	2.8	NS	NS	NS	NS	–
			E: 60		7035		72*		37.9		1.1		NS		NS		
ARISTOTLE, 2011[63]	Multi-nation	21.6*	A: 5	≥40	9120	9081	70*	70*	35.5	35.0	2.1	2.1	NS	NS	NS	NS	–
Mao et al, 2014[66]	China	NS	R: 15, 20	NS	177	176	75*	75*	39.0	37.5	3.4	3.4	NS	NS	NS	NS	–
J-ROCKET, 2012[65]	Japan	30	R: 15, 20	NS	639	639	71.0	71.2	17.1	21.8	3.3	3.2	NS	NS	NS	NS	–
ROCKET AF, 2011[62]	Multi-nation	23.6*	R: 15, 20	NS	7131	7133	73*	73*	39.7	39.7	3.5	3.5	NS	NS	NS	NS	–
RE-LY, 2009[61]	Multi-nation	24*	D: 110	NS	6015	6022	71.4	71.6	35.7	36.7	2.1	2.1	NS	NS	NS	NS	–
			D: 150		6076		71.5		36.8		2.2		NS		NS		
Observational studies																	
Chan et al, 2016[26]	Taiwan	18	D: 110, 150	72.1	9940	9913	75.0	76.0	42.0	42.0	NS	NS	4.1	4.2	2.6	2.6	1,† 2,† 8,† 9,† 12,† 13,† 15,† 16†
Korenstra et al, 2016[27,‡]	The Netherlands	24	D: 110, 150	NS	383	383	70.6	72.3	46.5	48.8	1.6	1.7	3.0	3.2	1.4	1.4	1,† 2,† 3,† 8,† 9,† 11, 12, 13,† 15,† 16†
Nishtala et al, 2016[28]	New Zealand	17	D: 110, 150	100	4385	4385	77.3	77.4	46.9	48.0	NS	NS	NS	NS	NS	NS	1,† 2,† 4,† 8,† 9,† 10,† 15,† 16†
Tsadok et al, 2016[29]	Canada	24	D: 110, 150	NS	110 mg <75 y, 1277	14,262	NS	NS	41.5	38.5	NS	NS	2.4	2.3	3.7	3.8	1,† 8, 9,† 15, 16
					150 mg <75 y, 5093		NS		35.3		NS		2.0		3.2		
			D: 110, 150		110 mg ≥75 y, 7649	32,930	NS	NS	57.2	56.9	NS	NS	2.4	2.4	2.5	2.7	
					150 mg ≥75 y, 1899		NS		45.6		NS		2.0		2.4		
Abraham et al, 2015[30]	United States	35	D: 75, 150	100	7749	7749	67.2	67.5	35.9	35.7	NS	NS	NS	NS	NS	NS	1,† 4,† 8,† 15†
			R: NS		5166	5166	69.0	69.1	39.0	38.7	NS	NS	NS	NS	NS	NS	
Bouillon et al, 2015[31,‡]	France	10	D: 75/110, 150 R: 10/15, 20	61.5	6705	10,705	75*	75*	47.8	47.9	NS	NS	NS	NS	NS	NS	6, 8, 9, 12, 15, 16
Graham et al, 2015[32]	United States	26	D: 75, 150	NS	67,207	67,207	NS	NS	51.0	52.0	NS	NS	NS	NS	NS	NS	1,† 2,† 4,† 5, 6, 8, 9, 11, 13, 15, 16

(continued)

Table I. (continued).

Study, Year	Country	Follow-up Duration, mo	NOAC Dosage, mg	% Naive Patients	Patients, n		Mean Age, y		% Female		Mean $CHADS_2$		Mean CHA_2DS_2-VASc		Mean HAS-BLED		Adjusted Covariates
					NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	
Hernandez et al, 2015[33]	United States	15	D: 75, 150	100	1302	8102	75.1	75.6	57.9	59.0	NS	NS	NS	NS	NS	NS	1, 2, 4, 8, 9, 11,† 15, 16, 19†
Ho et al, 2015[34]	Hong Kong	36	D: 110, 150	NS	393	1428	74.5	76.2	54.2	52.5	4.1	4.2	NS	NS	2.3	2.3	–
Lauffenburger et al, 2015[35]	United States	27	D: 75, 150	100	21,070	43,865	67.5	71.4	36.6	41.7	2.3	2.9	NS	NS	NS	NS	1,† 2,† 5,† 8,† 9,† 10,† 12,† 14,† 15,† 16,† 19†
Maura et al, 2015[36,‡]	France	3	D: 75/110, 150 R: 10/15, 20	100	8443 4651	16,014 9301	74.0 73.6	73.9 73.4	46.2 45.3	46.4 45.2	NS NS	NS NS	3.2 3.1	3.2 3.1	2.3 2.3	2.3 2.2	1,† 2,† 5,† 8,† 9,† 12,† 13,† 15,† 16,† 18†
Seeger et al, 2015[37]	United States	27	D: 150 D: 150	100	15,529 3660	15,529 3660	68.7 63.4	68.3 63.1	38.2 30.7	37.4 29.6	1.9 1.9	1.9 1.9	3.1 2.8	3.0 2.8	2.2 2.2	2.2 2.2	1,† 2,† 5,† 8,† 9,† 11,† 12, 13, 15,† 16†
Staerk et al, 2015[38]	Denmark	16.3	D: 110, 150	72.3	110 mg ex,1143	4534	79.6	70.3	51.0	42.0	2.3	1.4	3.9	2.6	2.4	1.9	1, 2, 8, 9, 15, 16
					150 mg ex,1748		67.7		32.2		1.5		2.6		1.9		
					110 mg *na*,1168		80.0		54.6		2.0		3.6		2.3		
					150 mg na,1844		65.9		38.4		1.1		2.2		1.8		
Tsadok et al, 2015[39]	Canada	24	D: 110, 150	NS	110 mg men, 4019	22,978	80.3	76.8	0	0	2.4	2.3	2.8	2.7	2.6	2.6	1,† 2,† 8, 9,† 15, 16, 17
					150 mg men, 4327		69.5		0		1.7		1.9		2.1		
			D: 110, 150		110 mg women, 4907	24,214	82.3	80.8	100	100	2.5	2.5	4.0	3.9	2.5	2.6	
					150 mg women, 2665		71.5		100		1.7		3.0		2.1		
Villines et al, 2015[40]	United States	26.7	D: 75, 150	100	12,793	12,793	73.8	74	41.2	41.1	NS	NS	3.9	3.9	3.4	3.4	1, 2, 8, 9, 10,† 11, 12, 13, 15, 16, 17
Yap et al, 2015[41]	Malaysia	10.5* (NOAC) 11.8* (VKA)	D: 110, 150	NS	500	500	65.3	66.8	38.0	39.8	2.7	3.4	NS	NS	1.6	1.7	–
Alonso et al, 2014[42]	United States	48	D: 75,150	NS	101	2290	75.1	76.1	46.5	44.5	3.1	3.1	4.6	4.5	3.2	2.8	1, 2, 8,† 9,† 11, 14
Aslan et al, 2014[43]	Turkey	15*	D: 110 D: 150	100	96 124	219	76* 61*	68*	61.5 48.4	52.5	NS NS	NS	4* 3*	3*	2* 2*	2*	–
Laliberté et al, 2014[44]	United States	14	R NS	NS	3654	14,616	73.3	73.7	51.0	51.5	2.0	2.0	3.4	3.5	1.9	1.9	1,† 2,† 8,† 9,† 10,† 11,† 12,† 13,† 14,† 19†

(continued)

Table I. (continued).

Study, Year	Country	Follow-up Duration, mo	NOAC Dosage, mg	% Naive Patients	Patients, n		Mean Age, y		% Female		Mean $CHADS_2$		Mean CHA_2DS_2-VASc		Mean HAS-BLED		Adjusted Covariates
					NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	
Larsen et al, 2014[45]	Denmark	18	D: 110, 150	62.4	110 mg ex, 2038	8504	82*	73*	54.4	38.4	2.1	1.5	3.9	3.0	2.3	2.0	1, 12, 13, 17
					150 mg ex, 2214		67*		35.2		1.3		2.6		1.7		
					110 mg na, 3045	14,126	82*	74*	55.1	41.3	1.9	1.3	3.7	2.8	2.2	1.9	
					150 mg na, 4018		69*		36.6		0.9		2.1		1.8		
Larsen et al, 2014[46]	Denmark	18	D: 110, 150	53.2	110 mg ex, 547	1918	82*	75*	55.0	38.7	3.5	3.2	5.4	4.7	3.0	2.8	1, 12, 13, 17
					150 mg ex, 412		70*		38.8		2.9		4.3		2.7		
					110 mg na,793	1825	83*	76*	56.2	44.0	3.4	3.2	5.2	4.8	3.2	3.1	
					150 mg na, 646		69*		35.9		2.6		3.9		2.7		
Larsen et al, 2014[45]	Denmark	18	D: 110, 150	19.6	110 mg ex, 1554	49,868	82*	75*	54.6	37.9	2.1	1.6	3.9	3.1	2.2	1.9	1, 8, 12, 13, 17
					150 mg ex, 1825		69*		35.9		1.3		2.6		1.9		
					110 mg na, 2124	8133	82*	72*	55.5	42.2	1.9	1.3	3.7	2.7	2.3	1.9	
					150 mg na, 2694		68*		37.6		1.0		2.2		1.8		
Sarrazin et al, 2014[48]	United States	15	D: 150	0	1394	83,950	69.7	74.4	1.4	1.4	2.1	2.2	NS	NS	2.7	2.6	8, 9, 11, 13
Larsen et al, 2013[49]	Denmark	17	D: 110	100	2739	4940	74.7	72.4	29.5	45.9	1.3	1.3	NS	NS	NS	NS	1,† 2,† 8,† 9,† 15,† 16†
			D: 150		2239	3996	67.4	66.3	65.5	33.3	1.0	1.0	NS	NS	NS	NS	
Sørensen et al, 2013[50]	Denmark	4.3	D: 110	10.9	1612	49,640	79.6	73.5	52.7	39.0	1.8	1.5	3.4	2.9	2.3	2.1	1, 2, 8, 9, 11, 12, 13, 15, 16
			D: 150		1114		67.9		36.7		1.0		2.2		1.9		
Ho et al, 2012[51] VTE	Hong Kong	23	D: 110, 150	NS	122	122	70.0	70.1	44.3	47.5	2.5	2.3	NS	NS	NS	NS	–
Randomized controlled trials																	
Hokusai-VTE, 2013[72]	Multi-nation	12	E: 30, 60	NS	4118	4122	55.7	55.9	42.7	42.8	–	–	–	–	NS	NS	–
AMPLIFY, 2013[71,‡]	Multi-nation	6	A: 5, 10	NS	2601	2704	57.2	56.7	39.7	40.9	–	–	–	–	NS	NS	–
EINSTEIN-PE, 2012[70,‡]	Multi-nation	3, 6, 12	R: 15, 20	100	2419	2413	57.9	57.5	45.9	48.3	–	–	–	–	NS	NS	20

(continued)

Table I. (continued).

Study, Year	Country	Follow-up Duration, mo	NOAC Dosage, mg	% Naive Patients	Patients, n		Mean Age, y		% Female		Mean $CHADS_2$		Mean CHA_2DS_2-VASc		Mean HAS-BLED		Adjusted Covariates
					NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	NOAC	VKA	
EINSTEIN, 2010[69,‡]	Multi-nation	3, 6, 12	R: 15, 20	NS	1731	1718	55.8	56.4	42.6	43.7	–	–	–	–	NS	NS	20
RE-MEDY, 2013[73]	Multi-nation	36	D: 150	NS	1430	1426	55.4	53.9	39.1	38.9	–	–	–	–	NS	NS	–
RE-COVER II, 2014[68]	Multi-nation	6	D: 150	NS	1280	1288	54.7	55.1	39.0	39.8	–	–	–	–	NS	NS	7, 20
RE-COVER, 2009[67]	Multi-nation	6	D: 150	NS	1273	1266	55.0	54.4	42.0	41.1	–	–	–	–	NS	NS	7, 20
Observational studies																	
Ageno et al, 2016[52,‡]	Multi-nation	8.0[*] (NOAC), 9.5[*] (VKA)	R: 15, 20	NS	2619	2149	59[*]	66[*]	45.5	48.1	–	–	–	–	NS	NS	1,[†] 2,[†] 3,[†] 7, 8,[†] 9[†]

A = apixaban; AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ATRIA = anticoagulation and risk factors in atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischemic attack (double risk weight); CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years (double risk weight), diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism (double risk weight), vascular disease, age 65-74 years, (female) sex category); D = dabigatran; E = edoxaban; EINSTEIN PE: Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; ENGAGE AF-TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; ex = vitamin K antagonist experienced; na = vitamin K antagonist naive; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly; J-ROCKET-AF = Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NS = not specified; R = rivaroxaban; RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-LY = Randomized Evaluation of Long-term Anticoagulant Therapy; RE-MEDY: Secondary Prevention of Venous Thrombo Embolism; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Covariates were as follows: (1) age; (2) sex; (3) weight; (4) race/ethnicity; (5) region; (6) social deprivation index (income, education, and unemployment); (7) active cancer; (8) history of cardiovascular diseases (eg, heart failure); (9) other noncardiovascular comorbidities; (10) comorbidity score/index; (11) $CHADS_2$ score; (1_2) CHA_2DS_2-VAS score; (13) HAS-BLED score; (14) ATRIA score; (15) use of cardiovascular medications (eg, antiplatelets); (16) use of other medications (eg, NSAIDs); (17) time to index exposure; (18) alcohol/smoking use; (19) insurance eligibility; and (20) history of pulmonary embolism or deep vein thrombosis.

[*]Medians were reported if mean was not reported.

[†]Included in propensity score matching method; otherwise covariates were adjusted with multivariable models.

[‡]Studies used non-warfarin vitamin K antagonist in the VKA group.

Table II. Summary of the meta-analysis results for atrial fibrillation according to study design: dabigatran, rivaroxaban, apixaban, and edoxaban versus vitamin K antagonists.[*]

	Dabigatran			Rivaroxaban				Apixaban		Edoxaban	
Variable	RCT (n = 1)	No. of Patients	Observational Studies (n = 25)[†]	No. of Patients	RCTs (n = 3)	No. of Patients	Observational Studies (n = 4)[†]	No. of Patients	RCT (n = 1)	No. of Patients	RCT (n = 1)	No. of Patients
Efficacy/effectiveness												
Stroke or systemic embolism	0.77 (0.57–1.03)	18,113	1.03 (0.83–1.27)	145,448	0.80 (0.67–0.95)[‡]	15,798	0.78 (0.59–1.04)	34,079	0.79 (0.66–0.95)[‡]	18,201	0.99 (0.77–1.28)	21,105
Stroke	0.77 (0.54–1.10)	18,113	0.94 (0.83–1.08)	147,373	0.82 (0.68–0.98)[‡]	15,770	NR	NR	0.79 (0.65–0.96)[‡]	18,201	0.44 (0.26–0.69) [‡]	21,105
Ischemic stroke	0.92 (0.64–1.32)	18,113	0.80 (0.68–0.94)[‡]	284,166	0.90 (0.73–1.12)	15,770	0.81 (0.57–1.15)	18,270	0.92 (0.74–1.14)	18,201	1.19 (0.85–1.67)	21,105
Hemorrhagic stroke	0.29 (0.19–0.44)[‡]	18,113	0.48 (0.39–0.61)[‡]	130,143	0.80 (0.60–1.05)	15,770	1.11 (0.13–9.54)	18,270	0.51 (0.35–0.75)[‡]	18,201	0.43 (0.26–0.69)[‡]	21,105
MI	1.36 (1.09–1.72)[‡]	18,113	0.84 (0.70–1.01)	439,463	0.82 (0.64–1.06)[§]	15,798	0.67 (0.35–1.28)	13,040	0.88 (0.66–1.17)	18,201	1.06 (0.84–1.34)	21,105
All-cause mortality	0.90 (0.82–0.98)[‡]	18,113	0.66 (0.51–0.86)[‡]	194,011	0.85 (0.70–1.03)	14,143	NR	NR	0.89 (0.80–0.99)[‡]	18,201	0.89 (0.83–0.96)[‡]	21,105
Safety												
Major bleeding	0.86 (0.75–1.00)	18,113	0.85 (0.72–1.01)	421,801	0.99 (0.97–1.01)	15,867	1.03 (0.81–1.32)	34,071	0.69 (0.60–0.80)[‡]	18,140	0.61 (0.36–1.03)	21,026
GI bleeding	1.29 (0.95–1.75)	18,113	1.11 (0.97–1.28)	424,454	1.32 (0.48–3.59)[§]	15,867	1.10 (0.81–1.49)	28,602	0.89 (0.69–1.14)	18,140	0.91 (0.50–1.65)	21,026
ICH	0.35 (0.26–0.48)[‡]	18,113	0.42 (0.34–0.51)[‡]	347,618	0.85 (0.58–1.23)	14,589	1.17 (0.66–2.06)	18,270	0.42 (0.30–0.58)[‡]	18,140	0.38 (0.24, 0.59)[‡]	21,026

GI = gastrointestinal; ICH = intracranial hemorrhage; MI = myocardial infarction; NR = not reported; RCT = *randomized controlled trial*.

[*]Pooled hazard ratios are reported as the primary outcomes. Please note that direct comparisons of the non–vitamin K antagonist oral anticoagulant agents are not possible until head-to-head RCTs are available.

[†]In total, there were 26 observational studies for atrial fibrillation (22 were for dabigatran, 3 were for dabigatran and rivaroxaban, and 1 study was for rivaroxaban).

[‡]There was a significant difference (based on 95% CIs) between non-vitamin K antagonist oral anticoagulants and vitamin K antagonists in terms of relevant outcomes.

[§]Pooled odds ratio was reported.

Table III. Summary of the meta-analysis results for venous thromboembolism (VTE) according to study design: dabigatran, rivaroxaban, apixaban, and edoxaban versus vitamin K antagonists.*

	Dabigatran		Rivaroxaban			Apixaban		Edoxaban	
Efficacy/Effectiveness	RCT (n = 3)	No. of Patients	RCTs (n = 2)	No. of Patients	Observational Study (n = 1)	No. of Patients	RCT (n = 1)	No. of Patients	RCT (n = 1)	No. of Patients
Recurrent VTE or fatal PE	1.17 (0.86, 1.61)	7963	0.88 (0.54–1.43)	8281	0.91 (0.54–1.54)	4515	0.84 (0.60–1.18)	5244	0.89 (0.70–1.13)	8240
Recurrent DVT	1.20 (0.82–1.76)	7963	0.72 (0.35–1.50)	8281	0.36 (0.19–0.69)†	4768	0.61 (0.35–1.06)	5244	0.91 (0.64–1.29)	8240
Nonfatal PE	1.23 (0.53–2.85)	7963	1.13 (0.73–1.75)	8281	0.82 (0.42–1.61)	4768	1.18 (0.68–2.05)	5244	0.83 (0.57–1.21)	8240
All-cause mortality	0.96 (0.68–1.35)	7963	0.88 (0.53–1.46)	8246	0.26 (0.14–0.49)†	4768	0.79 (0.53–1.18)	5368	1.05 (0.82–1.33)†	8240
Safety										
Major bleeding	0.68 (0.47–0.97)†	7963	0.54 (0.36–0.79)†	8246	0.77 (0.40–1.49)	4515	0.31 (0.17–0.56)†	5365	0.84 (0.59–1.20)	8240
GI bleeding	1.38 (1.02–1.87)†	7963	NR	NR	0.14 (0.04–0.47)†	4768	0.39 (0.16–0.94)†	5365	NR	NR
ICH	0.35 (0.12–1.04)‡	7963	0.25 (0.07–0.89)†	4768	NR	NR	0.50 (0.13–2.01)	5365	0.28 (0.10–0.75)†	8240

DVT = deep vein thrombosis; GI = gastrointestinal; ICH = intracranial hemorrhage; NR = not reported; PE = pulmonary embolism; RCT = *randomized controlled trial.*
*We reported pooled hazard ratios as our primary outcomes. Please note that direct comparisons of the non-vitamin K antagonist oral anticoagulant agents are not possible until head-to-head RCTs are available.
†There was a significant difference between non-vitamin K antagonist oral anticoagulants and vitamin K antagonists in terms of relevant outcomes.
‡Pooled odds ratio was reported.

Primary Efficacy/Effectiveness Outcomes for VTE: Recurrent VTE/Fatal PE

As seen in Figure 3, NOACs and VKAs had no difference in risk reduction of recurrent VTE/fatal PE in RCTs (dabigatran [n = 3]: HR, 1.17 [95% CI, 0.86–1.61]; rivaroxaban [n = 2]: HR, 0.88 [95% CI, 0.54–1.43]; apixaban [n = 1]: HR, 0.84 [95% CI, 0.60–1.18; edoxaban [n = 1]: HR, 0.89 [95% CI, 0.70–1.13]) and in an observational study of rivaroxaban (HR, 0.91 [95% CI, 0.54–1.54]).[52]

Primary Safety Outcome for both AF and VTE: Major Bleeding

For AF, Figure 4 illustrates substantial heterogeneity in the results of major bleeding among dabigatran observational studies, although there was no difference in the pooled risk of major bleeding between dabigatran and VKAs (1 RCT: HR, 0.86 [95% CI, 0.75–1.00]; I^2 = 52.2%; 15 observational studies: HR, 0.88 [95% CI, 0.75–1.03]; I^2 = 92.2%). Figure 5 also shows no difference in major bleeding risk between rivaroxaban compared with VKAs (3 RCTs: HR, 0.99 [95% CI, 0.97–1.01]; I^2 = 0%; 3 observational studies: HR, 1.03 [95% CI, 0.81–1.32]; I^2 = 0%). Apixaban had a 31% risk reduction in major bleeding (HR, 0.69 [95% CI, 0.60–0.80) compared with VKAs in the ARISTOTLE RCT. The pooled HR of 30- and 60-mg edoxaban from a single RCT showed no difference in major bleeding risk compared with VKA (HR, 0.61 [95% CI, 0.36–1.03]; I^2 = 96.6%).

For VTE (Figure 6), RCTs showed a 32% to 69% decreased risk in major bleeding for dabigatran (3 RCTs: HR, 0.68 [95% CI, 0.47–0.97]; I^2 = 0%), rivaroxaban (2 RCTs: HR, 0.54 [95% CI, 0.36–0.79]; I^2 = 0%), and apixaban (1 RCT: HR, 0.31 [95% CI, 0.17–0.56]) compared with VKAs. The decreased effect was not seen in an observational study for rivaroxaban (HR, 0.77 [95% CI, 0.40–1.49]) or in an RCT for edoxaban (HR, 0.84 [95% CI, 0.59–1.20]).

Secondary Efficacy/Effectiveness Outcomes

Stroke, Ischemic Stroke, Hemorrhagic Stroke, MI and All-Cause Mortality in AF Studies

As presented in Supplemental Figure 2 (see the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), there was no difference in stroke risk reduction between dabigatran and VKAs (1 RCT: HR, 0.77 [95% CI, 0.54–1.10]; I^2 = 80.6%; 6

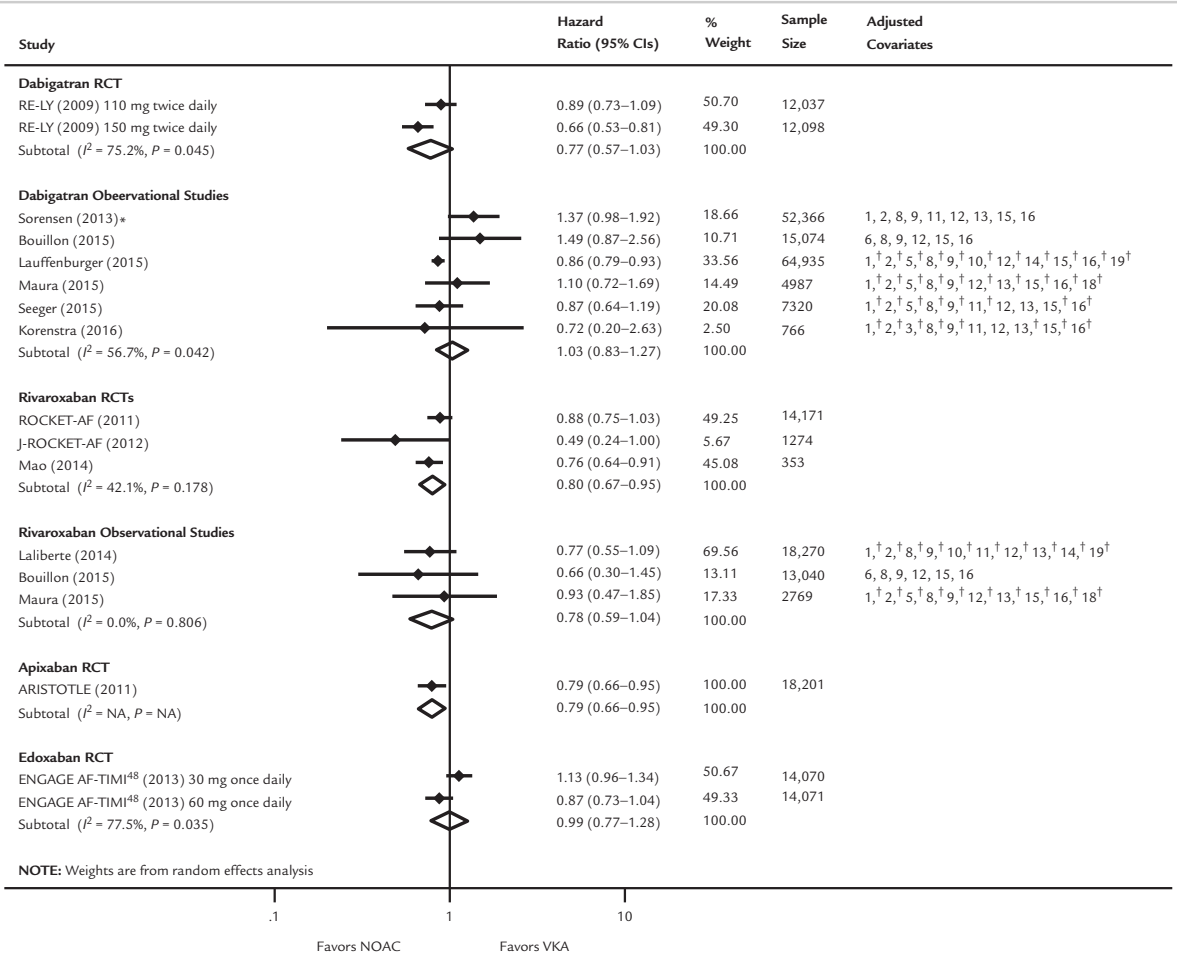

Figure 2. Forest plot for the risk of stroke or systemic embolism in patients with atrial fibrillation: non-vitamin K antagonist oral anticoagulants (NOACs) versus vitamin K antagonists (VKAs). *The study reported stratified relative risk, and the overall relative risk was estimated from fixed effect meta-analysis. †Included in the propensity score matching method; otherwise, the covariates were adjusted in the multivariable models. Covariates were as follows: (1) age; (2) sex; (3) weight; (4) race/ethnicity; (5) region; (6) social deprivation index (income, education and unemployment); (7) active cancer; (8) history of cardiovascular diseases (eg, heart failure); (9) other comorbidities (noncardiovascular diseases); (10) comorbidity score/index; (11) $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke/transient ischemic attack [double risk weight]) score; (12) CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years [double risk weight], diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism [double risk weight], vascular disease, age 65–74 years, [female] sex category) score; (13) HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [aged >65 years], drugs/alcohol concomitantly) score; (14) ATRIA (anticoagulation and risk factors in atrial fibrillation) score; (15) use of cardiovascular medications (eg, antiplatelets); (16) use of other medications (eg, NSAIDs); (17) time to index exposure; (18) alcohol/smoking use; (19) insurance eligibility; and (20) history of pulmonary embolism or deep vein thrombosis. ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; NA = not applicable; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-term Anticoagulant Therapy; RE-LY = Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) With Dabigatran Etexilate; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

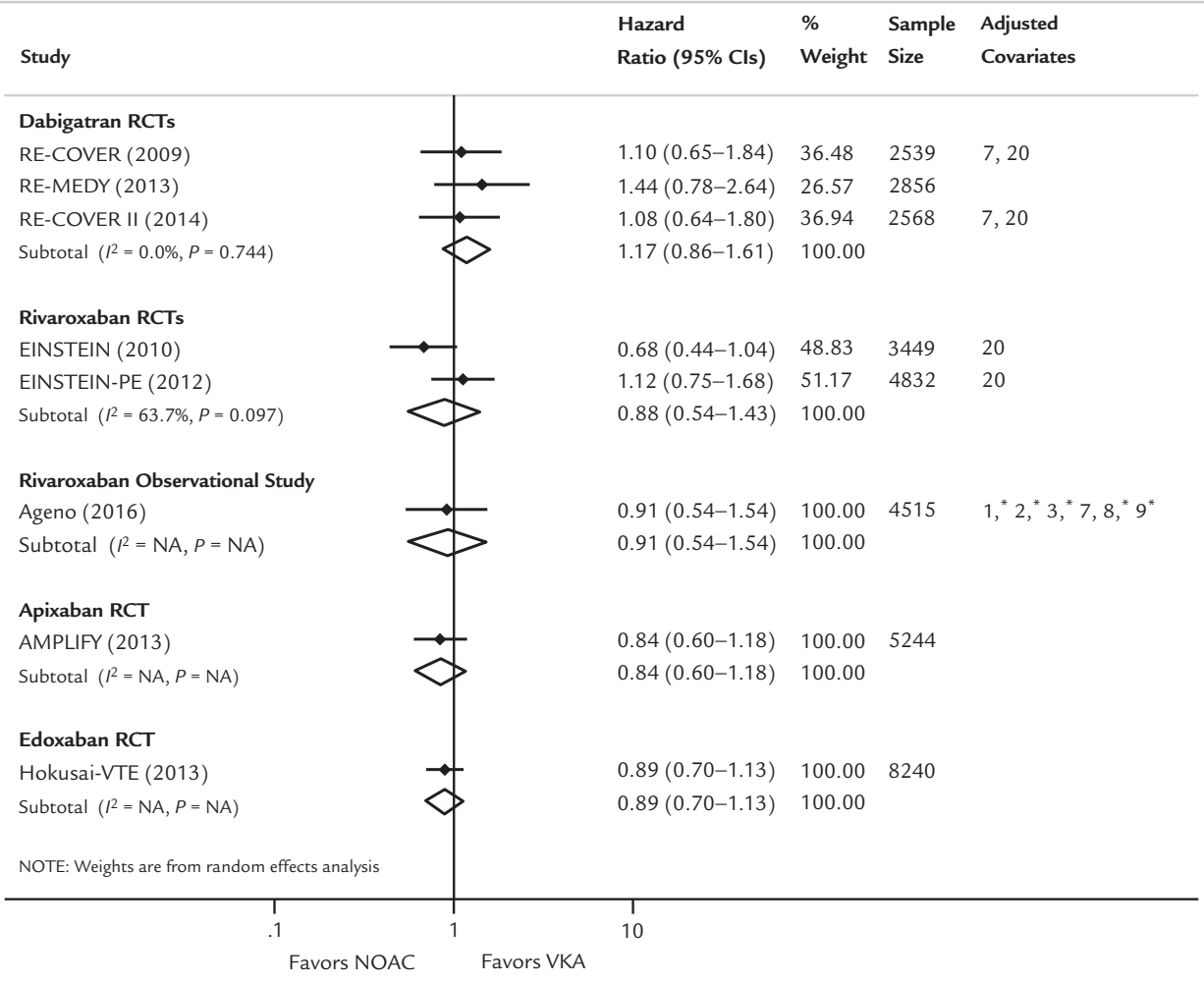

Figure 3. Forest Plot for the risk of recurrent venous thromboembolism (VTE) or fatal pulmonary embolism (PE) in patients with VTE: non–vitamin K antagonist oral anticoagulants (NOACs) versus vitamin K antagonist (VKAs). *Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates were as follows: (1) age; (2) sex; (3) weight; (4) race/ethnicity; (5) region; (6) social deprivation index (income, education, and unemployment); (7) active cancer; (8) history of cardiovascular diseases (eg, heart failure); (9) other comorbidities (noncardiovascular diseases); (10) comorbidity score/index; (11) $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke/transient ischemic attack [double risk weight]) score; (12) CHA_2DS_2-VASc (congestive heart failure, hypertension, age 75 years [double risk weight], diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism [double risk weight], vascular disease, age 65–74 years, [female] sex category) score; (13) HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly ($>$65 years), drugs/alcohol concomitantly) score; (14) ATRIA (anticoagulation and risk factors in atrial fibrillation) score; (15) use of cardiovascular medications (eg, antiplatelets); (16) use of other medications (eg, NSAIDs); (17) time to index exposure; (18) alcohol/smoking use; (19) insurance eligibility; and (20) history of pulmonary embolism or deep vein thrombosis. AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; EINSTEIN = Oral Rivaroxaban for Symptomatic Venous Thromboembolism; EINSTEIN-PE = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; NA = not applicable; RCT = randomized controlled trial; RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-MEDY = Secondary Prevention of Venous Thrombo Embolism.

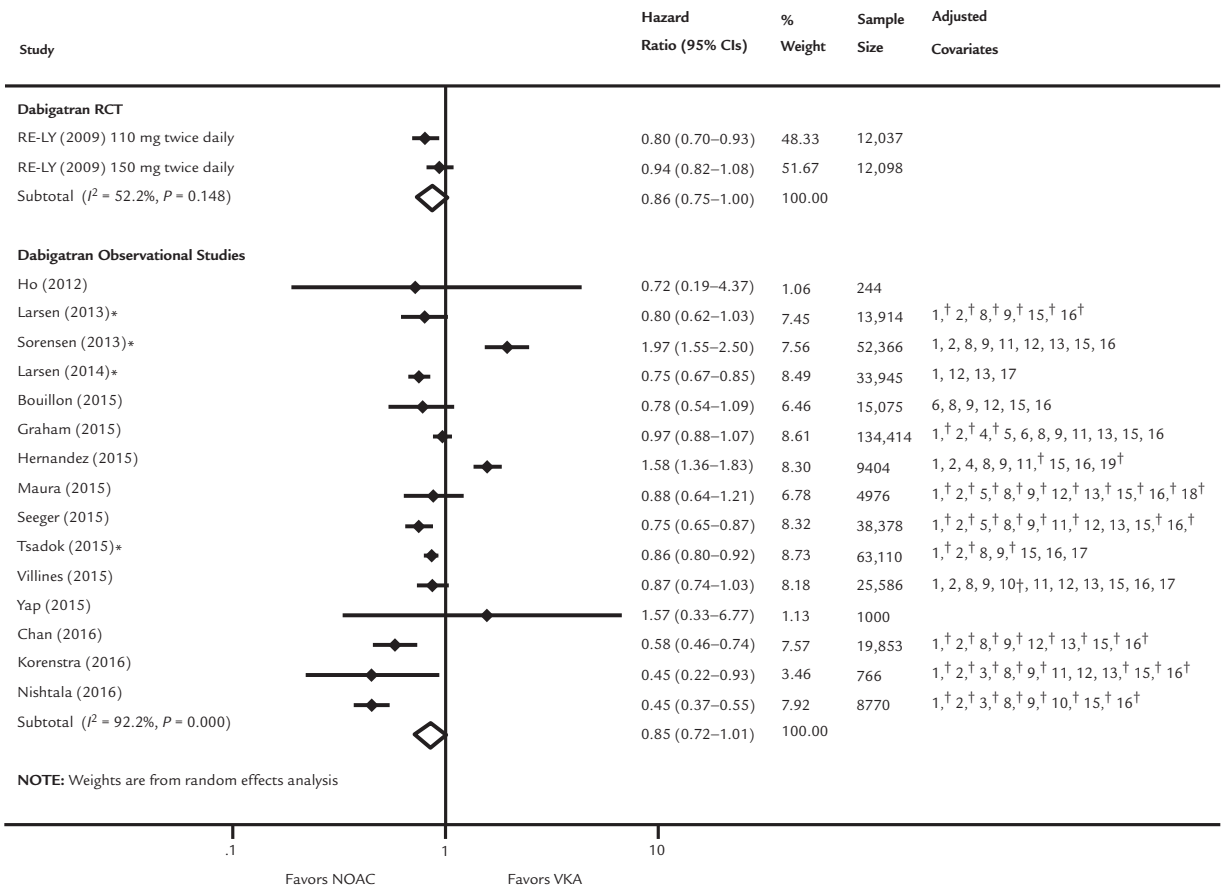

Figure 4. Forest plot for the risk of major bleeding in patients with atrial fibrillation: dabigatran versus vitamin K antagonists (VKAs). *The study reported stratified relative risk, and the overall relative risk was estimated from fixed effect meta-analysis. †Included in the propensity score matching method; otherwise, the covariates were adjusted in the multivariable models. Covariates were as follows: (1) age; (2) sex; (3) weight; (4) race/ethnicity; (5) region; (6) social deprivation index (income, education and unemployment); (7) active cancer; (8) history of cardiovascular diseases (eg, heart failure); (9) other comorbidities (non-cardiovascular diseases); (10) comorbidity score/index; (11) $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke/transient ischemic attack [double risk weight]) score; (12) CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years [double risk weight], diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism [double risk weight], vascular disease, age 65–74 years, [female] sex category) score; (13) HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly ($>$65 years), drugs/alcohol concomitantly) score; (14) ATRIA (anticoagulation and risk factors in atrial fibrillation) score; (15) use of cardiovascular medications (eg, antiplatelets); (16) use of other medications (eg, NSAIDs); (17) time to index exposure; (18) alcohol/smoking use; (19) insurance eligibility; and (20) history of pulmonary embolism or deep vein thrombosis. NOAC = non–vitamin K antagonist oral anticoagulant; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-term Anticoagulant Therapy.

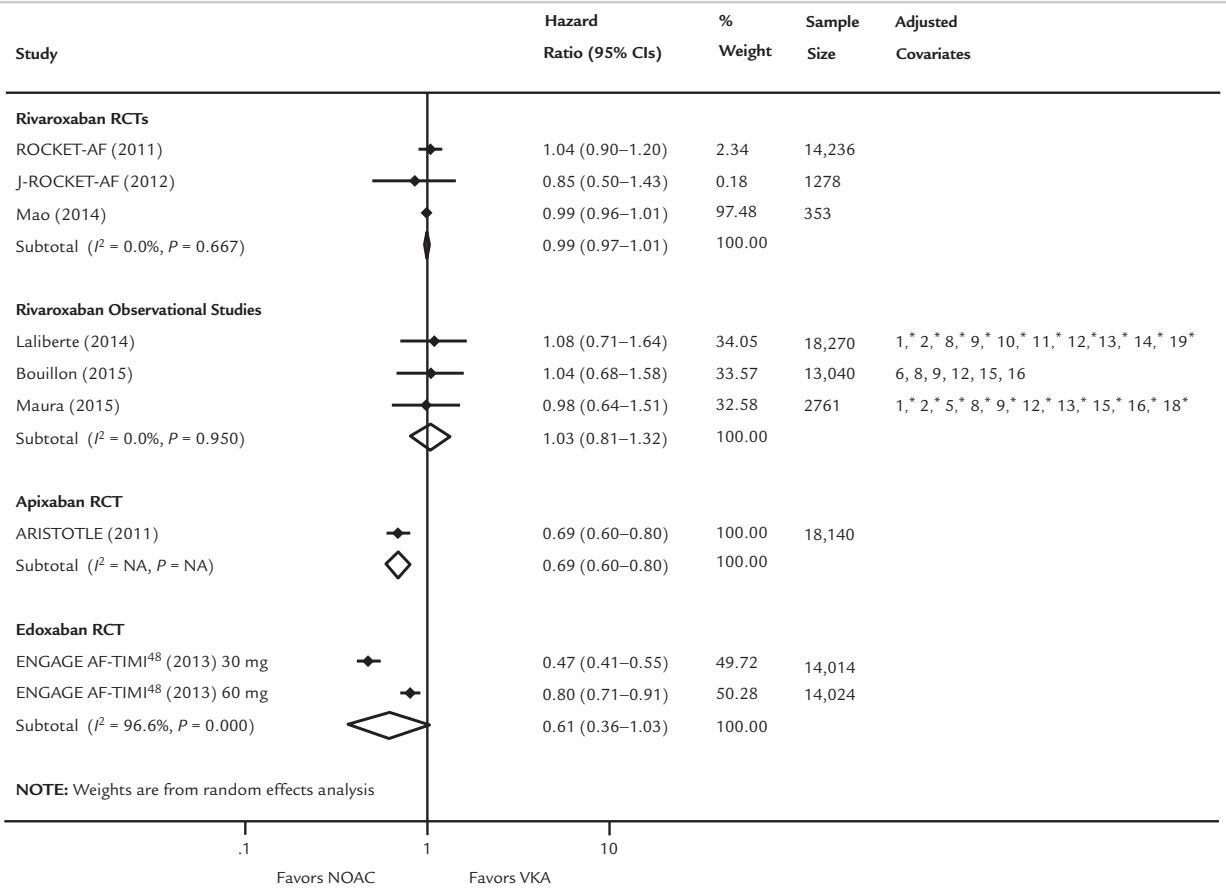

Figure 5. Forest plot for the risk of major bleeding in patients with atrial fibrillation: rivaroxaban, apixaban, or edoxaban versus vitamin K antagonists (VKAs). *Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates were as follows: (1) age; (2) sex; (3) weight; (4) race/ethnicity; (5) region; (6) social deprivation index (income, education, and unemployment); (7) active cancer; (8) history of cardiovascular diseases (eg, heart failure); (9) other comorbidities (noncardiovascular diseases); (10) comorbidity score/index; (11) $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke/transient ischemic attack [double risk weight]) score; (12) CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years [double risk weight], diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism [double risk weight], vascular disease, age 65–74 years, [female] sex category) score; (13) HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly ($>$65 years), drugs/alcohol concomitantly) score; (14) ATRIA (anticoagulation and risk factors in atrial fibrillation) score; (15) use of cardiovascular medications (eg, antiplatelets); (16) use of other medications (eg, NSAIDs); (17) time to index exposure; (18) alcohol/smoking use; (19) insurance eligibility; and (20) history of pulmonary embolism or deep vein thrombosis. ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; J-ROCKET-AF = Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NA = not applicable; NOAC = non–vitamin K antagonist oral anticoagulant; RCT = randomized control trial; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

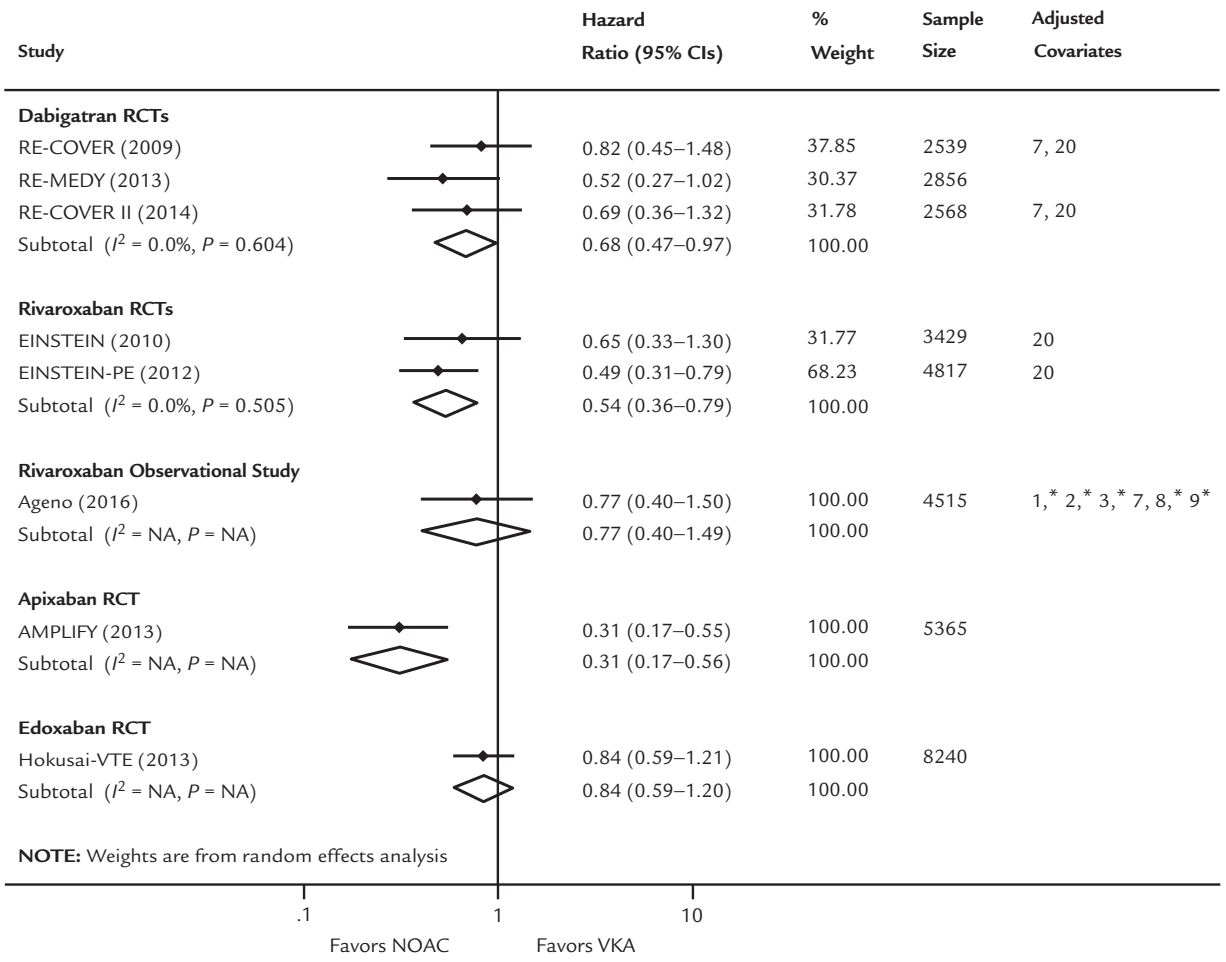

Figure 6. Forest plot for the risk of major bleeding in patients with venous thromboembolism (VTE): non–vitamin K antagonist oral anticoagulants (NOACs) versus vitamin K antagonist (VKAs). *Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates were as follows: (1) age; (2) sex; (3) weight; (4) race/ethnicity; (5) region; (6) social deprivation index (income, education, and unemployment); (7) active cancer; (8) history of cardiovascular diseases (eg, heart failure); (9) other comorbidities (noncardiovascular diseases); (10) comorbidity score/index; (11) $CHADS_2$ (congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke/transient ischemic attack [double risk weight]) score; (12) CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$75 years [double risk weight], diabetes mellitus, previous stroke/transient ischemic attack/arterial embolism [double risk weight], vascular disease, age 65–74 years, [female] sex category) score; (13) HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly ($>$65 years), drugs/alcohol concomitantly) score; (14) ATRIA (anticoagulation and risk factors in atrial fibrillation)score; (15) use of cardiovascular medications (eg, antiplatelets); (16) use of other medications (eg, NSAIDs); (17) time to index exposure; (18) alcohol/smoking use; (19) insurance eligibility; and (20) history of pulmonary embolism or deep vein thrombosis. AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; EINSTEIN = Oral Rivaroxaban for Symptomatic Venous Thromboembolism; EINSTEIN-PE = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; RCT = randomized controlled trial; RE-COVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-MEDY: Secondary Prevention of Venous ThromboEmbolism.

observational studies: HR, 0.94 [95% CI, 0.83–1.08]). Rivaroxaban, apixaban, and edoxaban had an 18% (3 RCTs: HR, 0.82 [95% CI, 0.68–0.98]), 21% (1 RCT: HR, 0.79 [95% CI, 0.65–0.96]), and 57% (1 RCT: HR, 0.43 [95% CI, 0.26–0.69]) risk reduction in stroke, respectively, compared with VKAs in RCTs. For ischemic stroke (see **Supplemental Figures 3A** and **3B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), dabigatran had a 20% risk reduction in 6 observational studies (HR, 0.80 [95% CI, 0.68–0.94]; $I^2 = 64.9\%$), but RCTs of dabigatran and other NOACs found no risk reduction. For hemorrhagic stroke (see **Supplemental Figure 4** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), a 52% to 71% decreased risk was seen with dabigatran (1 RCT: HR, 0.29 [95% CI, 0.19–0.44]; 5 observational studies: HR, 0.48 [95% CI, 0.39–0.61]), apixaban (1 RCT: HR, 0.51 [95% CI, 0.35–0.75]), and edoxaban (1 RCT: HR, 0.43 [95% CI, 0.26–0.69]) compared with VKAs, but such a decreased risk was not seen with rivaroxaban (RCT [n = 1]: HR, 0.80 [95% CI, 0.60–1.05]; $I^2 = 30.6\%$; observational study [n = 1]: HR, 1.11 [95% CI, 0.13–9.54]).

For MI (see **Supplemental Figures 5A** and **5B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), dabigatran had a 36% increased risk (1 RCT: HR, 1.36 [95% CI, 1.09–1.72]) compared with VKAs in 1 RCT. This risk increase was not seen in 9 observational studies (HR, 0.84 [95% CI, 0.70–1.01]; $I^2 = 80.1\%$) or studies of other NOACs.

For all-cause mortality (see **Supplemental Figures 6A** and **6B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), there was a 10% to 34% decreased risk associated with the use of dabigatran (1 RCT: HR, 0.90 [95% CI, 0.82–0.98]; $I^2 = 0\%$; 5 observational studies: HR, 0.66 [95% CI, 0.51–0.86]; $I^2 = 90.5\%$), apixaban (1 RCT: HR, 0.89 [95% CI, 0.80–0.99]), and edoxaban (1 RCT: HR, 0.89 [95% CI, 0.83–0.96]) compared with VKAs. However, no such decrease in all-cause mortality was found in 3 observational studies of dabigatran reporting ORs (OR, 0.53 [95% CI, 0.26–1.08]; $I^2 = 81.6\%$) or in a rivaroxaban RCT (HR, 0.85 [95% CI, 0.70–1.03).

Recurrent DVT, Nonfatal PE, and All-Cause Mortality in VTE Studies

One observational study showed that rivaroxaban had a 64% decreased risk of recurrent DVTs (OR, 0.36 [95% CI, 0.19–0.69]) and a 74% decreased risk of all-cause mortality (OR, 0.26 [95% CI, 0.14–0.49]) compared with VKAs, but the results from the RCTs did not show a difference between NOACs and VKAs for recurrent DVT, nonfatal PE, or all-cause mortality (see **Supplemental Figures 7–9B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358).

Secondary Safety Outcomes

GI Bleeding and ICH in AF Studies

Supplemental Figures 10A and **10B** (in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358) show no overall difference between NOACs and VKAs in GI bleeding. For ICH (see **Supplemental Figures 11A** and **11B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), there was a 58% to 65% decreased risk with dabigatran (1 RCT: HR, 0.35 [95% CI, 0.26–0.48]; 10 observational studies: HR, 0.42 [95% CI, 0.34–0.51]), apixaban (1 RCT: HR, 0.42 [95% CI, 0.30–0.58]), and edoxaban (1 RCT: HR, 0.38 [95% CI, 0.24–0.59]). This decrease in risk was not seen in studies of rivaroxaban or dabigatran reporting ORs.

GI Bleeding and ICH in VTE Studies

For GI bleeding (see **Supplemental Figure 12** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), studies using dabigatran had a 38% increase (3 RCTs: OR, 1.38 [95% CI, 1.02–1.87]) compared with VKAs. Conversely, apixaban (1 RCT: OR, 0.39 [95% CI, 0.16–0.94]) and rivaroxaban (1 observational study: OR, 0.14 [95% CI, 0.04–0.47]) had a decreased risk. As seen in **Supplemental Figure 13** (in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), rivaroxaban and edoxaban each had a single RCT that showed a decreased risk of ICH (rivaroxaban: OR, 0.25 [95% CI, 0.07–0.89]; edoxaban: OR, 0.28 [95% CI, 0.10–0.75]), but such risk reduction was not significant for dabigatran (3 RCTs: OR, 0.35 [95% CI, 0.12–1.04]) or apixaban (1 RCT: OR, 0.50 [95% CI, 0.13–2.01]).

Heterogeneity Assessment

There was high heterogeneity ($I^2 > 75\%$) among observational AF studies of dabigatran examining major bleeding (**Figure 4**), MI (see **Supplemental Figure 5A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), all-cause mortality (see **Supplemental Figures 6A** and **6B** in the online

version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), and GI bleeding (see **Supplemental Figure 10A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358). Most of the additional stratification analyses according to VKA/NOAC naive status, and/or dabigatran dose, and outcome definition of major bleeding did not significantly improve heterogeneity (see **Supplemental Figures 14–25** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358). Specifically, for major bleeding (see **Supplemental Figure 16** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358), stratifications according to dose and naive status showed a decreased risk in patients who took dabigatran 150 mg and had previous exposure to VKAs/NOACs (HR, 0.62 [95% CI, 0.48–0.79]; $I^2 = 0\%$). The heterogeneity reduced significantly in the studies using the specific ISTH definition of major bleeding (ISTH definition: HR, 0.79 [95% CI, 0.70–0.89]; $I^2 = 63.3\%$) but not in the studies using a broader definition (HR, 1.04 [95% CI, 0.63–1.74]; $I^2 = 97.9\%$) (see **Supplemental Figure 17** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358). For MI risk, dabigatran 75 or 150 mg was associated with a decreased risk in naive patients (HR, 0.88 [95% CI, 0.80–0.96]; $I^2 = 0\%$) (see **Supplemental Figure 20** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358). Dabigatran 150 mg was associated with a decreased risk of all-cause mortality (HR, 0.52 [95% CI, 0.39–0.70]; $I^2 = 0\%$) (see **Supplemental Figure 22** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358) compared with VKAs. For GI bleeding, dabigatran was associated with an increased risk among patients with previous exposure to VKAs (HR, 1.34 [95% CI, 1.17–1.53]) (see **Supplemental Figure 23** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.05.358).

DISCUSSION

The present systematic review and meta-analyses yielded 3 key findings regarding the use of NOACs compared with VKAs. First, the overall findings from the RCTs and observational studies were consistent in that the efficacy/effectiveness and safety of NOACs for AF and VTE are comparable or superior to VKAs, with a few notable inconsistencies in the risk of ischemic stroke and MI for dabigatran, stroke/systemic embolism for rivaroxaban in AF, and major bleeding for rivaroxaban in VTE. Second, the risk association and magnitude varied widely among RCTs and observational studies across different NOACs as well as the measured effectiveness and safety outcomes. For example, a 10% to 71% decreased risk of major bleeding, MI, hemorrhagic stroke, all-cause mortality, and ICH was associated with dabigatran, apixaban, and edoxaban used for AF but not with rivaroxaban. Third, the pooled results showed high heterogeneity among the observational studies. Additional stratification analyses found that the beneficial effects in patients with AF were mainly found in patients taking dabigatran 150 mg who had no prior exposure to NOACs/VKAs (ie, naive patients).

To our knowledge, this study is the first to assess evidence in separate meta-analyses of RCTs (n = 13) and observational studies (n = 27) for NOACs compared with VKAs in AF and VTE. Our findings were generally consistent with the previous meta-analyses of RCTs and 2 recent meta-analyses, including a small number (n = 8) of observational studies of dabigatran.[2,7–14,16–23] Follow-up pragmatic RCTs or well-designed observational studies provide valuable information on comparative effectiveness and safety of newly marketed drugs.[74] However, because such studies take extensive time and effort to conduct, rigorous meta-analyses of existing RCTs and observational data provide a good basis for evidence-based decision-making when results from observational studies are mixed. Furthermore, current evidence suggests that a rigorous meta-analysis of observational studies provides similar findings compared with the results from the RCTs regardless of type of study design, heterogeneity in population characteristics, or use of propensity score adjustment.[75,76] The observational studies in our meta-analyses had a wider range in age, $CHADS_2$ score, and follow-up duration than the RCTs, providing evidence about these new agents used in a broader patient population than RCTs. Nonetheless, our overall results showing that the NOACs are comparable or superior to VKAs in efficacy/effectiveness and safety indicate that the inclusion of patients with higher baseline risk (eg, older adults) in observational studies did not lead to greater safety risks. The NOACs may be a particularly good option for patients who are ineligible for or intolerable to warfarin or in whom international normalized ratio monitoring cannot be performed adequately.

We found that the magnitude of risk and benefit varied across NOACs on outcomes evaluated,

especially for dabigatran and rivaroxaban. For dabigatran in AF, the risk of MI and GI bleeding increased when using the 150-mg dose compared with the 110-mg dose or other NOACs. In VTE, dabigatran also had a 38% increased risk of GI bleeding compared with VKAs, but other NOACs had a decreased risk. A possible explanation of these variations may be the pharmacologic properties of dabigatran. Dabigatran has a single renal route of elimination and a 5-fold variability in patients receiving the same dose (18% having subtherapeutic blood levels; 40% having higher blood levels than needed), which may increase the bleeding risk, especially when using a higher dose.[77,78] Similarly, it is notable that the results from the observational studies using rivaroxaban for AF did not find a decreased risk of stroke/systemic embolism compared with VKAs as seen in the RCTs. Moreover, unlike other NOACs, rivaroxaban used in AF did not have a decreased risk in hemorrhagic stroke, all-cause mortality, and ICH risk, compared with VKAs. In VTE, an observational study of rivaroxaban did not show a decreased risk in major bleeding compared with VKAs as seen in the RCTs and with other NOACs.

The 2015 US FDA MedWatch reports mirror the effectiveness and safety concerns of rivaroxaban, in which rivaroxaban accounted for the largest number of domestic serious adverse events among all the reported agents (n = 10,674; 10.9% embolic-thrombotic events, 80.9% hemorrhage events).[5] There are also concerns about rivaroxaban due to its 5- to 9-hour half-life, as the current once-daily regimen may result in insufficient concentrations at the end of a 24-hour day and be less effective due to its rapid elimination. Due to these pharmacologic properties, dabigatran and rivaroxaban may require more individualized dosing.

Although limited by a single RCT each, apixaban and edoxaban use in patients with AF showed superior efficacy and safety (eg, stroke/systemic embolism, hemorrhagic stroke, all-cause mortality, major bleeding, ICH). However, apixaban and edoxaban currently have no postmarketing observational studies due to their limited time on the market (apixaban since December 2012; edoxaban since January 2015). Postmarketing surveillance and research are needed to refute or solidify the evidence for apixaban and edoxaban. Until head-to-head pragmatic RCTs or well-designed observational studies comparing NOACs against one another are conducted, any conclusions on the comparative effectiveness and safety of the NOACs need to be drawn cautiously.[73]

Substantial heterogeneity existed among observational AF studies of dabigatran examining major bleeding, MI, all-cause mortality, and GI bleeding. Possible explanations for inconsistencies and high heterogeneity include patient samples from diverse countries and data sources, different follow-up durations, mixed study cohorts of NOAC/VKA-naive and experienced patients, varying operational definitions of the outcomes, different risk assessment tools used, adjusting for different covariates, and unmeasured confounders.[10] For example, although the definition of major bleeding varied across the observational studies, restriction to the ISTH definition significantly decreased the heterogeneity. In addition, the $CHADS_2$ risk assessment tool was used in RCTs (n = 6), whereas CHA_2DS_2-VASc was adopted in most of the observational studies (n = 15) for predicting the risk of stroke in patients with AF, which is the currently recommended population-based risk stratification and thus more closely mirrors clinical practice. Despite high heterogeneity, evidence from our rigorous meta-analysis of observational studies provides similar findings compared with the results from the RCTs. Given the heterogeneity in observational studies, to treat specific patient populations, clinicians would be best served by using the specific observational study that best matches their patient population and outcome of interest.

Our study has several additional limitations. First, different studies were adjusted for different confounding factors, which made it challenging to compare the results across the studies. However, findings from the sensitivity analysis excluding a small number of observational studies (n = 4) without any adjustment for covariates drew results similar to the overall findings.[34,41,43,51] Second, the results for apixaban and edoxaban relied on a single RCT each with no observational data. Third, we did not have resources to review non-English publications. However, we included articles from an extensive search of broad databases and are confident that this study covered the majority of high-quality and well-designed studies. Finally, as expected, the current study results may not be generalizable to the population that was not evaluated in the included studies.

CONCLUSIONS

The overall findings from the RCTs and observational studies were consistent in that efficacy/effectiveness and safety of NOACs for AF and VTE are comparable or superior to VKAs. Although no observational studies were currently available for apixaban and edoxaban, a few notable inconsistencies exist in the risk of ischemic stroke and MI for dabigatran and stroke/systemic embolism for rivaroxaban in AF, and major bleeding for rivaroxaban in VTE. More evidence from observational studies is needed for apixaban and edoxaban on their effectiveness and safety in the real-world settings.

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CONFLICTS OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.clinthera.2017.05.358.

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SUPPLEMENTARY MATERIAL

Figure S1-S25.

Table SI.

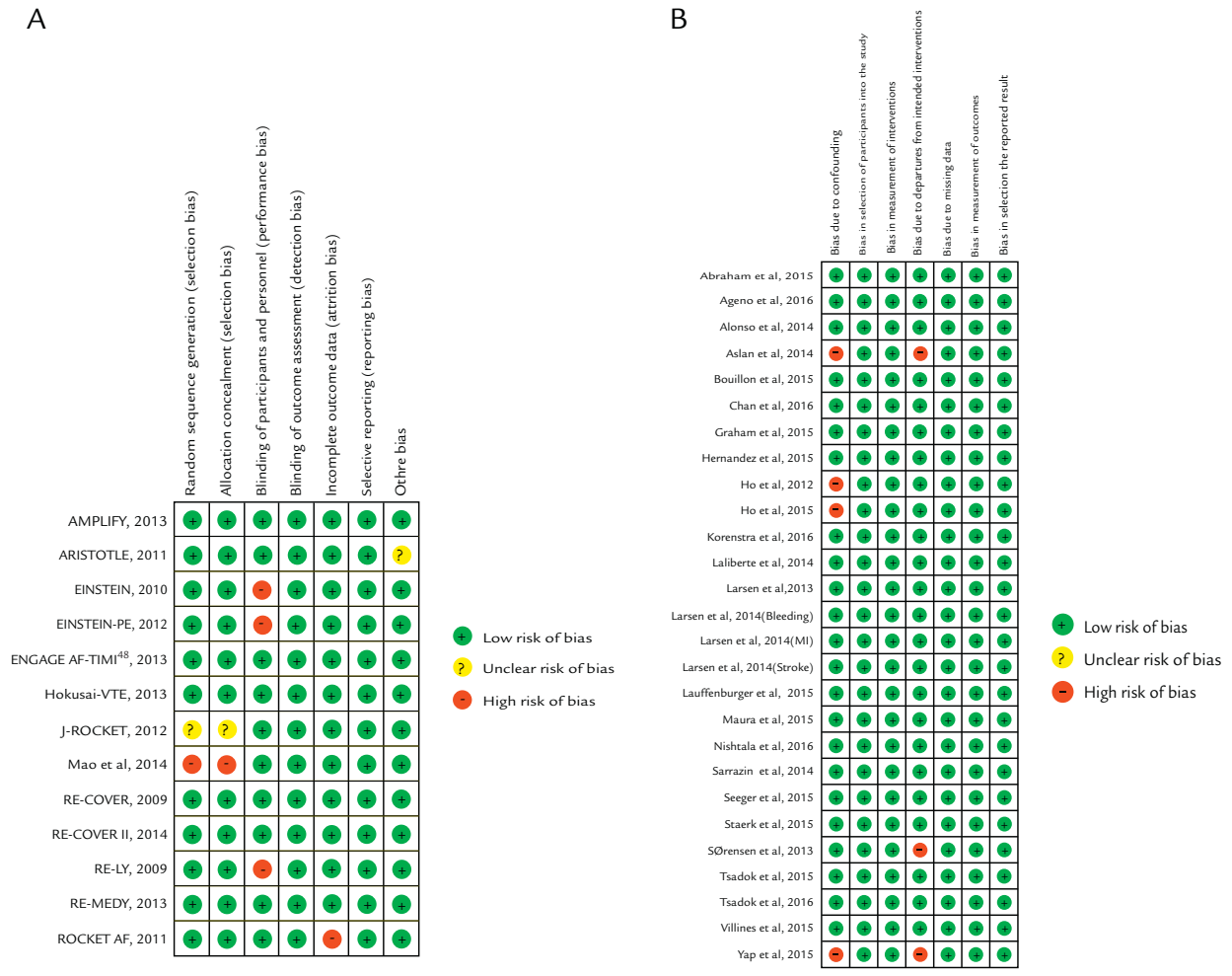

Figure S1. (A) Bias Assessment for the 13 Randomized Controlled Trials.
(B) Bias Assessment for the 27 Observational Studies.

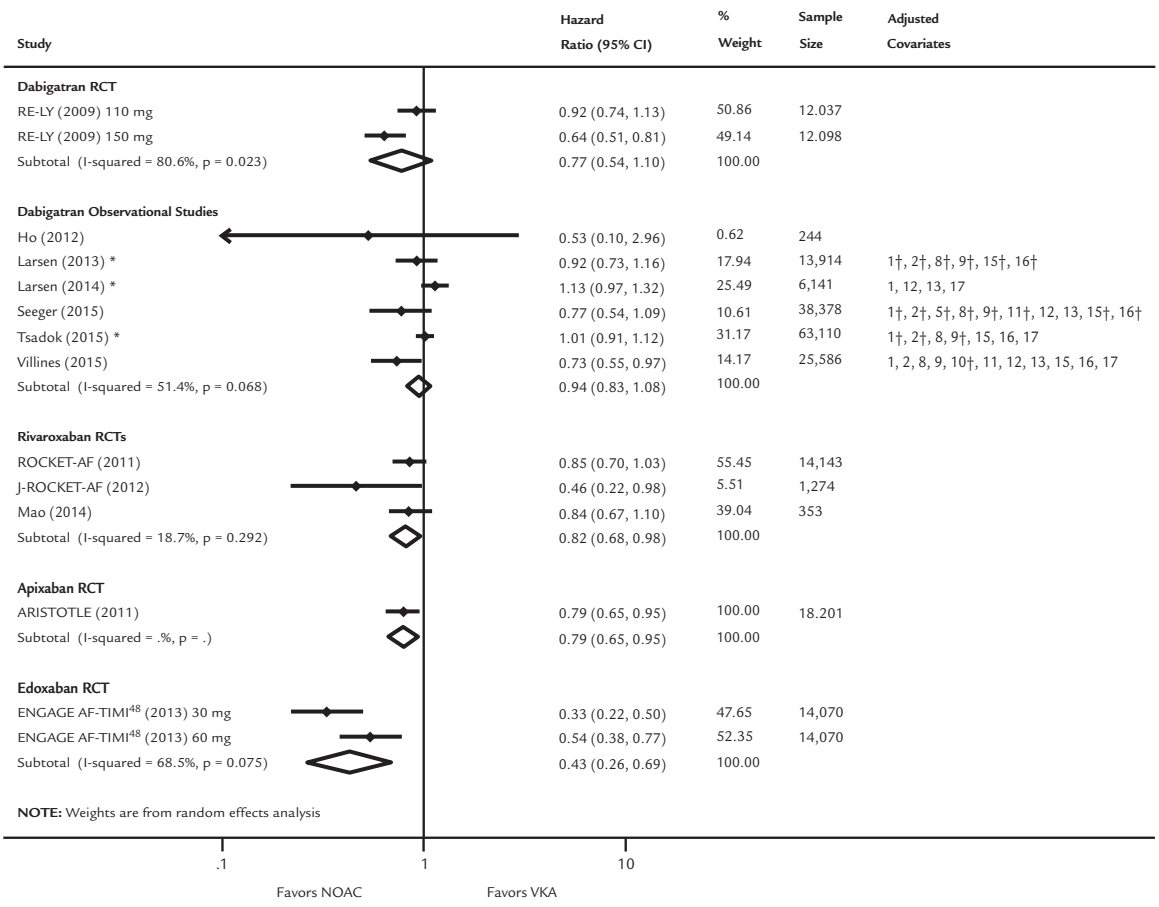

Figure S2. Forest Plot for the Risk of Stroke in Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control trial*; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

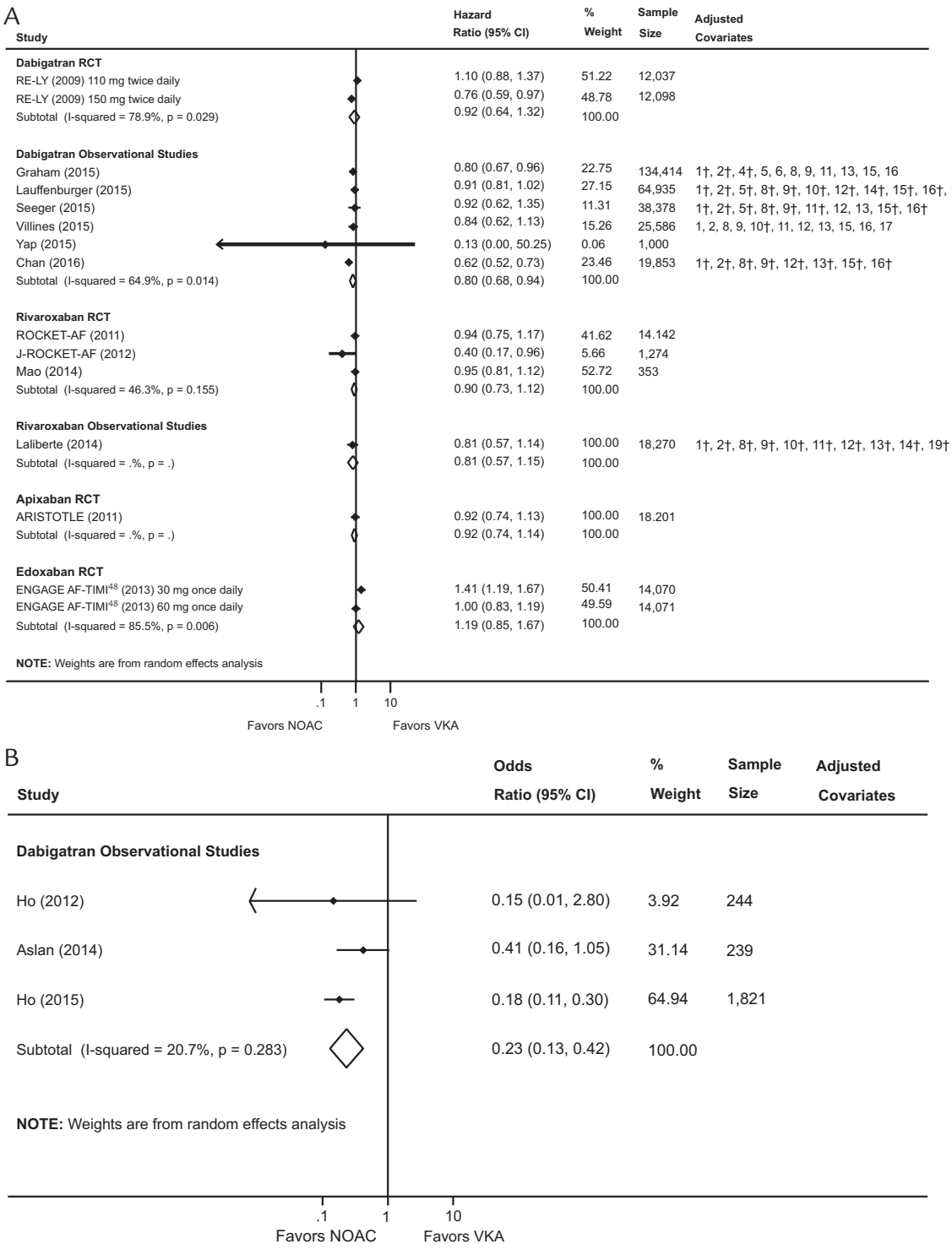

Figure S3. (A) Forest Plot for the Risk of Ischemic Stroke in Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension,

Abnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis. (B) Forest Plot for the Risk of Ischemic Stroke in Atrial Fibrillation Studies Reporting Odds Ratios. Abbreviations: **RCT:** *randomized control trial*; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included stu.

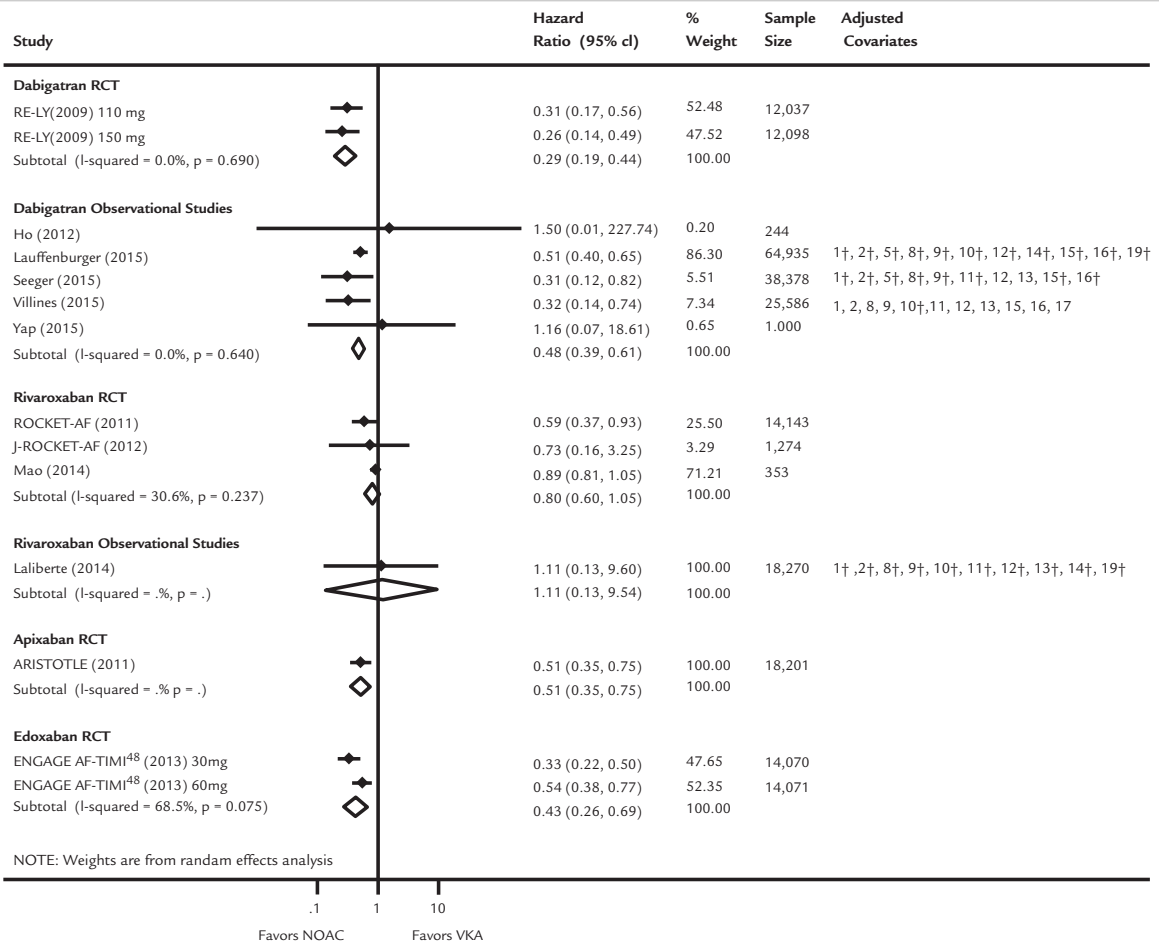

Figure S4. Forest Plot for Risk of Hemorrhagic Stroke in Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

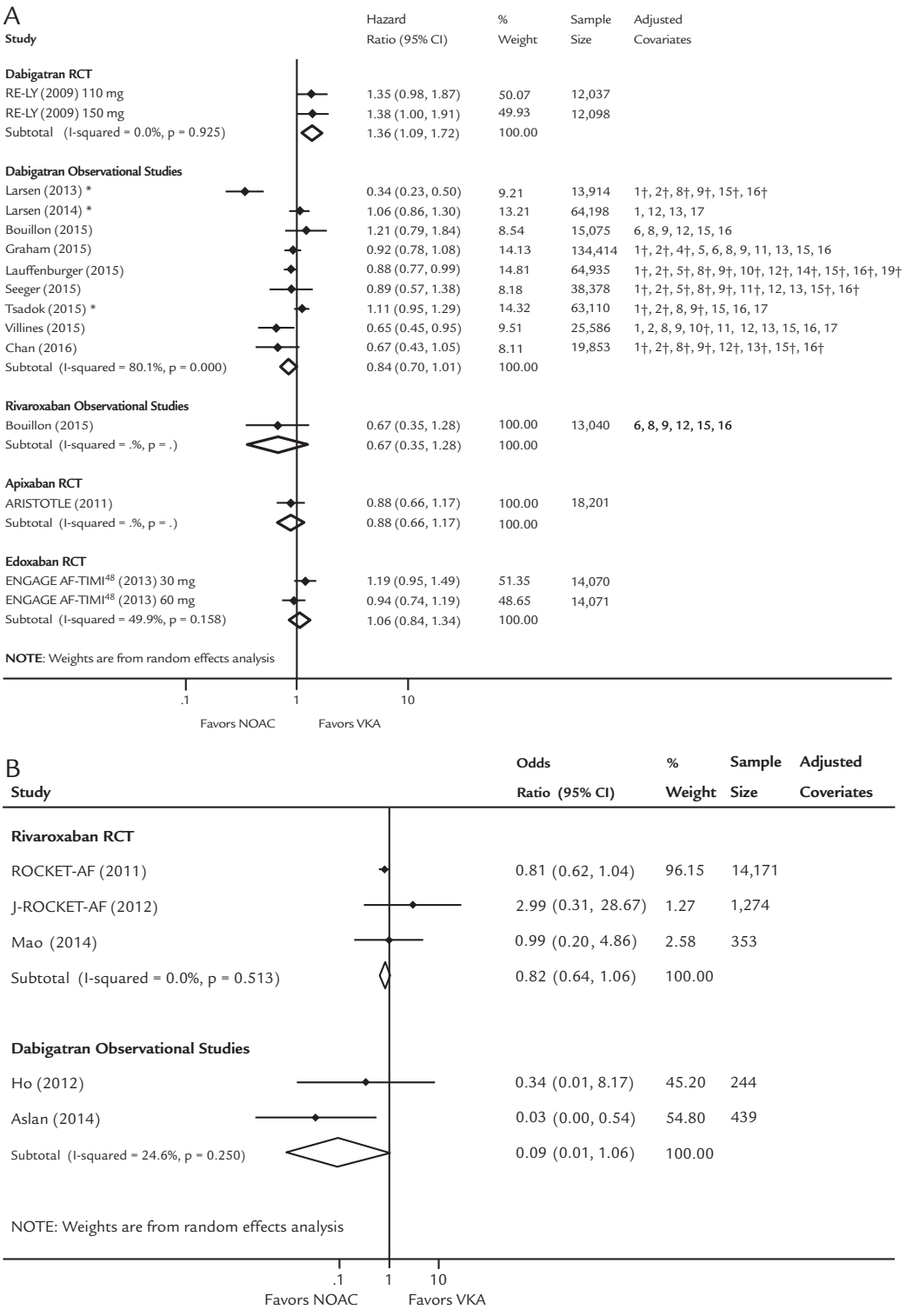

Figure S5. (A) Forest Plot for the Risk of Myocardial Infarction in Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension,

Age≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis. (B) Forest Plot for Risk of Myocardial Infarction in the Atrial Fibrillation Studies Reporting Odds Ratios. Abbreviations: **RCT***: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

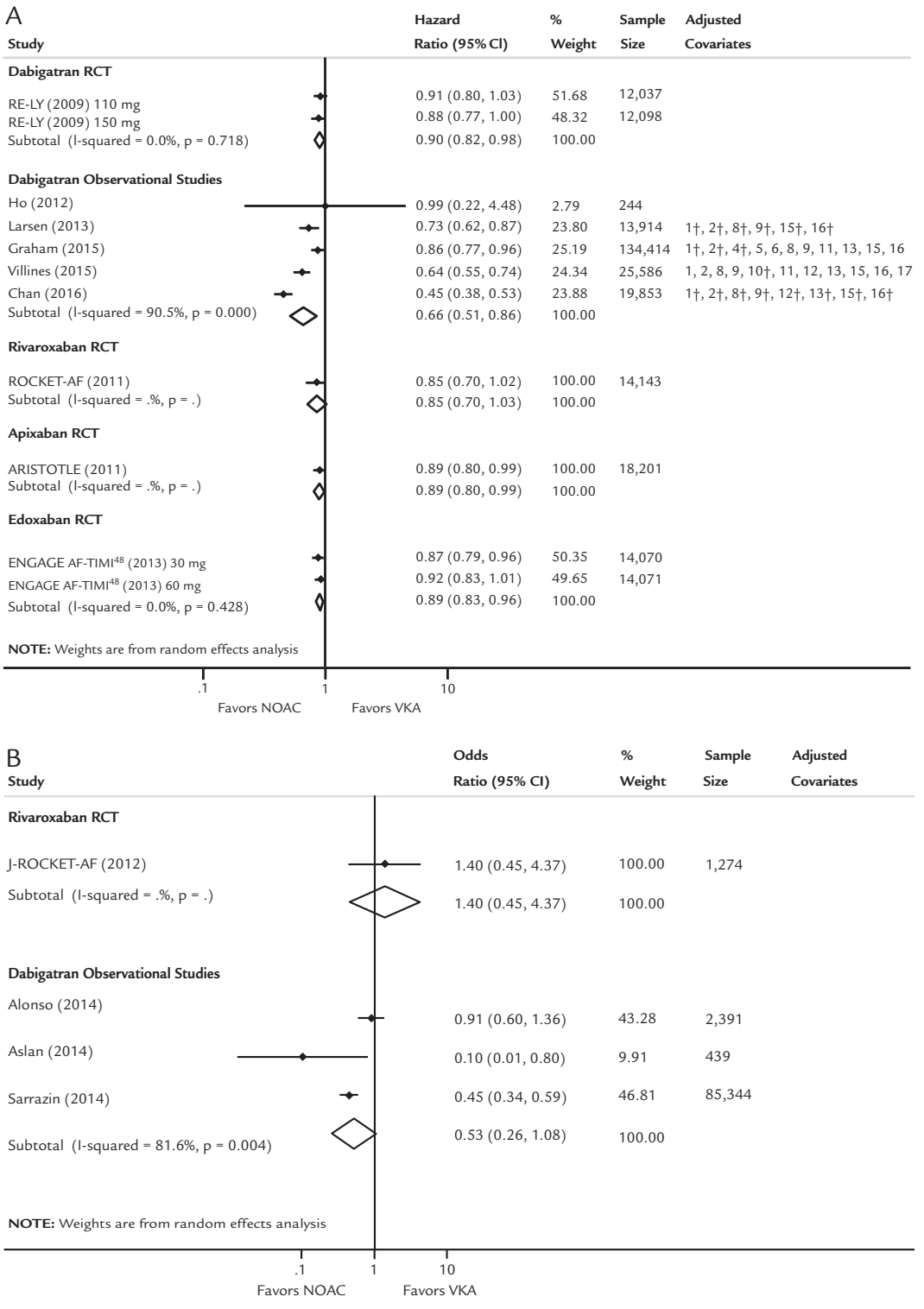

Figure S6. (A) Forest Plot for the Risk of All-cause Mortality in Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (Congestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus,

prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis. (B) Forest Plot for Risk of All-cause Mortality in the Atrial Fibrillation Studies Reporting Odds Ratios. Abbreviations: **RCT***: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

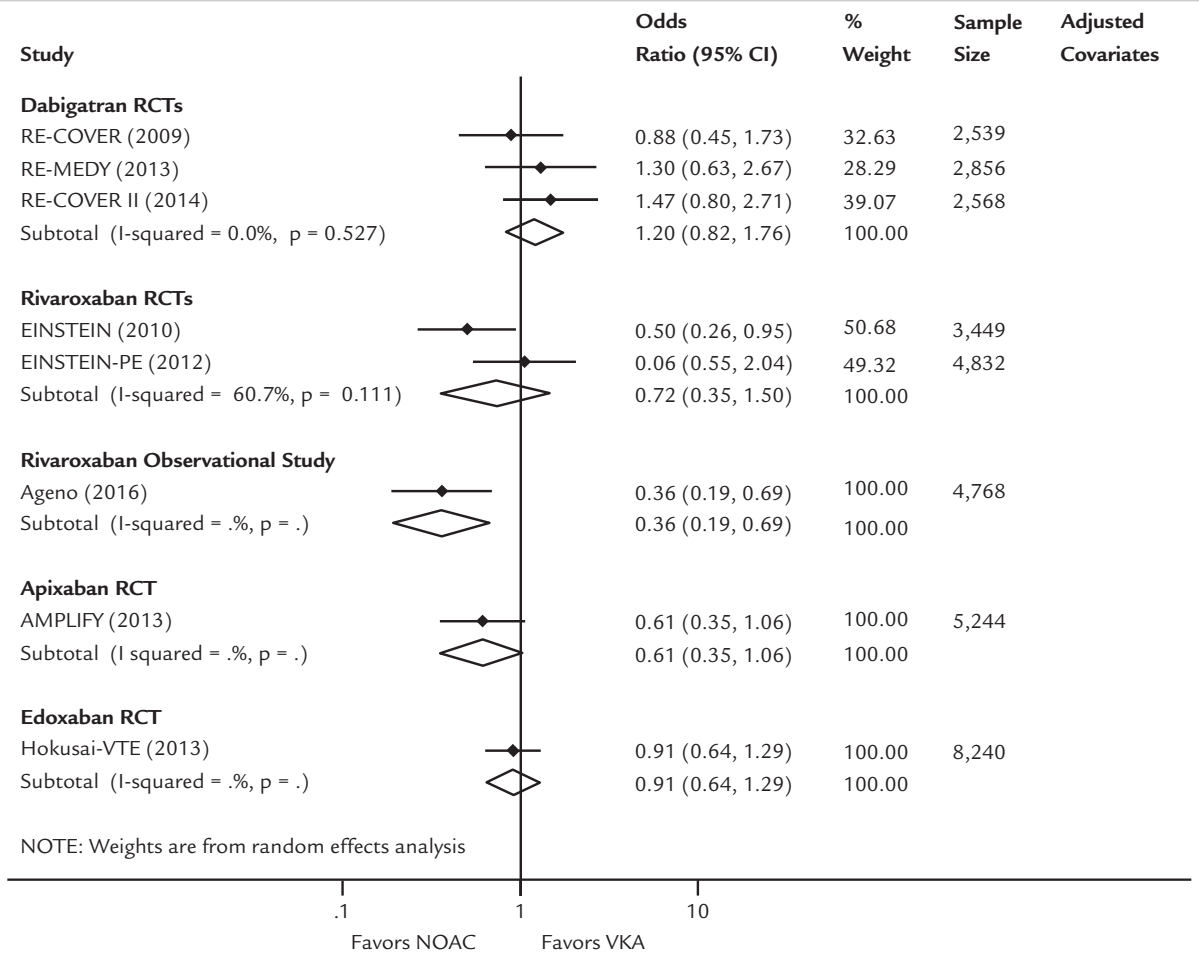

Figure S7. Forest Plot for the Risk of Recurrent Deep Vein Thrombosis in Venous Thromboembolism Studies Reporting Odds Ratios. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

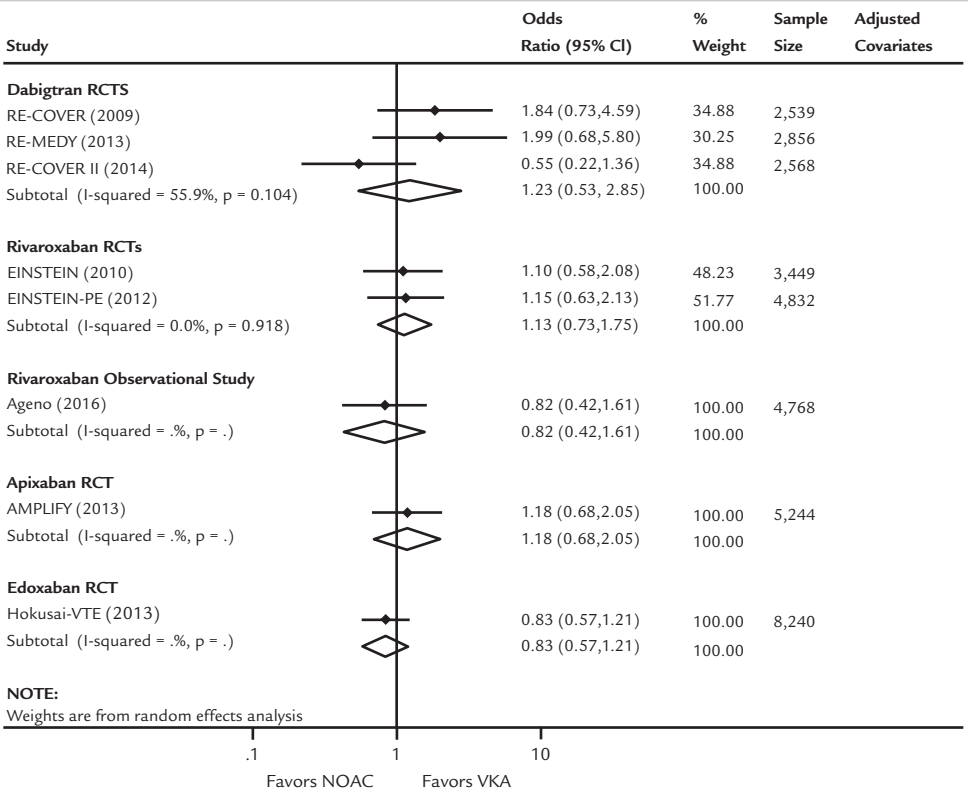

Figure S8. Forest Plot for the Risk of Non-Fatal Pulmonary Embolism in Venous Thromboembolism Studies Reporting Odds Ratios. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

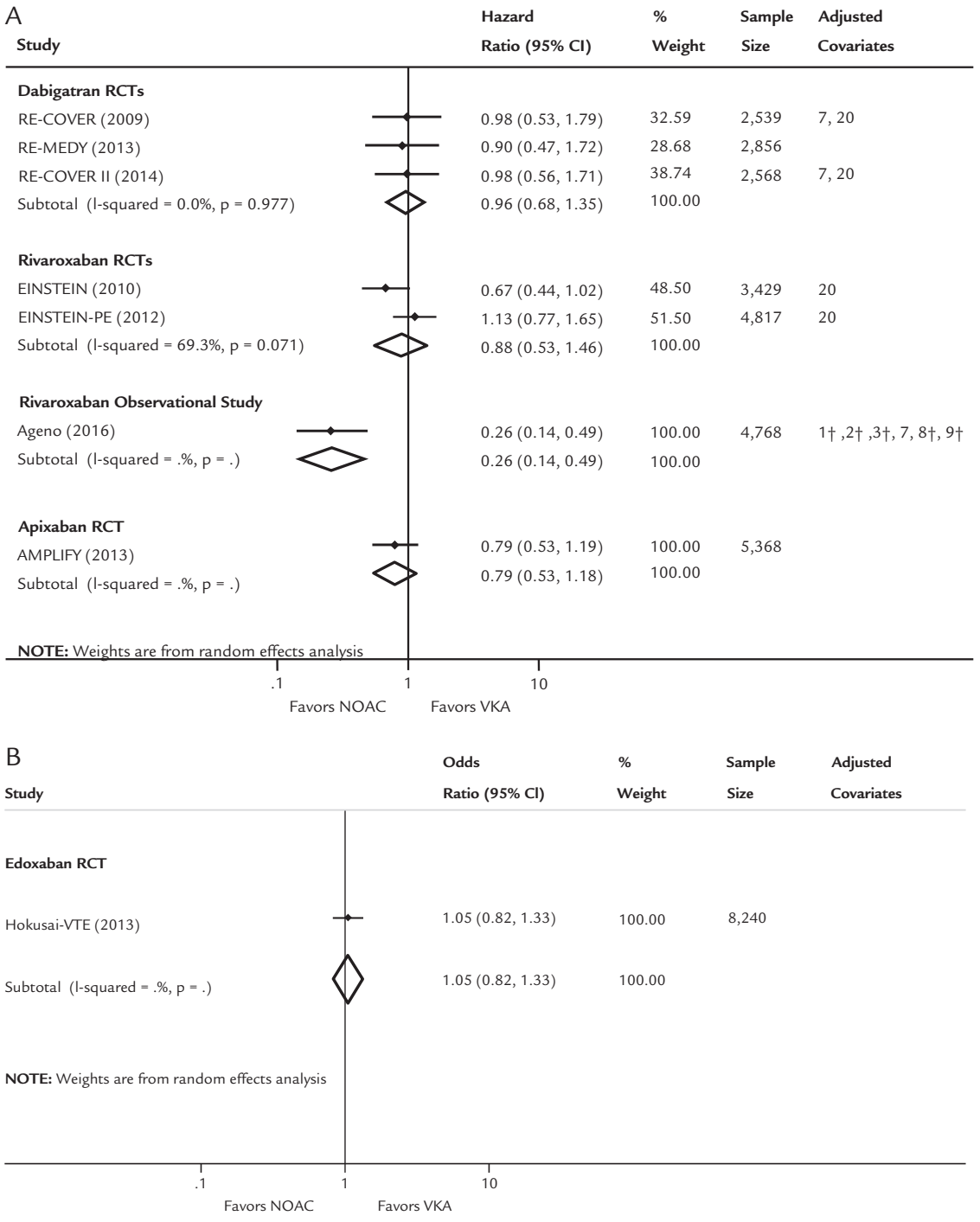

Figure S9. (A) Forest Plot for the Risk of All-Cause Mortality in Venous Thromboembolism Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/ arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory);

HAS-BLED, (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis. (B) Forest Plot for the Risk of All-Cause Mortality in Venous Thromboembolism Studies Reporting Odds Ratios. Abbreviations: **RCT***: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

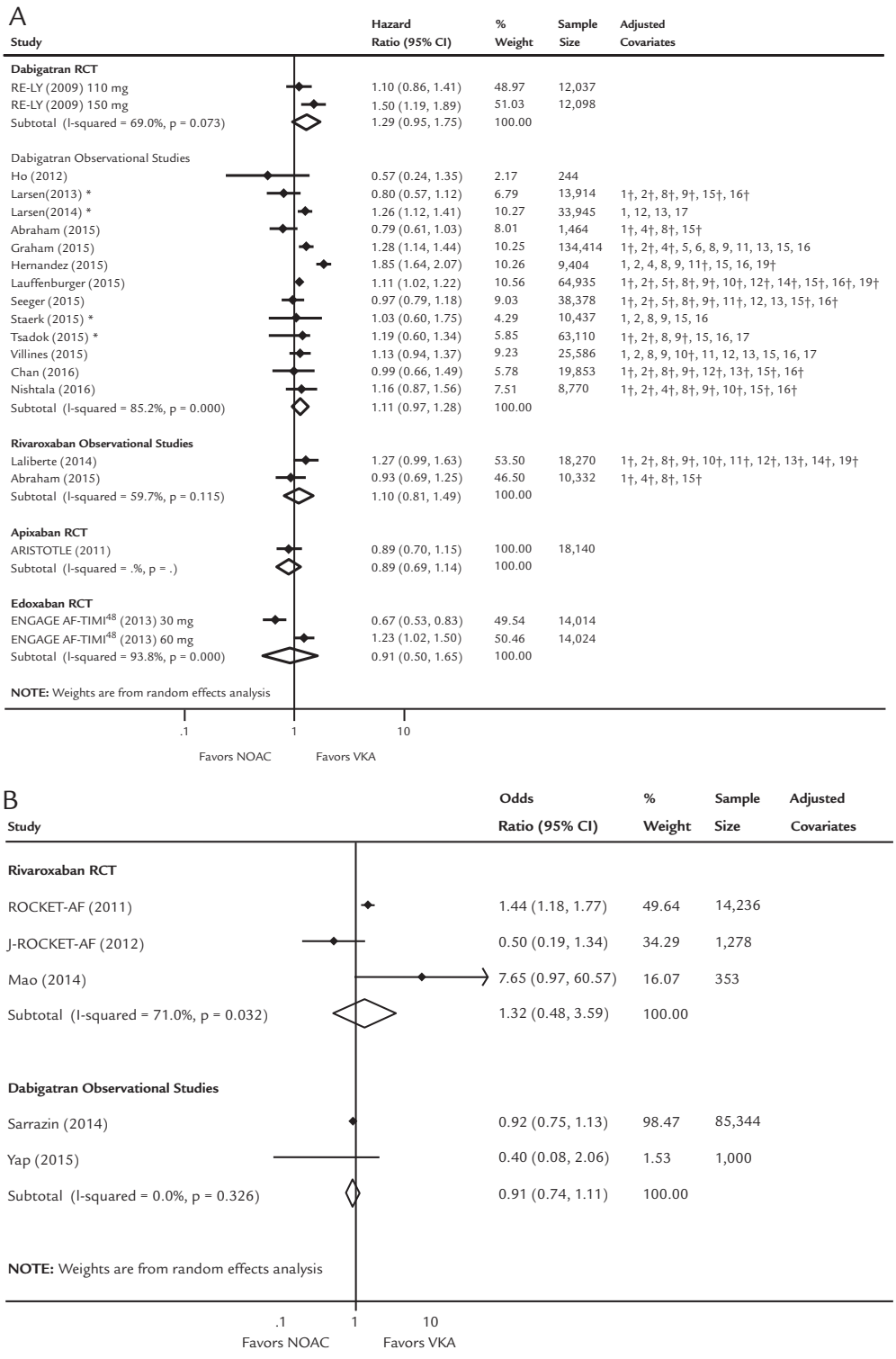

Figure S10. (A) Forest Plot for the Risk of Gastrointestinal Bleeding in Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (Congestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus,

prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis. (B) Forest Plot for the Risk of Gastrointestinal Bleeding in the Atrial Fibrillation Studies Reporting Odds Ratios. Abbreviations: **RCT***: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

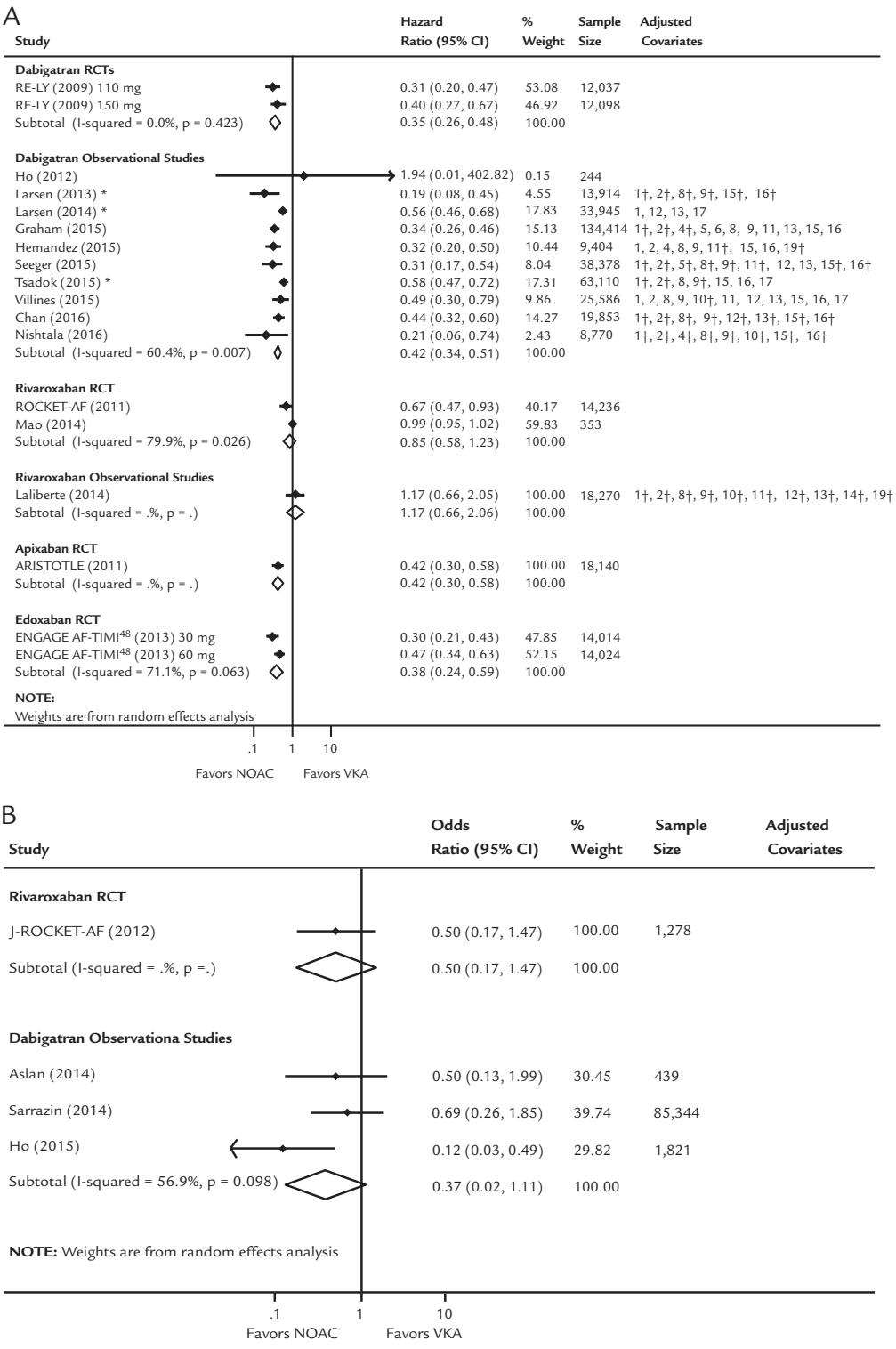

Figure S11. (A) Forest Plot for the Risk of Intracranial Hemorrhage in the Atrial Fibrillation Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (Congestive heart failure, Hypertension, Age≥75 years,

Diabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis. (B) Forest Plot for the Risk of Intracranial Hemorrhage in the Atrial Fibrillation Studies Reporting Odds Ratios. Abbreviations: **RCT**: *randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

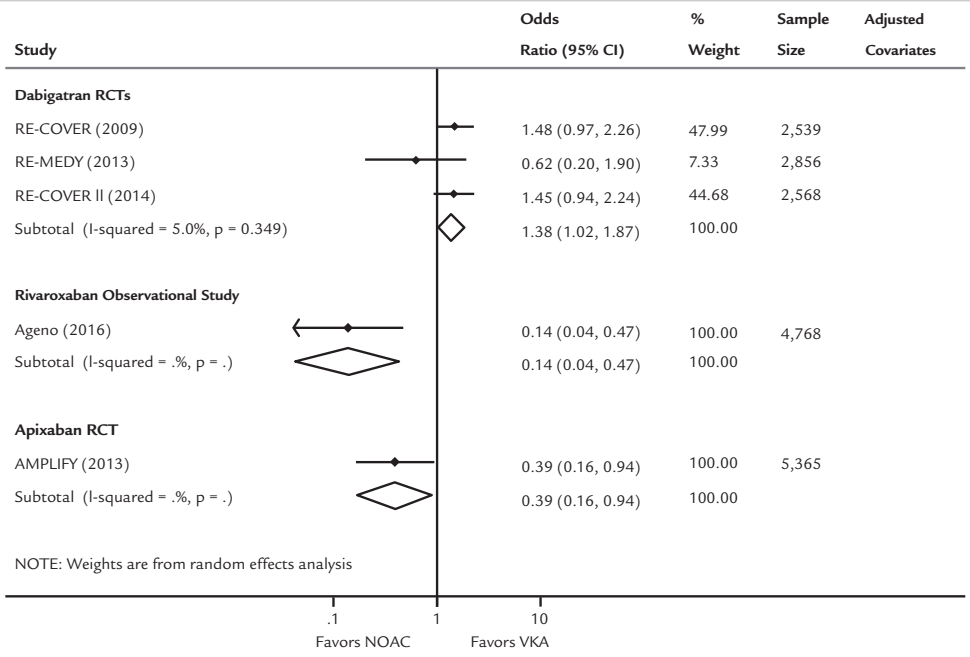

Figure S12. Forest Plot for the Risk of Gastrointestinal Bleeding in in Venous Thromboembolism Studies Reporting Odds Ratios. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjusted covariates reported in the included studies.

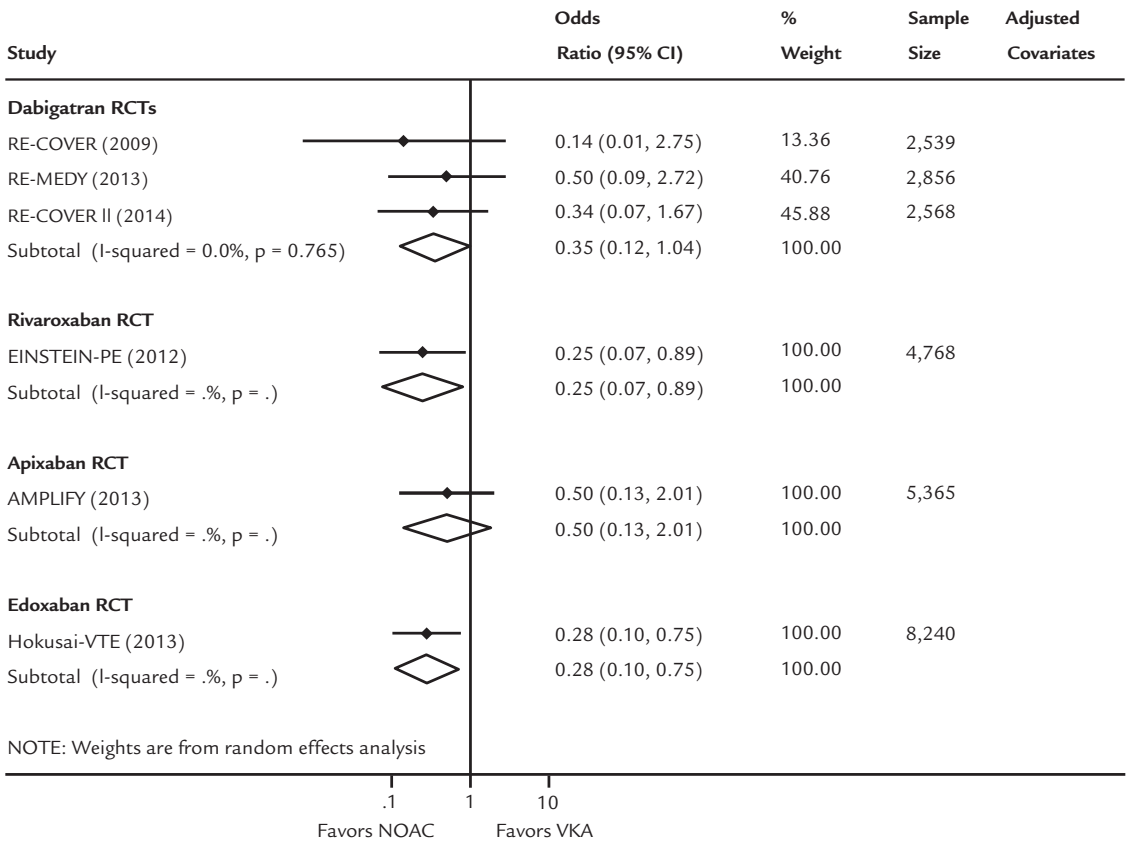

Figure S13. Forest Plot for the Risk of Intracranial Hemorrhage Venous Thromboembolism Studies Reporting Odds Ratios. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist. Note: no adjus ted covariates reported in the included studies.

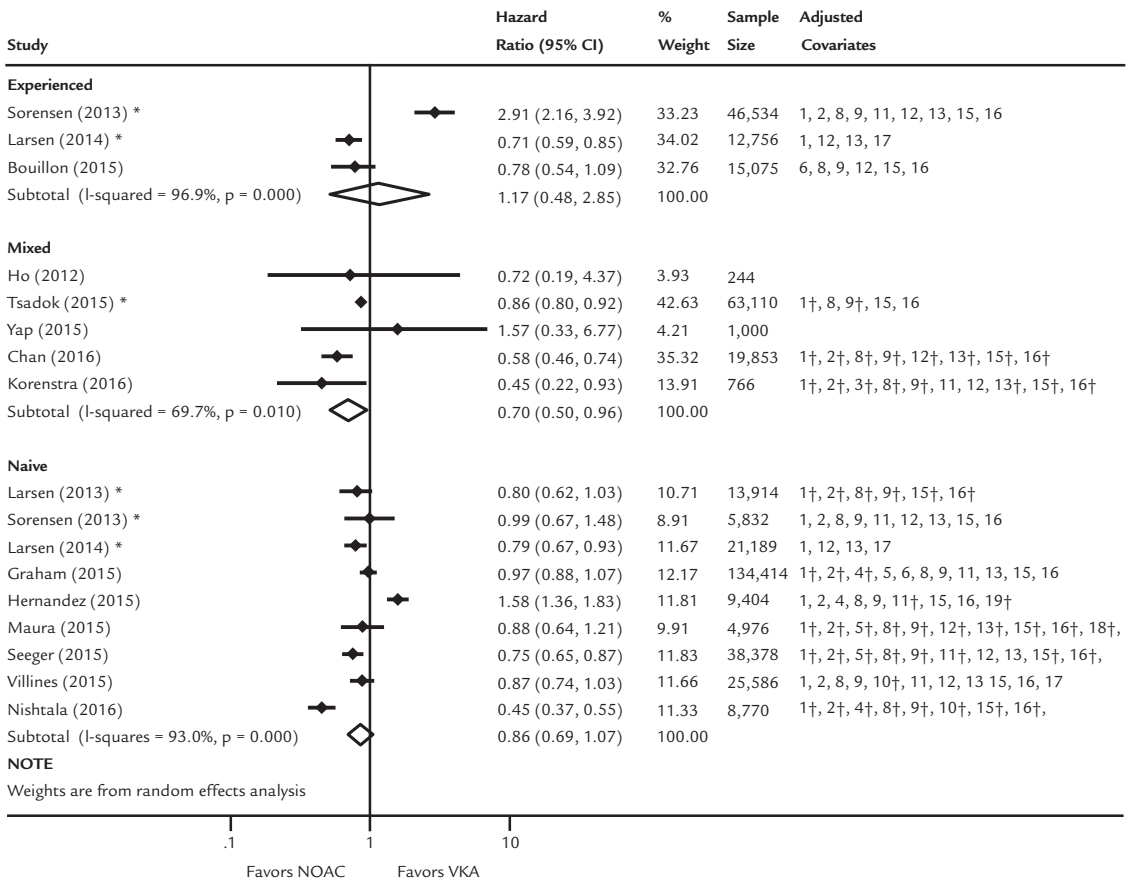

Figure S14. Forest Plot for the Risk of Major Bleeding in the Observational Studies of Dabigatran for Atrial Fibrillation: By Naïve Status. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

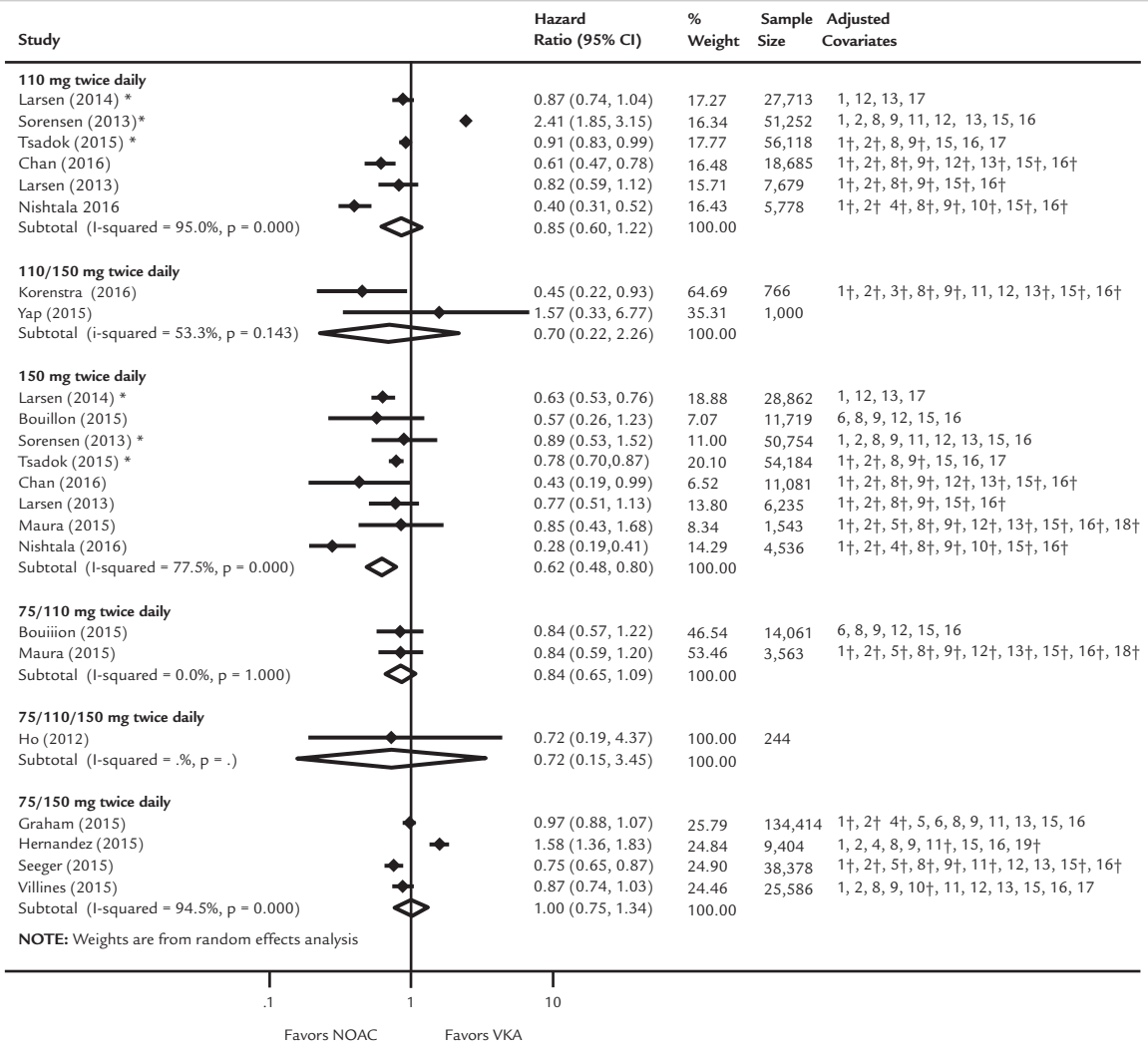

Figure S15. Forest Plot for the Risk of Major Bleeding in the Observational Studies of Dabigatran for Atrial Fibrillation: By Dabigatran Dose. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(> 65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

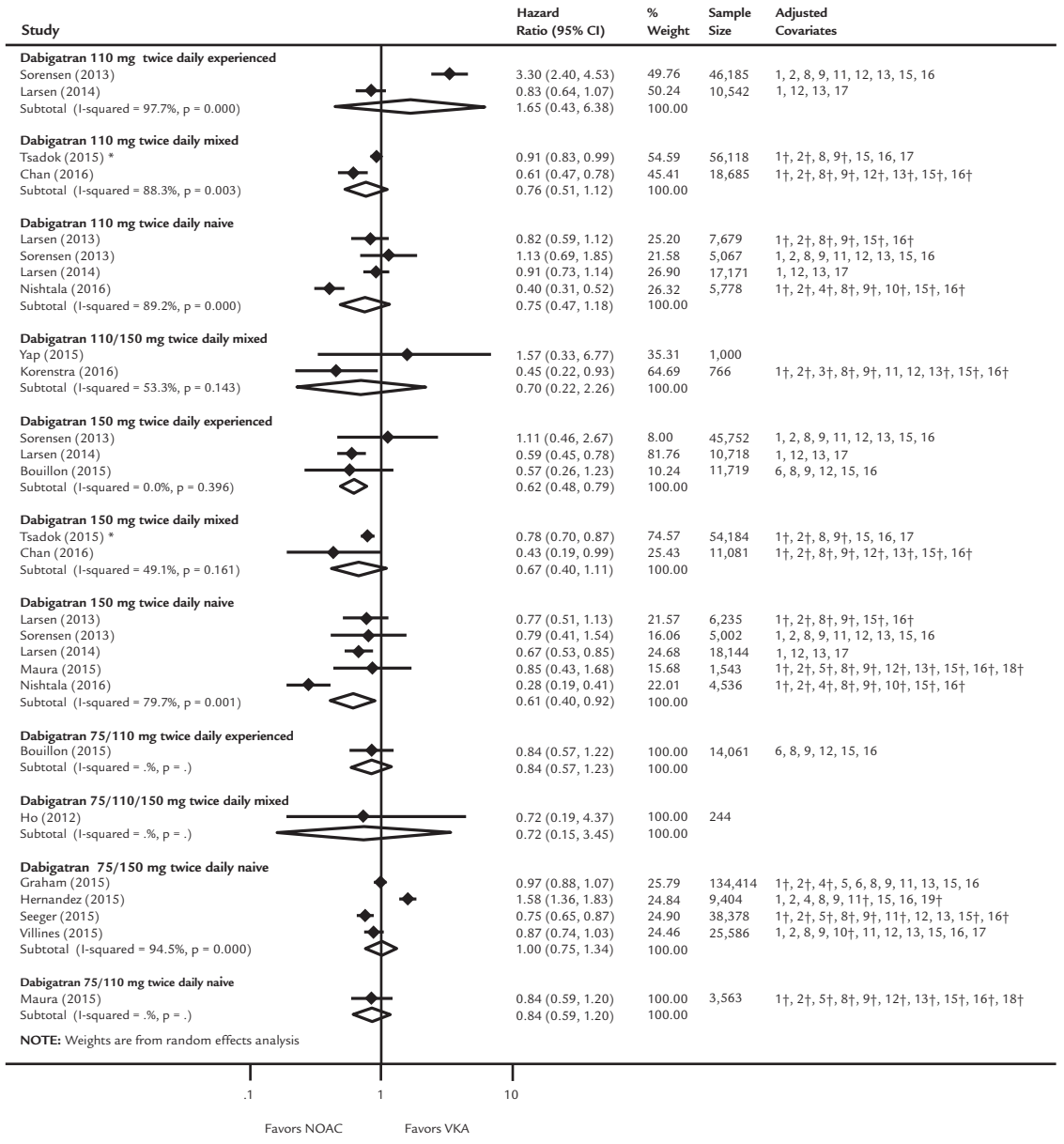

Figure S16. Forest Plot for the Risk of Major Bleeding in the Observational Studies of Dabigatran for Atrial Fibrillation: By Dabigatran Dose and Naïve Status. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index

(income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

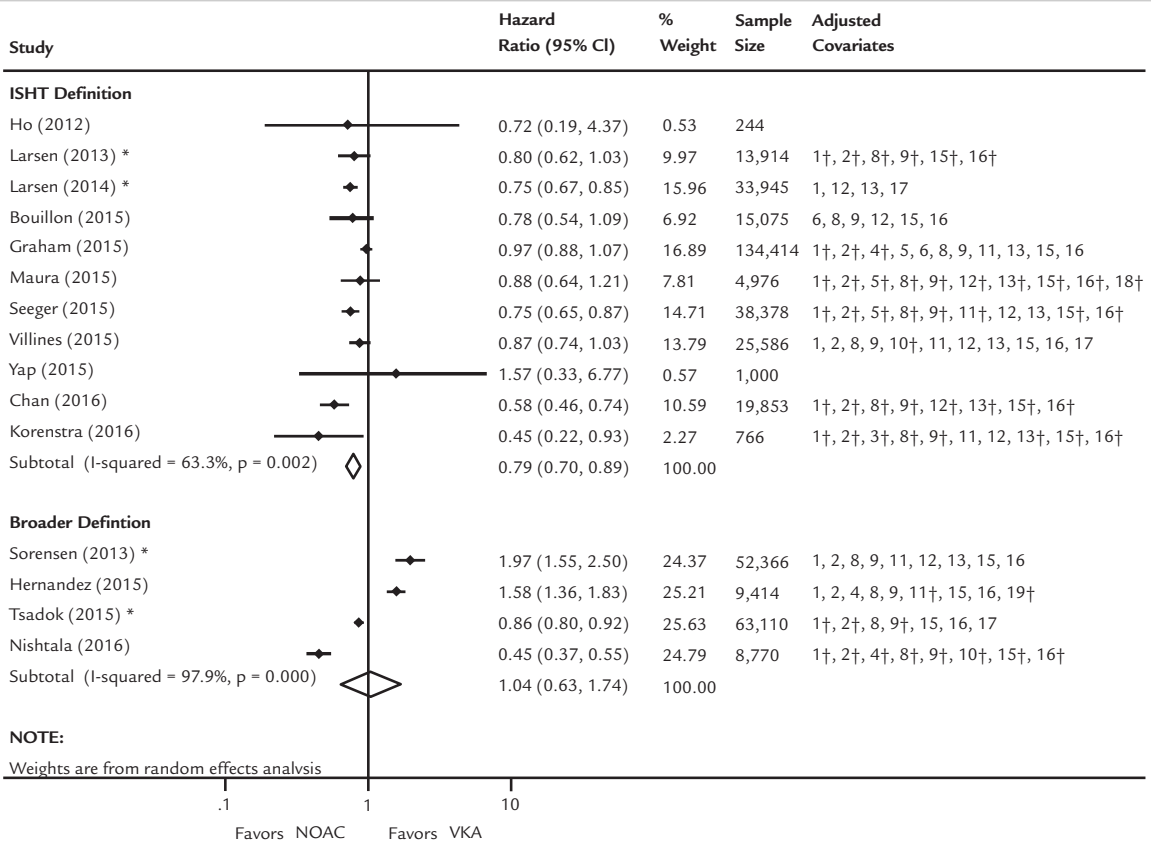

Figure S17. Forest Plot for the Risk of Major Bleeding in the Observational Studies of Dabigatran for Atrial Fibrillation: By Using the Definition of Major Bleeding from the International Society On Thrombosis and Hemostasis vs. A Broader Definition. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

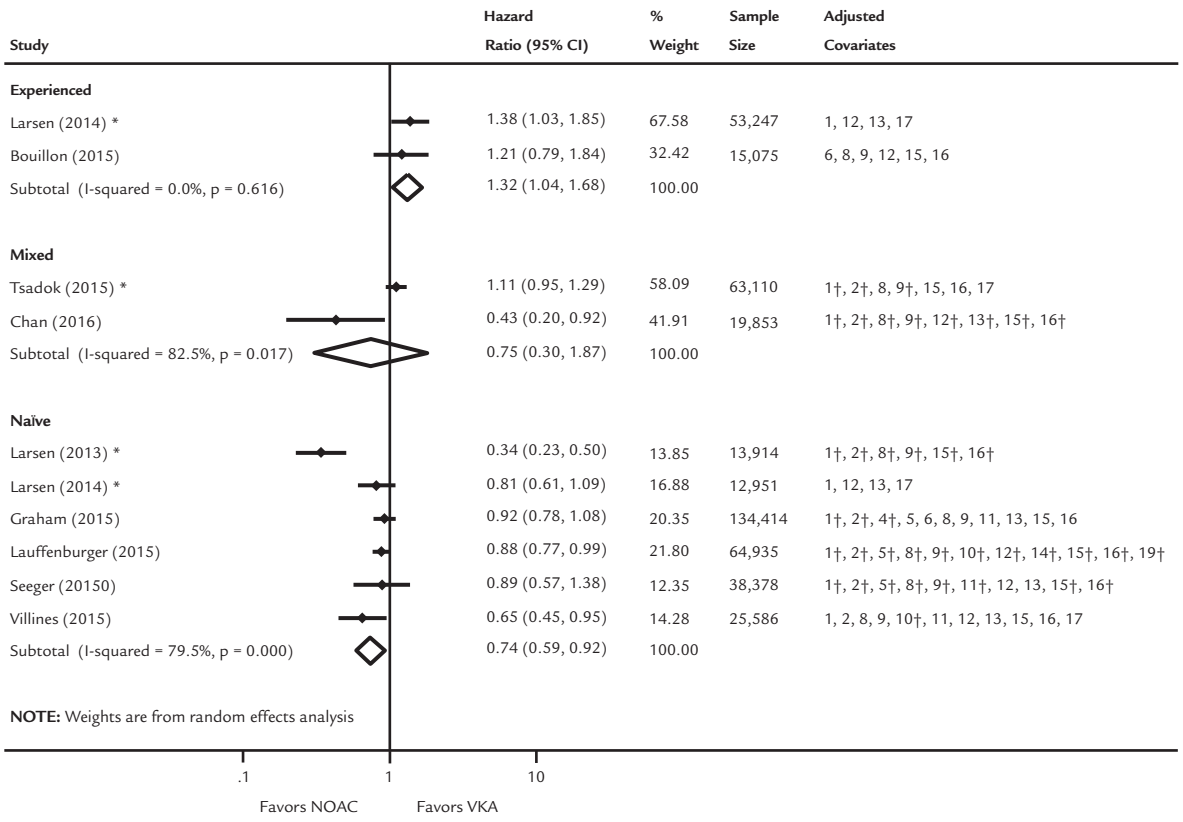

Figure S18. Forest Plot for Risk of Myocardial Infarction in the Observational Studies of Dabigatran for Atrial Fibrillation: By Naïve Status. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

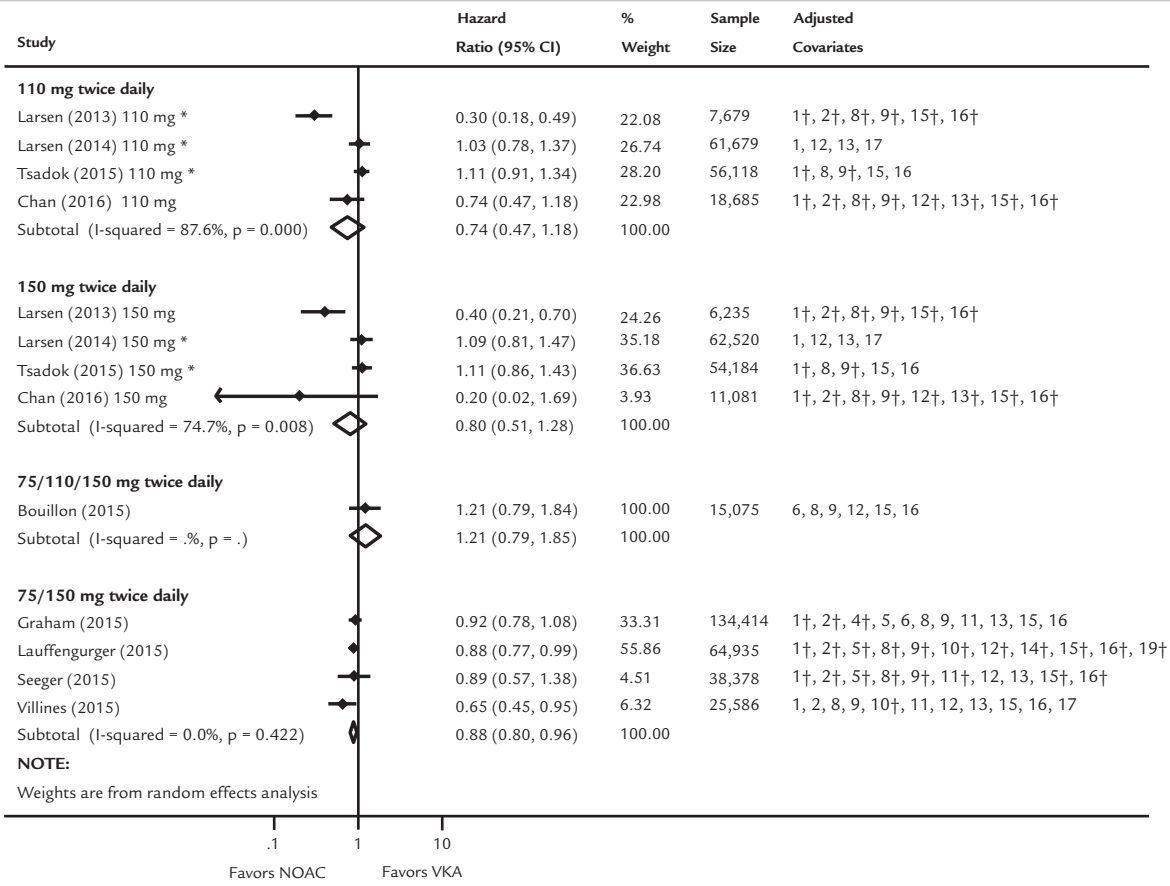

Figure S19. Forest Plot for Risk of Myocardial Infarction in the Observational Studies of Dabigatran for Atrial Fibrillation: By Dabigatran Dose. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

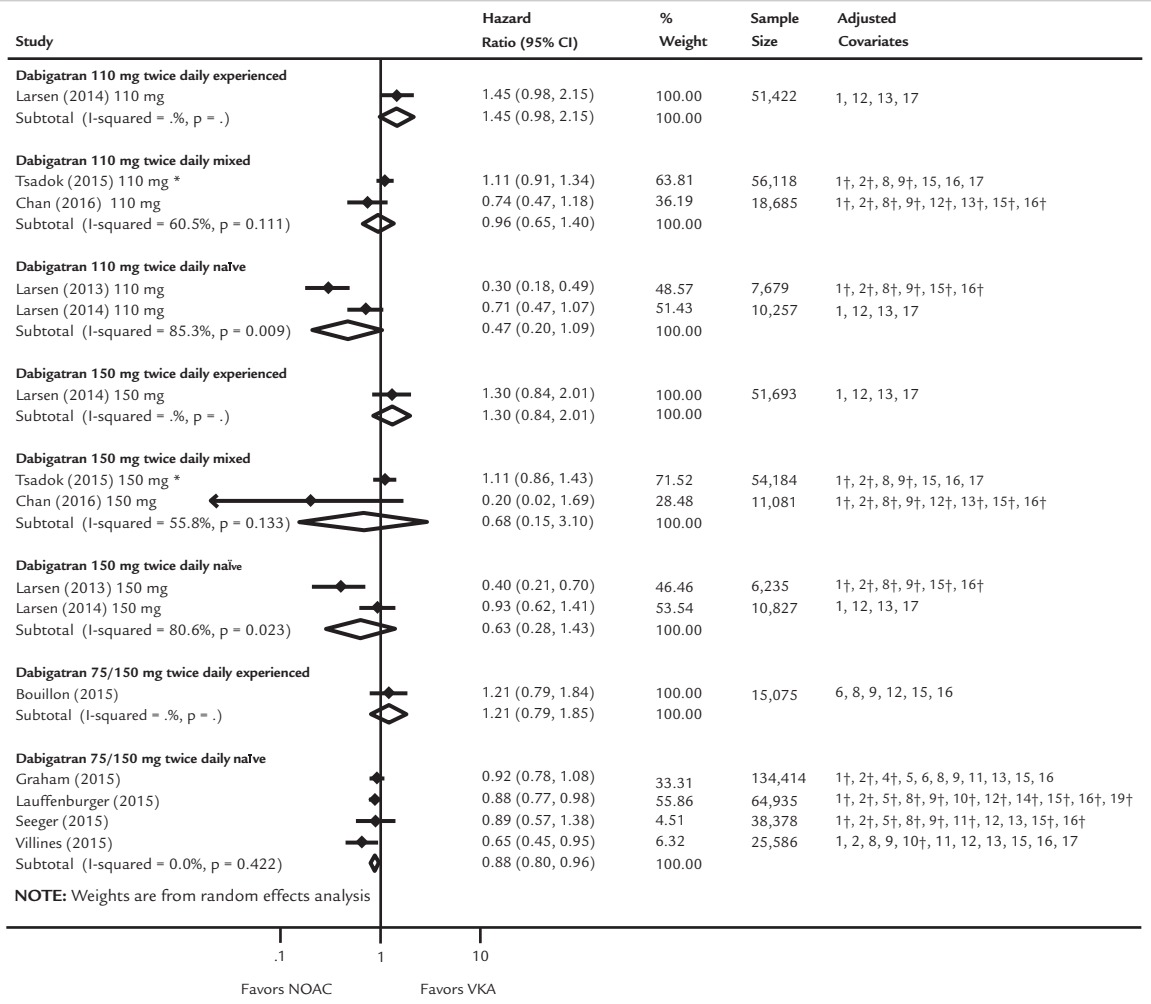

Figure S20. Forest Plot for Risk of Myocardial Infarction in the Observational Studies of Dabigatran for Atrial Fibrillation: By Dabigatran Dose and Naïve Status. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

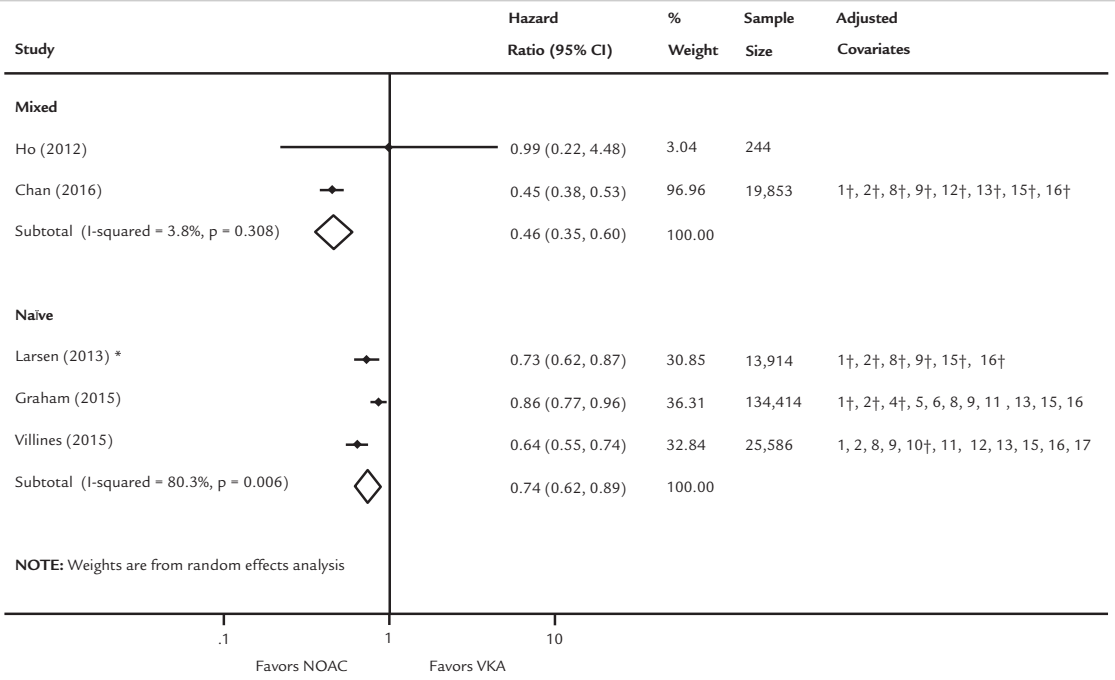

Figure S21. Forest Plot for Risk of All-Cause Mortality in the Observational Studies of Dabigatran for Atrial Fibrillation: By Naïve Status. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

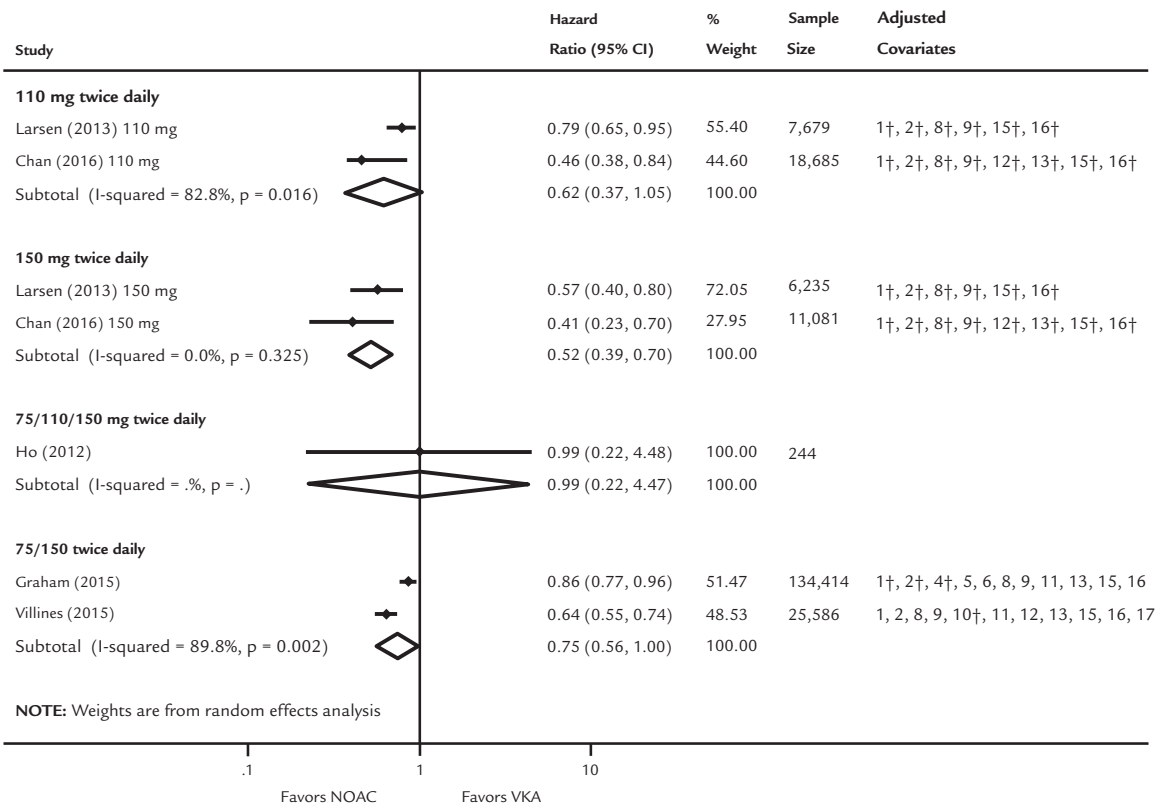

Figure S22. Forest Plot for Risk of All-Cause Mortality in the Observational Studies of Dabigatran for Atrial Fibrillation: By Dabigatran Dose. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

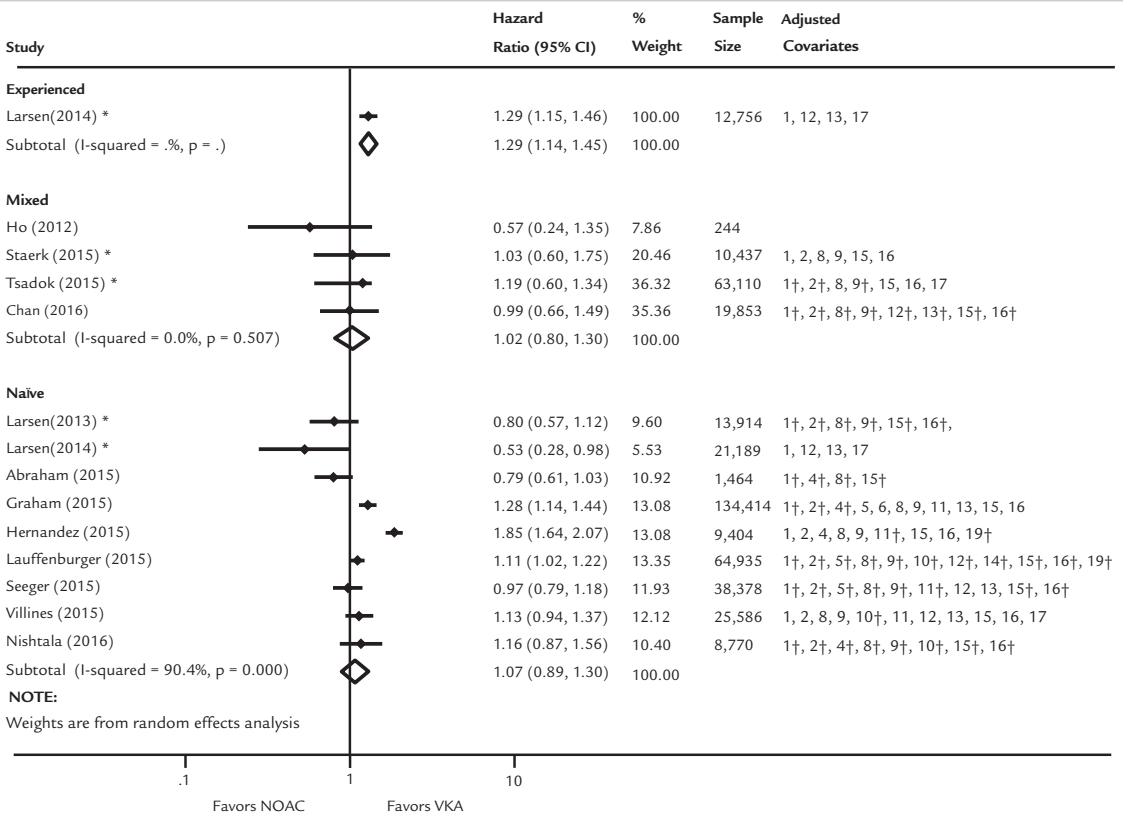

Figure S23. Forest Plot for Risk of Gastrointestinal Bleeding in the Observational Studies of Dabigatran for Atrial Fibrillation: By Naïve Status. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

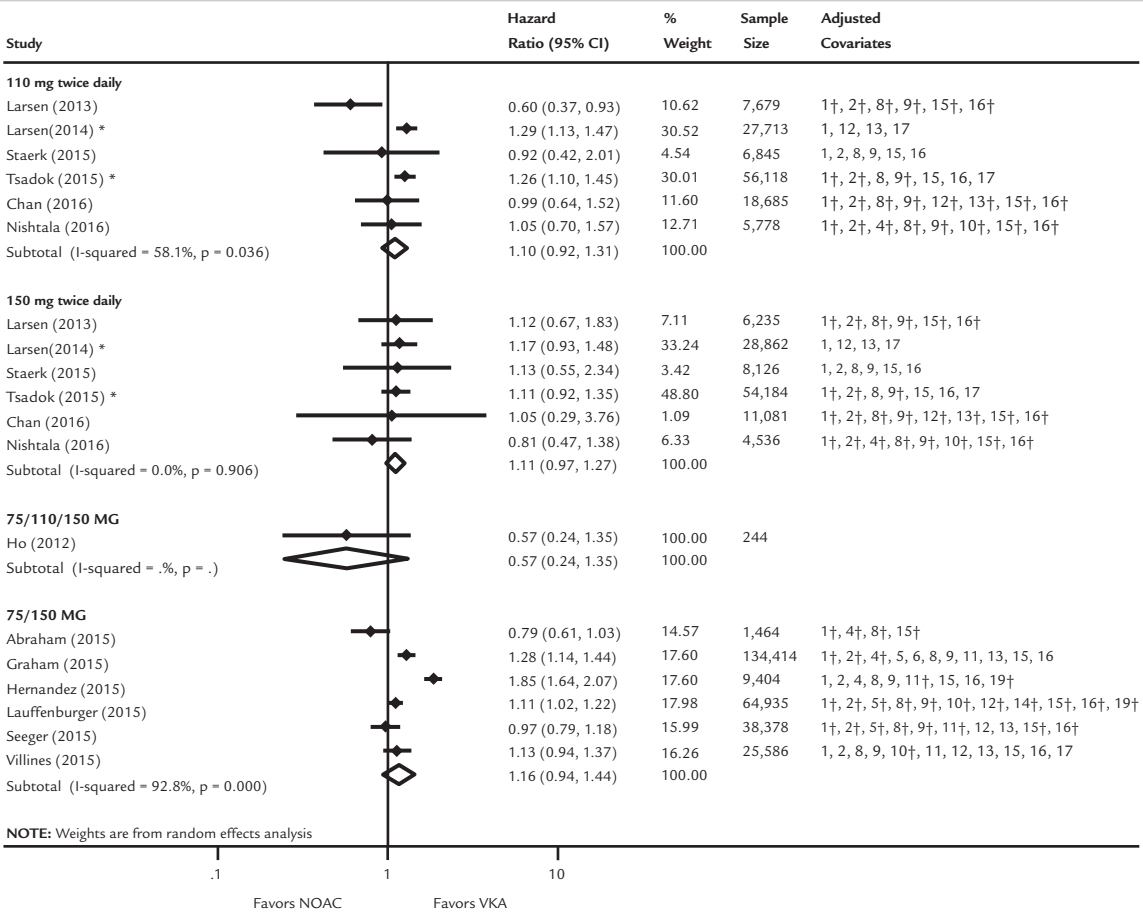

Figure S24. Forest Plot for Risk of Gastrointestinal Bleeding in the Observational Studies of Dabigatran for Atrial Fibrillation: By Dabigatran Dose. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

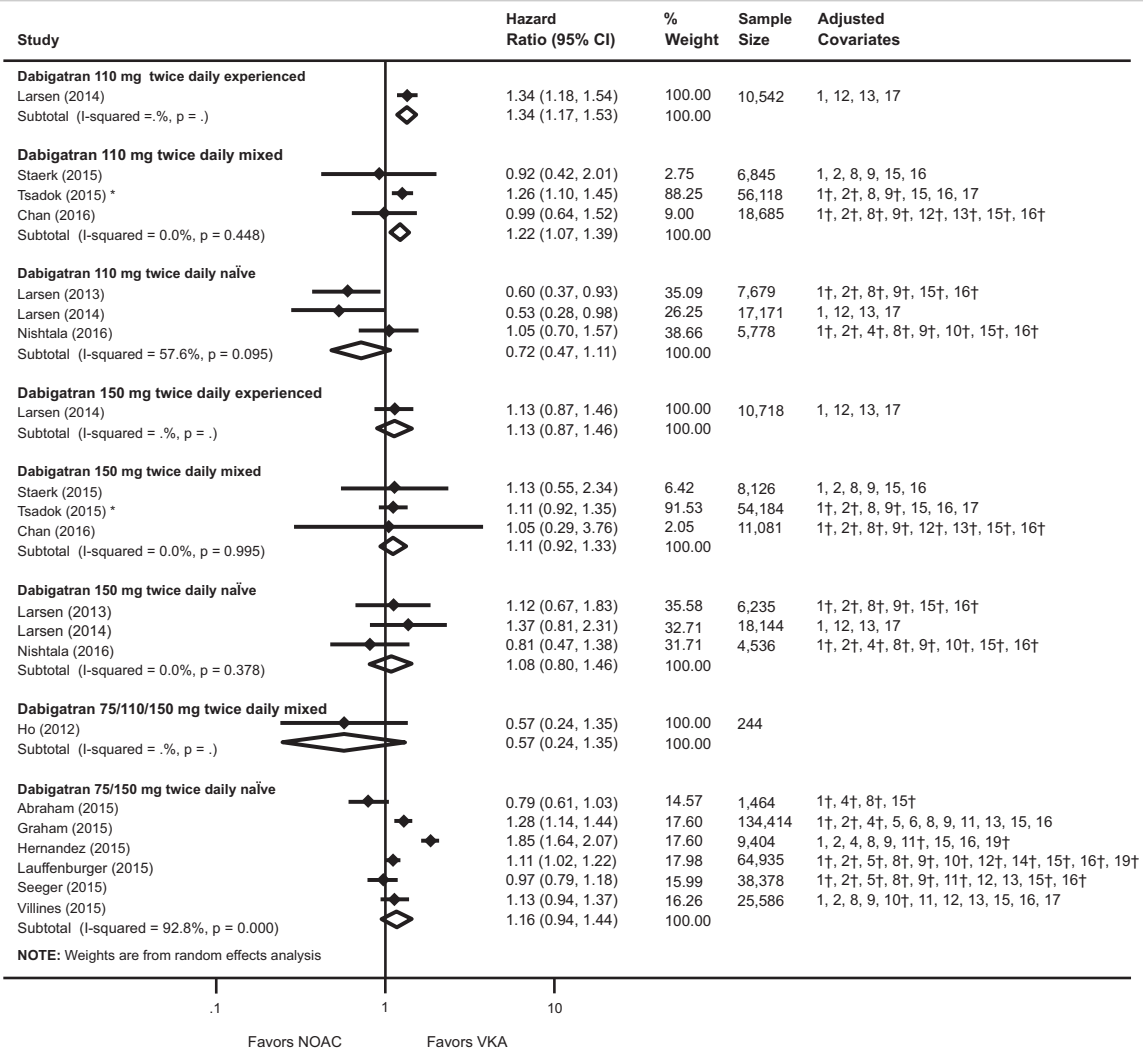

Figure S25. Forest Plot for Risk of Gastrointestinal Bleeding in Atrial Fibrillation Studies Stratified by Dose and Naïve Status for Dabigatran from Observational Studies. Abbreviations: *RCT: randomized control* trial; **NOAC**: non-vitamin K antagonist oral anticoagulant; **VKA**: vitamin K antagonist; **$CHADS_2$,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes mellitus, prior **S**troke/TIA (double risk weight)); **CHA_2DS_2-VASc,** (**C**ongestive heart failure, **H**ypertension, **A**ge≥75 years (double risk weight), **D**iabetes mellitus, previous **S**troke/TIA/arterial embolism (double risk weight), **V**ascular disease, **A**ge 65-74 years, (female) **S**ex **c**ategory); **HAS-BLED,** (**H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR (international normalized ratio), **E**lderly(>65 years), **D**rugs/Alcohol Concomitantly); **ATRIA** (anticoagulation and risk factors in atrial fibrillation). * The study reported stratified relative risk and the overall relative risk was estimated from fixed effect meta-analysis. † Included in the propensity score matching method; otherwise the covariates were adjusted in the multivariable models. Covariates: (1) age, (2) sex, (3) weight, (4) race/ethnicity, (5) region, (6) social deprivation index (income, education and unemployment), (7) active cancer, (8) history of cardiovascular diseases (e.g. heart failure), (9) other comorbidities (non-cardiovascular diseases), (10) comorbidity score/index, (11) $CHADS_2$ score, (12) CHA_2DS_2-VASc score, (13) HAS-BLED score, (14) ATRIA score, (15) use of cardiovascular medications (e.g. antiplatelets), (16) use of other medications (e.g. nonsteroidal anti-inflammatory drugs), (17) time to index exposure, (18) alcohol/smoking use, (19) insurance eligibility, (20) history of pulmonary embolism or deep-vein thrombosis.

Table SI. Search Strategies.

Sources	Search strategies
Medline/PubMed	((((“Atrial Fibrillation”[Mesh] OR “Atrial Flutter”[Mesh] OR “Venous Thrombosis”[Mesh] OR “Venous Thromboembolism”[Mesh] OR “Thromboembolism”[Mesh] OR “Pulmonary Embolism”[Mesh] OR “Thrombosis”[Mesh] OR “heart atrium flutter” OR “vein thrombosis” OR “venous thromboembolism” OR “atrial fibrillation” OR “atrial flutter” OR “AF” OR “non-valvular atrial fibrillation” OR “non valvular atrial fibrillation” OR “NVAF” OR “auricular fibrillation” OR “auricular fibrillations” OR “atrial fibrillations” OR “atrial flutters” OR “non-valvular atrial fibrillations” OR “non valvular atrial fibrillations” OR “deep vein thromboses” OR “deep vein thrombosis” OR “deep venous thromboses” OR “deep venous thrombosis” OR “DVT” OR “thromboses” OR “thrombosis” OR “thromboembolism” OR “VTE” OR “pulmonary embolisms” OR “pulmonary embolism” OR “PE” OR “lung embolism” OR “lung embolisms” OR “pulmonary thromboembolism” OR “pulmonary thromboembolisms”))) AND ((“Anticoagulants”[Mesh] OR “Antithrombins”[Mesh] OR “Factor Xa Inhibitors”[Mesh] OR “blood clotting factor 10a inhibitor” OR “dabigatran” OR “dabigatran etexilate” OR “rivaroxaban” OR “apixaban” OR “edoxaban” OR pradaxa OR pradax OR pradaxar OR prazaxa OR rendix OR xarelto OR eliquis OR savaysa OR lixiana OR “target-specific oral anticoagulants” OR “target specific oral anticoagulants” OR tsoacs OR tsoac OR “new oral anticoagulants” OR “new oral anticoagulant” OR “novel oral anticoagulants” OR “novel oral anticoagulant” OR noacs OR noac OR “direct oral anticoagulants” OR “direct oral anticoagulant” OR doacs OR doac OR “antithrombin” OR “anticoagulant” OR “anticoagulants” OR “factor xa inhibitor”))) AND ((“Warfarin”[Mesh] OR “Coumarins”[Mesh] OR “Acenocoumarol”[Mesh] OR “Phenprocoumon”[Mesh] OR “Phenindione”[Mesh] OR “warfarin” OR “coumadin” OR “courmarin anticoagulant” OR “vitamin k antagonist” OR “antivitamin k” OR “phenprocoumon” OR “phenprocumon” OR “acenocumarol” OR “acenocoumarol” OR “fluindione” OR “phenindione” OR “anisindione”))
Embase	#1 ‘atrial fibrillation’/exp OR ‘heart atrium flutter’/exp OR ‘deep vein thrombosis’/exp OR ‘vein thrombosis’/exp OR ‘venous thromboembolism’/exp OR ‘lung embolism’/exp OR ‘atrial fibrillation’ OR ‘atrial flutter’ OR ‘af’ OR ‘non-valvular atrial fibrillation’ OR ‘non valvular atrial fibrillation’ OR ‘nvaf’ OR ‘auricular fibrillation’ OR ‘auricular fibrillations’ OR ‘atrial fibrillations’ OR ‘atrial flutters’ OR ‘non-valvular atrial fibrillations’ OR ‘non valvular atrial fibrillations’ OR ‘deep vein thrombosis’ OR ‘deep vein thromboses’ OR ‘deep venous thrombosis’ OR ‘deep venous thromboses’ OR ‘dvt’ OR ‘thrombosis’ OR ‘thromboses’ OR ‘thromboembolism’ OR ‘vte’ OR ‘pulmonary embolism’ OR ‘pe’ OR ‘lung embolism’ OR ‘pulmonary thromboembolism’ OR ‘pulmonary thromboembolisms’ AND #2 ‘anticoagulant agent’/exp OR ‘anticoagulation’/exp OR ‘blood clotting factor 10a inhibitor’/exp OR ‘antithrombin’/exp OR ‘dabigatran’/exp OR ‘dabigatran etexilate’/exp OR ‘rivaroxaban’/exp OR ‘apixaban’/exp OR ‘edoxaban’/exp OR dabigatran OR rivaroxaban OR apixaban OR edoxaban OR pradaxa OR pradax OR pradaxar OR prazaxa OR rendix OR xarelto OR eliquis OR savaysa OR lixiana OR ‘target-specific oral anticoagulants’ OR ‘target specific oral anticoagulants’

(continued)

Table SI. (continued).

Sources	Search strategies
	OR tsoacs OR tsoac OR 'new oral anticoagulants' OR 'new oral anticoagulant' OR 'novel oral anticoagulants' OR 'novel oral anticoagulant' OR noacs OR noac OR 'direct oral anticoagulants' OR 'direct oral anticoagulant' OR doacs OR doac OR 'antithrombin' OR 'anticoagulant' OR 'anticoagulants' OR 'factor xa inhibitor' AND #3 'coumarin anticoagulant'/exp OR 'warfarin'/exp OR 'antivitamin k'/exp OR warfarin OR coumadin OR 'courmarin anticoagulant' OR 'vitamin k antagonist' OR 'antivitamin k' OR phenprocoumon OR phenprocumon OR acenocumarol OR acenocoumarol OR fluindione OR phenindione OR anisindione
Web of Science	TS=('heart atrium flutter' OR 'vein thrombosis' OR 'venous thromboembolism' OR 'atrial fibrillation' OR 'atrial flutter' OR 'af' OR 'non-valvular atrial fibrillation' OR 'non valvular atrial fibrillation' OR 'nvaf' OR 'auricular fibrillation' OR 'auricular fibrillations' OR 'atrial fibrillations' OR 'atrial flutters' OR 'non-valvular atrial fibrillations' OR 'non valvular atrial fibrillations' OR 'deep vein thrombosis' OR 'deep vein thromboses' OR 'deep venous thrombosis' OR 'deep venous thromboses' OR 'dvt' OR 'thrombosis' OR 'thromboses' OR 'thromboembolism' OR 'vte' OR 'pulmonary embolism' OR 'pe' OR 'lung embolism' OR 'pulmonary thromboembolism' OR 'pulmonary thromboembolisms') AND TS=('blood clotting factor 10a inhibitor' OR 'dabigatran' OR 'dabigatran etexilate' OR 'rivaroxaban' OR 'apixaban' OR 'edoxaban' OR pradaxa OR pradax OR pradaxar OR prazaxa OR rendix OR xarelto OR eliquis OR savaysa OR lixiana OR 'target-specific oral anticoagulants' OR 'target specific oral anticoagulants' OR tsoacs OR tsoac OR 'new oral anticoagulants' OR 'new oral anticoagulant' OR 'novel oral anticoagulants' OR 'novel oral anticoagulant' OR noacs OR noac OR 'direct oral anticoagulants' OR 'direct oral anticoagulant' OR doacs OR doac OR 'antithrombin' OR 'anticoagulant' OR 'anticoagulants' OR 'factor xa inhibitor') AND TS=(warfarin OR coumadin OR 'courmarin anticoagulant' OR 'vitamin k antagonist' OR 'antivitamin k' OR phenprocoumon OR phenprocumon OR acenocumarol OR acenocoumarol OR fluindione OR phenindione OR anisindione)
Academic search complete	('heart atrium flutter' OR 'vein thrombosis' OR 'venous thromboembolism' OR 'atrial fibrillation' OR 'atrial flutter' OR 'af' OR 'non-valvular atrial fibrillation' OR 'non valvular atrial fibrillation' OR 'nvaf' OR 'auricular fibrillation' OR 'auricular fibrillations' OR 'atrial fibrillations' OR 'atrial flutters' OR 'non-valvular atrial fibrillations' OR 'non valvular atrial fibrillations' OR 'deep vein thrombosis' OR 'deep vein thromboses' OR 'deep venous thrombosis' OR 'deep venous thromboses' OR 'dvt' OR 'thrombosis' OR 'thromboses' OR 'thromboembolism' OR 'vte' OR 'pulmonary embolism' OR 'pe' OR 'lung embolism' OR 'pulmonary thromboembolism' OR 'pulmonary thromboembolisms') AND

(continued)

Table SI. (continued).

Sources	Search strategies
	('blood clotting factor 10a inhibitor' OR 'dabigatran' OR 'dabigatran etexilate' OR 'rivaroxaban' OR 'apixaban' OR 'edoxaban' OR pradaxa OR pradax OR pradaxar OR prazaxa OR rendix OR xarelto OR eliquis OR savaysa OR lixiana OR 'target-specific oral anticoagulants' OR 'target specific oral anticoagulants' OR tsoacs OR tsoac OR 'new oral anticoagulants' OR 'new oral anticoagulant' OR 'novel oral anticoagulants' OR 'novel oral anticoagulant' OR noacs OR noac OR 'direct oral anticoagulants' OR 'direct oral anticoagulant' OR doacs OR doac OR 'antithrombin' OR 'anticoagulant' OR 'anticoagulants' OR 'factor xa inhibitor') AND (warfarin OR coumadin OR 'courmarin anticoagulant' OR 'vitamin k antagonist' OR 'antivitamin k' OR phenprocoumon OR phenprocumon OR acenocumarol OR acenocoumarol OR fluindione OR phenindione OR anisindione)
CINAHL	('heart atrium flutter' OR 'vein thrombosis' OR 'venous thromboembolism' OR 'atrial fibrillation' OR 'atrial flutter' OR 'af' OR 'non-valvular atrial fibrillation' OR 'non valvular atrial fibrillation' OR 'nvaf' OR 'auricular fibrillation' OR 'auricular fibrillations' OR 'atrial fibrillations' OR 'atrial flutters' OR 'non-valvular atrial fibrillations' OR 'non valvular atrial fibrillations' OR 'deep vein thrombosis' OR 'deep vein thromboses' OR 'deep venous thrombosis' OR 'deep venous thromboses' OR 'dvt' OR 'thrombosis' OR 'thromboses' OR 'thromboembolism' OR 'vte' OR 'pulmonary embolism' OR 'pe' OR 'lung embolism' OR 'pulmonary thromboembolism' OR 'pulmonary thromboembolisms') AND ('blood clotting factor 10a inhibitor' OR 'dabigatran' OR 'dabigatran etexilate' OR 'rivaroxaban' OR 'apixaban' OR 'edoxaban' OR pradaxa OR pradax OR pradaxar OR prazaxa OR rendix OR xarelto OR eliquis OR savaysa OR lixiana OR 'target-specific oral anticoagulants' OR 'target specific oral anticoagulants' OR tsoacs OR tsoac OR 'new oral anticoagulants' OR 'new oral anticoagulant' OR 'novel oral anticoagulants' OR 'novel oral anticoagulant' OR noacs OR noac OR 'direct oral anticoagulants' OR 'direct oral anticoagulant' OR doacs OR doac OR 'antithrombin' OR 'anticoagulant' OR 'anticoagulants' OR 'factor xa inhibitor') AND (warfarin OR coumadin OR 'courmarin anticoagulant' OR 'vitamin k antagonist' OR 'antivitamin k' OR phenprocoumon OR phenprocumon OR acenocumarol OR acenocoumarol OR fluindione OR phenindione OR anisindione)
Cochrane Library	#1 MeSH descriptor: [Atrial Fibrillation] explode all trees #2 MeSH descriptor: [Atrial Flutter] explode all trees #3 MeSH descriptor: [Venous Thrombosis] explode all trees #4 MeSH descriptor: [Pulmonary Embolism] explode all trees #5 MeSH descriptor: [Venous Thromboembolism] explode all trees #6 MeSH descriptor: [Embolism and Thrombosis] explode all trees

(continued)

Table SI. (continued).

Sources	Search strategies
	#7 #1 or #2 or #3 or #4 or #4 or #5 or #6 or 'heart atrium flutter' or 'vein thrombosis' or 'venous thromboembolism' or 'atrial fibrillation' or 'atrial flutter' or 'af' or 'non-valvular atrial fibrillation' or 'non valvular atrial fibrillation' or 'nvaf' or 'auricular fibrillation' or 'auricular fibrillations' or 'atrial fibrillations' or 'atrial flutters' or 'non-valvular atrial fibrillations' or 'non valvular atrial fibrillations' or 'deep vein thrombosis' or 'deep vein thromboses' or 'deep venous thrombosis' or 'deep venous thromboses' or 'dvt' or 'thrombosis' or 'thromboses' or 'thromboembolism' or 'vte' or 'pulmonary embolism' or 'pe' or 'lung embolism' or 'pulmonary thromboembolism' or 'pulmonary thromboembolisms' #8 MeSH descriptor: [Blood Coagulation Factor Inhibitors] explode all trees #9 MeSH descriptor: [Anticoagulants] explode all trees #10 MeSH descriptor: [Antithrombins] explode all trees #11 MeSH descriptor: [Factor Xa Inhibitors] explode all trees #12 #8 or #9 or #10 or #11 or 'blood clotting factor 10a inhibitor' or 'dabigatran' or 'dabigatran etexilate' or 'rivaroxaban' or 'apixaban' or 'edoxaban' or pradaxa or pradax or pradaxar or prazaxa or rendix or xarelto or eliquis or savaysa or lixiana or 'target-specific oral anticoagulants' or 'target specific oral anticoagulants' or tsoacs or tsoac or 'new oral anticoagulants' or 'new oral anticoagulant' or 'novel oral anticoagulants' or 'novel oral anticoagulant' or noacs or noac or 'direct oral anticoagulants' or 'direct oral anticoagulant' or doacs or doac or 'antithrombin' or 'anticoagulant' or 'anticoagulants' or 'factor xa inhibitor' #13 MeSH descriptor: [Warfarin] explode all trees #14 MeSH descriptor: [Coumarins] explode all trees #15 MeSH descriptor: [Acenocoumarol] explode all trees #16 MeSH descriptor: [Phenprocoumon] explode all trees #17 MeSH descriptor: [Phenindione] explode all trees #18 #13 OR #14 OR #15 OR #16 OR #17 OR warfarin OR coumadin OR 'courmarin anticoagulant' OR 'vitamin k antagonist' OR 'antivitamin k' OR phenprocoumon OR phenprocumon OR acenocumarol OR acenocoumarol OR fluindione OR phenindione OR anisindione #19 #7 AND #12 AND #18