Supplementary Online Content

Sun MT, Wood MK, Chan WO, et al. Risk of intraocular bleeding with novel oral anticoagulants compared with warfarin: a systematic review and meta-analysis. *JAMA Ophthalmol*. Published online July 6, 2017. doi:10.1001/jamaophthalmol.2017.2199

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6-7 + Supplement
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7 + Supplement
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7 + Supplement
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7 + Supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7 + Supplement
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from	6-7 + Supplement

		investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7 + Supplement
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8 + Supplement
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8 + Supplement
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8 + Supplement

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8 + Supplement
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8 + Supplement
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9+10+ Figures + Supplement
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9+10+ Figures + Supplement
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9+10+ Figures + Supplement
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9+10+ Figures + Supplement
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9+10+ Figures + Supplement

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9+10+ Figures + Supplement
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9+10+ Figures + Supplement
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

eTable 2. Risk of Bias Summary
Study – EINSTEIN-DVT

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: In both studies, patients were randomly assigned to a study group with the use of a computerized voice–response system, with stratification by country.
Allocation concealment (selection bias)	Low risk	Quote: In both studies, patients were randomly assigned to a study group with the use of a computerized voice–response system, with stratification by country.
Blinding of participants and personnel (performance bias)	High risk	Quote: open-label trial Comment: Authors comment this may have led to diagnostic-suspicion bias. The number of patients with suspected events was higher in the rivaroxaban group suggesting the bias may have been against this group. Either way as the study relied on patients reporting symptoms the patients' knowledge of which treatment they are receiving may have introduced bias wither way.
Blinding of outcome assessment (detection bias)	Low risk	Quote: All suspected outcome events were classified by a central adjudication committee whose members were unaware of the treatment assignments.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: For both studies, the primary efficacy analysis was performed on an intention-to-treat basis. Comment: 11.3% and 14.2% in the rivaroxaban and standard treatment groups prematurely discontinued treatment. There is statistically significant difference between these figures.
Selective reporting (reporting bias)	Low risk	Comment: Study protocol available, outcomes pre-specified
Other		Quote: Sponsored by Bayer Schering Pharma and Ortho-McNeil.

Study – AMPLIFY

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Randomization was performed with the use of an interactive voice-response system and was stratified according to the qualifying diagnosis

Allocation concealment (selection bias)	Low risk	Quote: Randomization was performed with the use of an interactive voice-response system and was stratified according to the qualifying diagnosis
Blinding of participants and personnel (performance bias)	Low risk	Quote: Double-Blinded. Patients were assigned to receive apixaban tablets plus placebo enoxaparin injections and placebo warfarin tablets or conventional therapy with enoxaparin injections and warfarin tablets plus placebo apixaban tablets. The study used blinded INR monitoring with a point-of-care device that generated an encrypted code for INR results. Comment: Considerable effort to ensure blinding of both participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	Quote: An independent committee, whose members were unaware of the study-group assignments, adjudicated the qualifying diagnosis, the anatomical extent of the initial deep-vein thrombosis or pulmonary embolism, and all suspected outcomes.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: All efficacy analyses included data for patients in the intention-to-treat population Comment: 377 (14.0%) and 413 (15.3%) participants discontinued the study prematurely in the apixaban and conventional therapy groups respectively.
Selective reporting (reporting bias)	Low risk	Comment: Study protocol available, outcomes pre-specified
Other		Quote: The trial was sponsored by Bristol-Myers Squibb and Pfizer.

STUDY – HOKUSAI-VTE

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Randomization was performed with the use of an interactive Web-based system, with stratification
Allocation concealment (selection bias)	Low risk	Quote: Randomization was performed with the use of an interactive Web-based system, with stratification
Blinding of participants and personnel (performance bias)	Low risk	Quote: Edoxaban or warfarin was administered in a double-blind, double-dummy fashion. All measurements were performed by means of a point-of-care device that provided an actual INR value for patients receiving warfarin and a sham INR value for

		patients receiving Edoxaban.
Blinding of outcome assessment (detection bias)	Low risk	Quote: An independent committee, whose members were unaware of the study-group assignments, adjudicated all suspected outcomes and the results of baseline imaging tests and assessed the anatomical extent of thrombosis.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: All efficacy analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization and received at least one dose of the study drug. Comment: 181 (4.4%) from Edoxaban and 167 (4.1%) from warfarin group failed to complete study. Similar and low numbers from both groups.
Selective reporting (reporting bias)	Low risk	Comment: Protocol available online with predefined outcomes.
Other		Quote: Supported by Daiichi-Sankyo.

Study: EINSTEIN-PE

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Randomization was performed with the use of a computerized voice-response system and was stratified
Allocation concealment (selection bias)	Low risk	Quote: Randomization was performed with the use of a computerized voice-response system
Blinding of participants and personnel (performance bias)	High risk	Quote: open-label trial Comment: Authors comment this may have led to diagnostic-suspicion bias. The number of patients with suspected events was higher in the rivaroxaban group suggesting the bias may have been against this group. Either way as the study relied on patients reporting symptoms the patients' knowledge of which treatment they are receiving may have introduced bias wither way.
Blinding of outcome assessment (detection bias)	Low risk	Quote: A central committee whose members were unaware of the study-group assignments adjudicated the results of all baseline lung-imaging tests and all suspected outcome events.
Incomplete outcome data	Low risk	Quote: The primary efficacy analysis was

addressed (attrition bias)		performed on an intention-to-treat basis. Comment: 10.7% and 12.3% in the rivaroxaban and standard therapy groups respectively prematurely discontinued treatment. No statistically significant difference between these figures.
Selective reporting (reporting bias)	Low risk	Comment: Study protocol available, outcomes pre-specified
Other		Quote: The trial was sponsored by Bayer Health- Care and Janssen Pharmaceuticals.

Study: J-ROCKET

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Central randomisation using Interactive Voice Response System stratified according to country, prior Warfarin use and history of prior stroke, TIA or non-CNS systemic embolism.
Allocation concealment (selection bias)	Low risk	Quote: Central randomisation using Interactive Voice Response System stratified according to country, prior Warfarin use and history of prior stroke, TIA or non-CNS systemic embolism.
Blinding of participants and personnel (performance bias)	Low risk	Quote: A double-blind, double-dummy design. patients in each group also received a tablet of either titrated warfarin placebo or rivaroxaban placebo, respectively, to preserve the treatment blind. INR monitoring procedures to maintain double-blinding are described.
Blinding of outcome assessment (detection bias)	Low risk	Quote: An independent clinical endpoint committee adjudicated all suspected strokes, systemic embolisms, myocardial infarctions (MIs), deaths, and bleeding events contributing to the prespecified endpoints.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: ITT population analyses included all randomized patients. Of the 1,280 randomized patients, 1,278 (639 in each group) received ≥1 dose of study medication and were included in the safety population, and 1,274 patients were included in the per-protocol population. Comment: Apparently small numbers (3 per group) of incomplete data.
Selective reporting	Low risk	Comment: Protocol not available however

(reporting bias)		apparently pre-defined outcomes appear as you would expect for this trial.
Other		Quote: The rivaroxaban clinical development program is co-sponsored by Janssen Pharmaceuticals, Inc (Raritan, NJ, USA) and Bayer HealthCare Pharmaceuticals AG (Leverkusen, Germany). The trial was funded by Bayer Healthcare Pharmaceuticals AG's Japanese subsidiary, Bayer Yakuhin Ltd.

Study: RECOVER II

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Patients were randomized by use of an interactive voice response system and a computer-generated randomization scheme in blocks of 4.
Allocation concealment (selection bias)	Low risk	Quote: Patients were randomized by use of an interactive voice response system and a computer-generated randomization scheme in blocks of 4.
Blinding of participants and personnel (performance bias)	Low risk	Comment: Initially single and then double dummy phase. Uses placebos and sham INR measurements.
Blinding of outcome assessment (detection bias)	Low risk	Quote: A central adjudication committee, the members of which were unaware of the treatment assignments, classified all suspected outcome events, bleeding events, and deaths.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: Modified intention to treat analysis. Comment: Study drug stopped before planned treatment completion in 14.6% of dabigatran group and 14.1% of warfarin group. Planned observation time for analysis was not completed in 9.8% of Dabigatran group and 9% of warfarin group. Similar size and reasons in both groups.
Selective reporting (reporting bias)	Low risk	Comment: Subgroups apparently predefined.
Other		Quote: The study was designed, conducted, and funded and the data were analyzed by Boehringer Ingelheim

Study: RECOVER

Entry	Judgement	Support

Random sequence generation (selection bias)	Low risk	Quote: We used a computer-generated randomization scheme with variable block sizes, stratified
Allocation concealment (selection bias)	Low risk	Quote: We used a computer-generated randomization scheme with variable block sizes, stratified. The treatment-group assignment was concealed from all the investigators and their staff at the coordinating center and the clinical centers and from the clinical monitors.
Blinding of participants and personnel (performance bias)	Low risk	Quote: Warfarin or a placebo that looked identical to warfarin (then). Administration of dabigatran or a placebo that looked identical to dabigatran was initiated, and the parenteral anticoagulant was stopped. Double Dummy. Comment: Also used sham INR monitoring.
Blinding of outcome assessment (detection bias)	Low risk	Quote: The treatment-group assignment was concealed from all the investigators and their staff at the coordinating center and the clinical centers and from the clinical monitors. All suspected outcome events and deaths were classified by central adjudication committees, whose members were unaware of the treatment assignments.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: We analyzed efficacy according to a modified intention-to-treat principle, since patients who did not receive any study drug were excluded from all analyses, as was prespecified in the protocol. Comment: The drug was stopped before 6 months in 16% of dabigatran and 14.5% of warfarin. Observation time was shorter than 6 months in 7.9% of dabigatran group and 7.7% of warfarin group. Similar reasons and size for missing data in both groups.
Selective reporting (reporting bias)	Low risk	Quote: All safety analyses and secondary efficacy analyses were predefined.
Other		Quote: Supported by Boehringer Ingelheim.

STUDY – ROCKET-AF

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Randomization was performed with the use of a central 24-hour, computerized, automated voice-response system.
Allocation concealment (selection bias)	Low risk	Quote: Randomization was performed with the use of a central 24-hour, computerized,

		automated voice-response system.
Blinding of participants and personnel (performance bias)	Low risk	Quote: Double-blind trial. Patients in each group also received a placebo tablet in order to maintain blinding. Sham INR results were generated.
Blinding of outcome assessment (detection bias)	Low risk	Quote: An independent clinical end-point committee applied protocol definitions to adjudicate all suspected cases of stroke, systemic embolism, myocardial infarction, death, and bleeding events that contributed to the prespecified end points.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: Testing for noninferiority and superiority was also performed in the intention-to-treat population. The proportions of patients who permanently stopped their assigned therapy before an end-point event and before the termination date were 23.7% in the rivaroxaban group and 22.2% in the warfarin group. Only 32 patients were lost to follow up. Comment: 2 groups of patients were excluded from the analysis due to violations in good clinical practise and issues with data quality.
Selective reporting (reporting bias)	Low risk	Comment: Protocol available with predefined outcomes
Other		The study was supported by Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare.

Study: RE-LY

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: The patients were randomized by a central randomization service, through an interactive voice response system (IVRS)
Allocation concealment (selection bias)	Low risk	Quote: The patients were randomized by a central randomization service, through an interactive voice response system (IVRS)
Blinding of participants and personnel (performance bias)	High risk	Quote: Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug. Warfarin was administered in an unblended fashion. The use of open-label warfarin could have introduced a bias in the reporting or adjudication of events. This risk was reduced by the implementation of several validated procedures, including blinded evaluation of

		outcome events. The unexpectedly different rates of myocardial infarction and gastrointestinal bleeding among the three treatment groups support an absence of bias Comment: As some of the outcomes rely on patient reported symptoms this may have introduced performance bias as patients may underreport symptoms on dabigatran in attempt to please the investigators for example..
Blinding of outcome assessment (detection bias)	Low risk	Quote: Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: All analyses were based on the intention-to-treat principle. Complete follow-up was achieved in 99.9% of patients, with 20 patients lost to follow-up. The rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively, at 1 year and 20.7%, 21.2%, and 16.6% at 2 years.
Selective reporting (reporting bias)	Low risk	Comment: Protocol published ahead of results with predefined outcomes
Other		Quote: The study was funded by Boehringer Ingelheim

STUDY – RE-MEDY

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Patients underwent randomization by means of an interactive voice-response system.
Allocation concealment (selection bias)	Low risk	Quote: Patients underwent randomization by means of an interactive voice-response system.
Blinding of participants and personnel (performance bias)	Low risk	Quote: patients were assigned in a 1:1 ratio to receive active dabigatran and a warfarin-like placebo or active warfarin and a dabigatran-like placebo. True or sham INR was then obtained by means of an interactive voice-response system with a central computer that had been programmed with the randomization schedule.
Blinding of outcome assessment (detection bias)	Low risk	Quote: Central committees, whose members were not aware of the treatment assignments, adjudicated suspected cases of recurrent

		venous thromboembolism, bleeding, death, acute coronary events (as well as cerebrovascular events in the placebo-control study), and liver function abnormalities (according to clinical and routine laboratory data).
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: In both trials, a modified intention-to-treat analysis was performed for efficacy, with exclusion of patients who did not receive any dose of the study drug. In the active-control study, the study drug was stopped early in 276 patients (19.3%) in the dabigatran group (in 147 because of an adverse event, 23 because of nonadherence, 2 because of loss to follow-up, 64 because of their decision to stop taking the study medication, and 40 for other reasons) and in 281 patients (19.7%) in the warfarin group (in 129 because of an adverse event, 34 because of nonadherence, 6 because of loss to follow-up, 58 because of their decision to stop taking the study medication, and 54 for other reasons). Comment: Similar numbers in missing data for both groups.
Selective reporting (reporting bias)	Low risk	Comment: Trial protocol available online with predefined outcomes.
Other		Quote: Both studies were funded, designed, and conducted, and the data analyzed, by Boehringer Ingelheim in conjunction with the steering committee.

Study: ARISTOTLE

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Randomization is stratified by investigative site and prior warfarin use status. Randomisation performed using Interactive Voice Response System with randomization schedules generated centrally. (per study protocol supplement)
Allocation concealment (selection bias)	Low risk	Quote: Randomization is stratified by investigative site and prior warfarin use status. Randomisation performed using Interactive Voice Response System with randomization

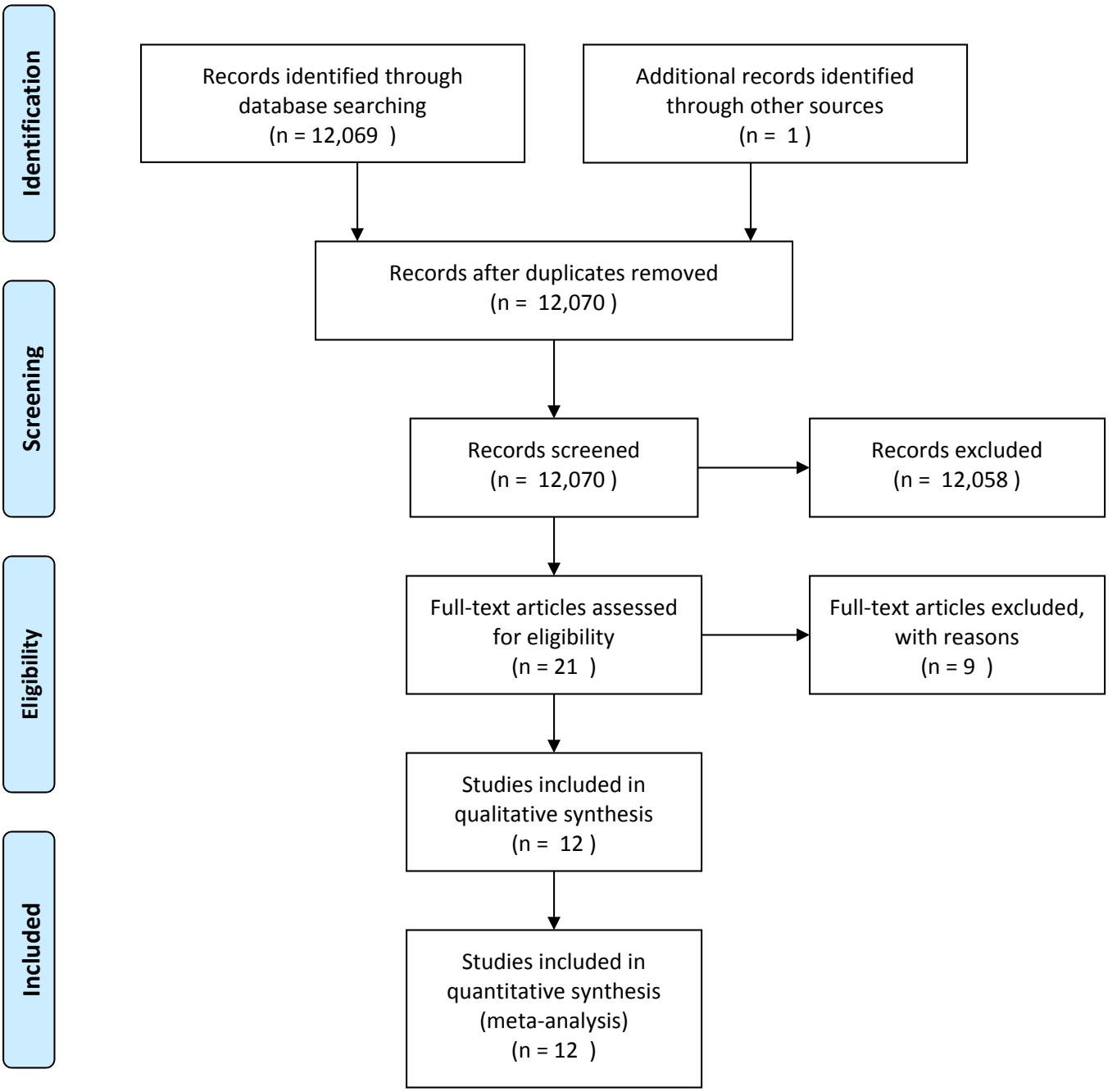
		schedules generated centrally. (per study protocol supplement)
Blinding of participants and personnel (performance bias)	Low risk	Quote: Double-blind trial. To maintain blinding, study medications are packaged using a double-dummy design. Subjects, investigators, members of the steering and adjudication committees, and the sponsor's staff conducting the study do not have access to individual subject treatment assignments.
Blinding of outcome assessment (detection bias)	Low risk	Quote: An independent, blinded, clinical events committee (CEC) adjudicates all suspected hemorrhagic and non-hemorrhagic strokes, TIAs, systemic emboli, major and clinically relevant non-major bleeding, myocardial infarction, and cause of death.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: Data on vital status at the end of the trial were missing for 380 patients (2.1%). The absence of data on vital status was due to withdrawal of consent in the case of 92 patients in the apixaban group (1.0%) and 107 patients in the warfarin group (1.2%) and was due to loss to follow-up in the case of 35 patients in the apixaban group (0.4%) and 34 in the warfarin group (0.4%). Comment: Similar and small number of incomplete data in both groups
Selective reporting (reporting bias)	Low risk	Comment: Trial protocol available predefined outcomes
Other		Quote: sponsors (Bristol-Myers Squibb and Pfizer)

Study: ENGAGE-AF

Entry	Judgement	Support
Random sequence generation (selection bias)	Low risk	Quote: Randomization was performed with the use of a central, 24-hour, interactive, computerized response system
Allocation concealment (selection bias)	Low risk	Quote: Randomization was performed with the use of a central, 24-hour, interactive, computerized response system
Blinding of participants and personnel (performance bias)	Low risk	Quote: Double Dummy. Each patient received two sets of study drugs: either active edoxaban and a placebo matching warfarin, or a placebo matching edoxaban and active warfarin. To maintain blinding, sham INR values were generated.

Blinding of outcome assessment (detection bias)	Low risk	Quote: An independent clinical end-point committee, whose members were unaware of the study assignment, adjudicated all deaths and suspected cerebrovascular events, systemic embolic events, myocardial infarctions, bleeding events, and hepatic events.
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: Analysis included data from patients who underwent randomization and received at least one dose of the study drug during the treatment period (modified intention- to-treat population). The very low rate of missing data (0.5%) underscores the robustness of these observations Comment: Similar numbers lost to follow up in 3 groups (63, 61 and 68)(0.9%, 0.9% and 1%)
Selective reporting (reporting bias)	Low risk	Comment: Protocol available online – predefined clinical endpoints
Other		Quote: Supported by Daiichi Sankyo Pharma Development.

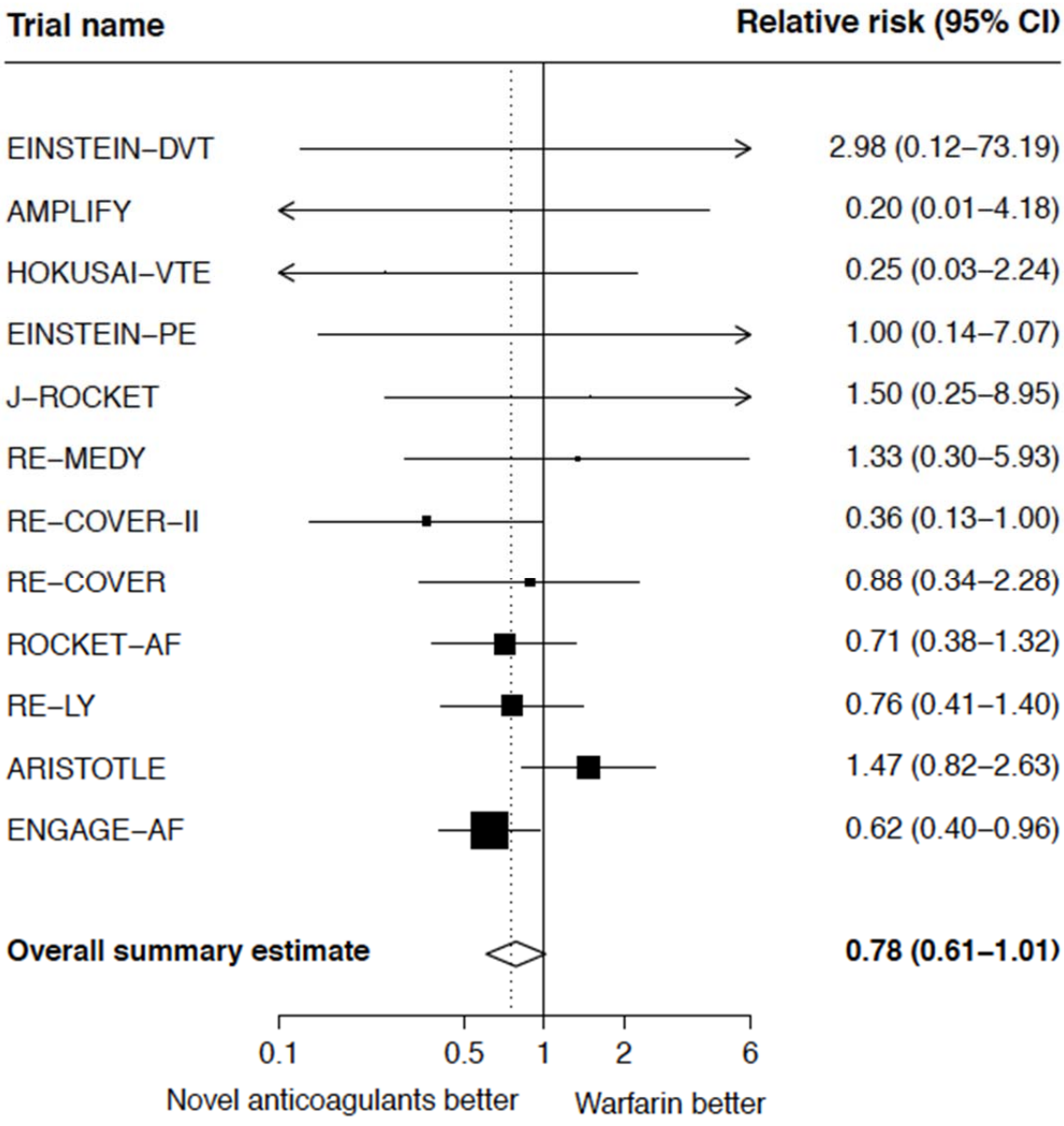
eFigure 1. PRISMA Flow Diagram



eFigure 2. Risk of Bias Graph

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
EINSTEIN-DVT	+	+	-	+	+	+	+
AMPLIFLY	+	+	+	+	+	+	+
HOKUSAI-VTE	+	+	+	+	+	+	+
EINSTEIN-PE	+	+	-	+	+	+	+
J-ROCKET	+	+	+	+	+	+	+
RE-COVER-II	+	+	+	+	+	+	+
RE-COVER	+	+	+	+	+	+	+
ROCKET-AF	+	+	+	+	+	+	+
RE-LY	+	+	-	+	+	+	+
RE-MEDY	+	+	+	+	+	+	+
ARISTOTOLE	+	+	+	+	+	+	+
ENGAGE-AF	+	+	+	+	+	+	+

eFigure 3. Risk of Intraocular Bleeding in Trials of Novel Anticoagulants Compared to Warfarin Therapy With Random Effects Meta-Analysis



eFigure 4. Subgroup Analyses According to Indication and Type of Novel Anticoagulant With Random Effects Meta-Analysis