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DIPLOMA THESIS :

TITLE:

ASSESS THE REPORTING QUALITY OF META-ANALYSES OF RANDOMIZED-CONTROLLED TRIALS EXPLORING THE EFFICACY AND SAFETY OF THE NEW ANTICOAGULANTS VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION,BASED ON PRISMA STATEMENT.

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ABSTRACT:

Introduction: Over the last decade there has been a number of guidelines published, aimed at improving the quality of reporting in published studies and reviews. In systematic reviews and meta-analyses this may be measured by their compliance with the PRISMA statement.

Aims: Our aim is to assess the reporting quality of meta-analyses of randomized-controlled trials exploring the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation, using the prisma checklist.

Methods: A search was performed on MEDLINE and EMBASE databases. The meta-analyses that we found were assessed with the prisma checklist, where each checklist item was scored with 1 point. The meta-analysis which received the most points was assessed as the best and most complete.

Results: Five meta-analyses were pooled, which were all eligible according to their title and abstract. The assessment of these meta-analyses was performed with the prisma checklist and each checklist item was scored with 1 point. Compliance with the PRISMA statement was generally good. Meta-analyses No2 and 5 received the most points (24). Meta-analyses No1 and 4 received 23 points and meta-analysis No3 received two points (though its assessment was not complete as we were not able to have access to the full text).

Conclusion: Meta-analyses No 2 and 5 are the most complete in terms of the prisma checklist assessment. However, there were not big differences in the scores that all meta-analyses received. All scores were high. This indicates that the meta-analyses of randomized-controlled trials exploring the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation have a good reporting quality.

INTRODUCTION:

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an overall prevalence of 5.5% that increases up to 17.8% in individuals 85 years of age. AF is a major risk factor for stroke, with a 30-day mortality rate of 24% in the absence of treatment. Vitamin K antagonists (VKAs) are highly effective for the prevention of stroke, mainly of ischemic origin, in patients with AF, resulting in a 64% risk reduction

compared with placebo and a 37% risk reduction compared with antiplatelet therapy. For this reason, VKAs are currently recommended in all AF patients at moderate to high risk for stroke or systemic embolism (SE). However, VKAs have significant limitations, particularly their unpredictable anticoagulant response and numerous food and drug interactions, mandating regular laboratory monitoring. These limitations make treatment with VKAs problematic for many patients; as a result, only about half of all potentially eligible AF patients are treated with VKAs. Over the last several years, novel oral anticoagulant drugs (NOACs), including direct thrombin inhibitors and factor Xa inhibitors, have been developed. These drugs have the potential to address some of the limitations of VKAs. These agents have fewer food and drug interactions and a more predictable anticoagulant effect, thus allowing fixed dosing without the need for laboratory monitoring. Furthermore, their shorter half-life may produce additional advantages, eg, if temporary interruption is required for a surgical procedure or in the case of an hemorrhagic complication.

There are meta-analyses of randomized-controlled trials, which explore the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation. In order to assess the reporting quality of these meta-analyses, we are going to use the PRISMA statement. The aim of the PRISMA Statement is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses. The 27 checklist items pertain to the content of a systematic review and meta-analysis, which include the title, abstract, methods, results, discussion and funding.

Methods:

We performed a search in the databases MEDLINE and EMBASE using the following search string :“atrial fibrillation AND warfarin AND (apixaban OR dabigatran OR edoxaban OR rivaroxaban OR ximelagatran) AND meta-analyses”. Five meta-analyses were pooled, which were all eligible according to their title and abstract. The quality of the reporting of the included meta-analyses was assessed according to the level of compliance with the PRISMA guidelines. These guidelines incorporate 27 items pertaining to each section of the review, including title, abstract, introduction, methods, results, discussion, conclusion, and funding. Each checklist item was scored with 1 point. The meta-analysis which received the most points was assessed as the best and most complete.

Results:

Meta-analysis No1:

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doi: 10.1097/FJC.0000000000000129
Original Article

Meta-analysis of Efficacy and Safety of the New Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation

Prisma Checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. Meta-analysis of Efficacy and Safety of the New Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation	368
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. Objective: To assess the efficacy and safety of the new oral anticoagulants versus warfarin in patients with atrial fibrillation by the meta-analyses performed for 5 studies ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, ROCKET-AF, and J-ROCKET. Methods: The events including primary efficacy endpoint (stroke and systemic embolism), ischemic stroke, hemorrhagic stroke, all-cause mortality, and myocardial infarction were used for efficacy analysis and those including major bleeding, intracranial hemorrhage, and gastrointestinal bleeding were used for safety analysis. Instead of combining both doses to 1 meta-analysis, the high-dose groups of RE-LY (150 mg twice daily) and ENGAGE AF-TIMI 48 (60 mg twice daily) were combined with the single dose studies ARISTOTLE, ROCKET-AF, and J-ROCKET. A separate meta-analysis was done for the low-dose groups of RE-LY	368

		(110 mg twice daily) and ENGAGE AF-TIMI 48 (30 mg twice daily). Results: The high-dose regimen had better performance than low dose in efficacy. In addition, low-dose regimen demonstrated to significantly reduce the risk of hemorrhagic stroke, all-cause mortality, and intracranial hemorrhage. Conclusions: The new oral anticoagulants demonstrated promising alternatives to warfarin in prevention of stroke in patients with atrial fibrillation.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Atrial fibrillation (AF) is a kind of arrhythmia, and there are about 8 million patients with AF in China, 2.2 million in the United States and 4.5 million in Europe Union.[1] It is known that AF is one of the independent risk factors for stroke and might increase its risk by up to 5-fold. The AF-related strokes are associated with higher risk of mortality and morbidity than non-AF strokes.[2] For a half-century, clinicians have prescribed aspirin or vitamin K antagonist (most commonly warfarin) for the patients with AF. Warfarin is always a preferred option to prevent stroke or systemic embolism events.[3,4]Although with the proven efficacy, its use is limited by some drawbacks including the narrow therapeutic window requiring frequent international normalized ratio (INR) monitoring and a high risk of bleeding.[5,6]	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). Therefore, as a result, some new oral anticoagulants (NOACs) inhibiting either activated factor X (factor Xa) or thrombin have been developed to provide a more promising option.[7,8] The 4 large phase III randomized controlled trials (RCTs) RE-LY (Dabigatran randomized evaluation of long-term anticoagulant therapy), 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), ARISTOTLE (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation), and ENGAGE AF-TIMI 48 (Edoxaban once daily to prevent stroke or systemic embolism)[9] have separately examined the long-term effect of NOACs compared with warfarin to prevent stroke and systemic embolism in patients with AF. Although these NOACs have been proved more efficacious than	

		warfarin for the primary efficacy endpoint of stroke and systemic embolism, the conclusion for the secondary efficacy endpoints and safety endpoints are heterogeneous.[10,11] Therefore, it is important to comprehensively compare efficacy and safety of NOACs versus warfarin in the patients with AF. Several meta-analyses for NOACs versus warfarin[12,13] have been published, but these publications included only 3 phase 3 studies: RE-LY, ROCKET-AF, and ARISTOTLE. In this article, except the above 3 studies, we added 22,385 patients by including J-ROCKET AF (Rivaroxaban Clinical Trial in Japan),[14] and ENGAGE AF-TIMI 48 published recently. This allowed us to perform a more comprehensive comparative analysis of NOACs versus warfarin. Moreover, different from previous analyses, we performed separate meta-analyses for the high-dose groups of RE-LY (150 mg twice daily) and ENGAGE AF-TIMI 48 (60 mg twice daily) combined with the single dose studies ARISTOTLE, ROCKET-AF, and J-ROCKET AF and the low-dose groups of RE-LY (110 mg twice daily) and ENGAGE AF-TIMI 48 (30 mg twice daily), respectively. This will not merge the benefit and risk of different doses. Although with a reduced INR target level of 1.6–2.6 in J-ROCKET AF than the regular therapeutic range 2.0–3.0,[15] the design was similar and the results were consistent with those of ROCKET AF for the primary efficacy endpoint, principal safety outcome, and major bleeding. Therefore, to include J-ROCKET AF in the meta-analysis would not introduce bias.	
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. We systematically searched the publications of RCTs comparing NOACs to warfarin in patients with AF from the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest in December 2013. The keywords or medical terms included "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "DABIGATRAN," "RIVAROXABAN," "APIXABAN," "EDOXABAN," "BETRIXABAN," "YM-150," "RE-LY," "LY-517717," "ENGAGE AF-TIMI 48," and "WARFARIN." We only searched clinical trials from the Embase and MEDLINE. The Science Citation Index Expanded and ProQuest searches were limited to the reports with full-text available. In addition, we manually searched the clinical databases such as the website of ClinicalTrials, related review, and reports for further eligible studies. Two authors selected the studies independently, and the disagreements were resolved by discussion among all the authors.	
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. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of RCTs was used for this analysis.[16] The criteria for studies included in our analysis were as following: (1) they were RCTs between NOACs and warfarin, (2) all the patients were randomized to warfarin or NOACs, and (3) the target population was the patients with AF. Except double-blinded, the open-label studies were also included in the search because of the need of frequent INR monitoring for warfarin. The data extracted from these studies included patients' age, median follow-up time, mean $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, biabetes mellitus, stroke (doubled)] scores,[17] gender, mean time in the therapeutic range of warfarin, and some specific medical history. For all the included studies, the primary efficacy endpoint was composite of stroke and systemic embolism. The secondary efficacy endpoints included ischemic stroke, hemorrhagic stroke, all-cause mortality, and myocardial infraction. For safety evaluation, the main endpoint was major bleeding defined as fatal bleeding or bleeding in a critical site, and the	

		secondary endpoint included gastrointestinal and intracranial bleeding. We only considered the studies approved or in development so the studies for ximelagatran, which had been withdrawn,[18] and studies for darexaban, which is no longer in development[19] were excluded from our analysis.	
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. We systematically searched the publications of RCTs comparing NOACs to warfarin in patients with AF from the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest in December 2013. The keywords or medical terms included "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "DABIGATRAN," "RIVAROXABAN," "APIXABAN," "EDOXABAN," "BETRIXABAN," "YM-150," "RE-LY," "LY-517717," "ENGAGE AF-TIMI 48," and "WARFARIN." We only searched clinical trials from the Embase and MEDLINE. The Science Citation Index Expanded and ProQuest searches were limited to the reports with full-text available. In addition, we manually searched the clinical databases such as the website of ClinicalTrials, related review, and reports for further eligible studies. Two authors selected the studies independently, and the disagreements were resolved by discussion among all the authors.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. We systematically searched the publications of RCTs comparing NOACs to warfarin in patients with AF from the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest in December 2013. The keywords or medical terms included "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "DABIGATRAN," "RIVAROXABAN," "APIXABAN," "EDOXABAN," "BETRIXABAN," "YM-150," "RE-LY," "LY-517717," "ENGAGE AF-TIMI 48," and "WARFARIN." We only searched clinical trials from the Embase and MEDLINE. The Science Citation Index Expanded and ProQuest searches were limited to the reports with full-text available. In addition, we manually searched the clinical databases such as the website of ClinicalTrials, related review, and reports for further eligible studies. Two authors selected the studies independently, and the disagreements were resolved by discussion among all the authors.	

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). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses of RCTs was used for this analysis.[16] The criteria for studies included in our analysis were as following: (1) they were RCTs between NOACs and warfarin, (2) all the patients were randomized to warfarin or NOACs, and (3) the target population was the patients with AF. Except double-blinded, the open-label studies were also included in the search because of the need of frequent INR monitoring for warfarin. The data extracted from these studies included patients' age, median follow-up time, mean $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, biabetes mellitus, stroke (doubled)] scores,[17] gender, mean time in the therapeutic range of warfarin, and some specific medical history. For all the included studies, the primary efficacy endpoint was composite of stroke and systemic embolism. The secondary efficacy endpoints included ischemic stroke, hemorrhagic stroke, all-cause mortality, and myocardial infraction. For safety evaluation, the main endpoint was major bleeding defined as fatal bleeding or bleeding in a critical site, and the secondary endpoint included gastrointestinal and intracranial bleeding. We only considered the studies approved or in development so the studies for ximelagatran, which had been withdrawn,[18] and studies for darexaban, which is no longer in development[19] were excluded from our analysis. The Cochrane Collaboration's tool was used to conduct quality assessment to risk of bias.[20] It evaluated bias in a RCT within the following domains: sequence generation; allocation concealment; blinding of participants, personal, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. In each domain, the risk of bias was classified into high, low, or unclear for each RCT.	

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 investigators. We systematically searched the publications of RCTs comparing NOACs to warfarin in patients with AF from the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest in December 2013. The keywords or medical terms included "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "DABIGATRAN," "RIVAROXABAN," "APIXABAN," "EDOXABAN," "BETRIXABAN," "YM-150," "RE-LY," "LY-517717," "ENGAGE AF-TIMI 48," and "WARFARIN." We only searched clinical trials from the Embase and MEDLINE. The Science Citation Index Expanded and ProQuest searches were limited to the reports with full-text available. In addition, we manually searched the clinical databases such as the website of ClinicalTrials, related review, and reports for further eligible studies. Two authors selected the studies independently, and the disagreements were resolved by discussion among all the authors.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. We systematically searched the publications of RCTs comparing NOACs to warfarin in patients with AF from the Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest in December 2013. The keywords or medical terms included "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "DABIGATRAN," "RIVAROXABAN," "APIXABAN," "EDOXABAN," "BETRIXABAN," "YM-150," "RE-LY," "LY-517717," "ENGAGE AF-TIMI 48," and "WARFARIN." We only searched clinical trials from the Embase and MEDLINE. The Science Citation Index Expanded and ProQuest searches were limited to the reports with full-text available. In addition, we manually searched the clinical databases such as the website of ClinicalTrials, related review, and reports for further eligible studies. Two authors selected the studies independently, and the disagreements were resolved by discussion among all the authors.	

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. The Cochrane Collaboration's tool was used to conduct quality assessment to risk of bias.[20] It evaluated bias in a RCT within the following domains: sequence generation; allocation concealment; blinding of participants, personal, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. In each domain, the risk of bias was classified into high, low, or unclear for each RCT.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Based on the random-effects model by DerSimonian and Laird,[21] we calculated the pooled relative risks (RRs) and their corresponding 95% confidence intervals (CIs).	
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. The presence of between-study variability was assessed by the Q statistic ($P < 0.10$ was used as indicator of statistically significant result), and the proportion of heterogeneity was assessed by the I^2 index. All the analyses were conducted in statistical software Stata 11.0 (StataCorp LP, College Station, TX).	

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). The Cochrane Collaboration's tool was used to conduct quality assessment to risk of bias.[20] It evaluated bias in a RCT within the following domains: sequence generation; allocation concealment; blinding of participants, personal, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. In each domain, the risk of bias was classified into high, low, or unclear for each RCT.	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
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. Eight hundred nine publications were identified though database search (Fig. 1). By study selection process, the 5 studies from 56 publications (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, ROCKET-AF, and J-ROCKET) assessing the efficacy and safety of NOACs compared with warfarin in patients with AF were evaluated for eligibility. The primary objective was to determine whether the new drug was noninferior to warfarin about the composite of stroke and systemic embolism.	

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. Forty-three thousand fifty patients received NOACs and 29,911 received warfarin. Baseline characteristics of the populations are listed in Table 1. The average age and proportion of female were similar between NOACs and warfarin groups among the 5 studies. The underlying risk for stroke indicated by the proportion of patients with $CHADS_2$ was significantly different across studies. It can be observed the studies ENGAGE AF-TIMI 48, ROCKET-AF, and J-ROCKET enrolled more patients with higher risk of stroke than ARISTOTLE and RE-LY. The median follow-up time in all studies ranged from 1.6 to 2.8 years, and the median time in therapeutic range of patients assigned to warfarin ranged from 44% to 68%.	
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). The risk of bias was assessed by Cochrane Collaboration's tool. In RE-LY, dabigatran was administered in a blinded fashion, whereas warfarin was administered in an unblinded fashion to locally adjust INR within the therapeutic range 2.0–3.0. However, all the investigators, coordinating center members, the steering committee, and the sponsor were kept blinded during event ascertainment and analyses process.[22] Therefore, the risk of bias due to blind was low for RE-LY. For ROCKET-AF, the efficacy was analyzed based on intention-to-treat and bleeding on safety analysis data sets (1 site including 93 patients was excluded due to good clinical practice violation).[10] This should not introduce additional selection bias.	
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. For the high-dose regimen analysis, NOACs demonstrated noninferior to warfarin in the prevention of stroke and systemic embolism in each study. NOACs further demonstrated superior to warfarin at the above endpoint in ARISTOTLE and RE-LY (Fig. 2). In respect to the major bleeding prevention, NOACs showed superiority to warfarin in ARISTOTLE and ENGAGE AF-TIMI 48, whereas other studies showed comparable risk of major bleeding (Fig. 3). The pooled risk of stroke and systemic embolism in the patients randomized to NOACs was 20% lower (RR = 0.80; 95% CI, 0.71–0.91) than those randomized to warfarin. This	

		benefit was mostly driven by the large reduction of hemorrhagic stroke (RR = 0.50; 95% CI, 0.41–0.62) and the reduction of all-cause mortality (RR = 0.90; 95% CI, 0.85–0.95). For safety, the pooled risk of major bleeding events in the patients randomized to NOACs was reduced by 14% (RR = 0.86; 95% CI, 0.74–0.99) compared with the risk of those on warfarin because of the large reduction of intracranial hemorrhage (RR = 0.48; 95% CI, 0.41–0.56) (Fig. 4). For the low-dose regimen meta-analysis, NOACs demonstrated similar efficacy to warfarin for prevention of stroke and systemic embolism in each study. The similar conclusion was drawn for the pooled group (RR = 1.03; 95% CI, 0.84–1.27). If differentiated by stroke types, the large reduction in the risk of hemorrhagic stroke (RR = 0.33; 95% CI, 0.23–0.46) was offset by the increase in ischemic stroke (RR = 1.31; 95% CI, 1.14–1.49). For low-dose regimens, there was also a reduction in the risk of all-cause mortality (RR = 0.89; 95% CI, 0.83–0.96) but a higher risk of myocardial infarction (RR = 1.25; 95% CI, 1.04–1.50). For safety, although with the significant difference for the risk of major bleeding events in each study, the pooled RR of NOACs compared with warfarin (RR = 0.63; 95% CI, 0.38–1.04) was inconclusive. When differentiated by bleeding types, there was a large risk of decrease in intracranial hemorrhage (RR = 0.31; 95% CI, 0.24–0.41) and also a risk of decrease in gastrointestinal bleeding (RR = 0.85; 95% CI, 0.72–1.00) (Fig. 5).	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. From the combined results of the high-dose and low-dose regimens, the inclusion of low-dose diminished the magnitude of risk reduction in stroke and systemic embolism (RR = 0.86; 95% CI, 0.75–0.99) by NOACs but resulting in lower risk of major bleeding events (RR = 0.78; 95% CI, 0.64–0.94).	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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). Based on the design of each study, in this article, we considered meta-analyses for high-dose regimen, low-dose regimen, and their combination. Five phase III RCTs including ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, ROCKET-AF, and J-ROCKET were included in our analysis. It was found that randomization to NOACs reduced the risk of stroke and systemic embolism compared with warfarin. This benefit was mainly driven by the substantial reduction of hemorrhagic stroke. Although as a part of the efficacy assessment of NOACs, hemorrhagic stroke is also a complication of anticoagulant treatment.[23] The rough half reduction in risk of hemorrhagic stroke by NOACs indicated the benefit of the treatment. NOACs were also found to be associated with lower risk of hemorrhagic stroke and all-cause mortality compared with warfarin. A lower risk in ischemic stroke (RR = 0.87; 95% CI, 0.77–0.99) between NOACs and warfarin was reported by Miller et al,[12] which was different from our inconclusive result. However, for the prevention of ischemic stroke, the NOAC is effective due to the reduction of the risk by two thirds compared with placebo.[5] The pooled risk of major bleeding events was similar between NOACs and warfarin. The combined results of efficacy and safety support use of the NOACs as alternatives to warfarin for long-term prevention in the patients with AF. The separate meta-analyses of the high-dose and low-dose regimens showed that the high-dose regimen has better performance than low dose in efficacy. Although with similar risks of stroke and systemic embolism and major bleeding events, low-dose regimen was found to significantly reduce the risk of hemorrhagic stroke, all-cause mortality, and intracranial hemorrhage. Consequently, the low-dose regimen could be an appealing option for the patients with high risk of bleeding with full-dose anticoagulation therapy. Warfarin has been underused due to concerns over the need of frequent INR monitoring and the risk of bleeding.[24] Only about a half of patients with AF received warfarin. Furthermore, the patients receiving it might have 30%–50% of time not within the therapeutic range 2.0–3.0. Therefore, the development of NOACs seems necessary. Moreover, there are already 2 compounds dabigatran and rivaroxaban approved by the US Food and Drug Administration.[25,26] It is necessary to compare them with warfarin on efficacy and safety by meta-analysis so that the informed clinical decisions can be made.	

		From the meta-analysis, we observed that the estimates are inconsistent across all the studies. We believe that these large phase III studies have enough power to evaluate the primary efficacy but may not have sufficient power to compare the secondary endpoints. Especially for the inconclusive results from individual study, they cannot always show us a real conclusion. One example is: the conclusive result for all-cause mortality is only benefited by apixaban and low-dose edoxaban. This also indicates the ability of meta-analysis in the assessment of the relative benefits of NOACs compared with warfarin. Another example is: different studies enrolled different proportions of patients with $CHADS_2$ scores. It would have been difficult to provide an overall description for NOACs compared with warfarin on their efficacy and safety without performing a meta-analysis. Actually, by working mechanisms, rivaroxaban, apixaban, and edoxaban should be factor Xa inhibitors, whereas dabigatran is the thrombin inhibitor. A sensitivity analysis was done by excluding dabigatran from the high-dose regimen. The risk of stroke and systemic embolism (RR = 0.85; 95% CI, 0.77–0.93) was similar but the risk of major bleeding (RR = 0.84; 95% CI, 0.69–1.01) became inconclusive. However, the 5 studies could be pooled together for below reasons: they are all phase 3 warfarin-controlled trials with similar designs, and they are NOACs by specific inhibitors of important factors in the coagulation cascade, and previous meta-analyses took a similar approach.[27]	
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). There were 2 potential limitations for our meta-analyses: First, the patients in clinical trials were often at lower risk of adverse events than those seen in routine clinical practice. This might affect the generalizability of the results based on the clinical trials.[28] Second, the patients taking warfarin in routine clinical practice often had less time of INR well-controlled in the therapeutic range.[29] This variability could not be applied to the NOACs in the meta-analysis.	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. In general, our meta-analyses have shown the balance between safety and efficacy of the NOACs compared with warfarin. NOACs demonstrated promising alternatives to warfarin in prevention of stroke in patients with AF.	
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.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: **www.prisma-statement.org**.

Meta-analysis No 2:

Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation

Prisma Checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation A Systematic Review and Meta-Analysis of the Literature	2381
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. **Background**—Novel oral anticoagulants (NOACs) have been proposed as alternatives to vitamin K antagonists for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Individually, NOACs were at least noninferior to vitamin K antagonists, but a clear superiority in overall and vascular mortality was not consistently proven. **Methods and Results**—We performed a meta-analysis of phase II and phase III randomized, controlled trials comparing NOACs with vitamin K antagonists in patients with atrial fibrillation. The MEDLINE and EMBASE databases, supplemented with conference abstract books and www.clinicaltrials.gov, were searched up to the first week of July 2012 with no language	2381

		restriction. Two reviewers performed independent article review and study quality assessment. Data on overall and cardiovascular mortality, stroke or systemic embolism, ischemic stroke, major and intracranial bleeding, and myocardial infarction were collected. NOACs were pooled to perform a comparison with vitamin K antagonists, calculating pooled relative risks (RRs) and associated 95% confidence intervals (CIs). We retrieved 12 studies (3 administering dabigatran, 4 administering rivaroxaban, 2 administering apixaban, and 3 administering edoxaban) enrolling a total of 54 875 patients. NOACs significantly reduced total mortality (5.61% versus 6.02%; RR, 0.89; 95% CI, 0.83–0.96), cardiovascular mortality (3.45% versus 3.65%; RR, 0.89; 95% CI, 0.82–0.98), and stroke/systemic embolism (2.40% versus 3.13%; RR, 0.77; 95% CI, 0.70–0.86). There was a trend toward reduced major bleeding (RR, 0.86; 95% CI, 0.72–1.02) with a significant reduction of intracranial hemorrhage (RR, 0.46; 95% CI, 0.39–0.56). No difference in myocardial infarction was observed. **Conclusions**—NOACs are associated with an overall clinical benefit compared with vitamin K antagonists. Additional research is required to confirm these findings outside the context of randomized trials.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an overall prevalence of 5.5% that increases up to 17.8% in individuals ≥85 years of age.[1] AF is a major risk factor for stroke,[2] with a 30-day mortality rate of 24% in the absence of treatment.[3] Clinical Perspective on p 2391 Vitamin K antagonists (VKAs) are highly effective for the prevention of stroke, mainly of ischemic origin, in patients with AF, resulting in a 64% risk reduction compared with placebo and a 37% risk reduction compared with antiplatelet therapy.[4] For this reason, VKAs are currently recommended in all AF patients at moderate to high risk for stroke or systemic embolism (SE).[5] However, VKAs have significant limitations, particularly their unpredictable anticoagulant response and numerous food and drug interactions, mandating regular laboratory monitoring.[6] These limitations make treatment with VKAs problematic for many patients; as a result, only about half of all potentially eligible AF patients are treated with VKAs.[6] Over the last several years, novel oral anticoagulant drugs (NOACs), including direct thrombin inhibitors and factor Xa inhibitors, have been developed. These drugs have the potential to address some of the limitations of VKAs.[7] These agents have fewer food and drug interactions and a more predictable anticoagulant effect, thus allowing fixed dosing without the need for laboratory	2381, 2382

		monitoring. Furthermore, their shorter half-life may produce additional advantages, eg, if temporary interruption is required for a surgical procedure or in the case of an hemorrhagic complication. The NOACs have been compared with warfarin for the prevention of stroke and SE in patients with AF.[8–10] These trials have been favorable for the NOACs but have not consistently demonstrated superiority over warfarin, particularly in terms of overall and vascular mortality.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). To better assess the clinical benefit, we carried out a systematic review of the literature and a meta-analysis of phase II and phase III randomized, clinical trials (RCTs) of these agents compared with VKAs for the prevention of stroke or SE in patients with AF.	2382
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. A protocol for this review was prospectively developed that detailed the specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods. This protocol is available for review through the investigators.	2382

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. Two reviewers (N.R. and F.D.) performed study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer (W.A.) if necessary. Studies were considered potentially eligible for this systematic review if they met the following criteria: They were phase III RCTs or phase II RCTs including at least one of the evaluated dosages subsequently used in phase III trials; NOACs were compared with therapeutic doses of VKAs in patients with AF; and thromboembolic and bleeding events were objectively assessed in both groups. For trials that were reported in >1 publication, we extracted data from the most complete publication and used other publications to clarify data. To assess the agreement between reviewers for study selection, we used the κ statistic, which measures agreement beyond chance.[11]	2382
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. We identified all published studies that compared the risk of thromboembolic and/or major bleeding (MB) events in AF patients randomized to VKAs (warfarin, phenprocoumon, acenocumarol, fluindione, and tecarfarin) or NOACs (dabigatran, AZD0837, sofigatran, rivaroxaban, apixaban, edoxaban, betrixaban, eribaxaban, LY517717, YM150, TAK442, and TTP889) using the MEDLINE (1966 to week 1 of July 2012) and the EMBASE (1980 to week 1 of July 2012) electronic databases. The term ximelagatran was excluded from the search because this drug has been withdrawn from the market	2382

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. The search strategy was developed without any language restriction and used the medical subject headings and text words presented in Table 1 in the online-only Data Supplement. We supplemented our search by reviewing abstracts books from the congresses of the International Society on Thrombosis and Haemostasis (2003–2011), European Society of Cardiology (2005–2011), American Society of Hematology (2004–2011), and American College of Cardiology (2008–2011) and by manually reviewing the reference lists of all retrieved articles. We also searched on the www.clinicaltrials.gov Web site to identify unpublished trials.	2382
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). Two reviewers (N.R. and F.D.) performed study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer (W.A.) if necessary. Studies were considered potentially eligible for this systematic review if they met the following criteria: They were phase III RCTs or phase II RCTs including at least one of the evaluated dosages subsequently used in phase III trials; NOACs were compared with therapeutic doses of VKAs in patients with AF; and thromboembolic and bleeding events were objectively assessed in both groups. For trials that were reported in >1 publication, we extracted data from the most complete publication and used other publications to clarify data. To assess the agreement between reviewers for study selection, we used the κ statistic, which measures agreement beyond chance.[11]	2382

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 investigators. We extracted and presented data according to the Providing Innovative Service Models and Assessment (PRISMA) criteria.[12] If outcome data for extraction could not be identified, we contacted the study authors by e-mail, with a reminder after 15 days. For unpublished trials, we also contacted the pharmaceutical companies. Two reviewers (N.R. and F.D.) independently assessed study quality using a validated scale[14] based on the following criteria: methods used to generate the randomization sequence, method of double blinding, and description of patient withdrawals and dropouts. A score of 1 point was given for each criterion satisfied, and 1 additional point was given for high quality of randomization and double blinding, for a maximum of 5 points. Studies with a score >2 were considered high quality, and studies with a score ≤2 were considered low quality. Although concealed treatment allocation is not part of this rating scale, it was included in our study quality assessment. We resolved disagreements about study data extraction by consensus or by discussion with a third reviewer (W.A.).	2382
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. Two reviewers (N.R. and F.D.) independently extracted data on study (year of publication, design), population characteristics (number of patients, mean age, sex), and treatment (therapeutic indication, type of drug, dose, and duration). Information on the following outcomes was collected in the 2 groups: number of total and ischemic strokes (ISs), SE, total and cardiovascular mortality, MB and intracranial bleeding, and myocardial infarctions (MIs). No attempt was made to reclassify bleeding events. However, in the included studies, MBs were classified mostly according to International Society on Thrombosis and Haemostasis criteria[13] as bleeding causing a fall in hemoglobin levels of ≥2 g/dL, bleeding leading to transfusion of ≥2 U whole blood or red cells, symptomatic bleeding in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, intrarticular, pericardial, or intramuscular with compartment syndrome), or bleeding events leading to death.	2382

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. The presence of publication bias was investigated by the use of funnel plots of effect size versus standard error.[20]	2382
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). We determined pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) for all-cause and cardiovascular mortality in AF patients who received VKAs or treatment with a NOAC. Furthermore, the pooled RR of any cardioembolic event (which included stroke or SE), IS, MB and intracranial bleeding, and MI in the 2 arms of treatment was calculated. Because transient ischemic attacks are frequently subjective, seldom consistently reported, and not usually considered a primary outcome in AF trials, we decided not to include them in our analysis.	2382
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. From phase II dose-ranging RCTs, we summed all groups whose total daily dose was equal to the regimens used in phase III RCTs. For all the treatment effects that were statistically significant, we determined the absolute risk reduction (ARR) or the absolute risk increase and the corresponding number needed to treat (NNT) or number needed to harm. Data were pooled by use of a fixed-effects model (Mantel-Haenszel method),[15] and results were compared with the results obtained with a random-effects (RE) model (DerSimonian-Laird method).[16] A value of $P<0.05$ was considered statistically significant. All analyses were performed with Review-Manager software (RevMan, version 5.1.6 for Windows; The Cochrane Collaboration, Oxford, UK; 2008). Because combining trials with extremely low or zero event rates can yield biased results, we repeated the analyses using Comprehensive Meta-Analysis software, version 2 (Biostat Software Corp, Englewood, NJ), which provides exact fixed-effect point and interval estimates for the odds ratio.[17] The appropriateness of pooling data across studies was assessed with the use of the Cochran Q and the I^2 test for heterogeneity, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error.[18] For the preparation of the forest plots, we also used the Meta Data Viewer software version 1.02 (National Toxicology Program, Research Triangle Park, NC).[19] The presence of publication bias was investigated by the use of funnel plots of effect size versus standard error.[20]	2382

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). The presence of publication bias was investigated by the use of funnel plots of effect size versus standard error.[20]	2382
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **Sensitivity Analyses** We repeated sensitivity analyses by using only studies that satisfied each item of our prespecified quality evaluation.[21] Furthermore, separate analyses of studies published in peer-reviewed journals were provided. **Subgroup Analyses** We planned to perform separate analyses of studies assessing short-term outcomes (1–3 months) and long-term outcomes (>1 year). We also performed separate analyses including, from phase II trials, only the exact same dose regimen of the NOAC that was subsequently used in phase III trials and, in a separate analysis, excluding the lower dosage of dabigatran (110 mg twice daily), which is not licensed by the US Food and Drug Administration.	2383
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. We identified 1454 potentially relevant studies: 364 from MEDLINE and 1090 from EMBASE. A total of 317 studies were duplicated, and 1106 studies were excluded after title and abstract screening. The remaining 31 studies were retrieved in full for detailed evaluation. A list of the 24 excluded studies and reasons for exclusion is available on request. Two additional studies were identified from a personal library.[22,23] We identified 3 more studies by searching unpublished trials on www.clinicaltrials.gov.[24–26] A review of the reference lists of included studies did not provide any additional references. Twelve studies were therefore included in this systematic review.[8–10,22–30] Interobserver agreement for study selection was almost perfect (κ=0.89). The study identification and selection progression are summarized in Figure I in the online-only Data Supplement. Data from 2 studies were supplemented with information extracted from more recent publications.[31,32] Supplementary data for 7 trials were provided by the investigators involved in the trial or the pharmaceutical companies.[22–27,29] Data on dabigatran and rivaroxaban were also supplemented with information from their Food and Drug Administration reviews.[33,34]	2383

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. Baseline characteristics of patients included in the studies are summarized in the Table. For 4 NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), a phase III RCT was published or was ongoing. The comparator VKA was warfarin in all studies. All studies were published in English. Study size ranged from 100 patients[26] to 18 201 patients,[10] for a total of 54 875 included patients. Eight studies were phase II RCTs[22,24–30] and 4 studies were phase III RCTs.[8–10,23] Three studies involved dabigatran,[8,24,30] 4 involved rivaroxaban,[9,23,25,26] 2 involved apixaban,[10,27] and 3 involved edoxaban.[22,28,29]	2383
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). The presence of publication bias was investigated by the use of funnel plots of effect size versus standard error.	2382
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.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **Sensitivity Analyses** Sensitivity analyses including only high-quality[8–10,23,28,29] and published[8–10,22,23,27–30] studies confirmed the results of the primary analyses (Figures IV–VII in the online-only Data Supplement). Similarly, repeating our analyses with Comprehensive Meta Analysis software including trials with extremely low or zero event rates did not change the results of the primary analyses (results available on request). **Subgroup Analyses**	2385, 2386

		In the subgroup analysis that included only studies with short-term follow-up,[22,24–30] only the rate of stroke and SE appears to be significantly reduced in patients randomized to NOACs, whereas the rates of cardiovascular and total death, IS, MB, intracranial bleeding, and MI were similar in the 2 groups. In contrast, the subgroup analyses that included only studies with long-term follow-up[8–10,23] and only the dose regimens used in phase III studies provided the same results as the primary analyses. The analysis excluding the lower dosage of dabigatran showed a reduction of IS with NOACs compared with VKAs (RR, 0.86; 95% CI, 0.76–0.99; I^2=30%) using a fixed-effects model. This result was not statistically significant with an RE model (RR, 0.85; 95% CI, 0.70–1.02; Figures IV–VII in the online-only Data 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). This is, to the best of our knowledge, the first systematic review and meta-analysis of phase II and phase III RCTs that compared the NOACs with warfarin for the prevention of stroke and SE in patients with AF. Our analysis, incorporating >50 000 patients, found a statistically significant 11% RR reduction in the incidence of both total mortality and cardiovascular mortality, which corresponds to an NNT of 244 patients to prevent 1 death and to an NNT of 500 patients to prevent 1 cardiovascular death. The observed advantage of the NOACs is consistent for all outcomes, including stroke and SE reduction (RR reduction, 23%; NNT, 137) and MB reduction (RR reduction, 14%; NNT, 157). Following the favorable results of the individual clinical trials, dabigatran and rivaroxaban have received approval from the regulatory agencies and apixaban is expected to be licensed in the near future. However, the cost-effectiveness of these compounds remains unclear. This lack of clarity exists, in part, as a result of the observation that single studies have reported small and often nonstatistically significant differences between the NOACs and warfarin for hard end points such as overall mortality and vascular mortality. We believe that our study could provide more accurate estimates of the expected clinical benefits of the NOACs. Taken together, our results suggest that the use of the NOACs not only provides practical advantages over the VKAs but also is associated with an overall clinical benefit, suggesting their cost-effectiveness. More important, the NOACs both reduce clinical events and offer the possibility of increasing the use of adequate prophylactic strategies in patients with AF. It is well known that AF remains a major cause of stroke[2] and that the severity of stroke is greater in patients with AF than in other subgroups.[35] Despite this evidence, the use of VKAs in the real world of patients with AF remains unacceptably low, with an overall prevalence of treated high-risk patients not exceeding 70%.[36] The availability of NOACs has the potential to reduce the incidence of AF-related strokes and SE because of both their superior efficacy and their potential to be more widely used compared with the VKAs. In this meta-analysis, we have combined the results of clinical	2386, 2387

trials carried out with 4 NOACs. These drugs present some important differences in terms of mechanisms of action; 1 drug (dabigatran etexilate) is a direct thrombin inhibitor and 3 drugs (rivaroxaban, apixaban, and edoxaban) are direct factor Xa inhibitors. Moreover, there are some differences in the mechanisms of excretion, in their mean half-lives, and in the drug-drug interactions, among others.[37] These differences may suggest that combining the results of these drugs may not be appropriate. However, there were no signs of heterogeneity when the outcomes of total and cardiovascular mortality, stroke, or SE were analyzed, thus suggesting that the advantages in terms of efficacy are consistent among all the new agents included in our study. On the other hand, significant heterogeneity was documented when the outcome of MB was analyzed.

This finding may be due in part to some drug-specific or regimen-specific differences in terms of safety, although none of the NOACs were less safe than warfarin, and to patient-specific characteristics. Indeed, some studies enrolled an intermediate-risk population with a mean $CHADS_2$ score of ≈2,[8,10,22,27–29] whereas other studies enrolled a population at higher risk not only for thromboembolic but also for bleeding complications, with a mean $CHADS_2$ score >3.[9,23]

When the analysis was repeated with the exclusion of the lower dose of dabigatran, which is not approved in the United States and is recommended for more fragile patients in other countries, the results were fully comparable to those of the main analysis in terms of total mortality and safety, whereas a tendency toward a greater benefit in the reduction of IS was observed.

There is great interest in the potential increased risk of MI with the use of the NOACs, particularly dabigatran. The results of a recent meta-analysis of trials involving dabigatran for the primary and secondary prevention of cardiovascular diseases found a 33% RR increase in acute coronary events with the novel direct thrombin inhibitors compared with traditional anticoagulant drugs.[38] Another recent analysis comparing warfarin with other antithrombotic drugs (ximelagatran, dabigatran, idraparinux, and clopidogrel) in AF clinical trials found a 23% RR reduction in the rate of MI with warfarin, suggesting the protective effect of the VKA.[39] In this meta-analysis, we failed to detect any difference in the overall risk of MI, with a 1.29% rate in both NOAC- and VKA-treated patients. Of interest, no statistically significant difference was detected after subgroup analysis.

The strengths of this study include the rigorous methodological

		approach, the selection of all the studies performed with the 4 NOACs considered, and the consistency of the results of sensitivity analyses. Furthermore, to the greatest extent possible, we confined our analysis to clinically relevant events, and because all the studies were performed as a component of product registration, it is likely that all reported outcome events were objectively confirmed.	
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). The study has a number of limitations. First, because this was a study-level meta-analysis, we were unable to confirm the overall results in specific subgroups of patients according to their baseline stroke or bleeding risk. Population characteristics were quite different among the single studies; however, several subgroup analyses have already been published suggesting the consistency of the principal findings across different subgroups such as patients with previous stroke[31,40,41] or more advanced age.[42] Second, we could not compare the patients receiving NOACs with different subgroups of warfarin-treated patients according to the time in therapeutic range, and it has been shown that the magnitude of the	2389

		benefit of the NOACs compared with standard treatment is dependent on the quality of control of warfarin.[43] Third, the results of our meta-analysis are driven mainly by 3 large RCTs involving dabigatran,[8] rivaroxaban,[9] and apixaban,[10] whereas fewer data are available on edoxaban because the phase III RCT is currently ongoing. Fourth, the funnel plot for stroke or SE was asymmetrical with a lack of studies on the right part of the plot, suggesting that unpublished studies likely to demonstrate an increased risk of stroke or SE with NOACs were not included in our meta-analysis. Instead, the funnel plot for MI was lacking studies on the left side of the plot, suggesting that studies demonstrating a reduction in the risk of MI with NOACs were not included. However, because we performed an extensive research of the literature, including abstracts presented at congresses of several international societies, and because we contacted pharmaceutical companies asking for unpublished trials, the existence of other trials not included in our systematic review is extremely unlikely.	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. NOACs reduced overall and cardiovascular mortality, stroke and SE, and MB and intracranial bleeding compared with warfarin. These favorable efficacy and safety profiles now need to be confirmed in postmarketing studies.	2389
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. Dr Crowther discloses having served on advisor boards for Leo Pharma, Pfizer, Bayer, Boehringer Ingelheim, Alexion, CSL Behring, and Artisan Pharma. Dr Crowther has prepared educational materials for Pfizer, Octapharm, and CSL Behring; has provided expert testimony for Bayer; and holds a Career Investigator Award from the Heart and Stroke Foundation of Ontario and the Leo Pharma Chair in Thromboembolism Research at McMaster University. Dr Crowther's institution has received funding for research projects from Boehringer Ingelheim, Octapharm, Pfizer, and Leo Pharma. Dr Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. Dr Ageno has served on the advisory boards for Bayer, BMS/Pfizer, and Daiichi Sankyo; has received honoraria for speaking activities from Boehringer Ingelheim, Bayer, BMS, Pfizer, Sanofi, GlaxoSmithKline; and has received funding for research projects from Bayer,	2389, 2390

		GlaxoSmithKline, and Alexion. Dr Turpie has served on advisory boards for Bayer, Astellas, and Takeda and has received honoraria for speaking activities from Boehringer Ingelheim, Bayer, BMS, Pfizer, Sanofi, and GlaxoSmithKline. Drs Dentali and Riva report no conflicts.	

Meta-analysis No3:

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

The access to the full article of this meta-analysis is not free, so we can only assess its title and summary.

Prisma Checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials	
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. **Background** Four new oral anticoagulants compare favourably with warfarin for stroke prevention in patients with atrial fibrillation; however, the balance between efficacy and safety in subgroups needs better definition. We aimed to assess the relative benefit of new oral anticoagulants in key subgroups, and the effects on important secondary outcomes. **Methods**	

We searched Medline from Jan 1, 2009, to Nov 19, 2013, limiting searches to phase 3, randomised trials of patients with atrial fibrillation who were randomised to receive new oral anticoagulants or warfarin, and trials in which both efficacy and safety outcomes were reported. We did a prespecified meta-analysis of all 71 683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials. The main outcomes were stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding. We calculated relative risks (RRs) and 95% CIs for each outcome. We did subgroup analyses to assess whether differences in patient and trial characteristics affected outcomes. We used a random-effects model to compare pooled outcomes and tested for heterogeneity.

Findings

42 411 participants received a new oral anticoagulant and 29 272 participants received warfarin. New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0·81, 95% CI 0·73–0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (0·49, 0·38–0·64; p<0·0001). New oral anticoagulants also significantly reduced all-cause mortality (0·90, 0·85–0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39–0·59; p<0·0001), but increased gastrointestinal bleeding (1·25, 1·01–1·55; p=0·04). We noted no heterogeneity for stroke or systemic embolic events in important subgroups, but there was a greater relative reduction in major bleeding with new oral anticoagulants when the centre-based time in therapeutic range was less than 66% than when it was 66% or more (0·69, 0·59–0·81 *vs* 0·93, 0·76–1·13; p for interaction 0·022). Low-dose new oral anticoagulant regimens showed similar overall reductions in stroke or systemic embolic events to warfarin (1·03, 0·84–1·27; p=0·74), and a more favourable bleeding profile (0·65, 0·43–1·00; p=0·05), but significantly more ischaemic strokes (1·28, 1·02–1·60; p=0·045).

Interpretation

This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

Funding

		None.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
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.	
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.	
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.	

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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 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.	
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.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
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.	

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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
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.	
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.	

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).	
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.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
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.	

Meta-analysis No4:

http://www.ajconline.org/article/S0002-9149%2812%2901065-X/fulltext

Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran, Rivaroxaban, Apixaban*) Versus *Warfarin* in Patients With Atrial Fibrillation

Prisma Checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran*, *Rivaroxaban*, *Apixaban*) Versus *Warfarin* in Patients With Atrial Fibrillation	
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. New oral anticoagulants are categorized, on the basis of their targets, as direct thrombin or factor Xa inhibitors.[1] Direct thrombin inhibitors include AZD0837 and dabigatran, and direct factor Xa inhibitors include apixaban, betrixaban, edoxaban, LY-517717, rivaroxaban, and ym-150. Recently, 3 large phase III randomized controlled trials (RCTs), the Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,[2] the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[3] and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF),[4] have examined the long-term use of new oral anticoagulants. Although these trials established that new oral anticoagulants were more efficacious than warfarin with respect to the primary end point of combined stroke and systemic embolism, their results pertaining to important secondary efficacy end points as well as safety outcomes were inconclusive or heterogenous. We therefore performed a systematic review and meta-analysis to examine the long-term efficacy and safety of the new oral anticoagulants compared to warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation (AF).	
INTRODUCTION			

Rationale	3	Describe the rationale for the review in the context of what is already known. We therefore performed a systematic review and meta-analysis to examine the long-term efficacy and safety of the new oral anticoagulants compared to warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation (AF).	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
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. We systematically searched the published medical research for RCTs comparing new oral anticoagulants to warfarin in patients with AF. The Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest's Dissertations and Theses databases were searched from inception through July 2011 without language restriction. The following were used as Medical Subject Heading terms and/or keywords: “new oral anticoagulants,” “oral thrombin inhibitors,” “oral factor Xa inhibitors,” “dabigatran,” “rivaroxaban,” “apixaban,” “edoxaban,” “betrixaban,” “ym-150,” and “LY-517717.”	

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. Studies were included if (1) they were RCTs, (2) they randomized subjects to warfarin or to non–vitamin K antagonist oral anticoagulants, (3) they were conducted in patients with AF, and (4) they were published in peer-reviewed journals. Studies examining ximelagatran were excluded because it has since been removed from the market because of hepatotoxicity.[6] Conference abstracts and presentations were also excluded, because their results may not be final, and such publications undergo more limited peer review. Open-label and blinded studies were included, because warfarin's need for monitoring makes blinding difficult. Finally, to assess the long-term efficacy and safety of these agents, only RCTs with follow-up durations of >1 year were included. Data extracted from each RCT included patient- and study-level characteristics as well as outcomes. Extracted patient- and study-level characteristics included average age, median follow-up times, discontinuation rates, mean $CHADS_2$ scores,[7] gender distribution, mean time in the therapeutic range of warfarin, and proportion of patients with relevant co-morbidities present at baseline. The main efficacy outcome of interest was a composite end point of stroke (including hemorrhagic stroke) and systemic embolism. Other efficacy outcomes were ischemic and unidentified stroke, hemorrhagic stroke, all-cause mortality, vascular mortality, and myocardial infarction. The main safety outcome of interest was major bleeding. Other safety outcomes were gastrointestinal bleeding and intracranial bleeding.	
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. We systematically searched the published medical research for RCTs comparing new oral anticoagulants to warfarin in patients with AF. The Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest's Dissertations and Theses databases were searched from inception through July 2011 without language restriction. The following were used as Medical Subject Heading terms and/or keywords: “new oral anticoagulants,” “oral thrombin inhibitors,” “oral factor Xa inhibitors,” “dabigatran,” “rivaroxaban,” “apixaban,” “edoxaban,” “betrixaban,” “ym-150,” and “LY-517717.” We did not restrict our search to studies conducted in patients with AF, to avoid excluding trials that reported subgroup data on patients with AF. The Embase and MEDLINE searches were limited to clinical trials, and the Embase search was further limited to studies performed in humans. The Science Citation Index Expanded and ProQuest searches were limited to full-text reports. Clinical trial databases, relevant	

		reviews, and the reference lists of retrieved reports were hand searched for potentially relevant studies not identified in our electronic database search.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. The following were used as Medical Subject Heading terms and/or keywords: "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "dabigatran," "rivaroxaban," "apixaban," "edoxaban," "betrixaban," "ym-150," and "LY-517717."	
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). Studies were included if (1) they were RCTs, (2) they randomized subjects to warfarin or to non–vitamin K antagonist oral anticoagulants, (3) they were conducted in patients with AF, and (4) they were published in peer-reviewed journals. Studies examining ximelagatran were excluded because it has since been removed from the market because of hepatotoxicity.[6] Conference abstracts and presentations were also excluded, because their results may not be final, and such publications undergo more limited peer review. Open-label and blinded studies were included, because warfarin's need for monitoring makes blinding difficult. Finally, to assess the long-term efficacy and safety of these agents, only RCTs with follow-up durations of >1 year were included.	

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 investigators. Two reviewers independently extracted data from the RCTs. Disagreements were resolved by consensus or, if necessary, by a third party. Data extracted from each RCT included patient- and study-level characteristics as well as outcomes. Extracted patient- and study-level characteristics included average age, median follow-up times, discontinuation rates, mean $CHADS_2$ scores,[7] gender distribution, mean time in the therapeutic range of warfarin, and proportion of patients with relevant co-morbidities present at baseline. The main efficacy outcome of interest was a composite end point of stroke (including hemorrhagic stroke) and systemic embolism. Other efficacy outcomes were ischemic and unidentified stroke, hemorrhagic stroke, all-cause mortality, vascular mortality, and myocardial infarction. The main safety outcome of interest was major bleeding. Other safety outcomes were gastrointestinal bleeding and intracranial bleeding.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. The following were used as Medical Subject Heading terms and/or keywords: “new oral anticoagulants,” “oral thrombin inhibitors,” “oral factor Xa inhibitors,” “dabigatran,” “rivaroxaban,” “apixaban,” “edoxaban,” “betrixaban,” “ym-150,” and “LY-517717.” We did not restrict our search to studies conducted in patients with AF, to avoid excluding trials that reported subgroup data on patients with AF.	
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. Quality assessment of included trials was conducted using the Cochrane Collaboration's tool for assessing risk for bias.[8] This assessment tool evaluates bias in an RCT within the following domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity. The risk for bias in each domain was classified as high, low, or unclear for each RCT.	

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). We estimated pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) using DerSimonian and Laird random-effects models, which account for within- and between-study variability. The presence of between-study variability was assessed using the Q statistic (with p <0.10 considered significant), and the proportion of heterogeneity due to between-study variability was estimated using the I^2 index. All analyses were conducted using Stata version 11.0 (StataCorp LP, College Station, Texas).	
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. The presence of between-study variability was assessed using the Q statistic (with p <0.10 considered significant), and the proportion of heterogeneity due to between-study variability was estimated using the I^2 index. All analyses were conducted using Stata version 11.0 (StataCorp LP, College Station, Texas).	

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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
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. Our electronic search identified a total of 3,167 reports (Figure 1). After removing duplicates, we screened titles and abstracts, and the full text of 44 publications was retrieved and evaluated for eligibility. Three trials that met our inclusion criteria were identified and included in the present study. One trial was published as an original report[3] with a follow-up report providing additional data.[9] The other 2 trials were presented as ClinicalTrials.gov entries and were subsequently published in peer-reviewed journals.[2, 4] No additional studies were identified from Cochrane systematic reviews, manual searches of the reference lists of retrieved reports, relevant reviews, or clinical trial databases.	
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. In ARISTOTLE, 18,201 patients with nonvalvular AF were randomized to either apixaban 5 mg twice daily or to warfarin.[2] In RE-LY, 18,113 patients with nonvalvular AF were randomized to 1 of 3 treatment arms: dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or warfarin.[3, 9] The 150-mg dose was used in our analysis because it is the dose administered to patients with AF. ROCKET AF compared a 20 mg/day dose of rivaroxaban to warfarin in 14,264 patients with nonvalvular AF.[4] These 3 trials randomized a total of 44,563 patients, 22,327 to new oral anticoagulants and 22,236 to warfarin. The mean length of follow-up ranged from 657 to 730 days, and the average age ranged from 70 to 73 years. Mean $CHADS_2$ scores were between 2.1 and 3.5. Women constituted 35% to 40% of the study populations, and the mean time in the therapeutic range of warfarin ranged from 55% to 64%.	

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). Quality assessment of included trials was conducted using the Cochrane tool for assessing risk for bias. In RE-LY, patients were unblinded with respect to dabigatran or warfarin assignment.[3, 10] However, all investigators, coordinating center members, the steering committee, the event adjudication committee, and the sponsor were blinded during event ascertainment and analyses. As such, the risk for bias for RE-LY was described as low for the domain of blinding.	
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. When data were pooled across RCTs, patients randomized to new oral anticoagulants had a 22% RR reduction for the composite end point of stroke and systemic embolism compared to those randomized to warfarin (RR 0.78, 95% CI 0.67 to 0.92; Figure 2). The risks for ischemic and unidentified stroke (RR 0.87, 95% CI 0.77 to 0.99), hemorrhagic stroke (RR 0.45, 95% CI 0.31 to 0.68; Figure 2), and all-cause mortality (RR 0.88, 95% CI 0.82 to 0.95; Supplemental Figure 1) were also lower in patients randomized to new oral anticoagulants compared to patients randomized to warfarin. The risk for vascular mortality, using data from the RE-LY and ROCKET AF trials, was significantly reduced among those randomized to new oral anticoagulants (RR 0.87, 95% CI 0.77 to 0.98; Supplemental Figure 1); ARISTOTLE was excluded from this analysis because only event rates, rather than count data, were reported. Risk for myocardial infarction was similar between new oral anticoagulants and warfarin (RR 0.96, 95% CI 0.73 to 1.26; Supplemental Figure 2).Safety outcome analyses included major bleeding, gastrointestinal bleeding, and intracranial bleeding (Figure 3). Analyses of the risks of major bleeding (RR 0.88, 95% CI 0.71 to 1.09) and gastrointestinal bleeding events (RR 1.25, 95% CI 0.91 to 1.72) were inconclusive because of wide 95% CIs. However, randomization to a new oral anticoagulant was associated with a significant reduction in the risk for intracranial bleeding (RR 0.49, 95% CI 0.36 to 0.66).	

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. When data were pooled across RCTs, patients randomized to new oral anticoagulants had a 22% RR reduction for the composite end point of stroke and systemic embolism compared to those randomized to warfarin (RR 0.78, 95% CI 0.67 to 0.92; Figure 2). The risks for ischemic and unidentified stroke (RR 0.87, 95% CI 0.77 to 0.99), hemorrhagic stroke (RR 0.45, 95% CI 0.31 to 0.68; Figure 2), and all-cause mortality (RR 0.88, 95% CI 0.82 to 0.95; Supplemental Figure 1) were also lower in patients randomized to new oral anticoagulants compared to patients randomized to warfarin. The risk for vascular mortality, using data from the RE-LY and ROCKET AF trials, was significantly reduced among those randomized to new oral anticoagulants (RR 0.87, 95% CI 0.77 to 0.98; Supplemental Figure 1); ARISTOTLE was excluded from this analysis because only event rates, rather than count data, were reported. Risk for myocardial infarction was similar between new oral anticoagulants and warfarin (RR 0.96, 95% CI 0.73 to 1.26; Supplemental Figure 2).Safety outcome analyses included major bleeding, gastrointestinal bleeding, and intracranial bleeding (Figure 3). Analyses of the risks of major bleeding (RR 0.88, 95% CI 0.71 to 1.09) and gastrointestinal bleeding events (RR 1.25, 95% CI 0.91 to 1.72) were inconclusive because of wide 95% CIs. However, randomization to a new oral anticoagulant was associated with a significant reduction in the risk for intracranial bleeding (RR 0.49, 95% CI 0.36 to 0.66).	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15). Quality assessment of included trials was conducted using the Cochrane tool for assessing risk for bias. In RE-LY, patients were unblinded with respect to dabigatran or warfarin assignment.[3, 10] However, all investigators, coordinating center members, the steering committee, the event adjudication committee, and the sponsor were blinded during event ascertainment and analyses. As such, the risk for bias for RE-LY was described as low for the domain of blinding. ROCKET AF, a trial whose primary objective was one of noninferiority, performed its efficacy and safety analyses on the basis of per protocol and as-treated populations rather than the intention-to-treat population.[4] Although such analyses are appropriate for noninferiority designs, they disturb the integrity of randomization, leading to potential confounding and selection bias. Although an intention-to-treat analysis was provided for the primary efficacy outcome of combined stroke and systemic embolism, it was not provided for other efficacy and safety outcomes.[4] Consequently, ROCKET AF was considered unclear in the domain of other sources of bias. Importantly, the as-treated	

		population excluded only 28 of 14,264 patients included in the intention-to-treat analyses. ARISTOTLE, another noninferiority trial, used an intention-to-treat analysis for all efficacy outcomes but not for safety outcomes, for which only patients who received ≥1 dose of study drug were considered.[2] It was therefore considered unclear in the domain of other sources of bias. These safety analyses excluded 61 of 18,201 patients included in the intention-to-treat population.	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
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). In our meta-analysis, we found that the new oral anticoagulants reduced the risk for a composite end point of stroke and systemic embolism compared to warfarin. New oral anticoagulants were also found to be associated with a lower risk for key secondary efficacy outcomes, including ischemic and unidentified stroke, hemorrhagic stroke, all-cause mortality, and vascular mortality, compared to warfarin. Our meta-analysis was inconclusive with respect to major bleeding and gastrointestinal bleeding but found a substantial decrease in the risk for intracranial bleeding. Overall, our results support the use of the new oral anticoagulants as alternatives to warfarin for long-term anticoagulation therapy in patients with AF.	
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). Our study had 3 potential limitations. First, there was heterogeneity among the included trials. They examined different oral anticoagulants, and some of the between-trial differences may be due to the use of different agents. There was also some heterogeneity with respect to the study designs and included populations. Therefore, we used random-effects models that account for between-study heterogeneity. Second, patients in clinical trials are often at lower overall risk for adverse events than patients seen in everyday clinical practice.[27] Although this may affect the generalizability of our results, it likely did not result in bias. Third, patients taking warfarin in the included studies were more likely to be within its therapeutic range than in real practice. One study found that patients in studies monitored by community physicians spent 12.2% less time in the therapeutic range compared to patients in randomized trials.[12] Similar variability is unlikely to apply to the same extent to the new oral anticoagulants, because of	

		their fixed dosing and more predictable pharmacokinetic and pharmacodynamic properties. The safety and efficacy profiles of the new agents relative to that of warfarin may therefore be augmented when used outside the controlled clinical trial setting.	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. In our meta-analysis, we found that the new oral anticoagulants reduced the risk for a composite end point of stroke and systemic embolism compared to warfarin. New oral anticoagulants were also found to be associated with a lower risk for key secondary efficacy outcomes, including ischemic and unidentified stroke, hemorrhagic stroke, all-cause mortality, and vascular mortality, compared to warfarin. Our meta-analysis was inconclusive with respect to major bleeding and gastrointestinal bleeding but found a substantial decrease in the risk for intracranial bleeding. Overall, our results support the use of the new oral anticoagulants as alternatives to warfarin for long-term anticoagulation therapy in patients with AF.	
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. We would like to thank Tara Dourian (Jewish General Hospital/McGill University) for her help with data extraction.	

Meta-analysis No5:

http://www.researchgate.net/publication/266796982_A_meta-analysis_of_phase_III_randomized_controlled_trials_with_new_oral_anticoagulants_in_atrial_fibrillation_Comparisons_between_direct_thrombin_inhibitors_vs._factor_Xa_inhibitors_and_different_dosing_regimens

A meta-analysis of phase III randomized controlled trials with new oral anticoagulants in atrial fibrillation: Comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens

Prisma Checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			

Title	1	Identify the report as a systematic review, meta-analysis, or both. A meta-analysis of phase III randomized controlled trials with new oral anticoagulants in atrial fibrillation: Comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens	1253
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. Aims: Previous studies evaluating the ability of novel oral anticoagulants (NOAC) to prevent thromboembolism in patients with non-valvular atrial fibrillation (AF) have identified differences between the efficacy and safety of the drugs tested. Whether these differences reflect differences in direct thrombin or Xa inhibition, different dosing regimens or specific aspects of each agent or trial has not yet been explored. Methods: A search was performed on MEDLINE, EMBASE and COCHRANE, and ongoing studies were tracked on clinicaltrials.gov. Phase III randomized controlled trials of direct thrombin inhibitors (DTI) and factor Xa inhibitors (FXaI) vs. warfarin in patients with AF were eligible. Data were pooled using random-effects, according to the Mantel-Haenszel model. Sensitivity analyses were performed on DTI, FXaI, once-daily and twice-daily regimens. Results: Seven studies were pooled, including a total of 80,290 patients. Both DTI and FXaI outperformed warfarin regarding stroke or systemic embolism, intracranial bl eeding, total and cardiovascular mortality. No signifi cant differences were found between DTI and FXaI or between once-daily and twice-daily regimens. Some drugs performed worse than warfarin regarding some secondary endpoints, including: edoxaban 30 mg bid on ischaemic stroke, dabigatran on acute myocardial infarction, dabigatran 150 mg bid and rivaroxaban 20mgod on gastrointestinal bleeding. Conclusion: Our pooled data do not support the hypothesis of a signi ficant class-effect of DTI or FXaI, nor the benefit of once-daily vs. twice-daily dosing in the setting of AF, reinforcing that the choice of NOAC should be adapted to the specific patient and focused on the agent itself, rather than the pharmacological class or dosing regimen.	1253

INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Patients with atrial fibrillation (AF) have an increased risk of death [1] and stroke [2]. So far, vitamin-K antagonists (VKA) have been the mainstay in the prevention of thromboembolism in patients with AF [3]. However, the use of these anticoagulants is often challenging due to inter and intra-individual variability in dosing, need of frequent monitoring and interaction with other drugs or food, and this has led to the development of other pharmacological alternatives [4]. In recent years, several new non-VKA oral anticoagulants (NOAC), belonging to one of two different classes (direct thrombin inhibitors [DTI] and direct factor Xa inhibitors [FXaI]), have been evaluated in patients with non-valvular AF [5].	1253
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). In the phase III randomized controlled trials, differences regarding effi cacy and safety have been observed between some of these drugs in comparison with warfarin. Whether these differences reflect a DTI or FXaI class-effect, different drug pharmacokinetics or dosing regimens or relate to specific aspects of each agent or trial has never been explored. A meta-analysis including data from all phase III randomized controlled trials provides the best opportunity to test the existence of differences between DTI and FXaI drugs and once and twice-daily agents, since head-to-head randomized controlled trials are not likely to be performed. Indirect drug comparisons between trials may be obtained, thus providing a possible way of filling this knowledge gap.	1253
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. We performed a search in the databases MEDLINE, EMBASE and COCHRANE (from inception to November 21, 2013) using the following search string: “atrial fibrillation AND warfarin AND (apixaban OR Dabigatran OR edoxaban OR rivaroxaban OR ximelagatran)”.	1253, 1254

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. All phase III randomized controlled trials investigating NOAC versus warfarin in patients withnon-valvular AF were considered for inclusion. Despite being left out of most previous pooled NOAC analyses, trials involving ximelagatran provide an important opportunity of accessing DTI behaviour, since this is the only agent of this class besides dabigatran to be tested in patients with AF. Therefore, all trials of NOAC were included irrespective of commercial availability of the study drug. Assessment of efficacy and safety endpoints during follow-up was mandatory. Substudies of randomized controlledtrials,phase II randomized con- trolled trials, observational real-world experience with NOAC and controlled trials in the setting of interventions (e.g. catheter ablation of AF) were not eligible for analysis. The population, intervention, comparison and outcome (PICO) approach was used for conducting the meta-analysis[6]. The population of interest included patients with non-valvular AF, and the intervention was oral anticoagulation. Comparisons were performed between the following groups: warfarin versus NOAC; DTI versus warfarin; FXaI versus warfarin; DTI versus FXaI; once-daily NOAC vs. warfarin; twice-daily NOAC vs. warfarin, and once vs. twice-daily NOAC. The outcomes were: stroke or systemic embolic events, total mortality, cardiovascular mortality, ischaemic stroke, acute myocardial infarction, major bleeding, intracranial bleeding and gastrointestinal bleeding.	1254
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. We performed a search in the databases MEDLINE, EMBASE and COCHRANE (from inception to November 21, 2013) using the following search string: "atrial fibrillation AND warfarin AND (apixaban OR dabigatran OR edoxaban OR rivaroxaban OR ximelagatran)". Reference lists of all accessed full-text articles were further searched for sources of potentially relevant information. Ongoing studies on other NOAC in non-valvular AF were searched on ClinicalTrials.gov, and experts in the field were contacted to ensure that all important studies had been included. Authors of full-text papers and congress abstract authors were also contacted by email to retrieve additional information.	1254

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. We performed a search in the databases MEDLINE, EMBASE and COCHRANE (from inception to November 21, 2013) using the following search string: "atrial fibrillation AND warfarin AND (apixaban OR dabigatran OR edoxaban OR rivaroxaban OR ximelagatran)".	1254
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). All phase III randomized controlled trials investigating NOAC versus warfarin in patients withnon-valvular AF were considered for inclusion. Despite being left out of most previous pooled NOAC analyses, trials involving ximelagatran provide an important opportunity of accessing DTI behaviour, since this is the only agent of this class besides dabigatran to be tested in patients with AF. Therefore, all trials of NOAC were included irrespective of commercial availability of the study drug. Assessment of efficacy and safety endpoints during follow-up was mandatory. Substudies of randomized controlledtrials,phase II randomized con- trolled trials, observational real-world experience with NOAC and controlled trials in the setting of interventions (e.g. catheter ablation of AF) were not eligible for analysis.	1254
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 investigators. To ensure that all trials met the pre-specified inclusion criteria, search results were reviewed by two investigators (RP and SBa), who needed to reach consensus on study selection; if necessary, a third in- vestigator (SBo) intervened. Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group [7]. Study quality was formally evaluated using the Del- phi Consensus criteria [8].	1254

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. The population, intervention, comparison and outcome (PICO) approach was used for conducting the meta-analysis [6]. The population of interest included patients with non-valvular AF, and the intervention was oral anticoagulation. Comparisons were performed between the following groups: warfarin versus NOAC; DTI versus warfarin; FXaI versus warfarin;DTI versus FXaI; once-daily NOAC vs. warfarin;twice-daily NOAC vs. warfarin, and once vs. twice-daily NOAC. The outcomes were:stroke or systemic embolic events, total mortality, cardiovascular mortality, ischaemic stroke, acute myocardial infarction, major bleeding, in- tracranial bleeding and gastrointestinal bleeding.	1254
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. Using funnel plots for evaluation the presence of publication bias was not considered appropriate, since less than 10 studies (minimum number for assuring the appropriateness of the method) were included [11] . Heterogeneity-adjusted trial sequential analysis was applied to the meta-analysis to reduce the risk of random error due to repetitive testing of accumulating data [12].	1254
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Comparison of the treatment effect of adjusted-dose warfarin vs. NOAC was performed using risk ratios (number of events or the incidence in each treatment group) and respective 95% confidence intervals. Pairwise comparisons were performed for all assessed endpoints. Data were used from the intention-to-treat populations unless otherwise specified.	1254

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. Statistical heterogeneity on each outcome of interest was assessed and quantified using the Cochran Q test and the I2 statistic, respectively. The I2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. Values below 25%, 25% to 50% and higher than 50% are, by convention, classified as low, moderate, and high degrees of heterogeneity. Using funnel plots for evaluation the presence of publication bias was not considered appropriate, since less than 10 studies (minimum number for assuring the appropriateness of the method) were included[11]. Heterogeneity-adjusted trial sequential analysis was applied to the meta-analysis to reduce the risk of random error due to repetitive testing of accumulating data [12]. The optimal information size with adaptation of monitoring boundaries, and the cumulative Z-statistics after each trial were assessed (Supplementary material). This was based on an α significance level of 5% and A β of 20% (80% power), the observed risk reduction, incidence rate in the control group and the variation across trials (I2).	1254

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). Using funnel plots for evaluation the presence of publication bias was not considered appropriate, since less than 10 studies (minimum number for assuring the appropriateness of the method) were included.	1254

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. Three sensitivity analysis were performed: the first excluding data from the "stroke prevention using oral thrombin inhibition in atrial fibrillation" (SPORTIF) III and V trials, since the drug was withdrawn from development after lack of approval by the Federal Drug Agency as a result of hepatotoxicity [5]; the second excluded data from "Japanese Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation" (J-ROCKET AF) since, according to Japanese guidelines, patients above 70 years had a target international normalized ratio of 1.6 to 2.6[10], and therefore, different from the one used in other trials (2.0 to 3.0). Moreover, a lower dose of rivaroxaban (15 mg once-daily) was used; the third excluded data from all three studies.	1254
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. A total of 2,821 entries were retrieved for analysis of titles and abstracts. Of these, 2,677 were excluded as they were either duplicates or deemed unsuitable for the purpose of our meta-analysis (editorials, letters, reviews or case-reports). The remaining 144 results were care-fully screened, and after analysis of the full-text (in case of journal articles), 7 studies[13–19]were considered adequate for the purpose of our meta-analysis. The selection process is illustrated in Fig. 1. There was a good agreement between investigators on the inclusion of the selected trials. No ongoing phase III NOAC trials in patients with AF were found on clinicaltrials.gov.	1254

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. Baseline data and the design of selected trials are summarized in Tables 1 and 2.	1254
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). .	
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. When analyzing DTI and FXaI together, NOAC were associated with a lower incidence of stroke or systemic embolism (RR = 0.84; CI 95%0.74-0.95; P = 0.006) and major bleeding (RR = 0.79; CI 95% 0.67-0.93; P = 0.004) (Fig. 2). Results favouring a better outcome with NOAC were also found for total mortality (RR = 0.90; CI95% 0.86-0.95; Pb 0.0001), cardiovascular mortality (RR = 0.88; CI 95% 0.83-0.94; P = 0.0002) (Fig. 3) and intracranial bleeding (RR = 0.49; CI 95% 0.37-0.63; Pb 0.00001) (Fig. 4). However, no significant differences between the NOAC and warfarin were found concerning the incidence of ischaemic stroke (RR = 0.97; CI95% 0.83-1.14; P = 0.74), myocardial infarction (RR = 1.01; CI95% 0.83-1.24; P = 0.90) and gastrointestinal bleeding (RR = 1.07; CI 95% 0.86-1.34; P = 0.53) (Figs. 4 and 5). Concerning total mortality and cardiovascular mortality (Fig. 3), a significant risk reduction was observed for FXaI when compared with warfarin (RR = 0.89; CI 95% 0.84-0.95; P = 0.0002; I2= 0% and RR = 0.88; CI 95% 0.81-0.94; P = 0.0006; I2 = 0%, respectively). A non-significant absolute reduction was observed for both endpoints for DTI (RR = 0.92; CI 95% 0.84-1.01; P = 0.07; I2= 0% and RR = 0.96; CI 95% 0.73-1.25; P = 0.75; I2= 41%, respectively), despite the marginally sig- Nificant trend for a reductionin the“Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate” (RE-LY) trial[15]. When compared with warfarin, only FXaI reduced the incidence of stroke or systemic embolism (FXaI: RR = 0.83; CI 95% 0.72-0.95; P = 0.006; I2= 36%; DTI: RR = 0.91; CI 95%0.64-1.28; P = 0.58; I2= 68%). The neutral result of DTI is explained by the less favourable results of the SPORTIF V trial (Fig. 2). DTI were associated with a lower risk of major bleeding when compared with warfarin (RR = 0.85; CI 95%	1254, 1255, 1256

		0.77-0.95; P = 0.003; I2= 0%) and a similar trend was found for FXaI, despite the neutral results of the two rivaroxaban trials (RR = 0.78; CI 95% 0.61-1.01; P = 0.06; I2=90%)(Fig. 2). Regarding myocardial infarction and ischaemic stroke, no significant differences were found when comparing all DTI or FXaI trials with warfarin (Figs. 5). Moreover, a moderate to high heterogeneity of study results in each pharmacologic class was observed, thus making the existence of specific class effects for this event very unlikely. The forest plot of Fig. 4 shows that only FXaI were associated with a significant reduction of intracranial bleeding (RR = 0.47; CI 95% 0.36-0.62; Pb 0.00001; I2= 52%). Despite the clear benefit observed with dabigatran, pooling of data with ximelagatran displayed a numerical but non-significant reduction in this endpoint (RR = 0.64; CI 95% 0.28-1.48; P = 0.30; I 2=75%). Regarding gastrointestinal bleeding (Fig. 4), FXaI performed similarly to warfarin (RR = 1.00; CI 95% 0.74-1.36; P = 0.98; I2=81%),despite the results of the"Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation" (ROCKET-AF) trial, whereas DTI were associated with a significant increase in gastrointestinal bleeding (RR = 1.28; CI 95% 1.05-1.56; P = 0.02; I2 = 0%), explained by the results of the RE-LY trial.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). In the sensitivity analysis that excluded the SPORTIF III and SPORTIF V trials, treatment with DTI (i.e. dabigatran) led to a significant reduction in stroke or systemic embolism and intracranial bleeding (Table 3). Moreover, a strong trend towards an increase in acute myocardial infarction was also uncovered (RR = 1.29; CI 95% 0.99-1.69; P = 0.06). In the two scenarios that exclude the J-ROCKET AF trial, no changes in the FXaI vs. warfarin comparisons were observed.	1256

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). Three main conclusions can be drawn from this meta-analysis: Firstly, the pooled results confirm the overall benefit of NOAC over warfarin for most effi cacy and safety endpoints among patients with non- valvular AF. Secondly, the observed heterogeneity in results does not provide support for a possible class-effect of DTI or FXaI but rather suggests that specific properties characterise particular agents or trials. Thirdly, no clear benefits were observed in favour of any NOAC dosing regimen (once vs. twice-daily).	1258
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). Several limitations are commonly linked to the methodology of meta-analyses. Cross-study comparisons deal with some drawbacks, as previously discussed (e.g. control groups treated with warfarin were not identical in TTR, patients population, etc). Moreover, trials with DTI provided a much smaller population than FXaI and featured only two drugs, which may have impacted on comparisons between DTI and FXaI. Second, FXaI and DTI, as separate drug classes among the NOAC, have been previously assessed in other meta-analyses of randomized controlled trials [27-29]. However, some differences between the present study and previous ones should be highlighted. Besides AF [29], these included other clinical settings (venous thromboembolism [27] or AF and venous thromboembolism [28]). In all three of them [27–29], DTI and FXaI were compared with warfarin [27–29], placebo [27] or low molecular weight heparin [28], whereas no direct comparisons between the two NOAC classes were performed. The same applies to comparisons between once and twice-daily dosing regimens of NOAC in AF[28,29]. Randomized controlled trials with edoxaban, the most recent NOAC, were not included in any of them. One of these studies included randomized controlled trials with ximelagatran and was also the only one to provide data on optimal information size assessed through trial sequential analysis[29]. Third, due to the limited number of included studies the results obtained from methods assessing study heterogeneity	1263

		(like the I2) must be interpreted with caution. Also, a restricted sample size can be an issue when performing of a meta-regression. The Cochrane handbook suggests a minimum of 10 studies for using this method[11]. Finally, differences exist in the definition of major bleeding (Table VI– Supplementary material).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. In patients with AF, NOAC have an overall favourable effect when compared with warfarin regarding the risk of stroke or systemic embolism, major bleeding, total and cardiovascular mortality and intracranial bleeding. When restricting the analysis to the two different pharmacologic classes, DTI and FXaI, and to different dosing regimens, once-daily and twice-daily NOAC, a high heterogeneity between studies and no pronounced effect in favour of any of these were found. All differences and trends in the comparisons could be explained by results of isolated trials that were not reproduced by other agents of thesame class or with the same dosing regimen. Thus, current evidence shows that the choice of a NOAC for AF thromboembolic prophylaxis should be adapted to the individual patient and focused on the drug itself, rather than its pharmacologic class.	1263
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. Sources of funding None. Acknowledgements None.	1263

According to the checklist items that were fullfilled, meta-analysis No1 received 23 points, meta-analysis No2 received 24 points and meta-analysis No3 received 2 points (although we did not have access to the full text, so the assessment is not complete). Meta-analysis No4 received 23 points and meta-analysis No5 received 24 points. The results are shown at table 1.

Table 1:

Summary of the results of applying the PRISMA statement to the individual meta-analyses										
PRISMA statement results										
				SCORE						
			Meta-analysis No1		**Meta-analysis No2**		**Meta-analysis No3**		**Meta-analysis No4**	**Meta-analysis No5**
Title	1	Title	1		1		1		1	1
Abstract	2	Structured summary	1		1		1		1	1
Introduction	3	Rationale	1		1		0		1	1
Methods	4	Objectives	1		1				0	1
	5	Protocol and registration	1		1		0		1	1
	6	Eligibility criteria	1		1		0		1	1
	7	Information sources	1		1		0		1	1

	8	Search	1		1		0		1	1
	9	Study selection	1		1		0		1	1
	10	Data collection process	1		1		0		1	1
	11	Data items	1		1		0		1	1
	12	Risk of bias in individual studies	1		1		0		1	1
	13	Summary measures	1		1		0		1	1
	14	Synthesis of results	1		1		0		1	1
	15	Risk of bias across studies	1		1		0		0	1
	16	Additional analyses	0		1		0		0	1
Results	17	Study selection	1		1		0		1	1
	18	Study characteristics	1		1		0		1	1
	19	Risk of bias within studies	1		1		0		1	0
	20	Results of individual studies	1		0		0		1	1
	21	Synthesis of results	1		0		0		1	0
	22	Risk of bias across studies	0		0		0		1	0
	23	Additional analyses	0		1		0		0	1

Discussion	24	Summary of evidence	1		1		0		1	1
	25	Limitations	1		1		0		1	1
	26	Conclusions	1		1		0		1	1
Funding	27	Funding	0		1		0		1	1
Total			23		24		2		23	24

CONCLUSION:

Generally, most of the meta-analyses found received high scores. Title, abstract and introduction met the prisma criteria. Synthesis of results, risk of bias across studies and additional analyses are the checklist items for which most of the meta-analyses did not get a point. This indicates a deficiency of the studies as far as these three checklist items are concerned. According to the prisma checklist, meta-analyses No2 and No5 received the highest score. Therefore, these meta-analyses are more complete and adequate, compared with the other three meta-analyses found. However, the fact that most studies received high scores indicates that the meta-analyses of randomized-controlled trials exploring the efficacy and safety of the new anticoagulants versus warfarin in patients with atrial fibrillation have a good reporting quality.

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