

# Supplementary Material

## METHODS

### Search Strategy

An updated systematic search of the three databases was conducted for the period of March 1, 2013 to December 18, 2013, with the objective of capturing new subgroup analyses from phase 3 trials of dabigatran, rivaroxaban, and apixaban. No limits in terms of publication date or language were included in this search strategy.

### Data Extraction

A total of 43 variables were extracted using a standardized data abstraction form developed in Microsoft Excel (Table A-1). In addition, data for the outcomes of interest, if available, were extracted from the trials that compared a new oral anticoagulant versus warfarin in patients with CHADS<sub>2</sub> score  $\geq 2$  at baseline. In addition, edoxaban data were extracted from the clinical study report or post hoc analysis of ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48) if needed.

### Statistical Methods

The mixed Poisson regression model specific to this analysis can be described as follows:

$$y_{ij} \sim \text{Poisson}(\lambda_{ij}E_{ij})$$

$$\log(\lambda_{ij}) = t_j + s_i$$

where

- $y_{ij}$  is the number of events that occurred among the patients who received treatment  $j$  in study  $i$
- $\lambda_{ij}$  is the risk of events among the patients who received treatment  $j$  in study  $i$
- $E_{ij}$  is the exposure time contributed by the patients who received treatment  $j$  in study  $i$ , generally given in the format of person-years
- $t_j$  is the mean logarithm of risk for treatment  $j$
- $s_i$  are random study effects following a normal distribution with mean zero and unknown variance that account for the correlation between  $y_{ij}$  and  $y_{ij'}$  for  $j \neq j'$  when treatment groups come from the same study

It therefore follows that the risk of event due to treatment  $i$  is  $\lambda_i = \exp(t_i)$ , and the risk ratio (RR) of treatment  $a$  versus treatment  $b$  is defined as  $\lambda_a/\lambda_b = \exp(t_a - t_b)$ .

In this model, we assumed that risk is constant over the follow-up period. Suppose there are 1,000 person-years from one treatment  $j$  and study  $i$  after 1 year follow-up, then the mean of observed number of events is  $1,000\lambda_{ij}$ . If we follow up the patients for another 1.2 years and have a total of 2,000 person-years, then the mean number of events should be  $2,000\lambda_{ij}$ . This assumption is not true when the chance of events is varied according to the exposure time (e.g., for a type of adverse event that occurs immediately after the first treatment).

For each outcome analyzed using a model based on the Poisson distribution, the risk for specified treatment was estimated by  $\exp(\widehat{\beta}_1)$  with 95% confidence interval (CI) and the RR was estimated by  $\exp(\widehat{\beta}_1 - \widehat{\beta}_2)$  with 95% CI. The estimated risk, RR, and 95% CI are presented in the tables and forest plots. For consistency, person-years were derived by the ratio of number of events versus risk, even if person-years were provided separately.

## RESULTS

### Systematic Review and Summary of Included Trials

Of the 1,357 records identified in the initial literature search, 51 publications met the inclusion criteria. Eleven additional publications were identified from an updated systematic search of the literature. A total of 33 publications were identified as relevant. Of them, four phase 3 trials that compared a new oral anticoagulant versus warfarin and two publications<sup>1,2</sup> of these trials evaluating outcomes by CHADS<sub>2</sub> score were included in this meta-analysis. The four phase 3 trials were ARISTOTLE (apixaban),<sup>3</sup> ROCKET-AF (rivaroxaban),<sup>4</sup> RE-LY (dabigatran),<sup>5</sup> and ENGAGE AF-TIMI 48 (edoxaban).<sup>6</sup> The PRISMA checklist is presented in table A-2 and a list of excluded publications is presented in table A-3.

The average age of patients was similar among trials, as were the proportion of women recruited and the percentage of patients with prior myocardial infarction. However, there were a number of differences across these four trials in trial design, patients enrolled, and populations analyzed:

- The ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 trials were double-blind, double-dummy trials. In contrast, in the RE-LY trial, the assignments to dabigatran or warfarin were not concealed, and warfarin was administered as an open-label treatment.
- The RE-LY trial publication based all efficacy and safety analyses on the intention-to-treat (ITT) principle. In the ARISTOTLE trial publication, efficacy analyses were conducted on the ITT population and safety analyses on the on-treatment population. Analyses of efficacy in the ROCKET-AF trial publication were conducted on the ITT population only for the primary efficacy endpoint, and on a per-protocol population to demonstrate non-inferiority, with superiority and safety analyses run on the on-treatment population. In the ENGAGE AF-TIMI 48 trial, efficacy analyses were conducted on the ITT/modified ITT (mITT) overall study period and on-treatment populations, and safety analyses were conducted on the safety population during the on-treatment and overall study periods.
- Median follow-up ranged from 1.8 years in ARISTOTLE to 2.8 years in ENGAGE AF-TIMI 48.
- Subjects were enrolled in the ARISTOTLE, ENGAGE AF-TIMI 48, and RE-LY trials if they had a CHADS<sub>2</sub> score of  $\geq 1$ , whereas ROCKET-AF enrolled a higher-risk population (CHADS<sub>2</sub> score  $\geq 2$ ). At baseline, the mean CHADS<sub>2</sub> score for the ROCKET-AF trial was 3.4, compared with 2.1 for both RE-LY and ARISTOTLE.
- A larger proportion of patients with previous stroke or transient ischemic attack, with heart failure, or with diabetes were enrolled in ROCKET-AF than in the other trials.

- The mean percentage of time in which the international normalized ratio was in the therapeutic range of 2.0-3.0 for warfarin was 64% in the RE-LY trial, 62% in the ARISTOTLE trial, 55% in the ROCKET-AF trial, and 65% in the ENGAGE AF-TIMI 48 trial.

**Table A-1. Data Abstraction Form**

<b>Worksheet</b>	<b>Fields</b>
Study characteristics	<ul style="list-style-type: none"> <li>▪ Record number</li> <li>▪ Reference</li> <li>▪ Follow-up duration; study duration</li> <li>▪ Study design</li> <li>▪ Study phase</li> <li>▪ Intention-to-treat analysis</li> <li>▪ Inclusion criteria</li> <li>▪ Exclusion criteria</li> <li>▪ Concomitant medications at baseline</li> </ul>
Baseline characteristics by arm	<ul style="list-style-type: none"> <li>▪ Record number</li> <li>▪ Age</li> <li>▪ Female (% patients)</li> <li>▪ BP</li> <li>▪ Type of AF</li> <li>▪ Diabetes (% patients)</li> <li>▪ Hypertension (% patients)</li> <li>▪ CHADS<sub>2</sub> score</li> <li>▪ Creatinine clearance</li> <li>▪ VKA naïve (% patients)</li> <li>▪ Definition of VKA naïve</li> <li>▪ Comments</li> </ul>
Treatments per arm	<ul style="list-style-type: none"> <li>▪ Record number</li> <li>▪ Treatment group</li> <li>▪ Number randomized</li> <li>▪ Dosing schedule</li> <li>▪ Time in therapeutic range (% patients)</li> <li>▪ Dyspepsia, n (%)</li> <li>▪ Lost to follow-up, n (%)</li> <li>▪ Discontinuations, n (%)</li> </ul>

Worksheet	Fields
Outcomes per arm <sup>a</sup>	<ul style="list-style-type: none"> <li>▪ Record number</li> <li>▪ Composite of stroke and systemic embolism</li> <li>▪ systemic embolism</li> <li>▪ Ischemic stroke</li> <li>▪ Hemorrhagic stroke</li> <li>▪ All-cause death</li> <li>▪ Cardiovascular mortality</li> <li>▪ MI</li> <li>▪ Composite of major bleeding or clinically relevant nonmajor bleeding</li> <li>▪ Major bleeding<sup>b</sup></li> <li>▪ Major gastrointestinal bleeding</li> <li>▪ Clinically relevant non-major bleeding</li> <li>▪ Fatal bleeding</li> <li>▪ Intracranial hemorrhage</li> </ul>

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CHADS<sub>2</sub>, stroke risk factor scoring system in which 1 point is given for history of congestive heart failure, hypertension, age ≥ 75 years, and diabetes, and 2 points are given for history of stroke or transient ischemic attack; CI, confidence interval; ITT, intention to treat; MACE, major adverse cardiac event; MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist.

<sup>a</sup> For each treatment arm, definition, type of analysis (e.g., ITT, per-protocol population), total number of patients analyzed, number of patients with events, and event rate (%/patient-year) were extracted for each outcome. In addition, hazard ratios between treatment groups with CIs, standard errors, and *P* values were also extracted.

<sup>b</sup>The Subcommittee on Control of Anticoagulation, of the Scientific and Standardization Committee of the ISTH, endorses the following criteria for major bleeding in non-surgical patients: (i) fatal bleeding, and/or (ii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome, and/or (iii) bleeding causing a fall in hemoglobin level of 20g L (-1) (1.24 mmol/L[-1]) or more, or leading to a transfusion of two or more units of whole blood or red cells.

**Table A-2. PRISMA Checklist**

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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.	1
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-6
<b>METHODS</b>			
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.	NA
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4
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.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6



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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
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.	6-7
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).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
<b>RESULTS</b>			
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.	4
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.	5
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).	5
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.	8-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
<b>DISCUSSION</b>			
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).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14

<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

NA= not available;

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. Available at [www.prisma-statement.org](http://www.prisma-statement.org). Accessed on 29 July 2015.

**Table A-3. Excluded Studies and Reasons for Exclusion**

Reference	Ref ID	Reason
<b>Level 1 Screening (n = 1,101)</b>		
[Embolic complications in atrial fibrillation. Data of the Studio Italiano Fibrillation Atriale (SIFA)]. G Chir 1995 Mar;16(3):137-9.	464	Study Design
[INR self monitoring: large study shows no prognostic value]. MMW Fortschr Med 2008 Nov 20;150(47):14.	191	Intervention/Comparators
Aalbers J, Bryer A, Klug E. FDA committee unanimously recommends approval of dabigatran etexilate for stroke prevention in atrial fibrillation. Cardiovasc J Afr 2010 Nov;21(6):341.	129	Study Design
Aalbers J, Wagenaar P, Klug E. New anti-coagulant therapies set to revitalise clinical haematology practice. Cardiovasc J Afr 2010 Nov;21(6):323-6, 337.	130	Study Design
Aalbers J, Wagenaar P, Klug E. New anti-coagulant therapies set to revitalise clinical haematology practice: Annual meeting of the Southern African Society of Thrombosis and Haemostasis. Cardiovascular Journal of Africa 2010;21(6):323-6+337.	734	Study Design
Aalbers J. New anticoagulants offer consistent stroke-reduction benefit in atrial fibrillation. Cardiovascular Journal of Africa 2012;23(3):168.	612	Study Design
Aalbers J. Rivaroxaban equals warfarin treatment in atrial fibrillation patients at high risk of stroke. Cardiovasc J Afr 2010 Nov;21(6):342-3.	128	Intervention/Comparators
Abdelhafiz AH, Myint MP, Tayek JA, Wheeldon NM. Anemia, hypoalbuminemia, and renal impairment as predictors of bleeding complications in patients receiving anticoagulation therapy for nonvalvular atrial fibrillation: a secondary analysis. Clin Ther 2009 Jul;31(7):1534-9.	175	Study Design
Abdelhafiz AH, Wheeldon NM. Results of an open-label, prospective study of anticoagulant therapy for atrial fibrillation in an outpatient anticoagulation clinic. Clinical Therapeutics 2004;26(9):1470-8.	946	Intervention/Comparators
Abi nasr I, Mansencal N, Dubourg O. Management of atrial fibrillation in heart failure in the elderly. International Journal of Cardiology 2008;125(2):178-82.	843	Study Design
Abrol R, Page RL. Azimilide dihydrochloride: A new class III anti-arrhythmic agent. Expert Opinion on Investigational Drugs 2000;9(11):2705-15.	1060	Study Design

<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
ACTIVE-W: warfarin beats clopidogrel/aspirin in atrial fibrillation. <i>Cardiovasc J S Afr</i> 2006 Mar;17(2):91.	260	Intervention/Comparators
Ad N, Henry L, Schlauch K, Holmes SD, Hunt S. The CHADS score role in managing anticoagulation after surgical ablation for atrial fibrillation. <i>Annals of Thoracic Surgery</i> 2010;90(4):1257-62.	736	Study Design
Adam SS, McDuffie JR, Ortel TL, Nagi A, Williams JW. 2012 Apr.	41	Study Population
Adams Jr HP. 10 Most Commonly Asked Questions about which Antiplatelet Agent to Prescribe. <i>Neurologist</i> 2003;9(6):318-22.	971	Study Design
Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. <i>Lancet</i> 1996 Sep 7;348(9028):633-8.	448	Intervention/Comparators
Agarwal S, Bennett D, Smith DJ. Predictors of warfarin use in atrial fibrillation patients in the inpatient setting. <i>Am J Cardiovasc Drugs</i> 2010;10(1):37-48.	155	Intervention/Comparators
Agbahiwe SO, Okeke C, Okonkwo O. Janssen pharmaceuticals' xarelto. <i>Pharm.Times</i> 77. 2011.	648	Study Design
Agno W, Crowther M, Steidl L, Ultori C, Mera V, Dentali F, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: A randomized controlled trial. <i>Thrombosis and Haemostasis</i> 2002;88(1):48-51.	1013	Study Population
Aguirre FV, McMahon RP, Mueller H, Kleiman NS, Kern MJ, Desvigne-Nickens P, et al. Impact of age on clinical outcome and postlytic management strategies in patients treated with intravenous thrombolytic therapy: Results from the TIMI II study. <i>Circulation</i> 1994;90(1):78-86.	1148	Study Design
Ahmad Y, Lip GYH, Apostolakis S. New oral anticoagulants for stroke prevention in atrial fibrillation: Impact of gender, heart failure, diabetes mellitus and paroxysmal atrial fibrillation. <i>Expert Review of Cardiovascular Therapy</i> 2012;10(12):1471-80.	521	Study Design
Ahrens I, Bode C. Oral anticoagulation with edoxaban. Focus on current phase III clinical development. <i>Hamostaseologie</i> 2012;32(3):212-5.	34	Study Design
Ahrens I, Lip GY, Peter K. What do the RE-LY, AVERROES and ROCKET-AF trials tell us for stroke prevention in atrial fibrillation? <i>Thromb Haemost</i> 2011 Apr;105(4):574-8.	122	Study Design
Aizawa Y, Kohsaka S, Suzuki S, Atarashi H, Kamakura S, Sakurai M, et al. Comparison of antiarrhythmics used in patients with paroxysmal atrial fibrillation: Subanalysis of J-RHYTHM study. <i>Circulation Journal</i> 2010;74(1):71-6.	776	Intervention/Comparators
Akdeniz B, Badak O, Baris N, Aslan O, Kirimli O, Goldeli O, et al. Left atrial appendage-flow velocity predicts cardioversion success in atrial fibrillation. <i>Tohoku Journal of Experimental Medicine</i> 2006;208(3):243-50.	897	Study Design
Akdeniz B, Turker S, Ozturk V, Badak O, Okan T, Aslan O, et al. Cardioversion under the guidance of transesophageal echocardiography in persistent atrial fibrillation: Results with low molecular weight heparin. <i>International Journal of Cardiology</i> 2005;98(1):49-55.	934	Intervention/Comparators

<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
Akins PT, Feldman HA, Zoble RG, Newman D, Spitzer SG, Diener HC, et al. Secondary stroke prevention with ximelagatran versus warfarin in patients with atrial fibrillation: pooled analysis of SPORTIF III and V clinical trials. <i>Stroke</i> 2007 Mar;38(3):874-80.	241	Intervention/Comparators
Al Suwaidi J, Zubaid M, Al-Mahmeed WA, Al-Rashdan I, Amin H, Bener A, et al. Impact of fasting in Ramadan in patients with cardiac disease. <i>Saudi Medical Journal</i> 2005;26(10):1579-83.	916	Study Population
Albage A, van der Linden J, Lindblom D, Kenneback G, Nygren AT, Svedenhag J, et al. The maze operation for treatment of atrial fibrillation. <i>Scandinavian Cardiovascular Journal</i> 2000;34(5):480-5.	1058	Intervention/Comparators
Albers GW, Atwood JE, Hirsh J, Sherman DG, Hughes RA, Connolly SJ. Stroke prevention in nonvalvular atrial fibrillation. <i>Ann Intern Med</i> 1991 Nov 1;115(9):727-36.	492	Study Design
Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. <i>Chest</i> 2001;119(1 SUPPL.):194S-206S.	1051	Study Design
Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. <i>JAMA</i> 2005 Feb 9;293(6):690-8.	296	Intervention/Comparators
Albers GW. Antithrombotic therapy for prevention and treatment of ischemic stroke. <i>Journal of Thrombosis and Thrombolysis</i> 2001;12(1):19-22.	1024	Study Design
Albers GW. Atrial fibrillation and stroke: Three new studies, three remaining questions. <i>Archives of Internal Medicine</i> 1994;154(13):1443-8.	1146	Study Design
Alex J, Guvendik L. Evaluation of ventral cardiac denervation as a prophylaxis against atrial fibrillation after coronary artery bypass grafting. <i>Annals of Thoracic Surgery</i> 2005;79(2):517-20.	932	Study Population
Alexander R, Ferretti AC, Sorensen JR. Stop the nonsense not the anticoagulants: a matter of life and death. <i>N Y State Dent J</i> 2002 Nov;68(9):24-6.	349	Study Design
Alexander W, Connolly S, Arnesen H. European Society of Cardiology: Apixaban or aspirin in decreasing stroke risk (The AVERROES Trial). <i>P and T</i> 2010;35(10):580-1.	737	Intervention/Comparators
Algra A, Koundstaal PJ, Van Gijn J. Secondary prevention after cerebral ischaemia: Monotherapy with acetylsalicylic acid still first choice? <i>Nederlands Tijdschrift voor Geneeskunde</i> 1998;142(6):277-80.	1103	Intervention/Comparators
Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Warfarin anticoagulation and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction. <i>J Am Coll Cardiol</i> 1998 Mar 15;31(4):749-53.	438	Intervention/Comparators
Al-Khatib SM, Hafley G, Harrington RA, Mack MJ, Ferguson TB, Peterson ED, et al. Patterns of management of atrial fibrillation complicating coronary artery bypass grafting: Results from the PROject of Ex-vivo Vein graft ENgineering via Transfection IV (PREVENT-IV) Trial. <i>Am Heart J</i> 2009 Nov;158(5):792-8.	166	Intervention/Comparators
Al-Khatib SM, Pieper KS, Lee KL, Mahaffey KW, Hochman JS, Pepine CJ, et al. Atrial fibrillation and mortality among patients with acute coronary syndromes without ST-segment elevation: Results from the PURSUIT trial. <i>American Journal of Cardiology</i> 2001;88(1):76-9.	1044	Study Population

Reference	Ref ID	Reason
Almroth H, Hoglund N, Boman K, Englund A, Jensen S, Kjellman B, et al. Atorvastatin and persistent atrial fibrillation following cardioversion: A randomized placebo-controlled multicentre study. <i>European Heart Journal</i> 2009;30(7):827-33.	808	Intervention/Comparators
Alonso-Coello P, Zhou Q, Guyatt G. Home-monitoring of oral anticoagulation vs. dabigatran: An indirect comparison. <i>Thrombosis and Haemostasis</i> 2012;108(4):647-53.	564	Intervention/Comparators
Alreja G, Chandrasekaran D, Trikalinos T, Rothberg M. Oral anticoagulants for secondary prophylaxis of stroke in coronary artery disease and cerebrovascular accident. <i>J Am Coll Cardiol</i> 2011;57(14):E1509.	701	Study Population
Amabile G, Matteoli S, Fattapposta F, Lavezzari M, Trappolini M, Heiman F, et al. [Italian Study on Atrial Fibrillation (SIFA): status report]. <i>Cardiologia</i> 1993 Dec;38(12 Suppl 1):327-32.	475	Intervention/Comparators
Amin A. New oral anticoagulants for stroke prevention in atrial fibrillation: An update for managed care and hospital decision-makers. <i>Formulary</i> 2012;47(8):299-305.	522	Study Design
Amin AN, Lin J, Thompson S, Wiederkehr D. Inpatient and outpatient occurrence of deep vein thrombosis and pulmonary embolism and thromboprophylaxis following selected at-risk surgeries. <i>Ann Pharmacother</i> 2011 Sep;45(9):1045-52.	87	Study Design
Andersen LV, Lip GY, Lindholt JS, Frost L. Upper limb arterial thromboembolism: A systematic review on incidence, risk factors, and prognosis including a meta-analysis of risk-modifying drugs. <i>J Thromb Haemost</i> 2013 Feb 25.	2	Study Population
Anderson DC, Buckingham T, Hart RG, Kelley RE, Litin SC, McBride R, et al. Design of a multicenter randomized trial for the stroke prevention in atrial fibrillation study. <i>Stroke</i> 1990;21(4):538-45.	1165	Study Design
Anderson DC. Progress report of the Stroke Prevention in Atrial Fibrillation Study. <i>Stroke</i> 1990 Nov;21(11 Suppl):III12-III17.	498	Study Design
Anderson J, O'Donnell M. Clinical trials of new anticoagulants. <i>Vnitri Lekarstvi</i> 2006;52(SUPPL. 1):123-6.	895	Study Design
Antiplatelet agents for stroke patients. <i>MeReC Bulletin</i> 2003;14(2):5-8.	975	Study Design
Antonielli E, Pizzuti A, Gandolfo N, Sclavo M, Tanga M, Riva G, et al. Short-term anticoagulation before electrical cardioversion of chronic atrial fibrillation. <i>Giornale Italiano di Cardiologia</i> 1997;27(8):803-10.	1108	Intervention/Comparators
Apixaban in other situations? <i>Prescrire Int</i> 2012 Sep;21(130):203.	25	Study Design
Apixaban superior to warfarin in preventing stroke or systemic embolism. <i>Australian Journal of Pharmacy</i> 2012;93(1104):93.	601	Study Design
Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. <i>J Am Coll Cardiol</i> 2012 Aug 28;60(9):861-7.	28	Intervention/Comparators
Apostolakis S, Marin F, Lip GYH. Antiplatelet therapy in stroke prevention. <i>Adv.Cardiol.</i> 47, 141-154. 2012.	580	Study Design

Reference	Ref ID	Reason
Appadu B, Morosan M. Drugs affecting coagulation. <i>Anaesthesia and Intensive Care Medicine</i> 2013;14(1):32-8.	518	Study Design
Aramendi JI, Mestres CA, Campos V, Martinez-Leon J, Pontes C, Munoz G, et al. Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (TRAC): Rationale and design for a prospective, randomized, co-operative trial. <i>Interactive Cardiovascular and Thoracic Surgery</i> 2003;2(2):170-4.	992	Study Design
Aramendi JI, Mestres CA, Martinez-Leon J, Campos V, Munoz G, Navas C. Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (trac): prospective, randomized, co-operative trial. <i>Eur J Cardiothorac Surg</i> 2005 May;27(5):854-60.	294	Study Design
Archer SL, James KE, Kvernen LR, Cohen IS, Ezekowitz MD, Gornick CC. Role of transesophageal echocardiography in the detection of left atrial thrombus in patients with chronic nonrheumatic atrial fibrillation. <i>Am Heart J</i> 1995 Aug;130(2):287-95.	460	Intervention/Comparators
Arentz T, Weber R, Burkle G, Herrera C, Blum T, Stockinger J, et al. Small or large isolation areas around the pulmonary veins for the treatment of atrial fibrillation? Results from a prospective randomized study. <i>Circulation</i> 2007 Jun 19;115(24):3057-63.	228	Intervention/Comparators
Ariesen MJ, Algra A, Koudstaal PJ, Rothwell PM, Van Walraven C. Risk of Intracerebral Hemorrhage in Patients with Arterial Versus Cardiac Origin of Cerebral Ischemia on Aspirin or Placebo: Analysis of Individual Patient Data from 9 Trials. <i>Stroke</i> 2004;35(3):710-4.	964	Intervention/Comparators
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<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
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Wensley S, Keir S, Caine S, Mac MM. Additional risk factors in atrial fibrillation patients not receiving warfarin. <i>Age Ageing</i> 1999 Jul;28(4):355-7.	421	Study Design
Westphal K. Long-term oral anticoagulation: Evidence favors self-management. <i>MMW-Fortschritte der Medizin</i> 2004;146(42):58-9.	942	Study Design
White HD, Gruber M, Feysi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. <i>Arch Intern Med</i> 2007 Feb 12;167(3):239-45.	238	Intervention/Comparators
Wiegand UKH, LeJeune D, Boguschewski F, Bonnemeier H, Eberhardt F, Schunkert H, et al. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery: Influence of patient morbidity, operation strategy, and perioperative antiplatelet/anticoagulation therapy. <i>Chest</i> 2004;126(4):1177-86.	944	Intervention/Comparators
Wilson SJA, Wells PS, Kovacs MJ, Lewis GM, Martin J, Burton E, et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: A randomized controlled trial. <i>Canadian Medical Association Journal</i> 2003;169(4):293-8.	987	Intervention/Comparators
Witt DM. Initiation and Reinitiation of Anticoagulation Therapy. <i>Seminars in Hematology</i> 2011;48(4):295-301.	665	Study Design
Witte K, Thackray S, Clark AL, Cooklin M, Cleland JG. Clinical trials update: IMPROVEMENT-HF, COPERNICUS, MUSTIC, ASPECT-II, APRICOT and HEART. <i>Eur J Heart Fail</i> 2000 Dec;2(4):455-60.	383	Study Design
Wittkowsky AK. A systematic review and inventory of supplement effects on warfarin and other anticoagulants. <i>Thrombosis Research</i> 2005;117(1-2):81-6.	907	Study Population
Wolfram O, Hammwoehner M, Gramley F, Goette A. Update on pharmacologic approaches to prevent thromboembolism in atrial fibrillation: Are thrombin and factor Xa inhibitors the ultimate answer? <i>Current Vascular Pharmacology</i> 2011;9(3):350-7.	682	Study Design
Wolzt M, Eriksson UG, Gouya G, Leuchten N, Kapiotis S, Elg M, et al. Effect on perfusion chamber thrombus size in patients with atrial fibrillation during anticoagulant treatment with oral direct thrombin inhibitors, AZD0837 or ximelagatran, or with vitamin K antagonists. <i>Thromb Res</i> 2012 Apr;129(4):e83-e91.	81	Intervention/Comparators
Wolzt M, Samama MM, Kapiotis S, Ogata K, Mendell J, Kunitada S. Effect of edoxaban on markers of coagulation in venous and shed blood compared with fondaparinux. <i>Thromb Haemost</i> 2011 Jun;105(6):1080-90.	106	Intervention/Comparators
Wroe CD. 22nd Congress of the European Society of Cardiology, Amsterdam. <i>International Journal of Clinical Practice</i> 2000;54(7):459-60.	1063	Study Design
Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. <i>N Engl J Med</i> 2002 Dec 5;347(23):1825-33.	348	Intervention/Comparators

<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
Wyse DG. Rhythm versus rate control trials in atrial fibrillation. <i>Journal of Cardiovascular Electrophysiology</i> 2003;14(9 SUPPL.):S35-S39.	983	Intervention/Comparators
Wyse DG. Some Recent Randomized Clinical Trials in the Management of Atrial Fibrillation. <i>Journal of Interventional Cardiac Electrophysiology</i> 2003;9(2):223-8.	976	Study Design
Ximelagatran matches warfarin in AF. <i>British Journal of Diabetes and Vascular Disease</i> 2003;3(6):442.	972	Intervention/Comparators
Xu XS, Moore K, Burton P, Stuyckens K, Mueck W, Rossenu S, et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban in patients with acute coronary syndromes. <i>British Journal of Clinical Pharmacology</i> 2012;74(1):86-97.	587	Study Design
Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation : a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolic Secondary Prevention Cooperative Study Group. <i>Stroke</i> 2000 Apr;31(4):817-21.	382	Intervention/Comparators
Yamase M, Nakazato Y, Daida H. Effectiveness of amiodarone versus bepridil in achieving conversion to sinus rhythm in patients with persistent atrial fibrillation: A randomised trial. <i>Heart</i> 2012;98(14):1067-71.	588	Intervention/Comparators
Yamashita T, Ogawa S, Aizawa Y, Atarashi H, Inoue H, Ohe T, et al. Investigation of the optimal treatment strategy for atrial fibrillation in Japan : The J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) study design. <i>Circulation Journal</i> 2003;67(9):738-41.	982	Intervention/Comparators
Yamashita T. Frontiers of anticoagulation therapy for atrial fibrillation. <i>Journal of Cardiology</i> 2011;58(1):1-5.	679	Study Design
Yamashita T. Therapy of atrial fibrillation: Rate control or rhythm control? <i>Respiration and Circulation</i> 2003;51(10):1049-53.	977	Study Design
Yarmohammadi H, Varr BC, Puwanant S, Lieber E, Williams SJ, Klostermann T, et al. Role of CHADS2 score in evaluation of thromboembolic risk and mortality in patients with atrial fibrillation undergoing direct current cardioversion (from the ACUTE Trial Substudy). <i>Am J Cardiol</i> 2012 Jul 15;110(2):222-6.	49	Study Design
Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. <i>Internal Medicine</i> 2001;40(12):1183-8.	1027	Intervention/Comparators
Yigit Z, Kucukoglu MS, Okcun B, Sansoy V, Guzelsoy D. The safety of low-molecular weight heparins for the prevention of thromboembolic events after cardioversion of atrial fibrillation. <i>Japanese Heart Journal</i> 2003;44(3):369-77.	967	Intervention/Comparators
Yokota Y, Tsumura Y, Takarada A, Kawai H, Yokoyama M. The effect of recent advances in pharmacologic management on the prognosis of dilated cardiomyopathy. <i>Japanese Circulation Journal</i> 1993;57(11):1038-46.	1158	Study Population
You JHS, Tsui KKN, Wong RSM, Cheng G. Cost-effectiveness of Dabigatran versus genotype-guided management of Warfarin therapy for stroke prevention in patients with Atrial fibrillation. <i>PLoS ONE</i> 2012;7(6).	590	Study Design

Reference	Ref ID	Reason
Yousef ZR, Tandy SC, Tudor V, Jishi F, Trent RJ, Watson DK, et al. Warfarin for non-rheumatic atrial fibrillation: five year experience in a district general hospital. <i>Heart</i> 2004 Nov;90(11):1259-62.	305	Study Design
Zehnder BS, Schaer BA, Jeker U, Cron TA, Osswald S. Atrial fibrillation: estimated excess rate of stroke due to lacking adherence to guidelines. <i>Swiss Med Wkly</i> 2006 Dec 2;136(47-48):757-60.	243	Intervention/Comparators
Zeuthen EL, Lassen JF, Husted SE. Haemostatic activity in patients with atrial fibrillation treated with low-molecular-weight heparin before and after electrical cardioversion. <i>Journal of Thrombosis and Thrombolysis</i> 2004;17(3):185-9.	956	Intervention/Comparators
Zeuthen EL, Lassen JF, Husted SE. Is there a hypercoagulable phase during initiation of antithrombotic therapy with oral anticoagulants in patients with atrial fibrillation? <i>Thromb Res</i> 2003 Mar 15;109(5-6):241-6.	337	Intervention/Comparators
Zhao L, Zhang Z, Kolm P, Jasper S, Lewis C, Klein A, et al. Cost in the Use of Enoxaparin Compared With Unfractionated Heparin in Patients With Atrial Fibrillation Undergoing a Transesophageal Echocardiography-Guided Cardioversion (from Assessment of Cardioversion Using Transesophageal Echocardiography [ACUTE] II Randomized Multicenter Study). <i>American Journal of Cardiology</i> 2008;101(3):338-42.	845	Study Design
Zhu BP, Fan L, Li XY. Long-term effect and reliability of warfarin and aspirin for primary prevention of cardio-cerebral vessels events in patients with peripheral arteriosclerotic occlusive disease: A randomized, single-blind, controlled clinical trial with two-year follow-up. <i>Chinese Journal of Clinical Rehabilitation</i> 2005;9(15):10-1.	928	Study Population
Zimetbaum P. Amiodarone for atrial fibrillation. <i>New England Journal of Medicine</i> 2007;356(9):935-41+894.	868	Study Design
Zimmermann M. [Atrial fibrillation: anticoagulants or not?]. <i>Schweiz Med Wochenschr</i> 1994 Sep 3;124(35):1560-5.	467	Study Design
Zolfaghari S, Harenberg J, Marx S, Wehling M. Indirect comparisons of the new oral anticoagulants in patients with non-valvular atrial fibrillation. <i>Blood</i> 2012;120(21).	536	Study Design
Zuo HJ, Su JL, Zeng H, Yuan BH, Yao CH. Anticoagulation treatment in real-life practice of patient with nonvalvular atrial fibrillation in Beijing city. <i>National Medical Journal of China</i> 2007;87(33):2328-31.	854	Study Design

## Level 2 Screening (n = 57)

Adams HP, Jr. Antiplatelet aggregating versus anticoagulant agents in preventing early recurrent stroke among patients with atrial fibrillation. <i>Curr Neurol Neurosci Rep</i> 2001 Jan;1(1):11-2.	367	Study Design
Agarwal S, Hachamovitch R, Menon V. Improvement in thromboembolic outcomes with warfarin in patients with non-valvular atrial fibrillation over the last two decades. <i>J Am Coll Cardiol</i> 2012;59(13):E1836.	618	Study Design
Aguilar M, I, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. <i>Cochrane Database of Systematic Reviews</i> 2007.	1169	Study Design

<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: A meta-analysis. <i>Heart</i> 2008;94(12):1607-13.	822	Study Design
Artang R, Rome E, Vidaillet H. Dabigatran and myocardial infarction, drug or class effect. Meta-analysis of randomized trials with oral direct thrombin inhibitors. <i>J Am Coll Cardiol</i> 2012;59(13):E571.	619	Study Design
Baker WL, Phung O. Do differences exist between oral anticoagulants in patients with nonvalvular atrial fibrillation? an adjusted indirect comparison meta-analysis. <i>J Am Coll Cardiol</i> 2012;59(13):E597.	616	Study Design
Biondi Zoccai G, Marietta M, Malavasi V, Lotrionte M, D'Ascenzo F, Abbate A, et al. Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: Evidence from pair-wise and warfarincontrolled network meta analyses. <i>Blood Transfusion</i> 2012;10:s61.	561	Study Design
Camm AJ. The RE-LY study: Randomized Evaluation of Long-term anticoagulant therapy: Dabigatran vs. warfarin. <i>European Heart Journal</i> 2009;30(21):2554-5.	781	Study Population
Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients. <i>Int J Cardiol</i> 2012 Apr 9.	51	Study Design
Chatterjee S, Sharma A, Uchino K, Biondi-Zoccai G, Lichstein E, Mukherjee D. Rivaroxaban use is associated with reduced risk of myocardial infarction-insights from a meta-analysis and trial sequential analysis of randomized clinical trials. <i>Circulation</i> 2012;126(21).	533	Study Design
Connolly SJ. RELY: Randomized evaluation of long-term anticoagulant therapy. <i>European Journal of Heart Failure</i> 2009;11(12):1215.	780	Study Population
Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. <i>Arch Intern Med</i> 2006 Jun 26;166(12):1269-75.	256	Study Design
Cowburn P, Cleland JGF. SPAF-III results. <i>European Heart Journal</i> 1996;17(7):1129.	1120	Study Population
Cucherat M. Bias-corrected indirect comparison meta-analysis of new oral anticoagulant in atrial fibrillation. <i>Value in Health</i> 2012;15(7):A364.	547	Study Design
Dentali F, Riva N, Crowther M, Turpie AGG, Lip GYH, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation : A systematic review and meta-analysis of the literature. <i>Circulation</i> 2012;126(20):2381-91.	538	Study Design
Di PG, Palareti G. [The BAFTA study]. <i>G Ital Cardiol (Rome)</i> 2008 Nov;9(11):735-9.	194	Study Design
Dogliotti A, Paolasso E, Giugliano RP. Novel Oral Anticoagulants in Atrial Fibrillation: A Meta-analysis of Large, Randomized, Controlled Trials vs Warfarin. <i>Clin Cardiol</i> 2013 Feb;36(2):61-7.	7	Study Design

<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
Edwards SJ, Hamilton V, Nherera L, Trevor N, Barton S. A mixed treatment comparison (MTC) to compare the efficacy of anti-thrombotic agents in the prevention of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation (NVAf). <i>Value in Health</i> 2012;15(7):A363.	546	Study Design
Gomez-Outes A, Terleira-Fernandez A, Suarez-Gea ML, Vargas-Castrillon E. New oral anticoagulants versus warfarin on primary and secondary prevention of stroke in patients with atrial fibrillation: A metaanalysis. <i>Basic and Clinical Pharmacology and Toxicology</i> 2012;111:32.	543	Study Design
Green CJ, Hadorn DC, Bassett K, Kazanjian A. Anticoagulation in chronic nonvalvular atrial fibrillation: a critical appraisal and meta-analysis. <i>Can J Cardiol</i> 1997 Sep;13(9):811-5.	439	Study Design
Harenberg J, Marx S, Diener HC, Lip GYH, Marder VJ, Wehling M, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. <i>International Angiology</i> 2012;31(4):330-9.	571	Study Design
Harenberg J, Marx S, Krejczy M, Weiss C. Indirect comparison of new oral anticoagulants for patients with atrial fibrillation using network meta-analysis. <i>Hamostaseologie</i> 2012;32(1):A72.	562	Study Design
Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. <i>Ann Intern Med</i> 1999 Oct 5;131(7):492-501.	414	Study Design
Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. <i>Ann Intern Med</i> 2007 Jun 19;146(12):857-67.	227	Study Design
Jacobs LG. The sin of omission: a systematic review of antithrombotic therapy to prevent stroke in atrial fibrillation. <i>J Am Geriatr Soc</i> 2001 Jan;49(1):91-4.	379	Study Design
Koefoed BG, Feddersen C, Gullov AL, Petersen P. Effect of fixed minidose warfarin, conventional dose warfarin and aspirin on INR and prothrombin fragment 1 + 2 in patients with atrial fibrillation. <i>Thromb Haemost</i> 1997 May;77(5):845-8.	443	Outcomes
Koretsune Y, Inoue H, Kawai Y, Uchiyama S, Yamaguchi T. The oral factor Xa inhibitor DU-176b in Japanese warfarin-naive patients with atrial fibrillation: Results of two phase II open-label, dose-escalation studies. <i>J Am Coll Cardiol</i> 2009;53(10):A430-A431.	816	Intervention/Comparators
Kwong JS, Lam YY, Yan BP, Yu CM. Bleeding of new oral anticoagulants for stroke prevention in atrial fibrillation: a meta-analysis of randomized controlled trials. <i>Cardiovasc Drugs Ther</i> 2013 Feb;27(1):23-35.	13	Study Design
Lega JC, Mismetti P, Fassier T, Bertolotti L, Cucherat M, Vital-Durand D, et al. Double blind vs. open design on treatment effect of new oral anticoagulants in atrial fibrillation: A meta-analysis. <i>Fundamental and Clinical Pharmacology</i> 2012;26:17.	610	Study Design
Lip GY, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. <i>J Am Coll Cardiol</i> 2012 Aug 21;60(8):738-46.	45	Study Design
Lip GYH, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: A systematic review and meta-analysis. <i>Thrombosis Research</i> 2006;118(3):321-33.	887	Study Design



<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
Mak KH. Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomised trials. <i>BMJ Open</i> 2012;2(5).	20	Study Design
Mant J, Hobbs R, Fletcher K, Roalfe A. Is warfarin a safe alternative to aspirin in elderly patients with atrial fibrillation? <i>Cardiology Review</i> 2008;25(7):32-6.	835	Study Design
Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation (Provisional abstract). <i>American Journal of Cardiology</i> 2012;110:453-60.	1179	Study Design
Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. The efficacy and safety of new oral anticoagulants versus warfarin in patients with atrial fibrillation: A systematic review and meta-analysis. <i>Journal of Population Therapeutics and Clinical Pharmacology</i> 2012;19(2):e124.	541	Study Design
O'Dell KM, Igawa D, Hsin J. New Oral Anticoagulants for Atrial Fibrillation: A Review of Clinical Trials. <i>Clinical Therapeutics</i> 2012;34(4):894-901.	609	Study Design
Optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation: a systematic review of the clinical evidence. <i>CADTH Technol Overv</i> 2012;2(3):e2304.	26	Study Design
Patel MR, Hellkamp AS, Lokhnygina Y, Piccini JP, Zhang Z, Mohanty S, et al. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: Analysis from the ROCKET AF trial (Rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). <i>J Am Coll Cardiol</i> 2013;61(6):651-8.	509	Outcomes
Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. <i>N Engl J Med</i> 1990 Mar 22;322(12):863-8.	501	Intervention/Comparators
Rasmussen LH, Larsen TB, Graungaard T, Skjoth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. <i>BMJ</i> 2012;345:e7097.	15	Study Design
Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. <i>Arch Intern Med</i> 1994 Jul 11;154(13):1449-57.	469	Study Design
Roskell NS, Lip GY, Noack H, Clemens A, Plumb JM. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. <i>Thromb Haemost</i> 2010 Dec;104(6):1106-15.	137	Study Design
Roskell NS, Samuel M, Noack H, Monz BU. Major bleeding in patients with atrial fibrillation receiving vitamin K antagonists: a systematic review of randomized and observational studies. <i>Europace</i> 2013 Feb 13.	3	Study Design
Roversi S, Malavasi V, D'Ascenzo F, Abbate A, Castagno D, Van Tassell B, et al. Picking the best novel oral anticoagulant for atrial fibrillation: Evidence from a warfarin-controlled network meta-analysis. <i>J Am Coll Cardiol</i> 2012;59(13):E598.	615	Study Design

<b>Reference</b>	<b>Ref ID</b>	<b>Reason</b>
Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. <i>Circ Cardiovasc Qual Outcomes</i> 2012 Jul 1;5(4):480-6.	33	Study Design
Segal JB, McNamara R, Miller M, Powe N, Goodman SN, Robinson KA, et al. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. <i>Cochrane Database of Systematic Reviews</i> 2006.	1168	Study Design
Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs. <i>J Gen Intern Med</i> 2000 Jan;15(1):56-67.	405	Study Design
Simon TA, Jakouloff D, Mitchell SA, Raza SA, Lockhart I, Drost P. Heterogeneity in published evidence for stroke prevention in patients with atrial fibrillation: A systematic review. <i>Pharmacoepidemiology and Drug Safety</i> 2012;21:247-8.	573	Study Design
Sobieraj DM, White CM, Alikhanov S, Winkler S, Mediouni M, Kluger J, et al. The impact of antiplatelet and anticoagulant therapies on gastrointestinal symptoms in patients with atrial fibrillation: A systematic review. <i>Annals of Pharmacotherapy</i> 2012;46(9):1220-31.	563	Study Design
Stroke Prevention in Atrial Fibrillation Study. Final results. <i>Circulation</i> 1991 Aug;84(2):527-39.	494	Intervention/Comparators
Taylor FC, Cohen H, Ebrahim S. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. <i>BMJ</i> 2001 Feb 10;322(7282):321-6.	380	Study Design
Testa L, Agnifili M, Latini RA, Mattioli R, Lanotte S, De Marco F, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. <i>QJM</i> 2012;105(10):949-57.	555	Study Design
Uchino K, Hernandez AV. Dabigatran is associated with higher risk of myocardial infarction or acute coronary syndromes: A meta-analysis of non-inferiority randomized controlled trials. <i>Circulation</i> 2011;124(21).	649	Study Design
Van Latum JC. The 'European atrial fibrillation study': Secondary prevention of thromboembolic complications with oral anticoagulants or acetylsalicylic acid in patients with non-rheumatic atrial fibrillation. <i>Nederlands Tijdschrift voor Geneeskunde</i> 1994;138(20):1025-31.	1149	Study Design
van WC, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. <i>JAMA</i> 2002 Nov 20;288(19):2441-8.	350	Study Design
Wasserlauf G, Grandi SM, Fillion KB, Eisenberg MJ. Safety of rivaroxaban versus vitamin K antagonists: A systematic review and meta-analysis. <i>Circulation</i> 2012;126(21).	530	Study Design
Yasaka M, Inoue H, Kawai Y, Yamaguchi T, Uchiyama S, Matsumoto M, et al. Randomized, parallel group, warfarin control, multicenter phase II study evaluating safety of DU-176b in Japanese subjects with non-valvular atrial fibrillation (NVAf). <i>Journal of Thrombosis and Haemostasis</i> 2009;7(S2):692.	792	Study Design

### **Studies Excluded from the Meta-analysis (n = 29)**

Reference	Ref ID	Reason
Al-Khatib, S. M.; Thomas, L.; Wallentin, L.; Lopes, R. D.; Gersh, B.; Garcia, D.; Ezekowitz, J.; Alings, M.; Yang, H.; Alexander, J. H.; Flaker, G.; Hanna, M.; Granger, C. B. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: Results from the ARISTOTLE trial. <i>European Heart Journal</i> 2013, 34 (31), 2464-2471.	R_127	Subgroup of no interest
BAY59-7939 in Atrial Fibrillation Once Daily (OD). NCT00973245. Available at <a href="http://clinicaltrials.gov/ct2/show/NCT00973245?term=anticoagulant&amp;cond=atrial+fibrillation&amp;intr=anticoagulant&amp;phase=123&amp;rank=34">http://clinicaltrials.gov/ct2/show/NCT00973245?term=anticoagulant&amp;cond=atrial+fibrillation&amp;intr=anticoagulant&amp;phase=123&amp;rank=34</a> . Accessed March 26, 2013.		Not enough information
BAY59-7939 Japanese in Atrial Fibrillation (2nd). NCT00973323. Available at <a href="http://clinicaltrials.gov/ct2/show/NCT00973323?term=anticoagulant&amp;cond=atrial+fibrillation&amp;intr=anticoagulant&amp;phase=123&amp;rank=33">http://clinicaltrials.gov/ct2/show/NCT00973323?term=anticoagulant&amp;cond=atrial+fibrillation&amp;intr=anticoagulant&amp;phase=123&amp;rank=33</a> . Accessed March 26, 2013.		Not enough information
Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. <i>Arch Intern Med</i> 1996 Feb 26;156(4):409-16.	454	Methodological differences
Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. <i>N Engl J Med</i> . 2010 Nov 4;363(19):1875-6.		Supporting document
FDA Briefing Information 2010. Clinical Review: Pradaxa (dabigatran)		Supporting document
FDA Draft Briefing Document for Xarelto® (rivaroxaban) 2011		Supporting document
FDA Medical Review on Apixaban 2012		Supporting document
Gullov AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. <i>Atrial Fibrillation Aspirin and Anticoagulation. Arch Intern Med</i> 1999 Jun 28;159(12):1322-8.	424	Subgroup of no interest
Halperin HL, Hankey GJ, Wojdyla D, Piccini JP, Lokhnygina Y, Patel MR, Breithardt G, Singer DE, Becker RC, Hacke W, Paolini JP, Nessel CC, Mahaffey KW, Califf RM, Fox KA. Efficacy and Safety of Rivaroxaban Compared with Warfarin Among Elderly Patients with Nonvalvular Atrial Fibrillation in the ROCKET-AF Trial. Presented at: American Heart Association (AHA) Scientific Sessions 2012; Feb 02.		Not enough information
Hankey GJ, Stevens S, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL, Patel MR, Breithardt G, Singer DE, Becker RC, Paolini JP, Nessel CC, Hacke W, Fox KA, Califf RM. Predictors of Intracranial Hemorrhage Among Anticoagulated Patients with Atrial Fibrillation: Insights from 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). Presented at: American Heart Association (AHA) Scientific Sessions 2012; Feb 02.		Subgroup of no interest
Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. <i>Stroke</i> 2012 Jun;43(6):1511-7.	52	Subgroup of no interest

Reference	Ref ID	Reason
Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. <i>Eur Heart J</i> . 2012 Nov;33(22):2821-30 [Abstract]		Not enough information
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