SUPPLEMENTARY MATERIAL

METHODS

We established a systematic review protocol according to the methodological guidance provided by the Cochrane Collaboration[1] and have reported the findings according to the PRISMA statement.[2]

With the main objective to assess the efficacy of new oral anticoagulants, this systematic review addressed the following clinical question: **What is the comparative effectiveness of new oral anticoagulants vs vitamin K antagonists in terms of a reduction in the risk of stroke or bleeding in patients with nonvalvular atrial fibrillation?**

Inclusion Criteria

To respond to the clinical question of the review, we considered eligible studies with the following criteria (studies should meet all of them):

- Participants: patients diagnosed with nonvalvular atrial fibrillation (NVAF) with or without a previous stroke;
- Interventions: direct oral anticoagulants (DOACs: apixaban, dabigatran, and rivaroxaban; any dose);
- Control: vitamin K antagonists (VKAs), focusing on warfarin;
- Outcomes: the primary outcome for effectiveness was ischemic stroke. Major and intracranial bleeding were considered the primary safety outcomes. The secondary outcomes of interest were gastrointestinal and fatal bleeding. Additionally, we also considered a composite end point of stroke/systemic embolism. Because all studies reported time-to-event outcomes, in order to be included in the meta-analysis, studies had to not only provide rates, but also effect measures (hazard ratios [HRs]). Otherwise, studies were excluded;
- Study design: we limited the inclusion to observational studies (either prospective or retrospective) reporting on any of the above outcomes from routinely collected health data. To be

included, studies had to use national or regional registries or registries covering a large population across multiple sites. Single-center studies using local registries were excluded unless they had more than 1000 patients. For studies that used the same registry and were performed in the same (or very similar) period, the most complete publication was selected, discarding the rest in order to avoid including the same patients in duplicate in the meta-analysis. Only when it was perceived that the degree of overlap between studies was low were all publications included.

Study Identification

- To retrieve the studies of interest for the review, MEDLINE (through PubMed) and EMBASE (through Ovid) were searched up to March 2017. Search algorithms (Table 1 of the supplementary material) were designed that were adapted to the requirements of each database; these algorithms included a combination of controlled vocabulary search terms and filters to retrieve clinical trials and cohort studies. The bibliography sections of eligible studies were also searched for additional studies.

Data Extraction

- One reviewer extracted data to describe the included studies according to the following variables: reference, objective, country, design, data source, time period, DOAC, control, outcomes, outcome definitions, population (eligibility), population (study sample), population (baseline participant characteristics), and analysis.
- All of the data obtained in this step are included in tables showing the characteristics of the included studies. In addition, 1 researcher extracted data on the effects estimates for the outcomes of interest reported in the included studies, and a second reviewer checked the data extraction for accuracy.

Risk of Bias Assessment

- We assessed the risk of bias of included studies and judged the bias across outcomes of interest. We used the ROBINS-I tool to assess risk of bias because it was specifically designed to assess nonrandomized studies when they are used to measure the impact of interventions[3] (Table 2 of the supplementary material).
- The assessment of threats of validity for the study designs included in the review is a complex task because studies based on routine collected health data do not fit the classical observational design and do not typically collect data with a specific research question,[4] complicating the appraisal of some domains.
- For each study, we assessed confounding, selection bias, bias in measurement interventions, bias due to deviations from intended interventions, bias due to missing data, bias in outcome assessment, and bias in the selection of the reported results. We adapted the original ROBINS-I tool to fit the design of the included studies and their specificities.
- We established some questions to assess the different biases of interest and appraised each included study. We appraised the different domains according to the main outcome of interest in the included studies. Each domain was classified as having low, moderate, or serious risk of bias and we made a final assessment for each study according to the bias across domains. We considered a study to be at (1) low risk of bias if all of the domains were assessed as low risk; (2) moderate risk if all of the domains were assessed as low or moderate risk; and (3) serious risk if the study was considered to be at serious risk in at least 1 domain.

Data Analysis

Timepoints and Effect Measures

- Most studies presented results up to 1 year, with only a few reporting results from longer follow-up periods (2 years or more). The timepoint chosen for the main comparison was 1 year, with secondary analyses defined for longer follow-up results.

- The effect measures were HRs and their corresponding 95% confidence intervals. In all cases, the data extracted were adjusted by the HR reported in the main analyses of the original papers or, exceptionally, by the HR obtained with the most complete adjustment model.
- When available, the data reported in the main analysis corresponds to the most general population: all doses (standard and reduced), all participants (switch and naïve), all ages, and all purposes (primary and secondary prevention). Whenever a study presented only disaggregated data for 1 or more of these subgroups, the most complete nonoverlapping data were used for the main analysis. Whenever a study presented data for only some level of the subgroups (ie, only including naïve participants), these data were included in the main analysis as well as in the corresponding subgroup analysis.

Data Synthesis

- The main comparison of interest was DOACs vs control, presenting results disaggregated by type of DOAC. The control was warfarin but could also be other VKAs. Other main comparisons of interest were head-to-head comparisons between the different DOACs. However, the meta-analysis was only meaningful for the rivaroxaban vs dabigatran comparison because the included studies presented few data for the other head-to-head comparisons. Thus, there are only 2 main comparisons.
- Pooled estimates of effect for the main comparisons (DOACs vs control, and rivaroxaban vs dabigatran) were computed with a random-effects model applying the inverse-variance meta-analysis method. Meta-analyses were conducted for all primary and secondary outcomes assessed at 1 year.
- For secondary analyses (subgroup analyses, sensitivity analyses, and analysis at 2 years), only the primary outcomes of stroke, major bleeding, and intracranial bleeding were analyzed.

- All meta-analyses were stratified by DOACs and included a pooled category with the trials that presented aggregated data for all DOAC. Because most trials provided data for different categories of DOACs, no total was computed for any meta-analysis.

Heterogeneity Assessment

- All of the included studies were observational real-life studies and all of them implemented some kind of procedure to adjust for differences between the cohort of participants taking warfarin, apixaban, dabigatran, or rivaroxaban. The procedures implemented varied across studies (ie, propensity scores or adjusted Cox models), and the number and type of factors adjusted for varied considerably. For these reasons, large clinical heterogeneity was expected in all of the analyses.
- Between-study heterogeneity was assessed through the I^2 statistic, which can take a range of values from 0% (meaning all observed variability in results can be explained by random variation) to 100% (none of the observed variability in results can be explained by random variation). Cutoff values were defined for the I^2 to help in the interpretation of results: values lower than 20% were considered to correspond to unimportant heterogeneity; values between 21% and 65% were considered moderate heterogeneity; and I^2 values over 65% were considered to be highly heterogeneous.

Subgroup and Sensitivity Analyses

- Several secondary analyses were conducted. First of all, secondary analyses were conducted for each of the planned subgroups (naïve and switched participants, standard and reduced doses).
- A secondary analysis was conducted using the longer-term data available in each study.

RESULTS

Search Results and Eligibility

The PRISMA flowchart shows the search results and the decisions made during the eligibility process (Figure 1 of the manuscript). We obtained 4244 references from MEDLINE and EMBASE searches and screened 3391 unique references after eliminating duplicates. We excluded 3312 references based on their title or abstract and obtained 79 full-text studies for the final decision.

After a detailed assessment of the full texts, we excluded 49 studies:

- 19 did not assess an outcome of interest or reported outcome data in a way that could not be analyzed in the meta-analysis (crude data and rates, without providing an effect measure such as the HR) (Avgil-Tsadok et al.,[5] Badal et al.,[6] Bochatay et al.,[7] Chan et al.,[8] Demir et al.,[9] Ellis et al.,[10] Fontaine et al.,[11] Gorst-Rasmussen et al.,[12] Kodani et al.,[13] Kono et al.,[14] Larsen et al.,[15] Lee et al.,[16] Maura et al.,[17] Michel et al.,[18] Palamaner et al.,[19] Shevelev et al.,[20] Sorensen et al.,[21] Steinberg et al.,[22] and Yap et al.[23]);
- 18 did not obtain data from a reliable source (Al-Khalili et al.,[24] Aslan et al.,[25] Ho et al.,[26] Khan et al.,[27] Kilickiran Avci et al.,[8] Konigsbrugge et al.,[29] Korenstra et al.,[30] Kwon et al.,[31] Labaf et al.,[32] Lee et al.,[33] Leef et al.,[34] Marques-Matos et al.,[35] Naganuma et al.,[36] Riley et al.,[37] Saji et al.,[38] Sherid et al.,[39] Yap et al.,[40] and Yavuz et al.[41]);
- 8 reported overlapping data with other included studies (Abraham et al.,[42] Ho et al.,[43] Lamberts et al.,[44] Larsen et al.,[45] Lauffenburger et al.,[46] Lip et al.,[47] Staerk et al.,[48] and Staerk et al.[49]) (overlaps with Yao et al.,[50] overlaps with Li et al.,[51] overlaps with Larsen et al.,[52] and Nielsen et al.,[53] overlaps with Larsen et al.[52] and Nielsen et al.,[53] overlaps with Bengtson et al.,[54] overlaps with Lip et al.,[55] overlaps with Gorst-Rasmussen et al.,[12] overlaps with Larsen et al.[50] and Nielsen et al.,[53] respectively);
- 2 studies did not assess new oral anticoagulants (Guo et al.[56] and Lip et al.[57]);
- 1 reported data from an ineligible population (anticoagulation resumption after a first major bleed in NVAF patients) (Hernandez et al.[58]);
- and 1 did not adjust data for the comparison (the reference group for the comparison comprised patients treated with warfarin and with a time in therapeutic range ≥ 65%) (Li et al.[51]).

Finally, we included 27 different studies publishing data in 30 publications (3 studies published relevant data in 2 separate papers): Arihiro et al.[59] (Japan), Avgil-Tsadok et al.[60] (Canada), Bengtson et al.[54] (US), Bouillon et al.[61] (France), Chan et al.[62,63] a+b (Taiwan), Chang et al.[64] (US), Coleman et al.[65] (US), Forslund et al.[66] (Sweden), Gieling et al.[67] (UK), Graham et al.[68] (US), Graham et al.[69] (US), Halvorsen et al.[70] (Norway), Hernandez et al.[71] (US), Hernandez et al.[72] (US), Hohnloser et al.[73] (Germany), Lai et al.[74] (Taiwan), Laliberté et al.[75] (US), Larsen et al.[76,77] a+b (Denmark), Larsen et al.[52] (Denmark), Li et al.[78] (US), Lip et al.[79] (US), Nielsen et al.[53] (Denmark), Nishtala et al.[80] (New Zealand), Noseworthy et al.[81] (US), Seeger et al.[82] (linked to Yao et al.), Vaughan Sarrazin et al.[83] (US), Villinies et al.[84] (US), and Yao et al.[85] (US) (Table 3 of the supplementary material).

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Table 1 of the suplementary material

Search Algorithms for Database Searches

DATABASE	SEARCH ALGORITHM
MEDLINE (PubMed) 20/04/2017	#1 "Dabigatran"[Mesh] 1986 #2 "Rivaroxaban"[Mesh] 1658 #3 "Dabigatran"[nm] 1986 #4 "Rivaroxaban"[nm] 1658 #5 "edoxaban"[nm] 291 #6 "apixaban"[nm] 893 #7 oral anticoagula*[ti] 4625 #8 NOAC*[tiab] 1188 #9 DOAC*[tiab] 466 #10 dabigatran[tiab] 3209 #11 apixaban[tiab] 1799 #12 rivaroxaban[tiab] 2855 #13 edoxaban[tiab] 728 #14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 9668 #15 "Warfarin"[Mesh] 16800 #16 "Warfarin"[nm] 16800 #17 warfarin[tiab] 20278 #18 vitamin K antagonist*[tiab] 3966 #19 VKA[tiab] 1109 #20 #15 OR #16 OR #17 OR #18 OR #19 28384 #21 #14 AND #20 4531 #22 systematic[sb] 319651 #23 #21 AND #22 486 #24 #21 NOT #23 4045 #25 "Atrial Fibrillation"[Mesh] 42760 #26 atrial fibrillation[tiab] 52480 #27 #25 OR #26 62436 #28 #24 AND #27 2257 #29 "Stroke"[Mesh] 104004 #30 stroke[tiab] 187995 #31 #29 OR #30 220619 #32 #24 AND #31 1808 #33 #28 OR #32 2401 #34 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals [mh] NOT humans [mh]) 3461777 #35 #33 AND #34 1628 #36 #33 NOT #35 773 #37 "Comparative Study"[pt] 1761255 #38 "Cohort Studies"[Mesh] 1610475 #39 "Propensity Score"[Mesh] 3672 #40 "Registries"[Mesh] 71305 #41 cohort*[tiab] 401749 #42 observational[ti] 18306 #43 registr*[tiab] 162502 #44 nationwide[tiab] 34597 #45 administrative[tiab] 35085 #46 claims[tiab] 37903 #47 propensity[tiab] 40617 #48 #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR

	#46 OR #47 3483871 #49 #36 AND #48 178 #50 real world[tiab] 21984 #51 #50 AND #35 84 #52 #49 OR #51 262 #53 #23 OR #35 OR #52 2292
EMBASE Ovid EMBASE 1974 to 2017 May 04 05/05/2017	1 exp dabigatran/ (8519) 2 exp rivaroxaban/ (9537) 3 exp dabigatran/ (8519) 4 exp edoxaban/ (2024) 5 oral anticoagula*.ti. (6962) 6 NOAC*.ti,ab. (2373) 7 DOAC*.ti,ab. (756) 8 dabigatran.ti,ab. (6042) 9 apixaban.ti,ab. (3240) 10 rivaroxaban.ti,ab. (5569) 11 edoxaban.ti,ab. (1028) 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (20002) 13 exp warfarin/ (77810) 14 warfarin.ti,ab. (31108) 15 vitamin K antagonist*.ti,ab. (6367) 16 VKA.ti,ab. (2366) 17 13 or 14 or 15 or 16 (84711) 18 exp atrial fibrillation/ (23981) 19 atrial fibrillation.ti,ab. (87233) 20 18 or 19 (93552) 21 exp cerebrovascular accident/ (144845) 22 stroke.ti,ab. (281422) 23 21 or 22 (327274) 24 20 or 23 (395950) 25 12 and 17 and 24 (6634) 26 conference.so. (334589) 27 25 not 26 (6350) 28 exp comparative effectiveness/ (30861) 29 Controlled Study/ (5355982) 30 Cohort Studies/ (168942) 31 exp propensity score/ (12496) 32 exp cohort analysis/ (284218) 33 exp propensity score/ (12496) 34 exp register/ (96627) 35 cohort*.ti,ab. (642060) 36 registr*.ti,ab. (222027) 37 nationwide.ti,ab. (48510) 38 administrative.ti,ab. (45967) 39 claims.ti,ab. (52149) 40 propensity.ti,ab. (53788) 41 observational.ti. (25334) 42 real world.ti,ab. (33695) 43 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (6171570) 44 27 and 43 (1868)

Table 2 of the supplementary material

Risk of Bias Assessment for the Included Studies

Study ID	**Arihiro et al.**[59]	**Avgil-Tsadok et al.**[60]	**Bengtson et al.**[54]	**Bouillon et al.**[61]	**Chan et al.**[62]
Cohort design	Prospective	Retrospective	Retrospective	Nationwide	Nationwide
Data source	Clinical registry	Administrative data	Administrative data	Administrative data	Administrative data
Primary outcome	Stroke or embolism and bleeding (major)	Stroke or TIA, bleeding (any), and AMI	Stroke, bleeding, and AMI	Bleeding (any)	Stroke, bleeding, AMI, and mortality
Confounding (baseline) Researchers implemented appropriate methods to control for prognostic confounders	**Low risk** Propensity score (unclear analysis)	**Low risk** Propensity score (matching)	**Low risk** Propensity score (high dimensional)	**Moderate risk** Cox conditional model (matched adjustment)	**Low risk** Inverse probability weighting
Confounding (of intervention) Researchers implemented appropriate methods to avoid an impact of prognostic factors on the choice of drug prescribed	**No information**	**No information**	**No information**	**No information**	**No information**
Selection bias Researchers selected a sample of newly diagnosed patients or new drug users and measured outcomes from the start of treatment	**Serious risk** AF diagnosed after a first stroke and patients had recently received their prescription	**Low risk**	**Low risk**	**Low risk** Study of switchers but index date for NOACs appropriately defined	**Low risk**
Selection bias Researchers described any exclusion during eligibility	**Low risk**	**Moderate risk** Reduced dabigatran doses excluded	**Low risk**	**Low risk**	**Low risk**
Bias in measurement of interventions Researchers avoided the definition and categorization of interventions without knowledge of outcomes	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**

Bias due to deviations from intended interventions Researchers measured and controlled differences in co-interventions between groups	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Missing data Researchers measured and controlled differences in the extent of and reasons for missing data between groups	**Moderate risk** Missing data for drop outs	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in outcome measurement Researchers avoided different measures of outcomes depending on the drug	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in the selection of reported findings Researchers reported complete findings for the outcomes of interest	**Serious risk** Main outcome findings reported only as composite	**Moderate risk** Main outcome effect estimates reported only as composite	**Low risk**	**Moderate risk** Findings for composite outcome not described in Methods	**Low risk**
OVERALL RISK OF BIAS	**SERIOUS**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**

AMI, acute myocardial infarction; NOACs, nonvitamin K antagonist oral anticoagulants; TIA, transient ischemic attack.

Study ID	**Chan et al.[63]**	**Coleman et al.[65]**	**Forslund et al.[66]**	**Gieling et al.[67]**	**Graham et al.[68]**	**Graham et al.[69]**
Cohort design	Nationwide	Retrospective	Nationwide	Retrospective	Retrospective	Retrospective
Data source	Administrative data	Administrative data	Population registry	Primary care database	Administrative data	Administrative data
Primary outcome	Stroke, bleeding, AMI, and mortality	Stroke or bleeding (intracranial)	Bleeding (major)	Bleeding (major)	Stroke and major bleeding	Stroke, major bleeding, and mortality
Confounding (baseline) Researchers implemented an appropriate method to control for prognostic confounders	**Low risk** Inverse probability weighting	**Low risk** Propensity score (matching)	**Low risk** Inverse probability weighting	**Moderate risk** Cox proportional hazards regression	**Low risk** Propensity score (matching)	**Low risk** Inverse probability weighting
Confounding (of intervention) Researchers implemented appropriate methods to avoid an impact of prognostic factors on the choice of drug prescribed	**No information**	**No information**	**No information**	**No information**	**No information**	**No information**
Selection bias	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**

Researchers selected a sample of new drug users and measured outcomes from the start of treatment						
Selection bias Researchers described any exclusion during eligibility	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in measurement of interventions Researchers avoided the definition and categorization of interventions without knowledge of outcomes	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias due to deviations from intended interventions Researchers measured and controlled differences in co-interventions between groups	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Missing data Researchers measured and controlled differences in the extent of and reasons for missing data between groups	**Low risk**	**Low risk**	**Low risk**	**Moderate risk** Excluded patients with the outcome at baseline	**Low risk**	**Low risk**
Bias in outcome measurement Researchers avoided different measures of outcomes depending on the drug	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in the selection of reported findings Researchers reported complete findings for the outcomes of interest	**Low risk**	**Low risk**	**Moderate risk** Composite outcome reported in findings not described in the Methods	**Low risk**	**Low risk**	**Low risk**
OVERALL RISK OF BIAS	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**

Study ID	**Halvorsen et al.[71]**	**Hernandez et al.[72]**	**Hernandez et al.[73]**	**Hohnloser et al.[74]**	**Laliberté et al.[76]**	**Lai et al.[75]**
Cohort design	Nationwide	Retrospective	Retrospective	Retrospective	Retrospective	Nationwide
Data source	Population registry	Administrative data	Administrative data	Administrative data	Administrative data	Administrative data
Primary outcome	Bleeding (major or clinically relevant)	Bleeding (any)	Stroke, other thromboembolism	Bleeding (major)	Stroke or embolism and bleeding (any)	Mortality
Confounding (baseline) Researchers implemented an appropriate method to control for prognostic confounders	**Moderate risk** Cox proportional hazards regression	**Low risk** Inverse probability weighting	**Low risk** Inverse probability weighting	**Low risk** Propensity score (matching)	**Low risk** Propensity score (matching)	**Low risk** Propensity score (matching)

Confounding (of intervention) Researchers implemented appropriate methods to avoid an impact of prognostic factors on the choice of drug prescribed	**No information**	**No information**	**No information**	**No information**	**No information**	**No information**
Selection bias Researchers selected a sample of new drug users and measured outcomes from the start of treatment	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Selection bias Researchers described any exclusion during eligibility	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in measurement of interventions Researchers avoided the definition and categorization of interventions without knowledge of outcomes	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias due to deviations from intended interventions Researchers measured and controlled differences in co-interventions between groups	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Missing data Researchers measured and controlled differences in the extent of and reasons for missing data between groups	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in outcome measurement Researchers avoided different measures of outcomes depending on the drug	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in the selection of reported findings Researchers reported complete findings for the outcomes of interest	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
OVERALL RISK OF BIAS	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**

Study ID	**Larsen et al.[76,77](*)**	**Larsen et al.[52,53](*)**	**Li et al.[79]**	**Lip et al.[80]**	**Nishtala et al.[81]**
Cohort design	Nationwide	Nationwide	Retrospective	Retrospective	Nationwide
Data source	Population registry	Population registry	Administrative	Administrative	Population registry

			data	data	
Primary outcome	Bleeding (any)	Stroke or embolism, mortality, and bleeding (any)	Stroke or embolism and bleeding (major)	Bleeding (major)	Bleeding (any)
Confounding (baseline) Researchers implemented an appropriate method to control for prognostic confounders	**Moderate risk** Cox conditional model (matched adjustment)	**Low risk** Inverse probability weighting	**Low risk** Propensity score (matching)	**Moderate risk** Cox proportional hazards regression	**Low risk** Propensity score (matching)
Confounding (of intervention) Researchers implemented appropriate methods to avoid an impact of prognostic factors on the choice of drug prescribed	**No information**	**No information**	**No information**	**No information**	**No information**
Selection bias Researchers selected a sample of new drug users and measured outcomes from the start of treatment	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Selection bias Researchers described any exclusion during eligibility	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in measurement of interventions Researchers avoided the definition and categorization of interventions without knowledge of outcomes	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias due to deviations from intended interventions Researchers measured and controlled differences in co-interventions between groups	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Missing data Researchers measured and controlled differences in the extent of and reasons for missing data between groups	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Bias in outcome measurement Researchers avoided different measures of	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**

outcomes depending on the drug					
Bias in the selection of reported findings Researchers reported complete findings for the outcomes of interest	**Low risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
OVERALL RISK OF BIAS	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**	**MODERATE**

*Larsen 2014 risk of bias assessment applies to Larsen 2014a and Larsen 2014b; Larsen 2016 risk of bias assessment also applies to Nielsen 2017

Table 3 of the supplementary material

Characteristics of the Included Studies

Study ID	Arihiro et al.[59]
Reference	Arihiro S, Todo K, Koga M, Furui E, Kinoshita N, Kimura K, et al. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: The SAMURAI-Nonvalvular Atrial Fibrillation (NVAF) study. *Int J Stroke.* 2016;11:565-574. doi:10.1177/1747493016632239
Objective	To determine the risk-benefit profile within 3 months of warfarin or NOAC receipt in acute stroke/TIA
Country	Japan
Design	Prospective cohort study
Data source	Web-based registration system, covering 18 Japanese stroke centers
Time period	September 2011 to March 2014
NOAC (all dosages are recommended for Japan)	Dabigatran 300 mg or 220 mg daily Rivaroxaban 15 mg or 10 mg daily Apixaban 10 mg or 5 mg daily
Control	Warfarin Target INR 2.0-3.0 for those < 70 years of age 1.6-2.6 for those ≥70 years of age
Outcomes (all assessed within 3 months of OAC initiation)	**Effectiveness** Stroke or systemic embolism Any ischemic event (including recurrence of ischemic stroke or TIA, systemic embolism, acute coronary syndrome, aortic dissection, aortic aneurysm rupture, peripheral artery disease requiring hospitalization, venous thromboembolism, and revascularization such as carotid endarterectomy, carotid artery stenting, and percutaneous coronary intervention) Ischemic stroke or TIA **Safety** Major bleeding Intracranial hemorrhage All-cause mortality
Outcome definitions	Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a fall in the hemoglobin level of 2.0 g/dL or more or leading to the transfusion of 2 or more units of whole blood or red blood cells
Population (eligibility)	Patients with nonvalvular AF who were hospitalized within 7 days of onset of ischemic stroke/TIA Excluded: rheumatic mitral valve disease, a history of prosthetic valve replacement or mitral valve surgical repair, active infectious endocarditis, or lack of written informed consent
Population (study sample)	**Study population** N = 1137 Warfarin, n = 662 (58.2%) Dabigatran, n = 205 (18.0%) Rivaroxaban, n = 245 (21.5%) Apixaban, n = 25 (2.2%) **Target population** 1192 patients; 55 patients not taking oral anticoagulants after the index stroke/TIA, mainly due to severe neurological deficits, were excluded

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**All participants**
Women	32.0	33.0	38.7	48.8	43.3
Age, mean (SD)	74.0 (12.0)	73.1 (8.8)	75.8 (9.0)	79.3 (9.7)	77.7 (9.9)
>65 years	-	-	-	-	-
>75 years	-	-	-	-	-
>85 years	-	-	-	-	-

CHA_2DS_2VASc, median (IQR)	5 (4-6)	5 (4-6)	5 (4-6)	6 (5-6)	5 (4-6)
CHA_2DS_2, median (IQR)	4 (3-4)	3 (3-4)	4 (3-4)	4 (3-5)	4 (3-4)
$CHA_2DS_2 \geq 4$	-	-	-	70.7	62.3
HAS-BLED, median (IQR)	3 (3-4)	3 (3-4)	3 (2-4)	3 (3-4)	3 (3-4)
Standard dose	-	26.3	54.3	-	-
Reduced dose	-	73.7	45.7	-	-
Comorbidities					
Ischemic stroke, or systemic embolism, or TIA	100	100	100	100	100
Heart failure	-	-	-	-	-
Myocardial infarction	-	-	-	-	-
Vascular disease	-	-	-	-	-
Renal dysfunction	-	-	-	-	-
Previous bleeding	-	-	-	-	-
Hypertension	-	-	-	-	-
Diabetes	-	-	-	-	-
Cancer	-	-	-	-	-
Concomitant medication					
Aspirin	-	-	-	15.3	14.5
Beta-blocker	-	-	-	-	-
NSAID	-	-	-	-	-
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Cumulative rates of primary and secondary events **Comparison of the risk of an end point between groups** Chi-square test Cox proportional hazards model **Confounding** Cox proportional hazards model adjusted by potential confounding factors (sex, age, $CHADS_2$ score, admission National Institutes of Health Stroke Scale score, creatinine clearance) **Sensitivity analysis** Not reported **Supplementary analyses** Complementary analyses using propensity scores as an adjustment covariate **Software for statistical analysis** JMP 11.0.2 statistical software (SAS Institute, Inc, Cary, North Carolina) **Statistical significance reference** $P < .05$

INR, International Normalized Ratio; IQR, interquartile range; NOACs, nonvitamin K antagonist oral anticoagulants; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Avgil-Tsadok et al.[60]
Reference	Avgil-Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Behlouli H, Pilote L. Dabigatran use in elderly patients with atrial fibrillation. *Thromb Haemost*. 2016;115:152-160. doi:10.1160/TH15-03-0247
Objective	To assess dabigatran effectiveness and safety in elderly patients in real-world practice
Country	Canada
Design	Nationwide cohort study
Data source	Administrative databases in Quebec: The provincial hospital discharge database (*Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière-Med-Echo*) was linked to the provincial physician and prescription claims database (*la Régie de l'assurance maladie du Quebec* [RAMQ]) using patients' encrypted health insurance numbers. Linkage using unique identifiers, such as health insurance numbers, is considered preferable to deterministic or probabilistic linkages using patient characteristics, such as age and sex. The Quebec prescription claims database has previously been determined to be a reliable source of filled medication prescriptions The hospital discharge database was used to obtain information on patient characteristics such as comorbidities and to calculate the CHA_2DS_2-VASc and HAS-BLED scores
Time period	1999-2013
NOAC	• Dabigatran 110 mg • Dabigatran 150 mg
Control	Warfarin
Outcomes	**Effectiveness** Stroke/TIA **Safety** Bleeding events
Outcome definitions	Outcomes were defined using the International Classification of Diseases-9th/10th (ICD-9/10) revision, codes 427.3, 427.31, or 427.32/I48. Stroke was defined as ischemic cerebrovascular disease, with the inclusion of TIA and retinal infarct. Bleeding events included intracranial hemorrhage (ICH), gastrointestinal (GI) bleeding, and other hemorrhages. The outcomes of ICH and GI bleeding were also separately analyzed
Population (eligibility)	Participants were Quebec residents discharged alive from hospitalization with a primary diagnosis of AF or a major comorbid diagnosis (secondary diagnosis) of AF during the study period
Population (study sample)	**Study population** < 75 years, N = 20 632 Warfarin, n = 14 262 Dabigatran 110 mg twice daily, n = 1277 Dabigatran 150 mg twice daily, n = 5093 ≥ 75 years, N = 42 478 Warfarin, n = 32 930 Dabigatran 110 mg twice daily, n = 7649 Dabigatran 150 mg twice daily, n = 1899

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	< 75 (N = 20 632)			**≥ 75 (N = 42 478)**		
	Warfarin	**Dabigatran (110 mg)**	**Dabigatran (150 mg)**	**Warfarin**	**Dabigatran (110 mg)**	**Dabigatran (150 mg)**
Women	38.5	41.5	35.3	56.9	57.2	45.6
Age	-	-	-	-	-	-
>65 years	-	-	-	-	-	-
>75 years	-	-	-	-	-	-
>85 years	-	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	2.3 (1.3)	2.4 (1.3)	2.0 (1.3)	3.8 (1.2)	3.7 (1.2)	3.2 (1.2)
Modified HAS-BLED, mean (SD)	2.4 (1.2)	2.4 (1.1)	2.0 (1.0)	2.7 (1.0)	2.5 (1.0)	2.4 (1.0)

Standard dose						
Reduced dose						
Comorbidities						
Ischemic stroke, or systemic embolism, or TIA (see below)	-	-	-	-	-	-
History of stroke	10.2	8.8	9.1	12.2	11.6	11.6
Heart failure (see below)	-	-	-	-	-	-
Valvular heart disease	31.8	17.3	15.6	30.8	22.8	21.0
Myocardial infarction	21.8	21.0	14.7	20.5	18.0	16.5
Vascular disease	15.9	13.9	9.1	16.3	13.8	13.6
Renal dysfunction (acute or chronic renal disease)	23.6	22.0	10.3	35.0	25.1	15.1
Previous bleeding	10.1	10.1	5.4	11.5	9.5	8.7
Hypertension	70.5	73.8	67.8	79.9	78.1	75.2
Diabetes	35.2	34.2	28.5	28.4	24.9	24.1
Cancer (any malignancy)	8.7	11.0	7.7	11.5	9.5	8.7
Concomitant medication						
Aspirin	-	-	-	-	-	-
Beta-blocker (other than sotalol)	42.1	35.5	38.2	46.8	39.9	41.0
NSAID	0.6	0.9	1.0	0.3	0.5	0.6
Calcium channel blocker	-	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-	-
ACE inhibitor	21.8	18.3	19.8	22.1	19.4	19.1
Statin	21.6	19.2	23.4	20.7	20.2	24.9
Aspirin	20.5	21.4	19.5	17.4	17.0	17.3
Digoxin	15.9	14.1	13.6	19.0	17.1	16.0
Angiotensin receptor blocker	11.3	12.2	14.1	13.7	13.8	16.5
Diltiazem	10.1	10.2	11.0	12.6	11.8	13.4
Amiodarone	9.8	13.3	8.5	8.1	7.1	6.7
Clopidogrel	2.5	4.2	1.9	1.7	2.3	1.9
Other antiarrhythmic	2.5	1.3	4.7	1.5	1.9	2.8
Sotalol	2.2	2.5	3.6	1.6	1.9	3.2
Verapamil	1.2	1.3	1.5	1.3	1.4	1.8

Analysis	**Measure of the risk of an end point** Crude Kaplan-Meier analysis was conducted to compare time to stroke and bleeding events in the 2 age groups for the 2 dabigatran doses and warfarin. The rate estimates were compared by the log-rank test To account for differences in baseline characteristics, 3 sets of propensity scores were calculated (ie, the predicted probability that a patient would be a user of dabigatran or warfarin, given baseline covariates) for (1) any dabigatran dose; (2) the 110 mg twice daily dose; and (3) the 150 mg twice daily dose. The propensity scores were calculated separately for the different age groups **Comparison of the risk of an end point between groups** Cox proportional hazards models: in the multivariable Cox proportional hazards models, dabigatran use was considered a time-fixed binary variable, where it was assumed that patients who were prescribed dabigatran remained on the same prescription throughout the follow-up period. This approach is akin to intention-to-treat analyses in RCTs

	Sensitivity analysis The analyses were repeated by defining elderly patients as 80 years and older rather than 75 years and older **Software for statistical analysis** SAS (version 9.2) statistical software package (SAS Institute Inc, Cary, North Carolina) **Statistical significance reference** All statistical tests were 2-sided. *P*-value

ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drugs; RCT, randomized clinical trial; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Bengtson et al.[54]
Reference	Bengtson LGS, Lutsey PL, Chen LY, MacLehose RF, Alonso A. Comparative effectiveness of dabigatran and rivaroxaban versus warfarin for the treatment of non-valvular atrial fibrillation. *J Cardiol*. 2017;69:868-876. doi:10.1016/j.jjcc.2016.08.010
Objective	To evaluate if the effectiveness of dabigatran and rivaroxaban (vs warfarin) in ischemic stroke prevention differs between switchers from warfarin to NOACs and anticoagulant-naïve patients and to assess the overall safety profile of oral anticoagulants
Country	United States
Design	Retrospective cohort study
Data source	US MarketScan databases: Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database (enrollment data and health insurance claims for inpatient and outpatient services as well as outpatient pharmacy services)
Time period	January 1, 2009 through December 31, 2012
NOAC	• Dabigatran 75 mg twice daily • Dabigatran 150 mg twice daily • Rivaroxaban 10 mg once daily • Rivaroxaban 15 mg once daily • Rivaroxaban 20 mg once daily
Control	Warfarin
Outcomes	**Effectiveness** • Ischemic stroke • Myocardial infarction • Hip/pelvic fracture **Safety** • Intracranial bleed • Gastrointestinal bleed
Outcome definitions	Outcomes were defined based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 427.3, 427.31, and 427.32, in any position
Population (eligibility)	Individuals with medical and outpatient pharmaceutical data, with ≥ 6 months of continuous enrollment prior to first anticoagulant use. Patients were eligible if they had at least 1 inpatient claim or 2 outpatient claims for AF and at least 1 prescription for warfarin or for 2 of the NOACs (dabigatran or rivaroxaban) after their initial AF diagnosis Patients with ICD-9-CM diagnostic codes for valvular disease or procedure codes for valvular repair or replacement before or at AF diagnosis were excluded because NOACs have received FDA approval for nonvalvular AF only
Population (study sample)	**Study population** N = 61 648 anticoagulant initiators Dabigatran, n = 18 981 Rivaroxaban, n = 2100 Warfarin, n = 40 567 N = 84 018 switchers Dabigatran, n = 13 937 Rivaroxaban, n = 1202 Warfarin, n = 68 880

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	New users		**Switchers**		**Pooled (new users and switchers)**	
	Dabigatran	**Warfarin**	**Dabigatran**	**Warfarin**	**Rivaroxaban**	**Warfarin**
Women	36.2	38.8	37.9	38.0	39.8	41.2
Age, mean (SD)	68.5 (12.3)	70.8 (12.1)	70.9 (11.3)	71.5 (11.4)	70.4 (12.0)	72.5 (12.2)
>65 years	-	-	-	-	-	-
>75 years	-	-	-	-	-	-
>85 years	-	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)						
HAS-BLED, mean (SD)						

Standard dose	91.7	-	93.4	-	-	-
Reduced dose	8.3	-	6.6	-	-	-
Comorbidities						
Ischemic stroke, or systemic embolism, or TIA	20.6	22.3	25.4	24.0	26.3	30.9
Heart failure	24.3	30.4	35.2	36.6	31.5	39.3
Myocardial infarction	7.6	9.5	7.6	9.2	10.5	11.7
Vascular disease (see below)	-	-	-	-	-	-
Peripheral arterial disease	15.5	18.0	19.8	20.3	21.4	25.6
Renal dysfunction	7.6	12.9	10.0	13.0	11.2	16.0
Previous bleeding (see below)	-	-	-	-	-	-
GI bleed	7.6	8.3	10.4	11.4	13.2	14.5
Other bleed	3.6	5.0	7.9	8.4	7.6	9.5
Hypertension	75.2	72.9	82.0	80.2	85.6	84.7
Diabetes	28.6	32.1	32.2	33.8	30.7	35.4
Metastatic cancer	1.6	2.3	1.4	2.2	1.9	2.5
Concomitant medication						
Aspirin (see below)	-	-	-	-	-	-
Antiplatelet	2.1	2.0	1.5	1.6	2.9	2.3
Beta-blocker	71.1	64.8	79.4	76.2	77.6	76.4
NSAID	-	-	-	-		
Calcium channel blocker	41.7	39.4	48.9	44.4	48.3	46.5
Renin angiotensin system inhibitor	-	-	-	-	-	-
Digoxin	14.9	16.2	28.9	27.6	21.9	25.3
Clopidogrel	14.0	12.0	10.8	10.1	15.7	13.0
Angiotensin-converting enzyme inhibitor	36.0	37.6	42.5	43.3	40.3	43.9
Angiotensin receptor blocker	23.5	20.5	28.1	23.9	29.3	25.7
Antiarrhythmic medication	29.4	20.4	39.3	29.1	41.5	29.4
Statin	54.3	51.7	64.2	61.5	61.3	62.5
Diabetes medication	21.5	23.7	24.0	24.8	21.2	24.8

Analysis	**Measure of the risk of an end point** Cox proportional hazards models were used to assess the association between anticoagulant type (separately for dabigatran and rivaroxaban vs warfarin) and the time to each outcome Propensity score-adjusted Cox regression was used to calculate hazard ratios and 95% confidence intervals for relevant end points in NOACs vs warfarin users **Comparison of the risk of an end point between groups** Separate analyses were conducted to compare anticoagulant-naïve users of NOACs and those switching from warfarin High-dimensional propensity scores were calculated for each of the main comparisons. The methodology included the following dimensions: age, sex, inpatient diagnostic codes, inpatient procedure codes, outpatient diagnostic codes, outpatient procedure codes, and outpatient pharmacy claims. High-dimensional propensity scores were calculated with Rassen's SAS macros and included both empirical variables and the covariates described above. For each outcome, Cox proportional hazards models were adjusted for the high-dimensional propensity score decile as well as the age, sex, and $CHADS_2$ score, to allow stratification of the results by these 3 covariates **Sensitivity analysis** A sensitivity analysis was performed among high-dimensional propensity score-matched dabigatran and warfarin users A greedy matching technique, which is an efficient approximation of a nearest neighbor matching approach, where the comparator with the closest propensity score is selected, was implemented with a published SAS macro for the matched analysis. Kaplan-Meier survival curves were used to calculate the survival-free probability of each outcome of interest separately for dabigatran and warfarin new users and switchers. Effect measure modification by sex, age (≤ 75 and > 75), and $CHADS_2$ score (0-1 classified as low risk and ≥ 2 classified as moderate/high risk) was explored via stratified analysis. Due to the small number of rivaroxaban users and correspondingly few events, new users and switchers were pooled for

	analysis **Software for statistical analysis** SAS 9.3 **Statistical significance reference** *P* < .05 was considered statistically significant

NOACs, nonvitamin K antagonist oral anticoagulants; SD, standard deviation.

Study ID	Bouillon et al.[61]
Reference	Bouillon K, Bertrand M, Maura G, Blotière PO, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol*. 2015;2:e150-59. doi:10.1016/S2352-3026(15)00027-7
Objective	To compare the risk of bleeding between individuals who switched and those who remained on a vitamin K antagonist (nonswitchers) in real-world conditions
Country	France
Design	Nationwide cohort study
Data source	The French national health insurance database (*Système National d'Information Inter-Régimes de l'Assurance Maladie* [SNIIRAM]) contains anonymized individual data on all reimbursements for patient health expenditure, including drugs and outpatient medical and nursing care, that have been prescribed or done by health care professionals. The SNIIRAM database does not provide any direct information on the medical indication for each reimbursement but does contain the patient's status with respect to full reimbursement of care related to severe and costly long-term conditions listed in the International Classification of Diseases, 10th edition (ICD-10). The SNIIRAM also includes important status information but not cause of death. Information from the SNIIRAM database was also cross-referenced to the French hospital discharge data base (*Programme de Medicalisation des Systemes d'Information* [PMSI]), which provides medical information on all patients admitted to hospital in France, including discharge diagnoses coded in the ICD-10, medical procedures, and French diagnosis-related groups
Time period	January 1, 2011, and November 30, 2012
NOAC	Dabigatran Rivaroxaban
Control	Vitamin K antagonists (acenocoumarol, fluindione, warfarin)
Outcomes	**Effectiveness** • Ischemic stroke • Systemic embolism • First or recurrent myocardial infarction • Death • Composite outcomes **Safety** • Bleeding events
Outcome definitions	Outcomes were defined based on the ICD-10
Population (eligibility)	Patients who were aged 18 years or older; had their first prescription of a vitamin K antagonist between January 1, 2011, and November 30, 2012, without having had a vitamin K antagonist reimbursed in the 12 months before January 1, 2011; and were starting vitamin K antagonists for nonvalvular atrial fibrillation. In France, 3 vitamin K antagonists are available—fluindione, warfarin, and acenocoumarol. Patients who had switched from one type of vitamin K antagonist to another and those who had dementia were excluded. Because all individuals on a vitamin K antagonist could theoretically have been switched to a NOAC, patients with contraindications for NOACs were also excluded—ie, those with surgery for valvular heart disease, recent cancer, dialysis for kidney failure, current or recent gastroduodenal ulceration, hepatic impairment or liver disease, and any lesion or condition with a substantial risk of severe bleeding such as anemia
Population (study sample)	**Study population** N = 17 410 (10 705 nonswitchers, 6705 switchers) **Target population** N = 445 735 eligible individuals identified in the SNIIRAM registry Excluded: N = 106 914 • Age < 18 years, n = 1506 • Switched from 1 type of VKA to another, n = 16 513 • Had a prescription of 2 different oral anticoagulants, n = 680Had heart valve disease or surgery for this condition, n = 33 090 • Had cancer, 23 918

	• Were receiving kidney dialysis, n = 1926 • Had anemia or another blood disorder, n = 38 308 • Had cirrhosis, fibrosis, or liver failure, n = 5704 • Had a gastroduodenal ulcer, n = 793 • Had undergone lower limb surgery, n = 9740 N = 199 578 • Unswitched and unmatched individuals, n = 141 206 • Switched but unmatched individuals, n = 1777 • Unswitched, matched individuals with a duration of VKA treatment shorter than that of switched individuals, n = 56 595 N = 43 624 • Used a VKA or DOA ≤ 0 day after the index date, n = 10 596 • Died before the index date, n = 145 • Had an index date ≥ 1 December 1, 2012, n = 1980 • Admitted to hospital 45 days before the index date, n = 11 951 • Had dementia, n = 4007 • Were switched or unswitched individuals without their matching pair, n = 14 945 N = 57 868 unswitched individuals excluded because of different INR numbers between switched and unswitched individuals N = 20 341 • Unswitched individuals not randomly selected, n = 8670 • Switched individuals without their matching pair, n = 4261 • Unswitched and switched individuals with an oral anticoagulation indication for DVT/PE or a nondetermined indication, n = 7410 unswitched and 2815 switched

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Nonswitchers	**Switchers**
Women	48	48
Age		
>65 years	-	-
67-82 years	75	75
>85 years	-	-
Modified CHA_2DS_2VASc, median (IQR)	4 (3-4)	3 (2-4)
Modified HAS-BLED, median (IQR)	2 (2-3)	2 (2-3)
Standard dose		
Reduced dose		
Comorbidities		
Ischemic stroke, or systemic embolism, or TIA	1	1
Heart failure	47	46
Myocardial infarction		
Vascular disease (see below)	-	-
Peripheral arterial disease	3	2
Renal dysfunction (see below)	-	-
Chronic renal impairment	3	2
Previous bleeding		
Intracranial	<1	<1
Gastrointestinal	<1	<1
Other	<1	<1
Hypertension	86	84
Diabetes	20	17
Cancer	-	-

Concomitant medication		
Aspirin (antiplatelet agents)	22	24
Beta-blocker	-	-
NSAID	6	8
Calcium channel blocker	-	-
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Chi-square tests and *t* tests were used to assess the similarity of switchers and nonswitchers according to the matching variables. Additionally, the standardized difference between these groups was calculated as the difference in means or proportions divided by the pooled SD. An imbalance between the groups was defined as an absolute value greater than 0.10. Univariate associations between exposure and covariates were analyzed with chi-square and Fisher's exact tests for classified variables, as well as a Cochran-Mantel-Haenszel trend test for ordered variables and a *t* test and analysis of variance for continuous variables **Comparison of the risk of an end point between groups** A log-rank test was used to examine differences between switchers and nonswitchers in the occurrence of events. For the multivariate analysis, a conditional Cox model was used to estimate hazard ratios and their 95% confidence intervals of bleeding, ischemic stroke or systemic embolism, myocardial infarction, and of composite events, at a median follow-up of 10 months (interquartile range, 9.8-10.0) **Software for statistical analysis** SAS software, version 9.3

CI, confidence interval; DOACs, direct oral anticoagulants; DVT, deep venous thrombosis; PE, pulmonary embolism; VKAs, vitamin K antagonists.

Study ID	Chan et al.[62]
Reference	Chan YH, Kuo CT, Yeh YH, Chang SH, Wu LS, Lee HF, et al. Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in Asians with nonvalvular atrial fibrillation. *J Am Coll Cardiol.* 2016;68:1389-1401. doi:10.1016/j.jacc.2016.06.062
Objective	To compare the risk for thromboembolic events, bleeding, and mortality associated with rivaroxaban and dabigatran vs warfarin in Asians with nonvalvular atrial fibrillation (NVAF)
Country	Taiwan
Design	Nationwide retrospective cohort study
Data source	Taiwan National Health Insurance Research Database, covering > 99% of the Taiwanese population in 2014
Time period	February 2013 to December 2013
NOAC	Dabigatran 300 mg or 220 mg daily Rivaroxaban 20 mg or 15 mg or 10 mg daily
Control	Warfarin
Outcomes	**Effectiveness** Ischemic stroke Systemic embolism Myocardial infarction **Safety** Intracranial hemorrhage Gastrointestinal bleeding All hospitalizations for bleeding All-cause mortality
Outcome definitions	All outcomes were required to be discharge diagnoses, using the respective ICD codes
Population (eligibility)	Patients with NVAF treated with rivaroxaban, dabigatran, or warfarin Exclusion criteria: Pulmonary embolism or deep vein thrombosis within 6 months before AF diagnosis Joint replacement or valvular surgery within 6 months before AF diagnosis End-stage renal disease < 30 years of age Rivaroxaban or dabigatran users switched to warfarin
Population (study sample)	**Study population** N = 15 088 Warfarin, n = 5251 (34.8%) Dabigatran 300 mg daily, n = 620 (0.4%) Dabigatran 220 mg daily, n = 5301 (35.1%) Rivaroxaban 20 mg daily, n = 491 (3.2%) Rivaroxaban 15 mg daily, n = 3009 (19.9%) Rivaroxaban 10 mg daily, n = 416 (2.7%) **Target population** 80 365 dabigatran, rivaroxaban, or warfarin users; 65 227 met the above exclusion criteria and were excluded

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**All participants**
Women	-	42	46	44	44
Age, mean (SD)	-	75 (9)	76 (9)	71 (12)	-
>65 years	-	87	89	69	81
>75 years	-	58	60	43	53
>85 years	-	16	17	13	15
CHA_2DS_2VASc, mean (SD)	-	4.1 (1.6)	4.1 (1.6)	3.3 (1.8)	-
HAS-BLED, mean (SD)	-	3.1 (1.1)	3.1 (1.1)	2.7 (1.3)	-
Standard dose (for rivaroxaban, 20 or 15 mg daily, depending on serum Cr clearance; for dabigatran, 150 to 300 mg daily)	-	10	13	-	-
Reduced dose	-	90	87	-	-

Comorbidities					
Ischemic stroke, or systemic embolism, or TIA	-	37	34	22	31
Heart failure	-	16	16	16	16
Myocardial infarction	-	3	4	3	3
Vascular disease	-	0	0	0	0
Renal dysfunction	-	22	22	21	22
Previous bleeding	-	2	2	2	2
Hypertension	-	86	87	75	82
Diabetes	-	41	41	36	39
Cancer	-	-	-	-	-
Concomitant medication					
Aspirin	-	45	41	54	47
Beta-blocker	-	-	-	-	-
NSAID	-	25	23	26	25
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Incidence rates, estimated using the total number of study outcomes during the follow-up period divided by person-years at risk **Comparison of the risk of an end point between groups** Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis **Confounding** The inverse probability of treatment weights of propensity scores was used to balance covariates across the 3 study groups regarding time-to-event analyses (incidence rate, log-rank test, and Cox proportional hazards model) The balance of covariates at baseline among study groups was assessed using the absolute standardized mean difference **Sensitivity analysis** Not reported **Supplementary analyses** Subgroup analysis to determine whether the NOACs had protective effects for 4 outcomes vs warfarin Subgroup analysis on the basis of age, presence of chronic kidney disease, and CHA_2DS_2-VASc and HAS-BLED scores **Software for statistical analysis** SAS 9.4 (SAS Institute, Cary, North Carolina) **Statistical significance reference** *P* < .05 was considered statistically significant

NOACs, nonvitamin K antagonist oral anticoagulants; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Chan et al.[63]
Reference	Chan YH, Yen KC, See LC, Chang SH, Wu LS, Lee HF, et al. Cardiovascular, bleeding, and mortality risks of dabigatran in Asians with nonvalvular atrial fibrillation. *Stroke.* 2016;47:441-449. doi:10.1161/STROKEAHA
Objective	To investigate the ischemic and bleeding outcomes associated with dabigatran in Asian patients with nonvalvular atrial fibrillation (AF) vs warfarin
Country	Taiwan
Design	Nationwide cohort study
Data source	The Taiwan National Health Insurance Research, which is a national billing administrative database of health care services with >23 million enrollees, covering >99% of the population of Taiwan in 2014
Time period	June 2012 to December 2013
NOAC	Dabigatran
Control	Warfarin
Outcomes	**Effectiveness** Ischemic stroke Myocardial infarction **Safety** Intracranial hemorrhage Major gastrointestinal bleeding All major bleeding events All-cause mortality
Outcome definitions	All outcomes had to be a discharge diagnosis Major gastrointestinal bleeding was defined as a hospitalized gastrointestinal bleeding event requiring transfusion Major hospitalized bleeding events were defined as the total events of intracranial hemorrhage plus major gastrointestinal bleeding
Population (eligibility)	Patients with NVAF treated with dabigatran or warfarin Exclusion criteria: Pulmonary embolism or deep vein thrombosis within 6 months before AF was diagnosed Joint replacement or valvular surgery within 6 months before AF was diagnosed End-stage renal disease < 30 years of age Dabigatran users switched to warfarin Use of warfarin before June 2012
Population (study sample)	**Study population** N = 19 853 Warfarin, n = 9913 (50%) Dabigatran, n = 9940 (50%) 300 mg daily, n = 1168 (12%) 220 mg daily, n = 8772 (88%) **Target population** 89 705 patients diagnosed with AF and prescribed dabigatran or warfarin, of whom 69 852 met the above exclusion criteria and were excluded

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**All participants**
Women	-	42	-	44	43
Age, mean (SD)	-	75 (10)	-	71 (12)	-
>65 years	-	87	-	71	79
>75 years	-	58	-	44	51
>85 years	-	15	-	13	14
CHA_2DS_2VASc, mean (SD)	-	3.1 (1.6)	-	3.4 (1.8)	-
HAS-BLED, mean (SD)	-	2.6 (1.0)	-	2.1 (1.2)	-
Standard dose	-	100	-	-	-
Reduced dose	-	0	-	-	-
Comorbidities					

Ischemic stroke, or systemic embolism, or TIA	-	39	-	24	32
Heart failure	-	16	-	15	16
Myocardial infarction	-	3	-	3	3
Vascular disease	-	-	-	-	-
Renal dysfunction	-	23	-	21	22
Previous bleeding	-	1	-	1	1
Hypertension	-	87	-	77	82
Diabetes	-	41	-	35	38
Cancer	-	-	-	-	-
Concomitant medication					
Aspirin	-	44	-	55	50
Beta-blocker	-	-	-	-	-
NSAID	-	25	-	27	26
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Incidence rates were estimated using the total number of study outcomes during the follow-up period divided by person-years at risk **Comparison of the risk of an end point between groups** The risk of study outcomes over time for dabigatran vs warfarin (reference) was obtained using survival analysis (Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis) **Confounding** The inverse probability of treatment weights of propensity scores was used to balance covariates across the 2 study groups The balance of potential confounders at baseline (index date) between the 2 study groups was assessed using the absolute standardized mean difference **Sensitivity analysis** Not reported **Supplementary analyses** Analysis stratified by age Subgroup analysis by dabigatran dose (ie, 300 mg and 220 mg daily) **Software for statistical analysis** SAS 9.2 (SAS Institute Inc, Cary, North Carolina) **Statistical significance reference** $P < .05$

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Chang et al.[62]
Reference	Chang HY, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ.* 2015;350:h1585. doi:10.1136/bmj.h1585
Objective	To determine the real-world safety of dabigatran or rivaroxaban vs warfarin in terms of gastrointestinal bleeding
Country	United States
Design	Retrospective cohort study
Data source	IMS Health LifeLink Health Plan Claims Database. This database contains commercial health plan information from managed care plans and other sources (such as Medicare and Medicaid) throughout the United States
Time period	October 1, 2010 and March 31, 2012
NOAC	Dabigatran 150 mg twice daily Rivaroxaban
Control	Warfarin
Outcomes	**Safety** Time to gastrointestinal bleeding
Outcome definitions	Outcome defined according to ICD-9 codes and CPT codes validated in a recent study
Population (eligibility)	Enrollees with a prescription of warfarin, dabigatran, or rivaroxaban between October 1, 2010 and March 31, 2012, who were aged 18 years or older, had continuous enrollment and no oral anticoagulant use during the 6 months before the entry date, with known age and sex, and with no gastrointestinal bleeding for at least 6 months before the cohort entry date
Population (study sample)	**Study population** N = 46 163 Dabigatran, n = 4907 Rivaroxaban, n = 1649 Warfarin, n = 3906 **Target population** N = 244 872 Excluded: • Age < 18 years, n = 1057 • Without continuous medical enrollment over 6 months before the cohort entry date, n = 74 289 • Without continuous drug enrollment over 6 months before the cohort entry date, n = 87 722 • Not new user, n = 119 026 • First prescription of oral anticoagulant after March 31, 2012, n = 7880 • Missing sex information, n = 395 • Had previous bleeding, n = 12 979 (10 693 in prebaseline period and 3533 in baseline period)

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Dabigatran (n = 4907)	**Rivaroxaban (n = 1649)**	**Warfarin (n = 39 607)**	**All participants (n = 46 163)**
Women	30.9	51.5	46.9	45.3
Age, mean (SD)	62.0 (12.0)	57.6 (9.8)	57.4 (13.5)	57.6 (13.3)
≥ 65 years	32.8	17.5	22.4	23.3
>75 years	-	-	-	-
>85 years	-	-	-	-
CHA_2DS_2VASc, mean (SD)				
HAS-BLED, mean (SD)				
Standard dose	100			
Reduced dose	-			
Comorbidities				
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-
Heart failure	-	-	-	-
Myocardial infarction	-	-	-	-

Vascular disease	-	-	-	-
Renal dysfunction	-	-	-	-
Renal failure	4.2	2.1	5.1	4.9
Previous bleeding	-	-	-	-
Hypertension	-	-	-	-
Diabetes	-	-	-	-
Cancer	-	-	-	-
Concomitant medication				
Aspirin	-	-	-	-
Beta-blocker	-	-	-	-
NSAID	15.6	43.7	23.9	23.7
Calcium channel blocker	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-

Analysis	**Measure of the risk of an end point** Rate of gastrointestinal bleeding (per 100 person-years) **Comparison of the risk of an end point between groups** Hazard ratios were derived from Cox proportional hazard models with propensity score weighting and robust estimates of errors **Confounding** Propensity score weighting **Sensitivity analysis** Two additional models were evaluated: 1 including all variables as regression covariates and another including all variables as stratification factors. Secondly, the length of the washout period was varied from 7 to 30 to 45 days to check the robustness of the results. Thirdly, all inpatient records were censored due to the lack of prescription information during hospital admission in order to examine whether such an exclusion would affect the findings. Finally, the HAS-BLED bleeding risk score was additionally included in the model to control for a patient's risk of bleeding and examine whether the results would change. Due to the lack of laboratory data, the labile International Normalized Ratio was excluded from the construction of this risk score **Software for statistical analysis** SAS 9.2 **Statistical significance reference** Statistical significance was determined with 95% confidence intervals and 2-tailed *P* values ($P \leq .05$)

NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Coleman et al.[65]
Reference	Coleman CI, Antz M, Bowrin K, Evers T, Simard EP, Bonnemeier H, Cappato R. Real-World Evidence of Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation in the United States: the REVISIT-US Study. *Curr Med Res Opin*. doi:10.1080/03007995.2016.1237937
Objective	To assess the effectiveness and safety of rivaroxaban or apixaban vs warfarin in nonvalvular atrial fibrillation (NVAF) patients treated outside of clinical trials
Country	United States
Design	Retrospective cohort study
Data source	MarketScan covers all age groups and contains claims from about 100 employers, health plans, and government and public organizations representing about 170 million covered lives in the US (health plan enrollment records, limited participant demographics, International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis and procedure codes, admission and discharge dates, inpatient mortality data, and outpatient medical services and prescription drug dispensing records). It combines 2 separate databases: • Commercial • Medicare supplemental database
Time period	January 2012 to October 2014
NOAC	Rivaroxaban 15 mg once daily Rivaroxaban 20 mg once daily Apixaban 2.5 mg twice daily Apixaban 5 mg twice daily
Control	Warfarin
Outcomes	**Effectiveness** Ischemic stroke Intracranial hemorrhage (ICH) ICH and ischemic stroke combined **Safety** ICH
Outcome definitions	ICD-9-CM
Population (eligibility)	Patients had to be oral anticoagulant (OAC) treatment-naïve in the 180 days prior to the day of the first qualifying OAC dispensing, newly initiated on rivaroxaban, apixaban, or warfarin, ≥ 18 years of age on the day of the first qualifying OAC dispensing (index date), with a baseline CHA_2DS_2-VASc score ≥ 2, ≥ 2 ICD-9-CM diagnosis codes for NVAF (427.31), and ≥ 180 days of continuous medical and prescription coverage prior to OAC initiation Patients with valvular heart disease, a transient cause of NVAF, venous thromboembolism, hip or knee replacement surgery, malignant cancer, or pregnancy, and patients receiving OAC before the index date, or prescribed > 1 OAC agent on the index date or during follow-up were excluded. In addition, patients with a prior history of stroke, systemic embolism, or ICH were excluded from the analysis to prevent misclassification of past events as new events
Population (study sample)	**Study population** N = 38 831 NVAF patients newly initiated on rivaroxaban Rivaroxaban, n = 12 748 Warfarin, n = 26 083 N = 18 591 NVAF patients newly initiated on apixaban Apixaban, n = 4332 Warfarin, n = 14 259 **Target population** From the 38 831 patients with rivaroxaban, 10.5% could not be adequately matched and were therefore excluded from the analyses. Following propensity-scoring, 11 411 rivaroxaban (17.3% received the reduced 15 mg once daily) and 11 411 warfarin users were matched From the 18 591 apixaban, 5.7% patients could not be adequately matched and were therefore excluded from the analyses. Following propensity-scoring, 4083 apixaban and 4083 warfarin users were included
Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)	

	Rivaroxaban	Warfarin	Apixaban	Warfarin
Women	46.4	46.1	46.8	46.4
Age, mean (SD)	70.66 (10.99)	70.72 (11.35)	71.00 (11.25)	71.15 (11.32)
>65 years	-	-	-	-
>75 years	-	-	-	-
>85 years	-	-	-	-
CHA_2DS_2VASc, mean (SD)	3.46 (1.37)	3.48 (1.35)	3.47 (1.38)	3.47 (1.35)
HAS-BLED, mean (SD)	1.62 (0.69)	1.62 (0.71)	1.65 (0.69)	1.66 (0.72)
Standard dose	82.7	-	84.5	-
Reduced dose	17.3	-	15.5	-
Comorbidities				
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-
Heart failure	19.8	20.0	19.1	19.0
Myocardial infarction	-	-	-	-
Vascular disease	-	-	-	-
Renal failure	1.2	1.2	1.8	1.8
Previous bleeding				
Hypertension	93.4	93.7	94.9	94.6
Diabetes mellitus	34.3	34.9	34.1	33.8
Cancer	-	-	-	-
Concomitant medication				
Aspirin (see below)	-	-	-	-
Antiplatelet medication	11.0	10.9	10.8	10.8
Beta-blocker	51.1	51.4	56.0	55.3
NSAID	16.3	16.0	16.7	16.7
Calcium channel blocker	34.4	34.6	37.1	35.8
Renin angiotensin system inhibitor	-	-	-	-

Analysis	**Measure of the risk of an end point** Incidence rates of end points (number of events per 100 person-years or %/year) **Comparison of the risk of an end point between groups** Cox proportional hazards regression analysis was performed to estimate hazard ratios with 95% confidence intervals for the development of each end point **Software for statistical analysis** Aetion Evidence Generation Platform - Effectiveness Evaluation Application version R2.0.20160113_2214-0 g6871884 **Statistical significance reference** $P < .05$ was considered statistically significant

NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Ellis et al.[10]
Reference	Ellis MH, Neuman T, Bitterman H, Dotan SG, Hammerman A, Battat E, et al. Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: A retrospective population-based cohort study. *Eur J Intern Med.* 2016;33:55-59. doi:10.1016/j.ejim.2016.05.023
Objective	To determine the incidence of bleeding in patients with atrial fibrillation (AF) receiving dabigatran, rivaroxaban, or warfarin
Country	Israel
Design	Retrospective population-based cohort study
Data source	Nationwide computerized database, covering 4.3 million subjects
Time period	January 2011 to December 2013
NOAC	Rivaroxaban 20 mg once daily Dabigatran 300 mg daily or 220 mg daily
Control	Warfarin (2.5 mg dose tablets) Target INR 2.0-3.0
Outcomes	**Effectiveness** None **Safety** Any bleeding Intracranial hemorrhage Gastrointestinal bleeding Mortality within 30 days of hemorrhage
Outcome definitions	Not provided
Population (eligibility)	Patients with AF, prescribed warfarin, dabigatran (300 or 220 mg daily), or rivaroxaban for the first time and for a minimum of 3 consecutive months between January 2011 and December 2013
Population (study sample)	**Study population** 18 249 Warfarin, n = 9564 (52.4%) Dabigatran, n = 5976 (32.7%): 1806 (9.9%) received the recommended dose (300 mg daily) 4170 (22.8%) received the reduced dose (220 mg daily) Rivaroxaban, n = 2709 (14.8%) **Target population** 18 249 patients with AF, admitted to hospital with hemorrhage, receiving dabigatran, rivaroxaban, or warfarin

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**All participants**
Women	-	46.4	38.6	43.8	43.9
Age, median	-	-	82	79	-
>65 years	-	-	-	-	-
>75 years	-	-	-	-	-
>85 years	-	-	-	-	-
CHA_2DS_2VASc, median	-	-	4	3	-
HAS-BLED, mean (SD)	-	-	-	-	-
Standard dose	-	30.2	100	100	77.1
Reduced dose	-	69.8	0	0	22.9
Comorbidities	-	-	-	-	-
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-	-
Heart failure	-	-	-	-	-
Myocardial infarction	-	-	-	-	-
Vascular disease	-	-	-	-	-
Renal dysfunction	-	-	-	-	-
Previous bleeding	-	-	-	-	-
Hypertension	-	-	-	-	-
Diabetes	-	-	-	-	-
Cancer	-	-	-	-	-

Concomitant medication					
Aspirin (reported as antiplatelet drug use)	-	39.5	55	52	48.3
Beta-blocker	-	-	-	-	-
NSAID	-	-	-	-	-
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Rates of bleeding per 100 patient-years and associated 95% confidence intervals **Comparison of the risk of an end point between groups** Assessment of whether the 95% confidence intervals for bleeding rates in the groups overlap Cox regression analysis of time to bleeding or censoring (warfarin as reference) **Confounding** Cox regression analysis adjusted for age, sex, serum creatinine, $CHADS_2$ score, and aspirin use **Sensitivity analysis** Not reported **Supplementary analyses** Not reported **Software for statistical analysis** SPSS version 21 **Statistical significance reference** $P < .05$

AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Fontaine et al.[11]
Reference	Fontaine GV, Mathews KD, Woller SC, Stevens SM, Lloyd JF, Evans RS. Major bleeding with dabigatran and rivaroxaban in patients with atrial fibrillation: A real-world setting. *Clin Appl Thromb Hemost*. 2014;20:665-672. doi:10.1177/1076029614536606
Objective	To assess risk of bleeding among "real-world" patients with atrial fibrillation (AF) taking novel oral anticoagulants
Country	United States
Design	Nationwide cohort study (retrospective electronic medical record and chart review)
Data source	Enterprise Data Warehouse (EDW) at Intermountain Healthcare: the EDW is a central data repository that houses all medical record data for patient encounters at Intermountain Healthcare hospitals, clinics, and pharmacies
Time period	October 2010 and November 2012
NOAC	Dabigatran Rivaroxaban
Control	Warfarin
Outcomes	**Safety** Major bleeding
Outcome definitions	Major bleeding was defined as fatal bleeding, bleeding into a critical organ or organ space including intracranial, intraspinal, intraocular, intraarticular, peritoneal, and pericardial, or other bleeding in the setting of the transfusion of ≥ 2 units of packed red blood cells. This included bleeding into the gastrointestinal or genitourinary tracts. Omitted from the definition of major bleeding was a solitary drop in hemoglobin of ≥ 2 mg/dL in the absence of clinically overt bleeding due to the lack of specificity (eg, hemoglobin changes can occur for reasons other than bleeding, such as hydration)
Population (eligibility)	Patients were included if they had a diagnosis of AF and were receiving either dabigatran or rivaroxaban To ensure that the included patients were actively receiving a novel oral anticoagulant and had not been initially provided a prescription for a novel oral anticoagulant and then were switched back to warfarin, patients with an International Normalized Ratio (INR) of ≥ 1.8 in the 90 days following initiation of either dabigatran or rivaroxaban were excluded from the final analysis
Population (study sample)	**Study population** N = 2579 patients **Target population** N = 6910 Excluded: Encounters were removed because of patient duplication, n = 1951 Without atrial fibrillation, n = 1884 Not experiencing major bleeds, n = 487 Major bleeding while not taking a novel oral anticoagulant within the previous 7 days, n = 2 Major bleeding after transitioning back to warfarin therapy, n = 5 No evidence of major bleeding on manual chart review, n = 2

Study ID	Forslund et al.[66]
Reference	Forslund T, Wettermark B, Andersen M, Hjemdahl P. Stroke and bleeding with non-vitamin K antagonist oral anticoagulant or warfarin treatment in patients with non-valvular atrial fibrillation: a population-based cohort study. *Europace*. 2017;20:420-428. doi:10.1093/europace/euw416
Objective	To evaluate both effectiveness and safety outcomes with NOAC vs warfarin treatment in OAC-naïve patients with NVAF in routine care, including primary care, in a large region with decentralized OAC treatment
Country	Sweden
Design	Nationwide cohort study
Data source	The Stockholm administrative health data register (VAL), which contains pseudonymized data on diagnoses, age, sex, prescription claims, hospitalizations and other health care consultations, migration, and death for all individuals in the region. The VAL also contains individual level data on all prescription drugs dispensed anywhere in Sweden to inhabitants in the region since July 2010: amounts, expenditures and reimbursement, patient age and sex, copayments, and prescriber category
Time period	January 2012 until December 2015
NOAC	Dabigatran Rivaroxaban Apixaban
Control	Warfarin
Outcomes	**Effectiveness** TIA/ischemic or unspecified stroke/death **Safety** Severe bleeds
Outcome definitions	Severe bleeds were defined as intracranial bleeds, gastrointestinal bleeds, esophageal bleeds from varicose veins, hemothorax, hemopericardium, intraocular bleeding, or anemia due to an acute major bleed
Population (eligibility)	All individuals with nonvalvular AF who had a first claim of either a NOAC or warfarin from January 2012 until December 2015 were included Patients were excluded if they had no diagnosis of AF from 2003 until the first claim of the drug of inclusion or if they had a prior diagnosis or procedure code for a mechanical valve or mitral stenosis. Each individual was only included once, that is, at the date of the first treatment claimed
Population (study sample)	**Study population** Initiation of anticoagulant treatment with warfarin (n = 12 919) or NOAC (n = 9279) in OAC-naïve patients with NVAF Dabigatran, n = 3322 Rivaroxaban, n = 2370 Apixaban, n = 3587 **Target population** N = 20 588 Excluded: No previous diagnosis of atrial fibrillation: warfarin, n = 7786; NOAC, n = 7113 Diagnosis of or procedure code for mechanical valve or mitral stenosis: warfarin, n = 253; NOAC, n = 134 Prior anticoagulant treatment: warfarin, n = 633; NOAC, n = 4062

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Warfarin	**NOAC**	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Women	44.6	43.5	40.0	45.4	45.4
Age, median (SD)	74.1 (11.0)	72.9 (11.1)	69.9 (11.3)	74.0 (10.3)	75.0 (10.8)
65-74 years	32.1	36.3	39.5	35.8	33.7
75-79 years	16.8	15.4	13.6	17.3	15.7
>80 years	34.4	29.2	20.1	31.5	36.1
CHA_2DS_2VASc, mean (SD)	3.68 (1.91)	3.42 (1.91)	3.01 (1.89)	3.59 (1.88)	3.69 (1.90)
HAS-BLED, mean (SD)					
Comorbidities					

Ischemic stroke, or systemic embolism, or TIA	-	-	-	-	-
Ischemic stroke/TIA or peripheral embolus	21.1	20.4	18.2	20.4	22.4
Heart failure	26.3	23.0	19.4	25.0	25.0
Myocardial infarction	-	-	-	-	-
Vascular disease	30.2	24.5	20.1	27.8	26.3
Renal dysfunction	7.9	5.0	2.1	5.5	7.4
Previous bleeding (see below)	-	-	-	-	-
Gastric/duodenal bleeding	1.0	0.9	0.7	1.0	1.1
Intracranial bleed	1.8	2.9	2.6	3.0	3.3
Any severe bleed	7.6	9.4	7.5	10.0	10.8
Hypertension	70.1	67.8	63.1	68.4	71.7
Diabetes	20.1	17.1	15.0	18.1	18.4
Cancer	22.2	22.1	18.6	22.3	25.2
Concomitant medication					
Aspirin (see below)	-	-	-	-	-
Prior low-dose aspirin	47.8	44.9	42.6	51.1	42.8
Beta-blocker	-	-	-	-	-
NSAID	-	-	-	-	-
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Crude estimates with data presented as proportions or mean values with 95% confidence intervals, as appropriate **Comparison of the risk of an end point between groups** Cox regression analyses were performed for crude and adjusted estimates evaluating 2 coprimary end points: the composite end point–TIA/ischemic or unspecified stroke/death (adjusted for individual CHA_2DS_2-VASc criteria with age as a continuous variable)–and severe bleeds, adjusted for sex and adapted HAS-BLED criteria (anemia, severe bleed, TIA/stroke, liver disease, renal disease, alcoholism, and prior antiplatelet therapy) with age as a continuous variable **Software for statistical analysis** SAS Enterprise Guide 6.1 (SAS Institute Inc, Cary, North Carolina) **Statistical significance reference** A 5% level of significance was considered

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Gieling et al.[67]
Reference	Gieling EM, van den Ham HA, van Onzenoort H, Bos J, Kramers C, de Boer A. Risk of major bleeding and stroke associated with the use of vitamin K antagonists, nonvitamin K antagonist oral anticoagulants and aspirin in patients with atrial fibrillation: A cohort study. *Br J Clin Pharmacol*. 2017;83:1844-1859. doi:10.1111/bcp.13265
Objective	To evaluate the risk of major bleeding and stroke in AF patients using NOACs, VKAs, or aspirin
Country	United Kingdom
Design	Retrospective cohort study
Data source	The Clinical Practice Research Datalink Database (includes demographic information, laboratory tests, specialist referrals, hospital admissions, prescription details, and lifestyle variables such as body mass index, smoking, and alcohol consumption)
Time period	March 2008 to October 2014
NOAC	NOACs VKAs Aspirin
Control	Warfarin
Outcomes	**Effectiveness** Ischemic stroke Hemorrhagic stroke **Safety** Major bleeding, gastrointestinal bleeding, intracranial bleeding, stroke
Outcome definitions	The UK Read code system was used to define outcomes. Major bleeding was defined as bleeding at a critical site or organ and the selected read-codes were reviewed by a clinician for relevancy
Population (eligibility)	All patients aged ≥ 18 with a first-ever recorded diagnosis of AF during a patient's period of valid data collection. Only patients with a follow-up time between 18 March 2008 (the date of market introduction of the NOACs) and 1 October 2014 were included. Within this cohort of AF patients, new users of antithrombotic drugs were identified: VKAs, NOACs, and low-dose (≤ 325 mg) aspirin. New users were defined as patients who had never been exposed to any of the drugs of interest
Population (study sample)	**Study population** Cohort: stroke, N = 29 446 NOAC users, n = 1128 VKA users, n = 12 445 Aspirin users, n = 15 471 Mixed users, n = 402 Cohort: major bleeding, N = 30 418 NOAC users, n = 1247 VKA users, n = 13 177 Aspirin users, n = 15 551 Mixed users, n = 443 **Target population** N = 211 126 Excluded: • Under 18 years at AF diagnosis, n = 142 • AF diagnosis outside valid data collection or study period, n = 131 478 • Patient's year of birth was after the left censoring date, n = 24 • Patients with AF but without prescription of interest before or after AF diagnosis, n = 83 473 • Patients with prior use of eligible study drug, n = 38 531 • Patients with previous stroke, n = 2051 • Patients with previous major bleed, n = 1079

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Cohort outcome bleed				**Cohort outcome stroke**			
	NOAC	**VKA**	**Aspirin**	**Mixed**	**NOAC**	**VKA**	**Aspirin**	**Mixed**
Women	45.4	46.1	49.9	35.9	44.4	45.7	49.5	35.3
Age, mean (SD)	72.4	71.9	73.5	72.2	72.0	71.7	73.4	71.8

	(12.6)	(11.9)	(12.7)	(10.6)	(12.8)	(12.0)	(12.7)	(10.5)
60-69 years	20.2	22.3	23.1	26.4	21.0	22.4	23.2	27.4
70-79 years	32.2	34.1	27.4	36.1	31.0	33.9	27.4	35.6
≥80 years	30.5	28.9	36.2	26.2	30.1	28.6	35.9	25.1
CHA_2DS_2VASc, mean (SD)	2.6 (1.5)	2.6 (1.5)	2.5 (1.5)	2.6 (1.4)	2.4 (1.5)	2.5 (1.5)	2.5 (1.4)	2.5 (1.4)
HAS-BLED, mean (SD)	-	-	-	-	-	-	-	-
Comorbidities								
Ischemic stroke, or systemic embolism, or TIA								
Congestive heart failure	7.2	10.1	5.8	14.9	7.5	10.4	5.8	15.7
Myocardial infarction (see below)	-	-	-	-	-	-	-	-
Ischemic heart disease	8.3	10.2	9.0	25.1	7.7	10.1	8.9	26.1
Vascular disease (see below)	-	-	-	-	-	-	-	-
Peripheral artery disease	5.1	5.0	3.9	5.9	5.4	5.0	4.0	6.0
Renal dysfunction (see below)	-	-	-	-	-	-	-	-
Chronic renal failure	0.5	1.1	1.0	<5	0.5	1.0	1.0	<5
Acute renal failure	0.6	0.5	0.7	<5	0.4	0.5	0.7	<5
Previous bleeding (see below)	-	-	-	-	-	-	-	-
GI bleed	<5	<5	<5	<5	2.8	2.6	2.5	1.5
Hypertension	54.1	53.3	49.6	5.2	53.6	53.0	49.4	51.0
Diabetes	-	-	-	-	-	-	-	-
Cancer	0.9	0.9	0.7	0.9	1.3	1.0	0.8	1.0
Concomitant medication								
Aspirin (see below)	-	-	-	-	-	-	-	-
Antiplatelet drug	0.7	1.4	0.6	<5	0.4	1.0	0.4	<5
Beta-blocker	-	-	-	-	-	-	-	-
NSAID	11/2	11.8	13.3	13.5	10.9	12.1	13.4	13.7
Calcium channel blocker	-	-	-	-	-	-		-
Renin angiotensin system inhibitor	-	-	-	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Crude incidence rates of outcomes within 1 year per 1000 person-years were calculated **Comparison of the risk of an end point between groups** Cox proportional hazards regression analysis estimated the adjusted hazard ratios **Confounding** Potential confounders were included in the final model if they independently changed the beta-coefficient for current use with the outcome of interest by at least 5% or when a consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature **Software for statistical analysis** SAS 9.2 PHREG procedure

AF, atrial fibrillation; GI, gastrointestinal; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack; SD, standard deviation, VKAs, vitamin K antagonists.

Study ID	Gorst-Rasmussen et al.[12]
Reference	Gorst-Rasmussen A, Lip GY, Bjerregaard Larsen T. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care. *Pharmacoepidemiol Drug Saf*. 2016;25:1236-1244. doi:10.1002/pds.4034
Objective	To evaluate the effectiveness and safety of rivaroxaban vs warfarin or dabigatran etexilate in nonvalvular atrial fibrillation (AF) patients
Country	Denmark
Design	Nationwide cohort study
Data source	Three nationwide Danish registries: • The Danish National Prescription Registry (with information on all prescription purchases in Denmark since 1995, coded using Anatomical Therapeutic Chemical classification codes) • The Danish National Patient Register (containing > 99% of all hospital discharge diagnoses in Denmark since 1976, coded according to the International Classification of Diseases [ICD]) • The Danish Civil Registration System (containing information on date of birth, sex, and residency)
Time period	February 2012 to August 2014
NOAC	• Rivaroxaban 15 mg • Rivaroxaban 20 mg • Dabigatran 110 mg • Dabigatran 150 mg
Control	Warfarin (any dose)
Outcomes	**Effectiveness** • Ischemic stroke/systemic embolism (SE)/transient ischemic attack (TIA) • All-cause death • Myocardial infarction • Venous thromboembolism **Safety** • Any bleeding • Intracranial bleeding • Gastrointestinal bleeding • Major bleeding events
Outcome definitions	End points were ascertained according to the International Classification of Disease, 10th revision (ICD-10)
Population (eligibility)	Patients with an existing diagnosis of atrial fibrillation with a first-time purchase of the NOAC of interest or warfarin during the study time period Excluded patients who had purchased oral anticoagulants (warfarin, rivaroxaban, dabigatran, or apixaban) within 2 years of baseline Excluded patients for whom either of the following applied: immigrated within 1 year before baseline; prior venous thromboembolism diagnosis; knee or hip surgery within 30 days before baseline; prior valvular surgery; and prior diagnosis of mitral stenosis
Population (study sample)	**Study population** N = 22 358 Rivaroxaban, n = 2405 (15 mg, n = 776; 20 mg, n = 1629) Dabigatran, n = 8908 (110 mg, n = 3588; 150 mg, n = 5320) Warfarin, n = 11 045 **Target population** N = 33 243 Excluded: • Prior valvular surgery/mitral stenosis, n = 526 • Knee or hip surgery < 6 weeks before, n = 179 • Prior venous thromboembolism, n = 1594 • Anticoagulant purchase < 2 years before, n = 8549 • Immigrated < 1 year before, n = 37

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Rivaroxaban	Dabigatran	Warfarin

	15 mg	20 mg	110 mg	150 mg	
Women	59.7	48.9	56.8	36.5	43.0
Age, mean (SD)	82.8 (8.7)	72.8 (9.9)	80.8 (8.0)	66.0 (8.5)	72.6 (11.3)
≥65 years	96.1 (746)	82.0 (1336)	95.5 (3427)	62.4 (3319)	78.3 (8649)
≥75 years	82.6 (641)	39.2 (639)	81.4 (2921)	12.4 (659)	45.1 (4984)
>85 years	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	2.3 (1.2)	1.5 (1.3)	2.0 (1.2)	1.0 (1.0)	1.6 (1.3)
HAS-BLED, mean (SD)	2.8 (1.1)	2.3 (1.1)	2.6 (1.1)	1.9 (1.2)	2.4 (1.2)
Standard dose	-	68	-	60	100
Reduced dose	32	-	40	-	-
Comorbidities					
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-	-
Prior stroke	20.9	18.2	16.9	9.4	12.2
Heart failure	17.4	5.3	8.6	3.7	9.9
Myocardial infarction	-	-	-	-	-
Vascular disease	22.2	12.2	18.1	9.9	20.5
Renal dysfunction	-	-	-	-	-
Renal disease	10.1	1.5	2.5	1.1	6.5
Previous bleeding	17.0	14.3	16.8	10.1	14.3
Hypertension	38.4	35.2	36.5	27.7	35.3
Diabetes	17.4	13.8	14.0	12.9	16.8
Cancer	-	-	-	-	-
Concomitant medication					
Aspirin	55.8	44.0	48.9	36.1	48.1
Beta-blocker	-	-	-	-	-
NSAID	21.5	21.2	22.4	24.7	23.1
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-
Clopidogrel	11.5	10.2	10.8	6.1	8.9

Analysis	**Measure of the risk of an end point** Crude event rates for all end point and treatment combinations **Comparison of the risk of an end point between groups** Restricted attention to contrasts between clinically meaningful treatment alternatives: R15 vs warfarin, R15 vs D110, R20 vs warfarin, and R20 vs D150 **Confounding** Propensity score (PS) methods were subsequently used to control for baseline differences. Each of the 4 contrasts defined a subcohort of patients receiving either rivaroxaban or a comparison treatment. Within each subcohort, we derived a PS for the probability of rivaroxaban therapy using boosted logistic regression models. Standardized mean differences were used to check the balance of treatment groups Cox proportional hazards models stratified by deciles of the trimmed PS were then used to compare event rates within each subcohort **Sensitivity analysis** First, the trimmed PS was entered in "standardized mortality reweighted" Cox models estimating the average treatment effect on the treated patients. Secondly, an alternative PS was obtained using the high-dimensional propensity score technique. Cox models were then stratified for the primary end points by deciles of this PS after performing asymmetric trimming, as previously described Finally, the primary analysis was repeated after truncation of follow-up when there was evidence of discontinuation; additionally, patients were censored if they were deemed to have been off treatment for more than 30 days or if they switched treatment **Software for statistical analysis** R version 3.0.2 with the "twang" add-on **Statistical significance reference** A 2-sided *P* value less than .05 was considered statistically significant

AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Graham et al.[68]
Reference	Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation*. 2015;131:157-164. doi:10.1161/CIRCULATIONAHA.114.012061
Objective	To evaluate the safety of dabigatran vs warfarin for treatment of nonvalvular atrial fibrillation
Country	United States
Design	Retrospective cohort study
Data source	Medicare health insurance databases: • Medicare Part A (hospitalization) • Medicare Part B (office-based medical care) • Medicare Part D (prescription drugs)
Time period	October 2010 and December 2012
NOAC	• Dabigatran 75 mg twice daily • Dabigatran 150 mg twice daily
Control	Warfarin
Outcomes	**Effectiveness** • Ischemic stroke • Acute myocardial infarction • Death • Intracranial hemorrhage **Safety** • Major bleeding • Gastrointestinal bleeding
Outcome definitions	International Classification of Diseases, Ninth Revision, Clinical Modification codes were used to define these outcomes Major bleeding was defined as a fatal bleeding event, a hospitalized bleeding event requiring transfusion, or hospitalization with hemorrhage into a critical site (ie, intracranial, intraspinal, intraarticular, intraocular, pericardial, retroperitoneal, or intramuscular with compartment syndrome) Intracranial hemorrhage was defined with the use of codes for a traumatic hemorrhage, with a positive predictive value of 89% to 97%, and codes for hemorrhage with closed head trauma, which have not been validated
Population (eligibility)	All patients with any inpatient or outpatient diagnoses of AF or atrial flutter based on International Classification of Diseases, Ninth Revision coding who also filled at least 1 prescription for either drug during the study period. Patients discharged from the hospital on the same day as their index dispension were included Patients were excluded if they had < 6 months of enrollment in Medicare before their index dispensing, were aged < 65 years, received prior treatment with a study medication or rivaroxaban or apixaban (anticoagulants approved during the study), were in a skilled nursing facility or nursing home, or were receiving hospice care on the date of their cohort-qualifying prescription. Patients were also excluded if they had a hospitalization that extended beyond the index dispensing date. Patients undergoing dialysis and kidney transplant recipients were also excluded. Additionally, because warfarin is approved for indications other than AF, patients with diagnoses indicating the presence of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement surgery in the preceding 6 months were also excluded
Population (study sample)	**Study population** Dabigatran, N = 67 207 Warfarin, N = 67 207 **Target population** N = 341 414 Dabigatran-treated, n = 67 494 Warfarin-treated, n = 273 920
Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)	
	Dabigatran **Warfarin**

Women	51	52
Age, median (IQR)		
≥65-74 years	42	41
≥75-84 years	43	43
≥85 years	16	16
CHA_2DS_2VASc (scores greater than 2)	-	-
HAS-BLED (scores greater than 2)	91	91
Standard dose	85	100
Reduced dose	15	-
Comorbidities		
Ischemic stroke or systemic embolism	-	-
Stroke in past 1-30 d	2	2
Stroke in past 31-183 d	1	2
TIA	7	7
Heart failure (hospitalized)	4	4
Heart failure (not hospitalized)	14	14
Acute myocardial infarction in past 1-30 d	1	1
Acute myocardial infarction in past 31-183 d	1	1
Vascular disease	-	-
Coronary revascularization	16	16
Other cerebrovascular disease	13	13
Renal dysfunction	-	-
Kidney failure (acute)	5	5
Kidney failure (chronic)	13	13
Previous bleeding (hospitalized)	1	1
Previous bleeding (not hospitalized)	3	3
Hypertension	87	87
Diabetes mellitus	33	34
Cancer	-	-
Concomitant medication		
Aspirin	-	-
Beta-blocker	70	71
NSAID	15	15
Calcium channel blocker	42	42
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Incidence rates were estimated with the use of event counts and exposure follow-up time **Comparison of the risk of an end point between groups** Cox proportional hazards regression was used to compare time-to-event in dabigatran vs warfarin (reference) cohorts **Confounding** Propensity score matching **Sensitivity analysis** (1) Restriction of the analysis to patients with initial prescriptions of ≤ 30 days duration (2) Restriction of the analysis to patients with at least 2 prescription fills of a study drug (3) An increased gap allowance between anticoagulant prescriptions from 3 to 14 days **Software for statistical analysis** R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc, Cary, North Carolina) **Statistical significance reference** Statistical significance was determined with 95% confidence intervals and 2-tailed *P* values (*P* ≤ .05)

IQR, interquartile range; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack.

Study ID	Graham et al.[69]
Reference	Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med.* 2016;176:1662-1671. doi:10.1001/jamainternmed.2016.5954
Objective	To compare the risks of thromboembolic stroke, intracranial hemorrhage (ICH), major extracranial bleeding including major gastrointestinal bleeding, and mortality in patients with nonvalvular AF who initiated dabigatran or rivaroxaban treatment for stroke prevention
Country	United States
Design	Nationwide cohort study
Data source	Medicare: • Part A (hospitalization) • Part B (outpatient medical care) • Part D (prescription drugs)
Time period	November 4, 2011 to June 30, 2014
NOAC	Dabigatran 150 mg, twice daily Rivaroxaban 20 mg, once daily
Control	No control with VKAs
Outcomes	**Effectiveness** • Thromboembolic stroke • ICH • Mortality • Acute myocardial infarction **Safety** • Major extracranial bleeding events • Major gastrointestinal bleeding • Hospitalized extracranial bleeding events
Outcome definitions	Outcomes were defined using previously validated algorithms based on ICD-9 diagnosis codes. These algorithms have reported positive predictive values ranging from 86% to 97%
Population (eligibility)	New users with nonvalvular AF who were 65 years or older, enrolled in fee-for-service Medicare, and who initiated treatment with dabigatran or rivaroxaban during the study period Patients enrolled in Medicare Advantage (Part C), which provides care through private insurance companies, were not included because claims for medical encounters and hospitalizations were not reliably captured by Medicare during the study period Patients were excluded if they had less than 6 months of enrollment in Medicare Parts A, B, and D, were younger than 65 years, had received prior treatment with warfarin or any NOAC, resided in a skilled nursing facility or nursing home, or were receiving hospice care on the date of their cohort-qualifying prescription (index date). Patients with a hospitalization extending beyond the index date were also excluded, as were kidney transplant recipients and patients undergoing dialysis. Additionally, patients with diagnoses indicating a potential alternative indication for anticoagulation in the 6 months preceding study entry (mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement) were also excluded
Population (study sample)	**Study population** 15 524 and 20 199 person-years of on-treatment follow-up Dabigatran, n = 52 240 Rivaroxaban, n = 66 651

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Unweighted cohorts		**Weighted cohorts**	
	Dabigatran	**Rivaroxaban**	**Dabigatran**	**Rivaroxaban**
Women	47	47	47	47
Age				
65-74 years	50	51	50	50
75-84 years	40	40	40	40
≥85 years	10	9	47	47
CHA_2DS_2VASc				
HAS-BLED				

Standard dose	100	100	100	100
Reduced dose	-	-	-	-
Comorbidities				
Ischemic stroke, or systemic embolism, or TIA (see below)	-	-	-	-
Transient ischemic attack	6	6	6	6
Stroke in past 1-30 d	2	2	2	2
Stroke in past 31-180 d	1	1	1	1
Heart failure				
Hospitalized	3	3	3	3
Outpatient	13	11	12	12
Acute myocardial infarction in past 1-30 d	1	1	1	1
Acute myocardial infarction in past 31-183 d	1	1	1	1
Vascular disease (see below)				
Coronary revascularization	14	15	15	15
Cardioablation	2	2	2	2
Cardioversion	9	9	9	9
Renal dysfunction				
Acute	3	3	3	3
Chronic	10	8	9	9
Previous bleeding	<1	<1	<1	<1
Hypertension	86	86	86	86
Diabetes	34	32	33	33
Cancer	-	-	-	-
Concomitant medication				
Aspirin (see below)	-	-	-	-
antiplatelet	13	15	14	14
Beta-blocker	70	71	71	71
NSAID	14	14	14	14
Calcium channel blocker	42	42	42	42
Renin angiotensin system inhibitor	-	-	-	-
Estrogen therapy	2	2	2	2
Histamine H2 antagonist	5	5	5	5
Proton pump inhibitor	26	27	27	27
Selective serotonin reuptake inhibitor antidepressant	13	12	13	13
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	59	58	59	58
Antiarrhythmic	25	25	25	25
Anticoagulant (injectable)	7	9	8	8
Digoxin	14	12	13	13
Diuretic				
Loop	25	22	23	23
Potassium-	8	8	8	8

sparing				
Thiazide	30	30	30	30
Nitrate	9	9	9	9
Statin	58	57	57	57
Fibrate	5	4	4	4
Diabetes related				
Insulin	6	6	6	6
Metformin	15	15	15	15
Sulfonylurea	9	8	9	9
Other	6	6	6	6
Metabolic inhibitor				
Amiodarone	9	10	9	9
Dronedarone	4	4	4	4
Azole antifungal	<1	<1	<1	<1
Prescriber speciality				
Cardiology	54	60	57	57
Family medicine	12	8	10	10
Internal medicine	21	19	20	20
Other	13	13	13	13

Analysis	**Measure of the risk of an end point** Adjusted hazard ratios (HRs) for the primary outcomes. Adjusted incidence rate differences (AIRDs) were also estimated. All analyses were based on IPTW-adjusted cohorts and therefore accounted for potential confounding by baseline factors Weighted Kaplan-Meier cumulative incidence plots were generated to characterize risk over time **Comparison of the risk of an end point between groups** Weighted Cox proportional hazards regression with robust estimation was used to estimate the time-to-event in rivaroxaban vs dabigatran (reference) cohorts. Adjusted incidence rate differences were estimated using weighted event counts and follow-up time within cohorts **Confounding** To adjust for potential confounding, inverse probability of treatment weighting (IPTW) based on the propensity score was used. The propensity score (predicted probability of initiating dabigatran treatment given baseline characteristics) was used to generate patient-specific stabilized weights that control for covariate imbalances. Covariate balance between the weighted cohorts was assessed using standardized mean differences. A standardized difference of 0.1 or less indicates a negligible difference between groups. The distributions of propensity scores and stabilized weights were inspected for outliers **Sensitivity analysis** A number of sensitivity analyses were performed. To assess whether the main analyses were affected by a misclassification of exposure time, analyses were restricted to patients with at least 2 prescription fills of a study drug and the gap allowance between anticoagulant prescriptions was increased from 3 to 14 days. The main analysis was repeated using multivariable Cox regression, which included all covariates used in the weighted analysis. In post hoc sensitivity analyses, the CHA_2DS_2-VASc was substituted for the $CHADS_2$ score; censoring was no longer performed for initiation of dialysis or kidney transplantation, or admission to a nursing home, skilled nursing facility, or hospice; and the competing risks of death were adjusted for using the subdistribution of hazards approach **Software for statistical analysis** R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute Inc) **Statistical significance reference** Statistical significance was determined using 95% confidence intervals and 2-tailed *P* values ($P \leq .05$)

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

Study ID	Halvorsen et al.[70]
Reference	Halvorsen S, Ghanima W, Fride Tvete I, Hoxmark C, Falck P, Solli O, Jonasson C. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. *Eur Heart J Cardiovasc Pharmacother*. 2017;3:28-36. doi:10.1093/ehjcvp/pvw031
Objective	To evaluate bleeding risk in clinical practice in patients with atrial fibrillation (AF) being prescribed dabigatran, rivaroxaban, or apixaban vs warfarin
Country	Norway
Design	Nationwide cohort study
Data source	Two nationwide registries: • The Norwegian Patient Registry (NPR), which includes emergency visits, hospitalizations, outpatient consultations, length of stay, and surgical and medical procedures • The Norwegian Prescription Database (NorPD), which covers all prescriptions dispensed at pharmacies nationwide, information on date of dispensation, quantity, and strength dispensed and the time of all-cause death
Time period	January 1, 2013 to June 30, 2015
NOAC	• Apixaban twice daily • Dabigatran twice daily • Rivaroxaban once daily
Control	Warfarin
Outcomes	**Safety** • Major bleeding • Clinically relevant nonmajor (CRNM) bleeding • Gastrointestinal bleeding (GI) • Intracranial bleeding (ICH) • Other site bleeding
Outcome definitions	Bleeding was defined as all bleeding events recorded in the NPR between the index date and 30 days after the calculated end of OAC supply Major bleeding was defined as any bleeding event that occurred in a critical area or organ or any bleeding event that was accompanied by blood transfusion ≤ 10 days after the hospital admission date CRNM bleeding was defined in accordance with the ISTH classification as any bleeding requiring medical intervention by a health care professional, leading to hospitalization or increased level of care or prompting a face-to-face evaluation, that did not fit the criteria for major bleeding The bleeding events were also categorized by organ system into GI, ICH, or bleeding from other sites. Bleeding end points took into account all bleeds with the prespecified ICD-10 codes and were not restricted to admissions with bleeding as the primary (first) code
Population (eligibility)	The study included all patients ≥ 18 years diagnosed with nonvalvular AF with at least 1 warfarin or NOAC dispensation in the study period but who were anticoagulant-naïve before the start of the study Patients with venous thromboembolism during the last 180 days and those who had knee or hip replacement surgery during the last 35 days before OAC initiation were excluded
Population (study sample)	**Study population** N = 32 675 patients starting treatment with an OAC Dabigatran, n = 7925 Rivaroxaban, n = 6817 Apixaban, n = 6506 Warfarin, n = 11 427 **Target population** N = 68 215 Excluded: • Patients < 18 years, n = 4 • Patients with any OAC dispensation in the 180 days prior to the index date, n = 34 066 • Patients with VTE in the 180 days prior to the index date, n = 912 • Patients with knee/hip surgery in the 35 days prior to the index date, n = 336 • Patients with 2 different OACs dispensed at the index date, n = 6 • Patients dispensed OAC tablet strengths not indicated for AF at the index date, n = 216

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Women	41	38	45.6	45
Age, mean (SD)	74.6 (11.9)	70.8 (11.3)	74.7 (10.7)	74.5 (11.1)
>65 years	-	-	-	-
≥75 years	6248 (54.7)	2967 (37.4)	3524 (51.7)	3295 (50.6)
>85 years	-	-	-	-
CHA_2DS_2VASc, mean (SD)				
HAS-BLED, mean (SD)	42.8	37.0	47.0	46.6
Standard dose				
Reduced dose				
Comorbidities				
Ischemic stroke, or systemic embolism, or TIA (see below)	-	-	-	-
Stroke, TIA, and thromboembolism	11.6	9.4	16.1	13.9
Chronic heart failure	29.0	15.8	20.4	20.6
Myocardial infarction (see below)	-	-	-	-
Ischemic heart disease	35.9	21.4	25.5	27.6
Vascular disease (see below)	-	-	-	-
Anemia (last year)	4.8	2.0	3.0	3.1
Renal dysfunction (see below)	-	-	-	-
Chronic kidney disease	5.0	0.73	2.0	2.5
Previous bleeding (see below)	-	-	-	-
Previous bleeding hospitalization	16.8	11.2	14.8	15.1
Hypertension	67.0	59.0	66.0	65.4
Diabetes	14.7	10.4	11.7	12.3
Active cancer (last year)	10.0	7.4	9.2	8.6
Concomitant medication				
Aspirin (see below)	-	-	-	-
Low-dose aspirin (last year)	47.4	46.5	53.1	50.8
Beta-blocker				
NSAID (last year)	19.8	24.4	23.2	23.0
Calcium channel blocker	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-
Nonaspirin antiplatelet inhibitor (last year)	2.4	2.3	3.4	2.9

Analysis	**Measure of the risk of an end point** Crude incidence rates were also calculated as the first bleeding episode per 100 person-years. Relative risks were given as hazard ratios with 95% confidence intervals. Post hoc subgroup analyses for the primary end point of major or CRNM bleeding were performed for elderly patients (≥ 75 years old) as well as for OAC dose levels at the index date (standard and reduced dose) vs warfarin **Comparison of the risk of an end point between groups** Cox proportional hazards regression analyses were conducted to determine the risk of bleeding for the different NOACs vs. warfarin, both unadjusted and adjusted for known patient characteristics: age, sex, previous bleeding, previous OAC use, comorbidities, and concomitant medications at baseline Each bleeding end point was compared with the entire cohort and not in contrast to nonbleeders only, that is, for the major bleeding end point, the comparison was with all nonmajor bleedings **Software for statistical analysis** R (version 3.1.1, R Development Core Team) **Statistical significance reference** All statistical tests were 2-tailed and *P* values < .05 were considered significant

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Hernández et al.[71]
Reference	Hernández I, Baik SH, Piñera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med.* 2015;175:18-24. doi:10.1001/jamainternmed.2014.5398
Objective	To compare the risk of bleeding associated with dabigatran and warfarin using Medicare data
Country	United States
Design	Retrospective cohort study
Data source	Centers for Medicare & Medicaid Services (CMS)
Time period	October 1, 2010 to October 31, 2011
NOAC	Dabigatran at any dose. The report did not explicitly describe the dose of interest
Control	Warfarin
Outcomes	**Safety** Major bleeding events: • Intracranial hemorrhage • Hemoperitoneum • Inpatient or emergency department stays for gastrointestinal • Hematuria • Not otherwise specified (NOS) hemorrhage Minor bleeding events: • Epistaxis • Hemoptysis • Vaginal hemorrhage • Hemarthrosis • Any outpatient claim for hematuria • Gastrointestinal • NOS hemorrhage Any bleeding (including major and minor bleeding events)
Outcome definitions	Secondary International Classification of Diseases, Ninth Revision (ICD-9)
Population (eligibility)	Patients who were newly diagnosed as having AF who filled a prescription for either dabigatran or warfarin within 2 months of the first diagnosis Those who filled prescriptions for dabigatran and warfarin during the first 2 months after diagnosis were excluded
Population (study sample)	**Study population** Dabigatran, n = 1302 Warfarin, n = 8102

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Dabigatran	**Warfarin**
Women	57.7	59.1
Age, median (IQR)	75.7 (8.5)	75.0 (10.4)
>65 years	-	-
>75 years	-	-
>85 years	-	-
CHA_2DS_2VASc, mean (SD)		
HAS-BLED, mean (SD)		
Standard dose		
Reduced dose		
Comorbidities		
Ischemic stroke, or systemic embolism, or TIA (previous stroke or TIA)	18.3	23.0
Congestive heart failure	41.2	52.4
Acute myocardial infarction	8.9	6.2
Vascular disease	-	-
Renal dysfunction	-	-
Chronic kidney disease	23.5	34.2
Previous bleeding (history of bleeding)	6.8	11.7

Hypertension	88.6	87.5
Diabetes mellitus	36.1	45.0
Cancer	-	-
Concomitant medication		
Aspirin (included in the group below)	-	-
Use of antiplatelet (aspirin, clopidogrel, prasugrel, dipyridamole, ticlopidine, and ticagrelor)	6.8	8.2
Beta-blocker	-	-
NSAID	8.9	8.7
Calcium channel blocker	-	-
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Incidence rates **Comparison of the risk of an end point between groups** Cox proportional hazards regression models to evaluate the risk of bleeding **Confounding** Propensity score weighting conducted in 2 stages. A multivariate logistic regression was performed to predict the probability of an individual being a dabigatran or warfarin user, controlling for all of the listed covariates. In the second stage, Cox proportional hazards regression models were constructed to compare the hazard rates of bleeding between dabigatran and warfarin groups, using the inverse of the propensity score as a weight **Supplementary analyses** The incidence of bleeding was further examined in subgroups stratified by age (< 75 or ≥ 75 years) and among African Americans, users with renal impairment, and patients with at least 7 priority CMS conditions other than AF. Subgroup analyses were performed following the same methods and controlling for all covariates except for the one defining the subgroup **Software for statistical analysis** The CMS-RxHCC score was calculated using the CMSP prescription Drug Hierarchical Condition Categories software

IQR, interquartile range; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Hernandez et al.[72]
Reference	Hernandez I, Zhang Y. Comparing stroke and bleeding with rivaroxaban and dabigatran in atrial fibrillation: Analysis of the US Medicare Part D data. *Am J Cardiovasc Drugs.* 2017;17:37-47. doi:10.1007/s40256-016-0189-9
Objective	To compare effectiveness and safety between rivaroxaban 20 mg/dabigatran 150 mg and rivaroxaban 15 mg/dabigatran 75 mg among patients with atrial fibrillation (AF)
Country	United States
Design	Prospective cohort study
Data source	Pharmacy and medical data for a 5% random sample of US Medicare beneficiaries from the Centers for Medicare and Medicaid Services (CMS)
Time period	November 2011 to December 2013
NOAC	Dabigatran 300 mg daily Rivaroxaban 20 mg daily
Control	Dabigatran 150 mg daily Rivaroxaban 15 mg daily
Outcomes	**Effectiveness** Ischemic stroke, other thromboembolic events, and all-cause mortality **Safety** Any bleeding event and major bleeding Specifically reported were intracranial hemorrhage and gastrointestinal bleeding
Outcome definitions	Ischemic stroke was defined as having 1 inpatient, emergency room, or outpatient claim with primary or secondary International Classification of Diseases, Ninth Revision (ICD-9) codes 433, 434, or 436 Other thromboembolic events included inpatient, emergency room, or outpatient claims for systemic embolism (ICD-9 = 444), transient ischemic attack (ICD-9 = 435), and pulmonary embolism (ICD-9 = 415.1) Major bleeding events included intracranial hemorrhage, hemoperitoneum, and inpatient or emergency room stays for gastrointestinal, hematuria, or not otherwise specified hemorrhage
Population (eligibility)	Patients who filled a prescription for dabigatran or rivaroxaban between November 4, 2011 (the approval date for rivaroxaban) and December 31, 2013. Patients were required to have a diagnosis of AF any time before the index date according to the CMS Chronic Condition Warehouse definition of AF **Exclusion criteria** Patients who had a claim for dabigatran or rivaroxaban in the 3 months before the index date Patients receiving rivaroxaban 10 mg
Population (study sample)	**Study population** N = 17 507 Dabigatran 300 mg daily, n = 7322 Dabigatran 150 mg daily, n = 1818 Rivaroxaban 20 mg daily, n = 5799 Rivaroxaban 15 mg daily, n = 2568 **Target population** N = 44 621 Patients who filled a prescription for dabigatran or rivaroxaban between November 4, 2011 (the approval date for rivaroxaban) and December 31, 2013. Of the 44 621 identified patients, 27 116 met the exclusion criteria and were excluded

Population (baseline participant characteristics after matching) (values expressed as percentages unless otherwise stated)

	Dabigatran High-dose	**Rivaroxaban High-dose**	**Dabigatran Low-dose**	**Rivaroxaban Low-dose**
Women	52.0	52.1	66.6	66.7
Age, mean (SD)	.	.	.	.
>65 years	94.5	94.4	98.1	98.1
>75 years	55.6	55.5	83.6	83.3
>85 years	.	.	.	.
CHA_2DS_2, mean (SD)	3.28 (1.75)	3.28 (1.96)	3.83 (1.99)	3.83 (1.68)

HAS-BLED, mean (SD)	.	.	.	.
Standard dose	100	100	0	0
Reduced dose	0	0	100	100
Comorbidities				
Ischemic stroke, or systemic embolism, or TIA	22.9	23.0	34.3	34.1
Heart failure	51.3	51.3	69.3	69.1
Acute myocardial infarction	6.8	6.8	10.8	11.0
Vascular disease	.	.	.	.
Renal dysfunction	27.2	27.2	51.9	51.8
Previous bleeding	19.6	19.5	24.8	24.9
Hypertension	92.9	92.9	96.9	96.8
Diabetes	43.8	43.9	50.1	50.0
Cancer	.	.	.	.
Concomitant medication				
Antiplatelets	6.6	6.4	7.7	7.7
Beta-blocker	.	.	.	.
NSAID	13.9	13.7	11.1	11.0
Calcium channel blocker	.	.	.	.
Renin angiotensin system inhibitor	.	.	.	.

Analysis	**Measure of the risk of an end point** Number of events and cumulative incidence rates at 1-year follow-up **Comparison of the risk of an end point between groups** To compare the unadjusted cumulative incidence of effectiveness and safety outcomes at 1-year follow-up, Kaplan-Meier time-to-event curves were constructed Cox proportional hazards models to compare effectiveness and safety outcomes between groups, using the inverse of the propensity score for each individual as a weight. Cox models included 1 indicator variable for rivaroxaban initiation as well as all predefined covariates (below) **Confounding** Adjustment for demographic variables and clinical characteristics, all of which were measured at the index date. Demographic variables included age, race, and Medicaid eligibility. Clinical characteristics included $CHADS_2$ score, chronic kidney disease, hypertension, a history of stroke or TIA, prior acute myocardial infarction, diabetes, congestive heart failure, acquired hypothyroidism, number of other CMS priority comorbidities, a history of bleeding, concomitant use of nonsteroidal anti-inflammatory drugs, and concomitant use of antiplatelet drugs Using the above covariates, propensity score weighting was done in 2 steps. First, a logistic regression controlling for all of the covariates listed above was constructed to calculate the probability of initiating rivaroxaban (propensity score). Standardized differences in covariate means between 2 treatment groups were calculated to evaluate whether covariates were balanced between treatment groups after propensity score weighting **Sensitivity analysis** By excluding subjects who filled a prescription for warfarin 6 months before the index date By including and excluding patients who had a history of stroke or TIA before the index date Analysis robustness was assessed after excluding patients who filled a prescription for NSAIDs or antiplatelet agents after the index date **Supplementary analyses** Subgroup analysis of the effectiveness and safety of dabigatran and rivaroxaban among 3 subgroups of patients: those aged > 75 years, patients with chronic kidney disease, or those with at least 7 CMS priority conditions other than AF. For each subgroup identified, the propensity score was recalculated and Cox models were constructed to compare effectiveness and safety outcomes following the same methodology as the overall sample **Software for statistical analysis** SAS 9.4 (Cary, North Carolina) **Statistical significance reference** Not stated

AF, atrial fibrillation; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack; SD, standard deviation.

Study ID	Hohnloser et al.[73]
Reference	Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a post-marketing surveillance study. *Clin Res Cardiol*. 2017;106:618-628. doi:10.1007/s00392-017-1098-x
Objective	To assess the comparative risks of bleeding leading to hospitalization during therapy with NOACs and phenprocoumon in AF patients
Country	Germany
Design	Retrospective cohort study
Data source	Research database from the Health Risk Institute (HRI): comprises longitudinal information on medical and drug claims from an age- and sex-representative sample of about 4 million statutory health-insured subjects in Germany. Data available from each medical claim include date/quarter of service, place of service, diagnoses (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification [ICD-10-GM]), and procedures performed/services rendered. Data available for each drug claim include the agent dispensed (as set forth by the Anatomical Therapeutic Chemical System), dispensing/prescription date, and quantity dispensed. Selected demographic and eligibility information (including age/year of birth, sex, dates of enrollment) is also available for subjects in the HRI database
Time period	January 1, 2013 to March 31, 2015
NOAC	Any NOAC Apixaban Dabigatran Rivaroxaban Phenprocoumon
Control	Warfarin
Outcomes	Major bleeding event Gastrointestinal bleeding events Any bleeding event A composite net clinical outcome consisting of ischemic stroke, systemic embolism, or major bleeding
Outcome definitions	Major bleeding consisted of an emergency hospital admission with an ICD-10-GM hospital discharge diagnosis Gastrointestinal bleeding was defined as bleeding at any time during exposure time with localization in the gastrointestinal tract and documented ICD-10-GM hospital discharge diagnosis Any bleeding was defined using prespecified primary or secondary ICD-10-GM hospital discharge diagnoses at any time
Population (eligibility)	Adult patients (≥ 18 years) with nonvalvular AF who were new users of apixaban, dabigatran, rivaroxaban, and phenprocoumon during the study period were identified. A new user was required to have no prior prescription for any of the above-listed substances in the 12 months before initiation of medication. All patients were required to have at least 1 primary or secondary hospital discharge diagnosis of AF in the previous or same quarter of the index date or, alternatively, at least 2 ambulatory verified diagnoses of AF in the period between January 1, 2010 and the index date Patients were excluded if they were not continuously represented in the HRI database for at least 1 year prior to January 1, 2013, which was defined as the baseline period. Patients with valvular AF, deep vein thrombosis, hemodialysis, pregnancy, or anticoagulation therapy (ie, heparin, low-molecular-weight heparin, vitamin K antagonists, or NOACs) for any other indication during the 4 quarters prior to or on the index date were excluded
Population (study sample)	**Study population** N = 35 013 Dabigatran, n = 3138 Apixaban, n = 3633 Rivaroxaban, n = 12 063 Phenprocoumon, n = 16 179 **Target population** N = 154 603 Excluded:

	• Patients without AF or atrial flutter diagnosis in the same or preceding quarter of the index treatment, n = 50 401 • Restricted to age ≥ 18 years, n = 2 • Patients with dialysis/valvular disorder/thrombosis/gravidity in the 4 quarters before or at start date, n = 7230 • Patients with heparin at the start date, n = 2906 • Patients with NOAC or phenprocoumon prescription in the 4 quarters before the start date, n = 59 051

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Phenprocoumon (n = 16 179)	Any NOAC (n = 18 834)	Apixaban (n = 3633)	Dabigatran (n = 3138)	Rivaroxaban (n = 12 063)
Women	49.9	48.8	50.8	48.1	48.3
Age, mean (SD)	76.1 (9.1)	73.7 (11.2)	75.5 (10.8)	72.6 (11.2)	73.4 (11.3)
>65 years	-	-	-	-	-
>75 years	-	-	-	-	-
>85 years	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	4.1 (1.6)	3.8 (1.8)	4.1 (1.8)	3.8 (1.8)	3.7 (1.8)
HAS-BLED, mean (SD)	2.7 (1.1)	2.7 (1.2)	2.9 (1.2)	2.6 (1.2)	2.6 (1.2)
Standard dose					
Reduced dose					
Comorbidities					
Ischemic stroke, or systemic embolism, or TIA	12.2	16.1	22.4	21.9	12.7
Congestive heart failure	40.4	34.6	37.1	31.7	34.6
Myocardial infarction	7.5	5.0	5.6	5.1	4.8
Vascular disease					
Coronary heart disease	46.9	37.6	39.7	36.7	37.2
Renal insufficiency	23.9	17.3	21.4	13.3	17.1
Previous bleeding (see below)					
Major bleeding	1.3	1.4	2.0	1.6	1.1
GI bleeding	2.1	1.9	2.1	2.1	1.8
Any bleeding event	8.6	8.3	9.7	7.5	8.0
Hypertension	88.5	85.7	88.2	85.0	85.2
Diabetes	36.8	32.6	34.2	29.9	32.8
Cancer	19.7	18.4	19.2	17.9	18.3
Concomitant medication					
Aspirin (see below)					
Antiplatelet drugs	22.7	24.7	27.0	25.5	23.7
Aspirin	17.5	19.7	21.8	19.4	19.2
Beta-blocker					
NSAID	34.8	36.9	37.4	36.0	36.9
Calcium channel blocker		-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-
Proton pump inhibitor	43.9	44.1	46.0	44.0	43.6

Analysis	**Measure of the risk of an end point** Unadjusted event rates were estimated for each treatment group and were expressed per 100 person-years **Comparison of the risk of an end point between groups** Cox proportional hazard models were used to estimate the hazard ratios of major bleeding, gastrointestinal bleeding, any bleeding, and net clinical outcome adjusted for prespecified baseline demographics and clinical factors **Confounding** A Cox proportional hazard model was used to compare end points in each of the propensity score-matched cohorts **Sensitivity analysis** Propensity score matching was performed as a sensitivity analysis. To assess the impact of different dosages on the primary findings, the risk of major bleeding, gastrointestinal

	bleeding, and any bleeding with phenprocoumon was compared only with that of those patients who received the highest approved dose of NOACs only (2 × 5 mg/day for apixaban, 2 × 150 mg/day for dabigatran, 1 × 20 mg/day for rivaroxaban) The respective risks of different bleeding events for each treatment were compared when prescribed in the study period or until death or the end of the insurance status. Hence, the date of a switch or of discontinuation of the OAC treatment was not used as a censoring date. Instead, the exposure times of patients who switched from 1 substance to another were assessed based on their actual exposure time under each successive anticoagulant received during follow-up
NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.	

Study ID	Kodani et al.[13]
Reference	Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H; J-RHYTHM Registry Investigators. Beneficial effect of non-vitamin k antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation - Results of the J-RHYTHM Registry 2. *Circ J.* 2016;80:843-51. doi:10.1253/circj.CJ-16-0066
Objective	To investigate the long-term outcomes of warfarin therapy vs nonvitamin K antagonist oral anticoagulants (NOACs) in Japanese patients with nonvalvular atrial fibrillation (AF)
Country	Japan
Design	Prospective cohort study
Data source	Multicentre registry (131 institutions)
Time period	January 2010 to July 2010
NOAC (dosages not specified)	Dabigatran Rivaroxaban Apixaban
Control	Warfarin 36.7% had baseline INR values of 1.6-1.99 29.0% had baseline INR values of 2.0-2.59 2.6% had baseline INR ≥ 3.0
Outcomes	**Effectiveness** Symptomatic stroke including transient ischemic attack (TIA) Systemic thromboembolism All-cause mortality **Safety** Major bleeding including intracranial hemorrhage requiring hospitalization All-cause mortality
Outcome definitions	Symptomatic stroke including TIA Systemic thromboembolism Major bleeding including intracranial hemorrhage All outcomes had to be confirmed by computed tomography or magnetic resonance imaging
Population (eligibility)	Outpatients aged ≥ 20 years who had at least 1 episode of AF on a standard 12-lead electrocardiogram and who had maintained sinus rhythm for more than 1 year
Population (study sample)	**Study population** N = 6616 Warfarin, n = 3964 (59.9%) Dabigatran, n = 325 (4.9%) Rivaroxaban, n = 403 (6.1%) Apixaban, n = 184 (2.8%) Unknown NOAC, n = 11 (0.2%) Unknown OAC, n = 976 (14.8%) No OAC, n = 753 (11.4%) **Target population** Of the 7937 patients in the original registry, 909 patients did not give consent for extended follow-up and were thus excluded. Of the 7027 patients with AF who had been enrolled in this extended study, 364 were excluded for valvular AF. Of the remaining 6663 patients with NVAF, 47 (0.7%) were lost to follow-up. Therefore, 6616 patients with NVAF were included in the analyses

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	Dabigatran	Rivaroxaban	Warfarin	All participants
Women	-	-	-	28.8	29.0
Age, mean (SD)	-	-	-	70.1 (9.4)	69.7 (9.9)
>65 years	-	-	-	-	-
>75 years	-	-	-	35.3	34.0
>85 years	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	-	-	-	1.7 (1.2)	1.7 (1.2)
HAS-BLED, mean (SD)	-	-	-	-	-
Standard dose	-	-	-	-	-

Reduced dose	-	-	-	-	-
Comorbidities	-	-	-		
Ischemic stroke, or systemic embolism, or TIA	-	-	-	14.7	13.8
Heart failure	-	-	-	30.1	27.2
Myocardial infarction	-	-	-	-	-
Vascular disease	-	-	-	-	-
Renal dysfunction	-	-	-	-	-
Previous bleeding	-	-	-	-	-
Hypertension	-	-	-	61.1	60.1
Diabetes	-	-	-	18.7	18.2
Cancer	-	-	-	-	-
Concomitant medication	-	-	-		
Aspirin	-	-	-	20.7	18.0
Beta-blocker	-	-	-	-	-
NSAID	-	-	-	-	-
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Event rates in 3 groups according to the final status of anticoagulation therapy at the time of the event or at the end of follow-up: patients taking warfarin (Warfarin group), any NOAC (NOAC group), and no anticoagulant (No-OAC group) **Comparison of the risk of an end point between groups** Frequencies of events were compared using chi-square or Fisher's exact test Kaplan-Meier curves for time to events were compared with log-rank tests A Cox proportional hazard model **Confounding** Odds ratios for each event in the Warfarin and NOAC groups were calculated by multivariate logistic regression analysis adjusted for the components of the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, history of ischemic stroke or TIA, vascular disease [coronary artery disease], age 65-74 years, and female sex) and antiplatelet use, using the No-OAC group as a reference **Sensitivity analysis** Not reported **Supplementary analyses** Multivariate Cox regression analysis of the effect of the INR subgroup on the risk of thromboembolic events and major hemorrhage Multivariate logistic regression analysis of the effect of warfarin on all-cause and cardiovascular mortality **Software for statistical analysis** IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, New York) **Statistical significance reference** A 2-sided *P* value < .05

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Lai et al.[74]
Reference	Lai CL, Chen HM, Liao MT, Lin TT, Chan KA. Comparative effectiveness and safety of dabigatran and rivaroxaban in atrial fibrillation patients. *J Am Heart Assoc*. 2017;6:e005362. doi:10.1161/JAHA.116.005362
Objective	To examine the comparative effectiveness and safety between dabigatran and rivaroxaban in atrial fibrillation patients
Country	China
Design	Nationwide cohort study
Data source	National Health Insurance claims database
Time period	June 1, 2012 to May 31, 2014
NOAC	• Dabigatran 110 mg • Dabigatran 150 mg • Rivaroxaban 10 mg • Rivaroxaban 15 mg • Rivaroxaban 20 mg 86% of patients in the dabigatran group received 110 mg; 75% of patients in the rivaroxaban group received 15 mg, 21% received 20 mg, and 4% received 10 mg. Therefore, patients receiving different doses of the same study medication (110 and 150 mg for dabigatran; 10, 15, and 20 mg for rivaroxaban) were pooled into 1 study group for their respective drugs
Control	No control
Outcomes	**Effectiveness** • Death • Ischemic stroke • Acute myocardial infarction • Arterial embolism/thrombosis **Safety** • Intracranial hemorrhage • Gastrointestinal hemorrhage
Outcome definitions	International Classification of Diseases, 9th Revision (ICD-9-CM)
Population (eligibility)	All adult beneficiaries aged ≥ 20 years with a diagnosis of atrial fibrillation and flutter and prescriptions of study medications within the enrollment period were identified. The date of the first prescription of dabigatran or rivaroxaban was operationally defined as the index date. In addition, subjects having diagnoses of deep vein thrombosis, pulmonary embolism, mitral stenosis or procedures including valvular replacement, mitral commissurotomy, heart transplantation, or extracorporeal circulatory support within the 6-month period prior to the index date were excluded. Finally, patients receiving 2 study medications at the same time or having concomitant antiplatelet agents such as aspirin, clopidogrel, ticlopidine, or dipyridamole on the index date were excluded
Population (study sample)	**Study population** N = 15 234 subjects were included Dabigatran, n = 10 625 Rivaroxaban, n = 4609 After applying a PS-matching procedure, 4600 dabigatran users were successfully matched to 4600 rivaroxaban users **Target population** N = 18 278 Excluded: • Sex missing, n = 31 • Diagnosis of DVT or PE within 6 months prior to the index date, n = 162 • Diagnosis of MS within 6 months prior to the index date, n = 118 • Valve replacement, commissurotomy, heart transplantation, or extracorporeal circulation within 6 months prior to the index date, n = 4 • Two study medications prescribed on the index date, n = 48 • Prescription of aspirin, clopidogrel, ticlopidine, or dipyridamole on the index date, n = 2681
Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)	
	Overall population **PS-matched population**

	Dabigatran	Rivaroxaban	Dabigatran	Rivaroxaban
Women	43.3	45.3	45.4	45.2
Age, median (IQR)	76 (69-82)	76 (70-82)	76 (70-82)	76 (70-82)
<65 years	12.9	12.0	11.6	12.0
65-74 years	29.8	30.5	30.1	30.5
≥75 years	57.3	57.6	58.4	57.5
CHA_2DS_2VASc, mean (SD)	3.3 (1.5)	3.3 (1.5)	3.3 (1.5)	3.3 (1.5)
HAS-BLED, mean (SD)	-	-	-	-
Standard dose				
Reduced dose				
Comorbidities				
Ischemic stroke, or systemic embolism, or TIA	23.8	19.4	19.1	19.5
Heart failure (see below)				
Valvular heart disease	24.4	26.4	26.1	26.3
Myocardial infarction	1.1	1.3	1.4	1.3
Vascular disease	3.5	3.4	3.3	3.4
Renal dysfunction (failure)	4.7	4.7	4.8	4.7
Previous bleeding (see below)				
Intracranial hemorrhage	1.1	1.2	1.1	1.2
Hypertension	49.0	49.7	49.4	49.7
Diabetes mellitus	20.2	20.2	20.4	20.2
Cancer (see below)				
Solid tumor without metastasis	5.7	5.7	5.3	5.7
Concomitant medication				
Aspirin	42.8	44.3	44.3	44.3
Beta-blocker	52.3	53.9	53.7	53.8
NSAID	55.5	58.0	57.6	57.9
Calcium channel blocker	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-
Warfarin	51.0	46.3	46.2	46.3
Clopidogrel	8.1	9.5	9.2	9.5
Ticlopidine	2.6	2.7	2.6	2.7
Dipyridamole	8.2	9.0	8.6	9.0
Digoxin	26.3	25.0	24.8	25.0
Amiodarone	17.4	18.7	19.0	18.7
Dronedarone	2.4	4.2	4.0	4.2
Verapamil	3.5	4.0	3.5	3.9
Diltiazem	20.4	20.2	19.9	20.2
Dihydropyridine CCB	34.7	33.5	33.3	33.4
ACEI	14.4	13.6	13.8	13.5
ARB	53.1	52.2	51.4	52.2

Loop diuretic	30.1	33.9	33.3	33.8
Thiazide	7.1	6.5	6.5	6.5
Spironolactone	12.3	14.7	14.6	14.6
Statin	28.1	28.2	27.7	28.2
OAD	23.8	23.6	23.0	23.6
Insulin	6.6	6.9	6.9	6.9
PPI	11.0	12.3	12.1	12.3
H2-blocker	29.0	30.6	30.5	30.6

Analysis	**Measure of the risk of an end point** Incidence rates of various clinical outcomes are presented as cases per 100 person-years among the overall population and the PS-matched population **Comparison of the risk of an end point between groups** The marginal proportional hazards model was applied for estimation of the relative risks (hazard ratios) of various clinical outcomes between the dabigatran group and the rivaroxaban group among the PS-matched population as the primary analysis Using a chi-square test for categorical variables and the 2-sample *t* test for normally distributed continuous variables, baseline characteristics were compared between the dabigatran group and the rivaroxaban group in the overall population. The standardized difference was also used to measure covariate balance, whereby an absolute standardized difference greater than 0.10 represented meaningful imbalance **Confounding** A PS was derived using logistic regression to model the probability of receipt of rivaroxaban (or dabigatran) as a function of all of the potential confounders **Software for statistical analysis** SAS software, version 9.4 (SAS Institute, Inc, Cary, North Carolina) **Statistical significance reference** All reported *P* values were 2-sided, and the significance level was set at < .05

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DVT, deep venous thrombosis; IQR, interquartile range; MS, mitral stenosis; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Laliberté et al.[75]
Reference	Laliberté F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin.* 2014;30:1317-1325. doi:10.1185/03007995.2014.907140
Objective	To assess real-world safety, effectiveness, and persistence associated with rivaroxaban and warfarin in nonvalvular AF patients
Country	United States
Design	Retrospective cohort study
Data source	Symphony Health Solutions' (SHS) Patient Transactional Datasets
Time period	May 2011 to July 2012
NOAC	Rivaroxaban 20 mg
Control	Warfarin
Outcomes	**Effectiveness** • Composite stroke and systemic embolism (ischemic stroke, hemorrhagic stroke, systemic embolism) • Venous thromboembolism events (deep vein thrombosis and pulmonary embolism) **Safety** • Major bleeding • Intracranial hemorrhage • Gastrointestinal bleeding
Outcome definitions	International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM): 427.31 Composite stroke and systemic embolism end points were required to be identified during a hospitalization or emergency department visit as a primary or secondary diagnosis VTE events were required to be identified during either (1) a hospitalization or emergency department visit or (2) during an outpatient visit with a 6-month washout (to ensure the identification of a new VTE event) Hemorrhagic stroke was defined as the occurrence of both a diagnosis of ICH and a diagnosis of late effects of cerebrovascular disease during the same hospitalization
Population (eligibility)	Patients newly initiated on rivaroxaban or warfarin after November 2011 (the time of rivaroxaban approval for nonvalvular AF in the US), were ≥ 18 years of age, had a $CHADS_2$ score ≥ 1 during the 180-day baseline period, and had ≥ 2 diagnoses of AF during the baseline or follow-up period. The study patients were required to have at least 6 months of clinical activity (a variable included in the SHS data) prior to the index date (baseline period). Patients with prior use of warfarin but who initiated rivaroxaban after its approval in November 2011 were classified in the rivaroxaban cohort, consistent with recent clinical trials studying the use of novel oral anticoagulants by AF patients that have combined VKA-experienced and -naïve patients Patients diagnosed at baseline with valvular involvement, pregnancy, malignant cancers, and transient causes of AF were excluded from the study
Population (study sample)	**Study population** Rivaroxaban, n = 3654 Warfarin, n = 26 825 **Target population** N = 1 083 888 Excluded: • Less than 180 days of continuous activity: rivaroxaban, n = 4968; warfarin, n = 180 030 • Not newly initiated (180-day washout period): warfarin, n = 600 817 • Less than 2 AF diagnoses, n = 0 • Less than 18 years of age, n = 0 • Valvular involvement, pregnancy, malignant cancer, transient causes of AF: rivaroxaban, n = 1378; warfarin, n = 12 397

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Rivaroxaban	Warfarin
Women	51.0	51.5
Age, mean (SD)	73.3 (8.4)	73.7 (8.3)
>65 years	-	-

>75 years	-	-
>85 years	-	-
CHA_2DS_2VASc, mean (SD)	3.4 (1.4)	3.5 (1.4)
HAS-BLED, mean (SD)	1.9 (0.8)	1.9 (0.8)
Standard dose	100	100
Reduced dose	-	-
Comorbidities		
Ischemic stroke, or systemic embolism, or TIA	-	-
Cerebrovascular accident (stroke)	9.8	9.8
Heart failure	19.6	20.8
Myocardial infarction	-	-
Vascular disease	-	-
Renal dysfunction	-	-
Renal disease	12.2	13.0
Chronic kidney disease	7.5	8.2
Previous bleeding	7.8	8.0
Hypertension	71.9	71.3
Diabetes	25.2	26.4
Cancer	-	-
Concomitant medication	-	-
Aspirin	-	-
Beta-blocker	-	-
NSAID	12.7	11.9
Calcium channel blocker	-	-
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Hazards ratios **Comparison of the risk of an end point between groups** Cox proportional hazard models were used to compare event and persistence rates **Confounding** Propensity score matching was performed to minimize sample selection bias and the risk of confounding between rivaroxaban and warfarin users Propensity scores were calculated using a multivariate logistic regression model, incorporating the following baseline characteristics: demographics, insurance type comorbidities, and risk factors for bleeding, stroke and VTE events **Sensitivity analysis** Conducted for the analysis of persistence with therapy for rivaroxaban and warfarin users, where the use of other oral anticoagulants (ie, dabigatran) during follow-up was allowed (not considered a gap in therapy) **Software for statistical analysis** SAS 9.3 (SAS Institute Inc, Cary, North Carolina) **Statistical significance reference** Statistical significance was assessed with 2-sided tests at a significant level of .05

AF, atrial fibrillation; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack; SD, standard deviation; VTE, venous thromboembolism.

Study ID	Larsen et al.[76]
Reference	Larsen TB, Gorst-Rasmussen A, Rasmussen LH, Skjøth F, Rosenzweig M, Lip GY. Bleeding events among new starters and switchers to dabigatran compared with warfarin in atrial fibrillation. *Am J Med*. 2014;127:650-656. doi:10.1016/j.amjmed.2014.01.031
Objective	To assess bleeding safety of dabigatran relative to warfarin within each stratum of VKA-naïve and VKA-experienced patients with atrial fibrillation
Country	Denmark
Design	Nationwide cohort study
Data source	Three Danish nationwide databases: • Danish National Prescription Registry (purchase date, Anatomical Therapeutic Chemical classification code, and package size for every prescription purchase in Denmark since 1994) • Danish National Patient Register (admission/discharge date, and discharge International Classification of Diseases diagnoses for > 99% of somatic hospital admissions in Denmark) • Danish Civil Registration System (with information on sex, date of birth, and vital and emigration status)
Time period	August 1, 2011 (dabigatran market entry) to May 30, 2013 August 1, 2009 to May 30, 2013 (warfarin)
NOAC	• Dabigatran 110 mg • Dabigatran 150 mg
Control	Warfarin (according to VKA experience status)
Outcomes	**Safety** • Major bleeding • Intracranial bleeding • Fatal bleeding • Gastrointestinal bleeding • Any bleeding
Outcome definitions	End points were ascertained according to the International Classification of Disease, 10th revision (ICD-10). Major bleeding, intracranial bleeding (including retinal bleeding and traumatic intracranial bleeding), fatal bleeding (death within 30 days from any bleeding event), gastrointestinal bleeding, and any of the preceding ("any bleeding")
Population (eligibility)	Included: first-time purchases of dabigatran and warfarin purchases during the study time period Excluded: purchases made by patients without a prior hospital diagnosis of atrial fibrillation; or with a prior hospital diagnoses of mitral stenosis, venous thromboembolism, or valvular surgery; or with a previous purchase of phenprocoumon
Population (study sample)	**Study population** Patients with a first-time dabigatran purchase, n = 11 315 VKA-naïve, n = 7063; VKA-experienced, n = 4252 Warfarin, n = 22 630 (VKA-naïve, n = 14 126; VKA-experienced, n = 8504)

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	VKA-naïve stratum			**VKA-experienced stratum**		
	Dabigatran 110 mg	**Dabigatran 150 mg**	**Warfarin**	**Dabigatran 110 mg**	**Dabigatran 150 mg**	**Warfarin**
Women	55.1	36.6	41.3	54.4	35.2	38.4
Age, median (IQR)	82 (77-86)	67 (62-72)	73 (66-80)	82 (77-86)	69 (64-73)	74 (67-81)
≥65 years	95.3	63.6	76.8	96.9	70.9	81.8
≥75 years	80.1	13.7	42.5	80.3	18.3	46.2
>85 years	-	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	3.70 (1.47)	2.12 (1.41)	2.80 (1.67)	3.89 (1.47)	2.59 (1.54)	3.01 (1.59)
HAS-BLED, mean (SD)	2.32 (1.04)	1.70 (1.11)	1.97 (1.18)	2.22 (1.01)	1.83 (1.08)	1.87 (1.03)
Standard dose	100	100	100	100	100	100
Reduced dose	-	-	-	-	-	-
Comorbidities						
Ischemic stroke, or	26.5	16.3	16.9	27.9	19.0	19.6

systemic embolism, or TIA						
Heart failure	-	-	-	-	-	-
Myocardial infarction	-	-	-	-	-	-
Vascular disease	-	-	-	-	-	-
Renal dysfunction	3.1	1.3	7.0	4.7	2.8	4.6
Previous bleeding	18.7	11.1	13.4	22.1	15.1	16.0
Hypertension	34.8	33.0	34.1	37.9	44.7	39.6
Diabetes	13.6	11.2	14.7	16	15.9	16.8
Cancer	-	-	-	-	-	-
Concomitant medication						
Aspirin	41.1	32.9	38.6	24.0	21.4	18.4
Beta-blocker	-	-	-	-	-	-
NSAID	5.9	6.0	5.3	4.9	4.5	4.5
Calcium channel blocker	-	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-	-
Clopidogrel	8.1	5.0	6.1	3.4	2.3	1.2

Analysis	**Measure of the risk of an end point** Crude cumulative incidences of bleeding were estimated with the Aalen-Johansen method under competing risks of death **Comparison of the risk of an end point between groups** Risk time from the baseline date until the first occurrence of the relevant bleeding event, emigration, death, or July 31, 2013 Cox proportional hazards regression models to estimate hazard ratios of bleeding events for each of the 6 different combinations of treatment (D110, D150, and warfarin) and VKA experience status, with VKA-naïve warfarin users as a reference **Confounding** Regression models were adjusted for the following baseline characteristics: age (continuous; cubic spline); components of CHA_2DS_2VASc and HAS-BLED (binary); months since August 2011 (continuous; cubic spline). In the analyses restricted to the VKA-experienced stratum, time since initiation of VKA therapy (continuous; cubic spline) was also adjusted for **Sensitivity analysis** Per-protocol-type sensitivity analysis was used to investigate the effect of continuous treatment, censoring individuals at the time of nonpersistence (time of treatment switching or > 30 days discontinuation, ascertained from previous package sizes and a standard daily dose) **Supplementary analyses** To assess the extent to which subjects followed the assumed treatment, 3-month persistence probabilities were also estimated with the Aalen-Johansen method under competing risks of death **Software for statistical analysis** Stata/MP version 12.1 **Statistical significance reference** A 2-sided *P* value < .05 was considered statistically significant

IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

Study ID	Larsen et al.[77]
Reference	Larsen TB, Rasmussen LH, Gorst-Rasmussen A, Skjøth F, Lane DA, Lip GY. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: A nationwide cohort study. *Am J Med*. 2014;127:1172-1178. doi:10.1016/j.amjmed.2014.07.023
Objective	To evaluate the effectiveness of dabigatran relative to warfarin for secondary prevention of stroke/transient ischemic attack among "new starters" on anticoagulant therapy
Country	Denmark
Design	Nationwide cohort study
Data source	Three Danish nationwide databases: • The Danish National Prescription Registry (with information on purchase date, Anatomical Therapeutic Chemical classification code, and package size for every prescription purchase in Denmark since 1994) • The Danish National Patient Register, established in 1977, which includes admission/discharge date and discharge International Classification of Diseases diagnoses for > 99% of somatic hospital admissions in Denmark • The Danish Civil Registration System (with information on sex, date of birth, and vital and emigration status)
Time period	August 1, 2011 (dabigatran market entry in Denmark) to May 30, 2013, alongside all purchases of warfarin from August 1, 2009 to May 30, 2013
NOAC	• Dabigatran 110 mg twice daily • Dabigatran 150 mg twice daily
Control	Warfarin
Outcomes	**Effectiveness** • Stroke • Transient ischemic attack • Composite stroke/transient ischemic attack • Fatal strokes/transient ischemic attacks **Safety** • Bleeding risk
Outcome definitions	End points were ascertained according to the International Classification of Disease, 10th revision (ICD-10) • Ischemic stroke (I63, I64.9) • Transient ischemic attack (G45) • Fatal stroke, not including hemorrhagic stroke (ischemic stroke or transient ischemic attack followed by death within 30 days)
Population (eligibility)	Patients with atrial fibrillation and a history of stroke/transient ischemic attack making a first-time dabigatran purchase, alongside patients making a first-time warfarin purchase (controls) during the study period Excluded purchases not preceded by a hospital diagnosis of atrial fibrillation, or preceded by a hospital diagnosis of mitral stenosis, venous thromboembolism, or valvular surgery, or preceded by phenprocoumon use. In accordance with the focus on secondary prevention, purchases not preceded by a hospital diagnosis of stroke/transient ischemic attack were excluded
Population (study sample)	**Study population** VKA-naïve: Dabigatran, n = 1439; warfarin, n = 1825 VKA-experienced: Dabigatran, n = 959; warfarin, n = 1918 **Target population** N = 731 407 (naïve, n = 41 613; experienced, n = 689 794) Excluded: • No prior stroke, n = 598 285 (naïve, n = 35 633; experienced, n = 562 652) • No prior AF, n = 32 143 (naïve, n = 2338; experienced, n = 29 805) • Other exclusion criteria: other hospital diagnosis of mitral stenosis, venous thromboembolism, valvular surgery, or prior phenprocoumon use, n = 20 203 (naïve, n = 378; experienced, n = 19 825)
Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)	

	Vitamin K antagonist-naïve			Vitamin K antagonist-experienced		
	Warfarin	**Dabigatran 110 mg**	**Dabigatran 150 mg**	**Warfarin**	**Dabigatran 110 mg**	**Dabigatran 150 mg**
Women	41.4	54.7	36.7	37.9	54	34.4
Age, median (IQR)	72 (65-79)	81 (76-86)	67 (62-72)	74 (67-80)	81 (76-85)	68 (64-73)
>65 years	-	-	-	-	-	-
>75 years	-	-	-	-	-	-
>85 years	-	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	1.73 (1.06)	2.01 (0.90)	1.50 (1.02)	1.66 (0.91)	1.94 (0.87)	1.63 (1.00)
HAS-BLED, mean (SD)	0.96 (0.88)	1.38 (0.82)	0.61 (0.74)	1.16 (0.90)	1.54 (0.87)	0.91 (0.86)
Standard dose	100	100	100	100	100	100
Reduced dose	-	-	-	-	-	-
Comorbidities						
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-	-	-
Prior ischemic stroke	75.3	81.2	74.9	75.7	82.1	76.5
Prior transient ischemic attack	36.3	32.0	35.8	37.2	32.4	34.7
Heart failure	-	-	-	-	-	-
Myocardial infarction (see below)	-	-	-	-	-	-
Prior myocardial infarction, unstable angina, or cardiac arrest	17.6	17.5	8.4	19.8	25.0	22.1
Vascular disease	-	-	-	-	-	-
Renal dysfunction	9.5	3.9	0.9	6.0	3.3	3.2
Previous bleeding	16.2	20.9	13.0	19.2	24.5	19.7
Hypertension	36.4	33.0	29.6	37.7	36.7	38.1
Diabetes	16.1	15.4	13.0	18.0	14.1	20.6
Cancer	-	-	-	-	-	-
Concomitant medication						
Aspirin	43.0	42.7	34.8	23.0	25.6	21.8
Beta-blocker						
NSAID	5.2	4.2	4.8	4.3	4.4	4.9
Calcium channel blocker	-	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-	-
Clopidogrel	21.4	20.1	20.3	3.0	6.4	5.8
Clopidogrel and aspirin/NSAID	7.7	6.2	5.0	0.4	2.0	1.5

Analysis	**Measure of the risk of an end point** Crude cumulative incidences of stroke/transient ischemic attack were calculated with the Aalen-Johansen method under competing risk of death **Comparison of the risk of an end point between groups** Time-to-event analysis was used to compare the risk of stroke/transient ischemic attack between treatment groups within the 2 VKA-experienced strata (naïve/experienced), measuring risk time from baseline and until the relevant event, emigration, death, or July 31, 2013, whichever came first Cox regression was used to contrast event rates between dabigatran users and warfarin controls within each of the VKA-experienced strata **Confounding** Regression analyses were adjusted for the baseline values of the following indications: age (continuous; cubic spline); components of the CHA_2DS_2-VASc and HAS-BLED (binary); and months since August 2011 (continuous; cubic spline). In the VKA-experienced stratum, time since initiation of VKA therapy (continuous; cubic spline) was also adjusted for **Sensitivity analysis** Repeated regression analyses after individual censoring at the time of nonpersistence in order to quantify the effect of continuous treatment (implicitly assuming censoring to be noninformative conditionally on baseline covariates)

	Regression analyses were also repeated when requiring end points to have been registered as the primary diagnosis in connection with hospitalization for at least 1 night Repeated a subset of the main analyses in the primary prevention group, that is, the analogously defined 2 VKA-experienced strata based on the subset of the warfarin/dabigatran purchase data that excluded subjects with a prior diagnosis of stroke/transient ischemic attack **Software for statistical analysis** Stata/MP version 12.1 (StataCorp LP, College Station, Texas) **Statistical significance reference** A 2-sided *P* value < .05 was considered statistically significant

AF, atrial fibrillation; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

Study ID	Larsen et al.[52]
Reference	Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. *BMJ.* 2016;353:i3189. doi:10.1136/bmj.i318
Objective	To evaluate the effectiveness and safety of the novel oral anticoagulants (dabigatran, rivaroxaban, and apixaban) vs warfarin in anticoagulant-naïve patients with atrial fibrillation
Country	Denmark
Design	Nationwide cohort study
Data source	Three Danish nationwide databases • Danish National Prescription Registry (with information on every drug prescriptions claimed since 1994) • Danish National Patient Register (admission and discharge information [dates, discharge diagnoses] for more than 99% of hospital admissions since 1977) • Danish Civil Registration System (with information on sex, date of birth, and vital and emigration status; all individuals in Denmark have a unique identification number)
Time period	August 2011 to October 2015
NOAC	Apixaban 5 mg twice daily Dabigatran 150 mg twice daily Rivaroxaban 20 mg once daily
Control	Warfarin (2.5 mg dose tablets)
Outcomes	**Effectiveness** Ischemic stroke Composite of ischemic stroke or systemic embolism Death Composite of ischemic stroke, systemic embolism, or death **Safety** Any bleeding Intracranial bleeding Major bleeding
Outcome definitions	Ischemic stroke: ICD-10 revision codes. This outcome has been validated, with a positive predictive value of more than 97% Systemic embolism: ICD-10 revision codes Bleeding events: intracranial, major, gastrointestinal, and traumatic intracranial Major bleeding: extracranial bleeding with anemia, hemothorax, hematuria, epistaxis, and bleeding in the eye
Population (eligibility)	People diagnosed with atrial fibrillation with a first-time purchase of the NOAC of interest (to standard doses) or a new warfarin prescription during the study time period Restriction to standard doses because patients who receive reduced dosage regimens have more comorbidities and are of a more advanced age (> 80 years) Restriction to naïve patients (exclusion of patients who had used any oral anticoagulant within 1 year before the study period) Exclusion of patients with valvular atrial fibrillation (mitral stenosis or mechanical heart valves) or venous thromboembolism (pulmonary embolism or deep vein thrombosis)
Population (study sample)	**Study population** N = 61 678 Apixaban, n = 6349 (10%) Dabigatran, n = 12 701 (21%) Rivaroxaban, n = 7192 (12%) Warfarin, n = 35 436 (57%) **Target population** N = 122 068 patients as new users of NOACS Exclusion of 35 035 patients receiving 1 of the nonvitamin K antagonist oral anticoagulants with reduced doses and 25 355 patients with an indication for valvular atrial fibrillation or venous thromboembolism

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	Dabigatran	Rivaroxaban	Warfarin	All participants
Women	39.7	33.9	43.1	41.2	39.8
Age, median (IQR)	71.3 (65.8-77.2)	67.6 (62.0-72.4)	71.8 (65.7-78.9)	72.4 (64.7-79.8)	70.9 (64.3-77.7)

>65 years	78.2	64.4	77.7	74.2	73.0
>75 years	33.7	13.9	38.1	41.4	34.5
>85 years	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	2.8 (1.6)	2.2 (1.4)	2.8 (1.6)	2.8 (1.7)	2.7 (1.6)
HAS-BLED, mean (SD)	2.3 (1.2)	2.0 (1.1)	2.2 (1.2)	2.2 (1.2)	2.2 (1.2)
Standard dose	100	100	100	100	100
Reduced dose	-	-	-	-	-
Comorbidities					
Ischemic stroke, or systemic embolism, or TIA	21.1	13.2	16.8	14.8	15.3
Heart failure	15.9	9.3	12.6	10.4	11.0
Myocardial infarction	-	-	-	-	-
Vascular disease	13.9	10.4	12.2	18.1	15.4
Renal dysfunction	2.4	1.1	1.8	6.6	4.5
Previous bleeding	14.0	9.9	12.8	11.8	11.8
Hypertension	48.8	47.0	48.6	50.6	49.4
Diabetes	15.8	13.8	14.0	15.6	15.0
Cancer	16.1	11.8	16.1	16.5	15.5
Concomitant medication					
Aspirin	37.8	38.2	38.3	42.0	40.4
Beta-blocker	38.6	40.1	38.9	41.0	40.3
NSAID	22.4	24.5	22.1	24.3	23.9
Calcium channel blocker	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Crude incidence (number of events divided by person-time) **Comparison of the risk of an end point between groups** Time-to-event analysis (risk time from initial prescription until the relevant event, emigration, death, or end of follow-up) Intention-to-treat analysis for all end points Cox regression (warfarin as the primary reference) **Confounding** Inverse probability of treatment weighted analysis Generalized boosted models (based on 10 000 regression trees to calculate weights for the optimal balance between the treatment populations and obtain estimates representing population average treatment effects) Propensity model including treatment predictors of age (continuous); binary indicators for sex; ischemic stroke or systemic embolism or transient ischemic attack; vascular disease; hypertension; diabetes; cancer; recent prescription of aspirin, beta-blockers, nonsteroidal anti-inflammatory drugs, or statins; and CHA_2DS_2-VASc and HAS-BLED scores Graphical inspection of the weight distributions to evaluate the balance between treatment populations by standardized differences of all baseline covariates, using a threshold of 0.1 to indicate imbalance. Ordinary logistic regression to evaluate the association of baseline characteristics on treatment choice vs any of the alternatives **Sensitivity analysis** Analyses repeated by restriction to the cohort of patients with: *a)* a hospital discharge diagnosis of atrial fibrillation either before or within 30 days of the first prescription of a NOAC; *b)* dabigatran treatment postponed to February 2012; *c)* populations younger and older than 65; *d)* according to previous experience of stroke, systemic embolism, or transient ischemic attack **Supplementary analyses** Continuous treatment analysis (censoring follow-up if the patient was prescribed another treatment than that initiated) **Software for statistical analysis** Stata/MP version 14 and R version 3.1.1 **Statistical significance reference** A 2-sided *P* value of less than .05

IQR, interquartile range; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Li et al.[78]
Reference	Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost*. 2017;117:1072-1082. doi:10.1160/TH17-01-0068
Objective	To assess the effectiveness and safety of apixaban vs warfarin in nonvalvular atrial fibrillation patients in "real-world" clinical practice
Country	United States
Design	Retrospective cohort study
Data source	Four large, nationally-representative claims databases in the US: Two containing information from employer-provided health plans, with reported potential duplicates of only 0.5% in a study using both datasets: • Truven MarketScan® Commercial Claims Encounter and Medicare Supplemental and Coordination of Benefits Database ("MarketScan") • IMS PharMetrics Plus™ Database ("PharMetrics") Two containing information on beneficiaries from unique insurance plans, which guarantees no duplicates on the health plan level when pooled with other datasets: • Optum Clinformatics™ Data Mart ("Optum") • Humana Research Database ("Humana") The 4 datasets include claims from over 163 million members of commercial and Medicare Advantage/supplemental plans. The datasets contain information on patient demographics and enrollment history as well as medical claims from inpatient hospitals, outpatient hospitals, the emergency room, physician offices, and surgery centers
Time period	January 1, 2013 to September 30, 2015
NOAC	• Apixaban 5 mg • Apixaban 2.5 mg
Control	Warfarin
Outcomes	**Effectiveness** Stroke/systemic embolism (SE): • Ischemic stroke, • Hemorrhagic stroke • SE **Safety** Major bleeding events: • Gastrointestinal (GI) bleeding • Intracranial hemorrhage (ICH) • Other major bleeding
Outcome definitions	Identified using the first-listed ICD-9-CM diagnosis of inpatient claims. The diagnosis codes used for stroke/SE and major bleeding were based on a validated administrative claim-based algorithm as well as the International Society on Thrombosis and Haemostasis definition of major bleeding, as used in the ARISTOTLE trial
Population (eligibility)	NVAF patients who were aged ≥ 18 years and had ≥ 1 pharmacy claim for apixaban or warfarin during the identification were included in the study. AF patients were identified using ICD-9-CM code 427.31, a validated code used to identify AF patients with a median positive predictive value of 89%. The date of the first apixaban or warfarin pharmacy claim during the identification period was designated as the index date. Patients were required to have the AF diagnosis before or on the index date and have continuous medical and pharmacy health plan enrollment for ≥ 12 months prior to the index date Patients with evidence of valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity), or heart valve replacement/transplant during the 12 months prior to or on the index date, or with pregnancy during the study period were excluded. Patients treated with any OACs within 12 months before the index date or with > 1 OAC on the index date were also excluded
Population (study sample)	**Study population** N = 76 940 Warfarin, n = 38 470 Apixaban, n = 38 470 **Target population**

	NVAF patients, N = 115 186 Apixaban, n = 41 867 Warfarin, n = 73 319

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Warfarin**
Women	40.4	40.2
Age, mean (SD)	70.9 (12.0)	70.9 (11.9)
>65-74 years	27.7	27.7
≥75 years	40.7	40.5
>85 years	-	-
CHA_2DS_2VASc, mean (SD)		
HAS-BLED, mean (SD)		
Standard dose		
Reduced dose		
Comorbidities		
Ischemic stroke, or systemic embolism, or TIA	-	-
Stroke/SE	10.2	9.9
Transient ischemic attack (TIA)	6.2	6.1
Congestive heart failure	24.2	23.9
Myocardial infarction	8.9	8.8
Vascular disease (see below)	-	-
Nonstroke/SE peripheral vascular disease	45.1	44.9
Renal disease	19.8	19.9
Previous bleeding	-	-
Bleeding history	16.6	16.4
Hypertension	82.5	82.3
Diabetes mellitus	32.5	32.8
Cancer	-	-
Concomitant medication		
Aspirin (see below)	-	-
Antiplatelet	15.8	15.6
Beta-blocker	60.1	59.8
NSAID	23.5	23.3
Calcium channel blocker	-	-
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Cumulative incidence and hazard ratios **Comparison of the risk of an end point between groups** Propensity score matching was conducted between the warfarin and apixaban cohorts. Patients were matched 1:1 within each dataset on the propensity scores generated by logistic regressions based on age, sex, geographic region, Charlson Comorbidity Index score, baseline bleeding and stroke/SE history, comorbidities, and baseline comedications Cox proportional hazard models with robust sandwich estimates were performed to evaluate the risk of stroke/SE and major bleeding between the 2 matched cohorts **Sensitivity analysis** A sensitivity analysis was conducted without restricting the follow-up period to 1 year. In this analysis, patients were not censored at the 1 year postindex date **Software for statistical analysis** STATinMED **Statistical significance reference** *P* < .05 was considered statistically significant

NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation, SE, systemic embolism; TIA, transient ischemic attack.

Study ID	Lip et al.[79]
Reference	Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, Hamilton M. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost*. 2016;116:975-986. doi:10.1160/TH16-05-0403
Objective	To assess major bleeding risks among newly anticoagulated NVAF patients who initiate warfarin, apixaban, dabigatran, or rivaroxaban when used in the "real world" clinical practice
Country	United States
Design	Retrospective cohort study
Data source	Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Databases (containing medical and drug data for several million individuals annually, allowing for comprehensive longitudinal analysis)
Time period	January 2012 to December 2014
NOAC	Apixaban 5 mg twice daily Dabigatran 150 mg twice daily Rivaroxaban 20 mg once daily
Control	Warfarin
Outcomes	**Safety** Major bleeding
Outcome definitions	Major bleeding was defined as bleeding requiring hospitalization during the period of drug use or within 30 days after the last day of supply of the treatment prescription The definition of major bleeding was based on a published administrative claims-based algorithm as well as clinical trial definitions of major bleeding. This definition accounts for major bleeding at key sites including, but not limited to, intracranial, gastrointestinal, liver, splenic, and ocular hemorrhage requiring hospitalization with a diagnosis for bleeding
Population (eligibility)	AF patients (ICD-9-CM codes: 427.31 or 427.32) ≥ 18 years who newly initiated OACs (warfarin, dabigatran, rivaroxaban, and apixaban) during the study period were included. The first OAC pharmacy claim date was designated as the index date. Patients with continuous health plan enrollment with medical and pharmacy benefits for at least 12 months before the index date (baseline period) were included in the study. Patients with a prescription claim for warfarin, rivaroxaban, dabigatran, or apixaban prior to the index date were excluded. Patients with evidence of transient AF (thyrotoxicosis, pericarditis), cardiac surgery, venous thromboembolism (VTE), valvular heart disease, or pregnancy were excluded
Population (study sample)	**Study population** Newly anticoagulated NVAF patients, N = 45 361 Warfarin, n = 15 461 (34.1%) Apixaban, n = 7438 (16.4%) Rivaroxaban, n = 17 801 (39.2%) Dabigatran, n = 4661 (10.3%) **Target population** N = 101 138 Excluded: • Patients without AF or atrial flutter diagnosis at baseline, n = 14 214 • Restricted to age ≥ 18, n = 13 • Transient AF, n = 9962 • Patients with heart surgery, n = 2259 • Patients with VTE, n = 7002 • Patients with valvular heart disease, n = 22 255 • Pregnant patients, n = 54

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Warfarin**	**Dabigatran**	**Warfarin**	**Rivaroxaban**	**Warfarin**
Women	39.0	38.4	35.8	36.1	39.1	38.9
Age, mean (SD)	69.1 (12.3)	69.0 (12.3)	66.9 (12.2)	67.5 (12.3)	69.7 (11.9)	70.1 (12.0)
>65 years	-	-	-	-	-	-
>75 years	-	-	-	-	-	-

>85 years	-	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	2.9 (1.7)	2.8 (1.6)	2.6 (1.7)	2.6 (1.7)	2.9 (1.7)	3.0 (1.6)
Modified HAS-BLED, mean (SD)	2.2 (1.3)	2.2 (1.2)	2.0 (1.2)	2.0 (1.2)	2.2 (1.2)	2.2 (1.2)
Standard dose	100	-	100	-	100	-
Reduced dose	-	-	-	-	-	-
Comorbidities						
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-	-	-
Transient ischemic attack	5.4	5.4	4.5	3.8	5.11	5.25
Ischemic stroke	8.4	7.8	7.0	6.6	8.9	9.3
Congestive heart failure	20.1	19.7	19.1	18.9	22.1	22.0
Myocardial infarction	6.5	6.7	5.6	5.9	7.4	7.3
Vascular disease (see below)	-	-	-	-	-	-
Coronary artery disease	32.6	31.6	28.0	26.8	32.0	32.1
Renal disease	9.0	9.4	7.4	7.7	10.2	10.6
Previous bleeding	14.1	13.8	11.9	11.6	15.7	16.0
Hypertension	74.3	73.8	69.8	69.7	72.1	72.3
Diabetes	28.8	28.5	27.6	26.4	30.2	29.9
Cancer	-	-	-	-	-	-
Concomitant medication						
Aspirin	-	-	-	-	-	-
Beta-blocker	-	-	-	-	-	-
NSAID	-	-	-	-	-	-
Calcium channel blocker	-	-	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-	-	-

Analysis	**Measure of the risk of an end point** The incidence rate of major bleeding was calculated as the number of first major bleeding events divided by the total time at risk for major bleeding within the study period and described as the number of bleeding events per 100 person-years **Comparison of the risk of an end point between groups** Propensity score matching pairwise comparisons were conducted between each cohort, matching NOACs to warfarin and also matching among NOACs. Propensity scores were estimated by unconditional logistic regression that incorporated potential predictors of treatment as independent variables in the regression, and group status (eg, apixaban initiators vs warfarin initiators) as the outcome The cumulative incidence of major bleeding was compared and presented using Kaplan-Meier curves. Cox proportional hazard models for the propensity score-matched cohorts were used to estimate the relative risk of major bleeding with 95% confidence intervals **Confounding** Propensity score matching was used to balance age, sex, region, baseline comorbidities, and comedications **Sensitivity analysis** Sensitivity analysis was conducted to test the robustness of the study results. Because a dose-based interaction effect may be observed with major bleeding, the treatment effect associated with risk of major bleeding was assessed among patients prescribed the standard dose for all OACs (warfarin, apixaban 5 mg twice daily, rivaroxaban 20 mg once daily, or dabigatran 150 mg twice daily)

	Software for statistical analysis SAS 9.3 **Statistical significance reference** *P* < .05 was considered statistically significant

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack; VTE, venous thromboembolism.

Study ID	Nielsen et al.[53]
Reference	Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ*. 2017;356:j510. doi:10.1136/bmj.j510
Objective	To examine the clinical effectiveness and safety of apixaban 2.5 mg, dabigatran 110 mg, and rivaroxaban 15 mg vs warfarin among patients with atrial fibrillation who had not previously taken an oral anticoagulant
Country	Denmark
Design	Nationwide cohort study
Data source	Three Danish nationwide administrative databases: • The Danish National Prescription Registry (with information on purchase date, Anatomical Therapeutic Chemical classification code, and package size for every prescription claim since 1994) • The Danish Civil Registration System (with information on sex, date of birth, and vital and emigration status) • The Danish National Patient Register (admission/discharge date, and discharge International Classification of Diseases diagnosis codes for hospital admissions since 1977)
Time period	August 2011 to February 2016
NOAC	• Dabigatran 110 mg twice daily • Rivaroxaban 15 mg once daily • Apixaban 2.5 mg twice daily
Control	Warfarin
Outcomes	**Effectiveness** • Combined ischemic stroke/systemic embolism • Ischemic stroke • All-cause mortality **Safety** • Hemorrhagic stroke • Major bleeding • Gastrointestinal bleeding • Composite of any bleeding events
Outcome definitions	End points were ascertained according to the International Classification of Disease, 10th revision (ICD-10) Major bleeding was defined as bleeding with anemia, hemothorax, hematuria, epistaxis, and bleeding in the eye
Population (eligibility)	Eligible patients were identified as those with a first-time prescription claim for an NOAC, defined as apixaban (introduced December 10, 2012), dabigatran (introduced August 1, 2011), or rivaroxaban (introduced February 1, 2012), as well as individuals who started warfarin treatment (since August 1, 2011) up to February 28, 2016. Patients who had taken any oral anticoagulant within the previous year were excluded to establish a naïve cohort. All NOACs were restricted to reduced doses approved for stroke prevention in atrial fibrillation (in Europe) as follows: apixaban 2.5 mg, dabigatran 110 mg, and rivaroxaban 15 mg. To focus on nonvalvular atrial fibrillation, patients with previous hospital diagnoses indicating valvular atrial fibrillation (mitral stenosis or mechanical heart valves) were excluded. All patients with an indication for oral anticoagulant treatment other than atrial fibrillation (history of pulmonary embolism, deep venous thrombosis, or recent hip/knee surgery) were excluded
Population (study sample)	**Study population** N = 55 644 69.9% warfarin 7.9% apixaban 15.9% dabigatran 6.3% rivaroxaban **Target population** N = 88 141 Excluded: • Oral anticoagulant treatment other than atrial fibrillation, n = 31 852

	• Previous use of phenprocoumon within the past year for unknown reasons, n = 645

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban 2.5 mg twice/day (n = 4400)	Dabigatran 110 mg twice/ day (n = 8875)	Rivaroxaban 15 mg once/ day (n = 3476)	Warfarin (n = 38 893)	All
Women	60.6	53.7	53.2	40.4	44.9
Age, mean (SD)	83.9	79.9	77.9	71.0	73.9
≥65 years	97.2	93.6	85.7	74.6	80.1
≥75 years	88.1	78.1	66.8	41.3	52.5
≥85 years	48.3	28.4)	35.2	11.1	18.3
CHA_2DS_2VASc, mean (SD)	4.3 (1.5)	3.8 (1.5)	3.6 (1.8)	3.0 (1.7)	3.3 (1.7)
HAS-BLED, mean (SD)	2.8 (1.1)	2.7 (1.0)	2.5 (1.2)	2.4 (1.2)	2.4 (1.2)
Standard dose	-	-	-	-	-
Reduced dose	100	100	100	-	100
Comorbidities					
Previous ischemic stroke	22.9	16.0	15.2	11.0	13.0
Ischemic heart disease	29.9	26.3	26.7	26.8	27.0
Heart failure/LVD	20.3	15.5	18.9	15.5	16.1
Myocardial infarction	-	-	-	-	-
Vascular disease	22.0	17.7	18.2	19.0	19.0
Renal dysfunction	9.5	3.9	9.1	8.3	7.8
Previous bleeding	17.3	14.3	15.0	11.4	12.5
Hypertension	63.5	64.0	58.1	60.3	61.0
Diabetes	17.3	14.9	16.5	16.3	16.1
Cancer	22.2	18.3	20.0	16.7	17.6
Concomitant medication					
Aspirin	48.2	50.3	44.4	46.8	47.3
Beta-blocker	60.0	62.1	50.5	63.0	61.9
NSAID	18.5	24.5	21.8	24.4	23.7
Calcium channel blocker	33.8	35.6	30.5	33.1	33.4
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Cumulative incidence rates (calculated as number of events divided by person-time) **Comparison of the risk of an end point between groups** Person-years of follow-up were calculated from the date of first prescription claim to the occurrence of the first end point (death, emigration, or end of follow-up), whichever came first Cox regression (warfarin as the primary reference) Failure curves were used to depict how risks of events evolved over time. Specifically, the Aalen-Johansen estimator was used to calculate absolute risk of events taking into account the competing risk of death and the Kaplan-Meier estimator for all-cause mortality **Confounding** Applied an inverse probability of treatment weighted approach **Sensitivity analysis** Ordinary crude and Cox multivariate adjusted analysis to compare the results obtained from the weighted analyses Standardized morbidity ratio weights to address the (hypothetical) casual situation of all patients receiving warfarin treatment rather than an NOAC **Supplementary analyses** Supplemented the main analysis by a sensitivity analysis stratified by age category—for instance, age ≥ 80 years Sensitivity analysis restricted to patients with a hospital diagnosis of atrial fibrillation to increase the likelihood of the treatment indication Repeated the main analysis confined to the time period where all 3 NOACs were available in Denmark—that is, from 12 December 2012, when apixaban (the latest market drug) became available in Denmark

	Software for statistical analysis Stata version 14 (StataCorp) and R version 3.1.1 (R Foundation for Statistical Computing) **Statistical significance reference** A 2-sided *P*<.05 was considered significant

LVD, left ventricular dysfunction; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

Study ID	Nishtala et al.[80]
Reference	Nishtala PS, Gnjidic D, Jamieson HA, Hanger HC, Kaluarachchi C, Hilmer SN. 'Real-world' haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand. *Int J Cardiol.* 2016;203:746-752. doi:10.1016/j.ijcard.2015.11.067
Objective	To examine the risk of hemorrhage in a large population-based cohort of older individuals with atrial fibrillation (AF) who recently commenced treatment with warfarin or dabigatran and to compare the risk of hemorrhage with varying doses of dabigatran with warfarin, controlling for comorbidities
Country	New Zealand
Design	Nationwide cohort study
Data source	The National Minimum Dataset, which is a collection of all public and private hospital discharge information, including data on inpatients and day patient stays. These data were linked to those on prescriptions, diagnoses, and mortality, provided by the Ministry of Health
Time period	July 2011 to December 2011 but hospital admission records were retrieved up to December 2012
NOAC	Dabigatran 300 mg or 220 mg or 150 mg daily
Control	Warfarin
Outcomes	**Effectiveness** None **Safety** Bleeding Mortality
Outcome definitions	Any admission to hospital for hemorrhage while taking dabigatran or warfarin
Population (eligibility)	Individuals prescribed dabigatran or warfarin during the study period Excluded: Those prescribed warfarin during 18 months prior to the study and those who switched between the 2 drugs Age < 65 years Additionally, those prescribed dabigatran 150 mg daily (low dose) were excluded from the second cohort
Population (study sample)	**Study population** N = 12 842 Warfarin, n = 7079 (51.6%) Dabigatran, n = 5763 (42.1%) **Target population** 23 583 new users of all ages, of whom 10 741 met the above exclusion criteria and were excluded

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Apixaban	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**All participants**
Women	-	46.9	-	48.0	47.3
Age, mean (SD)	-	77.3 (6.4)	-	77.4 (6.6)	-
>65 years	-	-	-	-	-
>75 years	-	-	-	-	-
>85 years	-	-	-	-	-
CHA_2DS_2VASc, mean (SD)	-	-	-	-	-
HAS-BLED, mean (SD)	-	-	-	-	-
Standard dose (for dabigatran, all doses, ie, 300 mg, 210 mg, or 150 mg daily were considered standard, depending on age)	-	100	-	-	-
Reduced dose	-	-	-	-	-
Comorbidities					
Ischemic stroke, or systemic embolism, or TIA	-	18.8	-	19.4	19.1
Heart failure	-	22.4	-	21.9	22.2
Myocardial infarction	-	13.0	-	13.6	13.3
Vascular disease	-	2.8	-	2.8	2.8

Renal dysfunction	-	7.6	-	7.2	7.4
Previous bleeding	-	-	-	-	-
Hypertension	-	-	-	-	-
Diabetes	-	15.6	-	15.9	15.7
Cancer	-	3.6	-	3.5	3.5
Concomitant medication					
Aspirin	-	71.5	-	70.4	70.9
Beta-blocker	-	-	-	-	-
NSAID	-	-	-	-	-
Calcium channel blocker	-	2.7	-	2.1	2.4
Renin angiotensin system inhibitor	-	-	-	-	-

Analysis	**Measure of the risk of an end point** Bleeding rates per person-year **Comparison of the risk of an end point between groups** Two propensity score-matched cohort were created: the first was based on drug type (ie, dabigatran vs warfarin, binary matching), and the second was based on drug type and the 2 dosages of dabigatran (ie, 300 mg and 220 mg daily, nonbinary matching), creating 2 groups of dabigatran users and 1 group of warfarin users Cox proportional hazards models were used to compare adjusted hazard ratios of bleeding in the 2 matched cohorts **Confounding** The 2 cohorts were matched by propensity score, derived from age, sex, ethnicity, chronic disease score, impaired renal function, other comorbidities, and medication use **Sensitivity analysis** Analyses according to different persistence levels (prescription gaps of 30 days vs 60 days) **Supplementary analyses** Subgroup analysis of mortality in the first cohort (ie, dabigatran vs warfarin) **Software for statistical analysis** SPSS (IBM SPSS Statistics) version 22 and R statistics software version 3.1.2 **Statistical significance reference** Not stated

NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Noseworthy et al.[81]
Reference	Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. *Chest.* 2016;150:1302-1312. doi:10.1016/j.chest.2016.07.013
Objective	To compare the effectiveness and safety of dabigatran, rivaroxaban, and apixaban in clinical practice
Country	United States
Design	Retrospective analysis using administrative claims data
Data source	The American administrative claims database Optum Labs Data Warehouse (OLDW). The OLDW contains more than 100 million privately insured and Medicare Advantage enrollees from the last 20 years throughout the US, with greatest representation from the South and Midwest
Time period	October 2010 to February 2015
NOAC	Dabigatran Rivaroxaban Apixaban
Control (pairwise comparisons)	Dabigatran Rivaroxaban Apixaban
Outcomes	**Effectiveness** First inpatient admission for stroke or systemic embolism, including ischemic stroke, hemorrhagic stroke, and systemic embolism **Safety** First inpatient admission for major bleeding, which included gastrointestinal bleeding, intracranial bleeding, and bleeding from other sites The secondary outcomes were ischemic stroke, hemorrhagic stroke, and intracranial bleeding
Outcome definitions	In the Supplementary Material, not available
Population (eligibility)	All adult users (≥ 18 years) of dabigatran, rivaroxaban, and apixaban for nonvalvular atrial fibrillation At least a 12-month continuous enrollment in both medical and pharmaceutical health plans prior to the index date, defined as the baseline period At least 1 inpatient or outpatient AF diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification diagnosis 427.31) at baseline **Exclusion criteria:** Patients who only had a diagnosis of atrial flutter but no diagnosis of atrial fibrillation at baseline were excluded Patients who had valvular heart disease, dialysis, or kidney transplant were excluded
Population **(study sample)**	**Study population,** difficult to define because of overlaps between the cohorts The rivaroxaban and dabigatran cohort, N = 31 574 The apixaban and dabigatran cohort, N = 13 084 The apixaban and rivaroxaban cohort, N = 13 130 **Target population** Not explicitly defined

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Rivaroxaban (N = 15 787)	**Dabigatran (N = 15 787)**	**Apixaban (N = 6542)**	**Dabigatran (N = 6542)**	**Apixaban (N = 6565)**	**Rivaroxaban (N = 6565)**
Women	40.3	41.1	45.9	46.1	46.0	
Age, median (IQR)	70 (62-78)	71 (62-78)	73 (65-81)	73 (65-81)	73 (65-81)	73 (65-81)
>65 years	66.4	68.1	75.9	75.5	76	75.2
>75 years	35.2	37.0	45.5	45.4	47.5	45.5
>85 years	.	.	.	.	.	.
CHA_2DS_2VASc, median (IQR)	4 (2-5)	4 (2-5)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
0-1	14.5	14.0	9.2	9.4	9.1	9.7
2-3	33.5	32.8	30.0	30.7	29.9	30.1
≥4	52.1	53.2	60.9	59.9	61.0	60.2
HAS-BLED, median (IQR)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)

≥ 3	38.3	39.5	44.7	43.9	44.9	43.7
Standard dose	76.9	90.1	81.9	87.0	81.7	71.3
Reduced dose	23.1	9.9	18.1	13.0	18.3	28.7
Comorbidities						
Ischemic stroke, or systemic embolism, or TIA	14.2	14.0	15.4	15.7	15.4	15.6
Heart failure	27.2	27.5	31.3	31.0	31.4	31.7
Myocardial infarction	.	.	.	.	.	.
Vascular disease	46.8	46.6	50.0	48.8	50.0	48.8
Renal dysfunction	13.3	13.7	18.8	18.3	19.1	19.0
Previous bleeding	30.2	30.8	31.4	30.2	31.5	31.0
Hypertension	84.3	84.4	86.5	85.8	86.5	86.3
Diabetes	34.4	34.1	35.4	35.2	35.5	35.0
Cancer	.	.	.	.	.	.
Concomitant medication						
Antiplatelet or NSAID	10.8	11.1	12.2	11.9	12.3	11.7
Beta-blocker	.	.	.	.	.	.
Calcium channel blocker	.	.	.	.	.	.
Renin angiotensin system inhibitor	.	.	.	.	.	.
Warfarin-experienced	39.3	37.7	29.6	29.0	18.3	28.7

Analysis	**Measure of the risk of an end point** Event rate per 100 person-years **Comparison of the risk of an end point between groups** Cox proportional hazards regression was used to compare outcomes in each of the propensity score-matched cohorts, with robust sandwich estimates to account for the clustering within matched sets **Confounding** Three matched cohorts (rivaroxaban vs dabigatran, apixaban vs rivaroxaban, and apixaban vs dabigatran) were created using 1-to-1 propensity score matching without replacement and with a caliper of 0.01. Patients were matched on baseline sociodemographic characteristics, comorbidities, and prior warfarin use. Baseline characteristics were presented descriptively and the standardized difference was used to assess the balance of covariates after matching. A standardized difference less than 10% was considered acceptable. Because all baseline characteristics were balanced after propensity score matching, the Cox proportion hazards regression only included treatment as an independent variable **Sensitivity analysis** There were 4 sensitivity analyses: First, effectiveness outcomes were compared including all events that occurred between the index date and the end of the enrollment or study period (an analog of "intention-to-treat" analysis in clinical trials). This analysis was performed to assess the potential for the primary findings using an on-treatment analytic approach to be affected by differential censoring between treatment groups Second, to investigate whether dosing affects the comparative effectiveness or safety, additional analyses adjusting for whether a patient received a reduced dose were conducted in the Cox proportional hazards model Third, the study population was limited to patients initiating NOACs from January 1, 2013 to February 28, 2015 to minimize the impact of unmeasured secular trends that may have contributed to the differential effect observed with dabigatran (first to market) and apixaban (last to market) Fourth, an additional analysis was performed to censor patients at 6 months to minimize the impact of the variable follow-up time with each drug **Supplementary analyses** Subgroup analyses stratified by CHA_2DS_2-VASc score (0 or 1, 2 or 3, and ≥ 4), as well as HAS-BLED score (0-2 and ≥ 3) **Software for statistical analysis** SAS 9.3 (SAS Institute Inc, Cary, North Carolina) and Stata 13.1 (Stata Corp, College Station,

	Texas) **Statistical significance reference** Not stated

AF, atrial fibrillation; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack.

Study ID	Seeger et al.[82]
Reference	Seeger JD, Bykov K, Bartels DB, Huybrechts K, Zint K, Schneeweiss S. Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation. *Thromb Haemost*. 2015;114:1277-1289. doi:10.1160/TH15-06-0497
Objective	To assess the comparative effectiveness and safety of dabigatran vs warfarin among patients with nonvalvular atrial fibrillation in routine care
Country	United States
Design	Retrospective cohort study
Data source	Two commercial health insurance databases (MarketScan [Truven] and Clinformatics [Optum]) that are nationwide in geographical coverage and include some patients with Medicare supplement coverage
Time period	October 2010 to December 2012
NOAC	Dabigatran 150 mg twice daily
Control	Warfarin
Outcomes	**Effectiveness** • Stroke or systemic embolism • Ischemic stroke • Hemorrhagic stroke • Stroke of uncertain cause • Transient ischemic attack (TIA) • Myocardial infarction • Venous thromboembolism • Deep vein thrombosis • Pulmonary embolism **Safety** • Major intracranial bleeding • Major extracranial bleeding • Major gastrointestinal (GI) bleeding • Major upper GI bleeding • Major lower GI bleeding • Major urogenital bleeding • Major other bleeding
Outcome definitions	Secondary International Classification of Diseases, Ninth Revision (ICD-9). The primary outcomes have demonstrated high positive predictive values in claims databases
Population (eligibility)	Patient had no receipt of any oral anticoagulant in the preceding year Adults ≥ 18 years with recorded sex were eligible for inclusion provided they had a diagnosis of atrial fibrillation and no suggestion of valvular disease in their prior history. A CHA_2S_2-VASC score of 1 or more was also required Patients with a nursing home stay at or before cohort entry were excluded
Population (study sample)	**Study population** Dabigatran, n = 23 543 Warfarin, n = 50 288 **Target population** N = 385 861

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Dabigatran	**Warfarin**
Women	36.3	39.3
Age, mean (SD)	12.3	12.2
>65-74 years	22.0	22.2
>75 years	29.3	40.8
>85 years	-	-
CHA_2DS_2VASc, mean (SD)	2.87 (1.6)	3.44 (1.6)
HAS-BLED, mean (SD)	2.14 (1.0)	2.39 (1.1)
Standard dose	100	
Reduced dose	-	
Comorbidities		

Ischemic stroke, or systemic embolism, or TIA	-	-
Prior stroke	7.9	10
Previous TIA	3.9	4.3
Heart failure	16.3	22.0
Myocardial infarction	3.9	4.8
Peripheral vascular disease	2.6	4.1
Renal dysfunction	9.0	16.7
Previous bleeding (see below)	-	-
Upper GI bleed	0.3	0.6
Lower/unspecified GI bleed	2.0	3.2
Hypertension	96.6	95.5
Diabetes	19.9	23.4
Cancer	9.6	12.5
Concomitant medication		
Aspirin	-	-
Beta-blocker	73.6	71.0
NSAID	21.5	19.7
Calcium channel blocker	41.5	41.1
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Incidence rates **Comparison of the risk of an end point between groups** Hazard ratios for the comparison between dabigatran and warfarin were estimated in each data base using a Cox proportional hazards regression model **Confounding** Using propensity score matching of dabigatran and warfarin initiators, explicit comparisons were made between contemporaneous initiators of the compared medications in a manner that addressed confounding arising from differences in patient characteristics between the compared medications **Sensitivity analysis** An intention-to-treat analytic approach was applied that maintained patients in their initial exposure group (dabigatran or warfarin) by carrying this exposure forward for 365 days or until the occurrence of a study outcome, disenrollment from the database, admission to a nursing home, or the end of the study period. This analysis was performed to assess the potential for the primary (as-treated) results to be affected by differential censoring between treatment groups but has its own limitations due to increasing exposure misclassification with longer follow-up **Supplementary analyses** High-dimensional propensity score (hdPS) analyses were applied, which improve validity in claims-based studies. The hdPS was estimated by logistic regression in a model including 200 empirically identified covariates with the greatest potential to bias the association between dabigatran and the ischemic or hemorrhagic outcomes (separate hdPS models were developed for each of these), in addition to the investigator-specified covariates **Software for statistical analysis** Not reported

NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

Study ID	Vaughan Sarrazin et al.[83]
Reference	Vaughan Sarrazin MS, Jones M, Mazur A, Chrischilles E, Cram P. Bleeding rates in Veterans Affairs patients with atrial fibrillation who switch from warfarin to dabigatran. *Am J Med*. 2014;127:1179-1185. doi:10.1016/j.amjmed.2014.07.024
Objective	To assess the relative risks of any, gastrointestinal, intracranial, and other bleeding for Veterans Affairs patients who switched to dabigatran after at least 6 months on warfarin vs patients who continued on warfarin
Country	United States
Design	Nationwide cohort study
Data source	National Veterans Affairs administrative encounter and pharmacy data
Time period	June 2011 to September 2012
NOAC	Dabigatran 150 mg
Control	Warfarin
Outcomes	**Effectiveness** Death **Safety** Bleeding events, including gastrointestinal, intracranial, and other hemorrhage
Outcome definitions	Outcomes were defined using International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes validated previously and used in previous studies of anticoagulation
Population (eligibility)	Patients with atrial fibrillation who had been taking warfarin for at least 180 days before June 2011, with the most recent fill date within 90 days before June 2011 Patients without a diagnosis of atrial fibrillation (ICD-9-CM code 427.31) as identified on VA inpatient and outpatient encounter data during the 12 months before June 2011 were excluded, as were patients with a glomerular filtration rate < 30 mL/min/1.73 m^2 during the prior 12 months (based on National Laboratory Extracts) or with a prosthetic heart valve (based on ICD-9-CM diagnosis and procedure codes from the prior 12 months) because dabigatran use is not appropriate for patients with severe renal disease or valvular atrial fibrillation
Population (study sample)	**Study population** The final sample included 85 344 total patients, of whom 1394 (1.7%) switched from warfarin to dabigatran (150 mg)

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Patients who never initiated dabigatran use	Patients initiating dabigatran use
Women	1.4	1.4
Age, mean (SD)	74.4 (10.1)	69.7 (9.0)
55-64 years	15.8	26.3
65-74 years	30.0	39.2
75-84	33.3	24.2
≥85 years	18.9	6.5
CHA_2DS_2VASc, mean (SD)	-	-
$CHADS^2$, mean (SD)	2.21 (1.12)	2.08 (1.12)
HAS-BLED, mean (SD)	2.63 (1.18)	2.67 (1.23)
Standard dose	100	100
Reduced dose	-	-
Comorbidities		
Ischemic stroke, or systemic embolism, or TIA	-	-
Cardiomyopathy	10.3	13.9
Other dysrhythmia	15.3	20.5
Heart failure	29.8	34.1
Myocardial infarction	4.4	5.8
Vascular disease	-	-

Rheumatic/other valve disorder	8.8	7.3
Renal dysfunction (see below)		
Kidney function (GFR, mL/min/1.73 m^2)		
Normal GFR or mild disease (GFR ≥ 60)	52.2	64.9
Moderate (GFR 30-59)	31.2	23.4
Previous bleeding	-	-
Hypertension	-	-
Diabetes	-	-
Cancer	-	-
Concomitant medication		
Aspirin	-	-
Beta-blocker	-	-
NSAID	-	-
Calcium channel blocker	-	-
Renin angiotensin system inhibitor	-	-

Analysis	**Measure of the risk of an end point** Marginal structural models were used to determine the odds of any bleeding, gastrointestinal hemorrhage, intracranial hemorrhage, other hemorrhage, or death for patients taking dabigatran relative to warfarin. Marginal structural models reduce bias by weighting the contribution of each patient during a given week by "stabilized" weights, where stabilized weights reflect both baseline and time-varying patient covariates. Two sets of weights were calculated for each patient-week, the first reflecting patient covariates that affect anticoagulant selection, and the second reflecting characteristics that affect censoring events. Weighting observations effectively creates, for each week, a pseudopopulation in which patient covariates are no longer related to dabigatran use or censoring **Comparison of the risk of an end point between groups** The relationship between dabigatran use and each outcome was determined using separate weighted pooled logistic regression models for each outcome. Models were estimated using generalized estimating equations and robust standard errors **Confounding** The study uses marginal structural logistic regression models, which address potential bias in time-to-event studies when a time-dependent covariate is a risk factor for the event and predicts subsequent exposure **Sensitivity analysis** Three sets of sensitivity analyses were generated for each outcome. First, because bleeding events that are recorded on outpatient visits may be relatively minor, bleeding episodes were also defined using inpatient claims only (as a proxy for severe bleeds). Second, rather than censoring patients who died in analysis of bleeding events, a composite outcome was defined as bleeding or death. Finally, in contrast to the primary analysis in which patients were censored on the day their medication supply ran out, an "intention-to-treat" approach was used For each sensitivity analysis, stabilized weights were recalculated and weighted pooled logistic regression models were generated **Software for statistical analysis** SAS 9.3 (SAS Institute Inc, Cary, North Carolina)

GFR, glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Villines et al.[84]
Reference	Villines TC, Schnee J, Fraeman K, Siu K, Reynolds MW, Collins J, Schwartzman E. A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system. *Thromb Haemost*. 2015;114:1290-1298. doi:10.1160/TH15-06-0453
Objective	To compare the safety and effectiveness of dabigatran and warfarin in clinical practice
Country	United States
Design	Retrospective cohort study
Data source	US Department of Defense (DoD) claims database
Time period	October 1, 2009 to July 31, 2013
NOAC	• Dabigatran 150 mg • Dabigatran 75 mg
Control	Warfarin
Outcomes	**Effectiveness** • Stroke (both hemorrhagic and ischemic) • Ischemic stroke • Hemorrhagic stroke • Transient ischemic attack **Safety** • Major bleeding • Major intracranial bleeding • Major extracranial bleeding • Major gastrointestinal (GI) bleeding (major upper GI bleeding, major lower GI bleeding) • Major urogenital bleeding • Major other bleeding
Outcome definitions	Study outcomes were identified by ICD-9 codes for inpatient admitting and primary inpatient diagnosis codes on the inpatient claim. Only 1 study outcome was assigned per hospitalization
Population (eligibility)	Oral anticoagulant treatment-naïve NVAF patients with their first prescription for either dabigatran (either FDA-approved dose) or warfarin during the study period. Patients had to be aged 18 to 89 years at the index date, to have had ≥ 1 AF diagnosis at the index date or within the baseline period, and to have been continuously enrolled in the health plan during the baseline period Patients were excluded if they had a diagnosis of hyperthyroidism during the baseline period, ≥ 1 claim with a diagnosis of cardiac surgery, pericarditis, myocarditis, or pulmonary embolism within 3 months of the first diagnosis of AF (to exclude patients with transient causes of AF), or ≥ 1 medical claim for valvular heart disease during the baseline period
Population (study sample)	**Study population** Dabigatran, n = 14 813 Warfarin, n = 24 500 **Target population** N = 167 364

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)

	Before propensity score matching		**After propensity score matching**	
	Dabigatran	**Warfarin**	**Dabigatran**	**Warfarin**
Women	40.9	42.1	41.2	41.1
Age, mean (SD)	73.1 (9.6)	74.5 (9.2)	73.8 (9.3)	74.0 (9.0)
>65 years	-	-	-	-
>75 years	-	-	-	-
>85 years	-	-	-	-
CHA_2DS_2VASc, mean (SD)	3.8 (1.7)	4.2 (1.8)	3.9 (1.7)	3.9 (1.7)
HAS-BLED, mean (SD)	3.4 (1.3)	3.6 (1.3)	3.4 (1.2)	3.4 (1.3)
Standard dose	-	-	88	-
Reduced dose	-	-	12	-

Comorbidities				
Ischemic stroke, or systemic embolism, or TIA	-	-	-	-
Ischemic stroke	3.4	5.4	3.7	3.3
TIA	1.6	2.1	1.7	1.6
Heart failure	11.4	18.7	12.9	12.3
Myocardial infarction	-	-	-	-
Vascular disease	-	-	-	-
Coronary heart disease	18.3	25.3	19.8	19.4
Renal dysfunction (see below)	-	-	-	-
Kidney disease	10.2	19.8	11.7	11.1
Previous bleeding	-	-	-	-
Hypertension (see below)	-	-	-	-
Hypertension diagnosis	36.3	47.6	38.3	37.2
Hypertension diagnosis or treatment	96.1	96.5	96.5	95.7
Diabetes mellitus	13.6	19.7	14.9	14.4
Cancer	-	-	-	-
Concomitant medication				
Other antihypertensive (beta-blockers, calcium channel blockers, or diuretics or other antihypertensive agents)	9.6	12.1	10.3	9.8
Aspirin	-	-	-	-
Beta-blocker	-	-	-	-
NSAID	-	-	-	-
Calcium channel blocker	-	-	-	-
Renin angiotensin system inhibitor	-	-	-	-

Analysis	**Measure of the risk of an end point** Event rates for each outcome were calculated on an on-treatment basis as the total number of patients in each group who had the outcome during follow-up, divided by the total person-time of that event for the group. Person-time was calculated separately for each outcome; person-time consisted of the entire follow-up period for patients who did not have the outcome and the time to first occurrence for patients who did have the outcome **Comparison of the risk of an end point between groups** The time-to-event was evaluated using Kaplan-Meier survival analyses. Log-rank tests were used to assess whether statistically significant differences existed between groups. Cox proportional hazards models were used to evaluate the association between the time-to-event and treatment, adjusting for appropriate covariates if propensity score matching left an imbalance between groups **Confounding** Propensity score matching **Sensitivity analysis** Hazard ratios were also calculated for a propensity score-matched subgroup of patients with prescriptions for dabigatran 150 mg or warfarin. This subgroup included patients taking dabigatran 150 mg at index and having at least 1 postindex day of dabigatran 150 mg. Patients with both dabigatran 150 mg and dabigatran 75 mg at index (n = 8) were excluded, and follow-up was stopped when the patient started using another oral anticoagulant, including dabigatran 75 mg **Software for statistical analysis** SAS 9.3 (SAS Institute, Cary, North Carolina) **Statistical significance reference** A conventional alpha of .05 and 2-tailed level of significance were used

AF, atrial fibrillation; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; TIA, transient ischemic attack.

Study ID	Yao et al.[85]
Reference	Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5:e003725. doi:10.1161/JAHA.116.003725
Objective	To evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban vs warfarin in nonvalvular atrial fibrillation
Country	United States
Design	Retrospective cohort study
Data source	The OptumLabs Data Warehouse (OLDW), which contains > 100 million privately insured and Medicare Advantage enrollees from the past 20 years throughout the United States
Time period	October 1, 2010, and June 30, 2015
NOAC	• Apixaban 2.5 mg twice daily • Apixaban 5 mg twice daily • Dabigatran 150 mg • Dabigatran 75 mg • Rivaroxaban • Rivaroxaban
Control	Warfarin
Outcomes	**Effectiveness** • Stroke or systemic embolism, including ischemic stroke, hemorrhagic stroke, and systemic embolism **Safety** • Major bleeding, including gastrointestinal bleeding, intracranial bleeding, and bleeding from other sites
Outcome definitions	Outcomes were identified using ICD-9 codes in the primary or secondary diagnosis positions of inpatient claims. The positive predictive value in general ranged from 85% to 95%
Population (eligibility)	Adult patients (aged ≥ 18 years) with nonvalvular AF who were users of apixaban, dabigatran, rivaroxaban, and warfarin during the study period were identified Patients were required to have at least 12 months of continuous enrollment in both medical and pharmacy insurance plans prior to the index date, defined as the baseline period. For patients who only filled warfarin and never filled NOACs, the index medication was defined as the first warfarin fill after enrolling in health plans for at least 12 months; therefore, both warfarin and NOAC cohorts included patients who had previous warfarin exposure but none had previous NOAC exposure. All patients were required to have at least 1 inpatient or outpatient AF diagnosis at either primary or secondary positions on the index date or at baseline Patients who had valvular heart disease, end-stage chronic kidney disease, kidney transplant, or dialysis at any time were excluded. Also excluded were patients who underwent hip or knee replacement surgery within 6 weeks prior to the index date and who had a diagnosis of deep vein thrombosis or pulmonary embolism at baseline
Population (study sample)	**Study population** Apixaban, n = 7698 Dabigatran, n = 14 881 Rivaroxaban, n = 16 795 Warfarin, n = 85 869 **Target population** N = 339 606 Excluded: • Patients with AF diagnosis at baseline, n = 162 883 • Patients without dialysis, kidney transplant, end-stage renal disease, or valvular heart disease, n = 29 989 • Patients without VTE at baseline or joint replacement within 6 weeks prior to the index date, n = 20 556 • Adult patients who had valid demographic data, were not admitted for primary outcomes or died on the index date, and the index medication was not edoxaban, n = 935

Population (baseline participant characteristics) (values expressed as percentages unless otherwise stated)						
	Apixaban	**Warfarin**	**Dabigatran**	**Warfarin**	**Rivaroxaban**	**Warfarin**
Women	46.9	46.8	39.7	40.4	43.2	43.7
Age, median (IQR)	73 (66-81)	73 (66-81)	70 (62-78)	70 (61-78)	72 (64-79)	72 (64-80)
>65-74 years	30.9	30.9	31.5	30.4	32.9	32.8
≥75 years	46.4	46.1	34.4	34.6	41.8	41.4
>85 years	-	-	-	-	-	-
CHA_2DS_2VASc, median (IQR)	4 (3-5)	4 (3-5)	3 (2-5)	3 (2-5)	4 (2-5)	4 (2-5)
HAS-BLED, median (IQR)	2 (2-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (2-3)
Standard dose	81.9	-	91.2	-	78.5	-
Reduced dose	18.1	-	8.8	-	21.5	-
Comorbidities						
Ischemic stroke, or systemic embolism, or TIA	15.1	15.5	13.8	14.2	14.0	14.4
Congestive heart failure	31.4	31.9	27.2	27.3	28.9	29.5
Myocardial infarction	-	-	-	-	-	-
Vascular disease	28.3	28.4	23.1	23.4	26.9	27.5
Abnormal renal function	10.1	10.1	5.6	5.6	7.4	7.3
Bleeding history or predisposition	31.4	31.8	29.4	30.1	30.7	31.5
Hypertension	87.5	87.5	85.2	84.9	85.7	85.9
Diabetes mellitus	35.0	34.3	34.0	34.0	34.6	35.1
Cancer	-	-	-	-	-	-
Concomitant medication						
Aspirin (see below)	-	-	-	-	-	-
Antiplatelets/NSAID	12.1	12.5	10.3	10.2	11.6	11.6
Beta-blocker	47.5	47.8	44.6	44.5	45.6	45.0
NSAID	-	-	-	-	-	-
Other calcium channel blocker	16.6	16.3	13.3	13.4	14.9	14.7
Renin angiotensin system inhibitor	47.1	47.2	45.4	45.0	45.5	46.0
Amiodarone	9.6	10.1	8.4	8.4	8.3	8.8
Dronedarone	2.8	2.6	3.7	4.2	2.4	2.6
Other antiarrhythmic drug	11.1	10.7	12.8	12.9	11.0	11.2
Digoxin	8.9	9.1	13.6	13.6	10.8	11.1
Diltiazem	16.9	17.0	17.5	17.3	17.5	17.9
Verapamil	1.3	1.3	1.9	1.9	1.7	1.7
Statin	45.6	46.7	41.5	41.2	43.0	43.9
Other cholesterol reducer	5.9	5.9	7.3	7.6	5.7	5.7
Diuretics	32.3	31.8	28.5	28.5	29.6	29.6
Metformin	11.1	10.7	10.2	9.9	10.6	11.0
Sulfonylurea	6.0	6.0	6.0	5.9	6.0	5.9
Thiazolidinedione	0.8	0.8	1.5	1.3	0.9	0.9
Insulin	7.3	7.3	6.8	7.1	7.1	7.5
Other diabetes drug	3.1	2.9	2.8	2.9	2.7	2.9
Antiulcer agent	21.9	21.4	18.4	18.4	20.3	21.2
Antidepressant	16.2	16.1	14.5	15.0	15.3	15.6

Analysis	**Measure of the risk of an end point** Three matched cohorts (dabigatran vs warfarin, rivaroxaban vs warfarin, and apixaban vs warfarin) using 1:1 propensity score matching without replacement and with a caliper of 0.01. Propensity scores for NOAC treatment were estimated using logistic regression **Comparison of the risk of an end point between groups** Cox proportional hazards regression was used to compare outcomes in each of the propensity score-matched cohorts **Sensitivity analysis** The risk of stroke or systemic embolism was compared, including all events that occurred between the index date and the end of the enrollment or study period (an intention-to-treat

	analytic approach). The study population was limited to patients initiating NOACs from January 1, 2013 to June 30, 2015 Because apixaban became available in the United States in December 2012, apixaban users had a shorter follow-up time than those of other agents. Sensitivity analyses were conducted to censor patients at 6 months so that all drugs had a similar follow-up time Patients who had catheter ablation within 2 months prior to the index medication and those who had cardioversion 1 month before and 1 month after the index medication were excluded Subgroup analyses were conducted based on baseline time in therapeutic range (TTR) in patients with prior warfarin experience and based on follow-up TTR. The TTR was calculated using Rosendaal's method, which uses linear interpolation to assign an INR value to each day between successive observed INR values. Gaps of 56 days between INR values were not interpolated. After interpolation, the percentage of time during which the interpolated INR values lay between 2.0 and 3.0 (from 0% to 100%) was calculated. The follow-up TTRs of NOAC-treated patients were assigned based on the TTRs of their matched warfarin controls. A labile INR was defined as TTR < 60% **Software for statistical analysis** SAS 9.4 (SAS Institute Inc) and Stata 14.1 (Stata Corp)
AF, atrial fibrillation; IQR, interquartile range; NOACs, nonvitamin K antagonist oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack; TTR, time in therapeutic range; VTE, venous thromboembolism.	

FIGURE LEGEND

Figure of the supplementary material. HRs with 95%CIs for ischemic stroke (A), ischemic stroke plus systemic embolism (B), major bleeding (C), and intracranial hemorrhage (D) in patients with AF treated with DOACs vs VKAs using the longer-term data available in each study. 95%CI, 95% confidence interval; AF, atrial fibrillation; DOACs, direct oral anticoagulants; HR, hazard ratio; IV, interval variable, SE, systemic embolism, VKAs, vitamin K antagonists.