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ORIGINAL RESEARCH

Effectiveness and Safety of NOAC Versus Warfarin in Patients With Atrial Fibrillation and Aortic Stenosis

Line Melgaard, MSc, PhD; Thure Filskov Overvad, MD, PhD; Martin Jensen, MSc; Thomas Decker Christensen, MD, DMSc, PhD; Gregory Y. H. Lip, MD;* Torben Bjerregaard Larsen, MD, PhD; Peter Brønnum Nielsen, MSc, PhD, MPH*

BACKGROUND: Guideline recommendations on the use of non–vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients with aortic stenosis are based on studies including a low number of patients with aortic stenosis. The aim of this study was to estimate the effects of NOAC versus warfarin on thromboembolism and major bleeding among AF patients with aortic stenosis.

METHODS AND RESULTS: We emulated a target trial using observational data from Danish nationwide registries between 2013 and 2018. Thromboembolism was defined as a hospital diagnosis of ischemic stroke and/or systemic embolism, and major bleeding was defined as a hospital diagnosis of intracranial bleeding, gastrointestinal bleeding, or major or clinically relevant bleeding in other anatomic sites. Treatment effect estimates were based on an intention-to-treat and per-protocol approach. A total of 3726 patients with AF and aortic stenosis claimed a prescription for either a NOAC (2357 patients) or warfarin (1369 patients) and met the eligibility criteria for the trial. During 3 years of follow-up, the adjusted hazard ratios for thromboembolism and major bleeding were 1.62 (95% CI, 1.08–2.45) and 0.73 (0.59–0.91) for NOAC compared with warfarin in the intention-to-treat analyses. Similar results were observed in the per-protocol analyses.

CONCLUSIONS: In this observational study, we observed a higher risk of thromboembolism but a lower risk of major bleeding for treatment with NOACs compared with warfarin in patients with AF and aortic stenosis. This observation needs confirmation in large randomized trials in these commonly encountered patients.

Key Words: atrial fibrillation ■ stroke ■ valvular heart disease

Atrial fibrillation (AF) and valvular heart disease (VHD) often coexist, and aortic stenosis is one of the most prevalent VHD subtypes in developed countries,[1–3] affecting a large proportion of the elderly population.[4] The prevalence of both aortic stenosis and AF increases with age, and the number of patients diagnosed with aortic stenosis and AF will increase considerably in line with the rapidly increasing elderly population.[5–7] Approximately 16% to 36% of all patients with aortic stenosis have concomitant AF, and most of these patients are in lifelong thromboprophylaxis with oral anticoagulant therapy.[3,8–10] Importantly, patients with aortic stenosis have been identified as a high-risk subgroup in terms of the risk of thromboembolism and bleeding in anticoagulated patients with AF, which complicates the risk-benefit ratio of oral anticoagulation.[11–14]

Randomized, controlled trials have evaluated different oral anticoagulants, such as warfarin and non-vitamin K antagonist oral anticoagulants (NOACs), for

Correspondence to: Peter Brønnum Nielsen, MSc, MPH, PhD, Department of Cardiology, Aalborg University Hospital, Sdr. Skovvej 15, DK-9000, Denmark. E-mail:pbn@rn.dk

*G. Y. H. Lip and P. B. Nielsen are co-senior authors.

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CLINICAL PERSPECTIVE

What Is New?

- In patients with atrial fibrillation and aortic stenosis, non–vitamin K antagonist oral anticoagulants may be less effective than warfarin for preventing ischemic events but safer with respect to bleeding.

What Are the Clinical Implications?

- Based on the findings of our study and inconsistent data in the literature on the effectiveness and safety of non–vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and aortic stenosis, the optimal oral anticoagulant strategy remains unclear.
- The observed increased risk of thromboembolism in the non–vitamin K antagonist oral anticoagulants group in our study requires further investigation because it was not observed in the post hoc analyses of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials.

Nonstandard Abbreviations and Acronyms

ITT	intention-to-treat
NOAC	Non–vitamin K antagonist oral anticoagulant
PP	Per protocol
VHD	valvular heart disease

the prevention of thromboembolism in patients with AF; however, these trials excluded patients with significant VHD.[15–18] Patients with mechanical heart valves or moderate to severe mitral stenosis were excluded in all trials, and patients with any other VHD, such as aortic stenosis, were minimally represented. Only a few post hoc sub-analyses of the existing randomized, controlled trials have examined patients with both AF and VHD, and the proportion of patients with aortic stenosis was underrepresented (6%–12%),[12,19–21] despite aortic stenosis being one of the most prevalent VHDs in recent patients with AF and VHD (17%–62% with aortic stenosis).[2,22–24] Consequently, the effectiveness and safety of NOAC versus warfarin in AF patients with aortic stenosis has not been specifically investigated, although guidelines currently allow for use of NOACs in AF patients with aortic stenosis (and without a mechanical heart valve or concomitant moderate/severe mitral stenosis).[25,26]

The aim of the present study was to emulate a target trial using observational data from Danish nationwide registries to estimate the effects of NOAC versus warfarin on thromboembolism and major bleeding among AF patients with aortic stenosis.

METHODS

Study Design and Data Sources

This study was conducted using the "target trial" principles.[27,28] Briefly, we specified the protocol of a target trial (a hypothetical randomized experiment) to estimate the effectiveness and safety of NOAC versus warfarin in AF patients with aortic stenosis and then attempted to emulate this trial using observational data from the Danish nationwide registries. The specifications of each component in the target trial and the emulated trial are provided in Table S1.

Four Danish nationwide registries were used: The Danish Civil Registration System,[29] the National Prescription Registry,[30] the Danish National Patient Registry,[31] and the Danish National Laboratory Register. Data from these registries were linked via a unique personal identification number, which is used across all Danish nationwide registries. Data S1 provides a description of the registries.

Permissions to access data from the nationwide registries were obtained through the Danish Health Data Agency. Requests to access the data set may be sent to The Danish Health Data Agency at forskerservice@sundhedsdata.dk. Dr Melgaard, Mr Jensen, and Dr Nielsen had full access to all the data in the study and take responsibility for its integrity and the data analysis. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Eligibility Criteria

We identified patients in the Danish nationwide registries who met the target trial eligibility criteria (Table S1). The study population included patients with a first-time prescription for a NOAC or warfarin (baseline date) and a diagnosis of both AF and aortic stenosis at baseline or within 30 days after baseline. To ensure that patients were eligible for stroke prevention with oral anticoagulant therapy according to contemporary guidelines,[32] a CHA_2DS_2-VASc score level threshold of ≥1 for male and ≥2 for female patients was also an eligibility criterion. Patients with other indications for oral anticoagulant therapy or potential contraindications for NOAC or warfarin treatment were excluded. Patients with

dispensation of both a NOAC and warfarin within the first 30 days after baseline were excluded. Lastly, only patients who were alive and event-free after the first month were included due to the data setup and the statistical methods used (see Figure 1 for a flowchart of the study population). For details on the definition of AF, aortic stenosis, contraindications, comorbidities, and co-medication, please see Table S2.

Treatment Strategies

The Danish National Prescription Registry was used to identify patients who redeemed a first-time prescription for a NOAC (apixaban, dabigatran, rivaroxaban, or edoxaban) or warfarin between January 2013 and October 2018 (oral anticoagulation naïve users only). Patients were considered exposed to treatment irrespective of any subsequent dosage changes.

Outcomes

The effectiveness outcome was a hospital diagnosis of ischemic stroke and/or systemic embolism defined as a composite endpoint of "thromboembolism." The safety outcome was major bleeding leading to hospital admission (either intracranial bleeding, gastrointestinal bleeding, or major or clinically relevant bleeding in other anatomic sites). For details about the definition of the outcomes, please see Table S2.

Follow-Up Period

Each patient was followed up in the registries for the outcomes of interest. Follow-up started 30 days after treatment assignment (baseline) and ended at outcome diagnosis, death, administrative end of follow-up (3 years or December 2018), or emigration (loss to follow-up), whichever occurred first.

Causal Contrasts

To compare the 2 treatment strategies, we estimated the intention-to-treat (ITT) effect and per-protocol (PP) effect.

Statistical Analysis

The baseline characteristics of the study population were described according to treatment exposure category (NOAC or warfarin) using means and standard deviation for continuous variables, and proportions for categorical variables. The exposure category (ie, NOAC or warfarin) of each patient was based on the prescription claim at the baseline date, and this category remained unchanged throughout the study duration.

Counterfactual outcomes were investigated at 3 years and data arranged in such a way that each patient-month was represented by a single row (maximum of 36 rows per individual, corresponding to 3 years). To account for the non-randomization of the treatment assignment, we derived stabilized inverse probability of treatment weights. To compute these weights, we estimated the propensity of being assigned each treatment by a logistic regression including the following baseline confounding factors: age (as a restricted cubic spline) and dichotomous covariates on sex, heart failure, hypertension, diabetes, myocardial infarction, ischemic heart disease, renal disease, prior bleeding, prior thromboembolic event, diagnosis of atrial fibrillation, aortic stenosis or valve surgery (including bioprosthetic valve implantation) within 60 days before or 30 days after the baseline date, and use of statin or antiplatelet therapy within the last year.

The assessment of outcomes was based on an ITT approach and a PP approach (please see details in Data S1). When estimating the ITT treatment effects, treatment status was assessed at the date of first prescription claim (NOAC or warfarin) and remained unchanged throughout follow-up disregarding actual treatment. When estimating the PP treatment effects, treatment status was assessed continuously using a recommended daily dose and quantity of pills per pack in each prescription (a 60-day grace period between each prescription claim was allowed). The variable dose regimen of warfarin was modeled by continuous adaption of an (individual) estimated daily dose. Patients were considered adherent to the initial treatment strategy (NOAC or warfarin) unless a clinical event that fully or partly contraindicated treatment or had a major clinical impact on the anticoagulant therapy strategy occurred. If such an event occurred, we stopped updating the censoring weight for that patient, but kept the patient in the analysis. For the ITT and PP analyses, pooled logistic regression models were used to estimate the average treatment effects by means of hazard ratios (HRs) for the outcomes. In detail, we derived odds ratios from pooled logistic regressions, which are approximations of HRs when the investigated outcome is rare in all time intervals.[33] The calculated stabilized inverse probability of treatment weights were applied in pooled logistic regression models. For the PP analyses, we calculated stabilized inverse probability of censoring weights to account for the dependence between measured post-baseline time-varying prognostic factors (heart failure, hypertension, diabetes, ischemic heart disease, myocardial infarction, and use of statin or antiplatelet therapy [all included as dichotomous covariates]) and censoring, and these weights were multiplied by the stabilized inverse probability of treatment weights of baseline confounding factors and applied in the weighted pooled logistic regression models to estimate the PP treatment effects.[34]

In addition, standardized event-free survival curves were constructed, which depict the estimated counterfactual event-free survival had every individual receiving either treatment. All statistical analyses were performed using SAS 9.3 (SAS Institute) and Stata version 16 (StataCorp LP).

Sub-Analysis and Sensitivity Analyses

Some patients had an aortic valve surgery/procedure before inclusion in the study, which may affect the treatment effects, especially if the surgery/procedure was performed close to the baseline date. Therefore, we performed a sub-analysis in which we restricted the population to the following subpopulations and repeated the main analyses: (1) those who had an aortic valve surgery/procedure within 60 days before or 30 days after baseline, (2) those who had an aortic valve surgery/procedure at any time before or 30 days after baseline, and (3) those who never had an aortic valve surgery/procedure.

Two sensitivity analyses were performed to investigate the robustness of the analytical strategy in the main analyses. We performed a sensitivity analysis of the PP analysis in which we changed the assessment of continuous treatment status by allowing a grace period of 90 days as a treatment gap. Additionally, 2 "falsification outcomes" were examined, which were expected to have a null association with the exposure.[35] In detail, we emulated an individual target trial with pneumonia as the outcome and an individual target trial with cancer as the outcome using the described features from the ITT analyses.

Ethical Considerations

The study was conducted in compliance with General Data Protection Regulation Article 30, recorded at Aalborg University Hospital and Aalborg University (project no. 2017-40). No ethical approval or patient consent are required for studies based on data from administrative Danish registries according to Danish laws.

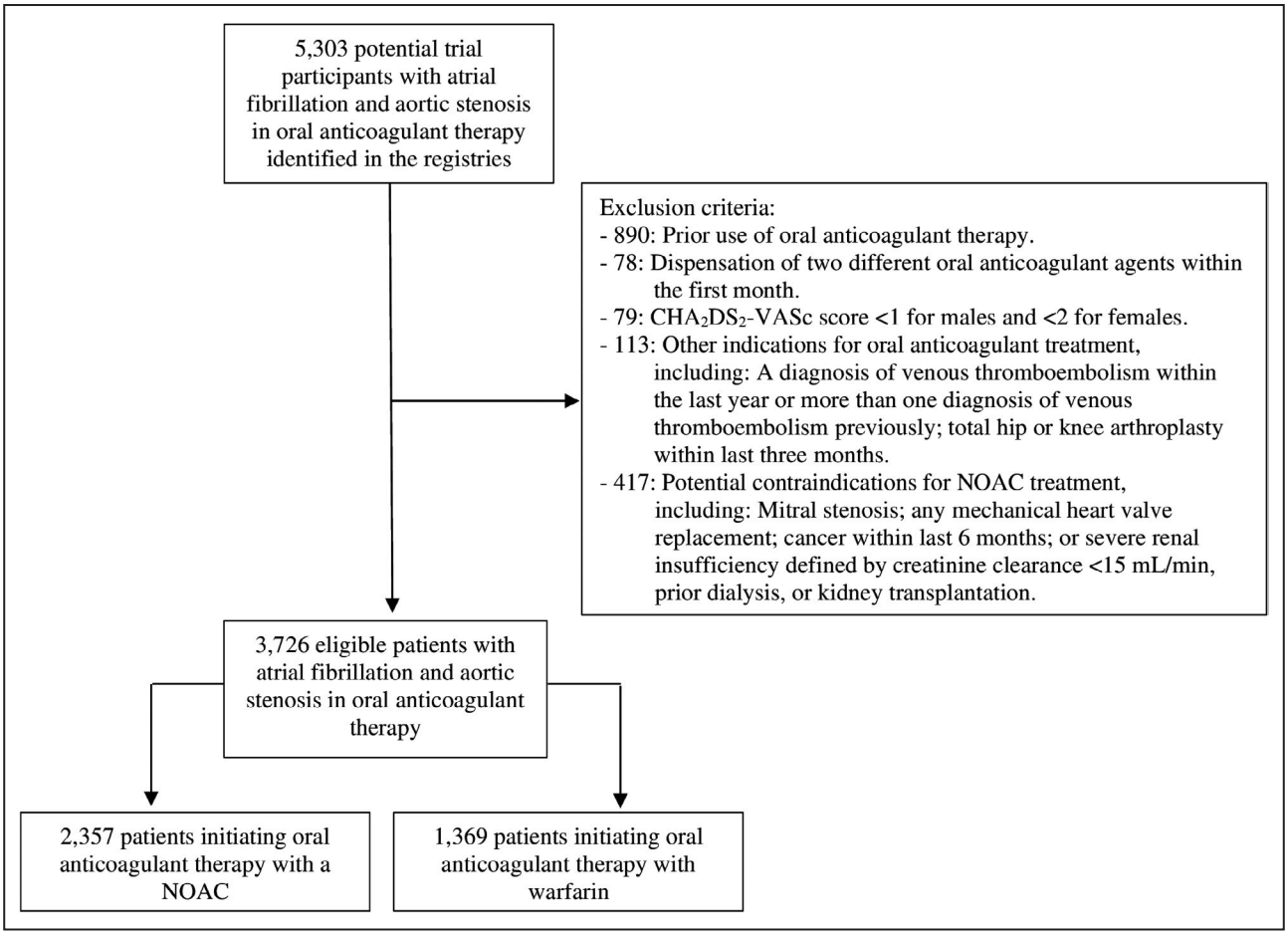

Figure 1. Flowchart of eligible patients to emulate the target trial.
CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, prior stroke/transient ischemic attack/systemic embolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–74 years, sex category [female]; and NOAC, non–vitamin K antagonist oral anticoagulant.

RESULTS

Of 5303 patients with AF and aortic stenosis who claimed a prescription for either a NOAC or warfarin between January 2013 and October 2018, 3726 were eligible for the target trial emulation (Figure 1). The study group comprised 1369 patients who claimed a prescription for warfarin and 2357 patients claimed a prescription for a NOAC: apixaban, 1105; dabigatran, 323; edoxaban, 38; and rivaroxaban, 891. The baseline characteristics of the study population are summarized in Table 1.

Effectiveness Outcome

During a median follow-up of 14 months (interquartile range [IQR]: 6–23 months), 113 thromboembolic events were observed. In the ITT analysis, the adjusted HR for thromboembolism was 1.62 (95% CI, 1.08–2.45) for NOACs compared with warfarin (Table 2). In the ITT analysis, the estimated 3-year thromboembolic-free survival was 94.0% for NOACs and 96.0% for warfarin (Figure 2).

In the PP analysis, the median follow-up was 11 months (IQR: 5–20 months), and 81 events were observed. A total of 3079 patients (82.6%) had a censoring event. The adjusted HR for thromboembolism was 1.92 (95% CI, 1.11–3.30) for NOACs compared with warfarin in the PP analysis. In the PP analysis, the estimated 3-year thromboembolic-free survival was 93.9% for NOACs and 97.0% for warfarin (Figure 2).

Safety Outcome

During a median follow-up of 13 months (IQR: 6–23 months), 355 major bleeding events were observed: 66 intracranial bleeds, 176 gastrointestinal bleeds, and 121 major or clinically relevant bleeds in other anatomic sites (some patients had more than one bleeding event on the same day). In the ITT analysis, the adjusted HR for major bleeding was 0.73 (95% CI, 0.59–0.91) for NOACs compared with warfarin (Table 2). In the ITT analysis, the estimated 3-year major bleeding-free survival was 87.6% for NOACs and 83.6% for warfarin (Figure 3).

In the PP analysis, the median follow-up was 11 months (IQR: 5–20 months), and 282 major bleeding events were observed: 53 intracranial bleeds, 143 gastrointestinal bleeds, and 90 major or clinically relevant bleeds in other anatomic sites (some patients had more than one bleeding event on the same day). A total of 2931 patients (78.7%) had a censoring event. The adjusted HR for major bleeding was 0.78 (95% CI: 0.60–0.99) for NOACs compared to warfarin in the PP analysis. In the PP analysis, the estimated 3-year major bleeding-free survival was 87.4% for NOACs and 85.1% for warfarin (Figure 3).

Table 1. Baseline Characteristics of Eligible Patients to Emulate the Target Trial

	Warfarin	NOAC
N (%)	1369	2357
Women, n (%)	590 (43.1)	1170 (49.6)
Age in years, median (IQR)	79 (73–85)	82 (75–88)
Days since diagnosis of AF, median (IQR)	15 (6–235)	11 (4–170)
Days since diagnosis of aortic stenosis, median (IQR)	360 (23–1528)	515 (18-1780)
Previous aortic valve intervention*, n (%)	432 (31.6)	497 (21.1)
Days since aortic valve intervention, median (IQR)	22 (13–100)	67 (17–1104)
Year of inclusion:		
2013, n (%)	393 (28.7)	197 (8.4)
2014, n (%)	364 (26.6)	310 (13.2)
2015, n (%)	285 (20.8)	379 (16.1)
2016, n (%)	202 (14.8)	484 (20.5)
2017, n (%)	97 (7.1)	570 (24.2)
2018, n (%)	28 (2.0)	417 (17.7)
Comorbidities: n (%)		
Heart failure	670 (48.9)	1008 (42.8)
Hypertension	957 (69.9)	1616 (68.6)
Diabetes	290 (21.2)	429 (18.2)
Prior thromboembolic event	276 (20.2)	571 (24.2)
Prior major bleeding event	272 (19.9)	500 (21.2)
Vascular disease	448 (32.7)	658 (27.9)
Prior myocardial infarction	270 (19.7)	380 (16.1)
Ischemic heart disease	599 (43.8)	881 (37.4)
Prior percutaneous coronary intervention	181 (13.2)	295 (12.5)
Prior coronary artery bypass grafting	206 (15.0)	231 (9.8)
Alcohol abuse	53 (3.9)	109 (4.6)
Chronic obstructive pulmonary disorder	231 (16.9)	430 (18.2)
Chronic kidney disease	159 (11.6)	152 (6.4)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
HAS-BLED score, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Co-medication: n (%)*		
NOAC agent:		
Apixaban	…	1105 (46.9)
Dabigatran	…	323 (13.7)
Edoxaban	…	38 (1.6)
Rivaroxaban	…	891 (37.8)
Aspirin	765 (55.9)	1185 (50.3)
Other antiplatelet therapy	224 (16.4)	472 (20.0)
Beta-blockers	639 (46.7)	991 (42.0)
ARB/ACE-inhibitors	755 (55.1)	1265 (53.7)
Calcium channel blockers	519 (37.9)	863 (36.6)

(*Continued*)

Table 1. Continued

	Warfarin	NOAC
Amiodarone	48 (3.5)	44 (1.9)
Digoxin	93 (6.8)	135 (5.7)
Non-loop diuretics	600 (43.8)	1012 (42.9)
Loop diuretics	553 (40.4)	838 (35.6)
NSAIDs	225 (16.4)	406 (17.2)
Statins	763 (55.7)	1184 (50.2)

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; IQR, Interquartile range; and N, Number.

*Primarily bioprosthetic aortic valve replacement.

†Patients with a redeemed prescription within 180 days prior to or 30 days after the diagnosis of atrial fibrillation.

Sub-Analysis and Sensitivity Analyses

In the sub-analysis, we restricted the population to 512 patients who had an aortic valve surgery/procedure within 60 days before or 30 days after baseline, 888 patients who had an aortic valve surgery/procedure at any time before or 30 days after baseline, and 2838 patients who never had an aortic valve surgery/procedure. We observed too few events in the 2 subpopulations with a history of valve surgery/procedure to perform the pre-planned analyses. However, we repeated the main analyses in the patients with no prior aortic valve surgery/procedure (ie, patients with native aortic stenosis) and found similar results as in the main analysis (Table S3).

In the sensitivity analysis, allowing a 90-day treatment gap in the estimate of continuous treatment, we observed similar results as in the main analysis. The PP analysis yielded an adjusted HR for thromboembolism of 1.87 (95% CI, 1.12–3.10) and an adjusted HR for major bleeding of 0.71 (95% CI, 0.56–0.90). The estimated 3-year survivals were materially unchanged, and reflecting results found in the main analysis (data not shown).

In the "falsification outcome" analyses using the ITT approach, the adjusted HR for the pneumonia outcome was 0.94 (95% CI, 0.80–1.11) for NOACs compared with warfarin and the adjusted HR for the cancer outcome was 1.15 (95% CI, 0.91–1.44) for NOACs compared with warfarin.

DISCUSSION

In this study, we used observational data to emulate a target trial estimating the average treatment effects of NOAC versus warfarin on thromboembolism and major bleeding among patients with AF and aortic stenosis. We observed a significantly higher risk of thromboembolism in the NOAC group compared with the warfarin group in both the ITT and PP analyses. In addition, we observed a significantly lower risk of major bleeding in the NOAC group compared with the warfarin group.

Table 2. Treatment Effects of NOAC Versus Warfarin on Thromboembolism and Bleeding After 3 Years of Follow-Up

Analytical strategy	Intention-to-treat analysis		Per-protocol analysis	
	Warfarin	NOAC	Warfarin	NOAC
Thromboembolism				
Event count	36	77	19	62
HR (95% CI)	Ref.	1.62 (1.08–2.45)	Ref.	1.92 (1.11–3.30)
Major bleeding†				
Event count	171	184	119	163
HR (95% CI)	Ref.	0.73 (0.59–0.91)	Ref.	0.78 (0.60–0.99)

HR indicates hazard ratio; and NOAC, non–vitamin K antagonist oral anticoagulant.

*Composite of intracranial bleeding, gastrointestinal bleeding, and major or clinically relevant bleeding in other anatomic sites.

Large randomized, controlled trials evaluating the efficacy and safety of NOACs versus warfarin for prevention of thromboembolic events in patients with AF demonstrated that the NOACs are associated with similar or lower rates of both ischemic stroke and major bleeding and less than half the risk of intracranial hemorrhage compared with adjusted dose warfarin.[15–18] Previous post hoc studies of these randomized, controlled trials examining NOACs versus warfarin in anticoagulated patients with AF with and without VHD generally observed comparable outcomes of stroke or systemic embolism and major bleeding in patients treated with regular doses of NOACs and patients treated with warfarin, with the exception of 20 mg rivaroxaban, which was associated with higher rates of major bleeding compared with warfarin.[12,19–21] Data on outcomes comparing NOACs to warfarin in AF patients with aortic stenosis have only been reported in 2 post hoc analyses of the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials.[12,20] In the post hoc analysis of the ROCKET AF trial, which included 214 AF patients with aortic stenosis,[12] AF patients with aortic stenosis on 20 mg rivaroxaban daily had similar stroke or systemic embolism rates compared to patients on warfarin (HR not reported) but higher rates of major bleeding (HR, 1.73; 95% CI, 0.73–4.12) and major bleeding/non-major clinically relevant bleeding (HR, 1.18; 95% CI, 0.70–1.97). In the post hoc analysis of the ARISTOTLE trial, which included 1150 AF patients with aortic valve disease, 384 of which had aortic stenosis,[20] AF patients with aortic valve disease on 5 mg apixaban twice daily had lower risk of stroke or systemic embolism (HR, 0.55; 95% CI, 0.30–1.01) and major bleeding (HR, 0.72; 95% CI, 0.44–1.18)

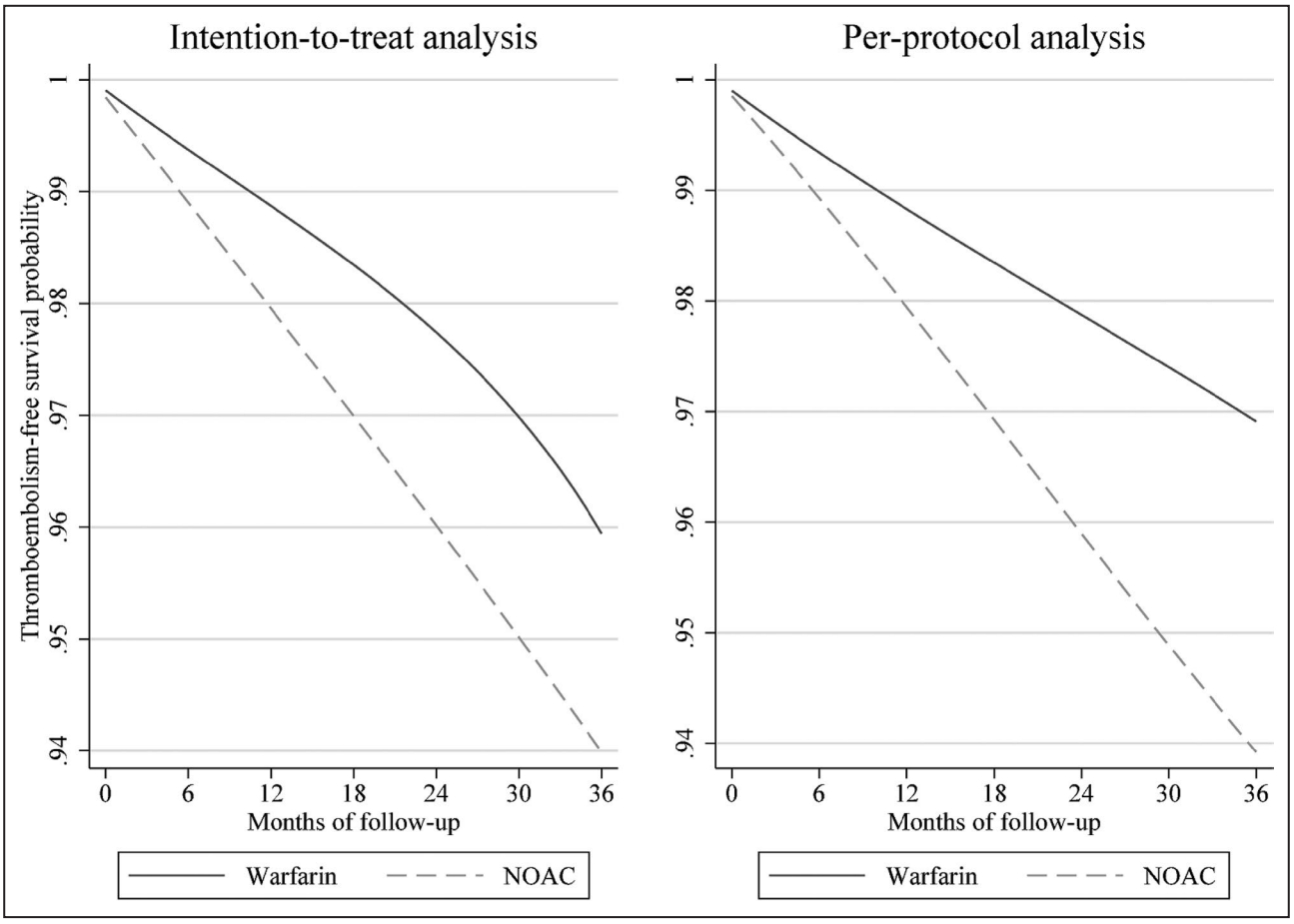

Figure 2. Standardized survival curve free from thromboembolic events.
Thromboembolism-free survival probability according to treatment strategy (NOAC or warfarin) for the intention-to-treat analysis and the per-protocol analysis. NOAC indicates non–vitamin K antagonist oral anticoagulant.

compared with patients on warfarin. In these 2 post hoc trials,[12,20] the finding of a lower or similar risk of thromboembolism in the NOAC group compared with the warfarin group is different from the findings in our study, where we observed a significantly higher risk of thromboembolism in the NOAC group compared with the warfarin group (HR, 1.62; 95% CI, 1.08–2.45 in ITT analysis; HR, 1.92; 95% CI, 1.011–3.30 in PP analysis). This observation may be explained by the nonrandomized setup in our study, though, we derived stabilized inverse probability of treatment weights to account for the non-randomization of the treatment assignment, and the falsification outcome analyses revealed minimal risk of residual bias. Therefore, our observation could also reflect an actual increased risk of thromboembolism in the NOAC group.

The trial subgroups were small and the CIs wide, and recent studies examining the effectiveness and safety of NOAC versus warfarin in AF patients with aortic stenosis undergoing transcatheter aortic valve replacement also observed an increased risk of thromboembolism in the NOAC group[36] and rivaroxaban-related safety concerns.[37] Furthermore, our study may better mirror the clinical reality, as we included a more diverse group of patients with AF and aortic stenosis than the ARISTOTLE and ROCKET AF trials.

The finding of major bleeding in our study is in line with the findings of the post hoc analysis in the ARISTOTLE trial, as we also observed a lower risk of major bleeding in the NOAC group compared with the warfarin group (HR, 0.73;95% CI, 0.59–0.91 in ITT analysis; HR, 0.78; 95% CI, 0.60–0.99 in PP analysis). In the ROCKET AF trial, the higher rates of major bleeding in patients treated with rivaroxaban were also observed in patients with other VHDs[12]; thus, the increased risk of major bleeding associated with rivaroxaban could be clinically important in patients with VHD, though we observed a considerably lower risk of major bleeding in the NOAC group in our study (38.0% of the patients in the NOAC group were in oral anticoagulant therapy with rivaroxaban).

Unfortunately, our data did not allow us to examine each NOAC agent or dose individually because of the

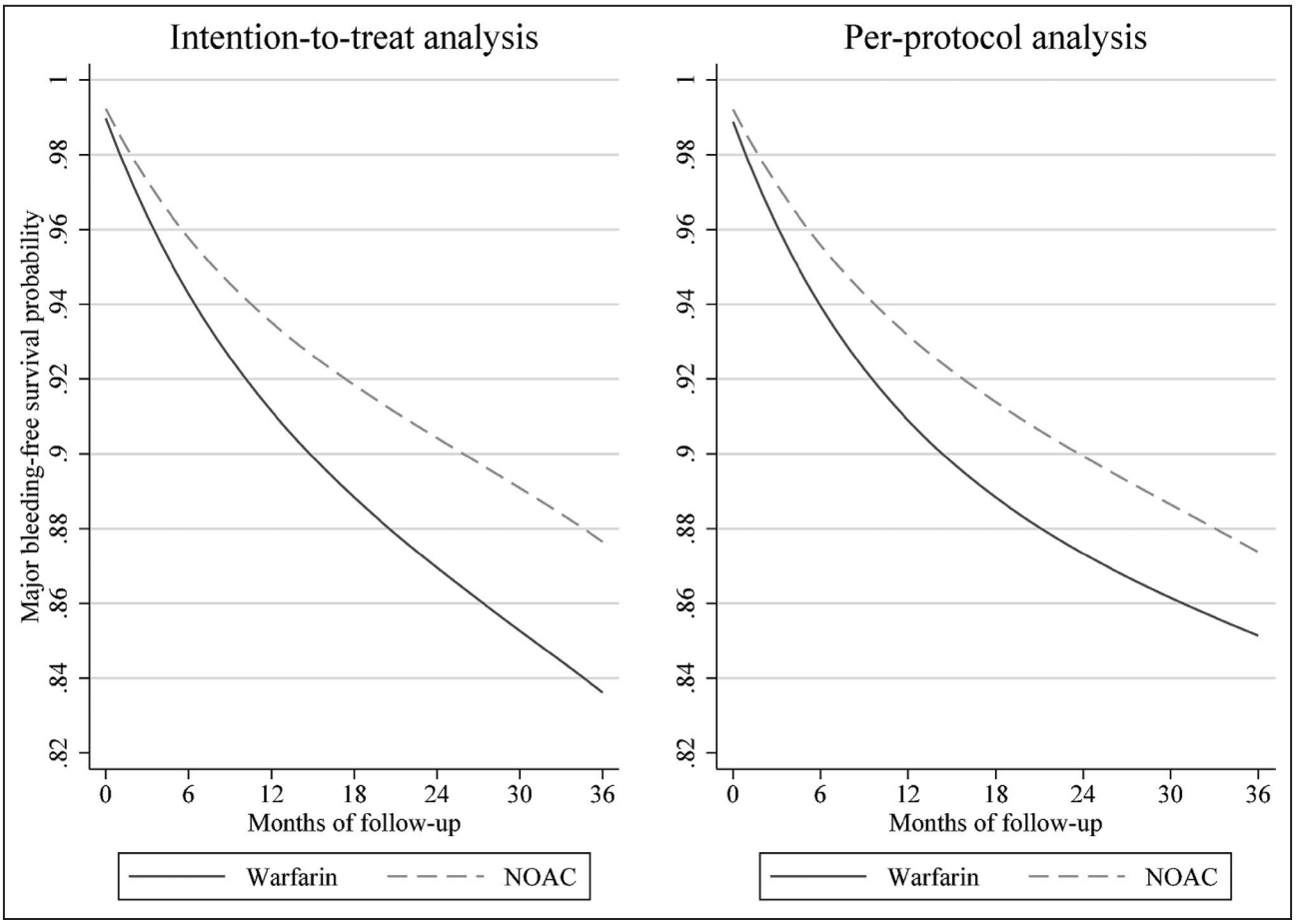

Figure 3. Standardized survival curve free from major bleeding events.
Major bleeding-free survival probability according to treatment strategy (NOAC or warfarin) for the intention-to-treat analysis and the per-protocol analysis. NOAC indicates non–vitamin K antagonist oral anticoagulant.

limited sample size. In our study, the proportion of patients in the NOAC group using apixaban was 46.8%, so our findings are mainly driven by therapy with apixaban or rivaroxaban. The proportion of patients in oral anticoagulant therapy with either dabigatran or edoxaban was low (13.7% and 1.6%, respectively) and randomized and observational data on outcomes of dabigatran and edoxaban in patients with AF and aortic stenosis are lacking in general.

Clinical Implications and Future Directions

International guidelines for patients with AF recommend NOAC as an alternative to warfarin in patients with native VHD, including aortic stenosis.[25,26] However, these guideline recommendations on the use of NOAC in AF patients with aortic stenosis are based on post hoc trial analyses including a small and widely underrepresented number of patients with aortic stenosis.[12,19–21] Furthermore, the results of these post hoc analyses were inconsistent, as outlined above.[12,20] Generally, caution is warranted when interpreting post-hoc trial analyses.[38]

The observations in our study suggest that NOAC may be less effective than warfarin for preventing ischemic events, but safer with respect to bleeding, in the population with AF and aortic stenosis. Thus, individual assessment of the thromboembolic risk and bleeding risk in this population might be necessary before deciding which oral anticoagulant agent the patient should be prescribed. Generally, the clinician should be aware of the overall increased risk of thromboembolism and bleeding in this typically aged, multimorbid population.

Based on the findings of our study and the existing inconsistent data on the effectiveness and safety of NOAC versus warfarin in patients with AF and aortic stenosis, the optimal oral anticoagulant strategy is not clear at this point and more research is necessary. Similarly, the safety of every NOAC agent is questionable because rivaroxaban may be associated with an increased risk of major bleeding and major bleeding/non-major clinically relevant bleeding in patients with AF and aortic stenosis,[12] whereas apixaban seems to be associated with an appealing safety profile[20] but data on dabigatran and edoxaban are lacking. Importantly, the observed increased risk of thromboembolism in the NOAC group in our study requires

further investigation, preferably in a large randomized trial, as this finding was not observed in the post hoc analyses of the ROCKET AF and ARISTOTLE trials.[12,20]

Strengths and Limitations

We examined the effect of NOAC versus warfarin on thromboembolism and bleeding using the "target trial" principle,[27] which has the advantage of avoiding common pitfalls that occur when conducting comparative effectiveness analyses using observational data.[27,39] Due to the non-randomized design, all confounding factors may not have been accounted for; for example, lifestyle factors were not available in the registries we utilized.

The diagnoses of AF and aortic valve disease have been validated with positive predictive values of 93% and 98%, respectively.[40–42] Patients with aortic stenosis is a broad group of patients with varying severity of valve disease. We did not have access to echocardiographic data or individual blood pressure measurements; therefore, we did not have information about the severity of aortic stenosis or degree of hemodynamic influence.

The diagnoses of ischemic stroke and intracranial hemorrhage have been validated with positive predictive values of 80%–90% and 88%, respectively.[43–45] No validation studies for the diagnoses of other major bleedings currently exist. However, we examined only diagnoses of major bleeding leading to a hospital admission to ensure that the bleeding was truly major and clinically relevant.[46] By this approach, bleeds registered in outpatients were not examined, but some of these bleeds could have been clinically relevant.

We observed an increase in NOAC users and a decrease in warfarin users during the years of inclusion, which are in line with observations in other AF populations.[47,48] NOAC has gradually become the preferred oral anticoagulant drug in patients with AF, both among new-users and prevalent users.[47,48] In our study, we only included patients with a first-time prescription of any oral anticoagulant agent, and, therefore, the increase in NOAC users in our study reflects the increased use of NOAC as the first choice of oral anticoagulant agent in new-users and not the switch to NOACs among prevalent users (which may have a different clinical profile and risks of adverse events than new-users). However, the lack of randomization in our study is a major limitation and, therefore, our findings need confirmation in large prospective randomized trials.

CONCLUSIONS

In this observational study, we observed a higher risk of thromboembolism but a lower risk of major bleeding for treatment with NOACs compared with warfarin in patients with AF and aortic stenosis. This observation needs confirmation in large, randomized trials in these commonly encountered patients. Importantly, the clinician must be aware of the increased risk of thromboembolism and bleeding in this population in general.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark (L.M., T.F.O., T.B.L., P.B.N.); ; Department of Clinical Medicine, Aalborg Thrombosis Research Unit, Faculty of Health, Aalborg University, Aalborg, Denmark (L.M., T.F.O., M.J., G.Y.L., T.B.L., P.B.N.); ; Department of Cardiothoracic and Vascular Surgery & Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark (T.D.C.); and Liverpool Centre for Cardiovascular Sciences, University Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK (G.Y.L.).

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Supplementary Material

Data S1
Table S1–S3

REFERENCES

1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. *Eur Heart J*. 2003;24:1231–1243. doi: 10.1016/S0195-668X(03)00201-X
2. Banerjee A, Allan V, Denaxas S, Shah A, Kotecha D, Lambiase PD, Jacob J, Lund LH, Hemingway H. Subtypes of atrial fibrillation with concomitant valvular heart disease derived from electronic health records : phenotypes, population prevalence, trends and prognosis. *Europace*. 2019;220:1–9. doi: 10.1093/europace/euz323
3. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B, Sundquist K, Smith JG. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart*. 2017;103:1696–1703. doi: 10.1136/heartjnl-2016-310894
4. Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, Lereun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol*. 2013;62:1002–1012. doi: 10.1016/j.jacc.2013.05.015

5. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8
6. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol*. 2011;8:162–172. doi: 10.1038/nrcardio.2010.202
7. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
8. Tarantini G, Mojoli M, Windecker S, Wendler O, Lefèvre T, Saia F, Walther T, Rubino P, Bartorelli AL, Napodano M, et al. Prevalence and Impact of Atrial Fibrillation in Patients With Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. *JACC: Cardiovascular Interventions*. 2016;9:937. –946. http://dx.doi.org/10.1016/j.jcin.2016.01.037
9. Zhang H, El-Am EA, Thaden JJ, Pislaru SV, Scott CG, Krittanawong C, Chahal AA, Breen TJ, Eleid MF, Melduni RM, et al. Atrial fibrillation is not an independent predictor of outcome in patients with aortic stenosis. *Heart*. 2020;106:280–286. doi: 10.1136/heartjnl-2019-314996
10. Andreasen C, Gislason GH, Køber L, Abdulla J, Martinsson A, Smith JG, Torp-Pedersen C, Andersson C. Incidence of ischemic stroke in individuals with and without aortic valve stenosis: a Danish retrospective cohort study. *Stroke*. 2020;51:1364–1371. doi: 10.1161/STROKEAHA.119.028389
11. Melgaard L, Overvad TF, Jensen M, Lip GYH, Larsen TB, Nielsen PB. Thromboembolism and bleeding complications in anticoagulated patients with atrial fibrillation and native aortic or mitral valvular heart disease: a descriptive nationwide cohort study. *Eur Hear J - Cardiovasc Pharmacother*. 2021;7:f101–f110. doi: 10.1093/ehjcvp/pvaa008
12. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Lokhnygina Y, Halperin JL, Singer DE, Hankey GJ, Hacke W, et al. Native valve disease in patients with non-valvular atrial fibrillation on warfarin or rivaroxaban. *Heart*. 2016;102:1036–1043. doi: 10.1136/heartjnl-2015-308120
13. Elvira-Ruiz G, Caro-Martínez C, Flores-Blanco PJ, Cerezo-Manchado JJ, Albendín-Iglesias H, Lova-Navarro A, Arregui-Montoya F, Muñoz-Franco FM, García-Iniesta N, García-Alberola A, et al. Aortic valve stenosis provides complementary information to bleeding risk scores in non-valvular atrial fibrillation patients initiating anticoagulation. *J Geriatr Cardiol*. 2020;17:141–148. doi: 10.11909/j.issn.1671-5411.2020.03.005
14. Chugh Y, Patel K, Maraboto Gonzalez CA, Li D, Gössl M. Anticoagulation in patients with aortic stenosis and atrial fibrillation. *Struct Hear*. 2020;4:360–368. doi: 10.1080/24748706.2020.1797257
15. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561
16. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: 10.1056/NEJMoa1009638
17. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. doi: 10.1056/NEJMoa1107039
18. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. doi: 10.1056/NEJMoa1310907
19. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, Clemens A, Reilly PA, Connolly SJ, Yusuf S, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). *Circulation*. 2016;134:589–598. doi: 10.1161/CIRCULATIONAHA.115.020950
20. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, Pais P, Erol C, Diaz R, Bahit MC, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (Aristotle) trial. *Circulation*. 2015;132:624–632. doi: 10.1161/CIRCULATIONAHA.114.014807
21. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, Ruff CT, Antman EM, Braunwald E, Giugliano RP. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. *J Am Coll Cardiol*. 2017;69:1372–1382. doi: 10.1016/j.jacc.2016.12.031
22. Strange J, Sindet-Pedersen C, Staerk L, Grove E, Gerds T, Torp-Pedersen C, Gislason GH, Olesen JB. All-cause mortality, stroke, and bleeding in patients with atrial fibrillation and valvular heart disease. *Eur Hear J - Cardiovasc Pharmacother*. 2021;7:f93–f100. doi: 10.1093/ehjcvp/pvaa011
23. Melgaard L, Jensen M, Overvad TF, Larsen TB, Lip GYH, Nielsen PB. Thromboembolic and bleeding complications in patients with atrial fibrillation and valvular heart disease: a descriptive nationwide cohort study. *Int J Clin Pr*. 2020;74:e13589. doi: 10.1111/ijcp.13589
24. Doi K, Ogawa H, Ishigami K, Ikeda S, Aono Y, Hamatani Y, Fujino A, An Y, Ishii M, Iguchi M, et al.; Fushimi AF Registry Investigators. Impact of valvular heart disease on mortality, thromboembolic and cardiac events in Japanese patients with atrial fibrillation - the Fushimi AF registry. *Circ J*. 2020;84:714–722.
25. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. doi: 10.1093/eurheartj/ehx391
26. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:1159–1195. doi: 10.1161/CIR.0000000000000503
27. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758–764. doi: 10.1093/aje/kwv254
28. Labrecque JA, Swanson SA. Target trial emulation: teaching epidemiology and beyond. *Eur J Epidemiol*. 2017;32:473–475. doi: 10.1007/s10654-017-0293-4
29. Pedersen CBC. The Danish civil registration system. *Scand J Public Health*. 2011;39:22–25. doi: 10.1177/1403494810387965
30. Kildemoes HW, Sørensen HT, Hallas J. The Danish national prescription registry. *Scand J Public Health*. 2011;39:38–41. doi: 10.1177/1403494810394717
31. Lynge E, Sandegaard J, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39:30–33. doi: 10.1177/1403494811401482
32. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210
33. Thompson W. On the treatment of grouped observations in life studies. *Biometrics*. 1977;33:463–470. doi: 10.2307/2529360
34. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15:615–625. doi: 10.1097/01.ede.0000135174.63482.43
35. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21:383–388. doi: 10.1097/EDE.0b013e3181d61eeb
36. Jochheim D, Barbanti M, Capretti G, Stefanini GG, Hapfelmeier A, Zadrozny M, Baquet M, Fischer J, Theiss H, Todaro D, et al. Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2019;12:1566–1576. doi: 10.1016/j.jcin.2019.03.003
37. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:120–129. doi: 10.1056/NEJMoa1911425
38. Peto R. Current misconception 3: that subgroup-specific trial mortality results often provide a good basis for individualising patient care. *Br J Cancer*. 2011;104:1057–1058. doi: 10.1038/bjc.2011.79
39. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70–75. doi: 10.1016/j.jclinepi.2016.04.014
40. Thygesen S, Christiansen C, Christensen S, Lash T, Sørensen H. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish national registry of patients. *BMC Med Res Methodol*. 2011;11:83. doi: 10.1186/1471-2288-11-83

41. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J*. 2012;46:149–153. doi: 10.3109/14017431.2012.673728
42. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832. doi: 10.1136/bmjopen-2016-012832
43. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of diagnostic codes for acute stroke in administrative databases: a systematic review. *PLoS One*. 2015;10:e0135834. doi: 10.1371/journal.pone.0135834
44. Krarup L, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28:150–154. doi: 10.1159/000102143
45. Hald SM, Sloth CK, Hey SM, Madsen C, Nguyen N, Rodríguez LAG, Al-Shahi Salman R, Möller S, Poulsen FR, Pottegård A, et al. Intracerebral hemorrhage: positive predictive value of diagnosis codes in two nationwide danish registries. *Clin Epidemiol*. 2018;10:941–948. doi: 10.2147/CLEP.S167576
46. Friberg L, Skeppholm M. Usefulness of health registers for detection of bleeding events in outcome studies. *Thromb Haemost*. 2016;116:1131–1139. doi: 10.1160/TH16-05-0400
47. Gadsbøll K, Staerk L, Fosbøl EL, Sindet-Pedersen C, Gundlund A, Lip GYH, Gislason GH, Olesen JB. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *Eur Heart J*. 2017;38:899–906. doi: 10.1093/eurheartj/ehw658
48. Maura G, Billionnet C, Drouin J, Weill A, Neumann A, Pariente A. Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011–2016. *BMJ Open*. 2019;9:e026645. doi: 10.1136/bmjopen-2018-026645

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Study design and data sources

This study was conducted using the 'target trial' principles.(23) Briefly, we specified the protocol of a target trial (a hypothetical randomized experiment) to estimate the effectiveness and safety of NOAC vs. warfarin in atrial fibrillation patients with aortic stenosis and then attempted to emulate this trial using observational data from the Danish nationwide registries. This approach has the advantage of avoiding pitfalls that can occur when conducting comparative effectiveness analyses using observational data.(35) The specifications of each component in the target trial and the emulated trial are provided in **Table S1**.

Longitudinal observational data from four Danish nationwide registries was used: i)The Danish Civil Registration System, which holds information on sex, date of birth, vital and emigration status of all persons living in Denmark,(25) ii) the National Prescription Registry,(26) which contains data on all prescriptions dispensed from Danish pharmacies, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System, iii) the Danish National Patient Registry, (27) which has registered dates of hospital admissions and discharges, outpatient and emergency room contacts, and discharge diagnoses classified according to the 10th revision of the International Classification of Diseases (ICD) for more than 99% of hospital admissions in Denmark, iv) the Danish National Laboratory Register, which includes information on laboratory values from 4 out of 5 regions in Denmark. The Danish National Patient Registry also holds information about surgical procedures and clinical examinations coded according to the Danish version of the Nordic NOMESCO Classification of Surgical Procedure provided by the Danish Health Data Agency. Data from these registries were linked via a unique personal identification number, which is used across all Danish national registries.

Eligibility criteria

We identified patients in the Danish nationwide registries who met the target trial eligibility criteria (**Table S1**). The study population included patients with a diagnosis of both atrial fibrillation and aortic stenosis at baseline or within 30 days after baseline; both diagnoses could be primary or secondary diagnoses given during a hospital admission or at an outpatient clinic. To ensure that patients were eligible for stroke prevention with oral anticoagulant therapy according to contemporary guidelines,(28) a CHA_2DS_2-VASc score level threshold of ≥1 for males and ≥2 for females was also an eligibility criterion. The score is comprised of congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74 years, sex category [female].

Patients with other indications for oral anticoagulant therapy were excluded, such as patients with a venous thromboembolism within the last year (or more than one previous diagnosis of venous thromboembolism) and patients undergoing knee/hip surgery within the last 3 months. Patients with potential contraindications for NOAC or warfarin treatment were excluded, including patients with mitral stenosis, any mechanical heart valve replacement, registered cancer diagnosis within the last 6 months (to reflect active cancer), or severe renal insufficiency (defined by creatinine clearance <15 mL/min, prior dialysis, or kidney transplantation). Patients with dispensation of both a NOAC and warfarin within the first 30 days after baseline were excluded. Lastly, only patients who were alive and event-free after the first month were included (see **Figure 1** for a flowchart of the study population). See **Table S2** for details on the definition of atrial fibrillation, aortic stenosis, contraindications, comorbidities, and co-medication.

Outcomes

The effectiveness outcome was a hospital diagnosis of ischemic stroke and/or systemic embolism defined as a composite endpoint of 'thromboembolism'. Given the severity of the diagnosis of ischemic stroke/systemic embolism, we only considered events if the patient was admitted to the hospital. Additionally, we only considered primary diagnoses of thromboembolism. An event of 'unspecified stroke' was included as an outcome since outcome adjudication assessment was not performed and since most strokes coded as such are of ischemic origin.(40) The safety outcome was a major bleeding leading to hospital admission (either intracranial bleeding, gastrointestinal bleeding, major or clinically relevant bleeding in other anatomic sites). We did not consider outpatient diagnoses for this outcome, but both primary and secondary inpatient diagnoses of major bleeding were included because of clinical coding practice. For both the effectiveness and safety outcomes, emergency room codes were not included due to a general low positive predictive value (see **Table S2** for details about the definition of the outcomes).

Follow-up period

Each patient was followed up in the registries for the outcomes of interest. Follow-up started 30 days after treatment assignment (baseline) and ended at outcome diagnosis, death, administrative end of follow-up (3 years or December 2018), or emigration (loss to follow-up), whichever occurred first.

Treatment strategies

The Danish National Prescription Registry were used to identify patients who redeemed a first-time prescription for a NOAC (apixaban, dabigatran, rivaroxaban, or edoxaban) or warfarin between January 2013 and October 2018 (oral anticoagulation naïve users only). The date of first prescription

claim was used as the baseline date. Shift between NOAC agents and/or changes in dosage during follow-up were left to the treating physician's discretion. Treatment groups were assumed exchangeable at baseline conditional on covariates that could confound the exposure-outcome association.

Causal contrasts

To compare the two treatment strategies, we estimated the intention-to-treat (ITT) effect and per-protocol (PP) effect.

Statistical analysis

The baseline characteristics of the study population were described according to treatment exposure category (NOAC or warfarin), using means and standard deviation for continuous variables, and proportions for categorical variables. The exposure category (i.e. NOAC or warfarin) of each patient was based on the prescription claim at the baseline date, and this category remained unchanged throughout the study duration.

Counterfactual outcomes were investigated at 3 years and data were arranged such that each patient-month was represented by a single row (maximum of 36 rows per individual, corresponding to 3 years). To account for the non-randomization of the treatment assignment, we derived stabilized inverse probability of treatment weights (IPTW). To compute these weights, we estimated the propensity of being assigned each treatment by a logistic regression including the following baseline confounding factors: age (as a restricted cubic spline) and dichotomous covariates on sex, heart failure, hypertension, diabetes, myocardial infarction, ischemic heart disease, renal disease, prior bleeding, prior thromboembolic event, diagnosis of atrial fibrillation within 60 days before or 30 days after the baseline date, diagnosis of aortic stenosis within 60 days before or 30 days after the baseline

date, valve surgery including bioprosthetic valve implantation within 60 days before or 30 days after the baseline date, and use of statin or antiplatelet therapy within the last year.

The assessment of outcomes was based on an ITT approach and a PP approach (see details in the following sections). When estimating the ITT treatment effects, treatment status remained unchanged throughout follow-up disregarding actual treatment. When estimating the PP treatment effects, continuous treatment status was assessed using a recommended daily dose and quantity of pills per pack in each prescription (a 60-day grace period between each prescription claim was allowed). The variable dose regimen of warfarin was modeled by continuous adaption of an (individual) estimated daily dose. Patients were considered adherent to the initial treatment strategy (NOAC or warfarin) unless a clinical event that fully or partly contraindicated treatment or had a major clinical impact on the anticoagulant therapy strategy occurred. Such an event included primary diagnoses/codes for the following diseases or procedures: chronic kidney disease or procedure code for dialysis, cancer, mitral stenosis, procedure code for any mechanical heart valve replacement or any other valve surgery, major bleeding (when investigating the thromboembolic outcome), or thromboembolism (when investigating the major bleeding outcome). If such an event occurred, we stopped updating the censoring weight for that patient, but kept the patient in the analysis. Statistical analyses were performed using SAS 9.3 (SAS Institute) and Stata version 16 (StataCorp LP).

Intention-to-treat analyses

Pooled logistic regression models were used to estimate the average treatment effects by means of hazard ratios (HRs) for the effectiveness and safety outcomes (with the warfarin group used as reference). In detail, we derived odds ratios from pooled logistic regressions, which are approximations of HRs when the outcome investigated is rare in all time intervals.(29) The baseline hazard rate function was estimated by a linear and a quadratic term of months of follow-up in the

study. In the adjusted analyses, the calculated IPTWs were applied in the weighted pooled logistic regression models. The risks of the effectiveness and safety (counterfactual) outcomes in both treatment groups were also estimated through the weighted pooled logistic regressions models with the additional inclusion of interaction terms on treatment exposure and time variables (in order to construct standardized event-free survival curves, which depict the estimated counterfactual event-free survival had every individual receiving either treatment).

Per-protocol analyses

For the PP analyses, a similar approach was used as in the ITT approach with the addition of administratively censoring follow-up if/when subjects deviated from their initial treatment. Because this censoring may be informative if post-baseline time-varying prognostic factors are not included into the analytic strategy, we calculated stabilized inverse probability of censoring weights to account for the dependence between measured post-baseline time-varying prognostic factors and censoring.(30) To compute these weights, we estimated the propensity of being censored by a logistic regression including post-baseline time-varying prognostic factors (heart failure, hypertension, diabetes, ischemic heart disease, myocardial infarction, and use of statin or antiplatelet therapy (all included as dichotomous covariates)) for each patient month. The calculated weights to account for this censoring process were multiplied by the IPTWs of baseline confounding factors and applied in the weighted pooled logistic regression models to estimate the PP treatment effects. Similarly, as in the ITT approach, the per-protocol standardized event-free survival curves were also estimated.

Sub-analysis and sensitivity analyses

Some patients had an aortic valve surgery/procedure before inclusion in the study, which may affect the treatments effects, especially if the surgery/procedure were performed close to the baseline date. Therefore, we performed a sub-analysis in which we restricted the population to the following

subpopulations and repeated the main analyses: i) those who had an aortic valve surgery/procedure within 60 days before or 30 days after baseline, ii) those who had an aortic valve surgery/procedure at any time before or 30 days after baseline, and iii) those who never had an aortic valve surgery/procedure.

Two sensitivity analyses were performed to investigate the robustness of the analytical strategy in the main analyses. In the PP analysis, a grace period of 60 days was allowed. However, we performed a sensitivity analysis in which we changed the assessment of continuous treatment status by allowing a grace period of 90 days as treatment gap. Additionally, two 'falsification outcomes' were examined, which were expected to have a null association with the exposure.(31) In detail, we emulated an individual target trial with pneumonia as the outcome and an individual target trial with cancer as the outcome using the described features from the ITT analyses.

Table S1. Specifications of the target trial and the emulated trial using observational data.

Protocol component	**Target trial specifications**	**Emulated trial specifications**
Eligibility criteria	Diagnosis of both atrial fibrillation and aortic stenosis. Age ≥18 years. A CHA_2DS_2-VASc score ≥1 for males, and ≥2 for females. No previous prescription of oral anticoagulants (oral anticoagulant naïve participants). No other indications for oral anticoagulant treatment, including: • A diagnosis of venous thromboembolism within the last year or several diagnoses at earlier times. • Knee or hip procedure within last three months. Potential contraindications for NOAC treatment, including: • Diagnosis of mitral stenosis or heart valve replacement. • Cancer diagnosis within last 6 months. • Renal insufficiency defined as creatinine clearance <15 mL/min, prior dialysis, or kidney transplantation.	Same as for target trial with the following specifications: Residents of Denmark for at least 1 year and with valid identifier information between January 2013 and October 2018. Diagnosis of atrial fibrillation before first prescription claim or up to 30 days later (using ICD-10 codes, both primary and secondary diagnoses given during hospitalization or in outpatient clinics) [see **Table S2** for details]. Diagnosis of aortic stenosis before first prescription claim or up to 30 days later (using ICD-10 codes, both primary and secondary diagnoses given during hospitalization or in outpatient clinics) [see **Table S2** for details]. Exclude participants with dispensation of both a NOAC and warfarin within the first 30 days after baseline. Other indications for oral anticoagulant treatment or potential contraindications were defined on the basis of recorded ICD-10 codes or procedure codes [see **Table S2** for details].
Treatment strategies	1. Initiation of warfarin 2. Initiation of a NOAC (apixaban, edoxaban, dabigatran, or rivaroxaban) The treatment strategy allows for shift in NOAC agent or dosage after initial assignment (left to physician's discretion). Patients were considered adherent to the initial treatment strategy unless a clinical event that fully or partly	First prescription claim of either: warfarin (ATC: B01AA) or NOAC (ATC: B01AE07; B01AF01; B01AF02; or B01AF03). Shift between NOAC agents or dosage during follow-up was allowed. Same accepted reasons for treatment non-adherence as in target trial (using ICD-10 codes or procedure codes to identify these deviations) [see **Table S2** for details].

	contraindicated treatment or had a major clinical impact on the anticoagulant therapy strategy occurred., including: • Development of chronic kidney disease or need for dialysis. • Primary diagnosis of cancer. • Diagnosis of mitral stenosis. • Mechanical heart valve replacement. • Any valve-related operation. • Major bleeding (for the effectiveness outcome). • Thromboembolism (for the safety outcome).	
Assignment procedure	Study participants were randomly assigned to receive either warfarin or a NOAC. The participants and investigators were aware of the treatment (no blinding).	The exposure category (i.e. NOAC or warfarin) of each study participant was based on first prescription claim during the study period, and this category remained unchanged throughout the study duration. Randomization was emulated by estimating stabilized inverse probability of treatment weights to adjust for pre-baseline prognostic factors [see details in Statistical methods].
Follow-up	For each participant, follow-up started at treatment assignment and ended at diagnosis of outcome, death, administrative end of follow-up (3 years or December 2018), or emigration (loss to follow-up), whichever occurred first.	Same as for the target trial, but follow-up started at prescription claim using ATC codes. Information of follow-up were obtained from the registries.
Outcomes definitions	Effectiveness outcome: A diagnosis of ischemic stroke and/or systemic embolism defined as a composite endpoint of 'thromboembolism' leading to a hospital admission. Safety outcome: A diagnosis of major bleeding (either intracranial bleeding, gastrointestinal bleeding, and major or clinically relevant bleeding in other anatomic sites) leading to a hospital admission.	Same as for target trial with the following specifications: Outcomes were defined by records of ICD-10 codes [see **Table S2** for details]. Given the severity of the diagnosis of ischemic stroke/systemic embolism, an event was only considered if the participant was admitted to the hospital. Additionally, only a primary diagnosis of thromboembolism was considered. An event of 'unspecified stroke' was included as an outcome since outcome adjudication assessment was not performed. A major bleeding event was only considered if the participant was admitted to the

		hospital; thus, outpatient diagnosis of a major bleeding event was not included, but both primary and secondary diagnoses of major bleeding were included due to clinical coding practice. For both outcomes, emergency room codes were not included due to a general low positive predictive value.
Causal contrasts	Intention-to-treat effect and per-protocol effect.	Average treatment effect in the population estimated with observational analogue of the intention-to-treat effect and per-protocol effect.
Statistical analyses	Estimation of the intention-to-treat effect comparing risk of the outcomes among participants assigned to NOAC vs. risk of the outcomes among participants assigned to warfarin. Estimation of the per-protocol effect with censoring of participants if/when they deviate from their assigned treatment strategy, unless a clinical event that fully or partly contraindicated treatment or had a major clinical impact on the anticoagulant therapy strategy occurred. Stabilized inverse probability of censoring weights was used to adjust for post-baseline time-varying prognostic factors associated with treatment adherence to avoid potential selection bias from informative censoring.	Same intention-to-treat and per-protocol effect analyses as for the target trial. However, the analyses only included participants who were alive and outcome-free 30 days after baseline due to data setup. In both the intention-to-treat and per-protocol analyses, stabilized inverse probability of treatment weights were used to adjust for pre-baseline prognostic factors. When estimating the per-protocol treatment effects, continuous treatment status was assessed using a recommended daily dose and quantity of pills per pack in each prescription (a 60 days grace period between each prescription claim was allowed). If an event with a major clinical impact on the anticoagulant therapy strategy occurred, we stopped updating the censoring weight for that patient, but kept the patient in the analysis.

Table S2. ICD-codes, procedure codes, and ATC-codes used to define study population, interventions, contraindications, comorbidities, medical therapies, and outcomes.

		Data source		
	Variable definition	**ICD-10 code/ Procedure code**	**ATC drug code***	**Registry sources**
Comorbidities				
Atrial fibrillation	Yes/no	I48		Danish National Patient Registry
Aortic stenosis / Aortic valve surgery	Yes/no	DI350; DI352; DI060; DI062; DQ230; KFMD10; KFMD11; KFMD12A; KFMD14; KFMA00; KFMA10; KFMA20; KFMA32; KFMA32A; KFMA96		Danish National Patient Registry
Heart failure	Yes/no	I501; I509; I110; I130; I132; I420; I50 or	C03C and C09	Danish National Patient Registry National Prescription Registry
Hypertension	Yes/no		Minimum 2 of: C02A; C02B; C02C; C02DA; C02L; C03A; C03B; C03D; C03EA; C03X; C07C; C07D; C08G; C09BA; C09DA; C09XA52; C02DB; C02DD; C02DG; C04; C05; C07; C07F; C08; C09BB; C09DB; C09	National Prescription Registry
Diabetes mellitus	Yes/no	E100; E101; E109; E110; E111; E119 or	A10	Danish National Patient Registry National Prescription Registry
History of thromboembolism	Yes/no	I63; I64; I74;		Danish National Patient Registry
Vascular disease	Yes/no	I21; I23; I700; I702-I709; I71; I739		Danish National Patient Registry
Ischemic heart disease	Yes/no	I20; I21; I22; I23; I24; I25		Danish National Patient Registry
Myocardial infarction	Yes/no	I21; I23		Danish National Patient Registry
Cancer	Yes/no	C		Danish National Patient Registry
Liver disease	Yes/no	B150; B160; B162; B190; K704; K72; K766; I85		Danish National Patient Registry

Alcohol abuse	Yes/no	E244; E529A; F10; G312; G621; G721; I426; K292; K70; K860; L278A; O354; T51; Z714; Z721		Danish National Patient Registry
Chronic obstructive pulmonary disorder	Yes/no	J40-J47; J60-J65; J67; J684; J701; J703; J841; J920; J921; J982; J983		Danish National Patient Registry
Chronic kidney disease	Yes/no	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61		Danish National Patient Registry
Venous thromboembolism	Yes/no	I26; I801; I802; I803; I808; I809; I828; I829; I822; I823; O223; O229; O871; O879; O882		Danish National Patient Registry
Mitral stenosis	Yes/no	I050; I052; I081A; I342; Q232		Danish National Patient Registry
Total hip or knee arthroplasty	Yes/no	KNGB; KNGC; KNGU; KNFB; KNFC; KNFU		Danish National Patient Registry
Coronary artery bypass graft	Yes/no	KFNA; KFNC; KFND; KFNE		Danish National Patient Registry
Percutaneous coronary intervention	Yes/no	KFNG		Danish National Patient Registry
Bioprosthetic valve implantation	Yes/no	KFMD10; KFKD10; KFJF10; KFGE10		Danish National Patient Registry
Mechanical prosthetic valve implantation	Yes/no	KFMD00; KFKD00; KFJF00; KFGE00		Danish National Patient Registry
Kidney transplantation	Yes/no	KKAS00; KKAS10; KKAS20		Danish National Patient Registry
Outcomes				
Thromboembolism	Yes/no	I63; I64; I74		Danish National Patient Registry
Major bleeding (composite outcome)	Yes/no	I60-I62; I690-I692; I850; I864A; K226; K228F; K250; K252; K254; K256; K260; K262; K264; K266; K270; K272; K274; K276; K280; K282; K284; K286; K290; K298A; K625; K638B; K638C; K661; K838F; K868G; K920; K921; K922; S063C; S064; S065; S066; S068B; S068D; S141C; S141D; S141E; S241D; S241E; S241F; S341D; S341E; S341F; E078B; E274B; G951A;		Danish National Patient Registry

		I312; I319A; I230; J942; M250; R04; S259A; S368A; S368B; S368D; T143C; T144A; D500; D62; D683; D698; D699; R58; T792A; T792B		
Intracranial bleeding	Yes/no	I60-I62; I690-I692		Danish National Patient Registry
Gastrointestinal bleeding	Yes/no	I850; I864A; K226; K228F; K250; K252; K254; K256; K260; K262; K264; K266; K270; K272; K274; K276; K280; K282; K284; K286; K290; K298A; K625; K638B; K638C; K661; K838F; K868G; K920; K921; K922		Danish National Patient Registry
Major clinically relevant bleeding located elsewhere	Yes/no	S063C; S064; S065; S066; S068B; S068D; S141C; S141D; S141E; S241D; S241E; S241F; S341D; S341E; S341F; E078B; E274B; G951A; I312; I319A; I230; J942; M250; R04; S259A; S368A; S368B; S368D; T143C; T144A; D500; D62; D683; D698; D699; R58; T792A; T792B		Danish National Patient Registry
Comedication				
Warfarin			B01AA03	National Prescription Registry
Non-vitamin K antagonist oral anticoagulant (Dabigatran Rivaroxaban Apixaban Edoxaban)			B01AE07 B01AF01 B01AF02 B01AF03	National Prescription Registry
Aspirin			B01AC06	National Prescription Registry
Other antiplatelets (Thienopyridines)			B01AC04; B01AC24; B01AC22	National Prescription Registry
Beta-blockers			C07	National Prescription Registry
Renin-angiotensin system inhibitors (ACEi/ARBs)			C09	National Prescription Registry

Calcium channel blockers			C07F; C08; C09BB; C09DB	National Prescription Registry
Amiodarone			C01BD01	National Prescription Registry
Digoxin			C01AA05	National Prescription Registry
Non-loop diuretics			C02DA; C02L; C03A; C03B; C03D; C03EA; C03X; C07C; C07D; C09BA; C09DA; C09XA52	National Prescription Registry
Loop diuretics			C03C; C03EB	National Prescription Registry
Non-steroidal anti-inflammatory drugs			M01AA; M01AB; M01AC; M01AE; M01AG; M01AH; M01AX01	National Prescription Registry
Statin			C10	National Prescription Registry

* Prescription data from 180 days before or 30 days after diagnosis of atrial fibrillation.

Table S3. Sub-analysis (participants with no prior aortic valve operation/procedure before baseline date): Treatment effects of NOAC vs. warfarin on thromboembolism and bleeding after 3 years of follow-up.

Analytical strategy:	Intention-to-treat analysis		Per-protocol analysis	
	Warfarin	NOAC	Warfarin	NOAC
THROMBOEMBOLISM				
Event count	23	71	12	56
Estimated 3-years event-free survival, %	96.4	92.6	97.6	93.0
HR (95% CI)	Ref.	2.10 (1.29-3.41)	Ref.	2.41 (1.25-4.66)
MAJOR BLEEDING*				
Event count	129	152	87	135
Estimated 3-years event-free survival, %	82.7	86.7	85.6	86.8
HR (95% CI)	Ref.	0.72 (0.56-0.91)	Ref.	0.78 (0.59-1.04)

Abbreviations: CI: Confidence interval, HR: Hazard ratio; NOAC: Non–vitamin K antagonist oral anticoagulant.
*Composite of intracranial bleeding, gastrointestinal bleeding, and major or clinically relevant bleeding in other anatomic sites.