**Thromboembolism and bleeding complications in anticoagulated patients with atrial fibrillation and native aortic or mitral valvular heart disease:**

**A descriptive nationwide cohort study**

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ABSTRACT

Aims: To describe the risks of thromboembolism and major bleeding complications in anticoagulated patients with atrial fibrillation (AF) and native aortic or mitral valvular heart disease using data reflecting clinical practice.

Methods and results: Descriptive cohort study of anticoagulated patients with incident AF and native aortic or mitral valvular heart disease, identified in nationwide Danish registries from 2000-2018. A total of 10,043 patients were included, of which 5,190 (51.7%) patients had aortic stenosis, 1,788 (17.8%) patients had aortic regurgitation, 327 (3.3%) patients had mitral stenosis, and 2,738 (27.3%) patients had mitral regurgitation. At 1 year after AF diagnosis, the risk of thromboembolism was 4.6% in patients with mitral stenosis taking a VKA, and 2.6% in patients with aortic stenosis taking a VKA or NOAC. For patients with aortic or mitral regurgitation, the risks of thromboembolism ranged between 1.5-1.8% in both treatment groups. For the endpoint of major bleeding, the risk was approximately 5.5% in patients with aortic stenosis or mitral stenosis treated with a VKA, and 3.3-4.0% in patients with aortic or mitral regurgitation. For patients treated with a NOAC, the risk of major bleeding was 3.7% in patients with aortic stenosis and approximately 2.5% in patients with aortic or mitral regurgitation.

Conclusion: When using data that reflects clinical practice, our observations suggest that one year after a diagnosis of AF, anticoagulated patients with aortic or mitral valvular heart disease had dissimilar risk of thromboembolism and major bleeding complications. Specifically, patients with aortic stenosis or mitral stenosis were high-risk subgroups. This observation may guide clinicians regarding intensity of clinical follow-up.

**Keywords:** native valvular heart disease, atrial fibrillation, anticoagulation, thromboembolism, bleeding complications.

INTRODUCTION

The combination of atrial fibrillation and valvular heart disease (VHD) is common, and many of these patients have native VHD.(1–3) Both atrial fibrillation and VHD has been associated with an increased risk of thromboembolism and bleeding events.(4–7) Anticoagulation for prevention of thromboembolism in patients with atrial fibrillation has been an area of much research.(8–11) However, randomized controlled trials evaluating oral anticoagulation (vitamin K antagonist (VKA) vs. non-vitamin K antagonist oral anticoagulant (NOAC)) for prevention of thromboembolism in patients with atrial fibrillation have excluded patients with significant VHD.(8–11) Patients with moderate/severe mitral stenosis were excluded in all trials and patients with any other native VHD such as aortic stenosis, aortic regurgitation, or mitral regurgitation were minimally represented.(8–11) Only few post hoc sub-analyses of the existing randomized controlled trials have examined patients with atrial fibrillation and native VHD, and only one included valve specific analyses.(7,12) Consequently, the risks of thromboembolism and bleeding complications in the anticoagulated patients with atrial fibrillation and native VHD are sparsely described, both in patients treated with a VKA and in patients treated with a NOAC.

Assessing the risks of thromboembolism and bleeding complications in anticoagulated patients with atrial fibrillation and different subtypes of native VHD may guide clinicians regarding intensity of clinical follow-up and recognition of high-risk subgroups. Therefore, in a large nationwide cohort study based on data reflecting clinical practice, we aimed to describe the risks of thromboembolism and major bleeding complications in anticoagulated patients with incident atrial fibrillation and native aortic or mitral VHD.

METHODS

*Study design and data sources*

This study was a register-based nationwide cohort study using data from three Danish nationwide registries: i) The Danish Civil Registration System, which holds information on sex, date of birth, vital and emigration status of all persons living in Denmark(13); ii) the National Prescription Registry(14), which contains data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System; iii) the Danish National Patient Registry(15), 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 since 1994. The Danish National Patient Registry also holds information about surgical procedures and clinical investigations coded according to the Danish version of the Nordic NOMESCO Classification of Surgical Procedure provided by the Danish Health Data Agency. Data were linked via a unique personal identification number used across all Danish national registries.

*Study population*

The study population consisted of all Danish citizens (age ≥18) with an incident diagnosis of atrial fibrillation between January 2000 and July 2018. To focus on patients with native VHD, only patients with a diagnosis of aortic stenosis/regurgitation or mitral stenosis/regurgitation who had not undergone any transcatheter or surgical valve intervention before the diagnosis of atrial fibrillation were included (see **eTable 1** in Supplementary for details about the definition of native VHD). Patients with multiple valve diseases may be regarded as a heterogeneous group of patients with a number of combinations of stenosis and regurgitation in the heart valves, and therefore often requires individual clinical assessment and treatment strategies. Since we did not have information on VHD severity, we were not able to accurately categorize these patients in relation to their most important VHD, and we thus excluded these patients. Additionally, only those patients using anticoagulant therapy within 180 days before or 30 days after the diagnosis date of atrial fibrillation were included. A NOAC is not recommended in patients with moderate/severe mitral stenosis and, therefore, we excluded all patients with mitral stenosis who were treated with a NOAC, since we could not estimate the severity of the VHD or obtain information about the clinical rationale for this potentially inappropriate use of NOACs.

Hospital diagnosis date of incident atrial fibrillation was the index date (baseline date) for this study, and patients were followed in the National Patient Registry for the outcomes of interest. Additional comorbidities at baseline were identified using the Danish National Patient Registry and the Danish National Prescription Registry. Ascertainment of baseline medication status was based on medication purchase within 180 days before or 30 days after the diagnosis date of atrial fibrillation. ICD-codes and ATC-codes used to define comorbidities and medical therapies are provided in Supplementary [see **eTable 2** in Supplementary].

*Outcomes*

The primary outcomes were thromboembolism (defined as ischaemic stroke or systemic embolism) and major bleeding (defined as intracranial bleeding, gastrointestinal bleeding, or clinically relevant bleeding located elsewhere; detailed information about the definition of the outcomes is available in **eTable 2** in Supplementary). To have information about the location of the major bleeding, we separately examined the endpoint of intracranial bleeding, gastrointestinal bleeding, and clinically relevant bleeding located elsewhere. All-cause death was also included as an endpoint, because of the fact that in administrative registries some deaths may be due to undiagnosed stroke. Given the severity of the diagnosis of thromboembolism, we only considered events if the patient was admitted to the hospital. Similarly, we were only interested in major bleedings leading to a hospital admission; hence, we did not consider outpatient diagnoses for this outcome. Additionally, we only considered primary diagnoses of thromboembolism, but both primary and secondary diagnoses of major bleeding due to clinical coding practice. Emergency room codes were not included due to a general low positive predictive value(16).

*Statistical analyses*

Baseline characteristics were described separately for each native VHD subtype using means/medians and standard deviation/interquartile range (IQR) for continuous variables, and proportions for categorical variables.

Time-to-event analysis was applied to describe the association between each native VHD and risk of the endpoints. Time at risk was measured from baseline date (date of atrial fibrillation diagnosis) and until an event of thromboembolism/major bleeding, date of death, emigration, or end of study (December 31, 2018), whichever came first.

Separately for each native VHD, cumulative incidence curves for thromboembolism and major bleeding were constructed based on the Aalen-Johansen estimator(17) for competing risk data assuming death as a competing risk. Additionally, crude cumulative incidence curves for the endpoint of all-cause death were constructed. To estimate the absolute risk of all endpoints for each native VHD at 1 year after AF diagnosis, the pseudo-value method was used in order to take into account the competing risks of death, where censored observations (for which the event status is not observed) are replaced with pseudo-observations based upon Aalen-Johansen cumulative incidence estimates. For comparison with other studies, which mainly present incidence rates, the crude event rate for all endpoints in each native VHD subtype were calculated as events per 100 person-years at risk. Additionally, risks and rates were estimated separately for patients treated with a VKA or a NOAC (baseline treatment status).

Statistical analyses were performed using SAS 9.3 (SAS Institute) and Stata version 15 (StataCorp LP).

*Ethical considerations*

The Danish Health Data Agency provided the data for the study. The study was in compliance with the General Data Protection Regulation and, therefore, a part of North Denmark Region’s record of processing activities (project no. 2017-40). No ethical approval is required for studies based on data from administrative Danish registries according to Danish laws.

RESULTS

We identified 10,043 incidentatrial fibrillation patients with native VHD from 2000-2018, of which 5,190 patients had isolated aortic stenosis, 1,788 patients had isolated aortic regurgitation, 327 patients had isolated mitral stenosis, and 2,738 patients had isolated mitral regurgitation [**eFigure 1**]. The median follow-up time for the endpoint of all-cause death was 4.2 years (inter-quartile range (IQR): 1.2 to 6.0).

Baseline patient characteristics according to the native VHD subtype are summarized in **Table 1**.Median age ranged between 74-81 years, and percentage of females ranged between 44.4-71.6%. The mean Charlson Comorbidity Index score ranged between 1.1-1.5, and the mean CHA2DS2-VASc and HAS-BLED scores were similar in all subtypes, approximately 3.8 and 2.5, respectively. A history of thromboembolism was more prevalent in patients with isolated mitral stenosis than in the other subtypes (20.2% vs. 10.3-16.1%), whereas the prevalence of prior major bleeding was relatively similar between all subtypes, except for patients with isolated mitral regurgitation where the prevalence was slightly lower (14.8% vs. 16.2-18.2%). Patients included before 2012 were all treated with a VKA. After the introduction of NOACs, on average 37.2-100.0% were anticoagulated with a VKA, whereas 56.6-62.8% were anticoagulated with a NOAC.

Cumulative incidence curves depicting events according to the native VHD and oral anticoagulant agent demonstrated a steep increase during the first month(s) after AF diagnosis, followed by a steady increase during the following months [**Figure 1** and **Figure 2**].

The absolute risks and rates of all events at 1-year follow-up according to native VHD subtype and oral anticoagulant agent are presented in **Table 2** and **Table 3**. At 1 year after atrial fibrillation diagnosis, the risk of thromboembolism was 4.6% in patients with isolated mitral stenosis taking a VKA, and 2.6% in patients with isolated aortic stenosis taking a VKA or NOAC. For patients with isolated aortic or mitral regurgitation, the risk ranged between 1.5-1.8% in both treatment groups.

For the endpoint of major bleeding, the risk was approximately 5% in patients with isolated aortic stenosis or isolated mitral stenosis treated with a VKA at 1 year after atrial fibrillation diagnosis, and between 3.3-4.0% in patients with isolated aortic or mitral regurgitation. For patients treated with a NOAC, the risk was 3.7% in patients with isolated aortic stenosis at 1 year after atrial fibrillation diagnosis, and approximately 2.5% in patients with isolated aortic or mitral regurgitation. Generally, most major bleeding events were other bleedings than intracranial and gastrointestinal bleedings.

The risk of all-cause death was approximately 19% at 1 year after atrial fibrillation diagnosis in patients with isolated aortic stenosis or mitral stenosis treated with a VKA and 25.1% in patients with isolated aortic stenosis when treated with a NOAC. For patients with isolated aortic or mitral regurgitation, the risk ranged between 11.3-14.9% in both treatment groups.

In general, few events across all endpoints were observed in patients with isolated mitral stenosis.

DISCUSSION

In this large cohort study of anticoagulated patients with incident atrial fibrillation and native VHD using data that reflects clinical practice, our main observations suggest as follows: (i) One year after a diagnosis of atrial fibrillation, anticoagulated patients with different native VHD had dissimilar risk of thromboembolism and bleeding complications, both in patients treated with a VKA and in patients treated with a NOAC. (ii) Specifically, patients with isolated aortic stenosis and patients with isolated mitral stenosis were high-risk subgroups.

*Aortic stenosis*

Aortic stenosis is the most common VHD in the Western countries. The risks of thromboembolism and bleeding complications in anticoagulated patients with atrial fibrillation and native aortic stenosis have only been sparsely described previously. In our study, we observed a 2.6% risk of thromboembolism and a 3.7-5.7% risk of bleeding complications in anticoagulated patients with isolated aortic stenosis at 1 year after atrial fibrillation diagnosis. In an explorative post hoc subanalysis of the ROCKET AF trial,(7) anticoagulated patients with atrial fibrillation and native aortic stenosis (although not isolated aortic stenosis) had a slightly higher thromboembolic rate (4.21 vs. 2.98 (VKA)/3.16 (NOAC) events per 100 person-years) and bleeding rate (7.61 vs. 6.66 (VKA)/4.43 (NOAC) events per 100 person-years) compared to the rates in our study. In the post hoc randomized trial subanalysis, patients with aortic stenosis were identified as a high-risk subgroup regarding thromboembolic and bleeding risk. Another study did not find a higher risk in atrial fibrillation patients with aortic stenosis compared to those without aortic stenosis,(6) but a recent study confirmed the findings of the post hoc analysis.(4)

We observed a 1-year mortality risk of 19.1% and 25.1% in patients with isolated aortic stenosis treated with a VKA and a NOAC, respectively, which was higher than what has been reported in some other studies,(18,19) but similar to the risk reported in a study published recently.(20) In our study, the high cumulative death incidences are likely related to the high median age of 81 years, as well as high CHA2DS2-VASc and Charlson Comorbidity Index scores in these patients together with the fact that the study population consisted of patients with diagnoses of atrial fibrillation and VHD requiring hospital contact.

Patients with aortic stenosis are often older, have many comorbidities, and thus, high CHA2DS2-VASc and HAS-BLED scores, as seen in our study. Therefore, it is possible that the observed risks in our study were primarily influenced by the presence of cardiovascular risk factor, rather than the heart valve disease itself. Irrespective of the causal explanation, this anticoagulated patient group is a high-risk subgroup that needs careful consideration and follow-up regarding bleeding complications and thromboembolic risk.

*Mitral stenosis*

It is generally agreed that mitral stenosis is the subtype of native VHD with the highest risk of thromboembolism, probably related to the low-flow patterns occurring in the left atrium and with a frequent location of the thrombus outside of the left atrial appendage.(21) Patients with mitral stenosis were generally excluded in previous trials testing anticoagulation in patients with atrial fibrillation, as mitral stenosis has been associated with a very high stroke risk in previous studies.(22–25) In our study, the observed high risk of thromboembolism at 1 year after atrial fibrillation diagnosis was expected (4.6%), even though we examined an anticoagulated patient group. The observed rate of thromboembolism in our study was slightly higher than the rates observed in another study (5.26 vs. 2.22-4.19 events per 100 person-years).(26) We observed a 5.2% risk of major bleeding. Mitral stenosis is the only native VHD, where NOACs are contraindicated due to potentially higher risk and different mechanisms of thrombosis, as well as the lack of sufficient data on the efficacy of NOACs in these patients.(21,27,28) No randomized controlled trial has examined the use of anticoagulation, nor specifically NOACs, in patients with native mitral stenosis. A recent explorative observational study of patients with atrial fibrillation and native mitral stenosis demonstrated lower rates of thromboembolism and intracranial haemorrhage in patients treated with a NOAC compared to those treated with a VKA;(26) however, future studies are necessary to confirm these results. Currently, the optimal anticoagulant therapy in patients with rheumatic VHD (rheumatic fever is the main cause of mitral stenosis globally) and atrial fibrillation is being investigated in the INVICTUS-VKA trial,(29) which is expected to complete in 2020.

*Aortic and mitral regurgitation*

In patients with atrial fibrillation, most studies indicate that aortic regurgitation and mitral regurgitation do not independently increase the thromboembolic risk beyond the atrial fibrillation alone and do not act as additional risk factors.(6,7,30–32) In the anticoagulated atrial fibrillation patients with isolated aortic or mitral regurgitation, we observed a ≤1.8% risk of thromboembolism at 1 year after atrial fibrillation diagnosis. In the post hoc subanalysis of the ROCKET AF trial,(7) anticoagulated patients with atrial fibrillation and native aortic or mitral regurgitation had similar thromboembolic rate as in our study (2.01 vs. 1.68-2.00 events per 100 person-years), but slightly higher bleeding rate than in our study (4.86 vs. 2.64-4.37 events per 100 person-years). In the post hoc subanalysis, the rate of major bleeding was higher among anticoagulated atrial fibrillation patients with aortic or mitral regurgitation compared to those without VHD – consistent with the findings of another study.(5) We observed a 2.4-4.0% risk of major bleeding in these subgroups at 1 year after atrial fibrillation diagnosis. Thus, risk of bleeding complications should receive attention in this anticoagulated patient group.

*Clinical implications*

In current guidelines, a NOAC is considered a reasonable alternative to a VKA in patients with atrial fibrillation and aortic stenosis, aortic regurgitation or mitral regurgitation based on post hoc sub-analyses of randomized controlled trials.(27,28) In our study, we aimed to describe the real-world risks of thromboembolism and major bleeding complications in anticoagulated patients with incident atrial fibrillation and different native aortic or mitral valve disease and, therefore, comparison of risks of events in patients treated with a VKA or a NOAC cannot be made based on this study as the study was not designed for this. Additionally, we did not have information about the quality of anticoagulant control (e.g. time in therapeutic range for patients in VKA therapy), which has a major impact on the risk of events.(33) Future trials need to investigate the effectiveness and safety of these anticoagulant agents in patients with atrial fibrillation and different subtypes of native VHD. Furthermore, even though our observations indicate that anticoagulated patients with atrial fibrillation and isolated aortic or mitral stenosis may be particular high-risk subgroups that requires intensive follow-up, we cannot elucidate whether these high risks are caused by the heart valve disease itself or the presence of other risk factors. To make any additional recommendations about the optimal antithrombotic management in these patients, a randomized trial specifically designed to investigate the optimal antithrombotic therapy in these patients is necessary. Nevertheless, our findings give an indication of the risk of events within the different subtypes of VHD and anticoagulant agents in clinical practice.

*Strengths and limitations*

The large sample size, uniquely possible with nationwide registry studies, minimizes the risk of random error. Bias from a selection into the study was likely low, since we investigated a nationwide population cohort of consecutive incident atrial fibrillation patients using administrative data, which also implies virtually no loss to follow-up.

The diagnoses of atrial fibrillation and VHD were based on a hospital contact resulting in a diagnosis of atrial fibrillation and/or VHD and, therefore, the study population may not be representative of all patients with atrial fibrillation and VHD, such as patients only seen in general practice. The diagnosis of atrial fibrillation has previously been validated with a positive predictive value of 93%.(34,35) Similarly, the diagnosis of different types of VHD have previously been validated with a positive predictive value of 96-98%.(36) We did not have access to echocardiographic data as well as individual-level blood pressure measurements, and therefore, we were unable to explore subcategories of the valve lesion, e.g., by severity or degree of hemodynamic influence. The risks of thromboembolism and bleeding may be dependent on whether the VHD is mild or severe, and therefore, the lack of information on this matter is a limitation. Furthermore, since we did not have information on VHD severity, we were not able to accurately categorize these patients in relation to their most important VHD, and we thus excluded patients with multiple valve disease.

In Denmark, every patient presenting with symptoms of a thromboembolism is admitted to and examined in a hospital setting. Hence, the accuracy of our findings depends on proper ICD-10 coding. The diagnosis of ischaemic stroke has been validated and found to have a positive predictive value of 80-90%.(37,38) However, the risk of ischaemic stroke can only be estimated with some uncertainty in our study. Firstly, we included unspecified stroke in the definition of ischaemic stroke, as the majority of such strokes are of ischaemic origin,(38) secondly, we did not include transient ischaemic attacks due to a low positive predictive value in the registries, and thirdly, some patients may experience a fatal thromboembolic event without an admission to the hospital. We were unable to estimate how many patients experienced such a fatal event without simultaneously being given a hospital discharge diagnosis, but this is likely to some extent to have underestimated thromboembolic incidence. Fourthly, the baseline prevalence of previous thromboembolism differed across subgroups. Since the positive predictive value of thromboembolism post-atrial fibrillation diagnosis is likely different depending on whether the patient has had a previous thromboembolic event, for which the subsequent event would be a recurrent event with perhaps a lower positive predictive value, this may contribute to a relative overestimation of thromboembolism among those with previous thromboembolism versus those without such a history.

The diagnosis of intracranial haemorrhage has been validated and found to have a positive predictive value of 88%.(39) No validation studies for the diagnosis of other major bleeding currently exist. However, we examined only diagnoses of major bleeding leading to a hospital admission to ensure that the bleeding was actually major and of clinical relevance. By this approach, major bleedings registered in outpatients were not examined, but some of these bleedings could be clinically relevant.

Lastly, the study was carried out as a nationwide study in the Danish population, which is ethnically homogeneous; thus, future studies are needed to evaluate if our findings hold in more ethnically diverse populations with atrial fibrillation and aortic or mitral VHD.

**Conclusion**

When using data that reflects clinical practice, our observations suggest that one year after a diagnosis of atrial fibrillation, anticoagulated patients with different native VHD had dissimilar risk of thromboembolism and bleeding complications, both in patients treated with a VKA and in patients treated with a NOAC. Specifically, patients with isolated aortic stenosis and patients with isolated mitral stenosis were high-risk subgroups. This observation may guide clinicians regarding intensity of clinical follow-up.

REFERENCES

1. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey J-Y, Schilling RJ, Schmidt J, Zamorano JL. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events--European Registry in Atrial Fibrillation (PREFER in AF). Europace. 2014;16:6–14.

2. Sharma SK, Verma SH. A Clinical Evaluation of Atrial Fibrillation in Rheumatic Heart Disease. J Assoc Physicians India. 2015;63:22–5.

3. Diker E, Aydogdu S, Ozdemir M, Kural T, Polat K, Cehreli S, Erdogan A, Göksel S. Prevalence and predictors of atrial fibrillation in rheumatic valvular heart disease. Am J Cardiol. 1996;77:96–8.

4. 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.

5. Bisson A, Bodin A, Clementy N, Bernard A, Babuty D, Lip GYH, Fauchier L. Stroke, thromboembolism and bleeding in patients with atrial fibrillation according to the EHRA valvular heart disease classification. Int J Cardiol. 2018;260:93–8.

6. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Babuty D, Angoulvant D, Lip GYH, Fauchier L. Prognostic value of CHA2DS2-VASc score in patients with “non-valvular atrial fibrillation” and valvular heart disease: The Loire Valley Atrial Fibrillation Project. Eur Heart J. 2015;36:1822–30.

7. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Lokhnygina Y, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Califf RM, Fox KAA, Patel MR. Native valve disease in patients with non-valvular atrial fibrillation on warfarin or rivaroxaban. Heart. 2016;102:1036–43.

8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.

9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, ROCKET AF Investigators. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011;365:883–91.

10. Granger CB, Alexander JH, McMurray JJ V, Lopes RD, Hylek EM, Hanna M, ARISTOTLE Committee and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.

11. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.

12. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, Clemens A, Reilly PA, Connolly SJ, Yusuf S, Wallentin L. 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;134:589–98.

13. Pedersen CBC. The Danish Civil Registration System. Scand J Public Health. 2011;39:22–5.

14. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011;39:38–41.

15. Lynge E, Sandegaard J, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39:30–3.

16. Lühdorf P, Overvad K, Schmidt EB, Johnsen SP, Bach FW. Predictive value of stroke discharge diagnoses in the Danish National Patient Register. Scand J Public Health. 2017;45:630–6.

17. Gooley T, Leisenring W, Crowley J, Storer B. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999;18:695–706.

18. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, Chambers J, Rosenhek R, Habib G, Lloyd G, Nistri S, Garbi M, Marchetta S, Fattouch K, Coisne A, Montaigne D, Modine T, Davin L, Gach O, Radermecker M, Liu S, Gillam L, Rossi A, Galli E, Ilardi F, Tastet L, Capoulad R, Zilberszac R, Vollema M, Delgado V, Cosyns B, Lafitte S, Bernard A, Pierard LA, Bax JJ, Pibarot P, Oury C. Outcomes of Patients with Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. JAMA Cardiol. 2018;3:1060–8.

19. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, on behalf of the CURRENT AS Registry Investigators. Initial Surgical Versus Conservative Strategies in Patients with Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2015;66:2827–38.

20. Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, Ilton M, Joseph M, Codde J, Playford D. Poor Long-Term Survival in Patients With Moderate Aortic Stenosis. J Am Coll Cardiol. 2019;74:1851–63.

21. Caterina R De, Camm AJ. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis : the concept for a trial. Europace. 2016;18:6–11.

22. Wolf PA, Dawber TR, Thomas HE, William B. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The framingham Study. Neurology. 1978;28:973–8.

23. Rider OJ, Malhotra A, Newton JD. Free Floating Left Atrial Ball Thrombus : A Rare Cause of Stroke. J Stroke Cerebrovasc Dis. 2013;22:238–9.

24. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Br Hear J. 1962;24:349–57.

25. Santos PM, Lopez EB, Barrio EE, Marrupe LH, Valtierra JJ, Gonzalez FP, et al. Massive left atrium thrombus. Int J Cardiovasc Imaging. 2013;30:67.

26. Kim JY, Kim S, Myong J, Kim YR, Kim T, Kim J, Jang S, Oh Y, Lee MY, Rho T. Outcomes of Direct Oral Anticoagulants in Patients With Mitral Stenosis. J Am Coll Cardiol. 2019;73:1123–31.

27. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Riestra A, Ruiz RC, Rodriguez JB. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739–91.

28. Nishimura RA, Otto CM, Bonow R, Carabello B, Erwin J, Fleisher L, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 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;135:1159–95.

29. INVICTUS-VKA. https://clinicaltrials.gov/ct2/show/NCT02832544.

30. De Caterina R, Camm AJ. What is “valvular” atrial fibrillation? A reappraisal. Eur Heart J. 2014;35:3328–35.

31. Erwin JP, Iung B. Current recommendations for anticoagulant therapy in patients with valvular heart disease and atrial fibrillation : the ACC / AHA and ESC / EACTS Guidelines in Harmony … but not Lockstep ! Heart. 2018;104:968–70.

32. Bisson A, Bernard A, Bodin A, Clementy N, Babuty D, Lip GYH, Fauchier L. Stroke and Thromboembolism in Patients With Atrial Fibrillation and Mitral Regurgitation. Circ Arrhythmia Electrophysiol. 2019;12:1–3.

33. White HD, Gruber M, Feyzi J, Kaatz S, Tse H-F, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med. 2007 Mar;167:239–45.

34. 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.

35. 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;46:149–53.

36. 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.

37. 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.

38. Krarup L, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28:150–4.

39. Hald SM, Sloth CK, Hey SM, Madsen C, Nguyen N, Rodríguez LAG, Salman R, Möller S, Poulsen FR, Pottegård A, Gaist D. Intracerebral hemorrhage: Positive predictive value of diagnosis codes in two nationwide danish registries. Clin Epidemiol. 2018;10:941–8.

FIGURE LEGENDS

**Figure 1.** Cumulative incidence of thromboembolism and major bleeding in the VKA-treated population, according to native VHD subtype. AF: Atrial fibrillation, VKA: Vitamin K antagonist.

**Figure 2.** Cumulative incidence of thromboembolism and major bleeding in the NOAC-treated population, according to native VHD subtype. AF: Atrial fibrillation, NOAC: Non-vitamin K antagonist oral anticoagulant.

**Figure 3.** Cumulative incidence of all-cause death in the VKA-treated and NOAC-treated population, according to native VHD subtype. AF: Atrial fibrillation, NOAC: Non-vitamin K antagonist oral anticoagulant, VKA: Vitamin K antagonist.

## Supplementary:

**eTable 1.** Discharge codes used for definition of native valvular heart disease.

**eTable 2**. ICD-codes and ATC-codes used to define comorbidities, medical therapies, and outcomes.

**eFigure 1**. Flowchart of study population.