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Thromboembolic and bleeding outcomes in patients with atrial fibrillation and valvular heart disease

A descriptive nationwide cohort study

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Thromboembolic and bleeding outcomes in patients with atrial fibrillation and valvular heart disease: A descriptive nationwide cohort study

Short title: Outcomes in AF patients with valvular disease

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Conflicts of interest

Professor Lip: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally. Professor Larsen: Investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim. Speaker for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. No fees are received personally. Mr. Nielsen: Speaking fees Boehringer Ingelheim, consulting fees from Bayer, and grant support from BMS/Pfizer. Ms. Melgaard: Grant support from BMS/Pfizer. Other authors: no conflict of interest. All authors have read and approved the submitted manuscript.

Abstract

Aims: The risks of thromboembolism and bleeding in patients with atrial fibrillation (AF) and valvular heart disease (VHD) are sparsely described. We described the risk of events in non-anticoagulated and anticoagulated patients with AF and VHD according to the EHRA classification, EHRA Type 1 and Type 2 VHD, and within subgroups of EHRA Type 1 and Type 2 VHD.

Methods and results: Cohort study of AF patients with coexisting VHD, identified in nationwide Danish registries from 2000-2018. Risk of thromboembolism and bleeding after 1 year of follow-up were calculated in each group. We identified 28,770 incident AF patients with VHD. Not surprisingly, we observed the highest risks of thromboembolism in the non-anticoagulated AF patients with EHRA Type 1 and Type 2 VHD (4.9% vs. 2.6% and 3.2% vs. 1.9%) and the highest risks of bleeding in the anticoagulated AF patients with EHRA Type 1 and Type 2 VHD (6.6% vs. 4.3% and 6.1% vs. 4.9%). However, within the subgroups of AF patients with EHRA Type 1 and Type 2 VHD, we observed a large proportion of non-anticoagulated patients (32.9-49.2%), despite a CHA₂DS₂-VASc score of $2 \leq$ in the majority of these patients (81.9-95.6%).

Conclusions: When using data reflecting contemporary clinical practice, we observed markedly different risks of thromboembolism and bleeding in EHRA Type 1 and Type 2 VHD. Additionally, we observed a potential underuse of oral anticoagulation within the subgroups of AF patients with EHRA Type 1 and Type 2 VHD, underlining need for further attention on this patient group.

Keywords

Atrial fibrillation; valvular heart disease; thromboembolism; bleeding; anticoagulation.

What's already known about this topic:

- Atrial fibrillation (AF) and valvular heart disease (VHD) often coexist. They are independent causes of mortality and morbidity, and both have been associated with risk of thromboembolism and bleeding events.
- However, no study has thoroughly described the risk of thromboembolism and major bleeding according to this newly proposed EHRA classification.
- Specifically, no study has described the risk in subgroups within EHRA Type 1 VHD and EHRA Type 2 VHD.

What does this article add:

- When using data reflecting contemporary clinical practice, we observed markedly different risks of thromboembolism and bleeding in EHRA Type 1 and Type 2 VHD, emphasizing the differences in these two underlying diseases.
- Additionally, we observed a potential underuse of oral anticoagulation within the subgroups of AF patients with EHRA Type 1 and Type 2 VHD, underlining an unmet need for appropriate anticoagulation in this patient group.
- Future studies examining the optimal antithrombotic treatment strategy in each subgroup of EHRA Type 1 VHD and EHRA Type 2 VHD are needed.

Introduction

Atrial fibrillation (AF) and valvular heart disease (VHD) often coexist [1–3]. They are independent causes of mortality and morbidity, and both have been associated with risk of thromboembolism and bleeding events [4–6]. Patients with AF have historically been categorized as ‘valvular AF’ or ‘non-valvular AF’. However, these terms have lacked clear-cut definitions, which challenged physicians and caused confusing terminology in medical research [7–10]. This led to the proposal of a new classification of AF patients with VHD: the ‘Evaluated Heartvalves, Rheumatic or Artificial’ (EHRA) valve classification, categorizing patients into: (i) EHRA Type 1 VHD, which refers to AF patients with ‘VHD needing therapy with a Vitamin K antagonist (VKA)’ and (ii) EHRA Type 2 VHD, which refers to AF patients with ‘VHD needing therapy with a VKA or a non-VKA oral anticoagulant (NOAC)’ [11,12]. EHRA Type 1 VHD comprises AF patients with mitral stenosis (moderate-severe, of rheumatic origin) or a mechanical prosthetic valve replacement with an indisputable high thromboembolic risk. Guidelines generally agree that this group requires lifelong anticoagulation with a VKA. EHRA Type 2 VHD includes AF patients with any other heart valve disease or a bioprosthetic valve replacement [11]. The thromboembolic risk in this heterogeneous group is more uncertain and, thus, antithrombotic treatment recommendations are less consistent.

The EHRA classification has been examined in two previous studies validating the CHA₂DS₂-VASc and HAS-BLED scores in AF patients with VHD [12,13]. However, no study has thoroughly described the risk of thromboembolism and major bleeding according to the newly proposed EHRA classification. Furthermore, EHRA Type 1 VHD and EHRA Type 2 VHD include a variety of valve lesions, which may have different etiologies and, therefore, different prognoses. Yet, no study has described the risk in these subgroups within EHRA Type 1 VHD and EHRA Type 2 VHD. Therefore, the aim of the present study was to describe the risk of thromboembolism and major bleeding in non-anticoagulated and anticoagulated patients with AF and VHD according to the EHRA classification, EHRA Type 1 and Type 2, and within subgroups of EHRA Type 1 and Type 2 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 [14]; ii) the National Prescription Registry [15], 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 [16], 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 AF diagnosis (ICD-10: I48) between January 2000 and July 2018. To focus on AF patients with VHD, only patients with a concomitant diagnosis of VHD either prior to or within 30 days after AF diagnosis were included. Hospital diagnosis date of incident AF was the index date (baseline) for this study. VHD was defined by a diagnosis/procedural code of mechanical prosthetic valve replacement (aortic or mitral/mitro-aortic) or mitral stenosis (categorized as EHRA Type 1 VHD) or a diagnosis/procedural code of mitral regurgitation, aortic stenosis/regurgitation, bioprosthetic aortic valve replacement, bioprosthetic mitral valve replacement, or other valve disease/procedure (tricuspid stenosis/regurgitation, pulmonary valve stenosis/regurgitation, or multiple valve disease) (categorized as EHRA Type 2 VHD) (See **eTable 1** and **eTable 2** in the Online Resources for details on the definition of EHRA Type 1 VHD and EHRA Type 2 VHD). All patients were classified as either EHRA Type 1 VHD or EHRA Type 2 VHD according to diagnostic and procedural information at index date. Patients with both a diagnosis in EHRA Type 1 VHD and in EHRA Type 2 VHD were classified as EHRA Type 1 VHD. We did not have access to echocardiographic data and, therefore, both patients with mild, moderate, and severe VHD were included. As oral anticoagulation with a VKA is recommended in all patients with a mechanical prosthetic valve replacement, we excluded those patients with a mechanical prosthetic valve replacement who were not in oral anticoagulation or were in anticoagulant therapy with a NOAC,

since we could not obtain information about the clinical rationale for this inappropriate anticoagulation status.

Outcomes

The primary outcomes were thromboembolism (defined as ischemic stroke or systemic embolism) and major bleeding (defined as intracranial bleeding, gastrointestinal bleeding, or major clinically relevant bleeding located elsewhere) (Detailed information about the definition of the outcomes is available in **eTable 3** in the Online Resources). Given the severity of the diagnoses of thromboembolism, we only considered events if the patient was admitted to the hospital; hence, we did not consider outpatient diagnoses for this outcome. Additionally, we only considered primary diagnoses of thromboembolism. For the endpoint of major bleeding, both primary and secondary diagnoses in out- and inpatient were considered due to clinical coding practice, and to allow for full clinical insight (i.e. bleeding leading to hospital contact). Emergency room codes were not included due to a general low positive predictive value [17]. All-cause death was included as a secondary outcome to elucidate the mortality risk, which may influence the methodological approach of estimating absolute risk in a diminishing at-risk population.

Statistical analyses

Baseline characteristics were described separately for patients in subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD using means/medians and standard deviation (SD)/interquartile range (IQR) for continuous variables, and proportions for categorical variables.

Time-to-event analysis was applied to describe the association between the EHRA categorization or subgroup of EHRA Type 1 VHD and EHRA Type 2 VHD and the risk of thromboembolism and major bleeding. Time at risk was measured from baseline date and until an event of thromboembolism or major bleeding, date of death, emigration, or end of study (November 30, 2018), whichever came first. Time at risk was measured separately for each event of interest (thromboembolism or major bleeding); thus, patients were followed until the event of interest (or a censoring event, e.g. death) and were allowed to experience a thromboembolic event before the bleeding event, and vice versa.

To depict risk development over time according to subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD, we calculated the cumulative incidence of thromboembolism and major bleeding based on the Aalen-Johansen estimator taking competing risk of death into consideration [18], since this is a group of AF patients with considerable comorbidity and elevated mortality risk. Additionally, cumulative incidence curves for all-cause death were constructed to show the mortality risk over time in each subgroup. The absolute risks of thromboembolism and major bleeding at 1 year after the AF diagnosis were based upon the Aalen-Johansen cumulative incidence estimates. The absolute risks were estimated in each group according to the baseline status of oral anticoagulant therapy. For the non-anticoagulated group, patients were censored if they initiated oral anticoagulant therapy during follow-up. Due to the low number of patients in the non-anticoagulated subgroup with a bioprosthetic mitral valve replacements, a reliable risk estimate will not be obtainable and, therefore, the absolute risks of events were not calculated in this subgroup. Since patients with mitral regurgitation that is related to ischemic heart disease have functional different characteristics compared to those without ischemic heart disease, we performed a subanalysis estimating the risk of events separately for patients with mitral regurgitation with and without coexisting ischemic heart disease (defined as the presence of a previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting). Additionally, we described the baseline characteristics of the two subgroups with mitral regurgitation in a supplemental table. Furthermore, as the study period extended over a long time period (2000-2018), we performed a subanalysis where we split the study period into two time spans, 2000-2009 and 2010-2018, and described the risk of events in EHRA Type 1 VHD and EHRA Type 2 VHD in the two periods. Statistical analyses were performed using SAS 9.3 (SAS Institute) and Stata version 15 (StataCorp LP).

Ethical considerations

This is an observational 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.

Data accessibility

Data for this study, obtained from Danish Health Data Agency, comprise sensitive personal information and due to data protection regulation, data cannot be made available to the public.

Accepted Article

Results

We identified 28,770 incident AF patients with VHD, of which 2,701 patients were categorized as EHRA Type 1 VHD and 26,069 patients were categorized as EHRA Type 2 VHD [Fig. 1 in the Online Resources].

Baseline patient characteristics

Baseline patient characteristics according to subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD are summarized in **Table 1**. Median age ranged from 62 to 76 years among patients with EHRA Type 1 VHD and from 74 to 82 years among patients with EHRA Type 2 VHD. Percentage of females ranged from 24.7% to 66.9% in patients with EHRA Type 1 VHD and from 37.8% to 51.9% in patients with EHRA Type 2 VHD. Prevalence of previous thromboembolism and mean CHA₂DS₂-VASc score were highest in patients with isolated mitral stenosis in EHRA Type 1 VHD and highest in patients with isolated aortic stenosis in EHRA Type 2 VHD. Similarly, the mean HAS-BLED score was highest in patients with isolated mitral stenosis in EHRA Type 1 VHD, but highest in patients with bioprosthetic aortic valve replacement in patients with EHRA Type 2 VHD. Regarding anticoagulation status at baseline, we observed a large proportion of non-anticoagulated patients (32.9-49.2%), despite a CHA₂DS₂-VASc score of 2 or above in the majority of these patients (81.9-95.6%).

Risk of thromboembolism and major bleeding

Both in the non-anticoagulated and anticoagulated patients, cumulative incidence curves depicting thromboembolism and major bleeding according to subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD demonstrated a steep increase during the first month(s) after AF diagnosis, followed by a steady increase during the following months [Fig. 2 and Fig. 3 in the Online Resources]. A similar pattern was observed for the endpoint of all-cause death [Fig. 4 in the Online Resources]. Separately for the non-anticoagulated and anticoagulated patients, risks of thromboembolism and major bleeding after 1 year of follow-up according to EHRA classification and subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD are presented in **Table 2** and **Table 3**. Overall, we observed the highest risks of thromboembolism in the non-anticoagulated AF patients with EHRA Type 1 and Type 2 VHD (4.9% vs. 2.6% and 3.2% vs. 1.9%, respectively) and the highest risks of bleeding in the anticoagulated AF patients with EHRA Type 1 and Type 2 VHD (6.6% vs. 4.3% and 6.1% vs. 4.9%, respectively). For the subgroups, we observed the highest risk of

thromboembolism in non-anticoagulated patients with mitral stenosis, both in the anticoagulated and non-anticoagulated patients. For the endpoint of major bleeding, we observed the highest risk in non-anticoagulated patients with a bioprosthetic aortic valve replacement and in the anticoagulated patients with 'other valve disease/procedure'. Due to the low number of patients in the non-anticoagulated subgroup with a bioprosthetic mitral valve replacement, a reliable risk estimate will not be obtainable and, therefore, the absolute risks of events were not calculated in this subgroup.

Subanalyses

The baseline characteristics of patients with mitral regurgitation and coexisting/no ischemic heart disease are described in **eTable 4** in the Online Resources. Generally, patients with mitral regurgitation and ischemic heart disease were more often males, had a higher prevalence of comorbidities such as diabetes, hypertension, heart failure and peripheral artery disease, and were more often taking antiplatelet therapy. We observed the highest risk of thromboembolisms in the non-anticoagulated patients with ischemic heart disease and the highest risk of major bleeding in the anticoagulated patients with ischemic heart disease [**eTable 5** in the Online Resources].

When splitting the study period into two time spans, we overall observed similar risks of events in the two time spans, except for the non-anticoagulated patients with EHRA Type 1 VHD where the risks of events were considerably higher in the time span 2010-2018 [**eTable 6** in the Online Resources]. Additionally, we observed slightly higher risks of major bleeding in the anticoagulated patients with EHRA Type 2 VHD in the time span 2010-2018 than in the first time span.

Discussion

In this nationwide cohort of AF patients with VHD, we overall observed the highest thromboembolic risks in the non-anticoagulated AF patients with EHRA Type 1 and Type 2 VHD and the highest bleeding risks in the anticoagulated AF patients with EHRA Type 1 and Type 2 VHD, as expected. However, within the subgroups of AF patients with EHRA Type 1 and Type 2 VHD we observed a large proportion of non-anticoagulated patients, despite a CHA₂DS₂-VASc score of 2 or above in the majority of these patients.

The proposal of the EHRA classification was an important step to clarify the definition of VHD in the AF population and to direct clinicians regarding choice of anticoagulant agent in these patients. In our study, we described the risk of thromboembolism and major bleeding in non-anticoagulated and anticoagulated AF patients with EHRA Type 1 VHD and EHRA Type 2 VHD, and in subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD. Our aim was not to compare the risk between the EHRA groups or subgroups, as each group/subgroup includes patients with several different, probably incomparable, problems with the heart valves. We cannot elucidate whether the observed risks are caused by the heart valve disease itself or the presence of other risk factors. However, based on the variations in baseline characteristics, including age, comorbidity and medicine use, together with the existing knowledge on the thromboembolic physiology of the different valve diseases, differences in thromboembolic and major bleeding risk between EHRA Type 1 and EHRA Type 2 VHD, and between the subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD, were expected.

Previously, only few studies have specifically investigated the thromboembolic and major bleeding risks in subgroups of VHD patients with concurrent AF [19–23]. A recent study examined the risk of a composite endpoint of ischemic/hemorrhagic stroke and all-cause mortality in AF patients with different types of VHD [22]. However, the study only included patients from 1998-2010, where the NOACs were not available, and did not specifically examine the endpoint of thromboembolism or major bleeding alone. Therefore, our study extends and specifies the findings of this previous study and adds important clinical insight since the NOACs have been widely adopted into clinical practice for stroke prevention in AF. Since our study period extended over a long time period (2000-2018), we performed a subanalysis where we split the study period into two time spans, 2000-2009 and 2010-2018. For the time span, where the NOACs were available (2010-2018), we generally observed slightly higher risks of major bleeding in the anticoagulated

patients with EHRA Type 2 VHD than in the first time span. However, based on *our* study we cannot make any definitive conclusions regarding this finding, as we did not describe the risk of events according to the anticoagulant agent used; thus, further studies are necessary.

We described the risk of thromboembolism and major bleeding separately for non-anticoagulated and anticoagulated patients. Not surprisingly, we overall observed the highest thromboembolic risks in the non-anticoagulated AF patients with EHRA Type 1 and Type 2 VHD and the highest bleeding risks in the anticoagulated AF patients with EHRA Type 1 and Type 2 VHD. However, these estimates should be interpreted with care as the aim of our study was solely to describe the risk of thromboembolism and bleeding in AF patients with EHRA Type 1 VHD and EHRA Type 2 VHD when using data reflecting contemporary clinical practice and not to compare the non-anticoagulated and anticoagulated patients. Additionally, the proportion of patients in antithrombotic therapy at baseline may not accurately describe the association with outcomes due to the limitations of assessing medication use using purchase data from registries. For example, the baseline antithrombotic medication status was used throughout the follow-up period; thus, adherence to therapy is an important, but unknown, factor. We censored patients in the non-anticoagulated group if they initiated oral anticoagulation during follow-up. However, in the anticoagulated patients we did not have information about the quality of anticoagulant control (e.g. time in therapeutic range for patients in VKA therapy and actual intake of oral anticoagulants), which impact the risk of events [24]. In our study, we observed similar risk of bleeding in the anticoagulated and non-anticoagulated patients of some subgroups and similar risk of thromboembolism in patients with a mechanical prosthetic valve replacement and in patients with EHRA Type 2 VHD despite a lower median age of patients with a mechanical prosthetic valve replacement. As our study was not designed to compare the risk in non-anticoagulated versus the risk in anticoagulated AF patients with VHD or the risk between subgroups, we can only speculate on these observations. Possible differences in baseline characteristics and risk profiles, which influence treatment strategy, are likely explanations for the similar risks.

Clinical implications and future research directions

The observations in our study provide the clinician with an overview of the thromboembolic and bleeding risks in AF patients with VHD in contemporary clinical practice. Moreover, this large study describes the clinical profile and medication status of a nationwide AF population with VHD. Within the subgroups of AF patients with EHRA Type 1 and Type 2 VHD, we observed a

large proportion of non-anticoagulated patients, despite a CHA₂DS₂-VASc score of 2 or above in the majority of these patients. This observation might be explained by methodological limitations of our study (as our aim was not to investigate differences in anticoagulation use), but could also reflect an actual underuse of oral anticoagulation for stroke prevention in AF patients with VHD in clinical practice. A previous study demonstrated that the lack of a clear-cut definition of 'valvular AF' until recently has challenged physicians and caused variable antithrombotic treatment strategy in these patients, in particular with regard to the use of NOACs [10]. The observed potential underuse of oral anticoagulation in AF patients with VHD underline the need for further attention on this patient group, both in clinical practice and in research. Future studies examining the optimal antithrombotic management in each subgroup of EHRA Type 1 VHD and EHRA Type 2 VHD are needed. Several studies have examined the effectiveness and safety of NOAC versus warfarin in AF patients with VHD, primarily in patients with EHRA Type 2 VHD[25–32]. Meta-analyses of post-hoc analyses of previous randomized trials examining NOAC versus warfarin in AF patients with VHD showed that when pooling the results there was a reduced risk of thromboembolism in the NOAC group and no difference in the risk of major bleeding[33–36]. However, in several comparative analyses based on real-world data, the benefits of NOAC compared to warfarin were inconsistent[25–28,32]. Until more evidence regarding the antithrombotic management of this population is available, clinicians are encouraged to use the EHRA classification and international guideline recommendations for guidance regarding stroke prevention in AF patients with VHD [11].

Our observations indicate that anticoagulated patients with AF and isolated mitral stenosis may be a particular high-risk subgroup that requires intensive follow-up. In another recent study from our group, we have also made this observation [37]. However, a randomized trial specifically designed to investigate the optimal antithrombotic therapy regime in patients with AF and mitral stenosis is necessary to make any additional recommendations about the optimal antithrombotic management of this subgroup of AF patients with VHD. In Denmark, the majority of the patients with mitral stenosis have non-rheumatic mitral stenosis (70% in our study). This influences the generalizability of our observations in this subgroup to other populations, where rheumatic disease is the dominating cause of mitral stenosis. Additionally, we included all patients with a diagnosis of mitral stenosis regardless of the severity of the valve disease and the baseline anticoagulant therapy. This could also influence the generalizability of our observations if we primarily included patients with very mild or very severe mitral stenosis.

We did not examine individual risk factors of thromboembolism and major bleeding in AF patients with different subtypes of VHD, as this analysis was outside the scope of our study; thus, we encourage future studies to look into this matter.

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 AF patients using administrative data, which also implies virtually no loss to follow-up.

The diagnoses of AF and VHD were based on a hospital contact resulting in a diagnosis of AF and/or VHD and, therefore, the study population may not be representative of all patients with AF and VHD, such as AF patients only seen in general practice. Nevertheless, the diagnosis of AF has previously been validated with a positive predictive value of 93% [38,39]. Similarly, the diagnosis of different types of VHD have previously been validated with a positive predictive value of 96-98%, and VHD is generally not diagnosed outside hospitals [40]. We did not have access to echocardiographic data and for that reason, we could not report information about the severity of the VHD. The risk 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.

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 ischemic stroke has been validated and found to have a positive predictive value of 80-90% [41,42]. However, the risk of ischemic stroke can only be estimated with some uncertainty in our study. Firstly, we included unspecified stroke in the definition of ischemic stroke, as the majority of such strokes are of ischemic origin [42]. Secondly, we did not include transient ischemic attacks due to a low positive predictive value in the registries, and thirdly, some patients may experience a fatal stroke and are never admitted to the hospital. Our definition of major bleeding only included bleedings leading to a hospital contact, however, some bleedings do not lead to a hospital contact and, therefore, these, probably minor, bleedings were not included in the endpoint.

According to guidelines, patients with moderate/severe mitral stenosis are recommended anticoagulation. However, in our study, some patients with mitral stenosis were not in anticoagulant therapy. This non-anticoagulated group could represent patients with mild mitral

stenosis or reflect the limitations when assessing the baseline medication status using administrative registries. Unfortunately, we could not estimate the severity of the VHD or obtain information about the clinical rationale for the anticoagulation status.

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 AF populations.

Conclusions

When using data reflecting contemporary clinical practice, we observed markedly different risks of thromboembolism in EHRA Type 1 and Type 2 VHD, and likewise differences in bleeding risk, emphasizing the differences in these two underlying diseases. Additionally, we observed a potential underuse of oral anticoagulation within the subgroups of AF patients with EHRA Type 1 and Type 2 VHD, underlining an unmet need for appropriate anticoagulation in this patient group. Future studies examining the optimal antithrombotic treatment strategy in each subgroup of EHRA Type 1 VHD and EHRA Type 2 VHD are needed.

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Table 1. Baseline characteristics of patients according to subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD.

<i>EHRA categorization</i>	EHRA Type 1 VHD			EHRA Type 2 VHD					
<i>Valve lesion:</i>	Isolated mitral stenosis	Mechanical prosthetic aortic valve replacement	Mechanical prosthetic mitral or mitro-aortic valve replacement	Isolated aortic stenosis	Isolated aortic regurgitation	Isolated mitral regurgitation	Bioprosthetic aortic valve replacement	Bioprosthetic mitral valve replacement	Other valve disease/procedure‡
N	789	1,475	437	10,279	3,343	6,016	4,384	362	1,685
Age in years, median (IQR)	76 (67-83)	64 (57-71)	62 (55-69)	82 (76-88)	76 (68-82)	74 (66-81)	77 (72-82)	74 (69-80)	76 (67-83)
Female sex	66.9 (528)	24.7 (365)	41.2 (180)	51.9 (5,337)	46.9 (1,568)	46.9 (2,823)	37.8 (1,658)	39.5 (143)	50.6 (852)
Comorbidities									
Diabetes mellitus	13.8 (109)	11.7 (173)	8.0 (35)	14.1 (1,445)	6.9 (232)	9.1 (550)	16.4 (721)	11.3 (41)	10.4 (175)
Hypertension	40.1 (316)	44.2 (652)	26.8 (117)	52.0 (5,348)	51.3 (1,716)	39.0 (2,349)	59.1 (2,593)	42.5 (154)	45.8 (771)
Heart failure	39.9 (315)	28.8 (425)	40.7 (178)	32.4 (3,326)	27.5 (919)	35.9 (2,161)	32.5 (1,426)	39.8 (144)	34.6 (583)
Peripheral vascular disease	13.6 (107)	21.8 (322)	5.7 (25)	14.3 (1,467)	18.0 (601)	9.6 (577)	16.2 (711)	9.9 (36)	12.2 (206)
History of myocardial infarction	14.1 (111)	12.2 (180)	15.3 (67)	18.1 (1,865)	14.3 (479)	17.5 (1,052)	18.2 (800)	24.3 (88)	16.4 (276)
Pacemaker or implantable cardioverter defibrillator	6.0 (47)	9.6 (141)	12.1 (53)	5.9 (610)	6.2 (208)	5.6 (335)	9.1 (398)	11.3 (41)	6.7 (113)
Hyperlipidemia/hypercholesterolemia	17.0 (134)	22.6 (333)	16.9 (74)	16.6 (1,709)	15.8 (527)	16.1 (971)	34.7 (1,522)	23.8 (86)	18.2 (306)
Chronic kidney disease	9.9 (78)	8.6 (127)	9.2 (40)	9.2 (943)	8.0 (267)	7.1 (430)	12.2 (533)	19.9 (72)	8.5 (144)
History of cancer	13.8 (109)	10.2 (151)	14.4 (63)	19.5 (2,003)	18.3 (611)	14.7 (886)	16.7 (733)	19.6 (71)	15.4 (260)
Chronic obstructive pulmonary disease	22.3 (176)	13.4 (198)	16.5 (72)	18.4 (1,891)	17.4 (583)	14.9 (895)	17.8 (780)	14.6 (53)	16.5 (278)
History of thromboembolism	17.7 (140)	11.3 (167)	12.4 (54)	16.1 (1,651)	13.8 (462)	10.0 (601)	14.1 (619)	14.4 (52)	10.4 (175)
History of bleeding	19.3 (152)	18.4 (271)	21.3 (93)	19.1 (1,962)	18.4 (614)	15.9 (957)	20.6 (903)	20.2 (73)	16.9 (285)

CHA ₂ DS ₂ -VASc score (mean ±SD)	3.8 (1.9)	2.5 (1.8)	2.6 (1.8)	4.1 (1.6)	3.5 (1.8)	3.3 (1.9)	3.9 (1.6)	3.6 (1.7)	3.5 (1.8)
HAS-BLED score (mean ±SD)	2.4 (1.3)	1.9 (1.3)	1.8 (1.2)	2.6 (1.1)	2.4 (1.2)	2.2 (1.2)	2.9 (1.1)	2.7 (1.1)	2.4 (1.2)
Charlson comorbidity index score (mean ±SD)	1.5 (1.7)	1.2 (1.6)	1.3 (1.7)	1.6 (1.8)	1.4 (1.8)	1.2 (1.7)	1.6 (1.8)	1.6 (2.0)	1.2 (1.7)
Time since VHD diagnosis:									
Within 6 months before index date	36.8 (290)	33.1 (488)	30.9 (135)	41.5 (4,261)	34.1 (1,139)	42.3 (2,543)	36.4 (1,597)	44.2 (160)	34.9 (588)
Median, days (IQR)	526 (1-2,106)	881 (21-3,231)	1,295 (72-3,305)	315 (0-1,425)	702 (0-2,350)	283 (0-1,894)	622 (87-2,112)	295 (44-1,680)	901 (6-2,453)
Comedication[†]									
Beta-blockers	55.8 (440)	66.5 (981)	65.4 (286)	58.8 (6,041)	62.8 (2,098)	62.4 (3,751)	66.2 (2,904)	60.2 (218)	60.8 (1,025)
ARB/ACE-inhibitors	43.0 (339)	52.0 (767)	49.7 (217)	46.8 (4,807)	55.4 (1,851)	54.9 (3,302)	54.4 (2,383)	53.6 (194)	50.8 (856)
Calcium channel blockers	25.0 (197)	27.8 (410)	17.8 (78)	35.2 (3,614)	32.9 (1,100)	25.3 (1,521)	32.8 (1,440)	19.1 (69)	29.4 (496)
Amiodarone	7.4 (58)	21.2 (312)	17.8 (78)	6.7 (692)	5.7 (189)	8.9 (533)	22.1 (968)	17.1 (62)	5.5 (92)
Digoxin	38.4 (303)	15.9 (234)	27.5 (120)	31.5 (3,239)	24.9 (831)	34.8 (2,093)	15.9 (699)	17.7 (64)	30.1 (507)
Non-loop diuretics	37.3 (294)	38.0 (561)	35.9 (157)	44.7 (4,596)	40.8 (1,364)	38.2 (2,298)	43.8 (1,918)	37.8 (137)	43.6 (735)
Loop diuretics	61.2 (483)	45.1 (665)	57.9 (253)	57.6 (5,917)	41.8 (1,399)	52.7 (3,172)	58.8 (2,579)	62.2 (225)	54.2 (913)
NSAIDs	16.1 (127)	18.1 (267)	13.0 (57)	14.9 (1,533)	16.0 (536)	14.7 (886)	16.6 (728)	11.6 (42)	16.0 (270)
Statins	38.3 (302)	45.3 (668)	33.9 (148)	39.6 (4,068)	35.9 (1,201)	33.4 (2,010)	60.6 (2,655)	42.5 (154)	36.0 (607)
Antithrombotic therapy: §									
Aspirin	46.1 (364)	38.1 (562)	29.5 (129)	50.8 (5,218)	45.8 (1,530)	46.4 (2,789)	67.1 (2,943)	51.1 (185)	49.2 (829)
Other antiplatelet	8.7 (69)	3.8 (56)	3.0 (13)	13.0 (1,341)	9.4 (314)	7.6 (458)	16.1 (705)	9.4 (34)	8.8 (148)
No oral anticoagulant therapy	37.5 (296)	-	-	49.2 (5,060)	45.7 (1,527)	40.7 (2,448)	34.9 (1,529)	32.9 (119)	45.9 (773)
CHA ₂ DS ₂ -VASc score = 0	3.4 (10)	-	-	1.0 (51)	6.4 (98)	6.5 (158)	1.1 (17)	- ¶	4.8 (37)
CHA ₂ DS ₂ -VASc score = 1	6.8 (20)	-	-	3.4 (174)	9.4 (144)	11.6 (285)	5.1 (78)	- ¶	9.2 (71)
CHA ₂ DS ₂ -VASc score = 2+	89.9 (266)	-	-	95.6 (4,835)	84.2 (1,285)	81.9 (2,005)	93.8 (1,434)	- ¶	86.0 (665)

Vitamin K antagonists/VKA	54.0 (426)	100.0 (1,475)	100.0 (437)	33.1 (3,398)	34.3 (1,148)	44.5 (2,676)	48.0 (2,103)	53.0 (192)	42.9 (723)
Non-vitamin K antagonist oral anticoagulants/NOAC	8.5 (67)	0.0 (0)	0.0 (0)	17.7 (1,821)	20.0 (668)	14.8 (892)	17.2 (752)	14.1 (51)	11.2 (189)
Oral anticoagulant therapy (patients included in 2016-2018):									
No oral anticoagulant therapy	25.0 (24)	-	-	29.2 (563)	25.8 (170)	25.6 (230)	29.7 (278)	25.8 (25)	32.0 (62)
Vitamin K antagonists/VKA	39.6 (38)	100.0 (195)	100.0 (47)	17.6 (339)	16.8 (111)	19.8 (178)	19.6 (183)	42.3 (41)	17.5 (34)
Non-vitamin K antagonist oral anticoagulants/NOAC	35.4 (34)	0.0 (0)	0.0 (0)	53.2 (1,025)	57.4 (378)	54.7 (492)	50.7 (475)	32.0 (31)	50.5 (98)

All numbers are in % with number of patients in brackets, unless otherwise stated.

Abbreviations: ACE: Angiotensin converting enzyme, ARB: Angiotensin II receptor blocker, CHA₂DS₂-VASc: Congestive heart failure or left ventricular disease, hypertension, age≥75, diabetes, stroke, vascular disease, age>65, female sex, EHRA: Evaluated Heartvalves, Rheumatic or Artificial valve classification, HASBLED: Hypertension, age>65, stroke, prior bleeding, labile INR, liver or kidney disease, medication predisposing bleeding or alcohol use, IQR: Interquartile range, NSAID: Non-steroidal anti-inflammatory drug, SD: Standard deviation, VHD: Valvular heart disease.

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

‡Patients with tricuspid stenosis/regurgitation, pulmonary valve stenosis/regurgitation, or multiple valve disease.

§Antithrombotic therapy status at baseline, based on information from the entire study period (2000-2018).

¶Exact number not allowed to be shown due to General Data Protection Regulations of The Danish Health Data Agency.

Table 2. Absolute risk of thromboembolism and major bleeding at 1 year after AF diagnosis according to EHRA classification and anticoagulation status at baseline.

<i>EHRA classification</i> (number of patients)	EHRA Type 1 VHD		EHRA Type 2 VHD	
	No OAC therapy (296)	OAC therapy (2,405)	No OAC therapy (11,456)	OAC therapy (14,613)
Absolute risk at 1 year of follow-up[†], % (number of events)				
Thromboembolic event	4.9 (13)	2.6 (63)	3.2 (333)	1.9 (277)
Major bleeding event [‡]	4.3 (11)	6.6 (158)	4.9 (498)	6.1 (884)
Abbreviations: EHRA classification: Evaluated Heartvalves, Rheumatic or Artificial valve classification, OAC: Oral anticoagulation, VHD: Valvular heart disease.				
[†] Calculated using the Aalen-Johansen estimator taking competing risk of death into consideration.				
[‡] Defined as intracranial bleeding, gastrointestinal bleeding, or major clinically relevant bleeding located elsewhere.				

Table 3. Absolute risk of thromboembolism and major bleeding at 1 year after AF diagnosis according to subgroups of EHRA Type 1 VHD and EHRA Type 2 VHD and anticoagulation status at baseline.

<i>EHRA categorization</i>	EHRA Type 1 VHD			EHRA Type 2 VHD					
	Isolated mitral stenosis	Mechanical prosthetic aortic valve replacement	Mechanical prosthetic mitral or mitro-aortic valve replacement	Isolated aortic stenosis	Isolated aortic regurgitation	Isolated mitral regurgitation	Bioprosthetic aortic valve replacement	Bioprosthetic mitral valve replacement§	Other valve disease¶
<i>Valve lesion:</i>									
Absolute risk at 1 year of follow-up†, % (number of events)									
<u>No OAC therapy</u> (number of patients)	(296)	-	-	(5,060)	(1,527)	(2,448)	(1,529)	(119)	(773)
Thromboembolic event	4.9 (13)	-	-	3.7 (169)	3.1 (43)	3.0 (67)	2.2 (29)	-	3.2 (22)
Major bleeding event‡	4.3 (11)	-	-	4.9 (226)	3.7 (51)	4.9 (105)	5.8 (77)	-	4.9 (34)
<u>OAC therapy</u> (number of patients)	(493)	(1,475)	(437)	(5,219)	(1,816)	(3,568)	(2,855)	(243)	(912)
Thromboembolic event	4.7 (23)	1.8 (26)	3.2 (14)	2.6 (135)	2.0 (36)	1.5 (53)	1.2 (34)	2.1 (5)	1.5 (14)
Major bleeding event‡	6.6 (32)	6.5 (96)	6.9 (30)	7.2 (372)	5.3 (95)	4.5 (161)	5.7 (162)	7.5 (18)	8.4 (76)

Abbreviations: EHRA classification: Evaluated Heartvalves, Rheumatic or Artificial valve classification, OAC: Oral anticoagulation, VHD: Valvular heart disease.

†Calculated using the Aalen-Johansen estimator taking competing risk of death into consideration.

‡Defined as intracranial bleeding, gastrointestinal bleeding, or major clinically relevant bleeding located elsewhere.

§Due to the low number of patients in the non-anticoagulated subgroup with a bioprosthetic mitral valve replacement, a reliable risk estimate will not be obtainable and, therefore, the absolute risks of events were not calculated in this subgroup.

¶Patients with tricuspid stenosis/regurgitation, pulmonary valve stenosis/regurgitation, or multiple valve disease.