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Dabigatran and The Risk of Staphylococcus Aureus Bacteremia

- A Nationwide Cohort Study

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Summary:

Treatment with dabigatran, compared with rivaroxaban and apixaban, was associated with a significantly lower incidence rate of *Staphylococcus aureus* bacteremia. This finding may have important implications for evolvement of prevention and treatment strategies for *Staphylococcus aureus* bacteremia and warrant further investigation.

Abstract

Background: Treatment with dabigatran, an oral direct thrombin inhibitor, reduces the virulence of *Staphylococcus aureus* in *in vitro* and *in vivo* models. However, it remains to be determined whether dabigatran reduces the risk of *S. aureus* infections in humans. We investigated the incidence rate of *Staphylococcus aureus* bacteremia (SAB) in patients with atrial fibrillation treated with the direct thrombin inhibitor, dabigatran, compared with patients treated with the factor Xa-inhibitors, rivaroxaban, apixaban, and edoxaban.

Methods: In this observational cohort study, 112,537 patients with atrial fibrillation who initiated treatment with direct oral anticoagulants (August 2011-December 2017) were identified from Danish nationwide registries. The incidence rates of SAB in patients treated with dabigatran versus patients treated with the factor Xa-inhibitors were examined by multivariable Cox regression accounting for time-dynamic changes of exposure status during follow-up.

Results: A total of 112,537 patients were included. During a median follow-up of 2.0 years, 186 patients in the dabigatran group and 356 patients in the factor Xa-inhibitor group were admitted with SAB. The crude incidence rate of SAB was lower in the dabigatran group compared with the factor Xa-inhibitor group (22.8 [95%CI,19.7-26.3] and 33.8 [95%CI,30.5-37.6] events per 10.000 person-years, respectively). In adjusted analyses, dabigatran was associated with a significantly lower incidence rate of SAB compared with factor Xa-inhibitors (incidence rate ratio 0.76 [95%CI,0.63-0.93]).

Conclusions: Treatment with dabigatran was associated with a significantly lower incidence rate of SAB compared with treatment with factor Xa-inhibitors.

Key words:

S. aureus; dabigatran; epidemiology.

Introduction

Staphylococcus aureus (*S. aureus*) is a leading cause of bacteremia and infective endocarditis (IE).[1] A common feature of this pathogen is its coagulase activity, which differentiates *S. aureus* from the less virulent coagulase-negative staphylococci. Its ability to activate the human coagulation system is explained by the secretion of two coagulases, staphylocoagulase and von Willebrand factor-binding protein, which bind to prothrombin to form the enzymatically active staphylothrombin complex.[2,3] This complex converts fibrinogen into fibrin strands,[2] which may not only aid in the resilience of *S. aureus* to antibiotics and contribute to less intravascular and localized immune clearance of this pathogen, but also facilitate platelet aggregation,[4,5] a step considered crucial in the induction and progression of IE.[6–9]

Treatment with anticoagulants, including heparins, vitamin K antagonists, and factor Xa-inhibitors, does not alter the function of staphylothrombin as the formation of this complex bypasses the coagulation cascade and its physiological regulation.[2,10] However, dabigatran, an oral direct thrombin inhibitor mainly used for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation inhibits staphylothrombin and thus the formation of fibrin by binding competitively to the active site of thrombin.[11] Although dabigatran has recently been shown to reduce the virulence of *S. aureus* in *in vitro* and *in vivo* animal models,[4,12,13] it remains to be determined whether treatment with dabigatran reduces the risk of *S. aureus* bacteremia (SAB) in humans.[14] Such knowledge is of great importance as it may add further to the understanding of the virulence of *S. aureus* and ultimately contribute to the evolvement of prevention and treatment strategies for SAB. This gap in knowledge prompted us to conduct a Danish nationwide retrospective cohort study to examine the incidence rate of SAB in patients with atrial fibrillation treated with the direct thrombin inhibitor, dabigatran, compared with patients treated with the factor Xa-inhibitors,

rivaroxaban, apixaban, and edoxaban. We hypothesized that dabigatran was associated with a lower incidence rate of SAB as compared with factor Xa-inhibitors.

Methods

Data sources

All residents in Denmark are assigned a unique and permanent civil registration number allowing accurate linkage of nationwide administrative registries at an individual level over time. For this study, data from the nationwide administrative registries, The Danish National Patient Registry, the Danish National Prescription Registry, and the Danish Civil Registration System were linked with the Danish Staphylococcal Bacteremia Database, which contains clinical data on more than 95% of all positive *S. aureus* isolates identified by the Departments of Clinical Microbiology in Denmark.[18] The Danish registries are validated and of high quality and have been described in detail previously.[15–18]

Study population

All Danish residents aged between 30 and 100 years with a first-time redeemed prescription of a direct oral anticoagulant (DOAC), i.e. dabigatran, rivaroxaban, apixaban, edoxaban between August 22, 2011 and December 30, 2017 were identified. Patients were included in the study if they received anticoagulation for atrial fibrillation, defined as: (1) a discharge or outpatient diagnosis code of atrial fibrillation and no registered diagnosis code of deep vein thrombosis or pulmonary embolism in the 6 months prior to inclusion, or (2) no registered diagnosis code of deep vein thrombosis or pulmonary embolism any time prior to inclusion. This definition was applied to ensure that patients who were diagnosed with atrial fibrillation and initiated oral anticoagulation therapy by

their general practitioner without a hospital contact were included. Patients were excluded if they had undergone hip or knee replacement in the 8 weeks prior to inclusion (Figure 1). The study population was restricted to patients with atrial fibrillation receiving DOAC to ensure a homogeneous population. The inclusion date was defined as the date of the claimed prescription of a DOAC.

Dabigatran and factor Xa-inhibitors

Exposure to dabigatran and factor Xa-inhibitors (i.e. rivaroxaban, apixaban, and edoxaban) was determined continuously for each individual during follow-up using an algorithm based on claimed prescriptions, taking date of claimed prescriptions, dosage and packing size into account, as described previously.[19,20] Patients could change exposure status, i.e. discontinue or switch treatment, during follow-up according to claimed prescriptions. To ensure that patients were only considered at risk when exposed to the respective drug, exposure status was included as a time-dependent covariate in the analyses.

Covariates

Comorbidity was obtained using in-hospital and outpatient diagnoses any time prior to inclusion (Appendix Table 1 for ICD codes). Patients with diabetes and hypertension were identified using claimed drug prescriptions as described previously (Appendix Table 2 for ATC codes).[21,22] Surgical procedures were assessed prior to inclusion (Appendix Table 1 for NCSP codes).

Outcomes

The primary outcome was SAB. The Danish Staphylococcal Bacteremia Database contains clinical data on more than 95% of all positive *S. aureus* isolates identified by the Departments of Clinical Microbiology in Denmark.[18] SAB complicated by development of IE was a secondary outcome and defined as a hospital discharge diagnosis of IE (ICD-10 codes I33, I38, I398) within 3 months after admission for SAB.[23] The diagnosis of IE in the Danish National Patient Registry has previously been validated with a positive predictive value of 90% in patients with a length of hospital stay of at least 14 days.[24] In Denmark, all patients with IE are admitted for at least 14 days. Consequently, patients with a diagnosis of IE and a length of hospital stay of <14 days were not considered as having IE, unless they died during admission. Patients were followed from inclusion (i.e. the date of the claimed prescription of a DOAC) until occurrence of the outcome of interest, death, emigration, or end of the study (December 31, 2017), whichever came first.

Statistical analysis

Baseline characteristics were reported as frequencies with percentages or medians with 25^{th}-75^{th} percentiles. Crude incidence rates were calculated as number of events per 10,000 person-years. Cox regression models with time-dependent covariates were used to estimate incidence rate ratios (IRR) with 95% confidence intervals (CI). Drug exposure, diabetes, chronic kidney disease, presence of a cardiac implantable device and heart valve prosthesis were included as time-dependent covariates, with information updated daily during follow-up. Drug exposure status was included as a time-dependent covariate in the models to account for shift or discontinuation of treatment during follow-up. The models were adjusted for age (categorical variable: 30-66, 66-75, 76-80, 81-100), sex, a history of SAB and IE due to any microorganism, diabetes, chronic kidney disease, congenital heart disease, presence of a cardiac implantable device and heart valve prosthesis. Factor Xa-inhibitors

served as the reference group in the analysis comparing dabigatran and factor Xa-inhibitors. In the analysis comparing each of the DOAC, rivaroxaban served as the reference group. Only the first event was considered in patients experiencing multiple events. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA). The level of statistical significance was set at 5%. There were no missing data for any of the covariates or outcomes.

Ethics

This study was approved by the Danish Data Protection Agency (No. 2007-58-0015; internal reference: *GEH-2014-011,* I-Suite no. 02720). In Denmark, ethical approval is not required for register-based studies in which individuals cannot be identified. Due to the Danish Act on Processing of Personal Data, we cannot report any number less than four observations.

Results

From August 22, 2011 to December 30, 2017, 152,045 patients redeemed a first-time prescription of a DOAC. After exclusion criteria were applied, 112,537 patients comprised the study population. A flow-chart of the study population selection process is presented in Figure 1. The median age of the study population was 73 years (25^{th}-75^{th} percentile 65-81) and 54.8% were men. Baseline characteristics according to the initiated DOAC drug at inclusion are summarized in Table 1. Patients initiating dabigatran were younger, were more often males, and had a lower prevalence of comorbidities compared with patients initiating factor Xa-inhibitors.

S. aureus bacteremia

The median follow-up was 2.0 years (25^{th}-75^{th} percentile 0.8-3.6 years). Total patient-years of follow-up were 81,709 and 105,180 years in the Dabigatran and factor Xa-inhibitor group, respectively. During follow-up, 186 patients in the dabigatran group and 356 patients in the factor Xa-inhibitor group were admitted with SAB. The crude incidence rates of bacteremia were 22.8 (95%CI,19.7-26.3) and 33.8 (95%CI,30.5-37.6) events per 10.000 person-years in the dabigatran and factor Xa-inhibitor group, respectively (Figure 2). In the rivaroxaban and apixaban group, the crude incidence rates of bacteremia were 37.1 (95%CI,32.3-42.7) and 30.7 (95%CI,26.2-35.9), events per 10.000 person-years, respectively. In the edoxaban group, less than 4 patients were admitted with SAB. In Cox regression analysis, treatment with dabigatran was associated with a significantly lower incidence rate of bacteremia compared with treatment with factor Xa-inhibitors (unadjusted IRR 0.64 [95%CI,0.53-0.77], adjusted IRR 0.76 [95%CI,0.63-0.93]). Likewise, treatment with dabigatran, but not apixaban, was associated with a significantly lower incidence rate of bacteremia compared with treatment with rivaroxaban (adjusted IRR 0.68 [95%CI,0.55-0.84] and 0.87 [95%CI,0.73-1.10], respectively).

S. aureus IE

During follow-up, 20 patients in the dabigatran group and 36 patients in the factor Xa-inhibitor group were admitted with *S. aureus* IE. The crude incidence rates of IE were 2.4 (95%CI,1.6-3.8) and 3.4 (95%CI,2.5-4.7) events per 10.000 person-years in the dabigatran and factor Xa-inhibitor group, respectively (Figure 2). In the rivaroxaban and apixaban group, the crude incidence rates of IE were 3.7 (95%CI,2.4-5.8) and 3.1 (95%CI,1.9-5.1) events per 10.000 person-years, respectively. In the edoxaban group, less than 4 patients were admitted with IE. In Cox regression analysis, treatment with dabigatran was not associated with a significantly different incidence rate of IE compared with

treatment with factor Xa-inhibitors (unadjusted IRR 0.74 [95%CI,0.42-1.32], adjusted IRR 0.79 [95%CI,0.44-1.40]). Treatment with dabigatran and apixaban was not associated with a significantly different incidence rate of IE compared with treatment with rivaroxaban (adjusted IRR 0.70 [95%CI,0.37-1.32] and 0.88 [95%CI,0.50-1.61], respectively).

Sensitivity analysis

A number of sensitivity analyses were performed to test the robustness of our findings: 1) The inclusion period was restricted to January 1, 2013 and December 30, 2017 to ensure that the majority of DOAC agents were available at the time of inclusion (dabigatran was approved in 2011, rivaroxaban and apixaban in 2012, and edoxaban in 2016). There was a trend towards a lower incidence rate of bacteremia with dabigatran compared with factor Xa-inhibitors (adjusted IRR 0.80 [95%CI,0.64-1.01]). 2) The study population was restricted to anticoagulant-naïve AF patients initiating DOAC, i.e. patients who did not redeem any prescription of a vitamin K antagonist oral anticoagulants in the 6 months prior to inclusion. In line with the main finding, this analysis also demonstrated that dabigatran was significantly associated with a lower incidence rate of bacteremia (adjusted IRR 0.77 [95%CI,0.61-0.97]), as compared with factor Xa-inhibitors. 3) The study population was extended to all patients who redeemed a prescription of a DOAC irrespective of the indication (i.e. including patients with a diagnosis of deep vein thrombosis or pulmonary embolism and patients who underwent hip or knee replacement in the 8 weeks prior to inclusion). As in the main analysis, dabigatran was associated with a significantly lower incidence rate of bacteremia (adjusted IRR 0.75 [95%CI,0.62-0.90]) compared with factor Xa-inhibitors. 4) The study population was restricted to patients without a history of SAB. In line with the main finding, this analysis demonstrated that dabigatran was significantly associated with a lower incidence rate of bacteremia (adjusted IRR 0.76 [95%CI,0.62-0.92]) compared with factor Xa-inhibitors. 5) The study population was restricted to patients who did not initiate edoxaban. As in the main analysis, dabigatran was

significantly associated with a lower incidence rate of bacteremia (adjusted IRR 0.76 [95%CI,0.63-0.92]) compared with factor Xa-inhibitors.

The 2-year follow-up period began at day of inclusion and patients were followed until the occurrence of outcome, death, emigration, shift or discontinuation of initiated treatment, or 31 December 2016

Discussion

In this nationwide cohort study, we examined the incidence rate of SAB in patients with atrial fibrillation treated with the direct thrombin inhibitor, dabigatran, compared with patients treated with the factor Xa-inhibitors, rivaroxaban, apixaban, and edoxaban. The major finding of this study was that treatment with dabigatran, compared with treatment with factor Xa-inhibitors, was associated with a significantly lower incidence rate of SAB.

Mounting evidence suggests that the ability of dabigatran to inhibit the coagulase activity of *S. aureus* may reduce its virulence in *in vitro* and *in vivo* animal models. Recently, treatment with dabigatran was shown to enhance leukocyte activation and reduce bacterial survival *in vitro*.[4] In a mouse abscess model, dabigatran was associated with reduced abscess size compared with placebo.[4] Likewise, dabigatran reduced the vegetation size, bacterial load, and inflammation in experimental S. *aureus* IE rat model.[13] In addition, dabigatran significantly lowered the incidence of *S. aureus* IE in a rat model of experimental IE.[12] Whether these findings can be extrapolated to humans has yet not been studied. Recently, Peetermans et al. conducted a single center, randomized, controlled feasibility and safety trial of staphylothrombin inhibition with direct thrombin inhibitors in a subset of patients with SAB.[14] In total, 94 patients were randomized 1:1 to direct thrombin inhibitors (oral dabigatran or intravenous argatroban) or subcutaneous enoxaparin. The authors reported that enoxaparin did not significantly alter staphylothrombin activity, whereas the direct thrombin inhibitors inhibited staphylothrombin activity, with increasing inhibition at higher levels of dabigatran and argatroban.[14] Further, the direct thrombin inhibitors

were associated with a numerically lower number of persistently positive blood cultures. However, the authors did not observe any differences in clinical outcomes among groups, though the study was not designed nor powered to detect such differences.[14]

To our knowledge, our study is the first to test the hypothesis that treatment with dabigatran is associated with lower incidence rate of SAB in humans. We found that dabigatran was associated with a lower incidence rate of SAB compared with factor Xa-inhibitors in patients with atrial fibrillation. Likewise, we found that dabigatran, but not apixaban or edoxaban, was associated with a lower incidence rate of SAB than rivaroxaban. However, despite a numerically lower crude incidence rate of *S. aureus* IE in the dabigatran group, the adjusted incidence rate was not significantly lower in patients treated with dabigatran compared with those treated with factor Xa-inhibitors. The lack of statistical significance may be explained by the low incidence rate of *S. aureus* IE in patients with atrial fibrillation treated with DOACs. Yet, these findings indicate that inhibition of the staphylothrombin complex via dabigatran may reduce the incidence rate of SAB and thus support the data from preclinical studies. However, no causal inference can be drawn from observational findings and our results warrant more studies on the antibacterial activity of dabigatran against *S. aureus* infections in humans.

In light of the numerically low incidence of SAB in general in patients with atrial fibrillation treated with DOACs, the choice of anticoagulant therapy in atrial fibrillation should not be guided be our findings. It is important to emphasize that the data from this observational and exploratory study should not be used to imply a beneficial effect of dabigatran over factor Xa-inhibitors and thus not encourage a change in the choice of anticoagulant therapy in atrial fibrillation. Such decisions should rely on data from large randomized trials investigating more prevalent and important safety and efficacy endpoints, including arterial thromboembolism and bleeding. Further, it is important to emphasize that prophylactic use of dabigatran for the prevention of SAB and IE in patients, in whom anticoagulation is not warranted, is not reasonable

due to the high risk of bleeding. Rather, our findings add further to the understanding of the virulence of *S. aureus* in humans and may ultimately contribute to the evolvement of prevention and treatment strategies for SAB and IE. Potential strategies to reduce the virulence of *S. aureus* may include specific inhibition of the staphylothrombin complex without inhibiting thrombin and thus without any anticoagulant effect.14 In line with this, a specific staphylocoagulase inhibitor (i.e. a murine monoclonal antibody directed against staphylocoagulase) is currently being tested in a lethal *S. aureus* sepsis murine model and preliminary data suggest that specific staphylocoagulase inhibition is associated with prolonged survival.[25] Despite these promising results, more data on the efficacy of specific staphylocoagulase inhibition on the virulence of *S. aureus* are warranted.

An interesting finding of this study was the incidence rate of SAB in the study population. In a recent Danish nationwide study, the incidence rate of SAB during the period 2008-2015 was 8.1 and 14.5 events per 10,000 person-years among Danish individuals aged 70-79 and 80-89 years, respectively.[26] Thus, the incidence rate of SAB in our study population is higher than in individuals from the background population with a similar age. However, it is well-known that male sex and comorbidities portend an increased risk of SAB. It is, therefore, possible that the higher rate of SAB observed in our study may, in part, reflect a higher burden of comorbid conditions, including atrial fibrillation, and a higher proportion of men.

Strengths and limitations

The main strength of this study is the completeness of data from nationwide administrative registries and the Danish Staphylococcal Bacteremia Database. The Danish healthcare system, funded by taxes, provides equal access to healthcare services for all residents regardless of socioeconomic or insurance status. In Denmark, oral anticoagulants can be purchased only through prescription. Due to partial reimbursement of drug expenses by the Danish healthcare system,

pharmacies are required to register all redeemed prescriptions ensuring complete and accurate registration. The findings of this study should be viewed in the context of a number of limitations. The observational nature of this study precludes the assessment of cause-effect relationships. Residual confounding cannot be excluded despite adjustment for potential confounders, and it is likely that these adjustments were not sufficient to even out the differences between the groups, including differences in age and prevalence of chronic kidney disease. In addition, confounding by indication cannot be omitted in pharmacoepidemiologic studies, though we attempted to minimize the impact of this limitation by restricting the selection of the study population to a more homogenous population (i.e. atrial fibrillation as the indication for DOAC treatment). Although dabigatran was associated with a numerically lower incidence rate of *S. aureus* endocarditis compared with factor Xa-inhibitors, the study was not powered to detect a significant difference between dabigatran and factor Xa-inhibitors with respect to this outcome given the low rate of *S. aureus* endocarditis in the study population. Finally, during the study period, the proportion of patients initiating treatment with dabigatran decreased,[27,28] and the incidence of SAB in the general Danish population increased.[26] To minimize the impact of these time trends on our findings, we performed a sensitivity analysis, in which the inclusion period was restricted to January 1, 2013-December 30, 2017.

Conclusions

Treatment with dabigatran was associated with a significantly lower incidence rate of SAB. This finding may have important implications for the evolvement of prevention and treatment strategies for SAB and warrant further investigation.

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Conflict of Interest Disclosures

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Table 1. Baseline characteristics of the study population according to exposure at inclusion

Characteristics	Dabigatran N=35,568	Factor Xa-inhibitors N=76,969	*Rivaroxaban N=41,003*	*Apixaban N=34,819*	*Edoxaban N=1,147*
Demographics					
Age (years), median (interquartile range)	73 (66-80)	75 (67-82)	*72 (65-81)*	*76 (69-84)*	*75 (69-82)*
Male, N (%)	20,450 (57·5)	41,641 (54·1)	*22,498 (54·9)*	*18,472 (53·1)*	*671 (58·5)*
Comorbidities, N (%)					
Ischemic heart disease	8,377 (26·4)	20,436 (26·6)	*10,023 (24·4)*	*10,086 (29·0)*	*327 (28·5)*
Heart failure	6,395 (18·0)	14,287 (18·6)	*6,716 (16·4)*	*7,396 (21·2)*	*175 (15·3)*
Stroke	5,120 (14·4)	12,213 (15·9)	*5,424 (13·2)*	*6,639 (19·1)*	*150 (13·1)*
Peripheral arterial disease	1,472 (4·1)	3,678 (4·8)	*1,777 (4·3)*	*1,845 (5·3)*	*56 (4·9)*
Hypertension	19,314 (54·3)	39,397 (51·2)	*19,968 (48·7)*	*18,758 (53·9)*	*671 (58·5)*
Diabetes	6,582 (18·5)	13,129 (17·1)	*6,657 (16·2)*	*6,276 (18·0)*	*196 (17·1)*
Malignancy	6,206 (17·5)	15,995 (20·8)	*8,015 (19,6)*	*7,732 (22·2)*	*248 (21·6)*
Chronic kidney disease	1,164 (3·3)	4,672 (6·1)	*2,088 (5·1)*	*2,510 (7·2)*	*74 (6·5)*
Chronic obstructive pulmonary disease	3,907 (11·0)	9,98 (13·0)	*4,825 (11·8)*	*5,010 (14·4)*	*147 (12·8)*
Liver disease	752 (2·1)	1,937 (2·5)	*973 (2·4)*	*933 (2·7)*	*31 (2·7)*
Congenital heart disease	218 (0·6)	492 (0·6)	*294 (0·7)*	*195 (0·6)*	*< 4*
Heart valve prosthesis	589 (1·7)	1,736 (2·3)	*854 (2·1)*	*858 (2·5)*	*24 (2·1)*
Cardiac implantable electronic device	2,609 (7·3)	6,105 (7·9)	*2,908 (7·1)*	*3,098 (8·9)*	*99 (8·6)*
Prior infective endocarditis	141 (0·4)	401 (0·5)	*196 (0·5)*	*198 (0·6)*	*7 (0·6)*
Prior *S. aureus* bacteremia	181 (0·5)	586 (0·8)	*298 (0·7)*	*280 (0·8)*	*8 (0·7)*

Figure legends

Figure 1. Flow chart of the study population

AF, atrial fibrillation; VTE, venous thromboembolism (i.e. deep vein thrombosis of pulmonary embolism)

Figure 2. Unadjusted incidence rates and adjusted incidence rate ratios of *S. aureus* bacteremia and IE according to exposure

Figure 1

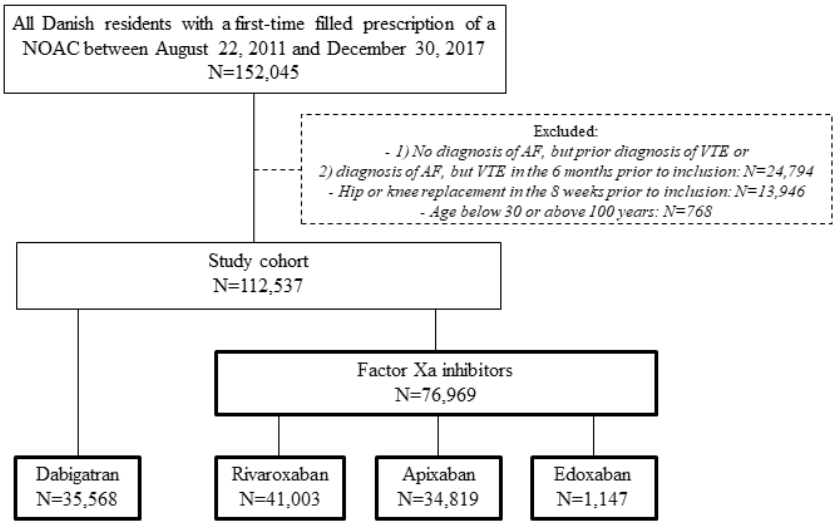

Figure 2