Thromboembolic and bleeding complications in patients with liver cirrhosis and atrial fibrillation – a population-based cohort study

Research year report

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Preface

This report is based on a study I conducted from February 2018 to January 2019, during my time as a research year student at the Department of Clinical Epidemiology (DCE). I am forever grateful for the opportunity to spend a year in such an amazing and supportive environment.

First, I would like to thank my four supervisors. Lars, for always having time for my questions and always taking the time to supervise me. Without your help and guidance I would have drowned in data, but you always kept me afloat. Second, I would like to thank Henrik. You opened the door at DCE for me. You have patiently answered my questions and supported me all the way through. Furthermore, I would like to thank Kasper. You unraveled the world of clinical epidemiology to me. And by your challenging questions you always made me improve and inspired me to do better. You always made me feel that you had infinite time to supervise me. Last, but absolutely not least, I would like to thank Anette. Had it not been for you I would never have embarked on this journey. You inspired me to start this project and you have supported and guided me ever since. I would also like to thank Søren, who helped me start the project and made it financially possible.

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Emil Riahi, April 2019

Content

Abstract

Objectives: We aimed to examine the risk of thromboembolic and bleeding complications in patients with atrial fibrillation and flutter (AFF), with and without a history of liver cirrhosis.

Methods: This population-based cohort study was based on data retrieved from Danish nationwide health registries. We identified all patients with a first-time hospital diagnosis of AFF in 1995─2015. Patients with AFF were categorized according to the presence or absence of a liver cirrhosis diagnosis. We computed crude incidence rates per 1,000 person years and hazard ratios (HRs) with [95% confidence intervals], based on Cox regression analyses adjusted for age, the CHA_2DS_2VASc score, and the Charlson Comorbidity Index score.

Results: We identified 273,225 patients with a hospital-based AFF diagnosis. Of those, 1,463 (0.54%) had a history of liver cirrhosis. During the first year of follow-up, patients with a history of liver cirrhosis had higher rates of hemorrhagic stroke, subdural hemorrhage, and gastrointestinal hemorrhage, than those without a liver cirrhosis history. We found no substantial differences in the rates of ischemic stroke, myocardial infarction, or venous thromboembolic events between patients with and without liver cirrhosis. Adjusted HRs showed that a history of liver cirrhosis was associated with ischemic stroke (HR: 1.77 [1.39-2.24]) and hemorrhagic stroke (HR: 1.55 [0.86-2.80]); in addition, liver cirrhosis was associated with venous thromboembolic events, subdural hemorrhage, and gastrointestinal hemorrhage (HRs of 2-fold, 3-fold, and 3.5-fold, respectively, compared to no liver cirrhosis), during the first year of follow-up. We found no association with myocardial infarction.

During the 2-5 year follow-up period, patients with a history of liver cirrhosis had higher rates of ischemic stroke, subdural hemorrhage, venous thromboembolic events, and gastrointestinal hemorrhage, but not myocardial infarction or hemorrhagic stroke, compared to patients without a liver cirrhosis history. Moreover, during 2-5 years of follow-up, a history of liver cirrhosis was associated with an increased risk of myocardial infarction, venous thromboembolic events, and gastrointestinal hemorrhage (HRs were 2-fold, 1.5-fold, and 4-fold, respectively, compared to no liver cirrhosis). Adjusted HRs showed no association between a history of liver cirrhosis and ischemic stroke, hemorrhagic stroke, or subdural hemorrhage.

Conclusion: In patients with AFF, liver cirrhosis was associated with ischemic stroke, venous thromboembolism, hemorrhagic stroke, subdural hemorrhage, and gastrointestinal hemorrhage during the first year of follow-up, compared to patients with AFF without liver cirrhosis. During the 2-5 year follow-up period, liver cirrhosis was associated with myocardial infarction, venous thromboembolic events, and gastrointestinal hemorrhage.

Dansk resume

Formål: At undersøge risikoen for tromboemboliske og blødningskomplikationer ved atrieflimren- eller flagren hos patienter med og uden levercirrose.

Metoder: Ved hjælp af nationale danske registre, udførte vi et populationsbaseret kohortestudie. Vi identificerede alle patienter med en førstegangsdiagnose for atrieflimren- eller flagren i perioden 1995-2015. Patienterne med atrieflimren- eller flagren blev kategoriseret efter hvorvidt de havde en tidligere levercirrose diagnose. Vi estimerede rå incidensrater per 1000 person år og hazardratioer med 95% konfidensintervaller. Ved estimeringen af hazardratioer benyttede vi en Cox regression og justerede for alder, CHA_2DS_2VASc score, og Charlson Comorbidity Index score

Resultater: Vi identificerede 273,225 patienter med en hospitalsbaseret atrieflimren- eller flagren diagnose. Ud af disse var 1,463 tidligere diagnosticeret med levercirrose. I løbet af et års follow-up, havde patienter med levercirrose en højere incidensrate af hæmoragisk slagtilfælde, subdurale blødninger og gastroinstestinale blødninger. Vi fandt ingen større forskelle i raten af iskæmisk slagtilfæde, myokardieinfarkt og venøse tromboembolier. I den justerede hazard ratio var levercirrose associeret med iskæmisk slagtilfæde (HR: 1.77 [1.39-2.24]) og hæmoragisk slagtilfælde (HR: 1.55 [0.86-2.80]) i løbet af det første år. Ligeledes var hazard ratioen øget for henholdsvis venøse tromboembolier, subdurale blødninger og gastrointestinale blødninger (2-fold, 3-fold og 3.5-fold) i løbet af det første års follow-up. Vi fandt ingen association til myokardieinfarkt.

I løbet af 2-5 års follow-up havde patienter med levercirrose en øget incidensrate af iskæmisk slagtilfælde, venøse tromboembolier, subdurale blødninger og gastro-intestinale blødninger. Vi fandt ikke en øget incidensrate af myokardieinfarkt eller hæmoragisk slagtilfælde. I samme tidsperiode var levercirrose associeret med en øget risiko for myokardieinfarkt, venøse tromboembolier og gastrointestinale blødninger (2-fold, 1.5-fold og 4-fold øget hazardratio). I den justerede hazardratio var der ingen sammenhæng mellem levercirrose og iskæmisk slagtilfælde, hæmoragisk slagtilfælde eller subdural blødning.

Konklusion: Hos patienter med atrieflimren- eller flagren er levercirrose associeret med iskæmisk slagtilfælde, venøse tromboembolier, hæmoragisk slagtilfælde, subdurale blødninger og gastrointestinale

blødninger i løbet af det første års follow-up. I løbet af 2-5 års follow-up var levercirrose associeret med myokardieinfarkt, venøse tromboembolier og gastrointestinal blødning.

Manuscript

Introduction

Atrial fibrillation and atrial flutter (AFF) are the most common cardiac arrhythmias, and the incidence and prevalence of AFF continues to increase (1,2). During 1994-2012, AFF was the sixth most common discharge diagnosis in Danish hospitals. It was included in 142,849 inpatient diagnoses and 105,710 outpatient clinic diagnoses (3). Several conditions have been associated with an increased risk of AFF, including; hypertension, ischemic heart disease, diabetes, obstructive sleep apnea, and hyperthyroidism (4–6). Furthermore, AFF is an important risk factor for ischemic stroke, peripheral embolism, heart failure, and early death (7,8). According to current clinical guidelines, patients with AFF that have other risk factors for thrombosis, graded according to the CHA_2DS_2VASc score, should receive oral anticoagulants to reduce the risk of ischemic stroke (9–11).

Comorbidities, such as diabetes and chronic kidney disease, are known to increase the risk of thromboembolic events in patients with AFF (12,13). It is less clearly understood whether liver cirrhosis might affect the thromboembolic risk in patients with AFF. Patients with liver cirrhosis were previously considered to be 'auto' anticoagulated, due to a clinical bleeding tendency and low levels of procoagulant factors (14). However, recent evidence has suggested that patients with liver cirrhosis had a 1.5-fold increased risk of venous thromboembolic events compared to those without liver cirrhosis (14–18).

In the European Union, the number of adults over 55 years old with AFF is expected to double from 8.8 million individuals, in 2010, to 17.9 million, in 2060 (19). However, the prevalence of liver cirrhosis has nearly doubled from 664 per 100,000, in 2001, to 1,058 per 100,000, in 2013, in a cohort of U.S. veterans (20). In Denmark alone, 12,976 patients were diagnosed with liver cirrhosis from 1999 through 2008 (21). Thus, it is important to understand the clinical interaction between these two diseases. Furthermore, it is unclear how treatment with oral anticoagulants for AFF might interact with liver cirrhosis. Only a few studies have investigated the interaction between AFF and liver cirrhosis (22–27). Moreover, some previous studies were limited by small sample sizes (with 321, 26, or 465 patients) (22,24,26). Although one study included nearly 290,000 patients with AFF, it included few potential events, such as systemic

thromboembolism and bleeding complications (23). Thus, to address these gaps in knowledge, we examined the risk of thromboembolism and bleeding complications in a Danish cohort of patients with AFF, with or without liver cirrhosis. Furthermore, we assessed how oral anticoagulants interacted with liver cirrhosis.

Methods

Setting and design

We conducted a population-based cohort study from January 1, 1995 to December 31, 2015, based on prospectively collected routine data retrieved from the Danish National Patient Registry (DNPR), the Danish National Prescription Registry, and the Civil Registration System (3,28,29). All Danish inhabitants are assigned a unique civil registration number at birth or upon immigration (29). This civil registration number enables the linkage of valid, anonymized, individual-level data between registries (29). The Danish national healthcare program is tax-funded, which ensures equal access to health services to the entire population (30).

Data sources

The DNPR holds records of all inpatient admissions to somatic hospitals, starting from 1977. It also holds records of all outpatient, emergency room, and psychiatric admissions starting from 1995. The information contained in the registry includes one primary discharge diagnosis and up to 19 secondary diagnoses; the setting (*i.e.*, hospital, outpatient clinic, or emergency room), and the admission and discharge dates. The diagnoses in the DNPR were classified according to the *International Classification of Diseases, Eighth Revision* (ICD-8), from 1977-1993, and according to the *International Classification of Diseases* (ICD-10) thereafter (3).

The Danish National Prescription Registry holds records on all reimbursed prescriptions filled from outpatient or municipality-based pharmacies, starting from 1995 (28). Information recorded in the registry includes the drug dispensed, the dispensation date, and the defined daily dosages. Dispensed drugs were classified according to the *Anatomical Therapeutic Chemical* (ATC) classification system codes.

Study population and exposure

We searched the DNPR to identify all patients with a first-time, inpatient or outpatient diagnosis of AFF, recorded between January 1, 1995 and December 31, 2015. The patients were identified with ICD-10 codes. Patients that were diagnosed with AFF before January 1, 1995 were identified in the DNPR, based on the respective ICD codes, and excluded from the study (3).

We divided the cohort of patients with AFF into two groups, according to the presence or absence of a hospital diagnosis of liver cirrhosis, recorded any time before the diagnosis of AFF. The Danish National Prescription Registry was used to classify patients as either users or non-users of oral anticoagulant treatment, based on ATC codes (28). Thus, the entire AFF cohort was divided into four exposure groups (Figure 1). Both a history of liver cirrhosis and the use of oral anticoagulants on the index date were assessed as exposures.

Users of oral anticoagulant treatment were defined as those that filled at least one reimbursed prescription of either vitamin K antagonists or a direct oral anticoagulant (DOAC), within 90 days after a first-time AFF diagnosis. Non-users of oral anticoagulant treatment were defined as those that did not fill a reimbursed prescription of either vitamin K antagonists or DOAC within the first 90 days of a first-time AFF diagnosis. To avoid an immortal time bias, the index date was defined as 90 days after the AFF diagnosis for all patients (31).

The ICD and ATC codes used to identify and classify study subjects are given in Supplementary table 1. The ICD diagnosis of AFF was validated in previous studies. The positive predictive value for AFF was 95% (32).

Outcomes

Thromboembolic outcomes were ischemic stroke, myocardial infarction, and venous thromboembolism. Ischemic stroke diagnoses comprised both specified ischemic stroke and unspecified stroke, because two thirds of unspecified strokes are known to be ischemic in origin (33).

Bleeding outcomes were hemorrhagic stroke, subdural hemorrhage, bleeding in the respiratory system or urinary tract, and gastrointestinal hemorrhage. Bleeding from the respiratory system or urinary tract was considered one collective outcome. Outcomes were identified in the DNPR, based on ICD-10 codes for

primary and secondary diagnoses given at inpatient and outpatient visits. Cardiovascular outcomes are accurately registered in the DNPR. Validation studies have reported a positive predictive value of 97% for ischemic stroke and myocardial infarction, 88% for first-time venous thromboembolism, and 74% for intracranial hemorrhage (3,32,33).

The ICD codes used for identifying outcomes are given in supplementary Table 2.

Covariates

The DNPR was accessed to determine the medical history of all patients prior to the index date. Based on all inpatient and outpatient discharge diagnoses, we extracted information on the comorbidity of study subjects. The comorbidities were used to calculate the CHA_2DS_2VASc score for each patient (11). We also calculated a Charlson Comorbidity Index score for each patient. We used a modified Charlson Comorbidity Index, which included only the comorbidities that were not included in the CHA_2DS_2VASc score (34). For both the CHA_2DS_2VASc score and the Charlson Comorbidity Index score, we grouped the scores into categories of 0-1, 2-3, 4-5, >6, and patients were classified according to these categories.

The DNPR was accessed to determine the year of the AFF diagnosis. For patients with liver cirrhosis, we also determined the time interval from the date of the liver cirrhosis diagnosis to the date of the AFF diagnosis.

Lastly, we accessed the Danish National Prescription Registry to extract information on co-medications. We defined co-medications as medications filled for at least one reimbursed prescription, recorded within 90 days prior to the index date.

The ICD and ATC codes that were used to identify covariates are given in Supplementary tables 3-6.

Statistical analysis

We followed patients from their index dates until death, emigration, or the end-of-study, on December 31 2016 (to ensure at least 9 months of follow-up), whichever came first. When patients experienced one adverse outcome, they remained at risk of the other adverse outcomes. For example, any patient that experienced a venous thromboembolic event remained at risk of an ischemic stroke, and vice versa.

In our main analysis, we compared patients with AFF without liver cirrhosis to patients with both AFF and liver cirrhosis. We calculated incidence rates per 1,000 person years during first year (0-1 year) and the

second to fifth years (2-5 years) of follow-up. Additionally, we constructed a Cox regression model and computed hazard ratios (HRs) with [95% confidence intervals] to estimate the risk of a thromboembolic or bleeding event during the 0-1 and 2-5 year periods. We computed adjusted hazard ratios (aHRs) based on two models. In the first model, we adjusted for age and gender. In the second model, we adjusted for age, the CHA_2 DS_2VASc score, and the Charlson Comorbidity Index score. In the latter analysis, we did not adjust for gender separately, because it was included in the CHA_2DS_2VASc score. With log-log plots, we assessed the assumption of proportional hazards and found no violations during the 0-1 year or the 2-5 year periods.

In an additional analysis, we compared all four exposure groups (Figure 1). In this analysis, we also calculated the incidence rates and HR, based on the same follow-up periods and regression models that we used in our main analysis.

We also conducted two stratified analyses, where we stratified patients by oral anticoagulant treatment or by liver cirrhosis. In the stratified analyses, we computed incidence rates and the HR, based on both Cox regression models, for the 0-1 year and 2-5 year periods. When stratifying by oral anticoagulant treatment, we also generated 21-year cumulative incidence plots of ischemic stroke and hemorrhagic stroke, and we treated death as a competing risk (35).

We used Stata version 15.1 for Windows 64-bit x86-64, for all data management, statistical computations, and cumulative incidence plots (36). The Danish Data Protection agency approved the study (record number: 707026). According to Danish legislation, registry-based studies do not require approval from an Ethics Committee or informed consent from patients.

Results

We identified 273,225 patients that received hospital-based diagnoses of AFF during 1995-2015 (Table 1). Patients with liver cirrhosis had a lower median age (68 years *vs*. 74 years), a larger proportion of males, (63.77% *vs.* 53.98%), and a lower CHA_2DS_2VASc score than patients without liver cirrhosis. Furthermore, more patients with liver cirrhosis had a Charlson Comorbidity Index score of two or more, compared to patients without liver cirrhosis (22% *vs*. 12.4%, respectively). The baseline prevalence of selected

comorbidities and co-medications are shown in Supplementary table 7. The prevalence of ischemic stroke, hemorrhagic stroke, and ischemic heart diseases were comparable between patients with and without liver cirrhosis. However, patients with liver cirrhosis had a higher prevalence of hypertension (41.56% *vs.* 34.75%), diabetes (20.51% *vs.* 10.00%), and chronic pulmonary diseases (36.09% *vs.* 25.36%), compared to those without liver cirrhosis.

Incidence of thromboembolic complications

During the 0-1 year follow-up period, patients with and without a history of liver cirrhosis had similar rates of ischemic stroke, myocardial infarction, or venous thromboembolic events. During the 2-5 year follow-up period, patients with a history of liver cirrhosis had increased rates of ischemic stroke (27.51 *vs.* 19.03 per 1000 person-years) and venous thromboembolic events (9.83 *vs*. 4.87 per 1000 person-years) compared to patients without a history of liver cirrhosis. We found no difference in the rates of myocardial infarction between these groups.

During the 0-1 year follow-up period, the rates of ischemic stroke and myocardial infarction were comparable between patients with a history of liver cirrhosis, including both users and non-users of oral anticoagulants, and those without a history of liver cirrhosis that did not use oral anticoagulants. During the 2-5 year follow-up period, among patients that did not use oral anticoagulants, those with a history of liver cirrhosis had increased rates of ischemic stroke (29.38 *vs.* 20.81 per 1,000 person-years) and venous thromboembolic events (11.57 *vs.* 5.47 per 1,000 person-years), compared to those without liver cirrhosis.

Risk of thromboembolic complications

During the 0-1 year follow-up period, a history of liver cirrhosis was associated with ischemic stroke (aHR: 1.77 [1.39-2.24]) and venous thromboembolic events (aHR: 2.14 [1.45-3.15]). No association was observed with myocardial infarction (aHR: 0.92 [0.61-1.40]). During the 2-5 year follow-up period, a history of liver cirrhosis was associated with myocardial infarction (aHR: 1.79 [1.06-3.02]) and venous thromboembolic events (aHR: 1.61 [0.77-3.38]). We found no clear association between a history of liver cirrhosis and ischemic stroke (aHR: 1.23 [0.75-2.01]). During the 0-1 year follow-up period, a history of liver cirrhosis, in the absence of oral anticoagulant use, was associated with ischemic stroke (aHR: 1.82 [1.38-2.40]) and venous thromboembolic events (aHR: 2.32 [1.51-3.57]), but not myocardial infarction

(aHR: 0.92 [0.57-1.51]). During the 2-5 year follow-up period, a history of liver cirrhosis was not associated with ischemic stroke, myocardial infarction, or venous thromboembolic events, regardless of oral anticoagulant use.

Incidence of bleeding complications

During the 0-1 year follow-up period, patients with a history of liver cirrhosis had higher rates of hemorrhagic stroke (9.35 *vs.* 4.05 per 1,000 person-years), subdural hemorrhage (7.76 *vs.* 1.89 per 1000 person-years), and gastrointestinal hemorrhage (43.68 *vs.*12.18 per 1000 person-years), but not hemorrhage of the lung or urinary tract, compared to patients without a history of liver cirrhosis (Table 2). During the 2-5 year follow-up period, we found similar differences in rates when comparing patients with a history of liver cirrhosis to patients without a history of liver cirrhosis. During the 0-1 year follow-up period, compared to patients without liver cirrhosis that did not use oral anticoagulants, patients with a history of liver cirrhosis that used oral anticoagulants had increased rates of hemorrhagic stroke (13.45 *vs.* 3.75 per 1,000 person-years) and gastrointestinal hemorrhage (47.14 *vs.* 12.86 per 1,000 person-years), but not hemorrhage of the lung and urinary tract (Table 3). During the 0-1 year follow-up period, non-users with a history of liver cirrhosis showed no differences in the rates of hemorrhagic stroke or hemorrhage of the lung or urinary tract, compared to non-users without liver cirrhosis.

Risk of bleeding complications

During the 0-1 year follow-up period, a history of liver cirrhosis was associated with hemorrhagic stroke (aHR: 1.55 [0.86-2.80]), subdural hemorrhage (aHR: 3.18 [1.76-5.77]), hemorrhage of the lung or urinary tract (aHR: 1.89 [1.48-2.41]), and gastrointestinal hemorrhage (aHR: 3.66 [2.91-4.59]). During the 2-5 year follow-up period, we found a similar association between a history of liver cirrhosis and gastrointestinal hemorrhage (aHR: 3.86 [2.68-5.57]). During the 2-5 year follow-up period, we found no clear associations between a history of liver cirrhosis and hemorrhagic stroke (aHR: 1.36 [0.51-3.63]), subdural hemorrhage (aHR: 1.26 [0.31-5.05]), or hemorrhage of the lung or urinary tract (aHR: 1.08 [0.64-1.82]).

During the 0-1 year and the 2-5 year follow-up periods, regardless of the use or non-use of oral anticoagulants, a history of liver cirrhosis was associated with hemorrhagic stroke, hemorrhage of the lung or urinary tract, and gastrointestinal hemorrhage.

Stratified analyses

When we stratified patients by oral anticoagulant treatment status, we found that patients with a history of liver cirrhosis had a lower 21-year risk of ischemic stroke than patients without a history of liver cirrhosis, in both strata (Figures 2 and 3). In contrast, patients with a history of liver cirrhosis had a higher 21-year risk of hemorrhagic stroke than patients without liver cirrhosis, in both strata (Figures 4 and 5). During the 0-1 year follow-up period, within each strata, a history of liver cirrhosis was associated with ischemic stroke and gastrointestinal hemorrhage. During the same time interval, in the strata of no oral anticoagulant use, a history of liver cirrhosis was associated with venous thromboembolic events and hemorrhage of the lung and urinary tract. During the 2-5 year follow-up period, within each strata, a history of liver cirrhosis was associated with venous thromboembolic events and gastrointestinal hemorrhage. During the 2-5 year follow-up period, within the strata of oral anticoagulant use, a history of liver cirrhosis was associated with myocardial infarction and gastrointestinal hemorrhage. The incidence rates per 1,000 person years and HRs are presented in Supplementary table 8.

When we stratified patients by the history of liver cirrhosis, among patients without a history of liver cirrhosis, users of oral anticoagulants were at lower risks of ischemic stroke, myocardial infarction, and venous thromboembolic events during the 0-1 and 2-5 year follow-up periods, compared to non-users without a history of liver cirrhosis. However, within the strata of patients without a history of liver cirrhosis, the use of oral anticoagulants was associated with all hemorrhagic events during the entire follow-up period. Within the strata of patients with a history of liver cirrhosis, we found no differences in the rates or risks of any adverse events, during either the 0-1 year or the 2-5 year follow-up period. Incidence rates per 1,000 person years and HRs are presented in Supplementary table 9.

Discussion

Main findings

In this population-based cohort study of patients with AFF, a history of liver cirrhosis was associated with an increased risk of ischemic stroke and venous thromboembolic events, during the first year of follow-up. The association between a history of liver cirrhosis and an increased risk ischemic stroke did not persist

during the 2-5 year follow-up period. However, during the 2-5 year follow-up period, patients with a history of liver cirrhosis had an increased rate of ischemic stroke compared to patients without liver cirrhosis. In the analysis stratified by oral anticoagulant treatment status, within each strata, a history of liver cirrhosis was associated with ischemic stroke, during the 0-1 year follow-up period.

Strengths and limitations

The main strength of our study was the nationwide coverage in a setting that ensured virtually complete follow-up. Thus, the risk of selection bias was minimal. Furthermore, we had a large cohort of more than 270,000 patients and the ability to follow the patients for more than 20 years. Additionally, our access to the medical history of each patient and the ability to link each patient to the prescription registry allowed us to take a range of potential confounders into account. Diagnostic codes of cardiovascular events were accurately coded in the DNPR, which ensured a valid classification of both exposures and outcomes (3).

However, this study had several limitations. Although our entire cohort was large, we had relatively few patients with liver cirrhosis. The small size of this group could lead to imprecise estimates. In addition, we did not assess our exposures as time-varying variables. Indeed, patients without a history of liver cirrhosis could develop liver cirrhosis during the study period, and the inability to track these changes could cause a misclassification bias. Similarly, both users and non-users of oral anticoagulants could potentially either terminate or initiate treatment with oral anticoagulants during the study period.

Other limitations were that we had no detailed information on the severity of the liver cirrhosis and no clinical scores, such as the Child-Pugh score or the Model of End-stage Liver Disease (MELD) score. There was also a risk of confounding by indication. For example, it was possible that only patients with the lowest clinical bleeding risk were treated with oral anticoagulants. This selective treatment could have led to an underestimation of the risk of bleeding complications associated with oral anticoagulant treatment (37). Furthermore, although we adjusted for potential confounders in our analyses, we could not rule out the risk of potential residual confounding factors, such as smoking. The increased risk of ischemic stroke in patients with liver cirrhosis, during the 0-1 year follow-up period might have been mediated by lifestyle factors, such as smoking and obesity, rather than by the history of liver cirrhosis. However, we did not observe any association between a history of liver cirrhosis and myocardial infarction during the 0-1 year follow-up

period. Based on the fact that ischemic stroke and myocardial infarction share risk factors, the impact of this potential confounder was likely to be minor (38,39).

Contribution to the literature

Of six previous studies focused on AFF and liver cirrhosis (22-27), four were conducted with either a South-Korean (22,26) or Taiwanese population (23,25). In East Asia, the most common etiology of liver cirrhosis is chronic infection with hepatitis B or C virus (40). In contrast, alcohol consumption and nonalcoholic fatty liver diseases are far more common etiologies of liver cirrhosis in Western Europe and North America (20,41). Of the six previous studies, three had smaller study populations than ours (22,24,26) and three did not include patients treated with DOAC (22,23,26)

Six studies have investigated the risk of thromboembolic and bleeding complications in patients with AFF and a history of liver cirrhosis (22–27). In a Taiwanese setting, Kuo *et al*. studied 289,559 patients with AFF. Of those patients, 10,336 had a history of liver cirrhosis (23). Kuo *et al.* compared patients with and patients without a history of liver cirrhosis, and the patients were stratified by stroke prevention strategies (*i.e.*, no treatment, treatment with antiplatelet agents, or treatment with warfarin). Similar to our study, Kuo *et al.* reported an increased risk of ischemic stroke among untreated patients with AFF and a history of liver cirrhosis (HR: 1.10 [1.00-1.20]) (23). However, in contrast to our study, Kuo *et al*. reported that, among patients treated with warfarin, those with liver cirrhosis were not at increased risk of either ischemic stroke (HR: 0.89 [0.71-1.12]) or intra-cranial hemorrhage (HR: 1.17 [0.81-1.68]), compared to patients without liver cirrhosis (23).

In another Taiwanese study, Lai *et al*. compared 3,490 patients with AFF and no liver disease to 433 patients with AFF and a diagnosis of chronic liver disease. They reported an increased risk of cerebral infarction among patients with AFF and chronic liver disease, compared to patients with AFF and no history of chronic liver disease (HR:1.50 [1.21-1.87]) (25). However, they did not find an increased risk of cerebral hemorrhage among patients with chronic liver disease compared to those without chronic liver disease.

Kuo *et al*. examined the risk of ischemic stroke and intracranial hemorrhage in patients with liver cirrhosis and AFF. They found that patients that used warfarin exhibited a lower risk of ischemic stroke

(HR: 0.76 [0.58-0.99]), but no difference in the risk of intracranial hemorrhage (HR: 1.27 [0.82-1.95]), compared to patients that did not use warfarin (23).

In the two Korean studies, Lee *et al*. and Choi *et al*. identified patients with AFF and a concomitant diagnosis of liver cirrhosis, with or without exposure to treatment with vitamin K antagonists. Lee *et al*. reported that patients with AFF and liver cirrhosis that received vitamin K antagonists had a lower risk of ischemic stroke than patients that did not receive vitamin K antagonists (HR: 0.32 [0.15-0.66]). However, patients that received oral anticoagulants also had an increased risk of major bleeding events compared to those that did not receive anticoagulants (HR: 1.68 [1.08-2.61]) (22). Choi *et al*. did not find a lower risk of ischemic stroke, but did report an increased risk of major bleeding events, among patients treated with oral anticoagulants compared to those not treated with anticoagulants (26). In our study, when we stratified by liver cirrhosis, we found that, within the group with liver cirrhosis, users and non-users of anticoagulants had comparable risks of both bleeding and thromboembolic events. Thus, it remains unclear whether patients with AFF and liver cirrhosis might benefit from oral anticoagulant treatment.

Possible mechanisms

Liver cirrhosis has long been recognized as a condition associated with increased risk of bleeding (42). The bleeding tendency associated with liver cirrhosis is thought to be caused by reduced synthesis of pro-coagulant factors, thrombocytopenia, and hemodynamic abnormalities, including portal hypertension (14,15,42,43). However, within the past decade, a number of studies have suggested that liver cirrhosis is also a pro-thrombotic state (16,44). This pro-thrombotic state is thought to be caused by the simultaneous reduction in anticoagulant factor synthesis and the reduction in von Willebrand factor clearance (14,15). These considerations might explain why we observed a simultaneous increase in the risks of both thrombotic and bleeding events in our study.

Implications

Despite the low number of patients with both AFF and a history of liver cirrhosis, this study showed that liver cirrhosis was not exclusively associated with a bleeding tendency; instead, it was associated with a combined risk of bleeding and thrombosis. More research is needed to grasp the clinical implications of this

combined bleeding and thrombosis tendency and to identify which patients are at risk of bleeding , which are at risk of thrombosis, and which are at risk of both.

Conclusion

In this study of patients with AFF, we found that a history of liver cirrhosis was associated with ischemic stroke and venous thromboembolism, during the first year of follow-up, and with myocardial infarction and venous thromboembolism, during the second to fifth years of follow up. However, a history of liver cirrhosis was also associated with all evaluated bleeding complications during the first year of follow-up. After that, liver cirrhosis only remained associated with gastrointestinal hemorrhage.

Due to the low number of events, our estimates are imprecise, and we could not clearly assess the interaction between liver cirrhosis and oral anticoagulants.

Supplementary Information

Background

Atrial fibrillation and flutter

AFF is characterized by rapid, uncoordinated, atrial contractions. AFF can be asymptomatic, but it is often characterized by dyspnea, angina pectoris, dizziness, syncope, and tiredness (45). AFF is related to three cardinal problems; reduced cardiac output, due to impaired atrial contractile function; unfavorable tachycardia at modest physical exertion; and increased risk of thromboembolic complications (45). The cause of the increased risk of thromboembolic complications associated with AFF has not been fully elucidated. However, the main contributing factor is thought to be the stasis of blood in the left atrial appendage, which leads to the formation of thrombi and secondarily emboli (4,45). Nevertheless, irrespective of the exact biological mechanism, AFF is recognized to be associated with increased risks of ischemic stroke and systemic embolism (7,8). Oral anticoagulants are effective in reducing the risk of ischemic stroke in patients with AFF (9,10). Current clinical guidelines recommend treating patients with AFF with oral anticoagulants, according to their CHA_2DS_2VASc score (11). However, anticoagulant therapy increases the risk of major hemorrhage (46).

Liver cirrhosis

Liver cirrhosis is characterized by irreversible fibrosis of the liver, which causes altered hepatic hemodynamics, reduced metabolic capacity, and reduced hepatic protein synthesis (45).

Formerly, patients with liver cirrhosis were considered to be 'auto' anticoagulated, because some patients presented with increased clotting times (expressed as the International Normalized Ratio [INR]), low levels of procoagulant factors, and a low platelet count (14). Specifically, the reduced synthesis of procoagulant factors has been of major concern (15). However, in recent years, evidence has arisen, which indicated that patients with liver cirrhosis had an increased risk of venous thromboembolic events, due to simultaneous reductions in anticoagulant factor synthesis and von Willebrand factor clearance (14–18). Despite the increasing evidence that patients with liver cirrhosis are at increased risk of venous thromboembolic events, it remains unclear how liver cirrhosis affects the risk of thromboembolic events in patients with AFF.

Furthermore, it is unclear how oral anticoagulant treatment might affect the risk of bleeding complications in patients with AFF and liver cirrhosis.

Systematic literature search

To obtain relevant data, we performed a systematic literature search before initiating the present study. We searched the NCBI database, PubMed. The search strategy was to assign the multiple search phrases to three categories (*i.e.*, 'atrial fibrillation' or 'liver cirrhosis') ; the first category was the population (e.g., patients with AFF), the second category was the exposure (e.g., liver cirrhosis), and the third category was the intervention (e.g., oral anticoagulant therapy). In each category, the search phrases were divided by the command 'OR'; in each search, the categories were divided by the command 'AND'. We used both index terms and free terms in the search phrases. The search was conducted on August 22, 2017, and it yielded seven results. However, only three studies were relevant, based on the abstracts (22–24). Next, to broaden the literature search, we conducted a second search with only the terms 'Atrial fibrillation' and 'liver cirrhosis'. This search identified one additional study (27).

Considerations regarding the study design

To address our research question, we chose a cohort study design. A cohort is a group of individuals with a common exposure; for example, symptoms, disease, job exposure, drug use etc. A cohort study measures the incidence of an event in one or more cohorts (47). Studies that include more than one cohort generally compare results between cohorts with different exposures. In our study, we combined two cohort studies in one. In the first study, a history of liver cirrhosis was considered the exposure; thus, we compared two cohorts: patients with (exposed) and patients without (unexposed) a history of liver cirrhosis. As shown in Figure 1, we also analyzed patients stratified by both a history of liver cirrhosis and the use of oral anticoagulants. This led to a total of four cohorts with different exposure combinations.

The cohort study has numerous advantages, compared to other types of observational studies. One advantage is the prospective nature of a cohort study. Our data on exposure (*i.e.,* a history of liver cirrhosis or the use of oral anticoagulants) were collected before the outcomes occurred; therefore, it was nearly

impossible for the outcomes to have an effect on the exposure classification (47). Additionally, the data used in our study were routinely collected for administrative purposes, not as part of a specific study protocol. This factor could diminish the risk of bias. Moreover, as opposed to case-control studies, cohort studies offer the possibility of estimating absolute risks. Thus, the choice of a cohort study enabled us to estimate incidence rates and cumulative incidences. However, as in all observational studies, cohort studies are subject to confounding. One might try to mitigate the effects of confounding in various ways, including matching study subjects on age, gender, geographical area, income etc; by stratifying subjects based on covariables; or by adjusting for covariables in a regression model. However, unmeasured confounding will always be possible, and due to their nature, these confounders are difficult to adjust for.

An alternative to observational studies is the randomized controlled trial (RCT). The RCT is interventional in nature, because subjects are actively allocated to either an exposure or non-exposure group. When the allocation is randomized, and the study population is sufficiently large, it should, in theory, evenly distribute potential confounding factors among the exposed and non-exposed study subjects, and thus, confounding can be avoided. Furthermore, when the RCT is performed as a double-blinded study, the risk of bias can be further diminished (47). However, the RCT has several drawbacks. The study subjects in RCTs often do not reflect the same distributions of sex, age, and ethnicity as the target population; this drawback leads to low external validity. Furthermore, RCTs have some logistic drawbacks compared to a registry-based cohort study. In a RCT, study participants need to be enrolled, provide informed consent, and complete the follow-up period. Had we chosen to conduct a RCT of the same size as our cohort study, it would have required immense man-power and finances to recruit 273,000 study subjects, and then conduct a 21-year follow-up, before we could perform our final statistical test. Lastly, there are some ethical considerations regarding the RCT. In the RCT, the study subjects are actively assigned to an exposure; however, it is unethical to assign study subjects to an exposure regarded harmful. In the current study plan, we suspected that exposing patients with liver cirrhosis to oral anticoagulants would increase the risk of bleeding complications. Therefore, it would have been unethical to conduct this study as a RCT. Consequently, for all these reasons, we chose to conduct a cohort study.

Exposure and outcome

The individuals of a cohort are identified by the presence or absence of a given exposure. Thus, exposure status is the key variable in a cohort study. Exposure can be seen as dichotomous, categorical, or continuous (47). Each method has its advantages and drawbacks. If we had chosen to treat liver disease as a continuous exposure, we would have required more data on liver function (e.g., plasma concentrations of coagulation factors, albumin, and bilirubin) and histological features (e.g., fibrosis, steatosis etc.). With that data, we could have treated liver disease as a continuous exposure, ranging from no liver disease to severe liver cirrhosis. Alternatively, we could have categorized liver disease, based on disease severity (e.g., mild disease, chronic disease, or Child-Pugh A, B , and C). With exposure treated as either a continuous or categorical variable, we could perhaps have elucidated a dose-response relationship between the severity of liver disease and the risk of thromboembolic and bleeding complications. However, that would have required a totally different logistical setup and different data sources; moreover, it would not have been possible to recruit such a large cohort, with the currently available data. Therefore, we chose to view the exposure as dichotomous; i.e., the presence or absence of a liver cirrhosis history.

Our primary exposure was liver cirrhosis. In addition, we assessed the use of oral anticoagulants as a secondary exposure. We classified subjects based on data from the DNPR and the Danish National Prescription Registry. Although the diagnoses in the DNPR generally have a high positive predictive value, the sensitivity of these registry data might be low. The DNPR only stores data for patients that were assessed and diagnosed at a hospital; thus, there was a possibility that some patients with liver cirrhosis were never recorded in the DNPR. This omission could have led to a misclassification of exposure. In a similar vein, the Danish National Prescription Registry only recorded reimbursements of dispensed oral anticoagulants. Thus, although we knew that the patients classified as users of oral anticoagulants retrieved their medication, we could not be sure that those patients actually used the dispensed drugs. This caveat could also have led to a potential exposure misclassification.

We also used the DNPR to detect the occurrence of outcomes. We chose to include a variety of thromboembolic and bleeding events to emphasize any differences in risks or incidence rates between exposure groups.

Statistical considerations

To estimate the absolute risk of thromboembolic or bleeding complications, we estimated the incidence rates and the cumulative incidence. The incidence rate was calculated as the number of events per 1,000 person-years (47). The cumulative incidence was calculated as the number of new events divided by the number of persons at risk, during the entire 21 years of follow-up (47). In this study, we did not estimate all-cause mortality; therefore, we chose to include competing risks in the calculations of cumulative incidence. Had we not chosen to account for competing risks, dead subjects would have been included in the groups at risk of given events; *e.g.*, ischemic stroke. Therefore, failure to account for competing risk could potentially lead to overestimation of the cumulative incidence (48).

Additionally, we constructed a Cox regression model to estimate the HRs [95% confidence intervals] of thromboembolic and bleeding events. In contrast to the incidence rate and cumulative incidence, the HR is a relative estimate. It estimates the instantaneous risk of an event in the exposed cohort, compared to the unexposed cohort. We assessed the assumption of proportional hazards via log-log plots. We found that estimations of HRs for the 0-5 year period would have violated the assumption of proportional hazards. Thus, we split up the follow-up into two intervals, namely 0-1 year and 2-5 years. However, this approach also had potential implications for our estimates, because it introduced a selection bias (49). When estimating a given HR for the 2-5 year period, patients eligible for the analysis had to be alive and free of a prior event at the beginning of the second year of follow-up. The potential implication of this is clear, if we consider of the risk of ischemic stroke in our study. As depicted in Table 2, liver cirrhosis was associated with an increased risk of ischemic stroke during the first year of follow-up. However, this association had diminished during the 2-5 year follow-up period. The mechanism underlying this effect was discussed previously by Hernán (49). Briefly, patients with liver cirrhosis that were most susceptible to experiencing an ischemic stroke would have experienced it during the first year of follow-up; thus, these patients were ineligible for the analysis of the 2-5 year follow-up period. Consequently, the patients eligible for the analysis of the 2-5 year follow-up period were those least susceptible to an ischemic stroke, which led to a diminished HR. To counter this bias, we could have chosen to estimate the HR with an ever-increasing follow-up interval (*i.e.*, 0-1 year, 0-2 years, 0-3 years, and so forth). However, that approach would have

violated the assumption of proportional hazards. Nevertheless, Hernán argued that the crossing of hazard functions "is meaningless from a practical standpoint", because hazard functions might simply cross due to a depletion of susceptible individuals, and not due to a crossing of the cumulative incidence curves (49).

Validity, bias, and confounding

The aim of any scientific study is to provide valid estimates of the truth. In epidemiology, the goal is to provide valid estimates of various associations. Estimates are not the true value of these associations, only approximations, intended to be as close to the true associations as possible. Estimates close to the true values are considered valid estimates.

When assessing the validity of a study, two major components are assessed; first, the internal validity; *i.e.*, the results of the study are valid for the study population considered; second, the external validity; *i.e.*, the results of the study are valid for populations outside the study population (47).

There are mainly two types of error that affect the internal validity; random error and systematic error. Random error refers to random variability in the data (or more precisely, variation in the data that we cannot explain with current knowledge) (47). Random error leads to imprecise estimates. A common way to reduce random error and increase the precision of the estimates is to increase the size of the study population; this approach diminishes the effect of random variation in data, and leads to more precise estimates (47).

Systematic errors lead to biased estimates. Generally, the sources of systematic errors are classified as: selection bias, information bias, and confounding (47).

Selection bias

Selection bias results from a distortion in the procedures used to select study participants and from factors that influence participation in the study. Selection bias can arise when the association between exposure and outcome in the study population is different from that of the entire population theoretically eligible for the study (47). In our study, this bias would apply if the associations between liver cirrhosis and thromboembolic and bleeding complications were different in patients with undiagnosed AFF from those observed in patients with diagnosed AFF. This selection bias could have rendered our estimates of the

association between liver cirrhosis and thromboembolic and bleeding complications invalid in patients with AFF.

Information bias

Information bias refers to the bias that can occur due to errors in the measurement or classification of a variable. The direction of information bias can either be towards or away from the null. The direction of the bias relies on whether the error depends on the value of the variable, the value of other variables, or the error in measuring other variables (47). A measurement error in variables with a finite number of possible values is called misclassification. When the misclassification depends on the values of other variables, it is called a differential misclassification (47). An example in our study could be the observation that patients with liver cirrhosis were at increased risk of gastrointestinal hemorrhage. However, if patients with liver cirrhosis had undergone diagnostic tests more often, due to the concern over gastrointestinal hemorrhage, then gastrointestinal hemorrhage might be diagnosed more often. Thus, the association would not have reflected a biological effect of liver cirrhosis; instead, it would have reflected the fact that the presence of liver cirrhosis had affected the detection of gastrointestinal hemorrhage, which is known as a detection bias (47). However, when the outcome is severe (for example hemorrhagic stroke), the detection bias would only effect the time of diagnosis, not the determination of the diagnosis.

Another form of misclassification is called nondifferential misclassification. Nondifferential misclassification is when the misclassification does not depend on the value of other variables. In our study, the AFF diagnosis provides an example. A proportion of the included patients might have been misclassified, because they do not actually have AFF (the predictive value positive was not 100% (32)). However, we suspect that this misclassification did not depend on whether the patient was diagnosed with liver cirrhosis. Therefore, the proportion of misclassified subjects did not depend on their exposure status; hence, it was a nondifferential misclassification.

Confounding

Confounding may be described as the confusion or mixing of effects. Often, confounding is used to describe instances where the apparent effect of an exposure is entirely, or partially, due to the effect of an extraneous factor. Confounding can lead to either overestimation and underestimation of an association, and

it can even change the direction of an effect (47). Thus, it is clear that confounder control is crucial for obtaining a valid estimate. To grasp the concept of confounding, one must consider the methods for estimating the effects. In our study, we wanted to estimate how liver cirrhosis (the exposure) affected the occurrence of thromboembolic and bleeding complications (the outcome) in patients with AFF. For that, we would have to estimate the occurrence of the outcome in exposed patients in the unexposed condition, and then compare that estimate to the observed occurrence of outcomes among the same patients in the exposed condition. However, this was not possible, because patients with liver cirrhosis had been exposed, by definition; thus, it was not possible to estimate the occurrence of outcome in this population in the absence of exposure. The solution to this problem is quite simple: the use of a substitute population. In other words, the occurrence of outcomes in the absence of exposure was estimated in a population of patients with AFF, but without liver cirrhosis. However, this solution created a different problem; the population without liver cirrhosis might not be identical to the population with liver cirrhosis, in terms of a number of factors that could affect the outcome. Thus, the use of patients without liver cirrhosis as a comparison population might be confounded by those factors (47).

For a variable to be considered a confounder, it must meet three criteria: 1) it must be an extraneous risk factor for the outcome or a surrogate marker for an extraneous risk factor; 2) it must be associated with the exposure of interest; and 3) it cannot be an intermediate step in the causal pathway from exposure to outcome (47). A potential confounder in our study was chronic pulmonary disease, because this disease might confound the association between liver cirrhosis and ischemic stroke. We used chronic pulmonary disease as a surrogate marker for smoking, because we did not have direct data on the smoking status of our study subjects. Chronic pulmonary disease met all three criteria for a confounder: 1) chronic pulmonary disease was a surrogate marker of an extraneous risk factor (smoking), because it is highly associated with smoking, and smoking is an independent risk factor of ischemic stroke (38,50); 2) chronic pulmonary disease was more prevalent among patients with liver cirrhosis than among patients without liver cirrhosis (36.09% *vs.* 25.36%; Supplementary table 7); and 3) chronic pulmonary disease was not an intermediate step on the causal pathway from liver cirrhosis to ischemic stroke; *i.e.*, we do not believe that liver cirrhosis caused smoking.

A confounding effect from chronic pulmonary disease could potentially indicate that the observed association between liver cirrhosis and ischemic stroke, during the 0-1 year follow-up period, was influenced by the fact that patients with liver cirrhosis had a higher prevalence of smoking. However, we did not observe an association between liver cirrhosis and myocardial infarction during the same time interval. Because myocardial infarction and ischemic stroke share risk factors, we concluded that the observed association was not entirely due to confounding factors (38,39).

In pharmacoepidemiological studies, two relevant sources of confounding are the indication and the contraindications. In daily clinical practice, treatment is administered for a reason, and conversely, the decision not to administer a specific treatment is also made for a reason. This selective administration of treatments can be a potential source of confounding (37). We found that, among the patients with liver cirrhosis, there was no clear association between oral anticoagulant treatment and a bleeding complication. However, a clear association was observed for patients without liver cirrhosis (Supplementary table 9). This finding could indicate that confounding by contraindication had occurred; in other words, only patients with liver cirrhosis that had the lowest tendency of bleeding were administered oral anticoagulants (37). However, we did not have data on the clinical bleeding tendency; therefore, we could not control for this potential confounding factor with our study design.

External validity

In contrast to the global population, in Denmark, excess alcohol consumption is the most common etiology of liver cirrhosis (40,41). Additionally, the ethnic composition of Danish patients with AFF and liver cirrhosis was not similar to the ethnic composition of the global population. Nevertheless, we believe that our results have high external validity. We do not believe that the etiological cause of liver cirrhosis or the ethnic composition of the population had a substantial effect on the association between liver cirrhosis and thromboembolic and bleeding complications in patients with AFF. Thus, the disparities between our study population and the global population should not have a substantial effect on external validity.

In fact, we believe that the factors with the largest potential of affecting external validity are age and gender distribution, because both age and gender are risk factors for stroke (38). Thus, our results might not

be generalizable to populations with AFF and liver cirrhosis that have age and gender distributions different from the distributions of our patient population (see Table 1).

Study limitations

Here, we have discussed the choices made in designing this study. We have mentioned some potential alternative choices. However, a few other alternative choices deserve a brief mention.

We chose not to evaluate liver cirrhosis and oral anticoagulation treatment as time-varying exposures. This choice was somewhat counterintuitive, because some patients might develop liver cirrhosis during the study period, and other patients might initiate or terminate oral anticoagulative treatment after the index date. Had we chosen to evaluate these exposures as time-varying variables, we might have achieved less misclassification bias.

Furthermore, propensity-score matching of our study subjects could have provided us with a higher level of confounder control (51). In particular, our outcomes were rather rare, and this feature limited the number of variables that could be included in our regression model.

Future studies

Consistent with current literature, our study showed that patients with AFF and liver cirrhosis were at increased risk of both thromboembolic and bleeding complications (22,23,25,26). However, several questions remain unanswered. Future studies should focus on three primary questions: 1) which patients with AFF and liver cirrhosis could potentially benefit from oral anticoagulant treatment? 2) How does oral anticoagulant treatment interact with liver cirrhosis? And 3) should either vitamin K antagonists or DOAC treatment be preferred for patients with liver cirrhosis?

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Tables and figures

Table 1. Characteristics of patients with atrial fibrillation or flutter, with and without liver cirrhosis, in the period of 1995-2015

Characteristic	Patients without liver cirrhosis N=271,762	Patients with liver cirrhosis N=1,463	Patients without liver cirrhosis N=271,762		Patients with liver cirrhosis N=1,463	
			Non-users of oral anticoagulants N=152,323	Users of oral anticoagulants N=119,439	Non-users of oral anticoagulants N=1,051	Users of oral anticoagulants N=412
Gender						
Male	146,700 (53.98)	933 (63.77)	75,659 (49.67)	71,041 (59.48)	679 (64.61)	254 (61.65)
Age, years						
Median (IQR)	74 (65 – 82)	68 (61 – 75)	75 (64-84)	73 (66-80)	67 (60-75)	69 (62-75)
CHA_2DS_2VASc score						
0-1	77,202 (28.41)	525 (35.89)	40,620 (26.67)	36,582 (30.63)	385 (36.63)	140 (33.98)
2-3	139,558 (51.35)	658 (44.98)	78,269 (51.38)	61,289 (51.31)	481 (45.77)	177 (42.96)
4-5	48,646 (17.90)	249 (17.02)	29,241(19.20)	19,405 (16.25)	166 (15.79)	83 (20.15)
>6	6,356 (2.34)	31 (2.12)	4,193 (2.75)	2,163 (1.81)	19 (1.81)	12 (2.91)
Charlson Comorbidity Index score						
0-1	238,100 (87.61)	1,140 (77.92)	130,773 (85.85)	107,327 (89.86)	815 (77.55)	325 (78.88)
2-3	27,942 (10.28)	244 (16.68)	17,533 (11.51)	10,409 (8.71)	177 (16.84)	67 (16.26)
4-5	3,224 (1.19)	56 (3.83)	2,209 (1.45)	1,015 (0.85)	40 (3.81)	16 (3.88)
>6	2,496 (0.92)	23 (1.57)	1,808 (1.19)	688 (0.58)	19 (1.81)	<5 (NA)

Values are the number (%), unless otherwise specified. Abbreviations: IQR: inter quartile range; CHA2DS2VASc score: assessment of stroke risk in atrial fibrillation

Table 2. Incidence rate and hazard ratios (HRs) with 95% confidence intervals (95% CIs) of thromboembolic and bleeding complications, during the first year (0-1 year) and the second to fifth years (2-5 years) after the index date, in patients with atrial fibrillation or flutter, with and without liver cirrhosis, in Denmark from 1995 through 2016

Complication and exposure to liver cirrhosis	0-1 year			2-5 years		
	IR (95% CI)	Partially adjusted HR* (95% CI)	Fully adjusted HR¤ (95% CI)	IR (95% CI)	Partially adjusted HR* (95% CI)	Fully adjusted HR¤ (95% CI)
Ischemic stroke						
Without liver cirrhosis	28.49 (27.83 - 29.17)	Reference	Reference	19.03 (18.70-19.37)	Reference	Reference
With liver cirrhosis	34.05 (25.17-46.08)	1.81 (1.42-2.29)	1.77 (1.39 – 2.24)	27.51 (21.73-34.83)	1.24 (0.76-2.04)	1.23 (0.75-2.01)
Myocardial infarction						
Without liver cirrhosis	14.30 (13.84-14.78)	Reference	Reference	10.08 (9.85-10.33)	Reference	Reference
With liver cirrhosis	14.18 (8.93-22.51)	0.97 (0.64-1.47)	0.92 (0.61-1.40)	8.32 (5.48-12.64)	1.86 (1.10-3.15)	1.79 (1.06-3.02)
Venous thromboembolic events						
Without liver cirrhosis	7.08 (6.76-7.41)	Reference	Reference	4.87 (4.71-5.04)	Reference	Reference
With liver cirrhosis	7.85 (4.22-14.58)	2.26 (1.53-3.32)	2.14 (1.45-3.15)	9.83 (6.69-14.44)	1.68 (0.80-3.53)	1.61 (0.77-3.38)
Hemorrhagic stroke						
Without liver cirrhosis	4.05 (3.81-4.31)	Reference	Reference	3.07 (2.94-3.20)	Reference	Reference
With liver cirrhosis	9.35 (5.31-16.46)	1.58 (0.87-2.87)	1.55 (0.86-2.80)	4.10 (2.27-7.40)	1.39 (0.52-3.70)	1.36 (0.51-3.63)
Subdural hemorrhage						
Without liver cirrhosis	1.89 (1.73-2.07)	Reference	Reference	1.56 (1.47-1.65)	Reference	Reference
With liver cirrhosis	7.76 (4.17-14.42)	3.23 (1.78-5.86)	3.18 (1.76-5.77)	4.10 (2.27-7.40)	1.25 (0.31-5.00)	1.26 (0.31-5.05)
Hemorrhage of the lung or urinary tract						
Without liver cirrhosis	17.64 (17.12-18.17)	Reference	Reference	14.24 (13.96-	Reference	Reference
With liver cirrhosis	23.00 (15.98-33.10)	1.90 (1.49-2.42)	1.89 (1.48-2.41)	25.38 (19.90-	1.07 (0.64-1.82)	1.08 (0.64-1.82)
Gastrointestinal hemorrhage						
Without liver cirrhosis	12.18 (11.75-12.61)	Reference	Reference	9.73 (9.50-9.97)	Reference	Reference
With liver cirrhosis	43.68 (33.46-57.04)	3.82 (3.04-4.80)	3.66 (2.91-4.59)	29.95 (23.89-	3.98 (2.76-5.73)	3.86 (2.68-5.57)

*Adjusted for age and sex; ¤ Adjusted for age, sex, CHA_2DS_2VASc score, and Charlson Comorbidity index score

Abbreviations: IR: incidence rate; CI: confidence interval; HR: hazard ratio

Table 3. Incidence rate and hazard ratios (HRs) with 95% confidence intervals (95% CIs) of thromboembolic and bleeding complications, during the first year (0-1 year) and the second to fifth years (2-5 years) after the index date, in patients with atrial fibrillation or flutter, with and without liver cirrhosis that either used (user) or did not use (non-user) oral anticoagulants, in Denmark from 1995 through 2016

Complication and exposures to liver cirrhosis and oral anticoagulants	0-1 year			2-5 years		
	IR (95% CI)	Partially adjusted HR* (95% CI)	Fully adjusted HR¤ (95% CI)	IR (95% CI)	Partially adjusted HR* (95% CI)	Fully adjusted HR¤ (95% CI)
Ischemic stroke						
Without liver cirrhosis						
Non-users	32.77 (31.81-33.75)	Reference	Reference	20.81 (20.34-21.29)	Reference	Reference
Users	23.24 (22.36-24.17)	0.84 (0.81-0.87)	0.85 (0.82-0.88)	16.96 (16.50-17.43)	0.91 (0.87-0.96)	0.92 (0.88-0.97)
With liver cirrhosis						
Non-users	36.26 (25.64-51.27)	1.83 (1.39-2.41)	1.82 (1.38-2.40)	29.38 (22.33-38.66)	1.11 (0.60-2.07)	1.11 (0.60-2.07)
Users	28.51 (15.34-52.98)	1.38 (0.87-2.19)	1.34 (0.84-2.13)	23.31 (14.69-37.00)	1.30 (0.58-2.90)	1.30 (0.58-2.83)
Myocardial infarction						
Without liver cirrhosis						
Non-users	16.65 (15.98-17.35)	Reference	Reference	11.28 (10.94-11.64)	Reference	Reference
Users	11.48 (10.87-12.12)	0.76 (0.72-0.80)	0.80 (0.76-0.84)	8.71 (8.39-9.04)	0.79 (0.73-0.84)	0.84 (0.79-0.91)
With liver cirrhosis						
Non-users	12.18 (6.75-22.00)	0.93 (0.57-1.52)	0.92 (0.57-1.51)	8.83 (5.41-14.42)	1.10 (0.49-2.44)	1.09 (0.49-2.43)
Users	19.10 (9.10-40.06)	0.72 (0.32-1.60)	0.70 (0.31-1.56)	7.21 (3.24-16.06)	2.74 (1.37-5.49)	2.79 (1.39-5.58)
Venous thromboembolic events						
Without liver cirrhosis						
Non-users	7.82 (7.37-8.30)	Reference	Reference	5.47 (5.24-5.71)	Reference	Reference
Users	6.16 (5.72-6.64)	0.77 (0.71-0.82)	0.78 (0.73-0.83)	4.17 (3.95-4.40)	0.77 (0.70-0.85)	0.79 (0.72-0.87)
With liver cirrhosis						
Non-users	7.68 (3.66-16.11)	2.40 (1.56-3.69)	2.32 (1.51-3.57)	11.57 (7.55-17.75)	1.99 (0.89-4.44)	1.95 (0.87-4.35)
Users	NA	1.22 (0.51-2.93)	1.14 (0.48-2.75)	6.02 (2.51-14.47)	0.64 (0.09-4.53)	0.61 (0.09-4.34)
Hemorrhagic stroke						
Without liver cirrhosis						
Non-users	3.75 (3.44-4.08)	Reference	Reference	2.67 (2.51-2.84)	Reference	Reference
Users	4.42 (4.06-4.83)	1.32 (1.21-1.44)	1.35 (1.24-1.47)	3.52 (3.32-3.73)	1.30 (1.17-1.46)	1.34 (1.20-1.50)
With liver cirrhosis						
Non-users	7.68 (3.66-16.11)	1.67 (0.79-3.52)	1.65 (0.79-3.48)	3.80 (1.81-7.98)	1.79 (0.57-5.55)	1.77 (0.57-5.50)

Users	13.45 (5.60-32.32)	1.98 (0.74-5.28)	1.93 (0.72-5.16)	NA	1.13 (0.16-8.07)	1.12 (0.16-7.97)
Subdural hemorrhage						
Without liver cirrhosis						
Non-users	1.60 (1.40-1.83)	Reference	Reference	1.23 (1.12-1.35)	Reference	Reference
Users	2.24 (1.98-2.53)	1.57 (1.39-1.77)	1.65 (1.46-1.86)	1.93 (1.79-2.09)	1.35 (1.16-1.56)	1.41 (1.22-1.63)
With liver cirrhosis						
Non-users	7.64 (3.64-16.03)	6.07 (3.33-11.06)	6.10 (3.35-11.12)	6.01 (3.33-10.85)	2.24 (0.56-8.98)	2.22 (0.55-8.92)
Users	NA	NA	NA	NA	NA	NA
Hemorrhage of the lung or urinary tract						
Without liver cirrhosis						
Non-users	14.75 (14.12-15.49)	Reference	Reference	12.12 (11.76-12.48)	Reference	Reference
Users	21.16 (20.33-22.03)	1.28 (1.23-1.33)	1.38 (1.32-1.44)	16.74 (16.29-17.20)	1.22 (1.15-1.28)	1.30 (1.23-1.37)
With liver cirrhosis						
Non-users	22.26 (14.36-34.51)	2.29 (1.72-3.05)	2.34 (1.76-3.12)	26.73 (20.09 - 35.58)	1.29 (0.70-2.41)	1.29 (0.70-2.41)
Users	24.83 (12.92-47.72)	1.81 (1.14-2.87)	1.92 (1.21-3.05)	22.42 (14.13-35.59)	0.96 (0.36-2.57)	1.04 (0.39-2.76)
Gastrointestinal hemorrhage						
Without liver cirrhosis						
Non-users	12.86 (12.27-13.47)	Reference	Reference	9.78 (9.47-10.11)	Reference	Reference
Users	11.35 (10.75-11.99)	1.01 (0.96-1.06)	1.05 (1.00-1.10)	9.68 (9.34-10.02)	1.10 (1.03-1.18)	1.15 (1.08-1.23)
With liver cirrhosis						
Non-users	42.26 (30.62-58.33)	3.90 (2.97-5.14)	3.86 (2.93-5.08)	30.25 (23.05-39.69)	4.75 (3.12-7.23)	4.72 (3.10-7.19)
Users	47.14 (29.30-75.82)	3.62 (2.40-5.45)	3.49 (2.32-5.27)	29.30 (19.47-44.10)	3.04 (1.45-6.38)	3.05 (1.45-6.41)

*Adjusted for age and sex; ¤ Adjusted for age, sex, CHA_2DS_2VASc score, and Charlson Comorbidity index score
Abbreviations: IR: incidence rate; CI: confidence interval; HR: hazard ratio

Figure 1 Classification of patients into exposure groups

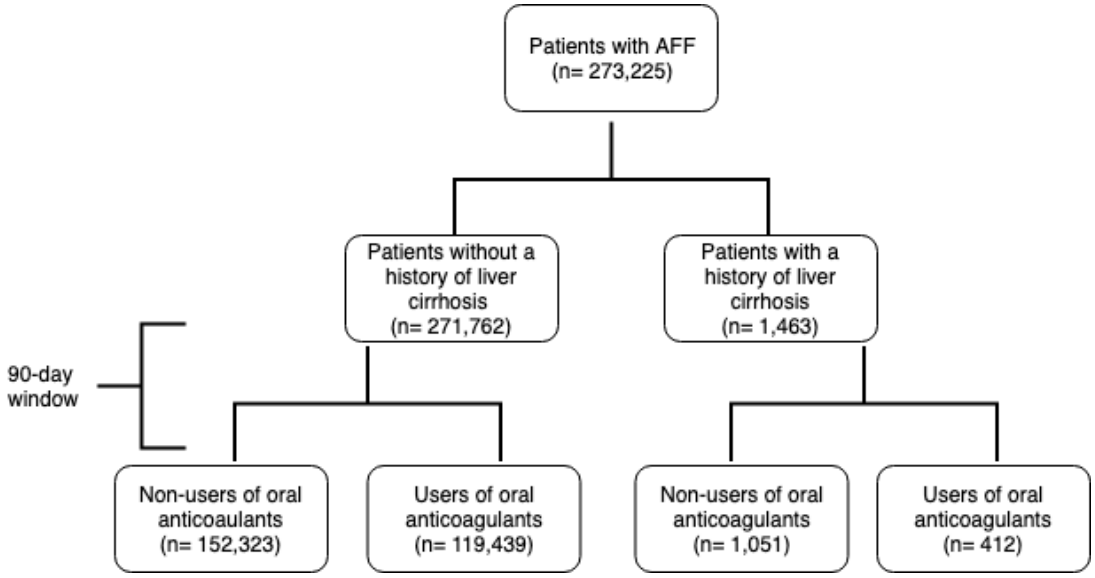


Figure 2 Cumulative 21-year incidence of ischemic stroke in patients with atrial fibrillation or flutter that did not use oral anticoagulants. Blue line: patients without liver cirrhosis; red line: patients with liver cirrhosis. Death was taken as a competing risk; analysis was not adjusted for age

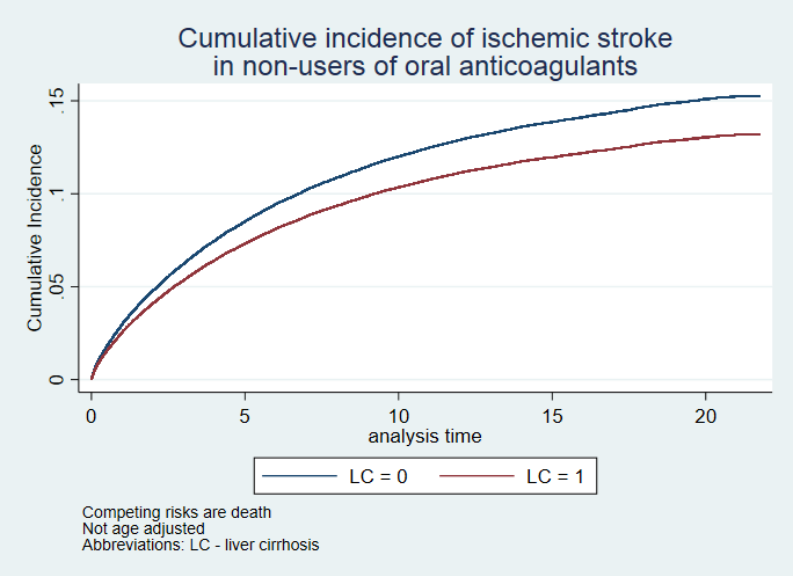


Figure 3 Cumulative 21-year incidence curve of ischemic stroke in patients with atrial fibrillation or flutter that used oral anticoagulants. Blue line: patients without liver cirrhosis; red line: patients with liver cirrhosis. Death was taken as a competing risk; analysis was not adjusted for age

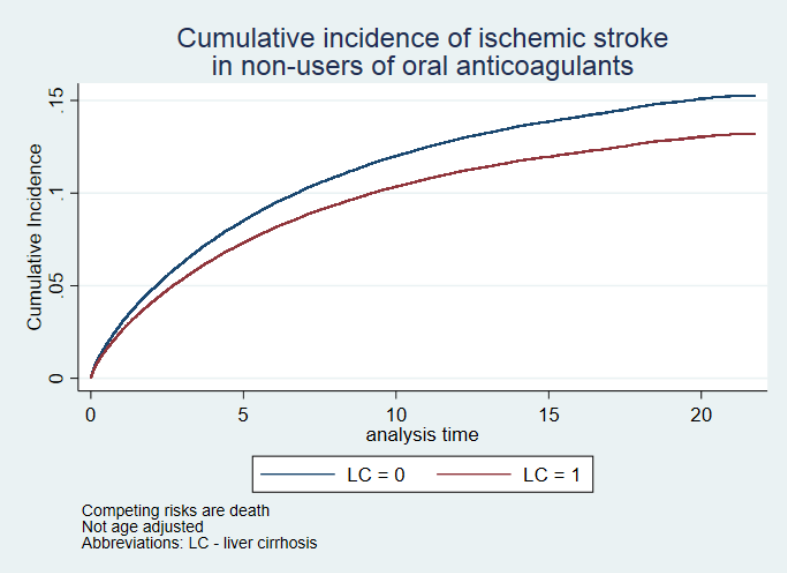


Figure 4 Cumulative 21-year incidence of hemorrhagic stroke in patients with atrial fibrillation or flutter that did not use oral anticoagulants. Blue line: patients without liver cirrhosis; red line: patients with liver cirrhosis. Death was taken as a competing risk; analysis was not adjusted for age.

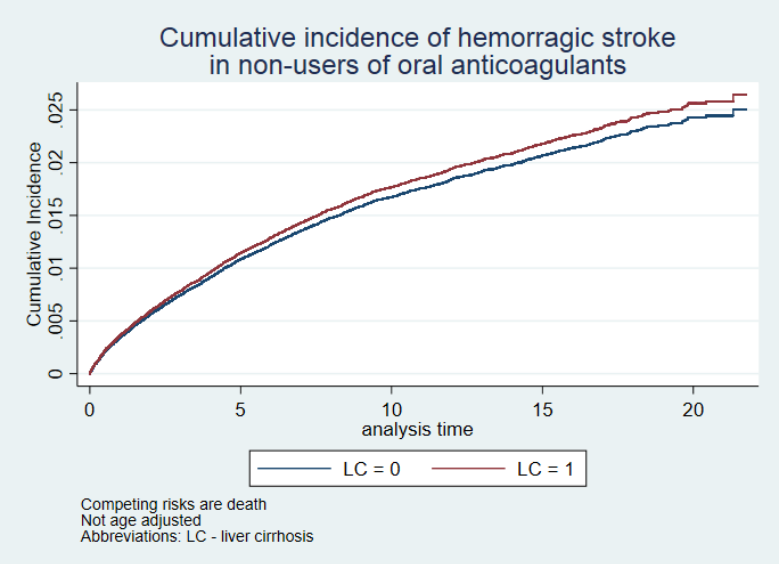
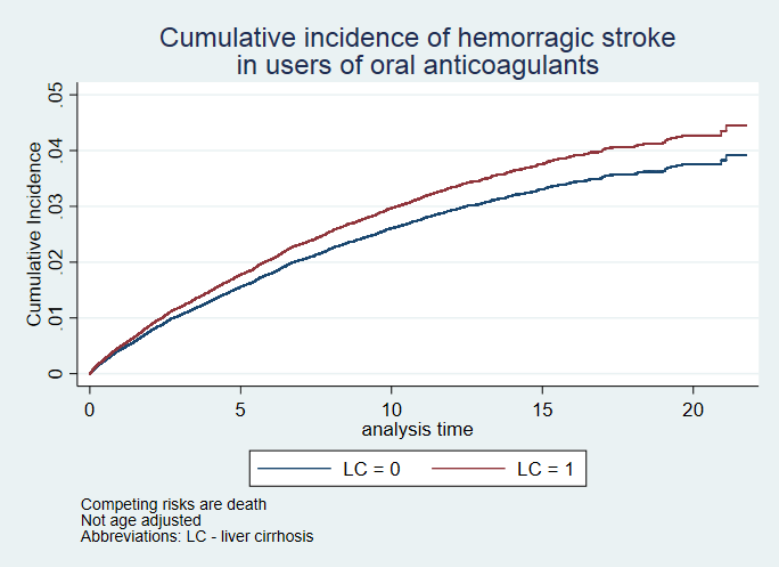


Figure 5 Cumulative 21-year incidence of hemorrhagic stroke in patients with atrial fibrillation or flutter that used oral anticoagulants. Blue line: patients without liver cirrhosis; red line: patients with liver cirrhosis. Death was taken as a competing risk; analysis was not adjusted for age



Supplementary tables

Supplementary table 1. Discharge diagnoses and Anatomical Therapeutic Chemical (ATC) codes used to identify and classify study subjects

Discharge diagnosis or type of anticoagulant	ATC code	ICD-8 and ICD-10 code
Atrial fibrillation and flutter	NA	ICD-8: 427.93-427.94; ICD-10: I48
Liver cirrhosis		
Alcoholic cirrhosis of liver	NA	ICD-8: 571.09; ICD-10: K70.3
Toxic liver disease with fibrosis and cirrhosis of liver	NA	ICD-8: NA; ICD-10: K71.7
Primary and secondary biliary cirrhosis	NA	ICD-8: 571.90, 571.91; ICD-10: K74.3, K74.4
Biliary cirrhosis, unspecified	NA	ICD-8: NA; ICD-10: K74.5
Chronic hepatic failure	NA	ICD-8: NA; ICD-10: K72.1
Other and unspecified cirrhosis of liver	NA	ICD-8: 571.92, 571.99; ICD-10: K74.6
Oral anticoagulants		
Warfarin (VKA)	B01AA03	NA
Phenprocoumon (VKA)	B01AA04	NA
Dabigatranetexilat (DOAC)	B01AE07	NA
Rivaroxaban (DOAC)	B01AF01	NA
Apixaban (DOAC)	B01AF02	NA
Edoxaban (DOAC)	B01AF03	NA

Abbreviations: VKA: vitamin K antagonists; DOAC: direct oral anticoagulants

Supplementary table 2. Discharge diagnoses used as indications of thromboembolic and bleeding outcomes

Diagnosis	ICD-8 code	ICD-10 code
Ischemic stroke	433-434	I63-I64
Myocardial infarction	410.09, 410.99	I21
Venous thromboembolic events	450.99, 451.00, 451.90	I26, I80.1-I80.3
Hemorrhagic stroke	430-431 (except 431.01)	I60-I61
Subdural hemorrhage	431.01	I620, S065
Hemorrhage of the lung or urinary tract	NA	J94.2, N02, R04, R31

Supplementary table 3. Discharge diagnoses used to characterize comorbidities in study subjects

Diagnosis	ATC code	ICD-8 code	ICD-10 code
Ischemic stroke	NA	433-434	I63, I64
Hemorrhagic stroke	NA	430-431	I60, I61
Ischemic heart diseases	NA	411-414	I20, I23-I25
Acute myocardial infarction	NA	410	I21
Arterial embolism and thrombosis	NA	444	I74
Heart failure	NA	427.09-427.11, 427.19, 428.99, 782.49	I11.0, I13.0, I13.2, I50.0, I50.1, I50.2, I50.3, I50.8, I50.9
Valvular diseases	NA	394-397424.00, 424.01, 424.02, 424.08, 424.09, 424.10, 424.11, 424.12, 424.18, 424.19, 424.90, 424.91, 424.92,	I05-I08, I09.9, I34-I37, I39
Cardiomyopathy	NA	425	I42-I43
Hypertension	C02A, C02B, C02C, C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, C02DB, C02DD, C02DG, C04, C05, C07	400-404	I10-I15, I67.4
Deep venous thrombosis and pulmonary embolism	NA	450.99, 451.00, 451.90	I26, I80.1-I80.3
Hyperlipidemia	NA	272.00	E78.0-E78.5
Diabetes mellitus	A10	249, 250 (excluding 249.02, 250.02)	E10-E14, H36.0
Obesity	NA	277	E65, E66
Chronic kidney disease	NA	249.02, 250.02, 403-405, 582-585, 590.09, 593.20, 753.10-753.19, 792	E10.2, E11.2, E14.2, N03, N05, N11.0, N14, N16, N18-N19, N26.9, Q61.1-Q61.4
Chronic pulmonary diseases	R03	490-493, 515- 518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2-J98.3
Thyrotoxicosis	NA	242	E05
Autoimmune rheumatic disease	NA	712, 734.19, 734.90	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35,D86
Inflammatory bowel disease	NA	563.00, 563..01, 563.02, 563.19	K50, K51
Cancer	NA	140-163,170-174,180-199, 200-209	C00-C96
Peptic ulcer	NA	531-533	K25-K27
Portal vein thrombosis and mesenteric vein thrombosis	NA	452	I81, K55.0H
Varices of the upper gastrointestinal tract without bleeding	NA	456.00	I85.9, I86.4 (excluding I86.4A), I98.2
Esophageal varices with bleeding	NA	456.01	I85.0
Ascites	NA	785.39	R18

Supplementary table 4. ATC codes used to determine comedications used by study subjects

Comedication	ATC-code
Calcium channel blockers	C08
Non-selective, non-combined beta-blockers	C07AA
All other beta-blockers	C07 (excluding C07AA)
Medications that affect the renin-angiotensin axis	C09
Digoxin	C01AA05
Statins	C10AA, C10B,
Acetylsalicylic acid	B01AC06, N02BA01
Non-aspirin, nonsteroidal anti-inflammatory drugs	M01A, (excluding M01AX05)
Diuretics, excluding aldosterone antagonists	C03 (excluding C03DA)
Aldosterone antagonist	C03DA
Amiodarone	C01BD01
Platelet inhibitors (clopidogrel, dipyrammol, ticagrelor)	B01AC04, B01AC07, B01AC24

Supplementary table 5. Discharge diagnoses used to identify variables included in the CHA_2DS_2VASc score

Diagnosis	ATC code	ICD-8 code	ICD-10 code
Stroke/ transient ischemic attack /peripheral embolism	NA	433-435, 444, 450.99	G45.8, G45.9, I26, I63, I64, I74
Vascular disease	NA	410, 440	I21, I70.0, I70.1–I70.9,
Congestive heart failure	NA	425, 427.09, 427.19	I11.0, I13.0, I13.2 I42, I50
Hypertension	C02A, C02B, C02C, C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, C02DB, C02DD, C02DG, C04, C05, C07	400-404	I10-I15, I67.4
Diabetes mellitus	A10	249, 250 (excluding 249.02, 250.02)	E10-E14, H36.0

Supplementary table 6. Discharge diagnoses used to determine the Charlson Comorbidity Index

Diagnosis	ATC code	ICD-8 code	ICD-10 code	score
Dementia	NA	290, 293.09	F00-F03, F05.1, G30	1
Chronic obstructive pulmonary diseases	R03	490-493, 515-518	J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2-J98.3	1
Connective tissue disease	NA	135.99, 446, 712, 716,	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35,D86	1
Peptic ulcer	NA	531-534	K25-K28	1
Hemiplegia	NA	344	G81-G82	2
Chronic kidney disease	NA	249.02, 250.02, 403-405, 582-585, 590.09, 593.20, 753.10-753.19, 792	E10.2, E11.2, E14.2, N03, N05, N11.0, N14, N16, N18-N19, N26.9, Q61.1-Q61.4	2
Any tumor	NA	140-195	C00-C75	2
Leukemia	NA	204-208	C91-C95	2
Lymphoma	NA	200-204	C81-C85, C88, C90, C96	2
Metastatic solid tumor	NA	195-200	C76-C80	6
Acquired immune deficiency syndrome (AIDS)	NA	079.83	B21-B24	6

Supplementary table 7. Characteristics of patients with atrial fibrillation or flutter, with and without liver cirrhosis, in the period 1995-2015

Characteristic	Patients without liver cirrhosis N=271,762	Patients with liver cirrhosis N=1,463	Patients without liver cirrhosis N=271,762		Patients with liver cirrhosis N=1,463	
			Non-users of oral anticoagulants N=152,323	Users of oral anticoagulants N=119,439	Non-users of oral anticoagulants N=1,051	Users of oral anticoagulants N=412
Year of diagnosis of atrial fibrillation or flutter						
1995-1999	43,648 (16.06)	172 (11.76)	30,043 (19.72)	13,605 (11.39)	136 (12.94)	36 (8.74)
2000-2003	48,882 (17.99)	229 (15.65)	30,597 (20.09)	18,285 (15.31)	170 (16.18)	59 (14.31)
2004-2007	51,185 (18.83)	306 (20.92)	28,195 (18.51)	22,990 (19.25)	222 (21.12)	84 (20.39)
2008-2011	57,023 (20.98)	333 (22.76)	31,841(20.90)	25,182 (21.08)	253 (24.07)	80 (19.42)
2012-2015	71,024 (26.13)	423 (28.91)	31,647 (20.78)	39,377 (32,97)	270 (25.69)	153 (37.14)
Time since diagnosis of liver cirrhosis						
0-1 years	NA	1,037 (70.88)	NA	NA	755 (71.84)	282 (68.45)
2-5 years	NA	120 (8.20)	NA	NA	95 (9.04)	25 (6.07)
6-9 years	NA	88 (6.02)	NA	NA	58 (5.52)	30 (7.28)
>10 years	NA	218 (14.90)	NA	NA	143 (13.61)	75 (18.20)
Comorbidities						
Ischemic stroke	9,841 (3.62)	56 (3.83)	5,402 (3.55)	4,439 (3.72)	40 (3.81)	16 (3.88)
Hemorrhagic stroke	720 (0.26)	9 (0.62)	495 (0.32)	225 (0.19)	6 (0.57)	<5 (NA)
Ischemic heart diseases	6,697 (2.46)	38 (2.60)	4,158 (2.73)	2,539 (2.13)	20 (1.90)	18 (4.37)
Acute myocardial infarction	5,886 (2.17)	27 (1.85)	3,521 (2.31)	2,365 (1.98)	16 (1.52)	11 (2.67)
Arterial embolism and thrombosis	362 (0.13)	<5 (NA)	230 (0.15)	132 (0.11)	<5 (NA)	<5 (NA)
Heart failure	29,490 (10.85)	197 (13.47)	17,570 (11.53)	11,920 (9.98)	127 (12.08)	70 (16.99)
Valvular diseases	13,209 (4.86)	69 (4.72)	6,373 (4.18)	6,836 (5.72)	36 (3.43)	33 (8.01)
Cardiomyopathy	3,862 (1.42)	47 (3.21)	1,898 (1.25)	1,964 (1.64)	28 (2.66)	19 (4.61)
Hypertension	94,424 (34.75)	608 (41.56)	54,887 (36.03)	39,537 (33.10)	440 (41.86)	168 (40.78)
Deep venous thrombosis and/or pulmonary embolism	4,277 (1.57)	37 (2.53)	2,208 (1.45)	2,069 (1.73)	25 (2.38)	12 (2.91)
Hyperlipidemia	18,760 (6.90)	105 (7.18)	10,251 (6.73)	8,509 (7.12)	72 (6.85)	33 (8.01)
Diabetes mellitus	27,168 (10.00)	300 (20.51)	14, 881 (9.77)	12,287 (10.29)	208 (19.79)	92 (22.33)
Obesity	2,685 (0.99)	32 (2.19)	1,445 (0.95)	1,240 (1.04)	19 (1.81)	13 (3.16)
Chronic kidney disease	6,400 (2.36)	83 (5.67)	3,977 (2.61)	2,423 (2.03)	55 (5.23)	28 (6.80)
Chronic pulmonary diseases	68,920 (25.36)	528 (36.09)	40,913 (26.86)	28,007 (23.45)	367 (34.92)	161 (39.08)

Thyrotoxicosis	1,274 (0.47)	5 (0.34)	800 (0.53)	474 (0.40)	<5 (NA)	<5 (NA)
Autoimmune rheumatic disease	1,073 (0.39)	8 (0.55)	705 (0.46)	368 (0.31)	6 (0.57)	<5 (NA)
Inflammatory bowel disease	901 (0.33)	11 (0.75)	590 (0.39)	311 (0.26)	9 (0.86)	<5 (NA)
Cancer	21,013 (7.73)	146 (9.98)	13,481 (8.85)	7,532 (6.31)	106 (10.09)	40 (9.71)
Peptic ulcer	10,346 (3.81)	217 (14.83)	6,754 (4.43)	3,592 (3.01)	174 (16.56)	43 (10.44)
Portal vein thrombosis and mesenteric vein thrombosis	11 (0.00)	<5 (NA)	6 (0.00)	5 (0.00)	<5 (NA)	<5 (NA)
Varices of the upper gastrointestinal tract without bleeding	81 (0.03)	123 (8.41)	52 (0.03)	29 (0.02)	99 (9.42)	24 (5.83)
Varices of the upper gastrointestinal tract with bleeding	51 (0.02)	92 (6.29)	37 (0.02)	14 (0.01)	77 (7.33)	15 (3.64)
Ascites	12 (0.00)	17 (1.16)	5 (0.00)	7 (0.01)	13 (1.24)	<5 (NA)
Comedications						
Calcium channel blockers	56,976 (20.97)	221 (15.11)	28,506 (18.71)	28,470 (23.84)	135 (12.84)	86 (20.87)
Non-selective, non-combined beta-blockers	16,550 (6.09)	125 (8.54)	9,932 (6.52)	6,618 (5.54)	100 (9.51)	25 (6.07)
All other beta-blockers	115,819 (42.62)	538 (36.77)	51,582 (33.86)	64,237 (53.78)	330 (31.40)	208 (50.49)
Medication targeting the renin-angiotensin axis	87,881 (32.34)	346 (23.65)	39,041 (25.63)	48,840 (40.89)	196 (18.65)	150 (36.41)
Digoxin	90,784 (33.41)	529 (36.16)	45,673 (29.98)	45,111 (37.77)	366 (34.82)	163 (39.56)
Statins	55,915 (20.57)	218 (14.90)	24,962 (16.39)	30,953 (25.92)	129 (12.27)	89 (21.60)
Acetylsalicylic acid	80,585 (29.65)	363 (24.81)	55,499 (36.44)	25,086 (21.00)	280 (26.64)	83 (20.15)
Non-aspirin NSAIDs	20,660 (7.60)	111 (7.59)	13,424 (8.81)	7,236 (6.06)	81 (7.71)	30 (7.28)
Diuretics, excluding aldosterone antagonists	118,332 (43.54)	739 (50.51)	62,479 (41.02)	55,853 (46.76)	511 (48.62)	228 (55.34)
Aldosterone antagonist	17,925 (6.60)	382 (26.11)	8,537 (5.60)	9,388 (7.86)	294 (27.97)	88 (21.36)
Amiodarone	12,601 (4.64)	73 (4.99)	5,145 (3.38)	7,456 (6.24)	39 (3.71)	34 (8.25)
Platelet inhibitors (clopidogrel, dipyrammol, ticagrelor)	17,496 (6.44)	96 (6.56)	12,507 (8.21)	4,989 (4.18)	70 (6.66)	26 (6.31)

Values are the number (%), unless indicated otherwise.

Supplementary table 8. Incidence rate and hazard ratios (HRs) with 95% confidence intervals (95% CIs) of arterial thromboembolic events, venous thromboembolic events, major bleeding events, and other bleeding events during 0-1 year and 2-5 years after the index date, in patients with atrial fibrillation or flutter, with and without liver cirrhosis that either used (user) or did not use (non-user) oral anticoagulants, in Denmark from 1995 through 2016; patients were stratified by anticoagulant treatment status

Events and exposure to liver cirrhosis and oral anticoagulants	0-1 year			2-5 years		
	IR (95% CI)	Partially adjusted HR(95% CI)	Fully adjusted HR (95% CI)	IR (95% CI)	Partially adjusted HR(95% CI)	Fully adjusted HR (95% CI)
Ischemic stroke						
Non-users of oral anticoagulants - without liver cirrhosis	32.77 (31.81 - 33.75)	Reference	Reference	20.81 (20.34-21.29)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	36.26 (25.64-51.27)	1.83 (1.39-2.41)	1.81 (1.38-2.40)	29.38 (22.33-38.66)	1.11 (0.60-2.07)	1.11 (0.60-2.07)
Users of oral anticoagulants - without liver cirrhosis	23.24 (22.36-24.17)	Reference	Reference	16.96 (16.50-17.43)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	28.51 (15.34-52.98)	1.60 (1.01-2.54)	1.53 (0.96-2.43)	23.31 (14.69-37.00)	1.48 (0.66-3.30)	1.43 (0.64-3.19)
Myocardial infarction						
Non-users of oral anticoagulants - without liver cirrhosis	16.65 (15.98-17.35)	Reference	Reference	11.28 (10.94-11.64)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	12.18 (6.75-22.00)	0.93 (0.57-1.52)	0.92 (0.57-1.51)	8.83 (5.41-14.42)	1.10 (0.49-2.44)	1.09 (0.49-2.43)
Users of oral anticoagulants - without liver cirrhosis	11.48 (10.87-12.12)	Reference	Reference	8.71 (8.39-9.04)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	19.10 (9.10-40.06)	0.93 (0.42-2.07)	0.84 (0.38-1.87)	7.21 (3.24-16.06)	2.74 (1.37-5.49)	3.21 (1.60-6.45)
Venous thromboembolic events						

Non-users of oral anticoagulants - without liver cirrhosis	7.82 (7.37-8.30)	Reference	Reference	5.47 (5.24-5.71)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	7.68 (3.66-16.11)	2.40 (1.56-3.69)	2.32 (1.51-3.57)	11.57 (7.55-17.75)	2.00 (0.89-4.44)	1.95 (0.87-4.35)
Users of oral anticoagulants - without liver cirrhosis	6.16 (5.72-6.64)	Reference	Reference	4.17 (3.95-4.40)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	NA	1.56 (0.65-3.76)	1.44 (0.60-3.46)	6.02 (2.51-14.47)	0.78 (0.11-5.58)	0.72 (0.10-5.13)
Hemorrhagic stroke						
Non-users of oral anticoagulants - without liver cirrhosis	3.75 (3.44-4.08)	Reference	Reference	2.67 (2.51-2.84)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	7.68 (3.66-16.11)	1.67 (0.79-3.52)	1.65 (0.79-3.48)	3.80 (1.81-7.98)	1.79 (0.57-5.55)	1.77 (0.57-5.50)
Users of oral anticoagulants - without liver cirrhosis	4.42 (4.06-4.83)	Reference	Reference	3.52 (3.32-3.73)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	13.45 (5.60-32.32)	1.59 (0.59-4.23)	1.54 (0.58-4.12)	NA	0.90 (0.13-6.39)	0.87 (0.12-6.22)
Subdural hemorrhage						
Non-users of oral anticoagulants - without liver cirrhosis	1.60 (1.40-1.83)	Reference	Reference	1.23 (1.12-1.35)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	7.64 (3.64-16.03)	6.07 (3.33-11.06)	6.10 (3.35-11.12)	6.01 (3.33-10.85)	2.24 (0.56-8.98)	2.22 (0.55-8.92)
Users of oral anticoagulants - without liver cirrhosis	2.24 (1.98-2.53)	Reference	Reference	1.93 (1.79-2.09)	Reference	Reference

Users of oral anticoagulants - with liver cirrhosis	NA	NA	1.05 (1.04-1.06)	NA	NA	NA
Hemorrhage of the lung or urinary tract						
Non-users of oral anticoagulants - without liver cirrhosis	14.75 (14.12-15.49)	Reference	Reference	12.12 (11.76-12.48)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	22.26 (14.36-34.51)	2.29 (1.72-3.05)	2.34 (1.76-3.12)	26.73 (20.09 - 35.58)	1.29 (0.70-2.41)	1.29 (0.70-2.41)
Users of oral anticoagulants - without liver cirrhosis	21.16 (20.33-22.03)	Reference	Reference	16.74 (16.29-17.20)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	24.83 (12.92-47.72)	1.44 (0.91-2.29)	1.40 (0.88-2.22)	22.42 (14.13-35.59)	0.80 (0.30-2.14)	0.81 (0.31-2.17)
Gastrointestinal hemorrhage						
Non-users of oral anticoagulants - without liver cirrhosis	12.86 (12.27-13.47)	Reference	Reference	9.78 (9.47-10.11)	Reference	Reference
Non-users of oral anticoagulants - with liver cirrhosis	42.26 (30.62-58.33)	3.90 (2.97-5.14)	3.86 (2.93-5.08)	30.25 (23.05-39.69)	4.75 (3.16-7.23)	4.72 (3.10-7.19)
Users of oral anticoagulants - without liver cirrhosis	11.35 (10.74-11.99)	Reference	Reference	9.68 (9.34-10.02)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	47.14 (29.30-75.82)	3.62 (2.40-5.46)	3.30 (2.19-4.97)	29.84 (11.88-43.90)	2.73 (1.30-5.75)	2.55 (1.22-5.37)

*Adjusted for age and sex; ¤ Adjusted for age, sex, CHA_2DS_2VASc score, and Charlson Comorbidity index score
Abbreviations: IR: incidence rate; CI: confidence interval; HR: hazard ratio

Supplementary table 9. Incidence rate and hazard ratios (HRs) with 95% confidence intervals (95% CIs) of arterial thromboembolic events, venous thromboembolic events, major bleeding events, and other bleeding events, during 0-1 year and 1-5 years after the index date, in patients with atrial fibrillation or flutter, with and without liver cirrhosis that either used (user) or did not use (non-user) oral anticoagulants, in Denmark from 1995 through 2016; patients were stratified by liver cirrhosis

Event and exposure to liver cirrhosis and oral anticoagulants	0-1 year			2-5 years		
	IR (95% CI)	Partially adjusted HR(95% CI)	Fully adjusted HR (95% CI)	IR (95% CI)	Partially adjusted HR(95% CI)	Fully adjusted HR (95% CI)
Ischemic stroke						
Non-users of oral anticoagulants - without liver cirrhosis	32.77 (31.81-33.75)	Reference	Reference	20.81 (20.34-21.29)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	23.24 (22.36-24.17)	0.84 (0.81-0.87)	0.85 (0.82-0.88)	16.96 (16.50-17.43)	0.91 (0.87-0.96)	0.92 (0.88-0.97)
Non-users of oral anticoagulants - with liver cirrhosis	36.26 (25.64-51.27)	Reference	Reference	29.38 (22.33-38.66)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	28.51 (15.34-52.98)	0.76 (0.45-1.31)	0.76 (0.44-1.31)	23.31 (14.69-37.00)	1.16 (0.41-3.24)	1.21 (0.44-3.34)
Myocardial infarction						
Non-users of oral anticoagulants - without liver cirrhosis	16.65 (15.98-17.35)	Reference	Reference	11.28 (10.94-11.64)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	11.48 (10.87-12.12)	0.76 (0.72-0.80)	0.80 (0.76-0.84)	8.71 (8.39-9.04)	0.79 (0.73-0.85)	0.84 (0.79-0.91)
Non-users of oral anticoagulants - with liver cirrhosis	12.18 (6.75-22.00)	Reference	Reference	8.83 (5.41-14.42)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	19.10 (9.10-40.06)	0.81 (0.32-2.07)	0.82 (0.32-2.10)	7.21 (3.24-16.06)	2.59 (0.89-7.55)	2.44 (0.83-7.20)
Venous thromboembolic events						

Non-users of oral anticoagulants - without liver cirrhosis	7.82 (7.37-8.30)	Reference	Reference	5.47 (5.24-5.71)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	6.16 (5.72-6.64)	0.77 (0.72-0.82)	0.78 (0.73-0.83)	4.17 (3.95-4.40)	0.77 (0.70-0.85)	0.79 (0.72-0.87)
Non-users of oral anticoagulants - with liver cirrhosis	7.68 (3.66-16.11)	Reference	Reference	11.57 (7.55-17.75)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	NA	0.50 (0.19-1.34)	0.50 (0.19-1.33)	6.02 (2.51-14.47)	0.31 (0.04-2.59)	0.36 (0.04-3.09)
Hemorrhagic stroke						
Non-users of oral anticoagulants - without liver cirrhosis	3.75 (3.44-4.08)	Reference	Reference	2.67 (2.51-2.84)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	4.42 (4.06-4.83)	1.32 (1.21-1.44)	1.35 (1.24-1.47)	3.52 (3.32-3.73)	1.30 (1.17-1.46)	1.34 (1.20-1.50)
Non-users of oral anticoagulants - with liver cirrhosis	7.68 (3.66-16.11)	Reference	Reference	3.80 (1.81-7.98)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	13.45 (5.60-32.32)	1.26 (0.37-4.32)	1.16 (0.34-4.01)	NA	0.60 (0.06-6.06)	0.65 (0.07-6.37)
Subdural hemorrhage						
Non-users of oral anticoagulants - without liver cirrhosis	1.60 (1.40-1.83)	Reference	Reference	1.23 (1.12-1.35)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	2.24 (1.98-2.53)	1.57 (1.39-1.77)	1.65 (1.46-1.86)	1.93 (1.79-2.09)	1.35 (1.17-1.56)	1.41 (1.22-1.63)
Non-users of oral anticoagulants - with liver cirrhosis	7.64 (3.64-16.03)	Reference	Reference	6.01 (3.33-10.85)	Reference	Reference

Users of oral anticoagulants - with liver cirrhosis	NA	NA	NA	NA	NA	NA
Hemorrhage of the lung or urinary tract						
Non-users of oral anticoagulants - without liver cirrhosis	14.75 (14.12-15.49)	Reference	Reference	12.12 (11.76-12.48)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	21.16 (20.33-22.03)	1.28 (1.23-1.33)	1.38 (1.32-1.44)	16.74 (16.29-17.20)	1.22 (1.15-1.28)	1.30 (1.23-1.37)
Non-users of oral anticoagulants - with liver cirrhosis	22.26 (14.36-34.51)	Reference	Reference	26.73 (20.09 - 35.58)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	24.83 (12.92-47.72)	0.79 (0.46-1.37)	0.83 (0.48-1.42)	22.42 (14.13-35.59)	0.77 (0.24-2.46)	0.82 (0.26-2.63)
Gastrointestinal hemorrhage						
Non-users of oral anticoagulants - without liver cirrhosis	12.86 (12.27-13.47)	Reference	Reference	9.78 (9.47-10.11)	Reference	Reference
Users of oral anticoagulants - without liver cirrhosis	11.35 (10.74-11.99)	1.01 (0.96-1.06)	1.05 (1.00-1.10)	9.68 (9.34-10.02)	1.10 (1.03-1.18)	1.15 (1.08-1.23)
Non-users of oral anticoagulants - with liver cirrhosis	42.26 (30.62-58.33)	Reference	Reference	30.25 (23.05-39.69)	Reference	Reference
Users of oral anticoagulants - with liver cirrhosis	47.14 (29.30-75.82)	0.95 (0.58-1.56)	0.96 (0.59-1.57)	29.84 (11.88-43.90)	0.73 (0.31-1.72)	0.63 (0.27-1.49)

*Adjusted for age and sex; ¤ Adjusted for age, sex, CHA_2DS_2VASc score, and Charlson Comorbidity index score
Abbreviations: IR: incidence rate; CI: confidence interval; HR: hazard ratio

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