# Thromboembolism and bleeding in patients with atrial fibrillation and liver disease - a nationwide register-based cohort study

*Thromboembolism and bleeding in liver disease*

Steensig, Kamilla; Pareek, Manan; Krarup, Anne Lund; Sogaard, Peter; Maeng, Michael; Tayal, Bhupendar; Lee, Christina Ji-Young; Torp-Pedersen, Christian; Lip, Gregory Y. H.; Holland-Fischer, Peter; Kragholm, Kristian Hay

*Published in:*
Clinics and research in hepatology and gastroenterology

*DOI (link to publication from Publisher):*
10.1016/j.clinre.2022.101952



*Publication date:*
2022

*Document Version*
Publisher's PDF, also known as Version of record

Clinics and Research in Hepatology and Gastroenterology 46 (2022) 101952

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE

# Thromboembolism and bleeding in patients with atrial fibrillation and liver disease — A nationwide register-based cohort study

# Thromboembolism and bleeding in liver disease

Kamilla Steensig[a,*,1], Manan Pareek[b,*,1], Anne Lund Krarup[c,d], Peter Sogaard[a], Michael Maeng[e], Bhupendar Tayal[a], Christina Ji-Young Lee[f,g], Christian Torp-Pedersen[a,g], Gregory YH Lip[a,h], Peter Holland-Fischer[d,i], Kristian Hay Kragholm[a,j]

[a] *Department of Cardiology, Aalborg University Hospital, Denmark*
[b] *Department of Cardiology, North Zealand Hospital, Hilleroed, Denmark*
[c] *Department of Neurogastroenterological Research and Centre for Clinical Research, North Denmark Regional Hospital, Denmark*
[d] *Department of Clinical Medicine, Aalborg University, Denmark*
[e] *Department of Cardiology, Aarhus University Hospital, Denmark*
[f] *Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Denmark*
[g] *Department of Clinical Research, North Zealand Hospital, Denmark*
[h] *Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, United Kingdom*
[i] *Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark*
[j] *Unit of Clinical Biostatistics and Epidemiology, Aalborg University Hospital, Denmark*

Available online 21 May 2022

**KEYWORDS**
Atrial fibrillation;
Bleeding;
Liver disease;

**Abstract**
*Background:* Balancing the risk of thromboembolism and bleeding in patients with liver disease and atrial fibrillation/flutter is particularly challenging.

*Abbreviations:* AF, atrial fibrillation and flutter; ARR, average risk ratios; DOAC, direct oral anticoagulant; ICD-10, International Classification of Diseases, Tenth Revision; GDPR, General Data Protection Regulation; INR, international normalised ratio; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease-Sodium; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulation; TE, thromboembolic events; TIA, transient ischaemic attack; VK, Avitamin K antagonist.

* Corresponding author: Manan Pareek, MD, PhD, FAHA, FESC, Department of Cardiology, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark.
*E-mail addresses:* mananpareek@dadlnet.dk, manan.pareek@regionh.dk (M. Pareek).
[1] Equal contribution as co-first authors.

https://doi.org/10.1016/j.clinre.2022.101952

Oral anticoagulants;
Stroke;
Thromboembolism

*Purpose:* To examine the risks of thromboembolism and bleeding with use/non-use of oral anticoagulation (including vitamin K-antagonists and direct oral anticoagulants) in patients with liver disease and AF.

*Methods:* Danish nationwide register-based cohort study of anticoagulant naive individuals with liver disease, incident atrial fibrillation/flutter, and a $CHA_2DS_2$-VASc-score$\geq$1 (men) or $\geq$2 (women), alive 30 days after atrial fibrillation/flutter diagnosis. Thromboembolism was a composite of ischaemic stroke, transient ischaemic attack, or venous thromboembolism. Bleeding was a composite of gastrointestinal, intracerebral, or urogenital bleeding requiring hospitalisation, or epistaxis requiring emergency department visit or hospital admission. Cause-specific Cox-regression was used to estimate absolute risks and average risk ratios standardised to covariate distributions. Because of significant interactions with anticoagulants, results for thromboembolism were stratified for CHA2DS2-VASc-score, and results for bleeding were stratified for cirrhotic/non-cirrhotic liver disease.

*Results:* Four hundred and nine of 1,238 patients with liver disease and new atrial fibrillation/flutter initiated anticoagulants. Amongst patients with a CHA2DS2-VASc-score of 1–2 (2–3 for women), five-year thromboembolism incidence rates were low and similar in the anticoagulant (6.5%) versus no anticoagulant (5.5%) groups (average risk ratio 1.19 [95%CI, 0.22–2.16]). In patients with a CHA2DS2-VASc-score>2 (>3 for women), incidence rates were 16% versus 24% (average risk ratio 0.66 [95%CI, 0.45–0.87]). Bleeding risks appeared higher amongst patients with cirrhotic versus non-cirrhotic disease but were not significantly affected by anticoagulant status.

*Conclusion:* Oral anticoagulant initiation in patients with liver disease, incident new atrial fibrillation/flutter, and a high CHA2DS2-VASc-score was associated with a reduced thromboembolism risk. Bleeding risk was not increased with anticoagulation, irrespective of the type of liver disease.



## Introduction

Atrial fibrillation and flutter (AF) and liver disease are chronic conditions associated with significant morbidity and mortality [1]. They are both highly prevalent and often coexist because of shared risk factors [2]. Patients with liver disease have an increased risk of bleeding, but while they were traditionally thought to be protected from thromboembolic events (TE) without a need for therapeutic anticoagulation, recent evidence appears to contradict this concept [1,3,4]. Indeed, balancing TE and bleeding risk in these individuals is particularly challenging because of decreased concentrations of endogenous anticoagulants, increased levels of procoagulants, and reduced platelet production [5].

TE risk in patients with non-valvular AF is assessed by the $CHA_2DS_2$-VASc score [6]. Contemporary US and European guidelines for AF recommend initiation of oral anticoagulation (OAC) for TE prevention in men with a $CHA_2DS_2$-VASc score $\geq$2 and women with a score $\geq$3 (class I recommendation) [7–9]. They further suggest consideration of OAC in men and women with $CHA_2DS_2$-VASc scores of 1 and 2, respectively (class IIa recommendation) [7–9]. However, randomized evidence to guide management in patients with these low $CHA_2DS_2$-VASc scores is lacking [10]. Nevertheless, although patients with AF generally benefit from therapeutic anticoagulation, patients with liver disease have generally been excluded from randomised controlled trials evaluating the efficacy and safety of OAC [11–14].

Therefore, we aimed to compare the risks of TE and bleeding in relation to OAC initiation (including both vitamin K antagonists [VKA] and direct OAC [DOAC]) in patients with liver disease, first diagnosed AF, and a $CHA_2DS_2$-VASc score of $\geq$1 in men and $\geq$2 in women.

## Methods

We conducted a register-based cohort study using Danish nationwide administrative registries. The national healthcare system in Denmark is taxpayer funded and public, ensuring free access to healthcare for all Danish residents. At birth or upon immigration, each resident is issued a unique 10-digit personal identifier by the Danish Civil Registration System. This identifier is used throughout every regional and national register and ensures accurate cross-linkage of healthcare information.

### Patient selection

Consecutive patients with pre-existing liver disease and a first episode of AF diagnosed January 1, 2010 through December 31, 2017 who were alive after 30 days were included. The latter cut-off was selected to allow time for redemption of OAC prescriptions. Details on medications, diseases and severity, and laboratory values are presented below in separate paragraphs. Relevant International Classification of Diseases, Tenth Revision (ICD-10) codes for liver disease are listed in *Supplemental Table 1*. Patients who had been treated with OAC within the last 6 months prior to study inclusion and patients who switched anticoagulant agent within the first 30 days of follow-up were excluded. Those without an indication for OAC in the setting of nonvalvular AF ($CHA_2DS_2$-VACs scores <1 in men and <2 in women, respectively) were also excluded.

## Patient exposure

Patients were compared according to whether OAC was initiated and their $CHA_2DS_2$-VASc score, with 1 point assigned for heart failure, hypertension, age 65−74 years, diabetes mellitus, vascular disease (prior myocardial infarction or peripheral artery disease), and female sex, and 2 points assigned for age ≥75 years and prior stroke/transient ischaemic attack (TIA)/venous thromboembolism. Furthermore, liver cirrhosis was defined as 1) an ICD-10 diagnosis of liver cirrhosis (excluding primary biliary cholangitis) or 2) a diagnosis of liver disease or primary biliary cholangitis plus at least one of the following: oesophageal or gastric varices, ascites, or hepatorenal syndrome.

## Study variables and data sources

Data on age and sex were retrieved from the Danish Civil Registration System [15]. Information on vital status was obtained from the Danish Register of Causes of Death [16]. Clinically relevant comorbidities were acquired through the Danish National Patient Register that contains information on all hospital-based inpatient and outpatient diagnoses in Denmark since 1977 [17]. We obtained information on previous ischaemic stroke, TIA, venous thromboembolism (pulmonary embolism, superficial thrombophlebitis, deep vein thrombosis, or portal vein thrombosis), peripheral artery disease, myocardial infarction, other ischaemic heart disease, and heart failure. Information on hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease was also acquired. Bleeding events within the last 5 years prior to study inclusion included gastrointestinal, urogenital, and intracerebral bleedings requiring hospitalisation, and epistaxis requiring emergency department visit or hospital admission.

Medication data were obtained from the Danish National Prescription Register that contains information on all pharmacy-dispensed prescriptions since 1995 [18]. Data on antiplatelet agents (aspirin and $P2Y_{12}$ inhibitors), lipid lowering agents (statins, fibrates, bile acid sequestrants, nicotinic acid and derivates, and combined lipid lowering drugs), nonsteroidal anti-inflammatory drugs (NSAID), and OAC including VKA (warfarin and phenprocoumon) and DOAC (rivaroxaban, apixaban, dabigatran, and edoxaban) were collected. Less than three patients were treated with edoxaban or phenprocoumon which were combined into "other anticoagulant therapy".

Laboratory results were available from four of the five national healthcare regions in Denmark and were acquired from the clinical laboratory information system "LABKA". Laboratory results relevant for calculating HAS-BLED, the Model for End-Stage Liver Disease (MELD), and MELD-Na scores were included. The HAS-BLED score is used to predict bleeding risk in patients with AF who initiate OAC [19]. A modified version of this score was used: hypertension defined as an ICD-10 diagnosis or treatment with ≥2 antihypertensive agents, abnormal renal/liver function (defined as at least twice weekly dialysis, kidney transplantation, creatinine >200 $\mu$mol/L, an ICD-10 diagnosis of chronic kidney disease and/or liver cirrhosis, alkaline phosphatase >315 U/L, alanine aminotransferase >210 U/L in men or >135 U/L in women, aspartate aminotransferase >135 U/L in men or >105 U/L in women), prior stroke, prior bleeding event (within 5 years using the aforementioned definition), age >65 years, and medications predisposing to bleeding (antiplatelet agents and NSAID), and alcohol-associated diagnoses *(Supplemental Table 2)*. MELD and MELD-Na predict survival in patients with chronic liver disease [20,21]. Laboratory variables relevant for these scores were international normalised ratio (INR), total bilirubin, and creatinine, with the addition of sodium in MELD-Na.

## Clinical endpoints

Endpoints of interest were 1) 5-year composite TE, including ischaemic stroke, TIA, or venous thromboembolism and 2) 5-year composite bleeding, including gastrointestinal, intracerebral, or urogenital bleeding requiring hospitalisation, or epistaxis requiring emergency department visit or hospital admission.

## Statistical analysis

We estimated the risks of TE and bleeding in relation to initiation of OAC therapy. Follow-up began 30 days after incident AF and continued until the occurrence of an event, death, emigration, a maximum follow-up time of 5 years, or end of follow-up on December 31, 2018, whichever came first. We performed cause-specific Cox regression to estimate absolute risks and average risk ratios (ARR) standardised to the covariate distribution of all patients. Average absolute risk for TE risk for patients with versus without OAC initiation was standardised for the $CHA_2DS_2$-VASc score distribution of the entire study population by using g-formula methods based on multivariable Cox regression [22,23]. Standardisation was used to ensure that exposure groups had comparable characteristics, i.e., that they had similar age, sex, selected comorbidity and pharmacotherapy distributions, to properly examine the impact of the actual exposure on outcomes. The average absolute risk for bleeding risk for patients with versus without OAC initiation was standardised for the HAS-BLED score and cirrhotic versus non-cirrhotic liver disease status distributions of the entire study population using the same methods. Prior to presentation of the results, we performed planned interaction analyses between OAC initiation and both $CHA_2DS_2$-VASc score and type of liver disease. Patients were then stratified according to OAC and $CHA_2DS_2$-VASc score ($CHA_2DS_2$-VASc score 1−2 (2−3 for women) versus $CHA_2DS_2$-VASc score >2 (>3 for women)) because of an interaction between OAC initiation and $CHA_2DS_2$-VASc score when determining TE risk ($P<0.001$). Similarly, due to an interaction between OAC initiation and type of liver disease (cirrhotic versus non-cirrhotic) in determining bleeding risk ($P<0.001$), we stratified patients by cirrhotic versus non-cirrhotic type liver disease for this analysis. A two-sided P-value <0.05 was considered statistically significant. Data management and analyses were performed using SAS, version 9.4 (Cary, NC, USA) and R, version 3.6.1 [24].

## Ethical considerations

This study complies with the Declaration of Helsinki and was approved by the Data Responsible Institute in the Capital Region of Denmark (Record no. P-2019−395) in accordance with the General Data Protection Regulation (GDPR). In agreement with the legislation of Statistics Denmark, data cannot be shared but can be assessed through Statistics Denmark with proper permission.

## Results

A total of 1238 OAC-naive patients with liver disease, first diagnosed AF, and a $CHA_2DS_2$-VASc score ≥1 (men) and ≥2 (women), who were alive 30 days after incident AF were included. Study inclusion is depicted in *Fig. 1*. Four hundred and nine patients initiated OAC, i.e., 122/426 (28.0%) of those with a $CHA_2DS_2$-VASc score 1−2 (men) or 2−3 (women), and 287/802 (25.8%) of those with a $CHA_2DS_2$-VASc score >2 (men) or >3 (women).

### Baseline characteristics

Baseline characteristics stratified for OAC initiation are presented in *Table 1*, associated laboratory results in *Supplemental Table 3*, and concomitant medications in *Supplemental Table 4*. Patients who were prescribed OAC more often had a history of heart failure, but less often cirrhotic liver disease, alcoholic fatty liver disease, other alcohol-associated diagnoses, prior bleeding events, ischaemic stroke, venous thromboembolism, and chronic kidney disease. They also appeared to represent a somewhat less sick liver disease population from a biochemical perspective and were less often on antiplatelet therapy. Characteristics of the study population according to OAC initiation and type of liver disease are shown in *Supplemental Table 5*, while *Supplemental Table 6* displays these characteristics categorized for guideline-recommended thresholds of the $CHA_2DS_2$-VASc score and whether or not an OAC was initiated.

### Risk of thromboembolism

Standardised absolute risks of TE are depicted in *Fig. 2*. Amongst patients with $CHA_2DS_2$-VASc scores 1−2 (2−3 in

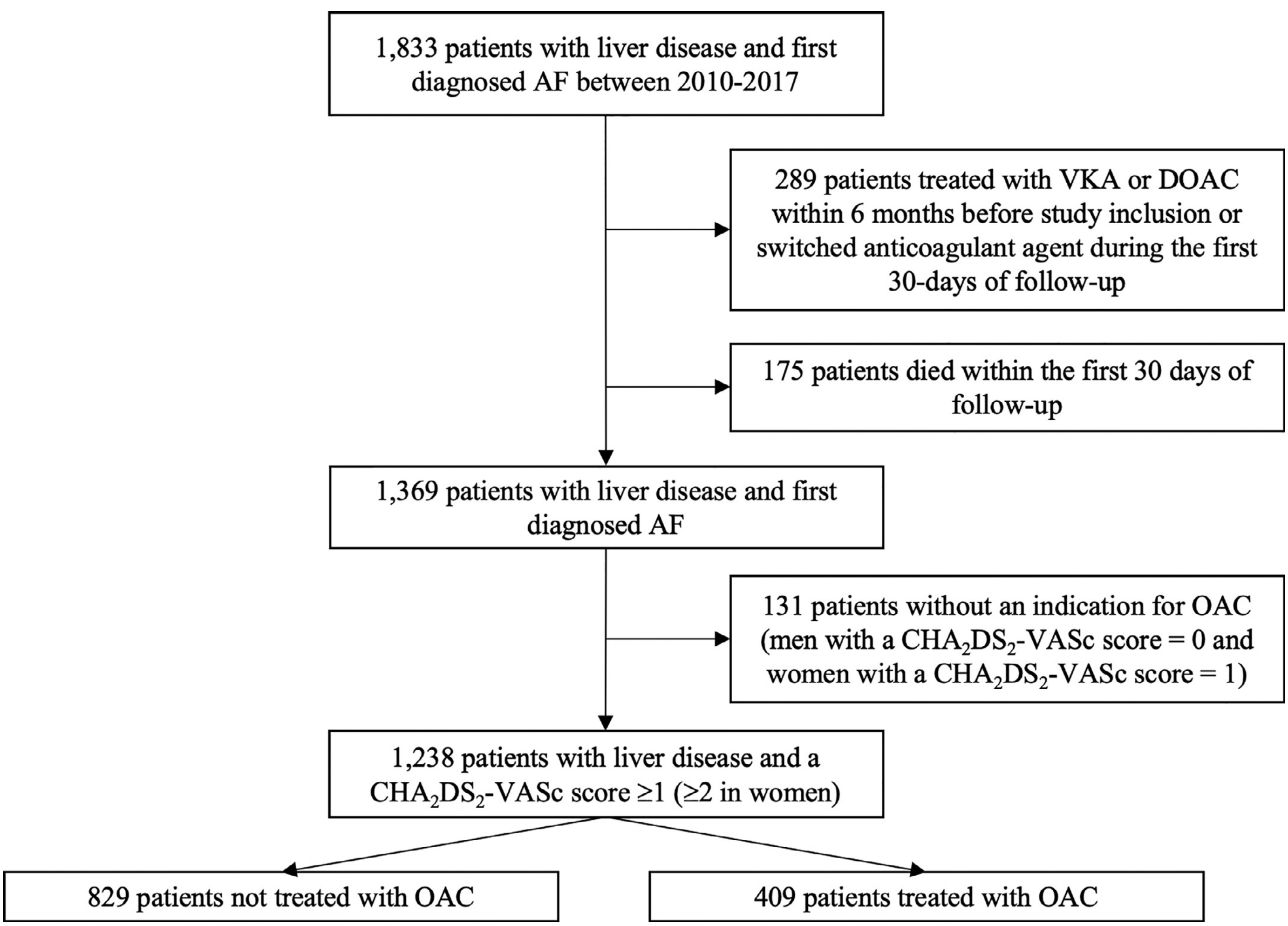


**Fig. 1 Patient flow chart.** The flow chart illustrates the inclusion of 1238 patients with liver disease, first diagnosed AF, and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women) between January 1, 2010 and December 31, 2017.
AF, atrial fibrillation or flutter; DOAC, direct oral anticoagulants; OAC, oral anticoagulant therapy (including VKA and DOAC); VKA, vitamin K antagonists.

**Table 1** Baseline characteristics for 1238 patients with liver disease, first diagnosed AF, and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women).

| Variable | Patients not treated with OAC (*n* = 829) | Patients treated with OAC (*n* = 409) | p-value |
|---|---|---|---|
| Age, median [IQR] | 69 [62–75] | 71 [65–78] | <0.001 |
| Male, *n* (%) | 493 (59.5) | 233 (57.0) | 0.44 |
| *Comorbidities* | | | |
| Heart failure, *n* (%) | 137 (16.5) | 104 (25.4) | <0.001 |
| Hypertension, *n* (%) | 636 (76.7) | 301 (73.6) | 0.26 |
| Diabetes mellitus, *n* (%) | 221 (26.7) | 116 (28.4) | 0.57 |
| Ischaemic stroke, *n* (%) | 139 (16.8) | 52 (12.7) | 0.08 |
| Transient ischaemic attack, *n* (%) | 19 (2.3) | 16 (3.9) | 0.15 |
| Ischaemic stroke/transient ischaemic attack, *n* (%) | 146 (17.6) | 60 (14.7) | 0.22 |
| Peripheral artery disease, *n* (%) | 96 (11.6) | 52 (12.7) | 0.63 |
| Ischaemic heart disease, *n* (%) | 181 (21.8) | 93 (22.7) | 0.77 |
| Acute myocardial infarction, *n* (%) | 69 (8.3) | 29 (7.1) | 0.52 |
| Venous thromboembolism, *n* (%) | 61 (7.4) | 20 (4.9) | 0.13 |
| Pulmonary embolism, *n* (%) | 20 (2.4) | 11 (2.7) | 0.92 |
| Superficial and deep thrombophlebitis, *n* (%) | 33 (4.0) | 8 (2.0) | 0.09 |
| Portal vein thrombosis, *n* (%) | 11 (1.3) | 3 (0.7) | 0.52 |
| Chronic obstructive pulmonary disease, *n* (%) | 200 (24.1) | 98 (24.0) | >0.99 |
| Any malignancy, *n* (%) | 166 (20.0) | 52 (12.7) | 0.002 |
| Previous alcohol diagnosis*, *n* (%) | 481 (58.0) | 136 (33.3) | <0.001 |
| Liver cirrhosis, *n* (%) | 355 (42.8) | 98 (24.0) | <0.001 |
| Primary biliary cholangitis, *n* (%) | 33 (4.0) | 23 (5.6) | 0.24 |
| Non-cirrhotic alcoholic fatty liver disease, *n* (%) | 217 (26.2) | 60 (14.7) | <0.001 |
| Non-alcoholic fatty liver disease, *n* (%) | 174 (21.0) | 79 (19.3) | 0.54 |
| Hepatocellular carcinoma, *n* (%) | 15 (1.8) | 4 (1.0) | 0.38 |
| Oesophageal and gastric varices, *n* (%) | 95 (11.5) | 30 (7.3) | 0.03 |
| Ascites, *n* (%) | 131 (15.8) | 28 (6.8) | <0.001 |
| Hepatorenal syndrome, *n* (%) | 13 (1.6) | 0 (0.0) | 0.02 |
| Chronic kidney disease, *n* (%) | 94 (11.3) | 34 (8.3) | 0.12 |
| Previous bleeding within 5 years†, *n* (%) | 132 (15.9) | 31 (7.6) | <0.001 |
| *Risk scores* | | | |
| $CHA_2DS_2$-VASc 1–2 (men) or 2–3 (women), *n* (%) | 314 (37.9) | 122 (29.8) | 0.006 |
| $CHA_2DS_2$-VASc>2 (men) or >3 (women), *n* (%) | 515 (62.1) | 287 (70.2) | |
| HAS-BLED (median [IQR]) | 3.0 [2.0–4.0] | 3.0 [2.0–4.0] | <0.001 |
| MELD (median [IQR]) | 9.0 [7.0–13.0] | 10.0 [7.0–13.8] | >0.99 |
| Missing | 513 (61.9) | 315 (77.0) | |
| MELD-Na (median [IQR]) | 10.0 [8.0–16.0] | 10.5 [8.0–15.0] | 0.66 |
| Missing | 513 (61.9) | 315 (77.0) | |
| *Medication* | | | |
| Lipid lowering treatment, *n* (%) | 256 (30.9) | 164 (40.1) | 0.002 |
| Aspirin, *n* (%) | 220 (26.5) | 127 (31.1) | 0.11 |
| $P2Y_{12}$ inhibitor treatment, *n* (%) | 80 (9.7) | 56 (13.7) | 0.04 |
| NSAID, *n* (%) | 147 (17.7) | 65 (15.9) | 0.47 |
| *Oral anticoagulants* | | | |
| Warfarin, *n* (%) | 0 (0.0) | 173 (42.3) | <0.001 |
| Rivaroxaban, *n* (%) | 0 (0.0) | 82 (20.0) | <0.001 |
| Apixaban, *n* (%) | 0 (0.0) | 102 (24.9) | <0.001 |
| Dabigatran, *n* (%) | 0 (0.0) | 50 (12.2) | <0.001 |
| Other anticoagulant therapy, *n* (%) | 0 (0.0) | N/A‡ | – |

AF, atrial fibrillation or flutter; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulants (including vitamin K antagonists and direct oral anticoagulants).
*Previous alcohol diagnoses were used to identify patients with complications due to excessive alcohol consumption *(Supplemental Table 2)*.
†Defined as gastrointestinal, intracerebral, or urogenital bleeding requiring hospitalisation, or epistaxis requiring emergency department visit or hospital admission.
‡N/A, not available due to cell count <3.

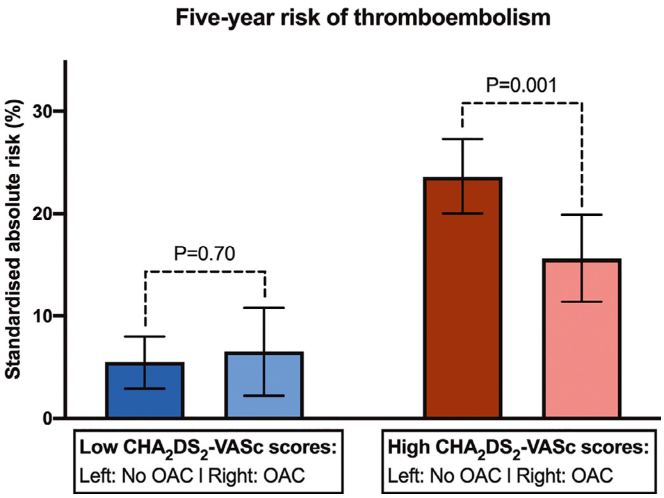


**Fig. 2** Absolute risk of thromboembolism standardised to the distribution of $CHA_2DS_2$-VASc score and OAC therapy in 1238 patients with liver disease, first diagnosed AF, and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women).
Thromboembolic endpoints included ischaemic stroke, TIA, or venous thromboembolism. Low $CHA_2DS_2$-VASc scores were defined as a score of 1–2 in men and 2–3 in women. High $CHA_2DS_2$-VASc scores were defined as $CHA_2DS_2$-VASc >2 in men and >3 in women.
AF, atrial fibrillation or flutter; OAC, oral anticoagulant therapy (including direct oral anticoagulants and vitamin K antagonists); TIA, transient ischaemic attack.

women), TE risks were low, irrespective of OAC initiation. Conversely, the risks in patients with a $CHA_2DS_2$-VASc score >2 (>3 in women) were overall substantially higher, although significantly reduced amongst those taking any OAC (*Table 2*). TE events according to type of OAC are provided in *Table 4*. Analyses of TE risk using guideline-recommended $CHA_2DS_2$-VASc thresholds are presented in *Supplemental Table 7*, and the cumulative incidences of TE stratified for OAC initiation, type of liver disease, and $CHA_2DS_2$-VASc score are listed in *Supplemental Table 8*. TE risks adjusted for concomitant medications are shown in *Supplemental Table 9*.

### Risk of bleeding

Standardised absolute risks of bleeding are shown in *Fig. 3*. These risks appeared higher amongst patients with cirrhotic compared with non-cirrhotic liver disease but were not significantly affected by OAC status (*Table 3*). Bleeding risks for the different OAC are shown in *Table 5*, and cumulative incidences of bleeding stratified by $CHA_2DS_2$-VASc score and OAC use are listed in *Supplemental Table 10*. Bleeding risks adjusted for use of concomitant medication are presented in *Supplemental Table 11*.

## Discussion

In this register-based cohort study of 1238 individuals with liver disease and incident AF, use of OAC was associated with a reduced TE risk in men with a $CHA_2DS_2$-VASc score >2 and women with a $CHA_2DS_2$-VASc score >3, but not amongst those with lower scores. The risk of bleeding was not affected.

Patients with liver disease who have an indication for anticoagulation have traditionally been treated with warfarin despite their often-elevated baseline INR and lack of a well-defined target INR [1]. For example, in a register-based retrospective cohort study of Taiwanese patients with liver cirrhosis, AF, and a $CHA_2DS_2$-VASc score ≥2, warfarin significantly reduced the risk of ischaemic stroke without affecting the risk of intracranial haemorrhage when compared with no treatment or antiplatelet therapy [25]. A newer study using the same database showed comparable risks of TE and intracranial haemorrhage in cirrhotic individuals with AF taking

**Table 2** Risk of thromboembolism for 1238 patients with liver disease, AF, and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women) expressed as cumulative incidence at 5 years.

A) Standardised absolute risk of thromboembolic events

| Treatment | Risk | 95% CI |
|---|---|---|
| $CHA_2DS_2$-VASc 1–2 (men) or 2–3 (women) | | |
| No OAC | 5.5% | (2.9%–8.0%) |
| OAC | 6.5% | (2.2%–10.8%) |
| $CHA_2DS_2$-VASc >2 (men) or >3 (women) | | |
| No OAC | 23.6% | (20.0%–27.3%) |
| OAC | 15.6% | (11.4%–19.9%) |

B) Average risk ratio for patients treated with versus without OAC

| Treatment | Risk ratio | 95% CI | p-value |
|---|---|---|---|
| $CHA_2DS_2$-VASc 1–2 (men) or 2–3 (women) | | | |
| OAC versus no OAC | 1.19 | (0.22–2.16) | 0.70 |
| $CHA_2DS_2$-VASc >2 (men) or >3 (women) | | | |
| OAC versus no OAC | 0.66 | (0.45–0.87) | 0.001 |

AF, atrial fibrillation or flutter; CI, confidence interval; OAC, oral anticoagulants (including vitamin K antagonists and direct oral anticoagulants).

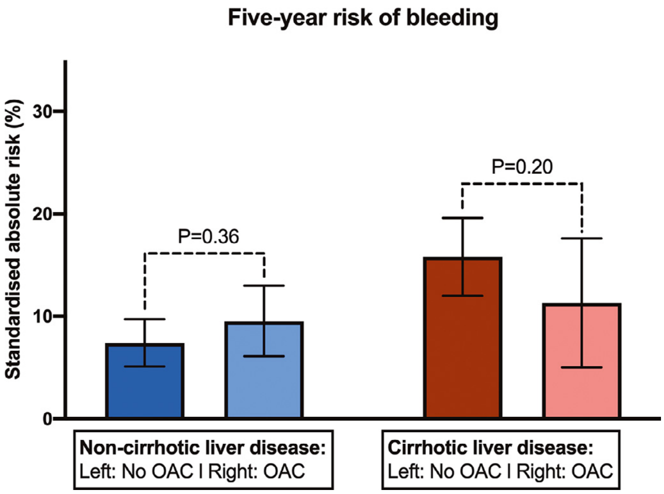


**Fig. 3** Absolute risk of bleeding events standardised to the distribution of cirrhotic versus non-cirrhotic liver disease, HAS-BLED score, and OAC therapy in 1238 patients with liver disease, first diagnosed AF and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women). Bleeding events included gastrointestinal, intracerebral or urogenital bleeding requiring hospitalisation, or epistaxis requiring emergency department visit or hospital admission.
AF, atrial fibrillation or flutter; OAC, oral anticoagulant therapy (including direct oral anticoagulants and vitamin K antagonists).

DOAC (>90% on low-dose DOAC) or warfarin, but overall rates of major bleeding were lower with DOAC [26]. A Korean study using a similar methodology found superior efficacy and safety of DOAC (~50% on low-dose DOAC) versus warfarin in patients with active liver disease [27]. Finally, a large Italian population-based cohort study reported that AF patients with concomitant liver disease had a favourable benefit/risk ratio when treated with OAC, even in high risk subgroups; however, information on OAC type was not available [28]. Recent meta-analyses corroborate the overall conclusions that can be drawn from both our and prior experiences, i.e., a reduction of stroke risk without an increase in bleeding risk with OAC versus no OAC, and a reduction in bleeding risk, but not a reduction in stroke with DOAC versus warfarin, in patients with advanced liver disease and AF [29,30].

While it is well-known that the degree of hepatic elimination varies substantially between OAC types, anticoagulant potencies of these agents may also differ between cirrhotic and non-cirrhotic patients. Dabigatran seems to act more potently in plasma from patients with cirrhosis while rivaroxaban may have decreased anticoagulant activity in this setting [31]. Furthermore, apixaban appears to have substantially reduced potency in patients with moderate and advanced liver cirrhosis [32]. These results are compatible with our findings of a relatively lower bleeding risk with rivaroxaban compared with warfarin, and a relatively higher risk with dabigatran compared with warfarin.

Differences in use and non-use of OAC in our cohort may reflect medical decisions, but it is also possible that patients not on OAC may have had lower compliance and not redeemed their prescription. Overall, our results suggest that the benefits on TE risk may outweigh the risk of bleeding in patients with liver disease and AF, in particular amongst cirrhotic patients with high $CHA_2DS_2$-VASc scores. Interestingly, Proietti et al. suggested a lower $CHA_2DS_2$-VASc threshold than ours as the point for when the net clinical benefit of OAC becomes favourable in patients with liver disease [28]. On the other hand, a recent consensus document from the European Society of Cardiology regarding OAC therapy in AF patients with a $CHA_2DS_2$-VASc score of 1 in men (2 in women) highlighted that TE risk in this group might be lower than anticipated and that additional prognostic information should be considered for risk refinement [10].

**Table 3** Risk of bleeding events in 1238 patients with liver disease, AF, and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women) expressed as cumulative incidence at 5 years.

A) Standardised absolute risk of bleeding events

| Treatment | Risk | 95% CI |
|---|---|---|
| Cirrhotic patients | | |
| No OAC | 15.8% | (12.0%–19.6%) |
| OAC | 11.3% | (5.0%–17.6%) |
| Non-cirrhotic patients | | |
| No OAC | 7.4% | (5.1%–9.7%) |
| OAC | 9.5% | (6.1%–13.0%) |

B) Average risk ratio for patients treated with versus without OAC

| Treatment | Risk ratio | 95% CI | p-value |
|---|---|---|---|
| Cirrhotic patients | | | |
| OAC versus no OAC | 0.72 | (0.28–1.15) | 0.20 |
| Non-cirrhotic patients | | | |
| OAC versus no OAC | 1.28 | (0.67–1.90) | 0.36 |

AF, atrial fibrillation or flutter; CI, confidence interval; OAC, oral anticoagulants (including vitamin K antagonists and direct oral anticoagulants).

**Table 4** Comparisons of OAC treatment and risk of thromboembolic events in 1238 patients with liver disease, first diagnosed AF, and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women). A) Standardised absolute risk of thromboembolic events for different OAC at five years. B) Risk ratios between different OAC.

A) Standardised absolute risk of thromboembolic events

| Treatment | Risk | 95% CI |
|---|---|---|
| No OAC (*n* = 829) | 17.2% | (14.6%—19.8%) |
| Warfarin (*n* = 173) | 11.9% | (7.3%—16.5%) |
| Any DOAC (*n* = 234) | 12.6% | (8.4%—16.9%) |
| Rivaroxaban (*n* = 82) | 8.6% | (2.6%—14.6%) |
| Apixaban (*n* = 102) | 14.6% | (8.1%—21.1%) |
| Dabigatran (*n* = 50) | 15.2% | (4.8%—25.6%) |

B) Risk ratios between patients treated with DOAC, warfarin, and no OAC

| Treatment | Risk ratio | 95% CI |
|---|---|---|
| Warfarin versus no OAC | 0.69 | (0.41—0.98) |
| DOAC versus no OAC | 0.74 | (0.47—1.00) |
| Rivaroxaban versus no OAC | 0.50 | (0.14—0.86) |
| Apixaban versus no OAC | 0.85 | (0.45—1.25) |
| Dabigatran versus no OAC | 0.88 | (0.27—1.50) |
| DOAC versus warfarin | 1.06 | (0.52—1.60) |
| Rivaroxaban versus warfarin | 0.72 | (0.15—1.30) |
| Apixaban versus warfarin | 1.23 | (0.51—1.95) |
| Dabigatran versus warfarin | 1.28 | (0.28—2.28) |
| Apixaban versus rivaroxaban | 1.70 | (0.29—3.11) |
| Dabigatran versus rivaroxaban | 1.77 | (0.04—3.50) |
| Dabigatran versus apixaban | 1.04 | (0.20—1.89) |

AF, atrial fibrillation or flutter; DOAC, direct oral anticoagulants; OAC, oral anticoagulants (including vitamin K-antagonists and direct oral anticoagulants).

**Table 5** Comparisons of OAC treatment and risk of bleeding events in 1238 patients with liver disease, first diagnosed AF and a $CHA_2DS_2$-VASc score ≥1 (≥2 in women). A) Standardised absolute risk of bleeding events for different OAC at five years. B) Risk ratios between different OAC.

A) Standardised absolute risk of bleeding events

| Treatment | Risk | 95% CI |
|---|---|---|
| No OAC (*n* = 829) | 10.7% | (8.7%—12.8%) |
| Warfarin (*n* = 173) | 11.6% | (6.7%—16.5%) |
| Any DOAC (*n* = 234) | 9.4% | (5.4%—13.4%) |
| Rivaroxaban (*n* = 82) | 4.6% | (0.0%—9.7%) |
| Apixaban (*n* = 102) | 9.5% | (3.6%—15.4%) |
| Dabigatran (*n* = 50) | 16.7% | (5.9%—27.6%) |

B) Risk ratios between patients treated with DOAC, warfarin, and no OAC

| Treatment | Risk ratio | 95% CI |
|---|---|---|
| Warfarin versus no OAC | 1.08 | (0.58—1.58) |
| DOAC versus no OAC | 0.88 | (0.47—1.29) |
| Rivaroxaban versus no OAC | 0.43 | (0.00—0.91) |
| Apixaban versus no OAC | 0.87 | (0.31—1.47) |
| Dabigatran versus no OAC | 1.56 | (0.51—2.61) |
| DOAC versus warfarin | 0.81 | (0.33—1.29) |
| Rivaroxaban versus warfarin | 0.40 | (0.00—0.87) |
| Apixaban versus warfarin | 0.82 | (0.20—1.44) |
| Dabigatran versus warfarin | 1.44 | (0.34—2.54) |
| Apixaban versus rivaroxaban | 2.06 | (0.00—4.66) |
| Dabigatran versus rivaroxaban | 3.62 | (0.00—8.22) |
| Dabigatran versus apixaban | 1.76 | (0.17—3.35) |

AF, atrial fibrillation or flutter; DOAC, direct oral anticoagulants; OAC, oral anticoagulants (including vitamin K-antagonists and direct oral anticoagulants).

Ongoing studies are evaluating OAC as part of antifibrotic treatment, since development of portal vein thrombosis and thrombotic occlusions in small hepatic veins may contribute to fibrosis development [4]. Prophylactic anticoagulant therapy with enoxaparin in cirrhotic patients may prevent portal vein thrombosis, delay hepatic decompensation, and improve survival [33]. A mortality benefit with warfarin or DOAC versus no anticoagulation was also observed in a retrospective longitudinal study of US veterans [34].

Notably, only about one-third of patients (~20% amongst those with cirrhotic liver disease and ~40% of those with non-cirrhotic liver disease) were treated with OAC. While this may reflect accurate patient selection, we cannot rule out that a larger group could have derived benefit from anticoagulation. We suggest that OAC therapy should be considered in patients with liver disease and incident AF, particularly in those with a $CHA_2DS_2$-VASc score >2 (>3 for women). Further investigation of factors related to TE and bleeding risks as well as studies on efficacy and safety of OAC, preferably randomised controlled trials, in patients with liver disease, including cirrhosis are warranted.

## Limitations

The observational nature of this study prevents us from making finite inferences about causality. Although the suggested benefits of OAC may in part reflect confounding by indication, particularly since not prescribed OAC appeared to represent an overall sicker population, standardised regression analysis is a robust method for obtaining adjusted estimates in such settings. Nevertheless, we were unable to explore specific reasons for not prescribing OAC. Patient characteristics, including risk scores, were only assessed at baseline and may have changed over time [35,36]. However, since most included conditions are chronic, these scores are much more likely to increase rather than decrease over time. We used a modified version of the HAS-BLED score because of lack of information on uncontrolled hypertension, and our definition may potentially have overestimated bleeding risk. Similarly, we were unable to incorporate data on labile INR. It is also not possible to differentiate between mild and end-stage liver disease when using our registries. Hepatic encephalopathy was not included in the definition of cirrhotic liver disease due to lack of a specific diagnostic code, but patients with hepatic encephalopathy usually have advanced chronic liver disease and associated stigmata like ascites. Still, the absence of this information hindered calculation of the Child-Pugh score, the score suggested by regulatory agencies to guide the choice of OAC agent in patients with liver disease despite lack of high-quality evidence to support such categorization [1,37,38]. Finally, although we relied on administrative registries, most of the diagnostic codes have been previously validated [17].

## Conclusions

OAC initiation in patients with liver disease and incident AF was associated with reduced TE risk in men with a $CHA_2DS_2$-VASc score >2 and in women with a $CHA_2DS_2$-VASc score >3. Bleeding risk was not increased with OAC, irrespective of type of liver disease. Only a minority of AF patients with cirrhotic liver disease were treated with OAC, indicating a potential for reducing TE burden in this population.

## Author contribution

KS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing – original draft. MP and KHK: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, visualization, writing – original draft, writing – review and editing. ALK, PS, MM, BT, CJL, CTP, GYHL, and PHF: conceptualization, investigation, methodology, writing – review and editing.

## Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Source of Funding

This is an academic study funded by the Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.

## Acknowledgements

None.

## Data Availability

Due to Statistics Denmark regulations, data cannot be shared, but can be accessed on secure servers upon receiving appropriate permissions.

## Disclosures

MP has received speaker's fees from AstraZeneca, Bayer, Boehringer Ingelheim, and Janssen-Cilag, and served on advisory boards for AstraZeneca and Janssen-Cilag. MM has received lecture fees and consulting honoraria from Novo Nordisk, Bayer, Boston Scientific, AstraZeneca, Boehringer Ingelheim, and Bristol Myers Squibb. CTP has received grants from Novo Nordisk and Bayer. GYHL is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo, and has served as a speaker for Bayer, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo; no fees have been directly received personally. KS, ALK, KHK, CJL, PHF, BT, and PS have no disclosures in relation to this manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2022.101952.

## References


[1] Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. J Am Coll Cardiol 2018;71(19):2162–75.

[2] Wijarnpreecha K, Boonpheng B, Thongprayoon C, Jaruvongvanich V, Ungprasert P. The association between non-alcoholic fatty liver disease and atrial fibrillation: a meta-analysis. Clin Res Hepatol Gastroenterol 2017;41(5):525–32.

[3] Søgaard KK, Horváth-Puhó E, Grønbæk H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case—control study. Am J Gastroenterol 2009;104(1):96–101.

[4] Tripodi A, Primignani M, Mannucci PM, Caldwell SH. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol 2017;112(2):274–81.

[5] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365(2):147–56.

[6] Lip GYH, Nieuwlaat R, Pisters R, Lane DAA, Crijns HJGMJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263–72.

[7] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42(5):373–498.

[8] Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest 2018;154(5):1121–201.

[9] January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland Jr. JC, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74(1):104–32.

[10] Sulzgruber P, Wassmann S, Semb AG, Doehner W, Widimsky P, Gremmel T, Kaski JC, Savarese G, Rosano GMC, Borghi C, Kjeldsen K, Torp-Pedersen C, Schmidt TA, Lewis BS, Drexel H, Tamargo J, Atar D, Agewall S, Niessner A. Oral anticoagulation in patients with non-valvular atrial fibrillation and a CHA2DS2-VASc score of 1: a current opinion of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Council on Stroke. Eur Heart J Cardiovasc Pharmacother 2019;5(3):171–80.

[11] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.

[12] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J. Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365 (11):981–92.

[13] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–51.

[14] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus Warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.

[15] Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. Eur J Epidemiol 2014;29 (8):541–9.

[16] Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39(7 Suppl):26–9.

[17] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90.

[18] Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39(7):38–41.

[19] Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093–100.

[20] Said A, Williams J, Holden J, Remington P, Gangnon R, Musat ALM. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. J Hepatol 2004;40 (6):897–903.

[21] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31(4):864–71.

[22] Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. Ann Stat 1982;10(4):1100–20.

[23] Hernán MRJ. Causal inference - Part 2. Boca Raton: Chapman & Hall/CRC; 2018.

[24] R: The R Project for Statistical Computing [Internet]. [cited 2021 Mar 25]. Available from: https://www.r-project.org/

[25] Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? J Am Heart Assoc 2017;6(6):e005307.

[26] Lee H, Chan Y, Chang S, Tu H, Chen S, Yeh Y, Wu L, Kuo C, Kuo C, See L. Effectiveness and safety of non-vitamin k antagonist oral anticoagulant and warfarin in cirrhotic patients with nonvalvular atrial fibrillation. J Am Heart Assoc 2019;8(5):e011112.

[27] Lee S, Lee H, Choi E, Han K, Jung J, Cha M, Oh S, Lip GYH. Direct oral anticoagulants in patients with atrial fibrillation and liver disease. J Am Coll Cardiol 2019;73(25):3295–308.

[28] Proietti M, Marzona I, Vannini T, Colacioppo P, Tettamanti M, Foresta A, Fortino I, Merlino L, Lip GYH, Roncaglioni MC. Impact of liver disease on oral anticoagulant prescription and major adverse events in patients with atrial fibrillation: analysis from a population-based cohort study. Eur Heart J Cardiovasc Pharmacother 2020.

[29] Chokesuwattanaskul R, Thongprayoon C, Bathini T, Torres-Ortiz A, O'Corragain OA, Watthanasuntorn K, et al. Efficacy and safety of anticoagulation for atrial fibrillation in patients with

cirrhosis: a systematic review and meta-analysis. Dig Liver Dis 2019;51(4):489–95.
[30] Violi F, Vestri A, Menichelli D, Di Rocco A, Pastori D, Pignatelli P. Direct oral anticoagulants in patients with atrial fibrillation and advanced liver disease: an exploratory meta-analysis. Hepatol Commun 2020;4(7):1034–40.
[31] Potze W, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Meijers JCM, et al. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. PLoS ONE 2014;9(2):e88390.
[32] Potze W, Adelmeijer J, Lisman T. Decreased in vitro anticoagulant potency of Rivaroxaban and Apixaban in plasma from patients with cirrhosis. Hepatology 2015;61(4):1435–6.
[33] Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, Turola E, Fornaciari G, Schianchi S, Ferrari A, Valla D. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012 Nov;143(5) 1253—60.e4.
[34] Serper M, Weinberg EM, Cohen JB, Reese PP, Taddei TH, Kaplan DE. Mortality and hepatic decompensation in patients with cirrhosis and atrial fibrillation treated with anticoagulation. Hepatology 2021;73(1):219–32.
[35] Chao T, Lip GYH, Liu C, Lin Y, Chang S, Lo L, Hu Y, Tuan T, Liao J, Chung F, Chen T, Chen S. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. J Am Coll Cardiol 2018;71(2):122–32.
[36] Yoon M, Yang P, Jang E, Yu HT, Kim T, Uhm J, et al. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in Asian Patients with atrial fibrillation: a nationwide cohort study. Thromb Haemost 2018;118(7):1296–304.
[37] Eliquis (apixaban). Highlights of prescribing information. [Internet]. [citedMar 25]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf.
[38] Eliquis (apixaban). Summary of product characteristics. [Internet]. [citedMar 25]. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_%20Information/human/%20002148/WC500107728.pdf.