American Journal of Gastroenterology

Association Between Non-vitamin K Antagonist Oral Anticoagulants or Warfarin and Liver Injury: A Cohort Study

--Manuscript Draft--

Manuscript Number:	AJG-19-2621R1
Full Title:	Association Between Non-vitamin K Antagonist Oral Anticoagulants or Warfarin and Liver Injury: A Cohort Study
Article Type:	Article
Section/Category:	Liver
Abstract:	OBJECTIVES: The risk of liver injury in patients with atrial fibrillation (AF) using non-vitamin K antagonist oral anticoagulants (NOACs) has not been previously examined using liver function tests as the primary outcome in the real-world setting. This study assessed the association between NOACs (dabigatran, rivaroxaban, apixaban) and warfarin and the risk of liver injury, as defined by laboratory tests. METHODS: Patients newly diagnosed with AF and prescribed NOACs or warfarin between 2010-2016, identified using the Hong Kong Clinical Database and Reporting System, were matched on age, sex, health status scores, comorbidities and medications by propensity score at a 1:1 ratio. Risk of liver injury, defined as laboratory test values >3 times the upper limit of normal of alanine aminotransferase or aspartate aminotransferase and >2 times the upper limit of normal of total bilirubin, was compared between NOAC and warfarin users using Cox proportional hazards regression. RESULTS: After propensity score matching, 13,698 patients were included, of which 141 (2.1%) NOAC users and 232 (3.4%) warfarin users developed liver injury. The hazard ratio (HR) for NOAC vs warfarin users was 0.71 (95% CI: 0.58-0.89). When comparing individual NOACs, only dabigatran (HR: 0.63; 95% CI: 0.48-0.82) was associated with a lower risk of liver injury. DISCUSSION: Among patients with atrial fibrillation, NOACs as a group, as well as dabigatran alone, were associated with a significantly lower risk of laboratory-based liver injury when compared to warfarin. However, liver injury occurs more frequently in real-world practice than in NOAC randomized controlled trials.
Response to Reviewers:	Dear Drs. Lacy and Spiegel, RE: Manuscript ID AJG-19-2621 - “Association Between Non-vitamin K Antagonist Oral Anticoagulants or Warfarin and Liver Injury: A Cohort Study”: response to the reviewers’ comments for the manuscript Thank you very much for the comments in the recent decision letter dated 3 February 2020. We appreciate this opportunity to further revise our manuscript. Our responses to the reviewers’ comments are given point-by-point below in red. Editor/Editorial Board: 1.Please indicate if any subjects had cholestatic liver injury defined by R value or ratio of serum ALT to serum alkaline phosphatase as a multiple of upper limit of normal R<2. Thank you for your comment. To address this point, and several other comments regarding the clinical details of patients who experienced our outcome definition of liver injury, we have added an additional table to the main text (Table 2, p. 31). As per the EASL Clinical Practice Guidelines: Drug-induced liver injury, we have described the number (%) of patients with the primary outcome by their ALT/ALP ratio (R) (i.e. R ≤2 cholestatic pattern, R >2 to <5 mixed pattern, and R ≥5 hepatocellular pattern) on the outcome date. In the complete cohort, a total of 332 (64.7%) of patients had a cholestatic pattern of liver injury (208 [66.5%] warfarin users and 124 [62.0%] NOAC users). Further details by drug are shown in Table 2 (p. 31). 2.How many patients had imaging of the liver with either ultrasound, CT or MRI? As mentioned in comment #1, we have added Table 2 (p. 31) to provide additional clinical information about patients who meet our definition of liver injury. Of these, a total of 114 (22.2%) patients (65 [20.8%] warfarin users and 49 [24.5%] NOAC users)

had a procedure date within 90 days after the outcome date for either ultrasound (liver, abdomen), CT (abdomen), or MRI (abdomen). This proportion may be lower than what is observed in US clinical practice, because of the extensive wait times for diagnostic imaging within the Hong Kong public healthcare system. We have also added the list of diagnostic imaging procedure codes to the Supplementary Appendix Table 2.

Reviewer #1:

1.The authors chose ALT 3XULN plus Bilirubin 2XULN as outcome parameter that reflects Hy's Law cases. International consensus criteria define DILI as ALT 5xULN or ALP 2xULN or Hy's Law (EASL Clinical Practice Guidelines: Drug-induced liver injury, Andrade, Raúl J.Aithal, Guruprasad P.Karlsen, Tom H. et al. Journal of Hepatology, Volume 70, Issue 6, 1222 - 1261), while Hy's Law (in the FDA-Definition also requiring a ratio of ALTxULN/APxULN>=5) is considered as an indicator of severe liver injury in the case that competing diagnoses have thoroughly been ruled out. By confining liver injury cases to the Hy's Law positive cases incidence of DILI with NOAC/warfarin might be underestimated. An important question that should be addressed is the exclusion of other possible causes in the investigated patients (Hyptension, Shock, viral Hepatitis, Biliary Obstruction) to corroborate the use of Hy's Law.

Thank you for your comment regarding the outcome definition. We agree with the reviewer that using a definition of Hy's Law cases may underestimate the true incidence of liver injury, which is why we used a broader definition of "liver injury" which appears to capture a greater number of patients and different patterns of liver injury. We selected our primary outcome (liver injury) in accordance with the laboratory test thresholds as defined in Hy's Law, specifically an ALT or AST > 3x the upper limit of normal (ULN) and a total bilirubin > 2x ULN. Our intention is not to suggest that each patient with the outcome satisfied all three components of Hy's Law (i.e. Hy's Law cases). As the reviewer has noted, a criteria of Hy's Law requires that other causes of liver injury be ruled out. It is very challenging to rule out or determine other potential causes for elevations in serum aminotransferase and bilirubin levels using electronic health record data, thus we have not defined the outcome as Hy's Law cases and describe the outcome as "liver injury". This outcome was selected because it is a common liver function safety endpoint reported in RCTs on NOAC effectiveness and safety. Thus, it allows us to compare the rate of liver injury in clinical practice to the rates observed in a more selective RCT population.
Furthermore, we have added descriptive results for the patients who experienced our outcome during follow-up (Table 2, p. 31). On the outcome date, of the 513 cases who met our outcome definition during follow-up, 144 (28%) had ALP > 2x ULN. When applying the definition of drug-induced liver injury (DILI) according to the guidelines (ALT ≥ 5x ULN or ALP ≥ 2xULN), 353 (69%) of patients met either criteria. As we were unable to perform a causality assessment, and with the challenges of ruling out other causes, we have not used this definition as the primary outcome in this study.

2.Causality is a big issue in DILI and especially in patients receiving multiple comedications. Was statistical testing performed concerning the occurrence of liver injury in the patients and the use of comedications with known DILI-liability (e.g. NSAR, Antiinfectives, antiTb, Antipeileptics etc)?

Due to the challenges in assessing liver injury using electronic health databases, we have not performed a causality assessment. No statistical testing was performed regarding co-medications prior to liver injury. However, as presented in Table 1, we identified baseline exposures to key classes of hepatotoxic medications, and these baseline exposures were well balanced after propensity score matching. Furthermore, we have included additional descriptive details for those patients who experienced our outcome definition of liver injury. Recent exposure to hepatotoxic medications are described in Table 2 (p. 31). For example, about half of the patients with liver injury were also dispensed prescriptions for antibacterial agents, lipid lowering drugs, and antiarrhythmic drugs, but at most 5% of patients were dispensed NSAIDs, antituberculosis agents, and antiepileptics. The distribution of drug exposure prior to liver injury appears to be similar for NOAC and warfarin users.

3.The cases with acute liver failure should be described in detail, since this is the worst possible outcome of DILI. The finding that NOAC-HR for acute liver failure is higher

than warfarin is especially interesting, since one would expect liver failure to occur more often with warfarin due to the effects of the drug on INR. It would be interesting to have these data discussed and more information in the supplement (especially on causality)

We have added Appendix Table 6, which provide additional details of patients with liver injury who were also diagnosed with acute liver failure using ICD-9-CM codes. In addition, we have expanded our results (p.11 lines 11-20) and our discussion (p. 14 lines 6-17) to further discuss the findings for patients with acute liver failure.

Reviewer #2:
1.It will be interesting to see a graphic distribution of latency between the drug start and the onset of liver injury, likewise for the dechallenge separated by drug.

Thank you for your comment. We have included additional clinical details about those patients who experienced our outcome definition of liver injury in Table 2 (p.31). We describe the time from drug initiation to the onset of liver injury in 6 categories (<1 month, ≥1 to <3 months, ≥3 to <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24 months). Furthermore, we have changed our survival curve (Appendix Figure 2) to a cumulative incidence curve and have shortened the plot axes in order to better visualize the curve. The survival curves are shown for each oral anticoagulant group and by specific drug. Taken together, this additional data should give readers a clearer understanding of the temporal onset of liver injury in our cohort.
Regarding dechallenge and resolution of elevations in liver function tests, we cannot determine the true date of discontinuation based on dispensing records. As with nearly all pharmacoepidemiology studies, we assume that patients who are dispensed a medication actually consume it as per the dispensing record.

2.How was causality assessed or is this just the description of elevation occurring, which would be ok too.

Thank you for the question. The objective of this study was to investigate the association between the use of NOACs vs warfarin and the risk of liver injury. We agree with the reviewer that a causality assessment is often required to determine whether cases can be classified as DILI. Because of the challenges in determining DILI from database studies, we have defined our outcome only as liver injury. Without a detailed review of each patient's medical records, we cannot determine what caused the outcome to occur. We have described laboratory tests at baseline and described the distribution of the relevant laboratory tests for the 513 patients who experienced the primary outcome of liver injury (Table 2, p. 31).

3.Please confirm, you truly observe a 2% Hy's law criteria, that is 3 ULN of ALT & Bilirubin >2ULN.

We selected our primary outcome (liver injury) in accordance with the laboratory test thresholds as defined in Hy's Law, specifically an ALT or AST > 3x the upper limit of normal (ULN) and a total bilirubin > 2x ULN. We can confirm that, as presented in Table 3 and Appendix Table 15, in the propensity score matched cohort, the risk of liver injury during follow-up was about 2%. As shown in Table 1 we included patients with a history of liver disease and gallbladder disease, which may contribute to the higher rate of liver injury in this study. Furthermore, as described in comment #4, changing the thresholds for the upper limits of normal (ALT and total bilirubin) reduced the number of cases with liver injury. With the modified ALT and total bilirubin thresholds as suggested in comment #4, a total of 221 patients in the matched cohort experienced the outcome (Appendix Table 10). The risk (number with event / total number in treatment group) of the revised outcome was as follows: warfarin 1.94% (133/6,849), dabigatran 1.23% (45/3,663), rivaroxaban 1.14% (23/2,016), and apixaban 1.71% (20/1,170). In conditions of actual use, the risk still appears to be modestly higher than observed in randomized controlled trials. This may be due to the fact that NOACs are prescribed to individuals who would have been excluded from randomized controlled trials and that our study has a somewhat longer duration of follow-up.

4.How does this change if you would use 2.5mg as threshold for Bilirubin, and ALT of

120 instead of 75 for ALT in women, and 150 instead of 105 for men. The later thresholds were more likely used in the clinical trials.

Thank you for your comment. We would like to first clarify our ALT thresholds in the main analysis were 75 for women and 99 for men (as shown in Appendix Table 1). We ran the main analysis with the same exclusion criteria, but changed the outcome definition as suggested (ALT > 75 U/L increased to > 120 U/L [women], ALT > 99 increased to >150 [men], bilirubin > 2 mg/L increased to > 2.5 mg/L [both sexes], and excluded AST from the outcome definition). A total of 221 patients (88 NOAC users and 133 warfarin users) in the propensity score matched cohort experienced the outcome with the increased ALT and total bilirubin thresholds. The results for the propensity matched cohort are similar to the main analysis, although not statistically significant because of the reduced number of events. In the main paper, they are shown in the results (p. 13 lines 2-3), Figure 2, and Appendix Table 10.

5.As a related question: Is the onset of liver injury usually occurring at time point not covered by randomized controlled trials?

As reported in the Caldeira et al systematic review of 29 NOAC randomized controlled trials, the weighted mean duration of follow-up was 16.4 months and ranged from 2 weeks to 2 years. Of the 513 patients who experienced the primary outcome, 158 (30.8%) experienced liver injury ≥ 2 years after initiation of oral anticoagulants. The longer follow-up in this observational study adds to the safety evidence obtained in randomized controlled trials. It also helps explain why we have observed a higher risk of liver injury since about one third of cases occur in a follow-up period that is excluded from randomized controlled trials. As stated previously, we have included the distribution of patients with the outcome according to follow-up time in Table 2 (p. 31). In addition, we have revised the discussion regarding the onset of liver injury (p. 14 lines 18-21).

6.Can you further report on number of death/Liver Transplantation total and liver related, as you study may suggest that liver injury may be more frequent on Warfarin, relevant clinical outcome may be more frequent with NOAC.

Similar to comment #5, we have now described the number (%) of patients who experienced liver transplant, all-cause mortality, and liver failure related mortality, within 90 days after the outcome date in Table 2 (p. 31). No patients underwent liver transplant, and the small number of deaths makes it difficult to draw firm conclusions. However, the reviewer is correct in that there is a signal that NOAC users with our primary outcome experience more severe clinical outcomes such as all-cause mortality, death from liver causes, and a diagnosis of acute liver failure. Therefore, we have added this point to the results (p.11 lines 12-20).

7.How did you assess causality in the people with elevated ALT/AST and Bilirubin?

Please see our previous response to comment #2. We have not assessed causality for patients who experienced the outcome of liver injury. We feel that the new Table 2 (p. 31) better informs the reader about the patients who experienced liver injury. Unfortunately, we do not have the resources to perform causality assessment, which requires manual review of medical records for each of the 513 patients with liver injury. We want to emphasize that our outcome definition is liver injury and not DILI, since without a comprehensive review of the complete medical record, we cannot attribute causality to a specific drug exposure.

8.What were r-values at onset by drug?

We have included the R values on the outcome date, for warfarin and NOACs, and for each NOAC drug in Table 2 (p. 31).

9.Can you comment on phenprocoumon, albeit not used in Hong Kong, I suspect, it has frequently be implicated in DILI.

Thank you for your question. We confirm that phenprocoumon is not licensed for sale in Hong Kong (Hong Kong Drug Office Drug Database, available at

	www.drugoffice.gov.hk/eps/do/en/consumer/search_drug_database.html). Hence, we do not have first-hand experience to inform further on the frequency or magnitude of effects on DILI specifically on the Chinese population in Hong Kong. However, we agree with the comment that phenprocoumon may be implicated in DILI as reported in the international literature. Thank you for your time and reconsideration of our manuscript.
Order of Authors:	Jiaxi Zhao, MSc
	Joseph E Blais, BScPharm
	Celine S.L. Chui, PhD
	In-Hye Suh, PharmD
	Esa Y.H. Chen, BPharm
	Wai-Kay Seto, MD
	Michael T Mok, MBBS
	Vincent K.C. Yan, BPharm
	Wallis C.Y. Lau, PhD
	Ian C.K. Wong, PhD
	Esther W Chan, PhD
Manuscript Classifications:	ALT; Anticoagulation; AST; Bilirubin; Drug-Induced Liver Injury; Epidemiology; Warfarin
Suggested Reviewers:	
Opposed Reviewers:	

Association Between Non-vitamin K Antagonist Oral Anticoagulants or Warfarin and Liver Injury: A Cohort Study

Jiaxi Zhao, MSc[1,8], Joseph E Blais, BScPharm[1], Celine S.L. Chui, PhD[1], In-Hye Suh, PharmD[1], Esa Y.H. Chen, BPharm[2], Wai-Kay Seto, MD[3,4,5], Michael T. Mok, MBBS[6], Vincent K.C. Yan, BPharm[1], Wallis C.Y. Lau, PhD[1,7], Ian C.K. Wong, PhD[1,7], Esther W. Chan, PhD[1,8]

[1.]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[2.]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Victoria, Australia

[3.]Department of Medicine, The University of Hong Kong, Hong Kong SAR, China

[4.] State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong SAR, China

[5.]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

[6.]Department of Cardiology, University Hospital Geelong and Deakin University, Geelong, Victoria, Australia

[7.]Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom

[8.]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

Corresponding author

Dr. Esther W Chan

General Office, L02-56 2/F, Laboratory Block LKS Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China.

Tel: +852-28315110; Email: ewchan@hku.hk

Abstract

OBJECTIVES: The risk of liver injury in patients with atrial fibrillation (AF) using non-vitamin K antagonist oral anticoagulants (NOACs) has not been previously examined using liver function tests as the primary outcome in the real-world setting. This study assessed the association between NOACs (dabigatran, rivaroxaban, apixaban) and warfarin and the risk of liver injury, as defined by laboratory tests.

METHODS: Patients newly diagnosed with AF and prescribed NOACs or warfarin between 2010-2016, identified using the Hong Kong Clinical Database and Reporting System, were matched on age, sex, health status scores, comorbidities and medications by propensity score on a 1:1 ratio. Risk of liver injury, defined as laboratory test values >3 times the upper limit of normal of alanine aminotransferase or aspartate aminotransferase and >2 times the upper limit of normal of total bilirubin, was compared between NOAC and warfarin users using Cox proportional hazards regression.

RESULTS: After propensity score matching, 13,698 patients were included, of which 141 (2.1%) NOAC users and 232 (3.4%) warfarin users developed liver injury. The hazard ratio (HR) for NOAC vs warfarin users was 0.71 (95% CI: 0.58-0.89). When comparing individual NOACs, only dabigatran (HR: 0.63; 95% CI: 0.48-0.82) was associated with a lower risk of liver injury.

DISCUSSION: Among patients with atrial fibrillation, NOACs as a group, as well as dabigatran alone, were associated with a significantly lower risk of laboratory-based liver injury when compared to warfarin. However, liver injury occurs more frequently in real-world practice than in NOAC randomized controlled trials.

Keywords: Oral anticoagulants, liver injury, liver function test, atrial fibrillation, safety

List of Abbreviations

AF = atrial fibrillation

ALT = alanine aminotransferase

ALP = alkaline phosphatase

AST = aspartate aminotransferase

CDARS = Clinical Data Analysis and Reporting System

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification

IPTW = inverse probability of treatment weighting

ITT = intention-to-treat

LFT = liver function test

NOAC = Non-vitamin K antagonist oral anticoagulant

Word count: 3554

INTRODUCTION

Safety signals from pharmacovigilance databases and case reports have emerged warning of potential risk for liver injury associated with non-vitamin K antagonist oral anticoagulants (NOACs)(1-4). These reports are particularly concerning considering the case of an earlier direct thrombin inhibitor, ximelagatran, which was withdrawn from the market due to hepatotoxicity(5). In light of the heightened concern for hepatotoxicity, guidelines from the American Heart Association and European Heart Rhythm Association recommend routine monitoring of liver function among patients with atrial fibrillation (AF) using NOACs(6-8).

To date, one systematic review(9), and two population-based observational studies have been conducted to assess the risk of liver injury associated with NOACs(10, 11). However, the results were not consistent among the three studies. NOACs were found to be significantly associated with a lower risk of liver injury compared with warfarin in a US cohort study(10), but no such association was identified in the other two(9, 11). Notably the observational studies did not include laboratory tests in the determination of liver injury. The use of diagnostic coding to define the outcome of liver injury is also particularly challenging using electronic databases as such data may be inaccurate or incomplete without thorough case validation. The validity of International Statistical Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes used to identify acute liver injury in three European data sources found a wide range of positive predictive values using different outcome definitions (8%-84%)(12). Low positive predictive values using ICD codes alone, may bias the results due to misclassification of outcomes.

The objective of this study was to compare the risk of laboratory-measured liver injury, between the use of NOACs and warfarin in patients with AF.

METHODS

Data source

We accessed data from the Clinical Data Analysis and Reporting System (CDARS), an electronic health record database of the Hong Kong Hospital Authority. Since 1991, the Hospital Authority is the statutory body responsible for managing public hospitals and institutions, specialist and general out-patient clinics in Hong Kong, and serves over 7 million residents in the region(13, 14). CDARS contains clinical information including demographics, date of hospital admission and discharge, diagnoses (coded ICD-9-CM), medical and surgical procedures, laboratory tests and prescription records. Various high-quality large population-based pharmacoepidemiological studies have used CDARS in the past(13-16). The validation of the database was demonstrated by high coding accuracy for the diagnoses of AF, with PPV of 95%(13, 14). This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468). Informed consent was not required for the use of de-identified data in the absence of patient contact.

Study design and selection of patients

A population-based, new-user, active-comparator, cohort study was conducted. Patients newly diagnosed with AF (ICD-9-CM code 427.3) between January 1, 2010 and December 31, 2016 were identified from CDARS. Index date was defined as prescription start date of the first record of oral anticoagulant following the first date of AF diagnosis (AF-date).

Patients with a history of valvular heart diseases, hyperthyroidism or a valve replacement surgery on or before AF-date were excluded. Patients with records of cardiac surgery, myocarditis,

pericarditis and pulmonary embolism within 90 days prior to AF-date (potential transient cases of AF), were also excluded. Patients were removed if they were <18 years, had missing information on sex or date of birth, died on or before AF-date, or were never exposed to any oral anticoagulants including warfarin, dabigatran, rivaroxaban and apixaban since the AF-date. Patients were considered as prior users, and hence excluded, if they had received any oral anticoagulants within 180 days prior to index date. Patients, who had been exposed to multiple oral anticoagulants on the index date, or who had elevated liver enzymes (same definition as outcome, Appendix Table 1 in the supplement) during a 90-day baseline window prior to the index date, or who had specific liver disease diagnoses (Appendix Table 2 in the supplement) before the index date, were also removed (Figure 1).

The remaining patients were divided into two groups based on the initial oral anticoagulant they took since the AF-date (NOACs vs. warfarin). The groups were followed up from index date until the earliest occurrence of the outcome, death, switching or discontinuation of the index oral anticoagulant (>30 day gap between two consecutive prescriptions of the same oral anticoagulant), or end of study (December 31, 2017).

Outcome

The outcome of interest was liver injury, defined as the earliest occurrence of an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) serum level greater than 3 times the upper limit of normal, and a total bilirubin level greater than 2 times the upper limit of normal in accordance with Hy's law(17, 18) (Appendix Table 1 in the supplement). Hy's law is used by the FDA(19) to detect potential liver injury for new drug therapies. The same transaminase and bilirubin thresholds have also been widely used in NOAC randomized controlled trials (RCTs)(20-22). Applying the same criteria to that used in RCTS provides a

more valid and comparable outcome definition. Furthermore, for patients with liver injury, we described the clinical characteristics and outcomes including mortality; liver transplant; diagnosis of acute liver failure; diagnostic imaging; time to onset of liver injury; comorbidities; medication use; distribution of serum concentrations of ALT, ALP, and total bilirubin on the outcome date; and the ALT/ALP ratio (R value).

Confounding control

All covariates potentially associated with liver injury or suspected to influence oral anticoagulant treatment selection were considered to be confounders. These covariates(10, 11, 23-25) were baseline demographic characteristics on the index date including age and sex; health status scores including Charlson Comorbidity Index, CHA2DS2-VASc on the index date; comorbidities identified on and before index date including viral hepatitis, non-viral liver diseases, alcoholism, gallbladder diseases, kidney diseases, diabetes mellitus, myocardial infarction, congestive heart failure, hypertension, anemia, coagulopathy, gastrointestinal bleeding, intracranial bleeding, other bleedings, ischemic stroke, peripheral vascular diseases, cancer, as well as concomitant medications used within 90 days prior to index date including antibacterial agents, antifungal agents, acetaminophen, proton pump inhibitors, H2-receptor antagonists, and medications used within 365 days prior to index date as listed in Appendix Tables 2-3 in the supplement.

Propensity score matching, was used to reduce the imbalance in baseline characteristics between the comparison groups. All aforementioned variables were used for propensity score estimation, regardless of its statistical significance or collinearity in logistic regression model(26). Patients prescribed either NOACs or warfarin were matched on a 1:1 ratio on the propensity score using a nearest-neighbor matching algorithm with a caliper of 0.1 (Appendix Figure 1 in the

supplement). To assess the balance in baseline characteristics after matching, the standardized mean difference (SMD), calculated as the difference in means or proportions over the pooled standard deviation (SD), was used. The negligible difference was defined as a SMD less than 0.1.

Statistical analysis

Patient characteristics were summarized as mean (SD) or median (interquartile range [IQR]) for continuous variables and in frequencies (percentages) for categorical variables.

The incidence rate, calculated as the number of events divided by the duration of follow-up in person-years, as well as 95% confidence interval (CI), were obtained via Poisson regression model. We estimated hazard ratios (HR) and 95% CIs using a Cox proportional hazards model for the risk of liver injury between NOACs and warfarin users. Subgroup analyses were conducted to investigate the risk of liver injury in NOACs and warfarin users by sex and age group (<65, 65-74, and ≥75 years).

Eight sensitivity analyses were performed to assess the robustness of our results. First, different prescription gap lengths of 5 and 15 days were used to assess possible misclassification of exposure due to drug discontinuation. Second, an intention-to-treat approach (ITT) was conducted to test the quality of our cohort with respect to compliance and deviation of allocation of exposure(27). Third, in order to test the impact of missing values on the results, we excluded patients who did not have any ALT, AST, total bilirubin, or alkaline phosphatase (ALP) test, during the 90-day baseline window. Fourth, we increased the upper limits of normal for serum ALT and bilirubin (and excluded AST), with liver injury defined as an ALT greater than three times the upper limit of normal (i.e. > 120 U/L [women] and >150 U/L [men]) and total bilirubin

greater than 2 times the upper limit of normal (i.e. > 2.5 mg/L). Furthermore, we defined liver injury and acute liver failure using ICD-9-CM codes to assess consistency with the primary analysis. Finally, we controlled for potential confounders used in the primary analysis through a multivariate regression model and inverse probability of treatment weighting (IPTW). Data analyses were conducted by JZ with independent cross-checking conducted by JEB and EYC.

Statistical significance was defined as $P<0.05$; all alternative hypotheses were 2-sided. All analyses were performed using R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Among the 71,630 patients newly diagnosed with AF identified in CDARS between 2010-2016, 18, 281 new users of NOACs and warfarin remained after applying the exclusion criteria. A total of 13,698 patients were included in the main analysis after matching on a 1:1 ratio with good balance in baseline characteristics (Figure 1, Table 1; Appendix Tables 4-5 in the supplement). The mean (SD) age of the whole cohort was 73.9 (10.6) years, and 6,602 (48.2%) were women. The median (IQR) follow-up period was 1.2 (2.1) years for NOAC users, and 1.1 (3.0) years for warfarin users.

Risk of liver injury

Characteristics of patients with liver injury

In the overall cohort, a total of 513 (2.8%) patients experienced liver injury during follow-up (Table 2). None received a liver transplant within 90 days after the outcome date. The proportion of patients who underwent diagnostic imaging of the liver were diagnosed with acute liver failure, died from any cause, or died from liver failure was consistently greater in NOAC users compared to warfarin users. Similarly, NOAC users on average had greater elevations in serum ALT, ALP, and total bilirubin. For warfarin and NOAC users, most cases of liver injury occurred within 2 years of initiating treatment. Nearly two-thirds of patients had a cholestatic pattern of liver injury as indicated by ALT/ALP ratio ≤ 2. Characteristics of patients with liver injury and a diagnosis of acute liver failure are shown in Appendix Table 6.

Primary analysis

In the matched cohort, 373 of 13,698 patients (2.7%) developed liver injury: 141 NOAC users (2.1%), of which 72 were dabigatran users (2.0%); 40 were rivaroxaban users (2.0%); 29 were apixaban users (2.5%); and 232 warfarin users (3.4%). The use of NOACs was significantly associated with a lower risk of liver injury compared with the use of warfarin. The adjusted HR was 0.71 (95% CI: 0.58-0.89) (Table 3). When comparing individual NOAC agents to warfarin, dabigatran was associated with a lower risk of liver injury (HR: 0.63; 95% CI: 0.48-0.82). However, there was no statistically significant association between liver injury and use of rivaroxaban (HR: 0.72; 95% CI: 0.51-1.01) or use of apixaban (HR: 1.13; 95% CI: 0.77-1.68). Kaplan-Meier curves for liver injury are presented in Appendix Figure 2 in the supplement.

Subgroup analyses

When stratified by sex, a similar association between liver injury and use of NOACs compared with use of warfarin was only found to be statistically significant in men (NOACs vs warfarin: HR: 0.69; 95% CI: 0.52-0.92; dabigatran vs warfarin: HR: 0.57; 95% CI: 0.40-0.83) (Table 4). In contrast, no statistically significant associations were found in women. For subgroup analyses of different age groups, NOACs (HR: 0.38; 95% CI: 0.22-0.69) as well as dabigatran (HR: 0.17; 95% CI: 0.06-0.47) were significantly associated with lower risk of liver injury for patients aged <65 years and in patients aged ≥75 years (NOACs vs warfarin: HR: 0.73; 95% CI: 0.56-0.96; dabigatran vs warfarin: HR: 0.67; 95% CI: 0.48-0.95). The association was not observed among patients in the 65-74 age group.

Sensitivity analyses

The results of all sensitivity analyses were generally consistent with the primary analysis (Figure 2; Appendix Tables 7-14 in the supplement). Compared with warfarin, NOACs and dabigatran

were all statistically significantly associated with lower risk of liver injury, except in the sensitivity analyses where the upper limits of normal for serum ALT and bilirubin were increased (HR: 0.81; 95% CI: 0.61-1.06), and ICD-9-CM codes used to identify liver injury (HR: 0.82; 95% CI: 0.63-1.07) and acute liver failure (HR: 1.41; 95% CI: 0.58-3.38). Rivaroxaban showed a statistically significant association with lower risk of liver injury compared with warfarin in the sensitivity analyses which used a 5-day (HR: 0.60; 95% CI: 0.40-0.89) and 15-day gap (HR: 0.61; 95% CI: 0.42-0.89) as discontinuation, and which used partial covariate adjustment (HR: 0.75; 95% CI: 0.57-1.00) and IPTW with 1% truncation (HR: 0.76; 95% CI: 0.58-1.00).

DISCUSSION

In this population-based study, we investigated the risk of liver injury associated with the use of NOACs compared with warfarin in patients with AF, and found that NOACs were associated with a lower risk of liver injury. This decreased risk of liver injury relative to warfarin remained whether NOACs were evaluated as a class or by individual agent, with dabigatran associated with the lowest risk of liver injury among the three NOAC agents examined. Several sensitivity analyses, with the exception of acute liver failure, were consistent with the primary analysis.

Clinical outcomes and onset of liver injury

Despite being associated with a lower risk of liver injury, our results suggest that if a patient experiences liver injury while using oral anticoagulants, the clinical outcomes may be more severe with NOACs. Average serum concentrations of ALT, ALP, and total bilirubin appeared to be higher for NOAC users than warfarin users. While no significant difference between groups was observed for the outcome of acute liver failure, the point estimate suggested potential harm from NOAC use. Extreme elevations in ALT and an R $\geq$5 indicate a predominantly hepatocellular pattern of liver injury in patients also diagnosed with acute liver failure. Thus, it appears that NOAC use is associated with a lower overall risk of liver injury but may result in more severe presentation if liver injury does occur.

A systematic review and meta-analysis of 29 NOAC RCTs did not identify an increased risk of liver injury for NOACs versus control(9). However, the maximum duration of follow-up for the included RCTs was 2 years, and our findings suggest that the time to onset among patients who developed liver injury was $\geq$ 2 years in 35% of warfarin and 25% of NOAC users. The risk of liver injury (as per our study definition) in NOAC RCTs ranged from 0.1% to 0.5%(20, 28, 29),

which is much lower compared to our estimates of 2.0%-2.5% (Appendix Table 15-16 in the supplement). Increasing the thresholds for ALT and bilirubin in a sensitivity analysis still suggests a higher risk in clinical use versus RCTs (1.1%-1.9%). In contrast to RCTs, a longer duration of follow-up and inclusion of patients with a history of liver disease and gallbladder disease may account for our findings. Therefore, hepatic function should continue to be monitored in patients taking oral anticoagulants for the management of atrial fibrillation.

Comparison to previous observational studies

Recently, two observational studies(10, 11) investigated the association between liver injury and use of NOACs. Alonso *et al.*[10] found that NOACs were associated with lower risk of liver injury hospitalization compared with warfarin. However, this conclusion might be biased by the investigators' use of the ITT approach, which could not eliminate the effect of differential misclassification of exposure(30). On the other hand, while Douros *et al.*[11] improved their study design by considering switching/discontinuation therapy, and found no association between use of NOACs and increased risk of liver injury compared to warfarin, the estimates had reduced precision likely due to very few identified events. Notably, neither of the two studies used liver function tests (LFTs) to identify liver injury.

Consistent with the findings by Alonso *et al.*(10), dabigatran was associated with a lower risk of liver injury. However, in our study, neither the lower risk observed with rivaroxaban or the higher risk observed with apixaban was statistically significant. Ximelagatran induced hepatotoxicity was identified in long-term (up to 6 months) post-marketing surveillance studies(31-33). Ongoing surveillance with long-term follow-up will be important particularly for further assessment of the potential risk associated with apixaban as the number of exposed individuals in this study was small and the point estimate favored warfarin.

Effects of sex and age

A significant association between use of NOACs and lower risk of liver injury was only found in men. Generally, women are more likely to present with drug-induced hepatotoxicity than men(34, 35). In females, a relatively smaller plasma volume, higher proportion of body fat, lower basal metabolic rate and lower renal blood flow, may cause drugs to more readily accumulate leading to potential liver injury(36). A pharmacokinetic study showed that both the maximum serum concentration and the area under the curve of dabigatran and apixaban are higher in women than men(37). Further studies are warranted considering the marginal 95% CI for women from our results.

The strongest association of NOACs, especially dabigatran, on risk reduction of liver injury compared to warfarin was seen in patients <65 years. This suggests that younger patients may obtain more clinical hepatic safety benefit than older patients. Aging reduces the ability to maintain homeostasis due to structural alteration or dysfunction, and is noted to be a major risk factor for liver diseases and injury(38). In Spain, 45% of cases of drug-induced liver injury reported from 1994-2004 occurred in patients aged >60 years(39). Increased body fat paired with decreased basal metabolic rate and renal blood flow could change the distribution and clearance of drugs in older individuals, increasing their vulnerability to hepatotoxicity. In dabigatran users ≥65 years, the area under the curve is 1.7-2.0 fold higher than that in younger subjects(37, 40). This may explain the increasing trends in liver injury in NOAC users, especially in patients taking dabigatran and rivaroxaban. The nonsignificant finding observed in the 65-75 age group may be attributed to a drop in the incidence rate of warfarin users.

Possible biological basis for study findings

Different pharmacokinetic profiles of oral anticoagulants may help explain differences in hepatic safety profiles(37). High-energy reactions involving cytochrome-P450 enzymes causing decline of adenosine triphosphate levels, loss of ionic gradients, cell swelling, and rupture could be one reason(17). Compared to warfarin, which is almost 100% hepatically eliminated(29), dabigatran is not a substrate, inhibitor, nor an inducer of cytochrome-P450(37), and is hydrolyzed from dabigatran etexilate into active form by an esterase(41). Only 20% of dabigatran is eliminated by the liver(29). In addition, the hydrolyzed form of dabigatran is not a substrate of P-glycoprotein(37), which plays an important role in removing foreign substances from cells(42). Although, rivaroxaban does not induce or inhibit P-glycoprotein(37, 43), it is metabolized by cytochrome-P450 and approximately 65% is eliminated by the liver(29, 37). This may relate to the observation that the reduction on risk of liver injury is less pronounced than that of dabigatran. In contrast, apixaban potentially poses the highest burden on the liver, as 75% of the drug is metabolized in the liver via cytochrome-P450 which is also a substrate for P-glycoprotein(29, 37).

Strengths and limitations

Our study design has a number of strengths. To our knowledge, this is the first study to adopt a laboratory test outcome as an objective measure for the definition of liver injury. We further used ICD-9-CM codes to define outcome events and to confirm the robustness of our results. Importantly, we accounted for therapy switching between warfarin and NOACs, drug discontinuation to avoid misclassification of exposures. The profile of drug hepatotoxicity is considerably different between western and Asian population(44) and as data on Asian cohorts

are limited, this study provides a unique insight into the liver safety of NOACs and may enable comparisons between ethnicities.

Considering the observational nature of this study, we cannot rule out the possibility of residual confounding. It is possible that awareness of the potential risk of liver injury with NOACs may have resulted in channeling bias, with patients at risk of potential liver injury being preferentially prescribed warfarin, particularly in patients with a history of chronic liver disease. However, both NOACs and warfarin are not recommended for patients with severe hepatic impairment in Hong Kong according to the pharmaceutical product regulator(45). To reduce the potential for bias, we excluded patients with any ICD-9-CM codes or laboratory values indicative of liver injury before the index date, and also used propensity score matching on 40 covariates with good balance in our matched cohort. The sample size for apixaban users is likely too small to draw a conclusion about risk of liver injury. Another potential limitation is that although 99.9% of patients in this study had LFTs during the study period, approximately 15% did not have a LFT at baseline. To test the impact of missing values on results, we removed those without baseline LFTs in one of the sensitivity analyses. The results were still consistent with our primary analysis.

In conclusion, among patients with atrial fibrillation, NOACs as a group, as well as dabigatran alone, were associated with a significantly lower risk of laboratory-based liver injury when compared to warfarin. However, the risk of liver injury appears to be higher than that observed in landmark clinical trials of NOACs, and patients using NOACs who experience liver injury may have more severe clinical outcomes.

Study Highlights

WHAT IS KNOWN

- Two cohort studies have investigated the association of NOACs and liver injury using claims databases in the United States and Canada.
- The association between NOACs and liver injury was inconsistent and the outcomes did not include liver function laboratory tests.
- Inclusion of Asian patients is limited in both randomized controlled trials (RCTs) and cohort studies.

WHAT IS NEW HERE

- This is the first population-based cohort study that used liver function tests to assess the association between NOACs and the risk of liver injury in an Asian population.
- NOACs were associated with improved hepatic safety compared to warfarin among adults with atrial fibrillation.
- Liver injury appears to be more frequent in clinical practice than in NOAC RCTs.

REFERENCES

1. Liakoni E, Ratz Bravo AE, Krahenbuhl S. Hepatotoxicity of new oral anticoagulants (NOACs). Drug Saf 2015;38:711-720.

2. Rochwerg B, Xenodemetropoulos T, Crowther M, Spyropoulos A. Dabigatran-induced acute hepatitis. Clin Appl Thromb Hemost 2012;18:549-550.

3. Clarke SA, Alsaad AA, Mack A, Phillips MB. Apixaban-induced liver injury. BMJ Case Rep 2016;2016.

4. Liakoni E, Ratz Bravo AE, Terracciano L, Heim M, Krahenbuhl S. Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban. JAMA Intern Med 2014;174:1683-1686.

5. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handb Exp Pharmacol 2010:407-418.

6. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013;15:625-651.

7. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330-1393.

8. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, 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;74:104-132.

9. Caldeira D, Barra M, Santos AT, de Abreu D, Pinto FJ, Ferreira JJ, Costa J. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart 2014;100:550-556.

10. Alonso A, MacLehose RF, Chen LY, Bengtson LG, Chamberlain AM, Norby FL, Lutsey PL. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. Heart 2017;103:834-839.

11. Douros A, Azoulay L, Yin H, Suissa S, Renoux C. Non-vitamin K antagonist oral anticoagulants and risk of serious liver injury. J Am Coll Cardiol 2018;71:1105-1113.

12. Forns J, Cainzos-Achirica M, Hellfritzsch M, Morros R, Poblador-Plou B, Hallas J, Giner-Soriano M, et al. Validity of ICD-9 and ICD-10 codes used to identify acute liver injury: a study in three European data sources. Pharmacoepidemiol Drug Saf 2019;28:965-975.

13. Lau WC, Chan EW, Cheung CL, Sing CW, Man KK, Lip GY, Siu CW, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. JAMA 2017;317:1151-1158.

14. Law SWY, Lau WCY, Wong ICK, Lip GYH, Mok MT, Siu CW, Chan EW. Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation. J Am Coll Cardiol 2018;72:271-282.

15. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for helicobacter pylori: a population-based study. Gut 2018;67:28-35.

16. Wong AY, Wong IC, Chui CS, Lee EH, Chang WC, Chen EY, Leung WK, et al. Association between acute neuropsychiatric events and helicobacter pylori therapy containing clarithromycin. JAMA Intern Med 2016;176:828-834.

17. Arora N, Goldhaber SZ. Anticoagulants and transaminase elevation. Circulation 2006;113:e698-702.

18. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol 2017;112:18-35.

19. Food and Drug Administration. Drug induced liver injury: premarketing clinical evaluation; 2009.

20. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151.

21. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, investigators A-. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807-815.

22. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J 2012;76:2104-2111.

23. Jinjuvadia K, Kwan W, Fontana RJ. Searching for a needle in a haystack: use of ICD-9-CM codes in drug-induced liver injury. Am J Gastroenterol 2007;102:2437-2443.

24. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008;135:1924-1934, 1934 e1921-1924.

25. Bjornsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol 2015;89:327-334.

26. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69:345-357.

27. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999;319:670-674.

28. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.

29. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. J Am Coll Cardiol 2018;71:2162-2175.

30. Gupta SK. Intention-to-treat concept: a review. Perspect Clin Res 2011;2:109-112.

31. Petersen P, Grind M, Adler J, Investigators SI. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. J Am Coll Cardiol 2003;41:1445-1451.

32. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690-698.

33. Agnelli G, Eriksson BI, Cohen AT, Bergqvist D, Dahl OE, Lassen MR, Mouret P, et al. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. Thromb Res 2009;123:488-497.

34. Guy J, Peters MG. Liver disease in women: the influence of gender on epidemiology, natural history, and patient outcomes. Gastroenterol Hepatol (N Y) 2013;9:633-639.

35. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study G. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065-2076.

36. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009;48:143-157.

37. Gelosa P, Castiglioni L, Tenconi M, Baldessin L, Racagni G, Corsini A, Bellosta S. Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs). Pharmacol Res 2018;135:60-79.

38. Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Curr Opin Gastroenterol 2015;31:184-191.

39. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512-521.

40. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost 2009;15 Suppl 1:9S-16S.

41. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos 2008;36:386-399.
42. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003;42:59-98.
43. Gnoth MJ, Buetehorn U, Muenster U, Schwarz T, Sandmann S. In vitro and in vivo P-glycoprotein transport characteristics of rivaroxaban. J Pharmacol Exp Ther 2011;338:372-380.
44. Suk KT, Kim DJ. Drug-induced liver injury: present and future. Clin Mol Hepatol 2012;18:249-257.
45. Drug Office Department of Health The Government of the Hong Kong SAR. Oral anticoagulants and antiplatelet drugs. In; 2014.

Acknowledgment

We thank Dr. Eric Y.F. Wan and Dr. Kenneth K.C. Man, who provided statistical consultation, Ms. Pat Wong, who provided administrative support for this study, and Ms. Lisa Y.L. Lam for proofreading the manuscript.

CONFLICT OF INTEREST

Guarantor of the article: First author Jiaxi Zhao, MSc, and corresponding author Esther W Chan, PhD, take full responsibility for the conduct of the study and have had access to the data and have control of the decision to publish.

Specific author contributions: All authors have contributed to and approved the final version of the manuscript. The respective roles of each author are the following: concept and design by Zhao, Blais, Suh, Wong and Chan; acquisition, analysis, or interpretation of data by all authors; drafting of the manuscript by Zhao, Blais, Suh, Chan; critical revision of the manuscript for important intellectual content by All authors; statistical analysis by Zhao, Blais, Chen.

Financial support: None.

Potential competing interests: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr. Joseph E Blais is supported by the Hong Kong Research Grants Council as a recipient of the Hong Kong PhD Fellowship Scheme. Prof. Ian CK Wong received grants from the Research Grants Council (RGC, Hong Kong), Innovative Medicines Initiative (IMI), Shire, Janssen-Cilag, Eli-Lily, Pfizer, Bayer, European Union FP7 program, outside the submitted work. Ian Wong is a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group, the British Association for

Psychopharmacology ADHD guideline group, and advisor to Shire. Dr. Esther W Chan has received honorarium from the Hospital Authority and research funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau of HKSAR, Hong Kong; National Natural Science Fund of China, China; Wellcome Trust, United Kingdom; Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen and Takeda, for work unrelated to this study. No other disclosures were reported.

Figure Legends

Figure 1. Study Flow Chart of NOACs and Warfarin New Users Selection

Abbreviations: AF, atrial fibrillation; CDARS, Clinical Data Analysis and Reporting System (of the Hong Kong Hospital Authority); ICD-9-CM, International Statistical Classification of Diseases, Ninth Revision, Clinical Modification; LFT, liver function test; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulant; PS, propensity score.

Figure 2. Forest Plots with the Primary Analyses and All Sensitivity Analyses

Abbreviations: HR, hazard ratio; ICD-9-CM, International Statistical Classification of Diseases, Ninth Revision, Clinical Modification; IPTW, inverse probability of treatment weighting; LFTs, liver function tests; NOACs, non -vitamin K antagonist oral anticoagulants; ULN, upper limit of normal. Forest plot with HRs for use of NOACs compared with use of warfarin associated with liver injury. Full covariate adjustment indicates that all covariates, which were in propensity score matching, were adjusted for in the Cox regression model. Partial covariate adjustment indicates that only selected covariates (age, sex, Charlson Comorbidity Index, kidney diseases, congestive heart failure, antibacterial agents, proton pump inhibitors, lipid-lowering agents, angiotensin-converting-enzyme inhibitors, diuretics and digoxin) were adjusted for in the Cox regression model. Inverse probability weighting with no truncation indicates that no changed in estimated weights. Inverse probability of treatment weighting with 1% truncation indicates that the individuals with weights below or above the 1st or 99th percentile respectively, were set to the truncation threshold.

Table 1. Baseline Characteristics of Warfarin and NOAC Users Before and After Propensity Score Matching

Baseline characteristic*	Before propensity score matching			After propensity score matching		
	Warfarin (n=8,519)	NOACs (n=9,762)	SMD†	Warfarin (n=6,849)	NOACs (n=6,849)	SMD†
Age, mean (SD), y	72.6 (11.6)	75.1 (10.2)	0.231	73.9 (10.7)	73.9 (10.5)	0.004
Women	3,905 (45.8)	4,937 (50.6)	0.095	3,280 (47.9)	3,322 (48.5)	0.012
Health status score on index date						
CCI, mean (SD)‡	1.7 (1.7)	1.4 (1.5)	0.197	1.5 (1.5)	1.5 (1.5)	0.031
$CHADS_2$, mean (SD)§	2.2 (1.5)	2.2 (1.5)	0.022	2.2 (1.5)	2.2 (1.5)	0.010
CHA_2DS_2-VASc, mean (SD)‖	3.7 (1.9)	3.7 (1.8)	0.024	3.7 (1.9)	3.7 (1.9)	0.013
Laboratory tests ¶ within 90 days prior to index date						
ALT, median (IQR), U/L	21.1 (18.0)	20.0 (15.5)	0.116	21.0 (16.4)	21.0 (16.0)	0.049
AST, median (IQR), U/L	27.5 (19.0)	25.0 (15.1)	0.145	27.0 (17.6)	25.0 (15.0)	0.131
ALP, median (IQR), U/L	75.0 (29.4)	72.8 (28.7)	0.115	74.0 (28.9)	72.7 (28.5)	0.070
Total bilirubin, median (IQR), mg/dL	0.74 (0.50)	0.71 (0.45)	0.085	0.73 (0.47)	0.71 (0.47)	0.013
Comorbidities on or before index date						
Viral hepatitis	163 (1.9)	188 (1.9)	0.001	136 (2.0)	136 (2.0)	0
Non-viral liver diseases	2 (<0.1)	4 (<0.1)	0.010	2 (<0.1)	3 (<0.1)	0.008
Alcoholism	91 (1.1)	92 (0.9)	0.013	67 (1.0)	62 (0.9)	0.008
Gallbladder diseases	208 (2.4)	230 (2.4)	0.006	158 (2.3)	169 (2.5)	0.011
Kidney diseases	1,051 (12.3)	549 (5.6)	0.236	459 (6.7)	513 (7.5)	0.031
Diabetes mellitus	2,064 (24.2)	2,132 (21.8)	0.057	1,540 (22.5)	1,583 (23.1)	0.015
Myocardial infarction	756 (8.9)	610 (6.2)	0.099	485 (7.1)	501 (7.3)	0.009
Congestive heart failure	2,644 (31.0)	2,070 (21.2)	0.225	1,654 (24.1)	1,766 (25.8)	0.038
Hypertension	4,481 (52.6)	5,041 (51.6)	0.019	3,564 (52.0)	3,582 (52.3)	0.005
Anemia	854 (10.0)	743 (7.6)	0.085	562 (8.2)	596 (8.7)	0.018
Coagulopathy	73 (0.9)	74 (0.8)	0.011	50 (0.7)	52 (0.8)	0.003
Gastrointestinal bleeding	727 (8.5)	740 (7.6)	0.035	535 (7.8)	548 (8.0)	0.007
Intracranial bleeding	265 (3.1)	300 (3.1)	0.002	210 (3.1)	210 (3.1)	0
Other bleedings	707 (8.3)	819 (8.4)	0.003	561 (8.2)	575 (8.4)	0.007
Ischemic stroke	2,705 (31.8)	3,204 (32.8)	0.023	2,216 (32.4)	2,184 (31.9)	0.010
Peripheral vascular diseases	247 (2.9)	152 (1.6)	0.091	117 (1.7)	136 (2.0)	0.021
Cancers	1,166 (13.7)	1,512 (15.5)	0.051	993 (14.5)	1,006 (14.7)	0.005
Medications use within 90 days prior to index date						
Antibacterial agents	2,697 (31.7)	2,614 (26.8)	0.107	1,950 (28.5)	2,022 (29.5)	0.023
Antifungal agents	24 (0.3)	23 (0.2)	0.009	15 (0.2)	13 (0.2)	0.006
Acetaminophen	3,179 (37.3)	3,539 (36.3)	0.022	2,487 (36.3)	2,497 (36.5)	0.003
PPIs	2,118 (24.9)	2,865 (29.3)	0.101	1,732 (25.3)	1,748 (25.5)	0.005
H2-receptor antagonists	4,490 (52.7)	5,264 (53.9)	0.024	3,672 (53.6)	3,658 (53.4)	0.004
Medications use within 365 days prior to index date						

Antiplatelet agents	6,597 (77.4)	7,709 (79.0)	0.037	5,313 (77.6)	5,319 (77.7)	0.002
Lipid lowering drugs	4,030 (47.3)	5,549 (56.8)	0.192	3,500 (51.1)	3,492 (51.0)	0.002
Antiarrhythmics	1,645 (19.3)	1,804 (18.5)	0.021	1,247 (18.2)	1,262 (18.4)	0.006
NSAIDs	960 (11.3)	1,061 (10.9)	0.013	775 (11.3)	766 (11.2)	0.004
ACEIs	3,634 (42.7)	3,621 (37.1)	0.114	2,717 (39.7)	2,771 (40.5)	0.016
ARBs	540 (6.3)	862 (8.8)	0.094	471 (6.9)	483 (7.1)	0.007
Beta blockers	4,920 (57.8)	6,053 (62.0)	0.087	4,115 (60.1)	4,068 (59.4)	0.014
CCBs	5,133 (60.3)	6,207 (63.6)	0.069	4,220 (61.6)	4,273 (62.4)	0.016
Diuretics	3,690 (43.3)	3,242 (33.2)	0.209	2,503 (36.5)	2,628 (38.4)	0.038
Digoxin	2,278 (26.7)	2,035 (20.8)	0.139	1,591 (23.2)	1,601 (23.4)	0.003
Nucleoside analogs	45 (0.5)	55 (0.6)	0.005	41 (0.6)	39 (0.6)	0.004
Antituberculosis agents	28 (0.3)	23 (0.2)	0.018	16 (0.2)	17 (0.2)	0.003
Antiepileptics	148 (1.7)	168 (1.7)	0.001	116 (1.7)	112 (1.6)	0.005
Immunosuppressants	37 (0.4)	43 (0.4)	0.001	30 (0.4)	27 (0.4)	0.007

Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; CCBs, calcium channel blockers; CCI, Charlson Comorbidity Index; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SMD, standardized mean difference.

* Values are expressed as frequency (%) unless otherwise specified.

† SMD indicates difference in mean or proportion of covariates in NOAC group vs warfarin group divided by the pooled standard deviation. SMD of less than 0.1 indicates a negligible difference between groups. After matching, only AST showed a slightly higher value of 0.131.

‡ CCI indicates patients with myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, acquired immune deficiency syndrome. The severity of comorbidity was categorized into three grades based on the score: mild with scores of 1-2; moderate with scores of 3-4; severe with scores of 5 or above (higher score indicates a higher risk of mortality).

§ $CHADS_2$ indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or systemic embolism. The score ranges from 0 to 6 (higher score indicates a higher risk of stroke).

‖ CHA_2DS_2-VASc indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, age 65 to 74, prior stroke or transient ischemic attack or systemic embolism, vascular disease, and sex category (women). The score ranges from 0 to 9 (higher score indicates a higher risk of stroke).

¶ There were 13 684 (99.9%) patients who ever had a LFT during the whole study period. A total of 1842 (13.4%) patients did not have any hepatic function laboratory tests within 90 days prior to index date:1849 (13.5%) patients were missing ALT, 10 835 (79.1%) were missing AST, 1855 (13.5%) were missing total bilirubin, and 1852 (13.5%) were missing ALP. SI conversion factors: To convert ALT/AST to µkat/L, multiply values by 0.0167; to convert total bilirubin to µmol/L, multiply values by 17.104.

Table 2. Characteristics of Warfarin and NOAC Users with Liver Injury Before Propensity Score Matching (n=513)

	Warfarin (n=313)	NOACs (n=200)	Dabigatran (n=93)	Rivaroxaban (n=63)	Apixaban (n=44)
Diagnostic imaging*					
Diagnostic imaging of the liver within 90 days after the outcome date	65 (20.8)	49 (24.5)	27 (29.0)	12 (19.0)	10 (22.7)
Acute liver failure, transplant and death					
Acute liver failure diagnosis within 90 days after outcome date	18 (5.8)	14 (7.0)	6 (6.5)	8 (12.7)	0 (0)
Liver transplant within 90 days after the outcome date	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death from any cause within 90 days after the outcome date	102 (32.6)	69 (34.5)	31 (33.3)	26 (41.3)	12 (27.3)
Death from liver causes within 90 days after the outcome date	1 (0.3)	3 (1.5)	2 (2.2)	1 (1.6)	0 (0)
Time from oral anticoagulant initiation to liver injury					
<1 month	37 (11.8)	23 (11.5)	11 (11.8)	7 (11.1)	5 (11.4)
≥1 month to <3 months	33 (10.5)	19 (9.5)	6 (6.5)	9 (14.3)	4 (9.1)
≥3 month to <6 months	33 (10.5)	17 (8.5)	12 (12.9)	1 (1.6)	4 (9.1)
≥6 to <12 months	40 (12.8)	36 (18.0)	13 (14.0)	13 (20.6)	10 (22.7)
≥12 to <24 months	61 (19.5)	56 (28.0)	22 (23.7)	17 (27.0)	17 (38.6)
≥24 months	109 (34.8)	49 (24.5)	29 (31.2)	16 (25.4)	4 (9.1)
Laboratory tests on outcome date					
ALT, median (IQR), U/L	177.3 (247.9)	184.2 (308.5)	210.0 (321.0)	204.0 (482.5)	146.5 (214.0)
≥5 times ULN	182 (58.1)	119 (59.5)	60 (64.5)	37 (58.7)	22 (50.0)
≥10 times ULN	93 (29.7)	75 (37.5)	39 (41.9)	24 (38.1)	12 (27.3)
≥20 times ULN	52 (16.6)	40 (20.0)	18 (19.4)	17 (27.0)	5 (11.4)
ALP, median (IQR), U/L	129.0 (116.0)	139.5 (132.5)	149.0 (176.0)	120 (70)	183.5 (297.5)
≥2 times ULN	82 (26.2)	62 (31.0)	32 (34.4)	9 (14.3)	21 (47.7)
≥4 times ULN	22 (7.0)	24 (12.0)	12 (12.9)	1 (1.6)	11 (25.0)
Total bilirubin, median (IQR), mg/dL	2.91 (1.80)	3.04 (1.85)	3.00 (2.67)	2.69 (1.65)	3.17 (1.46)
≥3 times ULN	146 (46.6)	101 (50.5)	46 (49.5)	27 (42.9)	28 (63.6)
≥5 times ULN	44 (14.1)	46 (23.0)	25 (26.9)	9 (14.3)	12 (27.3)
ALT/ALP ratio (R)					
≤2 (cholestatic)	208 (66.5)	124 (62.0)	58 (62.4)	31 (49.2)	35 (79.5)
>2 to <5 (mixed)	54 (17.3)	39 (19.5)	15 (16.1)	17 (27.0)	7 (15.9)
≥5 (hepatocellular)	51 (16.3)	37 (18.5)	20 (21.5)	15 (23.8)	2 (4.5)
Comorbidities within 30 days prior to outcome date					
Viral hepatitis	7 (2.2)	3 (1.5)	3 (3.2)	0 (0)	0 (0)
Non-viral liver diseases	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alcoholism	2 (0.6)	1 (0.5)	0 (0)	0 (0)	1 (2.3)
Gallbladder diseases	62 (19.8)	44 (22.0)	23 (24.7)	9 (14.3)	12 (27.3)

Myocardial infarction	26 (8.3)	15 (7.5)	8 (8.6)	5 (7.9)	2 (4.5)
Congestive heart failure	118 (37.7)	61 (30.5)	30 (32.3)	20 (31.7)	11 (25.0)
Hypertension	67 (21.4)	48 (24.0)	24 (25.8)	12 (19.0)	12 (27.3)
Shock/hypotension	33 (10.5)	23 (11.5)	15 (16.1)	7 (11.1)	1 (2.3)
Medication use within 30 days prior to outcome date					
Antibacterial agents	158 (50.5)	115 (57.5)	57 (61.3)	33 (52.4)	25 (56.8)
Antifungal agents	3 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
Acetaminophen	156 (49.8)	106 (53.0)	47 (50.5)	33 (52.4)	26 (59.1)
PPIs	168 (53.7)	113 (56.5)	47 (50.5)	34 (54.0)	32 (72.7)
H2-receptor antagonists	133 (42.5)	84 (42.0)	43 (46.2)	27 (42.9)	14 (31.8)
Antiplatelet agents	101 (32.3)	61 (30.5)	28 (30.1)	19 (30.2)	14 (31.8)
Lipid lowering drugs	160 (51.1)	122 (61.0)	45 (48.4)	44 (69.8)	33 (75.0)
Antiarrhythmics	74 (23.6)	47 (23.5)	20 (21.5)	23 (36.5)	4 (9.1)
NSAIDs	5 (1.6)	9 (4.5)	6 (6.5)	1 (1.6)	2 (4.5)
Nucleoside analogs	6 (1.9)	1 (0.5)	1 (1.1)	0 (0)	0 (0)
Antituberculosis agents	4 (1.3)	6 (3.0)	4 (4.3) †	0 (0)	2 (4.5)
Antiepileptics	6 (1.9)	6 (3.0)	2 (2.2)	2 (3.2)	2 (4.5)
Immunosuppressants	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; ULN, upper limit of normal.
Values are expressed as frequency (%) unless otherwise specified.
* See supplementary appendix for ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) procedure codes.
† Liver injury attributed to antituberculosis medications in diagnosis comment for one dabigatran user.

Table 3. Crude and Adjusted Estimates of Liver Injury Before and After Propensity Score Matching

	Before propensity score matching			After propensity score matching		
Exposure	**Total No. / No. of events/person-years / Incidence per 1000 person-years (95% CI)**	**Crude HR (95% CI)**	***P* value**	**Total No. / No. of events / person-years / Incidence per 1000 person-years (95% CI)**	**Adjusted HR (95% CI)**	***P* value**
Warfarin	8,519 / 313 / 16,369 / 19.1 (17.1 to 21.3)	1.00 (reference)		6,849 / 232 / 13,179 / 17.6 (15.4 to 20.0)	1.00 (reference)	
NOACs	9,762 / 200 / 15,173 / 13.2 (11.4 to 15.1)	0.65 (0.55 to 0.78)	<0.001	6,849 / 141 / 10,727 / 13.1 (11.1 to 15.4)	0.71 (0.58 to 0.89)	0.002
Dabigatran	5,125 / 93 / 8,861 / 10.5 (8.5 to 12.8)	0.53 (0.42 to 0.67)	<0.001	3,663 / 72 / 6,391 / 11.3 (8.9 to 14.1)	0.63 (0.48 to 0.82)	<0.001
Rivaroxaban	2,924 / 63 / 4,312 / 14.6 (11.3 to 18.5)	0.71 (0.54 to 0.94)	0.02	2,016 / 40 / 3,014 / 13.3 (9.6 to 17.8)	0.72 (0.51 to 1.01)	0.05
Apixaban	1,713 / 44 / 2,000 / 22.0 (16.1 to 29.1)	1.04 (0.75 to 1.43)	0.83	1,170 / 29 / 1,321 / 22.0 (14.9 to 30.9)	1.13 (0.77 to 1.68)	0.53

Abbreviations: CI, confidence interval; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulants.

Table 4. Estimates of Liver Injury Risk After Propensity Score Matching Stratified by Sex and by Age Group

Stratified by sex

Exposures	Men (n=7,096)		Women (n=6,602)		*P* value for interaction
	Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	
Warfarin	3,569 / 129 / 6,878 / 18.8 (15.7 to 22.2)	1.00 (reference)	3,280 / 103 / 6,302 / 16.3 (13.4 to 19.7)	1.00 (reference)	
NOACs	3,527 / 73 / 5,411 / 13.5 (10.6 to 16.8)	0.69 (0.52 to 0.92)	3,322 / 68 / 5,315 / 12.8 (10.0 to 16.1)	0.75 (0.55 to 1.03)	0.68
Dabigatran	1,893 / 36 / 3,276 / 11.0 (7.8 to 15.0)	0.57 (0.40 to 0.83)	1,770 / 36 / 3,115 / 11.6 (8.2 to 15.8)	0.70 (0.48 to 1.02)	0.48
Rivaroxaban	1,041 / 24 / 1,495 / 16.1 (10.5 to 23.4)	0.81 (0.52 to 1.26)	975 / 16 / 1,519 / 10.5 (6.2 to 16.6)	0.62 (0.36 to 1.05)	0.43
Apixaban	593 / 13 / 640 / 20.3 (11.2 to 33.4)	0.99 (0.56 to 1.77)	577 / 16 / 681 / 23.5 (13.8 to 37.0)	1.30 (0.76 to 2.23)	0.46

Stratified on age group

Exposures	< 65 years (n=2,767)		65-74 years (n=3,775)		≥ 75 years (n=7,156)		*P* value for interaction
	Total No. / No. of event / person-years / Incidence per 1,000 person-years (95% CI)	Adjusted HR (95% CI)	Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	
Warfarin	1,451 / 51 / 3,177 / 16.1 (12.0 to 20.9)	1.00 (reference)	1,815 / 47 / 3,792 / 12.4 (9.2 to 16.3)	1.00 (reference)	3,583 / 134 / 6,210 / 21.6 (18.1 to 25.4)	1.00 (reference)	
NOACs	1,316 / 15 / 2,038 / 7.4 (4.2 to 11.7)	0.38 (0.22 to 0.69)	1,960 / 40 / 3,389 / 11.8 (8.5 to 15.8)	1.00 (0.65 to 1.55)	3,573 / 86 / 5,299 / 16.2 (13.0 to 19.9)	0.73 (0.56 to 0.96)	0.21
Dabigatran	751 / 4 / 1,307 / 3.1 (0.9 to 7.1)	0.17 (0.06 to 0.47)	1,097 / 24 / 2,106 / 11.4 (7.4 to 16.6)	0.97 (0.59 to 1.59)	1,815 / 44 / 2,979 / 14.8 (10.8 to 19.6)	0.67 (0.48 to 0.95)	0.07
Rivaroxaban	399 / 5 / 539 / 9.3 (3.3 to 19.9)	0.45 (0.18 to 1.14)	579 / 11 / 931 / 11.8 (6.1 to 20.2)	1.03 (0.52 to 2.01)	1,038 / 24 / 1,544 / 15.5 (10.1 to 22.6)	0.70 (0.45 to 1.08)	0.61
Apixaban	166 / 6 / 191 / 31.3 (12.5 to 63.5)	1.43 (0.61 to 3.35)	284 / 5 / 353 / 14.2 (5.1 to 30.4)	1.18 (0.46 to 3.02)	720 / 18 / 776 / 23.2 (14.1 to 35.6)	1.02 (0.62 to 1.68)	0.34

Abbreviations: CI, confidence interval; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulant.

Association Between Non-vitamin K Antagonist Oral Anticoagulants or Warfarin and Liver Injury: A Cohort Study

Jiaxi Zhao, MSc[1,8], Joseph E Blais, BScPharm[1], Celine S.L. Chui, PhD[1], In-Hye Suh, PharmD[1], Esa Y.H. Chen, BPharm[2], Wai-Kay Seto, MD[3,4,5], Michael T. Mok, MBBS[6], Vincent K.C. Yan, BPharm[1], Wallis C.Y. Lau, PhD[1,7], Ian C.K. Wong, PhD[1,7], Esther W. Chan, PhD[1,8]

[1.]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[2.]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Victoria, Australia

[3.]Department of Medicine, The University of Hong Kong, Hong Kong SAR, China

[4.] State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong SAR, China

[5.]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

[6.]Department of Cardiology, University Hospital Geelong and Deakin University, Geelong, Victoria, Australia

[7.]Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom

[8.]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

Corresponding author

Dr. Esther W Chan

General Office, L02-56 2/F, Laboratory Block LKS Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong SAR, China.

Tel: +852-28315110; Email: ewchan@hku.hk

Abstract

OBJECTIVES: The risk of liver injury in patients with atrial fibrillation (AF) using non-vitamin K antagonist oral anticoagulants (NOACs) has not been previously examined using liver function tests as the primary outcome in the real-world setting. This study assessed the association between NOACs (dabigatran, rivaroxaban, apixaban) and warfarin and the risk of liver injury, as defined by laboratory tests.

METHODS: Patients newly diagnosed with AF and prescribed NOACs or warfarin between 2010-2016, identified using the Hong Kong Clinical Database and Reporting System, were matched on age, sex, health status scores, comorbidities and medications by propensity score on a 1:1 ratio. Risk of liver injury, defined as laboratory test values >3 times the upper limit of normal of alanine aminotransferase or aspartate aminotransferase and >2 times the upper limit of normal of total bilirubin, was compared between NOAC and warfarin users using Cox proportional hazards regression.

RESULTS: After propensity score matching, 13,698 patients were included, of which 141 (2.1%) NOAC users and 232 (3.4%) warfarin users developed liver injury. The hazard ratio (HR) for NOAC vs warfarin users was 0.71 (95% CI: 0.58-0.89). When comparing individual NOACs, only dabigatran (HR: 0.63; 95% CI: 0.48-0.82) was associated with a lower risk of liver injury.

DISCUSSION: Among patients with atrial fibrillation, NOACs as a group, as well as dabigatran alone, were associated with a significantly lower risk of laboratory-based liver injury when compared to warfarin. However, liver injury occurs more frequently in real-world practice than in NOAC randomized controlled trials.

Keywords: Oral anticoagulants, liver injury, liver function test, atrial fibrillation, safety

List of Abbreviations

AF = atrial fibrillation

ALT = alanine aminotransferase

ALP = alkaline phosphatase

AST = aspartate aminotransferase

CDARS = Clinical Data Analysis and Reporting System

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification

IPTW = inverse probability of treatment weighting

ITT = intention-to-treat

LFT = liver function test

NOAC = Non-vitamin K antagonist oral anticoagulant

Word count: 3554

INTRODUCTION

Safety signals from pharmacovigilance databases and case reports have emerged warning of potential risk for liver injury associated with non-vitamin K antagonist oral anticoagulants (NOACs)(1-4). These reports are particularly concerning considering the case of an earlier direct thrombin inhibitor, ximelagatran, which was withdrawn from the market due to hepatotoxicity(5). In light of the heightened concern for hepatotoxicity, guidelines from the American Heart Association and European Heart Rhythm Association recommend routine monitoring of liver function among patients with atrial fibrillation (AF) using NOACs(6-8).

To date, one systematic review(9), and two population-based observational studies have been conducted to assess the risk of liver injury associated with NOACs(10, 11). However, the results were not consistent among the three studies. NOACs were found to be significantly associated with a lower risk of liver injury compared with warfarin in a US cohort study(10), but no such association was identified in the other two(9, 11). Notably the observational studies did not include laboratory tests in the determination of liver injury. The use of diagnostic coding to define the outcome of liver injury is also particularly challenging using electronic databases as such data may be inaccurate or incomplete without thorough case validation. The validity of International Statistical Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes used to identify acute liver injury in three European data sources found a wide range of positive predictive values using different outcome definitions (8%-84%)(12). Low positive predictive values using ICD codes alone, may bias the results due to misclassification of outcomes.

The objective of this study was to compare the risk of laboratory-measured liver injury, between the use of NOACs and warfarin in patients with AF.

METHODS

Data source

We accessed data from the Clinical Data Analysis and Reporting System (CDARS), an electronic health record database of the Hong Kong Hospital Authority. Since 1991, the Hospital Authority is the statutory body responsible for managing public hospitals and institutions, specialist and general out-patient clinics in Hong Kong, and serves over 7 million residents in the region(13, 14). CDARS contains clinical information including demographics, date of hospital admission and discharge, diagnoses (coded ICD-9-CM), medical and surgical procedures, laboratory tests and prescription records. Various high-quality large population-based pharmacoepidemiological studies have used CDARS in the past(13-16). The validation of the database was demonstrated by high coding accuracy for the diagnoses of AF, with PPV of 95%(13, 14). This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468). Informed consent was not required for the use of de-identified data in the absence of patient contact.

Study design and selection of patients

A population-based, new-user, active-comparator, cohort study was conducted. Patients newly diagnosed with AF (ICD-9-CM code 427.3) between January 1, 2010 and December 31, 2016 were identified from CDARS. Index date was defined as prescription start date of the first record of oral anticoagulant following the first date of AF diagnosis (AF-date).

Patients with a history of valvular heart diseases, hyperthyroidism or a valve replacement surgery on or before AF-date were excluded. Patients with records of cardiac surgery, myocarditis,

pericarditis and pulmonary embolism within 90 days prior to AF-date (potential transient cases of AF), were also excluded. Patients were removed if they were <18 years, had missing information on sex or date of birth, died on or before AF-date, or were never exposed to any oral anticoagulants including warfarin, dabigatran, rivaroxaban and apixaban since the AF-date. Patients were considered as prior users, and hence excluded, if they had received any oral anticoagulants within 180 days prior to index date. Patients, who had been exposed to multiple oral anticoagulants on the index date, or who had elevated liver enzymes (same definition as outcome, Appendix Table 1 in the supplement) during a 90-day baseline window prior to the index date, or who had specific liver disease diagnoses (Appendix Table 2 in the supplement) before the index date, were also removed (Figure 1).

The remaining patients were divided into two groups based on the initial oral anticoagulant they took since the AF-date (NOACs vs. warfarin). The groups were followed up from index date until the earliest occurrence of the outcome, death, switching or discontinuation of the index oral anticoagulant (>30 day gap between two consecutive prescriptions of the same oral anticoagulant), or end of study (December 31, 2017).

Outcome

The outcome of interest was liver injury, defined as the earliest occurrence of an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) serum level greater than 3 times the upper limit of normal, and a total bilirubin level greater than 2 times the upper limit of normal in accordance with Hy's law(17, 18) (Appendix Table 1 in the supplement). Hy's law is used by the FDA(19) to detect potential liver injury for new drug therapies. The same transaminase and bilirubin thresholds have also been widely used in NOAC randomized controlled trials (RCTs)(20-22). Applying the same criteria to that used in RCTS provides a

more valid and comparable outcome definition. Furthermore, for patients with liver injury, we described the clinical characteristics and outcomes including mortality; liver transplant; diagnosis of acute liver failure; diagnostic imaging; time to onset of liver injury; comorbidities; medication use; distribution of serum concentrations of ALT, ALP, and total bilirubin on the outcome date; and the ALT/ALP ratio (R value).

Confounding control

All covariates potentially associated with liver injury or suspected to influence oral anticoagulant treatment selection were considered to be confounders. These covariates(10, 11, 23-25) were baseline demographic characteristics on the index date including age and sex; health status scores including Charlson Comorbidity Index, CHA2DS2-VASc on the index date; comorbidities identified on and before index date including viral hepatitis, non-viral liver diseases, alcoholism, gallbladder diseases, kidney diseases, diabetes mellitus, myocardial infarction, congestive heart failure, hypertension, anemia, coagulopathy, gastrointestinal bleeding, intracranial bleeding, other bleedings, ischemic stroke, peripheral vascular diseases, cancer, as well as concomitant medications used within 90 days prior to index date including antibacterial agents, antifungal agents, acetaminophen, proton pump inhibitors, H2-receptor antagonists, and medications used within 365 days prior to index date as listed in Appendix Tables 2-3 in the supplement.

Propensity score matching, was used to reduce the imbalance in baseline characteristics between the comparison groups. All aforementioned variables were used for propensity score estimation, regardless of its statistical significance or collinearity in logistic regression model(26). Patients prescribed either NOACs or warfarin were matched on a 1:1 ratio on the propensity score using a nearest-neighbor matching algorithm with a caliper of 0.1 (Appendix Figure 1 in the

supplement). To assess the balance in baseline characteristics after matching, the standardized mean difference (SMD), calculated as the difference in means or proportions over the pooled standard deviation (SD), was used. The negligible difference was defined as a SMD less than 0.1.

Statistical analysis

Patient characteristics were summarized as mean (SD) or median (interquartile range [IQR]) for continuous variables and in frequencies (percentages) for categorical variables.

The incidence rate, calculated as the number of events divided by the duration of follow-up in person-years, as well as 95% confidence interval (CI), were obtained via Poisson regression model. We estimated hazard ratios (HR) and 95% CIs using a Cox proportional hazards model for the risk of liver injury between NOACs and warfarin users. Subgroup analyses were conducted to investigate the risk of liver injury in NOACs and warfarin users by sex and age group (<65, 65-74, and ≥75 years).

Eight sensitivity analyses were performed to assess the robustness of our results. First, different prescription gap lengths of 5 and 15 days were used to assess possible misclassification of exposure due to drug discontinuation. Second, an intention-to-treat approach (ITT) was conducted to test the quality of our cohort with respect to compliance and deviation of allocation of exposure(27). Third, in order to test the impact of missing values on the results, we excluded patients who did not have any ALT, AST, total bilirubin, or alkaline phosphatase (ALP) test, during the 90-day baseline window. Fourth, we increased the upper limits of normal for serum ALT and bilirubin (and excluded AST), with liver injury defined as an ALT greater than three times the upper limit of normal (i.e. > 120 U/L [women] and >150 U/L [men]) and total bilirubin

greater than 2 times the upper limit of normal (i.e. > 2.5 mg/L). Furthermore, we defined liver injury and acute liver failure using ICD-9-CM codes to assess consistency with the primary analysis. Finally, we controlled for potential confounders used in the primary analysis through a multivariate regression model and inverse probability of treatment weighting (IPTW). Data analyses were conducted by JZ with independent cross-checking conducted by JEB and EYC.

Statistical significance was defined as $P<0.05$; all alternative hypotheses were 2-sided. All analyses were performed using R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Among the 71,630 patients newly diagnosed with AF identified in CDARS between 2010-2016, 18, 281 new users of NOACs and warfarin remained after applying the exclusion criteria. A total of 13,698 patients were included in the main analysis after matching on a 1:1 ratio with good balance in baseline characteristics (Figure 1, Table 1; Appendix Tables 4-5 in the supplement). The mean (SD) age of the whole cohort was 73.9 (10.6) years, and 6,602 (48.2%) were women. The median (IQR) follow-up period was 1.2 (2.1) years for NOAC users, and 1.1 (3.0) years for warfarin users.

Risk of liver injury

Characteristics of patients with liver injury

In the overall cohort, a total of 513 (2.8%) patients experienced liver injury during follow-up (Table 2). None received a liver transplant within 90 days after the outcome date. The proportion of patients who underwent diagnostic imaging of the liver were diagnosed with acute liver failure, died from any cause, or died from liver failure was consistently greater in NOAC users compared to warfarin users. Similarly, NOAC users on average had greater elevations in serum ALT, ALP, and total bilirubin. For warfarin and NOAC users, most cases of liver injury occurred within 2 years of initiating treatment. Nearly two-thirds of patients had a cholestatic pattern of liver injury as indicated by ALT/ALP ratio ≤2. Characteristics of patients with liver injury and a diagnosis of acute liver failure are shown in Appendix Table 6.

Primary analysis

In the matched cohort, 373 of 13,698 patients (2.7%) developed liver injury: 141 NOAC users (2.1%), of which 72 were dabigatran users (2.0%); 40 were rivaroxaban users (2.0%); 29 were apixaban users (2.5%); and 232 warfarin users (3.4%). The use of NOACs was significantly associated with a lower risk of liver injury compared with the use of warfarin. The adjusted HR was 0.71 (95% CI: 0.58-0.89) (Table 3). When comparing individual NOAC agents to warfarin, dabigatran was associated with a lower risk of liver injury (HR: 0.63; 95% CI: 0.48-0.82). However, there was no statistically significant association between liver injury and use of rivaroxaban (HR: 0.72; 95% CI: 0.51-1.01) or use of apixaban (HR: 1.13; 95% CI: 0.77-1.68). Kaplan-Meier curves for liver injury are presented in Appendix Figure 2 in the supplement.

Subgroup analyses

When stratified by sex, a similar association between liver injury and use of NOACs compared with use of warfarin was only found to be statistically significant in men (NOACs vs warfarin: HR: 0.69; 95% CI: 0.52-0.92; dabigatran vs warfarin: HR: 0.57; 95% CI: 0.40-0.83) (Table 4). In contrast, no statistically significant associations were found in women. For subgroup analyses of different age groups, NOACs (HR: 0.38; 95% CI: 0.22-0.69) as well as dabigatran (HR: 0.17; 95% CI: 0.06-0.47) were significantly associated with lower risk of liver injury for patients aged <65 years and in patients aged ≥75 years (NOACs vs warfarin: HR: 0.73; 95% CI: 0.56-0.96; dabigatran vs warfarin: HR: 0.67; 95% CI: 0.48-0.95). The association was not observed among patients in the 65-74 age group.

Sensitivity analyses

The results of all sensitivity analyses were generally consistent with the primary analysis (Figure 2; Appendix Tables 7-14 in the supplement). Compared with warfarin, NOACs and dabigatran

were all statistically significantly associated with lower risk of liver injury, except in the sensitivity analyses where the upper limits of normal for serum ALT and bilirubin were increased (HR: 0.81; 95% CI: 0.61-1.06), and ICD-9-CM codes used to identify liver injury (HR: 0.82; 95% CI: 0.63-1.07) and acute liver failure (HR: 1.41; 95% CI: 0.58-3.38). Rivaroxaban showed a statistically significant association with lower risk of liver injury compared with warfarin in the sensitivity analyses which used a 5-day (HR: 0.60; 95% CI: 0.40-0.89) and 15-day gap (HR: 0.61; 95% CI: 0.42-0.89) as discontinuation, and which used partial covariate adjustment (HR: 0.75; 95% CI: 0.57-1.00) and IPTW with 1% truncation (HR: 0.76; 95% CI: 0.58-1.00).

DISCUSSION

In this population-based study, we investigated the risk of liver injury associated with the use of NOACs compared with warfarin in patients with AF, and found that NOACs were associated with a lower risk of liver injury. This decreased risk of liver injury relative to warfarin remained whether NOACs were evaluated as a class or by individual agent, with dabigatran associated with the lowest risk of liver injury among the three NOAC agents examined. Several sensitivity analyses, with the exception of acute liver failure, were consistent with the primary analysis.

Clinical outcomes and onset of liver injury

Despite being associated with a lower risk of liver injury, our results suggest that if a patient experiences liver injury while using oral anticoagulants, the clinical outcomes may be more severe with NOACs. Average serum concentrations of ALT, ALP, and total bilirubin appeared to be higher for NOAC users than warfarin users. While no significant difference between groups was observed for the outcome of acute liver failure, the point estimate suggested potential harm from NOAC use. Extreme elevations in ALT and an R ≥5 indicate a predominantly hepatocellular pattern of liver injury in patients also diagnosed with acute liver failure. Thus, it appears that NOAC use is associated with a lower overall risk of liver injury but may result in more severe presentation if liver injury does occur.

A systematic review and meta-analysis of 29 NOAC RCTs did not identify an increased risk of liver injury for NOACs versus control(9). However, the maximum duration of follow-up for the included RCTs was 2 years, and our findings suggest that the time to onset among patients who developed liver injury was ≥ 2 years in 35% of warfarin and 25% of NOAC users. The risk of liver injury (as per our study definition) in NOAC RCTs ranged from 0.1% to 0.5%(20, 28, 29),

which is much lower compared to our estimates of 2.0%-2.5% (Appendix Table 15-16 in the supplement). Increasing the thresholds for ALT and bilirubin in a sensitivity analysis still suggests a higher risk in clinical use versus RCTs (1.1%-1.9%). In contrast to RCTs, a longer duration of follow-up and inclusion of patients with a history of liver disease and gallbladder disease may account for our findings. Therefore, hepatic function should continue to be monitored in patients taking oral anticoagulants for the management of atrial fibrillation.

Comparison to previous observational studies

Recently, two observational studies(10, 11) investigated the association between liver injury and use of NOACs. Alonso *et al.*[10] found that NOACs were associated with lower risk of liver injury hospitalization compared with warfarin. However, this conclusion might be biased by the investigators' use of the ITT approach, which could not eliminate the effect of differential misclassification of exposure(30). On the other hand, while Douros *et al.*[11] improved their study design by considering switching/discontinuation therapy, and found no association between use of NOACs and increased risk of liver injury compared to warfarin, the estimates had reduced precision likely due to very few identified events. Notably, neither of the two studies used liver function tests (LFTs) to identify liver injury.

Consistent with the findings by Alonso *et al.*(10), dabigatran was associated with a lower risk of liver injury. However, in our study, neither the lower risk observed with rivaroxaban or the higher risk observed with apixaban was statistically significant. Ximelagatran induced hepatotoxicity was identified in long-term (up to 6 months) post-marketing surveillance studies(31-33). Ongoing surveillance with long-term follow-up will be important particularly for further assessment of the potential risk associated with apixaban as the number of exposed individuals in this study was small and the point estimate favored warfarin.

Effects of sex and age

A significant association between use of NOACs and lower risk of liver injury was only found in men. Generally, women are more likely to present with drug-induced hepatotoxicity than men(34, 35). In females, a relatively smaller plasma volume, higher proportion of body fat, lower basal metabolic rate and lower renal blood flow, may cause drugs to more readily accumulate leading to potential liver injury(36). A pharmacokinetic study showed that both the maximum serum concentration and the area under the curve of dabigatran and apixaban are higher in women than men(37). Further studies are warranted considering the marginal 95% CI for women from our results.

The strongest association of NOACs, especially dabigatran, on risk reduction of liver injury compared to warfarin was seen in patients <65 years. This suggests that younger patients may obtain more clinical hepatic safety benefit than older patients. Aging reduces the ability to maintain homeostasis due to structural alteration or dysfunction, and is noted to be a major risk factor for liver diseases and injury(38). In Spain, 45% of cases of drug-induced liver injury reported from 1994-2004 occurred in patients aged >60 years(39). Increased body fat paired with decreased basal metabolic rate and renal blood flow could change the distribution and clearance of drugs in older individuals, increasing their vulnerability to hepatotoxicity. In dabigatran users ≥65 years, the area under the curve is 1.7-2.0 fold higher than that in younger subjects(37, 40). This may explain the increasing trends in liver injury in NOAC users, especially in patients taking dabigatran and rivaroxaban. The nonsignificant finding observed in the 65-75 age group may be attributed to a drop in the incidence rate of warfarin users.

Possible biological basis for study findings

Different pharmacokinetic profiles of oral anticoagulants may help explain differences in hepatic safety profiles(37). High-energy reactions involving cytochrome-P450 enzymes causing decline of adenosine triphosphate levels, loss of ionic gradients, cell swelling, and rupture could be one reason(17). Compared to warfarin, which is almost 100% hepatically eliminated(29), dabigatran is not a substrate, inhibitor, nor an inducer of cytochrome-P450(37), and is hydrolyzed from dabigatran etexilate into active form by an esterase(41). Only 20% of dabigatran is eliminated by the liver(29). In addition, the hydrolyzed form of dabigatran is not a substrate of P-glycoprotein(37), which plays an important role in removing foreign substances from cells(42). Although, rivaroxaban does not induce or inhibit P-glycoprotein(37, 43), it is metabolized by cytochrome-P450 and approximately 65% is eliminated by the liver(29, 37). This may relate to the observation that the reduction on risk of liver injury is less pronounced than that of dabigatran. In contrast, apixaban potentially poses the highest burden on the liver, as 75% of the drug is metabolized in the liver via cytochrome-P450 which is also a substrate for P-glycoprotein(29, 37).

Strengths and limitations

Our study design has a number of strengths. To our knowledge, this is the first study to adopt a laboratory test outcome as an objective measure for the definition of liver injury. We further used ICD-9-CM codes to define outcome events and to confirm the robustness of our results. Importantly, we accounted for therapy switching between warfarin and NOACs, drug discontinuation to avoid misclassification of exposures. The profile of drug hepatotoxicity is considerably different between western and Asian population(44) and as data on Asian cohorts

are limited, this study provides a unique insight into the liver safety of NOACs and may enable comparisons between ethnicities.

Considering the observational nature of this study, we cannot rule out the possibility of residual confounding. It is possible that awareness of the potential risk of liver injury with NOACs may have resulted in channeling bias, with patients at risk of potential liver injury being preferentially prescribed warfarin, particularly in patients with a history of chronic liver disease. However, both NOACs and warfarin are not recommended for patients with severe hepatic impairment in Hong Kong according to the pharmaceutical product regulator(45). To reduce the potential for bias, we excluded patients with any ICD-9-CM codes or laboratory values indicative of liver injury before the index date, and also used propensity score matching on 40 covariates with good balance in our matched cohort. The sample size for apixaban users is likely too small to draw a conclusion about risk of liver injury. Another potential limitation is that although 99.9% of patients in this study had LFTs during the study period, approximately 15% did not have a LFT at baseline. To test the impact of missing values on results, we removed those without baseline LFTs in one of the sensitivity analyses. The results were still consistent with our primary analysis.

In conclusion, among patients with atrial fibrillation, NOACs as a group, as well as dabigatran alone, were associated with a significantly lower risk of laboratory-based liver injury when compared to warfarin. However, the risk of liver injury appears to be higher than that observed in landmark clinical trials of NOACs, and patients using NOACs who experience liver injury may have more severe clinical outcomes.

Study Highlights

WHAT IS KNOWN

- Two cohort studies have investigated the association of NOACs and liver injury using claims databases in the United States and Canada.
- The association between NOACs and liver injury was inconsistent and the outcomes did not include liver function laboratory tests.
- Inclusion of Asian patients is limited in both randomized controlled trials (RCTs) and cohort studies.

WHAT IS NEW HERE

- This is the first population-based cohort study that used liver function tests to assess the association between NOACs and the risk of liver injury in an Asian population.
- NOACs were associated with improved hepatic safety compared to warfarin among adults with atrial fibrillation.
- Liver injury appears to be more frequent in clinical practice than in NOAC RCTs.

REFERENCES

1. Liakoni E, Ratz Bravo AE, Krahenbuhl S. Hepatotoxicity of new oral anticoagulants (NOACs). Drug Saf 2015;38:711-720.

2. Rochwerg B, Xenodemetropoulos T, Crowther M, Spyropoulos A. Dabigatran-induced acute hepatitis. Clin Appl Thromb Hemost 2012;18:549-550.

3. Clarke SA, Alsaad AA, Mack A, Phillips MB. Apixaban-induced liver injury. BMJ Case Rep 2016;2016.

4. Liakoni E, Ratz Bravo AE, Terracciano L, Heim M, Krahenbuhl S. Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban. JAMA Intern Med 2014;174:1683-1686.

5. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. Handb Exp Pharmacol 2010:407-418.

6. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013;15:625-651.

7. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330-1393.

8. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, 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;74:104-132.

9. Caldeira D, Barra M, Santos AT, de Abreu D, Pinto FJ, Ferreira JJ, Costa J. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart 2014;100:550-556.

10. Alonso A, MacLehose RF, Chen LY, Bengtson LG, Chamberlain AM, Norby FL, Lutsey PL. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. Heart 2017;103:834-839.

11. Douros A, Azoulay L, Yin H, Suissa S, Renoux C. Non-vitamin K antagonist oral anticoagulants and risk of serious liver injury. J Am Coll Cardiol 2018;71:1105-1113.

12. Forns J, Cainzos-Achirica M, Hellfritzsch M, Morros R, Poblador-Plou B, Hallas J, Giner-Soriano M, et al. Validity of ICD-9 and ICD-10 codes used to identify acute liver injury: a study in three European data sources. Pharmacoepidemiol Drug Saf 2019;28:965-975.

13. Lau WC, Chan EW, Cheung CL, Sing CW, Man KK, Lip GY, Siu CW, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. JAMA 2017;317:1151-1158.

14. Law SWY, Lau WCY, Wong ICK, Lip GYH, Mok MT, Siu CW, Chan EW. Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation. J Am Coll Cardiol 2018;72:271-282.

15. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for helicobacter pylori: a population-based study. Gut 2018;67:28-35.

16. Wong AY, Wong IC, Chui CS, Lee EH, Chang WC, Chen EY, Leung WK, et al. Association between acute neuropsychiatric events and helicobacter pylori therapy containing clarithromycin. JAMA Intern Med 2016;176:828-834.

17. Arora N, Goldhaber SZ. Anticoagulants and transaminase elevation. Circulation 2006;113:e698-702.

18. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol 2017;112:18-35.

19. Food and Drug Administration. Drug induced liver injury: premarketing clinical evaluation; 2009.

20. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151.

21. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, investigators A-. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807-815.

22. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J 2012;76:2104-2111.

23. Jinjuvadia K, Kwan W, Fontana RJ. Searching for a needle in a haystack: use of ICD-9-CM codes in drug-induced liver injury. Am J Gastroenterol 2007;102:2437-2443.

24. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008;135:1924-1934, 1934 e1921-1924.

25. Bjornsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol 2015;89:327-334.

26. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69:345-357.

27. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 1999;319:670-674.

28. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.

29. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. J Am Coll Cardiol 2018;71:2162-2175.

30. Gupta SK. Intention-to-treat concept: a review. Perspect Clin Res 2011;2:109-112.

31. Petersen P, Grind M, Adler J, Investigators SI. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. J Am Coll Cardiol 2003;41:1445-1451.

32. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690-698.

33. Agnelli G, Eriksson BI, Cohen AT, Bergqvist D, Dahl OE, Lassen MR, Mouret P, et al. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. Thromb Res 2009;123:488-497.

34. Guy J, Peters MG. Liver disease in women: the influence of gender on epidemiology, natural history, and patient outcomes. Gastroenterol Hepatol (N Y) 2013;9:633-639.

35. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study G. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065-2076.

36. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009;48:143-157.

37. Gelosa P, Castiglioni L, Tenconi M, Baldessin L, Racagni G, Corsini A, Bellosta S. Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs). Pharmacol Res 2018;135:60-79.

38. Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Curr Opin Gastroenterol 2015;31:184-191.

39. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129:512-521.

40. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost 2009;15 Suppl 1:9S-16S.

41. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos 2008;36:386-399.
42. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003;42:59-98.
43. Gnoth MJ, Buetehorn U, Muenster U, Schwarz T, Sandmann S. In vitro and in vivo P-glycoprotein transport characteristics of rivaroxaban. J Pharmacol Exp Ther 2011;338:372-380.
44. Suk KT, Kim DJ. Drug-induced liver injury: present and future. Clin Mol Hepatol 2012;18:249-257.
45. Drug Office Department of Health The Government of the Hong Kong SAR. Oral anticoagulants and antiplatelet drugs. In; 2014.

Acknowledgment

We thank Dr. Eric Y.F. Wan and Dr. Kenneth K.C. Man, who provided statistical consultation, Ms. Pat Wong, who provided administrative support for this study, and Ms. Lisa Y.L. Lam for proofreading the manuscript.

CONFLICT OF INTEREST

Guarantor of the article: First author Jiaxi Zhao, MSc, and corresponding author Esther W Chan, PhD, take full responsibility for the conduct of the study and have had access to the data and have control of the decision to publish.

Specific author contributions: All authors have contributed to and approved the final version of the manuscript. The respective roles of each author are the following: concept and design by Zhao, Blais, Suh, Wong and Chan; acquisition, analysis, or interpretation of data by all authors; drafting of the manuscript by Zhao, Blais, Suh, Chan; critical revision of the manuscript for important intellectual content by All authors; statistical analysis by Zhao, Blais, Chen.

Financial support: None.

Potential competing interests: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr. Joseph E Blais is supported by the Hong Kong Research Grants Council as a recipient of the Hong Kong PhD Fellowship Scheme. Prof. Ian CK Wong received grants from the Research Grants Council (RGC, Hong Kong), Innovative Medicines Initiative (IMI), Shire, Janssen-Cilag, Eli-Lily, Pfizer, Bayer, European Union FP7 program, outside the submitted work. Ian Wong is a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group, the British Association for

Psychopharmacology ADHD guideline group, and advisor to Shire. Dr. Esther W Chan has received honorarium from the Hospital Authority and research funding from The Hong Kong Research Grants Council, The Research Fund Secretariat of the Food and Health Bureau, Narcotics Division of the Security Bureau of HKSAR, Hong Kong; National Natural Science Fund of China, China; Wellcome Trust, United Kingdom; Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen and Takeda, for work unrelated to this study. No other disclosures were reported.

Figure Legends

Figure 1. Study Flow Chart of NOACs and Warfarin New Users Selection

Abbreviations: AF, atrial fibrillation; CDARS, Clinical Data Analysis and Reporting System (of the Hong Kong Hospital Authority); ICD-9-CM, International Statistical Classification of Diseases, Ninth Revision, Clinical Modification; LFT, liver function test; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulant; PS, propensity score.

Figure 2. Forest Plots with the Primary Analyses and All Sensitivity Analyses

Abbreviations: HR, hazard ratio; ICD-9-CM, International Statistical Classification of Diseases, Ninth Revision, Clinical Modification; IPTW, inverse probability of treatment weighting; LFTs, liver function tests; NOACs, non -vitamin K antagonist oral anticoagulants; ULN, upper limit of normal. Forest plot with HRs for use of NOACs compared with use of warfarin associated with liver injury. Full covariate adjustment indicates that all covariates, which were in propensity score matching, were adjusted for in the Cox regression model. Partial covariate adjustment indicates that only selected covariates (age, sex, Charlson Comorbidity Index, kidney diseases, congestive heart failure, antibacterial agents, proton pump inhibitors, lipid-lowering agents, angiotensin-converting-enzyme inhibitors, diuretics and digoxin) were adjusted for in the Cox regression model. Inverse probability weighting with no truncation indicates that no changed in estimated weights. Inverse probability of treatment weighting with 1% truncation indicates that the individuals with weights below or above the 1st or 99th percentile respectively, were set to the truncation threshold.

Table 1. Baseline Characteristics of Warfarin and NOAC Users Before and After Propensity Score Matching

Baseline characteristic*	Before propensity score matching			After propensity score matching		
	Warfarin (n=8,519)	NOACs (n=9,762)	SMD†	Warfarin (n=6,849)	NOACs (n=6,849)	SMD†
Age, mean (SD), y	72.6 (11.6)	75.1 (10.2)	0.231	73.9 (10.7)	73.9 (10.5)	0.004
Women	3,905 (45.8)	4,937 (50.6)	0.095	3,280 (47.9)	3,322 (48.5)	0.012
Health status score on index date						
CCI, mean (SD)‡	1.7 (1.7)	1.4 (1.5)	0.197	1.5 (1.5)	1.5 (1.5)	0.031
$CHADS_2$, mean (SD)§	2.2 (1.5)	2.2 (1.5)	0.022	2.2 (1.5)	2.2 (1.5)	0.010
CHA_2DS_2-VASc, mean (SD)‖	3.7 (1.9)	3.7 (1.8)	0.024	3.7 (1.9)	3.7 (1.9)	0.013
Laboratory tests ¶ within 90 days prior to index date						
ALT, median (IQR), U/L	21.1 (18.0)	20.0 (15.5)	0.116	21.0 (16.4)	21.0 (16.0)	0.049
AST, median (IQR), U/L	27.5 (19.0)	25.0 (15.1)	0.145	27.0 (17.6)	25.0 (15.0)	0.131
ALP, median (IQR), U/L	75.0 (29.4)	72.8 (28.7)	0.115	74.0 (28.9)	72.7 (28.5)	0.070
Total bilirubin, median (IQR), mg/dL	0.74 (0.50)	0.71 (0.45)	0.085	0.73 (0.47)	0.71 (0.47)	0.013
Comorbidities on or before index date						
Viral hepatitis	163 (1.9)	188 (1.9)	0.001	136 (2.0)	136 (2.0)	0
Non-viral liver diseases	2 (<0.1)	4 (<0.1)	0.010	2 (<0.1)	3 (<0.1)	0.008
Alcoholism	91 (1.1)	92 (0.9)	0.013	67 (1.0)	62 (0.9)	0.008
Gallbladder diseases	208 (2.4)	230 (2.4)	0.006	158 (2.3)	169 (2.5)	0.011
Kidney diseases	1,051 (12.3)	549 (5.6)	0.236	459 (6.7)	513 (7.5)	0.031
Diabetes mellitus	2,064 (24.2)	2,132 (21.8)	0.057	1,540 (22.5)	1,583 (23.1)	0.015
Myocardial infarction	756 (8.9)	610 (6.2)	0.099	485 (7.1)	501 (7.3)	0.009
Congestive heart failure	2,644 (31.0)	2,070 (21.2)	0.225	1,654 (24.1)	1,766 (25.8)	0.038
Hypertension	4,481 (52.6)	5,041 (51.6)	0.019	3,564 (52.0)	3,582 (52.3)	0.005
Anemia	854 (10.0)	743 (7.6)	0.085	562 (8.2)	596 (8.7)	0.018
Coagulopathy	73 (0.9)	74 (0.8)	0.011	50 (0.7)	52 (0.8)	0.003
Gastrointestinal bleeding	727 (8.5)	740 (7.6)	0.035	535 (7.8)	548 (8.0)	0.007
Intracranial bleeding	265 (3.1)	300 (3.1)	0.002	210 (3.1)	210 (3.1)	0
Other bleedings	707 (8.3)	819 (8.4)	0.003	561 (8.2)	575 (8.4)	0.007
Ischemic stroke	2,705 (31.8)	3,204 (32.8)	0.023	2,216 (32.4)	2,184 (31.9)	0.010
Peripheral vascular diseases	247 (2.9)	152 (1.6)	0.091	117 (1.7)	136 (2.0)	0.021
Cancers	1,166 (13.7)	1,512 (15.5)	0.051	993 (14.5)	1,006 (14.7)	0.005
Medications use within 90 days prior to index date						
Antibacterial agents	2,697 (31.7)	2,614 (26.8)	0.107	1,950 (28.5)	2,022 (29.5)	0.023
Antifungal agents	24 (0.3)	23 (0.2)	0.009	15 (0.2)	13 (0.2)	0.006
Acetaminophen	3,179 (37.3)	3,539 (36.3)	0.022	2,487 (36.3)	2,497 (36.5)	0.003
PPIs	2,118 (24.9)	2,865 (29.3)	0.101	1,732 (25.3)	1,748 (25.5)	0.005
H2-receptor antagonists	4,490 (52.7)	5,264 (53.9)	0.024	3,672 (53.6)	3,658 (53.4)	0.004
Medications use within 365 days prior to index date						

Antiplatelet agents	6,597 (77.4)	7,709 (79.0)	0.037	5,313 (77.6)	5,319 (77.7)	0.002
Lipid lowering drugs	4,030 (47.3)	5,549 (56.8)	0.192	3,500 (51.1)	3,492 (51.0)	0.002
Antiarrhythmics	1,645 (19.3)	1,804 (18.5)	0.021	1,247 (18.2)	1,262 (18.4)	0.006
NSAIDs	960 (11.3)	1,061 (10.9)	0.013	775 (11.3)	766 (11.2)	0.004
ACEIs	3,634 (42.7)	3,621 (37.1)	0.114	2,717 (39.7)	2,771 (40.5)	0.016
ARBs	540 (6.3)	862 (8.8)	0.094	471 (6.9)	483 (7.1)	0.007
Beta blockers	4,920 (57.8)	6,053 (62.0)	0.087	4,115 (60.1)	4,068 (59.4)	0.014
CCBs	5,133 (60.3)	6,207 (63.6)	0.069	4,220 (61.6)	4,273 (62.4)	0.016
Diuretics	3,690 (43.3)	3,242 (33.2)	0.209	2,503 (36.5)	2,628 (38.4)	0.038
Digoxin	2,278 (26.7)	2,035 (20.8)	0.139	1,591 (23.2)	1,601 (23.4)	0.003
Nucleoside analogs	45 (0.5)	55 (0.6)	0.005	41 (0.6)	39 (0.6)	0.004
Antituberculosis agents	28 (0.3)	23 (0.2)	0.018	16 (0.2)	17 (0.2)	0.003
Antiepileptics	148 (1.7)	168 (1.7)	0.001	116 (1.7)	112 (1.6)	0.005
Immunosuppressants	37 (0.4)	43 (0.4)	0.001	30 (0.4)	27 (0.4)	0.007

Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; CCBs, calcium channel blockers; CCI, Charlson Comorbidity Index; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SMD, standardized mean difference.

* Values are expressed as frequency (%) unless otherwise specified.

† SMD indicates difference in mean or proportion of covariates in NOAC group vs warfarin group divided by the pooled standard deviation. SMD of less than 0.1 indicates a negligible difference between groups. After matching, only AST showed a slightly higher value of 0.131.

‡ CCI indicates patients with myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, acquired immune deficiency syndrome. The severity of comorbidity was categorized into three grades based on the score: mild with scores of 1-2; moderate with scores of 3-4; severe with scores of 5 or above (higher score indicates a higher risk of mortality).

§ $CHADS_2$ indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or systemic embolism. The score ranges from 0 to 6 (higher score indicates a higher risk of stroke).

‖ CHA_2DS_2-VASc indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, age 65 to 74, prior stroke or transient ischemic attack or systemic embolism, vascular disease, and sex category (women). The score ranges from 0 to 9 (higher score indicates a higher risk of stroke).

¶ There were 13 684 (99.9%) patients who ever had a LFT during the whole study period. A total of 1842 (13.4%) patients did not have any hepatic function laboratory tests within 90 days prior to index date:1849 (13.5%) patients were missing ALT, 10 835 (79.1%) were missing AST, 1855 (13.5%) were missing total bilirubin, and 1852 (13.5%) were missing ALP. SI conversion factors: To convert ALT/AST to µkat/L, multiply values by 0.0167; to convert total bilirubin to µmol/L, multiply values by 17.104.

Table 2. Characteristics of Warfarin and NOAC Users with Liver Injury Before Propensity Score Matching (n=513)

	Warfarin (n=313)	NOACs (n=200)	Dabigatran (n=93)	Rivaroxaban (n=63)	Apixaban (n=44)
Diagnostic imaging*					
Diagnostic imaging of the liver within 90 days after the outcome date	65 (20.8)	49 (24.5)	27 (29.0)	12 (19.0)	10 (22.7)
Acute liver failure, transplant and death					
Acute liver failure diagnosis within 90 days after outcome date	18 (5.8)	14 (7.0)	6 (6.5)	8 (12.7)	0 (0)
Liver transplant within 90 days after the outcome date	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death from any cause within 90 days after the outcome date	102 (32.6)	69 (34.5)	31 (33.3)	26 (41.3)	12 (27.3)
Death from liver causes within 90 days after the outcome date	1 (0.3)	3 (1.5)	2 (2.2)	1 (1.6)	0 (0)
Time from oral anticoagulant initiation to liver injury					
<1 month	37 (11.8)	23 (11.5)	11 (11.8)	7 (11.1)	5 (11.4)
≥1 month to <3 months	33 (10.5)	19 (9.5)	6 (6.5)	9 (14.3)	4 (9.1)
≥3 month to <6 months	33 (10.5)	17 (8.5)	12 (12.9)	1 (1.6)	4 (9.1)
≥6 to <12 months	40 (12.8)	36 (18.0)	13 (14.0)	13 (20.6)	10 (22.7)
≥12 to <24 months	61 (19.5)	56 (28.0)	22 (23.7)	17 (27.0)	17 (38.6)
≥24 months	109 (34.8)	49 (24.5)	29 (31.2)	16 (25.4)	4 (9.1)
Laboratory tests on outcome date					
ALT, median (IQR), U/L	177.3 (247.9)	184.2 (308.5)	210.0 (321.0)	204.0 (482.5)	146.5 (214.0)
≥5 times ULN	182 (58.1)	119 (59.5)	60 (64.5)	37 (58.7)	22 (50.0)
≥10 times ULN	93 (29.7)	75 (37.5)	39 (41.9)	24 (38.1)	12 (27.3)
≥20 times ULN	52 (16.6)	40 (20.0)	18 (19.4)	17 (27.0)	5 (11.4)
ALP, median (IQR), U/L	129.0 (116.0)	139.5 (132.5)	149.0 (176.0)	120 (70)	183.5 (297.5)
≥2 times ULN	82 (26.2)	62 (31.0)	32 (34.4)	9 (14.3)	21 (47.7)
≥4 times ULN	22 (7.0)	24 (12.0)	12 (12.9)	1 (1.6)	11 (25.0)
Total bilirubin, median (IQR), mg/dL	2.91 (1.80)	3.04 (1.85)	3.00 (2.67)	2.69 (1.65)	3.17 (1.46)
≥3 times ULN	146 (46.6)	101 (50.5)	46 (49.5)	27 (42.9)	28 (63.6)
≥5 times ULN	44 (14.1)	46 (23.0)	25 (26.9)	9 (14.3)	12 (27.3)
ALT/ALP ratio (R)					
≤2 (cholestatic)	208 (66.5)	124 (62.0)	58 (62.4)	31 (49.2)	35 (79.5)
>2 to <5 (mixed)	54 (17.3)	39 (19.5)	15 (16.1)	17 (27.0)	7 (15.9)
≥5 (hepatocellular)	51 (16.3)	37 (18.5)	20 (21.5)	15 (23.8)	2 (4.5)
Comorbidities within 30 days prior to outcome date					
Viral hepatitis	7 (2.2)	3 (1.5)	3 (3.2)	0 (0)	0 (0)
Non-viral liver diseases	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alcoholism	2 (0.6)	1 (0.5)	0 (0)	0 (0)	1 (2.3)
Gallbladder diseases	62 (19.8)	44 (22.0)	23 (24.7)	9 (14.3)	12 (27.3)

Myocardial infarction	26 (8.3)	15 (7.5)	8 (8.6)	5 (7.9)	2 (4.5)
Congestive heart failure	118 (37.7)	61 (30.5)	30 (32.3)	20 (31.7)	11 (25.0)
Hypertension	67 (21.4)	48 (24.0)	24 (25.8)	12 (19.0)	12 (27.3)
Shock/hypotension	33 (10.5)	23 (11.5)	15 (16.1)	7 (11.1)	1 (2.3)
Medication use within 30 days prior to outcome date					
Antibacterial agents	158 (50.5)	115 (57.5)	57 (61.3)	33 (52.4)	25 (56.8)
Antifungal agents	3 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
Acetaminophen	156 (49.8)	106 (53.0)	47 (50.5)	33 (52.4)	26 (59.1)
PPIs	168 (53.7)	113 (56.5)	47 (50.5)	34 (54.0)	32 (72.7)
H2-receptor antagonists	133 (42.5)	84 (42.0)	43 (46.2)	27 (42.9)	14 (31.8)
Antiplatelet agents	101 (32.3)	61 (30.5)	28 (30.1)	19 (30.2)	14 (31.8)
Lipid lowering drugs	160 (51.1)	122 (61.0)	45 (48.4)	44 (69.8)	33 (75.0)
Antiarrhythmics	74 (23.6)	47 (23.5)	20 (21.5)	23 (36.5)	4 (9.1)
NSAIDs	5 (1.6)	9 (4.5)	6 (6.5)	1 (1.6)	2 (4.5)
Nucleoside analogs	6 (1.9)	1 (0.5)	1 (1.1)	0 (0)	0 (0)
Antituberculosis agents	4 (1.3)	6 (3.0)	4 (4.3) †	0 (0)	2 (4.5)
Antiepileptics	6 (1.9)	6 (3.0)	2 (2.2)	2 (3.2)	2 (4.5)
Immunosuppressants	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; ULN, upper limit of normal.
Values are expressed as frequency (%) unless otherwise specified.
* See supplementary appendix for ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) procedure codes.
† Liver injury attributed to antituberculosis medications in diagnosis comment for one dabigatran user.

Table 3. Crude and Adjusted Estimates of Liver Injury Before and After Propensity Score Matching

Exposure	Before propensity score matching			After propensity score matching		
	Total No. / No. of events/person-years / Incidence per 1000 person-years (95% CI)	**Crude HR (95% CI)**	***P* value**	**Total No. / No. of events / person-years / Incidence per 1000 person-years (95% CI)**	**Adjusted HR (95% CI)**	***P* value**
Warfarin	8,519 / 313 / 16,369 / 19.1 (17.1 to 21.3)	1.00 (reference)		6,849 / 232 / 13,179 / 17.6 (15.4 to 20.0)	1.00 (reference)	
NOACs	9,762 / 200 / 15,173 / 13.2 (11.4 to 15.1)	0.65 (0.55 to 0.78)	<0.001	6,849 / 141 / 10,727 / 13.1 (11.1 to 15.4)	0.71 (0.58 to 0.89)	0.002
Dabigatran	5,125 / 93 / 8,861 / 10.5 (8.5 to 12.8)	0.53 (0.42 to 0.67)	<0.001	3,663 / 72 / 6,391 / 11.3 (8.9 to 14.1)	0.63 (0.48 to 0.82)	<0.001
Rivaroxaban	2,924 / 63 / 4,312 / 14.6 (11.3 to 18.5)	0.71 (0.54 to 0.94)	0.02	2,016 / 40 / 3,014 / 13.3 (9.6 to 17.8)	0.72 (0.51 to 1.01)	0.05
Apixaban	1,713 / 44 / 2,000 / 22.0 (16.1 to 29.1)	1.04 (0.75 to 1.43)	0.83	1,170 / 29 / 1,321 / 22.0 (14.9 to 30.9)	1.13 (0.77 to 1.68)	0.53

Abbreviations: CI, confidence interval; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulants.

1

Table 4. Estimates of Liver Injury Risk After Propensity Score Matching Stratified by Sex and by Age Group

Stratified by sex						
	Men (n=7,096)			**Women (n=6,602)**		
Exposures	**Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)**	**Adjusted HR (95% CI)**		**Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)**	**Adjusted HR (95% CI)**	***P* value for interaction**
Warfarin	3,569 / 129 / 6,878 / 18.8 (15.7 to 22.2)	1.00 (reference)		3,280 / 103 / 6,302 / 16.3 (13.4 to 19.7)	1.00 (reference)	
NOACs	3,527 / 73 / 5,411 / 13.5 (10.6 to 16.8)	0.69 (0.52 to 0.92)		3,322 / 68 / 5,315 / 12.8 (10.0 to 16.1)	0.75 (0.55 to 1.03)	0.68
Dabigatran	1,893 / 36 / 3,276 / 11.0 (7.8 to 15.0)	0.57 (0.40 to 0.83)		1,770 / 36 / 3,115 / 11.6 (8.2 to 15.8)	0.70 (0.48 to 1.02)	0.48
Rivaroxaban	1,041 / 24 / 1,495 / 16.1 (10.5 to 23.4)	0.81 (0.52 to 1.26)		975 / 16 / 1,519 / 10.5 (6.2 to 16.6)	0.62 (0.36 to 1.05)	0.43
Apixaban	593 / 13 / 640 / 20.3 (11.2 to 33.4)	0.99 (0.56 to 1.77)		577 / 16 / 681 / 23.5 (13.8 to 37.0)	1.30 (0.76 to 2.23)	0.46
Stratified on age group						
	< 65 years (n=2,767)		**65-74 years (n=3,775)**		**≥ 75 years (n=7,156)**	
Exposures	**Total No. / No. of event / person-years / Incidence per 1,000 person-years (95% CI)**	**Adjusted HR (95% CI)**	**Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)**	**Adjusted HR (95% CI)**	**Total No. / No. of event / person-years / Incidence per 1000 person-years (95% CI)**	**Adjusted HR (95% CI)**	***P* value for interaction**
Warfarin	1,451 / 51 / 3,177 / 16.1 (12.0 to 20.9)	1.00 (reference)	1,815 / 47 / 3,792 / 12.4 (9.2 to 16.3)	1.00 (reference)	3,583 / 134 / 6,210 / 21.6 (18.1 to 25.4)	1.00 (reference)	
NOACs	1,316 / 15 / 2,038 / 7.4 (4.2 to 11.7)	0.38 (0.22 to 0.69)	1,960 / 40 / 3,389 / 11.8 (8.5 to 15.8)	1.00 (0.65 to 1.55)	3,573 / 86 / 5,299 / 16.2 (13.0 to 19.9)	0.73 (0.56 to 0.96)	0.21
Dabigatran	751 / 4 / 1,307 / 3.1 (0.9 to 7.1)	0.17 (0.06 to 0.47)	1,097 / 24 / 2,106 / 11.4 (7.4 to 16.6)	0.97 (0.59 to 1.59)	1,815 / 44 / 2,979 / 14.8 (10.8 to 19.6)	0.67 (0.48 to 0.95)	0.07
Rivaroxaban	399 / 5 / 539 / 9.3 (3.3 to 19.9)	0.45 (0.18 to 1.14)	579 / 11 / 931 / 11.8 (6.1 to 20.2)	1.03 (0.52 to 2.01)	1,038 / 24 / 1,544 / 15.5 (10.1 to 22.6)	0.70 (0.45 to 1.08)	0.61
Apixaban	166 / 6 / 191 / 31.3 (12.5 to 63.5)	1.43 (0.61 to 3.35)	284 / 5 / 353 / 14.2 (5.1 to 30.4)	1.18 (0.46 to 3.02)	720 / 18 / 776 / 23.2 (14.1 to 35.6)	1.02 (0.62 to 1.68)	0.34

Abbreviations: CI, confidence interval; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulant.

Figure1

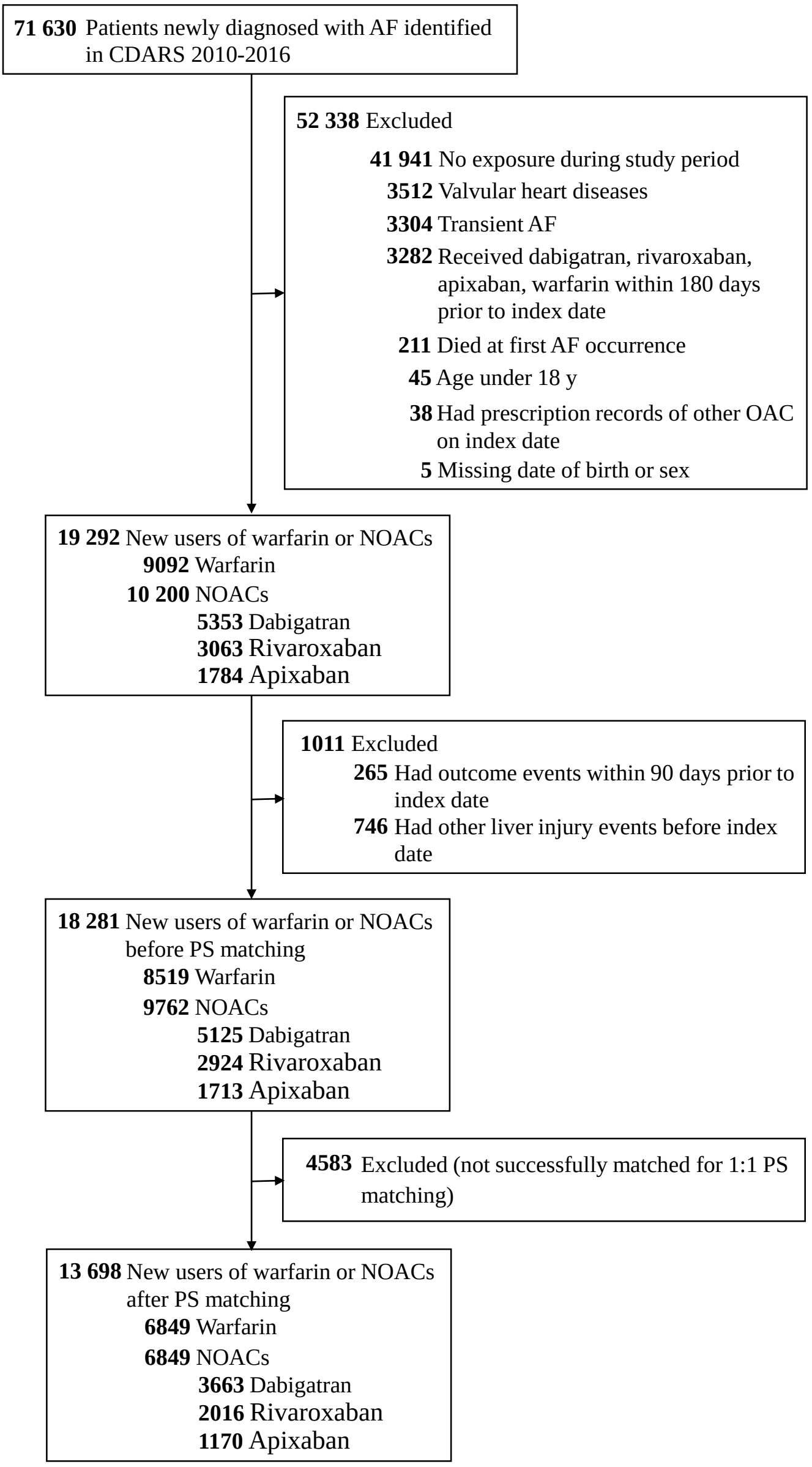
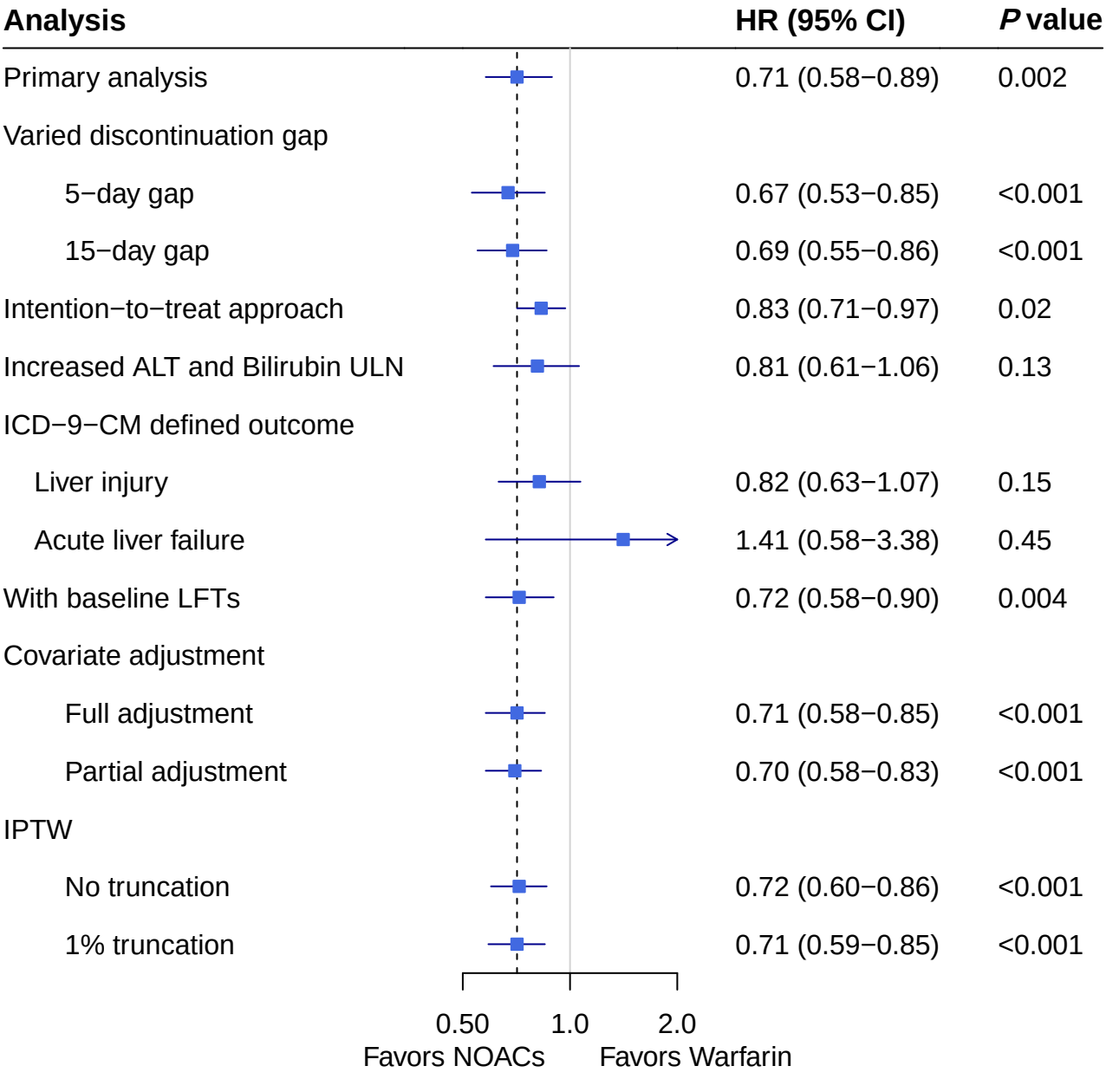

71 630 Patients newly diagnosed with AF identified in CDARS 2010-2016
52 338 Excluded
41 941 No exposure during study period
3512 Valvular heart diseases
3304 Transient AF
3282 Received dabigatran, rivaroxaban, apixaban, warfarin within 180 days prior to index date
211 Died at first AF occurrence
45 Age under 18 y
38 Had prescription records of other OAC on index date
5 Missing date of birth or sex
19 292 New users of warfarin or NOACs
9092 Warfarin
10 200 NOACs
5353 Dabigatran
3063 Rivaroxaban
1784 Apixaban
1011 Excluded
265 Had outcome events within 90 days prior to index date
746 Had other liver injury events before index date
18 281 New users of warfarin or NOACs before PS matching
8519 Warfarin
9762 NOACs
5125 Dabigatran
2924 Rivaroxaban
1713 Apixaban
4583 Excluded (not successfully matched for 1:1 PS matching)
13 698 New users of warfarin or NOACs after PS matching
6849 Warfarin
6849 NOACs
3663 Dabigatran
2016 Rivaroxaban
1170 Apixaban

Figure2


Analysis
HR (95% CI)
P value
Primary analysis
0.71 (0.58−0.89)
0.002
Varied discontinuation gap
5−day gap
0.67 (0.53−0.85)
<0.001
15−day gap
0.69 (0.55−0.86)
<0.001
Intention−to−treat approach
0.83 (0.71−0.97)
0.02
Increased ALT and Bilirubin ULN
0.81 (0.61−1.06)
0.13
ICD−9−CM defined outcome
Liver injury
0.82 (0.63−1.07)
0.15
Acute liver failure
1.41 (0.58−3.38)
0.45
With baseline LFTs
0.72 (0.58−0.90)
0.004
Covariate adjustment
Full adjustment
0.71 (0.58−0.85)
<0.001
Partial adjustment
0.70 (0.58−0.83)
<0.001
IPTW
No truncation
0.72 (0.60−0.86)
<0.001
1% truncation
0.71 (0.59−0.85)
<0.001
0.50
1.0
2.0
Favors NOACs
Favors Warfarin

Supplementary Content

Appendix Figure 1. Distribution of Propensity Score Before and After Matching for NOAC and Warfarin Users

Appendix Figure 2. Kaplan-Meier Curves for Liver Injury after PS Matching for NOAC and Warfarin Users

Appendix Table 1. Upper Limits of Normal for Laboratory Tests Used in the Study

Test*	Sex	Upper Limit of Normal (ULN)
Alanine aminotransferase (ALT)	Female	25 U/L
	Male	33 U/L
Aspartate aminotransferase (AST)	Female	25 U/L
	Male	40 U/L
Total bilirubin	Female	1.0 mg/dL
	Male	1.0 mg/dL
Alkaline phosphatase (ALP)	Female	93 U/L
	Male	110 U/L

* SI conversion factors: To convert ALT, AST, or ALP to µkat/L, multiply values by 0.0167; to convert total bilirubin to µmol/L, multiply values by 17.104.

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study**

ICD-9-CM	Description
Atrial fibrillation	
427.3	Atrial fibrillation and flutter
Valvular atrial fibrillation	
Valvular heart disease	
394.0	Mitral stenosis
Hyperthyroidism	
242	Thyrotoxicosis with or without goitre
Valve replacement (procedure codes)	
35.20	Open and other replacement of unspecified heart valve
35.22	Open and other replacement of aortic valve
35.24	Open and other replacement of mitral valve
35.26	Open and other replacement of pulmonary valve
35.28	Open and other replacement of tricuspid valve
Transient atrial fibrillation	
Cardiac surgery (procedure codes)	
00.5	Other cardiovascular procedures
35	Operations on valves and septa of heart
36	Operations on vessels of heart
37	Other operations on heart and pericardium
Myocarditis	
130.3	Myocarditis due to toxoplasmosis
391.2	Acute rheumatic myocarditis
398.0	Rheumatic myocarditis
422	Acute myocarditis
429.0	Myocarditis, unspecified
032.82	Diphtheritic myocarditis
036.43	Meningococcal myocarditis
074.23	Coxsackie myocarditis
093.82	Syphilitic myocarditis
Pericarditis	
391	Rheumatic fever with heart involvement
393	Chronic rheumatic pericarditis
420	Acute pericarditis
423.2	Constrictive pericarditis
036.41	Meningococcal pericarditis
074.21	Coxsackie pericarditis
093.81	Syphilitic pericarditis
098.83	Gonococcal pericarditis
Pulmonary embolism	
415.1	Pulmonary embolism and infarction

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Charlson Comorbidity Index	
Myocardial infarction	
410	Acute myocardial infarction
412	Old myocardial infarction
Congestive heart failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
425.4	Other primary cardiomyopathies
425.5	Alcoholic cardiomyopathy
425.7	Nutritional and metabolic cardiomyopathy
425.8	Cardiomyopathy in other diseases classified elsewhere
425.9	Secondary cardiomyopathy, unspecified
428	Heart failure
Peripheral vascular disease	
093.0	Aneurysm of aorta, specified as syphilitic
437.3	Cerebral aneurysm, non-ruptured
440	Atherosclerosis
441	Aortic aneurysm and dissection
443.1	Thromboangiitis obliterans [Buerger's disease]
443.2	Other arterial dissection
443.8	Other specified peripheral vascular diseases
443.9	Peripheral vascular disease, unspecified
447.1	Stricture of artery
557.1	Chronic vascular insufficiency of intestine
557.9	Unspecified vascular insufficiency of intestine
V43.4	Blood vessel replaced by other means
Cerebrovascular disease	
362.34	Transient retinal arterial occlusion
430-438	Cerebrovascular disease

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Charlson Comorbidity Index (continued)	
Chronic obstructive pulmonary disease	
416.8	Other chronic pulmonary heart diseases
416.9	Chronic pulmonary heart disease, unspecified
490-496	Chronic Obstructive Pulmonary Disease and Allied Conditions
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to other silica or silicates
503	Pneumoconiosis due to other inorganic dust
504	Pneumonopathy due to inhalation of other dust
505	Pneumoconiosis, unspecified
506.4	Respiratory conditions due to chemical fumes and vapors
508.1	Fibrosis of lungs
508.8	Respiratory conditions due to other specified external agents
Dementia	
290	Dementias
294.1	Dementia in conditions classified elsewhere
331.2	Senile degeneration of brain
Hemiplegia or paraplegia	
334.1	Hereditary spastic paraplegia
342	Hemiplegia and hemiparesis
343	Infantile cerebral palsy
344.0	Quadriplegia and quadraparesis
344.1	Paraplegia
344.2	Diplegia of upper limbs
344.3	Monoplegia of lower limb
344.4	Monoplegia of upper limb
344.5	Unspecified monoplegia
344.6	Cauda equina syndrome
344.9	Paralysis, unspecified
Diabetes without chronic complication	
250.0	Diabetes mellitus without mention of complication
250.1	Diabetes with ketoacidosis
250.2	Diabetes with hyperosmolarity
250.3	Diabetes with other coma
250.8	Diabetes with other specified manifestations
250.9	Diabetes with unspecified complication
Diabetes with chronic complication	
250.4	Diabetes with renal manifestations
250.5	Diabetes with ophthalmic manifestations
250.6	Diabetes with neurological manifestations
250.7	Diabetes with peripheral circulatory disorders

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Charlson Comorbidity Index (continued)	
Renal disease	
403.01	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease
403.11	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease
403.91	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
404.02	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.12	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.92	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
582	Chronic glomerulonephritis
583.0	Nephritis and nephropathy, not specified as acute or chronic, with lesion of proliferative glomerulonephritis
583.1	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
583.2	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
583.6	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal cortical necrosis
583.7	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal medullary necrosis
585	Chronic kidney disease
586	Renal failure, unspecified
588.0	Renal osteodystrophy

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Charlson Comorbidity Index (continued)	
Mild liver disease	
070.22	Chronic viral hepatitis B with hepatic coma without hepatitis delta
070.23	Chronic viral hepatitis B with hepatic coma with hepatitis delta
070.32	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta
070.33	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
070.44	Chronic hepatitis C with hepatic coma
070.54	Chronic hepatitis C without mention of hepatic coma
070.6	Unspecified viral hepatitis with hepatic coma
070.9	Unspecified viral hepatitis without mention of hepatic coma
570	Acute and subacute necrosis of liver
571	Chronic liver disease and cirrhosis
573.3	Hepatitis, unspecified
573.4	Hepatic infarction
573.8	Other specified disorders of liver
573.9	Unspecified disorder of liver
V42.7	Liver replaced by transplant
Moderate-severe liver disease	
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without bleeding
456.2	Esophageal varices in diseases classified elsewhere
572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
Peptic ulcer disease	
531	Gastric ulcer
532	Duodenal ulcer
533	Peptic ulcer site unspecified
534	Gastrojejunal ulcer
Rheumatic disease	
446.5	Giant cell arteritis
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.2	Sicca syndrome
710.3	Dermatomyositis
710.4	Polymyositis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.8	Other specified inflammatory polyarthropathies
725	Polymyalgia rheumatica

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Charlson Comorbidity Index (continued)	
Acquired Immune Deficiency Syndrome	
042	Human immunodeficiency virus [HIV] disease
Malignancy	
140-149	Malignant neoplasm of lip, oral cavity, and pharynx
150-159	Malignant neoplasm of digestive organs and peritoneum
160-165	Malignant neoplasm of respiratory and intrathoracic organs
170-172, 174-176	Malignant neoplasm of bone, connective tissue, and breast
179-189	Malignant neoplasm of genitourinary organs
190-195	Malignant neoplasm of other sites
200-208	Malignant neoplasm of lymphatic and hematopoietic tissue
238.6	Neoplasm of uncertain behavior of plasma cells
Metastatic solid tumor	
196	Secondary and unspecified malignant neoplasm of lymph nodes
197	Secondary malignant neoplasm of respiratory and digestive systems
198	Secondary malignant neoplasm of other specified sites
199	Malignant neoplasm without specification of site

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
$CHADS_2$ / CHA_2DS_2-VASc	
Congestive heart failure (the same as that in Charlson Comorbidity Index)	
Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
Diabetes mellitus	
250	Diabetes mellitus
Ischemic stroke	
433	Occlusion and stenosis of precerebral arteries
434	Occlusion of cerebral arteries
436	Acute, but ill-defined, cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
438	Late effects of cerebrovascular disease
Transient ischemic attack	
435	Transient cerebral ischemia
Vascular disease	
410	Acute myocardial infarction
411	Other acute and subacute forms of ischemic heart disease
412	Old myocardial infarction
413	Angina pectoris
414	Other forms of chronic ischemic heart disease
443.8	Other specified peripheral vascular diseases
443.9	Peripheral vascular disease, unspecified
Thromboembolism	
444	Arterial embolism and thrombosis
445	Atheroembolism

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Other baseline comorbidities	
Viral hepatitis	
070	Viral hepatitis
V02.61	Hepatitis B carrier
V02.62	Hepatitis C carrier
Non-viral liver disease	
456.1	Esophageal varices without mention of bleeding
456.21	Esophageal varices in diseases classified elsewhere, without mention of bleeding
573.4	Hepatic infarction
Alcoholism	
265.2	Pellagra
291.1	Alcohol-induced persisting amnestic disorder
291.2	Alcohol-induced persisting dementia
291.3	Alcohol-induced psychotic disorder with hallucinations
291.5	Alcohol-induced psychotic disorder with delusions
291.8	Other specified alcohol-induced mental disorders
291.9	Unspecified alcohol-induced mental disorders
303.0	Acute alcoholic intoxication
303.9	Other and unspecified alcohol dependence
305.0	Nondependent alcohol abuse
357.5	Alcoholic polyneuropathy
425.5	Alcoholic cardiomyopathy
535.3	Alcoholic gastritis
571.1	Acute alcoholic hepatitis
571.2	Alcoholic cirrhosis of liver
571.3	Alcoholic liver damage, unspecified
980	Toxic effect of alcohol
V11.3	Personal history of neurosis
Transient ischemic attack	
435	Transient cerebral ischemia
Gallbladder disease	
575	Other disorders of gallbladder
576	Other disorders of biliary tract

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Other baseline comorbidities (continued)	
Kidney disease	
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
580	Acute glomerulonephritis
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis and nephropathy not specified as acute or chronic
584	Acute kidney failure
585	Chronic kidney disease
586	Renal failure, unspecified
588	Disorders resulting from impaired renal function
590.0	Chronic pyelonephritis
593.3	Stricture or kinking of ureter
753.1	Cystic kidney disease
V42.0	Kidney replaced by transplant
V45.1	Postsurgical renal dialysis status
V56	Encounter for dialysis and dialysis catheter care
Anemia	
280	Iron deficiency anemias
281	Other deficiency anemias
282	Hereditary hemolytic anemias
283	Acquired hemolytic anemias
284	Aplastic anemia and other bone marrow failure syndromes
285	Other and unspecified anemias
Coagulopathy	
286	Coagulation defects
287.1	Qualitative platelet defects
287.3	Primary thrombocytopenia
287.4	Secondary thrombocytopenia
287.5	Thrombocytopenia, unspecified

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Other baseline comorbidities (continued)	
Gastrointestinal bleeding	
455.2	Internal hemorrhoids with other complication
455.5	External hemorrhoids with other complication
456.0	Esophageal varices with bleeding
456.20	Esophageal varices in diseases classified elsewhere, with bleeding
530.7	Gastroesophageal laceration-hemorrhage syndrome
530.82	Esophageal hemorrhage
531.0	Acute gastric ulcer with hemorrhage
531.2	Acute gastric ulcer with hemorrhage and perforation
531.4	Chronic or unspecified gastric ulcer with hemorrhage
531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
532.0	Acute duodenal ulcer with hemorrhage
532.2	Acute duodenal ulcer with hemorrhage and perforation
532.4	Chronic or unspecified duodenal ulcer with hemorrhage
532.6	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
533.0	Acute peptic ulcer of unspecified site with hemorrhage
533.2	Acute peptic ulcer of unspecified site with hemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
533.6	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
534.0	Acute gastrojejunal ulcer with hemorrhage
534.2	Acute gastrojejunal ulcer with hemorrhage and perforation
534.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
534.6	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation
535.01	Acute gastritis, with hemorrhage
535.11	Atrophic gastritis, with hemorrhage
535.21	Gastric mucosal hypertrophy, with hemorrhage
535.31	Alcoholic gastritis, with hemorrhage
535.41	Other specified gastritis, with hemorrhage
535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage
535.61	Duodenitis, with hemorrhage
562.02	Diverticulosis of small intestine with hemorrhage
562.03	Diverticulitis of small intestine with hemorrhage
562.12	Diverticulosis of colon with hemorrhage
562.13	Diverticulitis of colon with hemorrhage
568.81	Hemoperitoneum (nontraumatic)
569.3	Hemorrhage of rectum and anus
569.85	Angiodysplasia of intestine with hemorrhage
569.86	Dieulafoy lesion (hemorrhagic) of intestine
578	Gastrointestinal hemorrhage
579.1	Tropical sprue

Appendix Table 2. ***International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*** **Codes Used in the Study (continued)**

ICD-9-CM	Description
Other baseline comorbidities (continued)	
Intracranial bleeding	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
852	Subarachnoid subdural and extradural hemorrhage following injury
Other bleeding	
423.0	Hemopericardium
459.0	Hemorrhage, unspecified
593.81	Vascular disorders of kidney
599.7	Hematuria
623.8	Other specified noninflammatory disorders of vagina
626.2	Excessive or frequent menstruation
626.6	Metrorrhagia
719.1	Hemarthrosis
784.7	Epistaxis
784.8	Hemorrhage from throat
786.3	Hemoptysis
Liver injury (for baseline exclusion and sensitivity analysis)	
277.4	Disorders of bilirubin excretion
570	Acute and subacute necrosis of liver
571.4	Chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
571.9	Unspecified chronic liver disease without mention of alcohol
572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
573.3	Hepatitis, unspecified
573.8	Other specified disorders of liver
573.9	Unspecified disorder of liver
576.8	Other specified disorders of biliary tract
782.4	Jaundice, unspecified, not of newborn
V42.7	Liver replaced by transplant
50.59	Liver transplant, not elsewhere classified
Descriptive variables of patients with liver injury (in addition to previously listed comorbidities)	
Diagnostic imaging of liver	
88.01	C.A.T. scan of abdomen
88.74	Dx ultrasound-digestive
88.76	Dx ultrasound-abdomen
88.97	MRI - abdomen
Acute liver failure	
570	Acute and subacute necrosis of liver
Liver transplant	
V42.7	Liver replaced by transplant
50.59	Liver transplant, not elsewhere classified
Death from liver failure (ICD-10)	
K71	Toxic liver disease

K72	Hepatic failure, not elsewhere classified
Shock and hypotension	
458	Hypotension
785.5	Shock without mention of trauma

Appendix Table 3. Drugs for Propensity Score Matching Used in the Study

Drug category	Drug name
Short term use	
Antibacterial agents	Amoxicillin, Azithromycin, Clarithromycin, Cloxacillin, Dapsone, Doxycycline, Erythromycin, Minocycline, Nitrofurantoin, Trimethoprim
Antifungal agents	Fluconazole, Itraconazole, Ketoconazole
H2-receptor antagonist	Cimetidine, Nizatidine, Ranitidine
Acetaminophen	Acetaminophen
Proton pump inhibitors (PPIs)	Dexlansoprazole, Esomeprazole, Omeprazole, Pantoprazole, Rabeprazole
Long term use	
Antiarrhythmics	Amiodarone, Disopyramide, Dofetilide, Dronedarone, Flecainide, Propafenone, Rythmodan, Sotalol
Antiepileptics	Carbamazepine, Phenytoin, Valproate
Antihypertension agents	
Angiotensin-converting enzyme inhibitors (ACEI)	Benazepril, Captopril, Cilazapril, Enalapril, Fosinopril, Imidapril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril
Angiotensin II Receptor Blockers (ARBs)	Azilsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan
Beta blockers	Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carvedilol, Celiprolol, Labetalol, Metoprolol, Nadolol, Nebivolol, Oxprenolol, Pindolol, Propranolol, Sotalol
Calcium channel blockers (CCBs)	Amlodipine, Diltiazem, Felodipine, Lacidipine, Lercanidipine, Nicardipine, Nifedipine, Nimodipine, Verapamil
Diuretics	Amiloride, Bumetanide, Chlorthalidone, Eplerenone, Furosemide, Hydrochlorothiazide, Indapamide, Metolazone, Spironolactone, Torsemide, Triamterene
Antiplatelet agents	Abciximab, Aspirin, Clopidogrel, Dipyridamole, Eptifibatide, Prasugrel, Ticagrelor, Ticlopidine, Tirofiban
Antituberculosis agents	Ethambutol, Isoniazid, Pyrazinamide, Rifampicin, Rifabutin
Digoxin	Digoxin
Immunosuppressants	Azathioprine, Cyclosporine, Methotrexate

Appendix Table 3. Drugs for Propensity Score Matching Used in the Study (continued)

Drug category	Drug name
Long term use (continued)	
Lipid lowering drugs	Atorvastatin, Benfluorex, Ezetimibe, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Celecoxib, Diclofenac, Etodolac, Etoricoxib, Ibuprofen, Indomethacin, Meloxicam, Nabumetone, Sulindac
Nucleoside analogs	Abacavir, Adefovir, Entecavir, Lamivudine, Telbivudine, Tenofovir, Zidovudine

Appendix Table 4. Sex Specified Comparison of Warfarin and NOAC Users Baseline Characteristics Before and After Propensity Score Matching

	Men (n=7,096)			Women (n=6,602)		
Baseline Characteristics*	**Warfarin (n=3,569)**	**NOACs (n=3,527)**	**SMD†**	**Warfarin (n=3,280)**	**NOACs (n=3,322)**	**SMD†**
Age, mean (SD), y	72.1 (10.6)	71.8 (10.8)	0.026	76.0 (10.4)	76.1 (9.7)	0.017
Women	N/A	N/A	N/A	N/A	N/A	N/A
Health status score on index date						
CCI, mean (SD)‡	1.5 (1.5)	1.5 (1.5)	0.024	1.5 (1.5)	1.6 (1.5)	0.038
$CHADS_2$, mean (SD)§	2.0 (1.4)	2.0 (1.4)	0.013	2.3 (1.5)	2.3 (1.5)	0.031
CHA_2DS_2-VASc, mean (SD)‖	3.0 (1.7)	3.0 (1.7)	0.015	4.4 (1.8)	4.4 (1.8)	0.035
Laboratory tests¶ within 90 days prior to index date						
ALT, median (IQR), U/L	22.0 (16.5)	22.3 (17.0)	0.004	20.0 (17.0)	19.1 (15.7)	0.089
AST, median (IQR), U/L	27.0 (16.0)	25.5 (14.1)	0.070	28.0 (20.9)	25.0 (16.9)	0.180
ALP, median (IQR), U/L	72.0 (28.5)	70.0 (26.2)	0.085	76.7 (28.5)	75.7 (29.0)	0.057
Total bilirubin, median (IQR), mg/dL	0.78 (0.52)	0.78 (0.50)	0.008	0.68 (0.43)	0.65 (0.43)	0.017
Comorbidities on or before index date						
Viral hepatitis	90 (2.5)	76 (2.2)	0.024	46 (1.4)	60 (1.8)	0.032
Non-viral liver diseases	0 (0)	1 (<0.1)	0.024	2 (<0.1)	2 (<0.1)	0
Alcoholism	61 (1.7)	59 (1.7)	0.003	6 (0.2)	3 (0.1)	0.025
Gallbladder diseases	77 (2.2)	90 (2.6)	0.026	81 (2.5)	79 (2.4)	0.006
Kidney diseases	249 (7.0)	281 (8.0)	0.038	210 (6.4)	232 (7.0)	0.023
Diabetes mellitus	775 (21.7)	771 (21.9)	0.004	765 (23.3)	812 (24.4)	0.026
Myocardial infarction	276 (7.7)	274 (7.8)	0.001	209 (6.4)	227 (6.8)	0.019
Congestive heart failure	813 (22.8)	848 (24.0)	0.030	841 (25.6)	918 (27.6)	0.045
Hypertension	1744 (48.9)	1713 (48.6)	0.006	1820 (55.5)	1869 (56.3)	0.016
Anemia	239 (6.7)	250 (7.1)	0.015	323 (9.8)	346 (10.4)	0.019
Coagulopathy	31 (0.9)	30 (0.9)	0.002	19 (0.6)	22 (0.7)	0.011
Gastrointestinal bleeding	270 (7.6)	304 (8.6)	0.039	265 (8.1)	244 (7.3)	0.028
Intracranial bleeding	121 (3.4)	115 (3.3)	0.007	89 (2.7)	95 (2.9)	0.009
Other bleedings	321 (9.0)	321 (9.1)	0.004	240 (7.3)	254 (7.6)	0.013
Ischemic stroke	1151 (32.2)	1096 (31.1)	0.025	1065 (32.5)	1088 (32.8)	0.006
Peripheral vascular diseases	66 (1.8)	76 (2.2)	0.022	51 (1.6)	60 (1.8)	0.020
Cancers	476 (13.3)	470 (13.3)	0	517 (15.8)	536 (16.1)	0.010

Appendix Table 4. Sex Specified Comparison of Warfarin and NOAC Users Baseline Characteristics Before and After Propensity Score Matching (continued)

	Men (n=7,096)			Women (n=6,602)		
Baseline Characteristics*	**Warfarin (n=3,569)**	**NOACs (n=3,527)**	**SMD†**	**Warfarin (n=3,280)**	**NOACs (n=3,322)**	**SMD†**
Medications use within 90 days prior to index date						
Antibacterial agents	947 (26.5)	990 (28.1)	0.034	1003 (30.6)	1032 (31.1)	0.011
Antifungal agents	9 (0.3)	9 (0.3)	0.001	6 (0.2)	4 (0.1)	0.016
Acetaminophen	1132 (31.7)	1124 (31.9)	0.003	1355 (41.3)	1373 (41.3)	0
PPIs	875 (24.5)	910 (25.8)	0.030	857 (26.1)	838 (25.2)	0.021
H2-receptor antagonists	1845 (51.7)	1800 (51.0)	0.013	1827 (55.7)	1858 (55.9)	0.005
Medications use within 365 days prior to index date						
Antiplatelet agents	2788 (78.1)	2741 (77.7)	0.010	2525 (77.0)	2578 (77.6)	0.015
Lipid lowering drugs	1872 (52.5)	1843 (52.3)	0.004	1628 (49.6)	1649 (49.6)	0
Antiarrhythmics	574 (16.1)	615 (17.4)	0.036	673 (20.5)	647 (19.5)	0.026
ACEIs	1483 (41.6)	1513 (42.9)	0.027	1234 (37.6)	1258 (37.9)	0.005
NSAIDs	401 (11.2)	384 (10.9)	0.011	374 (11.4)	382 (11.5)	0.003
ARBs	198 (5.5)	198 (5.6)	0.003	273 (8.3)	285 (8.6)	0.009
Beta blockers	2074 (58.1)	1974 (56.0)	0.043	2041 (62.2)	2094 (63.0)	0.017
CCBs	2095 (58.7)	2066 (58.6)	0.003	2125 (64.8)	2207 (66.4)	0.035
Diuretics	1177 (33.0)	1211 (34.3)	0.029	1326 (40.4)	1417 (42.7)	0.045
Digoxin	686 (19.5)	712 (20.2)	0.017	895 (27.3)	889 (26.8)	0.012
Nucleoside analogs	31 (0.9)	24 (0.7)	0.021	10 (0.3)	15 (0.5)	0.024
Antituberculosis agents	13 (0.4)	15 (0.4)	0.010	3 (<0.1)	2 (<0.1)	0.011
Antiepileptics	55 (1.5)	64 (1.8)	0.021	61 (1.9)	48 (1.4)	0.033
Immunosuppressants	8 (0.2)	8 (0.2)	0.001	22 (0.7)	19 (0.6)	0.013

Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; CCBs, calcium channel blockers; CCI, Charlson Comorbidity Index; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SMD, standardized mean difference.

* Values are expressed as frequency (%) unless otherwise specified.

† SMD indicates difference in mean or proportion of covariates in NOAC group vs warfarin group divided by the pooled standard deviation. SMD of less than 0.1 indicates a negligible difference between groups.

‡ CCI indicates patients with myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, acquired immune deficiency syndrome. The severity of comorbidity was categorized into three grades based on the score: mild with scores of 1-2; moderate with scores of 3-4; severe with scores of 5 or above (higher score indicates a higher risk of mortality).

§ CHADS2 indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or systemic embolism. The score ranges from 0 to 6 (higher score indicates a higher risk of stroke)

‖ CHA2DS2-VASc indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, age 65 to 74, prior stroke or transient ischemic attack or systemic embolism, vascular disease, and sex category (women). The score ranges from 0 to 9 (higher score indicates a higher risk of stroke)

¶ There were 13 684 (99.9%) patients who ever had a LFT during the whole study period. A total of 1842 (13.4%) patients did not have any hepatic function laboratory tests within 90 days prior to index date:1849 (13.5%) patients were missing ALT, 10 835 (79.1%) were missing AST, 1855 (13.5%) were missing total bilirubin, and 1852 (13.5%) were missing ALP. SI conversion factors: To convert ALT/AST to µkat/L, multiply values by 0.0167; to convert total bilirubin to µmol/L, multiply values by 17.104.

Appendix Table 5. Age Group Specified Comparison of Warfarin and NOAC Users Baseline Characteristics Before and After Propensity Score Matching

	<65 years (n=2,767)			65-74 years (n=3,775)			≥75 years (n=7,156)		
Baseline Characteristics*	**Warfarin (n=1,451)**	**NOACs (n=1,316)**	**SMD†**	**Warfarin (n=1,815)**	**NOACs (n=1,960)**	**SMD†**	**Warfarin (n=3,583)**	**NOACs (n=3,573)**	**SMD†**
Age, mean (SD), y	58.1 (6.0)	57.6 (6.3)	0.087	70.3 (2.9)	70.0 (3.0)	0.078	82.2 (4.9)	82.0 (4.6)	0.037
Women	524 (36.1)	432 (32.8)	0.069	762 (42.0)	863 (44.0)	0.041	1994 (55.7)	2027 (56.7)	0.022
Health status score on index date									
CCI, mean(SD)‡	1.1 (0.4)	1.1 (0.4)	0.001	1.4 (0.4)	1.4 (0.4)	0.022	1.7 (0.5)	1.8 (0.5)	0.041
$CHADS_2$, mean (SD)§	1.3 (0.4)	1.3 (0.4)	0.027	1.5 (0.4)	1.5 (0.4)	0.004	2.8 (0.5)	2.8 (0.5)	0.010
CHA_2DS_2-VASc, mean (SD)‖	1.8 (0.4)	1.8 (0.4)	0.001	3.2 (0.4)	3.1 (0.5)	0.004	4.7 (0.5)	4.7 (0.5)	0.004
Laboratory tests¶ within 90 days prior to index date									
ALT, median (IQR), U/L	26.5 (20.7)	26.4 (21.0)	0.058	21.0 (16.5)	21.5 (15.1)	0.035	19.0 (15.0)	19.0 (14.6)	0.047
AST, median (IQR), U/L	29.1 (21.4)	26.0 (16.0)	0.175	26.0 (16.7)	25.9 (16.0)	0.053	27.0 (17.6)	25.0 (14.9)	0.144
ALP, median (IQR), U/L	72.1 (29.9)	71.5 (29.0)	0.070	74.1 (28.5)	72.0 (27.5)	0.132	75.0 (29.0)	73.6 (28.5)	0.039
Total bilirubin, median (IQR), mg/dL	0.78 (0.52)	0.71 (0.49)	0.114	0.70 (0.47)	0.71 (0.47)	0.055	0.72 (0.46)	0.72 (0.45)	0.002

Appendix Table 5. Age Group Specified Comparison of Warfarin and NOAC Users Baseline Characteristics Before and After Propensity Score Matching (continued)

	<65 years (n=2,767)			65-74 years (n=3,775)			≥75 years (n=7,156)		
Baseline Characteristics*	**Warfarin (n=1,451)**	**NOACs (n=1,316)**	**SMD†**	**Warfarin (n=1,815)**	**NOACs (n=1,960)**	**SMD†**	**Warfarin (n=3,583)**	**NOACs (n=3,573)**	**SMD†**
Comorbidities on or before index date									
Viral hepatitis	60 (4.1)	39 (3.0)	0.063	38 (2.1)	55 (2.8)	0.046	38 (1.1)	42 (1.2)	0.011
Non-viral liver diseases	0 (0)	0 (0)	N/A	1 (<0.1)	2 (0.1)	0.017	1 (<0.1)	1 (<0.1)	0
Alcoholism	28 (1.9)	19 (1.4)	0.038	24 (1.3)	24 (1.2)	0.009	15 (0.4)	19 (0.5)	0.016
Gallbladder diseases	16 (1.1)	15 (1.1)	0.004	37 (2.0)	34 (1.7)	0.022	105 (2.9)	120 (3.4)	0.025
Kidney diseases	51 (3.5)	64 (4.9)	0.067	106 (5.8)	121 (6.2)	0.014	302 (8.4)	328 (9.2)	0.027
Diabetes mellitus	281 (19.4)	254 (19.3)	0.002	438 (24.1)	456 (23.3)	0.020	821 (22.9)	873 (24.4)	0.036
Myocardial infarction	57 (3.9)	67 (5.1)	0.056	94 (5.2)	115 (5.9)	0.030	334 (9.3)	319 (8.9)	0.014
Congestive heart failure	326 (22.5)	282 (21.4)	0.025	331 (18.2)	347 (17.7)	0.014	997 (27.8)	1137 (31.8)	0.087
Hypertension	526 (36.3)	493 (37.5)	0.025	889 (49.0)	948 (48.4)	0.012	2149 (60.0)	2141 (60.0)	0.001
Anemia	73 (5.0)	62 (4.7)	0.015	100 (5.5)	127 (6.5)	0.041	389 (10.9)	407 (11.4)	0.017
Coagulopathy	6 (0.4)	2 (0.2)	0.049	12 (0.7)	10 (0.5)	0.020	32 (0.9)	40 (1.1)	0.023
Gastrointestinal bleeding	59 (4.1)	46 (3.5)	0.030	108 (6.0)	135 (6.9)	0.038	368 (10.3)	367 (10.3)	0
Intracranial bleeding	48 (3.3)	35 (2.7)	0.038	53 (2.9)	68 (3.5)	0.031	109 (3.0)	107 (3.0)	0.003
Other bleedings	97 (6.7)	81 (6.2)	0.022	150 (8.3)	152 (7.8)	0.019	314 (8.8)	342 (9.6)	0.028
Ischemic stroke	363 (25.0)	350 (26.6)	0.036	548 (30.2)	606 (30.9)	0.016	1305 (36.4)	1228 (34.4)	0.043
Peripheral vascular diseases	12 (0.8)	13 (1.0)	0.017	29 (1.6)	30 (1.5)	0.005	76 (2.1)	93 (2.6)	0.032
Cancers	166 (11.4)	136 (10.3)	0.036	266 (14.7)	293 (14.9)	0.008	561 (15.7)	577 (16.1)	0.013

Appendix Table 5. Age Group Specified Comparison of Warfarin and NOAC Users Baseline Characteristics Before and After Propensity Score Matching (continued)

	<65 years (n=2,767)			65-74 years (n=3,775)			≥75 years (n=7,156)		
Baseline Characteristics*	**Warfarin (n=1,451)**	**NOACs (n=1,316)**	**SMD†**	**Warfarin (n=1,815)**	**NOACs (n=1,960)**	**SMD†**	**Warfarin (n=3,583)**	**NOACs (n=3,573)**	**SMD†**
Medications use within 90 days prior to index date									
Antibacterial agents	285 (19.6)	258 (19.6)	0.001	417 (23.0)	461 (23.5)	0.013	1248 (34.8)	1303 (36.5)	0.034
Antifungal agents	0 (0)	2 (0.2)	0.055	6 (0.3)	6 (0.3)	0.004	9 (0.3)	5 (0.1)	0.025
Acetaminophen	410 (28.3)	339 (25.8)	0.056	621 (34.2)	660 (33.7)	0.011	1456 (40.6)	1498 (41.9)	0.026
PPIs	282 (19.4)	282 (21.4)	0.049	418 (23.0)	445 (22.7)	0.008	1032 (28.8)	1021 (28.6)	0.005
H2-receptor antagonists	751 (51.8)	692 (52.6)	0.017	1006 (55.4)	1046 (53.4)	0.041	1915 (53.4)	1920 (53.7)	0.006
Medications use within 365 days prior to index date									
Antiplatelet agents	1068 (73.6)	978 (74.3)	0.016	1432 (78.9)	1523 (77.7)	0.029	2813 (78.5)	2818 (78.9)	0.009
Lipid lowering drugs	680 (46.9)	663 (50.4)	0.070	990 (54.5)	1056 (53.9)	0.013	1830 (51.1)	1773 (49.6)	0.029
Antiarrhythmics	313 (21.6)	344 (26.1)	0.107	321 (17.7)	363 (18.5)	0.022	613 (17.1)	555 (15.5)	0.043
ACEIs	530 (36.5)	493 (37.5)	0.019	694 (38.2)	758 (38.7)	0.009	1493 (41.7)	1520 (42.5)	0.018
NSAIDs	188 (13.0)	165 (12.5)	0.013	216 (11.9)	262 (13.4)	0.044	371 (10.4)	339 (9.5)	0.029
ARBs	73 (5.0)	68 (5.2)	0.006	142 (7.8)	136 (6.9)	0.034	256 (7.1)	279 (7.8)	0.025
Beta blockers	910 (62.7)	868 (66.0)	0.068	1124 (61.9)	1239 (63.2)	0.027	2081 (58.1)	1961 (54.9)	0.064
CCBs	691 (47.6)	674 (51.2)	0.072	1105 (60.9)	1161 (59.2)	0.034	2424 (67.7)	2438 (68.2)	0.012
Diuretics	415 (28.6)	352 (26.7)	0.041	586 (32.3)	595 (30.4)	0.042	1502 (41.9)	1681 (47.0)	0.103
Digoxin	369 (25.4)	318 (24.2)	0.029	397 (21.9)	438 (22.3)	0.011	825 (23.0)	845 (23.6)	0.015
Nucleoside analogs	18 (1.2)	14 (1.1)	0.017	12 (0.7)	15 (0.8)	0.012	11 (0.3)	10 (0.3)	0.005
Antituberculosis agents	3 (0.2)	0 (0)	0.064	6 (0.3)	7 (0.4)	0.005	7 (0.2)	10 (0.3)	0.017
Antiepileptics	23 (1.6)	23 (1.7)	0.013	40 (2.2)	33 (1.7)	0.038	53 (1.5)	56 (1.6)	0.007
Immunosuppresants	9 (0.6)	2 (0.2)	0.076	12 (0.7)	13 (0.7)	0	9 (0.3)	12 (0.3)	0.016

Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARBs, angiotensin II receptor blockers; AST, aspartate aminotransferase; CCBs, calcium channel blockers; CCI, Charlson Comorbidity Index; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SMD, standardized mean difference.

* Values are expressed as frequency (%) unless otherwise specified.

† SMD indicates difference in mean or proportion of covariates in NOAC group vs warfarin group divided by the pooled standard deviation. SMD of less than 0.1 indicates a negligible difference between groups.

‡ CCI indicates patients with myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, acquired immune deficiency syndrome. The severity of comorbidity was categorized into three grades based on the score: mild with scores of 1-2; moderate with scores of 3-4; severe with scores of 5 or above (higher score indicates a higher risk of mortality).

§ CHADS2 indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or systemic embolism. The score ranges from 0 to 6 (higher score indicates a higher risk of stroke).

‖ CHA2DS2-VASc indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, age 65 to 74, prior

stroke or transient ischemic attack or systemic embolism, vascular disease, and sex category (women). The score ranges from 0 to 9 (higher score indicates a higher risk of stroke).
¶ There were 13 684 (99.9%) patients who ever had a LFT during the whole study period. A total of 1842 (13.4%) patients did not have any hepatic function laboratory tests within 90 days prior to index date:1849 (13.5%) patients were missing ALT, 10 835 (79.1%) were missing AST, 1855 (13.5%) were missing total bilirubin, and 1852 (13.5%) were missing ALP. SI conversion factors: To convert ALT/AST to μkat/L, multiply values by 0.0167; to convert total bilirubin to μmol/L, multiply values by 17.104.

Appendix Table 6. Characteristics of Warfarin and NOAC* Users with a Diagnosis of Acute Liver Failure Within 90 Days After Liver Injury

	Warfarin (n=18)	NOACs (n=14)	Dabigatran (n=6)	Rivaroxaban (n=8)
Diagnostic imaging†				
Diagnostic imaging of the liver within 90 days after the outcome date	8 (44.4)	4 (28.6)	3 (50.0)	1 (12.5)
Death				
Death from any cause within 90 days after the outcome date	7 (38.9)	8 (57.1)	3 (50.0)	5 (62.5)
Death from liver causes within 90 days after the outcome date	1 (5.6)	2 (14.3)	1 (16.7)	1 (12.5)
Time from oral anticoagulant initiation to liver injury				
<6 months	8 (44.4)	6 (42.9)	3 (50.0)	3 (37.5)
≥6 to <12 months	3 (16.7)	3 (21.4)	0 (0.0)	3 (37.5)
≥12 to <24 months	3 (16.7)	1 (7.1)	1 (16.7)	0 (0.0)
≥24 months	4 (22.2)	4 (28.6)	2 (33.3)	2 (25.0)
Laboratory tests‡ on outcome date				
ALT, median (IQR), U/L	360.5 (409.8)	1,799.5 (2,646.7)	1,288.5 (3,121.3)	1,799.5 (1,275.3)
≥5 times ULN	13 (72.2)	12 (85.7)	5 (83.3)	7 (87.5)
≥10 times ULN	11 (61.1)	12 (85.7)	5 (83.3)	7 (87.5)
≥20 times ULN	5 (27.8)	10 (71.4)	3 (50.0)	7 (87.5)
ALP, median (IQR), U/L	114.5 (46.5)	117.0 (35.3)	111.5 (35.5)	117.0 (33.5)
≥2 times ULN	2 (11.1)	2 (14.3)	1 (16.7)	1 (12.5)
≥4 times ULN	1 (5.6)	1 (7.1)	1 (16.7)	0 (0.0)
Total bilirubin, median (IQR), mg/dL	3.46 (1.49)	2.91 (3.37)	4.17 (10.54)	2.51 (2.16)
≥3 times ULN	13 (72.2)	7 (50.0)	4 (66.7)	3 (37.5)
≥5 times ULN	3 (16.7)	5 (35.7)	3 (50.0)	2 (25.0)
ALT/ALP ratio (R)				
≤2 (cholestatic)	8 (44.4)	2 (14.3)	1 (16.7)	1 (12.5)
>2 to <5 (mixed)	3 (16.7)	2 (14.3)	2 (33.3)	0 (0.0)
≥5 (hepatocellular)	7 (38.9)	10 (71.4)	3 (50.0)	7 (87.5)
Comorbidities within 30 days prior to outcome date				
Viral hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-viral liver diseases	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alcoholism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gallbladder diseases	0 (0.0)	1 (7.1)	1 (16.7)	0 (0.0)
Myocardial infarction	2 (11.1)	3 (21.4)	0 (0.0)	3 (37.5)
Congestive heart failure	11 (61.1)	6 (42.9)	2 (33.3)	4 (50.0)
Hypertension	4 (22.2)	3 (21.4)	1 (16.7)	2 (25.0)
Shock/hypotension	3 (16.7)	3 (21.4)	1 (16.7)	2 (25.0)
Medication use within 30 days prior to outcome date				
Antibacterial agents	9 (50.0)	7 (50.0)	3 (50.0)	4 (50.0)
Antifungal agents	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acetaminophen	10 (55.6)	4 (28.6)	1 (16.7)	3 (37.5)
PPIs	9 (50.0)	8 (57.1)	2 (33.3)	6 (75.0)
H2-receptor antagonists	9 (50.0)	6 (42.9)	2 (33.3)	4 (50.0)
Antiplatelet agents	6 (33.3)	5 (35.7)	0 (0.0)	5 (62.5)
Lipid lowering drugs	10 (55.6)	11 (78.6)	4 (66.7)	7 (87.5)

Antiarrhythmics	7 (38.9)	6 (42.9)	1 (16.7)	5 (62.5)
NSAIDs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nucleoside analogs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antituberculosis agents	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Antiepileptics	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressants	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; ULN, upper limit of normal.
Values are expressed as frequency (%) unless otherwise specified.
* No apixaban users were diagnosed with acute liver failure.
† See Appendix Table 2 for ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) procedure codes.
‡ See Appendix Table 1 for ULN. To convert ALT/ALP to µkat/L, multiply values by 0.0167; to convert total bilirubin to µmol/L, multiply values by 17.104.

Appendix Table 7. Adjusted Estimates of Liver Injury Risk after Propensity Score Matching Using 5-Day as the Gap of Discontinuation Therapy

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	*P* value
Warfarin	6,849	186 / 11,085	16.8 (14.5 to 19.3)	1.00 (reference)	
NOACs	6,849	111 / 9,289	11.9 (9.9 to 14.3)	0.67 (0.53 to 0.85)	<0.001
Dabigatran	3,663	58 / 5,442	10.7 (8.1 to 13.6)	0.61 (0.46 to 0.82)	0.001
Rivaroxaban	2,016	29 / 2,701	10.7 (7.3 to 15.1)	0.60 (0.40 to 0.89)	0.01
Apixaban	1,170	24 / 1,147	20.9 (13.6 to 30.4)	1.10 (0.71 to 1.69)	0.67

Abbreviations: HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants.

Appendix Table 8. Adjusted Estimates of Liver Injury Risk after Propensity Score Matching Using 15-Day as the Gap of Discontinuation Therapy

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	*P* value
Warfarin	6,849	218 / 12,584	17.3 (15.1 to 19.7)	1.00 (reference)	
NOACs	6,849	128 / 10,195	12.6 (10.5 to 14.9)	0.69 (0.55 to 0.86)	<0.001
Dabigatran	3,663	68 / 6,027	11.3 (8.8 to 14.2)	0.63 (0.48 to 0.83)	<0.001
Rivaroxaban	2,016	33 / 2,911	10.7 (7.9 to 15.7)	0.61 (0.42 to 0.89)	0.001
Apixaban	1,170	27 / 1,256	21.5 (14.4 to 30.6)	1.11 (0.74 to 1.67)	0.61

Abbreviations: HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants.

Appendix Table 9. Adjusted Estimates of Liver Injury Risk after Propensity Score Matching Using Intention-to-Treat Approach

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	*P* value
Warfarin	6,849	424 / 24,126	17.6 (16.0 to 19.3)	1.00 (reference)	
NOACs	6,849	271 / 17,486	15.5 (13.7 to 17.4)	0.83 (0.71 to 0.97)	0.02
Dabigatran	3,663	159 / 10,962	14.5 (12.3 to 16.9)	0.80 (0.67 to 0.97)	0.02
Rivaroxaban	2,016	70 / 4,655	15.0 (11.8 to 18.8)	0.79 (0.61 to 1.02)	0.07
Apixaban	1,170	42 / 1,869	22.5 (16.3 to 30.0)	1.12 (0.81 to 1.55)	0.49

Abbreviations: HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants.

Appendix Table 10. Adjusted Estimates of Liver Injury Risk after Propensity Score Matching Using Increased ALT and Bilirubin ULN* to Define Liver Injury Outcome Events

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	*P* value
Warfarin	6,849	133 / 13,306	10.0 (8.4 to 11.8)	1.00 (reference)	
NOACs	6,849	88 / 10,761	8.2 (6.6 to 10.0)	0.81 (0.61 to 1.06)	0.13
Dabigatran	3,663	45 / 6,409	7.0 (5.2 to 9.3)	0.70 (0.50 to 0.99)	0.04
Rivaroxaban	2,016	23 / 3,028	7.6 (4.9 to 11.1)	0.75 (0.48 to 1.17)	0.20
Apixaban	1,170	20 / 1,324	15.1 (9.4 to 22.7)	1.45 (0.90 to 2.35)	0.13

Abbreviations: ALT, , alanine aminotransferase; ULN, upper limit of normal; HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants.

* ULN for ALT in female is 40U/L, in male is 50U/L; ULN for total bilirubin in both female and male is 1.25mg/dL. To convert ALT to μkat/L, multiply values by 0.0167; to convert total bilirubin to μmol/L, multiply values by 17.104.

Appendix Table 11. Adjusted Estimates of Liver Injury Risk after Propensity Score Matching Using ICD-9-CM Codes to Define Liver Injury Outcome Events*

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	*P* value
Liver injury†					
Warfarin	6,849	134 / 13,266	10.1 (8.5 to 11.9)	1.00 (reference)	
NOACs	6,849	93 / 10,738	8.7 (7.0 to 10.5)	0.82 (0.63 to 1.07)	0.15
Dabigatran	3,663	45 / 6,389	7.0 (5.2 to 9.3)	0.68 (0.48 to 0.96)	0.03
Rivaroxaban	2,016	27 / 3,025	8.9 (6.0 to 12.7)	0.85 (0.56 to 1.29)	0.44
Apixaban	1,170	21 / 1,324	15.9 (10.0 to 23.6)	1.43 (0.89 to 2.28)	0.14
Acute liver failure‡					
Warfarin	6,849	10 / 13,426	0.7 (0.4 to 1.3)	1.00 (reference)	
NOACs	6,849	11 / 10,802	1.0 (0.5 to 1.7)	1.41 (0.58 to 3.38)	0.45
Dabigatran	3,663	2 / 6,433	0.3 (0.1 to 1.0)	0.45 (0.10 to 2.05)	0.30
Rivaroxaban	2,016	6 / 3,036	2.0 (0.8 to 4.0)	2.91 (1.00 to 8.40)	0.05
Apixaban	1,170	3 / 1,333	2.3 (0.6 to 5.8)	3.09 (0.80 to 11.87)	0.10

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants.

* ICD-9-CM codes for liver injury outcome events are presented in Appendix Table 2.

† General liver injury indicates the liver injury outcome as identified by ICD-9-CM codes as presented in Appendix Table 2.

‡ Acute liver failure indicates the liver injury outcome as identified by ICD-9-CM code 570.

Appendix Table 12. Adjusted Estimates of Liver Injury Risk after Propensity Score Matching among the Patients* with Baseline Liver Function Laboratory Tests

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Adjusted HR (95% CI)	*P* value
Warfarin	5,944	214 / 11,285	19.0 (16.5 to 21.6)	1.00 (reference)	
NOACs	5,944	132 / 9,244	14.3 (12.0 to 16.9)	0.72 (0.58 to 0.90)	0.004
Dabigatran	3,159	64 / 5,449	11.7 (9.1 to 14.9)	0.61 (0.46 to 0.81)	<0.001
Rivaroxaban	1,763	40 / 2,601	15.7 (11.1 to 20.7)	0.77 (0.55 to 1.09)	0.14
Apixaban	1,022	28 / 1,194	23.4 (15.8 to 33.2)	1.14 (0.76 to 1.70)	0.53

Abbreviations: HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

* Patients who do not have any result for ALT, AST, ALP or total bilirubin during the period of index date – 90 to index date – 1 were removed.

Appendix Table 13. Adjusted Estimates of Liver Injury Risk Using Covariate Adjustment Approach

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	Full* adjusted HR (95% CI; *P* value)	Partial† adjusted HR (95% CI; *P* value)
Warfarin	8,519	313 / 16,370	19.1 (17.1 to 21.3)	1.00 (reference)	1.00 (reference)
NOACs	9,762	200 / 15,173	13.2 (11.4 to 15.1)	0.71 (0.58 to 0.85; *P*<0.001)	0.70 (0.58 to 0.84; *P*<0.001)
Dabigatran	5,125	93 / 8,861	10.5 (8.5 to 12.8)	0.60 (0.47 to 0.76; *P*<0.001)	0.59 (0.46 to 0.74; *P*<0.001)
Rivaroxaban	2,924	63 / 4,312	14.6 (11.3 to 18.5)	0.76 (0.57 to 1.00; *P*=0.05)	0.75 (0.57 to 1.00; *P*=0.05)
Apixaban	1,713	44 / 2,000	22.0 (16.1 to 29.1)	1.01 (0.72 to 1.40; *P*=0.96)	1.01 (0.73 to 1.40; *P*=0.97)

Abbreviations: HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants; CCI, Charlson Comorbidity Index; SMD, standardized mean difference; PPIs, proton pump inhibitors; ACEI, angiotensin-converting-enzyme inhibitor;

* Full adjusted HR indicates that all variables for propensity score matching were used for covariate adjustment.

† Partial adjusted HR indicates that variables including age, sex, CCI, as well as the comorbidities and medications with SMD greater than 0.1 before propensity score matching which are congestive heart failure, kidney diseases, antibacterial agents, PPIs, lipid lowering agents, ACEI, diuretics, digoxin, were used for covariate adjustment.

Appendix Table 14. Adjusted Estimates of Liver Injury Risk Using Inverse Probability of Treatment Weighting Approach

Exposure	Total No.	No. of events / person-years	Incidence per 1000 person-years (95% CI)	IPTW adjusted HR (95% CI; *P* value)	IPTW with 1% truncation* adjusted HR (95% CI; *P* value)
Warfarin	8,519	313 / 16,370	19.1 (17.1 to 21.3)	1.00 (reference)	1.00 (reference)
NOACs	9,762	200 / 15,173	13.2 (11.4 to 15.1)	0.72 (0.60 to 0.86; *P*<0.001)	0.71 (0.59 to 0.85; *P*<0.001)
Dabigatran	5,125	93 / 8,861	10.5 (8.5 to 12.8)	0.60 (0.48 to 0.76; *P*<0.001)	0.59 (0.47 to 0.75; *P*<0.001)
Rivaroxaban	2,924	63 / 4,312	14.6 (11.3 to 18.5)	0.77 (0.59 to 1.01; *P*=0.06)	0.76 (0.58 to 1.00; *P*=0.05)
Apixaban	1,713	44 / 2,000	22.0 (16.1 to 29.1)	1.13 (0.81 to 1.56; *P*=0.47)	1.11 (0.80 to 1.54; *P*=0.52)

Abbreviations: HR, hazard ratio; CI, confidence interval; NOACs, non-vitamin K antagonist oral anticoagulants; IPTW, inverse probability of treatment weighting.

* Inverse probability of treatment weighting with 1% truncation indicates that the individuals with weights below or above the 1st or 99th percentile respectively, were set to the truncation threshold.

Appendix Table 15. Follow-up Period of the Cohort after Propensity Score Matching

Exposure	Total No.	No. of events (%)	Median (IQR) of overall follow-up period, years	Median (IQR) of follow-up period of patients who developed outcome events, years
Warfarin	6,849	232 (3.4)	1.12 (3.04)	1.19 (2.45)
NOACs	6,849	141 (2.1)	1.16 (2.09)	1.05 (1.48)
Dabigatran	3,663	72 (2.0)	1.20 (2.46)	1.11 (1.84)
Rivaroxaban	2,016	40 (2.0)	1.27 (2.07)	0.84 (1.65)
Apixaban	1,170	29 (2.5)	0.97 (1.38)	1.02 (1.15)

Abbreviations: IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants.

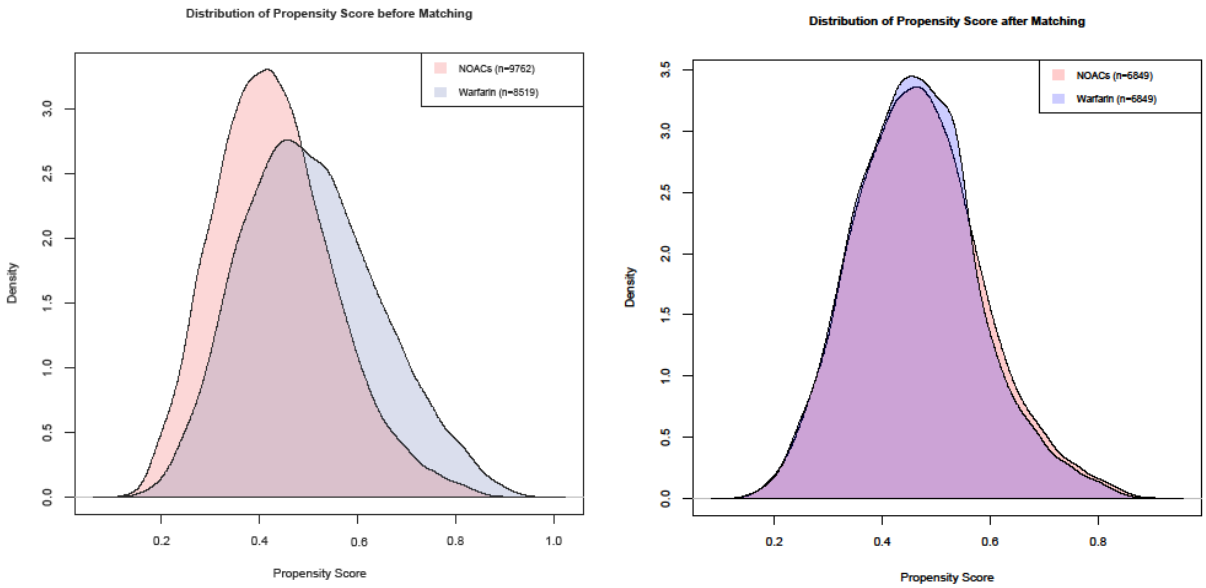
Appendix Table 16. Occurrence of Elevated* ALT/AST and Total Bilirubin in the Current Study Compared to Randomized Controlled Trials of Dabigatran, Rivaroxaban, and Apixaban

Study†	NOAC group		Control group		Hazard Ratio or Risk Ratio (95% CI)
	Subjects	Number of outcome events (%)	Subjects	Number of outcome events (%)	
Dabigatran					
Current study	3,663	72 (2.0)	6,849	232 (3.4)	0.63 (0.48 to 0.82)
RE-COVER	1,055	2 (0.2)	1,106	4 (0.4)	0.52 (0.10 to 2.86)
RE-LY	12,091	26 (0.2)	6,022	21 (0.3)	0.62 (0.35 to 1.09)
RE-MEDY	1,430	2 (0.1)	1,426	1 (<0.1)	1.99 (0.18 to 21.97)
RE-MOBILIZE	1,728	2 (0.1)	868	2 (0.2)	0.50 (0.07 to 3.56)
RE-NOVATE II	1,010	2 (0.2)	1,003	0 (0)	4.97 (0.24 to 103.30)
RE-SONATE	681	0 (0)	682	0 (0)	Not estimable
Rivaroxaban					
Current study	2,016	40 (2.0)	6,849	232 (3.4)	0.72 (0.51 to 1.01)
ATLAS ACS2-TIMI 51	10,350	21 (0.2)	5,176	10 (0.2)	1.05 (0.49 to 2.23)
EINSTEIN Acute DVT	1,682	2 (0.1)	1,648	4 (0.2)	0.49 (0.09 to 2.67)
EINSTEIN DVT Continued	591	0 (0)	586	0 (0)	Not estimable
EINSTEIN-PE	2,412	5 (0.2)	2,405	4 (0.2)	1.25 (0.34 to 4.64)
J-ROCKET	639	3 (0.5)	639	3 (0.5)	1.00 (0.20 to 4.94)
MAGGELLAN	3,364	7 (0.2)	3,382	7 (0.2)	1.01 (0.35 to 2.86)
RECORD1	2,128	1 (<0.1)	2,129	1 (<0.1)	1.00 (0.06 to 15.98)
RECORD3	1,220	2 (0.2)	1,239	0 (0)	5.08 (0.24 to 105.66)
RECORD4	1,150	1 (<0.1)	1,156	3 (0.3)	0.34 (0.03 to 3.22)
ROCKET-AF	7,111	33 (0.5)	7,125	35 (0.5)	0.94 (0.59 to 1.52)
Apixaban					
Current study	1,170	29 (2.5)	6,849	232 (3.4)	1.13 (0.77 to 1.68)

ADVANCE-1	1,596	0 (0)	1,588	2 (0.1)	0.20 (0.01 to 4.14)
ADVANCE-2	1,501	3 (0.2)	1,508	1 (<0.1)	3.01 (0.31 to 28.94)
ADVANCE-3	2,673	7 (0.3)	2,659	3 (0.1)	2.32 (0.60 to 8.97)
AMPLIFY-EXT	1,653	1 (<0.1)	829	3 (0.4)	0.17 (0.02 to 1.60)
APPRAISE2	3,673	2 (<0.1)	3,642	2 (<0.1)	0.99 (0.14 to 7.04)
ARISTOTLE	9,088	30 (0.3)	9,052	31 (0.3)	0.96 (0.58 to 1.59)
AVERROES	2,808	6 (0.2)	2,791	10 (0.4)	0.60 (0.22 to 1.64)

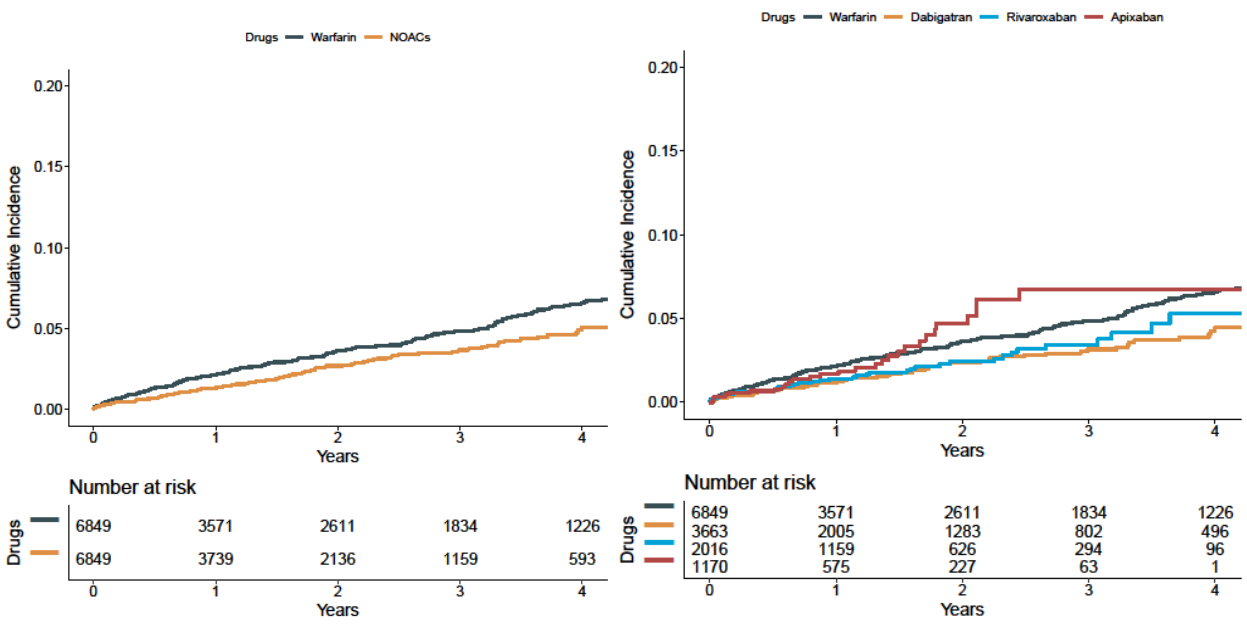
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
* The elevated ALT/AST was defined as > 3 times the upper limit of normal; elevated total bilirubin was defined as > 2 times the upper limit of normal.

† Individual clinical trial data as reported in Caldeira D, Barra M, Santos AT, et al. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart. 2014;100(7):550-556.



Appendix Figure 1. Distribution of Propensity Score Before and After Matching for NOAC and Warfarin Users

Abbreviations; NOAC, non-vitamin K antagonist oral anticoagulants. The curves indicate the distribution of the probability of a patient receiving NOACs given the observed patient characteristics. The probability was calculated using logistic regression in which NOAC treatment (yes/no) was the dependent variable and observed patient characteristics were independent variables.



Appendix Figure 2. Kaplan-Meier Curves for Liver Injury after PS Matching for NOAC and Warfarin Users

Abbreviations; NOACs, non-vitamin K antagonist oral anticoagulants.

25 February 2020

Brian E. Lacy, MD, PhD, FACG and Brennan Spiegel, MD, MSHS, FACG
Editors-in-Chief, *American Journal of Gastroenterology*

Dear Drs. Lacy and Spiegel,

RE: Manuscript ID AJG-19-2621 - "Association Between Non-vitamin K Antagonist Oral Anticoagulants or Warfarin and Liver Injury: A Cohort Study": response to the reviewers' comments for the manuscript

Thank you very much for the comments in the recent decision letter dated 3 February 2020. We appreciate this opportunity to further revise our manuscript. Our responses to the reviewers' comments are given point-by-point below in red.

Editor/Editorial Board:

1. Please indicate if any subjects had cholestatic liver injury defined by R value or ratio of serum ALT to serum alkaline phosphatase as a multiple of upper limit of normal R<2.

Thank you for your comment. To address this point, and several other comments regarding the clinical details of patients who experienced our outcome definition of liver injury, we have added an additional table to the main text (Table 2, p. 31). As per the EASL Clinical Practice Guidelines: Drug-induced liver injury, we have described the number (%) of patients with the primary outcome by their ALT/ALP ratio (R) (i.e. R ≤2 cholestatic pattern, R >2 to <5 mixed pattern, and R ≥5 hepatocellular pattern) on the outcome date. In the complete cohort, a total of 332 (64.7%) of patients had a cholestatic pattern of liver injury (208 [66.5%] warfarin users and 124 [62.0%] NOAC users). Further details by drug are shown in Table 2 (p. 31).

2. How many patients had imaging of the liver with either ultrasound, CT or MRI?

As mentioned in comment #1, we have added Table 2 (p. 31) to provide additional clinical information about patients who meet our definition of liver injury. Of these, a total of 114 (22.2%) patients (65 [20.8%] warfarin users and 49 [24.5%] NOAC users) had a procedure date within 90 days after the outcome date for either ultrasound (liver, abdomen), CT (abdomen), or MRI (abdomen). This proportion may be lower than what is observed in US clinical practice, because of the extensive wait times for diagnostic imaging within the Hong Kong public healthcare system. We have also added the list of diagnostic imaging procedure codes to the Supplementary Appendix Table 2.

Reviewer #1:

1. The authors chose ALT 3XULN plus Bilirubin 2XULN as outcome parameter that reflects Hy's Law cases. International consensus criteria define DILI as ALT 5xULN or ALP 2xULN or Hy's Law (EASL Clinical Practice Guidelines: Drug-induced liver injury, Andrade, Raúl J.Aithal, Guruprasad P.Karlsen, Tom H. et al. Journal of Hepatology, Volume 70, Issue 6, 1222 - 1261), while Hy's Law (in the FDA-Definition also requiring a ratio of ALTxULN/APxULN>=5) is

considered as an indicator of severe liver injury in the case that competing diagnoses have thoroughly been ruled out. By confining liver injury cases to the Hy's Law positive cases incidence of DILI with NOAC/warfarin might be underestimated. An important question that should be addressed is the exclusion of other possible causes in the investigated patients (Hyptension, Shock, viral Hepatitis, Biliary Obstruction) to corroborate the use of Hy's Law.

Thank you for your comment regarding the outcome definition. We agree with the reviewer that using a definition of Hy's Law cases may underestimate the true incidence of liver injury, which is why we used a broader definition of "liver injury" which appears to capture a greater number of patients and different patterns of liver injury.

We selected our primary outcome (liver injury) in accordance with the laboratory test thresholds as defined in Hy's Law, specifically an ALT or AST > 3x the upper limit of normal (ULN) and a total bilirubin > 2x ULN. Our intention is not to suggest that each patient with the outcome satisfied all three components of Hy's Law (i.e. Hy's Law cases). As the reviewer has noted, a criteria of Hy's Law requires that other causes of liver injury be ruled out. It is very challenging to rule out or determine other potential causes for elevations in serum aminotransferase and bilirubin levels using electronic health record data, thus we have not defined the outcome as Hy's Law cases and describe the outcome as "liver injury". This outcome was selected because it is a common liver function safety endpoint reported in RCTs on NOAC effectiveness and safety. Thus, it allows us to compare the rate of liver injury in clinical practice to the rates observed in a more selective RCT population.

Furthermore, we have added descriptive results for the patients who experienced our outcome during follow-up (Table 2, p. 31). On the outcome date, of the 513 cases who met our outcome definition during follow-up, 144 (28%) had ALP > 2x ULN. When applying the definition of drug-induced liver injury (DILI) according to the guidelines (ALT ≥ 5x ULN or ALP ≥ 2xULN), 353 (69%) of patients met either criteria. As we were unable to perform a causality assessment, and with the challenges of ruling out other causes, we have not used this definition as the primary outcome in this study.

2. Causality is a big issue in DILI and especially in patients receiving multiple comedications. Was statistical testing performed concerning the occurrence of liver injury in the patients and the use of comedications with known DILI-liability (e.g. NSAR, Antiinfectives, antiTb, Antipeileptics etc)?

Due to the challenges in assessing liver injury using electronic health databases, we have not performed a causality assessment. No statistical testing was performed regarding co-medications prior to liver injury. However, as presented in Table 1, we identified baseline exposures to key classes of hepatotoxic medications, and these baseline exposures were well balanced after propensity score matching. Furthermore, we have included additional descriptive details for those patients who experienced our outcome definition of liver injury. Recent exposure to hepatotoxic medications are described in Table 2 (p. 31). For example, about half of the patients with liver injury were also dispensed prescriptions for antibacterial agents, lipid lowering drugs, and antiarrhythmic drugs, but at most 5% of patients were dispensed NSAIDs, antituberculosis agents, and antiepileptics. The distribution of drug exposure prior to liver injury appears to be similar for NOAC and warfarin users.

3. The cases with acute liver failure should be described in detail, since this is the worst possible outcome of DILI. The finding that NOAC-HR for acute liver failure is higher than warfarin is especially interesting, since one would expect liver failure to occur more often with warfarin due to the effects of the drug on INR. It would be interesting to have these data discussed and more information in the supplement (especially on causality)

We have added Appendix Table 6, which provide additional details of patients with liver injury who were also diagnosed with acute liver failure using ICD-9-CM codes. In addition, we have expanded our results (p.11 lines 11-20) and our discussion (p. 14 lines 6-17) to further discuss the findings for patients with acute liver failure.

Reviewer #2:

1. It will be interesting to see a graphic distribution of latency between the drug start and the onset of liver injury, likewise for the dechallenge separated by drug.

Thank you for your comment. We have included additional clinical details about those patients who experienced our outcome definition of liver injury in Table 2 (p.31). We describe the time from drug initiation to the onset of liver injury in 6 categories (<1 month, ≥1 to <3 months, ≥3 to <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24 months). Furthermore, we have changed our survival curve (Appendix Figure 2) to a cumulative incidence curve and have shortened the plot axes in order to better visualize the curve. The survival curves are shown for each oral anticoagulant group and by specific drug. Taken together, this additional data should give readers a clearer understanding of the temporal onset of liver injury in our cohort.

Regarding dechallenge and resolution of elevations in liver function tests, we cannot determine the true date of discontinuation based on dispensing records. As with nearly all pharmacoepidemiology studies, we assume that patients who are dispensed a medication actually consume it as per the dispensing record.

2. How was causality assessed or is this just the description of elevation occurring, which would be ok too.

Thank you for the question. The objective of this study was to investigate the association between the use of NOACs vs warfarin and the risk of liver injury. We agree with the reviewer that a causality assessment is often required to determine whether cases can be classified as DILI. Because of the challenges in determining DILI from database studies, we have defined our outcome only as liver injury. Without a detailed review of each patient's medical records, we cannot determine what caused the outcome to occur. We have described laboratory tests at baseline and described the distribution of the relevant laboratory tests for the 513 patients who experienced the primary outcome of liver injury (Table 2, p. 31).

3. Please confirm, you truly observe a 2% Hy's law criteria, that is 3 ULN of ALT & Bilirubin >2ULN.

We selected our primary outcome (liver injury) in accordance with the laboratory test thresholds as defined in Hy's Law, specifically an ALT or AST > 3x the upper limit of normal (ULN) and a total

bilirubin > 2x ULN. We can confirm that, as presented in Table 3 and Appendix Table 15, in the propensity score matched cohort, the risk of liver injury during follow-up was about 2%. As shown in Table 1 we included patients with a history of liver disease and gallbladder disease, which may contribute to the higher rate of liver injury in this study. Furthermore, as described in comment #4, changing the thresholds for the upper limits of normal (ALT and total bilirubin) reduced the number of cases with liver injury. With the modified ALT and total bilirubin thresholds as suggested in comment #4, a total of 221 patients in the matched cohort experienced the outcome (Appendix Table 10). The risk (number with event / total number in treatment group) of the revised outcome was as follows: warfarin 1.94% (133/6,849), dabigatran 1.23% (45/3,663), rivaroxaban 1.14% (23/2,016), and apixaban 1.71% (20/1,170). In conditions of actual use, the risk still appears to be modestly higher than observed in randomized controlled trials. This may be due to the fact that NOACs are prescribed to individuals who would have been excluded from randomized controlled trials and that our study has a somewhat longer duration of follow-up.

4. How does this change if you would use 2.5mg as threshold for Bilirubin, and ALT of 120 instead of 75 for ALT in women, and 150 instead of 105 for men. The later thresholds were more likely used in the clinical trials.

Thank you for your comment. We would like to first clarify our ALT thresholds in the main analysis were 75 for women and 99 for men (as shown in Appendix Table 1). We ran the main analysis with the same exclusion criteria, but changed the outcome definition as suggested (ALT > 75 U/L increased to > 120 U/L [women], ALT > 99 increased to >150 [men], bilirubin > 2 mg/L increased to > 2.5 mg/L [both sexes], and excluded AST from the outcome definition). A total of 221 patients (88 NOAC users and 133 warfarin users) in the propensity score matched cohort experienced the outcome with the increased ALT and total bilirubin thresholds. The results for the propensity matched cohort are similar to the main analysis, although not statistically significant because of the reduced number of events. In the main paper, they are shown in the results (p. 13 lines 2-3), Figure 2, and Appendix Table 10.

5. As a related question: Is the onset of liver injury usually occurring at time point not covered by randomized controlled trials?

As reported in the Caldeira et al systematic review of 29 NOAC randomized controlled trials, the weighted mean duration of follow-up was 16.4 months and ranged from 2 weeks to 2 years. Of the 513 patients who experienced the primary outcome, 158 (30.8%) experienced liver injury ≥ 2 years after initiation of oral anticoagulants. The longer follow-up in this observational study adds to the safety evidence obtained in randomized controlled trials. It also helps explain why we have observed a higher risk of liver injury since about one third of cases occur in a follow-up period that is excluded from randomized controlled trials. As stated previously, we have included the distribution of patients with the outcome according to follow-up time in Table 2 (p. 31). In addition, we have revised the discussion regarding the onset of liver injury (p. 14 lines 18-21).

6. Can you further report on number of death/Liver Transplantation total and liver related, as you study may suggest that liver injury may be more frequent on Warfarin, relevant clinical outcome may be more frequent with NOAC.

Similar to comment #5, we have now described the number (%) of patients who experienced liver transplant, all-cause mortality, and liver failure related mortality, within 90 days after the outcome date in Table 2 (p. 31). No patients underwent liver transplant, and the small number of deaths makes it difficult to draw firm conclusions. However, the reviewer is correct in that there is a signal that NOAC users with our primary outcome experience more severe clinical outcomes such as all-cause mortality, death from liver causes, and a diagnosis of acute liver failure. Therefore, we have added this point to the results (p.11 lines 12-20).

7. How did you assess causality in the people with elevated ALT/AST and Bilirubin?

Please see our previous response to comment #2. We have not assessed causality for patients who experienced the outcome of liver injury. We feel that the new Table 2 (p. 31) better informs the reader about the patients who experienced liver injury. Unfortunately, we do not have the resources to perform causality assessment, which requires manual review of medical records for each of the 513 patients with liver injury. We want to emphasize that our outcome definition is liver injury and not DILI, since without a comprehensive review of the complete medical record, we cannot attribute causality to a specific drug exposure.

8. What were r-values at onset by drug?

We have included the R values on the outcome date, for warfarin and NOACs, and for each NOAC drug in Table 2 (p. 31).

9. Can you comment on phenprocoumon, albeit not used in Hong Kong, I suspect, it has frequently be implicated in DILI.

Thank you for your question. We confirm that phenprocoumon is not licensed for sale in Hong Kong (Hong Kong Drug Office Drug Database, available at www.drugoffice.gov.hk/eps/do/en/consumer/search_drug_database.html). Hence, we do not have first-hand experience to inform further on the frequency or magnitude of effects on DILI specifically on the Chinese population in Hong Kong. However, we agree with the comment that phenprocoumon may be implicated in DILI as reported in the international literature.

Thank you for your time and reconsideration of our manuscript.

Yours sincerely,

Dr. Esther W. Chan
Associate Professor and Research Lead, Centre for Safe Medication Practice and Research
Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong
Associate Research Fellow, The University of Hong Kong Shenzhen Institute of Research and Innovation
General Office, L02-56 2/F, Laboratory Block LKS Faculty of Medicine, The University of Hong Kong
21 Sassoon Road, Pokfulam, Hong Kong SAR, China
Tel: +852-28315110
Email: ewchan@hku.hk