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ORIGINAL ARTICLE

Utilization and long-term persistence of direct oral anticoagulants among patients with nonvalvular atrial fibrillation and liver disease

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Aims: We characterized the utilization and long-term treatment persistence of direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation (NVAF) and liver disease.

Method: Using the UK Clinical Practice Research Datalink, we assembled a population-based cohort of NVAF patients with liver disease initiating oral anticoagulants between 2011 and 2020. Logistic regression estimated odds ratios (ORs) and 95% confidence intervals (CIs) of the association between patient characteristics and initiation of DOACs *vs* vitamin K antagonists (VKAs). Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs of the association between patient characteristics and the switch from VKAs to DOACs *vs* remaining on VKAs. We also assessed the 5-year treatment persistence with DOACs *vs* VKAs, and whether ischemic stroke or bleeding preceded treatment discontinuation.

Results: Our cohort included 3167 NVAF patients with liver disease initiating DOACs (n = 2247, 71%) or VKAs (n = 920, 29%). Initiators of DOACs were more likely to have prior ischemic stroke (OR 1.44, 95% CI 1.12-1.85) than VKA initiators but less likely to have used antiplatelet agents (OR 0.66, 95% CI 0.53-0.82). Patients switching to DOACs were more likely to have used selective serotonin reuptake inhibitors (HR 1.64, 95% CI 1.13-2.37) than those remaining on VKAs. At 5 years, 31% of DOAC initiators and 9% of VKA initiators remained persistent. Only few patients were diagnosed with ischemic stroke or bleeding prior to treatment discontinuation.

Conclusion: Most NVAF patients with liver disease initiated treatment with DOACs. Long-term persistence with DOACs was higher than with VKAs but remained relatively low.

KEYWORDS
anticoagulation, antithrombotic treatment, cardiovascular disease, hepatic disease

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) are currently recommended as first-line treatments for stroke prevention in nonvalvular atrial fibrillation (NVAF).[1,2] These recommendations are based on results from large randomized controlled trials (RCTs) that showed similar or better efficacy and safety for DOACs compared with the therapeutic alternative vitamin K antagonists (VKAs).[3–6] Moreover, DOACs require less monitoring than VKAs and are easier to use due to their more rapid onset of anticoagulation and lower potential for food-drug and drug-drug interactions.[7]

Given these advantages, it has been debated whether treatment persistence with DOACs would be improved compared to VKAs.[8] To answer this question, several studies assessed the persistence with DOACs in the overall NVAF population, generally showing higher estimates than with VKAs.[9] However, there are no data on the persistence of DOACs and only limited data about other aspects of DOAC utilization such as treatment initiation or treatment switch in patients with NVAF and liver disease,[10,11] a high-risk group which accounts for up to 5% of the overall NVAF population.[10,12,13] Reasons for the elevated baseline risk of this group include the association between liver disease and an increased risk of both thrombosis[14] and bleeding,[15] as well as the potential effects of hepatic impairment on the pharmacology of DOACs.[16–19]

Since patients with liver disease were systematically excluded from the landmark RCTs which assessed the efficacy and safety of DOACs,[3–6] there are no specific recommendations on oral anticoagulation in NVAF patients with liver disease.[2,20,21] Thus, there is a need to understand how DOACs are used in this high-risk population in the setting of routine clinical practice. To this end, we conducted a population-based study to assess factors associated with the initiation of DOACs and the switch from VKAs to DOACs as well as the long-term persistence with DOACs in NVAF patients with liver disease.

What is already known about this subject

- Direct oral anticoagulants (DOACs) have shown a generally higher treatment persistence than vitamin K antagonists (VKAs) in patients with nonvalvular atrial fibrillation (NVAF).
- Treatment persistence and other aspects of DOAC utilization remain poorly understood in the high-risk group of NVAF patients with underlying liver disease.

What this study adds

- Most NVAF patients with liver disease initiated treatment with DOACs, with the probability of DOAC versus VKA initiation increasing over time.
- Treatment persistence at 5 years was higher with DOACs than with VKAs, but remained relatively low.
- The results were similar when focusing on NVAF patients with liver cirrhosis.

2 | METHODS

2.1 | Data source

We conducted this study using the UK Clinical Practice Research Datalink (CPRD), which is a primary care database containing electronic medical records of 19 million patients seen in >700 general practices.[22] The CPRD is representative of the UK general population in terms of age, sex, socioeconomic status and geographical spread.[22] Medical diagnoses and procedures are recorded by general practitioners using the Read code classification.[23] Drugs prescribed by general practitioners are coded using the UK Prescription Pricing Authority dictionary and are automatically recorded in the CPRD. The CPRD also contains information on anthropometric variables such as body mass index, lifestyle variables such as smoking and alcohol consumption, and laboratory test results. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 20_026) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

2.2 | Study cohort

We included all patients with a first diagnosis of atrial fibrillation between 1 January 2011 (when dabigatran was approved as the first DOAC for stroke prevention in NVAF) and 21 January 2020. We excluded patients <18 years old, with <365 days of medical history in the CPRD or with a prescription for an oral anticoagulant in the 365 days before their atrial fibrillation diagnosis. To restrict the cohort to NVAF, we excluded patients diagnosed with valvular disease, valvular repair or hyperthyroidism at any time before the diagnosis of atrial fibrillation. The date of cohort entry was defined as the date of the first prescription for a DOAC (ie, apixaban, dabigatran, edoxaban or rivaroxaban) or a VKA after the NVAF diagnosis. Patients not receiving treatment with an oral anticoagulant were not included in the cohort. To ensure the link between NVAF and oral anticoagulant use, we finally excluded patients diagnosed with venous thromboembolism or who underwent orthopaedic surgery (other approved indications for oral anticoagulation) between the NVAF diagnosis and cohort entry.

We further restricted the cohort to patients with liver disease. Liver disease was defined as (i) chronic or severe liver disease (eg, chronic infectious or noninfectious hepatitis, alcoholic fatty liver disease, other alcoholic liver disease, nonalcoholic fatty liver disease, liver necrosis, liver fibrosis, liver cirrhosis, gastroesophageal varices, hepatic failure, hepatic encephalopathy, hepatorenal syndrome, liver cancer, liver transplantation, major hepatectomy, Wilson's disease, hemochromatosis or Budd-Chiari syndrome) diagnosed at any time before cohort entry or (ii) acute liver disease (eg, acute infectious or noninfectious hepatitis, liver hematoma, liver injury or minor hepatectomy) diagnosed in the 6 months before cohort entry. This was our study cohort, in which all analyses

were conducted (see below). Patient numbers permitting, we also conducted the analyses restricting the study cohort to NVAF patients with liver cirrhosis to explore the potential impact of disease severity on the utilization of DOACs.

2.3 | Baseline characteristics

We assessed the following patient characteristics at cohort entry: calendar year, age, sex, smoking (current, former, never, unknown), body mass index (<25 kg/m^2, 25-29 kg/m^2, ≥30 kg/m^2, unknown; last measurement before cohort entry), arterial hypertension, congestive heart failure, hyperlipidaemia, coronary artery disease, peripheral vascular disease, diabetes mellitus, ischemic stroke or transient ischemic attack (TIA), and any bleeding (all measured at any time before cohort entry). We also assessed chronic kidney disease using related diagnoses and procedures at any time before cohort entry[24] and cancer (except nonmelanoma skin cancer) in the year before cohort entry. Moreover, we assessed drugs that are associated with the risk of ischemia or bleeding, including antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors and H_2 blockers (all measured in the year before cohort entry).

We calculated for each cohort member the CHA_2DS_2-VASc (congestive heart failure, arterial hypertension, age ≥75 years, diabetes, previous stroke/TIA, vascular disease, age 65-74 years, female sex) score to assess the thromboembolic risk related to NVAF[25] and the HAS-BLED (uncontrolled arterial hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelet agents or alcohol-related disorders) score to assess the risk of major bleeding related to the use of oral anticoagulants in NVAF.[26] Since all patients in the cohort had liver disease, they were assumed to have abnormal liver function. International normalized ratio was not considered in the calculations since it is not systematically recorded in the CPRD. Thus, the maximum HAS-BLED score was 8 instead of 9.

2.4 | Treatment initiation

We described the baseline characteristics of NVAF patients with liver disease initiating oral anticoagulant treatment, stratified by drug class (DOAC *vs* VKA) and individual DOAC. We then used logistic regression to estimate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of the association between baseline characteristics and initiation of DOACs *vs* VKAs, as well as initiation of apixaban *vs* rivaroxaban. Our drug-specific analyses focused on rivaroxaban and apixaban, the two DOACs most commonly used for stroke prevention in NVAF in the UK.[27]

2.5 | Treatment switch

We also described the baseline characteristics of NVAF patients with liver disease initiating VKAs and then switching to DOACs, a well-established trend in current anticoagulant treatment in NVAF.[28] Our second focus was patients initiating rivaroxaban and then switching to apixaban, an anticipated trend given recent data on DOAC utilization in patients with NVAF from the UK.[27] Moreover, we used Cox proportional hazards models to estimate crude and adjusted hazard ratios (HRs) and 95% CIs of the association between baseline characteristics and the switch to DOACs *vs* remaining on VKAs, as well the switch to apixaban *vs* remaining on rivaroxaban. In these analyses, treatment switch was defined as the date of the prescription for an oral anticoagulant (class) different than the index oral anticoagulant (class). Finally, in a post hoc descriptive analysis, we assessed clinical events potentially affecting oral anticoagulant treatment (ie, ischemic stroke/TIA, major bleeding and any bleeding) that occurred in the 180 days prior to treatment switch from VKAs to DOACs. Major bleeding was defined as intracranial bleeding, intraocular bleeding, intraarticular bleeding, hemopericardium, retroperitoneal bleeding, any bleeding combined with hospitalization or transfusion within 7 days, or intramuscular bleeding combined with compartment syndrome within 7 days.

2.6 | Treatment persistence

We assessed the persistence with DOACs *vs* VKAs and with apixaban *vs* rivaroxaban in the first 5 years (3 years in the analyses in the liver cirrhosis subcohort due to the lower number of patients). Patients were considered continuously exposed to an anticoagulant if the duration of one prescription overlapped with the date of the subsequent prescription. In the event of nonoverlap, a 30-day grace period between the end of one prescription and the beginning of the next was permitted to account for delays in refilling. Treatment persistence was quantified for each patient as the time to treatment discontinuation or switch. For the DOACs *vs* VKAs analysis, we allowed intra-class switches among different DOACs. We did not consider competing events such as death or administrative censoring as treatment discontinuation to avoid inflating discontinuation rates.[8] We used Kaplan-Meier curves to depict the probability of persistence with DOACs *vs* VKAs and with apixaban *vs* rivaroxaban. We also conducted a sensitivity analysis extending the grace period to 60 days. In a post hoc descriptive analysis, we assessed clinical events potentially affecting oral anticoagulant treatment (ie, ischemic stroke/TIA, major bleeding [definition available in the previous section] and any bleeding) that occurred in the 180 days prior to the discontinuation of DOACs or VKAs. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patients with NVAF and liver disease

Among 111 960 patients with NVAF initiating oral anticoagulant treatment during the study period, 3167 (3%) had liver disease (Figure 1; common liver conditions listed in Table A1). Of those, 2247 (71%) initiated treatment with a DOAC (1231 [39%] apixaban,

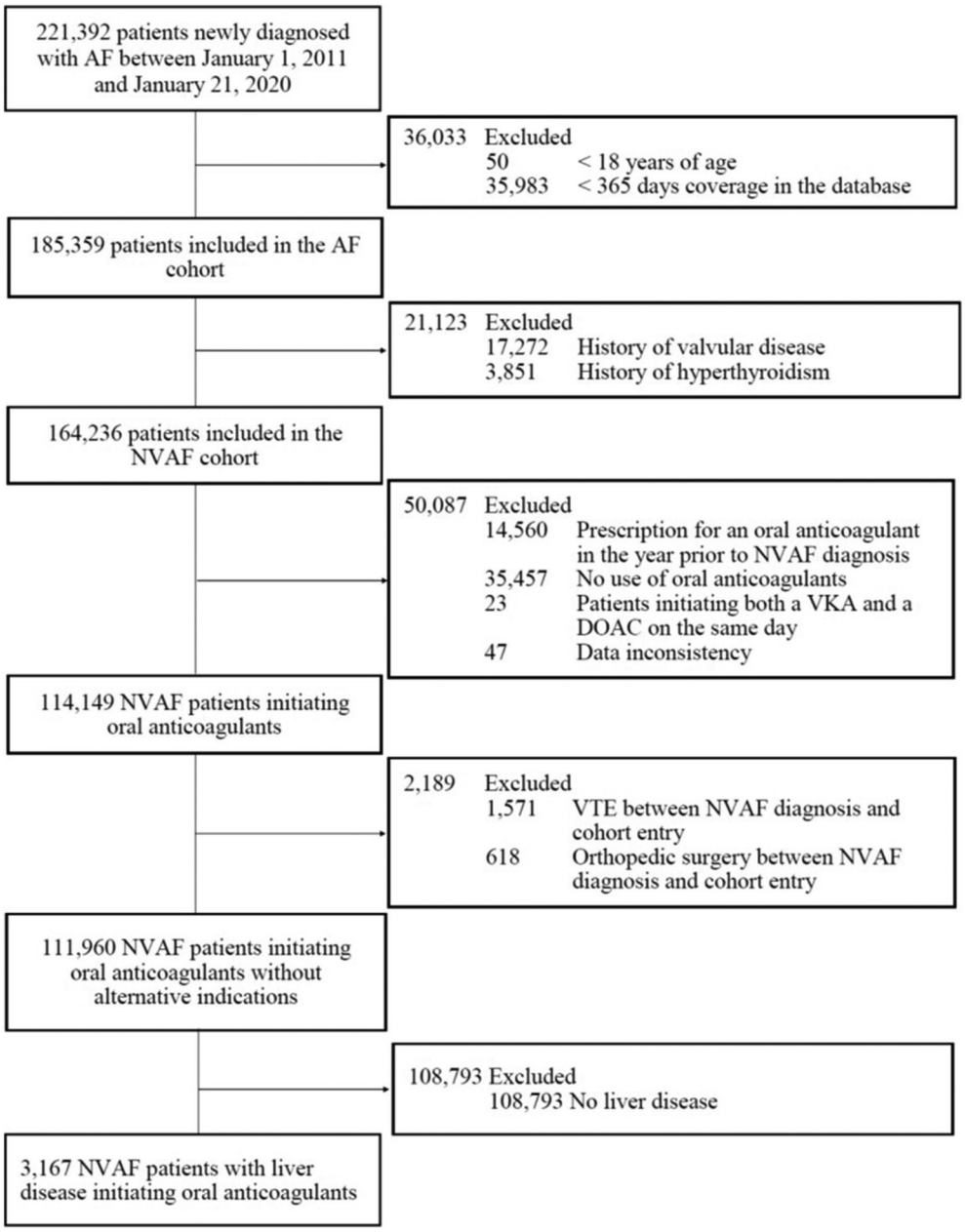

FIGURE 1 Flowchart showing the construction of the study cohort. AF, atrial fibrillation; DOACs, direct oral anticoagulants; NVAF, nonvalvular atrial fibrillation; VKAs, vitamin K antagonists; VTE, venous thromboembolism

121 [4%] dabigatran, 137 [4%] edoxaban, 758 [24%] rivaroxaban) and 920 (29%) with VKAs, with the probability of DOAC initiation increasing over time (Table 1). DOAC initiators were more likely to have prior ischemic stroke/TIA or to have used SSRIs than VKA initiators, but they were less likely to have used antiplatelet agents. We also observed that the probability of initiating apixaban *vs* rivaroxaban increased over time (Table A2). Apixaban initiators were more likely to be older, to have prior ischemic stroke/TIA or a higher baseline thromboembolic risk than rivaroxaban initiators, but they were less likely to be overweight.

Among the 920 NVAF patients with liver disease initiating treatment with VKAs, 323 (35%) switched to DOACs during follow-up (the percentage of DOAC initiators switching to VKAs was only 2%). The probability of switching from VKAs to DOACs increased over time (Table 2). Patients switching to DOACs were more likely to have used NSAIDs or SSRIs than those remaining on VKAs, but they were less likely to be overweight or to have used antiplatelet agents. In the 180 days prior to the treatment switch from VKAs to DOACs, 24 (7%) patients had a diagnosis of ischemic stroke or TIA and 19 (6%) patients had a diagnosis of any bleeding. Only a few patients (<2%) had a diagnosis of major bleeding. Among rivaroxaban initiators, 54 (7.5%) switched to apixaban during follow-up (Table A3), and they tended to have a higher baseline thromboembolic risk and bleeding risk than those remaining on rivaroxaban.

At 5 years, 31% of DOAC and 9% of VKA initiators remained persistent (difference DOACs *vs* VKAs 22% [95% CI 11-33%]), with the Kaplan-Meier curves diverging early in the first year (Figure 2). Median persistence was higher with DOACs (27 [95% CI 25-32] months) than with VKAs (10 [95% CI 9-12] months). In the 180 days

TABLE 1 Crude and adjusted ORs of treatment initiation with DOACs versus VKAs by baseline characteristics of NVAF patients with liver disease[a]

	DOACs (n = 2247)		VKAs (n = 920)		Crude OR (95% CI)	Adjusted[b] OR (95% CI)
Age in years, mean (SD)	70.7 (10.6)		70.1 (9.7)			
18-69	952	42.4	408	44.4	(reference)	(reference)
≥70	1295	57.6	512	55.7	1.08 (0.93-1.27)	1.06 (0.87-1.31)
Male sex	1349	60.0	560	60.9	0.97 (0.83-1.13)	1.10 (0.90-1.35)
Calendar year						
2011-2016	642	28.6	799	86.9	(reference)	(reference)
2017-2020	1605	71.4	121	13.2	16.51 (13.36-20.41)	16.58 (13.31-20.64)
Smoking status						
Current	S[c]	S[c]	S[c]	S[c]	0.99 (0.76-1.29)	0.95 (0.69-1.32)
Former	999	44.5	444	48.3	0.86 (0.73-1.01)	0.88 (0.72-1.08)
Never	988	44.0	376	40.9	(reference)	(reference)
Unknown	S[c]	S[c]	S[c]	S[c]	NA	NA
Body mass index in kg/m^2						
<25	347	15.4	133	14.5	(reference)	(reference)
25-29	704	31.3	260	28.3	1.04 (0.81-1.33)	1.08 (0.80-1.45)
≥30	1161	51.7	506	55.0	0.88 (0.70-1.10)	0.88 (0.67-1.17)
Unknown	35	1.6	21	2.3	NA	NA
Comorbidities						
Arterial hypertension	1638	72.9	684	74.4	0.93 (0.78-1.11)	0.94 (0.75-1.17)
Ischemic stroke/TIA	408	18.2	149	16.2	1.15 (0.94-1.41)	1.44 (1.12-1.85)
Congestive heart failure	463	20.6	207	22.5	0.89 (0.74-1.08)	0.94 (0.75-1.19)
Hyperlipidaemia	1068	47.5	421	45.8	1.07 (0.92-1.25)	1.37 (1.12-1.68)
Coronary artery disease	596	26.5	262	28.5	0.91 (0.76-1.08)	1.02 (0.81-1.30)
Peripheral vascular disease	198	8.8	76	8.3	1.07 (0.81-1.42)	1.17 (0.83-1.64)
Diabetes mellitus	953	42.4	412	44.8	0.91 (0.78-1.06)	0.87 (0.71-1.06)
Any bleeding	111	4.9	37	4.0	1.24 (0.85-1.81)	1.32 (0.83-2.09)
Chronic kidney disease	1092	48.6	464	50.4	0.93 (0.80-1.08)	0.93 (0.76-1.13)
Cancer	143	6.4	54	5.9	1.09 (0.79-1.51)	0.80 (0.54-1.20)
Comedications						
Antiplatelet agents	899	40.0	489	53.2	0.59 (0.50-0.69)	0.66 (0.53-0.82)
NSAIDs	317	14.1	130	14.1	1.00 (0.80-1.24)	1.24 (0.95-1.63)
SSRIs	300	13.4	80	8.7	1.62 (1.25-2.10)	1.50 (1.09-2.04)
Proton pump inhibitors	1299	57.8	505	54.9	1.13 (0.97-1.31)	1.07 (0.88-1.30)
H_2 blockers	135	6.0	68	7.4	0.80 (0.59-1.08)	0.67 (0.46-0.97)
CHA_2DS_2-VASC[d]						
0-2	647	28.8	265	28.8	(reference)	
≥3	1600	71.2	655	71.2	1.00 (0.85-1.19)	
HAS-BLED[d,e]						
1-2	491	21.9	182	19.8	(reference)	
≥3	1756	78.2	738	80.2	0.88 (0.73-1.07)	

CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; CI, confidence interval; DOACs, direct oral anticoagulants; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelets or alcohol-related disorders; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

[a]Baseline characteristics presented as numbers and percentages unless indicated otherwise.

[b]Adjusted estimates are joint association and should not be interpreted as causal or as a prediction model.

[c]Suppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

[d]The analyses for the CHA_2DS_2-VASC and HAS-BLED score were conducted using separate logistic regression models.

[e]Minimum HAS-BLED score was 1 because patients were assumed to have abnormal liver function and maximum HAS-BLED score was 8 because the international normalized ratio was not considered in the calculations.

TABLE 2 Crude and adjusted HRs of treatment switch from VKAs to DOACs versus remaining on VKAs by baseline characteristics of NVAF patients with liver disease[a]

	Switch to DOACs (n = 323)		Remain on VKAs (n = 597)		Crude HR (95% CI)	Adjusted[e] HR (95% CI)
Age in years, mean (SD)	69.3 (10.0)		70.6 (9.6)			
18-69	160	49.5	248	41.5	(reference)	(reference)
≥70	163	50.5	349	58.5	0.94 (0.76-1.17)	1.04 (0.81-1.32)
Male sex	197	61.0	363	60.8	0.97 (0.78-1.21)	0.97 (0.77-1.24)
Calendar year						
2011-2016	300	92.9	499	83.6	(reference)	(reference)
2017-2020	23	7.1	98	16.4	1.72 (1.11-2.68)	1.66 (1.06-2.61)
Smoking status						
Current	S[b]	S[b]	S[b]	S[b]	1.03 (0.71-1.49)	1.03 (0.69-1.52)
Former	147	45.5	297	49.8	0.91 (0.72-1.14)	0.95 (0.75-1.21)
Never	142	44.0	234	39.2	(reference)	(reference)
Unknown	S[b]	S[b]	S[b]	S[b]	NA	NA
Body mass index in kg/m^2						
<25	43	13.3	90	15.1	(reference)	(reference)
25-29	83	25.7	177	29.7	0.64 (0.44-0.92)	0.60 (0.41-0.88)
≥30	188	58.2	318	53.3	0.85 (0.61-1.19)	0.78 (0.54-1.11)
Unknown	9	2.8	12	2.0	NA	NA
Comorbidities						
Arterial hypertension	236	73.1	448	75.0	1.07 (0.84-1.37)	1.15 (0.88-1.51)
Ischemic stroke/TIA	46	14.2	103	17.3	0.82 (0.60-1.12)	0.86 (0.62-1.18)
Congestive heart failure	63	19.5	144	24.1	0.92 (0.70-1.21)	1.03 (0.77-1.37)
Hyperlipidaemia	147	45.5	274	45.9	1.04 (0.84-1.30)	1.08 (0.84-1.37)
Coronary artery disease	88	27.2	174	29.2	1.02 (0.80-1.30)	1.19 (0.89-1.58)
Peripheral vascular disease	24	7.4	52	8.7	1.12 (0.74-1.69)	1.16 (0.75-1.80)
Diabetes mellitus	140	43.3	272	45.6	0.97 (0.78-1.20)	1.02 (0.80-1.29)
Any bleeding	9	2.8	28	4.7	0.75 (0.39-1.45)	0.58 (0.27-1.24)
Chronic kidney disease	139	43.0	325	54.4	0.86 (0.69-1.07)	0.83 (0.66-1.06)
Cancer	15	4.6	39	6.5	1.29 (0.77-2.17)	1.28 (0.75-2.20)
Comedications						
Antiplatelet agents	162	50.2	327	54.8	0.74 (0.59-0.92)	0.71 (0.55-0.92)
NSAIDs	60	18.6	70	11.7	1.42 (1.07-1.88)	1.45 (1.08-1.95)
SSRIs	35	10.8	45	7.5	1.56 (1.09-2.21)	1.64 (1.13-2.37)
Proton pump inhibitors	173	53.6	332	55.6	1.04 (0.83-1.29)	1.02 (0.81-1.29)
H_2 blockers	23	7.1	45	7.5	1.10 (0.72-1.68)	1.04 (0.67-1.60)
CHA_2DS_2-VASC[c]						
0-2	114	35.3	151	25.3	(reference)	
≥3	209	64.7	446	74.7	0.89 (0.71-1.13)	
HAS-BLED[c,d]						
1-2	74	22.9	108	18.1	(reference)	
≥3	249	77.1	489	81.9	0.87 (0.67-1.13)	

CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; CI, confidence interval; DOACs, direct oral anticoagulants; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelets or alcohol-related disorders; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

[a]Baseline characteristics presented as numbers and percentages unless indicated otherwise.

[b]Suppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

[c]The analyses for the CHA_2DS_2-VASC and HAS-BLED score were conducted using separate Cox proportional hazards models.

[d]Minimum HAS-BLED score was 1 because patients were assumed to have abnormal liver function and maximum HAS-BLED score was 8 because the international normalized ratio was not considered in the calculations.

[e]Adjusted estimates are joint associations and should not be interpreted as causal or as a prediction model.

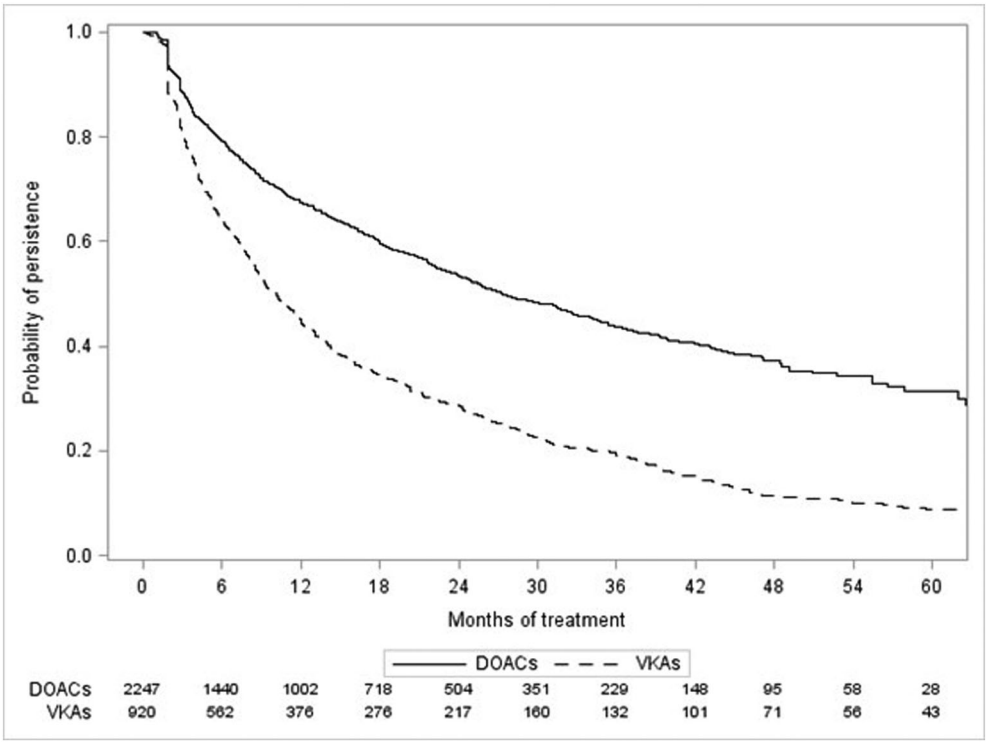

FIGURE 2 Treatment persistence with DOACs versus VKAs in patients with NVAF and liver disease in the first 5 years. $P < .0001$. DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists

prior to DOAC discontinuation, 64 (7%) patients had a diagnosis of ischemic stroke or TIA, 18 (2%) patients had a diagnosis of major bleeding and 100 (11%) patients had a diagnosis of any bleeding. In the 180 days prior to VKA discontinuation, 32 (5%) patients had a diagnosis of ischemic stroke or TIA, 14 (2%) patients had a diagnosis of major bleeding and 76 (11%) patients had a diagnosis of any bleeding. Moreover, we observed that the percentage of persistent patients at 5 years was 39% for apixaban and 27% for rivaroxaban (difference apixaban *vs* rivaroxaban 12% [95%CI 4-20%]) (Figure A1), and that median persistence was higher with apixaban (27 [95% CI 25-33] months) than with rivaroxaban (21 [95% CI 17-24] months). The results did not change when the grace period was extended to 60 days (data not shown).

3.2 | Patients with NVAF and liver cirrhosis

During the study period, 376 NVAF patients with liver cirrhosis initiated oral anticoagulants. Of those, 246 (65%) initiated treatment with a DOAC (mostly apixaban and rivaroxaban) and 130 (35%) with VKAs, and the probability of DOAC initiation increased over time (Table A4). DOAC initiators with liver cirrhosis were more likely to have used SSRIs but less likely to have hyperlipidaemia than VKA initiators. We also observed that the probability of initiating apixaban *vs* rivaroxaban increased over time, and that apixaban initiators were more likely to have prior ischemic stroke/TIA than rivaroxaban initiators (Table A5). The low number of NVAF patients with liver cirrhosis switching anticoagulants during follow-up precluded analyses on treatment switch in this population.

At 3 years, 39% of DOAC and 18% of VKA initiators remained persistent (difference DOACs *vs* VKAs 21% [95% CI 11-31%]), with the Kaplan-Meier curves diverging in the first year (***Figure A2***). Median persistence was higher with DOACs (26 [95% CI 18-33] months) than with VKAs (9 [95% CI 6-12] months). In the 180 days prior to DOAC discontinuation, 12 (13%) patients had a diagnosis of ischemic stroke or TIA, 5 (5%) patients had a diagnosis of major bleeding and 7 (7%) patients had a diagnosis of any bleeding. In the 180 days prior to VKA discontinuation, 14 (17%) patients had a diagnosis of any bleeding, while only few patients had a diagnosis of ischemic stroke or TIA or major bleeding (<5%). We also observed that the fraction of persistent patients at 3 years was 46% for apixaban and 32% for rivaroxaban (difference apixaban *vs* rivaroxaban 14% [95% CI 1-27%]) (Figure A3), and that median persistence was higher with apixaban (33 [95% CI 21 to *inestimable*] months) than with rivaroxaban (17 [95% CI 9-32] months). The results did not change when the grace period was extended to 60 days (data not shown).

4 | DISCUSSION

Our study showed that most NVAF patients with liver disease initiated oral anticoagulant treatment with DOACs. The probability of DOAC *vs* VKA initiation increased over time, and apixaban was the most preferred compound. Moreover, every third patient initiating treatment with VKAs eventually switched to DOACs. Long-term persistence with DOACs was higher than with VKAs but remained relatively low, and persistence with apixaban was higher than with rivaroxaban. The results did not materially change when focusing on NVAF patients with liver cirrhosis.

The utilization of DOACs in the high-risk group of NVAF patients with liver disease is poorly described, with previous population-based

studies providing limited information.[10,11] In a study conducted by our group using administrative data from the Canadian province of Quebec from 2011 to 2014, that is the first 3 years following DOAC market approval, the ratio of DOAC to VKA initiators in NVAF patients with liver disease was 0.4, and DOAC patients were younger and had a lower prevalence of comorbidities than VKA patients.[10] In another study based on administrative data from South Korea from 2014 to 2016, the ratio of DOAC to VKA initiators was 2:1, and DOAC users were older and had a higher thromboembolic risk than VKA users.[11] Our results on treatment initiation align more with the results from South Korea and less with those from our previous study. Similar to the study from South Korea, we also observed a predominance of DOACs, and DOAC users were more likely to have prior ischemic stroke/TIA than VKA users. This is not surprising, however, since our previous study had focussed on DOAC use in the initial post-approval period.

The probability of DOAC *vs* VKA initiation in our study increased substantially over time, and every third VKA initiator eventually switched to a DOAC. Thus, combining the available evidence, it seems that after an initial phase following DOAC market approval, characterized by a modest uptake and use in relatively healthy individuals, there has been a steep increase in the uptake of DOACs and a shift to users with a higher comorbidity burden. Of note, a similar shift in the characteristics of DOAC patients has also been described for the overall NVAF population.[27]

The DOACs most commonly used to initiate treatment in NVAF patients with liver disease in our study were apixaban and rivaroxaban. Due to the lack of data from RCTs on the efficacy and safety of DOACs in NVAF patients with liver disease, guidelines do not include specific recommendations for this high-risk population.[2,20,21] Moreover, recommendations from regulatory agencies are based on pharmacokinetic data and are very similar for all DOACs, with only severe liver dysfunction being a contraindication.[29] Thus, the predominance of apixaban and rivaroxaban in our study seems to be related to their increased use in the overall NVAF population,[27] rather than based on liver specific considerations. This hypothesis is also supported by the fact that apixaban and rivaroxaban were the most common DOACs also among patients with liver cirrhosis, in whom hepatic function should be even more compromised.

Persistence with DOACs was relatively low, with 35% of NVAF patients with liver disease remaining on treatment after 5 years, but it was still higher than with VKAs, where only 10% were persistent. Since patients could have reinitiated treatment later on, however, the absolute numbers should be interpreted with caution. However, the higher persistence with DOACs corroborates previous studies on oral anticoagulant persistence in the overall NVAF population.[9] Moreover, the fact that the results did not materially change when focussing on NVAF patients with liver cirrhosis argues against a major impact of liver disease severity on persistence.

Of note, the percentage of patients with relevant clinical events preceding oral anticoagulant treatment discontinuation was relatively low both among DOAC users (liver disease cohort 7% ischemic stroke/TIA and 11% bleeding; liver cirrhosis cohort 13% ischemic stroke/TIA and 7% bleeding) and VKA users (liver disease cohort 5% ischemic stroke/TIA and 11% bleeding; liver cirrhosis cohort <5% ischemic stroke/TIA and 17% bleeding). This suggests that effectiveness and safety can only partly explain the decreased treatment persistence with oral anticoagulants overall among NVAF patients with liver disease. Moreover, effectiveness and safety do not seem to account for the difference in persistence observed between DOACs and VKAs.

We also observed a slightly higher persistence with apixaban *vs* rivaroxaban, despite the once daily-dosing scheme of rivaroxaban (as opposed to the twice-daily dosing of apixaban), which has been linked to improved persistence with other cardiovascular drugs.[30] Since apixaban has been associated with a decreased risk of bleeding compared to rivaroxaban,[31] the observed difference in persistence could reflect apixaban's more favourable safety profile.

Our study has several strengths. It is the first study to focus on DOAC utilization in NVAF patients with liver disease, a high-risk group that was systematically excluded from the pivotal DOAC RCTs. Moreover, the study was based on a very recent and relatively large cohort, which allowed the calculation of contemporary and precise estimates for factors associated with oral anticoagulant initiation and switching. Due to the size of the cohort, we could also conduct analyses in NVAF patients with liver cirrhosis, a group where the knowledge gap in anticoagulant utilization is further amplified.[32] Finally, with the study period spanning from 2011 to 2020, we were able to assess the long-term persistence of oral anticoagulant treatment.

Our study also has limitations. Due to the low number of patients on dabigatran or edoxaban, specific analyses with these compounds were not feasible. However, our analyses with apixaban and rivaroxaban, the most commonly used DOACs for anticoagulation in NVAF[27,33,34] should be informative for the majority of patients. Second, given the relatively low number of NVAF patients with liver cirrhosis, we could not assess factors associated with treatment switch in this population. Third, given the lack of linkage to hospitalization data, the number of clinical events preceding treatment switch or discontinuation may have been underestimated. Finally, the CPRD records prescriptions and not dispensations, which could introduce misclassification. However, we do not expect this misclassification to be differential among different compounds.

Despite the knowledge gap regarding the effects of DOACs in NVAF patients with liver disease, most patients initiate oral anticoagulant treatment with these drugs and especially apixaban and rivaroxaban, possibly reflecting current trends in the overall NVAF population. Moreover, while the long-term persistence with DOACs was relatively low, it was still higher than with the therapeutic alternative VKAs.

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CONTRIBUTORS

A.D. conceived and designed the study, provided funding, contributed to data analysis, interpreted the data, and wrote and revised the manuscript. Y.C. analysed and interpreted the data, and reviewed the manuscript. R.W.P., K.B.F. and G.S. reviewed the study design, interpreted the data and reviewed the manuscript. C.R. contributed to the concept and the design of the study, provided supervision, interpreted the data and revised the manuscript.

COMPETING INTEREST

R.W.P. has received personal fees from Amgen, Analysis Group, Merck, and Pfizer, all outside of the submitted work. All other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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APPENDIX A

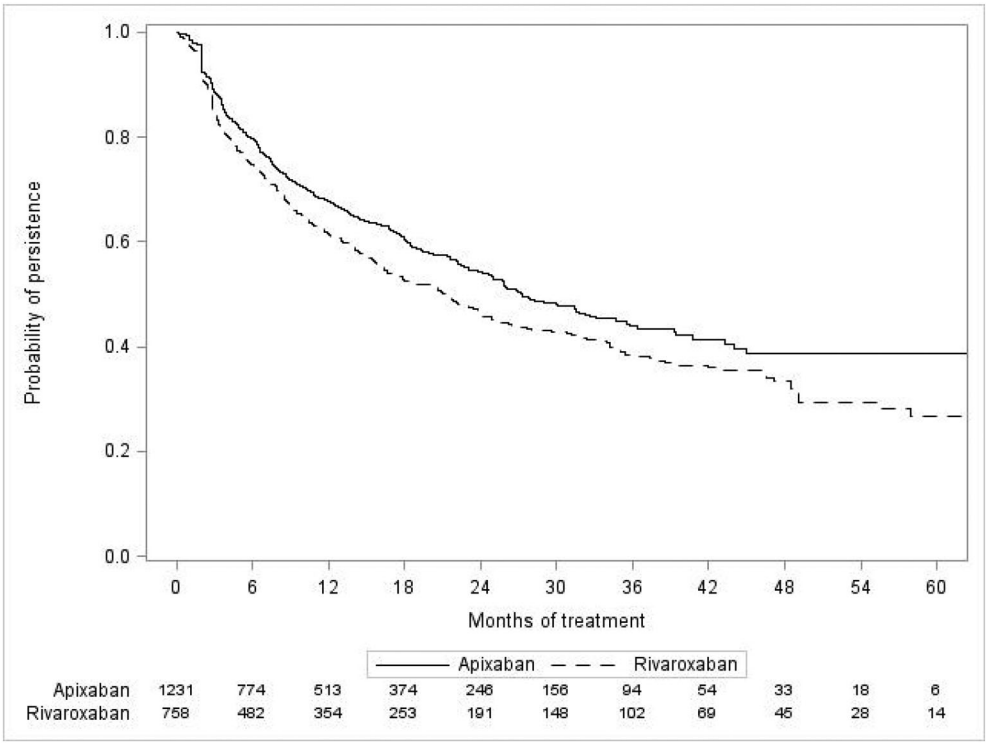

FIGURE A1 Treatment persistence with apixaban versus rivaroxaban in patients with NVAF and liver disease in the first 5 years. NVAF, nonvalvular atrial fibrillation; $P = .0026$

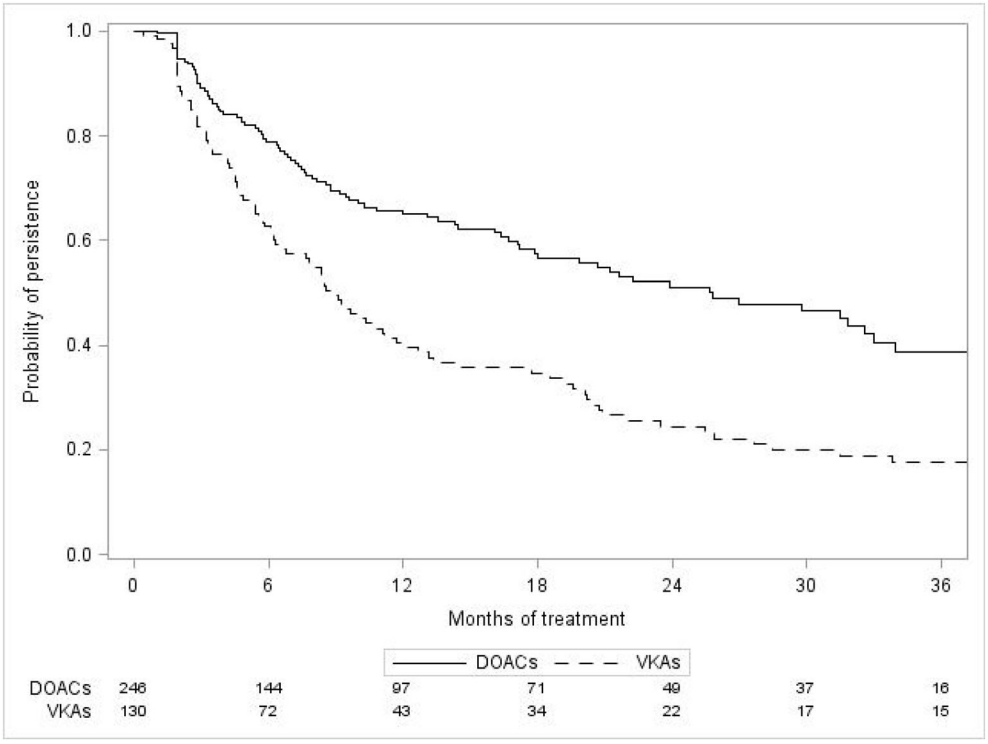

FIGURE A2 Treatment persistence with DOACs versus VKAs in patients with NVAF and liver cirrhosis in the first 3 years. DOACs, direct oral anticoagulants; NVAF, nonvalvular atrial fibrillation; VKAs, vitamin K antagonists; $P < .0001$

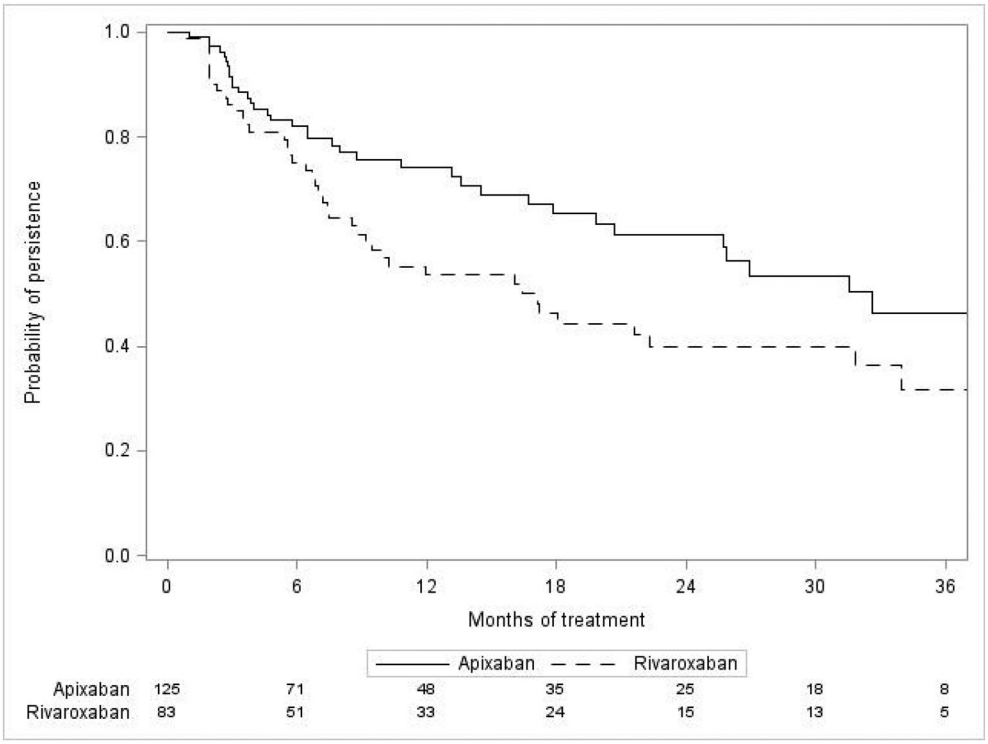

FIGURE A3 Treatment persistence with apixaban versus rivaroxaban in patients with NVAF and liver cirrhosis in the first 3 years. NVAF, nonvalvular atrial fibrillation; $P = .0365$

TABLE A1 Most common liver disease diagnoses

Diagnosis	n	%
Nonalcoholic fatty liver disease	916	28.7
Fatty liver disease unspecified	679	21.8
Abnormal liver function test[a]	326	10.2
Liver cirrhosis	230	7.2
Hemochromatosis	171	5.4
Alcoholic fatty liver disease	123	3.9
Alcoholic liver disease unspecified	96	3.0

[a]In the 6 months before cohort entry.

TABLE A2 Crude and adjusted ORs of treatment initiation with apixaban versus rivaroxaban by baseline characteristics of NVAF patients with liver disease[a]

Characteristic	Apixaban (n = 1231)		Rivaroxaban (n = 758)		Crude OR (95% CI)	Adjusted[e] OR (95% CI)
Age in years, mean (SD)	71.6 (10.6)		69.8 (10.6)			
18-69	481	39.1	353	46.6	(reference)	(reference)
≥70	750	60.9	405	53.4	1.36 (1.13-1.63)	1.28 (1.04-1.58)
Male sex	718	58.3	467	61.6	0.87 (0.73-1.05)	0.98 (0.80-1.20)
Calendar year						
2011-2016	249	20.2	319	42.1	(reference)	(reference)
2017-2020	982	79.8	439	57.9	2.87 (2.35-3.50)	2.85 (2.32-3.50)
Smoking status						
Current	S[b]	S[b]	S[b]	S[b]	0.91 (0.67-1.22)	0.94 (0.68-1.30)
Former	534	43.4	350	46.2	0.87 (0.72-1.06)	0.85 (0.69-1.05)
Never	555	45.1	318	42.0	(reference)	(reference)
Unknown	S[b]	S[b]	S[b]	S[b]	NA	NA

(Continues)

TABLE A2 (Continued)

Characteristic	Apixaban (n = 1231)		Rivaroxaban (n = 758)		Crude OR (95% CI)	Adjusted[e] OR (95% CI)
Body mass index in kg/m^2						
<25	212	17.2	95	12.5	(reference)	(reference)
25-29	376	30.5	242	31.9	0.70 (0.52-0.93)	0.71 (0.52-0.96)
≥30	623	50.6	409	54.0	0.68 (0.52-0.90)	0.74 (0.55-0.99)
Unknown	20	1.6	12	1.6	NA	NA
Comorbidities						
Hypertension	893	72.5	565	74.5	0.90 (0.74-1.11)	0.85 (0.68-1.06)
Ischemic stroke/TIA	245	19.9	118	15.6	1.35 (1.06-1.72)	1.46 (1.12-1.90)
Congestive heart failure	266	21.6	149	19.7	1.13 (0.90-1.41)	1.10 (0.87-1.40)
Hyperlipidaemia	575	46.7	371	48.9	0.91 (0.76-1.10)	0.91 (0.74-1.11)
Coronary artery disease	341	27.7	192	25.3	1.13 (0.92-1.39)	1.20 (0.93-1.56)
Peripheral vascular disease	104	8.5	78	10.3	0.80 (0.59-1.10)	0.76 (0.54-1.06)
Diabetes mellitus	540	43.9	309	40.8	1.14 (0.95-1.36)	1.18 (0.96-1.45)
Any bleeding	63	5.1	31	4.1	1.27 (0.82-1.96)	1.18 (0.74-1.88)
Chronic kidney disease	624	50.7	352	46.4	1.19 (0.99-1.42)	1.12 (0.91-1.38)
Cancer	90	7.3	40	5.3	1.42 (0.96-2.08)	1.29 (0.86-1.94)
Comedications						
Antiplatelets	481	39.1	308	40.6	0.94 (0.78-1.13)	0.85 (0.67-1.09)
NSAIDs	156	12.7	125	16.5	0.74 (0.57-0.95)	0.82 (0.62-1.09)
SSRIs	148	12.0	106	14.0	0.84 (0.64-1.10)	0.86 (0.64-1.14)
Proton pump inhibitors	725	58.9	432	57.0	1.08 (0.90-1.30)	1.08 (0.88-1.32)
H_2 blockers	89	7.2	36	4.8	1.56 (1.05-2.33)	1.44 (0.95-2.18)
CHA_2DS_2-VASC[c]						
0-2	316	25.7	241	31.8	(reference)	
≥3	915	74.3	517	68.2	1.35 (1.11-1.65)	
HAS-BLED[c,d]						
1-2	266	21.6	173	22.8	(reference)	
≥3	965	78.4	585	77.2	1.07 (0.86-1.33)	

CI, confidence interval; CHA_2DS_2-VASC, congestive heart failure, arterial hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; HAS-BLED, uncontrolled arterial hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelets or alcohol-related disorders; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack.

[a]Baseline characteristics presented as numbers and percentages unless indicated otherwise.

[b]Suppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

[c]The analyses for the CHA_2DS_2-VASC and HAS-BLED score were conducted using separate logistic regression models.

[d]Minimum HAS-BLED score was 1 because patients were assumed to have abnormal liver function and maximum HAS-BLED score was 8 because the international normalized ratio was not considered in the calculations.

[e]Adjusted estimates are joint associations and should not be interpreted as causal or as a prediction model.

TABLE A3 Crude and adjusted HRs of treatment switch from rivaroxaban to apixaban versus remaining on rivaroxaban by baseline characteristics of NVAF patients with liver disease[a]

	Switch to apixaban (n = 54)		Remain on rivaroxaban (n = 670)		Crude HR (95% CI)	Adjusted[e] HR (95% CI)
Age in years, mean (SD)	71.0 (9.4)		69.7 (10.6)			
18-69	23	42.6	314	46.9	(reference)	(reference)
≥70	31	57.4	356	53.1	1.23 (0.72-2.11)	0.94 (0.50-1.76)
Male sex	28	51.9	417	62.2	0.65 (0.38-1.11)	0.66 (0.37-1.18)
Calendar year						
2011-2016	25	46.3	267	39.9	(reference)	(reference)
2017-2020	29	53.7	403	60.2	1.47 (0.81-2.65)	1.29 (0.70-2.41)
Smoking status						
Current	S[b]	S[b]	S[b]	S[b]	1.11 (0.44-2.77)	1.54 (0.57-4.10)
Former	28	51.9	306	45.7	1.34 (0.75-2.41)	1.55 (0.84-2.85)
Never	19	35.2	283	42.2	(reference)	(reference)
Unknown	S[b]	S[b]	S[b]	S[b]	NA	NA
Body mass index in kg/m^2						
<25	S[b]	S[b]	S[b]	S[b]	(reference)	(reference)
25-29	15	27.8	217	32.4	0.99 (0.39-2.56)	1.10 (0.42-2.89)
≥30	31	57.4	359	53.6	1.19 (0.50-2.86)	1.22 (0.48-3.05)
Unknown	S[b]	S[b]	S[b]	S[b]	NA	NA
Comorbidities						
Hypertension	45	83.3	498	74.3	1.67 (0.81-3.41)	1.81 (0.82-3.98)
Ischemic stroke/TIA	13	24.1	98	14.6	1.74 (0.93-3.25)	1.94 (0.98-3.84)
Congestive heart failure	12	22.2	131	19.6	1.26 (0.66-2.39)	1.25 (0.64-2.47)
Hyperlipidaemia	24	44.4	330	49.3	0.81 (0.47-1.38)	0.68 (0.38-1.24)
Coronary artery disease	18	33.3	167	24.9	1.58 (0.90-2.78)	1.71 (0.82-3.54)
Peripheral vascular disease	S[b]	S[b]	S[b]	S[b]	0.32 (0.08-1.31)	0.32 (0.08-1.37)
Diabetes mellitus	22	40.7	272	40.6	1.05 (0.61-1.80)	0.95 (0.52-1.74)
Any bleeding	S[b]	S[b]	S[b]	S[b]	1.77 (0.64-4.92)	1.83 (0.62-5.43)
Chronic kidney disease	30	55.6	307	45.8	1.54 (0.90-2.63)	1.52 (0.82-2.81)
Cancer	S[b]	S[b]	S[b]	S[b]	0.68 (0.16-2.77)	0.33 (0.04-2.57)
Comedications						
Antiplatelets	23	42.6	272	40.6	1.04 (0.61-1.79)	0.73 (0.36-1.47)
NSAIDs	9	16.7	109	16.3	0.91 (0.44-1.85)	0.88 (0.41-1.88)
SSRIs	S[b]	S[b]	S[b]	S[b]	0.49 (0.18-1.35)	0.41 (0.14-1.14)
Proton pump inhibitors	37	68.5	375	56.0	1.74 (0.98-3.10)	1.70 (0.92-3.15)
H_2 blockers	S[b]	S[b]	S[b]	S[b]	1.50 (0.47-4.80)	1.39 (0.42-4.62)
CHA_2DS_2-VASC[c]						
0-2	12	22.2	217	32.4	(reference)	
≥3	42	77.8	453	67.6	1.63 (0.86-3.10)	
HAS-BLED[c,d]						
1-2	6	11.1	161	24.0	(reference)	
≥3	48	88.9	509	76.0	2.28 (0.98-5.33)	

CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; CI, confidence interval; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelets or alcohol-related disorders; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack.

[a]Baseline characteristics presented as numbers and percentages unless indicated otherwise.

[b]Suppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

[c]The analyses for the CHA_2DS_2-VASC and HAS-BLED score were conducted using separate Cox proportional hazards models.

[d]Minimum HAS-BLED score was 1 because patients were assumed to have abnormal liver function and maximum HAS-BLED score was 8 because the international normalized ratio was not considered in the calculations.

[e]Adjusted estimates are joint associations and should not be interpreted as causal or as a prediction model.

TABLE A4 Crude and adjusted ORs of treatment initiation with DOACs versus VKAs by baseline characteristics of NVAF patients with liver cirrhosis[a]

Characteristic	DOACs (n = 246)		VKAs (n = 130)		Crude OR (95% CI)	Adjusted[d] OR (95% CI)
Age in years, mean (SD)	71.9 (10.2)		71.7 (8.9)			
18-69	104	42.3	48	36.9	(reference)	(reference)
≥70	142	57.7	82	63.1	0.80 (0.52-1.24)	1.05 (0.58-1.88)
Male sex	141	57.3	69	53.1	1.19 (0.77-1.82)	1.13 (0.63-2.01)
Calendar year						
2011-2016	83	33.7	109	83.9	(reference)	(reference)
2017-2020	163	66.3	21	16.2	10.19 (5.96-17.43)	9.33 (5.17-16.87)
Smoking status						
Current	37	15.0	15	11.5	1.02 (0.51-2.04)	1.02 (0.43-2.43)
Former	100	40.7	70	53.9	0.59 (0.37-0.94)	0.60 (0.34-1.07)
Never	109	44.3	45	34.6	(reference)	(reference)
Body mass index in kg/m^2						
<25	62	25.2	28	21.5	(reference)	(reference)
25-29	77	31.3	32	24.6	1.09 (0.59-2.00)	1.34 (0.64-2.82)
≥30	102	41.5	64	49.2	0.72 (0.42-1.24)	0.70 (0.35-1.41)
Unknown	5	2.0	6	4.6	NA	NA
Comorbidities						
Hypertension	175	71.1	95	73.1	0.91 (0.56-1.46)	0.94 (0.50-1.77)
Ischemic stroke/TIA	40	16.3	26	20.0	0.78 (0.45-1.34)	0.88 (0.44-1.79)
Congestive heart failure	55	22.4	31	23.9	0.92 (0.56-1.52)	1.11 (0.56-2.21)
Hyperlipidaemia	90	36.6	68	52.3	0.53 (0.34-0.81)	0.54 (0.31-0.96)
Coronary artery disease	63	25.6	40	30.8	0.78 (0.48-1.24)	0.91 (0.46-1.81)
Peripheral vascular disease	27	11.0	10	7.7	1.48 (0.69-3.16)	2.14 (0.83-5.55)
Diabetes mellitus	99	40.2	67	51.5	0.63 (0.41-0.97)	0.70 (0.40-1.22)
Any bleeding	11	4.5	6	4.6	0.97 (0.35-2.68)	0.86 (0.25-2.97)
Chronic kidney disease	114	46.3	73	56.2	0.67 (0.44-1.03)	0.70 (0.40-1.22)
Cancer	15	6.1	7	5.4	1.14 (0.45-2.87)	1.63 (0.50-5.30)
Comedications						
Antiplatelets	95	38.6	64	49.2	0.65 (0.42-1.00)	0.94 (0.52-1.70)
NSAIDs	21	8.5	17	13.1	0.62 (0.32-1.22)	0.59 (0.25-1.41)
SSRIs	33	13.4	6	4.6	3.20 (1.31-7.86)	3.38 (1.09-10.50)
Proton pump inhibitors	152	61.8	76	58.5	1.15 (0.75-1.77)	1.23 (0.70-2.16)
H_2 blockers	12	4.9	9	6.9	0.69 (0.28-1.68)	0.84 (0.28-2.57)
CHA_2DS_2-VASC[b]						
0-2	63	25.6	26	20.0	(reference)	
≥3	183	74.4	104	80.0	0.73 (0.43-1.22)	
HAS-BLED[b,c]						
1-2	54	22.0	18	13.9	(reference)	
≥3	192	78.1	112	86.2	0.57 (0.32-1.02)	

CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; CI, confidence interval; DOACs, direct oral anticoagulants; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelets or alcohol-related disorders; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

[a]Baseline characteristics presented as numbers and percentages unless indicated otherwise.

[b]The analyses for the CHA_2DS_2-VASC and HAS-BLED score were conducted using separate logistic regression models.

[c]Minimum HAS-BLED score was 1 because patients were assumed to have abnormal liver function and maximum HAS-BLED score was 8 because the international normalized ratio was not considered in the calculations.

[d]Adjusted estimates are joint associations and should not be interpreted as causal or as a prediction model.

TABLE A5 Crude and adjusted ORs of treatment initiation with apixaban versus rivaroxaban by baseline characteristics of NVAF patients with liver cirrhosis[a]

Characteristic	Apixaban (n = 125)		Rivaroxaban (n = 83)		Crude OR (95% CI)	Adjusted[e] OR (95% CI)
Age in years, mean (SD)	73.2 (10.0)		71.6 (9.8)			
18-69	47	37.6	37	44.6	(reference)	(reference)
≥70	78	62.4	46	55.4	1.34 (0.76-2.35)	1.56 (0.75-3.26)
Male sex	73	58.4	46	55.4	1.13 (0.65-1.98)	1.26 (0.62-2.56)
Calendar year						
2011-2016	27	21.6	43	51.8	(reference)	(reference)
2017-2020	98	78.4	40	48.2	3.90 (2.13-7.15)	4.98 (2.48-9.97)
Smoking status						
Current	15	12.0	15	18.1	0.60 (0.26-1.37)	0.63 (0.23-1.71)
Former	53	42.4	34	41.0	0.93 (0.51-1.70)	0.91 (0.45-1.84)
Never	57	45.6	34	41.0	(reference)	(reference)
Body mass index in kg/m^2						
<25	S[b]	S[b]	S[b]	S[b]	(reference)	(reference)
25-29	37	29.6	29	34.9	0.62 (0.29-1.32)	0.73 (0.31-1.72)
≥30	49	39.2	37	44.6	0.64 (0.31-1.32)	0.73 (0.32-1.68)
Unknown	S[b]	S[b]	S[b]	S[b]	NA	NA
Comorbidities						
Hypertension	91	72.8	56	67.5	1.29 (0.71-2.36)	1.36 (0.63-2.90)
Ischemic stroke/TIA	24	19.2	10	12.1	1.73 (0.78-3.85)	2.68 (1.01-7.09)
Congestive heart failure	30	24.0	18	21.7	1.14 (0.59-2.22)	0.93 (0.42-2.05)
Hyperlipidaemia	42	33.6	32	38.6	0.81 (0.45-1.44)	0.58 (0.29-1.18)
Coronary artery disease	34	27.2	22	26.5	1.04 (0.55-1.94)	1.31 (0.56-3.06)
Peripheral vascular disease	14	11.2	9	10.8	1.04 (0.43-2.52)	1.34 (0.41-4.41)
Diabetes mellitus	48	38.4	33	39.8	0.94 (0.54-1.67)	0.95 (0.47-1.91)
Any bleeding	S[b]	S[b]	S[b]	S[b]	0.38 (0.09-1.65)	0.35 (0.06-2.23)
Chronic kidney disease	59	47.20	36	43.4	1.17 (0.67-2.04)	1.11 (0.55-2.23)
Cancer	S[b]	S[b]	S[b]	S[b]	1.58 (0.40-6.30)	3.66 (0.77-17.52)
Comedications						
Antiplatelets	49	39.2	31	37.4	1.08 (0.61-1.92)	0.96 (0.44-2.08)
NSAIDs	8	6.4	8	9.6	0.64 (0.23-1.78)	0.41 (0.12-1.48)
SSRIs	17	13.6	9	10.8	1.29 (0.55-3.06)	1.38 (0.49-3.84)
Proton pump inhibitors	78	62.4	54	65.1	0.89 (0.50-1.59)	0.76 (0.38-1.52)
H_2 blockers	S[b]	S[b]	S[b]	S[b]	2.77 (0.57-13.38)	4.93 (0.81-30.04)
CHA_2DS_2-VASC[c]						
0-2	26	20.8	24	28.9	(reference)	
≥3	99	79.2	59	71.1	1.55 (0.82-2.94)	
HAS-BLED[c,d]						
1-2	27	21.6	19	22.9	(reference)	
≥3	98	78.4	64	77.1	1.08 (0.55-2.1)	

CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65-74 years, female sex; CI, confidence interval; DOACs, direct oral anticoagulants; HAS-BLED, uncontrolled hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile international normalized ratio, age >65 years, use of NSAIDs or antiplatelets or alcohol-related disorders; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors; TIA, transient ischemic attack; VKAs, vitamin K antagonists.

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[c]The analyses for the CHA_2DS_2-VASC and HAS-BLED score were conducted using separate logistic regression models.

[d]Minimum HAS-BLED score was 1 because patients were assumed to have abnormal liver function and maximum HAS-BLED score was 8 because the international normalized ratio was not considered in the calculations.

[e]Adjusted estimates are joint associations and should not be interpreted as causal or as a prediction model.