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
Direct oral anticoagulants (DOACs) are currently recommended as first-line treatments for stroke prevention in nonvalvular atrial fibrillation (NVAF). 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). 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.

Given these advantages, it has been debated whether treatment persistence with DOACs would be improved compared to VKAs. To answer this question, several studies assessed the persistence with DOACs in the overall NVAF population, generally showing higher estimates than with VKAs. However, there is 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, a high-risk group which accounts for up to 5% of the overall NVAF population. Reasons for the elevated baseline risk of this group include the association between liver disease and an increased risk of both thrombosis and bleeding, as well as the potential effects of hepatic impairment on the pharmacology of DOACs.

Since patients with liver disease were systematically excluded from the landmark RCTs which assessed the efficacy and safety of DOACs, there are no specific recommendations on oral anticoagulation in NVAF patients with liver disease. 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.

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 (i.e., 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 (e.g., 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 (e.g., acute infectious or noninfectious hepatitis, liver hematomata, 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/m², 25-29 kg/m², ≥30 kg/m², 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 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 H₂ blockers (all measured in the year before cohort entry).

We calculated for each cohort member the CHA²DS₂-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 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. 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.

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. 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. 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, intracocular 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. 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,
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 initiatorsswitching 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
| Baseline Characteristics                      | DOACs (n = 2247) | VKAs (n = 920) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------------------|------------------|---------------|-------------------|---------------------|
| **Age in years, mean (SD)**                  |                  |               |                   |                     |
| 18-69                                         | 70.7 (10.6)      | 70.1 (9.7)    |                   |                     |
| ≥70                                           | 1295             | 57.6          | 512               | 1.08 (0.93-1.27)    | 1.06 (0.87-1.31)   |
| **Male sex**                                  |                  |               |                   |                     |
|                                               | 1349             | 60.0          | 560               | 0.97 (0.83-1.13)    | 1.10 (0.90-1.35)   |
| **Calendar year**                             |                  |               |                   |                     |
| 2011-2016                                     | 642              | 28.6          | 799               | (reference)         | (reference)        |
| 2017-2020                                     | 1605             | 71.4          | 121               | 16.51 (13.36-20.41) | 16.58 (13.31-20.64) |
| **Smoking status**                            |                  |               |                   |                     |
| Current                                      | 54                 | 23            | 92                | 0.99 (0.76-1.29)    | 0.95 (0.69-1.32)   |
| Former                                       | 999              | 44.5          | 444               | 0.86 (0.73-1.01)    | 0.88 (0.72-1.08)   |
| Never                                        | 988              | 44.0          | 376               | (reference)         | (reference)        |
| Unknown                                      | 35               | 1.6           | 21                | NA                 | NA                 |
| **Body mass index in kg/m²**                  |                  |               |                   |                     |
| <25                                          | 347              | 15.4          | 133               | 0.88 (0.70-1.10)    | 0.88 (0.67-1.17)   |
| 25-29                                        | 704              | 31.3          | 260               | 1.04 (0.81-1.33)    | 1.08 (0.80-1.45)   |
| ≥30                                          | 1161             | 51.7          | 506               | 1.08 (0.80-1.30)    | 1.08 (0.72-1.35)   |
| Unknown                                      | 35               | 1.6           | 21                | NA                 | NA                 |
| **Comorbidities**                             |                  |               |                   |                     |
| Arterial hypertension                        | 1638             | 72.9          | 684               | 0.93 (0.78-1.11)    | 0.94 (0.75-1.17)   |
| Ischemic stroke/TIA                          | 408              | 18.2          | 149               | 1.15 (0.94-1.41)    | 1.44 (1.12-1.85)   |
| Congestive heart failure                     | 463              | 20.6          | 207               | 0.89 (0.74-1.08)    | 0.90 (0.75-1.19)   |
| Hyperlipidaemia                              | 1068             | 47.5          | 421               | 1.07 (0.92-1.25)    | 1.37 (1.12-1.68)   |
| Coronary artery disease                      | 596              | 26.5          | 262               | 0.91 (0.76-1.08)    | 1.02 (0.81-1.30)   |
| Peripheral vascular disease                  | 198              | 8.8           | 76                | 1.07 (0.81-1.42)    | 1.17 (0.83-1.64)   |
| Diabetes mellitus                            | 953              | 42.4          | 412               | 0.91 (0.78-1.06)    | 0.87 (0.71-1.06)   |
| Any bleeding                                 | 111              | 4.9           | 37                | 1.24 (0.85-1.81)    | 1.32 (0.83-2.09)   |
| Chronic kidney disease                       | 1092             | 48.6          | 464               | 0.93 (0.80-1.08)    | 0.93 (0.76-1.13)   |
| Cancer                                       | 143              | 6.4           | 54                | 1.09 (0.79-1.51)    | 0.80 (0.54-1.20)   |
| **Comedications**                             |                  |               |                   |                     |
| Antiplatelet agents                          | 899              | 40.0          | 489               | 0.59 (0.50-0.69)    | 0.66 (0.53-0.82)   |
| NSAIDs                                       | 317              | 14.1          | 130               | 1.00 (0.80-1.24)    | 1.24 (0.95-1.63)   |
| SSRIs                                        | 300              | 13.4          | 80                | 1.62 (1.25-2.10)    | 1.50 (1.09-2.04)   |
| Proton pump inhibitors                       | 1299             | 57.8          | 505               | 1.13 (0.97-1.31)    | 1.07 (0.88-1.30)   |
| H₂ blockers                                  | 135              | 6.0           | 68                | 0.80 (0.59-1.08)    | 0.67 (0.46-0.97)   |
| **CHA²DS²-VASC**                             |                  |               |                   |                     |
| 0-2                                          | 647              | 28.8          | 265               | (reference)         | (reference)        |
| ≥3                                           | 1600             | 71.2          | 655               | 1.00 (0.85-1.19)    |                     |
| **HAS-BLED**                                 |                  |               |                   |                     |
| 1-2                                          | 491              | 21.9          | 182               | (reference)         | (reference)        |
| ≥3                                           | 1756             | 78.2          | 738               | 0.88 (0.73-1.07)    |                     |

CHA²DS²-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.

*Baseline characteristics presented as numbers and percentages unless indicated otherwise.
*Adjusted estimates are joint association and should not be interpreted as causal or as a prediction model.
*Suppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.
*The analyses for the CHA²DS²-VASC and HAS-BLED score were conducted using separate logistic regression models.
*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

|                            | Switch to DOACs (n = 323) | Remain on VKAs (n = 597) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-----------------------------|---------------------------|---------------------------|-------------------|----------------------|
| **Age in years, mean (SD)** |                           |                           |                   |                      |
| 18-69                       | 69.3 (10.0)               | 70.6 (9.6)                |                   |                      |
| ≥70                         | 160 49.5                  | 248 41.5                  | 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                     | Sb Sb                     | Sb Sb                     | 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                     | Sb Sb                     | Sb Sb                     | NA                | NA                   |
| **Body mass index in kg/m²**|                           |                           |                   |                      |
| <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)     |
| **Comediations**            |                           |                           |                   |                      |
| 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)     |
| H2 blockers                 | 23 7.1                    | 45 7.5                    | 1.10 (0.72-1.68)  | 1.04 (0.67-1.60)     |
| **CHA2DS2-VASCc**           |                           |                           |                   |                      |
| 0-2                         | 114 35.3                  | 151 25.3                  | (reference)       |                      |
| ≥3                          | 209 64.7                  | 446 74.7                  | 0.89 (0.71-1.13)  |                      |
| **HAS-BLEDc,d**             |                           |                           |                   |                      |
| 1-2                         | 74 22.9                   | 108 18.1                  | (reference)       |                      |
| ≥3                          | 249 77.1                  | 489 81.9                  | 0.87 (0.67-1.13)  |                      |

CHA2DS2-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.

*Baseline characteristics presented as numbers and percentages unless indicated otherwise.

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

CHA2DS2-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.

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*Baseline characteristics presented as numbers and percentages unless indicated otherwise.

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

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. 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. Thus, the predominance of apixaban and rivaroxaban in our study seems to be related to their increased use in the overall NVAF population, 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. Moreover, the fact that the results did not materially change when focusing 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. Since apixaban has been associated with a decreased risk of bleeding compared to rivaroxaban, 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. 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 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.

ACKNOWLEDGMENTS

Dr Douros is supported by a salary support award from the Fonds de recherche du Québec – Santé (FRQS). Dr Filion is supported by a senior salary support award from the FRQS and a William Dawson Scholar award from McGill University. Dr Platt holds the Albert Boehringer I Chair in Pharmacoepidemiology. Dr Renoux is supported...
by a salary support award from the FRQS. This study was supported by the Canadian Institutes of Health Research (Grant number: PJT-165954).

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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How to cite this article: Douros A, Cui Y, Platt RW, Filion KB, Sebastiani G, Renoux C. Utilization and long-term persistence of direct oral anticoagulants among patients with nonvalvular atrial fibrillation and liver disease. *Br J Clin Pharmacol*. 2022;88(3):994-1009. doi:10.1111/bcp.15046
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; $P < .0001$
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\(d\) OR (95% CI) |
|---------------------------------------|----------------------|-----------------------|-------------------|---------------------------|
| Age in years, mean (SD)               | 71.6 (10.6)          | 69.8 (10.6)           | (reference)       | (reference)               |
| 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                         | 249                  | 20.2                  | 319               | 42.1                      | (reference)               | (reference)               |
| 2011-2016                             | 982                  | 79.8                  | 439               | 57.9                      | 2.87 (2.35-3.50)          | 2.85 (2.32-3.50)          |
| Smoking status                        | Current              | 534                   | 43.4              | 350                        | 46.2                      | 0.87 (0.72-1.06)          | 0.85 (0.69-1.05)          |
|                                       | Former               | 555                   | 45.1              | 318                        | 42.0                      | (reference)               | (reference)               |
|                                       | Never                | 83                    | 6.5               | 33                         | 4.4                       | NA                        | NA                        |

\(a\)In the 6 months before cohort entry.

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 A2  (Continued)

| Characteristic | Apixaban (n = 1231) | Rivaroxaban (n = 758) | Crude OR (95% CI) | Adjusted\* OR (95% CI) |
|----------------|----------------------|-----------------------|------------------|------------------------|
| **Body mass index in kg/m²** | | | | |
| <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) |
| H₂ blockers | 89 | 7.2 | 36 | 4.8 | 1.56 (1.05-2.33) | 1.44 (0.95-2.18) |
| **CHA²DS²-VASC** | | | | |
| 0-2 | 316 | 25.7 | 241 | 31.8 | (reference) | (reference) |
| ≥3 | 915 | 74.3 | 517 | 68.2 | 1.35 (1.11-1.65) | |
| **HAS-BLED** | | | | |
| 0-2 | 316 | 25.7 | 241 | 31.8 | (reference) | (reference) |
| ≥3 | 965 | 78.4 | 585 | 77.2 | 1.07 (0.86-1.33) | |

CI, confidence interval; CHA²DS²-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.

\*Baseline characteristics presented as numbers and percentages unless indicated otherwise.

\*Suppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

\*The analyses for the CHA²DS²-VASC and HAS-BLED score were conducted using separate logistic regression models.

\*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.

\*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

| Characteristic | 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) | (reference) | (reference) |
| 18-69 | 23 | 42.6 | 314 | 46.9 | 1.23 (0.72-2.11) | 0.94 (0.50-1.76) |
| ≥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 | $^b$ | $^b$ | $^b$ | $^b$ | 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 | $^b$ | $^b$ | $^b$ | $^b$ | NA | NA |
| Body mass index in kg/m² | | | | | | |
| <25 | $^b$ | $^b$ | $^b$ | $^b$ | (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 | $^b$ | $^b$ | $^b$ | $^b$ | 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 | $^b$ | $^b$ | $^b$ | $^b$ | 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 | $^b$ | $^b$ | $^b$ | $^b$ | 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 | $^b$ | $^b$ | $^b$ | $^b$ | 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 | $^b$ | $^b$ | $^b$ | $^b$ | 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) |
| H₂ blockers | $^b$ | $^b$ | $^b$ | $^b$ | 1.50 (0.47-4.80) | 1.39 (0.42-4.62) |
| CHA2DS2-VASCc | | | | | | |
| 0-2 | 12 | 22.2 | 217 | 32.4 | (reference) | (reference) |
| ≥3 | 42 | 77.8 | 453 | 67.6 | 1.63 (0.86-3.10) | (reference) |
| HAS-BLEDc,d | | | | | | |
| 1-2 | 6 | 11.1 | 161 | 24.0 | (reference) | (reference) |
| ≥3 | 48 | 88.9 | 509 | 76.0 | 2.28 (0.98-5.33) | (reference) |

CHA2DS2-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.

aBaseline characteristics presented as numbers and percentages unless indicated otherwise.

bSuppressed: numbers <5 not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

The analyses for the CHA2DS2-VASC and HAS-BLED score were conducted using separate Cox proportional hazards models.

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.

Adjusted estimates are joint associations and should not be interpreted as causal or as a prediction model.
| Characteristic                              | DOACs (n = 246) | VKAs (n = 130) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------------|----------------|----------------|------------------|---------------------|
| Age in years, mean (SD)                   | 71.9 (10.2)    | 71.7 (8.9)     | (reference)      | (reference)         |
| 18–69                                      | 104            | 42.3           | 48               | 36.9 (0.52-1.24)    |
| ≥70                                        | 142            | 57.7           | 82               | 63.1               |
| Male sex                                   | 141            | 57.3           | 69               | 53.1 (0.77-1.82)    |
| Calendar year                              |                |                |                  |                     |
| 2011–2016                                  | 83             | 33.7           | 109              | 83.9 (reference)    |
| 2017–2020                                  | 163            | 66.3           | 21               | 16.2 (10.19-17.43)  |
| Smoking status                             |                |                |                  |                     |
| Current                                    | 37             | 15.0           | 15               | 11.5 (1.02 (0.51-2.04)) |
| Former                                     | 100            | 40.7           | 70               | 53.9 (0.59 (0.37-0.94)) |
| Never                                      | 109            | 44.3           | 45               | 34.6 (0.72 (0.42-1.24)) |
| Body mass index in kg/m²                   |                |                |                  |                     |
| <25                                        | 62             | 25.2           | 28               | 21.5 (reference)    |
| 25–29                                      | 77             | 31.3           | 32               | 24.6 (1.09 (0.59-2.00)) |
| ≥30                                        | 102            | 41.5           | 64               | 49.2 (0.72 (0.42-1.24)) |
| Unknown                                    | 5              | 2.0            | 6                | 4.6 (NA)           |
| Comorbidities                              |                |                |                  |                     |
| Hypertension                               | 175            | 71.1           | 95               | 73.1 (0.91 (0.56-1.46)) |
| Ischemic stroke/TIA                        | 40             | 16.3           | 26               | 20.0 (0.78 (0.45-1.34)) |
| Congestive heart failure                   | 55             | 22.4           | 31               | 23.9 (0.92 (0.56-1.52)) |
| Hyperlipidaemia                            | 90             | 36.6           | 68               | 52.3 (0.53 (0.34-0.81)) |
| Coronary artery disease                    | 63             | 25.6           | 40               | 30.8 (0.78 (0.48-1.24)) |
| Peripheral vascular disease                | 27             | 11.0           | 10               | 7.7 (1.48 (0.69-3.16)) |
| Diabetes mellitus                          | 99             | 40.2           | 67               | 51.5 (0.63 (0.41-0.97)) |
| Any bleeding                               | 11             | 4.5            | 6                | 4.6 (0.97 (0.35-2.68)) |
| Chronic kidney disease                     | 114            | 46.3           | 73               | 56.2 (0.67 (0.44-1.03)) |
| Cancer                                     | 15             | 6.1            | 7                | 5.4 (1.14 (0.45-2.87)) |
| Comedications                              |                |                |                  |                     |
| Antiplautelets                             | 95             | 38.6           | 64               | 49.2 (0.65 (0.42-1.00)) |
| NSAIDs                                     | 21             | 8.5            | 17               | 13.1 (0.62 (0.32-1.22)) |
| SSRIs                                      | 33             | 13.4           | 6                | 4.6 (3.20 (1.31-7.86)) |
| Proton pump inhibitors                     | 152            | 61.8           | 76               | 58.5 (1.15 (0.75-1.77)) |
| H₂ blockers                                | 12             | 4.9            | 9                | 6.9 (0.69 (0.28-1.68)) |
| CHA₂DS₂-VASCb                              |                |                |                  |                     |
| 0–2                                        | 63             | 25.6           | 26               | 20.0 (0.73 (0.43-1.22)) |
| ≥3                                         | 183            | 74.4           | 104              | 80.0 (0.57 (0.32-1.02)) |
| HAS-BLEDb,c                                |                |                |                  |                     |
| 1–2                                        | 54             | 22.0           | 18               | 13.9 (reference)    |
| ≥3                                         | 192            | 78.1           | 112              | 86.2 (0.57 (0.32-1.02)) |

CHA₂DS₂-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.

aBaseline characteristics presented as numbers and percentages unless indicated otherwise.

bThe analyses for the CHA₂DS₂-VASC and HAS-BLED score were conducted using separate logistic regression models.

cMinimum 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.

dAdjusted 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

| Characteristic                              | Apixaban (n = 125) | Rivaroxaban (n = 83) | Crude OR (95% CI) | Adjusted* OR (95% CI) |
|---------------------------------------------|--------------------|----------------------|-------------------|-----------------------|
| **Age in years, mean (SD)**                 | 73.2 (10.0)        | 71.6 (9.8)           |                   |                       |
| 18-69                                        | 47                 | 37                   | 44.6 (reference)  |                       |
| ≥70                                          | 78                 | 46                   | 55.4              | 1.13 (0.65-1.98)      |
| Male sex                                     | 73                 | 46                   | 55.4              | 1.26 (0.62-2.56)      |
| **Calendar year**                            |                    |                      |                   |                       |
| 2011-2016                                    | 27                 | 43                   | 51.8 (reference)  |                       |
| 2017-2020                                    | 98                 | 40                   | 48.2              | 3.90 (2.13-7.15)      |
| Smoking status                               |                    |                      |                   |                       |
| Current                                      | 15                 | 15                   | 18.1              | 0.60 (0.26-1.37)      |
| Former                                       | 53                 | 34                   | 41.0              | 0.93 (0.51-1.70)      |
| Never                                        | 57                 | 34                   | 41.0              | (reference)           |
| **Body mass index in kg/m²**                 |                    |                      |                   |                       |
| <25                                          | Sb                 | Sb                   | Sb                | Sb                    |
| 25-29                                        | 37                 | 29                   | 34.9              | 0.62 (0.29-1.32)      |
| ≥30                                          | 49                 | 37                   | 44.6              | 0.64 (0.31-1.32)      |
| Unknown                                      | Sb                 | Sb                   | Sb                | NA                    |
| **Comorbidities**                            |                    |                      |                   |                       |
| Hypertension                                 | 91                 | 56                   | 67.5              | 1.29 (0.71-2.36)      |
| Ischemic stroke/TIA                          | 24                 | 10                   | 12.1              | 1.73 (0.78-3.85)      |
| Congestive heart failure                     | 30                 | 18                   | 21.7              | 1.14 (0.59-2.22)      |
| Hyperlipidaemia                              | 42                 | 32                   | 38.6              | 0.81 (0.45-1.44)      |
| Coronary artery disease                      | 34                 | 22                   | 26.5              | 1.04 (0.55-1.94)      |
| Peripheral vascular disease                  | 14                 | 9                    | 10.8              | 1.04 (0.43-2.52)      |
| Diabetes mellitus                            | 48                 | 33                   | 39.8              | 0.94 (0.54-1.67)      |
| Any bleeding                                 | Sb                 | Sb                   | Sb                | Sb                    |
| Chronic kidney disease                       | 59                 | 36                   | 43.4              | 1.17 (0.67-2.04)      |
| Cancer                                       | Sb                 | Sb                   | Sb                | 1.58 (0.40-6.30)      |
| **Comedications**                            |                    |                      |                   |                       |
| Antiplatelets                                | 49                 | 31                   | 37.4              | 1.08 (0.61-1.92)      |
| NSAIDs                                       | 8                  | 8                    | 9.6               | 0.64 (0.23-1.78)      |
| SSRIs                                        | 17                 | 9                    | 10.8              | 1.29 (0.55-3.06)      |
| Proton pump inhibitors                       | 78                 | 54                   | 65.1              | 0.89 (0.50-1.59)      |
| H₂ blockers                                  | Sb                 | Sb                   | Sb                | 2.77 (0.57-13.38)     |
| **CHA₂DS₂-VASC**                             |                    |                      |                   |                       |
| 0-2                                          | 26                 | 24                   | 28.9              | (reference)           |
| ≥3                                           | 99                 | 59                   | 71.1              | 1.55 (0.82-2.94)      |
| **HAS-BLED**                                 |                    |                      |                   |                       |
| 1-2                                          | 27                 | 19                   | 22.9              | (reference)           |
| ≥3                                           | 98                 | 64                   | 77.1              | 1.08 (0.55-2.1)       |

CHA₂DS₂-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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