ORIGINAL RESEARCH

Prescribing Trends of Oral Anticoagulants in US Patients With Cirrhosis and Nonvalvular Atrial Fibrillation

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BACKGROUND: Many patients with cirrhosis have concurrent nonvalvular atrial fibrillation (NVAF). Data are lacking regarding recent oral anticoagulant (OAC) usage trends among US patients with cirrhosis and NVAF.

METHODS AND RESULTS: Using MarketScan claims data (2012–2019), we identified patients with cirrhosis and NVAF eligible for OACs (CHA₂DS₂-VASc score \geq 2 [men] or \geq 3 [women]). We calculated the yearly proportion of patients prescribed a direct OAC (DOAC), warfarin, or no OAC. We stratified by high-risk features (decompensated cirrhosis, thrombocytopenia, coagulopathy, chronic kidney disease, or end-stage renal disease). Among 32 487 patients (mean age=71.6 years, 38.5% women, 15.1% with decompensated cirrhosis, mean CHA₂DS₂-VASc=4.2), 44.6% used OACs within 180 days of NVAF diagnosis, including DOACs (20.2%) or warfarin (24.4%). Compared with OAC nonusers, OAC users were less likely to have decompensated cirrhosis (18.6% versus 10.7%), thrombocytopenia (19.5% versus 12.5%), or chronic kidney disease/end-stage renal disease (15.5% versus 14.0%). Between 2012 and 2019, warfarin use decreased by 21.0% (32.0% to 11.0%), whereas DOAC use increased by 30.6% (7.4% to 38.0%), and among all DOACs between 2012 and 2019, apixaban was the most commonly prescribed (46.1%). Warfarin use decreased in all subgroups, including in compensated and decompensated cirrhosis, thrombocytopenia, coagulopathy, chronic kidney disease/end-stage renal disease, thrombocytopenia, coagulopathy, by 30.6% (7.4% to 38.0%), and among all DOACs between 2012 and 2019, apixaban was the most commonly prescribed (46.1%). Warfarin use decreased and DOAC use increased in all subgroups, including in compensated and decompensated cirrhosis, thrombocytopenia, coagulopathy, chronic kidney disease/end-stage renal disease, and across CHA₂DS₂-VASc categories. Among OAC users (2012–2019), DOAC use increased by 58.9% (18.7% to 77.6%). Among DOAC users, the greatest proportional increase was with apixaban (61.2%; *P*<0.001).

CONCLUSIONS: Among US patients with cirrhosis and NVAF, DOAC use has increased substantially and surpassed warfarin, including in decompensated cirrhosis. Nevertheless, >55% of patients remain untreated, underscoring the need for clearer treatment guidance.

Key Words: anticoagulation atrial fibrillation cirrhosis usage

Over the past decade, the prevalence of cirrhosis has doubled in the United States,^{1,2} and rates of cirrhosis-related hospitalizations and mortality are projected to triple by the year 2030.³ Nonvalvular atrial fibrillation (NVAF) and its thromboembolic sequelae disproportionately affect up to 15% of patients with cirrhosis and lead to substantial excess morbidity and mortality.^{4,5} For most adults with NVAF, there is a clear net clinical benefit in favor of initiating oral anticoagulants (OACs)

for the prevention of major thromboembolic events.⁶ Furthermore, over the past decade, studies in the general population with NVAF have demonstrated that direct oral anticoagulants (DOACs; ie, apixaban, rivaroxaban, dabigatran, or edoxaban) are equivalent or superior to warfarin for stroke prevention, while consistently conferring a much lower risk of intracranial hemorrhage.^{7–13} However, the optimal OAC strategy for patients with cirrhosis and NVAF is still unclear, as patients with cirrhosis

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CLINICAL PERSPECTIVE

What Is New?

- This is the first nationwide US study to evaluate recent changes in prescribing trends of specific oral anticoagulants (OACs) in patients with cirrhosis and nonvalvular atrial fibrillation.
- Between 2012 and 2019, over 50% of patients with cirrhosis and nonvalvular atrial fibrillation did not use any OACs, despite having an elevated stroke risk; however, direct OAC use increased substantially over that period and now surpasses warfarin use, even among patients with decompensated cirrhosis, thrombocytopenia, and coagulopathy.
- Among direct OAC users, the greatest proportional increase in use over time was found with apixaban.

What Are the Clinical Implications?

- Currently, data are lacking regarding the safety and effectiveness of direct OACs in patients with cirrhosis and nonvalvular atrial fibrillation.
- Yet, this study demonstrates that a growing number of patients with cirrhosis and nonvalvular atrial fibrillation are using direct OACs, including high-risk patients with decompensated cirrhosis, thrombocytopenia, or coagulopathy.
- Given the excess risks of bleeding and thrombosis that accompany cirrhosis, robust data are urgently needed to help define the optimal OAC strategy for this vulnerable population.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulant
HRS	hepatorenal syndrome
LAA	left atrial appendage
NVAF	nonvalvular atrial fibrillation
OAC	oral anticoagulant

were systematically excluded from all of the major OAC randomized controlled trials for NVAF, largely because of concerns regarding potential bleeding risks in the setting of coagulopathy, thrombocytopenia, and altered hepatic drug metabolism. Given the lack of robust data in this vulnerable population, current guidelines for the management of atrial fibrillation do not include specific OAC recommendations for patients with cirrhosis,^{14,15} who are at increased risk of both bleeding and thrombotic events.

To date, little is known about how prescribing trends of DOACs and warfarin have changed over time in US patients with cirrhosis and NVAF. Given the disproportionate burden of NVAF in cirrhosis, understanding these usage patterns represents an important unmet need. Thus, we sought to examine recent trends in prescribing patterns of OACs, including warfarin and DOACs, among US patients with cirrhosis and NVAF.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files).

The use of this data set for research was approved by the institutional review board (#2021P003597) of the Brigham and Women's Hospital, Boston, MA, and a data use agreement is in place.

Data Sources

This study used longitudinal claims data from a nationwide, US administrative data set, IBM MarketScan. MarketScan includes patient-level information from over 245 million unique individuals since 1995, who are commercially insured or who have primary traditional (parts A and B but not D) Medicare insurance plus a supplemental health plan with a pharmacy benefit, permitting construction of a nationally representative sample of Americans with employer-provided health insurance. For each insured individual. MarketScan includes demographic information, health plan enrollment status, and longitudinal, patient-level information regarding all reimbursed medical services, including inpatient and outpatient clinical diagnoses and procedures, together with records of all dispensed prescription medications, including medication start date, number of refills, strength, quantity, and days' supply.

Study Population

The study cohort included all patients over the age of 18 years with cirrhosis and a new diagnosis of NVAF in MarketScan, between January 1, 2012, and December 31, 2019. The date of the first recorded diagnosis of NVAF was defined as the cohort entry date, and all patients were required to have at least 6 months of continuous enrollment with medical and prescription coverage before cohort entry, which was defined as the baseline assessment period. Based on data ascertained during the baseline assessment period, we required the study population to have (1) CHA_2DS_2VASc score ≥ 2 (among men) or ≥ 3 (among women), (2) no valvular heart disease or mechanical heart valve, and (3) a diagnosis of cirrhosis (see Table S1 for details). Cirrhosis was defined as at least 1 inpatient or at least 2 outpatient International Classification of Diseases, Ninth Revision (ICD-9) codes (571.2, 571.5, 571.6) or Tenth Revision (ICD-10) codes (K70.3, K74, K74.3, K74.4, K74.5, K74.6, K74.60, K74.69). In previous validation studies, analogous *ICD-9* and *ICD-10* claims-based definitions of cirrhosis have yielded positive predictive values consistently >85% to 90%.¹⁶⁻²⁰ Atrial fibrillation was defined as at least 1 inpatient or at least 1 outpatient *ICD-9* code (427.3, 427.31, 427.32) or *ICD-10* code (I48.0–4, I48.91, I48.92), which has been shown in prior validation studies to have a positive predictive value between 84% and 96%²¹⁻²⁴ (median overall positive predictive value of 87%).²⁵

Patient Characteristics and Medication Use

Information regarding patient characteristics, including demographics, clinical comorbidities, and medication use was ascertained for each patient during the baseline assessment period. Clinical characteristics included age, sex, calendar year, severity of cirrhosis (defined by prior decompensation events, including ascites, spontaneous bacterial peritonitis, bleeding esophageal varices, hepatic encephalopathy, and hepatorenal syndrome), coagulopathy, thrombocytopenia, prior bleeding events, chronic kidney disease or end-stage renal disease (CKD/ESRD), CHA2DS2VASc score (calculated as 1 point each for congestive heart failure, hypertension, age ≥75 [point doubled], diabetes, prior stroke or transient ischemic attack or thromboembolism [point doubled], vascular disease, age 65-74, female sex), and HAS-BLED score (calculated as 1 point each for hypertension, abnormal renal function, abnormal liver function or cirrhosis [all patients received this point], prior stroke, prior major bleeding or predisposition to bleeding, a labile international normalized ratio, age >65 years, prior alcohol or drug use history, or use of medications that predispose to bleeding).^{14,26} All comorbidities were identified by ICD-9 and ICD-10 codes (see Table S1 for details).

Within the study cohort, the primary outcome was prescription of an OAC (including warfarin and the individual DOACs, apixaban, rivaroxaban, or dabigatran) in the 6 months following (and including) the cohort entry date, between 2012 and 2019.

Statistical Analysis

We stratified the OAC usage assessment by calendar year of cohort entry date. We assessed usage patterns of warfarin and DOACs (ie, use of any OAC in the 180 days following the cohort entry date) and the proportion of nonusers (ie, no OAC use in the 180 days following the cohort entry date). Patient characteristics at the time of cohort entry were cross-tabulated according to OAC use overall and according to warfarin or DOAC use and summarized with descriptive statistics. Subgroup analyses were conducted in patients with and without

decompensated cirrhosis, underlying coagulopathy, thrombocytopenia, prior bleeding events, and CKD/ ESRD, and based on CHA₂DS₂VASc category (ie, <5 versus \geq 5). We also conducted additional analyses according to age categories (<65 years, 65 to <75 years, and ≥75 years). We used the Cochran-Armitage test to assess time trends of OAC use.²⁷ In additional analyses, we identified patients who underwent left atrial appendage (LAA) closure within the original 180day follow-up period, as well as those who underwent LAA closure at any time point of follow-up. Finally, in sensitivity analyses, we restricted the study population to new OAC initiators, by further excluding any patient with an OAC prescription during the 6-month baseline assessment period, before the cohort entry date. All analyses were conducted using the Aetion platform and R, version 3.1.2.5 (R Foundation for Statistical Computing), which has been previously validated for use in nonrandomized studies^{28,29} and for predicting clinical trial findings.³⁰

RESULTS

We identified a total of 32487 patients in the MarketScan cohort between 2012 and 2019 with cirrhosis and NVAF, with a mean age of 71.6 years (38.5% women), and a mean CHA₂DS₂VASc score of 4.2, and a mean HASBLED score was 2.3 (Table). Among them, 15.1% had decompensated cirrhosis (including 10.2% with ascites or spontaneous bacterial peritonitis or hepatorenal syndrome [HRS], 10.5% with hepatic encephalopathy, and 7.4% with esophageal varices), 16.3% had thrombocytopenia, 22.7% had coagulopathy, 14.8% had CKD/ESRD, and 2.7% had a history of major bleeding events.

Within the study cohort, 14501 patients (44.6%) used OACs within 180 days of NVAF diagnosis, including 6560 (20.2%) DOAC users and 7941 (24.4%) warfarin users (Table). Compared with OAC nonusers, OAC users were less likely to have decompensated cirrhosis (18.6% versus 10.7%), hepatic encephalopathy (12.5% versus 7.7%), ascites or spontaneous bacterial peritonitis or HRS (12.7% versus 6.9%), or esophageal varices (9.0% versus 5.4%), and they also were less likely to have thrombocytopenia (19.5% versus 12.5%) or CKD/ESRD (15.5% versus 14.0%). The 2 groups were broadly similar in terms of age, sex, underlying coagulopathy, prior major bleeding events, and both CHA₂DS₂VASc and HASBLED scores (Table). Among all 32487 patients, 24 (<0.1%) underwent LAA closure within 180 days of NVAF diagnosis, and only 90 patients (0.3%) underwent LAA closure at any time after NVAF diagnosis. Among those 90 patients, 32 (35.6%) had decompensated cirrhosis, 57 (63.3%) had a prior major bleeding event, and 11 (12.2%) had CKD.

Table.	Characteristics of Patients With Cirrhosis and Nonvalvular Atrial Fibrillation in MarketScan (2012–2019)
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Characteristics*	All patients	Nonuse [†]	Any OAC	Warfarin	DOAC
Number of patients	32487	17986	14501	7941	6560
Female sex	12517 (38.5)	7230 (40.2)	5263 (36.3)	3028 (35.4)	2460 (37.5)
Age, y,- mean (SD)	71.6 (11.9)	70.9 (12.1)	72.6 (11.4)	73.3 (11.4)	71.6 (11.4)
Calendar year, n (%) [‡]					
2012	6916 (21.3)	4191 (60.6)	2725 (39.4)	2213 (32.0)	512 (7.4)
2013	5109 (15.7)	2886 (56.5)	2223 (43.5)	1528 (29.9)	695 (13.6)
2014	5132 (15.8)	2799 (54.5)	2333 (45.5)	1356 (26.4)	977 (19.0)
2015	4085 (12.6)	2197 (53.8)	1888 (46.2)	999 (24.5)	889 (21.8)
2016	3932 (12.1)	2094 (53.3)	1838 (46.7)	843 (21.4)	995 (25.3)
2017	2926 (9.0)	1549 (52.9)	1377 (47.1)	487 (16.6)	890 (30.4)
2018	2138 (6.6)	1122 (52.5)	1016 (47.5)	268 (12.5)	748 (35.0)
2019	2249 (6.9)	1148 (51.0)	1101 (49.0)	247 (11.0)	854 (38.0)
Comorbidities, %					
Decompensated cirrhosis	4897 (15.1)	3345 (18.6)	1552 (10.7)	821 (9.6)	731 (11.1)
Ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome	3329 (10.2)	2284 (12.7)	1045 (6.9)	556 (6.5)	489 (7.5)
Hepatic encephalopathy	3399 (10.5)	2248 (12.5)	1151 (7.7)	559 (7.0)	592 (9.0)
Esophageal varices	2419 (7.4)	1618 (9.0)	801 (5.4)	429 (5.4)	372 (5.7)
Thrombocytopenia	5324 (16.3)	3507 (19.5)	1817 (12.5)	1000 (12.6)	817 (12.5)
Coagulopathy	7388 (22.7)	4155 (23.1)	3233 (22.3)	2052 (25.8)	1181 (18.0)
Prior major bleeding event	889 (2.7)	467 (2.6)	422 (2.9)	258 (3.2)	164 (2.5)
Chronic kidney disease or end-stage renal disease	4810 (14.8)	2787 (15.5)	2023 (14.0)	1377 (17.3)	646 (9.8)
CHA ₂ DS ₂ VASc score – mean (SD)	4.2 (1.5)	4.1 (1.5)	4.3 (1.4)	4.4 (1.4)	4.2 (1.4)
HASBLED score – mean (SD)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)

DOAC indicates direct oral anticoagulant; and OAC, oral anticoagulant.

*All characteristics reported as N (%) or mean (SD).

 $^{\rm t}{\rm No}$ use of any OAC in the 180 days following a diagnosis of nonvalvular atrial fibrillation.

[‡]Proportions (%) reported by calendar year for all patients are percentages of the full cohort (N=32487), whereas the proportions reported by calendar year for the OAC user and nonuser groups are proportions of the total number of patients included in that calendar year.

During the study period (2012–2019), the proportion of OAC users increased (39.4% in 2012 to 49.0% in 2019; P<0.001). Between 2012 and 2019, there was a marked decline in warfarin use (32.0% to 11.0%, a decrease of 21.0%; P<0.001) and an increase in DOAC use (7.4% to 38.0%, an increase of 30.8%; P<0.001) (Figure 1). Similarly, increasing trends in DOAC use over time were observed among patients with decompensated cirrhosis (from 4.2% in 2012 to 36.1% in 2019, an increase of 31.9%; P<0.001) and in those with compensated cirrhosis (from 10.9% in 2012 to 39.5% in 2019, an increase of 28.6%; P<0.001).

Overall, the most frequently prescribed DOAC during the study period was apixaban (46.1% of all DOACs), followed by rivaroxaban (38.5% of all DOACs) and dabigatran (18.6% of all DOACs). In analyses of individual DOAC use over time, we observed increasing trends of apixaban use between 2013 (as apixaban was approved for stroke prevention in atrial fibrillation [AF] on December 28, 2012) and 2019 (0.8% to 26.4%,

an increase of 25.6%; P<0.001) and rivaroxaban use (2.3% in 2012 [given rivaroxaban was approved for stroke prevention in AF in 2011] to 10.5% in 2019, an increase of 8.2%; P<0.001), and a decline in dabigatran use (5.1% in 2012 to 1.1% in 2019, a decrease of 4.0%; P<0.001) (Figure 1). These trends resulted in a substantial increase in DOACs use over time, such that DOACs comprised 77.6% of all OAC use in 2019, compared with just 18.7% of all OAC use in 2012; P<0.001 (Figure 2).

Trends in warfarin and DOAC prescriptions as a proportion of all OAC prescriptions over time in key subgroups are shown in Figure 2. We observed consistent, increasing trends in DOAC use (as a proportion of all OAC use) over time in all subgroup analyses, including among patients with thrombocytopenia (from 18.2% in 2012 to 79.6% in 2019; *P*<0.001), coagulopathy (from 17.2% in 2012 to 80.6% in 2019; *P*<0.001), and underlying CKD/ESRD (from 11.3% in 2012 to 70.7% in 2019; *P*<0.001). We also observed consistent,



Figure 1. Proportions of warfarin and DOAC prescriptions, among patients with cirrhosis and NVAF in MarketScan, 2012 to 2019.

A, Total population; (**B**) compensated cirrhosis; (**C**) decompensated cirrhosis; (**D**) thrombocytopenia; (**E**) no thrombocytopenia; (**F**) coagulopathy; (**G**) no coagulopathy. DOAC indicates direct oral anticoagulant; and NVAF, nonvalvular atrial fibrillation.



Figure 2. Warfarin and DOAC prescriptions as a proportion of all OAC prescriptions, among patients with cirrhosis and NVAF in MarketScan, 2012 to 2019.

A, Total population; (B) compensated cirrhosis; (C) decompensated cirrhosis; (D) thrombocytopenia; (E) no thrombocytopenia; (F) coagulopathy; (G) no coagulopathy. DOAC indicates direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation; and OAC, oral anticoagulant.

increasing trends in DOAC use (as a proportion of all OAC use) in patients with compensated cirrhosis (from 24.4% in 2012 to 79.1% in 2019; *P*<0.001), and this trend appeared to be amplified in decompensated cirrhosis (from 12.2% in 2012 to 75.7% in 2019; *P*<0.001). Additionally, there was evidence of similar trends of increasing DOAC use and decreasing warfarin use across CHA₂DS₂VASc categories. Specifically, in the most recent calendar year with available data (2019), among patients with CHA₂DS₂VASc score <5, 79.1% of all OAC prescriptions were for DOACs, compared with 76.5% among patients with CHA₂DS₂VASc score ≥5. We also observed similar trends across additional subgroups defined by age (<65 years, 65 to <75 years, and ≥75 years) (not shown).

Among all DOAC users, the greatest proportional increase in use over time was observed with apixaban (61.2%; from 9.0% in 2013 to 70.2% in 2019; P<0.001) (Figure S1). In contrast, the proportion of DOAC users who used rivaroxaban increased by 2.9% between 2012 and –2019 (25.2% to 28.1%; P<0.001), whereas the proportion who used dabigatran decreased by 73.1% between 2012 and 2019 (74.8% to 1.7%; P<0.001). These trends were consistent across all subgroups (not shown).

Finally, we conducted sensitivity analyses focused on new initiators of OACs by excluding any patient with a recorded OAC prescription during the 6-month period before the cohort entry date. After this additional exclusion, there were 19553 remaining eligible patients in MarketScan with cirrhosis and NVAF. Among them, 6007 patients (30.7%) initiated an OAC within 180 days of NVAF diagnosis, including 2921 warfarin initiators (14.9%) and 3508 DOAC initiators (17.9%). Only 9 patients underwent LAA closure within 180 days of NVAF diagnosis, and 42 patients (0.2%) underwent LAA closure at any time-point of follow-up. Between 2012 and 2019, the proportion of patients initiating any OAC increased by 9.5% (29.4% in 2012 to 38.9% in 2019; P<0.001). There was a declining trend of warfarin initiation over the study period (23.9% to 5.4%, a decrease of 18.5%; P<0.001), and an increasing trend of DOAC initiation (5.5% to 33.6%, an increase of 28.1%; P<0.001). Overall, between 2012 and 2019, DOAC initiation (as a proportion of all new OAC initiations) increased by 67.0% (19.0% to 86.0%; P<0.001) (Figure S2). Apixaban was the most frequently initiated DOAC by 2019 (comprising 63.9% of all new OAC initiations and 85.6% of all DOAC initiations, in 2019).

DISCUSSION

In a large, population-based US cohort of commercially insured patients with cirrhosis and NVAF, we found more than half of the eligible patients were not anticoagulated. From 2012 to 2019, DOAC use has increased substantially, whereas warfarin use dropped precipitously. Apixaban has become the most frequently prescribed OAC, accounting for over 53% of all OAC prescriptions by the end of the study period. The trends of increasing DOAC use over time were consistent across all age groups and CHA₂DS₂VASc risk categories, and they also were evident in high-risk patients with underlying thrombocytopenia, coagulopathy, and decompensated cirrhosis. Notably, the most pronounced increases in DOAC use over time were found in patients with decompensated cirrhosis, whereas relatively smaller increases were found in patients with compensated cirrhosis.

Warfarin has historically been the most commonly prescribed OAC in patients with cirrhosis and NVAF,^{31,32} largely owing to the limited evidence in patients with chronic liver disease and the lack of cirrhosis-specific guidelines for AF management.^{14,26} Concern also remains regarding DOAC use in patients with progressive or decompensated cirrhosis, given the risks of aberrant hepatic drug metabolism and adverse bleeding events, coupled with the lack of cirrhosis-specific safety and efficacy data from published DOAC randomized controlled trials, which actively excluded patients with cirrhosis. Moreover, among the few observational studies focused on chronic liver disease, none directly compared individual DOACs in a head-to-head manner; thus, it is unclear whether one DOAC should be preferred over another. Given these uncertainties, it is often recommended that patients with NVAF and advanced cirrhosis avoid DOAC therapy.^{31,33–35} Nevertheless, we observed a progressive change over time in prescribing preferences for patients with cirrhosis and NVAF that increasingly favors DOACs, particularly apixaban, over warfarin, including in patients with decompensated cirrhosis and high-risk features such as thrombocytopenia and coagulopathy. These changing practice patterns could reflect variability in patient, provider, or formulary preferences; however, they did not appear to be explained by differences in patient age, or in the proportions of patients with underlying coagulopathy, thrombocytopenia, or prior major bleeding events, in our analyses stratified by these factors.

Overall, we found that over 50% of patients with cirrhosis and NVAF who were eligible for anticoagulation (ie, CHA₂DS₂VASc scores \geq 2 [men] or \geq 3 [women]) did not receive an OAC. Such low rates of OAC use were consistently observed in patients at the highest risk of stroke (ie, CHA₂DS₂VASc score \geq 5), including in those without clear contraindications to therapy, such as patients with compensated cirrhosis and those without coagulopathy, thrombocytopenia, or prior bleeding events. These findings are supported by data from the general population, which similarly describe modest rates of overall OAC use among adults with NVAF and elevated risk of stroke.³⁶ Other studies have suggested marked discordance between clinical recommendations for OAC use and actual patterns of real-world use, such that 20% to 55% of patients with AF and a CHA₂DS₂VASc score \geq 2 do not receive anticoagulation, whereas in contrast, 40% to 53% of patients with a CHA₂DS₂VASc score of 0 are treated with OAC therapy,³⁷⁻⁴⁰ including in studies with rigorously defined NVAF and comorbidities and valid assessments of CHA₂DS₂VASc scores.^{39,40} Such figures raise understandable concern because patients with AF who fail to receive guideline-congruent OAC therapy suffer from high rates of preventable stroke.⁴¹

Our findings show a progressive increase over time in the uptake of DOACs in patients with cirrhosis and NVAF, together with a concurrent decline in warfarin use, patterns that have also been described in the general population with NVAF.⁴²⁻⁴⁴ By the end of our study period (2019), DOACs accounted for 77.6% of all OAC prescription claims in MarketScan, and the most commonly prescribed DOAC was apixaban. Yet, there remains a lack of robust data regarding the use, safety, and effectiveness of DOACs, including apixaban, in patients with cirrhosis and NVAF. Thus, as the worldwide prevalence of cirrhosis continues to grow, and as DOACs continue to be integrated into clinical practice, it is imperative that future research studies identify the optimal DOAC strategy for this high-risk and vulnerable population, particularly for patients with advanced, decompensated cirrhosis.

We acknowledge several limitations. First, despite its large size, our study population included only enrollees of commercial insurance plans and thus may not be generalizable to Medicare or uninsured populations. Second, we did not have access to data regarding race, ethnicity, or income; to clinical notes; or to laboratory data to calculate Model for End-Stage Liver Disease scores or Child Turcotte-Pugh class or to measure renal function or thrombocytopenia, and we also lacked formulary information, which could have driven some of the observed trends. Third, in this administrative data set we lacked information regarding why providers might not have prescribed OAC to selected patients with cirrhosis, despite elevated risks of stroke. Fourth, we used ICD algorithms to define cirrhosis and liver decompensation; however, these algorithms are well validated, with positive predictive values >85% to 90%,^{16–20} which minimizes potential misclassification. Similarly, ICD diagnoses of thrombocytopenia and CKD/ESRD are likely specific and thus may underestimate the prevalence of those conditions. Finally, medication usage information corresponds only to filled prescriptions; thus, the OAC exposure status could be misclassified if a medication were filled but not taken by a patient.

Conclusions

In conclusion, this study found decreasing use of warfarin and increasing use of DOACs in a nationwide cohort of patients with cirrhosis and NVAF. These trends were particularly pronounced in patients with decompensated cirrhosis, a vulnerable group for whom DOAC safety data are scarce. Our study also demonstrated that over 50% of patients with NVAF and cirrhosis with high CHA₂DS₂VASc scores do not receive anticoagulation. Given the changing patterns of OAC prescribing in patients with cirrhosis and NVAF, further research is needed to evaluate the safety and effectiveness of DOACs compared with warfarin and with one another, including in high-risk patients with advanced, decompensated cirrhosis. Future studies should also investigate clinical outcomes of patients with cirrhosis and NVAF who are not initiated on guideline-based OAC therapy,^{14,26} in order to optimize stroke prevention strategies for this vulnerable and understudied population.

ARTICLE INFORMATION

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Disclosures

Dr Simon previously served as a consultant to Aetion and reports grants to the institution from Amgen, for unrelated work. Dr Schneeweiss (ORCID# 0000-0003-2575-467X) is participating in investigator-initiated grants to the Brigham and Women's Hospital from Boehringer Ingelheim unrelated to the topic of this study. He is a consultant to Aetion Inc., a software manufacturer of which he owns equity. His interests were declared, reviewed, and approved by the Brigham and Women's Hospital and Partners HealthCare System in accordance with their institutional compliance policies. Dr Singer has received research funding from Bristol Myers Squibb and has served as a consultant to Bristol Myers Squibb and Pfizer. The remaining authors have no disclosures to report.

Supplemental Material

Table S1 Figure S1–S2

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SUPPLEMENTAL MATERIAL

Variable Name	ICD-9	ICD-10
CHA ₂ DS ₂ VASc score ¹	Congestive heart failure: "428", "428.1", "428.2", "428.20", "428.22", "428.23", "428.3", "428.31", "428.33", "428.4", "428.42", "428.0", "428.21", "428.30", "428.32", "428.41", "428.43", "428.9", "429.9" Hypertension: "401.1", "401.9", "405", "405.0", "405.01", "405.11", "405.19", "405.9", "401", "401.0", "405.09", "405.1", "405.91", "405.99"	Congestive heart failure: "I50.1", "I50.20", "I50.21", "I50.22", "I50.32", "I50.41", "I50.42", "I50.814", "I50.82", "I50.84", "I50.89", "I50.23", "I50.30", "I50.31", "I50.33", "I50.40", "I50.43", "I50.810", "I50.811", "I50.812", "I50.813" Hypertension: "I15.8", "I15.9", "I16.1", "N26.2", "I10", "I15.0", "I15.1", "I15.2", "I16.0", "I16.9"
	Diabetes: "249.0", "249.10", "249.20", "249.21", "249.30", "249.31", "249.40", "249.50", "249.51", "249.6", "249.60", "249.61", "249.7", "249.80", "249.81", "249.90", "249.91", "250", "250.0", "250.00", "250.01", "250.02", "250.1", "250.10", "250.11", "250.12", "250.2", "250.20", "250.21", "250.22", "250.30", "250.33", "250.40", "250.60", "250.61", "250.62", "250.60", "250.61", "250.62", "250.82", "250.83", "250.90", "250.82", "250.83", "250.90", "250.91", "249", "249.00", "249.01", "249.1", "249.11", "249.2", "249.3", "249.4", "249.41", "249.5", "249.70", "250.13", "250.23", "250.3", "250.31", "250.32", "250.53", "250.43", "250.61", "250.52", "250.70", "250.73", "250.81", "250.9", "250.92", "250.93" Stroke, TIA, or Thromboembolism:	Diabetes: "E08.00", "E08.01", "E08.10", "E08.11", "E08.22", "E08.311", "E08.319", "E08.3211", "E08.3212", "E08.3219", "E08.3292", "E08.3311", "E08.3219", "E08.3292", "E08.3392", "E08.3411", "E08.3412", "E08.3392", "E08.3511", "E08.3512", "E08.3513", "E08.3511", "E08.3521", "E08.3523", "E08.3541", "E08.3524", "E08.3549", "E08.3551", "E08.3559", "E08.36", "E08.3551", "E08.3559", "E08.44", "E08.621", "E08.622", "E08.630", "E08.638", "E08.641", "E08.649", "E08.638", "E08.641", "E08.649", "E08.638", "E08.641", "E09.10", "E09.3219", "E09.3291", "E09.3292", "E09.3311", "E09.3393", "E09.3413", "E09.3419", "E09.3553", "E09.3513", "E09.3533", "E09.3553", "E09.3591", "E09.3593", "E09.40", "E09.41", "E09.39", "E09.52", "E09.610",
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"997 02" " <i>1</i> 15 11" " <i>1</i> 30" " <i>1</i> 33 0"	"E10.51" "E10.59" "E10.610"
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	"F13 621" "F13 622" "F12 620"
	"F13 638" "F12 6/0"
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	"G46.2", "I26.01", "I26.02", "I26.09",
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	"I82.A12". "I82.A13". "I82.A19".
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	"007.2", "088.213", "088.83",
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	"G45.8", "G45.9", "G46.1", "G97.31",
	"G97.32", "I26.99", "I60.01", "I60.11",
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Vascular Disease: "E08.51", "E09.51", "E09.52", "E10.51", "E10.59", "E10.65", "E11.51", "E11.52", "E11.65", "E13.51", "E13.59", "I21.01", "I21.02", "I21.11", "I21.29", "I21.4", "I21.A9", "I22.0", "I22.1", "I25.10", "I25.111", "I25.118", "I25.70", "I25.71", "I25.718", "I25.720", "I25.721", "I25.729", "I25.738", "I25.751", "I25.759", "I25.760", "I25.761".		088.82 , 181./18A , 181./2XA
"E08.51", "E09.51", "E09.52", "E10.51", "E10.59", "E10.65", "E11.51", "E11.52", "E11.65", "E13.51", "E13.59", "I21.01", "I21.02", "I21.11", "I21.29", "I21.4", "I21.A9", "I22.0", "I22.1", "I25.10", "I25.111", "I25.718", "I25.708", "I25.700", "I25.718", "I25.708", "I25.709", "I25.718", "I25.720", "I25.721", "I25.729", "I25.738", "I25.751", "I25.759", "I25.760", "I25.761".		Vascular Diseaso:
"E108.51', 'E05.52', "E10.65", "E10.51", "E10.59", "E10.65", "E11.51", "E11.52", "E11.65", "E13.51", "E13.59", "I21.01", "I21.02", "I21.11", "I21.29", "I21.4", "I21.A9", "I22.0", "I22.1", "I25.10", "I25.111", "I25.0", "I25.70", "I25.70", "I25.708", "I25.708", "I25.709", "I25.718", "I25.720", "I25.721", "I25.729", "I25.738", "I25.751", "I25.759", "I25.760", "I25.761".		"EQ2 51" "EQ2 51" "EQ2 52"
"E10.31', 'E10.33', 'E10.33', 'E10.33', ''E11.51", ''E11.52", ''E11.65", ''E11.51", ''E11.52", ''E11.65", ''E13.51", ''E13.59", ''I21.01", ''I21.02", ''I21.11", ''I21.29", ''I21.4", ''I21.A9", ''I22.0", ''I25.11", ''I25.118", ''I25.3", ''I25.10", ''I25.700", ''I25.701", ''I25.708", ''I25.709", ''I25.701", ''I25.708", ''I25.729", ''I25.729", ''I25.729", ''I25.729", ''I25.751", ''I25.759", ''I25.760", ''I25.761".		"E10 E1" "E10 E0" "E10 EE"
"E11.31', 'E11.32', 'E11.33', "E13.51", "E13.59", "I21.01", "I21.02", "I21.11", "I21.29", "I21.4", "I21.A9", "I22.0", "I22.1", "I25.10", "I25.111", "I25.718", "I25.708", "I25.700", "I25.718", "I25.708", "I25.709", "I25.718", "I25.720", "I25.721", "I25.729", "I25.738", "I25.751", "I25.759", "I25.760", "I25.761".		"E11 51" "E11 52" "E11 65"
" " " " " " " " " " " " " " " " " " "		"E12 E1" "E12 E0" "I21 01" "I21 02"
"121.11, 121.25, 121.4, 121.A9, "122.0", "122.1", "125.10", "125.111", "125.118", "125.3", "125.41", "125.700", "125.701", "125.708", "125.709", "125.718", "125.720", "125.721", "125.729", "125.738", "125.751", "125.759". "125.760". "125.761".		"121.01", L13.35", 121.01", 121.02", "121.11" "121.20" "121.4" "121.40"
"122.0", 122.1", 123.10", 123.111", "125.118", "125.3", "125.41", "125.700", "125.701", "125.708", "125.709", "125.718", "125.720", "125.721", "125.729", "125.738", "125.751", "125.759". "125.760". "125.761".		"I22 Ω" "I22 1" "I25 1Ω" "I25 111"
"125.718", 125.3", 125.41, 125.700", "125.701", "125.708", "125.709", "125.718", "125.720", "125.721", "125.729", "125.738", "125.751", "125.759". "125.760". "125.761".		"125 118" "125 2" "125 <u>1</u> 1" "125 700"
"I25.701", "I25.708", "I25.709", "I25.718", "I25.720", "I25.721", "I25.729", "I25.738", "I25.751", "I25.759". "I25.760". "I25.761".		"125 701" "125 708" "125 709"
"125.729", "125.729", "125.721", "125.729", "125.738", "125.751", "125.759". "125.760". "125.761".		"125.718", "125.700", "125.705", "125.718", "125.720" "125.721"
"I25.759". "I25.760". "I25.761".		"I25 729", "I25 738", "I25 751"
		"I25.759", "I25.760", "I25.761".

		"125.769", "125.798", "125.799", "125.810", "125.811", "125.83", "125.89", "125.9", "170.0", "173.9", "179.1", "179.8", "E08.52", "E10.52", "E11.59", "E13.52", "121.09", "121.19", "121.21", "121.3", "121.9", "121.A1", "122.2", "122.8", "122.9", "125.110", "125.119", "125.2", "125.42", "125.5", "125.6", "125.710", "125.711", "125.719", "125.728", "125.730", "125.731", "125.739", "125.750", "125.758", "125.768", "125.790", "125.791", "125.812", "125.82", "125.84"
HAS-BLED score ²	Abnormal Liver Function:	Abnormal Liver Function:
	"794.8"	"R94.5"
	Abnormal Repair Eunction:	Abnormal Repair Function:
	"794.4"	"R94.4"
	Drug or Alcohol Abuse:	Drug or Alcohol Abuse:
	"303.02", "303.90", "303.92",	"F10.10", "F10.20", "F10.21",
	"303.93", "305.01", "305.02", "V11.3",	"F10.220", "Z65.8", "F10.11",
	"303.00", "303.01", "303.03",	"F10.120", "F10.129", "F10.229"
	"303.91", "305.00", "305.03"	
		Stroke:
	Stroke:	"163.013", "163.019", "163.031", (163.022", (162.112", (162.112")
	433.91 , 434.01 , 434.11 , "424.01" "422.01" "422.11"	163.032 , 163.112 , 163.113 , (162.110" (162.122" (162.212"
	434.91 , 433.01 , 433.11 , "422 21" "422 21" "422 81"	103.119 , 103.132 , 103.212 , "IG2 210" "IG2 222" "IG2 20"
	455.21 , 455.51 , 455.61	"I63 313" "I63 320" "I63 331"
	Hypertension:	"I63 332" "I63 333" "I63 341"
	"A01 1" "A01 9" "A02 0" "A02 00"	"I63 342" "I63 343" "I63 349"
	401.1, 401.9 , 402.0 , 402.00 , 402.01" 402.01 " 402.01 "	"I63 39" "I63 40" "I63 411"
	"403 1" "403 10" "403 9" "403 90"	"163 421" "163 429" "163 431"
	"403 91" "404 00" "404 1" "404 12"	"I63 433", "I63 439", "I63 441",
	"404.13". "404.90". "404.91".	"163.49". "163.50". "163.511".
	"404.92", "404.93", "405.0", "405.01",	"163.519", "163.522", "163.529",
	"405.11", "405.19", "405.9", "401.0",	"163.532", "163.533", "163.541",
	"402.1", "402.10", "402.11", "402.90",	"163.542", "163.543", "163.6", "163.8",
	"402.91", "403.00", "403.11", "404.0",	"I63.00", "I63.011", "I63.012",
	"404.01", "404.02", "404.03",	"163.02", "163.033", "163.039",
	"404.10", "404.11", "404.9", "405.09",	"I63.09", "I63.10", "I63.111", "I63.12",
	"405.1", "405.91", "405.99"	"I63.131", "I63.133", "I63.139",
		"I63.19", "I63.20", "I63.211",
	Bleeding:	"I63.213", "I63.22", "I63.231",
	"280.8", "280.9", "281.0", "281.4",	"I63.232", "I63.239", "I63.29",
	"281.8", "282.1", "282.2", "282.4",	"I63.311", "I63.312", "I63.319",
	"282.40", "282.42", "282.44", "202.45" "202.47" "202.5" "202.6"	"163.321", "163.322", "163.323",
	282.45°, "282.47°, "282.5°, "282.6°, "282.6°, "282.6°, "282.6°, "282.6°, "282.6°,	163.339", "163.412", "163.413",
	282.64", "282.69", "282.9", "283.10",	163.419", "163.422", "163.423",
	283.2°, "283.9", "284.09", "284.1",	ib3.432°, "ib3.442°, "ib3.443″,

	"284.19", "284.8", "284.89", "285.0",	"I63.449", "I63.512", "I63.513",
	"285.2", "285.22", "285.29", "285.8",	"163.521", "163.523", "163.531",
	"280.0", "280.1", "281.1", "281.2",	"163.539", "163.549", "163.59", "163.9"
	"281 3" "281 9" "282 0" "282 3"	
	"282 A1" "282 A2" "282 A6"	Hypertension:
	(100, 40) (100,	"111 0" "112 10" "112 2" "115 9"
	202.45, 202.00 , 202.01 ,	111.9, 115.10 , 115.2 , 115.6 ,
		115.9 , 116.1 , N26.2 , 110 ,
	"282.8", "283.0", "283.1", "283.11",	"111.0", "112.0", "112.9", "113.0",
	"283.19", "284.0", "284.01", "284.11",	"I13.11", "I15.0", "I15.1", "I15.2",
	"284.12", "284.2", "284.81", "284.9",	"I16.0", "I16.9"
	"285.1", "285.21", "285.3", "285.9"	
		Bleeding:
		"D50.8", "D50.9", "D51.0", "D51.2",
		"D51.3", "D51.8", "D52.0", "D52.1",
		"D52.8", "D53.2", "D53.8", "D53.9",
		"D55.0". "D55.1". "D55.8". "D56.4".
		"D57.00" "D57.01" "D57.02"
		"D57 1" "D57 211" "D57 219"
		"D57.11", "D57.211", "D57.215",
		D37.40 , D37.411 , D37.60 ,
		D58.8 , D59.0 , D59.1 , D59.2 ,
		"D59.3", "D59.4", "D59.5", "D59.6",
		"D60.0", "D60.1", "D60.8", "D61.2",
		"D61.811", "D61.82", "D61.9",
		"D63.1", "D63.8", "D64.0", "D64.1",
		"D64.89", "D50.0", "D50.1", "D51.1",
		"D51.9", "D52.9", "D53.0", "D53.1",
		"D55.2", "D55.3", "D55.9", "D56.0",
		"D56.1", "D56.2", "D56.3", "D56.5",
		"D56.8", "D56.9", "D57.20".
		"D57 212" "D57 3" "D57 412"
		"D57 419" "D57 819" "D58 0"
		"D58 1" "D58 9" "D50 8" "D50 9"
		"DS0.1 , DS0.5 , DS5.8 , DS5.9 , "DS0.9" "DS1.01" "DS1.09" "DS1.1"
		D00.3, $D01.01$, $D01.03$, $D01.1$,
		D01.3 , D01.810 , D01.818 ,
	<u> </u>	"D64.3", "D64.4", "D64.81", "D64.9"
Thrombocytopenia	"287.3", "287.30", "287.31", "287.32",	"D69.3", "D69.41", "D69.42",
	"287.33", "287.39", "287.4", "287.41",	"D69.49", "D69.51", "D69.59",
	"287.49", "287.5"	"D69.6"
Coagulopathy	"286", "286.0", "286.1", "286.2",	"D65", "D66", "D67", "D68", "D68.0",
	"286.3", "286.4", "286.5", "286.52",	"D68.1", "D68.2", "D68.3", "D68.31",
	"286.53", "286.59", "286.6", "286.7",	"D68.311", "D68.312", "D68.318",
	"286.9", "287.1", "287.3", "287.4",	"D68.32", "D68.4", "D68.5", "D68.51",
	"287.5"	"D68.52". "D68.59". "D68.6".
		"D68.61", "D68.62". "D68.69".
		"D68 8" "D68 9" "D69 1" "D69 3"
		"D69 4" "D69 41" "D69 42"
		"D60 40" "D60 5" "D60 51"
		"D60 50" "D60 6"
iviajor Bleeding	Hospitalization for major bleeding	Hospitalization for major bleeding
	event:	event:

C	DX {"336.1", "363.61", "363.62",	DX {"G95.19", "H05.233", "H05.239",
"	'372.72", "377.42", "379.23", "431",	"H11.30", "H11.32", "H11.33",
"	'432", "432.0", "432.1", "432.9",	"H31.301", "H31.303", "H31.313",
"	'719.11", "719.15", "719.18",	"H31.322", "H31.323", "H43.11",
"	'719.19". "852.02". "852.03".	"H47.021". "H47.022". "H47.023".
"	(852.04", "852.09", "852.10",	"H47.029" "I60.00" "I60.02"
	(852 11" "852 12" "852 15"	"I60 10" "I60 12" "I60 2" "I60 30"
"	(852.10" "852.21" "852.2 <i>1</i> "	"I60 50" "I60 51" "I60 6" "I61 0"
"	(VED DO" "VED D" "VED D1" "VED D2"	"IG1 1" "IG1 2" "IG1 8" "IG2 00"
	032.23, 032.3 , 032.31 , 032.33 ,	(162.01" (162.02" (162.02" (162.00")
	852.34 , 852.35 , 852.30 , 852.4 ,	102.01 , 102.02 , 102.03 , 10125.00 ,
	852.41 , 852.42 , 852.43 ,	M25.012 , M25.019 , M25.021 ,
	·852.44″, "852.54″, "852.55″,	"M25.022", "M25.029", "M25.031",
	'852.59″, "853.00″, "853.01″,	"M25.039", "M25.041", "M25.049",
"	'853.04", "853.06", "853.12",	"M25.051", "M25.052", "M25.061",
<i>u</i>	'853.15", "853.19", "363.63",	"M25.062", "M25.069", "M25.074",
"	'376.32", "430", "719.12", "719.13",	"M25.075", "M25.076", "S06.340A",
"	'719.14", "719.16", "719.17",	"S06.341A", "S06.346A", "S06.350A",
"	'729.92", "852.0", "852.00", "852.01",	"S06.352A", "S06.354A", "S06.356A",
	'852.05", "852.06", "852.1", "852.13",	"S06.357A", "S06.358A", "S06.360A",
"	'852.14", "852.16", "852.2", "852.20",	"S06.361A", "S06.363A", "S06.365A",
"	'852.22 ["] , "852.23 ["] , "852.25 ["] ,	"S06.369A", "S06.4X1A", "S06.4X2A",
"	'852.26 ["] . "852.30 ["] . "852.32 ["] .	"S06.4X3A". "S06.4X5A". "S06.4X6A".
	(852.39", "852.40", "852.45",	"S06 4X7A", "S06 4X8A", "S06 4X9A",
	(852 46" "852 49" "852 5" "852 50"	"SO6 5X04" "SO6 5X14" "SO6 5X34"
"	(852 51" (852 52" (852 52")	"SOE 5X5A" "SOE 5X6A" "SOE 5X8A"
"	(952.51, 852.52, 852.55, (952.56, "952.0" "952.03" "952.03"	"SOE EVON" "SOE EVIN" "SOE EVEN"
	032.30 , 033.0 , 033.02 , 033.03 ,	"SOC. SASA, SUC. OATA, SUC. OATA, "SOC EXTA" "SOC EXEA" "SOT OATA"
	655.05 , 655.09 , 655.1 , 655.10 ,	SUD.DA/A , SUD.DAOA , SS/.U4IA ,
	853.11 , 853.13 , 853.14 ,	537.051A , H05.231 , H05.232 ,
	853.16", "866.01", "866.02",	"H11.31", "H31.302", "H31.309",
	866.11", "866.12"}	"H31.311", "H31.312", "H31.319",
		"H31.321", "H31.329", "H43.10",
C	OR	"H43.12", "H43.13", "I60.01",
		"I60.11", "I60.31", "I60.32", "I60.4",
F	Hospitalization AND transfusion:	"160.52", "160.7", "160.8", "160.9",
C	DX {"423.0", "455.7", "456.0",	"I61.2", "I61.4", "I61.5", "I61.6",
"	'456.20", "530.1", "531.00", "531.01",	"I61.9", "I62.9", "M25.011",
"	'531.1", "531.20", "531.21", "531.3",	"M25.032", "M25.042", "M25.059",
"	'531.40", "531.5", "531.60", "532.00",	"M25.071", "M25.072", "M25.073",
"	'532.01", "532.20", "532.5", "532.60",	"M25.08", "M79.81", "S06.342A",
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u	'533.3", "533.40", "533.41". "533.7".	"S06.347A", "S06.348A", "S06.349A".
u	'534.20", "534.3", "535.00". "535.10".	"S06.351A", "S06.353A". "S06.355A".
"	'535.30", "535.31". "537.83".	"S06.359A", "S06.362A". "S06.364A".
	(562.00", "562.02", "562.10"	"S06.366A", "S06.367A", "S06.368A"
	(562 12", "562 13", "578 1", "599 7"	"SO6 4X0A", "SO6 4X4A", "SO6 5X2A"
	(626.2" (784.8" (786.3" (700.02")	"SOG 5X44" "SOG 5X74" "SOG 6X04"
	(280.0" "285 1" "285 0" "166.0"	"SOG 622A" "SOG 622A" "SOG 622A"
	200.0 , 200.1 , 200.7 , 400.0 , (ASS 1" "ASS 0" "ASS 0" "ASS 1"	"SOG. GYEA" "SOG GYOA" "SOL OALA"
	455.1 , 455.2 , 455.3 , 455.4 ,	JUULONDA , JUULONDA , JJLUULA , "CDZ DD1 A" "CDZ DD2 A" "CDZ DD0 A"
	455.5 , 455.0 , 455.8 , 455.9 ,	557.USTA , 537.USZA , "537.USYA",
	459.0°, "530.7", "530.82", "531.41",	"S37.04ZA", "S37.049A", "S37.05ZA",
	531.61", "531.7", "531.9", "532.1",	"537.059A"}
"	'532.21", "532.3", "532.40", "532.41",	

"532.61'	', "533.01", "533.20",	OR
"533.21'	', "533.5", "533.60", "533.61",	
"533.9",	"534.00", "534.01", "534.1",	Hospitalization AND transfusion:
"534.21'	', "534.40", "534.41". "534.5"	DX {"D62", "D64.9". "K22.6". "K25.0".
"534 GO"		"K25.2". "K25.6". "K26.0" "K26.2"
"535 O1'	' "535 11" "535 20"	"K26 4" "K26 6" "K27 0" "K27 2"
"535.01 "535.21"	/ "535 <i>/</i> 0" "535 <i>/</i> 1"	"K27 6" "K28 0" "K28 2" "K28 4"
555.21 "525 50'	, 555.40, 555.41, / "E25 E1" "E25 60"	"K20.01" "K20.01" "K20.2 , K20.4 ,
555.50 (FDE 61)	, 555.51 , 555.00 , / "E62.01" "E62.02"	NZ9.01 , NZ9.41 , NZ9.31 , "VEF 21" "VE7 00" "VE7 01"
555.01	, 302.01 , 302.03 , / "FC9.91" "FC0.2" "FC0.95"	NSS.21 , NS7.00 , NS7.01 , "VET 11" "VET 12" "VET 22"
502.11	, 508.81 , 509.3 , 509.85 , "570 0" "622 0" "626 6"	K57.11 , K57.13 , K57.32 ,
578.0°,	5/8.9 , 623.8 , 626.6 ,	K57.40 , K57.41 , K57.51 ,
"/84./"}	AND PX {"99.03", "99.04",	"K57.52", "K57.92", "K57.93", "K62.5",
"99.05 <i>"</i> ,	"99.06"}	"K64.0", "K64.3", "K64.4", "K64.8",
		"K64.9", "K66.1", "K92.2", "N92.1",
OR		"R04.0", "K22.8", "K25.4", "K27.4",
		"K28.6", "K29.21", "K29.31", "K29.61",
Hospital	ization AND CPT/HCPC code	"K29.71", "K29.81", "K29.91",
for blood	d/blood product:	"K31.811", "K57.12", "K57.20",
DX {"423	8.0", "455.7", "456.0",	"K57.21", "K57.31", "K57.33",
"456.20'	', "530.1", "531.00", "531.01",	"K57.53", "K57.80", "K57.81",
"531.1" <i>.</i>	"531.20", "531.21", "531.3".	"K57.91", "K64.1", "K64.2", "K92.1".
"531.40"	. "531.5". "531.60". "532.00".	"N92.0". "R04.1". "R79.1"} AND PX
"532.01"	, "532.20", "532.5", "532.60".	{"30230H1", "30230M1", "30230N1",
"532 7"	"532 9" "533 00" "533 1"	"30230P1" "30230B1" "30230W1"
"533 3"	"533 <i>A</i> 0" "533 <i>A</i> 1" "533 <i>7</i> "	"30233I 1" "30233V1" "30233W1"
(⁵ 524.20)	2 "524 2" "525 00" "525 10"	"30233E1, 30233V1, 30233W1, "30240H1" "20240N1" "30240N1"
(525 20) (525 20)	, 554.5 , 555.00 , 555.10 , ' "E2E 21" "E2T 92"	30240111, 302401011 , 30240101 , $(2024011)^{2}$ (20240101) $(20240101)^{2}$ (20240101)
555.50 "F62.00"	, 555.51 , 557.65 , / "EC2 02" "EC2 10"	5024011, 5024001, 50240001, "20242011", "20242011", "202420001,
562.00	, 502.02 , 502.10 ,	30243H1 , 30243L1 , 30243N1 ,
562.12	, 562.13 , 578.1 , 599.7 ,	30243P1, 30243Q1, 30243R1,
"626.2", "222.2"	"784.8", "786.3", "790.92",	"3024311", "30250H1", "30250M1",
"280.0",	"285.1 <i>",</i> "285.9 <i>"</i> ,"455.0 <i>"</i> ,	"30250W1", "30253H1", "30253K1",
"455.1",	"455.2", "455.3", "455.4",	"30253M1", "30253N1", "30253P1",
"455.5",	"455.6", "455.8", "455.9",	"30253R1", "30253T1", "30253V1",
"459.0",	"530.7", "530.82", "531.41",	"30253W1", "30260H1", "30260L1",
"531.61"	', "531.7", "531.9", "532.1",	"30260M1", "30260N1", "30260P1",
"532.21'	', "532.3", "532.40", "532.41",	"30263M1", "30263R1", "30263W1",
"532.61'	', "533.01", "533.20",	"30230K1", "30230L1", "30230T1",
"533.21'	', "533.5", "533.60", "533.61",	"30230V1", "30233H1", "30233K1",
"533.9",	"534.00", "534.01", "534.1",	"30233M1", "30233N1", "30233P1",
"534.21'	', "534.40", "534.41", "534.5",	"30233Q1", "30233R1", "30233T1",
"534.60'	, "534.61", "534.7", "534.9",	"30240K1", "30240L1", "30240P1",
"535.01'	. "535.11". "535.20".	"30240R1". "30243K1". "30243N1".
"535.21'	, "535.40", "535.41".	"30243V1", "30243W1", "30250K1",
"535 50'	' "535 51" "535 60"	"30250L1" "30250N1" "30250P1"
"535.50 "535.61"	, 555.51 , 555.60 , ' "562 01" "562 03"	"30250E1", "30250T1", "30250T1", "30250E1", "30250T1", "30250V1",
	, 502.01 , 502.05 , ' "568 81" "560 2" "560 25"	"3025311" "30260K1" "20260P1"
۵۵۷.۱۱ ۲۵۰ (۲۵۵ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰ - ۲۵۰	"578 Q" "672 Q" "676 C"	"30255LI, 50200NI, 50200NI, "30260T1" "30260\/1" "20260\//1"
, ט.איכ וייד גסדיי	AND CDT/UCDC ("DO011"	3020011, 3020001 , 30200001 , " 20262011 " " 2026204 " " 2026214 "
(100047)	AND CF1/ACPC { P9011 ,	50203FL, 50203KL, 30203LL,
"P901/"	, P9UZZ [*] , P9U3Z [*] , "P9U34 [*] ,	30263N1°, "30263P1°, "3026311″, "20262N4"
"P9035"	, "P9036", "P9037", "P9051", "P9055", "P9037", "P9051",	"3U2b3V1"}
"P9054"	, "P9056", "P9057", "P9010",	
"P9016"	, "P9019", "P9020", "P9021",	OR

"P9023", "P9031", "P9033", "P9038",	
"P9039", "P9040", "P9044", "P9052",	Hospitalization AND CPT/HCPC code
"P9053", "P9055", "P9058", "P9059",	for blood/blood product:
"P9060"}	DX {"D62", "D64.9", "K22.6", "K25.0",
	"K25.2", "K25.6", "K26.0", "K26.2",
OR	"K26.4", "K26.6", "K27.0", "K27.2",
	"K27.6", "K28.0", "K28.2", "K28.4",
Hospitalization AND revenue code for	"K29.01", "K29.41", "K29.51",
blood/blood product:	"K55 21" "K57 00" "K57 01"
DX {"423 0" "455 7" "456 0"	"K57 11" "K57 13" "K57 32"
"456 20" "530 1" "531 00" "531 01"	"K57 40" "K57 41" "K57 51"
"521 1" "521 20" "521 21" "521 2"	"K57 52" "K57 92" "K57 92" "K62 5"
"521 AO" "521 5" "521 60" "522 00"	"K64 0" "K64 2" "K64 4" "K64 8"
551.40 , 551.5 , 551.00 , 552.00 , "E22.01" "E22.20" "E22.E" "E22.60"	K04.0 , K04.3 , K04.4 , K04.8 , "VCA 0" "VCC 1" "V02 2" "N02 1"
552.01 , 552.20 , 552.5 , 552.00 , "F22 7" "F22 0" "F22 00" "F22 1"	NO4.9 , NOO.1 , N92.2 , N92.1 ,
532.7 , 532.9 , 533.00 , 533.1 , "F22.2" "F22.40" "F22.41" "F22.7"	RU4.U , KZZ.8 , KZ5.4 , KZ7.4 ,
535.5 , 535.40 , 535.41 , 535.7 , (524.20) (524.2) (525.00) (525.40)	K28.0 , K29.21 , K29.31 , K29.01 ,
534.20 , 534.3°, 535.00°, 535.10°, "F2F 20" "F2F 24" "F27 22"	NZY./I, NZY.81, NZY.91,
535.3U", "535.31", "537.83",	K31.811°, K57.12°, K57.20°,
562.00°, "562.02", "562.10",	K5/.21°, "K5/.31°, "K5/.33″,
"562.12", "562.13", "578.1", "599.7",	"K57.53", "K57.80", "K57.81",
626.2 , 784.8 , 786.3 , 790.92 ,	K57.91, K04.1, K04.2, K92.1,
280.0 , 285.1 , 285.9 , 455.0 , "AFE 4" "AFE 2" "AFE 2" "AFE 4"	N92.0 , R04.1 , R79.1 } AND
455.1 , 455.2 , 455.3 , 455.4 ,	CP1/HCPC { P9010 , P9011 ,
"455.5", "455.6", "455.8", "455.9",	"P9016", "P9017", "P9019", "P9031",
"459.0", "530.7", "530.82", "531.41",	"P9037", "P9038", "P9040", "P9055",
"531.61", "531.7", "531.9", "532.1",	"P9057", "P9058", "P9059", "P9060",
"532.21", "532.3", "532.40", "532.41",	"P9020", "P9021", "P9022", "P9023",
"532.61", "533.01", "533.20",	"P9032", "P9033", "P9034", "P9035",
"533.21", "533.5", "533.60", "533.61",	"P9036", "P9039", "P9044", "P9051",
"533.9", "534.00", "534.01", "534.1",	"P9052", "P9053", "P9054", "P9056"}
"534.21", "534.40", "534.41", "534.5",	0.5
"534.60 <i>"</i> , "534.61 <i>"</i> , "534.7 <i>"</i> , "534.9 <i>"</i> ,	OR
"535.01", "535.11", "535.20",	
"535.21 <i>"</i> , "535.40 <i>"</i> , "535.41 <i>"</i> ,	Hospitalization AND revenue code for
"535.50 <i>"</i> , "535.51 <i>"</i> , "535.60 <i>"</i> ,	blood/blood product:
"535.61 <i>"</i> , "562.01 <i>"</i> , "562.03 <i>"</i> ,	DX {"D62", "D64.9", "K22.6", "K25.0",
"562.11 <i>"</i> , "568.81 <i>"</i> , "569.3 <i>"</i> , "569.85 <i>"</i> ,	"K25.2", "K25.6", "K26.0", "K26.2",
"578.0", "578.9", "623.8", "626.6",	"K26.4", "K26.6", "K27.0", "K27.2",
"784.7" } AND Revenue Code {"0381",	"K27.6", "K28.0", "K28.2", "K28.4",
"0382", "0383", "0384", "0387"}	"K29.01", "K29.41", "K29.51",
	"K55.21", "K57.00", "K57.01",
	"K57.11", "K57.13", "K57.32",
	"K57.40", "K57.41", "K57.51",
	"K57.52", "K57.92", "K57.93", "K62.5",
	"K64.0", "K64.3", "K64.4", "K64.8",
	"K64.9", "K66.1", "K92.2", "N92.1",
	"R04.0", "K22.8", "K25.4", "K27.4",
	"K28.6", "K29.21", "K29.31", "K29.61",
	"K29.71", "K29.81", "K29.91",
	"K31.811", "K57.12", "K57.20",
	"K57.21", "K57.31", "K57.33",
	"K57.53", "K57.80", "K57.81",

		"K57.91", "K64.1", "K64.2", "K92.1",
		"N92.0", "R04.1", "R79.1"} AND
		Revenue Code {"0381", "0382",
		"0383", "0384", "0387"}
Chronic Kidney Disease	"585.4", "585.5", "585.6"	"N18.4", "N18.5", "N18.6"
(CKD) or End-Stage Renal		
Disease (ESRD)		
Decompensated Cirrhosis	"070.2", "070.22", "070.44", "070.6",	"K70.3", "K70.30", "K72.10", "K72.11",
	"456.0", "456.1", "456.2", "456.20",	"K74.4", "K74.5", "K74.6", "K74.60",
	"572.2", "789.5", "070.23", "070.4",	"K70.31", "K71.7", "K72.1", "K74",
	"070.49", "070.71", "456.21",	"K74.3", "K74.69", "P78.81", "C22",
	"567.23", "572.4", "789.59", "155",	"C22.9", "I85", "I85.0", "I85.1",
	"155.0", "571", "572.8", "571.2",	"I85.10", "K65.2", "K70.10", "K70.11",
	"571.5", "571.6", "571.9", "572.3"	"K70.30", "K70.4", "K70.40", "K70.41",
		"К71.10", "К72.0", "К72.10", "К72.11",
		"K72.90", "K72.91", "K76.7", "T86.40",
		"T86.42", "T86.49", "Z48.23", "C22.0",
		"C22.1", "C22.4", "C22.7", "C22.8",
		"I85.00", "I85.01", "I85.11", "K70.31",
		"K71.1", "K71.11", "K71.50", "K71.51",
		"K72", "K72.00", "K72.01", "K72.1",
		"K72.9", "R18", "R18.0", "R18.8",
		"T86.4", "T86.41", "T86.43", "Z94.4"
Hepatic Encephalopathy	"572.2"	"G92", "G93.4", "G93.40", "G93.41",
		"G93.49"
Esophageal Varices	"456.0", "456.1", "456.2", "456.20",	"185", "185.0", "185.1", "185.10",
	"456.21"	"185.00", "185.01", "185.11", "186.4"
Ascites or Spontaneous	"789.5", "789.59", "567.23",	"K65.2", "K70.11", "K76.7", "K70.31",
Bacterial Peritonitis or	"572.4", "571", "572.8", "571.2",	"K71.51", "R18", "R18.0",
Hepatorenal syndrome	"571.5", "571.6", "571.9", "572.3"	"R18.8", "K70.3", "K70.30", "K72.10",
		"K72.11", "K74.4", "K74.5", "K74.6",
		"K74.60", "K70.31", "K71.7", "K72.1",
		"K74", "K74.3", "K74.69", "P78.81"

 1 CHA₂DS₂VASc score calculated as follows: 1 point each for, congestive heart failure, hypertension, age \geq 75 [point doubled], diabetes, prior stroke, or transient ischemic attack [TIA] or thromboembolism [point doubled], vascular disease, age 65-74, female sex.

²HAS-BLED score calculated as follows: 1 point each for, hypertension, abnormal renal function, abnormal liver function or cirrhosis [note: all patients in this cohort receive 1 point for cirrhosis], stroke, prior bleeding event elevated INR, age >65 years, prior alcohol or drug usage, and use of medications that predispose to bleeding [i.e., antiplatelets or anticoagulants].

Figure S1. Apixaban, Rivaroxaban and Dabigatran as a Proportion of all DOAC Prescriptions, Among Patients with Cirrhosis and NVAF in MarketScan, 2012-2019











DOAC, direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation

C. Decompensated Cirrhosis





G. No Coagulopathy

100%



Figure S2. Warfarin and DOAC Initiation as a Proportion of all New OAC Initiations, Among Patients with Cirrhosis and NVAF in MarketScan, 2012-2019



DOAC, direct oral anticoagulant; NVAF, nonvalvular atrial fibrillation