Journal of the American Heart Association

ORIGINAL RESEARCH

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

Tracey G. Simon, MD, MPH; Sebastian Schneeweiss, MD, ScD; Daniel E. Singer, MD; Sushama Kattinakere Sreedhara, MBBS, MPH; Kueiyu Joshua Lin, MD, ScD

**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 ($CHA_2DS_2$-VASc score ≥2 [men] or ≥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 $CHA_2DS_2$-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 and DOAC use increased in all subgroups, including in compensated and decompensated cirrhosis, thrombocytopenia, coagulopathy, chronic kidney disease/end-stage renal disease, and across $CHA_2DS_2$-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

Correspondence to: Kueiyu Joshua Lin, MD, PhD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont St, Suite 3030, Boston, MA. Email: jklin@bwh.harvard.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026863

For Sources of Funding and Disclosures, see page 8.



*JAHA* is available at: www.ahajournals.org/journal/jaha

## 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), $CHA_2DS_2VASc$ 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 $CHA_2DS_2VASc$ category (ie, <5 versus ≥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 180-day 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 32 487 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 $CHA_2DS_2VASc$ 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, 14 501 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 $CHA_2DS_2VASc$ and HASBLED scores (Table). Among all 32 487 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)**

| Characteristics* | All patients | Nonuse† | Any OAC | Warfarin | DOAC |
|---|---|---|---|---|---|
| Number of patients | 32 487 | 17 986 | 14 501 | 7941 | 6560 |
| Female sex | 12 517 (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) |
| $CHA_2DS_2VASc$ 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).
†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=32 487), 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,

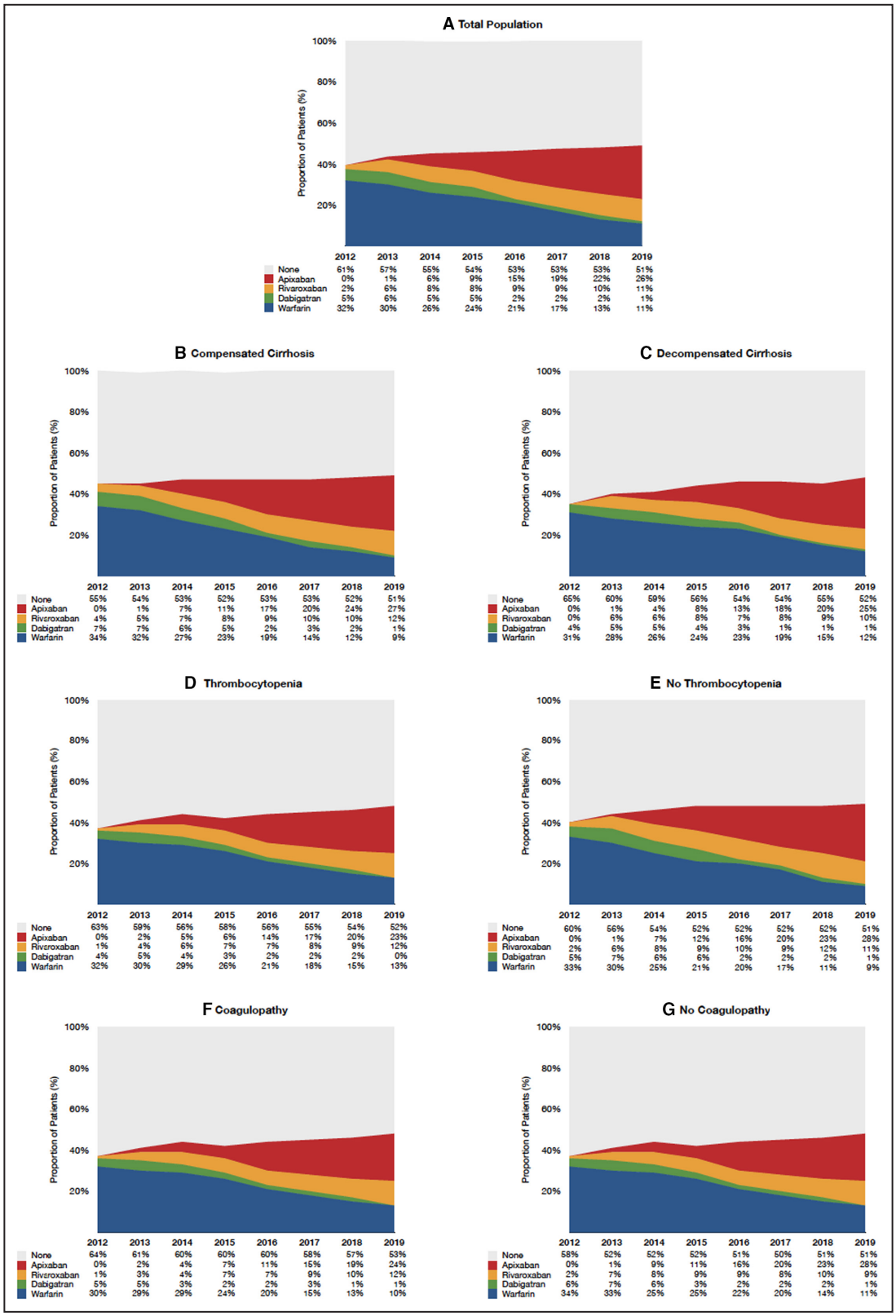



**Figure 1. Proportions of warfarin and DOAC prescriptions, among patients with cirrhosis and NVAF in MarketScan, 2012 to 2019.**

**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.

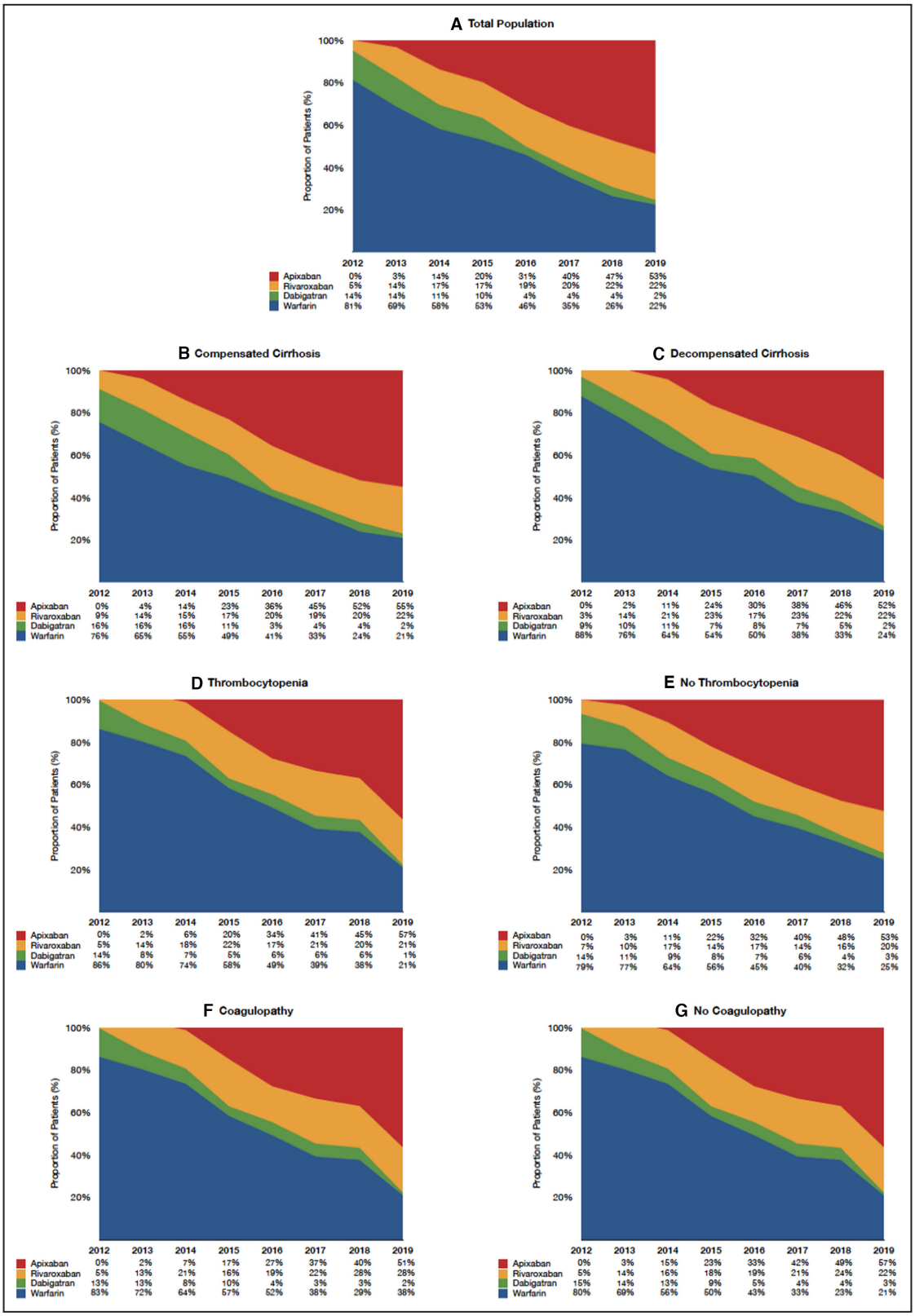



**Figure 2. Warfarin and DOAC prescriptions as a proportion of all OAC prescriptions, among patients with cirrhosis and NVAF in MarketScan, 2012 to 2019.**

**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 $CHA_2DS_2VASc$ categories. Specifically, in the most recent calendar year with available data (2019), among patients with $CHA_2DS_2VASc$ score <5, 79.1% of all OAC prescriptions were for DOACs, compared with 76.5% among patients with $CHA_2DS_2VASc$ 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 19 553 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 $CHA_2DS_2VASc$ 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, $CHA_2DS_2VASc$ scores ≥2 [men] or ≥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, $CHA_2DS_2VASc$ score ≥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 $CHA_2DS_2VASc$ score ≥2 do not receive anticoagulation, whereas in contrast, 40% to 53% of patients with a $CHA_2DS_2VASc$ score of 0 are treated with OAC therapy,[37–40] including in studies with rigorously defined NVAF and comorbidities and valid assessments of $CHA_2DS_2VASc$ 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 $CHA_2DS_2VASc$ 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

Received May 18, 2022; accepted November 30, 2022.

### Affiliations

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital (T.G.S., S.S., S.K.S., K.J.L.); and Division of Gastroenterology and Hepatology, Department of Medicine, Massachusetts General Hospital (T.G.S.), Harvard Medical School, Boston, MA; and Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA (D.E.S., K.J.L.).

### Acknowledgments

Study concept and design: Simon, Lin; Acquisition of data: Simon, Lin; Statistical analysis: Simon; Interpretation of data: all coauthors; Drafting of article: Simon; Critical revision of the article: all coauthors; Supervision and guarantor of the article: Lin. All authors contributed to the interpretation of the results and critical revision of the articlefor important intellectual content and approved the final version of the article. The corresponding author (Lin) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The corresponding author (Lin) affirms that the articleis an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

### Sources of Funding

This work was supported by National Institutes of Health K23 DK122104 (T.G.S.) and 1RF1AG063381–01 (K.J.L.). The funding sources did not participate in the design or conduct of this study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the article.

### 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

## REFERENCES


1. Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001–2013. *Gastroenterology.* 2015;149:1471–1482. E1475; quiz e1417-1478.
2. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. *BMJ.* 2018;362:k2817.
3. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology.* 2018;67:123–133. doi: 10.1002/hep.29466
4. Chokesuwattanaskul R, Thongprayoon C, Bathini T, O'Corragain OA, Sharma K, Preechawat S, Wijarnpreecha K, Kroner PT, Ungprasert P, Cheungpasitporn W. Epidemiology of atrial fibrillation in patients with cirrhosis and clinical significance: a meta-analysis. *Eur J Gastroenterol Hepatol.* 2019;31:514–519. doi: 10.1097/MEG.0000000000001315
5. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA.* 2001;285:2370–2375. doi: 10.1001/jama.285.18.2370
6. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med.* 2009;151:297–305. doi: 10.7326/0003-4819-151-5-200909010-00003
7. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992. doi: 10.1056/NEJMoa1107039
8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561
9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891. doi: 10.1056/NEJMoa1009638
10. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–2104. doi: 10.1056/NEJMoa1310907
11. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M, et al. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation.* 2015;131:157–164. doi: 10.1161/CIRCULATIONAHA.114.012061
12. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc.* 2016;5:e003725.
13. Chan YH, Yen KC, See LC, Chang SH, Wu LS, Lee HF, Tu HT, Yeh YH, Kuo CT. Cardiovascular, bleeding, and mortality risks of dabigatran in asians with nonvalvular atrial fibrillation. *Stroke.* 2016;47:441–449. doi: 10.1161/STROKEAHA.115.011476
14. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
15. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation.* 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
16. Nehra MS, Ma Y, Clark C, Amarasingham R, Rockey DC, Singal AG. Use of administrative claims data for identifying patients with cirrhosis. *J Clin Gastroenterol.* 2013;47:e50–e54. doi: 10.1097/MCG.0b013e3182688d2f
17. Kramer JR, Davila JA, Miller ED, Richardson P, Giordano TP, El-Serag HB. The validity of viral hepatitis and chronic liver disease diagnoses in veterans affairs administrative databases. *Aliment Pharmacol Ther.* 2008;27:274–282. doi: 10.1111/j.1365-2036.2007.03572.x
18. Goldberg D, Lewis J, Halpern S, Weiner M, Lo Re V III. Validation of three coding algorithms to identify patients with end-stage liver disease in an administrative database. *Pharmacoepidemiol Drug Saf.* 2012;21:765–769. doi: 10.1002/pds.3290
19. Mellinger JL, Shedden K, Winder GS, Tapper E, Adams M, Fontana RJ, Volk ML, Blow FC, Lok ASF. The high burden of alcoholic cirrhosis in privately insured persons in the United States. *Hepatology.* 2018;68:872–882. doi: 10.1002/hep.29887
20. Mapakshi S, Kramer JR, Richardson P, El-Serag HB, Kanwal F. Positive predictive value of international classification of diseases, 10th revision, codes for cirrhosis and its related complications. *Clin Gastroenterol Hepatol.* 2018;16:1677–1678. doi: 10.1016/j.cgh.2018.01.042
21. Antani MR, Beyth RJ, Covinsky KE, Anderson PA, Miller DG, Cebul RD, Quinn LM, Landefeld CS. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *J Gen Intern Med.* 1996;11:713–720. doi: 10.1007/BF02598984
22. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. *Stroke.* 1997;28:2382–2389. doi: 10.1161/01.STR.28.12.2382
23. Flaker GC, McGowan DJ, Boechler M, Fortune G, Gage B. Underutilization of antithrombotic therapy in elderly rural patients with atrial fibrillation. *Am Heart J.* 1999;137:307–312. doi: 10.1053/hj.1999.v137.91403
24. Shen AY, Yao JF, Brar SS, Jorgensen MB, Wang X, Chen W. Racial/ethnic differences in ischemic stroke rates and the efficacy of warfarin among patients with atrial fibrillation. *Stroke.* 2008;39:2736–2743. doi: 10.1161/STROKEAHA.107.508580
25. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol Drug Saf.* 2012;21:141–147. doi: 10.1002/pds.2317
26. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol.* 2019;74:104–132. doi: 10.1016/j.jacc.2019.01.011
27. Armitage P. Tests for linear trends in proportions and frequencies. *Biometrics.* 1955;10:417–451. doi: 10.2307/3001775
28. Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and reproducibility of observational cohort studies using large healthcare databases. *Clin Pharmacol Ther.* 2016;99:325–332. doi: 10.1002/cpt.329
29. Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med.* 2017;376:2300–2302. doi: 10.1056/NEJMc1701990
30. Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, Schneeweiss S. Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a multidatabase cohort study. *Arthritis Rheumatol.* 2017;69:1154–1164. doi: 10.1002/art.40084
31. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. *J Am Coll Cardiol.* 2018;71:2162–2175. doi: 10.1016/j.jacc.2018.03.023
32. Davis KA, Joseph J, Nisly SA. Direct oral anticoagulants and warfarin in patients with cirrhosis: a comparison of outcomes. *J Thromb Thrombolysis.* 2020;50:457–461. doi: 10.1007/s11239-019-02035-0
33. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202155s012lbl.pdf. Accessed November 01.
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s017lbl.pdf. Accessed November 01.

35. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s028lbl.pdf. Accessed November 01.
36. Buck J, Kaboli P, Gage BF, Cram P, Vaughan Sarrazin MS. Trends in antithrombotic therapy for atrial fibrillation: data from the veterans health administration health system. *Am Heart J.* 2016;179:186–191. doi: 10.1016/j.ahj.2016.03.029
37. Zimetbaum PJ, Thosani A, Yu HT, Xiong Y, Lin J, Kothawala P, Emons M. Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? *Am J Med.* 2010;123:446–453. doi: 10.1016/j.amjmed.2009.11.015
38. Liu J, Sylwestrzak G, Barron J, Rosenberg A, White J, Whitney J, Redberg R, Malenka D. Evaluation of practice patterns in the treatment of atrial fibrillation among the commercially insured. *Curr Med Res Opin.* 2014;30:1707–1713. doi: 10.1185/03007995.2014.922061
39. Akao M, Chun YH, Esato M, Abe M, Tsuji H, Wada H, Hasegawa K, Fushimi AFRI. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circ J.* 2014;78:2166–2172. doi: 10.1253/circj.CJ-14-0344
40. Cullen MW, Kim S, Piccini JP Sr, Ansell JE, Fonarow GC, Hylek EM, Singer DE, Mahaffey KW, Kowey PR, Thomas L, et al. Risks and benefits of anticoagulation in atrial fibrillation: insights from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) registry. *Circ Cardiovasc Qual Outcomes.* 2013;6:461–469. doi: 10.1161/CIRCOUTCOMES.113.000127
41. Lip GY, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res.* 2006;118:321–333. doi: 10.1016/j.thromres.2005.08.007
42. Perreault S, de Denus S, White-Guay B, Cote R, Schnitzer ME, Dube MP, Dorais M, Tardif JC. Oral anticoagulant prescription trends, profile use, and determinants of adherence in patients with atrial fibrillation. *Pharmacotherapy.* 2020;40:40–54. doi: 10.1002/phar.2350
43. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. *Pharmacotherapy.* 2018;38:907–920. doi: 10.1002/phar.2158
44. Wong SL, Marshall LZ, Lawson KA. Direct oral anticoagulant prescription trends, switching patterns, and adherence in Texas medicaid. *Am J Manag Care.* 2018;24:SP309–SP314.

# SUPPLEMENTAL MATERIAL

**Table S1. Variable Definitions.**

| Variable Name | ICD-9 | ICD-10 |
|---|---|---|
| $CHA_2DS_2VASc$ score[1] | Congestive heart failure:<br>"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"<br><br>Hypertension:<br>"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"<br><br>Diabetes:<br>"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", "250.41", "250.42", "250.5", "250.50", "250.60", "250.61", "250.62", "250.71", "250.72", "250.8", "250.80", "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", "249.71", "249.8", "249.9", "250.03", "250.13", "250.23", "250.3", "250.31", "250.32", "250.4", "250.43", "250.51", "250.52", "250.53", "250.6", "250.63", "250.7", "250.70", "250.73", "250.81", "250.9", "250.92", "250.93"<br><br>Stroke, TIA, or Thromboembolism:<br>"415.1", "415.12", "415.13", "415.19", "431", "432", "432.0", "432.1", "432.9", "433", "433.00", "433.1", "433.2", "433.20", "433.30", "433.8", "433.9", "433.90", "433.91", "434.01", "434.11", "434.91", "435", "435.2", "435.3", "435.8", "435.9", "437.3", "451.11", "451.19", "453.4", "453.41", "453.42", "453.5", "453.52", "453.8", "453.83", "453.84", "453.85", "453.86", "453.89", "453.9", "634.60", | Congestive heart failure:<br>"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"<br><br>Hypertension:<br>"I15.8", "I15.9", "I16.1", "N26.2", "I10", "I15.0", "I15.1", "I15.2", "I16.0", "I16.9"<br><br>Diabetes:<br>"E08.00", "E08.01", "E08.10", "E08.11", "E08.22", "E08.311", "E08.319", "E08.3211", "E08.3212", "E08.3219", "E08.3292", "E08.3311", "E08.3313", "E08.3391", "E08.3392", "E08.3411", "E08.3412", "E08.3499", "E08.3511", "E08.3512", "E08.3513", "E08.3519", "E08.3521", "E08.3523", "E08.3541", "E08.3542", "E08.3549", "E08.3551", "E08.3559", "E08.36", "E08.37X1", "E08.37X2", "E08.44", "E08.49", "E08.51", "E08.618", "E08.621", "E08.622", "E08.630", "E08.638", "E08.641", "E08.649", "E08.69", "E08.8", "E09.01", "E09.10", "E09.3219", "E09.3291", "E09.3292", "E09.3311", "E09.3393", "E09.3413", "E09.3419", "E09.3491", "E09.3493", "E09.3499", "E09.3511", "E09.3513", "E09.3522", "E09.3523", "E09.3532", "E09.3533", "E09.3553", "E09.3591", "E09.3593", "E09.36", "E09.37X1", "E09.39", "E09.40", "E09.41", "E09.51", "E09.52", "E09.610", "E09.620", "E09.621", "E09.622", "E09.628", "E09.630", "E09.641", "E09.65", "E10.11", "E10.21", "E10.22", "E10.29", "E10.319", "E10.3212", "E10.3293", "E10.3299", "E10.3311", "E10.3319", "E10.3411", "E10.3413", "E10.3419", "E10.3491", "E10.3492", "E10.3499", "E10.3511", "E10.3512", "E10.3513", "E10.3531", "E10.3543", "E10.3549", "E10.3553", "E10.3559", "E10.3591", "E10.3592", |

| | | |
|---|---|---|
| | “634.61”, “634.62”, “635.62”, “636.61”, “636.62”, “637.62”, “673.22”, “673.83”, “673.84”, “997.02”, “415.11”, “430”, “433.0”, “433.01”, “433.10”, “433.11”, “433.21”, “433.3”, “433.31”, “433.80”, “433.81”, “435.0”, “435.1”, “437.1”, “451.1”, “451.2”, “453.40”, “453.50”, “453.51”, “453.81”, “453.82”, “453.87”, “635.60”, “635.61”, “636.60”, “637.60”, “637.61”, “638.6”, “639.6”, “673.20”, “673.21”, “673.23”, “673.24”, “673.80”, “673.81”, “673.82”<br><br>Vascular Disease:<br>“250.71”, “250.72”, “410”, “410.00”, “410.01”, “410.02”, “410.11”, “410.20”, “410.21”, “410.40”, “410.42”, “410.5”, “410.52”, “410.6”, “410.60”, “410.61”, “410.62”, “410.71”, “410.72”, “410.81”, “410.92”, “414”, “414.00”, “414.02”, “414.03”, “414.06”, “414.07”, “414.1”, “414.11”, “414.8”, “414.9”, “443.9”, “250.7”, “250.70”, “250.73”, “410.0”, “410.1”, “410.10”, “410.12”, “410.2”, “410.22”, “410.3”, “410.30”, “410.31”, “410.32”, “410.4”, “410.41”, “410.50”, “410.51”, “410.7”, “410.70”, “410.8”, “410.80”, “410.82”, “410.9”, “410.90”, “410.91”, “412”, “414.0”, “414.01”, “414.04”, “414.05”, “414.10”, “414.12”, “414.19”, “414.2”, “414.3”, “414.4”, “440.0”, “443.81” | “E10.3599”, “E10.36”, “E10.37X9”, “E10.39”, “E10.40”, “E10.41”, “E10.42”, “E10.44”, “E10.49”, “E10.51”, “E10.59”, “E10.610”, “E10.618”, “E10.628”, “E10.641”, “E10.65”, “E10.9”, “E11.01”, “E11.21”, “E11.22”, “E11.311”, “E11.3211”, “E11.3212”, “E11.3213”, “E11.3219”, “E11.3311”, “E11.3312”, “E11.3319”, “E11.3391”, “E11.3392”, “E11.3393”, “E11.3399”, “E11.3411”, “E11.3493”, “E11.3499”, “E11.3511”, “E11.3513”, “E11.3519”, “E11.3521”, “E11.3522”, “E11.3529”, “E11.3532”, “E11.3533”, “E11.3552”, “E11.3592”, “E11.3593”, “E11.3599”, “E11.37X1”, “E11.37X2”, “E11.37X3”, “E11.39”, “E11.40”, “E11.51”, “E11.52”, “E11.618”, “E11.638”, “E11.641”, “E11.65”, “E11.9”, “E13.00”, “E13.10”, “E13.11”, “E13.319”, “E13.3211”, “E13.3212”, “E13.3213”, “E13.3219”, “E13.3291”, “E13.3292”, “E13.3293”, “E13.3312”, “E13.3313”, “E13.3393”, “E13.3419”, “E13.3491”, “E13.3492”, “E13.3511”, “E13.3512”, “E13.3519”, “E13.3529”, “E13.3533”, “E13.3541”, “E13.3543”, “E13.3551”, “E13.3552”, “E13.3553”, “E13.3559”, “E13.37X9”, “E13.39”, “E13.40”, “E13.41”, “E13.42”, “E13.44”, “E13.49”, “E13.51”, “E13.59”, “E13.628”, “E13.641”, “E13.65”, “E13.69”, “E13.8”, “E13.9”, “E08.21”, “E08.29”, “E08.3213”, “E08.3291”, “E08.3293”, “E08.3299”, “E08.3312”, “E08.3319”, “E08.3393”, “E08.3399”, “E08.3413”, “E08.3419”, “E08.3491”, “E08.3492”, “E08.3493”, “E08.3522”, “E08.3529”, “E08.3531”, “E08.3532”, “E08.3533”, “E08.3539”, “E08.3543”, “E08.3552”, “E08.3553”, “E08.3591”, “E08.3592”, “E08.3593”, “E08.3599”, “E08.37X3”, “E08.37X9”, “E08.39”, “E08.40”, “E08.41”, “E08.42”, “E08.43”, “E08.52”, “E08.59”, “E08.610”, “E08.620”, “E08.628”, “E08.65”, “E08.9”, “E09.00”, “E09.11”, “E09.21”, “E09.22”, “E09.29”, “E09.311”, “E09.319”, “E09.3211”, “E09.3212”, “E09.3213”, “E09.3293”, “E09.3299”, “E09.3312”, “E09.3313”, “E09.3319”, |

| | | |
|---|---|---|
| | | “E09.339”, “E09.3391”, “E09.3399”, “E09.3412”, “E09.3512”, “E09.3519”, “E09.3542”, “E09.3551”, “E09.3552”, “E09.3592”, “E09.3599”, “E09.37X9”, “E09.42”, “E09.43”, “E09.44”, “E09.49”, “E09.59”, “E09.618”, “E09.638”, “E09.649”, “E09.69”, “E09.8”, “E09.9”, “E10.10”, “E10.311”, “E10.3211”, “E10.3213”, “E10.3219”, “E10.3291”, “E10.3292”, “E10.3312”, “E10.3313”, “E10.3391”, “E10.3392”, “E10.3393”, “E10.3399”, “E10.3412”, “E10.3493”, “E10.3519”, “E10.3521”, “E10.3522”, “E10.3523”, “E10.3529”, “E10.3532”, “E10.3533”, “E10.3539”, “E10.3541”, “E10.3542”, “E10.3551”, “E10.3552”, “E10.3593”, “E10.37X1”, “E10.37X2”, “E10.37X3”, “E10.43”, “E10.52”, “E10.620”, “E10.621”, “E10.622”, “E10.630”, “E10.638”, “E10.649”, “E10.69”, “E10.8”, “E11.00”, “E11.10”, “E11.11”, “E11.29”, “E11.319”, “E11.3291”, “E11.3292”, “E11.3293”, “E11.3299”, “E11.3313”, “E11.3412”, “E11.3413”, “E11.3419”, “E11.3491”, “E11.3492”, “E11.3512”, “E11.3523”, “E11.3531”, “E11.3539”, “E11.3541”, “E11.3542”, “E11.3543”, “E11.3549”, “E11.3551”, “E11.3553”, “E11.3559”, “E11.3591”, “E11.36”, “E11.37X9”, “E11.41”, “E11.42”, “E11.43”, “E11.44”, “E11.49”, “E11.59”, “E11.610”, “E11.620”, “E11.621”, “E11.622”, “E11.628”, “E11.630”, “E11.649”, “E11.69”, “E11.8”, “E13.01”, “E13.21”, “E13.22”, “E13.29”, “E13.311”, “E13.3299”, “E13.3311”, “E13.3319”, “E13.3391”, “E13.3392”, “E13.3399”, “E13.3411”, “E13.3412”, “E13.3413”, “E13.3493”, “E13.3499”, “E13.3513”, “E13.3521”, “E13.3522”, “E13.3523”, “E13.3531”, “E13.3532”, “E13.3539”, “E13.3542”, “E13.3549”, “E13.3591”, “E13.3592”, “E13.3593”, “E13.3599”, “E13.36”, “E13.37X1”, “E13.37X2”, “E13.37X3”, “E13.43”, “E13.52”, “E13.610”, “E13.618”, “E13.620”, “E13.621”, “E13.622”, “E13.630”, “E13.638”, “E13.649”<br><br>Stroke, TIA, or Thromboembolism: |

| | | |
|---|---|---|
| | | “G45.0”, “G45.1”, “G45.2”, “G46.0”, “G46.2”, “I26.01”, “I26.02”, “I26.09”, “I26.90”, “I26.92”, “I60.00”, “I60.02”, “I60.10”, “I60.12”, “I60.2”, “I60.30”, “I60.50”, “I60.51”, “I60.6”, “I61.0”, “I61.1”, “I61.3”, “I61.8”, “I62.00”, “I62.01”, “I62.02”, “I62.03”, “I62.1”, “I63.013”, “I63.019”, “I63.031”, “I63.032”, “I63.112”, “I63.113”, “I63.119”, “I63.132”, “I63.212”, “I63.219”, “I63.233”, “I63.30”, “I63.313”, “I63.329”, “I63.331”, “I63.332”, “I63.333”, “I63.341”, “I63.342”, “I63.343”, “I63.349”, “I63.39”, “I63.40”, “I63.411”, “I63.421”, “I63.429”, “I63.431”, “I63.433”, “I63.439”, “I63.441”, “I63.49”, “I63.50”, “I63.511”, “I63.519”, “I63.522”, “I63.529”, “I63.532”, “I63.533”, “I63.541”, “I63.542”, “I63.543”, “I63.6”, “I63.8”, “I65.02”, “I65.09”, “I65.1”, “I65.21”, “I65.29”, “I65.8”, “I67.1”, “I67.81”, “I67.848”, “I80.11”, “I80.12”, “I80.13”, “I80.221”, “I80.222”, “I80.223”, “I80.231”, “I80.233”, “I80.292”, “I80.3”, “I82.210”, “I82.401”, “I82.402”, “I82.403”, “I82.409”, “I82.411”, “I82.431”, “I82.432”, “I82.439”, “I82.443”, “I82.491”, “I82.492”, “I82.499”, “I82.4Z1”, “I82.501”, “I82.502”, “I82.509”, “I82.511”, “I82.519”, “I82.521”, “I82.523”, “I82.531”, “I82.533”, “I82.541”, “I82.542”, “I82.549”, “I82.599”, “I82.5Y1”, “I82.5Y2”, “I82.5Y9”, “I82.5Z1”, “I82.5Z3”, “I82.5Z9”, “I82.611”, “I82.613”, “I82.A12”, “I82.A13”, “I82.A19”, “I82.B11”, “I82.B13”, “I82.B19”, “I82.C13”, “I82.C19”, “I97.821”, “O07.2”, “O88.213”, “O88.83”, “T80.0XXA”, “T82.817A”, “T82.818A”, “G45.8”, “G45.9”, “G46.1”, “G97.31”, “G97.32”, “I26.99”, “I60.01”, “I60.11”, “I60.31”, “I60.32”, “I60.4”, “I60.52”, “I60.7”, “I60.8”, “I60.9”, “I61.2”, “I61.4”, “I61.5”, “I61.6”, “I61.9”, “I62.9”, “I63.00”, “I63.011”, “I63.012”, “I63.02”, “I63.033”, “I63.039”, “I63.09”, “I63.10”, “I63.111”, “I63.12”, “I63.131”, “I63.133”, “I63.139”, |

| | | |
|---|---|---|
| | | “I63.19”, “I63.20”, “I63.211”, “I63.213”, “I63.22”, “I63.231”, “I63.232”, “I63.239”, “I63.29”, “I63.311”, “I63.312”, “I63.319”, “I63.321”, “I63.322”, “I63.323”, “I63.339”, “I63.412”, “I63.413”, “I63.419”, “I63.422”, “I63.423”, “I63.432”, “I63.442”, “I63.443”, “I63.449”, “I63.512”, “I63.513”, “I63.521”, “I63.523”, “I63.531”, “I63.539”, “I63.549”, “I63.59”, “I63.9”, “I65.01”, “I65.03”, “I65.22”, “I65.23”, “I65.9”, “I67.82”, “I67.841”, “I80.10”, “I80.201”, “I80.202”, “I80.203”, “I80.209”, “I80.229”, “I80.232”, “I80.239”, “I80.291”, “I80.293”, “I80.299”, “I82.290”, “I82.412”, “I82.413”, “I82.419”, “I82.421”, “I82.422”, “I82.423”, “I82.429”, “I82.433”, “I82.441”, “I82.442”, “I82.449”, “I82.493”, “I82.4Y1”, “I82.4Y2”, “I82.4Y3”, “I82.4Y9”, “I82.4Z2”, “I82.4Z3”, “I82.4Z9”, “I82.503”, “I82.512”, “I82.513”, “I82.522”, “I82.529”, “I82.532”, “I82.539”, “I82.543”, “I82.591”, “I82.592”, “I82.593”, “I82.5Y3”, “I82.5Z2”, “I82.601”, “I82.602”, “I82.603”, “I82.609”, “I82.612”, “I82.619”, “I82.621”, “I82.622”, “I82.623”, “I82.629”, “I82.890”, “I82.90”, “I82.91”, “I82.A11”, “I82.B12”, “I82.C11”, “I82.C12”, “I97.810”, “I97.811”, “I97.820”, “O03.2”, “O03.7”, “O04.7”, “O08.2”, “O88.211”, “O88.212”, “O88.219”, “O88.22”, “O88.23”, “O88.811”, “O88.812”, “O88.813”, “O88.819”, “O88.82”, “T81.718A”, “T81.72XA”<br><br>Vascular Disease:<br>“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”, “I25.3”, “I25.41”, “I25.700”, “I25.701”, “I25.708”, “I25.709”, “I25.718”, “I25.720”, “I25.721”, “I25.729”, “I25.738”, “I25.751”, “I25.759”, “I25.760”, “I25.761”, |

| | | |
|---|---|---|
| | | “I25.769”, “I25.798”, “I25.799”, “I25.810”, “I25.811”, “I25.83”, “I25.89”, “I25.9”, “I70.0”, “I73.9”, “I79.1”, “I79.8”, “E08.52”, “E10.52”, “E11.59”, “E13.52”, “I21.09”, “I21.19”, “I21.21”, “I21.3”, “I21.9”, “I21.A1”, “I22.2”, “I22.8”, “I22.9”, “I25.110”, “I25.119”, “I25.2”, “I25.42”, “I25.5”, “I25.6”, “I25.710”, “I25.711”, “I25.719”, “I25.728”, “I25.730”, “I25.731”, “I25.739”, “I25.750”, “I25.758”, “I25.768”, “I25.790”, “I25.791”, “I25.812”, “I25.82”, “I25.84” |
| HAS-BLED score[2] | Abnormal Liver Function:<br>“794.8”<br><br>Abnormal Renal Function:<br>“794.4”<br><br>Drug or Alcohol Abuse:<br>“303.02”, “303.90”, “303.92”, “303.93”, “305.01”, “305.02”, “V11.3”, “303.00”, “303.01”, “303.03”, “303.91”, “305.00”, “305.03”<br><br>Stroke:<br>“433.91”, “434.01”, “434.11”, “434.91”, “433.01”, “433.11”, “433.21”, “433.31”, “433.81”<br><br>Hypertension:<br>“401.1”, “401.9”, “402.0”, “402.00”, “402.01”, “402.9”, “403.0”, “403.01”, “403.1”, “403.10”, “403.9”, “403.90”, “403.91”, “404.00”, “404.1”, “404.12”, “404.13”, “404.90”, “404.91”, “404.92”, “404.93”, “405.0”, “405.01”, “405.11”, “405.19”, “405.9”, “401.0”, “402.1”, “402.10”, “402.11”, “402.90”, “402.91”, “403.00”, “403.11”, “404.0”, “404.01”, “404.02”, “404.03”, “404.10”, “404.11”, “404.9”, “405.09”, “405.1”, “405.91”, “405.99”<br><br>Bleeding:<br>“280.8”, “280.9”, “281.0”, “281.4”, “281.8”, “282.1”, “282.2”, “282.4”, “282.40”, “282.42”, “282.44”, “282.45”, “282.47”, “282.5”, “282.6”, “282.64”, “282.69”, “282.9”, “283.10”, “283.2”, “283.9”, “284.09”, “284.1”, | Abnormal Liver Function:<br>“R94.5”<br><br>Abnormal Renal Function:<br>“R94.4”<br><br>Drug or Alcohol Abuse:<br>“F10.10”, “F10.20”, “F10.21”, “F10.220”, “Z65.8”, “F10.11”, “F10.120”, “F10.129”, “F10.229”<br><br>Stroke:<br>“I63.013”, “I63.019”, “I63.031”, “I63.032”, “I63.112”, “I63.113”, “I63.119”, “I63.132”, “I63.212”, “I63.219”, “I63.233”, “I63.30”, “I63.313”, “I63.329”, “I63.331”, “I63.332”, “I63.333”, “I63.341”, “I63.342”, “I63.343”, “I63.349”, “I63.39”, “I63.40”, “I63.411”, “I63.421”, “I63.429”, “I63.431”, “I63.433”, “I63.439”, “I63.441”, “I63.49”, “I63.50”, “I63.511”, “I63.519”, “I63.522”, “I63.529”, “I63.532”, “I63.533”, “I63.541”, “I63.542”, “I63.543”, “I63.6”, “I63.8”, “I63.00”, “I63.011”, “I63.012”, “I63.02”, “I63.033”, “I63.039”, “I63.09”, “I63.10”, “I63.111”, “I63.12”, “I63.131”, “I63.133”, “I63.139”, “I63.19”, “I63.20”, “I63.211”, “I63.213”, “I63.22”, “I63.231”, “I63.232”, “I63.239”, “I63.29”, “I63.311”, “I63.312”, “I63.319”, “I63.321”, “I63.322”, “I63.323”, “I63.339”, “I63.412”, “I63.413”, “I63.419”, “I63.422”, “I63.423”, “I63.432”, “I63.442”, “I63.443”, |

| | | |
|---|---|---|
| | “284.19”, “284.8”, “284.89”, “285.0”, “285.2”, “285.22”, “285.29”, “285.8”, “280.0”, “280.1”, “281.1”, “281.2”, “281.3”, “281.9”, “282.0”, “282.3”, “282.41”, “282.43”, “282.46”, “282.49”, “282.60”, “282.61”, “282.62”, “282.63”, “282.68”, “282.7”, “282.8”, “283.0”, “283.1”, “283.11”, “283.19”, “284.0”, “284.01”, “284.11”, “284.12”, “284.2”, “284.81”, “284.9”, “285.1”, “285.21”, “285.3”, “285.9” | “I63.449”, “I63.512”, “I63.513”, “I63.521”, “I63.523”, “I63.531”, “I63.539”, “I63.549”, “I63.59”, “I63.9”<br><br>Hypertension:<br>“I11.9”, “I13.10”, “I13.2”, “I15.8”, “I15.9”, “I16.1”, “N26.2”, “I10”, “I11.0”, “I12.0”, “I12.9”, “I13.0”, “I13.11”, “I15.0”, “I15.1”, “I15.2”, “I16.0”, “I16.9”<br><br>Bleeding:<br>“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”, “D57.40”, “D57.411”, “D57.80”, “D57.811”, “D57.812”, “D58.2”, “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”, “D59.8”, “D59.9”, “D60.9”, “D61.01”, “D61.09”, “D61.1”, “D61.3”, “D61.810”, “D61.818”, “D61.89”, “D62”, “D63.0”, “D64.2”, “D64.3”, “D64.4”, “D64.81”, “D64.9” |
| Thrombocytopenia | “287.3”, “287.30”, “287.31”, “287.32”, “287.33”, “287.39”, “287.4”, “287.41”, “287.49”, “287.5” | “D69.3”, “D69.41”, “D69.42”, “D69.49”, “D69.51”, “D69.59”, “D69.6” |
| Coagulopathy | “286”, “286.0”, “286.1”, “286.2”, “286.3”, “286.4”, “286.5”, “286.52”, “286.53”, “286.59”, “286.6”, “286.7”, “286.9”, “287.1”, “287.3”, “287.4”, “287.5” | “D65”, “D66”, “D67”, “D68”, “D68.0”, “D68.1”, “D68.2”, “D68.3”, “D68.31”, “D68.311”, “D68.312”, “D68.318”, “D68.32”, “D68.4”, “D68.5”, “D68.51”, “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”, “D69.49”, “D69.5”, “D69.51”, “D69.59”, “D69.6” |
| Major Bleeding | Hospitalization for major bleeding event: | Hospitalization for major bleeding event: |

| | | |
|---|---|---|
| | DX {“336.1”, “363.61”, “363.62”, “372.72”, “377.42”, “379.23”, “431”, “432”, “432.0”, “432.1”, “432.9”, “719.11”, “719.15”, “719.18”, “719.19”, “852.02”, “852.03”, “852.04”, “852.09”, “852.10”, “852.11”, “852.12”, “852.15”, “852.19”, “852.21”, “852.24”, “852.29”, “852.3”, “852.31”, “852.33”, “852.34”, “852.35”, “852.36”, “852.4”, “852.41”, “852.42”, “852.43”, “852.44”, “852.54”, “852.55”, “852.59”, “853.00”, “853.01”, “853.04”, “853.06”, “853.12”, “853.15”, “853.19”, “363.63”, “376.32”, “430”, “719.12”, “719.13”, “719.14”, “719.16”, “719.17”, “729.92”, “852.0”, “852.00”, “852.01”, “852.05”, “852.06”, “852.1”, “852.13”, “852.14”, “852.16”, “852.2”, “852.20”, “852.22”, “852.23”, “852.25”, “852.26”, “852.30”, “852.32”, “852.39”, “852.40”, “852.45”, “852.46”, “852.49”, “852.5”, “852.50”, “852.51”, “852.52”, “852.53”, “852.56”, “853.0”, “853.02”, “853.03”, “853.05”, “853.09”, “853.1”, “853.10”, “853.11”, “853.13”, “853.14”, “853.16”, “866.01”, “866.02”, “866.11”, “866.12”}<br><br>OR<br><br>Hospitalization AND transfusion:<br>DX {“423.0”, “455.7”, “456.0”, “456.20”, “530.1”, “531.00”, “531.01”, “531.1”, “531.20”, “531.21”, “531.3”, “531.40”, “531.5”, “531.60”, “532.00”, “532.01”, “532.20”, “532.5”, “532.60”, “532.7”, “532.9”, “533.00”, “533.1”, “533.3”, “533.40”, “533.41”, “533.7”, “534.20”, “534.3”, “535.00”, “535.10”, “535.30”, “535.31”, “537.83”, “562.00”, “562.02”, “562.10”, “562.12”, “562.13”, “578.1”, “599.7”, “626.2”, “784.8”, “786.3”, “790.92”, “280.0”, “285.1”, “285.9”, “455.0”, “455.1”, “455.2”, “455.3”, “455.4”, “455.5”, “455.6”, “455.8”, “455.9”, “459.0”, “530.7”, “530.82”, “531.41”, “531.61”, “531.7”, “531.9”, “532.1”, “532.21”, “532.3”, “532.40”, “532.41”, | DX {“G95.19”, “H05.233”, “H05.239”, “H11.30”, “H11.32”, “H11.33”, “H31.301”, “H31.303”, “H31.313”, “H31.322”, “H31.323”, “H43.11”, “H47.021”, “H47.022”, “H47.023”, “H47.029”, “I60.00”, “I60.02”, “I60.10”, “I60.12”, “I60.2”, “I60.30”, “I60.50”, “I60.51”, “I60.6”, “I61.0”, “I61.1”, “I61.3”, “I61.8”, “I62.00”, “I62.01”, “I62.02”, “I62.03”, “M25.00”, “M25.012”, “M25.019”, “M25.021”, “M25.022”, “M25.029”, “M25.031”, “M25.039”, “M25.041”, “M25.049”, “M25.051”, “M25.052”, “M25.061”, “M25.062”, “M25.069”, “M25.074”, “M25.075”, “M25.076”, “S06.340A”, “S06.341A”, “S06.346A”, “S06.350A”, “S06.352A”, “S06.354A”, “S06.356A”, “S06.357A”, “S06.358A”, “S06.360A”, “S06.361A”, “S06.363A”, “S06.365A”, “S06.369A”, “S06.4X1A”, “S06.4X2A”, “S06.4X3A”, “S06.4X5A”, “S06.4X6A”, “S06.4X7A”, “S06.4X8A”, “S06.4X9A”, “S06.5X0A”, “S06.5X1A”, “S06.5X3A”, “S06.5X5A”, “S06.5X6A”, “S06.5X8A”, “S06.5X9A”, “S06.6X1A”, “S06.6X6A”, “S06.6X7A”, “S06.6X8A”, “S37.041A”, “S37.051A”, “H05.231”, “H05.232”, “H11.31”, “H31.302”, “H31.309”, “H31.311”, “H31.312”, “H31.319”, “H31.321”, “H31.329”, “H43.10”, “H43.12”, “H43.13”, “I60.01”, “I60.11”, “I60.31”, “I60.32”, “I60.4”, “I60.52”, “I60.7”, “I60.8”, “I60.9”, “I61.2”, “I61.4”, “I61.5”, “I61.6”, “I61.9”, “I62.9”, “M25.011”, “M25.032”, “M25.042”, “M25.059”, “M25.071”, “M25.072”, “M25.073”, “M25.08”, “M79.81”, “S06.342A”, “S06.343A”, “S06.344A”, “S06.345A”, “S06.347A”, “S06.348A”, “S06.349A”, “S06.351A”, “S06.353A”, “S06.355A”, “S06.359A”, “S06.362A”, “S06.364A”, “S06.366A”, “S06.367A”, “S06.368A”, “S06.4X0A”, “S06.4X4A”, “S06.5X2A”, “S06.5X4A”, “S06.5X7A”, “S06.6X0A”, “S06.6X2A”, “S06.6X3A”, “S06.6X4A”, “S06.6X5A”, “S06.6X9A”, “S31.001A”, “S37.031A”, “S37.032A”, “S37.039A”, “S37.042A”, “S37.049A”, “S37.052A”, “S37.059A”} |

| | | |
|---|---|---|
| | "532.61", "533.01", "533.20", "533.21", "533.5", "533.60", "533.61", "533.9", "534.00", "534.01", "534.1", "534.21", "534.40", "534.41", "534.5", "534.60", "534.61", "534.7", "534.9", "535.01", "535.11", "535.20", "535.21", "535.40", "535.41", "535.50", "535.51", "535.60", "535.61", "562.01", "562.03", "562.11", "568.81", "569.3", "569.85", "578.0", "578.9", "623.8", "626.6", "784.7"} AND PX {"99.03", "99.04", "99.05", "99.06"}<br><br>OR<br><br>Hospitalization AND CPT/HCPC code for blood/blood product:<br>DX {"423.0", "455.7", "456.0", "456.20", "530.1", "531.00", "531.01", "531.1", "531.20", "531.21", "531.3", "531.40", "531.5", "531.60", "532.00", "532.01", "532.20", "532.5", "532.60", "532.7", "532.9", "533.00", "533.1", "533.3", "533.40", "533.41", "533.7", "534.20", "534.3", "535.00", "535.10", "535.30", "535.31", "537.83", "562.00", "562.02", "562.10", "562.12", "562.13", "578.1", "599.7", "626.2", "784.8", "786.3", "790.92", "280.0", "285.1", "285.9", "455.0", "455.1", "455.2", "455.3", "455.4", "455.5", "455.6", "455.8", "455.9", "459.0", "530.7", "530.82", "531.41", "531.61", "531.7", "531.9", "532.1", "532.21", "532.3", "532.40", "532.41", "532.61", "533.01", "533.20", "533.21", "533.5", "533.60", "533.61", "533.9", "534.00", "534.01", "534.1", "534.21", "534.40", "534.41", "534.5", "534.60", "534.61", "534.7", "534.9", "535.01", "535.11", "535.20", "535.21", "535.40", "535.41", "535.50", "535.51", "535.60", "535.61", "562.01", "562.03", "562.11", "568.81", "569.3", "569.85", "578.0", "578.9", "623.8", "626.6", "784.7"} AND CPT/HCPC {"P9011", "P9017", "P9022", "P9032", "P9034", "P9035", "P9036", "P9037", "P9051", "P9054", "P9056", "P9057", "P9010", "P9016", "P9019", "P9020", "P9021", | OR<br><br>Hospitalization AND transfusion:<br>DX {"D62", "D64.9", "K22.6", "K25.0", "K25.2", "K25.6", "K26.0", "K26.2", "K26.4", "K26.6", "K27.0", "K27.2", "K27.6", "K28.0", "K28.2", "K28.4", "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 PX {"30230H1", "30230M1", "30230N1", "30230P1", "30230R1", "30230W1", "30233L1", "30233V1", "30233W1", "30240H1", "30240M1", "30240N1", "30240T1", "30240V1", "30240W1", "30243H1", "30243L1", "30243M1", "30243P1", "30243Q1", "30243R1", "30243T1", "30250H1", "30250M1", "30250W1", "30253H1", "30253K1", "30253M1", "30253N1", "30253P1", "30253R1", "30253T1", "30253V1", "30253W1", "30260H1", "30260L1", "30260M1", "30260N1", "30260P1", "30263M1", "30263R1", "30263W1", "30230K1", "30230L1", "30230T1", "30230V1", "30233H1", "30233K1", "30233M1", "30233N1", "30233P1", "30233Q1", "30233R1", "30233T1", "30240K1", "30240L1", "30240P1", "30240R1", "30243K1", "30243N1", "30243V1", "30243W1", "30250K1", "30250L1", "30250N1", "30250P1", "30250R1", "30250T1", "30250V1", "30253L1", "30260K1", "30260R1", "30260T1", "30260V1", "30260W1", "30263H1", "30263K1", "30263L1", "30263N1", "30263P1", "30263T1", "30263V1"}<br><br>OR |

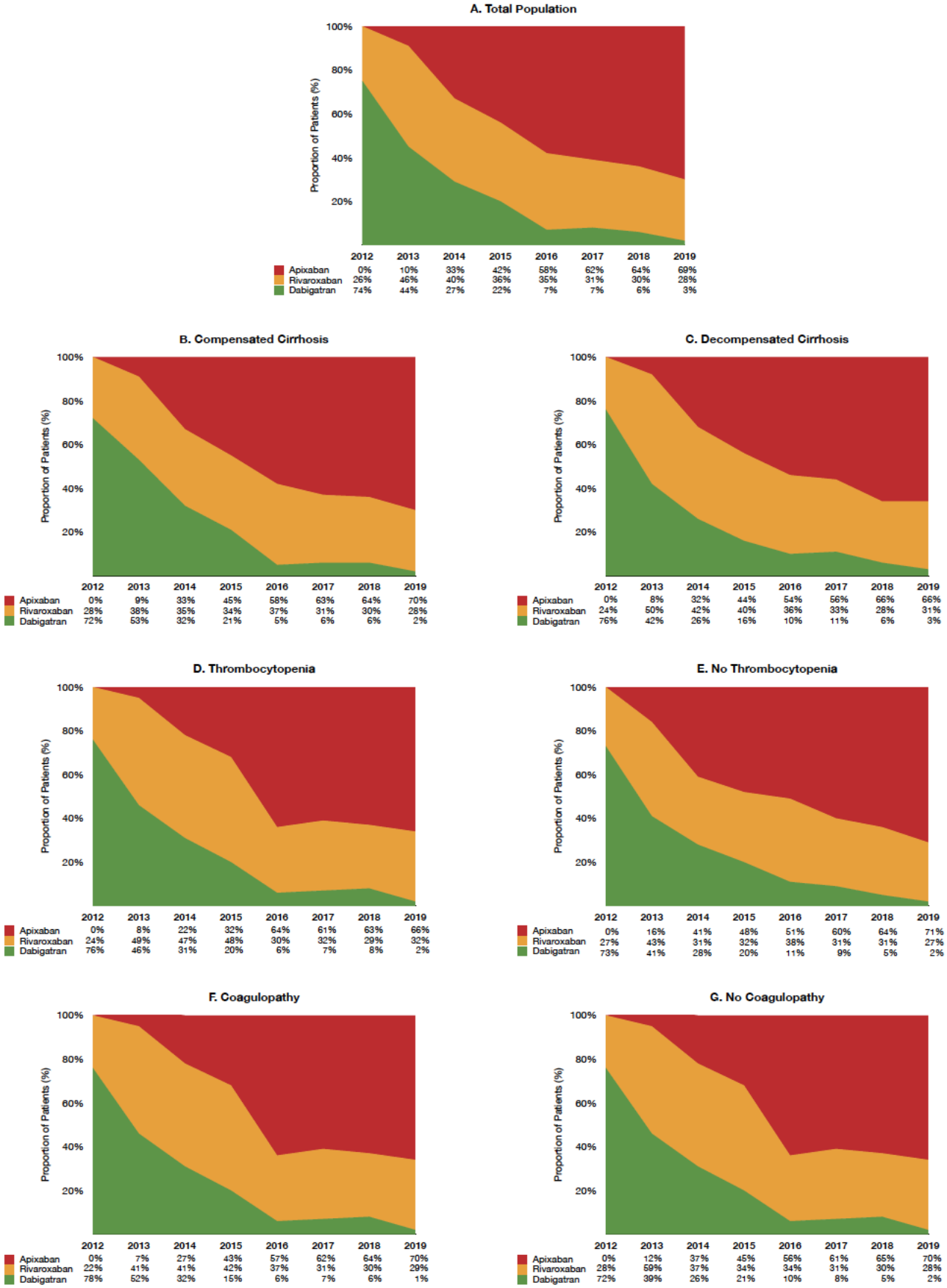
| | | |
|---|---|---|
| | "P9023", "P9031", "P9033", "P9038", "P9039", "P9040", "P9044", "P9052", "P9053", "P9055", "P9058", "P9059", "P9060"}<br><br>OR<br><br>Hospitalization AND revenue code for blood/blood product:<br>DX {"423.0", "455.7", "456.0", "456.20", "530.1", "531.00", "531.01", "531.1", "531.20", "531.21", "531.3", "531.40", "531.5", "531.60", "532.00", "532.01", "532.20", "532.5", "532.60", "532.7", "532.9", "533.00", "533.1", "533.3", "533.40", "533.41", "533.7", "534.20", "534.3", "535.00", "535.10", "535.30", "535.31", "537.83", "562.00", "562.02", "562.10", "562.12", "562.13", "578.1", "599.7", "626.2", "784.8", "786.3", "790.92", "280.0", "285.1", "285.9", "455.0", "455.1", "455.2", "455.3", "455.4", "455.5", "455.6", "455.8", "455.9", "459.0", "530.7", "530.82", "531.41", "531.61", "531.7", "531.9", "532.1", "532.21", "532.3", "532.40", "532.41", "532.61", "533.01", "533.20", "533.21", "533.5", "533.60", "533.61", "533.9", "534.00", "534.01", "534.1", "534.21", "534.40", "534.41", "534.5", "534.60", "534.61", "534.7", "534.9", "535.01", "535.11", "535.20", "535.21", "535.40", "535.41", "535.50", "535.51", "535.60", "535.61", "562.01", "562.03", "562.11", "568.81", "569.3", "569.85", "578.0", "578.9", "623.8", "626.6", "784.7"} AND Revenue Code {"0381", "0382", "0383", "0384", "0387"} | Hospitalization AND CPT/HCPC code for blood/blood product:<br>DX {"D62", "D64.9", "K22.6", "K25.0", "K25.2", "K25.6", "K26.0", "K26.2", "K26.4", "K26.6", "K27.0", "K27.2", "K27.6", "K28.0", "K28.2", "K28.4", "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 CPT/HCPC {"P9010", "P9011", "P9016", "P9017", "P9019", "P9031", "P9037", "P9038", "P9040", "P9055", "P9057", "P9058", "P9059", "P9060", "P9020", "P9021", "P9022", "P9023", "P9032", "P9033", "P9034", "P9035", "P9036", "P9039", "P9044", "P9051", "P9052", "P9053", "P9054", "P9056"}<br><br>OR<br><br>Hospitalization AND revenue code for blood/blood product:<br>DX {"D62", "D64.9", "K22.6", "K25.0", "K25.2", "K25.6", "K26.0", "K26.2", "K26.4", "K26.6", "K27.0", "K27.2", "K27.6", "K28.0", "K28.2", "K28.4", "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 (CKD) or End-Stage Renal Disease (ESRD) | "585.4", "585.5", "585.6" | "N18.4", "N18.5", "N18.6" |
| Decompensated Cirrhosis | "070.2", "070.22", "070.44", "070.6", "456.0", "456.1", "456.2", "456.20", "572.2", "789.5", "070.23", "070.4", "070.49", "070.71", "456.21", "567.23", "572.4", "789.59", "155", "155.0", "571", "572.8", "571.2", "571.5", "571.6", "571.9", "572.3" | "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", "C22", "C22.9", "I85", "I85.0", "I85.1", "I85.10", "K65.2", "K70.10", "K70.11", "K70.30", "K70.4", "K70.40", "K70.41", "K71.10", "K72.0", "K72.10", "K72.11", "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", "456.21" | "I85", "I85.0", "I85.1", "I85.10", "I85.00", "I85.01", "I85.11", "I86.4" |
| Ascites or Spontaneous Bacterial Peritonitis or Hepatorenal syndrome | "789.5", "789.59", "567.23", "572.4", "571", "572.8", "571.2", "571.5", "571.6", "571.9", "572.3" | "K65.2", "K70.11", "K76.7", "K70.31", "K71.51", "R18", "R18.0", "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]$CHA_2DS_2VASc$ score calculated as follows: 1 point each for, congestive heart failure, hypertension, age ≥75 [point doubled], diabetes, prior stroke, or transient ischemic attack [TIA] or thromboembolism [point doubled], vascular disease, age 65-74, female sex.

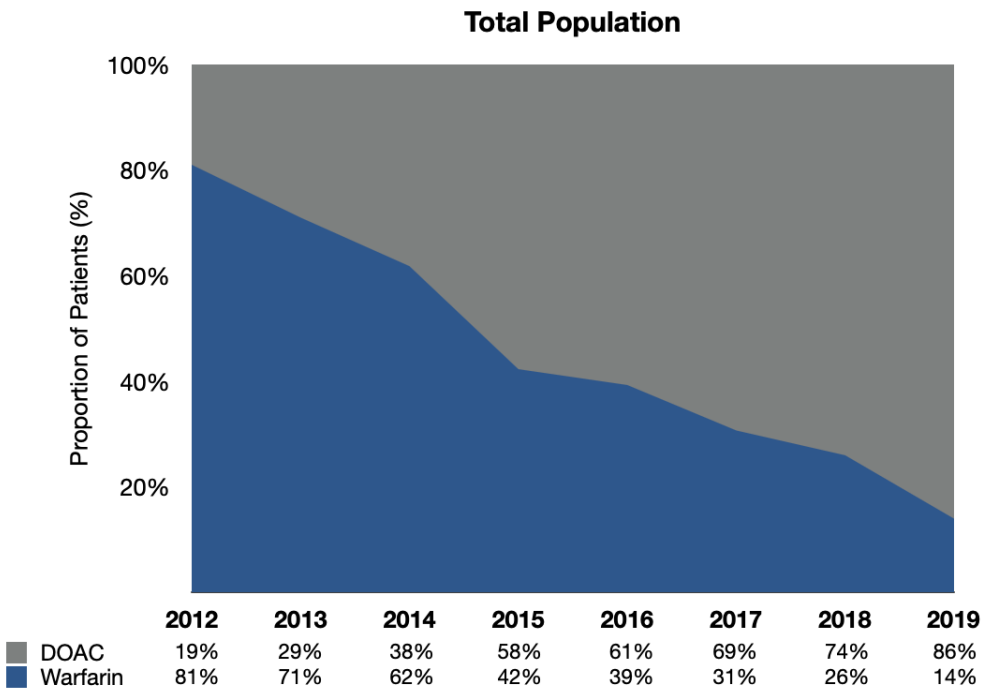
[2]HAS-BLED score calculated as follows: 1 point each for, hypertension, abnormal renal function, abnormal liver function or cirrhosis [note: all patients in this cohort receive 1 point for cirrhosis], stroke, prior bleeding event elevated INR, age >65 years, prior alcohol or drug usage, and use of medications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

**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