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ORIGINAL ARTICLE

Safety of DOACs in patients with Child-Pugh Class C cirrhosis and trial fibrillation

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Abstract

Background: Anticoagulation (AC) is used for stroke prevention in atrial fibrillation (AF). Direct Oral Anticoagulants (DOACs) are safe in patients with AF without cirrhosis, they are hardly studied in patients with advanced cirrhosis. Our study evaluates the safety and outcomes of DOACs in patients with Child-Pugh class C cirrhosis (CPC).

Methods: We queried TriNetX Database. Patients with CPC and AF were divided into three cohorts: patients on DOACs, no AC, and warfarin. Three study arms were created using a 1:1 propensity score matching system (PSM).

Results: Totally 16 029 patients met the inclusion criteria. Of those, 20.2% ($n = 3235$) were on DOACs, 47.1% ($n = 7552$) were not on AC, and 32.7% ($n = 5242$) were on warfarin. First arm comparing AC *versus* no AC, a statistically significant benefit was identified in 3-year mortality risk (47% *vs* 71%, $P < 0.0001$) and transplant status (17% *vs* 5%, $p < 0.0001$) with AC. However, no significant difference was identified regarding intracranial hemorrhage and GI bleeding risk. Second arm comparing patients on DOACs *versus* no AC, we identified mortality benefit (40% *vs* 72%, $P < 0.0001$) and a higher transplant rate (9% *vs* 3.2%, $P < 0.0001$) with DOACs. Intracranial hemorrhage rates (6% *vs* 4%, $P = 0.03$) were higher in patients on DOACs. Third arm comparing patients on DOACs *versus* Warfarin, a statistically significant lower risk of intracranial hemorrhage (6.6% *vs* 8.7%, $P = 0.004$) and GI bleed (2% *vs* 2.4%, $P < 0.0001$) were identified in patients on DOACs.

Conclusion: Anticoagulation is safe in patients with CPC with AF and may provide a mortality benefit. DOACs are a safer alternative to warfarin.

Introduction

Anticoagulation is often recommended for thromboprophylaxis for stroke prevention in patients with atrial fibrillation (AF). Cirrhosis is a known risk factor for the development of atrial fibrillation and therefore is a common condition in these patients. The hemostatic pathways in cirrhosis are imbalanced, which makes their response to anticoagulation unpredictable. Traditional agents and newer novel agents are both used for anticoagulation. Traditional agents require monitoring or parenteral administration and are burdensome to both patients and providers. Direct oral anticoagulants (DOACs) are oral medications and do not require frequent monitoring as traditional agents do. Although well-studied and approved for use in AF, these agents are not approved for use in patients with coexisting advanced liver disease. Therefore, this study aims to assess safety and outcomes of anticoagulation use patients with AF and Child-Pugh C cirrhosis.

Methods

The study was approved by the Institution Board Review Committee at Charleston Area Medical Center under number 22-899 on 11/28/2022. Written informed consent from patients was waived due to the de-identified nature of the TriNetX clinical database. The TriNetX (Cambridge, MA) database is a global federal research network that combines real-time data with electronic medical records. Patients aged ≥18 years with Child-Pugh Class C cirrhosis who have atrial fibrillation from January 2012 to December 2022. Patients with Child-Pugh Class C cirrhosis were identified using the codes from International Classification of Diseases (ICD)-10. A full description of study definitions and variables used to query the TriNetX database and their corresponding ICD codes are provided in the Supplementary Materials. The identified patients were divided into two major cohorts: patients who have Child-Pugh C cirrhosis and atrial fibrillation who are not taking any anticoagulation

and the other with patients receiving anticoagulation. The anticoagulation group was further divided into two cohorts: patients on warfarin and patients on DOACs. The DOACs included in the study were rivaroxaban and apixaban. Patients with Child-Pugh C cirrhosis that were included were any combination of lab or diagnostic values that would add up to a Child-Pugh C classification. A study flow diagram is shown in Figure 1.

The outcomes studied include the rates of intracranial hemorrhage, embolic stroke, gastrointestinal (GI) bleed, mortality and median survival rate, and transplant status. Outcomes ICD-10 codes were also provided in the Supplementary Material. Outcome analysis was performed after propensity score matching. The platform uses 1:1 PSM using a logistic regression for scores of the different metrics used in analysis. The PSM uses Python libraries. PSM was done using patient's demographics such as age at index, gender, and ethnicity, as well as comorbidities including chronic obstructive lung disease (COPD), nicotine dependence, heart failure, chronic kidney disease (CKD), hypertension, and diabetes mellitus. Baseline patient's characteristics and comorbidities are highlighted in Tables 1–3. Kaplan–Meier curves and log-rank tests were used to investigate the differences in all-cause mortality between groups. Risk Ratios (RR) with 95% confidence intervals (CI) were calculated for each outcome. A P-value of <0.05 was considered statistically significant. All statistical analyses were conducted on the TriNetX platform.

Result

A total of 16 029 patients met our inclusion criteria, and two major cohorts were created as highlighted in methods: patients with CPC cirrhosis and AF not on any anticoagulation ($n = 7552$; 47.1%) and patients with CPC cirrhosis and AF on anticoagulation. The latter cohort was further divided into warfarin group ($n = 5242$; 32.7%) and DOACs group ($n = 3235$; 20.2%) as in Figure 1. Three study arms were created. The first study arm compared patients with CPC cirrhosis with AF who are not taking any anticoagulation to patients with CPC cirrhosis who are taking anticoagulation. The second arm compared patients on DOACs to patients not on any anticoagulation. The

third arm compared patients on DOACs to patients who are on warfarin for thromboprophylaxis. Propensity matching score (PSM) in a 1:1 fashion was performed in all three study arms. Patient characteristics before and after propensity matching are highlighted in Tables 1–3.

In the first arm comparing two well matched PSM groups on AC and not on AC ($n = 5092/5092$), there was no significant statistical difference in safety outcomes of intracranial hemorrhage (3% vs 2.7%, $P = 0.19$) and GI bleeding (18.8% vs 19.5%, $P = 0.3$). The rate of embolic stroke was higher in patients on AC (0.9% vs 0.5%, $P = 0.03$). Even though patients on AC had a higher rate of stroke at baseline, there was no significant statistical difference in the rate of new stroke events at 3 years (0.49% vs 0.3%, $P = 0.08$). Patients on AC had a lower mortality rate at 3 years compared to patients who are not on any AC (47.4% vs 71.2%, $P = 0.00001$), with a median survival of 715 days compared with 66 days. Rates of Liver transplantation were significantly higher among patients on AC compared to those who were not on AC. (17% vs 5.2%, $P = 0.0001$).

In the second arm we compared patients with patients with Child-Pugh C cirrhosis with atrial fibrillation who are on DOACs to the patients not on any anticoagulation. After equally matched PSM groups were created ($n = 2625/2625$), there was no significant statistical difference was identified between the two groups in terms of GI bleed (18.8% vs 19.5%, $P = 0.3$). Patients on DOACs had a higher rate of intracranial hemorrhage (6.2% vs 4.9%, $P = 0.03$). A mortality benefit in the DOACs group at 3 years (40.1% vs 72.4%, $P = 0.00001$) was seen with a median survival of 898 days compared to 65 days. Liver transplantation rates were significantly higher among patients on DOACs (9.3% vs 3.2%, $P = 0.0001$).

The third Arm compared outcomes among PSM matched patients ($n = 2696/2696$) on DOACs to patients on warfarin as thromboprophylaxis. Patients on DOACs had lower rates of intracranial hemorrhage (6.6% vs 8.7%, $P = 0.004$) and GI bleeding (2% vs 2.4%, $P = 0.0001$). There was no difference in mortality rate at 3 years between the two groups (42% vs 43.7%, $P = 0.2$) and a similar rate of transplant status (8.3% vs 7.1%, $P = 0.092$) was identified. Summary of the results of all three study arms shown in Table 4. Comparative ratio graphs, Kaplan–Meier curves and Log-Rank test of each outcome between all three study arms are shown in Tables 5–9.

Discussion

Anticoagulation is used to prevent thromboembolic complications of atrial fibrillation (AF). Although AF is very common in the general population, cirrhosis on its own is a risk factor for AF occurrence. Therefore, AF is more prevalent in patients with cirrhosis.[1] Anticoagulation has a clear benefit of reducing the risk of ischemic stroke in patients with AF, and available observational data also suggest benefit in patients with cirrhosis[2,3] Multiple factors need to be considered when choosing an anticoagulation regimen, and the latest American Association for the Study of Liver Diseases (AASLD) guidelines recommend that such a decision should be tailored based on the degree of underlying liver and kidney dysfunction, bleeding risk, drug pharmacokinetics and patient/provider preference.[4] Patients with cirrhosis often have underlying portal hypertension with

1st Arm: AC vs No AC
2nd Arm: DOACs vs No AC
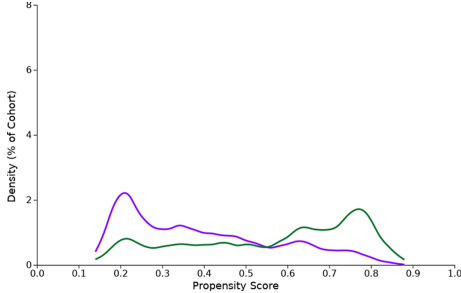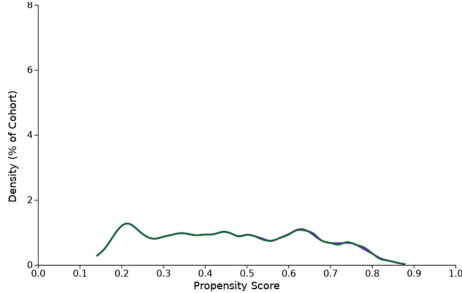3rd Arm: DOACs vs Warfarin
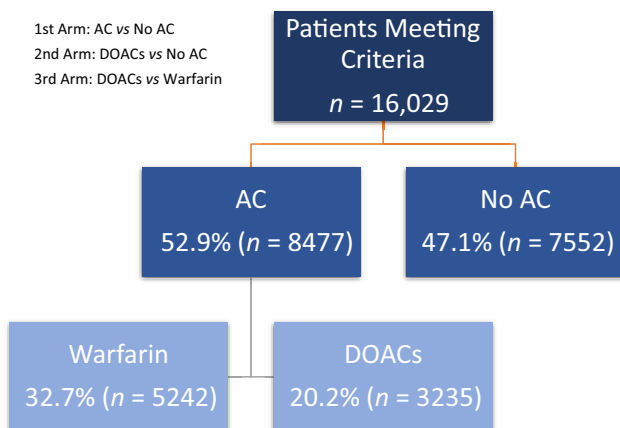
Figure 1 Study design flow diagram. AC, anticoagulation; DOACs, Direct Oral Anticoagulants.

Table 1 Patient characteristics of AC cohort and No AC cohort before and after PSM

AC cohort and No AC cohort patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
AC	8367	5092
No AC	8150	5092

Propensity score density function—before and after matching (AC—purple, No AC—green)

	Before PSM			After PSM		
	AC ($n = 8367$)	No AC ($n = 8150$)	P-value	AC ($n = 5092$)	No AC ($n = 5092$)	P-value
Demographics						
Age at Index, mean ± SD	64.2 ± 11.7	63.4 ± 11.2	<0.001	64.0 ± 11.6	64.0 ± 11.3	0.7
Female	32.2% ($n = 2689$)	35.3% ($n = 2853$)	<0.001	33.9% ($n = 1728$)	34% ($n = 1729$)	0.98
Not Hispanic or Latino	70.8% ($n = 5917$)	67.7% ($n = 5479$)	<0.001	70.1% ($n = 3568$)	69.8% ($n = 3552$)	0.73
Hispanic or Latino	5.6% ($n = 470$)	6.4% ($n = 517$)	<0.001	5.7% ($n = 289$)	6% ($n = 303$)	0.7
Comorbidities						
COPD	27.2% ($n = 2278$)	16.1% ($n = 1306$)	<0.001	21.8% ($n = 1112$)	21.4% ($n = 1088$)	0.56
Nicotine dependence	26.2% ($n = 2190$)	21.3% ($n = 1725$)	<0.001	24.1% ($n = 1226$)	24.9% ($n = 1269$)	0.32
Heart failure	69.5% ($n = 5808$)	34% ($n = 2752$)	<0.001	53.4% ($n = 2720$)	53.3% ($n = 2712$)	0.87
CKD	58.2% ($n = 4863$)	29.8% ($n = 2410$)	<0.001	44.8% ($n = 2281$)	44.4% ($n = 2451$)	0.7
Hypertension	77.5% ($n = 6483$)	56.6% ($n = 4584$)	<0.001	71.4% ($n = 3635$)	72.3% ($n = 3680$)	0.3
Diabetes mellitus	54.8% ($n = 4578$)	36.6% ($n = 2961$)	<0.001	48.7% ($n = 2481$)	48.1% ($n = 2451$)	0.55

AC, anticoagulation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PSM, Propensity-Score Matching; SD, standard deviation.

associated gastroesophageal varices. Also, these patients have a complex coagulation system that puts them at risk for both bleeding and clotting. Traditional tests to monitor the efficacy of treatment are often abnormal in those patients, and drug metabolism and clearance must be considered in the setting of potential underlying liver and kidney dysfunction. The prevalence of cirrhosis in the United States is 0.27%, and the overall prevalence of AF is 1%–2%.[5,6] In West Virginia, cirrhosis was responsible for a death rate of 16.1 per 100 000 patient population in 2020 and 17.9 per 100 000 in 2021.[7] With such a large population, determining the clinical benefit of anticoagulation in patients with cirrhosis and AF is of utmost importance.

The hemostatic pathways in patients with chronic liver disease are directly affected by disease progression and hepatic decompensation. Current evidence supports a paradigm recognizing that both anti- and procoagulant pathways are altered, resulting in a rebalanced coagulation system favoring thrombosis. Important changes in advanced liver disease include decreased

protein C and antithrombin and increased endothelial-derived von Willebrand factor and factor VIII that counterbalances the deficiencies in the procoagulant pathways. The fibrinolytic system that regulates clot remodeling and breakdown is also affected by liver disease in both pro-and anti-fibrinolytic directions, therefore causing an imbalance tilted toward either thrombosis or accelerated fibrinolysis leading to diffuse mucosal wound bleeding.[8]

Traditional anticoagulants include vitamin K antagonists (VKA) and low-molecular-weight heparin (LMWH). Studies including prophylactic and therapeutic doses of traditional anticoagulation are limited to small retrospective cohorts.[9,10] Furthermore, all therapeutic anticoagulation studies in cirrhotic patients include patients with portal vein thrombosis (PVT) as an indication of therapy. Consequently, extrapolation is necessary when considering therapy in cirrhotic patients with AF.

Warfarin is a vitamin K antagonist (VKA) that competitively inhibits vitamin K epoxide reductase complex, which is an

Table 2 Patient characteristics of DOACs cohort and No AC cohort before and after PSM

DOACs cohort and No AC cohort patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
DOACs	3162	2625
No AC	7200	2625

Propensity score density function—before and after matching (DOACs—purple, No AC—green)

	Before PSM			After PSM		
	DOACs (*n* = 3162)	No AC (*n* = 7200)	*P*-value	DOACs (*n* = 2625)	No AC (*n* = 2625)	*P*-value
Demographics						
Age at Index, mean ± SD	66.8 ± 11.3	63.4 ± 11.2	<0.001	66.2 ± 11.2	66.3 ± 11.2	0.77
Female	33.5% (*n* = 1059)	35.5% (*n* = 2556)	0.04	33.9% (*n* = 879)	34.4% (*n* = 903)	0.68
Not Hispanic or Latino	82.4% (*n* = 2607)	75.4% (*n* = 5385)	<0.001	81.4% (*n* = 2136)	81.9% (*n* = 2151)	0.59
Hispanic or Latino	5% (*n* = 157)	6.5% (*n* = 464)	0.044	5.3% (*n* = 140)	5.7% (*n* = 150)	0.54
Comorbidities						
COPD	32.4% (*n* = 1025)	17.4% (*n* = 1242)	<0.001	29% (*n* = 762)	27.7% (*n* = 727)	0.28
Nicotine dependence	34.5% (*n* = 1091)	24.3% (*n* = 1734)	<0.001	32.1% (*n* = 843)	31.5% (*n* = 828)	0.65
Heart failure	70.2% (*n* = 2221)	34.3% (*n* = 2449)	<0.001	64.3% (*n* = 1687)	62.7% (*n* = 1647)	0.25
CKD	54.4% (*n* = 1720)	31.7% (*n* = 2264)	<0.001	50.1% (*n* = 1316)	49.4% (*n* = 1296)	0.58
Hypertension	80.6% (*n* = 2550)	58% (*n* = 4142)	<0.001	77.9% (*n* = 2046)	79% (*n* = 2075)	0.33
Diabetes Mellitus	59.6% (*n* = 1884)	39.2% (*n* = 2801)	<0.001	55.7% (*n* = 1462)	56.5% (*n* = 1483)	0.56

AC, anticoagulation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DOACs, Direct Oral Anticoagulants; PSM, Propensity-Score Matching; SD, standard deviation.

essential enzyme for activating the vitamin K available in the body. Subsequently, warfarin can deplete functional vitamin K reserves, which reduces the synthesis of factors II, VII, IX, and X as well as protein C and S. Warfarin is metabolized in the liver through the CYP2C9 enzyme. According to the manufacturer's drug labeling, no dosage adjustments are necessary for hepatic impairment.[11] However, the response to oral anticoagulants may become enhanced in patients with cirrhosis. Therefore, INR needs to be closely monitored. In a study of 321 patients with cirrhosis, VKA was beneficial CPA Cirrhosis. However, it increased the risk of major bleeding in CPB that overwhelmed stroke reduction.[12] Another study of 465 patients with cirrhosis showed that anticoagulation with warfarin may not significantly reduce the risk of stroke but significantly increase the risk of major bleeding.[13] A study by Kuo L, Chao TF et al. in Taiwan found that the use of anticoagulation (warfarin) in patients with cirrhosis and AF was associated with a lower risk of ischemic stroke and a positive net clinical benefit compared with no anticoagulation. This supports the recommendation of using anticoagulation in patients with cirrhosis.[3] However, none of the studies specified Child class of cirrhosis or specifically included patients with CPC.

DOAC's are approved for a variety of indications and are often the most preferred by both patients and providers. Patients with cirrhosis were excluded from large clinical trials on DOACs. Therefore, our knowledge of the pharmacology of these agents in cirrhotic patients is very limited, and it is based on small pharmacodynamic studies.[14] We included patients on rivaroxaban and apixaban in our study. We excluded patients on dabigatran in our study considering the high bleeding risk in this population and since dabigatran has been associated with higher risk of GI bleeding even in general population.

Rivaroxaban is not recommended for use in patients with CPB or CPC. This was based on a small study evaluating a single dose of rivaroxaban in patients with hepatic impairment vs. healthy controls.[15] This study only included patients with

Table 3 Patient characteristics of DOACs cohort and warfarin cohort before and after PSM

DOACs cohort and warfarin cohort patient count before and after propensity score matching

Cohort	Patient count before matching	Patient count after matching
DOACs	3321	2696
Warfarin	5281	2696

Propensity score density function—before and after matching (DOACs—purple, warfarin—green)
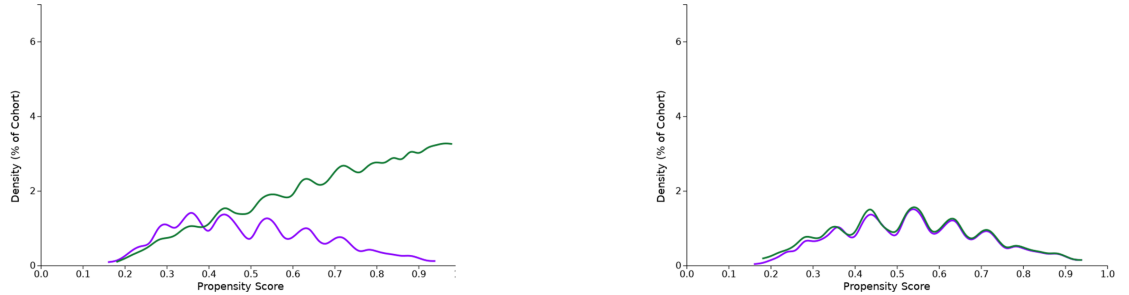
	Before PSM			After PSM		
	DOACs ($n = 3321$)	Warfarin ($n = 5281$)	P-value	DOACs ($n = 2625$)	No AC ($n = 2625$)	P-value
Demographics						
Age at Index, mean ± SD	66.8 ± 11.2	65.3 ± 12.4	<0.001	66.6 ± 11.1	66.7 ± 12.6	0.69
Female	33.6% ($n = 1115$)	33.2% ($n = 1746$)	0.72	33.7% ($n = 909$)	32.8% ($n = 885$)	0.49
Not Hispanic or Latino	82.7% ($n = 2747$)	82% ($n = 4314$)	0.41	83.2% ($n = 2243$)	84.3% ($n = 2272$)	0.29
Hispanic or Latino	5.3% ($n = 175$)	7% ($n = 368$)	0.001	5.7% ($n = 155$)	5.6% ($n = 151$)	0.8
Comorbidities						
COPD	32.3% ($n = 1072$)	29.7% ($n = 1564$)	0.013	32.3% ($n = 870$)	33.1% ($n = 892$)	0.5
Nicotine dependence	34.2% ($n = 1137$)	29.6% ($n = 1557$)	<0.001	34.2% ($n = 921$)	34.2% ($n = 922$)	0.98
Heart failure	69.7% ($n = 2315$)	70.6% ($n = 3713$)	0.37	70.5% ($n = 1901$)	71.5% ($n = 1927$)	0.43
CKD	54.2% ($n = 1799$)	55.9% ($n = 2938$)	0.12	56.4% ($n = 1520$)	56.3% ($n = 1518$)	0.96
Hypertension	80.2% ($n = 2664$)	77.3% ($n = 4064$)	0.001	80.3% ($n = 2164$)	81.4% ($n = 2195$)	0.28
Diabetes Mellitus	58.9% ($n = 1955$)	56.2% ($n = 2955$)	0.02	59.1% ($n = 1592$)	59.3% ($n = 1598$)	0.87

AC, anticoagulation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DOACs, Direct Oral Anticoagulants; PSM, Propensity-Score Matching; SD, standard deviation.

Table 4 Summary of all three study arms' results

|	AC	No AC	P-Value	DOACs	No AC	P-Value	DOACs	Warfarin	P-Value
Intracranial hemorrhage	3%	2.7%	0.19	6.2%	4.9%	0.03	6.6%	8.7%	0.004
Embolic stroke	0.9%	0.5%	0.03	1.1%	0.5%	0.009	1.2%	1.4%	0.63
GI bleed	18.8%	19.5%	0.3	19.4%	21.5%	0.065	2%	2.4%	0.0001
Mortality in 3 years	47.4%	71.2%	0.0001	40.1%	72.4%	0.0001	42%	43.7%	0.2
Median survival days	715 days	66 days		898 days	65 days				
Transplant	17%	5.2%	0.0001	9.3%	3.2%	0.0001	8.3%	7.1%	0.092

AC, anticoagulation; DOACs, Direct Oral Anticoagulants; GI, gastrointestinal.

CPA and CPB. Patients with CPB had a significantly elevated level of drug exposure compared with CPA and healthy controls. In vitro analysis showed that CPC demonstrated a reduced anticoagulant effect.[16] Later, some case reports demonstrated rivaroxaban safety in CPA for the treatment of portal vein thrombosis (PVT).[17] Another clinical series involving rivaroxaban showed that rates of major bleeding were similar between patients on DOACs and patients on traditional AC.[9]

Apixaban has no dose adjustment in CPA cirrhosis, as per manufacturer FDA approved label.[18] There are no recommendations

Table 5 Comparison between all three study arms in incidence rate, Kaplan–Meier survival analysis, and hazard ratio of intracranial hemorrhage
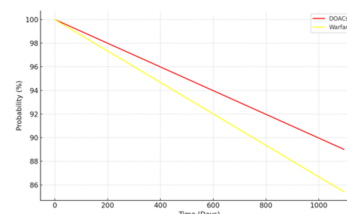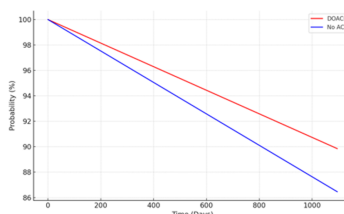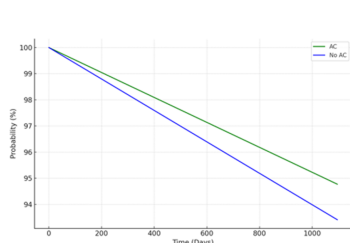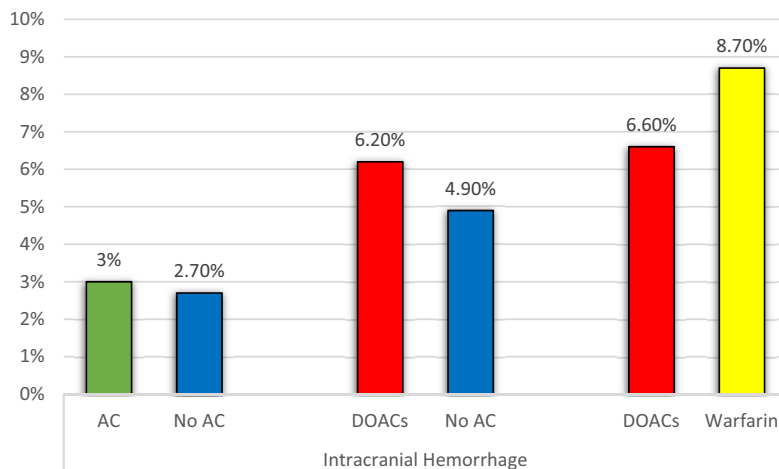
Kaplan–Meier survival analysis for ICH

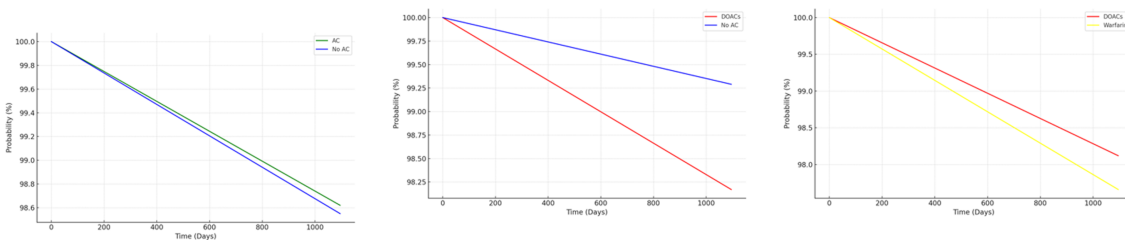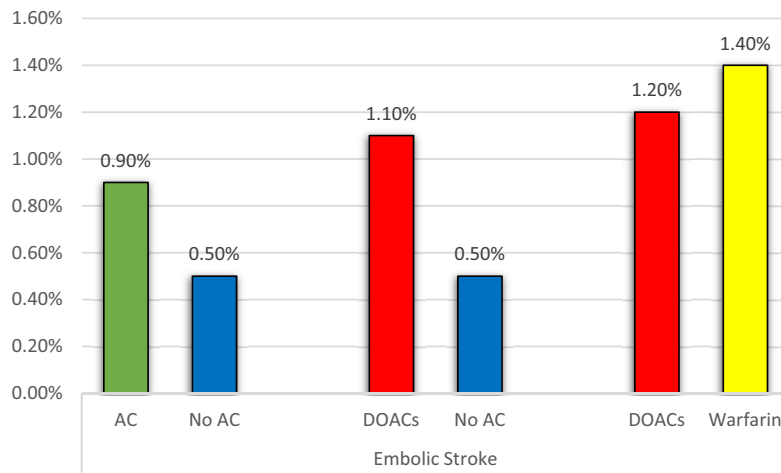| Cohort		Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window
1	AC	5092	160	94.77%	DOACs	2625	164	89.85%	DOACs	2696	178	89.01%
2	No AC	5092	138	93.41%	No AC	2625	128	86.46%	Warfarin	2696	234	85.42%
Log-rank test		χ^2	df	P		χ^2	df	P		χ^2	df	P
		4.249	1	0.039		2.135	1	0.144		9.880	1	0.002
Hazard ratio and proportionality		HR	95% CI	P	HR	95% CI	P	HR	95% CI	P		
		0.786	(0.625, 0.989)	0.700	0.840	(0.664, 1.062)	0.039	0.732	(0.603, 0.890)	0.874		

AC, anticoagulation; CI, confidence interval; DOACs, Direct Oral Anticoagulants; HR, hazard ration; ICH, intracranial hemorrhage.

for its use in CPB cirrhosis, and it is not recommended to be used in CPC cirrhosis. A study showed that rivaroxaban has a reduced effect in more advanced cirrhosis. Another case series showed that apixaban is safe and effective in CPA when used for PVT treatment.[19] A larger retrospective study showed similar rates of major bleeding in CPA and CPB when compared to healthy controls.[9]

There are two large studies comparing DOACs with VKA in cirrhosis patients. A study of 19 789 patients with AF and cirrhosis favored AC as thromboprophylaxis compared as compared to not using AC. It also concluded that compared to VKA, DOACs were associated with a lower risk of bleeding.[2] Another study involving 2694 veterans in 2017 also addressed the safety of DOACs and VKA. It showed that both forms of AC were associated with reduced all-cause mortality.[20] Neither study specified the severity of cirrhosis or the Child-Pugh class. A meta-analysis by Chokesuwattanaskul R et al. assessing the efficacy

Table 6 Comparison between all three study arms in incidence rate, Kaplan–Meier survival analysis and hazard ratio of embolic strokes

Kaplan–Meier survival analysis for embolic strokes

Cohort	Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window
1 AC	5092	44	98.62%	DOACs	2625	30	98.17%	DOACs	2696	33	98.12%
2 No AC	5092	26	98.55%	No AC	2625	13	99.29%	Warfarin	2696	37	97.66%
Log-rank test	χ^2	df	P	χ^2	df	P		χ^2	df	P	
	0.365	1	0.546	2.739	1	0.098		0.356	1	0.551	
Hazard ratio and proportionality	HR	95% CI	P	HR	95% CI	P		HR	95% CI	P	
	1.162	(0.713, 1.895)	0.270	1.733	(0.897, 3.349)	0.853		0.867	(0.542, 1.386)	0.173	

AC, anticoagulation; CI, confidence interval; DOACs: direct oral anticoagulants; HR, hazard ration.

and safety of anticoagulation for atrial fibrillation in patients with cirrhosis supports the findings of our study. They found that anticoagulation use was associated with a reduced risk of stroke without a significant increase in the risk of bleeding when compared with no anticoagulation. Furthermore, they also found out that the use of DOACs was associated with a lower risk of bleeding when compared to warfarin.[2] Both studies, however, did not classify clinical stage of cirrhosis in their patient population.

Safety of DOACs in terms of drug induced liver injury has been evaluated in a large meta-analysis that found no significant risk of liver injury with the use of DOACs. However, there

are no appropriately powered studies examining the safety of these agents in patients with cirrhosis. Furthermore, patients with advanced cirrhosis, CPB, and CPC were excluded from drug trials, which makes it very challenging when choosing an anticoagulant regimen for moderate–severe liver impairment.

Our study specifically targeted patients with CPC cirrhosis to assess the efficacy and safety of AC, and specifically DOACs, in this patient population. One of the major strengths of our study is the very specific nature of our inclusion criteria using only the laboratory data to identify patients, which ensures the inclusion of patients with CPC cirrhosis only. Also, the large

Table 7 Comparison between all three study arms in incidence rate, Kaplan–Meier survival analysis and hazard ratio of gastrointestinal bleed
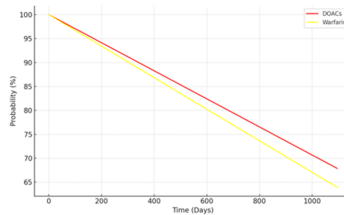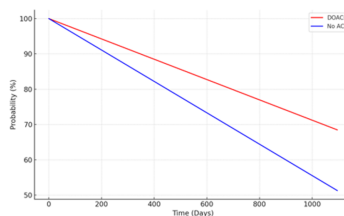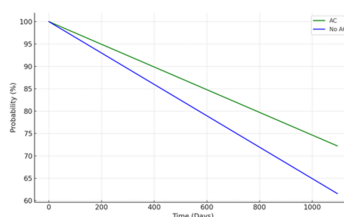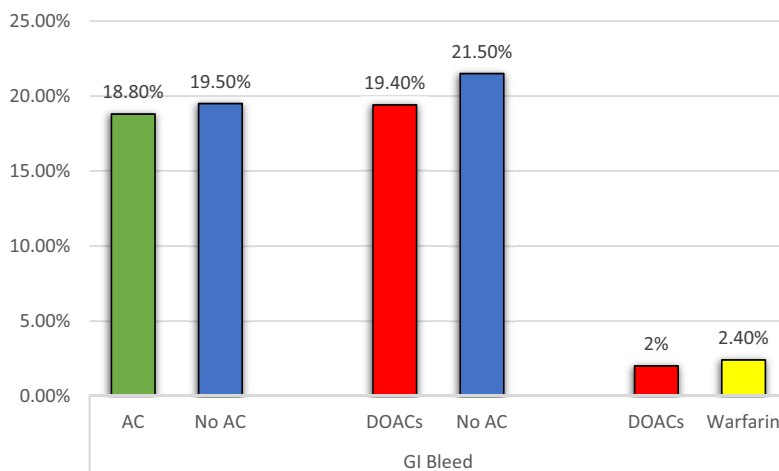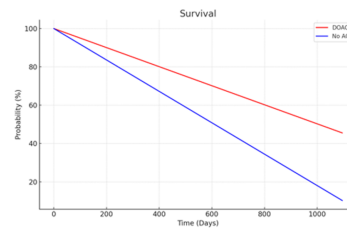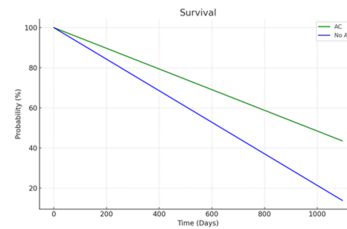

Kaplan–Meier survival analysis for GIB

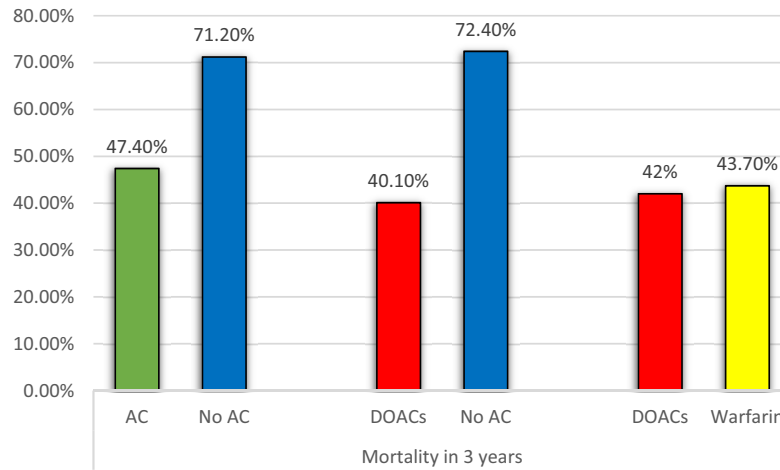| Cohort		Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window
1	AC	5092	959	72.22%	DOACs	2625	510	68.48%	DOACs	2696	541	67.87%
2	No AC	5092	995	61.57%	No AC	2625	564	51.29%	Warfarin	2696	648	63.90%

| Log-rank test	χ^2	df	χ^2	df	χ^2	df	df
	78.176	1	74.144	1	16.461	1	1
Hazard ratio and proportionality	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
	0.670	(0.612, 0.732)	0.927	0.589	(0.522, 0.666)	0.589	0.790	(0.705, 0.886)	0.044

AC, anticoagulation; CI, confidence interval; DOACs, Direct Oral Anticoagulants; GI, gastrointestinal; GIB, gastrointestinal bleed; HR, hazard ration.

Table 8 Comparison between all three study arms in incidence rate, Kaplan–Meier survival analysis and hazard ratio of mortality/survival

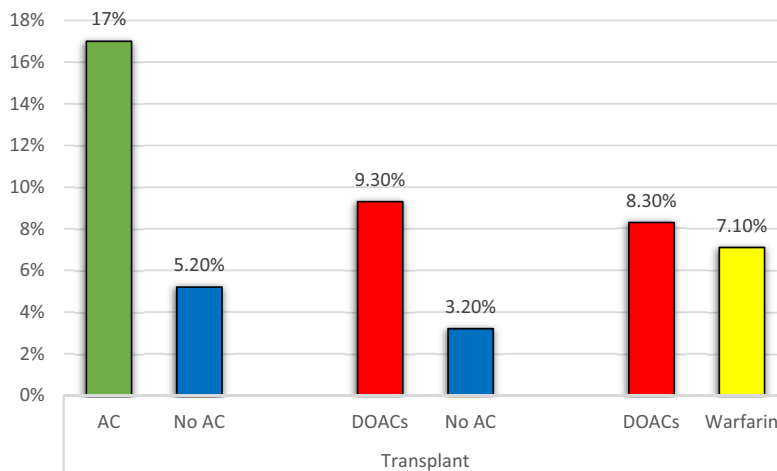(*Continues*)

Table 8 (Continued)
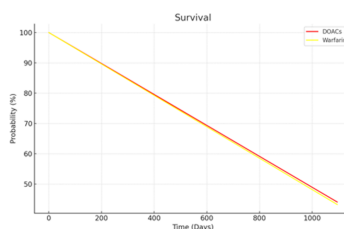
Kaplan–Meier survival analysis for mortality/survival

Cohort		Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window
1	AC	5092	2414	43.52%	DOACs	2625	1052	45.52%	DOACs	2696	1133	44.07%
2	No AC	5092	3626	13.81%	No AC	2625	1901	10.23%	Warfarin	2696	1179	43.25%

Log-rank test	χ^2	df	P	χ^2	df	P	χ^2	df	P
	1196.147	1	0.000	942.051	1	0.000	3.406	1	0.065

| Hazard ratio and proportionality	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
	0.411	(0.390, 0.433)	0.266	0.320	(0.296, 0.345)	0.006	0.926	(0.854, 1.005)	0.058

AC, anticoagulation; CI, confidence interval; DOACs, Direct Oral Anticoagulants; HR, hazard ratio.

Table 9 Comparison between all three study arms in incidence rate, Kaplan–Meier survival analysis, and hazard ratio of liver transplant

(*Continues*)

Table 9 (Continued)
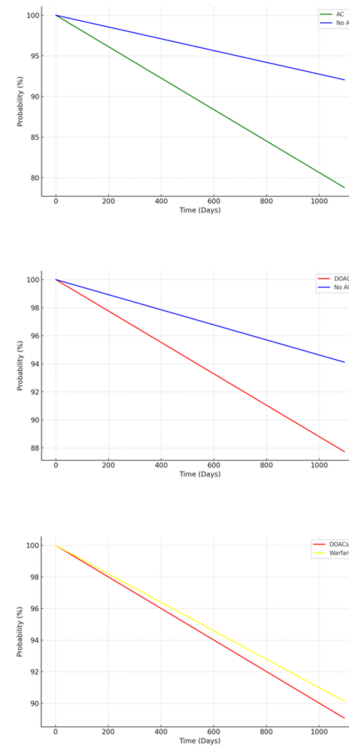
Kaplan–Meier survival analysis for liver transplant

Cohort		Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window	Cohort	Patients in cohort	Patients with outcome	Survival at end of window
1	AC	5092	865	78.80%	DOACs	2625	245	87.73%	DOACs	2696	224	89.06%
2	No AC	5092	264	92.06%	No AC	2625	83	94.11%	Warfarin	2696	191	90.13%

Log-rank test	χ^2	df	P	χ^2	df	P	χ^2	df	P
	251.640	1	0.000	52.787	1	0.000	2.606	1	0.106

Hazard ratio and proportionality	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
	2.901	(2.527, 3.331)	0.492	2.454	(1.911, 3.152)	0.004	1.172	(0.966, 1.422)	0.024

AC, anticoagulation; CI, confidence interval; DOACs, Direct Oral Anticoagulants; HR, hazard ratio.

patient population included in our study, makes the power of the findings very strong and increases the ability to generalize these findings on AC safety among patients with CPC cirrhosis.

There are several limitations to our study. First, we used ICD codes to identify patients, therefore we were unable to obtain any pathological data from liver biopsy or imaging such as liver ultrasound. Second, we could not verify medication compliance and we presumed that all prescribed medications were taken by patients as reported. Additionally, the impact of antiplatelets which can lead to increased risk of bleeding were not studied, due to limited ability to include more components in PSM secondary to our very selective inclusion criteria. We attempted to mitigate any selection bias by using highest risk comorbid conditions in our PSM to ensure comparability of our cohorts. Furthermore, the ability to reproduce similar results by rerunning our selective inclusion criteria and PSM components through all three study arms, indicates that we achieved true comparability and that cohorts are appropriately matched. Third, a selection bias does exist as evident by higher rates of embolic stroke at baseline among patient groups on anticoagulation as patients with stroke are more likely to be placed on anticoagulation. Fourth, we opted to report all-cause mortality and were unable to specify the cause. This is due to the innate nature of our de-identified database in TriNetX which hinders retrospective identification of cause of death and inability to access individual patients' charts. Finally, this is a retrospective study which needs future prospective studies to confirm the finding.

Conclusion

Anticoagulation is safe in patients with Child-Pugh Class C cirrhosis with atrial fibrillation and may provide a mortality benefit. DOACs are a safer alternative to warfarin, with a lower risk of intracranial hemorrhage and GI bleeding.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Data S1. Supporting information.