Digestive and Liver Disease 51 (2019) 489–495

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Efficacy and safety of anticoagulation for atrial fibrillation in patients with cirrhosis: A systematic review and meta-analysis

Ronpichai Chokesuwattanaskul[a,*], Charat Thongprayoon[b], Tarun Bathini[c], Aldo Torres-Ortiz[d], Oisin A. O'Corragain[e], Kanramon Watthanasuntorn[f], Ploypin Lertjitbanjong[f], Konika Sharma[f], Somchai Prechawat[a], Patompong Ungprasert[g], Paul T. Kröner[h], Karn Wijarnpreecha[h], Wisit Cheungpasitporn[d]

[a] Division of Cardiology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand
[b] Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
[c] Department of Internal Medicine, University of Arizona, Tucson, AZ, USA
[d] Department of Medicine, University of Mississippi Medical Center, MS, USA
[e] Department of Internal Medicine, Temple University Hospital, Philadelphia, PA, USA
[f] Department of Internal Medicine, Bassett Medical Center, NY, USA
[g] Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[h] Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Jacksonville, FL, USA

ARTICLE INFO

Article history:
Received 21 October 2018
Received in revised form
16 November 2018
Accepted 1 December 2018
Available online 13 December 2018

Keywords:
Anticoagulation
Atrial fibrillation
Cirrhosis
Liver failure
Meta-analysis
Systematic review

ABSTRACT

Objective: The atrial fibrillation-related stroke is clearly prevented by anticoagulation treatment, however, management of anticoagulation for AF in patients with cirrhosis represents a challenge due to bleeding concerns. To address this issue, a systematic review and meta-analysis of the literature was performed.
Methods: A literature search for studies reporting the incidence of AF in patients with cirrhosis was conducted using MEDLINE, EMBASE and Cochrane Database, from inception through July 2018.
Results: 7 cohort studies including 19,798 patients with AF and cirrhosis were identified. The use of anticoagulation (%) among included studies ranged from 8.3% to 53.9%. Anticoagulation use for AF in patients with cirrhosis was significantly associated with a reduced risk of stroke, with a pooled HR of 0.58 (95%CI: 0.35–0.96). When compared with no anticoagulation, the use of anticoagulation was not significantly associated with a higher risk of bleeding, with a pooled HR of 1.45 (95%CI: 0.96–2.17). Compared to warfarin, the use of direct oral anticoagulants (DOACs) was associated with a lower risk of bleeding among AF patients with cirrhosis.
Conclusion: Our study demonstrates that anticoagulation use for AF in patients with cirrhosis is associated with a reduced risk of stroke, without increasing significantly the risk of bleeding, when compared to those without anticoagulation.

1. Introduction

Cirrhosis is commonly characterized by damage to the liver parenchyma, resulting in fibrotic changes and regenerative nodules that lead to metabolic derangements and coagulopathy [1,2]. The liver produces many hemostasis-facilitating factors, and therefore chronic liver disease usually results in bleeding tendency [3]. Even though there is a decrease in coagulation factors, some pro-coagulant factors such as factor VIII and von Willebrand factor may be elevated in the setting of liver cirrhosis, which can potentially counterbalance the risk of bleeding in cirrhotic patients [4].

Atrial fibrillation (AF) currently affects about thirty-three million people worldwide, and it is one of the most common arrhythmias diagnosed in the elderly [5]. Among the cirrhosis patients, the overall estimated prevalence of AF is approximately 5%, which is higher than in its prevalence in the general population reported by previous studies [6–12]. Not only oral anticoagulation has shown to be an efficacious therapy for primary stroke prevention, but it has also proven to confer a mortality benefit in patients with AF. Systemic anticoagulation has been employed for many years for this purpose, and therapies continue to evolve in the

* Corresponding author.
E-mail addresses: drronpichaic@gmail.com, dr_ronpichai_c@yahoo.com (R. Chokesuwattanaskul).

https://doi.org/10.1016/j.dld.2018.12.001
1590-8658/

search of drugs that provide a better safety, yet efficacious profile, while reducing the incidence of stroke [13]. Vitamin K antagonists (VKAs) were the standard of treatment for primary stroke prevention until DOACs were released into the market almost a decade ago. These novel oral anticoagulants have proven by landmark, well-designed studies, to confer a lower risk of bleeding compared to VKAs, while reducing the incidence of stroke [14–17].

Cirrhosis and AF are common among the elderly population, and both conditions share common risk factors for bleeding events. Due to the bleeding propensity in cirrhotic patients, some clinicians believe that this condition may play a role as a protective mechanism for the occurrence of stroke in AF, and therefore many of them decide not to prescribe oral anticoagulation in patients with these clinical characteristics [18,19]. However, most of the studies that support the use of anticoagulation excluded patients with chronic liver disease, hence; the guidelines do not provide specific recommendations for the use of anticoagulation in patients with cirrhosis [13]. Many of the studies that have aimed to demonstrate the benefit of anticoagulation treatment in patients with cirrhosis have provided conflicting results [8,18–25]. We performed a systematic review in order to summarize evidence regarding the risks of stroke and bleeding in patients with cirrhosis on oral anticoagulation for AF.

2. Methods

2.1. Literature review and search strategy

The protocol for this meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018102664). A systematic literature search of MEDLINE (1946 through July 2018), EMBASE (1988 through July 2018), and the Cochrane Database of Systematic Reviews (database inception through July 2018) was conducted to assess the risks of stroke and bleeding in patients with cirrhosis on oral anticoagulation for AF.

The systematic literature review was conducted independently by two investigators (R.C. and C.T.) applying a search approach that incorporated the terms “atrial fibrillation” combined with the term “cirrhosis”, which is provided in “Online Supplementary data 1”. A manual search for relevant studies using references from the included articles was also performed. No language restrictions were applied. This study was performed in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [26] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, Online Supplementary data 2 [27].

2.2. Selection criteria

Eligible studies were only observational studies (cohort, case-control, or cross-sectional studies), that reported our outcomes of interest (stroke and bleeding), in patients with cirrhosis taking oral anticoagulation for AF. Studies needed to provide data on the risks of stroke or bleeding among these patients. Study size was not a limitation. Retrieved articles were individually reviewed for eligibility by the two investigators (R.C. and C.T.). Discrepancies were discussed and resolved by a third researcher (W.C.). The Newcastle–Ottawa quality assessment scale was used to evaluate the quality of the study for case-control studies, and outcomes of interest for cohort studies [28]. The modified Newcastle–Ottawa scale was used for cross-sectional studies [29], as shown in Table 1.

2.3. Data abstraction

A structured data collecting form was utilized to gather information from each study including title, year of the study, name of the first author, publication year, country where the study was conducted, demographics and characteristics of the patients with cirrhosis, methods used to diagnose AF, follow-up time, and stroke and bleeding risks.

Table 1
Main characteristic of studies included in meta-analysis of anticoagulation for AF in patients with cirrhosis.

	Grewal et al. [8]	Lee et al. [25]	Lai et al. [24]	Choi et al. [19]
Country	USA	South Korea	Taiwan	South Korea
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Year	2014	2015	2016	2017
Total number	136,050 liver cirrhosis patients	321 AF/cirrhotic (LC: liver cirrhosis)	AF/liver (N = 433) or AF/non-liver (N = 3490) cohort	465 nonvalvular AF/cirrhosis
Age	N/A	62.1 ± 10.3	72.8 ± 12.6	63.5
Follow up time	N/A	9 years	3.3 ± 1.4 years	37.6 months
Exposure definition	Cirrhosis patients with elevated INR from database (abnormal INR: on warfarin vs. off)	Early and advanced LC prognosis with VKA as primary stroke prevention in AF.	Compare between liver disease and without liver disease AF patient	AF/cirrhotic patient on warfarin 113 warfarin-treated patients vs. 352 non-users.
Newcastle-Ottawa scale	S4, C1, O0.	S4, C2, O3.	S4, C2, O3.	S4, C2, O3.
	Kuo et al. [23]	**Pastori et al. [20]**	**Goriacko et al. [18]**	
Country	Taiwan	Italy	USA	
Study design	Retrospective cohort	Retrospective cohort study	Retrospective cohort	
Year	2017	2018	2018	
Total number	9056 AF/cirrhosis with CHA2DS2-VASc ≥2 (VKA 754, antiplatelet 2770, others; not use any)	129 AF/liver fibrosis (77 on VKA, 52 on DOAC)	75 DOAC/158 warfarin (cirrhotic/AF)	
Age	73.4 ± 9.9	78.9 ± 7.5	66	
Follow up time	11 years	VKA (3622 patients/years), DOACs(1508 patients/years)	7 years	
Exposure definition	AF/cirrhosis patient on antiplatelet/VKA/no therapy for stroke prevention.	OAC in AF patient with liver fibrosis diagnosed with High FIB-4	AF/chronic liver disease started on anticoagulation treatment with either VKA or DOACs	
Newcastle–Ottawa scale	S4, C2, O3.	S4, C2, O3	S4, C2, O3	

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulation; ICH, intracranial hemorrhage; LC, liver cirrhosis; GIB, gastrointestinal bleeding; N/A, not available; OAC, oral anticoagulation; VKA, vitamin K antagonist; S, C, O, selection, comparability, and outcome.

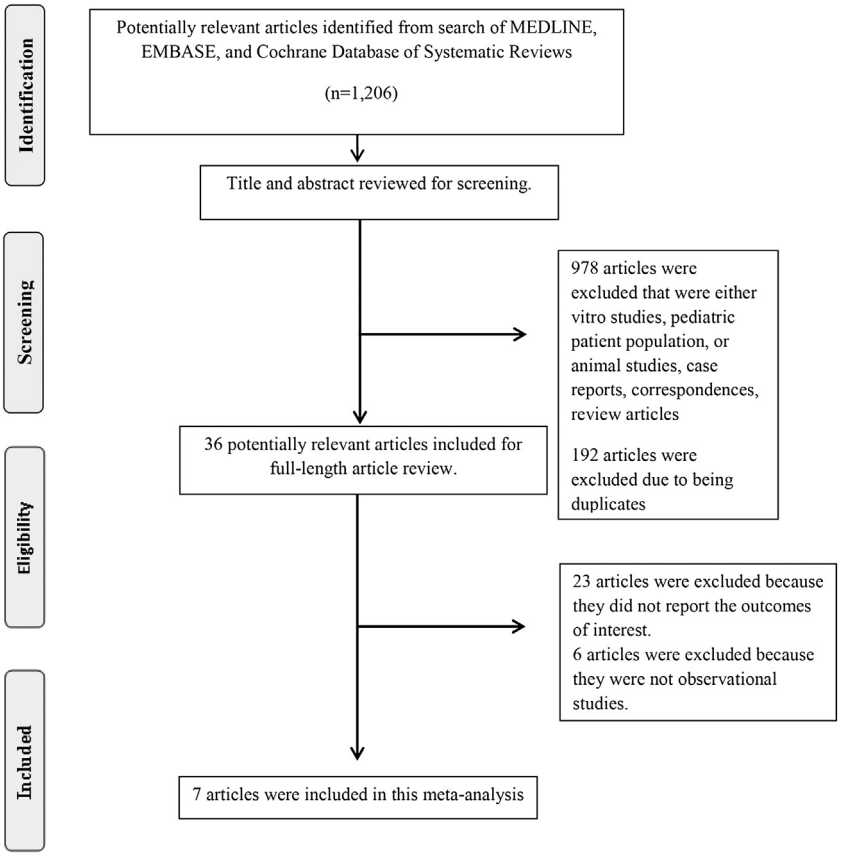

Fig. 1. Outline of our search methodology.

2.4. Statistical analysis

Data analysis was performed utilizing the Comprehensive Meta-Analysis software (version 3.3; Biostat. Inc., Englewood, NJ, USA). Adjusted point estimates from each included study were combined by the generic inverse variance approach of DerSimonian and Laird, which designated the weight of each study based on its variance [30]. Given the possibility of inter-study variance, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were applied to determine the inter-study heterogeneity. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity [31]. The publication bias was assessed using the Egger test [32]. Raw data for this review are publicly available, through the Open Science Framework (https://osf.io/xe624/?view_only=d4e5c375e0104d82bba1b434aa882a25).

3. Results

A total of 1206 potentially eligible articles were identified using our search strategy. After the exclusion of 978 articles that were either in vitro studies, pediatric patient population, or animal studies, case reports, correspondences, review articles, and 192 duplicate articles, 36 articles were included for full-length review. Among these, 23 were excluded because the outcomes of interest (stroke and bleeding in patients with cirrhosis taking oral anticoagulation for AF) were not reported and 6 articles were excluded because they were not observational studies. The final analysis included 7 cohort studies, including 19,798 patients with AF and cirrhosis with a mean follow-up time of 11 years. The kappa coefficient of agreement for the two investigators was 0.89.

The use of anticoagulation (%) among included studies ranged from 8.3% to 53.9%. The literature retrieval, review, and selection process are illustrated in Fig. 1. The characteristics and quality assessment of the included studies are presented in Table 1. Data on risks of stroke and bleeding in AF Patients with cirrhosis from included studies are provided in Table 2.

3.1. Definition of cirrhosis

Most of the included studies utilized the health database system and ICD-9 codes for extracting the diagnosis of liver cirrhosis [8,18,19,23,24]. Lee et al. defined liver cirrhosis was by clinical diagnosis, lab test, imaging (Doppler ultrasound, Computed Tomography scan), and biopsy when performed [25]. Pastori et al. used noninvasive liver imaging, a FIB-4 value of more than 3.25 as a cut-off, to define significant liver fibrosis [20].

The stage of liver cirrhosis reported by the included studied also were analyzed. The studies by Goriacko et al. and Lee et al. revealed that about two third of the studied population has an early stage (Child-Pugh A) liver cirrhosis [18,25]. The etiology of liver cirrhosis are alcoholic liver disease, NASH and viral hepatitis infection [18,25]. Lee et al. also demonstrated that the use of VKA increased the risk of bleeding in advanced liver cirrhosis (Child-Pugh B and C) but not in early liver cirrhosis (Child-Pugh A) [25]. For bleeding complications, most patients presented with gastrointestinal bleeding and central nervous system bleeding [18,20,24,25].

3.2. Anticoagulation use and risk of stroke in patients with AF and cirrhosis

Anticoagulation use for AF in patients with cirrhosis was significantly associated with a reduced risk of stroke with a pooled

Table 2
Data on risks of stroke and bleeding in AF Patients with cirrhosis from included studies.

Study	Anticoagulation N (%)	Stroke — anticoagulation (N)	Stroke — control (N)	HR — stroke	Bleeding — anticoagulation (N)	Bleeding — control (N)	HR — bleeding
Lee et al. [25]	173/321 (53.9)	Ischemic stroke All: 11/173 Early cirrhosis: 6/108 Advanced cirrhosis: 5/65	Ischemic stroke All: 23/148 Early cirrhosis: 20/107 Advanced cirrhosis: 3/41	Ischemic stroke All 0.30 (0.14–0.62) Early cirrhosis 0.23 (0.09–0.58) Advanced cirrhosis 0.60 (0.15–2.42)	Major bleeding All: 58/173 Early cirrhosis 23/108 Advanced cirrhosis 35/65	Major bleeding All: 30/148 Early cirrhosis: 19/107 Advanced cirrhosis: 11/41	Major bleeding All 1.87 (1.13–3.09) Early cirrhosis 0.89 (0.48–1.66) Advanced cirrhosis 2.98 (1.23–7.19)
Lai et al. [24]	163/433 (37.6%)	Hospitalization-requiring cerebrovascular event: 46/163	Hospitalization-requiring cerebrovascular event: 63/270	Hospitalization-requiring cerebrovascular event 1.09 (0.15–7.86) CHA2DS2-VASC = 0 1.06 (0.22–6.80) CHA2DS2-VASC = 1 0.49 (0.27–2.78) CHA2DS2-VASC ≥ 2 1.43 (0.34–5.10)	N/A	N/A	No difference in cerebral hemorrhage (p = .37)
Choi et al. [19]	113/465 (24.3%)	Ischemic stroke: 4/113	Ischemic stroke: 13/352	Ischemic stroke: 0.75 (0.21–2.78)	Major bleeding: 21/113	Major bleeding: 19/352	Major bleeding 2.60 (1.32–5.12)
Kuo et al. [23]	754/9056 (8.3%)	Ischemic stroke: 65/754	Ischemic stroke Propensity score matching: 74/754 All: 447/5532	Ischemic stroke Propensity score matching 0.71 (0.51–0.99) All 0.76 (0.58–0.99)	Intracranial hemorrhage 27/754	Intracranial hemorrhage Propensity score matching: 17/754 All: 107/5532	Intracranial hemorrhage Propensity score matching 1.10 (0.62–1.94) All 1.27 (0.82–1.95)
Pastori et al. [20]	Warfarin 1297 (55.7%) DOAC 1033 (44.3%)	Cardiovascular events Warfarin: 136/1297 DOAC: 33/1033	N/A	N/A	Warfarin Any bleeding: 261/1297 Major bleeding: 80/1297 DOAC Any bleeding: 96/1033 Major bleeding: 40/1033	N/A	N/A
Goriacko et al. [18]	Warfarin 158 (67.8%) DOAC 75 (32.2%)	N/A	N/A	N/A	Any bleeding Warfarin: 25/158 DOAC: 10/75	N/A	N/A
Grewal et al. [8]	N/A	N/A	N/A	N/A	GI bleeding: 790/3310 Intracranial hemorrhage: 120/3310	GI bleeding: 840/3650 Intracranial hemorrhage: 110/3650	GI bleeding 1.05 (0.94–1.17) Intracranial hemorrhage 1.21 (0.93–1.58)

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulation; ICH, intracranial hemorrhage; LC, liver cirrhosis; GIB, gastrointestinal bleeding; N/A, not available; OAC, oral anticoagulation; VKA, vitamin K antagonist; S, C, O, selection, comparability, and outcome.

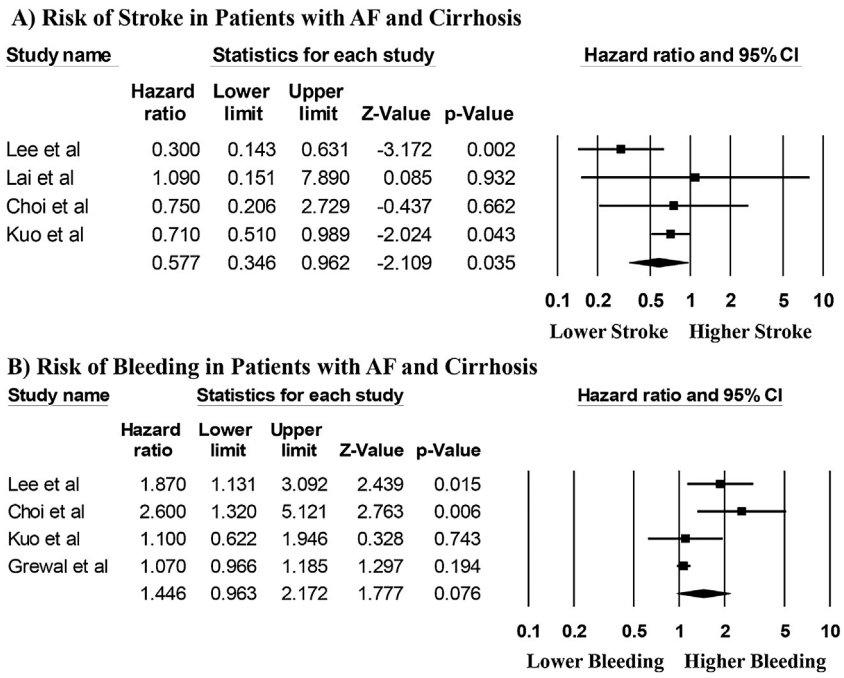

Fig. 2. Forest plots of the included studies assessing (A) risk of stroke and (B) risk of bleeding in the use of anticoagulation for AF in patients with cirrhosis.

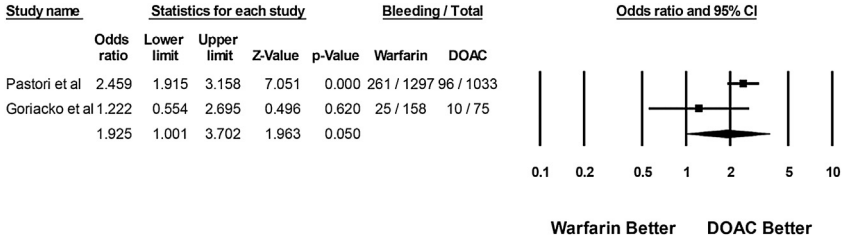

Fig. 3. Forest plots of the included studies assessing the risk of bleeding among AF patients with cirrhosis on warfarin vs. DOAC.

hazard ratio (HR) of 0.58 (95%CI: 0.35–0.96, I^2 = 35%, Fig. 2(A)), when compared to those without anticoagulation. The data on the anticoagulation use in AF patients with advanced cirrhosis was limited. Lee et al. demonstrated comparable stroke rates among AF patients with cirrhosis who were treated with anticoagulation (7.7%) and without anticoagulation (7.3%) (HR = 0.60 (95%CI: 0.15–2.42)) [25].

3.3. Anticoagulation use and risk of bleeding in patients with AF and cirrhosis

When compared with no anticoagulation, the use of anticoagulation was not significantly associated with a higher risk of bleeding with a pooled HR of 1.45 (95%CI: 0.96–2.17, I^2 = 72%, Fig. 2(B)). Compared to warfarin, the use of direct oral anticoagulants (DOAC) was associated with a lower risk of bleeding among AF patients with cirrhosis with a pooled odds ratio (OR) of 1.93 (95%CI: 1.001–3.70, I^2 = 63%, Fig. 3).

Data on anticoagulation use in AF patients with advanced cirrhosis and the risk of bleeding was limited. Lee et al. demonstrated a significantly increased risk of bleeding among AF patients with advanced cirrhosis treated with anticoagulation with a HR of 2.98 (95%CI: 1.23–7.19)[25].

3.4. Evaluation for publication bias

Funnel plots (Figs. S1–S2) and Egger's regression asymmetry tests were performed to evaluate for publication biases in analyses evaluating the risks of stroke and bleeding associated with the use of anticoagulation for AF in patients with cirrhosis. There were no significant publication biases identified ($p > 0.05$ for all analyses).

4. Discussion

Our study demonstrates an association between decreased risks of stroke without significant risk of bleeding among cirrhotic patients using oral anticoagulation for primary stroke prevention in AF. With respect to the type of drug, our study showed more favorable outcomes with the use of direct oral anticoagulation rather than VKAs.

The coagulation status in cirrhotic patients is the result of the balance between the decreased production of both pro-coagulant and anticoagulant factors. Certain conditions, especially among patients with decompensated liver cirrhosis, contribute to a higher bleeding tendency. These conditions include portal hypertension-related hemodynamic changes, endothelial dysfunction, and production of heparin-like agents by bacterial overgrowth and renal failure [33–37]. On the other hand, some patients develop a pro-coagulant state, manifested clinically by some of the common complications in cirrhotic patients, such as peripheral vein thrombosis, portal vein thrombosis, atherothrombotic disease and progression of liver fibrosis [38,39]. The balance between both pro-coagulant and anticoagulant factors is a dynamic and evolving process; hence, the coagulation status at any given time may vary and be unpredictable in each individual patient. This pathophys-

iological explanation suggests that there is interplay of complex mechanisms of the coagulation cascades that are not limited to a cellular level, but it is also related to the degree of liver dysfunction which varies from patient to patient. Therefore no single laboratory test can confirm the actual coagulation status of cirrhotic patients [3].

With respect to primary stroke prevention in AF, our study shows that the use of antithrombotic drugs in cirrhotic patients, either antiplatelet or anticoagulation therapy, is associated with better outcomes compared to those without these therapies. Based on scientific evidence that cirrhosis is associated not only to a bleeding diathesis but also with a pro-thrombotic state, our study found better outcomes with the use of oral anticoagulation with careful monitoring, over antiplatelet therapy. This is consistent with findings in the general population that demonstrate the futility of antiplatelet therapy for stroke prevention in AF [40].

Our study suggests that anticoagulation treatment in cirrhotic patients with AF may be beneficial. Hence, rather than refraining cirrhotic patients from systemic anticoagulation due to bleeding diathesis concerns, patients should be prescribed this type of therapy with close clinical and laboratory surveillance, in order to timely detect and manage any potential bleeding complications. The results from this study will hopefully encourage clinicians to prescribe systemic anticoagulation in this subset of patients, when indicated.

In a systematic review which included five retrospective cohort studies on the use of DOACs vs. AKAs for any thromboembolic event not limited to AF in 239 cirrhotic patients, they demonstrated a better safety and efficacy profile of DOACs over AKAs [35–39]. These results are in concordance with our study despite being performed in a different type of population.

Limitations in our study are noteworthy. Firstly, the diagnosis of AF was variable among studies, and patients with asymptomatic paroxysmal AF may not have been included. Secondly, anticoagulant agents in each individual study ranged from VKAs to different kinds of DOACs. This heterogeneity may have confounded the results and, theoretically, this data may be inappropriate for representation in a cumulative analysis manner. Thirdly, included studies did not provide a definition of major and minor bleeding, resulting in a variable incidence of bleeding across studies, hence, to generalize and to draw conclusions from these results may be challenging. In addition, the majority of data was obtained from observational studies, which confers the risks of the biases inherent to these types of studies. As a result, we can only establish an association between the use of anticoagulation and its clinical benefit, but we cannot determine a causal relationship.

In summary, our study demonstrates the benefit of the use of oral anticoagulation as primary stroke prevention in cirrhotic patients with AF. DOACs seem to provide a benefit over VKA for this particular purpose. However, further well-designed clinical studies need to be conducted to validate our findings.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.12.001.

References

[1] Saleh T, Matta F, Alali F, Stein PD. Venous thromboembolism with chronic liver disease. Am J Med 2011;124(1):64–8.
[2] Hytiroglou P, Theise ND. Regression of human cirrhosis: an update, 18 years after the pioneering article by Wanless et al. Virchows Arch 2018;473(1):15–22.
[3] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365(2):147–56.
[4] Wada H, Usui M, Sakuragawa N. Hemostatic abnormalities and liver diseases. Semin Thromb Hemost 2008;34(8):772–8.
[5] Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. Circulation 2014;129(8):837–47.
[6] Bhatia S, Mallam S, Singh V, Agnihotri K, Arora S, Patel P, et al. Atrial fibrillation is associated with worse outcomes in patients with cirrhosis. J Am Coll Cardiol 2017;69(11):493.
[7] Faroqui R, Niazi O. Prevalence and characteristics of atrial fibrillation in patients with end stage liver disease. J Cardiovas Electrophysiol 2017;28(5):604–5.
[8] Grewal H, Dangayach N. Warfarin in patients with liver cirrhosis and atrial fibrillation. . .worth the risk? Critic Care Med 2014;42(12):A1459.
[9] Huang WA, Dunipace E, Sorg JM, Vaseghi M. Liver disease as a novel risk factor for atrial fibrillation. Circulation 2016;134.
[10] Lee H, Choi EK, Rhee TM, Lee SR, Lim WH, Kang SH, et al. Cirrhosis is a risk factor for atrial fibrillation: a nationwide, population-based study. Liver Int 2017;37(11):1660–7.
[11] Mwalitsa JP, Maimone S, Filomia R, Alibrandi A, Saitta C, Caccamo G, et al. Atrial fibrillation in patients with cirrhosis. Liver Int 2016;36(3):395–400.
[12] Zamirian M, Sarmadi T, Aghasadeghi K, Kazemi MB. Liver cirrhosis prevents atrial fibrillation: a reality or just an illusion? J Cardiovas Dis Res 2012;3(2):109–12.
[13] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33(21):2719–47.
[14] Steffel J, Giugliano RP, Braunwald E, Murphy SA, Mercuri M, Choi Y, et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 Analysis. J Am Coll Cardiol 2016;68(11):1169–78.
[15] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–92.
[16] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–91.
[17] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–51.
[18] Goriacko P, Veltri KT. Safety of direct oral anticoagulants vs warfarin in patients with chronic liver disease and atrial fibrillation. Eur J Haematol 2018;100(5):488–93.
[19] Choi J, Kim J, Shim JH, Kim M, Nam GB. Risks versus benefits of anticoagulation for atrial fibrillation in cirrhotic patients. J Cardiovas Pharmacol 2017;70(4):255–62.
[20] Pastori D, Lip GYH, Farcomeni A, Del Sole F, Sciacqua A, Perticone F, et al. Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. Int J Cardiol 2018;264:58–63.
[21] Girleanu I, Trifan A, Stoica O, Huiban L, Stanciu C. Anticoagulant treatment for atrial fibrillation and decompensation rate in patients with liver cirrhosis. J Hepatol 2018;68:S710.
[22] Yu HT, Kim K, Kim TH, Uhm JS, Sung JH, Kim JY, et al. Favorable effect of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with liver cirrhosis. Eur Heart J 2017;38:615–6.
[23] Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? J Am Heart Assoc 2017;6(6).
[24] Lai HC, Chien WC, Chung CH, Lee WL, Wu TJ, Wang KY, et al. Atrial fibrillation, liver disease, antithrombotics and risk of cerebrovascular events: a population-based cohort study. Int J Cardiol 2016;223:829–37.
[25] Lee SJ, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B. The safety and efficacy of vitamin K antagonist in patients with atrial fibrillation and liver cirrhosis. Int J Cardiol 2015;180:185–91.
[26] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4(10):e296.
[27] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[28] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
[29] Herzog R, Alvarez-Pasquin MJ, Diaz C, Del Barrio JL, Estrada JM, Gil A. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health 2013;13:154.
[30] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
[31] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
[32] Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337(8746):867–72.

[33] Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology 2006;44(4):1039–46.
[34] Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362(9):823–32.
[35] Montalto P, Vlachogiannakos J, Cox DJ, Pastacaldi S, Patch D, Burroughs AK. Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. J Hepatol 2002;37(4):463–70.
[36] de Franchis R, Baveno VF. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53(4):762–8.
[37] Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? Blood 1999;94(8):2569–74.
[38] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137(6):2105–11.
[39] Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, Iannuzzi F, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. Hepatology 2010;52(1):249–55.
[40] Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev 2007;(3):CD006186.