



REVIEW

Direct Oral Anticoagulants in Patients with Liver Disease in the Era of Non-Alcoholic Fatty Liver Disease Global Epidemic: A Narrative Review

Stefano Ballestri · Mariano Capitelli · Maria Cristina Fontana ·
Dimitriy Arioli · Elisa Romagnoli · Catia Graziosi · Amedeo Lonardo ·
Marco Marietta · Francesco Dentali · Giorgio Cioni

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ABSTRACT

Atrial fibrillation (AF) and venous thromboembolism (VTE) are highly prevalent and relevant healthcare issues. Direct oral anticoagulants (DOACs) are now the first-choice for anticoagulant treatment of these conditions displaying a better efficacy/safety profile than vitamin-K antagonists, mainly due to significantly reduced risk of major bleeding, especially of intracranial haemorrhage. Nonalcoholic fatty liver disease

(NAFLD) is the most common liver disease in developed countries showing a continuously growing prevalence. Nonalcoholic steatohepatitis (NASH), its evolutive form, will be the leading cause for liver transplantation by 2020. NAFLD is independently associated with an increased risk of abnormalities of cardiac structure and function, including cardiac rhythm disorders (mainly AF). Moreover, data suggest an increased risk of unprovoked VTE associated with NAFLD/NASH. Therefore, a growing number of patients with chronic liver disease (CLD) will be candidate for anticoagulant therapy in the near future. Cirrhosis of any etiology is characterized by an unstable thrombosis/bleeding haemostatic balance, making anticoagulant therapy particularly challenging in this condition. Given that patients with significant active liver disease and cirrhosis were excluded from all pivotal randomized controlled trials on DOACs, this comprehensive review aims at critically discussing real-world evidence, including the latest population studies, regarding the use of DOACs in patients with CLD/cirrhosis.

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S. Ballestri (✉) · M. Capitelli · M. C. Fontana ·
C. Graziosi · G. Cioni
Internal Medicine Unit, Pavullo Hospital, Azienda
USL, Modena, Italy
e-mail: s.ballestri@ausl.mo.it

D. Arioli · E. Romagnoli
Internal Medicine and Critical Care Unit, Azienda
Ospedaliero-Universitaria, Modena, Italy

A. Lonardo
Metabolic Syndrome Unit, Ospedale Civile di
Baggiovara, Azienda Ospedaliero-Universitaria,
Modena, Italy

M. Marietta
Hematology Unit, Azienda Ospedaliero-
Universitaria, Modena, Italy

F. Dentali
Department of Clinical and Experimental Medicine,
Insubria University, Varese, Italy

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Key Summary Points

Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH), a globally epidemic condition, is independently associated with an increased risk of atrial fibrillation (AF) and unprovoked venous thromboembolism (VTE). Therefore, a growing mole of patients with chronic liver disease (CLD) will be a candidate for anticoagulant therapy in the forthcoming years.

Patients with significant active liver disease and cirrhosis have been excluded from all pivotal randomized controlled trials (RCTs) on direct oral anticoagulants (DOACs).

Anticoagulant therapy is challenging in cirrhotic patients, who exhibit an unstable balance hemostatic between thrombosis and bleeding.

Accumulating real world data suggest that, compared to warfarin, DOACs have similar efficacy and reduced bleeding complications in cirrhotic patients with AF or VTE.

RCTs evaluating efficacy, safety and possible dose adaptation rules in patients with cirrhosis are needed.

BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an age-dependent global prevalence of 1–3% in the adult population, exceeding 15% in people aged 80 years and over [1, 2]. It is estimated that subjects over 65 years affected by AF in Europe will increase by 89% from 7.6 to 14.4 million within the next 40 years, with prevalence rising from 7.8 to 9.5% [2]. Moreover, AF is significantly associated with an increased risk of thromboembolic

events [5-times higher risk of stroke], hospitalization and mortality [1, 2].

Similarly, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), carries a high financial burden being the third most frequent acute cardiovascular syndrome after myocardial infarction and stroke, and ranking high among the causes of cardiovascular mortality (more or less 300,000 deaths per year in United States and Europe) [3].

Direct oral anticoagulants (DOACs) have become the first-line drugs in the treatment of non-valvular AF (NVAF) and VTE with proven similar or better efficacy than vitamin-K antagonists (VKAs) such as warfarin and significantly reduced risk of major bleeding, mainly intracranial haemorrhage (ICH) [3, 4]. However, patients with liver disease and cirrhosis were excluded from pivotal randomized controlled trials (RCTs) of DOACs and evidences in this particular setting are limited [5].

Nonalcoholic fatty liver disease (NAFLD), now the most common chronic liver disease (CLD) in developed countries, embraces a spectrum of histopathological conditions ranging from simple relatively benign simple steatosis to nonalcoholic steatohepatitis (NASH), which is associated with progression to fibrosis/cirrhosis and hepatocellular carcinoma [6]. NASH will be the leading cause for liver transplantation by 2020 [7, 8]. NAFLD is independently associated with an increased risk of abnormalities of cardiac structure and function, including cardiac rhythm disorders (mainly AF) [9, 10]. Moreover, emergent data suggest NAFLD being associated with an increased risk of idiopathic VTE [11, 12]. Therefore, a growing number of patients with advanced fibrosis/cirrhosis will be candidate for anticoagulant therapy in the near future.

Cirrhosis of any etiology carries an increased risk of both thrombotic and bleeding complications, making anticoagulant therapy challenging in this condition. Given that patients with significant active liver disease and cirrhosis were excluded from trials on DOACs, this review aims at critically discussing real-world data, including the latest population studies, regarding the use of DOACs in patients with

CLD/cirrhosis. To this end we searched the PubMed database for publications up to February 2020, using pertinent terms and their combination: cirrhosis, chronic liver disease, direct oral anticoagulants, apixaban, dabigatran, edoxaban, rivaroxaban, venous thromboembolism, atrial fibrillation. Clinical trials, observational studies and case series were considered if relevant to the issue. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

THROMBOEMBOLISM IN LIVER DISEASES

Mechanisms: Hemostatic Balance and its Evaluation in Cirrhotic Patients

Preserved liver function is essential for the balance between haemostasis and thrombosis. Advanced liver disease of any etiology is typically associated with disorders of coagulation which are key in many scores of severity and outcome of liver disease [13].

Our understanding of the hemostatic balance in liver disease has progressed dramatically over the last decades. The prolongation of prothrombin time (PT)/international normalized ratio (INR) commonly found in advanced liver disease was traditionally considered protective from thrombo-embolic events. However, accumulating evidence has dismantled the theory of “auto-anticoagulation” in cirrhosis showing a high risk of VTE in cirrhotic patients, despite PT/INR values [14–16].

In cirrhotic patients, pro-hemorrhagic and prothrombotic drivers co-exist. Pro-hemorrhagic conditions include: (a) reduced plasma levels of coagulation factors synthesized by the liver [fibrinogen, factor (F)II, FV, FVII, FIX, FX, FXI, and FXII] reflected by prolonged PT and activated partial thromboplastin time (aPTT) (b) thrombocytopenia due to splenic sequestration and reduced thrombopoietin synthesis and (c) increased fibrinolysis secondary to elevated levels of tissue plasminogen activator, reduced levels of plasmin inhibitor and thrombin-activatable fibrinolysis inhibitor [17]. Conversely,

pro-thrombotic conditions include: (a) decreased endogenous anticoagulants synthesized by the liver: protein C, protein S and antithrombin (AT) (b) increased pro-coagulant endothelial-derived FVIII (c) increased platelet aggregation due to increased endothelial-derived von Willebrand factor (vWF) and reduced ADAMTS13, a natural inhibitor of vWF activity (d) reduced hepatic synthesis of plasminogen causing hypo-fibrinolysis [17].

The combination of these pro- and anti-coagulant factors results in a fragile balance (“re-balanced haemostasis”) in the stable cirrhotic patient that can be easily broken by precipitating factors (hepatic decompensation, sepsis, volume status, renal failure or invasive procedures) evolving into either thrombosis or bleeding [13, 16] (Fig. 1).

Recognizing the effect of liver disease on those laboratory tests of coagulation which are commonly used to monitor the therapeutic effects of anticoagulants is mandatory to appropriately evaluate and manage anticoagulant therapy in cirrhotic patients [18].

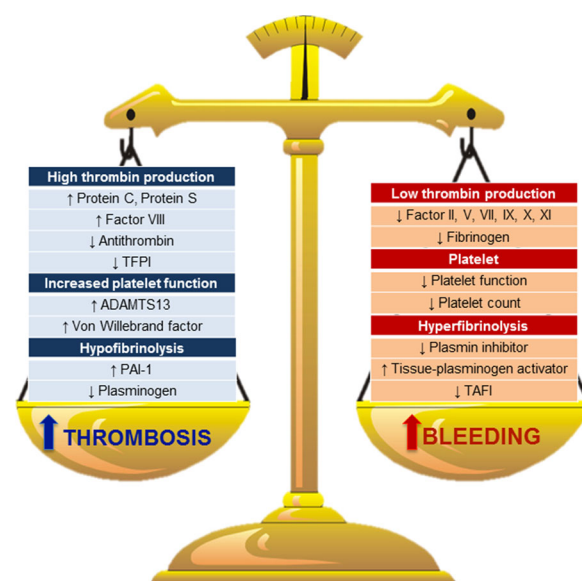


Fig. 1 Balance between thrombosis and bleeding in liver disease. ADAMTS13 ADAM metalloproteinase with thrombospondin type 1 motif 13, PAI plasminogen activator inhibitor, TAFI thrombin-activatable fibrinolysis inhibitor, TFPI tissue factor pathway inhibitor

Increased baseline INR/aPTT levels in the absence of anticoagulants and decreased anti-activated factor X (anti-Xa) levels after unfractionated/low-molecular weight heparin (UFH/LMWH) administration have been found in cirrhosis, correlating with the severity of liver disease [18–20]. Patients with cirrhosis can be unusually sensitive to the anticoagulant effects of warfarin and this may also be a clue to identifying latent disease [21].

INR does not appear to be a reliable tool to monitor haemostasis in cirrhotic patients because it only measures the activity of some procoagulants factors (FI, FII, FV, FVII and FX), but not that of anticoagulant proteins C/S [13]. Specific clotting tests (e.g. thromboelastography) may overcome the diagnostic limits of INR but lack validated target levels and are not routinely used [13, 22]. Similar challenges exist in using aPTT test for monitoring UFH therapy as with INR test for VKAs. Indeed, aPTT target ranges are unclear in cirrhotic patients, often carrying an aPTT already prolonged at baseline [18–20].

Anti-Xa levels are positively correlated with AT levels, which are reduced in cirrhotic patients [18, 20, 23, 24]. Therefore, the anti-Xa assay cannot be used to monitor AT-dependent anticoagulant drugs (LMWH/UFH) in patients with cirrhosis, given that it substantially underestimates drug levels. Conversely, the direct FXa and thrombin (FIIa) inhibitors can be monitored through the respective anti-Xa and anti-IIa assays in cirrhotic patients [19].

AF and VTE in Cirrhosis of Various Etiology

Published studies yielded inconsistent results regarding the incidence and prevalence of AF in patients with liver cirrhosis. In addition, temporal trends in risk profiles and clinical outcomes of hospitalized cirrhotic patients with concomitant AF are still unclear [25]. Patients with AF and concurrent liver cirrhosis have typically been excluded from RCTs of oral anticoagulant therapy, both VKAs and DOACs, for stroke prevention; therefore, AF guidelines are not able to provide specific

recommendation on anticoagulation in patients with cirrhosis [4]. In a recent nationwide registry study, the use of warfarin was associated with a reduced risk of ischemic stroke and positive net clinical benefit compared to non-treatment in patients with AF and cirrhosis, suggesting that thrombo-prophylaxis should be considered for such patients [26]. Conversely, a much smaller study reported that the incidence of stroke was similar in AF cirrhotic patients with and without warfarin use, whereas the incidence of major bleeding events was significantly higher in the warfarin group [27]. A recent large retrospective population-based Italian cohort study has shown that AF patients with concomitant liver disease had an increased risk of any of the primary study outcomes (stroke, major bleeding and all-cause death) compared to those without it (median follow-up time of 3.8 years); moreover, oral anticoagulation (97% VKAs, 3% DOACs) in patients with liver disease was associated with a significant benefit/risk ratio compared to non-treatment [28].

Hospitalized patients with cirrhosis have a 0.5–6.3% incidence of newly-diagnosed PE or DVT, similar to those without liver disease [29]. Validated risk stratification scores that predict VTE within hospitalized patients, also appear to accurately predict VTE among hospitalized patients with CLD [30]. Interestingly, a recent meta-analysis has shown that the risk of all VTE events was higher in patients with cirrhosis than in controls with an odds ratio (OR) of 1.7 [15]. Moreover, patients with cirrhosis and VTE may have increased mortality over 30 days as compared to those with VTE without cirrhosis [31, 32]. Nevertheless, prophylactic anticoagulation for VTE in hospitalized cirrhotics is significantly lower than in non-cirrhotics [33].

Aside from DVT/PE, a major issue for patients affected by CLD is splanchnic vein thrombosis, including mesenteric, portal and hepatic vein thrombosis [32]. Portal vein thrombosis (PVT) is the most common VTE event in cirrhosis with a prevalence ranging from nearly 1% in compensated to 8–25% in decompensated cirrhosis [34, 35]. Mechanistic factors involved in the development of PVT in cirrhotic patients are likely to be multi-factorial.

Prior VTE, thrombophilia, low portal vein flow velocity, malignancy, intra-abdominal infection, and recent surgery all increase the risk for PVT [32]. Of note, patients with cirrhosis who develop PVT and have no other history of clotting do not require a hypercoagulable workup [13]. The clinical presentation is variable and stability, regression, or resolution appear more common than clot progression [36]. Anticoagulation with LMWH appears safe and effective for PVT in cirrhosis [13, 37, 38].

AF and VTE in the NAFLD Spectrum

The epidemiology of liver diseases has significantly changed over the last years owing to NAFLD continuously growing prevalence in parallel with the decline of chronic hepatitis C virus (HCV) thanks to the advent of highly-effective direct-acting antiviral agents [8]. NAFLD is a multi-system disease representing a relevant health care issue [39]. Beyond its inherent liver-related morbidity and mortality, NAFLD also has a strong mutual, bi-directional relationship with type 2 diabetes (T2D)/metabolic syndrome (MetS) [40, 41]. Moreover, it is associated with an increased incidence and prevalence of fatal and non-fatal cardiovascular disease (CVD) events, mainly coronary heart disease (CHD), independently of classical cardiovascular risk factors [42–45]. Interestingly, several observational studies reported an association between NAFLD and increased risk of AF in patients with and without T2D, after adjustment for multiple potential confounders [46]. A recent metanalysis showed that NAFLD was independently associated with increased risk of prevalent (OR 2.07) and, only in T2D patients, incident [hazard ratio (HR) 4.96] AF [47]. Studies investigating whether the reversal of NAFLD will reduce the risk of AF are eagerly awaited. Conversely, longitudinal studies have already proven that NAFLD reversal/improvement or even its transient remission will reduce the risk of incident T2D (reviewed in [48]).

Emerging data suggest an association between NAFLD and VTE. One study showed a significantly higher prevalence of NAFLD in hospitalized patients with unprovoked VTE as

compared to healthy sex/age/body mass index (BMI) matched controls (81% vs 30%), even after adjustment for inherited thrombophilia. NAFLD was independently predicted by VTE (OR 1.8) at multivariate analysis [11]. A recent study has shown that NASH-related cirrhosis is independently associated with an increased risk of VTE among hospitalized patients with cirrhosis after adjustment for confounding factors (OR 2.46) [12]. The risk of PVT is significantly increased in patients with NASH-cirrhosis (OR 1.55) compared to cirrhosis owing to non-NASH etiologies independently of other risk factors [49] and those aged > 60 years, with BMI > 30 kg/m², arterial hypertension and T2D appear at a particularly high-risk of pre-liver transplant PVT (OR 2.11) [50].

Consistently, some studies provided evidence of a pro-coagulant state in NAFLD patients. An increased activity of some circulating coagulation factors (FVIII, FIX, FXI and FXII) has been found in patients of NAFLD, independently of age, gender and BMI [51, 52]. NAFLD has independently been associated with increased plasminogen activator inhibitor-1 (PAI-1) in obese patients in a manner related to histological severity [53]. A procoagulant-imbalance has been observed across the spectrum of NAFLD histological severity progressing from simple steatosis to NASH-cirrhosis and resulting from increased FVIII (procoagulant) and reduced protein C (anticoagulant) [54]. The findings of one study which found that haemostasis (i.e., platelets, coagulation and fibrinolysis) was rebalanced in NAFLD may have been influenced by unusually higher than expected FVIII levels in lean controls [55, 56]. In conclusion the coagulopathy observed across the NAFLD spectrum is an intriguing and as yet incompletely defined area. Therefore, more research is needed in this field.

Potential Role of Coagulation System on the Development of the Histogenesis of Cirrhosis and its Complications

Experimental and clinical data suggest an association between inflammation, activation of

coagulation system and development of hepatic fibrosis and portal hypertension in CLD [57].

Histopathological studies on cirrhotic livers have shown that micro-thrombotic occlusion of small intrahepatic veins and sinusoids, secondary to hepatic necroinflammation, frequently occurs; this event is followed by progressive venous obstruction and enhanced fibrogenesis through a process called parenchymal extinction, which may eventually lead to liver dysfunction, worsening of portal hypertension and PVT [58–60]. A pathogenic model of NASH progression has been proposed based on lipotoxic necrotic damage, leading to direct inflammatory injury of hepatic veins and, finally, venous obstruction with secondary collapse, fibrous septation and cirrhosis [61].

The activation of hepatic stellate cells (HSC) is the key pathogenic mechanism of hepatic fibrogenesis. Experimental animal models support a biological link between coagulation and fibrosis showing that thrombin and FXa can activate HSC [62, 63] and, conversely, their inhibition by anticoagulants may prevent or reduce fibrogenesis [57].

Prothrombotic genetic risk factors such as FV Leiden or prothrombin G20210A mutations have been associated with an increased risk of clinically relevant liver fibrosis (assessed by transient elastography) in the general population [64].

Taken collectively, these observations suggest that anticoagulation may represent also an effective tool to prevent and to treat liver fibrosis and, therefore, portal hypertension.

A milestone small RCT has shown that daily prophylactic administration of LMWH (enoxaparin) for 12 months in patients with advanced compensated cirrhosis [Child-Turcotte-Pugh (CTP) score B7-C10] prevented PVT development, hepatic decompensation and also improved survival [63]. It was speculated that the protective effect of enoxaparin on liver disease might have been due to an improvement in intestinal microcirculation with secondary reduction in bacterial translocation and thus liver inflammation, rather than by merely preventing PVT [65]. Few other studies on patients with hepatitis B virus (HBV)-related liver fibrosis/cirrhosis or post-liver transplant HCV

recurrence-related fibrosis treated with LMWH or warfarin have also shown improved liver function and decreased collagen levels/fibrosis (reviewed in [57]).

Recent data have shown that anticoagulant therapy (LMWHs or VKAs) in patients with cirrhosis and PVT is safe and does improve outcome in advanced cirrhosis [38, 66].

While currently available direct-acting antivirals will probably erase the burden of chronic viral hepatitis, effective antifibrotic drugs for CLD are still lacking [62]. Patients with metabolic disease (NAFLD/NASH) with indication to anticoagulation are continuously rising and would represent the ideal candidates for future studies evaluating the effect of long-term anticoagulation, including DAOCs, on fibrogenesis and portal hypertension.

DOACS IN ADVANCED CHRONIC LIVER DISEASE

Overview on DOACs and Liver Disease

The four DOACs available for clinical use include apixaban, rivaroxaban and edoxaban which are direct inhibitors of FXa and dabigatran which is a direct inhibitor of thrombin (FIIa). DOACs have become the first-choice anticoagulant drugs in the prevention and treatment of stroke-systemic embolism and VTE in the great majority of patients, provided that renal function is adequate. However, patients with active liver disease, defined as acute or chronic hepatitis, cirrhosis or elevated alanine transaminase (ALT) or aspartate transaminase (AST) > 2 or 3-times the upper limit of normal (ULN) or total bilirubin \geq 1.5–2 times the ULN, have all been excluded in all the pivotal RCTs of DOACs [5].

Compared to warfarin, DOACs are less reliant on hepatic clearance and have a shorter half-life. These pharmacodynamic characteristics make them attractive for use also in patients with liver disease [5, 67]. However, DOACs also have hepatorenal body clearance, plasma protein binding and cytochrome P450 metabolism. These pharmacokinetic properties can all be affected by liver disease to varying degrees,

suggesting caution in their use in patient with altered hepatic function [5, 67]. Apixaban and rivaroxaban are principally cleared by the liver (75% and 65% respectively), followed by edoxaban (50%) and lastly by dabigatran (20%), which is mainly eliminated by the kidney. Dabigatran etexilate is the only pro-drug DAOC undergoing the biotransformation to active drug by ubiquitous esterases; thus, its metabolism is not limited to the liver. Some DOACs have a high plasma protein binding capacity (rivaroxaban 95%, apixaban 85%, edoxaban 55%, and dabigatran 35%) which can be associated with increased free drug fraction levels when liver albumin synthesis is impaired. Apixaban and rivaroxaban are predominantly metabolized by cytochrome P450 enzymes, whose activity is reduced by liver disease, while dabigatran and edoxaban have minimal to none cytochrome P450 metabolism. Biliary excretion of all DOACs is reduced by liver disease. Finally, also renal clearance of DOACs may be impaired when liver disease is either associated with hepatorenal syndrome or other kidney diseases co-exist.

The CTP scoring system, the prognostic model universally used to predict mortality in cirrhosis, incorporates five parameters: serum bilirubin, serum albumin, prothrombin time, ascites severity and encephalopathy grade [68, 69]. Based on the sum of these items the individual patient is categorized into one of three CTP classes of growing severity (A, B, or C) which predict survival outcomes. Survival rates at 1 and 2-year are respectively 95% and 90% for CTP class A patients, while they are 80% and 70% for CTP class B and 45% and 38% for class C patients [70].

Therefore, it can be assumed that the risk of bleeding outweighs the potential benefits of anticoagulant therapy in cirrhotic CTP class C subjects, whose 1-year survival rate is less than 50% without liver transplantation. In patients with CTP class B anticoagulation should be balanced against the presence of portal hypertension, oesophageal varices, hypertensive gastropathy, thrombocytopenia, coagulopathy, baseline high risk of bleeding, impaired drug metabolism and impaired renal function.

On these grounds, both drug regulatory agencies (European Medicines Agency: EMA; Food and Drug Administration: FDA) and current guidelines recommend all four DOACs in patients with cirrhosis CTP class A, while contraindicate their use in patients with liver disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhosis CTP class C. DOACs are variably recommended in CTP class B liver disease [5, 67]. Rivaroxaban was contraindicated due to a > twofold increase in drug exposure in these patients [71] while dabigatran, apixaban and edoxaban may be used with caution based on low-grade evidence from few small retrospective studies [5, 67]. The U.S. FDA does not recommend also Edoxaban in CTP class B [72], although one study found no difference in drug exposure in patients with CTP A and B after a single low-dose of Edoxaban (15 mg) [73]. The European society of cardiology (ESC) recommends that the prescription and follow-up of anticoagulant therapy in cirrhotic patients should be performed in specialized centres featuring a multidisciplinary medical team (including a hepatologist and an expert of coagulation disorders) [67].

Evidence from Real-World Studies

Real-world data on the use of DOACs in patients with CLD are continuously accumulating. Several new studies have been published since the release of the latest guidelines [67] and previous reviews on the use of DOACs in patients with cirrhosis [5, 74–76]. Original studies evaluating the use of DOACs vs traditional anticoagulants in patients with CLD are reported in Table 1 [77–89].

The first data came from retrospective case series or relatively small-sized cohort studies showing that the hemorrhagic risk with DOACs was lower than or similar to warfarin in cirrhotic patients anticoagulated for various indications. However, the sample size of these studies did not usually allow for adequate comparison of thromboembolic outcomes [74]. A seminal retrospective analysis on 39 cirrhotic patients (approximately 50% in CTP class B)

Table 1 Studies evaluating DOACs vs traditional anticoagulants in patients with CLD

Author (reference)	Population characteristics	AC Indication study/ctrl, n	Age study/ctrl	CTP study/ctrl, %	Varices study/ctrl, n (%)	DOACs type	DOACs dose	AC duration study/ctrl	Efficacy outcomes study vs ctrl, n (%)	Safety outcomes study vs ctrl, n (%)
Intagliata [77]	USA, retrospective cohort, 39 cirrhotic pts (DOACs 20, warfarin/LMWH 13/6)	AF 4/1 VTE 4/12 SpVT 12/6	Mean (range) 57 (50–64)/ 60 (55–64)	A: 45/47 B: 55/53 C: 0/0	10 (50) 7 (41)	Apixaban 55% Rivaroxaban 45%	2.5 or 5 mg BID 10 or 20 mg OD	Mean 267/478 days	NA	Any bleeding rate: 20% vs 16% (ns) Major bleeding rate: 5% vs 11% (ns)
Kunk [78]	USA, retrospective cohort, 69 cirrhotic pts (DOACs only)	AF 22 PVT/DVT 47	Median (range) 73 (44–92)	A: 48 B: 38 C: 14	36 (52)	Apixaban 54% Rivaroxaban 36% Dabigatran 10%	NA	6 months	AF: none developed clot VTE: 81% resolution, 13% unchanged, 6% progression	Any bleeding rate: 16 (23) Major bleeding rate: 8 (12)
Hum [79]	USA, retrospective cohort, 45 cirrhotic pts (DOACs 27, warfarin/LMWH 15/3)	AF 15/9 DVT 12/8 PVT 4/3	Mean (range) 61 (26–90)/ 58 (34–80)	A: 41/39 B: 44/50 C: 15/11	4 (15) 72 (11)	Rivaroxaban 63% Apixaban 47%	15 mg OD ± 20 mg load 5 mg BID ± 10 mg load	Median 225/317 days	Failed efficacy: 1 (6) vs 1 (4) (p = 1.00)	Any bleeding rate: 8 (30) vs 10 (56) (p = 0.12) Major bleeding rate: 1 (4) vs 5 (28) (p = 0.03)
De Gottardi [80]	Europe, retrospective cohort, 36 cirrhotic pts vs 58 non-cirrhotic ctrls (all DOACs only)	SpVT 27/42 DVT 4/0 AF 5/12 Other 0/6	Median (range) 49.5 (16–82)/ 64.9 (32–82)	Median (range) 6 (5–8)	23 (64) 724 (41)	Rivaroxaban 83% Apixaban 11% Dabigatran 5%	5 to 20 mg TDD 2.5 to 10 mg TDD 110 to 220 mg TDD	Mean 9.6/ 13.1 months	NA	All bleeding rate: 5 (14) vs 9 (15.5) Major bleeding rate: 1 (3) vs 2 (3.5)
Goriacko [81]	USA, retrospective cohort, 233 CLD pts (DOACs 75, warfarin 158)	AF 75/158	Median (IQR) 66 (61, 75)/ 65 (59, 73)	A: 64/35 B: 35/59 C: 1/6	1 (1.3)/ 11 (7)	Dabigatran 47% Rivaroxaban 39% Apixaban 15%	NA	NA	NA	Any bleeding rate: 8.4% vs 8.8% per year (ns) Major bleeding rate: 3.3% vs 3.9% per year (ns)

Table 1 continued

Author (reference)	Population characteristics	AC Indication study/ctrl, n	Age study/ctrl	CTP study/ctrl, %	Varices study/ctrl, n (%)	DOACs type	DOACs dose	AC duration study/ctrl	Efficacy outcomes study vs ctrl, n (%)	Safety outcomes study vs ctrl, n (%)
Nagasaki [82]	Japan, retrospective cohort, 50 cirrhotic pts (DOACs 20, warfarin 30; INR target 1.5–2)	PVT 20/30	9 (53–74)/67 (24–83)	A: 75/50 B: 25/33 C: 0/17	16 (80)/26 (87)	Edoxaban 100%	60 mg (20%) or 30 mg (80%) OD	6/6 months	PVT resolution: 14 (70) vs 6 (20) $p < 0.001$ PVT progression: 1 (5) vs 14 (47) $p < 0.001$	Any bleeding rate: NA Major bleeding rate: 3 (15) vs 2 (7) (ns)
Pastori [83]	Italy, retrospective cohort, 129 pts with advanced liver fibrosis (i.e. FIB-4 > 3.25) (DOACs 52, VKAs 77); 2201 ctrls (DOACs 981, VKAs 1220)	FIB-4 > 3.25:AF 52/77 FIB-4 < 3.25:AF 981/1220	Mean \pm SD 74.4 \pm 9.3/ 78.9 \pm 7.5	NA	NA	Apixaban 35% Rivaroxaban 35% Dabigatran 27% Edoxaban 3% (pts + ctrls n.1033)	Standard	NA	FIB-4 not significantly associated with CV events neither in DOACs or VKAs pts at MVA $p = 0.001$	FIB-4 associated with major bleedings only in VKAs pts (HR: 3.075, $p = 0.001$)
Hanafy [84]	Egypt, RCT, 80 HCV-related cirrhotic CTP A-B pts (DOACs 40, warfarin 40)	Acute PVT 40/40	Mean \pm SD 46 \pm 5/ 41 \pm 2	A: NA B: NA C: 0	Grade \geq 2: 27(68)/29 (73)	Rivaroxaban 100%	10 mg every 12 h	NA	PVT resolution: 85% vs 45%. Short-term survival rate: 20.4 \pm 2.2 vs 10.6 \pm 1.8 months	GI bleeding: 0 (0) vs 17 (43.3)
Davis [85]	USA, retrospective cohort, 109 CLD pts (DOACs 27, warfarin 82)	DVT 9/41 PE 10/21 PVT 8/20	Median (IQR) 60 (53–62)/55 (50–64)	A: 41/22 B: 59/60 C: 0/18	3 (11)/17 (21)	Apixaban 44.5% Rivaroxaban 44.5% Dabigatran 11%	NA	NA	Recurrent VTE: 3 (11) vs 10 (12) at 3 months (ns)	Major bleeding rate: 2 (7.4) vs 7 (13.4) (ns) Admission for non-major one: 1 (3.7) vs 5 (6.1) (ns)

Table 1 continued

Author (reference)	Population characteristics	AC Indication study/ctrl, n	Age study/ctrl	CTP study/ctrl, %	Varices study/ctrl, n (%)	DOACs type	DOACs dose	AC duration study/ctrl	Efficacy outcomes study vs ctrl, n (%)	Safety outcomes study vs ctrl, n (%)
Davis [86]	USA, retrospective cohort, 167 cirrhotic pts (DOACs 57, warfarin 110)	DVT 10/32 PE 9/18 PVT 3/19 AF 23/28 Other 10/24	Median (IQR) 63 (58–72)/ 59 (52–67)	A: 61.4/ 39.1 B: 19.3/ 48.2 C: 5.3/6.4	7 (12)/28 (26)	Apixaban 52.6% Rivaroxaban 45.6% Dabigatran 1.8%	NA	NA	Stroke and recurrent embolism at 90 days: 1 (1.8) vs 0 (0) and 1 (1.8) vs 2 (1.8) (both ns)	Major bleeding rate at 90 days: 3 (5.2) vs 10 (9.1) (ns)
Wang [87]	Taiwan, population retrospective cohort, 633 pts with ILF (DOACs 342, warfarin 394)	AF 342/394	Mean ± SD 77 ± 36.9 all	NA	NA	Rivaroxaban 51% Dabigatran 28% Apixaban 19% Edoxaban 2%	NA	NA	No difference in IS or SE risk. Lower risk of death (aHR 0.64, 0.49–0.83)	No difference in major or GI bleeding
Lee [88]	Korea, population retrospective cohort, 4942 patients with significant active LD (DOACs 3115, warfarin 1827) from 37,353 total population	AF 3,115/ 1,827	Mean ± SD 67.9 ± 10.2/ 68.1 ± 10.8	NA	NA	Rivaroxaban 43% Dabigatran 27% Apixaban 23% Edoxaban 7% (total population)	51% reduced dose	F-up 15 months	Reduced risk of IS (HR 0.445, 0.312–0.636) and composite outcome ^a (HR 0.691, 0.577–0.827)	Lower risk of ICH (HR 0.424, 0.241–0.723), hospitalization for major bleeding (HR 0.622, 0.442–0.870)

Table 1 continued

Author (reference)	Population characteristics	AC Indication study/ctrl, n	Age study/ctrl	CTP study/ctrl, %	Varices study/ctrl, n (%)	DOACs type	DOACs dose	AC duration study/ctrl	Efficacy outcomes study vs ctrl, n (%)	Safety outcomes study vs ctrl, n (%)
Lee [89]	Taiwan, population retrospective cohort, 2428 cirrhotic pts (DOACs 1438, warfarin 990)	AF 1438/990	Mean \pm SD 72.8 \pm 11.1/ 72.4 \pm 11.2	NA	NA	Rivaroxaban 51% Dabigatran 37% Apixaban 12%	95% 10–15 mg OD 89% 110 mg BID 69% 2.5 mg BID	Mean F-up 1.13/ 1.30 years	Comparable risk of IS/SE	Lower risk of GI (HR 0.51, 0.32–0.79) and all (HR 0.51, 0.32–0.74) major bleeding. Comparable risk of ICH

^a Six items (ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, major bleeding, all-cause death), International Society on Thrombosis and Haemostasis (ISTH) definition was largely adopted for major bleeding in the reported studies

AC anticoagulation, AF atrial fibrillation, aHR adjusted hazard ratio, BID bis in die, CLD chronic liver disease, CTP Child-Turcotte-Pugh, ctrl control, CV cardiovascular, DOACs direct oral anticoagulants, DVT deep vein thrombosis, F-up follow-up, GI gastrointestinal, HCV hepatitis C virus, HR hazard ratio, ILF impaired liver function, INR international normalized ratio, IQR interquartile range, IS ischemic stroke, LMWH low-molecular weight heparin, MVA multivariate analysis, NA not available, ns not statistically significant, OD once daily, PE acute pulmonary embolism, pts patients, PVT portal vein thrombosis, RCT randomized controlled trial, SD standard deviation, SE systemic embolism, SpVT splanchnic vein thrombosis, TDD total daily dose, VTE venous thromboembolism, VKAs vitamin K antagonists

receiving anticoagulant therapy (20 on DOACs and 19 on traditional anticoagulation: warfarin or LMWH) for either splanchnic/non-splanchnic VTE or AF showed no significant difference in the risk of any/major bleeding between the two treatment groups (4/1 vs 3/19) over a 3-year period. The prevalence of oesophageal varices was high in both groups (50% DOACs and 41% warfarin) [77]. Another retrospective analysis performed at the same University Hospital on 69 cirrhotic patients on DOACs for AF or VTE, including several with advanced liver disease (CTP class A/B/C: 33/26/10), reported that all major bleeding (12% of patients) were observed in those with CTP class B/C: mainly non-variceal gastrointestinal (GI) bleeding occurring, despite the fact that the majority of patients did have oesophageal varices [78]. A retrospective cohort study conducted on 45 cirrhotic patients, mostly in CTP class B, treated with anticoagulants (38% rivaroxaban, 22% apixaban, 33% warfarin, 7% enoxaparin) for AF stroke prevention or VTE (mainly DVT) found a significantly lower frequency of major bleeding (4% vs 28%), mainly due to less ICH (0% vs 17%), in patients taking DOACs as compared to those taking either warfarin or enoxaparin over a 3-year follow-up [79].

A retrospective cohort study on 233 patients with CLD anticoagulated for AF with DOACs (n. 75: 15% apixaban, 47% dabigatran, 39% rivaroxaban; mostly CTP A) or warfarin (n. 58; mostly CTP B), showed similar all-cause bleeding and major bleeding rates between the two treatment groups [81]. A recent single-centre, retrospective study on a population of 109 cirrhotic patients (59% CTP class B) diagnosed with acute VTE (PE, DVT or PVT) has shown no statistical difference in recurrent VTE or major bleeding events among patients treated with all four DOACs (n. 27) compared to those with warfarin (n. 82) over a short (3-months) follow-up period; however, the DOACs group did not include CTP class C patients [85]. A subsequent study by the same group, including subjects with AF,

confirmed no statistically significant difference in both recurrent embolism/stroke and major bleeding at 90 days in cirrhotic patients under either DOACs or warfarin [86].

Three relatively small sampled studies have investigated the use of DOACs in cirrhotic patients with prevalent or exclusive indication to anticoagulant therapy for PVT. A multicentre retrospective study of 94 patients anticoagulated with DOACs (83% rivaroxaban, 11% dabigatran and 6% apixaban) mainly for PVT (about 65%) showed a similar over-all adverse events rate (17% vs 19%) in those with cirrhosis (*n.* 36, CTP class A–B only) and without it (*n.* 58), including 1 recurrent PVT and 1 major bleeding (lower GI) in cirrhotic and 2 major bleeding in non-cirrhotic patients without any fatal case due to DOACs during follow-up (mean 13.1 and 9.6 months, respectively). Patients with cirrhosis were prescribed more often with a reduced dose of all three DOACs not related to an adaptation to kidney dysfunction [80]. In another retrospective cohort of 50 cirrhotic patients (CTP A/B/C 30/15/5) with PVT, treated initially for 2 weeks with LMWH and then switched to oral anticoagulation, a greater resolution of PVT at 6 months was found among patients on DOAC (edoxaban) as compared to those on warfarin, without significant differences in the incidence of bleeding, however, it should be noted that the dose of warfarin was in the sub-therapeutic range (INR target 1.5 to 2.0) [82]. Finally, a recent RCT on 80 patients with HCV-related compensated cirrhosis with acute PVT showed a higher rate of resolution of PVT and improved short-term survival without any complication, including major bleeding, in patients treated with low-dose rivaroxaban (10 mg every 12 h) as compared to those receiving warfarin [84].

A recent post-hoc analysis of a prospective large multicentre study on AF outpatients treated with either VKAs (*n.*1297) or DOACs (*n.*1033) has shown that advanced fibrosis, assessed non-invasively by the validated FIB-4 score > 3.25, was significantly associated with major bleeding events in AF patients treated with VKAs but not in those on DOACs [83].

Three recent large retrospective Asian population studies have investigated the use of oral

anticoagulants in patients with liver disease and NVAF. A multicentre Taiwan cohort study based on electronic medical records, including 6451 anticoagulated AF patients over 65-years, has shown that DOACs were associated with a significantly reduced risk of death (HR 0.64) but with no difference in stroke/systemic embolism, major bleeding or GI bleeding as compared to warfarin in 633 patients with impaired liver function, defined as ALT or AST > twofold or total bilirubin > 1.5-fold ULN [87]. Another study, using the Korean National Health Insurance Service database, reported that, compared to warfarin, the use of DOACs (43% rivaroxaban, 27% dabigatran, 23% apixaban, 7% edoxaban) was associated with lower risk of ischemic stroke, ICH, GI bleeding, major bleeding, all-cause death and composite outcome in a population of 37,353 subjects with active liver disease defined by claims for diagnostic codes [International Classification of diseases (ICD)] during a mean 1.2-year follow-up [88]. All 4 DOACs showed risk reduction in all six clinical outcomes compared with warfarin, except for rivaroxaban which showed comparable hospitalization rates owing to GI bleeding. In a subgroup of 4942 patients with significant active liver disease (defined by positive ICD codes for liver cirrhosis, viral hepatitis, or ALT or AST > twofold ULN) a significantly reduced risk for ischemic stroke (HR 0.445), ICH (HR 0.424), hospitalization for major bleeding (HR 0.622) and composite outcome (HR 0.691) was confirmed in those on DOACs (63%) as compared to those on warfarin (39%). In patients with cirrhosis, no significant difference for efficacy and safety outcome was observed with DOACs use (*n.* 446) compared to warfarin (*n.* 322) [88]. Finally, a study on 2428 liver cirrhotic patients with AF, from the Taiwan National Health Insurance Research Database, has shown that the group taking DOACs (*n.* 1438; 51% rivaroxaban, 37% dabigatran, 12% apixaban) had a risk of ischemic stroke/systemic embolism and ICH comparable to that of the warfarin group (*n.* 990) and significantly lower GI (HR 0.51) and all (HR 0.51) major bleeding risk during a mean 1.2-year follow-up [89]. A subgroup analysis indicated that both dabigatran and rivaroxaban, but not apixaban, showed a

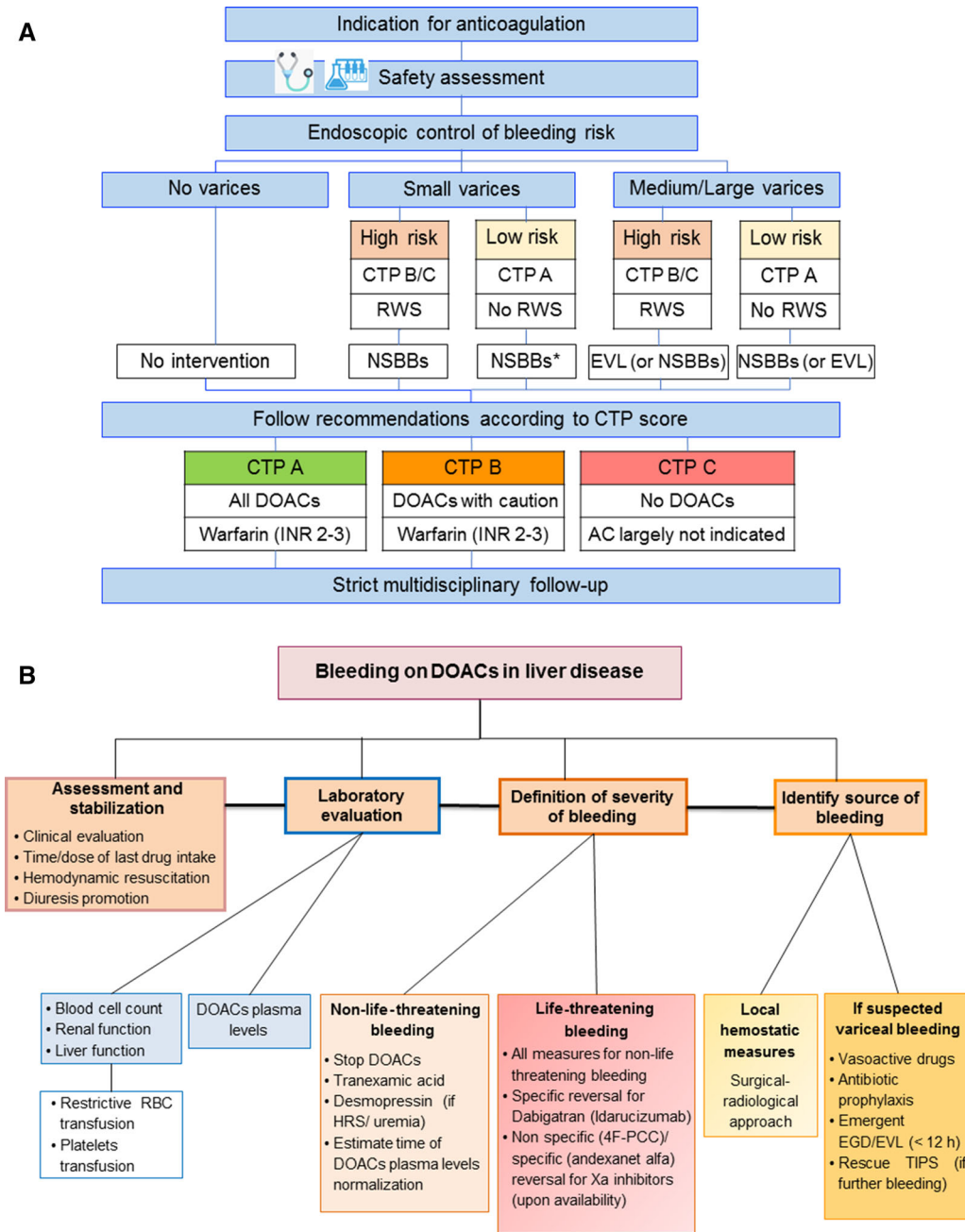


Fig. 2 Management of anticoagulation in patient with CLD/cirrhosis. **a** DOACs initiation. AC anticoagulation, CTP Child Turcotte-Pugh, DOACs direct oral anticoagulants, EGD esophagogastroduodenoscopy, EVL endoscopic variceal ligation, INR international normalized ratio, NSBBs non-selective beta-blockers, RWS red wale

signs. *can be used. **b** Management of bleeding complications. DOACs direct oral anticoagulants, EVL endoscopic variceal ligation, HRS hepatorenal syndrome, 4F-PCC four factor-prothrombin complex concentrate, RBC red blood cells, TIPS transjugular intrahepatic portosystemic shunt

significant lower risk of all major bleeding than warfarin. The authors argue that this finding in the apixaban group may be due to several

explanations: a higher proportion of standard-dose prescriptions, a small sample size insufficient for statistical significance, increased drug

exposure due to higher hepato-biliary clearance. Moreover, the advantage of lower GI and all major bleeding with DOACs over warfarin was observed only in subjects with either nonalcoholic or non-advanced liver cirrhosis (i.e. without complications including ascites, hepatic encephalopathy, spontaneous bacterial peritonitis or bleeding oesophageal varices) [89].

In summary, these population studies suggest that DOACs have at least comparable effectiveness and possibly a better safety than warfarin in patients with CLD/cirrhosis and AF. However, these results should be interpreted with caution [90, 91]. The strengths of these studies are the large population-based sample and that propensity score weighting methods were used to balance covariates between the two anticoagulation treatment groups in the two largest studies [88, 89]. Nevertheless, they have several weaknesses. As observational studies they are prone to confounding by indication and no adjustment method can fully resolve it [92]. In one study the definition of significant active liver disease was too broad including a spectrum of conditions ranging from mild elevation of aminotransferases to viral hepatitis with fibrosis of unknown severity and cirrhosis based on ICD codes. The impact of functional and prognostic scoring systems of cirrhosis (e.g. CTP) was not assessed [88]. Reduced doses of DOACs were prescribed from 50–60% [86] to 90% [89] of patients. In one study no data were provided about DOACs dosage [87]. The quality of anticoagulation control as reflected by time in therapeutic range (TTR) in the warfarin group was not evaluated. Previous data suggest that, in Asian populations, the quality of warfarin anticoagulation may be suboptimal [93]. Moreover, Asian individuals show pharmacokinetic and pharmacodynamic profiles of DOACs quite different from those of Caucasian individuals [94]. Therefore, some caution is needed in generalizing the results of these studies to Western populations.

Finally, two previously published meta-analyses have evaluated the use of warfarin and DOACs in cirrhotic patients including some of the above reported studies. The first including 19,798 cirrhotic patients with AF from seven cohort studies, two of which comparing DOACs

vs warfarin [81, 83], had two main findings: (a) the use of warfarin was associated with a lower risk of stroke compared with no anticoagulation (HR 0.58) without a significantly increased bleeding risk (HR 1.45), (b) the use of DOACs was associated with a lower risk of bleeding among AF patients with cirrhosis (OR 1.93) [95]. The second, including 447 cirrhotic patients from five studies [77, 79, 81, 82, 84] undergoing anticoagulant therapy (DOACs vs warfarin/LMWH) owing to various indications, found that patients treated with DOACs had no significantly increased risk of all-cause bleeding [relative risk (RR) 0.72] and major bleeding (OR 0.46) as compared to those who received traditional anticoagulants [96]. Updated meta-analyses including the most recent data from large Asian population studies are eagerly awaited.

In conclusion, real-world data suggest that DOACs can safely be used in CTP A patients and cautiously in CTP B cirrhotic patients with comparable efficacy and possibly better safety than warfarin. Interestingly, Rivaroxaban and Edoxaban have been used in CTP B cirrhotic patients in some studies without significant adverse events, despite their contraindication in these patients according to EMA/FDA and FDA, respectively.

Prospective studies and RCTs evaluating the efficacy and safety of DOACs in large subgroups of patients with compensated (CTP A) and decompensated (CTP B) cirrhosis are needed to establish appropriate dose adaptation rules based on bleeding/thromboembolic outcomes, aminotransferases/bilirubin cut-offs for DOACs use, risk factors for serious complications such as bleeding and, finally, which DOACs are more effective and safer in these patients.

A Practical Approach to the Prescription of DOACs

Patients with CLD candidate to any type of anticoagulant treatment including DOACs should undergo a complete clinical, laboratory and instrumental examination to assess the severity/functional prognostic class of liver disease and the burden of thrombotic and haemorrhagic risk (Fig. 2a).

Indication to anticoagulation should be based on currently available general guidelines for AF and VTE, given the lack of specific guideline recommendations and evidence from RCTs in cirrhotic patients [3, 67, 97]. Standard stratification tools such as the CHA₂DS₂-VASc score [67] should be used in selecting potential candidates for anticoagulation in AF. As far the complex scenario of PVT treatment in cirrhotic patients is concerned, updated clinical practice recommendations have recently been published by the American Society of Gastroenterology (AGA) [13].

All patients should undergo laboratory examination to determine hepato-renal function, platelet count and coagulation at baseline and at regular intervals during treatment. CTP scoring should be assessed regularly in patients with CLD. Screening and counselling for alcohol misuse should be provided. The decision of starting anticoagulation should be fully shared with the patients explaining expected benefits and possible adverse effects. DOACs dose reduction should be applied according to standard rules taking into consideration age, renal function, weight and current medications [67]. Anticoagulation should be interrupted/reduced in the presence of severe thrombocytopenia (platelet count $< 50 \times 10^9/L$ to $< 70 \times 10^9/L$), depending on the thrombotic risk of the patient [67, 97]. INR > 1.8 and/or platelet count $< 50 \times 10^9/L$ has been defined as significant coagulopathy in cirrhotic [22, 98]. However, conventional coagulation tests show a limited value in estimating haemostatic competency in patients with cirrhosis, as reported in Sect. [Mechanisms: Haemostatic Balance and its Evaluation in Patients with Cirrhosis](#).

Upper endoscopy should be performed in all cirrhotic patients to screen for oesophageal varices in order to reduce the bleeding risk before starting any type of anticoagulant: treatment with either non-selective beta-blockers or endoscopic variceal ligation (EVL) is recommended based on varices size and risk of bleeding [76, 99].

As previously stated, DOACs are recommended in cirrhotic patients in CTP class A while should be prescribed with caution in selected CTP class B cirrhotic patients weighing

the increased risk of bleeding, considering severity of portal hypertension, presence of active coagulopathy and previous GI bleeding. Warfarin, unlike DOACs, may be used in selected patients with CTP class C; however, given the high risk of bleeding and poor prognosis, anticoagulation is generally contraindicated in these patients.

Cardiologists, hepato-gastroenterologists and hematologists should collaborate to optimize anticoagulant treatment in patients with CLD: no evidence is available on which DOAC has the best efficacy and safety profile in such patients. In clinical practice the choice between different DOACs should consider their pharmacodynamic properties, patient characteristic, data from RCTs and prospective cohort studies on general population and from accumulating studies on liver disease patients.

Dabigatran has the lowest hepatic clearance and binding to albumin, conversely apixaban has the highest percentage of hepatic metabolism but evidence in the general population suggest that is associated to the best safety profile for GI bleeding [100–102]. Rivaroxaban and partly edoxaban are contraindicated in CTP class B patients, although in some studies they have been used in these patients at variable dosage (Table 1).

Management of Bleeding Complications

The management of bleeding complications in patients with liver disease should follow the general approach recommended by current guidelines (Fig. 2b) [67, 103]. The type of bleeding (non-major, major non-life threatening or life-threatening) and patient/drug characteristics (time of last DOAC dose intake, prescribed dosing regimen, renal function, comedication, indication for anticoagulation and underlying thrombotic risk) are key aspects guiding the strategy for bleeding management. Major bleeding is defined by the association with at least one of the following conditions: (a) hemodynamic compromise (b) occurrence at an anatomically critical site (e.g. central nervous system, thoracic, intra-abdominal, retroperitoneal intra-articular, intra-muscular)

given that it may cause severe disability and require surgical procedures for haemostasis or (c) associated with a decrease of haemoglobin (Hb) ≥ 2 g/dL (when baseline is known) or requiring the transfusion of ≥ 2 unit of packed red blood cells (RBC) [104]. Intra-luminal GI bleeding is not considered a critical bleeding site; however, it can produce hemodynamic instability.

Given the short half-lives of DOACs, most non-major bleeding complication can safely be managed only by treatment discontinuation and supportive measures including local haemostasis, fluid replacement, diuresis promotion, monitoring and blood transfusions when appropriate, following a restrictive transfusion strategy (target Hb level of 7–8 g/dL) [101, 105]. Activated charcoal may be administered to reduce the intestinal absorption if the DOAC was ingested within 2 h, but it may impair endoscopic visualization in the case of GI bleeding [106]. Procedural/surgical management of the bleeding site may also be considered. Anti-fibrinolytic therapy with tranexamic acid should be considered in major bleeding especially in trauma patients [67, 103].

In case of either critical-site/life-threatening bleeding or severe major bleeding not responding to the above reported general measures of control, reversal of anticoagulation represents a life-saving measure [67, 103]. Idarucizumab, a humanized anti-dabigatran monoclonal antibody, is available for reversing dabigatran anticoagulant activity [67, 103]. Andexanet alfa, a factor Xa decoy already marketed in the USA and now entering Europe, is indicated as specific reversal agent for FXa inhibitors. If it is not available, a 4-factor prothrombin complex concentrate (4F-PCC) should be administered to reverse the anticoagulant effect of a FXa-inhibitor. Specific coagulation assays measuring the anticoagulant activity of DOACs [diluted thrombin time (dTT) and anti-Xa chromogenic assay] may assist in the management of bleedings which are not immediately life-threatening, aiding to select patients before administering reversal agents [107, 108].

Specific management measures may help in controlling bleeding in patients with advanced

liver disease (Fig. 2b) [13, 99, 109]: optimization of renal function to prevent uremic platelet dysfunction and haemostatic changes; platelet transfusion in actively bleeding patients with severe thrombocytopenia ($< 50 \times 10^9/L$); standard treatment of acute variceal bleeding with a combination of a vaso-active drugs (immediate use of either terlipressin or somatostatin) and endoscopic procedures (< 12 h); early antibiotic prophylaxis to prevent infections (causing release of endothelial derived “heparinoids”); proton-pump inhibitors (PPIs) have no efficacy on portal-hypertension-related bleeding and increase the risk of spontaneous bacterial peritonitis, but a short course PPIs therapy after EVL may reduce post-banding ulcer size; transjugular intrahepatic portosystemic shunt (TIPS) as rescue therapy of choice in persistent bleeding; desmopressin (an endothelial stimulant that increases FVIII and vWF) can be used to improve platelet function only in patients with liver disease complicated by hepato-renal syndrome and uremia.

HEPATIC ADVERSE EFFECTS OF DOACS

DOACs pharmacokinetic properties (in particular liver metabolism of anti-Xa inhibitors) have raised concerns about potential drug induced liver injury (DILI) (i.e. transaminases $> 3 \times$ ULN with total bilirubin $> 2 \times$ ULN). Apart from Ximelagatran, an oral direct thrombin inhibitor which was rapidly withdrawn from the market in 2006 owing to a high risk of hepatotoxicity, DOACs have generally demonstrated an adequate liver safety profile [5].

A meta-analysis of 29 phase III RCTs has shown that all DOACs as a class, and also the individual drugs, do not increase the risk of DILI as compared to standard anticoagulation (VKA/LMWH) or placebo [110].

Real-life data have shown that all DOACs rarely cause DILI (incidence between 1:100 to 1:1000 patients) which, after GI disorders, is the non-bleeding leading cause of drug withdrawal worldwide. The underlying mechanism is

unknown but an idiosyncratic reaction is suspected [111, 112].

A recent study, using data from a large healthcare utilization database in the United States, has shown a lower rate of hospitalizations for DILI in patients on DOACs as compared to those on warfarin (5 vs. 9 per 1000 person-years) among a cohort of 113,717 patients with NVAF receiving a first-time oral anticoagulant prescription (50% warfarin and 50% DOACs). Among DOACs, dabigatran had the lowest relative risk of hospitalization owing to DILI [113]. History of hepato-biliary disease, alcoholism, kidney disease, heart failure, anemia and cancer are risk factors for hospitalization owing to DILI [113].

Another study on 51,887 patients with AF (including 3778 patients with concomitant liver disease) from a Canadian healthcare insurance database, who were followed for 68,739 person-years, showed no significant difference in the rates of serious DILI (i.e. hospitalization or death) with DOACs versus warfarin, irrespective of baseline liver status [114].

Currently available data reassure clinicians and patients regarding the hepatic safety of DOACs but, although rare, there is the possibility of clinically relevant DILI with DOACs. Therefore, clinical vigilance is necessary. European Heart Rhythm Association (EHRA) guidelines generally recommend annual monitoring of liver tests in patients treated with DOACs and closer six months monitoring in older individuals, in those with CLD and unstable medical conditions that may affect hepatic or renal function [67].

CONCLUSIONS

The proportion of patients affected by CLD in whom anticoagulation is indicated will likely be increasing owing to the ongoing NAFLD epidemic. Data suggest that NAFLD and NASH are independently associated with both AF and VTE, indicating a procoagulant state in these patients. Cirrhosis of any etiology features an unstable haemostatic balance making anticoagulant treatment challenging. Cardiovascular doctors should be prepared to prescribe

anticoagulants to an ever-growing number of patients with CLD and cirrhosis in the forthcoming years. Optimal medical assistance should offer a multidisciplinary approach based on a coordinated collaboration among the different specialists involved. Based on accumulating real-world data showing at least comparable efficacy and better safety than warfarin, DOACs are a good option for the treatment of AF and VTE in patients with liver disease. The management of bleeding complications in patients with liver disease may take advantage of specific reversal agents now available for all DOACs. No data are available to suggest a specific DOACs with better efficacy/safety profile to be preferentially used in cirrhotic patients. RCTs on the use of DOACs in patients with cirrhosis are urgently needed.

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Data Availability. All data generated or analyzed during this study are included in this published article.

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