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REVIEW

Anticoagulation in Patients with Liver Cirrhosis: Friend or Foe?

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Abstract
Concepts regarding the status of the coagulation process in cirrhosis are rapidly changing. Instead of a disease defined by excessive bleeding risk, recent studies have shown cirrhosis to be associated with a fragile state of rebalanced hemostasis, easily swayed in either direction, thrombosis, or bleeding. These findings, combined with the ever-growing population of patients with cirrhosis with an indication for anticoagulation (AC) and the emergence of the non-alcoholic fatty liver disease epidemic, have prompted a reexamination of the use of AC in patients with cirrhosis, either as a treatment for a concurrent thrombotic disorder or even as a possible therapeutic option that could influence the natural course of the disease and its complications. In recent years, a significant number of studies have been formulated to evaluate these possibilities. These studies evaluated, among others, the efficacy and safety of AC in thrombotic disorders or thrombotic complications of cirrhosis, its effect on survival, and the class of anticoagulants which is more suitable for patients with cirrhosis, depending on disease severity. This review examines recent studies investigating the use of AC in patients with cirrhosis and attempts to provide a simple guide for clinicians regarding the use of AC in patients with cirrhosis and its potential risks and benefits.

Keyword Cirrhosis · Anticoagulation · Thrombosis · Portal hypertension · Bleeding

Coagulation Imbalance in Patients with Cirrhosis

Coagulation imbalance has been a well-studied feature of liver cirrhosis for many years. Earlier reports emphasized the impairment of the hemostatic process observed in these patients [1], designating liver cirrhosis as a disease manifesting with an elevated bleeding propensity. Recent studies have disputed this theory, demonstrating that coagulation imbalance in cirrhosis is much more complex, with multiple components of the coagulation cascade being affected, each of them tipping the scales of the coagulation imbalance toward either side but ultimately achieving a fragile state of rebalanced hemostasis [2]. This state is achieved by conflicting changes in coagulation parameters such as (i) thrombocytopenia and platelet defects in contrast to elevated levels of von Willebrand factor and decreased levels of ADAMT-13 [3–5], (ii) depleted levels of most coagulation factors in contrast to elevated levels of factor VIII and decreased levels of proteins S and C, and antithrombin [6–8], and (iii) hyperfibrinolysis attributed to elevated levels of tissue plasminogen activator (tPA) and decreased levels of thrombin-activatable fibrinolysis inhibitor (TAFI) in contrast to decreased levels of plasminogen and elevated levels of plasminogen activator inhibitor 1 (PAI-1) [9, 10]. A summary of the alterations observed in critical components of the coagulation cascade is summarized in Fig. 1. While many tests have been proposed to identify and analyze parts of the hemostasis process in patients with cirrhosis, none have been evaluated as suitable for guiding decisions in a clinical environment [11, 12]. The re-evaluation of the coagulation imbalance status in patients with cirrhosis also brought forward the hypothesis that procoagulant drivers may be partly responsible for disease progression, mainly by the formation of microthrombi inside the liver parenchyma, which further augments hepatic congestion, promoting liver fibrosis [13, 14].

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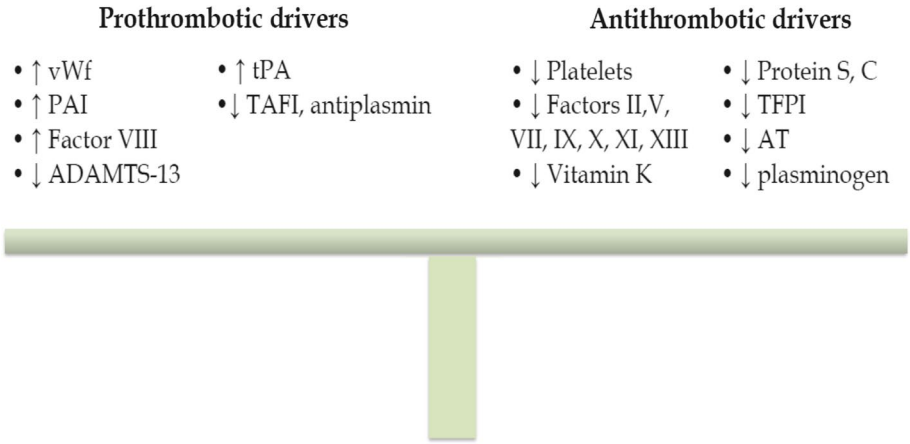

Fig. 1 Alterations in components of the coagulation cascade in patients with cirrhosis. *vWf* von Willebrand factor, *PAI* plasminogen activator inhibitor, *tPA* tissue plasminogen activator, *TAFI* thrombin-activatable fibrinolysis inhibitor, *TFPI* tissue factor pathway inhibitor

Most importantly, these changes in the concept of cirrhotic coagulopathy have underscored the need for prophylactic or therapeutic anticoagulation (AC) in these patients when indicated. In past decades, patients with cirrhosis were considered "Auto-Anticoagulated" and therefore were not prescribed anticoagulants, even when there was a clear indication, such as venous thromboembolism (VTE) or atrial fibrillation (AF). This assumption was primarily based on the alterations in blood tests, such as thrombocytopenia and prolongation of the international normalized ratio (INR) present in cirrhosis. However, studies have shown that simple blood tests cannot be indicative of the bleeding tendency of patients with cirrhosis while also demonstrating that transfusion with blood products to correct anticoagulation factor deficits confers more harm than benefit [15–17]. Furthermore, owing to the significant improvements in terms of the survival of patients with cirrhosis and the significant increase of patients with cirrhosis due to non-alcoholic steatohepatitis (NASH) [18], the number of patients with cirrhosis that require AC rises constantly. Therefore, to avoid depriving patients of a therapeutic option that may positively impact their prognosis, clinicians must be aware of recent developments in this field.

This review aims to examine the efficacy and safety of AC in patients with liver cirrhosis, both in terms of treating prothrombotic disorders and in terms of its effect on the progression of liver disease.

Anticoagulation in AF and VTE: Known Benefit with Questionable Harm

Many studies have evaluated AC therapy in disorders with a clear indication for it by assessing efficacy in terms of prevention and resolution of thrombotic events and safety in terms of minor or major bleeding events.

Atrial fibrillation is the most frequent disorder associated with AC in patients with cirrhosis, and it has been shown that patients with cirrhosis who suffer from concomitant AF have higher in-hospital mortality rates compared to those who do not [19, 20]. Due to the high prevalence of the disease, many studies have evaluated the use of AC in patients with concomitant cirrhosis. The first studies focused mainly on patients receiving vitamin K antagonists (VKA) versus patients without AC. Kuo et al. examined this relationship in a retrospective study of 9056 patients with cirrhosis and AF with a CHA2DS2-VASc score ≥ 2 [21]. It was found that patients who received warfarin had a significantly lower risk of ischemic stroke than those receiving antiplatelet therapy or no treatment (HR = 0.76; 95%CI 0.58–0.99). Interestingly, this net gain was not accompanied by an increase in bleeding tendency since all groups maintained similar risks of intracranial hemorrhage. While this study provided some positive signs, the absence of data regarding Child–Pugh (CP) classification (although it was reported that < 10% had a previous decompensation event) generated even more questions in terms of the specific group of patients with cirrhosis that would be benefited by the use of anticoagulation. A study by Lee et al. examined 321 patients with cirrhosis and concomitant AF, though it employed further sub-analysis for patients with CP B or C [22]. While patients receiving warfarin with CP A exhibited a lower risk of stroke (HR 0.23; 95%CI 0.09–0.58) and similar bleeding risks compared to patients without treatment, patients with CP B or C exhibited an overwhelming increase in terms of bleeding events (HR 2.98; 95%CI 1.23–7.19), surpassing the reduction of stroke events and resulting in a net increase in terms of clinically significant events (HR 2.01; 95%CI 1.06–3.83). Another study by Choi et al. displayed no reduction in stroke risk combined with an increase in hemorrhagic complications in patients receiving warfarin compared to patients without treatment [23]. A significant point raised in these studies was the difficulty of designating suitable INR target values in patients with liver failure, which remains a significant deterrent against the use of VKAs in patients with cirrhosis.

The difficulties surrounding the use of VKAs and the rise of direct-oral anticoagulants (DOACs) provided new data from studies comparing them to no treatment or directly to one another. A retrospective study by Serper et al. explored the incidence of stroke and bleeding complications in 2694 patients with AF and cirrhosis, divided into groups receiving warfarin, DOACs, or no treatment [24]. At least 75% of the patients were classified as CP A. Both DOACs and warfarin showed an advantage in terms of stroke incidence and overall mortality compared to no treatment, while there was no increase in bleeding complications. Furthermore, DOACs were shown to maintain significantly less bleeding risk than warfarin (HR 0.49; 95%CI 0.26–0.94). Additionally, another retrospective study with 2428 patients showed a significantly lower risk of gastrointestinal and major bleeding with DOACs, compared to warfarin [25]. A meta-analysis by Chokesuwattanaskul et al. that included seven cohort studies with 19,798 patients further confirmed these findings [26], as was the case for another meta-analysis of three studies and 4011 patients by Lee et al. [27]. With the consensus shifting toward the need for AC in patients with AF and concomitant cirrhosis, more and more studies examined the differences between VKAs and DOACs, without enrolling patients not on AC. The results of these studies are inconsistent, showing either an advantage of DOACs, mainly in terms of fewer bleeding complications [25, 26, 28], or similar outcomes between the two drug classes [29]. Common limitations of these studies are their retrospective nature and not taking into account the severity of liver disease, either by not including CP or Model For End-Stage Liver Disease (MELD) classifications for the patients or by failing to account for the more frequent use of VKAs in patients with CP B or C compared to DOACs, which are mainly used in patients with CP A. Notably, in many studies, DOACs were prescribed in sub-therapeutic doses, with one study even demonstrating superiority of reduced-dose DOACs over warfarin, in terms of both bleeding and thrombotic complications [28].

Another common syndrome that warrants AC for at least a period of some months is VTE. Research suggests that patients with cirrhosis are at a higher risk of developing VTE than the general population [30–32], either pulmonary embolism or deep venous thrombosis, for which a significant relationship has been independently established [30]. An even higher risk is reported in patients with cirrhosis due to non-alcoholic steatohepatitis (NASH) [33]. Moreover, one study exhibited that patients with VTE and cirrhosis experience higher 30-day mortality rates than patients without cirrhosis [34]. Finally, there have been studies investigating the prophylactic use of low molecular weight heparin (LMWH) in hospitalized patients with cirrhosis, with results showing no increase in terms of bleeding complications, albeit no advantage in terms of VTE prevention [35, 36].

To sum up, AC has been effectively established as a mainstay in the treatment of thrombotic disorders in patients with liver disease. Not only has it been shown that AC is more effective than no treatment, but there are also no signs of additional risks in terms of bleeding complications. Accordingly, the consensus has finally shifted, with current practice guidelines advocating in favor of the use of AC both in patients with AF and patients in need of VTE thromboprophylaxis [37]. When it comes to the choice of anticoagulation, most recent studies show an advantage of DOACs compared to VKAs, effectively rendering DOACs as the first-choice treatment for patients with cirrhosis and atrial fibrillation.

AC in Patients with Portal Vein Thrombosis (PVT): Necessary or Risky?

Portal vein thrombosis represents a significant complication of cirrhosis with a variety of effects on the course of the disease. While there are conflicting data concerning the effect of PVT on the overall mortality of patients with cirrhosis [38–40], its effects on decompensation events [38, 39, 41] and transplantation feasibility and mortality [42] are indisputable. The main complication of portal vein thrombosis is the development or escalation of previous clinically significant portal hypertension, leading to variceal bleeding [43]. Therefore, the use of AC in these patients has been highly debated due to the fear of bleeding [44]. However, the concept of AC inducing portal hypertension-related bleeding is contradicted by the fact that the resolution of portal vein thrombosis due to AC leads to improvement of portal hypertension.

Efficacy and safety of AC in PVT are difficult to assess due to the small number of randomized controlled trials (RCTs) on this subject and the fact that two of them investigate PVT in special situations [45, 46], while the third does not have a control group without AC [47]. That leaves only one RCT to explore the treatment of chronic PVT [48]. Therefore, most data are extracted from observational studies and subsequent meta-analyses.

With regard to efficacy, most studies focus on portal vein recanalization rates and the absence of thrombus expansion. In the only RCT by Zhou et al., recanalization rates at six months were independently associated with AC (1-month nadroparin followed by five months of warfarin) (OR 4.9; 95%CI 1.7–14.5) [48]. A higher recanalization rate was independently associated with AC in all observational and meta-analysis studies, regardless of the type of AC [49–58]. Moreover, a study by Rodriguez-Castro et al. showed that prompt initiation of anticoagulation was independently associated with successful recanalization [59]. Nevertheless, efficacy was never in question; safety was. With respect

to that, most studies showed that there was no association between bleeding complications and AC treatment, with a meta-analysis of 26 studies and 1475 patients by Valeriani et al. showing even a decreased risk of major bleeding in patients receiving AC (RR 0.52; 95%CI 0.28–0.97) [55]. Furthermore, meta-analyses investigating specifically the occurrence of variceal bleeding showed a decreased risk in patients receiving AC [53, 56, 57]. While these data further bolster the case for AC in PVT, the outcome that would settle the debate once and for all is the overall mortality of the patients. The results with regard to this endpoint are still inconsistent, with the largest observational studies reporting conflicting data [49, 52], showing either significant benefit or no difference, while a smaller study showed a survival benefit only in patients with MELD > 15 [50]. The most positive data yet have come from the abovementioned study by Valeriani et al., where overall mortality was significantly related to AC treatment (RR 0.42; 95%CI 0.24–0.73) [55].

With most of the data favoring the use of AC in PVT, the next question is which class of drugs is the preferred one, with DOACs presenting advantages over LMWH in terms of their pill form and VKAs due to their fixed dosage, irrespectively of INR value. As a consequence, there have been studies evaluating DOACs in the treatment of PVT, although the only studies to compare DOACs to traditional AC in chronic PVT have been two network meta-analyses by Ng et al. and Koh et al. that have encompassed studies with different treatment groups in order to formulate a comparison [60, 61]. In the first study by Ng et al., DOACs appear more effective in terms of recanalization compared to both LMWH (RR 2.3; 95%CI 1.04–5.1) and warfarin (RR 1.76; 95%CI 1.02–3.1), while in the second study, they maintain a higher risk of recanalization compared to VKAs (RR 1.67; 95%CI 1.02, 2.74). There is no significant difference in the risk of bleeding complications between the different drug classes in both studies. Significant studies investigating the use of anticoagulation in patients with cirrhosis and PVT are presented in Table 1.

In Which Patients? Which Anticoagulant? For How Long?

As explored in both cardiovascular thrombotic disorders and PVT, AC is generally found to have comparable safety to no treatment in patients with cirrhosis. Accordingly, the debate today primarily concerns the groups of patients that should be treated and the class of drugs that should be used. It should be noted that there is a consensus among guidelines that anticoagulation for chronic PVT (> 6 months) should be recommended only in patients awaiting LT, patients with a concurrent thrombophilic disorder, and patients with documented thrombus progression [62, 63]. In terms of liver disease severity, there have been many studies emphasizing the significant increase of bleeding complications in patients with CP B and especially CP C. Lee et al. showed that VKA treatment was responsible for higher bleeding risk in patients with CP B or C (HR 2.98; 95% CI 1.23–7.19), but not in patients with CP A, compared to no treatment [22]. These findings were further corroborated by Pettinari et al., who found significantly increasing bleeding rates with the progression of the CP stage in patients receiving AC (mainly LMWH) [49]. Two more recent studies have explicitly examined the safety of DOACs, with ambivalent results. Mort et al. found that a significant percentage (21%) of patients discontinued DOACs after a median follow-up of 181 days, albeit identified no relationship to CP status [64]. On the contrary, Semmler et al. found that 22% of CP B and C patients receiving DOACs developed major bleeding at 12 months, significantly higher than the percentage of CP A patients (5%) (HR: 5.82; 95%CI 2–16.9) [65]. Both studies recruited a large number of patients with CP B and C (> 50 in total for each study, > 50% of patients with cirrhosis), significantly larger than in previous studies, which could explain the increased prevalence of bleeding complications. Furthermore, studies have shown that patients with higher CP scores are less likely to achieve recanalization of PVT with AC [48, 57, 59]. As a consequence of these studies and the drug's manufacturer's recommendations, AC should be used with caution in patients with CP B and is generally not recommended in patients with CP C unless there is a significant indication or it would be administered for a limited period. A reduced dose could be an option in patients with CP B or C since studies have shown that physicians often use reduced doses in patients with cirrhosis without any apparent loss of efficacy [28, 66].

In terms of the duration of therapy, specific patients' characteristics define the need for AC cessation after both successful and unsuccessful therapy for PVT and also after bleeding events. Recent Baveno guidelines highlight the need for continuous AC regardless of PVT outcome in patients listed for liver transplantation (LT) [63]. However, there are contradictory guidelines in terms of continuing anticoagulation after six months in patients that are not listed for LT. While guidelines of the American College of Gastroenterologists (ACG) recommend cessation of therapy after recanalization or failure of recanalization at six months, Baveno guidelines suggest that anticoagulation may be continued after six months, with the intention of achieving recanalization or, in the event of recanalization, in order to prevent rethrombosis [62, 63]. Taking into account recent studies that show benefit of AC in terms of overall survival, it seems that chronic anticoagulation may be suitable for most patients with cirrhosis and PVT. Finally, for patients with significant thrombocytopenia (platelets $< 50 \times 10^9$/L) and patients experiencing bleeding events, a thorough

Table 1 Significant studies investigating the efficacy and safety of anticoagulation in patients with cirrhosis and portal vein thrombosis

Study–year—type	Study population–Groups	Efficacy—Safety	Comments
Meta-Analysis [56]	8 studies–353 patients AC: 199 (VKAs: 97, LMWH: 52, unknown: 50)	–AC associated with a higher recanalization rate (OR 4.8; 95%CI 2.7–8.7) –Similar bleeding rate between AC and no AC –AC associated with lower rates of variceal bleeding (OR 0.23; 95%CI 0.06–0.94)	–Mean FU ≈ 2 years –No data regarding the severity of cirrhosis
Prospective [50]	80 patients–AC: 37 (VKAs: 22, LMWH: 15)	–AC not associated with a higher recanalization rate (HR. 0.6; 95%CI 0.31–1.17) –AC not associated with overall OLT-free mortality –Patients on AC with MELD ≥ 15 had higher OLT-free survival compared to no AC ($p = 0.011$)	–Median FU ≈ 25.5 months –No data regarding bleeding events
Retrospective [59]	65 patients–all treated with enoxaparin	–66% responded to anticoagulation after a median of 4.4 months –CP A, Portal cavernoma, complete PVT, time to AC commencement: independent factors of not achieving recanalization –6% bleeding rate	FU ≥ 12 months
Retrospective [49]	182 patients–81 AC (LMWH: 56, FDPX: 15, VKAs:10)	–Higher recanalization rate with AC ($p < 0.0001$) –AC associated with lower mortality (HR 0.30; 95%CI 0.1–0.91) –No significant difference in terms of bleeding events –Higher bleeding rates and mortality with the progression of CP stage in patients receiving AC	–Median FU ≈ 19 months
RCT [48]	62 patients–32 AC (1-month nadroparin followed by 5 months WF)	–AC associated with a higher recanalization rate (OR 6.3; 95%CI 1.6–24.7) –No significant difference in terms of bleeding events AC group: significantly better CP score at 6 months ($p < 0.01$)	6-month FU
Meta-Analysis [54]	17 studies–744 patients–AC: 648 (VKAs: 315, DOACs:70, LMWH: 155)	–AC associated with a higher recanalization rate (OR 5.1; 95%CI 2.5–10.2) –No significant difference in terms of bleeding events –No difference between different drugs in terms of recanalization or bleeding rates –No influence of CP stage on bleeding and recanalization rates	
Prospective [51]	80 patients–40 AC (DOACs)	–Higher rate of recanalization in the DOAC group ($p < 0.05$) –Similar rate of bleeding between the two groups	–Groups by propensity matching –6-month FU
Meta-Analysis [58]	13 studies–6005 patients – AC: 1774 (LMWH, VKAs and DOACs)	–Higher rate of recanalization in the AC group (OR 4.3; 95%CI 3–6.1) –Similar mortality rates between the two groups –Higher rate of bleeding in the AC group (OR 1.16; 95%CI 1.02–1.32)	–FU > one year for most studies included –Biggest study only listed as an abstract (5310 patients)

Table 1 (continued)

Study–year—type	Study population–Groups	Efficacy—Safety	Comments
Meta-Analysis [55]	26 studies–1475 patients – AC: 947 (LMWH: 396, VKAs: 472, DOACs: 79)	–Higher rate of recanalization in the AC group (RR 3.2; 95%CI 1.42–7.2) –AC associated with lower rates of major bleeding (OR 0.52; 95%CI 0.28–0.97) –AC associated with lower overall mortality rates (OR 0.42; 95%CI 0.24–0.73)	–Median FU ≈ 20.4 months
Retrospective [52]	214 patients–86 AC (LMWH: 42, VKAs: 26, DOACs: 18)	–Higher rate of recanalization in the AC group (HR 4.9; 95%CI 1.91–12.3) –Similar rates of major bleeding between the two groups –Similar mortality rates between the two groups	–Median FU ≈ 27 months
Meta-Analysis [53]	9 studies–474 patients –AC: 256 (LMWH and VKAs)	–Higher rate of recanalization in the AC group (RR 2.3; 95%CI 1.8–2.9) –Similar rates of major bleeding between the two groups –AC associated with lower rates of variceal bleeding (OR 0.15; 95%CI 0.04–0.55) –No influence of CP stage on recanalization rates	
Meta-Analysis [57]	33 studies–1696 patients AC included LWMH, VKAs, DOACs and others	–Higher rate of recanalization in the AC group (RR 2.6; 95%CI 1.99–3.4) –Similar rates of major bleeding between the two groups –AC associated with lower overall mortality rates (OR 0.42; 95%CI 0.24–0.73) –AC associated with lower rates of variceal bleeding (OR 0.26; 95%CI 0.11–0.65) –Higher CP stage and MELD score were associated with lower recanalization rates	–14/33 (42%) of studies published only as abstracts
Meta-Analysis [60]	10 studies–527 patients—including LMWH, DOACs, VKAs and no AC	–DOACs were superior to LMWH (RR 2.3; 95%CI 1.04–5.1), VKAs (RR 1.76; 95%CI 1.02–3.1) and no treatment (RR 3.5; 95%CI 1.39–8.7) in terms of complete recanalization –Similar rates of major bleeding between all groups –Similar mortality rates between all groups	–Network Meta-Analysis
Meta-Analysis [61]	11 studies–552 patients–all AC (DOACs: 217, VKAs: 335)	–Higher rate of recanalization in the DOAC group (RR 1.67; 95%CI 1.02–2.74) –Similar rates of major bleeding between the two groups –Similar mortality rates between the two groups	–FU 3–12 months –Only AC groups

AC anticoagulation, *VKA* Vitamin K antagonists, *LMWH* Low-molecular-weight heparin, *OR* odds ratio, *FU* follow-up, *HR* hazard ratio, *OLT* orthotopic liver transplant, *CP* Child–Pugh, *PVT* Portal vein thrombosis, *FDPX* fondaparinux, *WF* warfarin, *DOAC* Direct oral anticoagulant, *RR* risk ratio, *MELD* Model For End-Stage Liver Disease

Table 2 Main characteristics of anticoagulation drug classes and their use in patients with cirrhosis

Drug Class	LMWH	VKAs	DOACs
Method of administration	Subcutaneous (difficult for patients to use for an extended period)	Oral	Oral
Monitoring efficacy	No	INR (difficulty assessing in patients with cirrhosis)	No
Adequate data on safety in patients with cirrhosis	Yes	Yes	No, but rapidly developing
Child–Pugh A	Yes	Yes	First choice
Child–Pugh B	Yes	Yes, but efficacy and safety uncertain due to INR variations	Yes, with caution
Child–Pugh C	First choice, only after careful consideration in patients with a significant need for anticoagulation	No	Pending more data, only after careful consideration in patients with a significant need for anticoagulation

LMWH Low-weight-molecular heparin, *VKA* Vitamin K antagonist, *DOAC* Direct oral anticoagulant, *INR* International normalized ratio

evaluation of the potential positive or negative effects of AC should be undertaken before the decision regarding the initiation or prolongation of AC is made.

Concerning the choice of AC drug class, the first step should be to avoid red flags in terms of special populations. For instance, in recent guidelines, DOACs are not recommended for CP C patients due to the lack of data [63, 67]. In contrast, VKAs are recommended only in CP A patients due to the significant difficulties of setting a target INR and associating it with therapeutic effects [67]. These guidelines assert LMWH as the primary therapeutic option for CP C patients, at least until more data are available for the use of DOACs. Furthermore, the presence and severity of varices in each patient should be considered and treated accordingly when AC needs to be implemented. An additional parameter to be considered is renal function, with hospitalized patients with decompensated cirrhosis experiencing some level of chronic kidney disease (CKD) in a percentage of > 45% in a recent study [68]. Regarding CKD, recent guidelines regarding the management of atrial fibrillation encourage the use of DOACs even in patients with a glomerular filtration rate (GFR) of 15 to 30 mL/min, albeit in a reduced dose [69]. However, it must be stressed that there is a great debate regarding the use of AC in patients on dialysis due to the high incidence of bleeding complications and conflicting data on stroke prevention [70]. All things considered the use of AC in patients with cirrhosis and GFR < 30 should be recommended only in specific situations and after careful consideration of potential benefits and harms. Finally, on paper, there are significant differences between DOACs in terms of hepatic and renal clearance. While guidelines for CKD patients clearly differentiate between DOACs [69], there is no such guidance for patients with liver cirrhosis. Theoretically, dabigatran demonstrates the advantage of minimal hepatic clearance (20%); however, this has not yet translated into clinical benefit. The main characteristics of drug classes and their advantages and disadvantages are summarized in Table 2.

Effect on the Natural History of Liver Cirrhosis

Following the gradual acceptance of AC in patients with cirrhosis, the next frontier is to determine whether anticoagulation can improve the natural history of the disease and improve survival. Many experimental studies have documented the role of AC in improving liver fibrosis or portal hypertension [13, 71–73]. However, the clinical debate emerged after a landmark clinical study by Villa et al. that prospectively assigned 70 patients with CP B and C cirrhosis to receive prophylactic enoxaparin (4000 IU/day) or placebo for 48 weeks [74]. After a follow-up of 144 weeks, patients in the enoxaparin group were statistically less likely to develop PVT, decompensate, or die. Meanwhile, there were only three reported bleeding episodes in this study. While this study provided promising data, its results have not been replicated. Only studies with an already established reason for AC have published results regarding its effect on overall mortality, with many establishing significantly better survival in patients receiving anticoagulation, as previously described [24, 49, 50, 55]. These studies have even prompted the recent Baveno guidelines to endorse the use of AC in patients with CP A and B due to its possible effect on overall survival [63]. However, to directly link these results to the improvement of liver fibrosis or portal hypertension (aside

from the effect of recanalization), there must be more studies investigating the effect of AC in patients with cirrhosis without a specific thrombotic syndrome.

Conclusions

It seems that for most cases, the debate is settled: AC is safe and effective in patients with cirrhosis. However, physicians should carefully determine each patient's characteristics before initiating AC, such as the severity of cirrhosis, presence of varices, renal insufficiency, and suitability of the selected anticoagulant. Furthermore, pending more studies, AC may in future be regarded as a therapeutic regimen for patients with cirrhosis, preventing decompensation and increasing survival. As for the choice of anticoagulation, DOACs appear to be safer and more effective than traditional anticoagulation with every new study published and, with some notable exceptions, are soon, if not already, going to be the drug of choice for patients with cirrhosis.

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Declarations

Conflict of interest The authors have not disclosed any conflict of interests.

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