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Particularities of Noac in Atrial Fibrillation Associated With liver Cirrhosis

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Case Report

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Abstract

Introduction: Patients with liver cirrhosis (LC) have a higher prevalence of atrial fibrillation (AFI) than the general population. If until the beginning of the 21st century, anticoagulant treatment in LC involved the use of low molecular weight heparins and vitamin K antagonists (VKAs) the possible administration of new oral anticoagulants (NOACs) is currently being investigated.

Purpose of the study: The present study investigates the efficacy and safety of NOACs use in patients with LC and AFI, by analyzing the literature.

Methods and materials: We conducted an extensive literature search to identify studies that report AFI anticoagulant therapy in patients with liver cirrhosis. The search was conducted in MEDLINE, Google Scholar, and PubMed and Thompson ISI in order to identify articles in English on this topic. To find relevant up-to-date data on the peculiarities of NOACs in AFI associated with cirrhosis, we used the following as keywords for current research: "atrial fibrillation", "liver cirrhosis", "anticoagulation", "direct-acting anticoagulants". Out of a total of 43 abstracts, only 36 full articles were considered that were directly related to the research topic, such as reviews or meta-analysis, published between 2008 and 2022, over a period of 14 years.

Results: NOACs have superior pharmacological characteristics to VKAs, but have a number of side effects that should be considered when administering to patients with AFI and decompensated LC. To date, there are several trials that have shown that since Dabigatran, Rivaroxaban, Apixaban and Edoxaban are metabolized in both the kidneys and the liver, patients with LC and AFI should be monitored continuously for their liver and kidney function. The use of NOACs is a reasonable alternative to VKAs in patients with LC and AFI, but the severity of liver disease should be considered, as anticoagulation is effective in patients with LC class Child-Pugh A, but is not recommended for those in Child-Pugh C class. In patients with moderate hepatic impairment (Child-Pugh B), NOACs are variably recommended.

Conclusion: More and more data have appeared in recent years that seem to encourage the administration of new oral anticoagulants in patients with decompensated liver cirrhosis and atrial fibrillation as these new coagulants seem to offer a benefit over VKAs.

INTRODUCTION

Atrial fibrillation (AFI) already affects 1–4% of the general population. In 2016, this pathology had an estimated prevalence of>43 million individuals worldwide [1,2]. Furthermore, the AFI is estimated to affect 6-12 million people in the United States by 2050 and 17.9 million in Europe by 2060. The consequences of the AFI are significant for an individual's health and include an increase in the rate of stroke and systemic embolism. if oral anticoagulant therapy is not administered [1]. AFI is often associated with multiple other comorbidities, most often with heart failure, as they are linked by common risk factors such as aging, high blood pressure, diabetes, and structural heart disease [3]. Some studies have shown that patients with liver cirrhosis (LC), especially alcoholic etiology, have both a diastolic dysfunction and a marked decrease in sympathetic activity, with less significant impairment of the vagal component [4]. Also, among patients with LC, the estimated overall prevalence of AFI is approximately 5%, thus being higher than its prevalence in the general population. A variety of common risk factors between AFI and LC may explain this increased prevalence. These factors range from alcohol consumption and metabolic risk factors to increasing the lifespan of individuals. There appears to be an association between worsening the severity of underlying liver disease and newly diagnosed AFI [5]. Until the beginning of the 21st century, anticoagulant treatment in LC involved the use of low molecular weight heparins and VKAs. The possible administration of NOAC is currently being investigated. NOACs, a newer class of anticoagulants, have become the most commonly prescribed oral agents to prevent ischemic stroke in AFI. However, studies for these agents have specifically excluded patients with advanced liver disease due to safety concerns. Retrospective studies and meta-analyses generally support the efficacy and safety of both warfarin and NOACs in patients with LC and AFI, and newer data suggest that NOACs are as effective as warfarin in preventing ischemic stroke. However, data evaluating liver decompensating and mortality with these drugs are limited [6]. The new oral anticoagulants have been shown to have a lower risk of bleeding compared to VKAs. However, most studies supporting the use of anticoagulation have excluded patients with chronic liver disease. In addition, many of the studies that aimed to demonstrate the benefit of anticoagulant treatment in patients with LC have provided conflicting results [7]. The aim of this study is to investigate the efficacy and safety of NOACs in patients with liver cirrhosis and atrial fibrillation by reviewing the literature.

MATERIALS AND METHODS

We conducted an extensive literature search to identify studies that report AFI anticoagulant therapy in patients with liver cirrhosis. The search was conducted in MEDLINE, Google Scholar, and PubMed and Thompson ISI in order to identify articles in English on this topic. To find relevant up-to-date data on the peculiarities of NOAC in AFI associated with cirrhosis, we used the following as keywords for current research: "atrial fibrillation", "liver cirrhosis", "anticoagulation", "direct-acting anticoagulants". Out of a total of 43 abstracts, only 36 full articles were considered that were directly related to the research topic, such as reviews or meta-analysis, published from 2008 to April 2022, on a period of 14 years. Thus, the premises for a narrative review were set.

RESULTS AND DISCUSSION

Coagulopathy associated with liver cirrhosis

The coagulation cascade consists of the intrinsic pathway (activation by FXII contact with the sub endothelial connective tissue in the affected tissue) and the extrinsic pathway (triggered rapidly due to tissue trauma or vascular injury, when the tissue factor activates and forms a complex with FVII in the presence of calcium (Ca^{++}). Each of these two ways is involved in the process of activation of enzymes and their cofactors, that lead to a following cascade reaction to form fubrin polymers, thus activating the development of a trombus [8].

Being one of the most important trigger of primary (platelet-mediated) and secondary (coagulation-mediated) haemostasis, thrombin could also have a great role in clot development through the polymerization of fibrin, activation of platelet receptor and the starting up of factors V, VIII, XI and XIII. LC is usually characterized by damage to the liver parenchyma, resulting in fibrotic changes and regenerative nodules that lead to both metabolic disorders and coagulopathy as the liver plays a central role in all four phases of the coagulation process (initiation and formation of platelet plug, the propagation of the coagulation process by the coagulation cascade, the end of coagulation by antithrombotic mechanisms and the removal of clots by fibrinolysis), as it synthesizes most of the coagulation factors and proteins involved in fibrinolysis, as well as thrombo protein, which is responsible for the production of platelets in megakaryocytes [9]. Most pro coagulant factors in the coagulation cascade, such as fibrinogen and factors II, V, X, VII, VIII, IX, XI, XII, are synthesized in the liver. Therefore, in LC, the serum level of pro coagulant factors decreases in proportion to the degree of hepatic impairment. In particular, FV and FVII have the lowest values in patients with hepatic impairment. Patients with liver disease may have vitamin K deficiency due to poor diet or mal absorption caused by decreased bile production or biliary obstruction. However, for example FVII, being synthesized by endothelial cells, not only in the liver, may have normal or elevated levels in cirrhotic patients due to continuous production by endothelial cells despite decreased liver production. Patients with compensated LC have a normal coagulation balance, but under decompensating conditions, due to a significant reduction in the levels of pro- and anticoagulant proteins produced in the liver, the capacity of the coagulation system is affected, including the coagulation cascade, and an unstable balance between thrombosis and bleeding. Many pathological processes associated with LC, such as portal hypertension and endothelial dysfunction, as well as comorbid conditions, can also alter the coagulation process [10]. Thus, either pro-haemorrhagic conditions may be predominate, namely: (a) low plasma levels of synthesized liver coagulation factors [fibrinogen, factor (F) II, FV, FVII, FIX, FX, FXI and FXII], thrombocytopenia; and

increased fibrinolysis due to elevated tissue plasminogen activator levels, decreased plasma inhibitor levels, and thrombin-activated fibrinolysis inhibitor, or predominant pro-thrombotic conditions, including: a decrease in anticoagulants synthesized by the liver : protein C, protein S and ant thrombin (AT),an increase in endothelium-derived pro-coagulant FVIII an increase in platelet aggregation due to increased endothelium-derived von Willebrand factor (vWF),and reduced hepatic plasminogen synthesis [11]. When patients with LC combine AFI and heart failure, anticoagulant treatment is a real challenge, but management must follow the integrated ABC pathway: A: Anticoagulation/Avoidance of stroke, with NOAC/AVK administration; B: more effective control of symptoms; with Betablocant/Digoxin administration; and C: cardiovascular and comorbidity optimization [12]. Potential candidates for the use of oral anticoagulants in patients with LC and AFI should be selected on the basis of traditional risk stratification tools, such as LCA2DS2-VASc and HAS-BLED scores. Also, as these patients have severe liver damage, it is necessary to investigate liver function (total bilirubin, serum albumin) and to look for ascites and encephalopathy to determine the Child-Pugh class. However, before initiating NOACs, it is recommended to identify the coagulation profile as well as to monitor their values during treatment. As a result, patients with LC and AFI may benefit from the advantages of the new oral anticoagulants; however, the medical literature includes limited data on the efficacy and safety of new oral anticoagulants in this particular medical condition [13].

Classification of NOAC mechanisms of action

Anticoagulants are the basic medicines for the prevention and treatment of thrombosis, stroke and systemic embolism in patients with atrial fibrillation (AF) or flutter. They can also be used to prevent and treat venous thromboembolism (VTE) [14]. Anticoagulants can inhibit thrombogenesis by altering the various pathways in the coagulation cascade or by directly selecting thrombin, diminishing thrombin formation. Indirect inhibitors (heparins), however, select and bind to natural plasma cofactors, such as AT, catalysing this reaction with coagulation enzymes [8]. Vitamin K antagonists, such as warfarin, which inhibits vitamin K-dependent coagulation factors, were formally approved for human use by the U.S. Food and Drug Administration (FDA) in 1954. For 50 years, warfarin was the only oral anticoagulant used in LC. Since 2009, new oral anticoagulants have been introduced in medical practice, comprised of direct-acting thrombin inhibitors and direct-acting factor Xa inhibitors, as alternatives to oral coagulants, to be used in the prevention of thrombosis [15].

NOACs are fast-acting, target-specific anticoagulants that act through two different mechanisms. Based on the mechanism of action, they are grouped into two classes: direct thrombin inhibitors and direct factor Xa inhibitors [16-18]. They inhibit both free and bound serine activated proteases, unlike heparin which can produce only the inhibitionof free proteases. Direct inhibitors of Factor Xa (Apixaban, Rivaroxaban, Edoxaban) bind directly to the catalytic site of Factor Xa and inhibit both free Factor Xa and prothrombinase binding [18].

Characteristics of NOACs

Benefits

The thrombin inhibitor (Dabigatran), designed to occupy and inactivate the proteolytic serine patch of thrombin, prevents thrombin from activating fibrinogen to produce fibrin [19]. Thus preventing the cleavage of prothrombin and its changing into thrombin NOACs have superior pharmacological characteristics to VKAs because they have a short half-life (several hours) and have therapeutic window wide. NOACs have few drug-drug interactions (unlike vitamin K antagonists) and do not require parenteral administration (unlike heparin) [15,16,20].

NOACs side effects

NOACs accumulate in patients with renal impairment, and can cause even fatal bleeding, mainly because no widely available monitoring tests to measure its anticoagulant activity have been identified and no specific antidotes are currently available to neutralize it in case of overdose and/or severe bleeding. The actual concentration of the drug may be required for specific patients, such as those with impaired renal function, before surgery, bleeding or thrombotic episodes and suspected overdoses and in order to control adherence to therapy [19]. NOACs have a number of side effects that should be considered when administering to patients with AFI, which may have other comorbidities. Rivaroxaban is associated with a low incidence of gastrointestinal bleeding but is lower than with warfarin [21]. Dabigatran is associated with an increased incidence of non-bleeding upper gastrointestinal symptoms, such as dyspepsia and heartburn, compared with warfarin [22,23]. But these adverse GI events are rarely an absolute contraindication to the use of this NOAC. Apixaban has a lower risk of gastrointestinal bleeding compared to other NOACs [24].

Absolute contraindications to direct oral anticoagulants

There are some absolute contraindications to NOACs. In case of severe renal impairment (Creatinine Clearance <30 mL/min) and severe hepatic impairment (Child Pugh C liver cirrhosis) the administration of Dabigatran, Apixaban and Rivaroxaban is excluded because the lack of renal/hepatic clearance accumulates in the body and there is a risk major bleeding compared to warfarin.

NOACs are also contraindicated if the patient has current active bleeding or has been diagnosed with coagulopathy. NOACs should not be used to identify a previous bleeding or documented anaphylaxis with a direct oral anticoagulant as it would endanger the patient's life during treatment with these anticoagulants [24,25].

Limitations on the use of NOACs

Although NOACs have brought more advantages over VKAs, there are currently some limitations in their use. First, more clinical evidence is needed to ensure the safe and effective use of these drugs. Second, the costs of purchasing medicines are higher for NOACs than for VKAs, and this is the main reason why the healthcare system prefers warfarin over NOACs [16]. Another disadvantage of using NOACs is that there are no specific antidotes for these drugs, but there is ongoing research. Although inactivated or activated 4-factor pro thrombin complex concentrate (4F-PCC) may be effective in reversing the anticoagulant effects of NOACs, clinical data in patients with severe bleeding limited.

Recent data on anticoagulant treatment with NOACs in patients with atrial fibrillation and liver cirrhosis:

Oral anticoagulation has proven to be an effective therapy not only for the primary prevention of stroke, but it also provides a benefit in terms of mortality in patients with AFI and LC [7]. The ideal anticoagulant in LC should have as low a protein binding as possible (hypoalbuminemia causes a higher concentration of the drug and a higher effect in case of a high binding rate), have an antidote (to be able to be antagonized in case of bleeding), have a low risk of bleeding and do not interfere with liver function [26]. NOACs have a comparable effectiveness to VKA, with a better safety profile. In general, novel oral anticoagulants (NOACs) are associated with a lower incidence of bleeding events. In subgroup analyses, Dabigatran and Rivaroxaban were associated with a lower risk for all major bleeding events compared to warfarin [26]. Because the metabolism and elimination of NOACs involve the liver and kidney, their pharmacokinetics may be influenced by liver disease to various degrees, indicating caution in their use in patients with impaired liver function. In addition, renal clearance of NOACs may be at risk when liver disease associates either hepatorenal syndrome or other kidney disease [11].

It becomes of importance for clinicians to take into consideration that European international guidelines approve the use of Apixaban and Rivaroxaban in patients with creatinine clearance (CrCl) up to 15 ml/min, but contraindicate their administration to LC Child Pugh C, if there is a current active angina or coagulopathy, in the event of a life-threatening previous haemorrhage during treatment with NOACs, and if the patient has a previous documented anaphylaxis with a direct oral anticoagulant [26]. As Dabigatran, Rivaroxaban, Apixaban and Edoxaban are metabolised by the liver and excreted both by the liver and by the kidneys, in patients with LC and AFI it is necessary to monitor liver function by monitoring serum Alanine Transaminase (ALT) values, and Aspartate Transaminase (AST), total bilirubin, platelet count, and haemoglobin level. It was identified that ALT or AST> 1.5-2 times the upper limit of normal, total bilirubin ≥1.5 × upper limit, platelet count <100,000/mm^3, and decreased haemoglobin level <9-10 g/dL represents exclusion criteria for NOACs administration to patients with impaired liver function [24]. Also, if a chronic kidney disease is associated, it is important to determine the clearance of creatinine because, at values <30 ml/min, NOACs are no longer administered due to the possibility of accumulation of these drugs in the body and due to the increased risk of bleeding. Lee et al. [26]. Demonstrated that the use of VKAs increased the risk of bleeding in advanced LC (Child-Pugh B and C), but not in early LC (Child-Pugh A). For bleeding complications, most patients presented with gastrointestinal bleeding and central nervous system bleeding. These authors demonstrated comparable rates of stroke among patients with AFI and LC who were treated with and without anticoagulation. Chokesuwattanasku et al. Study suggests that anticoagulant treatment in cirrhotic patients with AFI may be beneficial and concludes that, rather than administering systemic anticoagulation in cirrhotic patients due to the suspicion that bleeding diathesis may occur, it would be much better to prescribe this kind of therapy to these patients, under close clinical and laboratory supervision, in order to detect and manage in a timely manner any bleeding complications. Randomized clinical trials on the administration of NOACs in AFI have excluded patients with decompensated LC due to the high risk of bleeding, especially intracranial, due to their excessive accumulation in the body. According to the study by Elhosseiny et al. (2019) on two groups of patients with LC and treated, one with classic anticoagulants and the other with NOACs, both groups presented haemorrhagic events, but the haemorrhagic episodes were less significant in the group treated with NOACs. A recent study conducted by researchers in Taiwan (2018), patients with AFI and LC were divided into 3 groups as follows: with no treatment administrated, antiplatelet therapy and warfarin therapy only. The use of warfarin was associated with a lower risk of ischemic stroke and a net positive clinical outcome in comparison to the untreated group. Therefore, warfarin may be a desirable anticoagulant choice for these patients. However, the recommended limit value of INR required still further investigation [27]. On the other hand, other study in Taiwan (2018) on patients with LC indicated that NOAC therapy was associated with a significantly lower risk of death compared to warfarin therapy, but no difference was found in the development of stroke or systemic embolism, major bleeding, or gastrointestinal bleeding [28]. Serper et al. [6] analysed 15,767 patients with existing LC and newly onset AFI, from which patients with AFI or a history of valve disease previously LC or patients diagnosed before the onset of NOACs were excluded. The remaining patients were divided into three groups as follows: the first group received warfarin, the second group received NOACs, and the third group did not receive anticoagulation for 90 days after diagnosis of AFI.

Both warfarin therapy, although theoretically less appropriate for patients with LC, given its potential to further decrease vitamin K-dependent anticoagulant factors, and NOACs have been associated with a reduced incidence of general mortality, compared with the absence of anticoagulation, characterized by high values of mortality rate. The mechanism involved appears to be both a reduction in macro vascular thrombosis and a reduction in micro thrombosis that occurs under LC conditions, characterized by local reduction in S protein expression in hepatocytes and sinusoidal endothelium which thus becomes dysfunctional and can lead to micro thrombosis in the acinar microcirculation. The same authors found a low risk of stroke with both NOACs and warfarin, compared to when no anticoagulants were given. At the same time, NOACs are associated with a lower risk of bleeding compared to warfarin. At the same time, patients who did not receive any anticoagulants had lower rates of bleeding compared to warfarin and similar rates of bleeding compared to those on NOACs [6]. Violi et al. (2020) mentioned in a meta-analysis the effectiveness of NOACs and VKAs in patients who presented decompensated LC and AFI. These authors found that, compared to the use of

VKAs, NOACs could play an important role in diminishing the major bleeding risk, intracranial haemorrhage and gastrointestinal bleeding, but the analysis of the efficacy of the two types of anticoagulation didn't show great difference in comparison of the groups [29].

Practical recommendations:

The studies conducted so far have led to some useful conclusions for clinicians who need to treat the patient with LC and AFI. Both the US FDA and the European Medicines Agency (EMA) have made a number of recommendations regarding the administration of NOACS to such patients, depending on the severity of the liver disease. Thus, Warfarin can be used in the case of all patients with LC, regardless of the Child-Pugh class, with constant monitoring of INR. Chronic kidney disease and advanced chronic liver disease in patients with AFI could produce an increased risk of both bleeding and thrombosis. Furthermore, impaired renal and hepatic function may be a factor of complication in the metabolism and elimination of NOACs, which could produce the accumulation of these drugs in the body and an increased risk of bleeding [12]. Based on the limited data from studies to date, NOACs may be an acceptable choice in light of the comparable efficacy of warfarin and possibly better safety compared to it. On the other hand, based on the pharmacokinetic and pharmacodynamic evaluation of the four NOACs (Apixaban, Dabigatran, Edoxaban and Rivaroxaban), patients with LC-Class Child-Pugh A can be treated with any of the four NOACs, without adjusting the dose of the drug. Direct oral thrombin inhibitors (e.g., Dabigatran) and direct oral factor Xa inhibitors (e.g., Rivaroxaban, Apixaban) have recently emerged as an alternative to VKAs for the impediment of stroke development in AFI. NOACs acts rapidly and have a foreseeable and stabilized dose-related anticoagulant effect, noticing a few applicable drug interactions. The novel oral anticoagulants are used in fixed doses without the need to regularly monitor the intensity of the anticoagulation. However, there are certain distinct pharmacological properties for each of these drugs that could influence optimal clinical use [30,31]. However, the coexistence of AFI in patients with liver cirrhosis not only increases the risk of ICH, but also increases the risk of ischemic stroke.

Therefore, the use of NOACs in patients with AFI and liver cirrhosis remains a challenge. Some randomized clinical trials with NOAC for the prevention of stroke in atrial fibrillation have particularly ruled out patients with liver cirrhosis due to a specific degree of hepatic metabolism present in all NOACs [32]. The traditional risk scores, such as LCA2DS2-VASc and HAS-BLED scores, play an important role in the selection of potential candidates who could be administrated oral anticoagulation in AFI. In all patients that could be at risk for liver disease, the following are required: investigation of liver function tests, determination of Child-Pugh class, platelet count, coagulation profile before initiating NOAC, their values should be monitored during treatment. Severe thrombocytopenia (platelet count <50,000 to <70,000/ml) should indicate avoidance of the anticoagulant therapy, according to the patient's risk for thrombosis [33]. In patients with moderate hepatic impairment (Child-Pugh B), due to limited data and side effects of bleeding, NOACs are variably recommended. Thus caution is advised when using Apixaban and Dabigatran andthere is indicated careful monitoring of anticoagulation in the presence of portal hypertension, esophageal varices, hypertensive gastropathy, thrombocytopenia, coagulopathy, high initial risk of bleeding, impaired drug metabolism and impaired renal function. However, between the two, current literature indicates that Apixaban would be more appropriate for decompensated liver cirrhosis in Child-Pugh A and B classes. Due to limited data and side effects of bleeding in patients with moderate hepatic impairment (Child-Pugh B), caution is advised when using Apixaban. Edoxaban and Rivaroxaban in such patients are not recommended [33]. Patients with severe hepatic impairment (LC-Child-Pugh C class) is not recommended for any of the four NOACs, because in this particular situation the risk of bleeding defeats the benefits that the anticoagulant therapy might offer [32]. Chronic kidney disease and advanced chronic liver disease in patients with AFI trigger an increased risk of bleeding and thrombosis. Furthermore, impaired renal and hepatic function may complicate the metabolism and elimination of NOACs, which may lead to the accumulation of these drugs in the body and increase the risk of bleeding. Based on the limited data obtained from studies to date, NOACs could be a reasonable choice in the context of a better efficacy and a possibly better safety compared to warfarin [34].

CONCLUSION

It could be said that in cirrhosis there exists a pro coagulant state and these patients are thus prone to thrombosis, despite their altered hemostasis. In this case, they may benefit from the new oral anticoagulants; however, the specialty literature appears to still need gathering more data on how efficient or safe NOACs are in this particular patient population [33]. Due to the fact that NOACs are predominantly metabolized in the kidneys, their use in patients with liver cirrhosis, heart failure and AFI is a good alternative for anticoagulant treatment (26). In recent years, more and more data have appeared that seem to encourage the administration of Direct-acting Oral Anticoagulants in patients with decompensated cirrhosis and atrial fibrillation as as a primary prevention of stroke, as these new coagulants appear to provide a benefit over VKAs [11].

The ideal anticoagulant to be administered to patients with AFIand cirrhosis should: havea protein binding as low as possible (hypoalbuminemia causes a higher concentration of the drug and a higher effect in case of a high binding rate), have a hepatic metabolism as low as possible and have, as well, a risk of bleeding as low as possible [26]. Both Dabigatran and Rivaroxaban are associated with a low incidence of gastrointestinal bleeding, but compared to warfarin, this incidence is increased. Dabigatran is associated with an increased incidence of non-bleeding upper gastrointestinal symptoms, such as dyspepsia and heartburn. It has as side effects gastrointestinal symptoms unrelated to bleeding, has predominantly renal elimination, because 80% is eliminated this way and only 20% is metabolized and eliminated in the liver. But these adverse GI events are rarely an absolute contraindication to the use of NOAC. Apixaban has a lower risk of gastrointestinal bleeding compared to other NOACs [33]. In clinical practice, as shown in the study; NOACs can be used in patients with AFI in Child-Pugh A and Child-Pugh B only if the dose

is adjusted according to the needs of the patient [35]. In the case of patients with liver cirrhosis and atrial fibrillation, two aspects can be considered: If given anticoagulant therapy (with regular INR check), the patient may be at risk of bleeding If not given anticoagulant therapy, he may be at risk for a pulmonary embolism. In this case, the anticoagulation profile should be considered. If the coagulation parameters (INR, platelet count) are within normal limits, then there is a possibility of anticoagulant therapy, including NOACs [36]. The European Society of Cardiology (ESC) recommends an inter-pluri-disciplinary approach when it comes to the prescription and follow-up of anticoagulant therapy in cirrhotic patients that should be carried out in specialist centers [12].

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