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### *Recent advances*

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# Atrial fibrillation in patients with liver disease: Recent advances

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## ABSTRACT

Atrial fibrillation is associated with significant morbidity and mortality, and its incidence is increasing globally. The primary complication of atrial fibrillation is ischemic stroke, whose risk may be reduced with oral anticoagulant agents, i.e., either vitamin K antagonists or direct oral anticoagulants. Patients with atrial fibrillation often have concomitant hepatic impairment, particularly because of increasing rates of non-alcoholic liver disease. However, anticoagulation in patients with liver disease is challenging due to the pathophysiological changes of the coagulation cascade and, as a result, an increased risk of major bleeding in such individuals. Furthermore, monitoring of the degree of anticoagulation is complicated in patients with liver disease due to issues such as spontaneous international normalized ratio (INR) elevation, changes in hepatic drug elimination, and thrombocytopenia. We review the current evidence on atrial fibrillation and anticoagulation in patients with liver disease. We suggest having a strong focus on risk factor management and argue that the risk of ischemic stroke often outweighs the risk of hemorrhagic events in this setting.

**Key words:** anticoagulants, atrial fibrillation, liver diseases, liver failure

## INTRODUCTION

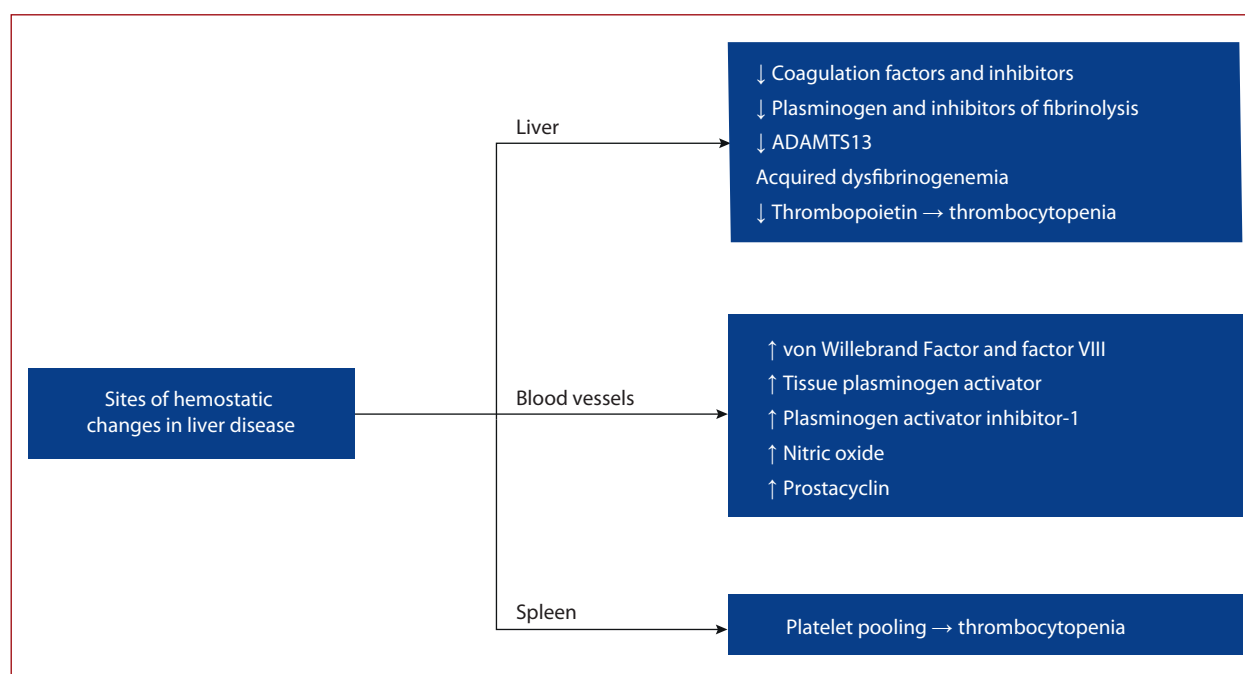
Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated prevalence of 2%–4% in adults [1]. Several modifiable and non-modifiable risk factors for AF have been uncovered, including age, sex, obesity, and a range of cardiac and non-cardiac conditions [2–7]. Early intervention with modifiable risk factor control may decrease the lifetime risk of AF and, in turn, reduce morbidity and mortality as well as the economic and societal burden [1]. Most of the excess morbidity and mortality related to AF is due to an increased risk of ischemic stroke, whose management involves oral anticoagulant therapy (OAC) [1]. Conditions that predispose to AF, such as alcohol intake and metabolic dysfunction, are also associated with increased risk of liver disease [3, 8–16]. Individuals with concomitant hepatic impairment and AF pose unique management challenges due to adverse changes in the coagulation cascade, platelet dysfunction,

increased risk of hemorrhagic stroke, and the presence of esophageal varices [17–19].

## RISK OF ATRIAL FIBRILLATION IN PATIENTS WITH ALCOHOLIC AND NON-ALCOHOLIC LIVER DISEASE

Liver cirrhosis is the end stage of most chronic liver diseases [20] and has multiple etiologies, including hepatitis C and B virus, and alcoholic and non-alcoholic liver disease. Unfavorable trends in both alcoholic and non-alcoholic liver disease have been observed [20, 21]. Alcohol consumption is associated with increased risk of incident AF, even among light drinkers, and relapse arrhythmia induced by alcohol binges is well described (holiday heart syndrome) [3, 22]. Finally, alcohol is a well-known risk factor for liver disease [14].

Metabolic dysfunction, i.e., diabetes, obesity, or hypertension, is also related to increased risks of both AF and non-alcoholic



**Figure 1.** Overview of hemostatic changes in liver disease related to anatomical locations. The hemostatic changes in liver disease can be related to four principal mechanisms: (1) reduced hepatic synthetic capacity resulting in thrombocytopenia and low levels of coagulation factors and inhibitors; (2) systemic intravascular coagulation with depletion of platelets and hemostatic factors increased fibrinolysis due to reduced hepatic capacity of metabolism of, for example, tissue plasminogen activator; (3) continuous systemic low-grade activation of the endothelium with release of hemostatic proteins, e.g., von Willebrand Factor; (4) cirrhosis results in splenomegaly, which allows for platelet pooling in the enlarged spleen

fatty liver disease (NAFLD) [15, 16]. The incidence of NAFLD is increasing, and it is now the leading cause of chronic liver disease [23]. A recent meta-analysis suggested a two-fold increase in the risk of AF in NAFLD patients [24]. NAFLD is considered the hepatic manifestation of metabolic syndrome, and while it is an umbrella term for a spectrum of liver disorders, an international consensus recently proposed renaming the disease as metabolic dysfunction-associated fatty liver disease to reflect the pathogenesis more appropriately [25, 26].

The reported prevalence of AF in individuals with liver cirrhosis varies globally from 0.2% to 20.2% [8–13]. Lower incidence rates of AF in liver cirrhosis patients have been reported from Middle Eastern countries, where the most common cause of cirrhosis is viral hepatitis [10, 27]. On the other hand, a high frequency of AF in liver cirrhosis patients is reported in Germany where the majority of cirrhosis is related to alcohol [8, 28]. Nevertheless, it remains unclear whether the presence of alcoholic liver disease or NAFLD are independent risk factors for AF or if they simply reflect underlying risk factors, e.g., alcohol consumption or metabolic dysfunction [29]. Nonetheless, the findings underscore the importance of risk factor control.

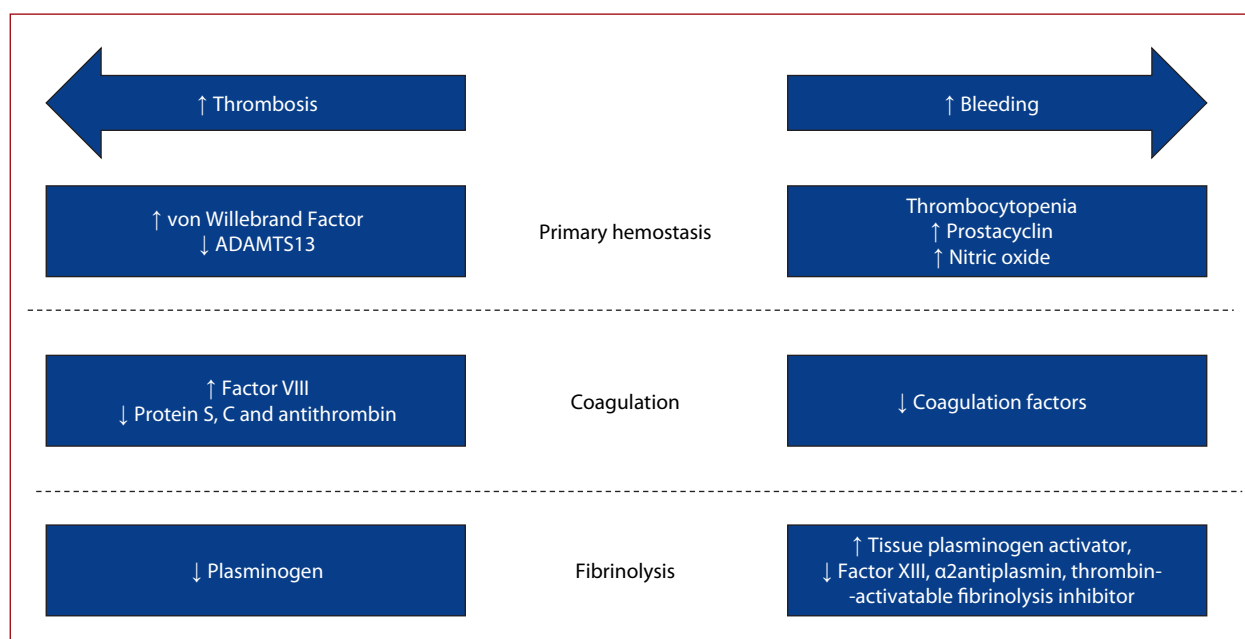
Several conditions known to be associated with AF are also associated with systemic inflammation. The inflammatory response, mediated through cytokines and extracellular remodeling, may lead to electrical and structural remodeling, contributing to the pathophysiology of AF [30, 31]. The systemic inflammation and autonomic dysfunction

present in alcoholic and non-alcoholic liver disease are some of the reasons why liver disease may be considered an independent risk factor for new-onset AF [11]. Indeed, it has been suggested that greater severity of liver disease increases the risk of new-onset AF [24]. This is supported by data from the Framingham Heart Study showing that elevated levels of serum transaminases were independently associated with new-onset AF, even when adjusted for moderate-to-severe alcohol intake [32].

## HEMOSTATIC CONSEQUENCES OF HEPATIC IMPAIRMENT

Under normal physiological circumstances, the liver plays a fundamental role in the hemostatic system by synthesizing most of the pro- and anticoagulation factors and by producing thrombopoietin which induces platelet production [33].

A comprehensive report of the impact of liver disease on the hemostatic system is beyond the scope of this review and has been extensively discussed elsewhere [34–36]. In brief, the impact of an adversely altered hepatic function on the coagulation pathway is systemic, complex, and bi-directional. It is capable of inducing both hyper- and hypocoagulability due to reduced plasma concentration of coagulation factors, altered endothelial function, increased fibrinolysis, thrombocytopenia, etc. [37] (Figure 1). Nearly all the pro- and anticoagulant factors are derived from the liver, and the most common means to monitor coagulopathy is activated partial thromboplastin time,



**Figure 2.** Hemostatic changes caused by liver disease and their pro- and antihemostatic impact

**Table 1.** The HAS-BLED score, a tool to estimate bleeding risk in patients with atrial fibrillation receiving warfarin and its' relation to risk of bleeding episodes per 100 patient-years

HAS-BLED score		Points
H	Hypertension, i.e., uncontrolled systolic blood pressure $\geq 160$ mm Hg	+1
A	Abnormal liver function: chronic hepatic impairment (e.g., cirrhosis) or biochemical evidence of significant hepatic impairment (i.e., bilirubin $\geq 2$ times upper normal limit AND aspartate transaminase, alanine transaminase, or alkaline phosphatase $\geq 3$ times upper normal limit)	+1
	Abnormal renal function: chronic dialysis, renal transplantation, or serum creatinine $\geq 200$ $\mu\text{mol/l}$	+1
S	History of stroke	+1
B	Bleeding tendency or predisposition	+1
L	Labile INR and/or TTI $< 60\%$	+1
E	Age $\geq 65$ years	+1
D	Drugs, i.e., concomitant treatment with aspirin or NSAID	+1
	Excess alcohol intake	+1
<b>Maximal score</b>		<b>9</b>
Bleeds per 100 patient-years [97, 98]		Total score
1.88		2
3.74		3
8.7		4
Insufficient data		$\geq 5$

Abbreviations: INR, international normalized ratio; TTI, time in therapeutic interval; NSAID, nonsteroidal anti-inflammatory drugs

prothrombin time, and internationalized normalized ratio (INR) — the ratio of the patient's prothrombin time relative to a normative prothrombin time value [38]. INR is also used to monitor the degree of anticoagulation for patients on vitamin K antagonists (VKA) and is frequently spontaneously elevated in patients with liver disease — something that is often interpreted as an indication of hypocoagulability. Conversely, it has been proposed that liver disease mediates a mixed coagulopathy, paradoxically predisposing to both thromboembolism and bleeding episodes [39–43] although these imbalances might induce an “auto-anticoagulated” state, i.e., protected from thrombotic events but prone to hemorrhagic complications, in compensated

liver cirrhosis [44, 45] (Figure 2). Nevertheless, the current consensus is that liver disease seems to increase the risk of thrombotic events, and the focus should be on preventing complications of such events [37].

Impaired liver function is included in the HAS-BLED score (Table 1) used in daily practice to estimate bleeding risk [46–49]. While the relation between liver disease and gastrointestinal bleeding is well understood, intracranial bleeding events in patients with cirrhosis are less well delineated. Two Danish, retrospective, registry-based studies suggested a significantly increased risk of intracranial hemorrhage (ICH) in persons with liver cirrhosis or non-cirrhotic alcoholic liver disease [50, 51]. This was

corroborated by a large US-based analysis of 56 220 individuals with liver disease that uncovered an independent relationship between liver disease and increased risk of ICH when compared with individuals who did not have hepatic impairment [17]. One of the above-mentioned Danish registry-based studies by Riahi and colleagues compared AF patients with and without liver cirrhosis. In addition to the data on intracranial bleeding risk, they found that the risk of ischemic stroke significantly increased in patients with liver cirrhosis compared with those without (incidence rate 29.7 vs. 21.6; hazard ratio, 1.3; 95 % confidence interval [CI], 1.1–1.6) [51] underscoring the complex effect of liver disease on the coagulation system.

### OUTCOMES IN PATIENTS WITH ATRIAL FIBRILLATION AND LIVER DISEASE

Frequent hospitalizations are common in patients with decompensated cirrhosis, and mortality rates are high [52]. A recent retrospective study from the US investigated clinical outcomes in 309 959 patients with end-stage liver disease of whom 32 858 had concomitant AF [13]. The coexistence of these conditions was related to longer length of hospital stay, increased cost of hospitalization, and worse in-hospital survival compared with end-stage liver disease without AF. The findings are in line with other recent studies [53–55]. The prevalence of congestive heart failure was 31.2% in the AF cohort, which is relatively high given that the prevalence of heart failure in AF patients is generally said to range from 15%–27% [56–60]. In contrast, a Korean study of a non-end-stage liver cirrhosis population reported a significant association between liver cirrhosis and incident AF compared with individuals without liver cirrhosis but did not find an association between AF and mortality in patients with cirrhosis [61]. However, the inclusion criteria were alcoholic and viral cirrhosis and while the distribution of causes of cirrhosis is not mentioned in the article, etiology might be an important factor when evaluating the coexistence and impact of AF and hepatic impairment, as mentioned earlier. Although the causal link between heart failure and AF is still an area of active research, it has been proposed that rather than considering AF an independent risk factor of mortality, it should be viewed as a predictor of adverse outcomes [62]. Assuming that this hypothesis is correct, it is possible that AF could be considered a marker of advanced end-stage liver disease rather than an independent risk factor for mortality.

### GENERAL MANAGEMENT OF ATRIAL FIBRILLATION

Atrial fibrillation is associated with a 5-fold increased risk of ischemic stroke compared with sinus rhythm, and high stroke risk in this setting is traditionally managed with OAC [1]. OACs for AF consist of either a VKA or a direct oral anticoagulant (DOAC). The therapeutic effect of VKAs

is monitored via INR, while DOACs do not require routine monitoring of the anticoagulant effect.

Stroke risk for an AF patient depends on several risk factors and markers [63–68]. In clinical practice, the yearly stroke risk in patients with non-valvular AF is estimated using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [69]. A CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in men and 2 in women should prompt consideration of OACs while OACs are clearly recommended in men and women with a score of  $\geq 2$  and  $\geq 3$ , respectively [70]. The most common concern when prescribing OACs is an increased risk of bleeding, and the HAS-BLED score is a commonly used clinical tool to assess bleeding risk (Table 1). A score  $\geq 3$  is considered high [71]. There is a considerable overlap between stroke and bleeding risk factors [72] and while a high HAS-BLED score indicates the need for regular clinical review of treatment, it is not a reason to withhold OACs *per se*.

### CONSIDERATIONS OF ANTICOAGULANT THERAPY IN PATIENTS WITH DISRUPTED HEMOSTASIS

VKAs have traditionally been the drug of choice in patients with liver disease despite several potential issues, i.e., the elimination pathway through the liver's cytochrome P450 enzyme system, lack of a well-defined INR target for this patient group, and its propensity to significantly interact with other drugs, food, and alcohol [37]. Considering DOACs, all of them undergo some degree of hepatic metabolism, and the European Medicines Agency has issued specific recommendations for each drug's use in patients with liver disease (Table 2). For this reason, DOACs represent a dual problem in patients with liver disease due to the changes in the coagulation cascade as well as the possible effect of liver injury on drug metabolism. In addition, patients with hepatic impairment have been either under-represented in, or simply excluded from, randomized clinical trials investigating OACs [73–77]. As such, most of the evidence on OAC use in patients with concurrent AF and liver disease is of a retrospective observational nature. Table 3 summarizes the main exclusion criteria related to hepatic impairment of the recent phase III randomized clinical trials investigating OACs for stroke prevention in AF patients.

### OBSERVATIONAL EVIDENCE ON ORAL ANTICOAGULANT TREATMENT IN PATIENTS WITH HEPATIC IMPAIRMENT

A large retrospective Taiwanese study demonstrated a net clinical benefit associated with OACs in liver cirrhosis patients [78]. The investigators included 289 559 patients with AF of whom 10 336 had concomitant liver cirrhosis. Overall, AF patients with liver cirrhosis had higher rates of both ICH and ischemic stroke compared with controls, and warfarin treatment significantly reduced the risk of ischemic stroke, with no concomitant increase in ICH. Notably, despite

**Table 2.** Overview of direct oral anticoagulant (DOAC) drugs, mechanism of action, elimination, and clinical considerations in patients with liver disease

Drug	Mechanism of action	Degree of hepatic elimination [37]	EMA recommendation	Child-Pugh class
Apixaban	Factor Xa inhibitor	75%	Testing of liver function prior to initiation of therapy. Not recommended in patients with liver-related coagulopathy and/or clinically relevant, increased bleeding risk [90]	A–B
Rivaroxaban	Factor Xa inhibitor	65%	Not recommended in moderate or severe hepatic impairment or liver-associated coagulopathies [87]	A
Edoxaban	Factor Xa inhibitor	50%	Assumed safe in patients with mild-moderate hepatic impairment. Not recommended in case of severe liver disease [89]	A–B
Dabigatran	Thrombin inhibitor	20%	Discourages use in patients with ALAT $\geq 2$ times upper normal limit or presence of liver disease with expected impact on survival [88]	A–B

Abbreviations: EMA, European Medicines Agency; ALAT, alanine aminotransferase

**Table 3.** Overview of liver-related exclusion criteria in large, randomized studies in patients with atrial fibrillation

Study	Exclusion criteria related to hepatic impairment
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) [73]	Known significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis) or ALT $> 3$ times the upper normal limit
Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) [74]	ALT or AST $> 2$ times upper normal limit or total bilirubin $\geq 1.5$ times upper normal limit
Edoxaban versus Warfarin in Patients with Atrial Fibrillation (ENGAGE AF-TIMI 48) [75]	Active liver disease or persistent (confirmed by repeat assessments $\geq 1$ week apart) elevations of ALT/AST $\geq 2$ times upper normal limit or bilirubin $\geq 1.5$ times upper normal limit. Known positive hepatitis B antigen or Hepatitis C antibody prior to randomization
Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RE-LY) [76]	Active liver disease, e.g.: persistent ALT/AST/alk phos $> 2$ times the upper limit, active hepatitis C, B, or A etc.
Apixaban in Patients with Atrial Fibrillation (AVERROES) [77]	ALT/AST $> 2$ times the upper limit of normal range or bilirubin $> 1.5$ times the upper limit of normal range

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; alk phos, alkaline phosphatase

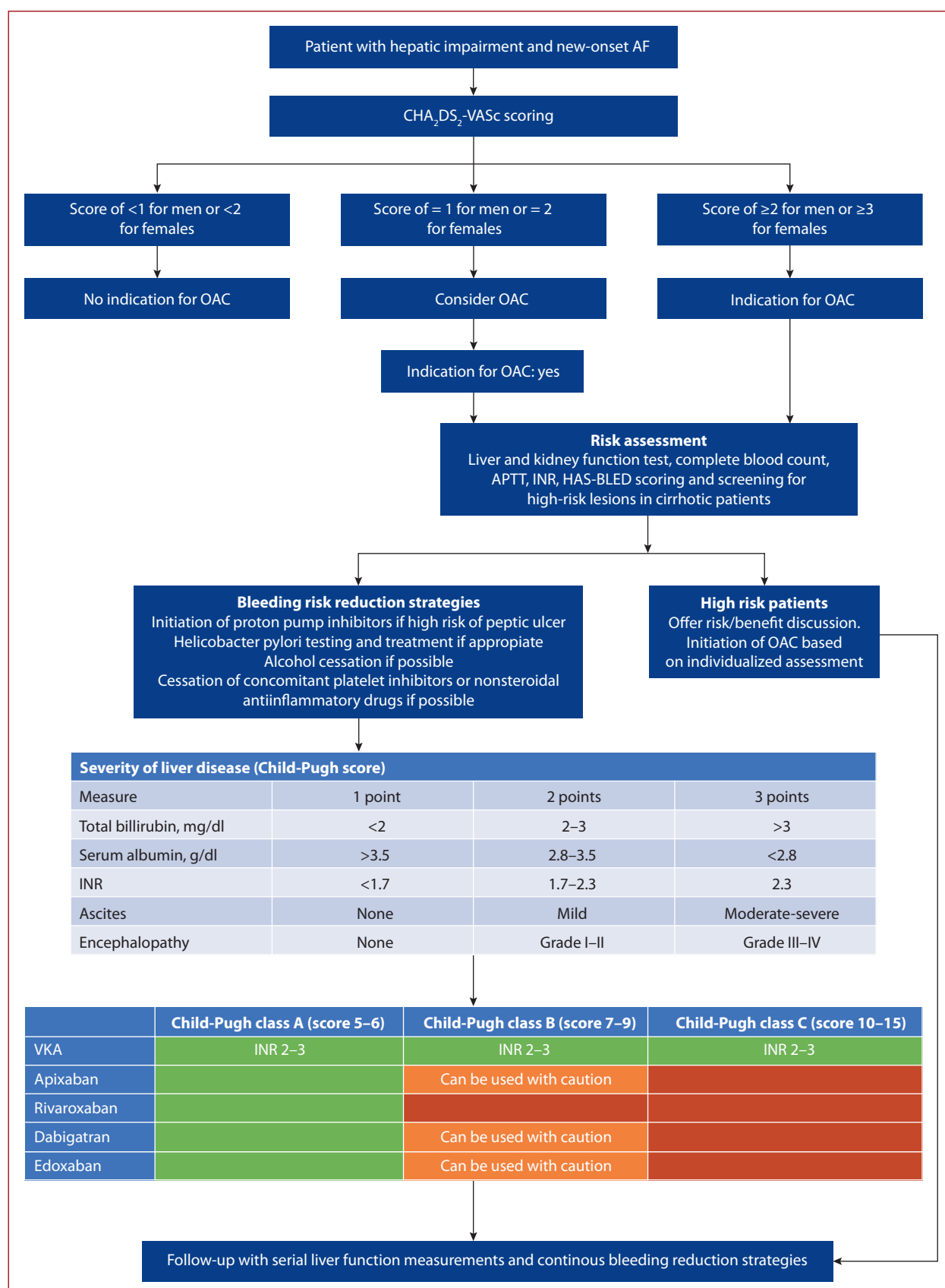
having a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$ , more than 90% of liver cirrhosis patients included in the study received either no treatment or treatment with a platelet inhibitor instead of OACs.

Supporting the Taiwanese study, a Danish, nationwide, cohort study by Steensig et al. also reported a benefit of OACs in individuals with liver disease and AF, though only in the case of a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$  for men and  $\geq 3$  for women [79]. The authors included a total of 1238 OAC naïve patients with liver disease, newly diagnosed atrial fibrillation, and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 1$  for men and  $\geq 2$  for women and compared initiation of OACs with no OACs. Initiation of OACs was associated with significantly reduced risk of thromboembolism, and the positive effect of OAC increased with the rising CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Additionally, the bleeding risk was not affected by initiation versus non-initiation of OACs.

In a retrospective analysis of 103 897 patients from the US Veterans Affairs health system receiving VKAs, of whom 1763 had liver disease, the time in therapeutic range was significantly lower in the liver disease group [80]. While there was no clear tendency for INR to be either above or below the therapeutic range, the results indicated an association between poor anticoagulation control and an up to 2-fold increased risk of major bleeding. Due to the high prevalence of spontaneous INR elevation as well as inherent coagulation dysfunction in patients with liver disease, physicians might be tempted to prescribe DOACs in off-label (reduced) doses to reduce bleeding risk; a practice

that has not been associated with lower bleeding rates, at least in an emergency department setting [81], and it is not recommended by the European Society of Cardiology or the European Medicines Agency. Nevertheless, a recent Polish study explored reduced dose apixaban, rivaroxaban, or dabigatran in 42 patients with concomitant liver cirrhosis (Child-Pugh score A–B) and AF, with an average CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 [82]. The investigators reported an annual rate of major bleeding of 2.4% and an annual rate of stroke of 1.8%. In comparison, annual stroke rates were 1.7%, 1.3%, and 1.1%, and annual bleeding risks were 3.6%, 2.1%, and 3.1% in the phase III randomized trials of rivaroxaban, apixaban, and dabigatran, respectively [73, 74, 76] although they notoriously excluded patients with significant liver disease.

Meta-analyses of the efficacy and safety of DOACs versus warfarin have consistently found DOACs to be at least non-inferior to warfarin treatment in patients with liver disease, even in those who have progressed to liver cirrhosis [83]. A systematic review including a pooled analysis of 41 859 patients with liver disease and AF found DOACs associated with a significantly reduced risk of ischemic stroke and bleeding risk compared with VKAs [84]. An observational Korean study of individuals with AF and liver disease compared 12 778 patients treated with VKA and 24 575 treated with DOACs. In that large Asian population, DOAC treatment was associated with a lower risk of ischemic stroke, and major bleeding events (including ICH and gastrointestinal bleeding) compared with warfarin.



**Figure 3.** Potential algorithm for initiating oral anticoagulation in patients with atrial fibrillation and liver disease. Adapted from [48]

Abbreviations: AF, atrial fibrillation; APTT, activated partial thromboplastin time; CHA<sub>2</sub>DS<sub>2</sub>-VASc, Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age 65–74 years, Sex category (female); HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol; OAC, oral anticoagulant; VKA, vitamin K antagonist; other — see [Table 1](#)



DOACs consistently seem to perform better in terms of efficacy and safety, even in patients with significant active liver disease [85].

## **GUIDELINES AND RECOMMENDATIONS**

The most recent European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the management of AF do not offer specific recommendations related to the concomitant presence of liver disease [1, 86]. The ESC guidelines underscore the existence of retrospective data, suggesting that the benefit of stroke prophylaxis with OACs might outweigh the risk of bleeding in patients with liver disease. Additionally, they highlight observational results suggesting a lower bleeding risk of DOACs compared with VKAs. The European Medicines Agency suggests that DOACs are safe to administer in Child-Pugh class A liver disease, and that apixaban, dabigatran, and edoxaban can be used with caution in Child-Pugh class B liver disease. However, they are all contraindicated in Child-Pugh class C liver disease [87–90]. The American Food and Drug Administration has similar recommendations, though it only recommends apixaban and dabigatran in Child-Pugh class B liver disease [91–94].

Decisions on initiation of OACs in patients with concomitant hepatic impairment and AF should be made as usual with CHA<sub>2</sub>DS<sub>2</sub>-VAsC risk stratification. Many patients with hepatic impairment are likely to benefit from OACs, but drug choice depends on the type and severity of liver disease (i.e., Child-Pugh score [Figure 3]). A risk assessment should be performed before initiating OACs by calculating the HAS-BLED score and doing blood tests that include liver function, platelet count, and clotting function. A platelet count <100 000/μl was an exclusion criterion for the three pivotal phase III randomized trials that examined dabigatran, apixaban, and edoxaban, respectively, in patients with non-valvular AF [74–76]. The lower limit was <90 000/μl in the rivaroxaban trial [73]. However, depending on individual thrombotic and bleeding risks, a lower limit of 50 000/μl to 70 000/μl may be acceptable in patients with hepatic impairment [37]. Furthermore, screening for high bleeding-risk lesions is recommended when a diagnosis of cirrhosis is made to evaluate bleeding risk related to portal hypertension [95]. Patients with an indication for OACs, but at high risk of a major bleeding event, should be offered a thorough consultation on the risks and benefits of initiation versus no initiation of OACs. Furthermore, AF risk factor management reduces the burden of recurrent AF [96]. In patients with hepatic impairment, alcohol cessation is particularly important.

## **CONCLUSIONS**

AF is associated with significant morbidity and mortality. The primary complication of AF is ischemic stroke, whose risk may be reduced with oral anticoagulant agents. AF patients often have concomitant hepatic impairment.

However, anticoagulation in patients with liver disease is challenging due to the pathophysiological changes of the coagulation cascade and, as a result, the increased risk of major bleeding in such individuals. Furthermore, monitoring of the degree of anticoagulation is complicated in patients with liver disease. We suggest a strong focus on risk factor management and argue that the risk of ischemic stroke often outweighs the risk of hemorrhagic events in this setting.

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