Update and Unmet Needs on the Use of Nonvitamin K Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation

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Abstract: The landscape of stroke prevention in patients with atrial fibrillation (AF) is rapidly changing after the introduction of nonvitamin K oral anticoagulants (NOACs) that are replacing in many countries the use of vitamin K antagonists in virtue of their similar efficacy and better safety. The European Heart Rhythm Association has proposed a new classification for AF patients with valvular heart disease (VHD), which has clinical implications for the most appropriate choice of antithrombotic strategy. Furthermore, a growing body of evidence is available on the use of NOACs in patients with VHD. Beyond VHD, several other factors may help tailoring the antithrombotic therapy to the characteristics of patients. Thus, a new risk factors-based approach to improve the management of AF patients, namely *Atrial fibrillation Better Care (ABC)* pathway has been recently proposed. This includes "A" avoid stroke by adequate anticoagulant therapy, "B" better control of symptoms related to AF, and "C" optimal management of comorbidities focusing on modifiable cardiovascular risk factors.

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Another recent update regards the use of NOACs in patients undergoing myocardial revascularization, where the association of NOACs with antiplatelet offers a new safe option in the first period after the procedure. Finally, there are still some patients in whom NOACs have not been systematically studied, and the clinician has to decide whether to prescribe or not NOACs balancing the risk of bleeding and stroke. This review aims to summarize the most recent evidence to consider when choosing an anticoagulant therapy in AF patients. (Curr Probl Cardiol 2021;46:100410.)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, affecting 0.12%-0.16% of adults aged ≤49 years, 3.7%-4.2% of patients aged 60-70 years, and 9%-17% of patients aged ≥80 years.[1] Consolidated evidence showed that AF is an important risk factor for ischemic stroke and myocardial infarction.[2]

The goal of oral anticoagulation (OAC) is to prevent ischemic stroke and systemic thromboembolism, and Vitamin K Antagonists (VKAs) have been long used at this purpose, with a risk reduction of 64%.[8] Although these drugs are effective for the prevention of thromboembolism, their use is limited by a narrow therapeutic range that needs frequent monitoring and dose adjustments resulting in substantial low quality of anticoagulant therapy in real-world settings, and a high-risk for bleedings.[3] Thus, the risk of intracranial hemorrhage (ICH) in patients treated with VKAs is 0.30%-0.44%.

All these reasons lead to the development of the nonvitamin K oral anticoagulants (NOACs) that have demonstrated similar efficacy and higher safety compared to VKAs in terms of major bleeding reduction, with a significant lower incidence of ICH.[3] The introduction of NOACs has certainly improved the therapeutic possibilities for thromboprophylaxis in AF, but their use in specific subgroups of patients is still uncertain.

In this review, we will report recent updates for the management of patients with AF, focusing on (1) new classification of "valvular AF" and choice of NOACs vs VKAs, (2) Risk factors-based approach for the management of patients with AF, (3) recent data on ischemic heart disease, and (4) special categories of patients in whom benefit of NOACs is still uncertain.

AF and Valvular Heart Disease

The use of NOACs is limited to patients with "nonvalvular" AF, as some preliminary studies suggested that NOACs may increase the risk of bleeding in patients with valvular heart disease (VHD), such as those with mechanical heart valves. At this regard, to better define the term "valvular AF," the European Heart Rhythm Association (EHRA) has recently proposed a new classification for patients with AF and VHD, identifying 2 groups of patients[4]: (1) EHRA Type 1 refers to AF patients with moderate-severe mitral stenosis (mainly of rheumatic origin) and mechanical prosthetic valve. (2) EHRA Type 2 that includes AF patients with all other types of VHD including bioprosthetic valve replacement, mitral valve repair, or transaortic valve intervention.

The efficacy and safety of NOACs have been tested in relation to the presence of valve disease in post hoc analysis from clinical trials.

In the ROCKET AF trial, 2003 patients had VHD: 89.6% mitral regurgitation, 24.8% aortic regurgitation, and 11.0% aortic stenosis. The incidence of stroke or systemic embolism was comparable between patients with and without VHD treated with Rivaroxaban or Warfarin.[5] However, an increase in major bleeding in patients treated with Rivaroxaban was observed (hazard ratio [HR] 1.56; 95% confidence interval [CI] 1.14-2.14), but with a similar rate of ICH.[5]

In the ARISTOTLE trial,[6] 4808 patients had a VHD: 73.3% mitral regurgitation, 18.4% aortic regurgitation, and 8.0% aortic stenosis. The study showed a lower incidence of stroke or systemic embolism in patients with VHD treated with Apixaban as compared to Warfarin (HR 0.70; 95% CI 0.51-0.97), with a similar rate of major bleeding and a reduction in ICH (HR 0.28, 95%CI 0.14-0.57).[6]

Dabigatran was also studied in a post hoc analysis of the RELY trial.[7] In 3950 VHD patients, Dabigatran 110 mg showed a similar incidence of thromboembolic events to warfarin, while a reduction in thromboembolic events (HR 0.59, 95%CI 0.37-0.93) was observed with Dabigatran 150 mg. Regarding the safety, a lower incidence of major bleeding was registered with Dabigatran 110 mg (HR 0.73; 95% CI 0.56-0.95), while no significant difference was found with Dabigatran 150 mg.[7] Both Dabigatran 150 mg (HR 0.36, 95%CI 0.17-0.77) and 110 mg (HR 0.29, 95%CI 0.13-0.68) were associated to a lower incidence of ICH compared to Warfarin.[7]

In the ENGAGE-AF TIMI 48 trial, 2824 had VHD: 79.7% mitral regurgitation, 13.1% aortic regurgitation, and 5.8% aortic stenosis.[8] High-dose Edoxaban showed similar efficacy in the prevention of

thromboembolic events and major bleeding in patients with VHD, with a reduction of ICH (HR 0.39, 95%CI 0.15-0.98) compared to Warfarin.[8] Low-dose Edoxaban showed similar efficacy and safety of Warfarin in VHD patients.[8]

A recent meta-analysis including 71,526 AF patients, of whom 13,574 had VHD[9] showed that NOACs globally reduce the incidence of stroke and systemic embolism (HR 0.70; 95% CI 0.60-0.82) compared to Warfarin, along with a similar rate of major bleeding and lower ICH (HR 0.47; 95% CI 0.24-0.92).[9]

Based on this evidence, the use of NOACs is indicated only in AF patients with VHD Type 2.

Patients With AF and Coronary Artery Disease

Atrial fibrillation and coronary artery disease (CAD) are 2 closely related diseases.[2] Treatment with VKAs is only marginally effective for cardiovascular prevention in AF.[10] NOACs showed better efficacy to reduce the risk of MI compared to VKAs; indeed, in a study of 31,739 patients the annual risk of MI was 1.6% for VKAs, 1.2% for Apixaban (HR 0.74, 95%CI 0.57-0.95), 1.2% for Dabigatran (HR 0.75, 95%CI 0.57-0.98), and 1.1% for Rivaroxaban (HR 0.68, 95%CI 0.51-0.91) without significant difference among NOACs.[11]

NOACs have been tested in patients undergoing percutaneous coronary intervention (PCI) due to an acute coronary syndrome (ACS) or to an elective procedure. In particular, in the REDUAL-PCI Trial,[12] the association of Dabigatran with $P2Y_{12}$ inhibitor resulted in a reduction of major bleedings for both 110 mg (HR 0.52, 95%CI 0.42-0.63) and 150 mg (HR 0.72, 95%CI 0.58-0.88). There was also a reduction of ICH for Dabigatran 150 mg compared with the standard triple therapy of warfarin + $P2Y_{12}$ inhibitor + Aspirin, with similar efficacy.

In the PIONEER AF-PCI[13] trial, the addition of Rivaroxaban 15 mg od with single antiplatelet (HR 0.59, 95%CI 0.47-0.76, $P < 0.001$) or Rivaroxaban 2.5 mg od + double antiplatelet (HR 0.63, 95%CI 0.50-0.80, $P < 0.001$) was safer than standard triple therapy with warfarin and double antiplatelet with comparable efficacy.

Based on this evidence, the 2018 ESC guidelines for myocardial revascularization[14] suggest that NOACs should be preferred over VKAs in association to antiplatelet therapy (Fig 1).

In particular, Dabigatran 110 mg bid, Apixaban 5 mg bid or Edoxaban 60 mg od could be considered as part of the triple antithrombotic therapy.[15] Triple therapy may be continued for 1-6 months, depending on the

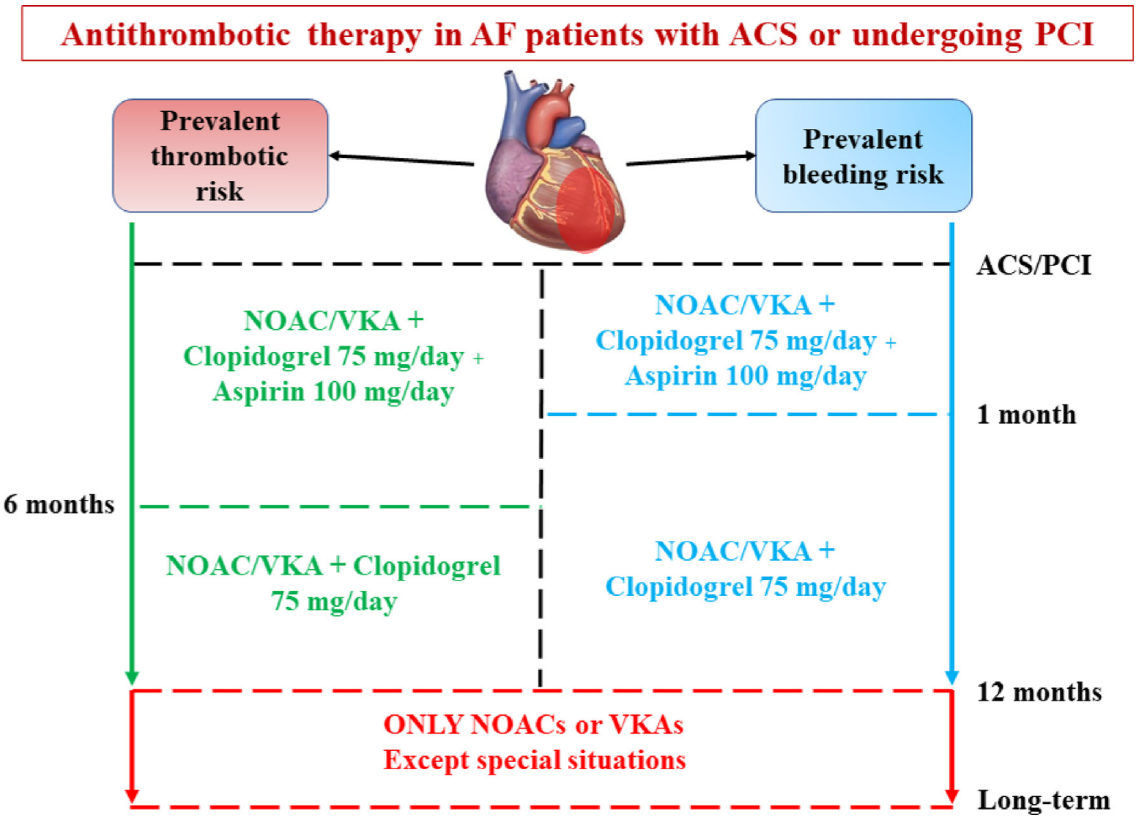

FIG 1. Antithrombotic therapy in atrial fibrillation (AF) patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).

thromboembolic and haemorrhagic risk (Fig 1). In association to double antiplatelet, a regimen containing Dabigatran 150 mg plus P_2Y_{12} is preferred (or Dabigatran 110 mg bid when dose reduction criteria are present). Rivaroxaban 15 mg od rather than 20 mg od may be considered to reduce the risk of bleeding.[15] Given the lack of data, the use of reduced dose Apixaban and Edoxaban in the PCI setting are based on their respective approved labels.

After withdrawal of antiplatelet drugs after 6-12 months from the index event, Apixaban 5 mg bid and Edoxaban 60 mg od could be used. Regarding the decision on whether or not to increase Dabigatran 110 mg to 150 mg bid is at physician discretion, based on the individual risk of stroke and bleeding.

Risk Factors-Based Approach for the Management of Patients With AF

Data here reported suggest that a holistic approach to the management of patients with AF is warranted to reduce the risk of thromboembolism and coronary artery disease. Recently, a risk factors-based approach to improve integrate care of patients with AF, namely the Atrial fibrillation Better Care (ABC) pathway has been proposed[16] (Fig 2). The (A) point of this pathway is to avoid the stroke by anticoagulation with NOACs or well-managed VKA.[17] The (B) consists of the assessment of AF-related symptoms, eventually evaluated by the EHRA score.[18] Finally, the (C) indicates the need for careful assessment and management of comorbidities, such as hypertension, heart failure, diabetes, dyslipidaemia, sleep apnoea, myocardial ischemia, concomitantly to an improvement of lifestyle, including reduction of alcohol consumption, withdrawn of tobacco consumption, adherence to a Mediterranean diet and carrying out regular physical activity.

The ABC pathway was applied in a post hoc analysis of AFFIRM trial that included 3169 patients randomized to a rhythm or rate control strategy.[19] Overall, only 222 (7.0%) patients were well managed (ABC compliant), while the remaining 2947 had at least one uncontrolled risk factor (ABC noncompliant).[19] The study showed a reduction of total mortality (HR 0.35, 95%CI 0.17-0.75), a composite endpoint of stroke/major bleeding/cardiovascular death (HR 0.35, 95%CI 0.18-0.68) and of hospitalization (HR 0.65; 95% CI 0.53-0.80)[19] in ABC-compliant patients.

The ABC pathway was also investigated in a prospective real-world study of 907 AF patients treated with VKAs.[20] In this study "A" was defined as a Time in therapeutic range (TiTR) > 65%, "B" as an EHRA

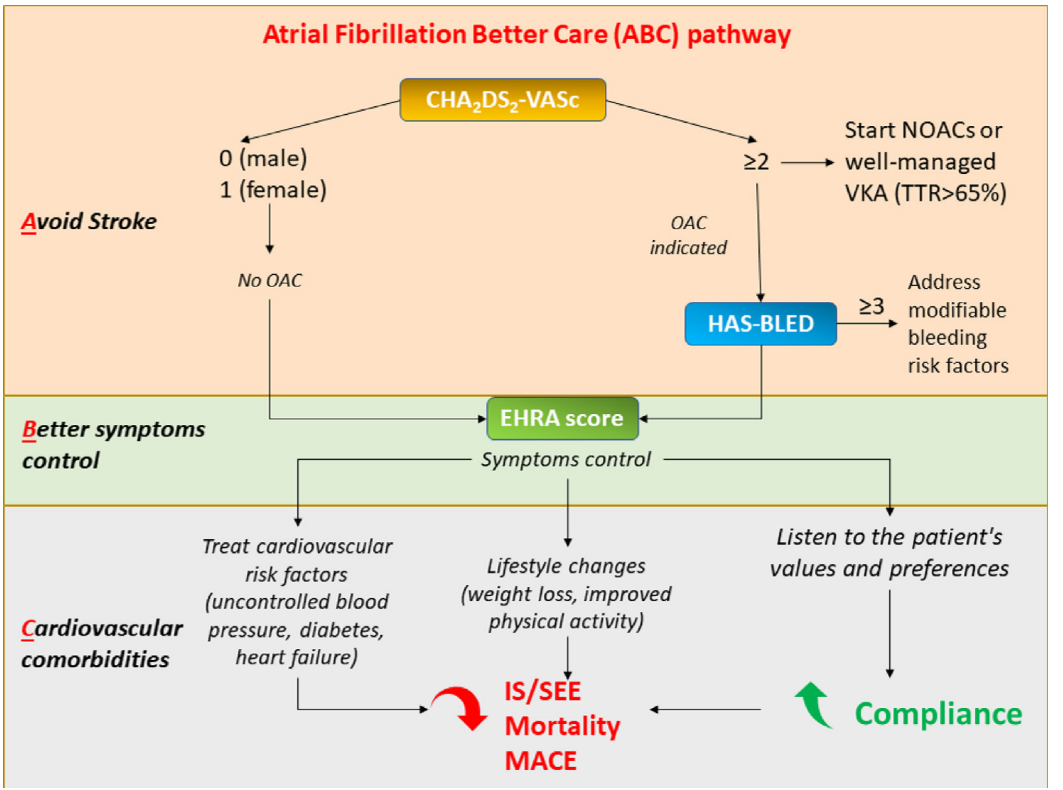

FIG 2. The Atrial Fibrillation Better Care (ABC) pathway. CVD, cardiovascular disease; IS, ischaemic stroke; MACE, major adverse cardiovascular events; NOAC, direct oral anticoagulant; OAC, oral anticoagulant; SEE, systemic embolism.

score of I-II, and "C" as an optimized management of cardiovascular risk factors (arterial hypertension, diabetes mellitus, heart failure, previous cardiovascular, and cerebrovascular events). Optimally managed patients in the ABC group (n = 198, 21.8%) had a lower risk of cardiovascular events (CVEs) (1.8% vs 4.5%/year, $P = 0.0013$) as compared to those presenting with at least one suboptimal ABC factor (adjusted HR 0.439, 95%CI 0.241-0.800, $P = 0.007$).[20]

Altogether, these data show that an integrated approach to the management of patients with AF may help improve outcomes in patients with AF.

Special Categories of Patients

The use of NOACs in particular subgroups of AF patients requires an accurate risk-benefit evaluation. These patients include those at low risk of ischemic stroke, those affected by obesity or patients with chronic liver disease (Fig 3).

a) *Low-risk of ischemic stroke*

There is clear evidence that patients with CHA_2DS_2-VASc score ≥ 2 in men and ≥ 3 in women should always be treated with OAC. However, a zone of uncertainty is represented by patients at intermediate risk of stroke, such as those with a CHA_2DS_2-VASc score 1 in men or 2 in women, for whom risk benefit of OAC should be evaluated.

A study including 8203 with CHA_2DS_2-VASc score 1 not on OAC, showed that the event rate of hospital admission or death due to thromboembolism at 1 year was 2.01, reduced to 1.23 by the treatment with VKAs,[21] suggesting a benefit of antithrombotic therapy also in patients with intermediate risk.

In a retrospective study on 140,420 AF patients from Swedish nationwide health registries,[22] the annual rate of ischemic stroke in patient with CHA_2DS_2-VASc of 1, was 0.5%-0.7% in men and 0.1%-0.2% in women. In this cohort, 46.2% of men and 22.5% of women were on warfarin at baseline.[22]

A recent study including 8962 patients with CHA_2DS_2-VASc score = 1 in men and 2 in women, showed a net benefit for the use of oral anticoagulant (HR 0.59, 95% CI 0.40-0.86, $P < 0.007$).[23] A retrospective analysis of discharge medical records of 182,678 subjects with AF,[24] showed a net clinical benefit for the use of anticoagulation in most of AF patients, with the exception of those at very low risk of stroke (ie, CHA_2DS_2-VASc 0-1).[24]

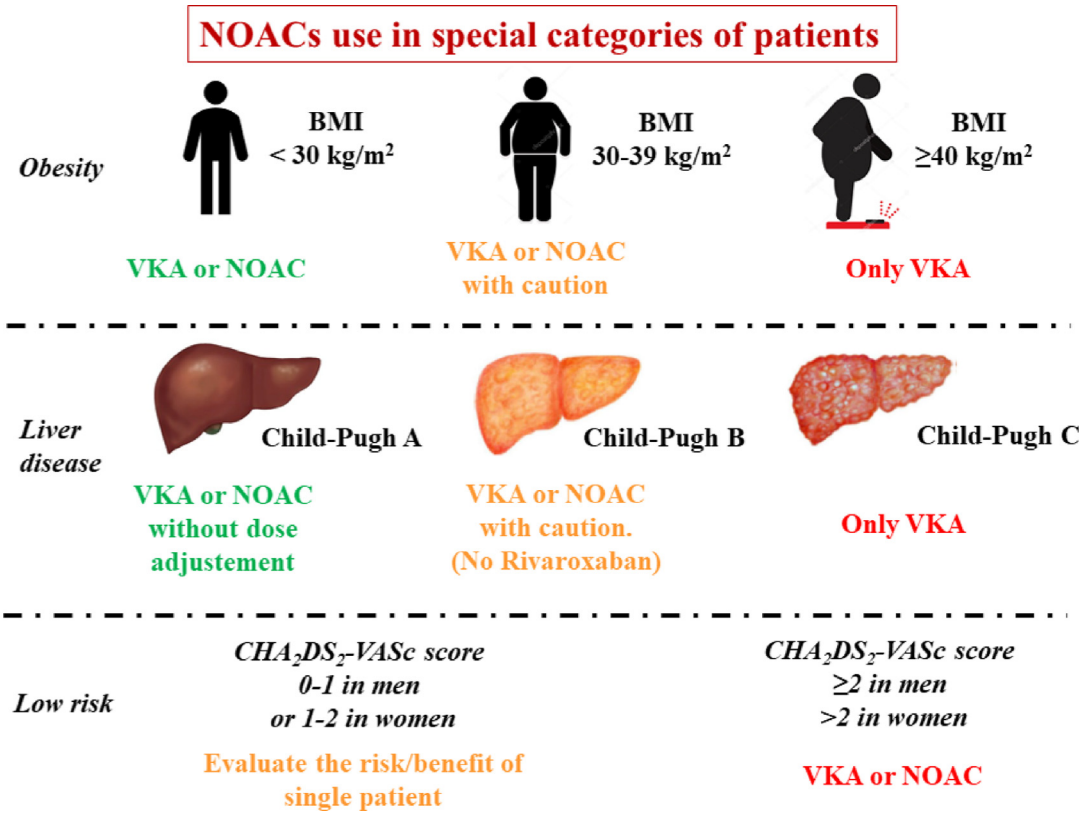

FIG 3. Use of NOACs in special subgroups of patients.

The evaluation of bleeding was performed[25] on 39,400 AF patients, of whom 23,572 were not treated, 5,353 on aspirin, and 10,475 on warfarin. In a mean follow-up of 5.9 years, the annual stroke event rate in untreated low-risk patients (CHA_2DS_2-VASc = 0 [male], 1 [female]) was 0.49 per 100 person-years, the addition of 1 risk factor increased the risk of stroke by 3 fold (1.55 per 100 person-years).[25]

In addition, an analysis from the National Health Insurance Research Database[26] that enrolled 186,570 AF patients not treated with anticoagulation or antiplatelet therapy with CHA_2DS_2-VASc score 1 [males] or 2 [females]. The study showed that when an additional risk factor beyond sex is present, the risk of thromboembolism significantly increases with advancing age and diabetes being the 2 strongest risk factors.[26]

In conclusion, anticoagulation treatment seems to be beneficial in patients with 1 additional stroke risk factor beyond sex. Most available data stem from VKA treatment, while NOACs efficacy and safety should be further investigated in this subgroup of patients.

b) *Obesity*

Obese population is not well represented in clinical trials and few clinical studies on obese patients treated with NOACs are available. Thus, while VKA therapy allows a dose adjustment based on INR values, bioavailability of NOACs in obese and very obese patients is uncertain.

A recent meta-analysis of randomized clinical trials[27] showed that AF patients with high (>100 kg) vs nonhigh body weight had a lower risk of thromboembolism (Relative Risk [RR] 0.43; 95% CI 0.28-0.67; P = 0.0002), with no difference in bleeding outcomes.[27]

These data were recently confirmed by a study from the Dresden NOAC registry, including 3432 AF patients, of whom 1,077 (31.4%) were obese.[28] The Authors found a progressive reduction of the incidence of the combined endpoint of stroke/TIA/systemic embolism of VTE according to BMI categories.[28]

A guidance from the ISTH recommends that NOACs can be prescribed at full dose in patients with BMI ≤40 kg/m^2, or body weight ≤120 kg, give the relative stability of pharmacokinetics of NOACs in these patients.[29] Conversely, if a NOAC is used in patients with BMI >40 kg/m^2, or body weight >120 Kg, drug-specific peak and through level should be tested (anti-Xa activity for Apixaban, Edoxaban and Rivaroxaban, and ecarin clotting time or diluted thrombin time for Dabigatran).[29] If levels of NOACs are within the normal levels, it is reasonable to continue the

therapy, while if the level is below the normal range, switching to VKAs is advised.

A similar indication comes from the 2018 position paper of ESC Working group, that suggests a full standard dose of NOACs in patients with normal/grade I obesity (BMI < 35 kg/m^2), with no/insufficient data for apixaban, edoxaban, and dabigatran for obesity class II-III; conversely Rivaroxaban full dose can be administered with caution in patients with class II obesity (BMI 35-39.9 kg/m^2).[30]

c) *Chronic liver disease (CLD)*

CLD represents a clinical challenge for patients treated with OAC, as patients with advanced CLD may have hemostatic abnormalities, which may favor bleeding.

The incidence of ischemic and hemorrhagic complications in patients with AF and coexisting CLD is difficult to estimate given the paucity of data on this topic.[31]

In VKA-treated patients, CLD is associated with a lower TiTR,[32] thus leaving patients potentially exposed to an increased risk of thromboembolism. Patients with AF and CLD, defined as liver cirrhosis or persistent increase of liver function tests (alanine transaminase or aspartate transaminase ≥ 2-3 times the upper limit of normal) or total bilirubin ≥1.5 times the upper limit of normal, have been excluded from trials with NOACs.[4]

A prospective observational study evaluating the safety and efficacy of NOACs in patients with CLD were performed on 2330 AF patients, 1033 on NOACs, and 1297 on VKAs.[33,34] CLD was defined by the noninvasive index of advanced liver fibrosis, namely FIB-4 (ie, >3.25).[33] CLD was present in 5.9% of patients on VKAs and 5.0% of patients on NOACs. During a mean follow-up of 33.6 months, 357 bleeding events occurred: of these 261 in the VKA (7.2%/year) and 96 (6.4%/year) in the NOAC group.[33]

Patients with CLD experienced a higher rate of major bleeding in the VKA (14.3% vs 5.6%, log-rank test $P < 0.001$) but not in the NOAC (5.8% vs 9.5%, log-rank test $P = 0.374$) group.[33]

Furthermore, in the NOACs group no significative difference was found in CVEs incidence between patients with and without CLD.[33]

In the 2018 EHRA practical guide all NOACs are contraindicated in patients with liver cirrhosis stage Child-Turcotte-Pugh (CTP) C, and in patient with elevated hemorrhagic risk (Fig 3).[4]

In patients with liver cirrhosis CTP class A-B, Edoxaban, Apixaban, and Dabigatran may be used with caution, while the use of Rivaroxaban

is contraindicated in CTP-B,[4] due to pharmacodynamic studies showing increased plasma concentrations of Rivaroxaban in these patients.

In conclusion, there are not sufficient data to evaluate the efficacy and safety of NOACs in patients with AF and CLD, especially for patients with end-stage liver disease. Available observational studies are encouraging showing a good safety and efficacy of NOACs in cirrhotic patients with AF,[35] but studies with larger sample are needed.

Conclusions

Despite recent advances in the thromboprophylaxis strategy for patients with AF, a high rate of cardiovascular events and mortality is still present. A holistic approach in the management of these patients is therefore necessary. Most patients with AF starting OAC are prescribed on NOACs, but their efficacy and safety in some specific subgroups are still uncertain.

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