European Heart Journal Supplements (2022) **24** (Supplement A), A11–A18
The Heart of the Matter
https://doi.org/10.1093/eurheartj/suab154

Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with advanced chronic kidney and liver diseases

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KEYWORDS
AF;
NOAC;
Chronic kidney disease;
Chronic liver disease

Advanced chronic kidney disease (CKD) or chronic liver disease (CLD) is frequent in patients with atrial fibrillation (AF) because of their common risk factors. Chronic kidney disease and CLD superimposed on AF are associated with increased risks of thrombosis and bleeding, which further complicates the use of oral anticoagulants (OACs). Because currently approved non-vitamin K antagonist oral anticoagulants (NOACs) undergo certain degrees of metabolism and clearance in the liver and kidney, increased exposure to medications and risk of bleeding are major concerns with the use of NOACs in patients with advanced CKD and CLD. Besides, these patients were mostly excluded from landmark trials of NOACs and related cohort studies are also limited. Therefore, the optimal strategy for the use of NOACs in this population remains unclear. This review would go through current evidence regarding the safety and efficacy of NOACs in AF patients with advanced CKD and CLD and provide a comprehensive discussion for clinical practices.

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia globally[1,2] and it accounts for 20–30% of all ischaemic strokes.[3] Oral anticoagulant (OAC) is the mainstream management in AF patients with high risks of ischaemic stroke as stratified by the CHA_2DS_2-VASc score.[3–5] In the recent decades, a paradigm shift from vitamin K antagonists (VKA) towards non-vitamin K antagonist oral anticoagulants (NOACs) has been proposed because of its non-inferiority to VKA for comparable risk reduction of ischaemic stroke and less bleeding.[5–12] The European Society of Cardiology (ESC) Guidelines for AF management clearly claim NOACs as the first-line therapy of OAC for AF patients eligible for stroke prevention.[3] However, the effect of NOACs on AF patients with advanced chronic kidney disease (CKD) and chronic liver disease (CLD) remains challenging because these patients are mostly excluded from landmark trials.[7–10] A paucity of robust data and bleeding tendency with CKD and CLD further complicate the use of NOACs. Therefore, this review aims to provide a comprehensive overview of the current evidence regarding the use of NOACs in AF patients with advanced CKD and CLD.

Chronic kidney disease

Chronic kidney disease is associated with bleeding diathesis and thromboembolism

Chronic kidney disease is common in AF patients[13,14] and conveys to a higher risk of thromboembolism,[15,16] haemorrhagic strokes, and major bleeding.[16,17] Potential

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pathophysiological mechanisms underlying excess risks of haemorrhage or ischaemic stroke with advanced CKD,[18] include an increased prevalence of anaemia, accelerated calcific atherosclerosis, platelet dysfunction, and other uraemic sequelae.[19] The use of OAC is more challenging for AF patients with CKD considering the tendency to bleed and the increased concentration of medications because of impaired renal clearance.

The use of non-vitamin K antagonist oral anticoagulants in relation to impaired renal functions in landmark trials

All NOACs possess variable degrees of renal clearance and different criteria of dose reduction in relation to renal function impairment have been proposed.[20-23] In landmark trials of NOACs, patients with a creatinine clearance (CrCl) rate <30 mL/min were excluded except in Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF (ARISTOTLE) which included patients with a CrCl rate between 25 and 30 mL/min.[20-23] Among patients with a CrCl rate of 25–50 mL/min in ARISTOTLE, apixaban presented with a comparable risk of ischaemic stroke/systemic embolism (IS/SE) and less major bleeding compared to warfarin.[24] The results remained the same in patients with a CrCl rate of 25–30 mL/min,[25] with a trend towards less major bleeding with apixaban compared to those with a CrCl rate >30 mL/min.[25] Standard dose of apixaban (for patients without age or body weight criterion to warrant dose adjustment) compared to warfarin in patients with a CrCl rate of 25–30 mL/min was associated with a trend of less major bleeding, whereas apixaban at a dose of 2.5 mg twice daily in patients meeting the dose reduction criteria decreased 73% of major bleeding. In the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), rivaroxaban is non-inferior to warfarin for IS/SE with a similar risk of bleeding compared to warfarin in patients with a CrCl rate of 30 to <50 mL/min.[26] In ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48), edoxaban was comparable to warfarin for preventing IS/SE and resulting in significantly less major bleeding in patients with a CrCl rate of 30 to <50 mL/min.[27] The net clinical outcomes were more favourable with edoxaban in this subgroup. In RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy), dabigatran (150 mg) taken twice daily in patients with a CrCl rate of 30 to <50 mL/min decreased risk of IS/SE with similar major bleeding compared to warfarin, while dabigatran at a dose of 110 mg twice daily was associated with similar risk of IS/SE and major bleeding[28] (*Table 1*).

In general, RCTs for the efficacy and safety in AF patients with advanced CKD are lacking, but subgroup analyses from landmark trials of NOACs showed a comparable or less risk of bleeding with similar efficacy compared to warfarin in patients with advanced CKD (*Figure 1*).

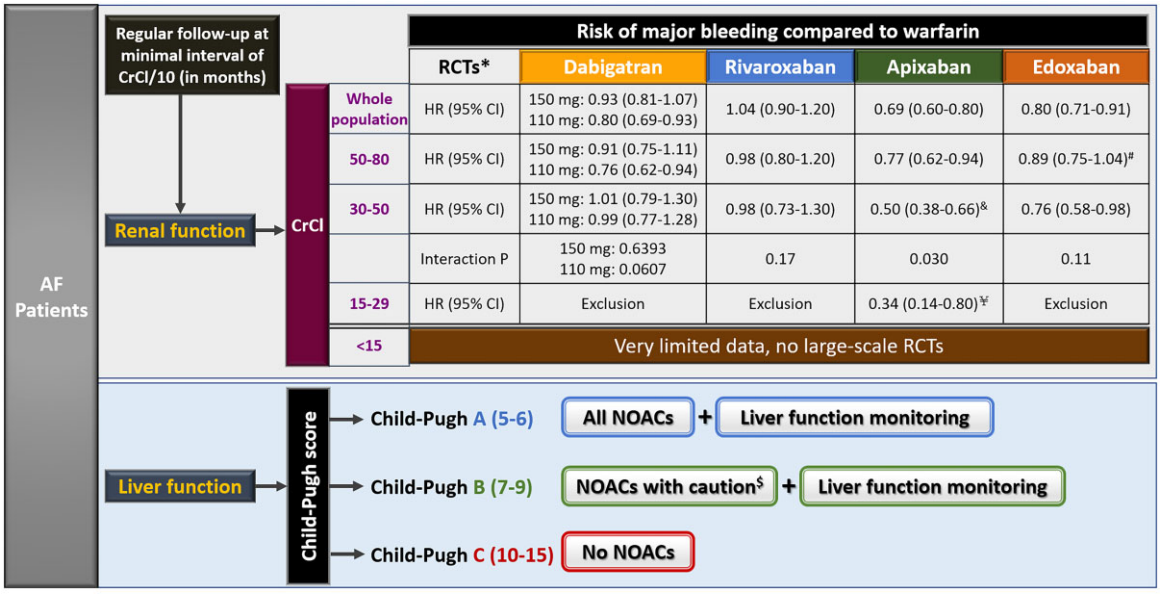
Real-world studies about the use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with advanced chronic kidney disease

Although robust data from RCTs on the use of NOAC in AF patients with advanced CKD are lacking, real-world cohort studies with variable sample sizes and designs may provide useful information (*Table 2*). A nationwide cohort study using propensity score-matching in patients with a CrCl rate range of 30–50 mL/min by Yu *et al.*[29] observed less IS/SE and bleeding with a daily dose of edoxaban (60 mg) compared to warfarin, whereas edoxaban (30 mg) was associated with less IS/SE and similar bleeding. Another small-sized cohort study reported less bleeding or thrombosis with apixaban compared to warfarin in patients with a CrCl rate <25 mL/min, but not all patients had AF.[30] The use of NOAC in AF patients receiving dialysis is even more difficult and complex. A prospective multicentre RCT, including 132 AF patients receiving dialysis by De Vriese *et al.*,[31] found that rivaroxaban (10 mg) was associated with fewer cardiovascular events and major bleeding compared to warfarin, but premature and permanent

Table 1 Efficacy and safety of different NOACs compared to warfarin in relation to impaired renal function from landmark trials

Trial	CrCl, mL/min	Patient number	Safety: major bleeding	Efficacy: stroke or systemic embolism
ARISTOTLE trial[24]	25 to ≤ 50	3017 (733 patients at low apixaban dose)	HR: 0.50, 95% CI: 0.38-0.66	HR: 0.79, 95% CI: 0.55-1.14
ARISTOTLE trial[25]	25 to 30	269 (48 patients at low apixaban dose)	HR: 0.34, 95% CI: 0.14-0.80	HR: 0.55, 95% CI: 0.2-1.5
ENGAGE AF-TIMI 48[27]	30 to <50	2740	HR: 0.76, 95% CI: 0.58-0.98	HR 0.87, 95% CI: 0.65-1.18
ROCKET AF trial[26]	30 to <50	2950	HR: 0.98, 95% CI: 0.73-1.30	HR: 0.84, 95% CI: 0.57-1.23
RE-LY trial[28]	30 to <50	3374	Dabigatran 150 mg: HR: 1.01, 95% CI: 0.79-1.30 Dabigatran 110 mg: HR: 0.99, 95% CI: 0.77-1.28	Dabigatran 150 mg: HR: 0.56, 95% CI: 0.37-0.85 Dabigatran 110 mg: HR: 0.85, 95% CI: 0.59-1.24

CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.



* Data from sub-analysis of RCTs (ARISTOTLE , ENGAGE AF–TIMI 48, RE-LY, ROCKET AF)
& CrCl 25-50 mL/min in ARISTOTLE trial; # CrCl 50-95 mL/min in ENGAGE AF–TIMI 48 trial; ¥ CrCl 25-29 mL/min; $ except rivaroxaban

Figure 1 Regular follow-up of renal functions is recommended in patients with impaired renal functions (upper panel). Subgroup analyses from landmark trials of NOACs observed no increase in major bleeding with NOACs even with declining CrCl rates. There are still knowledge gaps for patients with a CrCl rate <15 mL/min. The Child-Pugh score is recommended to stratify patients with different severity of liver function impairment and to choose appropriate NOACs (lower panel). Regular monitoring of liver functions should be done in patients receiving NOACs. *Data presented in the figure were adopted from the original analysis and sub-analysis of RCTs (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, ROCKET AF).[7-10, 24-28] &CrCl 25-50 mL/min in ARISTOTLE trial; #CrCl 50-95 mL/min in ENGAGE AF-TIMI trial; □CrCl 25-29 mL/min; $except rivaroxaban. AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance, mL/min; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulants; RCTs, randomized controlled trials.

discontinuation of OAC occurred in 25% of patients. However, a retrospective cohort study with meta-analysis reported no additional benefit of NOACs over warfarin regarding effectiveness and safety.[32,33] A similar result was found in the comparison of individual NOAC with warfarin in the meta-analysis except for higher bleeding risks with dabigatran and lower bleeding risks with apixaban.[32] Another cohort study also observed comparable efficacy and less bleeding with apixaban in AF patients receiving dialysis.[34] Furthermore, in another cohort study, rivaroxaban and apixaban showed similar efficacy and safety in patients undergoing dialysis.[35]

There were dose-identification studies with pharmacokinetic data investigating the potential drug accumulation in patients with advanced CKD.[36] Data obtained from the simulation model of RE-LY trial showed that a dose of dabigatran (75 mg twice daily) in patients with a CrCl rate range of 15–30 mL/min have target plasma level and exposure data largely within a safe and effective concentration range in patients with a CrCl rate >30 mL/min receiving 150 mg twice daily, suggesting dabigatran (75 mg twice daily) for patients with a CrCl 15–30 mL/min.[37] Another study analysing apixaban area under the curve (AUC) between eight patients with advanced CKD receiving dialysis using a single dose of apixaban (5 mg) showed a modest increase (36%) in apixaban AUC compared to eight healthy individuals without renal impairment.[38] Likewise, Chang *et al.*[39] revealed an increase in apixaban AUC by 44% with a single dose of apixaban (10 mg) in patients with a 24-h CrCl rate of 15 mL/min, but there was no difference in anti-factor Xa activity compared to subjects with normal renal function. Meanwhile, a small-sized study in seven patients with dialysis found accumulating drug levels with apixaban (2.5 mg twice daily) and supratherapeutic levels with apixaban (5 mg twice daily), suggesting 2.5 mg twice daily to be the maximum dose of apixaban in dialysis patients.[36]

In summary, real-world cohort studies observed better safety and comparable or even better efficacy of NOACs compared to warfarin in AF patients with moderate CKD without dialysis. For those with ESRD under dialysis, however, both retrospective cohort studies and meta-analyses showed no additional benefit with NOACs compared with warfarin except for apixaban which might be associated with better safety. Albeit, more data from large-scale RCTs are needed for a strong conclusion.

Accurate estimation of renal function is important for non-vitamin K antagonist oral anticoagulant dosing

About three in 10 Asian AF patients were treated with off-label dosing of NOACs, and either underdosing or overdosing is associated with higher risks of adverse events.[40] In AF patients with severe CKD, off-label dosing is also frequent and may be associated with worse safety and no additional benefit.[41] Therefore, it is important to have an accurate estimation of renal function when determining the dosages of NOACs. Most RCTs adopted the Cockcroft–Gault (CG) formula for dose adjustment, whereas the Modified Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas are frequently used in real-world practice. Chao *et al.*[42] found that the MDRD and CKD-EPI formulas overestimated the glomerular filtration

Table 2 Cohort studies regarding safety and efficacy of NOACs in AF patients with CKD

Study	Study design and patient number	Renal function	Safety: major bleeding	Efficacy: stroke or systemic embolism
Yu *et al.*[29]	Retrospective propensity score-matched cohort study: edoxaban 60 mg daily ($n=2840$) vs. warfarin ($n=2840$)	CrCl >30 to 50 mL/min	HR: 0.12, 95% CI: 0.02-0.88	HR: 0.25, 95% CI: 0.07-0.84
	Retrospective propensity score-matched cohort study: edoxaban 30 mg daily ($n=3016$) vs. warfarin ($n=3016$)	CrCl >30 to 50 mL/min	HR: 0.56, 95% CI: 0.26-1.23	HR: 0.38, 95% CI: 0.19-0.76
Hanni *et al.*[30]	Retrospective cohort study: apixaban ($n=128$, 57% at 2.5 mg twice daily) vs. warfarin ($n=733$) * (not all patients are AF)	CrCl <25 mL/min	Bleeding or thrombosis: HR: 0.47, 95% CI: 0.25-0.92	
Weir *et al.*[33]	Retrospective cohort study: rivaroxaban ($n=781$, 15% at 20 mg, 60% at 15 mg, 21% at a dose <15 mg, once daily) vs. warfarin ($n=1536$)	Stage 4 or 5 CKD ± dialysis	HR: 0.91, 95% CI: 0.62-1.28	HR: 0.93, 95% CI: 0.46-1.90
Miao *et al.*[35]	Retrospective cohort study: rivaroxaban ($n=787$) vs. apixaban ($n=1836$)	ESRD ± dialysis	HR: 1.00, 95% CI: 0.63-1.58	HR: 1.18, 95% CI: 0.53-2.63
Siontis *et al.*[34]	Retrospective cohort study: apixaban ($n=2351$) vs. warfarin ($n=23\,172$)	Dialysis patients	HR: 0.72, 95% CI: 0.59-0.87	HR: 0.88, 95% CI: 0.69-1.12
See *et al.*[32]	Retrospective cohort study: NOACs ($n=490$) vs. warfarin ($n=2747$)	Dialysis patients	HR: 0.98, 95% CI: 0.64-1.51	HR: 1.21, 95% CI: 0.76-1.92
	Meta-analysis: NOACs ($n=5343$) vs. warfarin ($n=20337$)	Stage 4 or 5 CKD receiving dialysis	HR: 0.80, 95% CI: 0.57-1.13	HR: 0.90, 95% CI: 0.71-1.16
	Meta-analysis: apixaban ($n=2512$) vs. warfarin ($n=9873$)	Stage 4 or 5 CKD receiving dialysis	HR: 0.56, 95% CI: 0.32-0.99	HR: 0.87, 95% CI: 0.69-1.10
	Meta-analysis: dabigatran ($n=431$) vs. warfarin ($n=10811$)	Stage 4 or 5 CKD receiving dialysis	HR: 1.47, 95% CI: 1.22-1.77	HR: 1.48, 95% CI: 0.84-2.61
	Meta-analysis: rivaroxaban ($n=2515$) vs. warfarin ($n=15952$)	Stage 4 or 5 CKD receiving dialysis	HR: 0.82, 95% CI: 0.52-1.31	HR: 0.84, 95% CI: 0.39-1.82
De Vriese *et al.*[31]	Prospective multicentre randomized controlled trial: rivaroxaban 10 mg vs. rivaroxaban 10 mg plus vitamin K2 vs. VKA ($n=132$)	Dialysis	Rivaroxaban: HR: 0.39, 95% CI: 0.17-0.90; Rivaroxaban plus vitamin K2: HR: 0.48, 95% CI: 0.22-1.08	*Fatal and non-fatal cardiovascular events Rivaroxaban: HR: 0.41, 95% CI: 0.25-0.68; Rivaroxaban plus vitamin K2: HR: 0.34, 95% CI: 0.19-0.61

CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; ERSD, end-stage renal disease; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

*Fatal and nonfatal cardiovascular events Rivaroxaban: HR: 0.41, 95% CI: 0.25-0.68, P=0.0006; Rivaroxaban plus vitamin K2: HR: 0.34, 95% CI: 0.19-0.61, P=0.0003.

rates in older patients with low body weights compared with the CG equation, leading to inappropriate dosing and attenuating the benefits of NOACs. Therefore, the CG equation should be the preferred formula for renal function evaluation and NOAC dosing.[42]

Chronic liver disease

The association between atrial fibrillation and chronic liver disease

Advanced CLD is prone to thrombosis as well as bleeding[43] because of altered regulation of platelet count, platelet aggregation, coagulation factors, natural inhibitors, and fibrinolysis.[44] The severity of hepatic impairment is usually determined according to the Child-Pugh classification with Class A, B, C representing mild, moderate, and severe hepatic impairment, respectively.[45] The reduction of coagulation factors generally correlates well with the severity of hepatic impairment.[46] CLD is frequent[47-50] in AF patients because they both share common risk factors. Although liver disease does not account for any point in most risk stratification schemes for AF, the presence of liver cirrhosis was found to be associated with an increased risk of ischaemic stroke.[51]

The use of oral anticoagulants in atrial fibrillation patients with impaired liver function is complicated

Oral anticoagulants are sometimes needed in patients with AF and CLD to prevent IS/SE or to treat liver disease-related venous thrombosis.[52,53] The old belief that elevated international normalized ratio (INR) in CLD is associated with bleeding tendency and a lower risk of thromboembolism has been revolutionized because an increased prevalence of thrombosis has been recognized.[51,54,55] However, the use of OACs in CLD is complicated by the imbalance in endogenous procoagulant and anticoagulant factors. Hepatic impairment also alters usual metabolism in the liver, leading to increased accumulation of medications and the need for dose adjustment.[46] For a long time, warfarin has been deemed as the main OACs in patients with CLD, but the narrow therapeutic range makes clinical management difficult. Besides, many patients with advanced CLD already have an INR level above 2.0 at baseline, which is the recommended therapeutic range for INR. Interaction with diet and medications, the need for frequent INR monitoring, and higher risks of intracranial haemorrhage (ICH) are also major concerns with warfarin use in patients with CLD. Large-scale RCTs on OAC use in AF patients with CLD are lacking and the available knowledge is mostly derived from real-world cohort studies. Chao *et al.*[51] reported a decreased risk of ischaemic stroke and a similar risk of ICH with warfarin use compared to no antithrombotic therapies or antiplatelet therapy from a nationwide cohort, including 9056 AF patients with liver cirrhosis. The results were consistent with a meta-analysis, including 7 cohorts, 19 798 patients with cirrhosis.[56]

Exclusion criteria in relation to liver function impairment in landmark trials of non-vitamin K antagonist oral anticoagulants

Most NOACs undergo certain degrees of liver metabolism, especially cytochrome p450 enzymes for some NOACs. Thus, impaired liver functions have been believed to increase drug levels and risks of bleeding.[57] In large-scale RCTs, patients with active or persistent liver disease were usually excluded (*Table 3*). Anaemia and thrombocytopenia, which are probably present in CLD, were also excluded in landmark RCTs.[20-23]

Data on the use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with chronic liver disease

In a large Asian population with AF and liver disease, NOACs showed better effectiveness and safety than warfarin, which was consistent in those with significant active liver disease defined as cirrhosis, viral hepatitis, or alanine

Table 3 Exclusion criteria in relation to impaired liver function in landmark trials of NOACs

Trial	NOAC	NOAC metabolism	Exclusion criteria
RE-LY trial[21]	Dabigatran	20% hepatic, 80% renal	• Active liver disease, including a. persistent ALT, AST, Alk Phos $>2\times$ ULN b. known active hepatitis C c. known active hepatitis B d. known active hepatitis A • Anaemia (haemoglobin level <100 g/L) • Thrombocytopenia (platelet count $<100\,000/mm^3$)
ROCKET AF trial[20]	Rivaroxaban	65% hepatic, 35% renal	• Known significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) or ALT $>3\times$ ULN • Anaemia (haemoglobin level <10 g/dL)
ARISTOTLE trial[23]	Apixaban	75% hepatic, 25% renal	• ALT or AST $>2\times$ ULN or a total bilirubin $\geq 1.5\times$ UL • Haemoglobin level <9 g/dL • Platelet count $\leq 100\,000/mm^3$
ENGAGE AF-TIMI 48 trial[22]	Edoxaban	50% hepatic, 50% renal	• Active liver disease or persistent elevation of liver enzymes/bilirubin a. ALT or AST ≥ 2 times the ULN b. Total bilirubin ≥ 1.5 times the ULN • Known positive hepatitis B antigen or hepatitis C antibody • Haemoglobin <10 g/dL • Platelet count $<100\,000/mm^3$

ALT, alanine transaminase; Alk Phos, alkaline phosphatase; AST, aspartate transaminase; NOAC, non-vitamin K antagonist oral anticoagulant; ULN, upper limit of normal.

transaminase (ALT)/aspartate transaminase (AST) >2× upper limit of normal (ULN).[58] A small-sized cohort study[59] observed a significantly lower risk of death, but similar IS/SE or major bleeding with NOACs compared to warfarin. One meta-analysis also demonstrated a beneficial role of NOAC in reducing the risks of stroke without increasing the risk of bleeding compared with when no anticoagulation was used.[56] In general, real-world cohort studies were in favour of the use of NOACs in AF patients with CLD, but a solid conclusion based on large-scale RCTs is lacking.

The concern of non-vitamin K antagonist oral anticoagulants-induced liver injury

Chronic liver disease may affect hepatic clearance and drug metabolism, hence, affecting drug response and facilitating drug-induced liver injury (DILI).[60] Severe DILI due to cardiovascular drugs are relatively uncommon, so the premarketing clinical trials are underpowered to detect differences until the post-marketing experience. The concern of NOACs-induced liver injury has been raised because of the hepatotoxic side effects of ximelagatran, a direct thrombin inhibitor, which causes severe liver injury in 8% of treated patients.[61] In landmark trials of NOACs, there was no significant difference in the risks of hepatotoxicity between warfarin and NOACs. However, they are underpowered, and the follow-up period may be too short to recognize rare adverse reactions.

Except for dabigatran, other approved NOACs are metabolized by the liver (mainly CYP3Q4 enzyme is involved) and are probably associated with increases in abnormal liver functions. A meta-analysis, including 29 RCTs, 152 116 patients under dabigatran or FX-a inhibitors observed no increased risk of DILI, with comparable results for individual NOACs. Besides, the risks of elevations in transaminases (>3 × ULN) were lower among NOAC-treated patients, especially in comparison with low molecular weight heparin.[62] However, patients with active liver disease were excluded, so it is difficult to ascertain the risks of DILI with NOACs in patients with baseline CLD. A French nationwide cohort study by Maura *et al.*[63] did not suggest an increase in the 1-year risk of acute liver injury with NOAC, and the incidence of acute liver injury was much higher in those with a history of liver disease or alcoholism. Canadian administrative database-linked cohort study reported[64] no significant difference in the rates of serious liver injury with NOACs compared with warfarin in patients with or without liver disease. Another study, including 113 717 patients with AF (50% warfarin and 50% NOACs), further reported a lower risk of liver injury with NOACs compared to warfarin. Although real-world observations generally showed no significant increase of DILI with NOACs, close monitoring over a long term through post-marketing surveys is still recommended.

Guideline recommendations on the use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with chronic liver disease

There is very little discussion of this issue in current guidelines. Generally, the Child-Pugh score is recommended to classify patients into different severity of liver function impairment. In the 2021 European Heart Rhythm Association Practical Guide for NOACs, all NOACs are not recommended in patients with a Child-Pugh class C (score >9), while all NOACs at normal dose can be used in patients with a Child-Pugh class A (score <7). For those with a Child-Pugh class B (score 7–9), dabigatran, apixaban, and edoxaban can be used with caution and rivaroxaban is not recommended due to a > two-fold increase in drug exposure.[65,66] The AHA/ACC/HRS Guidelines suggested that NOACs are not recommended in patients with severe hepatic dysfunction and hepatic function should occasionally be monitored for the use of factor Xa inhibitors.[4] Besides, annual monitoring of liver function should be done in patients treated with NOACs[66,67] (*Figure 1*).

Conclusions

Advanced CKD and CLD in AF patients are associated with increased risks of bleeding and thrombosis. Moreover, the altered kidney and liver functions may complicate the metabolism and clearance of NOACs, leading to the concern of drug accumulation and bleeding risk. Based on the limited data from subgroup analyses of RCTs and real-world cohort studies, NOACs might be an acceptable choice in light of comparable efficacy and possibly better safety compared to warfarin. Besides, accurate estimation of renal function using the CG formula is recommended for dosing of NOACs. Furthermore, the status of liver function impairment as determined by the Child-Pugh classification is pivotal for choosing NOACs. For patients with CLD and receiving NOACs, regular monitoring of liver function is mandatory. There is an urgent need for large-scale RCTs to provide solid data weighing efficacy from safety in this vulnerable population.

Funding

This work was supported in part by grants from the Ministry of Science and Technology (MOST 107-2314-B-075-062-MY3), Taipei Veterans General Hospital (V108B-015, V108B-027, V108C-090, V109C-042, and V109C-186), the Research Foundation of Cardiovascular Medicine, and the Szu-Yuan Research Foundation of Internal Medicine, Taipei, Taiwan. This paper was published as part of a supplement financially supported by Daiichi Sankyo Europe GmbH.

Conflict of interest: none declared.

Data availability

All data shown in this review article were adopted from published studies with corresponding citations.

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