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Review

When anticoagulation management in atrial fibrillation becomes difficult: Focus on chronic kidney disease, coagulation disorders, and cancer

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ABSTRACT

Anticoagulation therapy (AT) is fundamental in atrial fibrillation (AF) treatment but poses challenges in implementation, especially in AF populations with elevated thromboembolic and bleeding risks. Current guidelines emphasize the need to estimate and balance thrombosis and bleeding risks for all potential candidates of antithrombotic therapy. However, administering oral AT raises concerns in specific populations, such as those with chronic kidney disease (CKD), coagulation disorders, and cancer due to lack of robust data. These groups, excluded from large direct oral anticoagulants trials, rely on observational studies, prompting physicians to adopt individualized management strategies based on case-specific evaluations. The scarcity of evidence and specific guidelines underline the need for a tailored approach, emphasizing regular reassessment of risk factors and anticoagulation drug doses. This narrative review aims to summarize evidence and recommendations for challenging AF clinical scenarios, particularly in the long-term management of AT for patients with CKD, coagulation disorders, and cancer.

1. Introduction

Patients with atrial fibrillation (AF) have a 5-fold higher risk of stroke [1]. AF-related strokes are more severe than non-AF strokes, causing greater neurological disability and mortality [2]. Although anticoagulation therapy (AT) is the cornerstone of treatment in AF, its implementation in everyday clinical practice is challenging, especially in specific AF populations with high thromboembolic and bleeding risks (Fig. 1). Current guidelines recommend estimating and balancing the risk of thrombosis and bleeding in all patients who are candidates for antithrombotic therapy. In the case of AF, AT with direct oral anticoagulants (DOACs) is the standard of care [3,4] and has been proven effective and safe in the long-term management of the arrhythmia.

However, there are specific populations in which the administration of oral AT raises concerns [5–7]. For example, AT therapy in patients with chronic kidney disease (CKD), coagulation disorders, and cancer remains a real dilemma in daily clinical practice [8,9]. These patients are largely excluded from the large randomized trials of DOACs, and the available data comes mainly from observational studies, while physicians frequently apply individualized management based on a case-by-case evaluation.

This narrative review aims to summarize the available evidence and recommendations in difficult AF clinical scenarios concerning the long-term management of AT in patients with CKD, coagulation disorders, and cancer.

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2. Chronic kidney disease

AF is common among CKD patients, as this arrhythmia occurs in one in five CKD non-dialysis patients and one in three dialysis patients [10]. Also, the lower estimated glomerular filtration rate (eGFR), the higher the incidence of AF. According to a cohort study of 235,818 patients, the prevalence of AF increased by 57% when eGFR is lower than <30 ml/ min/1.73 m^2, in contrast to eGFR 30–59 ml/ min/1.73 m^2, where the AF prevalence increased only by 32%. Conversely, AF was associated with the development of kidney disease. The same cohort study included patients who had already AF. These patients had lower eGFR in comparison with those without AF and during the follow-up period, 3.3% developed kidney function decline and 4.9% proteinuria [11].

This bidirectional relationship between kidney disease and AF explains why these two conditions often co-exist and multiple pathogenetic mechanisms have been proposed. Kidney dysfunction predispose to both hypercoagulable and bleeding diathesis and CKD patients are at increased risk of stroke, coronary syndrome, deep vein thrombosis, bleeding manifestation, and death. Uremic toxins lead to both prothrombotic and bleeding diathesis, as a result of changes in hemostatic mechanism [12]. For example, uremia-induced cerebral microbleed can cause intracerebral hemorrhage and stroke. Focal deposit of hemosiderin is another pathophysiological mechanism for cerebrovascular events in patients with CKD. Common risk factors, like hypertension, diabetes mellitus and dyslipidemia, are met in both stroke and CKD. Also increased levels and activity of pro-inflammatory factors, like CRP, interleukin-6, TNF, factor VII, VIII, IX-XII, homocysteine, von Willebrand factor, fibrinogen etc. are responsible for hypercoagulable states [13]. In addition, clot lysis time is prolonged in dialysis patients, and specifically in peritoneal dialysis patients. Not only CKD patients, but also kidney transplant recipients have increased levels of pro-inflammatory factors, so these patients even after kidney transplantation are still at high risk for pro-thrombotic major and minor complications [14]. Bleeding manifestation in patients with CKD is a result of multiple mechanisms, involving platelet dysfunction and impaired interaction between platelet and endothelium [12]. It is a common knowledge that AF is a risk factor for stroke and death. AF in CKD patients is associated with a greater risk of stroke, heart failure, end-stage renal disease and death [13].

The options for oral anticoagulant drugs for stroke prevention in AF are vitamin-K antagonists (VKAs) and DOACs. VKAs are cleared mostly by the liver [15]. DOACs are partly renally cleared (dabigatran 80%, edoxaban 50%, rivaroxaban 33% and apixaban 27%) [16]. In CKD patients, CHA_2DS_2-VASc and HAS-BLED scores for stroke and bleeding risk assessment, respectively, can be used, but a careful balance between thromboembolic and bleeding complications is necessary [17].

Warfarin, which is not renally excreted, could be a good option, but as renal function declines, it is more difficult to achieve an international normalized ratio (INR) between 2 and 3 and these patients are more prone to bleeding [15]. In addition, warfarin is associated with more major bleeding complications, including intracranial hemorrhage, when compared to DOACs in the randomized controlled trials (RCTs) RE-LY, ARISTOTLE, ROCKET-AF and ENGANGE-AF-TIMI 48 [18–21].

Another recently recognized problem is warfarin's harmful effect on renal function, so-called anticoagulant-related nephropathy (ARN). ARN is an acute kidney injury of unknown origin in a patient receiving anticoagulants, which is usually present within the first two months after starting anticoagulant drugs. Although there are cases of DOACs-related ARN, most data focus on warfarin [22]. Patients who suffer from systemic lupus erythematosus, IgA nephropathy, diabetic nephropathy, postinfectious nephritis, nephrosclerosis, and segmental glomerulosclerosis have a higher risk for ARN [23]. Other risk factors, like age, sex, body weight, CKD, and concomitant use of CYP3A4 inhibitors, may play different roles depending on the prescribed anticoagulant drug (warfarin or DOACs) [24]. In a retrospective cohort study from Taiwan, dabigatran, even though it is excreted primarily from the kidneys, was associated with fewer ARN episodes compared to warfarin in patients with or without CKD [25]. Similar results about apixaban and rivaroxaban in comparison to warfarin came from a second retrospective study from Taiwan [26]. Data about edoxaban are limited; use of this latest DOAC does not appear to cause kidney dysfunction [23].

2.1. *Management of CKD patients with eGFR 30–59 ml/min/1.73 m^2*

Patients with CKD stage 3 and AF are at higher risk for thromboembolic and bleeding manifestations compared to patients who have normal kidney function and AF [27]. RCTs enrolled patients with normal eGFR and patients with eGFR 30–59 ml/min /1.73 m^2 (for

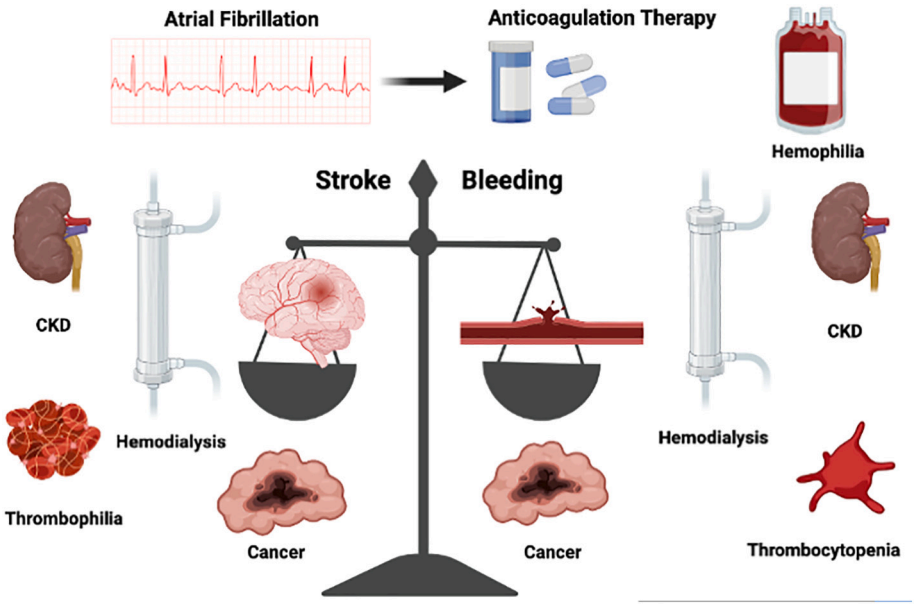

Fig. 1. When anticoagulation management in atrial fibrillation (AF) becomes difficult. Balancing the risks of stroke and bleeding in AF patients. CKD: Chronic kidney disease.

ARISTOTLE eGFR >25 ml/min /1.73 m^2) [18–21]. A recent Swedish study of real-world AF/CKD patients showed a gradual increase in DOACs use, especially for mild and moderate CKD [28]. As mentioned above, dabigatran is associated with high percentage of renal excretion, which raises concerns in moderate-severe CKD patients. Whereby, apixaban could be a better and safer option for these patients [29]. In addition, a study of patients with normal and mildly reduced kidney function (eGFR ≥50 ml/min/1.73 m^2) claimed that rivaroxaban reduced the rate of renal decline in comparison with warfarin [30]. The same outcomes have been reported by other studies [31,32] (Table 1). Dose reduction criteria based on renal function should also be applied and Cockcroft-Gault (CG) formula was used to calculate eGFR in RCTs of DOACs. Other equations for eGFR calculation are Modified Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas. Data from a multicenter cohort study of 39,239 patients in Taiwan support the use of CG rather than MDRD and CKD-EPI, after a comprehensive comparison between differences of eGFRs after using this 3 eGFRs formulas and subsequent changes on DOACs dosages and clinical findings. MDRD and CKD-EPI equations lead to DOACS mainly overdosing, especially for patients aged >75 years and weighted <50 kg. Moreover, regular follow-up of kidney function is required in order to change the dose. An inappropriately dose reduction could increase thromboembolic risk, while conversely, a high dose of an anticoagulant could increase bleeding complications [3].

2.2. Management of CKD patients with eGFR 15–29 ml / min / 1.73 m^2

Patients at stage 4 CKD (eGFR: 15–29 ml/min / 1.73 m^2) were excluded from all major DOACs RCTs, except for the ARISTOTLE trial, which included patients with an eGFR between 25 and 29 ml/min/1.73 m^2, hence the management of patients with AF and severe renal failure is difficult [18–21]. In addition, these patients have a greater thromboembolic and bleeding risk compared to those with mild and moderate renal disease. Most authors recommend an individualized approach balancing risks and benefits of anticoagulant therapy, as there are no RCTs-derived data for this patient category. If the HAS-BLED score is 2 or greater, AT may be omitted [10,33]. When the decision for anticoagulation is made, the next step concerns the type of oral anticoagulation. Although there is limited safety and efficacy data about DOACs in patients with eGFR <30 ml/min/1.73 m^2, low doses of apixaban, edoxaban, and rivaroxaban have been approved in both Europe, and the United States of America [3,34]. In addition, for these patients, only the U.S. Food and Drug Administration (FDA) has approved the use of 75 mg b.i.d. dabigatran [34].

During recent years, the use of DOACs has progressively increased in patients with CKD stage 4, a group previously treated exclusively with VKAs. A UK survey published in 2023 concerning the prescribing practice in CKD patients showed a clear preference for DOACs over warfarin, and apixaban was the most commonly prescribed DOAC in AF patients with CKD stage 4 [35]. A closer collaboration among cardiologists and nephrologists is necessary as eGFR declines and RCTs-derived data are lacking. Nevertheless, a physician-based survey among European Heart Rhythm Association (EHRA) and European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) revealed the suboptimal collaboration among cardiologists and nephrologists in the management of AF/CKD patients. In respect to anticoagulation treatment, estimation of thromboembolic risk, and shared decision-making instead of bleeding risk calculation was observed in CKD patients. The final choice and dosing of the anticoagulant drug was of great range, not only across CKD stages, but also among specialities [36].It is also crucial to avoid VKA in patients, who are at high risk for vascular calcification, calciphylaxis, and glomerular or other hemorrhage [10].

One meta-analysis of 43,850 patients and retrospective studies including individuals with eGFR <30 ml/min/1.73m^2 confirmed significantly fewer major bleeding events with DOACs compared to warfarin [31,37]. In addition, a subanalysis of ARISTOTLE trial compared apixaban with warfarin in patients with 25 to 30 ml/min/1.73 m^2 and showed that apixaban presents a better safety profile, as it caused less bleeding complications. Moreover, bleeding episodes were fewer in these patients compared to those with eGFR >30 ml/min/1.73 m^2 [38]. In respect to renal complications in patients with CKD stage 3 and 4, XARENO study, favored rivaroxaban. In this prospective study, 1455 AF patients with an eGFR between 15 and 49 ml/min/1.73m^2 were included. Rivaroxaban was the treatment of choice for 764 patients and the rest of them received VKA. Adverse renal outcomes (progression to stage 5, need for chronic dialysis and acute kidney injury), as well as net clinical benefit (stroke/embolism, acute coronary syndromes, major bleeding, and cardiovascular death) were examined. After a 2,1-year follow up period, treatment with rivaroxaban was associated with less adverse renal events (HR: 0.62; 95% CI: 0.43–0.88) and lower all-cause mortality (HR 0.76; 95% CI: 0.59–0.98) [39].

When warfarin is the treatment of choice, a lower dose is required for patients with advanced renal disease (stages 4 and 5) to achieve an INR between 2 and 3 [40]. DOACs seem like a feasible option for patients with AF and CKD at stage 4, but an individual approach after a discussion among cardiologists and nephrologists is recommended in order to avoid major bleeding complications.

Table 1
Summary of cohort studies regarding renal events after rivaroxaban and warfarin treatment in patients with atrial fibrillation.

First author, year	Study design	Sample size	CKD stage ml/min/ 1.73m^2	Comparison	Endpoints	Findings
Coleman, 2019 [31]	Cohort study	72,599	>15	-Rivaroxaban vs Warfarin	-AKI -Progression to stage 5 or dialysis	Favours Rivaroxaban
González-Pérez, 2022 [30]	Cohort study	11,652	≥50	-Rivaroxaban 20 mg vs Warfarin	-Doubling serum creatinine - ≥ 30% decline in eGFR -Progression to ESRD	Favours Rivaroxaban
Vaitsiakhovich, 2022 [32]	Cohort study	7368	>15	-Rivaroxaban 15 mg vs Warfarin	-kidney function worsening	Favours Rivaroxaban
Kreutz, 2024 (XARENO) [39]	Cohort study	1455	3–4 (eGFR <49 ml/min/ 1.73m^2)	Rivaroxaban vs VKA	-AKI -Progression to stage 5 or dialysis -Stroke -Systemic Embolism -Major bleeding -ACS -Cardiovascular death	-Favours Rivaroxaban *(Lower incidence of adverse kidney events)*

AKI: Acute Kidney Injury; eGFR: estimated glomerular filtration rate; ESRD: End-stage renal disease; VKA: Vitamin K antagonist; ACS: Acute Coronary Syndrome

2.3. Management of CKD patients with eGFR ≤ 15 ml/ min/ 1.73 m^2 and dialysis patients

Patients with an eGFR lower than 15 ml/min/1.73 m^2 (stage 5 CKD) are considered to have end-stage renal disease (ESRD). As mentioned above, there are no RCTs concerning patients with an eGFR <25–30 ml/ min /1.73 m^2 and the effect of DOACs or VKA on those patients. Both ESRD and dialysis patients have the highest ischemic and bleeding risk among CKD patients. In addition, the lack of RCT-derived data supporting the benefit over the risk of anticoagulants in this patient population poses more challenges in the management of CKD stage 5. Although, data concerning the use of risk scores (e.g., CHA_2DS_2-VASc and HAS-BLED) in these patients are limited, there are a few cohort studies that confirm the similar predictive ability in comparison to the general AF As in CKD stage 4, an individualized approach using these two risk scores is necessary before introducing an anticoagulant treatment [41]. At the moment, DOACs are not recommended for patients with AF and CKD stage 5 in Europe [3]. In contrast, the FDA has approved the use of the full dose of apixaban (5 mg b.i.d.) and rivaroxaban 15 mg for ESRD and on dialysis patients [42].

Recent American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline for diagnosis and management of AF recommends warfarin or evidence-based dose of apixaban for oral anticoagulation in AF patients with ESRD or on dialysis (Class IIb) [34]. However, robust data concerning the appropriate dose of DOACS are still missing. A study concerning apixaban pharmacokinetics at steady state in hemodialysis patients demonstrated that achieved drug exposure at dose of 2.5 mg b.i.d. is comparable with 5 mg b.i.d in patients without renal failure. Moreover, a dose of 5 mg b.i.d. in dialysis patients resulted in supratherapeutic levels [43]. Kidney Disease Improving Global Outcomes (KDIGO) guideline for CKD and arrythmias underlined the aforementioned considerations about appropriate apixaban dose and the safety rule “first do not harm” in ESRD [44]. A recent study of 4313 AF patients with stage 4 and 5 CKD compared 2.5 and 5 mg b.i.d. of apixaban and found that the full dose is associated with more bleeding events without a decrease in embolic episodes or death [45].

Data concerning VKAs are also conflicting. A retrospective cohort study from 2014 demonstrated that VKAs were associated with a significantly lower risk of all-cause mortality among dialysis patients [46]. On the other hand, a subsequent meta-analysis including 37,349 dialysis patients with AF failed to prove a benefit of warfarin on stroke protection and mortality. Moreover, warfarin was associated with an increased risk of major hemorrhage [47]. A second meta-analysis of 71,877 dialysis patients published in 2020 also showed that AT did not lead to a reduction of thromboembolism risk in this patient population, and the oral anticoagulants warfarin, rivaroxaban, and dabigatran presented a higher bleeding risk in dialysis patients than apixaban and no anticoagulant [48]. It is known that calculation of Time in Therapeutic range (TTR) is necessary for the assessment of the efficacy of VKA and TTR ≥ 70% is considered as an optimal anticoagulation management. TTR is affected by VKA dose, possible drug-drug interactions, and patient's comorbidities. TTR control is more difficult to achieve in CKD patients on VKA. According to a Swedish cohort study of 7738 newly diagnosed AF patients on warfarin, poor TTR control was independently associated with low eGFR and as eGFR declines, the percentage of TTR declines too. The most common adverse outcome was death, followed by non- hemorrhagic stroke. Also, TTR ≥ 70% is associated with less adverse events, even if advance renal dysfunction is present [49].

RCTs concerning patients with advanced kidney failure are required in order to choose among DOACs, VKAs, and no anticoagulation. Unfortunately, RENAL-AF, a PROBE (prospective randomized open blinded end point) study comparing apixaban 5 mg/2.5 mg b.i.d vs. warfarin in AF patients on dialysis had a premature termination due to enrollment issues [50]. AXADIA-AFNET 8, also a PROBE study with recruitment issues, finally randomized a total of 97 AF/ dialysis patients to apixaban 2.5 mg b.i.d or phenprocoumon. Safety and efficacy outcomes were similar between these two anticoagulants and both patient groups presented a high percentage of cardiovascular events [51]. Evidence from ongoing trials or trials in the recruiting phase will elucidate this difficult clinical scenario [e.g., AVKDIAL,DANWARD, SACK and SAFE-D] [16].

2.4. Management of kidney transplant recipients

Kidney transplantation is another gray area where the adequate DOAC dose needs to be selected according to renal function and possible interactions with immunosuppressive medication [29].

This patient group was also excluded from RCTs; hence, there are no specific guidelines for the management of AT. Like CKD patients, they are facing a high ischemic and bleeding risk. As mentioned above, AF in kidney transplant recipients increases graft loss and stroke incidences, as well as mortality. However, a greater risk may arise from immunosuppression and possible interactions between anticoagulants and immunosuppressants [52,53].

Warfarin is the most commonly used anticoagulant drug, but lately, DOACs are being prescribed to an increasing number of kidney transplant recipients. Calcineurin inhibitors (CNIs) are the most important immunosuppressants for renal transplantation, and they block a large number of metabolizing enzymes and drug transporters, which are used by DOACs; therefore, interactions between these two drug categories are not impossible. A recent study brings to light positive results about the safety and efficacy of rivaroxaban and apixaban in patients with a history of kidney transplantation and AF and no significant drug interactions were recorded [54–56]. At present, there are no RCTs studying drug-drug interactions between DOACs and immunosuppressants, like CNIs, tacrolimus, and ciclosporin. Close monitoring of these patients is necessary in order to prevent serious complications following AF and AT. Table 2 summarizes studies regarding AT in AF patients with severely impaired renal function or kidney transplant recipients AF patients.

3. Coagulopathies

3.1. Thrombocytopenia

Thrombocytopenia is defined as a platelet count below 150 × 10^9 /l, which is associated with a higher risk of death in general population [57]. Although thrombocytopenic AF patients also display a high mortality rate, this fact may be attributed to the severe comorbidities of this group of patients rather than thrombocytopenia per se [58]. One large registry and an observational retrospective cohort shows that a lower platelet count is associated with a significantly lower risk for subsequent stroke (Hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.40–0.80, $p = 0.002$) and higher bleeding risk [59,60]. In contrast, VTE-thrombocytopenic patients appear to have a high thrombotic risk [61,62].

There is no safe cutoff above which anticoagulation is harmless in thrombocytopenic patients. The cut-off of platelet count in large, randomized studies comparing DOACs with VKAs in AF was below 100 × 10^9 /l (ENGAGE TIMI 48 [21], ARISTOTLE [20], and RE-LY [18] for edoxaban, apixaban, and dabigatran, respectively) and below 90 × 10^9 /l (ROCKET AF [19] for rivaroxaban). Given the lack of evidence, an individualized approach conducted by a multidisciplinary team with close monitoring of platelet count is advised. Thrombocytopenic patients treated with VKAs display a greater risk of minor bleeding complications with a higher tendency for major bleeding than normal subjects, whereas the ischemic risk is similar [63]. In addition, a recent study by Iyengar et al. [64] showed that oral anticoagulation in thrombocytopenic AF patients significantly increased the risk of clinically relevant and major bleeding compared to normal patients (24.5 vs 16.7 % P =0.005 and 13.3 vs 5.7 % , P < 0.001, respectively). Moreover, in a retrospective study of 8239 AF patients, DOAC therapy in thrombocytopenic patients is associated with a lower risk of major bleeding

Table 2
Summary of studies regarding anticoagulation therapy in atrial fibrillation patients with severely impaired renal function or kidney transplant recipients.

First author, year	Study design	Sample size	CKD stage	Comparison	Endpoints	Findings
Granger, 2011 (ARISTOTLE) [20]	RCT	18,201	≥ 4 (eGFR >25 ml/min/ 1.73m^2)	Apixaban vs warfarin	-Stroke or Embolism -Bleeding -Death	Favours apixaban
Nochaiwong, 2016 [47]	Meta-analysis	37,349	dialysis	Warfarin vs no warfarin therapy	-Stroke or Embolism -Bleeding -All-cause death	Favours no warfarin therapy
Mavrakanas, 2017 [43]	Cohort study	7	dialysis	Apixaban 2.5 mg b.i.d. vs 5 mg b.i.d	-Apixaban Pharmacokinetics at steady state patients	Favours apixaban 2.5 mg b.i.d. (apixaban 5 mg b.i.d leads to supratherapeutic levels)
Chokesuwattanaskul, 2018 [56]	Meta-analysis	43,850 4–5 dialysis		Apixaban vs warfarin	-Stroke or Embolism -Bleeding	Favours apixaban
Siontis, 2018 [42]	Cohort study	25,523	dialysis	Apixaban vs warfarin	-Stroke or Embolism -Bleeding (major, gastrointestinal, intracranial) -Death	Favours apixaban (*a dose of 5 mg b.i.d offers greater protection against thromboembolic events)*
Coleman, 2019 [31]	Cohort study	72,599	Normal kidney function or CKD1–4	Rivaroxaban vs warfarin	-AKI -Progression to stage 5 or dialysis	Favours rivaroxaban
Kuno, 2020 [48]	Meta-analysis	71,877	dialysis	- Apixaban 5 mg b.i.d vs apixaban 2.5 mg b.i.d vs no-anticoagulant *(Stroke or Embolism & All-cause death*) - Apixaban 5 mg b.i.d vs apixaban 2.5 mg b.i.d vs rivaroxaban vs dabigatran vs no-anticoagulant *(Major bleeding)*	-Stroke or Embolism -Major Bleeding -All-cause death	Favours: -No OACs for stroke prevention. -Apixaban 5 mg for lower risk mortality. -Apixaban and no anticoagulant for major bleeding prevention.
Bixby, 2020 [122]	Cohort study	197	Kidney Transplant Recipients	DOACs vs warfarin	-Major bleeding -Thromboembolic events	-Favours apixaban *(Lower incidence of bleeding compared to all other OACs, but no statistically difference between DOACs and warfarin)*
Parker, 2021 [55]	Cohort study	31	Kidney Transplant Recipients	Apixaban vs Rivaroxaban vs Edoxaban	-DOAC levels -CNIs levels -Thrombotic events -Bleeding events	-Favours Apixaban and Rivaroxaban - Limited data regarding edoxaban
De Vriese, 2021 (Valkyrie Study) [123]	RCT	132	dialysis	VKA (INR 2–3) vs Rivaroxaban 10 mg vs VKA + vitamin K2	-Stroke -Cardiovascular events -Major/minor bleeding -Gastrointestinal bleeding	-Favours rivaroxaban 10 mg
Reinecke,2023 (AXADIA-AFNET-8) [51]	RCT	97	dialysis	VKA (INR 2–3) vs apixaban 2.5 mg bid	-Ischemic stroke -all-cause of death -myocardial infarction -DVT/P.E. - Major/minor bleeding	-No differences in efficacy and safety points of apixaban compared to VKA
Xu, 2023 [45]	Cohort study	4313	4–5 (non-dialysis)	Apixaban 5 mg b.i.d. vs 2.5 mg b.i.d.	-Stroke -Systemic Embolism -Death -Bleeding	-Favours apixaban 2.5 mg *(Lower incidence of bleeding, no difference in risk of stroke/systemic embolism and death)*
Kreutz, 2024 (XARENO) [39]	Cohort study	1455	3–4 (eGFR <49 ml/min/ 1.73m^2)	Rivaroxaban vs VKA	-AKI -Progression to stage 5 or dialysis -Stroke -Systemic Embolism -Major bleeding -ACS -Cardiovascular death	-Favours Rivaroxaban *(Lower incidence of adverse kidney events and lower all-cause mortality)*

eGFR: estimated glomerular filtration rate; RCT: Randomized Controlled Trial; DOAC: Direct Oral Anticoagulant; OAC: Oral anticoagulant; AKI: Acute Kidney Injury; CNI: Calcineurin inhibitors; b.i.d.: twice a day; VKA: Vitamin K antagonist

compared to warfarin (aHR 0.45, 95% CI 0.16–1.14) [65]. In a recent retrospective cohort study [66] including AF patients with thrombocytopenia and/or anemia, the subgroup of patients with low platelet count (<100 × 10^9 /l) treated with DOACs showed no difference in intracranial hemorrhage or major bleeding compared to no oral anticoagulant (non-OAC) treated thrombocytopenic patients. Conversely, the composite risk of ischemic stroke /systemic embolism or intracranial hemorrhage was lower in DOACs group compared to non-OAC group. However, in case of thrombocytopenia with concomitant anemia (Hb <10 mg /dl), there was no difference between DOACs and non-OAC treated patients. Data regarding the safety of these agents in patients with lower platelet counts is derived mainly from trials of DOACs in the treatment of cancer related VTE [67–69]. Janion-Sadowska et al. [70], in a small prospective trial found no difference between AF patients with mild thrombocytopenia (50–100 × 10 ^{9}/l) on reduced dose of anticoagulants (apixaban 2.5 mg bid, dabigatran 110 mg bid, rivaroxaban 15 mg od) and the AF patients with a normal platelet count on the recommended doses of the DOACs. No significant difference in major

Table 3
Summary of studies regarding the use of anticoagulants in atrial fibrillation patients with thrombocytopenia.

Author/year/ (REF)	Study design	Sample size	Platelet count ($x10^9$/l)	Anticoagulation	Comparison	Outcomes	Findings
Lai et al.,2017 [63]	Cohort	137	<100	Warfarin	Thrombopenic patients in warfarin vs normal subjects in warfarin	BleedingThrombosis	Higher bleeding risk in group with thrombocytopenia
Caro et al,2018 [124]	Case series		50	Warfarin			No major bleeding, thrombosis
			58	Rivaroxaban			No major bleeding, thrombosis
			46	Warfarin			No major bleeding, thrombosis
Janion-Sadowska et al.,2018 [70]	Cohort	62	50–100	Rivaroxaban 15 mg OD (33%)/Dabigatran 110 mg BID (54,3%)/ apixaban 2,5 mg BID (11,7%)	Reduced doses of DOACs in trombopenic patients vs recommended doses in normal patients	Major bleeding,CRNMB, Death	Reduced doses are safe and effective
Wang et al., 2019 [65]	Cohort	367	<100	DOACs (181 pts), warfarin (186 pts)	DOACs vs warfarin	IS/SE, major bleeding, death	Lower tendency in major bleeding in DOACs group
Michowitz et al., 2019 [60]	Cohort	1617	<150	DOACs (712 pts), warfarin (905 pts)	DOACs vs warfarin	Mortality, Myocardial infraction, TIA/CVA, bleeding SE	Favours DOACs
Yeh et al.,2022 [66]	Cohort (37,094 AF pts)	1665	<100	DOACs Warfarin No OACs	DOACs vs No OACs	IS/SE, Intracranial hemorrhage, Major bleeding	Favours DOACs
		849	<100 (Concomitant anemia Hb < 10 mg/ dl)	DOACs Warfarin No OACs	DOACs vs No OACs	IS/SE, Intracranial hemorrhage, Major bleeding	No difference
Xu et al, 2023 [141]	Cohort	154	<100	Rivaroxaban, Dabigatran	Rivaroxaban vs Dabigatran	Total bleeding, major bleeding, minor bleeding, thrombois, major bleeding or thrombosis	No significant difference
Iyengar et al.,2023 [64]	Cohort	1070	<100	Warfarin (47,8%)DOACs (52,2%)	Bleeding rates between thrombocytopenic and normal pts. who began oral anticoagulation	Major bleeding,CRNMB	Increased risk of CRB at the time of starting

DOAC: DirectOral Anticoagulants; OAC: Oral anticoagulants; OD: once daily; BID: twice a day; pts: patients; IS: Ischemic Stroke; SE: Systematic embolism; TIA: Transient ischemic attack; CVA: Cerebrovascular accident; CRNMB: Clinically relevant non-major bleeding; CRB: Clinically relevant bleeding; Hb: Hemoglobin.

bleeding and thrombosis was reported in a recent study between rivaroxaban and dabigatran in thrombocytopenic AF patients [141] (Table 3).

In the EHRA practical guide [29] consideration of half dose DOACs in patients with a platelet count between 20-50 $\times$ 10^9 especially if a bleeding risk factor coexist, and the avoidance of them below the cutoff of 20 $\times$ 10^9 platelets. Rivaroxaban is the most studied agent in the setting of heparin induced thrombocytopenia, and although large-scale trials are lacking it seems to be an effective treatment strategy [71].

3.2. Hemophilia

Hemophilia is an inherited bleeding disorder caused by mutations in genes encoding coagulation factor VIII and factor IX (Hemophilia A and B respectively). Given the advances in treatment of these patients and the consequential life prolongation, the coexistence of hemophilia with age related cardiovascular diseases such as AF is inevitable. In a large European cohort of hemophiliacs, the prevalence of AF was found to be 3,4% in patients older than 60 years old [72] while in a recent observational study the prevalence was 2,3% [73]. Although CVD risk seems to be lower in hemophilia patients especially in those with severe deficiency of coagulation factor [74], there are no data supporting the ultimate protection of hemophiliacs from embolic events. However, there is a paucity of evidence-based guidelines concerning AT in patients with hemophilia. Antithrombotic treatment is based on consensus and expert opinions [75–78].

The HAS-BLED score [79] is thought to underestimate the bleeding risk in hemophiliacs, not including parameters such as the severity of the disease and the presence of inhibitors, although a recent study demonstrates the association between HAS-BLED >3 and increased bleeding risk [80]. Algorithms incorporate baseline FVIII/FIX levels as an estimation of the bleeding risk [75–78].

AT was considered safe in the presence of FVIII/FIX trough levels $\geq$30% [75,76,78]. However, in COCHE study [80] no significant difference in bleeding events found between hemophiliacs with basal FVIII/FIX levels $\geq$20% and the control group. The more recent algorithm proposed by Schutgens at al [81], recommends AT to hemophiliacs with basal FVIII/FIX levels $\geq$20% and CHA_2DS_2-$VAS_C \geq 2$. In patients with severe hemophilia, endogenous thrombin potentials are analogous to those of patients in VKAs [82]. Therefore, in severe deficiency FVIII/FIX levels (< 1%) anticoagulation is not recommended regardless of the ischemic risk. Patients with FVIII/FIX levels 1–19% or patients with severe disease under FVIII/IX prophylaxis are candidates for ablation or low dose aspirin if CHA_2DS_2-$VAS_C \geq 4$. In the presence of an inhibitor, AT should be avoided [75].

In general, DOACs are preferred over VKAs due to their superior safety profile [83]. There are limited data regarding the use of DOACs in hemophiliacs. The successful use of reduced doses of apixaban (2,5 mg BID) [84], rivaroxaban (10 mg O.D.) [85] and low doses of dabigatran (110 mg BID) [125,126] have been reported in AF ablation and left atrial appendage occlusion (Table 4).

Table 4
Summary of case reports regarding the use of anticoagulants in patients with atrial fibrillation (AF) and hemophilia who underwent left atrial appendage occlusion and/or AF ablation.

Author /year/(REF)	Patient age	Severity of hemophilia	Procedure	Anticoagulant -duration of treatment	Coagulation replacement	Outcome
Van Der Valk et al, 2019 [126]	70	Mild HA	Catheter ablation	VKA 3 months/Dabigatran 110 mg BID	FVIII level > 20% while on anticoagulants	Post-procedure severe anemia
	72	Severe HA	Catheter ablation	VKA 1 month SAPT with aspirin 2 months	FVIII level > 20% while on anticoagulants	Post-procedure severe anemia
	59	Mild HA	Catheter ablation	Dabigatran 110 mg BID	FVIII level > 20% while on anticoagulants	No compications
	50	Severe HA	Catheter ablation	VKA 6 weeks	FVIII level > 20% while on anticoagulants	No complications
	55	Mild HA	Catheter ablation	Dabigatran 110 mg BID 6 weeks	FVIII level > 20% while on anticoagulants	No complications
Santoro et al., 2021 [84]	56	moderate HB	LAA closure	Apixaban 2,5 mg BID / 5 months	eftrenonacog alfa	No bleeding complications
Serrano et al., 2021 [125]	61	mild HA	Cryoablation	Dabigatran 110 mg BID /2 months	Prophylactic rFVIII	No bleedings
Kramer et al., 2021 [85]	65	HA -FVIII 38%	LAA closure	Rivaroxaban 10 mg(Pre-procedural)	FVIII: 30 IU/kg	No complications
	74	HA – FVIII 30%	LAA closure	Apixaban 2.5 mg BID	FVIII: 30 IU/kg	No compications

HA: Hemophilia A; BID: twice a day; LAA: Left Atrial Appendage; REF: Reference; rFVIII: recombinant factor VIII; VKA: Vitamin K antagonist; SAPT: Single antiplatelet therapy. HB: Hemophilia B.

3.3. Thrombophilia

Management of oral anticoagulation in patients with AF and thrombophilia may be challenging [86]. Although the efficacy and safety of DOACs in patients with AF have well been established, guidelines on the management of patients with concomitant thrombophilia are lacking due to limited data.

The efficacy and safety of DOACs in patients with inherited thrombophilia are described in several cohorts. Due to the lack of evidence of the use of DOACs in AF patients, the data regarding the use of DOACs come from the prevention of VTE. The START2 registry [87] included 446 thrombophilic patients among 4866 patients with acute VTE. In this subgroup, no difference was found in major bleeding [3 (1.1%) vs. 3 (1.8%)] or thrombotic events [3 (1.1%) vs. 1 (0.6%)] between DOACs and conventional anticoagulant therapy. Serrao et al. [86], documented no thromboembolic or bleeding events in major thrombophilic patients with acute VTE, treated with DOACs, in the median follow up period of 29 months. In 2020, a prospective cohort study by Campello et al. [88] demonstrated a lower 2-year VTE recurrence risk after discontinuation of anticoagulation in patients with inherited thrombophilia treated with DOACs versus heparin/VKA therapy (HR, 0.61 [95% CI, 0.47–0.82]).

Table 5
Summary of studies regarding the anticoagulation therapy in patients with thrombophilia in the era of DOACs.

Author /year/(REF)	Study design	Sample size	Type of thrombophilia	Comparison	Outcomes	Findings
Dufrost et al.,2018 [127]	Metanalysis	477	APS	DOACS (rivaroxaban 290 pts-dabigatran 144 pts-apixaban 13 pts) versus warfarin	VTE recurrences	Favours warfarin especially in triple positive group of patients
Pengo et al.,2018 [89](TRAPS)	Randomized trial	120	APS (Triple positive)	Rivaroxaban (59 pts) vs warfarin (61 pts)	Thromboembolic events, Major bleeding, Vascular death	Favours warfarin
Serao et al.,2019 [86]	Cohort	45	Major thrombophilia	DOACs`	Hemorrhagic /thrombotic complications	No events-median follow up 29 months
Malec et al. 2019 [128]	Cohort	172	APS	DOACs vs warfarin	VTE, cerebrovascular ischemic events,myocardial infraction, CRNMB	Favours warfarin
Ordi-Ros et al. 2019 [90]	Randomized trial	190	APS	Rivaroxaban vs VKA	Major bleeding, thrombosis	Favours VKA
Margaglione et al.,2020 [87] (START2 registry)	Cohort	446 (Subgroup of 4866 VTE pts)	Inherited thrombophilia	DOACs vs heparin and VKA	Bleeding/Thrombosis	Favours DOACs
Pengo et al., 2021] (TRAPS- 2 years outcomes) [129]	Cohort	115	APS (Triple positive)	DOACs vs warfarin	Thromboembolic events, Major bleeding, Vascular death	Favours warfarin
Franke et al., 2022 [95]	Retrospective cohort	200	APS	DOACs (119 pts) vs VKA (81 pts)	Recurrent thromboembolism	No difference
Woller et al., 2022 [91]	Randomized trial	48	APS	Apixaban (23 pts) vs warfarin (25 pts)	Arterial/Venous Thrombosis Vascular Death Bleedng	Favours warfarin
Campelo et al.,2023 [88]	Cohort	577	Inherited thrombophilia	DOACS (255 pts) vs Heparine and VKAs (322 pts)cs	-VTE recurrence-bleeding complications-residual vein thrombosis-VTE reccurence after discontinuation of anticoagulant	Lower 2-year risk of VTE recurrence after discontinuation in DOACs group

APS: Antiphospholipid syndrome; VKA: Vitamin K Antagonists; DOAC: DirectOral Anticoagulant; VTE: Venous Thromboembolism; pts:patients; CRNMB: Clinically relevant non-major Bleeding.

Moreover, the use of DOACs in patients with antiphospholipid syndrome (APS) is controversial. According to an RCT, which was published in 2018, treatment with rivaroxaban in patients with triple positivity [lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2-glycoprotein-I (aβ2-GPI)] is associated with higher thrombotic risk versus warfarin [89]. Another RCT, published one year later, did not show the noninferiority of rivaroxaban versus VKA in APS patients [90]. Apixaban has also been tested in an RCT of 48 APS patients. This study ended prematurely and supports the use of warfarin over apixaban for prevention of recurrent thrombotic episodes [91].

Therefore, the 2019 ESC [92] and 2020 ASH [93] VTE guidelines recommend against the use of DOACs in APS patients. However, 2020 ISTH guidance [94] suggested the discrimination of the APS phenotype and considering DOACs as a possible option in non-high-risk APS patients with specific characteristics such as INR instability, inability of INR monitoring, or severe adverse events of VKA treatment. Additionally, Franke et al. [95] in a recent retrospective study showed that DOACs might be a safe choice in low-risk APS patients. (Table 5).

Importantly, the pathophysiology of thrombosis in the setting of APS is not well understood and is driven by a great release of thrombin, tissue factor, and an increased activation of multiple coagulation factors. The efficacy of DOACs is questioned as their selective mechanism of action may provide inadequate protection in patients suffering from antiphospholipid syndrome. Until robust data are available, VKA is the standard of care unless allergy, intolerance, or suboptimal control exists.

4. Anticoagulation management for AF in oncology patients

4.1. Epidemiology and pathophysiology

Evidence derived from large cohorts supports a potent connection between AF and cancer, as there is an increased incidence of AF in patients with a recent diagnosis of malignancy and vice versa [96,97]. Patients with newly diagnosed or active cancer face a 4.4 times higher risk of developing AF during the first year of diagnosis [98] whereas, there is a higher risk of cancer in patients with a recent AF diagnosis, particularly during the first 3 months of AF onset, identifying AF as a potential marker of occult cancer [98]. Several mechanisms have been suggested as possible causes or triggers for the pathogenesis of AF in patients with cancer, including a primary cardiac tumor, metastatic disease in the heart or adjacent tissues, as well as paraneoplastic syndromes [99] (Fig. 2). Furthermore, several anticancer drug categories, such as alkylating agents, anthracyclines, antimetabolites, taxanes, bruton kinase inhibitors, BCR-Abl inhibitors, proteasome inhibitors, immune checkpoint inhibitors, and immunomodulatory agents have been associated with the induction of AF [100–102].

4.2. Challenges in anticoagulation management

Patients with AF and cancer present a higher thrombotic risk compared to those without cancer, due to various characteristics of different cancer types, as well as the administration of antineoplastic therapies [103]. At the same time, some cancer types including leukemia, myeloma, lymphoma, liver and pancreatic cancer are followed by greater risk of major bleeding in patients with AF requiring a careful bleeding risk stratification, according to evidence derived from meta-analyses and databases [104,105]. Scores and algorithms that are widely recommended and used for the estimation of thromboembolic and hemorrhagic risk in the general AF population have not been validated for patients with cancer and AF. The CHA_2DS_2VASc score may underestimate the actual thromboembolic risk [106]. Oncology patients with AF, and CHA2DS2-VASc score 0 (men) or 1 (women) may be considered for therapeutic anticoagulation after assessment of the bleeding risk, according to current ESC Guidelines on cardio-oncology, as they may face a higher thrombotic risk than patients without cancer [107]. Additionally, the HAS-BLED score, used for the estimation of bleeding risk may differ between AF patients with and without cancer, as it seems to underrate this risk in patients with cancer and AF [108]. A retrospective cohort study including 399,344 hospitalized patients with cancer and AF investigated and compared the predictive role of different bleeding risk scores. The HAS-BLED score performed better than others for intracranial bleeding prediction, while the ORBIT score showed the best predictivity for major bleeding and gastrointestinal bleeding [105].

Data from the EORP-AF General Long-Term Registry support that patients with cancer and AF had a sub-optimal level of adherence to Atrial Fibrillation Better Care (ABC) pathway, associated with higher risk of adverse events [109]. Furthermore, the scarcity of evidence regarding the efficacy and safety of the available anticoagulants due to

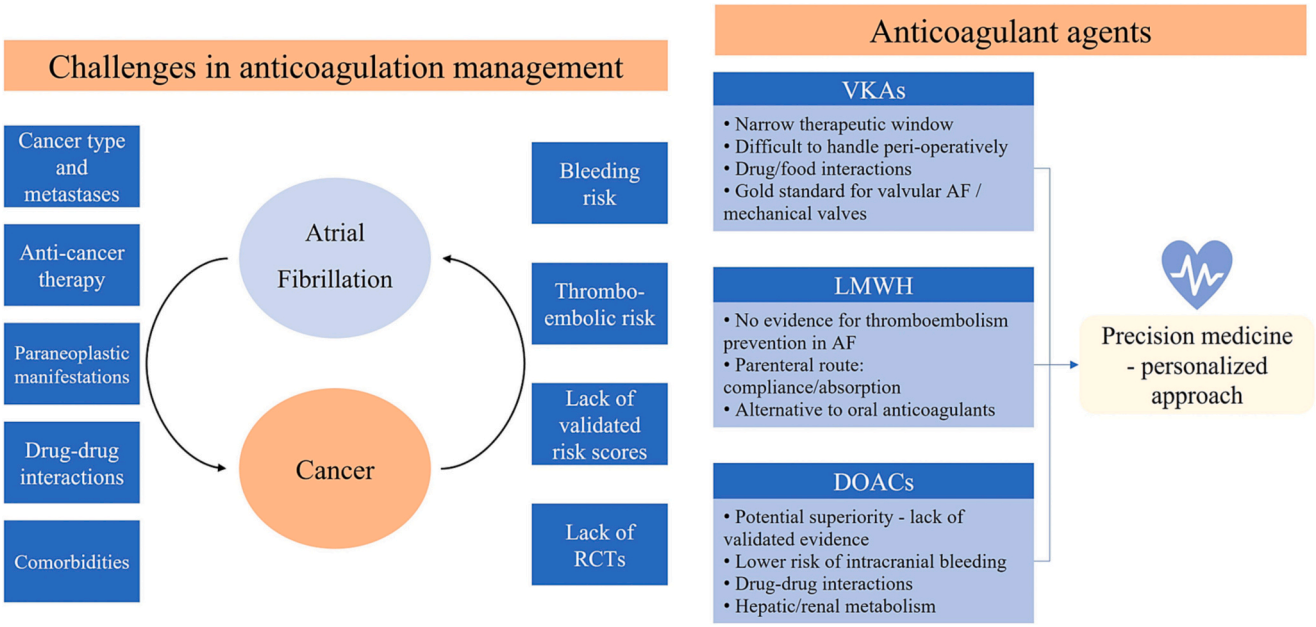

Fig. 2. Overview of atrial fibrillation anticoagulation management in oncology patients.
AF: Atrial fibrillation; RCT: Randomized Controlled Trials; VKA: Vitamin K antagonist; DOAC: Direct oral anticoagulant; LMWH: Low-molecular weight heparin.

the lack of RCTs [3] complicate the management of AT in the setting of AF and cancer and add an important challenge to decision-making [110] (Fig. 2).

4.3. Anticoagulation agents in cancer

4.3.1. Vitamin K antagonists (VKAs)

The use of VKAs in the setting of cancer is accompanied by many challenges, as they are associated with several risks that may affect patients with cancer. First of all, they present multiple food and drug-drug interactions with many widely used chemotherapeutics and other medications, as they share common metabolic pathways with certain drugs. Several antineoplastic therapies, such as fluoropyrimidines and tamoxifen inhibit the metabolism of warfarin, so co-administration with them should be avoided. A moderate degree of interaction has been reported between warfarin and other cytotoxic agents, such as carboplatin, vincristine, doxorubicin, and tyrosin kinase inhibitors, such as ibrutinib; therefore, a high level of awareness should be present [100,111]. VKAs also have a narrow therapeutic window, making it difficult to achieve optimal time in therapeutic range (TTR), while peri-operative handling is also challenging. Furthermore, intolerance to these agents due to cancer complications such as vomiting, malnutrition, and hepatic dysfunction is a common phenomenon in oncologic patients [111]. Finally, the risk of intracranial bleeding is higher compared with other anticoagulants; therefore, their use should be avoided in patients with brain cancer or metastases [110]. According to Ording et al., warfarin remains the most widely used anticoagulant between patients with AF and cancer, however discontinuation and switching rates are higher for those using warfarin than DOACs [112].

4.3.2. Low-molecular weight heparin (LMWH)

There is significant experience with the use of LMWH in the primary

Table 6
Overview of studies comparing DOACs vs. warfarin regarding thromboembolism, bleeding complications and mortality in AF patients with cancer.

First author, year[ref]	Study design	Country	Population (n)	Follow up (y)	DOACs compared	Most common cancer type	Efficacy outcomes	Safety outcomes	Findings
Melloni, 2017 [116]	Post hoc analysis (ARISTOTLE trial)	International, multicenter	1236	1.8	A	Prostate	IS/SE, MI, all-cause mortality	Major[a] and all bleeding	NS difference
Ording, 2017 [130]	Retrospective cohort study	Denmark	11,855	1	NA	Urological	Thromboembolic complications	Bleeding complications	NS difference
Fanola, 2018 [117]	Post hoc analysis (ENGAGE AF-TIMI 48 trial)	International, multicenter	1153	2.8	E	GI	IS/SE, MI, all-cause and CV mortality	Major[a] and all bleeding	NS difference
Kim, 2018 [131]	Retrospective cohort study	Korea	776	1.8	A, D, R	Gastric	IS/SE, all-cause mortality	Major[a] bleeding	Favours DOACs
Sawant, 2018 [132]	Retrospective cohort study	USA	196,521	1	A, D, R	NA	IS, all-cause mortality	Major[a] bleeding	Favours DOACs in all cause-mortality and major bleeding, NS difference in IS
Shah, 2018 [133]	Retrospective cohort study	USA	16,096	1	A, D, R	Genitourinary	IS	Major[a] bleeding	NS difference in IS, Favours A in major bleeding
Chen, 2019 [115]	Post hoc analysis (ROCKET AF trial)	International, multicenter	640	1.9	R	Prostate	IS/SE, MI, all-cause and CV mortality	Major[a] and all bleeding	NS difference
Yasui, 2019 [134]	Retrospective cohort study	Japan	224	1	A, D, E, R	GI	IS/SE	Major[a] bleeding	NS difference
Wu, 2020 [135]	Retrospective cohort study	Taiwan	672	0.5 and 1	A, D, E, R	NA	IS/SE, MI, all-cause mortality	Major[a] bleeding	Favours DOACs in IS/SE, major bleeding, NS difference in MI, GI bleeding, all-cause mortality
Chan, 2021 [136]	Retrospective cohort study	Taiwan	7955	1.45/ 1.73[b]	A, D, E, R	GI	IS/SE, MI	Major[a] bleeding	Favours DOACs
Deitelzweig, 2021 [137] [ref	Retrospective cohort study	USA	40,271	0.6–0.8	A, D, R	Prostate	IS/SE	Major[a] bleeding	Favours A in IS/SE and major bleeding
Ording, 2021 [138]	Retrospective study	Denmark	2128	12	A, D, E, R	Colorectal	NA	GI bleeding	NS difference
Mehta, 2022 [139]	Retrospective cohort study	USA	7675	NA	A, D, R	NA	IS/SE, MI, all-cause and CV mortality	Major[a] bleeding	NS difference in IS/SE, MI and CV mortality, Favours DOACs in all-cause mortality
Potter, 2022 [140]	Retrospective cohort study	USA	1133	4.1	A, D, E, R	Hematologic	IS, all-cause mortality	Major[a] bleeding	NS difference

A: apixaban; CV: cardiovascular; D: dabigatran; E: edoxaban; GI: gastrointestinal; ICH: intracranial hemorrhage; IS: ischemic stroke; MI: myocardial infraction; n: number; NA: Not available; NS: not significant; R: rivaroxaban; Ref: reference; SE: systemic embolism; vs: versus; y: years.

[a] Major bleeding includes any ICH, GI bleeding, hemorrhagic stroke, blood transfusion, admission for any bleeding, life-threatening bleeding or vital organ hemorrhage.

[b] For patients treated with DOACs and warfarin respectively.

and secondary prevention of venous thromboembolism (VTE) in oncology patients [9], being the preferred choice for a long time [3,113]; however there is no clear evidence on their effectiveness in patients with AF [113]. LMWH has some essential characteristics, including anti-tumor, anti-metastatic, and anti-angiogenic properties, while the parenteral route of administration does not affect their absorption by cancer complications. Moreover, they are often used as periprocedural bridging, while they lack major interactions with antineoplastic medications [110].

4.3.3. Direct oral anticoagulants (DOACs)

The net clinical benefit of DOACs in patients with active cancer and venous thromboembolism was found to be similar or more favorable than usual anticoagulation (VKAs or LMWH) in a recent meta-analysis [114]. Currently, DOACs are recommended as the first-line therapy for stroke and systemic embolism prevention in the general AF population, as they present similar rates of efficacy and lower rates of intracranial bleeding compared to VKAs [3]. However, recommendations from guidelines cannot be extended to AF patients with cancer due to the underrepresentation of these patients in landmark clinical trials. The percentage of patients with a history of cancer in ROCKET-AF was 4.5% [115], in ARISTOTLE 6.6% of enrolled patients had a history of malignancy [116], while patients with cancer were excluded in RE-LY and ENGAGE-AF trials [18,117].

Two published meta-analyses, including data from post-hoc analyses of randomized trials, along with observational retrospective data, support the notion that DOACs are associated with lower or similar rates of thromboembolic and bleeding events in oncology patients with "non-valvular AF". These results remain consistent among patients with active cancer [118,119]. Similarly, the meta-analysis of Casula et al. [120] including only randomized data, demonstrated that DOACs have similar efficacy and a safer profile than warfarin in cancer patients with AF. Table 6 summarizes the studies comparing DOACs to VKAs in cancer patients with AF. In a retrospective database analysis by Lin et al., assessing the mortality outcomes in oncology patients with AF, those who received dabigatran were associated with lower risks of cancer-related death, all-cause mortality and major bleeding compared to rivaroxaban study arm [121].

On the other hand, DOACs have some notable interactions with anticancer medications. Dabigatran is a substrate for P-glycoprotein, and the co-administration with other medications that are potent inhibitors or inducers of that enzyme should be avoided. Additionally, rivaroxaban and apixaban are also metabolized by cytochrome P450 (CYP3A4) and should be prescribed with caution along with other inducers or inhibitors of that cytochrome [100,111]. Moreover, DOACs have variable degrees of renal clearance, so their activity may be affected in patients with impaired renal function. These agents are administered orally, therefore, they may have unpredictable absorption by the gastrointestinal track as a result of cancer complications [100,102].

5. Conclusions and future considerations

There are clinical scenarios in AF management where the decision about the long-term administration of AT is difficult and challenging. In particular, the long-term administration of AT in AF patients with end-stage kidney diseases, coagulation disorders, and cancer is not currently supported by robust data. AT in these populations is of great interest, and the clinicians should balance the thromboembolic and bleeding risks, while a case-by-case evaluation is applied in most cases. The relationship between cancer and AF appears to be bidirectional, as these two conditions share common risk factors and pathophysiological mechanisms. The scarcity of evidence and specific guidelines indicate a personalized approach in each patient, based on cancer type, particular treatments, thromboembolic and hemorrhagic risk, comorbidities, and other individualized characteristics. RCTs are needed to assess the safety and effectiveness of new oral anticoagulation agents in patients with severe CKD and coagulation disorders. Individualized management is essential, with regular reassessment of risk factors and anticoagulation drugs doses. Since new evidence has become available (e.g. new anticoagulation agents), clinicians should be prepared to adapt their daily clinical practice in the future settings of AT. Future research and more clinical trials with better design and methodology should be conducted in order to establish an optimal management algorithm in that heterogeneous clinical setting.

Practice points

- AF is common among CKD patients, as this arrhythmia occurs in one in five CKD non-dialysis patients and one in three dialysis patients. The lower the eGFR, the higher the incidence of AF.
- Dose reduction criteria based on renal function should be applied in CKD patients and Cockcroft-Gault (CG) formula should used to calculate eGFR.
- In stage 4 CKD patients, most authors recommend an individualized approach balancing risks and benefits of anticoagulant therapy, as there are no RCTs-derived data for this patient category.
- Both end-stage renal disease and dialysis patients have the highest ischemic and bleeding risk among CKD patients. RCT-derived data supporting the benefit over the risk of anticoagulants in this patient population is lacking.
- Kidney transplantation is another gray area where the adequate DOAC dose needs to be selected according to renal function and possible interactions with immunosuppressive medication.
- There is no safe cutoff above which anticoagulation is harmless in thrombocytopenic patients. A half dose DOACs in patients with a platelet count between 20-50 $\times$ 10^9 especially if a bleeding risk factor coexist, and the avoidance of them below the cutoff of 20 $\times$ 10^9 platelets should be considered.
- Although cardiovascular risk seems to be lower in hemophilia patients especially in those with severe deficiency of coagulation factor, there are no data supporting the ultimate protection of hemophiliacs from embolic events. In general, DOACs are preferred over VKAs due to their superior safety profile. There are limited data regarding the use of DOACs in hemophiliacs.
- Guidelines on the management of AF patients with concomitant thrombophilia are lacking due to limited data. The use of DOACs in patients with antiphospholipid syndrome (APS) is controversial.
- Scores and algorithms that are widely recommended and used for the estimation of thromboembolic and hemorrhagic risk in the general AF population have not been validated for patients with cancer and AF.

Research agenda

- RCTs regarding the AT in severe CKD (stage 4 or 5) patients.
- RCTs to prove the efficacy and safety of AT in dialysis patients.
- Robust data to establish the possible drug-drug interactions between immunosuppressant drugs and AT.
- Establish the precise safety cut-off of platelets for administering AT.
- Large RCTs to study the safety and efficacy of DOACs in patients with hemophilia and thrombophilia.
- Drug-drug interactions between cancer-related therapies and DOACs. Safety and efficacy of DOACs in among different types of cancer.

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