REVIEW ARTICLE

Oral anticoagulation in patients with active cancer and atrial fibrillation: current challenges

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ABSTRACT

Atrial fibrillation and cancer are common comorbidities. Given an increased risk of arterial thrombosis caused by the former and an increased risk of bleeding in patients with the latter, the management of anticoagulation in patients in whom they coexist is complex. On the basis of generally low-quality evidence, numerous documents have been published in the past 3 years providing practice points for physicians to offer the best treatment plan to their patients. The present review begins with a summary of these recommendations and then proceeds to outline 9 practical challenges that fit into the larger questions of when and in whom anticoagulation is indicated, and what is the best agent in patients with atrial fibrillation and active cancer. For each of these 9 challenges, the evidence available is presented, the author's personal practical advice is given and the most pressing need to move the field forward is stated. I conclude by emphasizing the need for high-quality evidence and, more practically, by stressing 1) the importance of patient preference and values in the decision on whether and how to anticoagulate, and 2) the need for periodic reassessment of the benefits of anticoagulation with changes in cancer status and treatment plan.

Introduction Patients with active cancer have an increased risk of thromboembolic events. The risk of venous thromboembolism (VTE) is increased 4- to 8-fold in patients with cancer[1,2] while the risk of stroke and myocardial infarction is 2-fold higher.[3] Importantly, the incidence of these thromboembolic events varies widely within the population of patients with cancer. It is the highest in the most aggressive malignancies, with high tumor burden and metastatic disease, and the lowest in patients with less aggressive cancers as well as in disease-free patients in whom the risk of stroke may be similar to that of the general population.[3-6] The risk of bleeding is also increased in patients with cancer because of local barrier disruption, thrombocytopenia, disseminated intravascular coagulation, and frequent invasive procedures. Patients with cancer also frequently require anticoagulation because of the high incidence of VTE. In patients with cancer receiving anticoagulation, the incidence of major bleeding can be up to 10% per year.[7-10]

Atrial fibrillation (AF) and cancer are both frequent comorbidities and they appear to be associated with each other to some extent.[11-13] This is partially because of the shared risk factors and increased medical surveillance and testing that come with the diagnostic workup of either, but there may be causal connections between the two. Atrial fibrillation increases the risk of thrombotic events, particularly stroke, and often requires anticoagulation.[14,15] Given the high bleeding risk and difficulties in anticoagulation of patients with active cancer, the coexistence of both conditions is of high clinical complexity. This is compounded by the fact that the risk of stroke in patients with AF and active cancer is not clearly increased over those in patients with AF in the general population.[16,17] Although studies have shown somewhat inconsistent results, likely due to different inclusion criteria and study populations, the totality of evidence indicates that, if the risk of cardioembolic stroke is increased, the effect size is very small[9,16-25] and far smaller than the increase in the risk of bleeding. This state of affairs leads to uncertainty regarding the clinical benefit of anticoagulation in patients with AF and cancer. Furthermore, the evidence to support anticoagulation recommendations in this clinical setting is weak, as there have been no randomized trials and very few prospective studies to guide these decisions. Nevertheless, in the last few months,

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several authors and societies have offered guidance for these patients and their physicians. They are outlined in TABLE 1.[14,25-34]

This review aims to present some of the challenges of anticoagulant treatment in patients with AF and active cancer, examine the evidence behind the most relevant questions, and determine the needs in each area. It does not deal with the epidemiology of AF and stroke in patients with cancer or with the biological basis of the increased thromboembolic risk in patients with cancer. These topics have been recently reviewed elsewhere.[13,29,30,35,36]

Assessment of stroke and bleeding risk in patients with cancer and atrial fibrillation

How should stroke risk be assessed in patients with active cancer and atrial fibrillation? In the general population, there is a widespread consensus in the use of the CHA_2DS_2VASc score to determine the risk of stroke.[14,15] Neither the CHA_2DS_2VASc nor any other score have been prospectively validated in patients with active cancer and AF. Yet, although not uniformly, retrospective data[16,18,19,22,37] largely support an increase in stroke risk with an increasing CHA_2DS_2VASc score. Similarly, patients with a CHA_2DS_2VASc score 0 to 1 are at a low risk of stroke, which is in line with the idea that strokes in patients with AF and cancer have a similar mechanism to that in the general population (predominantly due to cardioembolism)[38] and that cancer is not a major contributor to stroke risk in patients with AF. Data from the Mayo Clinic, in some of the largest available single-center studies of patients with cancer and AF, show a 1.2-fold increase in the risk of stroke per 1-point increase in the CHA_2DS_2VASc (and 1.4-fold per 1-point increase in the $CHADS_2$).[19,37] There is also evidence that, similar to the general population, patients with cancer and AF with a low CHA_2DS_2VASc-score do not benefit from anticoagulation, while those with a high CHA_2DS_2VASc score do so.[39] One likely caveat to this consideration is that, as argued in the section below entitled Does stroke risk depend on whether AF was present at baseline?, CHA_2DS_2VASc may be accurate in patients with AF already present at the time of cancer diagnosis but not necessarily in AF diagnosed after cancer.[18,40]

Conclusion and future needs There are no risk scores specific to patients with active cancer and AF, and the CHA_2DS_2VASc should be used to assess stroke risk,[34,41] particularly when AF was already present at the time of cancer diagnosis. However, prospective validation studies, preferable with a parallel goal of assessing other risk factors that may be relevant in patients with cancer, are needed.

Should cancer or cancer type be considered a risk factor for stroke? The risk of stroke in patients with cancer is higher than in the general population.[3,4,42] This has led some authors to suggest that cancer should be added to the CHA_2DS_2VASc score, but there is no evidence that the CHA_2DS_2VASc + cancer status predicts stroke better than the CHA_2DS_2VASc alone in patients with AF. The increase in stroke risk in patients with cancer seems to be due to strokes of unclear mechanism (which are presumably due to hypercoagulability)[4,43-45] and there is no solid evidence to support the idea that patients with AF and active cancer have a clinically relevant increase in stroke over those with AF but no cancer.[16,17,20-23,36] Furthermore, the Khorana score, which predicts VTE, does not seem to predict ischemic stroke in patients with cancer and AF.[37] Perhaps as importantly, it is unlikely that all cancers increase the risk of stroke to the same extent and that they do so at all stages of the disease. Regarding the former, stroke risk is not increased in all cancers, particularly the least aggressive ones.[3,5] Some of the most common cancers, that is, breast and prostate cancer, are associated with only a very small or no increase in stroke.[3,42,46] Regarding the latter, patients with metastatic cancer or with a recent diagnosis of cancer have a higher risk of stroke than those that are disease-free.[3,4,42,47-50] Therefore, the claim that cancer (ie, all and any cancer) should be added to the CHA_2DS_2VASc is a simplistic one and should be nuanced before any serious proposals are put forward.

Conclusion and future needs There is no consistent evidence that cancer increases stroke risk in patients with AF. It is unlikely that a potentially small increase associated with cancer would make a clinically relevant difference in patients with AF, in whom standard cardioembolism (unrelated to cancer-associated hypercoagulability) is likely to cause a majority of strokes.

Does stroke risk depend on whether atrial fibrillation was present at baseline? The published evidence suggests that AF present at the time of cancer diagnosis (baseline AF) behaves similarly to AF in the general population. Aside from the indirect evidence provided by the predictive power of the CHA_2DS_2VASc score in patients with cancer,[18,19,39] there is also indirect evidence from randomized trials. A post-hoc substudy of the ENGAGE AF-TIMI48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial, which randomized patients with AF to edoxaban or warfarin, compared the 2 drugs in patients with active cancer developed (or recurring) after randomization. The incidence of stroke and systemic embolism in each treatment arm was similar in patients with cancer and in those without cancer (1.43% per year and 1.58% per year, respectively, in the high-dose edoxaban arm and 2.38% per year and 1.77% per year, respectively, in the warfarin arm).[51]

Contrary to baseline AF, AF diagnosed after the diagnosis of cancer (new-onset AF) is often secondary to a specific stressor, such as anemia, sepsis, or hypoxia.[29,35] In the general population,

secondary AF unquestionably increases the risk of early death while it is unclear to what extent the risk of stroke is increased; it likely depends on many variables, including the specific triggering event.[52-57] In patients with cancer, the relationship between new-onset AF and early death has also been consistently reported.[29,40,58-60] In one study, 24% of patients with cancer and new-onset AF who sought care in the emergency room died within 4 weeks.[58] In another study, 7 out of 16 patients (43%) with non-Hodgkin lymphoma who developed AF died with in 3 weeks.[40] In this same study, patients with secondary AF had higher mortality than those with primary new-onset AF. There is no data on the risk of AF recurrence and risk of stroke in patients with cancer and secondary AF.

Conclusion and future needs Secondary AF seems to indicate a high risk of early death in patients with active cancer. It is unclear what are the mid- to long-term implications of a time-limited episode of secondary AF in patients with cancer so a longer follow-up of these patients is needed to know the risk of AF recurrence and stroke.

How should hemorrhagic risk be assessed in patients with cancer and atrial fibrillation? Patients with active cancer have a high risk of bleeding derived from local barrier disruption, surgery and other procedures, thrombocytopenia due to therapy or bone marrow metastases, and frequent anticoagulation due to a high incidence of thromboembolism. Several risk factors for bleeding are known in these patients. The presence of gastrointestinal mass, history of hemorrhage, low platelet count or antiplatelet drug use, age, frailty, metastatic disease (particularly in the bone marrow), anemia, renal failure, and surgery increase bleeding risk.[8,61-63] However, no score has been convincingly validated in these patients and the effect sizes for each risk factor are inconsistent across studies, likely due to differences in the study population and endpoint definitions. Furthermore, these risk factors are often transient and are not included in bleeding scores developed and validated in the general population, such as the HAS-BLED, CHA_2DS_2VASc, and $HEMORR_2HAGES$ (the latter does include malignancy as a binary variable, although the role of cancer status is unclear). Therefore, these scores, which already have modest accuracy and little value in the general population,[14,34,64-66] are unlikely to be useful in predicting bleeding in patients with active cancer. Indeed, in line with this concept, D'Souza et al[16] showed that the predictive value of the CHA_2DS_2VASc score was very limited, with 2-year incidences of bleeding leading to hospitalization of 4.3%, 4.4%, and 6.8% in patients with CHA_2DS_2VASc of 0, 1, and 2 to 9, respectively, in a cohort of patients hospitalized with AF and with a history of recent (<5 years) cancer.

Conclusion and future needs While risk factors for bleeding in patients with cancer receiving anticoagulation are well established, there is no way to predict in which patients bleeding will occur. Rather than more observational studies determining even more risk factors and deriving bleeding risk scores, results from treatment protocols that include well-defined risk factors to make treatment decisions (such as the one my group or others have suggested)[26,29] are needed.

Challenges regarding anticoagulant treatment in patients with active cancer and atrial fibrillation

Which patients with atrial fibrillation and active cancer should receive anticoagulation? Generally, patients with AF should receive anticoagulation when the mortality and morbidity risk derived from ischemic stroke without anticoagulation overcomes that of the consequences of bleeding under anticoagulation. In the general population, patients with the CHA_2DS_2VASc score greater than 1 should generally be offered anticoagulation.[14,15] Bleeding risk should generally play no role in the decision because it is so correlated with stroke risk that even patients with a high bleeding risk derive a net benefit from anticoagulation. In patients with cancer, this concept seems to apply as well. Atterman et al[39] found that patients with AF and cancer derive the same benefit from anticoagulation (in terms of the composite endpoint of ischemic stroke or systemic embolism, major bleeding, and death) as patients with AF without cancer (hazard ratio for the composite outcome in anticoagulated vs not anticoagulated is 0.81 in both cancer and noncancer cohorts). This benefit was seen in patients with high, but not low, CHA_2DS_2VASc in both cohorts. Unlike patients without cancer, patients with cancer and intermediate CHA_2DS_2VASc also benefited from anticoagulation, a finding that aligns with a previous study suggesting that patients with cancer and AF with the CHA_2DS_2VASc score of 1 have a higher risk of stroke than those without cancer.[16]

As mentioned above, patients with cancer have specific bleeding risk factors. Their presence increases major bleeding risk much more than classic risk factors and does so often for a relatively short period of time. These factors are, furthermore, not strongly associated with stroke risk. Therefore, temporary withholding anticoagulation is likely beneficial for some patients with AF and cancer, even though this remains unproven. In an interesting study including more than 2000 patients with cancer and AF with almost 4 years of follow-up, Lee et al[47] reported that most ischemic and hemorrhagic events occurred within the first year after cancer diagnosis and that there were no outcome differences between patients who received and those who did not receive anticoagulation in this first year. The balance changed after the first year, when patients treated with anticoagulation (and with time in range >60%) had improved survival. While the specific results will vary based on the population included, it is likely that the net benefit of anticoagulation is dynamic in most populations with active cancer and

careful and periodic assessment of patient- and cancer-related factors have to be regarded. A relevant consideration, perceptively pointed out by Delluc et al,[28] is that before recommending against anticoagulation because of high bleeding risk under specific therapies, one should consider whether the benefits of anticoagulation could be greater than those of such antineoplastic therapies. They offer the example of adjuvant chemotherapy as the situation in which this question can most often come up. In such case, it should be discussed with the patient and the oncologist what are the potential downsides of omitting this therapy as compared with omitting anticoagulation for the period it would be administered.

Conversely, anticoagulation may not be warranted in some patients beyond stroke or bleeding risk assessment, such as for those with a short life expectancy,[67] for whom anticoagulation is likely not beneficial regardless of their score in any scoring system.

There is very little evidence in patients with cancer and mechanical heart valves, but Plaja et al[68] reported outcomes for 48 such patients (all treated with a vitamin K antagonist [VKA]) and a matched cohort of patients without cancer. In line with the evidence in AF, these patients did not have an increased risk of stroke or valve thrombosis. However, the incidence of major bleeding was high in the cancer cohort, particularly in relation to surgical procedures.

Conclusion and future needs While patients with cancer and no bleeding risk factors most likely benefit from anticoagulation similarly to the general population, some patients are unlikely to benefit at least at specific times in the course of their disease. In the absence of strong evidence and given the apparent dynamic nature of bleeding risk in patients with active cancer, our approach is to recommend against anticoagulation in patients with major risk factors, regardless of the CHA_2DS_2VASc (TABLE 1), and recommend anticoagulation in patients with a CHA_2DS_2VASc greater than 1 and no bleeding risk factors. In patients with minor risk factors for bleeding, our group recommends anticoagulation when the CHA_2DS_2VASc is very high.[26] Most importantly, however, this general recommendation is accompanied by 2 fundamental precepts. First, it should be accompanied by an in-depth discussion with the patient; given the lack of strong evidence, patient preferences should weigh heavily in the final recommendation. Secondly, the recommendation should be reassessed whenever there is a change in disease status, treatment plan, or other events in the course of the disease. Going forward, it is imperative that patients are treated within prospective protocols, particularly during periods when the net benefit of anticoagulation is more questionable, such as early after diagnosis of a gastrointestinal malignancy, patients with a history of bleeding, or when drugs inducing moderate to severe thrombocytopenia are administered. The results of these prospective protocols should guide clinical practice. Finally, the subset of patients with cancer and AF with a CHA_2DS_2VASc of 1 should also be closely scrutinized, as they may benefit from anticoagulation.[16,39]

Should the risk of venous thromboembolism play a role in recommending anticoagulation for atrial fibrillation? Some authors have pointed out that therapeutic anticoagulation may protect patients with active cancer and AF not only from cardioembolic stroke but also from VTE, the incidence of which is high in some subsets of patients with cancer.[69] Thus, the question has been raised of whether a high risk of VTE should be factored into the decision of offering anticoagulation to patients with cancer and AF.

The standard VTE prophylaxis warrants only prophylactic-dose anticoagulation, which is associated with a much lower risk of bleeding than therapeutic-dose anticoagulation.[10,70] Conversely, there is no evidence that prophylactic-dose anticoagulation is protective against cardioembolic stroke. Absent major risk factors and in the presence of a CHA_2DS_2VASc greater than 1, most patients with AF should be recommended therapeutic-dose anticoagulation. Our group finds it unlikely that the added benefit of VTE prevention would justify full-dose anticoagulation (over prophylactic-dose anticoagulation, which would already be recommended because of high risk of VTE) for patients in whom anticoagulation is not warranted for AF.

Conclusion and future needs A high-risk of VTE should not be used to offer full-dose anticoagulation to patients with cancer and AF in whom anticoagulation is not otherwise indicated. Given the complexity of the question (ie, does full-dose anticoagulation in patients with cancer, at high-risk of VTE, with AF but with no indication for full-dose anticoagulation offer a greater net benefit [prevention of stroke and venous thrombosis minus major bleeding, preferably weighted according to the clinical severity of each endpoint] than prophylactic-dose anticoagulation?) and the small differences expected in outcome, a randomized trial would be required to provide definitive answer. It is unlikely that this trial can be conducted, given the marginal potential gain (ie, it is unlikely that the effort required to launch it should be devoted to it, rather than to answering other more relevant questions), the very small target population, and the large sample size required.

Is there a place for treatment with a low-dose direct oral anticoagulant or lower-target international normalized ratio in atrial fibrillation and cancer? Undertreatment of AF, either in the form of no anticoagulation or in the use of an inappropriately low-dose direct oral anticoagulant (DOAC; a low dose in patients for whom a standard dose is approved) is a common practice in the general

TABLE 1 Outline of recommendations regarding anticoagulation in patients with atrial fibrillation and cancer

Author	Year	Indication for anticoagulation	Agent[a]
Farmakis et al[29]	2014	No anticoagulation if high bleeding risk (the authors mention intracranial tumor, hematologic malignancies with coagulation defects, thrombocytopenia, severe metastatic hepatic disease, etc). If no high bleeding risk features, anticoagulation recommended for $CHA_2DS_2VASc \geq 1$ and HAS-BLED <3, and optional for CHA_2DS_2VASc 0 or HAS-BLED ≥ 3.	VKA preferred (lack of data with LMWH and DOACs)
Zamorano et al[41] (ESC)	2016	$CHA_2DS_2VASc \geq 2$ and platelet count $>50\,000/\mu l$	VKA preferred
Tufano et al[33]	2018	–	LWMH often preferred. Among DOACs, dabigatran preferred due to the availability of a reversal agent.
Steffel et al[34] (EHRA)	2018	Based on CHA_2DS_2VASc and cancer- and treatment--related factors (type or site of cancer, liver metastases, coagulopathy, renal function, thrombocytopenia, surgery, among others mentioned)	VKAs are the standard of care, DOACs are a possible alternative (consider drug interactions and dose reductions or treatment interruption in thrombocytopenia, bleeding)
Sorigue and Miljkovic[26]	2019	Anticoagulation generally not recommended if major bleeding risk factors present (gastrointestinal mass, previous major bleeding, antiplatelet treatment, platelet count $<50\,000/\mu l$) and recommended for $CHA_2DS_2VASc > 5$ and 1 minor bleeding risk factor (age >80 y, metastatic disease, platelet count of 50 000–100 000/μl, glomerular filtration rate <30 ml/min/1.73m^2, drug interactions) and $CHA_2DS_2VASc > 1$ and no bleeding risk factors. Dynamic and periodic reassessment is essential.	If already receiving a DOAC or VKA at cancer diagnosis, likely continue the same agent (consider time in the therapeutic range, foreseen drug interactions). If anticoagulation is started anew, there is no evidence for DOAC as compared with VKA; base decisions on patient, cancer, and treatment features (Asian vs non-Asian, interactions, gastrointestinal mass, etc)
Chu et al[30]	2019	As in the general population	
Delluc et al[28] (ISTH)	2019	–	If already receiving a DOAC or VKA at cancer diagnosis, continue the same agent unless drug interactions are foreseen. If anticoagulation is started, DOACs are preferred unless drug interactions or gastrointestinal bleeding risk
Lopez-Fernandez et al[31] (Expert position paper)	2019	$CHA_2DS_2VASc \geq 2$ but consider bleeding risk (HASBLED). In complex patients, consider using ABC and $HEMORR_2HAGES$ scores.	DOACs are preferred. Consider drug interactions to choose the appropriate DOAC
Rhea et al[27]	2019	$CHA_2DS_2VASc \geq 2$ but consider cancer status, stage, response to treatment, and prognosis (if life expectancy <12 months or high bleeding risk); consider against anticoagulation	DOACs are generally preferred
Undas and Drabik[32]	2020	As in the general population	DOACs are preferred

This table aims to summarize a complex issue. The reader is referred to the original manuscripts for a nuanced recommendation and its justification.

a The agent preferred should be read keeping in mind the rapid changes in the field, as clinical practice data with DOAC in patients with cancer is rapidly accruing.

Almost all authors emphasize the need to individualize treatment (although what factors should be considered is not always specified) as well as the value of a multidisciplinary assessment of optimal treatment decisions.

Abbreviations: DOAC, direct oral anticoagulant; ESC, European Society of Cardiology; EHRA, European Heart Rhythm Association; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist

population, despite robust evidence of worse outcomes, that is, lower efficacy with no safety gains.[39,71,72] A diagnosis of cancer appears to increase the odds of receiving an inappropriately low dose of a DOAC[73] (as well as the odds of not receiving anticoagulation).[39] In a small retrospective study of patients with cancer and AF, a worryingly high incidence of anticoagulation failure was seen in patients treated with low-dose DOACs.[74]

Conclusion and future needs Inappropriately low--dose DOACs or low-target international normalized ratio (INR) should not be used as prevention of cardioembolic stroke. If anticoagulation is deemed appropriate, the approved DOAC doses and INR target should be used. Patients with cancer and AF in whom full-dose anticoagulation is deemed too risky due to the risk of bleeding are probably better off not receiving any therapeutic anticoagulation rather than inappropriately low doses (although prophylactic-dose anticoagulation may still be warranted for VTE prevention in some patients). While a clinical trial specific to patients with cancer could potentially settle this question definitively, previous data in the general population seem conclusive, and our group would not consider this an ideal use of resources.

What is the ideal anticoagulant agent for patients with cancer and atrial fibrillation? Today, VKAs and 4 DOACs are available for AF. The differences between the 2 classes are well known.

Based on data from randomized trials, DOACs are at least as effective as and safer than VKAs in the general population.[75] They are more convenient, as they require no monitoring[14] due to less drug and food interactions and a broader therapeutic window. Conversely, even when needed, they cannot be easily monitored. Efficacy data with both classes of agents in patients with cancer largely come from retrospective studies and post hoc subanalyses of randomized trials in the general population[50,51,76,77] while safety data are also available from randomized trials for cancer-associated VTE.[78-81] Overall, both VKAs and DOACs increase bleeding risk and appear to be similarly efficacious for stroke prevention in patients with cancer.[9,25,39,49-51,76,77,82] However, this comparative data are limited by the study designs. Most importantly, the concept of "patient with cancer" is heterogeneous across studies and often includes patients with cancer that is cured or in remission (or with unknown status), which have notably lower risks than patients with active cancer,[9,24] so data obtained in one should not inform the other. Similarly, patients with cancer differ in baseline characteristics from those without, patients who receive anticoagulation differ from those who do not, and those treated with DOACs differ from those treated with VKAs. This may lead to unreliable data, even with the use of methods to reduce bias, such as propensity score.[83,84]

With these caveats, data from studies on DOACs reveal a generally favorable safety profile. In line with results obtained in the general population, edoxaban and rivaroxaban seem to increase gastrointestinal bleeding,[9,25,28,76,79,80] while apixaban does not.[76,78,81] There is less data from patients with active cancer treated with dabigatran, although a large study reported similar results to those with rivaroxaban.[76] Importantly, some patient subsets remain understudied and DOACs may not be sufficiently tested as to be justified outside of a treatment protocol.[85] As in the general population, these include patients with renal failure or extreme body weights but in patients with cancer, this mainly involves treatment with drugs with potential interactions (see below: What direct oral anticoagulant–drug interactions are clinically relevant?).

While undoubtably less convenient, unlike DOACs, VKAs can be easily monitored, which can be an upside when facing potential drug interactions. Much has been made of the lower time in therapeutic range in patients with cancer, and indeed a large database study found cancer to be associated with a supratherapeutic INR,[86] but a single institution audit only showed a temporal 6% decrease in TTR that was of no clinical relevance.[21] Therefore, VKAs remain an acceptable therapeutic option in patients with cancer and AF.

Ultimately, with the limitations of the available data, DOACs and VKAs have similar efficacy and safety results.[22,47,48,50,51,76,77,87] The 2 classes have differential features (convenience, half-life, use in kidney failure, availability of reversal agents, drug interaction profile) that should be used to find the optimal agent for each patient. A possible exception are Asian patients, a population where DOACs appear consistently better than VKAs in those with cancer, consistent with the greater net benefit seen in Asians over non-Asians in the general population.[48,87,88]

In patients with cancer, in whom major bleeding is common, the availability of a reversal agent has been pointed to as a relevant consideration. Vitamin K antagonists have broadly available reversal agents (prothrombin complex concentrate or, less ideally, fresh frozen plasma).[89] Dabigatran has an approved reversal agent, idarucizumab,[90] although it is less widely available. Finally, the most recently approved reversal agent, andexanet alfa, approved for the reversal of anticoagulation in patients with major bleeding under treatment with apixaban and rivaroxaban, is not available in most institutions.[91] It should be noted, however, that there is no evidence that the use of idarucizumab and, particularly, andexanet alfa, offers better outcomes than supportive care and use of nonspecific reversal agents.

There are differences among DOACs. Twice-daily regimens have lower peak-trough variability[92] and this could potentially offer better results, even though there is no direct comparison between DOACs. Dabigatran at a dose of 150 mg twice a day is often considered the most efficacious option while apixaban (or dabigatran at a dose of 110 mg twice a day) has consistently shown the best safety profile.[93-97] Indirect comparisons suggest this is also the case in patients with cancer.[78-80] Conversely, twice-daily regimens are less convenient.

Low-molecular-weight heparin (LMWH) has not been investigated and is not approved for the treatment of AF.[34] In patients with cancer, LMWH is not safer than VKAs.[10]

Conclusion and future needs It is unlikely that either DOACs or VKAs are ideal for all patients, and specific patient-, cancer- and treatment-related factors should be assessed to make a decision. It is essential to discuss pros and cons with the patient. Our group concurs[26] with the International Society on Thrombosis and Haemostasis (ISTH) that one might want to continue the anticoagulant the patient was taking, if any, while DOACs are likely the first choice in patients who have to start anticoagulation and in whom no drug interactions are foreseen and gastrointestinal bleeding is not a concern.[28] The availability of a reversal agent is not a major consideration in our decision. If DOACs are chosen and the patient does not have a strong preference for a once-daily drug, our team favors twice-daily options (particularly apixaban, with which there is more evidence in patients with cancer than with dabigatran), because we hypothesize that the lower peak-trough variability could be clinically relevant in a population at a high bleeding risk such as patients

with cancer. Indirect comparisons do indicate greater safety with apixaban. Edoxaban can be the best option in some clinical setting because it is less dependent on CYP3A4 than the other anti-Xa, yet, unlike with dabigatran, some strong glycoprotein-P inhibitors can be concomitantly administered with dose adjustment.[98] Our team finds a very small role for LMWH in patients with cancer and AF, likely limited to persistent oral intolerance. If oral anticoagulation is not considered safe, one should consider withholding anticoagulation altogether before recommending LMWH.

Prospective data confirming the good early results with DOACs in patients not at risk for gastrointestinal bleeding are still needed. While our group does not expect a clinical trial comparing VKAs with DOAC or comparing different DOACs, there is a need for results of prospective treatment protocols, with well-defined parameters, that offer efficacy and safety data with each of the clinical options. This will help support decisions, particularly outside of large research institutions, which may already have protocols and where patients may routinely receive close specialized follow-up regarding their anticoagulation.

What direct oral anticoagulant–drug interactions are clinically relevant? There are fewer drug interactions with DOACs than VKA. However, unlike VKAs, these agents are dosed based on patient-specific variables rather than drug levels or activity. Therefore, while it is known that all DOACs (and dabigatran etexilate to a greater extent) are glycoprotein-P substrates and that apixaban and rivaroxaban are mainly metabolized through CYP3A4, the extent to which each DOAC interacts with each chemotherapeutic agent and the relevance of these interactions is not clear. In addition, determining drug concentration is not available in all institutions, or turnaround time may be slow. Finally, it has not been shown that modifying the dose of a DOAC to target a chosen concentration improves clinical outcomes.

Numerous documents have specified drugs that may interact with DOACs,[30-35,85,98-100] but most of these interactions are based on theoretical considerations or small studies on healthy volunteers. As a general rule, strong glycoprotein-P or CYP3A4 inducers or inhibitors should be avoided, because concomitant use may lead to significant alterations of DOAC concentrations. However, a majority of chemotherapy drugs are not strong glycoprotein-P or CYP3A4 inducers or inhibitors but rather have small to moderate effects. The effect they may have on DOAC concentrations, as well as the clinical relevance of that effect, is unknown.

So far, 4 randomized clinical trials have tested DOACs compared with LMWH for the treatment of cancer-associated VTE.[78-81] A large proportion of these patients received anticoagulation concomitantly with chemotherapy and the incidence of major bleeding has been reasonable in this population with a generally high bleeding risk. Therefore, many DOAC–chemotherapy interactions are likely not clinically relevant, but more robust evidence will be needed going forward.

Some may advocate for the use of laboratory tests to determine drug concentrations (ecarin clotting time or diluted thrombin time for dabigatran and anti-Xa activity for anti-Xa agents),[92] as concentrations close to the expected range can be reassuring. When this is not the case, one can potentially switch the DOAC or, less convincingly, change the dose to reach a target concentration.[34] However, none of these options are evidence based.

Conclusion and future needs Dabigatran should not be used concomitantly with strong glycoprotein-P inducers or inhibitors and apixaban and rivaroxaban with strong glycoprotein-P and CYP3A4 inducers or inhibitors. Edoxaban is less dependent on these metabolic pathways. When a clinically relevant interaction cannot be ruled out, VKAs with a close monitoring of INR should be considered. Alternatively, one can consider plasma testing for DOAC concentrations and verifying that levels are within the range reported in the general population.[34,92] Our team would not change the dose of a DOAC based on results but rather switch the anticoagulant if levels are not within the expected range. There is a need for pharmacokinetic data on the concomitant use of DOAC and mild or moderate glycoprotein-P and CYP3A4 inducers or inhibitors. Finally, efficacy and safety data focusing on specific patient subsets, including specific treatment regimens, are needed and likely to become available in upcoming years.

Summary and final conclusions The use of oral anticoagulation for stroke prevention in patients with AF and active cancer is challenging due to the mortality and morbidity associated with cardioembolic stroke and major bleeding. There is no solid data on how best to assess stroke or bleeding risk in these patients and, relatedly, on the decision of whether to recommend anticoagulation (and what agent to use). In this regard, we eagerly await the results of the ongoing Blitz-AFCancer registry, a prospective, international, observational study (ClinicalTrials.gov identifier, NCT03909386) collecting data on the management of patients with cancer and AF. The investigators aim to include 1500 patients and the study is expected to end in 2023. Our group hopes the results of this and other studies that may be published in the meantime will lead to solid treatment protocols. The present manuscript aimed to summarize the evidence available to date and what is needed to answer each of posed questions. In essence, retrospective data have been published but biases are likely to play a big role in the results reported and prospective data are urgently needed. Clinical trials would be desirable but few are likely to be conducted because of the sample size needed to establish efficacy data with an acceptable confidence as well as the heterogeneity of the "cancer" population.

However, the attention given to the question over the optimal treatment of AF in patients with cancer is growing, as is the number of cardio-oncology units within which these patients will be best cared for. In the next few years, prospective data will be available to help improve outcomes in these patients. Until then, the choices are based on low-quality evidence. Patient preferences and values should be particularly attended to and, regardless of the initial choice, the benefits and harms of anticoagulation and anticoagulants should be reassessed periodically.

ARTICLE INFORMATION

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REFERENCES

1 Cohen AT, Katholing A, Rietbrock S, et al. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer: a population-based cohort study. Thromb Haemost. 2017; 117: 57-65.

2 Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013; 122: 1712-1723.

3 Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. J Am Coll Cardiol. 2017; 70: 926-938.

4 Navi BB, Iadecola C. Ischemic stroke in cancer patients: a review of an underappreciated pathology. Ann Neurol. 2018; 83: 873-883.

5 Navi BB, Howard G, Howard VJ, et al. The risk of arterial thromboembolic events after cancer diagnosis. Res Pract Thromb Haemost. 2019; 3: 639-651.

6 Chen PC, Muo CH, Lee YT, et al. Lung cancer and incidence of stroke: a population-based cohort study. Stroke. 2011; 42: 3034-3039.

7 Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002; 100: 3484-3488.

8 Trujillo-Santos J, Nieto JA, Tiberio G, et al. Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost. 2008; 100: 435-439.

9 Vedovati MC, Giustozzi M, Verdecchia P, et al. Patients with cancer and atrial fibrillation treated with DOACs: a prospective cohort study. Int J Cardiol. 2018; 269: 152-157.

10 Posch F, Königsbrügge O, Zielinski C, et al. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res. 2015; 136: 582-589.

11 Hung YP, Hu YW, Liu CJ, et al. Risk and predictors of subsequent cancers of patients with newly-diagnosed atrial fibrillation – a nationwide population-based study. Int J Cardiol. 2019; 296: 81-86.

12 Jakobsen CB, Lamberts M, Carlson N, et al. Incidence of atrial fibrillation in different major cancer subtypes: a nationwide population-based 12 year follow up study. BMC Cancer. 2019; 19: 1105.

13 Rahman F, Ko D, Benjamin EJ. Association of atrial fibrillation and cancer. JAMA Cardiol. 2016; 1: 384-386.

14 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37: 2893-2962.

15 January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019; 74: 104-132.

16 D'Souza M, Carlson N, Fosbøl E, et al. CHA_2DS_2-VASC score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. Eur J Prev Cardiol. 2018; 25: 651-658.

17 Aspberg S, Yu L, Gigante B, et al. Risk of ischemic stroke and major bleeding in patients with atrial fibrillation and cancer. J Stroke Cerebrovasc Dis. 2020; 29: 104560.

18 Hu Y, Liu C, Chang PM, et al. Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. Int J Cardiol. 2013; 165: 355-357.

19 Patell R, Gutierrez A, Rybicki L, Khorana AA. Usefulness of $CHADS_2$ and CHA_2DS_2-VASc scores for stroke prediction in patients with cancer and atrial fibrillation. Am J Cardiol. 2017; 120: 2182-2186.

20 Denas G, Pengo V, Joppi R, Prandoni P. Cancer as a risk factor for stroke in atrial fibrillation patients receiving long-term oral anticoagulant therapy. Thromb Res. 2015; 136: 488.

21 Ambrus DB, Reisman JI, Rose AJ. The impact of new-onset cancer among veterans who are receiving warfarin for atrial fibrillation and venous thromboembolism. Thromb Res. 2016; 144: 21-26.

22 Ording AG, Horváth-Puhó E, Adelborg K, et al. Thromboembolic and bleeding complications during oral anticoagulation therapy in cancer patients with atrial fibrillation: a Danish nationwide population-based cohort study. Cancer Med. 2017; 6: 1165-1172.

23 Rose AJ, Sharman JP, Ozonoff A, et al. Effectiveness of warfarin among patients with cancer. J Gen Intern Med. 2007; 22: 997-1002.

24 Sato T, Aizawa Y, Fuse K, et al. The impact of cancer on major bleeding and stroke/systemic emboli in patients using direct oral anticoagulants: from the database of a single-center registry. J Atr Fibrillation. 2018; 11: 2105.

25 Pardo Sanz A, Rincón LM, Guedes Ramallo P, et al. Current status of anticoagulation in patients with breast cancer and atrial fibrillation. Breast. 2019; 46: 163-169.

26 Sorigue M, Miljkovic MD. Atrial fibrillation and stroke risk in patients with cancer: a primer for oncologists. J Oncol Pract. 2019; 15: 641-650.

27 Rhea IB, Lyon AR, Fradley MG. Anticoagulation of cardiovascular conditions in the cancer patient: review of old and new therapies. Curr Oncol Rep. 2019; 21: 45.

28 Delluc A, Wang TF, Yap ES, et al. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH. J Thromb Haemost. 2019; 17: 1247-1252.

29 Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology. J Am Coll Cardiol. 2014; 63: 945-953.

30 Chu G, Versteeg HH, Trines SA, et al. Atrial fibrillation and cancer – an unexplored field in cardiovascular oncology. Blood Rev. 2019; 35: 59-67.

31 López-Fernández T, Martín-García A, Roldán Rabadán I, et al. Atrial fibrillation in active cancer patients: expert position paper and recommendations. Rev Esp Cardiol. 2019; 72: 749-759.

32 Undas A, Drabik L. Non-vitamin K antagonist oral anticoagulants (NOACs) in cancer patients with atrial fibrillation. Anatol J Cardiol. 2020; 23: 10-18.

33 Tufano A, Galderisi M, Esposito L, et al. Anticancer drug-related nonvalvular atrial fibrillation: challenges in management and antithrombotic strategies. Semin Thromb Hemost. 2018; 44: 388-396.

34 Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018; 39: 1330-1393.

35 Mery B, Guichard JB, Guy JB, et al. Atrial fibrillation in cancer patients: hindsight, insight and foresight. Int J Cardiol. 2017; 240: 196-202.

36 Fitzpatrick T, Carrier M, Le Gal G. Cancer, atrial fibrillation, and stroke. Thromb Res. 2017; 155: 101-105.

37 Gutierrez A, Patell R, Rybicki L, Khorana AA. Predicting outcomes in patients with cancer and atrial fibrillation. Ther Adv Cardiovasc Dis. 2019; 13: 1753944719860676.

38 Hart RG, Pearce LA, Miller VT, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. Cerebrovasc Dis. 2000; 10: 39-43.

39 Atterman A, Friberg L, Asplund K, Engdahl J. Net benefit of oral anticoagulants in patients with atrial fibrillation and active cancer: a nationwide cohort study. Europace. 2020; 22: 58-65.

40 Sorigue M, Gual-Capllonch F, Garcia O, et al. Incidence, predictive factors, management, and survival impact of atrial fibrillation in non-Hodgkin lymphoma. Ann Hematol. 2018; 97: 1633-1640.

41 Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J. 2016; 37: 2768-2801.

42 Navi BB, Reiner AS, Kamel H, et al. Association between incident cancer and subsequent stroke. Ann Neurol. 2015; 77: 291-300.

43 Grazioli S, Paciaroni M, Agnelli G, et al. Cancer-associated ischemic stroke: a retrospective multicentre cohort study. Thromb Res. 2018; 165: 33-37.

44 Cocho D, Gendre J, Boltes A, et al. Predictors of occult cancer in acute ischemic stroke patients. J Stroke Cerebrovasc Dis. 2015; 24: 1324-1328.

45 Schwarzbach CJ, Schaefer A, Ebert A, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. Stroke. 2012; 43: 3029-3034.

46 D'Souza M, Smedegaard L, Madelaire C, et al. Atrial fibrillation and anticoagulation in patients with breast cancer. Scand Cardiovasc J. 2019; 53: 247-254.

47 Lee YJ, Park JK, Uhm JS, et al. Bleeding risk and major adverse events in patients with cancer on oral anticoagulation therapy. Int J Cardiol. 2016; 203: 372-378.

48 Kim K, Lee YJ, Kim TH, et al. Effect of non-Vitamin K antagonist oral anticoagulants in atrial fibrillation patients with newly diagnosed cancer. Korean Circ J. 2018; 48: 406-417.

49 Melloni C, Shrader P, Carver J, et al. Management and outcomes of patients with atrial fibrillation and a history of cancer: the ORBIT-AF registry. Eur Hear J - Qual Care Clin Outcomes. 2017; 3: 192-197.

50 Melloni C, Dunning A, Granger CB, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE trial. Am J Med. 2017; 130: 1440-1448.e1.

51 Fanola CL, Ruff CT, Murphy SA, et al. Efficacy and safety of edoxaban in patients with active malignancy and atrial fibrillation: analysis of the engage AF-TIMI 48 trial. J Am Heart Assoc. 2018; 7: e008987.

52 Lubitz SA, Yin X, Rienstra M, et al. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. Circulation. 2015; 131: 1648-1655.

53 Quon MJ, Behlouli H, Pilote L. Anticoagulant use and risk of ischemic stroke and bleeding in patients with secondary atrial fibrillation associated with acute coronary syndromes, acute pulmonary disease, or sepsis. JACC Clin Electrophysiol. 2018; 4: 386-393.

54 Verma A. Does "secondary" atrial fibrillation really exist? JACC Clin Electrophysiol. 2017; 4: 394-396.

55 Jabre P, Jouven X, Adnet F, et al. Atrial fibrillation and death after myocardial infarction: a community study. Circulation. 2011; 123: 2094-2100.

56 Klein Klouwenberg PMC, Frencken JF, Kuipers S, et al. Incidence, predictors, and outcomes of new-onset atrial fibrillation in critically ill patients with sepsis a cohort study. Am J Respir Crit Care Med. 2017; 195: 205-211.

57 Quon M, Pilote L. Does reversible AF exist? Or is AF just AF? Can J Gen Intern Med. 2018; 13 (SP1).

58 Imperatori A, Mariscalco G, Riganti G, et al. Atrial fibrillation after pulmonary lobectomy for lung cancer affects long-term survival in a prospective single-center study. J Cardiothorac Surg. 2012; 7: 4.

59 Lardaro T, Self WH, Barrett TW. Thirty-day mortality in ED patients with new onset atrial fibrillation and actively treated cancer. Am J Emerg Med. 2015; 33: 1483-1488.

60 Amioka M, Sairaku A, Ochi T, et al. Prognostic significance of new--onset atrial fibrillation in patients with non-Hodgkin's lymphoma treated with anthracyclines. Am J Cardiol. 2016; 118: 1386-1389.

61 Elting LS, Martin CG, Kurtin DJ, et al. The bleeding risk index: a clinical prediction rule to guide the prophylactic use of platelet transfusions in patients with lymphoma or solid tumors. Cancer. 2002; 94: 3252-3262.

62 Nieto J, Solano R, Ruiz-Ribo M, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2010; 8: 1216-1222.

63 Angelini DE, Radivoyevitch T, McCrae KR, Khorana AA. Bleeding incidence and risk factors among cancer patients treated with anticoagulation. Am J Hematol. 2019; 94: 780-785.

64 Apostolakis S, Lane DA, Guo Y, et al. Performance of the HEMORR$_2$HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol. 2012; 60: 861-867.

65 Edmiston MK, Lewis WR. Bleeding risk scores in atrial fibrillation: helpful or harmful? J Am Heart Assoc. 2018; 7: e010582.

66 Friberg L, Rosenqvist M, Lip GYH. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation. 2012; 125: 2298-2307.

67 Guha A, Dey A, Jneid H, et al. Atrial fibrillation in the era of emerging cancer therapies. Eur Hear J. 2019; 40: 3007-3010.

68 Plaja A, Berastegui E, Nieto-Moragas J, et al. Thromboembolism and bleeding in patients with cancer and mechanical heart valves. J Thromb Thrombolysis. 2019; 47: 454-461.

69 Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008; 111: 4902-4907.

70 Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med. 2019; 380: 711-719.

71 Steinberg BA, Shrader P, Thomas L, et al. Off-label dosing of non--vitamin K antagonist oral anticoagulants and adverse outcomes. J Am Coll Cardiol. 2016; 68: 2597-2604.

72 Gallagher AM, Setakis E, Plumb JM, et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost. 2011; 106: 968-977.

73 Xing LY, Barcella CA, Sindet-Pedersen C, et al. Dose reduction of non--vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a Danish nationwide cohort study. Thromb Res. 2019; 178: 101-109.

74 Stępień K, Nowak K, Zalewski J, Undas A. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and colorectal cancer: a single-center experience. Kardiol Pol. 2019; 77: 1186-1189.

75 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383: 955-962.

76 Shah S, Norby FL, Datta YH, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv. 2018; 2: 200-209.

77 Cavallari I, Verolino G, Romano S, Patti G. Efficacy and safety of non-vitamin K oral anticoagulants in patients with atrial fibrillation and cancer: a study-level meta-analysis. Thromb Haemost. 2020; 120: 314-321.

78 Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020; 382: 1599-1607.

79 Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018; 378: 615-624.

80 Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018; 36: 2017-2023.

81 McBane RD, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost. 2020; 18: 411-421.

82 Russo V, Rago A, Papa AA, et al. Use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with malignancy: clinical practice experience in a single institution and literature review. Semin Thromb Hemost. 2018; 44: 370-376.

83 Haukoos JS, Lewis RJ. The propensity score. JAMA. 2015; 314: 1637-1638.

84 Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research. JAMA. 2020; 323: 466-467.

85 Sorigue M, Cañamero E, Siguenza P, et al. Recent developments and persisting challenges in the prevention and treatment of venous thromboembolism in patients with hematological malignancies. Leuk Lymphoma. 2020; 61: 1277-1291.

86 Martín-Pérez M, Gaist D, De Abajo FJ, García Rodríguez LA. Predictors of over-anticoagulation in warfarin users in the UK General population: a nested case-control study in a primary health care database. Thromb Haemost. 2019; 119: 66-76.

87 Wu VCC, Wang CL, Huang YT, et al. Novel oral anticoagulant versus warfarin in cancer patients with atrial fibrillation: an 8-year population-based cohort study. J Cancer. 2020; 11: 92-99.

88 Wang KL, Lip GYH, Lin SJ, Chiang CE. Non-vitamin K antagonist oral anticoagulants for stroke prevention in asian patients with nonvalvular atrial fibrillation: meta-Analysis. Stroke. 2015; 46: 2555-2561.

89 Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013; 128: 1234-1243.

90 Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med. 2017; 377: 431-441.

91 Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019; 380: 1326-1335.

92 Samuelson BT, Cuker A. Measurement and reversal of the direct oral anticoagulants. Blood Rev. 2017; 31: 77-84.

93 Schaefer JK, McBane RD, Wysokinski WE. How to choose appropriate direct oral anticoagulant for patient with nonvalvular atrial fibrillation. Ann Hematol. 2016; 95: 437-449.

94 Dawwas GK, Brown J, Dietrich E, Park H. Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. Lancet Haematol. 2019; 6: e20-e28.

95 López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta--analysis, and cost effectiveness analysis. BMJ. 2017; 359: j5058.

96 Aryal MR, Gosain R, Donato A, et al. Systematic review and meta--analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. Blood Adv. 2019; 3: 2381-2387.

97 Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism. JAMA. 2014; 312: 1122.

98 Bellesoeur A, Thomas-Schoemann A, Allard M, et al. Pharmacokinetic variability of anticoagulants in patients with cancer-associated thrombosis: clinical consequences. Crit Rev Oncol Hematol. 2018; 129: 102-112.

99 Short NJ, Connors JM. New oral anticoagulants and the cancer patient. Oncologist. 2014; 19: 82-93.

100 Kraaijpoel N, Carrier M. How I treat cancer-associated venous thromboembolism. Blood. 2019; 133: 291-298.