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 the increase in arterial thrombosis caused by the former and the increased in bleeding risk in patients with the latter, 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 three years providing practice points for physicians to offer the best treatment plan to their patients. The present review begins by summarizing these recommendations and then proceeds to outline nine practical challenges that fit into the larger questions of when and for whom anticoagulation is indicated and what is the best agent in patients with AF and active cancer. For each of these nine 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. The author concludes by emphasizing the need for high-quality evidence and, more practically, by stressing 1) the importance of patient preference and values in the decision of whether and how to anticoagulate and 2) that periodic reassessment of the benefits of anticoagulation with changes in cancer status and treatment plan.
ORAL ANTICOAGULATION IN PATIENTS WITH ACTIVE CANCER AND ATRIAL FIBRILLATION: CURRENT CHALLENGES

0. INTRODUCTION

Patients with active cancer have an increased risk of thromboembolic events. The risk of venous thromboembolism (VTE) is increased four to eight-fold in patients with cancer [1,2] while the risk of stroke and myocardial infarction is increased twofold [3]. Importantly, the incidence of these thromboembolic events varies widely within the cancer population, being highest in the most aggressive malignancies, with high tumor burden and metastatic disease and lowest in patients with less aggressive cancers and while disease-free, when 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 require frequent anticoagulation because of the high incidence of VTE. In patients with cancer receiving anticoagulation the incidence of major bleeding can be up to 10%/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 shared risk factors and the increased medical surveillance and testing that come with diagnosis of either, but there may be causal connections between the two. AF increases the risk of thrombotic events, particularly stroke, and often requires anticoagulation [14,15]. Given the high bleeding risk and the difficulty of managing anticoagulation optimally in 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 the 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 bleeding risk. This state of affairs leads to uncertainty regarding the clinical benefit of anticoagulation for patients with AF and cancer. Furthermore, the evidence basis to support anticoagulation recommendations in this clinical setting is weak, as there are no randomized trials and very few prospective studies to guide these decisions. Nevertheless, in the last few months, several authors and societies have offered guidance for these patients and their physicians. Table 1 [14,26–34] outlines them.

The present 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].

1. ASSESSMENT OF STROKE AND BLEEDING RISK IN PATIENTS WITH CANCER AND ATRIAL FIBRILLATION

1.1 How should stroke risk be assessed in patients with active cancer and AF?

In the general population there is widespread consensus in the use of the CHA₂DS₂VASc score to determine the risk of stroke [14,15]. Neither CHA₂DS₂VASc 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 increasing CHA\textsubscript{2}DS\textsubscript{2}VASc and that patients with CHA\textsubscript{2}DS\textsubscript{2}VASc 0-1 are at low risk of stroke, which is in line with the idea that strokes in patients with AF and cancer are of similar mechanism than 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 single center studies published of patients with cancer and AF, show a x1.2 risk of stroke per CHA\textsubscript{2}DS\textsubscript{2}VASc 1 point increase (and 1.4x per CHADS\textsubscript{2} 1 point increase) [19,37]. There is also evidence that, similar to the general population, patients with cancer and AF with a low CHA\textsubscript{2}DS\textsubscript{2}VASc score do not benefit from anticoagulation while those with a high CHA\textsubscript{2}DS\textsubscript{2}VASc score do so [39]. One likely caveat to this consideration is that, as argued in question 1.3, CHA\textsubscript{2}DS\textsubscript{2}VASc 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: Absent risk scores specific to patients with active cancer and AF, CHA\textsubscript{2}DS\textsubscript{2}VASc 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.

1.2 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\textsubscript{2}DS\textsubscript{2}VASc score, but there is no evidence that CHA\textsubscript{2}DS\textsubscript{2}VASc + cancer status predicts stroke better than CHA\textsubscript{2}DS\textsubscript{2}VASc alone in patients with AF. The increase in stroke 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] and 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. Concerning the former, stroke risk is not increased in all cancers, particularly the least aggressive ones [3,5]. Some of the most common cancers, i.e., breast and prostate cancer, have either only a very small or no increase in stroke [3,42,46]. Concerning 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 (i.e., all and any cancer) should be added to CHA2DS2VASc 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.

1.3 Does stroke risk depend on whether AF 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 CHA2DS2VASc score in these patients [18,19,39], there is also indirect evidence from randomized trials. A post-hoc substudy of the ENGAGE AF-TIMI48, which randomized patients with AF to
edoxaban or warfarin, compared the two 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 no cancer (1.43%/year and 1.58%/year, respectively, in the high-dose edoxaban arm and 2.38%/year and 1.77%/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 an emergency room died within 4 weeks and we reported that 7/16 (43%) of patients with non-Hodgkin lymphoma who developed AF died within 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 risk of AF recurrence and stroke risk in patients with cancer and secondary AF.

Conclusion: 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 there is a need for a longer follow-up of these patients to know the risk of AF recurrence and stroke.

1.4 How should hemorrhagic risk be assessed in patients with cancer and AF?

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 a gastrointestinal mass, a history of hemorrhage, low platelet count or antiplatelet drug use, age, frailty, metastatic disease (particularly in bone marrow), anemia, renal failure and surgery increase bleeding risk [8,61–63]. However, no score has been robustly 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 temporary and are not included in bleeding scores developed and validated in the general population, such as HAS-BLED, CHA₂DS₂VASc and HEMORR₂HAGES (the latter of which 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 idea, D'Souza et al [16] showed that the predictive value of the CHA₂DS₂VASc score was very limited, with 2-year incidences of bleeding leading to hospitalization of 4.3%, 4.4% and 6.8% in patients with CHA₂DS₂VASc of 0, 1 and 2-9, 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 what patients will suffer bleeding. 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 we or others have suggested [26,29]) are needed.
2. CHALLENGES REGARDING ANTICOAGULANT TREATMENT IN PATIENTS WITH ACTIVE CANCER AND ATRIAL FIBRILLATION

2.1 What patients with AF 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 CHA\textsubscript{2}DS\textsubscript{2}VASc >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/systemic embolism, major bleeding, and death) as patients with AF without cancer (hazard ratio for the composite outcome in anticoagulated vs. not-anticoagulated: 0.81 in both cancer and no-cancer cohorts). This benefit was seen in patients with high, but not low, CHA\textsubscript{2}DS\textsubscript{2}VASc in both cohorts. Unlike patients without cancer, patients with cancer and intermediate CHA\textsubscript{2}DS\textsubscript{2}VASc also benefited from anticoagulation, a finding that aligns with a previous study suggesting that patients with cancer and AF with a CHA\textsubscript{2}DS\textsubscript{2}VASc of 1 have a higher risk of stroke than those without cancer [16].

As mentioned above, patients with cancer have specific bleeding risk factors. These risk factors increase major bleeding much more than classical risk factors and do so often for a relatively short period of time. These factors are, furthermore, not strongly associated with stroke risk. Therefore, temporary withholding of anticoagulation is likely beneficial for some patients with AF and cancer, even though this remains unproven. In
an interesting study including more than 2,000 patients with cancer and AF with almost 4 years of follow-up, Lee et al [47] reported that 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 anti-neoplastic therapies. They offer the example of adjuvant chemotherapy as the time when this question can most often come up. In these instances, a decision has to be made with the patient and the oncologist about what are the potential downsides of omitting this therapy vs. omitting anticoagulation for the period it would be administered.

Conversely, anticoagulation may not be warranted for some patients beyond stroke/bleeding risk assessment, such as for those with a short life expectancy [67], for whom anticoagulation is likely not beneficial regardless of 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 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/valve thrombosis. However, the
incidence of major bleeding was high in the cancer cohort, particularly in relation to surgical procedures.

Conclusion and 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 CHA\textsubscript{2}DS\textsubscript{2}VASc (table 1), and recommend anticoagulation in patients with CHA\textsubscript{2}DS\textsubscript{2}VASc >1 and no bleeding risk factors. In patients with minor risk factors for bleeding we recommend anticoagulation when CHA\textsubscript{2}DS\textsubscript{2}VASc is very high [26]. Most importantly, however, this general recommendation is accompanied by two 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 cancer and AF with CHA\textsubscript{2}DS\textsubscript{2}VASc of 1 should also be closely scrutinized as they may benefit from anticoagulation [16,39].

2.2 Should risk of VTE play a role in recommending anticoagulation for AF?
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 CHA₂DS₂VASc>1, most patients with AF should be recommended therapeutic-dose anticoagulation. We find 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 (i.e., 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 definitively answer the question. It is likely that this trial can be conducted, given the marginal potential gain (i.e., 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.

2.3 Is there place for treatment with low-dose direct oral anticoagulant (DOAC) or lower target INR in AF and cancer?

Undertreatment of AF, either in the form of no anticoagulation or in the use of inappropriately low-dose DOAC (low-dose in patients for whom standard-dose is approved) is a common practice in the general population, despite robust evidence of worse outcomes, i.e., lower efficacy with no safety gains [39,71,72]. A diagnosis of cancer appears to increase the odds of receiving inappropriately low-dose DOAC [73] (as well as those 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 DOAC [74].

Conclusion and future needs: Inappropriately low-dose DOAC or low target 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 bleeding risk 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 seems conclusive and we would not consider this an ideal use of resources.

2.4 What is the ideal anticoagulant agent for patients with cancer and AF?
VKA and four DOACs are available for AF today. The differences between the two classes are well known. Based on randomized trial data, DOAC are at least as effective as and safer than VKA 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 is also available from randomized trials for cancer-associated VTE [78–81]. Overall, both VKA 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 is limited by the study designs. Most importantly, the concept “patient with cancer” is heterogeneous across studies and often includes patients with cancer cured/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 to those who do not, and those treated with DOAC differ from those treated with VKA. 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 with DOAC reveal a generally favorable safety picture. 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 of patients with active cancer treated with dabigatran, although a large study reported similar results than with rivaroxaban [76]. Importantly, some patient subsets remain understudied and DOAC 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 question 2.5 below).

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

Ultimately, with the limitations of the available data, DOACs and VKA have similar efficacy and safety results [22,47,48,50,51,76,77,87]. The two 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 VKA in patients 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. VKA have broadly available reversal agents (prothrombin complex or, less ideally, fresh frozen plasma [89]). Dabigatran has an approved reversal agent, idarucizumab [90], although it less widely available. Finally, the most recently approved reversal agent, andexanet alfa, approved for 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 use of idarucizumab and, particularly,
andexanet alfa, offers better outcomes than supportive care and use of non-specific 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 150/12h is often considered the most efficacious option while apixaban (or dabigatran 110/12h) 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 VKA [10].

Conclusion and future needs: It is unlikely that either DOACs or VKA are ideal for all patients and assessment of specific patient-, cancer- and treatment-related factors should be used to make a decision. It is essential to discuss pros and cons with the patient. We concur [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 a 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, we favor 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 high bleeding risk population 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]. We find 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 GIT bleeding is still needed. While we do not expect a clinical trial comparing VKA vs. DOAC or comparing different DOACs, there is a need for results of prospective treatment protocol, 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.

2.5 What DOAC-drug interactions are clinically relevant?

DOACs have fewer drug-interactions than VKA. However, unlike VKA, these agents are dosed based on patient-specific variables, rather than on 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 interact 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 DOAC dose to target a chosen concentration improves clinical outcomes.
Numerous documents have specified drugs that may interact with DOAC [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/inhibitor should be avoided, because concomitant use may lead to significant alterations of DOAC concentration. However, a majority of chemotherapy drugs are not strong glycoprotein-P or CYP3A4 inducers/inhibitors but rather have small to moderate effects. The effect they may have on DOAC concentration, as well as the clinical relevance of that effect, is unknown.

So far, four randomized clinical trials have tested DOAC vs 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 generally high bleeding risk population. Therefore, many DOAC-chemotherapy interactions are likely not clinically relevant, but more and more robust evidence will be needed going forward.

Some may advocate for the use of laboratory tests to determine drug concentration (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 DOAC or, less convincingly, change dose to reach a target concentration [34]. However, none of these options are evidence-based.

Conclusions and future needs: Dabigatran should not be used concomitantly with strong glycoprotein-P inducers/inhibitors and apixaban and rivaroxaban with strong glycoprotein-P and CYP3A4 inducers/inhibitors. Edoxaban is less dependent on these metabolic pathways. When a clinically relevant interaction cannot be ruled out, use of VKA with close INR monitoring should be considered. Alternatively, one can consider
testing for DOAC plasma and verifying that levels are within the range reported in the general population [34,92]. We would not change DOAC dose based on results but rather switch 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/inhibitors. Finally, efficacy and safety data focusing on specific patient subsets, including specific treatment regimens, is 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 of stroke or bleeding risk in these patients and, relatedly, on the decision of whether to recommend anticoagulation (and what agent). In this regard, we eagerly await the results of the ongoing Blitz-AFCancer registry, a prospective, international, observational study (NCT03909386) collecting data on the management of patients with cancer and AF. The investigators aim to include 1500 patients and the projected study end date is in 2023. We hope 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 these questions. In essence, retrospective data has been published but biases are likely to play a big role in the results reported and prospective data is 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.

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Table 1. Outline of recommendations regarding anticoagulation for patients with atrial fibrillation and cancer.

| Author                  | Year | Indication for anticoagulation                                                                                                                                                                                                                                                                                                                                 | Agent                                                                                      |
|-------------------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| 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$_2$DS$_2$VASc $\geq$ 1 and HASBLED < 3 and optional for CHA$_2$DS$_2$VASc 0 or HASBLED $\geq$ 3. | VKA preferred (lack of data with LMWH and DOAC)                                           |
| Zamorano et al [41] (ESC)| 2016 | CHA$_2$DS$_2$VASc $\geq$ 2 and platelet count > 50/nL                                                                                                                                                                                                                                                                                                     | 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$_2$DS$_2$VASc and cancer- and treatment-related factors (type/site of cancer, liver metastases, coagulopathy, renal function, thrombocytopenia, surgery, among others mentioned)                                                                                                                                                   | VKA are standard of care, DOACs as possible alternative (consider drug interactions and dose reductions / treatment interruption in thrombocytopenia, bleeding) |
| Sorigue & Miljkovic [26] | 2019 | Anticoagulation generally not recommended if major bleeding risk factors present (gastrointestinal mass,                                                                                                                                                                                                                                                   | If already receiving DOAC or VKA at cancer diagnosis, likely continue the same agent (consider time in range, |
|                         |      |                                                                                                                                                                                                                                                                                                                                                         | |


| Reference                        | Year | Description                                                                 | Notes                                                                                                                                                                                                 |
|---------------------------------|------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chu et al [30]                  | 2019 | previous major bleeding, antiplatelet treatment, (thrombocytopenia < 50/nL) | If anticoagulation is started anew, no evidence for DOAC vs VKA, base decisions upon patient, cancer and treatment features (Asian vs. non-Asian, interactions, gastrointestinal mass, etc) |
| Delluc et al [28] (ISTH)        | 2019 | --                                                                          | If already receiving DOAC or VKA at cancer diagnosis, continue the same agent unless drug interactions are foreseen. If anticoagulation is started, DOAC preferred unless drug interactions or gastrointestinal bleeding risk |
| Lopez-Fernandez et al [31]     | 2019 | CHA$_2$DS$_2$VASc $\geq$ 2 but consider bleeding risk (HASBLED).            | DOAC preferred.                                                                                                                          |
|                                 |      | In complex patients consider using ABC and HEMORR$_3$HAGES scores.         | Consider drug interactions to choose amongst them                                                                                                                                                |
| Rhea et al [27]                 | 2019 | CHA$_2$DS$_2$VASc $\geq$ 2 but consider cancer status, stage,              | DOAC generally preferred                                                                                                                                                                           |
|                                 |      | response to treatment, and prognosis (if life expectancy < 12 months or high bleeding risk) consider against anticoagulation |                                                                                                                                                                                                        |
Abbreviations: VKA: vitamin K antagonists; LMWH: low molecular weight heparin; DOAC: direct oral anticoagulant; ESC: European Society of Cardiology; EHRA: European Heart Rhythm Association; ISTH: International Society on Thrombosis and Haemostasis

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

NB2: This 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.

NB3: Almost all authors emphasize the need to individualize treatment (although the what factors should be considered for it is not always specified) as well as the value of a multidisciplinary assessment of optimal treatment decisions.