clinical reviews

Atrial Fibrillation and Stroke Risk in Patients With Cancer: A Primer for Oncologists

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abstract

Cancer and atrial fibrillation (AF) are common conditions, but for patients affected with both, there is a lack of data about management of anticoagulation and cerebrovascular outcomes. In the first section of this review, we summarize the most relevant studies on stroke risk and management of AF in patients with active cancer, attempting to answer questions of whether to anticoagulate, whom to anticoagulate, and what agents to use. In the second section of the review, we suggest a decision algorithm on the basis of the available evidence and provide practical recommendations for each of the anticoagulant options. In the third section, we discuss the limitations of the available evidence. On the basis of low-quality evidence, we find that patients with cancer and AF have a risk of stroke similar to that of the general population but a substantially higher risk of bleeding regardless of the anticoagulant agent used; this makes anticoagulation-related decisions complex and evidence from the general population not immediately applicable. In general, we suggest stopping anticoagulation in patients with high risk of bleeding and in those with a moderate bleeding risk without a high thromboembolic risk and recommend anticoagulation as in the general population for patients at a low risk for bleeding. However, regardless of initial therapy, we recommend reassessing whether anticoagulation should be given at each point in the clinical course of the disease. High-quality evidence to guide anticoagulation for AF in patients with cancer is needed.

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INTRODUCTION

Cancer is one of the leading causes of death worldwide, and its incidence increases as the population ages. Therapeutic decision making must consider not only the heterogeneity of the disease itself but also patient comorbidity and fitness.

Atrial fibrillation (AF) is a common condition in the general population.[1] Like cancer, its incidence increases with age. Importantly, AF is often accompanied by a host of cardiovascular comorbidities, such as diabetes, hypertension, or heart disease. These comorbidities are at the same time risk factors for AF development and compound its impact on a patient's fitness. The most feared complication of AF is cardioembolic stroke, which constitutes 20% to 30% of ischemic strokes and is the subtype of stroke with the highest mortality and functional repercussion. Cardioembolic stroke can be effectively prevented by oral anticoagulants.[2]

Until recently, the examined relationship between AF and cancer has been limited to epidemiologic data showing that the diagnosis of either one increases the odds of being diagnosed with the other,[3] although common risk factors and the increased medical vigilance that comes with either diagnosis might confound the analysis. Yet, the clinical significance and optimal management of AF in patients with active cancer remains uncertain because of a lack of studies and the complexities surrounding them, which hinder obtaining clinically useful data.

In this review, we provide oncologists with a brief overview of the data on the risk of stroke in patients with active cancer and AF and the scarce evidence regarding the management of anticoagulation in these patients. We then describe our personal approach to this clinical scenario. We believe the oncologist needs to take an active part in the choice and follow-up of the anticoagulation, because bleeding and thrombosis are frequent clinical events in these patients, and their optimal management is an important part of successful anticancer treatment.

AF, CARDIOEMBOLIC STROKE, AND ANTICOAGULATION IN THE GENERAL POPULATION AND IN PATIENTS WITH ACTIVE CANCER

Incidence

General population. The incidence of AF in the general population depends on the presence of cardiovascular

ASSOCIATED CONTENT

See accompanying commentary on page 651

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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comorbidities, particularly age. The prevalence of AF increases from 0.1% in patients younger than 55 years of age to 10% in those older than 85 years.[1]

Cancer population. Approximately 2% to 5% of patients diagnosed with cancer have AF at the time of diagnosis, largely associated with the same factors as the general population.[4-6] However, the incidence of new-onset AF in patients with a diagnosis of cancer is higher than in the general population[3] for many reasons, including shared risk factors (for both cancer and AF) and cancer-induced inflammation.[7] In addition, patients with cancer may be more likely to suffer secondary AF (ie, AF triggered by an outside stressor, such as surgery, anemia, sepsis, or hypoxemia).[6-8] An increase in incidence has been best documented in the setting of lung and colon cancer surgery (which can be higher than 10% in the former and 5% in the latter),[8] but this is likely to be the result of the greater prevalence of these cancers in the general population, because there is no evidence that AF is less likely to occur in patients with other cancers requiring surgery. Finally, certain drugs also promote the development of AF. Some, such as anthracyclines, do so indirectly, by causing heart failure, which increases the risk of AF.[7] Other drugs cause AF directly, such as ibrutinib, which increases the risk of AF three to four times through off-target tyrosine kinase inhibition.[9]

Risk of Stroke

General population. The risk of stroke in patients with AF is assessed by means of the $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75, diabetes mellitus [1 point each] and previous stroke/transient ischemic attack [2 points]) and CHA_2DS_2VASc scores (congestive heart failure, hypertension, age 65-74, diabetes mellitus, vascular disease, female sex [1 point each] and age ≥ 75, previous stroke/transient ischemic attack/thromboembolism [2 points each]) (Data Supplement). For CHA_2DS_2-VASc, the risk of stroke ranges from 0.2%/y for those with 0 points to 12%/y to 14%/y for those with 9 points.[10]

Cancer population. Similarly to the risk of venous thromboembolic disease (VTE), the risk of arterial thromboembolism, including stroke, is increased in most cancer types, particularly in the few months after diagnosis.[11,12] In an analysis of more than 250,000 patients with cancer paired with as many without cancer, the cumulative incidence of stroke at 6 months was 3% and 1.6%, respectively. Although this presents a two-fold increase in stroke risk over the general population, this is strongly dependent on cancer type (eg, patients with lung cancer had four times the risk, and those with breast or prostate cancer did not seem to have an increased risk of stroke).[12] This increase in the incidence of stroke in patients with cancer is the result of an increase in the frequency of unexplained strokes, believed to be secondary to hypercoagulability or noninfectious endocarditis.[11] However, cardioembolic stroke is not increased in patients with cancer.[11,13] This is of major practical consequence, given the increased risk of bleeding in cancer,[14-16] and renders the assessment of the net clinical benefit of anticoagulation for AF even more complex.

Table 1 lists the data from published series assessing the risk of stroke in patients with cancer and AF.[4-6,17-29] Although these studies are heterogeneous, a distinction that seems consistently relevant in terms of risk of stroke is that between baseline AF and new-onset AF.

Baseline AF. Baseline AF is any AF already diagnosed at the time of cancer diagnosis. One of the most relevant studies in this setting is a cohort of more than 2,000 patients with recently diagnosed cancer and AF reported by Patell et al,[5] who, along with a relatively low risk of stroke (1.9%/y), found that $CHADS_2$ and CHA_2DS_2VASc scores were predictive of stroke. Denas et al[24] and Ambrus et al[25] reported no difference in stroke risk in patients with AF treated with warfarin on the basis of the presence or absence of cancer. Overall, the risk of stroke in patients with cancer and baseline AF seems to be similar to that of the general population, with $CHADS_2$ and CHA_2DS_2VASc being predictive of stroke risk.[5] However, the heterogeneity of the studies, particularly regarding anticoagulant treatment and the population included, still calls for more evidence, preferably gathered prospectively.

New-onset AF. New-onset AF is that diagnosed at the time of, or at any point after, the diagnosis of cancer. Contrary to baseline AF, some studies indicate that the $CHADS_2$ and CHA_2DS_2VASc scores may not predict stroke risk in new-onset AF.[4,29]

Although the distinction between baseline and new-onset AF needs additional support, it would align with the idea that AF in patients with cancer is frequently secondary. According to this idea, resolution of the trigger could resolve secondary AF, leading to a lower risk of stroke.[30] Importantly, new-onset AF in patients with cancer may reveal a low homeostatic reserve and a high risk of death.[6,31,32]

Anticoagulation

General population. The approach to a patient with AF requires many considerations that fall outside the scope of this review, but an essential question is whether the patient should receive anticoagulation. In most clinical scenarios, patients should receive anticoagulation because the benefits clearly outweigh the risks (ie, bleeding).[1,2] CHA_2DS_2VASc scores of 2 or greater are generally an indication to anticoagulate.[1,33] Bleeding risk should not factor into the equation for most patients, because most risk factors for bleeding are also risk factors for stroke, so that patients with the highest bleeding risk are often the ones who benefit the most from anticoagulation.[1,34]

Cancer population. When considering anticoagulation for AF, patients with cancer have two differential features: the risks of VTE and of noncardioembolic stroke are higher than in the general population and may have to factor into the decision for some cancer subtypes,[12,35] and bleeding risk is much higher than in the general population[14,15,17,18,23,25,36] (particularly in patients with GI cancers) because of local

TABLE 1. Published Series Reporting Cardiovascular Outcomes in Patients With Cancer and AF

Study	Study Population	No. of Patients in Study Group	Control Group	CHA_2DS_2VASc	Risk of Ischemic Stroke (or ischemic stroke/systemic embolism)	Conclusion and Comments
Rose[20]	Active cancer and warfarin for non-VTE indications	65	Matched 193 patients	NR	2 strokes in 65 patients in 11 months	The two strokes occurred when patients had interrupted warfarin
						TTR was lower in patients with cancer
Hu[4]	Cancer and AF	584 (baseline AF) 423 (new-onset AF)	Patients with cancer w/o AF	NR	For $CHADS_2$* 0-1, 2-3, and 4-6: baseline AF: 7%, 16%, 27%; New-onset AF: 30%, 28%, 54%	New-onset AF is associated with increased thromboembolism but not mortality
						Baseline AF is associated with increased mortality
						$CHADS_2$ predicts thromboembolism in baseline AF and mortality in new-onset AF
						Thrombotic risk includes pulmonary embolism (which may be a large proportion of the composite end point)
						New-onset AF is associated with an unusually high thrombotic risk
Denas[24]	Cancer and baseline AF	505	AF w/o cancer	NR	2.3% at 2 years under warfarin; 3.7% at 2 years w/o warfarin	Cancer does not increase stroke risk
						Prospective study
						Does not adjust for other risk factors
Lee[23]	Cancer and baseline AF	2,118	None	Mean CHA_2DS_2VASc, 2.7-3.5	7%-8% at 3.9 years (both with and w/o anticoagulation)	High risk of event in the first year
						Oral anticoagulation offers no benefit
						$CHADS_2$ has minimal predictive power
						Poor TTR
						Did not use a competing risk model
Ambrus[25]	Recently diagnosed cancer and baseline AF treated with warfarin	1,936	Patients with AF w/o cancer	Mean $CHADS_2$, 2.3	1.7% the first year	Patients with cancer have a similar stroke risk and higher bleeding risk than those w/o cancer
						TTR decreases 6.5% the first 6 months after cancer diagnosis
Ording[22]	Patients with a history of cancer and AF receiving anticoagulation	11,855 (only 21%-27% with cancer diagnosed < 2 years before AF)	Patients with AF receiving anticoagulation. No history of cancer	Median CHA_2DS_2VASc, 3	3%-3.4% at 1 year	Similar stroke and bleeding risks in cancer *v* no cancer, warfarin *v* DOAC
						Most patients had a remote history of cancer
Melloni[27]	AF and a history of cancer (ORBIT-AF registry)	2,318	AF w/o cancer	96% $CHA_2DS_2VASc \geq 2$	1.96%/y	Patients with a history of cancer have higher cardiovascular and bleeding risk factors
						Cancer details unknown but patients with < 6-month life expectancy were excluded

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TABLE 1. Published Series Reporting Cardiovascular Outcomes in Patients With Cancer and AF (continued)

Study	Study Population	No. of Patients in Study Group	Control Group	CHA_2DS_2VASc	Risk of Ischemic Stroke (or ischemic stroke/systemic embolism)	Conclusion and Comments
Patell[5]	Cancer and baseline AF	2,037	None	Median CHA_2DS_2VASc, 3	1.9%/y	$CHADS_2$ and CHA_2DS_2VASc are predictive of stroke and mortality
						Hematological and GIT malignancies as well as liver metastasis also increase stroke risk
						Only 36% of patients received anticoagulation
Melloni[26]	AF treated with apixaban and a history of cancer	1,236 (157 active in the year before)	AF treated with apixaban and no history of cancer	Mean CHA_2DS_2VASc, 3.6-3.8	1%/y	Patients with no cancer, active cancer, and remote cancer have similar risk of major bleeding and of ischemic stroke
						Subanalysis of the randomized ARISTOTLE trial
Elbadawi[28]	Patients with lung, breast, colon, or esophageal cancer and AF admitted to hospital	15,802	Patients with AF w/o cancer admitted to hospital	Median CHA_2DS_2VASc, 4	4% of patients with cancer and AF had in-hospital cerebrovascular accidents	Lower risk of stroke among inpatients with cancer
						CHA_2DS_2VASc did not predict main outcome
						Potential risk of biases (higher use of anticoagulation, competing risk of death, fewer diagnostic maneuvers)
D'Souza[29]	Patients with recent cancer (< 5 years) and new-onset AF	12,014	Patients w/o history of cancer	84% $CHA_2DS_2VASc \geq 2$	1.7%, 3.2%,7.1% at 2 years in CHA_2DS_2VASc 0, 1, and ≥ 2, respectively†	Patients with cancer have a higher bleeding risk and those with CHA_2DS_2VASc of 1 also a higher stroke risk
						The authors claim CHA_2DS_2VASc is not of value in patients with recent cancer but include all patients with $CHA_2DS_2VASc \geq 2$ in the same group
						Patients with AF were only included if hospitalized
						Excluded anticoagulated patients
Sorigue[6,21]	Patients with non-Hodgkin lymphoma and AF	23 (baseline AF); 40 (new-onset AF)	None	Median CHA_2DS_2VASc, 3	1.8%/y	Heterogeneous management of anticoagulant treatment
						Lower overall survival in patients with secondary AF
Kim[17]	Active cancer and baseline AF receiving anticoagulation	1,651	None	Median CHA_2DS_2VASc, 3.4-3.8	1.3%-5.5%/y	Lower stroke and bleeding risk with DOACs than warfarin
						Low TTR

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TABLE 1. Published Series Reporting Cardiovascular Outcomes in Patients With Cancer and AF (continued)

Study	Study Population	No. of Patients in Study Group	Control Group	CHA_2DS_2VASc	Risk of Ischemic Stroke (or ischemic stroke/systemic embolism)	Conclusion and Comments
Shah[18]	Active cancer and baseline AF receiving anticoagulation	16,096	None	CHA_2DS_2VASc, 4-4.6	0.7%-1.1%/y	Similar stroke risk between DOAC and warfarin.
						Apixaban and dabigatran lower bleeding risk
						Similar results to patients w/o cancer
Vedovati[19]	Cancer and AF receiving DOACs	289 patients with cancer (104 active)	Patients w/o history of cancer treated with DOACs	Mean CHA_2DS_2VASc, 4.2 (SD, 1.5)	3.6%/y (subgroup with active cancer)	Prospective study
						Incidence of stroke/transient ischemic attack in active cancer higher than in cancer-free patients
						Patients with a history of cancer similar outcome as cancer-free patients
						High incidence of major bleeding in patients with active cancer (12.8%/y)

Abbreviations: AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial; $CHADS_2$, congestive heart failure, hypertension, age ≥ 75, diabetes mellitus (1 point each) and previous stroke/transient ischemic attack (2 points); CHA_2DS_2VASc, congestive heart failure, hypertension, age 65-74, diabetes mellitus, vascular disease, female sex (1 point each) and age ≥ 75, previous stroke/transient ischemic attack/thromboembolism (2 points each); DOAC, direct oral anticoagulant; GIT, GI tract; NR, not reported; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; SD, standard deviation; TTR, time in therapeutic range; VTE, venous thromboembolism; w/o, without.

*Composite end point: stroke, peripheral embolism, and pulmonary embolism.

†Defined as admission/death as a result of stroke and bleeding, respectively.

barrier disruption, invasive procedures, treatment- or disease-related thrombocytopenia, and disseminated intravascular coagulation.[36] Of note, bleeding in patients with cancer may be more severe than in the general population.[16,37]

This uncertainty over the risk-benefit of anticoagulation in AF and cancer is reflected in the recent European Society of Cardiology guidelines, which do not make specific recommendations but rather suggest that each patient be assessed individually.[35] If the decision is made to anticoagulate, the immediate question is which agent to use. Table 2 lists the basic characteristics of the available options in the general population.

Vitamin K antagonists (VKAs) have several downsides that particularly affect patients with cancer. These include interaction with chemotherapeutic agents or other drugs, oral intolerance as a result of nausea, unsteady diet, and treatment

TABLE 2. Pros, Cons, and Practical Considerations of Each Anticoagulant Option for AF

Category	VKA	DOAC (as a group)*	LMWH
Advantage	More experience (particularly long-term data)	Rapid onset of action	Rapid onset of action
	Can be quantitatively monitored	Shorter half-life (less time to spontaneous reversal)	Short half-life
	No renal excretion	Predictable PK and wider therapeutic margin leading to no need for routine monitoring	Predictable PK
	Less GI bleeding	Lower risk of intracranial hemorrhage	No drug interactions
	Less affected by one missed dose	Fewer drug interactions†	
	Anticoagulant of choice in mechanical heart valves or mitral stenosis		
Disadvantage	Long half-life	Only approved for nonvalvular AF	No evidence in, and not approved for, AF
	Narrow therapeutic window	Monitoring tests not available everywhere, particularly on an emergency basis (standard blood tests such as the prothrombin time and the activated partial thrombin time do not allow for quantitative assessment of anticoagulation activity)	Expensive
	Drug and food interactions	Renal excretion	Inconvenient administration route
	Higher intracranial bleeding risk (absolute risk remains low)	Short half-life (one missed dose has a larger effect on serum concentration)	Renal excretion
Practical considerations with each agent	At the start of chemotherapy, check INR weekly. If time in therapeutic range is poor, consider stopping anticoagulation or switching to DOAC.	If possible, avoid in patients with high risk or history of GI bleeding.	We recommend against LMWH for AF because there is no evidence supporting its effectiveness, it does not have a better safety profile than other anticoagulants in cancer, it is more expensive and more inconvenient, and the rate of discontinuation is higher than with oral agents.
		Monitor renal function regularly, particularly when renal failure is already present. Preferably avoid dabigatran in renal failure.	
		To choose among them, consider potential drug interactions (dabigatran is dependent on glycoprotein-P but is not metabolized through cytochrome P450 3A4, unlike anti-Xa agents).	
		We generally favor twice daily agents (dabigatran or apixaban) because of less peak-trough variability and better results in indirect comparisons in AF in the general population.	

NOTE. The European Society of Cardiology currently recommends DOACs over VKAs as first-choice agents in most patients with AF.[1] Although this opinion is not supported by all scientific bodies and professionals, DOACs should definitely be used in patients with a low time in therapeutic range with VKAs or VKA therapeutic failure.

Abbreviations: AF, atrial fibrillation; CYP3A4, cytochrome P450 3A4; DOAC, direct oral anticoagulant; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PK, pharmacokinetics; VKA, vitamin K antagonists.

*Includes dabigatran, an anti-IIa agent, and apixaban, rivaroxaban, and edoxaban, anti-Xa agents.

†Dabigatran is a P-glycoprotein substrate, and the anti-Xa agents are metabolized through CYP3A4 (and are also substrates for P-glycoprotein, although they are less dependent on it than dabigatran). Strong inducers or inhibitors of these enzymes (most notably: azole antifungals, cyclosporine, tacrolimus, phenytoin, carbamazepine, St John wort, as well as many chemotherapeutic agents)[49] can interact with DOACs.

discontinuation due to invasive procedures. Furthermore, they are less efficacious than low-molecular-weight heparin (LMWH) for the treatment of cancer-associated VTE.[38] However, most of the available evidence does not suggest a notably higher incidence of stroke than the general population with AF[24,25] or a higher risk of bleeding than either LMWH or direct oral anticoagulants (DOACs).[16,36,39]

Until recently, because of lack of evidence and fear of potential drug interaction, DOACs were not recommended in patients with cancer. However, recent trials in the prevention and treatment of cancer-associated VTE[40,41] indicate that DOACs are effective and generally safe. The international society on Thrombosis and Haemostasis now accepts them as a valid option for the treatment of VTE in patients with cancer.[42] Although there are no trials in patients with AF and cancer, and the retrospective evidence available is more limited, a large retrospective comparative analysis for AF[18] suggested that the efficacy and safety of DOACs compared with warfarin are similar to those in the general population (incidence of ischemic stroke and severe bleeding of 0.8%/y and 2%/y with DOACs and 1%/y and 3%/y with warfarin, respectively). A relevant nuance is that trials in patients with VTE have shown that GI bleeding is increased in patients receiving full-dose DOACs, so particular caution is needed in patients at risk for GI bleeding (largely those with GI cancers and those with previous GI bleeding).[42,43] LMWH has not been studied for stroke prevention in AF and is not approved for that indication.

Periprocedural Management

General population. A plethora of retrospective trials and a subsequent randomized trial[44] have shown that LMWH increases major bleeding without decreasing stroke risk in patients with AF receiving VKAs undergoing ambulatory procedures. Therefore, most patients should interrupt VKA without bridging, at least for ambulatory procedures. Given the short half-life of DOACs and lack of evidence of benefit, bridging with LMWH is generally not advised.

Cancer population. Prospective data are lacking in patients with cancer. A large retrospective series showed that bridging with LMWH in patients with cancer (anticoagulated for any indication, not only AF) increased bleeding without decreasing thrombotic risk.[45]

Management of Bleeding

Severe bleeding is not common in the general population, but any-grade bleeding is a frequent complication of anticoagulant treatment. The therapeutic approach to bleeding should be step based, with more aggressive measures added to more basic ones as the severity of the bleeding episode increases[46,47] (Appendix Fig A1, online only).

As a general principle, it is important to keep in mind that anticoagulation does not cause bleeding on its own (it prevents clotting in the presence of bleeding). Therefore, a cause or trigger needs to be looked for and, if possible, treated (eg, endoscopic or angiographic examination). It should also be remembered that these patients have a high thrombotic risk (up to 6% to 8% of patients with major bleeding develop VTE[48]), both because of the indication for which they receive anticoagulation and because acute bleeding is a prothrombotic environment. Therefore, it is essential to restart anticoagulation (most often prophylactic-dose LMWH) as soon as the bleeding has subsided and the risk of rebleeding is low.[46,47]

MY APPROACH: ASSESSMENT AND MANAGEMENT OF AF IN PATIENTS WITH CANCER

Risk Assessment

Given the lack of prospective evidence and the many factors involved in decision-making (Fig 1), an individualized approach is essential, in line with the European Society of Cardiology guidelines recommendations.[35] Unfortunately, most prothrombotic factors also increase bleeding risk, and it is uncertain how much weight, if any, each risk factor should have.

Although some data indicate that there are no truly low-risk patients with cancer,[29] there is insufficient evidence that patients with cancer and AF with a CHA_2DS_2VASc 0 to 1 obtain a net benefit from anticoagulation. In patients with CHA_2DS_2VASc of 2 or more, in the general population, anticoagulation is generally recommended (even at the expense of a higher bleeding risk with treatment), because cardioembolic strokes generally have worse functional outcomes than most bleedings (except intracranial, which are rare), and this is often used to justify treatment even in patients with high bleeding risk.[51] However, major bleeding increases mortality[52] and thrombotic risk in the acute phase and decreases adherence to antithrombotic medication. In the general population, a 1%/y risk of stroke is the threshold to recommend anticoagulation,[33] knowing that anticoagulation carries a risk of major bleeding between 2% and 5%/y.[2] Similar data from patients with active cancer are difficult to obtain, given the differences between studies, but most of them show a consistently higher risk of bleeding: 4% in the first 3 months of anticoagulation, 4% to 6% at 6 months, and up to 10%/y to 15%/y.[14,15,19,36,38] Assuming that the mortality of bleeding in patients with cancer is the same, although it may be higher,[16,37] a consistent stroke risk of at least 4%/y to 5%/y without anticoagulation (which does not seem to be the case for a majority of patients; Table 1) would be required to justify anticoagulation. It has been argued that, because anticoagulation may also offer protection against VTE, one may have a lower threshold for anticoagulation in patients with a high risk of VTE.[35] Although worth investigating, at present we would generally not recommend anticoagulation in a patient with AF on the basis of VTE risk, given that many patients with a high risk of VTE also have high bleeding risks. Ultimately, given how variable and dynamic bleeding risk is in patients with cancer,

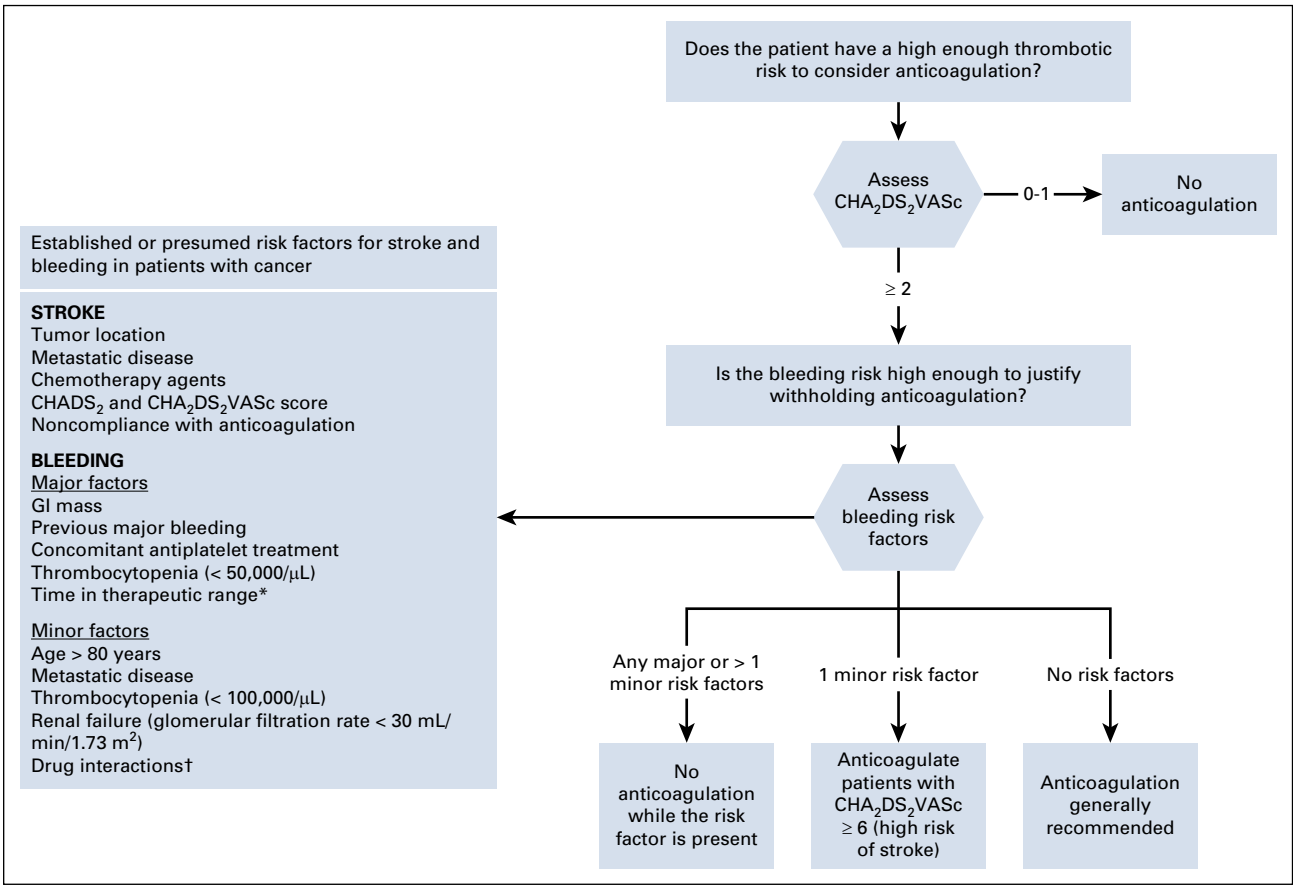

FIG 1. Established or presumed risk factors for stroke and bleeding in patients with cancer: proposed algorithm to decide whether patients with active cancer should receive anticoagulation for atrial fibrillation. (*) If time in therapeutic range is poor, consider switching to a direct oral anticoagulant. (†) See Short and Connors[49] and Kraajipoel and Carrier.[50] $CHADS_2$, congestive heart failure, hypertension, age ≥ 75, diabetes mellitus (1 point each) and previous stroke/transient ischemic attack (2 points); CHA_2DS_2VASc, congestive heart failure, hypertension, age 65-74, diabetes mellitus, vascular disease, female sex (1 point each) and age ≥ 75, previous stroke/transient ischemic attack/thromboembolism (2 points each).

an in-depth discussion with the patient, including periodic assessment of the need to anticoagulate, is warranted.

Initiating Anticoagulation

Primary AF. In patients with a CHA_2DS_2VASc of 0 or 1, we would recommend against anticoagulation for AF. For CHA_2DS_2VASc of 2 or more, we would first gauge bleeding risk. This was already suggested by Farmakis et al[8] in 2014, and all evidence published subsequently supports their position. In patients with a high bleeding risk (any major or more than one minor risk factor from Fig 1), we would generally suggest stopping anticoagulation during chemotherapy and restarting later, when tumor burden is lower and risk of thrombocytopenia is back to baseline. Conversely, we would tend to treat patients with a low bleeding risk (no bleeding risk factors) as one would the general population. For patients with a moderate risk (only one minor risk factor), we would generally favor anticoagulation for patients with a previous stroke or a CHA_2DS_2VASc of 6 or more (stroke risk approximately 10%/y[10]; Fig 1).

Secondary AF. For patients with secondary AF, anticoagulation may be a less-relevant concern. The trigger should be dealt with, and attention must be paid to a potential low homeostatic reserve that indicates high risk of an unfavorable clinical outcome. A cardiology consultation to rule out underlying cardiac damage and to aid with management of the acute episode is recommended. These patients may have a higher risk of developing permanent AF in the long term, but if the triggering event is resolved, the risk of stroke and the benefits of anticoagulation seem uncertain.[30] We would therefore argue for clinical follow-up (with or without temporary anticoagulation until the end of the AF episode) rather than up-front indefinite anticoagulation.

Periprocedural bridging and bleeding. We recommend against periprocedural bridging for most patients receiving anticoagulation for AF. In patients who suffer a major bleed, the risk of rebleeding is high, so we would favor stopping anticoagulation, at least until the trigger (eg, GI mass) has been resolved. However, in the acute phase of the bleeding episode, the risk of VTE is high, so prophylactic-dose LMWH

should be administered as soon as the bleeding has subsided and until hospital discharge.[46,47]

Choices of agents. Concerning specific anticoagulant agents, we generally continue with the drug (VKA or DOAC) the patient is taking if AF was previous to the diagnosis of cancer and anticoagulation is warranted. If the patient is diagnosed with new-onset AF, there is no evidence to choose one over another, and we would consider each of them on a case-by-case basis, generally following the considerations in Table 2.

SHORTCOMINGS OF THE EXISTING DATA AND FUTURE CHALLENGES

Data are insufficient for us to have a firm grasp on the risk of ischemic stroke in patients with AF and cancer. A summary of what we perceive are the most relevant limitations can be found in the Data Supplement. However, the major limitation with the available data is that patients with cancer are considered a single population. Different cancer sites and histological subtypes have widely different clinical courses, which should probably make physicians consider AF differently in these patients. Similarly, the risk-benefit balance of anticoagulation for AF likely changes during the course of the disease, particularly bleeding risk, which is higher when tumor burden is largest and treatment is administered.

CONCLUSION

AF in patients with cancer remains an underexamined topic. Given the thrombotic and hemorrhagic risk of these patients, evidence cannot be extrapolated from the general population. The available evidence, severely limited in amount and quality, points toward a risk of ischemic stroke that is not much higher than in the general population. Bleeding risk is higher, and the optimal anticoagulation strategy remains uncertain. Therefore, and at least until higher-grade evidence becomes available, an individualized and dynamic approach is essential and arguably more important than the initial strategy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JOP.18.00592.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: Marc Sorigue
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Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Atrial Fibrillation and Stroke Risk in Patients With Cancer: A Primer for Oncologists

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APPENDIX

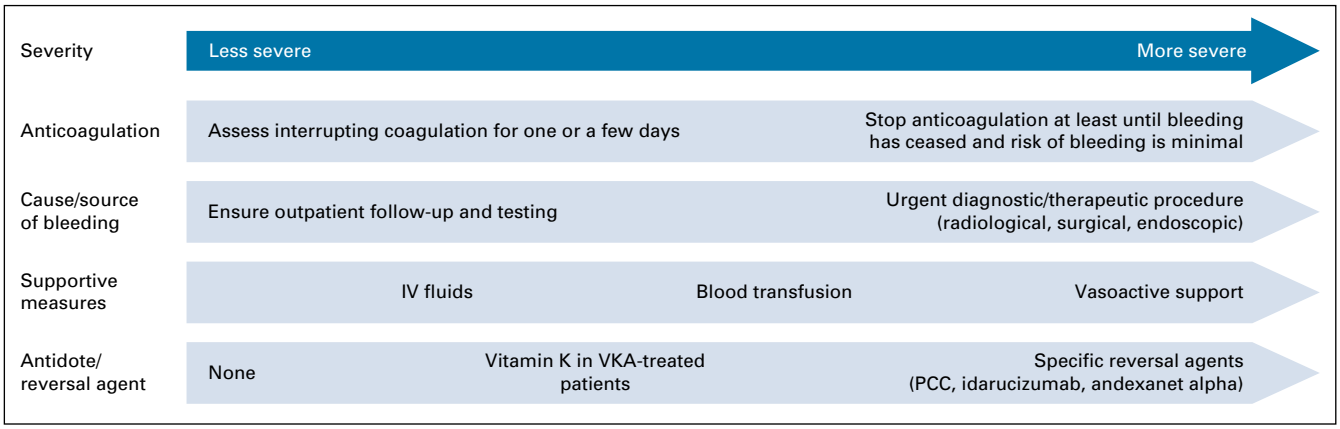

FIG A1. Stepwise management of bleeding in patients under anticoagulation. PCC, prothrombin complex concentrate; VKA, Vitamin K antagonist.