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Atrial fibrillation and ischemic stroke in cancer: the latest scientific evidence, current management, and future directions

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Abstract
Atrial fibrillation is the most common cardiac arrhythmia and is a major risk factor for ischemic stroke. Atrial fibrillation and ischemic stroke are major cardiovascular complications in cancer patients, who have a higher burden and worse outcomes than the general population. Clinical risk stratification scores for stroke and bleeding, commonly used in the general population to estimate thromboembolic and bleeding risk, respectively, are less well validated in cancer patients, who have historically been excluded in clinical trials. There is a lack of consensus opinion on how to effectively risk-stratify cancer patients based on the currently available tools and a need for cancer-specific scores that offer a tailored approach to each patient in order to more effectively stratify ischemic stroke and bleeding risk in this cohort of patients. Cancer-mediated physiologic changes and adverse effects of antineoplastic therapy have been implicated as etiologies of the increased risk for both atrial fibrillation and ischemic stroke. Risk stratifying scores such as CHA_2DS_2-VASc and HAS-BLED, commonly used in the general population, are less well validated in cancer patients. There is a need for cancer-specific scores that can more effectively stratify ischemic stroke and bleeding risk in cancer patients, although given the heterogeneity of cancers, whether a "one score fits all" is uncertain.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1] with the global prevalence of AF increasing from 33.5 million to 59 million between 2010 and 2019 [2]. The prevalence of AF is low among younger individuals (0.12 −0.16% in age < 49) but increases with age (10 −17% in age > 80) [3]. AF is a significant risk factor for ischemic stroke and patients with AF have a fivefold increased risk of stroke compared to the general population, though anticoagulation in eligible patients can reduce this risk by around 65% [4].

AF and ischemic stroke are common cardiovascular complications in cancer patients, with data demonstrating a 63% higher risk of AF in cancer patients when compared to those without cancer [5], and a two-fold increased stroke risk in

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cancer patients compared to those without cancer [6]. Additionally, the risk of all-cause mortality, major bleeding, and intracranial hemorrhage is increased in cancer patients with AF [7]. AF and comorbid cancer are also associated with an increased hospital length of stay and healthcare costs [8].

The higher risk of AF in cancer patients can be explained by shared risk factors between both conditions, such as age, smoking, obesity, and alcohol use [5, 9, 10]; the cardiotoxicity of common anti-neoplastic modalities predisposing to the development of AF [5, 11] and cancer-mediated inflammation leading to the development of AF [5, 11]. The higher risk of ischemic stroke in cancer patients can partly be explained by the higher incidence of AF in this population [5], alterations in the expression of coagulation factors due to both cancer and the inflammatory response, along with abnormalities in platelet activity resulting in a hypercoagulable state [12, 13].

Further complicating the clinical picture is the mixed data from cancer patients with AF, and the major heterogeneity of a "cancer" population in published studies. For example, one study found that prostate and breast cancers are associated with increased ischemic stroke risk, while hematologic, lung, prostate, and colorectal cancers are associated with increased bleeding risk [14]. Another study found that lung, breast, colon, and prostate cancer had increased thromboembolic risk [15], making the decision to initiate anticoagulation in cancer patients with AF challenging. Finally, patients with AF and a history of cancer have historically been excluded from clinical studies validating the traditional clinical risk stratifying scores as well as those that determined efficacy of the various anticoagulants, making it challenging to apply evidence-based management to this cohort of patients [11, 14, 16].

This narrative review article aims to highlight the latest research surrounding the pathophysiology of AF and ischemic stroke in cancer patients, the accuracy of common clinical risk stratification scores (such as CHA_2DS_2-VASc and HAS-BLED) in estimating thromboembolic and bleeding risk, respectively, in cancer patients, and the current management of ischemic stroke risk in cancer patients with AF. We included studies that are recent, extensively cited in the literature, and are relevant to the intersection of AF, ischemic stroke and cancer. Additionally, we cited guidelines and statements from major cardiology societies to provide a comprehensive perspective on contemporary practice.

Pathophysiology of the increased risk for atrial fibrillation in cancer patients

Compared to noncancer patients, cancer patients are at an increased risk of developing AF, with one meta-analysis showing that solid cancer patients had a 47% increased risk of AF compared to noncancer patients, with the risk peaking within 90 days after diagnosis [17]. Cancer patients generally have a worse prognosis compared to noncancer patients [10]. Cancer treatments, when combined with pre-existing conditions like dyslipidemia and hypertension, create a high-risk profile for AF [6, 10]. Therapies for prostate cancer and hematologic malignancies disrupt metabolic pathways and have found to increase the risk for AF and other arrythmias [18, 19]. Similarly, breast cancer and its treatment options, such as anthracyclines are linked to myocardial toxicity, arrhythmias, and stroke [20, 21]. Risk factors such as older age, male sex, and lifestyle choices such as smoking also increase the risk of AF in cancer patients. Lung cancer and colorectal cancer are particularly impacted due to the high burden of comorbidities [22]. Additionally, cancer patients are at an increased risk for hypertension [23], diabetes [24], and cardiovascular disease [25] compared to noncancer patients, which further increases the risk of AF and stroke. The difference in the prevalence of AF between cancer and non-cancer patients persists even after adjusting for sociodemographic and cardiovascular risk factors [26].

The pathophysiology of cancer associated AF is multifaceted [10]. Chronic inflammation in cancer patients significantly contributes to atrial remodeling. Cytokines like IL-6 (interleukin-6) and CRP (C-reactive protein) enhance oxidative stress, fibrosis, and electrical remodeling, thereby facilitating the development of AF [27]. Elevated CRP levels have been independently associated with both the presence and future onset of AF, and CRP may promote structural remodeling by aiding in the clearance of apoptotic myocytes and promoting replacement fibrosis [28]. In the context of lung cancer, systemic hypoxia intensifies oxidative stress, creating a particularly arrhythmogenic environment [5].

Disruptions in the balance between sympathetic and parasympathetic autonomic control also induce changes in atrial electrophysiology, contributing to the increased incidence of AF [29]. Cancer and cancer therapeutic interventions are associated with autonomic disruption through direct effects, such as primary autonomic tumors and autonomic symptoms arising from brain tumors or metastatic lesions, and indirect effects, such as cancer treatment, pain response, and paraneoplastic autonomic syndromes. For example, chemotherapy agents may induce autonomic neuropathy, leading to irregular heart rates, while surgical interventions can result in transient autonomic dysfunction, both of which heighten the risk of AF and subsequent thromboembolic events [30].

Other underlying pathophysiological factors include hyperthyroidism due to aberrant release of thyroid-stimulating hormone or T3-like peptides by tumors and autoimmune paraneoplastic responses targeting atrial structures as antigens [31]. Classes of cancer therapies such as alkylating agents, anthracyclines, antimetabolites, and tyrosine kinase

inhibitors have been associated with AF and other arrhythmias. Arrhythmogenic effects can result from direct electrophysiological disruptions such as interference with cardiac ion channels and pumps [32]. Cancer treatments have also been associated with cardiotoxicities and/or cardiovascular morbidities such as arterial hypertension, myocarditis, ventricular dysfunction, and heart failure [33]. These can result in structural heart remodeling evidenced by histopathologic findings, including myocyte necrosis, fibrosis, and inflammatory infiltrates [34]. Immune checkpoint inhibitors have been theorized to cause similar sequelae due to T-lymphocyte-mediated inflammation targeting antigens in the heart [35].

Finally, radiation therapy has been implicated as a factor that increases the risk of AF, as the structural changes in the heart as a consequence of fibrosis could result in a pro-arrhythmogenic state [36, 37]. These risks are summarized in the figure below (Fig. 1).

Pathophysiology of the increased risk for ischemic stroke in cancer patients

Cancer patients are at an increased risk for ischemic stroke compared to the general population [38] and strokes in cancer patients tend to be more severe and associated with worse neurological and mortality outcomes compared to noncancer patients [39]. Among those with newly diagnosed cancer, those with a history of ischemic stroke were almost 3 times as likely to experience a recurrent stroke after cancer diagnosis (aHR, 2.68 [95% CI, 2.41–2.98]), with the risk being even higher if the stroke occurred within a year preceding the cancer diagnosis (aHR, 3.68 [95% CI, 3.22–4.22]) [40]. One study found that this risk is the highest in lung, pancreatic, and colorectal cancers, with increased risk being the highest 3 months after cancer diagnosis and attenuating by 1 year after diagnosis compared to noncancer controls [41].

Similar to the increased risk for AF, the pathophysiology behind the increased risk for ischemic stroke is also

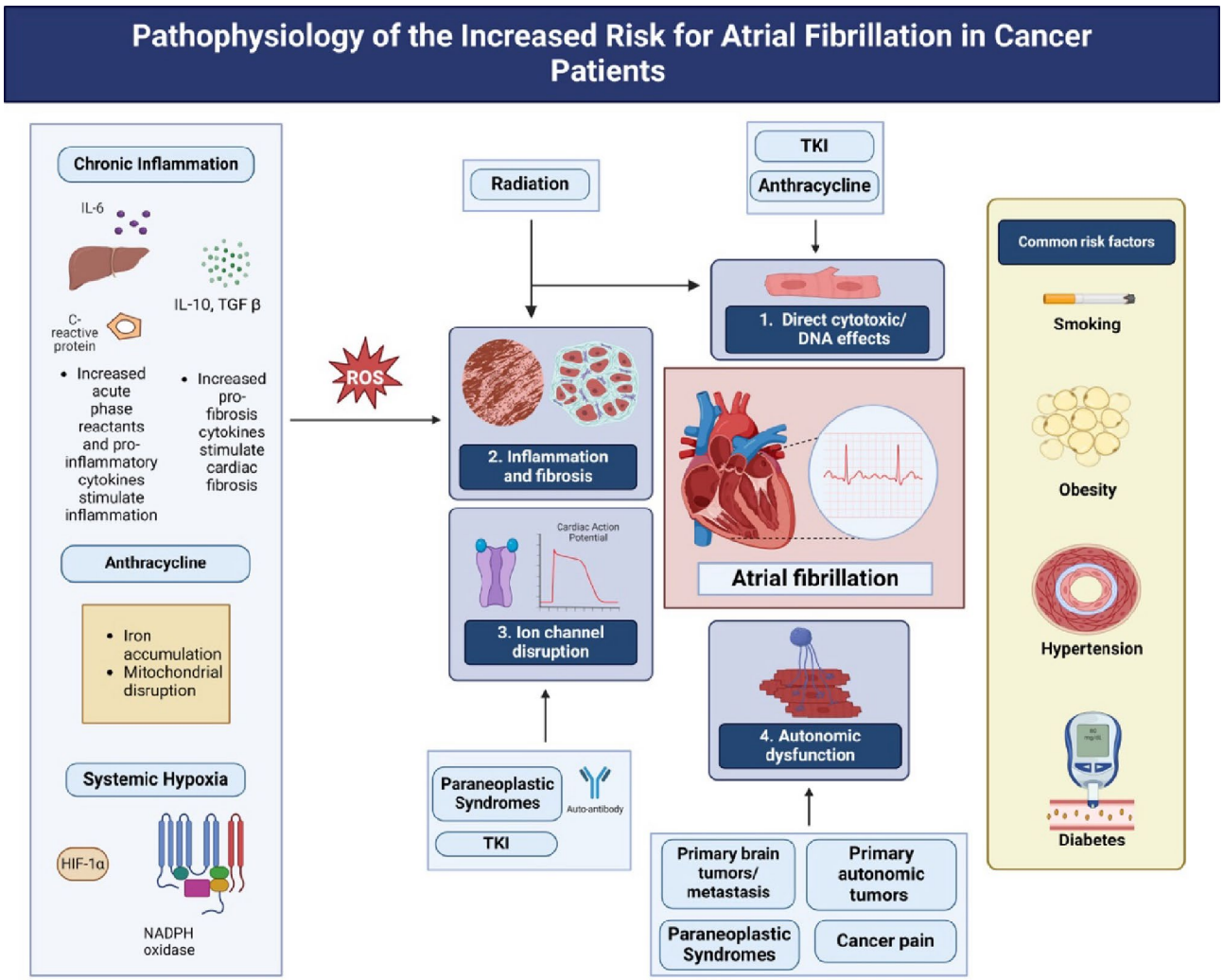

Fig. 1 Pathophysiology of the increased risk for AF in cancer patients. "Created with BioRender.com"

multifaceted, with both cancer-mediated hypercoagulability and the adverse effects of anti-neoplastic therapy playing significant roles. Tumors secrete procoagulants like tissue factor, which activate the clotting cascade, predisposing patients to thromboembolism [13]. Tissue factor, which is constitutively expressed by certain tumors, is involved in initiating the extrinsic coagulation pathway and thereby increases downstream activation of thrombin [42]. Cancer cells can also activate hypercoagulability in normal cells by interacting with endothelial cells, platelets, and leukocytes, resulting in the release of soluble mediators such as inflammatory cytokines (TNF-α, IL-1β), growth and proangiogenic factors (VEGF, bFGF, G-CSF), and platelet aggregation agents (ADP, thrombin) [43]. Additional mechanisms include the activation of platelets through direct cell-cell adhesion and releasing platelet-activating molecules, as well as cancer cell expression of adhesion molecules that enable binding to vessel walls and blood cells [43, 44]. Chemotherapy agents such as cisplatin and 5-fluorouracil worsen this hypercoagulable state by inducing endothelial damage from reactive oxygen species [20]. ADT-associated metabolic and pro-inflammatory alterations in immune cells, along with androgen-modulated platelet activity, contribute to increased atherosclerotic stroke risk [45]. Less common mechanisms for ischemic stroke include non-bacterial thrombotic endocarditis, which significantly increases the risk of arterial thromboembolism and may be an underdiagnosed cause of embolic stroke of undetermined source (ESUS) associated with cancer [46]. Venous thromboembolism, given that cancer is a hypercoagulable state, may also occur as a paradoxical embolism via a patent foramen ovale or another right-to-left intra-cardiac shunt [47]. These factors are summarized in the table below (Table 1).

Types of cancer that increase the risk for atrial fibrillation and ischemic stroke

Hematologic cancers

Hematologic malignancies such as lymphoma, leukemia and multiple myeloma are associated with an increased risk for AF [5]. Common treatment modalities such as stem cell transplantation and antineoplastic agents such as ibrutinib and melphalan are also associated with an increased risk for AF [19, 79, 80]. Additionally, hematologic malignancies such as multiple myeloma and Hodgkin lymphoma are associated with an increased risk for ischemic stroke [81–83].

Lung cancer

Of all the cancers, lung cancer poses the highest risk for AF and ischemic stroke, which may be due to systemic hypoxia and inflammation [5, 84]. One Swedish study identified lung cancer as having more than two times the risk of ischemic stroke 6 months after cancer diagnosis (SIR: 2.2 [95% CI:1.9, 2.4]) [58], and a SEER-Medicare study noted lung cancer as having the highest 6-month cumulative incidence of ischemic stroke compared to controls [57]. Lung cancer has also previously been associated with poor survival [85] secondary to hypercoagulability [86].

Prostate cancer

AF was associated with worse prognosis and clinical outcomes among patients with prostate cancer [87]. ADT for prostate cancer heightens AF risk by altering metabolic and hormonal pathways [88]. Abiraterone acetate appears to have the highest risk for AF among anti-androgen therapies for prostate cancer [20]. The decrease in the incidence of AF after normalization of testosterone in men with hypogonadism following testosterone replacement therapy may suggest the impact on androgens as the mechanism by which these therapies increase PC risk [89]. Compared to other cancers, prostate cancer had the lowest incidence rate ratio for AF, though still significant [90].

Breast cancer

Breast cancer and its treatments, such as anthracycline-based treatments increase arrhythmogenic risks [20, 21]. Doxorubicin demonstrates dose-dependent cardiotoxicity attributed to iron accumulation and formation of reactive oxygen species rather than double-strand breaks from inhibition of topoisomerase II [91]. Chemotherapy agents such as doxorubicin often target rapidly dividing cells, whereas mature cardiomyocytes are mostly quiescent [92].

Colorectal cancer

Postoperative AF frequently occurs following colorectal cancer surgery [93]. However, increased AF risk occurs within 90 days after colorectal cancer diagnosis exclusively, with no greater risk than for other cancers [94]. A meta-analysis investigating the relationship between cancer and the risk of developing AF found a 54% higher risk of developing AF in patients with colorectal cancer compared to patients without colorectal cancer [17]. In a Danish nationwide study of stroke patients, there was an increased risk of colorectal cancer in the first year after diagnosis, with the highest risk in patients with comorbid diabetes and obesity.

Table 1 Pathophysiology of the increased risk for ischemic stroke in cancer patients

Category	Mechanism/Factors	Pathophysiology
Cancer-Associated Factors	Prothrombotic state Cancer stage	• Increased levels of circulating microparticles, procoagulants and cancer mucin leads to the overexpression of tissue factor and factor X [42, 48–50] • Increased platelet production and activation by cancer cells through elevated thrombopoietin (TPO) levels, and p-selectin and ADP activity, respectively [43, 51] • Cancer cell-derived extracellular vesicles [52, 53] • Hyperviscosity [54] • Thromboinflammatory state: tumors secrete pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-8), activating endothelial cells, increasing vascular permeability, procoagulant activity, platelet production, and acute-phase reactants [55, 56] • Thromboembolic risk increases with cancer stage, with the highest risk in patients with stage III/IV cancer and those with distant metastases [12, 57, 58]
	Tumor embolism	• Leads to large vessel occlusion stroke in rare cases of lung cancer and lymphoma [59, 60]
	Non-bacterial thrombotic endocarditis	• Increases the risk of arterial thromboembolism [46]
Host-Related Factors	Obesity [61]	• Adipocytokine secretion: excess adipose tissue secretes leptin, which leads to platelet aggregation and activation [62, 63] • Chronic inflammation [62, 63] • Elevated PAI-1 levels inhibit fibrinolysis and promote thrombosis [62–64]
	Advanced age [65]	• Cognitive decline [66] • Acceleration of age-related changes due to cancer: DNA damage, epigenetic changes, cellular senescence, inflammation [66]
	Hypertension	• Poorly controlled hypertension significantly increases the risk for chemotherapy-induced cardiomyopathy and heart failure [67]
	Underlying uncontrolled diabetes	• Hyperglycemia-induced oxidative stress leads to endothelial damage and a prothrombotic state [68] • Advanced glycation end products (AGEs) interact with their receptors (RAGE) on endothelial cells [69]
	Underlying thrombophilia or predisposition to hypercoagulability [70]	• Factor V Leiden mutation • Prothrombin G20210A mutation • Deficiencies in antithrombin, protein C, or protein S
Treatment-Related Factors	Cancer directed surgery	• Hypercoagulability, inflammation, stress, and catabolic states post-surgery [71, 72]
	Radiation therapy (especially when directed at the head, neck, or chest)	• Accelerated atherosclerosis and direct damage to the myocardium [73, 74]
	Breast cancer hormone therapy (e.g., tamoxifen)	• Estrogen receptor modulation leads to a small increased venous thromboembolism risk [75]
	Prostate cancer hormone therapy (e.g., androgen deprivation therapy)	• Metabolic changes: insulin resistance, lipid dysregulation [76] • Vascular effects: impaired vasodilation, increased stiffness, endothelial dysfunction [76]
	Immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab)	• Inhibiting immune checkpoint proteins enhances immune responses, which leads to vasculitis, increased atherosclerosis, and endothelial dysfunction [77]
	Anti-angiogenic agents (e.g., bevacizumab)	• Damage the integrity of vascular endothelial cells, inhibit the expression of prostaglandin and nitric oxide, and promote platelet aggregation [78]
	Platinum-based chemotherapies (e.g., cisplatin)	• Endothelial damage from reactive oxygen species [20]
	Drugs that increase the risk of atrial fibrillation: tyrosine kinase inhibitors, anthracyclines, radiotherapy to chest, hematopoietic stem cell transplantation (HSCT)	• Increased thrombotic risk [36]

This may be a sequela of occult bleeding from colorectal cancer or a paraneoplastic syndrome causing hypercoagulability [95]. Other mechanisms include procoagulants and direct compression, which are not specific to colorectal cancer [96].

The risks of AF and stroke in common cancers are summarized below (Table 2).

The utility of common risk stratification scores in predicting thromboembolic and bleeding risk in cancer patients with atrial fibrillation

CHA_2DS_2-VASc and HAS-BLED are standard risk stratification scores used by clinicians to aid in the decision-making process for initiating anticoagulation in patients with AF. The CHA_2DS_2-VASc score is a risk stratification score with regards to the initiation of anticoagulation in patients with AF and has a maximum score of 9, with 1 point each allotted for a history of congestive heart failure, hypertension, diabetes mellitus, female sex, age 65–74 years old, and vascular disease (prior myocardial infarction, aortic plaque, peripheral artery disease) and 2 points each allotted for a prior stroke/transient ischemic attack and age ≥ 75 [106, 107]. More recent data show that female sex is a risk modifier rather than a risk factor for stroke, and given that in recent years, the female-male difference in stroke risk is nonsignificant [108, 109], such that there was no significant difference between the CHA_2DS_2-VASc score and the non-sex CHA_2DS_2-VASc score (i.e. CHA_2DS_2-VA) [110]. The 2024 European Society of Cardiology (ESC) guidelines reflect this data and recommend using the CHA_2DS_2-VA when making decisions on anticoagulation therapy [111]. Nevertheless, these scores have not been well validated in cancer patients with AF, with only a few studies addressing this issue [112, 113].

Table 2 Increased risk of AF and ischemic stroke and the mechanisms associated with this risk stratified by specific cancer

Type of Cancer	Risk of Atrial Fibrillation and Ischemic Stroke	Factors/Mechanisms Associated with Increased Risk
Hematologic Cancers	• Leukemia, lymphoma and multiple myeloma are associated with an increased risk for AF [5] • Stem cell transplantation and antineoplastic agents such as ibrutinib and melphalan are associated with an increased risk for AF [19, 79, 80] • Hodgkin lymphoma and multiple myeloma are associated with an increased risk for ischemic stroke [81–83]	• Shared risk factors between cardiovascular disease and hematologic malignancy (old age, pre-existing diastolic dysfunction, weight gain, pre-existing cardiovascular disease) [79] • Ibrutinib inhibits the phosphoinositide 3-kinase (PI3K)-Akt pathway, which is a regulator of cardiac protection [19, 80]
Lung Cancer	• Highest risk for AF among cancers [5] • Highest arterial thromboembolic risk 6 months after diagnosis [57] • Smoking confounds risk, but does not fully explain elevated stroke incidence [97] • Poor survival linked to hypercoagulability [85, 86]	• Systemic hypoxia and inflammation [5, 84] • Dose-dependent AF risk from smoking [98] • Immunotherapy (PD-1/PD-L1) associated with arrhythmias [99] • Radiotherapy (localized NSCLC): 5-year cumulative AF incidence 11.1%), higher pulmonary vein max dose = higher AF risk [100]
Prostate Cancer	• AF associated with worse prognosis and clinical outcomes [87] • Lowest incidence rate ratio of AF among common cancers but still significant [90] • Incidence of stroke 12% higher with ADT associated with 13% increased stroke risk [76] • Among ADT therapies, GnRH, GnRH + oral anti-androgens, and orchiectomy all linked to elevated stroke risk [101]	• ADT disrupts metabolic/hormonal pathways [88] • Abiraterone acetate confers higher AF risk among anti-androgens [20] • Testosterone normalization linked to decreased AF in hypogonadal men [89] • Orchiectomy and combination GnRH + anti-androgens can further elevate stroke risk [101]
Breast Cancer	• Anthracycline-based therapies (e.g., doxorubicin) heighten arrhythmogenic risks [20] • Doxorubicin cardiotoxicity is dose-dependent [91] • Radiotherapy (localized breast cancer): 5-year cumulative AF incidence of 1.3%, increased with higher pulmonary vein max dose [100] • Aromatase inhibitor (AI) use is associated with an increased incidence of new onset AF compared to tamoxifen use [102]	• Direct cardiotoxic effects (ROS generation, iron accumulation) rather than solely topoisomerase II inhibition [91] • Chemotherapy targeting rapidly dividing cells can also damage quiescent cardiomyocytes [92] • Radiation therapy dose to pulmonary vein area potentially increasing AF risk [100] • Depletion of estrogen has been associated with an increased AF risk; AIs deplete estrogen in the cardiovascular system [102]
Colorectal Cancer	• Postoperative AF common after CRC surgeries [93] • Within 90 days of CRC diagnosis: elevated AF risk [94] • 54% higher AF risk vs. non-CRC patients [17] • Increased stroke risk in first year post-diagnosis, especially in patients with diabetes, obesity [95] • Arrhythmias (2.0%) with capecitabine in metastatic CRC [103]	• Hypercoagulability/paraneoplastic mechanisms [95, 96] • Procoagulants released by CRC cells and direct tumor compression of vessels [96] • Capecitabine-associated cardiotoxicities (MI, arrhythmias) [103, 104] • Bevacizumab (VEGF inhibitor) elevates relative risk of cerebrovascular ischemic events (RR = 3.22, up to 6.22 in metastatic CRC) [105] • Surgical stress contributing to AF [93]

Bleeding risk can be assessed by various bleeding risk stratification scores [114]. The most validated simple clinical score is the HAS-BLED score, which has a maximum score of 9, with 1 point each allotted for a history of hypertension, abnormal renal function, abnormal liver function, bleeding history or predisposition, labile international normalized ratio (INR), age > 65, use of drugs, and use of alcohol [115]. A HAS-BLED score of ≥ 3 indicates caution when prescribing oral anticoagulation and necessitates early and more frequent follow-up. Bleeding risk is the interaction of modifiable and non-modifiable bleeding risks, and are not static but dynamic, changing over time and impacting outcomes [116, 117]. However, bleeding risk scores have been less well validated in AF patients with cancer, although some studies have been published [118].

Common risk stratifying scores have not been well validated in cancer patients

Despite the utility of these risk-stratifying scores in guiding clinical decision-making in the general population, one significant drawback is that these scores have not been well validated in a population of cancer patients with AF [6, 11, 113, 119]. Moreover, these scores do not take into account a history of or type of cancer, the hypercoagulable state due to the cancer itself, and the prothrombotic effects of specific anti-neoplastic therapies, along with the increased bleeding risk due to cancer and anti-neoplastic-related coagulopathy and thrombocytopenia [14, 93]. Patients with cancer and AF have a higher incidence of stroke when compared to the general population [3, 113] but similar risk factors, which could be due to cancer-specific risk factors for stroke that are not accounted for in traditional risk-stratification scores [113].

Further complicating the clinical picture is that cancer patients have both a higher risk of stroke and a higher risk of bleeding, making the decision to initiate anticoagulation even more challenging [16, 113].

The predictive value of CHA_2DS_2-VASc for thromboembolism in cancer patients

The predictive value of CHA_2DS_2-VASc for stroke risk in cancer patients with AF is summarized in the evidence table below (Table 3).

The predictive value of HAS-BLED for bleeding in cancer patients

Regarding bleeding risk, the discriminative capacity of the HAS-BLED score in predicting bleeding events was modest in cancer patients with a history of AF [119, 123]. This could be due to the dynamic nature of the components of the score, such as uncontrolled hypertension, labile INR, and drug use, leading to patients switching risk categories from their baseline assignment [119]. Importantly, bleeding risk in cancer patients with AF is not static and requires close review and reassessment at follow-up appointments.

Current management of thromboembolic risk in cancer patients

Although guidelines recommend routine screening of all members of the general population above the age of 65 for AF [88], except for patients receiving Bruton tyrosine kinase inhibitor therapy, in whom EKG before initiation of the therapy and serial EKGs are recommended [125], there are currently no specific recommendations in the recent cardio-oncology guidelines for screening cancer patients for AF that differ from the general population [126]. As with the general population, primary prevention of stroke in cancer patients requires an individualized risk calculation to determine the steps for primary prevention; however, a uniform method to calculate cancer patients' risk for stroke has not been established in this cohort [127]. As with primary prevention of stroke in cancer patients with AF, secondary prevention faces similar challenges, as there is limited literature and a lack of consensus regarding secondary prevention of stroke in cancer patients with AF [39, 128]. The uncertainty about the best antithrombotic regimen to treat the hypercoagulable state in cancer [128] combined with the difficulty in identifying a known source of the stroke in cancer patients leads many neurologists to employ a personalized approach or rely on institutional practice patterns to determine which antithrombotic agents to utilize in this cohort [39].

As mentioned above, current guidelines recommend similar strategies for initiating anticoagulation in cancer patients with AF as with noncancer patients, with the DOACs (direct oral anticoagulants) preferred to low molecular weight heparin (LMWH) and vitamin K antagonist (VKA) in patients without mechanical heart valves or moderate-to-severe mitral stenosis [88, 126, 129]. A nationwide cohort study found that DOACs were associated with a lower risk of major adverse cardiovascular events (defined as ischemic stroke/systemic embolism or acute myocardial infarction, major adverse limb events, venous thrombosis and major bleeding compared with warfarin use [16], while a meta-analysis found that DOACs were associated with a lowered risk of stroke/systemic embolism (SE) and major bleeding compared to VKA [130].

A subgroup analysis of the ARISTOPHANES study that investigated safety and efficacy of different classes of anticoagulants for cancer patients with nonvalvular AF found

Table 3 Predictive value of CHA_2DS_2-VASc for stroke risk in cancer patients with AF

Study	Pertinent Population	Key Findings
Ajabnoor et al., 2024 [119]	Patients with nonvalvular AF and breast, prostate, colorectal, lung or hematological cancer who did not use anticoagulation > 14 days before AF diagnosis	CHA_2DS_2-VASc had good to modest discrimination in: • Prostate cancer (c-statistic = 0.74, [95% CI: 0.71, 0.77)] • Hematological cancer (c-statistic = 0.71, [95% CI: 0.66, 0.76]) • Colorectal cancer (c-statistic = 0.70, [95% CI: 0.66, 0.75]) • Breast cancer (c-statistic = 0.70, [95% CI: 0.66, 0.74]) • Lung cancers (c-statistic = 0.69, [95% CI: 0.60, 0.79]) • AF and no cancer (c-statistic = 0.73, [95% CI: 0.72, 0.74])
D'Souza et al., 2018 [120]	Patients with nonvalvular AF and a cancer diagnosis within 5 years who did not use anticoagulation within 6 months preceding the admission for AF or within the first 7 days following discharge	• Patients with cancer and a CHA_2DS_2-VASc score of 1 had a fourfold increased risk for thromboembolism compared to patients without cancer and a CHA_2DS_2-VASc score of 0
Leader et al., 2023 [121]	Patients with AF and cancer with a CHA_2DS_2-VASc score of 0–2 not on anticoagulation within 90 days of inclusion in the study	• Patients with a CHA_2DS_2-VASc score of 0–2 who were not on anticoagulation had almost a threefold risk of arterial thromboembolism in the first 12 months after cancer diagnosis (HR: 2.7, [95% CI: 1.65–4.41]) • Patients at intermediate risk (defined as men with a CHA_2DS_2-VASc score of 1 and women with a CHA_2DS_2-VASc score of 2) had more than a sixfold risk for arterial thromboembolism in the first 12 months after cancer diagnosis (HR: 6.07, [95% CI: 2.45–15.01])
Matetic et al., 2023 [122]	Patients with nonvalvular AF and breast, prostate, colorectal, lung or hematological, or other cancer	• CHA_2DS_2-VASc had poor discriminative capacity for ischemic stroke and statistically insignificant area under the curve (AUC) values in cancer patients (AUC: 0.538, [95% CI 0.477–0.598], $p = 0.238$)
Pastori et al., 2021 [7]	Patients hospitalized with AF and a history of cancer	• CHA_2DS_2-VASc was significantly associated with thromboembolic risk, but its predictive value was modest and significantly lower in cancer patients with AF compared to patients without cancer
Raposeiras-Roubin et al., 2022 [123]	Patients with AF with cancer treated with and without anticoagulation	• In patients treated with anticoagulation, the c-statistic of CHA_2DS_2-VASc was similar in cancer patients (0.63) and noncancer patients (0.60), $p > 0.05$ for the comparison • In patients not treated with anticoagulation, the c-statistic of CHA_2DS_2-VASc was poor and significantly lower in patients with cancer (0.49) than in patients without cancer (0.69), $p < 0.001$ for the comparison
Ullah et al., 2023 [124]	Patients with AF and breast, prostate, colorectal, lung or hematological, or other cancer	• CHA_2DS_2-VASc had modest predictive capacity for ischemic stroke in the overall cancer cohort (AUC: 0.624, [95% CI: 0.617–0.631], $p < 0.0001$) • CHA_2DS_2-VASc was not predictive for ischemic stroke in prostate cancer (AUC: 0.527, [95% CI: 0.498–0.555], $p = 0.079$) and colorectal cancer (AUC: 0.558 [95% CI: 0.495–0.621], $p = 0.1$)

that apixaban had a lower risk of stroke/SE and major bleeding when compared to warfarin while dabigatran and rivaroxaban had similar risk for stroke/SE and major bleeding when compared to warfarin. In terms of DOAC-DOAC comparison, for stroke/SE, apixaban had a lower risk compared to dabigatran and a similar risk compared to rivaroxaban. For major bleeding, apixaban had a lower risk when compared to rivaroxaban and a similar risk when compared to dabigatran [131].

Another study found that patients receiving LMWH or warfarin had an increased risk of VTE (venous thromboembolism) recurrence compared with those prescribed DOACs, and patients receiving LMWH were associated with an increased risk of all-cause mortality and hospitalizations for major bleeding compared with those prescribed DOACs [132].

Regarding interventional management, LAAO (left atrial appendage occlusion) devices are an option for stroke prevention in those who cannot take long term oral anticoagulation [133, 134] but rarely used in clinical practice for cancer patients due to complications associated with the procedure [126]. There are mixed results concerning the safety of the procedure. One study found an increased risk of in-hospital ischemic stroke/TIA with active cancer, but not with prior cancer [135] and another study found an increased risk of periprocedural complications in patients with active cancer [134]. Two other studies demonstrated no difference in stroke, mortality, or bleeding in cancer patients vs. noncancer patients [136, 137].

Current guidelines for the management of ischemic stroke in the general population recommend the utilization of IV alteplase if the patient presents within 4.5 h of symptom onset and/or endovascular therapy, though there are no specific guidelines for patients with AF [138]. Although there are emerging data demonstrating the benefit of IV alteplase in patients with AF [139], eligibility for therapy in this cohort of patients is a challenge because IV alteplase is contraindicated if a dose of oral anticoagulation has been used within 48 h [138]. Further complicating the clinical picture is that there are not readily available laboratory tests to measure the therapeutic effect of DOACs and reversal of DOACs is not generally recommended due

to the prothrombotic risks [139]. In cancer patients with stroke, there is minimal knowledge and trial data about the safety and efficacy of these therapies [39, 140]. Although the American Heart Association (AHA) guidelines state that cancer patients (except those with brain cancer) who do not have contraindications for thrombolytic therapy are eligible for therapy, the utilization of this therapy during acute stroke is more than 3% lower for those with malignancy compared to those without [141]. Data from two studies, along with a scientific rationale from the AHA with regards to the inclusion and exclusion criteria of this therapy, suggest that IV alteplase does not increase bleeding risk in cancer patients [142–144], although it is important to note the small sample size of these studies. With regards to endovascular therapy in cancer patients, studies have shown similar rates of successful reperfusion [145, 146] and intracranial hemorrhage [145–147], but worse functional outcomes [145, 146], 3-month all-cause mortality [146] and risk of recurrent stroke within 3 months [145] when compared to noncancer patients.

Drug interactions between DOACs and cancer treatments

Although DOACs have fewer drug-drug interactions (DDIs) than warfarin, all DOACs are substrates for the P-glycoprotein (P-gp) system, while rivaroxaban and apixaban are additionally metabolized by the cytochrome P3A4 (CYP3A4) pathway [148–150]. Coadministration of DOACs with other medications that alter the activity of these two systems can result in supra or subtherapeutic drug levels. P-gp or CYP3A4 inducers may reduce the plasma concentration of the DOAC, thereby increasing thrombotic risk, while P-gp or CYP3A4 inhibitors may increase the plasma concentration of the DOAC, thereby increasing bleeding risk [148, 150]. This is important to consider because these two systems play an important role in metabolizing commonly prescribed classes of antineoplastic agents such as anthracyclines, antimitotic agents, tyrosine kinase inhibitors, hormonal agents, and immune-modulating agents. Further complicating the clinical picture is the variability within classes of antineoplastic agents with regards to induction or inhibition of the CYPA4 and P-gp systems [151] and the limited literature documenting the real world risk of adverse events as a result of DOAC DDIs [148]. The 2018 European Heart Rhythm Association guidelines do not recommend DOAC use in combination with drugs that are strong inducers or inhibitors of both the CYPA4 and P-gp systems, but offer no specific recommendations for moderate inhibitors/inducers [151].

Discussion

This narrative review article illustrates the latest scientific evidence surrounding the risk of AF and ischemic stroke in patients with cancer. We highlight the latest research regarding the pathophysiology of both AF and ischemic stroke in cancer patients, the current management of AF and ischemic stroke risk in cancer patients, and evidence on clinical risk stratifying scores such as CHA_2DS_2-VASc and HAS-BLED.

The latest ESC cardio-oncology guidelines from 2022 highlight the complexity behind risk stratifying stroke risk in cancer patients with AF and give a class IIa recommendation for using CHA_2DS_2-VASc as a risk stratifying tool for stroke, noting that it may underestimate actual thromboembolic risk in this population [126]. Despite this, the current class of evidence to initiate anticoagulation in cancer patients with AF and a CHA_2DS_2-VASc score of 1 for males and 2 for females or 0 for males and 1 for females is IIa and IIb, respectively [126]. This aligns with the AHA's scientific statement on arrythmias in cardio-oncology, which highlights the growing evidence that the CHA_2DS_2-VASc and HAS-BLED may be less accurate in cancer patients because they do not account for cancer specific factors [152]. The decision to initiate anticoagulation in this population is individualized, taking into account cancer prognosis, cancer type, and the individual risk profile of each patient [14, 93, 126, 127], highlighting the lack of consensus opinion on how to effectively risk-stratify cancer patients with AF based on current available scores and guidelines.

Further research could focus on developing more effective risk stratification tools for bleeding and stroke risk in cancer patients with AF. Cancer patients are at a higher risk for AF, bleeding, and ischemic stroke than the general population, yet traditional risk stratifying scores are not validated in this population and have poor predictive capacity for thromboembolic and bleeding events in this cohort of patients. Moreover, there is variability in which cancers increase the risk of thromboembolism versus which increase the risk of bleeding. The lack of evidence-based guidelines has significant implications in clinical practice, as suboptimal use of anticoagulation in cancer patients with AF and high stroke risk, with even worse utilization of anticoagulation in cancer patients receiving chemotherapy [153], along with worse stroke outcomes in cancer patients [154] and cancer patients with AF [155], has been reported in the literature.

We recommend creating cancer-specific risk scores that offer a tailored approach to each patient and incorporate variables such as cancer characteristics and anti-cancer therapy that are not commonly captured in traditional risk stratification scores to more effectively stratify ischemic stroke and bleeding risk in this cohort of patients. This is

consistent with the previously referenced AHA scientific statement, which emphasizes the need for cancer-specific risk prediction algorithms to guide clinical decision making on initiation of anticoagulation in cancer patients with AF [152]. We highlight the pathophysiology behind cancer patients' increased risk for both thrombosis and bleeding, the lack of clear clinical guidelines concerning how to effectively manage the competing bleeding and thrombotic risk in cancer patients with AF, and the underwhelming performance of current risk stratification scores for both in cancer patients with AF. An ideal score would incorporate the propensity for both bleeding and thrombosis based on cancer and patient-specific risk factors in guiding management concerning which patients would benefit most from initiating anticoagulation. A new cancer-specific risk score would consist of patient variables that are readily available to providers and can be easily implemented in a clinic setting, although given the heterogeneity of cancers, whether a "one score fits all" is possible remains to be seen.

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Data availability No datasets were generated or analysed during the current study.

Declarations

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