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STATE OF THE ART

Cancer and arterial thrombosis: therapeutic options

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Abstract

A State of the Art lecture titled "Cancer and Arterial Thrombosis: Therapeutic Options" was presented at the International Society on Thrombosis and Haemostasis Congress in 2023. This State of the Art review delves into the complex relationship between cancer and arterial thromboembolism (ATE), encompassing acute coronary syndrome, ischemic strokes, and peripheral arterial disease.

The burden of cancer-associated ATE is not well defined, but studies indicate elevated risks, particularly in the 6 months after a cancer diagnosis. Incidence varies among cancer subtypes, with lung cancer displaying the highest rates. Additionally, the pathophysiology of cancer-associated ATE involves a multifaceted interplay of cancer-induced hypercoagulopathy, cancer therapy–related thrombosis, and personal risk factor contributors.

ATEs are clinically heterogeneous and in the context of cancer have particular mechanistic differences compared with ATE patients without cancer. This requires modifications in approach and tailored management considerations. Specific etiologies contributing to ATE, such as coronary vasospasm and non–bacterial-thrombotic endocarditis, need to be considered. The diagnosis of cancer alone usually does not contraindicate patients to standard guideline-based therapies for the management of ATE, although nuances in treatment may need to be considered in light of the underlying cancer.

Atrial fibrillation in cancer patients further complicates the thrombotic landscape. Cancer patients with atrial fibrillation are at a higher risk of ATE, necessitating careful consideration of anticoagulation therapy as clinical benefits and bleeding risks need to be weighed. ATE may also be a presenting sign of underlying malignancy, which requires increased awareness and focused clinical evaluation for cancer in selected cases. Finally, we summarize relevant new data on this topic presented during the 2023 International Society on Thrombosis and Haemostasis Congress.

KEYWORDS
acute coronary syndrome, atrial fibrillation, neoplasms, stroke, thromboembolism, thrombosis

Essentials

- Cancer patients are at an increased risk of both venous thromboembolism and arterial thromboembolism (ATE).
- ATE is an important contributor to morbidity and mortality in cancer patients.
- Cancer and anticancer treatment contribute to the increased risk of ATE.
- The management of ATE in cancer patients warrants specific considerations.

1 | INTRODUCTION

The association between cancer and thromboembolism has been well established since the 19th century when Armand Trousseau described migratory thrombophlebitis in patients with visceral cancer [1]. Traditionally, the literature on cancer-associated thrombosis (CAT) has focused on venous thromboembolism (VTE) and there has been limited attention and published data on arterial thromboembolism (ATE) in cancer. ATE includes a wide spectrum of diseases, including acute coronary syndrome (ACS), ischemic stroke, and peripheral arterial disease (PAD) [2]. Recent literature has suggested that patients with cancer are at an increased risk of ATE [3,4]

In this State of the Art review article, we aim to review cancer-associated ATE, including the burden of disease, the specific pathophysiology associated with cancer, and its management. This review will focus on ATE associated with active cancer and not the late cardiovascular effects of cancer and its therapy. We will not cover myeloproliferative neoplasms associated with ATE [5,6].

2 | THE BURDEN OF CANCER-ASSOCIATED ATE: INCIDENCE AND IMPACT

Data on the epidemiology of cancer-associated ATE were limited until recently. In addition, it is difficult to compare between most studies due to the heterogeneity in diagnosis of ATE, study design, and patient cohorts (Table) [7–15]. For example, the diagnosis of myocardial infarction may be based on different parameters, including electrocardiogram changes, cardiac biomarkers, and angiogram findings. These variations would result in differences in reporting, affecting the incidence rates. In addition, in many studies reporting ATE incidence, most relied on International Classification of Diseases claim codes rather than specific adjudicated outcome definitions, hence affecting accuracy of the data.

In the analysis of a Surveillance, Epidemiology, and End Results (SEER) database in the United States, which included 279,719 patients with newly diagnosed cancer and matched controls, the incidence of ATE (ischemic stroke or myocardial infarction) was 4.7% compared with 2.2% in the control cohort at 6 months, with a hazard ratio for ATE of 2.2 (95% CI: 2.1-2.3) [4]. Such consolidated cancer-associated ATE data are scarce since most reported data are in specific ATE or cancer subtypes. Emerging data demonstrate an increasing incidence of cancer-associated ATE [16,17].

Cancer-associated ATE incidence also differs between cancer subtypes. In the SEER study, lung cancer had the highest incidence of ATE, with a 6-month cumulative incidence of acute myocardial infarction (AMI) of 3.2% and stroke of 5.6% [4]. Overall, rates also differed with histopathology, with adenocarcinoma demonstrating the highest rates of stroke recurrence [4]. Lung cancer also had the highest ATE rate at 12 months in other studies [3,14]. Different types of ATE may be associated with different cancer locations. Wang et al. [18] looked at the incidence and risk of various types of ATE in patients with cancer and reported that ischemic strokes were more commonly found in brain cancer (relative risk [RR] = 4.04), that acute mesenteric ischemia was typically associated with gastrointestinal cancers (RR = 6.53 with pancreatic cancer), and that acute renal infarction was associated with renal cancer (RR = 4.52) when compared with a cohort of Medicare enrollees without cancer. Detection bias due to site-specific cancer imaging may explain some of the excess ATE risk in these patients.

The risk of ATE in cancer patients is time-dependent. The highest risk has been demonstrated in the first month after the cancer diagnosis, with a hazard ratio of 7.3 for AMI and 4.5 for ischemic stroke, with the risk tapering with time [4]. Longer-term data on ATE risk are limited. In a population cohort study of cancer patients in Sweden, while the overall risk of cancer-associated ATE declined with time, it was still elevated after 10 years postcancer diagnosis with a standardized incidence ratio of 1.07 [15]. Some of the long-term ATE risk may be explained by the late cardiovascular effects of cancer therapy, such as accelerated atherosclerosis associated with radiation therapy, and not by active cancer itself.

The diagnosis of cancer-associated ATE also has a prognostic impact. Cancer patients with ATE had an increased risk for mortality (HR: 4.0; 95% CI: 4.0-4.1), and this remained significant after adjustment for cancer stage and other matching factors [4]. The 30-day mortality after an ATE in patients with cancer was also higher at 17.6% compared with a matched control population who had an ATE without cancer at 11.6% [4]. In an analysis of patients with AMI requiring percutaneous coronary intervention (PCI) from the National Heart, Lung, and Blood Institute Dynamic Registry, cancer was a significant predictor of 1-year mortality [19]. In cancer patients with ischemic strokes, 30-day mortality rates were as high as 25% to 50% [20,21].

3 | THE PATHOPHYSIOLOGY OF CANCER-ASSOCIATED ATE

Virchow's triad describes 3 main domains that explain the development of vascular thrombosis: coagulopathy, endothelial dysfunction, and stasis of blood flow. In the context of cancer-associated ATE, specific etiologies across these domains include cancer-induced hypercoagulopathy, cancer therapy–associated thrombosis, and cancer genomic contributors (Figure 1). Additionally, patients with shared

TABLE Selected studies reporting the epidemiology of cancer-associated ATE in various cancer patient cohorts.

Study	Study design	Cohort	Country	Cancer types[d]	Period	Total patients	Median age (y)	Follow-up (mo)	ATE *n* (%)	ACS *n* (%)	Ischemic stroke *n* (%)	PAD *n* (%)
Grilz et al. [8]	Prospective observational cohort study	Patients with cancer[e]	Austria	All	2003-2013	1880	61	24[a]	48 (2.6%)	20 (1.1%)	16 (0.9%)	NA
Zoller at al. [9,15]	Retrospective population-based cohort study	Patients with a diagnosis of cancer	Sweden	All	1987-2008	820,491	Not available	Not available	NA	34,666 (4.2%)	31,524 (3.8%)	NA
Navi et al. [4]	Retrospective multicentre cohort study	Patients from US SEER database with new primary diagnosis of cancer	USA	8 cancer subtypes[b]	2002-2011	279,718	74	24	Cumulative incidence 1 y: 6.5% 2 y: 9.1%	Cumulative incidence 1 y: 2.6% 2 y: 3.7%	Cumulative incidence 1 y: 4.3% 2 y: 5.8%	NA
Mulder et al. [3]	Retrospective population-based cohort study	Patients with cancer	Demark	All	1997-2017	458,462	69	12	Cumulative incidence 6 mo: 1.5% 1 y: 2.1%	Cumulative incidence 6 mo: 0.5% 1 y: 0.8%	Cumulative incidence 6 mo: 0.9% 1 y: 1.2%	Cumulative incidence 6 mo: 0.1% 1 y: 0.1%
Feldman et al. [14]	Retrospective cohort study	Patients with solid organ cancer[e]	USA	Solid organ cancers	2014-2016	11,871	66	12[c]	160 (1.3%)	53 (0.4%)	106 (0.9%)	1 (0.1%)
Noumegni et al. [10]	Prospective multicentre cohort study	Patients with CA-VTE	France	All	1992-2019	914	68	68[a]	57 (6.2%)	8 (0.9%)	43 (4.7%)	5 (0.6%)
Brenner et al. [11]	Prospective registry study	RIETE cohort with active CA-VTE[e]	USA, Europe, South America, Israel, Iran, Vietnam, Japan	All	2009-2014	5717	67	12	63 (1.1%)	15 (0.3%)	42 (0.7%)	6 0 (0.1%)

ACS, acute coronary syndrome; ATE, arterial thromboembolism; CA-VTE, cancer-associated venous thromboembolism; PAD, peripheral arterial disease; RIETE, Registro Informatizado de Enfermedad TromboEmbolica; US, United States; SEER, Surveillance Epidemiology and End Results–Medicare.

[a]Median follow-up.

[b]Breast cancer, lung cancer, prostate cancer, colorectal cancer, bladder cancer, pancreatic cancer, gastric cancer, non-Hodgkin lymphoma.

[c]Patients were indexed on the date of tissue-matched blood control accession and followed until first ATE event or death, for up to 12 months.

[d]Patients indexed at time of cancer diagnosis, unless otherwise specified.

[e]Patients with prior ATE excluded from study.

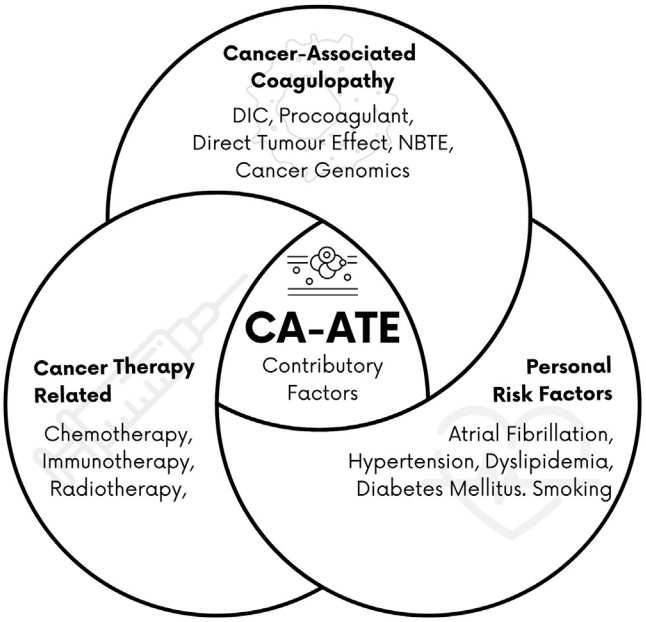

FIGURE 1 Contributing factors to cancer-associated arterial thromboembolism. CA-ATE, cancer-associated arterial thromboembolism; DIC, disseminated intravascular coagulation; NBTE, nonbacterial thrombotic endocarditis.

risk factors such as a history of smoking are at increased risk for cancer-associated ATE, while risk factors such as hypertension and atrial fibrillation (AF) are more prevalent in certain groups of cancer patients (eg, due to targeted anticancer therapy such as Bruton tyrosine kinase inhibitors) [22].

3.1 | Cancer-induced hypercoagulopathy

Cancer-induced hypercoagulopathy involves a complex interplay of direct and indirect effects of cancer on the coagulation system. Malignant cells express procoagulants that directly contribute to prothrombotic states. These procoagulant proteins include tissue factor, podoplanin, plasminogen activator inhibitor, and protein disulfide isomerase [23]. Tissue factor, in particular, plays an important role in arterial thrombosis. Malignant cells release tissue factor-rich macrovesicles, which may interact with tissue factor expression on macrophages in atherosclerotic plaques [24,25]

At the cellular level, activated platelets and neutrophil extracellular traps (NETs) also contribute to thrombosis. NETosis is chronically induced in the presence of malignancy and contributes to accelerated arterial thrombosis development [26]. NETs provide the structural backbone for red blood cells, platelets, and fibrin, thereby promoting thrombosis [27]. In addition, the components of NETs such as extracellular DNA, histones, and serine proteases enhance thrombosis. Histones impair thrombomodulin-dependent protein C activation, inhibiting natural anticoagulant activity, while neutrophil serine proteases cause proteolysis of tissue factor pathway inhibitor, enhancing tissue factor and contact factor-mediated hemostasis [28]. These components may serve as biomarkers for risk prediction and diagnosis of cancer-associated ATE [29].

3.2 | Cancer therapy–associated thrombosis

Anticancer therapies, including cytotoxic chemotherapy, immunotherapy, targeted therapy, and radiotherapy, have off-target adverse effects that include thrombosis. Figure 2 shows the differential mechanism, vascular effect, and preferential sites of ATE of various cancer therapies. The underlying mechanism of therapy-associated thrombosis is multifactorial, including endothelial dysfunction, induced coagulopathy, and platelet activation. These effects are layered upon the prothrombotic effects of the underlying cancer, further increasing the risk of thrombosis. The data on cancer therapy–induced VTE are more robust than those on ATE, and the risk profiles

Pathophysiology of ATE	Platelet activation	Procoagulant effects	Endothelial dysfunction
	BCR-ABL Inhibitors IMiDs	VEGF Inhibitor VEGF TKI Platinum-based agents	VEGF Inhibitor VEGF TKI Fluoropyrimidines Immune Checkpoint Inhibitors Platinum-based agents Radiation

Effect on arterial flow	Vasospasm	Acute arterial thrombosis	Accelerated atherosclerosis
	Fluoropyrimidines Platinum-based agents VEGF Inhibitor VEGF TKI Vinca alkaloids	BCR-ABL Inhibitors Immune Checkpoint Inhibitors IMiDs	Radiation BCR-ABL Inhibitors VEGF Inhibitor VEGF TKI Immune Checkpoint Inhibitors

Type of ATE	Acute coronary syndrome	Ischemic stroke	Peripheral vascular disease
	Fluoropyrimidines Platinum-based agents IMiDs VEGF Inhibitor VEGF TKI BCR-ABL Inhibitors Immune Checkpoint Inhibitors	Platinum-based agents IMiDs VEGF Inhibitor VEGF TKI BCR-ABL Inhibitors	Platinum-based agents BCR-ABL Inhibitors

FIGURE 2 Anticancer therapies associated with ATE, stratified for mechanism and site of ATE. ATE, arterial thromboembolism; BCR-ABL: Breakpoint Cluster Region-Abelson; IMiDs, immunomodulatory drugs; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

do differ. Therapies with the highest risk of ATE include vascular endothelial growth factor inhibitors and Breakpoint Cluster Region-Abelson (BCR-ABL) tyrosine kinase receptor inhibitors (TKI) [30].

For example, ponatinib, a BCR-ABL TKI, was associated with a prohibitively high rate of ATE in initial studies. A phase 3 trial had to be stopped prematurely due to a 6% incidence of serious ATE prior to study termination [31]. Several mechanisms for ponatinib-associated ATE have been suggested, including platelet hyperactivation and thrombotic microangiopathy involving increased von Willebrand factor [32,33]. Traditional cytotoxic chemotherapy, such as platinum-based therapies and vinca alkaloids, also carries a significant risk of ATE. ATE accounted for 16.6% of all reported cardiovascular events in a 30-year review of the US Food and Drug Administration registry data [34]. Newer cancer therapies, including immune checkpoint inhibitors (ICIs), also carry an increased risk of ATE. In a retrospective cohort study comparing patients who received ICI with a control cohort of patients who did not receive ICI, the ICI group had an RR of 2.01 for developing ATE, with the RR increasing to 1.41 at 1 year and 1.97 at 4 years [35].

ATEs are also associated with radiotherapy through radiation-induced arteritis. The early effects of radiation manifest as endothelial apoptosis, with subsequent long-term effects of vascular fibrosis accelerating arteriosclerosis [36]. In patients receiving radiotherapy for head and neck tumors, the incidence of carotid stenosis was 21% at 36 months [37]. These vascular changes mean that clinical manifestations of ATE may arise years after the initial radiation therapy [38].

3.3 | Cancer genomic contributors

Cancer genetic polymorphisms could also contribute to the risk profile of cancer-associated ATE [16]. These observations provide insights into understanding the pathophysiology of cancer-associated ATE. Such genetic alterations may also affect pathways controlling hemostasis, including platelet reactivity, NET formation, and tissue factor expression [39]. Furthermore, in a retrospective analysis of non–small-cell lung cancer patients, ALK rearrangement was associated with a three-fold increase in ATE risk [40]. Other oncogenes associated with hypercoagulability through elevated tissue factor expression include EGFR, PTEN, and p53 [41].

Overall, understanding the pathophysiology of cancer-associated ATE involves recognizing the complex interplay of cancer-induced hypercoagulopathy, cancer therapy–associated thrombosis, and cancer genomic contributors. Accurate risk assessment and improved reporting are essential for identifying at-risk agents and quantifying the risk of ATE in cancer patients.

4 | A DEEP DIVE INTO ATES IN THE SETTING OF CANCER

ATEs are clinically heterogeneous, and specific ATE types will have unique mechanisms contributing to risk and hence require modifications to approaches and specific management considerations in the setting of cancer [42]. We will focus our discussion on the 3 most common ATEs – ACS, ischemic stroke, and PAD.

4.1 | ACS

4.1.1 | Mechanism

ACS encompasses myocardial infarction and myocardial ischemia. Navi et al. [4] reported that the excess risk of ACS varies by cancer type and stage, with lung, gastric, and pancreatic cancers exhibiting the highest rates of ACS. The development of ACS involves multifactorial and complex mechanisms, ranging from coronary artery vasospasm to acute arterial thrombosis and accelerated atherosclerosis [43,44]. Proposed mechanisms include direct endothelial injury and changes in vascular smooth muscle cell reactivity [45]. ACS can also be triggered by destabilization of atherosclerotic lesions, leading to plaque rupture and immediate term accelerated atherosclerosis [46]. The classical cytotoxic agent associated was cisplatin; however, multiple targeted therapies such as BCR-ABL TKI, ICI, and vascular endothelial growth factor inhibitors have such off-target effects.

4.1.2 | Diagnostic workup

The clinical presentation of ACS in cancer patients differs from that in the general population, necessitating modifications in clinical suspicion and evaluation. The most common presenting complaint of ACS in patients with cancer is dyspnea rather than the classical presentation of chest pain. Furthermore, there is a higher prevalence of silent ischemia, likely attributed to concurrent analgesic use and neurotoxicity from cancer therapy, which can affect the interpretation of angina symptoms [47]. Due to the latency of the clinical effects of some treatments, patients may have been asymptomatic after initial therapy and present years after. For instance, testicular cancer patients treated with chemotherapy have a 3.1-fold higher risk of AMI after 10 years, with an absolute risk of ATEs at 8% [48].

4.1.3 | Management

Management of ACS in cancer patients should generally follow the principles and approaches used for noncancer ACS patients, particularly if the patient's cancer prognosis exceeds 6 months [49]. Real-world data, however, indicate that cancer patients with ACS often do not receive guideline-recommended management, such as the use of statins, antiplatelet therapies, and PCIs [50,51]. Nevertheless, managing ACS in the context of cancer necessitates consideration of additional clinical complexities.

An important clinical dilemma in the decision to use antiplatelet therapy arises when cancer patients present with thrombocytopenia. Despite the increased bleeding risk, studies have demonstrated that antiplatelet drugs, like aspirin, improve outcomes in ACS patients with

cancer [52]. Thrombocytopenia exposes individuals to bleeding complications, but it is not protective for further thrombotic risk. Hence, balancing the bleeding risk and potential benefits of antiplatelet therapy must be carefully considered. To guide the use of antiplatelet therapy, guidelines have been developed to provide advice on platelet level cut-offs for antiplatelet use in the setting of cancer [53,54].

While PCI remains the gold standard for managing AMI, there has been a trend toward less invasive strategies in cancer patients [55]. Traditionally, bare-metal stents were preferred in cancer patients undergoing PCI as it requires a shorter course of dual antiplatelet therapy [56]. However, improving stent technology has allowed for a shorter duration of dual antiplatelet therapy with dual eluting stents [57]. The European Society of Cardiology Cardio-Oncology guidelines for acute ACS management hence recommend "An invasive strategy" for patients with a prognosis of more than 6 months and that patients with high bleeding risk treated with ACS be considered for short-duration dual antiplatelet therapy [49]. It is important to note that cancer still impacts outcomes, as ACS patients with cancer who undergo PCI have a higher risk of in-stent thrombosis, with reported rates of 5.56% compared with 0.78% in noncancer patients, despite standard dual antiplatelet therapy post PCI [58].

The type and duration of antiplatelet therapy in the context of the cancer patient may also differ, considering higher bleeding risk. For patients requiring dual antiplatelet therapy, aspirin, and clopidogrel carry a lower bleeding risk compared with aspirin with ticagrelor or prasugrel, especially with patients, and may be preferred for patients who are at high risk of bleeding [59]. A shorter duration of therapy should be considered, especially when multiple antithrombotic agents are used to mitigate the bleeding risk [49].

Conducting a review of medications that may contribute to ACS is essential, and temporary cessation of the implicated drug is usually recommended (Figure 2). The decision to rechallenge a drug should involve a multidisciplinary discussion, considering the patient's consensus, risk, and alternative cancer therapies available [49]. In cases of suspected coronary vasospasm where a drug rechallenge is being considered due to the lack of viable alternative therapy, the use of nitrates and calcium channel blockers as pretreatment may be considered, with close clinical and cardiac monitoring of the patient during administration [60].

4.2 | Ischemic stroke

4.2.1 | Mechanisms

The connection between ischemic stroke and cancer is well established. Recent acute ischemic stroke registry data from Switzerland demonstrated that 5.4% of patients had cancer, of whom 28% had newly diagnosed cancer while the remainder had known active cancer at the time of stroke [61]. Cancer and stroke share similar risk factors including smoking and advanced age, but beyond these shared risk factors, data suggest that cancer and its therapy are direct contributors to stroke development. This is supported by a prospective cohort study which demonstrated that cancer patients with stroke (compared with those with stroke or cancer only) have an increase in hypercoagulable markers (eg, D-dimer), higher levels of molecules indicating platelet and endothelial activation (eg, P-selectin), and more microembolic signals (on transcranial Doppler), suggesting a cardiovascular source [62,63]. Furthermore, thrombus composition in cancer patients with stroke is different from that in stroke patients without cancer, in line with these mechanistic findings [64]. This indicates that cancer-associated stroke is a specific entity [63].

Identifying the mechanism of stroke is important. Traditionally, ischemic strokes can be subdivided into lacunar and nonlacunar strokes; 45% of nonlacunar strokes are considered cryptogenic [65]. A new terminology, embolic strokes of undetermined source (ESUS), was proposed to describe cryptogenic strokes of ischemic origin with no clear underlying etiology after standard workup [66]. In one study of patients who were initially diagnosed as ESUS, subsequent underlying malignancy was diagnosed in 10% to 20% [67]. Furthermore, it is important to differentiate between cancer patients with a traditional stroke mechanism not directly explained by cancer and those with active cancer and its therapy as a suspected driver of the stroke. Researchers recently used a novel categorization of potentially cancer-related stroke mechanisms based on expert opinion and pathophysiologic considerations to classify stroke occurring in cancer patients [61]. The stroke was defined as cancer-related in 42.5% of patients and was further classified as cancer-treatment related (20.5% of all strokes in cancer) and hypercoagulable mechanism (22.7%). After applying this classification strategy, only 16% of strokes remained cryptogenic. The subgroup of patients with hypercoagulable cancer-associated stroke is an important subgroup when considering the therapeutic approach and future research avenues.

4.2.2 | Diagnostic workup

Patients with cancer-associated ischemic strokes should have their strokes classified using clinical and imaging characteristics and receive the same standard workup for etiology as noncancer patients. If the stroke is nonlacunar, this workup would include cardiac rhythm assessment for AF, head and neck vascular imaging to identify large vessel atherosclerosis, and transthoracic echocardiography (TTE) [65]. Potentially culprit anticancer therapy should be identified, and if the patient has cancer-associated ESUS, additional workup should be considered as previously reviewed. This may include testing for D-dimer, performing transesophageal echocardiography (TEE), and (where available) continuous transcranial Doppler [68]. This work up can lead to identification of specific underlying etiologies with therapeutic implications such as nonbacterial thrombotic endocarditis (NBTE), intravascular coagulopathy, and paradoxical clots.

4.2.3 | NBTE

Cancer is the leading cause of NBTE, and autopsy studies have shown a high incidence of malignancy among NBTE cases [64]. Vascular

distribution and additional markers (such as D-dimer) suggest that NBTE is a common etiology of cancer-associated ESUS but retrospective cohort studies show a low prevalence of NBTE (1.9% in a recent study) suggesting underdiagnosis [61]. This is because TTE has a low diagnostic yield and because many patients do not undergo TEE, which is the gold standard. This is supported by a recent study showing that 30% (7/23) cancer patients with stroke undergoing thrombectomy had NBTE [61].

NBTE is characterized by cardiac valvular vegetations and multisite cerebral infarcts and is frequently associated with mucin-releasing adenocarcinoma [69]. Investigations should include blood cultures and microbiology serologic tests to exclude underlying infective pathology. D-dimer is often markedly elevated as well. The significance of D-dimer testing has been demonstrated in various studies, including its association with transcranial Doppler embolic signals in stroke patients without a detectable underlying stroke mechanism [62]. Cardiac imaging via TTE should be performed, and if negative, a TEE should be considered to evaluate for cardiac valve vegetations [62]. The diagnostic workup and management of NBTE in cancer patients was recently reviewed [70]. In brief, NBTE requires multidisciplinary team management, and anticoagulation with low-molecular-weight heparin is a cornerstone of therapy to address the hypercoagulable state [71]. It is important to rule out NBTE in patients with CAT, especially if a hypercoagulable, cardioembolic source is suspected, because of therapeutic implications.

4.2.4 | Management

Outcomes in cancer-associated strokes are poorer than conventional stroke patients, with higher rates of neurologic deterioration, recurrence, and mortality. In a study of patients with cancer and stroke, the 6-month cumulative rate of recurrent ischemic stroke was 16%, with similar findings in a recent registry (20% recurrent stroke rate at 12 months) [61,68]. Hence, optimization of management approaches is critical. A crucial step is to reassess the cancer status, and, if the cancer is newly diagnosed or progressing, to treat the cancer (or modify therapy) as soon as possible. This calls for early involvement of an oncologist and multidisciplinary management.

Cancer itself is not a contraindication to reperfusion therapy, which remains an important management option for acute ischemic strokes. Nonetheless, a major concern in the setting of cancer-associated strokes is the risk of intracranial bleeding, which may occur as a hemorrhagic conversion of ischemic areas or as a complication to antithrombotic therapy. Some small studies have demonstrated that the use of intravenous thrombolysis did not increase the risk of intracranial bleeding complications in cancer patients without additional bleeding risk factors [72,73]. This highlights that although consideration of bleeding risk is important in the setting of cancer-associated stroke, there are patients for whom systemic thrombolysis remains a potentially beneficial therapeutic option in acute ischemic stroke. In a study of outcomes of endovascular recanalization therapy, recanalization rates were lower in cancer-related stroke patients at 63% as compared with cardioembolic stroke patients at 84% [74].

There are no high-quality clinical data to direct the choice of antithrombotic therapy (antiplatelet vs anticoagulation) in cancer-associated stroke, and antiplatelet therapy remains the default antithrombotic class even in ESUS [68]. The efficacy of anticoagulation and the optimal type of anticoagulation in the setting of cancer-associated stroke, especially ESUS, is unknown. Clinical trials of the use of direct oral anticoagulants (DOACs) (apixaban and rivaroxaban) in a general population of patients with undifferentiated ESUS did not show superiority over aspirin for prevention of recurrent ischemic stroke [75,76]. It is possible that therapeutic effects differ between now-recognized subtypes of ESUS, one of which is patients with cancer. However, the subgroup analysis of the cancer population in one of these studies demonstrated similar recurrent stroke rates with rivaroxaban and aspirin. Like all post-hoc analyses, this substudy is limited by inherent bias and does not rule out a therapeutic effect of DOACs, but this remains to be proven [77]. Moreover, retrospective cohort data demonstrated no difference in recurrent cancer-associated stroke between anticoagulation and antiplatelet therapy, but confounding by indication is possible. In support of a theoretical role of antiplatelet therapy, some studies on clots in cancer-associated stroke show that these are platelet rich [64,78]. Finally, there is evidence that cancer-associated stroke occurs despite therapeutic dose oral anticoagulation given for other indications [61,79]. To summarize, once NBTE and other specific causes have been ruled out, there is still equipoise regarding the use of anticoagulation or antiplatelet therapy in cancer-associated ESUS, but decisions on management must be taken on a case-by-case basis.

4.3 | PAD

Among the subtypes of ATEs in cancer, PAD has been understudied. There is limited reporting of PAD incidence in most cancer-associated ATE studies. However, PAD and its association with cancer should not be disregarded. In a Danish study, for patients with a lower limb arterial thrombosis, the 6-month standardized incidence ratio for cancer was 3.28 [80]. BCR-ABL TKIs, specifically nilotinib and ponatinib, are associated with an increase in PAD risk (including severe cases) manifesting as accelerated atherosclerosis and acute limb ischemia [81]. While the literature suggests that the incidence of PAD is not as high as other ATE subtypes, it remains vital to recognize the risk for PAD. This may be via individual risk stratification such as the European Society of Cardiology score [82]. Patients who are at higher risk, should be evaluated and counseled carefully when deciding on starting on anticancer agents which carry a higher risk of ATE, and lower risk alternatives considered when appropriate. In addition, monitoring clinical symptoms and biomarkers in patients receiving high-risk anticancer therapies, using tools like the ankle-brachial index may be considered [83].

5 | CANCER AND AF

The risk of ATE in cancer patients is compounded by the presence of AF. A growing body of evidence suggests that cancer patients are at a higher risk of developing AF and subsequent ATEs than patients without cancer. There are several potential mechanisms leading to the increased risk of AF in patients with cancer, including cancer therapy–induced AF, atrial remodeling due to cancer-induced inflammation, and autonomic dysregulation [22,84,85]. The contribution of cancer to the ATE risk in AF is exemplified in a recent study reporting an increased 12-month incidence of ischemic stroke, transient ischemic attack, or systemic thromboembolism in AF patients with newly diagnosed cancer (no anticoagulation; CHA2DS2-VASc score = 0-2) compared with those without cancer (2.13% and 0.8% respectively; HR: 2.70; 95% CI: 1.65-4.41) [86]. The management of anticoagulation in the setting of cancer has multiple challenges like the risk of bleeding. In a retrospective cohort study of patients with cancer and AF with a CHA2DS2-VASc score of 2 or more, 44.3% did not receive anticoagulation, despite an indication [87]. This reflects the difficult balance between the ATE-protective benefits of anticoagulation vs the bleeding risk associated with anticoagulation [86]. In addition, there is increasing data to support that the CHA2DS2-VASc score, used for stroke risk stratification in AF patients, underestimates the stroke risk in cancer patients [86,88,89]. The European Society of Cardiology Cardio-Oncology guidelines provide recommendations on various aspects related to cancer and AF. Notably, there is a recommendation to consider anticoagulation in cancer patients with a CHA2DS2-VASc score of 0 for men and 1 for women after weighing the bleeding risk (Class IIb, Grade C) due to the higher stroke risk in cancer patients [49].

6 | PREVIOUSLY UNDIAGNOSED MALIGNANCY IN ATE

VTE, especially when unprovoked, has been recognized as a presenting manifestation of cancer, but there is less awareness of ATE as a condition preceding the diagnosis of cancer. In an analysis of a SEER database of cancer admissions in the United States, the risk of ATE increased 6 months before the diagnosis of cancer [3,90]. This suggests that ATE might precede the diagnosis of cancer as well. Furthermore, a recent population-based cohort study reported an absolute incidence of underlying cancer of 2.4% at 12 months after an ATE, with a slightly increased risk compared with matched controls (hazard ratio of 1.68) [91]. The RR for a cancer diagnosis at 12 months post-ATE was highest (up to 3.49) in 3 prespecified subgroups without selected conventional cardiovascular risk factors (so-called unexplained ATE). A similar trend was observed in a cohort study of young stroke patients (aged 15-49 years) who had up to a 5-fold increased risk of cancer at 1-year post-stroke (compared with patients without stroke), while this risk was only slightly elevated in older patients [92,93].

Consequently, in cases of unexplained ATE, the clinical question arises whether a workup for an occult malignancy should be considered. Some authors have suggested the use of biomarkers to detect cancer. For instance, Zhao et al. [94] studied the predictive value of D-dimer for predicting previously undiagnosed cancer in stroke patients and found that a D-dimer > 5.5 mg/L had a high positive predictive value for cancer [94]. Considering the low absolute incidence of cancer in the months after unexplained ATE and lack of evidence, no specific screening is recommended for occult malignancy. We recommend increased awareness of the possibility of occult cancer in ATE patients, especially in the absence of conventional risk factors, and a focused clinical evaluation involving history-taking and physical examination. Any abnormalities in this workup and in routine laboratory tests (eg, iron deficiency anemia) should be thoroughly investigated, as would be the case for unprovoked VTE. Furthermore, age and sex-based screening for malignancy, as recommended by general population screening guidelines, should be encouraged.

7 | INTERNATIONAL SOCIETY OF THROMBOSIS AND HEMOSTASIS 2023 CONGRESS REPORT

During the International Society of Thrombosis and Hemostasis (ISTH) Congress in 2023, several abstracts were presented concerning cancer and ATE. In a population-based study, the incidence of stroke was evaluated in colorectal cancer patients receiving cetuximab, an epidermal growth factor receptor inhibitor. Ischemic stroke occurred in 0.53% of patients receiving cetuximab plus chemotherapy, while chemotherapy alone had a rate of 0.31% (HR: 1.67; 95% CI: 1.11-2.52) [95]. These findings highlight the additional thrombosis risk associated with cancer therapy, as previously discussed.

Several abstracts discussed various pathophysiological contributors to ATE in cancer. In a study involving combined DNA and RNA analysis of lung cancer patients, significant enrichment in coagulation and fibrinolysis genes was observed [96]. Nopps et al. [97] also demonstrated that elevated levels of growth differentiation factor-15, a novel biomarker, were associated with the risk of VTE, ATE, and all-cause death in cancer patients. These findings illustrate the diverse procoagulant landscapes across different cancer subtypes, potentially serving as a basis for future molecular prediction models and treatment targets. At the cellular level, non–small-cell lung cancer patients exhibited fibrinolytic deficiency, as evidenced by elevated levels of tissue plasminogen activator and lower levels of urokinase-type plasminogen activator [98]. In addition, a mouse cancer model indicated that NETs contribute to myocardial inflammation and stress, increasing the risk of ACS [99].

Regarding management considerations, while anticoagulation is generally a treatment option for CAT, breakthrough thrombosis can occur. Larsen et al. [100] reported a 5.4% ATE rate at 6 months (mainly ischemic stroke) in patients treated with apixaban for venous thrombosis, with recurrent ATE associated with pancreatic and ovarian cancer. A population-based study of anticoagulant use and prognosis in patients with AF and cancer, demonstrated a shift away

from the use of heparin and warfarin toward DOACs. While there was a decrease in the incidence of VTE in the AF-cancer population, overall survival did not decrease [101]. Apart from anticoagulation, other agents to modify the outcomes of thrombosis patients are needed. In a study of high-risk thrombosis patients with cancer undergoing chemotherapy, atorvastatin was associated with a reduction in inflammatory cytokines such as IL-6 and lower F1+2 levels [102].

8 | FUTURE DIRECTIONS

While there is a growing awareness of the risk of ATE in cancer, much remains to be understood about the factors contributing to ATE development in cancer. This knowledge gap becomes especially apparent with the introduction of new anticancer agents, such as immunologic and cellular therapies. To overcome the challenges in data collection, standardization of the definitions of ATE and improved reporting are essential. Initiatives such as the ISTH Common Data Elements and toolkit for collection of thrombosis-related data elements serves to address this issue [103]. Currently, signals are emerging, indicating an increased incidence of ATE associated with these newer agents like ICIs [28]. There is a need for a deeper understanding of the distinctions between VTE and ATE pathophysiology, as well as the contributing risk factors, as they are not identical disease processes. The development of specific risk stratification tools for cancer-associated ATE, akin to the Khorana score for VTE, is also imperative [104]. The identification of suitable biomarkers for ATE would aid in risk stratification and disease monitoring [105]. We suggest studies differentiating between the types of ATE (ie, stroke and ACS), since the underlying etiologies may differ. Furthermore, there is a demand for cancer-specific risk scoring for AF to assess thrombotic and bleeding risks, given the increasing prevalence of AF among cancer patients. The optimal antithrombotic therapies in the context of cancer-associated ATE remains uncertain, including the choice between anticoagulation or antiplatelet therapy. The role of adjunctive therapies in ATE prophylaxis is also unclear [79,106]. In summary, substantial research is needed to advance our understanding of the relationship between ATE and cancer, ultimately enhancing the support and outcomes of oncological care for patient.

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