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Permalink

https://escholarship.org/uc/item/3vh6v1vx

Journal

Stroke, 57(4)

ISSN

0039-2499

Authors

Navi, Babak B
Kasner, Scott E
Cushman, Mary
et al.

Publication Date

2026-02-02

DOI

10.1161/str.0000000000000517

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AHA Scientific Statement

Classification and Management of Ischemic Stroke in Patients with Active Cancer

A Scientific Statement from the American Heart Association

Babak B. Navi, MD, MS, Chair[1,2]; Scott E. Kasner, MD, MSCE, FAHA[3]; Mary Cushman, MD, MSc, FAHA[4]; Tochi M. Okwuosa, DO, FAHA[5]; Nathaniel H. Fleming, MD, MS[6]; Jacqueline M. Behr, NP, RN, MS[7]; Jennifer J Yang, PharmD[8]; Ajay Gupta, MD, MS[9]; Lisa M. DeAngelis, MD, Vice Chair[1,2]; on behalf of the American Heart Association Stroke Council; and Council on Cardiovascular and Stroke Nursing

[1]Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, NY

[2]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY

[3]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA

[4]Division of Hematology and Oncology, Department of Medicine, Vermont Center for Cardiovascular and Brain Health, University of Vermont Larner College of Medicine, Burlington, VT

[5]Department of Internal Medicine, Division of Cardiology, Rush University Medical Center, Chicago, IL

[6]Department of Neurology, University of California, San Francisco, CA

[7]Division of Neuro-Oncology, Department of Neurology and Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY

[8]Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, NY

[9]Department of Radiology, Columbia University Vagelos College of Physicians and Surgeons, New York, NY

Correspondence:

Babak Navi, MD

420 East 70th Street, Room 411

New York, NY 10021

212-746-0225

ban9003@med.cornell.edu

Short title: Cancer-related stroke

Tables: 3

Figures: 1

References: 67

Abstract word count: 250

Word count excluding title page, abstract, references, tables, and figure legends: 5,076

Abstract

About 10-15% of patients with ischemic stroke have a history of cancer, half of whom have active malignancy at the time of stroke. With improved cancer treatments extending patient survival, the co-prevalence of these diseases has increased steadily since 2000. This has sparked considerable growth in research and knowledge on this topic. Approximately half of ischemic strokes in patients with active cancer are due to conventional mechanisms, although cancer-related factors may contribute. The remaining half of ischemic strokes in this population are typically classified cryptogenic or attributed to cancer-specific mechanisms. These cryptogenic strokes often have characteristic risk markers and clinical features and are extremely high risk for recurrent stroke and other adverse events, distinguishing them from other stroke subgroups. Recent epidemiological, translational, and histopathological data indicate that many of these events are likely caused by the cancer itself through multifactorial prothrombotic processes. In this scientific statement incorporating multidisciplinary expertise, we critically appraise and synthesize recent evidence and provide clinical suggestions on the epidemiology, presentation, evaluation, pathophysiology, and treatments for ischemic stroke in patients with active cancer. Additionally, we propose a novel classification for ischemic stroke attributed to cancer itself, which we define as

"cancer-related stroke", to enable consistent nomenclature and harmonize stroke classification across clinical practice and research. This system is based on routinely-available clinical data and includes different categories for certainty of causality, relating to patient's distinctive clinical features and estimated risk for recurrent thromboembolism. We hope this framework spurs dedicated controlled trials to address areas of clinical uncertainty.

Key Words: AHA Scientific Statements, cancer, ischemic stroke, classification, antithrombotic therapy

Non-standard Abbreviations and Acronyms

AF, atrial fibrillation

AIS, acute ischemic stroke

DIC, disseminated intravascular coagulation

DOAC, direct oral anticoagulant therapy

ESUS, embolic stroke of undetermined source

LMWH, low molecular weight heparin

NBTE, nonbacterial thrombotic endocarditis

TCD, transcranial Doppler

VEGF, vascular endothelial growth factor

VTE, venous thromboembolism

vWF, von Willebrand factor

Introduction

Cancer is the second and stroke is the fourth leading cause of death in the US.[1] There is a strong interplay between cancer, its treatments, and the vascular system, leading to an increased incidence of acute ischemic stroke (AIS) in patients who harbor or were previously treated for an underlying malignancy.[2] Given the growing incidence of cancer with more than 2 million new cancer diagnoses annually in the US, and the longer survival associated with improved therapeutics, there will be over 21 million American cancer survivors by 2030, representing over 6% of the population.[3,4] This degree of prevalence will further increase the odds of these two major diseases developing in the same individual, and the burgeoning number of publications over the past decade on AIS in patients with cancer reflects the diagnostic and therapeutic challenges associated with this co-occurrence.

This AHA statement is designed to review the epidemiology of this clinical problem, its presentation, diagnosis, treatment, and the steps clinicians can take to prevent recurrence. While care reflects the standard approach to any patient with stroke,[5,6] prior or concurrent cancer frequently changes the pathophysiology and clinical impact of cerebral ischemia, necessitating a different work-up, and extra considerations and vigilance when deciding on thrombolytics, clot retrieval,

antithrombotic agents, and future cancer treatments. Despite the spate of recent papers, prospective randomized trial data are generally lacking, resulting in a dependence upon observational studies, expert opinion, and individual clinical judgment.

A major goal of this statement on cancer-related ischemic stroke is to outline what is known, codify current expert opinion through a proposed nomenclature and classification system, and clarify the opportunities for future study. This proposed classification is meant to supplement prevailing systems and is intended for strokes currently classified as cryptogenic after standard diagnostic evaluation (i.e., embolic stroke of undetermined source [ESUS]) or those that fall under defined mechanistic categories but are directly related to the systemic effects of cancer (i.e., nonbacterial thrombotic endocarditis [NBTE]). Under this proposed schema, these “cancer-related strokes” would instead be categorized under the “stroke of other determined etiology” subtype. Meanwhile, stroke mechanisms with defined categories that are not directly related to the systemic effects of cancer would continue to be categorized per conventional criteria even if mediated by cancer or its treatments (i.e., large artery atherosclerosis after radiotherapy). As this statement is focused on active cancer, we define it here as a pathological diagnosis or treatment of any cancer other than cutaneous squamous or basal cell

carcinoma in the past 6 months; known recurrent, regionally advanced, or metastatic cancer; or cancer not in complete remission. Major points and clinical suggestions from each section are summarized in Table 1.

Epidemiology and Primary Prevention

Among patients with known active cancer there is an approximately 2-fold increased risk of AIS compared to the general population, and this increased risk is borne primarily during the first year after cancer diagnosis.[7,8] This increased risk is associated with all types and stages of cancer, but the greatest risks are seen with metastatic cancers of the pancreas, lung, and gastrointestinal tract.[2,9] Adenocarcinoma histology, particularly mucinous and clear cell adenocarcinomas, may especially predispose to stroke.[10] Cancer genomic mutations further modulate stroke risk, especially alterations in KRAS and STK11.[11]

Several cancer treatments are associated with an increased risk of stroke. Surgery is an established risk factor for stroke and is often required in patients with cancer for diagnosis or treatment.[12] Patients with cancer have an estimated 30-40% higher risk of perioperative stroke than patients without cancer after adjusting for demographics, comorbidities, and surgical factors.[12] Certain chemotherapies have

been linked to stroke risk, including platinum-based compounds, vascular endothelial growth factor (VEGF) agents, tyrosine kinase inhibitors, and hormonal agents (Table 2).[13,14] However, unraveling causal associations of treatments from confounding-by-indication bias in these studies is difficult. Radiotherapy promotes endothelial injury, inflammation, oxidative stress, and atherosclerosis, which can result in small- or large-vessel vasculopathy and subsequent AIS; this often takes years to develop.[15] For this reason and because of delayed cardiac toxicity after some chemotherapies, many cancer survivors face an elevated risk of stroke throughout their lifetime.[16]

Overall, in a retrospective analysis of the US National Inpatient Sample of adults hospitalized from 2007-2019 with a primary diagnosis of AIS, 12.7% had a previous or active cancer (81% solid, 19% hematologic).[17] The prevalence of cancer among Americans with AIS increased from 10.7% in 2007 to 14% in 2019.[17] Whether this increased prevalence is related to more frequent surveillance brain MRIs for cancer staging is uncertain. In a prospective multicenter study of Dutch patients with a first ischemic cerebrovascular event, 12% had a history of cancer.[18]

For the primary prevention of stroke in patients with cancer, the effect of antithrombotics and statins is uncertain. In ASPREE, a phase 3 randomized trial

investigating aspirin vs placebo in older people, there were 1,392 participants diagnosed with incident cancer during follow-up, and their risk of stroke was similar across treatment arms.[19] A meta-analysis of 14 randomized trials comparing anticoagulation with no anticoagulation among ambulatory patients with cancer found similar risks of stroke between groups but higher risks of bleeding with anticoagulant use.[20] Results did not vary by cancer site or anticoagulant type, dose, or duration.[20] International studies using administrative datasets suggest that statins may reduce stroke risk in patients with newly diagnosed or historical cancer, especially those treated with radiation to the head, neck, or thorax, although confirmatory prospective studies are lacking.[21,22]

Clinical Presentation

Cancer Presenting as Stroke

Stroke is occasionally the presenting sign of an occult cancer.[23] Anywhere from 1.5%-10% of patients with AIS will be diagnosed with a new malignancy within one year, with cryptogenic mechanisms and dedicated cancer screening conferring higher risks.[23,24] The OCCULT-5 score uses older age, female sex, multi-territorial infarction pattern, elevated D-dimer, and an ESUS phenotype to predict occult

malignancy in patients with AIS.[25] However, because of the low pre-test probability, the positive predictive value of an elevated score is modest.[25]

Ongoing prospective studies, INVISIBLE-1 (NCT06100718) and INCOGNITO (NCT05733416), are evaluating the diagnostic utility and clinical impact of dedicated cancer screening in patients with cryptogenic stroke. In the absence of strong evidence, our approach is to assess all patients with AIS for typical symptoms and signs of cancer through a thorough history and exam and laboratory testing of blood counts and liver function to direct any cancer diagnostic evaluations. If symptoms or signs of cancer are present, then we typically pursue focused cancer screening targeting the organ or system involved. We also ensure that patients with AIS are up-to-date with appropriate guideline-directed cancer screening, such as mammography, colonoscopy, low-dose chest CT, and prostate specific antigen testing.[26] While it is not unreasonable to consider body imaging with contrast-enhanced CT or PET-CT in patients with cryptogenic stroke and clinical characteristics associated with cancer-related stroke such as very elevated D-dimer levels or multi-territorial infarction patterns, it is important to note that this approach is not supported by data, and it remains to be proven whether earlier identification of occult cancer in patients with AIS improves outcomes. Additionally, D-dimer has imperfect sensitivity and specificity, and can

be elevated from trauma, procedures, atrial fibrillation (AF), and other thromboembolic events.[27] Lastly, there are downsides to obtaining contrast-enhanced body imaging, including radiation exposure and the potential for nephropathy, anaphylaxis, and incidental findings.

Stroke with Known Cancer

Compared to the general AIS population, patients with comorbid cancer tend to be older and have lower rates of hypertension and dyslipidemia but higher rates of smoking and venous thromboembolism (VTE).[9,28,29] Malignancy-associated infarcts are frequently multi-focal,[28-30] manifested clinically with higher average stroke severity due to more widespread cerebral involvement and encephalopathy.[2,9,29] Radiographically, the “three-territory sign”, describing involvement of the bilateral anterior and posterior cerebral circulations, is more common in malignancy-associated stroke, occurring in 30-50% of cases.[28,29]

In patients with cancer and AIS, markers of systemic hypercoagulability and inflammation are often elevated, with D-dimer being the most validated hematological biomarker to discriminate malignancy-associated AIS.[23,29,31] Low hemoglobin and elevated neutrophil-to-lymphocyte ratio have also been

described.[23,29,32] On transcranial Doppler (TCD) ultrasound, microembolic signals are common and often bilateral.[28,29]

Biological Pathways Implicated in Heightened Stroke Risk

Several factors are responsible for increased stroke risk in patients with cancer, including cancer treatment effects and frequent interruptions of antithrombotic therapy for procedures, thrombocytopenia, and bleeding. However, in general, the largest driver of stroke risk in patients with cancer is cancer-mediated hypercoagulability, a complicated multifactorial process involving several linked pathways, including broad activation of the platelet, coagulation, and endothelial systems.[9,29] In the prospective MOST-Cancer study, markers of platelet (P-selectin), coagulation (D-dimer), and endothelial (thrombomodulin, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1) activation were higher in patients with active cancer and AIS (n=50) than in AIS-only matched controls (n=50).[28] Of the markers tested, D-dimer had the largest absolute and relative numeric difference between groups.[28] Von Willebrand factor (vWF), a glycoprotein that mediates platelet adhesion and aggregation at sites of vascular injury, is also implicated in the pathogenesis of cancer-related stroke.[33] In the prospective SCAN study, among 90 patients with active cancer and AIS, vWF

antigen levels were associated with stroke severity, multi-territorial infarctions, cryptogenic mechanisms, and mortality at 1 year.[33] However, as vWF is an acute phase reactant associated with infarct size, its relationship with cancer-related stroke may be an epi-phenomenon and not causal.[34]

Thromboinflammation via neutrophil extracellular trap formation (NETosis) is another important contributor to AIS development in patients with cancer. Activated neutrophils release decondensed chromatin leading to extracellular DNA lattices that can trap other blood cells and cause thrombus formation. It has been postulated that circulating cancer cells interact with neutrophils to trigger NETosis and subsequently AIS.[35] In the prospective OASIS-Cancer study, compared to 100 matched controls, including those with AIS-only or cancer-only, 38 patients with cancer-related AIS had higher plasma DNA and nucleosome levels, and these NETosis markers correlated with D-dimer levels.[35]

The OASIS-Cancer study also highlighted the role of extracellular microvesicles in cancer-related stroke.[36] The investigators reported that cancer cell-derived extracellular microvesicle levels were higher in the cancer-related stroke group than in control groups, and the microvesicle levels were associated with hypercoagulability, measured by D-dimer, through tissue-factor independent

pathways.[36] These circulating microvesicles are small spherical cell fragments shed by tumors or blood cells, often in response to inflammatory signaling, that promote activation of the coagulation cascade by expressing procoagulant proteins and exposing surface phospholipids. Besides these biological pathways, which likely vary by cancer type, there are probably others involved in cancer-related stroke, including secretion of mucin, release of tissue factor, and expression of fibrinolysis inhibitors and inflammatory cytokines.[9] However, it is clear that no single factor can be targeted to eliminate cancer-mediated hypercoagulability other than the cancer itself, the driving force behind all of these pathways.

Stroke Mechanisms

Conventional stroke mechanisms account for about half the burden of AIS in patients with active cancer, although cancer-related factors sometimes mediate these mechanisms (Figure 1/Central Illustration).[28,32] Large artery atherosclerosis is a frequent stroke mechanism in the oncological population because of high smoking rates and the long-term effects of cancer treatments. Immunotherapy with immune checkpoint inhibitors has been associated with accelerated progression of atherosclerosis and a threefold higher risk for ischemic

cardiovascular events.[37] Radiotherapy also promotes atherosclerosis, most often affecting the cervical internal carotid arteries in patients with head and neck cancer and the intracranial vasculature in patients with primary brain tumors.[2,15] Cardioembolism is common in patients with malignancy because cancer increases the risk for atrial fibrillation (AF),[38] and some cancer treatments, particularly anthracyclines, trastuzumab, cyclophosphamide, and taxanes, can cause cardiomyopathy.[39] Additionally, immunosuppression and indwelling venous catheters are common in patients with cancer, predisposing them to infective endocarditis and septic emboli. Finally, cancer greatly heightens VTE risk, and this can lead to paradoxical embolization through right-to-left shunts.[40] However, the attributable risk of patent foramen ovale for stroke may be lower in patients with cancer than in the general population. Among 2,236 patients with AIS who had transesophageal echocardiography in Bern, Switzerland, patients with active cancer (n=103) had lower median ROPE scores (4 vs 5) and fewer right-to-left shunts (23% vs 36%) than patients without cancer, although confounding by indication was possible.[40]

The remaining 50% of AIS in patients with active cancer are either of undetermined source or due to known cancer-specific mechanisms.[9,28,32] Many of these undetermined cases have distinctive clinical features and are likely caused by

cancer-mediated prothrombotic processes.[9] The typical phenotype for what historically has been labeled “cancer-related ESUS” is a patient with disseminated solid cancer that is recently diagnosed and untreated or that has progressed through treatment, who has embolic-appearing AIS in multiple vascular territories with very elevated blood prothrombotic markers and microemboli on TCD. When a cerebral arterial occlusion is detected on vessel imaging, the susceptibility vessel sign is usually absent on brain MRI, indicating an erythrocyte-poor thrombus.[41] Further, if thrombectomy is performed, the retrieved thrombus is generally confirmed as platelet- and fibrin-rich.[42]

Many of these cancer-related ESUS patients may have occult NBTE, which shares a similar clinical phenotype, and is characterized by platelet-fibrin vegetations on cardiac valves.[43] However, NBTE is rarely confirmed, even when suspected, because the valvular vegetations tend to be small and friable and thus difficult to detect.[44] Therefore, attention should be paid to “valve thickening” on echocardiography, which may represent NBTE lesions in the appropriate context. Disseminated intravascular coagulation (DIC) causing in situ cerebral artery thrombosis is another possible mechanism for ESUS in patients with cancer, although formal criteria for overt DIC are rarely met.[9] Another cancer-specific stroke mechanism is tumor embolization, which arises from centrally-located primary or metastatic lung

cancers that invade the pulmonary veins or cardiac chambers.[2] This mechanism should be suspected if months later metastases form at the site of stroke. Lastly, non-stenosing large artery atherosclerosis is an underappreciated stroke mechanism, including in cancer patients; high-risk plaque features on imaging may help identify culprit lesions.[30]

Rarely, cancer drugs can cause stroke.[13,14] This includes VEGF inhibitors, VEGF and BCR-ABL targeting tyrosine kinase inhibitors, immunomodulatory antiangiogenic agents, and hormonal therapies.[39,45] However, assigning causality to these medications is challenging because of confounding by indication.[14] Many cancer therapeutic agents linked to stroke risk are typically administered to patients with disseminated cancers or as second-line treatment after progression of disease, and therefore delineating whether the cancer and its hematological effects caused the stroke or whether it was the drug given to treat the cancer is difficult.[14] This is compounded by the fact that many patients with cancer receive multiple treatments in combination. We therefore stress caution in assigning causality to individual cancer therapies, which could lead to inappropriate cessation of potentially life-saving treatments and produce a self-fulfilling prophecy. Further, if one considered these relationships causal, stroke secondary prevention therapies could mitigate future AIS risk regardless of ongoing cancer treatments.

Diagnostic Evaluation

The diagnostic approach to patients with suspected stroke and active cancer must account for additional layers of complexity related to the dual disease process.[6] For example, a hypodensity on head CT could represent an infarction, metastasis, or infection; therefore, MRI is preferred, although even MRI may be insufficient for an immediate definitive diagnosis. MRI findings that favor AIS over tumor include true restricted diffusion (i.e., bright hyperintensity on diffusion-weighted images with accompanying hypointensity on apparent diffusion coefficient images), wedge-shaped lesion(s) corresponding to cerebrovascular territories, edema that involves the cortex and is proportionate to the size of the diffusion-weighted hyperintensity, and lack of enhancement.[46] In some cases, especially when the diffusion restricting areas are small or MRI is performed subacutely (when enhancement from infarcts is expected), a repeat MRI in 1-2 months is necessary to confirm stroke.

Given the complicated relationships between stroke, cancer, and cancer treatments, these patients often need more testing than other AIS patients. Notably, vascular imaging should include the aortic arch among patients with prior

chest radiation, and thus CTA may be preferred over MRA. Blood cultures should be considered to assess for infectious endocarditis, especially those that are immunosuppressed, have indwelling venous catheters, or endorse systemic symptoms. Measuring plasma D-dimer is generally advised as it can be helpful in relating the cancer to the stroke, stratifying the risk of future stroke and death, and measuring the response to treatment.[31,47] We typically measure D-dimer during the index stroke hospitalization and every few months thereafter. In patients treated with intravenous thrombolysis or thrombectomy, early D-dimer measurements may be falsely elevated, so checking towards the end of the hospitalization may be prudent. Echocardiography should generally include an agitated saline injection to assess for right-to-left shunts, as the risk of VTE is markedly elevated with cancer and could lead to paradoxical embolism.[40,44] If a right-to-left shunt is identified, then venous ultrasound of the extremities may be warranted. Transesophageal echocardiography should be considered because it views the cardiac valves better than transthoracic echocardiography and is more likely to diagnose NBTE.[44] As cancer is associated with a heightened risk of AF, prolonged cardiac rhythm monitoring is generally advised.[38] In select patients, chest CT might also be considered to assess a centrally-located cancer which could cause tumor embolization. Conversely, it should be noted that while these tests may provide useful information, they can be burdensome, especially for patients with active

cancer who may be frail and overwhelmed by their cancer treatment. Therefore, decisions about which diagnostic tests to obtain should be individualized and shared with the patient.

New Classification for Cancer-Related Stroke

About 50% of AIS in patients with cancer are currently categorized as ESUS by predominant classification systems such as TOAST.[9,28,48] However, it is increasingly clear based on epidemiological, translational, and histopathological studies that many of these strokes are related to the systemic effects of the cancer itself.[8,28,35,36,49] Yet, there is no standardized classification schema for "cancer-related stroke", and existing literature is ripe with inconsistent nomenclature when referring to this phenotype. Therefore, like the PASCAL classification for patent foramen ovale-associated stroke,[50] we propose a novel classification system with varying degrees of certainty to attribute a stroke to cancer itself (Table 3). The different categories for certainty of causality (probable vs possible vs unlikely) have been adapted from a recent international consensus statement on subgroups of ESUS, and relate to a patient's distinctive clinical features and their estimated risk for recurrent thromboembolism.[27] The proposed criteria are based on data that are routinely available in clinical practice. The probable category encompasses

standard criteria for NBTE, overt DIC, or tumor embolism, while the possible category includes the most robust clinical, laboratory, and radiographic risk markers for AIS in patients with cancer.[9,27,28] A D-dimer threshold of >2,500 ng/ml FEU was selected to assign possible causality because it is near most published cutoffs for identifying occult cancer or positing causation to known cancer in patients with AIS, and it is roughly five times the upper limit of normal.[23,27-29,31] Meanwhile, cancer therapies were omitted from the proposed criteria because strokes attributed to them have uncertain mechanisms and their treatment may differ from therapy directed towards a cancer-related stroke, and thus we believe they should be classified separately. Importantly, cancer-related stroke is not a homogenous entity, and some patients meeting criteria for cancer-related stroke may have stroke from non-neoplastic etiologies; therefore, it is imperative that clinicians comprehensively address patients' overall cardiovascular risk profile, including hypertension, smoking, diabetes, hyperlipidemia, etc. We hope that this novel framework will harmonize stroke classification in patients with cancer, thereby enabling consistent nomenclature across clinical practice and research, and setting the stage for therapeutic trials in this growing high-risk population.

Goals of Care

Patients with cancer-related stroke face high rates of disability as well as cancer- and treatment-related complications.[2] In a prospective survey, patients with active cancer and AIS reported that stroke disability and cancer pain had the largest impact on their quality of life, while cognitive impairment and functional dependence were their biggest concerns for the future.[51] This cohort was generally more concerned about future stroke than bleeding events and preferred a more aggressive antithrombotic strategy, although wide variability existed.[51] Given these factors, it is imperative to periodically reassess these patients' goals of care, especially as they may change over the course of their illness. Additionally, palliative care to control symptoms and enhance quality-of-life should always be considered alongside disease-targeting medical therapies. For an in-depth discussion on palliative care for patients with cardiovascular disease, we refer readers to the AHA's scientific statement on this topic.[52]

Acute Treatment

Patients with AIS and cancer should be considered for acute treatment with intravenous thrombolysis. Cancer is not a contraindication to such treatment;[5] however, an additional layer of vigilance is warranted when assessing eligibility. As hematologic derangements are common in patients with cancer, clinicians may

want to wait for the results of complete blood counts and coagulation studies prior to administering treatment. Further, a very careful review of baseline brain imaging must not only exclude hemorrhage but also metastatic disease. If brain metastases are present, we would defer intravenous thrombolysis because of the high risk for hemorrhagic complications. In general, patients with cancer are roughly one-third less likely to receive thrombolysis because of factors such as thrombocytopenia, anticoagulation, recent invasive procedures, and concern for tumoral bleeding.[53] Short-term outcomes after intravenous thrombolysis, including symptomatic intracerebral hemorrhage and in-hospital mortality, are similar in properly selected patients with and without cancer.[54] However, long-term outcomes are typically worse in oncological patients, although this is primarily driven by the effects of the cancer, and a sizeable number achieve functional independence.[55]

Similarly, patients with cancer may be eligible for mechanical endovascular thrombectomy if a large vessel occlusion is identified. This procedure has similar rates of technical success and short-term outcomes in patients with vs without cancer.[56,57] However, patients with cancer face a greater probability of death and stroke recurrence because of their malignancy.[56,57]

Overall, patients with cancer and AIS should be considered on an individual basis for these acute stroke interventions with the aim of reducing disability and optimizing quality of life. While all treatment decisions must be considered in the context of the long-term goals of care and perceived risks and benefits, the potential for substantial reversal of stroke-related deficits is likely to be worthwhile for most patients. Conversely, in patients who have a large core infarct on baseline imaging and are likely to suffer permanent severe disability even with reperfusion, a more palliative approach may be more appropriate.[51] As patients' wishes for such scenarios may be unknown to treating neurologists acutely, we encourage emergent consultation with the involved oncologist(s) to assist with medical decision making.

Risk of Recurrent Stroke and Other Adverse Events

Cancer-related stroke is one of the highest risk subgroups for stroke recurrence.[2,47] Compared with the general stroke population, patients with active cancer have a 2- to 3-fold increased risk of recurrent stroke at 1-year, with rates ranging from 14-29%.[9,58] Most of these events occur within 3 months, an especially high risk period for recurrence.[10,47] These patients also face substantially increased risks of other ischemic events.[47] Among 263 patients with active cancer and AIS at a quaternary

cancer center, the 6-month rate of major ischemic events was 37% and nearly half the events were VTE.[10] Patients who had a recurrent thromboembolism were twice as likely to die than those who did not.[10]

There is a U-shaped curve for incident and recurrent stroke risk in patients with cancer, with the highest risk soon after cancer diagnosis (peak hypercoagulability due to amplified cancer activity and treatment), then a reduction in risk during the years following cancer control or cure, followed by a subsequent progressive rise in stroke risk associated with cancer recurrence or long-term effects of cancer treatments.[2] Historically, the coexistence of cancer and stroke was associated with poor prognosis and high mortality.[43,59] Fortunately, advancements in supportive care and oncological treatments, especially immunotherapy and targeted therapy, have improved survival in patients with cancer.[4,60] Paradoxically, this may also prolong the window during which thromboembolic complications can occur.

Patients with cancer and AIS are also high risk for major bleeding because of frequent thrombocytopenia, invasive tumors, or cancer therapies impairing hemostasis.[29] In a prospective cohort of patients with active cancer and AIS, the estimated 1-year cumulative incidence of major bleeding was 24%.[47] Balancing the prevention of recurrent ischemic events – with anticoagulants and antiplatelet

medications – while mitigating bleeding risks poses significant clinical challenges that require judicious decision-making.

Secondary Stroke Prevention

For Patients with Known Mechanisms

Secondary stroke prevention in patients with cancer should be tailored to the stroke mechanism if known.[6] For instance, antiplatelet therapy and aggressive risk factor control should be implemented for small vessel disease, while direct oral anticoagulant (DOAC) therapy should be administered for nonvalvular AF. Stroke from radiation-induced atherosclerosis of the extracranial carotid artery should generally be treated with revascularization, typically endovascular stenting because of the perceived higher risks of adverse events related to open surgical dissection through fibrotic soft tissue; consultation with proceduralists with expertise in this population is suggested. In patients with confirmed NBTE or overt DIC, therapeutic-dose anticoagulants are typically prescribed, although supportive clinical trial data is admittedly lacking, and a reasonable argument could be made to administer antiplatelets to patients with confirmed NBTE because of their platelet-rich vegetations.[2] Many begin with unfractionated or low molecular weight

heparin (LMWH), particularly for overt DIC which frequently causes bleeding thereby favoring a short-acting anticoagulant. Long-term, DOACs may be preferred because of their oral administration and comparable safety and efficacy vs LMWH for other forms of cancer-associated thromboembolism.[9,29]

For Patients with Unknown Mechanisms

When the stroke is categorized as ESUS according to current construct (or possible "cancer-related stroke" as proposed in this statement), the optimal antithrombotic strategy is uncertain, and equipoise exists between anticoagulant and antiplatelet therapy.[9] While theoretical considerations may prompt some physicians to use anticoagulants, current observational and clinical trial data do not indicate that is a clearly superior approach. At a major cancer center, among 172 patients with active cancer and AIS, 90 were prescribed an anticoagulant at hospital discharge and 82 were prescribed an antiplatelet medication alone.[10] Rates of recurrent stroke, recurrent thromboembolism, and death were comparable between groups, although confounding by indication was likely.[10] Subgroup analyses of two large randomized trials in ESUS were similarly neutral. Among 543 patients with history of cancer enrolled into the NAVIGATE-ESUS trial, recurrent AIS rates were 7.7% with rivaroxaban 15 mg daily and 5.4% with aspirin 100 mg daily (HR, 1.43; 95% CI, 0.71-

2.87).[61] In the ARCADIA trial, 137 patients had a history of cancer, and the risk of a major ischemic or hemorrhagic event was 21.1% in patients randomized to apixaban 5 mg twice daily vs 13.1% in patients randomized to aspirin 81 mg daily (HR, 0.61; 95% CI, 0.26-1.43).[62] An important caveat to these subgroup analyses is that data on cancer activity, type, and stage were unavailable.

There have been two randomized trials dedicated to secondary stroke prevention in patients with cancer. The TEACH trial compared therapeutic-dose enoxaparin to standard-dose aspirin in patients with active cancer and AIS and no clear indication for anticoagulant or antiplatelet therapy.[63] This trial focused on feasibility of enrollment, and demonstrated that patients and physicians are generally willing to enroll in a trial comparing these antithrombotic strategies, especially if an oral anticoagulant were used.[63] The small number of patients (n=20) prevented meaningful efficacy analyses.[63] The ENCHASE trial randomized 40 patients with cancer and ESUS to edoxaban 60 mg daily or enoxaparin 1 mg/kg twice daily; there was no antiplatelet arm.[64] This trial focused on prothrombotic and embolic biomarkers, and demonstrated that D-dimer levels at 7 days and TCD microemboli rates at 90 days were similar between groups, indicating that DOACs and LMWHs have comparable effects in this population.[64]

Vitamin K antagonists have not been studied in clinical trials focused on AIS with cancer. However, they are generally avoided in this population because of their narrow therapeutic window, interactions with cancer treatments, and inferiority to other anticoagulants for the treatment of cancer-associated VTE. Furthermore, in a retrospective study of cancer-related stroke (n=79), warfarin use was associated with higher follow-up D-dimer levels and nominally more recurrent stroke than LMWH use.[65]

Phase 3 randomized trials of different antithrombotic strategies, particularly DOACs vs aspirin, are needed to determine the optimal approach for ESUS with cancer. Combined anticoagulant-antiplatelet therapy should also be explored as both coagulation factors and platelets are implicated in cancer-related stroke; however, this approach could further increase an already high bleeding risk. The role of statins in cancer-related stroke is also uncertain, although observational data suggest that statins may improve survival in patients with cancer and AIS regardless of stroke mechanism.[66] In the absence of clear indications, decisions surrounding secondary stroke prevention should be individualized and guided by multidisciplinary discussions between neurologists and oncologists. Drug-drug interactions should be considered when selecting medications, particularly DOACs because of their CYP3A4 and P-glycoprotein metabolism.[67]

Aggressive oncological treatment is critical to reduce the prothrombotic effects of cancer. Cancer activity drives the multifactorial hypercoagulable process that promotes stroke, and this is best addressed by eliminating cancer cells.[9] Therefore, chemotherapy, especially targeted agents that cause less systemic toxicity, should not be postponed in AIS patients with reasonable performance status. One exception is when the index stroke is attributed to a cancer medication, in which case the medication should be substituted for comparable alternatives. Another occasional exception is cancer surgery for which there are competing risks that require consideration. Operating soon after AIS will delay or interrupt antithrombotic therapy, which may trigger recurrence, especially if an active thromboembolic source is present. Conversely, postponing surgery for prolonged periods will enable cancer dissemination and progression of cancer-mediated hypercoagulability, which unquestionably will promote stroke recurrence. Therefore, we generally advise not postponing surgery beyond a few weeks unless the stroke was severely disabling, or the surgical risks are too high.

Conclusion

Cancer-related stroke is a growing and high-risk subgroup of AIS, with distinctive clinical features, mechanisms, and outcomes. As cancer treatments continue to improve, the prognosis of cancer-related stroke will likely follow suit. Translational studies have increased our understanding of the molecular and cellular pathogenesis of cancer-related stroke, although much work remains, including a better delineation of the biological causal pathway from cancer to AIS. In general, if standard exclusions are absent, patients with cancer and AIS should be treated with acute reperfusion interventions. Furthermore, all management decisions, including the type of antithrombotic therapy should be individualized and employed according to the patient's goals-of-care and priorities. In this statement, we propose a novel classification system for cancer-related stroke to remove it from the ESUS umbrella and enable consistent nomenclature across clinical practice and research. We hope that this novel classification will spur dedicated controlled trials to determine the optimal strategies for acute treatment and secondary prevention for these complex patients.

Acknowledgements

The authors thank Ms. Anne Leonard for her invaluable guidance and support for this statement; Dr. Eric Yang, Dr. Gregory Goldgof, Dr. Jennifer Jantz, Mr. Richard Genova, Dr. Jana Ivanidze, and the NewYork-Presbyterian/Weill Cornell Medical Center Clinical Microbiology Laboratory for assisting in image acquisition; and Mr. Patrick Lane for designing the central illustration.

Sources of Funding

None.

Conflicts of Interest and Financial Disclosures

Dr. DeAngelis discloses receiving consulting fees from Break Through Cancer and Starlight Therapeutics. Dr. Cushman discloses receiving research grants from the National Institutes of Health. Dr. Kasner discloses receiving research grants from Bayer, Daichi Sankyo, and DiaMedica; and receiving consulting fees from AstraZeneca, Medtronic, Boehringer Ingelheim, Genentech, and WL Gore. The other authors report no disclosures.

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Figure Legend

Figure 1 (Central Illustration)

Title: Ischemic Stroke Mechanisms Related to Cancer or its Treatments and their Corresponding Diagnostic Findings.

Legend: This figure depicts important mechanisms of ischemic stroke related to the effects of cancer or its treatments, and their corresponding diagnostic findings, as described below. Nonbacterial thrombotic endocarditis: the three-territory sign on magnetic resonance imaging (MRI), characterized by acute infarcts in all three cerebrovascular territories; high intensity transient signals (HITS) on transcranial Doppler (TCD), which are surrogates for circulating microemboli; a mitral valve vegetation on transesophageal echocardiography (TEE) with negative blood cultures. Disseminated intravascular coagulation: a blood smear demonstrating abundant schistocytes. Tumor embolism: a computed tomography (CT) scan showing a centrally located primary lung cancer abutting and invading the great vessels and the right mainstem bronchus. Paradoxical embolism: an acute deep vein thrombosis (DVT) on venous ultrasound; a Spencer grade 5 right-to-left shunt on a TCD bubble study. Cancer therapy-related cardiomyopathy: late gadolinium

enhancement in multiple cardiac walls on MRI indicating myocardial edema and fibrosis due to immune checkpoint inhibitor-related myocarditis. Atherosclerosis after radiotherapy: a complicated non-stenosing internal carotid artery (ICA) plaque with areas of low attenuation that likely represent high-risk components on CT angiography; a complex aortic arch atheroma with a lipid-rich necrotic core on CT angiography. Infective endocarditis: gram-positive cocci in pairs and chains on blood culture from *Streptococcus gallolyticus* bacteremia; eccentric, circumscribed fluorodeoxyglucose (FDG) avidity associated with a prosthetic aortic valve on PET (positron emission tomography)-CT.

Table 1. Summary of Major Points and Clinical Suggestions from Each Section

Section	Major Points and Clinical Suggestions
Introduction	Given the growing incidence of cancer, and the falling mortality associated with improved therapeutics, there will be over 21 million American cancer survivors by 2030, representing over 6% of the population. Shared decision-making and close collaboration between neurology and oncology is essential when managing a patient with cancer and AIS and should consider cancer prognosis and the perceived risks and benefits of potential diagnostic tests and treatments.
Epidemiology and primary prevention	Both active and historical cancers are risk factors for AIS, though the specific risks vary over time and by cancer type, histology, stage, genomics, and treatments. Based on secondary analyses of primary prevention trials, neither aspirin nor anticoagulant therapy appears to reduce the risk of AIS in patients with cancer. Conversely, observational data suggest that statins may reduce AIS risk in patients with cancer, particularly in those treated with radiotherapy to the head, neck, or thorax.
Clinical presentation	In the year after AIS, 1.5%-10% of patients are newly diagnosed with incident cancer. Risks are highest in patients with elevated D-dimer, cryptogenic mechanisms, and multi-territorial cerebral infarctions. Controlled studies are needed to determine whether routine screening for occult cancer in patients with AIS improves clinical outcomes. Compared to the general ischemic stroke population, patients with cancer and AIS tend to be older, have fewer stroke risk factors, higher stroke severity, more widespread infarcts, and increased blood markers of thrombosis and inflammation.
Biological pathways implicated in heightened stroke risk	Prospective studies indicate that, compared to stroke-only controls, patients with active cancer and AIS have higher levels of platelet, coagulation, and endothelial activation, neutrophil extracellular trap formation, and circulating cancer- and platelet-derived extracellular vesicles. As multiple biological pathways are implicated in the pathogenesis of cancer-related AIS, no single target exists for preventing recurrent thromboembolism in these patients.
Stroke mechanisms	Conventional stroke mechanisms, such as cardioembolism and atherosclerosis, account for about half the burden of AIS in patients with active cancer. However, cancer-related factors, such as radiation and chemotherapy, sometimes mediate these mechanisms. The remaining 50% of AIS in patients with active cancer are either of undetermined source or due to known cancer-specific mechanisms. Among the cryptogenic cases, many are suspected to be due to covert NBTE based on clinical and histopathologic data. Stroke from cancer drugs is rare and limited to select classes and agents.
Diagnostic evaluation	The diagnostic approach to patients with suspected stroke and active cancer must account for additional layers of complexity related to the dual disease process.

	In addition to the standard diagnostic evaluation for AIS, D-dimer is generally advised for cancer patients. Blood cultures, right-to-left shunt assessments, TEE, chest CT, and more prolonged cardiac rhythm monitoring should also be strongly considered for these patients.
New classification for cancer-related stroke	We propose a novel classification system with varying degrees of certainty to attribute some strokes to cancer itself. These "cancer-related strokes" would then be categorized under the "stroke of other determined etiology" subtype. The different categories for certainty of causality (probable vs possible vs unlikely) relate to patients' distinctive clinical features and their risk for recurrent thromboembolism. The probable category encompasses standard criteria for NBTE, overt DIC, or tumor embolism, while the possible category includes the most robust clinical, laboratory, and radiographic risk markers for AIS in patients with cancer.
Goals of care	We suggest periodically outlining the goals of care for patients with active cancer and AIS, as they may change over the course of their disease. Palliative care to control symptoms and enhance quality-of-life should be implemented alongside disease-targeting medical therapies.
Acute treatment	Patients with AIS and active cancer should be considered for IVT according to standard criteria. However, an additional layer of vigilance is warranted when assessing eligibility. We suggest checking complete blood counts and coagulation studies prior to treatment. Further, if brain metastases are present, we generally advise against IVT because of the high risk for hemorrhagic complications. Mechanical thrombectomy is associated with similar rates of technical success and in-hospital outcomes but higher rates of stroke recurrence and death in patients with vs without active cancer. Patients with cancer and LVO-stroke should be considered on an individual basis for thrombectomy while accounting for their long-term goals of care, cancer prognosis, and the perceived risks and benefits of the procedure.
Risk of recurrent stroke and other adverse events	Cancer-related stroke is one of the highest risk subgroups for recurrent thromboembolism. Compared with the general stroke population, patients with active cancer have a 2- to 3-fold increased risk of recurrent stroke at 1-year, with rates ranging from 14-29%. There is a U-shaped curve for incident and recurrent AIS risk in patients with cancer, with highest risk soon after cancer diagnosis from peak hypercoagulability due to amplified cancer activity and treatment, then a reduction in risk during the years following cancer control or cure, followed by a subsequent progressive rise in stroke risk associated with tumor recurrence or the long-term effects of cancer treatments.
Secondary stroke prevention	Secondary stroke prevention in patients with cancer should be tailored to the stroke mechanism if known. For instance, antiplatelet therapy and aggressive risk factor control is advised for small vessel disease, while DOACs should be administered for nonvalvular AF. Further, most patients with cancer and AIS should be treated with a statin.

	When a defined stroke mechanism is absent in a patient with active cancer, and the stroke is categorized as ESUS (or possible “cancer-related stroke as proposed in this statement), equipoise exists between anticoagulant and antiplatelet therapy. There are strong theoretical arguments for either approach, and current observational and clinical trial data do not indicate one to be clearly superior to the other. Dedicated randomized-controlled trials are needed.
Conclusion	Cancer-related AIS is a growing and high-risk subgroup of ischemic stroke. Recent studies have improved our understanding of its risk markers, pathophysiology, clinical features, and outcomes. We have proposed in this statement a novel classification system for cancer-related stroke to enable consistent nomenclature across practice and research, which we hope will spur controlled trials to determine the optimal strategies for acute treatment and secondary prevention in this population.

1 Nonstandard abbreviations: AIS, acute ischemic stroke; AF, atrial fibrillation; CT, computed
2 tomogram; DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; ESUS,
3 embolic stroke of undetermined source; IVT, intravenous thrombolysis; LVO, large vessel occlusion;
4 NBTE, nonbacterial thrombotic endocarditis; TEE, transesophageal echocardiogram.

Table 2. Cancer Medications Potentially Associated with Increased Ischemic Stroke Risk*

Class†	Medication	Indication by Cancer Type	Postulated Mechanism for Stroke
Alkylating agents	Cyclophosphamide	Lymphoma, leukemia, myeloma, breast, ovarian, neuroblastoma, retinoblastoma	Endothelial injury, increased platelet aggregation
Anthracyclines	Daunorubicin Doxorubicin Epirubicin Idarubicin	Leukemia, lymphoma, bladder, breast, ovarian, sarcoma, thyroid, neuroblastoma, lung, Wilm's tumor, endometrial, hepatocellular, myeloma, renal cell, thymic	Cardioembolism from cardiomyopathy, endothelial injury, platelet activation, increased tissue factor activity
Anti-CD52 monoclonal antibody	Alemtuzumab	Leukemia, lymphoma	Cervicocephalic artery dissection, endothelial injury, immune dysregulation, hypertension
Aromatase inhibitors	Anastrozole Letrozole Exemestane	Breast	Altered lipid metabolism
BCR-ABL targeted receptor tyrosine kinase inhibitors	Ponatinib Nilotinib Dasatinib	Leukemia	Endothelial injury, platelet activation, hypertension
CYP 17A1 inhibitors	Abiraterone	Prostate	Hypertension
Gonadotropin releasing hormone agonists	Leuprolide Goserelin Triptorelin Buserelin	Prostate	Atherosclerotic plaque rupture, metabolic syndrome
Immune checkpoint inhibitors	Ipilimumab Nivolumab Pembrolizumab Atezolizumab Avelumab Durvalumab	Melanoma, breast, bladder, cervical, colon, head and neck, lymphoma, hepatobiliary, lung, renal cell, stomach, esophageal, colorectal	Increased systemic inflammation, accelerated atherosclerosis, cardioembolism from myocarditis
Immunomodulatory antiangiogenic agents	Lenalidomide Thalidomide	Myeloma, lymphoma, myelodysplastic syndromes	Endothelial injury, increased platelet activation, hypertension
Platinum-based compounds	Carboplatin Oxaliplatin Cisplatin	Lung, breast, ovarian, head and neck, testicular, cervical, bladder,	Endothelial injury, increased platelet aggregation

		esophageal, colorectal, sarcoma, lymphoma	
Proteasome inhibitors	Bortezomib Carfilzomib	Myeloma and lymphoma	Endothelial injury including PRES, vascular oxidative stress, hypertension
Protein synthesis inhibitors	Pegasparaginase Erwinia Asparaginase	Acute lymphoblastic leukemia, lymphoma	Cerebral vein thrombosis from decreased anticoagulant proteins, particularly antithrombin; increased tissue factor expression
Selective estrogen receptor modulator	Tamoxifen	Breast	Increased procoagulant proteins, decreased anticoagulant proteins, increased platelet aggregation
VEGF receptor targeted tyrosine kinase inhibitors	Sorafenib Sunitinib Axitinib Pazopanib Vandetinib	Renal cell, hepatocellular, thyroid, sarcoma, neuroendocrine	Endothelial injury, mitochondrial oxidative stress, hypertension, impaired pericyte function and survival
VEGF monoclonal antibody	Bevacizumab	Cervical, colorectal, hepatocellular, lung, ovarian or fallopian tube, primary peritoneal, renal cell, glioblastoma	Endothelial injury, mitochondrial oxidative stress, hypertension, increased antifibrinolytic proteins

1 Nonstandard abbreviations: CYP, cytochrome P450; PRES, posterior reversible
2 encephalopathy syndrome; VEGF, vascular endothelial growth factor
3 *This list of medications is not exhaustive nor definitive and is restricted to medications
4 with the most robust data and biological plausibility for a potential association with
5 increased stroke risk.
6 †Listed in alphabetical order
7

Table 3. Proposed Etiological Classification for the Diagnosis of Cancer-Related Ischemic Stroke*†

Degree of	**Probable**	**Possible**	**Uncertain Causal Link**
Criteria	Meeting ≥1 of the following criteria: -Cardiac vegetation(s) with negative blood cultures (i.e., NBTE) -ISTH DIC Score ≥5 fulfilling criteria for overt DIC‡ -Radiographic evidence for tumor invading the left atrium or ventricle, pulmonary veins, or cervicocephalic arteries with acute infarction confined to the corresponding cerebrovascular territories§	-Cryptogenic ischemic stroke after standard diagnostic evaluation in a patient with active cancer that has spread beyond the primary site *OR* recently progressed *AND* meeting ≥1 of the following criteria: -D-dimer >2500 ng/ml FEU in the absence of an acute venous thromboembolism -Acute infarction in multiple cerebrovascular territories (i.e., bilateral anterior, unilateral anterior and posterior, or bilateral anterior and posterior)	Not meeting criteria for Probable or Possible causality

Nonstandard abbreviations: DIC, disseminated intravascular coagulation; FEU, fibrinogen equivalent units; HITS, high intensity transient signals; ISTH, International Society of Thrombosis and Haemostasis; NBTE, nonbacterial thrombotic endocarditis; TCD, transcranial Doppler.

*This classification is specific to patients with active cancer. The prevailing definition for active cancer in prospective studies is a pathological diagnosis or treatment of any cancer other than basal or squamous cell carcinoma of the skin within the past 6 months; known recurrent, regionally advanced, or metastatic cancer; or cancer not in complete remission.

†This proposed classification is meant to supplement prevailing classification systems such as TOAST. It is intended for strokes that are currently classified as cryptogenic or those that fall under defined mechanistic categories but are directly related to the systemic effects of cancer (i.e., NBTE, DIC, tumor embolism). Under this proposed schema, these “cancer-related strokes” should instead be categorized under the “stroke of other determined etiology” subtype. Stroke mechanisms with defined categories that are not directly related to the systemic effects of cancer should be categorized per conventional criteria even if mediated by cancer or its treatments (i.e., large artery atherosclerosis after radiotherapy).

‡The ISTH DIC Score ranges from 0 to 8. A score ≥5 fulfills criteria for overt DIC. Points are assigned based on platelet count (2 points for values <50 x 10^3/uL or 1 point for

values 51-100 x 10^3/uL), fibrin-related markers such as D-dimer (3 points for severely increased values [>10X upper limit of normal] or 2 points for moderately increased values [>1 to <10X upper limit of normal]), prothrombin time (2 points if prolonged ≥6 seconds or 1 point if prolonged 3 to 6 seconds), and fibrinogen level (1 point if <100 mg/dL).

§Radiographic evidence can include echocardiography, computed tomogram, or magnetic resonance imaging.

||The susceptibility vessel sign describes a hypointense signal within an occluded intracranial artery seen on magnetic resonance imaging T2-weighted gradient-recalled echo images and is associated with erythrocyte-rich thrombi.