Peripheral arterial ischemic events in cancer patients

Saurabh Sanon¹, Daniel J Lenihan² and Elie Mouhayar³

Abstract
Thromboembolic complications are the second leading cause of death in cancer patients. In contrast to the large body of literature on venous thromboembolism (VTE), relatively few reports have focused on the pathogenesis, incidence, management and outcomes of arterial thromboembolic events in patients with malignancy. The purpose of this article is to review the current literature on the etiology, mechanisms, and prognosis of arterial thromboembolic events in cancer patients and outline appropriate screening and management guidelines that may help lower the rates of morbidity and mortality related to these events.

Keywords
arterial ischemic event; arterial occlusive diseases; arterial thromboembolic events; arterial thrombosis; cancer; thromboembolism; thrombosis

Introduction
Peripheral artery disease and cancer are prevalent conditions that often coexist. Thromboembolic complications are the second leading cause of death in cancer patients.¹ In contrast to the large number of studies on venous thromboembolism (VTE), relatively few reports have focused on the pathogenesis, incidence, management and outcomes of arterial ischemic events in patients with malignancy. The annual incidence of these events in cancer patients is not well studied. Prevalence is in the range of 1.5–3.1%.²,³ Multifactorial mechanisms have been implicated and the outcome following these events is poor.⁴ Acute limb ischemia in patients with cancer carries a high mortality rate.²,⁴ In a cohort study by El Sakka et al., 50% of all patients presenting to an institution with critical limb ischemia and malignancy died within 6 months, compared with 20.6% of patients without underlying malignancy.² The purpose of this review is to describe the etiology and mechanisms of arterial thromboembolic events in cancer patients and outline appropriate screening and management guidelines that may help lower the rates of morbidity and mortality related to these events.

Epidemiology
Hypercoagulable states associated with malignancy or certain hematological disorders can present with diverse clinical ischemic syndromes. This includes venous and arterial thromboembolic events. In contrast to VTE, most of the available data regarding arterial ischemic events is based on case series and reports. Very few epidemiologic studies looked at the prevalence of arterial thromboembolic events in this patient population. Khorana et al. reported a prevalence rate of 1.5–3.1%.²,³ There has been a 124% increase in reported similar events from 1995 to 2002,² likely related to improved detection of such events and improved survival of patients with cancer. The presence of comorbidities including pulmonary disease, renal disease, infection, blood transfusion, chemotherapy and obesity are associated with a higher risk of arterial events. There is no observed difference in incidence between subgroups divided by type of malignancy and presence or absence of metastatic disease. Reported events included acute coronary syndrome, stroke and peripheral artery thromboembolism.² Schattner and colleagues reported a prevalence rate...
Table 1. Causes of arterial thromboembolic events in non-cancer patients

<table>
<thead>
<tr>
<th>Embolic etiology</th>
<th>Thrombotic etiology</th>
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<tr>
<td>Atrial fibrillation</td>
<td>Atherosclerosis</td>
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<td>Acute myocardial infarction</td>
<td>Shock/low flow state</td>
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<td>Mitral stenosis</td>
<td>Thrombophilia</td>
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<td>Valvular prosthesis</td>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>Infective endocarditis</td>
<td>Protein C and S deficiency</td>
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<tr>
<td>Non-bacterial thrombotic endocarditis</td>
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<td>Aortic arch atherosclerosis</td>
<td>Heparin-induced thrombocytopenia</td>
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<tr>
<td>Aneurysms (aortic, carotid, popliteal)</td>
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<tr>
<td>Paradoxical emboli</td>
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<td>Cardiac tumor</td>
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Etiology and pathophysiology

Acute ischemic arterial events can have thrombotic or embolic etiologies. The two causes have different diagnostic and therapeutic approaches; however, the exact mechanism can sometimes be difficult to establish.

Hypercoagulability

In addition to the typical causes of arterial ischemia related to traditional cardiovascular conditions, patients with underlying malignancy or hematologic disorders have added risks for in situ thrombosis related to the inherent thrombophilia associated with their malignancy and its therapy (Table 1). Malignancy is a common cause of acquired thrombophilia. Complex mechanistic etiologies have been implicated in this process; however, a key initiating factor is the release of procoagulants such as tissue factor and cancer procoagulant, which activate factor X and the clotting cascade. Inflammatory cytokines secreted by tumor cells lead to endothelial dysfunction and prime the vascular endothelium into a prothrombotic state. Patients with malignancy also have increased levels of clotting factors (fibrinogen, factors V, VIII, IX, XII), thrombocytosis, impaired fibrinolytic activity, and decreased protein C and S levels.

Antiphospholipid antibody syndrome (APLS) is diagnosed on the basis of thrombosis in the presence of anticardiolipin antibodies, lupus anticoagulant and/or an anti-beta 2 glycoprotein I antibody. Zuckerman et al. reported that 21.8% of their patients with malignancies were positive for anticardiolipin antibodies (the most common type of antiphospholipid antibodies – APL), compared to 3.4% in the control group; similarly, 27.7% of the anticardiolipin-positive patients experienced thromboembolic events, compared to 14.2% of the anticardiolipin-negative patients ($p < 0.05$). In recent years, a higher prevalence of APL has been found in patients with solid tumors compared to controls. Research has suggested that these antibodies are produced in response to tumor antigens rather than secreted from the tumor cells themselves and that the antibodies are involved in the production of monoclonal immunoglobulin that might have lupus anticoagulant and anticardiolipin activities. Adequate long-term management depends on accurate diagnosis, as these patients may benefit from long-term therapy with vitamin K antagonists. While screening for hypercoagulability in cancer patients with VTE is controversial and rarely needed, those patients that present with arterial thromboembolic events without an obvious source or clear etiology, it may be warranted to assess for APLS since the long-term management is clearly altered with anticoagulation in this situation.

Thromboembolic events

Non-bacterial thrombotic endocarditis (NBTE), tumor-cell emboli and paradoxical embolus from deep venous thrombosis (DVT) through a patent foramen ovale are typical examples of embolic etiologies in these patients. NBTE is characterized by the presence of sterile platelet-fibrin vegetations on the contact margins of cardiac valvular leaflets. A majority of patients presenting with NBTE are found to have cancer, and the vegetations are thought to form as a result of focal valvular endothelial injury associated with the hypercoagulability of cancer. These vegetations can cause arterial thromboembolic events after dislodgement, leading to strokes, splenic infarctions and acute limb ischemia. Hagmann et al. reported NBTE in 4% of all patients with cancer in their study population. Dutta et al. reported an 18% prevalence of NBTE in their cohort of patients with active cancer. Transesophageal echocardiography is the preferred imaging modality in this setting and treatment includes low-molecular-weight heparin or unfractionated heparin (UFH).

Figure 1. Non-bacterial thrombotic endocarditis involving the mitral valve in a 45-year-old male with pancreatic cancer.
Paradoxical embolization is another mechanism that is typically detected on the basis of the concomitant presence of arterial and venous thrombosis; this finding should trigger evaluation for patent foramen ovale or atrial septal defect responsible for intracardiac right-to-left shunt (RLS). Iguchi et al. reported RLS in 55% of their cohort of cancer patients presenting with ischemic stroke. They also reported that over 50% of these patients with RLS had underlying DVT or pulmonary embolisms. Diagnostic modalities for paradoxical embolization include contrast-transcranial Doppler imaging, contrast transthoracic echocardiography or transesophageal echocardiography. Systemic anticoagulation is preferred in this setting; however, patent foramen ovale closure is an attractive option for recurrent events despite anticoagulation (Figure 2).

Other causes of arterial ischemia
Several other mechanisms can lead to arterial ischemic events in patients with malignancy. For example, the risk of coronary artery thrombosis is two to five times higher in cancer patients with known atherosclerotic disease who are undergoing chest radiation therapy. Other potential predisposing factors include chronic deconditioning resulting in immobility and mechanical compression of blood vessels by the neoplastic process or endothelial damage caused by iatrogenic mechanisms related to blood vessel catheterization, surgery and chemotherapeutic agents. Low-flow states and shock associated with sepsis secondary to cancer-mediated or chemotherapy-induced immunosuppression can lead to vascular stasis, arterial thrombosis and limb ischemia, especially in the presence of underlying obstructive atherosclerotic disease and hypercoagulability. Management is typically focused on reversing the low-flow state.

Arterial ischemic events associated with specific malignancies
Table 2 lists some causes of arterial thromboembolic events associated with malignancy, hematologic disorders or cancer therapy.

Acute leukemia
Although acute leukemia is classically associated with hemorrhagic complications, the disease course can be complicated by thrombotic events, the incidence of which depends upon the type of leukemia and the chosen therapy. De Stefano et al. reported a 9.6% incidence of thrombosis at the time of presentation in patients with acute promyelocytic leukemia and a 1.4% incidence in patients with acute lymphocytic leukemia (ALL). The incidence was reported to increase to 10.6% with 1-asparaginase treatment for ALL. In this study, more than 50% of the thrombotic events occurred as the presenting manifestation before cytoreductive therapy was started, with 20% of these events involving an arterial bed. Mechanisms for thrombosis in acute leukemia include increased fractional volume of leukocytes, reduced cell deformability, increased blast cell secretion of tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β) and subsequent induction of endothelial tissue factor expression, and thrombomodulin down-regulation and adhesion molecule up-regulation. Therapeutic options include leukapheresis and immediate chemotherapy. Surgical thromboembolectomy should be considered for large vessel occlusion (Figure 3).

Myeloproliferative disorders
Clinical vascular events in myeloproliferative disorders (MPDs), such as polycythemia vera (PV) and essential thrombocytopenia (ET), are characterized by microcirculatory disturbances responsible for forming platelet and fibrin plugs in terminal arterial coronary, cerebral, cutaneous and peripheral circulatory beds, leading to visual and aural symptoms, intractable headaches, Raynaud’s
phenomenon, ischemic cerebrovascular accidents and acute coronary syndromes. Various studies have reported the incidence of thrombosis upon PV and ET diagnosis at 9.7–38.6%, with 64–96.7% of these events involving the arterial bed. Others have reported the tendency for thrombophilia to manifest 5–6 years before an MPD diagnosis. Pathophysiologic mechanisms of thrombosis in MPDs include the effects of erythrocytosis and thrombocytosis; biochemical changes in the red blood cell (RBC) membrane such as JAK2-dependent phosphorylation of the Lutheran blood group, leading to increased cellular adhesiveness; increased plasma levels of β-thromboglobulin and platelet factor 4, leading to increased platelet activation; leukocytosis; and increased leukocyte alkaline phosphatase and intracellular elastase. Thrombotic prevention in MPD patients warrants the use of aspirin, which has been demonstrated to significantly lower the risk of cardiovascular events. In symptomatic patients and in those with platelet counts greater than 600,000, hydroxyurea, anagrelide and/or phlebotomy appear to have some clinical benefit (Figure 4).

**Figure 3.** A 26-year-old patient with leukemia presenting with two episodes of left-side transient hemiparesis over 2 weeks. (A) Carotid duplex Doppler imaging shows focal stenosis/soft plaque in the right bulb and proximal internal carotid artery. (B) Turbulent flow and increased velocity was consistent with 50–69% stenosis of the right internal carotid artery.

**AL-Amyloidosis**

Light-chain amyloidosis (AL) is a monoclonal plasma cell dyscrasia in which secreted immunoglobulin is deposited in many organs including the heart. AL-amyloid can occur in association with multiple myeloma, Waldenström’s macroglobulinemia or non-Hodgkin’s lymphoma. Cardiac involvement in the form of intracardiac thrombosis and thromboembolic events is found in 26–33% patients with primary amyloidosis, particularly the immunocyte-derived (AL)
A 55-year-old patient with cerebrovascular accident, bowel ischemia and platelet counts of greater than 1,000,000 subsequently diagnosed with essential thrombocytosis. Her echocardiogram shows a left ventricular apical thrombus (arrow) in the presence of normal wall motion and normal left ventricular systolic function.

A 42-year-old patient with multiple myeloma and secondary amyloidosis presenting with recurrent transient ischemic attacks. The transesophageal echocardiogram shows a 0.9 × 0.7-cm left atrial appendage clot (calipers). No ischemic events occurred after warfarin therapy was initiated.

Although a variety of malignancies have been associated with arterial thromboembolic events, no single cancer type dominates. In their large cohort, Khorana et al. reported the association of arterial thromboembolic events with prostate, lung and colon cancer. Javid et al. studied a sample of 20 cancer patients who presented with arterial thrombosis. Amongst these patients, two (10%) had lung cancer, three (15%) had adenocarcinoma of unknown primary, three (15%) had colorectal cancer, five (25%) had breast cancer, two (10%) had ovarian cancer, one (5%) had leukemia, one (5%) had transitional cell carcinoma, one (5%) had melanoma, one (5%) had squamous cell carcinoma and one (5%) had non-Hodgkin’s lymphoma. The mechanistic etiologies implicated in these cases included a hypercoagulable state of malignancy, peripheral embolization and direct tumor compression of the arterial walls.

Neurofibromatosis
Neurofibromatosis type I (NF1) is a genetic disorder associated with the development of neurofibromas, malignant nerve sheath tumors, myelogenous leukemia and pheochromocytoma. NF1 is an autosomal dominant disorder characterized by mutations in the NF1 gene, which encodes neurofibromin, a GTPase-activating protein that down-regulates the p21-ras cellular proto onco gene. Neurofibromin has also been found in the vascular endothelial and smooth muscle cells. Abnormal or loss of neurofibromin function has been hypothesized to alter vascular histiogenesis, leading to NF1-associated vasculopathy characterized by the development of arteriovenous malformations, aneurysms and stenosis. Intrinsic arterial wall lesions in patients with NF1 vasculopathy are thought to be related to spindle cell proliferation, fibromuscular dysplasia, intimal thickening and intramural nerve cell proliferation. Clinical implications of NF1 vasculopathy include severe hypertension from renal artery stenosis and ruptured aortic aneurysms in addition to direct arterial compression by the neural tumor. Treatment of NF1 vasculopathy depends on the patient’s age and medical condition and the lesions’ locations and characteristics; options include observation and monitoring for asymptomatic patients, and percutaneous intervention and surgical repair for symptomatic individuals.

Malignancy treatment-related thrombotic events
Chemotherapy
Chemotherapeutic agents are now identified as an independent risk factor for thrombosis in cancer patients. The true incidence of vascular events with these agents remains largely unknown, with most available data generated from case reports. In general, mechanisms for these events have included chemotherapy-induced expression of macrophage-monocyte tissue factor, endogenous procoagulant-anticoagulant mismatch, accentuated tumor and endothelial cell death, and cytokine release resulting in increased expression of tissue factor and enhanced endothelial cell reactivity to platelets. Certain chemotherapy agents (Table 3) have been associated with arterial thromboembolic events more than others: 5-fluorouracil can decrease protein C levels and increase fibrinopeptide A levels besides leading to endothelial...
damage and even endothelial-independent vasoconstriction via protein kinase C. Gemcitabine has been associated with vascular events ranging from digital ischemia, VTE, thrombotic microangiopathy and systemic capillary leaks. Cisplatin, a central component of several chemotherapeutic regimens, induces thrombosis by causing endothelial damage, activating platelets and increasing monocyte tissue factor activity, with a 12–17.6% risk of strokes, recurrent peripheral arterial thromboembolic events and/or aortic thrombosis (Figure 6). Recently developed biologically targeted therapies such as bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, have been associated with an increased risk of serious arterial thromboembolic events and/or aortic thrombosis (Figure 6). Endothelial damage, reduction of endothelial renewal capacity, exposure of subendothelial collagen, subsequent tissue factor activation and overexpression of proinflammatory cyclooxygenase-2 and E-selectin genes all lead to activation of the coagulation pathway, thereby causing intravascular thrombosis. Scappaticci et al. reported the absolute rate of arterial thromboembolic events as 5.5 events per 100 person-years in their population of patients concurrently receiving bevacizumab and chemotherapy. Pereg and Lisher reported that low-dose aspirin effectively prevented cardiovascular complications in patients receiving bevacizumab who were 65 years or older with a prior history of cardiovascular ischemic events.

Sunitinib and sorafenib are two other VEGF receptor inhibitors with the mechanism of action involving tyrosine kinase inhibition. These agents have been shown to improve the clinical outcome of patients with different types of malignancies (renal, hepatic, thyroid, gastrointestinal stromal tumors) and their use is expected to increase significantly in the future since these drugs are being assessed for activity in multiple other cancer types. A recent meta-analysis by Choueiri et al. found a significant increase in the risk of arterial thromboembolic events with these agents (relative risk 3.03 (95% CI, 1.25–7.37; \( p = 0.015 \)) compared with control patients.

More recently, Shahani et al. have reported a possible association between androgen-deprivation therapy (GnRH agonists or antagonists, or androgen receptor antagonists used in conjunction with GnRH analogs) for prostate cancer and increased cardiovascular mortality via the development of metabolic syndrome, insulin resistance, diabetes and dyslipidemia. Long-term prospective studies are needed to further elucidate such an association.

**Radiation therapy**

Arterial disease secondary to radiation therapy has been linked to accelerated atherosclerosis, with the risk depending on the radiation dose and technique, extent of vascular exposure and type of cancer. Ionizing radiation has been proposed to cause oxidative stress resulting in accelerated atherosclerosis; endothelial damage and fibrin deposition by activating the coagulation cascade; and accelerated transforming growth factor beta (TGF-\( \beta \))-mediated transformation of fibroblasts to fibrocytes, all of which predispose patients to arterial thromboembolic events. Prevention of radiation-induced atherosclerosis and subsequent thrombosis involves reducing traditional atherosclerotic risk factors.

### Table 3. Chemotherapeutic agents associated with specific arterial ischemic events

<table>
<thead>
<tr>
<th>Chemotherapeutic agent</th>
<th>Arterial ischemic events</th>
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<tbody>
<tr>
<td>L-Asparaginase</td>
<td>Cerebrovascular accidents</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Cerebrovascular accidents, peripheral arterial events, aortic thrombosis</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Coronary vasospasm-mediated cardiac ischemia</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Coronary thrombosis-mediated cardiac ischemia, cerebrovascular accidents</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Digital ischemia, thrombotic microangiopathy</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Arterial thrombosis (rare)</td>
</tr>
<tr>
<td>Sorafenib / Sunitinib</td>
<td>Myocardial infarction, cerebrovascular accidents</td>
</tr>
</tbody>
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**Figure 6.** A 57-year-old patient with bladder cancer presenting with an acute thromboembolic event involving the left external iliac, common femoral, deep femoral and tibialis vessels. (A) Arterial duplex study shows a thrombus in the deep femoral artery (arrow). (B) Angiogram shows multiple filling defects consistent with thrombi in the common femoral and tibialis vessels (arrow). Pathology samples following surgery found no evidence of atherosclerosis. A cardioembolic source of embolization and antiphospholipid antibody syndrome were ruled out by further testing. The cause was subsequently attributed to chemotherapy.
with diet and lifestyle modifications including smoking cessation. This is in addition to adequately managing diabetes, hypertension and dyslipidemia. Pharmacologic intervention includes lifelong antiplatelet therapy; additionally, statin therapy may be beneficial, given its anti-inflammatory and antithrombotic effects on the irradiated endothelium. Since surgical interventions may be difficult in scarred tissue, percutaneous angioplasty with stenting is becoming an attractive treatment modality when revascularization is indicated. For radiation-induced renal, iliac and femoral disease, balloon angioplasty with or without stenting has shown favorable results (Figure 7).

**Supportive therapies related to arterial thromboembolism**

**Erythropoetin (EPO)**

Although most available data report the incidence of VTE with EPO use, EPO has also been implicated in the risk of arterial thromboembolic events in cancer patients, especially when used in combination with chemotherapy. Studies have reported rates of arterial and venous thrombosis of 13–27%. Data regarding the role of altered protein C and S, factor VIII, and von Willebrand factor levels secondary to EPO administration are inconsistent, and proposed novel mechanisms point to increased c-reactive protein activity, nitric oxide and thrombin-activatable fibrinolysis inhibitor (TAFI) as the causative factors for EPO-related thrombosis.

**Blood and blood component transfusion**

Khorana et al. retrospectively analyzed a cohort of 70,542 cancer patients and reported an arterial thromboembolic event rate of 5.2% in those receiving RBC transfusions versus 3.1% in non-transfused patients ($p < 0.001$). Both RBC and platelet transfusion were found to be predictors of an arterial thromboembolic event (RBCs: OR, 1.53; 95% CI, 1.46–1.61; $p < 0.001$; platelets: OR, 1.55; 95% CI, 1.40–1.71; $p < 0.001$) and associated with an increased risk of in-hospital mortality (RBCs: OR, 1.34; 95% CI, 1.29–1.38; $p < 0.001$; platelets: OR, 2.40; 95% CI, 2.27–2.52; $p < 0.001$). Possible mechanisms of transfusion-induced thrombosis include inadvertent delivery of prothrombotic mediators such as activated platelets, platelet microparticles and sCD40L, increased circulating RBC mass and consequent vascular stasis; vasoconstriction due to nitric oxide-depleted RBCs, and delivery of increased redox-active iron, resulting in oxidative stress.

**Suggested algorithm for evaluation of arterial thromboembolic events in patients with underlying malignancy**

The clinical presentation and management of arterial thromboembolic events in general vary based on the arterial bed and the organ involved; the clinical spectrum includes stroke, myocardial infarction, and visceral and limb ischemia. The rest of the discussion in this review will focus mainly on the management of limb ischemia in patients with malignancy.

Standard evaluation for these patients should include a complete physical examination, complete blood count, basic metabolic panel, prothrombin time, partial thromboplastin time and international normalized ratio. Initial evaluation should also include electrocardiography to identify
arrhythmia, and echocardiography to detect a potential source of embolus. There should be a low threshold for performing transesophageal echocardiography (TEE) because of the high prevalence of NBTE in this patient population. If these preliminary test results are unremarkable, computed tomographic angiography of the chest and abdomen may be necessary to detect a vascular source. In addition, carotid and subclavian artery duplex imaging should be performed in the setting of a suspected embolic event involving the central nervous system or affecting the upper extremities, respectively. Agitated saline contrast echocardiography and TEE are reasonable modalities for excluding an intracardiac shunt in the presence of a suspected paradoxical embolism. When a thrombotic arterial ischemic event is suspected, further testing may be necessary to exclude the presence of APL antibody or tumor-induced blood vessel compression. If the aforementioned work-up is non-diagnostic, a chemotherapy-induced arterial thromboembolic event should be suspected (Figure 8).

It is not clear if extensive screening for cancer is justified in patients who present with an idiopathic arterial thromboembolic event. Oktar et al. recommended a moderate screening strategy utilizing chest X-ray, basic laboratory tests and abdominopelvic ultrasonography to search for occult cancer in patients presenting with idiopathic VTE and a more extensive screening strategy in patients with high-risk features for malignancy, such as thrombosis in unusual sites. El Sakka et al. recommended chest X-ray as a screening modality based on findings from their study, in which lung cancer was the predominant malignancy in patients presenting with critical leg ischemia; however, the absence of a single predominant malignancy in other studies does not support this recommendation.

Management (Figure 9)
Following the diagnosis of critical limb ischemia, urgent intervention is typically directed toward reversing ischemia and minimizing organ damage, followed by long-term therapy and secondary prevention. The decision to use medical therapy versus a surgical or percutaneous approach to treat the acute event should be based on the

![Figure 9](image-url)
Table 4. Therapeutic interventions of potential benefit for arterial ischemic events observed in the setting of malignancy or hematologic disorders

<table>
<thead>
<tr>
<th>Arterial thromboembolic events associated with:</th>
<th>Treatment options</th>
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<tbody>
<tr>
<td>Myeloproliferative disorders</td>
<td>Aspirin (for primary and secondary prevention)</td>
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<td></td>
<td>Cell reduction therapy</td>
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<td></td>
<td>(i.e. phlebotomy, hydroxyurea, anagrelide, interferon alpha)</td>
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<tr>
<td>Acute leukemia</td>
<td>Leukapheresis</td>
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<td></td>
<td>Chemotherapy</td>
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<td></td>
<td>Surgical thromboembolectomy</td>
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<tr>
<td>Cardiac amyloidosis</td>
<td>Systemic anticoagulation</td>
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<tr>
<td>Neurofibromatosis</td>
<td>Percutaneous intervention</td>
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<td></td>
<td>Surgical repair</td>
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<tr>
<td>NBTE, non-bacterial thrombotic endocarditis</td>
<td>Systemic anticoagulation</td>
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<tr>
<td>Paradoxical embolization</td>
<td>Systemic anticoagulation</td>
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<td></td>
<td>PFO closure for recurrent events</td>
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<tr>
<td>APLS, antiphospholipid antibody syndrome</td>
<td>Systemic anticoagulation</td>
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<tr>
<td>Radiation therapy</td>
<td>Diet and lifestyle modifications</td>
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<td></td>
<td>Antplatelet therapy</td>
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<td>Statin therapy</td>
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<td></td>
<td>Percutaneous angioplasty with or without stenting</td>
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<tr>
<td>Low-flow states</td>
<td>Early goal-directed therapy for shock reversal</td>
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<tr>
<td>Bevacizumab</td>
<td>Aspirin (for primary prevention in patients &gt; 65 years old or with a history of cardiovascular events)</td>
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</table>

NBTE, non-bacterial thrombotic endocarditis; PFO, patent foramen ovale; APLS, antiphospholipid antibody syndrome.

patient’s general condition and the availability of local expertise.

Management of limb-threatening ischemia should include discontinuation of chemotherapy, early goal-directed therapy to reverse shock (if present) and anticoagulation with UFH or low-molecular-weight heparin and antiplatelet agents. Urgent surgical intervention is indicated if an embolic event is highly suspected. If the mechanism is not well defined, arteriography should determine the further course of action: percutaneous revascularization, embolectomy, catheter-based thrombolysis or surgical bypass. Long-term anticoagulation for primary and secondary prevention should be individualized and tailored to the patient’s underlying pathologic process and balanced against his risk of bleeding. Table 4 summarizes the therapeutic interventions of potential benefit previously discussed separately with each clinical condition.

Prognosis

The prognosis of cancer patients presenting with arterial thromboembolic events is not well defined. It most likely depends on the patient’s baseline condition, the underlying malignancy and the extent of organ damage. Khorana et al. observed a high mortality rate following an arterial thromboembolic event in hospitalized cancer patients undergoing chemotherapy. In patients with MPDs or radiation-induced atherosclerosis, a simple intervention like initiating antiplatelet therapy and lipid management can significantly improve their outcome. Conversely, the outlook for patients with critical limb ischemia associated with solid tumors is poor, regardless of any intervention that might be tried. Arterial thrombosis in such settings can be agonizing for many of these patients. Increased awareness and vigilance regarding this condition may lead to earlier detection and treatment, and thereby possibly alleviate some of the morbidities associated with these events.

Conclusion

Despite the significant morbidity and mortality rates associated with arterial thromboembolic events in patients with cancer, there is a relative paucity of literature on this pathology. Through this review we attempt to substantiate the cancer–arterial ischemic event relationship and provide suggested diagnostic and management guidelines, so as to improve the detection and treatment of this condition in clinical practice, and possibly alleviate some of the morbidity associated with it.

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References


