Yemen Journal of Medicine

https://yemenjmed.com

Article information

DOI: 10.63475/yjm.v5i2.0436

Article history:
Received: 05 June 2026
Accepted: 15 August 2026
Published: 20 August 2026

Correspondence to:
Mohammed Alkhanafsa
Email: mohammed-alkhanafsa@outlook.com
ORCID: 0009-0002-4983-2855

How to cite this article
Alkhanafsa M, Alqatati F. Cancer-associated nonbacterial thrombotic endocarditis: Current evidence and clinical challenges. Yemen J Med. 2026;5(2):264-273.

Copyright License: *© 2026 authors. This scholarly article is disseminated in accordance with the provisions of the Creative Commons Attribution License, thereby permitting unrestricted utilization, distribution, or reproduction across any medium, provided that credit is given to the authors and the journal*

Review Article

Cancer-Associated Nonbacterial Thrombotic Endocarditis: Current Evidence and Clinical Challenges

Mohammed Alkhanafsa[1], Fadel Alqatati[1]

1 Resident, Department of Medicine, Hamad Medical Corporation, Doha, Qatar

ABSTRACT

Nonbacterial thrombotic endocarditis (NBTE) is an uncommon but clinically important manifestation of cancer-associated thrombosis, characterized by sterile platelet-fibrin vegetations, usually on the mitral or aortic valve. It is most often associated with advanced adenocarcinoma and systemic hypercoagulability and commonly presents through systemic embolization, particularly multifocal ischemic stroke. Diagnosis is challenging because vegetations may be small, blood cultures are typically negative, and findings overlap with infective endocarditis, autoimmune valvulopathy, and degenerative lesions. Transthoracic echocardiography (TTE) is an appropriate initial test, but transesophageal echocardiography (TEE) is substantially more sensitive and should be performed when clinical suspicion remains high despite a negative or nondiagnostic TTE. Cardiac magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography/computed tomography may be useful adjuncts in selected diagnostically uncertain cases. Management is supported predominantly by observational cohorts, case series, and expert opinion rather than randomized NBTE-specific trials. Therapeutic unfractionated heparin or low-molecular-weight heparin is commonly favored when bleeding risk is acceptable, while evidence for direct oral anticoagulants remains limited and mixed. Control of the underlying malignancy is central to reducing recurrent embolic risk. This review summarizes current evidence on pathogenesis, presentation, diagnosis, anticoagulation, prognosis, and research priorities in cancer-associated NBTE.

Key words: nonbacterial thrombotic endocarditis, cancer-associated thrombosis, marantic endocarditis, ischemic stroke, adenocarcinoma, anticoagulation, transesophageal echocardiography

INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE) is a noninfective valvular disorder characterized by sterile thrombotic vegetations composed mainly of platelets and fibrin. [1–4] The term marantic endocarditis is commonly used for the malignancy-associated form, whereas Libman-Sacks endocarditis refers more specifically to immune-mediated sterile valvular lesions associated with systemic lupus erythematosus or antiphospholipid syndrome; these terms are related but not fully interchangeable. [5–7] Unlike infective endocarditis, NBTE generally lacks microorganisms, destructive valve infection, abscess formation, and persistent bacteremia.

Cancer-associated NBTE remains underrecognized because its clinical manifestations are usually embolic rather than cardiac. Patients may present with ischemic stroke, myocardial infarction, splenic or renal infarction, mesenteric ischemia, acute limb ischemia, or digital ischemia before a valvular source is considered. The condition lies at the intersection of malignancy-associated hypercoagulability, arterial thromboembolism, valvular disease, and embolic stroke of undetermined source. [4,5,8] Contemporary evidence remains

limited and is derived mainly from retrospective cohorts, single-center echocardiographic series, clinicopathological studies, and case-based literature. [8–11]

This clinically focused narrative review summarizes current evidence on cancer-associated NBTE, with emphasis on epidemiology, pathogenesis, embolic presentation, multimodality diagnosis, anticoagulation controversies, surgery, prognosis, and practical evidence gaps. **Figure 1** provides an overview of the pathophysiology, clinical presentation, diagnostic approach, differentiation from infective endocarditis, and management principles of cancer-associated NBTE.

METHODS

A structured narrative literature review was conducted using PubMed/MEDLINE and Google Scholar. The final search was completed on July 14, 2026, and covered database inception through that date. Search combinations included "nonbacterial thrombotic endocarditis," "marantic endocarditis," "cancer," "malignancy," "adenocarcinoma," "stroke," "echocardiography," "transesophageal echocardiography," "cardiac magnetic resonance," "FDG PET," "transcranial Doppler," "anticoagulation," "heparin," and "direct oral anticoagulants." Reference lists of key reviews, guidelines, and cohort studies were hand-searched for additional eligible publications. Embase, Scopus, and the Cochrane Library were not independently searched, which is acknowledged as a limitation.

English-language adult human studies were considered. Priority was given to original cohorts, echocardiographic or clinicopathological series, systematic or state-of-the-art reviews, major society guidelines, and landmark pathological studies. Case reports and small case series were included selectively when they provided unique information on multimodality imaging, recurrent embolism, direct oral anticoagulants (DOAC) failure or success, or uncommon management decisions; they were not used to estimate incidence or comparative treatment effects. Pediatric-only reports, studies focused exclusively on infective endocarditis, and non-cancer NBTE reports without relevance to differential diagnosis or management were excluded. When publications arose from overlapping institutional populations, each report was used only for the distinct outcome it addressed, reducing the risk of double counting.

This review was designed as a clinically focused narrative, non-systematic synthesis rather than a scoping review or meta-analysis. Formal duplicate screening, risk-of-bias assessment, and a PRISMA flow diagram were therefore not performed. Methodological reporting was informed by selected transparency items from the PRISMA Extension for Scoping Reviews (PRISMA-ScR) and by the Scale for the Assessment of Narrative Review Articles (SANRA) quality framework [12,13], without representing the review as PRISMA-ScR compliant. The final cited synthesis included 33 publications. Because the search was iterative and Google Scholar results are dynamic, formal deduplication and exact retrieved and screened record counts were not prospectively recorded and cannot be reconstructed reliably; this is an explicit methodological limitation.

Epidemiology and Cancer Associations

The true incidence of NBTE is difficult to determine because many cases are diagnosed postmortem, after an embolic event, or only when transesophageal echocardiography (TEE) is performed. Classic autopsy studies established its association with wasting illnesses, advanced malignancy, and

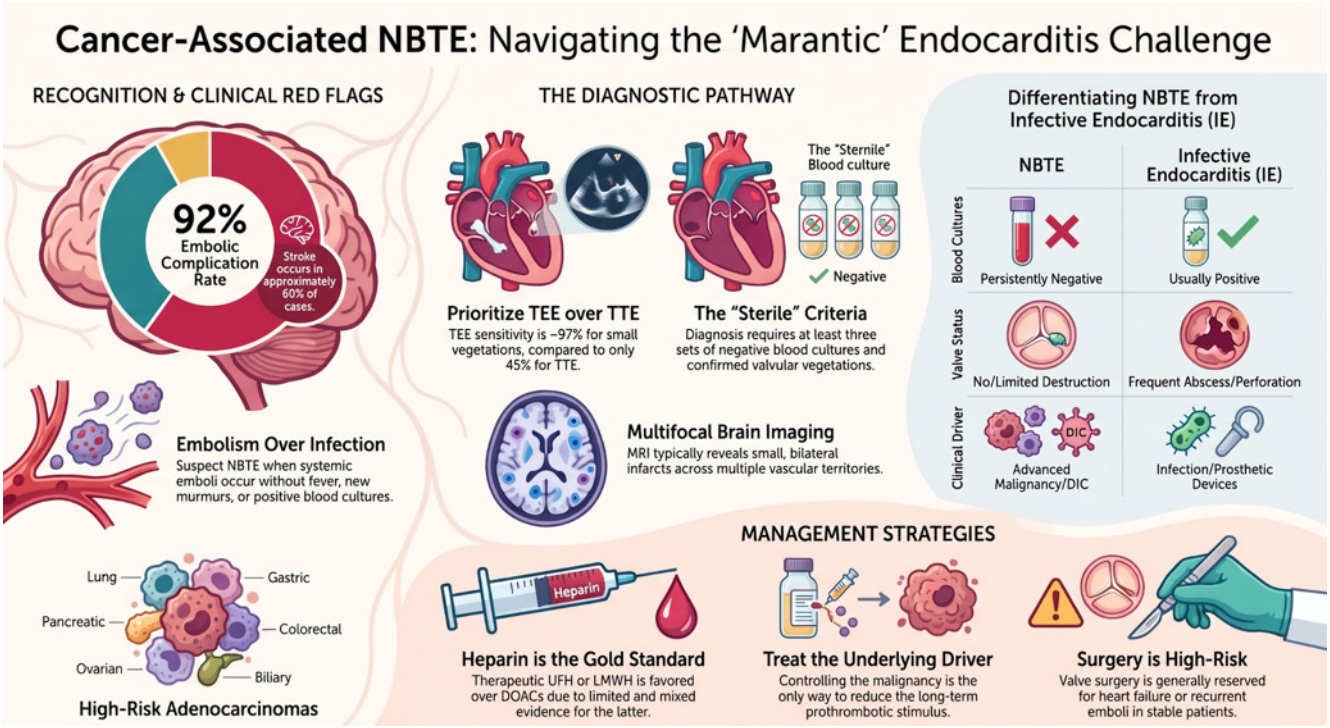

Figure 1: Overview of the clinical recognition, diagnostic pathway, differential diagnosis, and management of cancer-associated NBTE.

systemic coagulopathy. [1,2] Contemporary cohorts continue to identify malignancy as one of the most frequent underlying conditions. [8–10]

Cancer-associated NBTE is most strongly linked to adenocarcinomas, particularly lung, pancreatic, gastric, colorectal, ovarian, and biliary tract cancers. [4,8,14] Among published cases, lung adenocarcinoma is frequently reported, but pooled case reports and individual-patient meta-analyses are vulnerable to publication, referral, and ascertainment bias and cannot establish population-level cancer rankings. [14] The apparent prominence of lung cancer may reflect both biological factors and more frequent thoracic imaging, metastatic evaluation, neurologic surveillance, or echocardiography in symptomatic patients.

NBTE may occur in patients with known metastatic cancer or precede the diagnosis of an occult malignancy. Unexplained sterile valvular vegetations accompanied by multifocal arterial emboli, markedly elevated D-dimer, disseminated intravascular coagulation (DIC), weight loss, anemia, or constitutional symptoms should therefore prompt a focused evaluation for malignancy. [5,7,8] A pragmatic approach includes a detailed history and examination, a complete blood count, renal and liver profiles, a review of age-appropriate cancer screening, and targeted computed tomography of the chest, abdomen, and pelvis when clinical features warrant it. Indiscriminate tumor marker panels or repeated whole-body imaging without clinical direction are unlikely to be high-yield.

The contribution of modern anticancer therapy is incompletely defined. Immune checkpoint inhibitors (ICIs) are associated with venous and arterial thrombotic events in broader oncology cohorts, and isolated temporal associations with NBTE have been described, but causality cannot be separated from advanced cancer and other treatment-related risks. [15] Plausible mechanisms include cytokine-driven endothelial activation, tissue factor expression, platelet activation, and immune-mediated myocardial or valvular inflammation. Targeted therapies, antiangiogenic agents, hormonal therapy, central venous devices, surgery, hospitalization, and progressive tumor burden may also modify thrombotic risk and should be considered in individual assessment.

Pathogenesis

The pathogenesis of cancer-associated NBTE is multifactorial. Tumor cells and the tumor microenvironment promote coagulation through tissue factor expression, inflammatory cytokines, endothelial injury, platelet activation, neutrophil extracellular traps, and impaired endogenous anticoagulant pathways. [4,5,16] Cancer-derived extracellular vesicles and microparticles may expose tissue factor and negatively charged phospholipids, providing catalytic surfaces for thrombin generation. Although these mechanisms are well established in cancer-associated thrombosis, their specific contribution to valvular deposition in NBTE remains incompletely quantified. [16]

Mucin-producing adenocarcinomas may further promote thrombosis through selectin-mediated interactions between tumor-derived mucins, platelets, leukocytes, and endothelium. [17,18] These mechanisms provide a biological link between NBTE, Trousseau syndrome, DIC, and mucinous adenocarcinoma. Valvular endothelial injury, high-shear flow, and systemic inflammation probably facilitate local deposition of platelet-fibrin thrombi along the lines of valve closure. [3,4]

The mitral and aortic valves are most frequently involved, consistent with left-sided high-pressure flow and contemporary echocardiographic series. [3,4,11] Vegetations are typically friable, weakly attached, minimally inflammatory, and may cause little valve destruction despite a high embolic potential. Cancer-associated NBTE should therefore be viewed as one phenotype within the broader spectrum of cancer-associated thrombosis rather than an isolated cardiac disorder; patients may simultaneously have venous thromboembolism (VTE), arterial thrombosis, DIC, or recurrent embolic stroke. [19]

No inherited thrombophilia has been consistently established as a specific predisposition to cancer-associated NBTE. The malignancy-driven hypercoagulable state appears to be the dominant mechanism. [4,5,7] Routine broad thrombophilia testing is therefore not recommended solely because NBTE is present, but selective testing may be reasonable in unusually young patients, those with a strong family history, recurrent thrombosis disproportionate to cancer activity, or clinical suspicion of antiphospholipid syndrome.

Clinical Presentation

The clinical presentation of cancer-associated NBTE is dominated by embolic complications rather than cardiac symptoms. Fever, a new murmur, severe valve dysfunction, and heart failure are less common than in infective endocarditis, although their absence does not exclude either condition. Stroke was the most common presentation in the Cleveland Clinic cohort, occurring in 59.5% of patients. [9] In the 111-patient Mayo Clinic cancer-associated NBTE echocardiographic series, 91.9% experienced an embolic complication, underscoring the strongly embolic phenotype. [11]

Neurological events are particularly important. Brain magnetic resonance imaging often demonstrates multiple small acute infarcts of different ages, frequently involving both hemispheres and both anterior and posterior circulations. Cortical and cortical-subcortical lesions are common, although solitary or single-territory infarcts can occur and do not exclude NBTE. [20–22] This multifocal pattern differs from a typical single large-vessel territorial infarct and should prompt evaluation for a central embolic source when atrial fibrillation, intracardiac thrombus, and large-artery atherosclerosis are not explanatory.

Other manifestations include myocardial infarction, splenic infarction, renal infarction, mesenteric ischemia, acute limb ischemia, and digital ischemia. Recurrent embolization may occur despite anticoagulation, particularly when the underlying cancer remains uncontrolled, or DIC persists. Because embolic events are often the first clinical clue, the transition from clinical presentation to diagnosis should be immediate: unexplained multifocal arterial ischemia in a patient with active cancer warrants prompt echocardiographic and microbiological evaluation. The principal clinical clues that should raise suspicion for cancer-associated NBTE are summarized in **Table 1**.

Table 1: Clinical clues suggesting cancer-associated NBTE.

Clinical clue	Typical finding	Why it matters
Multifocal ischemic stroke	Small, bilateral cortical or cortical-subcortical infarcts across multiple vascular territories	Suggests a central embolic source, particularly when atrial fibrillation and large-vessel disease are absent. [20–22]
Recurrent embolism despite therapy	New stroke, splenic or renal infarction, limb ischemia, or myocardial infarction	Raises concern for persistent valvular thrombus, inadequate anticoagulant exposure, DIC, or uncontrolled cancer. [4,5,8]
Known advanced adenocarcinoma	Lung, pancreatic, gastric, colorectal, ovarian, or biliary cancer	These tumor types are repeatedly associated with NBTE and Trousseau syndrome. [4,14,17,18]
Negative blood cultures with valvular vegetation	Sterile-appearing vegetation without persistent bacteremia	Supports NBTE only after infective and culture-negative endocarditis have been carefully excluded. [7,23]
Marked systemic coagulopathy	Elevated D-dimer, thrombocytosis or thrombocytopenia, prolonged coagulation indices, or DIC	Platelet counts may be high, normal, or low; thrombocytopenia is common in advanced cancer, chemotherapy, and consumptive coagulopathy. [4,5,19]
Occult malignancy presentation	Embolic stroke or systemic infarction without another source	NBTE may precede cancer diagnosis and should prompt a focused malignancy evaluation. [5,8]

Diagnostic Approach

No single test confirms NBTE in living patients. Diagnosis requires integration of echocardiographic evidence of valvular vegetations, a negative and sufficiently complete microbiological evaluation, systemic embolization, and an underlying prothrombotic condition such as active malignancy. [7,24] Histopathology remains definitive but is rarely available unless surgery or autopsy is performed. A practical diagnostic and management algorithm for patients with suspected cancer-associated NBTE is shown in **Figure 2**.

Echocardiography

Transthoracic echocardiography (TTE) is the appropriate first-line cardiac test because it is rapid, noninvasive, and widely available. However, its sensitivity is limited for small or minimally mobile vegetations. In the Cleveland Clinic cohort, TTE identified NBTE in 45.2% of cases, whereas TEE identified vegetations in 33 of 34 patients in whom it was performed (97.1%). [9] TEE is particularly important for vegetations smaller than approximately 5 mm, lesions on the atrial surface of the mitral valve, or cases in which TTE image quality is suboptimal. [7,25] Consequently, a negative TTE does not exclude NBTE when clinical suspicion is high.

Typical echocardiographic findings include small, broad-based, irregular, or sessile vegetations on the mitral or aortic valve, often with limited independent motion and little surrounding tissue destruction. [3,4,7,11] However, morphology alone cannot reliably distinguish NBTE from infective endocarditis, papillary fibroelastoma, Lambl excrescences, degenerative nodules, or thrombus. The absence of abscess, perforation, severe new regurgitation, or destructive valve changes favors NBTE but is not diagnostic. [7,23]

Microbiological and Laboratory Evaluation

Infective endocarditis, including culture-negative infective endocarditis, must be actively excluded before valvular vegetations are attributed to NBTE. At least three sets of blood cultures should be obtained before antibiotics when clinically feasible. Depending on epidemiology and exposure history, serology or polymerase chain reaction testing may be required for *Coxiella burnetii*, *Bartonella* species, *Brucella* species, *Tropheryma whipplei*, fungi, or other fastidious organisms. [23] Inflammatory markers, complete blood count, coagulation profile, fibrinogen, D-dimer, renal and hepatic function, and peripheral smear may assist in assessing DIC, bleeding risk, and alternative diagnoses but are not individually diagnostic.

Brain Imaging and Transcranial Doppler

Brain magnetic resonance imaging with diffusion-weighted sequences is preferred when neurological symptoms are present because it can identify small, multifocal, and temporally heterogeneous infarcts. [20–22] Transcranial Doppler may demonstrate high-intensity transient microembolic signals in cerebral arteries and can support the presence of ongoing embolization, particularly in patients with recurrent neurologic events. [5] It is not a stand-alone diagnostic test, but serial monitoring may be useful in selected patients when available.

Cardiac MRI and 18F-FDG PET/CT

Cardiac magnetic resonance imaging can be considered when echocardiography is inconclusive or when a cardiac tumor, mural thrombus, papillary fibroelastoma, or inflammatory mass remains in the differential. Potential advantages include multiplanar tissue characterization, perfusion assessment, and late gadolinium enhancement; however, NBTE-specific diagnostic-accuracy data are sparse, and small mobile valvular vegetations may remain difficult to visualize. [7,25] Cardiac magnetic resonance should therefore be regarded as an adjunct rather than a replacement for TEE.

18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) may be useful when the distinction from infective endocarditis remains unresolved or when occult malignancy staging is required. Marked focal valvular or perivalvular uptake supports active infection or inflammation, whereas NBTE may show absent or low uptake; nevertheless, absent uptake does not establish NBTE, native-

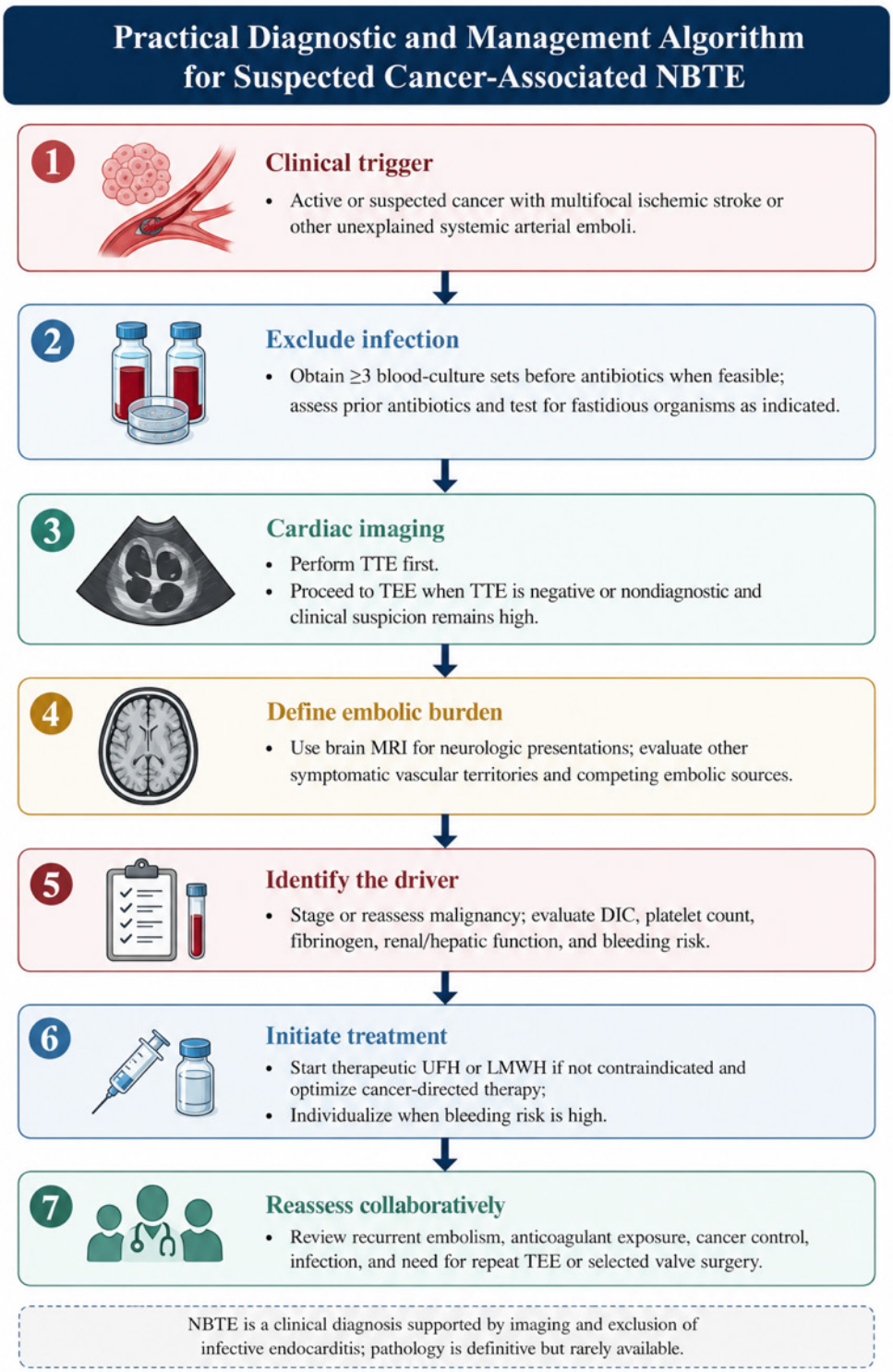

Figure 2: Practical diagnostic and management algorithm for suspected cancer-associated NBTE. The pathway begins with recognition of multifocal or otherwise unexplained arterial embolization in a patient with active or suspected cancer, followed by exclusion of infective endocarditis, TTE and TEE as indicated, definition of embolic burden, evaluation of the prothrombotic driver and bleeding risk, therapeutic anticoagulation when appropriate, cancer-directed therapy, and multidisciplinary reassessment. [4,5,7,9,23,25,26]

valve sensitivity is imperfect, prior antibiotics can reduce inflammatory signal, and concurrent cancer can complicate interpretation. [7,23] FDG PET/CT findings must therefore be integrated with blood cultures, serology, valve morphology, and the clinical context.

Occult Malignancy Evaluation

When NBTE is suspected without a known cancer, evaluation should be clinically directed. Recommended first steps are a detailed history and examination, review of age-appropriate

screening, complete blood count and metabolic profile, urinalysis, chest imaging, and targeted cross-sectional imaging based on symptoms, examination, laboratory abnormalities, and embolic distribution. Computed tomography of the chest, abdomen, and pelvis is reasonable when clinical suspicion is substantial. Tissue diagnosis should be pursued for any suspicious lesion before assuming a cancer type solely from the NBTE presentation. [5,7,25] The recommended work-up and major differential diagnoses are summarized in **Table 2**, while the key clinical and echocardiographic features distinguishing NBTE from infective endocarditis are summarized in **Table 3**.

Management

Management has three objectives: prevent recurrent embolization, treat the underlying malignancy or other prothrombotic condition, and ensure that infective endocarditis has not been missed. No randomized trial has compared anticoagulants specifically in NBTE, and recommendations must distinguish direct NBTE evidence from extrapolation based on cancer-associated VTE.

Anticoagulation

Therapeutic anticoagulation is the cornerstone of treatment when there is no prohibitive bleeding risk. [4,5,25,26] Unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is commonly favored in active cancer-associated NBTE, particularly after arterial embolism, recurrent stroke, DIC, fluctuating renal function, or when rapid interruption may be required. [4,5,25,26] This preference reflects historical experience, observational evidence, case-based reports, expert opinion, and biological plausibility; it has not been established by head-to-head randomized NBTE trials.

Table 2: Diagnostic work-up and differential diagnosis of suspected NBTE.

Condition	Key features	Suggested evaluation
Cancer-associated NBTE	Sterile vegetation, systemic emboli, active or occult malignancy, and hypercoagulability	TTE followed by TEE if suspicion remains high; blood cultures; coagulation profile and D-dimer; brain MRI when neurologic symptoms are present; cancer staging or focused malignancy evaluation. [5,7,9,11]
Infective endocarditis	Fever, persistent bacteremia, valve destruction, abscess, inflammatory or peripheral stigmata	At least three blood-culture sets, inflammatory markers, TTE/TEE, and organism-directed testing; apply contemporary infective-endocarditis criteria. [23]
Culture-negative infective endocarditis	Negative routine cultures with infectious risk factors, prior antibiotics, or systemic inflammatory features	Serology/PCR for selected organisms and review of antibiotic exposure, travel, animal exposure, and immunosuppression. [23]
Libman-Sacks endocarditis	Systemic lupus erythematosus or antiphospholipid syndrome; sterile lesions may involve either valve surface	Antinuclear antibody, anti-double-stranded DNA antibodies, complement levels, and antiphospholipid antibodies, interpreted with the clinical phenotype. [6,7]
Degenerative valve disease or Lambl excrescences	Calcification, chronic thickening, thin filamentous strands, no systemic hypercoagulable syndrome	Detailed TEE characterization and correlation with embolic pattern and clinical context. [7]
Cardiac tumor or thrombus	Intracardiac mass with an atypical attachment site or tissue characteristics	TEE, cardiac CT, or cardiac MRI when echocardiography is inconclusive. [7,25]

Table 3: Echocardiographic and clinical features that may help distinguish NBTE from infective endocarditis.

Feature	NBTE	Infective endocarditis
Clinical context	Advanced malignancy, DIC, antiphospholipid syndrome, or systemic lupus erythematosus	Bacteremia risk, prosthetic valve/device, injection drug use, recent procedure, or focal infection
Blood cultures	Persistently negative after adequate sampling	Often positive; may be negative after antibiotics or with fastidious organisms.
Vegetation morphology	Often small, broad-based, irregular or sessile; may occur along closure lines	Variable size and mobility; may be pedunculated or highly mobile
Valve distribution	Predominantly mitral and aortic; multivalve disease can occur	Any valve; right-sided disease common in injection drug use or devices
Valve destruction	Usually absent or limited	Perforation, abscess, fistula, or severe new regurgitation may occur
Embolic pattern	Frequent multifocal systemic or cerebral emboli, often with advanced cancer	Septic emboli may be accompanied by fever, mycotic aneurysm, or metastatic infection.
FDG PET/CT	Often absent or low valvular inflammatory uptake; evidence is limited	Focal valvular/perivalvular uptake may support active infection, especially prosthetic-valve infection
Definitive diagnosis	Pathology shows sterile platelet-fibrin thrombi	Microorganisms or inflammatory destruction on culture/histopathology

Cancer-associated VTE guidelines support LMWH or selected DOACs for conventional venous thrombosis, but they do not specifically address sterile valvular vegetations or recurrent arterial embolism. [27–29] Those recommendations constitute indirect evidence and should not be presented as NBTE-specific guidance. Published NBTE case literature includes recurrent embolism during DOAC therapy as well as satisfactory outcomes, particularly when the underlying cancer is controlled; however, publication bias, heterogeneous follow-up, and the absence of comparative cohorts prevent reliable estimates. [5,25,30] In a patient who develops NBTE or recurrent arterial emboli while receiving a DOAC, adherence, absorption, drug interactions, renal and hepatic function, and dose appropriateness should be reviewed, with strong consideration given to switching to UFH or LMWH.

Cancer-associated VTE findings should not be generalized uniformly across individual DOACs. In the CARAVAGGIO trial, apixaban was noninferior to dalteparin for recurrent cancer-associated VTE without a statistically significant increase in major bleeding. [31] The CANVAS trial likewise supported direct oral anticoagulation as a reasonable alternative to LMWH for cancer-associated VTE. [32] These trials enrolled patients with venous thrombosis rather than NBTE and do not establish equivalence for valvular thrombi or arterial embolization. Apparent differences in gastrointestinal or genitourinary bleeding among apixaban, rivaroxaban, and edoxaban are based on indirect cross-trial comparisons and should not be interpreted as proof of NBTE-specific superiority.

Full therapeutic dosing is generally used for active NBTE. Dose-reduced anticoagulant regimens used for extended secondary prevention of cancer-associated VTE have not been studied in active NBTE and should not be assumed to prevent valvular thrombus propagation or arterial embolization. [4,5,25] Duration is individualized and commonly continues while cancer is active, vegetations persist, or embolic risk remains high, with periodic reassessment of bleeding risk, goals of care, and cancer response.

Antiplatelet therapy alone is not an established treatment for NBTE and should not substitute for anticoagulation. Combination antiplatelet and anticoagulant therapy may substantially increase bleeding and should be reserved for a separate compelling indication, such as recent coronary stenting or acute coronary syndrome, after multidisciplinary assessment.

Management of Thrombocytopenia, DIC, and Bleeding Risk

Advanced cancer, chemotherapy, liver dysfunction, marrow infiltration, and DIC can produce thrombocytopenia rather than thrombocytosis. Anticoagulant decisions should therefore incorporate platelet count and trend, fibrinogen, active bleeding, recent procedures, intracranial lesions, gastrointestinal or genitourinary tumors, renal function, and anticipated cancer treatment. UFH may be preferable when rapid reversal or frequent procedural interruption is expected. Dose modification, platelet support, or temporary interruption may be necessary, but there are no NBTE-specific platelet thresholds validated in prospective studies.

Cancer-Directed Therapy

Control of the underlying malignancy is central to reducing the prothrombotic stimulus. Persistent or progressive cancer can sustain tissue factor activity, inflammatory signaling, DIC, and recurrent embolization despite anticoagulation. [4,5,8] When feasible, systemic therapy, surgery, radiotherapy, or targeted treatment should be optimized. The balance between anticancer benefit, thrombosis control, bleeding risk, treatment toxicity, and prognosis requires multidisciplinary review involving oncology, hematology, cardiology, neurology, infectious diseases, and palliative care.

Role of Surgery

Valve surgery is uncommon in cancer-associated NBTE because patients often have advanced malignancy, coagulopathy, recent embolic stroke, poor functional status, and a very high perioperative risk. Potential indications include severe valve dysfunction causing heart failure, large mobile vegetations with recurrent emboli despite adequate anticoagulation and cancer treatment, or persistent diagnostic uncertainty when infection or tumor cannot be excluded. [23–25] These indications are adapted largely from broader valve and endocarditis practice rather than supported by NBTE-specific comparative outcomes. Published surgical experience consists of highly selected reports and small series; therefore, a reliable quantitative operative-mortality or survival estimate cannot be provided for routine counseling. Decisions should be individualized by a multidisciplinary heart team and aligned with oncologic prognosis and patient goals. The main management challenges, practical approaches, and evidence limitations are summarized in **Table 4**.

Prognosis

The prognosis of cancer-associated NBTE is generally poor because the condition often reflects advanced malignancy, severe systemic hypercoagulability, and a high embolic burden rather than isolated valvular disease. [8–11] Contemporary cohorts consistently report substantial mortality, but their estimates are not directly comparable because populations, index dates, cancer stages, outcome definitions, and follow-up intervals differ. Accordingly, the available literature does not support a single reliable 6-month or 1-year mortality estimate for cancer-associated NBTE.

Quantitative contemporary data nevertheless illustrate the burden of disease. Stroke occurred in 59.5% of the Cleveland Clinic cohort, and TEE detected vegetations in 33 of 34 examined patients (97.1%), compared with 45.2% detection by TTE. [9] In the 111-patient Mayo Clinic cancer-associated NBTE echocardiographic series, 91.9% had an embolic complication. [11] Recurrent embolism despite anticoagulation is clinically well recognized, but contemporary studies use nonuniform definitions and do not provide a sufficiently consistent anticoagulation-adjusted recurrence rate for pooling. Patients with treatable malignancy, lower tumor burden, early recognition, preserved performance status, cancer control, and effective anticoagulation may stabilize or show vegetation resolution; disseminated cancer, DIC, persistent thrombocytopenia, recurrent multifocal stroke, and poor functional status are adverse features.

Table 4: Management challenges in cancer-associated NBTE.

Challenge	Practical approach	Evidence limitation	Key references
Initial anticoagulant	Use therapeutic UFH or LMWH when not contraindicated, particularly after arterial embolism or in unstable patients.	No randomized NBTE-specific anticoagulation trial; recommendation is based mainly on observational evidence and expert opinion.	[4,5,25,26]
DOAC use	Consider only in selected stable patients when heparin is unsuitable; reassess promptly if embolism recurs.	Case-based NBTE evidence plus indirect extrapolation from cancer-VTE trials; both failures and successes are reported.	[25,27–33]
DOAC selection	Apixaban has strong cancer-VTE trial data, but no DOAC has proven superiority for NBTE.	Cancer-VTE data only; no DOAC has demonstrated NBTE-specific superiority.	[31,32]
Dose and duration	Use full therapeutic dosing during active NBTE; continue while cancer, vegetations, or embolic risk remain active.	Reduced-dose extended-VTE strategies and the optimal NBTE duration are unvalidated.	[4,5,27–29]
Recurrent embolism	Confirm adherence and dosing; repeat TEE; reassess cancer progression, DIC, and infection; consider switching to UFH/LMWH.	Mostly case series and expert opinion; recurrence definitions vary.	[4,5,8,25,30]
Bleeding or thrombocytopenia	Individualize according to platelet trend, active bleeding, renal function, central nervous system disease, gastrointestinal or genitourinary cancer, procedures, and goals of care.	No prospectively validated NBTE-specific platelet thresholds.	[27–29]
Antiplatelet therapy	Do not use alone for NBTE; combine with anticoagulation only for a separate compelling indication.	No established NBTE benefit; combination therapy increases bleeding risk.	[25,26]
Valve surgery	Reserve for selected patients with heart failure, recurrent emboli despite therapy, or diagnostic uncertainty.	Highly selected reports; advanced cancer, coagulopathy, and poor functional status markedly increase operative risk.	[23–25]

Clinicians should communicate that anticoagulation reduces but may not eliminate embolic risk, and that prognosis depends heavily on the reversibility of the underlying cancer-related hypercoagulable state. Follow-up TEE can be considered when results would alter anticoagulant strategy, surgical assessment, or cancer treatment, but the optimal surveillance interval is unknown.

Clinical Challenges and Evidence Gaps

The central evidence gap is the absence of prospective NBTE registries and randomized anticoagulation trials. Future studies should distinguish cancer-associated NBTE from autoimmune sterile endocarditis, use standardized echocardiographic definitions, report vegetation size and valve distribution, document neurologic imaging patterns, and provide uniform outcomes including recurrent arterial embolism, major bleeding, vegetation resolution, 6- and 12-month survival, and cancer control.

The relationship between ICIs and NBTE deserves focused study. Broader ICI cohorts demonstrate venous and arterial thrombotic events [15], while plausible mechanisms include cytokine-driven endothelial activation, tissue factor expression, platelet activation, and immune-mediated myocardial or valvular inflammation. However, isolated temporal associations cannot distinguish drug causality from the thrombotic effect of advanced cancer itself.

Potential biomarkers include D-dimer, fibrinogen, tissue-factor activity, tissue-factor-bearing extracellular vesicles, platelet-activation markers, inflammatory cytokines, and circulating tumor DNA. [16] Tissue-factor activity and extracellular-vesicle assays may better reflect tumor-driven thrombin generation, whereas circulating tumor DNA may eventually support occult malignancy detection or cancer-response monitoring. None is currently validated as a stand-alone diagnostic or prognostic test for NBTE, and future biomarker studies should be linked to echocardiographic, neurologic-imaging, recurrent-embolism, and cancer-control outcomes.

Multimodality imaging is another priority. Prospective comparisons of TTE, TEE, cardiac MRI, FDG PET/CT, and transcranial Doppler could define when adjunctive tests add value and whether microembolic-signal monitoring predicts recurrent stroke. Finally, future guidance should clearly separate direct NBTE evidence from extrapolation based on cancer-associated VTE, infective endocarditis, or autoimmune valvular disease.

CONCLUSIONS

Cancer-associated NBTE is an underrecognized manifestation of malignancy-related hypercoagulability and an important cause of multifocal ischemic stroke and systemic arterial embolization. TTE is an appropriate initial test, but TEE should be performed when suspicion remains high because it is substantially more sensitive for small vegetations. Cardiac magnetic resonance, FDG PET/CT, and transcranial Doppler may provide adjunctive information in selected cases but do not replace careful microbiological evaluation

and TEE. Therapeutic UFH or LMWH remains the most commonly favored anticoagulant approach, based primarily on observational evidence and expert opinion rather than randomized NBTE-specific trials. DOAC evidence is limited, mixed, and largely extrapolated from cancer-VTE studies. Effective cancer treatment, individualized bleeding assessment, and multidisciplinary care are essential. Prospective registries and comparative studies are needed to define diagnostic criteria, anticoagulant selection, recurrence risk, and survival.

ACKNOWLEDGMENTS

The authors thank the Department of Internal Medicine, Hamad Medical Corporation, Doha, Qatar, for academic support.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

SOURCE OF FUNDING

None.

CONFLICT OF INTEREST

None.

REFERENCES

1. MacDonald RA, Robbins SL. The significance of nonbacterial thrombotic endocarditis: An autopsy and clinical study of 78 cases. Ann Intern Med. 1957;46(2):255–273. https://doi.org/10.7326/0003-4819-46-2-255
2. Deppisch LM, Fayemi AO. Non-bacterial thrombotic endocarditis: Clinicopathologic correlations. Am Heart J. 1976;92(6):723–729. https://doi.org/10.1016/S0002-8703(76)80008-7
3. Lopez JA, Ross RS, Fishbein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: A review. Am Heart J. 1987;113(3):773–784. https://doi.org/10.1016/0002-8703(87)90719-8
4. El-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: Pathogenesis, diagnosis, and treatment. Oncologist. 2007;12(5):518–523. https://doi.org/10.1634/theoncologist.12-5-518
5. Itzhaki Ben Zadok O, Spectre G, Leader A. Cancer-associated non-bacterial thrombotic endocarditis. Thromb Res. 2022;213 Suppl 1:S127–S132. https://doi.org/10.1016/j.thromres.2021.11.024
6. Hurrell H, Roberts-Thomson R, Prendergast BD. Non-infective endocarditis. Heart. 2020;106(13):1023–1029. https://doi.org/10.1136/heartjnl-2019-315204
7. Tonutti A, Scarfò I, La Canna G, Selmi C, De Santis M. Diagnostic work-up in patients with nonbacterial thrombotic endocarditis. J Clin Med. 2023;12(18):5819. https://doi.org/10.3390/jcm12185819
8. Patrzalek P, Wysokinski WE, Kurmann RD, Houghton D, Hodge D, Kuczmik W, et al. Cancer-associated non-bacterial thrombotic endocarditis: Clinical series from a single institution. Am J Hematol. 2024;99(4):596–605. https://doi.org/10.1002/ajh.27239
9. Zmaili MA, Alzubi JM, Kocyigit D, Bansal A, Samra GS, Grimm R, et al. A contemporary 20-year Cleveland Clinic experience of nonbacterial thrombotic endocarditis: Etiology, echocardiographic imaging, management, and outcomes. Am J Med. 2021;134(3):361–369. https://doi.org/10.1016/j.amjmed.2020.06.047
10. Quintero-Martinez JA, Hindy JR, El Zein S, Michelena HI, Nkomo VT, DeSimone DC, et al. Contemporary demographics, diagnostics and outcomes in non-bacterial thrombotic endocarditis. Heart. 2022;108(20):1637–1643. https://doi.org/10.1136/heartjnl-2022-320970
11. Kurmann RD, Klarich KW, Wysokinska E, Houghton D, Kaminska A, Patrzalek P, et al. Echocardiographic findings in cancer-associated non-bacterial thrombotic endocarditis: Clinical series of 111 patients from a single institution. Eur Heart J Cardiovasc Imaging. 2024;25(9):1255–1263. https://doi.org/10.1093/ehjci/jeae112
12. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med. 2018;169(7):467-473. https://doi.org/10.7326/M18-0850
13. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5. https://doi.org/10.1186/s41073-019-0064-8
14. Rahouma M, Khairallah S, Dabsha A, Elkharbotly IAMH, Baudo M, Ismail A, et al. Lung cancer as a leading cause among paraneoplastic non-bacterial thrombotic endocarditis: A meta-analysis of individual patient data. Cancers (Basel). 2023;15(6):1848. https://doi.org/10.3390/cancers15061848
15. Moik F, Chan WE, Wiedemann S, Hoeller C, Tuchmann F, Aretin MB, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. Blood. 2021;137(12):1669–1678. https://doi.org/10.1182/blood.2020007878
16. Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood. 2017;130(13):1499–1506. https://doi.org/10.1182/blood-2017-03-743211
17. Wahrenbrock M, Borsig L, Le D, Varki N, Varki A. Selectin-mucin interactions as a probable molecular explanation for the association of Trousseau syndrome with mucinous adenocarcinomas. J Clin Invest. 2003;112(6):853–862. https://doi.org/10.1172/JCI18882
18. Varki A. Trousseau's syndrome: Multiple definitions and multiple mechanisms. Blood. 2007;110(6):1723–1729. https://doi.org/10.1182/blood-2006-10-053736
19. Sack GH Jr, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: Clinical, pathophysiologic, and therapeutic features. Medicine (Baltimore). 1977;56(1):1–37. https://doi.org/10.1097/00005792-197756010-00001

20. Biller J, Challa VR, Toole JF, Howard VJ. Nonbacterial thrombotic endocarditis. A neurologic perspective of clinicopathologic correlations of 99 patients. Arch Neurol. 1982;39(2):95–98. https://doi.org/10.1001/archneur.1982.00510140029007
21. Rogers LR, Cho ES, Kempin S, Posner JB. Cerebral infarction from non-bacterial thrombotic endocarditis. Clinical and pathological study including the effects of anticoagulation. Am J Med. 1987;83(4):746-756. https://doi.org/10.1016/0002-9343(87)90908-9
22. Oakley CI, Wysokinska EM, Kaminska A, Mohammed MA, Patrzalek P, Houghton D, et al. Topography of ischemic strokes in cancer-associated non-bacterial thrombotic endocarditis: A single-institution descriptive case series. J Stroke Cerebrovasc Dis. 2025;34(2):108171. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.108171
23. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J. 2023;44(39):3948–4042. https://doi.org/10.1093/eurheartj/ehad193
24. Eiken PW, Edwards WD, Tazelaar HD, McBane RD, Zehr KJ. Surgical pathology of nonbacterial thrombotic endocarditis in 30 patients, 1985-2000. Mayo Clin Proc. 2001;76(12):1204–1212. https://doi.org/10.4065/76.12.1204
25. Al Chalaby S, Makhija R, Sharma S, Majure DT. Nonbacterial thrombotic endocarditis: Presentation, pathophysiology, diagnosis and management. Rev Cardiovasc Med. 2022;23(4):137. https://doi.org/10.31083/j.rcm2304137
26. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e576S–e600S. https://doi.org/10.1378/chest.11-2305
27. Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Adv. 2021;5(4):927–974. https://doi.org/10.1182/bloodadvances.2020003442
28. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. J Clin Oncol. 2023;41(16):3063–3071. https://doi.org/10.1200/JCO.23.00294
29. Falanga A, Ay C, Di Nisio M, Gerotziafas G, Jara-Palomares L, Langer F, et al. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(5):452–467. https://doi.org/10.1016/j.annonc.2022.12.014
30. Akiki E, Ahmad A, El-Am EA, Casanegra AI, Klarich KW, Kurmann RD. Case Report: New is not always better: Treatment of non-bacterial thrombotic endocarditis. Front Cardiovasc Med. 2023;10:1208190. https://doi.org/10.3389/fcvm.2023.1208190
31. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al; Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020;382(17):1599–1607. https://doi.org/10.1056/NEJMoa1915103
32. Schrag D, Uno H, Rosovsky R, Rutherford C, Sanfilippo KM, Villano JL, et al. Direct oral anticoagulants versus low-molecular-weight heparin and recurrent venous thromboembolism in patients with cancer: A randomized clinical trial. JAMA. 2023;329(22):1924–1933. https://doi.org/10.1001/jama.2023.7843
33. Lee AYY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146–153. https://doi.org/10.1056/NEJMoa025313