Cancer-Associated Thrombosis: Risk Factors, Molecular Mechanisms, Future Management

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Abstract
Venous thromboembolism (VTE) is a major health problem in patients with cancer. Cancer augments thrombosis and causes cancer-associated thrombosis (CAT) and vice versa thrombosis amplifies cancer progression, termed thrombosis-associated cancer (TAC). Risk factors that lead to CAT and TAC include cancer type, chemotherapy, radiotherapy, hormonal therapy, anti-angiogenesis therapy, surgery, or supportive therapy with hematopoietic growth factors. There are some other factors that have an effect on CAT and TAC such as tissue factor, neutrophil extracellular traps (NETs) released in response to cancer, cancer procoagulant, and cytokines. Oncogenes, estrogen hormone, and thyroid hormone with its integrin αvβ3 receptor promote angiogenesis. Lastly, patient-related factors can play a role in development of thrombosis in cancer. Low-molecular-weight heparin and direct oral anticoagulants (DOACs) are used in VTE prophylaxis and treatment rather than vitamin K antagonist. Now, there are new directions for potential management of VTE in patients with cancer such as euthyroid, blockade of thyroid hormone receptor on integrin αvβ3, sulfated non-anticoagulant heparin, inhibition of NETs and stratifying low and high-risk patients with significant bleeding problems with DOACs.

Keywords
angiogenesis, anticoagulants, cancer, coagulation, heparins, inflammation, integrin αvβ3, non-anticoagulant heparin, oral anticoagulant, thrombosis, thyroid hormone

Date received: 21 April 2020; revised: 10 July 2020; accepted: 10 August 2020.

Introduction
In 1865, a French physician named Armand Trousseau described the first association between thrombosis and cancer, which was later called the Trousseau syndrome. Several clinical trials have revealed the link between venous thrombosis and cancer and demonstrated an increase in the prevalence of venous thrombosis in patients with cancer. In 1977, Sack et al. discovered that the Trousseau syndrome was chronically disseminated vascular coagulation associated with non-bacterial thrombotic endocarditis and arterial thrombosis in malignant patients.¹ A vicious cycle between cancer and thrombosis is termed cancer-associated thrombosis (CAT) where cancer amplifies the risk of thrombosis. Vice versa, where thrombosis amplifies the cancer progression, this is termed thrombosis-associated cancer (TAC) (Figure 1). Venous thromboembolism (VTE) includes the conditions of deep vein thrombosis (DVT) and pulmonary embolism.² The most important VTE-related risk is cancer; 20%-30% of VTE occurrences are assumed to be associated with cancer.³ The risk of developing arterial and venous thromboembolism is significantly increased in patients with cancer.⁴ Mortality is increased in cancer patients with VTE compared to cancer patients without VTE.⁵ It has been reported that the annual incidence of VTE in patients with cancer is 0.5% compared to 0.1% in the non-cancer population.⁶ Survival of patients with VTE was poorer in CAT.⁷ This review focuses on the interplay between cancer and thrombosis and the impact on a cancer patient’s management, with special emphasis on treatment of CAT.

Risk Factors for CAT
Cancer Type and Stage
Cancer is a heterogeneous illness because it has different types and stages, which may have effects on VTE.⁸ CAT is common

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in many types of cancer such as pancreatic, brain, lung, and ovarian cancers. Patients with prostate cancer usually have a relatively low risk, and patients with breast cancer are reported to develop VTE 3 to 4 times more often than patients of equivalent age without breast cancer. The aggressiveness of cancer, early metastatic development, and short survival were particularly associated with a high incidence of VTE. The risk of VTE occurrence is higher in advanced metastatic cancer than in localized cancer. Previous studies confirmed that tumor grade and stage were significantly associated with risk of venous thrombosis. Moreover, the risk of VTE was high in the first 3 months after the cancer diagnosis and then decreased gradually during the 10 years after the cancer diagnosis. This may be because multiple cancer therapies (e.g., chemotherapy, radiotherapy) boost VTE risk. Also, a percentage of patients with cancer enter a remission phase, which reduces the danger of VTE. Another reason is that a large proportion of cancer patients will succumb to the disease over time. This contesting event (death) prevents the observation of thrombotic events.

Cancer Treatment

Tumor pressure on blood vessels results in stasis and VTE. Some medications that are used in treatment of cancer are related to high risk of thrombosis. Examples of these medications are hormonal therapy such as tamoxifen, chemotherapy (e.g., paclitaxel, doxorubicin, thalidomide), molecular targeted therapy such as osimertinib, anti-angiogenesis therapy (e.g., bevacizumab, ramucirumab), immunotherapies and radiation therapies.

Chemotherapy. Using combination therapy of chemotherapeutic drugs increases the risk of arterial thrombosis occurrence in patients with breast cancer, but the mechanism is not clear. Also, chemotherapy increases the risk of VTE and produces a
prothrombotic condition through a number of distinct mechanisms\textsuperscript{18} that can harm the endothelium directly,\textsuperscript{19} decrease endogenous anticoagulant substances, and/or boost the procoagulant protein.\textsuperscript{20} Chemotherapy also can cause apoptosis and cytokine release, which can in turn lead to enhanced endothelial and monocyte tissue factor (TF) expression that is considered as the physiologic initiator of coagulation.\textsuperscript{21} Chemotherapy can ultimately lead to platelet activation.\textsuperscript{22}

Both cytotoxic and targeted chemotherapy are associated with VTE. For example, cisplatin induces endothelial cell apoptosis and results in the release of procoagulant endothelial microparticles.\textsuperscript{23} L-asparaginase causes depletion of key proteins in the regulation of the coagulation pathway\textsuperscript{24}—therefore VTE is a complication in patients with acute lymphoblastic leukemia receiving asparaginase inhibitor chemotherapy and these symptomatic VTEs can be reduced by low-molecular-weight heparin (LMWHs).\textsuperscript{25} 5-Fluorouracil causes depletion of protein C, increases thrombin activity,\textsuperscript{26} and damages endothelial cells to promote thrombus formation.\textsuperscript{27} Another example is tamoxifen, an anti-estrogen drug. Its estrogenic activity might elevate the risk of VTE through depletion of protein C and protein S.\textsuperscript{27,28}

Not only is chemotherapy associated with increased VTE risk but also cancer type is associated with further increase in VTE risk.\textsuperscript{29} Patients with advanced pancreatic ductal adenocarcinoma have high risk of VTE, and chemotherapy can further increase that risk. Moreover, thromboprophylaxis with LMWH for 3 months decreased that risk, however, further anticoagulation expansion may be helpful to limit a future thromboembolic risk.\textsuperscript{30} Because there are growing risks of CAT due to additional new antineoplastic drugs, immunotherapies, or chemotherapy combinations, a prospective registry named TESCO and promoted by the Spanish Society of Medical Oncology data highlight the evolution of CAT, with new agents and thrombotic risk factors.\textsuperscript{31}

Radiotherapy. Radiotherapy can be used when VTE risk is high in early phases of cancer,\textsuperscript{11} or as part of localized treatment, with or without chemotherapy for localized tumors.\textsuperscript{32} As a result, there is increasing evidence that radiotherapy could affect the result of VTE anticoagulant therapy in cancer patients.\textsuperscript{33} Ionizing radiation influences protein C pathway and its thrombomodulin interaction.\textsuperscript{34} After radiation, procoagulant factors with activated factor VIII, pro-inflammatory nuclear factor kappa B, increased D-dimers and pro-thrombin fragments prompt pro-coagulant response.\textsuperscript{35} Radiation also induces primary hemostasis through TF and von Willebrand activation\textsuperscript{36} leading to endothelial dysfunction and thrombosis. Also, an in vitro study has shown that tumor irradiation activates cancer cell integrin αvβ3,\textsuperscript{37} which has a pivotal role in CAT, and that role will be discussed later in this review.

Hormonal therapy. Use of hormone therapy is a clear risk factor for the development of cancer\textsuperscript{38} and it elevates VTE risk,\textsuperscript{39} which can enhance the link between CAT and TAC.

Surgery. Major surgery is a well-known risk factor for VTE, and patients who develop VTE in the post-operative period have a higher mortality rate.\textsuperscript{40} Additionally, the length of surgery has been associated with an increased risk of VTE.\textsuperscript{41} A prothrombotic state may occur due to several processes including enhanced levels of fibrinogen, thrombin generation, activation of TF, decreased fibrinolysis and hemostasis.\textsuperscript{42} Furthermore, patient immobility after an operation can lead to venous stasis and cancer procoagulants’ overexpression that causes immediate damage to the vascular endothelium.\textsuperscript{19} Other factors that may increase the risks from surgery on VTE formation are pelvic dissection, the patient’s position during surgery, cancer, advanced age, heart or respiratory failure.\textsuperscript{43}

Supportive therapy with hematopoietic growth factors. Previous studies showed that patients treated with erythropoiesis-stimulant agents in addition to red blood cell transfusions have a higher risk of VTE than do patients without additional erythropoiesis-stimulant agents.\textsuperscript{44,45} Erythropoietin is found to be an activator to platelets and enhances factor VIII and thrombin generation and decreases protein C and protein S.\textsuperscript{46} Erythropoietin also promotes signaling pathways in endothelial cells and enhances their thrombogenicity.\textsuperscript{47}

Hormonal Risk Factors

Thyroid hormones. Thyroid hormones are key regulators of essential cellular processes including proliferation, differentiation, apoptosis, and metabolism.\textsuperscript{48} A prospective study reported that subclinical hyperthyroidism was associated with enhanced risk of cancer, particularly in lung, prostate, ovarian, pancreatic, and renal carcinoma.\textsuperscript{49} Thyroid hormone has an effect on cancer cell proliferation and angiogenesis\textsuperscript{50,51} The intracellular metabolically active hormone in normal cells is 3,5,3’-triiodo-L-thyronine (T3) from prohormone L-thyroxine (T4). The thyroid hormone action is done by genomic and non-genomic actions. Genomic action is initiated when T3 binds to thyroid receptors that interact with specific responding elements. Non-genomic actions modulate gene transcription by activating pathways and other transcription factors.\textsuperscript{52,53} The availability of T4 is the pivotal step for activation of the integrin and consequent transmembrane signaling into the cell. T3 and T4 bind to the plasma membrane protein integrin αvβ3, which mediates the signal across the membrane. At physiological concentrations, T4 is the primary ligand at αvβ3.\textsuperscript{54}

Thyroid hormone also has a pro-angiogenic effect initiated by several thyroid hormone analogs affecting coagulation by acting on platelet integrin αvβ3.\textsuperscript{55} Thyroid hormone stimulates the aggregation of platelet and the release of platelets’ adenosine triphosphate (ATP).\textsuperscript{56} All of the above may explain the association between thyroid hormone, platelets, and CAT.\textsuperscript{57} Concepts highlighted for future directions with regard to the role of thyroid hormone and integrin αvβ3 in CAT warrant clinical investigations.
Estrogen hormone. Estrogen has been associated with an increased risk of thromboembolic events in patients using combined hormone replacement or estrogens. Venous thromboembolism risk increases in patients with cancers such as breast cancer and endometrial cancer, which are positively correlated with serum estrogen levels. Estrogens have pleiotropic effects due to a large tissue distribution of their receptors in many tissues such as platelets with different effects. A high level of estrogen enhances the secretion of angiogenic cytokines such as VEGF that influence the expression of integrin zvβ3, which in turn contributes to angiogenesis. By influencing angiogenesis, these angiogenic factors affect the growth of cancer such as breast and ovarian.

Molecular Risk Factors

Oncogenes. CAT may be activated directly or indirectly through an oncogenic process. The indirect effect of oncogenes may happen through vascular invasion, metastasis, bleeding, vascular permeability, angiogenesis, recruitment of inflammatory cells and extracellular vesicles (EVs) that may reprogram coagulant phenotypes of endothelial cells or leukocytes. The direct effect of oncogenes on CAT includes the negative effect of an epidermal growth factor receptor (EGFR) antagonist on the expression of TF in cancer cells.

Examples for these oncogenes are K-RAS oncogene and p53 tumor suppressor gene. A previous study reported a link between integrin zvβ3 and p53 activity in that blockade of zvβ3 suppresses the expression and/or activity of p53. K-RAS alters the levels of crucial angiogenic mediators such as VEGF or thrombospondin and affects multiple facets of the cancer, recruitment of inflammatory cells, immune responses, and CAT. Other oncogenes may regulate TF, such as MET proto-oncogene EGFR, and erb-b2 receptor tyrosine kinase 2 (ERBB2).

Mechanisms Involved in CAT

Platelets. Cancer cells can activate platelets by direct and indirect mechanisms that lead to CAT. Tumor-cell induced platelet aggregation (TCIPA) was also linked to greater metastatic invasion. A significant TCIPA mechanism is secretion of thrombin by cancer cell procoagulants that turn fibrinogen into fibrin. Another mechanism is the activation of coagulation factors V, VIII, XI, XIII, and protease-activated receptors (PAR receptors) that are highly expressed on platelets. Tumor cells also express adenosine diphosphate (ADP) that activates platelets to release more ADP and thus activates more platelets. Platelets also express TF on their membrane, contributing to CAT. Platelets have many growth factors that are also present in the tumor microenvironment and cause development of the tumor and support angiogenesis.

Coagulation. Together with cells and platelets, TF is important for normal hemostasis. Coagulation occurs in 3 overlapping phases: initiation, amplification, and propagation. In the initiation phase, TF binds to factor VIIa to activate factor IX and factor X. Activation of factor IX works as the link between the extrinsic and intrinsic pathways. Factor Xa then binds to factor II to form thrombin. The amplification phase starts because the amount of thrombin generated is not enough to form a widespread clot, therefore positive feedback loops are present to bind thrombin with platelets. In the propagation phase, enzyme complexes (tenase complex and prothrombinase complex) on the platelet surface support high amounts of thrombin generation and platelet activation. This occurs to ensure continuous generation of thrombin and subsequently fibrin generation and polymerization to form a stable clot.

Tissue factor. The main cause of coagulation in patients with cancer is TF expression on the surface of cancer cells as shown in Figure 2. The coagulation extrinsic pathway is initiated by TF because it binds to factor VII and promotes proteolysis and activation to factor VIIa. The binary TF/factor VIIa complex activates factor IX and factor X, leading to the development of thrombin, culminating in the production of fibrin. The existence of TF in the blood as a component of EVs from vascular cells, and subsequently from tumor cells, increases the prothrombotic status of patients with cancer. Other cancer-related phenomena, such as the epithelial-mesenchymal transition, may also trigger the release of EVs containing TF.

Microvesicles. A heterogeneous population of small membrane-enclosed structures, EVs are released into the extracellular space. They have been divided into 3 main categories according to their origin: exosomes, microvesicles (MVs) and apoptotic bodies. The diversity of MVs’ origin is responsible for a variety of structures and composition in lipids, proteins and nucleic acids and thus MVs are involved in different pathophysiological processes such as coagulation, inflammation, angiogenesis or endothelial dysfunction. MVs have to be integrated in their complex vascular environment with all partners (innate immune cells such as polymorphonuclear cells, monocytes, endothelial cells, platelets, and tumor cells) contributing to thrombus formation.

Endothelial. Although TF is widely expressed on subendothelial cells such as fibroblasts, pericytes, and vascular smooth muscle cells, it is not expressed in normal endothelium; malignant tissue involving endothelial and tumor cells express TF constitutively. Platelets and endothelia cells have p-selectin on their surfaces. P-selectin could increase VTE through leukocyte recruitment.

Neutrophil extracellular traps. Cancer cells may release NETs and they have been shown to endorse venous and arterial thrombosis. NETs can activate endothelial cells and eventually increase the release of von Willebrand factor (a significant glycoprotein for platelet adherence and thrombosis aggregation) and serve as a platform to adhere and aggregate platelets, which is vital for thrombus formation. Cancers create a systemic environment that prevents NETs from releasing...
neutrophils that modulate different facets of the tumor biology, including metastasis.  

**Cancer procoagulant.** Cancer procoagulant (CP) is unlike TF in that it directly activates factor X independent of coagulation factor VII. It has been detected in different malignant cells such as leukemia and breast cancer and is present in solid and hematologic tumors but not in normal tissues.

**Monocytes.** Monocytes and macrophages express TF in an inactive form and then specific inflammatory agonist pathways convert it to totally procoagulant TF. Activation of TF on monocytes or macrophages requires an exchange of thiol-disulfide and involves protein disulfide isomerase (PDI). While the PDI can be released during vessel wall injury, in vitro research showed that PDI is present on the surface of intact cells in complex with TF and PDI-regulated TF activity on EVs.

**Cytokines.** Tumor cells release cytokines into the bloodstream. Leukocytes and vascular cells are both cytokine sources and targets for them. Hemostatic balance depends on the complex interactions between endothelial cells, blood cells, the coagulation-fibrinolytic system, and cytokines. Pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) induce TF in monocytes. Such cytokines not only trigger procoagulant activity but also impede the anticoagulation pathway of thrombomodulin/protein C and affect fibrinolysis by upregulating urokinase type plasminogen activator and type I inhibitor of such activation. Indeed, cytokine production is significantly increased in cancer patients by activating host cells, like monocytes and endothelial cells as well as by cytokine release itself through tumor cells. Cytokines like IFN-α, IFN-γ and TNF can boost the activity of tumor cell procoagulants and consequently activate clotting in patients with cancer.

**Current Management of CAT**

**Low-molecular-weight heparin.** LMWH inhibits coagulation by activating antithrombin III, which binds to and inhibits factor Xa and IIa. In the absence of contra-indications, LMWH is preferred over vitamin K antagonists (VKA) for the treatment of VTE in patients with cancer based on 4 previous studies that showed the high efficacy and superiority of LMWHs compared to VKAs. First, the Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) study compared dalteparin (LMWH) to warfarin and showed a 55% reduction in relative

![Figure 2. Relationship between integrin αvβ3, thyroid hormones, TF/FVIIa, angiogenesis, inflammation, and thrombus formation. When TF is released, it activates factor VII (VIIa) forming a complex that activates thrombus formation. TF is expressed on vascular endothelial cells, circulating monocyte and platelet where its activation upregulates VEGF that promotes angiogenesis. Non-genomic actions of thyroid hormones are initiated on integrin αvβ3. Thyroid hormones activate the NF-κB pathway, thus promoting the production of VEGF, cell proliferation and angiogenesis. Thrombus formation and angiogenesis stimulation affect inflammation pathway and vice versa. Either sulfated non-anticoagulant LMWH (SNACH) or integrin αvβ3 receptor blockade suppresses inflammation, angiogenesis, and indirectly the thrombosis processes. Abbreviations: ABP-280, actin-binding protein 280; NF-KB, nuclear factor kappa B; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TRES, thyroid hormone response elements; TRs, thyroid hormone receptors. (Modified with permission from Mousa SA. Heparin and low-molecular weight heparins in thrombosis and beyond. Methods Mol Biol 2010;663:109-132).](image-url)
risk of recurrent VTE without increasing major bleeding.\textsuperscript{114} Another study is the Comparison of Acute Treatments in Cancer Haemostasis (CATCH) trial that compared LMWH (tinzaparin) to warfarin and showed a trend toward reduction in VTE recurrence, but the difference was not statistically significant. Tinzaparin showed a safer profile in clinically relevant non-major bleeding than warfarin.\textsuperscript{116} The other 2 studies confirmed that warfarin is associated with a high bleeding rate in patients with cancer.\textsuperscript{113,115} Therefore, in CAT, LMWH is preferred in VTE prophylaxis and treatment.

**Direct oral anticoagulants (DOACs).** Four DOACs, including dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (direct factor Xa inhibitor), have been approved by the FDA for VTE therapy. They have benefits over VKAs including safety such as a lower incidence of major bleeding, more convenient to use, fewer drug and food interactions, a wide therapeutic index, and there is no periodic laboratory tracking required. Furthermore, unlike LMWHs, DOACs are taken orally and don’t require long-term subcutaneous injections.\textsuperscript{117}

Previous randomized clinical trials compared DOACs and LMWHs in the treatment of CAT, such as the Hokusai VTE Cancer,\textsuperscript{118} SELECT-D,\textsuperscript{119} and ADAM VTE\textsuperscript{120} trials. They reported that DOACs are not inferior to LMWHs for preventing VTE recurrence in patients with cancer. The Hokusai VTE trial and SELECT-D trial revealed that DOACs were non-inferior to subcutaneous LMWH, and the rate of recurrent VTE was lower, but the rate of major bleeding was higher with edoxaban (DOAC) than with dalteparin (LMWH).\textsuperscript{118,119} The SELECT-D study reported significant bleeding events as a side effect to DOACs.\textsuperscript{119} In patients treated with rivaroxaban (DOACs), more clinically relevant non-major bleeding did happen. Most bleeds were gastrointestinal, and the distinction in bleeding risk was most apparent for gastrointestinal cancer patients.\textsuperscript{118} Recently, a meta-analysis study reported that the risk of VTE recurrence in patients with cancer receiving DOACs as compared to LMWHs is reduced but with an increased number of episodes of major bleeding.\textsuperscript{112} Recently the results of the Caravaggio Investigators’ study showed that there was no difference between treatment with DOACs and LMWHs in the number of CAT relapses over a 6-month period. Moreover, it showed that in patients less than 65 years of age, apixaban prevented the recurrence of VTE more than dalteparin and the effect of apixaban was decreased in elderly patients. There were also no differences in the risk of major gastrointestinal bleeding and total mortality although the number of clinically relevant non-major bleeding episodes was higher after apixaban use.\textsuperscript{122} Table 1 summarizes data with LMWH versus warfarin and DOAC in CAT.

**Future Directions in the Management of CAT**

**Euthyroid.** Several studies have reported an increased thrombophilic risk profile in patients with overt hyperthyroidism and sub-clinical hyperthyroidism; this transforms the hemostatic balance through hypercoagulable and hypofibrinolytic state with elevated levels of factor VIII, factor IX, von Willebrand factor, and thromboxane A2, amongst other factors.\textsuperscript{123} These factors contribute to an increased risk of VTE and CAT in patients with hyperthyroidism.\textsuperscript{124} Conversely, patients with subclinical hyperthyroidism are at increased risk of developing hypercoagulability and a hypercoagulable state. These patients may be at increased risk of VTE, and CAT.\textsuperscript{125} Thus, these patients seem to be at increased risk of VTE and CAT.\textsuperscript{126}

**Hypothyroid.** There is some evidence to suggest that hypothyroidism is associated with an increased risk of VTE.\textsuperscript{127} The proposed mechanism involves an imbalance in the hemostatic balance, with hypothyroidism leading to an increased risk of VTE and CAT.\textsuperscript{128} Further studies are needed to better understand the role of hypothyroidism in the development and management of VTE and CAT.

**Subclinical Hypothyroid.** Subclinical hypothyroidism is a condition characterized by an elevated thyrotropin (TSH) level and normal free thyroxine (FT4) level.\textsuperscript{129} Several studies have reported an increased risk of VTE and CAT in patients with subclinical hypothyroidism.\textsuperscript{130} These patients may be at an increased risk of VTE and CAT due to an imbalance in the hemostatic balance. Further studies are needed to better understand the role of subclinical hypothyroidism in the development and management of VTE and CAT.
factor antigen (VWF: Ag), fibrinogen, and plasminogen activator inhibitor. \(^{123}\) The evidence suggests that hypothyroidism may have a biphasic effect on fibrinolysis, depending on disease severity. \(^{124}\) A previous study found that T3 may directly or indirectly control transcription of hepatic and vessel walls’ coagulation; this transcriptional modification resulted in a change in the plasma coagulation factors. \(^{125}\) Moreover, spontaneous or medically induced hypothyroidism may alter the clinical behavior of cancers such as breast cancer, \(^{126}\) glioblastoma \(^{127}\) and renal cell carcinoma. \(^{128}\) T3 reduces serum thyrotropin levels (TSH) and T4 level and also improves clinical and radiological conditions in cancer patients. \(^{129}\) In fact, T3 cannot induce tumor cell proliferation at physiological concentrations. \(^{130}\) When the T3 level increases, it can stimulate cancer cell proliferation at the receptor on integrin \(\alpha v\beta 3\). \(^{131}\) Nevertheless, in patients with euthyroidism and cancer, euthyroidism alone with a normal T3 level does not seem to promote the growth of the tumor. \(^{130}\) T4 has a significant action on tumor cells and coagulation when compared to T3. This may represent a novel, inexpensive and nontoxic approach for improving CAT and TAC. The paradigm should be tested in prospective controlled trials in a wider variety of patients with cancer. Thus future studies are needed to investigate the effect of euthyroid in CAT and TAC.

**Blockade of thyroid hormone receptors on integrin \(\alpha v\beta 3\).** The plasma membrane integrin \(\alpha v\beta 3\) acts as a membrane receptor for thyroid hormone. Integrin \(\alpha v\beta 3\) binding facilitates the hormone’s proliferative action on cancer cells and blood vessel cells. \(^{131}\) The primary thyroid hormone ligand of this receptor is T4, which activates \(\beta\)-catenin and induces metastasis. \(^{132}\) The activation and deactivation of thyroid hormones may also stimulate angiogenesis associated with primary or metastatic tumors. As stated above, various mechanisms stimulate angiogenesis among the non-genomic actions of T4 and T3 at \(\alpha v\beta 3\), of tumor cell proliferation, and of anti-apoptotic tumor defenses. \(^{133}\) These problems may be avoided by using an analog of T4, tetraiodothyroacetic acid (tetrac), which prevents binding of iodothyronines to integrin \(\alpha v\beta 3\). \(^{134}\) In order to limit tetrac to the cell surface of thyroid hormone receptor, diamino propane tetraiodothyroacetic acid (DAT) is preferred. Tetrad DAT as thyroid hormone derivatives influence gene expression after crossing cellular membranes. We conjugated tetrad to the polymeric nanoparticle poly (lactic-co-glycolic acid) (PLGA) resulting in nano-diamino-tetrac (NDAT). \(^{135}\) Many studies have shown that the formulation of NDAT is restricted to the extracellular area and to the integrin, thus slowing tumor development and vascularity. \(^{136}\) NDAT’s antitumor efficacy includes pro-apoptotic activity and gene transcription disturbance that are crucial to a number of mechanisms for cancer cell survival. \(^{137}\) Tetrad blocks the pro-angiogenic activity of VEGF and of basic fibroblast growth factor (bFGF; FGF2) in the chick chorioallantoic membrane and in an endothelial cell microtubule formation assay \(^{138}\) and PDGF. \(^{51}\) Moreover, tetrad prevents radioresistance of cancer cells resulting from the activation of integrin \(\alpha v\beta 3\). \(^{139}\) Another drug that can block thyroid hormone on integrin \(\alpha v\beta 3\) is compound XT199, which is an integrin antagonist that can block aggregatory effects on platelets. It acts at the cell surface via interaction with integrin \(\alpha v\beta 3\) and thyroid hormone receptors. \(^{140}\)

**SNACH (Sulfated non-anticoagulant heparin).** It was shown that the effect of SNACH in inhibiting cancer metastasis is not related to the heparin anticoagulant property. \(^{136}\) SNACH is a LMWH that has no effect on the systemic coagulation factors yet releases TF pathway inhibitor protein (TFPI), a key endogenous inhibitor of the TF/VIIa complex from the endothelium. \(^{141}\) (Figure 2). Release of TFPI may be responsible for the anti-angiogenic and antimetastatic activity. Like most of the non-antithrombin-mediated effects, TFPI release from the vascular endothelium is associated with N-sulfated regions of heparin and non-anticoagulant heparins. \(^{141}\) The additional finding that SNACH exhibits anti-angiogenesis activity suggests another mechanism that could contribute to its role in tumor suppression. \(^{141}\) As shown in Figure 2, it can be concluded that SNACH releases TFPI that affects inflammation and angiogenesis, and it has an inhibitory effect on TF/VIIa complex that affects activation of coagulation and platelets and consequently affects CAT.

**Inhibition of NETs.** In cancer, NETs circulate at high levels in blood, \(^{142}\) activate the occlusion of small vessels, \(^{143}\) activate the contact pathway of coagulation, \(^{144}\) and help in digesting the major coagulation inhibitors such as antithrombin III and TFPI. \(^{145}\) Dissolving NETs with DNase I restores normal perfusion of microvasculature in animal models. \(^{143}\) Also, DNase I proved its significance in inhibiting tumorigenicity of some cancer cell lines. \(^{146}\) There are many drugs that can be used as NET inhibitors by reducing NETs’ formation such as peptidyl arginine deiminase type 4 inhibitors, \(^{147}\) cyclooxygenase-2, \(^{148}\) and vitamin C. \(^{149}\) Based on the above findings, targeting intravascular NETs may similarly reduce thrombosis in patients with cancer.

**Risk stratification strategies.** Prevention and treatment of CAT can be achieved by a variety of risk stratification strategies. Risk factors are either patient-related factors, cancer-related factors, or treatment-related factors. \(^{150}\) The use of single clinical risk factors as a risk stratification failed. Therefore, the new American Society of Clinical Oncology (ASCO) guidelines recommend the use of a risk score that includes multiple variables to identify high-risk patients \(^{151,152}\) such as elevated platelet and leukocyte counts, decreased hemoglobin, elevated D-dimer, elevated prothrombin activation products, elevated soluble P-selectin, peak thrombin generation, and elevated levels of TF-bearing microparticles. \(^{153}\) Potential applications of risk factors stratification include educating patients about warning signs and symptoms of VTE, which could lead to early detection and treatment \(^{154}\) and targeted prophylaxis that supports the “precision medicine” approach that is the hallmark of anticancer therapy. \(^{155}\)
**The Link between CAT and TAC**

The strong link between cancer and thrombosis is illustrated in Figure 1 along with CAT and TAC. Tumor cells may activate the coagulation system and lead to thrombosis through the production of procoagulant, fibrinolytic, and pro-inflammatory and pro-angiogenic cytokines, leading to the pro-thrombotic state and tumor metastasis in patients with cancer.156

On the other hand, coagulation factors also affect the progression of cancer leading to TAC. Previous studies suggested that hemostatic abnormalities in patients with cancer can contribute to inflammatory cell recruitment, tumor stroma production, and angiogenesis.157 We know that TF is expressed on cancer cells and vasculature158 as well as on endothelial cells and platelets, and TF-bearing EVs contribute to the thrombotic phenotype in cancer patients.159 The TF/factor VIIa complex has an effect on processes of blood coagulation and has an effect on inflammation and angiogenesis.160 Higher TFPI-1 levels may be due to the TF uptake in tumor cells or to damaged endothelial cells in ongoing coagulation activation in patients with cancer and DVT or metastases.161 TF also regulates αvβ3 integrin, which as stated earlier, is expressed on platelets, cancer cells, and endothelium. Integrin αvβ3 activation facilitates tumor angiogenesis and tumor progression.162 In summary, TF isoforms, factor VII, PAR2, and αvβ3 integrin affect cell process and cell interaction with their environment, including angiogenic events.163

**Conclusion**

There is a two-way clinical relationship between cancer and VTE. Thrombotic events, especially idiopathic thrombosis, can sometimes be a cause of cancer. At the same time, VTE is a serious complication of cancer and the second most frequent cause of death in patients with cancer. Moreover, the prevention and treatment of VTE in cancer patients is challenging because the risk-benefit profile when using anticoagulants must be considered. Further data are needed to confirm future directions in the management of CAT or TAC by either euthyroid, blockade of thyroid hormone on integrin αvβ3 by NDAT or other agents, by sulfated non-anticoagulant heparin (SNACH), inhibition of NETs, stratifying low and high risk patients with significant bleeding problems with DOACs, or other appropriate therapies.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
16. Wall JG, Weiss RB, Norton L, et al. Arterial thrombosis associated with adjuvant chemotherapy for breast carcinoma: a cancer and leukemia group B study. Am J Med. 1989;87(5):501-504.

17. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost. 2006;4(3):529-535.

18. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. Thromb Res. 2006;118(5):555-568.

19. Cool RM, Herrington JD, Wong L. Recurrent peripheral arterial thrombosis induced by cisplatin and etoposide. Pharmacotherapy. 2002;22(9):1200-1204.

20. Mannucci PM, Bettega D, Chantarangkul V, Tripodi A, Sacchini V, Veronesi U. Effect of tamoxifen on measurements of hemos- tasis in healthy women. Arch Intern Med. 1996;156(16):1806-1810.

21. Mills PJ, Parker B, Jones V, et al. The effects of standard anthracycline-based chemotherapy on soluble ICAM-1 and vascular endothelial growth factor levels in breast cancer. Clin Cancer Res. 2004;10(15):4998-5003.

22. Walsh J, Wheeler HR, Geczy CL. Modulation of tissue factor by human monococytes by cisplatin and Adriamycin. Br J Haematol. 1992;81(4):480-488.

23. Lechner D, Kollars M, Gleiss A, Kyrl PA, Weltermann A. Chemotherapy-induced thrombin generation via procoagulant endothelial microparticles is independent of tissue factor activity. J Thromb Haemost. 2007;5(12):2445-2452.

24. Bezeaud A, Drouet L, Leverger G, Griffin JH, Guillou MC. Effect of L-asparaginase therapy for acute lymphoblastic leukemia on plasma vitamin K-dependent coagulation factors and inhibitors. J Pediatr. 1986;108(5 Pt 1):698-701.

25. Siabai H, Chen R, Liu X, et al. Anticoagulation prophylaxis reduces venous thromboembolism rate in adult acute lymphoblastic leukemia treated with asparaginase-based therapy. Br J Haematol. 2020. Epub May 13. doi:10.1111/bjh.16695.

26. Feffer SE, Carmosino LS, Fox RL. Acquired protein C deficiency in patients with breast cancer receiving cyclophosphamide, methotrexate, and 5-fluorouracil. Cancer. 1989;63(7):1303-1307.

27. Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden thrombophilia study. Lancet. 1993;342(8886-8887):1503-1506.

28. Liberti G, Bertina RM, Rosendaal FR. Hormonal state rather than age influences cut-off values of protein S: reevaluation of the thrombotic risk associated with protein S deficiency. Thromb Haemost. 1999;82(3):1093-1096.

29. Giustozzi M, Curcio A, Weijb B, et al. Variation in the association between antineoplastic therapies and venous thromboembolism in patients with active cancer. Thromb Haemost. 2020;120(5):847-856.

30. Maraveyas A, Haque F, Muazzam IA, Ilyas W, Bozas G. Increased dose primary thrombophrophylaxis in ambulatory patients with advanced pancreatic ductal adenocarcinoma, a single centre cohort study. Thromb J. 2020;18:1-9.

31. Carmona-Bayonas A, Gómez D, Martínez de Castro E, et al. A snapshot of cancer-associated thromboembolic disease in 2018-2019: first data from the TESEO prospective registry. Eur J Intern Med. 2020;78:41-49.

32. Guy JB, Falk AT, Chargari C, Bertoletti L, Magne N. Thromboembolic events following brachytherapy: case reports. J Contemp Brachyther. 2015;7(1):76-78.

33. Guy JB, Bertoletti L, Magne N, et al. Venous thromboembolism in radiation therapy cancer patients: findings from the RIETE registry. Crit Rev Oncol Hematol. 2017;113:83-89.

34. Geiger H, Pawar SA, Kerschen EJ, et al. Pharmacological targeting of the thrombomodulin-activated protein C pathway mitigates radiation toxicity. Nat Med. 2012;18(7):1123-1129.

35. Byrne M, Reynolds JV, O’Donnell JS, et al. Long-term activation of the pro-coagulant response after neoadjuvant chemoradiation and major cancer surgery. Br J Cancer. 2010;102(1):73-79.

36. Boerma M, Kruse JJ, van Loenen M, et al. Increased deposition of von Willebrand factor in the rat heart after local ionizing irradiation. Strahlenther Onkol. 2004;180(2):109-116.

37. Leith JT, Hercbergs A, Kenney S, Mousa SA, Davis PJ. Activation of tumor cell integrin αvβ3 by radiation and reversal of activation by chemically modified tetraiodothyroacetic acid (tetra). Endocr Res. 2018;43(4):215-219.

38. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progesterin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-333.

39. Mandalà M, Falanga A, Rolaia F. Management of venous thromboembolism (VTE) in cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2011;22(Suppl 6):v85-92.

40. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Arch. Intern. Med. 2003;163(14):1711-1717.

41. Jordan BJ, Matulewicz RS, Trihn B, Kundu S. Venous thromboembolism after nephrectomy: incidence, timing and associated risk factors from a national multi-institutional database. World J Urol. 2017;35(11):1713-1719.

42. Edelman JJ, Reddel CJ, Kritharides L, et al. Natural history of hypercoagulability in patients undergoing coronary revascularization and effect of preoperative myocardial infarction. J Thorac Cardiovasc Surg. 2014;148(2):536-543.

43. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2002;121(2 Suppl):e227S-e277S.

44. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietin and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006;98(10):708-714.

45. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008;299(8):914-924.

46. Smith KJ, Bleyer AJ, Little WC, Sane DC. The cardiovascular effects of erythropoietin. Cardiovasc Res. 2003;59(3):538-548.
Fuste B, Serradell M, Escolar G, et al. Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. *Thromb Haemost.* 2002;88(4):678-685.

Ortega Carvalho TM, Chiamolera MI, Pazos Moura CC, Wondisford FE. Hypothalamus-pituitary-thyroid axis. *Compr Physiol.* 2016;6(3):1387-1428.

Hellevik AI, Asvold BO, Bjoro T, Romundstad PR, Nilsen TI, Vatten LJ. Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(2):570-574.

Davis PJ, Davis FB, Mousa SA, Luidens MK, Lin HY. Membrane receptor for thyroid hormone: physiologic and pharmacologic implications. *Annu Rev Pharmacol Toxicol.* 2011;51:99-115.

Davis PJ, Glinsky GV, Lin HY, et al. Cancer cell gene expression modulation from plasma membrane integrin αvβ3 by thyroid hormone and nanoparticulate tetrac. *Front Endocrinol (Lausanne).* 2014;5:240.

Brent GA. Mechanisms of thyroid hormone action. *J Clin Invest.* 2012;122(9):3035-3043.

Cayrol F, Sterle HA, Díaz Flaque MC, Barreiro Arcos ML, Crema schi GA. Non-genomic actions of thyroid hormones regulate the growth and angiogenesis of T cell lymphomas. *Front Endocrinol.* 2019;10:63.

Bergh JJ, Lin HY, Lansing L, et al. Integrin αvβ3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. *Endocrinology.* 2005;146(7):2864-2871.

Davis PJ, Davis FB, Mousa SA. Thyroid hormone-induced angiogenesis. *Curr Cardiol Rev.* 2009;5(1):12-16.

Mousa SS, Davis FB, Davis PJ, Mousa SA. Human platelet aggregation and degranulation is induced in vitro by L-thyroxine, but not by 3,5,3′-triiodo-L-thyronine or diiodothyropropionic acid (DITPA). *Clin Appl Thromb Hemost.* 2010;16(3):288-293.

Meikle CKS, Kelly CA, Garg P, Wuescher LM, Ali RA, Worth RG. Cancer and thrombosis: the platelet perspective. *Front Cell Dev Biol.* 2017;4:147-147.

Hullely S, Grady D, Bush T, et al. Randomized trial of estrogen plus progesterin for secondary prevention of coronary heart disease in postmenopausal women. Heart and estrogen/progestin replacement study (HERS) research group. *JAMA.* 1998;280(7):605-613.

Bharti JN, Rani P, Kamal V, Agarwal PN. Angiogenesis in breast cancer and its correlation with estrogen, progesterone receptors and other prognostic factors. *J Clin Diag Res.* 2015;9(1):Ec05-07.

Zhang Y, Hua F, Ding K, Chen H, Xu C, Ding W. Angiogenesis changes in ovariectomized rats with osteoporosis treated with estrogen replacement therapy. *BioMed res int.* 2019;2019:1283717.

Couse JF, Korach KS. Estrogen receptor null mice: what have we learned and where will they lead us? *Endocr Rev.* 1999;20(3):358-417.

Jayachandran M, Miller VM. Human platelets contain estrogen receptor a, caveolin-1 and estrogen receptor associated proteins. *Platelets.* 2003;14(2):75-81.

Sar P, Peter R, Rath B, Das Mohapatra A, Mishra SK. 3, 3′5 Triiodo L thyronine induces apoptosis in human breast cancer MCF-7 cells, repressing SMP30 expression through negative thyroid response elements. *PLoS One.* 2011;6(6):e20861.

Andersen CL, Sikora MJ, Boisen MM, et al. Active estrogen receptor-alpha signaling in ovarian cancer models and clinical specimens. *Clin Cancer Res.* 2017;23(14):3802-3812.

Rak J, Milsom C, May L, Klement P, Yu J. Tissue factor factor in cancer and angiogenesis: the molecular link between genetic tumor progression, tumor neoangiogenesis, and cancer coagulopathy. *Semin Thromb Hemost.* 2006;32(1):54-70.

Ancrile B, Lim KH, Counter CM. Oncogenic Ras-induced secretion of IL6 is required for tumorigenesis. *Genes Dev.* 2007;21(14):1714-1719.

Chenakrishnaiah S, Meehan B, D’Asti E, et al. Leukocytes as a reservoir of circulating oncogenic DNA and regulatory targets of tumor-derived extracellular vesicles. *J Thromb Haemost.* 2018;16(9):1800-1813.

Garnder D, Magnus N, Lee TH, et al. Cancer cells induced to express mesenchymal phenotype release exosome-like extracellular vesicles carrying tissue factor. *J Biol Chem.* 2012;287(52):43565-43572.

Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. *Blood.* 2005;105(4):1734-1741.

Strömblad S, Becker JC, Yebra M, Brooks PC, Chresha DA. Suppression of p53 activity and p21WAF1/CIP1 expression by vascular cell integrin alphavbeta3 during angiogenesis. *J Clin Invest.* 1996;98(2):426-433.

Rak J, Klement G. Impact of oncogenes and tumor suppressor genes on deregulation of hemostasis and angiogenesis in cancer. *Cancer Metastasis Rev.* 2000;19(1-2):93-96.

Tape CJ, Ling S, Dimitriadi M, et al. Oncogenic KRAS regulates tumor cell signaling via stromal reciprocation. *Cell.* 2016;165(4):910-920.

Spranger S, Gajewski TF. Impact of oncogenic pathways on evasion of antitumour immune responses. *Nat rev Cancer.* 2018;18(3):139-147.

Unruh D, Schwarze SR, Khoury L, et al. Mutant IDH1 and thrombosis in gliomas. *Acta Neuropathol.* 2016;132(6):917-930.

Yu JL, Xing R, Milsom C, Rak J. Modulation of the oncogene-dependent tissue factor expression by kinase suppressor of Ras 1. *Thromb Res.* 2010;126(1):e6-10.

Xu XR, Zhang D, Oswald BE, et al. Platelets are versatile cells: new discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and angiogenesis. *Crit Rev Clin Lab Sci.* 2016;53(6):409-430.

Schlesinger M. Role of platelets and platelet receptors in cancer metastasis. *J Hematol Oncol.* 2018;11(1):125.

De Candia E. Mechanisms of platelet activation by thrombin: a short history. *Thromb Res.* 2012;129(3):250-256.

Menter DG, Tucker SC, Kopetz S, Sood AK, Crissman JD, Honn KV. Platelets and cancer: a casual or causal relationship: revisited. *Cancer Metastasis Rev.* 2014;33(1):231-269.
80. Lechner D, Weltermann A. Chemotherapy-induced thrombosis: a role for microparticles and tissue factor? *Semin Thromb Hemost*. 2008;34(2):199-203.

81. Gremmel T, Frelinger AL, Michelson AD. Platelet physiology. *Semin Thromb Hemost*. 2016;42(3):191-204.

82. Li N. Platelets in cancer metastasis: to help the “villain” to do evil. *Int J Cancer*. 2016;138(9):2078-2087.

83. Wojtukiewicz MZ, Sierko E, Hempel D, Tucker SC, Homn KV. Platelets and cancer angiogenesis nexus. *Cancer Metastasis Rev*. 2017;36(2):249-262.

84. Hoffmann M, Monroe DM. A cell-based model of hemostasis. *Thromb Haemost*. 2001;85(6):958-965.

85. Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian J Anaesth*. 2014;58(5):515-523.

86. Aleman MM, Byrnes JR, Wang JG, et al. Factor XIII activity mediates red blood cell retention in venous thrombi. *J Clin Invest*. 2014;124(8):3590-3600.

87. Evrenmay M, Young S, Gailani D, Schoenecker J, Hamm HE. Protease-activated receptor (PAR) 1 and PAR4 differentially regulate factor V expression from human platelets. *Mol Pharmacol*. 2013;83(4):781-792.

88. Neuenschwander PF, Fiore MM, Morrissey JH. Factor VII autoactivation proceeds via interaction of distinct protease-cofactor and zymogen-cofactor complexes. Implications of a two-dimensional enzyme kinetic mechanism. *J Biol Chem*. 1993;268(29):21489-21492.

89. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH. New fundamentals in hemostasis. *Physiol Rev*. 2013;93(1):327-358.

90. Ettelaie C, Collier ME, Featherby S, Benelhaj NE, Greenman J, Maraveyas A. Analysis of the potential of cancer cell lines to release tissue factor-containing microvesicles: correlation with tissue factor and PAR2 expression. *Thromb J*. 2016;14:2.

91. Boulanger CM, Loyer X, Rautou PE, Amabile N. Extracellular vesicles in coronary artery disease. *Nat Rev Cardiol*. 2017;14(5):259-272.

92. Ridger VC, Boulanger CM, Scherrer AA, et al. Microvesicles in vascular homeostasis and diseases. Position paper of the European society of cardiology (esc) working group on atherosclerosis and vascular biology. *Thromb Haemost*. 2017;117(7):1296-1316.

93. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol*. 2013;13(1):34-45.

94. Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers (Basel)*. 2018;10(10).

95. Ay C, Simanek R, Vormittag R, et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna cancer and thrombosis study (CATS). *Blood*. 2008;112(7):2703-2708.

96. Meier TR, Myers DD, Jr, Wrobleski SK, et al. Prophylactic P-selectin inhibition with PSI-421 promotes resolution of venous thrombosis without anticoagulation. *Thromb Haemost*. 2008;99(2):343-351.

97. Abdol Razak N, Elaskalani O, Metharom P. Pancreatic cancer-induced neutrophil extracellular traps: a potential contributor to cancer-associated thrombosis. *Int J Mol Sci*. 2017;18(3):487.

98. von Bruhl ML, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med*. 2012;209(4):819-835.

99. McDonald B, Davis RP, Kim SJ, et al. Platelets and neutrophil extracellular traps collaborate to promote intravascular coagulation during sepsis in mice. *Blood*. 2017;129(10):1357-1367.

100. Mauzacher LM, Posch F, Martinod K, et al. Cytokinurinated histone H3, a biomarker of neutrophil extracellular trap formation, predicts the risk of venous thromboembolism in cancer patients. *J Thromb Haemost*. 2018;16(3):508-518.

101. Demers M, Wagner DD. Neutrophil extracellular traps: a new link to cancer-associated thrombosis and potential implications for tumor progression. *Oncoimmunology*. 2013;2(2):e22946.

102. Falanga A, Consonni R, Marchetti M, et al. Cancer procoagulant and tissue factor are differently modulated by all-trans-retinoic acid in acute promyelocytic leukemia cells. *Blood*. 1998;92(1):143-151.

103. Reinhardt C, von Bruhl ML, Manukyan D, et al. Protein disulfide isomerase acts as an injury response signal that enhances fibrin generation via tissue factor activation. *J Clin Invest*. 2008;118(3):1110-1122.

104. Langer F, Spath B, Fischer C, et al. Rapid activation of monocyte tissue factor by antithymocyte globulin is dependent on complement and protein disulfide isomerase. *Blood*. 2013;121(12):2324-2335.

105. Ahamed J, Versteeg HH, Kerver M, et al. Disulfide isomerization switches tissue factor factor from coagulation to cell signaling. *Proc Natl Acad Sci USA*. 2006;103(38):13932-13937.

106. Rothmeier AS, Marchese P, Langer F, et al. Tissue factor prothrombotic activity is regulated by integrin-arf6 trafficking. *Arterioscler Thromb Vasc Biol*. 2017;37(7):1323-1331.

107. Grignani G, Maiolo A. Cytokines and hemostasis. *Haematologica*. 2000;85(9):967-972.

108. Dosquet C, Weill D, Wautier JL. Cytokines and thrombosis. *J Cardiovasc Pharmacol*. 1995;25(Suppl 2):S13-S19.

109. Puhlmann M, Weinreich DM, Farma JM, Carroll NM, Turner EM, Alexander HR, Jr. Interleukin-1b induced vascular permeability is dependent on induction of endothelial tissue factor (TF) activity. *J Transl Med*. 2005;3:37-37.

110. Yamamura M, Yamada Y, Momita S, Kamihira S, Tomonaga M. Circulating interleukin-6 levels are elevated in adult T-cell leukemia/lymphoma patients and correlate with adverse clinical features and survival. *Br J Haematol*. 1998;100(1):129-134.

111. Zucchella M, Pacchiarini L, Meloni F, et al. Effect of interferon alpha, interferon gamma and tumor necrosis factor on the procoagulant activity of human cancer cells. *Haematologica*. 1993;78(5):282-286.

112. Mulloy B, Hogwood J, Gray E, Lever R, Page CP. Pharmacology of heparin and related drugs. *Pharmacol Rev*. 2016;68(1):76-141.

113. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med*. 2002;162(15):1729-1735.
114. Lee AY, Levine MN, Baker RI, 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.

115. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med.* 2006;119(12):1062-1072.

116. Lee AYY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA.* 2015; 314(7):677-686.

117. Almarshad F, Alaklabi A, Bakhsh E, Pathan A, Almegren M. Use of direct oral anticoagulants in daily practice. *Am J Blood Res.* 2018;8(4):57-72.

118. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378(7):615-624.

119. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer and venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol.* 2018;36(20):2017-2023.

120. McBane II R, Loprinzi CL, Ashrani A, et al. Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE trial. *Thromb Haemost.* 2017;117(10): 1952-1961.

121. Fuentes HE, McBane RD, 2nd, Wysokinski WE, et al. Direct oral factor Xa inhibitors for the treatment of acute cancer-associated venous thromboembolism: a systematic review and network meta-analysis. *Mayo Clin. Proc.* 2019;94(12):2444-2454.

122. Agnelli G, Becattini C, Meyer G, et al. Apixaban and factor Xa inhibitors for the treatment of venous thromboembolism associated with cancer. *N Engl J Med.* 2020;382(17):1599-1607.

123. Stuijver DJ, van Zaane B, Romualdi E, Brandjes DP, Gerdes VE, Hercbergs A. Long-term response in high-grade optic glioma treated with medically induced hypothyroidism and carboplatin: a case report and review of the literature. *Anticancer Drugs.* 2013;24(3):315-323.

124. Lee AY, Levine MN, Baker RI, 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.

125. Salloum-Asfar S, Boelen A, Reitsma PH, van Vlijmen BJ. The immediate and late effects of thyroid hormone. *Horm Cancer.* 2018;9(6):420-432.

126. Li W, Yalcin M, Bharali DJ, et al. Pharmacokinetics, biodistribution, and anti-angiogenesis efficacy of diamino propane tetrathiodioacetic acid-conjugated biodegradable polymeric nanoparticle. *Sci Rep.* 2019;9(1):9006.

127. Davis PJ, Sudha T, Lin HY, Mousa SA. Thyroid hormone, hormone analogs, and angiogenesis. *Compr Physiol.* 2015;6(1):353-362.

128. Sudha T, Phillips P, Kanaan C, Linhardt RJ, Mousa SA. Inhibitory effect of non-anticoagulant heparin (S-NACH) on pancreatic cancer cell adhesion and metastasis in human umbilical cord vessel segment and in mouse model. *Clin Exp Metastasis.* 2012;29(5):431-439.

129. Mousa SA. Hypothyroidism in patients with renal cell carcinoma: blessing or curse? *Cancer.* 2011;117(3):534-544.
144. Oehmcke S, Mørgelin M, Herwald H. Activation of the human contact system on neutrophil extracellular traps. *J Innate Immun*. 2009;1(3):225-230.

145. Massberg S, Grahl L, von Bruehl ML, et al. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. *Nat Med*. 2010;16(8):887-896.

146. Hawes MC, Wen F, Elquza E. Extracellular DNA: A bridge to cancer. *Cancer Res*. 2015;75(20):4260-4264.

147. Lewis HD, Liddle J, Coote JE, et al. Inhibition of PAD4 activity is sufficient to disrupt mouse and human NET formation. *Nat Chem. Biol*. 2015;11(3):189-191.

148. Gonzalez RD, Martinez-Colón GJ, Smith AJ, et al. Inhibition of neutrophil extracellular trap formation after stem cell transplant by prostaglandin E2. *Am J Respir Crit Care Med*. 2016;193(2):186-197.

149. Mohammed BM, Fisher BJ, Kraskauskas D, et al. Vitamin C: a novel regulator of neutrophil extracellular trap formation. *Nutrients*. 2013;5(8):3131-3151.

150. Khorana AA, McCrae KR. Risk stratification strategies for cancer-associated thrombosis: an update. *Thromb Res*. 2014;133(Suppl 2):S35-S38.

151. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907.

152. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood*. 2010;116(24):5377-5382.

153. Pabinger I, Thaler J, Ay C. Biomarkers for prediction of venous thromboembolism in cancer. *Blood*. 2013;122(12):2011-2018.

154. Khorana AA. Risk assessment for cancer-associated thrombosis: what is the best approach? *Thromb Res*. 2012;129:S10-S15.

155. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. *Intern Emerg Med*. 2012;7(3):291-292.

156. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br J Cancer*. 2010;102(Suppl 1):S2-S9.

157. Nuttall GA. Hemostasis and thrombosis: basic principles and clinical practice, 5th ed. *Anesth Analg*. 2007;104(5):1317.

158. Contrino J, Hair G, Kreutzer DL, Rickles FR. In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease. *Nat Med*. 1996;2(2):209-215.

159. Rak J. Microparticles in cancer. *Semin Thromb Hemost*. 2010;36(8):888-906.

160. Versteeg HH, Ruf W. Emerging insights in tissue factor-dependent signaling events. *Semin Thromb Hemost*. 2006;32(1):24-32.

161. Fischer EG, Riewald M, Huang HY, et al. Tumor cell adhesion and migration supported by interaction of a receptor-protease complex with its inhibitor. *J Clin Invest*. 1999;104(9):1213-1221.

162. Bieker R, Kessler T, Schwoppe C, et al. Infarction of tumor vessels by NGR-peptide-directed targeting of tissue factor: experimental results and first-in-man experience. *Blood*. 2009;113(20):5019-5027.

163. van den Berg YW, Osanto S, Reitsma PH, Versteeg HH. The relationship between tissue factor and cancer progression: insights from bench and bedside. *Blood*. 2012;119(4):924-932.