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Cancer-Associated Thrombosis: A Taiwanese Perspective on Therapeutic Options with Focus on Non-Vitamin K Antagonist Oral Anticoagulants

Yu-Yun Shao,[1,2] Ching-Liang Ho,[3] Cheng-Shyong Chang,[4] Chia-Lun Chang,[5] Jen-Kuang Lee,[6] Hung-Ju Lin,[6] Hui-Hua Hsiao,[7] Ta-Chung Chao,[8] Ching-Yeh Lin[9] and Chuang-Chi Liaw[10]

Cancer-associated thrombosis (CAT) is a common complication of malignancies. Patients with CAT are at risk of venous thromboembolism recurrence, but also at risk of bleeding while anticoagulated. Taiwanese patients are perceived to have a lower incidence of CAT, likely leading to false reassurance for Taiwanese patients with cancer. Because of this, oncologists and cardiologists from multiple medical institutions in Taiwan have set forth to provide clinical consensus guidelines on the management of CAT, based on local clinical practices and guided by predominant international clinical practice guidelines.

This paper aims to describe the current disease burden of cancer-associated venous thromboembolism in Taiwanese cancer patients, and discusses the unmet needs and gaps in the management of this medical complication. It also outlines diagnostic and management strategies relevant to the different treatment options available, such as non-vitamin K antagonist oral anticoagulants.

Key Words: Cancer-associated thrombosis • Deep venous thromboembolism • Evidence-based guidelines • Non-vitamin K antagonist oral anticoagulants • Pulmonary embolism

Abbreviations

ASCO	American Society of Clinical Oncology
BNP	B-type natriuretic peptide
CAT	Cancer-associated thrombosis
Ccr	Creatinine clearance
CTPA	Computed tomographic pulmonary angiography
CYP3A4	Cytochrome P450 3A4
DVT	Deep vein thrombosis
ESC	European Society of Cardiology
ISTH	International Society on Thrombosis and Haemostasis
LWMH	Low molecular weight heparin
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMCR	Nonmajor clinically relevant
NOAC	Non-vitamin K antagonist oral anticoagulant
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
p-gp	Permeability glycoprotein
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VQ	Ventilation/perfusion
VTE	Venous thromboembolism

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[1]Department of Oncology, National Taiwan University Hospital; [2]Graduate Institute of Oncology, National Taiwan University College of Medicine; [3]Division of Hematology and Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei; [4]Division of Hematology-Oncology, Department of Internal Medicine, Chang Bing Show Chwan Memorial Hospital, Changhua; [5]Department of Hematology, Taipei Municipal Wanfang Hospital; [6]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei; [7]Division of Hematology and Oncology, Department of Internal Medicine, Kaohsiung Medical University and Kaohsiung Medical University Hospital, Kaohsiung; [8]Department of Oncology, Taipei Veterans General Hospital, Taipei; [9]Department of Hematology, Changhua Christian Hospital, Changhua; [10]Department of Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.
Corresponding author: Dr. Ching-Liang Ho, Division of Hematology and Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Chenggong Road, Neihu District, Taipei 114. Taiwan. Tel: 886-2-8792-3311; Fax: 888-2-8792-7134; E-mail: charileho22623@gmail.com

INTRODUCTION

Venous thromboembolism (VTE) is an umbrella term used to characterize a state of hypercoagulability where a number of factors lead to the formation of a clot or thrombus in the blood vessels, such as in deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis, and splanchnic vein thrombosis, an unusual site of VTE.[1] Cancer-associated thrombosis (CAT) is VTE that occurs in patients with cancer. CAT results directly from a hypercoagulability state or indirectly due to cancer cells or tumor compression of major blood vessels.[1] It is important to manage and treat CAT, as it negatively affects survival outcomes of cancer patients and increases the likelihood of mortality by two- to six-fold.[2]

The reported incidence of CAT varies depending on the patient population, duration of follow-up, and method of detecting and reporting thrombotic events. Active cancer is associated with a four- to seven-fold increased risk of developing CAT, and cancer patients make up about 20% to 30% of all new cases of VTE in the community.[3] In the Registro Informatizado de Enfermedad Trombo Embolica registry, a large prospective cohort of patients with VTE, about 18% of the patients had active cancer.[4]

Patients with cancer are at a four- to seven-fold higher risk of thrombosis than patients without cancer.[5] Epidemiology data have demonstrated yearly increases in the incidence of CAT in Asian patients, particularly in high-risk and elderly patients.[5] Overall, the estimated incidence of CAT in Taiwan was 185 per 100,000 person-years from 1997 to 2005.[6] A study based on the National Health Insurance Research Database in Taiwan used two algorithms to define CAT. Among 43,855 cancer patients, the investigators found CAT incidence rates of 9.9 (using algorithm 1) and 3.4 (using algorithm 2) per 1000 person-years.[5] In addition, analysis of medical records from January 2011 to December 2013 from the National Taiwan University Hospital showed that among 5620 patients diagnosed with lung, gastric and pancreatic cancer, and lymphoma, all of whom have a higher risk of VTE, the incidence rate of VTE was 36.3 per 1000 patient-years.[7]

International guidelines for managing CAT have used Western population data to derive recommendations. Therefore, such guidelines may not be entirely applicable to other racial or ethnic populations.[8] For instance, Taiwanese population studies have shown a lower incidence of CAT than in Western populations. Nonetheless, it remains unknown whether this lower incidence is attributable to ethnic differences or reflects discrepancies in study design, disease severity and physician practices.[5]

No large clinical trials have assessed the treatment of CAT in Taiwan, and consensus statements on the management of CAT have mostly been extrapolated from data about VTE in patients without cancer.[1,9] Since cancer patients have different clinical characteristics to the general population (i.e. hypercoagulable state, nutritional status), the efficacy and safety of CAT treatments should be evaluated separately from general VTE treatments.[1]

One of the recommended treatments for CAT is low molecular weight heparins (LMWHs), which are typically administered subcutaneously.[2] This may cause discomfort for patients, leading to poor compliance.[2,10] Some clinical trials have highlighted the use of non-vitamin K antagonist oral anticoagulants (NOACs) as secondary thromboprophylaxis, but have reported unknown risks and benefits for primary thromboprophylaxis.[1]

Splanchnic vein thrombosis is a rare manifestation of VTE, with an incidence around 25-fold lower than usual site VTE. However, the incidence of splanchnic vein thrombosis varies in different studies and presentation types. Digestive cancers, such as hepatocellular carcinoma, and liver cirrhosis are the major malignancies associated with splanchnic vein thrombosis, while other risk factors such as abdominal infection or surgery may also be associated. Nevertheless, around one fourth of cases are unprovoked.[11-13] Considering the complexity of splanchnic vein thrombosis and limited medical evidence, we aimed to outline the appropriate management of cancer-associated usual site VTE, including DVT and PE, based on local clinical scenarios and consensus of oncologists and cardiologists. The purpose of this consensus statement is to provide clinicians with evidence-based recommendations to effectively manage cancer-associated VTE in Taiwanese patients.

MATERIALS AND PROCESS

A meeting of Taiwan oncologists and cardiologists

was held with the aim of determining consensus statements on managing CAT.

The team collected and reviewed publications on managing CAT. A systematic review of related literature was done through a Medline and Google Scholar search using the following keywords: VTE, cancer-associated thrombosis, prophylaxis, treatment. A manual search was also performed if the publications were not available online. After comprehensive team discussions, consensus statements were generated. These recommendations were formulated by a final vote of agreement. The panelists' personal experiences and interpretations of the published data establish the basis for these recommendations.

RESULTS AND DISCUSSION

Review of studies

All available publications (clinical trials, meta-analyses, consensus statements, international guidelines) were selected, screened and reviewed by the listed authors. All statements were presented with supporting modifications based on feedback.

CAT risk assessment and diagnosis

Clinical risk factors for CAT include the primary site of cancer, chemotherapy, anti-angiogenic therapy, surgery and hospitalization.[14] In general, the following patient factors predispose patients to CAT: advanced stage of cancer; cancer of the brain, pancreas, stomach, bladder, kidney or lung; gynecologic or metastatic cancer; lymphoma; myeloproliferative neoplasms; regional bulky lymphadenopathy with extrinsic vascular compression; familial and/or acquired hypercoagulability (including pregnancy); medical comorbidities (e.g. infections, renal disease, pulmonary disease, congestive heart failure, arterial thromboembolism); poor performance status; older age (> 65 years); smoking history; obesity; and lack of activity.[2]

Some cancer therapies also increase the risk of CAT, such as platinum chemotherapy, anti-angiogenic therapy (e.g. bevacizumab), immunomodulators (e.g. thalidomide, lenalidomide), selective estrogen receptor modulators (e.g. tamoxifen), erythropoietin-stimulating agents and L-asparaginase.[2,15] Central venous access devices, which are commonly implanted in cancer patients for infusion access, also increase the risk of CAT.[2,15]

Predictive and candidate biomarkers include D-dimer, platelet and leukocyte counts, and hemoglobin. However, no single biomarker can accurately identify high-risk populations. Clinical risk scores incorporating clinical and laboratory variables, such as the Khorana score and the CAT Score, may help to categorize patients according to the risk of CAT.[16,17]

The National Comprehensive Cancer Network (NCCN) and National Institute for Health and Care Excellence (NICE) recommend that cancer patients should be promptly assessed for CAT at the first onset of symptoms. Baseline assessments include a complete history and physical examination.[10,18] CAT should be suspected if the patient experiences common presenting symptoms of DVT and PE, such as pain, extremity edema, erythema, dyspnea, or tachypnea.[2]

Symptomatic DVTs in femoral and popliteal veins can be directly diagnosed using noninvasive imaging such as duplex, compression or Doppler venous ultrasonography. Venography may be used as an alternative if ultrasonography is not feasible. To diagnose PE, computed tomographic pulmonary angiography (CTPA) is used to evaluate pulmonary vessels. Pulmonary ventilation/perfusion (VQ) scans may be considered as an alternative to CTPA. A 2D echocardiogram, CTPA, pro-B-type natriuretic peptide (pro-BNP) and troponin tests may be done to determine the severity of CAT.[2] Several studies have suggested that a low D-dimer level may indicate a low risk of CAT.[19,20]

For patients with symptoms similar to DVT, such as pain, extremity edema and erythema, but with negative imaging results, the D-dimer level could help exclude the diagnosis of DVT (Figure 1).[2,8]

Diagnostic and risk stratification consensus statements:

- A proposed CAT diagnostic algorithm for symptomatic DVT and PE (Figure 1) provides a simplified method of assessment.

Management of CAT

Several international and national organizations have published clinical practice guidelines for managing CAT. A summary of the guideline recommendations for CAT treatment with NOACs is shown in Table 1.[2,21-24]

The most widely used guidelines in Taiwan include

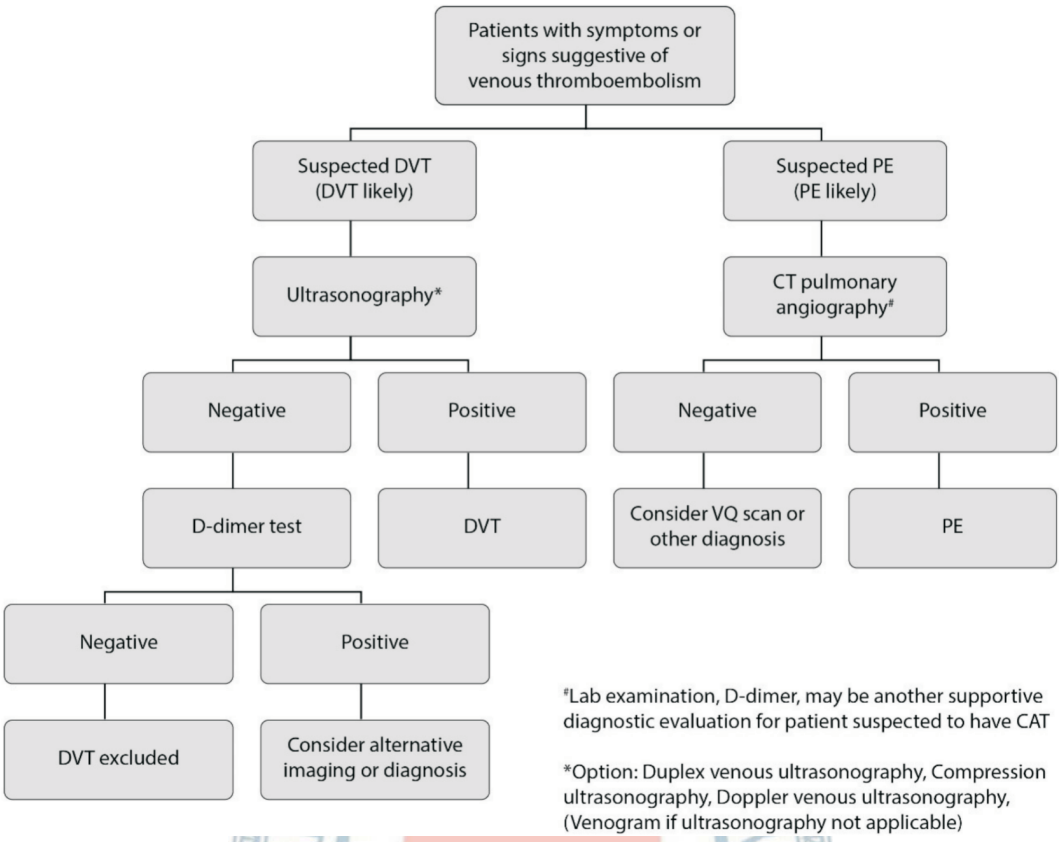

Figure 1. *CAT diagnosis flowchart.[8,19,20] CT, computed tomography; DVT, deep vein thrombosis; PE, pulmonary embolism; VQ, pulmonary ventilation-perfusion.*

those developed by the American Society of Clinical Oncology (ASCO), NCCN, European Society of Cardiology (ESC) and International Society on Thrombosis and Haemostasis (ISTH).[2,21,23,25,26]

Consensus statements shared by these guidelines include:[8]

- Timely administration of anticoagulation is essential.
- Conventional treatment involves parenteral LMWHs.
- Two strategies have been tested in four pivotal trials of NOACs for CAT treatment: the single-drug approach and the LMWH lead-in approach. Both strategies are adequate treatment for CAT. The pharmacological characteristics of NOACs are summarized in Table 2.

Low molecular weight heparins (LMWHs)

Clinical trials have shown that LMWHs, compared with vitamin K antagonists (VKAs), are more effective in preventing CAT recurrence without increasing the rate of major bleeding complications.[2,21-24] LMWHs are considered the standard treatment for CAT, and VKAs are not routinely recommended for treating acute VTE in patients with active cancer. However, LMWHs have disadvantages, including the need for daily injections, handling of the syringe, drug-induced thrombocytopenia, weight-adjusted dosage, and limited use in patients with renal insufficiency.[10,27,28] LMWHs are also contraindicated in patients who have experienced heparin-induced thrombocytopenia.[2]

Anticoagulation consensus statements:

- For patients with CAT in whom NOACs are not indicated, LMWHs are the treatment of choice.
- VKAs are not routinely recommended for treatment of acute VTE in patients with active cancer.

Non-vitamin K antagonist oral anticoagulants (NOACs)

Since becoming available in the 2000s, novel oral anticoagulants have rapidly replaced classic VKA anticoagulants, owing to their convenient route of administration and minimal monitoring requirements.[29] Compared

Table 1. Major guideline recommendations on the treatment of CAT[2,21-24]

	Anticoagulant choice	Duration of therapy
ISTH SSC 2018	• NOACs (edoxaban and rivaroxaban) and LMWH are the preferred agents. • Choice is dependent on the risk of bleeding (LMWH preferred in patients with a high risk of bleeding) and potential for DDIs.	• No recommendations provided.
ASCO 2019	• Initial anticoagulation (first 5-10 days): LMWH or rivaroxaban preferred. • Long-term (< 6 months): LMWH, edoxaban or rivaroxaban (VKAs are acceptable alternatives for long-term therapy if LMWH/NOACs are not available). • Extended therapy (≥ 6 months): LMWH, edoxaban or rivaroxaban, or VKAs.	• Extended therapy beyond 6 months can be considered for selected patients with active cancer.
ITAC 2019	• Initial anticoagulation (first 5-10 days): LMWH, rivaroxaban or edoxaban following ≥ 5 days of parenteral anticoagulation. • Long-term (< 6 months): LMWH or NOACs (to date evidence is only available for edoxaban and rivaroxaban). • Extended therapy (≥ 6 months): LMWH or NOACs.	• Treatment for a minimum of 6 months, following which termination or continuation of anticoagulation should be based on individual evaluation.
NCCN Version 1 2022	• NOACs (including edoxaban, rivaroxaban and apixaban) preferred for patients without gastric or gastroesophageal lesion. • LMWH preferred for patients with gastric or gastroesophageal lesion.	• Minimum 3 months. For non-catheter associated DVT or PE, indefinite anticoagulation is recommended while cancer is active, under treatment, or if risk factors for recurrence persist.
ESC 2019	• Long-term for patients with PE and cancer (< 6 months): LMWH are preferred over VKAs. • Edoxaban or rivaroxaban should be considered as an alternative to LMWH, with a word of caution for patients with GI cancer due to the increased risk of bleeding with NOACs.	• Extended therapy beyond 6 months should be considered for an indefinite period or until the cancer is cured.

ASCO, American Society of Clinical Oncology; CAT, cancer-associated thrombosis; DDI, drug-drug interactions; ESC, European Society of Cardiology; GI, gastrointestinal; ISTH SSC, International Society on Thrombosis and Haemostasis Scientific and Standardization Committee; ITAC, International Initiative on Thrombosis and Cancer; LMWH, low molecular weight heparin; NCCN, National Comprehensive Cancer Network; NOACs, non-vitamin K antagonist oral anticoagulants; PE, pulmonary embolism; VKA, vitamin K antagonist.

Table 2. Properties of NOACs used for the single-drug approach and the LMWH lead-in approach[21]

	Single-drug approach		Two-phase approach
	Rivaroxaban	Apixaban	Edoxaban
Target	Factor Xa	Factor Xa	Factor Xa
Time to peak	2-4 h	1-2 h	1-2 h
Half-life	7-11 h	8-14 h	5-11 h
Renal elimination	33%	27%	50%
Metabolism	P-gp/CYP3A4	P-gp/CYP3A4	P-gp/CYP3A4
Initial LMWH	Optional < 48 h	Optional < 36 h	Mandatory
Regimen	15 mg twice daily for the first 21 days, followed by 20 mg once daily.	10 mg twice daily for the first 7 days, followed by 5 mg twice daily.	LMWH or UFH for at least 5 days, followed by edoxaban* 60 mg once daily.

* 30 mg once daily if creatinine clearance 30-50 mL or body weight < 60 kg.
LMWH, low molecular weight heparin; UFH, unfractionated heparin.

with VKAs, NOACs have comparable efficacy and safety for the treatment of non-cancer VTE.[30-32] Recent clinical trials have shown that NOACs and LMWHs also have comparable safety and efficacy.[32]

Three NOACs have been compared with LMWHs for the treatment of CAT in randomized studies. Once-daily-based rivaroxaban and twice-daily-based apixaban can be used as a single-drug approach, but the dose in the acute phase has to be adjusted (Table 2). In the SELECT-D pilot study, rivaroxaban was associated with lower CAT recurrence compared with LMWHs.[31] In the Caravaggio study, apixaban was shown to be noninferior to LMWHs in preventing the recurrence of CAT.[33] Trials evaluating once-daily-based edoxaban have used a LWMH lead-in approach, in which the patients were required to receive at least 5 days of LMWHs or unfractionated heparin (UFH) before switching to edoxaban (Table 2). In the Hokusai VTE Cancer study, this approach was shown to be noninferior to LMWHs in a composite outcome of VTE recurrence or major bleeding.[34] Another non-vitamin K antagonist oral anticoagulant (NOAC), dabigatran, has not been examined in randomized studies as a treatment for CAT. Two clinical trials compared dabigatran with warfarin for the treatment of acute VTE.[35,36] Both studies confirmed the noninferiority of dabigatran to warfarin in the prevention of recurrent VTE. A post-hoc analysis further pooled the results of patients with VTE and cancer in these two clinical trials, and also showed similar clinical effects in the prevention of VTE recurrence and bleeding between dabigatran and warfarin.[37] Accordingly, warfarin is an inferior treatment to LMWHs for CAT. To date, no clinical trials have compared dabigatran with LMWHs as treatment for CAT.

Conventional anticoagulant therapies are associated with high treatment burden. VKAs have a narrow therapeutic window, require frequent monitoring of anticoagulation levels, and have substantial food and drug interactions. LMWHs require daily injections,[2,3] which is associated with shorter persistence compared with oral agents in patients with cancer-associated thrombosis.[38] In addition, once-daily dosing is related to better adherence than twice-daily dosing.[39-42] In the observational COSIMO study, rivaroxaban significantly decreased the treatment burden in patients who switched anticoagulation from VKAs or LMWHs to rivaroxaban. In addition, under a discrete choice experiment in the COSIMO study, the patients preferred oral intake compared with self-injection.[43,44] Therefore, NOACs, including rivaroxaban, apixaban and edoxaban, can be considered the new standard CAT treatment, and they can be provided to patients without contraindications. In addition, NOACs could be a suitable alternative for patients who experience heparin-induced thrombocytopenia.[45]

Patients with active cancer are at an increased risk of recurrent thrombosis. It is generally recommended to extend the anticoagulation treatment period in this population.[26,46] The ASCO 2019 and ESC 2019 guidelines state that extended treatment beyond 6 months can be considered for some patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.[21,23] A sub-analysis of the phase III Hokusai VTE Cancer clinical trial compared edoxaban with dalteparin for VTE treatment in patients with active cancer, and the results showed that edoxaban therapy was associated with low rates of recurrent VTE and major bleeding among patients with active cancer receiving extended anticoagulant therapy beyond 6 months.[47] Anticoagulation may be continued indefinitely in these patients,[21,23] however they should be assessed regularly to ensure the safety and efficacy of treatment.[23] The frequency of CAT evaluation is recommended to be every 6 months.[5]

The Expert Panel, based on international guidelines, available clinical evidence and extrapolation from patients with unprovoked VTE, recommends that extending anticoagulation beyond 6 months may be considered for patients at high risk of recurrence with active cancer.[21]

The renal elimination rates of edoxaban, rivaroxaban and apixaban are 50%, 35%, and 27%, respectively. Edoxaban has the highest rate of renal elimination, so it must be decreased to 30 mg once daily when creatinine clearance (Ccr) is between 30 and 50 ml/min.[48] The randomized clinical trials which have compared rivaroxaban, edoxaban, or apixaban with LWMHs have all excluded patients with renal insufficiency (defined as Ccr < 30 ml/min).[33,49,50] According to the NCCN guidelines, rivaroxaban, edoxaban and apixaban should not be used when the Ccr is < 30 ml/min.[2]

NOACs consensus statements:

- NOACs, such as rivaroxaban, apixaban and edoxaban, are preferred over LMWHs [except for patients with gastrointestinal (GI) cancer or active GI lesions].
- Treatment on an outpatient basis with a single-drug approach is preferred.
- A once-daily dosing regimen leads to better drug compliance.

- Treatment for an extended period beyond 6 months should be considered.

Management of CAT in patients with hematologic malignancies

Thrombocytopenia is a serious concern in patients with cancer. It can be transient due to chemotherapy or chronic due to the infiltration of tumor cells into the bone marrow, immune-mediated thrombocytopenia, disseminated intravascular coagulation or microangiopathic hemolytic anemia.[51] Patients with hematologic malignancies usually receive intensive chemotherapy which can induce severe thrombocytopenia, so using anticoagulants in these patients requires extra caution.

Absolute contraindications to anticoagulation therapy in patients with hematologic cancer include recent central nervous system bleeding, an intracranial or spinal lesion with high risk of bleeding, and active major bleeding. Relative contraindications include chronic, clinically significant measurable bleeding for more than 48 hours, severe platelet dysfunction, recent major surgery, underlying hemorrhagic coagulopathy, a high risk of falls, neural anesthesia and interventional spine and pain procedures.[52] When the platelet count drops below 50,000/μL, NOACs or LMWHs should be withheld until recovery to more than 50,000/μL.[2]

Prophylaxis for CAT may be considered in high-risk populations, such as Caucasian patients with multiple myeloma who are receiving thalidomide or lenalidomide combined with high-dose steroids.[2,52] However, such patients in Taiwan have a lower risk of CAT.[53] Therefore, routine prophylaxis in Taiwan may not be necessary.

Management of CAT in upper GI malignancies

NOACs exert an anticoagulation effect not only by systemic absorption through the GI tract, but also by local effects on intestinal mucosa. In the Hokusai VTE Cancer and SELECT-D studies, edoxaban and rivaroxaban, respectively, were associated with more gastrointestinal bleeding than LMWHs in patients with upper GI cancers.[2,47] In the Caravaggio study, the frequencies of major gastrointestinal bleeding were similar between apixaban and dalteparin. However, the sample size of GI tract cancer was too small to make a solid conclusion.[33] This suggests that using NOACs in patients with upper GI cancers requires caution and careful monitoring,[46] especially in those who have active gastric or gastroesophageal lesions. LMWHs may be considered in such patients.[2]

A recent retrospective study in Taiwan compared the use of LMWHs and NOACs in patients with CAT, and the results showed that NOAC and LWMH treatment resulted in a similar risk of recurrent VTE and major bleeding, both in patients with GI cancers and non-GI cancers. Using NOACs was associated with a significantly lower rate of GI bleeding. A possible explanation is that racial differences may be associated with different risks of GI bleeding in patients treated with NOACs or LMWHs for CAT.[55] Because of its retrospective study design, a validation study is required to confirm the results.[56]

Upper GI malignancy consensus statements:

- Patients with active primary upper gastric or gastroesophageal tumors may have an increased risk of GI bleeding with NOACs. Monitor these patients closely.
- LMWHs may be considered for patients with gastric or gastroesophageal lesions.

CAT prophylaxis

The decision to use anticoagulation for the prophylaxis of CAT should be informed by a valid stratification of risk, as there is a need to balance the benefits of preventing CAT with the risks of bleeding complications. Multiple risk assessment models have been proposed to identify patients who have an increased risk of CAT. The Khorana score is the most widely used prediction model, and is based on five criteria: type/site of cancer, prechemotherapy platelet count $\geq 350 \times 109$/L, hemoglobin < 10 g/dL and/or prechemotherapy erythrocyte and leukocyte count > 11,000/UL, and body mass index ≥ 35 kg/m^2.[56] However, several studies have shown that this score cannot adequately predict risk, has poor usability, and fails to consider ethnic differences.[57]

Recently, two phase III clinical trials, CASSINI and AVERT, evaluated the efficacy and safety of NOACs for thromboprophylaxis in ambulatory cancer patients with a Khorana score ≥ 2.[57,58] In the CASSINI trial, treatment with rivaroxaban, compared with placebo, led to a substantially lower incidence (2.6% vs. 6.4%) of CAT during the intervention period.[58] In the AVERT trial, apixaban therapy significantly lowered the rate of CAT compared with placebo (4.2% vs. 10.2%).[57] In both trials, the mod-

est reduction in CAT occurrence did not outweigh the increased risk of bleeding in patients with a Khorana score ≥ 2. Since the two studies enrolled very few Asian patients, the results may not be wholly applicable to Taiwanese patients. The study findings demonstrate that the key issue is selecting the high-risk patients who would benefit from CAT prophylaxis.

The CATScore is an externally validated clinical prediction model for CAT which uses tumor-site category and D-dimer concentration.[17] A study using the CATScore on the AVERT trial population found that a 6-month CAT risk threshold of ≥ 8% improved the efficiency of risk-targeted thromboprophylaxis, where the number needed to treat to prevent one CAT event was only six.[17]

Neither the Khorana score nor CATScore considers ethic differences. The SAVED score, a VTE assessment model for patients with multiple myeloma treated with immunomodulatory drugs, incorporates race as a factor.[59] However, it cannot be applied to patients with solid cancers.

A risk stratification scoring system by Taiwanese specialists has been established based on Taiwan National Health Insurance data. This system, scoring age and sex, prior history of VTE, and cancer subtypes classifies patients with cancer into four risk categories: very low risk, low risk, intermediate risk, and high risk, with incidence rates of CAT in each category of 0.5%, 0.9%, 1.5% and 8.7%, respectively. This risk scoring system could be helpful in deciding whether to give thromboprophylaxis to patients with cancer.[6] However, it has not been validated in prospective clinical trials. Meanwhile, most of the aforementioned scoring systems may not be adequate to evaluate the long-term risks of CAT.

Prophylaxis consensus statements:

- Risk assessment for CAT may be done using a scoring tool, but they should be applied and interpreted cautiously.
- Routine pharmacologic thromboprophylaxis should not be offered to all outpatients with cancer.

Drug interactions with NOACs

NOACs have significantly fewer drug interactions than warfarin. However, chemotherapy drugs that strongly affect cytochrome P450 3A4 (CYP3A4) enzyme and/or transporter permeability glycoprotein (P-gp) can alter the plasma concentration of NOACs, and lead to clinically significant alterations in the anticoagulant effects. This may either increase toxicity and bleeding or decrease the effectiveness of NOACs (Table 3).[1,60,61] If strong drug interactions between cancer therapy and oral anticoagulants are identified, LMWHs can be an alternative treatment.[2]

Please note that the list of drugs in Table 3 is not

Table 3. Common oncology drugs with possible interactions with NOACs[1,60,61]

No/minimal interaction: No effect on NOAC dosage	Enhances effect of NOAC: Consider dose reduction	Impairs effect of NOAC: Use full dose regimen	Strong interaction: Avoid concomitant use
• Antimetabolites: methotrexate, analogs of purines and pyrimidines (such as 5-fu gemcitabine). • Topoisomerase inhibitors: topotecan, irinotecan, etoposide. • Anthracyclines: daunorubicin, mitoxantrone. • Alkylating drugs: busulfan, bendamustine, chlorambucil, melphalan, carmustine. • Platinum preparations: cisplatin, carboplatin, oxaliplatin. • Intercalating drugs: bleomycin, mitomycin C. • Tyrosine kinase inhibitors: erlotinib, gefitinib. • Immunomodulatory drugs: everolimus, sirolimus.	• Immunomodulatory drugs: cyclosporin. • Hormonal drugs: tamoxifen. • Alkylating drugs: ifosfamide, cyclophosphamide. • Tyrosine kinase inhibitors: nilotinib, dasatinib.	• Antimitotic drugs: docetaxel, vincristine, vinorelbine, paclitaxel (for rivaroxaban and apixaban). • Monoclonal antibodies: bevacizumab. • Immunomodulatory drugs: prednisone, thalidomide, lenalidomide.	• Hormonal drugs: abiraterone (increase of activity), enzalutamide (weakening of effect). • Tyrosine kinase inhibitors: imatinib, crizotinib (potentiation). • Antimitotic drugs: vinblastine (weakening of action). • Anthracyclines: doxorubicin (weakening of effect). • Immunomodulatory drugs: dexamethasone (weakening of effect).

NOAC, non-vitamin K antagonist oral anticoagulant.

comprehensive; if any drug is not mentioned, please refer to a drug interaction checker, such as WebMD (https://www.webmd.com/interaction-checker/default.htm).

Interaction consensus statements:

- Identify all possible drug-drug interactions with NOACs by evaluating current systemic therapy (e.g. cancer therapy).
- The concomitant use of strong dual inhibitors/inducers of CYP3A4 and P-glycoprotein should be avoided with NOACs.

Management of NOAC-associated bleeding

The ISTH defines major bleeding as bleeding that; leads to death, occurs in a critical site (e.g. brain), or results in a blood transfusion of two or more units of packed red cells.[62] Nonmajor clinically relevant (NMCR) bleeding is bleeding that does not meet the criteria for major bleeding, but still requires a medical intervention or affects the patient's daily activities.[62] Minor bleeding is defined as any other overt bleeding episode that does not meet the criteria for major or NMCR bleeding.[62]

Patients with active bleeding should receive supportive measures, such as mechanical compression or minor surgery, to achieve hemostasis (Figure 2). Hemodynamic status, blood pressure, blood coagulation parameters, blood count and kidney function should also be assessed. For minor events, dose delay of one dose or one day may be done until bleeding regresses. For those with NMCR bleeding, the bleeding should be stopped and fluid replacement and blood transfusion considered.[63] Anticoagulation reversal should only be considered in patients with life-threatening major bleeding or those needing urgent invasive procedures. However, all anticoagulation reversals are associated with a higher risk of VTE.

Physicians are familiar with using protamine and vitamin K to reverse the effect of heparins and VKAs, respectively. In contrast, the reversal of NOACs is more complex. If the latest dose of NOACs was taken within 2 hours, oral charcoal can be considered and repeated for up to 6 hours to decrease absorption. Idarucizumab is an antidote for dabigatran, and andexanet alfa is an antidote for apixaban and rivaroxaban, although it is not currently available in Taiwan. However, these reversal drugs may be associated with thromboembolism.[2] In addition, one of the three available prothrombin complex concentrates (PCC) can be considered for the reversal of

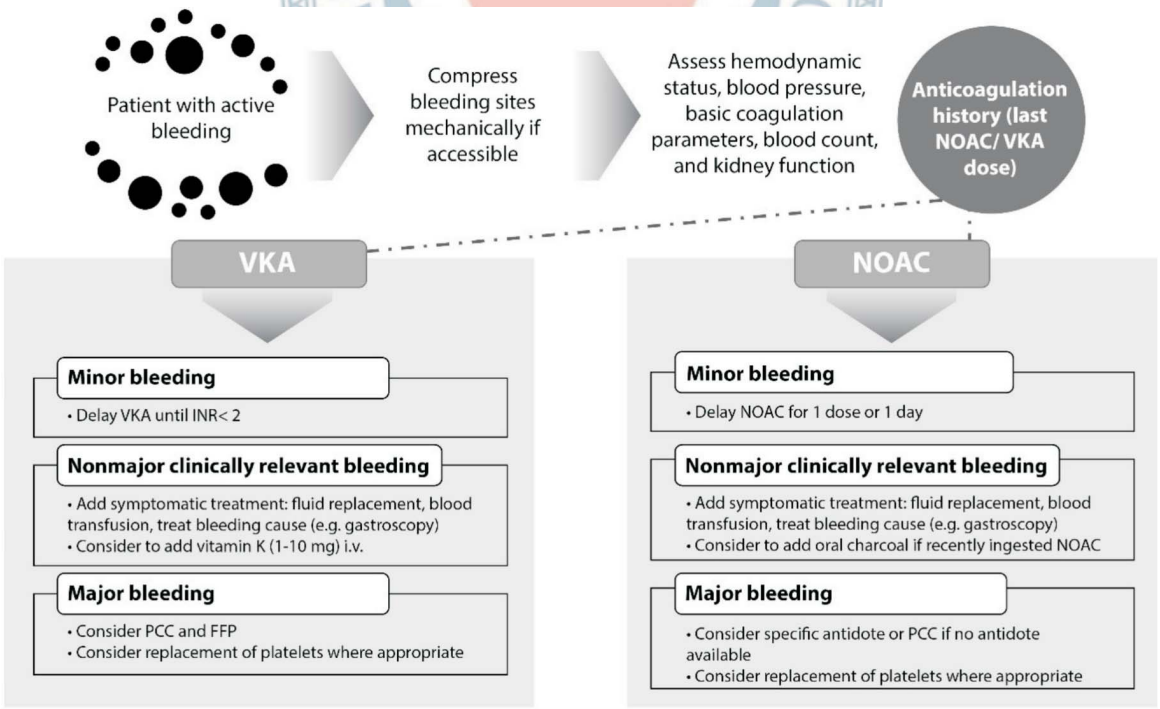

Figure 2. *Steps to manage active bleeding in patients on anticoagulation therapy.[63] FFP, fresh frozen plasma; INR, international normalized ratio; i.v., intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; PCC, prothrombin complex concentrates; VKA, vitamin K antagonist.*

direct factor Xa inhibitors: the activated PCC FEIBA®, and the 4-factor PCCs Profilnine® and Beriplex®.[2,63] PCCs can be beneficial for blood coagulation and can be effectively applied in cases of severe life-threatening bleeding or urgent surgery.[18,21,63,64] However, activated PCC and 4-factor PCC are not indicated as reversal drugs for NOACs and may contribute to a higher risk of thromboembolism. They have to be used with caution.[2,64]

Patients undergoing a planned invasive procedure

NOACs should be discontinued temporarily in patients undergoing surgery or an invasive procedure. NOACs should be withheld for at least 48 hours prior to a procedure with major bleeding risk and at least 24 hours prior to a procedure with minor bleeding risk, in patients with normal kidney function. For patients with severely impaired kidney function (Ccr 15-30 mL/min), it is recommended to interrupt factor Xa inhibitors for at least 36 hours and 48 hours prior to interventions carrying a minor and major bleeding risk, respectively. In general, NOACs can be resumed 6 to 8 hours following a procedure with immediate and complete hemostasis. However, for some procedures, resuming the full dose of anticoagulant therapy within the first 3 days increases the risk of bleeding. Careful monitoring is advised.[48]

NOAC-associated bleeding consensus statements:

- NOAC-associated bleeding in patients with CAT should be managed with standard interventions (e.g. mechanical compression, hemostasis, fluid/blood replacement) or antidotes, if available.
- Assess risk factors for bleeding, such as chemotherapy-induced thrombocytopenia, before starting treatment.

SUMMARY

Cancers highly predispose patients to thromboembolic diseases and may lead to poor survival. Asian populations, particularly in Taiwan, have a lower incidence of CAT compared with Western populations, but have similar outcomes in terms of mortality. LMWHs are recommended to treat CAT, but they are limited by the mode of administration and adverse events. NOACs, especially those administered via a single-drug approach and given once daily, are generally preferred by patients, and can improve compliance in patients without GI cancer or active GI lesions.

CONFLICT OF INTEREST

This study was supported by the Taiwan Society of Cancer Palliative Medicine; and it was the listed authors who developed the content and Yu-Yun Shao finalized the manuscript. All the authors declare no conflict of interest.

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