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ABOUT COVER

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MINIREVIEWS

Facing the challenge of venous thromboembolism prevention in patients undergoing major abdominal surgical procedures for gastrointestinal cancer

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Abstract

Venous thromboembolism (VTE) refers to a hypercoagulable state that remains an important and preventable factor in the surgical treatment of malignancies. VTE includes two identical entities with regards to deep vein thrombosis and pulmonary embolism. The incidence of VTE after major abdominal interventions for gastrointestinal, hepato-biliary and pancreatic neoplastic disorders is as high as 25% without prophylaxis. Prophylactic use of classic or low-molecular-weight heparin, anti-Xa factors, antithrombotic stocking, intermittent pneumatic compression devices and early mobilization have been described. Nevertheless, thromboprophylaxis is often discontinued after discharge, although a serious risk may persist long after the initial triggering event, as the coagulation system remains active for at least 14 d post-operatively. The aim of this review is to evaluate the results of the current practice of VTE prevention in cancer patients undergoing major abdominal surgical operations, with special attention to adequately elucidated guidelines

and widely accepted protocols. In addition, the recent literature is presented in order to provide an update on the current concepts concerning the surgical management of the disease.

Key words: Deep vein thrombosis; Pulmonary embolism; Gastro-intestinal cancer; Thromboprophylaxis; Venous thromboembolism

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Core tip: Venous thromboembolism (VTE) refers to a hypercoagulable state that remains an important and preventable factor in the surgical treatment of malignancies. The incidence of VTE after major interventions for gastro-intestinal, hepatobiliary and pancreatic neoplastic disorders is as high as 25% without prophylaxis. Prophylactic use of classic or low-molecular-weight heparin, anti-Xa factors, antithrombotic stocking, intermittent pneumatic compression devices and early mobilization have been described. The aim of this review is to evaluate the results of the current practice of VTE prevention in cancer patients undergoing major abdominal surgical operations, with attention to adequately elucidated guidelines and widely accepted protocols.

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INTRODUCTION

Venous thromboembolism (VTE) refers to a hypercoagulable state that remains an important and preventable factor in the surgical treatment of malignancies. VTE includes two identical entities with regards to deep vein thrombosis (DVT) and pulmonary embolism (PE)[1]. The incidence of VTE after major abdominal intervention for gastrointestinal (GI), hepatobiliary and pancreatic (HPB) neoplastic disorders is as high as 25% without prophylaxis[2]. Associated immobility, the Trendelenburg position, abdominal surgical procedure, potential compression of the vena cava, placement of intravenous catheters and chemotherapy have been proposed as major determinants of hypercoagulation and VTE prevalence. Neoadjuvant chemoradiotherapy followed by surgical resection as well as laparoscopic techniques have also been implicated. Recent surveys suggest that mechanical and pharmacological prophylaxis is effective in preventing post-operative VTE[3]. Prophylactic use of classic or low-molecular-weight heparin (LMWH), anti-Xa factors, antithrombotic stocking, intermittent pneumatic compression devices and early mobilization have been alternatively described[4]. Nevertheless, thromboprophylaxis is interrupted early in many cases, while relevant risk may exist long after discharge, as the activation of the coagulation system persists for at least 2 wk post-operatively. In 2007, the American Society of Clinical Oncology (ASCO) suggested an evidence-based clinical practice for the prophylactic and therapeutic approach to VTE. A subsequent update has recently been reported. However, there is still debate about the choice and duration of the appropriate anticoagulation therapeutic approach. Both guidelines recommend consideration of extended prophylaxis in high-risk patients, despite the lack of a relevant, specific definition[5]. The aim of this study was to elucidate the results of the current practice of VTE prevention in cancer patients undergoing major abdominal surgical operations, with special attention to adequately evaluated guidelines and widely accepted protocols. In addition, recent literature is presented to provide an update on current concepts in surgical management of the disease.

HISTOLOGY AND PATHOGENESIS

Although several predisposing factors in DVT have been meticulously investigated, mechanisms of thrombus development remain unclear. The classic Virchow triad refers to the combination of blood flow restriction, a hypercoagulable state and prothrombotic alterations in the vessel wall, and plays a pivotal role in thrombosis initiation[6]. Traditionally, a blood clot contains a mishmash of platelets, red blood cells and fibrin. Arterial clots are usually created under high shear stress after rupture of an atherosclerotic plaque or other vascular destruction. As they are platelet-rich, administration of antiplatelet drugs is often implemented. In contrast, venous clots are fibrin-rich and develop under lower shear stress on the surface of a macroscopically intact endothelium. The therapeutic approach always involves anticoagulant drug administration[7]. Disturbed blood flow remains a significant risk parameter, as it can provoke DVT due to long-term immobilization[8]. Hypoxia activates the endothelium, promotes the release of Weibel-Palade bodies (storage granules in endothelial cells), and facilitates blood coagulation. Weibel-Palade bodies are also responsible for the production of the von Willebrand factor, which has an important pathogenetic role in platelet recruitment.

The blood coagulation cascade is well-defined and divided into the extrinsic and intrinsic pathways. Deficiencies in the anticoagulants antithrombin and proteins C and S constitute significant genetic risk factors that contribute to the development of a hypercoagulable condition. Mild genetic alterations in von Leiden factor, prothrombin G20210A and fibrinogen C10034T predispose patients to decreased fibrinolysis[9]. It is common knowledge that the most frequent site of thrombus formation is the valve pocket sinus due to its vertical blood flow and inadequate oxygen tension. Therefore, small thrombi initiated within the valve pocket develop slowly and extend along the inside of the vein wall, resu-

lting in vascular occlusion. It has been proposed that, under abnormal conditions, tissue factor (TF) is expressed on both circulating leukocytes and activated endothelial cells together with the platelet inhibitors nitric oxide and prostacyclin[10]. In addition, recent surveys demonstrate that neutrophils accelerate thrombosis by releasing serine proteases that inactivate the anticoagulant TF pathway inhibitor, suggesting that interfering with the binding of leukocytes to the activated endothelium may represent a promising therapeutic strategy against DVT. Finally, post-thrombotic syndrome describes chronic venous insufficiency following DVT and is attributed to venous hypertension, which may result from persistent thrombotic occlusion or venous valvular reflux due to a previous thrombotic condition[11]. Additionally, inflammation may contribute to successive venous valvular damage.

CLINICAL PRESENTATION

Considering that VTE encompasses two clinical conditions, including DVT and PE, clinical findings refer to both nosologic entities. DVT typically presents with pain and lower limb oedema, the latter being the most specific symptom. If the thrombus is located in the ileac bifurcation, pelvic veins or the inferior vena cava, bilateral rather than unilateral oedema is usually apparent. Moreover, high partial obstruction often causes moderate oedema imitating that of heart, liver or renal insufficiency[12]. Pain with tenderness occurs in the majority of affected patients. Relevant clinical signs are considered nonspecific and remain independent of the size, location and extent of the thrombus. Warmth of the related limb, locoregional erythema, or discoloration and dilation of superficial veins may also be apparent. Homan's sign (calf pain on dorsiflexion of the foot) also presents in 50% of patients with DVT[13]. Furthermore, DVT should be differentially diagnosed from various other diseases including cellulitis, Baker's cyst, musculoskeletal injury, neoplasm, lymphedema, hematoma, sarcoma, venous or arterial aneurysms, and connective tissue disorders[14]. Finally, a very uncommon but hazardous form of DVT is Phlegmasia Cerulea Dolens, which is the consequence of extensive thrombotic occlusion of the major and collateral veins of a lower extremity, including the ileac and femoral veins. It is characterized by acute onset of pain, oedema, blue discoloration and swelling of the affected limb, which, if left untreated, will result in foot gangrene[15].

As far as PE is concerned, aetiology refers to air, septic and amniotic fluid emboli. Relevant clinical findings may vary from deadly hemodynamic collapse to progressive dyspnoea, and most patients with PE present with obscure symptoms. Taking into consideration the aforementioned clinical evidence, common signs of PE include sudden dyspnoea (73%) that worsens with exertion, pleuritic chest pain (66%) deteriorating with inhalation, or exertion and a productive cough (37%) that may lead to haemoptysis (13%)[16]. Similar findings upon physical examination include tachypnoea, rales, tachycardia, fever, cardiac galloping, lower limb oedema and cyanosis.

DIAGNOSTIC MODALITIES

Several imaging studies have been proposed for DVT diagnosis. Duplex Ultrasonography (B-mode and Doppler) remains the current first line examination performed, due to non-invasiveness and absence of irradiation or contrast material[17]. B-mode is based on the principle that normal venous structures easily collapse with the pressure applied by the transducer, while veins harboring thrombi will not compress and will therefore be visible. The Doppler color-flow imaging technique can reveal the potential adequacy of blood flow in an area where an isoechoic clot might not be depicted. Sensitivity and specificity are as high as 95% in symptomatic patients, but diminish with obesity, small and peripheral thrombi, as well as asymptomatic disease[18].

Venography with pedal vein cannulation, injection of contrast material, and serial limb radiographs remains the diagnostic modality of choice for DVT verification, with sensitivity and specificity reaching 100%. However, this technique is invasive and may induce serious consequences, such as hypersensitivity reactions, superficial phlebitis and renal toxicity. Another modality applied is Impedance Plethysmography, which is sensitive and specific in proximal vein thrombosis. It measures the electrical resistance of the calf, which reflects changes in blood volume[19]. Spiral multidetector-row CT venography from the popliteal fossa provides adequate diagnostic accuracy in association with sonographic assessment. Finally, magnetic resonance imaging remains the modality of choice for suspected ileac vein or inferior vena cava thrombosis, especially when CT venography is contraindicated or technically difficult[20]. Radiolabelled peptides that tend to connect to various thrombus components have also been studied. Apcitide, a technetium-labelled platelet glycoprotein IIb/IIIa receptor antagonist, is proposed for diagnostic investigations of DVT. Diagnostic modalities related to DVT detection are summarized in Table 1.

With regard to PE, common electrocardiographic abnormalities, including tachycardia, nonspecific ST-T disorders, right heart strain, atrial fibrillation and S_1 Q_3 T_3 pattern, are encountered in the minority of affected patients[21]. CT pulmonary angiography (CTPA) is considered as the initial imaging modality of choice for stable patients[22]. CTPA reveals emboli as an intraluminal filling defect after injection of contrast material, is non-invasive and widely available, and provides invaluable information for differential diagnosis[23]. Sensitivity and specificity are disproportionate to the size of the affected pulmonary artery. Nevertheless, PA is the criterion standard for diagnosing PE. With the use of contrast material, a filling defect or a sharp cut-off of the problematic artery is detected in anterior, posterior and lateral studies[24]. Essential to verifying PE, Ventilation/

Table 1 Diagnostic modalities applied for deep vein thrombosis detection

Deep vein thrombosis	U/S (B-mode)	U/S (Doppler)	Venography	Impedance plethysmography	CTV	MRI	Radiolabeled peptides
Mechanism of action	Veins with thrombi do not compress	Absent or abnormal blood flow when a thrombus is present	Pedal vein cannulation and injection of contrast material	Measures electrical resistance of the calf reflecting blood volume change	Spiral multidetector CT venography from popliteal fossa to the pelvis	-	Radiolabeled peptides that bind to various components of a thrombus
Sensitivity and specificity	95%	95%	100%	Sensitive and specific in proximal vein thrombosis	-	-	-
Advantages	Non-invasiveness Absence of radiation or contrast material	Non-invasiveness Absence of radiation or contrast material	High sensitivity and specificity	-	-	Ileac vein or inferior vena cava thrombosis, when CT venography is contraindicated or technically inadequate	Apcitide, a technetium-labeled platelet glycoprotein IIb/IIIa receptor antagonist
Disadvantages	Obesity, small peripheral thrombi, asymptomatic disease	Obesity, small peripheral thrombi asymptomatic disease	Invasiveness Hypersensitivity reactions Renal toxicity	-	Correlation with sonographic findings	-	Expensive

CTV: Computed tomography venography; MRI: Magnetic resonance imaging.

Perfusion Scanning may be used when CTPA or Pulmonary Angiography are contraindicated[25]. Finally, PE demonstrates increased signal intensity within the pulmonary artery during magnetic resonance angiography with intravenous administration of gadolinium. Sensitivity and specificity are high for central, lobar, and segmental emboli, while sub-segmental emboli render magnetic resonance angiography inadequate[26] (Table 2).

THERAPEUTIC APPROACH

VTE remains the second most common cause of death in cancer patients and constitutes an independent prognostic factor for mortality[27]. Moreover, recurrent VTE and major bleeding complications are higher in cancer patients, even if they receive anticoagulation therapy. Patients with upper GI malignancies, such as hepatobiliary and gastroesophageal cancer, are in great danger of VTE, with pancreatic cancer presenting the highest VTE prevalence. In advanced pancreatic cancer patients, relevant risk is as high as 25%, and asymptomatic VTE incidence is up to 60%. GI cancers are frequently treated with antiangiogenic or chemotherapeutic agents, such as cisplatin and irinotecan, which are associated with increased risk for VTE as well as combined neoadjuvant chemoradiotherapy[28]. It is estimated that chemotherapy provokes an inflammatory response due to endothelial disruption. In particular, IL-1 and TNF-a, among other cytokines, diminish the concentration of anticoagulant proteins, such as antithrombin Ⅲ and protein C. The procoagulant reaction is reinforced by increased TF expression, and is maintained for up to 6 mo after induction of chemoradiation, thus implying an increased long-term risk for VTE[29]. Major abdominal cancer surgery is also a risk factor for VTE, even after hospital discharge and discontinuation of the usual perioperative prophylaxis[30]. As for laparoscopic surgery, there is still no consensus as to whether the laparoscopic or open techniques abate morbidity related to VTE. Some investigators state that the risk is lessened due to overall reduction in postoperative morbidity, while others claim that the impact of pneumoperitoneum increases the risk, due to compression of the inferior vena cava and iliac veins. However, existing trials are not adequate to reliably evaluate these findings[31].

Pharmacologic thromboprophylaxis is strongly recommended in patients with GI cancer undergoing major surgery, as risk reduction up to 80% has been proven for VTE. Current guidelines suggest LMWH as the standard of care. ASCO recommendations propose unfractionated heparin, fondaparinux or LMWH as a first-line treatment, unless contraindicated due to high bleeding risk or active bleeding. Prophylactic dosages at levels of 3000-5000 anti-Fxa units per day have proven more effective than and as safe as lower doses. Treatment should begin 12-24 h pre- or 6-24 h postoperatively and last 7-10 d. The combination of pharmacologic and mechanical prophylaxis, such as compression stockings and intermittent pneumatic compression devices, may be more efficient, especially in the high-risk group of patients. Extended thromboprophylaxis up to 28 d should be taken into serious consideration only in high-risk patients who fulfill the following criteria, including cancer-related stage Ⅲ/Ⅳ, upper GI cancer, histological features of adenocarcinoma, thrombocytosis, leucocytosis, elevated D-dimer and CRP. Patient-related factors refer

Table 2 Imaging modalities for pulmonary embolism verification

PE	ECG	CTPA	V/Q Scan	MRA
Findings	Sinus tachycardia Non-specific ST-T disorders S1Q3T3 pattern Atrial fibrillation Right heart strain	Intraluminal filling defect of pulmonary artery after injection of contrast material	Ventilated area not perfused	Increased signal intensity of pulmonary thrombi within pulmonary artery after injection of gadolinium
Advantages	Immediate Costless	Criterion standard for diagnosis	Radiation dose lower than CTPA	High sensitivity and specificity for central, lobar, and segmental emboli
Disadvantages	Low sensitivity and specificity	Invasiveness Hypersensitivity reactions Renal toxicity	-	Inadequate for subsegmental emboli

CTPA: CT pulmonary angiography; V/Q: Ventilation/perfusion; MRA: Magnetic resonance angiography.

to ages older than 60 years, obesity, previous history of VTE, surgery lasting 2 h or longer, prolonged postoperative immobilization, and presence of infection or fever. Treatment-related determinants include chemotherapy, central-line or port catheter, parenteral nutrition and radiation therapy. On the other hand, European Society of Molecular Oncology (ESMO) guidelines do not suggest fondaparinux as the first line of treatment and recommend extended prophylaxis up to 28 d for all cancer patients undergoing abdominal or pelvic surgery. Given these differentiations, the newest ESMO and ASCO guidelines consort with each other. American Society of Haematology and Australian Government National Health and Medical Research Council recommendations coincide with ASCO guidelines, while Mayo Clinic VTE Prevention and Management and German guidelines go along with ESMO proposals.

As far as long-term prevention of VTE is concerned, ASCO guidelines suggest the use of LMWH as the standard of care. If this is unavailable, vitamin K antagonists (VKA) are used. Novel Oral Anticoagulants (NOACs) are currently not suggested for patients with GI cancer and VTE due to the limited data available in patients with malignancy. Treatment should last for 6 mo. ESCO and American Society of Haematology guidelines recommend the use of LMWH for 6 mo. ESCO specifically proposes an initial dose of LMWH 100% for 1 mo and 75%-80% of the initial dose for 5 mo thereafter. Additionally, the Mayo Clinic suggests that anticoagulants should be continued until there is no evidence of active malignancy, either as evidence of imaging or cancer-related treatment, while German guidelines propose LMWH for 3-6 mo and highlight that prophylaxis could last for a lifetime in persistent cancers[32].

Non-vitamin-K NOACs have been introduced in the treatment of VTE associated with GI cancer. As the aforementioned guidelines state, the use of NOACs are currently not recommended due to limited data in cancer patients. On the other hand, available anticoagulants exhibit certain disadvantages. Unfractionated heparin requires platelet monitoring and daily injections, which are highly inconvenient. Also, it is associated with heparin-induced thrombocytopenia, types Ⅰ and Ⅱ, bleeding and osteoporosis. LMWH is contraindicated in renal impairment, adding to its drawbacks. VKA, such as warfarin, require INR monitoring and have multiple drug and food interactions. A narrow therapeutic window, delayed onset of action and bleeding risk render VKA inadequate and inferior to LMWH[28].

The family of NOACs includes dabigatran etexilate, rivaroxaban, apixaban and edoxaban, each one with their own special pharmacokinetics and pharmacodynamics[33]. Dabigatran etexilate is a direct thrombin (factor IIa) inhibitor. It is administered orally and presents a half-life of 12-14 h and a rapid onset of action. Its bioavailability does not exceed 10% (3-7%), and its absorption is facilitated by acids. Its excretion is primarily in urine (80%), so caution is required for patients with renal impairment, as its half-life can be increased up to 34 h. More specifically, it is contraindicated when creatinine clearance (CrCl) is under 30 mL/min. Its clearance is also dependent on the P-glycoprotein transport pathway. In addition, routine monitoring is not required because of predictable pharmacokinetics. In the RE-COVER, RE-SONATE and RE-MEDY phase Ⅲ clinical trials, dabigatran showed non-inferiority to warfarin and superiority to placebo. It is FDA approved for VTE prophylaxis after hip and knee arthroplasty, stroke prevention in patients with non-valvular atrial fibrillation, and VTE treatment. As for adverse effects, dyspepsia is the only one that occurs more frequently with dabigatran than with warfarin[28,33].

Rivaroxaban is a direct inhibitor of factor Xa. It is orally administered and has a half-life of 7-11 h, with a rapid onset of action as well[34]. Its bioavailability is excellent (80%-100%). Significant food interactions have not been reported. It is a substrate of the cytochrome P450 system, especially CYP3A4 and P-glycoprotein, and is excreted by both the renal and hepatic systems, demanding extreme caution in patients with renal or hepatic insufficiency[33]. More specifically, it is contraindicated when CrCl is under 30 mL/min in haemodialysis and in patients with Child-Pugh B or C cirrhosis. Additionally, monitoring is not required. In the EINSTEIN-DVT and EINSTEIN-Extension phase Ⅲ clinical trials, rivaroxaban presented non-inferiority to VKA/LMWH

Table 3 Comparative evaluation of mechanism of action and contra-indications of novel oral anticoagulants

Novel oral anticoagulants	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin (factor IIa) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Route of administration	Per os	Per os	Per os	Per os
Half-life	12-14 h	7-11 h	12 h	8-10 h
Bioavailability	3%-7%	80%-100%	50%	62%
Metabolism	P-glycoprotein	P-glycoprotein Cytochrome P450 system (CYP3A4)	P-glycoprotein Cytochrome P450 system (CYP3A4)	P-glycoprotein Cytochrome P450 system (CYP3A4)
Excretion	Urine (80%)	Urine and HBR	Urine (25%)	Primarily: HBR Secondarily: Urine
Contraindication	CrCl < 30 mL/min	CrCl < 30 mL/min Hemodialysis Child Pugh B and C stage cirrhosis	CrCl < 15 mL/min	
FDA approval	VTE prophylaxis after hip and knee arthroplasty, Non valvular atrial fibrillation VTE treatment	VTE prophylaxis after hip and knee arthroplasty, Non valvular atrial fibrillation VTE treatment	Non valvular atrial fibrillation VTE treatment and prevention after major orthopedic surgery	Non valvular atrial fibrillation VTE treatment and prevention after major orthopedic surgery
Clinical trials	Non-inferiority to warfarin Superiority to placebo	Non-inferiority to VKA/ LMWH Superiority to placebo	-	
Dosage	100-150 mg × 2/24 h	10-30 mg × 1/24 h	2.5-5 mg × 2/24 h	15-30 mg × 1/24 h

HBR: Hepatobiliary route; VTE: Venous thromboembolism; VKA: Vitamin K antagonists; LMWH: Low molecular weight heparin.

and superiority to placebo, respectively. It is also FDA approved with the same indications as dabigatran[28].

Apixaban appears to have the same mode of action and route of administration as rivaroxaban. It has a half-life of 12 h, and a bioavailability of about 50%. It is metabolized by P-glycoprotein, the cytochrome 450 system, and the CYP3A4 pathway. Its excretion is in urine (25%), and the drug is contraindicated when CrCl is under 15 mL/min. Edoxaban inhibits factor Xa and is orally administered. It has a half-life of 8-10 h and good bioavailability (62%). It is excreted primarily by the hepatobiliary route and secondarily in the urine. Also, it is metabolized by both P-glycoprotein and the CYP3A4 pathway. As mentioned for the other NOACs, monitoring is not required. Both apixaban and edoxaban are FDA approved for non-valvular atrial fibrillation, VTE treatment and prevention after major orthopaedic surgery[28,33].

As far as dosing frequency is concerned, dabigatran and apixaban require 110-150 mg and 2.5-5 mg twice a day, respectively, while rivaroxaban and edoxaban necessitate 10-30 mg and 15-30 mg once daily, respectively[33]. Apixaban remains the safest of the NOACs, showing reduced risk of major or clinically-relevant minor bleeding at a statistically significant level, with dabigatran taking the second place. Additionally, apixaban and rivaroxaban pose a significantly lower risk for major bleeding compared with LMWH or VKA, a fact which may be of particular clinical importance[35]. In conclusion, differences between doses of dabigatran and apixaban, as well as the correlations between the safety and timing differences between dabigatran or apixaban and rivaroxaban or edoxaban, are summarized in Table 3.

CONCLUSION

VTE refers to both DVT and PE and is highly associated with malignancy, with HPB and gastric cancer ranking first[36]. CTPA is the initial diagnostic modality, while ultrasonography is preferred for DVT[37]. LMWH is used pre- or 6-24 h postoperatively and should continue for 7-10 d. Extension up to 28 d is highly recommended for major abdominal or pelvic surgical procedures[38-42]. NOACs are promised to revolutionize current treatment and bring together efficacy and many benefits for patients. However, the use of NOACs for VTE prophylaxis is certainly debatable. Potential drug interactions with chemotherapeutic components, GI abnormalities, and hepatic and renal insufficiency remain significant determinants of NOAC administration[43-45]. Therefore, bioavailability may not reach desirable levels[46]. The lack of rapid reversal agents also prevents the use of these agents for invasive procedures and thrombocytopenia. Furthermore, cancer patients are at a greater risk of bleeding than non-cancer patients due to chemotherapy-induced thrombocytopenia and antiangiogenic therapy. Moreover, a reduction in circulating proteins and albumins could influence the binding levels of NOACs. Thus, a comparative study of NOACs with the current curative approach, LMWH, may clarify this dispute.

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