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Management of Venous Thromboembolisms: Part I. The Consensus for Deep Vein Thrombosis

Kang-Ling Wang,[1] Pao-Hsien Chu,[2] Cheng-Han Lee,[3] Pei-Ying Pai,[4] Pao-Yen Lin,[5] Kou-Gi Shyu,[6] Wei-Tien Chang,[7] Kuan-Ming Chiu,[8] Chien-Lung Huang,[9] Chung-Yi Lee,[10] Yen-Hung Lin,[11] Chun-Chieh Wang,[12] Hsueh-Wei Yen,[13] Wei-Hsian Yin,[9] Hung-I Yeh,[14] Chern-En Chiang,[1] Shing-Jong Lin[15] and San-Jou Yeh[2]**

Deep vein thrombosis (DVT) is a potentially catastrophic condition because thrombosis, left untreated, can result in detrimental pulmonary embolism. Yet in the absence of thrombosis, anticoagulation increases the risk of bleeding. In the existing literature, knowledge about the epidemiology of DVT is primarily based on investigations among Caucasian populations. There has been little information available about the epidemiology of DVT in Taiwan, and it is generally believed that DVT is less common in Asian patients than in Caucasian patients. However, DVT is a multifactorial disease that represents the interaction between genetic and environmental factors, and the majority of patients with incident DVT have either inherited thrombophilia or acquired risk factors. Furthermore, DVT is often overlooked. Although symptomatic DVT commonly presents with lower extremity pain, swelling and tenderness, diagnosing DVT is a clinical challenge for physicians. Such a diagnosis of DVT requires a timely systematic assessment, including the use of the Wells score and a D-dimer test to exclude low-risk patients, and imaging modalities to confirm DVT. Compression ultrasound with high sensitivity and specificity is the front-line imaging modality in the diagnostic process for patients with suspected DVT in addition to conventional invasive contrast venography. Most patients require anticoagulation therapy, which typically consists of parenteral heparin bridged to a vitamin K antagonist, with variable duration. The development of non-vitamin K oral anticoagulants has revolutionized the landscape of venous thromboembolism treatment, with 4 agents available,including rivaroxaban, dabigatran, apixaban, and edoxaban. Presently, all 4 drugs have finished their large phase III clinical trial programs and come to the clinical uses in North America and Europe. It is encouraging to note that the published data to date regarding Asian patients indicates that such new therapies are safe and efficacious. Ultimately, our efforts to improve outcomes in patients with DVT rely on the awareness in the scientific and medical community regarding the importance of DVT.

Key Words: Anticoagulants • Deep vein thrombosis • Diagnosis • Treatment

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[1]General Clinical Research Center, Taipei Veterans General Hospital; School of Medicine, National Yang-Ming University; [2]Division of Cardiology, Department of Internal Medicine, Heart Failure Center, Healthcare Center, Chang Gung Memorial Hospital; College of Medicine, Chang Gung University; [3]Department of Internal Medicine, National Cheng Kung University Hospital; College of Medicine, National Cheng Kung University, ; [4]Division of Cardiology, Department of Internal Medicine, China Medical University Hospital; School of Medicine, China Medical University; [5]Division of Cardiovascular Surgery, Department of Surgery, National Cheng Kung University Hospital; [6]Division of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital; [7]Department of Emergency Medicine, National Taiwan University Hospital; [8]Division of Cardiovascular Surgery, Cardiovascular Center, Far Eastern Memorial Hospital; [9]Division of Cardiology, Department of Internal Medicine, Cheng Hsin General Hospital; [10]Department of Cardiovascular Surgery, Department of Surgery, Tri-Service General Hospital; [11]Department of Internal Medicine, National Taiwan University Hospital; [12]Department of Cardiology, Chang Gung Memorial Hospital; College of Medicine, Chang Gung University; [13]Division of Cardiology, Department of Internal Medicine; Kaohsiung Medical University Hospital; [14]Division of Cardiology, Department of Internal Medicine, Mackay Memorial Hospital; Mackay Medical College; [15]Department of Medical Research, Taipei Veterans General Hospital; School of Medicine, National Yang-Ming University.
Address correspondence and reprint requests to: Dr. Pao-Hsien Chu, Division of Cardiology, Department of Internal Medicine, Heart Failure Center, Healthcare Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan. Tel: 886-3-328-1200 ext. 8162; Fax: 886-3-327-1192; E-mail: taipei.chu@gmail.com
*Pao-Hsien Chu and San-Jou Yeh share equal contribution as corresponding authors.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a significant healthcare burden worldwide. For the past 150 years, DVT and PE have been categorized as two separate entities but share a common pathogenesis centered on Virchow's triad of blood flow stasis, vessel wall damage and increased blood viscosity. Actually, both conditions are related aspects of the same dynamic disease process, VTE, that not only share risk factors and treatment but also require a coordinated approach to make the timely diagnosis.[1] In particular, VTE may be lethal as PE may result in acute right ventricular failure.[2-4] In Europe, it has been estimated that more than 500,000 deaths per annum are attributable to VTE or its associated complications.[5] Besides the high fatality rate, VTE also has features of high recurrence rate,[6,7] and intractable thrombogenesis that may cause severe chronic sequela,[8,9] as well as poor patient quality of life.[10] The serious and chronic nature of VTE requires considerable healthcare resources to be properly managed.[11,12] Furthermore, VTE is predominantly a disease that affects the elderly.[13] In fact, the incidence rates of VTE increase exponentially as the patient population increases in age.[14,15] In addition, hospitalized patients undergoing major surgery and patients with acute exacerbations of a variety of medical conditions are at an increased risk for VTE.[16-18] Since a greater proportion of frail elderly patients have either complex medical or surgical conditions, it is expected that an ever-increasing number of patients would be diagnosed with VTE in their coming years.[19,20]

Clinically, it has been long postulated that PE is a sequel of DVT as clots, forming in the lower extremity or pelvic veins, break off and travel into the pulmonary circulation.[21] Indeed, more than 40% of patients with DVT have asymptomatic PE identified by imaging stduies,[1,22] and the majority of patients with fatal PE have demonstrable DVT on autopsy, mostly asymptomatic before death.[23] Even though DVT and PE are part of the same disease, VTE, early mortality rates are considerably different,[14,24,25] particularly a small proportion of patients with PE have substantially worse outcomes within the first 3 months.[2,26] Therefore, the clinical assessment, the diagnostic and therapeutic approaches for PE and DVT are manifestly different.[4]

In this document, experts have reviewed the updated information of DVT regarding epidemiology, diagnostic approaches, and pharmacological management. Ultimately, this document has made consensus recommendations for clinical practices. With these renewed efforts, we hope to remind the medical community of VTE as a mitigable disease that has been long overlooked.

EPIDEMIOLOGY

VTE is a common clinical condition in Western countries, with an incidence of 100 cases or greater in 100,000 person-years.[5,14,25,27] In general, incident symptomatic DVT occurs twice as frequently as incident symptomatic PE.[28,29] Among patients with lower extremity DVT, regardless of symptoms, isolated distal DVT without concomitant proximal extension represents the majority of all diagnoses with this illness.[30-32] However, most of the patients with symptomatic DVT also have extensive and proximal thrombosis.[33]

Studies conducted in various communities have reported that the incidence of DVT ranged from 93-124 cases per 100,000 person-years in West Europe,[25,34] 116 cases per 100,000 person-years in North America,[6] and 52-55 cases per 100,000 person-years in Australia and New Zealand.[35,36] It has been generally perceived that VTE, including DVT, is less common in Asian patients than in Caucasian patients.[36,37] The studies conducted in Asia, primarily in ethnic Chinese populations, consistently reported lower incidences of VTE in Asian patients with rates on average four-fold or more lower than in Caucasian patients.[38] The average incidences were 17, 12, and 6 cases per 100,000 person-years for VTE, DVT, and PE, respectively.[38] However, the information was comparable to data obtained in patients of Asian ethnicity who lived in Western countries.[36,37] The reported incidence of VTE among the general population in Taiwan was 16-17 cases per 100,000 person-years.[15,39] However, comparisons between Asian and Western data should be interpreted cautiously. Owing to the frequently stealthy nature of VTE, the diagnosis requires an elevated level of awareness both from patients and physicians, in conjunction with the comprehensive approaches and the sensitivity and specificity of

diagnostic modalities. The long-time belief that VTE is less common in Asian populations may have provided false reassurance and leads to a lack of awareness.[40] It remains unknown to what extent that the observed differences between Asian and Caucasian patients are genuine or reflect discrepancies between study designs, patient demographics, and physician practices. In addition, population-base epidemiology data has demonstrated yearly increases in incident VTE in Asian patients,[20] particularly in high-risk and elderly patients.[39,41]

Risk factors

DVT, as part of the continuum of VTE, is a multifactorial disease that represents the interaction of genetic and environmental factors. The majority of patients with incident or recurrent VTE have at least one recognized risk factor.[42,43] Common risk factors are listed in Table 1. Acquired risk factors are far more common than inherited thrombophilia. Additionally, advanced age, cancer, immobilization, recent trauma or surgery, and hospitalization are all important risk factors.[44,45]

Orthopedic surgery

Major orthopedic surgeries such as hip fracture repair and total hip/knee arthroplasty, including replacement surgery, represent a substantially high risk for VTE.[19] Prior to the 1980s, while no thromboprophylaxis was conducted, the rates of symptomatic VTE in patients after hip fracture surgery without prophylaxis ranged from 15 to 30%.[46] In the modern era, with thromboprophylaxis in Western populations, symptomatic VTE in patients undergoing major orthopedic surgery was 2.7%, of which 1.5% had DVT.[47] However, it should be noted that the asymptomatic DVT confirmed by venograms was 3 times higher than symptomatic DVT.[48] Recent meta-analysis also suggested that asymptomatic DVT accounted for most of the events in patients after knee arthroplasty.[49]

Customarily, it has been perceived that Asian patients are at a lower risk for VTE following orthopedic procedures.[50] However, evidence supporting an underestimated incidence of VTE in Asia stems from the review of postoperative VTE reported in Asian countries.[40,51,52] Overall, the adjusted incidences of total DVT were 13%, 16%, 50%, and 18% for general surgery, total hip replacement, total knee replacement, and hip fracture surgery, respectively.[40] Regardless of the methodologies used for diagnosing DVT, the reported incidences of post-operative DVT were notably high across Asian countries.[51] The SMART study was a prospective investigation of the incidence of symptomatic VTE up to 1 month postoperative in Asia.[53] Patients undergoing major orthopedic surgery without thromboprophylaxis were included, and patients from Taiwan were jointly enrolled in the study.[54] Among 2,420 Asian patients, postoperative symptomatic DVT occurred in 0.9% of patients; whereas in 326 evaluable venograms, 35.6% of patients had asymptomatic DVT.[54] The AIDA program also showed a similar result to the SMART venography study. Asian patients undergoing total knee replacement had the highest risk for incident DVT.[55] Findings of the SMART and AIDA studies were consistent with Western data.[40] Some studies based upon claims data inferred that the incidence of symptomatic VTE after knee or hip arthroplasty was low in Taiwan.[56,57] However, a single hospital report based on routine postoperative venograms indicated that 63.6% of patients with total knee arthroplasty had DVT, of which the majority were symptomatic distal DVT.[32] The risk of late DVT and thrombosis propagation was similar in patients in Taiwan with isolated distal DVT, or a more complicated DVT.[58] Apparently, further research is needed to elucidate those discrepancies.

Table 1. Risk factors for venous thromboembolism

Advancing age
Obesity
Recent surgery (including hip or knee replacement)
Major trauma (including fracture)
Active cancer
Acute medical illnesses (e.g. heart failure, respiratory failure)
Paralytic stroke or immobilization
Antiphospholipid syndrome
Inherited thrombophilia
Previous venous thromboembolism
Congenital venous malformation
Varicose veins
Central venous catheter or vena cava filter
Long-distance travel
Pregnancy/antepartum
Oral contraceptives or hormone replacement therapy

References[19,21,45]

Medical illness

VTE is also a common complication in patients who suffer critical illness.[59] In Europe and North America, VTE occurred in 14.9% of patients hospitalized for acute illness without thromboprophylaxis, of which 4.9% had proximal DVT on venograms.[60] Symptomatic DVT represented only 10% of the total number of asymptomatic events in patients with acute medical illness.[61] The risk of asymptomatic DVT, including both proximal and distal DVT, proven by venograms was as high as 9.0%.[62] Nevertheless, prospective observations in Asian countries indicated that the rate of symptomatic VTE without thromboprophylaxis in hospitalized non-surgical patients was 1.1%,[63] which was comparable to rates in Western populations.[64]

In addition, most of Asian patients were not assigned with thromboprophylaxis measures in the setting of acute illness or surgical conditions. The low reported incidence of symptomatic VTE may only reflect a reduced awareness by patients and physicians. Finally, autopsy data suggested a similar incidence of PE in Asia and in the West.[65-67] Some of the apparent differences in the incidence of symptomatic VTE between Western and Asian populations probably arose from variations in access to healthcare.[68]

Inherited thrombophilia

The common inheritable factors for thrombophilia include factor V Leiden, prothrombin G20210A, and deficiencies of natural inhibitors.[21,44,69] Factor V Leiden and prothrombin G20210A are more prevalent in Caucasians,[70,71] whereas protein S deficiency is the most common defect, followed by protein C and antithrombin deficiency in Asians.[40] In Taiwan, factor V Leiden and prothrombin genetic mutations are rare conditions; the most common inherited thrombophilia is protein S deficiency regardless of the presence of VTE.[72-75] The ethnic differences in the distribution of genetic predisposition to VTE are shown in Table 2.

It is important to realize the limitations of thrombophilia testing. Diagnosing a heritable thrombophilia has rarely changed the course of patient management. The presence of a heritable thrombophilia increases the risk of first thrombosis in varying degrees,[21] and it does not strongly predict the risk of recurrence after discontinuation of anticoagulation in unselected VTE patients.[19,76,77] It is generally recommended not to offer heritable thrombophilia testing to patients with provoked VTE.[78] In NICE recommendations, the only clear indications to perform heritable thrombophilia testing are when consideration is given to discontinuing anticoagulation following an unprovoked VTE, and for patients with a history of a first-degree relative with VTE.[79]

Recommendations

- Asian patients might have a lower risk for symptomatic VTE compared with Caucasian patients.
- Thromboprophylaxis should be incorporated into the daily care regimen for Asian patients complicated with high-risk medical or surgical conditions.
- Factor V Leiden and prothrombin G20210A mutation are rare in Asian patients with VTE, and therefore should not be routinely tested.

Table 2. Ethnic differences in the distribution of inherited thrombophilias

	Factor V Leiden	Prothrombin G20210A mutation	Protein S deficiency	Protein C deficiency	Antithrombin deficiency
General populations, %					
Caucasians	4.8[71]	2.0,[71] 2.7[40]	0.03-0.13[40]	0.2-0.4[71]	0.02-0.16[71]
Asians	0-0.2[40]	0-0.2[40]	0.06-3.7[40]	0.3-1.1[40]	0-2.3[40]
Taiwanese	NA	NA	6.4[74]	4.0[74]	6.4[74]
Patients with VTE, %					
Caucasians	18.8[71]	7.1[71]	2.3[71]	3.7[71]	1.9[71]
Asians	0[40]	0[40]	10.7-17.8[40]	8.9-10.7[40]	4.7-8.1[40]
Taiwanese	0[72,73,75]	0[73]	3.6,[75] 8.0,[73] 32.9,[72] 33.6[74]	4.0,[73] 10.7,[75] 17.2,[74] 18.8[72]	3.5,[72] 4.0,[73] 5.2,[74] 7.1[75]

NA, not applicable; VTE, venous thromboembolism.

Diagnosis

Venous thrombosis in the lower extremity can involve the superficial leg veins, the deep veins of the calf, and proximal veins, that include popliteal, superficial femoral, common femoral, and iliac veins. DVT at the calf is generally asymptomatic as complete dissolution of small thrombi occurs quite frequently.[30] These thrombi can extend proximally and become dangerous, whereas more proximal DVT results in symptoms associated with venous outflow obstruction, venous or perivascular inflammation, or PE.[80,81]

Diagnosing DVT is an ongoing clinical challenge for physicians. The accurate and timely diagnosis of this disease is mandatory in patients with suspected DVT because thrombi left untreated can result in detrimental PE, whereas anticoagulation in the absence of thrombosis is medically inappropriate. Common symptoms such as pain, swelling and tenderness make it sometimes difficult to distinguish DVT from other medical conditions such as heart failure, local infection, or the popliteal cyst.[82,83] As a result, the clinical diagnosis of DVT has been proven to be surprisingly unreliable.[84]

Contrast venography

Contrast venography is the benchmark for diagnosing DVT.[80] The diagnosis is established based on the presence of a constant intraluminal filling defect on at least two projections. Treatment with anticoagulants could be safely withheld in patients with a technically adequate normal venogram, and only 1.3% of patients developed symptomatic DVT within 3 months.[80] However, venography is invasive, not uniformly available, and has limitations for patients with renal insufficiency and allergic reactions to contrast medium. To illustrate the entire venous drainage of the lower extremity, a dorsal foot vein cannulation is necessary. The technical difficulties frequently encountered have been cannulation failure,[85] and inadequate visualization of a venous segment.[86]

A certain and reliable diagnosis of DVT can only be established by means of imaging. On the other hand, ruling out acute DVT can be safely achieved by using a standardized clinical probability assessment and a D-dimer blood test. The main advantage of such an approach is the reduction in the required number of imaging tests, which are in general time consuming, costly and associated with radiation exposure and other complications. Therefore, venography is currently seldom used, but still serves as a reference standard and should be used if other tests are unable to definitely confirm or exclude the diagnosis of DVT.[87]

Clinical assessment

An important first step is to assess the patient's pretest probability of DVT based on medical history and physical examination. Although several structured clinical probability scoring systems have been developed to stratify patients,[88-91] the system that has been most extensively studied and widely used is the Wells score.[84] This scoring system,which incorporates medical history and physical examination, is listed in Table 3. The rule that originally categorizes patients as having a low, moderate, or high probability of DVT has been extensively validated by more than 8,000 patients.[92,93] A simplified version of the Wells score dichotomizes patients as being unlikely (prevalence of DVT: 6%), or likely (prevalence of DVT: 28%) to have DVT for practical purposes.[94] It has been shown that the Wells scoring system has excellent interobserver reliability, regardless of the extent of physician experience.[84,95] However, except for Japanese population, the Wells score has not yet been extensively validated in Asian populations.[96]

When an extensive clinical history of the patient has

Table 3. MIB-PEDVT-HO2 acronym for Wells prediction rules for diagnosing deep vein thrombosis

Clinical characteristics	Points
Malignancy, active	+1
Immobilization of the lower extremities or paralysis	+1
Bed rest > 3 days or major surgery < 12 weeks	+1
Pitting edema confined to the symptomatic leg	+1
Engorgement of entire leg	+1
Diameter difference on affected calf > 3 cm	+1
Veins (superficial, nonvaricose) dilation of the affected leg	+1
Tenderness along the distribution of the deep veins	+1
History of deep vein thrombosis	+1
Other diagnoses at least as likely as deep vein thrombosis	-2

Three-level clinical probability (low, ≤ 0; intermediate, 1-2; high, ≥ 3) and two-level clinical probability (unlikely, < 2; likely, ≥ 2).
Reference[84,92,94]

been obtained, the clinician can get confirmation of whether any instances of active cancer (**M**alignancy), paraplysis that leads to immobilization (**I**mmobilization of the lower extremities or paralysis), and prolonged bed rest or a recent major surgery (**B**ed rest > 3 days or major surgery < 12 weeks) are major risk factors for DVT and thus related to the patient's course of disease. The presentation indicative of DVT includes leg swelling (**P**itting edema confined to the symptomatic leg and/or **E**ngorgement of the entire leg, and a **D**iameter difference on the affected calf > 3 cm), visible collateral circulation (**V**eins, nonvaricose superficial dilation of the affected leg), and leg pain (**T**enderness along the distribution of the deep veins). A prior history of DVT (**H**istory of deep vein thrombosis) is also an independent risk factor. Finally, if there is an alternative tentative diagnosis other than DVT (**O**ther diagnoses at least as likely as deep vein thrombosis), the likelihood of DVT is decreased. In this instance, the acronym MIB-PEDVT-HO2 is a convenient tool.

D-dimer

The major criticism in using the Wells score to assess DVT probability is the subjective element of considering an alternative diagnosis. This clinical probability can be subsequently supplemented by the combination with a determination of the level of D-dimer for better risk stratification.[94]

Fibrin D-dimer is the degradation product of cross-linked fibrin. D-dimer levels are typically elevated in patients with acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The sensitivity of an elevated level of D-dimer is high, but the specificity is rather moderate.[97] A high D-dimer level is also observed in conditions such as malignancy, infection, pregnancy, post surgery or trauma, and increasing age. Consequently, a negative result can facilitate the exclusion of VTE.[98]

A number of D-dimer assays are available. The meta-analysis of 217 D-dimer tests evaluated for DVT indicated that the sensitivities of the D-dimer enzyme-linked immunofluorescence assay, microplate enzyme-linked immunosorbent assay and latex quantitative assay are 96%, 94%, and 93%, respectively; they are superior to those of the whole-blood D-dimer assay, latex semi-quantitative assay and latex qualitative assay as the sensitivities are 83%, 85%, and 69%, respectively.[99] The higher sensitivity yields a higher negative predictive value and introduces fewer concerns regarding false-negative results. In addition, the age-dependent decrease in specificity of D-dimer with suspected PE was observed.[100] Recent investigations suggested that age-adjusted cut-offs (age × 10 ug/L above 50 years) improved specificity of D-dimer testing in the elderly with suspected PE.[101-103] The European guidelines have adopted the age-adjusted D-dimer cut-offs for the diagnosis of acute PE.[4] The clinical application of the aforementioned aspect regarding D-dimer testing has not been prospectively validated in patients with suspected DVT and not yet endorsed by American guidelines for the diagnosis of DVT.

Compression ultrasound

Compression ultrasound (CUS) is the front-line imaging modality in the diagnostic process for patients with suspected DVT. The sensitivity and specificity of the CUS in diagnosing proximal DVT is 94% and 98%, respectively.[104] However, the sensitivity decreases in detecting asymptomatic proximal DVT with similar specificity.[105] The sensitivity of CUS in diagnosing distal DVT is relatively low, at 57%,[104] and is only 48% for detecting asymptomatic calf vein thrombosis.[105] For proximal DVT, ultrasound studies have a positive predictive value of 100% and 71% for symptomatic and asymptomatic events, respectively, whereas the negative predictive value for symptomatic and asymptomatic events are 100% and 94%, respectively.[106]

Conventionally, 3 protocols are presently available. The proximal CUS (so-called 2-point CUS) assesses compressibility of the femoral and popliteal veins. Loss of compressibility of either segment is diagnostic for incident proximal DVT. The second approach is to conduct a complete CUS along the proximal till distal deep veins of the leg. The prior study suggested that only 0.5% of patients withholding anticoagulation after a single, negative, complete CUS had distal DVT within 3 months and no proximal DVT occurred.[82] Although it has good accuracy, complete CUS is time consuming and a modest proportion of imaging results are inadequate, particularly in the calf veins.[107] As an alternative to the aforementioned measures, repeated proximal CUS after 5-7 days is recommended in patients with an initial negative proximal CUS finding. This approach detects if any distal DVT propagates into the proximal vein that may increase

the risk of PE. The repeated proximal CUS strategy in the intermediate to high-risk patients is safe with regard to withholding anticoagulation.[108,109]

Computed tomography and magnetic resonance imaging

Both computed tomography venography (CTV) and magnetic resonance venography (MRV) are alternatives to CUS as a means to diagnose DVT.[110] In particular, CTV provides direct imaging of the inferior vena cava, pelvic and lower extremity veins immediately after computed tomography pulmonary angiography. Since DVT is the most important risk for PE, it seems ideal that a single examination simplifies and shortens VTE work-up. However, this single comprehensive imaging modality for VTE requires a larger amount of iodinated contrast medium to produce adequate opacification of the pulmonary arteries, and pelvic and lower extremity veins,[111,112] and exposure to ionizing radiation may be greater than for either test alone.[113,114] The pooled analysis showed that for the diagnosis of DVT, in particular proximal DVT, CTV had a sensitivity and specificity of 96% and 95%, respectively.[115] In addition, to facilitate the diagnosis of DVT, MRV has a sensitivity and specificity of 92% and 95%, respectively, and the sensitivity for the diagnosis of proximal DVT increases to 94%.[116]

The sensitivity and specificity of both CTV and MRV for the diagnosis of DVT are comparable to CUS. However, the safety of withholding anticoagulation on the basis of a normal CTV or MTV result has yet to be evaluated prospectively. Furthermore, CTV has generally been tested along with computed tomography pulmonary angiogram in patients with suspected PE. CTV, however, has yet to be more extensively assessed as a standalone diagnostic modality in patients with suspected DVT. Therefore, both imaging modalities should not be routinely used as front-line approaches.[87] It is reasonable to utilize CTV or MRV in conditions that CUS cannot be performed or is less reliable, such as for patients with morbid obesity or casts, and patients with suspected DVT in the iliac or inferior cava vein or suspected venous anomaly.[87,98,117]

Recommendations

- To diagnose DVT requires systematic assessment (Figure 1).
- An acronym of MIB-PEDVT-HO2 for the Wells score is the comprehensive initial to stratify patients.
- The combination of the Wells score and a D-dimer test is validated in deciding whether to initially withhold anticoagulation.
- CUS, either proximal, whole leg or repeated measure-

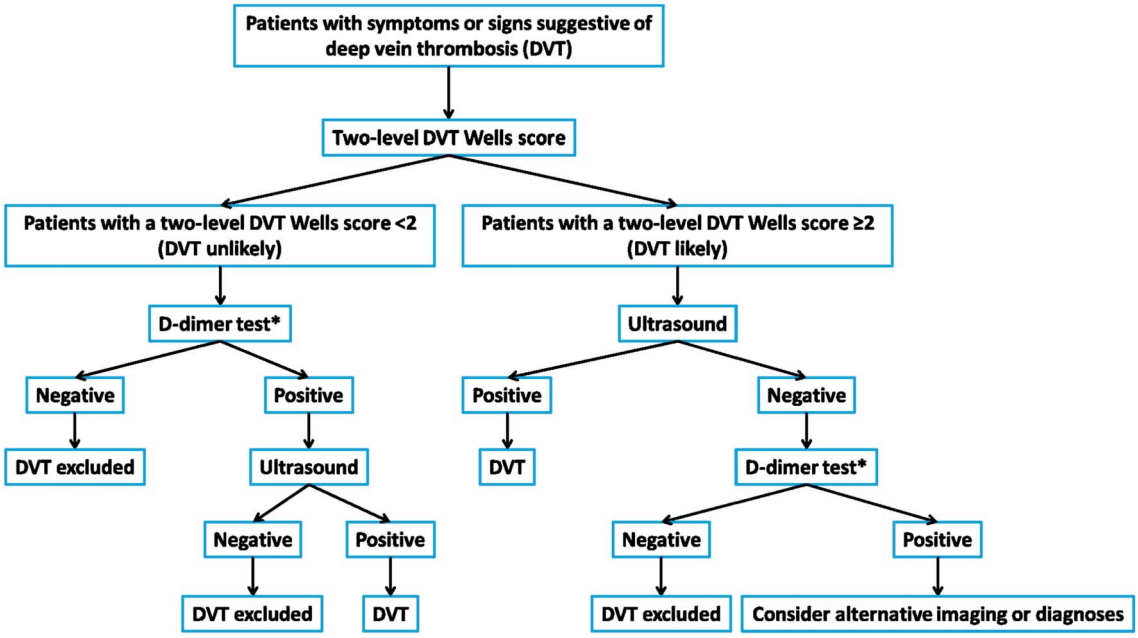

Figure 1. *Diagnosis flowchart. * Moderately or highly sensitive D-dimer test.*

ments, should constitute the first-line imaging for most patients with the increased likelihood of DVT.

- CTV and MRV have similar sensitivities and specificities to CUS in diagnosing DVT. However, those measures should be reserved for conditions where patients cannot be evaluated properly by CUS or thrombosis in pelvic veins, or inferior vena cava is suspected.
- Contrast venography is the reference modality for diagnosing DVT and is reserved for occasions when other tests are unable to definitely establish or exclude DVT.

Treatment

DVT can become complicated with PE, and has a high recurrence at the early stage without treatment.[118] The risk of recurrence and post-thrombotic syndrome (PTS) develop steadily after the first episode of DVT.[7,119] The most effective manner in which to prevent thrombus extension, recurrence and late complications primarily depends on effective pharmacological and/or mechanical treatment.[120]

Thrombolysis

Despite effective anticoagulation, only 20%, 39% and 58% of the patients had normal CUS at 3 months, 6 months and 1 year, respectively.[121] Other studies reported a similar rate of the presence of residual thrombus at 3 months and beyond.[122,123] The presence of residual thrombus has been associated with the risk of recurrence and the occurrence of PTS.[121,124,125] The possibility to reduce thrombus burden and to restore venous drainage in the early stage of DVT in patients with extreme high risk for thromboembolism complications is an appealing one. The evidence suggested that systemic thrombolysis had the potential to reduce PTS at the expense of an increase in major bleeding. As a result, systemic thrombolysis is not generally recommended by the current guidelines.[120,126] A variety of endovascular interventions have been tested in patients with iliofemoral DVT, including catheter-directed thrombolysis (CDT) and/or thrombectomy. CDT reduces PTS at 24 months with a number needed to treat of 7 in a randomized trial that involved 209 patients with iliofemoral DVT.[127] There was no significant reduction in recurrence by CDT in this small-sized trial. However, bleeding is a primary concern of a broad application of thrombolysis.[128] Currently, CDT is preferred for patients with iliofemoral DVT and/or limb-threatening circulatory compromise, acute or subacute symptoms, and a low risk of bleeding.[120,126]

Endovascular thrombectomy and stenting have reduced recurrence and PTS at 30 months compared with anticoagulation only in a randomized trial involving 169 patients with proximal DVT.[129] Whether pharmacomechanical CDT truly reduces recurrence and PTS in patients with proximal DVT is being evaluated currently in a larger trial with a target of more than 600 patients and a primary endpoint of PTS occurrence.[130]

Conventional anticoagulation

The initial and standard pharmacological approach in patients with DVT started with parenteral anticoagulants, either unfractionated or low-molecular-weight heparin, followed by long-term vitamin K antagonists (VKAs). The importance of effective initial parenteral anticoagulants has been emphasized by the results in early trials.[131,132] It has been suggested to start parenteral anticoagulation within a short period of time while waiting for the results of diagnostic tests in patients with intermediate to high clinical suspicion of acute DVT.[120] In general, twice-daily low-molecular-weight heparin (LMWH) administration is preferred over once-daily LMWH administration or unfractionated heparin for a lower risk of inducing major bleeding and heparin-induced thrombocytopenia.[133,134]

An oral VKA is preferably initiated on the same day as the start of parenteral anticoagulants, which should be continued for at least 5 days until the international normalized ratio (INR) is 2.0 or above for 2 consecutive days.[120,135] The targeted INR for VKA treatment is 2.0-3.0. The subtherapeutic dose is associated with higher recurrence,[136] and the occurrence of PTS.[137] To maintain adequate anticoagulation without an excessive risk of bleeding in the use of VKAs, primarily warfarin, is a lesson that every clinician has learned for the past 50 years due to the limitations of new effective treatment.[138]

Non-vitamin K oral anticoagulants (NOACs)

NOACs have been developed to optimize VTE management and overcome the limitations of traditional treatments. Five NOACs have been extensively tested in patients with VTE in clinical trials. Except for ximela-

gatran, which has been withdrawn, rivaroxaban, dabigatran, apixaban, and edoxaban have been approved in North America and Europe for VTE treatment; edoxaban has completed the largest clinical trial ever in VTE treatment. Except for acute treatment, rivaroxaban, dabigatran, and apixaban have been compared with placebo or warfarin in the setting of extended treatment for VTE.

Rivaroxaban

Patients with acute DVT or PE were enrolled in the EINSTEIN program. In the EINSTEIN DVT, 3,449 patients with acute symptomatic DVT were randomized to receive oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by warfarin for 3, 6, or 12 months.[139] In the EINSTEIN PE, 4,832 patients who had acute symptomatic PE with or without DVT, were randomized according to the same protocol.[140] In both the EINSTEIN DVT and EINSTEIN PE, a single-drug approach by rivaroxaban was non-inferior to the standard treatment with regard to VTE recurrence and had no excessive major or clinically relevant nonmajor bleeding.[139,140] In particular, there was no signal of excessive VTE recurrence by day 21, at the end of the twice-daily treatment. The pool analysis of 8,282 patients showed very similar results of separate trials but there was significantly less major bleeding in patients with rivaroxaban compared to the standard therapy (hazard ratio: 0.54; 95% confidence interval: 0.37-0.79, p = 0.002).[141]

Dabigatran

Dabigatran has been tested in 2 trials for acute VTE treatment (RE-COVER and RE-COVER II).[142,143] The RE-COVER series consisted of 2 trials because of low rate of recurrent VTE observed in the first trial with a small population. Dabigatran 150 mg twice daily was compared with warfarin for 6 months after the initial parenteral heparin. There were 2,564 and 2,589 patients with acute VTE enrolled in the RE-COVER and the RE-COVER II, respectively. In both trials, dabigatran was non-inferior to warfarin with regard to recurrent VTE but had significantly less major or clinically relevant nonmajor bleeding (hazard ratio: 0.63; 95% confidence interval: 0.47-0.84, in the RECOVER; hazard ratio: 0.62; 95% confidence interval: 0.45-0.84, in the RECOVER II). The extent of major bleeding was similar in patients with dabigatran or warfarin. The conclusions were consistent in the pooled analysis.[142]

Apixaban

In the AMPLIFY study, 5,400 patients with acute VTE were randomized to receive apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) or subcutaneous enoxaparin followed by warfarin for 6 months.[144] Apixaban, as a single-drug approach, was non-inferior to the standard treatment with respect to recurrent VTE. Both major bleeding or clinically relevant nonmajor bleeding were significantly less in patients with apixaban (relative risk: 0.44, 95% confidence interval: 0.36-0.55, p < 0.001; relative risk: 0.31, 95% confidence interval: 0.17-0.55, p < 0.001, respectively).

Edoxaban

Edoxaban has been compared with warfarin in the largest phase III clinical trial in VTE treatment. In the HOKUSAI VTE, 8,240 patients with acute VTE were randomly assigned to edoxaban (60 mg once daily or 30 mg once daily in patients with renal impairment or low body weight) or warfarin for 3 to 12 months after the initial parenteral heparin.[145] Edoxaban was non-inferior to warfarin with respect to recurrent VTE. Furthermore, edoxaban had significantly less major or clinically relevant nonmajor bleeding (hazard ratio: 0.81; 95% confidence interval: 0.71-0.94, p = 0.004), and had no excessive risk for major bleeding.

The risk of recurrent VTE and bleeding are fundamental considerations for recommendation of VTE management. Although clinical trials of NOACs in VTE treatment have differences with regard to the study designs, the conclusions are rather similar. The design and results of pivotal NOAC trials for VTE treatment are listed in Table 4 and 5. The availability of NOACs that do not require monitoring will create a treatment shift for patients with VTE as an effective, safer, and more convenient treatment for patients, physicians, and healthcare systems.[146] The additional advantage of NOACs against VKAs is that Asians are prone to bleeding when treated with VKAs, and the optimal INR use has yet to be determined in Asian patients.[147,148] In trials evaluating NOACs for stroke prevention in atrial fibrillation, NOACs have

Table 4. Patient characteristics in clinical trials of non-vitamin K oral anticoagulants for venous thromboembolism treatment

	EINSTEIN-DVT		EINSTEIN-PE		RE-COVER		RE-COVER II		AMPLIFY		HOKUSAI-VTE	
	Rivaroxaban	VKA	Rivaroxaban	VKA	Dabigatran	VKA	Dabigatran	VKA	Apixaban	VKA	Edoxaban	VKA
Number of patients	1,731	1,718	2,419	2,413	1,273	1,266	1,280	1,288	2,691	2,704	4,118	4,122
Design	Open-label		Open-label		Double-blinded		Double-blinded		Double-blinded		Double-blinded	
Treatment duration	3, 6 or 12 months*		3, 6 or 12 months*		6 months		6 months		6 months		3, 6 or 12 months*	
Initial treatment	Rivaroxaban 15 mg twice daily for 3 weeks	LMWH ≥ 5 days	Rivaroxaban 15 mg twice daily for 3 weeks	LMWH ≥ 5 days	LMWH or UFH ≥ 5 days		LMWH or UFH ≥ 5 days		Apixaban 10 mg twice daily for 7 days	LMWH or UFH ≥ 5 days	LMWH or UFH ≥ 5 days	
Long-term treatment	Rivaroxaban 20 mg once daily	INR: 2-3	Rivaroxaban 20 mg once daily	INR: 2-3	Dabigatran 150 mg twice daily	INR: 2-3	Dabigatran 150mg twice daily	INR: 2-3	Apixaban 5mg twice daily	INR: 2-3	Edoxaban 60 mg once daily[#]	INR: 2-3
Age, years	56	56	58	58	55	54	55	55	57	57	56	56
Female, %	43	44	46	48	42	41	39	40	42	41	43	43
Index event, %												
DVT	99	99	0	0	69	69	69	68	65	66	60	60
PE ± DVT	1	1	100	100	31	31	31	32	35	34	40	40
Risk factor, %												
Unprovoked	61	63	65	64	NR	NR	NR	NR	90	90	66	65
Prior VTE	19	19	19	20	26	25	19	16	17	15	19	18
Cancer	7	5	5	5	5	5	4	4	2	3	9	10
TTR, %	NA	58	NA	63	NA	60	NA	57	NA	60	NA	64

* Treatment duration was left to the discretion of the treating physician. [#] An edoxaban 30 mg once daily was administered in certain conditions.
DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NA, not applicable; NR, not reported; PE, pulmonary embolism; TTR, time in therapeutic range; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 5. Hazard ratio (95% confident interval) of selected outcomes for non-vitamin K oral anticoagulants in venous thromboembolism treatment

	Rivaroxaban vs. VKAs EINSTEIN pooled analysis	Dabigatran vs. VKAs RE-COVER pooled analysis	Apixaban vs. VKAs AMPLIFY*	Edoxaban vs. VKAs HOKUSAI-VTE
Recurrent VTE	0.89 (0.66-1.19)	1.09 (0.76-1.57)	0.84 (0.60-1.18)	0.82 (0.60-1.14)[#]
Major bleeding	0.54 (0.37-0.79)	0.73 (0.48-1.11)	0.31 (0.17-0.55)	0.84 (0.59-1.21)
Major or CRNM bleeding	0.93 (0.81-1.06)	0.62 (0.50-0.76)	0.44 (0.36-0.55)	0.81 (0.71-0.94)
Death	0.89 (0.67-1.18)	1.00 (0.67-1.51)	0.79 (0.53-1.19)	1.05 (0.82-1.35)

* Relative risks are reported for the AMPLIFY study. [#] Recurrent VTE during on-treatment period.
CRNM, clinically relevant nonmajor; VKA, vitamin K antagonist; VTE, venous thromboembolism.

less critical bleeding than VKAs in Asian patients than in patients with other ethnicities.[147,149,150] In trials evaluating NOACs for VTE treatment, both rivaroxaban and edoxaban have published data of Asian patients.[150,151] Both analyses reconfirmed the similar efficacy and the probable safety advantage of rivaroxaban and edoxaban against dose-adjusted VKAs.

Recommendations

- Timely administration of anticoagulation is essential in the treatment of DVT (Figure 2).
- Conventional treatment involves parenteral heparin bridging to VKAs with a maintenance target INR of 2.0-3.0.
- Two strategies have been tested in 6 pivotal trials of

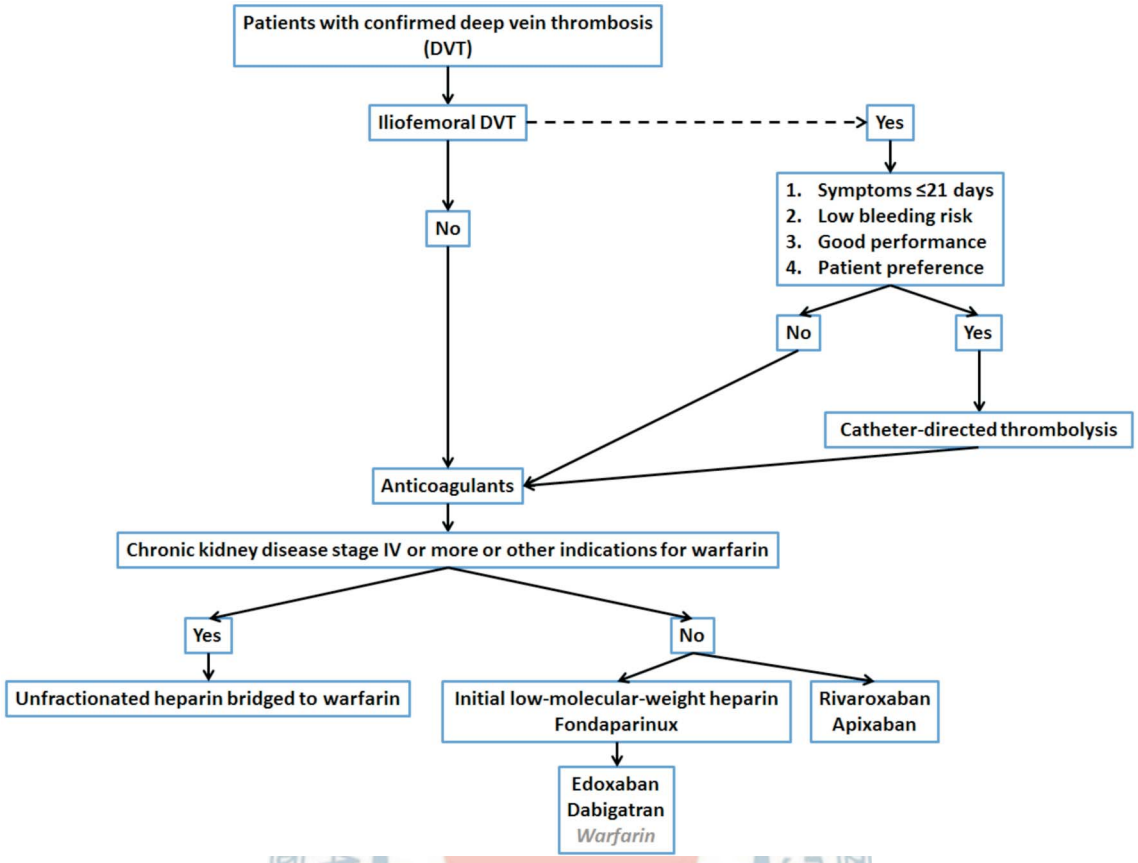

Figure 2. *Treatment flowchart.*

NOACs for VTE treatment; the single-drug approach using rivaroxban or apixaban, and the 2-phase approach using parenteral heparin bridged to dabigatran or edoxaban are as effective as the conventional treatment with regard to the recurrence of VTE.

- With respect to major bleeding, NOACs seem to be safer than the conventional treatment.

Duration

A 3-phase anticoagulation treatment is recommended by the current guidelines.[120] The initial phase of intensified anticoagulants is followed by minimal 3-month long-term oral anticoagulants for the majority of patients.[152-154] After the first 2 phases, whether patients require an extended phase of anticoagulants depends on balances between risk for VTE recurrence without and bleeding with anticoagulants,[155] and the preference of patients. DVT, as part of VTE, is a chronic disease with a high rate of recurrence. Previous epidemiological data indicated that more than 30% of patients developed recurrence within 10 years.[7,119,156,157] In general, the long-term recurrence rate is not extremely different between DVT and PE. Rather, recurrence is more likely to occur in the same clinical manifestation as the index event.[24,118]

According to the most recent data from randomized trials, the risk of early recurrence (on anticoagulant treatment) is about 1-2%.[158] Factors associated with recurrence are listed in Table 6. Risk factors for recurrence during anticoagulation include immobilization, cancer, and chronic pulmonary condition,[76] in which immobilization > 3 days is the strongest risk factor.[159] The risk of recurrence after terminating anticoagulant therapy markedly differs depending on whether the initial event is associated with one or more risk factors.[152,160,161] The long-term recurrence rate has been reported to reach 13% at 1 year, 23% at 5 years, and 30% at 10 years.[162] Risk factors for recurrence after discontinuing anticoagulation include male sex,[163] elevated body mass index,[164] low levels of high-density lipoprotein choles-

terol,[165] idiopathic presentation, thrombophilia, increasing age, shorter duration of anticoagulation, cancer, and residual thrombus.[7,121,166]

In fact, the provoked nature of an index event is a major determinant for the risk of VTE recurrence.[15,167] In patients with proximal DVT and PE, the estimated cumulative risk of recurrence after stopping anticoagulants is as follows: VTE provoked by surgery, 1% after 1 year and 3% after 5 years; VTE provoked by a nonsurgical reversible risk factor, 5% after 1 year and 15% after 5 years; and unprovoked VTE, 10% recurrence after 1 year and 30% after 5 years, and 15% annually for patients with cancer.[120]

Previous trials have compared different antithrombotic strategies in the reduction of VTE recurrence in patients with an unprovoked event.[152,160,168] These trials indicated that extending anticoagulation for 1 year has yet to eliminate long-term recurrence in patients with unprovoked VTE. Two trials have intended to extend the anticoagulation treatment beyond 1 year.[169,170] In the ELATE study, low-intensity warfarin (target INR of 1.5-1.9) has been compared with standard-intensity warfarin (target INR of 2.0-3.0), and patients have been followed for an average of 2.4 years. The recurrence rate was 1.9 per 100 patient-years in the low-intensity group compared with 0.7 per 100 patient-years in the standard-intensity group (p = 0.03).[170] In the PREVENT study, 508 patients with unprovoked VTE were randomized to low-intensity warfarin (target INR of 1.5-2.0) or placebo. The trial was terminated after 2 years of therapy due to extreme beneficial effect with warfarin. The recurrent VTE was 2.6 per 100 patient-years with warfarin compared with 7.2 per 100 patient-years with placebo (p < 0.001).[169] Incidentially, the major bleeding was remarkable low in both trials (around 1 per 100 patient-years in all treatment groups).

Besides warfarin, extended treatment trials for VTE involving rivaroxaban, dabigatran and apixaban have been completed, with variable treatment duration and comparators.[139,171,172] All 3 NOACs have largely reduced recurrent or fatal VTE and had no excessive risk for major bleeding compared with placebo. The recurrent or fatal VTE and major bleeding was similar with dabigatran and standard-intensity warfarin, but the risk of major or clinically relevant bleeding event was lower with dabigatran compared with standard-intensity warfarin.[171] The information associated with the NOACs trials involving extended treatment for VTE is listed in Table 7.

In addition to anticoagulants, aspirin has been used for VTE prevention in high-risk patients.[173] Recently, 2 extended treatment trials compared low-dose aspirin (100 mg once daily) with placebo in patients with unprovoked VTE.[174,175] The pool analysis of 2 trials indicated that the recurrence rate was 5.1% per year with

Table 6. Risk factors for recurrent venous thromboembolism

While taking anticoagulant drugs
Immobilization
Cancer
Chronic obstructive pulmonary disease
After anticoagulant drugs are discontinued
Unprovoked event or associated with cancer
Male sex
Obesity
Lack of recanalization of DVT on venous ultrasound examination
Presence of antiphospholipid antibody

Reference[76,152,161,162]

Table 7. Clinical trials of non-vitamin K oral anticoagulants in extended treatment for venous thromboembolism

	Dabigatran		Rivaroxaban	Apixaban	
	RE-MEDY	RE-SONATE	EINSTEIN-EXT	AMPLIFY-EXT	AMPLIFY-EXT
Comparator	Warfarin	Placebo	Placebo	Placebo	Placebo
Treatment	Dabigatran 150 twice daily	Dabigatran 150 twice daily	Rivaroxaban 20 mg once daily	Apixaban 2.5 mg twice daily	Apixaban 5 mg twice daily
Treatment duration	18 months	6 months	6 or 12 months	12 months	12 months
Recurrent VTE*	1.44 (0.78-2.64)	0.08 (0.02-0.25)	0.18 (0.09-0.39)	0.19 (0.11-0.33)	0.20 (0.11-0.34)
Major bleeding*	0.52 (0.27-1.02)	NA	NA	0.49 (0.09-2.64)	0.25 (0.03-2.24)

* Hazard ratio (95% confident interval).

NA, not applicable; VKA, vitamin K antagonist; VTE, venous thromboembolism.

low-dose aspirin compared with 7.5% per year with placebo (p = 0.008), whereas there was no excessive risk for major bleeding.[176]

Despite the probability that extended treatment is effective and generally safe in reducing VTE recurrence in patients with higher risk for recurrence, anticoagulation treatment of indefinite duration, or even probably for a lifetime, is a major undertaking both for patients and healthcare professionals.[177] The decision of the treatment duration for DVT requires a complex evaluation that balances the risks of recurrence in the absence of anticoagulation against the risks of bleeding complications with continued pharmacological therapy.[152,178] There is not yet a universally accepted method for predicting the risk of VTE recurrence in the absence of anticoagulation. The DASH scoring system and Vienna prediction model are newly developed assessment for patients with unprovoked VTE.[179,180] To address the risk of major bleeding with anticoagulation in the first 3 months of treatment, the practice guidelines recommend a complex matrix whereas the RIETE scoring is a simple assessment.[181]

Recommendations

- The long-term treatment comprises minimally a 3-month duration of oral anticoagulants.
- Patients without a transient reversible risk factor for VTE are more likely to develop recurrences after cessation of anticoagulant treatment.
- For extended treatment, normal or low intensity warfarin, dabigatran, rivaroxaban, apixaban, and aspirin are effective on the reduction of VTE recurrence in patients with unprovoked VTE.
- Whether patients require an extended phase of anticoagulants depends on balances between the risk of VTE recurrence without anticoagulants and bleeding with anticoagulants, and the preference of patients.
- There is not yet a widely accepted scoring system for prediction of VTE recurrence without anticoagulation and bleeding with anticoagulation.

Pregnancy-related VTE

Pregnancy is associated with a hypercoagulable state characterized by increased concentrations of procoagulant factors and by a simultaneous decrease of anticoagulant factors.[182] It is important to note that the likelihood of VTE is increased at least 4-fold during pregnancy compared with a non-pregnant status, and is a major cause of maternal mortality in the developed world.[183,184] The overall incidence of VTE in pregnancy is about 1-2 cases per 1,000 deliveries in the West, and around 1 case per 10,000 individuals in Asia.[20,185] The risk of VTE remains high until the first 6 weeks after delivery have passed.[186] Furthermore, VTE occurs at a rate of 5.4, 7.2, and 4.3 cases per 10,000 pregnancies for antepartum, peripartum, and postpartum, respectively.[185] Isolated DVT, particularly left iliac and/or femoral vein, is more common in pregnant patients due to the enlarged uterus' compressive effects on veins.[187]

The use of diagnostic algorithms for DVT, the combination of structured clinical prediction rules and the use of D-dimer testing, in non-pregnant patients is neither adequate nor validated when applied in pregnancy. Leg swelling, the cardinal sign and symptom of DVT, may be associated with a normal pregnancy and levels of D-dimer increase with the progression of a normal pregnancy.[188] The cornerstone of diagnosing DVT in pregnancy is the demonstration of presence of a clot by CUS. Compression maneuvers should be performed along the entire venous system from the femoral to the popliteal vein. The sensitivity and negative predictive value are 90.9% and 98.9%, respectively,[189] with a reduced accuracy for isolated calf- and iliac-vein thrombosis.[190] CUS could be repeated within 7 days if the initial study is negative,[191,192] or MRV could be used if the initial CUS study is negative or for detecting iliac-vein thrombosis.[193]

It is safe to withhold anticoagulation in pregnant patients with suspected DVT following negative serial CUS and iliac vein imaging.[194] Maternal complications from anticoagulant therapy are similar to those seen in non-pregnant patients.[195] However, additional considerations regarding the health and life of the fetus will affect patients' choices on anticoagulation therapy. For the treatment of acute DVT, particularly proximal DVT with or without PE, inpatient treatment with parenteral heparin is recommended and VKAs should only be considered in exceptional circumstances.[192,196] Pregnant women were excluded from participating in clinical trials evaluating NOACs, and NOACs are not approved for such conditions and should not be used in breast-feeding pa-

tients. In general, LMWH is recommended over unfractionated heparin for use in pregnant patients. It is reasonable to use the twice-daily regimen of LMWH in pregnancy, especially for the first month when the risk of recurrence is the greatest. This practice also stems from the altered renal elimination of LMWH and the impact of weight gain during pregnancy.

No study has assessed the optimal duration of anticoagulant therapy for treatment of pregnancy-related VTE. In non-pregnant patients with VTE, evidence supports a minimum duration of 3 months of treatment. Major guidelines recommend anticoagulants, which should be continued for at least 6 weeks postpartum (for a minimum total therapy duration of 3 months).[196,197] And for pregnant women with a prior history of VTE associated with transient risk factors, withholding antepartum anticoagulation therapy is generally safe.[198,199]

Cancer-related VTE

Patients with cancer are at the increased risk for VTE,[200] and carry a substantial risk for VTE recurrence.[15,201] Meanwhile, VTE can be attributed to major morbidity and mortality in patients with cancer,[202] and has a significant negative impact on quality of life in patients with cancer.[203] Although long-term VKAs are warranted and prevent recurrence in the majority of patients, VKA treatment therapy is problematic in patients with cancer because drug interactions, malnutrition, vomiting, and liver dysfunction can lead to unpredictable levels of anticoagulation in addition to the potential need for invasive procedures requiring interruption of VKAs.[204] These limitations may contribute to the higher risk of recurrent thromboembolism and bleeding in patients with cancer than in patients without cancer.

Weight-adjusted LMWH as a parenteral agent is effective and appealing for treatment in patients with cancer. The remote and recent clinical trials have demonstrated the advantage of treatment with LMWH over VKAs for 6 months.[205,206] NOACs had at least a similar clinical benefit as VKAs in the subgroup analyses,[141,207,208] and might be even comparable to LMWH in the pooled analyses.[209,210] However, additional studies are needed to confirm this concept and to compare NOACs with LMWH directly in patients with cancer.[211] Currently, 3 protocols that will randomize cancer patients with VTE to either NOACs or LMWH with a variable treatment duration are approved (NCT02583191, NCT02585713, NCT02073682). Despite practicing guidelines recommending LMWH for at least 3-6 months and possibly indefinitely for patients with active cancer, the optimal duration of LMWH treatment beyond 6 months is yet to be determined by the evidence from the randomized controlled trials.[212,213] In the Hokusai VTE-cancer study, patients will be treated for an extended period up to 12 months on the basis of the risk-benefit assessment by the treating physician and/or on patient preference.[214]

Areas with uncertainty

Although a large number of cohort studies have provided convincing data, and the clinical assessment pathway has been long constructed, these studies describe and have been validated mainly in Western populations. The therapeutic trials had a very low proportion of both young and elderly patients, and patients with minimal comorbidity. In addition, a small proportion of Asian patients participated in these trials. The NOACs have been tested in extended treatment with limited follow-up periods. It will be necessary to elaborate on (i) whether Asian patients indeed have a low risk for the development of DVT and PE, (ii) whether the diagnostic algorithm is feasible if Asian patients truly have a lower prevalence of DVT and PE, (iii) long-term recurrence without and bleeding risk with anticoagulation treatment in Asian patients, and (iv) whether treatment for VTE in patients with pregnancy or cancer is practical in Asian patients who might have different thrombosis and bleeding profiles. Nevertheless, the accumulation of clinical experience with new therapeutics in the real-world will have to proceed at a prudent pace. For those trials that enrolled but have yet to publish data regarding Asian patients, we welcome public dissemination of the research results, so that physicians, patients, and other health care professionals can benefit from the results.[215,216]

SUMMARY

The heavy burden of DVT, as part of VTE continuum, is seriously overlooked in Taiwan. Routine risk assess-

ment and thromboprophylaxis for high-risk patient have not been established, and the guidelines are not yet developed. On the other hand, the diagnosis of DVT requires a sophisticated evaluation from pre-test risk assessment until imaging confirmation. The implantation of the comprehensive diagnostic algorithm facilitates the timely administration of therapeutics for the appropriate patients. For patients with DVT, anticoagulation is essential to prevent thrombus extension and recurrence. The conventional strategy of initial parenteral heparin followed by warfarin is effective, but somehow inconvenient and has its limitations. Quickly-adopted NOACs as an alternative strategy for acute VTE treatment have their unique features with respect to each other. Some of the NOACs are taken once daily, others twice daily, some require the use of a parenteral heparin lead in, and others use the single-drug approach. The single-drug approach without preceding parenteral treatments is appealing to low risk outpatients whereas the conventional parenteral lead in strategy is feasible for intermediate/high risk inpatients. Nevertheless, NOACs have been proven effectively safe in the large-scale clinical trials, particularly with respect to the important outcome of bleeding. Finally, DVT is a chronic disease and unprovoked DVT carries a higher risk for recurrence. Extended treatment should be considered in such patients in part based upon the weight of prevention of recurrence and risk of bleeding. Growing studies have paid attention to the idea of constructing a more user-friendly scoring system to predict VTE recurrence without and bleeding events with anticoagulation. Finally, this consensus document hopefully can upsurge the awareness of DVT in the medical community, and improve patient outcomes during the acute phase and thereafter in the long run.

DISCLOSURE

Dr. Kang-Ling Wang received some benefit from Bayer, Boehringer Ingelheim, and Daiichi Sankyo. Dr. Kou-Gi Shyu has been on the speaker's bureau for AstraZeneca, Bayer, Daiichi Sankyo, MSD, Pfizer, Sanofi, and Takeda. Dr. Chern-En Chiang has been on the speaker's bureau for Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer.

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