

Diagnosis and Treatment of Lower Extremity Deep Vein Thrombosis: Korean Practice Guidelines

Seung-Keo Min¹, Young Hwan Kim², Jin Hyun Joh³, Jin Mo Kang⁴, Ui Jun Park⁵,
Hyung-Keo Kim⁶, Jeong-Hwan Chang⁷, Sang Jun Park⁸, Jang Yong Kim⁹, Jae Ik Bae¹⁰,
Sun Young Choi¹¹, Chang Won Kim¹², Sung Il Park¹³, Nam Yeol Yim¹⁴, Yong Sun Jeon¹⁵,
Hyun-Ki Yoon¹⁶, and Ki Hyuk Park¹⁷

¹Department of Surgery, Seoul National University College of Medicine, Seoul, ²Department of Radiology, Keimyung University College of Medicine, Daegu, ³Department of Surgery, Kyung Hee University School of Medicine, Seoul, ⁴Department of Surgery, Gachon University College of Medicine, Incheon, ⁵Department of Surgery, Keimyung University College of Medicine, Daegu, ⁶Department of Surgery, Kyungpook National University School of Medicine, Daegu, ⁷Department of Surgery, Chosun University College of Medicine, Gwangju, ⁸Department of Surgery, University of Ulsan College of Medicine, Seoul, ⁹Department of Surgery, Catholic University College of Medicine, ¹⁰Mint Intervention Clinic, Seongnam, ¹¹Department of Radiology, Ewha Womans University College of Medicine, Seoul, ¹²Department of Radiology, Pusan National University School of Medicine, Yangsan, ¹³Department of Radiology, Yonsei University College of Medicine, Seoul, ¹⁴Department of Radiology, Chonnam National University College of Medicine, Gwangju, ¹⁵Department of Radiology, Inha University College of Medicine, Incheon, ¹⁶Department of Radiology, University of Ulsan College of Medicine, Seoul, ¹⁷Department of Surgery, Daegu Catholic University College of Medicine, Daegu, Korea

Lower extremity deep vein thrombosis is a serious medical condition that can result in death or major disability due to pulmonary embolism or post-thrombotic syndrome. Appropriate diagnosis and treatment are required to improve symptoms and salvage the affected limb. Early thrombus clearance rapidly resolves symptoms related to venous obstruction, restores valve function and reduces the incidence of post-thrombotic syndrome. Recently, endovascular treatment has been established as a standard method for early thrombus removal. However, there are a variety of views regarding the indications and procedures among medical institutions and operators. Therefore, we intend to provide evidence-based guidelines for diagnosis and treatment of lower extremity deep vein thrombosis by multidisciplinary consensus. These guidelines are the result of a close collaboration between interventional radiologists and vascular surgeons. The goals of these guidelines are to improve treatment, to serve as a guide to the clinician, and consequently to contribute to public health care.

Key Words: Guideline, Venous thrombosis, Diagnosis and treatment

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Corresponding author: Ki Hyuk Park
Department of Surgery, Daegu Catholic University College of Medicine, 33 Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Korea
Tel: 82-53-650-4053
Fax: 82-53-624-7185
E-mail: khpark@cu.ac.kr
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INTRODUCTION

1) Background and purpose

Deep vein thrombosis (DVT) refers to the presence of thrombus within a deep vein of the body, most frequently

in the lower extremities. Many episodes are asymptomatic and the symptoms of acute DVT, including edema, pain, and erythema, are non-specific. At least three-quarters of patients having lower extremity symptoms consistent with DVT have a non-thrombotic cause of their symptoms. Therefore, confirmatory testing is almost always required,

not only to ensure appropriate treatment of those with confirmed DVT but also to prevent the complications of inappropriate anticoagulation in those with other disorders. The aim of the treatment of DVT is to prevent its complications—pulmonary embolism (PE), recurrent DVT, post-thrombotic syndrome (PTS), and death.

The standard treatment for acute DVT is systemic anticoagulation to decrease the propagation of the thrombus and prevent PE. However, anticoagulation alone has no significant thrombolytic activity and does not prevent PTS. Early thrombus clearance rapidly resolves symptoms related to venous obstruction, and can restore valve function so that it reduces the incidence of PTS. Recently, catheter-directed thrombolysis with or without mechanical thrombectomy has been established as a standard method for early thrombus removal. The indications for these interventional procedures are gradually increasing with the rapid development of equipment and procedures, and there are a variety of views regarding the indications and procedures among medical institutions and operators.

In the United States, the Society of Interventional Radiology, American College of Chest Physicians, Society of Vascular Surgeon, and American Venous Forum presented the recommended guidelines for the interventional procedures of acute DVT in 2006 and 2012. In Europe, the Scottish Intercollegiate Guidelines Network and National Clinical Guideline Center working group issued guidelines for management of venous thromboembolism (VTE) in 2010 and 2012. Through these efforts, by establishing standard procedures and raising awareness of physicians on the front lines of medicine to the importance of the procedures, a cautious approach is encouraging. Moreover, these guidelines can be used as basic standards for health insurance payment, review and assessment for reducing medical costs.

However, although a number of similar studies have been conducted, clinical guidelines for Korea have not yet been established. Thus, experts from academies (The Korean Society of Interventional Radiology and The Korean Society for Vascular Surgery) related to interventional procedures in Korea came together and agreed to develop clinical guidelines. We aim to propose recommendations by presenting evidence-based treatment recommendations through a multidisciplinary approach, which will guide interventional procedures by providing up-to-date and accurate information to healthcare providers working at primary, secondary and tertiary hospitals. Furthermore, we aim to help patients themselves choose medical services by providing accurate information and so contribute to public health promotion.

2) Guideline development

Considering that the development of de novo domestic clinical guideline is a difficult undertaking, these guidelines were developed by adapting the pre-existing guidelines of other countries. If no existing guidelines were available, we evaluated existing good-quality articles using the systemic literature review methodology.

The steering committee was composed of the executives of The Korean Society of Interventional Radiology and The Korean Society for Vascular Surgery. The steering committee fixed the subject and the goal, assigned the members of the guideline development committee and approved the guideline development budget. The guideline development committee comprised 22 members.

Guideline development committee members discussed the purpose of the guidelines, the range of development including writing topics, the subjects of the application and user groups, development method, determined the level of evidence (LOE), classified recommendations, selected the consensus development method, internal and external review processes, revision processes and formed the committee of detail associated with guideline development during the first conference. The committee of detail was composed of the guideline evaluation committee, the writing committee, and the editing committee. The guideline evaluation committee comprised four members and evaluated the pre-existing guidelines based on Appraisal of Guidelines for Research & Evaluation II (AGREE II). The writing committee had 17 members and were responsible for drawing up the draft guidelines and the proposal of recommendations. The editing committee was composed of four members and was responsible for reviewing the recommendation levels, the LOE, and the draft guidelines by performing peer review.

The LOE and the classification of recommendations (COR) followed the criteria used in the American College of Cardiology/American Heart Association (ACC/AHA) 2005 guidelines [1]. COR was divided into three categories: Recommendation I (strong recommendation), Recommendation II (weak recommendation), and Recommendation III (contraindication). Recommendation I was defined as conditions for which there was solid evidence for and/or general agreement that a given procedure or treatment is effective, useful, and beneficial and will not be changed by further research. Recommendation II was defined as conditions with conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. IIa was defined as cases for which the weight of evidence/opinion was in favor of usefulness/efficacy. IIb was defined as cases for which the

usefulness/efficacy was less well established by evidence/opinion. Recommendation III was defined as conditions for which there was evidence and/or general agreement that a procedure/treatment is not useful/effective and may be harmful in some cases (Table 1). LOE was classified into three steps: A, B, and C. Evidence A was defined as data derived from multiple randomized clinical trials or meta-analysis. Evidence B was defined as data derived from a single randomized clinical trial or non-randomized studies. Evidence C was defined as only a consensus opinion of experts, case studies, or standard of care (Table 2).

To select high-quality guidelines for use as a reference in the adaptation process, we searched for existing guidelines. We recovered 115 documents by mixing search index words, such as VTE, diagnosis, anticoagulation, thrombolysis, thrombectomy, and guidelines, using the PUBMED, SCOPUS, and COCHRANE search engines.

The guideline evaluation committee determined the inclusion and exclusion criteria for quote-worthy documents among the obtained documents. The inclusion criteria were set as evidence-based guidelines, international guidelines written in English, and guidelines written after 2005. Guidelines that did not represent the organization, those written by one person and translations of single guidelines were excluded.

Five guidelines were chosen based on these inclusion criteria. Four members of the guideline evaluation committee evaluated these guidelines based on AGREE II, which is the most commonly used tool internationally for the quality assessment of guidelines. AGREE II comprises 23 sub-items within six assessment categories, and each item is assigned a score on a 7-point Likert scale. Based on the evaluated results after opinion coordination, three

guidelines that had standardized scores of more than 50% in all categories were finally selected [2-4].

The guideline development committee selected the final key question after reviewing whether population, intervention, comparison, and outcome (PICO), the essential structural component of the key question, was well equipped and appropriate as a clinical question. The key question was agreed upon using the nominal group technique. Consensus was defined as more than 75% of the panel selecting 1 or 2 on the 5-point Likert scale (1, agree entirely; 2, agree generally; 3, agree partially; 4, do not agree generally; 5, do not agree entirely). If the consensus was less than 75%, a second round of voting was carried out after discussion and a modification of phrases. If agreement was not reached in the second round of voting, the key question was dismissed. Eleven members of the development committee participated as a panel, and 22 of a total of 42 key questions that were drawn up were agreed on by the committee members and were selected as the final clinical questions.

Writing committee members, who were assigned according to sub-themes, drew up the proposal of recommendations for clinical questions. A single draft of the proposal of recommendation was deduced by collecting common information and deleting unnecessary information after analyzing recommendations extracted from selected guidelines. If there were no data for reference in existing guidelines of clinical questions, a new proposal of recommendation was developed on the basis of the results after evaluating the quality of articles through a literature search and review. Thus, a total of 43 proposals of recommendation were drawn up. Ten of these recommendations were deleted because no final agreement

Table 1. Classification of recommendations

Class	Description
I	Conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
IIb	Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and is some cases may be harmful.

Table 2. Levels of evidence

Level	Description
A	Data derived from multiple randomized clinical trials or meta-analysis.
B	Data derived from a single randomized clinical trial or nonrandomized studies.
C	Only consensus opinion of experts, case studies, or standard of care.

was reached due to opinions that the information was ambiguous and difficult to understand despite modification of phrases or sentences and was impractical in Korea, etc. The remaining 33 recommendations were chosen by means of a Delphi consensus survey. We created a recommendation data extraction form, which was used by the panel as a reference during the Delphi consensus process.

For formal mutual agreement of the final adoption of recommendations, a modified Delphi technique was applied. The panel was composed of 26 members (The Korean Society of Interventional Radiology, 14; The Korean Society for Vascular Surgery, 12). To assist the panel, the recommendation data extraction form and related references were provided by e-mail. The vote was performed anonymously. After sending the disclosure sheet on conflict of interest to all panel members, the members signed the document confirming that they did not receive any support from interest groups related to the recommendation. The degree of consensus was quantitatively analyzed using a 9-point Likert scale (1, strongly disagree; 9, entirely agree). In the response scale, scores of 7-9 points were considered to indicate agreement with the recommendations. When more than 50% of the panel agreed, the proposal of recommendations was considered to have achieved consensus. During the first round of voting, all recommendations met the agreement condition. Based on the adopted recommendations, the writing committee members assigned to specific sub-themes wrote draft guidelines. The editing committee evaluated the draft guidelines based on the selected recommendations. The guidelines were internally evaluated through an expert advisory conference to discuss the expertise of relevant academies associated with the guidelines, including problems in the recommendations, background and description of the evidence, etc. Following this internal evaluation, the final guidelines were established by means of a public hearing involving experts in relevant fields and stakeholders.

CONTENTS

1) Symptoms

① Clinical presentation of acute lower extremity DVT

The clinical presentation of acute lower extremity DVT varies with the anatomic distribution, extent, and degree of occlusion of the thrombus. Symptoms may range from absence to massive swelling and cyanosis with impending venous gangrene. Three patterns of thrombosis are usually recognized: isolated calf vein (distal), femoropopliteal, and iliofemoral thrombosis, and symptoms tend to be more

severe as thrombosis extends more proximally. However, up to 50% of patients with acute DVT may lack specific signs or symptoms [5,6]. Postoperative patients are, in particular, more likely to have small, asymptomatic, distal, non-occlusive thrombi. When present, signs and symptoms of acute lower extremity DVT may include pain, edema, erythema, tenderness, fever, prominent superficial veins, pain with passive dorsiflexion of the foot (Homan's sign), and peripheral cyanosis. Phlegmasia cerulea dolens, characterized by the triad of massive swelling, cyanosis, and pain, is the most severe form of acute lower extremity DVT and results from complete thrombosis of an extremity's venous outflow [7]. In advanced cases, it is marked by severe venous hypertension with collateral and microvascular thrombosis, leading to venous gangrene. Venous gangrene is particularly associated with warfarin-mediated protein C depletion in patients with cancer or heparin-induced thrombocytopenia [8,9].

Unfortunately, the diagnosis of DVT based on clinical signs and symptoms is notoriously inaccurate. The signs and symptoms of DVT are non-specific and may be associated with other lower extremity disorders, including lymphedema, PTS, superficial venous thrombosis, cellulitis, musculoskeletal trauma, and Baker's cysts. Among patients referred to the vascular laboratory for exclusion of DVT, only 12%-31% will have a positive ultrasound (US) study [10-12]. The most common presenting symptoms have a wide range of reported sensitivities and specificities: calf pain, sensitivity 75%-91% and specificity 3%-87%; and calf swelling, sensitivity 35%-97% and specificity 8%-88% [13-18]. None of the signs or symptoms is sufficiently sensitive or specific, either alone or in combination, to accurately diagnose or exclude thrombosis [19].

② Complications of acute lower extremity DVT

(1) Pulmonary embolism: The potentially life-threatening consequences of PE make it the most important short-term complication of acute lower extremity DVT. Symptomatic PE accompanies approximately 10% of DVT [20]. However, respiratory symptoms correlate poorly with the presence or absence of objectively documented PE, and as many as 75% of pulmonary emboli may be asymptomatic [21,22].

(2) Post-thrombotic syndrome: PTS, the symptoms of which include pain, edema, skin changes, and ulceration, is the most important late complication of acute lower extremity DVT. Older studies, many with methodological flaws, reported post-thrombotic manifestations in up to two-thirds of patients with acute lower extremity DVT. More recent studies suggest that the PTS develops in 29.6% of those with proximal thrombosis and 30% of those with isolated calf vein thrombosis [23]. In addition to

the substantial economic costs, the physical limitations of patients with PTS are similar to those of patients with other serious chronic medical conditions [20].

(3) Mortality after acute lower extremity DVT: Mortality after an episode of acute lower extremity DVT exceeds that expected in an age-matched population. Although the in-hospital fatality rate for DVT is only 5%, 1-, 3-, and 5-year mortality rates of 22%, 30%, and 39%, respectively, have been noted [20]. Early mortality is most frequently secondary to cancer, PE and cardiac disease. Among patients older than 45 years, cancer is the most important predictor of early death (28-day mortality rate, 25.4%) compared with 12.6% in patients without cancer [24]. While deaths among cancer patients and idiopathic DVT remain high for at least 3 years beyond the index event, that for those with secondary VTE unrelated to cancer return to those of general population after 6 months [24]. Clinically, there appears to be an association between idiopathic VTE and cardiovascular events [25]. For instance, the 10-year cumulative risk of symptomatic vascular events among patients with idiopathic DVT is 25.4%, compared with 12.9% in those with secondary VTE [26]. Patients with idiopathic DVT also have a higher prevalence of atherosclerotic risk factors (diabetes, hypertension, and hypercholesterolemia) and coronary artery calcium than control group without VTE [27].

③ Natural history of acute lower extremity DVT

(1) Venous thrombogenesis: As Virchow proposed, three factors are important in the development of venous thrombosis—abnormalities of blood flow, abnormalities of blood coagulation, and vessel wall injury. The role of structural injury to the vein wall is disputable. Overt endothelial injury appears to be neither a necessary nor a sufficient condition for thrombosis [28]. In contrast, evidence is accumulating that biologic injury to the endothelium may play a more important role in venous thrombogenesis. Although most venous thrombi originate in areas of low blood flow, stasis alone is also an inadequate stimulus in the absence of low levels of activated coagulation factors [29,30]. Stasis may be a permissive factor for the other events required for thrombosis.

Imbalanced activation of the coagulation system appears to be the most important factor underlying many episodes of acute lower extremity DVT. Some components of imbalanced coagulation appear to be associated with thrombotic risk factors, including age, malignancy, surgery, trauma, primary hypercoagulable states, pregnancy, and oral contraceptive use.

Lower extremity thrombi originate in areas of localized imbalanced coagulation due to stasis, such as soleal sinuses,

behind venous valve pockets, and venous confluences. Propagation of thrombi beyond areas of stasis likely depends largely on the relative balance between activated coagulation and thrombolysis. In contrast to arterial thrombi, venous thrombi are composed largely of red cells and fibrin, with relatively few platelets.

(2) Recanalization: Once formed, the competing processes of recanalization and recurrent thrombosis characterize the natural history of acute lower extremity DVT. The development of chronic sequelae is closely related to the balance between recanalization and recurrence. Monocytes appear to play a particularly important role in thrombus organization and recanalization. Recanalization appears to be a complex process involving intrinsic and extrinsic fibrinolysis, peripheral fragmentation, neovascularization, and retraction. Thrombus organization begins in the attachment zone with the migration of surfacing cells, presumably derived from the endothelium, over the thrombus [31]. Most recanalization occurs within the first 6 weeks [32]. Although thrombus resolution proceeds at a similar rate in the proximal venous segment, some have found more rapid clearance from the tibial segments, perhaps reflecting the increased efficiency of thrombolysis in small veins [33].

The degree of recanalization is related to both the degree of activated coagulation and fibrinolytic inhibition. From a clinical perspective, more complete recanalization has been reported in older patients, those with asymptomatic postoperative thrombosis, and patients with involvement of only one venous segment [34]. Cancer is associated with less complete recanalization. The presence of permanent risk factors has been associated with an 11-fold higher risk of delayed recanalization [35].

(3) Recurrent venous thrombosis: Standard anticoagulation is effective in preventing recurrent VTE while patients are being treated. Among patients with proximal DVT, recurrent thromboembolic events occurred in 5.2% of patients treated with standard anticoagulation for 3 months [36], compared with 47% of patients inadequately treated with a 3-month course of low-dose subcutaneous heparin [37].

Not surprisingly, most symptomatic events occur after anticoagulation has been stopped. Sarasin and Bounameaux [38] calculated a theoretical recurrence rate of 0.9% per month after discontinuing anticoagulant therapy for proximal DVT, similar to annual recurrence rates of 7.0%–12.9% [39,40]. The risk of recurrent VTE is highest over the first 6–12 months after the index event, although cumulative rates can reach 24% at 5 years and 30% at 8 years after initial presentation [40–43]. The risk of recurrence is at least as great in the contralateral as in the ipsilateral extremity [42].

The risk of recurrence is highly related to the underlying thrombotic risk factors. Data from the Duration of Anti-coagulation (DURAC) trial suggest a 2-year recurrence rate of 12% in patients with idiopathic DVT or irreversible risk factors and 4.8% in patients with reversible risk factors if treated with 6 months of anticoagulants [43]. Others have similarly noted that patients with idiopathic DVT or thrombophilia are at three-fold greater risk for recurrent VTE than those with secondary thrombosis [40,41]. Other risk factors for symptomatic recurrent DVT include advanced age, male gender, increased body mass index, lower extremity paresis and active malignancy [44].

Recurrent VTE in the setting of thrombosis isolated to the calf veins requires special consideration. Limited data suggest that isolated calf vein thrombosis is associated with less extensive activation of coagulation than proximal venous thrombosis [45]. At least two types of calf vein thrombosis may be differentiated—those with involvement of the paired posterior tibial and peroneal vein (axial calf vein thrombosis) and those isolated to the veins draining the gastrocnemial and soleal muscles (muscular calf vein thrombosis); the natural history of these types may be different. In patients with thrombosis isolated to the axial calf veins, proximal propagation occurred in 23% of untreated patients and 10% of patients treated with only intravenous heparin [46]. As US technology has improved, muscular calf vein thrombi are identified more frequently and now account for approximately 40% of isolated calf vein thrombi. More information is needed regarding the natural history and management of these thrombi.

Recognized thrombophilic states, particularly the factor V Leiden mutation, lupus anticoagulant, and homocysteinemia, have been associated with recurrent thromboembolic events [47-49]. Others have reported a 2.2-fold to >5-fold increased risk of recurrent thrombosis among those with incomplete recanalization [34,40]. A D-dimer level of >500 ng/mL measured 1 month after discontinuing anticoagulants was associated with a 3.3-fold increased risk of recurrence [50].

2) Diagnosis of lower extremity DVT

① Clinical probability scores (clinical scores)

Patients suspected with DVT usually present with swelling, pain, redness, and warmth in the lower extremity. Currently, the diagnosis of DVT relies on imaging modalities such as compression and color Doppler US, and computed tomography (CT). However, only a minority of patients evaluated for suspected DVT with symptoms actually have the disease and the symptoms of many patients have other causes [51]. In addition, considering the cost and

invasiveness of diagnostic methods, the initial approach for patients with a possible DVT should be focused on the assessment of their individual pre-test probability (i.e., the likelihood that they have a DVT), and diagnostic tests should be selected according to the results of pre-test probability.

Clinical probability scores estimate the probability of DVT by incorporating signs, symptoms, and risk factors. This score stratifies patients into groups according to the probability, which influences the subsequent diagnostic strategy. Currently, several structured scoring systems have been developed and introduced; the most widely used and well-studied is the Wells score [52]. The original Wells scoring system published in 1997 consisted of a nine-component clinical prediction rule for DVT and stratified patients into three categories: 'high' (3 or more points) 'intermediate' (1-2 points), and 'low' (less than 1 point) (Table 3). The prevalence of DVT was estimated as 5.0% (95% confidence interval [CI], 4%-8%) in the low risk category, 17% (95% CI, 13%-23%) in the intermediate risk category, and 53% (95% CI, 44%-61%) in the high risk category [51]. In 2003, the original Wells score was modified. A further component, 'previously documented DVT', was added to the original Wells score, and instead of considering surgery within 4 weeks as a risk factor, the duration was extended to 12 weeks. In place of the three risk categories in the original version, this version has only two risk categories: 'likely' (≥ 2 points) or 'unlikely' (< 2 points) (Table 4) [53]. The prevalence of DVT according to this 'two-level' Wells was estimated as 28% (95% CI, 24%-32%) in the 'likely' group and 6% (95% CI, 4%-8%) in the 'unlikely' group [53].

According to the NICE guidelines, analysis involving 13,086 patients showed that the sensitivity and specificity for DVT of the Wells score ranged from 77% to 98% and 37% to 58%, respectively [3]. For the purpose of ruling out DVT, this means that 2 to 23 out of 100 patients with DVT will be missed using the Wells score; therefore, this test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 42 to 63 out of 100 of people without DVT will be identified as having the condition, suggesting that this score is not suitable for confirming the presence of DVT without further diagnostic testing. Thus, a clinical probability score, such as the Wells score, cannot be used as the sole diagnostic modality to confirm or rule out DVT. However, this score enables stratification of subjects into different risk categories, so that the most appropriate diagnostic or treatment pathway can be followed. The diagnosis of DVT should be made in conjunction with further diagnostic modalities.

Table 3. Wells score criteria for assessment of suspected DVT

Criterion	Score (point)
1. Active cancer (treatment ongoing or within the last 6 months or palliative)	1
2. Calf swelling >3 cm compared to the other calf (measured 10 cm below the tibial tuberosity)	1
3. Collateral superficial veins (non-varicose)	1
4. Pitting edema (greater in the symptomatic leg)	1
5. Swelling of the entire leg	1
6. Localized tenderness along the distribution of the deep venous system	1
7. Paralysis, paresis, or recent plaster cast immobilization of the lower extremities	1
8. Recently bedridden >3 days, or major surgery in the previous 4 weeks	1
9. Alternative diagnosis at least as likely as DVT	-2
Interpretation: for evaluation (low vs. moderate vs. high)	
Score of 0 or less: low probability of deep vein thrombosis	
Score of 1 or 2: moderate probability of deep vein thrombosis	
Score of 3 or higher: high probability of deep vein thrombosis	

DVT, deep vein thrombosis.

Table 4. Revised Wells score criteria for assessment of suspected DVT

Criterion	Score (point)
1. Active cancer (treatment ongoing or within the last 6 months or palliative)	1
2. Calf swelling >3 cm compared to asymptomatic calf (measured 10 cm below the tibial tuberosity)	1
3. Collateral superficial veins (non-varicose)	1
4. Pitting edema (greater in the symptomatic leg)	1
5. Swelling of the entire leg	1
6. Localized tenderness along the distribution of the deep venous system	1
7. Paralysis, paresis, or recent plaster cast immobilization of the lower extremities	1
8. Recently bedridden for ≥ 3 days, or major surgery requiring a regional or general anesthetic in the previous 12 weeks	1
9. Previously documented deep vein thrombosis	1
10. Alternative diagnosis at least as likely as DVT	-2
Interpretation: for dichotomized evaluation (likely vs. unlikely)	
Score of 2 or higher: deep vein thrombosis is 'likely'	
Score of less than 2: deep vein thrombosis is 'unlikely'	

DVT, deep vein thrombosis.

② D-dimer

After thrombus formation, a fibrinolytic response is immediately activated. The resultant generation of plasmin causes the release of fibrin degradation products (predominantly D-dimer) into the circulation. Therefore, the level of D-dimer, a degradation product of cross-linked fibrin, is typically elevated in patients with acute DVT. A negative D-dimer assay implies that thrombosis is not occurring and thus has a role in excluding a diagnosis of DVT. However, a positive D-dimer assay should be interpreted cautiously because D-dimer levels may also be increased in a variety of nonthrombotic disorders (e.g., liver disease, inflammatory conditions, malignancy, pregnancy, and following surgery

or trauma).

A wide variety of D-dimer assays are available. D-dimer can be tested by enzyme-linked immunofluorescence assays, microplate enzyme-linked immunosorbent assays (ELISAs), quantitative latex immunoturbidimetric assays, latex semiquantitative assays and the whole-blood D-dimer assay. Among these tests, ELISAs and enzyme-linked immunofluorescence assays, along with latex immunoturbidimetric assays, are generally termed highly sensitive due to their high sensitivity, whereas the whole blood D-dimer assay is considered moderately sensitive [51,54].

According to a meta-analysis published in 2006, the pooled sensitivity and specificity of all D-dimer tests was

90.5% and 54.7%, respectively [55]. In the NICE guidelines, the sensitivity and specificity for D-dimer tests ranged from 75% to 100% and 26% to 83%, respectively [3]. These results suggest that the D-dimer test generally has high sensitivity but lower specificity. In addition, this implies that this test is not suitable for confirming the presence of DVT but can assist ruling out of DVT due to its high sensitivity. In conclusion, the D-dimer test cannot be used as a sole diagnostic modality to confirm DVT, similar to a clinical probability score. However, in conjunction with further diagnostic tests, such as a clinical probability score or ultrasonography, D-dimer tests can be helpful to rule out DVT.

③ Diagnostic strategies for suspected lower extremity DVT

Sensitivity is the most important factor in diagnostic methods for suspected DVT because tests with high sensitivity can minimize the risk of missed diagnosis that might result in no treatment for patients with DVT. For this purpose, the clinical probability score, D-dimer, and Doppler ultrasonography have been investigated either alone or in combination with other tests. In contrast to western countries, the clinical probability score and D-dimer test are not widely used to rule out DVT in Korea. As described earlier, the clinical probability score alone cannot be used to confirm or rule out DVT. However, according to a multicenter randomized control trial of 1,723 patients published in 2013, the incidence of symptomatic VTE at 3 months was not significantly different between selective testing and uniform testing groups (0.5% in both). Selective testing (n=860) is defined as D-dimer testing for outpatients with low or moderate clinical pretest probability for DVT and ultrasonography without D-dimer testing for outpatients with high clinical pretest probability. Uniform testing (n=862) is defined as D-dimer testing for all participants. Selective testing reduced the proportion of patients who required D-dimer testing by 21.8%. In addition, it reduced the proportion of patients who required ultrasonography by 7.6% overall and by 21.0% in outpatients with a low clinical pretest probability [56]. Therefore, the sensitivity for ruling out DVT of clinical probability scores, such as the Wells score, can be enhanced by use in conjunction with other tests, and the number of diagnostic tests can be reduced.

In patients with a low or unlikely clinical probability score, further diagnostic tests, such as the D-dimer test and duplex ultrasonography, can be performed to rule out DVT. As described above, positive D-dimer test cannot be used as a sole diagnostic modality to confirm DVT, but a negative D-dimer test can be helpful to rule out DVT.

Therefore, the combination of a clinical probability score and D-dimer test has been investigated. According to a systemic review of the diagnostic properties of D-dimer in patients with suspected DVT published in 2006, the post-test probability of DVT was 0.7% in patients with a low clinical probability score and negative D-dimer test, which would result in 0.08 cases of fatal PE and 0.36 cases of nonfatal PE per 1,000 patients [54]. Moreover, the addition of a D-dimer test to a clinical probability score has been reported to decrease the rate of fatal and non-fatal PE by 90% compared to a clinical probability score alone [54]. In another cohort study, the prevalence of DVT in patients with a low clinical probability score and negative D-dimer test was 0.45% during 3 months of follow-up [57]. These results are comparable to those of other radiologic tests to rule out DVT in patients suspected to have the condition. The prevalence of DVT during 3 months of follow-up was 1.9% in patients with negative venography to rule out DVT [58], and 0.5-0.9% in patients with negative duplex ultrasonography to rule out DVT [59-61].

In a recent meta-analysis based on these results, the authors concluded that DVT could be excluded in patients with an 'unlikely' clinical probability score combined with a negative D-dimer test result [62]. However, further radiologic testing is necessary in patients with a high clinical probability score or positive D-dimer test considering the low specificity of these methods.

Recommendations

- A clinical probability score is useful for the diagnosis of DVT in patients with suspected lower extremity DVT. (Class I, Level B)
- A low clinical probability score and negative D-dimer test can be used as exclusive criteria for the diagnosis of DVT in patients with suspected lower extremity DVT. (Class I, Level B)
- If the clinical probability score is high or D-dimer test is positive, a further radiologic test is necessary for confirmative diagnosis of DVT in patients with suspected lower extremity DVT. (Class I, Level B)

④ Thrombophilia testing

Thrombophilia is an acquired or inherited predisposition to venous thrombosis. One of the important acquired thrombophilia is the anti-phospholipid antibody syndrome, which can be detected as a lupus anticoagulant or anti-cardiolipin antibodies. Inherited thrombophilia includes deficiencies in one of the three natural anticoagulants—antithrombin III, protein C and protein S, which have been linked with familial venous thrombosis. In addition, inherited thrombophilia can be caused by factor V Leiden

mutation or prothrombin G20210 mutation that can predispose patients to dysfunctional coagulation factors.

The intensity and duration of anticoagulation can be adjusted in patients with VTE and thrombophilia to decrease complications and mortality caused by recurrent VTE, although clinical evidence for such adjustment is currently insufficient. According to the international consensus statement published in 2005, screening for thrombophilia should be performed in 1) all patients with a first episode of spontaneous VTE; 2) patients with VTE under the age of 50 years even with a transient predisposing factor; 3) patients with VTE whose only risk factor is oral contraceptive therapy, estrogen replacement therapy, or pregnancy; and 4) patients with recurrent VTE irrespective of the presence of risk factors [63]. However, whether spontaneous VTE means the presence of thrombophilia is controversial. In a prospective cohort study by Baglin et al. [64], the prevalence of thrombophilia in 157 patients with idiopathic DVT was 32%; however, the prevalence of thrombophilia in 330 patients with clinical risk factors was also 26%. In addition, the risk of recurrence in patients with thrombophilia is similar (relative risk: factor V Leiden mutation, 1.4; prothrombin G20210A mutation, 1.7; protein S deficiency, 1.0; protein C deficiency, 1.8; and antithrombin III deficiency, 2.6), and the annual risk of recurrent VTE is higher in patients with idiopathic VTE compared to those with VTE associated with thrombophilia (3.3% vs. 2.5%) [64–66]. On the basis of these results, genetic thrombophilia testing is not routinely recommended in all patients with DVT for reasons of cost effectiveness.

The mutation spectrum of genetic thrombophilia in Korean patients is different to that in western countries. Activated protein C resistance caused by factor V Leiden mutation and increased plasma prothrombin caused by prothrombin G20210A mutation are the most common causes of VTE in Caucasians. However, natural anticoagulant deficiencies—such as protein C, protein S, and antithrombin III deficiencies—are the most common causes of genetic thrombophilia in Asian patients. Several studies of Chinese and Japanese VTE patients reported a paucity of factor V Leiden mutation [67–69]; indeed, one study of 418 Koreans reported no factor V Leiden mutation [70]. The prothrombin G20210A mutation is extremely rare in Japanese and Chinese patients [71,72]. Moreover, there has been no report of the prothrombin G20210A mutation in Korean patients. A study of natural anticoagulant deficiency in 127 Korean VTE patients reported that the most common deficiency was of protein C (50.7%), followed by antithrombin III (29.6%) and protein S (19.7%) [73].

Recommendations

- Genetic thrombophilia testing is not routinely recommended in all patients with DVT. (Class IIb, Level B)
- Thrombophilia tests for factor V Leiden or prothrombin G20210A mutation are not recommended for Korean patients with DVT. (Class III, Level C)

3) Imaging diagnosis of lower extremity DVT

① Imaging diagnosis of acute lower extremity DVT

We generally recommend against invasive diagnostic strategies when a comparably accurate non-invasive alternative is available for diagnosis of lower extremity DVT. This is because invasive tests are generally associated with greater patient discomfort, side effects (e.g., reactions to contrast) and radiation exposure than noninvasive tests. However, we recommend invasive testing over noninvasive testing if the benefits of a more accurate diagnosis outweigh these disadvantages. Individual patient preferences relating to test discomfort and tolerance for diagnostic uncertainty influence this decision.

(1) Ultrasound: US is widely used and preferred as a first-line imaging modality for the diagnosis of proximal DVT [2–4,74–76]. It is non-invasive, can easily be performed at the patient's bedside, and sufficiently reliable for serial evaluation. The inability to fully collapse a venous segment under gentle US probe pressure is considered diagnostic of DVT. US evaluation for DVT is often combined with real-time Doppler imaging, such as duplex, continuous-wave, and color-flow Doppler imaging. Duplex US imaging can assist in the characterization of a clot as obstructive or partially obstructive.

US examination has high sensitivity and specificity for the diagnosis of symptomatic proximal lower extremity DVT when compared to conventional venography [4]. However, the diagnostic performance of US is consistent in the femoral and popliteal vein, but less consistent in the ilio caval region and below the knee [74,75]. A recent meta-analysis found US to have very high sensitivity (range, 93.2%–95.0%; pooled sensitivity, 94.2%) and high specificity (range, 93.1%–94.4%; pooled specificity, 93.8%) for diagnosing proximal DVT, but much lower sensitivity (range, 59.8%–67.0%; pooled sensitivity, 63.5%) for diagnosis of distal DVT [77].

There are two methods in US examination of lower extremity DVT. Proximal compressive US examination assesses the compressibility of the femoral and popliteal veins. Whole leg US examination assesses the deep veins of both the proximal leg and calf. Distal DVT may be present in patients with a normal proximal compressive US; however, it is seldom associated with important clinical sequelae such

as PE or PTS [2]. Thus, whole leg US as a stand-alone test to exclude DVT has a risk of over-treatment. Nevertheless, as distal DVT may propagate proximally and lead to PE, additional investigations, such as whole leg US or a second (serial or repeat US) proximal US may be needed to exclude distal DVT or to detect early extension into the proximal veins [60,78,79].

The pretest clinical probability score and D-dimer result have a significant effect on the usefulness of US [2,75,80]. In patients with a low pretest probability of first lower extremity DVT, if the D-dimer is negative, further testing using US or venography is not recommended. If the D-dimer is positive, US is recommended over no test or venography. Initial testing with US is preferred over D-dimer if the patient has a comorbid condition associated with elevated D-dimer levels [2,74]. Whole leg US may be preferred over proximal US in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT [2]. In patients with a high pretest probability of first lower extremity DVT, US is recommended over a stand-alone D-dimer test. In patients with extensive unexplained leg swelling in a high probability group, if there is no DVT on US and D-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT [2,4].

Recurrent leg pain is common in patients after an episode of DVT and can be caused by recurrent disease, acute exacerbation of PTS, or non-thrombotic problems. Accurate diagnosis of recurrence is important because the consequences of misdiagnosis are considerable. US is preferable in patients suspected of having recurrent lower extremity DVT. However, persistent abnormalities of the deep veins following a first episode of thrombosis complicate evaluation using compressive US. Prospective follow-up studies have reported residual US abnormalities (non-compressibility) in approximately 80% of patients at 3 months and 50% of patients at 1 year after the diagnosis of proximal lower extremity DVT. Thus, the presence of a non-compressible venous segment on compressive US is not diagnostic of recurrent thrombosis [81]. Although the finding of a new non-compressibility of the common femoral or popliteal vein when compared with a previous US is considered diagnostic of recurrence, this finding occurs in only 10% to 20% of patients with recurrent DVT [2,81,82]. The presence of new non-compressibility of a previously normal popliteal or common femoral vein and/or a 2 mm increase in the residual venous diameter of one of these two veins, when measured in the transverse plane during maximal compression, has a sensitivity of 91% and specificity of 97% for diagnosis of recurrent DVT [81-83]. A 4 mm increase in venous diameter during compression

compared with a previous result on venous US has a sensitivity of 71% and specificity of 100% for diagnosis of recurrent DVT [84,85].

Recommendation

- US examination is one of the primary imaging modalities for diagnosis of acute lower extremity DVT. (Grade 1, Level B)

(2) Venography: Conventional contrast venography is the gold standard for the diagnosis of lower extremity DVT. In this technique, proximal compression tourniquets are applied, and a series of overlapping radiographs are obtained after injection of contrast medium into a dorsal vein in the foot to outline the entire deep venous system of the lower extremity. DVT is diagnosed by the presence of a constant intra-luminal filling defect that is present in more than one view; non-filling of a venous segment despite repeated injection is suspicious, but not diagnostic, of DVT [86]. However, venography is not uniformly available, uncomfortable for patients, and contraindicated in patients with renal insufficiency and severe allergic reactions to contrast medium. Further, inadequate imaging is common in venography; visualization of a venous segment is inadequate in 20% of cases. The dorsal foot vein cannot be cannulated in 5%. Also it can be difficult to interpret, and the designation of 'DVT present' or 'DVT absent' is subject to a considerable degree of intra- and inter-observer variation [2]. Thus, venography is now rarely used in clinical practice and many hospitals are unable to perform the procedure. However, venography is still the reference standard test for DVT, and can be used when other tests are unable to definitely exclude the diagnosis of DVT or for planning endovascular treatment.

(3) CT venography: Although ultrasonography is widely used for the diagnosis of DVT, CT venography has recently been documented as a rapid and available alternative to ultrasonography for lower extremity DVT, with sensitivity and specificity of 89%-100% and 94%-100%, respectively [87-92]. CT venography typically involves injection of contrast media into an arm vein, followed by multi-detector CT imaging timed to coincide with opacification of the deep veins of the legs to allow assessment of these veins for thrombus. Intravenous contrast media, ranging from 100-150 mL, is used with an injection rate of 3-4 mL/s. However, the specifics of the protocol may vary among institutions. CT venography can also be incorporated into a comprehensive examination that includes pulmonary CT angiography for evaluation for both PE and proximal DVT [93]. In patients with suspected PE, a recent meta-analysis found CT venography for the diagnosis of proximal DVT to have high

sensitivity (range, 71%-100%; pooled sensitivity, 95.9%) and high specificity (range, 93%-100%; pooled specificity, 95.2%), comparable to those of US [94]. CT venography is a noninvasive technique and has an inherent advantage of cross-sectional imaging to identify the extravascular sources of extrinsic compression, presumably an underlying cause of DVT. However, it shares the disadvantage with conventional contrast venography of requiring exposure to ionizing radiation and use of iodinated contrast media.

(4) Magnetic resonance venography: Magnetic resonance (MR) venography is a noninvasive imaging modality that shares many of the clinical advantages of US, such as preventing exposure to ionizing radiation or iodinated contrast media [95-98]. MR venography has the advantage of cross-sectional imaging for delineation of extravascular anatomy and identification of potential sources of extrinsic venous compression that may be an underlying cause of lower extremity DVT or suggest alternative conditions that mimic DVT. Therefore, MR venography may be the test of choice for patients in whom ultrasound is not feasible. MR venography can be applied using a variety of pulse sequences or techniques [95-98]. Some techniques such as time-of-flight or phase-contrast venography visualize blood flow without the need for contrast media. However, the imaging of vascular structures is often improved by the use of contrast media [98]. Despite the wide variety of techniques, a recent meta-analysis found MR venography to have both high sensitivity (range, 87.5%-94.5%; pooled sensitivity, 92%) and specificity (range, 92.6%-96.5%; pooled specificity, 95%) [98]. However, it should be noted that MR venography has fewer evaluations in studies, has contraindications, and is not recommended in certain patients, such as those with MRI unsafe devices.

Recommendation

- CT and MR venography are useful diagnostic modalities in patients with highly suspected iliac vein thrombosis with non-diagnostic results of US. (Class I, Level C)

② Imaging diagnosis of chronic lower extremity DVT

US examination has improved diagnostic accuracy and reproducibility and is the preferred first-line diagnostic test for patients with suspected chronic DVT [99,100]. Duplex US can evaluate both venous obstruction and reflux, and includes the following components: direct visualization of deep, superficial, and perforator venous anatomic segments; compressibility of the femoral and popliteal veins; phasic venous flow with and without augmentation maneuvers; and documentation of venous reflux with measurement of valve closure time [101].

Duplex US of the femoral vein may provide indirect evidence of outflow iliac vein obstruction with monophasic waveforms, loss of respiratory variation in the femoral tracing, or poor augmentation of the signal with distal limb compression [102]. The diagnostic accuracy of duplex US may be improved by performing direct duplex US examination of the ilio caval veins; however, reliable and reproducible imaging is limited by body habitus, intestinal gas, and operator variability [103]. For improved diagnostic accuracy, if additional information on the iliac vein is required, patients with suspected chronic thrombotic venous obstruction should undergo additional imaging studies by conventional venography, CT venography or MR venography [104-106]. Ascending venography can accurately identify the post-thrombotic changes in the deep venous system, the collateral patterns and status of ilio caval veins, and thus is useful for determining whether endovascular or surgical intervention is needed and which procedure is feasible [107]. Descending venography can determine the extent of the reflux, and may be useful for determining whether deep venous reconstructive surgery is needed and what type of surgery is feasible [63]. Imaging with intravascular US with cross-sectional views of the vein and adjacent structures has high diagnostic accuracy for ilio caval thrombus burden or ilio caval compression due to May-Thurner syndrome or other adjacent structures, which may influence the therapeutic options [108,109].

Recommendations

- US examination is one of the primary imaging modalities for diagnosis of chronic lower extremity DVT. (Class I, Level B)
- CT or MR venography can be performed in patients with chronic lower extremity DVT if additional information on the state of the iliac vein is required or for planning before surgical or endovascular interventions. (Class IIa, Level C)

4) Anticoagulation therapy

① Preliminary assessment

Before embarking upon anticoagulant therapy, consideration should be given to 1) investigating disorders underlying the development of DVT or PE, 2) ensuring it is safe to anticoagulate the patient, 3) ensuring that monitoring of anticoagulation can be carried out safely and accurately, and 4) clinical assessment of the risks of anticoagulation [4].

Good clinical history taking, physical examination and some laboratory tests are essential in the assessment of factors contributing to the development of DVT and the

fitness of the patient for anticoagulation. The presence of inherited thrombophilia does not influence the choice of initial anticoagulant therapy, the intensity of treatment or the duration of anticoagulation. Therefore, screening of thrombophilia is not always necessary [110]. Due to their pharmacology, the anticoagulants most often used in the management of DVT require assessment of baseline coagulation and renal function prior to embarking on therapy. Use of a vitamin K antagonist (VKA) or low-molecular-weight heparin (LMWH) in patients with impaired renal function could increase the bleeding risk. A baseline assessment of the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) is required to identify prolongation of clotting times, which might contraindicate anticoagulation or complicate monitoring [111-113]. Treatment with all forms of heparin is associated with a risk of developing heparin-induced thrombocytopenia. All patients embarking on anticoagulation with heparin or LMWH should have a baseline platelet count performed before starting. This involves a simple clinical assessment combined with a full blood count and assessment of serum creatinine [114]. Patient age, a history of gastrointestinal bleeding, a history of stroke and a history of concomitant medical illness are important in the assessment of bleeding risk. There is a well-documented association between cancer and DVT. A full clinical history and physical examination for symptoms and signs of underlying malignancy should be performed in patients presenting with apparently unprovoked DVT management. Laboratory tests for tumor markers or CT scan for detection of hidden malignancy is useful; however, the cost effectiveness and effect on the mortality and morbidity due to malignancy is unknown [115].

Recommendations

- All patients presenting with lower extremity DVT should have a full clinical history and examination undertaken with the aim of detecting underlying conditions contributing to the development of thrombosis and assessing suitability for antithrombotic therapy. (Class I, Level C)
- Patients commencing treatment with anticoagulant should have a baseline assessment of renal function, PT and aPTT. (Class IIa, Level C)
- Patients commencing treatment with VKA, heparin, or LMWH should undergo a full blood count. (Class I, Level C)

② Indications for anticoagulation

All patients diagnosed with DVT or PE should undergo anticoagulation. The effect of immediate anticoagulation

therapy was demonstrated in prospective studies [116,117]. This is also true when attempting invasive treatment. Despite differences in the duration and intensity of anticoagulation as well as the choice of anticoagulants according to patients, anticoagulation is the essential in DVT treatment. Certain drugs may be prohibited or used in reduced dose for specific patients. Patients with high risk of bleeding or who are currently bleeding should be excluded from anticoagulation.

Recommendation

- All patients diagnosed with lower extremity DVT require anticoagulation therapy to prevent recurrence and death unless they are bleeding or at risk of bleeding. (Class I, Level A)

③ Choice of anticoagulation therapy

Because anticoagulation therapy requires long-term treatment (>3 months), VKA oral anticoagulant is the standard treatment [118]. Unless the patient is pregnant, which is a contraindication for VKA, there are few reasons to choose other anticoagulants [119,120]. Adjusted-dose subcutaneous unfractionated heparin (UFH) is an effective alternative to VKA, but LMWH is more popular because UFH requires initial laboratory monitoring and twice-daily injection, and is associated with osteoporosis [121,122]. Synthetic pentasaccharides, such as fondaparinux and idraparinux, are not used widely because of concern over bleeding and the lack of an antidote [123]. Recently, new oral anticoagulants (NOACs), such as rivaroxaban, dabigatran, apixaban, and edoxaban, have been evaluated for treatment of DVT and are now available in many countries. These are attractive preferred alternatives to warfarin for long-term management of patients with VTE. However, whether the NOACs have a more favorable risk-benefit profile than warfarin during long-term treatment is unclear. Most studies regarding the choice of anticoagulant have compared them with VKA. LMWH is at least as effective as VKA for treatment of recurrent DVT, extension of thrombi, mortality and major bleeding, and was more effective than VKA in patients with cancer [124]. However, considerations favoring use of LMWH over VKA are limited because the evidence of the benefit of LMWH is of low quality, the estimated absolute advantage compared with VKA is small, and the high cost of LMWH. Recommendation to use LMWH over VKA in cancer patients with DVT is usually limited to those with metastatic disease, impaired liver function, poor nutritional status, or unstable nutritional status, and those who wish to avoid laboratory monitoring. A single study has directly compared rivaroxaban with parenteral anticoagulation/VKA in patients with acute DVT.

Their results have suggested that rivaroxaban is not inferior to VKA in terms of recurrent DVT, major bleeding, or death [125].

Recommendations

- VKA is the standard treatment of lower extremity DVT. (Class I, Level A)
- UFH, LMWH, and NOACs can be considered as alternatives to VKA therapy. (Class IIa, Level B)

④ Duration of anticoagulation

Anticoagulant therapy for DVT should be discontinued if the reduction of recurrent DVT no longer clearly outweighs the increase in bleeding or if patients prefer to stop treatment due to the financial burden, even if the reduction in DVT outweighs the increase in bleeding. The primary goal of trials regarding the optimal duration of anticoagulation is to identify the shortest duration of therapy that results in a post-treatment risk of recurrence is as low as can be achieved [2].

Four systematic reviews have addressed the duration of anticoagulation with VKA, principally warfarin, after an episode of proximal lower extremity DVT [126-129]. A meta-analysis of 15 studies revealed that shorter-term VKA treatment (median, 1.75 months) results in more recurrences than longer-term treatment (median, 6 months) [126]. In two studies comparing 6 and 3 months of treatment with VKA in patients with VTE which was unprovoked or provoked by a reversible risk factor, there was no difference in the risk of recurrence [130,131].

An elevated plasma concentration of D-dimer measured shortly after the discontinuation of a course of VKA treatment for VTE identifies patients at higher risk of recurrence [4]. In the PROLONG study, patients with an abnormal D-dimer level 1 month after discontinuation of anticoagulant for treatment of unprovoked VTE were randomized to resume warfarin or not. When the primary end-points of recurrent VTE and major bleeding were assessed, there were three events among the 103 patients who resumed warfarin therapy and 18 among the 120 who did not (adjusted hazard ratio [HR], 4.26; 95% CI, 1.23-14.6; $P=0.02$) [132].

Recommendation

- VKA should be continued for at least 3 months for treatment of lower extremity DVT. (Class I, Level A)

⑤ Monitoring during anticoagulation

VKA has a narrow therapeutic window and there is considerable inter-individual as well as temporal intra-individual variability, which necessitates regular monitoring. The PT, with the result expressed as international normalized ratio (INR), is the best measure of intensity

of VKA therapy. Cohort studies have established that high-quality INR control is associated with better clinical outcomes. During anticoagulant therapy, particularly the first 90 days, periods of INR >4.5 are associated with increased bleeding episodes (risk ratio [RR], 5.96; 95% CI, 3.68-9.67; $P<0.0001$) while periods of INR <2 are associated with increased thrombotic events (RR, 1.88; 95% CI, 1.16-3.07; $P<0.05$) [133,134]. Poor-quality INR control, as assessed by the percentage of time with INR <1.5 , is associated with a long-term higher risk of recurrent VTE after eventual anticoagulant cessation (RR, 2.7; 95% CI, 1.39-5.25; $P=0.003$) [135]. NOACs, such as dabigatran and rivaroxaban, directly inhibit thrombin or factor Xa, respectively. They have reproducible pharmacokinetics, which allows fixed dosing with no requirement for coagulation monitoring [4].

Recommendation

- The VKA dose should be adjusted to maintain a target INR of 2.0 to 3.0 irrespective of treatment duration in patients with lower extremity DVT. (Class I, Level B)

5) Compression therapy

PTS is a burdensome complication that develops in 25%-50% of patients after acute DVT [23,136]. Its clinical features range from minor limb swelling and discomfort to severe leg pain, edema, skin changes and even ulceration. Because no effective treatment options are available, prevention of PTS is crucial [137]. Compression stockings can prevent PTS by reducing venous hypertension and reflux, and can be used to both mitigate leg complaints and reduce the risk of PTS after acute DVT [138].

Two previous randomized trials suggested that wearing compression stockings for 2 years after proximal lower extremity DVT reduced the risk of developing PTS by 50% [139,140]. Guidelines for the treatment of DVT published in 2010 recommended the use of below-knee graduated elastic compression stockings, which provide 40 mmHg at the ankle, on the affected leg for 2 years after lower extremity DVT to reduce the incidence of PTS [4]. Both trials were small, performed in a single center, and were not placebo-controlled. In contrast, Kahn and colleagues reported the results of a multicenter randomized placebo-controlled trial of active treatment (knee-length stockings with 30-40 mmHg compression) versus placebo compression stocking (knee-length sham stockings without therapeutic compression) for 2 years in 806 patients to prevent PTS after a first proximal lower extremity DVT. The cumulative incidence of PTS was 14.2% for active compression stockings versus 12.7% for placebo compression stockings

(adjusted HR, 1.13; 95% CI, 0.73-1.76; P=0.58). These findings do not support routine wearing of compression stockings after DVT [141]. The efficacy of compression stockings in terms of reducing the incidence of PTS in patients with lower extremity DVT remains controversial.

Because there is no evidence of the benefit of continuing compression stockings use in patients beyond 2 years, this is a decision for the individual patient and their physician. However, compression stockings may be required by patients to control their PTS symptoms beyond 2 years. This is more as a treatment for PTS rather than prevention of PTS.

Regarding the length of compression stockings, there is little evidence from randomized controlled trials about the effectiveness of thigh-length stockings. Prandoni et al.'s trial [142] compared thigh-length compression stockings with below-knee compression stockings. This study failed to show any advantage of the thigh-length over the below-knee compression stockings. PTS developed in 32.6% of patients randomized to the thigh-length and in 35.6% to the below-knee compression stockings, for an adjusted HR of 0.93 (95% CI, 0.62-1.41). Furthermore, thigh-length stockings can be more difficult to fit and often roll down, creating a tourniquet effect. Below-knee compression stockings are thus preferred for prevention of PTS in patients with proximal lower extremity DVT. They have similar effectiveness as thigh-length compression stockings but better compliance and lower cost. However, physician judgment, patient preference and adherence are important issues when deciding on stocking length.

Recommendation

- Compression stockings reduce the risk of PTS in patients with lower extremity DVT. (Class IIa, Level A)

6) Endovascular treatment of acute lower extremity DVT

① Indications for endovascular treatment

DVT thrombolysis has the potential to reduce the risk of PE and the incidence of PTS. Endovascular therapy for DVT consists of catheter-directed thrombolytic therapy (CDT) and percutaneous mechanical thrombectomy (PMT). PMT is usually combined with thrombolysis and additionally involves mechanical agitation or disruption of the large thrombus. Similarly, the thrombus can be removed using suction catheters in combination with thrombolytic agents.

Carefully selected patients with low bleeding risk (often younger patients) with extensive proximal iliofemoral DVT may benefit from thrombolysis, particularly CDT, in which bleeding rates are lower than the systemic thrombolytic therapy [143-146]. CDT should be considered for patients with symptomatic iliofemoral DVT who have symptoms of

less than 14-day duration, good functional status, a life expectancy of 1 year or more and a low risk of bleeding. Especially, when phlegmasia cerulea dolens or venous gangrene is present, aggressive endovascular thrombus removal should be performed on an emergency basis for limb salvage [147-151].

The threshold for thrombus removal strategies in acute femoropopliteal DVT should be higher than that for iliofemoral DVT. Compared with iliofemoral DVT, femoropopliteal DVT is associated with less deranged hemodynamics and a lower risk of recurrent VTE, and many femoropopliteal DVT patients experience symptom resolution or no PTS when treated with anticoagulation and compression stockings alone [139,140]. Multicenter registries have suggested a less favorable outcome for femoropopliteal than iliofemoral DVT treated with thrombolytic therapy [152]. Therefore, endovascular therapy can be performed in selected patients with progression of acute femoropopliteal DVT despite of using anticoagulant therapy or those with severe symptoms [146].

Recommendations

- Endovascular treatment is not routinely recommended in patients with lower extremity DVT. (Class IIb, Level C)
- Endovascular treatment can be considered in patients with acute symptomatic iliofemoral DVT with a low risk of bleeding. (Class IIa, Level B)
- Endovascular treatment for femoropopliteal DVT can be considered in patients with progression of DVT despite anticoagulant therapy or those with severe symptoms. (Class IIb, Level B)
- Endovascular treatment should be considered in patients manifesting venous gangrene or phlegmasia cerulea dolens with a low risk of bleeding. (Class I, Level B)

② Catheter-directed thrombolysis

CDT inserts a catheter into the blood clot through which the thrombolytic agent is infused. Compared with systemic anticoagulation and systemic thrombolysis, CDT achieves early lysis of the blood clot, resulting in rapid relief of the symptoms, improved venous patency rates, and decreased occurrence of PE and PTS. PTS commonly occurs in acute iliofemoral DVT and subsequently, active removal of the thrombi in these circumstances is recommended. In a prospective multicenter registry, CDT using urokinase resulted in 88% successful thrombolysis in patients with acute iliofemoral DVT [152].

The results of randomized trials and meta-analyses suggest that CDT may reduce PTS and improve quality of life without an unacceptable increase in bleeding [153-156]. In a multicenter registry, the major bleeding complication

rate was up to 11.4%, whereas studies thereafter using recombinant tissue plasminogen activator (TPA) reported major bleeding rates of 2%-4% [153,157-160]. The lower major bleeding rates in the later studies may reflect the different drug regimen, US-guided puncture of the access vein, different patient selection criteria, or a combination of these factors. In addition to randomized trials, findings of observational studies suggest that CDT improves venous patency and preserve venous valve function. In a meta-analysis, there was no difference in the rate of PE [146].

Although there is no consensus on the optimal pharmacologic thrombolytic agent for endovascular DVT therapy, commonly used thrombolytic agents include urokinase and TPA. However, data collected for comparing the infusion rates of thrombolytic agents and durations of thrombolysis are currently insufficient [146]. Because the scientific basis is limited, physicians are encouraged to use individual judgment in adjusting doses based on individual patient considerations, including the clinical severity of the thrombotic process, the extent of thrombosis, and the estimated risk of bleeding. Commonly used dosing schemes for CDT of DVT are urokinase, 120,000 units/h; TPA, 0.5 mg/h; reteplase, 0.5 units/h; and tenecteplase, 0.25 mg/h [147].

Thrombolytic infusion times should be minimized and balanced against the lytic process to avoid complications. Follow-up venography is typically obtained every 8 to 24 hours after the infusion is initiated to evaluate residual thrombus. Although thrombolytic infusion time can be extended to remove residual thrombus, thrombolysis should be stopped within 48 hours due to the bleeding risk [161].

Recommendation

- Catheter-directed thrombolysis can be performed primarily in patients with acute symptomatic iliofemoral DVT with a low risk of bleeding. (Class IIa, Level A)

③ Pharmacomechanical thrombectomy

Mechanical thrombectomy can be combined with CDT through mechanical agitation or disruption of the thrombi to decrease the amount of thrombolytic agent needed and shorten the treatment time. High success rates of clot lysis have been reported in studies assessing the effect of combining CDT with PMT, balloon maceration, or aspiration thrombectomy [161-167]. Although these methods are generally considered as safe treatments with lower dose and shorter treatment time, they have not been documented by large randomized controlled trials. The PMT technique used varies according to local institutional resources and expertise. Commonly used mechanical thrombectomy devices include the Arrow-Trerotola PTD

(Arrow International Inc., Reading, PA, USA), Trellis (Covidien, Bacchus Vascular Inc., Santa Clara, CA, USA), Angiojet (Possis Medical, Bayer Healthcare Inc., Pittsburg, PA, USA), Oasis (Medi-Tech/Boston Scientific Inc., Natick, MA, USA), Hydrolyser (Cordis Corp., Inc., Roden, The Netherlands), EKOS (EKOS Corp., Inc., Camberley, UK).

In small retrospective studies, PMT without thrombolysis frequently fails to remove much of the thrombus [168,169], or is associated with a high risk of PE [170,171].

Recommendation

- Mechanical thrombectomy can be performed in combination with catheter-directed thrombolysis to shorten treatment time and reduce the thrombolytic dose. (Class IIb, Level C)

④ Concomitant anticoagulation treatment

When exogenous thrombolytic agents are infused around or within a clot, concurrent re-thrombosis may occur during thrombolysis due to release of thrombin from fibrin. Rapid and effective clot lysis during thrombolysis is dependent on inhibition of concurrent re-thrombosis using anticoagulants. Therefore, the empirical administration of intravenous UFH during CDT of DVT is recommended. Although the evidence regarding the heparin dose is insufficient, the optimal heparin dosing during CDT may differ among thrombolytic agents. Therapeutic level heparin may be appropriate for most patients receiving urokinase, and sub-therapeutic level heparin may be appropriate for most patients receiving TPA [147]. Maintenance doses of heparin (500-1,500 units/h) following 3,000-5,000 unit bolus injection are commonly given during urokinase thrombolytic procedures. The aPTT can be used to guide heparin therapy. Blood sampling should be performed for serial monitoring of hematocrit, platelet count, and aPTT every 6 to 8 hours. The heparin dose is adjusted to maintain the aPTT at 1.5-2.0 fold that of the control. It is recommended to follow a sub-therapeutic regimen consisting of a 2,500-unit heparin bolus followed by a continuous drip at 500 units/h when using TPA. It is desirable to maintain the aPTT time at 1.25-1.5 fold that of the control values [172].

⑤ Periprocedural use of inferior vena cava filter

Although CDT may be associated with asymptomatic radiographic evidence of PE, symptomatic PE appears to be a relatively rare complication of CDT. The incidence of clinical PE during CDT does not appear to exceed that in patients who receive anticoagulation therapy alone [152]. According to the Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) study, which

was the first reported multicenter randomized controlled trial, the incidence of DVT at 2 years after inferior vena cava (IVC) filter placement was significantly higher than that in the no IVC filter group. In contrast, the overall survival rate was not significantly different between the two groups [173]. Therefore, routine placement of permanent IVC filters in patients undergoing CDT for DVT is not recommended in terms of short-term efficacy and long-term complications [2,147,152,173-175].

The introduction of retrievable filters that can be placed and potentially removed when no longer indicated has contributed to their increased overall use. In the recently reported Filter Implantation to Lower Thromboembolic Risk in Percutaneous Endovenous Intervention (FILTER-PEVI) trial [176], IVC filter implantation during PMT reduced the risk of iatrogenic PE eightfold (1.4% vs. 11.3%), without reducing mortality. Similarly, the Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial [156] reported that venographic detection of entrapped thrombus by IVC filter was observed in 11% during or immediately after percutaneous endovascular intervention. However, Protack et al. [175] reported that PE did not occur during CDT. CDT without universal prophylactic IVC filter placement was safe and effective for treating acute DVT. The use of prophylactic IVC filter might be restricted in patients at high risk of PE, such as those with a free-floating thrombus extending into the IVC. Therefore, periprocedural retrievable IVC filter placement can be considered in selected patients after assessing the relative risks vs. benefits of filter placement for those with markedly limited cardiopulmonary reserve, free-floating thrombus in IVC, or with mechanical thrombectomy alone without CDT [148,156,175,176].

Recommendations

- Placement of a permanent IVC filter is not recommended in patients undergoing catheter-directed thrombolysis for lower extremity DVT in terms of short-term efficacy and long-term complications. (Class III, Level B)
- Placement of a retrievable IVC filter during endovascular therapy for lower extremity DVT can be considered after assessing the economic costs for filter placement and removal, cardiopulmonary reserve, presence of free-floating IVC thrombus, and mechanical thrombectomy alone. (Class IIb, Level B)

© Additional balloon angioplasty and stent

Additional endovascular therapy such as balloon angioplasty and stenting can be performed to treat residual

stenotic lesions after CDT. Additional endovascular treatment is necessary for venous obstructive lesion after thrombolysis in May-Thurner syndrome [147,148], although this has not been demonstrated in randomized controlled studies. AbuRahma et al. [177] have reported that adjuvant endovascular treatment is superior to CDT alone in terms of primary patency and long-term symptom resolution in their non-randomized prospective comparison study involving 51 patients with iliofemoral venous thrombosis.

Generally, stent is preferred over balloon angioplasty for treatment of iliac vein obstructive lesions because the fibrotic nature of venous stenosis often results in elastic recoil after balloon angioplasty [178]. Also, in cases of residual infrarenal ilio caval thrombus involving a short segment, stent placement may be preferred over continued thrombolytic infusion to reduce bleeding risk associated with prolonged thrombolysis and decrease procedure time [147,179]. However, for flow-limiting lesions in the femoropopliteal vein, balloon angioplasty is preferred. Because stent has not been thoroughly evaluated for treatment of femoral veins, and it has traditionally been considered desirable to avoid placing stent within mobile areas, such as the knee joint [148,152]. Indications for adjuvant endovascular treatment after CDT include residual flow-limiting reduction in vein diameter, visible flow stasis during contrast injection, opacification of collateral veins, presence of intraluminal filling defect (such as webs), and extrinsic compression [180].

The initial technical success of adjuvant endovascular treatment could be defined as restoration of continuous in-line venous flow from the iliofemoral vein into the IVC and abolition of abnormal collaterals. Reported technical success rate of adjuvant endovascular treatment ranges from 94% to 100% [181-186]. The primary patency rate, assisted primary patency rate, and secondary patency rate of adjuvant endovascular treatment have been reported in several studies. Primary patency is defined as preserved patency without any intervention after technically successful treatment. The 6-month primary patency rate is 82%-95.8% [183,187-189]. The 12-month primary patency rate is 74.1%-95% [177,182-190]. The 36-month primary patency ranges from 56.7% to 69% [177,191]. The 60-month primary patency rate is 38.1%-74% [177,186,192]. Assisted primary patency indicates a technically successful treatment, after which occlusion of the vein did not occur but intervention of any type had been performed to correct an abnormality of the treated segment. The 12-month assisted primary patency rate is 79.7%-96% [185,186,188,190]. The 24-month assisted patency rate ranges from 82.7% to 91% [187,188]. The 60-month assisted patency rate is 62.8% [186]. Secondary patency indicates

restoration of patency after an interventional treatment for venous occlusion. The 12-month secondary patency rate is 85.8%–100% [184–186,188]. The 24-month secondary patency rate approaches 100% [184,188]. The 60-month secondary patency rate was 73.8% and 84% [186,192]. Male sex, recent trauma history, age less than 40 years, and stent length of more than 6cm were reported to be associated with decreased primary patency [186,191].

The rate of symptomatic improvement after adjuvant endovascular treatment is 83% [188]. Moreover, development of venous valve dysfunction or PTS after adjuvant endovascular treatment is infrequent [187,188]. Husmann et al. [187], in their retrospective study of 11 patients, reported development of mild PTS after common iliac vein stenting in one patient after more than 12 months of follow up.

Recommendation

- Additional balloon angioplasty or stent placement can improve symptoms in patients with acute lower extremity DVT if venous flow is disturbed by iliac vein compression. (Class IIa, Level B)

⑦ Endpoint of endovascular treatment

To reduce progression to PTS, early restoration of venous patency and preservation of valvular function is important by completely removing the thrombus [148,153]. Although there is no randomized controlled study or large-scale observational study of adequate endpoints of endovascular treatment, the endpoint of endovascular treatment for acute DVT should be defined as anatomical success, such as restoration of continuous in-line venous flow.

The endpoint of endovascular treatment for acute DVT, in other words, successful restoration of venous flow and thrombus removal, can be determined by venography or color Doppler ultrasonography. Venographic findings include restoration of venous flow without remnant intraluminal thrombus such as a filling defect and abolition of collaterals throughout the iliofemoral vein segment into the IVC [181]. Color Doppler ultrasonography findings include color flow within the veins, normal respiratory variability and augmentation [181]. Unfortunately, adequate ultrasonography for iliac veins is often limited by body habitus, depth, overlying bowel gas, and incompressibility of the retroperitoneal veins. Hence, venography is preferred for monitoring the degree of venous restoration during or after endovascular treatment for DVT, and venographic results can be adopted as an indicator for technical success of endovascular treatment for DVT rather than color Doppler ultrasonography findings [152,153,191,193].

Recommendation

- Restoration of venous flow and presence of residual thrombus should be evaluated by venography prior to removal of sheath after endovascular treatment in patients with DVT. (Class IIa, Level C)

7) Surgical treatment of acute lower extremity DVT

Anticoagulation therapy is the main treatment option for acute femoropopliteal DVT, but anticoagulation only in extensive iliofemoral DVT is not sufficient to prevent later development of chronic venous insufficiency and postphlebotic syndrome [125,148,194]. Therefore, early thrombus removal is necessary [195,196]. However, surgical venous thrombectomy is an invasive treatment with possible complications of anesthesia, bleeding, or PE. Moreover, experienced expert vascular surgeons are not readily available [197,198]. Surgical venous thrombectomy is recommended in selected patients who are candidates for anticoagulation but in whom thrombolytic therapy is contraindicated. Especially in patients with limb-threatening venous ischemia, such as venous gangrene or phlegmasia cerulea dolens, aggressive thrombus removal should be considered if the patient's general condition is acceptable [7,199].

Surgical venous thrombectomy can be performed in selected patients; i.e., those with a first episode of acute iliofemoral DVT, symptoms <14 days in duration, a low risk of bleeding, ambulatory with good functional capacity and an acceptable life expectancy. These limitations are due to previous reports of worse outcomes in chronic DVT or with symptoms having 10–21 days in duration [200–206]. In cases with a bleeding risk, poor general condition, short life expectancy, absence of appropriate equipment or experienced vascular surgeon, conventional anticoagulation may be preferred over high-risk surgery.

The choice of surgical venous thrombectomy techniques is largely guided by expert opinion and case series rather than by comparative trials. Important contemporary techniques include the following: preoperative imaging to define the proximal extent of the thrombus, intraoperative use of positive end-expiratory pressure to reduce the risk of PE, intraoperative completion venography to ensure patency of the iliac vein, stenting of iliac vein stenosis, use of temporary arteriovenous fistula to reduce early thrombosis, and postoperative anticoagulation with careful monitoring [195,196].

Recommendations

- We recommend surgical venous thrombectomy in patients with venous gangrene or phlegmasia cerulea

dolens who are not candidates for catheter-directed thrombolysis. (Class IIa, Level A)

- Surgical venous thrombectomy can be performed in selected patients: a first episode of acute iliofemoral DVT, symptoms <14 days in duration, a low risk of bleeding, ambulatory with good functional capacity and an acceptable life expectancy. (Class IIb, Level C)

8) Endovascular treatment of chronic lower extremity DVT

The most common complication of DVT is PTS, which affects 25% to 60% of acute lower extremity DVT patients [207]. Despite therapeutic anticoagulation and elastic compression stocking therapy, a significant proportion of DVT patients may develop postthrombotic sequelae. Because the iliac vein rarely recanalizes, patients with chronic iliofemoral DVT develop valvular reflux and have persistent venous obstruction, a combination that tends to be associated with the worst forms of PTS [31,208]. Although the severity of PTS can vary, the signs and symptoms can be life-style limiting and include pain, edema, telangiectasia, hyperpigmentation, and ulceration. For this reason, endovascular treatment is often used as a nonsurgical alternative to venous bypass in highly symptomatic patients with chronic DVT [209]. In this setting, endovascular treatment is not expected to result in a normal limb, since it has usually sustained some degree of permanent venous damage. Instead, the primary goals of therapy are improvement in presenting symptoms, reduction of venous disability, and/or healing of existing venous ulcers [147]. CDT rarely produces complete thrombolysis in chronic DVT patients and is instead typically used to complement stent placement or to remove the superimposed acute thrombus in patients with acute-on-chronic DVT [147]. In many patients, particularly those in whom a predisposition to bleeding is identified during the pretreatment evaluation, stent placement may be performed without preceding CDT [181,210].

In reports from a group with extensive experience in venous recanalization, recanalization was technically successful in 83% of occluded iliac veins and in 98% of occluded filter-bearing IVCs; the 4-year primary and secondary patency rates were approximately 35% and 72%, respectively, for iliac vein recanalization and 40% and 80%, respectively, for IVC recanalization [211,212]. An European group assessed recanalization in 89 patients with primary iliac vein occlusion, and reported primary and secondary patency rates at 10 years of 83% and 93%, respectively [213].

The efficacy of this treatment lies in the ability to traverse the hard occlusive clot. This often takes time and perseverance because crossing extensive occlusions involving

the IVC, iliac, and femoral veins can take a full day to be successful. Although there are no high-level randomized controlled data, recanalization of chronic occlusive DVT can be performed safely and successfully and provide significant improvement in venous flow, which leads to symptom relief and improvement in the quality of life.

Recommendation

- Endovascular treatment can be considered in symptomatic patients with chronic lower extremity DVT. (Class IIb, Level C)

9) Surgical treatment of chronic lower extremity DVT

Patients with chronic DVT who are not candidates for endovascular repair or those who failed attempts of endovascular revascularization can undergo open surgical reconstruction. Adams et al. [214] reported successful surgical bypass for iliofemoral venous occlusion refractory to endovascular therapy. Hao et al. [215] successfully treated a patient with symptomatic chronic iliac vein occlusion with a femoro-caval bypass. Complex occlusion of the IVC and iliofemoral veins can lead to PTS. Anaya-Ayala et al. [216] reported a case of complex venous outflow reconstruction related to chronic occlusion of the left iliofemoral vein after failed endovascular interventions. Khanna and Singh [217] suggested that open procedures should be performed in cases of unsuccessful stenting attempts, stent failure, and long occlusions in which stenting may not be feasible.

Open reconstruction for chronic DVT showed reasonable results. Jost et al. [218] reported that venous reconstructions for iliofemoral or IVC obstruction offered 3-year patency rates of 62%. Puggioni et al. [219] have performed surgical reconstitution of postthrombotic deep veins with endophlebectomy of 23 deep venous segments in 13 patients with advanced PTS. Ten patients (77%) remained primarily patent at a median follow-up of 8 months (range, 1-28 months). Vogel et al. [220] analyzed symptom improvement and quality of life in patients with postthrombotic iliofemoral obstruction after common femoral endophlebectomy with iliocaval endoluminal recanalization. After a follow-up of more than 6 months, all patients demonstrated significant improvement in symptoms and venous scores postoperatively. Garg et al. [221] reported the long-term outcome after open surgical and hybrid reconstructions for chronic venous obstructions. Palma vein bypass and femoroiliac or iliocaval polytetrafluoroethylene (PTFE) bypasses showed excellent outcomes with good symptomatic relief.

Common open procedures for chronic DVT include a crossover bypass procedure (Palma-Dale procedure), in-

line bypass surgery, and endophlebectomy. The Palma-Dale procedure has remained a useful technique for venous reconstruction in patients with proximal outflow obstruction. This operation, which was designed for patients with chronic unilateral iliac vein obstruction of any etiology, requires a normal contralateral iliofemoral venous system to ensure venous drainage. In the crossover bypass, the great saphenous vein of the non-affected limb is exposed and rotated at the saphenofemoral junction. An alternative to use of the autologous saphenous vein is use of a 10 mm PTFE graft for femoro-femoral bypass procedures when an adequate-caliber saphenous vein is not available. Reported patency rates are between 70% and 85%, but follow-up periods were variable and objective graft assessment via imaging was not performed in all patients. In-line bypass surgery may be performed for femoroiliocaval obstruction associated with segmental obstruction. An expanded PTFE graft is most commonly used. An arteriovenous fistula is created distally to maintain adequate inflow. Life-long anticoagulation is usually required. Endophlebectomy is an open surgical technique in which the postthrombotic vein is longitudinally exposed at various segments and the synechiae attached to the intimal layer are carefully removed using scissors at the base. Endophlebectomy demonstrated significant improvement in venous scores postoperatively. The venous clinical severity score was decreased ($P=0.02$) from 17 to 9.8 after the operation and the Villalta scale was decreased ($P=0.002$) from 13.6 to 6.0 postoperatively [220].

Recommendation

- Open surgical reconstruction in patients with chronic DVT is reserved for symptomatic patients who are not candidates for endovascular treatment or who failed endovascular treatment. (Class IIb, Level B)

10) Postoperative care

① Anticoagulation therapy

After endovascular treatment is completed, the patient is typically treated with anticoagulants. This is not different from the guidelines for acute DVT patients. Immediately after removing the vascular sheath, anticoagulant therapy is recommended to prevent recurrent thrombosis in the thrombolyzed or stented venous segment and treat distal remnant venous thrombus at the same time. According to international guidelines, parenteral anticoagulation such as heparin, LMWH, fondaparinux is recommended as initial therapy. Oral VKA is the standard oral anticoagulant. However, NOACs of factor Xa blockers and thrombin antagonist may play more important role in the near future because of their relatively low incidence of bleeding complications. Post-procedural anticoagulation is required for all patients regardless of the results of the procedure (partial resolution, complete resolution, or failure) [148,151,175].

Recommendation

- Anticoagulation therapy should be administered after endovascular therapy for thrombus removal. This is not different from the guidelines for anticoagulation therapy in acute lower extremity DVT. (Class 1, Level B)

② Compression therapy

Post-procedural compression therapy is also necessary for all DVT patients. Although proximal thrombus is resolved by intervention, many patients still have leg swelling of variable severity. Compression therapy reduces tissue swelling and enhances calf muscle contractility. During the acute stage of DVT, 20–30 mmHg graduated compression stockings are recommended. This also prevents long-term post-thrombotic complications, such as venous ulcer and dermatitis.

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