Thromboembolic Disorders: Guidance for Return-to-Play

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Abstract:
Venous thromboembolism (VTE) is a major cause of morbidity and mortality. Treatment for VTE in athletes is similar to nonathletes. Early treatment of deep venous thrombosis (DVT) with bed rest and anticoagulation has given way to anticoagulation with early mobilization. Thrombolysis, preferably catheter-directed thrombolysis (CDT), may be used in select patients with upper extremity DVT (UEDVT). Surgical procedures should be reserved for those athletes with UEDVT who fail initial therapy. Compression devices are advocated for the treatment of postthrombotic symptoms (PTS) in lower extremity DVT (LEDVT) and UEDVT. Athletes with DVT should be encouraged to start a gradual return to activities of daily living (ADL) the day they begin anticoagulation therapy. A structured return-to-training program with progressive increase in intensity can begin shortly after ADL mastery, provided the athlete is monitored carefully for recurrence of VTE. Athletes should not engage in contact or collision sports until anticoagulation therapy is complete.

INTRODUCTION
Deep venous thrombosis (DVT) occurs annually in one in 1000 people among the general U.S. population (6,8,13). DVT, with its associated complications, is a significant source of morbidity and mortality. While physical activity and exercise appear to be protective against thromboembolic disorders, case reports of DVT in athletes do exist (1). Examples from published literature include lower extremity DVT (LEDVT) in triathletes (19,25), soccer players (6), runners (13), and a military cadet (8), as well as cases of upper extremity DVT (UEDVT) in football linemen (23), weight lifters (13), and baseball pitchers (9). Despite case reports, no estimates are available for the incidence of thromboembolic disorders in competitive athletes. While anticoagulation treatment guidelines are well established for DVT, no return-to-play guidelines currently exist for athletes with venous thrombosis. Additionally, no randomized controlled trials (RCT) or large cohort studies exist that document the safe timing of exercise in the DVT recovery process. This article discusses the evidence for safe return-to-exercise and competition for athletes with DVT.

EPIDEMIOLOGY
DVT affects more than 250,000 people in the United States each year. At least 116,000 people are diagnosed with their first DVT each year (8). The estimated incidence of DVT from all causes is 0.5 to 1.6/1000 year^-1, a number that may be underestimated because of the number of asymptomatic DVT and inaccuracies of clinical diagnosis (6). In the general population, the majority of DVT occur in the lower extremity. UEDVT is rare, occurring in approximately 2/100,000 person-year^-1 but is the most common vascular condition among athletes (8).

Delayed presentation with DVT is not uncommon. More than 50% of our patients diagnosed with DVT wait at least 3 d before seeking medical attention (8). Complications of DVT include death, pulmonary embolus (PE), recurrent DVT, and postthrombotic syndrome (PTS). Morbidity and mortality can be high. One to five percent of patients presenting with DVT will die from all-cause complications, mainly pulmonary embolism (25). In one study, 30% of patients presenting with their first DVT died within 30 d (8). Up to 50% of patients with DVT develop a PE (2). Despite optimal anticoagulant therapy, DVT symptoms such as leg swelling can take up to several weeks to subside. As many as 40% of patients with DVT develop PTS, symptoms of which include chronic leg pain, leg heaviness, leg swelling, and leg cramping aggravated with standing and alleviated with recumbence and elevation (21). PTS usually occurs in the first 6 months following DVT diagnosis, but its effects can last for years (27). Approximately 20% to 50% of patients with LEDVT and 15% to 25% of patients with
UEDVT develop PTS (6,9,10,23). PTS can be difficult to distinguish from recurrent occult thrombosis. The severity of symptoms may vary over time, and the most extreme manifestation is venous ulcers of the lower leg.

**PATHOPHYSIOLOGY**

Thrombosis development is summarized by Virchow’s Triad of endothelial injury, blood stasis, and increased blood viscosity. These three clot-predisposing factors initiate a cascade of procoagulant reactions that culminate with the formation of a thrombus. Endothelial injury has been highlighted as a primary factor in case reports of athletes with LEDVT involving acute traumatic knee dislocation and repetitive cyclist leg motion over a bicycle seat (6,8,13). Muscle hypertrophy impinging on blood vessels, causing both blood stasis and endothelial injury, has been implicated in both LEDVT and UEDVT (6,8,9,13,23). Compression of the subclavian vein by cervical ribs, clavicular anomalies, and musculoskeletal bands also have been reported in cases of UEDVT (also termed “effort thrombosis” or Paget Schroetter Syndrome). Increased blood viscosity, traditionally implicated in patients with hypercoagulable disorders, also plays a role in patients with erythrocytosis and marked dehydration (13).

**RISK FACTORS**

Standard risk factors for DVT are immobilization, pregnancy, recent surgery, malignancy, older age, smoking, hypercoagulable states, connective tissue disorders, sex steroid administration, severe dehydration, and major trauma (6,13). Competitive athletes often are placed under conditions where they are exposed to several risk factors. These risk factors can include orthopedic trauma, postinjury immobilization, frequent and prolonged travel, hemococoncentration after exertion, and polycythemia as seen with altitude training and exogenous Epo administration (13). While cast immobilization, hypoxic training, air travel, doping, misuse of nutritional supplements, and pathologic training potentially may contribute to an increased risk of thrombosis, there is no strong evidence to suggest that these factors clearly predispose the competitive athlete to thrombosis (1,10,13). Case reports have described athletes presenting with UEDVT after pitching and following heavy upper-body workouts involving repetitive arm abduction (9,23). Literature also describes athletes who presented with LEDVT following popliteal contusion, car rides longer than 3 h, and elective abortion (6,8,13). However, there is no consensus that elite athletes as a whole are at higher risk for venous thromboembolism (VTE). More study is needed.

**CLINICAL PRESENTATION**

Published case reports describe athletes presenting with DVT following heavy bouts of exertion, after competition travel, and orthopedic injury sustained during competition (6,13,19,23,25). Some cases have reported DVT in athletes following only mild to moderate activity (6). Patients with VTE typically present with complaints of limb edema and pain that is increased with provocative maneuvers. Low-grade fever, venous distension, increased limb circumference, extremity cyanosis, and tender palpable cords may be noticed (6,7,11,23).

**DIAGNOSIS**

Clinical examination has low sensitivity (11%) and a low predictive value (25%) for DVT; however, it has demonstrated moderate to high specificity (76%–85%) (8). History and physical exam findings alone have a predictive value of only 15% (18). Clinical prediction algorithms, which rely on the initial risk stratification of athletes based on pretest probability, have been developed to facilitate the diagnosis of VTE (9a). Pretest probability of DVT may be estimated by a well-validated clinical prediction rule, such as the Wells model, which takes into account the clinical features of active cancer (1 point), lower extremity paralysis, paresis, or immobilization (1 point), recent surgery with bed rest for 3 d (1 point), localized deep vein tenderness (1 point), full length leg swelling (1 point), unilateral calf swelling >3 cm (1 point), pitting edema (1 point), collateral superficial veins (1 point), and probable alternative diagnosis (−2 points) (26). A score of zero is considered low risk, while a score of one point or higher is considered moderate or high. Athletes with a moderate to high probability should undergo duplex venous ultrasound with compression to rule out LEDVT. Athletes with a low pretest probability may be screened first with a highly sensitive D-dimer assay. DVT is ruled out in low-risk athletes with a negative D-dimer assay. Those low-risk athletes with a positive D-dimer must have DVT ruled out via compression duplex ultrasound (18). Ultrasound is the initial test of choice because it is noninvasive, and it has high sensitivity (93% for proximal LEDVT, 96% for UEDVT) and specificity (98% for proximal LEDVT, 93.5% for UEDVT) in the investigation of peripheral DVT (14,17). If initial ultrasound results are negative and DVT is strongly suspected, ultrasound should be repeated in 3 to 7 d (18). Additionally, computed tomography (CT) venography (sensitivity 89%–100%; specificity 94%–100%) or magnetic resonance (MR) angiography (sensitivity 100%; specificity 100%) can be used to confirm the diagnosis (13,14,18).

**TREATMENT**

**LEDVT**

Anticoagulation remains the mainstay of VTE therapy whether the patient is a competitive athlete or a member of the general population. It maintains the patency of venous collaterals, reduces thrombus propagation, and reduces the incidence of thrombus embolization (11,13). Anticoagulation is begun with subcutaneous low molecular weight heparin (LMWH) or unfractionated heparin (UFH), and concurrent initiation of a vitamin K antagonist (VKA) like warfarin. LMWH or UFH is continued for at least 5 d and discontinued once a therapeutic international normalized ratio (INR) range of 2.0 to 3.0 has been achieved for 24 h (8). In patients with DVT, the dose of VKA should be adjusted to maintain an INR range of 2.0 to 3.0 (target of 2.5) for all treatment durations. For patients with DVT secondary to a transient risk factor, anticoagulation with VKA is continued for 3 months (11). Patients with unprovoked (i.e., idiopathic) DVT should be anticoagulated with a VKA for at least 3 months, then undergo risk-to-benefit ratio evaluation for long-term therapy. Patients with a first unprovoked VTE that is a proximal DVT, and in whom risk factors for bleeding are absent and for whom good anticoagulation monitoring is achievable, should undergo...
long-term anticoagulation when this is consistent with patient preference. For patients with a first unprovoked distal DVT, 3 months of anticoagulation is sufficient (11). In patients with extensive acute proximal DVT (e.g., iliopopliteal DVT with symptoms <14 d) who have a low bleeding risk, CDT followed by balloon angioplasty and stent placement may be used to reduce acute symptoms and postthrombotic morbidity, provided adequate expertise and resources are available (11).

UEDVT

Although no RCT have evaluated the use of anticoagulation for the initial treatment of UEDVT, several small prospective cohort studies have reported low rates of recurrent DVT, PE, and major bleeds using treatment protocols for UEDVT similar to those for patients with LEDVT (11,13,23). Thus, for patients with acute UEDVT, the American College of Chest Physicians (ACCP) recommends anticoagulation treatment as described for LEDVT. Although some studies report good success of thrombolytic therapy in establishing early and maintaining late venous patency, the overall quality of evidence remains low (11). It has been suggested that catheter-directed thrombolysis (CDT) may reduce PTS in athletes with UEDVT. It also has been suggested that CDT may yield higher rates of clot resolution and reduces risk of serious bleeding compared with systemic thrombolysis (11,13). However, the largest prospective study examining CDT reported a substantial follow-up recurrence rate of 23% (11). More study is needed to determine whether thrombolytic therapy is superior to anticoagulation in important clinical end points such as PE, recurrent VTE, bleeding, and PTS. The ACCP recommends against routine use of systemic or CDT therapy for most patients with UEDVT. However, in select patients with acute UEDVT who present with severe symptoms of recent onset (i.e., less than 7 d) and who pose a low risk of bleeding, CDT may be used for initial treatment, provided appropriate expertise and resources are available (11).

Surgery

A number of surgical reviews have advocated for thrombolysis and angioplasty or stent placement followed by early or late surgical decompression of thoracic outlet syndrome. However, the data and safety of these approaches are limited and derived from small, uncontrolled case series (9,11,23). For most patients with acute UEDVT, the ACCP recommends against the routine use of catheter extraction, surgical thrombectomy, transluminal angioplasty, stent placement, staged approach of lysis followed by interventional or surgical procedure, or superior vena cava filter placement. These interventions, however, including surgical decompression in cases of obstruction to thoracic vascular structures, may be considered in athletes with acute UEDVT and severe persistent symptoms who have failed conservative measures, including anticoagulation, structured physical therapy, weight loss, and nonsteroidal antiinflammatory drugs (NSAID) (11,13).

Compression Therapy

Venous compression devices long have been used in the initial treatment of LEDVT, despite a paucity of evidence-based literature to support their use. However, combined data from five trials over the last 10 yr suggest that the use of venous compression reduces the incidence of PTS (2,10,15). Mild to moderate PTS decreased from 37% to 22%, and severe PTS decreased from 12% to 5% (15). Overall, the number needed to treat with venous compression to prevent one episode of PTS was five (15). Given the potentially debilitating effects of PTS and the low potential for harm, the ACCP recommends elastic compression stockings with an ankle pressure gradient of 30 to 40 mm Hg for the prevention of PTS in patients with symptomatic proximal LEDVT. Compression therapy should be started as soon as possible after initiating anticoagulation and should be continued for a minimum of 2 yr. The treatment of PTS has been evaluated only in small or methodologically flawed trials. Based on limited data, for patients with severe edema of the leg due to PTS, a course of intermittent pneumatic compression is suggested. For patients with mild edema, elastic compression stockings are recommended (11).

Unlike lower extremity PTS, no controlled studies have evaluated the effectiveness of elastic bandages or compression sleeves in the prevention of upper extremity PTS. Thus the routine use of elastic compression is not recommended for the prevention of PTS after UEDVT (11). Likewise for treatment of upper extremity PTS, there exist no controlled studies evaluating the effectiveness of elastic bandages or compression sleeves. Anecdotal evidence, however, exists suggesting that patients with upper extremity PTS may derive symptomatic relief from elastic bandages or compression sleeves. Since their use is unlikely to cause harm, elastic bandages and compression sleeves are recommended in patients with UEDVT who have persistent pain and edema (11).

PROGNOSIS/COMPLICATIONS

Patients with VTE who undergo anticoagulation experience marked reductions in complications of VTE compared with those who remain untreated. Although radiographically demonstrable clot lysis occurs in only 50% of anticoagulated patients (6), heparin (UFH or LMWH) significantly reduces clot propagation, recurrent PE, and mortality (11). Mortality is high when anticoagulation is not used. Weight-appropriate unmonitored LMWH administered subcutaneously is as effective and as safe as intravenous UFH. In fact, a recent analysis of 17 studies demonstrated that LMWH was associated with fewer thrombotic complications and less major bleeding than UFH (11).

While many previously active patients with LEDVT attempt return to an active lifestyle, the long-term clinical outcomes often are complicated by persistent symptoms. One study found that 82% of patients with their first DVT suffered from recurrent symptoms at a mean follow-up of 6.6 yr (27). As previously mentioned, early ambulation and compression therapy may mitigate these symptoms. The general knowledge concerning quality of life and burden of illness in these patients is not known. More study is needed.

For patients with LEDVT, the overall prognosis is good. Of patients treated with thrombolyis, 80% to 90% returned to a long-term asymptomatic state (13). It also appears that the prognosis with anticoagulation is favorable. In a literature review of more than 2,500 patients, no superiority of
treatment was found between anticoagulation alone and thrombolysis for the general treatment of UEDVT (23).

In cases of external compression such as thoracic outlet syndrome or clavicular impingement, patients appear to benefit from acute correction of the anatomy. One study reported that all patients who underwent first rib resection were free of long-term symptoms. Another study that examined UEDVT in elite baseball players found that four players who underwent first rib resection were able to return-to-play at previous levels or better (11). While the overall data are positive, they are admittedly limited. Thus, it is suggested that surgical decompression be reserved for patients with severe persistent symptoms after failing conservative therapy (11,23).

RETURN-TO-ACTIVITY/PLAY

Traditionally, patients with active DVT were hospitalized and placed on bed rest for 7 to 10 d for fear of PE development in those who remain active. Soreness often precluded a return to daily activities in the first few weeks after DVT, especially in patients entering their sixth and seventh decades of life. Thus, sedentary patients generally followed a gradual 6-wk return to daily activities. Over the last two decades, however, this plan of care has been challenged, particularly for athletes. The early treatment of acute DVT with bed rest and anticoagulation has given way to anticoagulation with early mobilization (2,10,11,22).

Randomized trials and observational studies suggest that a majority of patients with DVT may begin ambulation within 24 hours of anticoagulation provided they have adequate cardiopulmonary reserve and no clinical evidence of active pulmonary embolism (2,10,21). Evidence suggests that these patients who ambulate early are not at higher risk for developing PE, nor does it aggravate acute DVT symptoms. In fact, early walking may reduce the risk of DVT extension, improve the resolution of DVT symptoms, and reduce the long-term symptoms of PTS. Provided that immediate rest, elevation, and anticoagulation have reduced the initial edema and inflammation, it thus seems prudent to permit, and even encourage, the athlete with DVT to engage in light ambulation as tolerated within the first 1 to 2 d after beginning anticoagulation.

While data for anticoagulation and early mobilization exist, data guiding return to physical activity are sparse. There are no RCT investigating when it is safe to return to sport following VTE. There are no expert consensus-derived clinical practice guidelines on the topic.

### Table 1.
Return-to-training recommendation in weeks after anticoagulation initiation.

<table>
<thead>
<tr>
<th>Weeks 1–3</th>
<th>Gradual return to ADL</th>
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<tbody>
<tr>
<td>Week 4</td>
<td>Start nonweight-bearing exercise (e.g., swimming)</td>
</tr>
<tr>
<td>Week 5</td>
<td>Start nonimpact-loading exercise (e.g., cycling)</td>
</tr>
<tr>
<td>Weeks 6+</td>
<td>Start impact-loading exercise (e.g., commence return-to-running program)</td>
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In their case report of a female triathlete with acute LEDVT, Roberts and Christie suggested a gradual progressive return to training program (Table 1) (19). At the start, they recommend the gradual introduction of activities of daily living (ADL) over the first 3 wk of anticoagulation. This is based off animal models of the natural history of venous thrombosis, which demonstrate that thrombus endothelialization and adhesion to vessel wall begin early in the first 3 wk after clot formation. Once endothelialization and adhesion take place, the potential for clot migration and embolism decreases. Thus, during the first 3 wk of anticoagulation, athletes should engage in gradual return to ADL. By weeks 4 to 6, clot lysis and recanalization have occurred. It is during weeks 4 through 6 of anticoagulation that Roberts and Christie suggest a gradual return-to-training regimen that begins with nonweight-bearing exercise (e.g., swimming) in week 4, then nonimpact-loading exercise (e.g., swimming and cycling) in week 5, followed by the gradual introduction of impact-loading exercise (e.g., running) in week 6. While a template for the gradual introduction of running is not specified, such might be accomplished by use of an 8-wk return-to-running protocol as outlined by O’Connor and Wilder (16) (Table 2). Athletes should be instructed to discontinue any activity that results in their case report of a female triathlete with acute LEDVT, Roberts and Christie suggested a gradual progressive return to training program (Table 1) (19). At the start, they recommend the gradual introduction of activities of daily living (ADL) over the first 3 wk of anticoagulation. 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in return of symptoms or signs and report any blood loss or bruising. While on warfarin, athletes will need weekly INR labs until a stable INR has been reached, at which point lab monitoring can be performed on a monthly basis (11).

Individuals with acute VTE should not participate in collision or contact sports. Individuals in noncontact sports may participate after appropriate counseling, unless that sport is a suspected cause for VTE or has additional environmental risks (e.g., SCUBA diving) (11).

Those with UEDVT who are determined to have an underlying cause for thrombus should not participate in aggravating activities until any structural abnormalities have been corrected (13).

If individuals have completed a course of anticoagulation and a hypercoagulability laboratory evaluation (as needed for a positive family history of VTE or personal history of recurrent idiopathic VTE) is negative, return-to-play with gradual increase in intensity is recommended with careful monitoring for recurrent VTE and management of PTS. Strong recommendations should be given to the athlete about the possible instigating factors that may have led to the initial event so that appropriate preventative measures can be instituted (13).

**PREVENTION**

Multiple studies have demonstrated the effectiveness of graduated compression stockings in the prevention of DVT in hospitalized patients (20). The study of graduated compression stockings in athletes is limited to a few small treadmill studies of healthy runners. Two studies found no significant physiologic benefit, while a third found that running performance was improved at anabolic and metabolic thresholds (4,5,12). Significantly decreased incidence of delayed onset muscle soreness and greater subjective comfort in runners wearing low-grade compression stockings were benefits noted in other studies (3,4). None of the studies involving athletes, however, evaluated the role of compression stockings in the primary prevention of DVT.

The role of exercise in the prevention of VTE has been the subject of much scrutiny. Chronic sports participation or endurance training is associated with overall decrease in risk of venous thrombosis and a reduction in various markers of coagulation. Light to moderate exercise thus is likely to be of benefit. However, there is enhanced platelet reactivity and coagulation in response to vigorous exercise (1). Since vigorous exercise is an integral part of the elite athlete's training regimen, some suggest that this may place elite athletes at a higher risk for thrombosis.

While there is not conclusive evidence that properly hydrated athletes have a decreased incidence of VTE, there is evidence of increased incidence of VTE in hemococoncentrated or polycythemic individuals. When combined with the observation that there is enhanced platelet reactivity and coagulation in response to vigorous exercise, it would seem prudent to recommend sufficient oral intake, particularly for those engaging in high-intensity workouts.

Those who suffer competition injury requiring immobilization greater than 3 d should receive early prophylactic anticoagulation in addition to physical antithrombotic measures (13). For athletes with a history of DVT using air travel, LMWH should be considered for prevention of DVT recurrence. In addition, Eichner has recommended eight strategies for prevention of clots. These include sitting in seats that allow leg extension, hourly aisle walks, not crossing legs, wearing of loose clothing, hydration with water or juices, consuming low-fat meals, fidgeting, and thinning blood with aspirin or LMWH if prone to clotting (7).

**CONCLUSION**

Venous thromboembolism can occur in athletes following strenuous exertion, prolonged air or automobile travel, and orthopedic injury. While it is not known whether elite athletes are at higher risk for VTE, the nature of their training and competition schedules exposes them to various risk factors. A high index of suspicion is needed to diagnosis VTE in the athlete, as many patients do not exhibit hallmark signs, and the rates of short- and long-term complications are high (6,8,18). Those athletes diagnosed with VTE should undergo anticoagulation therapy. Selected cases may warrant alternate additional therapies or procedures. Compression therapy and rapid mobilization are crucial to shorter recovery times and decreased long-term complications. Return-to-play should follow a structured program of gradual increased activity as tolerated by the patient. More study, preferably RCT or large cohort studies, is needed to examine the safe timing of return-to-play in the VTE recovery process.

**References**

Hypercoagulability in Athletes

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Introduction

An active 42-year-old man was diagnosed with a lower extremity deep vein thrombosis (DVT) and appropriately anticoagulated. He asked when and how to return to his normal physical activity; he did so and anticoagulation was discontinued 3 months later. Soon after, he was diagnosed with a recurrent DVT, and subsequently found to be protein S-deficient. In another case, an active 55-year-old man was diagnosed with atrial fibrillation and placed on long-term warfarin therapy. He asked if it was safe to run a marathon while on warfarin.

These two vignettes highlight questions about the management of coagulation and coagulation disorders in athletes. Does athletic competition increase an athlete’s thrombotic risk? Who should we screen and how? When can athletes return to activity and what limitations should be advised?

Venous thrombosis is a common disorder that affects one in 1000 per year [1] and can be associated with significant sequelae. Embolization is a significant risk and the acute symptoms of pain and swelling can be debilitating. Post-thrombotic syndrome may occur in as many as 60% of patients with DVT [2] and presents as chronic pain, edema, induration, pigmentation, venectasia, varicosis, and venous ulcers.

Remembering Virchow’s triad of stasis, endothelial injury, and hypercoagulability will help one identify risk factors for thrombosis. Athletes, especially elite athletes, are placed under conditions in which they are exposed to several of these risk factors such as trauma, immobilization after injury, frequent travel, hemoconcentration after exertion, and polycythemia. Female athletes on oral contraceptives have an added risk for thrombosis. Several articles [3–5] have been published regarding preventative measures for venous thromboembolism (VTE) in athletes, and multiple studies have outlined the most appropriate treatment for an acute VTE [6,7,8]. However, little has been published regarding recommendations for athletes who have had a VTE concerning activity and how they should be managed afterward.

Persons with a hypercoagulable disorder are at an added risk for an acute thrombotic event. Activated protein C (APC) resistance is the most common cause for hereditary thrombophilia and is most commonly associated with a factor V Leiden mutation (90%–95%) [9••]. Presence of this gene results in inability for APC to inactivate factors V and VIII, which in turn leads to unchecked coagulation [9••]. Allele frequency in the general population of white European subjects is 4%, but in nonwhite populations is extremely uncommon [9••]. The relative risk of thrombosis for carriers of the factor V mutation is thought to be increased seven times for heterozygotes and 80 times for homozygotes [10]. Another mutation involves a single nucleoside transition in the gene for prothrombin (prothrombin 20210A mutation). This mutation results in approximately 30% higher prothrombin levels in heterozygotes compared with healthy controls, which is presumed to be the mechanism for its thrombotic effects [11]. Prevalence of this mutation among healthy controls has varied in studies from 0.7% to 6.0%, and its presence has been associated with a relative risk of thrombosis of 2.8 [12]. This prothrombin 20210A mutation is uncommon in nonwhite populations [9••]. Antithrombin (AT) III, protein C and S deficiencies are also associated with thrombophilia. Gene frequency in the population for AT III, and proteins...
C and S is 0.1%, 0.33%, and 0.5%, respectively. Protein S deficiency has been related to 1.4% to 7.5% of hypercoagulability cases and protein C deficiency to 1.4% to 8.6% [13]. AT III is associated with 0.5% to 4.9% [9•] of cases although the risk for thrombosis with this deficiency is higher [14]. Hyperhomocysteinemia has been shown to be a risk for venous thrombosis and corresponds to an odds ratio of 2.5 when compared with healthy controls [9••]. Elevated levels of factors VIII and XI have also been found to result in a fivefold and 2.2-fold increased risk, respectively [9••], although the genetic relation of these elevated levels is being investigated. A study by Hilberg et al. [15] examined the prevalence of the main causes of hereditary thrombophilia in a German National athletic team and concluded that gene frequencies for these disorders corresponded to the general population.

Etiology
There are three major influences that predispose to thrombosis: injury to the endothelium, alterations in blood flow, and alterations in the blood itself. Endothelial damage results in local procoagulant functions [16]. Initial endothelial injury activates platelets, resulting in adhesion to subendothelial collagen with von Willebrand’s factor, shape changes, and aggregation (interadherence) [17]. These events lead to the release of several stored products, such as ADP and fibrinogen, and the synthesis of thromboxane A2. The complex that is formed in turn activates several coagulation factors in the intrinsic coagulation pathway. In addition, injured cells release tissue factor, which activates the extrinsic coagulation cascade. Both the intrinsic and extrinsic coagulation pathways entail a series of transformations of proenzymes to activated enzymes, ultimately resulting in formation of thrombin, which converts soluble fibrinogen into insoluble fibrin.

Several case studies have been published about the relationship of thrombosis and exercise [17–21]. Primary upper-extremity deep venous thrombosis (UEDVT) is thought to be related to trauma to the subclavian vein [22]. Heavy upper extremity exertion results in microtrauma to the axillo-subclavian vein leading to activation of the coagulation cascade [6••, 22], and has been termed effort thrombosis or Paget-Schroetter syndrome. Compression and stress of the subclavian vein can also develop in athletes with hypertrophied muscles who do heavy lifting or repetitively abduct their arms [6••]. Similar motions are commonly seen in rowing, wrestling, weight lifting, baseball, softball, gymnastics, basketball, hockey, tennis, golf, football, handball, squash, boxing, swimming, volleyball, and parachute jumping [6••, 23]. Additional risk factors for UEDVT are the presence of cervical ribs, long transverse processes of the cervical spine, musculoskeletal bands, and clavicular or first rib anomalies, which all favor subclavian vein compression [24].

Several case reports of lower extremity thrombosis in athletes have also been published [21,25]. Mechanisms of injury to endothelium include knee dislocation, ischemia from muscle hypertrophy, and repetitive microtrauma such as cyclist leg motion over seats [26]. Muscle hypertrophy can also lead to compression of venous structures, leading to stasis. Other risks for lower extremity thrombosis include injury associated with surgery or cast immobilization.

Risk Factors
Hemoconcentration
The significance of the contribution of hemoconcentration to thrombotic events is undetermined, although an increase in concentration has been demonstrated in several studies [26, 27]. Adequate hydration during and after exercise decreases this effect. Because most hemoconcentration is short lived with exercise, it may not be significant unless combined with other thrombotic risk factors.

Injury and immobilization
Recent trauma has been demonstrated to be associated with a 13-fold increased risk of VTE [28] in a population-based study. A higher incidence has been associated with head injury, lower extremity or pelvic fractures, and spinal cord injury. Even minor injuries resulting in minor trauma to endothelium can result in thrombosis as seen with Paget-Schroetter syndrome [22].

Stasis can localize coagulation proenzymes making them more likely to be converted to enzymes [29]. Meissner et al. [29] observed that patients with venous thromboembolism had a higher prevalence if immobilized for greater than 3 days. In addition they suggested in their discussion that hypercoagulability might persist for at least 1 month after injury after noting persistent elevations in markers for activated coagulation. However, their study suggested that duration of immobilization and obesity were the only significant predictors of thromboembolism in injured patients [29].

Travel
Athletes are traveling longer distances to tournaments, matches or games. A recent case control study by Ferrari et al. [30••] examined subjects who had a VTE and compared them with controls. They found that a history of recent travel by air, train, or car was found four times more frequently in the VTE group. Most commercial aircraft are pressurized to about 8000 feet of altitude. This results in mild hypoxia that may be concerning in certain medical conditions. Two studies by Bendz et al. [31, 32] examined the association between acute hypoxia seen during airplane flights and activation of coagulation and found that markers of activated coagulation transiently increased by two- to eightfold when subjects were rapidly exposed to a hypoxic and hypobaric environment of 76 kPa. Travel duration longer than 4 hours within the previous 2 months was also seen as an independent risk factor in 15.5% of patients presenting with a VTE [33].
Erythrocytosis
Training at high altitudes or simulating living in a high-altitude environment using modified hypoxic chambers is a technique used to increase the hemoglobin and hematocrit, and possibly improve performance when competing at sea level. Multiple studies have demonstrated that there is an increase in hemoglobin synthesis and a greater concentration in persons exposed to high-altitude environments [32,34,35,36••]; however, there is little published regarding the effects of this high concentration. A study by Jha et al. [36••], examined the incidence of stroke in a high-altitude area over several years. Although the subjects were not elite athletes, they were young soldiers of armed forces serving at altitudes greater than 4270 m. Stroke incidence was 13.7 per 1000 in high altitude compared with 1.05 per 1000 in low altitude, and 75% of cases were found to have polycythemia [36••]. This supports the idea that erythrocytosis may increase susceptibility to thrombus.

Multiple articles and commentaries have related the increased viscosity effects of recombinant human erythropoietin (rhEpo) to stroke and death of athletes [37–39]. Berglund and Ekblom [40] investigated the effects rhEpo on blood pressure and found that rhEpo induced a significant increase in systolic blood pressure of 14 mm Hg during exercise.

Platelet adhesiveness and aggregability changes after exercise Platelet adhesion to sites of endothelial injury is closely followed by platelet aggregation (platelet interadherence). Once the primary aggregation begins, thrombin is generated and the coagulation cascade is set in motion. Todd et al. [41] compared healthy older and younger men after exercise and found that older men have an increase in thromboxane B2 levels 30 minutes after exercise, and may be more predisposed to platelet activation. Another study by Wang et al. [42] examined the difference that moderate and strenuous endurance exercise has on platelet aggregation and adhesiveness. In their active healthy group, platelet adhesiveness and aggregation were enhanced by severe exercise and aggregation was decreased by moderate exercise. However, Ahmadizad and El-Sayed [43] state that the evidence for this increase in activation and function is not clear, as there have been studies that show an increase, a decrease, or no significant change after endurance exercise.

Hormonal therapy
Oral contraceptives are commonly used not only for birth control but also for medical management of amenorrhea and osteoporosis in the female athlete triad. Venous thrombosis has become less common with low-dose preparations of oral contraceptives, but their use still adds a significant fourfold increased risk. For athletes with a genetic thrombophilia the risk is even higher. Vandenbergroucke et al. [44] found that women who used low-dose contraceptives and had a heterozygous factor V Leiden mutation had a 30-fold increased risk for thrombosis and those with a homozygous mutation had an estimated 100-fold increased risk.

Screening
Initial evaluation of athletes during preparticipation examinations should focus on thrombotic episodes in family members or any personal history of thrombotic events. The history should identify the use of prothrombotic drugs such as oral contraceptives, hormone replacement therapy, or epogen, and unusual training practices such as high-altitude training. For athletes with a positive personal or family history of a thromboembolic event, it may be reasonable to review records for a prior evaluation [9••]. Appropriate evaluation for high-risk thrombotic states should include AT III, protein C, and protein S levels, in addition to presence of antiphospholipid antibodies, factor V Leiden, and prothrombin 20210A mutations and homocysteine levels [7••,9••]. Any laboratory evaluation that has not been done should be ordered. Routine screening for athletes without any significant history is not recommended. Hilberg et al. [15] state in their discussion of APC resistance that screening elite athletes is necessary to identify individuals at high risk so that measures for preventing thrombosis can be taken. This recommendation stems from the prevalence of APC resistance in the study group that was consistent with the prevalence in the general white population coupled with the previously mentioned added risks. Individual consideration should be made based upon the ethnicity of the athlete, as the incidence of prothrombin 20210A and factor V Leiden in nonwhite populations is low [7••,9••].

Diagnosis
Typical complaints of patients with VTE include edema and discomfort in the affected limb, and increased pain with provocative maneuvers. Physical examination may show low-grade fever, cyanosis in the limb, a tender palpable cord, edema with increased limb circumference, and possibly venous distention. Objective testing should be performed to confirm or exclude the diagnosis. Duplex ultrasound is the initial test of choice because it is noninvasive and has a high sensitivity and specificity for peripheral DVT [6••,45]. If ultrasound results are negative and DVT is strongly suspected, further studies include venography and magnetic resonance angiography [6••].

Management
The mainstay of therapy is anticoagulation. Anticoagulation maintains the patency of venous collaterals, reduces propagation of the thrombus, and reduces the incidence of embolic phenomenon [6••,7••,9••,46]. Initial medications should be either low molecular weight heparin (LMWH) or unfractionated heparin with concurrent initiation of warfarin [6••,7••,9••]. INR should be maintained between 2.0 and 3.0 [47••]. Patients with first episode of VTE that have a reversible or time-limited risk factor should be treated for at least 3 months, whereas those with an idiopathic VTE should be treated for 6 months. Patients with continuing risk factors or
with recurrent VTE should be treated for 12 months or longer. Anyone with three or more episodes of VTE should be on indefinite anticoagulation [47••]. Once medications have been started and symptoms of pain and swelling are controlled, patients may ambulate [48].

In athletes with UEDVT, it has been recommended that thrombolysis be strongly considered to prevent the long-term effects of post-thrombotic syndrome manifested by chronic arm and hand aching and swelling [6••,7•,46, 49,50•]. Catheter-directed thrombolysis is recommended over systemic thrombolysis as it achieves higher rates of complete clot resolution with lower doses of medication and reduces the risk of serious bleeding [6••,51]. The time of symptom onset to initiation of thrombolysis influences the success rate. The best success occurs if thrombolysis is begun within 7 days of onset of symptoms [7•,8•,21,46], although longer times (up to 3 weeks) have also been successful [21,50•,51].

In lower extremity DVT, the use of thrombolytic therapy is controversial as most patients treated with only anticoagulants have uncomplicated courses. Thrombolytics may be considered for patients without contraindications who have significant swelling and symptoms [52]. If used, they should be started at the earliest opportunity. Conservative measures such as graduated compression stockings have been shown to reduce the incidence of post-thrombotic syndrome in patients with lower extremity DVT [2], and may also be added.

If thoracic obstruction to vascular structures contributed to an UEDVT, further therapy involving conservative measures versus decompression of the restriction may be necessary [6••,8•,46,49,50•,51]. Joffe and Goldhaber [6••] report a preference of conservative therapy involving structured physical therapy, weight loss if needed, and nonsteroidal anti-inflammatory drugs rather than early surgical decompression after thrombolysis. If indicated, decompression involves surgical resection of part of the first rib or clavicle or lysis of dense adhesions around the subclavian vein [6••,51]. The aim is to relieve positional pinching by the subclavius muscle and the lower fibers of the anterior scalene against the first rib [46]. The exact timing of when to perform the decompression is still debated. Some advocate early decompression after thrombolysis during the same admission [45,46], but most cases are determined on the flow quality and severity of residual symptoms [8•,46,49]. Following decompression, subclavian stenting can also be performed for those athletes with persistent venous strictures [49,50•], but their long-term effectiveness has not been extensively studied. Stenting prior to decompression should not be attempted as positional pinching can lead to damage of the stent and a high risk of recurrent thrombosis [46].

Prognosis
A total of 80% to 90% of patients treated in the above manner for UEDVT returned to a long-term asymptomatic state, so overall prognosis is good [21,45], although failures have been reported in case studies [17,19]. Yilmaz et al. [8•] reported that all patients who underwent first rib resection were symptom free after long-term evaluation. DiFelice et al. [53] examined cases of effort thrombosis in elite baseball players and found that four players with UEDVT who underwent first rib resection were able to return to play at or above previous levels. Arko et al. [25] investigated 26 patients who had vascular complaints as a result of various athletic competitions and found that 11 of 14 patients with an arterial injury were able to return to their prior level of competition, and 12 of 12 patients with UEDVT returned to their usual level of activity.

If the cause of the VTE is determined to be from a thrombophilic disorder such as factor V Leiden, antiphospholipid syndrome, AT III deficiency, or protein C or S deficiency prothrombin 20210A mutation the prognosis is not as clear. The risk of primary or repeat embolism with these disorders can be high [9••,13] as previously mentioned, although De Stefano et al. [54] found that heterozygous carriers of factor V Leiden had no increase in recurrent thrombosis compared with controls. Individuals with more than one genetic defect (ie, factor V Leiden and prothrombin mutation), with two or more spontaneous VTEs, life-threatening VTE, presence of antiphospholipid antibody syndrome, or AT III deficiency should receive long-term anticoagulation according to recent recommendations [6••,13,54–56]. Two completed trials have shown continued efficacy with full-dose warfarin (INR 2.0–3.0), although rates of major bleeding were high during extended therapy [57•]. Recent studies examining long-term, low-intensity warfarin therapy with INR of 1.5 to 2.0 appears to be an effective method for preventing recurrent VTE [57•] and may be considered for athletes who travel, but their indication in patients with hypercoagulable states is not clear and is probably not recommended. In addition, a more recent study comparing low-intensity therapy with conventional therapy found that conventional therapy was more effective in preventing recurrent VTE, and there was no reduction in risk of clinically significant bleeding for patients using low-intensity therapy [58•].

Prevention
The key for preventing VTE is attention to general techniques to avoid clotting. Studies investigating a decreased incidence of VTE in athletes who are properly hydrated compared with those who are dehydrated were not found in a literature search. However, evidence lends toward the increased incidence of VTE with individuals who are hemoconcentrated as seen in individuals who are polycythemic; therefore, sufficient oral intake is recommended. Individuals who are injured during competition and are subsequently immobilized should receive early prophylactic anticoagulation if rapid mobilization is not anticipated within 3 days, in addition to physical anti-thrombotic measures [10].
Multiple studies have recommended the use of LMWH [3,4,15,31] for the prevention of venous thrombosis during airplane flights for those at an increased risk, but the cost is high. Aspirin may also show some benefits of protection [59], but its effectiveness is much less than LMWH [31,59]. Hilberg et al. [3,4,15] have recommended in several publications the use of LMWH and/or leg exercises during flights. In addition, Eichner [5] has recommended eight strategies for prevention of clots on flights, which include sitting in seats that allow leg extension, hourly aisle walks, not crossing legs, loose clothing, hydration with water or juices, low-fat meals, fidgeting, and thinning blood with an aspirin or LMWH if prone to clotting.

Athletes who participate in high-altitude training or utilize a hypoxic or altitude sleep tent should be warned regarding their use and the increased risk of thromboembolism. These athletes should be monitored while utilizing these devices by following the hemogram.

Clearance for Participation
In general, the guidance for clearing athletes to participate in competition if a blood disorder is suspected or determined has been minimal [60]. Athletes that are found to have a positive family or personal history of VTE should be evaluated further prior to participation, as the risk for an event for those with a genetic hypercoagulable disorder is high.

Individuals with an acute VTE on continued anticoagulation therapy should not participate in activities involved with collision or contact and strong recommendations on risks of continuing limited contact activities should be made. Individuals involved in noncontact sports may participate after appropriate counseling unless that activity is a suspected cause for VTE, or has additional environmental risks (such as scuba diving). One case presentation by Roberts and Christie [61] listed a return-to-training regimen for a triathlete with a calf DVT. Their suggestion was return to activities of daily living over the first 3 weeks of treatment, followed by the following gradual increase in training intensity: Swimming for 1 week, then swimming and cycling for 1 week, then gradual increase in running. Any activity that resulted in return of thrombosis symptoms should be discontinued.

Those with UEDVT who are determined to have an underlying cause for thrombus should not participate in aggravating activities until any structural abnormalities have been corrected.

If individuals have completed a course of anticoagulation and a hypercoagulability laboratory evaluation is negative, return-to-play with gradual increase in intensity is recommended with careful monitoring for recurrent VTE and management of post-thrombotic symptoms. Strong recommendations should be given to the athlete, however, about the possible instigating factors that may have led to the initial event, so that appropriate measures for prevention can be instituted.

Conclusions
Using these guidelines to manage our two scenarios, the 42-year-old man with the lower extremity DVT returned to activities of daily living after several weeks of anticoagulation with no symptoms of thrombosis. He began physical activity starting with no impact, gradually increasing to previous levels over several weeks with monitoring for any recurrence of symptoms. After completing 3 months anticoagulation, a hypercoagulable work-up was ordered. He had a recurrent DVT while awaiting results, and was found to be protein S-deficient, warranting life-long warfarin therapy. At the patient’s request, his children were screened for protein S deficiency and one son was also deficient. This lead to counseling regarding choice of activities, management after injury or surgery, and techniques to prevent VTE.

Our second patient with atrial fibrillation on long-term warfarin therapy was cleared to participate in the marathon with cautions about appropriate monitoring of his INR, and signs and symptoms of hemorrhagic complications.

Hypercoagulability and thromboembolic events are not restricted to the nonactive population. Sports and primary care providers should have a comfort level and a good understanding of these conditions and their relationship to the athlete’s chosen activity so they can render appropriate advice about restrictions, prophylaxis, and preventative measures.

Acknowledgment
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References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance


Discussion of pathophysiology and current treatment of UEDVT.
Offers additional opinion regarding UEDVT management.
Offers additional opinion regarding UEDVT management.
Gives support to idea that polycythemia increases susceptibility to thrombus.


Management of venous thromboembolism: an update

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Abstract

Venous thromboembolism (VTE), which constitutes pulmonary embolism and deep vein thrombosis, is a common disorder associated with significant morbidity and mortality. Landmark trials have shown that direct oral anticoagulants (DOACs) are as effective as conventional anticoagulation with vitamin K antagonists (VKA) in prevention of VTE recurrence and associated with less bleeding. This has paved the way for the recently published guidelines to change their recommendations in favor of DOACs in acute and long-term treatment of VTE in patients without cancer. The recommended treatment of VTE in cancer patients remains low-molecular-weight heparin. The initial management of pulmonary embolism (PE) should be directed based on established risk stratification scores. Thrombolysis is an available option for patients with hemodynamically significant PE. Recent data suggests that low-risk patients with acute PE can safely be treated as outpatients if home circumstances are adequate. There is lack of support for use of inferior vena cava filters in patients on anticoagulation. This review describes the acute, long-term, and extended treatment of VTE and recent evidence on the management of sub-segmental PE.

Keywords: Venous thromboembolism, Anticoagulation, Direct oral anticoagulants, Vitamin K antagonists

Abbreviations: ACCP, American College of Chest Physicians; CI, Confidence interval; CRNM, Clinically relevant non-major; CTEPH, Chronic thromboembolic pulmonary hypertension; CTPA, Computed tomography of the pulmonary angiography; DOAC, Direct oral anticoagulant; DVT, Deep vein thrombosis; IVC, Inferior vena cava; LMWH, Low-molecular weight heparin; PE, Pulmonary embolism; PESI, Pulmonary embolism severity index; SSPE, Sub-segmental pulmonary embolism; VKA, Vitamin K antagonists; VTE, Venous thromboembolism

Background

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is one of the most common cardiovascular diseases occurring for the first time in about 1 in 1000 people [1, 2]. Its incidence rises with increasing age, for example to about 5 per 1000 people among those over 70 years of age [3]. VTE is associated with significant morbidity and mortality with the 30-day mortality rate in the absence of treatment of about 3 % for DVT and 31 % for PE [4]. The long-term complications of VTE are post-thrombotic syndrome (PTS), which occurs in 20 to 50 % of patients with DVT [5], and chronic thromboembolic pulmonary hypertension (CTEPH), which occurs in 2 to 4 % of patients with PE [6]. Patients with CTEPH have progressive dyspnea and exercise intolerance and those with PTS have chronic leg pain and swelling, which in a minority of patients can progress to development of venous ulcers. These conditions can significantly reduce the patient’s quality of life. Furthermore, the management VTE is associated with substantial health care costs for not only the initial hospitalization but also for hospital re-admissions [7, 8]. Therefore, VTE is associated with significant morbidity and mortality.
Initial management
The initial management of patients with a PE should be based on risk stratification of the patient into low, intermediate, or high risk for 30-day mortality based on established risk scores such as pulmonary embolism severity index (PESI) or its simplified version (simplified PESI) [9, 10]. Low risk patients, who are hemodynamically stable, can be treated as outpatients if home circumstances are adequate [11, 12]. At the other extreme, patients with acute PE and hypotension or patients with DVT-associated phlegmasia of the lower leg should be considered for treatment with thrombolytic agents [13, 14].

Oral anticoagulants
Anticoagulants are the mainstay treatment of VTE and are given in three phases of acute, long-term (in the first 3 months), and extended treatment [14]. For many years initial treatment was started with a parenteral anticoagulant, for example low-molecular-weight heparin (LMWH), overlapping with a vitamin K antagonist (VKA), such as warfarin. The combination was continued for at least 5 days until the achievement of therapeutic anticoagulation with international normalized ratio of 2 to 3 [14]. Although conventional therapy with VKAs is effective and safe, it has some limitations including delayed onset, need for parental daily injections, and interactions with dietary vitamin K and numerous drugs. Over the past 5 years, 4 direct oral anticoagulants (DOACs) have been approved for acute and long-term treatment of VTE [15–20]. The DOACs were compared with conventional therapy and found to be as effective in prevention of VTE recurrence and associated with less bleeding. The recently published American College of Chest Physicians (ACCP) guidelines have changed their recommendations in favor of DOACs in acute and long-term treatment of VTE in patients without cancer [21]. In patients with cancer associated VTE, the recommended anticoagulation remains LMWH over VKA [21].

The aim of this review is to (1) describe the initial management of patients with acute PE including the role of thrombolytic agents in hemodynamically unstable patients and at the other extreme outpatient management of low risk patients, (2) summarize the evidence on acute, long-term, and extended treatment of VTE comparing DOACs versus VKA, and (3) review the recent data on the management of sub-segmental PE and the lack of support for use of inferior vena cava filters in patients on anticoagulation.

Review
Acute and long-term treatment of venous thromboembolism
Thrombolytic and interventional treatment for acute venous thromboembolism
Anticoagulant therapy alone is recommended over thrombolysis for most patients with an acute DVT with exception for those with extensive iliofemoral or proximal DVT at high risk of limb ischemia [14, 21]. Thrombolytic therapy (systemic or catheter-directed) increase clot lysis and reduce the incidence of PTS compared to anticoagulation alone [22, 23]. However, this is at the expense of higher rate of major bleeding and no difference in rate of recurrent VTE or mortality [22–24]. Massive proximal DVT or iliofemoral thrombosis associated with limb-threatening ischemia or severe symptomatic swelling may be treated with thrombolysis. Thrombolysis can be considered only after objective diagnosis of the DVT and in a patient with low bleeding risk. The CaVenT trial randomized 209 patients with iliofemoral DVT to catheter directed therapy (CDT) versus anticoagulation. They found that the patients treated with CDT had significantly less PTS at 2 years compared with those treated with anticoagulation (41 versus 56 %) [22]. Another study randomized 32 patients with iliofemoral DVT to receive either CDT or systemic thrombolysis, followed by anticoagulation [25]. The patients who were treated with CDT had less reflux in both the deep and superficial veins and more patients had venous valvular competence preserved compared with patients who underwent systemic thrombolysis. A large, multicenter trial (the ATTRACT trial) is currently underway that randomizes patients to receive pharmacomechanical catheter-directed thrombolysis (PCDT) plus standard therapy with anticoagulation versus standard therapy alone [26]. It will investigate whether PCDT should be routinely utilized to prevent PTS in patients with symptomatic proximal DVT [26].

Systemic thrombolysis is a widely accepted treatment for PE in patients with persistent hypotension (e.g., systolic blood pressure <90 mmHg for 15 min) and not at high risk of bleeding [14, 21]. The use of thrombolytic therapy in intermediate risk patients with acute PE associated with right ventricle (RV) dysfunction is controversial. The RV dysfunction is confirmed by echocardiogram or computed tomography and a positive troponin I/T. The potential indication for thrombolysis in this group is based on evidence that patients with severe RV dysfunction have worse prognosis than those without RV dysfunction [27]. Three recently published trials have examined the role of systemic thrombolysis in intermediate risk patients [28–30]. In the Moderate Pulmonary Embolism Treated Thrombolysis (MOPETT) trial, 121 patients were randomly assigned to receive heparin (unfractionated or LMWH) alone or the combination of tissue type plasminogen activator (tPA) plus heparin [28]. Compared to the heparin group, treatment with tPA resulted in lower rates of pulmonary hypertension and significantly lower pulmonary artery systolic pressures at 28 months. The rates of bleeding, recurrent PE, and mortality was similar in both groups [28]. In another trial comparing the combination of LMWH plus
an intravenous bolus of tenecteplase versus LMWH alone in intermediate risk PE patients, those treated with tenecteplase had fewer adverse outcomes and better functional capacity at 90 days [29]. In a large multicenter randomized trial (PEITHO), 1005 intermediate risk patients with PE were randomized to tenecteplase and heparin or to heparin therapy alone [30]. Thrombolysis therapy led to reduction in the primary composite outcome of death or cardiovascular collapse at seven days after randomization although it increased major bleeding (including intracranial bleeding) with no overall gained benefit from thrombolysis [30]. A meta-analysis of 16 trials comprising 2115 intermediate risk patients reported that 59 patients would need to be treated with thrombolysis to prevent one death, while a major bleeding occurs with every 18 patients treated [13]. Further studies are needed to identify subgroups of intermediate risk patients who will benefit from systemic thrombolytic therapy.

CDT may be used in patients with acute PE at increased risk of bleeding as a lower dose of a thrombolytic agent is infused directly into the pulmonary artery via a catheter [31]. CDT is also effective in lowering pulmonary arterial pressure and improving RV function [32]. In a randomized controlled trial of 59 patients with acute intermediate risk PE, ultrasound-assisted catheter-directed thrombolysis followed by heparin was compared to treatment with heparin alone [33]. At 24 h, CDT improved the hemodynamics compared to anticoagulation. At 90 days of follow-up, there was no difference in mortality or major bleeding between the two groups [33]. Most of the evidence is limited by small sample size and of low quality compared to the available evidence for systemic thrombolysis. Systemic thrombolysis is therefore currently recommended over CDT in patients with acute PE who are candidates for thrombolysis [21].

**Outpatient treatment of venous thromboembolism**

Home therapy is commonly employed for patients with an acute DVT in clinical practice with a few exceptions. Several randomized controlled trials and meta-analyses, which have compared home therapy with LMWH versus inpatient therapy with intravenous unfractionated heparin, suggest that outpatient therapy is safe and feasible in most patients with acute DVT [34–36]. Outpatient therapy should not be selected for those with massive symptomatic DVT, high risk of bleeding, or hemodynamic instability due to concurrent symptomatic PE [37].

The outpatient treatment of PE is suggested with grade 2B evidence in the most recent ACCP guidelines in low-risk patients with adequate home circumstances [21]. The decision for outpatient management should take into account the patient’s clinical condition, bleeding risk, their preference, and the available home support. Risk stratification scores such as PESI or simplified PESI may be utilized to identify low-risk patients without RV dysfunction who are potential candidates for short in-hospital stay or entirely outpatient management [11, 12, 38]. With the recent changed recommendations in favor of DOACs for acute and long-term VTE treatment, future research should focus on the safety and efficacy of DOACs in outpatient management of acute VTE.

**Vitamin K antagonists versus direct oral anticoagulants**

Four DOACs including dabigatran, rivaroxaban, apixaban, and edoxaban were compared with conventional therapy in the RE-COVER I and II, EINSTEIN-DVT and PE, AMPLIFY, and Hokusai-VTE trials, respectively [15–20]. The study design was double-blinded in all trials except for the ENSTEIN trials, which used a prospective, randomized, open-label, blinded end point evaluation design. The study designs and treat protocols are compared in Table 1. The study populations were similar in these trials. In the dabigatran and edoxaban trials, parental anticoagulation was added to both DOAC and conventional therapy arms, and after at least 5 days patients were switched to the DOAC. Therefore, in clinical practice, patients should be initiated on parenteral anticoagulation and either switched to dabigatran or edoxaban after 5 days or it should be overlapped with a vitamin K antagonist. In contrast, in the rivaroxaban and apixaban trials DOACs were started without the need for initial parental anticoagulation. The primary efficacy outcome was recurrent VTE or VTE-related mortality in all 6 trials. The primary safety outcome was either major bleeding or a composite of major and clinically relevant non-major bleeding (CRNMB). The efficacy and safety outcomes of these trials are listed in Table 2. All of the trials excluded patients with severe renal dysfunction, those with active bleeding or at high risk of bleeding, and patients already on therapeutic anticoagulation. A recent pooled analysis of these 6 trials reported that DOACs have similar efficacy as VKA in treatment of acute VTE and significantly lower risk of major bleeding than VKA [39]. Recurrent VTE occurred in 2 % of those given DOAC versus 2.2 % in patients that received VKA (relative risk [RR] 0.90; 95 % confidence interval [CI], 0.77 – 1.06) [39]. A 39 % reduction in risk of major bleeding was reported in DOAC recipients compared to those who received VKA therapy (RR 0.61; 95 % CI, 0.45 – 0.83). Compared with recipients of VKA therapy, intracranial bleeding, fatal bleeding, and CRNMB were significantly reduced in the DOAC group [39]. Given the better safety profile of DOACs with less major bleeding, similar efficacy in prevention of recurrent VTE, and the convenience of administration of DOACs, the recent ACCP guidelines suggested DOACs over VKA for the acute and long-term treatment of VTE in patients without cancer [21].
<table>
<thead>
<tr>
<th>Trial name</th>
<th>RE-COVER</th>
<th>RE-COVER II</th>
<th>EINSTEIN-DVT</th>
<th>EINSTEIN-PE</th>
<th>AMPLIFY</th>
<th>Hokusai-VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Double-blinded</td>
<td>Double-blinded</td>
<td>PROBE</td>
<td>PROBE</td>
<td>Double-blinded</td>
<td>Double-blinded</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>2539</td>
<td>2589</td>
<td>3449</td>
<td>4832</td>
<td>5395</td>
<td>8292</td>
</tr>
<tr>
<td>Indication for Anticoagulation</td>
<td>Acute VTE</td>
<td>Acute VTE</td>
<td>Acute DVT</td>
<td>Acute PE</td>
<td>Acute VTE</td>
<td>Acute VTE</td>
</tr>
<tr>
<td>DOAC Treatment Protocol</td>
<td>Dabigatran 150 mg twice daily</td>
<td>Dabigatran 150 mg twice daily</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks; then 20 mg once daily</td>
<td>Rivaroxaban 15 mg twice daily for 3 weeks; then 20 mg once daily</td>
<td>Apixaban 10 mg twice daily for days; then 5 mg twice daily</td>
<td>Edoxaban 60 mg once daily; patients with CrCl 30–50 mL/min, body weight ≤60 kg, or receiving strong P-glycoprotein inhibitors: edoxaban 30 mg once daily</td>
</tr>
<tr>
<td>Non-inferiority Margin for Hazard Ratio</td>
<td>2.75</td>
<td>2.75</td>
<td>2.0</td>
<td>2.0</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Need for initial Parenteral Anticoagulation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Therapy (months)</td>
<td>6</td>
<td>6</td>
<td>3, 6, or 12</td>
<td>3, 6, or 12</td>
<td>6</td>
<td>≤12</td>
</tr>
<tr>
<td>TTR (%)</td>
<td>60</td>
<td>57</td>
<td>58</td>
<td>63</td>
<td>61</td>
<td>64</td>
</tr>
</tbody>
</table>

DOAC direct oral anticoagulant, DVT deep vein thrombosis, PE pulmonary embolism, PROBE prospective, randomized, open-label, blinded end point, TTR time in therapeutic range for warfarin, VKA vitamin K antagonists, VTE venous thromboembolism, CrCl creatinine clearance.
Management of VTE in patients with cancer

The major society guidelines including the ACCP, American Society of Clinical Oncology, and the National Comprehensive Cancer Network recommend use of LMWH for treatment of VTE in cancer patients [21, 40, 41]. Treatment with LMWH is continued for the duration of active cancer given that the risk of recurrent VTE can reach an annual risk of 20% [42]. Five randomized trials have compared therapy with LMWH versus warfarin in cancer patients [43–47]. The details of these trials are outlined in Table 3. Two trials showed a reduction in the rates of recurrent VTE using LMWH with no effect on mortality or bleeding [44, 45], two showed no difference in any outcome [43, 46], and the recently published CATCH trial demonstrated a non-significant reduction in the rate of recurrent VTE and lower risk of CRNMB in those who received LMWH [47].

There are no published randomized trials that a priori have compared DOACs with VKA or LMWH for treatment of VTE in cancer patients. A meta-analysis of the subsets with DVT and cancer totaling 1132 patients in the six trials that compared DOACs versus VKA [15–20] has been published [48]. They found similar rates of VTE recurrence (3.9 versus 6%; odds ratio [OR] 0.63; 95% CI, 0.37–1.10) and major bleeding (3.2 versus 4.2%; OR 0.77; 95% CI, 0.41-1.44). Although these trials included cancer patients [15–20], they were typically not receiving active chemotherapy or radiation. The cancer patients included in these trials had usually completed treatment or had a previous history of cancer and are not a true representative

| Table 2 | Efficacy and safety outcomes for treatment of acute VTE: DOACs versus VKA |
|--------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Primary Efficacy | Recurrent symptomatic VTE or related mortality: 2.4 vs 2.1a | Recurrent symptomatic VTE or related mortality: 2.3 vs 2.2a | Recurrent symptomatic VTE: 2.1 vs 3.0a | Recurrent symptomatic VTE or related mortality: 2.1 vs 1.8a | Recurrent symptomatic VTE or related mortality: 3.2 vs 3.5a |
| Primary Safety Outcome(s) | Major bleeding: Any bleeding | Major bleeding: Any bleeding | Major or CRNM bleeding: Any bleeding | Major or CRNM bleeding: Any bleeding | Major or CRNM bleeding: Any bleeding | Major or CRNM bleeding: Any bleeding |
| Major Bleeding DOAC vs VKA (%) | 1.6 vs 1.9 | 1.2 vs 1.7 | 0.8 vs 1.2 | 1.1a vs 2.2 | 0.6a vs 1.8 | 1.4 vs 1.6 |
| Major or CRNM Bleeding DOAC vs VKA (%) | 5.6 vs 8.8 | 5.0 vs 7.9 | 8.1 vs 8.1 | 10.3 vs 11.4 | 4.3a vs 9.7 | 8.5a vs 10.3 |

CRNM clinically relevant non-major, DOAC direct oral anticoagulants, VKA vitamin K antagonists, VTE venous thromboembolism
aStatistically significant difference between the two groups

Table 3 Comparison of trials on LMWH versus VKA for treatment of VTE in cancer patients

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>CANTHANOX</th>
<th>CLOT</th>
<th>MAIN-LITE</th>
<th>ONCENOX</th>
<th>CATCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Open-label</td>
<td>Open-label</td>
<td>Open-label</td>
<td>Open-label</td>
<td>Open-label</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>146</td>
<td>676</td>
<td>200</td>
<td>122</td>
<td>900</td>
</tr>
<tr>
<td>Treatment Protocol</td>
<td>Enoxaparin 1.5 mg/kg daily</td>
<td>Dalteparin 200 IU/kg once daily for the first month then 150 IU/kg for 5 months</td>
<td>Tinzaparin 175 IU/kg once daily</td>
<td>Enoxaparin 1 mg/kg every 12 h for 5 days then enoxaparin 1 mg/kg or 1.5 mg/kg daily</td>
<td>Tinzaparin 175 IU/kg once daily</td>
</tr>
<tr>
<td>Duration of Therapy (months)</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Primary Efficacy Outcome</td>
<td>Recurrent symptomatic VTE: 10.5 vs 21.1</td>
<td>Recurrent symptomatic VTE: 9 vs 17</td>
<td>Recurrent symptomatic VTE: 7 vs 10</td>
<td>Recurrent symptomatic VTE: enoxaparin 1 mg vs. 1.5 mg vs VKA 6.8 vs 6.3 vs 10.0</td>
<td>Composite of recurrent symptomatic VTE, fatal PE, or incidental VTE: 7.2 vs 10.5</td>
</tr>
<tr>
<td>Safety Bleeding Outcomes</td>
<td>Major bleeding: 7 vs 16; Fatal bleeding: 0 vs 8a</td>
<td>Major bleeding: 6 vs 4; Any bleeding: 14 vs 19</td>
<td>Major bleeding: 7 vs 7; Any bleeding: 27 vs 24</td>
<td>Major bleeding: enoxaparin 1 mg vs. 1.5 mg vs VKA: 6.5 vs 11.1 vs 2.9</td>
<td>Major bleeding: 2.7 vs 2.4 CRNM bleeding: 10.9a vs 15.3</td>
</tr>
</tbody>
</table>

CRNM clinically relevant non-major, DOAC direct oral anticoagulants, LMWH low-molecular weight heparin, PE pulmonary embolism, VKA vitamin K antagonists, VTE venous thromboembolism
aStatistically significant difference between the two groups
of all cancer patients. The Hokusai VTE-cancer randomized open label trial is currently underway and will examine whether edoxaban is non-inferior to LMWH for treatment of VTE in cancer patients [49].

**Extended treatment of venous thromboembolism**

Extended anticoagulation can be employed in patients with unprovoked VTE to reduce the risk of recurrent VTE if the benefit/risk ratio favors continuation of anticoagulation while taking into account patient’s risk of bleeding. All DOACs except for edoxaban have been compared with placebo in randomized trials for extended secondary VTE prevention beyond the initial three months of anticoagulation [17, 50, 51]. The details of these trials are compared in Table 4. All trials showed marked superiority of the DOACs over placebo for the prevention of recurrent VTE without significant increase in major bleeding [17,50, 51]. However, compared to the placebo arms, all DOACs had higher rate of CRNMB [17, 50, 51]. Duration of extended anticoagulation was 6 to 12 months in the EINSTEIN [17] and AMPLIFY-Extension [50] studies and 6 months in the RE-SONATE trial [51]. Two doses of apixaban were evaluated in the AMPLIFY-Extension trial and the rate of bleeding was lower for apixaban 2.5 mg twice daily than 5 mg twice daily [50]. A single regimen of rivaroxaban (20 mg once daily) and dabigatran (150 mg twice daily) was used in the EINSTEIN and RE-SONATE studies.

Dabigatran is the only DOAC that has been compared with warfarin for extended VTE prevention in the REMEDY trial [51]. Dabigatran was non-inferior to warfarin in prevention of recurrent VTE (1.8 versus 1.3 %, hazard ratio [HR] 1.44; 95 % CI, 0.78–2.64) and had a significantly lower rate of major bleeding or CRNMB (HR 0.54; 95 % CI, 0.41–0.71). These results demonstrated that DOACs are effective in secondary VTE prevention with no significant increase in major bleeding. The ACCP guidelines recommend no change in the choice of anticoagulant agent in patients who need extended anticoagulation after the first 3 months of therapy [21]. Given the observed lower bleeding risk, the dose of apixaban may be reduced to 2.5 mg twice daily after the initial treatment.

Aspirin has been also evaluated in secondary VTE prevention in patients with first unprovoked VTE who have completed anticoagulant treatment. In this setting, randomized trials and a meta-analysis reported a 30 % reduction in rates of recurrent VTE compared to placebo or observation [52–55]. The ACCP guidelines suggest that aspirin is an available option in patients with unprovoked VTE that are stopping anticoagulant therapy if there are no contraindications to use of aspirin [21]. However, aspirin is not recommended as an alternative to anticoagulant therapy [21].

**Treatment of VTE in special situations**

**Management of sub-segmental pulmonary embolism**

The increase in utilization of a highly sensitive computed tomography pulmonary angiography (CTPA) has led to detection of incidental asymptomatic PE or small sub-segmental PE [56]. Whether or not patients with sub-segmental pulmonary embolism (SSPE) should be anticoagulated is controversial. It is unclear whether the SSPE detected by CTPA are artifacts and therefore false positive [57]. Furthermore, an isolated SSPE likely does not have the same risk of progression or VTE recurrence as a single segmental or lobar PE [57]. There are currently no published randomized trials for treatment of patients with SSPE. Retrospective studies have reported VTE recurrence in only a small number of patients with SSPE and without DVT, who were not anticoagulated.

<table>
<thead>
<tr>
<th>Table 4 Comparison of extended duration DOAC trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Name</strong></td>
</tr>
<tr>
<td>Design</td>
</tr>
<tr>
<td>Comparison Arm</td>
</tr>
<tr>
<td>Number of Patients</td>
</tr>
<tr>
<td>Treatment Protocol</td>
</tr>
<tr>
<td>Duration of Therapy (months)</td>
</tr>
<tr>
<td>Primary Efficacy Outcome</td>
</tr>
<tr>
<td>Major Bleeding DOAC vs VKA or Placebo (%)</td>
</tr>
<tr>
<td>Major and CRNM Bleeding DOAC vs VKA or Placebo (%)</td>
</tr>
</tbody>
</table>

DOAC direct oral anticoagulant, CRNM clinically relevant non-major, DOAC direct oral anticoagulants, VKA vitamin K antagonists, VTE venous thromboembolism

^a^Statistically significant difference between the two groups
Computed tomography pulmonary angiography, VTE and no detected proximal DVT. The optimal management strategy for patients with SSPE [21]. Future prospective studies are needed to determine mobilization, active cancer, previous history of VTE) high risk of VTE recurrence (e.g., recent surgery, immobilization, active cancer, previous history of VTE). The ACCP guidelines recommend performing bilateral ultrasounds to exclude proximal DVT before a decision is made not to treat a patient with SSPE [21]. If a DVT is detected then the patient should receive anticoagulation. However, if no proximal DVT is detected the guidelines suggest that the patient should receive anticoagulation. If an acute VTE already on anticoagulation with no absolute contraindication to anticoagulation (e.g., concurrent active bleeding) [67]. The IVC filter is removed once the bleeding risk is low and anticoagulation is given [14]. In patients with acute VTE already on anticoagulation with no absolute contraindications, studies suggest that there is lack of benefit to use of IVC filters in addition to anticoagulation [68–72]. In the PREPIC 1 trial, 400 patients with proximal DVT were randomized to either anticoagulation alone or anticoagulation plus IVC filter placement [68]. The initial 2-year PREPIC 1 study and a subsequently published 8-year follow-up reported that IVC filter insertion was associated with a reduction in the initial rate of PE, increase in the rate of DVT, and no difference in mortality [68, 69]. The PREPIC 2 trial examined the adjuvant role of IVC filters in patients with PE who received either anticoagulation alone or anticoagulation plus an IVC filter [70]. The filter was removed at 3 months. There was no difference in the rates of recurrent VTE or mortality between the two groups [70]. In addition to lack of benefit, IVC filters are associated with complications including IVC filter thrombosis, DVT, and guide wire entrapment [71, 72]. The ACCP guidelines recommend against the use of IVC filters in patients on anticoagulation for acute VTE [21].

**Conclusions**

VTE is a major cause of morbidity and mortality. DOACs are suggested over VKA for acute and long-term treatment of VTE in patients without cancer, as they have been shown to be as effective as VKA in reducing VTE recurrence and associated with significantly less major bleeding. Future studies are needed to examine different management strategies in this patient group.

**Role of inferior vena cava filter in management of acute venous thromboembolism**

Inferior vena cava (IVC) filters are typically used in patients with an acute VTE and an absolute contraindication to anticoagulation (e.g., concurrent active bleeding) [67]. The IVC filter is removed once the bleeding risk is low and anticoagulation is given [14]. In patients with acute VTE already on anticoagulation with no absolute contraindications, studies suggest that there is lack of benefit to use of IVC filters in addition to anticoagulation [68–72]. In the PREPIC 1 trial, 400 patients with proximal DVT were randomized to either anticoagulation alone or anticoagulation plus IVC filter placement [68]. The initial 2-year PREPIC 1 study and a subsequently published 8-year follow-up reported that IVC filter insertion was associated with a reduction in the initial rate of PE, increase in the rate of DVT, and no difference in mortality [68, 69]. The PREPIC 2 trial examined the adjuvant role of IVC filters in patients with PE who received either anticoagulation alone or anticoagulation plus an IVC filter [70]. The filter was removed at 3 months. There was no difference in the rates of recurrent VTE or mortality between the two groups [70]. In addition to lack of benefit, IVC filters are associated with complications including IVC filter thrombosis, DVT, and guide wire entrapment [71, 72]. The ACCP guidelines recommend against the use of IVC filters in patients on anticoagulation for acute VTE [21].

**Conclusion**

VTE is a major cause of morbidity and mortality. DOACs are suggested over VKA for acute and long-term treatment of VTE in patients without cancer, as they have been shown to be as effective as VKA in reducing VTE recurrence and associated with significantly less major bleeding. Future studies are needed to assess their safety and efficacy in outpatient treatment of acute VTE. LMWH is the current standard of care for treatment of VTE in cancer patients. Randomized trials are ongoing to examine the non-inferiority of DOACs versus LMWH in cancer patients. Lastly, it is currently unclear whether or not to treat patients with SSPE and no proximal DVT; future prospective studies are needed to examine different management strategies in this patient group.

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**Availability of data and material**

Not applicable.

**Authors’ contributions**

SP and SS are responsible for writing and editing of the manuscript. Both authors read and approved the final manuscript.

**Competing interests**

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Ethics approval and consent to participate
Not applicable.

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