

# Venous Thromboembolism

## A Public Health Concern

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**Abstract:** Venous thromboembolism (VTE), defined as deep vein thrombosis, pulmonary embolism, or both, affects an estimated 300,000–600,000 individuals in the U.S. each year, causing considerable morbidity and mortality. It is a disorder that can occur in all races and ethnicities, all age groups, and both genders. With many of the known risk factors—advanced age, immobility, surgery, obesity—increasing in society, VTE is an important and growing public health problem.

Recently, a marked increase has occurred in federal and national efforts to raise awareness and acknowledge the need for VTE prevention. Yet, many basic public health functions—surveillance, research, and awareness—are still needed. Learning and understanding more about the burden and causes of VTE, and raising awareness among the public and healthcare providers through a comprehensive public health approach, has enormous potential to prevent and reduce death and morbidity from deep vein thrombosis and pulmonary embolism throughout the U.S.

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### Introduction

Venous thromboembolism (VTE) is a condition in which the blood clots inappropriately, causing considerable morbidity and mortality. The term VTE encompasses a continuum that includes both deep vein thrombosis (DVT), clots in the deep veins of the body; and pulmonary embolism (PE), which occurs when a clot breaks free and enters the arteries of the lungs. All races and ethnicities are affected by VTE, as are both genders and all age groups. With many of the known risk factors—advanced age, immobility, surgery, obesity—increasing in society, it is an important and growing public health problem. Yet, until recently, this condition has received little attention from the public health community. Fortunately, in many cases, VTE is preventable; thus, the importance of research and prevention of VTE is being increasingly recognized. However, critical and essential public health pieces are still missing. The current paper provides an overview of the epidemiology of VTE; discusses some recent, key public health activities;

and identifies gaps in essential functions that are needed to prevent and reduce morbidity and mortality.

### Epidemiology

Clinically, patients with VTE can be defined as presenting with DVT, PE, or both. About two thirds of patients with VTE present for care with DVT, and the remaining one third present with PE, which is the primary cause of mortality associated with VTE, often resulting in sudden death. It is also the leading cause of preventable hospital death and a leading cause of maternal mortality in the U.S.<sup>1,2</sup>

### Incidence

Currently, there is no national surveillance for VTE, so the precise number of people affected by VTE is unknown. Based on analyses of clinical administrative databases and hospital- and community-based studies, the overall annual incidence of VTE in the U.S. is estimated to be between 1 and 2 per 1000 of the population, or 300,000–600,000 cases.<sup>3–5</sup> However, these incidence rates differ by age, race, and gender (Table 1). The incidence ranges from 1 per 100,000 in the young and increases to about 1 per 100 in people aged  $\geq 80$  years. The overall rate is higher among blacks and whites than among other races and ethnicities. Men have a slightly higher overall incidence rate than women, but women have a slight increase during the reproductive years.<sup>5,9–11</sup> However, because of the difficulty in documenting DVT

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**Table 1.** Estimated incidence of venous thromboembolism by age, race, and gender

Characteristics	Annual incidence per 1000
<b>Race/ethnicity</b>	
White	1.17 <sup>3</sup>
Black	0.77 <sup>6</sup> –1.41 <sup>5</sup>
Asian	0.29 <sup>7</sup>
Hispanic	0.61 <sup>7</sup>
<b>Age (years)</b>	
<15	<0.5 <sup>3,8</sup>
15–44	1.49 <sup>3</sup>
45–79	1.92 <sup>9</sup>
≥80	5–6 <sup>3,4,8,9</sup>
<b>Gender</b>	
Male	1.3 <sup>3</sup>
Female	1.1 <sup>3</sup>
<b>Overall</b>	1–2 <sup>3–5</sup>

and PE, the limitations of administrative databases, and the regional and racial specificity of community-based studies, VTE may be vastly under-reported.<sup>12,13</sup>

### Morbidity and Mortality

Venous thromboembolism is often fatal. Depending on case ascertainment and the use of autopsy data, studies estimate that 10%–30% of all patients suffer mortality within 30 days; the majority of deaths occur among those with PE, as an estimated 20%–25% of all PE cases present as sudden death.<sup>6,8–10</sup> Other serious complications of DVT and PE include increased risks of recurrent thromboembolism and chronic morbidity (e.g., venous insufficiency, pulmonary hypertension). Following a standard course of anticoagulant therapy, about one third of all VTE patients experience a recurrence within 10 years of the initial event, with the highest risk occurring within the first year, yet they remain at risk throughout their lives.<sup>6,14</sup> One third to one half of lower-extremity DVT patients develop post-thrombotic syndrome and chronic venous insufficiency, lifelong conditions characterized by pain, swelling, skin necrosis, and ulceration.<sup>6,15</sup>

Quality of life has been reported to be adversely affected up to 4 months after DVT, and for those with post-thrombotic syndrome, quality of life actually declines further during this period, with changes similar to those seen in individuals with chronic heart, lung, or arthritic disease.<sup>15</sup> In addition, subsets of VTE patients require long-term anticoagulation to prevent additional

clots, which also decreases quality of life and places them at an increased risk for adverse bleeding episodes.

### Economic Burden

Venous thromboembolism is complex and presents in both inpatient and outpatient settings, and although many cases have been attributed to hospitalization, about two thirds of cases occur in outpatients.<sup>16</sup> Although data are lacking on the exact cost attributed to VTE, a recent analysis of healthcare claims estimated that the total annual healthcare cost for VTE ranges from \$7594 to \$16,644 per patient.<sup>17</sup> With estimates of 300,000–600,000 incident cases per year, this cost equates to a total annual cost of \$2 billion to \$10 billion attributable to VTE.

### Etiology and Risk Factors

The etiology of VTE is not fully understood. It is a multifactorial condition involving genetic and both constant and transient acquired risk factors (Table 2). A threshold seems to exist, as the presence of one risk factor does not always result in disease status; however, an interactive effect of multiple triggers and events can lead to clot formation. Yet, in about 50% of cases there is no acquired risk factor identified (idiopathic), and in 10%–20% there is no acquired or genetic risk identified, signifying the effect of still unknown genetic and/or acquired risk factors.<sup>12,13,18</sup>

Known acquired risks include chronic disease, cancer, obesity, antiphospholipid antibodies, and advanced age.<sup>6,9,11,19–21</sup> Other acquired risks can be thought of as transient states, which include surgery, trauma, immobilization, infection, and hospitalization.<sup>6,8,19–21</sup> Women also have increased risk during pregnancy and the postpartum period and while taking hormonal contraceptives and hormone replacement therapy.<sup>11,22–25</sup> Hospitalization is an especially important risk factor as it provides a unique period in which multiple risk factors may be

**Table 2.** Identified risk factors for venous thromboembolism

Genetic	Acquired	Transient acquired
Family history	Advanced age	Pregnancy
Factor V Leiden	Antiphospholipid antibodies	Oral contraceptives
Prothrombin G20210A	Cancer	Hormone therapy
Protein C deficiency	Chronic disease	Hospitalization
Protein S deficiency	Obesity	Surgery
Antithrombin deficiency	—	Trauma
Sickle cell trait	—	Immobilization

present (surgery, trauma, intravenous catheters and access devices, immobilization, pregnancy, chronic conditions); it has been estimated that as many as half of outpatient VTE occurrences can be linked directly to a prior hospitalization up to 3 months postdischarge.<sup>16</sup> This finding indicates that the hospitalization period provides a unique intervention and prevention point.

Family history of VTE is associated with DVT and PE occurrence,<sup>19,26</sup> indicating that genetics also plays an important etiologic role. Several genetic risk factors, also known as inherited thrombophilias, have been identified and include factor V Leiden; prothrombin G20210A mutation; and deficiency of the natural anticoagulants protein C, protein S, and antithrombin. The prevalence of these mutations in the general population varies from <1%–5% and implies a three- to ten-fold increased risk of VTE in their heterozygous states.<sup>27,28</sup> Deficiencies of the natural anticoagulants confer the most risk, but these disorders are also less common in the population. Presence of one of these mutations does not always lead to the development of VTE, but it has been estimated that approximately 25%–35% of individuals with a first VTE express at least one of these five mutations in either the heterozygous or homozygous state.<sup>18,28,29</sup> Some of these genetic risk factors are much less common in non-white populations (e.g., factor V Leiden, prothrombin G20210A), and research into genetic risk factors among other races and ethnicities is needed. Recently, the Genetic Attributes and Thrombosis Epidemiology (GATE) study identified sickle cell trait to be associated with VTE.<sup>30</sup>

Interactions between risk factors in the form of both gene–gene and gene–environment interactions further

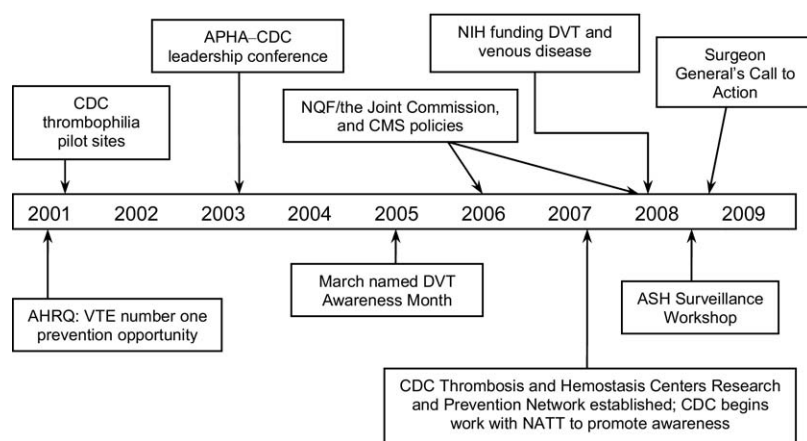
increase risk. For example, reports have shown even greater increased risk among women with factor V Leiden or sickle cell trait, while they are taking oral contraceptives. Among women with the factor V Leiden, taking oral contraceptives increased their risk fivefold.<sup>31</sup> Screening for factor V Leiden prior to prescription of oral contraceptives is not recommended in asymptomatic individuals, however, because the absolute risk is still low.<sup>32</sup> Among those with sickle cell trait, the risk was three times higher, much greater than the multiplicative effect of the two exposures.<sup>33</sup> Genetic risk also exacerbates the risk of VTE during pregnancy, with estimates of 20%–50% of pregnancy-related VTE associated with the presence of at least one thrombophilia.<sup>23,34,35</sup> As expected, individuals with more than one thrombophilia also have a greater risk than individuals having a single inherited risk factor.<sup>18,28,36</sup>

## Public Health Activities and Gaps

Recently, there has been a marked increase in federal and national efforts to raise awareness about VTE and acknowledge it as a growing and important public health problem (Figure 1). In 2001, the Agency for Healthcare Research and Quality (AHRQ) identified prevention of VTE through appropriate thromboprophylaxis as the number-one safety practice for hospitals.<sup>37</sup> In 2003, the American Public Health Association (APHA) and the Centers for Disease Control and Prevention (CDC) held a Leadership Conference on Deep Vein Thrombosis to stress the need for increased awareness of VTE.<sup>38</sup> In March 2005, the U.S. Senate, in honor of journalist David Bloom, passed a resolution declaring March as DVT Awareness Month.<sup>39</sup>

From 2006 through 2008, in recognition of the high attributable risk of hospitalization and the fact that PE is the most preventable cause of hospital death, the National Quality Forum, the Joint Commission, and the Centers for Medicare and Medicaid Services all instituted policies and measures to reduce VTE and promote appropriate prophylaxis to at-risk patients in the hospital setting.<sup>12,40,41</sup>

At the same time, CDC and the National Institutes of Health (NIH)



**Figure 1.** Timeline of recent public health activities and initiatives related to venous thromboembolism

AHRQ, Agency for Healthcare Research and Quality; APHA, American Public Health Association; ASH, American Society of Hematology; CMS, Centers for Medicare and Medicaid Services; DVT, deep vein thrombosis; NATT, National Alliance for Thrombosis and Thrombophilia; NQF, National Quality Forum

have increased their activities in public health and clinical research of VTE. In 2001, CDC began a Thrombosis and Hemostasis Centers pilot sites program to provide health-related services and conduct research directed toward the reduction or prevention of complications of thrombosis and thrombophilia.<sup>42</sup> Based on the initial work of these pilot sites, in July 2007, CDC implemented the Thrombosis and Hemostasis Centers Research and Prevention Network to foster collaborative epidemiologic research to identify risks (both genetic and acquired) among a U.S. population and ultimately improve diagnosis and treatment.<sup>43</sup> In 2008, NIH funded grantees to conduct research with the goal of improved diagnosis, therapy, and prevention of VTE.<sup>44</sup> The CDC and NIH are working together to encourage collaboration and interaction among grantees to further foster and improve clinical and public health research.

In 2007, CDC began supporting education and outreach activities to provide health promotion and wellness programs for people at risk for or affected by clotting disorders at both the community and national level. Working with the National Alliance for Thrombosis and Thrombophilia (NATT), CDC funded a health promotion and wellness initiative called “Stop the Clot” that develops and disseminates health information for people who have been affected by VTE.<sup>33</sup> The program conducts community education forums on clotting, sponsors a website with resources and information for the public, and has established support groups for people who have experienced VTE. Additionally, CDC and NATT have developed an online training program on the basics of VTE for nonphysician healthcare providers. This year, CDC will continue its work with NATT and has expanded its health promotion program to work with the Venous Disease Coalition (a coalition of healthcare professionals and organizations) to develop a program specifically for women who may be at risk for VTE.

To address the dramatic increased risk of VTE among the elderly, the American Society of Hematology (ASH) conducted a Thrombosis in the Elderly workshop in May 2006. Participants stressed the need for further research on mechanisms and risk factors for VTE and its complications among the elderly, as well as further development of safe and effective treatment strategies.<sup>45</sup> In June 2008, in recognition that the true burden of VTE is unknown, ASH, on behalf of the CDC, convened an expert panel for a National Workshop on Thrombosis Surveillance. The panel’s recommendations included the need for strengthened national surveillance of DVT and PE and increased public awareness.<sup>13</sup>

Most recently, in September 2008, the U.S. Surgeon General released a *Call to Action to Prevent Deep Vein*

*Thrombosis and Pulmonary Embolism*,<sup>12</sup> urging a coordinated, multifaceted plan to reduce the numbers of cases of DVT and PE nationwide, through the following:

- Increased public and provider awareness;
- Use of evidence-based practices for screening, preventing, diagnosing, and treating DVT and PE;
- More research on the causes, prevention, and treatment of DVT.

These important and much-needed activities have placed the spotlight on VTE as a serious and important public health problem and further emphasized the need for a public health response. Yet, there are still areas in all three of the core essential services of public health (assessment, policy development, and assurance) in which more knowledge and activities are needed.

## Public Health Surveillance

Presently, there is no national surveillance of VTE, and current prevalence and incidence estimates are likely underestimated. Because prevalence studies have focused mainly on whites, the risks—and more importantly, the true burden—of VTE for minority populations is unknown and unaccounted for in current estimates. Further, PE often presents as sudden death. Given that the number of autopsies performed in the U.S. is low, and that PE may be misdiagnosed as heart failure, current estimates of the number of PE events are probably low. Similarly, because DVT has many presentations and is diagnosed and cared for by multiple providers and in multiple settings (inpatient and outpatient), the overall burden of DVT is likely to be underestimated as well.

The purpose of public health surveillance is to assess public health status, define public health priorities, evaluate programs, and stimulate research.<sup>46</sup> Surveillance for DVT and PE must be the first step toward preventing morbidity and mortality and reducing burden from VTE. Without the important knowledge of why, where, and among whom VTE occurs, it is difficult to understand where to focus research and target prevention measures. Surveillance data will also provide a much-needed baseline upon which to assess the effectiveness of prevention efforts. The objectives that a strengthened surveillance system should meet include the ability to:

- Establish population-based estimates of VTE incidence, prevalence, and mortality;
- Facilitate longitudinal epidemiologic research of VTE to evaluate morbidity and mortality and further identify and quantify risks factors for VTE and its complications;



- Translate surveillance findings into targeted awareness and prevention messages and into hypotheses for public health epidemiologic research.

## Research

Further research into the causes, both acquired and genetic, and the complications of VTE is essential to preventing morbidity and mortality and reducing health disparities. More than 50% of VTE cases are spontaneous or unprovoked, indicating that many acquired risk factors have yet to be elucidated. The proportion of blacks who suffer from VTE is equal to or greater than that of whites; yet, some studies suggest that blacks may be more likely to present with PE and may have higher mortality rates from VTE, even though traditional (inherited and non-inherited) risk factors may not be as prevalent among blacks.<sup>7,19,47–50</sup> The strong association of family history of VTE with occurrence of VTE in whites and blacks suggests a genetic component, but few genetic markers have been found among non-white populations.<sup>19,47–50</sup> Knowledge of genetic risk factors historically has been of great interest because it could be used to predict which individuals are at risk for developing VTE. Such information could be used in conjunction with environmental factors to develop a risk profile that could be used for intervention and prevention strategies, particularly during high-risk situations such as surgery, pregnancy, or immobilization.

These genetic risks also warrant further investigation as they may be involved in other disorders such as adverse pregnancy outcomes. In addition, the long-term outcomes and complications of VTE, including post-thrombotic syndrome and recurrent VTE, need to be better understood in order to prevent long-term morbidity and improve the quality of life of those affected.

## Awareness

As noted at the APHA–CDC leadership conference and in the Surgeon General’s call to action, there is a lack of awareness among patients, providers, and the general public about VTE signs and symptoms.<sup>12,38</sup> To learn more about the public’s knowledge of DVT and identify its symptoms and risk factors, the CDC submitted DVT-related questions to the 2007 HealthStyles survey. Results showed that despite a low frequency of personal experience of DVT (14%), most respondents identified pain and swelling as symptoms (68% and 64%, respectively), and most knew that medical care should be sought for these symptoms (89%). However, only 38% of respondents knew that a DVT was a blood clot in a vein, and most could not identify common risk factors for DVT, such as aging or surgery (SEC, unpublished observations, 2009).

Early and accurate diagnosis of VTE is important for preventing deaths and having favorable long-term outcomes. Because these events can be silent, it is vital that all healthcare providers be aware of situations that put patients at risk, and provide appropriate tests, prophylaxis, and treatment. According to the call to action, much is known about effective prevention and treatment of VTE, yet this evidence is not applied consistently and systematically in healthcare settings.<sup>12</sup> Part of the difficulty lies in the complexity of VTE itself, as it occurs in many healthcare settings and, therefore, is diagnosed and managed by many providers (e.g., hematologists, surgeons, obstetricians, emergency physicians, primary care physicians). Yet, there is no national consensus by practitioners and hospitals on the best way to approach this condition. The most adhered-to guidelines have been published by the American College of Chest Physicians (ACCP); however, these guidelines are not accepted and followed by all specialties as evidenced by the differences between the ACCP guidelines and those of the American Academy of Orthopedic Surgeons for VTE prophylaxis for patients undergoing hip or knee surgery.<sup>12,51–54</sup> Moreover, with the increased focus on prevention of VTE, a risk of unnecessary treatment and bleeding from use of anticoagulant prophylaxis, screening, and testing arises. Development of consensus standards for screening, testing, managing, and preventing VTE is needed, with the ultimate goal of prevention and optimal health.

## Summary and Conclusion

Venous thromboembolism is a major public health problem that affects an estimated 300,000–600,000 individuals in the U.S. each year. With many of the known acquired risks increasing in the U.S. population, we can expect to see growing numbers of people affected by VTE. Increasing surveillance, research, and awareness of VTE must be a priority. By employing a comprehensive public health approach to learning about the burden and causes of VTE and raising awareness among the public and healthcare providers, enormous potential exists to prevent and reduce death and morbidity from DVT and PE throughout the U.S.

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