50

Epidemiology of Venous Thromboembolic Disease

Marc Carrier and Mary Cushman

INCIDENCE AND CLINICAL RELEVANCE OF VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cardiovascular disease after coronary heart disease and stroke. The age-standardized incidence rate is 1 to 2 per 1000 people per year. There is no surveillance for VTE, so the precise incidence and prevalence are not clear; three data sources present disparate results as recently reviewed.[1] Estimates from the United States Centers for Disease Control suggest there are 300,000 to 600,000 cases annually in the United States. In contrast, another study suggested 465,715 DVT, 296,000 PE, and 370,000 VTE deaths annually in six European countries with a population size together that is similar to the United States. The American Heart Association estimated that there were 676,000 DVT cases in the United States in 2014.

Estimation of lifetime risk is another way to consider the impact of VTE on the population. A report from an observational cohort of blacks and whites in the United States estimated that the lifetime risk of VTE after age 45 was 8.1% overall and 11.5% in blacks. Reflecting the association of common risk factors for VTE, lifetime risk was 10.9% in those with obesity and 17% to 18% in those with sickle cell anemia/trait or factor V Leiden (the most common genetic thrombophilia).[2] The risk of VTE differs by race-ethnicity, being lower in populations of Asian descent and perhaps higher in those of African descent, compared to Caucasians.[3]

VTE is a chronic disease that is associated with increased short- and long-term complications. In the short term, recurrent VTE and major bleeding predominate, while in the long term post-thrombotic syndrome (PTS), recurrent VTE and chronic thromboembolic pulmonary hypertension (CTEPH) cause morbidity and mortality. The case fatality rate for both recurrent VTE and major bleeding is approximately 11% during the first three months of anticoagulation therapy. PTS is a long-term complication in up to 25% to 50% of patients with DVT, and CTEPH complicates the course of approximately 1% of patients with PE.[4,5] Hence, VTE is an important cause of disability-adjusted life years lost and poses significant healthcare costs.[6,7] To reduce incidence and complications of VTE a better understanding of its incidence and associated risk factors is required.

SECULAR TRENDS IN INCIDENCE OF VENOUS THROMBOEMBOLISM

In North America, the overall incidence of VTE seems to have remained relatively unchanged over time. A large US population-based study reported an age- and sex-adjusted incidence of a first episode of VTE of 10.2 (95% CI: 10.2 to 10.3) per 10,000 person-years and demonstrated that the incidence did not change over a 30-year period (1991 to 2010).[8] A Canadian study also reported a stable age- and sex-adjusted incidence of VTE of 13.8 (95% CI: 13.7 to 14.0) per 10,000 person-years between 2004 and 2012.[9] Finally, a study from the Netherlands reported a stable overall age-adjusted incidence rate of first episode of VTE over a 10-year period from 2003 to 2012.[7] Interestingly, although the incidence rate of overall VTE remained stable over time, a number of studies have reported a decrease in the incidence of DVT but an increase in the incidence of PE. A French study comparing the 2013 incidence rate of VTE to that of 1998 using age- and sex-adjusted standardized incidence ratios (SIRs) reported a lower incidence for isolated DVT (without PE) in 2013 (SIR 0.53 [95% CI: 0.47 to 0.60]) but an increase in the incidence of isolated PE (without DVT) (SIR 1.29 [95% CI: 1.10 to 1.52]).[10] Other studies in the United States and the Netherlands also reported a decrease in the incidence of first (distal or proximal) DVT but an increase in the incidence of PE.[7,11] These observations are consistent with findings from the large population-based Norwegian Tromsø study that reported that the age-adjusted incidence of PE increased from 4.5 (95% CI: 2.3 to 6.7) per 10,000 person-years in 1996 to 11.3 (95% CI: 8.2 to 14.4) in 2010, whereas the incidence of isolated DVT in the same timeframe decreased from 11.2 (95% CI: 7.7 to 14.6) to 8.8 (95% CI: 6.1 to 11.5).[12] In contrast, as shown in Fig. 50.1, the 2018 statistical update of the American Heart Association reported a tripling of PE hospitalization and an approximate 50% increase in DVT hospitalization over the last two decades in the United States.[1] There are many potential reasons for this reported increase in DVT hospitalization. One explanation could relate to increased detection due to improvements in the sensitivity of imaging tests, such as using full-length leg ultrasonography, which may detect small distal DVTs that would not have been diagnosed with a diagnostic algorithm using proximal ultrasonography alone. However, the differences in findings from these studies with varied designs remain unexplained.

The reason for the increase in the overall incidence rate of PE over time remains unclear. The introduction of computed tomographic pulmonary angiography (CTPA) and its recent increasing availability in hospital emergency rooms is an important factor to consider. Detection of incidental PE, discussed below, might contribute. Advances in technology, more specifically the implementation of multiple-detector CTPA in clinical practice, has led to improvement in the sensitivity of PE diagnosis by allowing better resolution of the 2 to 3 mm diameter subsegmental pulmonary arteries. A large study from the US reported

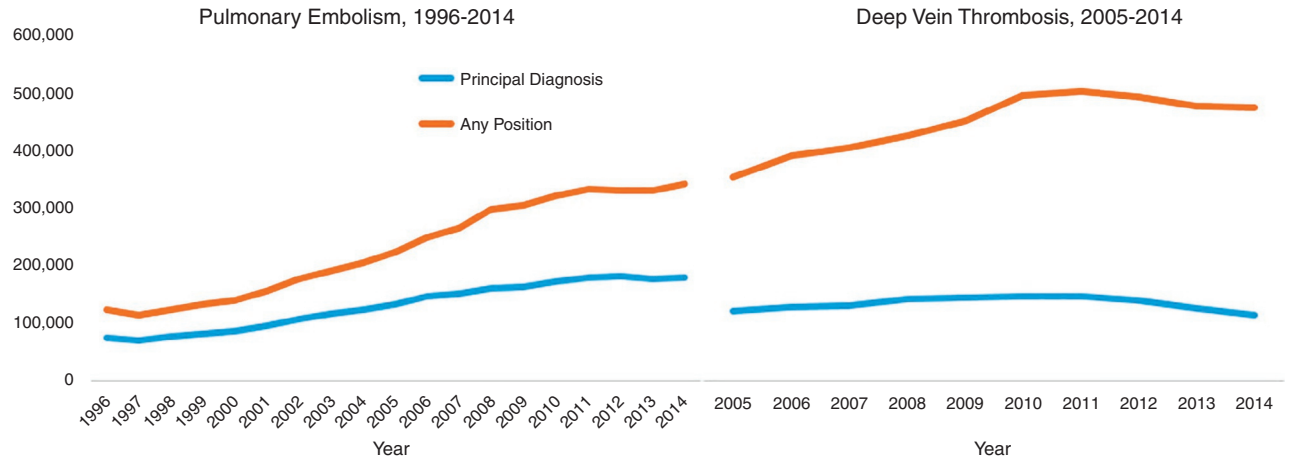

Fig. 50.1 Trend in hospitalized pulmonary embolism and deep vein thrombosis in the United States. Data is based on appearance of diagnosis codes in the principal position (*blue;* reason for the hospital stay) or any position *(orange)* in the list of discharge diagnosis codes. (From Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67–e492.)

that the increased use of multiple-detector CTPA for the diagnosis of PE seems to have led to a significant increase in the overall incidence of PE diagnosis.[13] Other factors besides improved sensitivity of CTPA may also be contributing, including improvements in effectiveness of PE diagnosis (using diagnostic algorithms including pre-test probability assessment), increased clinical awareness of healthcare providers to the diagnosis, a true increase in the incidence, or overdiagnosis. One study reported a decreasing age-adjusted, in-hospital case fatality rate from 12.1% to 7.8% between 1998 and 2006 without any significant change in overall mortality, suggesting that at least some of the increased PE diagnoses are less severe (or overdiagnosed).[13] Similar findings were reported in an Italian study assessing hospitalization for patients with acute PE. In this study, the incidence of PE increased from 4.0 to 6.2 per 10,000 person-years in women and from 3.5 to 4.6 in men between 2002 and 2012. The case-fatality rate decreased over the same time frame from 15.6% to 10.2% in women and 17.6% to 10.2% in men.[14]

The reported increased incidence of PE diagnosis since the introduction of multiple-detector CTPA may be correlated with an increase in the diagnosis of PE localized in the subsegmental pulmonary arteries without involvement in larger-order vessels (i.e., subsegmental PE, SSPE). A systematic review and meta-analysis of the literature reported that the rate of SSPE diagnosis among patients that underwent single-detector CTPA was 4.7% as compared to 9.4% for those that underwent multiple-detector CTPA.[15] Thus the rate of SSPE diagnosis seems to be increasing with the number of detectors used for PE diagnosis. These rates have been reported to range from 7% to 15% in patients undergoing 4- to 64-detector CTPA, respectively.

In summary, although not all reports agree, the overall incidence of VTE seems to have remained relatively unchanged over time, with lower-limb DVT decreasing and PE increasing in recent years. The rise in PE is likely, in part, a manifestation of the greater sensitivity of diagnostic tests for PE in smaller caliber vessels (e.g., subsegmental pulmonary arteries). The clinical importance of these isolated SSPE is not clear[15] and further studies are required to guide clinical management.

TABLE 50.1 Independent Risk Factors for Venous Thromboembolism

Risk Factor	Relative Risk
Established	
Age, per decade	2
Body mass index >30 kg/m^2	2
Body mass index >40 kg/m^2	3
Major surgery	20
Hospitalization for acute medical illness	5
Immobilization	2
Nursing home confinement	5
Trauma/fracture	5
Active cancer	15
Neurologic disease with leg paresis	6
Pregnancy or postpartum	4
Oral contraceptives	2–3
Postmenopausal oral hormones	2
Hereditary thrombophilia	2–12
Emerging	
Elevated factor VIII or von Willebrand factor	4
Elevated D-dimer	4
Height (per 10 cm)	1.5
Chronic kidney disease	2
Venous insufficiency	2
Sickle cell trait	1.6
African American ethnicity vs. Caucasian (in United States)	1.8

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Established Risk Factors

The incidence of VTE is dependent on the prevalence of its associated risk factors. A list including known important independent risk factors for VTE is depicted in Table 50.1. Most of these risk factors are transient (e.g., hospitalization) or modifiable (e.g., obesity). It is important to consider that the impact of combinations of risk factors tends to be at least additive and often multiplicative, such that the more factors present, the higher the risk. A well-known example is the combination of oral contraceptive pills (relative risk 2 to 3) and factor V Leiden (relative risk 4 to 7), which lead to a relative risk of 34 for VTE.

Hospitalization (due to acute medical illness or major surgery) is the most important risk factor, with about 40% of all VTE occurring after

hospital stay. The risk of VTE in hospitalized medically ill patients may be stratified further based on a combination of additional risk factors (e.g., age, obesity, previous VTE, or other co-morbid conditions). Risk assessment models for predicting VTE have been derived for this high-risk population, however the models are not fully validated so may not be generalizable to all settings.[16] Among surgical patients, who tend to have higher risk than medical patients, the incidence of postoperative VTE is greater in older patients (≥ 65 years old) and following certain types of procedures (e.g., major orthopedic surgery, abdominal, or pelvic surgery).[17] The total number of high-risk surgeries has been increasing over time. For example, hip and knee arthroplasties have doubled in the Netherlands between 1995 and 2010.[7] Given this increase in the prevalence of high-risk procedures and the fact that about 40% of all VTE occur during or shortly after hospitalization, there is a strong and unmet potential to prevent events and reduce the burden of disease.

Secular trends in two risk factors in particular are also important to consider in relation to VTE incidence in recent decades: the aging population and the obesity epidemic. Age is a critical determinant of this disease. The incidence of VTE ranges from 1 in 10,000 annually in young people, to 1 to 3 per 1000 in middle age, and nearly 1% per year in the very old; essentially the incidence doubles with every decade of age. As such, with the graying of the population, we could anticipate an increase in incidence over time. The second key factor is obesity, which is associated with a two- to threefold increased risk of VTE. Between 1990 and 2000, the obesity prevalence in the United States rose from 10% to 25%. We can calculate based on the change in population over this time that this factor alone would lead to 32,500 more cases of VTE annually in the United States. If the obesity rate had remained unchanged there would have been 21,000 events attributable to obesity in 2000 rather than an estimated 52,500 cases. Further, obesity seems to be more closely associated with PE than DVT,[18] so might relate to increases in PE diagnosis discussed above.

It can also be expected that the prevalence of cancer will increase in the upcoming years.[19] Active cancer accounts for approximately 20% of all incident VTE, and VTE is the second leading cause of death in this patient population. The risk of VTE is higher for patients with certain tumor types (e.g., brain, stomach, pancreas) and those with metastatic disease.

Emerging Risk Factors

As shown in Table 50.1, emerging risk factors for VTE include taller height, chronic kidney disease (CKD), sickle cell trait, elevated factor VIII/von Willebrand factor, elevated D-dimer, and African American ethnicity. While these factors are important risk factors, the clinical role of considering these risk factors is uncertain since they have rarely been incorporated into prediction scores for VTE. However, these risk factors are generally persistent risk factors, so consideration and understanding is important, especially for researchers.

Of these risk factors, D-dimer is probably the most widely used clinically, being present in risk prediction scores for cancer-related VTE[20] and recurrent VTE among patients with unprovoked first VTE.[21] While higher D-dimer is also strongly associated with risk of a first VTE in the future in healthy people[22] at this time there is no role for testing for predicting first VTE. There are also strong associations of coagulation factor VIII levels with first and recurrent VTE risk.[23]

Several studies investigated taller height or longer legs in relation to VTE risk with a hypothesis that venous return is impaired in taller people. More definitive data on height as a VTE risk factor was published by Roetker and colleagues who reported that a genetic risk score for taller height increased the risk of VTE, providing solid evidence of a causal relationship between height and VTE risk.[24] This association may be due to impaired venous return with taller height.

CKD has a global prevalence of 11% to 13%,[25] and increases the risk of VTE about twofold, although it is not yet clear whether stage 0 CKD or isolated albuminuria is related to risk.[26,27] Most of the association of CKD with VTE can be explained by a higher factor VIII level in the presence of CKD,[28] suggesting the mechanism might involve a procoagulant state or endothelial dysfunction in CKD as the link. This suggests that interventions to reduce procoagulation in CKD patients might be worthy of study.

About 8% of African Americans are carriers of the sickle cell trait, the heterozygous form of sickle cell disease. Several studies have now documented that sickle cell trait increases VTE risk, especially PE, which is a more fatal disease.[29] This finding may play a role in the known disparity in VTE affecting African Americans compared to whites in the United States, a disparity that is also partly explained by obesity.[3]

Overall, the prevalence of a majority of VTE risk factors is increasing over time and improvements in preventative strategies should hold promise for avoiding a concurrent increase in the incidence of VTE and its complications.

CLASSIFICATION OF VENOUS THROMBOEMBOLISM

The diagnostic classification of VTE is critical to consider as it leads directly to information on prognosis and on treatment duration. In general, VTE is either provoked by an acquired risk factor or unprovoked.[30] Acquired risk factors can be transient (e.g., major surgery) or persistent (e.g., metastatic carcinoma). VTE may be divided into unprovoked (~50% of cases), provoked with transient risk factors (~25% of cases), or provoked by persistent risk factors (~25% of cases).

Transient risk factors usually resolve after the VTE event (e.g., major surgery, trauma, etc.) and can be divided into major and minor risk factors. Patients with major and minor transient risk factors in the 2 to 3 months prior to VTE diagnosis, typically have a 50% lower recurrence risk than those with unprovoked VTE (Box 50.1). Patients with VTE provoked by a major transient risk factor (e.g., major surgery) are usually at very low risk of recurrent VTE after stopping treatment

BOX 50.1 Classification of Venous Thromboembolism (VTE)

VTE Provoked by a Transient Risk Factor

Major risk factors (up to 3 months prior to VTE)
- Surgery with general anesthesia for greater than 30 minutes
- Confined to bed ("bathroom privileges") for ≥3 days with acute illness
- Cast immobilization
- Cesarean section

Minor risk factors (up to 2 months prior to VTE)
- Surgery with general anesthesia for less than 30 minutes
- Admission to hospital for less than 3 days with an acute illness
- Estrogen therapy
- Pregnancy or puerperium
- Confined to bed out of hospital for less than 3 days with acute illness
- Leg injury associated with reduced mobility for at least 3 days

VTE Provoked by a Persistent Risk Factor
- Active cancer (ongoing treatment or metastatic/progressive disease)
- Neurologic disease with leg paresis

Unprovoked VTE
- Not in either of the above classifications

Modified from Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost.* 2016;14(7):1480–1483.

and short-term anticoagulation (3 months) is usually recommended. Patients with VTE provoked by persistent risk factors (e.g., metastatic cancer) are at high risk of recurrent VTE and extended treatment duration is often warranted to minimize the risk of recurrence. Transient risk factors may also fluctuate over time (e.g., inflammatory bowel disease) making it difficult to categorize and prognosticate the expected VTE recurrence rate. Patients with transient risk factors that fluctuate over time have a higher risk of recurrent VTE than those with truly transient risk factors, but lower than those with persistent risk factors. Guidelines recommend that clinicians tailor anticoagulation duration based of the risk benefit ratio and patient preference.[30]

Unprovoked VTE is not associated with any identifiable acquired risk factors (either transient or permanent) and can be considered a chronic disease in many patients. The term "unprovoked" is preferred over the previously used term "idiopathic" which suggests that there is no identifiable reason for the VTE. Patients may have non-acquired risk factors (e.g., hereditary thrombophilia) which do not qualify the VTE as provoked and may influence the underlying risk of recurrent VTE after stopping anticoagulation. Patients with unprovoked VTE have an intermediate risk of recurrent VTE after stopping therapy and need risk stratification and determination of patient preferences to help clinicians decide on length of anticoagulation. Essentially all of these patients are candidates for long-term anticoagulation, and consultation with a clinician experienced in VTE care is advisable.

INCIDENTAL VENOUS THROMBOEMBOLISM

The most common setting for incidental VTE is in cancer patients.[31] Approximately 50% of all VTE diagnosed in cancer patients are incidentally detected without any clinical suspicion of a symptomatic event. The prevalence of incidental VTE varies widely (from 1% to 15%) depending on tumor type and stage and type of diagnostic test used. Most incidental VTE are PE diagnosed on staging multi-detector CT. Approximately 60% of all incidental PEs involve the main or lobar pulmonary arteries and they are bilateral in about 30% of cases.[31] Small studies have suggested that incidental PE may present with a lower thrombotic burden when compared to symptomatic events.[32] However, these studies might have underestimated the actual embolic burden.

Data on the prevalence of incidental DVT of the extremities is scarce. The reported prevalence is variable from < 1% to 7%.[31] These estimates likely underestimate the actual prevalence of asymptomatic DVT in high-risk patients as imaging of the leg veins is not routinely performed. A recent prospective study reported that 9% of cancer patients initiating chemotherapy had asymptomatic DVT detected when screening lower extremity ultrasonography was performed.[33]

To consider treatment options for incidental VTE, prognosis must be considered. The prognosis seems to be similar for patients with incidental and symptomatic VTE.[34] A prospective cohort study reported rates of recurrent VTE of 11% among cancer patients with incidental VTE and 18% in those with symptomatic VTE.[35] The overall survival was 71% in both groups. Therefore, current clinical practice guidelines recommend treating incidental VTE using the same approach as symptomatic VTE.[36]

CONCLUSION

An understanding of the epidemiology and trends over time in VTE and its risk factors is important in considering diagnosis and management of this often-chronic disease. Correct diagnosis and classification are critical to designing treatment plans for patients since many patients are treated with long-term anticoagulants after a single event. Established and emerging risk factors discussed above should be considered by clinicians when they educate their patients. For example, occurrence of VTE in an obese patient should be accompanied by weight loss counseling. Proper interpretation of imaging findings has important clinical implications, for example in consideration of SSPE or incidental PE. The changing landscape of an individual's risk with aging and over time has implications for prevention as well.

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137(12):e67–e492.
2. Bell EJ, Lutsey PL, Basu S, et al. Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med*. 2016;129(3):339. e19-26.
3. Zakai NA, McClure LA, Judd SE, et al. Racial and regional differences in venous thromboembolism in the United States in 3 cohorts. *Circulation*. 2014;129(14):1502–1509.
4. Ten Cate-Hoek AJ. Prevention and treatment of the post-thrombotic syndrome. *Res Pract Thromb Haemost*. 2018;2(2):209–219.
5. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2).
6. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol*. 2014;34(11):2363–2371.
7. Scheres LJJ, Lijfering WM, Cannegieter SC. Current and future burden of venous thrombosis: not simply predictable. *Res Pract Thromb Haemost*. 2018;2(2):199–208.
8. Heit JA, Ashrani A, Crusan DJ, et al. Reasons for the persistent incidence of venous thromboembolism. *Thromb Haemost*. 2017;117(2):390–400.
9. Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. Secular trends in incidence and mortality of acute venous thromboembolism: the AB-VTE population-based study. *Am J Med*. 2016;129(8):879. e19-25.
10. Delluc A, Tromeur C, Le Ven F, et al. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. *Thromb Haemost*. 2016;116(5):967–974.
11. Huang W, Goldberg RJ, Anderson FA, et al. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985-2009). *Am J Med*. 2014;127(9):829–839. e5.
12. Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. *Eur J Epidemiol*. 2017;32(4):299–305.
13. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*. 2011;171(9):831–837.
14. Dentali F, Ageno W, Pomero F, et al. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy. *Thromb Haemost*. 2016;115(2):399–405.
15. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost*. 2010;8(8):1716–1722.
16. Rothberg MB. Venous thromboembolism prophylaxis for medical patients: who needs it? *JAMA Intern Med*. 2014;174(10):1585–1586.
17. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41(1):3–14.
18. Cushman M, O'Meara ES, Heckbert SR, et al. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: the Longitudinal Investigation of Thromboembolism Etiology. *Thromb Res*. 2016;144:127–132.
19. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
20. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol*. 2018;5(7):e289–e298.

21. Tosetto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). *J Thromb Haemost*. 2012;10(6):1019–1025.
22. Folsom AR, Alonso A, George KM, et al. Prospective study of plasma D-dimer and incident venous thromboembolism: the Atherosclerosis Risk in Communities (ARIC) Study. *Thromb Res*. 2015;136(4): 781–785.
23. Timp JF, Lijfering WM, Flinterman LE, et al. Predictive value of factor VIII levels for recurrent venous thrombosis: results from the MEGA follow-up study. *J Thromb Haemost*. 2015;13(10):1823–1832.
24. Roetker NS, Armasu SM, Pankow JS, et al. Taller height as a risk factor for venous thromboembolism: a Mendelian randomization meta-analysis. *J Thromb Haemost*. 2017;15(7):1334–1343.
25. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One*. 2016;11(7):e0158765.
26. Mahmoodi BK, Gansevoort RT, Naess IA, et al. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation*. 2012;126(16):1964–1971.
27. Cheung KL, Zakai NA, Folsom AR, et al. Measures of kidney disease and the risk of venous thromboembolism in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis*. 2017;70(2):182–190.
28. Cheung KL, Zakai NA, Callas PW, et al. Mechanisms and mitigating factors for venous thromboembolism in chronic kidney disease: the REGARDS Study. *J Thromb Haemost*. 2018;16(9):1743–1752.
29. Folsom AR, Tang W, Roetker NS, et al. Prospective study of sickle cell trait and venous thromboembolism incidence. *J Thromb Haemost*. 2015;13(1):2–9.
30. Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *J Thromb Haemost*. 2016;14(7):1480–1483.
31. Di Nisio M, Carrier M. Incidental venous thromboembolism: is anticoagulation indicated? *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):121–127.
32. den Exter PL, Kroft LJ, van der Hulle T, et al. Embolic burden of incidental pulmonary embolism diagnosed on routinely performed contrast-enhanced computed tomography imaging in cancer patients. *J Thromb Haemost*. 2013;11(8):1620–1622.
33. Khorana AA, Francis CW, Kuderer NM, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. *Thromb Res*. 2017;151:89–95.
34. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol*. 2011;29(17):2405–2409.
35. Font C, Farrus B, Vidal L, et al. Incidental versus symptomatic venous thrombosis in cancer: a prospective observational study of 340 consecutive patients. *Ann Oncol*. 2011;22(9):2101–2106.
36. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol*. 2015;33(6):654–656.