Medical Management of Venous Thromboembolism: What the Interventional Radiologist Needs to Know

Raj S. Kasthuri, M.D.¹ Nigel S. Key, M.D.¹

¹ Division of Hematology/Oncology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Semin Intervent Radiol 2012;29:3–9

Address for correspondence and reprint requests Raj S. Kasthuri, M.D., Division of Hematology/Oncology, University of North Carolina at Chapel Hill, CB # 7035, 321B Mary Ellen Jones Bldg, Chapel Hill, NC 27599 (e-mail: raj_kasthuri@med.unc.edu).

Abstract

Deep vein thrombosis and pulmonary embolism are considered manifestations of the same pathophysiological process and are together referred to as venous thromboembolism (VTE). VTE is a common disorder with an incidence of 1 to 3 in 1000 in the general population. It is estimated that the incidence of VTE is likely to increase as the average life expectancy of the U.S. population increases. Treatment of VTE consists of anticoagulation; the duration of anticoagulation is largely determined by the circumstances surrounding development of the thrombotic event. Vitamin K antagonists, the only oral anticoagulants approved for treatment of VTE in the United States, have several drawbacks and therefore new oral anticoagulants are currently in various stages of development. This review focuses on the risk factors for VTE and the approach to determining the duration of anticoagulation in patients with VTE. Results of clinical trials on the new oral anticoagulants that may soon be licensed for the treatment of VTE are also discussed.

Keywords

- ▶ venous thromboembolism
- ▶ thrombophilia testing
- ▶ anticoagulation
- ▶ medical management

Objectives: Upon completion of this article, the reader should be able to explain the management of patients with VTE and the results of clinical trials comparing new oral anticoagulants with warfarin for the treatment of VTE.

Accreditation: Tufts University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: Tufts University School of Medicine designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are related disorders with common risk factors. DVT and PE are considered manifestations of the same pathophysiological process and are together referred to as venous thromboembolism (VTE). VTE is a common disorder with an estimated annual incidence of 1 to 3 cases per 1000, and PE constitutes a third of all cases of VTE.¹ VTE is associated with

significant morbidity and mortality, and fatal PE is the first sign of VTE in a significant number of cases. The incidence of VTE increases with age from ~1 per 10,000 around age 20 to 10 per 1000 by age 80.² The incidence of VTE is likely to increase as the average life expectancy of the U.S. population increases. The signs and symptoms of VTE can be nonspecific, leading to significant delays in diagnosis and initiation of treatment. Increasing public awareness of VTE risk factors and the prevention of VTE has been the focus of recent efforts by the National Institutes of Health and the U.S. Department of Health and Human Services.³ This review focuses on the risk factors for VTE, duration of anticoagulation in patients with VTE, and new anticoagulant drugs.

Risk Factors for Venous Thromboembolism

Several factors increase the risk for developing VTE. These can be broadly divided into inherited risk factors, often referred to as inherited thrombophilias, and acquired risk factors (► **Table 1**).

Issue Theme Venous Thromboembolism; Guest Editors, Suresh Vedantham, M.D., F.S.I.R., and Nael Saad, M.D.

Copyright © 2012 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0032-1302445>.
ISSN 0739-9529.

Table 1 Risk Factors for Venous Thromboembolism

Inherited Risk Factors (Thrombophilias)	
Minor	
– Heterozygous factor V Leiden	
– Heterozygous prothrombin gene mutation	
Major	
– Protein S deficiency	
– Protein C deficiency	
– Antithrombin deficiency	
– Homozygous factor V Leiden	
– Homozygous prothrombin gene mutation	
– Compound heterozygosity for factor V Leiden and prothrombin gene mutation	
Acquired Risk Factors	
– Surgery	
Orthopedic surgery (hip and knee arthroplasty)	
Major surgery (abdominal surgery, bariatric surgery, neurosurgery)	
– Major trauma	
– Hormone-related risk factors	
Pregnancy	
Oral contraceptive use	
Hormone replacement therapy	
– Prolonged immobilization	
– Obesity	
– Smoking	
– Cancer	
– Antiphospholipid antibody syndrome	

This is a list of the most common risk factors and not intended to be a comprehensive list.

Inherited Risk Factors for VTE

Over the last 3 decades, several genetic mutations associated with increased thrombotic risk have been identified. All of these mutations affect or alter the function of one of the clotting factors or of the natural anticoagulants, thereby resulting in uncontrolled thrombin generation. The thrombophilias can be subclassified into low-risk and high-risk thrombophilias based on the extent to which they increase thrombotic risk. The most common inherited thrombophilia is heterozygosity for factor V Leiden (FVL). This is an arginine to glutamine substitution (R506Q) that affects the efficiency with which clotting factor V is degraded by activated protein C. Heterozygous FVL is present in ~5% of Caucasians in the United States and increases the risk for a first episode of VTE by three- to fivefold.^{4,5} The second most common inherited thrombophilia is heterozygosity for the prothrombin 20210 mutation (G20210A, PGM). PGM is also seen primarily in Caucasians and present in ~2 to 3% of that population. PGM

increases the risk for a first episode of VTE by two- to threefold.⁶ FVL and PGM are generally considered mild or low-risk thrombophilias given the relatively modest increase in risk for VTE associated with these mutations. However, inherited deficiencies of the natural anticoagulants protein C (PC), protein S (PS), and antithrombin (AT), sometimes referred to as the classic thrombophilias, are associated with a significantly greater (~5- to 10-fold) risk for VTE and are considered high-risk thrombophilias. The classic thrombophilias are rare, with PC and PS deficiency occurring in 1 in 500 individuals and AT deficiency occurring in 1 in 2000 to 3000 individuals.^{7–11} Homozygosity for FVL and PGM, as well as compound heterozygosity for these mutations, are rare and believed to be associated with a significantly higher risk for thrombosis compared with the low-risk thrombophilias.^{12,13} Mutations associated with increased circulating levels of several other coagulation factors, such as factors VIII, IX, XI, and fibrinogen, are also believed to confer an increased risk for thrombosis. However, these tend to be mild risk factors and are not routinely tested as part of laboratory evaluations for hypercoagulable states.

Finally, mutations in the methyltetrahydrofolate reductase gene (*MTHFR*) bear mention. Mutations in the *MTHFR* gene were believed to confer an increased risk for VTE. The mechanism underlying this increased risk appears to be related to an increase in homocysteine levels that can sometimes be associated with *MTHFR* mutations. Significant increases in homocysteine levels are associated with a modest (less than twofold) increase in risk for VTE.¹⁴ Thus, in situations where thrombophilia testing is considered, homocysteine levels could be measured, but testing for the presence of *MTHFR* mutations is not recommended. In terms of treatment, replacement of vitamins B6, B12, and folate can decrease the homocysteine level; however, this has not been shown to decrease the risk for recurrent VTE.¹⁵

Acquired Risk Factors for VTE

Several acquired or transient factors are associated with increased risk for VTE, summarized in **Table 1**. It is well established that the risk for VTE increases dramatically with age, and the risk at >80 years of age is ~100 times higher than in childhood.² In terms of gender, the data are more equivocal. Women of childbearing age may have a slightly increased risk for a first episode of VTE.¹⁶ Although it has been suggested that the risk for first VTE is higher in men after age 55, this still remains unclear.^{16,17} On the other hand, male gender appears to be an independent predictor of risk for recurrent (rather than first-time) VTE.^{18,19} Among the acquired risk factors for VTE, two warrant more discussion.

Obesity and Risk for VTE

The prevalence of obesity is increasing in most Western societies. Recent reports estimate that 60% of the U.S. population is overweight and ~30% are obese (as defined by a body mass index [BMI] >30). Obesity is an independent risk factor and confers a two- to threefold greater risk for VTE.²⁰ Furthermore, this risk continues to increase with increasing BMI and is greater in those that are morbidly obese. Of note,

the risk for VTE is higher when obesity occurs in the setting of other transient risk factors such as oral contraceptive use (>20-fold increase in risk) or inherited risk factors such as heterozygosity for FVL and PGM (~7-fold increase in risk).^{20,21}

Smoking and Risk for VTE

Although smoking is well established as a risk factor for arterial disease, its role in VTE has remained unclear until recently. Data from multiple epidemiological studies over the last few years have shown that smoking is also an independent risk factor for VTE, increasing the risk for VTE 1.5- to 2-fold.²¹⁻²³ Whereas the effect of smoking on VTE risk is mild, given that the prevalence of smokers is much higher in the general population compared to that of the inherited thrombophilias, the population attributable risk from smoking is likely to be significant.

Treatment of VTE

Treatment of VTE involves initiation of anticoagulation that can be divided into two phases: immediate treatment with the goal of preventing further extension and/or embolization of the thrombus (a risk that seems to extend for ~3 months after the event), and secondary prophylaxis with the goal of preventing recurrent VTE.²⁴ Anticoagulation is initiated with an immediate acting parenteral agent such as unfractionated heparin, low molecular weight heparin (LMWH), or the pentasaccharide fondaparinux. New immediate-acting oral agents are now available, albeit not yet licensed for the treatment of acute VTE, and are discussed separately later. Treatment with an oral vitamin K antagonist (e.g., warfarin) is started in conjunction with the parenteral anticoagulant, with the parenteral agent being continued until the prothrombin time (PT) or international normalized ratio (INR) is in the therapeutic range (INR: 2-3), a process known as "bridging." This phase usually takes 5 to 7 days. Warfarin is continued for at least 3 months.²⁵ This constitutes the immediate phase of treatment. In addition to preventing thrombus extension/embolization, anticoagulation also facilitates endogenous thrombolysis of the DVT/PE. Following completion of this phase of treatment, anticoagulation is either discontinued or continued longer for secondary prophylaxis against recurrent VTE, depending on the perceived risk-benefit ratio of additional therapy.

Duration of Anticoagulation

The decision to extend anticoagulation beyond 3 months is made taking into account the presence or absence of inherited and/or acquired risk factors, safety of continued anticoagulation, and comorbidities.²⁵ VTE that occurs in the presence of one or more acquired risk factors is considered a provoked event. Examples of this are thromboses that develop following prolonged hospitalization, surgery, or are associated with oral contraceptive use. In such cases, the provoking factor is usually reversible (e.g., discontinuation of oral contraceptive) and is not an ongoing cause for concern at the time discontinuation of anticoagulation is considered

usually 3 months after the acute event.²⁵ In patients with a provoked VTE treated with 3 months of anticoagulation, the risk for recurrence at 5 years is relatively low at ~5 to 10%.²⁶ This risk of recurrent thrombosis must be weighed against the risk of major bleeding over the same time period with continued anticoagulation (1 to 2% per year). Thus the risk-benefit ratio generally favors discontinuation of anticoagulation in patients with provoked VTE. However, in the case of VTE that occurs in the absence of such provoking factors, referred to as unprovoked VTE, the risk for recurrence following 3 months of anticoagulation is significantly higher at ~25 to 30% at 5 years.²⁶ In these patients, long-term and potentially lifelong anticoagulation should be considered, particularly if the patient is tolerating anticoagulation and there is no difficulty maintaining a therapeutic and relatively stable INR.

In determining the duration of anticoagulation in any given patient, it is important to bear in mind that some acquired risk factors may not be transient. One such example is cancer-associated VTE. If the cancer is incurable, the patient will benefit from long-term anticoagulation even though this could be considered a provoked event. One special situation in which long-term anticoagulation is recommended for the treatment of VTE occurring in association with an acquired risk factor is the antiphospholipid syndrome. Although only limited data are available on the natural history of this disease, they suggest that the risk of recurrent VTE in patients with the antiphospholipid syndrome may be as high as 75% at 8 years; therefore, indefinite anticoagulation is generally recommended for these patients.²⁷

Treating unprovoked VTE with long-term anticoagulation has the disadvantage of overtreating a significant number of patients who may not develop recurrent events. Thus there is a need to develop strategies to better stratify the risk for recurrence in patients with unprovoked VTE. One approach to improve risk stratification is the use of a clinical decision model developed by Rodger et al that includes assessment for evidence of postthrombotic syndrome (hyperpigmentation, edema, redness), measurement of D-dimer, BMI, age, and gender.²⁸ Patients are scored based on the presence or absence of these risk factors. This clinical decision model was able to identify women with unprovoked VTE that had a <3% annual risk of recurrence.²⁸ Another approach involves assessment for residual vein thrombosis using compression ultrasound after 3 months of anticoagulation, and continuation of anticoagulation if residual venous thrombosis is present.^{29,30} The drawback of this approach is the lack of standardization on what constitutes residual vein thrombosis. Yet another approach is the use of the D-dimer test to determine duration of anticoagulation, which is discussed later.

Risk Stratification Using the D-Dimer Test

The D-dimer test has been used to identify patients at high risk for recurrent VTE following discontinuation of anticoagulation. This approach was tested in the PROLONG study where the D-dimer was measured 1 month following discontinuation of anticoagulation in patients with a first,

unprovoked VTE.³¹ In this study, patients with a normal D-dimer did not resume anticoagulation, and patients with an abnormal D-dimer were randomized to either receive no further treatment or to resume anticoagulation. The recurrence rate among patients with an abnormal D-dimer that did not resume anticoagulation was 15% after an average follow-up of 16 months, as compared with 3% in patients who resumed anticoagulation. The recurrence rate in patients with a normal D-dimer (who did not receive anticoagulation) was only ~6%. This approach is now increasingly used in clinical practice, and a validation study with a longer duration of follow-up (total of 2 years) is ongoing. It is important to note, however, that there are many commercially available D-dimer assays, and an adequately validated assay should be used in this situation.

Impact of Thrombophilia Testing on the Duration of Anticoagulation

Over the last few years, physicians have become more conservative about the usefulness of thrombophilia testing in patients with VTE, given that treatment decisions are based more on the presence or absence of provoking clinical factors rather than the presence of a thrombophilia.³² Consider the example of a patient with a provoked VTE. Treatment of such a patient would involve anticoagulation for 3 months, assuming that the provoking factor is no longer present. In this case, the decision regarding the duration of anticoagulation would not change even if the patient was found to be heterozygous for FVL or PGM, the most common inherited thrombophilias. Indeed, a small number of such patients with a provoked VTE may carry one of the rare high-risk thrombophilias like PC, AT, or homozygous FVL. It is unclear whether these patients should be continued on long-term anticoagulation for secondary prophylaxis following a single provoked VTE. On the other hand, long-term anticoagulation should be considered in most patients with unprovoked VTE given the significant risk for recurrence. In such patients, the presence or absence of a thrombophilia would again not alter these recommendations. Thus thrombophilia testing in general does not have a material impact on treatment duration decisions and should therefore not be routinely pursued in all patients with VTE. The primary benefit of thrombophilia testing is from the genetic counseling standpoint in that the presence of thrombophilia might provoke counseling of the patient's family members on VTE prevention measures.

In general, when it is performed, thrombophilia testing should be avoided at the time of diagnosis of VTE for several reasons. First, the results will not have an immediate impact on treatment because the patient will require at least 3 months of anticoagulation. Second, depending on the extent of thrombosis, levels of PC and PS may be low as a result of the acute thrombosis and could result in misdiagnosis. Third, treatment with heparin, as would be indicated for treatment of VTE, can decrease AT activity and lead to misdiagnosis. Thus a more suitable time to pursue thrombophilia testing would be during an outpatient follow-up visit. One caveat to remember is that anticoagulation with warfarin will decrease PC and PS activity because they are also vitamin K dependent

proteins, and the patient should discontinue warfarin for at least 2 to 4 weeks before these tests are obtained. In patients with unprovoked VTE, this can be achieved by transitioning the patient to a LMWH for 4 weeks if thrombophilia testing is believed to be indicated.

Thrombolytic Therapy for VTE

It is widely accepted that systemic thrombolytic therapy should be considered in patients with massive PE (defined by hemodynamic compromise).²⁵ The role for thrombolysis, particularly catheter-directed thrombolysis (CDT), in other patients with DVT and/or PE is less well established. At present, it is our impression that most hematologists would favor CDT in the acute setting in young patients with significant iliofemoral DVT who are otherwise healthy and have a low risk for bleeding complications. The rationale here is that CDT may decrease the incidence and severity of postthrombotic syndrome and thereby improve future quality of life. This hypothesis is being systematically studied in an ongoing prospective randomized control trial (ATTRACT trial).

New Anticoagulants

The introduction of LMWH as a safe and effective alternative to unfractionated heparin led to a radical change ~15 years ago in the management of patients with VTE. LMWH made it possible to treat acute VTE in many patients entirely in the outpatient setting. These agents have better bioavailability and are administered subcutaneously once or twice daily. They do not require routine monitoring, although it is possible to monitor their levels if needed. However, for >50 years, vitamin K antagonists (warfarin) have been the only oral agents available for the treatment of VTE. Vitamin K antagonists have several limitations, such as: slow onset of action necessitating 5 to 7 days of bridging with one of the parenteral agents; a narrow therapeutic window; significant inter-individual variability in dose response (this is at least in part due to genetic polymorphisms in metabolic pathways); and numerous food and drug interactions that require continued monitoring of the PT/INR. The development of alternatives to vitamin K antagonists has been the holy grail of anticoagulation therapy. The properties of an ideal oral anticoagulant would be immediate onset of action, absence of food and drug interactions, wide therapeutic window, lack of the need for monitoring, and rapid reversibility in the event of bleeding.³³

Several oral anticoagulants have been developed over the last few years and are currently in clinical trials.³⁴ Most of these are direct inhibitors of factor Xa or factor IIa (thrombin). A few have already completed phase 3 clinical trials against LMWH or warfarin for the prevention or treatment of VTE; these are discussed later. It is important to highlight a few aspects common to all of these newer agents. First, routine coagulation tests like the PT/INR and partial thromboplastin time (aPTT) cannot be used to monitor these newer agents. ▶ **Table 2** summarizes the effect on the PT/INR and aPTT of the newer agents that are in advanced stages of development.^{35,36} Second, there is no specific antidote for these drugs if emergent reversal is required, such as in the event of bleeding complications. The current approach to

Table 2 Effect of New Anticoagulants on Screening Coagulation Tests

Drug name	Effect on PT/INR	Effect on aPTT
Dabigatran	Prolonged at therapeutic drug levels. Not sensitive for monitoring.	Prolonged in a curvilinear manner with increasing doses. Results vary based on reagent used.
Rivaroxaban	Minimal prolongation at therapeutic drug levels. Results vary based on thromboplastin used.	Less sensitive than PT. Results vary based on reagent used.
Apixaban	Prolongs PT/INR. Not sensitive for monitoring. Effect of different thromboplastins not known.	Minimal prolongation at therapeutic drug levels. Effects of different reagents not known.

PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

management of bleeding associated with these agents is primarily supportive and involves administration of fresh-frozen plasma, prothrombin complex concentrates, and/or recombinant VIIa. Finally, several these newer agents are excreted by the kidney and should therefore be avoided in patients with compromised renal function.

Dabigatran Etxilate (PRADAXA)

Dabigatran is an orally administered direct thrombin inhibitor administered as a prodrug. Dabigatran reaches peak plasma levels 2 hours after administration, has a half-life of 14 to 17 hours, and steady state plasma levels are achieved in 3 days.^{37,38} Dabigatran has undergone several phase 3 clinical trials evaluating its efficacy in the prevention of VTE following hip and knee arthroplasty, in the treatment of VTE, and in the prevention of stroke in patients with atrial fibrillation. It was found to be noninferior to enoxaparin (40 mg subcutaneously once daily) in the prevention of VTE following hip and knee arthroplasty.^{39–41} A separate investigation, the RECOVER trial, evaluated dabigatran (150 mg orally twice daily) versus warfarin (INR: 2 to 3) for the treatment of VTE.⁴² Of note, patients in both trial arms received initial treatment with a LMWH for bridging. This was a double-blind randomized controlled trial of 6 months of anticoagulation, and dabigatran was noninferior to warfarin in this trial with comparable rates of bleeding. In another report, the RE-LY trial studied the efficacy of dabigatran versus warfarin (INR: 2 to 3) for stroke prevention in patients with atrial fibrillation.⁴³ This was a double-blind, double-dummy randomized controlled trial, and two doses of dabigatran were studied: 110 mg twice daily and 150 mg twice daily, administered for 2 years. The lower dose of dabigatran was comparable with warfarin for stroke prevention with lower rates of bleeding, whereas the higher dose of dabigatran was more effective than warfarin for stroke prevention with comparable rates of bleeding. In this study of 18,000 subjects, 12% of participants receiving dabigatran reported dyspepsia. Based on the results of these studies, dabigatran is licensed for the prevention of VTE after hip and knee arthroplasty in Europe, and it is approved for the prevention of stroke in atrial fibrillation in the United States and Canada. We expect that it will be submitted to the U.S. Food and Drug Administration for licensing for the treatment of VTE in the near future.

Rivaroxaban (XARELTO)

Rivaroxaban is a direct factor Xa inhibitor. It is the only new agent that achieves steady state plasma levels after the first dose. Peak plasma levels are reached in 2 to 4 hours, and it has a half-life of 5 to 9 hours in younger individuals and 9 to 13 hours in the elderly.⁴⁴ Rivaroxaban (10 mg once daily) was evaluated against enoxaparin (40 mg once daily) for the prevention of VTE after hip and knee arthroplasty in the RECORD trials.^{45,46} These studies found rivaroxaban to be superior to enoxaparin in the prevention of VTE, with comparable bleeding rates. Based on these studies, rivaroxaban is licensed for the prevention of VTE following hip and knee arthroplasty in Europe and Canada. The EINSTEIN trials investigated rivaroxaban versus warfarin for the treatment of acute VTE. The EINSTEIN-DVT trial was an open-labeled study where patients were randomized to warfarin following LMWH bridging, or to rivaroxaban.⁴⁷ In this study, subjects on the rivaroxaban arm did not require bridging with LMWH. Instead, they received a higher dose of rivaroxaban, 15 mg twice daily for 3 weeks, after which the dose was reduced to 20 mg daily. This study showed rivaroxaban was comparable with warfarin for the treatment of VTE. The effect of continued anticoagulation for 18 months versus 6 months was evaluated in the EINSTEIN extension study where, following 6 months of anticoagulation, subjects were randomized to continuing rivaroxaban or placebo for an additional year. In this study, rivaroxaban significantly reduced recurrent VTE compared with placebo (2% versus 7.1%; hazard ratio: 0.28; 95% confidence interval, 0.15 to 0.53) without an increase in major bleeding. The EINSTEIN-PE study is ongoing. Finally, rivaroxaban was evaluated against warfarin for the prevention of stroke in patient with atrial fibrillation in the ROCKET AF trial,⁴⁸ the results of which demonstrated rivaroxaban (20 mg once daily) to be noninferior to warfarin.

Apixaban

Apixaban is another orally administered direct factor Xa inhibitor. Peak plasma levels are attained 1 hour after administration, and steady state levels are achieved by 3 days. It has a half-life of 12 hours and is administered twice daily.⁴⁹ Apixaban was studied against enoxaparin for the prevention of VTE following hip and knee arthroplasty in the ADVANCE trials.^{50,51} Apixaban was superior to enoxaparin with comparable rates of bleeding. Phase 3 trials on apixaban versus

warfarin for the treatment of VTE are ongoing (AMPLIFY and AMPLIFY-EXT). Two trials have been performed evaluating the efficacy of apixaban in the prevention of stroke in patients with atrial fibrillation. The AVERROES trial evaluated apixaban against aspirin in patients deemed unsuitable for warfarin.⁵² The incidence of stroke and systemic embolization were significantly lower in the apixaban group. Although the rates of major bleeding were comparable in both groups, apixaban was associated with higher rates of minor bleeding. Finally, the ARISTOTLE study compares apixaban versus warfarin for stroke prevention in atrial fibrillation; this study is ongoing.

Other New Anticoagulants

In addition to those already discussed, several other anticoagulants are in varying stages of development.³³

Summary

The treatment of patients with VTE is complex, including variations in the type of treatment, duration of treatment, and agents that are used. Specific algorithms for treatment, although helpful in some settings, should be used as a guideline to allow individual treatment variations based on clinical and laboratory factors specific to any given patient.

References

- Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol* 2008;28(3):370–372
- White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107(23, Suppl 1):14–18
- The surgeon general's call to action to prevent deep vein thrombosis and pulmonary embolism. 2008. Accessed October 16, 2011
- Juul K, Tybjaerg-Hansen A, Schnohr P, Nordestgaard BG. Factor V Leiden and the risk for venous thromboembolism in the adult Danish population. *Ann Intern Med* 2004;140(5):330–337
- Moll S. Thrombophilias—practical implications and testing caveats. *J Thromb Thrombolysis* 2006;21(1):7–15
- Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;88(10):3698–3703
- Demers C, Ginsberg JS, Hirsh J, Henderson P, Blajchman MA. Thrombosis in antithrombin-III-deficient persons. Report of a large kindred and literature review. *Ann Intern Med* 1992;116(9):754–761
- Allaart CF, Poort SR, Rosendaal FR, Reitsma PH, Bertina RM, Briët E. Increased risk of venous thrombosis in carriers of hereditary protein C deficiency defect. *Lancet* 1993;341(8838):134–138
- Tait RC, Walker ID, Reitsma PH, et al. Prevalence of protein C deficiency in the healthy population. *Thromb Haemost* 1995;73(1):87–93
- Makris M, Leach M, Beauchamp NJ, et al. Genetic analysis, phenotypic diagnosis, and risk of venous thrombosis in families with inherited deficiencies of protein S. *Blood* 2000;95(6):1935–1941
- Dykes AC, Walker ID, McMahon AD, Islam SI, Tait RC. A study of protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. *Br J Haematol* 2001;113(3):636–641
- Martinelli I, Bucciarelli P, Margaglione M, De Stefano V, Castaman G, Mannucci PM. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. *Br J Haematol* 2000;111(4):1223–1229
- Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood* 1995;85(6):1504–1508
- Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost* 2005;3(2):292–299
- Den Heijer M, Willems HP, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: a randomized, placebo-controlled, double-blind trial. *Blood* 2007;109(1):139–144
- Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158(6):585–593
- Tormene D, Ferri V, Carraro S, Simioni P. Gender and the risk of venous thromboembolism. *Semin Thromb Hemost* 2011;37(3):193–198
- Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med* 2004;350(25):2558–2563
- McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *Lancet* 2006;368(9533):371–378
- Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *Br J Haematol* 2007;139(2):289–296
- Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjønneland A, Overvad K. Smoking and venous thromboembolism: a Danish follow-up study. *J Thromb Haemost* 2009;7(8):1297–1303
- Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation* 2010;121(17):1896–1903
- Lutsey PL, Virnig BA, Durham SB, et al. Correlates and consequences of venous thromboembolism: the Iowa Women's Health Study. *Am J Public Health* 2010;100(8):1506–1513
- Key NS, Kasthuri RS. Current treatment of venous thromboembolism. *Arterioscler Thromb Vasc Biol* 2010;30(3):372–375
- Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):454S–545S
- Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet* 2010;376(9757):2032–2039
- Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;346(10):752–763
- Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* 2008;179(5):417–426
- Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood* 2008;112(3):511–515
- Prandoni P, Prins MH, Lensing AW, et al; AESOPUS Investigators. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. *Ann Intern Med* 2009;150(9):577–585
- Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006;355(17):1780–1789
- Moll S. Who should be tested for thrombophilia? *Genet Med* 2011;13(1):19–20
- Eikelboom JW, Weitz JI. New anticoagulants. *Circulation* 2010;121(13):1523–1532

- 34 Van Es J, Eerenberg ES, Kamphuisen PW, Büller HR. How to prevent, treat, and overcome current clinical challenges of VTE. *J Thromb Haemost* 2011;9(Suppl 1):265–274
- 35 Castellone DD, Van Cott EM. Laboratory monitoring of new anticoagulants. *Am J Hematol* 2010;85(3):185–187
- 36 Samama MM, Guinet C. Laboratory assessment of new anticoagulants. *Clin Chem Lab Med* 2011;49(5):761–772
- 37 Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008;36(2):386–399
- 38 Stangier J, Eriksson BI, Dahl OE, et al. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. *J Clin Pharmacol* 2005;45(5):555–563
- 39 Eriksson BI, Dahl OE, Huo MH, et al; RE-NOVATE II Study Group. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2011;105(4):721–729
- 40 Eriksson BI, Dahl OE, Rosensch N, et al; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;5(11):2178–2185
- 41 Eriksson BI, Dahl OE, Rosensch N, et al; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370(9591):949–956
- 42 Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361(24):2342–2352
- 43 Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139–1151
- 44 Kubitz D, Becka M, Wensing G, Voith B, Zuehlendorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct factor Xa inhibitor—after multiple dosing in healthy male subjects. *Eur J Clin Pharmacol* 2005;61(12):873–880
- 45 Eriksson BI, Borris LC, Friedman RJ, et al; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358(26):2765–2775
- 46 Kakkar AK, Brenner B, Dahl OE, et al; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372(9632):31–39
- 47 Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363(26):2499–2510
- 48 Ahrens I, Lip GY, Peter K. What do the RE-LY, AVERROES and ROCKET-AF trials tell us for stroke prevention in atrial fibrillation? *Thromb Haemost* 2011;105(4):574–578
- 49 Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;37(1):74–81
- 50 Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363(26):2487–2498
- 51 Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010;375(9717):807–815
- 52 Connolly SJ, Eikelboom J, Joyner C, et al; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364(9):806–817