Venous Thromboembolism and Atherothrombosis
An Integrated Approach
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Case presentation 1: A 45-year-old man with a history of obesity, hypertension, dyslipidemia, deep vein thrombosis (DVT) complicated by pulmonary embolism (PE) 12 years earlier, and non–ST-elevation myocardial infarction treated with angioplasty and stenting of the left anterior descending coronary artery 4 years earlier presented to the emergency department with sudden onset of substernal chest pain. His ECG showed anterolateral ST-segment elevation, and emergent coronary angiography demonstrated in-stent thrombosis of his left anterior descending coronary artery (Figure 1A).

Case Presentation 2: A 39-year-old man with a history of cigarette smoking, hypertension, dyslipidemia, and non–ST-elevation myocardial infarction 3 years earlier presented with progressive dyspnea and several hours of chest pressure. His ECG was unchanged, but his cardiac troponin I was elevated at 1.33 ng/mL (normal <0.1 ng/mL). Contrast-enhanced chest computed tomography demonstrated a large saddle PE (Figure 2).

Overview
Venous thromboembolism (VTE), including DVT and PE, is the third most common cardiovascular disorder after coronary artery disease and stroke. Furthermore, patients with acute coronary syndromes or stroke have an increased risk of VTE as a complication of hospitalization.1 Many risk factors for VTE, such as obesity, hypertension, dyslipidemia, diabetes, and smoking, overlap with those for atherothrombosis. Data from registry analyses and clinical trials suggest that clinicians should abandon “silo thinking” regarding VTE risk factors and integrate cardiovascular risk reduction strategies from coronary artery disease and stroke into the prevention of DVT and PE. As a novel paradigm, VTE is best considered as part of a pan-cardiovascular syndrome that includes coronary artery disease, peripheral artery disease, and cerebrovascular disease.

Risk Factors
The association of atherothrombosis and VTE was first suggested by Prandoni and colleagues,2 who found that the presence of carotid artery plaque was associated with a doubling in the risk of VTE. A subsequent study demonstrated that the risk of acute myocardial infarction is 4-fold higher among patients with a prior history of VTE than among those without such a history.3 Similarly, the risk of stroke is also increased after an initial VTE event.4

Shared risk factors help explain the increased risk of VTE in patients with atherothrombosis and the greater frequency of myocardial infarction and stroke in patients who have had DVT or PE. Established cardiovascular risk factors, including obesity, hypertension, dyslipidemia, diabetes mellitus, the metabolic syndrome, and tobacco use, also increase the risk of VTE. In addition, postmenopausal hormone replacement and hormonal contraceptive therapy increase the risk of atherothrombosis and VTE.

Obesity, a well-established risk factor for atherothrombosis, increases the risk of VTE. In a meta-analysis of 63 552 patients from 21 studies, obesity was associated with a doubling in VTE risk.5 In a cohort study from the US National Hospital Discharge Survey, obese women had a greater risk of DVT than obese men.6 In the all-...
female Nurses’ Health Study, obesity tripled the risk of unprovoked PE.7 Hypertension predisposes to both atherothrombosis and VTE. Hypertension is associated with a 50% increase in the risk of VTE.5 In the Nurses’ Health Study, hypertension was associated with a 2-fold increase in the risk of unprovoked PE.7 HDL cholesterol levels in particular are significantly lower in patients who experience VTE.5 Diabetes mellitus has been associated with a 42% increase in the risk of DVT or PE.5 A case-control study of 208 VTE patients and 300 control subjects from Korea demonstrated that both low levels of HDL cholesterol and elevated fasting glucose correlated with a doubling in the risk of VTE.8

The metabolic syndrome has emerged as a potent risk factor for atherothrombosis that affects up to 45% of the US population over 50 years old.9 Recent data also implicate the metabolic syndrome as a risk factor for VTE. A registry of 20,374 patients demonstrated that the metabolic syndrome increased the risk of VTE by 84%.10 However, abdominal adiposity, a prominent feature of the metabolic syndrome, accounted for the majority of the increased risk in men and was associated with a significantly increased risk of VTE in women.10 The metabolic syndrome was associated with a 50% increase in the risk of any VTE and a 70% greater risk of an unprovoked event in a large Korean population.8

Although a heart-healthy diet constitutes an important component of risk reduction in atherothrombosis, the contribution of nutritional factors to the risk of VTE has received scant attention. In a prospective study conducted over 12 years, 14,962 patients underwent assessments of dietary intake and were followed up for incident VTE.11 Greater daily consumption of fruits and vegetables was associated with a declining risk of VTE.11 Eating fish at least once weekly was associated with a 30% to 45% reduction in the incidence of VTE.11 The risk of VTE increased with greater consumption of red and processed meats.11 The top quintile of meat eaters had double the risk of DVT or PE compared with the bottom quintile.11

Hormonal contraception and replacement therapy have been linked to VTE and atherothrombotic events. Oral contraceptive pills, especially those that contain third-generation progestins, increase the risk of VTE.12 In the Women’s Health Initiative, women receiving estrogen-plus-progestin hormone replacement therapy demonstrated a 2-fold increase in the risk of VTE compared with those in the placebo group.13

Additional atherothrombotic risk factors of tobacco use and stress also increase the risk of VTE. Smoking is a particularly potent VTE risk factor among women, doubling the risk of unprovoked PE for those who smoke 25 to 34 cigarettes daily and tripling the risk for those who smoke 35 or more cigarettes daily compared with never-smokers.7 In a prospective cohort study of 69,586 Swedish men followed up for 28 years, persistent stress was independently associated with an increased frequency of PE.14

Pathophysiology

In addition to having risk factors in common, VTE and atherothrombosis
demonstrate shared pathophysiology (Figure 3). Inflammation, systemic and local hypercoagulability, and endothelial injury play integral mechanistic roles in the pathophysiology of atherothrombosis. An improved understanding of VTE integrates these same pathophysiological processes.

The role of inflammation in the pathogenesis of VTE has long been suspected on the basis of the observation of an increased frequency of DVT and PE in patients with chronic inflammatory disorders such as inflammatory bowel disease and systemic vasculitis. Elevations in C-reactive protein, a sensitive marker of systemic inflammation, have been linked to an increased risk of VTE. In an analysis of 10,505 participants in the Atherosclerosis Risk In Communities (ARIC) Study followed up for incident DVT or PE over 8.3 years, elevated C-reactive protein above the 90th percentile was associated with a 76% increase in the risk of VTE versus lower percentiles. Elevations in systemic inflammatory markers, including C-reactive protein, fibrinogen, and factor VIII, are particularly prevalent in patients who experience unprovoked DVT or PE compared with those with secondary VTE. Polymorphisms in genes encoding factor VII, interleukin-1β, and interleukin-10 modify the risk of unprovoked VTE. In an analysis of the randomized, controlled JUPITER study (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), rosuvastatin (20 mg orally daily) reduced the rate of symptomatic VTE by 43% in patients with elevated C-reactive protein and LDL cholesterol levels <130 mg/dL compared with placebo.

Hypercoagulability has been well established in the pathogenesis of VTE. Inherited thrombophilias, including activated protein C resistance due to factor V Leiden mutation, prothrombin gene mutation, and deficiencies of protein C, protein S, and antithrombin III, increase the risk of VTE. Although hyperhomocysteinemia may be inherited due to a deficiency in methylenetetrahydrofolate reductase, it is most often acquired because of dietary folate deficiency and has been associated with both VTE and atherothrombosis. Antiphospholipid antibody syndrome is an acquired thrombophilia that increases the risk for both VTE and arterial thromboembolism.

Endothelial injury plays a pathophysiological role in the development of VTE. Traumatic injury to the extremity may result in DVT due to a combination of local endothelial injury and immobility. However, even minor lower-extremity injuries that are not associated with surgery, limb casting, or immobility may increase the risk of DVT up to 5 times that of subjects without such trauma. Local endothelial injury from pacemaker and internal cardiac defibrillator leads and long-term indwelling central venous catheters increase the risk of upper-extremity DVT.

Prevention
Preventive efforts should begin with lifestyle measures to reduce the risk of VTE and atherothrombotic events. Overweight and obese patients should be counseled regarding diet and exercise to achieve sustained weight reduction. We advise our coronary heart disease and VTE patients to reduce their intake of red and processed meats and to increase consumption of fish, fruits, and vegetables. We counsel them regarding tobacco cessation and offer prescription of pharmacological aids and referral to support groups. Finally, referral for stress management and relaxation techniques may be beneficial.
Pharmacotherapeutic interventions for prevention of cardiovascular events in patients with VTE or atherothrombosis include treatment of risk factors and anticoagulation. Cardiovascular risk factors of hypertension, dyslipidemia, and diabetes should be treated according to goals set forth by guideline recommendations. In the JUPITER trial, rosuvastatin decreased the frequency of VTE events among nondyslipidemic patients with elevated C-reactive protein levels, which suggests that statins may reduce risk through modulation of inflammatory pathways.\(^{18}\)

Anticoagulation should be considered in patients who have had VTE according to the risk for recurrence. Patients who have had unprovoked, or idiopathic, VTE benefit from indefinite-duration anticoagulation because of a high rate of recurrent events.\(^{21–23}\) Patients with a history of provoked events due to trauma, surgery, or immobilization usually receive time-limited anticoagulation (often for 6 months) but require meticulous attention to VTE prophylaxis during subsequent high-risk situations such as hospitalization for medical illness. Although antiplatelet agents are not effective in reducing the risk of VTE, they do help prevent atherothrombosis. Some patients will require “triple therapy” with warfarin, aspirin, and clopidogrel or prasugrel.

Patients who have experienced atherothrombotic events represent an underrecognized population at risk for VTE. In an analysis of the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database, more than 1 million patients with atherothrombotic cardiovascular disease, including myocardial infarction and stroke, were at risk for VTE, which constitutes one of the largest proportions of hospitalized medical patients.\(^{1}\) Despite guideline recommendations for prevention of DVT and PE in hospitalized medical patients,\(^{24,25}\) including those with atherothrombotic cardiovascular disease, VTE prophylaxis remains underutilized.\(^{26,27}\) Implementation of computerized and “human-based” decision support strategies can improve VTE prophylaxis use in this vulnerable patient population.\(^{28–30}\)

**Policy Implications**
The link between atherothrombosis and VTE has public healthcare policy implications. In 2008, the US Surgeon General issued the “Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism” and estimated that 100 000 to 180 000 PE deaths occur annually in the United States alone.\(^{31}\) He cited PE as the most preventable cause of death among hospitalized patients.

Identification of individuals with established atherothrombotic cardiovascular disease or with risk factors for atherothrombotic cardiovascular disease provides additional targets for VTE prevention efforts. VTE complicating hospitalization for medical illness such as myocardial infarction and stroke burdens the healthcare system.\(^{32}\) Medicare has classified DVT and PE that occur after total knee or hip replacement as a “never event” and has stopped reimbursing hospitals for the additional costs incurred by this complication.\(^{33}\) A similar policy eventually could be applied to VTE that complicates a hospitalization for common medical illnesses such as myocardial infarction and stroke. Furthermore, the Joint Commission has placed increasing emphasis on VTE prevention as a critical patient safety issue. An improved understanding of the link between atherothrombotic cardiovascular disease and VTE provides clinicians with the ability to identify a previously underrecognized patient population at risk for DVT and PE. Fortunately, effective strategies can be implemented to reduce the frequency of these common cardiovascular illnesses.

**Case Resolutions**
**Case presentation 1:** This patient was treated successfully with emergent coronary angioplasty and stent placement in the left anterior descending coronary artery (Figure 1B). Aspirin and clopidogrel were added to his medication regimen, along with continued warfarin.

**Case presentation 2:** This patient was treated successfully for acute PE (Figure 2) with intravenous unfractionated heparin as a “bridge” to warfarin. Because his PE was idiopathic and unprovoked, warfarin was continued for indefinite duration.

**Case presentations 1 and 2:** Both patients were treated for pan-cardiovascular disease with aggressive risk factor reduction, including weight reduction, hypertension control, smoking cessation, lipid lowering, and counseling about diet and exercise. They were educated that a heart-healthy lifestyle is critical for the prevention of both myocardial infarction and PE.

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Disclosures

None.

References


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