

## REVIEW ARTICLE

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# Prophylaxis against Venous Thromboembolism in Ambulatory Patients with Cancer

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THE RISK OF VENOUS THROMBOEMBOLISM IS FOUR TO SEVEN TIMES AS high among patients with cancer as among persons without this disease.<sup>1,2</sup> This risk is highest for patients with certain types of solid tumors and hematologic cancers and is increased for patients who are receiving chemotherapy or radiotherapy, who have undergone operative procedures, who have metastatic disease, or who have inherited thrombophilias. Studies have indicated that the mechanisms of this effect may include mucin production by tumors, exposure of tissue factor-rich surfaces and tissue factor-bearing microparticles, cysteine proteinase production leading to thrombin generation, and local hypoxia.<sup>3,4</sup> Venous thromboembolism is the second leading cause of death in patients with cancer,<sup>5</sup> and overall mortality is increased among patients who have both conditions. In one study, the 1-year survival rate among these patients was one third the survival rate among patients who had cancer but did not have venous thromboembolism.<sup>6</sup> The incidence of cancer-associated thrombosis has increased,<sup>7-10</sup> probably because of a combination of improved treatment outcomes resulting in longer patient survival, more aggressive and prothrombotic treatment regimens, an aging population, and increased detection owing to improvements in imaging technology and the frequency of imaging.

Awareness of venous thromboembolism has increased considerably. As a result of the Surgeon General's call to action in 2008 to prevent deep-vein thrombosis and pulmonary embolism, programs have been created to assess and evaluate the occurrence of this condition. The Institute of Medicine declared hospital-acquired venous thromboembolism a medical error. The Agency for Healthcare Research and Quality has stated that providing prophylaxis against venous thromboembolism is one of the most important measures that can be taken to improve patient safety. The usefulness of prophylaxis against venous thromboembolism after orthopedic joint-replacement surgery is not questioned, and therefore, the Centers for Medicare and Medicaid Services has declared it a hospital-acquired condition, with a negative effect on reimbursement.

The use of prophylactic anticoagulation therapy in most hospitalized patients with cancer and in patients undergoing surgery for cancer has been endorsed despite limited data.<sup>11-13</sup> Empirical prophylaxis against venous thromboembolism in ambulatory patients who have cancer remains controversial. The largest studies of prophylaxis against venous thromboembolism, the Prophylaxis of Thromboembolism during Chemotherapy (PROTECHT) trial<sup>14</sup> and the SAVE-ONCO study,<sup>15</sup> showed decreased rates of events among patients who were receiving chemotherapy for cancer. Smaller studies involving selected patients at higher risk for venous thromboembolism, such as those with pancreatic cancer, have shown a greater magnitude of decrease in venous thromboembolism with the use of prophylaxis.<sup>16,17</sup> However, the effect of prophylaxis on morbidity, mortality, and cost has not been rigorously studied.

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N Engl J Med 2014;370:2515-9.

DOI: 10.1056/NEJMr1401468

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**RISKS AND RATES OF VENOUS THROMBOEMBOLISM**

The risk of venous thromboembolism varies among patients who have cancer, and it depends on a number of factors, including the type of cancer, treatments, and the presence or absence of coexisting disease. Data from a prospective observational study involving approximately 2700 patients with cancer were used by Khorana and colleagues<sup>18</sup> to derive a risk-scoring model (Table 1). Scores range from 0 to 7, with higher scores indicating a higher risk of venous thromboembolism. According to this model, the incidence of venous thromboembolism was 0.3% among low-risk patients (0 points), 2.0% among intermediate-risk patients (1 or 2 points), and 6.7% among high-risk patients ( $\geq 3$  points) over a median of 2.5 months. The ability of the model to identify patients with cancer who had a low or high risk of venous thromboembolism was subsequently confirmed in the validation study by Khorana et al., as well as in studies by others.<sup>19</sup>

In the PROTECHT and SAVE-ONCO clinical trials, patients with cancer were randomly assigned to venous thromboprophylaxis or placebo, but they were not separated prospectively according to risk of venous thromboembolism. In these clinical trials, the overall rates of venous thromboembolism among patients who were receiving placebo were low, ranging from roughly 3 to 4%. The PROTECHT study randomly as-

signed 1150 ambulatory patients with cancer to receive prophylactic nadroparin or placebo. The nadroparin group, as compared with the placebo group, had a 50% reduction in composite venous and arterial events (2.0% vs. 3.9%,  $P=0.02$ ).<sup>14</sup> The SAVE-ONCO trial randomly assigned 3212 ambulatory patients receiving chemotherapy for locally advanced solid tumors or metastatic cancer to receive a prophylactic dose of semuloparin or placebo.<sup>15</sup> The overall incidence of venous thromboembolism was 1.2% in the semuloparin group, as compared with 3.4% in the placebo group (hazard ratio, 0.36; 95% confidence interval, 0.21 to 0.60;  $P<0.001$ ).

A recent real-world retrospective analysis involving 27,479 patients in a health care claims database suggests that the actual rate of venous thromboembolisms may be higher than that reported in clinical trials.<sup>20</sup> This analysis was similar to the PROTECHT and SAVE-ONCO studies in that it assessed the rate of venous thromboembolism at 3.5 months after the initiation of chemotherapy, but it also reassessed the rate at 12 months. The rate of reported venous thromboembolism at 3.5 months after the initiation of chemotherapy was 7.3% (range, 4.6 to 11.6), with an increase over time to a cumulative rate of 13.5% (range, 9.8 to 21.3) at 12 months. Suggested reasons for the increased rates in this study, as compared with those in clinical trials, included possible selection of lower-risk patients in clinical trials and the detection of asymptomatic venous thromboembolism because of a longer time period for analysis in this retrospective study. In another retrospective study, however, 75% of patients with cancer who received a diagnosis of asymptomatic pulmonary embolism actually had chest symptoms that had previously been attributed to the cancer or its treatment.<sup>8</sup> A study comparing rates of recurrent venous thromboembolism, bleeding, and death between patients with cancer who received anticoagulation therapy for incidentally detected pulmonary embolism and those who received anticoagulation therapy for symptomatic pulmonary embolism showed no significant difference in outcome between the two groups.<sup>21</sup> Both studies confirm that patients with incidentally detected pulmonary embolism benefit from anticoagulation therapy as much as do patients with symptomatic pulmonary embolism.

Although prophylactic anticoagulation ther-

**Table 1. Risk-Assessment Model for Venous Thromboembolism, According to the Khorana Score.\***

| Variable  | Points | Odds Ratio (95% CI) |
|---|--------|---------------------|
| Type of cancer                                      |        |                     |
| Stomach or pancreatic                               | 2      | 4.3 (1.2–15.6)      |
| Lung, lymphoma, gynecologic, bladder, or testicular | 1      | 1.5 (0.9–2.7)       |
| Platelet count $\geq 350,000/\text{mm}^3$           | 1      | 1.8 (1.1–3.2)       |
| Hemoglobin $<10 \text{ g/dl}$                       | 1      | 2.4 (1.4–4.2)       |
| White-cell count $>11,000/\text{mm}^3$              | 1      | 2.2 (1.2–4.0)       |
| BMI $\geq 35$                                       | 1      | 2.5 (1.3–4.7)       |

\* Data are from Khorana et al.<sup>18</sup> The aggregate score is calculated by adding the individual component points. Complete blood counts before treatment should be used. An aggregate score of 0 indicates low risk, an aggregate score of 1 or 2 indicates intermediate risk, and an aggregate score of 3 or more indicates high risk. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Odds ratios are based on data from the derivation cohort. CI denotes confidence interval.

apy in ambulatory patients with cancer has been associated with a significant reduction in the relative risk of venous thromboembolism, the difference in absolute risk is small, and no survival benefit has yet been shown. The risk of bleeding associated with anticoagulation is higher among patients with cancer than among persons in the general population. The rates of minor bleeding in the PROTECHT and SAVE-ONCO trials were similar among the patients receiving prophylactic anticoagulant therapy and those receiving placebo. The PROTECHT study was not powered to detect differences in major bleeding. In the SAVE-ONCO study, no increase in major bleeding was observed in patients receiving prophylactic treatment as compared with placebo.

Additional risk factors for venous thromboembolism in ambulatory patients with cancer include prolonged immobilization and the use of hormone therapy and angiogenesis inhibitors. Other known risk factors that should be considered in the decision regarding the use of thromboprophylaxis include a history of deep-vein thrombosis, vascular compression due to tumor or adenopathy, and known inherited thrombophilia. For example, in my clinic, prophylactic anticoagulation therapy is used in patients with cancer who have a history of deep-vein thrombosis and require treatment with tamoxifen, as well as in those who have a strong family history of venous thromboembolism and a known factor V Leiden mutation. Prophylaxis against venous thromboembolism should be considered in patients with metastatic disease, a history of life-threatening pulmonary embolism or extensive lower-extremity deep-vein thrombosis, or clinically significant tumor-mediated compression of large veins such as the inferior vena cava, the hepatic and portal veins, and the subclavian, iliac, and other similar veins. The high risk of venous thromboembolism is similar among patients with hematologic cancer and those with pancreatic cancer; however, the risk of bleeding may be higher among patients with hematologic cancer because of marrow involvement and the use of myelosuppressive chemotherapy. These patients have generally been excluded from clinical trials of prophylaxis against venous thromboembolism in patients with cancer, but they would benefit from an individual assessment of the risk of venous thromboembolism and a discussion of the risks and benefits of prophylaxis. Recommenda-

tions regarding the use of prophylaxis against venous thromboembolism are described in Table 2. Additional information is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Anxiety about the risk of bleeding among patients with cancer is justified, but bleeding associated with anticoagulation therapy at prophylactic doses should be less than that associated with full-intensity anticoagulation therapy needed to treat acute venous thromboembolism. Ambulatory patients with cancer who are receiving chemotherapy and prophylaxis against venous thromboembolism can be closely monitored, and anticoagulation therapy can be withheld if there are changes in renal function or the platelet count that suggest an increased risk of bleeding. All guidelines suggest withholding any dose of anticoagulation drug if the platelet count is less than 50,000 per cubic millimeter; however, for very high-risk patients, the continued use of prophylactic anticoagulation therapy can be considered if the platelet count is more than 30,000 per cubic millimeter. Creative dosing strategies such as every-other-day dosing can be considered in patients with an increased risk of venous thromboembolism, such as patients with a prior life-threatening pulmonary embolism who require lenalidomide treatment for myeloma and in whom new thrombocytopenia or recent major bleeding has developed.

#### GUIDELINES

Current guidelines from the American College of Chest Physicians (ACCP),<sup>11</sup> the American Society of Clinical Oncology (ASCO),<sup>12</sup> and the National Comprehensive Cancer Network (NCCN)<sup>13</sup> have subtle differences, but all advise against the use of routine prophylaxis against venous thromboembolism in most ambulatory patients with cancer. An exception is made for patients with multiple myeloma who require treatment with thalidomide or lenalidomide with chemotherapy or dexamethasone; among these patients, rates of venous thromboembolism of 23 to 75% have been reported.<sup>22</sup> Either enoxaparin (at a dose of 40 mg subcutaneously daily or the equivalent) or warfarin is recommended, although recommended target international normalized ratios differ (ASCO guidelines recommend 1.5 and NCCN and ACCP guidelines recommend 2.0 to 3.0). For

**Table 2. Comparison of Recommendations Regarding Prophylaxis against Venous Thromboembolism.\***

| Potential Indication  | Recommended Use of Prophylaxis |         |          |          |
|---|--------------------------------|---------|----------|----------|
|   | Author                         | ACCP    | ASCO     | NCCN     |
| Treatment of multiple myeloma with thalidomide or lenalidomide with high-dose dexamethasone, doxorubicin, combination chemotherapy, or other risk factors | Yes†                           | Suggest | Yes      | Yes      |
| Cancer associated with high risk of venous thromboembolism (pancreatic or gastric)  |                                |         |          |          |
| With other risk factors   | Yes†                           | Suggest | Consider | Consider |
| Without other risk factors  | Consider‡                      | No      | Consider | Consider |
| Cancer associated with intermediate risk of venous thromboembolism (lung, ovarian, primary central nervous system, bladder, lymphoma)                     |                                |         |          |          |
| With other risk factors   | Consider‡                      | Suggest | Consider | No       |
| Without other risk factors  | No‡                            | No      | Consider | No       |
| Cancer associated with low risk of venous thromboembolism   |                                |         |          |          |
| With other risk factors   | Consider‡                      | Suggest | Consider | No       |
| Without other risk factors  | No                             | No      | Consider | No       |

\* Consensus guidelines of professional societies are not always explicit. Variations in the strength of recommendations exist because data are limited and often recommendations are extrapolated from other patient populations. All societies agree that high-risk patients with multiple myeloma should receive prophylaxis, although the wording of the American College of Chest Physicians (ACCP) is “suggest,” or a weak recommendation based on limited data. For other patient groups, “yes” indicates a definitive recommendation; “suggest,” a weak recommendation; and “consider,” a possible benefit but with no supporting data and therefore uncertainty regarding benefit. The ACCP<sup>11</sup> suggests the use of prophylaxis in patients with solid tumors, a low bleeding risk, and additional risk factors for venous thromboembolism. According to other societies and clinicians, additional risk factors for venous thromboembolism include previous venous thromboembolism, inherited thrombophilia, the use of hormonal therapy, the presence of metastatic disease, vascular compromise by tumor or lymphadenopathy, and a high Khorana risk score. The American Society of Clinical Oncology (ASCO) suggests that the use of prophylaxis should be considered on a case-by-case basis in highly selected outpatients who have solid tumors and are receiving chemotherapy, and the uncertainty of risks and benefits should be discussed. The National Comprehensive Cancer Network (NCCN) advises that prophylaxis against venous thromboembolism should not be used outside the setting of a clinical trial, although it can be considered for patients with a Khorana score of 3 or higher.

† Bleeding risk must be assessed and considered. High-risk factors for bleeding include a recent episode of major active bleeding or bleeding at a critical site, a platelet count of less than 50,000 per cubic millimeter, and the presence of untreated central nervous system metastases.

‡ The risk for the individual patient should be assessed, and the risk–benefit ratio should be discussed with that patient.

patients with an increased risk of venous thromboembolism, such as those with a Khorana score of 3 or higher or patients with pancreatic, lung, or stomach cancer, the ASCO and NCCN guidelines recommend conversations with the individual patient about the risks and benefits of prophylactic anticoagulation, and the ACCP guidelines recommend the use of prophylactic low-molecular-weight heparin or unfractionated heparin.

## CONCLUSIONS

Venous thromboembolism results in increased morbidity, mortality, and complexity of care in

all patient populations, but in patients with cancer, this complication may also lead to delays in surgery and the administration of chemotherapy as well as an increased risk of bleeding associated with full-intensity anticoagulation. The increased use of prophylaxis against venous thromboembolism in high-risk ambulatory patients with cancer who are eligible for this therapy could lead to improved outcomes. Further studies are needed to assess the effects of this prophylaxis on morbidity, mortality, and the costs of care for patients with cancer.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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