Cancer and venous thromboembolism: an overview

PAOLO PRANDONI, ANDREA PICCIOLI, ANTONIO GIROLAMI

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ABSTRACT

Background and Objective. Although the relationship between malignant diseases and venous thromboembolism has been convincingly demonstrated, the clinical implications of this association still have to be thoroughly elucidated. The aim of this study was to review briefly the mechanisms by which cancer may induce the development of thrombosis and to analyze critically the most recent clinical advances in this field.

Evidence and Information Sources. The material examined in the present review includes articles published in journals covered by the Science Citation Index® and Medline®.

State of the Art. Neoplastic cells can activate the clotting system directly, thereby generating thrombin, or indirectly, by stimulating mononuclear cells to synthesize and express various procoagulants. Cancer cells and chemotherapeutic agents can injure endothelial cells, thereby intensifying hypercoagulability. Currently, primary prevention of venous thrombosis should be considered for cancer patients during and immediately after chemotherapy, when long-term indwelling central venous catheters are placed, during prolonged immobilization from any cause, and following surgical interventions. Secondary prevention of recurrent venous thromboses usually necessitates long-term anticoagulation. In some patients with cancer the condition is resistant to warfarin, and long-term adjusted high-dose heparin is required. The diagnosis of venous thromboembolism may help to uncover previously occult carcinoma by prompting a complete physical examination and a few routine tests.

Perspectives. Further investigations are required to evaluate the cost-benefit ratio of extensive diagnostic screening for occult malignancy in all patients presenting with idiopathic venous thromboembolism, and to explore the potential of low molecular weight heparins for improving survival in patients with cancer.

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Key words: thrombosis, venous thromboembolism, cancer, anticoagulation, heparin, low molecular weight heparin, warfarin, chemotherapy

Since the initial observation by Armand Trousseau in 1865, numerous studies have addressed the relationship between cancer and thrombosis. Post-mortem studies have demonstrated a markedly increased incidence of thromboembolic disease in patients who died of cancer, particularly those with mucinous carcinomas of the pancreas, lung, and gastrointestinal tract.1,2 Cohort studies of surgical patients showed that the incidence of deep venous thrombosis (DVT) was markedly higher in patients with malignant disorders than in patients with other, non-malignant diseases.3-6 An increased risk of venous thromboembolism (VTE) is suggested by the high incidence of pulmonary embolism7 and subclinical activation of the coagulation system in non-surgical patients with cancer.8-11 The relationship between cancer and thrombosis is further supported by the greater risk of patients with idiopathic VTE developing overt malignancy than patients whose thrombotic episode is associated with a well recognized risk factor.12

This article reviews the relation between cancer and VTE and highlights some relevant clinical implications.

Pathogenesis

Pathogenetic mechanisms accounting for the development of thrombotic disorders in patients affected by cancer were described by Virchow more than a century ago. They include hypercoagulability, due to tumor cell activation of clotting, vessel wall injury, and stasis.

Hypercoagulability

Neoplastic cells can activate the clotting system directly, thereby generating thrombin, or indirectly by stimulating mononuclear cells to produce and express procoagulants. Several different procoagulant activities have been identified from tumor cell lines, extracts or sonicates of human and animal tumors. The best characterized tumor cell procoagulants are tissue factor, an integral membrane glycoprotein which can activate the extrinsic pathway through interaction with factor VIII, and factor X activators.13,14 Tissue factor procoagulant activity has been identified in some acute leukemias15 and in solid tumors of the ovary, stomach, and kidney.16 Direct factor X activation with the...
procoagulant cysteine proteinase has been found in some patients with lung, prostate, colon, breast, and kidney cancer and with leukemia. \textsuperscript{17, 18} Mucin-secreting adenocarcinomas are frequently associated with thrombosis because the sialic acid moiety can cause non-enzymatic activation of factor X to its active form, factor Xa. \textsuperscript{19} Consequently, adenocarcinomas of the lung, pancreas, gastrointestinal tract, and ovary are often associated with venous thrombosis. \textsuperscript{20}

Tumor cells can activate systemic coagulation by stimulating mononuclear cells to synthesize and express various procoagulant substances, including tissue factor and factor X activators. Normal monocytes and macrophages can be activated by tumor tissue factor and factor X activators. Normal monocytes and macrophages can be activated by tumor cells in the presence of lymphocytes. \textsuperscript{21} In patients with cancer, endothelial cells may be activated by cytokines such as tumor necrosis factor and interleukin-1 or interleukin-like substances that may induce tissue factor production. \textsuperscript{22} A peptide produced by a human bladder cancer cell line stimulates tissue factor expression in endothelial cells. \textsuperscript{23}

Clinical manifestations of increased thrombin generation may be accentuated by down-regulation of endothelial cell counterregulatory mechanisms, such as decreased hepatic synthesis of antithrombin and protein C. \textsuperscript{8, 10, 24, 25} In addition, normal endothelial cell function may be disrupted by various defects in platelet function. \textsuperscript{8, 10, 24, 25}

The enhanced clotting activation in patients with cancer is confirmed by the demonstration of increased levels of systemic hypercoagulability markers, such as fibrinopeptide A, prothrombin fragment F1+2 and thrombin-antithrombin complexes in most patients. \textsuperscript{26, 27}

As expected, the risk of (recurrent) venous thromboembolism is higher in those cancer patients who are also carriers of thrombophilia, such as the factor V Leiden mutation. \textsuperscript{28}

**Vessel wall damage**

There is increasing awareness that cancer cells can injure endothelium by direct vascular invasion, resulting in the onset of a prothrombotic state. \textsuperscript{24, 25} The adhesion of tumor cells to endothelium was evaluated in vivo by Naschitz and associates, who observed a complex interaction between endothelium, platelets, and tumor cells. \textsuperscript{29} Direct vessel wall injury, in association with rheologic abnormalities and catheter-associated thrombin formation, is most likely the explanation for the occurrence of the upper extremity DVT arising as a complication of central venous lines. \textsuperscript{30} Among mechanisms responsible for thrombotic events arising during the use of chemotherapeutic drugs, vascular endothelium damage probably plays a major role besides the reduction in the plasma concentration of natural anticoagulants. \textsuperscript{31, 34}

**Venous stasis**

Venous stasis predisposes to venous thrombosis by preventing activated coagulation factors from being diluted and cleared by normal blood flow. \textsuperscript{3} Moreover, hypoxic damage to endothelial cells due to stasis may produce prothrombotic alterations. Venous stasis develops as a consequence of immobility in severely debilitated cancer patients, in conjunction with cancer surgery, or as a result of venous obstruction due to extrinsic vascular compression in patients with bulky tumor masses. \textsuperscript{35}

**Clinical implications**

**Search for occult malignancies in patients with idiopathic VTE**

A number of studies have examined the relationship between DVT and the subsequent development of cancer.

In four studies, the incidence of newly diagnosed malignancy in patients with suspected VTE was compared with that in patients whom this diagnosis was excluded by normal objective diagnostic tests. \textsuperscript{36-39} In all four studies the risk for new malignancy was higher among the patients with confirmed venous thromboembolism (Table 1).

Other studies compared the development of cancer in patients with apparently idiopathic VTE (no known associated risk factors) versus secondary VTE (Table 2). \textsuperscript{40-50} In all studies but one \textsuperscript{40} the risk of developing subsequent malignancies was significantly higher in patients with idiopathic VTE than in those with secondary VTE. In the studies in which no extensive screening procedures were performed, the incidence of newly diagnosed malignancy was considerably lower than that observed in studies in which extensive investigation for occult malignancy was performed. \textsuperscript{41, 42, 44, 45, 47, 49} On average, the risk of patients with idiopathic VTE developing a new cancer was four to five times higher than that in patients in whom the thrombotic event was associated with well recognized risk factors.

Besides, two recent articles retrospectively calculated the standardized incidence ratio (SIR) for cancer (the ratio of observed numbers of incident cancers to expected numbers) in patients with idiopathic VTE. \textsuperscript{43, 44}

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**Table 1. Incidence (first year) of newly diagnosed malignancy in patients with VTE in comparison to in those without VTE.**

<table>
<thead>
<tr>
<th>Study</th>
<th>First-year incidence of malignancy</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Goer, 1982</td>
<td>10/133 (8.8)</td>
<td>0/128 (0)</td>
</tr>
<tr>
<td>Goldberg, 1987</td>
<td>14/370 (3.7)</td>
<td>16/1073 (1.5)</td>
</tr>
<tr>
<td>Griffin, 1987</td>
<td>4/113 (4.0)</td>
<td>10/517 (2.0)</td>
</tr>
<tr>
<td>Nordstrom, 1984</td>
<td>66/1383 (4.8)</td>
<td>37/2412 (1.5)</td>
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Table 2. Incidence of cancer in the follow-up of patients with idiopathic and secondary VTE.

<table>
<thead>
<tr>
<th></th>
<th>Frequency of cancer</th>
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<tbody>
<tr>
<td></td>
<td>Idiopathic VTE (%)</td>
</tr>
<tr>
<td>Aderka, 1986</td>
<td>12/35 (34.3)</td>
</tr>
<tr>
<td>Monreal, 1988</td>
<td>3/16 (18.7)</td>
</tr>
<tr>
<td>Monreal, 1991</td>
<td>7/31 (22.6)</td>
</tr>
<tr>
<td>Prandoni, 1992</td>
<td>11/145 (7.6)</td>
</tr>
<tr>
<td>Monreal, 1993</td>
<td>6/21 (28.6)</td>
</tr>
<tr>
<td>Bastounis, 1996</td>
<td>21/84 (25)</td>
</tr>
<tr>
<td>Ahmed, 1996</td>
<td>3/113 (2.7)</td>
</tr>
<tr>
<td>Monreal, 1997</td>
<td>13/105 (12.4)</td>
</tr>
<tr>
<td>Hettiarachchi, 1998</td>
<td>10/155 (6.4)</td>
</tr>
<tr>
<td>Achkar, 1997</td>
<td>13/78 (16.7)</td>
</tr>
<tr>
<td>Rajan, 1998</td>
<td>13/152 (8.6)</td>
</tr>
<tr>
<td>All</td>
<td>112/931 (12.0)</td>
</tr>
</tbody>
</table>

Although most studies have indicated a significant association between idiopathic VTE and cancer, the clinical implications of these findings are, as yet, unclear. As suggested by these results, an extensive diagnostic work-up might be justified at the time of referral for the venous thrombosis. Extensive screening with computer tomography scanning, gastrointestinal endoscopy and a number of tumor markers have indeed the potential to detect occult malignancies. However, it remains unclear whether identified malignancies are potentially treatable and whether treatment could favorably influence life expectancy or quality of life. Even if a recent decision analysis of screening for occult cancer in patients with idiopathic VTE revealed potential gains in life expectancy, it should not be forgotten that extensive screening procedures for malignancy are associated with high costs, and themselves carry some morbidity, thus they are only acceptable if life-saving. A clinical trial in which patients with unexplained thrombosis, but asymptomatic for malignant disease are randomized to either extensive screening or standard clinical care without screening, is currently in progress, and has the potential to identify the effect of screening for malignancy on the survival of these patients. In the mean time, clinical decisions must be based on indirect evidence. While waiting for the results of this trial, it is appropriate to maintain a low threshold of suspicion for malignancy when treating patients with unexplained VTE. Decisions to perform additional diagnostic tests can be based on the findings of an initial clinical evaluation, which includes medical history, physical examination, routine laboratory tests and chest X-ray. This approach has received recent support from the retrospective analysis of a wide cohort of patients with idiopathic DVT, conducted in the Boston area.

Primary prophylaxis of VTE

Because VTE is often encountered in patients with cancer, some clinicians have proposed that all patients with cancer should receive pharmacological prophylaxis. However, further trials are needed before this approach can be endorsed.

Currently, primary prevention should be considered for cancer patients in certain circumstances, such as after surgical interventions, during chemotherapy, and in those with indwelling central venous catheters.

Surgical interventions

Patients with cancer are at a markedly high risk of developing DVT. As shown in Table 3, the overall incidence of postoperative DVT in patients with cancer is about twice as high as that of patients free of malignancy. As recently demonstrated by Huber et al., the incidence of post-operative pulmonary embolism is remarkably higher in patients with cancer than in those without cancer. In order to reduce the risk of venous thrombosis, a Consensus Statement has recently recommended the use of low-dose, low molecular weight heparin (LMWH) or physical measures in patients with cancer when confined to bed for any reason, and when undergoing low-risk surgical procedures. Extensive abdominal or pelvic surgery places patients with cancer at a markedly high risk of developing post-operative DVT and pulmonary embolism. These patients, therefore, require prophylactic measures comparable to those usually recommended for major orthopedic surgery. These measures include adjusted-dose heparin, higher doses of heparin fractions (on average twice as high as those suggested for general surgery), or oral anticoagulants.
As compared to the standard heparin regimen that is used in the prevention of thromboembolism in patients with cancer who undergo surgery, no selective advantage has yet been shown with LMWHs. In a recent double-blind multicenter trial addressing the value of enoxaparin for prevention of DVT in elective cancer surgery, 1,115 patients were randomized to receive either enoxaparin, 40 mg once daily beginning 2 h before surgery, or unfractionated low-dose heparin, 5,000 U three times daily. Primary outcome was VTE as detected by mandatory bilateral venography or pulmonary scintigraphy. Venograms were inadequate in about 40% of patients. Of 631 evaluable patients, a total of 104 (16.5%) developed thromboembolic complications. The frequency was 18.2% in the heparin group and 14.7% in the enoxaparin group. There were no differences in bleeding events or other complications, nor were there differences in mortality at either 30 days or 3 months. Another study compared two doses of a LMWH (dalteparin, 5000 or 2500 units once daily) for thromboprophylaxis in 2070 patients undergoing elective general surgery for abdominal diseases, 63% of whom had malignant disease. The higher dosage schedule reduced the incidence of DVT from 12.6 to 6.7% at the expense of more hemorrhagic complications (4.7 versus 2.7%). This higher rate of bleeding was not seen among patients undergoing operations for cancer.

In this context glycosaminoglycans show promise. Danaparoid (a mixture of dermatan and heparan sulphate) has recently been shown to be as effective and safe as standard heparin for prevention of DVT after elective surgery for malignant disease. Finally, in a recent Italian multicenter trial addressing the value of dermatan sulphate for prevention of DVT in elective cancer surgery, 842 patients were randomized to receive either dermatan sulphate, 300 mg once daily, starting on the second day before surgery, or unfractionated low-dose heparin, 5000 U three times daily. Primary outcome was DVT, as assessed by bilateral contrast venography at the end of treatment. Adequate venography was obtained in 521 patients.

As shown in Table 4, patients with breast cancer are at a particularly high risk of developing both venous and arterial thromboses when they receive chemotherapeutic drugs. Moreover, a recent trial randomized a large series of women with breast cancer to receive either tamoxifen alone or in association with a 6-month course of chemotherapy. During the study period, thromboembolic events were observed among women allocated to receive the chemotherapy much more frequently than in women allocated to tamoxifen alone. The thrombotic risk of cancer patients receiving chemotherapy is probably increased by the use of hematopoietic colony-stimulating factors. Thromboembolism related to chemotherapy represents, therefore, a relatively common and serious complication of chemotherapy in cancer patients. This risk should be considered when assessing an adjuvant chemotherapy program.

Recently, a prospective double-blind randomized study showed that during chemotherapy very low-dose warfarin (1 mg/day) for six weeks, followed by doses that maintained the International Normalized Ratio (INR) at 1.3 to 1.9, was an effective and safe method for prevention of thromboembolism in patients with metastatic breast cancer. Based on data from this trial, a cost-effectiveness analysis was concluded, showing that warfarin at low doses can be given to women with metastatic breast cancer receiving chemotherapy with no increase in health care costs. Whether this strategy may also be utilized in patients with other oncologic patterns remains to be demonstrated.
In a recent prospective cohort study assessing embolism after discontinuation of warfarin therapy, cancer remains at a high risk of developing thrombosis during the course of proper anticoagulant therapy. The risk of extension and/or recurrence of venous thrombosis? The main controversies concern when facing cancer patients with an episode of DVT, the risk ratio of developing early and late symptomatic VTE recurrences in cancer patients was 1.74. This means that, after suffering an episode of DVT, cancer patients have a risk of recurrences which is almost twice as high as that observed in patients free from malignancies. In view of the persistently high risk for recurrent thrombotic events and the acceptable risk of bleeding, prolongation of warfarin should be considered for as long as the cancer is active. The suggested policy is to administer warfarin to maintain the INR between 2.0 and 3.0.

Recurrence of venous thromboembolism during oral anticoagulation

The literature contains many reports of persistent or recurrent thrombosis in cancer patients despite administration of therapeutic doses of oral anticoagulants. However, the exact frequency of these failures is unknown.

Recently, we reported the data from the long-term follow-up of 823 consecutive patients with DVT. All patients received oral anticoagulation for at least three months. Overall the frequency of thromboembolic recurrences during the first three months of anticoagulation was significantly higher in patients with cancer (Table 5). These findings have been confirmed by a multicenter trial addressing the value of LMWH for the initial treatment of acute VTE. More than 1000 patients with VTE were randomized to receive either fixed-doses LMWH or adjusted-dose unfractionated heparin. Irrespective of the study treatment, among the 232 patients with cancer at baseline, 20 (8.6%) had symptomatic recurrent VTE during the 3-month follow-up, as compared to only 32 (4.1%) of the remaining 789 patients (p<0.001). Proper studies are required to identify more effective therapeutic approaches in cancer patients suffering an episode of VTE.

The anticoagulation strategy in the treatment of patients with recurrent venous thromboembolism during oral anticoagulation is not rigidly standardized. Our policy is to administer a new course of full-dose unfractionated or low molecular weight heparin, followed by a higher dose of warfarin (such as to keep the INR between 3.0 and 4.5). We recommend the use of subcutaneous heparin in adjusted doses for patients who are resistant even to high doses of warfarin. In patients with a very poor prognosis, it seems reasonable to replace warfarin with heparin, without waiting for the eventual failure of higher doses of warfarin. If heparin therapy fails, the only option remains the insertion of a vena cava filter.

Table 5. Venous thromboembolism and bleeding complications during 3 months of oral anticoagulation. A prospective cohort study in 823 consecutive patients with DVT treated with heparin followed by warfarin (experience of the Padua center between 1985 and 1997).

<table>
<thead>
<tr>
<th></th>
<th>Cancer (n=189)</th>
<th>No cancer (n=634)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrence</td>
<td>27 (14.3%)</td>
<td>24 (3.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total bleeding</td>
<td>22 (12.6%)</td>
<td>47 (7.4%)</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>9 (4.8%)</td>
<td>18 (2.8%)</td>
<td>&gt; 0.2</td>
</tr>
</tbody>
</table>
Hemorrhagic risk related to anticoagulation

It is generally agreed that cancer patients are at high risk of hemorrhagic complications while receiving oral anticoagulant drugs. However, in our cohort of patients with DVT the risk of bleeding during oral anticoagulation was not different in patients with cancer than in those without cancer (Table 5). This finding is supported by a recent study. Bona et al. prospectively followed a large number of patients with and without cancer who required long-term anticoagulation. They did not find appreciable differences between the two groups in terms of hemorrhagic complications. The practical implication of these studies is that, at least in the absence of contraindications, there is no need to reduce the intensity of anticoagulation in cancer patients, as is often done in many centers, because of the fear of hemorrhagic complications. It is important to stress that a hemorrhagic complication of the gastrointestinal or genitourinary tract in a patient on oral anticoagulants within the range can be considered a hint in the direction of a hidden cancer.

Reduction of mortality

Anticoagulant treatment of cancer patients, particularly those with lung cancer, has been reported to improve survival. These interesting, although preliminary, results of controlled trials lent some support to the argument that activation of blood coagulation plays a role in the natural history of tumor growth.

Numerous studies have been performed in recent years that have addressed the value of LMWH in comparison to standard heparin in the treatment of venous thromboembolism, and an updated meta-analysis of the most adequate reports was published in 1997. In eight of the nine studies reporting on the long-term follow-up (three to six months) of enrolled patients, the analysis of total mortality exhibited a surprising trend in favor of LMWH (pooled relative risk, 0.74; 95% CI, 0.57-0.97). In the five studies that provided subgroup analyses, this effect was entirely attributable to the differences in the subgroup of patients with cancer (Table 6). This difference cannot be solely attributed to thrombotic or bleeding events. Since large numbers of cancer patients were included in the studies, it seems unlikely that those with more advanced tumors were present in the standard heparin group. While it is also possible that standard heparin increases cancer mortality, such an adverse effect has not been reported previously. These considerations suggest that LMWH might exert an inhibitory effect on tumor growth that is not apparent with standard heparin.

The evidence of lowered cancer mortality in patients on LMWH has stimulated renewed interest in these agents as antineoplastic drugs. A few multicenter studies aimed at investigating this fascinating hypothesis are now being carried out.

Conclusions

Patients with otherwise unexplained VTE have a relatively high risk of subsequent malignant disease. Although extensive screening at the time of a patient’s referral has the potential to detect occult malignancies, the cost-to-benefit ratio of an extensive diagnostic work-up still has to be demonstrated definitively.

During prolonged immobilization for any reason, and following surgical interventions, patients with cancer are at a remarkably higher risk of VTE than patients free from malignant disorders. Unfractionated heparin in adjusted doses or LMWH in doses commonly recommended for high risk surgical patients is the prophylactic treatment of choice for cancer patients undergoing an extensive abdominal or pelvic intervention. Furthermore, the risk of thrombotic episodes is increased in cancer patients by chemotherapy and by the use of indwelling central venous catheters. Recent data suggest a positive benefit-to-risk ratio of the systematic use of fixed mini-doses of warfarin or low doses of a LMWH.

After experiencing an episode of thrombosis, cancer patients remain at risk of recurrence for as long as the cancer is active. They should, therefore, be protected by a long-term course of oral anticoagulation. The risk of recurrent thrombotic events despite adequate anticoagulation is higher in patients with advanced cancer. Subcutaneous heparin therapy should be reserved for patients in whom warfarin has been ineffective.

Finally, in cancer patients affected by DVT, treatment with LMWHs has been reported to be associated with a lower mortality than treatment with unfractionated heparin therapy. This observation suggests that these agents might have an antineoplastic activity.

Contributions and Acknowledgments

PP planned the review and was responsible for writing the paper. AP critically read all potentially helpful articles and identified those suitable for reviewing. AG critically revised the manuscript for important intellectual content. All authors read the manuscript and approved its final version.


<table>
<thead>
<tr>
<th>Series</th>
<th>UFH no. (%)</th>
<th>LMWH no. (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandoni, 1992[98]</td>
<td>8/18 (44.4)</td>
<td>1/15 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Hull, 1992[99]</td>
<td>13/49 (26.5)</td>
<td>6/47 (12.8)</td>
<td></td>
</tr>
<tr>
<td>Koopman, 1996[101]</td>
<td>7/36 (19.4)</td>
<td>9/34 (26.4)</td>
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</tr>
<tr>
<td>Levine, 1996[101]</td>
<td>13/57 (22.8)</td>
<td>8/46 (17.4)</td>
<td></td>
</tr>
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<td>Columbus, 1997[101]</td>
<td>27/113 (23.9)</td>
<td>20/119 (16.8)</td>
<td></td>
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<tr>
<td>All</td>
<td>68/273 (24.9)</td>
<td>44/261 (16.8%)</td>
<td>0.03</td>
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UFH = unfractionated heparin; LMWH = low-molecular-weight heparin.
Disclosures
Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

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