Venous thromboembolism is performed, on average, 3 million times each year. Traditionally, elective knee arthroscopy has been considered an unlikely cause of thromboembolic events. Therefore, it is largely performed without thromboprophylaxis. Without thromboprophylaxis, the incidence of venous thromboembolism after knee arthroscopy varies widely, from 0.6% to 18%, depending on the diagnostic method used. In contrast, the incidence of venous thromboembolism in total knee arthroplasty is approximately 25%, and the incidence in total hip arthroplasty is approximately 27%. In a recent study, among 12,595 patients, 0.34% had symptomatic venous thromboembolism in the setting of knee arthroscopy and arthroscopy-assisted surgery without thromboprophylaxis. Despite the rare incidence of postarthroscopy venous thromboembolism, certain factors increase the risk, including personal or family history of venous thromboembolism.

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lism, history of malignancy, long-term use of anticoagulants, use of estrogen-progestin oral contraceptives or hormone replacement therapy, and history of vascular disease. Although thromboprophylaxis would be recommended in these higher-risk patients, despite the presence of known risk factors, most patients are not given postarthroscopy thromboprophylaxis. However, rivaroxaban is effective for postoperative oral thromboprophylaxis. Given the apparently low rate of postoperative venous thromboembolism, there are limited guidelines for prophylaxis after routine elective knee arthroscopy.

In the current study, 10 subjects (8 men, 2 women) who had venous thromboembolism within 6 months of arthroscopy were screened for familial and acquired thrombophilia. The study focused on the important role of previously undiagnosed familial thrombophilia in postarthroscopic venous thromboembolism. The findings suggest that screening for thrombophilia before arthroscopy can identify otherwise healthy high-risk patients who should receive postarthroplasty thromboprophylaxis, comparable to patients undergoing total hip or knee arthroplasty.

MATERIALS AND METHODS

Patients

The study was conducted according to a protocol approved by the institutional review board, and signed informed consent was obtained.

During a 10-year period (2005-2015), the authors assessed 10 otherwise healthy patients (8 men, 2 women) who were referred to their thrombosis center after documentation of symptomatic deep venous thrombosis (DVT) after elective routine knee arthroscopy. Patients were included if they did not have venous thromboembolism or a known thrombophilic disorder before surgery and if the subsequent venous thromboembolism occurred within 6 months after knee arthroscopy. All patients received conventional anticoagulation after venous thromboembolism.

After referral, polymerase chain reaction analysis was performed for major gene mutations associated with thrombosis, including factor V Leiden, G20210A prothrombin, plasminogen activator inhibitor 4G4G, and methylenetetrahydrofolate reductase. The authors performed serologic tests of thrombophilia (high levels of factors VIII and XI, homocysteine, antiphospholipid immunoglobulin G and immunoglobulin M antibodies, and lupus anticoagulant; low levels of antigenic protein C, S, and free S; and antithrombin III deficiency). Polymerase chain reaction and serologic tests were performed by Esoterix-LabCorp (Austin, Texas) with standard published analytic methods in blood obtained first thing in the morning after overnight fasting. Blood was obtained with the patient in the seated state.

Separately, the authors assessed 21 patients (15 men, 6 women) who were referred to their center (2004-2015) after symptomatic DVT occurred within 6 months of total hip or knee arthroplasty. Comparable to the group with postarthroscopy DVT, patients with venous thromboembolism after total hip or knee arthroplasty were included if they had no known thrombophilic disorder or venous thromboembolism events before surgery.

To provide a healthy control group, the authors systematically measured thrombophilia and hypofibrinolysis in 110 healthy normal subjects (48 men, 62 women) who had no history of venous thromboembolism.

Results

As seen in the Table, the 10 patients with venous thromboembolism after arthroscopy differed from the 110 control subjects in factor V Leiden heterozygosity, high homocysteine level, and high factor VIII level. When this group was compared with the 21 patients with venous thromboembolism after total hip or knee arthroplasty, findings for coagulation disorders in the 2 groups were very similar. The exception was heterozygosity for the factor V Leiden mutation, which was more common in the arthroscopy group than in patients who had undergone total hip or knee arthroplasty (40% vs 0%, P<.001) (Table). None of the 10 patients who had venous thromboembolism after arthroscopy met the current clinical-historical criteria for increased risk. Normally, thromboprophylaxis should be considered in patients who meet one of the following criteria: (1) history of malignancy, long-term use of anticoagulants, use of estrogen-progestin oral contraceptives or hormone replacement therapy, or history of vascular disease; or (2) two or more of the classic DVT risk factors described in the literature. The 21 patients undergoing total hip or knee arthroplasty differed from the
### Table

**Coagulation Disorders in Patients With Venous Thromboembolism After Knee Arthroscopy or Total Knee or Hip Arthroplasty and Healthy Normal Control Subjects**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Factor V</th>
<th>PTG</th>
<th>MTHFR</th>
<th>PAIG</th>
<th>Homocysteine</th>
<th>ACLA IgG</th>
<th>ACLA IgM</th>
<th>Lupus Anti-coagulant</th>
<th>Factor VIII</th>
<th>Factor XI</th>
<th>Protein C</th>
<th>Protein S</th>
<th>Free S</th>
<th>Anti-thrombin III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal range</td>
<td>TC, TT</td>
<td>TC, TT</td>
<td>TT</td>
<td>4G4G</td>
<td>Dated&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dated&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Positive</td>
<td>&gt;150%</td>
<td>&gt;150%</td>
<td>&lt;73%</td>
<td>&lt;63%</td>
<td>&lt;66%</td>
<td>&lt;80%</td>
<td></td>
</tr>
<tr>
<td>10 patients with venous thromboembolism after arthroscopy</td>
<td>4/10</td>
<td>0/8</td>
<td>3/10</td>
<td>3/10</td>
<td>3/10</td>
<td>0/10</td>
<td>1/10</td>
<td>0/10</td>
<td>5/10</td>
<td>1/10</td>
<td>2/8</td>
<td>0/8</td>
<td>1/6</td>
<td>1/8</td>
</tr>
<tr>
<td>21 patients with venous thromboembolism after total hip arthroplasty - total knee arthroplasty vs 10 patients with venous thromboembolism after arthroscopy</td>
<td>0/21</td>
<td>0/21</td>
<td>0/21</td>
<td>0/21</td>
<td>0/21</td>
<td>0/21</td>
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<tr>
<td>21 patients with venous thromboembolism vs 110 normal control subjects</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>i</td>
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</tbody>
</table>

**Abbreviations:** ACLA IgG, anticardiolipin antibody immunoglobulin G; ACLA IgM, anticardiolipin antibody immunoglobulin M; MTHFR, methylenetetrahydrofolate reductase; PAIG, plasminogen activator inhibitor 1 gene; PTG, prothrombin; TC, heterozygote; TT, homozygote normal.

<sup>a</sup>Dated cut point for homocysteine: high≥13.5 µmol/L (before 3/20/2005); ≥12 µmol/L (3/21/05-3/27/06); ≥10.4 µmol/L (3/28/06-4/14/08); ≥11.4 µmol/L (4/15/08-11/14/08); ≥15 µmol/L (11/15/08-12/21/14); ≥10.4 µmol/L (after 12/21/14).

<sup>b</sup>Dated cut point for immunoglobulin G: high≥23 GPL (before 10/31/12); ≥15 GPL (after 11/1/12).

<sup>c</sup>Dated cut point for immunoglobulin M: high≥13 MPL (before 4/30/12); ≥13 MPL (after 5/1/12).

<sup>d</sup>P<.05 for 10 patients with venous thromboembolism vs 110 normal control subjects by Fisher’s exact test.

<sup>e</sup>P<.01 for 10 patients with venous thromboembolism vs 110 normal control subjects by Fisher’s exact test.

<sup>f</sup>P<.001 for 10 patients with venous thromboembolism vs 21 patients with venous thromboembolism by Fisher’s exact test.

<sup>g</sup>P<.01 for 10 patients with venous thromboembolism vs 21 patients with venous thromboembolism by Fisher’s exact test.

<sup>h</sup>P<.05 for 21 patients with venous thromboembolism vs 110 normal control subjects by Fisher’s exact test.

<sup>i</sup>P<.001 for 21 patients with venous thromboembolism vs 110 normal control subjects by Fisher’s exact test.
feature article

(40% vs 0%, P<.01). Those who had total hip or knee arthroplasty were more likely than control subjects to have plasminogen activator inhibitor 4G4G homozygosity, high levels of antiphospholipid antibody immunoglobulin M, high levels of factors VIII and XI, and low levels of free protein S. Many patients receive anticoagulation for up to 35 days after total hip or knee arthroplasty,17-19 based on higher rates of venous thromboembolism after total hip or knee arthroplasty.

In the current literature on venous thromboembolism after knee arthroscopy, the reported incidence varies widely, from 0.6% to 18%, depending on the diagnostic method used.2-6 With the use of venography, 1 study reported an incidence of venous thromboembolism after knee arthroscopy of 14.9%, and only 3.7% of cases were symptomatic.1 This is particularly important for patients who have an asymptomatic and therefore unknown DVT that could become symptomatic later. There is no consensus on the appropriate thromboprophylaxis for patients undergoing knee arthroscopy.20 Krych et al9 stated that thromboprophylaxis should be considered in patients undergoing arthroscopy who meet one of the following criteria: (1) history of malignancy, long-term use of anticoagulants, use of estrogen-progestin oral contraceptives or hormone replacement therapy, or history of vascular disease; or (2) two or more of the classic DVT risk factors described in the literature.9,10 Bohensky et al21 identified additional risk factors for venous thromboembolism, including older age (>60 years), presence of comorbidity, marriage, major mechanical issues, and undergoing the procedure in a public hospital.21 As shown in the current study, a history of “classic” risk factors for venous thromboembolism in patients undergoing routine arthroscopy is very insensitive. However, a preoperative diagnosis of thrombophilia should be both specific and sensitive in identifying patients who are at risk for venous thromboembolism after either arthroscopy or total hip or knee arthroplasty.12

Although the rate of venous thromboembolism is low in patients undergoing routine elective knee arthroscopy,2-6 preoperative coagulation tests and risk assessment should be of benefit, with findings comparable to preoperative studies before total hip or knee arthroplasty.12,22 In a population-based cohort study, Bohensky et al23 found 6.4 adverse outcomes among 1000 elective knee arthroscopy procedures. Among 1000 elective knee arthroscopy procedures, they found 3.6 cases of DVT and 1 case of pulmonary embolism. Both DVT and pulmonary embolism, which has a high case fatality rate, incur major medical costs to diagnose and treat (approximately $10,804 and $16,644, respectively).23,25

As noted in the current study, preoperative measurement of risk factors such as factor V Leiden, homocysteine levels, and factor VIII levels, costing health care provider payments of approximately $400, would provide a much more sensitive and specific assessment of the risk of venous thromboembolism after arthroscopy than the current method of obtaining a history of classic risk factors alone. Routine testing for thrombophilia can better guide thromboprophylaxis in patients undergoing knee arthroscopy who are at high risk for DVT and pulmonary embolism and otherwise may be considered to have a low risk21 of thromboembolic events. Although the incidence of venous thromboembolism is low, rivaroxaban and bemiparin thromboprophylaxis for 3 weeks after knee arthroscopy efficiently and safely prevents this complication. The orthopedic surgeon’s choices for thromboprophylaxis for knee arthroplasty include none (which is associated with 6.4 adverse outcomes per 1000 knee arthroplasties),21 treatment of all patients for 3 weeks,20 or, as the authors suggest, treatment of patients who are at high risk as defined by thrombophilia screening.

Before knee arthroscopy, only 1 of the 10 patients in the current study had any of the classic risk factors,9,10,21 and this patient had previous testosterone use.16 Testosterone therapy was only recently implicated in venous thromboembolism in men with no other risk factors.16,27-29

Despite being diagnosed with a familial thrombophilia after arthroscopy and venous thromboembolism, none of the 10 study patients had a personal or family history of venous thromboembolism. Although they were at risk for venous thromboembolism their entire lives, previously, these patients had no overt thrombotic manifestations of thrombophilia. Preoperative risk was low as assessed with traditional risk factors.9,10,21 When assessed with traditional methods,9,10,21 none of the 10 patients in the current study who had postarthroscopy venous thromboembolism were given thromboprophylaxis. Evaluating a few common thrombophilias should identify high-risk patients who are otherwise healthy and are candidates for thromboprophylaxis for knee arthroscopy.

Anticoagulation is associated with bleeding risks that must be weighed against the benefit of reduced risk of venous thromboembolism. Previously, after total knee arthroplasty, anticoagulation was achieved with low-molecular-weight heparin or warfarin.30 In the Global Orthopaedic Registry,31 mean time to venous thromboembolism was 9.7 days for total knee arthroplasty. Therefore, most venous thromboembolism events occur in outpatients after discharge. Thromboprophylaxis with enoxaparin or warfarin can be cumbersome.30 For this reason, more recently, these patients have been treated with the direct thrombin inhibitor dabigatran or with 1 of the factor Xa inhibitors rivaroxaban or apixaban, which can be given orally and without close monitoring.32,33 Feng et al32 highlighted the efficacy of factor Xa inhibitors as venous thromboembolism prophylaxis after knee or hip arthroplasty; their anticoagulant effect did not come with an increased risk of
bleeding. Compared with enoxaparin, the factor Xa inhibitors apixaban and edoxaban had better anticoagulant effect without higher bleeding risks. Rivaroxaban, however, had an anticoagulant effect similar to that of the other factor Xa inhibitors, but had a high bleeding risk compared with enoxaparin.

A strength of the current study is robust analysis for familial thrombophilias in a relatively large cohort of patients with venous thromboembolism after knee arthroscopy. The study is limited by the small number of patients with venous thromboembolism after arthroscopy, which limits the power of comparisons with normal subjects and patients after total knee arthroplasty.

CONCLUSION

Factor V Leiden heterozygosity, elevated levels of factor VIII, and elevated levels of homocysteine were much more common in postarthroscopy patients with venous thromboembolism than in healthy normal control subjects. Values were comparable to those in patients with venous thromboembolism after total hip or knee arthroplasty, a patient group that currently receives routine thromboprophylaxis. Venous thromboembolism after knee arthroscopy is uncommon and is less common than after total hip or knee arthroplasty. However, the authors suggest routine measurement of 3 common familial thrombophilias, factor V Leiden, factor VIII, and homocysteine, before arthroscopy to identify patients who are at higher risk for postoperative venous thromboembolism. Keeping risk-benefit ratios in mind, identification of thrombophilia before arthroscopy can guide thromboprophylaxis in patients who otherwise would be considered to be at low risk for venous thromboembolism.

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