Prevention of Venous Thromboembolism in Total Knee and Hip Replacement
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Case presentation: A 69-year-old woman had a cemented hip replacement 15 years previously, which initially fared well but then gradually failed because of aseptic loosening. She developed pain in her hip and was scheduled for a revision total hip replacement. A formal venous thromboembolism (VTE) risk assessment was undertaken before surgery according to the Hospital’s policy for all orthopedic admissions. The risk assessment identified 2 conflicting issues. First, the patient had a particularly high risk of VTE, having had an above-knee deep vein thrombosis after her primary hip replacement and now required a major surgery, namely a revision hip arthroplasty. Second, she had a greater than usual risk of bleeding after surgery because of her obesity and the need for a large soft-tissue exposure, long-term aspirin, and supplementary bone graft from her iliac crest. The surgeon was faced with a common orthopedic problem, providing effective VTE prophylaxis without causing an equally important problem of surgical bleeding.

Introduction
Hip and knee replacement operations are now commonly performed, around 1 million annually in the United States and about the same number in Europe. These procedures are among the most successful and life-changing interventions available.

However, the release of thromboplastins from dissected soft tissue and especially reamed bone, as well as venous stasis both during surgery and during relative postoperative immobility, provoke a high rate of thromboembolism.

Several measures reduce the risk of VTE, but orthopedic surgeons are intuitively and properly concerned about the potential hemorrhagic side effect of pharmacological prophylaxis, which is associated with prolonged recovery, wound failure, and even periprosthetic infection. After all, following the Hippocratic principle of primum non nocere, the most thrombosceptic surgeons have even argued that whereas a thrombosis is an act of God, bleeding is caused by a surgeon. Who is to say that a symptomatic leg thrombosis is any more important than a symptomatic wound bleed or that a fatal embolism is more important than a fatal cerebral or retroperitoneal bleed? Studies of all-cause mortality in orthopedics have shown no clear change in mortality rates with or without prophylaxis. The symptomatic nonfatal VTE rate of around 3% to 4% without prophylaxis may be no different from the increased rate of bleeding induced by pharmacological prophylaxis. A balanced approach, individualized for each patient, is therefore required to secure the safest outcome.

Available Options and Evidence
There are many consensus statements and meta-analyses, a few of which we cite.

General
It is likely that early mobilization, careful surgical technique, and adequate rehydration will all reduce the risk of VTE after joint arthroplasty.

Mechanical
Graduated compression stockings are of some benefit but must be well fitted. Mechanical foot or calf compressors are effective as well in total hip arthroplasty and total knee arthroplasty, although probably not quite as effective as the best pharmacological methods. They have the drawbacks of impracticability and lack of compliance, espe-
Older Oral Agents

Aspirin and warfarin (Coumadin) are widely used in North America, although warfarin is now generally regarded as obsolete in Europe. Aspirin is controversial (Table 1).

Injectable Agents

Low–molecular-weight heparin has become the standard on the basis of >2 decades of clinical experience and a large number of well conducted studies. There is good evidence that, used carefully, low–molecular-weight heparin is effective and does not carry an unacceptable bleeding risk. Fondaparinux (pentasaccharide) is also very effective in reducing VTE but carries less risk of bleeding side effects.

New Oral Agents

The past 3 years have seen the advent of new oral agents, anti Xa or direct thrombin inhibitors. The anti Xa agent apixaban is now also approved for hip and knee arthroplasty. The data suggest that the thromboprophylactic efficacy and bleeding risk of these new agents is at least equivalent to the clinical trial comparator, enoxaparin. There are no direct comparisons between these new oral agents to test relative differences in efficacy or bleeding. These drugs have the important advantage over injectable agents of oral administration, which allows practical administration for a longer duration, especially after hospital discharge. They have the further advantage over existing oral agents relative to efficacy (aspirin), as well as avoidance of monitoring and potential drug interactions (warfarin). They are likely to change the way that prophylaxis is administered in orthopedic patients, in particular meeting the previously unmet need for pragmatic out-of-hospital prophylaxis.

The various pharmacological options are summarized in Table 2. There may be discrepancies between the official manufacturer’s product information, based on clinical trial programs, and the pragmatic and considered protocols advised by professional guidelines. These discrepancies are an underlying theme of this article.

When to Start, When to Finish

The thrombotic process starts as soon as the arthroplasty starts, and so thromboprophylaxis must be started as close to surgery as possible. Pharmacological prophylaxis can be started before surgery, but if too close there will be a risk of bleeding; if too far before surgery, the drug effect will have decayed before the thrombotic process commences. Preoperative administration is also compromised because an unexpected delay in surgery or an earlier than expected procedure will exacerbate these problems. Postoperative administration is therefore more reliable with regard to a precise time for com-

Table 1. Drawbacks of Warfarin and Aspirin, Advantages of New Oral Agents

<table>
<thead>
<tr>
<th>Drawbacks of Warfarin</th>
<th>Advantages of new oral agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs regular monitoring, which is expensive and time consuming</td>
<td>At least as effective as enoxaparin</td>
</tr>
<tr>
<td>If started too close to surgery or at too high a dose, there will be a risk of bleeding</td>
<td>Comparable bleeding profile</td>
</tr>
<tr>
<td>If started judiciously, later and at a lower dose, there will be an interval of several days during which the patient will be unprotected during his or her most thrombogenic phase</td>
<td>No drug interactions</td>
</tr>
<tr>
<td>Interaction with many drugs and alcohol</td>
<td>No monitoring</td>
</tr>
<tr>
<td>Probably not as effective as LMWH</td>
<td>Can be used for out-of-hospital prophylaxis</td>
</tr>
<tr>
<td>Caution in certain groups (eg, renal impairment)</td>
<td>Less prone to HIT than LMWH</td>
</tr>
<tr>
<td>Only recently available, no long-term experience (vs LMWH)</td>
<td>Poor reversibility</td>
</tr>
<tr>
<td></td>
<td>Caution in certain groups (eg, renal impairment)</td>
</tr>
<tr>
<td></td>
<td>Only recently available, no long-term experience (vs LMWH)</td>
</tr>
</tbody>
</table>

LMWH indicates low–molecular-weight heparin; NICE, National Institute for Health and Clinical Excellence; ACCP, American College of Chest Physicians; AAOS, American Academy of Orthopaedic Surgeons; and HIT, heparin induced thrombocytopenia.
mencement, but there is still a balance between giving the drug too soon (and risking bleeding) and too late (and risking thrombosis) (Figure 1). The duration of risk of VTE must also be considered. The risk after knee replacement is around 2 weeks and for hip replacement 4 to 6 weeks.14 The risk may be longer in some individuals with extra risk factors. Prophylaxis should be continued until the risk has diminished (Figure 2). Because joint replacement patients only remain in hospital for a few days, prophylaxis must be extended beyond hospital discharge. This raises practical issues which can be readily addressed with an effective oral agent. Injectable agents and mechanical devices are less practical after hospital discharge.

### Guidelines

Prophylaxis in the United States and Europe is now usually determined by hospital policy informed by guidelines. Guidelines distill the evidence and provide a reasoned and balanced practical summary for the surgeon.15 Regular application of guidelines should help facilitate the implementation of prophylaxis. Despite a similar evidence base, guidelines vary.16 The American Academy of Orthopaedic Surgeons prefers pulmonary embolism as an end point and, with a paucity of studies providing this end point, cannot make firm recommendations on the basis of comparative studies. The first version in 2007 tended toward aspirin and warfarin postoperatively; the latest 2011 iteration17 recommends the avoidance of aspirin before surgery and recommends postoperative pharmacological methods or mechanical methods for hip and knee arthroplasty. Those with a higher risk of thrombosis should have both; those with a higher risk of bleeding should have mechanical methods. Other guidelines, such as those of the American College of Chest Physicians4 and the International Consensus Statement8 are based on a venographic surrogate; this approach supports much firmer recommendations because there are a large number of studies with adequate sample size and significant differences in proportions between randomized groups. New iterations of each are due in 2012.

### Table 2. Pharmaceutical Options in Total Hip Arthroplasty and Total Knee Arthroplasty

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Class</th>
<th>Manufacturer</th>
<th>Route</th>
<th>Timing</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Lovenox (US)</td>
<td>LMWH</td>
<td>Sanofi-Aventis</td>
<td>sc</td>
<td>Postop &gt;12 hours</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Clexane (Europe)</td>
<td>LMWH</td>
<td>Sanofi-Aventis</td>
<td>sc</td>
<td>Preop 12 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>LMWH</td>
<td>Pfizer Inc/Eisai Inc</td>
<td>sc</td>
<td>Preop</td>
<td>Once daily</td>
</tr>
<tr>
<td>Tinzaparin (not yet licensed in US; approved in Europe)</td>
<td>Innohep</td>
<td>LMWH</td>
<td>Leo Pharmaceuticals</td>
<td>sc</td>
<td>Preop</td>
<td>Once daily</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Anxtra</td>
<td>Pentasaccharide</td>
<td>GlaxoSmithKline</td>
<td>sc</td>
<td>&gt;6–8 hours postop</td>
<td>Once daily</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Coumadin/Jantoven</td>
<td>Vitamin K antagonist</td>
<td>Bristol-Myers-Squibb/Upsher-Smith</td>
<td>po</td>
<td>variable</td>
<td>Once daily</td>
</tr>
<tr>
<td>Apixaban (not yet licensed in US; approved in Europe)</td>
<td>Eliquis</td>
<td>Anti-Xa</td>
<td>Bristol-Myx SQuib/Pfizer</td>
<td>po</td>
<td>12–24 hours postop</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xarelto</td>
<td>Anti-Xa</td>
<td>Bayer</td>
<td>po</td>
<td>Postop &gt;8 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Dabigatran (not yet licensed in US; approved in Europe)</td>
<td>Pradaxa</td>
<td>Direct thrombin inhibitor</td>
<td>Boeringher Ingelheim</td>
<td>po</td>
<td>Postop 1–4 hours</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

This is a guide only. Any drug on this table should only be prescribed after confirmation by the prescribing physician of all data on dose, duration, indications, and contra-indications. For duration of administration, refer to both professional guidelines and manufacturer’s product information. LMWH indicates low–molecular-weight heparin; sc, by injection; postop, after surgery; preop, before surgery; and po, by mouth.

### A Balanced Approach

It is generally held that hip and knee replacement have a risk of VTE high
enough to justify universal prophylaxis. However, the type of prophylaxis, the time of initiation, and the duration of administration are a matter for the clinician to judge, balancing the risk of thrombosis and of bleeding. Further, cost effectiveness is an increasingly relevant issue in financially constrained health economies.

### Mechanical–Pharmaceutical Combinations

To minimize bleeding risk yet maximize efficacy of VTE prophylaxis, mechanical and chemical methods are combined to exploit the advantages of each and avoid the disadvantages. A mechanical device is used on the contralateral leg during surgery, then on both legs as soon as the operation is finished. It is continued for as long as it is tolerated. A drug is started postoperatively, but only when the bleeding risk has diminished.

If the patient has a higher than usual risk of bleeding (for example, higher body mass, history of bleeding diathesis, or enlarged surgical incision for revision surgery), then a slightly higher risk of VTE might be accepted, which would indicate starting an anticoagulant later and covering the interim with an effective mechanical method.

#### The Solution in this Case

The surgeon weighed the conflicting risks of bleeding and VTE. Because the patient had a higher risk of bleeding, it was decided to delay the pharmacological prophylaxis until the day after surgery. Mechanical prophylaxis was instituted as early as possible. The patient was given well-fitting graduated compression stockings on arrival in hospital and was encouraged to wear these for 6 weeks. In the operating room, mechanical foot compressors were applied to the opposite leg and activated throughout the procedure. At the end of the procedure, the foot compressor was applied to the operated leg as well. Compression was continued until the patient started to mobilize. The device was then removed only when the patient was tentatively mobilizing but was reattached by the nurse or physiotherapist immediately afterward. By the fifth day, the patient was mobilizing well and was discharged. It was deemed impractical to use the device at home. A new oral agent (Rivaroxaban 10 mg once daily) was given at 9:00 AM on the day after surgery. This delay was judged sensible to bring the drug close enough to surgery for prophylactic effect but to allow adequate hemostasis. The drug was prescribed for 5 weeks. The patient developed no hematoma and no symptomatic VTE.

### Disclosures

Dr Warwick has received honoraria and traveling expenses from Boehringer Ingelheim (manufacturers of Dabigatran, a direct thrombin inhibitor) for 2 lectures in 2011 and 1 in 2010. The author received traveling expenses for his contribution to the International Consensus Statement Editorial Board in 2011.

### References

8. Nicolaides AN, Breddin HK, Carpenter P, Coccheri S, Conard J, De Stefano V, Elkoofy...


In the article by Warwick, “Prevention of Venous Thromboembolism in Total Knee and Hip Replacement,” which was published in the May 1, 2012 issue of the journal (Circulation. 2012;125:2151–2155), the following errors occurred:

In the legend to Table 1, the abbreviation “NICE” is expanded to “National Institute for Clinical Excellence.” The correct expansion of “NICE” is National Institute for Health and Clinical Excellence.

In Table 2, “GlaxoSmithKlein” should read “GlaxoSmithKline.” “Bristol Myer Squibb/Pfizer” should read “Bristol-Myers Squibb/Pfizer.”

Table 2, the brand name provided for the generic “Rivaroxaban” should be “Xarelto,” not “Pradaxa.”

These errors have been corrected in the current online version of the article. The authors regret the errors.