Prevention of Venous Thromboembolism in Total Knee and Hip Replacement
David Warwick, MD, FRCS, FRCS(Orth)

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 thrombocsectic 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.3–10

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 impracticality and lack of compliance, espe-
though warfarin is now generally re- 
widely used in North America, al-
Aspirin and warfarin (Coumadin) are
Older Oral Agents

Drawbacks of Warfarin

Needs regular monitoring, which is expensive and time consuming
If started too close to surgery or at too high a dose, there will be a risk of bleeding
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
Interaction with many drugs and alcohol
Probably not as effective as LMWH

Drawbacks of Aspirin

Only weak antithrombotic effect so limited efficacy
Evidence base controversial
GI bleeding, wound bleeding
Controversial professional support. Not recommended by NICE or ACCP, but recommended by first
Not licensed for thromboprophylaxis

Advantages of new oral agents
At least as effective as enoxaparin
Comparable bleeding profile
No drug interactions
No monitoring
Can be used for out-of-hospital prophylaxis
Less prone to HIT than LMWH

Disadvantages of new oral agents
Poor reversibility
Caution in certain groups (eg, renal impairment)
Only recently available, no long-term experience (vs LMWH)

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.

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

Drawbacks of Warfarin

Needs regular monitoring, which is expensive and time consuming
If started too close to surgery or at too high a dose, there will be a risk of bleeding
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
Interaction with many drugs and alcohol
Probably not as effective as LMWH

Drawbacks of Aspirin

Only weak antithrombotic effect so limited efficacy
Evidence base controversial
GI bleeding, wound bleeding
Controversial professional support. Not recommended by NICE or ACCP, but recommended by first
Not licensed for thromboprophylaxis

Advantages of new oral agents
At least as effective as enoxaparin
Comparable bleeding profile
No drug interactions
No monitoring
Can be used for out-of-hospital prophylaxis
Less prone to HIT than LMWH

Disadvantages of new oral agents
Poor reversibility
Caution in certain groups (eg, renal impairment)
Only recently available, no long-term experience (vs LMWH)

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.

Neuraxial Anesthesia
Neuraxial anesthesia reduces VTE in arthroplasty and also reduces overall mortality.9 However, the anesthetist
will need to consider whether the insertion of a spinal or epidural catheter may be compromised by the risk of a
neuraxial bleed when an anticoagulant is given concomitantly. Meticulous timing and adherence to published an-
esthetic guidelines is essential.

Older Oral Agents
Aspirin and warfarin (Coumadin) are
widely used in North America, al-
though warfarin is now generally re-
garded 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 stud-
ies. There is good evidence that, used
carefully, low–molecular-weight hepa-
rin is effective and does not carry an
unacceptable bleeding risk. Fondapa-
rinux (pentasaccharide) is also very
effective in reducing VTE but carries,
as do all pharmacological agents, a risk
of bleeding side effects.10

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
rivaroxaban is available in the United
States for VTE prophylaxis in total hip
arthroplasty and total knee arthro-
plasty. In Europe, the direct thrombin
inhibitor dabigatran and the anti Xa
agent apixaban are now also approved
for hip and knee arthroplasty.11,12 The
data suggest that the thromboprophyl-	hic efficacy and bleeding risk of
these new agents is at least equivalent
to the clinical trial comparator, enoxa-
parin. There are no direct comparisons
between these new oral agents to test
relative differences in efficacy or
bleeding. These drugs have the im-
portant advantage over injectable agents
of oral administration, which allows
practical administration for a longer
duration, especially after hospital dis-
charge. They have the further advan-
tage over existing oral agents relative
to efficacy (aspirin), as well as avoid-
ance 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 un-
met need for pragmatic out-of-hospital
prophylaxis.

The various pharmacological op-
tions are summarized in Table 2. There
may be discrepancies between the of-
icial manufacturer’s product informa-
tion, based on clinical trial programs,
and the pragmatic and considered pro-
tocols advised by professional guide-
lines. These discrepancies are an un-
derlying theme of this article.

When to Start, When

The thrombotic process starts as soon
as the arthroplasty starts, and so throm-
leftrightarrow
prophylaxis must be started as close
to surgery as possible.13 Pharmacolog-
ical prophylaxis can be started before
surgery, but if too close there will be a
risk of bleeding; if too far before sur-
gery, the drug effect will have decayed
before the thrombotic process com-
ences. Preoperative administration is
also compromised because an unex-
pected delay in surgery or an earlier
than expected procedure will exacer-
bate these problems. Postoperative ad-
ministration is therefore more reliable
with regard to a precise time for com-

When to Start, When

The thrombotic process starts as soon
as the arthroplasty starts, and so throm-
leftrightarrow
prophylaxis must be started as close
to surgery as possible.13 Pharmacolog-
ical prophylaxis can be started before
surgery, but if too close there will be a
risk of bleeding; if too far before sur-
gery, the drug effect will have decayed
before the thrombotic process com-
ences. Preoperative administration is
also compromised because an unex-
pected delay in surgery or an earlier
than expected procedure will exacer-
bate these problems. Postoperative ad-
ministration is therefore more reliable
with regard to a precise time for com-

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. 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. Regular application of guidelines should help facilitate the implementation of prophylaxis.

Despite a similar evidence base, guidelines vary. 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 iteration 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 Physicians and the International Consensus Statement 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.

### 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 VTE (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...


Prevention of Venous Thromboembolism in Total Knee and Hip Replacement

David Warwick

Circulation. 2012;125:2151-2155
doi: 10.1161/CIRCULATIONAHA.111.055731

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/17/2151

An erratum has been published regarding this article. Please see the attached page for:
/content/126/10/e159.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
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.