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Warfarin management in patients on continuous anticoagulation therapy undergoing total knee replacement

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We evaluated the safety and efficacy of total knee replacement in patients receiving continuous warfarin therapy.

We identified 24 consecutive patients receiving long-term warfarin therapy who underwent total knee replacement between 2006 and 2008 and compared them with a group of age- and gender-matched patients not on long-term anticoagulation. Primary observations were changes in haemoglobin, transfusion rates and complications. Secondary observations were fluctuations in the international normalised ratio (INR) and post-operative range of movement.

There was no significant difference between the two groups in pre- or post-operative haemoglobin, incidence of transfusion or incidence of post-operative complications. There were no surgical delays due to a high INR level. The mean change in INR during the peri-operative phase was minimal (mean 0.4; SD 0.7). There was no significant difference in the range of movement between the two groups after day two post-operatively.

Current American College of Chest Physicians guidelines recommend bridging therapy for high-risk patients receiving oral anticoagulation and undergoing major orthopaedic procedures. We have shown that a safe alternative is to continue the steady-state warfarin peri-operatively in patients on long-term anticoagulation requiring total knee replacement.

In 2009 there were 79 263 total knee replacements (TKRs) recorded in the National Joint Registry for England and Wales.[1] In Australia, 40 675 TKRs were performed in 2009 the majority of which were in patients over 60 years of age.[2] The proportion of the Australian population over 65 years is expected to increase from 12% to 21% by 2031.[3] In the population requiring TKR there is likely to be a proportional increase in patients with medical comorbidities requiring long-term warfarin therapy. The three most common indications for oral anticoagulation are atrial fibrillation, mechanical heart valves and venous thromboembolism (VTE).[4]

Warfarin selectively inhibits vitamin K-dependent coagulation factors II, VII, IX and X, as well as proteins C and S, resulting in impaired formation of fibrin.[5] It is rapidly absorbed from the upper gastrointestinal tract and reaches maximum blood concentration within 90 minutes after oral administration.[6] It is highly protein bound, mainly to albumin, but only the free fraction is pharmacologically active. The half-life is usually 36 to 42 hours and is independent of the dose. It is completely metabolised by the liver and eliminated by the kidneys. The dose-response relationship is influenced by genetic factors, diet, concomitant medications and disease states.[6,7]

The management of peri-operative anticoagulation therapy for patients receiving long-term warfarin who are at high risk of thromboembolism remains controversial. The risk of bleeding needs to be balanced against the risk of thromboembolism. If anticoagulation needs to be reversed before surgery, there will always be some risk of thromboembolism.[4] This is dependent on the underlying indication for anticoagulation, the patient's risk factors for thrombus formation, the type of surgical procedure taking place, the duration of cessation of anticoagulation, and whether the anticoagulation is completely or partially reversed. The last two variables can be modified to balance the hazards involved.

Current guidelines recommend discontinuation of warfarin pre-operatively, with a bridging regimen using low-molecular-weight heparin in the peri-operative phase while the INR (international normalised ratio) normalises.[8,9] Warfarin is then resumed after surgery and bridging therapy is stopped once the INR falls within the therapeutic range.[4,9,10] However, the evidence to support current protocols of peri-operative warfarin therapy is largely anecdotal.[8] There

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are currently no randomised controlled trials (RCT) on peri-operative bridging therapy. There is, however, an RCT in progress aiming to enroll 2500 patients with atrial fibrillation on warfarin therapy. Until this trial is published, we must rely on recommendations based on observational studies and guidelines issued by the relevant professional bodies.

A position statement has been published by the Australian Society of Thrombosis and Haemostasis which recommends a bridging regimen for high-risk patients.[8] In contrast, Carter et al[11-14] provided an evidence-based review of oral surgery and warfarin. Their prospective series showed that it was safe to leave patients on warfarin and control bleeding from various oral wounds, mainly dental extractions, by local measures.[11] They conclude that in terms of safety, convenience, cost, and from a medico-legal point of view, continuation of the patient's normal warfarin regimen is recommended for oral surgery when the INR is within the normal therapeutic range of 2 to 4.[11,15] This rationale is supported by the consideration that a stroke is a catastrophic event, whereas bleeding, albeit an inconvenience, is usually easily controlled.[16] We recognise that TKR carries an increased relative risk of bleeding compared to dental extractions, but the principle still applies. The population most at risk of cerebrovascular thrombosis are those with mechanical heart valves, who have a target INR of 3.5, and it is precisely these patients who would be most affected by reducing the INR to < 3.[11,17] Stopping warfarin in high-risk patients before endoscopy has been shown to result in an incidence rate of strokes of 3%.[18] Wahl[19] performed a meta-analysis in patients undergoing dental surgery and confirmed that the incidence of embolic complications when warfarin was stopped was 1%; this was three times more likely than bleeding complications.

Concerns about rebound hypercoagulability after withdrawal of warfarin have been supported by studies confirming increased thrombin activity after warfarin withdrawal.[20-23] Bridging therapy protocols may require extended hospital stays and increased costs.[11,24] There have been reports of large INR fluctuations during the first few days following surgery.[5] Inconsistent anticoagulation during this time could prove hazardous: even with effective thromboprophylaxis the rate of symptomatic pulmonary embolism (PE) has been reported as 1.3% to 5% [7,25] and of fatal PE 0.09% to 0.15%.[26,27]

Against this background we investigated whether it is safe to continue established long-term warfarin therapy during TKR. Our hypothesis was that continuity and consistency of a regimen of anticoagulation would be beneficial to all patients who require such therapy. Primary observations were changes in haemoglobin, transfusion rates, and complications of over- and under-anticoagulation. Secondary observations were fluctuations in the INR, range of movement, length of hospital stay and wound healing.

The ideal anticoagulation therapy regimen would simultaneously offer adequate prophylaxis against thromboembolism and afford adequate surgical haemostasis and low complication rates to allow a safe peri-operative period and recovery. Time and costs involved for patients and doctors when a regimen needs adjustment to accommodate surgery are also an important consideration.

Table I. Patient comorbidities in the warfarin-continued group

Indications for warfarin	Number
History of atrial fibrillation	12
History of pulmonary embolism	4
History of mechanical heart valve	3
History of coronary artery bypass graft	2
History of congestive cardiac failure	2
History of transient ischaemic attack	1

Patients and Methods

We retrospectively identified 24 consecutive patients receiving long-term warfarin therapy who required TKR between 2006 and 2008 (warfarin-continued group) under the care of the senior author (LP). As a control, we collected the same data from a group of age- and gender-matched patients not on long-term warfarin therapy undergoing routine TKR (control group). The warfarin-continued group had a higher incidence of significant comorbidities prior to surgery (Table I). The control group commenced a prophylactic anticoagulation regimen of warfarin (target INR 2.0 to 2.5), without bridging therapy on the day of surgery which was continued for six weeks after surgery, according to a once-daily dosing nomogram.[7] This is the preferred thromboprophylactic regimen in the Hospital of Special Surgery, New York, and is a validated[7] popular method in the United States and Australia, used routinely by the senior author (LP).

All patients gave informed consent for participation in the study, and institutional ethical approval was granted.

Pre-operatively, in the warfarin-continued group no changes were made to the patients' warfarin regimens. The INR was checked prior to surgery and daily post-operatively until discharge. An INR up to 3.0 was deemed safe for undergoing surgery. All procedures were carried out by the senior author in a single centre. A medial parapatellar approach was used under tourniquet control. No drains were used post-operatively. All patients wore an intermittent calf compression device and participated in the standard physiotherapy protocol for TKR.

The use of a spinal anaesthetic technique was contra-indicated because of the high INR values of our study population. All patients received a general anaesthetic and were assessed and optimised in a specific pre-operative anaesthetic clinic.

Medical records were reviewed to collect the relevant data, including patient demographics, pathology leading to arthritis, indications for warfarin therapy, range of movement, body mass index, daily INR and warfarin doses, pre- and daily post-operative haemoglobin, incidence and

Table II. Characteristics of patients undergoing total knee replacement (TKR) in the two groups

	Warfarin-continued group	Control group
Number of patients	24	24
Males (n)	15	16
Mean age (years) (range)	75 (64 to 90)	76 (64 to 87)
Mean BMI* (kg/m^2) (range)	29 (23 to 36)	28 (20 to 50)
Unilateral TKR (n)	21	21
Bilateral TKR (n)	3	3

* BMI, body mass index

quantity of blood transfused. Complications were categorised into haematoma formation, embolic events, delayed wound healing, infection or revision surgery. Any supplementary anticoagulation therapy or change in the patient's normal regimen was also noted. Clinical reviews were conducted at six weeks and 12 months post-operatively, and included range of movement, analgesics used and pain levels.

Statistical analysis. Statistical analysis was performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, Illinois). All data were assumed to be non-parametric. Statistical significance was set at $p < 0.05$. Linear variables were summarised by the mean, standard deviation (SD), median and 95% confidence intervals (CI). Linear variables were examined for change over time with the Wilcoxon signed-rank test, and differences between groups were assessed with the Mann-Whitney U test. Categorical variables were summarised by frequency. A *post-hoc* power study confirmed 81.4% power using an α-level of 0.05 and a calculated observed effect size (Cohen's d) of 0.7, using a sample size of 54 cases in total.

Results

Of the 24 patients who underwent TKR while continuing their normal warfarin therapy regimen (warfarin-continued group), three underwent bilateral TKR and were matched for procedure, age and gender with 24 control patients, three of whom also had bilateral surgery (control group) (Table II). Patient comorbidities requiring long-term warfarin therapy are shown in Table I.

International normalised ratio for warfarin-continued group. The mean INR was 2.2 (SD 0.46; 1.0 to 3.0) pre-operatively and 2.6 (SD 0.8; 1.5 to 5.0) post-operatively. There were no surgical delays caused by a high INR level. The mean change in INR during the peri-operative phase was minimal (mean 0.4; SD 0.7) (Fig. 1). Of the 24 patients in this group, the number who had an INR < 1.9 on each peri-operative day was low, involving only four patients pre-operatively and four patients between post-operative days one and six (Fig. 2).

Haemoglobin. The means and 95% CIs for the pre- and post-operative haemoglobin levels in both groups are shown in Figure 3.

Transfusion. The rates of blood transfusion were not dissimilar between the groups (Table III).

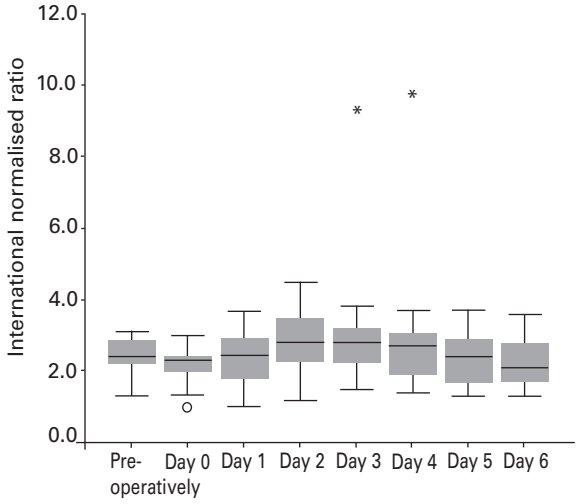

Fig. 1

Box plot showing the mean and 95% confidence interval for the daily international normalised ratio (INR) for the Warfarin Group. Outliers asterisked are described in the text.

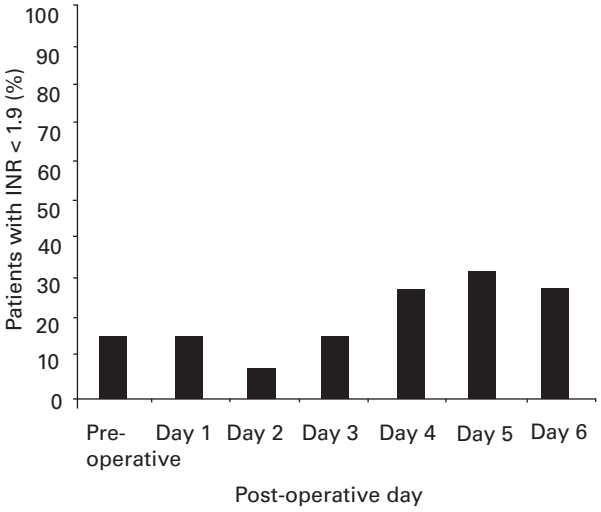

Fig. 2

Bar chart showing the proportion of patients in the warfarin-continued group (n = 24) with an international normalised ratio (INR) < 1.9 pre- and post-operatively.

Complications. There was no particular difference between the groups in the rate complications (Table IV).

A patient with known factor V Leiden thrombophilia developed a symptomatic below-knee deep-vein thrombosis (DVT) during the six-week post-operative period, suspected at two weeks and confirmed by ultrasound. The INR during the peri-operative period did not fall below 2.4. There were no other associated complications with this patient, who made a full recovery and a range of movement 0° to 100° at six weeks.

A patient with a mechanical heart valve suffered a transient ischaemic attack (TIA) affecting the left eye following bilateral TKR. The INR during the peri-operative period

Table III. Incidence of blood transfusion in warfarin-continued and total knee replacement (TKR) groups (Mann-Whitney U test)

	Number of packed red blood cell units	Warfarin-continued group	Control group	p-value
Unilateral TKR	Number of patients	21	21	
	0	16	13	0.178
	1		1	
	2	3	7	
	4	2		
Bilateral TKR	Number of patients	3	3	
	0	1	1	0.261
	2	1	1	
	3		1	
	4	1		

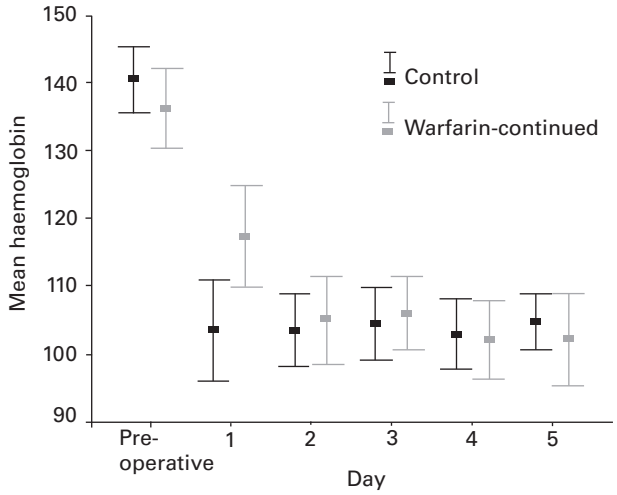

Fig. 3

Means plot showing the mean daily haemoglobin changes in the warfarin-continued group compared with the control group. There was a significant difference between the groups pre-operatively (p = 0.01) and on the first post-operative day (p = 0.001), and no significant difference at any other time (Day 2, p = 0.50; Day 3, p = 0.52; Day 4, p = 0.73; Day 5, p = 0.25). The error bars show the 95% confidence interval.

did not fall below 2.2. Ophthalmic opinion was that he would achieve a 95% recovery. No other sequelae were documented, and a range of movement of 0° to 130° with healed wounds was noted at six weeks.

One patient had delayed wound healing and underwent debridement and re-suturing. The INR ranged between 1.6 and 3.7. He made a full recovery, with a range of movement of 0° to 120°.

A patient with a history of hepatitis B, chronic renal failure, ischaemic heart disease and emphysema, despite being considered high risk at pre-operative evaluation, had a unilateral TKR. Despite optimal management and minimal blood loss, she developed renal and liver failure due to ischaemic hepatitis causing the INR to rise to 9.7 on days three and four post-operatively (Fig. 1). There was no evidence of haemorrhage, the haemoglobin remained stable with a base value of 8.6 g/dl, and no blood was transfused. The warfarin had not been given for three days prior to this event, as the INR values were respectively 2.2, 3.1 and 4.5 on the day of surgery and on days one and two post-operatively. She was treated with dialysis, vitamin K injections and fresh frozen plasma. Once the INR was stabilised, a subcutaneous heparin infusion was started, on day six. Warfarin was restarted on day seven when the renal and hepatic impairment had resolved. She was discharged on day 16. The range of movement was 0° to 100° at six weeks, pain was mild and the wound had healed.

There was no incidence of local haematoma formation around the TKR in either group.

Range of movement. There was a significant difference in the mean range of flexion between the groups at days one and two (p = 0.01 and 0.03, respectively, Mann-Whitney U test), but no differences at other review points (Fig. 4).

Length of hospital stay. The mean length of stay in the warfarin-continued group was 7.5 days (SD 2.5; 5 to 16), and 5.6 days (SD 0.8; 4 to 7) in the control group. This difference was significant (p < 0.01, Mann-Whitney U test). In the warfarin-continued group, one patient had a paralytic ileus, managed conservatively, that delayed discharge; another patient suffered acute-on-chronic renal failure (see above).

Discussion

This study has shown that maintaining warfarin therapy in patients undergoing TKR is safe and effective, with a stable therapeutic window of anticoagulation being achievable. The mean pre-operative INR was 2.2, with a mean change in INR of 0.4 in this group. Similar results have been reported by Rhodes et al,[5] with a mean pre-operative INR of 2.1 and a mean change in INR of 1.2. Larson, Zumberg and Kitchens[28] also showed INR ranges from 1.8 to 2.1 peri-operatively. In one patient the INR did rise to a level where reversal was necessary. This patient developed acute renal failure and secondary liver failure, exacerbated by existing comorbidities. The sudden rise in INR despite withholding warfarin for three days was probably the consequence of acute liver failure disturbing the coagulation pathway[29] and disrupting the hepatic metabolism of warfarin.[11] Nevertheless, haemorrhage did not ensue and transfusion was not necessary. It could be argued that if this

Table IV. Post-operative complications in the warfarin-continued and control groups

	Warfarin-continued group	Control group
Bleeding		
Delayed wound healing	1	
Gastric ulcer haemorrhage		1
Embolism		
Deep-venous thrombosis	1	2
Pulmonary emboli		2
Transient ischaemic attack	1	
Other		
Interruption of anticoagulant therapy	1	
Paralytic ileus	1	
Superficial wound infection		1
Total	5	6

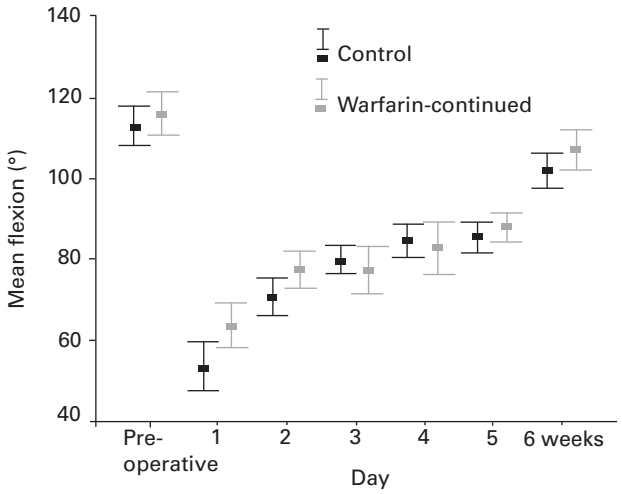

Fig. 4

Means plot showing the mean flexion range of movement (°) in the warfarin-continued group compared with the control group. There was a significant difference between the groups on the first and second post-operative day (p = 0.01 and p = 0.03, respectively), and no significant difference on the pre-operative day or on days 3 to 5 (p = 0.34, 0.41, 0.64 and 0.40, respectively). The error bars show the 95% confidence interval.

patient had been treated with heparin bridging therapy the renal failure might have been more severe, as heparin is nephrotoxic.[30,31] Complications in this high-risk population are not uncommon.

The mean daily change in haemoglobin was similar in the two groups and was within the expected range following TKR (Fig. 3).[32]

The incidence of bleeding following TKR in patients on warfarin therapy has been described in two studies.[5,28] In one, a 2% rate of major bleeding and a 4% rate of minor bleeding was reported in 100 consecutive patients continuing warfarin therapy during TKR or total hip replacement.[28] The other retrospective study[5] comparing bridging therapy (n = 39) with continuation of warfarin (n = 38) for TKR found no increase in the rate of haemorrhage for patients on continuous warfarin. In our series of 24 patients on continuous warfarin no major bleeding occurred and only one minor wound problem was encountered. The frequency of subtherapeutic INR was low, with only four patients having an INR < 1.9 pre-operatively and some dipping low on more than one occasion post-operatively (Fig. 2). A possible contributory factor to the low incidence of bleeding might have been the tamponade effect of not using a drain.

Reported rates of transfusion following primary TKR have ranged from 4% to 38% in unilateral and from 31% to 72% in bilateral cases.[32-35] In previous reports where warfarin was continued, the rate was 34% in one,[28] and in the other the therapeutic warfarin group had a lower transfusion requirement.[5] In our study the transfusion rates for the warfarin-continued group of 24% in unilateral TKR and 67% in bilateral TKR were comparable with those in the control group (38% and 67%, respectively) and differ little from previous studies; they also are within the normal limits of routine TKR performed on patients not on long-term warfarin therapy.

In the warfarin-continued group two patients suffered thromboembolic events comprising one DVT and one TIA, with no long-term sequelae, compared with two DVTs and two PEs in the control group. One study suggests that there is greater risk of embolic events when oral anticoagulant therapy is interrupted, compared to the background risk without anticoagulation.[18] Levels of markers of hypercoagulability, including fibrinopeptide A, activated factor VII, prothrombin fragments, thrombin-antithrombin III complexes and D-dimers, have been found to be elevated following abrupt cessation of warfarin.[20-23] Re-initiation of warfarin is also associated with marked decreases in protein C and S levels within the first 36 hours. This is prior to a reduction in factors X and II.[36-38] This leads to a rebound phenomenon and a transient hypercoagulable state. The potential increase in prothrombotic risk cannot be ignored. In addition, restoring the patient to their pre-operative steady-state INR is associated with increased costs, and in some instances a longer hospital stay.[24,37] Interruption of anticoagulation in patients on long-term warfarin therapy poses a major risk of morbidity and mortality[39,40] which has been attributed to the rebound phenomenon and hypercoagulable state.[41] We experienced only one patient with wound necrosis, which was easily managed by debridement, re-suturing and antibiotics. This problem did not appear to be warfarin-induced skin necrosis, which can occur either on initiation of warfarin or cessation of long-term administration.[37] Heparin-induced thrombocytopenia (HIT) is a much more common problem and may cause paradoxical thrombosis.[28] The continuation of warfarin therapy minimises the risk of warfarin skin necrosis and avoids HIT. Rhodes et al[5] report large fluctuations in the peri-operative INR in bridging therapy regimens.

The decision to continue warfarin throughout the peri-operative phase precludes spinal anaesthesia, because the risk of epidural haematoma is unacceptably high. Several studies have shown no increase mortality, cardiac morbidity or VTE between general and spinal anaesthesia.[42-44]

The weaknesses of this study are typical of a non-controlled observational case series. The numbers of patients are low and statistics reported are prone to type II error. However, the high-risk heterogeneous group of patients we are trying to investigate are infrequently encountered, making recruitment of large numbers for study difficult. The use of consecutive patients eliminates some potential bias. The strengths of the study include its simple design strategy, asking the simple question: is warfarin safe to continue throughout the peri-operative period?

Current American College of Chest Physicians guidelines recommend bridging therapy for high-risk patients receiving oral anticoagulation undergoing major orthopaedic procedures.[9,45] Our results suggest that it is safe to continue steady-state warfarin peri-operatively.

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References

1. **No authors listed.** National Joint Registry for England and Wales. 7th Annual Report, 2010. http://www.njrcentre.org.uk/NjrCentre/LinkClick.aspx?fileticket=QkPl7kk6B2E%3d&tabid=86&mid=523 (date last accessed 27 July 2011).
2. **Davidson D, Graves S, Tomkins A, et al.** Australian Orthopaedic Association National Joint Replacement Registry. Annual Report, 2010. http://www.dmac.adelaide.edu.au/aoanjrr/documents/aoanjrrreport_2010.pdf (date last accessed 27 July 2011).
3. **No authors listed.** Australian Bureau of Statistics. Australian Social Trends. Catalogue 4102.1, 1999. http://www.abs.gov.au/ausstats/abs@.nsf/2f762f95845417aeca25706c00834efa/63378ca41ac510aeca2570ec00114198!OpenDocument (date last accessed 27 July 2011).
4. **Grant PJ, Brotman DJ, Jaffer AK.** Perioperative anticoagulant management. *Med Clin North Am* 2009;93:1105–1121.
5. **Rhodes DA, Severson EP, Hodrick JT, Dunn HK, Hofmann AA.** Discontinuation of warfarin is unnecessary in total knee arthroplasty. *Clin Orthop* 2010;468:120–126.
6. **Hirsh J, Dalen J, Anderson DR, et al.** Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119(Suppl):8–21.
7. **Asnis PD, Gardner MJ, Ranawat A, et al.** The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. *J Arthroplasty* 2007;22:213–218.
8. **Baker RI, Coughlin PB, Gallus AS, et al.** Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis Haemostasis. *Med J Aust* 2004;181:492–497.
9. **Douketis JD, Berger PB, Dunn AS, et al.** The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(Suppl):299–339.
10. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(Suppl):338–400.
11. **Carter G, Goss AN, Lloyd J, Tocchetti R.** Current concepts of the management of dental extractions for patients taking warfarin. *Aust Dent J* 2003;48:89–96.
12. **Carter G, Goss A.** Tranexamic acid mouthwash: a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg* 2003;32:504–507.
13. **Carter G, Goss A, Lloyd J, Tocchetti R.** Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg* 2003;61:1432–1435.
14. **Carter G, Goss AN, Lloyd J, Tocchetti R.** Local haemostasis with autologous fibrin glue following surgical enucleation of a large cystic lesion in a therapeutically anticoagulated patient. *Br J Oral Maxillofac Surg* 2003;41:275–276.
15. **Kamien M.** Remove the tooth, but don't stop the warfarin. *Aust Fam Physician* 2006;35:233–235.
16. **Woods R, Savage N.** Managing dental patients receiving warfarin therapy. *Australian Prescriber* 2002;25:69.
17. **Malden NJ.** Warfarin and extractions. *Br Dent J* 2003;194:65.
18. **Blacker DJ.** Warfarin reversal: consensus guidelines on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 2005;182:365.
19. **Wahl MJ.** Myths of dental surgery in patients receiving anticoagulant therapy. *J Am DentAssoc* 2000;131:77–81.
20. **Poller L, Thomson J.** Evidence for "rebound" hypercoagulability after stopping anticoagulants. *Lancet* 1964;2:62–64.
21. **Harenberg J, Haas R, Zimmerman R.** Plasma hypercoagulability after termination of oral anticoagulants. *Thromb Res* 1983;29:627–633.
22. **Genewein U, Haeberli A, Straub P, Beer JH.** Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. *Br J Haematology* 1996;92:479–485.
23. **Palareti G, Legnani C.** Warfarin withdrawal: pharmacokinetic-pharmocodynamic consideration. *Clin Pharmacokinetics* 1996;30:300–313.
24. **McLemore EC, Harold KL, Cha SS, Johnson DJ, Fowl RJ**. The safety of open inguinal herniorraphy in patients on chronic warfarin therapy. *Am J Surg* 2006;192:860–864.
25. **Anderson DR, Wilson SJ, Blundell J, et al.** Comparison of a nomogram and physician adjusted dosage of warfarin for prophylaxis against deep-vein thrombosis after arthroplasty. *J Bone Joint Surg [Am]* 2002;84-A:1992–1997.
26. **Leiberman JR, Wollaeger J, Dorey F, et al.** The efficacy of prophylaxis with low dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. *J Bone Joint Surg [Am]* 1997;79-A:319–325.
27. **Pelligrini V, Donaldson C, Farber D.** The Mark Coventry Award: Prevention of readmission for venous thromboembolism after total knee arthroplasty. *Clin Orthop* 2006;452:21–27.
28. **Larson BJ, Zumberg MS, Kitchens CS.** A feasibility study of continuing dose-reduced warfarin for invasive procedures in patients with high thromboembolic risk. *Chest* 2005;127:922–927.
29. **Amitrano L, Guardascione MA, Brancaccio V, Balzano A.** Coagulation disorders in liver disease. *Semin Liver Dis* 2002;22:83–96.
30. **No authors listed.** Anticoagulants and protamine. In: Martin J, ed. *British national formulary*. Sixtieth ed. London: Pharmaceutical Press, 2010:141–144.
31. **Johanson NA, Lachiewicz PF, Lieberman JR, et al.** AAOS Clinical Practice Guideline Summary. Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty, 2009. http://www5.aaos.org/dvt/physician/ADU013/suppPDFs/OKO_ADU013_S10.pdf (date last accessed 27 July 2011).
32. **Bong M, Patel V, Chang E, et al.** Risks associated with blood transfusion after total knee arthroplasty. *J Arthroplasty* 2004;19:281–287.
33. **Keating EM, Meding JB, Faris PM, Ritter MA.** Predictors of transfusion risk in elective knee surgery. *Clin Orthop* 1998;357:50–59.
34. **Larocque BJ, Gilbert K, Brien WF.** A point score system for predicting the likelihood of blood transfusion after hip or knee arthroplasty. *Transfusion* 1997;37:463–467.
35. **Salido JA, Marín LA, Gómez LA, Zorrilla P, Martínez C.** Preoperative hemoglobin levels and the need for transfusion after prosthetic hip and knee surgery: analysis of predictive factors. *J Bone Joint Surg [Am]* 2002;84-A:216–220.
36. **Harrison L, Johnston M, Massicotte MP, et al.** Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997;126:133–136.
37. **Srinivasan AF, Rice L, Bartholomew JR, et al.** Warfarin induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. *Arch Intern Med* 2004;164:66–70.
38. **Weiss P, Soff GA, Halkin H, Seligsohn U.** Decline in proteins C and S and factors II, VII and X during the initiation of warfarin therapy. *Thromb Res* 1987;45:783–790.
39. **Kearon C, Hirsh J.** Management of anticoagulation before and after elective surgery. *N Engl J Med* 1997;336:1506–1511.
40. **No authors listed.** Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism: Research Committee of the British Thoracic Society. *Lancet* 1992;340:873–876.
41. **Sallah S, Thomas DP, Roberts HR.** Warfarin and heparin-induced skin necrosis and the purple toe syndrome: infrequent complications of anticoagulant treatment. *Thromb Haemost* 1997;78:785–790.
42. **Brinker MR, Reuben JD, Mull JR, et al.** Comparison of general and epidural anaesthesia in patients undergoing primary unilateral THR. *Orthopedics* 1997;20:109–115.
43. **Manolio TA, Beattie C, Christopherson R, Pearson TA.** Regional versus general anesthesia in high-risk surgical patients: the need for a clinical trial. *J Clin Anesth* 1989;1:414–421.
44. **Parker MJ, Urwin SC, Handoll HH, Griffiths R.** General versus spinal/epidural anaesthesia for surgery for hip fractures in adults. *Cochrane Database Syst Rev* 2000;2:CD000521.
45. **Kearon C, Kahn SR, Agnelli G, et al.** Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(Suppl):454–545.