Netherlands
The Journal of Medicine

REVIEW

Periprocedural reversal and bridging of anticoagulant treatment

M. Levi*, E. Eerenberg, P.W. Kamphuisen

Department of Vascular Medicine and Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, *corresponding author: tel. +31 (0)20 5662171, fax: +31 20 6919658, e-mail: m.m.levi@amc.uva.nl

ABSTRACT

Anticoagulants are effective agents in reducing the risk of thromboembolism but the most important adverse effect of these agents is the occurrence of bleeding. Bleeding complications may occur spontaneously but the risk of bleeding is particularly increased in case of trauma or around invasive procedures. If patients being treated with anticoagulants need to undergo an invasive intervention, physicians need to consider whether to interrupt the use of this medication or to allow its use to be continued. Suspending the use of anticoagulants increases the risk of thrombosis, whereas continued use may cause bleeding complications. To shorten the period in which anticoagulant treatment is interrupted, bridging strategies have been advocated. No evidence-based scientific research has been carried out regarding best practice for the perioperative use of anticoagulants. The periprocedural anticoagulation policy in patients should be individualised based on the risk of a thromboembolic complication (which can be estimated with available scoring systems) offset against the bleeding risk associated with the intervention.

KEYWORDS

Anticoagulants, hemorrhage, heparin, surgery, vitamin K antagonists, aspirin, clopidogrel, prasugrel, bridging

INTRODUCTION

Anticoagulant agents are often used for the prevention and treatment of a wide range of cardiovascular diseases. Most frequently used anticoagulants are heparin or its derivatives, vitamin K antagonists (such as warfarin or coumadin) and antiplatelet agents, including aspirin and thienopyridine derivatives, such as clopidogrel or prasugrel. A myriad of clinical studies have demonstrated that these agents (alone or in combination) can prevent or treat acute or chronic thromboembolic complications, in patients with atrial fibrillation or prosthetic heart valves, after myocardial infarction, percutaneous coronary interventions, or ischaemic stroke, and in patients with venous thrombosis or pulmonary embolism.[1] The most important complication of treatment with anticoagulants is haemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life-threatening.[2]

If a patient needs to undergo an urgent invasive procedure, such as emergency surgery, it may be required to reverse the anticoagulant effect of the various agents. However, in some patients reversal will increase the risk of thromboembolic complications. For such patients, the interruption of anticoagulation should be as short as possible. In many cases, so-called bridging strategies are used to shorten the duration of the period without anticoagulant cover. Depending on the clinical situation, i.e. the urgency and estimated risk of the invasive procedure, reversal may take place in a few hours, but in some cases immediate reversal is necessary.[3,4] Generally, each (immediate) reversal of anticoagulant treatment also needs to take into consideration the indication for the antithrombotic agents. For example, the interruption of combined aspirin and clopidogrel treatment in a patient in whom an intracoronary stent has recently been inserted will markedly increase the risk of acute stent thrombosis with consequent downstream cardiac ischaemia or infarction. Likewise, in a patient with a prosthetic mitral valve and atrial fibrillation, interruption of vitamin K antagonists may increase the risk of valve thrombosis and cerebral or systemic embolism. Each of these specific clinical situations requires a careful and balanced assessment of the benefits and risks of reversing

anticoagulants (and potential strategies to keep the period of reversal as short as possible). In general, the optimal periprocedural anticoagulant strategy encompasses a proper assessment of both bleeding risk associated with the intervention and the risk of a thromboembolic complication. In this manuscript we will focus on these risks, in particular for patients with atrial fibrillation, and discuss frequently used periprocedural bridging strategies.

ASSESSMENT OF THROMBOEMBOLIC RISK

The risk of a thromboembolic complication in patients with atrial fibrillation is generally estimated by means of the CHADS2 score. Based on various characteristics, namely the presence of heart failure, hypertension, age >75 years, diabetes mellitus and a history of, ischaemic stroke (ischaemic stroke) or transient ischaemic attack (TIA), one can determine the risk of thromboembolism. Patients with 0 to 2 points have an annual risk of a thromboembolic complication of 1 to 4%, whereas in patients with 3 to 6 points this is 6 to 18% per year.[5] Generally, patients with a CHADS2 score of >2 are treated with vitamin K antagonists and with lower scores by means of aspirin or without antithrombotic agents. Clinical studies have convincingly shown that treatment with anticoagulant agents in patients with atrial fibrillation substantially reduces the risk of thromboembolic complications.

There is only limited data on the perioperative thromboembolic risk. By using a large dataset of patients with atrial fibrillation who participated in a study on the outcome of restoration of sinus rhythm compared with control of ventricular rate,[6] the risk of bleeding and thrombosis around surgery in this cohort was investigated.[7] Of the 522 patients in this study 94 patients (mean 69.9 years) underwent 121 non-cardiac surgical procedures during a 29-month follow-up. In all patients the anticoagulant treatment was discontinued around the operation. In the months after surgery, no thrombotic complications occurred, compared with an incidence of 0.42%/month during the remaining months of the study (*table 1*). However, patients with atrial fibrillation and anticoagulation had a 3.6-fold increased risk of bleeding within one month after surgery. Severe haemorrhage occurred in one patient. Based on this retrospective analysis, it would appear that it is a safe policy to interrupt anticoagulation around invasive procedures in patients with atrial fibrillation. It is important to note, however, that the study population was a relatively young group in a relatively good cardiac condition. In addition, it should be taken into account that the existence of atrial fibrillation and the use of anticoagulation may have played a role in whether or not to perform surgery. The (slightly) increased risk of bleeding may be attributed to a changing institution of anticoagulant in a period after an interruption and surgery often with hospitalisation and use of various other drugs.

Table 1. *Incidence of thromboembolism and bleeding in the first month after surgery in patients with atrial fibrillation in whom the anticoagulants were interrupted compared with the incidence of these complications in a control period*

Outcome	1st month after surgery No. (% per month)	Control period No. (% per month)	Relative risk (95% CI)
Thromboembolism	0 (0)	11 (0.4)	-
Haemorrhage	3 (2.6)	19 (0.7)	3.6 (1.05-12.0)
- Major bleeding	1 (0.9)	8 (0.3)	2.8 (0.35-22.5)
- Minor bleeding	2 (1.7)	11 (0.4)	4.1 (0.91-18.4)
Both outcomes	3 (2.6)	30 (1.2)	1.2 (0.70-7.4)

95% CI = 95% confidence interval.

Notwithstanding the results mentioned above, it remains the question whether interruption of treatment in patients with a higher risk of thromboembolism could be potentially harmful.[8] In the consensus on antithrombotic treatment of the American College of Chest Physicians, stratification of patients according to their risk for perioperative thromboembolism is based on patients' clinical indication for antithrombotic therapy and the presence of comorbidities.[9] Although there is no validated risk stratification of such patients, the approach that was used in these guidelines is to separate patients into a high-risk, moderate-risk, or low-risk group according to their indication for antithrombotic therapy (*table 2*).

Table 2. *Estimated thromboembolic risk based on the ACCP consensus*

Risk stratum	Atrial fibrillation
High risk	CHADS2 score 5-6 Recent (within 3 months) stroke or TIA Rheumatic valvular heart disease Prosthetic heart valves
Moderate risk	CHADS2 score 3-4
Low risk	CHADS2 score 0-2 and no prior stroke or TIA

CHADS2 = congestive heart failure, hypertension, age >75 years, diabetes, stroke; TIA = transient ischaemic attack.

ASSESSMENT OF BLEEDING RISK

The most important complication of treatment with vitamin K antagonists (VKAs) is haemorrhage, which may be life-threatening.[2] In well-controlled patients in clinical trials treatment with VKAs increases the risk of major bleeding by 0.5%/year and the risk of intracranial haemorrhage

by about 0.2%/year.[10] The most important risk factor for haemorrhage in users of VKAs is the intensity of the anticoagulant effect.[10] Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twice as large as in studies with a target INR of 2.0 to 3.0.[11] Patient characteristics constitute another important determinant of the bleeding risk bleeding. Elderly patients have a twofold increased risk of bleeding[12] and the relative risk of intracranial haemorrhage (in particular at higher INRs) was 2.5 (95% CI 2.3 to 9.4) in patients >85 years compared with patients aged 70 to 74 years.[13] Comorbidity, such as renal or hepatic insufficiency, may also significantly increase the risk of bleeding. A case-control study in 1986 patients on VKAs showed that this comorbidity increased the risk of bleeding by about 2.5.[14] Another very important determinant of the risk of bleeding is the use of other medication, in particular agents affecting platelet function. Two meta-analyses, comprising six trials with a total of 3874 patients and ten trials with a total of 5938 patients, found a relative risk of major bleeding when VKAs were combined with aspirin of 2.4 (95% CI 1.2 to 4.8) and 2.5 (95% CI 1.7 to 3.7), respectively.[15,16]

There is no evidence that patients with atrial fibrillation have a different bleeding risk during invasive procedures compared with other patients. It may be, however, that patients with atrial fibrillation represent a relatively vulnerable population and thereby will have a somewhat enhanced risk of bleeding. Although bleeding is a treatable perioperative complication, there is emerging evidence that the clinical impact of bleeding is considerable and, perhaps, greater than previously appreciated.[9] Furthermore, postoperative bleeding delays the resumption of antithrombotic therapy, with the potential to further expose patients to an increased risk for thromboembolism. Stratifying patients according to their risk for perioperative bleeding can be based on the risk for bleeding associated with the surgery or procedure. Although there is no precise information that quantifies perioperative bleeding risk, special attention is warranted for certain surgical or other invasive procedures associated with a high risk for bleeding. These include coronary artery bypass or heart valve replacement surgery, intracranial or spinal surgery, major vascular surgery including aortic aneurysm repair or peripheral artery bypass, major orthopaedic surgery (such as hip or knee replacement), major cancer surgery and prostate and bladder surgery.

REVERSAL OF VITAMIN K ANTAGONIST TREATMENT

When interrupting the administration of VKAs important differences in the half-lives of the various agents (nine hours for acenocoumarol, 36 to 42 hours for warfarin, and 90 hours for phenprocoumon, respectively) need to be taken into account.[4,17] The most straightforward active intervention to counteract the effect of VKAs is the administration of vitamin K.[18] There is quite some debate on the use of vitamin K in patients with a too high INR who require surgery. Although a randomised controlled trial did not find any difference in bleeding or other complications in nonbleeding patients with INR values of 4.5 to 10 who were treated with vitamin K or placebo,[19] consensus-based guidelines advocate the use of small doses of vitamin K (2 mg orally) in patients with an INR >7 and using long-acting vitamin K antagonists. In patients who require subacute emergency surgery administration of vitamin K is crucial to reverse the anticoagulant effect of VKAs. Vitamin K can be given orally and intravenously, whereas the parenteral route has the advantage of a more rapid onset of the treatment.[20] After the administration of intravenous vitamin K, the INR will start to drop within two hours and will be completely normalised within 12 to 16 hours,[21] whereas after oral administration it will take up to 24 hours to normalise the INR.[18] Intramuscular injections of vitamin K should be avoided in patients who are anticoagulated and subcutaneous administration of vitamin K results in a less predictable bioavailability.[20] When the INR is below 7 a dose range of 2.5 to 5 mg of vitamin K has been advocated whereas with higher INRs a dose of 5 to 10 mg is required to correct the INR. Higher doses of vitamin K are equally effective but may lead to VKA resistance for more than a week, which may hamper long-term management.[22] A potential concern with the use of parenteral vitamin K is the occurrence of anaphylactic reactions, although the incidence of this complication is very low, in particular with the more modern micelle preparations.[23]

When immediate correction of the INR is necessary, this can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required to correct the INR is very large, carries the risk of fluid overload, and will probably take hours to administer.[24] Therefore, prothrombin complex concentrates (PCCs), most of which containing all vitamin K-dependent coagulation factors, are more useful. It should be mentioned that the exact composition of PCCs (i.e. the content of individual vitamin K dependent proteins) may significantly vary between preparations. Although PCCs can indeed be given using fixed dose schemes, it has been shown that individualised dosing regimens based on INR at presentation and body weight are more effective.[25] In a prospective cohort study of patients on VKAs who presented with major bleeding, PCCs were effective in reducing the INR below 2 in 56 out of 58 patients.[26] Another prospective study in patients using VKA and presenting with bleeding also found

that PCCs resulted in at least satisfactory and sustained haemostasis in 98%.[27] In recent years the safety of PCCs, in particular regarding the transmission of blood-borne infectious diseases, has markedly improved owing to several techniques, such as pasteurisation, nanofiltration, and addition of solvent detergent. The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from older literature and modern PCCs do not seem to be associated with eliciting DIC.[28]

REVERSAL OF ANTIPLATELET AGENTS

It has been shown that the use of aspirin is associated with increased perioperative blood loss in major procedures, although this does not necessarily translate into clinically relevant endpoints, such as the requirement for transfusion or re-operation.[29] Over the last years the approach to the patient who is taking aspirin and who presents with bleeding or needs to undergo an invasive procedure has changed considerably. In fact, in current clinical practice bleeding can almost always be managed with local haemostatic procedures or conservative strategies without interrupting aspirin and also most invasive procedures do not require the cessation of aspirin when adequate attention is given to local haemostasis. In contrast, interruption of aspirin has been associated with an increased risk of thromboembolic complications, potentially due to a rebound hypercoagulability. Obviously, in special clinical circumstances, such as the need to undergo a neurosurgical or ophthalmic procedure, the antihaemostatic effect of aspirin needs to be reversed immediately. The most rigorous measure to achieve that is the administration of platelet concentrate after cessation of aspirin. Another approach is the administration of de-amino d-arginin vasopressin (DDAVP, desmopressin). DDAVP is a vasopressin analogue that despite minor molecular differences has retained its antidiuretic properties but has much less vasoactive effects.[30,31] DDAVP induces release of the contents of the endothelial cell associated Weibel-Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII) and (also by yet unexplained additional mechanisms) a remarkable augmentation of primary haemostasis as a consequence.

Clopidogrel and prasugrel belong to the class of thienopyridine derivatives which act by blocking the adenosine diphosphate (ADP) receptor on the platelet. Importantly, the combination of aspirin and clopidogrel is vastly superior over aspirin alone in patients who have received intracoronary stents or in other patients with high-risk coronary artery disease. There is ample evidence that dual platelet inhibition of aspirin plus clopidogrel has a significantly higher efficacy than aspirin alone in patients with acute coronary syndromes who have undergone coronary interventions for at least a year (and possibly longer) after the event. However, the increased efficacy of the combined use of aspirin and clopidogrel is also associated with a significantly higher bleeding risk.[32] Prasugrel is another thienopyridine derivative that after rapid and almost complete absorption after oral ingestion irreversibly binds to the ADP receptor. Prasugrel has a stronger antiplatelet effect than clopidogrel because of more effective metabolism and less dependence of cytochrome P450 enzymes that may be subject to genetic polymorphisms.[33] The decision whether or not the interrupt or even reverse antithrombotic treatment with dual platelet inhibition in case of the need to perform an invasive procedure will depend on the specific clinical situation. Especially in patients with recent implantation of an intracoronary stent (in the last 6-12 weeks), cardiologists will often not or only reluctantly agree with cessation of treatment.[34] In this period re-endothelialisation of the stent has not yet occurred and the patient is very vulnerable to acute thrombotic occlusion of the stent. In patients with drug-eluting stents this period may be even longer. If, however, the decision is made to stop and even reverse the treatment with aspirin and clopidogrel, administration of platelet concentrate is probably the best way to correct the haemostatic defect.[35] In addition, DDAVP was shown to correct the defect in platelet aggregation caused by clopidogrel, so this may be another option.[36]

PERIPROCEDURAL ANTICOAGULATION INTERRUPTION AND/OR BRIDGING STRATEGIES IN PATIENTS WITH ATRIAL FIBRILLATION

A practical guide in selecting the most appropriate interruption and/or bridging strategy is outlined in *table 3*. In general, in patients undergoing interventions with a low risk of bleeding and major potential for adequate local haemostasis, continuation of antithrombotic treatment may be considered. In case of VKA treatment tapering the intensity of anticoagulation, for example to an INR of 1.5 to 2.0, is advocated.[9] For larger interventions, the optimal strategy is determined by the risk of thromboembolic complications when anticoagulant treatment is interrupted. In patients with low risk of thromboembolism, short-lasting interruption of anticoagulant treatment is advised. Anticoagulant treatment should not be resumed until 12 and preferably 24 hours after the intervention, to avoid bleeding complications.[37]

For patients with a high risk of thromboembolism, the window of no anticoagulant prophylaxis should be

Table 3. *Perioperative interruption and bridging strategy based on risk of thromboembolism and risk of perioperative bleeding*

Risk of thromboembolism	Risk of peri-operative bleeding: Low	Risk of peri-operative bleeding: High
High	• Consult with surgeon or operator • Continue VKA • Monitor INR • Target INR 1.5-2.0	• Stop treatment with VKA (warfarin or coumadin 3-4 days, phenprocoumon 5-7 days preoperatively) • Start therapeutic UFH or LMWH • Stop UFH 3 hrs preoperatively or LMWH 24 hrs preoperatively • Restart heparin 12-24 hrs post-operatively (if no bleeding) • Restart VKA 1-2 days postoperatively (if no bleeding) • Stop heparin when INR is in therapeutic range
Low		• Stop treatment with VKA (warfarin or coumadin 3-4 days, phenprocoumon 5-7 days preoperatively) • Restart VKA 12-24 hrs postoperatively (if no bleeding) • Usual prophylactic LMWH (prevention of venous thromboembolism)

Patients with an intermediate risk of thromboembolism are treated according to the low-risk stratum, although individual exceptions may be made based on patient characteristics and preferences of patients and doctors. VKA = vitamin K antagonists; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; INR = international normalised ratio.

minimised using heparin ('bridging'). In this strategy, therapeutic doses of heparin are administered after cessation or interruption of vitamin K antagonists. Shortly before the intervention, heparin is temporarily stopped and reinstated after termination of the procedure. The most precise bridging may be obtained by the administration of continuous intravenous unfractionated heparin, as the short half-life (about 90 minutes) may allow cessation of its administration only two to three hours before the intervention, whereas anticoagulation can be immediately resumed as soon as possible after the procedure. Also in this case it has been shown that resumption of heparin treatment before 12 to 24 hours after the intervention may lead to major bleeding complications.[38] The disadvantage of this strategy with unfractionated heparin is that it requires intravenous treatment, thereby potentially prolonging the hospital stay, and the variable intraindividual and interindividual effect, necessitating frequent laboratory monitoring with sequential aPTTs. An alternative to unfractionated heparin may be low-molecular-weight (LMW) heparin, which may be administered subcutaneously and has a more predictable anticoagulant effect. Bridging strategies with LMW heparin may be performed in an outpatient setting and in general do not require laboratory monitoring. The disadvantage of LMW heparin is its relatively longer half-life (8 to 12 hours), which may make it somewhat more difficult to precisely plan cessation of this agent relative to the timing of the intervention.

For patients with an intermediate risk of thromboembolic complications it is hard to formulate clear guidelines. Especially in this area individualised treatment decisions should be made in close consultation between cardiologist, haemostasis specialist, and surgeon. Most local guidelines now advocate to treat intermediate-risk patients as low-risk patients; however, in individual cases and dependent on the intervention, clinical circumstances, and preferences of patients and doctors, it seems justified to follow a bridging rather than an interruption strategy in selected patients.

CONCLUSION

The periprocedural anticoagulation policy in patients with atrial fibrillation should be individualised based on the risk of a thromboembolic complication offset against the bleeding risk associated with the intervention. A proper assessment should be made of the perioperative risk of thromboembolism after discontinuation of anticoagulant therapy versus the bleeding risk due to continuing this treatment around the invasive procedure. In case of a high risk of thromboembolic complications and a procedure with a high bleeding risk, bridging of anticoagulant treatment with heparin or LMW heparin to interrupt anticoagulant prophylaxis as short as possible should be considered.

REFERENCES

1. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):110S-112S.
2. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med. 2007;356(22):2301-11.
3. Levi M. Emergency reversal of antithrombotic treatment. Intern Emerg Med. 2009;4(2):137-45.
4. Levi MM, Eerenberg E, Lowenberg E, Kamphuisen PW. Bleeding in patients using new anticoagulants or antiplatelet agents: risk factors and management. Neth J Med. 2010;68(2):68-76.
5. Levi M, Hobbs FD, Jacobson AK, et al. Improving antithrombotic management in patients with atrial fibrillation: current status and perspectives. Semin Thromb Hemost. 2009;35(6):527-42.
6. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347(23):1834-40.
7. Vink R, Rienstra M, Van Dongen CJ, et al. The risk of thromboembolism and bleeding after general surgery in patients with atrial fibrillation. Am J Cardiol. 2005; September 15;96(6):822-4.

8. Douketis JD, Crowther MA, Cherian SS. Perioperative anticoagulation in patients with chronic atrial fibrillation who are undergoing elective surgery: results of a physician survey. Can J Cardiol. 2000;16(3):326-30.

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(6 Suppl):299S-339S.

10. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):257S-298S.

11. Saour JN, Sieck JO, Mamo LA, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med. 1990;322(7):428-32.

12. Hutten BA, Lensing AW, Kraaijenhagen RA, Prins MH. Safety of treatment with oral anticoagulants in the elderly. A systematic review. Drugs Aging. 1999;14(4):303-12.

13. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141(10):745-52.

14. Levi M, Hovingh GK, Cannegieter SC, Vermeulen M, Buller HR, Rosendaal FR. Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based. Blood. 2008;111(9):4471-6.

15. Hart RG, Benavente O, Pearce LA. Increased risk of intracranial hemorrhage when aspirin is combined with warfarin: A meta-analysis and hypothesis. Cerebrovasc Dis. 1999;9(4):215-7.

16. Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. Ann Intern Med. 2005;143(4):241-50.

17. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S-198S.

18. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. J Thromb Haemost. 2006;4(9):1853-63.

19. Crowther MA, Ageno W, Garcia D, et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin. Ann Intern Med. 2009;150:293-300.

20. Crowther MA, Douketis JD, Schnurr T, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med. 2002;137(4):251-4.

21. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med. 2003;163(20):2469-73.

22. van Geest-Daalderop JH, Hutten BA, Pequeriaux NC, de Vries-Goldschmeding HJ, Rakers E, Levi M. Invasive procedures in the outpatient setting: Managing the short-acting acenocoumarol and the long-acting phenprocoumon. Thromb Haemost. 2007;98(4):747-55.

23. Dentali F, Ageno W. Management of coumarin-associated coagulopathy in the non-bleeding patient: a systematic review. Haematologica. 2004;89(7):857-62.

24. Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. Mayo Clin Proc. 2007;82(1):82-92.

25. van Aart L, Eijkhout HW, Kamphuis JS, et al. Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: an open, prospective randomized controlled trial. Thromb Res. 2006;118(3):313-20.

26. Kessler CM. Urgent reversal of warfarin with prothrombin complex concentrate: where are the evidence-based data? J Thromb Haemost. 2006;4(5):963-6.

27. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost. 2008;6(4):622-31.

28. Levi M. Disseminated intravascular coagulation. Crit Care Med. 2007;35:2191-5.

29. Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis. 2004;17(1):21-7.

30. Richardson DW, Robinson AG. Desmopressin. Ann Intern Med. 1985;103(2):228-39.

31. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med. 2007;356:2301-11.

32. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.

33. Bhatt DL. Prasugrel in clinical practice. N Engl J Med. 2009;361(10):940-2.

34. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Catheter Cardiovasc Interv. 2007;69(3):334-40.

35. Vilahur G, Choi BG, Zafar MU, et al. Normalization of platelet reactivity in clopidogrel-treated subjects. J Thromb Haemost. 2007;5(1):82-90.

36. Leithauser B, Zielske D, Seyfert UT, Jung F. Effects of desmopressin on platelet membrane glycoproteins and platelet aggregation in volunteers on clopidogrel. Clin Hemorheol Microcirc. 2008;39(1-4):293-302.

37. Vink R, van den Brink RB, Levi M. Management of anticoagulant therapy for patients with prosthetic heart valves or atrial fibrillation. Hematology. 2004;9(1):1-9.

38. Fernandez-Fernandez FJ, del Castillo-Fraile M. Acute abdominal pain in a patient receiving enoxaparin. Neth J Med. 2009;67(6):243-4.