

# Anticoagulation for venous thromboembolism

## What if they bleed?

G. Palareti

Dept. of Angiology & Blood Coagulation, University Hospital of Bologna, Italy

### Keywords

VTE, anticoagulation, bleeding, haemorrhages

### Summary

Acute venous thromboembolism (VTE) is treated with parenteral administration of heparin or derivatives, in conjunction with oral vitamin K antagonists (VKAs) to reach and maintain INR values between 2.0 and 3.0 for at least 3 months; the duration of a further period of treatment for secondary prevention of recurrences is still matter of debate. If bleeding occurs during treatment the decision will be based on: a) type of bleeding (major or minor), and b) thrombotic risk if anticoagulation is withheld (characteristics of patients and time elapsed from the index VTE). In case of major bleeding anticoagulation should be stopped and reversed. A first but insufficient measure is i.v. vitamin K administration. Fresh frozen plasma is widely used; however, large volumes are needed (at least 15 mL/kg body weight) with risk for fluid overload. Prothrombin complex concentrate infusion, with 3 or (better) the 4 pro-coagulant factors, is a more efficient (fast and safe) measure. In patients at high thrombotic risk (first month or other conditions) and absolute contraindication for anticoagulation a caval filter is recommended, to avoid as much as possible life-threatening pulmonary embolism.

### Schlüsselwörter

VTE, Antikoagulation, Blutung, Hämorrhagien

### Zusammenfassung

Die Behandlung der akuten venösen Thromboembolie (VTE) besteht in der parenteralen Gabe von Heparin bzw. -derivaten, zusammen mit oralen Vitamin-K-Antagonisten (VKA), um INR-Werte zwischen 2,0 und 3,0 zu erreichen und für mindestens drei Monate aufrecht zu erhalten. Über die Dauer einer anschließenden sekundären Rezidivprophylaxe wird noch diskutiert. Falls während der Behandlung eine Blutung auftritt, richtet sich die Entscheidung nach: a) Art der Blutung (leichte oder schwere) und b) Thromboserisiko bei Absetzen der Antikoagulation (Patientencharakteristika und Zeitraum seit der Index-VTE). Im Falle einer großen Blutung sollte die Antikoagulation beendet und antagonisiert werden. Eine erste, jedoch unzureichende Maßnahme ist die i.v.-Gabe von Vitamin K. Gefrorenes Frischplasma wird häufig verwendet; es werden jedoch große Mengen benötigt (mindestens 15 ml/kg Körpergewicht), mit dem Risiko der Volumenüberlastung. Die Infusion eines Prothrombin-komplex-Konzentrats mit drei oder (besser) vier Gerinnungsfaktoren ist das effizientere Verfahren (schnell und sicher). Bei Patienten mit einem hohen Thromboserisiko (im ersten Monat oder bei Vorliegen anderer Erkrankungen) und einer absoluten Kontraindikation für eine Antikoagulation wird ein Vena-cava-Filter empfohlen, um möglichst eine lebensbedrohliche Lungenembolie zu vermeiden

### Correspondence to:

Prof. Gualtiero Palareti  
Dept. of Angiology & Blood Coagulation  
University Hospital of Bologna  
Via Albertoni 15, 40138 Bologna, Italy  
Tel. +39 0516362483, Fax +39 051341642  
gualtiero.palareti@unibo.it

### Anticoagulation bei venöser Thromboembolie – Was tun bei einer Blutung?

Hämostaseologie 2012; 32: 40–44

doi:10.5482/ha-1180

received: October 2, 2011;

accepted: October 6, 2011;

prepublished online: October 19, 2011;

## Anticoagulation for VTE

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent, clinically important and potentially lethal disease, whose annual incidence is estimated to range between 0.7 and 1.2 people every 1000 in the general population, although the rate increases markedly with age. Short term complications of VTE are represented by occurrence of potentially life-threatening PE and extension of thrombosis to other vein tracts. VTE recurrence (1) and post-thrombotic syndrome (2) are the medium and long-term possible complications.

Therapeutic dose anticoagulation is the standard medical intervention in patients with acute VTE. Though changes may soon occur with the foreseen clinical use of the so-called new oral anticoagulants, the current treatment of acute phase is based on the parenteral administration for the first few days (at least 5 days) of drugs that have an immediate anticoagulant effect (heparin or derivatives) in conjunction with oral vitamin K antagonists (VKAs), that require not less than five days to give a clinically effective anticoagulation; heparin or derivatives can be stopped when INR is > 2 for two consecutive days.

Guidelines recommend VKA therapy for at least three months as treatment of acute phase of the disease, followed by a further period of treatment targeted at the secondary prevention of recurrences (3); optimal duration of this extended treatment is affected by the nature of the index event and patient characteristics and is still matter of debate (4, 5).

## Bleeding during anticoagulation

The risk of bleeding is associated with therapeutic anticoagulation, whatever the drug used and throughout all the above mentioned periods of anticoagulant treatment. If bleeding occurs in a patient treated for VTE our approach and clinical decision will be based on

- type of bleeding event and associated risk, bearing in mind the site and/or entity of the bleed, and
- thrombotic risk for patient if anticoagulation is withheld, which is determined by the specific characteristics of each patient and by the time elapsed from the index VTE.

Bleeds are divided into major and minor on the basis of objective criteria, major bleeds being those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources. In line with these criteria the Control of Anticoagulation Subcommittee of the International Society of Thrombosis and Haemostasis recommends bleeds to be considered major if

- fatal, or in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome), or
- cause a fall in haemoglobin level of 20 g/l or more, or
- lead to transfusion of two or more units of whole blood or red cells (6).

All other bleeds can be considered minor.

There is general consensus that in case of major bleeding, anticoagulation should be stopped and completely reversed to obtain rapid and complete normalization of coagulation, with a view to offering patients more changes that bleeding spontaneously stops or to allow invasive maneuvers/surgery be performed to stop bleeding if indicated. The occurrence of a minor bleeding event does not per se indicate anticoagulation should be stopped or reversed; INR should be checked to adjust for possible overanticoagulation (7, 8) and, especially in case of therapeutic INR, to look for the presence of a remediable lesion as source of bleeding and take care of it.

## Reversal of VKAs

### Vitamin K

When the anticoagulant effect of VKAs needs neutralizing the important differences in the half-lives of these agents must be taken into account, requiring in turn that the big time differences needed to restore normal hemostasis after cessation of administration be calculated. The half-lives of VKAs are:

- 9 h for acenocoumarol,
- 6–42 h for warfarin and
- 90 h for phenprocoumon (9).

The time interval for complete restoration of haemostasis after administration is stopped may be estimated in

- 18–24 h for acenocoumarol,
- 60–80 h for warfarin and
- 8–10 days for phenprocoumon.

It is evident that simple cessation of therapeutic doses in case of major bleeding is not sufficient and other therapeutic measures are necessary. A first measure, though usually not enough on its own, is intravenous vitamin K administration (10).

A slow infusion of 5 to 10 mg of vitamin K, to be repeated after 12 h if necessary, leads to an effective reversal of anticoagulation within 8–16 h.

In cases of very serious or life-threatening bleeding an immediate correction of INR to normal values is mandatory and can be achieved by administering already active vitamin K-dependent pro-coagulant factors.

### Fresh frozen plasma

Fresh frozen plasma (FFP) is the natural source of factors II, VII, IX and X that are deficient due to the effect of VKAs, and infusion of blood group specific FFP is the most widely used measure to reverse anticoagulation (11). However, several factors limit the value of FFP as the best replacement treatment to reverse anticoagulation in case of major bleeding. First, large FFP volumes are needed to replace vitamin

K-dependent factors (the recommended FFP dose for warfarin reversal is at least 15 ml/kg body weight and therefore approximately 1000 ml for an adult weighing 70 kg) and this may lead to fluid overload and pulmonary oedema (12), especially in patients with compromised cardiovascular conditions. Furthermore, it has been shown that administration of the recommended dose of FFP is not enough to completely correct coumarin-induced coagulopathy, especially for persistently low factor IX levels (8). Finally, this treatment is difficult to administer quickly since the time needed to obtain and prepare the plasma (stored frozen at  $-20^{\circ}\text{C}$ ) is usually a cause of delay before transfusion.

### Prothrombin complex concentrates

A more efficient way of replacing missing clotting factors is to administer prothrombin complex concentrates (PCC) that can be given rapidly since there is no need for blood group matching or thawing, and is safe as regards transmission of blood-borne infectious diseases since prepared using viral inactivation methods (13). A number of studies have shown that a reverse of VKA-related anticoagulation is achieved more rapidly and INR corrections significantly better with PCC than FFP; for a review of the literature see Leissinger et al. (14). A dose of 30 U/kg is usually effective, and the following doses have been suggested: 25 U/kg for patients with an INR of 2.0–3.9, and 35 U/kg for an INR of  $> 4.0$ .

A recent update from the British Committee for Standards in Haematology recommends that PCCs should be administered in preference to FFP for reverse of VKA-related anticoagulation in patients with major bleeding (15). PCCs are available for clinical use in two main types, provided by various manufacturers:

- The 4-factor PCCs, that contain all the four pro-coagulant vitamin K-dependent factors and also the anticoagulant proteins C and S. These are considered more useful since they can rapidly replace all the deficient clotting factors. In a prospective study in VKA-treated patients presenting with major bleeding or requiring emergency surgical or urgent

invasive diagnostic intervention, administration of a PCC of this type resulted in satisfactory and sustained hemostasis in 98% of treated patients (16).

- The 3-factor PCCs contain little factor VII and are less effective for complete correction of INR levels (17).

Potential adverse effects of PCC administration regard mainly thrombotic events that have been reported after their transfusion in anticoagulated patients; this risk is, however, very small, especially in preparations containing antithrombin and heparin. Due to the potential risks, PCCs should be reserved for patients with major bleeding, especially those with intracranial hemorrhage in whom an immediate correction of coagulopathy is highly recommended (18).

## Thrombotic complications in non anticoagulated VTE patients

It has already been noted that if major bleeding occurs during anticoagulation the treatment should be stopped and anticoagulation reversed. However, this cannot be done without exposing patients to a risk of thrombotic complications. In patients treated for VTE this risk is not constant during the time following the occurrence of the index thrombotic event and is not the same for all patients.

One study showed a rate of recurrent VTE as high as 47% in patients with proximal DVT who were treated for only 10 days with adequate intravenous heparin therapy followed by three months of inadequate, low dose heparin (19). In another study, progression of thrombosis was found in 27% of patients with symptomatic DVT receiving only an anti-inflammatory drug and repeated venography after 30 days (20). It has been estimated that well performed anticoagulation with warfarin reduces the risk of recurrent VTE by about 80% (21), whereas thromboembolic complications can occur in 50% of cases during the first 3 months after onset of the thrombotic event if left untreated (22). However, the risk of thrombotic complications de-

clines rapidly in the first months after the acute episode (23).

In fact, if patients with acute VTE are left without anticoagulation the rate of thromboembolic complications reaches 40% during the first month, dropping to 10% during the second and third months (21).

## Vena cava filters

It is clear that if major bleeding (which is an absolute contraindication to anticoagulation) occurs in patients during the first month after acute proximal DVT or PE the risk of life-threatening or even fatal PE is too high to keep them without proper protection and a vena caval filter should be fitted. What to do if major bleeding occurs during the second or third months after onset of VTE, when the risk of recurrence has dropped sufficiently, is less clear and the decision should take account of the individual conditions of each patient. While in most patients vena cava interruption is not necessary, in some, such as those with chronic pulmonary heart disease, chronic thromboembolic pulmonary hypertension or minimal cardiopulmonary reserve, it may be an option to try and avoid PE events, even minor ones that could in any case be life threatening. Aggressive protection (filter implantation) may also be indicated in patients who have suffered a clinically important (hemodynamic) PE event, especially if idiopathic, and in whom anticoagulation should be stopped during the first months due to a major bleeding occurrence. It has been shown, in fact, that the risk of recurrence is higher in patients presenting with PE with the recurrent event often being another PE event, that may also be life-threatening (24).

The risk of adverse events after filter implantation is however not negligible and may include events related to filter insertion (e.g. haematoma, infections), or other complications such as migration, vena caval perforation or filter thrombosis (25). There is evidence suggesting that vena cava filters increase the risk of recurrent DVT, only partly reduce the risk of PE and do not affect mortality (26). When a caval filter is indicated for a temporary contraindication

to anticoagulation, such as a major bleed, a preferable option is to insert a retrievable filter and to remove it when anticoagulation can be restarted. However, in most cases these filters are not removed and it cannot be excluded that there may be more associated long-term complications than after permanent filter implantation. In general, whether in the presence of a filter or not, it is recommended to restart anticoagulation as soon as bleeding is no longer active though caution should be taken in managing anticoagulation if risk factors for bleeding are persistent.

## Major bleeding during long-term treatment period

An anticoagulant therapy for three months is recommended in patients with DVT and/or PE secondary to transient (and reversed) risk factors. In contrast, it is recommended that patients with an unprovoked VTE event should receive anticoagulation for no less than three months, after which they should be evaluated for the risk-benefit ratio of long-term therapy (3). Since in patients who receive long-term anticoagulant treatment the risk-benefit ratio of continuing such treatment should be reassessed at periodic intervals, the occurrence of major bleeding or clinically relevant non-major bleeding events may affect the evaluation of the risk-benefit ratio of extended anticoagulation. In this condition therefore anticoagulant treatment should not only be temporarily stopped but definitive withdrawal also considered. Long term anticoagulation is also recommended in patients with more than one unprovoked event due to their foreseen high risk of recurrence; in these patients a resumption of anticoagulation is always advisable when the major or clinically relevant non-major bleeding event is stopped.

## Anticoagulation restart after bleeding

The decision to restart anticoagulation after major or life-threatening bleeding should be taken on a case-by-case basis. The risk of thromboembolism during in-

terruption of anticoagulation should be weighed in single patients against the risk of recurrent bleeding and clinical risks associated with a possible recurrent event if anticoagulation is resumed. Many conditions should be taken into account:

- the actual site and
- the possible cause of bleeding,
- the severity of the event and
- the clinical impact of possible rebleeding.

For example, the clinical risks associated with intra-cerebral hemorrhage are higher than those associated with subdural bleeding, and in both cases the risk of recurrence is quite different depending on whether the index event was unprovoked or secondary to a transient cause, such as trauma. In most cases it is strongly advisable to reexamine the site of bleeding to ascertain whether bleeding is still ongoing and/or the state of the source of bleeding.

In a recent article (27) the authors distinguish three broad categories of major bleeds and propose different decisions on when to resume anticoagulation:

- Bleeds that are treatable (e. g. with surgery or invasive maneuvers) or self-limiting: In these cases anticoagulation may be resumed within one week of the initiation of treatment or after resolution of the bleeding.
- Bleedings that are not treatable but are expected to resolve over time (e. g., ischaemic bowel, intra-cerebral haemorrhagic stroke): VKAs may be resumed between two and four weeks after the bleed and if appropriate and timely investigations do not show evidence of ongoing or new bleeding.
- Bleeds that are untreatable and are unlikely to resolve spontaneously such as those associated with important impairment in haemostasis or those associated with cancer: In these cases the relative risks and benefits of resuming VKAs should be considered on a case-by-case basis and anticoagulation should only be resumed when the risk of thrombotic complications outweighs the risk associated with fresh bleeding.

In any case, it should be stressed that the decision to restart anticoagulation will depend on the patient's values and preferences with regards the relationship between the risk of a new bleeding and that of thrombotic complications (9).

### Minor bleeding

In general, stopping and reversing anticoagulation is not required in patients presenting with minor bleeds. The current level of anticoagulation should, however, be immediately checked and possible over-anticoagulation corrected with administration of small amounts of vitamin K (usually 2 mg given orally are sufficient to bring INR values within the therapeutic range).

What to do in cases of minor bleeding occurring when INR is within the therapeutic range depends on the clinician's judgment to which extent the patients are at the risk of complications and how long has elapsed from the index VTE event. Patients who are at high thromboembolic risk may be managed by lowering doses of warfarin to maintain INRs at the lower end of the therapeutic range, whereas anticoagulation can be temporarily stopped in those at low risk.

Indeed it needs to be borne in mind that VKA therapy can exacerbate bleeding.

Furthermore, in many cases of minor bleeds patients are likely to require invasive diagnostic procedures that can be associated with high haemorrhagic risk if performed during anticoagulation at therapeutic intensity (28). It has in fact been shown that short-term interruption of warfarin therapy is associated with a low risk of thromboembolism (29) and that isolated low INR values are rarely associated with thromboembolic complications (30). In cases where the bleeding source is not identified and persistent, the risks of bleeding if VKAs are resumed must be carefully weighed against thrombotic risk. Adjunctive measures, such as discontinuation of a concomitant antiplatelet therapy, can be adopted to minimize the risk of further bleeding.

## References

1. Palareti G, Cosmi B. Predicting the risk of recurrence of venous thromboembolism. *Curr Opin Hematol* 2004; 11: 192–197.
2. Kahn SR. Natural history of postthrombotic disease: Transition from acute to chronic disease. *J Vasc Surg* 2010; 52: 62S–64S.
3. Kearon C, Kahn SR, Agnelli G et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> ed). *Chest* 2008; 133: 454S–545S.
4. Kearon C. Indefinite anticoagulation after a first episode of unprovoked venous thromboembolism: yes. *J Thromb Haemost* 2007; 5: 2330–2335.
5. Baglin T. Unprovoked deep vein thrombosis should be treated with long-term anticoagulation – no. *J Thromb Haemost* 2007; 5: 2336–2339.
6. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.
7. Briz M, Talks K, Hanley J et al. Reversal of warfarin-induced over-anticoagulation with individualized dosing of oral vitamin K: a pilot study. *J Thromb Haemost* 2010; 8: 1123–1125.
8. Makris M, Greaves M, Phillips WS et al. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost* 1997; 77: 477–480.
9. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8<sup>th</sup> edition). *Chest* 2008; 133: 160S–198S.
10. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost* 2006; 4: 1853–1863.
11. Ozgonenel B, Omalley B, Krishen P, Eisenbrey AB. Warfarin reversal emerging as the major indication for fresh frozen plasma use at a tertiary care hospital. *Am J Hematol* 2007; 82: 1091–1094.
12. Lee SB, Manno EM, Layton KF, Wijidicks EFM. Progression of warfarin-associated intracerebral hemorrhage after INR normalization with FFP. *Neurology* 2006; 67: 1272–1274.
13. Lankiewicz MW, Hays J, Friedman KD et al. Urgent reversal of warfarin with prothrombin complex concentrate. *J Thromb Haemost* 2006; 4: 967–970.
14. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. *Am J Hematol* 2008; 83: 137–143.
15. Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (Warfarin): 3<sup>rd</sup> ed. – 2005 update. *Br J Haematol* 2006; 132: 277–285.
16. Pabinger I, Brenner B, Kalina U et al. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. *J Thromb Haemost* 2008; 6: 622–631.
17. Holland L, Warkentin TE, Refaai M et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supra-therapeutic international normalized ratio due to

- warfarin overdose. *Transfusion (Paris)* 2009; 49: 1171–1177.
18. Boullis NM, Bobek MP, Schmaier A, Hoff JT. Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery* 1999; 45: 1113–1118.
  19. Hull R, Delmore T, Genton E et al. Warfarin sodium versus low dose heparin in the long term treatment of venous thrombosis. *N Engl J Med* 1979; 301: 855–858.
  20. Nielsen HK, Husted SE, Krusell LR et al. Anticoagulant therapy in deep venous thrombosis – a randomized controlled study. *Thromb Res* 1994; 73: 215–226.
  21. Kearon C, Hirsh J. Current concepts: management of anticoagulation before and after elective surgery. *N Engl J Med* 1997; 336: 1506–1511.
  22. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003; 107: I22–I30.
  23. Coon WW, Willis PW 3<sup>rd</sup>. Recurrence of venous thromboembolism. *Surgery* 1973; 73: 823–827.
  24. Eichinger S, Weltermann A, Minar E et al. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. *Arch Intern Med* 2004; 164: 92–96.
  25. Imberti D, Prisco D. Retrievable vena cava filters: key considerations. *Thromb Res* 2008; 122: 442–449.
  26. Segal JB, Streiff MB, Hoffman LV et al. Management of venous thromboembolism: A systematic review for a practice guideline. *Ann Intern Med* 2007; 146: 211–222.
  27. Ageno W, Garcia D, Aguilar MI et al. Prevention and treatment of bleeding complications in patients receiving vitamin K antagonists, part 2: Treatment. *Am J Hematol* 2009; 84: 584–588.
  28. Hui AJ, Wong RM, Ching JY et al. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. *Gastrointest Endosc* 2004; 59: 44–48.
  29. Garcia DA, Regan S, Henault LE et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008; 168: 63–69.
  30. Clark NP, Witt DM, Delate T et al. Thromboembolic consequences of subtherapeutic anticoagulation in patients stabilized on warfarin therapy: The Low INR Study. *Pharmacotherapy* 2008; 28: 960–967.