PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

Cardiovascular Disease Educational and Research Trust (UK)
European Venous Forum
North American Thrombosis Forum
International Union of Angiology and
Union Internationale du Phlebologie

Periprocedural Management

Chapter 23

General Considerations

- **Periprocedural management of patients requiring temporary interruption of VKA (e.g. warfarin) due to an elective invasive procedure or elective surgery is a common clinical problem[1]**
  - In North America alone, an annual estimate of 1.3 million patients who are receiving antithrombotic therapy will be assessed for an elective surgical or invasive procedure[2]

1. Spyropoulos AC. J Thromb Thrombolysis 2010;29(2):192-8.
2. Kaatz S, et al. J Thromb Haemost 2010;8(5):884-90.

General Considerations

- **Bleeding and thrombotic risk assessment should be performed for patients undergoing a procedures to determine:**
  - If interruption of antithrombotic therapy is needed in the periprocedural period
  - If bridging anticoagulation is needed
- **Bridging anticoagulation**
  - Defined as the use of short-acting parenteral anticoagulants in the pre- and post-procedural period to maintain an anticoagulant effect during temporary interruption of VKA when the INR may be subtherapeutic

General Considerations

- **Impact of major bleeding in the periprocedural period may be associated with significant morbidity and a case-fatality rate of up to 9%[1]**
- **Postoperative bleeding delays the resumption of antithrombotic therapy, thereby placing patients at risk for thromboembolism[2]**

1. Linkins LA, et al. Ann Intern Med 2003;139(11):893-900.
2. Kovacs MJ, et al. Circulation 2004;110(12):1658-63.

General Considerations

- **Bleeding risk assessment involves considerations of patient- and procedure-related risk factors for bleeding**
  - History of prior bleeding, especially prior periprocedural bleeding, or the use of multiple antithrombotic drugs may place the patient at higher risk of bleeding
- **High bleeding risk procedures include:[1]**
  - Most major surgeries lasting >45 minutes
  - Vascular procedures
  - Major orthopedic procedures
  - Cardiothoracic procedures
  - Extensive cancer surgery
  - Prostate and bladder surgery

1. Douketis JD, et al. Chest 2008;133(6 Suppl):299S-339S.

General Considerations

- **Invasive procedures such as resection of colonic polyps, prostate, liver, or kidney biopsy, or pacemaker or defibrillator implantation may place the patient at increased risk of bleeding or significant pocket hematomas[1,2]**
- **Most surgeries lasting <45 minutes or minor invasive procedures including diagnostic gastrointestinal procedures, dermatological and dental procedures, and ophthalmologic procedures carry a low bleeding risk[3]**

1. Sorbi D, et al. Gastrointest Endosc 2000;51(6):690-6.
2. Wiegand UK, et al. Chest 2004;126(4):1177-86.
3. Spyropoulos AC, et al. Int Angiol 2008;27(4):333-43.

General Considerations

- **Thrombotic risk assessment is based on the three most common indications for VKA therapy**
  - Mechanical heart valve
  - Atrial fibrillation
  - VTE
- **Emerging data suggest an up to a 10-fold increased risk of arterial thromboembolism in the perioperative setting, especially among patients undergoing major surgery[1]**

1. Dunn AS, Turpie AG. Arch Intern Med 2003;163(8):901-8.

ACCP: Perioperative Thromboembolism[1]
Suggested Risk Stratification

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High: • >10%/year risk of ATE • or >10%/month risk of VTE	• Any mechanical mitral valve • Caged ball or tilting disc valve in mitral/aortic position • Recent (<6 month) stroke or TIA	• $CHADS_2$ score of 5 or 6 • Recent (<3 month) stroke or TIA • Rheumatic valvular heart disease	• Recent (<3 month) VTE • Severe thrombophilia • Deficiency of protein C, protein S or antithrombin • Antiphospholipid antibodies • Multiple thrombophilias
Moderate: • 4-10%/year risk of ATE • or 4-10%/month risk of VTE	• Bileaflet AVR *with* major risk factors for stroke	• $CHADS_2$ score of 3 or 4	• VTE within past 3–12 months • Recurrent VTE • Non-severe thrombophilia • Active cancer
Low: • <4%/year risk of ATE • or <2%/month risk of VTE	• Bileaflet AVR *without* major risk factors for stroke	• $CHADS_2$ score of 0–2 • (and no prior stroke or TIA)	• VTE more than 12 months ago

1. Douketis JD, et al. Chest 2008;133(6 Suppl):299S-339S.

General Considerations

- **Case-fatality of a major bleed is approximately 8-9%[1]**
  - Embolic stroke is associated with a case-fatality or permanent major neurologic defect approaching 70%[2]
- **Thrombosis of a heart valve can lead to fatality 15% of the time[3]**
- **For VTE, the case-fatality is approximately 5-9%[1]**
  - An INR >3.0 at the time of surgery may confer a higher risk for bleeding complications (OR 1.6; 95% CI: 0.4-4.0)[4]

1. Linkins LA, et al. Ann Intern Med 2003;139(11):893-900.
2. Tiede DJ, et al. Mayo Clin Proc 1998;73(7):665-80.
3. Longstreth WT, et al. Neurology 2001;56(3):368-75.
4. Torn M, Rosendaal FR. British Journal of Haematology 2003;123(4):676-82.

Periprocedural Management
Patients Undergoing Minor Procedures

- **Minor dental, dermatological, and ophthalmological procedures comprise ~20% of procedures of patients receiving VKA[1]**
- **Randomized trials and prospective cohort studies indicate that patients who continue VKA during dental extraction had similar rates of major and clinically significant non-major bleeding (<5%) and rare thromboembolic events (<1%), as did patients who discontinued VKA[2-4]**

1. Douketis JD, et al. Chest 2008;133(6 Suppl):299S-339S.
2. Zanon E, et al. Blood Coagul Fibrinolysis 2003;14(1):27-30.
3. Sacco R, et al. J Thromb Haemost 2006;4(3):688-9.
4. Evans IL, et al. Br J Oral Maxillofac Surg. 2002;40(3):248-52.

Periprocedural Management
Patients Undergoing Minor Procedures

- **Partial interruption of VKA 2-3 days prior to a dental procedure has also been associated with low bleed risk[1]**
- **Prospective cohort studies in patients undergoing dermatological and ophthalmological procedures were associated with a low incidence of major bleeding and support the notion that VKA can be continued around the time of certain minor procedures[2-4]**

1. White RH, et al. Ann Intern Med 1995;122(1):40-2.
2. Syed S, et al. J Am Acad Dermatol 2004;51(6):955-7.
3. Kallio H, et al. Br J Anaesth 2000;85(5):708-11.
4. Hirschman DR, et al. Nursing Forum 2006;41(1):30-7.

Periprocedural Management
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3. Kallio H, et al. Br J Anaesth 2000;85(5):708-11.
4. Hirschman DR, et al. Nursing Forum 2006;41(1):30-7.

Bridging Anticoagulation
Interruption of VKA

- **Basic principles**
  - Patients undergoing a high-bleeding risk procedure or surgery where there is intent to minimize the antithrombotic effect of VKA in the pre-procedural period, approximately 5 days of interruption of warfarin is needed, based on a half-life of approximately 36-42 hours[1]
  - Elderly patients or patients on a longer-lasting VKA such as the less widely-used phenprocoumon (with a half-life of 96-140 hours), longer periods of interruption may be necessary[2]

1. White RH, et al. Ann Intern Med 1995;122(1):40-2.
2. Hylek EM, et al. Ann Intern Med 2001;135(6):393-400.

Bridging Anticoagulation
Interruption of VKA

- **Basic principles**
  - There is a residual anticoagulant effect, as measured by anti- FXa ≥ 0.10 IU/ml, if therapeutic-dose LMWH is given within 12 hours of the start of the procedure[1]
  - Pre-operative administration of low-dose vitamin K orally (1-2.5 mg) in patients with an elevated INR (≥ 1.5) does not appear to be associated with resistance to re-anticoagulation after surgery[2]
  - Coagulation tests (aPTT, PT, and heparin anti-FXa level) are likely inadequate to measure the dual anticoagulant effects of VKA and UFH in the periprocedural period
    - Emerging tests (TG) may have improved sensitivity in detecting the global anticoagulant effects of both LMWH and VKA[3]

1. O'Donnell MJ, et al. Ann Intern Med 2007;146:184-7.
2. Woods K, et al. J Thromb Thrombolys 2007;in press.
3. Gerotziafas GT, et al. Thromb Haemost 2009;102(1):42-8.

Bridging Anticoagulation
Interruption of VKA

- **Basic principles**
  - Administration of antithrombotic therapy at close proximity to the procedure or at therapeutic versus prophylactic doses may increase bleeding risk
    - In high bleeding risk procedures, delaying resumption of bridging therapy (for 48-72 hours after the procedure), decreasing the dose of bridging therapy (i.e., prophylactic-dose), or avoiding post-procedure bridging anticoagulation may decrease the risk of bleeding[1]
  - No evidence non-therapeutic-dose bridging anticoagulation with UFH or LMWH is effective in preventing arterial thromboembolism[2]

1. Dunn AS, et al. Journal of Thrombosis & Haemostasis 2007;5(11):2211-8.
2. Bath PM, et al. Lancet 2001;358(9283):702-10.

Bridging Anticoagulation
Interruption of VKA

- **Basic principles**
  - Bridging therapy should be based on an explicit, evidence-based, and standardized protocol with careful consideration of patient and procedural risk factors for thrombosis and bleeding[1]
  - Substantial cost savings exist with the use of LMWH as bridging therapy due to facilitation of management in the outpatient setting compared with intravenous UFH used in-hospital[2]

1. Spyropoulos AC. Curr Hematol Rep 2005;4(5):405-13.
2. Spyropoulos AC, et al. Chest 2004;125(5):1642-50.

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- **Majority of MHV studies included therapeutic-dose LMWH regimens and none had control groups without bridging therapy[1-5]**
- **The pooled perioperative ATE event rate was low (~1%), with no reported episodes of MHV thrombosis, and the overall rate of major bleeding was ~3%**
- **A study of 172 patients with PHVs on chronic VKA needing temporary interruption found 1 arterial thromboembolic event and an overall adverse event rate of 5.5% using mostly outpatient-based treatment-dose LMWH as bridging therapy[2]**

1. Kovacs MJ, et al. Circulation 2004;110(12):1658-63.
2. Spyropoulos AC, et al. American Journal of Cardiology 2008;102(7):883-9.
3. Douketis JD, et al. Arch Intern Med 2004;164(12):1319-26.
4. Jaffer AK, et al. Am J Med;123(2):141-50.
5. Hammerstingl C, et al. Journal of Heart Valve Disease 2007;16(3):285-92.

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- **Recent cohort studies have assessed intermediate-dose LMWH as bridging therapy (i.e., 70 anti-Xa IU/kg twice-daily) with low thromboembolic and bleed rates[1]**
- **The incidence of thromboembolic events with older studies using IV UFH as bridging therapy found more variable arterial thromboembolic event rates[2]**
- **Mathematical modeling of a patient with a MHV not treated with a VKA in the periprocedural period is estimated at 0.046% per day or ~0.4% for 8 days**

1. Pengo V, et al. Circulation. Jun 9 2009;119(22):2920-2927.
2. Katholi RE, et al. Am Heart J. Aug 1978;96(2):163-165.

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- **There are prospective cohort studies in which mostly therapeutic-dose LMWH bridging anticoagulation has been assessed in patients with AF[1-5]**
  - The pooled risk of perioperative arterial thromboembolism was ~1%
- **Recent studies have included intermediate-dose LMWH bridging regimens with good outcomes in patient populations that have included patients with atrial fibrillation[6-8]**

1. Kovacs MJ, et al. Circulation 2004;110(12):1658-63.
2. Dunn AS, et al. J Thromb & Haemost 2007;5(11):2211-8.
3. Douketis JD, et al. Arch Intern Med 2004;164(12):1319-26.
4. Jaffer AK, et al. Am J Med;123(2):141-50.
5. Spyropoulos AC, et al. J Thromb & Haemost 2006;4(6):1246-52.
6. Pengo V, et al. Circulation. Jun 9 2009;119(22):2920-2927.
7. Malato A, et al. Haematologica 2006;91:10.
8. Hammerstingl C, et al. Thrombosis & Haemostasis 2009;101(6):1085-90.

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- **There is a need for placebo-controlled studies in VKA-treated patients with MHV or AF indications**
- **The PERIOP-2 (*clinicaltrials.gov/NCT00432796)* and BRIDGE (clinicaltrials.gov/NCT00786474) studies have been initiated and are actively enrolling VKA-treated patients who require elective surgery and will be randomly allocated to bridging or no bridging regimens**

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- **There are multiple prospective cohort studies that have evaluated bridging anticoagulation with therapeutic-, intermediate-, and low-dose regimens of various LMWHs in patients with VTE[1-5]**
- **The pooled risk for recurrent symptomatic VTE was low (<1%)**
- **These studies did not include control groups**

1. Dunn AS, et al. J Thromb & Haemost 2007;5(11):2211-8.
2. Douketis JD, et al. Arch Intern Med 2004;164(12):1319-26.
3. Spyropoulos AC, et al. J Thromb & Haemost 2006;4(6):1246-52.
4. Malato A, et al. Haematologica 2006;91:10.
5. Jaffer AK, et al. J Thromb Thrombolysis 2005;20(1):11-6.

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- There are no clinical data available to optimize periprocedural administration of the novel small molecule antithrombotic agents, dabigatran and rivaroxaban
- The pharmacological properties of these agents with their relatively short half-lives have the potential to eliminate the need for bridging therapy
- Perioperative guidelines on the use of these agents based on their pharmacokinetic and pharmacodynamic properties have been suggested[1-3]

1. Spyropoulos AC. Curr Opin Hematol 2010;17(5):444-9.
2. van Ryn J, et al. Thromb Haemost 2010;103(6):1116-27.
3. Douketis JD. Curr Pharm Des 2010;16(31):3436-41.

Bridging Anticoagulation
Patients with a MHV, AF or VTE Receiving VKA

- **Dabigatran can be discontinued 24 hours before a low bleed risk procedure and approximately 2-4 days before a high-bleed risk procedure in patients with a CrCl > 50 mL/min[1]**
  - In patients with moderate renal insufficiency (CrCl 30-50 mL/min), dabigatran should be discontinued at least 2 days before a low bleed risk procedure and 4 days before a high bleed risk procedure
- **Rivaroxaban can be stopped approximately 24 hours before a procedure[2]**
- **Resumption of therapy for both agents can occur within 24 hours after low bleed risk procedures and ~48-72 hours after high bleed risk procedures[2]**

1. van Ryn J, et al. Thromb Haemost 2010;103(6):1116-27.
2. Spyropoulos AC. Curr Opin Hematol 2010;17(5):444-9.

Recommendations
Periprocedural Management

- **In patients undergoing minor dermatological and ophthalmological procedures (specifically cataract extraction) and are receiving VKA, continuing VKA around the time of procedure should be considered**
  - Level of evidence: Low
- **For dental procedures, consider co-administration of an oral prohemostatic agent (tranexamic acid) while continuing VKAs**
  - Level of evidence: Moderate
- **In patients undergoing dental procedures, stopping VKA 2-3 days before the procedure is an option**
  - Level of evidence: Low

Recommendations
Periprocedural Management

- **In patients undergoing a high-bleeding risk procedure or surgery, discontinuation of VKA (warfarin) approximately 5 days prior to allow adequate time for the INR to normalize is indicated**
  - Level of evidence: Moderate
- **In patients who are receiving therapeutic-dose LMWH as bridging therapy, the last dose should be administered 24 hours before the procedure or surgery at approximately half the total daily dose**
  - Level of evidence: Low

Recommendations
Periprocedural Management

- **For intravenous UFH, we suggest stopping approximately 4 hours prior to the procedure or surgery**
  - Level of evidence: Low
- **In patients whose INR is still elevated 1-2 days before the procedure (INR ≥ 1.5), consider administering low-dose (1-2.5 mg) oral vitamin K to normalize the INR**
  - Level of evidence: Low
- **In patients undergoing a minor invasive or surgical procedure, bridging anticoagulation with LMWH should be resumed within 24 hours after the procedure if there is adequate hemostasis**
  - Level of evidence: Low

Recommendations
Periprocedural Management

- **In patients undergoing major surgery or high-bleeding risk procedures, consider one of three options: i) delay LMWH approximately 48-72 hours after surgery until hemostasis is achieved; ii) administer low-dose LMWH (usually within 24 hrs after a procedure); or iii) avoid post-procedural bridging therapy altogether**
  - Level of evidence: Low
- **LMWH should be used in the outpatient setting as bridging therapy over in-hospital UFH to avoid hospitalization**
  - Level of evidence: Low

Recommendations
Periprocedural Management

- **In patients with MHV and AF at high arterial thromboembolic risk or patients with VTE at high VTE risk, bridging therapy with LMWH or UFH in the periprocedural period during temporary interruption of VKA should be considered**
  - Level of evidence: Low
- **In patients at moderate arterial thromboembolic or VTE risk, assessment of individual patient- and surgery related factors should be considered over a standardized approach on whether to use bridging therapy**
  - Level of evidence: Low

Recommendations
Periprocedural Management

- **In patients at low arterial thromboembolic or VTE risk, no bridging over bridging therapy should be considered**
  - Level of evidence: Low
- **In all patients undergoing major procedures or surgeries for which there are international guideline recommendations for VTE prevention in the post-operative period, the use of the appropriate prophylactic agent should be used during re-initiation of VKA if postoperative heparin bridging is not used**
  - Level of evidence: Moderate