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**THROMBOSIS
WATCH**

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Editors:

Matthew T. Rondina, MD

Sara Vazquez, PharmD

Andrew Freeman, MD

Nikki M. Milne, PharmD Candidate

Adam Davies, PharmD Candidate



University Health Care

Thrombosis Service

REVIEW TOPIC: ANTITHROMBOTIC THERAPY FOR VENOUS THROMBOEMBOLIC DISEASE: AMERICAN COLLEGE OF CHEST PHYSICIANS EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES (8TH EDITION)

HIGHLIGHTS FROM THE NEW 2008 GUIDELINES

Long-Term Treatment of Acute Deep Vein Thrombosis/Pulmonary Embolism

Long-term treatment is defined as the treatment that continues after the initial therapy (UFH, LMWH, fondaparinux) has been completed. Two major goals are associated with long-term therapy. First is completion of treatment for the acute venous thromboembolism (VTE), usually the first 3 months of treatment. Second is the prevention of recurrent VTE, which follows the first 3 months of treatment.

Duration of Therapy

- ◆ Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) secondary to a reversible risk factor should be treated for 3 months with a Vitamin K antagonist (VKA).
- ◆ Unprovoked DVT/PE should be treated for at least 3 months with a VKA after which patients should be evaluated for long-term therapy. (Patients should receive treatment until the benefits are clearly outweighed by the risks of treatment).
Previously in 2004: Duration of therapy should be at least 6 to 12 months.
- ◆ In patients with unprovoked proximal DVT/PE, low risk of bleeding, and where good anticoagulation monitoring is possible, long-term treatment is recommended.
Previously in 2004: "We suggest that patients with first-episode idiopathic DVT be considered for indefinite anticoagulation therapy."
- ◆ Patients with second episode of unprovoked DVT/PE should receive long-term treatment.
- ◆ First unprovoked distal DVT should be sufficiently treated with 3 months of therapy.
(New for 2008)
- ◆ Patients with DVT and cancer should receive treatment for 3 to 6 months with LMWH and then treated indefinitely or until cancer resolves with a VKA or LMWH.
- ◆ Long-term anticoagulant therapy recipients should be periodically reassessed for risk-to-benefit ratio.
(New for 2008)

Intensity of Therapy

- ◆ DVT/PE patients on a VKA should be maintained with an INR of 2.5 (2.0 – 3.0) for the entire treatment duration.
- ◆ Low intensity therapy (INR range 1.5 to 1.9) with less frequent monitoring can be used in patients who have: 1) unprovoked DVT/PE, 2) been treated for 3 months with conventional-intensity therapy, and 3) would otherwise stop treatment.
Previously in 2004: "We recommend against low-intensity therapy (INR range, 1.5-1.9) compared to INR range of 2.0-3.0."
- ◆ High intensity therapy (INR range 3.1 to 4.0) should not be used.



WHAT'S NEW IN THE LITERATURE?

JOURNALS REVIEWED: AMERICAN JOURNAL OF MEDICINE, ANNALS OF INTERNAL MEDICINE, ARCHIVES OF INTERNAL MEDICINE, CHEST, JOURNAL OF THROMBOSIS AND HAEMOSTASIS, PHARMACOTHERAPY.

1. *Pulmonary Embolism Incidence is Increasing with Use of Spiral Computed Tomography.* DeMonaco NA, Dang Q, Kapoor WN, et al. *Am J Med.* 2008; 121:611-617.

This retrospective analysis of Pennsylvania hospital discharge data showed that the rising use of spiral CT has increased the incidence of pulmonary embolism (PE). PE diagnosis increased 0.004% per year ($p < 0.001$), and deaths from pulmonary embolism decreased from 12.8% to 11.1% ($p < 0.001$) from 1997 to 2001. The increased use of spiral CT is thought to help provide an earlier diagnosis leading to lower severity of pulmonary embolism and decreased mortality.

2. *Comparison Between Idiopathic Deep Vein Thrombosis of the Upper and Lower Extremity Regarding Risk Factors and Recurrence.* Lechner D, Weltermann A, Eischer L, et al. *J Thromb Haemost* 2008; 6:1269-74.

This prospective study of 50 patients with upper extremity deep vein thrombosis (UEDVT) and 841 patients with lower extremity deep vein thrombosis (LEDVT) investigated the difference in risk factors and recurrence between the two groups from 1992 and 2006. The study found that patients with UEDVT were younger ($p < 0.001$), had lower body weight ($p < 0.001$), had less frequent family history of VTE ($p = 0.06$), had lower incidence of factor V Leiden ($p = 0.009$), and less often had concomitant PE ($p = 0.001$). Recurrence of VTE occurred in two patients with UEDVT (4%) and 129 patients with LEDVT (15%), two of which were fatal. The likelihood of recurrence within 5 years was 2% with UEDVT compared to 19% with LEDVT.

3. *A Spontaneous Prothrombotic Disorder Resembling Heparin-Induced Thrombocytopenia.* Warkentin TE, Makris M, Jay RM, et al. *Am J Med.* 2008; 121:632-636.

Over 18 years, the investigators observed three patients with spontaneous heparin-induced thrombocytopenia (HIT) (positive test results by serotonin-release assay, and two enzyme immunoassays) in the absence of preceding heparin therapy. All three patients had a preceding infection or inflammation. Two patients presented with thrombocytopenia and thrombosis: one died and the other had a stroke and a limb amputation. The third patient did not present with thrombocytopenia but later had an anaphylactic reaction after receiving 2 injections of LMWH. This study suggests that a rare transient prothrombotic disorder similar to HIT can occur.

4. *Prevention of Venous Thromboembolism in Neurosurgery: A Metaanalysis.* Collen FJ, Jackson JF, Shorr AF, et al. *Chest.* 2008; 134:237-249.

This metaanalysis involved 30 studies published between 1960 and 2007 with a total of 7,779 patients who were undergoing neurosurgical procedures. Prophylaxis with LMWH and intermittent compression devices (ICDs) was effective in decreasing the risk of deep vein thrombosis after neurosurgical procedures (LMWH: RR 0.60, ICDs: RR 0.41). The study showed no statistical difference between LMWH and nonpharmacological methods in the rate of intracranial hemorrhage (LMWH: RR, 1.97), although there was a trend toward a higher rate of intracranial hemorrhage in heparin preparations. More studies are needed in this subset of patients, and therapy should be based on individual risks and benefits.

5. *Overweight, Obesity, and the Risk of Recurrent Venous Thromboembolism.* Eichinger S, Hron G, Bialonczyk C, et al. *Arch Intern Med.* 2008; 168:1678-1683.

This prospective study of 1107 patients with a first venous thromboembolism (VTE) looked at VTE recurrence in relation to body mass index (BMI). In a mean follow-up of 46 months, 168 patients experienced recurrent VTE. The probability of recurrence was 9.3% in normal weight subjects ($BMI < 25$), 16.7% in overweight subjects ($BMI = 25-30$), and 17.5% in obese subjects ($BMI > 30$). The hazard ratio for VTE recurrence in overweight subjects was 1.3 ($p = 0.20$), and 1.6 in obese subjects ($p = 0.02$) compared to normal weight subjects. This study provides more data for obesity as a risk factor for recurrent VTE.



6. *Low-Molecular-Weight Heparin versus Compression Stockings for Thromboprophylaxis after Knee Arthroscopy.* Camporese G, Bernardi E, Prandoni P, et al. *Ann Intern Med.* 2008; 149:73-82.

This randomized, single-blind, controlled trial of 1761 patients undergoing knee arthroscopy assessed the use of LMWH (nadroparin) and compression stockings (CS) 30-40 mm Hg at the ankle for thromboprophylaxis. The 3-month incidence of VTE was 3.2% in the CS group, 0.9% in the 7-day LMWH group, and 0.9% in the 14-day LMWH group ($p=0.005$). Bleeding incidence was 0.3% in the CS group, 0.9% in the 7-day LMWH group, and 0.5% in the 14-day LMWH group. The 14-day LMWH group was stopped early due to lack of benefit over the 7-day group. The authors of this study recommend that all patients undergoing knee arthroscopy should receive a 7-day regimen of LMWH.

7. *Catheter-Directed Embolectomy, Fragmentation, and Thrombolysis for the Treatment of Massive Pulmonary Embolism After Failure of Systemic Thrombolysis.* Kuo WT, van deen Bosch MAAJ, Hofmann LV, et al. *Chest.* 2008; 134:250-254.

This retrospective review observed 70 patients with suspected acute PE who were referred for pulmonary angiography or intervention. Twelve patients were referred to catheter-directed intervention (CDI), and seven of those twelve were referred because of failure with systemic thrombolysis. Post-CDI angiography showed improved pulmonary perfusion in all patients (as measured by the mean Miller index) from 0.88 to 0.47 ($p<0.01$). Hemodynamic improvement was seen in 10 of 12 patients post-CDI. Two patients who did not hemodynamically improve died of cardiac arrest. CDI may improve hemodynamic stability in patients with massive PE and could be recommended in patients who fail systemic thrombolysis.

8. *Testing for Inherited Thrombophilia Does Not Reduce the Recurrence of Venous Thrombosis.* Coppens M, Reijnders JH, Middeldorp S, et al. *J Thromb Haemost.* 2008; 6:1474-7.

This case-control study analyzed subjects from the Multiple Environmental and Genetic Assessment of risk factor for venous thrombosis (MEGA) study. The authors selected 197 patients with thrombosis recurrence and compared them to 324 control subjects. The investigators found that thrombophilia testing had been performed in 35% of cases and 30% of controls. The odds ratio for venous thromboembolism recurrence was 1.2 (CI=0.9-1.8) for those who underwent thrombophilia testing. These results suggest that thrombophilia testing does not reduce the incidence of recurrent VTE.

9. *Thromboembolic Consequences of Subtherapeutic Anticoagulation in Patients Stabilized on Warfarin Therapy: The Low INR Study.* Clark NP, Witt DM, Delate T, et al. *Pharmacotherapy.* 2008; 28:960-967.

This retrospective 90-day analysis included 2597 patients, 1080 with low INR (one INR value 0.5 or more units below their therapeutic range) and 1517 with therapeutic INR (no INR values below 0.2 or more units below their therapeutic range). Five thromboembolic events occurred: 4 in the low INR group and 1 in the therapeutic INR group ($p=0.214$). There was no difference in bleeding between the two groups. This suggests that patients who have a single subtherapeutic INR have a similar risk of thrombosis to those who maintained a therapeutic INR.

10. *Combined Clot Fragmentation and Aspiration in Patients with Acute Pulmonary Embolism.* Eid-Lidt G, Gaspar J, Sandoval J, et al. *Chest.* 2008; 134:54-60.

This study included 18 patients referred to the cardiac catheterization laboratory with a massive PE and right ventricular dysfunction (RVD). All 18 patients underwent clot fragmentation and 13 of the 18 also underwent thrombus aspiration. After catheterization investigators observed a significant increase of systolic blood pressure ($p=0.001$) and oxygen saturation ($p=0.001$), and a decrease in the shock index ($p=0.001$). The in-hospital major complications rate was 11.1% and includes one death from refractory shock, and one patient with intracerebral hemorrhage. No cardiovascular deaths or recurrent PE occurred, however the study was not designed to analyze this. These results suggest that clot fragmentation with or without aspiration can be a practical alternative treatment for patients with a massive PE and RVD.



UNIVERSITY HEALTHCARE THROMBOSIS SERVICE NEWS AND EVENTS:

General:

- ◆ As of Oct 27th we will have “Rapid Response” DVT Treatment team which will respond in real time to the vascular lab to facilitate safe outpatient management of DVT when appropriate.
- ◆ The 2008 American College of Chest Physicians Antithrombotic Guidelines are available in the June Supplement to Chest. You may access them at the following website: www.chestjournal.org.
- ◆ The Intermountain Medical Center in Murray is hosting their 2008 Department of Medicine Annual Update and Clinical Learning Day on Friday, October 24 through Saturday, October 25. Topics in the area of Venous Thromboembolism and Antithrombotic Therapy will be covered. Our very own Dr. Robert Pendleton and Dr. Matthew Rondina will be speaking at this event. For more information please visit www.intermountainhealthcare.org/cme/deptmedcld2008.

Research:

- ◆ We have been selected as a site for the BRIDGE trial, a landmark placebo controlled peri-procedural anticoagulation management study for patients with atrial fibrillation. Drs. Vinik and Pendleton will be co-Principal investigators and Dr. Andrew Freeman and Vicky Digregorio will be co-investigators.

Education:

- ◆ Our next Journal Club will be held on January 21, 2009. The topic of discussion will be “Tools and Tricks for Optimizing the Management of VKAs.” If you are interested in participating please contact Sharla Watts at 801-581-7818 or via email at sharla.watts@hsc.utah.edu.



QUESTIONS

(Answers Found at Bottom)

1. The appropriate treatment duration for a patient with an unprovoked DVT/PE according to the 2008 Chest guidelines is:
 - a) 6-12 months.
 - b) no more than 6 months.
 - c) 3 months then re-evaluate.
 - d) indefinite.

2. Thrombophilia testing reduces the recurrence of venous thromboembolism.
 - a) True.
 - b) False.

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Answers: 1. c, 2. b



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