Review

Antithrombotic Therapy for AF and VTE:

ACCP Treatment Guidelines

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The American College of Chest Physicians (ACCP) has recently published comprehensive guidelines on the use of antithrombotic therapy for the management of atrial fibrillation (AF) and venous thromboembolism (VTE), the two most common indications for anticoagulant therapy.[1-3]

AF

AF is an important risk factor for ischemic stroke and affects approximately two million adults in North America with a prevalence of about 7% in patients > 80 years old.[4]

Antithrombotic therapy for AF[1]

Current recommendations for antithrombotic therapy in patients with AF are as follows:

- Greater than 65 years of age and at least one major stroke risk factor (*i.e.*, prior stroke or transient ischemic attack, left ventricular dysfunction, hypertension, diabetes, or age > 75 years)**:** warfarin, administered to achieve an international normalized ratio (INR) range of 2.0 to 3.0 (Grade 1A)
- Between the ages of 65 years to 75 years and no stroke risk factors: warfarin administered to achieve an INR range of 2.0 to 3.0 (Grade 1A), or 81 mg q.d. to 325 mg q.d. of acetylsalicylic acid (ASA) (Grade 1A)
- Patients < 65 years and no stroke risk factors: 81 mg q.d. to 325 mg q.d. of ASA (Grade 1B)

Patients with chronic atrial flutter should receive antithrombotic therapy as though they have AF, since most of these patients have intermittent AF or are destined to develop chronic AF.

Lynne's case

Lynne, 30, presents at 36 weeks of gestation with swelling and pain in her left leg. She is diagnosed with deep vein thrombosis (DVT) of the left leg. Anticoagulation therapy, with subcutaneous low-molecular weight heparin (LMWH) b.i.d. is started and the insertion of a temporary vena cava filter is planned given the proximity of the diagnosis of DVT to the delivery date and the need to interrupt anticoagulant therapy in the peripartum period.

At 40 weeks of gestation, Lynne has a cesarean section. On the day before the delivery, LMWH is discontinued and an inferior vena cava filter is inserted. The delivery is uneventful. LMWH is resumed two days after surgery when hemostasis is secured. The following day, the inferior vena cava filter is removed and LMWH is continued. Lynne is started on warfarin, given to achieve a therapeutic international normalized ratio (INR) of 2.0 to 3.0; LMWH is stopped when the INR is therapeutic.

Lynne continues taking warfarin for three months, during which time she is safe to breastfeed.

For a discussion on DVT in pregnancy, turn to page 75.

Case discussion cont'd...

Discussion

Pregnancy and the peripartum period is associated with a five-fold higher risk for DVT compared to the risk in a non-pregnant woman:

- Over 90% of DVT that occurs during pregnancy is in the left leg, likely because the right iliac artery compresses the left iliac vein, reducing venous flow and, is likely exacerbated by the compressive effects of the overlying gravid uterus
- The initial treatment of DVT in pregnant women is heparin (unfractionated or LMWH), which does not cross the placenta. Warfarin therapy during pregnancy is problematic because of teratogenic effects, especially if given during the first trimester
- The use of a temporary inferior vena cava filter is a novel approach to prevent life-threatening pulmonary embolism in patients who temporarily cannot receive anticoagulant therapy because of bleeding or, as in this case, need surgery
- The duration of anticoagulant therapy for patients with pregnancy-associated DVT is three months, as with other episodes of DVT occurring in association with a transient risk factor

What to avoid?

Sub-therapeutic warfarin anticoagulation (INR < 2.0), should be avoided as it is associated with a sharp increase in the risk for stroke.[4]

New treatment approaches

A recent large randomized trial compared treatment with warfarin (INR 2.0 to 3.0) to treatment with a combination of 81 mg q.d. of ASA and 75 mg q.d. of clopidogrel.[5] This study found that combined ASA and clopidogrel were associated with a higher incidence of stroke and other cardiovascular events compared to warfarin (5.6% vs. 3.9%; relative risk = 1.45, p = 0.0002). Surprisingly, combined ASA and clopidogrel were not associated with a higher rate of major bleeding (2.4% vs. 2.2%; relative risk = 1.02; p = 0.67).

Alternative treatments to warfarin that are currently being investigated include direct thrombin inhibitors and oral anti-factor Xa inhibitors.

Preventing VTE

VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the most common preventable cause of in-hospital death. The ACCP recommends DVT prophylaxis with low-dose unfractionated heparin (UFH) or low-dose low-molecular weight heparin (LMWH) in a broad spectrum of patients. Recent research has focused on medical patients and patients who have had orthopedic surgery.

AF is an important independent risk factor for ischemic stroke and affects approximately two million adults in North America.

Medical patients

Current recommendations for DVT prevention in medical patients are as follows:

- Patients at moderate risk for VTE: low-dose UFH (*i.e.*, 5000 IU b.i.d. or t.i.d.) or low-dose LMWH (*i.e.*, 40 mg q.d. of enoxaparin, or 5000 IU q.d. of dalteparin) (Grade 1A)
- Patients at high risk for VTE (*i.e.*, prior VTE, lower limb paralysis, prolonged immobility): low-dose LMWH (Grade 1A)

- ICU patients at moderate risk for VTE: UFH or LMWH (Grade 1A)
- ICU patients at high-risk for VTE: LMWH (Grade 1A)
- Airline travel > 6 hours: compression stockings for low-to-moderate risk patients (Grade 1C) and compression stockings, or one dose of LMWH for high-risk patients (Grade 2B/2C)

Sub-therapeutic warfarin anticoagulation (INR < 2.0), should be avoided as it is associated with a sharp increase in the risk for stroke.

Orthopedic surgery

The following are the current recommendations for DVT prevention after orthopedic surgery:

- Hip fracture repair: 2.5 mg q.d. of fondaparinux (Grade 1A)
- Knee replacement: LMWH (*i.e.*, 40 mg q.d. of enoxaparin, or 5000 IU q.d. of dalteparin, or 4500 IU of tinzaparin), or warfarin (INR range 2.0 to 3.0), or fondaparinux (Grade 1A)
- Hip replacement: LMWH, or warfarin, or fondaparinux (Grade 1A)

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- Duration of prophylaxis after knee or hip replacement: at least seven days to 10 days with LMWH, warfarin or fondaparinux (Grade 1A)
- Duration of prophylaxis after hip fracture repair: 30 days with fondaparinux (Grade 1A)
- Duration of DVT prophylaxis after hip replacement (alternative management): 30 days with LMWH or warfarin (Grade 1A)

What to avoid?

After orthopedic surgery, avoid ASA as the only method of DVT prophylaxis in any patient (Grade 1A); avoid venous ultrasound screening for DVT in asymptomatic patients (Grade 1A).

Treating VTE

Initiating anticoagulant therapy

Current recommendations for the initial treatment of patients with DVT or PE include:

- Subcutaneous (SC) LMWH or SC/intravenous UFH as a short-acting anticoagulant (Grade 1A)
- Starting warfarin on the first day of treatment, given to achieve an INR range of 2.0 to 3.0 (Grade 1A)
- Administer LMWH therapy q.d. or b.i.d. for five days to 10 days (Grade 1A)
- Compression stockings for lower limb DVT (Grade 1A)
- Thrombolytic therapy for patients with massive PE that is associated with hemodynamic instability and/or respiratory failure, or massive DVT that is associated with limb ischemia (Grade 2B)

Duration of oral anticoagulant therapy

The duration of oral anticoagulant therapy, typically with warfarin (INR range 2.0 to 3.0), is based primarily on the etiology of the episode as outlined below:[3]

- VTE occurring in association with a transient risk factor (*i.e.*, surgery, trauma, or immobility within past three months): three months of warfarin
- VTE occurring in association with active cancer (treated within the last six months or palliative): three months to six months of LMWH (warfarin as secondary alternative)
- Unprovoked (idiopathic) VTE: at least six months of warfarin
- Unprovoked (idiopathic) VTE and prothrombotic risk factors: six months to 12 months of warfarin
- Two or more episodes of VTE: long-term (> 12 months) warfarin

What to avoid?

Avoid the following when using anticoagulant therapy:

- Routine anti-factor Xa testing to monitor the anticoagulant effect of LMWH; anti-factor Xa testing can be considered in special populations, such as those with renal insufficiency
- Thrombolytic therapy in patients with non-massive DVT or PE
- Prophylactic placement of an inferior vena cava filter in patients with DVT

New treatment approaches

A recent randomized trial compared treatment of SC LMWH and SC UFH with the latter administered in a fixed, weight-based dose of 250 IU/kg b.i.d. and without laboratory monitoring.[6]

Take-home message

- Warfarin therapy (INR range 2.0 to 3.0) remains the treatment-of-choice for AF, although alternatives (direct thrombin inhibitors, oral anti-factor Xa inhibitors) are being investigated in clinical trials
- The importance of VTE prevention after orthopedic surgery continues with increasing focus on VTE prevention in medical patients
- More options are available for the acute treatment of VTE, including unmonitored subcutaneous unfractionated heparin; new treatments, such as direct thrombin inhibitors and oral anti-factor Xa inhibitors, are under investigation

The study showed that both treatment approaches had comparable efficacy and safety, with no significant difference between UFH and LMWH for recurrent VTE (3.8% vs. 3.4%), or major bleeding (1.1% vs. 1.4%). Dx

References

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