Improving Quality: Anticoagulation Therapy

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Scope of the Problem

- Adverse Drug Events (ADEs)
  - ✓ Heparin and warfarin constitute 2 of the top 3 medications requiring ER visits due to complications
  - ✓ Anticoagulants are frequently cited in medical malpractice litigation

Wu KW, Pantaleo N. Am J Health-Syst Pharm 60(3):253-259, 2003

Scope of the Problem

- Adverse Drug Events (ADEs)
  - ✓ 1.5 million preventable ADEs in United States annually
  - ✓ Anticoagulants account for 4% of preventable ADEs and 10% of potential ADEs.

Committee on Identifying and Preventing Medication Errors. Aspden P, Wolcott J, Bootman JL, Cronenwett LR, Editors. *Preventing Medication Errors: Quality Chasm Series*. Washington, DC: National Academies Press; July 2006.

Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: Implications for prevention. ADE Prevention Study Group. *JAMA*. 1995;274:29-34.

Scope of the Problem

- Anticoagulation remains underused
  - ✓ Despite 29 studies showing efficacy of anticoagulation for stroke prevention in patients with Atrial Fibrillation:
  - ✓ In study of 12 stroke centers from 2003-2007,
  - ✓ Less than 10% of patients were therapeutically anticoagulated
  - ✓ 30% not on any anticoagulation therapy
  - ✓ 61% not on warfarin; of those treated, 29% subtherapeutic
  - ✓ Result: 597 pts c/ strokes; 60% disabled, 20% died

Gladstone, DJ, et al. Publication pending, Stroke 2009

Scope of the Problem

- Anticoagulation remains underused
  - ✓ HCFA/CMS data: 40,000 strokes/ $600,000,000 annually could be prevented by proper use
  - ✓ 1-2 million patients treated; 4-6 million patients have indications for treatment
  - ✓ Less than half of pts on treatment are in therapeutic range

Scope of the Problem

- Need for improved anticoagulation management widely recognized
  - ✓ Examples from the Internet:
    - (google mail banner)- "www._____.com - Our Experienced Lawyers Will Review Your Heparin Case For Free".
    - (another site)- "_____ assists attorneys evaluating cases involving anticoagulant therapy by considering the answers to these top ten questions and others applicable to the case:

1. Was the patient an appropriate candidate for anticoagulation?
2. Did the patient comply with outpatient blood tests needed to monitor response to the anticoagulants?

Scope of the Problem

- Need for improved anticoagulation management widely recognized:
  - ✓ Centers for Medicare
  - ✓ AHRQ
  - ✓ American College of Chest Physicians
  - ✓ Joint Commission
  - ✓ Leapfrog Coalition
  - ✓ Third party providers

Scope of the Problem

3. Were standardized protocols used to order anticoagulation?
4. How often were clotting times tested?
5. Were abnormally elevated clotting times acted upon with dosage adjustments?
6. Were there any signs of bleeding while the patient was on anticoagulation?
7. How quickly did the healthcare team respond to bleeding?
8. Did the nurses give Heparin or Coumadin as ordered?
9. Is there evidence that hemorrhage was the cause of the patient's death, or was some other cause more likely?
10. What type of medical expert is most appropriate to review the case?"

Joint Commission Requirements

- 2008 - National Patient Safety Goal 3E
  - ✓ Reduce the likelihood of patient harm associated with the use of anticoagulation therapy.
    - Full compliance required by all accredited systems as of 1/1/2009.
    - (Reference: OSUMC Grand Rounds, 11/13/08- "Anticoagulation Therapy and the Joint Commission")

DVT/PE - Prophylaxis

- Current ACCP guidelines - 8th Edition
  - ✓ Address what to do
  - ✓ When to do it
  - ✓ What to use
  - ✓ What not to use

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

Case #1

- 68 yo female admitted for left knee replacement
  - ✓ Surgery successful; on post-op day 15, pt found dead at home
  - ✓ Post mortem exam: cause of death massive pulmonary embolus
  - ✓ What may have happened? Was anything in this situation preventable?

DVT/PE - Prophylaxis

- What to use – Low Molecular Weight Heparins (LMWH)
  - ✓ Enoxaparin – 30mg SubQ twice daily, or 40mg SubQ daily
  - ✓ Dalteparin – 2500-5000 int units SubQ daily
  - ✓ Tinzaparin –not approved for VTE prophylaxis

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What to use – Fondaparinux
- Parenteral Factor Xa inhibitor
  - ✓Indicated for:
  - ✓DVT/PE
  - ✓VTE prophylaxis

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What to use – Low dose unfractionated heparin (LDUH or UFH)
  - ✓Dosing- 5,000 units SubQ bid or tid
  - ✓Compared to LMWH, LDUH is associated with increased risk of heparin induced thrombocytopenia

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What to use – Fondaparinux
- Dosing- varies by indication and body weight
  - ✓ VTE prophylaxis: 2.5mg SubQ daily, in pts > 50kg
  - ✓ DVT/PE treatment: 5mg SubQ daily (pts < 50kg)
    7.5 mg SubQ daily (pts 50-100kg)
    10 mg SubQ daily (pts > 100kg)

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What to use – Warfarin
  - ✓ Dosing- varies due to medications, genetic phenotype, diet. If used for prophylaxis:
  - ✓ VTE prophylaxis: INR goal should be 2.5, with acceptable INR range of 2-3.

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What NOT to do:
  - ✓ Nothing – avoidance of prophylaxis results in avoidable morbidity and mortality
  - ✓ Rely on Aspirin alone
  - ✓ Rely on mechanical devices alone, unless patient has high risk of bleeding

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What TO do: Prevent the Event!
  - ✓ For patients undergoing:
    - Hip or knee arthroplasty, hip fx repair-use LMWH, fondaparinux, or warfarin (goal INR 2.5), for at least 10 days
    - Consider Intermittent Pneumatic Compression as adjunct

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What TO do: Prevent the Event!
  - ✓ For patients undergoing:
    - Major general, gynecologic, or urologic surgery-use LMWH, unfractionated heparin (UFH) or fondaparinux
    - Consider Intermittent Pneumatic Compression as adjunct

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What TO do: Prevent the Event!
  - ✓ For patients with acute medical illness – use LMWH, UFH or fondaparinux
    - Consider Intermittent Pneumatic Compression as adjunct

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

DVT/PE - Prophylaxis

- What TO do: Prevent the Event!
  - ✓ Thromboprophylaxis is also important for patients in the following situations:
    - Intensive Care Unit
    - Major trauma
    - Spinal cord injury

Geerts, WH, et al. Prevention of Venous Thromboembolism. *Chest.* 2008; 133:381S-453.

Case #2

- Heparin Induced Thrombocytopenia
  - ✓ Severe adverse drug reaction to heparin
  - ✓ Caused by antibody mediated reaction
  - ✓ Associated with significantly increased risk of thrombosis

Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low molecularweight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335

Case #2

- 59 yo male admitted for CABG
  - ✓ Surgery successful; on post-op day 5, pt c/o of sudden pain in R leg
  - ✓ PE: R LE cool, c/ diminished DP pulse
  - ✓ Lab: Lytes BUN Cr WNL; CBC: H/H 9.2/29, WBC 11.5, Plts 63,000
  - ✓ What may have happened?

Heparin Induced Thrombocytopenia

- Early detection is effective
  - ✓ Consider regularly scheduled platelet counts (every 2-3 days) for all patients on UFH or LMWH.
  - ✓ A reduction in platelet counts of greater than 50% from baseline should trigger use of alternative agent for anticoagulation until laboratory evaluation confirms or rules out HIT.

Franchini M. Heparin Induced Thrombocytopenia: An Update. *Thrombosis Journal* 2005, 3:14

Heparin Induced Thrombocytopenia

- If HIT is suspected:
  - ✓ Clinical suspicion is key- don't wait for confirmation
  - ✓ If suspected, immediately stop all heparin, LMWH
  - ✓ Start alternative agent for anticoagulation; must not cross react with HIT associated antibodies.

Chong BH: Heparin-induced thrombocytopenia. *J Thromb Haemost* 2003, 1:1471-1478.
Franchini M. Heparin Induced Thrombocytopenia: An Update. *Thrombosis Journal* 2005, 3:14

HIT – Treatment

- Argatroban
  - ✓ Dosing - initial dose is 2 µg/kg/minute given intravenously
  - ✓ Adjust dose to achieve an aPTT 1.5 to 3 times the baseline value.
  - ✓ Drug of choice for patients with renal insufficiency

Franchini M. Heparin Induced Thrombocytopenia: An Update. *Thrombosis Journal* 2005, 3:14
Chong BH: Heparin-induced thrombocytopenia. *J Thromb Haemost* 2003, 1:1471-1478.

Heparin Induced Thrombocytopenia

- Treatment- alternative agents
  - ✓ Approved agents for HIT treatment; all directly inhibit thrombin activity or formation
    - Argatroban
    - Lepirudin
    - Danaparoid

Chong BH: Heparin-induced thrombocytopenia. *J Thromb Haemost* 2003, 1:1471-1478.
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Franchini M. Heparin Induced Thrombocytopenia: An Update. *Thrombosis Journal* 2005, 3:14

HIT – Treatment

- Danaparoid
  - ✓ Dosing - intravenous bolus dose of 2500 U followed by 400 U/hour for 4 hours, then 300 U/hour for 4 hours and subsequently 200 U/hour until anticoagulation is no longer required
  - ✓ Adjust the dose to maintain plasma anti-Xa levels within 0.5–0.8 U/mL.

Franchini M. Heparin Induced Thrombocytopenia: An Update. *Thrombosis Journal* 2005, 3:14
Chong BH: Heparin-induced thrombocytopenia. *J Thromb Haemost* 2003, 1:1471-1478.

HIT – Treatment

- Lepirudin
  - ✓ Dosing - 0.4 mg/kg as a bolus followed by 0.15 mg/kg/hour
  - ✓ Adjust the dose to achieve an aPTT of 1.5 to 3 times the baseline value.
  - ✓ Drug of choice for patients with liver dysfunction

Franchini M. Heparin Induced Thrombocytopenia: An Update. *Thrombosis Journal* 2005, 3:14
Chong BH: Heparin-induced thrombocytopenia. *J Thromb Haemost* 2003, 1:1471-1478.

Anticoagulants

- New medications in development – potential concerns
  - ✓ Cost
  - ✓ Coverage
  - ✓ Patient compliance
  - ✓ Unanticipated toxicities
  - ✓ Monitoring

Anticoagulants

- New medications in development – direct thrombin inhibitors
  - ✓ Apixaban
  - ✓ Rasaxaban
  - ✓ Rivoroxaban
  - ✓ Dabigatran

Anticoagulation Therapy: An Overview

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Objectives

- Precautions
- Risk Assessment
- Monitoring
- Bridge Therapy

Case #1

- Patient with a fib and history of GI bleed was recently started on warfarin. States he was told he can no longer eat greens and can't ever take antibiotics.

Case #1

- Patient with a fib and history of GI bleed was recently started on warfarin. States he was told he can no longer eat greens and can't ever take antibiotics.

Precautions: Adverse Effects

- Bleeding/Bruising
  - ✓ Gum bleeding, nosebleed, excessive menstrual bleeding, significant bruising
  - ✓ Red or dark brown urine, red or black tarry stools
  - ✓ Vomiting or coughing blood
- Skin necrosis and limb gangrene
- Teratogenicity
- Purple Toe Syndrome

Case #1

- Patient with a fib and history of GI bleed was recently started on warfarin. States he was told he cannot eat greens and can't ever take antibiotics.

Case #1

- Patient with a fib and history of GI bleed was recently started on warfarin. States he was told he can no longer eat greens and can never take antibiotics.

Precautions: Food Interactions

- Green leafy vegetables and certain oils contain Vitamin K
- Consistency, not avoidance
- Vitamin K ↓ warfarin effects
  - ✓ ↑ in Vit K means ↑ for clots
  - ✓ ↓ in Vit K means ↑ risk of bleeding
- Liquids
  - ✓ Cranberry juice, grapefruit juice, and alcohol

Precautions: Drug Interactions

- Prescription, OTC, and Natural products
- Antibiotics
- NSAIDs
- Cardiac Medications

Case #2

- 68 yo male comes in for clinic visit and is found to be in atrial fibrillation. PMH includes only HTN. Should he be initiated on aspirin or warfarin?

$CHADS_2$ for A Fib Risk Assessment

CHF	= 1 point
HTN	= 1 point
Age >75	= 1 point
Diabetes	= 1 point
S_2troke	= 2 points
	TOTAL

If ≥ 2, warfarin recommended

Low risk
0 points: 1.9%/year
1 point: 2.8%/year
2 points: 4.0%/year

Moderate risk
3 points: 5.9%/year
4 points: 8.5%/year

High risk
5 points: 12.5%/year
6 points: 18.2%/year

Gage BF et al. JAMA 2001; 285:2864-70; Singer DE et al. Chest. 2008;133(6 Suppl):546-92S

Risk Assessment Atrial Fibrillation

Stroke Risk Factors include: HTN, Age >75, DM, CHF

No risk factors	Aspirin 81-325mg/day
1 risk factor	Warfarin INR 2.5 or Aspirin 81-325mg/day
2 risk factors	Warfarin INR 2.5
History of stroke, TIA, or systemic embolism	Warfarin INR 2.5
Mitral stenosis or prosthetic heart valve	Warfarin INR 2.5 or higher valve-specific INR

Singer DE et al. Chest. 2008;133(6 Suppl):546-92S

Risk Assessment: Features of ACCP 2008

- Age 65-75 not a RF
- VKA or aspirin is acceptable for CHADS2 score of 1
- Chest guidelines do not endorse lower INR targets in elderly patients

Case #2

- 68 yo male comes in for clinic visit and is found to be in atrial fibrillation. PMH includes only HTN. Should he be initiated on aspirin or warfarin?

Monitoring

- Baseline INR, H&H, and Plt
- Starting warfarin dose:
  - ✓ 5-10mg/d for first 1-2 days
  - ✓ Elderly: ≤ 5mg/day
  - ✓ Recommend against the use of pharmacogenetic based initial dosing

Ansell J et al. *Chest.* 2008; 133(6 Suppl):160S-98S

Case #3

- The patient's physician from Case #2 decided to start him on warfarin. What now?

Monitoring

- Frequency recommendations
  - ✓ Outpatients: 2- 3 days/week until a stable dose response has been achieved
  - ✓ For stable patients, interval no longer than 4 weeks
- Testing more frequently will lead to greater TTR

Ansell J et al. *Chest.* 2008; 133(6 Suppl):160S-98S

Monitoring: Therapeutic INRs

2-3 times weekly

→ Every 1 week

→ Every 2 weeks

→ Every 4 weeks

Extend interval once INR is in range twice consecutively at the same weekly dose

Case #4

- 55 yo male with DM and HTN on warfarin for atrial flutter has been stable on 5mg daily for the last three months. He presents to clinic for four week follow-up, and his INR was 6.7. Of note, he has been recently ill with n/v/d.

Case #3

- The patient's physician from Case #2 decided to start him on warfarin. <u>What now?</u>

Monitoring

- Fluctuations
  - ✓ Concomitant medication change
  - ✓ Missed doses
  - ✓ Lifestyle changes
  - ✓ Other disease states
- For pts with variable INR, recommend trial of daily low-dose oral vitamin K (100 to 200mcg) with close monitoring

Ansell J et al. *Chest*. 2008; 133(6 Suppl):160S-98S

Monitoring: Nontherapeutic INRs

- Monitor trend and assess for bleeding/brusing
- Omit or Add dose(s)
  - ✓ Transient factors (recent illness, diet, missed dose, recent alcohol, smoking)
  - ✓ Always combine with education
- Maintenance dose adjustments
  - ✓ Consider risk vs. benefit
  - ✓ 5-20% of weekly dose
- Consider 1-2 week f/u for any dose change or INR more than 0.2 from goal range

Ansell J et al. *Chest.* 2008; 133(6 Suppl):160S-98S

Case #4

- 55 yo male with DM and HTN on warfarin for atrial flutter has been stable on 5mg daily for the last three months. He presents to clinic for four week follow-up, and his INR was 6.7. Of note, he has been recently ill with n/v/d.

  What now?

Management of Elevated INRs

INR	Serious Bleeding	Intervention*
< 5	N	Lower dose or omit dose
≥ 5 but < 9	N	Omit 1-2 doses, resume at adjusted dose when INR at goal *Alternate:* Omit 1 dose and give 1-2.5 mg po vitamin K if at increased risk of bleeding
≥ 9	N	Hold warfarin and give 2.5-5mg po vitamin K. Resume at adjusted dose when INR at goal.
Any INR	Y	Hold warfarin, give vitamin K 10mg by slow IV infusion, may supplement w/ FFP, PCC, or rVIIa

* Intervention should be followed by more frequent monitoring

Ansell J et al. *Chest.* 2008; 133(6 Suppl):160S-98S

Case #5

- 63 yo male on warfarin for LLE DVT <3 months ago is stable on warfarin. However, he is scheduled for an invasive procedure.
- Is bridge therapy warranted?
- What recommendations would you give?

Bridge Therapy

- **Goal is to decrease risk of procedure-related bleeding and still minimize risk of thromboembolism**
- **Continuation of VKA is recommended during minor dental procedures, minor dermatologic procedures, and cataract removal**

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

Case #5

- **63 yo male on warfarin for LLE DVT <3 months ago is stable on warfarin. However, he is scheduled for an invasive procedure.**
- **Is bridge therapy warranted?**
- **What recommendations would you give?**

Bridge Therapy: Thromboembolic Risk Assessment

HIGH	**- A fib and $CHADS_2$ of 5 or 6** **- Stroke or TIA w/I 3 mo** **- VTE w/i 3 mo** **- Mechanical mitral valve**	**- Tx dose LMWH** or **- IV UFH** ***LMWH>IV UFH***
Moderate	**- A fib and $CHADS_2$ of 3 or 4** **- Mech AV + one stroke RF** **- VTE w/i 3-12 mo or recurrent** **- Active cancer**	**- Tx dose LMWH** or **- IV UFH** or **- Low dose LMWH** ***Tx dose LMWH > other options***
LOW	**- A fib and $CHADS_2$ of 0 to 2** **- Mech AV and no stroke RF** **- VTE >12 mo ago**	**- Low-dose LMWH** or **- No bridging**

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

Case #5

- **63 yo male on warfarin for LLE DVT <3 months ago is stable on warfarin. However, he is scheduled for an invasive procedure.**
- **Is bridge therapy warranted?**
- **What recommendations would you give?**

Bridge Therapy

- **Warfarin**
  - ✓ **Discontinue 5 days prior to procedure**
  - ✓ **Resume 12-24 hours after procedure at perioperative dose**
- **Bridge therapy**
  - ✓ **Start 48 hours after stopping warfarin**
  - ✓ **Discontinue 24 hours prior to procedure**
  - ✓ **Consider resuming 24 hours after procedure or after assessment of postop hemostasis**

Questions?

Conclusions

- **Patient education is key**
- **Consider guidelines as a guide, not a blanket recipe**
- **Utilize clinical judgment per individual patient**