

Improving Quality: Anticoagulation Therapy

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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

- **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

- **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:**
 - **Centers for Medicare**
 - **AHRQ**
 - **American College of Chest Physicians**
 - **Joint Commission**
 - **Leapfrog Coalition**
 - **Third party providers**

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:

Scope of the Problem

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?**
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?**

Scope of the Problem

- 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.**

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

- **Current ACCP guidelines - 9th Edition**
 - **Address what to do**
 - **When to do it**
 - **What to use**
 - **What not to use**

CHEST 2012; 141(2)(Suppl):e227S–e277S453.

DVT/PE - Prophylaxis

- **What to use – Low Molecular Weight Heparins (LMWH)**
 - Enoxaparin – 30 mg SubQ twice daily, or 40 mg 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 – Fondaparinux**
- **Dosing- varies by indication and body weight**
 - **VTE prophylaxis:** 2.5 mg SubQ daily, in pts > 50kg
 - **DVT/PE treatment:** 5 mg 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 – 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 – 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 to use – Rivaroxaban**
 - **Dosing- 10 mg po daily:**
 - **VTE prophylaxis: for hip replacement: duration is 35 days**
 - **For knee replacement: duration is 12 days**

CHEST 2012; 141(2)(Suppl):e227S–e277S453.

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:**
 - **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 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 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.

DVT/PE - Prophylaxis

- **ACCP 9th guidelines changes:**
 - **Post-op ortho Rx duration- 10-35 days; consider new DTI's**
 - **Low risk medical pts may not require Rx**
 - **Outpts with CA but no other risks- no routine prophylaxis**

CHEST 2012; 141(2)(Suppl):e278S–e325S.

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?**

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

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

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.

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.

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, or requiring cardiac surgery**

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

Anticoagulation : New Guidelines and New Anticoagulants

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9th Edition CHEST Guidelines February 2012

- **What are some of the new recommendations**
- **What are some of the changes**
- **How do we apply these to patient care**

Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Chest February 2012 141:2 suppl 53S

Table 4—Strength of the Recommendations Grading System

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.



**Evidence-Based Management of Anticoagulant Therapy:
Antithrombotic Therapy and Prevention of Thrombosis, 9th
ed: American College of Chest Physicians Evidence-Based
Clinical Practice Guidelines
*Chest February 2012 141:2 suppl e152S-e184S***

2.1. For patients sufficiently healthy to be treated as outpatients, we suggest initiating Vitamin K Antagonist (VKA) therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on INR measurements rather than starting with the estimated maintenance dose (Grade 2C).

**Evidence-Based Management of Anticoagulant
Therapy: Antithrombotic Therapy and Prevention of
Thrombosis, 9th ed: American College of Chest
Physicians Evidence-Based Clinical Practice
Guidelines
*Chest February 2012 141:2 suppl e152S-e184S***

3.1. For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B)

**Evidence-Based Management of Anticoagulant Therapy:
Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:
American College of Chest Physicians Evidence-Based Clinical
Practice Guidelines**
Chest February 2012 141:2 suppl e152S-e184S

3.2. For patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic, we suggest continuing the current dose and testing the INR within 1 to 2 weeks (Grade 2C).

**Evidence-Based Management of Anticoagulant Therapy:
Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:
American College of Chest Physicians Evidence-Based Clinical
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Chest February 2012 141:2 suppl e152S-e184S

3.3. For patients with stable therapeutic INRs presenting with a single subtherapeutic INR value, we suggest against routinely administering bridging with heparin (Grade 2C).

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Practice Guidelines**

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9.1. (a) For patients taking VKAs with INRs between 4.5 and 10 and no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B)

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(b) For patients taking VKAs with INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered (Grade 2C).

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor PCC rather than with plasma (Grade 2C).

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

Case 1

- **LP is an 52 yo male with a history of recurrent thrombotic events on chronic warfarin therapy**
- **Patient has been stable within his desired therapeutic INR range of 2-3 on his current total weekly dose (TWD) of warfarin for 6 months**
- **Today he presents in clinic with an INR 1.6**
- **What should be done?**

Case 1

- According to the new CHEST guidelines:
 - The patient's current TWD should be continued and the patient should follow-up in 1-2 weeks
 - Bridge therapy does not need to be initiated at this time

Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
Chest February 2012 141:2 suppl e531S-e575S

Table 2—[Section 1.4.3] CHADS₂ Score³⁰ for Assessment of Stroke Risk in Patients With Nonrheumatic AF

Risk Factor	Points
Recent Congestive heart failure exacerbation	1
History of Hypertension	1
Age ≥ 75 y	1
Diabetes mellitus	1
Prior history of Stroke or transient ischemic attack	2

CHADS₂ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack. See Table 1 legend for expansion of other abbreviation.

Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Chest February 2012 141:2 suppl e531S-e575S

2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, CHADS₂ score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B). For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2 B) or combination therapy with aspirin and clopidogrel (Grade 2B).

Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, CHADS₂ score = 1), we recommend oral anticoagulation rather than no therapy (Grade 1B). We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily) (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B).

Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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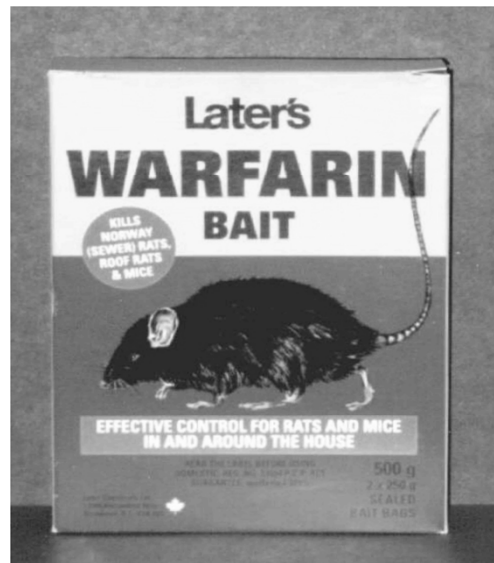
2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, CHADS₂ score \geq 2), we recommend oral anticoagulation rather than no therapy (Grade 1A), aspirin (75 mg to 325 mg once daily) (Grade 1B), or combination therapy with aspirin and clopidogrel (Grade 1B). For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily). (Grade 1B)

Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Chest February 2012 141:2 suppl e531S-e575S

2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation, we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0 – 3.0) (Grade 2B).

Remarks: Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of \leq 30 mL/min). Clinicians should be aware that there is no antidote for dabigatran.



Dabigatran (Pradaxa®)

PI: Pradaxa (dabigatran)oral tablets; Boehringer Ingelheim; Ridgefield, CT, 2010

- Direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

CrCl	Dose
>30 mL/min	150mg BID
15-30 mL/min	75mg BID*
<15 mL/min or hemodialysis	Unknown

* Based on pharmacokinetic modeling

Dabigatran (Pradaxa®)

Stangier J. Clin Pharmacokinet 2008;47:285-295

Bioavailability	6.5%
t _{max}	1.5-3 h (healthy patients) 3.7-4.5 h (day of surgery)
V _d	60-70 L
Elimination	80% renal unchanged
t _{1/2}	12-17 h
Protein binding	35%

Dabigatran (Pradaxa®)

Stangier J. Clin Pharmacokinet 2008;47:285-295

- **Holding for Procedures**

Creatinine Clearance	Hold for:
≥ 50 mL/min	1-2 days
< 50 mL/min	3-5 days

Consider holding longer for major surgery, spinal puncture, placement of spinal/epidural catheter

Dabigatran (Pradaxa®)

- **No cytochrome P-450 activity**
 - **Interaction with P-glycoprotein**
- **No dietary interactions**
- **Larger Therapeutic Index**
- **No monitoring recommended**

Rivaroxiban (Xarelto®)

PI: Xarelto (dabigatran) oral tablets; Bayer HealthCare AG, 51368
Leverkusen, Germany

- Rivaroxaban selectively inhibits factor Xa to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and to reduce the risk of deep vein thrombosis post knee and hip replacement surgery

Indication	CrCl	Dose
A-Fib	> 50 ml/min	20 mg daily
A-Fib	15 - 50 ml/min	15 mg daily
Post-Hip Replacement		10 mg daily (rec. duration of 35 days)
Post- Knee Replacement		10 mg daily (rec. duration of 12 days)

“The Ideal Anticoagulant”

	Warfarin	Dabigatran	Rivaroxiban
Oral dosage form	✓	✓	✓
Predictable, rapid effect		✓	✓
Few drug interactions		✓	✓
Reversibility	✓		
Inexpensive	✓		
No need for monitoring		✓	✓
Once daily dosing	✓		✓

Other Considerations for New Anticoagulants

- **No reversal agent**
- **Adverse reactions**
 - **Still bleeding risk**
 - **Dyspepsia (35% with dabigatran)**
- **Renal Dosing**
- **Lack of monitoring**

Other Considerations for New Anticoagulants

- **Compliance**
 - **Faster return to baseline (short half-life syndrome)**
 - **Cost**
 - **Twice daily dosing (dabigatran)**

Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
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Case 2

- JP is a 49yo female
- Thrombosis of the main portal vein May 2011,
- Rescanned February 2012 still showing portal vein thrombosis.
- Hx of stage I ER/PR positive breast cancer.
- Mastectomy and sentinel lymph node biopsy was performed on 01/30/2008
- No findings on Mammogram December 2011.
- Adjuvant hormone therapy with tamoxifen March 2008-May 2011. Changed to letrozole May 2011.
- Thrombosis risk tamoxifen vs. letrozole (1.7% vs 1.1%)

Case 2

- **Patient having laparoscopic surgery for small recurrent ventral hernia**
- **How do we handle her anticoagulation?**

First question – When do we stop her anticoagulation?

- **How long prior to her procedure should her warfarin be stopped?**
- **If bridged – when should her bridge therapy be stopped?**

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2.1. In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately 5 days before surgery instead of stopping VKAs a shorter time before surgery (Grade 1C).

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4.3. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 hours before surgery instead of 12 hours before surgery (Grade 2C).

What is the patients risk of a recurrent thrombotic event?

- High Risk
- Moderate Risk
- Low Risk

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Table 4.—[Introduction] Suggested Risk Stratification for Perioperative Thromboembolism

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High	<ul style="list-style-type: none"> Any mitral valve prosthesis Any aortic valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack 	<ul style="list-style-type: none"> CHADS₂ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Electromechanical heart disease 	<ul style="list-style-type: none"> Recent (within 3 mo) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple miscarriages)
Moderate	<ul style="list-style-type: none"> Bicuspid aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 y 	<ul style="list-style-type: none"> CHADS₂ score of 3 or 4 	<ul style="list-style-type: none"> VTE within the past 3-12 mo Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recent VTE Active cancer (treated within 6 mo or palliative)
Low	<ul style="list-style-type: none"> Bicuspid aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke 	<ul style="list-style-type: none"> CHADS₂ score of 0 to 2 (assuming no prior stroke or transient ischemic attack) 	<ul style="list-style-type: none"> VTE >12 mo previous and no other risk factors

CHADS₂ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.

*High-risk patients may also include those with a prior stroke or transient ischemic attack occurring >3 mo before the planned surgery and a CHADS₂ score <5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, transcatheter aortic valve replacement, major vascular surgery).

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High Risk Patients

2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during interruption of VKA therapy (Grade 2C).

***Remarks:* Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.**

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Low Risk Patients

In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no-bridging instead of bridging anticoagulation during interruption of VKA therapy (Grade 2C).

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Moderate Risk Patients

In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.

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Moderate Risk – Who do we consider bridge therapy?

- Patients with a mechanical bileaflet aortic valve and additional stroke risk factors comprising prior stroke or systemic embolism or transient ischemic attack, hypertension, diabetes, congestive heart failure, or age > 75 years
- Patients with atrial fibrillation and a CHADS₂ score of 3 or 4 or prior thromboembolism during interruption of warfarin
- Patients with VTE within the past 3 to 12 months, nonsevere thrombophilia, active cancer, and recurrent VTE

Answer: All Moderate Risk patients should be considered for bridge therapy

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Table 4—[Introduction] Suggested Risk Stratification for Perioperative Thromboembolism

Risk/Stroke	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	VTE
High	<ul style="list-style-type: none"> Any mitral valve prosthesis Any aortic-bi- or tri-leaflet aortic valve prosthesis Biocore (within 6 mo) stroke or transient ischemic attack 	<ul style="list-style-type: none"> CHA₂DS₂ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Electromechanical heart disease 	<ul style="list-style-type: none"> Recent (within 3 mo) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	<ul style="list-style-type: none"> Bi-leaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75 y 	<ul style="list-style-type: none"> CHA₂DS₂ score of 5 or 4 	<ul style="list-style-type: none"> VTE within the past 3-12 mo No severe thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
Low	<ul style="list-style-type: none"> Bi-leaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke 	<ul style="list-style-type: none"> CHA₂DS₂ score of 0 to 3 (assuming no prior stroke or transient ischemic attack) 	<ul style="list-style-type: none"> VTE >12 mo previous and no other risk factors

CHA₂DS₂ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.

*High-risk patients may also include those with a prior stroke or transient ischemic attack occurring >3 mo before the planned surgery and a CHA₂DS₂ score <5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, mitral mitralotomy, major vascular surgery).

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- **Other considerations**
 - **High-bleeding-risk procedures**
 - **Renal function**

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- **What dose of Low-Molecular-Weight-Heparin (LMWH) do we use to bridge?**
 - No published randomized, controlled trials on bridge therapy
 - In observational studies high-risk patients typically received therapeutic dose LMWH
 - **BRIDGE Study**

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4.2.2. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, we suggest prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B).

Remarks: Additional risk factors for venous thrombosis in outpatients with cancer include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide

What do we do with our patient

- **What risk category does she fall in?**
- **What other risk factors does she possess?**
- **What is the bleeding risk for this patient's procedure?**

What was decided

- **After discussion with the patient's Oncologist, it was determined to bridge this patient with enoxaparin**
- **Deemed patient was moderate risk**
 - **Acute event 3-12 months ago**
 - **Recent scan showing chronic thrombus**
 - **Patient is on hormonal therapy**
- **Bleeding risk deemed low for procedure**

What about post-procedure?

- **When do we restart the patients warfarin therapy?**
- **When do we restart the patient's bridge therapy?**

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2.2. In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 hours after surgery (evening of or next morning) and when there is adequate hemostasis instead of later resumption of VKAs (Grade 2C).

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4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 hours after surgery instead of resuming LMWH within 24 hours after surgery (Grade 2C). In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing *non-high-bleeding-risk* surgery, we suggest resuming therapeutic-dose LMWH approximately 24 hours after surgery instead of resuming LMWH more than 24 hours after surgery.

Summary of Bridge Therapy

- **Bridging guidelines still vague**
- **Still no published randomized, controlled clinical trials with bridge therapy (BRIDGE Study ongoing)**
- **Each patient still needs assessed individually**
 - **Guidelines will not encompass all patients and all patient risk factors**

Improving Quality: Anticoagulation Therapy

Mark Wurster, MD
Founder and Chief Medical Officer
Standing Stone, Inc.

The New Agents

- **Unresolved issues –**
 - **‘Short half-life syndrome’**
 - **Emergency reversal**
 - **Drug/Treatment costs**
 - **Efficacy of outcomes vs. AC care**
 - **Post marketing surveillance will be crucial**

Dabigatran

- **Pradaxa (Dabigatran)- current situation**
- **Numerous case reports of complications are being reported in US, New Zealand, Australia**
- **In December 2011, FDA requested additional information from physicians regarding Pradaxa**
- **Case reports are limited in terms of information gained, especially in terms of relative risk compared to other therapeutic options**

The New Agents- Clinical Use

- **Dabigatran Case Series – A prospective, observational cohort study**
- **Purpose-**
- **To evaluate the clinical outcomes of patients receiving anticoagulation therapy with dabigatran, using warfarin therapy as a comparison**

Dabigatran Case Series

- **Setting-**
- **Staten Island / Long Island Jewish hospital-**
- **Anticoagulation clinic currently follows approximately 2200 patients, the majority of which are POC testers**

Dabigatran Case Series

- **Design-**
- **Beginning 11/2010, all patients switched from warfarin to dabigatran followed prospectively for one year, with retrospective chart reviews covering one year prior while on warfarin**
- **Cohort design allows each patient to serve as their own control**
- **Endpoints- bleeds, thromboses, or other Rx complications that required med to be D/C'ed**

Dabigatran Case Series

- **Design-**
- **Endpoints- bleeds, thromboses, or other treatment related complications that required medication to be discontinued**
- **Results were compared by means of Fisher's exact test**

Dabigatran Case Series

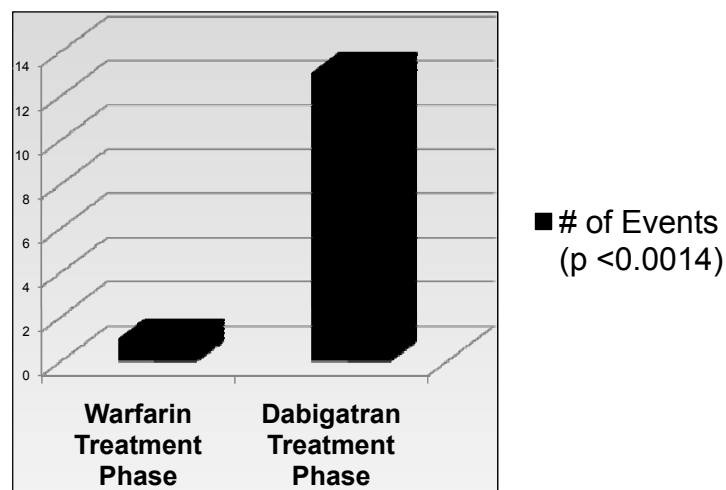
- **Preliminary Results-**
- **For 113 eligible patients after 6 months of warfarin therapy, followed by 6 months of dabigatran therapy:**
- **For almost all patients, reasons listed for switching therapy included physician or patient convenience; in one case, a patient who planned to be overseas needed an alternative to regular INR monitoring**

Dabigatran Case Series

- Preliminary Results-
- During warfarin treatment phase, one patient was admitted to the hospital for diagnosis of 'warfarin toxicity'

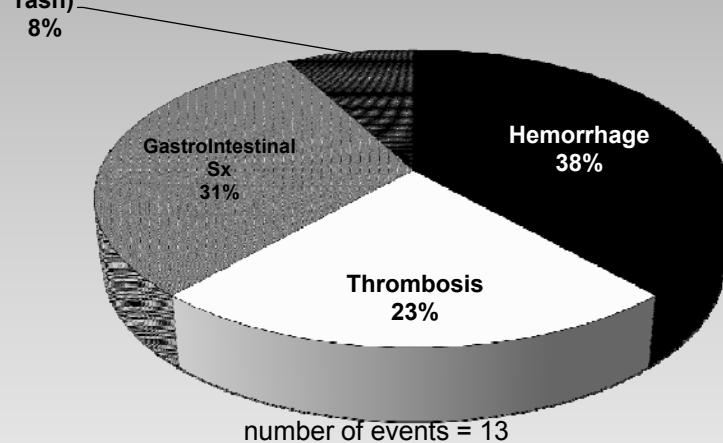
Dabigatran Case Series

Events Requiring Medication Stoppage



Dabigatran Case Series

Frequency of Dabigatran Complications by Type



Dabigatran Case Series

- **Preliminary Results-**
- **During dabigatran treatment phase: one death (GI bleed), four other bleeding episodes (two GI bleeds, one rectus sheath hemorrhage, one intracranial hemorrhage), one Deep Venous Thrombosis, one atrial thrombus, one Transient Ischemic Attack, one skin rash, and four GI reactions**

Dabigatran Case Series

- **Preliminary Results**
 - Incidence of endpoints during warfarin therapy phase was 0.83%
 - Incidence of endpoints during dabigatran therapy phase was 11.5 %
 - The difference was HIGHLY statistically significant
 - ($p < 0.0014$)
 - Relative risk of adverse event with dabigatran = 13.8

Dabigatran Case Series

- **Preliminary Results**
 - Why are the differences so striking, compared to prior studies?
 - Sampling error?
 - 'Usual care' versus study related close observation?
 - Use in inappropriate subjects?
 - Poor warfarin use in prior studies (TTR in RE-LY was 64% with huge variation internationally, compared to 70% for warfarin clinic in this study)

Dabigatran Case Series

- **The current study is still active –**
- **Goals for final report – continue observation of patients for a further 6 months, with emphasis on:**
 - **Demographics**
 - **Renal Function**
 - **Co-morbidities**
 - **Concomitant medications**
 - **Other possible factors that may influence appropriate patient selection for the medication**