

# ANTICOAGULATION UPDATE

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# DISCLOSURES

## **Research Support:**

AstraZeneca; BMS; Boehringer-Ingelheim; Eisai; GSK; Sanofi-Aventis

## **Consultant:**

BMS; Boehringer-Ingelheim; Eisai; Merck; Pfizer; Sanofi-Aventis

# TOPICS

- Immediate anticoagulation
- New LMWH indication in cancer; extended LMWH prophylaxis
- Warfarin dosing and genetics
- FDA warfarin labeling vs. NHLBI Randomized Clinical Trial
- Bridging
- Novel oral anticoagulants

# IMMEDIATE ANTICOAGULATION

1. Unfractionated heparin: target PTT between 60 to 80 seconds
2. Low molecular weight heparins: enoxaparin, dalteparin, tinzaparin
3. Fondaparinux
4. Direct thrombin inhibitors (HIT): argatroban, lepirudin, bivalirudin

# CANCER AND VTE

- **3-fold higher recurrence and bleeding, when treating cancer patients (Prandoni. Blood 2002; 100: 3484)**
- **LMWH Monotherapy halves recurrence, vs. warfarin. (FDA approved May 2007) (Lee AYY. NEJM 2003; 349:146)**
- **Extended Anticoagulation: Survival advantage? (“FAMOUS”--Kakkar AK. JCO 2004; 22: 1944) (“CLOT”--Lee AYY. JCO 2005; 23: 2130)**

# EXCLAIM: EXTENDED-DURATION ENOXAPARIN PROPHYLAXIS IN HIGH-RISK MEDICAL PATIENTS

| End points  | Outcome, extended prophylaxis, n=2052 (%) | Outcome, placebo, n=2062 (%) | RR reduction (%) | p     |
|-------------|---|------------------------------|------------------|-------|
| VTE events  | 2.8                                       | 4.9                          | 44%              | 0.001 |
| Symptomatic | 0.3                                       | 1.1                          | 73%              | 0.004 |
| No Sxs      | 2.5                                       | 3.7                          | 34%              | 0.032 |

(Hull RD et al. July 2007; ISTH; Geneva)

# WARFARIN PRESCRIPTIONS

In 2005, > 23 million USA warfarin prescriptions were written. Warfarin, the only available oral anticoagulant in the USA, was the 12<sup>th</sup> most commonly prescribed generic drug.

**(Verispan, Inc.)**

**Can Rapid Turnaround  
Genetic Testing Reduce  
the “Educated Guessing  
Game” and  
“Play of Chance” in  
Warfarin Dosing?**

# WARFARIN: ADVANTAGES

1. INR assesses anticoagulant level.
2. Multiple antidotes available.
3. Omitting 1-2 doses is not problematic.
4. Introduced in 1954. Has “stood the test of time.” No liver toxicity.
5. Ability to maintain target INR is improving. (Now > 60% in top facilities.)
6. No anticoagulant has demonstrated superior efficacy or safety.
7. Inexpensive.

# WARFARIN: WALKING A TIGHTROPE

- Excessive dose precipitates hemorrhage.
- Inadequate dose predisposes to stroke and pulmonary embolism.
- Dosing nomograms work poorly.
- Dosing by trial and error predominates.

# WARFARIN GENETIC TESTING

1. Cytochrome P450 2C9 genotyping can identify mutations associated with impaired warfarin metabolism.
2. Vitamin K receptor polymorphism testing can predict low, intermediate, or high doses of warfarin.
3. Major drawbacks in genotyping for warfarin dosing: a) slow turnaround time, b) \$300-\$500 cost, c) clinical factors that influence dosing.

# FDA “BLACK BOX” WARNING (October 6, 2006)

“Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR)...”

# FIRST MONTH WARFARIN HAS HIGH BLEEDING RATE

| Bleeding Type                        | Head Bleed                   | Major Non-Head Bleed        |
|--------------------------------------|------------------------------|-----------------------------|
| <b>1<sup>st</sup> Month Warfarin</b> | <b>0.92%</b><br>(annualized) | <b>1.2%</b><br>(annualized) |
| Subsequent Warfarin                  | 0.46% per year               | 0.61% per year              |

(Fang MC. J Am Geriatr Soc 2006; 54: 1231-1236)

**FDA ADDS “BLACK BOX”**  
**WARNING/ PRECAUTION**  
**FOR WARFARIN**

**October 6, 2006**

**WARNING: BLEEDING RISK**

**August 16, 2007**

**Precaution: “Consider a lower initial warfarin dose for patients with certain genetic variations.”**

# AMERICAN ENTERPRISE

## INSTITUTE-BROOKINGS REPORT

Incorporating routine genetic testing into warfarin dosing will result in an estimated:

- 85,000 fewer serious bleeds
- 17,700 fewer strokes
- \$1.1 billion saved

(November 2006)

# OBJECTIONS TO GENETIC TESTING: Warfarin

1. Considered costly, inconvenient.  
(Coverage by CMS just shifts costs.)
2. Slows down prescribing warfarin.
3. Not proven to be as good or superior to the current standard of care (“educated guess” approach)—which is getting better.

# OBJECTIONS TO GENETIC TESTING: Warfarin

4. Will genetic profiling improve maintenance dosing? If so, how?
5. Can Anticoag Clinics/ POC testing improve warfarin anticoagulation more than rapid turnaround genetic testing?
6. Novel anticoagulants—fixed dose, no coagulation monitoring

# GENOTYPE VS STANDARD WARFARIN DOSING (N=206)

## **Couma-Gen Trial**

- Rapid turnaround CYP2C9 and VKORC1 testing vs. “empiric”
- Primary endpoint: TTR
- Smaller and fewer dosing changes with genetic testing
- No difference in TTR

(Circulation 2007; 116: 2563-2570)

# Per-patient % out-of range INRs

| <u>Patient group</u>                 | <u>Genetic-dosing</u> | <u>Controls</u> | <u>p</u> |
|--------------------------------------|-----------------------|-----------------|----------|
| Whole population                     | 30.7 %                | 33.1 %          | NS       |
| Patients with 0 or multiple variants | 29 %                  | 39 %            | 0.03     |

Anderson JL et al. *Circulation* 2007; 116: 2563-2570

**NHLBI CONSIDERS GENETIC**  
**TESTING FOR WARFARIN**  
**UNPROVEN: PLANS**  
**MULTIMILLION DOLLAR TRIAL**

**1,500 Patients will be  
randomized to: 1) Genetic plus  
clinical nomogram,  
2) Clinical nomogram,  
3) Conventional warfarin dosing**

# NHLBI Randomized Controlled Trial: 2008-2011

## Primary Endpoint:

Percent of Time in Therapeutic Range  
(PTTR)

## Hypothesis:

60% PTTR in standard arm versus  
 $\geq$  72% PTTR in Genetics Plus Clinical  
Nomogram arm

# RISK FACTORS FOR AN ELEVATED INR (It's not all Genetics)

- Advanced Age (one-third dose)
- Abnormal Liver Function
- Decreased Vitamin K Intake (NPO, diarrhea, antibiotics)
- Alcohol in Binges
- Change in Warfarin Preparation
- Drug-drug and drug-food interactions

# BRIDGING TRIAL (N=1,293)

- Prospective cohort; all receiving long-term warfarin; average age: 72 years; mostly AF patients
- 80% had warfarin held  $\leq$  5 days
- 0.7% had thromboembolism; none had been bridged; 0.4% rate when warfarin was held  $\leq$  5 days
- Of those bridged, 3.7% had major bleed.

(Garcia DA, et al. Arch Intern Med 2008; 168: 63-69)

## Bridging: Bleeding Complication Risk

| <u>Bleeding</u>  | <u>Bridge</u> | <u>No bridge</u> |
|------------------|---------------|------------------|
| Major hemorrhage | 3.7 %         | 0.2 %            |
| Minor hemorrhage | 9 %           | 0.6 %            |

Garcia DA et al. *Arch Intern Med* 2008;  
168:63

# NOVEL ORAL ANTICOAGULANTS

1. Dabigatran: an oral DTI—twice daily fixed dose (renal clearance)
2. Rivaroxaban: direct factor Xa inhibitor (renal clearance)—once daily fixed dose
3. Apixaban: direct factor Xa inhibitor (hepatic clearance)—twice daily fixed dose

(Eikelboom JW, Weitz JI; Circulation 2007; 116: 131)

# NEW ORAL ANTICOAGULANTS: ADVANTAGES

1. No coagulation lab monitoring
2. No dose adjustment
3. No drug-food interactions
4. Rare drug-drug interactions
5. No “bridging” needed prior to invasive procedures or surgery

# NEW ORAL ANTICOAGULANTS: DISADVANTAGES

1. No specific antidote for overdose (“tincture of time”)
2. No anticoagulant effect if doses are “skipped” or “forgotten”
3. No lab test to monitor anticoagulant effect or intensity
4. No way to modulate dose for “outlier” BMI or chronic kidney disease
5. Expensive

# VTE AND ORTHOPEDIC SURGERY

- 700,000 elective THR and TKR annually in the USA
- The number one major complication is DVT and PE
- DVT and PE are the top cause of rehospitalization

# RECORD-1 THR Prophylaxis (5 weeks Rx both groups) N=4,541

| <u>Outcome</u>                                 | <u>Rivaroxaban</u><br><u>%</u> | <u>Enoxaparin</u><br><u>%</u> | <u>Relative risk</u><br><u>reduction, %</u> | <u>p</u> |
|--|--------------------------------|-------------------------------|---|----------|
| DVT,<br>nonfatal PE,<br>all-cause<br>mortality | 1.1                            | 3.7                           | 70  | <0.001   |
| Major VTE                                      | 0.2                            | 2.0                           | 88  | <0.001   |
| Major bleed                                    | 0.3                            | 0.1                           | —   | 0.178    |
| Minor bleed                                    | 5.8                            | 5.8                           | —   | 1.000    |

Eriksson B. American Society of Hematology;  
December 8-11, 2007; Atlanta, GA.

# RECORD-2 THR Prophylaxis (5 weeks rivaroxaban vs 10-14 days enoxaparin) N=2,509

| <u>Outcome</u>                 | <u>Rivaroxaban</u><br><u>%</u> | <u>Enoxaparin,</u><br><u>%</u> | <u>Risk reduced,</u><br><u>%</u> | <u>p</u> |
|--------------------------------|--------------------------------|--------------------------------|----------------------------------|----------|
| DVT, nonfatal<br>PE, mortality | 2.0                            | 9.3                            | 79                               | <0.001   |
| Major VTE                      | 0.6                            | 5.1                            | 88                               | <0.001   |
| Major bleed                    | 0.1                            | 0.1                            | —                                | 0.980    |
| Minor bleed                    | 6.5                            | 5.5                            | —                                | 0.246    |

Kakkar AK. American Society of Hematology;  
December 8-11, 2007; Atlanta, GA.

# MAXIMIZING “GOOD” A/C

1. Centralized anticoagulation services—often run by RN, PharmD
2. Point-of-care INR testing, including self-testing and self-dose-adjusting
3. LMWH monotherapy for cancer patients
4. Genetic testing for warfarin?
5. Novel oral anticoagulants:  
Rivaroxaban, Apixaban, Dabigatran  
(Circulation 2007; 116: 131-133)
6. Once weekly injectables, with antidote