

WARFARIN GENETICS AND
DOSING: THE NEW
PHARMACOGENOMIC FRONTIER

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February 15, 2007

WARFARIN PRESCRIPTIONS

In 2005, 23 million warfarin prescriptions were written in the USA.

Warfarin was the 12th most commonly prescribed generic drug.

(Verispan, Inc.)

WARFARIN: WALKING A TIGHTROPE

- Warfarin anticoagulation is prescribed to prevent thrombosis.
- It is dosed to achieve a target INR.
- Excessive dosing precipitates hemorrhage.
- Inadequate dosing predisposes to stroke and pulmonary embolism.
- Dosing nomograms work poorly.
- Dosing by trial and error predominates.

Elevated INR is a surrogate for increased risk of intracranial hemorrhage and other major bleeding complications.

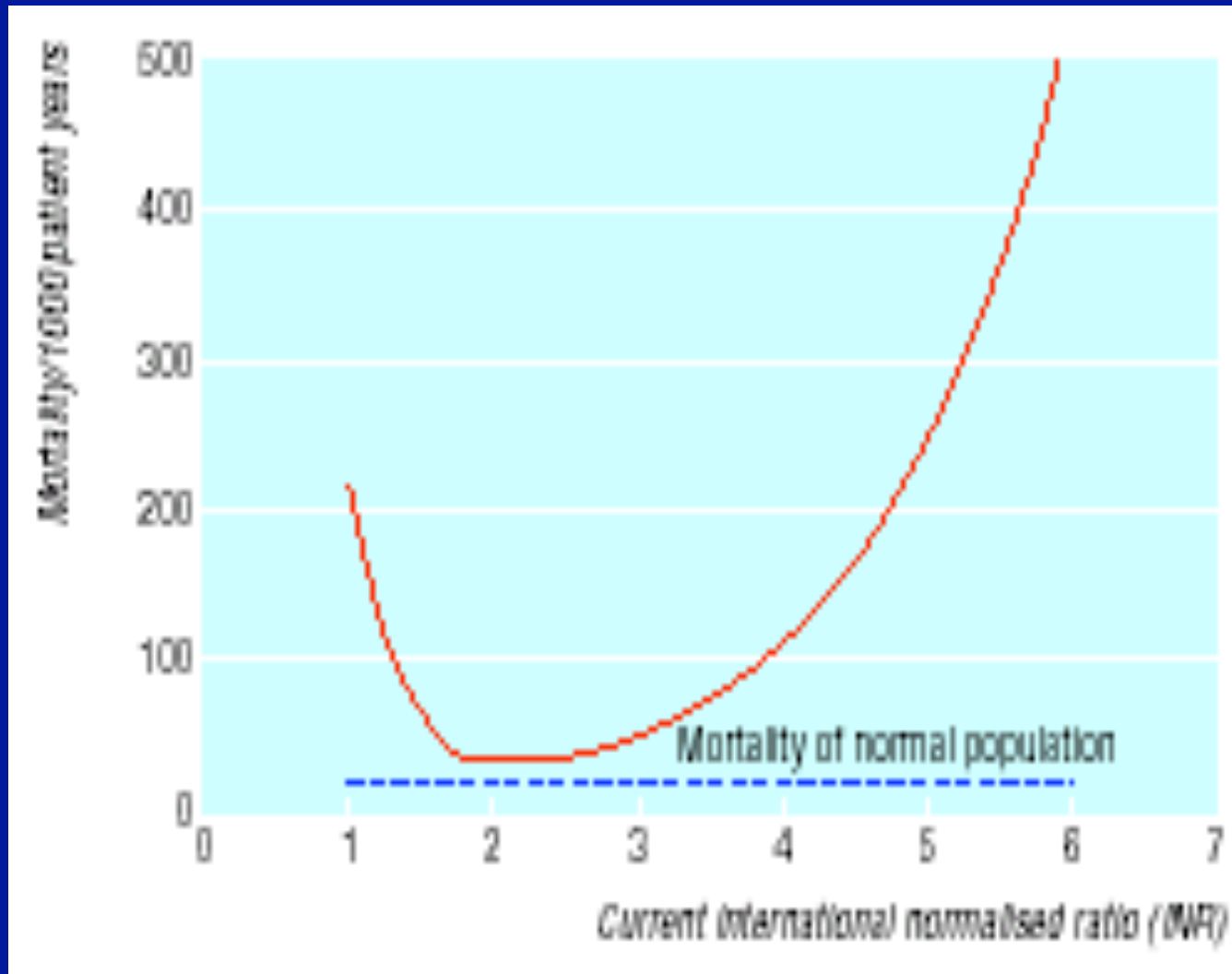
Subtherapeutic INR is a surrogate for thrombotic complications.

SWEDISH ANTICOAGULATION CLINICS

- 46 clinics
- 42,451 patients
- 3,533 deaths
- 1,250,000 INRs

(BMJ 2002;325:1073-1075)

DEATH RATE VS. INR



(BMJ 2002;325:1073)

NARROW RX'IC WINDOW

At INR = 2.2, risk of death is minimized.

Death rate doubles with every 1 unit increase in INR > 2.5

(BMJ 2002; 325:1073)

FDA ADDS “BLACK BOX”
WARNING FOR WARFARIN

October 6, 2006

WARNING: BLEEDING RISK

FDA “BLACK BOX” WARNING

“Warfarin sodium can cause major or fatal bleeding.

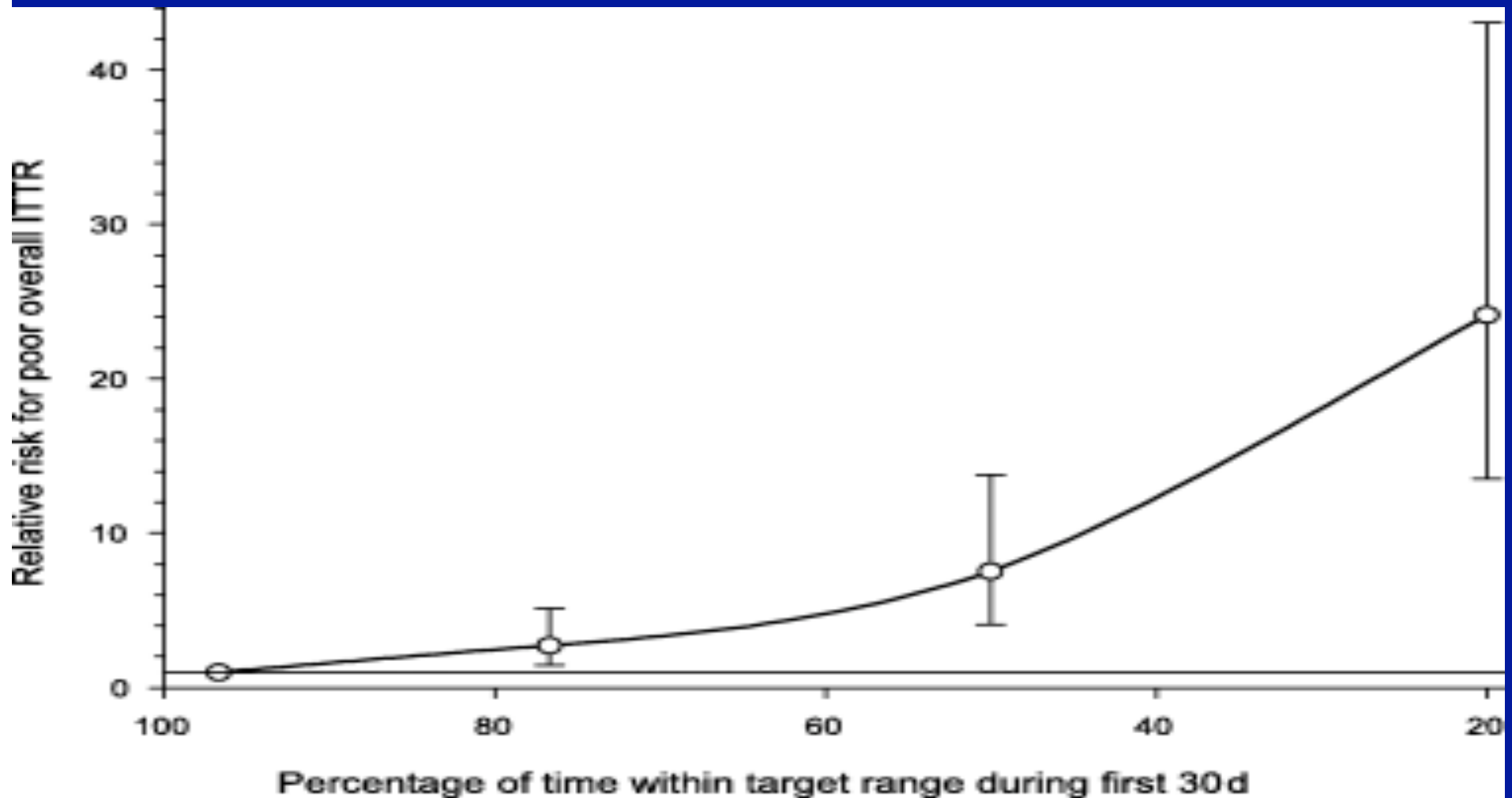
Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR)...”

FIRST MONTH WARFARIN HAS HIGH BLEEDING RATE

Bleeding Type	Head Bleed	Major Non-Head Bleed
1st Month Warfarin	0.92% (annualized)	1.2% (annualized)
Subsequent Warfarin	0.46% per year	0.61% per year

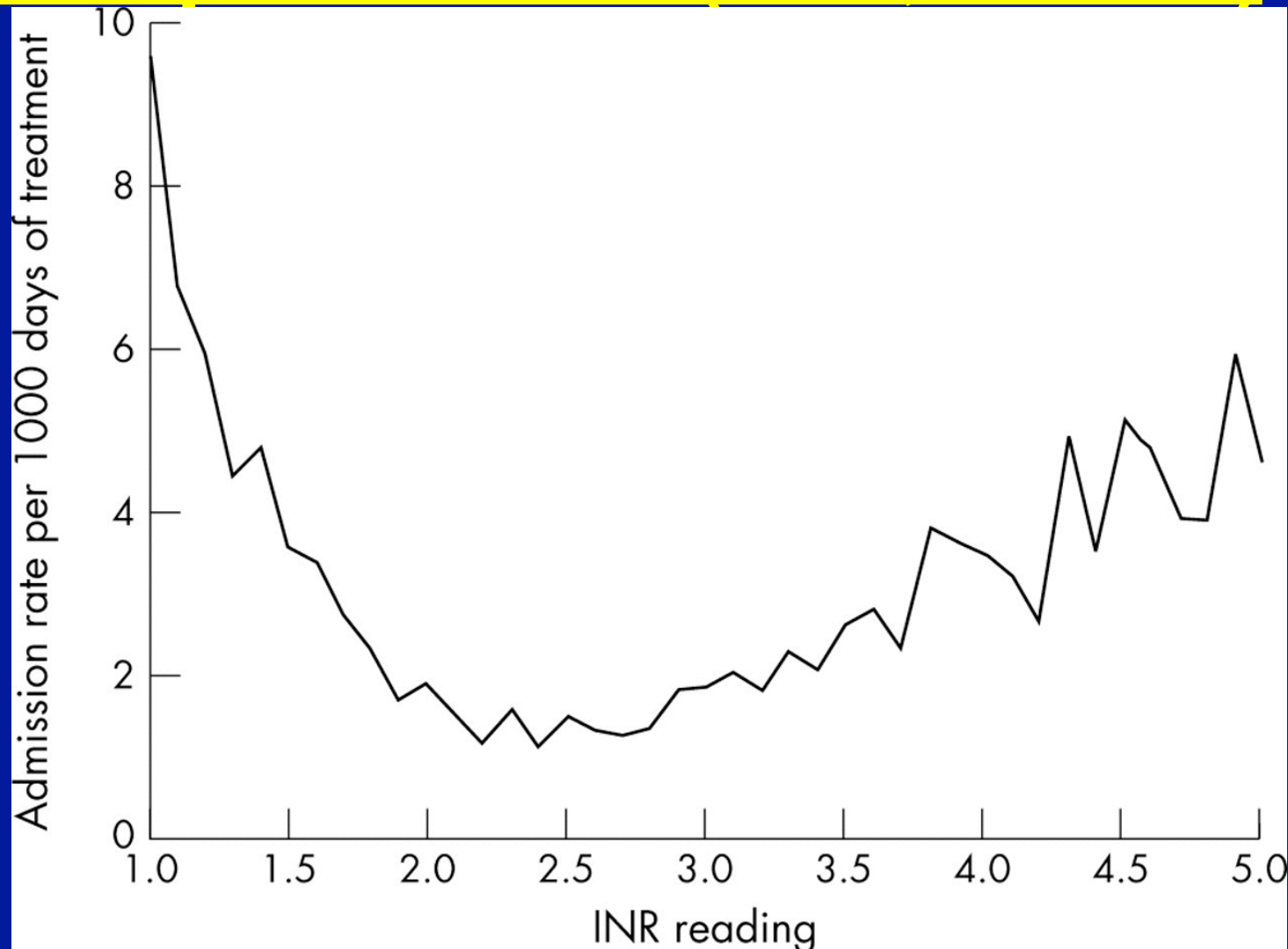
(Fang MC. J Am Geriatr Soc 2006; 54: 1231-1236)

INITIAL INR PREDICTS OVERALL INR (N=2,300)



(BJH 2005; 128: 513-519)

Out-of-Range INRs Lead to Hospitalization (N=2,223 AF)



(Heart 2005; 91: 472-477)

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

RISK FACTORS FOR AN ELEVATED INR

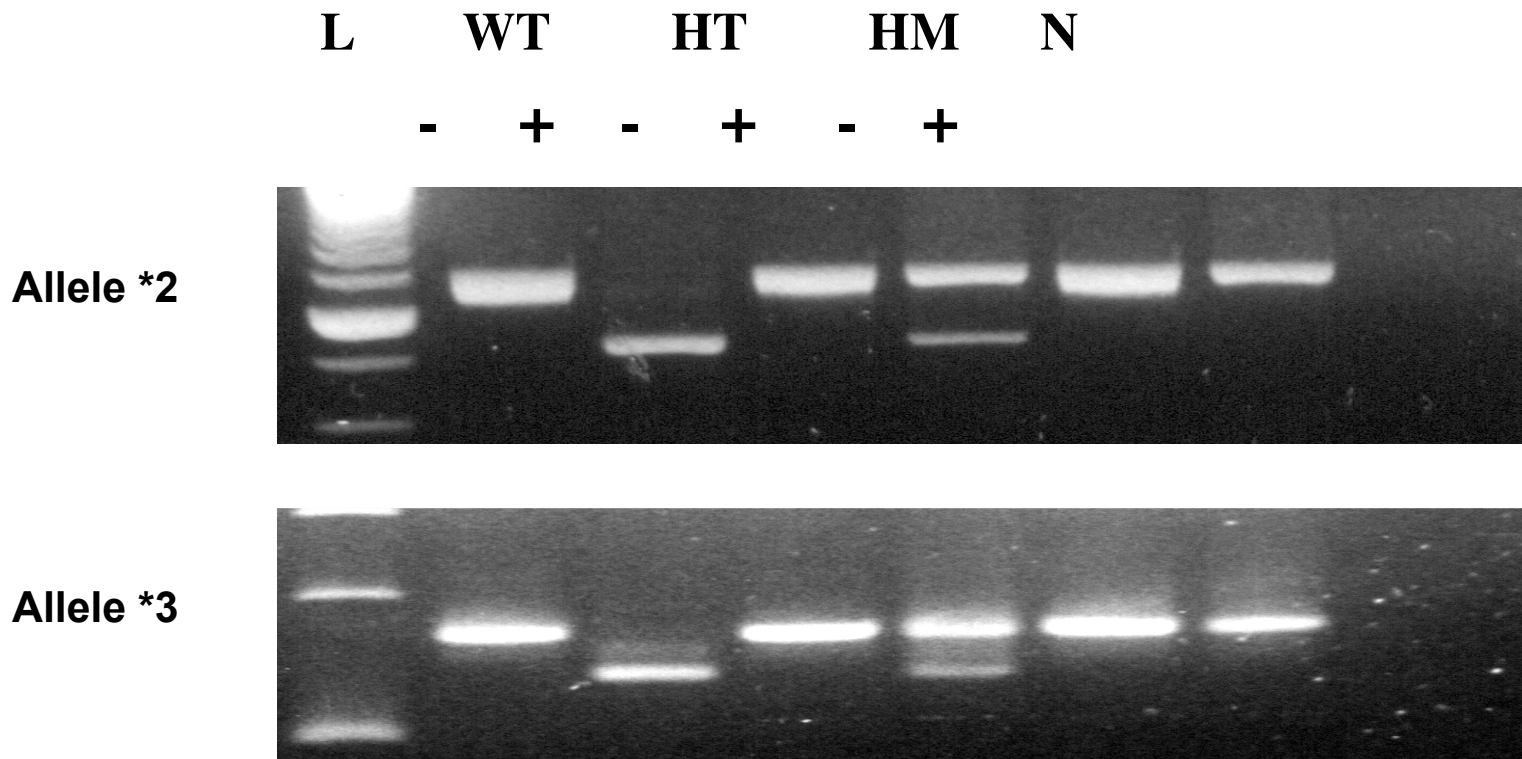
(It's not all Genetics)

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

GENETIC TESTING

1. Cytochrome P450 2C9 genotyping can identify mutations associated with impaired warfarin metabolism.
2. Vitamin K receptor polymorphism testing can identify whether patients require low, intermediate, or high doses of warfarin.
3. The major drawback in applying genotyping to warfarin dosing has been slow turnaround time.

CYP450 2C9*2 and *3 Polymorphisms



Joffe HV et al. Thromb Haemost 2004; 91: 1123-8

CYP2C9 POLYMORPHISMS: BWH

<u>WT</u>	<u>HT</u>	<u>HZ/cpd HT</u>
*1/*1	*1/*2	*2/*2
	*1/*3	*2/*3
		*3/*3

Dose 7.2 mg 4.1 mg 1.4 mg

(Joffe et al. Thromb Haemost 2004; 91: 1123-8)

VKORC1 HAPLOTYPES AND WARFARIN DOSE

<u>Haplotype</u>	<u>Dose</u>
A/A	2.7 mg
A/B	4.9 mg
B/B	6.2 mg

(Rieder et al. NEJM 2005; 352: 2285-93)

WARFARIN DOSE VARIANCE

1. 5 common *VKORC1* haplotypes account for 25% of warfarin dose variance.
2. CYP2C9 genotype accounts for 10% of warfarin dose variance.

(Rieder et al. NEJM 2005; 352: 2285-93)

WARFARIN NOMOGRAM: OBJECTIVE

Use clinical and genetic information to develop a warfarin nomogram that maintains warfarin naïve patients in the target INR range $> 70\%$ of the time.

IMPLICATIONS

A Partners Warfarin Nomogram that maintains patients in the target INR range > 70% of the time will:

- improve warfarin efficacy and patient safety
- reduce cost of frequent INR testing and treatment of warfarin complications
- demonstrate the role of genetic testing in clinical medicine

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)

WARFARIN NOMOGRAM:

Unique Aspects

1. Nomogram will incorporate genetic information prior to the 1st warfarin dose.
2. Nomogram will be fine tuned during the study.
3. Fills a > 50 year gap/ quest.
4. Begin a pharmacogenetic database for future trials.