UNIVERSITY of WASHINGTON

Warfarin Pharmacogenomics

David L. Veenstra, PharmD, PhD

Pharmaceutical Outcomes Research and Policy Program
Institute for Public Health Genetics
University of Washington
Seattle, WA

Warfarin—Current Situation

- Warfarin (Coumadin) is a commonly prescribed anticoagulant used to prevent clotting events in patients with mechanical heart valves, prior to major orthopedic surgery, deep vein thrombosis (DVT), and most commonly in atrial fibrillation (AF) patients.
- Warfarin has been used since 1954, and in 2004, over 16 million prescriptions were dispensed in the US.[1]
- Currently, there are no competing drugs on the market.

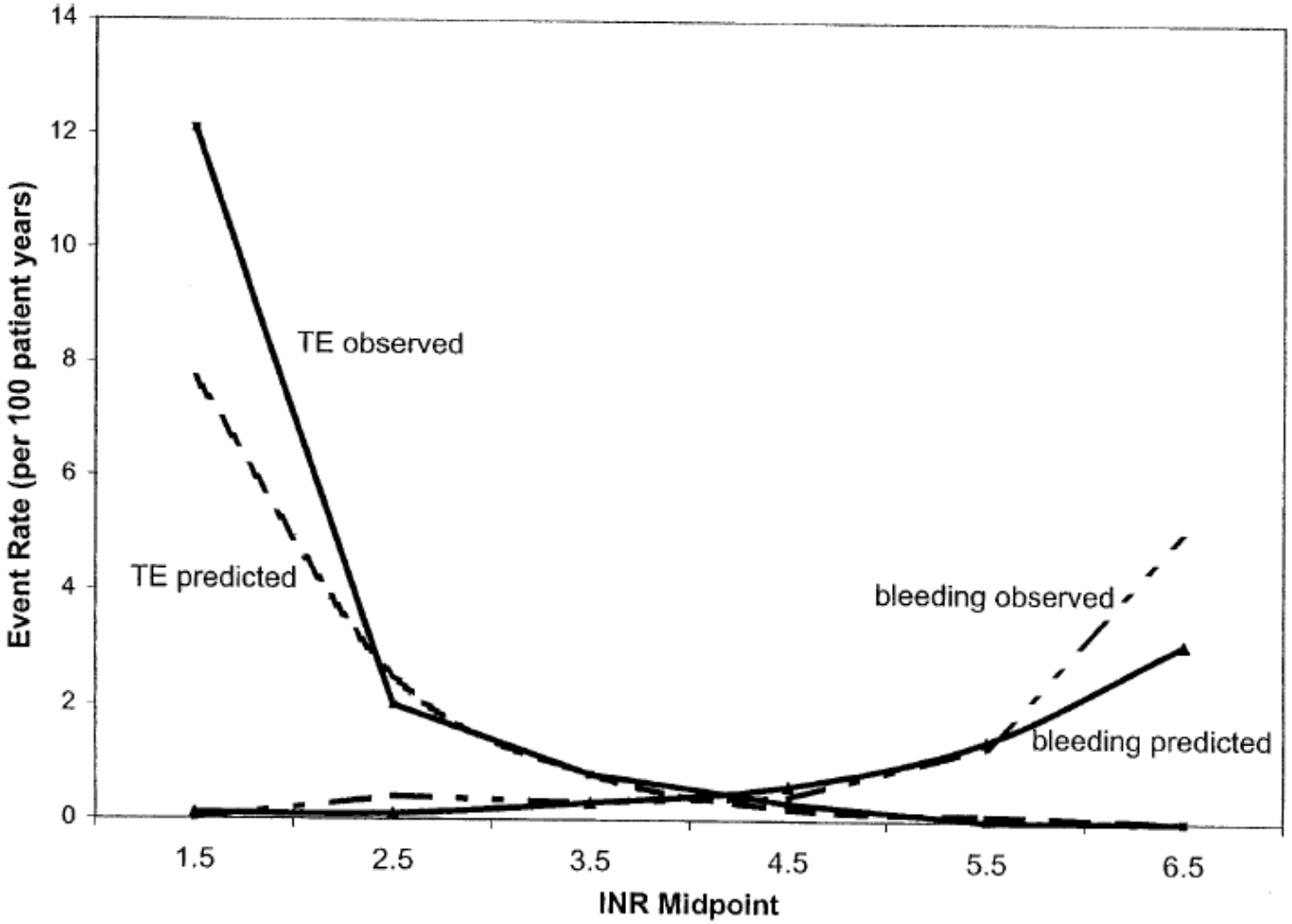
1) Drug Topics (2005)

Warfarin Efficacy

- Warfarin is a highly effective drug for reducing the risk of thromboembolic events
- Reduces ischemic stroke risk by 68% compared to no antithrombotic therapy and by 52% compared to aspirin in AF patients

1) Singer et al. (2004) Chest
2) Fihn et al. (1993) Ann Int Med

INR used to monitor patients



Samsa and Matchar, JTT 2000

Warfarin Safety

- The incidence of serious and life threatening bleeding events is approximately 2-10% in the first year and less thereafter
- Serious and life threatening bleeds are those requiring medical intervention, primarily gastrointestinal and intracranial
- Approximately 1% of serious/life threatening bleeds are fatal
- Costs
    - Serious: $3,000
    - Life threatening: $21,000
    - Fatal: $11,000
- Warfarin is underutilized, in part due to the perceived risk of bleeds

1) Fihn et al. (1993) Ann Int Med
2) Landefeld et al. (1989) Am J Med
3) Lafata et al. (2000) JGIM
4) Bungard et al. (2000) Arch Intern Med

Warfarin Initiation

- Clinical and demographic factors can have an important effect on warfarin dose requirement, necessitating chronic (e.g., lifetime) monitoring and dose adjustments.
  - Age, race, gender, comorbidities, comedications, and diet all effect INR and dose requirement
- Strategies for dose initiation
  1. Often 5mg for all patients
  2. Clinical “sensitivity factors” sometimes used, e.g., age, cancer, amiodarone use
  3. Formal dosing algorithms have been published, but not often used in clinical practice

Can Warfarin Management Be Improved?

- The percentage of time patients spend 'in range' varies from approximately 50 to 70%.
- Careful monitoring and dose adjustments (e.g., in anticoagulation clinics) can increase percent time INR in range by 10-20%

Thus, an individualized approach to warfarin management is the 'standard of care'.

Can this approach be improved using pharmacogenomics?

Clinical Validity

Warfarin and CYP2C9

- CYP2C9 first reported to metabolize warfarin in 1992[1]
- CYP2C9 variants discovered that affect dose a few years later[2]
  - *2 variant has 40% reduced warfarin metabolism
  - *3 variant has 90% reduced warfarin metabolism
  - CYP2C9 low dose variants: European 30% > African 4% > Asian 1%
  - ~10% of dose variation is determined by CYP2C9 genotype[3]

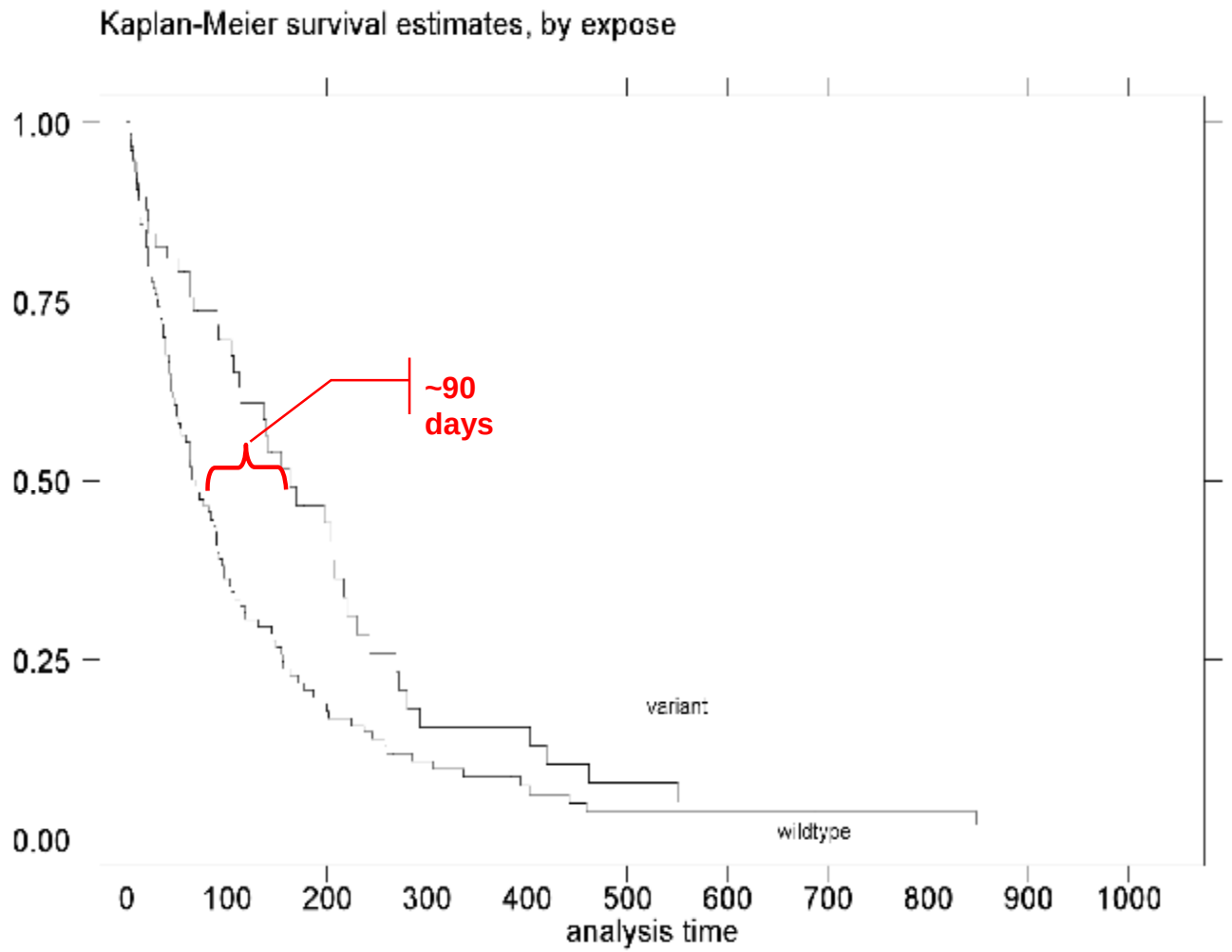
1) Rettie et al. (1992) Chem Res Toxicol
2) Steward et al. (1997) Pharmacogenetics
3) Reider et al. (2005) NEJM

CYP2C9 Variants and Bleeding Risk

- CYP2C9 variants *2 and *3 found to have significantly higher risk of serious or life threatening bleeds (HR 2.39)
- CYP2C9 variants have a 40% increased risk of a high INR (>4.0)

Higashi et al. (2002) JAMA

CYP2C9 and Time to Stable Dosing



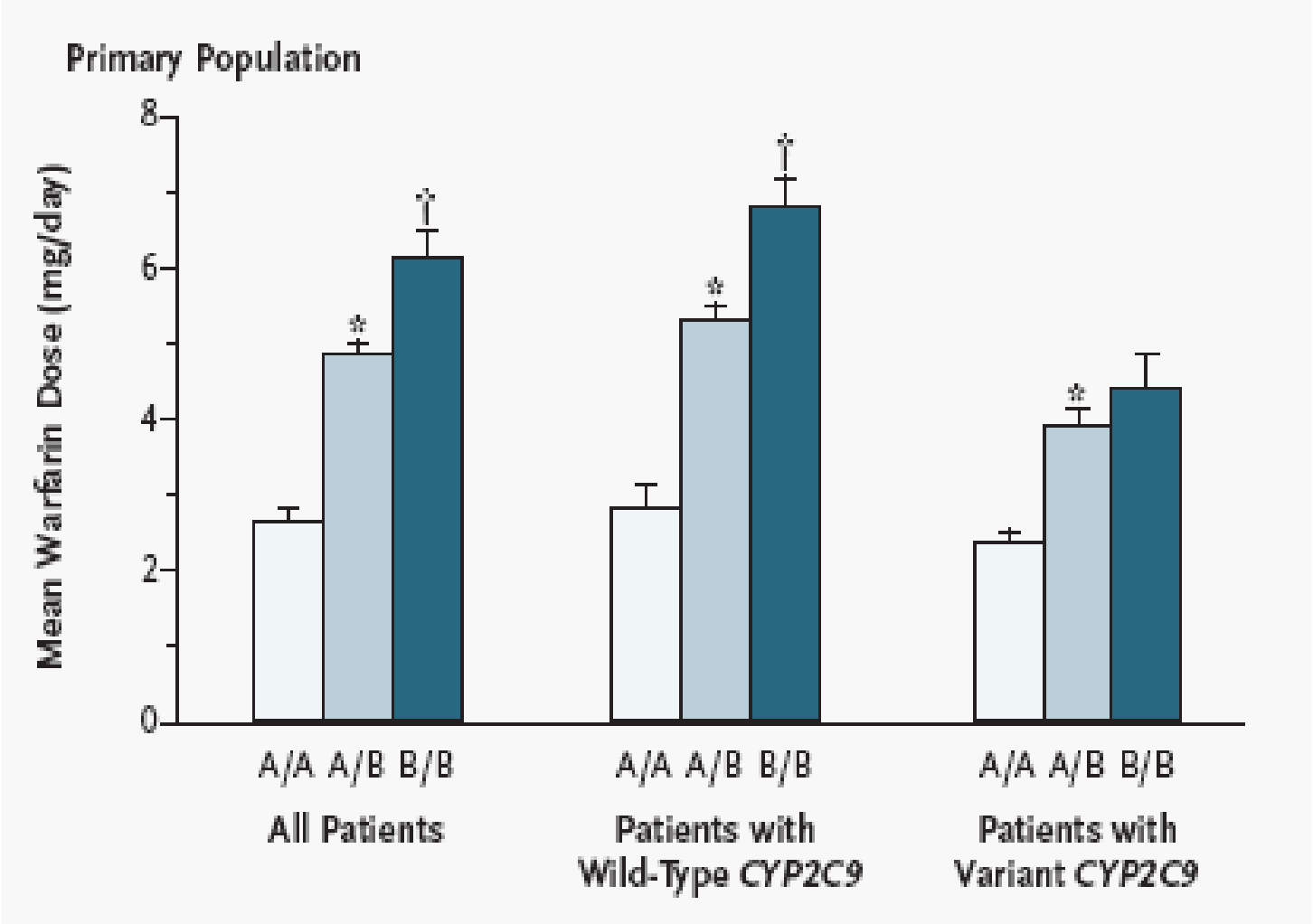
Higashi et al. (2002) JAMA

Warfarin and VKORC1

- VKORC1 (vitamin K epoxide reductase) gene identified in 2004
  - Variant form recognized as a reason for warfarin resistance
- VKORC1 codes for the warfarin drug target
  - 37% of whites, 14% of blacks and 89% of Asians have the A haplotype group associated with lower dose
  - 20-25% of dose is determined by VKORC1 genotype

1) Rost et al. (2004) Nature
2) Reider et al. (2005) NEJM

VKORC1 variants and dose



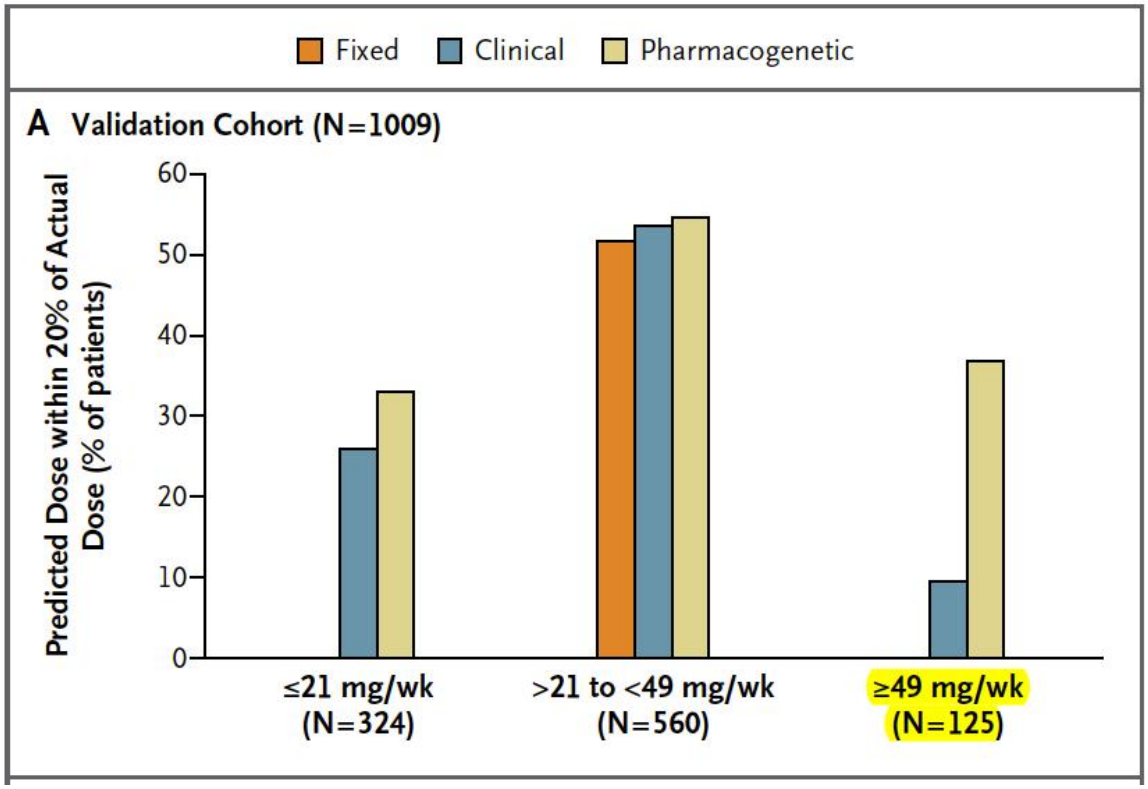
Reider et al. (2005) NEJM

Rationale for Genotype Testing

- If we can better determine the appropriate warfarin dose for an individual before treatment initiation, therapeutic, stable INR may be attained earlier, and thus there will be a decrease in bleeding (and clotting) events.
- May be additional benefits in subsequent management in regard to frequency of monitoring/visits etc.

International Warfarin PGx Consortium

- A warfarin dose prediction algorithm was recently developed by the International Warfarin Pharmacogenetics Consortium (IWPC), involving data from 5700 patients from 9 countries.



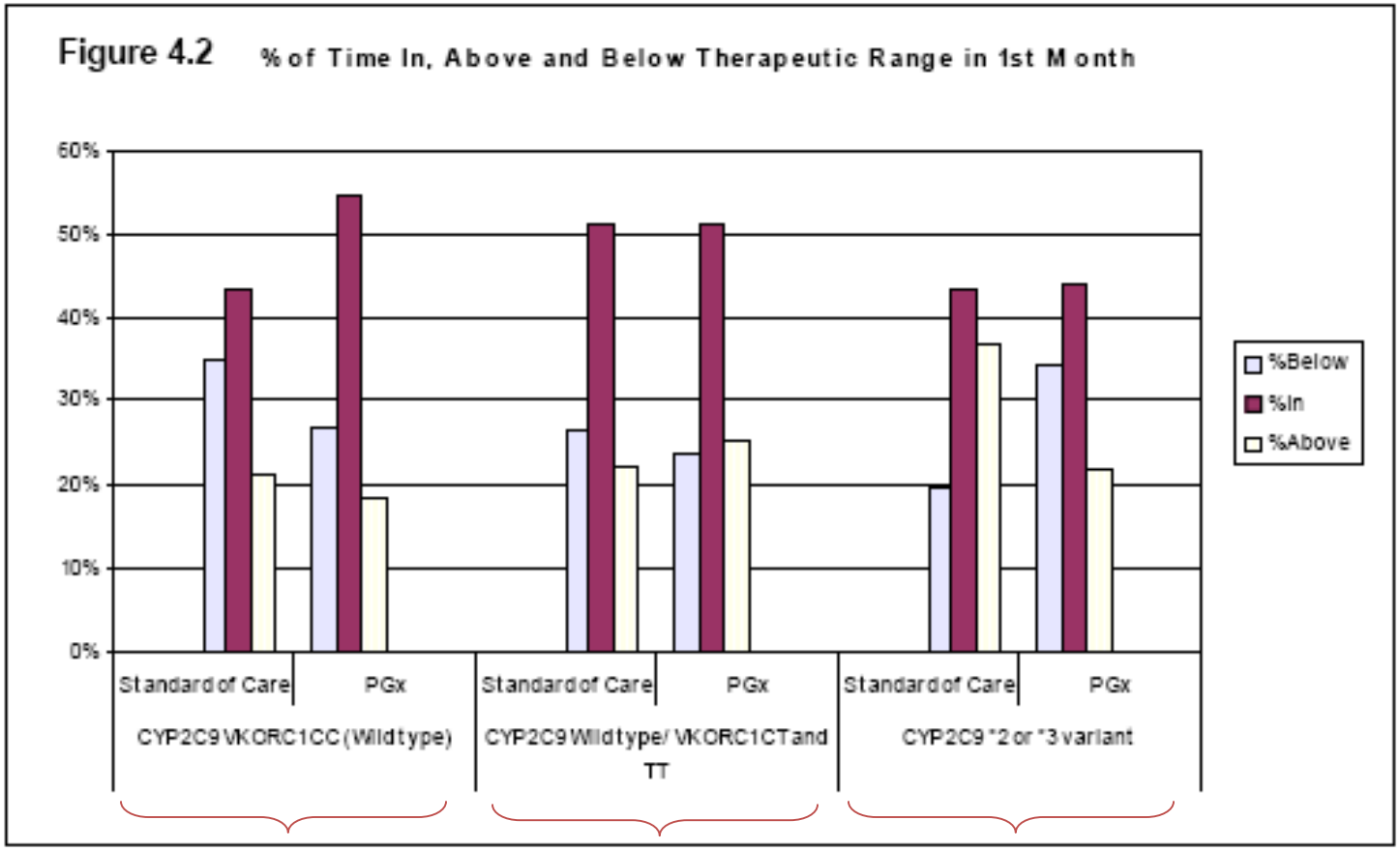
IWPC, NEJM 2009

Clinical Utility

RCT?

- Comparator
  - Standard of care vs. clinical algorithm vs. intense monitoring
- Bleeding as primary outcome
  - assuming 4-8% risk of major bleed in first year
  - 25% relative risk reduction in overall population
  - 5,000 – 10,000 patients required
- Consider use of surrogate marker
  - % time INR in-range common trial measure

Anderson et al, N=200



Wild-types: ↑ time in-range

VKOR variants: little change

CYP2C9 variants: trade-off

Anderson et al, Circulation 2007
Meckley et al, Pharmacoecon 2010

Caraco et al, N=185

Table 2 Anticoagulation details during the initiation phase (defined as first 8 days)

	Study group (*N*=95)	Control group (*N*=96)	*P*-values
Time to first INR > 2 (days)	4.80 ± 1.46	7.53 ± 3.06	< 0.001
Cumulative loading dose (mg) (until 1st ther. INR)	33.0 ± 13.9	46.8 ± 39.1	< 0.001
Average loading daily dose (mg)	8.55 ± 1.81	6.67 ± 2.05	< 0.001
Time spent at INR > 3 (days)	0.41 ± 0.86	0.44 ± 1.09	0.55

Table 3 Anticoagulation characteristics from induction to stable anticoagulation phase

	Study group (*N*=92)	Control group (*N*=93)	*P*-values
Time from induction to maintenance (days)	14.1 ± 6.9	32.2 ± 21.1	< 0.001
Maintenance dose (mg/day)	5.51 ± 3.09	6.23 ± 5.39	0.65
Maintenance INR	2.47 ± 0.20	2.46 ± 0.21	0.62
Time spent at INR > 3 (days)	1.77 ± 2.79 (12.6%)	6.58 ± 7.33 (20.4%)	< 0.001

- Drawing inferences from this study is difficult, due primarily to different follow-up periods for study and control groups

Caraco et al, Clin Pharm Ther 2007

NIH-Sponsored COAG Trial

- An NIH-funded RCT – the 'Clarification of Optimal Anticoagulation Through Genetics (COAG)' trial - has recently been initiated (S. Kimmel, PI)
  - 1200 patients
  - Clinical vs. clinical+genomic algorithms for dose initiation
  - Primary outcome: percentage of time in therapeutic range (INR) over the first month of treatment
- Scheduled for completion in the fall of 2011.

http://clinicaltrials.gov/ct2/show/NCT00839657

Systematic Reviews

- 2006 American College of Medical Genetics evidence-based review found
  - testing had analytic and clinical validity.
  - "no study has yet shown this intervention to be effective in reducing the incidence of high INR values, the time to stable INR, or the occurrence of serious bleeding events."
- A recent systematic review by Kangerelis and colleagues "did not find sufficient evidence to support the use of pharmacogenetics to guide warfarin therapy"

1. Flockhart et al, Gen Med 2008
2. Kangerelis et al, JGIM 2009

Recommendations and Guidelines

- The 2008 American College of Chest Physicians anticoagulation management guidelines state "we suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C)."

Ansell et al, Chest 2008

Cost Effectiveness

- An early analysis suggested testing could save $1B annually in the US. However, assumptions have been criticized.
- Several recent studies have similarly concluded that testing is unlikely to be cost effective unless:
  - testing costs drop significantly, and
  - effectiveness is established.

1. McWilliam et al, AEI-Brookings 2006
2. Veenstra, JTH 2007
3. Hughes et al, Pharmacoecon 2007
4. Patrick et al, Circ Card Qual Outcomes 2009
5. Eckman et al, Ann Int Med 2009
6. Meckley et al, Pharmacoecon 2010

Coverage Decisions

- In August 2009 CMS issued a coverage decision that specifies testing will only be reimbursed for patients initiating warfarin who are enrolled in an RCT that measures major bleeding and thromboembolic events (coverage with evidence development)

CMS, NCD 90.1

Regulatory

- On Jan. 22nd of 2010, FDA updated the drug label for warfarin to include dose ranges based on pharmacogenomic information.

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

- Testing is <u>not</u> required

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

Summary

- Validated relationships between variation in two genes and outcomes
- Plausible benefit
- Sparse evidence of clinical utility
- Evidence requirements variable