Contrasting Medical and Legal Standards of Evidence: Warfarin Case Study

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Warfarin

• Brand name: Coumadin
• Highly effective and commonly prescribed oral anticoagulant (stroke prevention)
  – 2 million new warfarin users annually
  – >20 million current U.S. prescriptions
• Prescribed following myocardial infarction, atrial fibrillation, stroke, venous thrombosis, prosthetic heart valve replacement, and following major surgery
• Works by blocking production of vitamin K dependent clotting factors
  – Takes time for depletion of existing clotting factors before PT (INR) affected
**Warfarin: Risks – Too Low of Dose**

- Too low of dose – risk of stroke
  - Risk of stroke in patients with atrial fibrillation
  - Warfarin prevents 20 strokes for each bleeding event
  - Only 50% of chronic AF patients are on warfarin – risk of stroke in untreated patients ∼ 12% per year
  - Risk of thrombotic blood clot or stroke when INR is < 2.0 (undertreated)

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**Warfarin: Risks – Too High of Dose**

- Too high of dose – risk of excessive bleeding
  - Results in bleeding (especially intracranial bleeding)
  - Major bleeding episodes in 1-2% of all patients; death in as many as 0.1-0.7%
  - One of the most common causes of serious adverse drug reactions (ADR)
    - 29,000 emergency room visits for bleeding events each year

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**Patient Monitoring**

- Risk of bleeding can be cut by more than 50% with proper monitoring
- Requires frequent and careful monitoring of the clotting parameter affected by warfarin, namely the prothrombin time (PT), expressed as International Normalized Ratio (INR)
  - PT - time to clot; Normal times are 10-13 sec (INR: Range 1.0 - 1.4)
- Initial testing should be every couple days until the INR is stabilized
- Once stabilized, subsequent testing is generally recommended once a month
- On warfarin therapy, a patient is kept at about 2-3x normal (PT = 20-39 seconds; INR = 2-3)
Vitamin K-dependent clotting factors (FII, FVII, FIX, FX, Protein C/S/Z)

Epoxide Reductase

\( \gamma \)-Carboxylase (GGCX)

Warfarin acts as a vitamin K antagonist

Warfarin

CYP2C9

Inactivation

CYP2C9 Polymorphisms

- CYP2C9 SNPs alter warfarin metabolism:
  - CYP2C9*1 (WT) - normal
  - CYP2C9*2 (Arg144Cys) - intermediate metabolizer
  - CYP2C9*3 (Ile359Leu) - poor metabolizer

- CYP2C9 alleles occur at:
  - European: *2 - 10.7%; *3 - 8.5%
  - Asian: *2 - 0%; *3 - 1-2%
  - African-American: *2 - 2.9%; *3 - 0.

Warfarin: Role of Pharmacogenetics

- CYP2C9 and VKORC1 genotypes account for up to 50% of the variability in dose recommendations
  - CYP2C9 - 18%
  - VKORC1 - 25%
  - Other factors include ethnicity, gender, other medications, weight/height, age

- Variants are common
  - 66% of Caucasians, 90% of east Asians have at least one CYP2C9 or VKORC1 variant
Once the Poster Child for Personalized Medicine

- Narrow therapeutic range
- Serious adverse effects of incorrect dose
  - Bleeding if too high
  - Clotting if too low
- Individual variation in dose requirements
- Known genetic variation that affects metabolism and dose requirement
- Early prediction of high clinical utility

Poster Child Promise Unfulfilled

- Three issues not adequately considered
  - Genetic information only assists with initial dose estimate
  - INR needs to be measured regardless
  - Dose adjustments usually needed either way
  - There was no clinical evidence of improved outcomes
2007: FDA Requires Genetic Warning Added to Label

- "In Milestone, FDA Pushes Genetic Tests Tied to Drug … warfarin's label will carry new information describing the role of genetics in dosing. The label will say that a lower initial warfarin dose 'should be considered for patients with certain genetic variations.'" WSJ
- "This information will benefit patients because it will describe why patients with a variation in the CYP2C9 and/or VKORC1 genes may need a lower warfarin dose than patients with the usual forms of these genes." U.S. FDA

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Ranges are derived from multiple published clinical studies. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

What is the Evidence for Clinical Utility?
Outcomes

• Patient oriented
  – Bleeding
  – Clotting
  – Death, disability
• Medical intermediate outcomes
  – Time to steady state INR
  – Percent of time in therapeutic range

Evidence Pyramid

• RCT, good design
• RCT, less rigorous design
• Cohort study
• Case control study
• Cross sectional study
• Correlation study
• Case reports (series)
• Common practice
• Expert opinion

Quality of Evidence Pyramid
RCT’s

- CoumaGen, 2007
- Marshfield, 2011
- COAG, 2015
- EU-PACT, 2015
  - J.K. Burmester et al., ’A Randomized Control Trial of Genotype‐based Coumadin Initiation, Genetics in Medicine 13, no. 6 (2011): 509‐518.

RCT Results

- No difference in out of range INR (3/4)
- No difference in PTTR (3/4)
- No difference in adverse reactions (4/4)
- More accurate prediction of steady state warfarin dose (1)
- Decreased bleeding at 6 months (not sure how gene testing affects this)
- Limitations: low power to detect adverse events, race issues, generalizability (special clinics)

Observational Studies

- Tend to find favorable intermediate outcomes
- Some have shown decreases in adverse events
- Concerns
  - Observational and non randomized controlled trials have high risk for bias
Meta Analyses

• No findings of increased adverse events
• One found decreased time to steady state INR but only when compared to fixed dose not adjusted dose comparison group

Clinical Guidelines and Current Practice

• AACP
  — Recommends against
• CPIC
  — Recommends using the genetic information if available
• General use (anecdotal)
  — Low to none

Insurance Coverage

• Medicare
  — Coverage with evidence development
• Aetna
  — Does not cover, considered investigational
• DRG
  — Hospitals then accept the cost
What are the implications for liability?

Relevant Factors for Physician Evaluation of Warfarin Genetic Testing

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Many warfarin medical malpractice cases

Anecdotal evidence of a handful of genetic/warfarin cases

More common is inadequate monitoring, medication and foods that affect need for dose change and monitoring

Lack of gene testing rarely the only cause of an adverse event and only effects initial dose estimate

Future Trends

• New oral anticoagulant medications
  – Cost, reversibility, rates of adverse effects, need to check INR

• Reduced cost of whole genome testing
  – Use of existing information

• Point of care tests
  – Makes more practical
Conclusions

• Outcome of a hypothetical med mal case for failure to recommend genetic test prior to prescribing warfarin by patient with major bleeding event likely a toss up
  – Likely to get to jury
  – And then?

• Once a malpractice case gets to the jury, the outcome is highly individualized and often unpredictable, often turning on the skills and effectiveness of the attorneys and expert witnesses involved, as well as the specific circumstances of the particular patient and the actions of the health care professional being sued.