GIFT: Genetics Informatics Trial of Warfarin Therapy for Deep Venous Thrombosis Prevention

Brian F. Gage, MD, MS\textsuperscript{1}, Anne R. Bass, MD\textsuperscript{2}, Hannah Lin\textsuperscript{1,3}, Scott C. Woller, MD\textsuperscript{4,5}, Scott M. Stevens, MD\textsuperscript{4,5}, Noor Al-Hammadi, MBChB, MPH\textsuperscript{1} and Charles S. Eby, MD on behalf of the GIFT Investigators

1 Washington University in Saint Louis, St. Louis;
2 Hospital for Special Surgery, New York;
3 University of Massachusetts, Worcester;
4 Intermountain Healthcare, Salt Lake City;
5 University of Utah, Salt Lake City;

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The Problem: Warfarin works, but

Warfarin causes more emergency department visits among the elderly than any other drug (N. Shehab *JAMA* 2016).

INR = International Normalized Ratio. Values > 3 or 4 predispose to bleeding.
Genetics Informatics Trial (GIFT) of Warfarin Therapy for DVT Prevention

• Hypothesis: Pharmacogenetic dosing of warfarin therapy decreases the rate of adverse events vs. clinical-algorithm dosing
CYP2C9
CYP1A1
CYP1A2
CYP3A4
Oxidized Vitamin K
Reduced Vitamin K
O2
Hypofunctional
F. II, VII, IX, X
Functional
F. II, VII, IX, X
GGCX
VKORC1
CO2
Warfarin
CALU
K1-OH
CYP4F2
CYP2C9
R-warfarin
S-warfarin

Gage B & Eby C. Pharmacogenomics J. 2004
Warfarin Pharmacogenetics

• Cytochrome P450 2C9 (CYP2C9) SNPs slow S-warfarin metabolism
• VKORC1-1639 G>A Vitamin K epoxide reductase increases warfarin sensitivity
• CYP4F2 V433M reduces vitamin K clearance
2 x 2 Factorial Design

Genetic Dosing

- INR 2.5
- INR 1.8

Clinical Dosing

- INR 2.5
- INR 1.8
Genotyping Strategy

• Initially: Genotyping at clinical sites with retrospective confirmation and DNA banking by Central Laboratory

• Later: Central laboratory provided pre-surgery genotyping for all clinical sites

• Genotype Method: Predominantly GenMarkDx eSensor instrument and reagents
Randomization & Double Blinding

• Randomized 1:1 to genetic vs. clinical dosing
  – stratified by arthroplasty site, self-identified race, and center: HSS, Intermountain Healthcare, Rush, University of Utah, UT Southwestern, and WUSTL

• Participants and study personnel were blind to study arm and genotype, but not to warfarin dose
Primary Outcome Was a Composite of:

• Major bleeding within 30 days,
• INR $\geq 4$ within 30 days,
• Death within 30 days, and
• Venous thromboembolism (VTE) confirmed by objective testing within 60 days of arthroplasty
  – Patients were screened for DVT using Duplex US
Statistical Analyses

• Modified intention-to-treat basis
  – included all randomized participants who received 1+ doses of warfarin.

• A priori high-risk subgroup:
  – Participants whose clinical and genetic predicted doses (on day 1) differed by $\geq 1.0$ mg/day.

• Two-sided alpha of 0.05, partitioned:
  – 0.044 alpha required in total cohort
  – Remaining alpha in high-risk subgroup

• 1600 participants provided 80% power
GIFT CONSORT Diagram

Randomized (n=1650)

Allocated to Genetic Dosing (n=831)
- Received allocated intervention (n=808)
- Did not receive intervention (n=23)

Allocated to Clinical Dosing (n=819)
- Received allocated intervention (n=789)
- Did not receive intervention (n=30)

Follow-Up

Lost to follow-up before day 30 (n=1)

Analysis

Lost to follow-up before day 30 (n=0)

Analyzed (n=808)
- Excluded from analysis (n=0)
- Duplex US missing (n=36)

Analyzed (n=789)
- Excluded from analysis (n=0)
- Duplex US missing (n=31)
## GIFT Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Genetic N=808</th>
<th>Clinical N=789</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (SD)</td>
<td>72.2 (5.3)</td>
<td>72.0 (5.5)</td>
</tr>
<tr>
<td>Indication: N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip Replacement</td>
<td>207 (25.6)</td>
<td>199 (25.2)</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>601 (74.4)</td>
<td>590 (74.8)</td>
</tr>
<tr>
<td>Female: N (%)</td>
<td>522 (64.6)</td>
<td>496 (62.9)</td>
</tr>
<tr>
<td>Race: N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>52 (6.4)</td>
<td>50 (6.3)</td>
</tr>
<tr>
<td>American Indians or Native</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asian or Indian Subcontinent</td>
<td>16 (2.0)</td>
<td>13 (1.7)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>735 (91.0)</td>
<td>719 (91.1)</td>
</tr>
<tr>
<td>Statin†: N (%)</td>
<td>365 (45.2)</td>
<td>402 (51.0)</td>
</tr>
<tr>
<td>Diabetes: N (%)</td>
<td>116 (14.4)</td>
<td>105 (13.3)</td>
</tr>
</tbody>
</table>

† P = 0.02.
From Days 1-11, WarfarinDosing.org Provided Guidance; Clinicians Did the Dosing

<table>
<thead>
<tr>
<th>Therapy Date</th>
<th>INR</th>
<th>Anticipated maintenance dose (mg/d)</th>
<th>Dose (mg) Taken</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 05-01-2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 05-02-2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 05-03-2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 05-04-2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Today’s recommendation:** ~4.0 mg
**Maintenance estimate:** ~3.6 mg/day.
From Days 1-11, WarfarinDosing.org Provided Guidance; Clinicians Did the Dosing

<table>
<thead>
<tr>
<th>Therapy Day</th>
<th>Date</th>
<th>INR</th>
<th>Today’s recommendation (mg)</th>
<th>Anticipated maintenance dose (mg/d)</th>
<th>Dose (mg) Taken</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>05-01-2011</td>
<td></td>
<td></td>
<td>1.5mg</td>
<td>4.0</td>
<td>PM</td>
</tr>
<tr>
<td>2</td>
<td>05-02-2011</td>
<td></td>
<td></td>
<td>1.5mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>05-03-2011</td>
<td></td>
<td></td>
<td>1.5mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>05-04-2011</td>
<td></td>
<td></td>
<td>1.5mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Today’s recommendation: ~4.0 mg
Maintenance estimate: ~3.6 mg/day.
Table 1: Primary Results (N = 1597)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Genotype Group, N = 808, % (N)</th>
<th>Clinical Group, N = 789, % (N)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed (days 1-30)</td>
<td>0.25% (2)</td>
<td>1.01% (8)</td>
<td>0.062</td>
</tr>
<tr>
<td>INR ≥ 4 (days 1-30)</td>
<td>6.9% (56)</td>
<td>9.8% (77)</td>
<td>0.041</td>
</tr>
<tr>
<td>VTE (days 1-60)</td>
<td>4.1% (33)</td>
<td>4.8% (38)</td>
<td>0.48</td>
</tr>
<tr>
<td>Death (days 1-30)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total</td>
<td>10.8% (87)</td>
<td>14.7% (116)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Genetic dosing reduced the relative risk of adverse outcomes by 27% \((RR=0.73; 95\% \ CI: 0.56 – 0.95)\).
Benefit of Genetic Dosing Was Consistent:

- There was no significant interaction in any of these subgroups
  - African-Americans
  - $CYP2C9$ genotype
  - Target INR 2.5 vs. 1.8
  - Hip vs. knee arthroplasty
Secondary Outcome: Percentage of Time in the Therapeutic Range (PTTR) During Days 4-28 of Warfarin Therapy

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Genotype-Group</th>
<th>Clinical Group</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>PTTR</td>
<td>N</td>
</tr>
<tr>
<td>Overall</td>
<td>803</td>
<td>54.7</td>
<td>785</td>
</tr>
<tr>
<td>High-risk</td>
<td>321</td>
<td>55.5</td>
<td>333</td>
</tr>
<tr>
<td>Stratified by Target INR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target 2.5 (2.0-3.0)</td>
<td>399</td>
<td>56.2</td>
<td>389</td>
</tr>
<tr>
<td>Target 1.8 (1.5-2.1)</td>
<td>404</td>
<td>53.3</td>
<td>396</td>
</tr>
</tbody>
</table>
GIFT Conclusions

• Algorithm-assisted warfarin dosing is safe
  – Dosing algorithms from WarfarinDosing.org should be integrated into EMRs

• Genotype-guided dosing reduced the relative risk of adverse outcomes by 27%
  – Improved INR control, especially among high-risk subgroup.

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