A Randomized Trial Comparing Genotype-Guided Dosing of Warfarin to Standard Dosing: The EU Pharmacogenetics of Anticoagulant Therapy (EU-PACT) Warfarin Study

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on behalf of the EU-PACT Warfarin Trial Investigators
Warfarin

- Number of users: 1-1.5% of population
- Dose (mg) range per day: 0.5-20

Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

McLeod and Jonas, 2009

FDA Label Changes (2007, 2010)
EU-PACT Warfarin RCT

AIM

- To determine whether genotype-guided dosing of warfarin was superior to standard clinical care over 3 months in patients with AF or VTE previously naïve to warfarin

DESIGN

- Pragmatic single-blind two-arm parallel group randomized controlled trial
Warfarin Dosing – Standard Clinical Care

Thrombotic disorder
- Clinical decision

Loading Dose
- 3 doses
- 10,5,5mg
- 5,5,5mg (over 75 years)

Day 4
- INR checked
- Dosing – using clinical practice

Day 6 onwards
- INR checked
- Dose adjusted according to INR – local clinical practice
The Genetic Warfarin Dosing Pathway

**Thrombotic disorder**
- Clinical decision

**Loading Dose**
- Individualised
- Algorithm developed with genetic and clinical factors

**Day 4**
- INR checked
- Dosing – individualised based on clinical and genetic factors

**Maintenance**
- INR checked
- Dose adjusted according to INR by computer software

**Usual clinical care**

**Dose revision algorithm**
Point-of-Care Genotyping Assay

Time <2 hours
Results for:
- **CYP2C9*2**
- **CYP2C9*3**
- **VKORC1 (-1639G>A)**
Randomized (n=455)

Allocation

- Allocated to genotype guided dosing (n=227)
  - Received Warfarin (n=222)
  - Did not start Warfarin for clinical reasons (n=5)

- Allocated to non genotype guided dosing (n=228)
  - Received Warfarin (n=225)
  - Did not start Warfarin for clinical reasons (n=3)

Follow-Up

- Dropped out before day 13 (n=11)
  - Lost to follow-up (n=1)
  - Withdrew consent (n=1)
  - Warfarin discontinued for clinical reasons (n=3)
  - Discontinued trial due to dosing errors (n=5)
  - Patient died (n=1)

- Dropped out before day 13 (n=9)
  - Withdrew consent (n=3)
  - Warfarin discontinued for clinical reasons (n=5)
  - Discontinued trial as patient did not want to take Warfarin (n=1)

Analysis

- Analysed (n=211)

- Analysed (n=216)

Dropped out after day 13 (n=11)
- Lost to follow-up (n=8)
- Warfarin discontinued for clinical reasons (n=1)
- Patient died (n=2)

Dropped out after day 13 (n=20)
- Lost to follow-up (n=5)
- Warfarin discontinued for clinical reasons (n=8)
- Discontinued trial as patient did not want to take Warfarin (n=3)
- Patient’s target INR changed (n=1)
- Patient died (n=2)
- Unable to obtain venous INR results (n=1)
Results: Baseline Variables

- Well matched between the two arms
- Most were males (61.0%; n=277),
- 98.5% (n=447) were White
- Mean age of 67.3 (SD 13.7) years.
- Majority of patients (72.1%, n=328) had AF
- Those with VTE received heparin for at least 5 days
- Genotype distributions between the two arms similar and consistent with the literature of allele frequencies
### Primary Outcome Measure

Percent time within therapeutic INR range 2.0-3.0 (TTR) during 12 weeks following the initiation of warfarin therapy

<table>
<thead>
<tr>
<th>Genotyped arm %TTR</th>
<th>Standard dosing (control) arm %TTR</th>
<th>Adjusted Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT ANALYSIS (n= 211 vs 216)</strong></td>
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<tr>
<td>67.4%</td>
<td>60.3%</td>
<td>7%</td>
<td>P&lt;0.001</td>
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<td><strong>PER-PROTOCOL (n=166 vs 184)</strong></td>
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<tr>
<td>68.9%</td>
<td>62.3%</td>
<td>6.6%</td>
<td>P=0.001</td>
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</table>

Sensitivity analyses did not change the conclusions of the primary analysis
## Differences in %Time in Therapeutics Range According to Treatment Month

<table>
<thead>
<tr>
<th></th>
<th>Genotyped arm (95% CI)</th>
<th>Control arm (95% CI)</th>
<th>Difference (%) (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted mean % Time in range</strong></td>
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<tr>
<td><strong>weeks 1-4</strong></td>
<td>55.72 (52.12, 59.33)</td>
<td>46.96 (43.36, 50.56)</td>
<td>8.77 (4.39, 13.14)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>weeks 5-8</strong></td>
<td>74.36 (69.57, 79.16)</td>
<td>64.19 (59.40, 68.98)</td>
<td>10.17 (4.36, 15.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>weeks 9-12</strong></td>
<td>75.47 (71.21, 79.72)</td>
<td>74.11 (69.81, 78.40)</td>
<td>1.36 (-3.84, 6.57)</td>
<td>0.607</td>
</tr>
</tbody>
</table>
Differences Between Genotyped-Guided Group and Control Group

International Normalized Ratio

Time in Therapeutic Range
**Secondary Outcomes**

- **Time to Reach Therapeutic INR**
  - HR 1.43 (95% CI 1.17, 1.76)
  - P<0.001

- **Time to Reach Stable Dose**
  - HR 1.40 (95% CI 1.12, 1.74) P<0.001

Genotyping reduced risk of, and % time above, an INR≥ 4.0
Genotyping reduced the number of dose adjustments
Bleeding and Thromboembolic Events

- No major bleeds (according to ISTH criteria)
- Three clinically serious bleeds (all in the standard dosing arm)
- No difference in minor bleeds between the two arms (35.1% vs 36.9%)
- Only one thromboembolic event
Conclusions

- Genotype guided dosing before starting warfarin was compared to standard dosing. This:
  - Increased the TTR by approximately 7% (the primary outcome)
  - Reduced over-anticoagulation (INR>4.0) by 69%
  - Reduced the time required to reach therapeutic INR by about 28%
  - Improved the time required to reach stable dose by 25%
  - Reduced the number of warfarin dose adjustments by 9%

- Novel algorithmic strategy
- POC assay produced results in 2h
- Limitation: evaluated a surrogate (INR) and did not have power to assess clinical events of bleeding and thrombosis
A Randomized Trial of Genotype-Guided Dosing of Warfarin

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ABSTRACT

BACKGROUND

The level of anticoagulation in response to a fixed-dose regimen of warfarin is difficult to predict during the initiation of therapy. We prospectively compared the effect of genotype-guided dosing with that of standard dosing on anticoagulation control in patients starting warfarin therapy.

METHODS

We conducted a multicenter, randomized, controlled trial involving patients with atrial fibrillation or venous thromboembolism. Genotyping for CYP2C9*2, CYP2C9*3, and VKORC1 (−1639G→A) was performed with the use of a point-of-care test. For patients assigned to the genotype-guided group, warfarin doses were prescribed according to pharmacogenetic-based algorithms for the first 5 days. Patients in the control (standard dosing) group received a 3-day loading-dose regimen. After the initiation period, the treatment of all patients was managed according to routine clinical practice. The primary outcome measure was the percentage of time in the therapeutic range of 2.0 to 3.0 for the international normalized ratio (INR) during

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- All patients who took part in the trial
- All Centers to recruited patients
- Nurses, data managers and monitors for help in running the trials
- LGC for the POC genotyping platform
- EU-FP7 Programme for funding the trial