Pharmacogenetic-guided and standard dosing did not differ for out-of-range INRs in patients initiating warfarin therapy


Clinical impact ratings: Cardiology ★★★★★☆☆ Hematol/Thrombo ★★★★★★★

**Question**
In patients initiating oral anticoagulation with warfarin, how do pharmacogenetic-guided dosing (PGD) and standard dosing (SD) compare for percentage of out-of-range international normalized ratios (INRs)?

**Methods**
Design: Randomized controlled trial (RCT).
Allocation: Unclear allocation concealment.*
Blinding: Blinded (clinicians and patients).*
Follow-up period: ≤ 3 months.
Setting: Anticoagulation clinic at Intermountain Healthcare, Utah, USA.
Patients: 206 patients 18 to 86 years of age (mean age 61 y, 53% men out of 200 patients) in whom anticoagulation with a target INR range of 2 to 3 was indicated. Exclusion criteria included pregnancy, lactation, and comorbid conditions precluding standard dosing (e.g., advanced physiologic age, serum creatinine level > 2.5 mg/dL, hepatic insufficiency, or terminal disease).
Intervention: Warfarin initiation with PGD (n = 101) or SD (n = 99). PGD was based on a regression equation that included genotype, age, sex, and weight and generated scores in 14 dose increments from 1 to 8 mg/d; twice the dose was given on the first 2 days, and subsequent dose modification was based on INR. SD was 10 mg/d given on the first 2 days, followed by 5 mg/d up to 90 days; dose adjustments on days 5 to 7 were based on INR measured at day 5, and dose adjustment after day 7 was based on a standardized warfarin dosing protocol.
Outcomes: Percentage of out-of-range INRs (< 1.8 or > 3.2) per patient. Secondary outcomes were time to first supratherapeutic INR (or use of vitamin K), duration within therapeutic INR range, proportion of patients reaching therapeutic INR at days 5 and 8, total number of INR measurements and dose adjustments, and adverse events. The study had 80% power to detect a 20% difference in out-of-range INRs between groups.
Patient follow-up: 97% (intention-to-treat analysis).

**Main results**
Groups did not differ for percentage of out-of-range INRs per patient (Table). The PGD group had fewer required dose adjustments per patient than did the SD group (difference between groups 0.62, 95% CI 0.04 to 1.19). Groups did not differ for any other secondary outcomes.

**Conclusion**
Pharmacogenetic-guided and standard dosing did not differ for out-of-range INRs in patients initiating warfarin therapy.

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<table>
<thead>
<tr>
<th>Outcome at ≤ 3 mo</th>
<th>Pharmacogenetic</th>
<th>Standard</th>
<th>RRR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out-of-range INRs per patient</td>
<td>31%</td>
<td>33%</td>
<td>7.9% (38 to 39)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

†INR = international normalized ratio; other abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article.

**Commentary**
In recent years, elegant scientific work (1) has shown that the CYP2C9 and VKORC1 enzymes play an important role in the effect of warfarin on coagulation. Many studies (1) have shown that certain genetic mutations of CYP2C9 and VKORC1 are associated with a ≤ 50% decrease (compared with wild type) in dose required to achieve a therapeutic anticoagulant effect. Supporters of genetic testing point out that, given the potential added costs of genetic testing (which were not assessed in this study), compelling evidence from well-designed RCTs is needed to show that genetic testing adds clinically meaningful and cost-effective benefits over standard warfarin management. Until then, clinicians should continue to rely on such factors as age, sex, weight, concomitant medications, comorbid conditions, and timely INR monitoring to safely initiate and manage warfarin therapy.

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**References**