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

Anderson JL, Horne BD, Stevens SM, et al. **Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation.** Circulation. 2007;116:2563-70.

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.

Sources of funding: Deseret Foundation; Heart and Lung Institute; LDS Hospital; Intermountain Healthcare; Critical-Path Institute.

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*See Glossary.

Pharmacogenetic vs standard dosing of warfarin in patients initiating oral anticoagulation therapy†

Outcome at ≤ 3 mo	Pharmacogenetic	Standard	RRR (95% CI)	NNT
Out-of-range INRs per patient	31%	33%	7.9% (–38 to 39)	Not significant

†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, when combined with other factors (e.g., age, sex, weight, concomitant medication use), knowledge of a patient's genotype can account for > 50% variation in warfarin dosage. Pharmacogenetic testing may help clinicians to select individual warfarin doses more accurately, which is appealing because warfarin has a narrow therapeutic index, and a disproportionately large number of bleeding complications occur early after the start of warfarin therapy (2).

The results of the timely RCT by Anderson and colleagues emphasize the need for caution before adopting genetic testing as part of routine management of warfarin-treated patients. Although the PGD group had fewer dosing changes and INR measurements, these differences may be partly explained by a key aspect of the study design: The SD group was given a fixed starting warfarin dose of 10 mg regardless of age, sex, and weight, whereas these variables, which are known to influence INR stability, were considered in the PGD group. Importantly, although this design should have favored the PGD group, genetic testing did not result in a difference in the primary endpoint, percentage of out-of-range INRs.

The results of this RCT do not exclude the possibility that genetic testing can simplify warfarin dosing and, through greater INR stability, reduce risk for bleeding and thromboembolic complications. However, 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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