Genetic dosing algorithm underestimates the warfarin dose requirement among patients having severe thrombosis and/or thrombophilia

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BACKGROUND AND OBJECTIVES

- Genetic profiling may help to predict warfarin dosing in certain patient groups (1)
- Despite anticoagulation some thrombophilia patients are at increased risk for thrombosis
- Data on the accuracy of genetic dosing algorithms in thrombophilia patients are limited

PATIENTS AND METHODS

- 50 patients with severe thrombosis and/or thrombophilia referred for consultation and thrombophilia testing to the Helsinki University Hospital Coagulation Center (Table 1-2)
- Samples for genetic profiling to analyze warfarin metabolism associated SNPs
  - *CYP2C9* common single nucleotide polymorphisms (SNP) *2 and *3
  - *VKORC1* SNP 1639G>A
- Warfarin dose was estimated with Gage and IWPC algorithms based on genotype (2-3)
- Height, weight, smoking and concurrent medication recorded from the archives (Table 1)
- Warfarin dose was recorded when stable INR levels had been reached
  = Real-life warfarin dose

CONCLUSIONS

- Thrombophilia patients using warfarin are, on average younger than conventionally
- Warfarin dose requirement in these patients is clearly higher than usually
- Real-life warfarin doses were higher than the genetically predicted doses

RESULTS

- Patients were young (mean <50 years, 68% women, Table 1)
- Half the patients (54%) carried a thrombophilia in laboratory screen
- Prevalence of warfarin metabolism associated SNPs was 72% (Table 3)
- 13 patients (26%) had more than one of these SNPs
- The dosing algorithm estimates were lower than the actual prescribed real-life dose ($p<0.05$, Figure, Table 4)
- Correlation between the dose estimates and real-life dose was poor (Figure)

Table 1: Patient characteristics, n=50

Age, years (range)	47 (20-76)
Women (%)	34 (68)
BMI (SD)	27 (6)
Smoking (%)	4 (8)
Statin use (%)	10 (20)
ASA use (%)	11 (22)

Table 2: Prevalence of thrombosis and/or thrombophilia, n=50

DVT or PE (%)	33 (66)
Stroke (%)	4 (8)
Arterial thrombosis (%)	4 (8)
Other thrombosis (%)	5 (10)
Valvular replacement (%)	4 (8)
FV Leiden (%)	14 (28)
FII variant (%)	6 (12)
AT, PC or PS deficiency (%)	4 (8)
Phospholipid antibodies (%)	7 (14)

DVT, deep vein thrombosis; PE, pulmonary embolism; AT, antithrombin; PC, protein C; PS, protein S

Table 3: Distribution of warfarin metabolism SNPs, n=50

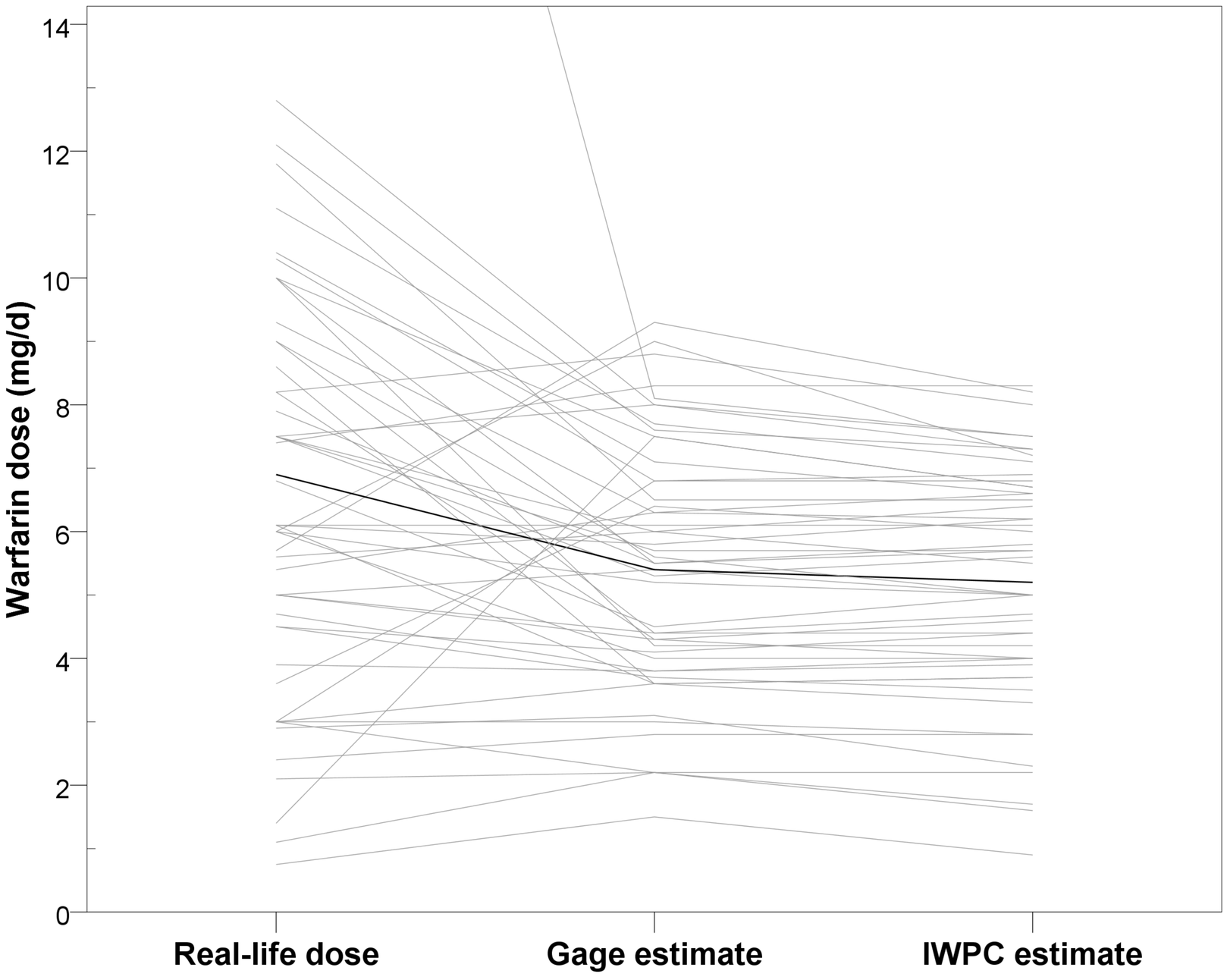
		VKORC1 c.-1639G/G	c.-1639G/A	c.-1639A/A	Total
CYP2C9	*1/*1	14	12	4	30
	*1/*2	4	1	3	8
	*1/*3	3	3	1	7
	*2/*3	2	1	2	5
Total		23	17	10	50

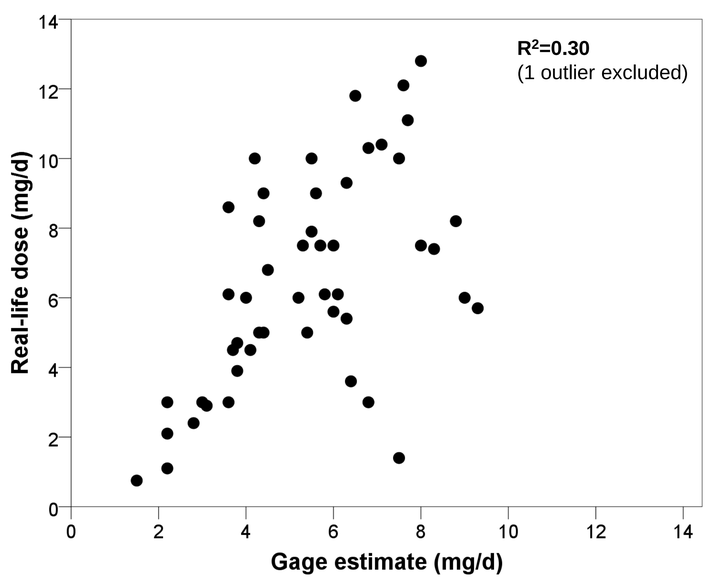
Table 4: Estimated and real-life warfarin dose (SD) n=50

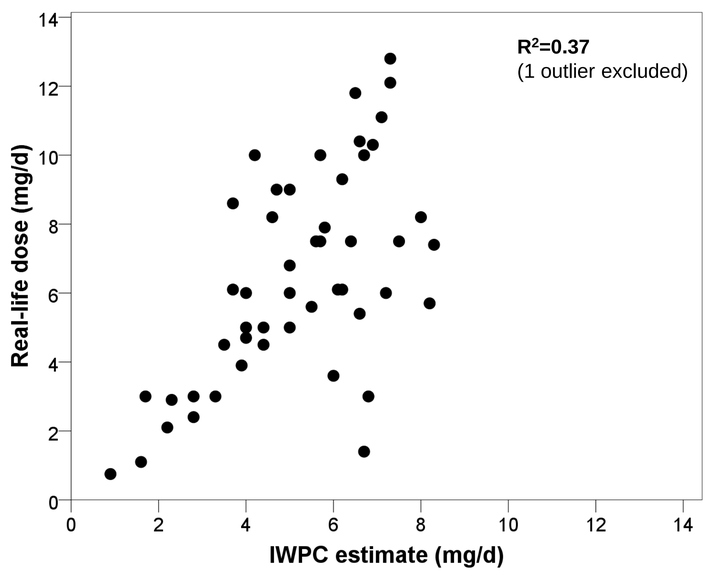
Gage dose estimate (2)	5.4 mg/d (2.0)*
IWPC dose estimate (3)	5.2 mg/d (1.9)*
Real-life dose	6.9 mg/d (4.5)

* $p<0.05$, for difference with real-life dose

Figure: Individual patient doses varied widely with higher dose trends than predicted by the algorithm estimates.







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