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A systematic analysis and comparison of warfarin initiation strategies

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Abstract

Objective—Randomized trials have reported inconsistent evidence regarding the effectiveness of algorithms that use genotypes to initiate warfarin therapy. The Clarification of Optimal Anticoagulation through Genetics (COAG) trial initiated therapy based on predicted maintenance doses, with a pharmacogenetic-guided algorithm in one study group and a clinically guided algorithm in the other. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) consortium initiated therapy based on loading doses, with an algorithm-based prediction in one study group and a fixed-dose regimen in the other. To understand the differences between these trials, we compared the initial doses between alternative dosing algorithms (the pharmacogenetic-guided and clinically guided algorithms developed by Gage and colleagues and those developed by the International Warfarin Pharmacogenetics Consortium), and between the COAG and EU-PACT dose-initiation strategies.

Methods—Secondary analysis of the COAG trial—a double-blind, randomized controlled trial (2009–2013)—conducted at 18 clinical centers in the United States, which included 1,010 adults initiating warfarin therapy, of whom 719 achieved maintenance dose.

Results—Among COAG participants, the distribution of initial doses differed between algorithms, but exhibited similar prediction accuracy for maintenance dose. However, had the COAG trial implemented the EU-PACT strategy, the 3-day initial dose would have been 4.8 mg greater among participants randomized to pharmacogenetic-guided dosing, but only 2.5 mg greater among participants randomized to clinically guided dosing ($P < 0.001$).

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Conclusions—Compared to the COAG trial, the EU-PACT trial used systematically larger loading doses in the pharmacogenetic-guided group and might have inadequately adjusted for clinical variability in warfarin dose requirements in the fixed-dose group.

Keywords

warfarin; algorithms; pharmacogenetic-guided; clinically guided; dose-initiation; dose-refinement

Introduction

Patients initiating warfarin therapy for the treatment or prevention of thromboembolism can have their initial warfarin dose determined from dosing algorithms [1]. These algorithms have been derived to predict a patient's maintenance dose based on clinical factors (e.g., age, race, body size, and use of concomitant medications) and polymorphisms in genes known to influence warfarin pharmacokinetics and pharmacodynamics (e.g., the cytochrome P-450 family 2 subfamily C polypeptide 9 enzyme gene, or *CYP2C9*, the principal enzyme responsible for warfarin metabolism, and the vitamin K epoxide reductase complex 1 gene, or *VKORC1*, the target protein for warfarin action) [1–3]. Warfarin dosing algorithms account for different dose requirements across groups defined by race, but the algorithms' prediction accuracy differs by race, with less accuracy among black compared to nonblack patients [4–7].

The Clarification of Optimal Anticoagulation through Genetics (COAG) trial—a double-blind, randomized controlled trial—recently showed that pharmacogenetic-guided initiation of warfarin did not improve anticoagulation control compared to clinically guided initiation, and might have worsened anticoagulation control among self-identified black patients [8–11]. Overall, there was no difference between dosing strategies in the percentage of time in the therapeutic INR range from completion of the intervention period on day 4 or 5 through day 28 of therapy [11]. However, there was a statistically significant interaction by race: black patients in the pharmacogenetic-guided group had a lower mean percentage of time in the therapeutic INR range than those in the clinically guided group [11]. Meanwhile, a single-blind randomized controlled trial conducted by the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) consortium found that pharmacogenetic-guided warfarin initiation with loading doses (based on predicted maintenance dose) improved anticoagulation control compared to a fixed-dose regimen [12]. The mean percentage of time in the therapeutic INR range during the first 12 weeks after initiation was significantly greater among those randomized to pharmacogenetic-guided dosing compared to standard dosing [12].

Two hypotheses might explain the discordant results between the COAG and EU-PACT trials: the pharmacogenetic-guided dosing algorithms used in the COAG trial, although shown to be accurate in validation cohorts, did not optimally dose participants; or the fixed-dose regimen prescribed in the EU-PACT 'control' group did not optimally dose participants because potentially meaningful clinical variability in dose requirements was ignored. It is important to differentiate between these hypotheses because warfarin is widely prescribed and modest errors in dosing can have catastrophic clinical consequences.

Our objective was to compare: predicted maintenance doses between pharmacogenetic-guided and clinically guided dosing algorithms, using simulations and data collected on COAG study participants; the accuracy of alternative algorithms to predict maintenance dose among COAG study participants; and warfarin doses between the COAG and EU-PACT dose-initiation strategies. We focused on the pharmacogenetic-guided and clinically guided dose-initiation and dose-refinement algorithms derived by Gage and colleagues, and the dose-initiation algorithms derived by the International Warfarin Pharmacogenetics Consortium (IWPC) (Supplemental Digital Content, Section 1.1) [4–6]. The COAG trial used the Gage algorithms in the pharmacogenetic-guided and clinically guided dosing groups [10]. The EU-PACT trial used a modified version of the IWPC dose-initiation algorithm and the Gage dose-refinement algorithm in the pharmacogenetic-guided dosing group [13].

Methods

Description of Trials

In the COAG trial (NCT00839657), dose-initiation algorithms derived by Gage and colleagues were used to calculate doses on days 1 through 3 [4]. To prevent under-dosing slow metabolizers, the first dose was not decreased for patients with *CYP2C9**2 or *3 variants [10]. Dose-refinement algorithms derived by Gage and colleagues were used to calculate doses on days 4 and 5 [5]. Subsequent dose revisions were determined based on standardized dose titration, such that treating physicians were informed only of the relative dose change [14,15]. A total of 1,015 patients were randomized, stratified by race (black or nonblack) and clinical center.

In the EU-PACT trial (NCT01119300), the pharmacogenetic-guided dosing group received doses over the first 3 days based on a modified IWPC pharmacogenetic-guided algorithm (race and enzyme inducer variables were excluded from the algorithm); the predicted doses on days 1–3 were then increased based on *CYP2C9* genotypes [13]. The dose on days 4 and 5 were determined from a modified Gage pharmacogenetic-guided dose-refinement algorithm (race, history of stroke, history of diabetes, and current fluvastatin use were excluded from the algorithm) [13]. For participants randomized to standard dosing, participants 75 years or younger received 10 mg on day 1, 5 mg on day 2, and 5 mg on day 3 (total, 20 mg); participants older than 75 years received 5 mg per day on days 1 through 3 (total, 15 mg). Subsequent dosing was based on usual local practice, but all study sites used standardized dose titration. A total of 455 patients were randomized; 98.5% reported their race as white.

Comparison of Dosing Algorithms using Data Simulations—First, we generated data for all possible combinations of *CYP2C9* (*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3), *VKORC1-1639* (G/G, A/G or G/A, A/A), age (50, 60, 70 years), race (black, nonblack), height (160, 170, 180 cm), weight (70, 80, 90 kg), current smoker (yes, no), current amiodarone use (yes, no), and primary indication for warfarin therapy (deep vein thrombosis or pulmonary embolism, other). Next, we calculated the initial dose in mg/day according to

the Gage and IWPC pharmacogenetic-guided and clinically guided dose-initiation algorithms. Full details are provided in Section 1.2 of the Supplemental Digital Content.

Comparison of Dosing Algorithms using COAG Trial Data—We applied the Gage and IWPC algorithms to the data from all COAG study participants, regardless of their assigned intervention and regardless of whether they achieved maintenance dose. This all-inclusive analysis was possible because in the COAG trial, all participants were genotyped, regardless of treatment assignment. Data were available for 1,010 participants; 5 participants withdrew from the study prior to genotyping. We used graphics, descriptive statistics, and two-sample Kolmogorov-Smirnov tests to compare the doses predicted from the Gage and IWPC pharmacogenetic-guided and clinically guided algorithms, stratified by race. Full details are provided in Section 1.3 of the Supplemental Digital Content.

Both overall and by race, we compared the accuracy of the Gage and IWPC pharmacogenetic-guided and clinically guided dose-initiation algorithms to predict the observed maintenance dose. Participants were analyzed according to their randomized intervention. This analysis was limited to the 719 participants who achieved maintenance dose. Summary statistics for prediction accuracy included partial R^2 from linear regression models that adjusted for clinical center, Spearman rank correlation, and the mean absolute difference between predicted and observed maintenance dose.

Comparison of COAG and EU-PACT Dose-Initiation Strategies—We used graphics, descriptive statistics, and Wilcoxon rank-sum tests to compare the observed doses over the first 3 days of therapy among COAG study participants to that which would have been predicted under the EU-PACT dosing strategy. First, we calculated the mean difference in the total dose between dosing strategies, stratified by treatment assignment. Second, among COAG study participants randomized to clinically guided dosing, we calculated the percent of participants who received a total dose that would have differed by more than 20% of the EU-PACT total dose, stratified by age (older than 75 years, 75 years or younger). Third, among COAG study participants who achieved maintenance dose, we divided the average dose over the first 3 days of therapy by the observed maintenance dose; a ratio of 1 indicated equality between the average initial dose and the maintenance dose.

All analyses were completed using R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). The COAG study protocol was approved by the institutional review board at the University of Pennsylvania and at each participating clinical center. All COAG study participants provided written informed consent.

Results

Comparison of Dosing Algorithms using Data Simulations

Across the range of input variables we considered, the Gage and IWPC pharmacogenetic-guided algorithms appeared to have a curvilinear relationship, which reflected the different functional form between the algorithm equations (i.e., exponential function for Gage algorithm and squared function for the IWPC algorithm) (Supplemental Digital Content Figure 1). On average, the Gage genotype initiation dose was larger than the IWPC genotype

dose, with no apparent differences by race. Compared to the pharmacogenetic-guided algorithms, the clinically guided algorithms provided a smaller range of doses (Supplemental Digital Content Figure 2). On average, the Gage clinical initiation dose was larger than the IWPC clinical dose. Full results are provided in Section 2.1 of the Supplemental Digital Content.

Comparison of Dosing Algorithms using COAG Trial Data

Among COAG study participants, there were notable differences between the Gage genotype and clinical initiation doses (Supplemental Digital Content Figure 3; $P<0.001$). Application of the Gage dose-refinement algorithms decreased the variability in predicted doses (Supplemental Digital Content Figure 4; $P=0.15$). There were also notable differences between the IWPC genotype and clinical initiation doses (Supplemental Digital Content Figure 5; $P<0.001$), but with less variability compared to the Gage initiation doses. Full results are provided in Section 2.2 of the Supplemental Digital Content.

The IWPC and Gage genotype initiation doses exhibited a similar curvilinear relationship that we observed in the simulated data (Supplemental Digital Content Figure 6; $P=0.001$). For Gage genotype initiation doses ≤ 5 mg/day, the IWPC initiation doses were similar, but for Gage genotype initiation doses >5 mg/day, the IWPC initiation doses were smaller, with no substantial differences by race (Supplemental Digital Content Table 1). Similarly, for Gage clinical initiation doses ≤ 5 mg/day, the IWPC initiation doses were similar, but for Gage clinical initiation doses >5 mg/day, the IWPC initiation doses were smaller ($P=0.010$), with no substantial differences by race (Supplemental Digital Content Figure 7 and Supplemental Digital Content Table 2). Full results are provided in Section 2.2 of the Supplemental Digital Content.

Among the 719 COAG study participants who achieved maintenance dose, the Gage and IWPC dose-initiation algorithms exhibited similar prediction accuracy for the observed maintenance dose (Table 1). The Gage and IWPC pharmacogenetic-guided algorithms both exhibited higher accuracy among nonblack participants (R^2 of 0.52 for both) and lower accuracy among black participants (R^2 of 0.21 and 0.17, respectively). The Gage and IWPC algorithms exhibited similar proportions of predicted minus observed doses within 1 mg/day, whereas the IWPC algorithms exhibited larger proportions less than -1 mg/day (i.e., the predicted dose was less than the observed maintenance dose by 1 mg/day or more).

Black study participants were less likely to achieve maintenance dose ($P=0.001$; Table 2). There was some evidence to suggest that those who achieved maintenance dose were older, less likely to smoke, and less likely to have *CYP2C9**3 variants ($0.05<P<0.1$). The distribution of other variables used in the algorithms was similar between those who did and did not achieve maintenance dose, including the study intervention ($P>0.1$). The mean absolute difference between the Gage and IWPC initiation doses was identical (0.4 mg/day) between those who did and did not achieve maintenance dose.

Comparison of COAG and EU-PACT Dose-Initiation Strategies

Among COAG study participants randomized to pharmacogenetic-guided dosing, all participants would have received a larger total dose over the first 3 days of therapy under the

EU-PACT dose-initiation strategy (Figure 1). On average, the EU-PACT total dose over the first 3 days would have been 4.8 mg greater than the total dose that COAG study participants received (Table 3). This difference is not surprising given that EU-PACT used a loading dose strategy and increased the algorithm-predicted dose based on *CYP2C9* genotypes (to a greater extent than did the COAG trial, which ignored *CYP2C9* genotypes on day 1 only). Had the COAG trial used *CYP2C9* genotypes on day 1, the average difference would have been very similar (5.1 mg rather than 4.8 mg). However, among COAG study participants randomized to clinically guided dosing, the disparity between COAG and EU-PACT dose-initiation strategies was smaller. On average, the EU-PACT total dose would have been 2.5 mg greater than the total dose that COAG study participants received (Table 3). Therefore, the impact of 'loading' would have differed between the intervention groups ($P<0.001$). Similar results were obtained among black ($P<0.001$) and nonblack ($P<0.001$) participants (Table 3), with a greater disparity between the EU-PACT and COAG dose-initiation strategies among black compared to nonblack participants.

Use of the clinical dose-initiation algorithm in the COAG trial also resulted in much larger variability in warfarin doses compared to the EU-PACT dose-initiation strategy (Figure 1). Among COAG study participants randomized to clinically guided dosing and older than 75 years ($n=64$), 63 participants (98%) received a total dose over the first 3 days that was less than the total dose they would have received under the fixed-dose regimen of EU-PACT (i.e., 15 mg total). Twenty-nine participants (45%) received a total dose that would have differed by more than 20% of the EU-PACT total dose (i.e., less than 12 mg or greater than 18 mg total). Among COAG study participants randomized to clinically guided dosing and 75 years or younger ($n=436$), 84 participants (19%) received a total dose that was greater than the total dose they would have received under the fixed-dose regimen of EU-PACT (i.e., 20 mg total); 352 participants (81%) received a total dose that was less than the total dose they would have received under the EU-PACT strategy. One hundred and eighty-two participants (42%) received a total dose that would have differed by more than 20% of the EU-PACT total dose (i.e., less than 16 mg or greater than 24 mg total).

The differences between the COAG and EU-PACT dose-initiation strategies were also evident when compared to the observed maintenance dose (Figure 2). Under the COAG strategy, the mean ratio of average initial dose to maintenance dose was 1.1 for both dosing groups (Table 3). Under the EU-PACT strategy, the mean was 1.5 and 1.3 for the pharmacogenetic-guided and clinically guided dosing groups, respectively (Table 3). The differences between group means (0 and 0.2 for the COAG and EU-PACT strategies, respectively) reflect the differential impact of loading under the EU-PACT strategy. Among the clinically guided dosing group, the larger coefficient of variation for the EU-PACT strategy (0.43 versus 0.35) likely reflects unaccounted-for clinical variability in dose requirements under the EU-PACT fixed-dose regimen. Similar results were obtained among black and nonblack participants, with a greater disparity between the EU-PACT and COAG dose-initiation strategies among black compared to nonblack participants (Table 3).

Discussion

Our study addressed the following questions: what if the COAG trial used the IWPC algorithms, rather than the Gage algorithms, and what if the COAG trial implemented the EU-PACT dose-initiation strategy? First, the results from our simulation study and from our analysis of the COAG trial data suggest that the Gage and IWPC algorithms provide similar initial warfarin doses on average, but with notable differences in their distributions. In addition, the Gage and IWPC algorithms exhibited similar prediction accuracy for maintenance dose among COAG study participants who achieved maintenance dose, and there were no systematic differences between the Gage and IWPC initial doses among those who did not achieve maintenance dose. Our results are consistent with previous research [16–18]. Therefore, had the IWPC algorithms been used in the COAG trial, we expect that the trial would have arrived at a similar conclusion: initiating warfarin therapy at a predicted maintenance dose based on a pharmacogenetic-guided algorithm does not improve anticoagulation control compared to initiating therapy at a predicted maintenance dose based on a clinically guided algorithm.

Second, the dosing strategies differed substantially between the COAG and EU-PACT trials: the COAG trial initiated warfarin therapy based on the predicted maintenance dose in both study groups; the EU-PACT trial initiated therapy based on loading doses, and used a modified algorithm-based prediction in one study group and a fixed-dose regimen in the other. Had the COAG trial implemented the EU-PACT dosing strategy, all participants randomized to pharmacogenetic-guided dosing would have received larger initial doses, but some participants randomized to clinically guided dosing would have received smaller initial doses. Thus, the EU-PACT dosing strategy would have ‘loaded’ the dose differently between the COAG intervention groups. A recent systematic review reported inconsistent evidence regarding the effectiveness of loading doses, but pooled analyses that achieved statistical significance indicated a benefit from loading doses on anticoagulation control [19]. In addition, the fixed-dose regimen in the EU-PACT ‘control’ group did not account for clinical variability in warfarin dose requirements. Therefore, the results of the EU-PACT trial showing an advantage of a pharmacogenetic-guided dosing algorithm could be due to inadequate adjustment for clinical variability in warfarin dose requirements in the ‘control’ group, and not to the use of a pharmacogenetic-guided dosing algorithm itself. Of course, there could be other explanations for the discordant results between the COAG and EU-PACT trials, including blinding, dose-titration methods, and the patient populations studied.

We compared and contrasted alternative dose-initiation strategies in both a cohort of patients initiating warfarin therapy and using simulated data. Strengths of our study include the comprehensiveness of our simulation study, the clinical relevance of our analysis using the COAG trial data, and the quality of data collection and large sample size of the COAG trial, which facilitated calculation of algorithm-based predictions for all participants and comparisons by race. Our simulation study is fully reproducible (see Supplemental Digital Content).

We acknowledge the following limitations. First, in our simulation study, we generated data for groups defined by race that were otherwise balanced on all other covariates, including

VKORC1 and *CYP2C9* variants. Therefore, although our simulation study provided an ideal setting in which to analyze all possible doses predicted by the dosing algorithms, its direct clinical relevance might be limited. Second, in our analysis of the prediction accuracy of dosing algorithms, we were limited to those COAG study participants who achieved maintenance dose, although there was no evidence to suggest that the Gage and IWPC initial doses differed between those who did and did not achieve maintenance dose. Third, we were unable to compare the COAG and EU-PACT dose-refinement strategies in the pharmacogenetic-guided group on days 4 and 5 because the COAG trial did not observe the post-randomization INRs (on days 2–4) that would have resulted from the EU-PACT dose-initiation strategy. In addition, there was no formalized dose-refinement strategy in the EU-PACT fixed-dose group. Fourth, we were unable to evaluate the prediction accuracy of the EU-PACT dosing strategy for maintenance dose because the EU-PACT dose-initiation strategy was based on loading doses. However, we were able to evaluate the accuracy of the IWPC algorithm upon which the EU-PACT loading doses were based. Fifth, COAG study participants who reported their race as ‘Asian’ were grouped with other nonblack participants. We were unable to make meaningful comparisons among Asian participants due to an inadequate sample size (n=18). Sixth, the COAG trial did not include genetic variants that might uniquely improve dose prediction in black populations [18,20,21].

Long-term anticoagulation control among the EU-PACT fixed-dose group was apparently superior to that among the COAG clinically guided group. Although the mean percentage of time in the therapeutic INR range among these groups was very similar at day 28 of therapy (45.7% versus 45.4%, respectively), there was a difference at week 12 (60.3% versus 50.2%, respectively). We are unable to speculate on the reasons for this difference. Comparing observed outcomes for individual arms between two different trials (e.g., the COAG clinically guided group and the EU-PACT fixed-dose group) is fraught with limitations because the study design, inclusion and exclusion criteria, and dose-titration strategies after warfarin initiation differed between the trials. Such a comparison is akin to making unadjusted comparisons between two groups in an observational study with a large potential for unmeasured confounding. This is why our analyses focused on comparing the differences between dosing strategies within trials, which are both valid comparisons and can be objectively quantified. Randomized trials are needed compare dosing algorithms to fixed-dose initiation strategies.

Our analysis and its limitations should be considered alongside clinical research regarding the use of genetic information in determining clinical outcomes for patients initiating warfarin therapy. In particular, Mega and colleagues recently performed a large observational study embedded within a randomized trial, and showed that patients with certain genetic variants had a higher risk of bleeding [22]. In an analysis stratified by HAS-BLED score, the authors reported an apparent increase in the incidence of overt bleeding across groups defined by *CYP2C9* and *VKORC1* genotypes, although they did not provide a formal statistical analysis of this result. The study by Mega and colleagues provides additional evidence that genotypes are associated with variability in warfarin dose requirements and clinical outcomes, but it was not a randomized trial of pharmacogenetic-guided initiation of warfarin therapy. With respect to the potential influence of clinically guided initiation on clinical outcomes, the COAG trial did not test a clinically guided

strategy relative to a strategy that did not include either genetic or clinical information in a dosing algorithm. The COAG trial did not conclude that clinical factors alone were adequate for optimal warfarin dosing, and we do not conclude this here.

Our study adds objective data to the ongoing debate regarding the benefits of pharmacogenetic-guided initiation of warfarin therapy on anticoagulation control [23–30]. First, our results suggest that use of the IWPC pharmacogenetic-guided algorithm would not improve anticoagulation control compared to the IWPC clinically guided algorithm. Second, our results indicate that the EU-PACT trial might have found a benefit of pharmacogenetic-guided dosing because of systematically different loading strategies between the study groups and unaccounted-for clinical variability in warfarin dose requirements among the fixed-dose group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Total warfarin doses over the first 3 days of therapy (mg) for the COAG and EU-PACT dose-initiation strategies among all COAG study participants (n=1,010).

Figure 2. Density plots that display the distribution of average warfarin doses over the first 3 days of therapy relative to maintenance dose for the COAG and EU-PACT dose-initiation strategies among COAG study participants who achieved maintenance dose (n=719).

Summary statistics of Gage and IWPC pharmacogenetic and clinical dose-initiation predictions of maintenance dose versus observed maintenance dose among 719 COAG study participants who achieved maintenance dose, for all participants and by race.

Table 1

	Pharmacogenetic-guided dosing			Clinically guided dosing		
	All participants	Black	Nonblack	All participants	Black	Nonblack
Achieved maintenance dose, n	370	84	286	349	89	260
<i>Gage dose-initiation algorithm</i> [*]						
Partial R ² †	0.48	0.21	0.52	0.27	0.33	0.17
Spearman rank correlation ‡	0.72	0.50	0.75	0.54	0.70	0.46
Mean absolute difference, mg/d §	1.3	1.6	1.2	1.5	1.4	1.6
Predicted – observed dose, % **						
1 mg/d	25	39	20	29	28	30
Within 1 mg/d	53	38	57	42	48	39
-1 mg/d	22	23	22	29	24	31
<i>IWPC dose-initiation algorithm</i>						
Partial R ² †	0.47	0.17	0.52	0.30	0.31	0.22
Spearman rank correlation ‡	0.70	0.49	0.73	0.54	0.69	0.46
Mean absolute difference, mg/d §	1.3	1.6	1.3	1.5	1.4	1.6
Predicted – observed dose, % **						
1 mg/d	21	30	19	23	24	23
Within 1 mg/d	51	40	54	41	40	41
-1 mg/d	28	30	27	36	36	36

^{*} Results for Gage dose-initiation algorithm were presented in Table S6 of the Supplementary Appendix to Kimmel *et al.*, 2013. 11

[†] Partial R² calculated from multivariable linear regression models of observed versus predicted maintenance dose, adjusted for clinical center.

[‡] Spearman rank correlation between predicted and observed maintenance dose.

[§] Mean absolute difference between predicted and observed maintenance dose, in mg/day.

^{**} Difference between predicted and observed maintenance dose, categorized as 1 mg/day, within 1 mg/day, and -1 mg/day.

Table 2

Participant characteristics at randomization among 1,010 COAG study participants who did and did not achieve maintenance dose. *

	Achieved maintenance dose (n=719)	Did not achieve maintenance dose (n=291)	P *
<i>Study intervention</i>			
Pharmacogenetic-guided dosing	370 (51)	140 (48)	0.36
<i>Demographic characteristics</i>			
Age, years, median	58 (47, 70)	57 (45, 68)	0.086
Black race	173 (24)	100 (34)	0.001
Current smoker	94 (13)	51 (18)	0.075
Height, cm, median	173 (165, 180)	170 (163, 179)	0.79
Weight, kg, median	87 (75, 105)	88 (74, 109)	0.55
Body surface area, m ² , median	2.02 (1.85, 2.20)	2.02 (1.83, 2.25)	0.72
<i>Warfarin and other therapies</i>			
DVT or PE as primary indication	448 (62)	170 (58)	0.25
Current amiodarone use	15 (2)	8 (3)	0.49
Current fluvastatin use	2 (<1)	1 (<1)	0.99
Current enzyme inducer use	8 (1)	4 (1)	0.75
<i>Medical history</i>			
Diabetes	161 (22)	77 (26)	0.19
Stroke	48 (7)	20 (7)	0.89
<i>Genetic variants</i>			
<i>CYP2C9*2</i>			0.96
No variants	597 (83)	240 (82)	
Heterozygous	114 (16)	48 (16)	
Homozygous	8 (1)	3 (1)	
<i>CYP2C9*3</i>			0.073
No variants	663 (92)	259 (89)	
Heterozygous	56 (8)	31 (11)	
Homozygous	0 (0)	1 (<1)	
<i>VKORC1 (VKORC1 3673G>A)</i>			0.91
No variants (GG)	344 (48)	143 (49)	
Heterozygous (AG or GA)	290 (40)	113 (39)	
Homozygous (AA)	85 (12)	35 (12)	
Total number of genetic variants [†]			0.27
0 variants	275 (38)	118 (41)	
1 variant	270 (38)	94 (32)	
>1 variant	174 (24)	174 (27)	

DVT, deep-vein thrombosis; PE, pulmonary embolism

* Summaries presented as n (%) unless otherwise indicated as median (25th, 75th percentile). P values obtained from Wilcoxon rank-sum tests for continuous variables and Fisher's exact test for categorical variables.

[†] Defined as total number of measured variants in *CYP2C9*2*, *CYP2C9*3*, and *VKORC1*.

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Table 3
Comparison of COAG and EU-PACT dose-initiation strategies among COAG study participants.

	All participants		Black participants		Nonblack participants	
	Pharmacogenetic-guided dosing	Clinically guided dosing	Pharmacogenetic-guided dosing	Clinically guided dosing	Pharmacogenetic-guided dosing	Clinically guided dosing
<i>Difference in total dose over first 3 days of therapy between EU-PACT and COAG strategies *</i>						
Mean (SD), mg	(n=510) 4.8 (1.8)	(n=500) 2.5 (3.4)	(n=139) 6.4 (1.5)	(n=134) 0.1 (3.9)	(n=371) 4.2 (1.5)	(n=366) 3.4 (2.7)
<i>Mean (SD) ratio of average initial dose to maintenance dose †</i>						
COAG strategy	(n=370) 1.1 (0.4)	(n=349) 1.1 (0.4)	(n=84) 1.2 (0.5)	(n=89) 1.1 (0.3)	(n=286) 1.1 (0.4)	(n=260) 1.1 (0.4)
EU-PACT strategy	1.5 (0.5)	1.3 (0.6)	1.6 (0.6)	1.1 (0.4)	1.4 (0.5)	1.3 (0.6)

SD = standard deviation

* For each COAG study participant (n=1,010), we first calculated the total dose over the first 3 days of therapy under the COAG and EU-PACT dose-initiation strategies. We then calculated the differences between strategies as the total dose under the EU-PACT strategy minus the total dose under the COAG strategy; a positive difference indicated a larger total dose under the EU-PACT dose-initiation strategy.

† For each COAG study participant who achieved maintenance dose (n=719), we first calculated the total dose over the first 3 days of therapy under the COAG and EU-PACT dose-initiation strategies. We then divided the average dose over the first 3 days of therapy by the observed maintenance dose; a ratio of 1 indicated equality between the average initial dose and the maintenance dose.