Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Table of Contents

1 Study Organization and Committees

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The following clinical centers are listed in descending order according to total enrollment, beginning with the highest-enrolling center.

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2 Additional Acknowledgments

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Tulane University: Supported in part by 1 U54 GM104940 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds the Louisiana Clinical and Translational Science Center.

3 Inclusion and Exclusion Criteria

3.1 *Inclusion Criteria*

- Age ≥ 18 years.
- Willingness and ability to sign informed consent.
- Able to be followed in outpatient anticoagulation clinic.
- Expected duration of warfarin therapy of at least 1 month.
- Anticoagulation management for the patient will be performed in-hospital and as an outpatient by clinicians that will adhere to the study dosing algorithms and dose-titration plans.
- Target INR 2–3.

3.2 *Exclusion Criteria*

- Currently taking warfarin.
- Prior warfarin therapy with known required stable dose.
- Clinician opinion that warfarin dosing needs to be adjusted for reasons not accounted for by dosing algorithm.
- Abnormal baseline INR (off warfarin), e.g., due to liver disease, antiphospholipid antibody
- Contraindication to warfarin treatment for at least 3 months.
- Life expectancy of less than 1 year.
- Pregnant women or childbearing women not using medically approved method of birth control.
- Inability to follow-up on a regular basis with anticoagulation practitioners participating in trial.
- Any factors likely to limit adherence to warfarin, e.g., dementia, alcohol or substance abuse, plans to move in the next 6 months, history of unreliability in medication taking or appointment keeping, significant concerns about participation in the study from spouse, significant other, or family members, lack of support from primary health care provider.
- Cognitive or other causes of inability to provide informed consent or follow study procedures.
- Participating in another trial that prohibits participation in the COAG trial or planned enrollment in such a trial within the first 6 months of warfarin therapy.
- Estimated blood loss of >1000 mL requiring blood transfusions within 48 hours before randomization.
- Genotype (*CYP2C9* or *VKORC1*) known to participant from prior testing.

4 Blinding

The COAG trial was double blind. Neither the treating clinicians nor participants knew the dosing algorithm used or the dispensed warfarin dose during the first 4 weeks. Study drug was over-encapsulated based on a previously published method.[1] Such over-encapsulation has been demonstrated not to alter warfarin pharmacokinetics. After 4 weeks of therapy (the primary outcome duration), clinicians were informed of the actual dose that the participant was taking (but not the initial doses in the first 4 weeks). Participants then received unblinded warfarin.

5 Dosing Algorithms

5.1 *Dose-Initiation Algorithms*

Pharmacogenetic dose-initiation algorithm[2]

The estimated daily dose in mg/day is:

$$\exp[0.9751 - (0.2066 \times \textit{CYP2C9*2}) - (0.4008 \times \textit{CYP2C9*3}) - (0.3238 \times \textit{VKORC1})$$

− (0.00745 × age in years)
− (0.0901 × black race)
+ (0.0922 × smokes)
+ (0.4317 × body surface area in m^2)
− (0.2538 × amiodarone use)
+ (0.2029 × target INR)
+ (0.0664 × DVT/PE as indication for warfarin therapy)],

for which: *CYP2C9*2* and *CYP2C9*3* SNPs are coded as 0 if absent (no variants), 1 if heterozygous, and 2 if homozygous; *VKORC1* is *VKORC1 3673G>A* (also known as *VKORC1* -1639, rs9923231) and is coded 0 (homozygous GG), 1 (heterozygous), or 2 (homozygous AA). Race is coded as 1 if black and 0 if nonblack. Smokes, amiodarone use, and DVT/PE as indication for warfarin therapy are coded as 1 if yes and 0 if no. Body surface area is calculated as $[(\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725}]/139.2$. In the COAG trial, target INR was fixed at 2.5.

In the COAG trial, the first dose in the genotype-guided dosing group did not incorporate *CYP2C9*. Thus, for first doses calculated from the pharmacogenetic dose-initiation algorithm, *CYP2C9*2* and *CYP2C9*3* were set to 0. The rational for this is based on prior studies that showed that *CYP2C9* variants have little influence on INR response early in therapy[3] and that decreasing the first dose in slow metabolizers delays the time until the INR is therapeutic and can negate the putative benefit of genotyping for *CYP2C9*.[4]

Clinical dose-initiation algorithm[2]

The estimated daily dose in mg/day is:

exp[0.613
− (0.0075 × age in years)
+ (0.156 × black race)
+ (0.108 × smokes)
+ (0.425 × body surface area in m^2)
− (0.257 × amiodarone use)
+ (0.216 × target INR)
+ (0.0784 × DVT/PE as indication for warfarin therapy)],

for which all variables are defined as in the pharmacogenetic dose-initiation algorithm above.

5.2 *Dose-Revision Algorithms*

Pharmacogenetic dose-revision algorithm[5]

The estimated daily dose in mg/day is:

1/7 × exp[(3.10894
– (0.14745 × *CYP2C9*2*)

– (0.30770 × *CYP2C9*3*)
– (0.23032 × *VKORC1*)
– (0.00767 × age in years)
– (0.09644 × black race)
+ (0.24597 × body surface area in m^2)
– (0.11216 × diabetes)
– (0.20590 × stroke)
– (0.10350 × amiodarone use)
– (0.19275 × fluvastatin use)
+ (0.26729 × target INR)
– (0.51611 × ln INR)
+ (0.01690 × $dose_{-2}$)
+ (0.02018 × $dose_{-3}$)
+ (0.01065 × $dose_{-4}$)],

for which: *CYP2C9*2* and *CYP2C9*3* SNPs are coded as 0 if absent (no variants), 1 if heterozygous, and 2 if homozygous; *VKORC1* is *VKORC1 3673G>A* (also known as *VKORC1* -1639, rs9923231) and is coded 0 (homozygous GG), 1 (heterozygous), or 2 (homozygous AA). Race is coded as 1 if black and 0 if nonblack. Diabetes, stroke, amiodarone use, fluvastatin use, and DVT/PE as indication for warfarin therapy are coded as 1 if yes and 0 if no. Target INR was fixed at 2.5. INR is the INR measured on the day of dosing, transformed using the natural log. $Dose_{-i}$ is the dose given *i* days before the INR is measured.

Clinical dose-revision algorithm[5]

The estimated daily dose in mg/day is:

1/7 × exp[(2.81602
– (0.00590 × age in years)
+ (0.07123 × black race)
+ (0.17675 × body surface area in m^2)
– (0.16759 × diabetes)
– (0.22844 × stroke)
– (0.11137 × amiodarone use)
– (0.25487 × fluvastatin use)
+ (0.27815 × target INR)
– (0.76679 × ln INR)
+ (0.03471 × $dose_{-2}$)
+ (0.03047 × $dose_{-3}$)
+ (0.01929 × $dose_{-4}$)],

for which all variables are defined as in the pharmacogenetic dose-revision algorithm above.

6 Calculation of Percent Time in Therapeutic INR Range

The protocol specified that INRs be measured twice per week in each of the first 2 weeks of therapy and then weekly thereafter for the next 2 weeks. Therapeutic INR range was defined as 2–3, inclusive. The percent time in therapeutic INR range (PTTR) from completion of the intervention period (day 4 or 5) through day 28 of therapy was calculated using a standard linear interpolation method between successive INR values.[6] All INRs measured after day 3 were included in the calculation. Any off-protocol INRs measured before day 4 were not included, for the following reasons: first, based on the pharmacokinetics and pharmacodynamics of warfarin, the drug has little effect on the INR during the first 2 days of therapy and the method of dosing would be unlikely to have an effect on INRs on day 2 or 3; second, INRs are not routinely collected in the first 2 days of therapy, primarily because they do not reflect the effect of warfarin; third, measuring PTTR beginning on day 4/5 ensures that we measured the outcome after completion of the intervention period; fourth, other pharmacogenetic trials have used similar approaches; for example, in Couma-Gen, below-range INRs were counted after day 4.[7]

For participants who had the drug held for up to 5 days, all available INRs were used in the PTTR calculation. For those who had the drug held for more than 5 days, any INRs measured in the 5 days after the drug was held were used in the PTTR calculation. If the drug was later restarted, then the first INR drawn was used to calculate PTTR from that point on. If a participant did not have an INR on day 28, then the next INR collected up through day 32 was used to interpolate the INR on day 28 for the PTTR calculation. Day 32 was selected as the cut-point for INR inclusion because the study protocol specified a visit window for the week-4 visit that extended to day 32.

Here we describe our approaches for any missing INRs. First, the PTTR for participants with no INRs after day 3 was set to missing (n=60). Second, if a participant had only 1 INR on day 4 or 5, and no INRs thereafter (n=19), then the following algorithm was used to impute PTTR:

- If day-4/5 INR was below range (<2), then PTTR=0;
- If day-4/5 INR was in range, then PTTR=0.5; or
- If day-4/5 INR was above range (>3), then PTTR=0.

Sensitivity analyses excluding those who had only 1 INR on day 4 or 5, and no INRs thereafter, had no substantive impact on the results.

Third, if a participant was missing an INR on day 4 and 5, but had INRs available thereafter (n=17), then the day-4 INR was set to 1 for the PTTR calculation. Sensitivity analyses excluding those missing an INR on day 4 and 5 had no substantive impact on the results.

7 Definitions of Adverse Events

Major bleeding was defined based on the Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT) definition[8] as fatal hemorrhage, intracranial bleeding documented by imaging or autopsy, or symptomatic bleeding requiring overnight hospitalization or major therapeutic intervention (transfusion, angiographic intervention, or surgery). Thromboembolism

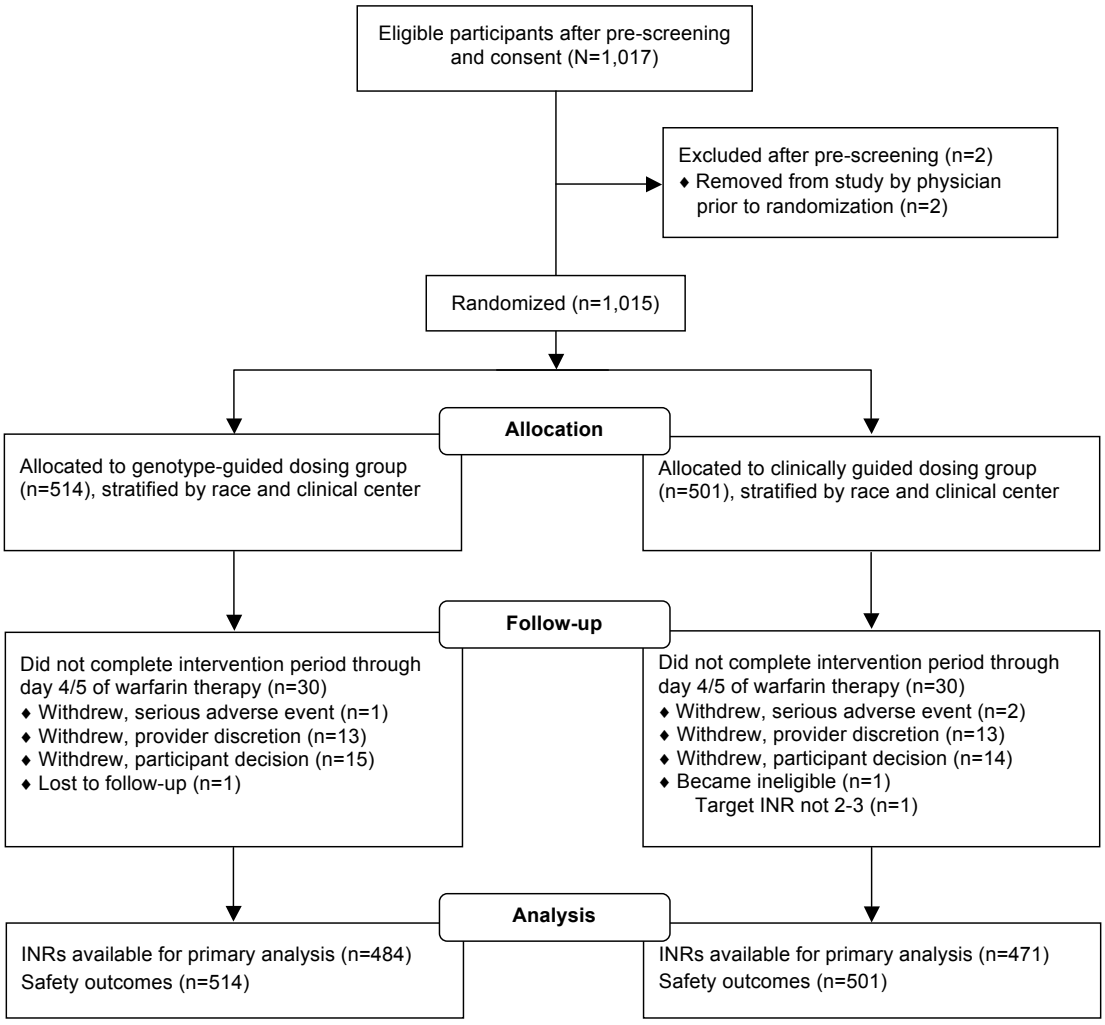
was defined as a deep venous thrombosis (confirmed by ultrasound, CT, MR, or contrast phlebography), pulmonary embolism (confirmed by CT angiography, MR angiography, catheter-based pulmonary angiography, 'high probability' ventilation-perfusion isotope imaging, or autopsy), or embolic stroke (based on clinical history, radiography, or autopsy). Clinically relevant major bleeding was defined[9,10] as a bleeding event that did not meet the definition of major bleeding, but that prompted medical evaluation, a diagnostic procedure, a non-surgical or non-endoscopic procedure (e.g., nasal packing), or bleeding resulting in interruption of anticoagulant treatment for 3 days or longer.

8 Adherence

At each visit during the first month of therapy, participants were asked if they missed any doses or took any extra doses in the prior week. The mean reported non-adherence across these visits was 3.7 to 9.2% in the genotype-guided dosing group and 5.2 to 12.6% in the clinically guided dosing group.

9 Supplementary Tables and Figures

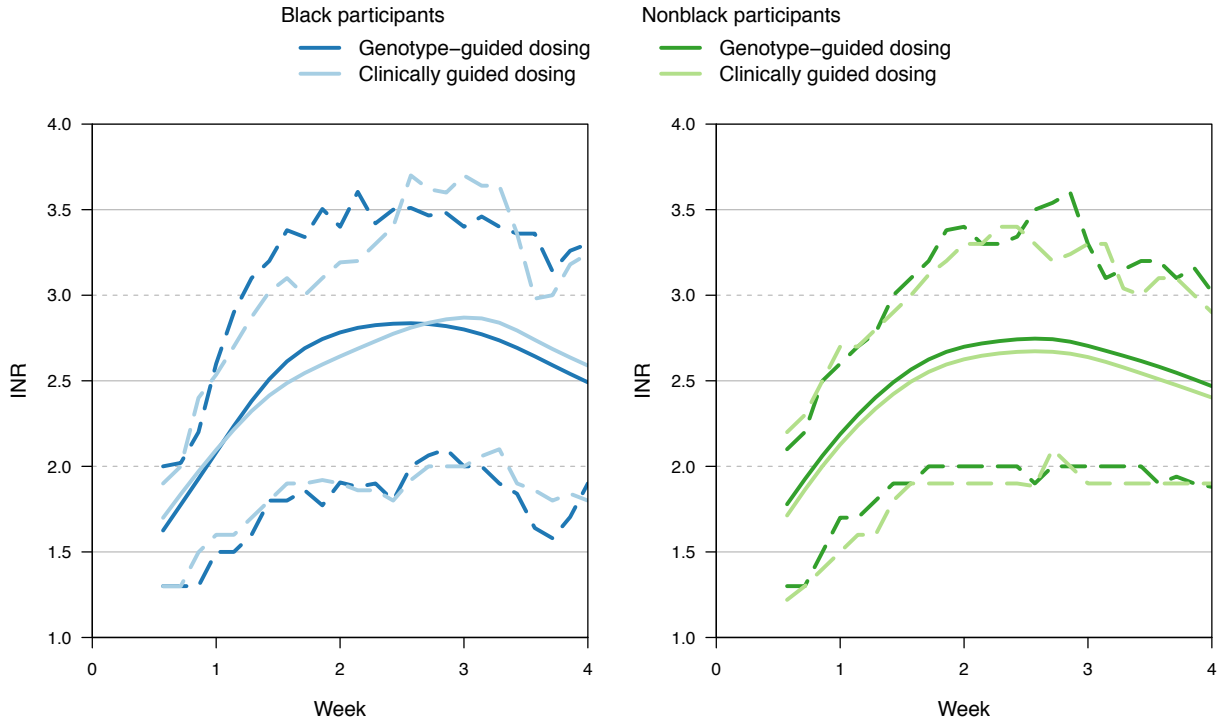
Figure S1: Participant flow diagram. *



* A preliminary assessment of a patient's potential eligibility was made to determine if further screening was warranted. Medical and/or pharmacy records were reviewed and initial inquiries made about potential study participants. Potential participants were provided with basic information about the study. Because detailed screening logs were not kept, accurate numbers of potential participants are not available. Based on periodic surveys at each clinical center, estimates of the reasons that patients were not enrolled were: patient admitted after hours or when the research coordinator was not available (12%); patient had already received their first dose of warfarin before screening (24%); patient had previous warfarin therapy with known stable dose (48%); patient declined (6%); patient did not meet other study criteria (9%); clinician decided not to initiate warfarin (1%). Thus, only approximately 6% of potentially eligible participants declined to enroll and an estimated 84% of potentially eligible participants did not enroll simply due to the logistics of identifying patients without prior warfarin therapy who had not yet received their first dose of warfarin. Randomization occurred after informed consent,

confirmation of eligibility, and collection of baseline information and blood for genotyping. Randomization was stratified by participating clinical centers and by self-reported race (black versus nonblack). Participants who did not complete the intervention period through day 4 or 5 of warfarin therapy did not have any available INRs, so that these participants were not included in the modified intention-to-treat analysis of the primary outcome, PTTR. All participants were included in analyses of safety outcomes.

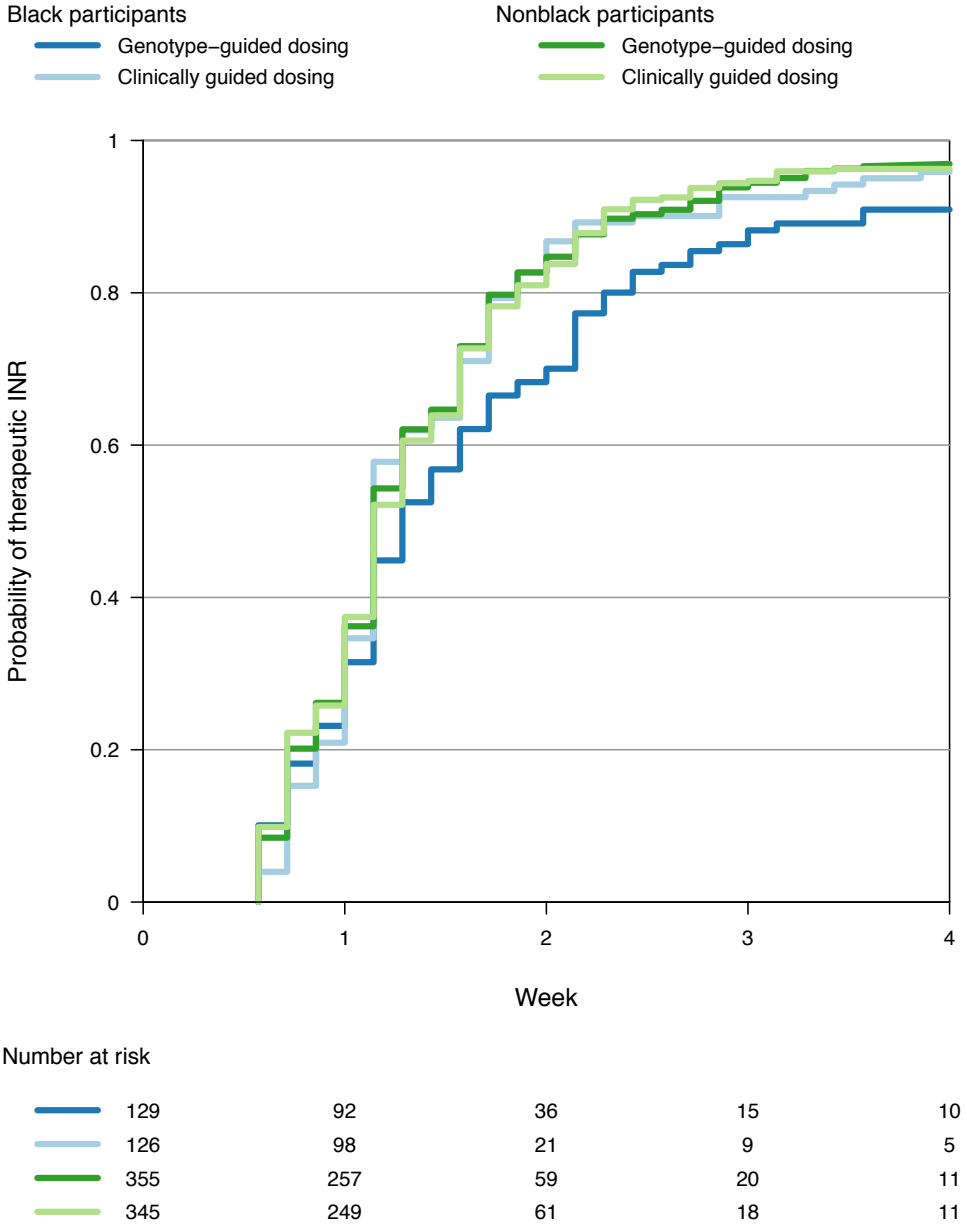
Figure S2: International normalized ratios (INRs) from completion of the intervention period to day 28 of therapy for the genotype-guided and clinically guided dosing groups among black participants (left panel) and nonblack participants (right panel). Solid lines represent smoothing splines with 5 degrees of freedom. Dashed lines represent the 20th and 80th percentiles of INR values calculated over a 3-day window. *†



* Mean PTTR from day 4/5 to day 14:
    Black participants:
        32.6% in the genotype-guided dosing group;
        39.4% in the clinically guided dosing group;
    Nonblack participants:
        43.1% in the genotype-guided dosing group;
        40.6% in the clinically guided dosing group.

† Mean PTTR from day 15 to day 28:
    Black participants:
        50.2% in the genotype-guided dosing group;
        58.0% in the clinically guided dosing group;
    Nonblack participants:
        63.2% in the genotype-guided dosing group;
        60.7% in the clinically guided dosing group.

Figure S3: Time to first therapeutic INR by dosing group and race.



Probability of achieving a therapeutic INR calculated as 1 minus the Kaplan-Meier survival estimate.

Figure S4: Predicted and observed daily maintenance dose (mg/day) according to genotype-guided and clinically guided dose-initiation (top row) and dose-revision (bottom row) algorithms among black participants (left column) and nonblack participants (right column). Data are shown for participants who achieved maintenance dose. Solid lines represent smoothing splines with 5 degrees of freedom.

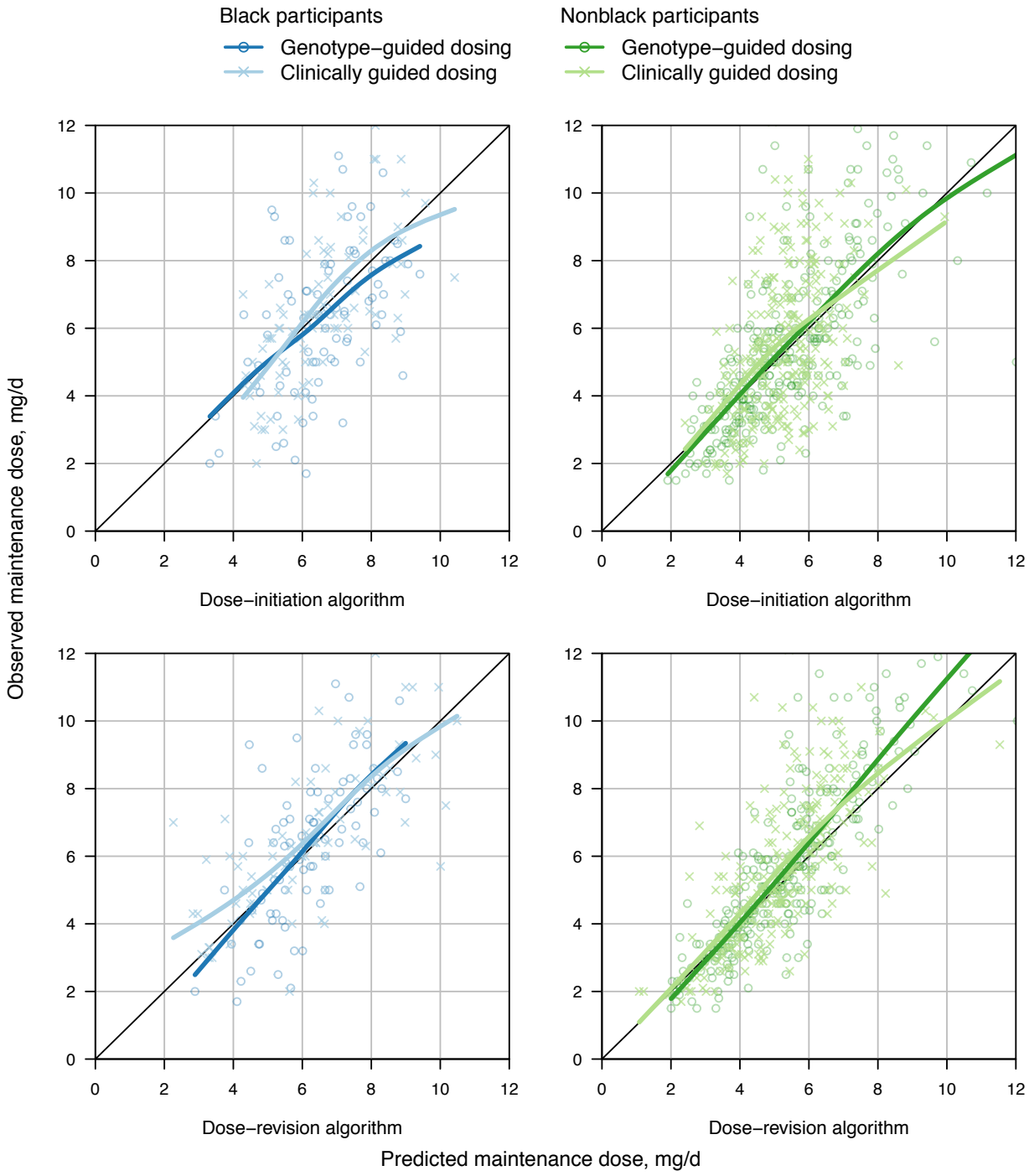


Table S1: Participant characteristics at randomization by race. *

	Black (n=275)	Nonblack (n=740)	P
Demographic characteristics			
Age, years, median †	53 (43, 65)	59 (48, 71)	< 0.001
Male gender	123 (45)	395 (53)	0.016
Hispanic ethnicity	4 (1)	61 (8)	< 0.001
Education			< 0.001
Did not complete high school	37 (13)	59 (8)	
High school degree only	106 (39)	158 (21)	
Post-secondary education	115 (42)	484 (65)	
Did not respond	17 (6)	39 (5)	
Current smoker †	59 (21)	86 (12)	< 0.001
Body surface area, m^2, median †	2.03 (1.87, 2.25)	2.01 (1.84, 2.20)	0.082
Warfarin and other therapies			
Inpatient warfarin initiation	213 (77)	467 (63)	< 0.001
Indication for warfarin therapy			0.24
DVT or PE only	163 (59)	426 (58)	
Atrial fibrillation/flutter only	56 (20)	165 (22)	
Other indication only	30 (11)	79 (11)	
Multiple indications	21 (8)	67 (9)	
No indication given	5 (2)	3 (<1)	
DVT or PE as primary indication †	169 (61)	453 (61)	> 0.99
Expected duration of warfarin therapy			0.009
1 month	8 (3)	58 (8)	
1–3 months	21 (8)	44 (6)	
>3 months	246 (89)	638 (86)	
Prior warfarin use	25 (9)	61 (8)	0.61
Current amiodarone use †	5 (2)	18 (2)	0.64
Current fluvastatin use †	1 (<1)	2 (<1)	> 0.99
Current heparin use	164 (60)	395 (53)	0.076
Medical history			
Congestive heart failure	54 (20)	73 (10)	< 0.001
Deep vein thrombosis	70 (25)	225 (30)	0.16
Diabetes †	80 (29)	159 (21)	0.013
Hypertension	182 (66)	358 (48)	< 0.001
Myocardial infarction	23 (8)	72 (10)	0.63
Pulmonary embolism	71 (26)	143 (19)	0.018
Stroke †	30 (11)	38 (5)	0.002
Genetic variants			
*CYP2C9*2* †			< 0.001
No variants	262 (95)	575 (78)	
Heterozygous	11 (4)	151 (20)	
Homozygous	0 (0)	11 (1)	
Withdrew prior to genotyping	2 (<1)	3 (<1)	
*CYP2C9*3* †			< 0.001
No variants	268 (97)	654 (88)	
Heterozygous	5 (2)	82 (11)	
Homozygous	0 (0)	1 (<1)	
Withdrew prior to genotyping	2 (<1)	3 (<1)	
VKORC1 (*VKORC1 3673G>A*) †			< 0.001
No variants (GG)	222 (81)	265 (36)	
Heterozygous (AG or GA)	50 (18)	353 (48)	
Homozygous (AA)	1 (<1)	119 (16)	
Withdrew prior to genotyping	2 (<1)	3 (<1)	

Table S1: Continued.

	Black (n=275)	Nonblack (n=740)	P
Total number of genetic variants ‡			< 0.001
0 variants	209 (76)	184 (25)	
1 variant	60 (22)	304 (41)	
>1 variant	4 (1)	249 (34)	
Withdrew prior to genotyping	2 (<1)	3 (<1)	

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

† Variable used in pharmacogenetic or clinical dose-initiation or dose-revision algorithm. Dosing algorithms are provided in Supplementary Appendix.

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

Table S2: Dispensed warfarin doses over the intervention period for the genotype-guided and clinically guided dosing groups, for all participants and by race.

	Genotype-guided dosing			Clinically guided dosing		
	All participants (n = 484) %	Black (n = 129) %	Nonblack (n = 355) %	All participants (n = 471) %	Black (n = 126) %	Nonblack (n = 345) %
Days 1–3 *						
< 4 mg/day	6	2	7	2	2	2
≥ 4 and ≤ 6 mg/day	53	30	62	65	37	74
> 6 mg/day	41	67	32	33	61	23
Days 4–5 †						
< 4 mg/day	21	4	27	17	14	19
≥ 4 and ≤ 6 mg/day	44	37	47	46	31	52
> 6 mg/day	35	59	26	37	55	30

* Average dispensed dose over days 1–3.

† Average dispensed dose over days 4–5.

Table S3: Comparison of above-range (>3) and below-range (<2) INRs through 4 weeks between the genotype-guided and clinically guided dosing groups, for all participants and by race.

	Genotype-guided dosing Mean percent time, % *	Clinically guided dosing Mean percent time, % *	Odds ratio (95% CI) †	P
Above range (INR>3)				
All participants (n=955)	23.8	21.9	1.1 (0.96, 1.3)	0.15
Race				0.013 ‡
Black (n=255)	27.4	22.5	1.5 (1.2, 2.1)	0.004
Nonblack (n=700)	22.4	21.6	1.0 (0.84, 1.2)	0.99
Below range (INR<2)				
All participants (n=955)	31.0	32.7	0.96 (0.84, 1.1)	0.56
Race				0.13 §
Black (n=255)	37.0	34.0	1.1 (0.88, 1.5)	0.31
Nonblack (n=700)	28.8	32.3	0.90 (0.77, 1.1)	0.21

CI, confidence interval.

* Percent time above and below therapeutic range was calculated using linear interpolation between successive INR values. Percent time in therapeutic range (PTTR) is provided in Table 2.

† Relative odds of above-range (below-range) INR between the genotype-guided and clinically guided dosing groups, for which in-range is the referent category, estimated from a multinomial logistic regression model, adjusted for race, clinical center, and cubic splines for day since initiation. All INRs collected in the first 4 weeks were used in the analysis, except for any INRs collected more than 5 days after the drug was held. A robust variance estimator was used to account for longitudinal correlation.[11] Probability weights equal to the inverse of the total number of INRs for each participant were used to account for heterogeneity in the number of INRs per participant.[12]

‡ Interaction P value to evaluate equality of above-range estimated odds ratios between race subgroups.

§ Interaction P value to evaluate equality of below-range estimated odds ratios between race subgroups.

Table S4: Comparison of time to first therapeutic INR (2–3) between the genotype-guided and clinically guided dosing groups.

	Genotype-guided dosing 14-day probability (95% CI) *	Clinically guided dosing 14-day probability (95% CI) *	Hazard ratio (95% CI) †	P
All participants (n=955)	0.81 (0.77, 0.84)	0.85 (0.81, 0.88)	0.94 (0.82, 1.1)	0.36
Primary subgroup ‡				0.097 §
Algorithms' difference ≥ 1.0 mg/d (n=392)	0.82 (0.76, 0.87)	0.80 (0.74, 0.85)	1.1 (0.87, 1.3)	0.48
Algorithms' difference < 1.0 mg/d (n=563)	0.80 (0.75, 0.84)	0.87 (0.83, 0.91)	0.86 (0.72, 1.0)	0.078
Race				0.072 §
Black (n=255)	0.70 (0.60, 0.77)	0.87 (0.79, 0.92)	0.76 (0.58, 0.99)	0.044
Nonblack (n=700)	0.85 (0.80, 0.88)	0.84 (0.79, 0.87)	1.0 (0.87, 1.2)	0.91
Total number of genetic variants **				0.99 §
1 variant (n=343)	0.85 (0.78, 0.89)	0.87 (0.81, 0.91)	0.94 (0.76, 1.2)	0.59
0 or >1 variant (n=612)	0.79 (0.74, 0.83)	0.83 (0.78, 0.87)	0.94 (0.80, 1.1)	0.50

CI, confidence interval.

* Probability of achieving a therapeutic INR by day 14, calculated as 1 minus the Kaplan-Meier survival estimate at day 14. See Supplementary Figure 2.

† Relative hazard of achieving a therapeutic INR between the genotype-guided and clinically guided dosing groups, estimated from multivariable Cox regression models, adjusted for race and clinical center. A hazard ratio >1 indicates that participants in the genotype-guided dosing group had, on average, shorter time to first therapeutic INR compared to those in the clinically guided dosing group. Follow-up began at completion of the intervention period. Censoring events were warfarin discontinuations longer than 5 days (censored at 5 days after the drug was held), study withdrawal, death, or administrative censoring at day 28.

‡ Defined as an absolute difference of ≥ 1.0 mg in the predicted initial daily dose between the pharmacogenetic and clinical dose-initiation algorithms.

§ Interaction P value to evaluate equality of estimated hazard ratios between subgroups.

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

Table S5: Comparison of time to maintenance dose between the genotype-guided and clinically guided dosing groups.

	Genotype-guided dosing 28-day probability (95% CI) *	Clinically guided dosing 28-day probability (95% CI) *	Hazard ratio (95% CI) †	P
All participants (n=946)	0.44 (0.39, 0.48)	0.46 (0.41, 0.50)	1.1 (0.91, 1.2)	0.45
Primary subgroup ‡				0.94 §
Algorithms' difference ≥ 1.0 mg/d (n=389)	0.44 (0.36, 0.50)	0.47 (0.39, 0.54)	1.1 (0.84, 1.3)	0.63
Algorithms' difference < 1.0 mg/d (n=557)	0.44 (0.38, 0.50)	0.45 (0.39, 0.51)	1.1 (0.88, 1.3)	0.48
Race				0.19 §
Black (n=249)	0.29 (0.20, 0.37)	0.42 (0.32, 0.50)	0.89 (0.65, 1.2)	0.44
Nonblack (n=697)	0.49 (0.44, 0.54)	0.47 (0.42, 0.53)	1.1 (0.94, 1.3)	0.19
Total number of genetic variants **				0.26 §
1 variant (n=341)	0.47 (0.39, 0.55)	0.45 (0.37, 0.52)	1.2 (0.93, 1.5)	0.16
0 or >1 variant (n=605)	0.42 (0.36, 0.48)	0.47 (0.40, 0.52)	1.0 (0.82, 1.2)	0.97

CI, confidence interval.

* Probability of achieving maintenance dose by day 28, calculated as 1 minus the Kaplan-Meier survival estimate at day 28.

† Relative hazard of achieving maintenance dose between the genotype-guided and clinically guided dosing groups, estimated from multivariable Cox regression models, adjusted for race and clinical center. A hazard ratio >1 indicates that participants in the genotype-guided dosing group had, on average, shorter time to maintenance dose compared to those in the clinically guided dosing group. Follow-up began at completion of the intervention period. Censoring events were warfarin discontinuations longer than 5 days (censored at 5 days after the drug was held), study withdrawal, death, or administrative censoring at the end of the study.

‡ Defined as an absolute difference of ≥ 1.0 mg in the predicted initial daily dose between the pharmacogenetic and clinical dose-initiation algorithms.

§ Interaction P value to evaluate equality of estimated hazard ratios between subgroups.

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

Table S6: Summary statistics of pharmacogenetic and clinical dose-initiation and dose-revision predictions of maintenance dose versus observed maintenance dose among all participants who achieved maintenance dose, for all participants and by race.

	Genotype-guided dosing			Clinically guided dosing		
	All participants	Black	Nonblack	All participants	Black	Nonblack
Achieved maintenance dose, n	370	84	286	349	89	260
Within 1 mg of 5 mg/day, % *	33	27	35	31	26	33
Dose-initiation algorithm						
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
Dose-revision algorithm						
Partial R^2 †	0.69	0.40	0.75	0.54	0.50	0.51
Spearman rank correlation ‡	0.84	0.66	0.87	0.77	0.77	0.77
Mean absolute difference, mg/d §	1.0	1.3	0.9	1.1	1.1	1.1
Predicted – observed dose, % **						
≥ 1 mg/d	14	24	12	12	11	13
Within 1 mg/d	62	50	66	61	63	61
≤ -1 mg/d	23	26	22	26	26	27

* Percent of participants whose observed maintenance dose would have been within 1 mg/day of 5 mg/day (had all participants started on a dose of 5 mg/day).

† Partial R^2 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 S7: Comparison of adverse events from randomization to day 28 of warfarin therapy between the genotype-guided and clinically guided dosing groups by race. Results for all participants are provided in Table 3.

Outcome	Genotype-guided dosing n/N (%)	Clinically guided dosing n/N (%)	Hazard ratio (95% CI) *	P
Any INR≥4, major bleeding, or TE †				0.19 ‡
Black	34/141 (24)	29/134 (22)	1.3 (0.81, 2.2)	0.26
Nonblack	71/373 (19)	74/367 (20)	0.90 (0.65, 1.2)	0.52
Any INR≥4				0.27 ‡
Black	33/141 (23)	27/134 (20)	1.4 (0.82, 2.3)	0.23
Nonblack	67/373 (18)	65/367 (18)	0.97 (0.69, 1.4)	0.86
Major bleeding §				0.78 ‡
Black	1/141 (1)	2/134 (1)	0.55 (0.05, 6.1)	0.63
Nonblack	3/373 (1)	8/367 (2)	0.38 (0.10, 1.4)	0.15
Thromboembolism				NA ‡
Black	1/141 (1)	0/134 (0)	NA	NA
Nonblack	4/373 (1)	4/367 (1)	1.0 (0.25, 4.1)	0.98
Clinically relevant non-major bleed **				0.31 ‡
Black	2/141 (1)	6/134 (4)	0.30 (0.06, 1.6) **	0.15
Nonblack	11/373 (3)	14/367 (4)	0.76 (0.33, 1.7) **	0.50
All-cause death				NA ‡
Black	1/141 (1)	1/134 (1)	NA	NA
Nonblack	1/373 (<1)	0/367 (0)	NA	NA

CI, confidence interval; TE, thromboembolism; NA, not available due to limited number of events.

* Relative hazard of an adverse event between the genotype-guided and clinically guided dosing groups, estimated from multivariable Cox regression models, adjusted for race and clinical center. A hazard ratio >1 indicates that participants in the genotype-guided dosing group had, on average, shorter time to an adverse event compared to those in the clinically guided dosing group. Follow-up time began at randomization. Censoring events for major bleeding and thromboembolic events were death and administrative censoring at day 28. The censoring event for death was administrative censoring at day 28.

† Principle secondary outcome.

‡ Interaction P value to evaluate equality of estimated hazard ratios between race subgroups.

§ The INR at the time of the bleeding event was available for all but 1 participant (clinically guided dosing group, nonblack), and was elevated (INR>3) in 3 participants in the genotype-guided dosing group (1 black and 2 nonblack) and in 1 participant (nonblack) in the clinically guided dosing group.
** Binary outcome of any clinically relevant non-major bleed was analyzed using a multivariable logistic regression model, adjusted for race and clinical enter. Point estimate and confidence interval are estimated odds ratios comparing the odds of a clinically relevant non-major bleed between the genotype-guided and clinically guided dosing groups.

Table S8: Comparison of adverse events from randomization to the end of follow-up between the genotype-guided and clinically guided dosing groups.

Outcome	Genotype-guided dosing n/N (%)	Clinically guided dosing n/N (%)	Hazard ratio (95% CI) *	P
Any INR≥4, major bleeding, or TE				
All participants	154/514 (30)	170/501 (34)	0.91 (0.73, 1.1)	0.42
Race				0.84 †
Black	42/141 (30)	51/134 (38)	0.95 (0.63, 1.4)	0.80
Nonblack	112/373 (30)	119/367 (32)	0.90 (0.69, 1.2)	0.43
Any INR≥4				
All participants	150/514 (29)	152/501 (30)	1.0 (0.80, 1.3)	0.99
Race				0.90 †
Black	41/141 (29)	46/134 (34)	1.0 (0.67, 1.6)	0.91
Nonblack	109/373 (29)	106/367 (29)	0.99 (0.76, 1.3)	0.96
Major bleeding ‡				
All participants	7/514 (1)	19/501 (4)	0.36 (0.15, 0.86)	0.021
Race				0.83 †
Black	2/141 (1)	5/134 (4)	0.42 (0.08, 2.2)	0.30
Nonblack	5/373 (1)	14/367 (4)	0.34 (0.12, 0.95)	0.039
Thromboembolism §				
All participants	6/514 (1)	9/501 (2)	0.67 (0.24, 1.9)	0.46
Race				0.82 †
Black	1/141 (1)	2/134 (1)	0.52 (0.05, 5.8)	0.60
Nonblack	5/373 (1)	7/367 (2)	0.72 (0.23, 2.3)	0.57
Clinically relevant non-major bleed **				
All participants	40/514 (8)	52/501 (10)	0.71 (0.46, 1.1) **	0.13
Race				0.22 †
Black	9/141 (6)	17/134 (13)	0.46 (0.19, 1.1) **	0.072
Nonblack	31/373 (8)	35/367 (10)	0.85 (0.50, 1.4) **	0.52
All-cause death				
All participants	6/514 (1)	11/501 (2)	0.55 (0.20, 1.5)	0.25
Race				0.097 †
Black	4/141 (3)	3/134 (2)	1.5 (0.33, 6.7)	0.61
Nonblack	2/373 (1)	8/367 (2)	0.24 (0.05, 1.1)	0.070

CI, confidence interval; TE, thromboembolism.
* Relative hazard of an adverse event between the genotype-guided and clinically guided dosing groups, estimated from multivariable Cox regression models, adjusted for race and clinical center. A hazard ratio >1 indicates that participants in the genotype-guided dosing group had, on average, shorter time to an adverse event compared to those in the clinically guided dosing group. Follow-up time began at randomization. Censoring events for major bleeding and thromboembolic events were death and administrative censoring at the end of the study. The censoring event for death was administrative censoring at the end of the study.
† Interaction P value to evaluate equality of estimated hazard ratios between race subgroups.
‡ The rate of any major bleeding serious adverse event among the genotype-guided and clinically guided dosing groups was 3.5% and 9.9% per year, respectively. Among the major bleeding events that occurred after the first 28 days, the INR was elevated at the time of the event in 2 participants in the genotype-guided dosing group and 2 participants in the clinically guided dosing group (all nonblack).
§ The rate of any thromboembolic serious adverse event among the genotype-guided and clinically guided dosing groups was 3.0% and 4.6% per year, respectively.
** Binary outcome of any clinically relevant non-major bleed was analyzed using a multivariable logistic regression model, adjusted for race and clinical enter. Point estimate and confidence interval are estimated odds ratios comparing the odds of a clinically relevant non-major bleed between the genotype-guided and clinically guided dosing groups.

Table S9a: Comparison of percent time in therapeutic INR range (PTTR) between COAG and other randomized controlled trials of pharmacogenetic dosing of warfarin.

Study	Mean PTTR, %	Timeframe, weeks *	Therapeutic INR range
COAG	40%	2 weeks	2–3
	45%	4 weeks	2–3
	62%	4 weeks	1.8–3.2
	51%	12 weeks	2–3
	68%	12 weeks	1.8–3.2
CoumaGen[7]	50-52%	12 weeks	2–3
	69%	12 weeks	1.8–3.2
CoumaGen-II[13]	69%	4 weeks	1.8–3.3 (target, 2.5) 2.25–3.85 (target, 3)
Marshfield[14]	29%	2 weeks	2–3.5 (target, 2.5 and 3)

* Timeframe indicates the time period for which PTTR was calculated.

Table S9b: Comparison of percent time in therapeutic INR range (PTTR) between COAG and randomized controlled trials that compared warfarin with new oral anticoagulants among warfarin-naïve patients, using the most comparable time periods for PTTR calculation.

Study	Mean PTTR, %	Timeframe, weeks *	Therapeutic INR range
COAG	45%	4 weeks	2–3
	51%	12 weeks	2–3
RELY[15] †	43%	4 weeks	2–3
ROCKET-AF[16] †	47%	84 weeks	2–3
ARISTOTLE[17] †	44% ‡	12 weeks	2–3

* Timeframe indicates the time period for which PTTR was calculated.
† Data presented are for the subset of participants that newly initiated warfarin therapy.
‡ Median PTTR.

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