

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

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ABSTRACT

BACKGROUND

The level of anticoagulation in response to a fixed-dose regimen of warfarin is difficult to predict during the initiation of therapy. We prospectively compared the effect of genotype-guided dosing with that of standard dosing on anticoagulation control in patients starting warfarin therapy.

METHODS

We conducted a multicenter, randomized, controlled trial involving patients with atrial fibrillation or venous thromboembolism. Genotyping for *CYP2C9**2, *CYP2C9**3, and *VKORC1* (−1639G→A) was performed with the use of a point-of-care test. For patients assigned to the genotype-guided group, warfarin doses were prescribed according to pharmacogenetic-based algorithms for the first 5 days. Patients in the control (standard dosing) group received a 3-day loading-dose regimen. After the initiation period, the treatment of all patients was managed according to routine clinical practice. The primary outcome measure was the percentage of time in the therapeutic range of 2.0 to 3.0 for the international normalized ratio (INR) during the first 12 weeks after warfarin initiation.

RESULTS

A total of 455 patients were recruited, with 227 randomly assigned to the genotype-guided group and 228 assigned to the control group. The mean percentage of time in the therapeutic range was 67.4% in the genotype-guided group as compared with 60.3% in the control group (adjusted difference, 7.0 percentage points; 95% confidence interval, 3.3 to 10.6; $P < 0.001$). There were significantly fewer incidences of excessive anticoagulation (INR ≥ 4.0) in the genotype-guided group. The median time to reach a therapeutic INR was 21 days in the genotype-guided group as compared with 29 days in the control group ($P < 0.001$).

CONCLUSIONS

Pharmacogenetic-based dosing was associated with a higher percentage of time in the therapeutic INR range than was standard dosing during the initiation of warfarin therapy. (Funded by the European Commission Seventh Framework Programme and others; ClinicalTrials.gov number, NCT01119300.)

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WARFARIN HAS PROVED TO BE EFFECTIVE in the management of thromboembolic disease¹ but has a narrow therapeutic index, with wide variation among patients in the daily doses required; this variation can lead to either excessive or insufficient anticoagulation.² An increase in the international normalized ratio (INR) above the therapeutic range confers a predisposition to bleeding,³ which is a common cause of hospital admission.⁴

Polymorphisms in two genes, *CYP2C9* (involved in the metabolism of the pharmacologically more potent *S*-enantiomer of warfarin) and *VKORC1* (involved in the vitamin K cycle),^{5,6} together with age and body-surface area, account for about 50% of the variability in the individual daily dose requirement.¹ Data showing the importance of these polymorphisms led the Food and Drug Administration to change the drug label for warfarin⁷ and include the statement, “The patient’s *CYP2C9* and *VKORC1* genotype information, when available, can assist in selection of the starting dose.”⁸ However, genotyping before prescription of warfarin is not recommended in clinical practice guidelines⁹ because of the lack of data from randomized trials and is not performed routinely in clinical practice.¹

A number of prospective studies and randomized, controlled trials have failed to show that genotyping improves anticoagulation control.^{1,10-14} These studies have had limitations with respect to sample size, dosing algorithms, or genotyping strategy.¹⁰ Although a recent study showed that genotype-guided dosing led to superior control of anticoagulation, the finding was based on a comparison with a nonrandomized, real-world parallel control group.¹⁵ In order to fill this evidence gap, our group, as part of the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) consortium,¹⁶ performed a randomized, controlled trial of genotype-guided dosing of warfarin as compared with standard clinical care.

METHODS

TRIAL DESIGN

The EU-PACT warfarin trial was a pragmatic, single-blind, randomized, controlled trial that was designed to determine whether genotype-guided warfarin dosing was superior to standard dosing. The trial methods have been described previously.¹⁶ The protocol (available with the full text of this article at NEJM.org) was approved by

the local research ethics committee in Liverpool, United Kingdom, and by the regional ethical review board in Uppsala, Sweden. Oversight was provided by a data and safety monitoring board. Data were collected by the investigators and were analyzed by a statistician (the second author), who vouches for the accuracy and completeness of the data reported. All the authors vouch for adherence of the study to the protocol. LGC (formerly the Laboratory of the Government Chemist) provided the point-of-care genotyping assay with funding from the European Union.

TRIAL PARTICIPANTS

We recruited patients in the United Kingdom (three centers) and Sweden (two centers). Eligible patients had not received previous treatment with warfarin and had either atrial fibrillation or venous thromboembolism that was deemed by their attending physician to require anticoagulation with warfarin with a target INR of 2.0 to 3.0. Recruitment occurred only after the decision to start warfarin had been made by the patient’s clinician. Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix, available at NEJM.org.¹⁶ All participants gave written informed consent before taking part in the trial.

TRIAL PROCEDURES

Patients were randomly assigned to either the genotype-guided dosing group or the standard dosing (control) group, with the use of a randomization schedule incorporated into online software for the case-report form. Block randomization was stratified according to center and indication (atrial fibrillation or venous thromboembolism). Patients were unaware of the study-group assignments.

Genotyping for the *CYP2C9**2, *CYP2C9**3, and *VKORC1* (–1639G→A) alleles was performed on a point-of-care platform with the use of HyBeacon probes (LGC), which provided results in approximately 2 hours.¹⁷ Genotyping was performed immediately after randomization for patients in the genotype-guided group and after trial completion for patients in the control group. Details concerning genotyping are provided in the Supplementary Appendix.

The dosing regimen in the genotype-guided group was determined in the following way: for days 1 through 3, the doses were determined on the basis of a loading-dose algorithm¹⁸; this algorithm incorporated predicted maintenance doses

from a slightly modified version of the International Warfarin Pharmacogenetics Consortium algorithm¹⁹ with the estimated half-life for the S-enantiomer of warfarin according to *CYP2C9* genotype. For days 4 and 5, the doses were determined on the basis of a dose-revision algorithm that was based on the INR value on day 4.²⁰ Both algorithms incorporated clinical and genetic factors (Table S1 in the Supplementary Appendix). The doses after day 5 were determined according to usual local clinical practice.

In the control group, patients 75 years of age or younger received 10 mg of warfarin on day 1, 5 mg on day 2, and 5 mg on day 3, whereas patients older than 75 years of age received 5 mg per day on days 1 through 3. The doses on days 4 and 5 and thereafter were determined according to usual local clinical practice.

All patients were followed for 3 months, with INR measured on days 1, 4, 6, 8, 15, 22, 57, and 85. Some patients had additional clinic visits and INR measurements, but these were determined by clinical need.

OUTCOME MEASURES

The primary outcome measure was the percentage of time in the therapeutic INR range of 2.0 to 3.0, calculated with the use of the method of Rosendaal et al.,²¹ during the 12 weeks after the initiation of warfarin therapy. The secondary outcome measures included the incidence of INR values of 4.0 or higher, the percentage of time with an INR of 4.0 or higher, the percentage of time with an INR of less than 2.0, the time to reach a therapeutic INR, and the time to reach a stable warfarin dose. Additional secondary outcome measures included major and minor bleeding events, defined according to the International Society on Thrombosis and Haemostasis (ISTH) classification²²; thromboembolic events; sensitivity to warfarin; resistance to warfarin; the number of adjustments in the dose of warfarin; and the clinical usefulness of the rapid point-of-care genotyping test. Definitions of the secondary outcome measures are detailed in the Supplementary Appendix.

STATISTICAL ANALYSIS

The original sample size was calculated with the use of data on time in the therapeutic range during the first 3 months of warfarin therapy from studies of warfarin use in patients with atrial fibrillation or venous thromboembolism.^{23,24} The

standard deviation of the primary outcome was estimated at 26.5%. We calculated that 442 patients would need to be enrolled in each group for the study to have 80% power to show an improvement with genotyping of 5 percentage points in the percentage of time in the therapeutic range, at a 5% significance level. Owing to challenges in recruitment, the sample size was recalculated, with the use of blinded data from the first 222 patients recruited, to give a new estimate of the standard deviation of 23%. The revised minimum target sample size was set at 200 patients per study group, which would provide 80% power to detect a slightly larger improvement in the primary outcome of 7 percentage points.

Participants who remained in the study on day 13 or later were included in the analysis according to the groups to which they were randomly assigned. Those who dropped out before day 13 were excluded from the analysis. A per-protocol analysis was also performed. The INR value for day 1 (the start of warfarin therapy) was assumed to be that measured at visit 1 (the randomization visit). If the INR at visit 1 was unavailable, it was assumed to be 1.0. When two different INR measurements were performed on the same day, the higher of the two values was used.

Linear regression was used for the statistical between-group comparison of the primary outcome and other numerical secondary outcomes. Categorical outcomes were compared with the use of logistic regression. Time-to-event outcomes are shown with the use of Kaplan–Meier curves and were compared between groups with the use of Cox regression. The number of dose adjustments was compared between groups with the use of Poisson regression. All regression analyses included the stratification factors of center and indication.

Three sensitivity analyses were performed for the primary outcome. The first included all patients with at least two INR measurements, including those who dropped out before day 13. The second excluded those who received a dose of warfarin before randomization, and the third analyzed the percentage of time in the therapeutic range from randomization to the end of the 3-month follow-up period rather than from the initiation of treatment to the end of the follow-up period. The model created for the regression analyses was assessed by examination of residuals. All analyses were performed with the use of SAS software, version 9.3.

RESULTS

PATIENTS

Recruitment took place from January 2011 through January 2013, with final follow-up in April 2013. A total of 455 patients (353 in the United Kingdom and 102 in Sweden) underwent randomization, with 227 assigned to the genotype-guided group and 228 to the control group (Fig. S1 in the Supplementary Appendix). Most of the patients were

men (61.0%), and 98.5% were white; the mean age was 67.3 years. The majority of patients (72.1%) had atrial fibrillation; those with venous thromboembolism received heparin for at least 5 days after the initial diagnosis. The two groups were well balanced with respect to the baseline characteristics (Table 1). The genotype distributions in the two groups were similar to those described in the literature.⁵

We included in the analysis only the 427 pa-

Table 1. Demographic and Baseline Clinical Characteristics of the Study Patients.*

Characteristic	All Patients			Patients Included in Primary Analysis		
	Genotype-Guided Group (N=227)	Control Group (N=228)	Total (N=455)	Genotype-Guided Group (N=211)	Control Group (N=216)	Total (N=427)
Center — no. (%)						
Enköping, Sweden	16 (7.0)	14 (6.1)	30 (6.6)	14 (6.6)	13 (6.0)	27 (6.3)
Liverpool, U.K.	97 (42.7)	98 (43.0)	195 (42.9)	89 (42.2)	94 (43.5)	183 (42.9)
Newcastle, U.K.	39 (17.2)	37 (16.2)	76 (16.7)	38 (18.0)	37 (17.1)	75 (17.6)
St. Helens, U.K.	40 (17.6)	42 (18.4)	82 (18.0)	35 (16.6)	37 (17.1)	72 (16.9)
Uppsala, Sweden	35 (15.4)	37 (16.2)	72 (15.8)	35 (16.6)	35 (16.2)	70 (16.4)
Indication — no. (%)						
Atrial fibrillation	164 (72.2)	164 (71.9)	328 (72.1)	153 (72.5)	157 (72.7)	310 (72.6)
Venous thromboembolism	63 (27.8)	64 (28.1)	127 (27.9)	58 (27.5)	59 (27.3)	117 (27.4)
Age — yr						
Mean	67.8±14.5	66.9±12.9	67.3±13.7	67.6±14.3	67.3±12.7	67.5±13.5
Range	23.7 to 90.2	22.0 to 90.2	22.0 to 90.2	24.5 to 90.2	22.0 to 90.2	22.0 to 90.2
Sex — no./total no. (%)						
Male	145/226 (64.2)	132/228 (57.9)	277/454 (61.0)	138/211 (65.4)	127/216 (58.8)	265/427 (62.1)
Female	81/226 (35.8)	96/228 (42.1)	177/454 (39.0)	73/211 (34.6)	89/216 (41.2)	162/427 (37.9)
Height — cm						
Mean	171.6±10.2	170.4±10.2	171.0±10.2	172.1±9.9	170.4±10.3	171.3±10.2
Range	142 to 195	147 to 194	142 to 195	142 to 195	147 to 194	142 to 195
Weight — kg						
Mean	85.6±19.9	87.4±21.0	86.5±20.4	86.3±19.6	87.6±21.4	87.0±20.5
Range	42.9 to 158.8	43.5 to 182.8	42.9 to 182.8	42.9 to 158.8	43.5 to 182.8	42.9 to 182.8
Race — no./total no. (%)†						
Black	3/226 (1.3)	2/228 (0.9)	5/454 (1.1)	2/211 (0.9)	2/216 (0.9)	4/427 (0.9)
White	222/226 (98.2)	225/228 (98.7)	447/454 (98.5)	208/211 (98.6)	213/216 (98.6)	421/427 (98.6)
Asian	1/226 (0.4)	1/228 (0.4)	2/454 (0.4)	1/211 (0.5)	1/216 (0.5)	2/427 (0.5)
Smoking status — no./total no. (%)						
Current smoker	23/223 (10.3)	29/227 (12.8)	52/450 (11.6)	20/210 (9.5)	27/215 (12.6)	47/425 (11.1)
Former smoker	93/223 (41.7)	105/227 (46.3)	198/450 (44.0)	88/210 (41.9)	101/215 (47.0)	189/425 (44.5)
Never smoked	107/223 (48.0)	93/227 (41.0)	200/450 (44.4)	102/210 (48.6)	87/215 (40.5)	189/425 (44.5)

Table 1. (Continued.)

Characteristic	All Patients			Patients Included in Primary Analysis		
	Genotype-Guided Group (N=227)	Control Group (N=228)	Total (N=455)	Genotype-Guided Group (N=211)	Control Group (N=216)	Total (N=427)
VKORC1 genotype — no./total no. (%) [‡]						
G/G	91/226 (40.3)	93/212 (43.9)	184/438 (42.0)	86/211 (40.8)	90/202 (44.6)	176/413 (42.6)
A/G	91/226 (40.3)	90/212 (42.5)	181/438 (41.3)	83/211 (39.3)	85/202 (42.1)	168/413 (40.7)
A/A	44/226 (19.5)	29/212 (13.7)	73/438 (16.7)	42/211 (19.9)	27/202 (13.4)	69/413 (16.7)
CYP2C9 genotype — no./total no. (%)						
*1/*1	150/226 (66.4)	141/213 (66.2)	291/439 (66.3)	142/211 (67.3)	133/203 (65.5)	275/414 (66.4)
*1/*2	47/226 (20.8)	45/213 (21.1)	92/439 (21.0)	42/211 (19.9)	45/203 (22.2)	87/414 (21.0)
*1/*3	21/226 (9.3)	20/213 (9.4)	41/439 (9.3)	20/211 (9.5)	18/203 (8.9)	38/414 (9.2)
*2/*2	6/226 (2.7)	2/213 (0.9)	8/439 (1.8)	5/211 (2.4)	2/203 (1.0)	7/414 (1.7)
*2/*3	2/226 (0.9)	4/213 (1.9)	6/439 (1.4)	2/211 (0.9)	4/203 (2.0)	6/414 (1.4)
*3/*3	0/226	1/213 (0.5)	1/439 (0.2)	0/211	1/203 (0.5)	1/414 (0.2)
Time from randomization to start of treatment — days [§]						
Median (interquartile range)	1 (0 to 2)	1 (0 to 1)	1 (0 to 2)	1 (0 to 2)	1 (0 to 1)	1 (0 to 2)
Range	-1 to 134	-1 to 46	-1 to 134	-1 to 134	-1 to 46	-1 to 134

* Plus-minus values are means ±SD. Patients included in the primary analysis were those for whom at least 13 days of data on the international normalized ratio were available. Unless otherwise indicated, there were no significant differences between the two groups in any baseline characteristic.

[†] Race was self-reported.

[‡] Persons with the G/G genotype have the highest dose requirements, and those with the A/A genotype have the lowest.

[§] P=0.02 for the comparison between the genotype-guided and control groups. The difference was due primarily to logistic and medical reasons (see Table S2 in the Supplementary Appendix). Of the patients included in the analysis, 19 in the genotype-guided group (9.0%) and 21 in the control group (9.7%) received a dose before randomization on day 1, so the doses on days 2 and 3 were adjusted to ensure that the total dose over a period of 3 days equaled the predicted genotype-determined dose or the standard 3-day dose.

tients who had at least 13 days of INR data: 211 in the genotyped-guided group and 216 in the control group (Table 1). The reasons that patients dropped out of the study are shown in Figure S1 in the Supplementary Appendix, and the protocol deviations are shown in Table S2 in the Supplementary Appendix. There were 7 deaths (5 in the genotype-guided group and 2 in the control group) during the trial, none of which were judged to be due to the use of, or indication for, warfarin

PRIMARY OUTCOME

The unadjusted percentage of time with an INR of 2.0 to 3.0 was 67.4% in the genotype-guided group as compared with 60.3% in the control group. This represents a difference of 7.0 percentage points (95% confidence interval, 3.3 to 10.6; P<0.001) (Table 2) after adjustment for cen-

ter and indication. In the per-protocol analysis, the corresponding values in the genotype-guided group (166 patients) and control group (184 patients) were 68.9% and 62.3%, with an adjusted difference of 6.6 percentage points (P=0.001). The findings of the sensitivity analyses were consistent with those of the primary analysis.

The differences in the mean INR between the two groups were greatest soon after the initiation of anticoagulation and became less pronounced during the 3-month follow-up period (Fig. 1A). The difference between the two groups in the mean percentage of time in the therapeutic range became apparent between 5 and 10 days after the initiation of warfarin therapy (Fig. 1B), with significant differences observed for weeks 1 through 4 and 5 through 8 but not for weeks 9 through 12 (Table 3). There was some variation

Table 2. Percentage of Time in the Therapeutic Range for International Normalized Ratio (INR).*

Analysis	Genotype-Guided Group		Control Group		Least-Squares Mean Difference†	
	No. of Patients	% Time in Therapeutic Range‡	No. of Patients	% Time in Therapeutic Range‡	Percentage Points (95% CI)§	P Value
Patients with ≥13 days of INR data	211	67.4±18.1	216	60.3±21.7	7.0 (3.3–10.6)	<0.001
Per-protocol analysis¶	166	68.9±16.9	184	62.3±21.2	6.6 (2.7–10.5)	0.001
Sensitivity analyses						
All randomly assigned patients with ≥1 subsequent INR measurement	215	66.6±19.1	223	59.2±22.5	7.3 (3.5–11.1)	<0.001
Percentage of time in therapeutic range from day of randomization	211	65.9±17.8	216	58.9±21.2	6.9 (3.3–10.5)	<0.001
Exclusion of patients who underwent randomization after 1 dose of warfarin	192	67.1±18.2	195	60.1±21.9	7.1 (3.2–11.0)	<0.001

* Plus–minus values are means ±SD. The percentage of time in the therapeutic INR range of 2.0 to 3.0 was calculated with the use of generalized linear models. Except in a sensitivity analysis, the time in the therapeutic INR was calculated from the time of initiation of therapy.

† The differences between groups were adjusted for center and indication (atrial fibrillation or venous thromboembolism).

‡ The percentage of time in the therapeutic range is the least-squares mean.

§ The difference in least-squares means is for the genotype-guided group minus the control group.

¶ The per-protocol analysis included all patients without a major protocol deviation.

|| Patients underwent randomization at visit 1, which ranged from 7 days before the start of warfarin therapy to 1 day after the start of warfarin therapy.

among centers in the control of anticoagulation in both trial groups, with the between-group difference in the time in the therapeutic range ranging from 1.7 to 11.4 percentage points (Table S3 in the Supplementary Appendix).

SECONDARY OUTCOMES

Patients in the genotype-guided group were less likely to have an INR of 4.0 or higher than were those in the control group (Table 3). The median time to reach a therapeutic INR — which was calculated as the median time to the first of two INR values, measured at least 1 week apart, that were within the target range — was shorter in the genotype-guided group than in the control group (Fig. 2A). A total of 173 patients (82.0%) in the genotype-guided group reached a stable dose by 3 months, as compared with 152 patients (70.4%) in the control group, with patients in the genotype-guided group reaching a stable dose more quickly than those in the control group (Table 3 and Fig. 2B). There were also fewer adjustments in the dose of warfarin in the genotype-guided group than in the control group. There was no significant difference between the two groups in the median number of additional

INR measurements (four in each group) above those required by the protocol.

No major bleeding events according to the ISTH classification²² were reported in the trial, and there was no significant difference in overall bleeding events between the two groups. Three bleeding events (all in the control group) were classified as clinically significant and required admission to the hospital. The majority of the minor bleeding episodes consisted of bruising (Table S4 in the Supplementary Appendix). There was only one thromboembolic event (in the control group). There were no significant differences in the other secondary outcomes between the two groups (Table 3).

An analysis performed at the end of the study showed that the genotyping by means of the point-of-care assay was incorrect in the case of six patients. This affected *VKORC1* genotyping only and was due either to problems with the stability of the genotyping reagents or operator error in the interpretation of results (Table S2 in the Supplementary Appendix). Despite these errors, the sensitivity and specificity values for genotyping for all three alleles were high (Table S5 in the Supplementary Appendix).

DISCUSSION

Our trial showed that genotype-based dosing at the initiation of warfarin therapy increased the time in the therapeutic range (the primary outcome) by 7 percentage points and reduced the incidence of excessive anticoagulation, the time required to reach a therapeutic INR, the time required to reach a stable dose, and the number of adjustments in the dose of warfarin. However, the median number of additional INR measurements did not differ between the two groups because the protocol required eight INR measurements over a period of 3 months after the initiation of warfarin. Our findings are consistent with those of observational studies of the effect of the *VKORC1* and *CYP2C9* genotypes on warfarin dose requirement,^{5,6} and the prospective, nonrandomized, parallel-group comparison performed by Anderson et al.,¹⁵ which showed a mean time in the therapeutic range of 71% in the genotype-guided group and 59% in the control group at 3 months.

In order to achieve rapid but safe anticoagulation, a new pharmacogenetic loading-dose algorithm¹⁸ was developed that took into account the effect of *CYP2C9* allelic variants on the pharmacokinetics of warfarin. Our algorithmic strategy reduced the likelihood of excessive anticoagulation (INR ≥ 4.0) in the early stages of anticoagulation, while reducing the time to achieve a therapeutic INR, suggesting that genotype-guided dosing may not only prove to be safer but may also reduce the time required for stabilization when adopting a loading-dose strategy. The difference in mean INR between the two groups was greatest near the start of the trial (Fig. 1A), a finding that is consistent with previous findings that genotype-guided dosing has the greatest effect during the early stages of warfarin therapy.²⁵

Our trial design was consistent with clinical practice in the United Kingdom and Sweden in two major respects. First, clinical algorithms are not used in either country; thus, the study was designed pragmatically to reflect clinical practice, assessing the potential benefits of genotype-guided dosing as compared with standard dosing. Although our trial could be criticized for not having compared a genotype-guided dosing algorithm with a clinical algorithm, the values for the percentage of time in the therapeutic range in

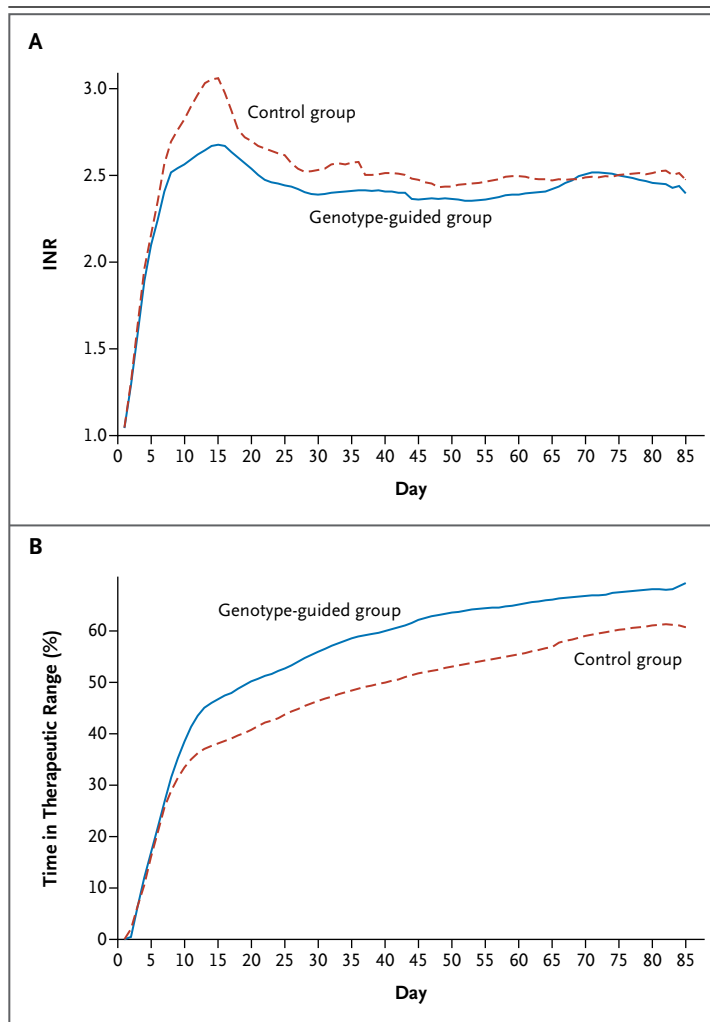


Figure 1. Mean International Normalized Ratio (INR) and Percentage of Time in the Therapeutic INR Range.

The differences between the genotype-guided dosing group and the standard dosing (control) group in the mean INR (Panel A) and the percentage of time in the therapeutic INR range of 2.0 to 3.0 (Panel B) are shown over a follow-up period of 3 months.

the control group were either equivalent to or exceeded those observed in previous studies (Table S6 in the Supplementary Appendix). Second, we used loading doses that follow the American College of Chest Physicians guidelines.⁹ This strategy has the advantage of reducing the time to reach a therapeutic INR²⁶ but increases the risk of excessive anticoagulation, particularly in the elderly.²⁷

A major limitation of our trial is that the primary outcome measure was the time in the therapeutic range, rather than the clinical out-

Table 3. Secondary Outcome Measures and Time-Dependent Analyses of the Primary Outcome Measure.*

Outcome	Genotype-Guided Group (N=211)	Control Group (N=216)	Comparison (95% CI)	P Value
INR \geq 4.0 — % of patients	57 (27.0)	79 (36.6)	0.63 (0.41 to 0.97)†	0.03
Percentage of time with INR \geq 4.0	2.3 \pm 6.4	5.3 \pm 10.3	-2.9 (-4.5 to -1.4)‡	<0.001
Percentage of time with INR <2.0	20.0 \pm 14.9	21.9 \pm 16.9	-2.0 (-4.9 to 1.0)‡	0.20
Time to reach therapeutic INR — days			1.43 (1.17 to 1.76)§	<0.001
Median	21	29		
Interquartile range	8 to 36	14 to 58		
Time to reach stable dose — days			1.40 (1.12 to 1.74)§	0.003
Median	44	59		
Interquartile range	35 to 70	41 to 86		
Dose adjustments — no.	4.9 \pm 2.6	5.4 \pm 3.0	0.91 (0.83 to 0.99)¶	0.02
Major bleeding events — no. of patients	0	0		
Bleeding events — no. of patients (%)	78 (37.0)	82 (38.0)	0.96 (0.62 to 1.49)†	0.87
Thromboembolic events — no. of patients (%)	0	1 (0.5)		
Warfarin sensitivity — no. of patients (%)	4 (1.9)	2 (0.9)		
Warfarin resistance — no. of patients (%)	4 (1.9)	3 (1.4)		
Percentage of time in therapeutic INR range**				
During wk 1–4	54.6 \pm 23.0	45.7 \pm 24.3	8.8 (4.4 to 13.1)‡	<0.001
During wk 5–8	73.9 \pm 28.0	63.5 \pm 33.1	10.2 (4.4 to 16.0)‡	<0.001
During wk 9–12	74.5 \pm 25.2	72.9 \pm 29.8	1.4 (-3.8 to 6.6)‡	0.61

* Plus-minus values are means \pm SD. All comparisons were adjusted for center and indication (atrial fibrillation or venous thromboembolism).

† The value is the odds ratio for the genotype-guided group.

‡ The value is the difference in percentage points (genotype-guided group minus the control group).

§ The value is the Cox proportional-hazards ratio for the genotype-guided group.

¶ The value is the incidence rate ratio for the genotype-guided group.

|| A statistical comparison was not performed owing to an insufficient number of events.

** This was a post hoc analysis.

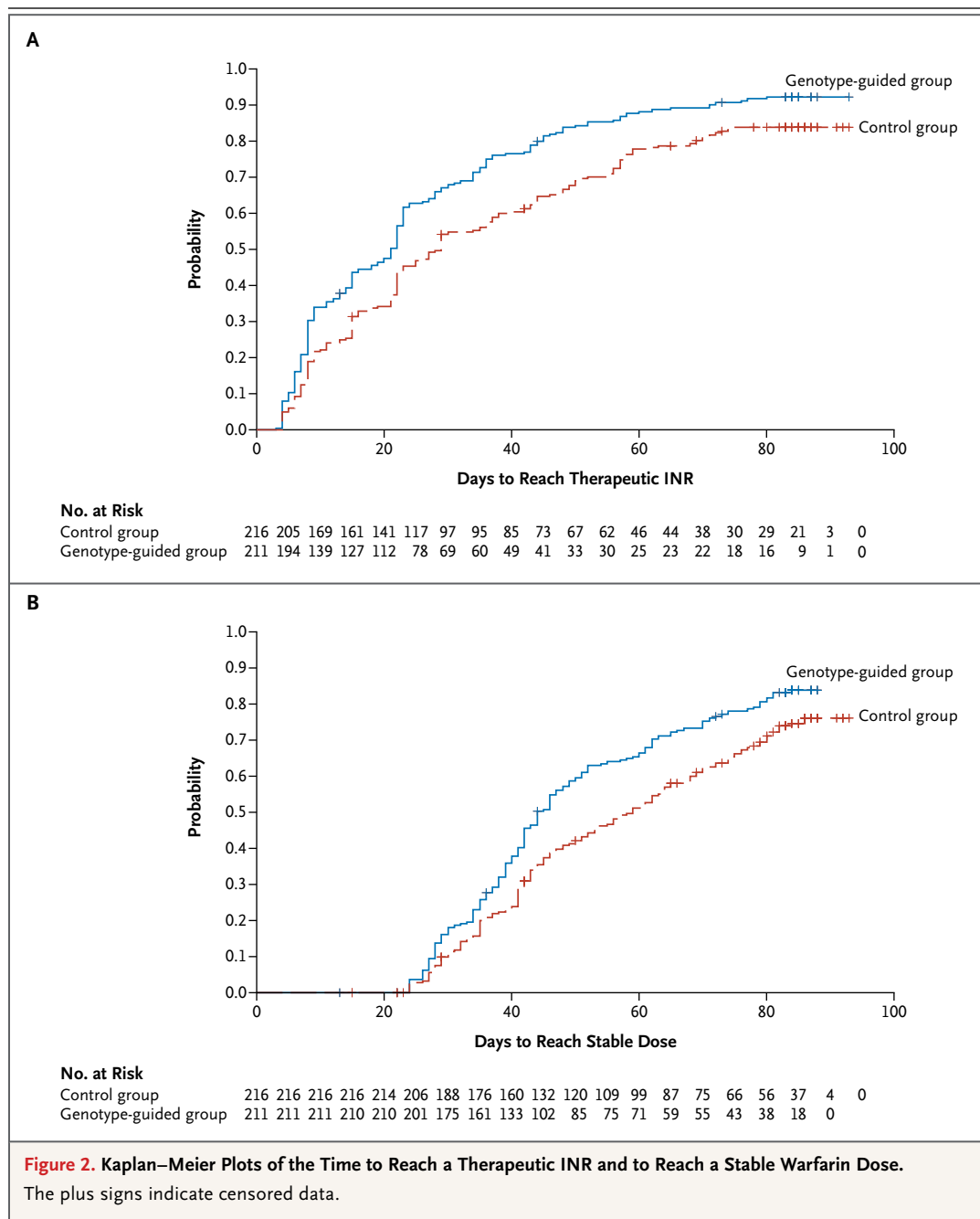
come measures of bleeding and thrombosis. On the basis of our finding that approximately 37% of the patients in the control group had bleeding events, we would have had to enroll 2916 patients to show a reduction of 5 percentage points in the rate of bleeding events (to 32%) in the genotype-guided group, with 80% power. However, bleeding events increase when the INR is 4.0 or higher,²⁸ and genotype-guided dosing in our trial reduced the incidence of, and the time with, an INR of 4.0 or higher.

Our trial did not use a double-blind design. Although this design would have been possible, it would have been more complex to implement. However, because dosing was based on a defined regimen in the genotype-guided group for the first 5 days and in the control group for the first 3 days and did not differ between the groups thereafter, we believe that the clinical care of pa-

tients was not influenced by treatment assignment. In addition, because we were using an objective and measurable end point (i.e., INR), we do not believe that the outcome assessment was biased.

The majority of our patients were of European ethnic background, and we cannot generalize our findings to other ethnic groups. Although the same genes determine warfarin dose requirements in different ethnic groups,²⁹ the frequency of the individual gene variants differs,^{29,30} and algorithms that are specific to ethnic groups will need to be developed. The development of a robust evidence-based algorithmic strategy is crucial for improving warfarin dosing in all ethnic groups.

In conclusion, we found that genotype-guided warfarin dosing was superior to standard dosing with respect to both the primary out-



come measure (time in the therapeutic INR range) and a number of secondary outcome measures. Whether this will translate to improved clinical outcomes is unclear.

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