Impact of CYP2C9-interacting Drugs on Warfarin Pharmacogenomics

Saaket Agrawal, B.S., Meredith S. Heiss, M.S., C.G.C., Remington B. Fenter, M.S., C.G.C, Tatiana V. Abramova, M.S., Minoli A. Perera, Pharm.D., Ph.D., Laura J. Rasmussen-Torvik, Ph.D., M.P.H., Maureen E. Smith, M.S., C.G.C., Jennifer A. Pacheco, M.S., and Alfred L. George, Jr., M.D.

SUPPLEMENTARY INFORMATION

Table of Contents

SUPPLEMENTARY METHODS

Genotyping

DNA samples were acquired from the NUgene biobank. All samples had a minimum DNA concentration of 40 ng/µl. Genotyping was performed in the NUSeq Core Facility using Applied Biosystems Taqman genotyping assays for *CYP2C9*2* (rs1799853), *CYP2C9*3* (rs1057910), *CYP2C9*4* (rs56165452), and *VKORC1* c.-1639 G>A (rs9923231). Information on the Taqman probes is presented in **Table S7.** Genotyping was performed according to the Applied Biosystems pharmacogenomics experiments application guide. Standard genotyping quality control procedures were performed, including the use of negative controls and duplicate samples.

INR Variability (INRvar) and Time in Therapeutic Range (TTR)

INRvarA is the statistical variance of INR. Standard deviation of INR, a related parameter, has been shown to have good predictive value for adverse events associated with warfarin therapy.[1] INRvarB was derived using the Fihn variance growth rate method, which is a time-dependent measure of INR variability – large changes between consecutive INR measurements with small time gaps will contribute more to the summation than those that occur with large time gaps.[2, 3]

TTRa was derived using the Rosendaal method that calculates the presumed time a person is in the therapeutic range (2.0 – 3.0, inclusive) assuming that INR changes linearly between consecutive measurements.[4] Notably, we did not linearly interpolate between consecutive measurements if there were more than 8 weeks between them. TTRb is the simplest measure

of long-term anticoagulation, measuring the fraction of INR measurements in the therapeutic range. The pros and cons of TTRa and TTRb have been outlined elsewhere.[5]

INRvarA, INRvarB, TTRa, and TTRb were calculated using all INR data points collected within the study period, defined as the time between 30 days after the first warfarin prescription and the date of the last warfarin prescription. One extreme INR value (INR = 21.5) was excluded from the analysis because it did not match the trend of surrounding INR values for that participant. For calculation of the four outcome measures, all INR values on the same day were averaged, which is a previously used strategy.[6] For calculation of INRvarB and TTRa, the smallest unit of time we allowed in our calculation was one day (i.e., hours and minutes between two data points were not considered).

Values for INRvarA and INRvarB deviated significantly from the normal distribution (**Figure S1**). Natural logarithm transformations of INRvarA and INRvarB, Ln(INRvarA) and Ln(INRvarB, respectively, yielded normally distributed data that we used for subsequent statistical analyses to minimize the probability of a type I error. Log transformed INRvarB has previously been shown to be a good predictor of adverse events associated with warfarin.[7] Three Ln(INRvarA) data points were determined to be far outliers (**Figure S2**) and omitted from the analyses to maintain a normal distribution (**Table S11**).

Impact of CYP2C9-interacting drug exposure on INR

The time period from which INR values were sampled was defined by a minimum date (30 days before the start of the interacting drug), and a maximum date defined as the earlier date between 30 days after the start date and 7 days after the end date. The complexity of the maximum date is to account for shorter courses of CYP2C9-interacting drugs. To be included in the analysis, the interacting drug/time period entry had to satisfy the following criteria: (1) there

were at least 14 days between the first day INR was measured and the start date of the drug, (2) there were at least 7 days between the last day INR was measured and the start of the drug, (3) at least 1 INR had to be measured within 2 weeks prior to the start date of the drug, and (4) at least 1 INR had to be measured within 1 week after the start date.

For each analyzed study period, the following parameters were collected: peak INR, trough INR, average INR, and number of INR data points in the [minimum date, medication start date] and [medication start date, maximum date] time periods (“pre” and “post”, respectively). A total of 121 instances that satisfied these criteria were analyzed. If more than 20 instances were available for a single drug, which was true for amiodarone, metronidazole, and sulfamethoxazole, then that drug was analyzed separately. The remaining CYP2C9 inhibitors were analyzed together, and the CYP2C9 inducers were analyzed together.

Table S1: Genotype and allele frequencies

A)

Genotype	Frequency
VKORC1 (c. -1639 G>A)	
G/G	139
G/A	188
A/A	71
Total	398
CYP2C9 *2	
C/C	297
C/T	91
T/T	11
Total	399
CYP2C9 *3	
A/A	352
A/C	47
C/C	0
Total	399

B)

Rs#	Gene (Allele)	Minor Allele	Minor Allele

			Frequency
rs1799853	*CYP2C9 (*2)*	T	0.142
rs1057910	*CYP2C9 (*3)*	C	0.059
rs9923231	*VKORC1*	T	0.415

A) Genotype frequencies for all successfully genotyped subjects. All alleles are in Hardy-Weinberg equilibrium.

B) Minor allele frequencies are shown for *CYP2C9*2*, *CYP2C9*3*, and *VKORC1*.

Table S2: Descriptive statistics

A. Outcome Measures

	Mean	Minimum	Maximum	Quartiles
Number of INR Measurements	77.9	14	1004	25, 48, 102
INRvarA (Statistical variance)	0.75	0.01	4.27	0.36, 0.57, 0.92
INRvarB (Fihn variance)	1.34	0.03	15.73	0.36, 0.70, 1.58
Ln(INRvarA)	-0.58	-4.61	1.45	-1.01, -0.57, -0.09
Ln(INRvarB)	-0.31	-3.58	2.76	-1.02, -0.36, 0.46
TTRa (Rosendaal method, %)	50.5	0	94.1	35.2, 53.9, 67.6
TTRb (% of INRs in range)	41.4	0	88	28.0, 42.9, 53.5

B. INR stratification in analyzed participants

	Frequency (%)
Subtherapeutic INR Value	9,618 (39.0)
Therapeutic INR Value	11,162 (45.3)
Supratherapeutic INR Value	3,830 (15.6)
Total	24,610 (100)

(A) These parameters are reported for the 302 subjects included in the analysis. Note that all INR values obtained in the same day were averaged before calculating INRvarA, INRvarB, Ln(INRvarA), Ln(INRvarB), TTRa, and TTRb. (B) Includes INR values within the study period (between 30 days after the 1st warfarin prescription start date and the last warfarin prescription end date) for the 302 subjects who were analyzed. Subtherapeutic is defined as any INR value less than 2, therapeutic is defined as any INR value between 2 and 3 (inclusive), and supratherapeutic is defined as any INR value greater than 3.

Table S3: Association of outcome measures with (A) genotype-predicted warfarin response and (B) CYP2C9-interacting drugs

Analysis A	**Normal**	**Sensitive**	**Highly Sensitive**	**p-value**
Ln(INRvarA)	-0.64* (-0.74, -0.53)	-0.39* (-0.54, -0.25)	-0.58 (-1.10, -0.05)	0.023
Ln(INRvarB)	-0.46* (-0.62, -0.31)	-0.04* (-0.25, 0.18)	-0.38 (-1.06, 0.30)	0.006
TTRa	50.9 (47.5, 54.4)	49.8 (45.5, 54.1)	52.1 (32.5, 71.6)	0.902
TTRb	42.4 (39.8, 45.1)	39.6 (36.3, 43.0)	42.1 (26.4, 57.9)	0.443

Analysis B	**0 Interacting drugs**	**1 Interacting drugs**	**2+ Interacting drugs**	**p-value**
Ln(INRvarA)	-0.69 (-0.86, -0.52)	-0.53 (-0.66, -0.41)	-0.43 (-0.58, -0.28)	0.064
Ln(INRvarB)	-0.64*† (-0.91, -0.38)	-0.24* (-0.42, -0.06)	-0.05† (-0.27, 0.16)	0.001
TTRa	54.8* (49.6, 60.0)	50.6 (46.4, 54.7)	46.2* (41.8, 50.6)	0.044
TTRb	47.0*† (42.8, 51.1)	39.9* (36.7, 43.1)	37.8† (34.4, 41.1)	0.002

For each subgroup, means are listed with 95% CI in parenthesis. Each p-value corresponds to a one-way ANOVA test for the INR outcome measure against the three categories. Post hoc pairwise comparisons were made using Tukey's HSD. * and † indicate a significant pairwise comparison at the $p < 0.05$ level. The list of interacting drugs utilized for (B) can be found in **Table 3**.

Table S4: Analysis of the interacting drug/genotype interaction

A. Significance of interaction term from two-way ANOVA

Outcome variable	**p-value**
Ln(INRvarA)	0.043*
Ln(INRvarB)	0.093
TTRa	0.183
TTRb	0.168

B. Subgroup analyses of outcome variables

LnINRvarA	**0 Interacting drugs**	**1 Interacting drugs**	**2+ Interacting drugs**	**p-value**
Normal	-0.91*†‡ (-1.09, -0.72)	-0.56* (-0.74, -0.39)	-0.49† (-0.67, -0.32)	0.005
Sensitive	-0.31‡ (-0.62, 0.004)	-0.51 (-0.70, -0.31)	-0.30 (-0.61, -0.002)	0.401
Highly Sensitive	-1.28 (-2.64, 0.09)	-0.23 (-1.39, 0.93)	-0.22 (-1.49, 1.05)	0.070
p-value	0.001	0.690	0.448	
Ln(INRvarB)	**0 Interacting drugs**	**1 Interacting drugs**	**2+ Interacting drugs**	**p-value**
Normal	-1.02*†‡ (-1.32, -0.73)	-0.32* (-0.57, -0.08)	-0.15† (-0.41, 0.11)	<0.001
Sensitive	-0.06‡ (-0.53, 0.42)	-0.10 (-0.36, 0.16)	0.10 (-0.36, 0.55)	0.779
Highly Sensitive	-1.15 (-2.10, -0.19)	-0.42 (-1.81, 0.97)	0.42 (-1.82, 2.67)	0.068

p-value	0.001	0.446	0.444	
TTRa	**0 Interacting drugs**	**1 Interacting drugs**	**2+ Interacting drugs**	**p-value**
Normal	59.1*† (52.4, 65.8)	48.6* (42.9, 54.4)	46.6† (41.1, 52.0)	0.011
Sensitive	48.2 (39.7, 56.6)	53.8 (47.5, 60.2)	44.8 (36.7, 53.0)	0.226
Highly Sensitive	60.4 (-31.6, 152.3)	45.8 (15.2, 76.4)	50.0 (-24.4, 124.5)	0.817
p-value	0.124	0.459	0.890	
TTRb	**0 Interacting drugs**	**1 Interacting drugs**	**2+ Interacting drugs**	**p-value**
Normal	51.0*†‡ (45.8, 56.1)	39.6* (35.1, 44.0)	38.4† (34.4, 42.4)	<0.001
Sensitive	40.7‡ (33.8, 47.5)	41.0 (36.2, 45.8)	36.0 (29.2, 42.7)	0.473
Highly Sensitive	53.6 (-16.0, 123.2)	31.6 (2.7, 60.5)	41.1 (-8.0, 90.3)	0.478
p-value	0.047	0.657	0.751	

(A) Two-way ANOVA was utilized with each outcome variable to check if the interacting drug/genotype interaction term significantly contributed to the model. * indicates statistical significance at the $p < 0.05$ level. (B) Subgroup analyses for each outcome variable. For each subgroup, means are listed with 95% CI in parenthesis. The p-values in the rows correspond to one-way ANOVA analyses for each genotype bin with interacting drugs as the independent variable. The p-values in the columns correspond to one-way ANOVA analyses for each interacting drug bin with genotype as the independent variable. Post hoc pairwise comparisons were made using Tukey's HSD. *, †, and ‡ indicate a significant pairwise comparison at the $p < 0.05$ level.

Table S5: INR behavior immediately before and after administration of CYP2C9-interacting drugs

Interacting drug Group	**INR Difference**	**Mean**	**95% CI**	**p-value**
Amiodarone (n = 34)	Maximum Change in INR (PostPeak – PreAvg)	1.04	(0.52, 1.57)	<0.001
	Change in Average INR (PostAvg – PreAvg)	-0.01	(-0.35, 0.34)	0.972
Metronidazole (n = 35)	Maximum Change in INR (PostPeak – PreAvg)	0.50	(0.19, 0.81)	0.003
	Change in Average INR (PostAvg – PreAvg)	-0.30	(-0.58, -0.02)	0.036
Sulfamethoxazole (n = 25)	Maximum Change in INR (PostPeak – PreAvg)	0.61	(0.15, 1.08)	0.012
	Change in Average INR (PostAvg – PreAvg)	-0.15	(-0.40, 0.11)	0.247
Other CYP2C9 inhibitors (n = 20)	Maximum Change in INR (PostPeak – PreAvg)	0.32	(-0.03, 0.68)	0.074
	Change in Average INR (PostAvg – PreAvg)	-0.11	(-0.37, 0.15)	0.382

CYP2C9 inducers (n = 7)	Maximum Change in INR (PostTrough – PreAvg)	-0.93	(-1.35, -0.51)	0.002
	Change in Average INR (PostAvg – PreAvg)	-0.53	(-1.09, 0.02)	0.058

Criteria for the study period are described in the Supplementary Methods. For each analyzed study period, the following parameters were collected: peak INR, trough INR, average INR, and # of INR data points in the [minimum date, interacting drug start date] and (interacting drug start date, maximum date] time periods (pre and post, respectively). A single participant could contribute multiple study periods to this analysis.

For each listed difference, the p-value corresponds to a t-test comparing the two sets of INRs included in the difference (i.e. PostAvg and PreAvg). Statistical significance was taken to be at the $p < 0.05$.

Table S6: Variable descriptions

Variable	Description
Age in 2017 or at death	Study participant's calculated age in 2017 or at the time of death if known to be deceased before 2017
Age at first warfarin prescription	Age was extracted from the NMEDW[a] for each warfarin prescription. Ages were sorted for each participant and the youngest age for each participant was recorded as his or her age at first warfarin prescription
Weight	Self-reported at the time of NUgene enrollment
BMI	Calculated from participant's self-reported weight and height at the time of NUgene enrollment.
Sex	Self-reported at the time of NUgene enrollment
Warfarin Indication	Diagnosis given on, or within 1 day of, initial warfarin prescription. Diagnoses were filtered by ICD9 code. All diagnoses with an ICD9 code between 400 and 499 or 745.5, 289.81, V43.3, V43.65, or V43.64 were retained. Duplicated and irrelevant diagnoses were removed. All remaining diagnoses were categorized into one of the four categories of warfarin indication (thrombosis, atrial fibrillation, stroke, or orthopedic). Of note, atrial fibrillation includes both atrial fibrillation and atrial flutter. Orthopedic includes both hip and knee joint replacement. Stroke also includes transient cerebral ischemia. Some participants had multiple warfarin indications, in which case they were counted in multiple categories, as appropriate. Remaining participants were classified as other or unknown. Other/unknown includes those with a warfarin indication that does not fall into one of the above 4 categories

	(e.g. antiphospholipid syndrome or heart valve replacement), as well as those for which either no diagnosis was recorded within 1 day of the warfarin prescription start date or all diagnoses recorded within this time appeared irrelevant to warfarin initiation.
INR Value	Filtered to remove duplicate recordings of the same INR value by excluding all values that were redundant in participant number, INR filed date, and INR value.
INR Filed Date	Date and time[b] of INR measurement
Days from start of first warfarin prescription	Calculated from INR filed date and initial warfarin prescription start date *(INR filed date[b]) – (first warfarin prescription start date[b])*
Days from end of last warfarin prescription	Calculated from INR filed date and final warfarin prescription start date *(INR filed date[b]) – (last warfarin prescription end date[b])*
Warfarin/interacting drug prescription start date	Date and time[b] when warfarin or interacting drug prescription started
Warfarin/ interacting drug prescription end date	Date and time[b] of when warfarin or interacting drug prescription ended

[a]Additional information about the NMEDW is available at http://nucats.northwestern.edu/resources/data-science-and-informatics/nmedw/index.html

[b]All date and time-based measures in a given participant's extracted EHR dataset are shifted by the same random time interval so that the each participant's clinical event timeline is preserved, while de-identifying each participant and eliminating Protected Health Information.

Table S7: Applied Biosystems Taqman assays

CYP2C9 *2 (rs1799853)
Chr.10: 94942290 on Build GRCh38
C/T, Transition Substitution
GATGGGGAAGAGGAGCATTGAGGAC**[C/T]**GTGTTCAAGAGGAAGCCCGCTGCCT

CYP2C9 *3 (rs1057910)
Chr.10: 94981296 on Build GRCh38
C/A, Transversion Substitution
TGTGGTGCACGAGGTCCAGAGATAC**[C/A]**TTGACCTTCTCCCCACCAGCCTGCC

CYP2C9 *4 (rs56165452)
Chr.10: 94981297 on Build GRCh38
C/T, Transition Substitution
GTGGTGCACGAGGTCCAGAGATACA**[C/T]**TGACCTTCTCCCCACCAGCCTGCCC

VKORC1 c. -1639 G>A (rs9923231)
Chr.16: 31096368 on Build GRCh38
C/T, Transition Substitution
GATTATAGGCGTGAGCCACCGCACC**[C/T]**GGCCAATGGTTGTTTTTCAGGTCTT

The context sequence **[VIC/FAM]** for each Taqman assay utilized is presented, labeled by gene and standard SNP nomenclature (bold), SNP ID (parentheses), chromosomal location (italics), and description of the nucleotide change (italics).

Table S8: CYP2C9 inhibitors and inducers

CYP2C9 inhibitors	CYP2C9 inducers
Amiodarone (193)	Aprepitant (0)
Capecitabine (2)	Bosentan (5)
Cotrimoxazole (0)	Carbamazepine (6)
Efavirenz (1)	Enzalutamide (0)
Etravirine (0)	Nevirapine (0)
Fenofibrate (39)	Phenobarbital (0)
Fluconazole (56)	Rifampin (12)
Fluvastatin (7)	Secobarbital (0)
Fluvoxamine (0)	St. John's Wort (0)
Isoniazid (3)	
Lovastatin (12)	
Metronidazole (109)	
Miconazole (14)	
Oxandrolone (0)	
Paroxetine (31)	
Phenylbutazone (0)	
Probenecid (3)	
Sertraline (84)	
Sulfamethoxazole (109)	
Sulfaphenazole (0)	
Sulfinpyrazone (0)	
Teniposide (0)	
Tigecycline (1)	
Voriconazole (6)	
Zafirlukast (2)	

This list was obtained by combining (1) CYP2C9 inhibitors and inducers on FDA label for warfarin [8] and (2) CYP2C9 inhibitors and inducers from the Flockhart Table of Drug Interactions [9]. The number in parenthesis is the number of times each drug occurs in the combined medical record of the 401 participants who meet the inclusion criteria for this study (see **Table 1**). Drugs that did not occur in this cohort were excluded from the analysis.

Table S9: Methodology for selecting CYP2C9 inhibitors and inducers

	References for Mechanistic Evidence (ME)	**References for Clinical Evidence (CE)**	**Criterion not met**
Criteria	Consistent in vitro or in vivo evidence of drug inhibiting or inducing CYP2C9	Clinical evidence that drug can produce change in PT/INR in setting of warfarin use (≥3 participants total)	
Amiodarone	[10-12]	[13, 14]	
Capecitabine	[15]	[16]	
Efavirenz	[17-19]	[20]	CE
Fenofibrate	[21]	[21, 22]	
Fluconazole	[23, 24]	[24]	
Fluvastatin	[25, 26]	[27-29]	
Isoniazid	[30, 31]	[32]	ME, CE
Lovastatin	[33]	[34]	ME, CE
Metronidazole	[35, 36]	[37]	
Miconazole[a]	[38, 39]	[40, 41]	
Paroxetine	[42, 43]	[44]	ME
Probenecid	[45, 46]	[47]	ME, CE
Sertraline	[42]	[48-50]	CE
Sulfamethoxazole	[51, 52]	[53, 54]	
Tigecycline	[55, 56]	[55]	ME, CE
Voriconazole	[39, 57]	[58]	
Zafirlukast	[59]	[60]	
Bosentan	[61]	[62]	
Carbamazepine	[63]	[64]	
Rifampin	[65, 66]	[67]	

[a]There is evidence of a CYP2C9-mediated miconazole-warfarin interaction for both the oral gel and topical cream formulations of miconazole.

For a given drug, the search terms “drug 2c9”, “drug cyp2c9”, and “drug warfarin” were used in Pubmed and Google Scholar to find references. Representative examples from the literature are included in the table above. The reasons for omitting drugs are indicated in the “Criterion not met” column. Excluded drugs contain references because examples from the literature regarding their interaction with CYP2C9 were found, but the evidence in those examples were determined to not meet the criteria outlined in the table.

Table S10: INR variability and time in therapeutic window calculations

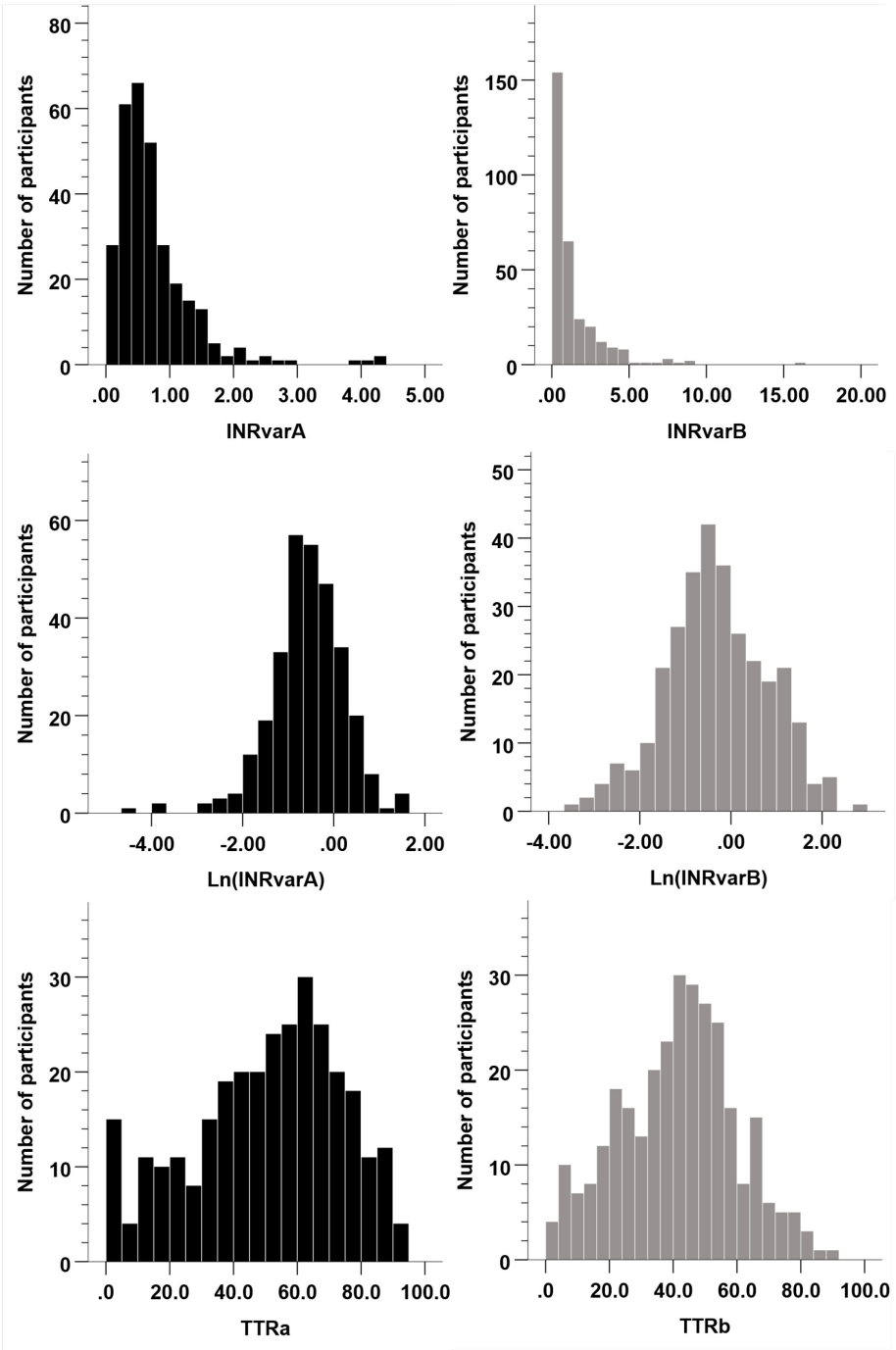
Outcome Variable	Calculation Method
INRvarA *Statistical variance method [1, 68]*	$\sigma^2 = \frac{\sum (\overline{X} - X)^2}{(n-1)}$ *Measure of the distribution of values from their mean*
INRvarB *Fihn variance growth rate method [2, 3, 69, 70]*	$\sigma^2 : \frac{1}{(n-1)} \sum \frac{(INR_{i+1} - INR_i)^2}{T_i}$ *Measure of time-weighted INR variance*
TTRa *Rosendaal Method [4, 71]*	Days in Therapeutic Range (2-3) / Total Days *Incorporates the frequency of INR measurements and assumes changes in INR are linear over time*
TTRb *Traditional Method [5]*	# of INR Measurements in Therapeutic Range (2-3) / Total # of INR Measurements

All INRs obtained in a given day were averaged when calculating these variables. All calculations were done in Python 2.7.15 on the Spyder IDE. T_i in the denominator of INRvarB (Fihn method) is entered as weeks.

Table S11: Characteristics of three participants omitted from Ln(INRvarA) analysis

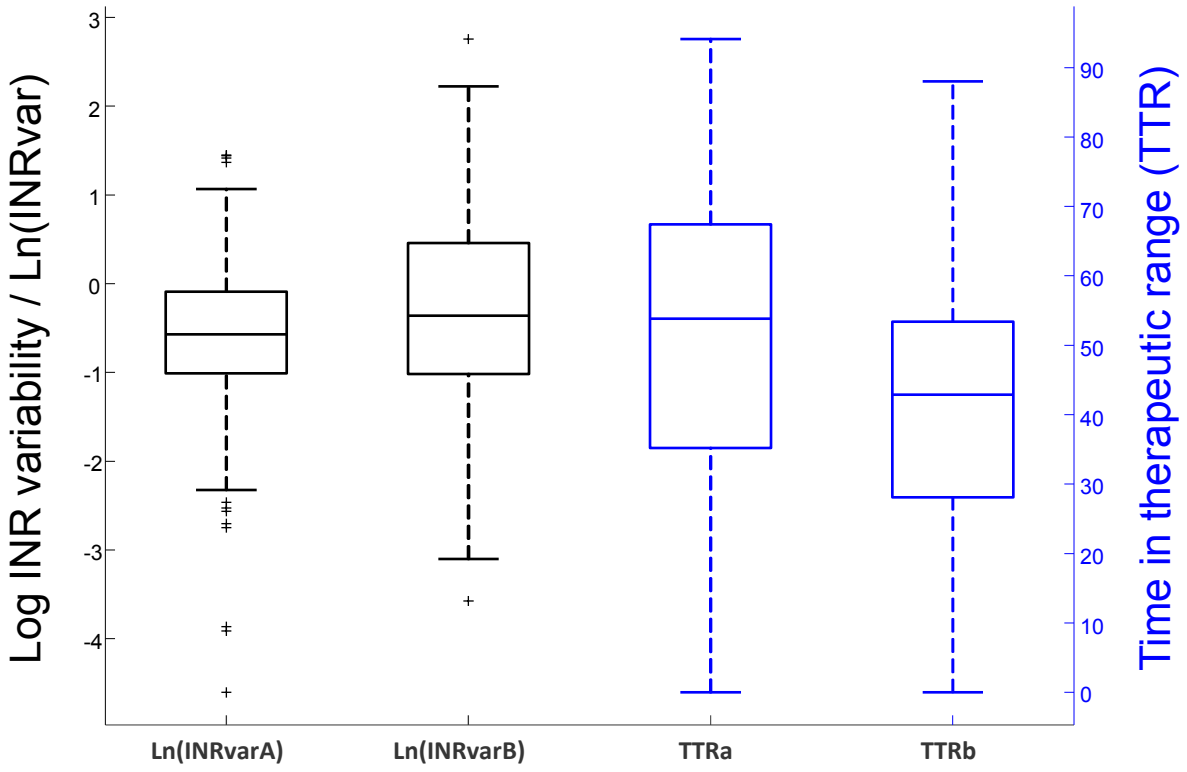
PtNum	*CYP2C9*	*VKORC1*	Interacting drugs	Ln(INRvarA)	Ln(INRvarB)	TTRa	TTRb	INR
1	*1*2	A/G	fenofibrate;fluconazole	-4.61	-2.92	0.0	0.0	18
2	*1*1	A/A		-3.91	-3.02	0.0	0.0	16
3	*1*1	A/G	fluconazole	-3.86	-2.06	0.0	0.0	15

Figure S1: Histograms of INRvarA, INRvarB, Ln(INRvarA), Ln(INRvarB), TTRa, TTRb



All histograms of the n = 302 participants remaining after applying the inclusion and exclusion criteria (**Figure 1**). INRvarA and INRvarB deviated too far away from normality to do ANOVA analyses (top). Hence, a natural logarithm transformation was applied to both variables, yielding Ln(INRvarA) and Ln(INRvarB) (middle), which are much better approximations of normal distributions.

Figure S2: Box Plots of Ln(INRvarA), Ln(INRvarB), TTRa, TTRb



The y-axis for Ln(INRvarA) and Ln(INRvarB) is found on the left side; the y-axis for TTRa and TTRb is found on the right side. The red checkmarks represent outliers. Based on these boxplots, we omitted the three most negative Ln(INRvarA) data points from the Ln(INRvarA) analysis. These three points (-4.61, -3.91, -3.86) are far outliers for this outcome measure (Ln(INRvarA) > Q_3 + 3*IQR). See **Table S11** for omitted participants.

SUPPLEMENTARY REFERENCES

1. Lind, M., et al., *Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation.* Thrombosis Research, 2012. **129**(1): p. 32-35.
2. Fihn, S.D., et al., *The risk for and severity of bleeding complications in elderly patients treated with warfarin.* Annals of internal medicine, 1996. **124**(11): p. 970-979.
3. Van Leeuwen, Y., F. Rosendaal, and S. Cannegieter, *Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants.* Journal of Thrombosis and Haemostasis, 2008. **6**(3): p. 451-456.
4. Rosendaal, F.R., et al., *A method to determine the optimal intensity of oral anticoagulant therapy.* Thrombosis and Haemostasis, 1993. **69**(3): p. 236-9.
5. Schmitt, L., J. Speckman, and J. Ansell, *Quality assessment of anticoagulation dose management: comparative evaluation of measures of time-in-therapeutic range.* Journal of Thrombosis and Thrombolysis, 2003. **15**(3): p. 213-216.
6. Limdi, N.A., et al., *Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across three racial groups.* 2010: p. blood-2009-12-255992.
7. Razouki, Z., et al., *Improving quality measurement for anticoagulation: adding international normalized ratio variability to percent time in therapeutic range.* 2014. **7**(5): p. 664-669.
8. *Warfarin sodium (warfarin tablet) [package insert]. Generic. Retrieved from https://dailymed.nlm.nih.gov/dailymed/index.cfm.* 2018.
9. Flockhart, D.I.U.S.o.M., *Drug interactions: cytochrome P450 drug interaction table.* 2007. **2010**.
10. Heimark, L.D., et al., *The mechanism of the interaction between amiodarone and warfarin in humans.* Clinical Pharmacology and Therapeutics, 1992. **51**(4): p. 398-407.
11. Naganuma, M., et al., *Role of desethylamiodarone in the anticoagulant effect of concurrent amiodarone and warfarin therapy.* J Cardiovasc Pharmacol Ther, 2001. **6**(4): p. 363-7.
12. McDonald, M., et al., *Warfarin-Amiodarone Drug-Drug Interactions: Determination of [I](u)/K(I),(u) for Amiodarone and its Plasma Metabolites.* Clin Pharmacol Ther, 2012. **91**(4): p. 709-17.
13. Lu, Y., et al., *Characteristics of the amiodarone–warfarin interaction during long-term follow-up.* American Journal of Health-System Pharmacy, 2008. **65**(10): p. 947-952.

14. Sanoski, C.A. and J.L. Bauman, *Clinical Observations With the Amiodarone/Warfarin Interaction: Dosing Relationships With Long-term Therapy.* Chest, 2002. **121**(1): p. 19-23.
15. Camidge, R., et al., *Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer.* Journal of Clinical Oncology, 2005. **23**(21): p. 4719-4725.
16. Shah, H.R., et al., *A Retrospective Study of Coagulation Abnormalities in Patients Receiving Concomitant Capecitabine and Warfarin.* Clinical Colorectal Cancer, 2006. **5**(5): p. 354-358.
17. Wanke, R., et al., *The role of competitive binding to human serum albumin on efavirenz–warfarin interaction: a nuclear magnetic resonance study.* International Journal of Antimicrobial Agents, 2013. **42**(5): p. 443-446.
18. Smith, P.F., R. DiCenzo, and G.D. Morse, *Clinical pharmacokinetics of non-nucleoside reverse transcriptase inhibitors.* Clinical pharmacokinetics, 2001. **40**(12): p. 893-905.
19. Xu, C. and Z. Desta, *In vitro analysis and quantitative prediction of efavirenz inhibition of eight cytochrome P450 (CYP) enzymes: major effects on CYPs 2B6, 2C8, 2C9 and 2C19.* Drug metabolism and pharmacokinetics, 2013. **28**(4): p. 362-371.
20. Bonora, S., et al., *Drug interactions between warfarin and efavirenz or lopinavir-ritonavir in clinical treatment.* Clin Infect Dis, 2008. **46**(1): p. 146-7.
21. Kim, K.Y. and M.A. Mancano, *Fenofibrate potentiates warfarin effects.* Ann Pharmacother, 2003. **37**(2): p. 212-5.
22. Ascah, K.J., G.A. Rock, and P.S. Wells, *Interaction between fenofibrate and warfarin.* Annals of Pharmacotherapy, 1998. **32**(7-8): p. 765-768.
23. Kunze, K.L., et al., *Warfarin-fluconazole. I. Inhibition of the human cytochrome P450-dependent metabolism of warfarin by fluconazole: in vitro studies.* Drug Metabolism and Disposition, 1996. **24**(4): p. 414-421.
24. Black, D.J., et al., *Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies.* Drug metabolism and disposition, 1996. **24**(4): p. 422-428.
25. Scripture, C.D. and J.A. Pieper, *Clinical pharmacokinetics of fluvastatin.* Clinical pharmacokinetics, 2001. **40**(4): p. 263-281.
26. Shaik, A.N., et al., *Mechanism of Drug-Drug Interactions Between Warfarin and Statins.* J Pharm Sci, 2016. **105**(6): p. 1976-1986.
27. Trilli, L.E., et al., *Potential interaction between warfarin and fluvastatin.* Annals of Pharmacotherapy, 1996. **30**(12): p. 1399-1402.

28. Andrus, M.R., *Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature.* Pharmacotherapy, 2004. **24**(2): p. 285-290.
29. Kim, M.-J., et al., *Effects of fluvastatin and cigarette smoking on CYP2C9 activity measured using the probe S-warfarin.* European journal of clinical pharmacology, 2006. **62**(6): p. 431-436.
30. Wen, X., et al., *Isoniazid is a mechanism-based inhibitor of cytochrome P 450 1A2, 2A6, 2C19 and 3A4 isoforms in human liver microsomes.* European journal of clinical pharmacology, 2002. **57**(11): p. 799-804.
31. Desta, Z., N.V. Soukhova, and D.A. Flockhart, *Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: potent inhibition of CYP2C19 and CYP3A.* Antimicrob Agents Chemother, 2001. **45**(2): p. 382-92.
32. Rosenthal, A.R., et al., *Interaction of isoniazid and warfarin.* JAMA, 1977. **238**(20): p. 2177-2177.
33. Neuvonen, P.J., J.T. Backman, and M. Niemi, *Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin.* Clinical pharmacokinetics, 2008. **47**(7): p. 463-474.
34. Ahmad, S., *Lovastatin: warfarin interaction.* Archives of internal medicine, 1990. **150**(11): p. 2407-2407.
35. O'Reilly, R.A., *The stereoselective interaction of warfarin and metronidazole in man.* New England Journal of Medicine, 1976. **295**(7): p. 354-357.
36. Levy, R.H., *Cytochrome P450 isozymes and antiepileptic drug interactions.* Epilepsia, 1995: p. S8-13.
37. Howard-Thompson, A., et al., *Intracerebral hemorrhage secondary to a warfarin-metronidazole interaction.* The American Journal of Geriatric Pharmacotherapy, 2008. **6**(1): p. 33-36.
38. O'Reilly, R.A., et al., *Mechanisms of the stereoselective interaction between miconazole and racemic warfarin in human subjects.* Clinical Pharmacology and Therapeutics, 1992. **51**(6): p. 656-667.
39. Niwa, T., T. Shiraga, and A. Takagi, *Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes.* Biological and Pharmaceutical Bulletin, 2005. **28**(9): p. 1805-1808.
40. Nutescu, E., I. Chuatrisorn, and E. Hellenbart, *Drug and dietary interactions of warfarin and novel oral anticoagulants: an update.* Journal of thrombosis and thrombolysis, 2011. **31**(3): p. 326-343.

41. Devaraj, A., et al., *Interaction between warfarin and topical miconazole cream.* BMJ, 2002. **325**(7355): p. 77.
42. Schmider, J., et al., *Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation.* British journal of clinical pharmacology, 1997. **44**(5): p. 495-498.
43. Anderson, L.L., et al., *Measuring Drug Metabolism Kinetics and Drug–Drug Interactions Using Self-Assembled Monolayers for Matrix-Assisted Laser Desorption-Ionization Mass Spectrometry.* Analytical Chemistry, 2016. **88**(17): p. 8604-8609.
44. Bannister, S., et al., *Evaluation of the potential for interactions of paroxetine with diazepam, cimetidine, warfarin, and digoxin.* Acta Psychiatrica Scandinavica, 1989. **80**(S350): p. 102-106.
45. Sahi, J., et al., *Regulation of cytochrome P450 2C9 expression in primary cultures of human hepatocytes.* Journal of biochemical and molecular toxicology, 2009. **23**(1): p. 43-58.
46. Runkel, R., et al., *Naproxen-probenecid interaction.* Clin Pharmacol Ther, 1978. **24**(6): p. 706-13.
47. Monig, H., et al., *The effects of frusemide and probenecid on the pharmacokinetics of phenprocoumon.* Eur J Clin Pharmacol, 1990. **39**(3): p. 261-5.
48. Apseloff, G., et al., *Effect of sertraline on protein binding of warfarin.* Clinical pharmacokinetics, 1997. **32**(1): p. 37-42.
49. Sayal, K., et al., *Psychotropic interactions with warfarin.* Acta Psychiatrica Scandinavica, 2000. **102**(4): p. 250-255.
50. Rapeport, W.G., et al., *Absence of effect of sertraline on the pharmacokinetics and pharmacodynamics of phenytoin.* J Clin Psychiatry, 1996. **57 Suppl 1**: p. 24-8.
51. O'Reilly, R.A., *Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man.* N Engl J Med, 1980. **302**(1): p. 33-5.
52. Wen, X., et al., *Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively.* Drug Metabolism and Disposition, 2002. **30**(6): p. 631-635.
53. Kaufman, J.M. and H.E. Fauver, *Potentiation of warfarin by trimethoprim-sulfamethoxazole.* Urology, 1980. **16**(6): p. 601-603.
54. Ahmed, A., et al., *Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin.* Journal of thrombosis and thrombolysis, 2008. **26**(1): p. 44-48.

55. Zimmerman, J.J., et al., *Evaluation of a Potential Tigecycline-Warfarin Drug Interaction.* Pharmacotherapy, 2008. **28**(7): p. 895-905.
56. McKeage, K. and G.M. Keating, *Tigecycline.* Drugs, 2008. **68**(18): p. 2633-2644.
57. Jeong, S., P.D. Nguyen, and Z. Desta, *Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A.* Antimicrobial agents and chemotherapy, 2009. **53**(2): p. 541-551.
58. Purkins, L., et al., *Voriconazole potentiates warfarin-induced prothrombin time prolongation.* British journal of clinical pharmacology, 2003. **56**: p. 24-29.
59. Shader, R.I., et al., *Inhibition of human cytochrome P450 isoforms in vitro by zafirlukast.* Biopharmaceutics and drug disposition, 1999. **20**(8): p. 385-388.
60. Calhoun, W.J., *Summary of clinical trials with zafirlukast.* American journal of respiratory and critical care medicine, 1998. **157**(6): p. S238-S246.
61. Dingemanse, J. and P.L. van Giersbergen, *Clinical pharmacology of bosentan, a dual endothelin receptor antagonist.* Clinical pharmacokinetics, 2004. **43**(15): p. 1089-1115.
62. Weber, C., et al., *Effect of the endothelin-receptor antagonist bosentan on the pharmacokinetics and pharmacodynamics of warfarin.* The Journal of Clinical Pharmacology, 1999. **39**(8): p. 847-854.
63. Herman, D., et al., *The influence of co-treatment with carbamazepine, amiodarone and statins on warfarin metabolism and maintenance dose.* Eur J Clin Pharmacol, 2006. **62**(4): p. 291-6.
64. Mannheimer, B., et al., *The effect of carbamazepine on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population.* J Thromb Haemost, 2016. **14**(4): p. 765-71.
65. Heimark, L.D., et al., *The mechanism of the warfarin-rifampin drug interaction in humans.* Clinical Pharmacology and Therapeutics, 1987. **42**(4): p. 388-394.
66. Chen, Y., et al., *Induction of human CYP2C9 by rifampicin, hyperforin, and phenobarbital is mediated by the pregnane X receptor.* Journal of Pharmacology and Experimental Therapeutics, 2004. **308**(2): p. 495-501.
67. Krajewski, K.C., *Inability to achieve a therapeutic INR value while on concurrent warfarin and rifampin.* The Journal of Clinical Pharmacology, 2010. **50**(6): p. 710-713.
68. Vanerio, G., *International Normalized Ratio Variability: A Measure of Anticoagulation Quality or a Powerful Mortality Predictor.* Journal of Stroke and Cerebrovascular Diseases, 2015. **24**(10): p. 2223-2228.

69. Ibrahim, S., et al., *The clinical evaluation of International Normalized Ratio variability and control in conventional oral anticoagulant administration by use of the variance growth rate.* Journal of Thrombosis and Haemostasis 2013. **11**(8): p. 1540-1546.

70. Iwuchukwu, O.F., et al., *Genetic determinants of variability in warfarin response after the dose-titration phase.* Pharmacogenetics and genomics, 2016. **26**(11): p. 510.

71. Singer, D.E., et al., *Alternative calculations of individual patient time in therapeutic range while taking warfarin: results from the ROCKET AF trial.* Journal of the American Heart Association, 2015. **4**(3): p. e001349-e001349.