

Table S1. Predictive models for logarithm of INR dose according to patients' clinical and genetics characteristics: sensitivity analysis including different models. Statistical test for model fit (R²) is reported for the whole group of subjects

WHITES-ACENOCOUMAROL									
Variable	Base model ^o +amiodarone (Model 1) N=4152/4154 (100%)			Base model ^o +all available drugs (Model 2) N=675/4154 (16%)			Model 1+smoking (Model 3) N=747/4154 (18%)		
	Parameter estimate	P-value	R ²	Parameter estimate	P-value	R ²	Parameter estimate	P-value	R ²
Intercept	4.036	<.0001	0.32	3.229	<.0001	0.57	3.148	<.0001	0.59
Age *	-0.013	<.0001		-0.010	<.0001		-0.010	<.0001	
BMI*	-0.002	0.15		0.011	0.0001		0.014	<.0001	
Male sex	0.039	0.01		0.004	0.88		0.010	0.66	
Indication for treatment [^]	-0.020	0.25		0.137	<.0001		0.125	<.0001	
<i>CYP2C9</i> *2 1-allele	-0.173	<.0001		-0.153	<.0001		-0.151	<.0001	
<i>CYP2C9</i> *2 2-alleles	-0.303	<.0001		-0.306	0.0005		-0.271	0.0003	
<i>CYP2C9</i> *3 1-allele	-0.395	<.0001		-0.447	<.0001		-0.418	<.0001	
<i>CYP2C9</i> *3 2- alleles	-1.087	<.0001		-1.301	<.0001		-1.241	<.0001	
<i>VKORC1</i> AG	-0.287	<.0001		-0.293	<.0001		-0.314	<.0001	
<i>VKORC1</i> AA	-0.744	<.0001		-0.704	<.0001		-0.738	<.0001	
<i>CYP4F2</i> CT	0.023	0.16		0.054	0.05		0.064	0.01	
<i>CYP4F2</i> TT	0.116	<.0001		0.229	<.0001		0.205	<.0001	
Amiodarone	-0.211	<.0001		-	-		-0.318	<.0001	
All CYP-inhibitors	-	-		0.104	0.0003		-	-	
All CYP-inducers	-	-		-0.102	0.01		-	-	
Smoking	-	-	-	-	0.051	0.24			
WHITES-WARFARIN									
Variable	N=3841/4548 (84%)			N=2308/4548 (51%)			N=3366/4548 (74%)		
	Parameter estimate	P-value	R ²	Parameter estimate	P-value	R ²	Parameter estimate	P-value	R ²
Intercept	4.016	<.0001	0.52	4.119	<.0001	0.54	3.999	<.0001	0.51
Age *	-0.010	<.0001		-0.011	<.0001		-0.010	<.0001	
BMI*	0.010	<.0001		0.010	<.0001		0.011	<.0001	
Male sex	0.132	<.0001		0.152	<.0001		0.125	<.0001	
Indication for	-0.043	0.0003		-0.040	0.01		-0.036	0.01	

treatment^								
<i>CYP2C9</i> *2 1-allele	-0.222	<.0001		-0.226	<.0001		-0.225	<.0001
<i>CYP2C9</i> *2 2-alleles	-0.524	<.0001		-0.531	<.0001		-0.523	<.0001
<i>CYP2C9</i> *3 1-allele	-0.388	<.0001		-0.393	<.0001		-0.387	<.0001
<i>CYP2C9</i> *3 2- alleles	-1.175	<.0001		-1.503	<.0001		-1.119	<.0001
<i>VKORC1</i> AG	-0.266	<.0001		-0.268	<.0001		-0.271	<.0001
<i>VKORC1</i> AA	-0.665	<.0001		-0.654	<.0001		-0.669	<.0001
<i>CYP4F2</i> CT	0.062	<.0001		0.070	<.0001		0.057	<.0001
<i>CYP4F2</i> TT	0.172	<.0001		0.190	<.0001		0.160	<.0001
Amiodarone	-0.238	<.0001		-	-		-0.244	<.0001
All CYP-inhibitors	-	-		-0.009	0.74		-	-
All CYP-inducers	-	-		-0.066	<.0001		-	-
Smoking	-	-		-	-		0.020	0.34

ASIANS-WARFARIN

	N=434/438 (99%)			N=113/438 (26%)			N=291/438 (66%)		
Intercept	3.421	<.0001		3.306	<.0001		3.421	<.0001	
Age *	-0.004	0.003		-0.011	0.01		-0.005	0.01	
BMI*	0.015	0.0002		0.029	0.003		0.016	0.0007	
Male sex	0.059	0.17		-0.112	0.22		0.051	0.37	
Indication for treatment^	-0.011	0.80		0.082	0.37		-0.035	0.56	
<i>CYP2C9</i> *2 1-allele	-0.073	0.45	0.45	0.844	0.11	0.35	-0.072	0.50	
<i>CYP2C9</i> *2 2-alleles	-	-		-	-		-	-	-
<i>CYP2C9</i> *3 1-allele	-0.210	0.01		-0.117	0.53		-0.150	0.13	
<i>CYP2C9</i> *3 2- alleles	-1.279	<.0001		-	-		-1.203	0.0005	
<i>VKORC1</i> AG	-0.378	<.0001		-0.508	0.01		-0.402	<.0001	
<i>VKORC1</i> AA	-0.787	<.0001		-0.757	<.0001		-0.880	<.0001	
<i>CYP4F2</i> CT	0.110	0.02		0.107	0.29		0.133	0.03	
<i>CYP4F2</i> TT	0.152	0.04		-0.035	0.86		0.119	0.24	
Amiodarone	-0.254	0.01		-	-		-0.185	0.09	
All CYP-inhibitors	-	-		0.285	0.56		-	-	
All CYP-inducers	-	-	0.038	0.70	-	-			
Smoking	-	-	-	-	0.024	0.87			

BLACKS-WARFARIN

	N=789/815 (97%)			N=239/815 (29%)			N=553/815 (67%)		
Intercept	3.815	<.0001	0.32	3.867	<.0001	0.27	3.786	<.0001	0.35

Age *	-0.008	<0.0001	-0.007	<0.0001	-0.008	<0.0001
BMI*	0.011	<0.0001	0.011	<0.0001	0.013	<0.0001
Male sex	0.139	<0.0001	0.103	0.06	0.179	<0.0001
Indication for treatment^	-0.040	0.18	-0.025	0.70	-0.051	0.14
<i>CYP2C9</i> *2 1-allele	-0.082	0.14	-0.178	0.17	-0.072	0.26
<i>CYP2C9</i> *2 2-alleles	-	-	-	-	-	-
<i>CYP2C9</i> *3 1-allele	-0.341	<0.0001	-0.190	0.32	-0.341	0.0001
<i>CYP2C9</i> *3 2- alleles	-	-	-	-	-	-
<i>CYP2C9</i> *5 1-allele	-0.375	0.002	-0.420	0.06	-0.386	0.01
<i>CYP2C9</i> *5 2-alleles	-	-	-	-	-	-
<i>VKORC1</i> AG	-0.292	<0.0001	-0.256	0.0001	-0.295	<0.0001
<i>VKORC1</i> AA	-0.284	0.03	-0.434	0.27	-0.241	0.09
<i>CYP4F2</i> CT	0.006	0.87	-0.064	0.41	0.014	0.72
<i>CYP4F2</i> TT	0.279	0.08	-0.208	0.58	0.384	0.04
Amiodarone	-0.335	<0.0001	-	-	-0.300	<0.0001
All CYP-inhibitors	-	-	0.006	0.96	-	-
All CYP-inducers	-	-	-0.086	0.12	-	-
Smoking	-	-	-	-	-0.041	0.36

Note: Due to significant heterogeneity, separate models are reported for different ethnic groups and drugs.

◦ Base model is that reported in table 4.

* Estimate for 1 unit increase

^ Estimate for the following indication for treatment: fibrillation/flutter, cardiomyopathy/LV dilation, post orthopedic

Table S2. Effect of concomitant drugs on warfarin dose and genetic polymorphisms of *CYP4F2* and *CYP2C9* genes: gene-drug interaction and subgroup analyses

Drug	Drug effect on warfarin dose (p-value)	<i>CYP4F2</i> interaction (p-value)	<i>CYP2C9*2</i> interaction (p-value)	<i>CYP2C9*3</i> interaction (p-value)	<i>CYP4F2</i> effect	<i>CYP4F2</i> effect	<i>CYP2C9*2</i> effect	<i>CYP2C9*2</i> effect	<i>CYP2C9*3</i> effect	<i>CYP2C9*3</i> effect
					(p-value) when no use of concomitant drug	(p-value) when use of concomitant drug	(p-value) when no use of concomitant drug	(p-value) when use of concomitant drug	(p-value) when no use of concomitant drug	(p-value) when use of concomitant drug
CAUCASIANS - ACENOCOUMAROL										
Amiodarone (N=4152)	-0.15 (<0.0001)	-0.01 (0.79)	-0.06 (0.26)	0.005 (0.95)	0.11 (<0.0001)	0.12 (0.02)	-0.12 (<0.0001)	-0.19 (<0.0001)	-0.37 (<0.0001)	-0.35 (0.0004)
Azoles (N=3081)	-0.06 (0.45)	-0.13 (0.42)	-0.28 (0.13)	-0.16 (0.68)	0.13 (<0.0001)	-0.06 (0.82)	-0.11 (<0.0001)	-0.24 (0.39)	-0.33 (<0.0001)	-0.86 (0.27)
<i>CYP2C9</i> -inhibitors (N=3081)	-0.05 (0.03)	-0.02 (0.57)	-0.03 (0.54)	0.07 (0.20)	0.13 (<0.0001)	0.11 (0.005)	-0.11 (<0.0001)	-0.14 (0.001)	-0.34 (<0.0001)	-0.25 (<0.0001)
Statin (N=3615)	-0.01 (0.50)	0.002 (0.96)	0.06 (0.16)	0.03 (0.54)	0.11 (<0.0001)	0.11 (0.006)	-0.20 (<0.0001)	-0.07 (0.09)	-0.20 (<0.0001)	-0.29 (<0.0001)
Aspirin (N=2493)	-0.01 (0.64)	0.02 (0.73)	0.05 (0.30)	-0.02 (0.77)	0.13 (<0.0001)	0.17 (0.0003)	-0.13 (<0.0001)	-0.07 (0.10)	-0.34 (<0.0001)	-0.37 (<0.0001)
All <i>CYP</i> -inhibitors (N=4152)	-0.05 (0.0002)	0.01 (0.77)	0.01 (0.84)	0.03 (0.45)	0.11 (<0.0001)	0.11 (<0.0001)	-0.12 (<0.0001)	-0.12 (<0.0001)	-0.37 (<0.0001)	-0.34 (<0.0001)
All <i>CYP</i> -inducers (N=676)	0.11 (0.0003)	-0.09 (0.16)	-0.01 (0.89)	0.14 (0.09)	0.11 (0.001)	0.03 (0.63)	-0.17 (<0.0001)	-0.18 (0.002)	-0.56 (<0.0001)	-0.43 (<0.0001)
CAUCASIANS - WARFARIN										
Amiodarone (N=3841)	-0.23 (<0.0001)	0.01 (0.83)	-0.07 (0.16)	-0.04 (0.55)	0.09 (<0.0001)	0.11 (0.02)	-0.23 (<0.0001)	-0.3 (<0.0001)	-0.41 (<0.0001)	-0.45 (<0.0001)
Azoles (N=1623)	-0.04 (0.49)	-0.02 (0.86)	0.17 (0.16)	-0.18 (0.36)	0.1 (<0.0001)	0.07 (0.65)	-0.24 (<0.0001)	-0.03 (0.86)	-0.44 (<0.0001)	-0.57 (0.05)

CYP2C9-inhibitors (N=2693)	-0.09 (<0.0001)	0.01 (0.67)	-0.06 (0.08)	0.00 (0.99)	0.09 (<0.0001)	0.10 (<0.0001)	-0.22 (<0.0001)	-0.27 (<0.0001)	-0.43 (<0.0001)	-0.43 (<0.0001)
Other CYP-inhibitors (N=603)	-0.08 (0.07)	0.10 (0.09)	-0.03 (0.63)	-0.11 (0.27)	0.02 (0.53)	0.13 (0.003)	-0.26 (<0.0001)	-0.29 (<0.0001)	-0.39 (<0.0001)	-0.49 (<0.0001)
CYP2C9-inducers (N=2308)	-0.01 (0.66)	0.07 (0.28)	-0.15 (0.04)	-0.02 (0.86)	0.09 (<0.0001)	0.15 (0.02)	-0.23 (<0.0001)	-0.37 (<0.0001)	-0.43 (<0.0001)	-0.44 (<0.0001)
Other CYP-inducers (N=1476)	0.14 (0.15)	-0.14 (0.57)	-0.42 (0.12)	0.20 (0.36)	0.10 (<0.0001)	0.55 (0.32)	-0.25 (<0.0001)	-1.47 (0.03)	-0.44 (<0.0001)	-0.04 (0.93)
Statin (N=3543)	-0.06 (<0.0001)	0.01 (0.80)	-0.05 (0.09)	-0.02 (0.56)	0.08 (<0.0001)	0.09 (<0.0001)	-0.22 (<0.0001)	-0.27 (<0.0001)	-0.41 (<0.0001)	-0.44 (<0.0001)
Aspirin (N=1981)	-0.04 (0.14)	0.00 (0.95)	-0.08 (0.14)	-0.13 (0.09)	0.08 (<0.0001)	0.10 (0.01)	-0.23 (<0.0001)	-0.30 (<0.0001)	-0.40 (<0.0001)	-0.51 (<0.0001)
Carbamazepina (N=1888)	0.10 (0.27)	0.17 (0.36)	-0.17 (0.46)	NE	0.10 (<0.0001)	0.41 (0.49)	-0.24 (<0.0001)	-0.09 (0.93)	-0.44 (<0.0001)	NE
PPI (N=603)	-0.05 (0.33)	0.12 (0.21)	-0.08 (0.50)	-0.18 (0.28)	0.05 (0.08)	0.17 (0.08)	-0.27 (<0.0001)	-0.29 (0.02)	-0.41 (<0.0001)	-0.57 (0.0008)
Rifampin (N=1623)	-0.02 (0.89)	-0.37 (0.15)	-0.72 (<0.0001)	-0.42 (0.34)	0.10 (<0.0001)	NE	-0.23 (<0.0001)	-1.66 (0.01)	-0.44 (<0.0001)	-0.35 (0.31)
All CYP-inhibitors (N=3876)	-0.09 (<0.0001)	0.01 (0.59)	-0.06 (0.03)	-0.03 (0.48)	0.08 (<0.0001)	0.09 (<0.0001)	-0.20 (<0.0001)	-0.26 (<0.0001)	-0.40 (<0.0001)	-0.43 (<0.0001)
All CYP-inducers (N=2308)	0.01 (0.78)	0.02 (0.78)	-0.19 (0.01)	0.02 (0.82)	0.09 (<0.0001)	0.11 (0.08)	-0.22 (<0.0001)	-0.40 (<0.0001)	-0.44 (<0.0001)	-0.41 (<0.0001)
ASIANS - WARFARIN										
Amiodarone (N=434)	-0.14 (0.19)	0.37 (0.10)	0.57 (0.13)	-0.61 (0.20)	0.04 (0.39)	0.37 (0.16)	-0.12 (0.26)	0.44 (0.25)	-0.23 (0.005)	-0.82 (0.09)
CYP2C9-inhibitors (N=289)	-0.07 (0.30)	-0.05 (0.69)	0.16 (0.50)	-0.05 (0.80)	0.05 (0.46)	-0.06 (0.56)	-0.11 (0.36)	-0.05 (0.82)	-0.16 (0.18)	-0.28 (0.12)
CYP2C9-inducers (N=113)	0.21 (0.62)	NE	NE	NE	0.01 (0.85)	NE	0.57 (0.17)	NE	-0.01 (0.94)	NE
Statin (N=291)	-0.02 (0.79)	-0.09 (0.45)	0.15 (0.56)	0.03 (0.91)	0.07 (0.30)	-0.10 (0.40)	-0.10 (0.40)	-0.03 (0.91)	-0.19 (0.09)	-0.26 (0.19)
Aspirin (N=289)	-0.08	0.03 (0.83)	-0.44 (0.23)	0.26 (0.25)	0.03 (0.62)	0.06 (0.67)	-0.09 (0.42)	-0.49 (0.19)	-0.23 (0.04)	-0.05 (0.81)

	(0.29)									
All CYP-inhibitors (N=434)	0.00 (0.99)	-0.08 (0.37)	0.03 (0.88)	0 (0.99)	0.07 (0.16)	-0.01 (0.92)	-0.11 (0.39)	-0.09 (0.59)	-0.24 (0.01)	-0.28 (0.06)
All CYP-inducers (N=113)	0.21 (0.62)	NE	NE	NE	0.01 (0.85)	NE	0.57 (0.17)	NE	-0.01 (0.94)	NE
BLACKS- WARFARIN										
Amiodarone (N=797)	-0.32 (<0.0001)	0.18 (0.32)	-0.35 (0.12)	0.38 (0.10)	0.02 (0.58)	0.06 (0.74)	-0.05 (0.37)	-0.65 (0.01)	-0.38 (<0.0001)	-0.20 (0.37)
CYP2C9-inhibitors (N=323)	-0.12 (0.01)	-0.20 (0.09)	0.00 (0.98)	-0.39 (0.14)	0.10 (0.13)	-0.10 (0.35)	-0.18 (0.08)	-0.16 (0.31)	-0.09 (0.51)	-0.41 (0.09)
CYP2C9-inducers (N=247)	-0.05 (0.68)	-0.74 (0.01)	0.30 (0.52)	NE	-0.02 (0.84)	-0.56 (0.04)	-0.16 (0.19)	-0.43 (0.24)	-0.20 (0.28)	NE
Statin (N=797)	-0.06 (0.04)	0.02 (0.83)	0.28 (0.02)	-0.38 (0.03)	0.03 (0.49)	0.05 (0.34)	-0.17 (0.02)	0.15 (0.14)	-0.23 (0.02)	-0.63 (<0.0001)
Aspirin (N=323)	-0.09 (0.08)	-0.04 (0.78)	0.58 (0.01)	-0.13 (0.63)	0.06 (0.40)	-0.01 (0.96)	-0.32 (0.001)	0.16 (0.47)	-0.20 (0.18)	-0.17 (0.51)
All CYP-inhibitors (N=797)	-0.12 (<0.0001)	0.09 (0.18)	0.18 (0.10)	-0.24 (0.15)	-0.01 (0.76)	0.08 (0.11)	-0.15 (0.03)	0.08 (0.40)	-0.26 (0.01)	-0.48 (0.0002)
All CYP-inducers (N=247)	-0.05 (0.68)	-0.74 (0.01)	0.30 (0.52)	NE	-0.02 (0.84)	-0.56 (0.04)	-0.16 (0.19)	-0.43 (0.24)	-0.20 (0.28)	NE
OTHERS- WARFARIN										
Amiodarone (N=162)	-0.27 (0.002)	-0.13 (0.49)	-0.04 (0.86)	NE	-0.02 (0.73)	-0.02 (0.93)	-0.17 (0.04)	-0.31 (0.20)	-0.29 (0.01)	NE
CYP2C9-inhibitors (N=162)	-0.17 (0.04)	-0.08 (0.58)	0.23 (0.19)	0.73 (0.08)	-0.02 (0.73)	-0.12 (0.41)	-0.26 (0.01)	0.03 (0.85)	-0.36 (0.001)	0.62 (0.20)
Statin (N=162)	-0.05 (0.70)	-0.23 (0.26)	0.35 (0.10)	0.64 (0.14)	0.00 (0.96)	-0.18 (0.53)	-0.25 (0.003)	0.11 (0.66)	-0.31 (0.004)	0.41 (0.54)
Aspirin (N=148)	0.10 (0.45)	0.14 (0.66)	0.09 (0.79)	NE	-0.01 (0.91)	NE	-0.21 (0.02)	NE	-0.26 (0.01)	NE

All CYP-inhibitors (N=162)	-0.11 (0.18)	-0.06 (0.70)	0.24 (0.15)	0.66 (0.12)	-0.03 (0.72)	-0.10 (0.42)	-0.28 (0.004)	0.05 (0.74)	-0.36 (0.001)	0.6 (0.21)
All CYP-inducers (N=44)	-0.6 (0.26)	NE	NE	NE	-0.03 (0.87)	NE	0.04 (0.80)	NE	-0.13 (0.69)	NE

NE=Not Estimable. Note: Due to significant heterogeneity, separate models are reported for different ethnic groups and drugs. Besides concomitant drug(s) and gene polymorphisms, models are adjusted by study, age, sex, BMI and indication for treatment. For each gene, the reference category is the gene polymorphism according to the dominant model (heterozygous+homozygous vs. wild type patients).

Table S3. Statistical test for model fit (R^2) of two previously published models for warfarin dose prediction (Gage 2008, Klein 2009) in comparison with the model presented here in Table 3 (“new model”): application to a subset of subjects from the validation cohort for whom both scores could be calculable on the basis of the available information.

Ethnicity	New model vs Gage 2008 (Gage et al. 2017)			New model vs Klein 2009 (Consortium et al. 2009)		
	R^2 new model	R^2 Gage	N subjects	R^2 new model	R^2 Klein	N subjects
Whites	0.41	0.43	938	0.47	0.43	775
Asians	0.44	0.42	86	not calculated*	0.11	34
Blacks	0.19	0.22	187	0.20	0.23	80

*not calculated because only 34 subjects can be included and this makes the estimate unreliable.

Consortium, International Warfarin Pharmacogenetics, T E Klein, R B Altman, N Eriksson, B F Gage, S E Kimmel, M-T M Lee, et al. 2009. “Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data.” *New England Journal of Medicine* 360 (8): 753–64. doi:10.1056/NEJMoa0809329.

Gage, Brian F., Anne R. Bass, Hannah Lin, Scott C. Woller, Scott M. Stevens, Noor Al-Hammadi, Juan Li, et al. 2017. “Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty.” *JAMA* 318 (12): 1115. doi:10.1001/jama.2017.11469.