

Table 1. Descriptive characteristics of studies included in the analysis

First author (ref)	PY	Country	Ethnicity	Subjects, n	Males (%)	Age, years (mean±sd)	Drug	INR target	Gene polymorphisms	Available confounders*
Aquilante CL ³⁶	2006	Florida (USA)	Whites (93%) Blacks (7%)	344	300 (87%)	69±11	Warfarin	2.5-3.5	CYP2C9*2, CYP2C9*3, CYP2C9*5, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment
Borgiani P ¹⁸	2009	Italy	Whites	141	75 (53%)	69±12	Warfarin	2.0-4.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, sex, indication for treatment
Borobia AM, ¹⁶ Tong HY ⁴³	2012-2016	Spain	Whites (Spanish)	679	345 (51%)	68±13	Acenocumarol	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Botton MR ²⁸	2011	Brazil	Whites	279	155 (57%)	63±14	Warfarin	1.8-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2 [^]	Age, BMI, sex, smoking, other drugs
Bourgeois S ⁴⁵	2016	UK	Whites	217	119 (55%)	71±11	Warfarin	2.0-4.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Caldwell MD ¹²	2008	Wisconsin (USA)	Whites	429	252 (59%)	69±11	Warfarin	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, indication for treatment, other drugs
Cavallari LH ²⁹	2010	Illinois (USA)	Blacks	208	57 (27%)	56±16	Warfarin	2.0-4.0	CYP2C9*2, CYP2C9*3, CYP2C9*5, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Cen HJ ³⁰	2010	China	Asians	221	103 (47%)	45±12	Warfarin	1.5-3.0	CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, other drugs
Cerezo-Manchado JJ (a) ⁴⁶	2013	Spain	Whites	943	459 (49%)	75±9	Acenocumarol	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, sex, indication for treatment, other drugs
Cerezo-Manchado JJ (b) ⁴⁶	2013	Spain	Whites	3882	1916 (49%)	74±10	Acenocumarol	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2 [^]	Age, sex, indication for treatment, other drugs
Cha PC ³¹	2010	Japan	Asians	440	293 (77%)	68±11	Warfarin	1.5-3.0	CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, indication for treatment, other drugs

Gong IY ³²	2011	UK	Whites (95%) Blacks (3%) Asians (2%)	167	96 (57%)	60±18	Warfarin	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, sex, indication for treatment
Hirai K ⁴⁷	2015	Japan	Asians	217	143 (66%)	68±10	Warfarin	1.5-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, sex, indication for treatment
Isaza C ⁴⁸	2010	Colombia	Hispanic	145	72 (50%)	55±15	Warfarin	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2 [^]	Age, BMI, sex, indication for treatment
Jiménez-Varo E ⁴⁹	2014-2015	Spain	Whites	162	89 (55%)	73±9	Acenocumarol	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2 [^]	Age, BMI, sex, smoking, indication for treatment, other drugs
Kringen MK ³³	2011	Norway	Whites	105	87 (83%)	60±9	Warfarin	1.9-3.6	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, sex, other drugs
Lee KE ⁵⁰	2012	Korea	Asians	188	62 (33%)	59±10	Warfarin	2.0-3.0	CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, other drugs
Lee MT ²⁷	2009	China	Asians	233	130 (56%)	63±13	Warfarin	1.7-3.0	CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, indication for treatment, other drugs
Lubitz SA ³⁴	2010	New York (USA)	Whites (68%) Blacks (20%) Asians (12%)	155	97 (63%)	69±14	Warfarin	2.0-3.0	CYP2C9*2, CYP2C9*3, CYP2C9*5, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Mazzaccara C ⁵¹	2013	Italy	Whites	256	142 (55%)	67±11	Warfarin	1.6-3.9	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, indication for treatment, other drugs
Ozer M ⁵²	2013	Turchia	Whites	107	53 (50%)	54±14	Warfarin	1.5-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment
Pathare A ³⁷	2012	Oman	Asians	188	88 (47%)	51±17	Warfarin	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Pautas E ³⁵	2010	France	Whites	272	65 (24%)	87±6	Warfarin	2.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, sex, other drugs
Pavani A ³⁸	2012	India	Indians	207	108 (52%)	40±13	Warfarin	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex
Perez-Andreu V ¹⁹	2009	Spain	Whites	100	100 (100%)	65±6	Acenocumarol	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age

Perini JA ²⁰	2010	Brazil	Whites (50%) Brown (30%) Blacks (20%)	390	186 (48%)	54±15	Warfarin	2.0-3.5	CYP2C9*2, CYP2C9*3, CYP2C9*5, VKORC1, CYP4F2 [^]	Age, BMI, sex, smoking, indication for treatment, other drugs
Ramirez AH ³⁹	2012	Tennessee (USA)	Whites	1029	586 (57%)	65±15	Warfarin	1.6-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Rathore SS ¹⁷	2012	India	Indians	217	145 (67%)	39±12	Acenocumarol	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2 [^]	Age, BMI, sex, smoking
Sagreiya H ²¹	2010	California (USA)	Whites (75%) Asians (17%) Blacks (8%)	101	58 (57%)	64±15	Warfarin	1.8-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Shain MH ²²	2011	Egypt	Egyptians	188	84 (44%)	48±15	Warfarin	1.5-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment
Shendre A ⁴⁰	2016	Alabama (USA)	Whites (58%) Blacks (41%) Asians (1%)	1169	610 (52%)	61±16	Warfarin	1.8-3.2	CYP2C9*2, CYP2C9*3, CYP2C9*5, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Suriapranata IM ²³	2011	Indonesia	Asians	85	48 (56%)	57±11	Warfarin	1.5-2.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs
Tan SL ⁴¹	2013	China	Asians	317	95 (30%)	45±10	Warfarin	1.8-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex
Tatarunas V ⁴²	2014	Lithuania	Whites	189	118 (62%)	65±11	Warfarin	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, other drugs
van Schie RM (a) ⁴⁴	2013	Netherlands	Whites	568	328 (58%)	70±11	Other (phenprocumon)	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, indication for treatment, other drugs
van Schie RM (b) ⁴⁴	2013	Netherlands	Caucasians	397	217 (55%)	73±9	Acenocumarol	2.0-3.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, indication for treatment, other drugs
Wells PS ²⁴	2010	Canada	Caucasians	246	136 (55%)	61±14	Warfarin	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment,

										other drugs
Zambon CF ²⁵	2011	Italy	Caucasians	371	231 (62%)	73±9	Warfarin	2.5	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment
Zhang JE ²⁶	2009	UK	Caucasians	202	120 (59%)	66±14	Warfarin	2.0-3.0	CYP2C9*2, CYP2C9*3, VKORC1, CYP4F2	Age, BMI, sex, smoking, indication for treatment, other drugs

PY=Publication Year

* Covariates with less than 20% of missing data are here indicated and used in the multivariate analysis

^ CYP2F4 not in HW equilibrium

Table 2. Subgroup analyses of association studies of the *CYP4F2* polymorphism on coumarin dose requirements

Variable	Subgroup (N studies)	Difference* (95%CI)	I ² (Q test p-value)	Meta-regression p-value
Ethnicity	Whites (26)	0.10 (0.08; 0.11)	15% (0.25)	0.002
	Asians (10)	0.08 (0.05; 0.11)	0% (0.85)	
	Blacks (5)	0.05 (-0.04; 0.14)	21% (0.28)	
	Others (5) [^]	0.01 (-0.05; 0.06)	0% (0.72)	
Drug	Acenocumarol (7)	0.11 (0.09; 0.13)	13% (0.33)	0.03
	Warfarin (31)	0.08 (0.06; 0.09)	9% (0.33)	
Sex	Males (39)	0.07 (0.06; 0.09)	16% (0.20)	0.03
	Females (38)	0.10 (0.08; 0.12)	19% (0.16)	
INR target	<2.5 (11)	0.08 (0.05; 0.11)	0% (0.79)	Reference
	2.5 (23)	0.09 (0.07; 0.11)	22% (0.17)	0.42
	>2.5 (18)	0.08 (0.06; 0.10)	0% (0.49)	0.93
Smoking	No (21)	0.09 (0.07; 0.11)	0% (0.68)	0.74
	Yes (12)	0.07 (-0.02; 0.15)	33% (0.12)	
Other drugs considered	No (7)	0.08 (0.03; 0.12)	47% (0.08)	0.72
	Yes (32)	0.09 (0.08; 0.10)	10% (0.31)	
HW equilibrium	No (6)	0.08 (0.04; 0.12)	53% (0.06)	0.92
	Yes (33)	0.09 (0.07; 0.10)	9% (0.33)	
Quality score	<5	0.08 (0.06; 0.10)	29% (0.11)	0.46
	≥5	0.09 (0.08; 0.11)	6% (0.39)	
CYP2C9	CYP2C9 *1*1	0.08 (0.07; 0.10)	18% (0.18)	0.73
	CYP2C9 *1*2/ *1*3/*2*2/*2*3/*3*3	0.09 (0.06; 0.12)	25% (0.10)	
VKORC11	VKORC1 GG	0.08 (0.06; 0.10)	4% (0.40)	0.13
	VKORC 1 AA/AG	0.10 (0.08; 0.11)	10% (0.30)	

* difference in logarithm of stable coumarin dose of subjects with *CYP4F2* polymorphism (CT+TT) compared to subjects with *CYP4F2* wild-type (CC), according to dominant model

[^] includes Indian, Egyptian, Brown, Hispanic

Table 3. Predictive model for logarithm of stable coumarin dose according to patients' clinical and genetics characteristics. Statistical test for model fit (R^2) is reported both for the test and validation cohorts

WHITES								
Variable	Acenocoumarol				Warfarin			
	Parameter estimate (95%CI)	P-value	R ² test (N=2744)	R ² validation (N=1410)	Parameter estimate (95%CI)	P-value	R ² test (N=3016)	R ² validation (N=1532)
Intercept	4.069 (3.883; 4.256)	<0.0001	0.33	0.28	3.981 (3.887; 4.075)	<0.0001	0.51	0.52
Age*	-0.014 (-0.015; -0.012)	<0.0001			-0.009 (-0.010; -0.008)	<0.0001		
BMI*	-0.002 (-0.006; 0.002)	0.28			0.010 (0.008; 0.012)	<0.0001		
Male sex	0.014 (-0.024; 0.052)	0.47			0.123 (0.098; 0.148)	<0.0001		
Indication for treatment [^]	0.000 (-0.042; 0.042)	0.98			-0.043 (-0.069; -0.017)	0.001		
<i>CYP2C9</i> *2 1-allele	-0.190 (-0.232; -0.147)	<0.0001			-0.231 (-0.261; -0.202)	<0.0001		
<i>CYP2C9</i> *2 2-alleles	-0.359 (-0.484; -0.234)	<0.0001			-0.513 (-0.600; -0.426)	<0.0001		
<i>CYP2C9</i> *3 1-allele	-0.394 (-0.446; -0.342)	<0.0001			-0.387 (-0.425; -0.350)	<0.0001		
<i>CYP2C9</i> *3 2-alleles	-1.214 (-1.522; -0.907)	<0.0001			-1.316 (-1.502; -1.131)	<0.0001		
<i>VKORC1</i> AG	-0.291 (-0.332; -0.249)	<0.0001			-0.266 (-0.292; -0.240)	<0.0001		
<i>VKORC1</i> AA	-0.762 (-0.816; -0.708)	<0.0001			-0.666 (-0.704; -0.629)	<0.0001		
<i>CYP4F2</i> CT	0.018 (-0.022; 0.058)	0.39			0.073 (0.047; 0.098)	<0.0001		
<i>CYP4F2</i> TT	0.100 (0.041; 0.159)	0.0009			0.191 (0.147; 0.235)	<0.0001		

ASIANS

Variable	Acenocoumarol				Warfarin			
	Parameter estimate	P-value	R ² test (N=0)	R ² validation (N=0)	Parameter estimate	P-value	R ² test (N=292)	R ² validation (N=146)
Intercept	-	-	-	-	3.484 (3.112; 3.855)	<.0001	0.45	0.42
Age *	-	-			-0.005 (-0.008; -0.001)	0.02		
BMI*	-	-			0.014 (0.004; 0.023)	0.004		
Male sex	-	-			0.058 (-0.050; 0.167)	0.29		
Indication for treatment^	-	-			-0.027 (-0.139; 0.084)	0.63		
CYP2C9*2 1-allele	-	-			-0.114 (-0.351; 0.124)	0.35		
CYP2C9*2 2-alleles	-	-			-	-		
CYP2C9*3 1-allele	-	-			-0.224 (-0.428; -0.020)	0.03		
CYP2C9*3 2-alleles	-	-			-1.065 (-1.717; -0.412)	0.002		
VKORC1 AG	-	-			-0.422 (-0.574; -0.271)	<.0001		
VKORC1 AA	-	-			-0.827 (-0.975; -0.679)	<.0001		
CYP4F2 CT	-	-			0.117 (0.003; 0.231)	0.04		
CYP4F2 TT	-	-			0.124 (-0.075; 0.324)	0.22		

BLACKS								
Variable	Acenocoumarol				Warfarin			
	Parameter estimate	P-value	R ² test (N=0)	R ² validation (N=0)	Parameter estimate	P-value	R ² test (N=534)	R ² validation (N=288)
Intercept	-	-			3.875 (3.692; 4.061)	<0.0001		
Age*	-	-			-0.009 (-0.011; -0.006)	<0.0001		
BMI*	-	-			0.010 (0.007; 0.015)	<0.0001		
Male sex	-	-			0.152 (0.086; 0.219)	<0.0001		
Indication for treatment [^]	-	-			-0.090 (-0.160; -.0183)	0.01		
CYP2C9*2 1-allele	-	-			-0.007 (-0.149;0.133)	0.93		
CYP2C9*2 2-alleles	-	-			-	-		
CYP2C9 *3 1-allele	-	-	-	-	-0.469 (-0.666;-0.270)	<0.0001	0.30	0.22
CYP2C9 *3 2-alleles	-	-			-	-		
CYP2C9 *5 1-allele	-	-			-0.436 (-0.736;-0.137)	0.005		
CYP2C9 *5 2-alleles	-	-			-	-		
VKORC1 AG	-	-			-0.284 (-0.585; -0.020)	0.07		
VKORC1 AA	-	-			-0.281 (-0.588;-0.020)	<0.0001		
CYP4F2 CT	-	-			-0.0382 (-0.124; 0.050)	0.40		
CYP4F2 TT	-	-			0.300 (-0.068; 0.664)	0.11		

CI= Confidence Interval

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

* Estimate for 1 unit increase; ^ Estimate for the following indication for treatment: fibrillation/flutter, cardiomyopathy/LV dilation, post orthopedic

Table 4. Beta coefficients (p-values) for single genes and gene-gene interaction.

Ethnicity	Drug	N subjects (N studies)	<i>CYP4F2</i>	<i>CYP2C9</i>	<i>VKORC1</i>	<i>CYP4F2*CYP2C9</i>	<i>CYP4F2*VKORC1</i>	<i>CYP2C9*VKORC1</i>
Whites	Acenocumarol	4154 (5)	0.08 (0.0002)	-0.22 (<0.0001)	-0.40 (<0.0001)	-0.02 (0.51)	-0.03 (0.21)	-0.01 (0.79)
	Warfarin	4548 (15)	0.08 (0.0001)	-0.30 (<0.0001)	-0.38 (<0.0001)	-0.001 (0.96)	0.02 (0.37)	-0.01 (0.55)
Asians	Acenocumarol	0 (0)	NE	NE	NE	NE	NE	NE
	Warfarin	438 (8)	0.10 (0.34)	-0.26 (0.05)	-0.46 (<0.0001)	0.12 (0.36)	-0.08 (0.48)	-0.004 (0.98)
Blacks	Acenocumarol	0 (0)	NE	NE	NE	NE	NE	NE
	Warfarin	815 (5)	0.04 (0.30)	-0.20 (0.0004)	-0.27 (<0.0001)	0.004 (0.97)	-0.02 (0.82)	0.02 (0.83)
Others	Acenocumarol	0 (0)	NE	NE	NE	NE	NE	NE
	Warfarin	701 (7)	-0.08 (0.13)	-0.19 (0.003)	-0.27 (<0.0001)	0.07 (0.31)	0.09 (0.13)	-0.05 (0.48)
All	All	11,435 (29)	0.07 (<0.0001)	-0.24 (<0.0001)	-0.37 (<0.0001)	0.02 (0.21)	0.02 (0.23)	-0.02 (0.12)

NE= Not estimated

Note: ethnicity- and drug-specific models are adjusted by study, age, sex, BMI and indication for treatment. The final model is also adjusted by ethnicity and drug. For each gene, the reference category is the gene polymorphism according to the dominant model (heterozygous+variant homozygous vs wt). For the analysis on Blacks, *CYP2C9* included, beyond *2 and *3, also *5 polymorphism.