Figure S1. Funnel plot for association studies of the CYP4F2 polymorphism on coumarin dose requirements.

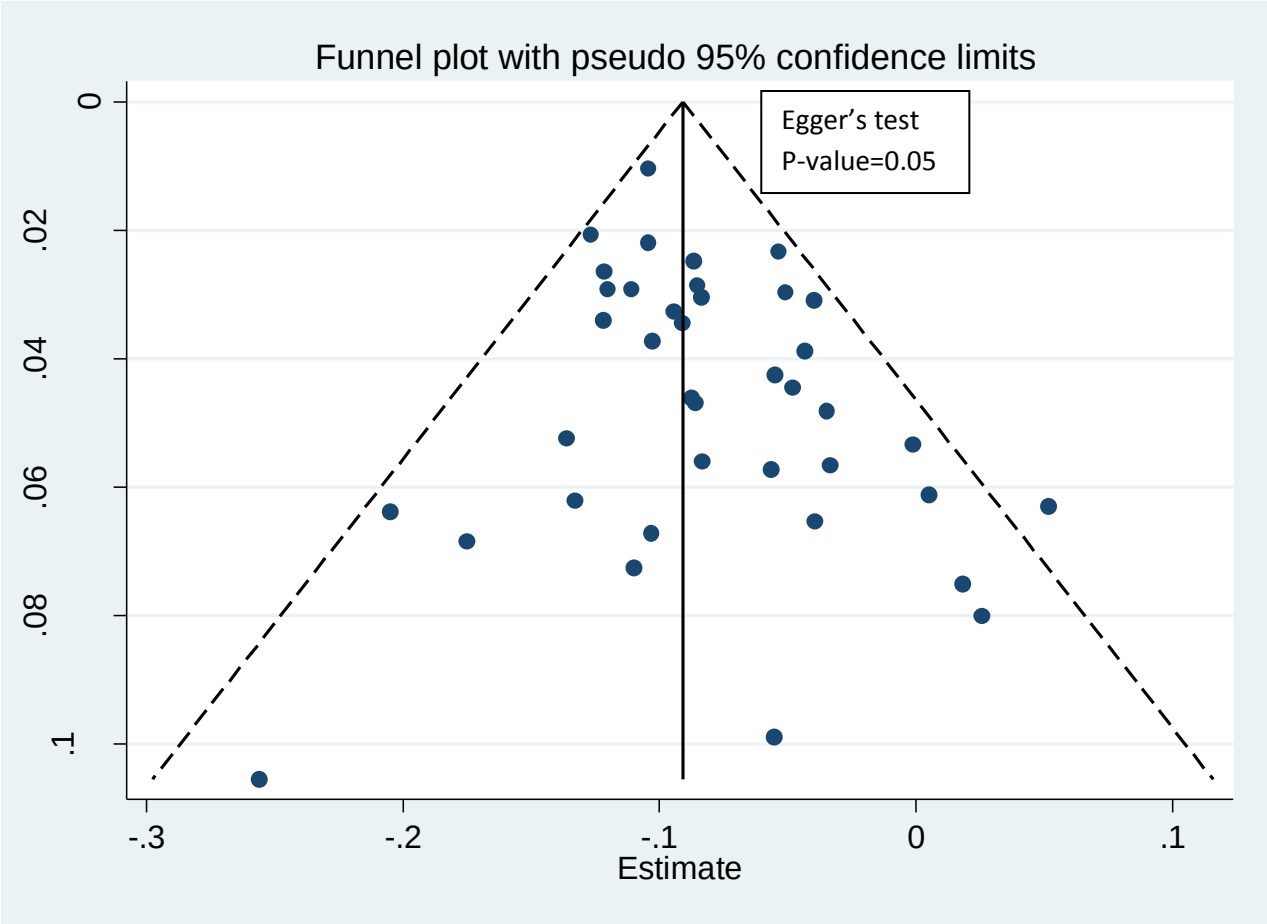


Figure S2a Forest plot for the difference in logarithm of stable coumarin dose* for subjects with *CYP4F2* polymorphism (CT) compared to subjects with *CYP4F2* wild-type (CC)

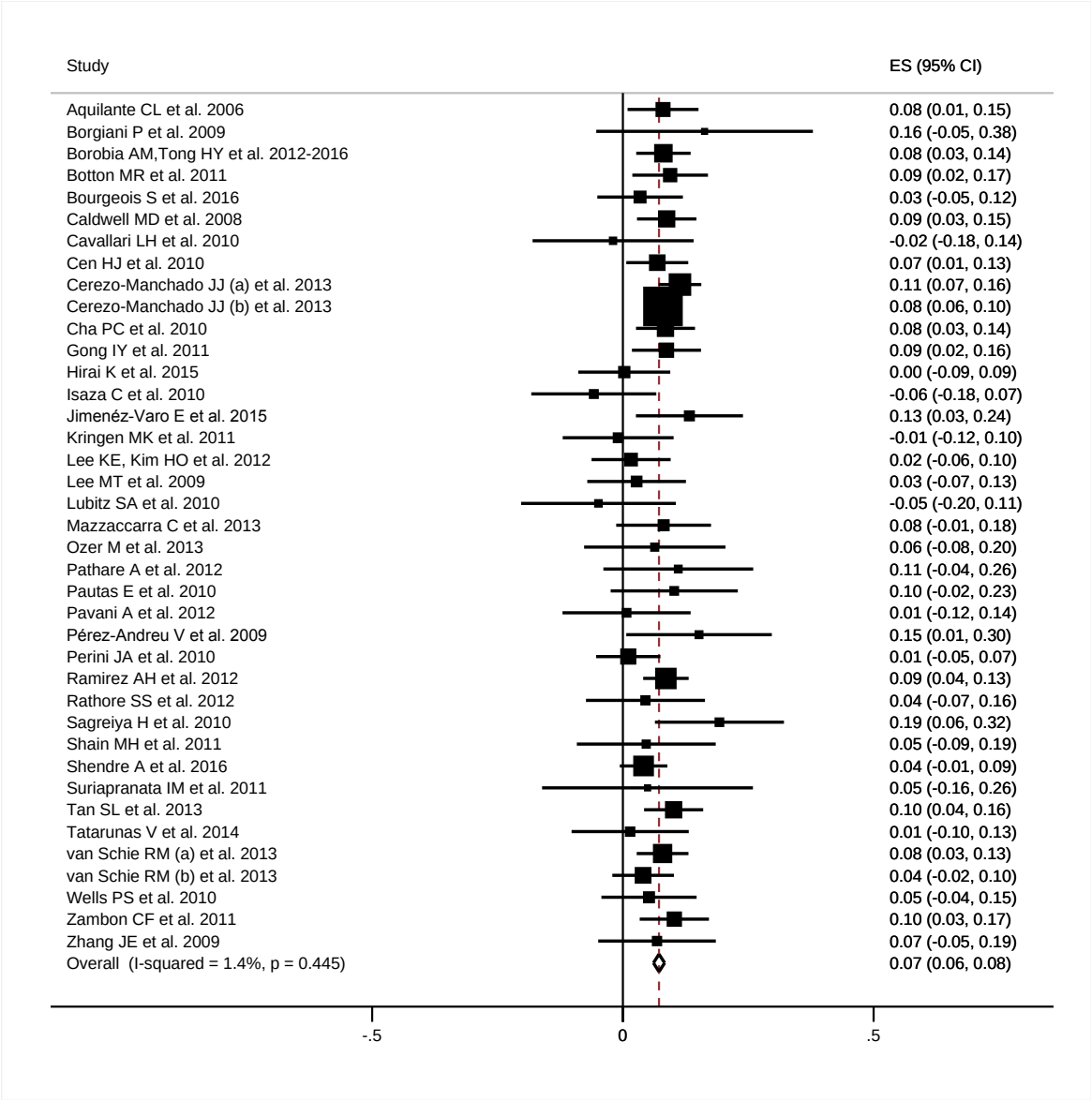
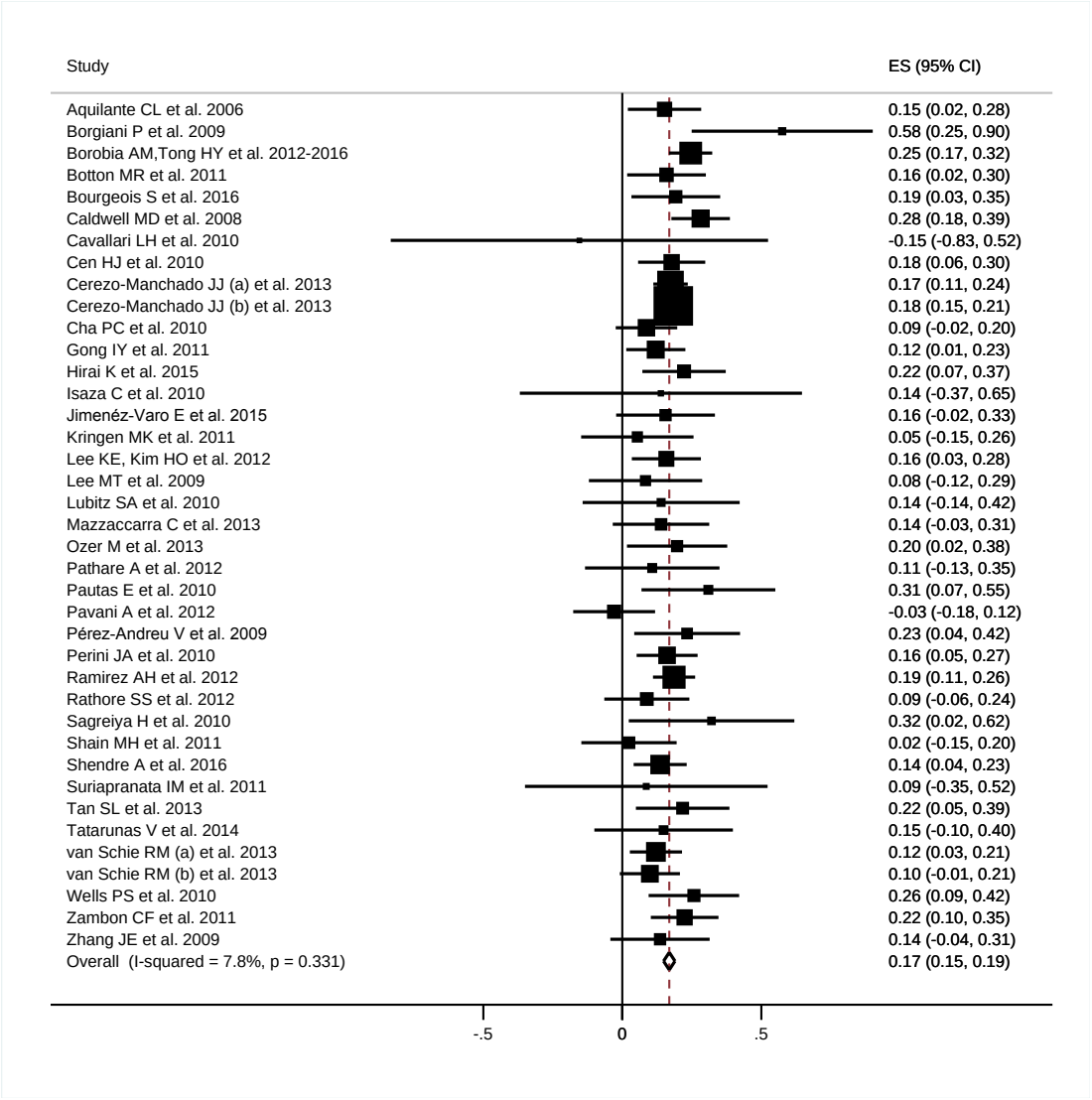


Figure S2b. Forest plot for the difference in logarithm of stable coumarin dose* for subjects with *CYP4F2* polymorphism (TT) compared to subjects with *CYP4F2* wild-type (CC)

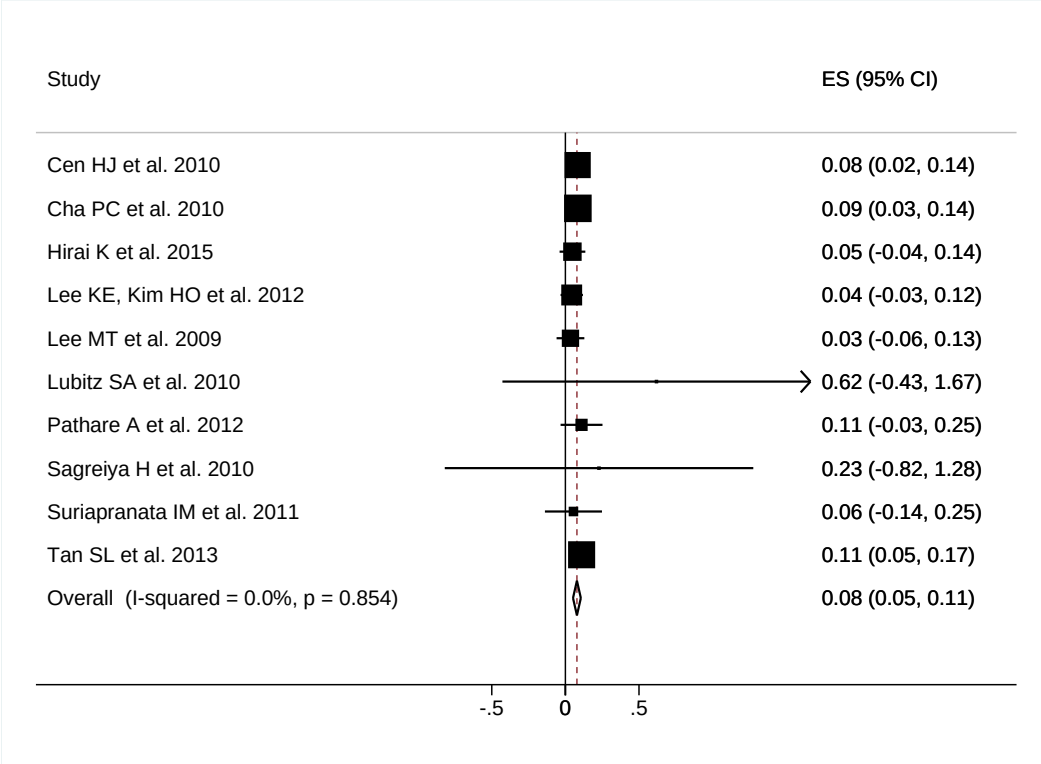


CI=Confidence Intervals; ES=Estimate

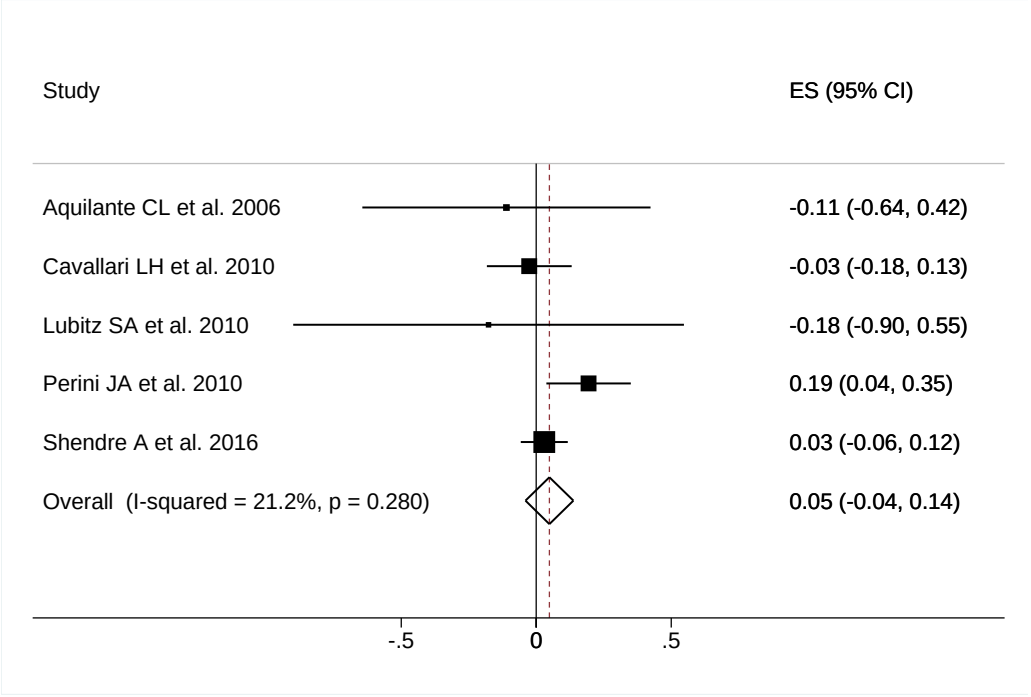
* exp(ES) gives the relative percentage difference as weekly dose in mg

Figure S3. Forest plot for the difference in logarithm of stable coumarin dose* for subjects with *CYP4F2* polymorphism (CT+TT) compared to subjects with *CYP4F2* wild-type (CC), according to dominant model and stratified by (A) ethnicity; (B) drug; (C) sex.

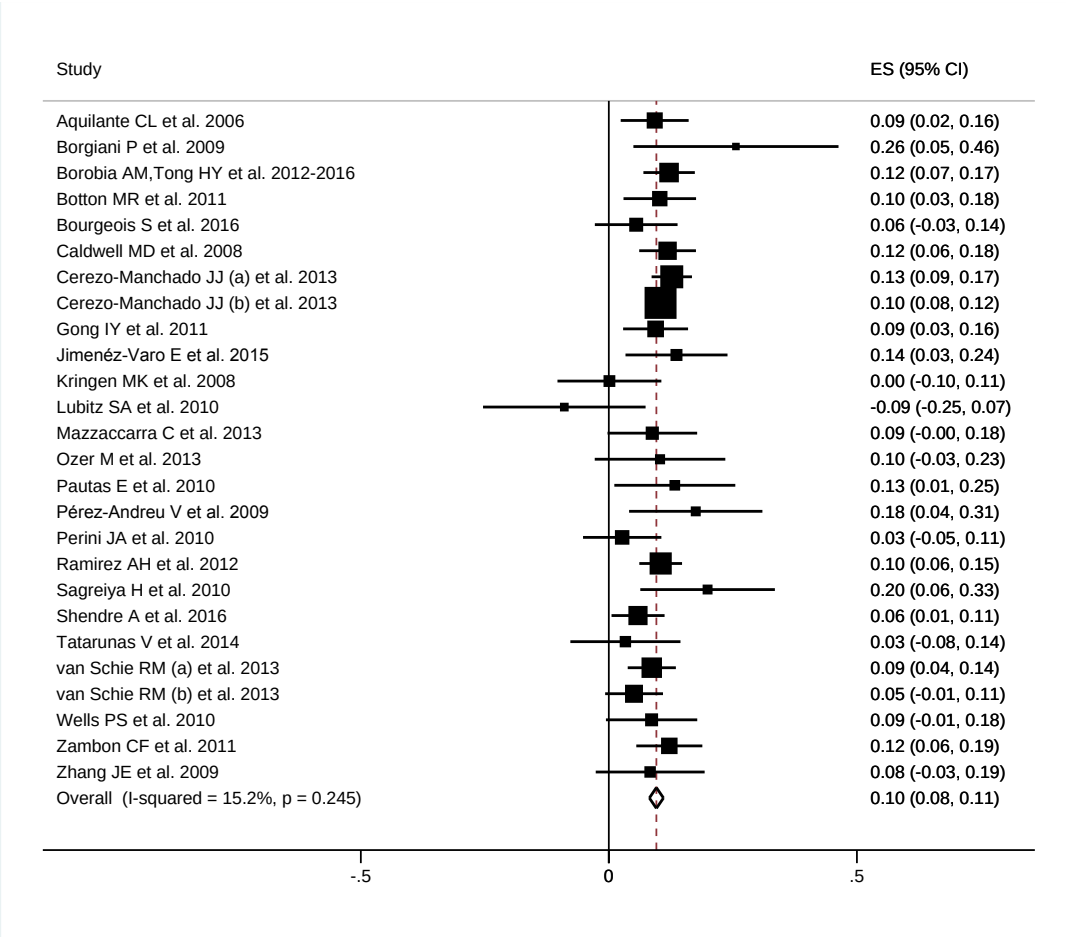
A) Asians



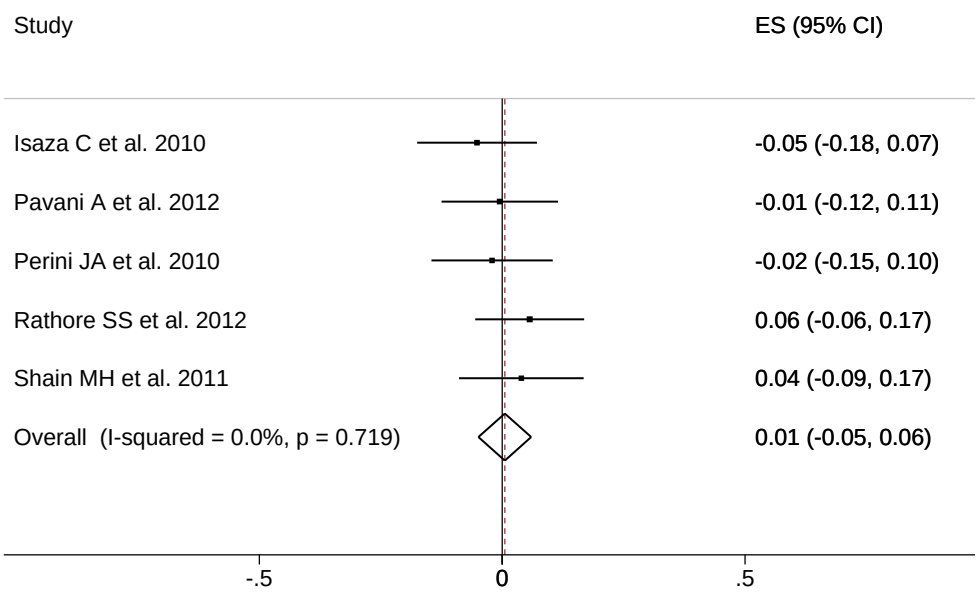
A) Blacks



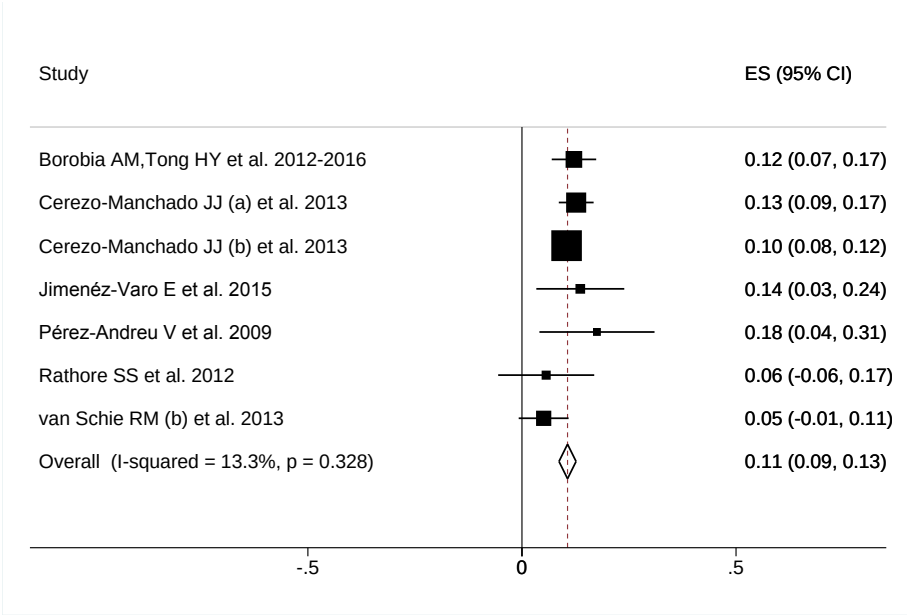
A) Whites



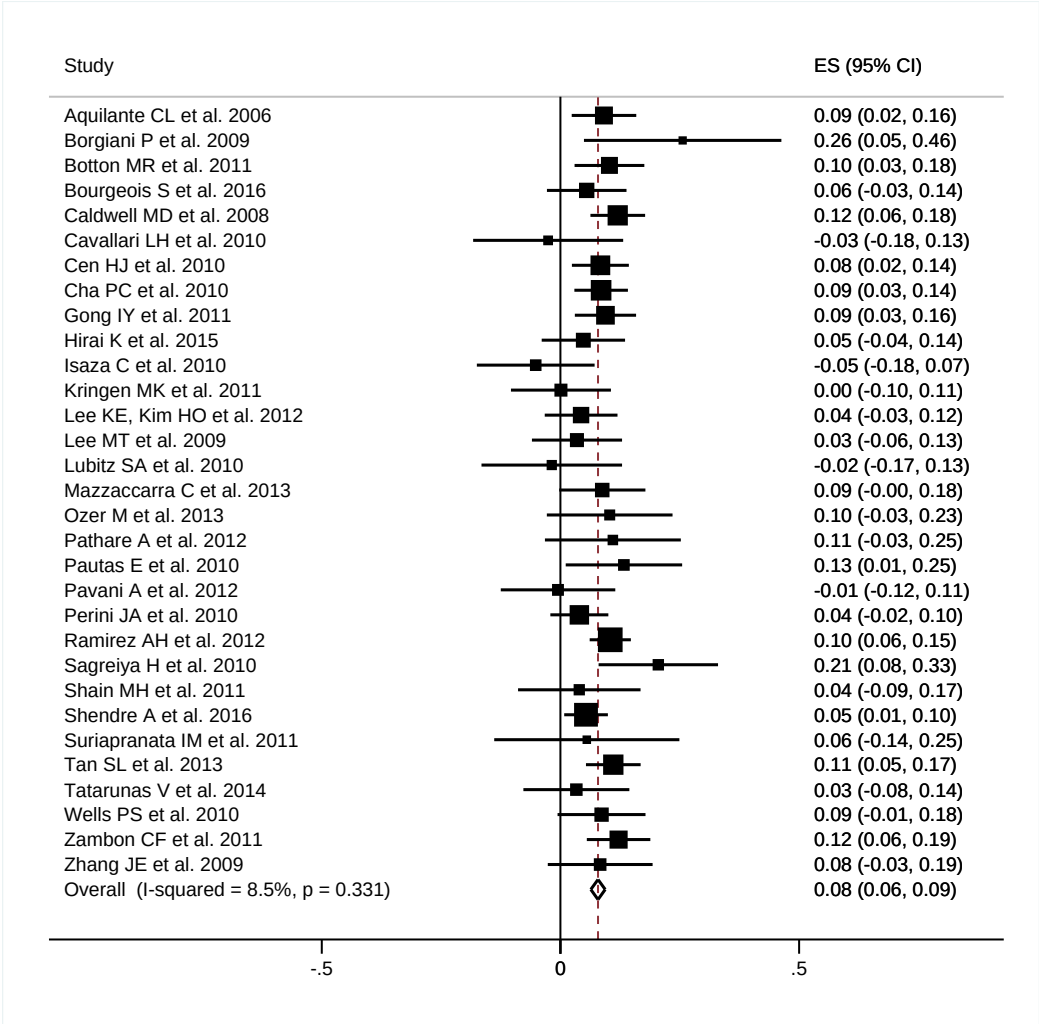
A) Others



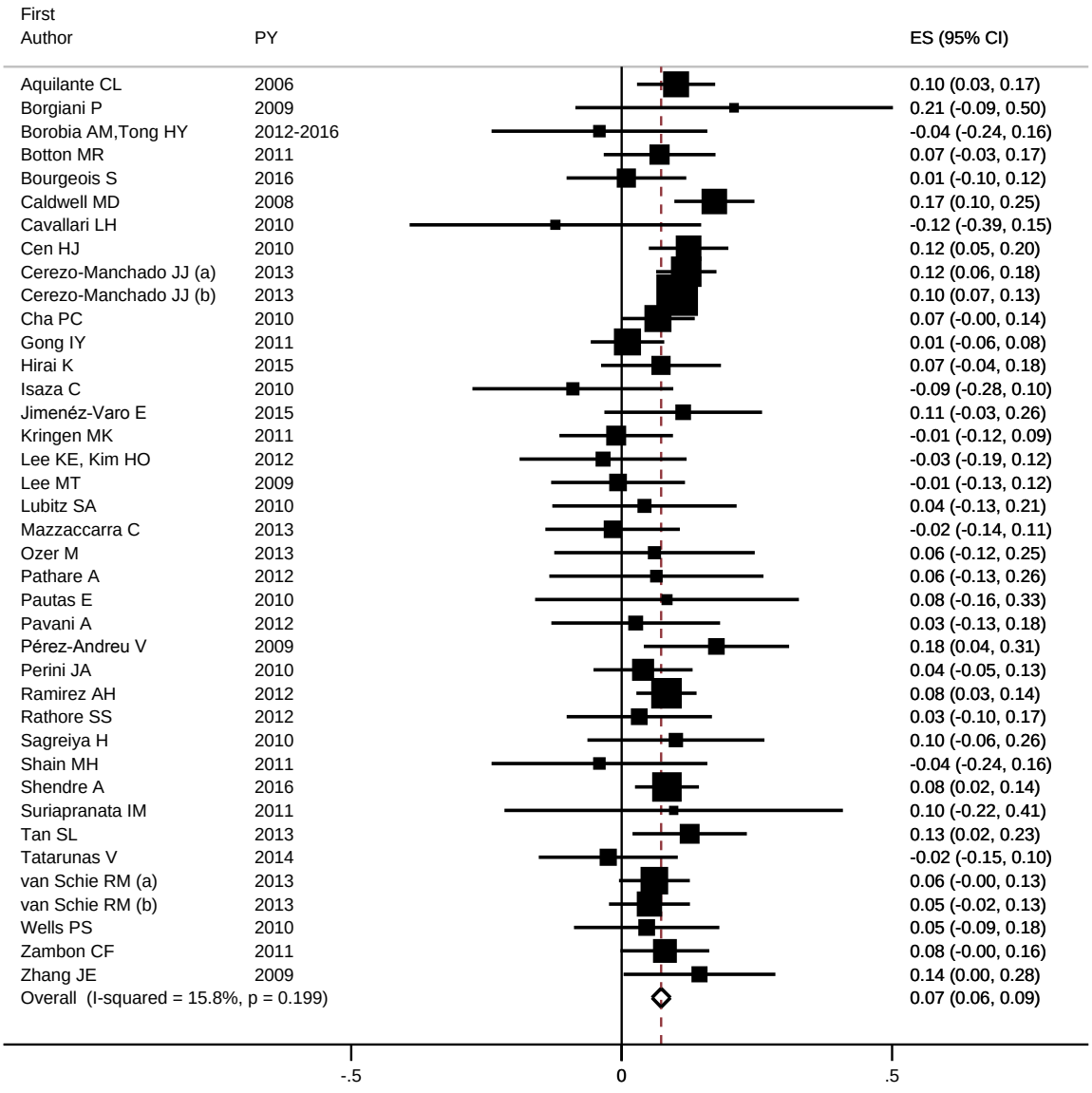
B) Acenocoumarol



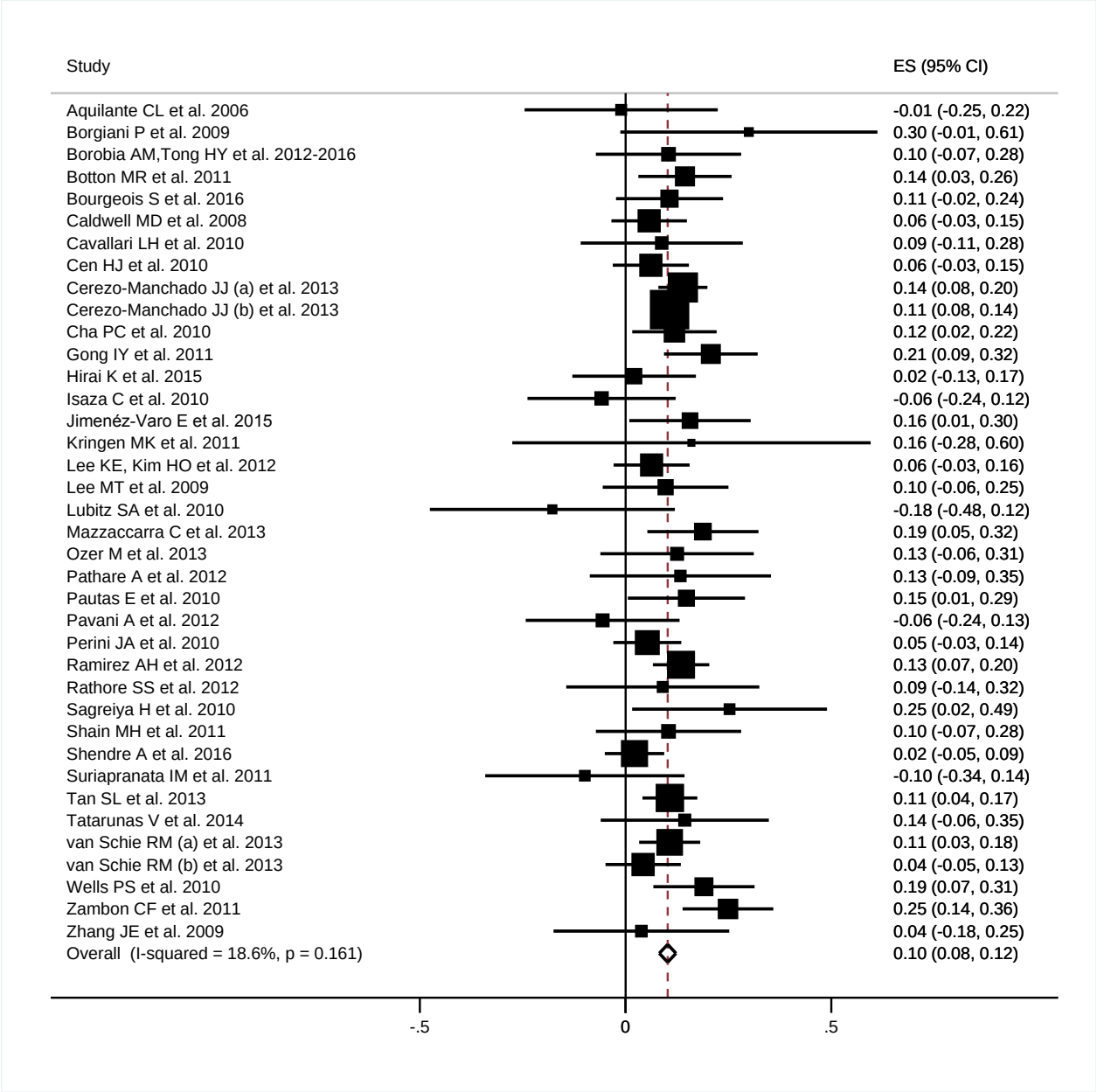
B) Warfarin



c) Males


First Author
PY
ES (95% CI)
Aquilante CL 2006 0.10 (0.03, 0.17)
Borgiani P 2009 0.21 (-0.09, 0.50)
Borobia AM,Tong HY 2012-2016 -0.04 (-0.24, 0.16)
Botton MR 2011 0.07 (-0.03, 0.17)
Bourgeois S 2016 0.01 (-0.10, 0.12)
Caldwell MD 2008 0.17 (0.10, 0.25)
Cavallari LH 2010 -0.12 (-0.39, 0.15)
Cen HJ 2010 0.12 (0.05, 0.20)
Cerezo-Manchado JJ (a) 2013 0.12 (0.06, 0.18)
Cerezo-Manchado JJ (b) 2013 0.10 (0.07, 0.13)
Cha PC 2010 0.07 (-0.00, 0.14)
Gong IY 2011 0.01 (-0.06, 0.08)
Hirai K 2015 0.07 (-0.04, 0.18)
Isaza C 2010 -0.09 (-0.28, 0.10)
Jimenéz-Varo E 2015 0.11 (-0.03, 0.26)
Kringen MK 2011 -0.01 (-0.12, 0.09)
Lee KE, Kim HO 2012 -0.03 (-0.19, 0.12)
Lee MT 2009 -0.01 (-0.13, 0.12)
Lubitz SA 2010 0.04 (-0.13, 0.21)
Mazzaccarra C 2013 -0.02 (-0.14, 0.11)
Ozer M 2013 0.06 (-0.12, 0.25)
Pathare A 2012 0.06 (-0.13, 0.26)
Pautas E 2010 0.08 (-0.16, 0.33)
Pavani A 2012 0.03 (-0.13, 0.18)
Pérez-Andreu V 2009 0.18 (0.04, 0.31)
Perini JA 2010 0.04 (-0.05, 0.13)
Ramirez AH 2012 0.08 (0.03, 0.14)
Rathore SS 2012 0.03 (-0.10, 0.17)
Sagreiya H 2010 0.10 (-0.06, 0.26)
Shain MH 2011 -0.04 (-0.24, 0.16)
Shendre A 2016 0.08 (0.02, 0.14)
Suriapranata IM 2011 0.10 (-0.22, 0.41)
Tan SL 2013 0.13 (0.02, 0.23)
Tatarunas V 2014 -0.02 (-0.15, 0.10)
van Schie RM (a) 2013 0.06 (-0.00, 0.13)
van Schie RM (b) 2013 0.05 (-0.02, 0.13)
Wells PS 2010 0.05 (-0.09, 0.18)
Zambon CF 2011 0.08 (-0.00, 0.16)
Zhang JE 2009 0.14 (0.00, 0.28)
Overall (I-squared = 15.8%, p = 0.199) 0.07 (0.06, 0.09)
-.5
0
.5

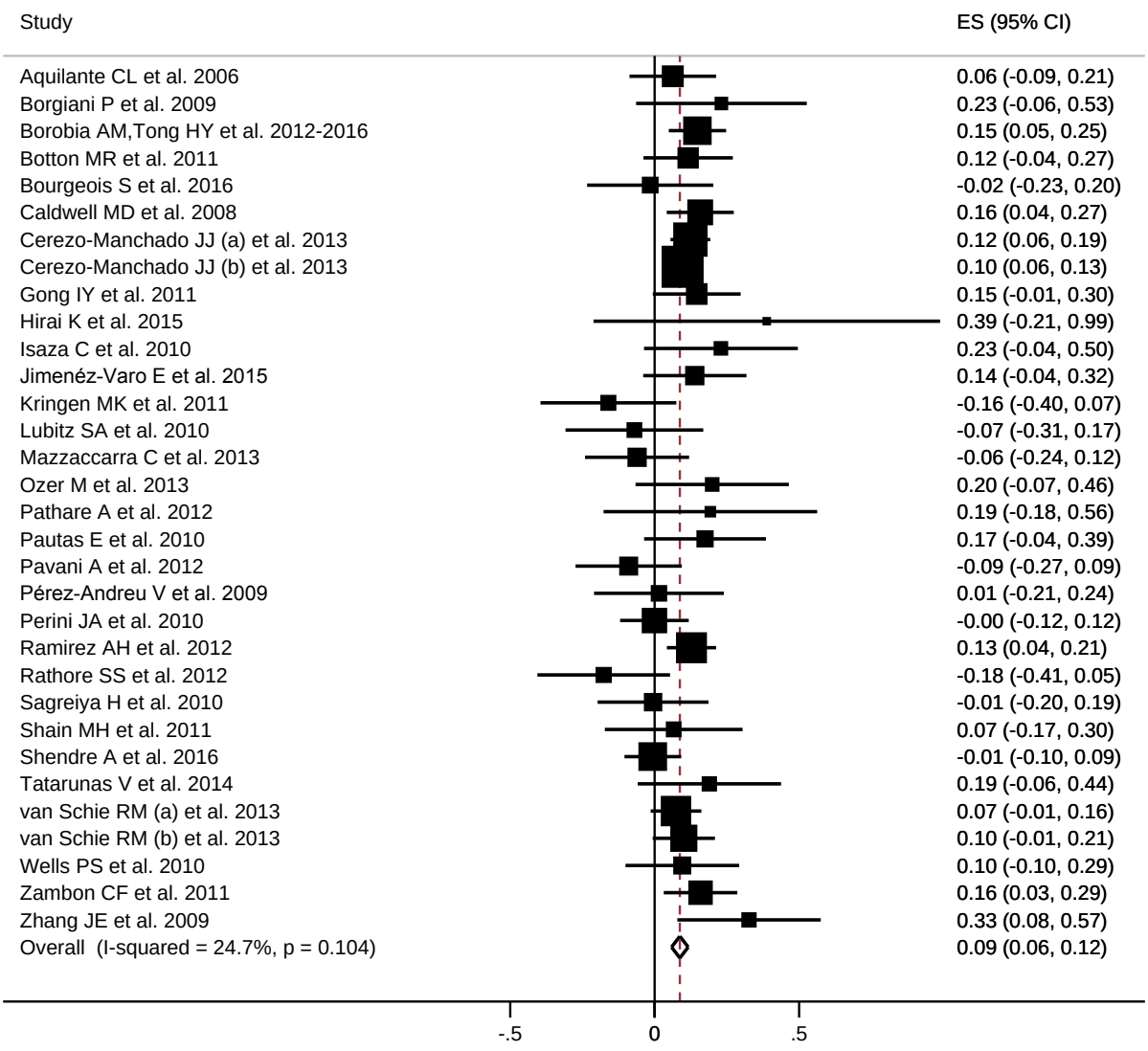
c) Females



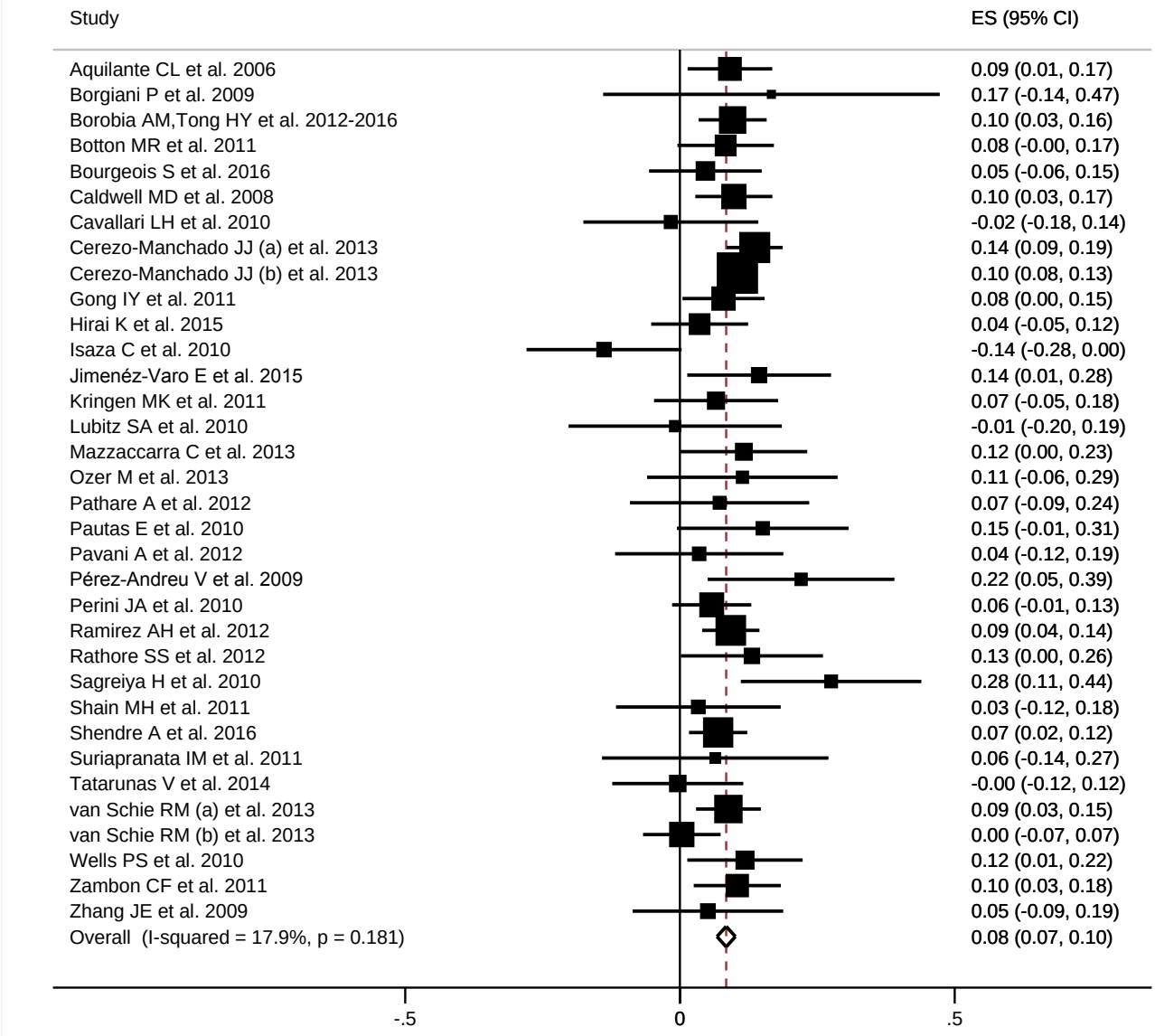
CI=Confidence Intervals; ES=Estimate
* exp(ES) gives the relative percentage difference as weekly dose in mg

Figure S4. Forest plot for the difference in logarithm of stable coumarin dose* for subjects with *CYP4F2* polymorphism (CT+TT) compared to subjects with *CYP4F2* wild-type (CC), according to dominant model and stratified by (A) CYP2C9; (B) *VKORC1*.

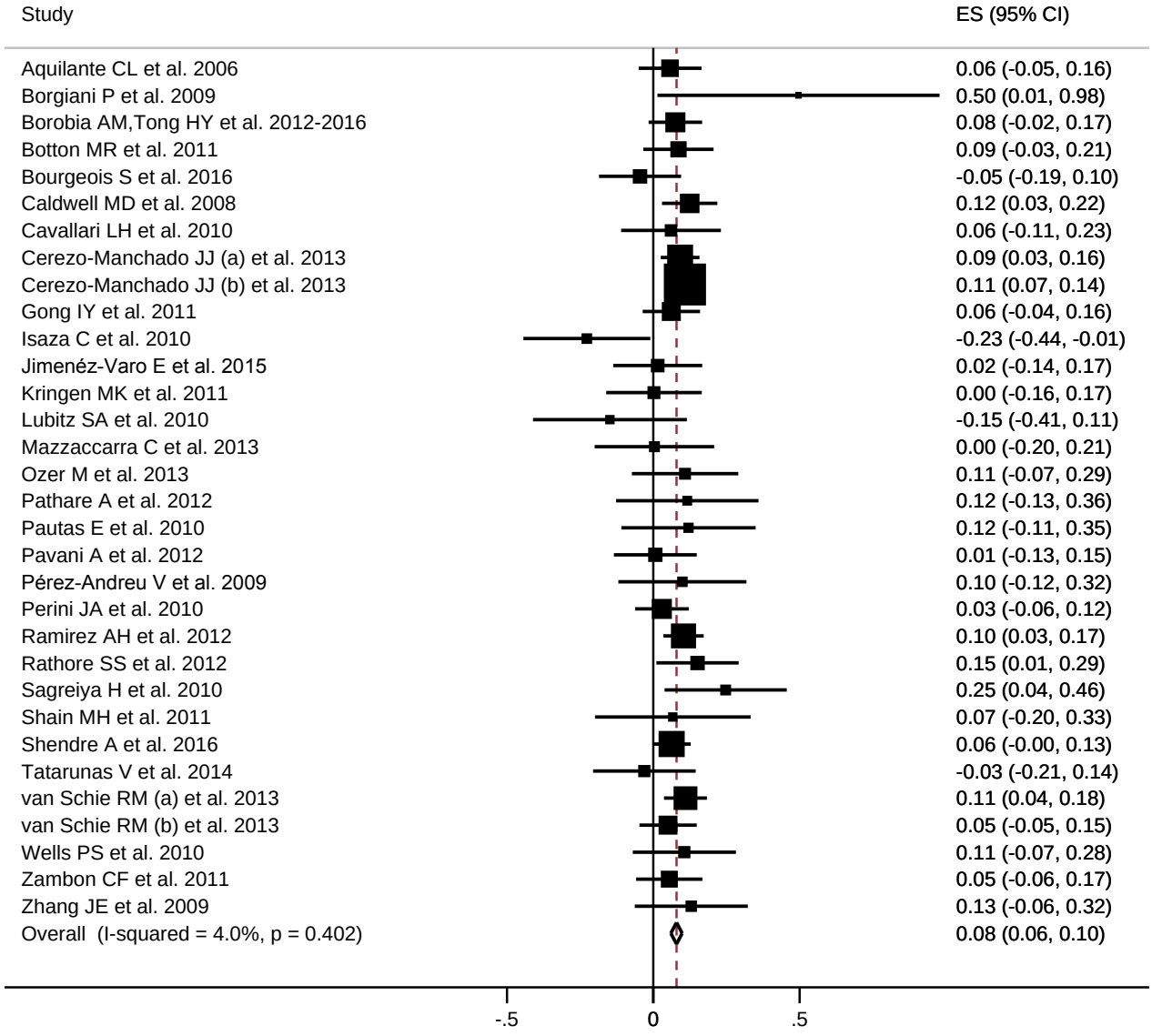
CYP2C9*2 or *3



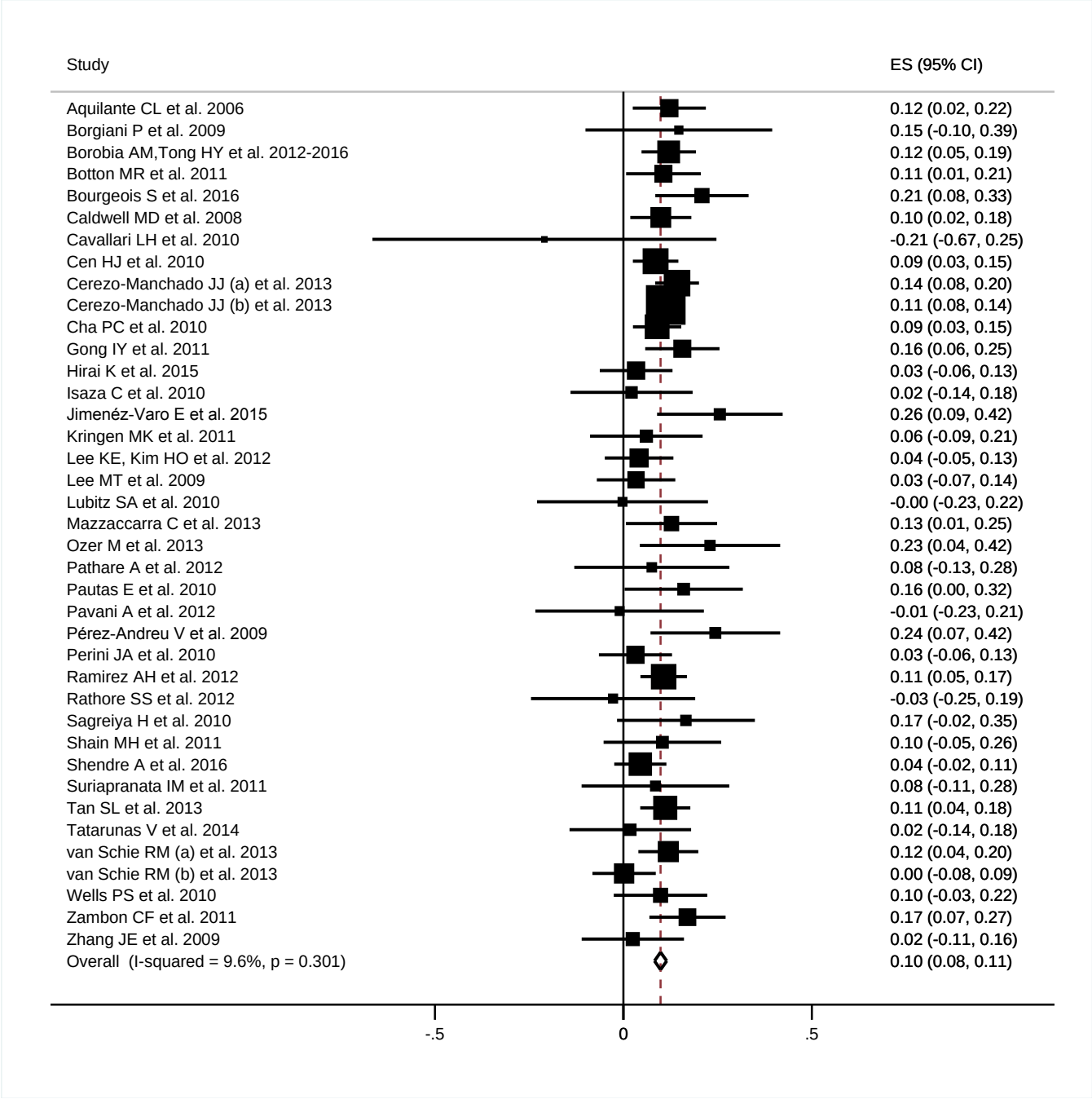
CYP2C9 wild type



VKORC1 rs9923231 GG (Wild type)



VKORC1 rs9923231 GA or AA (mutated)



CI=Confidence Intervals; ES=Estimate

* exp(ES) gives the relative percentage difference as weekly dose in mg

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 (R^2) is reported for the whole group of subjects

WHITES-ACENOCOUMAROL									
	Base model°+amiodarone (Model 1) N=4152/4154 (100%)			**Base model°+all available drugs (Model 2) N=675/4154 (16%)**			**Model 1+smoking (Model 3) N=747/4154 (18%)**		
Variable	**Parameter estimate**	**P-value**	**R^2**	**Parameter estimate**	**P-value**	**R^2**	**Parameter estimate**	**P-value**	**R^2**
Intercept	4.036	<.0001		3.229	<.0001		3.148	<.0001	
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	
*CYP2C9*2* 1-allele	-0.173	<.0001		-0.153	<.0001		-0.151	<.0001	
*CYP2C9*2* 2-alleles	-0.303	<.0001		-0.306	0.0005		-0.271	0.0003	
*CYP2C9*3* 1-allele	-0.395	<.0001		-0.447	<.0001		-0.418	<.0001	
*CYP2C9*3* 2- alleles	-1.087	<.0001	0.32	-1.301	<.0001	0.57	-1.241	<.0001	0.59
VKORC1 AG	-0.287	<.0001		-0.293	<.0001		-0.314	<.0001	
VKORC1 AA	-0.744	<.0001		-0.704	<.0001		-0.738	<.0001	
CYP4F2 CT	0.023	0.16		0.054	0.05		0.064	0.01	
CYP4F2 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									
	N=3841/4548 (84%)			**N=2308/4548 (51%)**			**N=3366/4548 (74%)**		
Intercept	4.016	<.0001		4.119	<.0001		3.999	<.0001	
Age *	-0.010	<.0001		-0.011	<.0001		-0.010	<.0001	
BMI*	0.010	<.0001	0.52	0.010	<.0001	0.54	0.011	<.0001	0.51
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^									
*CYP2C9*2* 1-allele	-0.222	<.0001		-0.226	<.0001		-0.225	<.0001	
*CYP2C9*2* 2-alleles	-0.524	<.0001		-0.531	<.0001		-0.523	<.0001	
*CYP2C9*3* 1-allele	-0.388	<.0001		-0.393	<.0001		-0.387	<.0001	
*CYP2C9*3* 2- alleles	-1.175	<.0001		-1.503	<.0001		-1.119	<.0001	
VKORC1 AG	-0.266	<.0001		-0.268	<.0001		-0.271	<.0001	
VKORC1 AA	-0.665	<.0001		-0.654	<.0001		-0.669	<.0001	
CYP4F2 CT	0.062	<.0001		0.070	<.0001		0.057	<.0001	
CYP4F2 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	
*CYP2C9*2* 1-allele	-0.073	0.45		0.844	0.11		-0.072	0.50	
*CYP2C9*2* 2-alleles	-	-		-	-		-	-	
*CYP2C9*3* 1-allele	-0.210	0.01	0.45	-0.117	0.53	0.35	-0.150	0.13	0.47
*CYP2C9*3* 2- alleles	-1.279	<.0001		-	-		-1.203	0.0005	
VKORC1 AG	-0.378	<.0001		-0.508	0.01		-0.402	<.0001	
VKORC1 AA	-0.787	<.0001		-0.757	<.0001		-0.880	<.0001	
CYP4F2 CT	0.110	0.02		0.107	0.29		0.133	0.03	
CYP4F2 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	<0.0001	0.32	3.867	<0.0001	0.27	3.786	<0.0001	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	
*CYP2C9*2* 1-allele	-0.082	0.14		-0.178	0.17		-0.072	0.26	
*CYP2C9*2* 2-alleles	-	-		-	-		-	-	
*CYP2C9*3* 1-allele	-0.341	<0.0001		-0.190	0.32		-0.341	0.0001	
*CYP2C9*3* 2- alleles	-	-		-	-		-	-	
CYP2C9 *5 1-allele	-0.375	0.002		-0.420	0.06		-0.386	0.01	
CYP2C9 *5 2-alleles	-	-		-	-		-	-	
VKORC1 AG	-0.292	<0.0001		-0.256	0.0001		-0.295	<0.0001	
VKORC1 AA	-0.284	0.03		-0.434	0.27		-0.241	0.09	
CYP4F2 CT	0.006	0.87		-0.064	0.41		0.014	0.72	
CYP4F2 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)	*CYP4F2* interaction (p-value)	*CYP2C9*2* interaction (p-value)	*CYP2C9*3* interaction (p-value)	*CYP4F2* effect (p-value) when no use of concomitant drug	*CYP4F2* effect (p-value) when use of concomitant drug	*CYP2C9*2* effect (p-value) when no use of concomitant drug	*CYP2C9*2* effect (p-value) when use of concomitant drug	*CYP2C9*3* effect (p-value) when no use of concomitant drug	*CYP2C9*3* effect (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)
CYP2C9-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 CYP-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 CYP-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.

Supplementary Material: Discussion and SAS Code

Assumption of patients' exchangeability

The assumption of patients' exchangeability underlies this analysis. Indeed, inference is a process whereby one passes from data on a set of units to statements about a further unit. This linkage can be formulated in terms of judgments of exchangeability between the unit and the data; or, alternatively expressed, judgments of which subpopulation the unit belongs to.[1] Specifically, we assumed that the optimal coumarin dose calculated for patients in our multicenter study may be applied to a further, new patient. Evidence of clinical utility for the studied markers is a key issue in translating pharmacogenomics into clinical practice and the extent to which the optimal coumarin dose differs between subgroups defined by the markers is an important component of assessing clinical utility. In order to properly take into account genetic differences across subpopulations, we assumed exchangeability within subgroups of individuals from the same race and taking the same type of drug (warfarin or acenocoumarol), and therefore performed separate analyses according to each race/drug combination.

Nevertheless, beyond the identification of appropriate subpopulations, another important aspect to be taken into account is the assumption of "no unmeasured confounders" underlying exchangeability assumption.[2] We tried to assess the issue of possible unmeasured confounding by creating, as sensitive analyses, new models including further covariates beyond the ones included in the main analysis, and we obtained similar R Square values. A possible residual confounding, however, could not be completely ruled out.

In general, when the assumption of exchangeability does not hold, possible alternative analyses may be performed, including promising Bayesian approaches that enables personalized treatment selection for new patients.[3,4] Indeed, implicit to the concept of precision medicine is heterogeneity of treatment benefit among patients and patient subpopulations. Further researches and different

types of analyses may be helpful in the future to obtain optimal coumarin doses estimates in the era of precision medicine.

References

1. Lindley, D. V., Novick, M. R. The Role of Exchangeability in Inference. *Ann. Stat.* 9, 45-58 (1981)
2. Greenland, S., Robins, J. M., Pearl, J. Confounding and collapsibility in causal inference. *Stat. Sci.* 14, 29-46 (1999)
3. Ma, J., Stingo, F. C., Hobbs, B. P. Bayesian predictive modeling for genomic based personalized treatment selection. *Biometrics* 72, 575-583 (2016)
4. Hobbs B.P., and Landin R. Bayesian basket trial design with exchangeability monitoring. *Stat. Med.* 37, 3557-3572 (2018)

SAS code

```
/*1)Two-stage analysis for the association between CYP4F2*3 polymorphism and
stable coumarin dose */

/*Study-specific estimates*/
/*PARAMETERS:
      COHORT: name of dataset containing subjects for each specific cohort;
      CLASS: study-specific categorical variables (i.e. race);
      COVARIATES: study-specific covariates as described in Table 1 + CYP2C9*2
and *3 combined and VKORC polymorphisms (both genes coded as 0, 1, 2 for no, 1
or 2 variant alleles)*/

%MACRO GLM_ANALYSIS (COHORT= , CLASS= , COVARIATES= );
proc glm data=&COHORT.;
class &CLASS.;
model lndose=CYP4F2_V433M_D &COVARIATES./solution; /*lndose=logarithmic
transformation of dose, CYP4F2_V433M_D coded as 0 (CC) or 1 (CT+TT)*/
ods output ParameterEstimates=beta;
run;quit;
%MEND;

/*meta-analysis and meta-regression with STATA, 'metan' command:
metan Beta StdErr **possible covariate for meta-regression**, random classic
lcols( Study ) sortby( newID ) nowarning  xlabel(-0.50, 0.00, 0.50) boxsca(50)
textsize(100)  nowt diamopt(lcolor(black))*/
```

```
/*2)Stable coumarin dose predictive model*/

/*A)MAIN ANALYSIS: TABLE 3*/
/*Sampling*/
proc surveyselect data=WAR method=srs samprate=0.66 seed=0 out=sampling;
strata cohort_n;
run;
data warfarin.test;
set sampling;
test=1;
run;
proc sort data=WAR;by IDcumulative;run;
proc sort data=warfarin.test;by IDcumulative;run;
data tot;
merge WAR warfarin.test;
by IDcumulative;
if test=. then test=0;
run;
data warfarin.valid;
set tot;
if test=0;
run;
/*Create different datasets for each available combination of race and drug and
perform analysis for each of these combinations*/
/*Example for whites+warfarin*/
data white_warfarin;/*test set*/
set warfarin.test;
if race='White';if Warfarin_0_Aceno_1=0;
run;
data white_warfarin_valid;/*validation set*/
set warfarin.valid;
if race='White';if Warfarin_0_Aceno_1=0;
run;
/*Glm models on training set and validation*/
/*COVARIATES:
Age_years: continuous;
BMI: continuous;
sex: 0=Female 1=Male;
IND: 0=DVT OR PE OR heart valve OR stroke OR others  1=fibrillation/flutter OR
cardiomyopathy/LV dilation OR post orthopedic;
CYP2C9_a2_3: 0=2 variant alleles    1=1 variant allele      2=0 variant alleles
(reference);
CYP2C9_a3_3: 0=2 variant alleles    1=1 variant allele      2=0 variant alleles
(reference);
*only for Blacks: CYP2C9_a5_3: 0=2 variant alleles   1=1 variant allele      2=0
variant alleles (reference)*;
VKORC_3:     0=2 variant alleles    1=1 variant allele      2=0 variant alleles
(reference);
CYP4F2_3:    0=2 variant alleles    1=1 variant allele      2=0 variant alleles
(reference)*/
proc glm data=white_warfarin;
class CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3 CYP4F2_3;
model lndose=AGE_years BMI sex IND CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3
CYP4F2_3/solution clparm;
store work.Score_white_warfarin;
run;quit;
```

```
proc plm restore=work.Score_white_warfarin;
score data=white_warfarin_valid out=Pred1;
run;
proc glm data=Pred1;
model lndose=predicted/solution;
run;quit;

/*B)SENSITIVITY ANALYSIS: SUPPLEMENTARY TABLE S1*/
/*Create different datasets for each available combination of race and drug and
perform analysis for each of these combinations*/
/*Example for whites+warfarin*/
data white_warfarin_all;/*test+validation cohort*/
set WAR;
if race='White';if Warfarin_0_Aceno_1=0;
run;
/*Glm models on the whole cohort*/
proc glm data=white_warfarin_all;
class CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3 CYP4F2_3;
model lndose=AGE_years BMI sex IND CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3 CYP4F2_3
amiodarone/solution;/*amiodarone code 0=no     1=yes*/
run;quit;
proc glm data=white_warfarin_all;
class CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3 CYP4F2_3;
model lndose=AGE_years BMI sex IND CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3 CYP4F2_3
CYPind CYPinhib/solution;/*CYPind (All CYP-inducers) code        0=no  1=yes
CYPinhib (All CYP-inhibitors) code  0=no  1=yes*/
run;quit;
proc glm data=white_warfarin_all;
class CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3 CYP4F2_3;
model lndose=AGE_years BMI sex INDICATION_01 CYP2C9_a2_3 CYP2C9_a3_3 VKORC_3
CYP4F2_3 amiodarone smokerstatus/solution;/*smokerstatus code 0=no     1=yes*/
run;quit;
```

```
/*C)PREVIOUS MODELS COMPARISON: SUPPLEMENTARY TABLE S3*/
/*Create different datasets for each available combination of race and drug and
perform analysis for each of these combinations*/
/*Example for whites+warfarin*/
/*Consortium IWP: create data set NE_validation from white_warfarin_valid by
recoding variables as follow:
age_dec: 1=10-19 years  2=2-29 years      3=30-39 years     ...;
heightcm:continuous;
weightkg: continuous;
VKORC1_NE:              0=GG/AA/missing              1=AG (dummy variable);
VKORC2_NE:              0=GG/AG/missing              1=AA (dummy variable);
VKORCmiss_NE:           0=GG/AG/AA                   1=missing (dummy variable);
CYP2C912_NE:            0=11/22/13/33/23/missing     1=12 (dummy variable);
CYP2C913_NE:            0=11/22/12/33/23/missing     1=13 (dummy variable);
CYP2C922_NE:            0=11/12/13/33/23/missing     1=22 (dummy variable);
CYP2C923_NE:            0=11/12/13/33/22/missing     1=23 (dummy variable);
CYP2C933_NE:            0=11/12/13/22/23/missing     1=33 (dummy variable);
CYP2C9miss_NE:          0=11/12/13/22/23/33          1=missing (dummy variable);
CYPind (All CYP-inducers):          0=no  1=yes;
Amiodarone:                         0=no  1=yes;
*/
data NE_model;
set NE_validation;
score_NE=5.6044-0.2614*age_dec+0.0087*heightcm+0.0128*weightkg-0.8677*VKORC1_NE-
1.6974*VKORC2_NE-0.4854*VKORCmiss_NE-0.5211*CYP2C912_NE-0.9357*CYP2C913_NE-
1.0616*CYP2C922_NE-1.9206*CYP2C923_NE-2.3312*CYP2C933_NE-
0.2188*CYP2C9miss_NE+1.1816*CYPind-0.5503*Amiodarone;
expscore_NE=score_NE*score_NE;
run;
proc glm data=NE_model;
model WEEKLYSTABLEDOSEmg=expscore_NE;
where score ne .;/*for comparison with our score: only in the subgroup of
subjects for which we can calculate our score*/
run;quit;
/*Gage: create data set GAGE_validation from white_warfarin_valid by recoding
variables as follow:
age_years: continuous;
BSA: sqrt(heightcm*weightkg/3600);
INRtarget: continuous;
VKORC11639GgtA_CF:      0=GG              1=AG        2=AA;
CYP2C9_a3_CF:           0=11/22/12        1=13/23     2=33;
CYP2C9_a2_CF:           0=11/33/13        1=12/23     2=22;
Amiodarone:             0=no  1=yes;
smokerstatus:           0=no  1=yes;
DVT_PE:                 0=no  1=yes;
*/
data GAGE_model;
set GAGE_validation;
score_GAGE=0.9751-0.00745*age_years+0.4317*BSA+0.2029*INRtarget-
0.3238*VKORC11639GgtA_CF-0.4008*CYP2C9_a3_CF-0.2066*CYP2C9_a2_CF-
0.2538*Amiodarone+0.0922*smokerstatus+0.0664*DVT_PE;
expscore_GAGE=7*(exp(score_GAGE));
run;
proc glm data=GAGE_model;
model WEEKLYSTABLEDOSEmg=expscore_GAGE;
```

```
where score ne .;/* for comparison with our score: only in the subgroup of
subjects for which we can calculate our score*/
run;quit;



/*D) GENE-GENE INTERACTION: TABLE 4*/
/*Create different datasets for each available combination of race and drug and
perform analysis for each of these combinations*/
/*Example for whites+warfarin*/
/*Gene codes:
CYP2C9:     0=11  1=12/22/13/33/23;
VKORC:      0=GG  1=AG/GG;
CYP4F2:     0=CC  1=CT/TT;
intCYP2C9: CYP2C9*CYP4F2;
intVKORC: VKORC*CYP4F2;
intCYP2C9VKORC: CYP2C9*VKORC;
*/
proc glm data=white_warfarin_all;
class cohort_n;
model lndose=cohort_n AGE_years BMI sex IND CYP2C9 VKORC CYP4F2 intCYP2C9
intVKORC intCYP2C9VKORC/solution;
run;quit;
```

```
/*E) GENE-DRUG INTERACTION AND STRATIFIED ANALYSIS: SUPPLEMENATARY TABLE S2*/
/*Create different datasets for each available combination of race and drug and
perform analysis for each of these combinations*/
/*Example for whites+warfarin*/
/*Gene codes:
CYP2C9_2:   0=11/13/33  1=12/22/23;
CYP2C9_3:   0=11/12/22  1=13/33/23;
VKORC:      0=GG        1=AG/GG;
CYP4F2:     0=CC        1=CT/TT;
*/
%MACRO DRUGS;
%let drugs = amiodarone azoli CYP2C9inducers CYP2C9inhibitors PPI Statin aspirin
carbamazepina otherCYPinducers otherCYPinhibitor rifampin CYPinhib CYPind;
%let i=1;
%do %while (%scan(&drugs, &i) ne );
   %let next_drug = %scan(&drug, &i);

proc glm data=white_warfarin_all; /*drug effect (column 1)*/
class cohort_n;
model lndose=cohort_n AGE_years BMI sex  IND &next_drug CYP2C9_2 CYP2C9_3 VKORC
CYP4F2/solution;
ods output Nobs=N&next_drug;
ods output ParameterEstimates=estimates&next_drug;
run;quit;

proc glm data=white_warfarin_all; /*gene-drug interaction (columns 2--4*/
class cohort_n;
model lndose=cohort_n AGE_years BMI sex IND &next_drug CYP2C9_2 CYP2C9_3 VKORC
CYP4F2 &next_drug*CYP2C9_2 &next_drug*CYP2C9_3 &next_drug*CYP4F2/solution;
ods output ParameterEstimates=int&next_drug;
run;quit;

proc sort data=white_warfarin_all;/*stratified analysis (columns 5--10 */
by &next_drug;run;
proc glm data=white_warfarin_all;
class cohort_n;
model lndose=cohort_n AGE_years BMI sex IND CYP2C9_2 CYP2C9_3 VKORC
CYP4F2/solution;
by &next_drug;
ods output ParameterEstimates=stratestimates&next_drug;
run;quit;

%let i = %eval(&i + 1);
%end;
%mend;
%DRUGS;
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The effect of *CYP4F2, VKORC1 and CYP2C9* polymorphisms in influencing mean coumarin dose. A single patient data meta-analysis in more than 15,000 individuals.

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Supplementary Methods

In addition to the primary studies already included in our previously published meta-analysis, we performed a new literature search scrutinizing Medline and Web of Science from September 1, 2011 to September 14, 2016, without language restrictions. The search algorithm combined the

categories for “drug,” “cytochrome,” and “gene” by the Boolean operator “AND.” The search terms (medical subject headings and text words) in each category were combined with the operator “OR.” The following search strategy was applied: (warfarin OR coumarin OR coumadin OR acenocoumarol OR phenprocoumon) AND (CYP4F2 OR 4F2 OR cytochrome) AND (gene OR genetic* OR genomic* OR pharmacogenet* OR pharmacogenom* OR polymorph*).

In addition, in order to identify advance online publications, we searched the online databases of the 10 journals with the highest frequency of eligible publications as indexed by ISI Web of Science. We manually searched the tables of contents of the issues of these journals for 2005–2011, along with the bibliographies of relevant articles to retrieve further potential publications.

Study selection and inclusion/exclusion criteria.

We considered as potentially eligible observational studies published in full text where the *CYP4F2* rs2108622 were genotyped along with the *CYP2C9* (at least one out of the two variants of interest rs1799853 and rs1057910) and/or *VKORC1* (rs9923231) in coumarin treated patients (see also main manuscript). The studies selected had to meet the following inclusion criteria: (i) clinical cohort or cross-sectional study in coumarin-treated patients, (ii) CYP4F2 genotyping performed in all patients or in a random selection of patients. There were no restrictions in the inclusion criteria with respect to patient demographic information, including age, body weight, height, use of interacting drugs, indication for coumarin use, and target INR range.

We excluded studies that were published only as abstracts, conference reports, case reports, reviews, and notes. Other exclusion criteria were: randomized clinical trials where specific algorithms were applied, studies in children, studies that selected participants on the basis of coumarin dose, case reports.

Quality of the primary studies

As for our previous meta-analysis, we graded the quality of epidemiologic studies in general, applying items taken from the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies,

indicators specific to the quality of genetic association studies, and indicators specific for coumarin (e.g., stable anticoagulation). We also checked for departure from Hardy–Weinberg equilibrium by Chi Square test in controls.

We applied a scale with a maximum score of 7 points. One point was assigned for each of the follow indicators: absence of large population stratification (ethnic homogeneity ≥90%), assessment of compliance to coumarin drug therapy, consideration of Vitamin K intake, consistency of observed genotype frequencies with the Hardy-Weinberg equilibrium (defined as $p>0.05$), exclusion of critical patients (e.g. patients with overt liver or renal disease, malignant disease, hospitalization within the earlier 4 weeks, congestive heart failure, thyroid disease or chronic gastrointestinal conditions), stable anticoagulation (defined as INR values within the therapeutic range occurring in three consecutive measurements or for a minimum period of three weeks), exclusion or consideration of medications potentially interacting with coumarin drugs.

Two investigators independently scored quality (ED, MM), and disagreements were resolved by consensus. In subgroup analyses, studies with a median scores <5 were compared against studies with median scores ≥5.

Statistical analysis

Two-stage analysis for the association between CYP4F2*3 polymorphism and stable coumarin dose

We calculated study-specific estimates, with 95% Confidence Intervals (CI), for the difference in log dose of coumarin for subjects with at least one *CYP4F2* T-allele (CT+TT) compared to wild-type (CC) subjects, according to a dominant model. Separate estimates for CT and TT genotypes were also calculated as a sensitivity analysis. These study-specific estimates were obtained by fitting general linear models with log dose of coumarin as the dependent variable and *CYP4F2*3* polymorphism as the independent variable. All the models were adjusted for available study-specific covariates, including: age, sex, race, BMI, smoking status, indication for coumarin treatment, INR target, concomitant drugs, *CYP2C9*2* and *3 polymorphisms, and *VKORC1* polymorphism.

Following the two-stage analysis approach,[1] we pooled study-specific estimates with random-effects models, using the DerSimonian and Laird method. We evaluated homogeneity among study-specific estimates by the

Q statistic and I^2, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.[2] We performed meta-regression analysis to assess the influence on Summary Estimates (SE) of different study features: type of drugs (acenocoumarol/warfarin), sex, ethnicity (Whites/Asians/Blacks/Others), INR target (<2.5/2.5/>2.5), current smoking status, study adjustment for concomitant drugs (yes/no), deviation from Hardy-Weinberg (HW) equilibrium, quality score (<5/≥5), *CYP2C9*2/*3* (wild-type/any polymorphism) and *VKORC1* (wild-type/any polymorphism). When significant differences according to specific study factors were suggested by meta-regression, stratified analyses were performed for *CYP4F2*3*-coumarin dose association on subgroups of significant factors.

We assessed possible participation bias by drawing funnel plots and by Egger's test.[3]

P-values <0.05 were considered statistically significant for all the tests apart from the Q statistic, where p-values<0.10 were considered statistically significant. The analysis was carried out using the SAS (version 9.4) and STATA (version 13) software.

Stable coumarin dose predictive model

Due to significant differences in coumarin dose and *CYP4F2*3* association for different drugs and ethnic groups, the individual data analysis on the pooled dataset was always reported for each type of drug (acenocoumarol/warfarin) and for each ethnic group.

For each ethnic and drug subgroup, we randomly chose 2/3 of patients as the "derivation cohort" for developing dose-prediction models, while the remaining 1/3 of the patients constituted the "validation cohort," which was used for testing the final selected model. In order to keep a large sample size for prediction model construction, we included covariates which were available in the majority of studies (Table 1): age, BMI, sex, indication for treatment, *CYP4F2*3*, *CYP2C9*2, *3* and **5* (for Blacks), and *VKORC1* polymorphisms, by using general linear models with log dose of coumarin as dependent variable. To use an additive genetic model, we coded the number of variant alleles at each locus as 0, 1, or 2. Sensitivity analyses were also conducted on the whole cohort of subjects by including further available covariates collected in a smaller number of studies (concomitant drugs, especially amiodarone, and smoking status), to assess their role in stable coumarin dose prediction. The coefficient of determination (R^2) was calculated both for the main prediction model on the "derivation cohort" and for models included in sensitivity

analyses. We applied the scores obtained from the main prediction model to the validation data set and also calculated the R^2 .

For the sake of comparison, we also applied scores obtained from two previously published models for warfarin dose prediction[4,5] to our validation cohort and converted the scores to units of mg/week. In order to correctly compare our proposed model with each of the two previously published models, R^2 was calculated on the subset of subjects for whom both scores could be calculated on the basis of available data. In order to assess the importance of *CYP4F2*3* on warfarin dose prediction in our data, we also compared dose predictions from our pharmacogenetic model including *CYP4F2*3* in the whole dataset with that from our model excluding *CYP4F2*3* by using the adjusted R^2 as defined by Darlington.[6]

Gene-gene and gene-drug interactions were investigated by adding an interaction term to the main prediction model fitted on the whole cohort of subjects (for each drug/ethnicity subgroup), in order to have the largest sample size to test for interaction. Moreover, we performed subgroup analyses according to the use or not of specific concomitant drugs, to evaluate whether the change in coumarin dose associated with specific gene polymorphisms were modified by concomitant drugs.

P-values <0.05 were considered statistically significant. The analyses were carried out using SAS (version 9.4) software.

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