Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon

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Methods

Inclusion and exclusion criteria

Inclusion criteria were diagnosed with atrial fibrillation or venous thromboembolism initiating acenocoumarol or phenprocoumon treatment for at least 12 weeks, target INR in low intensity range (2-3 in Greece and 2.5-3.5 in The Netherlands), age ≥ 18 years and ability to attend the scheduled visits. Exclusion criteria were presence of a mechanical heart valve, severe cognitive impairment, known *CYP2C9* or *VKORC1* genotype at the start of the study, previous treatment with any coumarin anticoagulant, pregnancy or lactation or non-eligibility according to the treating physician.

Recruitment

Patients were recruited at the department of Cardiology and the department of Internal medicine of the Democritus University of Thrace in Alexandroupolis, Greece, the Cardiology department of the Onassis Cardiac Surgery Center in Athens, Greece and at four anticoagulant clinics in The Netherlands (Atal-Medical Diagnostics Center in Amsterdam, Medial Diagnostics centre in Hoofddorp, Anticoagulant Clinic The Hague and Anticoagulant Clinic Leiden) from November 2010 to March 2013.

Treatment

The PGx group received a dose according to a genotype-guided algorithm for the first 3 days. In some cases, it was not possible to dose the patient according to the dose algorithm from day one on. The patient then received a standard dose on day 1 and the dose on day 2 and 3 was adjusted according to the dosage that the patient had already received at day 1. The standard dose on day one was determined by the physician who decided to start the treatment and this dose is normally 6mg acenocoumarol and 3 or 4 mg phenprocoumon. After 3 days, the patients received a

maintenance dose according to the genotype-guided dose revision algorithm. The control group was dosed according to a non-genotype-guided loading dose algorithm for the first 3 days. On day 4 or 5 (with possible exceptions due to weekends or bank holidays) doses were adjusted according to the genotype-guided or non-genotype-guided algorithm and first INR value. The dose algorithms included *VKORC1* and *CYP2C9* genotype (intervention arm only), age, sex, height, weight and amiodarone use. The development of these algorithms has been described elsewhere[1]. After the first two visits, the dose was adjusted according to the INR results using local clinical procedures. The coumarin treatment of patients with atrial fibrillation and patients with venous thromboembolism did not differ, as the same algorithm was used. However, patients with venous thromboembolism often also received a low molecular weight heparin until a therapeutic INR was reached. The heparin was prescribed by the physician who decided to initiate the coumarin treatment.

The type of coumarin administered was dependent on the type routinely used by the recruiting centre (acenocoumarol in all three centres in Greece and in Amsterdam (The Netherlands), phenprocoumon in Leiden (The Netherlands) and both coumarin anticoagulants in The Hague (The Netherlands) and Hoofddorp (The Netherlands)) depending on the experience of the prescribing physician. A validated rapid point of care test (POCT) was used to genotype *VKORC1* -1639G>A (rs9923231) and *CYP2C9* *2 (rs1799853) and *3 (rs1057910) [2]. For quality assurance, the first 10 blood samples of each centre and a further 10% of all samples were spotted onto classic FTA cards and sent to LGC for genotyping using the HyBeacon®assay on the Lighttyper. Although the target range in The Netherlands is normally 2.5-3.5 for patients with atrial fibrillation or venous thromboembolism, all patients were treated with a target range of 2.0-3.0 for the purpose of this trial.

Secondary endpoints

Secondary endpoints were time to and number of patients with INR≥4, percentage time spent with an INR≥4 or with an INR<2, time to reach therapeutic INR, time to reach stable dose, time to and number of minor and major bleeding events, time to and number of thromboembolic events and incidence of coumarin sensitivity and resistance. Because of the low number of patients (<50%) with ≥4, stable dose, bleeding events and thromboembolic events, we were not able to calculate the median time to event for these endpoints. A therapeutic INR was defined as the first INR within target range, providing that a subsequent INR ≥1 week later is also within target range. A stable dose was defined as INR within target range for a period of at least 3 weeks with at least three consecutive INR measurements within target range and <10% change in dose. A stable dose of ≤1.0 mg acenocoumarol or ≤1.5 mg phenprocoumon indicated coumarin sensitivity, while a dose of ≥8 mg acenocoumarol or ≥6 mg phenprocoumon indicated coumarin resistance. More definitions are described below. Because in earlier observational studies the difference in time in therapeutic range between different genotypes was only seen in the first month [3,4], we were also interested in the effect of genotyping on the percentage time in range in the first month only. We therefore also analysed the percentage time in range in the first 4 weeks, week 5-8 and week 9-12, separately.

Dose algorithms

Phenprocoumon

Loading dose algoritm

Loading doses for phenprocoumon as derived from the individual maintenance dose.‡

Dose day 1 (mg)	Dose day 2 (mg)	Dose day 3 (mg)	Maintenance Dose range (mg per day)
3	3	3	<1.04
6	3	3	1.04-1.31
6	6	3	1.31-1.61
6	6	6	1.61-1.85
9	6	6	1.85-2.92
9	9	6	>2.92*

‡ The lower limit of the maintenance dose range corresponds with the given loading dose, e.g. a loading regimen of 6-3-3 leads to a monitoring dose of 1.04 mg/day.
* Only for genotype-guided algorithm

Maintenance dose algorithm

Algorithms for phenprocoumon.‡

	Genotype- guided	Non-genotype-guided	Univariate R^2 (%) on the sqrt(dose)
Intercept	2.874	1.652	
CYP2C9 genotype			4.6
*1/*1	0#	-	
*1/*2	-0.259	-	
*1/*3	-0.342	-	
*2/*2	-0.447	-	
*2/*3	-0.684	-	
*3/*3	-0.681	-	
VKORC1 genotype			34.1
CC	0#	-	
CT	-0.601	-	
TT	-1.394	-	
Age, in years	-0.015	-0.011	8.1
Sex, if female	0.026	0.105	2.1
Height, in cm	0.011	0.011	7.3
Weight, in kg	0.008	0.013	12.8
Amiodarone use, if yes	-0.345	-0.343	0.5
Unadjusted R^2 of the algorithm	55.9%	17.3%	

‡ The outcome is the square root of the mean first stable maintenance dose in mg/week for the INR target range 2.0-3.5. If the target range 2.0-3.0 is used, all coefficients need to be divided by sqrt(1.07).
# The value of this parameter is zero because it is the reference group.

Note: The formula for, for example, the genotype-guided algorithm of phenprocoumon should be read as: Square root mean maintenance dose (mg/week)= 2.874 – 0 (if CYP2C9*1/*1) – 0.259 (if CYP2C9*1/*2) – 0.342 (if CYP2C9*1/*3) – 0.447 (if CYP2C9*2/*2) – 0.684 (if CYP2C9*2/*3) – 0.681 (if CYP2C9*3/*3) – 0 (if VKORC1 CC) – 0.601 (if VKORC1 CT) – 1.394 (if VKORC1 TT) – 0.0153 * age (years) + 0.026 (if female) + 0.0113 * height (cm) + 0.0085 * weight (kg) – 0.345 (if amiodarone is used).

Dose revision algoritms

Dose revision algorithms day 3

Dose revision for genotype-guided dosing algorithm after INR measurement on day 3:

INR day 3	**Correction factor**	**n**
<1.2	1.12	23
1.2-1.6	1 (actually 0.95)	40
>1.6	0.85	12

In addition, patients with an INR of >2.2 do not receive a dose on the day of the measurement.

Dose revision for non-genotype-guided dosing algorithm after INR measurement on day 3:

INR day 3	**Correction factor**	**n**
<1.2	1.32	26
1.2-1.6	1 (actually 1.03)	47
>1.6	0.65	28

In addition, patients with an INR of >2.2 do not receive a dose on the day of the measurement.

Dose revision algorithms day 4

Dose revision for genotype-guided dosing algorithm after INR measurement on day 4:

INR day 4	**Correction factor**	**n**
<1.3	1.13	30
1.3-2.3	1 (actually 0.96)	120
>2.3	0.78	15

In addition, patients with an INR of >2.8 do not receive a dose on the day of the measurement.

Dose revision for non-genotype-guided dosing algorithm after INR measurement on day 4:

INR day 4	**Correction factor**	**n**
<1.3	1.25	37
1.3-2.3	1 (actually 1.00)	138
>2.3	0.63	30

In addition, patients with an INR of >2.8 do not receive a dose on the day of the measurement.

Dose revision algorithms day 5

Dose revision for genotype-guided dosing algorithm after INR measurement on day 5:

INR day 5	**Correction factor**	**n**
<1.5	1.11	13
1.5-2.5	1 (actually 0.97)	21
>2.5	0.87	3

In addition, patients with an INR of >3.0 do not receive a dose on the day of the measurement.

Dose revision for non-genotype-guided dosing algorithm after INR measurement on day 5:

INR day 5	**Correction factor**	**n**
<1.5	1.31	16
1.5-2.5	1 (actually 0.92)	22
>2.5	0.75	7

In addition, patients with an INR of >3.0 do not receive a dose on the day of the measurement.

Note: We will always prescribe a loading dose for 3 days. So for patients who have an INR measurement on day 3 will finish the loading dose before adjustment of the dose on day 4. If the INR is to low on day 3 (<1.2) or 4 (<1.3) we will continue loading:

- First predicted maintenance dose (MD) between 0.75 and 0.85 tablets/day: 2 tablets on day 4 and 1 tablet on day 5. From day 6 on: MD*correction factor.
- First predicted MD >0.85 tablets/day: 2 tablets on day 4 and 2 on day 5. From day 6 on: MD*correction factor.

For patients with a too low INR on day 5 (INR<1.5):

- On day 4: prescribed dose according to calendar (MD: 0.75-1 → 1 tablet, MD: 1.05-1.5 → 1.5 tablet, ect) and on day 5: 2 tablets. From day 6 on: MD*correction factor.

Acenocoumarol

Loading dose algoritm

Loading doses for acenocoumarol as derived from the individual maintenance dose. ‡

Dose day 1 (mg)	Dose day 2 (mg)	Dose day 3 (mg)	Maintenance dose range (mg per day)
1	1	1	<1.00
2	1	1	1.00-1.25
2	2	1	1.25-1.75
2	2	2	1.75-2.00
3	2	2	2.00-2.25
3	3	2	2.25-2.75
3	3	3	2.75-3.00
4	3	3	3.00-3.25
4	4	3	3.25-3.75
4	4	4	3.75-4.00
5	4	4	4.00-4.25
5	5	4	4.25-4.75
5	5	5	4.75-5.00

‡ The lower limit of the maintenance dose range corresponds with the given loading dose.

Maintenance dose algorithm

Algorithms for acenocoumarol.‡

	Genotype- guided	Non-genotype-guided	Univariate R^2 (%) on the sqrt(dose)
Intercept	4.117	2.635	
CYP2C9 genotype			4.5
*1/*1	0#	-	
*1/*2	-0.093	-	
*1/*3	-0.519	-	
*2/*2	-0.435	-	
*2/*3	-0.466	-	
*3/*3	-1.375	-	
VKORC1 genotype			27.2
CC	0#	-	
CT	-0.572	-	
TT	-1.267	-	
Age, in years	-0.027	-0.027	14.1
Sex, if female	0.271	0.386	0.2
Height, in cm	0.009	0.013	6.3
Weight, in kg	0.010	0.013	11.8
Amiodarone use, if yes	-0.377	-0.167	0.2
Unadjusted R^2 of the algorithm	52.6%	23.7%	

‡ The outcome is the square root of the mean first stable maintenance dose in mg/week for the INR target range 2.0-3.5. If the target range 2.0-3.0 is used, all coefficients need to be divided by sqrt(1.07).

[#] The value of this parameter is zero because it is the reference group.

Dose revision algoritms

No distinguish will be made between the correction factors after INR measurement on day 3, 4 or 5, due to the short half-life of ACE.

The correction factors for the genotype-guided dosing arm after INR measurement on day 3, 4 and 5 are as follow:

INR	**Correction factor**	**n**
<1.5	1.1 (actually 1.01)	4
1.5-2.5	1.00	42
2.5-3.0	0.91	24
>3.0	0.76	42

The correction factors for the non-genotype-guided dosing arm after INR measurement on day 3, 4 and 5 are as follow:

INR	**Correction factor**	**n**
<1.5	1.42	6
1.5-2.5	1.00 (actually 1.04)	59
2.5-3.0	0.89	27
>3.0	0.69	58

Definitions

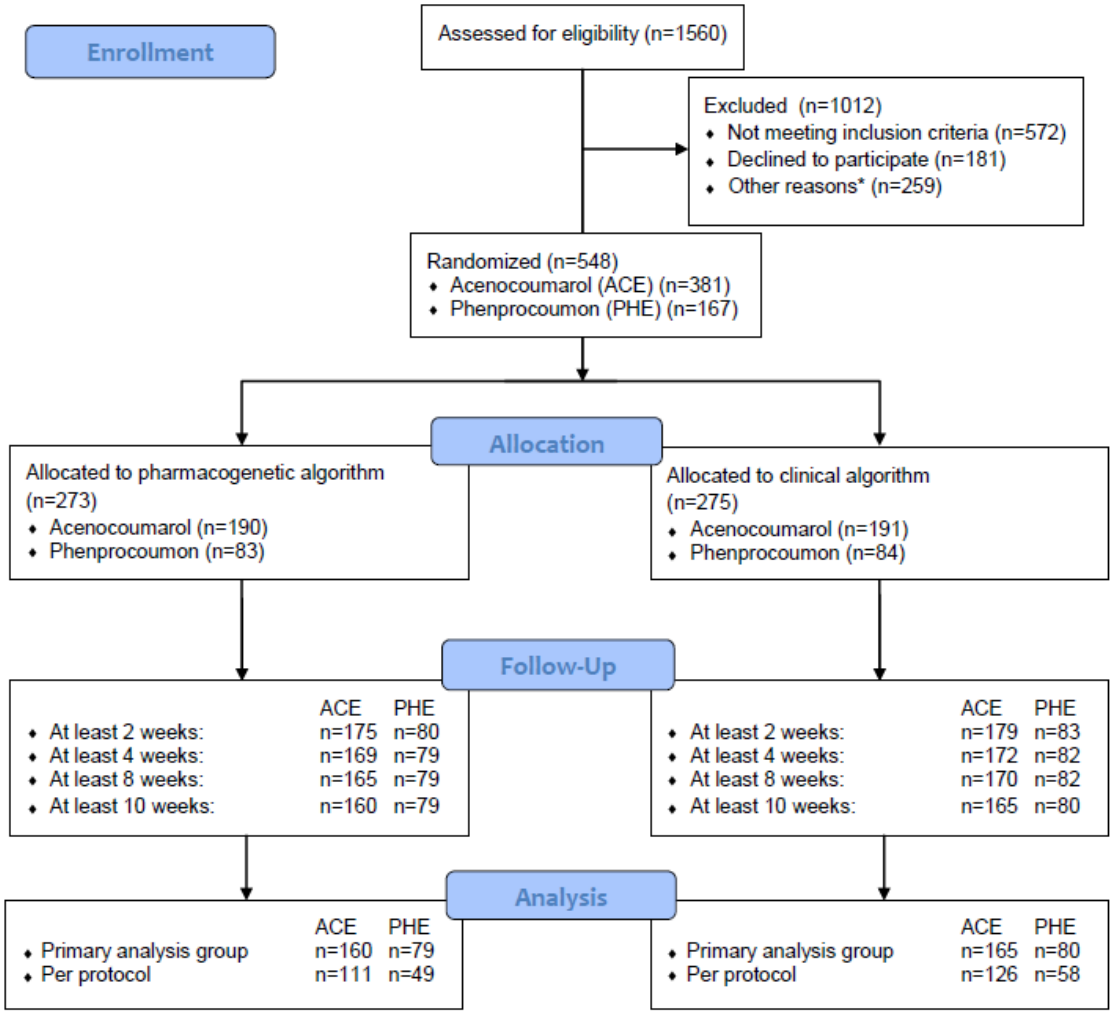
- *Therapeutic INR*: first INR within target range, provided that a subsequent INR ≥1 week later is also within target range
- *Stable dose*: the dose a patient used when the INR was within target range for a period of at least 3 weeks with at least three consecutive INR measurements within the target range and <10% change in dose
- *Acenocoumarol sensitivity*: ≤1mg acenocoumarol/day at stable dose within the therapeutic range. Patients using enzyme inhibitors are excluded from the sensitive group
- *Phenprocoumon sensitivity*: ≤1.5mg phenprocoumon/day at stable dose within the therapeutic range. Patients using enzyme inhibitors are excluded from the sensitive group
- *Acenocoumarol resistance:* ≥8mg acenocoumarol/day at stable dose within the therapeutic range. Patients using enzyme inducers are excluded from the sensitive group
- *Phenprocoumon resistance:* ≥6mg phenprocoumon /day at stable dose within the therapeutic range. Patients using enzyme inducers are excluded from the sensitive group
- *Enzyme inhibitors:* Amiodarone, Omeprazole, Simvastatin, Fluoxetine
- *Enzyme inducers:* Carbamazepine, Phenytoin, Phenobarbitone, Rifampicin
- *Adverse event (AE):* An AE is any untoward medical occurrence that does not necessarily have a causal relationship with the coumarin anticoagulant. An AE can be any unfavourable, unintended clinical sign, symptom, medical complaint or clinically relevant change in laboratory variables or clinical tests. Accidents, operations (not pre-planned), changes in medication or deterioration in concurrent illness are also considered as AEs
- *Serious adverse event (SAE):* A serious AE is any untoward medical occurrence that at any dose:
    - results in death
    - is life-threatening
    - requires inpatient hospitalisation or prolongation of existing hospitalization

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- any other relevant medical event, e.g. major bleeding

- *Major bleeding:* A bleeding that meets at least one of the following criteria*:*
  - A clinically overt bleeding associated with a drop in haemoglobin of ≥20g/l
  - A clinically overt blood loss needing transfusion of ≥2 units of whole blood or erythrocytes
  - Bleeding involving critical anatomical sites: intracranial, intraspinal, intramuscular with compartment syndrome, intraocular, retroperitoneal, pericardial, and atraumatic intra-articular bleeding.
  - Fatal bleeding
- *Minor bleeding:* All bleeding that does not fulfill the above criteria, including bleeding causing treatment cessation

Figures

Figure S1: Study enrolment flow chart.



* Other reasons for trial exclusion included not being able to contact the patient or not being able to make an appointment with the patient due to logistic reasons.

Tables

Table S1: Protocol violations and numbers of patients excluded from the per-protocol analyses.

	Genotype-guided Group	Control Group	All Patients
Error made with algorithm or genotype not available	21	4	25
Physician changed dose or patient did not take drug as prescribed after first 2 visits	34	31	65
No INR available on days 3 to 5 to calculate a revised dose	47	39	86
Target INR range changed during the study	1	5	6
Patient took more than one dose before starting on loading dose according to the algorithm	1	0	1
Total (some patients had 2 or more violations)	79	61	140

Table S2: Baseline characteristics of the randomized patients , including country data.

	Acenocoumarol						**Phenprocoumon**	
	Combined		Greece		The Netherlands		The Netherlands	
	PGx	Control	PGx	Control	PGx	Control	PGx	Control
n	**190**	**191**	**104**	**103**	**86**	**88**	**83**	**84**
Age, mean (SD)	68 (14)	68 (13)	72 (11)	72 (12)	63 (15)	64 (14)	67 (11)	67 (11)
Sex, male, n (%)	121 (64%)	107 (56%)	63 (61%)	61 (59%)	58 (67%)	46 (52%)	51 (61%)	47 (56%)
Ethnicity, white, n (%)*	184 (97%)	189 (99%)	103 (99%)	103 (100%)	81 (94%)	86 (98%)	79 (95%)	81 (96%)
Indication, AF, n (%)	158 (83%)	158 (83%)	95 (91%)	93 (90%)	63 (73%)	65 (74%)	68 (82%)	70 (83%)
Height, mean (SD) (cm)	172 (11)	171 (11)	168 (9)	167 (9)	176 (11)	175 (11)	174 (9)	173 (10)
Weight, mean (SD) (kg)	84 (15)	82 (18)	82 (13)	79 (16)	85 (18)	85 (20)	87 (17)	83 (16)
CYP2C9, n (%)	missing: 0	4 (2%)	0	2 (2%)	0	2 (2%)	0	3 (4%)
*1*1	111 (58%)	107 (57%)	57 (55%)	54 (54%)	54 (63%)	53 (62%)	55 (66%)	57 (70%)
*1*2	39 (21%)	33 (18%)	20 (19%)	18 (18%)	19 (22%)	15 (17%)	14 (17%)	14 (17%)
*1*3	29 (15%)	32 (17%)	17 (16%)	21 (21%)	12 (14%)	11 (13%)	11 (13%)	7 (9%)
*2*2	4 (2%)	11 (6%)	3 (3%)	5 (5%)	1 (1%)	6 (7%)	2 (2%)	2 (3%)
*2*3	5 (3%)	4 (2%)	5 (5%)	3 (3%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
*3*3	2 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
HWE, p-value	0.37	0.002	0.76	0.11	0.42	0.02	0.66	0.77
VKORC1, n (%)	missing:0	4 (2%)	0	2 (2%)	0	2 (2%)	0	3 (4%)
GG	70 (37%)	55 (29%)	31 (30%)	19 (19%)	39 (45%)	36 (42%)	24 (29%)	33 (41%)
GA	84 (44%)	93 (50%)	51 (49%)	57 (56%)	33 (38%)	36 (42%)	40 (48%)	33 (41%)
AA	36 (19%)	39 (20%)	22 (21%)	25 (25%)	14 (16%)	14 (16%)	19 (23%)	15 (19%)
HWE, p-value	0.23	0.97	0.90	0.18	0.13	0.33	0.77	0.20
Amiodarone use, n (%)	22 (12%)	23 (12%)	22 (21%)	23 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

No statistically significant ($p<0.05$) differences in baseline characteristics were found

HWE=Hardy-Weinberg equilibrium, *Determined by questionnaire filled in by the patient

Table S3: Sensitivity analysis of the primary outcome Percentage time in therapeutic INR-range during 12 weeks following initiation – patients with at least 2 weeks of follow-up

	PGx, mean % (SD) N = 255	Control, mean % (SD) N = 262	Difference, % (95% CI)	p-value
Acenocoumarol				
Greece	61.12 (27.1)	62.7 (23.9)	-1.53 (-8.93-5.87)	0.68
The Netherlands	61.11 (22.6)	58.04 (22.6)	3.07 (-3.79-9.94)	0.38
Combined	61.12 (24.9)	60.47 (23.4)	0.65 (-4.40-5.70)	0.79
Phenprocoumon				
The Netherlands	59.39 (21.8)	56.89 (23.3)	2.50 (-4.49-9.49)	0.48
Acenocoumarol + Phenprocoumon	60.58 (24.0)	59.36 (23.4)	1.24 (-2.85-5.33)	0.55

Table S4: Secondary outcomes for Acenocoumarol in Greece and The Netherlands separately

	Greece			The Netherlands		
Outcome	PGx	Control	p-value	PGx	Control	p-value
N	80	85		80	80	
PTIR weeks 1-4	54.71	52.47	0.57	54.29	48.17	0.14
PTIR weeks 5-8	66.39	67.92	0.92	65.64	58.33	0.17
PTIR weeks 9-12	67.12	73.30	0.28	64.86	68.44	0.51
Percentage of patients with INR≥4	28.8	32.9	0.56	37.5	33.8	0.62
Percentage time spent INR≥4	1.86	1.81	0.95	3.76	3.66	0.94
Percentage time spent INR<2	26.65	21.12	0.10	18.06	18.41	0.91
Percentage of patients with stable dose	37.5	43.5	0.43	50.0	55.0	0.53
Incidence of coumarin sensitivity, %	4.2	9.8	0.26	1.8	0	0.32
Incidence of coumarin resistance, %	0	0	-	0	0	-
Number of INR measurements	9.54	9.79	0.53	11.66	11.73	0.85
Absolute difference between calculated versus achieved stable dose	0.47	0.77	0.01	0.48	0.50	0.84
Safety						
Incidence rate of Adverse Events (AE) per person month	0.40	0.34	0.74	2.37	1.71	0.13
Incidence rate of Serious Adverse Events (SAE) per person month	0.07	0.05	0.68	0.06	0.06	0.97
Incidence rate of bleeding events per person month	0.01	0.03	0.43	0.86	0.80	0.63
Incidence rate of thromboembolic events, per person month	0.00	0.02	0.20	0.05	0.02	0.49

Table S5: Baseline characteristics of the patients included in the per protocol analysis

	Acenocoumarol						**Phenprocoumon**	
	Combined		Greece		The Netherlands		The Netherlands	
	PGx	Control	PGx	Control	PGx	Control	PGx	Control
n	**128**	**140**	**78**	**87**	**50**	**53**	**51**	**59**
Age, mean (SD)	69 (14)	70 (12)	73 (10)	72 (10)	62 (16)	67 (13)	68 (10)	66 (10)
Sex, male, n (%)	84 (66%)	82 (59%)	49 (63%)	53 (61%)	35 (70%)	29 (55%)	29 (57%)	34 (58%)
Ethnicity, white, n (%)	123 (96%)	140 (100%)	77 (99%)	87 (100%)	46 (92%)	53 (100%)	48 (94%)	59 (100%)
Indication, AF, n (%)	104 (81%)	122 (87%)	70 (90%)	79 (91%)	34 (68%)	43 (81%)	41 (80%)	48 (81%)
Height, mean (SD) (cm)	171 (11)	170 (10)	168 (9)	167 (9)	177 (11)	174 (11)	174 (9)	174 (10)
Weight, mean (SD) (kg)	83 (15)	82 (19)	84 (13)	80 (15)	83 (18)	86 (22)	87 (18)	83 (16)
CYP2C9, n (%)	missing: 0	2 (1%)	0	2 (2%)	0	0	0	1 (2%)
*1*1	74 (58%)	77 (56%)	44 (56%)	44 (52%)	30 (60%)	33 (62%)	33 (65%)	38 (66%)
*1*2	25 (20%)	24 (17%)	14 (18%)	16 (19%)	11 (22%)	8 (15%)	8 (16%)	11 (19%)
*1*3	19 (15%)	23 (17%)	11 (14%)	17 (20%)	8 (16%)	6 (11%)	7 (14%)	7 (12%)
*2*2	4 (3%)	10 (7%)	3 (4%)	5 (6%)	1 (2%)	5 (9%)	2 (4%)	2 (3%)
*2*3	5 (4%)	4 (3%)	5 (6%)	3 (4%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)
*3*3	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
VKORC1, n (%)	missing: 0	2 (1%)	0	2 (2%)	0	0	0	1 (2%)
GG	51 (40%)	37 (27%)	25 (32%)	14 (17%)	26 (52%)	23 (43%)	15 (29%)	23 (40%)
GA	53 (41%)	71 (51%)	37 (47%)	49 (58%)	16 (32%)	22 (42%)	27 (53%)	27 (47%)
AA	24 (19%)	30 (22%)	16 (21%)	22 (26%)	8 (16%)	8 (15%)	9 (18%)	8 (14%)
Amiodarone use, n (%)	18 (14%)	19 (14%)	18 (23%)	19 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table S6: Primary outcome Percentage time in therapeutic INR-range during 12 weeks following initiation – per protocol analysis

	PGx, mean % (SD) N = 160	Control, mean % (SD) N = 184	Difference, % (95% CI)	p-value
Acenocoumarol				
Greece	62.79 (26.5)	65.13 (24.0)	-2.34 (-10.78-6.09)	0.58
The Netherlands	68.01 (17.5)	60.50 (22.0)	7.52 (-0.55-15.59)	0.07
Combined	64.95 (23.2)	63.25 (23.2)	1.70 (-4.26-7.66)	0.58
Phenprocoumon				
The Netherlands	59.21 (19.6)	58.32 (23.1)	0.90 (-7.41-9.20)	0.83
Acenocoumarol + Phenprocoumon	63.20 (22.3)	61.70 (23.3)	1.50 (-3.35-6.35)	0.54

Table S7: Secondary outcomes for Acenocoumarol and Phenprocoumon – per protocol analysis

	Acenocoumarol			**Phenprocoumon**			**Acenocoumarol + Phenprocoumon**		
Outcome	PGx	Control	p-value	PGx	Control	p-value	PGx	Control	p-value
N	111	126		49	58		160	184	
PTIR weeks 1-4	56.07	52.35	0.26	47.94	42.19	0.23	53.68	49.22	0.11
PTIR weeks 5-8	70.17	65.35	0.28	60.75	60.49	0.97	67.35	63.84	0.34
PTIR weeks 9-12	68.50	72.15	0.43	68.94	72.72	0.57	68.63	72.33	0.33
Percentage of patients with INR≥4	28.8	29.4	0.93	26.5	29.3	0.75	28.1	29.3	0.80
Percentage time spent INR≥4	2.01	2.12	0.89	1.61	2.82	0.23	1.89	2.34	0.47
Percentage time spent INR<2	23.16	19.70	0.19	17.67	19.27	0.64	21.48	19.56	0.36
Percentage of patients with stable dose	45.9	50.0	0.53	63.3	65.5	0.81	51.2	54.9	0.50
Incidence of coumarin sensitivity, %	4.1	5.3	0.72	5.4	4.8	0.90	4.5	5.1	0.83
Incidence of coumarin resistance, %	0	0	-	0	0	-	0	0	-
Number of INR measurements	10.26	10.44	0.60	12.98	12.64	0.41	11.09	11.13	0.90
Absolute difference between calculated versus achieved stable dose	0.49	0.65	0.09	0.44	0.58	0.31	0.47	0.63	0.05
Safety									
Incidence rate of Adverse Events (AE) per person month	1.35	0.83	0.11	1.25	1.02	0.23	1.32	0.88	0.07
Incidence rate of Serious Adverse Events (SAE) per	0.09	0.06	0.55	0.20	0.02	0.16	0.12	0.05	0.16

person month									
Incidence rate of bleeding events per person month	0.36	0.34	0.78	0.30	0.40	0.21	0.35	0.36	0.84
Incidence rate of thromboembolic events, per person month	0.04	0.02	0.57	0.02	0	0.19	0.03	0.01	0.40

Table S8: Secondary outcomes for Acenocoumarol in Greece and The Netherlands separately – per protocol analysis

	Greece			The Netherlands		
Outcome	PGx	Control	p-value	PGx	Control	p-value
N	65	75		46	51	
PTIR weeks 1-4	55.55	54.76	0.86	56.85	48.74	0.11
PTIR weeks 5-8	65.92	69.05	0.61	76.54	59.87	0.009
PTIR weeks 9-12	67.33	72.11	0.44	70.14	72.19	0.76
Percentage of patients with INR≥4	24.6	29.3	0.53	34.8	29.4	0.57
Percentage time spent INR≥4	1.80	1.59	0.83	2.31	2.91	0.64
Percentage time spent INR<2	26.91	21.07	0.12	17.86	17.67	0.96
Percentage of patients with stable dose	38.5	44.0	0.51	56.5	58.8	0.49
Incidence of coumarin sensitivity, %	5.3	8.9	0.51	2.9	0	0.29
Incidence of coumarin resistance, %	0	0	-	0	0	-
Number of INR measurements	9.48	9.60	0.77	11.37	11.67	0.50
Absolute difference between calculated versus achieved stable dose	0.41	0.73	0.009	0.57	0.57	0.99
Safety						
Incidence rate of Adverse Events (AE) per person month	0.38	0.23	0.42	2.86	1.80	0.14
Incidence rate of Serious Adverse Events (SAE) per person month	0.08	0.04	0.51	0.09	0.07	0.86
Incidence rate of bleeding events per person month	0.01	0.04	0.49	0.91	0.85	0.67
Incidence rate of thromboembolic events, per person month	0.005	0.01	0.47	0.08	0.03	0.48

Table S9: Details of adverse events

	PGx (n=273)		Control (n=275)	
	Events, n	Participants, n (%)	Events, n	Participants, n (%)
Bleeding				
Minor	267	114 (42%)	265	121 (44%)
Haematoma or bruise (any site)	230	105 (38%)	233	111 (40%)
Bleeding gums	3	3 (1%)	0	0 (0%)
Colonic or rectal bleeding	9	9 (3%)	1	1 (0.4%)
Vaginal bleeding	2	1 (0.4%)	7	5 (2%)
Haematuria	4	2 (0.7%)	1	1 (0.4%)
Epistaxis	13	12 (4%)	14	13 (5%)
Ocular bleeding	3	3 (1%)	3	3 (1%)
Other/unspecified bleeding	3	3 (1%)	6	6 (2%)
Major - Gastrointestinal bleeding	0	0 (0%)	1	1 (0.4%)
Thromboembolism				
Minor	2	2 (0.7%)	1	1 (0.4%)
Major	4	3 (1%)	5	3 (1%)
Any adverse event	691	177 (65%)	666	175 (64%)
Any serious adverse event	21	18 (7%)	23	18 (7%)

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