EUropean Pharmacogenetics of AntiCoagulant Therapy trial

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To determine whether a dosing algorithm containing genetic information increases the time within therapeutic INR range during anticoagulation therapy with phenprocoumon compared to a dosing regimen that does not contain this genetic information....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON32884

Source
ToetsingOnline

Brief title
EU-PACT trial

Condition

- Cardiac arrhythmias
- Embolism and thrombosis

Synonym
atrial fibrillation, Thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Utrecht
Source(s) of monetary or material Support: European Community's Seventh Framework Programme;grant agreement number: HEALTH-F2-2009-223062

Intervention

Keyword: Coumarins, Dosing algorithm, Pharmacogenetics, Phenprocoumon

Outcome measures

Primary outcome

The % time within therapeutic INR range in the first 3 months of anticoagulation therapy.

Secondary outcome

1. Time to and the number of patients with INR above 4.0, which indicates over-anticoagulation.

2. Percent time spent above INR 4.0.

3. Percent time spent below INR 1.5, which indicates under-anticoagulation.

4. Time to reach therapeutic INR defined as the time to the first INR within target range, providing that a subsequent INR more than 1 week later is also within target range.

5. Time to reach stable dose defined as INR within target range for a period of at least 3 weeks with <10% change in dose.

6. Time to and number of minor and major bleeding events.

7. Time to and number of thromboembolic events (therapeutic failure).

8. The incidence of sensitivity defined as less than 1.5 mg phenprocoumon/day at stable dose within the therapeutic range. Patients who are on enzyme inhibitors will be excluded from the sensitive group.

9. The incidence of resistance defined as more than 6 phenprocoumon mg/day at stable dose within the therapeutic range. Patients who are on enzyme inducers will be excluded from the resistant group.

10. Number of coumarin dose adjustments.

11. The clinical utility of the rapid genotyping test developed by LGC.

12. Quality of life as reported by the patient tested by the EuroQol (EQ)-5D questionnaire.

13. The cost-effectiveness of genotype-guided dosing for each coumarin compared with non-genotype-guided dosing.

Study description

Background summary

The narrow therapeutic range and wide inter-patient variability in dose requirement make anticoagulation response to coumarin derivatives difficult to predict. As a result, patients require frequent monitoring to avert adverse effects and maintain therapeutic efficacy. Polymorphisms in cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex 1 (VKORC1) jointly account for about 40% of the inter-individual variability in dose requirements. To date, several pharmacogenetic-guided dosing algorithms for coumarin derivatives, predominately for warfarin, have been developed. However, the potential benefit of these dosing algorithms in terms of their safety and clinical utility has not been adequately investigated in randomized settings.

Study objective

To determine whether a dosing algorithm containing genetic information increases the time within therapeutic INR range during anticoagulation therapy with phenprocoumon compared to a dosing regimen that does not contain this genetic information. Secondary research-questions of the study include the cost effectiveness, number of thromboembolic and bleeding events, time to reach stable dose and number of supratherapeutic INR peaks.

Study design

This is consist of a two-armed, single-blinded, randomised controlled trial. In the intervention arm patients commencing anticoagulation therapy with phenprocoumon will be dosed according to a drug-specific genotype-guided dosing algorithm, which is based on genetic information, clinical data and (in the monitoring phase) previous INR. In the control arm patients will be dosed according to a non-genotype-guided dosing regimen which does not include

genetic information. The follow-up period per patient is 3 months.

Intervention

Patients will be dosed according to a newly developed dosing algorithm.

Study burden and risks

Burden: 7 extra blood samples (33mL) are taken from each participant at the start of the study, and 3 (15mL) at visit 8. Patients also have to attend 8 scheduled visits within the 3 months study period and are asked to fill in questionnaires before 6 visits (total time: 90 minutes).
Risks: As well the newly developed genotype-guided dosing algorithm as the newly developed nongenotype-guided dosing algorithm are anticipated to improve the accuracy of coumarin dosing and thus improve the safety (less bleedings) and efficacy (more time spent in INR range) of anticoagulation therapy.

Contacts

Public
Universiteit Utrecht

Sorbonnelaan 16, PO box 80082
3508 TB Utrecht
NL
Scientific
Universiteit Utrecht

Sorbonnelaan 16, PO box 80082
3508 TB Utrecht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients with either venous thromboembolism (VTE) or atrial fibrillation (AF) requiring treatment with phenprocoumon for at least 12 weeks and a target INR in the low intensity range (INR range 2-3 in the United Kingdom, Sweden, Germany, Austria, Greece and Spain and INR 2.5-3.5 in the Netherlands)
2. Age >= 18 years
3. Ability to attend scheduled visits
4. Signed informed consent

Exclusion criteria

1. Abnormal clotting function at baseline (at least one of):
a. INR >1.5
b. platelet count <100 x 10^9 per Liter blood
c. prolonged APTT >1.3 times the upper reference value that is not explained by presence of lupus anticoagulants
2. Presence of a mechanical heart valve
3. Severe cognitive impairment
4. Known genotype CYP2C9 or VKORC1 at start of the study
5. Previous or current treatment with any coumarin
6. Pregnancy or lactation
7. Non-eligible subject, e.g. fysical or mental health problems.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-10-2010
Enrollment:	610
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Acenocoumarol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-03-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-03-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-016994-13-NL
CCMO	NL29816.058.09