A Randomized Trial Comparing Genotype-Guided Dosing of Warfarin to Standard Dosing: The EU Pharmacogenetics of Anticoagulant Therapy (EU-PACT) Warfarin Study

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on behalf of the EU-PACT Warfarin Trial Investigators

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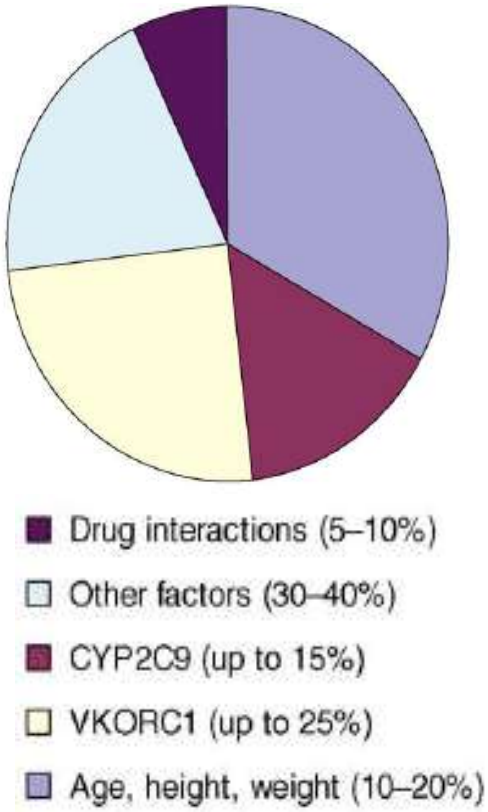
Warfarin

- Number of users:

  1-1.5% of population

- Dose (mg) range per day:

  0.5-20



McLeod and Jonas, 2009

FDA Label Changes (2007, 2010)

Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

CHEST 2012; 141(2)(Suppl):e152S–e184S

EU-PACT Warfarin RCT

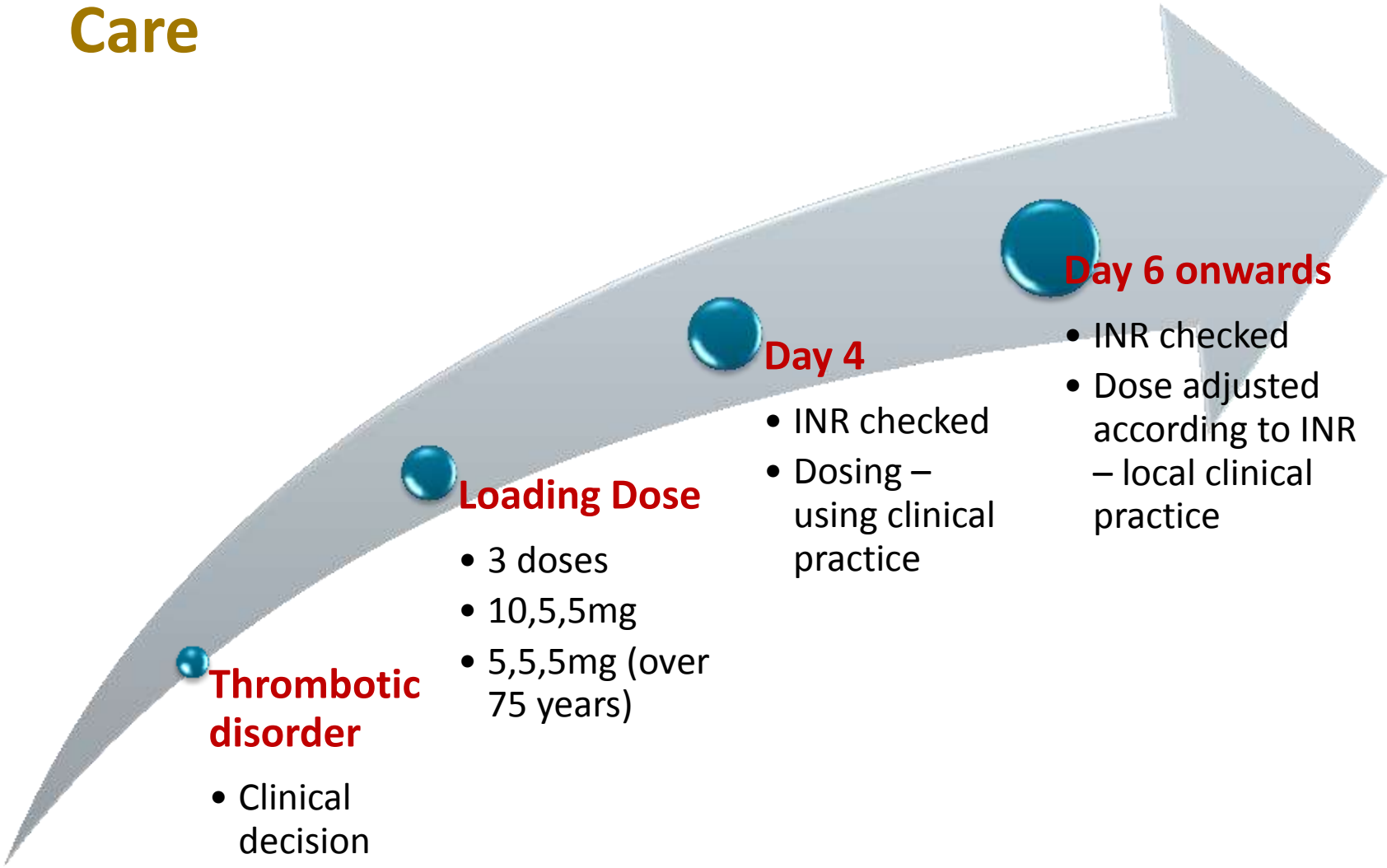
AIM

- To determine whether genotype-guided dosing of warfarin was superior to standard clinical care over 3 months in patients with AF or VTE previously naïve to warfarin

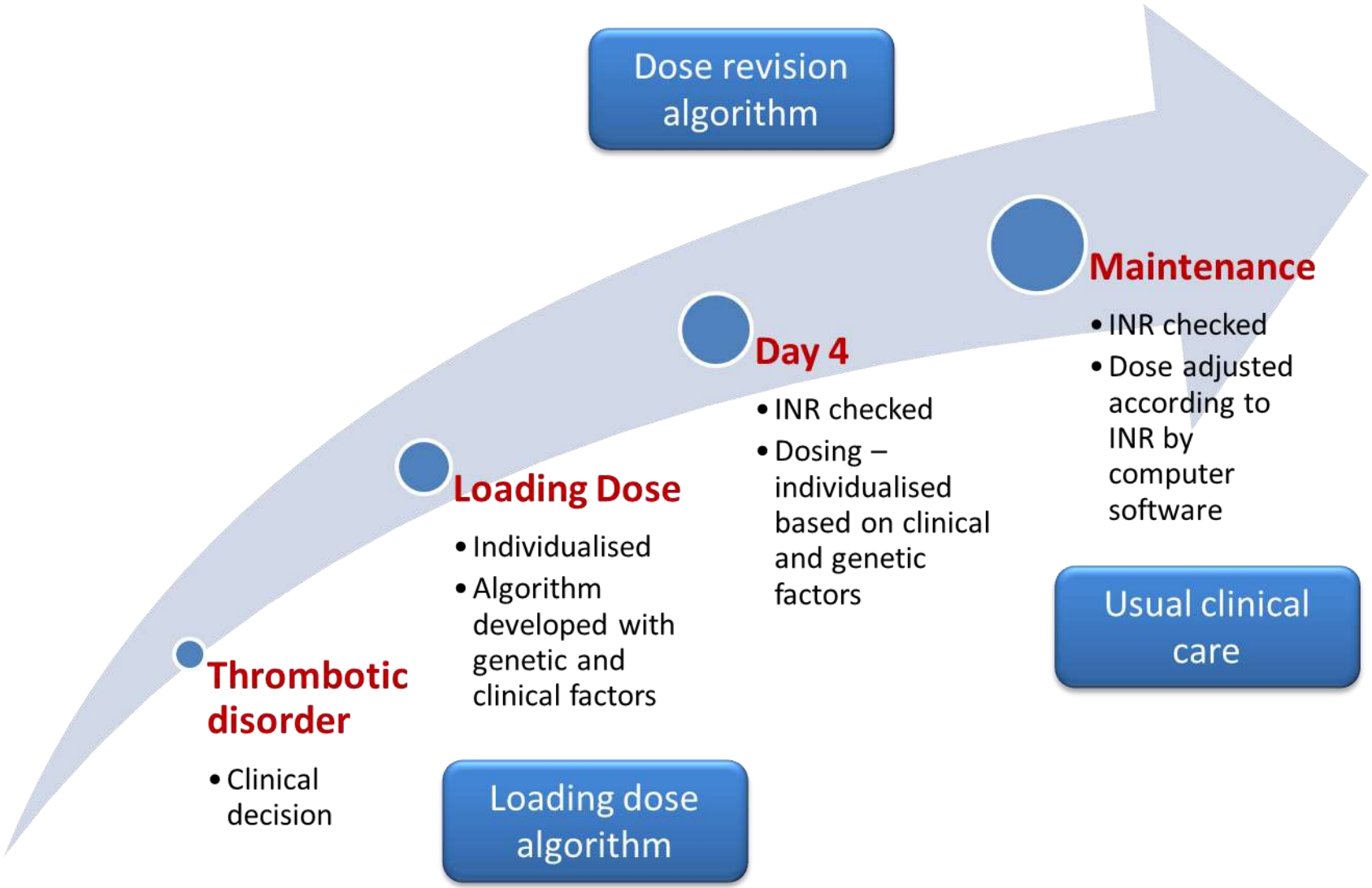
DESIGN

- Pragmatic single-blind two-arm parallel group randomized controlled trial

Warfarin Dosing – Standard Clinical Care



The Genetic Warfarin Dosing Pathway



Point-of-Care Genotyping Assay

Pipetting 5 µl blood to buffer A

↓

Transfer 1 µl of diluted blood to the test samples

↓

Perform PCR

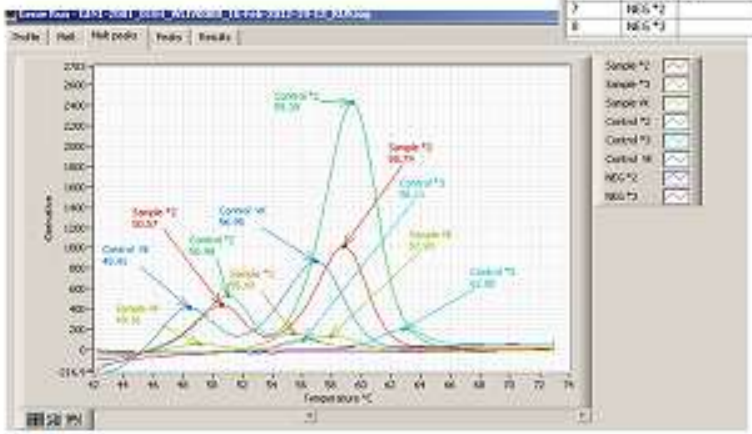
↓

Check on computer (PC) : shape and the temperature of the melt peaks comply with result table

A strip of 8 tubes containing prepared mastermix


Genie 1


Result Table


Melt peaks

Time <2 hours

Results for:

- *CYP2C9*2*
- *CYP2C9*3*
- *VKORC1 (-1639G>A)*

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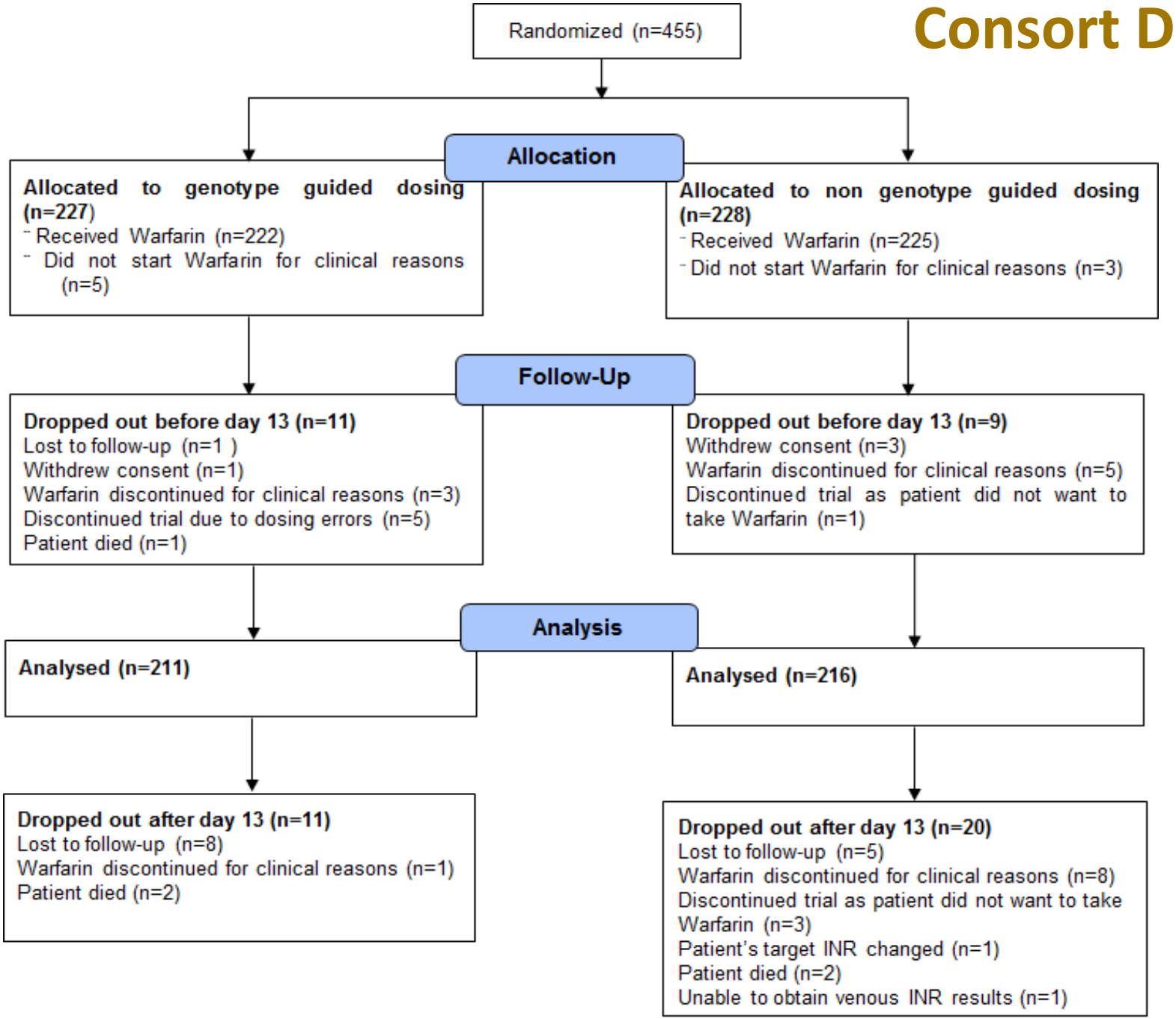
Consort Diagram



Results: Baseline Variables

- Well matched between the two arms
- Most were males (61.0%; n=277),
- 98.5% (n=447) were White
- Mean age of 67.3 (SD 13.7) years.
- Majority of patients (72.1%, n=328) had AF
- Those with VTE received heparin for at least 5 days
- Genotype distributions between the two arms similar and consistent with the literature of allele frequencies

Primary Outcome Measure

Percent time within therapeutic INR range 2.0-3.0 (TTR) during 12 weeks following the initiation of warfarin therapy

Genotyped arm %TTR	Standard dosing (control) arm %TTR	Adjusted Difference	P value
ITT ANALYSIS (n= 211 vs 216)			
67.4%	60.3%	7%	P<0.001
PER-PROTOCOL (n=166 vs 184)			
68.9%	62.3%	6.6%	P=0.001

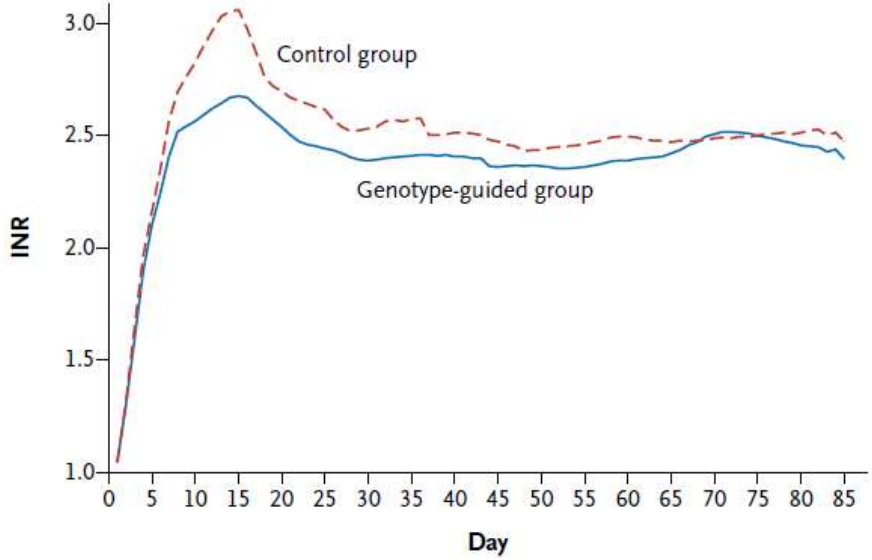
Sensitivity analyses did not change the conclusions of the primary analysis

Differences in %Time in Therapeutics Range According to Treatment Month

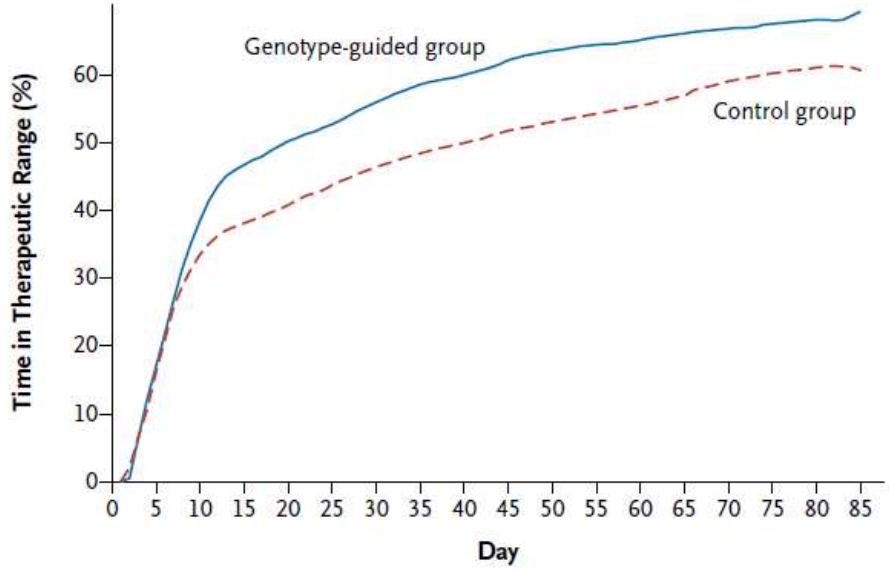
	Genotyped arm	Control arm	Difference (%)	P value
Adjusted mean (95% CI) % Time in range weeks 1-4	55.72 (52.12, 59.33)	46.96 (43.36, 50.56)	**8.77** (4.39, 13.14)	**<0.001**
Adjusted mean (95% CI) % Time in range weeks 5-8	74.36 (69.57, 79.16)	64.19 (59.40, 68.98)	**10.17** (4.36, 15.99)	**<0.001**
Adjusted mean (95% CI) % Time in range weeks 9-12	75.47 (71.21, 79.72)	74.11 (69.81, 78.40)	**1.36** (-3.84, 6.57)	0.607

Differences Between Genotyped-Guided Group and Control Group

International Normalized Ratio

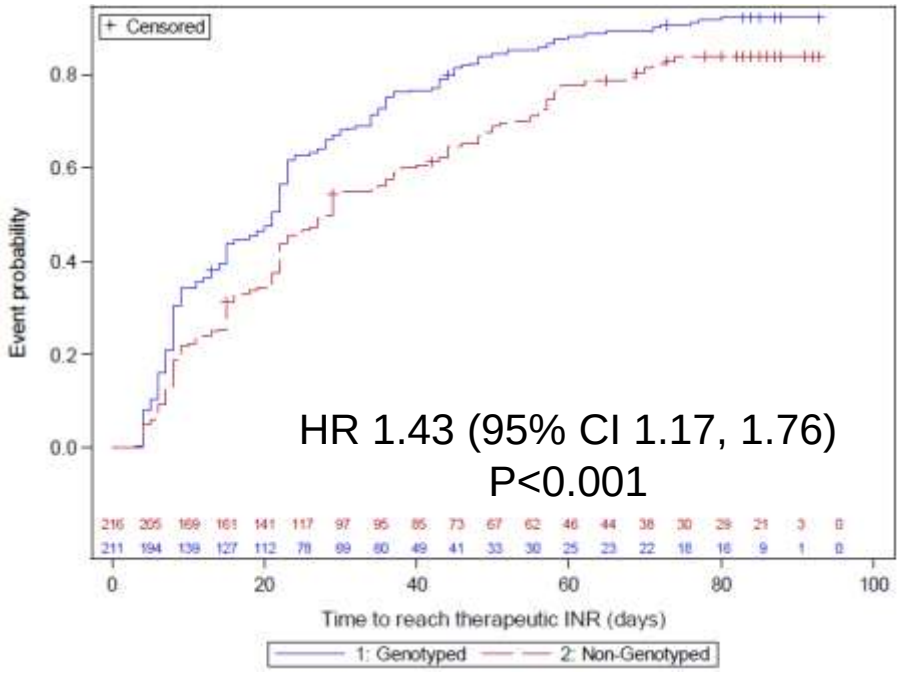


Time in Therapeutic Range

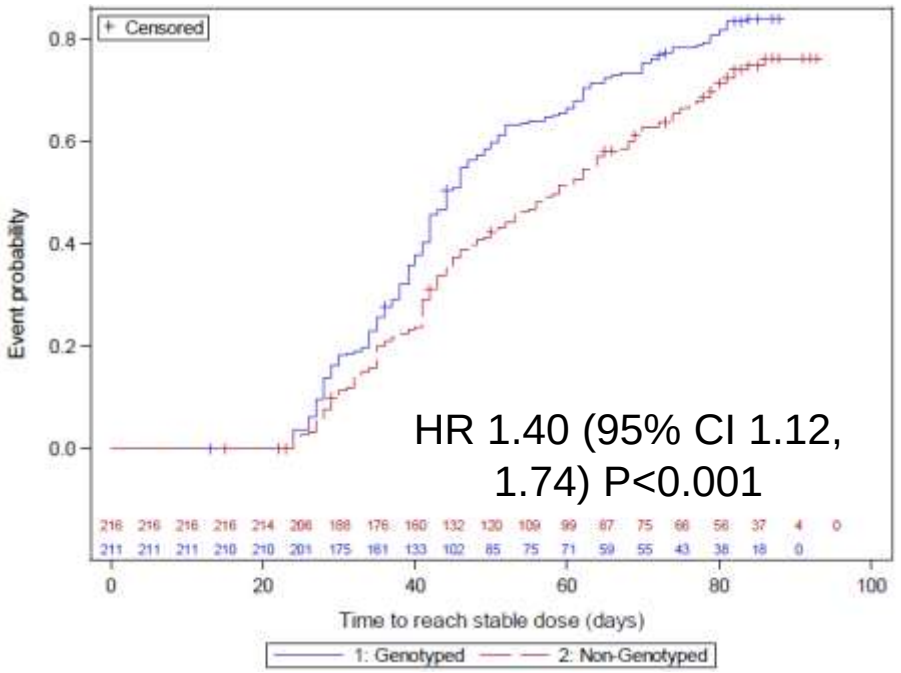


Secondary Outcomes

Time to Reach Therapeutic INR



Time to Reach Stable Dose



Genotyping reduced risk of, and % time above, an INR≥ 4.0
Genotyping reduced the number of dose adjustments

Bleeding and Thromboembolic Events

- No major bleeds (according to ISTH criteria)
- Three clinically serious bleeds (all in the standard dosing arm)
- No difference in minor bleeds between the two arms (35.1% vs 36.9%)
- Only one thromboembolic event

Conclusions

- Genotype guided dosing before starting warfarin was compared to standard dosing. This:
  - increased the TTR by approximately 7% (the primary outcome)
  - Reduced over-anticoagulation (INR>4.0) by 69%
  - Reduced the time required to reach therapeutic INR by about 28%
  - Improved the time required to reach stable dose by 25%
  - Reduced the number of warfarin dose adjustments by 9%
- Novel algorithmic strategy
- POC assay produced results in 2h
- Limitation: evaluated a surrogate (INR) and did not have power to assess clinical events of bleeding and thrombosis

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ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

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ABSTRACT

BACKGROUND

The level of anticoagulation in response to a fixed-dose regimen of warfarin is difficult to predict during the initiation of therapy. We prospectively compared the effect of genotype-guided dosing with that of standard dosing on anticoagulation control in patients starting warfarin therapy.

METHODS

We conducted a multicenter, randomized, controlled trial involving patients with atrial fibrillation or venous thromboembolism. Genotyping for *CYP2C9**2*, *CYP2C9**3*, and *VKORC1* (–1639G→A) was performed with the use of a point-of-care test. For patients assigned to the genotype-guided group, warfarin doses were prescribed according to pharmacogenetic-based algorithms for the first 5 days. Patients in the control (standard dosing) group received a 3-day loading-dose regimen. After the initiation period, the treatment of all patients was managed according to routine clinical practice. The primary outcome measure was the percentage of time in the

From the University of Liverpool (M.P., G.B., A.L.J., C.H.T., J.E.Z., P.R.W.) and Royal Liverpool and Broadgreen University Hospital National Health Service (NHS) Trust (M.P., C.H.T.), Liverpool, Whiston Hospital, Prescot (T.N.), and Newcastle upon Tyne NHS Trust (P.K.) and Newcastle University (J.B.L., A.K.D., P.A., F.K.), Newcastle upon Tyne — all in the United Kingdom; Uppsala University, Department of Medical Sciences (N.E., C.C., H.K., M.W.), Uppsala Clinical Research Center (N.E.) and Uppsala University Hospital (C.C., B.W., M.W.), Uppsala, and Enköping Hospital, Enköping (C.S.) — all in Sweden; and Utrecht University, Utrecht, the Netherlands (A.H.M.Z.). Address reprint requests to Dr. Pirmohamed at the Wolfson Centre for Personalised

Acknowledgments

- **Investigators**: Girvan Burnside[1], Jenni Stoddern[1], Clare Prince[1], Cheng Hok Toh[1], Toby Nicholson[2], Patrick Kesteven[3], Andrea Jorgensen[1], Ann Daly[5], Anke-Hilse Maitland-van der Zee[6], Paula Williamson[1], Niclas Eriksson[4], Peter Avery[5], Farhad Kamali[5], Mia Wadelius[4], for the EU-PACT Investigators. [1]The University of Liverpool, UK, [2]Whiston Hospital, Merseyside, [3]Newcastle upon Tyne Hospitals NHS Foundation Trust, UK, [4]Uppsala University, Sweden, [5]Newcastle University, UK, [6]Uetrecht University, The Netherlands
- All patients who took part in the trial
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- Nurses, data managers and monitors for help in running the trials
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