Implementation of genotype-guided dosing of warfarin to improve anticoagulation control

Andrea L Jorgensen[1], Gail Fitzgerald[2], Clare Prince[2], Ana Alfirevic[3], Julia Reynolds[4], Eunice Zhang[3], Jennifer Downing[3], Munir Pirmohamed[3]
[1] Department of Biostatistics, The University of Liverpool, Liverpool, United Kingdom, [2] RD&I, Royal Liverpool & Broadgreen University Hospital Trust, Liverpool, United Kingdom,
[3] Molecular and clinical pharmacology, The University of Liverpool, Liverpool, United Kingdom, [4] Innovation Agency, Academic Health Science Network for the North West Coast, United Kingdom

This pilot implementation was funded by NIHR CLAHRC NWC and the views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care..

Background

- Warfarin is an effective, widely used anticoagulant, but dosing is challenging due to its narrow therapeutic index and large interpatient variability in requirements.
- Needs close monitoring of international normalised ratio (INR), with target range typically 2-3. Important to establish therapeutic dose (that which maintains INR in target range) as soon as possible to reduce risk of adverse events (bleeding; thrombosis) and number of clinic visits required for INR monitoring.
- Many clinical, demographic and genetic factors associated with dose requirements, with variants in *CYP2C9* and *VKORC1* genes having the largest influence.
- EU-PACT trial[1] demonstrated genotype-guided dosing approach (GGD), using point-of-care genetic testing, led to patients spending 7% more time in target INR range and achieving target range sooner.
- We undertook an implementation project to determine whether GGD could translate into routine clinical practice in the UK.

Study design and follow-up

- Matched cohort design: 3 clinics using GGD approach (implementation group); 3 comparable clinics using standard approach (control group).
- Statistical power boosted by using routinely collected INR data from similar anticoagulation clinics using standard approach (dashboard data).
- Patients in implementation group genotyped using point-of-care assay and dosed according to GGD days 1-5; dosed according to usual clinic practice thereafter. Patients in control groups dosed according to usual practice throughout. All followed-up for 12 weeks.
- Data collected on: demographics, INR measurements, dose changes, withdrawals, hospital admissions.
- Patient and staff questionnaires completed at implementation group clinics to gain feedback on GGD approach.

Point-of-care genotyping assay and dose calculator

Genotyping assay:

- Buccal swab to obtain DNA, no DNA extraction required.
- ParaDNA point-of-care genotyping platform, developed by LGC.
- Results available in 45 minutes.

Dose calculator:

- Computerised web-based calculator incorporating loading dose (days 1-3) and maintenance dose (days 4/5) algorithms previously tested in EU-PACT.[1]

Outcomes

- **Primary outcome:** % time in target INR range during first 12 weeks
- **Secondary outcomes:**
  1. INR ≥ 4 in first week
  2. INR <2 in first week
  3. Total number clinic visits in first 12 weeks
  4. Patient adverse events (bleeds, mortality, other morbidity)
  5. Patient opinion of GGD
  6. Staff opinion of GGD

Statistical methods

- Time in target INR range calculated using method of Rosendaal et al.[2]
- Student's t-test, chi-square test and Mann-Whitney U test used as appropriate to compare between implementation and control groups (with and without dashboard data, where applicable). Significance threshold of 0.05 assumed.
- Descriptive analysis of questionnaire responses.

Results

Outcome	Implementation (n=122)	Control (n=733) (n=93 for adverse events outcome)	Comparison (95% CI)	p-value
% Time target range: mean (SD)	61.90 (21.09)	55.40 (22.60)	Diff: 6.50 (2.39-10.61)	0.002
INR ≥ 4 in first week: n(%)	3 (2.46)	54 (7.37)	OR=0.31 (0.09-0.99)	0.06
INR <2 in first week: n(%)	93 (76.23)	405 (55.25)	OR=2.60 (1.67-4.04))	<0.001
Number clinic visits: median (IQR)	10 (8-11)	10 (8-12)	-	0.55
Number adverse events	1	3	OR: 0.98 (0.66-1.43)	0.43

Table 1: Comparison of clinical outcomes

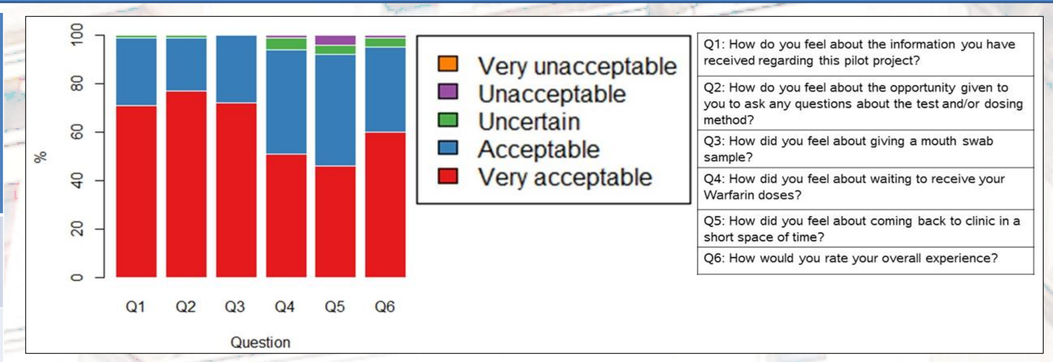

Figure 1: Patient Questionnaire Responses

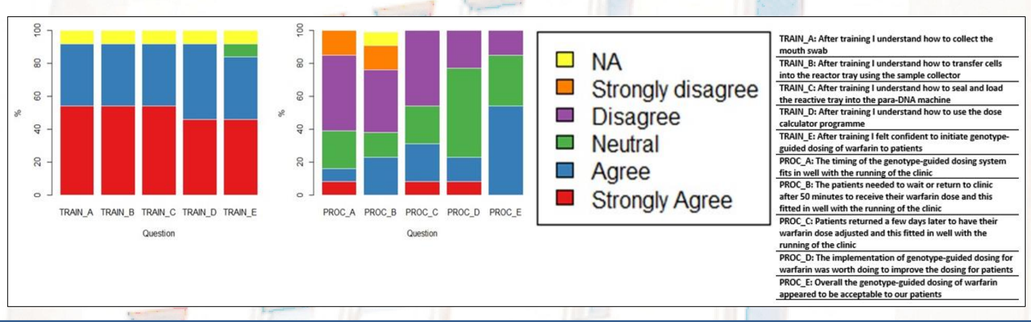

Figure 2: Staff Questionnaire Responses

Conclusions

Despite increasing popularity of direct acting oral anticoagulants (DOACs), warfarin remains the most cost-effective anticoagulant for a majority of patients. Further, DOACs are contraindicated for some patient subgroups including those with severe renal impairment, on certain interacting drugs and children. However, it is essential for effectiveness and patient safety that therapeutic dose of warfarin is achieved quickly and maintained. Results of our project demonstrate that the GGD approach supports this goal (Table 1), can be implemented smoothly into clinical practice with only a few minor modifications (Fig 2), and moreover is viewed positively by patients (Fig 1) and staff (Fig 2).

References
1. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. New England Journal of Medicine. 2013;369(24):2294-303.
2. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69(3):236-9.

Better Together