

SHORT REPORT

Anticoagulation control and cost of monitoring of older patients on chronic warfarin therapy in three settings in North East England

SALAH ABOHELAIKA¹, HILARY WYNNÉ², FARHAD KAMALI¹, PETER AVERY³, BRIAN ROBINSON⁴, PATRICK KESTEVEN⁴¹Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne NE1 7RU, UK²Newcastle upon Tyne Hospitals NHS Foundation Trust— Care of the Older People's Medicine, Freeman Hospital, Freeman Road, Newcastle upon Tyne NE7 7DN, UK³School of Mathematics and Statistics, Newcastle University, UK⁴Haematology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UKAddress correspondence to: Hilary Wynne. Tel: +44 0191 2231683; Fax: +44 0191 2231249. Email: hilary.wynne@nuth.nhs.uk

Abstract

Background: novel oral anticoagulants may be particularly cost-effective when INR control (TTR) with warfarin is poor or monitoring difficult.**Setting:** the Newcastle upon Tyne monitoring service, set in hospital or general practice and a domiciliary-based service for housebound patients.**Objectives:** to examine anticoagulation stability and costs of monitoring.**Subjects:** three hundred and twenty-six atrial fibrillation patients, 75 years and over, with target INR of two to three, accessing hospital ($n = 100$), general practice ($n = 122$) and domiciliary ($n = 104$) service.**Methods:** age, co-morbidities, length of warfarin treatment, medications, INR values and dose changes from January to December 2011 were recorded, and costs analysed.**Results:** home-monitored patients had taken warfarin for longer, mean 5.2 years, than hospital (3.7) or general practice (3.1) patients. Age and total number of drugs prescribed chronically were negatively related to TTR. INR measurements and dose changes were negatively associated with the duration of treatment, positively correlated with co-morbidities. The mean TTR was 78% in hospital, 71% in general practice and 68% in domiciliary monitored patients. INR was monitored more often in hospital and domiciliary groups than in general practice and more dose changes occurred in the domiciliary group than in others. Costs of warfarin and monitoring were £128 per patient per year for hospital, £126 for general practice and £222 for domiciliary patients.**Conclusions:** further exploration of the clinical effectiveness of novel anticoagulants in dependent patients is warranted to determine to what extent trial outcomes so far achieved in a fitter elderly population are influenced by the chronic co-morbidities of old age.**Keywords:** aged, anticoagulation costs, dependency, time in therapeutic range, warfarin, older people

Introduction

Novel oral anticoagulants, which act directly through inhibition of thrombin or factor Xa, were approved in 2012 by The National Institute of Health and Clinical Excellence (NICE) for use in patients with non-valvular atrial fibrillation (NVAF) aged 75 years or older in accordance with their license, as the incremental cost-effectiveness ratio is plausibly

less than £20,000 per QALY gained [1–3]. Doctors now have a choice of oral anticoagulants, but need evidence to guide prescribing decisions. Time spent in therapeutic range (TTR) is an important influence on outcomes of thrombo-embolic prophylaxis with warfarin, with patients with TTR of 70% or more having a 79% reduced risk of stroke compared with those with a TTR of <30% and lower mortality [4]. A meta-analysis of recent studies concerning thrombo-embolic

and major haemorrhagic events in NVAF in patients receiving warfarin therapy concluded that overall survival is improved where TTR is >40% [5], and a TTR of >58% is needed to be confident that patients will benefit from the treatment [6].

The RE-LY study of patients with NVAF suggested that dabigatran 150 mg bd might be cost-effective in high-risk patients unless INR control with warfarin is excellent (average TTR >72.6%), but warfarin is cost-effective in moderate-risk patients unless INR control is poor (average TTR <57.1%) [7, 8]. In a UK benefit-harm analysis, fewest net potential benefits of dabigatran versus warfarin were seen in centres which achieved a good TTR of $\geq 65.5\%$ [9]. Novel anticoagulation is at least as effective at reducing stroke and systemic embolism, and results in fewer bleeds, in particular intracranial bleeding, when compared with warfarin [10], including in patients aged 80 years and over [11]. Use might be particularly justified in patients exhibiting low TTR, for example, under 50% in spite of good patient adherence to therapy, and in those for whom monitoring is difficult or costly [12].

Difficulties with warfarin therapy are encountered by the very elderly using outpatient anticoagulation monitoring, including the missing of appointments and problems contacting them with dosing instructions [13], and gain from no monitoring requirements for novel anticoagulants has been recognised by NICE [1–3]. While domiciliary monitoring may address this issue, risk of warfarin-related bleeding is associated with dependency and domiciliary monitoring of INR [14].

Novel anticoagulants may be particularly cost-effective compared with warfarin for dependent older people, those whose anticoagulant control is erratic or for whom monitoring is not feasible [15]. We set out to examine TTR and service costs in patients housebound due to a high level of dependency using the Newcastle domiciliary service, and to compare these to patients monitored in general practice outreach clinics and patients choosing hospital monitoring for their convenience.

Methods

The inclusion criteria were to have atrial fibrillation with a target INR range of two to three, aged 75 years and over and to be on warfarin chronically since before December 2010. INR testing and warfarin dosing are performed throughout the unified service in accordance with a standard protocol facilitated by the DAWN computer dosing programme (version 6.10) [16] and trained staff. The DAWN software was given the order of inclusion criteria and selected 326 patients from those accessing hospital ($n = 100$), general practice ($n = 122$) and domiciliary ($n = 104$) services. INR values were collected retrospectively for 12 months (January to December 2011) for each patient, and dose changes and INR measurements recorded, as well as age, co-morbidities, drug therapy and duration of warfarin therapy. TTR was established using the linear extrapolation method of Rosendaal *et al.* [17].

Costs for the monitoring service in 2011 were obtained from the finance department at the Newcastle upon Tyne Hospitals NHS Foundation Trust. Methods followed those

set out by the *BMJ* guidelines for economic submissions [18]. Costs of all consumables, reagents, depreciation of INR testing equipment and quality control materials were calculated per test. Staff costs, transport, overheads and computer equipment were calculated per patient treated. Costs which were considered common and equal to all patients (medical advice, consultant supervision, treatment of adverse events) were not included. The price of portable coagulometer and computer (assuming a 5-year lifespan) has no impact and the cost of the hospital computer server, being common to all groups, was not included. The price of each domiciliary phlebotomy visit was calculated by dividing salary, car lease and insurance, petrol, consumables and sample transport by the number of tests. No patient relied upon NHS transport as domiciliary visits are used instead. We assumed that patient private travel costs were the same, whether to GP surgery or to the hospital clinic (all patients were eligible for free-public transport) and we did not collect data on these.

Data were coded and entered using Statistical Package for Social Sciences (SPSS) version 19. A one-way analysis of covariance (ANCOVA) model was fitted to test the difference in TTR, INR measurements and dose changes among the three groups. The influences of the other covariates were examined. Responses were adjusted for covariates (selected by stepwise regression) to ensure that differences between groups were not merely due to differences in the covariates. Square roots of some data were used to achieve approximate normality. The Chi-square test was used to compare categorical data.

Results

The mean age \pm SD of the hospital patients (54% male) was 83 ± 5 , of the general practice cohort (46% male) was 82 ± 4 and of the domiciliary patients (26% male) was 84 ± 5 years. The domiciliary patients were significantly older ($F(2,323) = 8.61$, $P < 0.0001$) with a larger proportion of females [χ^2 (df = 2) = 17.65, $P < 0.001$] than the other two groups.

The important covariates found, and hence allowed for, were age, co-morbidities, years on warfarin and total number of medications. Quality of anticoagulation control is shown in Table 1. Please see Supplementary material data, Appendix 1.

Patients used a median of six drugs (five cardiovascular medications including warfarin) and had a median of three chronic diseases (two cardiovascular diseases including atrial fibrillation, plus one other) with no significant difference between the groups. As age and total number of drugs increased, TTR fell ($P = 0.005$). As years on warfarin increased, the number of INR measurements ($P = 0.01$) and dose changes ($P = 0.003$) fell while, as co-morbidities increased, more INR measurements ($P = 0.004$) and dose changes ($P = 0.03$) occurred. One (domiciliary monitored) patient on 10 drugs for cardiovascular disease and malignancy, suffered intracranial bleeding, following a fall when his INR was 16. Workload and descriptive costs of monitoring are presented in Table 2; being similar in the three groups, it was not possible to calculate confidence intervals around these cost differences as we had no measure of variability of cost.

Table 1. Mean % of time in therapeutic range (TTR), number of INR monitoring and number of dose changes among the groups

	Hospital mean (95% CI)	General practice mean (95% CI)	Domiciliary mean (95% CI)	P-value
TTR %	78 (74, 82)	71 (67, 74)	68 (65, 72)	0.001
Number of INR monitoring events	13.1 (12.2, 14.1)	11 (10.2, 11.8)	14.2 (13.2, 15.1)	<0.0001
No. of dose changes	2.4 (1.8, 3.0)	1.8 (1.3, 2.3)	3.4 (2.8, 4.1)	0.001
No. of years of warfarin usage	3.7 (2.9, 4.5)	3.1 (2.5, 3.8)	5.2 (4.4, 6.0)	<0.0001

Table 2. Actual workload and costs (pounds sterling) of the anticoagulant monitoring service (for year 2011)

	Hospital	General practice	Domiciliary
Total number of patients monitored	1,430	2,150	520
Total INR tests performed	18,105	25,663	6,415
Cost (£)			
INR tests	5,612	7,955	20,996
Staff	134,848	195,410	19,916
Transport	–	4,196	59,050
Computers and software	2,615	3,933	951
Total cost (£)	143,075	211,494	100,903
Warfarin cost (£) /pt/yr (% of total cost)	28.2 (21.8)	28.2 (22.2)	28.2 (12.6)
Cost of warfarin monitoring per patient per annum including medication cost (£)	128	126	222

Discussion

In our population, TTR results for hospital and general practice patients were both in the upper quartile of patients in the RE-LY study, and even the domiciliary patients at 68% were in the second best quartile, consistent with the observation that the adequacy of anticoagulant control in routine practice can be broadly comparable to that reported in clinical trials [19], and our costs for the ambulatory services were similar to those estimated by NICE [1].

Our novel finding is that domiciliary-based patients had poorer anticoagulant control, compared with clinic monitored patients, in spite of having the highest number of INR measurements and dose changes, in a service which costs more than the clinic service per patient year to finance. As INR testing and warfarin dosing are performed throughout the service in accordance with a standard protocol facilitated by the DAWN computer dosing programme and trained staff, differences in stability of control are likely to be attributable to differences in patient characteristics.

Patients can move from ambulatory to domiciliary monitoring as their physical or mental condition deteriorates, the longer time that our home-monitored patients had been taking warfarin reflecting this. Although which patient characteristics influence outcomes is not known, domiciliary

monitoring and greater chronic disease burden are associated with risk of warfarin-related complications [8, 20–22]. The similar number of co-morbidities and prescribed drugs in our general practice and home-monitored patients is perhaps surprising, but it is likely that, as the risk–benefit profile of warfarin changed over time, for more dependent patients their warfarin was discontinued. Although, as this patient cohort was studied before publication of NICE guidance [1–3] no transfers to novel anticoagulants were made, the additional availability of this treatment option makes further exploration of their clinical effectiveness in this patient group of great importance. The findings of this small retrospective study may not be applicable to a wide population and a longitudinal study is required to better establish the relationship between patient characteristics such as dependency and clinically relevant outcomes of anticoagulation as current trial data derive from a fitter, heavier population with a mean age about a decade younger.

The limited long-term safety data, the increased bleeding risk for those of 80 years or older with impaired renal function or low body weight [23], drug interactions, and the lack of a direct antidote or laboratory measure of adherence and response and the need for good compliance in view of their short half-lives mean that warfarin will continue to have a role for thrombo-embolic prophylaxis in AF, including in patients with cardiac valve replacements for whom outcomes with novel anticoagulants can be significantly poorer [24]. Further exploration of effective interventions to increase the proportion of INR tests within target range would therefore be worthwhile.

Key points

- Those having domiciliary monitoring have a lower mean TTR at 68% than hospital (78%) and general practice (71%) monitored patients.
- TTR falls as age and total number of drugs prescribed chronically rise.
- The number of INR measurements and dose changes rise with number of co-morbidities.
- Outcomes from novel anticoagulants may be influenced by chronic co-morbidities of old age.
- Further exploration of the clinical effectiveness of novel anticoagulants in dependent patients is warranted.

Conflicts of interest

None declared.

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