ORIGINAL ARTICLE

A systematic review of outcome measures reported for the therapeutic effectiveness of oral anticoagulation

D A Fitzmaurice, P Kesteven, K M Gee, E T Murray, R McManus

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See end of article for authors' affiliations

Correspondence to: Dr D Fitzmaurice, Department of Primary Care and General Practice, The Medical School, University of Birmingham B15 2TT, UK; d.a.fitzmaurice@bham.ac.uk

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Aims: To evaluate the evidence of therapeutic international normalised ratio (INR) control reporting and to provide recommendations for future reporting, particularly for research and audit purposes.
Methods: A systematic review of literature published over a five year period describing therapeutic INR control. Papers were identified from the Medline electronic database, and those that met the quality criteria were reviewed independently by an academic general practitioner and a consultant haematologist.
Results: Fifteen papers were identified that met the quality criteria for review. The sample size of studies ranged from 53 to 2545 (mean, 483.9) patients. Follow up ranged from three months to 13 years. Twelve studies reported results from secondary care only, one from primary care only, and two from both primary and secondary care. Seven of the 15 papers reported percentage time in range, five of 15 papers reported mean INR, six of 15 papers reported the proportion of tests in range, and five of 15 papers reported mean warfarin dose. Additional methods of presenting INR results were: dose changes each month, distribution of INR results, deviation of INR value from mean, percentage dose changes, time between visits, and median INR value. Six papers reported only one outcome measure, six reported two outcomes, two papers reported three outcomes, and one paper reported five outcomes.
Conclusions: It is recommended that at least two outcome measures should be reported and measures should be selected so that both the INR determinations and dosing advice are monitored.

The past few years have seen an increase in interest in the therapeutic management of oral anticoagulation. Principally, this has been driven by the increasing numbers of patients receiving oral anticoagulation treatment as a result of trials demonstrating the effectiveness of oral anticoagulation in preventing strokes in patients with atrial fibrillation.[1] One criticism of the original studies demonstrating the effectiveness of oral anticoagulation in preventing stroke was that although target international normalised ratios (INRs) for treatment were stated, the achieved intensity of anticoagulation achieved was not. This is an important issue because achieved intensity of anticoagulation is related to the benefit derived from the treatment. Similarly, subsequent studies have used a wide range of outcome measures to determine performance levels of both individuals and anticoagulation clinics. Our own research has shown that using different outcome measures of anticoagulant clinic effectiveness produced different results on the same data sets.[2 3] The need for standardisation has previously been highlighted.[4]

> "The aims of our study were to establish the nature of outcome measures being reported for the therapeutic effectiveness of oral anticoagulation and to provide recommendations for international normalised ratio reporting in the future"

To our knowledge, there have been two attempts to introduce some standardisation into the process, with the description of point prevalence[5] (or last look in the book) and the per cent time spent in range.[6] It is now widely accepted that per cent time in range should be calculated assuming a linear change in INR values over time.[7] However it is not clear how widely these outcome measures are used. We have undertaken a systematic review of papers reporting INR data published in the past five years, subsequent to these recommendations. The aims of our study were to establish the nature of outcome measures being reported for the therapeutic effectiveness of oral anticoagulation and to provide recommendations for INR reporting in the future.

METHOD

A literature search from January 1995 to December 1999 was carried out using Medline. No attempts were made to access grey literature. The keywords used for the search were "anticoagulation" and "INR". Of the papers identified using the Medline search, DF excluded inappropriate papers based on their titles. Copies of the remaining papers were identified and the abstracts reviewed separately by EM and DF. Papers were excluded if they: (1) did not present results in terms of INR, (2) included less than 50 patients, (3) reported induction of warfarin only, (4) had a follow up period of less than three months, or (5) were written by members of the research team. Papers that were excluded by one reviewer only were reassessed by the team (DF, EM, and KG) and a consensus was taken on their eligibility for our study. Eligible papers were reviewed in full following a proforma devised by the study team (table 1) by a haematologist (PK) and a clinical research fellow (RMc) to establish the variety of outcome measures used to report therapeutic oral anticoagulation control.

RESULTS

Three hundred and fifty four papers were identified using a Medline search. Of these, 314 were excluded based on their titles. Of the remaining papers, 15 were included in the formal review. The sample size of the reviewed studies ranged from 53 to 2545 (mean, 484) patients. The duration of follow up ranged from three months to 13 years. Twelve studies reported results from secondary care only, one from primary care only, and two from both primary and secondary care. All but one of the studies reported results from adult populations. In terms of the presentation of INR results, seven of 15 papers reported percentage time in range, five of 15 papers reported mean INR,

Table 1 Presentation of international normalised ratio (INR) results

First author and ref	Sample size	Duration of follow up	Model of care	Adult /child	% Time in range	Mean INR	Proportion of tests in range	Mean dose	Other*
Schaufele[8]	181	4 months	Secondary	Adult			Yes		
MRC[9]	2545	13 years	Primary	Adult		Yes		Yes	
Malik[10]	480	2 years	Secondary	Adult	Yes		Yes		
Streif[11]	319	5 years	Secondary	Child			Yes	Yes	1
Blann[12]	867	3 months	Secondary	Adult		Yes		Yes	
Kulinna[13]	100	6 months	Secondary	Adult			Yes		
Morsdorf[14]	76	5 years	Primary and secondary	Adult		Yes			2
Sawicki[15]	179	6 months	Secondary	Adult			Yes		3
Poller[16]	285	3 months	Secondary	Adult	Yes	Yes	Yes		4, 5
Hsin[17]	53	3 months	Secondary	Adult	Yes				
Taylor[18]	241	12 months	Secondary	Adult	Yes				
SPIRIT Study[19]	1316	3 years	Secondary	Adult	Yes				
Palereti[20]	311	6 months	Secondary	Adult	Yes				
Pengo[21]	205	3 years	Secondary	Adult	Yes	Yes		Yes	
Koefoed[22]	100	3 months	Primary and secondary	Adult				Yes	6
Total	7258 (483.9)	Range 3 months to 13 years			7	5	6	5	

*Coded lists of "other" presentation of INR results: 1, dose changes each month; 2, distribution of INR results; 3, deviation of INR value from mean; 4, % dose changes; 5, time between visits; 6, median INR.

Table 2 Reasons for exclusion

Exclusion criteria							
Exclusion based on title	Follow up <3 months	Includes <50 patients	Does not report INR results	Reports only on induction	Written by DF, EM, PK	Reports only on induction and includes <50 patients	Total excluded
314	1	5	7	7	2	3	339

INR, international normalised ratio.

six of 15 papers reported proportion of tests in range, and five of 15 papers reported mean warfarin dose. Additional methods of presenting INR results were: dose changes each month, distribution of INR results, deviation of INR value from mean, percentage dose changes, time between visits, and median INR value. None of the papers reviewed reported point prevalence. Six papers reported only one outcome measure, six reported two outcomes, two papers reported three outcomes, and one paper reported five outcomes (table 1). The paper reporting five outcome measures was a randomised trial of computerised anticoagulant dosage, which reported time in range, mean INR, proportion of tests in range, the percentage of dose changes, and the mean time between visits.[16]

Excluded papers

In total 339 papers were excluded. Three hundred and fourteen papers were excluded on the basis of title alone. A further 25 papers were excluded following review by DF and EM for reasons given in table 2. Informal review of these papers by DF was undertaken following exclusion to identify any further parameters that had not been noted in the formal review. No further parameters were noted. Excluded papers are listed in table 3.

DISCUSSION

There has been increasing interest in the therapeutic management of oral anticoagulation following evidence for its beneficial thromboprophylactic effect in non-rheumatic atrial fibrillation. However, one of the difficulties in interpreting research findings has been the lack of consistency in expressing INR data. This inconsistency makes the comparison of findings between different centres very difficult. In a sense, this mirrors problems encountered within laboratory comparisons before the introduction of the INR system. Our own data have shown that there are differences in the observed efficacy depending upon the parameters chosen, with differences of up to 10% found in terms of INR control (table 4). This is important because INR control gives a proxy measure for clinical outcomes, which are relatively infrequent. Thus, improved INR control should correlate with improved clinical outcome.

> "It is unclear why point prevalence has not been more widely reported because this is a relatively easy statistic to generate"

The most surprising finding of our study was that none of the papers reviewed used one of the recommended methods of reporting, namely point prevalence. A large minority of papers reported only one outcome measure. The four most widely reported parameters were:

- percentage of time spent in range
- mean INR
- proportion of tests in range
- mean warfarin dose.

The first three of these measures relate to therapeutic control, whereas warfarin dose is only likely to be discrepant if there is a problem with the INR estimation between centres. The paper that reported five outcome measures centred around computerised dosing. The routine use of computerised data collection should allow the production of therapeutic control data in a variety of formats and should be encouraged.

In conclusion, we recommend that at least two outcome measures should be reported and that these should be selected from the four measures stated above. The measures should be

Table 3 Papers excluded from systematic review

1	Gedge J, Orme S, Hampton KK, *et al*. A comparison of a low-dose warfarin induction regimen with the modified Fennerty in elderly patients. *Age Ageing* 200;**29**:31–4.
2	Johnson MJ. Problems of anticoagulation within a palliative care setting: an audit of hospice patients taking warfarin. *Pall Med* 1997;**11**:306–12.
3	Roberts GW, Druskeit T, Jorgensen LE, *et al*. Comparison of an age adjusted warfarin loading protocol with empirical dosing and Fennerty's protocol. *Aust N Z J Med* 1999;**29**:731–6.
4	Motykie GD, Mokhtee D, Zebala LP, *et al*. The use of a Bayesian forecasting model in the management of warfarin therapy after total hip arthroplasty. *J Arthroplasty* 1999;**14**:988–93.
5	Vadher B, Patterson DL, Learning M. Prediction of the international normalized ratio and maintenance dose during the initiation of warfarin therapy. *Br J Clin Pharmacol* 1999;**48**:63–70.
6	Hobbs FD, Fitzmaurice DA, Murray ET, *et al*. Is the international normalised ratio (INR) reliable? A trial of comparative measurements in hospital laboratory and primary care settings. *J Clin Pathol* 1999;**52**:494–7.
7	Caprini JA, Arcelus JI, Motykie G, *et al*. The influence of oral anticoagulation therapy on deep vein thrombosis rates for four weeks after total hip replacement. *J Vasc Surg* 1999;**30**:813–20.
8	Caprini JA, Arcelus JI, Reyna JJ, *et al*. Deep vein thrombosis outcome and the level of oral anticoagulation therapy. *J Vasc Surg* 1999;**30**:805–11.
9	Sunderji R, Campbell L, Shalansky K, *et al*. Outpatient self-management of warfarin therapy: a pilot study. *Pharmacotherapy* 1999;**19**:787–93.
10	Morsdorf S, Erdlenbruch W, Taborski U, *et al*. Training of patients for self-management of oral anticoagulant therapy: standards, patient suitability and clinical aspects. *Thromb Haemost* 1999;**25**:109–15.
11	Schenk JF, Morsdorf S, Pindur G, *et al*. Analysis and occurrence of adverse events with oral anticoagulant therapy. *Thromb Haemost* 1999;**25**:65–71.
12	Crowther MA, Ginsberg JB, Kearon C, *et al*. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999;**159**:46–8.
13	Ageno W, Turpie AG. Exaggerated initial response to warfarin following heart valve replacement. *J Cardiol* 1999;**84**:905–8.
14	Cheung YF, Leung MP. Low dose oral anticoagulation therapy in Chinese children with congenital heart disease. *J Paediatr Child Health* 1998;**34**:563–7.
15	Gerstein FH, Evans MF. When the INR comes back too high. *Can Fam Physician* 1998;**44**:1841–2.
16	Oates A, Jackson PR, Austin CA, *et al*. A new regimen for starting warfarin therapy in out-patients. *Br J Clin Pharmacol* 1998;**46**:157–61.
17	The Newcastle Anticoagulation Study Group. Effectiveness of anticoagulation among patients discharged from hospital on warfarin. *Med J Aust* 1998;**169**:243–6.
18	Tait RC, Sefcick A. A warfarin induction regimen for out-patient anticoagulation in patients with atrial fibrillation. *Br J Haematol* 1998;**101**:450–4.
19	Fitzmaurice DA, Hobbs FDR, Murray ET. Primary care anticoagulant clinic management using computerized decision support and near patient international normalized ratio (INR) testing: routine data from a practice nurse-led clinic. *Fam Pract* 1998;**15**:144–6.
20	Seamark DA, Backhouse S, Barber P, *et al*. Validation of current practice and a near patient testing method for oral anticoagulant control in general practice. *J R S Med* 1997;**90**:657–60.
21	Palareti G, Manotti CD, Angelo A, *et al*. Thrombotic events during oral anticoagulant treatment: results of the inception cohort, prospective collaborative ISCOAT study. *Thromb Haemost* 1997;**78**:1438–43.
22	Dedden P, Chang B, Nagel D. Pharmacy managed program for treatment of deep vein thrombosis with enoxaparin. *American Journal of Clinical Pharmacy* 1997;**54**:1968–72.
23	Hasenkam JM, Kimose HH, Knudsen L, *et al*. Self management of oral anticoagulant therapy after heart valve replacement. *Eur J Cardiothorac Surg* 1997;**11**:935–42.
24	Carroll WE, Jackson RD. Warfarin monitoring independent of the international normalized ratio (INR): a pilot study. *Res Commun Mol Pathol Pharmacol* 1997;**95**:169–78.
25	Harrison L, Johnson M, Massicotte MP, *et al*. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997;**126**:133–6.

Table 4 Differences in observed values from the same international normalised ratio data sets

	Tests in range	Point prevalence	Time in range
Intervention	62	71	69
Control	58	64	62

Taken from Fitzmaurice *et al*.[2]

Take home messages

- At least two outcome measures should be reported, chosen from the following parameters: percentage of time spent in range, mean international normalised ratio (INR), proportion of tests in range, and mean warfarin dose
- Measures should be selected so that both the INR determinations and dosing advice are monitored
- There is a need for standardisation of reporting of INR

selected so that both the INR determinations and dosing advice are monitored. It is unclear why point prevalence has not been more widely reported because this is a relatively easy statistic to generate. Our study highlights the need for standardisation of reporting of INR. This will become increasingly important with the development of differing models of oral anticoagulation management if clinical governance is to be taken seriously.

Authors' affiliations
D A Fitzmaurice, K M Gee, E T Murray, R McManus, Department of Primary Care and General Practice, The Medical School, University of Birmingham B15 2TT, UK
P Kesteven, Department of Haematology, The Freeman Hospital, High Heaton, Newcastle upon Tyne, NE7 7DN, UK

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6 **Rosendaal FR**, Cannegieter SC, vd Meer FJM, *et al*. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;**69**:236–9.
7 **Azar AJ**, Deckers JW, Rosendaal FR, *et al*. Assessment of therapeutic control in a long-term anticoagulant trial in post-myocardial infarction patients. *Thromb Haemost* 1994;**72**:347–51.
8 **Schaufele MK**, Marciello MA, Burke DT. Dosing practices of physicians for anticoagulation with warfarin during inpatient rehabilitation. *Am J Phys Med Rehab* 2000;**79**:69–74.
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anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998;**351**:233–41.
10 **Malik AK**, Taylor AJ. Can warfarin randomized trials be reproduced in "real life"? Adherence to warfarin guidelines for intensity of anticoagulation in a university based warfarin clinic. *South Med J* 2000;**93**:58–61.
11 **Streif MA**, Marzinotto AV, Massicotte P, *et al*. Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999;**94**:3007–14.
12 **Blann A**, Hewitt J, Siddiqui F, *et al*. Racial background is a determinant of average warfarin dose required to maintain the INR between 2 and 3. *Br J Haematol* 1999;**107**:207–9.
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ECHO

Myopathy and an unusual serum antibody point to a defined syndrome

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A study of patients presenting over three years with syndromes affecting skeletal muscles has found that those with serum antibody to the signal recognition particle (SRP) represent a defined syndrome. Empirical evidence suggests that early corticosteroid treatment may improve muscle strength.

Seven patients had antibodies to SRP but no antibodies linked with other myopathies. Their age range was 32–70 years and five were women. In most patients the disease started in the autumn (August-January), and all had similar signs and symptoms—severe, rapidly increasing weakness of proximal muscles, leading to disability. Muscle strength was recorded in some proximal muscles as MRC grade 0/5 in five patients and 3/5 in two. The weakness was always greatest in the deltoid and psoas muscles. Sensation was unaffected. Creatine kinase was greatly increased, up to 3000–25 000 U/l, and active myopathy was confirmed by electromyography.

Biopsy specimens of affected muscles showed active degeneration and regeneration of muscle fibres and swollen, but sparse, endomysial capillaries containing deposits of the terminal C5b–9 components of the complement cascade. No inflammation was evident in any of the samples, marking out this syndrome from other immune myopathies.

Patients had a neuromuscular examination and biopsy of muscles of grade 4/5 strength. Frozen sections were examined by histochemical and immunocytochemical methods and compared with those from six normal controls.

Subgroups of myopathologic syndromes are starting to be recognised by their specific clinical, immunological, and pathological criteria, and some are associated with specific serum antibody, the best defined so far and most common is with anti-Jo-1.

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