

Title	Warfarin prevalence, indications for use and haemorrhagic events
Authors	Quirke, William; Cahill, Mary R.; Perera, Kanthi; Sargent, Jeremy; Conway, Jane
Publication date	2007-03
Original Citation	Quirke, W.; Cahill, M.R.; Perera, K.; Sargent, J.; Conway, J. (2007) 'Warfarin prevalence, indications for use and haemorrhagic events'. Irish Medical Journal, 100 (3):402-404.
Type of publication	Article (peer-reviewed)
Link to publisher's version	<a href="http://www.imj.ie//IMJPage_0_1.aspx?issueid=311#Original%20Papers">http://www.imj.ie//IMJPage_0_1.aspx?issueid=311#Original%20Papers</a>
Rights	© Irish Medical Journal 2007
Download date	2024-12-03 20:58:39
Item downloaded from	<a href="https://hdl.handle.net/10468/465">https://hdl.handle.net/10468/465</a>

# Warfarin Prevalence, indications for use and haemorrhagic events

Ir Med J. 2007 Mar;100(3):402-4

## Abstract

Warfarin, the standard oral anticoagulant drug used in Ireland, is a widely prescribed medication, particularly in the elderly. A HSE Mid-Western Area wide audit was undertaken over a 12-month period to examine the prevalence and indications for warfarin use and haemorrhagic complications associated with the drug. Every patient receiving warfarin therapy over a 13-week period was included (2564). The age standardised rate varied from 0.09% of 35-39 year olds to 6.1% of 80-84 year olds. Atrial fibrillation was the most common indication (54%) in patients attending the Mid-Western Regional Hospital anticoagulation clinic. The annual cumulative incidence of adverse haemorrhagic events in patients with a recorded INR=5.0 episode was 16.6%. The incidence of major and minor haemorrhagic events per INR=5.0 episode was 1.3% and 15.3% respectively. The most common sites of haemorrhage were genitourinary (39%) and gastrointestinal (27%). No fatal or intracranial haemorrhage relating to episodes of over-anticoagulation were reported during the audit period. The most frequent reason for over-anticoagulation was drug interaction (43%). In 74% of patients, the elevated INR was reversed by omitting or reducing warfarin dose. In 17% of cases, vitamin K was administered. Only 3% of incidents were treated with fresh frozen plasma or prothrombin complex concentrates.

## Introduction

Warfarin is effective in the prevention of venous thromboembolism, thromboses in patients with heart valve prostheses, embolic stroke in patients with chronic atrial fibrillation and cerebrovascular disease. It is also of proven benefit in patients with pulmonary embolism and as secondary prophylaxis after myocardial infarction. Nonetheless, warfarin is associated with a significant incidence of serious haemorrhage. In a review of observational studies, average annual rates of fatal, major and major/minor haemorrhages were 0.8, 4.9 and 15% respectively.

The incidence of haemorrhage in warfarinised patients is directly related to the adequacy of control. Systems for the control of warfarin are evolving and becoming more sophisticated. Quality improvements in systems include the increasing use of computerised dosing, specialist nursing input into monitoring patients and the use of near patient testing for selected patients. These have been initiated with set protocols recommended by the British Committee for Standards in Haematology.

The delivery of care to warfarinised patients in the HSE Mid-Western area has undergone major changes between 1999 and 2002. During this time a computerised nurse led anticoagulation clinic replaced the more traditional physician led system. This was achieved with cross-disciplinary co-operation and resources from the HSE Mid-Western area and the national partnership process. The audit was undertaken after this period of change.

This audit aimed to establish the age related incidence of warfarin use in the HSE Mid-Western area and determine the frequency of indications for its use. Causes of over-anticoagulation were examined which we hope will aid clinicians in the future management of warfarin patients. With increasing worries about prion-transmitted (nvCJD) infection, examination of the practice of transfusing fresh frozen plasma to reverse over-anticoagulated patients has gained in importance. We also audited the use of blood products, vitamin K and stopping warfarin as means of reversal of over-anticoagulated patients.

## Methods

### Identification of warfarinised patients (laboratory computer records)

To quantify patients on warfarin within the borders of the HSE Mid-Western area, hospital laboratory computer records were interrogated in its laboratories, i.e. Mid-Western Regional Hospital Limerick, St John's Hospital Limerick, Ennis and Nenagh General Hospitals. We achieved this through COGNOS, a data extracting software package for iLAB, the laboratory information system. This number was quantified from a 13-week period, August 1st 2002 to October 31st 2002, a timeframe we deemed to be the maximum review interval for a patient on warfarin. Patients who had an INR $\leq$ 1.5 on 4 occasions over 2 weeks or more were deemed to be on warfarin unless there was a defined exclusion. For example, a patient known to have an elevated INR secondary to other causes, e.g. hereditary bleeding disorders, disseminated intravascular coagulation (DIC) or liver abnormalities were excluded. To ensure completeness of the computerised record and to allow the denominator of the population of the HSE Mid-Western area to be accurately utilised, laboratories on the borders of the HSE Mid-Western Area (Tralee, Clonmel, Cashel, Galway, Mallow and Waterford) were contacted. This allowed us to establish whether any patients, with Mid-Western Area addresses, had their INR monitored outside our region. Patients whose INR was monitored exclusively by near patient testing (Coagucheck) were determined by liaison with Roche Diagnostics and their customers. The resulting data was analysed and age standardised (Irish population standard) using the direct method.

### Identification of over-anticoagulated patients (laboratory computer records)

Over-anticoagulated patients were quantified from August 1st 2002 to August 1st 2003. Patients with an INR=5.0 episode in the 12-month audit period were identified from computer records using COGNOS, in HSE Mid-Western area hospital laboratories, to determine the incidence and extent of haemorrhages in such instances. An INR of five or above was chosen because INR values greater than five have shown a consistent increase in haemorrhagic events.

### Investigation of over-anticoagulated patients and categorisation of associated haemorrhagic events

Patients with INRs=5.0 were linked to accident and emergency attendances or inpatient/clinic records. Anticoagulation nurses and haematology medical staff examined the casualty record and hospital chart. We examined the record to determine the suspected primary cause of loss of INR control, action taken for its reversal and if any blood loss was evident relating to the episode of over-anticoagulation. General practitioner surgeries or nursing homes within the HSE Mid-Western Area, in care of patients who presented with an INR=5.0, were supplied with a questionnaire for each patient to obtain more information about the over-anticoagulation incident. Haemorrhages were categorised as major if they were fatal, intracranial, retroperitoneal or lead to a drop in haemoglobin concentration of 4g/dl or more and/or required transfusion of a minimum of 2 units of blood. Minor haemorrhages were all cases of haemorrhage not classified as major.

## Results

The number of patients estimated to be receiving warfarin within the HSE Mid-Western area was 2564. As expected, the age standardised rates (Table 1) rose sharply with age and in-patient age range of 80-84 it reached a maximum of 6.1% of this population (61/1000 standardised to Irish census 2002). In the very elderly (>85 years), the rate declined to 3.6% (36.5/1000).

Age group	Number on warfarin	HSE Mid-West area population	Ireland population figures	Age specific rates per 1000 people mid-west
15-19	3	27936	313188	0.1
20-24	12	28048	328334	0.42
25-29	6	24914	312693	0.24
30-34	30	24839	304676	0.86
35-39	23	24530	290906	0.94
40-44	49	23387	271984	2.1
45-49	54	22085	249604	2.4
50-54	127	20892	230843	6.1
55-59	203	17771	197294	11.4
60-64	278	13728	154252	20.3
65-69	391	12024	133474	32.5
70-74	428	10080	112129	42.5
75-79	493	8338	89815	59.1

80-84	323	5295	58857	61.0
85+	137	3756	41726	36.5
<b>Total</b>	<b>2557</b>	<b>229591</b>	<b>3917203</b>	
	<b>Overall age</b>	<b>standardized</b>	<b>rate</b>	<b>7.2/1000</b>

Reasons for warfarin therapy in patients attending the Mid-Western Regional Hospital clinic are summarised in Table 2. The most common indication for treatment was atrial fibrillation (54%). The ratio of male to female patients was 1.4:1. The average age of the patient was 66.5 years.

Indication	n	% of total cases
Atrial Fibrillation	404	54.4
Pulmonary Embolism/ Deep Vein Thrombosis	135	18.2
Mechanical Prosthetic Valve Replacement	86	11.6
Post-operative Primary Prevention of DVT	37	5.0
Cerebrovascular Disease †	36	4.8
Cardiac Disease °	30	4.0
Peripheral Vascular Disease	10	1.4
More than 1 of the above recorded	5	<1.0
<b>Total</b>	<b>743</b>	<b>100</b>

† - Denotes CVA/Transient Ischaemic Attacks  
° - Denotes Cardiomyopathies/Ischaemic Heart Disease/Congenital Heart Disease/Prevention of Myocardial Infarction

The number of patients presenting with INR=5.0 episodes in the 12-month audit period was 463. Detailed information was available on 327 of these episodes from which confirmation of warfarinisation was made in 307 cases. Information on remaining 136 episodes was unavailable due to missing/non-documentation of over-anticoagulation events and the inability to access some community or general practitioner records.

Suspected primary cause of INR=5.0	n	% of total cases
Interacting medication	133	43.3
Accidental overdose	42	13.6
Overdose at Warfarin induction	30	9.9
Alcohol related	27	8.8
Prescription error	12	3.9
Hepatic dysfunction	8	2.6
Pre-analytical error	8	2.6
Malnutrition/Malabsorption of Vitamin K	3	1.0
Unknown	44	14.3
<b>Total</b>	<b>307</b>	<b>100.0</b>

Table 3 shows the suspected primary cause of INR=5.0 cases, the most common being drug interaction (43%).

Within the audit period, 51 patients (16.6%) who presented with an INR=5.0 experienced episodes of haemorrhage. Of these 47 (15.3%) had a minor haemorrhage while 4 (1.3%) had a major haemorrhage. No fatal haemorrhage relating to over-anticoagulated patients was reported during the audit period. The most common sites of haemorrhage were genitourinary (39.2%) and gastrointestinal (27.5%). Other types of haemorrhages discovered in over-anticoagulated patients were bruising/haematoma of soft tissue (11.8%), epistaxis (7.8%), haemoptysis (5.9%), gingival/oral mucosal (3.9%) and other sites (3.9%). While this audit focused on episodes of haemorrhage, it was also noted that in the 12-month audit period, only one of the 932 Mid-Western Regional Hospital anticoagulation clinic patients presented with a thromboembolism while on warfarin.

Action taken to counteract INRs=5.0	n	% of total cases
Warfarin dose omitted/reduced only	227	74.0
Vitamin K (Oral/IV)	53	17.3
Fresh Frozen Plasma (FFP)	7	2.3
Prothrombin Complex Concentrate (PCC)	3	1.0
Warfarin therapy terminated	9	2.9
None	8	2.6
<b>Total</b>	<b>307</b>	<b>100</b>

Table 4 details the action taken to counteract episodes of over-anticoagulation. The most frequently used method of INR reversal was warfarin dose omission/reduction.

Information not available on 7 patients whose INR was tested in laboratories outside the borders of the HSE-Western area.

No patients on warfarin between the ages of 0-14 were detected during the study period.

This table shows the number of patients on warfarin in different age groups. Column 4 shows the Irish figures from the census data for this age group and the last line of column four contains the total population figures. The rates in column 5 show the age specific rates in the Mid-West standardized against the Irish population to allow easy comparison with other areas.

### Discussion

Notable features from the audit included the calculation of age specific rates for warfarin patients in the Mid-Western area. Changes in the indications for anticoagulation have resulted in a progressive increase in patients requiring lifelong oral anticoagulant therapy, especially in the older age groups. The number of patients on oral anticoagulants has increased rapidly over the past five years, principally due to the large number of elderly patients with chronic atrial fibrillation commenced on this therapy for the prevention of stroke. This audit confirmed this with over half of patients (54%) attending the warfarin clinic with atrial fibrillation as their primary indication for treatment.

This audit also highlights the encouraging and predominant use of warfarin dose omission/reduction (74%) to counteract over-anticoagulated patients in accordance with hospital and British Committee for Standards in Haematology (BCSH) guidelines. Only 17% of over-anticoagulated patients were administered vitamin K. With increasing concern regarding transfusion-transmitted infection and prion disease, the use of fresh frozen plasma in only 7 and prothrombin complex concentrate in only 3 out of 307 patients is also encouraging. BCSH guidelines suggest that factor concentrates are more effective than frozen plasma (Octoplas) in the treatment of over-anticoagulation. Recent trends in the Mid-Western Regional Hospital confirm that prothrombin complex concentrate is now the preferred option for serious haemorrhage in over-anticoagulated patients where immediate correction is needed. It is issued after discussion with the consultant haematologist on-call who advises on appropriate correction of elevated INR.

Due to its narrow therapeutic index and its pharmacokinetic and pharmacodynamic properties, warfarin is highly susceptible to interactions with other drug components. The high incidence of interacting medication (43%) as a cause of loss of INR control needs to be addressed. The most common clinical picture associated with drug induced alterations in INR was the treatment of exacerbations of chronic obstructive pulmonary disease and infections. Antibiotics and antibiotic/steroid combinations were the most common category of interacting drugs. When prescribing new medications, ideally a non-interacting drug should be chosen. Where this is not possible, more frequent INR monitoring and dose alteration is necessary until the course of medication is completed or warfarin control has stabilised. This is routinely encouraged in the warfarin clinic.

Prescription and pre-analytical errors resulting in an elevated INR are amenable to reduction in the future. A typical example of a prescription error included clerical errors in dosage charts of in-patients resulting in overdosing, although some cases involved unexplained dosage increase by medical staff with the INR within therapeutic range. Three cases of minor haemorrhage were associated with prescription errors. Pre-analytical errors primarily involved

inappropriate methods of specimen collection. An example of these errors would include a specimen taken from a patient intravenous line resulting in dilution of patient plasma giving a falsely elevated INR. No episodes of haemorrhage were reported with these types of errors.

Initiating warfarin therapy is undoubtedly one of the most difficult aspects of warfarin management. As well as the frequent elderly age of the patient, the physician may encounter a previously unknown bleeding risk, sensitivity, or resistance to oral anticoagulant effects. One common pitfall is the unnecessary urgency to achieve a therapeutic INR for chronic conditions such as atrial fibrillation. A previous audit<sup>9</sup> of the start of anticoagulant treatment reported that 58% of INR results were not therapeutic upon patient discharge.

Most hospitals or surgeries initiate warfarin with high loading doses, most often ten milligrams on days one and two of therapy. This audit discovered 30 cases (9.9%) of INRs=5.0 with 1 associated minor haemorrhage event due to overdose at induction, thereby confirming this as a significant cause of over-anticoagulation. Multiple studies have confirmed the fallacy of relying on a high loading dose, which can potentially result in early over-anticoagulation and the development of a potential hypercoagulable state. It has been demonstrated that a 10-mg loading dose<sup>10, 11</sup> is unlikely to be more effective than a 5-mg dose in achieving a therapeutic INR by day 4 or 5 of therapy.

The annual incidence of major (1.3%) and minor (15.3%) haemorrhages per INR =5.0 episode appears to be broadly in line (allowing for differences in definition) with large clinic population studies showing major haemorrhage rates of 2% and minor haemorrhage rates of just over 5%.<sup>12</sup> Comparison is difficult because the criteria for defining the severity of bleeding vary considerably between studies, accounting in part for the variation in the rates of bleeding. We acknowledge the limitations in using INR=5.0 in calculating the incidence of haemorrhages, including the fact that patients experiencing haemorrhage within INR range or less than 5.0 were<sup>13</sup> not systematically identified. In addition, most intracranial haemorrhages occur with INR within therapeutic range. However, during the audit period, no fatal or intracranial haemorrhage in warfarinised patients (with any INR range) was reported. Of the 932 patients attending the MWRH clinic in the 12-month audit period, only one experienced a thromboembolic event. This patient was within INR therapeutic range at the time of the embolus being diagnosed.

There is a continuous need to monitor the standards of anticoagulation achieved and the quality of service delivered. The age standardised rates in this study allow more detailed service delivery planning which clearly needs to be targeted to the needs of the elderly population. The information in this audit may be useful to other HSE areas within Ireland to assist with benchmarking and service planning.

## References

1. Baglin T, Keeling D, & Watson H for the British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition â 2005 update. *British Journal of Haematology* 2005; 132: 277-285
2. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomised controlled trials. *Archives of Internal Medicine* 1994; 154: 1449-1457.
3. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; 348: 423-428.
4. Ryan P, Gilbert M, & Rose P. Computer control of anticoagulant dose for therapeutic management. *British Medical Journal* 1989; 299: 1207-1209.
5. British Committee for Standards in Haematology. Guidelines for near patient testing. *Clinical and Laboratory Haematology* 1995; 17: 301-310.
6. Rose P. Audit of anticoagulant therapy. *Journal of Clinical Pathology* 1996;49: 5-9.
7. Cannegieter S, Rosendaal F, Wintzen A, Van der Meer F, Vandenbroucke J & Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *New England Journal of Medicine* 1995; 333: 11-17.
8. Davidson J, Colvin B, Barrowcliffe T, et al. British Committee of Standards of Haematology Guidelines on Oral Anticoagulation, 2nd edition. *Journal of Clinical Pathology* 1990; 43: 177-183.
9. Tan G, Cohen H, Taylor F, & Gabby J. Audit of start of anticoagulation treatment in patients. *Journal of Clinical Pathology* 1993; 46: 67-71.
10. Harrison L, Johnston M, Massicotte M, Crowther M, Moffat K & Hirsh J. Comparison of 5-mg and 10-mg loading doses initiation of warfarin therapy. *Annals of Internal Medicine* 1997; 126: 133-136.
11. Crowther M, Ginsberg J, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Archives of Internal Medicine* 1999; 159: 46-48.
12. DiMarco JP, Flaker G, Waldo AL, Corley SD, Greene HL, Safford RE, Rosenfeld LE, Mitrani G, Nemeth M; AFFIRM Investigators. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation. Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005 Apr; 149(4): 650-6.
13. Butler A, & Tait R. Management of oral anticoagulant-induced intracranial haemorrhage. *Blood Reviews* 1998; 12: 35-44.

Comments: MR Cahill Department of Haematology, CUH, Wilton, Cork Email: <a href=mailto:MaryR.Cahill@mailp.hse.ie>MaryR.Cahill@mailp.hse.ie</a>