

# A comparison of a low-dose warfarin induction regimen with the modified Fennerty regimen in elderly inpatients

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## Abstract

**Objectives:** to compare a new low-dose warfarin induction regimen with the Fennerty regimen in elderly inpatients.

**Design:** age-stratified, randomized prospective study.

**Subjects:** 120 age-stratified elderly inpatients.

**Interventions:** each patient was randomized to either the new induction regimen or to a modified Fennerty regimen.

**Main outcomes measures:** days to therapeutic International Normalized Ratio (INR >2); days in the therapeutic range (INR 2–3) during induction; number of patients with INR >4.5; ability of day 4 INR to predict day 8 warfarin dose.

**Results:** the mean time to therapeutic INR was longer for the new induction regimen than modified Fennerty regimen in patients aged 65–75 years [4.6 (mean) ± 1.6 (SD) days *vs* 3.8 ± 0.8 days; *P* = 0.03] and in patients aged >75 years (4.5 ± 1.4 days *vs* 3.5 ± 0.7 days; *P* = 0.003). Patients spent more time in the therapeutic INR range with the new induction regimen [3.0 ± 1.3 days *vs* 2.7 ± 1.3 days (*P* = 0.03) for those aged 65–75 years and 2.9 ± 1.1 days *vs* 2.4 ± 1.3 days (*P* = 0.04 for those aged >75 years)]. Fewer patients using the new regimen had INRs >4.5 in the first 8 days [1 (3%) *vs* 6 (20%) for 65–75 years (*P* < 0.05) and 1 (3%) *vs* 11 (37%) for >75 years (*P* < 0.01)]. The ability to predict the maintenance dose to within 1 mg was 55% for both regimens.

**Conclusion:** the low-dose regimen has important clinical advantages over the Fennerty regimen for anticoagulating elderly inpatients.

**Keywords:** anticoagulation, protocols, warfarin

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## Introduction

Elderly people have an increased risk of haemorrhage associated with oral anticoagulants, particularly if they have co-morbid disease and an International Normalized Ratio (INR) of >4.5 [1, 2]. With ageing, less warfarin is required to provide the same degree of anticoagulation [3, 4] although no age-related differences in clotting factor degeneration have been demonstrated. Although warfarin pharmacokinetics may not change with age [5], there may be greater inhibition of vitamin K-dependent clotting factor synthesis at equivalent plasma warfarin levels in elderly subjects.

Following ingestion, there is rapid absorption of warfarin but the anticoagulant effect is usually delayed for 24–36 h. Warfarin induction regimens have become common practice, with the most widely recommended

being that reported by Fennerty *et al.* [6]. This was initially described in patients with a mean age of 52 years, but has been poorly validated in older groups [6–8]. A recent study in elderly inpatients has suggested that this regimen may be associated with over anticoagulation and may be poorly predictive of maintenance warfarin requirements [8]. Here, we describe a new low-dose warfarin induction regimen which aims to reduce over-anticoagulation, increase time in the therapeutic INR range during the induction period and be more predictive of maintenance warfarin requirements than the modified Fennerty regimen.

## Subjects and methods

Following approval by the local ethics committee,

Table 1. Morning International Normalized Ratios (INRs) and evening doses of warfarin for the two regimens

| Day | INR     | Warfarin dose (mg) |                   |
|-----|---------|--------------------|-------------------|
|     |         | New induction      | Modified Fennerty |
| 1   | <1.4    | 10                 | 10                |
| 2   | <1.8    | 5                  | 10                |
|     | 1.8-2.0 | 1                  | 1                 |
|     | >2.0    | -                  | -                 |
| 3   | <2.0    | 5                  | 10                |
|     | 2.0-2.2 | 4                  | 5                 |
|     | 2.3-2.5 | 4                  | 4                 |
|     | 2.6-2.9 | 3                  | 3                 |
|     | 3.0-3.2 | 2                  | 2                 |
|     | 3.3-3.5 | 1                  | 1                 |
|     | >3.5    | -                  | -                 |
|     | 4       | <1.4               | >7                |
| 4   | 1.4-1.5 | 7                  | 8                 |
|     | 1.6-1.7 | 6                  | 7                 |
|     | 1.8-1.9 | 5                  | 6                 |
|     | 2.0-2.3 | 4                  | 5                 |
|     | 2.4-3.0 | 3                  | 4                 |
|     | 3.1-3.2 | 2                  | 3                 |
|     | 3.3-3.5 | 1                  | 3                 |
|     | 3.6-4.0 | -                  | 3                 |
|     | >4.0    | -                  | - <sup>a</sup>    |

<sup>a</sup>Until INR <3.

consecutive elderly inpatients starting warfarin were recruited and randomized to either the new low-dose induction regimen or the modified Fennerty regimen (Table 1) to achieve a target INR of 2–3. Patients were age-stratified into 65–75 years and >75 years bands. Concomitant use of heparin and other medications did not influence randomization.

Baseline demographic data as well as the indications for anticoagulation, concomitant diagnoses and medication were recorded. Daily INR values and warfarin dosages were noted. The ability of each regimen to predict maintenance (day 8) warfarin dosage from the day 4 INR value was recorded.

### Sample collection

Morning blood samples were collected on days 2–8 for INR estimation and from this value an evening (1800 h) dosage of warfarin was prescribed. Patients' INRs were calculated after their prothrombin times had been

measured with Innovin (DADE). Synthasil (Ortho) was used for activated partial thromboplastin time (APPT) tests. All coagulation tests were performed on Sysmex CA6000 (Toa Medical Electronics Company Ltd). All patients had an INR of <1.4 before treatment, and no patient had an APPT ratio >10.

### Statistical analysis

Values are expressed as mean (standard deviation). Comparisons of the time taken to achieve a therapeutic INR and time within the therapeutic range during the first 8 days between the two regimens were performed by Mann-Whitney *U* tests for non-parametrically distributed data. The numbers of patients with INRs >4.5, and for whom the day 4 warfarin dose predicted day 8 maintenance dosage, were compared between the different groups using  $\chi^2$  analysis. A *P* value of <0.05 was taken as statistically significant.

### Results

One hundred and twenty-seven patients were randomized but seven were withdrawn due to failure to prescribe according to the randomized regimen (three for each regimen) or because their INR was not checked on day 4. For the remaining 120 patients there were no differences in age, sex, co-prescribed drugs (including heparin), concomitant diagnoses or indications for warfarin between the age-stratified groups (Table 2).

Over-anticoagulation was defined as an INR of >4.5 [6]. Fewer patients treated according to the new induction regimen had INRs >4.5 in the first 8 days than patients treated according to the modified Fennerty regimen [1 (3%) *versus* 6 (20%) for ages 65–75 years (*P* < 0.05) and 1 (3%) *versus* 11 (37%) for ages >75 years (*P* < 0.01); Figure 1]. There were no reported bleeding episodes during the study but one patient randomized to the modified Fennerty regimen received 1 mg of vitamin K when her INR was 10. Warfarin was omitted on 59 occasions during the first 8 days in those patients receiving the modified Fennerty regimen and on 18 occasions for patients those receiving the new regimen.

Patients in both age groups spent more time within the therapeutic INR range with the new regimen than the modified Fennerty regimen [ $3.0 \pm 1.3$  days *versus*  $2.7 \pm 1.3$  days (*P* = 0.03) for those aged 65–75 years and  $2.9 \pm 1.1$  days *versus*  $2.4 \pm 1.3$  days (*P* = 0.04) for those aged >75 years]. The mean time to therapeutic INR was longer for the new regimen both for subjects aged 65–75 years ( $4.6 \pm 1.6$  days *versus*  $3.8 \pm 0.8$  days; *P* = 0.03) and for those aged >75 years ( $4.5 \pm 1.4$  days *versus*  $3.5 \pm 0.7$  days; *P* = 0.003).

Day 8 warfarin dose was taken to be the maintenance warfarin dose. In those aged 65–75, day 4 INR

## Validation of low-dose warfarin induction regimen

Table 2. Patient characteristics, anticoagulation indications and concomitant diagnoses of patients receiving the two warfarin regimens

| Characteristic   | Subjects aged 65–75 years         |                                       | Subjects aged >75 years           |                                       |
|--|-----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|
|  | New induction<br>( <i>n</i> = 30) | Modified Fennerty<br>( <i>n</i> = 30) | New induction<br>( <i>n</i> = 30) | Modified Fennerty<br>( <i>n</i> = 30) |
| Mean age, years  | 70.3                              | 70.5                                  | 80.5                              | 80.6                                  |
| No. (and %) male   | 17 (57%)                          | 13 (43%) <sup>a</sup>                 | 12 (40%)                          | 18 (60%) <sup>b</sup>                 |
| Missing INRs (%)   | 6.3                               | 5.0                                   | 4.6                               | 3.3                                   |
| No. (and %) receiving heparin                            | 14 (47%)                          | 16 (53%)                              | 13 (43%)                          | 14 (47%)                              |
| No. of patient indications for warfarin                  |                                   |                                       |                                   |                                       |
| Atrial fibrillation                                      | 12                                | 10                                    | 17                                | 11                                    |
| Pulmonary embolism                                       | 8                                 | 13                                    | 5                                 | 9                                     |
| Venous thrombosis  | 9                                 | 6                                     | 8                                 | 9                                     |
| Other conditions   | 1                                 | 1                                     | 0                                 | 1                                     |
| No. of subjects with concomitant diagnoses               |                                   |                                       |                                   |                                       |
| Cardiovascular   | 17                                | 19                                    | 22                                | 19                                    |
| Cerebrovascular  | 5                                 | 2                                     | 9                                 | 7                                     |
| Infection  | 6                                 | 3                                     | 3                                 | 5                                     |
| Lung disease   | 7                                 | 7                                     | 6                                 | 8                                     |
| Malignancy   | 6                                 | 2                                     | 3                                 | 5                                     |
| Other  | 17                                | 23                                    | 27                                | 25                                    |
| No. of patients taking 0, 1 or ≥2 additional medications |                                   |                                       |                                   |                                       |
| 0  | 14                                | 13                                    | 8                                 | 8                                     |
| 1  | 13                                | 12                                    | 12                                | 14                                    |
| ≥2   | 3                                 | 5                                     | 10                                | 9                                     |

<sup>a</sup>*P* < 0.05; <sup>b</sup>*P* < 0.01; none of the other differences were statistically significant.  
INR, International Normalized Ratio.

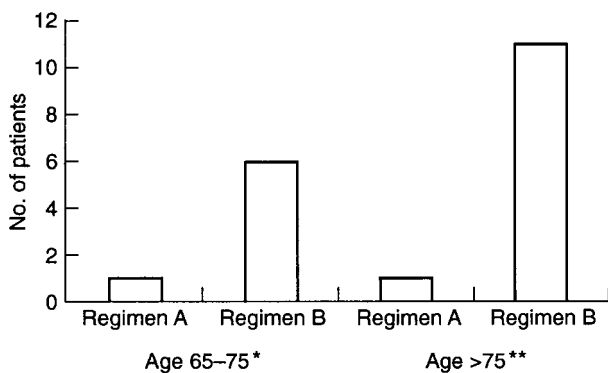


Figure 1. Number of patients with International Normalized Ratios >4.5 receiving regimen A (new induction) and B (modified Fennerty). Comparison between regimens A and B for each age group: \**P* < 0.05; \*\**P* < 0.01.

predicted warfarin maintenance dose exactly in seven patients (23%) receiving each regimen and to within 1 mg in 17 patients (57%) receiving the new regimen and 15 patients (50%) receiving the modified Fennerty regimen (not significant). Among those aged >75 years, day 4 INR predicted maintenance warfarin dose exactly in nine (30%) of the patients receiving the new regimen and eight (27%) of the patients receiving the modified Fennerty regimen and to within 1 mg in 16 (53%) of those receiving the new regimen and 18 (60%) of those receiving the modified Fennerty regimen (not significant).

## Discussion

This is a pragmatic study of a new low-dose warfarin induction regimen for elderly inpatients with standard indications. Implementation will depend upon medical

staff checking patient INRs daily and following the regimen closely. Unfortunately junior doctors often prescribe warfarin whilst on call for patients who are not their own (since the INRs are often returned after the end of the standard working day) or in circumstances when they may be unaware of the patient's age or do not have access to a printed regimen.

For both age groups, the new warfarin regimen was associated with more time in the therapeutic range than the modified Fennerty regimen but time to therapeutic INR was increased. The delay in achieving a therapeutic INR was <1 day on average but may be important if starting warfarin is the only reason for staying in hospital. Alternatively, an unstable INR may delay discharge and be associated with significant costs in terms of bed utilization, particularly in over-anticoagulation has required treatment. Warfarin can, however, be started safely as an outpatient [9].

The principal advantage of our new regimen lies in the reduction in over-anticoagulation. Although our patients were stratified because age >75 years has been shown to be an independent risk factor for haemorrhage [2], particularly with INR >4.5 [1], the incidence of over-anticoagulation was in favour of the new regimen in both age groups. The excess anticoagulation associated with the modified Fennerty regimen may be due to rapid reduction in factor VII levels, prior to a fall in levels of factors X and II [10].

The regimens were of similar value in predicting maintenance warfarin requirements. The absolute value of predictability is lower than in previous studies, which may reflect both the methodology used and our INR target range of 2–3 compared with the value of 2–4 which was used in previous studies [6, 7, 11].

In summary, this new regimen has significant advantages over the Fennerty regimen for inpatient anticoagulation of elderly people. Although the time to therapeutic INR is marginally longer, this is offset significantly by the greater time in the therapeutic range and lower incidence of significant over-anticoagulation associated with the new regimen.

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## Key points

- The new low-dose warfarin induction regimen results in less over-anticoagulation (INR >4.5), fewer omitted warfarin doses and more time in the therapeutic range (INR 2–3) than the modified Fennerty regimen.
  - The new regime takes slightly longer than the modified Fennerty regimen to achieve a therapeutic International Normalized Ratio.
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