

Dependency rather than old age increases the risk of warfarin-related bleeding

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SUMMARY

There is uncertainty about the safety of anticoagulation with warfarin in the elderly. This cohort study investigated the risk factors for warfarin-related bleeding in a primary care setting. In multiple regression analyses increased risk of bleeding was associated with domiciliary monitoring of international normalised ratio (INR), low proportion of INR tests in the target range, high intensity of anticoagulation, and male sex. Age was not associated with increased risk after adjustment. High levels of dependency, not old age, should raise concerns about the safety of anticoagulation with warfarin.

Keywords: aged; anticoagulants; dependency; haemorrhage; risk; warfarin.

Introduction

CAREFUL patient selection is a prerequisite to safe, cost-effective anticoagulation with warfarin, and depends on an assessment of each patient's risk of haemorrhagic complications. Understanding of the determinants of bleeding is improving, but uncertainties still exist, particularly about the role of age as an independent risk factor.¹ This unselected population cohort study was designed to investigate the risk factors for warfarin-related bleeding in a primary care setting.

Method

Patients were receiving treatment with warfarin and registered with one of four general medical practices, which provided surgery-based and domiciliary near-patient monitoring of anticoagulant therapy, during the period 1995–2000. A detailed account of this service has been reported previously.² International normalised ratio (INR) testing and warfarin dosing were performed in accordance with standard protocols by fully-trained nursing staff. During a cumulative follow-up of 664.8 person years, 380 episodes of warfarin treatment were monitored in 344 patients. Multiple episodes of anticoagulation were required in patients with recurrent venous thromboembolism and non-rheumatic atrial fibrillation, that recurred following cardioversion. In addition, patients who received continuous treatment with warfarin were considered to have had more than one episode of monitoring when the indication changed and in any situation where the INR target range was altered.

Fifty-six per cent of patients were female. Age at the time of enrolment ranged from 16 to 95 years with a median of 71 years. Sixty-nine (18%) episodes of monitoring were started when patients were 80 years or older. The most common indications for anticoagulation were non-rheumatic atrial fibrillation in 194/380 (51%) and venous thromboembolism in 70/380 (18%) episodes of monitoring. During 228 episodes all monitoring was performed in the surgery, in 84 episodes monitoring was in the patient's home (because they were unfit to attend the surgery), and in 68 episodes monitoring was carried out in both settings at different times.

Bleeding complications were classified as major when it was intracranial (documented by imaging); surgery or angiographic intervention were required to stop bleeding; bleeding resulted in a reduction in haemoglobin levels of 2 g/dl or more or necessitated transfusion of two or more units of blood; and when bleeding resulted in permanent loss of organ function, for example, intraocular bleeding causing blindness. Other bleeding events were classified as minor. Eighteen major bleeding events (four of which were fatal) occurred in 16 patients. A further 41 minor bleeding episodes in 27 patients resulted in hospital attendance for assessment or treatment.

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HOW THIS FITS IN

What do we know?

Careful patient selection is necessary to ensure that anticoagulation with warfarin is safe and effective. There is concern that old age may confer an increased risk of bleeding complications.

What does this paper add?

In this study, patients requiring domiciliary monitoring of international normalised ratio were at greatest risk of bleeding, and age had no independent effect. This finding indicates that it is not advanced age but dependency that should raise concerns about the safety of anticoagulation with warfarin.



This study was performed using previously anonymised data.² Analysis of time to first bleeding event was carried out separately for minor and major events using Cox's proportional hazard model, with the counting process approach to incorporate varying discrete time periods of warfarin exposure (episodes of treatment) in individual patients. Following initial unadjusted analyses, variables with $P < 0.3$ or judged to be of clinical importance were entered in multiple regressions. Risk factors included age, sex, location of monitoring, warfarin indication, INR target (minimum and maximum), percentage of time and percentage of tests in range, below range and above range, and maximum achieved INR. Previous minor bleeding episodes were included in analysis of risk factors for major bleeding. All analyses were carried out in SAS (version 8).

Results

In multiple regression analyses the following factors were associated with an increased risk of bleeding (Table 1):

- domiciliary monitoring,
- a low proportion of INR tests within the target range,
- high intensity of anticoagulation (maximum target INR), and
- male sex.

The fivefold increased risk of major bleeding after a minor event just failed to achieve statistical significance because of small numbers. Age was not strongly associated with increased risk after adjustment.

Discussion

Patients whose high level of dependency necessitated domiciliary monitoring were at greatest risk of warfarin-related bleeding, but increasing age had no independent effect.

This primary care-based service, serving an elderly population, provided an opportunity to compare differences in the outcome of anticoagulation in ambulant and housebound patients. The process of surgery and domiciliary monitoring (INR testing and warfarin dosage protocol) was the same and staff in both settings received identical training. Differences in outcome are therefore likely to be attributable to differences in patient characteristics rather than type of service provision.

It is taught that old age is associated with increased risk of bleeding.³ Anticoagulation is underused⁴ and many clinicians consider that it should be avoided in the elderly.⁵ However, our findings indicate that it is not advanced age but dependency that should encourage a cautious approach to treatment. We did not investigate which aspects of dependency explained the increased risk, but possible determinants include multiple morbidity, polypharmacy, cognitive impairment, tendency to falls, and frequent hospital admissions. The data suggest that the management of patients who need domiciliary monitoring should differ from that of patients who are still mobile enough to attend the surgery. For example, it may be necessary to apply more restrictive criteria for initiating treatment and to adopt a lower target INR in dependent patients. However, further prospective investigation is required to provide the evidence that such a policy will improve outcomes.

We have observed an increased risk of major bleeding in men which emerged only after adjustment for all other variables, notably domiciliary monitoring, which was three times more common in women. The explanation for this finding is unclear but may relate to some aspect of comorbidity or lifestyle.

Table 1. Adjusted hazard ratios and 95% CI for time to first minor and major bleeding event ($n = 344$ patients).

Variable	Minor bleed ($n = 27$ events)			Major bleed ($n = 16$ events)		
	Adjusted hazard ratio	95% CI	P-value	Adjusted hazard ratio	95% CI	P-value
Previous minor event	N/A	N/A	N/A	5.36	0.86 to 33.6	0.073
Monitoring						
(Domiciliary versus surgery)	3.08	1.03 to 9.27	0.045	14.04	2.82 to 70.0	0.001
(Domiciliary and surgery versus surgery)	2.29	0.83 to 6.35	0.110	4.54	1.01 to 20.5	0.049
Tests in range (+20%)	0.41	0.23 to 0.72	0.002	0.90	0.44 to 1.84	0.781
Maximum INR target (+1)	2.25	1.15 to 4.42	0.018	2.54	0.94 to 6.91	0.067
Maximum INR (+2)	0.74	0.47 to 1.16	0.189	1.27	0.89 to 1.81	0.185
Male versus female	1.38	0.58 to 3.26	0.465	3.68	1.05 to 12.9	0.001
Age (+10 years)	1.28	0.83 to 1.96	0.268	1.25	0.57 to 2.74	0.580

INR = international normalised ratio; N/A = not applicable.

The finding that the proportion of INR tests within target range is a predictor of risk of minor bleeding is of clinical relevance. This index of quality of long-term anticoagulation control is easily measured and should form part of the routine assessment of individual patients on warfarin.

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