The incidence of bleeding complications associated with warfarin treatment in general practice in the United Kingdom

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SUMMARY
The aim of this study was to estimate and explore the incidence of warfarin-related bleeding in a representative sample of patients in the United Kingdom. We identified 3958 patients aged 40 to 84 years, newly treated with warfarin and with no prior history of bleeding from the General Practice Research Database, and followed them for 12 months. The overall incidence of first-time, idiopathic bleeding was 15.2 per 100 patient-years of current warfarin exposure: the incidence of fatal/hospitalised and referred bleeding was 3.5 and 2.6 per 100 patient-years, respectively.
Keywords: *warfarin; bleeding; incidence; United Kingdom.*

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Introduction

WARFARIN is an effective therapy for both the treatment and prevention of thromboembolic events; however, bleeding is a relatively common, and sometimes serious, complication.[1] Bleeding rates reported under clinical trial conditions may be a poor guide to observed rates in real-life practice. The purpose of this study was to estimate the incidence of bleeding complications associated with the use of warfarin in general practice in the United Kingdom (UK), and to assess the effects of age, sex, and indication for treatment.

Method

Data were obtained from the General Practice Research Database (GPRD), which is a computerised database of longitudinal patient records collected from a panel of general practitioners (GPs) in the UK.[2] The information recorded includes demographics, medical diagnoses from GP visits, outpatient visits, hospitalisations, and prescriptions. Patients were eligible for inclusion in the study if they had a first-ever prescription of warfarin during the study period (1 January 1994 to 30 June 1996), were aged 40 to 84 years old at the time of that prescription, had been permanently registered with the practice for at least a year at the time of that prescription, had no record of prior bleeding or coagulation disorders, and were not pregnant and had at least one year of follow-up, or had died, during the study period.

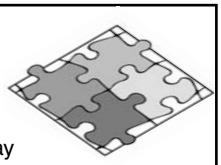
Patients were excluded if the indication for treatment could not be determined, if they were receiving fixed low-dose warfarin, or if the indication was solely post-surgical venous thromboebolism prophylaxis.

All patients in this cohort were followed from the start of treatment until the earliest occurrence of any the following events: occurrence of a bleed or development of a coagulation disorder, reaching the age of 85 years, death, or the end of the one-year follow-up period. The case definition was idiopathic, first-time bleeding events occurring during the follow-up period. Non-idiopathic bleeding, such as that directly relating to surgery or trauma, was excluded.

Potential cases were identified by searching the computer record for codes and/or comments that indicated a bleed during the follow-up period. These were manually reviewed and a questionnaire was sent to the GP to confirm the bleed and to obtain more information about the outcome. Anonymised copies of hospital letters were requested.

Bleeds were classified as: 'fatal' if the patient died of a bleeding-related cause within seven days of a bleeding event; 'hospitalised' if the patient was admitted as a result of the bleed or was already in hospital at the time of the bleed;

HOW THIS FITS IN



What do we know?

Clinical trial-based estimates of the incidence of warfarin-induced bleeding may not reflect rates in real-life practice; however, observational data are sparse for most indications.

What does this paper add?

This study describes the incidence of bleeding complications, by indication, in a large representative cohort of UK patients with no prior history of bleeding. Bleeding resulting in referral or hospitalisation is common. Rates of major bleeding reported in clinical trials provide an incomplete picture of the bleeding complications that patients and their physicians encounter in everyday practice.

'referred' if the patient was referred to an outpatient or casualty department; and 'minor' otherwise. Indication for treatment was classified from the computer record. Patients with both atrial fibrillation and cerebrovascular disease as an indication were included in the atrial fibrillation group. 'Current warfarin exposure' was defined as all patient time occurring within 0 to 30 days of a prescription. We studied only events occurring during current warfarin exposure, since exposure status was considered unknown for other periods**.** Poisson regression was used to estimate incidence rates and confidence intervals, and to assess the independent effects of indication, age, and sex.

Results

The final cohort consisted of 3958 warfarin users. A total of 400 incident, idiopathic bleeds occurred during follow-up, of which 245 occurred during current warfarin exposure. Gastrointestinal bleeding, epistaxis, intracranial bleeding, and haematuria were the most common forms of fatal/hospitalised bleeds (Table 1).

The overall incidence of bleeding was 15.2 bleeds per 100 patient-years of current exposure (Table 2). After adjusting for age and sex, the overall risk of bleeding varied by

Table 1. Characteristics of first-time idiopathic bleeds during current exposure to warfarin.

Site/system	Number of bleeds (%)			
	All	Fatal/hospitalised	Referred	Minor
Intracranial	5 (2)	5 (9)	0 (0)	0 (0)
Gastrointestinal	48 (20)	19 (34)	11 (26)[a]	18 (12)[a]
Genitourinary/haematuria	60 (25)	8 (14)	14 (33)	38 (26)
Epistaxis	49 (20)	14 (25)	8 (19)	27 (18)
Haemoptysis	10 (4)	3 (5)	2 (5)	5 (3)
Bruising/haematoma of soft tissue	32 (13)	3 (5)	0 (0)	29 (20)
Eye	22 (9)	0 (0)	4 (10)	18 (12)
Other	19 (8)	5 (9)	3 (7)	11 (8)
Total: all sites	245 (100)	57 (100)	42 (100)	146 (100)

[a]Predominantly rectal bleeding (possibly haemorrhoidal) or blood in the stools.

Table 2. Crude incidence rate (IR) per 100 patient-years and adjusted relative risk (RR) of bleeding during current warfarin exposure.

Patient characteristic	Number of Patients (%)	All bleeds			RR[a] of bleeding (95% CI)		
		Number of bleeds	IR (95% CI)[b]	RR[a] (95% CI)	Fatal/hospitalised	Referred	Minor
All	3958 (100)	245	15.2 (13.5–17.0)				
Fatal/hospitalised		57	3.5 (2.7–4.6)				
Referred		42	2.6 (1.9–3.5)				
Minor		146	9.1 (7.8–10.6)				
Age							
40–49	320 (8)	20	19.6 (13.1–28.4)	1	1	1	1
50–59	690 (17)	35	13.7 (10.0–18.4)	0.74 (0.4–1.3)	0.5 (0.2–1.8)	0.2 (0.1–1.1)	1.0 (0.5–2.1)
60–69	1148 (29)	72	15.4 (12.4–18.9)	0.84 (0.5–1.4)	0.6 (0.2–1.7)	1.0 (0.3–3.0)	0.9 (0.4–1.7)
70–79	1415 (36)	89	14.7 (12.1–17.8)	0.80 (0.5–1.3)	1.0 (0.4–2.5)	0.6 (0.2–2.0)	0.8 (0.4–1.5)
80–84	385 (10)	29	16.1 (11.5–22.2)	0.87 (0.5–1.5)	1.2 (0.4–3.5)	1.1 (0.3–3.9)	0.7 (0.3–1.6)
Sex							
Male	2280 (58)	129	13.8 (11.8–16.2)	1	1	1	1
Female	1678 (42)	116	17.1 (14.5–20.1)	1.17 (0.9–1.5)	1.3 (0.8–2.2)	0.6 (0.3–1.2)	1.3 (0.9–1.9)
Indication							
DVT/PE	1608 (41)	94	18.4 (15.0–22.5)	1	1	1	1
Atrial fibrillation	1071 (27)	76	14.2 (11.3–17.8)	0.79 (0.6–1.1)	0.7 (0.4–1.3)	0.7 (0.3–1.6)	0.9 (0.6–1.3)
Valve disorders	238 (6)	24	21.6 (14.3–31.8)	1.17 (0.7–1.8)	1.4 (0.6–3.3)	2.2 (0.9–5.4)	0.8 (0.4–1.6)
Cerebrovascular	295 (7)	21	14.3 (9.3–21.9)	0.80 (0.5–1.3)	0.6 (0.2–1.7)	0.9 (0.3–2.8)	0.8 (0.5–1.6)
CHD/PVD	746 (19)	30	9.9 (6.9–14.2)	0.55 (0.4–0.8)	0.4 (0.1–1.0)	0.4 (0.1–1.3)	0.7 (0.4–1.1)

[a]Relative risk adjusted by age, sex and indication using Poisson regression; [b]crude incidence rate per 100 person-years. DVT = deep vein thrombosis; PE = pulmonary embolism; CHD = coronary heart disease; PVD = peripheral vascular disease.

indication ($P = 0.04$) with the highest risk observed among patients with valve disorders. Age and sex effects were not significant at the 5% level, although there was a suggestion of a possible increase in the risk of fatal/hospitalised bleeding with age.

Discussion

In patients aged 40 to 84 years old who were newly treated with warfarin and with no prior history of bleeding, we found an overall incidence of bleeding of 15.2 per 100 patient-years of current exposure during the initial 12 months of treatment. These findings were consistent with a higher rate of bleeding in patients with heart valve prostheses/disorders and a possible increase in the risk of more serious bleeding at older ages, as has been reported elsewhere.[3]

One of the strengths of the present study is that, unlike many observational studies, our study population was not drawn from a selected, and often small, sample of clinics or hospitals. Furthermore, we expect to have captured a broadly representative sample of patients monitored in both anticoagulation clinics and general practice, since long-term medications required by outpatients are normally prescribed by GPs.

Incomplete ascertainment of bleeds is a potential problem in any retrospective study. Previous GPRD validation studies[4] report that close to 90% of events resulting in hospitalisation or referral are recorded, although the ascertainment of less severe diagnoses, such as minor bleeds, is probably less complete. Although we obtained confirmatory information from the GP for 90% of cases, some under-ascertainment of fatal bleeds is possible, since the cause of death was unknown in 15% of deaths in our sample. Thus the true rate of fatal bleeding may have been somewhat higher than the annual rate of fatal bleeds (0.6 per 100 patient years) that we report.

In conclusion, the bleeding rates reported here are not inconsistent with rates reported elsewhere;[5] however, they are not negligible and support the need for ongoing clinical audit and for the development of risk management strategies[6] to ensure that patients are safely anticoagulated.

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