



EUROPEAN  
HEMATOLOGY  
ASSOCIATION



Ferrata Storti  
Foundation

# A three-year prospective study of the presentation and clinical outcomes of major bleeding episodes associated with oral anticoagulant use in the UK (ORANGE study)

Laura Green,<sup>\*1,2,3</sup> Joachim Tan,<sup>\*1</sup> Joan K Morris,<sup>1</sup> Raza Alikhan,<sup>4</sup> Nicola Curry,<sup>5,6</sup> Tamara Everington,<sup>7,8</sup> Rhona Maclean,<sup>9</sup> Khalid Saja,<sup>10</sup> Simon Stanworth,<sup>5,6,11</sup> Campbell Tait<sup>12</sup> and Peter MacCallum<sup>1,2</sup>

Haematologica 2018  
Volume 103(4):738-745

<sup>1</sup>Barts and the London School of Medicine and Dentistry, Queen Mary University of London; <sup>2</sup>Barts Health NHS Trust, London; <sup>3</sup>NHS Blood and Transplant, Colindale; <sup>4</sup>University Hospital of Wales, Cardiff and Vale University Health Board; <sup>5</sup>Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford <sup>6</sup>Radcliffe Department of Medicine, University of Oxford, and Oxford BRC Haematology Theme; <sup>7</sup>Hampshire Hospitals NHS Foundation Trust; <sup>8</sup>Salisbury NHS Foundation Trust; <sup>9</sup>Sheffield Teaching Hospitals NHS Foundation Trust; <sup>10</sup>Barking, Havering and Redbridge University Hospitals NHS Trust; <sup>11</sup>Transfusion Medicine, NHS Blood and Transplant, Oxford and <sup>12</sup>Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde, UK

\*Joint first authors

## ABSTRACT

The outcomes of patients developing major bleeding while on oral anticoagulants remain largely unquantified. The objectives of this study were to: (i) describe the burden of major hemorrhage associated with all available oral anticoagulants in terms of proportion of bleeds which are intracranial hemorrhages, in-hospital mortality and duration of hospitalization following major bleeding; (ii) identify risk factors for mortality; and (iii) compare the characteristics of major hemorrhage between cases treated with warfarin and direct oral anticoagulants for the subgroups of patients with atrial fibrillation or venous thromboembolism. This was a multicenter, 3-year prospective cohort study of patients aged  $\geq 18$  years on oral anticoagulants who developed major hemorrhage leading to hospitalization. The patients were followed up for 30 days or until discharge or death, whichever occurred first. In total 2,192 patients (47% female, 81% on warfarin, median age 80 years) were reported between October 2013 and August 2016 from 32 hospitals in the UK. Bleeding sites were intracranial (44%), gastrointestinal (33%), and other (24%). The in-hospital mortality was 21% (95% CI: 19%-23%) overall, and 33% (95% CI: 30%-36%) for patients with intracranial hemorrhage. Intracranial hemorrhage, advanced age, spontaneous bleeding, liver failure and cancer were risk factors for death. Compared to warfarin-treated patients, patients treated with direct oral anticoagulants were older and had lower odds of subdural/epidural, subarachnoid and intracerebral bleeding. The mortality rate due to major bleeding was not different between patients being treated with warfarin or direct oral anticoagulants. Major bleeding while on oral anticoagulant therapy leads to considerable hospital stays and short-term mortality.

## Correspondence:

[laura.green@bartshealth.nhs.uk](mailto:laura.green@bartshealth.nhs.uk)

Received: October 6, 2017.

Accepted: January 22, 2018.

Pre-published: January 25, 2018.

doi:10.3324/haematol.2017.182220

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: [www.haematologica.org/content/103/4/x738](http://www.haematologica.org/content/103/4/x738)

©2018 Ferrata Storti Foundation

Material published in *Haematologica* is covered by copyright. All rights are reserved to the Ferrata Storti Foundation. Use of published material is allowed under the following terms and conditions:

<https://creativecommons.org/licenses/by-nc/4.0/legalcode>.

Copies of published material are allowed for personal or internal use. Sharing published material for non-commercial purposes is subject to the following conditions:

<https://creativecommons.org/licenses/by-nc/4.0/legalcode>, sect. 3. Reproducing and sharing published material for commercial purposes is not allowed without permission in writing from the publisher.



## Introduction

Oral anticoagulants (OAC) are highly effective for stroke prevention in patients with atrial fibrillation,<sup>1,2</sup> for the treatment and prevention of venous thromboembolism,<sup>3</sup> and for the prevention of thrombosis related to mechanical heart valves.<sup>4,5</sup> It is estimated that OAC therapy is required for 1.25 million people per year in the UK with approximately 70% being for those with atrial fibrillation.<sup>6</sup> This requirement is likely to continue to rise in an aging population, given that the prevalence

of atrial fibrillation<sup>7</sup> and the incidence of venous thromboembolism<sup>8</sup> both increase with age.

The foremost complication of OAC therapy is the development of major bleeding. In the phase III randomized clinical trials which compared warfarin and direct OAC – namely dabigatran etexilate, rivaroxaban, apixaban and edoxaban (DOAC hereafter) – in patients with atrial fibrillation and venous thromboembolism, this risk was reported to be 1-3% per year.<sup>9</sup> In clinical practice some studies have reported similar risks of major bleeding,<sup>10-12</sup> while others have found that it may be considerably higher.<sup>13,14</sup>

When DOAC were first introduced into clinical practice there was concern among clinicians that the lack of specific antidotes could be detrimental to patients' outcomes in the event of major bleeding. Recently, 'post-approval' observational studies have reported on the safety profile of DOAC; however, these studies have primarily focused

on patients with atrial fibrillation, using patients' clinical data obtained from national registries/databases which were designed for different purposes.<sup>15</sup> Moreover, these studies lacked detail on the acute management of the bleeds. The burden (with respect to in-hospital mortality, morbidity and duration of hospitalization) of major bleeding associated with all OAC, for any clinical indications, remains largely unknown. This dearth of knowledge is true even in the case of warfarin, which has been the mainstay of OAC therapy for more than 60 years. Moreover, the widespread and increasing use of OAC, particularly in the frail elderly, underscores the urgency of comparative studies to assess the burden of major bleeding events associated with warfarin and DOAC. Such information should be incorporated into the clinical assessment and counseling of patients prescribed OAC, as well as the optimization of strategies for the management of OAC-associated major bleeding events.

**Table 1.** Baseline characteristics by type of oral anticoagulant<sup>a</sup>.

	Total number (%)	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Total patients	2,192 (100)	1,771 (81)	46 (2)	283 (13)	89 (4)
Female	1,028 (47)	814 (46)	24 (52)	153 (54)	35 (39)
Age (years), median [IQR]	80 [72-86]	79 [71-85]	85 [79-88]	82 [74-88]	81 [76-86]
<65	284 (13)	246 (14)	2 (4)	29 (10)	7 (8)
65-74	408 (19)	348 (20)	6 (13)	42 (15)	12 (13)
75-84	863 (39)	714 (40)	12 (26)	96 (34)	39 (44)
≥85	637 (29)	463 (26)	26 (57)	116 (41)	31 (35)
Indications <sup>b</sup>					
Atrial fibrillation	1,575 (72)	1,265 (71)	38 (83)	193 (68)	76 (85)
Venous thromboembolism	456 (21)	352 (20)	3 (7)	89 (31)	11(12)
Mechanical heart valve	212 (10)	211 (12)	---	1 (<1)	---
Other	184 (8)	143 (8)	11 (24)	18 (6)	12 (13)
Prescribed anti-thrombotics					
Single antiplatelet therapy	193 (9)	144 (8)	3 (7)	35 (12)	11 (13)
Dual antiplatelet therapy	27 (1)	23 (1)	---	1 (<1)	3 (3)
LMWH/UHF	53 (2)	47 (3)	1 (2)	5 (2)	---
Co-morbidities (type)					
Congestive heart failure	342 (16)	278 (16)	4 (9)	46 (16)	14 (16)
Hypertension	1,181 (54)	949 (54)	28 (61)	154 (54)	50 (56)
Previous stroke/TIA	432 (20)	334 (19)	17 (37)	56 (20)	23 (26)
Liver failure <sup>d</sup>	35 (2)	28 (2)	1 (2)	6 (2)	---
Cancer	334 (15)	258 (15)	6 (13)	55 (19)	14 (16)
Diabetes	494 (23)	402 (23)	9 (20)	62 (22)	21 (24)
Peripheral vascular disease	66 (3)	49 (3)	2 (4)	13 (5)	2 (2)
Ischemic heart disease	570 (26)	456 (26)	15 (33)	69 (24)	29 (33)
Chronic kidney disease <sup>d</sup>	339 (15)	282 (16)	2 (4)	49 (17)	6 (7)
Alcohol dependence	48 (2)	39 (2)	1 (2)	7 (2)	1 (1)
Dementia	144 (7)	97 (5)	2 (4)	35 (12)	8 (9)
Recurrent falls	128 (6)	94 (5)	4 (9)	24 (8)	6 (7)
Previous major bleeding					
Intracranial hemorrhage <sup>e</sup>	81 (4)	64 (4)	2 (4)	11 (4)	4 (4)
Gastrointestinal bleed	87 (4)	71 (4)	2 (4)	10 (4)	4 (4)
Other bleeds	38 (2)	29 (2)	3 (7)	6 (2)	---
Bleed history unknown	626 (29)	513 (29)	11 (24)	73 (26)	28 (31)

LMWH: low molecular weight heparin; UHF: unfractionated heparin; TIA: transient ischemic attack; <sup>d</sup>Edoxaban patients not shown separately (n=3). <sup>e</sup>10% of patients had more than one indication. <sup>a</sup>See appendix for definitions of liver and renal failure. <sup>d</sup>Includes two with additional non-intracranial previous bleeds

The main objectives of this study were to: (i) describe the burden of major hemorrhage associated with all available OAC in terms of proportion of bleeds which are intracranial, in-hospital case-fatality and morbidity, and duration of hospitalization; (ii) identify risk factors for fatality; (iii) compare characteristics of major hemorrhage between patients treated with warfarin and DOAC for the subgroups anticoagulated for atrial fibrillation or venous thromboembolism, the clinical conditions for which DOAC are indicated.

## Methods

### Study design

The ORANGE (ORal ANticoagulant aGEnt-associated bleeding events reporting system) study was a prospective cohort study that collected information from multiple UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode while on OAC therapy. Ethics approval was obtained for the study from the National Health Service, Health Research Authority (East of England-

**Table 2. Bleeding characteristics and outcomes.**

	Number (%)	
Total patients	2,192 (100)	
All intracranial hemorrhage	<b>963 (44)</b>	
Subdural/epidural	386 (18)	
Intracerebral <sup>a</sup>	474 (22)	
Subarachnoid <sup>b</sup>	103 (5)	
All gastrointestinal bleeds	<b>712 (32)</b>	
Upper <sup>c</sup>	443 (20)	
Lower	269 (12)	
Other bleeds	<b>517 (24)</b>	
Visceral	<b>131 (6)</b>	
Genitourinary	<b>87 (4)</b>	
Musculoskeletal	<b>224 (10)</b>	
Miscellaneous (e.g. intra-ocular, puncture and surgical sites)	<b>75 (4)</b>	
Provocation of bleeding		
Spontaneous	1,434 (65)	
Trauma (excluding fall)	200 (9)	
Surgery or procedure	105 (5)	
Fall	432 (20)	
Unclassified <sup>d</sup>	21 (1)	
<b>Outcomes up to 30 days</b>		<b>Days to event, median[IQR]</b>
Died in hospital	446 (20)	3 [1-8]
Discharged from hospital	1,413 (64)	7 [3-13]
Still inpatient at 30 days	273 (12)	
Lost to follow-up		
Transferred to other hospital	47 (2)	2 [1-8]
Not submitted	13 (1)	
<b>Case fatality by groups</b>	<b>Followed-up, N</b>	<b>Died (%)</b>
Overall	2,132	446 (21)
Age, years		
<65	274	25 (9)
65-74	400	62 (16)
75-84	840	197 (23)
85+	618	162 (26)
Type of oral anticoagulant		
Warfarin	1,719	358 (21)
Direct oral anticoagulant	413	88 (21)
Site of bleed		
All intracranial	923	302 (33)
All gastrointestinal	704	91 (13)
Other	505	53 (11)

<sup>a</sup>Includes 32 with additional bleeds in other sites. <sup>b</sup>Includes 17 with additional subdural bleed. <sup>c</sup>Includes 18 with additional lower gastrointestinal bleed. <sup>d</sup>Reported as "unknown" or "not available".

Cambridge South Research Ethics Committee, reference: 12/EE/0431). Data on major bleeding events were submitted by multiple hospitals across England, Scotland, Wales and Northern Ireland between October 1, 2013 and August 31, 2016. Patients underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.

### Definition of major bleeding

The definition of major bleeding adopted was an augmented version of the International Society on Thrombosis and Haemostasis criteria.<sup>16</sup> It was defined as bleeding requiring hospitalization and at least one of the following: (i) resulting in death; (ii) transfusion of  $\geq 2$  units of red blood cells or a drop in hemoglobin of  $\geq 20$  g/L; (iii) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; (iv) transfusion of fresh-frozen plasma; (v) administration of prothrombin complex concentrate, recombinant activated factor VII, factor VIII inhibitor bypassing activity or fibrinogen concentrate. The rationale for appending (iv) and (v) was to ensure that the routes for case identification were as comprehensive as possible.

### Data collection

Any patient of 18 years or over on OAC therapy at the time when they developed major bleeding was eligible for the study.

Cases were reported consecutively and identified by clinical and research staff in participating hospitals from the emergency department, transfusion laboratory, pharmacy (if they stored hemostatic agents) and hematology doctors who were called to give medical advice on the management of these patients.

The study collected information on patients' baseline characteristics; type of OAC and indication(s), as well as co-morbidities and clinical outcomes at 30 days, death, or discharge, whichever occurred first. Further information on details of data collection/verification, and justification for sample size are given in the *Online Supplementary Material*.

### Statistical analysis

The first bleeding episode of each individual patient was analyzed, with all DOAC grouped together for comparisons. Associations between categorical variables were examined with a chi-squared or Fisher exact test and Mann-Whitney U tests were used for continuous variables (all two-sided at a 5% level of significance). Multinomial logit models were used to estimate the conditional odds ratios for DOAC *versus* warfarin on the site of bleeding (*versus* a reference site), adjusting for age and bleeding provocation. Risk factors for in-hospital 30-day mortality were investigated using mixed-effects multivariable logistic regression to take into account intra-hospital correlation, controlling for age, co-morbidities, bleeding provocation and indications for OAC therapy. All analyses were performed using STATA version 14 (StataCorp LP, USA).

**Table 3.** Comparison of warfarin and direct oral anticoagulants, for patients with atrial fibrillation and/or venous thromboembolism (n=1958).

	Warfarin	All DOAC number (%) or median[IQR]	P
Total patients	<b>1,557</b>	<b>401</b>	
Age, years	80 [72-85]	82 [75-88]	<0.001 <sup>a</sup>
Number of co-morbidities <sup>d</sup>			
None	227 (15)	57 (14)	0.724 <sup>b</sup>
1-2	868 (56)	216 (54)	
3-4	398 (26)	107 (27)	
5+	64 (4)	21 (5)	
CHA2DS2-VASc score	<b>3 [2-4]</b>	<b>3 [2-5]</b>	<b>0.1<sup>a</sup></b>
HAS-BLED score <sup>e</sup>	<b>2 [1-3]</b>	<b>2 [2-3]</b>	<b>0.1<sup>a</sup></b>
Sites of bleed			
Lower gastrointestinal	166 (11)	75 (19)	<0.001 <sup>b</sup>
Upper gastrointestinal	293 (19)	101 (25)	
Subdural	313 (20)	42 (10)	
Subarachnoid	74 (5)	17 (4)	
Intracerebral	342 (22)	92 (23)	
Other	369 (24)	74 (18)	
Patients followed-up	<b>1512</b>	<b>393</b>	
In-hospital deaths within 30 days	322 (21)	84 (21)	0.973 <sup>b</sup>
Days in hospital before death	3 [1-8]	3 [1-10]	0.948 <sup>a</sup>
Days in hospital for discharged patients	7 [3-13]	6 [3-11]	0.303 <sup>a</sup>
Number of complications in hospital			
None	1,184 (76)	308 (77)	0.977 <sup>c</sup>
1	229 (15)	60	
2	62 (4)	17 (4)	
3+	37 (2)	8 (2)	

DOAC: direct oral anticoagulants. <sup>a</sup>Mann Whitney test; <sup>b</sup>chi-squared test; <sup>c</sup>Fisher exact test; <sup>d</sup>co-morbidities as described in Table 1 <sup>e</sup> score does not include the labile International Normalized Ratio.

**Table 4.** Univariable and multivariable analysis of risk factors for mortality (n=2,132).

	OR [95%CI]	Univariable analysis P	Adjusted OR* [95%CI]	Multivariable analysis P
<b>Age (years)</b>				
<65	1		1	
65-74	1.84 [1.12,3.01]	0.016	1.50 [0.89,2.53]	0.12
75-84	3.07 [1.97,4.80]	<0.001	2.77 [1.73,4.44]	<0.001
85+	3.59 [2.28,5.65]	<0.001	3.78 [2.33,6.14]	<0.001
<b>Type of oral anticoagulant</b>				
Warfarin	1		1	
Direct oral anticoagulant <sup>b</sup>	0.99 [0.76, 1.31]	0.98	0.96 [0.71,1.28]	0.77
<b>Site of bleed</b>				
Other	1		1	
Lower gastrointestinal	0.65 [0.38, 1.12]	0.12	0.45 [0.25, 0.79]	0.005
Upper gastrointestinal	1.67 [1.14, 2.46]	0.01	1.17 [0.78, 1.75]	0.44
Subdural/epidural	2.43 [1.66, 3.55]	<0.001	2.55 [1.69, 3.84]	<0.001
Subarachnoid	2.72 [1.58, 4.68]	<0.001	3.23 [1.82, 5.71]	<0.001
Intracerebral	6.34 [4.51, 8.91]	<0.001	5.75 [4.01, 8.23]	<0.001
<b>Provocation<sup>c</sup></b>				
Spontaneous	1		1	
Trauma	0.82 [0.55,1.21]	0.31	0.54 [0.35, 0.83]	0.005
Surgery/procedure	0.23 [0.10,0.52]	0.001	0.50 [0.21, 1.19]	0.12
Fall	0.97 [0.74,1.28]	0.84	0.53 [0.38, 0.73]	0.001
Liver failure	2.08 [1.02,4.26]	0.04	3.86 [1.79, 8.36]	0.001
Cancer	1.29 [0.97,1.70]	0.08	1.37 [1.01, 1.84]	0.04

OR: odds ratio; \*Odds ratios adjusted for all other variables in model; <sup>b</sup>Includes dabigatran, rivaroxaban, apixaban and edoxaban; <sup>c</sup>unclassified provocations not displayed (n=21).

## Results

Cases were identified and reported by 32 hospitals across the UK, with the median number (inter-quartile range, IQR) of cases reported per hospital being 44 (25 – 88), and the median (IQR) duration for completing a case report (measured from the date of bleeding) being 38 (13–87) days. Table 1 shows the demographics, OAC therapy specifications and co-morbidities of 2,192 individual patients reported with major bleeding between October 2013 and August 2016; 34 (1.6%) had more than one episode during the study period (*data not shown*). All patients fulfilled the International Society of Thrombosis and Haemostasis criteria for major bleeding: 20% had a fatal bleed; 62% were transfused with  $\geq 2$  units of red blood cells or had a drop of  $\geq 20$ g/L hemoglobin; and 86% had symptomatic bleeding in a critical organ (overall, 67% of patients met more than one criteria). At the time of the bleed, the majority of patients were on warfarin (81%) with the remainder being on a DOAC. Patients taking an OAC for atrial fibrillation and venous thromboembolism made up 72% and 21% of the cohort respectively; approximately 10% had multiple indications.

Bleeding presentations and outcomes are shown in Table 2. All intracranial hemorrhages (subdural, subarachnoid and intracerebral bleeds combined), gastrointestinal bleeds (upper and lower) and other bleeds made up 44%, 32% and 24% of the total, respectively. Two-thirds of the bleeds were reported as spontaneous and one-fifth as resulting from a fall. Outcomes up to 30 days were reported for 2,132 (97%) patients. The overall in-hospital mortality rate was 20.9% (95% CI: 19.2% - 22.7%) but was 32.7% (95% CI: 29.7–35.9%) among patients with an

intracranial hemorrhage. Bleeding was mentioned as the cause of death in 70% of cases, while in 22% it was not, and in 8% the cause of death was unknown/ or referred to the coroner. Patients discharged within 30 days of bleeding stayed a median of 7 days in hospital. In-hospital complications included admission to an Intensive Care Unit (10%), ventilation or acute respiratory distress syndrome (5%), hemorrhagic stroke (3%), cardiac arrest (2%), sepsis or pneumonia (2%), thrombotic events (2%), and re-bleeding (2%).

For the management of bleeding, patients on warfarin were given any blood transfusion (31%), prothrombin complex concentrate (78%) and vitamin K (74%); patients on DOAC were given any blood transfusion (43%), prothrombin complex concentrate (39%) and tranexamic acid (28%). OAC therapy was resumed in 43% of survivors while they were in hospital. The proportions of patients (among survivors) who restarted OAC after a bleed varied by site of bleed: intracranial hemorrhage (24%), gastrointestinal (46%), other (65%), as well as indication: atrial fibrillation (36%), mechanical heart valves (86%), venous thromboembolism (50%), other (42%). One-third of patients on a DOAC were restarted on a different OAC, as were approximately one-fifth of patients with intracranial hemorrhage or venous thromboembolism. Out of 111 DOAC patients, 29 (26%) were switched to vitamin K antagonists and out of 610 patients on warfarin, 42 (7%) were switched to a DOAC.

Comparison of the 1,958 (89%) patients who were on OAC for atrial fibrillation and/or venous thromboembolism (Table 3) showed that those admitted on DOAC were significantly older than those on warfarin ( $P<0.001$ ), but there was no significant difference in the number of

co-morbidities between them. The type of OAC was associated with the site of bleeding ( $P < 0.001$ ); after adjusting for age and bleeding provocation using multinomial models, the conditional odds ratios of admission with a subdural/epidural, subarachnoid and intracerebral bleed (*versus* a lower gastrointestinal bleed) on DOAC compared to warfarin, were 0.28 (95% CI: 0.17-0.47;  $P < 0.001$ ), 0.52 (95% CI: 0.30-0.90;  $P = 0.02$ ) and 0.61 (95% CI: 0.41-0.92;  $P = 0.02$ ), respectively. Mortality rate, the number of complications following bleeding, and the duration of hospitalization were not significantly different between patients treated with warfarin or DOAC.

Table 4 shows the analysis of risk factors for fatality in 2,132 patients with known outcomes. After controlling for age, co-morbidities, bleeding site and provocation, there was no evidence that compared to warfarin, DOAC were associated with different odds of death (adjusted OR=0.96; 95% CI: 0.71-1.28;  $P = 0.77$ ). Intracerebral, subarachnoid and subdural/epidural bleeds were associated with 5.8 (95% CI: 4.0-8.2), 3.2 (95% CI: 1.8-5.7) and 2.6 (95% CI: 1.7-3.8) times higher odds of death, respectively, compared with other bleeds. Adjusting for other covariates, advanced age, spontaneous bleeding (compared to trauma or falls), liver failure and cancer were significantly associated with increased odds of dying, while indications for OAC were not predictors of an adverse outcome. There was negligible between-hospital variation (intra-class correlation coefficient=0.003). Given the relatively small number of patients for whom outcome was missing ( $n = 60$ ), sensitivity analyses were performed by assuming either all survived or died, and this did not materially alter the significance of the estimates.

## Discussion

The main objective of this study was to investigate the aggregate burden of major hemorrhage in patients receiving OAC, across all indications and drug types, in terms of ensuing mortality, morbidity and hospitalization. Our results showed a considerable death rate, with one-fifth of all patients, and one-third of those with intracranial hemorrhage, dying in hospital within 30 days of a major bleeding episode. Of those who were discharged within a month, half had spent 7-30 days in hospital. Our mortality rates, both overall and for the subgroup with intracranial hemorrhage, are comparable with those of other studies.<sup>17,18</sup> However, a recent Canadian study that used a similar definition of major bleeding as ours (including only patients >66 years) showed lower mortality rates than in our study (9.2% for DOAC and 15.2% for warfarin): this difference is likely to be due to the lower rate of intracranial hemorrhage (27% overall) seen in their study.<sup>19</sup>

The proportion of patients with intracranial hemorrhage (44%) was similar to that in the study by Becattini and colleagues,<sup>20</sup> but higher than that in other studies.<sup>19,21</sup> The higher rate may be due to: (i) one-third of our cases being from hospitals with specialist neurosurgical units (i.e. endpoints of inter-hospital referrals); (ii) our cohort including patients who were older than those in clinical trials and thus more prone to falls and the development of intracranial hemorrhage; (iii) our definition of major bleeding being more severe than those of clinical trials, as we identified only patients who developed major hemorrhage culminating in hospitalization; (iv) cases of intracranial

hemorrhage being more exhaustively documented (e.g. through administration of prothrombin complex concentrates), compared with gastrointestinal or other bleeds.

The pivotal randomized controlled trials of patients with atrial fibrillation and venous thromboembolism found lower rates of intracranial hemorrhage with all DOAC than with warfarin, and higher rates of gastrointestinal bleeding with dabigatran and rivaroxaban than with warfarin.<sup>9,21</sup> A systematic review of randomized clinical trials by Connolly and colleagues<sup>22</sup> concluded that “the risks of subdural hematoma were significantly higher with vitamin K antagonists compared with factor-Xa inhibitors and direct thrombin inhibitors” [meta-analysis odds ratio (95% CI): 2.9 (2.1–4.1) and 1.8 (1.2–2.7), respectively]. Our findings appear to be a corollary of the established evidence: while our study did not directly assess the incidence of bleeding on OAC, we observed increased odds of admission with all types of intracranial hemorrhage *versus* gastrointestinal bleeding on warfarin compared to DOAC, with the association being strongest for subdural/epidural bleeding. Further investigation into this association between warfarin and subdural hematoma would thus be an important topic in future research.

Analysis of risk factors for death showed that intracranial hemorrhage was a strong predictor of death. However, we saw no difference in the proportions of deaths between patients treated with warfarin or DOAC even though the proportion of intracranial hemorrhage was higher for the former. A likely explanation for this is that patients admitted on DOAC were significantly older than those on warfarin, and advanced age was also an independent risk factor for death. The participants in the clinical trials of warfarin *versus* DOAC were significantly younger than those in our study. However, our results provide reassurance for clinicians who prescribe DOAC therapy in that, where major bleeding is concerned, the outcome is no worse than that associated with warfarin despite the lack of antidotes and the advanced age of many patients in this study. Since DOAC antidotes are now becoming available it is important to perform similar studies to assess the effect that these have on outcomes, and thereby improve OAC choices in the future.

A key strength of this study is that the data were prospectively collected by over 30 hospitals across the UK, with information retrieved directly from patients' case notes and not from large databases in which data are collected for different reasons, or missed by administrative coding.<sup>23-26</sup> This has enabled us to document for the first time in the UK the characteristics and clinical outcomes of patients who develop major bleeding associated with different OAC when prescribed for any clinical indications. Additionally, over three-quarters of cases were fully reported within 90 days of the major bleeding episode, ensuring a high degree of fidelity with actual events and minimizing the chance of recall bias. Furthermore, we were able to collect data on the acute management of major bleeding, whereas this is not usually possible from large data sets. Our analysis showed a very low level of inter-hospital variation, which suggests that our findings should be generalizable to the wider population and potentially further afield. Moreover, the design of the study meant that we did not rely on patients' consent, a further potential source of selection bias.

Our study also provides data on the outcomes of major bleeding that are more generalizable to contemporary

practice than those observed in the randomized clinical trials. Patients in the latter were more highly selected, and the management of major bleeding in the trials appears different from current recommended practice; for example, among those with major bleeding in the open-label warfarin arm of the RELY trial only 27% received vitamin K and 1% received a prothrombin complex concentrate<sup>27</sup> in contrast to over 70% for both in our study.

We identified patients who developed major bleeding on OAC and were admitted to hospital, but it is possible that not every case was captured, because they were not triaged to emergency departments, and thus could have been missed by the research team. The upshot is that we may have collected data on the more severe bleeding cases with consequently worse outcomes, although we expect the numbers affected to be relatively small. Furthermore, it could be argued that warfarin cases would have been easier to capture through the prescription of prothrombin complex concentrate. However, the methods of case identification were designed to capture all cases of major bleeding from hospitals, independently of the type of OAC, but we recognize that some cases could have been inadvertently missed.

It is also possible that we may have missed some cases of fatal bleeding who died suddenly in the community; however, we think these numbers will likely be small because the majority would be taken to their local emergency department because of acute deterioration. Furthermore, we might have missed the outcome of patients who were discharged before 30 days; however, it seems a reasonable stipulation that patients were discharged from hospital if and when major bleeding had been successfully treated or resolved, and hence restricting follow-up to within the hospital is justifiable on the grounds that any post-discharge deaths would not be “following from the bleeding event”.

In conclusion, for clinicians who are responsible for counseling patients about oral anticoagulation our findings indicate that mortality from major bleeding on OAC that requires hospitalization is high, with one in five patients likely to die within 30 days. This is of concern given the widening use of these agents in an increasingly elderly and frail population. As far as DOAC are concerned, our results provide reassurance, in that they are

not associated with worse outcomes compared to warfarin despite the lack of antidotes at the time of the study. As the DOAC antidotes emerge, it would be important for future studies to investigate their impact on patients' outcomes compared to current practice.

### Funding

*This study was funded by the British Society for Haematology Early Stage Researcher Fellowship awarded to Dr Laura Green. The views expressed in this publication are those of the authors and not those of the funder. The funder had no role in the study design, data collection/analysis or preparation of this article.*

### Acknowledgments

*We would like to acknowledge all hospitals, NHS trusts and principal investigators who reported to the study: Newham University Hospital (Dr Olivia Kreze), Whipps Cross University Hospital (Dr Peter MacCallum); The Royal London Hospital (Dr Laura Green); Barking Havering and Redbridge University Hospitals (Dr Khalid Saja); John Radcliffe Hospital (Dr Nicola Curry); Glasgow Royal Infirmary (Dr Campbell Tait); University Hospital of Wales (Dr Raza Alikhan); Sheffield Teaching Hospitals (Dr Rhona Maclean); Basingstoke & North Hampshire Hospital and Salisbury District Hospital (Dr Tamara Everington); Ulster Hospital (Dr Margaret Bowers); Wexham Park Hospital (Dr Sarah Wilson); Witherby General Hospital (Dr Sumant Kundu); Newcastle upon Tyne Hospitals (Dr John Hanley); North Middlesex University Hospital (Dr John Luckit); Basildon and Thurrock Hospitals (Dr Godwin Simon); Torbay Hospital (Dr Nichola Rymes); University College Hospital (Dr Hannah Cohen); St George's Healthcare NHS Trust (Dr James Uprichard); Birmingham Heartlands Hospital (Dr Charalampos Kartsios); Royal Bournemouth Hospital (Dr Jason Mainwaring); Hull and East Yorkshire Hospitals NHS Trust (Dr Salama Aboasad); Northern Lincolnshire and Goole NHS Foundation Trust (Dr Sanjeev Jaliha); Dumfries and Galloway Royal Infirmary (Dr Mohamed Khan); University Hospitals of North Midlands (Dr Deepak Chandra); Gloucestershire Hospitals (Dr Oliver Miles); South Tees Hospitals (Dr Jamie Maddox); Glangwili General Hospital (Dr Saran Nicholas); Royal Berkshire NHS Foundation Trust (Dr Liza Keating); University Hospital Southampton (Dr Sara Boyce); Northumbria Healthcare NHS Foundation Trust (Dr Charlotte Bomken) and North Cumbria University Hospitals (Dr Roderick Oakes).*

## References

- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962.
- Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369-23429.
- Wolberg AS, Rosendaal FR, Weitz JI, et al. Venous thrombosis. *Nat Rev Dis Primers*. 2015;1:15006.
- Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89(2):635-641.
- van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124(12):1968-1975.
- NICE. Assumptions used in estimating a population benchmark. 2012. (Available from <http://www.nice.org.uk/usingguidance/commissioningguides/anticoagulation-therapyservice/popbench.jsp>). Accessed on 10 October 2017.
- Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. *Glob Heart*. 2014;9(1):113-119.
- Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. *Thromb Haemost*. 2014;112(2):255-263.
- Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. *Blood*. 2014;124(15):2450-2458.
- Hecker J, Marten S, Keller L, et al. Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. *Thromb Haemost*. 2016;115(5):939-949.
- Beyer-Westendorf J, Ebertz F, Forster K, et al. Effectiveness and safety of dabigatran therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. *Thromb Haemost*. 2015;113(6):1247-1257.
- Lip GY, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk

- among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost.* 2016;116(5):975-986.
13. Wang SV, Franklin JM, Glynn RJ, Schneeweiss S, Eddings W, Gagne JJ. Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: new initiator cohort study. *BMJ.* 2016;353:i2607.
  14. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation.* 2007;115(21):2689-2696.
  15. Nielsen PB, Skjoth F, Sogaard M, Kjaeldgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ.* 2017;356:j510.
  16. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3(4):692-694.
  17. Nieto JA, Solano R, Ruiz-Ribo MD, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost.* 2010;8(6):1216-1222.
  18. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA.* 2015;313(8):824-836.
  19. Xu Y, Schulman S, Dowlathshahi D, et al. Direct oral anticoagulant- or warfarin-related major Bleeding: characteristics, reversal strategies, and outcomes from a multicenter observational study. *Chest.* 2017;152(1):81-91.
  20. Becattini C, Franco L, Beyer-Westendorf J, et al. Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life. *Int J Cardiol.* 2017;227:261-266.
  21. Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol.* 2013;70(12):1486-1490.
  22. Connolly BJ, Pearce LA, Hart RG. Vitamin K antagonists and risk of subdural hematoma: meta-analysis of randomized clinical trials. *Stroke.* 2014;45(6):1672-1678.
  23. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ.* 2016;353:i3189.
  24. Li L, Geraghty OC, Mehta Z, Rothwell PM, Oxford Vascular S. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *Lancet.* 2017;390(10093):490-499.
  25. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc.* 2016;5(2). pii: e003074.
  26. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med.* 2016;176(11):1662-1671.
  27. Majeed A, Hwang HG, Connolly SJ, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation.* 2013;128(21):2325-2332.