Correction of International Normalised Ratio in major bleeding related to vitamin K antagonists is associated with better survival: a UK study

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Abstract

Background: The association between international-normalized-ratio (INR) correction and mortality in patients with major bleeding on vitamin-K-antagonists (VKA) is important for evaluating the efficacy of reversal agents for oral anticoagulants.

Objectives: We evaluate if INR correction (defined as ≤1.3) following intervention in major bleeding on VKA is associated with better survival, and if there is a dose-response relationship between Vitamin K (VK) and INR correction.

Methods: Data on patients' characteristics, haematological management and 30-day outcomes reported by 32 UK hospitals (October 2013 - August 2016) were analysed. Associations between INR correction and: (a) 30-day mortality; (b) VK dose were estimated using multivariable logistic regression, using multiple imputation to handle missing INR values.

Results: Of 1,771 patients, 77%, 73% and 33% received prothrombin-complex-concentrate (PCC), VK (92% intravenous) and red cells and fresh frozen plasma transfusion respectively. Proportionally more intracranial haemorrhage (ICH) cases (87%) than non-ICH cases (69%) received PCC. VK administration did not vary by ICH group, with 10mg (33%) and 5mg (28%) doses being the most common. Higher doses of VK (10mg) were more likely to correct INR than lower doses (5mg). Post-intervention INR>1.3 in treated patients was associated with 3.2 (95%CI: 2.1–4.9) times higher odds of death within 30 days, compared with INR≤1.3, with no difference between ICH and non-ICH.

Conclusions: INR correction after intervention to manage major bleeding on VKA is associated with better survival. Higher VK doses (10mg) improve INR correction more than lower doses (5mg) in major bleeding, but further studies are warranted to compare the relative benefits/risks of 5mg versus 10mg doses.

Keywords: major haemorrhage, warfarin, vitamin K, INR correction, outcomes

Introduction

Vitamin K antagonists (VKA) such as warfarin have been the mainstay of oral anticoagulation therapy (OAC) for many decades worldwide. Like all anticoagulant agents, VKA are associated with development of major bleeding and intracranial haemorrhage (ICH), whose annual incidence from recent studies has varied from 1.6% - 3% and <1%, respectively [1].

The UK guideline for the management of major bleeding associated with VKA recommends that prothrombin complex concentrate (PCC) and intravenous vitamin K (5mg) should be used to treat the bleeding, and that fresh frozen plasma (FFP) transfusion should only be given if PCC is not available [2]. However, only a few small randomised controlled trials have compared the efficacy and safety of FFP versus PCC in patients with major bleeding associated with warfarin [3, 4] and there have been no clinical trials to determine the most appropriate dose of vitamin K for treatment of major bleeding, in terms of its capacity to sustain the reversal action of PCC/FFP whilst avoiding potential difficulties with achieving therapeutic INR levels when anticoagulation is resumed [5].

Further, most trials that have compared PCC with FFP have used as a primary outcome laboratory markers such as the correction of the international normalised ratio (INR), rather than a clinical outcome measure [4, 6]. The main reason for this is the large sample sizes needed to perform such trials, which in turn will require a long period of time and incur significant costs delivering these trials in a challenging and unpredictable environment. Only a few small studies have evaluated the associations between INR correction and mortality in patients who have developed major bleeding on warfarin [7, 8]. Evaluating the relationship between correction of laboratory markers and clinical outcomes (particularly mortality) for management of major bleeding associated with OAC is important not only for warfarin, but also possesses relevance with the advent of new antidotes for direct oral anticoagulants (DOACs).

In this paper we describe the haematological management of major bleeding cases associated with VKA in the UK and in particular we evaluate: (a) if INR correction (defined as ≤ 1.3) following intervention is associated with lower in-hospital mortality up to 30 days; and (b) if there is a dose-response relationship between Vitamin K and correction of INR post-intervention.

Methods

The ORANGE study (October 2013 to August 2016) was a prospective cohort study that collected data from 32 UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode whilst on OAC therapy such as VKA or direct OACs, enabling the identification of key risk factors for mortality following OAC-associated major bleeding [9]. For this paper, data on a subgroup of patients reported to the ORANGE study who were on a VKA (predominantly warfarin) were extracted for analysis. Major bleeding was defined in accordance with the criteria set by the International Society on Thrombosis and Haemostasis[10]; additionally patients receiving transfusion of FFP, PCC or other haemostatic agents were also included. Details of study approvals, case definition, identification and validation have been described previously [9]. Data comprised information on patient demographics, co-morbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days (death, discharge or continued hospitalisation). Patients were not approached by the research teams and their management was not altered for the purpose of this study.

Bleeding sites were categorised into intracranial (intracerebral, subarachnoid and subdural bleeding), upper and lower gastrointestinal and "Other" (visceral, genitourinary, musculo-mucosal-skeletal and elsewhere not already mentioned); patients with multiple sites of bleeding would be assigned to a single category according to the above-stated order. Two sets of patients' laboratory results were collected: (T1) within 1 day of reported date of bleeding and prior to any treatment by haemostatic agents (such as PCC) or red cells and FFP transfusion; and (T2) the first result following administration of any treatment (PCC or vitamin K or FFP), provided it was within 2 days of reported date of bleeding. If more than one product was given, this would be the earliest result after the first product. If no intervention was given, the earliest available result following T1 INR and within 2 days of reported date of bleeding was used. The reason for setting an upper limit for inclusion of results is to evaluate the predictive value of INR that is measured proximally to onset of bleeding and time of intervention; even without intervention INR will tend to decrease over time once anticoagulation has been stopped. Test results for haemoglobin, platelet count, prothrombin time (PT), INR, activated partial thromboplastin time (APTT), serum creatinine and alanine aminotransferase (ALT) were extracted for this analysis. Information on red cells and FFP transfusion and reversal agents

administered within 2 days for management of bleeding were recorded. These included Vitamin K, PCC and FFP, as well as less commonly used haemostatic agents (recombinant activated factor VII, factor eight inhibitor bypassing activity, fibrinogen concentrate).

Statistical Analysis

Variables were summarised as frequencies/proportions, means/standard deviations or median/interquartile ranges, as appropriate. The association of T2 INR with primary outcome (in-hospital death within 30 days of admission for major bleeding) was investigated using multivariable logistic regression, adjusting for bleed site (grouped as ICH or non-ICH) and age. The time elapsed (in hours) between treatment and T2 INR was included as a potential confounder, on the basis that critically ill patients were more likely to be promptly monitored and thus return elevated INR readings. Patients who received no treatment within the 2-day window, or whose T2 INR preceded treatment, were considered untreated and the time between T1 and T2 INR results was used as proxy. Tests of interaction were used to examine whether the effect of INR on death would differ between: (a) treated and untreated patients; and (b) ICH and non-ICH patients. Random effects models were fitted to investigate potential hospital clustering effects. All tests were two-sided at 5% level of significance.

Due to missing values in the primary outcome (death) and main exposure (T2 INR), multiple imputation (MI) was used to create and analyse 60 multiply imputed datasets under the assumption that data were missing at random. Incomplete variables were imputed under fully conditional specification, using logistic regression for binary variables and predictive mean matching with 5 nearest neighbours for continuous variables, separately by treatment status to allow for investigation of interaction; variables were log- or power-transformed to an approximate normal distribution where required prior to imputation. Laboratory results that correlated ($r \geq 0.15$) with INR values (comprising PT, APTT, haemoglobin, platelet count, serum creatinine and ALT), as well as factors known to affect T2 INR (history of liver and renal disease, administration of PCC, FFP and vitamin K) were selected as auxiliary variables in the imputation model to improve prediction of missing values. The probability of INR being missing was postulated to be associated with a short hospital stay (whether due to discharge, transfer or death), absence of intervention/treatment and variation in INR monitoring practices across hospitals; for this, hospitals were grouped by proportion of their patients missing T1 INR results at admission (0%, 1-4%, 5-9% and ≥10%). Mann-Whitney and Chi-squared tests

were used to confirm the hypothesised associations. Finally the parameters of substantive interest were estimated in each imputed dataset separately and combined using Rubin's rules [11]. For comparison, the analysis was performed on the subset of complete cases.

For the secondary analysis, logistic regression was used to investigate the association between Vitamin K dose and T2 INR correction, adjusting for PCC dosing, ICH, T1 INR and T1 serum creatinine. Continuous variables were modelled using linear and quadratic functional forms as appropriate. Analysis was performed on both complete cases and the multiply imputed datasets and checked for agreement. The predicted probabilities of T2 INR correction were plotted for different Vitamin K doses, holding other covariates at fixed values, for non-ICH and ICH patients. All analyses were performed using STATA version 14 (StataCorp LP, USA).

Results

Over the study period 1,771 patients on VKA (1,763 Warfarin, 7 Sinthrome, 1 Phenindione) presented with major bleeding; patient characteristics and their co-morbidities have been detailed in a previous publication [9]. In summary, the median age (interquartile range) of patients was 79 (71–85) years and the main indications for VKA were atrial fibrillation (71%), venous thromboembolism (20%) and mechanical heart valve (12%), with 11% of patients having more than one indication. The distribution of bleeding sites is given in Figure 1; intracranial haemorrhage and gastrointestinal bleeding accounted for 46% and 30% of cases respectively.

Table 1 shows the haematological management of cases. Overall, 77% received PCC and this was proportionally higher in ICH cases (87%) than non-ICH cases (69%). Vitamin K was administered to 1,296 (73%) patients predominantly through the intravenous (IV) route (92% IV, 4% oral, <1% IV and oral, 4% not recorded). The most common doses prescribed were 10mg (33%) and 5mg (28%) with no difference between ICH and non-ICH cases; however, there were proportionally fewer patients receiving 10mg or more amongst those with a mechanical heart valve compared to those without (24% vs. 34%). Overall 33% of patients received red blood cells (RBC) and/or fresh frozen plasma (FFP); both RBC and FFP transfusion were more likely for non-ICH cases (57% and 6% respectively) than ICH cases (4% and 1% respectively).

Out of 1771 patients, 358 (20%) died in hospital within 30-days of admission for major bleeding, with 52 (3%) lost to follow-up. A valid T2 INR result was available for 1222 (69%) patients; for a subgroup of 955 patients for whom exact timings were available, the median (interquartile range) time elapsed between treatment (or T1 INR if not treated) and T2 INR measurement was 9.0 (3.6-19.9) hours and 9.9 (5.5-18.4) hours for the treated and untreated groups respectively. T2 INR remained uncorrected (>1.3) in 20% and 40% of ICH and non-ICH patients respectively (Figure 2). Analysis of complete cases (n=1191) showed that the effect of T2 INR>1.3 on 30-day mortality depended on treatment status; no significant association was seen in the untreated group whereas it was associated with 3.2 (95%CI: 1.9-5.2) times greater odds of death in the treated group, after adjusting for ICH and age. Additionally adjusting for time of measurement increased the corresponding odds in the treated group to 4.2 (95%CI: 2.1-8.3) times, but this was based on a smaller sample with available data (n=853). Analysis using 60 multiply-imputed datasets (n=1771) showed the odds of death were 3.2 (95%CI: 2.1-4.9) times higher in those with INR>1.3 compared to INR≤1.3 at T2 in the treated group, with borderline evidence of a lesser association in the untreated group. There was no evidence that the association between INR and mortality differed between those with ICH vs. non-ICH, and no evidence of hospital-level variation. The unadjusted and adjusted odds ratios in both analyses are presented in Table 2; further details of the imputation model are provided in Appendix 1 (supplementary table).

For the secondary analysis, a logistic regression model with T2 INR correction as the outcome was fitted with Vitamin K dose (linear and quadratic), PCC dose, ICH, T1 INR and T1 serum creatinine as covariates; additionally adjusting for a patient's weight and FFP administration did not change the estimated effect of Vitamin K and there was no evidence that its effect differed between ICH and non-ICH patients. Due to a relatively high number of missing T2 INR results (31%), only complete case (n=1046) results are reported; analysis of the multiply imputed datasets did not show materially different results. The predicted probabilities of T2 INR correction are illustrated in Figure 3 for a patient with pre-treatment INR of 3 and serum creatinine of 100 μmol/L. There is a discernible dose-response relationship, with the incremental effect being greatest in patients receiving no or lower doses of PCC, for both ICH and non-ICH cases; however, over the range of lower doses there is greater uncertainty as shown by wider confidence intervals.

Discussion

Key results

In this study we report on the haematological management and outcomes of 1,771 patients on VKA who were hospitalised for major bleeding in the UK and the association between INR correction and mortality. The overall mortality rate was 20% with the key results being:

- PCC, Vitamin K and FFP transfusion were administered to 77%, 73% and 4% of cases respectively. PCC administration was higher for ICH cases than non-ICH cases, while FFP was relatively more common for non-ICH cases.
- The adjusted odds of death were 3.2 (95%CI: 2.1-4.9) times higher in those whose INR was not corrected to ≤1.3 after receiving treatment; this association was the same for ICH and non-ICH cases.
- Vitamin K was administered most commonly in 10mg and 5mg doses (33% and 28% of all patients respectively), with no significant difference between ICH and non-ICH patients. Higher doses of Vitamin K were more likely to correct INR than lower doses.

Interpretation of results

This UK multicentre study is hitherto the largest to report on the haematological management of major bleeding associated with VKA and the association between INR correction and mortality, using prospectively collected hospital data as opposed to data linkage to healthcare databases. The use of PCC in this study was higher than other international studies [12, 13], because the UK guidelines recommend that PCC be used as a first line treatment in these cases, and FFP should only be given if PCC is not available [14]. It is noteworthy that PCC was more likely to be given to ICH patients whilst non-ICH patients were more likely to receive red cells and FFP transfusion. A possible explanation is that non-ICH bleeding would more likely involve significant blood loss and thus necessitate more red cells and FFP transfusion for volume replacement compared with ICH; however, there is a further question of whether non-ICH bleeds should also be treated with PCC, independently of whether blood components were administered, that current guidelines have yet to specifically address.

We identified that administration of Vitamin K was tri-modal, with none, 5mg and 10mg being the most common. This spread is not surprising given the lack of clinical trials investigating appropriate dosages for VKA associated major bleeding. This is also a reflection of differences in national guidelines, with some recommending 5mg (UK included) [14] and others

recommending as much as 10mg (Australia, USA) [15, 16]. Additionally, we noted that higher doses (≥10mg) of Vitamin K were less commonly given to heart valve patients, suggesting that there may be anxiety amongst clinicians that higher doses could complicate attainment of therapeutic INR in a group for whom restarting of anticoagulation is of greater priority [5]. Our analysis showed an approximately linear dose-dependence of Vitamin K on the probability of achieving INR correction, indicating therefore that 10mg would be beneficial for patients. The benefit-risk balance of prescribing 5mg versus 10mg of Vitamin K in major bleeding would nonetheless need to be confirmed by further interventional studies.

There are no official guidelines on the timing and frequency of INR monitoring in the management of major bleeding. We found that uncorrected INR (>1.3), measured after receipt of treatment, is an important risk factor for mortality in VKA associated major bleeding; this association is particularly strong in patients who have received some form of intervention and holds true for both ICH and non-ICH cases. In the case of ICH, one study of 853 patients demonstrated that a combination of INR reversal <1.3 within 4 hours and systolic blood pressure (BP) of <160 mmHg at 4 hours were associated with lower rates of hematoma enlargement (OR=0.28; 95%CI: 0.19-0.42; p<0.001) and in-hospital mortality (OR=0.60; 95%CI: 0.37-0.95; p=0.03) [17]; these are broadly consistent with our findings on the strength of association between INR and mortality, taking into account small differences in the subgroup specification and INR timings. Another smaller study using the electronic health records of 405 patients receiving FFP for major bleeding showed that failure to correct INR to ≤1.3 within 48 hours of FFP administration was associated with a significantly higher risk of death within 30 days of admission for ICH cases (adjusted Hazard Ratio=2.55; 95%CI: 1.04–6.28), but not for non-ICH cases [7]. With a larger sample size, we have more precisely estimated the association between INR correction and mortality, and in particular for treated patients. This finding is particularly relevant for the increasing adoption of direct oral anticoagulant agents and their specific antidotes, suggesting that haemostatic assay corrections, which are relatively quick to assess compared with longer-term clinical outcomes, could be used in future trials to predict the efficacy of reversal agents.

Strengths and limitations

The study data were prospectively collected using patients' clinical notes within a short timeframe of the major bleeding event and not retrospectively identified through administrative databases, thus minimising reporting and selection bias. The data had been submitted by

multiple hospitals across the UK, making our findings generalisable to major bleeding patients on VKAs for whom the mainline treatment consists of PCC and Vitamin K. The exact timing of onset of major bleeding prior to admission cannot be ascertained in most cases, but it seems a reasonable assumption that very few will be asymptomatic and delay presentation to hospital, and therefore hospital admission is an acceptable proxy. An upper limit of 2 days post-admission was set for inclusion of interventions and INR results for analysis; this was to ensure that only factors in close proximity to onset of bleeding were analysed, such that the prognostic value of post-intervention INR on outcomes could be assessed without being confounded by subsequent complications. Without complete data on the exact time treatments were administered, post-treatment INR results inevitably do not always correspond to the same elapsed time after intervention for each patient. This was addressed first by ascertaining whether treatment preceded or followed INR result, and examining the influence that time elapsed in hours (where available) had on the results. Furthermore, whilst we believe the classification of bleeding sites into ICH and non-ICH is the primary and most clinically significant distinction, we accept that additional data on other measures of bleeding severity could have enhanced findings; as in other observational studies, treatment decisions for patients will be influenced by perceived clinical severity and even after trying to adjust for this, the possibility of residual confounding remains. Lastly, the amount of missing data in post-intervention INR (31%) is a limitation. The use of multiple imputation which relied on clinical insight and exploratory analyses to inform auxiliary variable selection helped to make the missing at random assumption more plausible and, in turn, allowed data from all patients to be analysed and improved precision of estimates. For example, length of hospital stay was confirmed as an important predictor of INR being missing. The final results were in very close agreement to those from complete case analysis which give some assurance that the imputation model and missing data mechanism had been correctly specified.

In conclusion, failure of INR correction is an important risk factor for mortality in major bleeding associated with VKAs, for both ICH and non-ICH patients. The findings support the hypothesis that correction of haemostatic assays could be used as surrogates for a variety of clinical outcomes in order to assess efficacy of reversal agents for oral anticoagulant agent bleeding. Higher doses of Vitamin K are more efficacious in correcting INR, but further studies are warranted to compare the relative benefits and risks of 5mg versus 10mg doses.

Contribution to authorship:

JT, LG, PM and JKM designed the study, wrote the manuscript and made all subsequent revisions. JT and JKM performed the analyses. NC, SS and CT contributed to the design of the study and writing of the manuscript.

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Conflict of interests:

All authors declare the following: LG, JKM, JT, NC and SS have no conflicts of interest to disclose. CT has received consultancy and speaker honoraria, and travel support to attend scientific meetings from Bayer and Boehringer Ingelheim, and consultancy honoraria from BMS/Pfizer. PM has served as a speaker for Bayer and Daiichi-Sankyo, as a consultant for Daiichi-Sankyo, and has received travel support from Boehringer Ingelheim.

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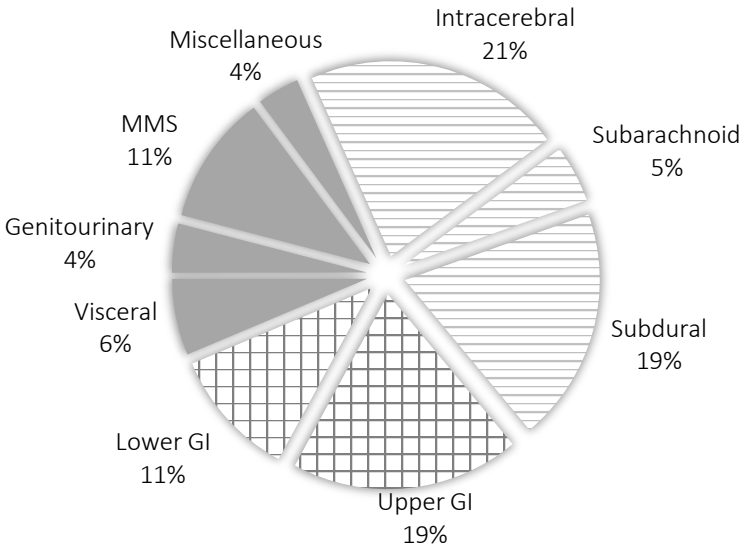
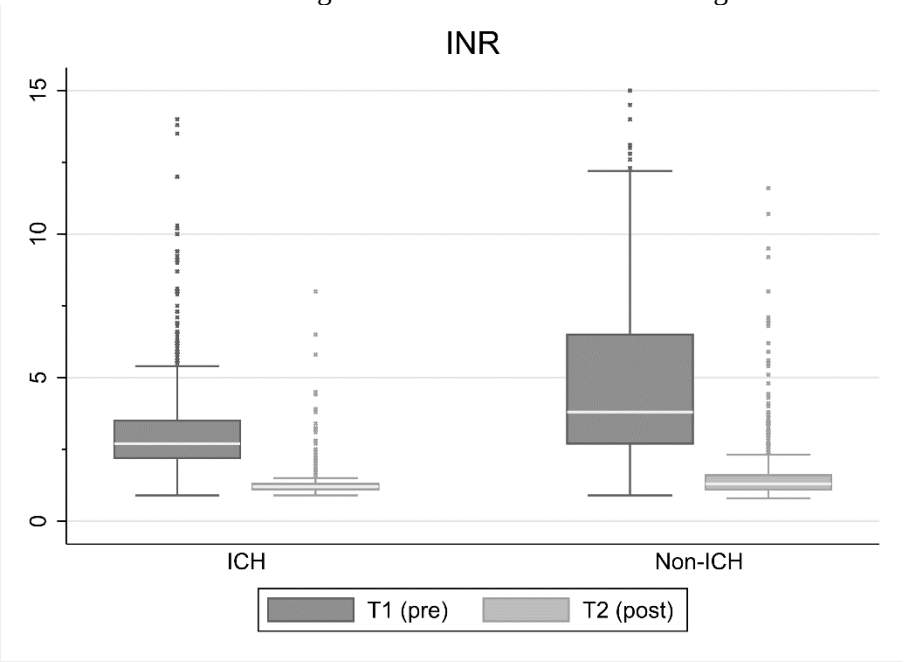
Figure 1: Sites of Bleeding (n = 1,771)



Explanation of Other	
Visceral	Haemoptysis; Pericardium; Retroperitoneal; Abdomen; Chest/Thoracic
Genitourinary	Haematuria/Urethral; Vaginal
Musculo-mucosal-skeletal (MMS)	Epistaxis or mucosal; Cutaneous or soft tissue; Intra-articular; Oral/Pharyngeal
Miscellaneous	Surgical site; Intraocular; Puncture site; Unknown; Other not covered above

(cases with more than 1 of the above classified according to priority described in text.)

Figure 2: INR results at T1 (pre-intervention) and T2 (post-intervention), intracranial haemorrhage vs. non-intracranial haemorrhage



	ICH		Non-ICH	
Time Period	n	INR, Median (IQR)	n	INR, Median (IQR)
T1	714	2.7 (2.2 – 3.5)	877	3.9 (2.7 – 7.1)
T2	509	1.2 (1.1 – 1.3)	713	1.3 (1.1 – 1.6)

INR: international normalised ratio; ICH: intracranial haemorrhage; IQR: interquartile range
(T1 INR >15 (n=35) not plotted)

Figure 3: Predicted probability of T2 INR correction, by Intracranial Haemorrhage (ICH), Prothrombin Complex Concentrate (PCC) dose and Vitamin K dose, for a patient with T1 INR=3 and serum creatinine=100 µmol/L, with 95% confidence intervals

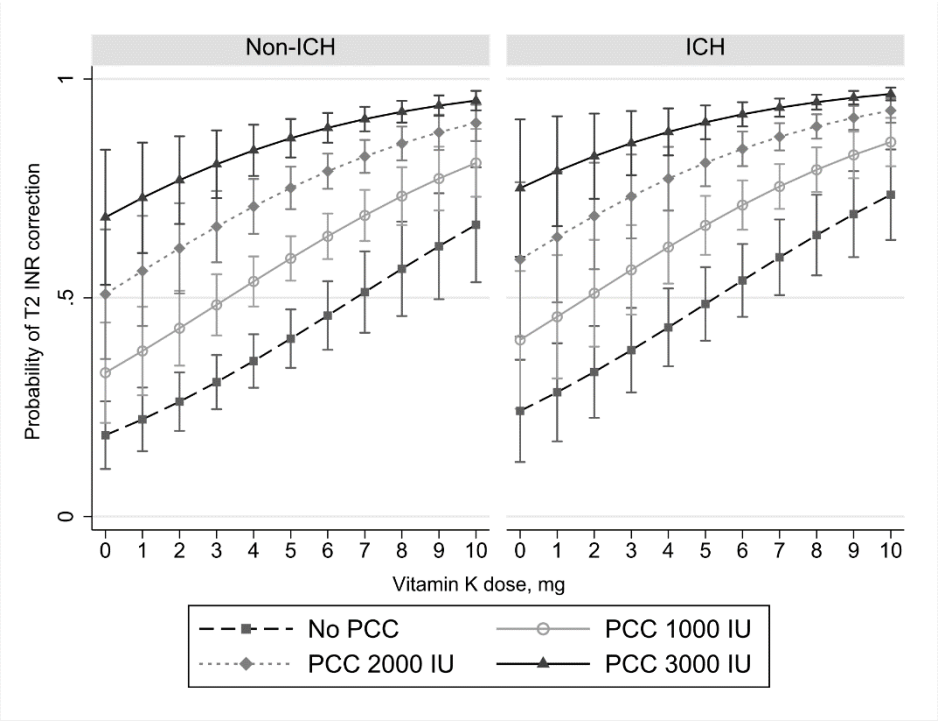


Table 1: Interventions (reversal agents and red cells and fresh frozen plasma administered) within 2 days for Management of Major Bleeding on VKA

	Total	**ICH**	**non-ICH**
	n (%)	**n (%)**	**n (%)**
Total	1771	808	963
Any intervention	1574 (85.9)	747 (92.5)	827 (85.9)
PCC (any dose)	1364 (77.0)	704 (87.1)	660 (68.5)
<1000 IU	37 (2.1)	17 (2.1)	20 (2.1)
1000 – 1999 IU	330 (18.6)	166 (20.5)	164 (17.0)
2000-2999 IU	624 (35.2)	349 (43.2)	275 (28.6)
3000+ IU	362 (20.4)	164 (20.3)	198 (20.6)
Unknown dose	11 (0.6)	8 (1.0)	3 (0.3)
Vitamin K (any dose)	1296 (73.2)	620 (76.7)	676 (70.2)
1-4 mg	116 (6.6)	23 (2.9)	93 (9.8)
5 mg	495 (27.9)	244 (30.2)	251 (26.1)
6-9 mg	15 (0.9)	4 (0.5)	11 (1.1)
10 mg	576 (32.5)	298 (36.9)	278 (28.9)
>10 mg	14 (0.8)	5 (0.6)	9 (0.9)
Unknown dose	80 (4.5)	46 (5.7)	34 (3.4)
Red Blood Cells	574 (32.4)	29 (3.6)	545 (56.6)
Fresh Frozen Plasma	68 (3.8)	8 (1.0)	60 (6.2)
FEIBA/FVIIa/FgC	3 (0.2)	0 (0.0)	3 (0.3)

ICH: intracranial haemorrhage; PCC: prothrombin complex concentrate; FEIBA: factor eight inhibitor bypassing activity; rVFIIa: recombinant activated factor VII: FgC: fibrinogen concentrate

Table 2: Analysis of association between T2 INR correction and 30-day in-hospital mortality by univariable and multivariable logistic regression models

	Complete cases (n=1191)				**Multiple Imputation (n=1771)**			
	OR	95%CI		p-value	OR	95%CI		p-value
Univariable analysis								
T2 INR ≤ 1.3	1				1			
T2 INR > 1.3	1.54	1.12	2.12	0.008	1.57	1.18	2.09	0.002
Multivariable analysis								
T2 INR >1.3 (in untreated group)	1.59	0.98	2.58	0.86	1.54	0.99	2.42	0.06
T2 INR >1.3 (in treated group)	3.18	1.93	5.23	<0.001	3.26	2.13	4.98	<0.001

OR = odds ratio; CI = confidence interval; INR= international normalized ratio
For multivariable analysis, odds ratios are adjusted for treatment (treated/untreated), intracranial haemorrhage (yes/no) and age (years).

Appendix 1 (Supplementary)

Table 3: Summary of multiple imputation variables and % missing (N=1771)

	Median	p25	p75	Number of missing records	% missing
Primary variables					
Death within 30 days of bleeding (Outcome)	-	-	-	52	3
T2 INR (Exposure)	1.2	1.1	1.4	549	31
Auxiliary variables					
T1 INR	3.2	2.4	5.1	180	10
T1 Prothrombin time, seconds	38.3	25.8	61.3	969	55
T2 Prothrombin time, seconds	13.4	12	16	1043	59
T1 Activated partial thromboplastin time, seconds	40	33	51	803	45
T2 Activated partial thromboplastin time, seconds	29.2	25.6	34	977	55
T1 Serum Creatinine, µmol/L	94	72	134	141	8
T1 Alanine transaminase, IU/L	19	14	28	562	32
T1 plasma haemoglobin, g/dL	11.6	8.9	13.4	81	5
T1 platelet count, $x10^9$/L	222	171	288	91	5
Length of hospital stay, days	7	3	17	12	<1
Weight, kg	73	62	86	872	49
Vitamin K dose, mg	5	0	10	80	4
Vitamin K dose squared, mg^2	25	0	100	80	4
Prothrombin Complex Concentrate dose, IU	2000	500	2500	11	1
Time between treatment and T2 INR, hours	9.5	5.0	18.8	816	46

T1: pre-intervention (within 1 day of admission for major bleeding)
T2: post-intervention (first result after intervention, or after T1 if no intervention given, and within 2 days of admission for major bleeding)
p25 – lower quartile; p75 – upper quartile
INR=international normalised ratio

Other auxiliary variables with no missing data
Age, years
Sex
Intracranial haemorrhage (ICH)
Did not receive any intervention before measurement of T2 INR
Administration of Prothrombin Complex Concentrate, any dose
Administration of Vitamin K, any dose
Transfusion of Fresh Frozen Plasma, units
Hospital proportion of patients with T1 INR recorded (proxy for quality of routine INR monitoring)
Indicated warfarin/VKA for mechanical heart valve
Haemorrhagic cerebrovascular accident during follow-up
Admission to ITU during follow-up
Any history of liver failure/cirrhosis, cancer or chronic renal failure