Review of Direct Oral Anti-Coagulants (DOACs) and Warfarin Reversal in Trauma Patients

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Glossary

Abbreviation	Meaning
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
CS	Clotting Screen
CT	Computer Tomography
DGH	District General Hospital
DOAC	Direct Oral Anti-Coagulants
FBC	Full Blood Count
GCS	Glasgow Coma Score
FFP	Fresh Frozen Plasma
MTC	Major Trauma Centre
PCC	Prothrombin Complex Concentrate
rFVIIa	Recombinant factor VIIa (Novoseven)
RBC	Red Blood Cell
RoTEM	Thromboelastometry
SHOT	Serious Hazards of Transfusion
TEG	Thromboelastograph
TU	Trauma Unit
TXA	Tranexamic acid
VTE	Venothromboembolic event

SUMMARY OF MAIN FINDINGS

The organisational survey was completed by 27 hospitals, whose classification was taken as reported by the data with 11 district general hospitals (DGH), 11 sites designated as trauma units (TU), 4 Major Trauma Centres (MTCs) and 1 other. Most of these sites are located in the London Regional Transfusion Committee (RTC) region. Not all sites who completed the organisational survey were able to contribute to individual case entry due to not having eligible patients attending their site during the audit period. Hence for each section there were differences noted.

A four factor Prothrombin Complex Concentrate (PCC) was available in all hospitals, 25/27 hospitals stocked recombinant Factor VIIa (rFVIIa), massive haemorrhage / trauma was stated as the reason for stocking rFVIIa in 19 hospitals, 15 hospitals stocked this for treating patients with bleeding disorders, 10 sites held stock for both indications. The majority of hospitals had the antidote for dabigatran, but very few patients were on dabigatran (2%). Very few sites had the NICE approved antidote Andexanet alfa for Rivaroxaban and Apixaban.

All hospitals had reversal guidelines for warfarin, only 21 (78%) hospitals had reversal guidelines for Direct Oral Anticoagulants (DOAC). The dosage of vitamin K and PCC was reported available on warfarin reversal guidelines in 89%, but there were no comments related to the dose of PCC for the DOAC group.

Eighteen sites submitted 50 cases on warfarin, and 26 sites supplied almost complete data sets for 245 cases on a DOAC, suggesting that more patients presenting to A+E are anticoagulated with a DOAC than a vitamin K antagonist. Apixaban was the most commonly used DOAC, and warfarin was the only vitamin K antagonist reported in this audit.

In both groups stroke prevention was the most commonly reported indication for anticoagulation and in both groups head injury was the most commonly reported reason for presentation (81% DOAC, 88% warfarin). A very small number of patients were also on antiplatelet therapy in both groups, with a small fraction of DOAC patients taking dual antiplatelet therapy.

A significant number of patients presented with complications from multiple co-morbidities which delayed identification of bleeding.

Time taken to take blood samples from patients, sending patients for imaging and availability of blood results were delayed in most patients (>80% in both groups) and administration of vitamin K, PCC and tranexamic acid was suboptimal.

Patients on a DOAC were more likely to need transfusion support with blood and other blood components than those taking warfarin.

INTRODUCTION

History and purpose of The London Haematology and Trauma Group

The Major Trauma Centres (MTC) with their associated trauma networks, were established in 2008 following the 2007 National Confidential Enquiry into Patient Outcome and Death report [1] which identified serious failings in the clinical and organisational aspects of trauma care in England. The London Haematology & Trauma Group was convened in 2010 to support the London Trauma System. This group was originally formulated as a sub-group of the London Regional Transfusion Committee (RTC), which reports to the National Blood Transfusion Committee (NBTC). The London Haematology & Trauma Group advises the London Trauma Steering Group in part through the provision of an annual report and hence contributes to the Trauma Governance framework. The original objectives of the group were to support a consistent approach to delivery of transfusion care across all London Major Trauma Centres within the four trauma networks. This group has expanded to include other centres designated as MTC including Oxford, Cambridge and more recently the group has expanded its membership further to include Southampton in 2021 and in 2022, Plymouth and Liverpool.

The key activities of the group are as follows:

1. Share good practice and guidelines in relation to transfusion support for trauma services.
2. Develop and undertake audit projects of trauma transfusion practice.
3. Support education and training across Trauma networks.
4. Support development of guidance for co-ordinated transfusion support as part of emergency planning.
5. Promote implementation of evidence-based practice.
6. Interact with Pan-London and national research infrastructure to support clinical research and participation in multi-centre clinical trials in trauma associated transfusion.
7. Support development of epidemiological, public health and health services research related to trauma and the provision of transfusion services.

Purpose of study

Since the introduction of the MTC and the associated networks, the transfusion support and management of the reversal of anticoagulation within MTC have been standardised through sharing of good practice and guidelines. Just prior to the start of the COVID-19 pandemic in 2020, this group was mandated by the London Major Trauma Steering Group with the task of 1) identifying if all trauma units (TU) had reversal guidelines for anticoagulation, particularly for the DOACs and 2) to assess if the guidance's were being followed.

Anticoagulants

Anticoagulants are commonly prescribed for the management of venous thromboembolism (treatment and prophylaxis), in patients with cardiac co-morbidities such as atrial fibrillation, congenital and valvular heart disease to prevent thrombotic complications. Bleeding is the commonest and most concerning adverse event associated with anticoagulants [(2)]. The vitamin K antagonist, warfarin has been available since the 1950s. The monitoring and reversal of this agent has long been established. Since the introduction of DOACs in 2010, this class of anticoagulants has become a more attractive alternative to vitamin K antagonist in all indications except mechanical heart valves and antiphospholipid syndrome. Compared to warfarin, the DOACs have more predictable pharmacokinetics, shorter half-lives (ranging from 5 to 17 hours). DOACs do not need regular monitoring with clotting assays and have reduced food and drug interactions. The bleeding incidence is thought to be lower than with warfarin and varies according to the type of DOAC used, the indication, and individual risk factors of the patients determining the incidence of fatal bleeding (i.e., intracranial haemorrhage). Until recently the only antidote available was for Dabigatran (a direct thrombin inhibitor) and reversal of FXa inhibitor (Rivaroxaban, Apixaban and Edoxaban) was empirically with Prothrombin Complex Concentrate. Reversal guidelines for DOAC have only recently been more widely available.

Survey: Oct 2020

In October 2020, a snap survey (appendix 1a) was sent to all hospitals in London and the South East Coast Region to determine if they had a guideline for the use of Prothrombin Complex Concentrate (PCC) for the reversal of anticoagulation associated bleeding (warfarin and DOACs). Hospitals were asked if they had undertaken an audit in the last 2 years to check if the reversal guidelines were being followed. Overall, 30 hospitals responded (21 from London, 9 from the South East Coast region). Twenty-nine (97%) hospitals responded that they had a Trust guideline for warfarin to be reversed with PCC but only 27% of hospitals had audited their practice. Twenty-seven (90%) hospitals had a guideline for DOAC reversal and only 25% of these had audited against these guidelines. There was a request from >70% of the respondents for an audit template to enable regular auditing against the guidelines.

METHODS

Pilot audit: June –July 2021

In response to the request for an audit template from the October 2020 survey, an organisational survey and audit templates for patients taking vitamin K antagonists and DOACs was created on an online platform. The goal of the organisational survey was to find out if hospitals had reversal guidelines. The audit templates were designed to enable entry of data from cases seen / admitted with trauma induced bleeding. The electronic platform allowed the anonymised data collection to be saved and resumed as information was gathered. Data entry was only complete for each case when submitted.

The aim of the pilot was to assess the format and usability of the templates. The pilot was originally planned for the month of June 2021 and / or collection of data from 10 cases, whichever was sooner. However, several of the 9 hospitals in the pilot (*table 1*) reported two common problems:

1) that they needed 2-4 weeks to get approval for the audit to be registered within their organisations
2) difficulty in identifying a member of staff from the emergency department to help with data collection

There were no other concerns raised about the feasibility and ease of use of the templates. The pilot period was extended to 2 months, running from 1st June - 31st July 2021.

Table 1: Names of hospitals partaking in the pilot

Croydon Hospital
Northwick Park Hospital
Chelsea & Westminster Hospital
Kingston Hospital
Princess Royal Hospital Farnborough
Milton Keynes Hospital
Royal Surrey Hospital
Medway & Maritime Hospital
East Surrey Hospital

The Audit: January –March 2022

The audit was planned to run for 3 months between January – March 2022 (or completion of up to 30 patient entries whichever was sooner), with data collection to be completed by the middle of April through the electronic portal in *Table 2*. The audit was advertised across London, The South East and

East of England regions through the Regional Transfusion Committees and Patient Blood Management Practitioners. NHS staff were sent instructions to guide data collection / entry on the platform, together with pdf versions of the surveys and data linkage documents to keep confidential demographic records of cases submitted, the linkage document was for local reference. Due to the additional pressures on the NHS workforce related to the rising number of cases of covid-19 infection, which in many places led to the deployment of NHS staff, the data entry into the electronic portal was extended to the end of the first week of July 2022.

Table 2: Audit landing page

See appendix 3 for the questions for organisational survey, DOAC and vitamin K antagonist templates.

Links to Audit Tools

Organisational Survey to Be Completed ONCE for Each Participating Organisation - Link below

Link: https://wh1.snapsurveys.com/s.asp?k=160916075240

Audit of Reversal of Vitamin K Antagonist Associated Bleeding

This audit template should only be completed for patients presenting with trauma related bleeding who at presentation were taking a vitamin K antagonist as anticoagulation (e.g. Warfarin / Acenocoumarol).

Complete audit form for up to 30 cases - link below

Link: wh1.snapsurveys.com/s.asp?k=161582425235

Audit of Reversal of DOAC Associated Bleeding

This audit template should only be completed for patients presenting with trauma related bleeding who at presentation were taking a DOAC

Complete audit form for up to 30 cases - link beow

Link: https://wh1.snapsurveys.com/s.asp?k=163705938660

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ORGANISATIONAL SURVEY RESULTS

The survey was sent out to 88 hospitals in the region, 27 hospitals responded, 5 sites submitted duplicate data which were removed from the analysis. Data was submitted by 11 DGH, 11 sites designated as TU, 4 MTCs and 1 site without an A+E *(figure 1)*, with most hospitals distributed across the London RTC region.

All hospitals had reversal guidelines for warfarin, and this was the only vitamin K antagonist reported to be in use. Twenty-four (89%) hospitals indicated that a dose of vitamin K and Prothrombin Complex Concentrate (PCC) was clearly stated on the warfarin reversal guidelines.

All hospitals stocked a licensed 4 factor PCC, with a 15 (56%) stocking Beriplex and 12 (44%) Octaplex. There were 18 responses citing weight tailored approaches (units/Kg), with 3 indicating a weight dependent approach combined with specific INR results and 5 responses specifying specific dosages ranging from 1500 to 5000 international units of PCC.

Guidelines for reversal of DOACs was reported as available in 21 (78%) hospitals. There were no comments related to the dose of PCC for this group. Twenty-five (92.5%) hospitals stocked the antidote to Dabigatran, 3 hospitals also commented that they stocked the antidote Andexanet alpha for reversal of Rivaroxaban and Apixaban. Two hospitals did not stock any antidote.

Recombinant factor VIIa was available in 24 hospitals, *figure 4* illustrates the reasons given for stocking this.

Figure 1: Classification of hospitals completing the organisational survey

Data was entered by 11 DGH, 11 TU, 4 MTC. Other was specified as hospital with ITU covering emergencies.

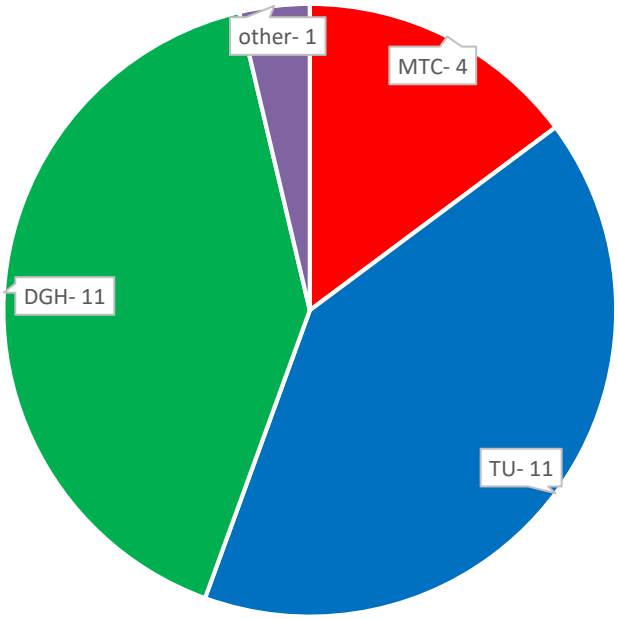


Figure 2: Availability of reversal guidelines

All hospitals had warfarin reversal guidelines; only 78% had DOAC reversal guidelines.

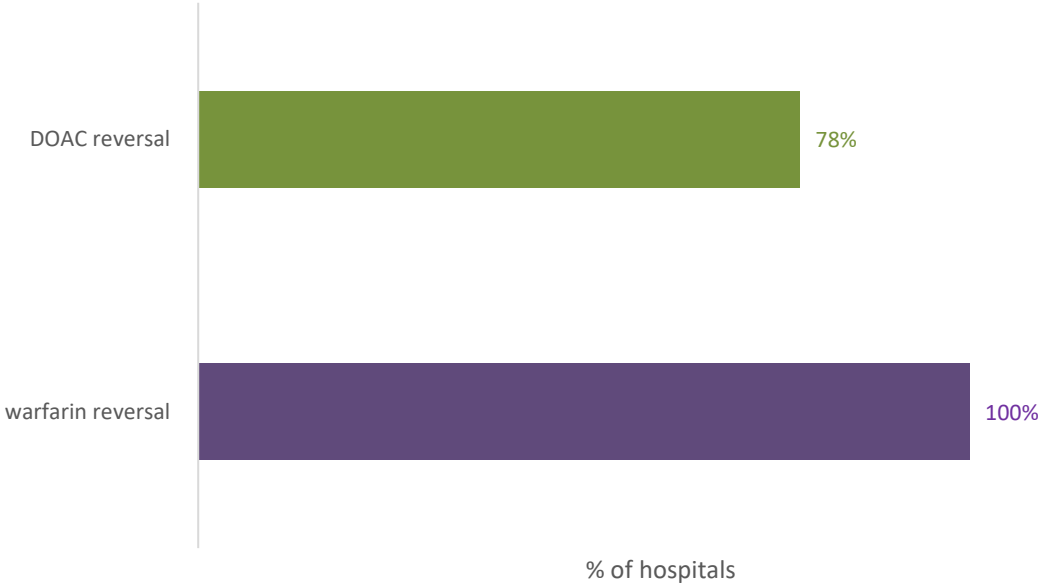


Figure 3: PCC availability

All hospitals stocked PCC, with 15 sites using Octaplex and 12 using Beriplex.

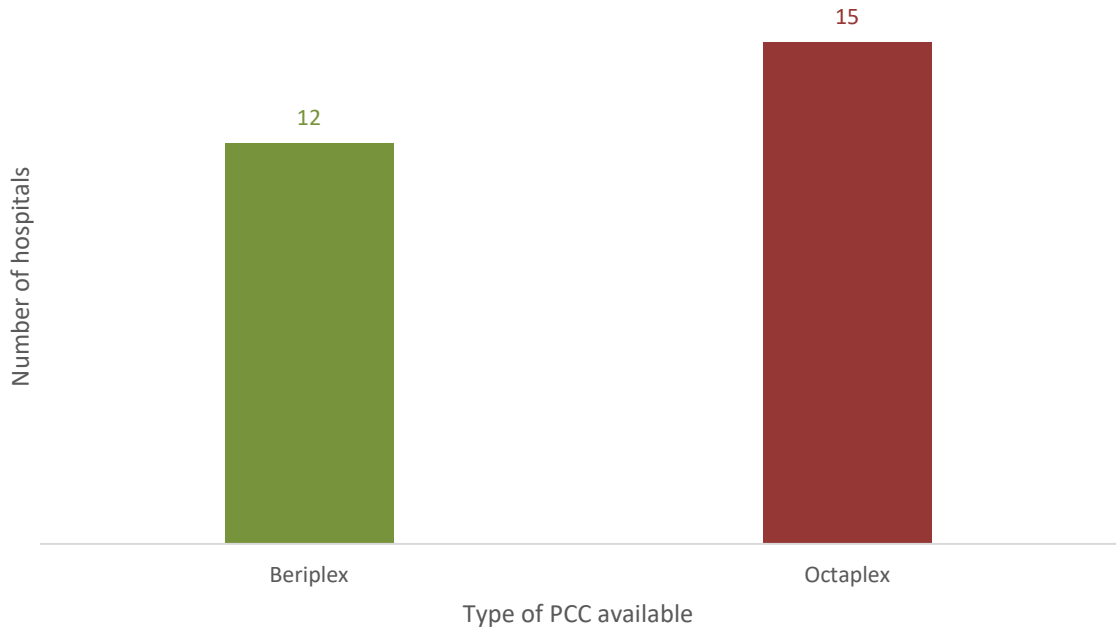
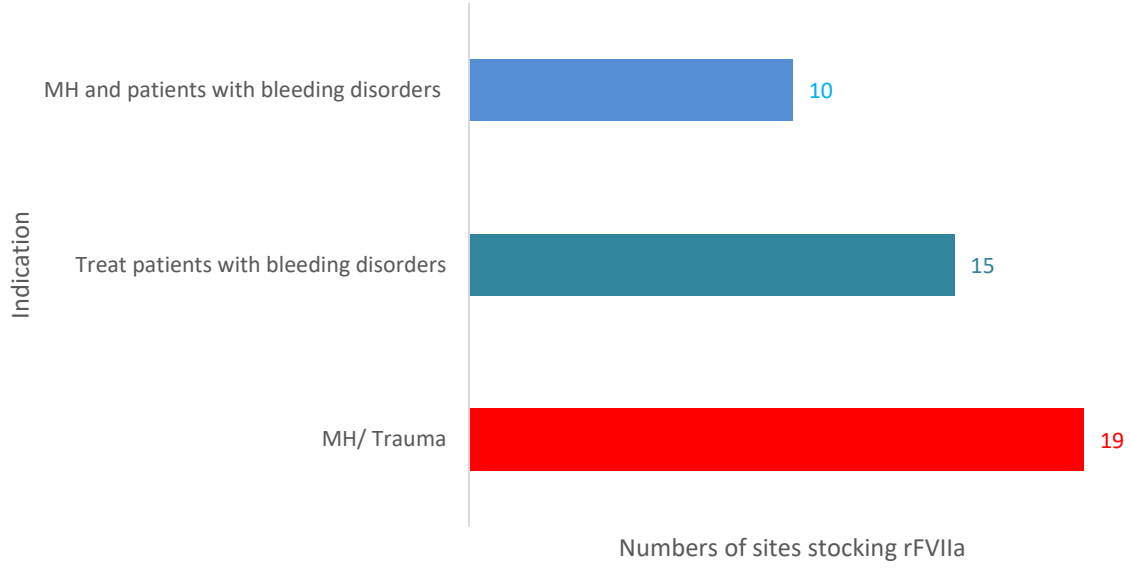


Figure 4: Purpose for stocking recombinant FVIIa

Massive haemorrhage / trauma was stated as the reason for stocking rFVIIa in 19 hospitals, 15 hospitals stocked this for treating patients with bleeding disorders, 10 sites reported holding stock for both indications. One site stated, "this was used as the last line of treatment for ongoing bleeding in massive trauma/obstetric PPH when all else failed". Two hospitals did not stock rFVIIa.

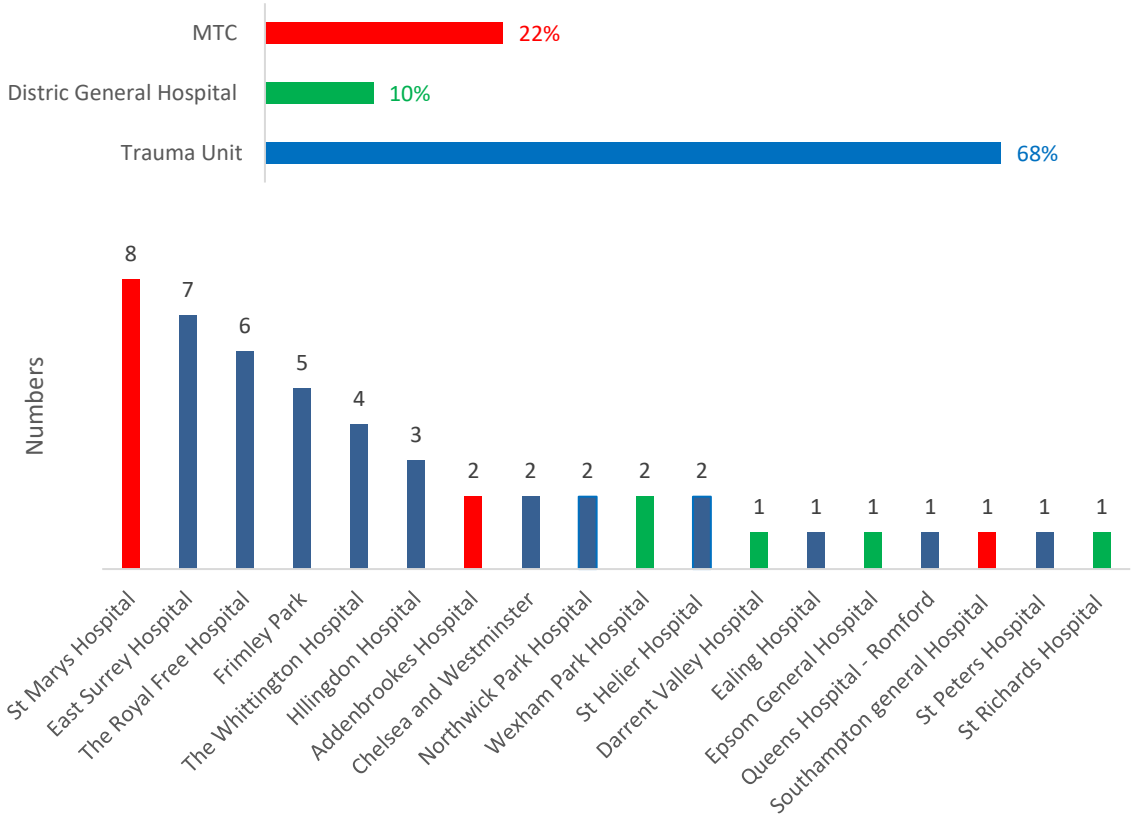


RESULTS OF AUDIT OF REVERSAL OF VITAMIN K ANTAGONIST ASSOCIATED BLEEDING

Cases were submitted by 18 hospitals. There were complete data sets on 50 cases, and warfarin was the only vitamin K antagonist reported in use. The largest number of cases entered by a single site was 8, the lowest was 1. *Figure 5* shows the number of cases reported by each hospital.

Figure 5: Hospitals submitting cases on warfarin

Data was entered by 11 hospitals classified as a trauma unit (blue bars) 3 MTC (red bars) and 4 DGH (green bars), 18 sites in total contributed 50 cases. The TU contributed 34 (68%) cases, DGH 5 (10%) cases and MTC 11 (22%) cases. The highest number of cases (8) was entered by St Mary's Hospital, (MTC). Seven hospitals submitted 1 case each (median 2 and mean 2.7).



Stroke prevention (50%) was the most common indication for anticoagulation with warfarin**.** VTE prophylaxis accounted for 27%, VTE treatment 10% and 15% of patients were on warfarin for a metallic heart valve (*figure 6*). A small number of patients (16%) were also on antiplatelet therapy, but none were on dual antiplatelet therapy. The majority of patients were admitted with head injury

(*figure 7*). In 15 cases initial presentation was due to complications of pre-existing medical conditions, however, subsequently 88% of these were reported as presenting with a head injury.

Figure 6: Indication for vitamin K antagonist use

Stroke prevention was the most common indication (50%) for anticoagulation with warfarin. VTE prophylaxis accounted for 27%, VTE treatment 10% and 15% of patients were on warfarin for a metallic heart valve. A small percentage were anticoagulated for more than one indication.

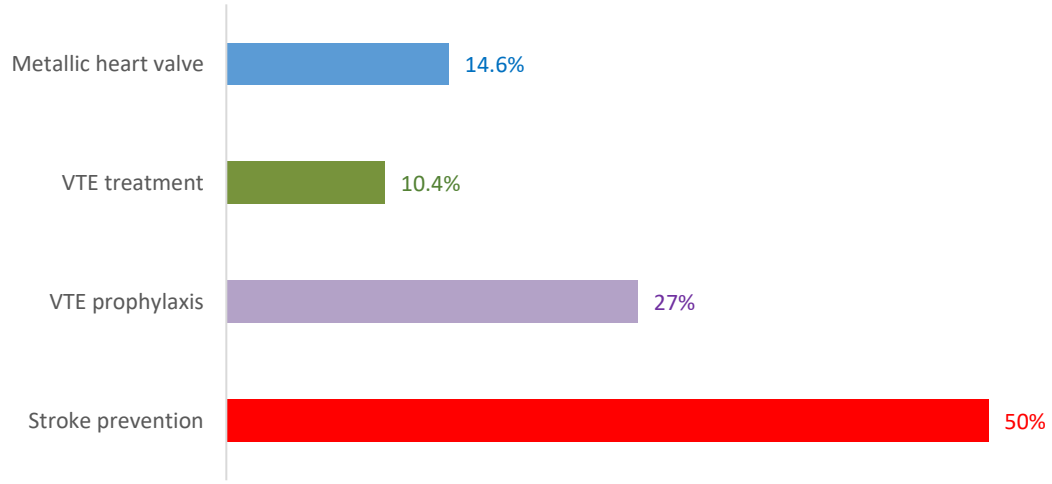
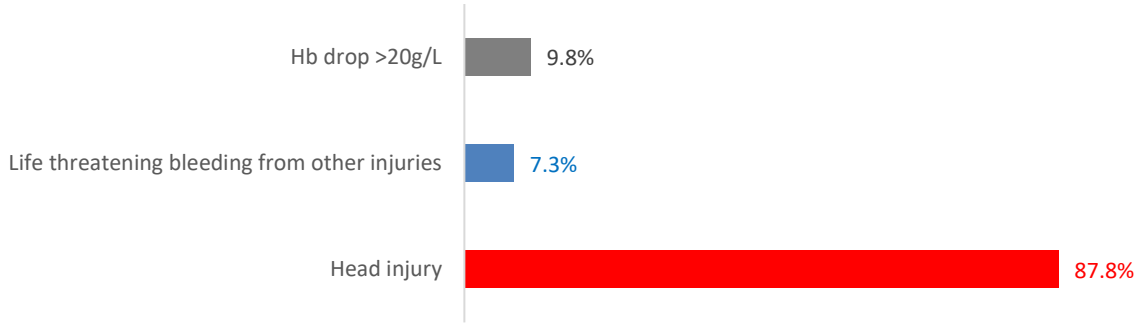


Figure 7: Reason for presentation whilst on warfarin

The majority of patients were admitted with head injury (87%), almost 10% presented with a drop in haemoglobin greater than 20g/L and very few presented with life threatening injuries. For a small percentage more than one indication was ticked.



Availability of Blood Results

In 82% of cases, treatment was delayed until blood results were available (*figure 8*). In approximately 1/3 (34%) of cases it took 30-60 minutes for patients to have blood tests taken. Only 20% of patients

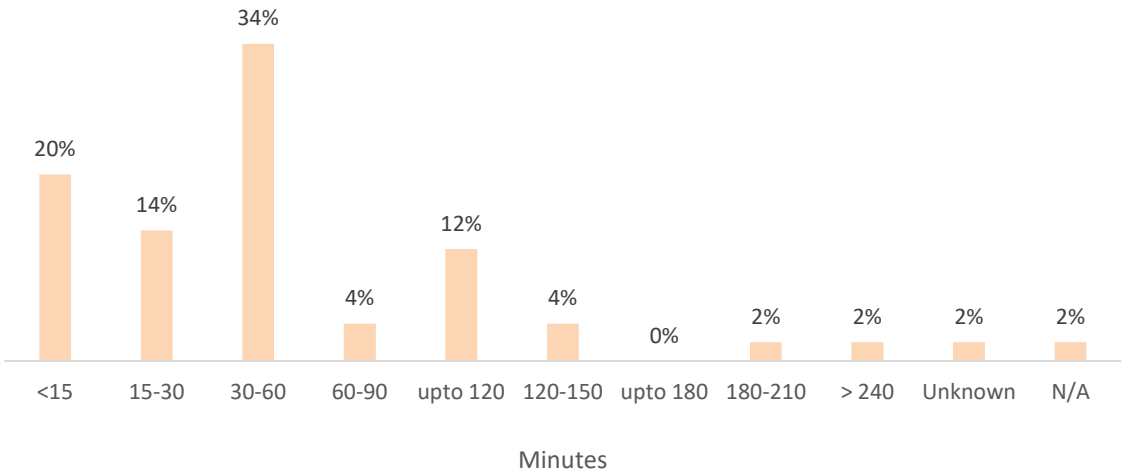
had bloods taken within 15 minutes and 14% had their bloods taken between 15-30 minutes of arrival to ED. *Figure 9* shows the range of time taken from arrival to the emergency department and having initial bloods taken.

Figure 8: Did treatment commence before blood results were returned?

The red bar shows that the majority of patients (82.9%) did not commence treatment before the results were available. Only 17% of patients had treatment started before blood results were obtained.

Figure 9: Time between arrival in ED and initial blood sampling

In 34% of cases, it took 30-60 minutes for patients to have blood tests taken. Only 20% of patients had bloods taken within 15 minutes and 14% were taken between 15-30 minutes of arrival to the emergency department. Data was missing for 4% of cases.



The time taken to get the full blood count authorised is shown in *figure 10*, and results for clotting screen are shown in *figure 11*. In 24% of cases, the time taken to get results back was unknown, but

in approximately 60% of cases the full blood count results were available within one hour, and approximately 50% of clotting results were back in this time period.

Figure 10: Time of FBC samples arriving in lab and authorisation of results

This chart shows the distribution of time taken to get FBC authorised by the laboratory. In approximately 60% of cases the full blood count results were available within one hour. Data was missing for 4% cases.

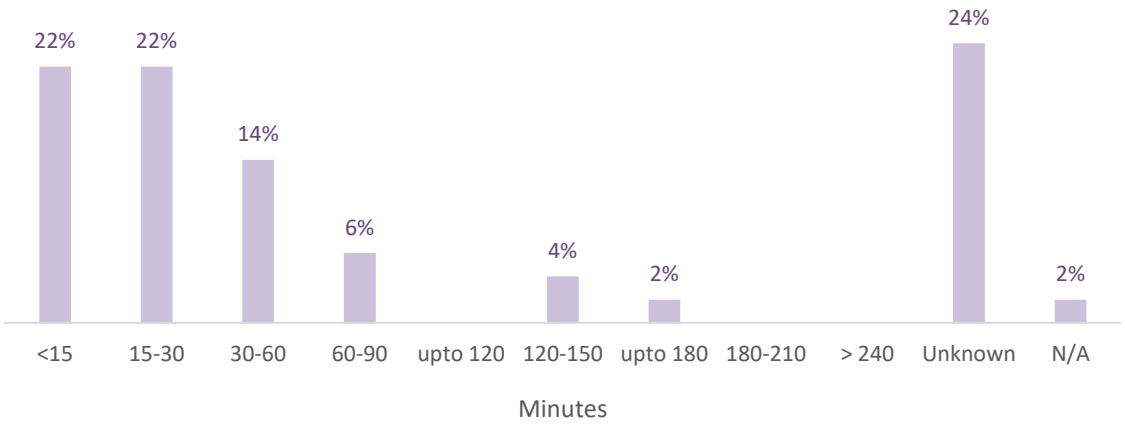
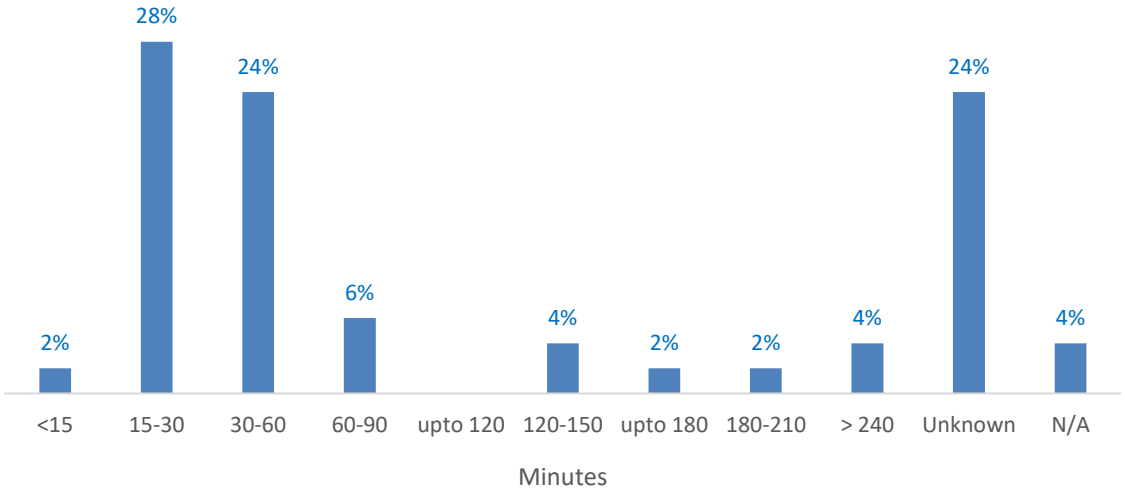


Figure 11: Time of clotting samples arriving in lab and authorisation of results

This chart shows the distribution of time taken to get clotting results authorised by the laboratory. In approximately 50% of cases the clotting screen count results were available within one hour.



Availability of Imaging Results

A small number of patients (18%) had a Computer Tomography (CT) scan within an hour of arrival to the emergency department. *Figure 12* below outlines the range of times taken from arrival to the emergency department to CT scan.

Figure 12: Time between arrival to ED and CT scan

This chart shows the distribution of time taken for patients to be sent for CT scan. Only 18% patients went to have a CT scan within 60 minutes of presentation to A+E, this increased to 46% by 2 hours. Data set incomplete; data provided for 78% of cases.

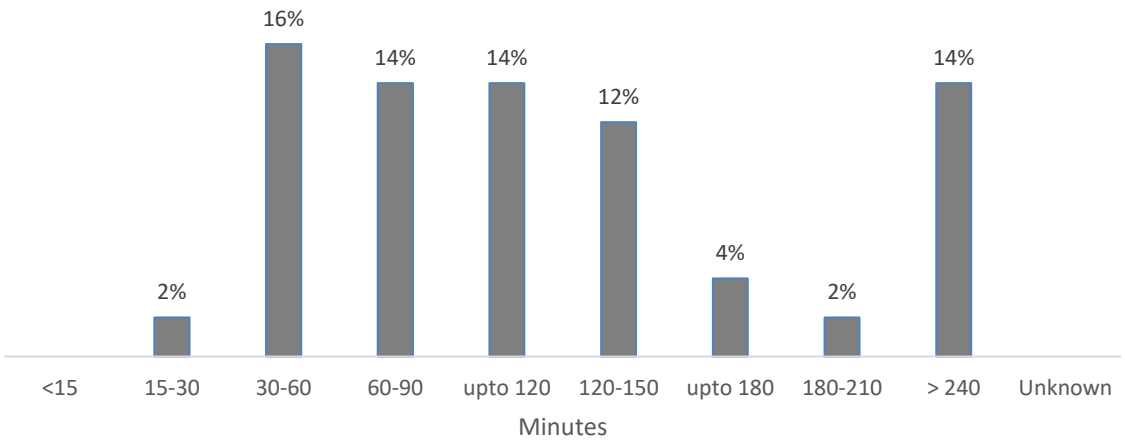
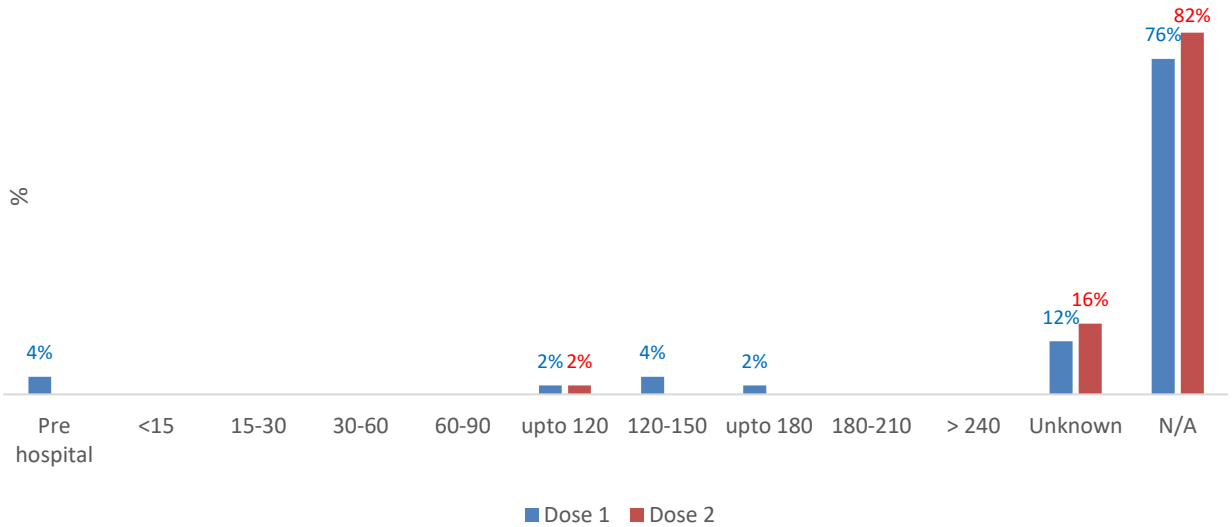


Figure 13: Time of first and second dose of Tranexamic Acid

Data entry on first and second dose of tranexamic acid was sparse, with majority stating not applicable or unknown.

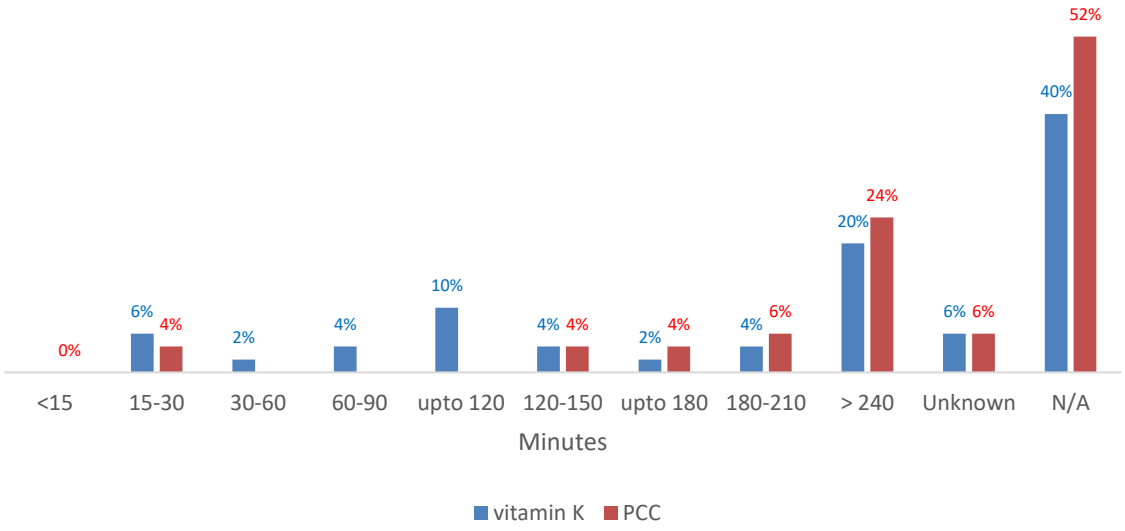


Vitamin K and PCC administration

Administration of vitamin K and PCC was poor. It was reported that in 40% of cases vitamin K administration was not applicable, where it was indicated, the majority waited more than 2 hours to receive this, the complete range of times is shown in *figure 14*. In >50% PCC was stated as not applicable, where it was given, 22% waited more than 4 hours to receive this.

Figure 14: Arrival time to ED to vitamin K and PCC administration

Approximately 8% of patients received vitamin K within 60 minutes of arrival to A+E, 10% of patient waited 2 hours, 20% waited more than 4 hours. For vitamin K, not applicable was stated for 40% of cases. In >50%, PCC was stated as not applicable, where it was stated applicable 24% waited more than 4 hours to receive this. Data submitted for 98% cases for vitamin K, and 100% for PCC.



There were 18 comments submitted in relation to patients taking warfarin. In two cases, presentation was delayed, in 15 cases initial presentation was thought to be related to complications of underlying pre-existing medical conditions.

Blood component usage

Only 9 units of blood was transfused in three patients, none of these received tranexamic acid. One patient who was on warfarin for stroke prevention presented with a collapse at home and was subsequently diagnosed with ruptured aortic aneurysm, received 5/9 of these units. This patient had reparative surgery but later died in intensive care. Another patient who received three units of blood was on warfarin for metallic heart valve and presented with haemoglobin drop >20g/L. Both of these patients also received PCC as per local guidelines. The third patient who was transfused 1 unit of blood

presented with symptomatic anaemia; this patient was anticoagulated for stroke prevention. No other blood component was transfused in this group.

Examples of cases

Two patients presented with subarachnoid bleeds; both were taking warfarin for the treatment of VTE. One of these patients arrived in the emergency department in the middle of the afternoon, from the time to arrival in the emergency department, it took up to an hour to take blood tests from the patient, up to 2 hours to get a CT scan, more than 4 hours to get blood results back, then the patient received both vitamin K and PCC to reverse warfarin. The second patient who arrived in the emergency department in the evening also waited up to 2 hours for a CT scan and 2.5 hours to get blood samples taken with results being available for both full blood count and clotting screen within 3.5 hours, but still did not receive vitamin K or PCC until more than 4 hours from time of arrival to the department. Both patients survived and were discharged home.

RESULTS OF AUDIT OF REVERSAL OF DOAC ASSOCIATED BLEEDING

In total 26 hospitals supplied data for patients admitted on a DOAC, almost complete datasets were supplied for 245 cases, the details of the hospitals and number of cases are shown below in *figure 15*. The most commonly reported DOAC in use was Apixaban and 78% of hospitals reported having reversal guidelines for DOACs. The antidote for Dabigatran was stocked by 92.5% of hospitals but only 2% of cases were reported to be taking this agent. Three hospitals stocked the antidote Andexanet alpha for reversal of Rivaroxaban and Apixaban. Two hospitals did not stock any antidote.

Stroke prevention was the most common indication for anticoagulation (81%), with 28% for VTE and only 3% for acute coronary syndrome (ACS).

There were 45 comments submitted in relation to DOAC use. Delayed presentation was reported for 18 cases, and time of injury unknown in 2 cases. In 22 cases, initial presentation was related to complications of co-morbidities.

Figure 15: Hospitals submitting cases on DOAC

Data submitted by 4 MTC, 11 TU and 11 DGH. The majority of cases 141 (57%) were submitted by trauma units, 75 (31%) DGH and 29 (12 %) cases were reported from Major Trauma Centres, in total 26 sites contributed 245 cases. The spread of cases entered is wide with highest number of cases reported by Frimley Park Hospital (TU), with 29 patients, with four hospitals entering a single case each (median 6, mean 9.4)

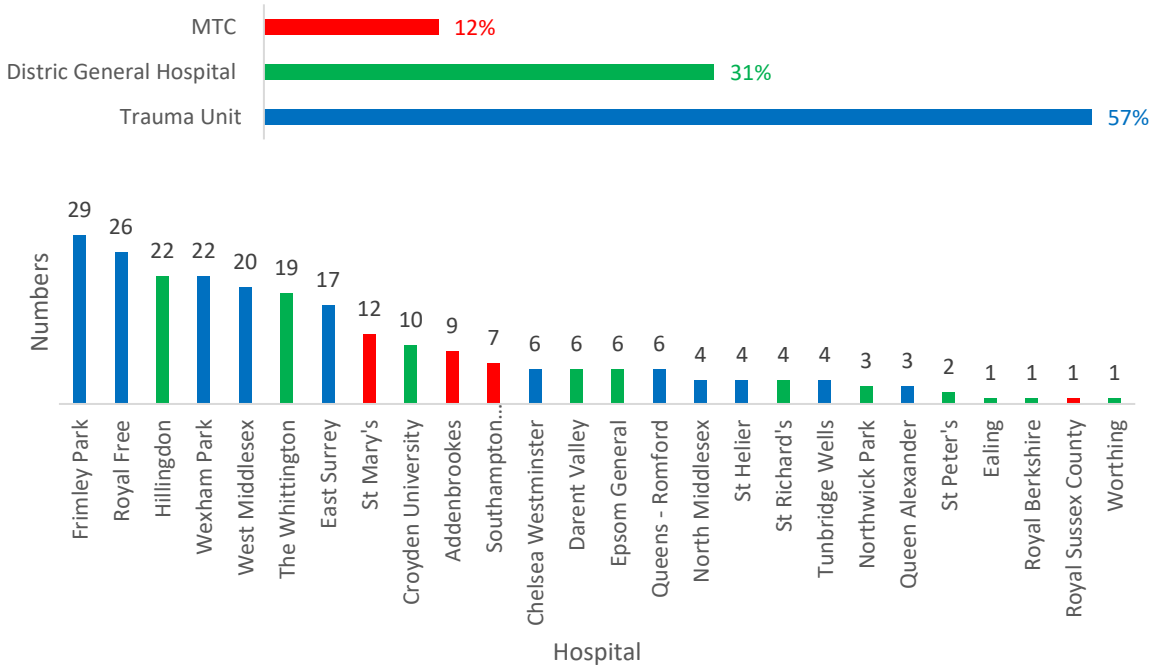


Figure 16: Types of DOAC patients taking

Apixaban was the most commonly used DOAC, followed by Rivaroxaban, then Edoxaban. Only 2% of patients were on Dabigatran.

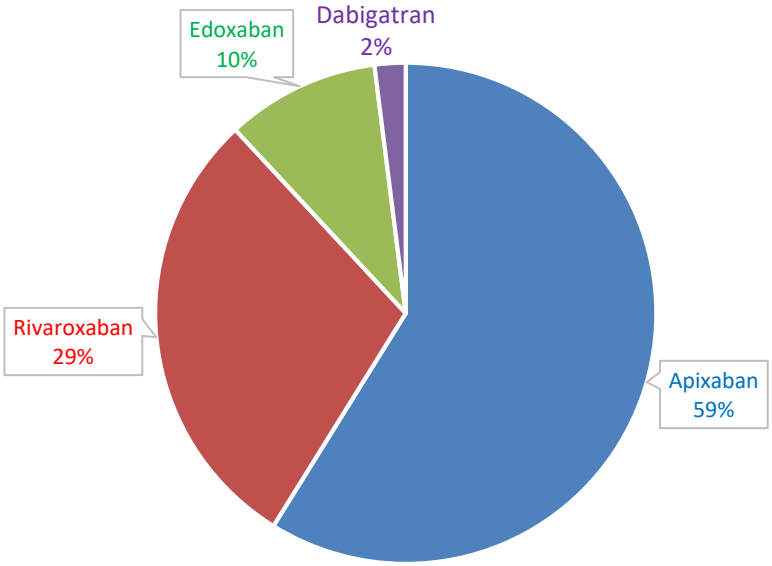


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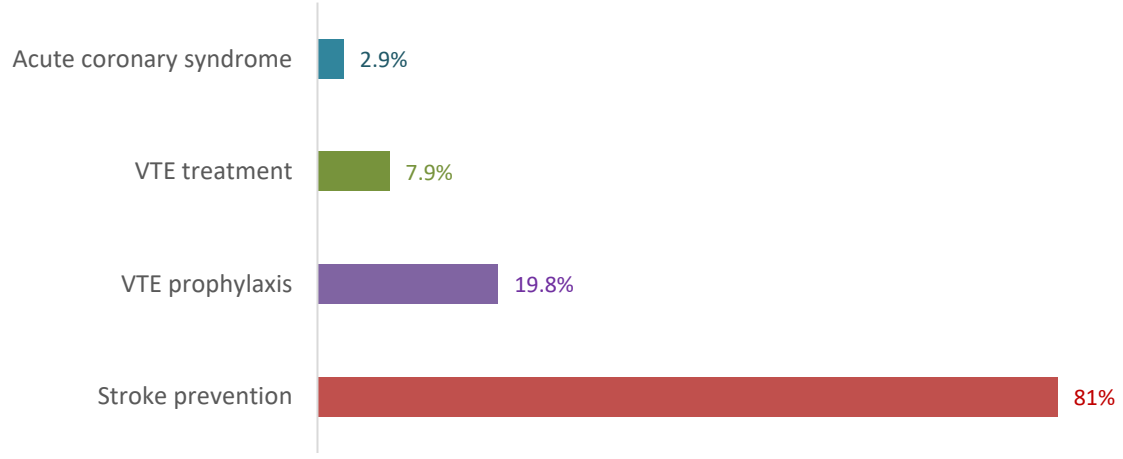
Figure 17: Indications for DOAC usage

Stroke prevention was the most common indication for being on a DOAC, 11% of cases were anticoagulated for more than one indication.



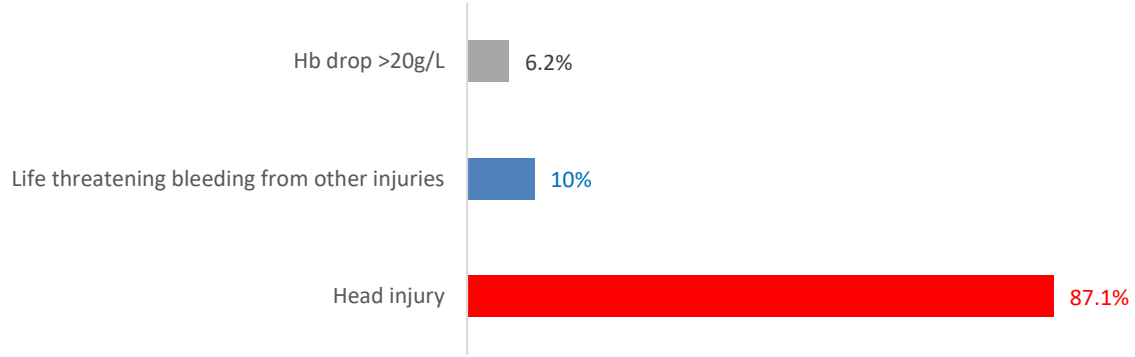
The majority (90%) of patients taking a DOAC were not taking an antiplatelet agent, of the 10% of patients who were on antiplatelet therapy (*figure 18*), 20% of these were on dual antiplatelet therapy. Indication for presentation is shown in *figure 19*, with almost 90% presenting with head injury.

Figure 18: Use of antiplatelet therapy with DOAC

Only 10% of patients were on a DOAC and antiplatelet drug, within this small group taking antiplatelet drugs, 20% if these reported as taking dual antiplatelet drugs with a DOAC.

Figure 19: Reason for presentation whilst on DOAC

Majority of patients presented with a head injury; small percentage presented with more than one indication.



Availability of Blood Results in DOAC Cases

In almost 1/3 patients, it took 30-60 minutes from time of arrival to ED to take initial blood tests and 84% waited for test results before commencing treatment. *Figures 20-22* outline the time taken between arrival to the emergency department to having blood tests taken and authorisation of results. Only 15% of patients received treatment before the blood results were available.

Figure 20: Time between arrival to ED and blood sampling

The graph shows the distribution of time taken for patients to have blood samples. Approximately half of patients had bloods taken within 60 minutes of arrival to the emergency department. Data available for 88% cases.

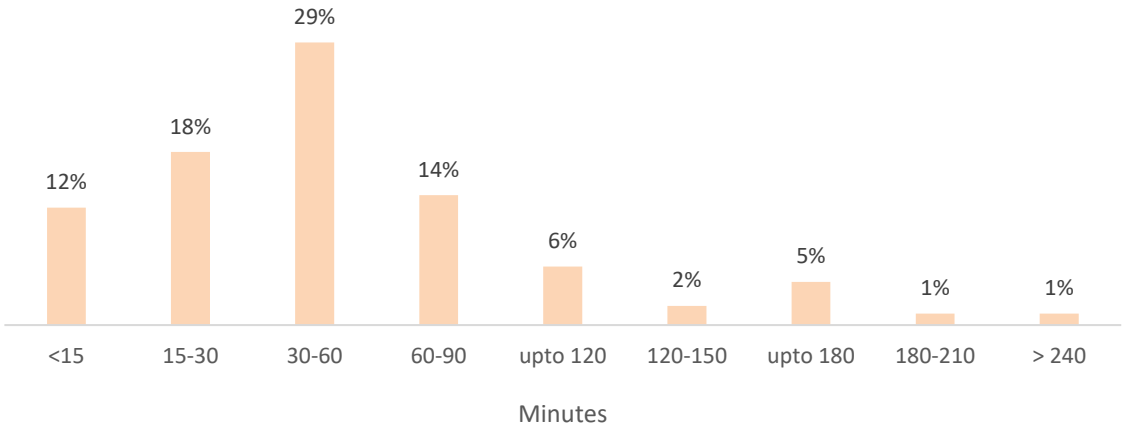


Figure 21: Time of FBC samples arriving in lab and authorisation of results

The graph outlines the distribution of time reported for availability of authorised FBC results. In almost 2/3 of patients, the FBC was authorised within 60 minutes. Data available for 98.8% cases.

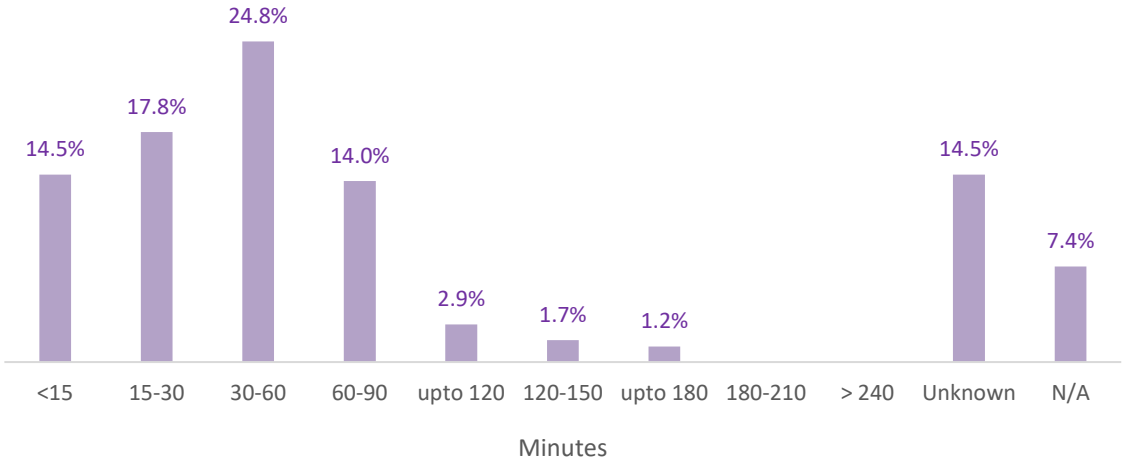


Figure 22: Time of clotting samples arriving in lab and authorisation of results

The graph shows the distribution time taken to obtain authorised clotting screen. In almost 18% of patients' results were authorised within 15-30 minutes. Less than 4% had clotting results available within 15 minutes. Combined this increased to 52% within 60 minutes. Data available for 75.2% cases.

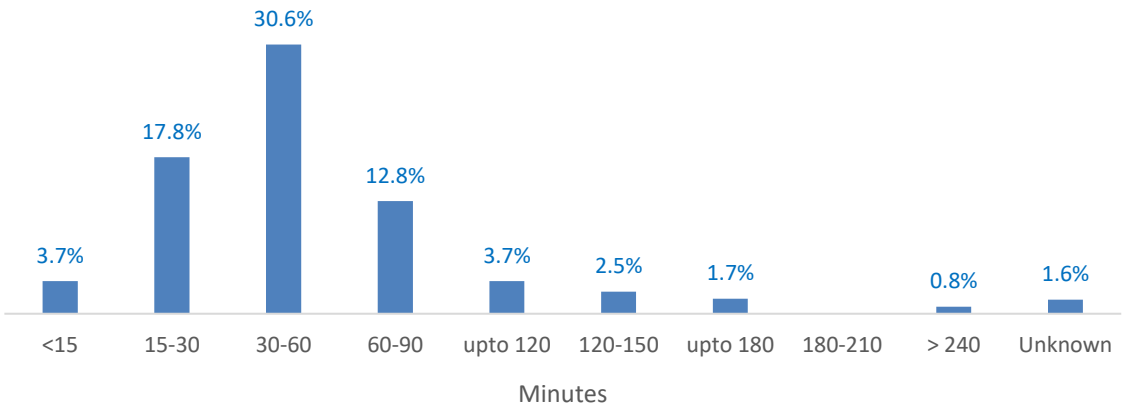
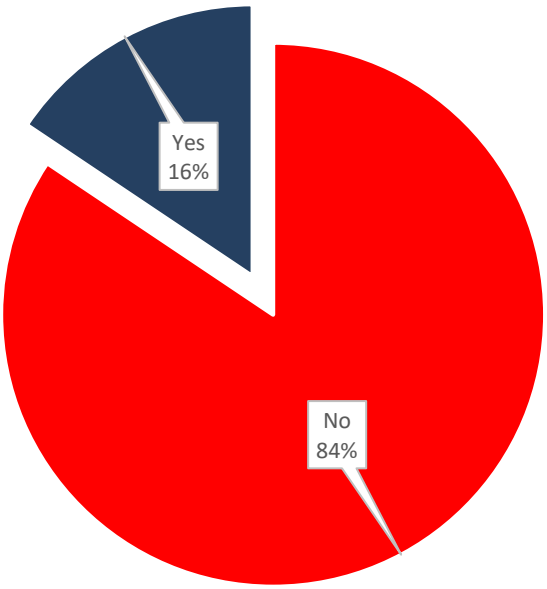


Figure 23: Was treatment commenced before test results available?

For the majority of patients (84%) treatment was only given after results were available, a small proportion (16%) were treated before the availability of blood results.

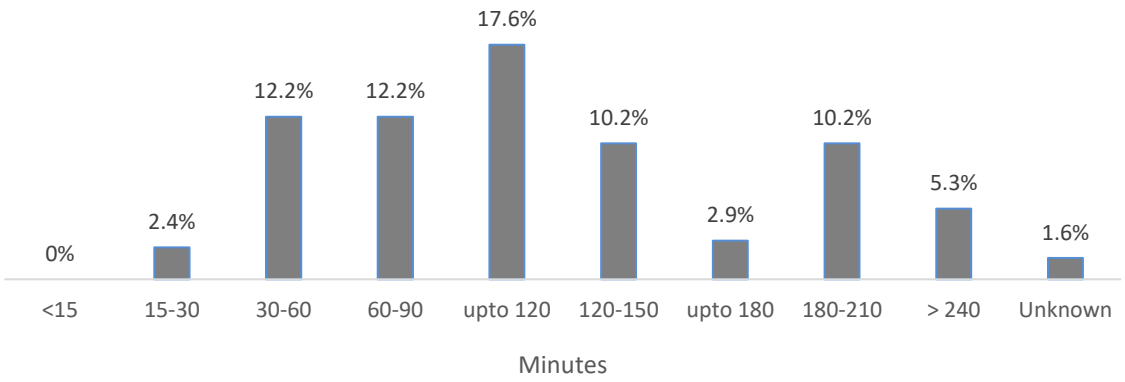


Availability of Imaging Results

The time to getting CT scans was up to 2 hours in approximately 50% of cases, with a quarter waiting longer. Data entry for this section was incomplete.

Figure 24: Time between arrival to ED and CT scan

Only 14.6% had a CT within 60 minutes of presenting to A+E, the majority of patients waited up to 2 hours and 30 minutes for a CT. Data available for 74.6% cases.

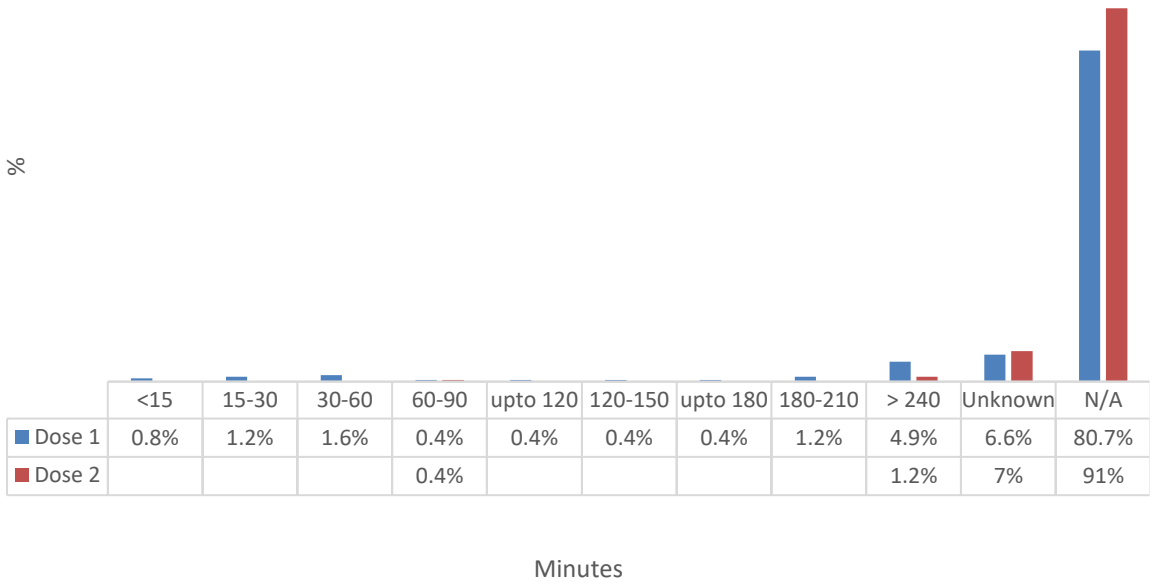


Tranexamic Acid

Administration of tranexamic acid was low with majority stating 1st and 2nd dose not applicable.

Figure 25: Time of first and second doses of Tranexamic acid

The majority of patients did not receive Tranexamic acid.



	<15	15-30	30-60	60-90	upto 120	120-150	upto 180	180-210	> 240	Unknown	N/A
Dose 1	0.8%	1.2%	1.6%	0.4%	0.4%	0.4%	0.4%	1.2%	4.9%	6.6%	80.7%
Dose 2				0.4%					1.2%	7%	91%

PCC administration and antidote usage

Two thirds of patients (66%) did not receive PCC. There were 3 reported cases of prescription for PCC being cancelled. Ninety-four percent reported that an antidote (e.g., Idarucizumab) was not given.

Figure 26: Time of arrival to ED and adminstration of PCC

PCC was given in 20% of cases after 4 hours from arrival to the emergency department and stated not applicable in 66% of patients.

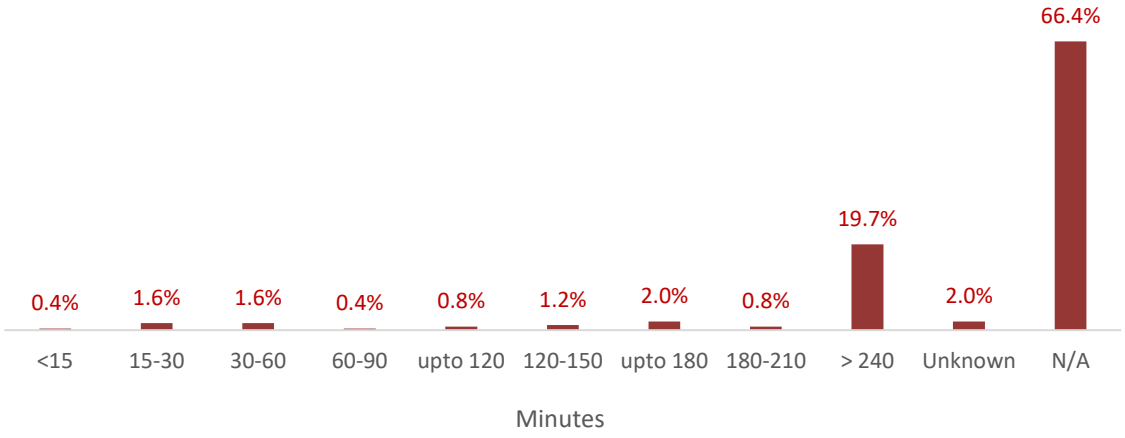
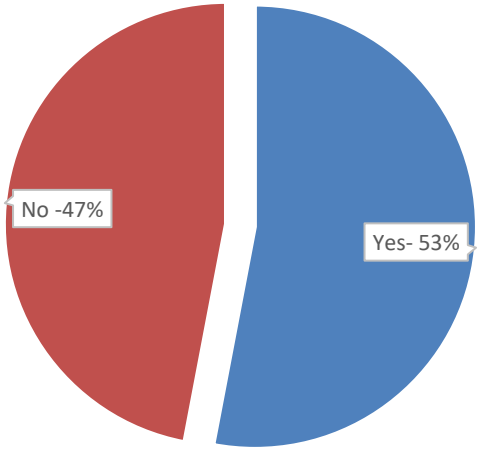


Figure 27: Was PCC given in line with local policy?

Just over half of patients (53%) received PCC in line with local policy.



Blood component usage in DOAC cases

Twenty-three patients received transfusion support in this group and transfusion support was much higher than the warfarin group with 40 units of red cells being transfused to 16 patients, 2 units of platelets were given to 2 patients, 14 units of fresh frozen plasma given to 4 patients, and 1 unit of cryoprecipitate to 1 patient. Of the patients receiving blood components, 9 were given tranexamic acid. PCC was not given to patients who were transfused.

Figure 28: Number of patients receiving transfusion and tranexamic acid

Twenty-three patients received blood component support, majority being red cells. Only 9/23 patients received tranexamic acid.

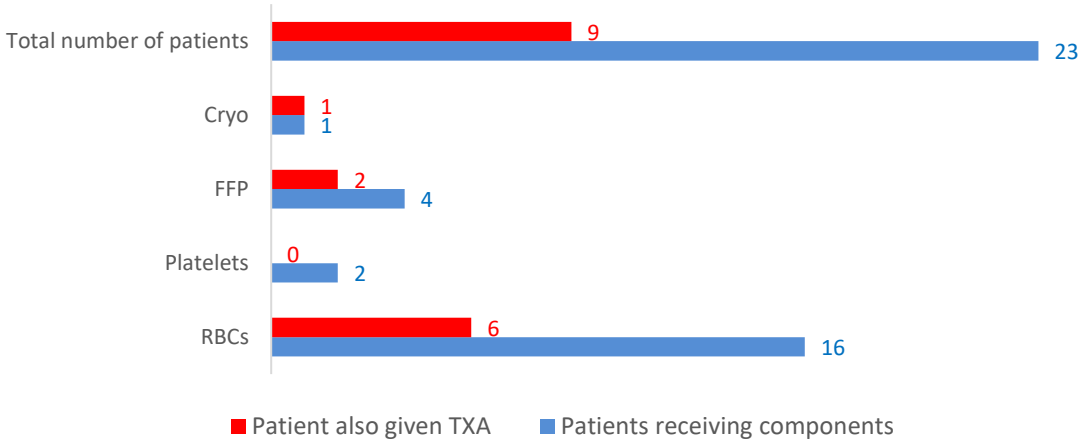
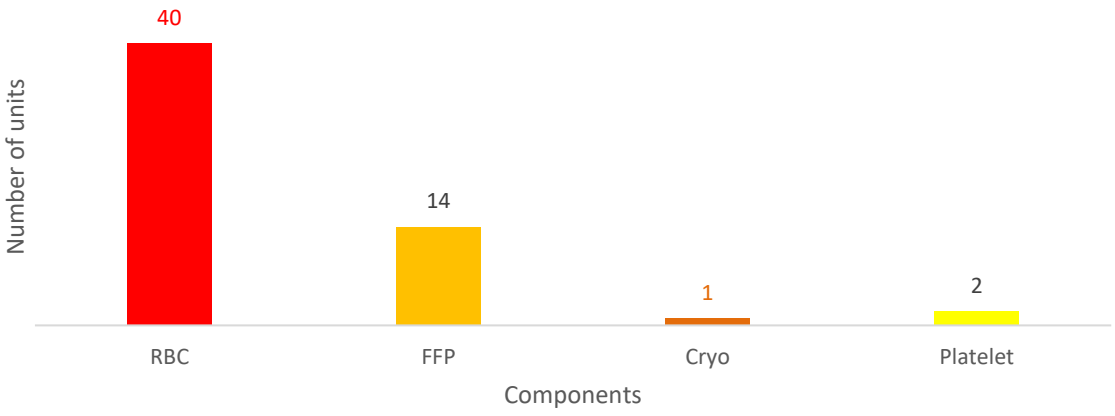


Figure 29: Blood component usage

Very few patients needed transfusion support but, in this group, red cells, fresh frozen plasma, platelets and cryoprecipitate were transfused.



DISCUSSION

For the organisational survey, the majority of hospitals who completed this were mainly from the London RTC region with 4 MTC, 11 TU and 11 DGH completing the survey. There were subtle differences in the hospitals submitting data for the organisational survey and those who entered actual case data for the two types of anticoagulation. Not all who completed the organisational survey were able to contribute to individual case entry due to not having eligible patients attending their site during the recruitment period.

Review of the trauma networks identified that a small number of sites incorrectly classified themselves as DGH rather than TU. The audit aim was to review the practices in TU, this objective was met as analysis of the datasets revealed the largest numbers of cases were entered by TU in both audit templates.

Apixaban was the most common DOAC in use and warfarin was the only vitamin K antagonist reported.

All hospitals had reversal guidelines for warfarin, only 21 (78%) of hospitals had reversal guidelines for DOAC, note this is lower than in the 2020 survey where 90% of hospitals reported having a DOAC reversal guideline. This is likely due to the scoping survey involving much fewer hospitals.

All hospitals stocked a licensed 4 factor PCC, this is recommended for the reversal of warfarin [3]. The dosage of vitamin K and PCC was reported available on warfarin reversal guidelines in 89%. There were no comments related to the dose of PCC for the DOAC group.

Recombinant Factor VIIa (rFVIIa) was available in 24 (89%) hospitals, with 15 (55%) hospitals keeping this for patients with bleeding disorders, 19 (70%) hospitals stating this was kept for use in massive haemorrhage / trauma, and 10 (37%) hospitals stocking this for both indications. However, the use of rFVIIa is not supported by the current BSH major haemorrhage guideline [4].

Eighteen sites submitted 50 cases on warfarin. The highest number of cases reported by a single site was a MTC, however 32 cases (64%) were entered by hospitals designated as trauma units.

There was more data entry for patients presenting to hospital on DOAC (245 cases from 26 hospitals), suggesting that more patients are likely to be anticoagulated with a DOAC. Again, data submission

was highest from those categorised as trauma units with 141 cases (57.5%), only 29 cases (11.8%) were reported by the MTCs, and 75 (30.6%) by District General Hospitals. The spread of cases entered was wide with highest number of cases (28) reported by hospitals designated as a trauma unit, with 9 hospitals submitting >10 cases each, 4 hospitals submitted 1 case, (median 6, mean 9.4). From this one can assume that the data reflects that a patient is now more likely to be anticoagulated with a DOAC than warfarin.

Although Dabigatran was reported in use in only 2% of patients, twenty-five (92.5%) hospitals stocked the antidote to Dabigatran which was NICE approved in 2016 [5], but just 6% reported using an antidote and only 3 hospitals commented that they stocked the antidote Andexanet Alpha for reversal of Apixaban and Rivaroxaban, this low number likely reflects that this antidote was only approved by NICE in 2021 [6] for reversal of these two Factor Xa inhibitor drugs.

In both groups stroke prevention was the most common indication for anticoagulation, 81% for DOAC, 50% for warfarin and unexpectedly head injury the most common reported reason for attendance to the emergency department (81% for DOAC, 88% for warfarin). Patients who are anticoagulated for stroke prevention are usually older and are not always recognised as trauma cases early. They are also more likely to have multiple pathologies which need simultaneous management, this was supported by additional comments entered in the audit. However, the audit was not designed to collect information on patient demographics and other co-morbidities. There is a scarcity of published data on the care and outcome of elderly patients who present as trauma and pre-hospital identification and triage of major trauma in elderly patients is challenging but key for delivery of optimal care [7] and outcomes.

Use of anticoagulation together with antiplatelet agent was low, in the warfarin group this was 16%, none were on dual antiplatelet therapy, whilst only 10% for the DOACs group were on antiplatelet therapy, 20% of these were taking more than one antiplatelet agent.

In the warfarin group looking at the time between arrival in the emergency department and initial bloods taken for clotting screen / FBC, in 34% of cases, it took 30-60 minutes for patients to have blood tests taken. Only 20% of patients had bloods taken within 15 minutes and 14% had their bloods taken between 15-30 minutes. There was complete data in 96% of cases. In comparison, in the DOAC group only 12% of patients had bloods taken within 15 minutes, in 18% this was done between 15-30

minutes, and almost 30% had this done between 30-60 minutes. In this group complete data was available in 91% of cases.

Authorisation of the full blood count results was completed in the majority (>96%) and within an hour in both groups, however in the warfarin group clotting results were available in 100% of cases but data was only available for 75% of patients on a DOAC. In both groups just over 50% of cases had clotting results authorised in the first hour but in both groups, treatment was similarly delayed until blood results were available in >80% of cases.

Data on the time of arrival to the emergency department and time taken to have a CT scan was provided in similar numbers in both groups, with 78% taking warfarin and 75% taking a DOAC. In both groups the majority of patients were documented to have had CT scan undertaken between 30 minutes and 2.5 hours. The 2014 NICE guidelines on assessment and early management of head injury [8] recommends that adults with the risk factors in *table 3* should have a CT head scan within 1 hour of presentation and a provisional written report within an hour of the scan. Concerns were raised by a coroner's letter in June 2019, that the 2014 NICE guideline did not adequately cover the management of indirect brain injuries in elderly patients. This led to a further review and update of this guideline. For those patients taking anticoagulant therapy and who had sustained a head injury with no other risk factors for brain injury, the 2019 revision recommended a CT head scan within 8 hours of the injury, with a provisional written radiology report within 1 hour of the scan being performed.

The dataset on time to CT scan reported in this audit appears to comply with NICE recommendations but it is important to note that as the audit did not request information on the Glasgow Coma Scale (GCS) of patients this has to be interpreted with caution.

Table 3: Criteria for CT head scan

Patients with a head injury and any of the following risk factors, NICE guideline [8] recommended CT head scan within 1 hour of the risk factor being identified:

1. GCS less than 13 on initial assessment in the emergency department.
2. GCS less than 15 at 2 hours after the injury on assessment in the emergency department.
3. Suspected open or depressed skull fracture.
4. Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
5. Post-traumatic seizure.
6. Focal neurological deficit.
7. More than 1 episode of vomiting.

Glasgow Coma Scale (GCS)

Although in the organisational survey, 89% reported that the dosage of vitamin K and PCC was stated on warfarin reversal guidelines, administration of both was poor. The 2015 NICE guideline [9] recommended that prothrombin complex concentrate should be offered immediately for the emergency reversal of warfarin anticoagulation in patients presenting with either severe bleeding or head injury with suspected intracerebral haemorrhage. In >50% of warfarin cases, PCC was stated as not applicable, where it was stated applicable 24% waited more than 4 hours to receive this. In the DOAC group 66% of cases were considered eligible for PCC but did not receive this, and almost 20% who received PCC did so after 4 hours of arrival to emergency department.

Only 5% of patients on warfarin received vitamin K within 60 minutes of arrival to A+E, 10% of patients waited 2 hours, 20% waited more than 4 hours, and not applicable was stated for 40% of cases. This is far below recommended best practice which is to give vitamin K and PCC immediately on identification of bleeding in anticoagulated patients particularly if head injury is suspected [1]. However, data from both groups reflected that a significant number of patients presented with what was initially thought to be complications of pre-existing medical conditions, this resulted in delayed identification of bleeding related to head injury.

Similarly, the use of tranexamic acid use was poor in both groups with the majority stating not applicable. The first dose of tranexamic acid should be given in pre-hospital setting in trauma patients; however, it is important to note that a significant number of patients were thought to have presented with complications of pre-existing medical complications and the identification of bleeding was

delayed, this may explain why not applicable was recorded for so many. Another consideration is that pre-hospital records are not easily located, and it is difficult to identify pre-hospital staff to complete records if not available.

Transfusion support was much higher on those taking DOAC than in the warfarin group. Whether this was due to the small numbers of patients taking dual antiplatelet drugs in the DOAC group, or failure to obtain clotting results or to identify coagulopathy risks in this group is unclear. It is important to note that the DOACs do not alter the clotting tests, and this may be why data collection was much lower at 75% compared to 100% for warfarin cases. The increased risk of bleeding in patients taking DOAC and antiplatelet agents, particularly dual agents, is unlikely to be apparent from the clotting results.

In total 40 units of red cells, 2 units of platelets, 14 units of FFP, and 1 unit of cryoprecipitate was transfused in the DOAC group in comparison to 9 units of blood transfused to 3 patients on warfarin (1 patient received 5 units), none of whom received tranexamic acid. For 2 cases, tranexamic acid was stated as 'not applicable' and for one 'don't know'. Only nine of the twenty–three patients transfused in the DOAC group received tranexamic acid.

CONCLUSION

The audit aim was to review the practices in TU, this objective was met as analysis of the datasets revealed the largest numbers of cases were entered by TU in both audit templates. Reversal guidelines were available for all sites for warfarin, but this was not the case for DOACs.

A larger data set was available for patients taking a DOAC than for warfarin, suggesting that the use of this class of anticoagulant is more prominent in the general population with Apixaban reported as the most commonly used DOAC, and warfarin was the only vitamin K antagonist reported in this audit.

In both groups, stroke prevention was the most reported indication for anticoagulation. Patients who are anticoagulated for stroke prevention are usually older with multiple co-morbidities needing simultaneous management. A significant number of patients presented with complications from multiple co-morbidities which delayed identification of bleeding.

In both groups head injury was the most common reported injury, as this was an unexpected finding, there was no question requesting data on the GCS of the patients at presentation. In both groups the majority of patients were documented to have had CT scan undertaken between 30 minutes and 2.5 hours, this meets the recommendation of 2014 NICE guidelines on assessment and early management of head injury [8], however as the audit was not set to collect data on the patients GCS on admission this should be taken with caution. The 2015 NICE guideline [9] recommended that prothrombin complex concentrate should be offered immediately, the data in this audit showed that this recommendation was not met by the majority.

A very small number of patients were also on antiplatelet therapy in both groups, with a small fraction of DOAC patients reported to be on dual antiplatelet therapy.

Authorisation of the full blood count results was completed within an hour in both groups, however in the warfarin group, clotting results were available in all cases but data was only available for 75% of patients on a DOAC. In both groups just over 50% of cases had clotting results authorised in the first hour but in both groups, treatment was similarly delayed until blood results were available in >80% of cases. In both groups administration of vitamin K, PCC and tranexamic acid was suboptimal.

Patients on a DOAC were more likely to need transfusion support with blood and other components than those taking warfarin.

The Central Alerting System in 2022 [10] issued recommendations that anticoagulation reversal should not be delayed by the need to obtain haematology authorisation for the use of PCC / reversal agents. This was prompted by the upward trend in blood delays reported to Serious Hazards of Transfusion (SHOT), in 2021[11]. It is hoped that this safety alert will result in all hospitals ensuring that their reversal protocols clearly state dose and location of PCC and antidotes so that patients receive prompt anticoagulation reversal treatment.

Limitations of audit identified

The data may be skewed as only 27 sites out of potential 88 responded, and complete data collection was not available on all cases submitted, paper records may have been difficult to locate, this may have been confounded by covid 19 pandemic restrictions.

The audit questions did not identify if hospitals had access to point of care testing devices such as INR machines, thromboelastograph (TEG) and thromboelastometry (RoTEM). These devices would negate sending samples to the laboratory immediately.

The audit was not designed to collect data on patient demographics and GCS.

More accurate data on tranexamic acid use may have been obtained if hospitals were asked 1) whether there was a contraindication to tranexamic use and 2) information could not be found.

Design of the audit limited data entry in many instances to drop down lists, it is likely that not applicable was ticked as a default when data not easily found.

RECOMMENDATIONS FOR HOSPITALS

1. All hospitals should have reversal guidelines for DOACs – see appendix 3 for examples.
2. All patient presenting to A+E on anticoagulation should be assessed as a priority to exclude bleeding particularly head injury in older patients.
3. Those patients who are thought to be at risk of bleeding should have blood tests (FBC and clotting screen (or POCT) and prioritised for imaging immediately.
4. Samples from these patients should be prioritised and processed urgently in the laboratory with availability of results within 30 minutes of receipt.
5. Vitamin K, and PCC should be administered to bleeding patients on warfarin immediately, (as recommended by CAS alert 2022 – preventing delays) without waiting for blood results.
6. PCC should be administered to patients on DOAC who present with bleeding immediately without waiting for blood results as these patients are more likely to need blood product support.
7. Tranexamic acid should be given to all bleeding patients on presentation unless a contraindication is identified such as gastrointestinal bleeding, see HALT-IT trial recommendations [13].
8. Recombinant VIIa should not be kept as stock for trauma / major haemorrhage.
9. Andexanet alpha should be used for patients taking Apixaban or Rivaroxaban who present with major gastrointestinal bleeding as per NICE guidance [6].

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Appendix 1 Questions in Survey 2020

Audit of Trauma Units – Questions for survey monkey

Name of Trusts…….

1) Does your Trust have a guideline for PCC to be used to reverse bleeding due to warfarin?
2) If answer to Q1 was yes, has an audit been undertaken to check this is followed in the last 2 years?
3) Does your Trust have a reversal guideline for DOACs?
4) If answer to Q3 was yes has an audit been undertaken to check this is followed in the last 2 years?
5) Do you have a protocol for paediatric major haemorrhage?
6) Do your guidelines recommend use of O positive red cells for unknown males?
7) What support would you require from this group to help you undertake audits of this nature?

Date

Name / Signature

Role

Appendix 2 Audit templates

Organisational survey

1. Please enter the name of your hospital
2. Please indicate if you are a
    a. Major Trauma Centre
    b. Hospital with a trauma unit
    c. District General Hospital with Accident and Emergency
    d. Other facilities for dealing with trauma not indicated above (please describe)
3. Does your Trust stock a licensed four-factor prothrombin complex concentrate? Is this
    a. Beriplex
    b. Octaplex
    c. Both
4. Does your organisation have a policy in place for emergency anticoagulation reversal?
    a. Yes, for warfarin,
    b. Yes, for DOAC
    c. No
5. Does your organisation's policy clearly state the dose of PCC to be administered and when to administer it?
    a. Yes
    b. No
6. Please indicate
    a. the dose advised in the policy,
    b. when it is to be administered e.g., within 1 hour of injury
7. Does your organisation's policy clearly state the dose of vitamin K to be administered?
    a. Yes
    b. No
8. If you stock factor VIIA, what is its intended purpose?
    a. Do not stock
    b. Massive haemorrhage/ trauma
    c. Patients with bleeding disorders
    d. Other purpose
9. Do you stock an antidote for DOAC on site? e.g., Idarucizumab.
    a. Yes
    b. No
10. Any other comments

Audit on reversal of DOAC associated bleeding/head injury

1. Please enter the name of your hospital
2. Please indicate if you are a
    a. Major Trauma Centre
    b. Hospital with a trauma unit
    c. District General Hospital with Accident and Emergency
    d. Other facilities for dealing with trauma not indicated above (please describe)
3. Which DOAC is your patient taking?
    a. Dabigatran
    b. Rivaroxaban
    c. Apixaban
    d. Edoxaban

4. What is the indication for the DOAC (select all that apply)?
    a. VTE prophylaxis
    b. VTE treatment
    c. Stroke prevention
    d. Acute coronary syndrome
5. Was the patient also on an antiplatelet agent?
    a. Yes
    b. No
6. If yes was this a dual antiplatelet agent
    a. Yes
    b. No
7. Did this patient present with … (tick all that apply)?
    a. Head injury
    b. Life threatening bleeding from other injuries
    c. Haemoglobin drop >20g/L
8. In relation to their injury, please indicate using the 24-hour clock … (hh:mm)
    a. Estimated time of injury
    b. Time of arrival in Emergency Department

In relation to their injury/presentation, please select, the approximate times involved in the patient journey from the list (select don't know or NA if not relevant to this) for question 9-16.

    a. Less than 15 minutes
    b. Between 15-30 minutes
    c. Between 30 minutes – 1 hour
    d. Between 1 hour and 1 hour 30 minutes
    e. Up to 2 hours
    f. Between 2 hours and 2 hours and 30 minutes
    g. Up to 3 hours
    h. Between 3 hours and 30 minutes
    i. Up to 4 hours
    j. More than 4 hours
    k. Not applicable to this case
    l. Don’t know

9. Time between arrival in ED and initial clotting screen/FBC being sent to the lab
10. Time between lab arrival and authorisation for FBC
11. Time between lab arrival and authorisation for the clotting screen
12. Time between ED arrival and CT scan
13. Time between arrival in ED and 1st dose of TXA given
14. Time between arrival in ED and 2nd dose of TXA given
15. Time between arrival in ED and PCC given
16. Time between arrival in ED and antidote given e.g., 5 g Idarucizumab
17. Were there any specific issues in relation to this patient?
    a. Yes (please describe)
    b. No
18. For this patient, was treatment commenced before results of tests became available?
    a. Yes
    b. No
19. If PCC was given, was this in line with local policy?
    a. Yes

    b. No
20. Was this patient transfused with RBC; if yes how many?
    a. Yes (How many?)
    b. No
21. Was this patient transfused with Platelets; if yes how many?
    a. Yes (How many?)
    b. No
22. Was this patient transfused with FFP; if yes how many?
    a. Yes (How many?)
    b. No
23. Was this patient transfused with Cryoprecipitate; if yes how many?
    a. Yes (How many?)
    b. No
24. Any other comments related to this patient?

Audit on reversal of Vitamin K antagonist associated bleeding/head injury

1. Please enter the name of your hospital
2. Please indicate if you are a
    a. Major Trauma Centre
    b. Hospital with a trauma unit
    c. District General Hospital with Accident and Emergency
    d. Other facilities for dealing with trauma not indicated above (please describe)
3. For THIS patient which vitamin K antagonist was the patient taking?
    a. Warfarin
    b. Acenocoumarol
4. What is the indication for the vitamin K antagonist?
    a. VTE prophylaxis
    b. VTE treatment
    c. Stroke prevention/ Atrial fibrillation
    d. Metallic heart valve
5. Was the patient also on antiplatelet agent?
    a. Yes
    b. No
6. If yes was this a dual antiplatelet agent?
    a. Yes
    b. No
7. Did this patient present with (tick all that apply)?
    a. Head injury
    b. Life threatening bleeding from other injuries
    c. Haemoglobin drop >20g/L
8. In relation to their injury, please indicate using 24-hour clock (hh:mm)
    a. Estimated time of injury
    b. Time of arrival in the Emergency Department (ED)

In relation to their injury/presentation, please select, the approximate times involved in this patient journey from the list (select don't know or NA if not relevant to this) for question 9-16.

    a. Less than 15 minutes
    b. Between 15-30 minutes

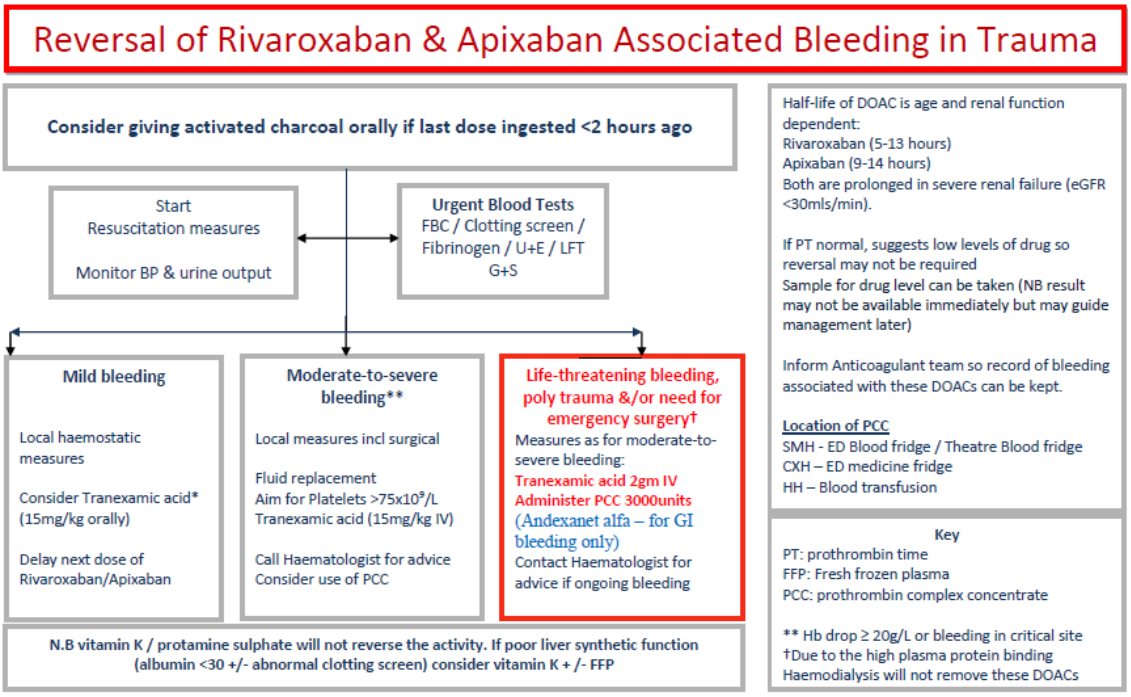
c. Between 30 minutes – 1 hour
d. Between 1 hour and 1 hour 30 minutes
e. Up to 2 hours
f. Between 2 hours and 2 hours and 30 minutes
g. Up to 3 hours
h. Between 3 hours and 30 minutes
i. Up to 4 hours
j. More than 4 hours
k. Not applicable to this case
l. Don't know

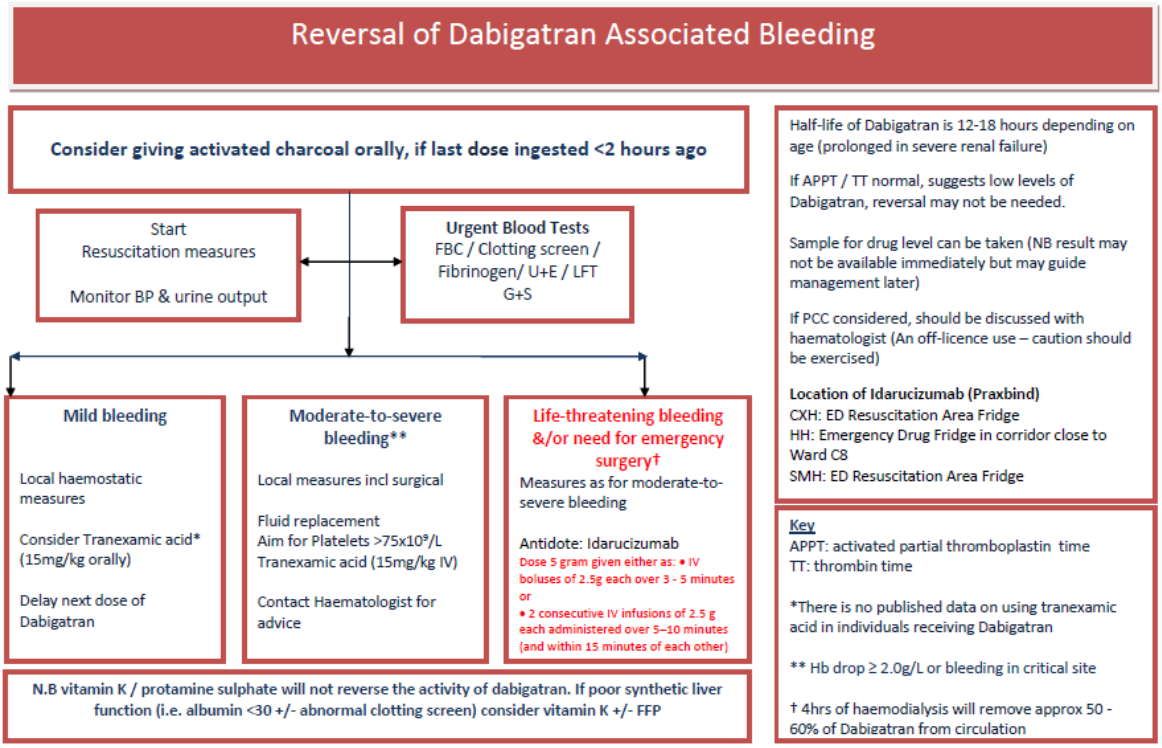
9. Time between arrival in ED and initial clotting screen/FBC being sent to the lab
10. Time between lab arrival and authorisation for FBC
11. Time between lab arrival and authorisation for the clotting screen
12. Time between ED arrival and CT scan
13. Time between arrival in ED and 1st dose of TXA given
14. Time between arrival in ED and 2nd dose of TXA given
15. Time between arrival to ED and Vitamin K given
16. Time between arrival to ED and PCC given

17. Were there any specific issues in relation to this patient?
    a. Yes (please describe)
    b. No
18. For this patient, was treatment commenced before results of tests became available?
    a. Yes
    b. No
19. If PCC was given, was this in line with local policy?
    a. Yes
    b. No
20. If vitamin K was given, was this in line with local policy?
    a. Yes
    b. No
21. Was this patient transfused with RBC; if yes how many?
    a. Yes (How many?)
    b. No
22. Was this patient transfused with Platelets; if yes how many?
    a. Yes (How many?)
    b. No
23. Was this patient transfused with FFP; if yes how many?
    a. Yes (How many?)
    b. No
24. Was this patient transfused with Cryoprecipitate; if yes how many?
    a. Yes (How many?)
    b. No
25. Any other comments related to this patient?

Appendix 3 Examples of DOAC reversal guidelines

Flow diagram for reversal of the FXa inhibitors (Rivaroxaban and Apixaban) is given below with dosage of PCC and antidote (where applicable) for life-threatening bleeding / trauma patients stated, clearly stating location of PCC. Flow diagram below for Dabigatran clearly stating dose and location of antidote. This follows the recommendation of the CAS Alert [10].





Acknowledgements

All hospitals and staff in theatres and anybody else who took the time to complete this survey during one of the busiest times in the history of the NHS – THANK YOU.

For setting up the online templates and analyzing data:
Brian Hockley, Data Analyst and Clinical Audit Manager, NHSBT

For helping with designing the survey:
Danny Gaskin, Biomedical Scientist, Patient Blood Management Practitioner, NHSBT
Selma Turkovic, Patient Blood Management Practitioner, London, NHSBT
Anwen Davies, Patient Blood Management Practitioner, South East, NHSBT
Emily Carpenter, Transfusion Practitioner, Kings College Hospital

For promotion of the survey:
Frances Moll, RTC Administrator, South East, NHSBT
Angela Pumfrey, RTC Administrator, London, NHSBT
Frances Sear, Patient Blood Management Practitioner, East of England, NHSBT

Sue Katic, Senior PA, NHSBT for coordinating the distribution of information to participating sites, collating feedback, responding to queries from data collectors and for proofreading this report.

Dr Sara Boyce, Consultant Haematologist, Southampton University Hospital for proofreading this report.

All the members of the Haematology and Trauma group.