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

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THE LONDON HAEMATOLOGY AND TRAUMA GROUP

Convened in 2010 to support the London Trauma System.

- 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.
- Group expansion to include MTC in Oxford, Cambridge, recently to include Southampton in 2021 and in 2022, Plymouth and Liverpool.

- The key activities of the group are:

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.

PURPOSE OF STUDY

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.

2) to assess if the guidance's were being followed.

Oct 2020 Survey

October 2020, snap survey sent to all hospitals in London and the South East Coast

Question

1) Reversal guidelines available for the use of Prothrombin Complex Concentrate (PCC) for the reversal of anticoagulation associated bleeding (warfarin and DOACs).
2) Audit undertaken

Oct 2020 Survey Results

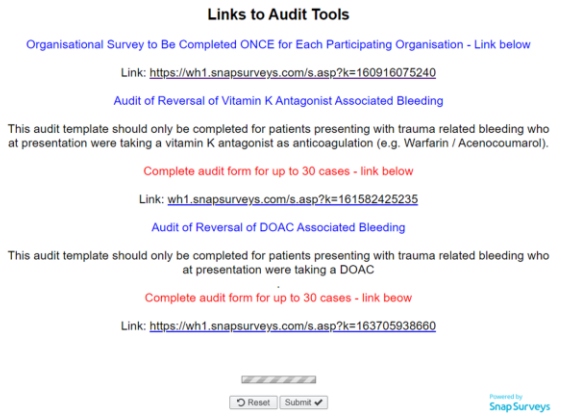
1) 30 hospitals responded
    1) 21 from London
    2) 9 from the South East Coast region

29/30 hospitals - guideline for warfarin reversal but only 27% of hospitals had audited.

27/30 hospitals - guideline for DOAC reversal and only 25% of these had audited.

>70% of the respondents requested an audit template to enable regular auditing against the guidelines.

Pilot audit: June –July 2021



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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- To assess the format and usability of the templates.
- Originally planned for the month of June 2021 and / or collection of data from 10 cases
- Several of the 9 hospitals in the pilot reported two common problems:

1. 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

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

Organisational survey

Audit of reversal of vitamin K associated bleeding

Audit of reversal of DOAC associated bleeding

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.

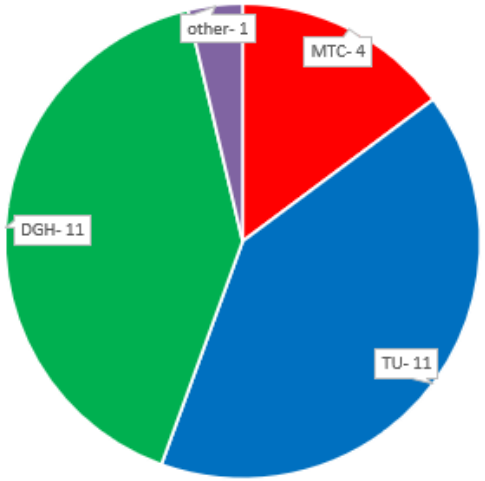


Figure 2: Availability of reversal guidelines

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

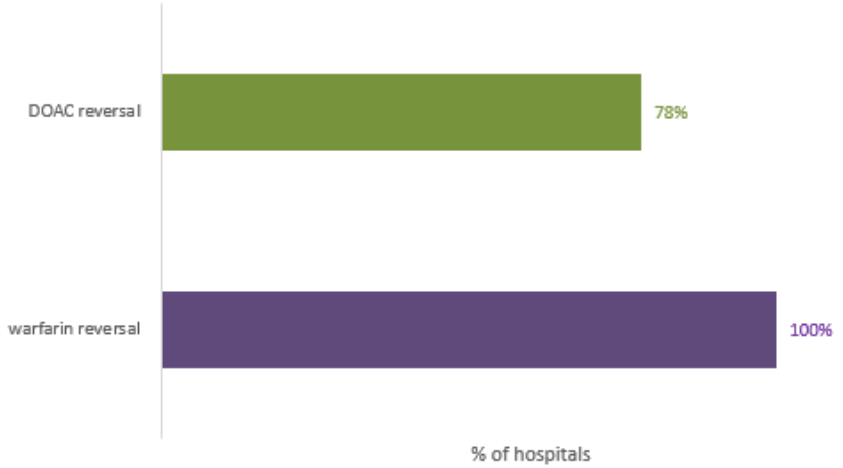


Figure 3: PCC availability

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

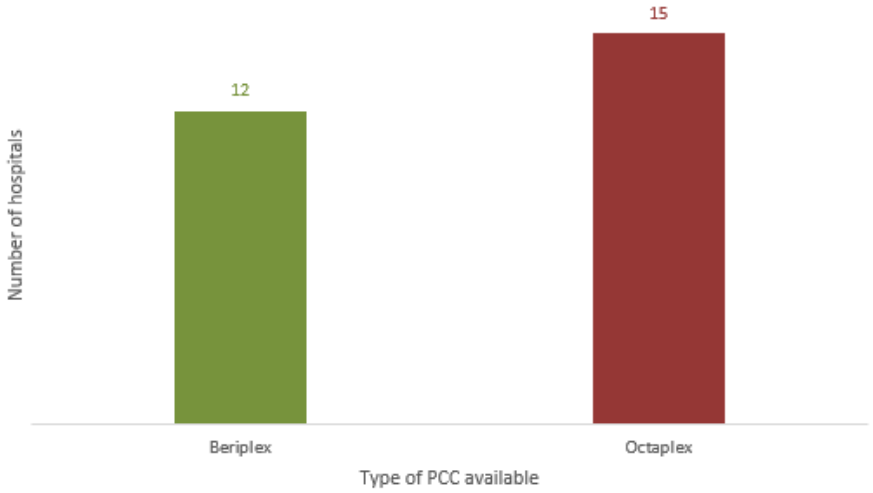
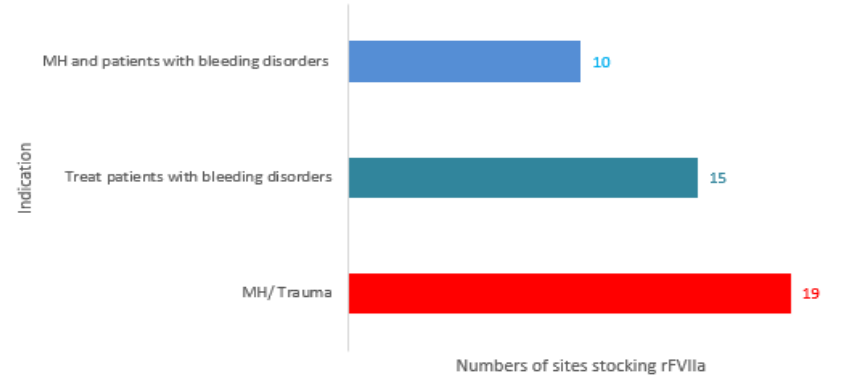


Figure 4: Purpose for stocking recombinant FVIIa

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.



ORGANISATIONAL SURVEY

RESULTS

RESULTS OF AUDIT OF REVERSAL OF VITAMIN K ANTAGONIST ASSOCIATED BLEEDING

Vitamin K Antagonist

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).

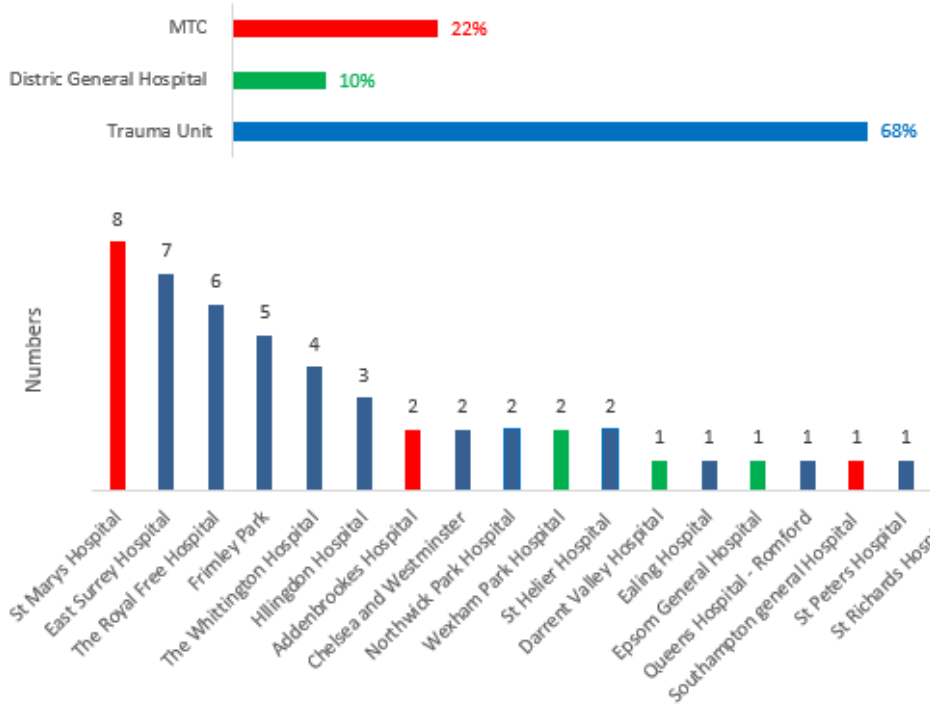


Figure 6: Indication for vitamin K antagonist use

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.

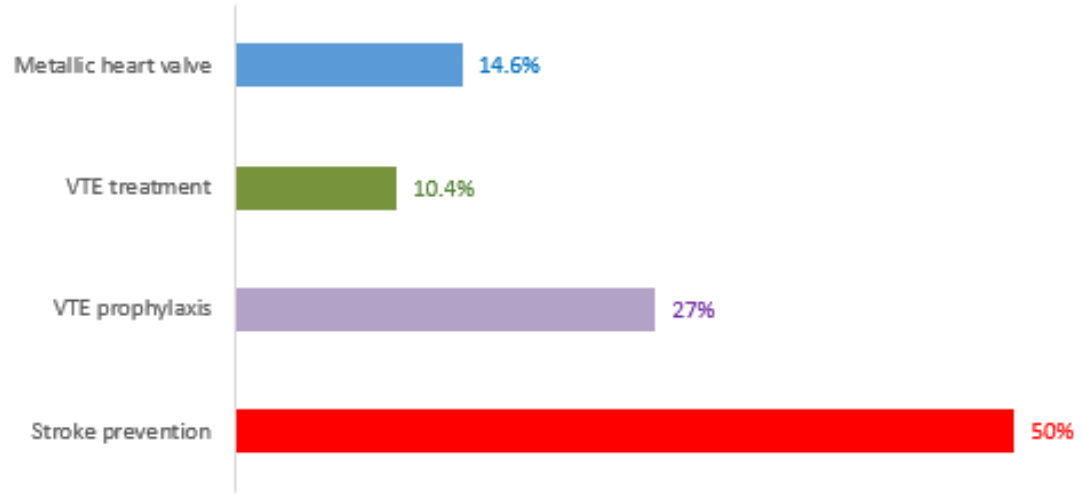


Figure 7: Reason for presentation whilst on warfarin

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.

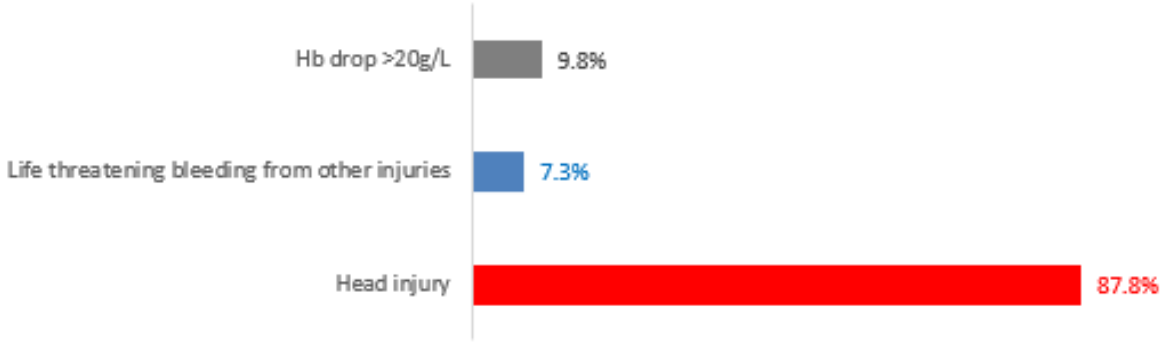


Figure 8: Did treatment commence before blood results were returned?

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.

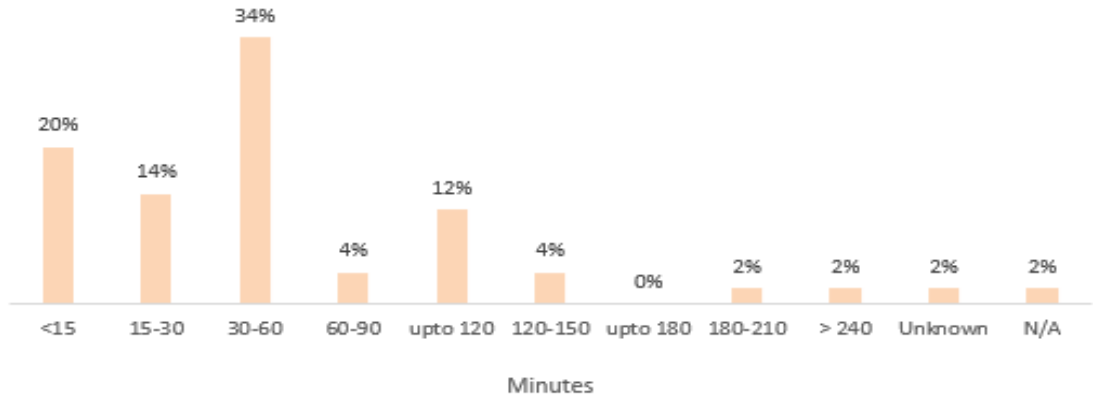


Figure 10: Time of FBC samples arriving in lab and authorisation of results

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.

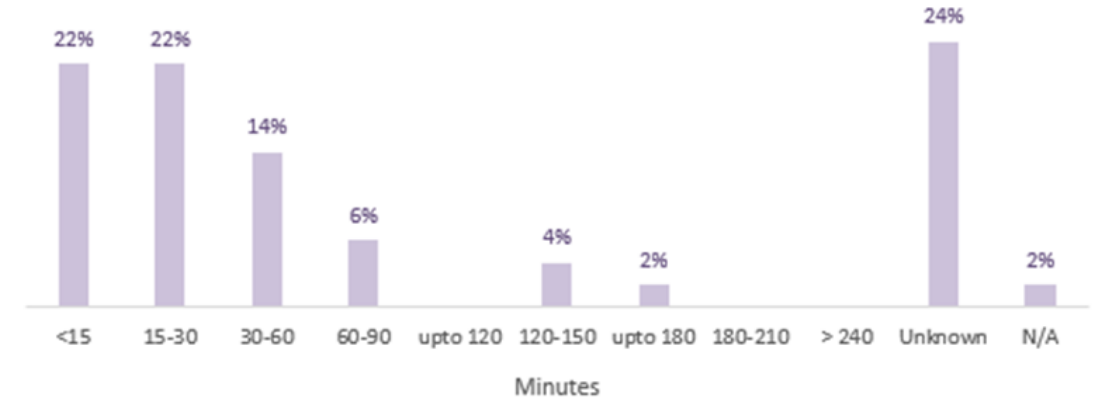


Figure 11: Time of clotting samples arriving in lab and authorisation of results

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.

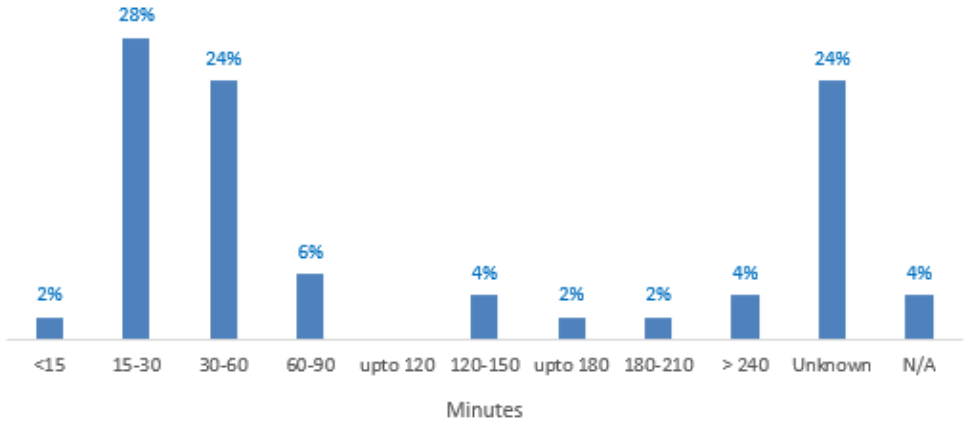


Figure 12: Time between arrival to ED and CT scan

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.

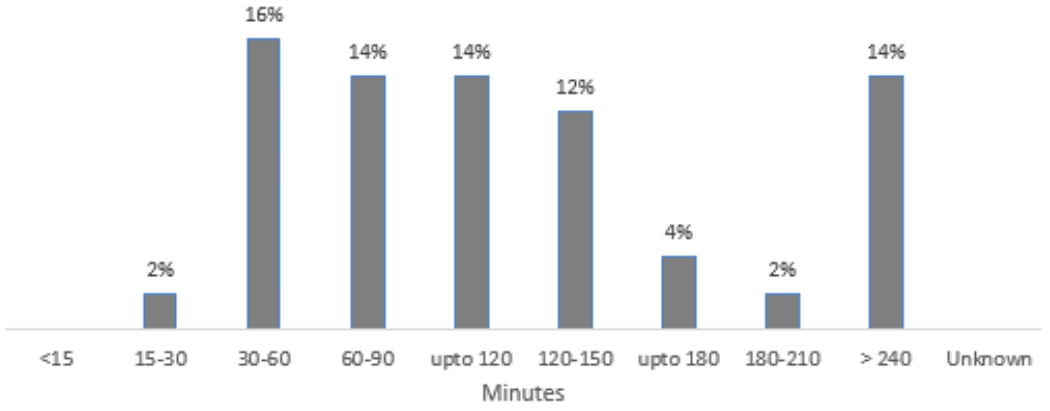


Figure 13: Time of first and second dose of Tranexamic Acid

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

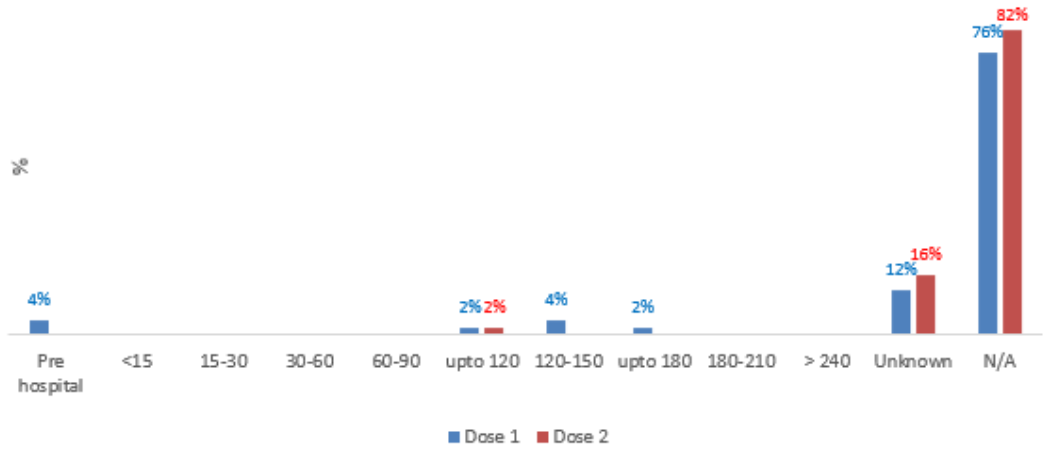
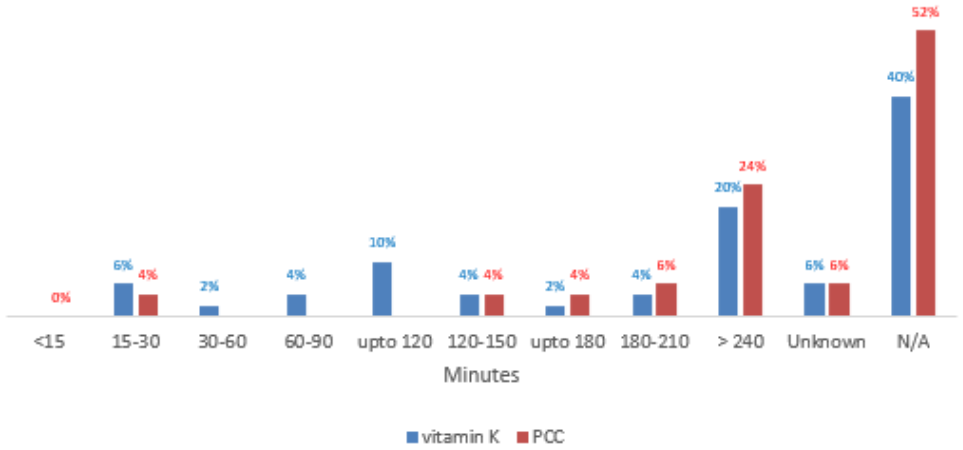


Figure 14: Arrival time to ED to vitamin K and PCC administration

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.



RESULTS OF AUDIT OF REVERSAL OF DOAC ASSOCIATED BLEEDING

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)

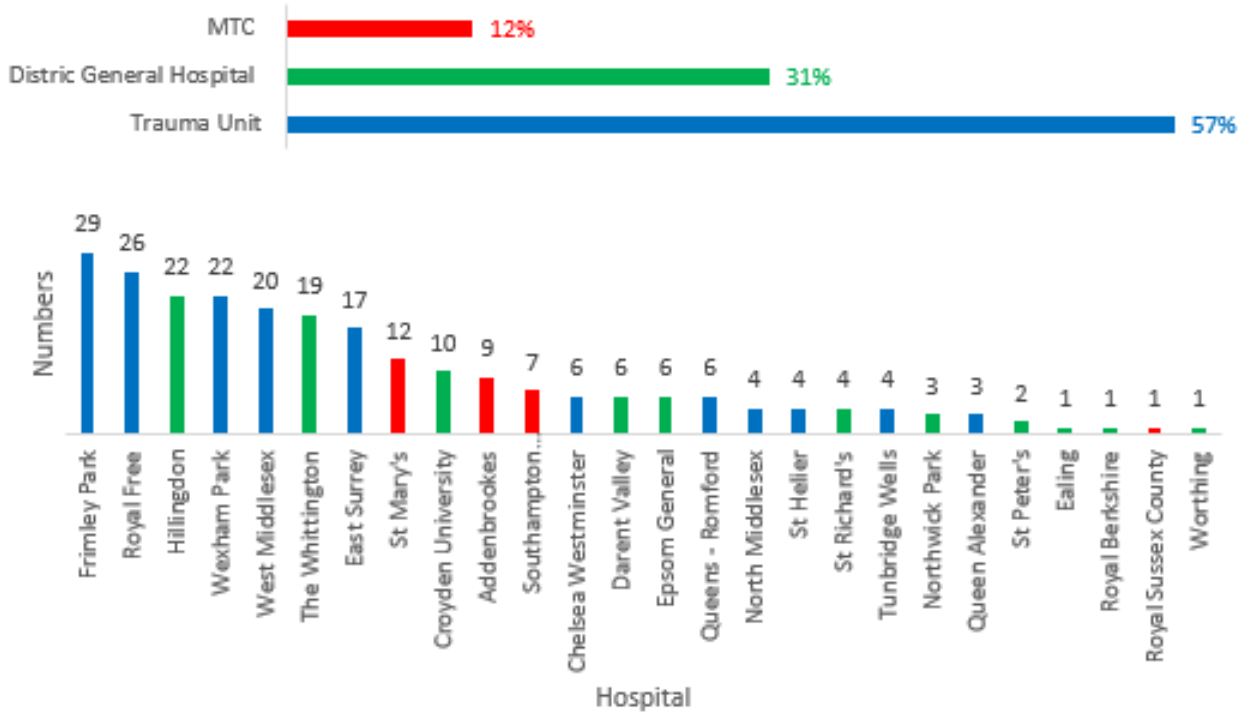


Figure 16: Types of DOAC patients taking

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

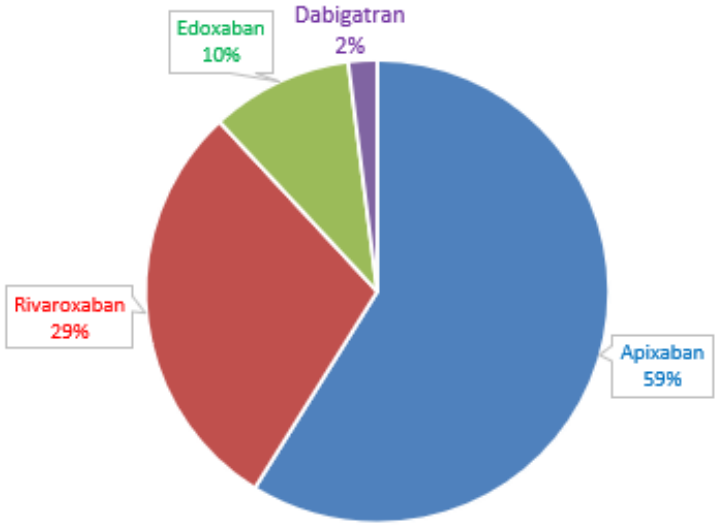


Figure 17: Indications for DOAC usage

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

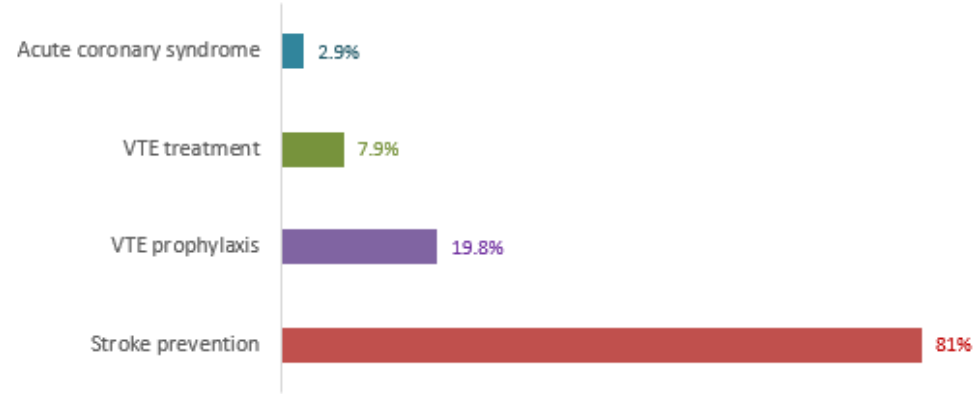


Figure 18: Use of antiplatelet therapy with DOAC

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.

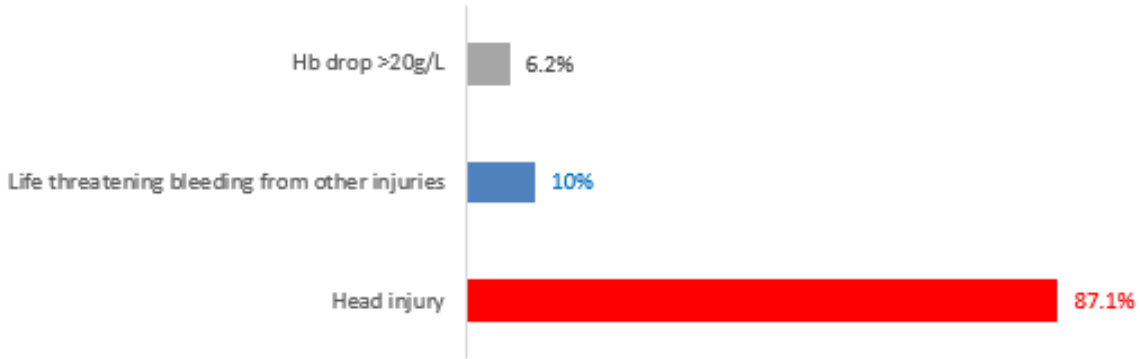


Figure 20: Time between arrival to ED and blood sampling

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.

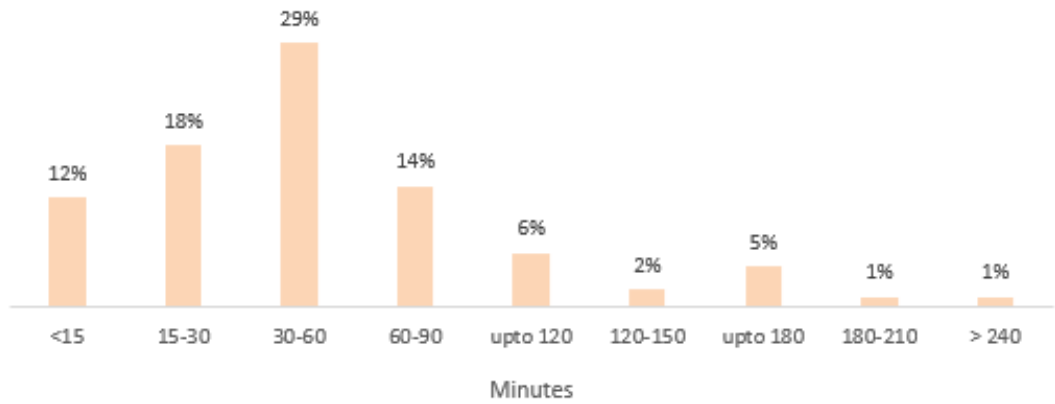


Figure 21: Time of FBC samples arriving in lab and authorisation of results

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.

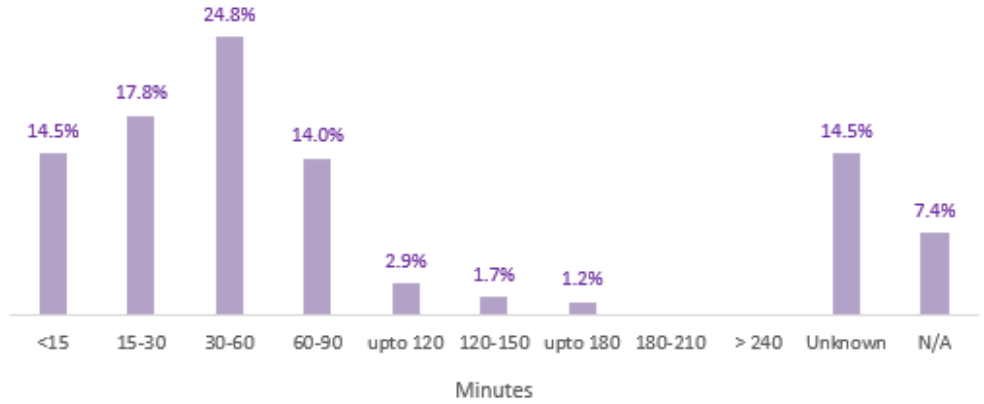


Figure 22: Time of clotting samples arriving in lab and authorisation of results

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.

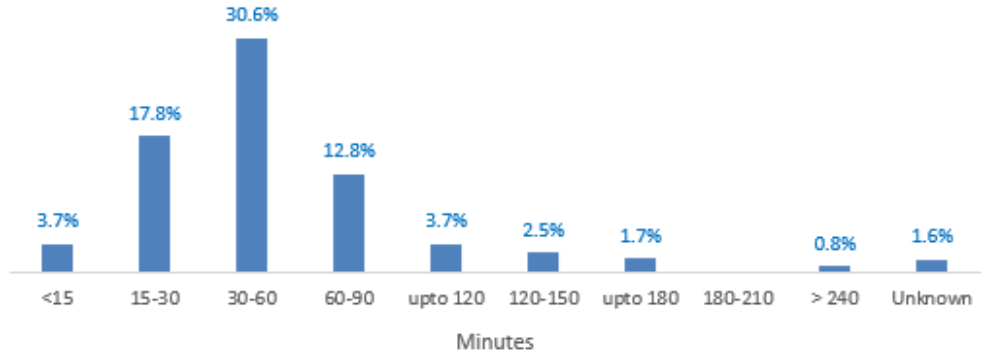


Figure 23: Was treatment commenced before test results available?

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.

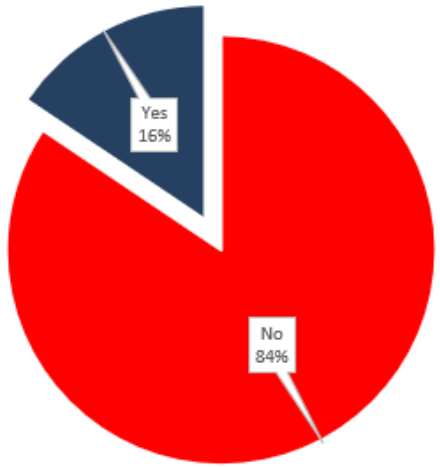


Figure 24: Time between arrival to ED and CT scan

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.

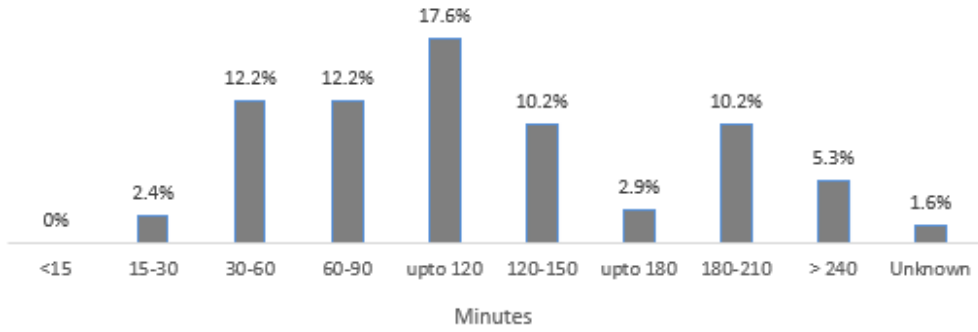
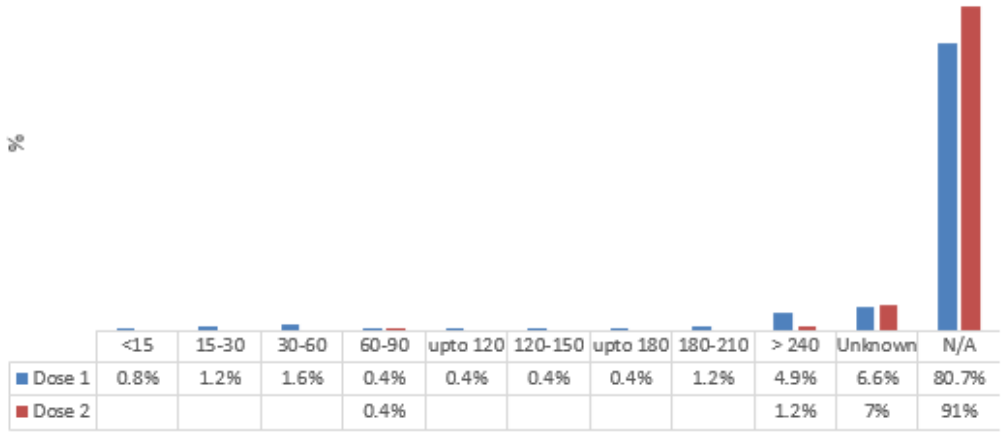


Figure 25: Time of first and second doses of Tranexamic acid

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%

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

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

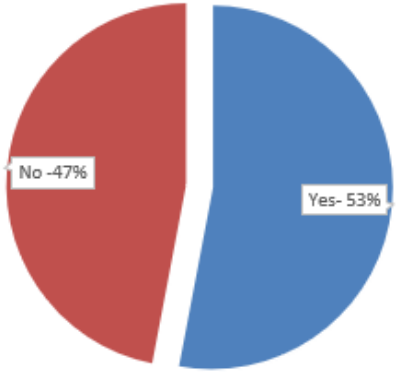
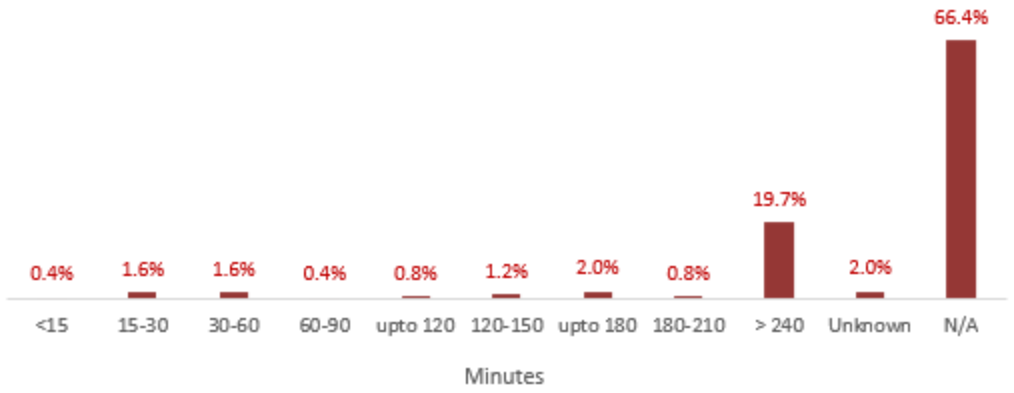


Figure 26: Time of arrival to ED and adminstration of PCC

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



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

NB 9 units used in 3 patients on warfarin

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.

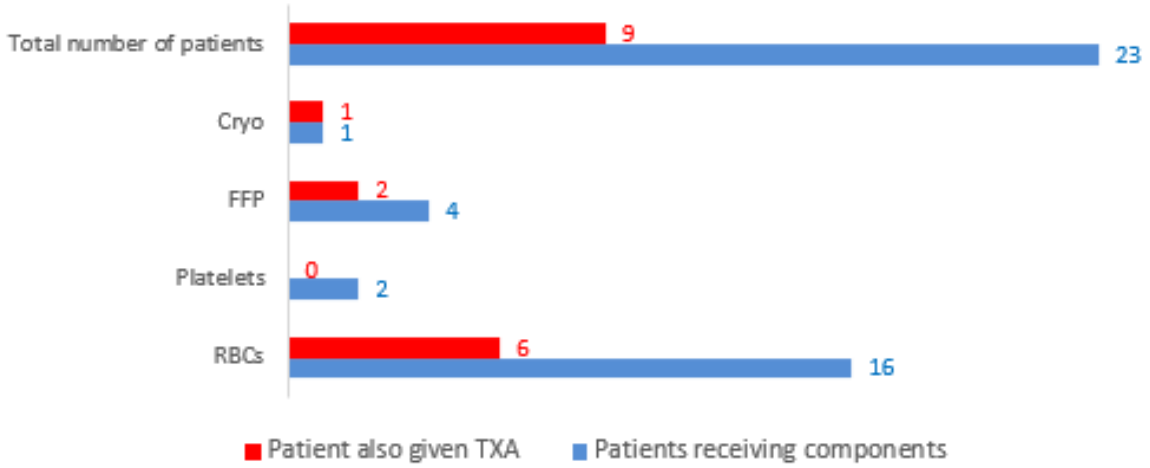
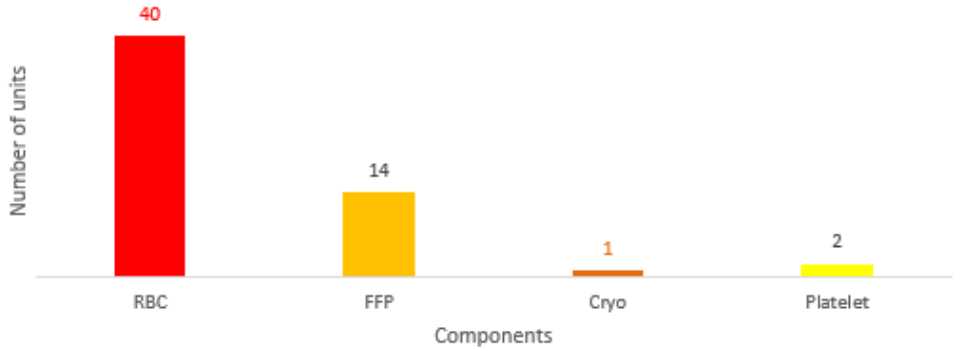


Figure 29: Blood component usage

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



Blood component use in DOAC cases

SUMMARY OF MAIN FINDINGS

- 27 hospitals -11 DGH, 11 TU, 4 Major Trauma Centres (MTCs), 1 other.
- PCC was available in all hospitals.
- All hospitals had reversal guidelines for warfarin with dosage of vitamin K and PCC in 89%.
- 21 (78%) hospitals had reversal guidelines for DOAC, no comments related to the dose of PCC for the DOAC group.

- 25/27 hospitals stocked rFVIIa - 19/27 massive haemorrhage / trauma, 15/27 for treating patients with bleeding disorders, 10/27 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.

SUMMARY OF MAIN FINDINGS

- 18 sites - 50 cases on warfarin, 34/50 cases submitted by TU.
- 26 sites- 245 cases on a DOAC (Apixaban most common) 141/245 cases submitted by TU.
- In both groups
  - stroke prevention - most commonly reported indication for anticoagulation
  - head injury - most commonly reported reason for presentation (81% DOAC, 88% warfarin).
- Small number on antiplatelet therapy in both groups, with a small fraction of DOAC patients taking dual antiplatelet therapy.
- 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.
- DOAC group needed more transfusion support with blood and other blood components than those on warfarin.

Discussion

- Largest data set from TU
- In both groups stroke prevention was the most common indication for anticoagulation and head injury was the most common reported injury, as this was an unexpected finding.
- 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, 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 recommended that prothrombin complex concentrate should be offered immediately, the data in this audit showed that this recommendation was not met by the majority.
- CAS Alert Blood delays Jan 2022 recommendations – also not met
- 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.

Limitations of audit identified

- Skewed data as only 27/88 sites responded,
- Complete data collection was not available on all cases submitted – difficulties in locating paper records confounded by covid 19 pandemic restrictions.
- No data on POCT (INR machines, thromboelastograph (TEG) and thromboelastometry (RoTEM)
- 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.
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.
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 .

Reversal of Rivaroxaban & Apixaban Associated Bleeding in Trauma

Consider giving activated charcoal orally if last dose ingested <2 hours ago

Start
Resuscitation measures

Monitor BP & urine output

Urgent Blood Tests
FBC / Clotting screen / Fibrinogen / U+E / LFT
G+S

Mild bleeding

Local haemostatic measures

Consider Tranexamic acid* (15mg/kg orally)

Delay next dose of Rivaroxaban/Apixaban

Moderate-to-severe bleeding**

Local measures incl surgical

Fluid replacement
Aim for Platelets >75x10^9/L
Tranexamic acid (15mg/kg IV)

Call Haematologist for advice
Consider use of PCC

Life-threatening bleeding, poly trauma &/or need for emergency surgery†

Measures as for moderate-to-severe bleeding:
Tranexamic acid 2gm IV
Administer PCC 3000units
(Andexanet alfa – for GI bleeding only)
Contact Haematologist for advice if ongoing bleeding

N.B vitamin K / protamine sulphate will not reverse the activity. If poor liver synthetic function (albumin <30 +/- abnormal clotting screen) consider vitamin K + /- FFP

Half-life of DOAC is age and renal function dependent:
Rivaroxaban (5-13 hours)
Apixaban (9-14 hours)
Both are prolonged in severe renal failure (eGFR <30mls/min).

If PT normal, suggests low levels of drug so reversal may not be required
Sample for drug level can be taken (NB result may not be available immediately but may guide management later)

Inform Anticoagulant team so record of bleeding associated with these DOACs can be kept.

Location of PCC
SMH - ED Blood fridge / Theatre Blood fridge
CXH – ED medicine fridge
HH – Blood transfusion

Key
PT: prothrombin time
FFP: Fresh frozen plasma
PCC: prothrombin complex concentrate

** Hb drop ≥ 20g/L or bleeding in critical site
†Due to the high plasma protein binding
Haemodialysis will not remove these DOACs

Reversal of Dabigatran Associated Bleeding

Consider giving activated charcoal orally, if last dose ingested <2 hours ago

Start
Resuscitation measures

Monitor BP & urine output

Urgent Blood Tests
FBC / Clotting screen / Fibrinogen/ U+E / LFT
G+S

Mild bleeding

Local haemostatic measures

Consider Tranexamic acid* (15mg/kg orally)

Delay next dose of Dabigatran

Moderate-to-severe bleeding**

Local measures incl surgical

Fluid replacement
Aim for Platelets >75x10^9/L
Tranexamic acid (15mg/kg IV)

Contact Haematologist for advice

Life-threatening bleeding &/or need for emergency surgery†

Measures as for moderate-to-severe bleeding

Antidote: Idarucizumab
Dose 5 gram given either as: • IV boluses of 2.5g each over 3 - 5 minutes or
• 2 consecutive IV infusions of 2.5 g each administered over 5–10 minutes (and within 15 minutes of each other)

N.B vitamin K / protamine sulphate will not reverse the activity of dabigatran. If poor synthetic liver function (i.e. albumin <30 +/- abnormal clotting screen) consider vitamin K +/- FFP

Half-life of Dabigatran is 12-18 hours depending on age (prolonged in severe renal failure)

If APPT / TT normal, suggests low levels of Dabigatran, reversal may not be needed.

Sample for drug level can be taken (NB result may not be available immediately but may guide management later)

If PCC considered, should be discussed with haematologist (An off-licence use – caution should be exercised)

Location of Idarucizumab (Praxbind)
CXH: ED Resuscitation Area Fridge
HH: Emergency Drug Fridge in corridor close to Ward C8
SMH: ED Resuscitation Area Fridge

Key
APPT: activated partial thromboplastin time
TT: thrombin time

*There is no published data on using tranexamic acid in individuals receiving Dabigatran

** Hb drop ≥ 2.0g/L or bleeding in critical site

† 4hrs of haemodialysis will remove approx 50 - 60% of Dabigatran from circulation