Bleeding on Novel Oral Anticoagulants
A Regional Survey

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Background

* Increasing use of Novel Oral Anticoagulants (NOACs) in the management of prophylaxis and management of venous thromboembolism and in stroke prevention in atrial fibrillation

* Can be used instead of traditional vitamin K antagonists - (warfarin)

* Oral effective treatment – once or twice daily
* No need for coagulation monitoring – less burden on anticoagulation clinics
* Increasing use by cardiology, general medicine, stroke physicians, elderly care

* Currently 3 NOACS approved by National Institute for Health and Care Excellence (NICE)

* Dabigatran
* Rivoraxaban
* Apixaban

Dabigatran

* Direct thrombin inhibitor
* prevention of venous thrombo-embolism after hip or knee replacement surgery in adults
* Prevention of stroke and systemic embolism in atrial fibrillation
* Under consideration for treatment /secondary prevention of deep vein thrombosis and pulmonary embolism

Rivoraxaban

* Directly inhibits activated Factor X
* Treatment of Pulmonary embolism and prevention of recurrent venous thromboembolism
* Treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism
* Prevention of stroke and systemic embolism in atrial fibrillation

Rivoraxaban

* Prevention of venous thromboembolism after knee or hip replacement surgery in adults

* Future use - ?Acute Coronary Syndrome

Apixaban

* Direct inhibitor of activated Factor X
* Stroke and systemic embolism prevention in non valvular atrial fibrillation
* Prevention of venous thromboembolism in adults after elective hip or knee replacement surgery

Apixaban

* Future use – treatment of deep vein thrombosis/ pulmonary embolism and secondary prevention

* Unlike vitamin k antagonists – no definitive antidote currently available
* Increasing queries and concern re management of bleeding

* No definitive reversal policies available – local hospital protocols ?Prothrombin Complex Concentrates/ Recombinant factor VII, FEIBA

* Despite not needing to be monitored - is there a role for coagulation testing in bleeding
* ?effects of impaired renal function
* Site of bleeding and severity
* Duration between last dose of NOAC and bleeding

Aim

* Aim of this survey was to gather experience of reported bleeding episodes on NOACS in the Northern Region

* ?definitive reversal protocols /more standard approach across region

Methods

* Online survey designed using a web based survey design tool
* Invitations issued to all members of the Haematology Northern Regional Group
* Consultants and haematology trainees

* 17 hospitals in the Northern Region
* Asked to complete survey if had been consulted for advice re a patient bleeding on a novel oral anticoagulant
* 25 questions in total

* Email reminders/prompts - at various points during survey collection

* Survey asked several key questions
* Demographics of patient/base hospital
* Indication for anticoagulation
* Which NOAC and dose
* Renal function at commencement of treatment - ?any deterioration at time of bleeding

* Interval between time of last dose (If known) and bleeding episode

* Coagulation results at time of bleeding episode – Prothrombin time/ Activated Partial Thromboplastin Time / Thrombin time

* Other relevant co-morbidity

* Severity judged according to International Society of Thrombosis and Haemostasis bleeding severity scale

* Use of blood products – red cells/ fresh frozen plasma/ cryoprecipitate and platelets

ISTH Bleeding Severity

* **Major**

one or more of Fatal Bleeding, bleed in critical site – intracranial, intraocular, retroperitoneal / pericardial/ intramuscular with compartment syndrome/ Fall in Hb of greater than 2 g/dL or requiring transfusion of 2 or more red cell units)

* **Clinically relevant non major** (does not fit with major criteria but requires medical or surgical intervention to stop bleeding)

* Minor (all other bleeding)

Definition of Major Bleeding

* ‘Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients‘

The subcommitte on control of anticoagulation - Scientific and standardization committee of the International Society of Thrombosis and Haemostasis – Journal of Thrombosis and Haemostasis –April 2005

Methods

* Management of bleeding episodes

* Cessation of NOAC
* Antifibrinolytics
* Surgical/endoscopic measures
* PCC (Beriplex), Recombinant Factor VIIa, FEIBA?

Methods

* Outcome of management
* Death ?related to bleeding

Methods

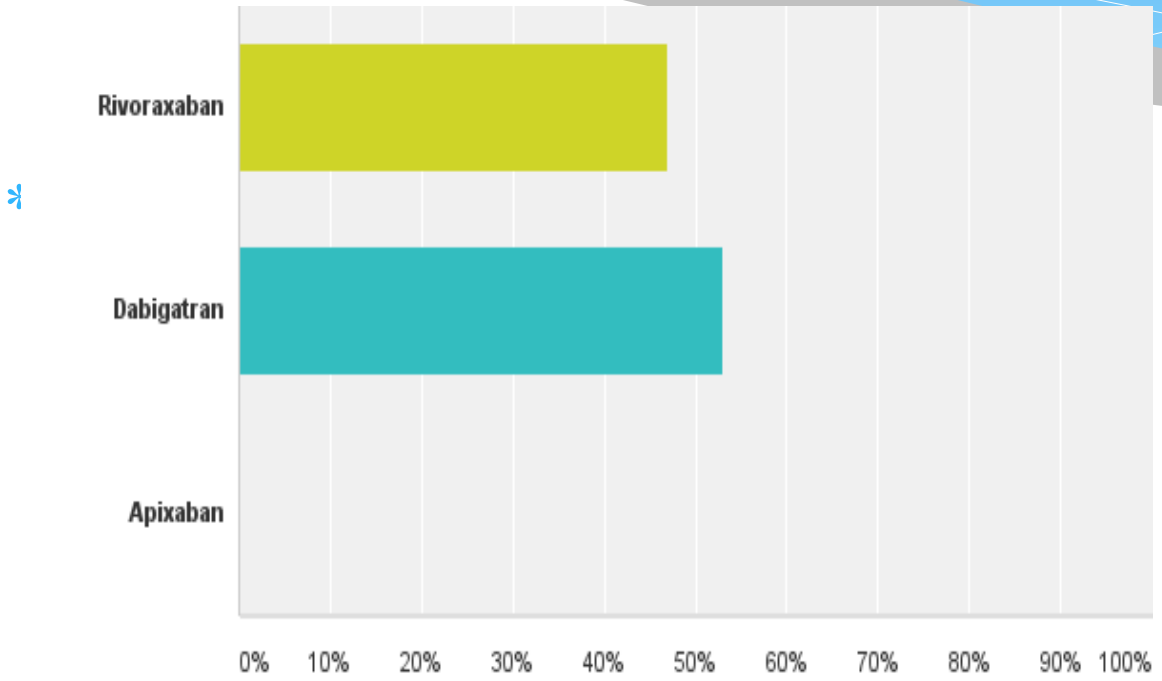
* Responses collected between April 2013 and October 2014

* HTC agreement obtained prior to collecting responses

Results

* 33 responses in total during survey collection period
* Survey monkey – survey collection tool

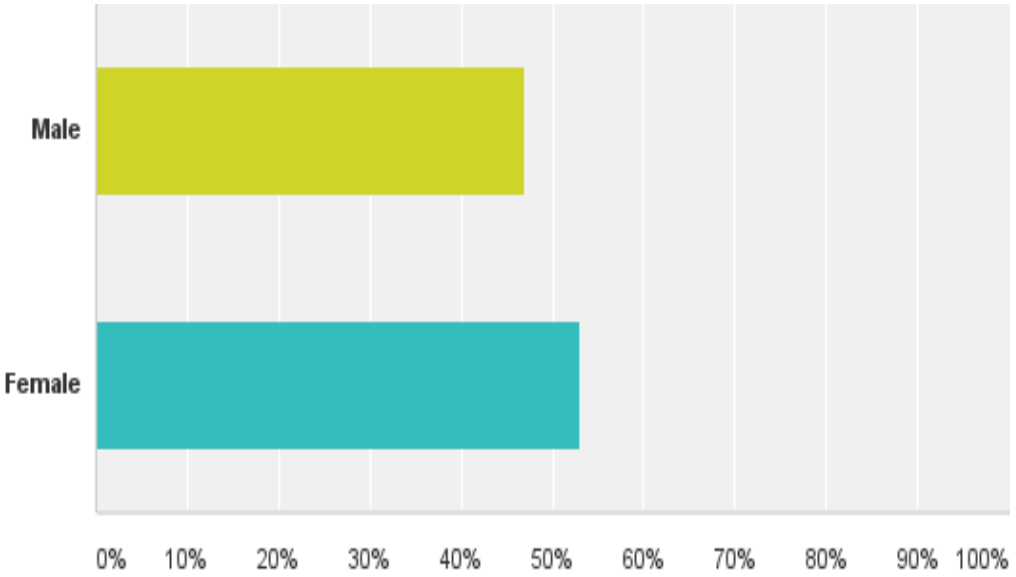
Q2: Which anticoagulant?



Q2: Which anticoagulant?

Answer Choices	Responses	
Rivoraxaban	46.88%	15
Dabigatran	53.13%	17
Apixaban	0.00%	0
Total Respondents: 32		

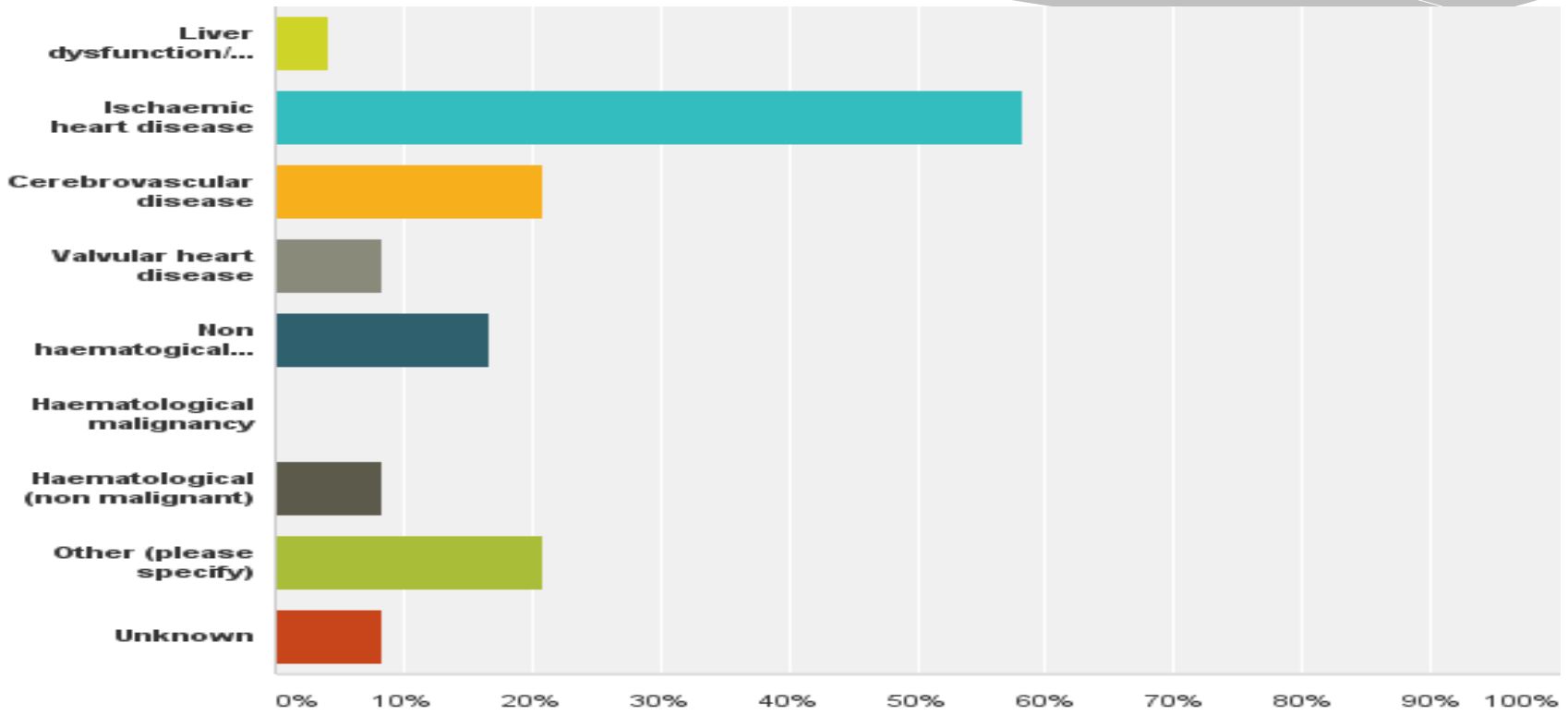
Q3: Gender of patient?



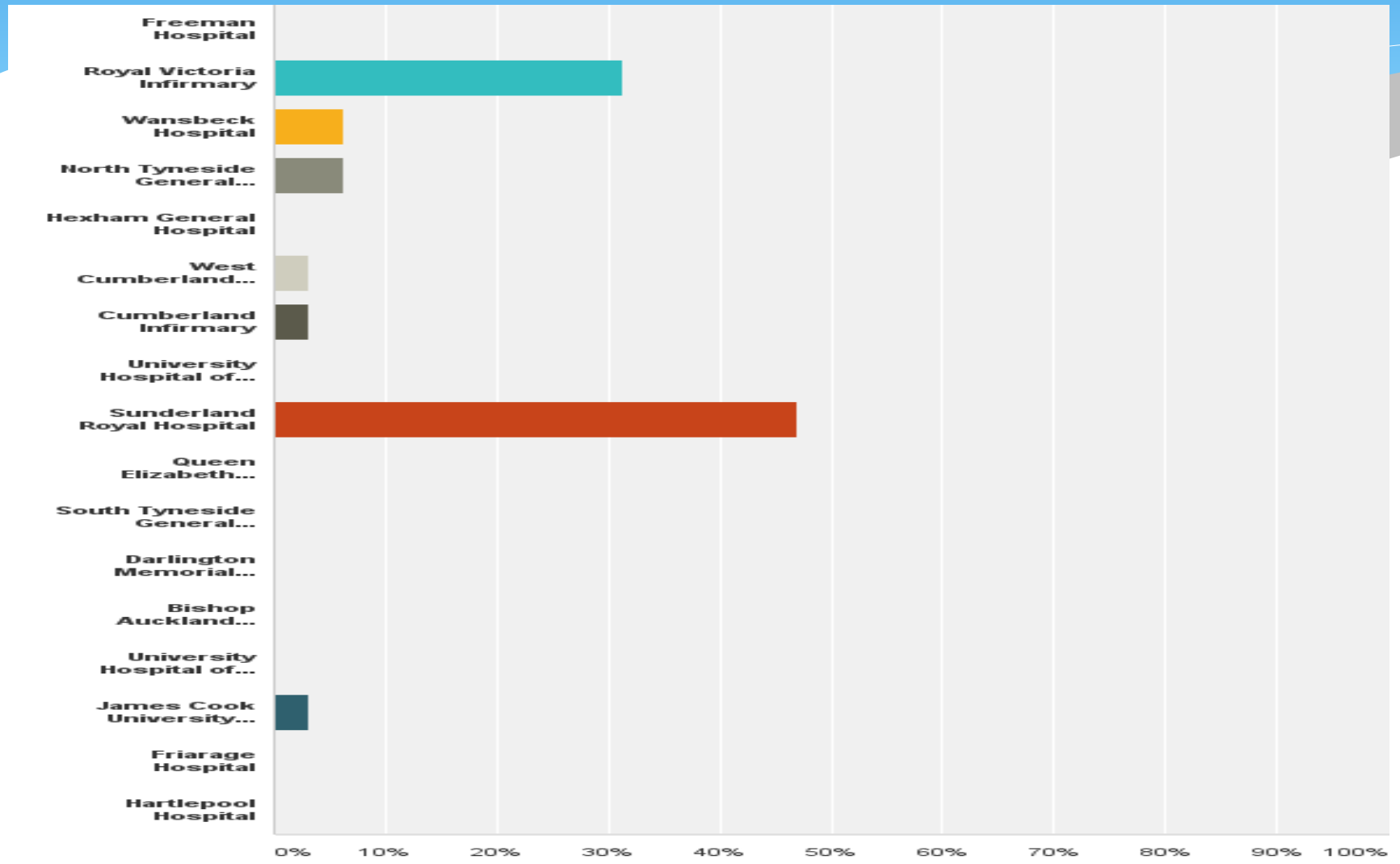
Male 46.88%

Female 53.13%

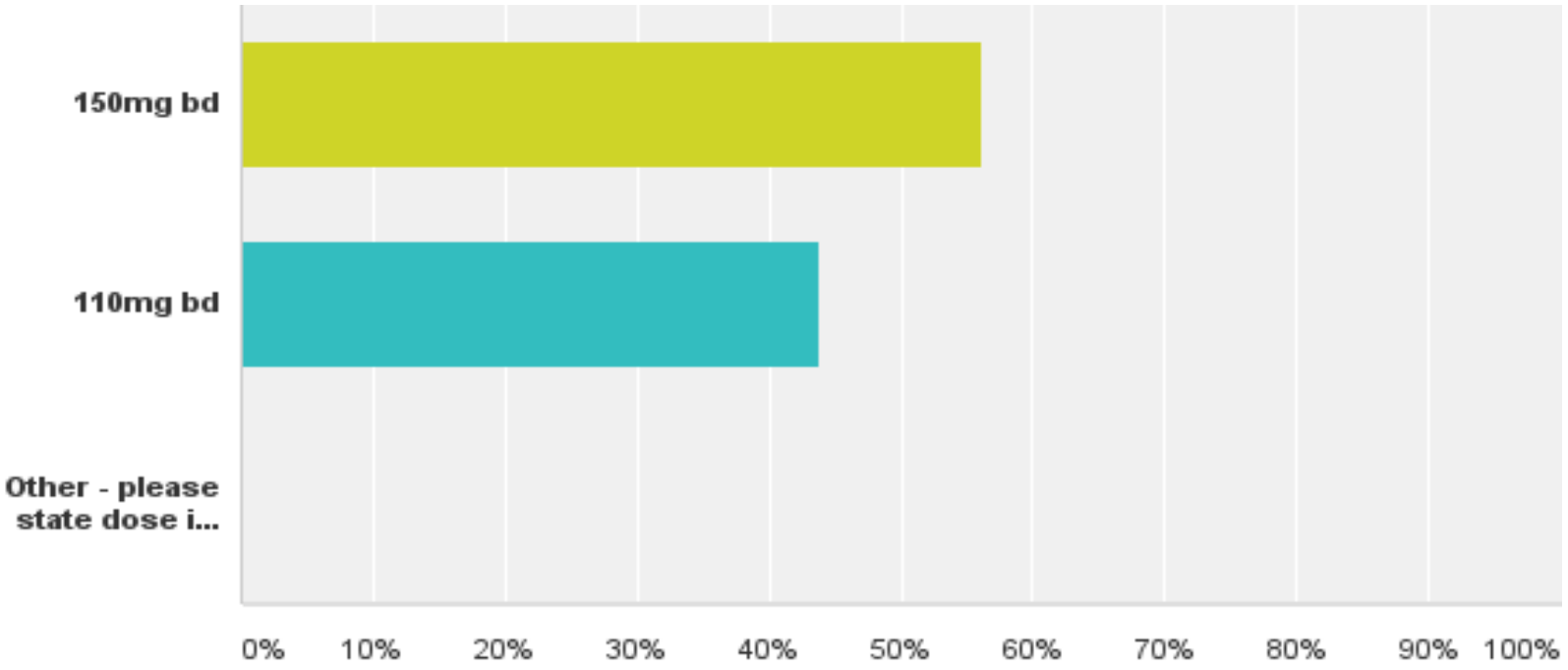
Q5: Other co-morbidity?



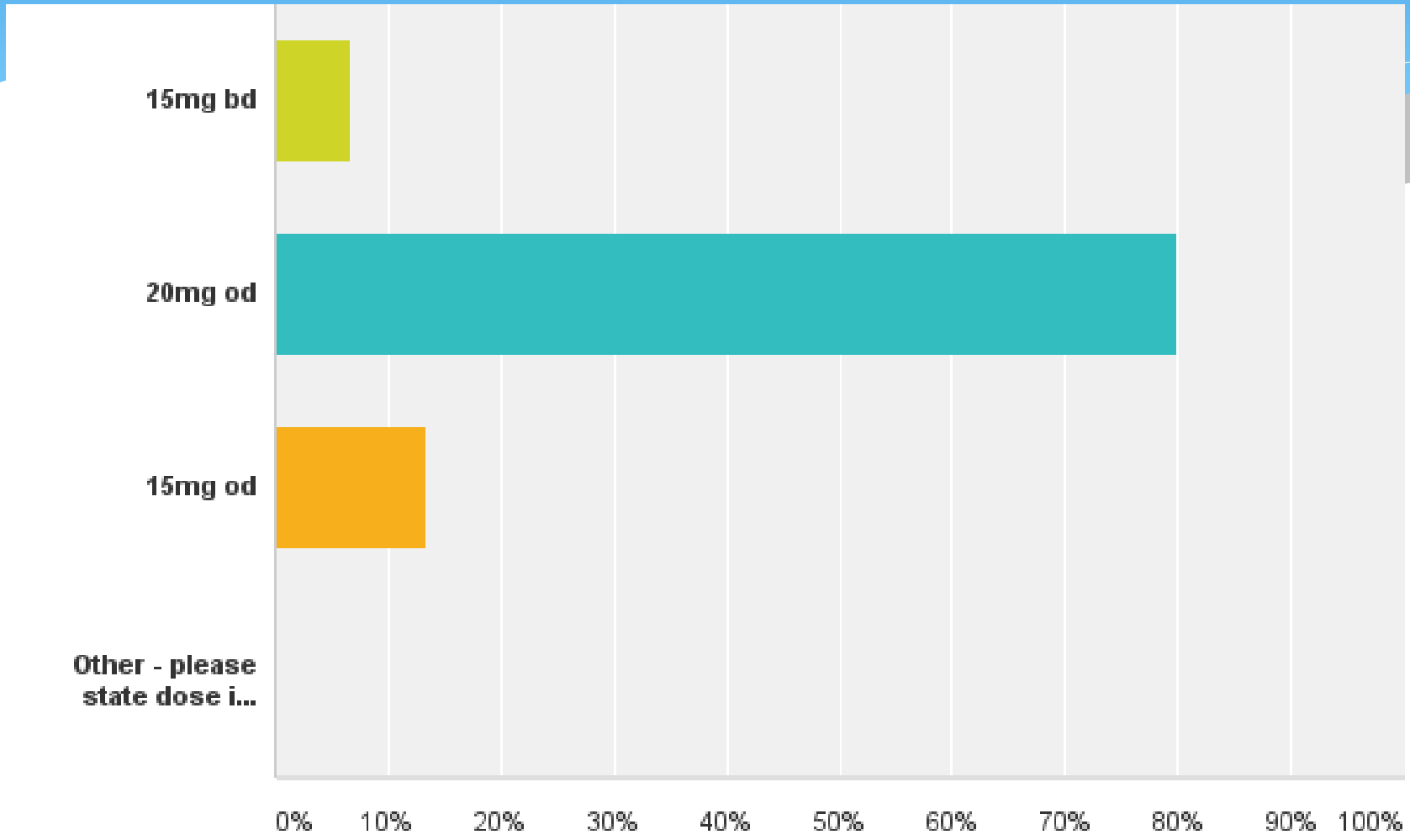
Q6: Base Hospital?



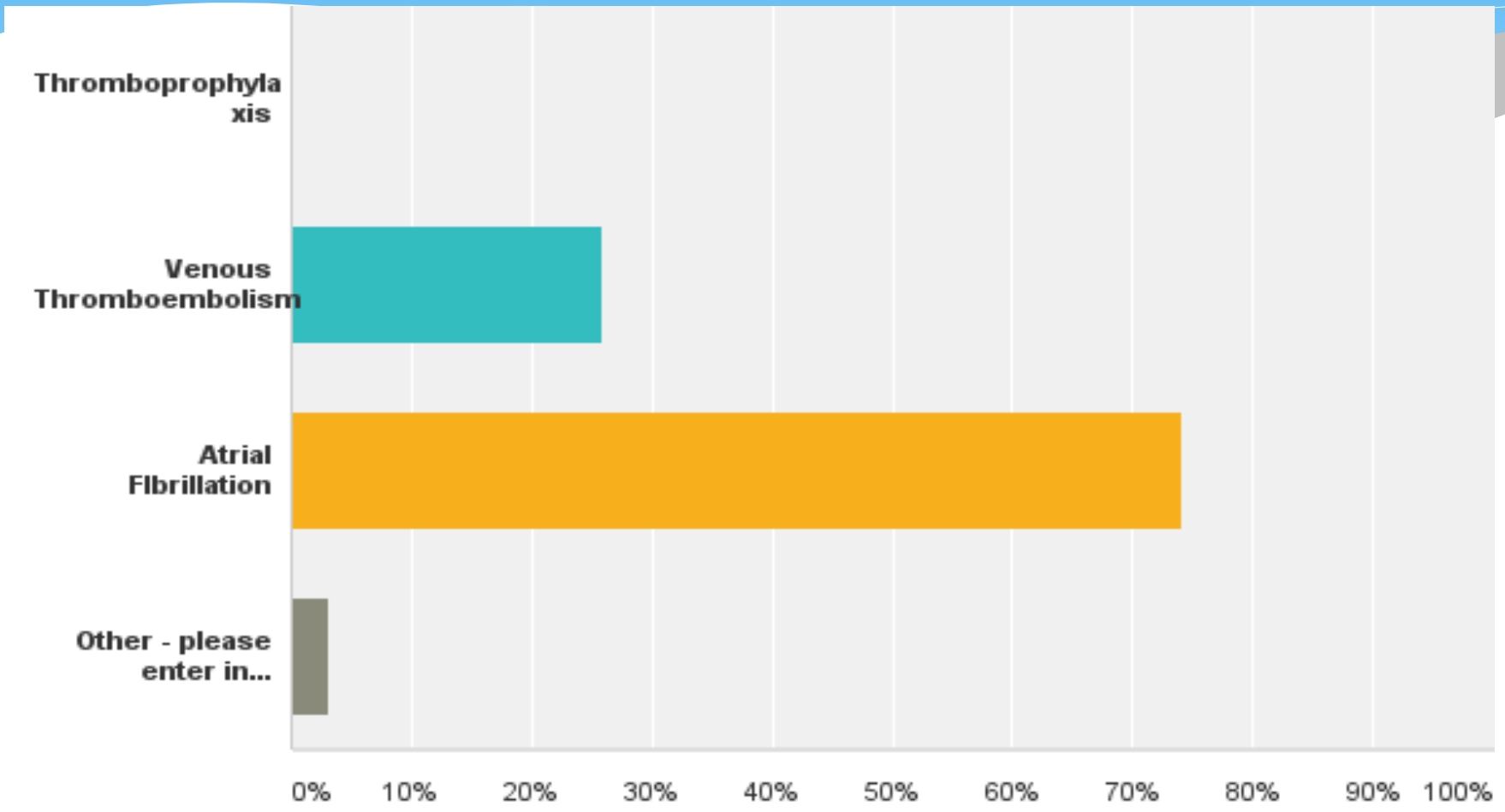
Q8: If Dabigatran - dose?



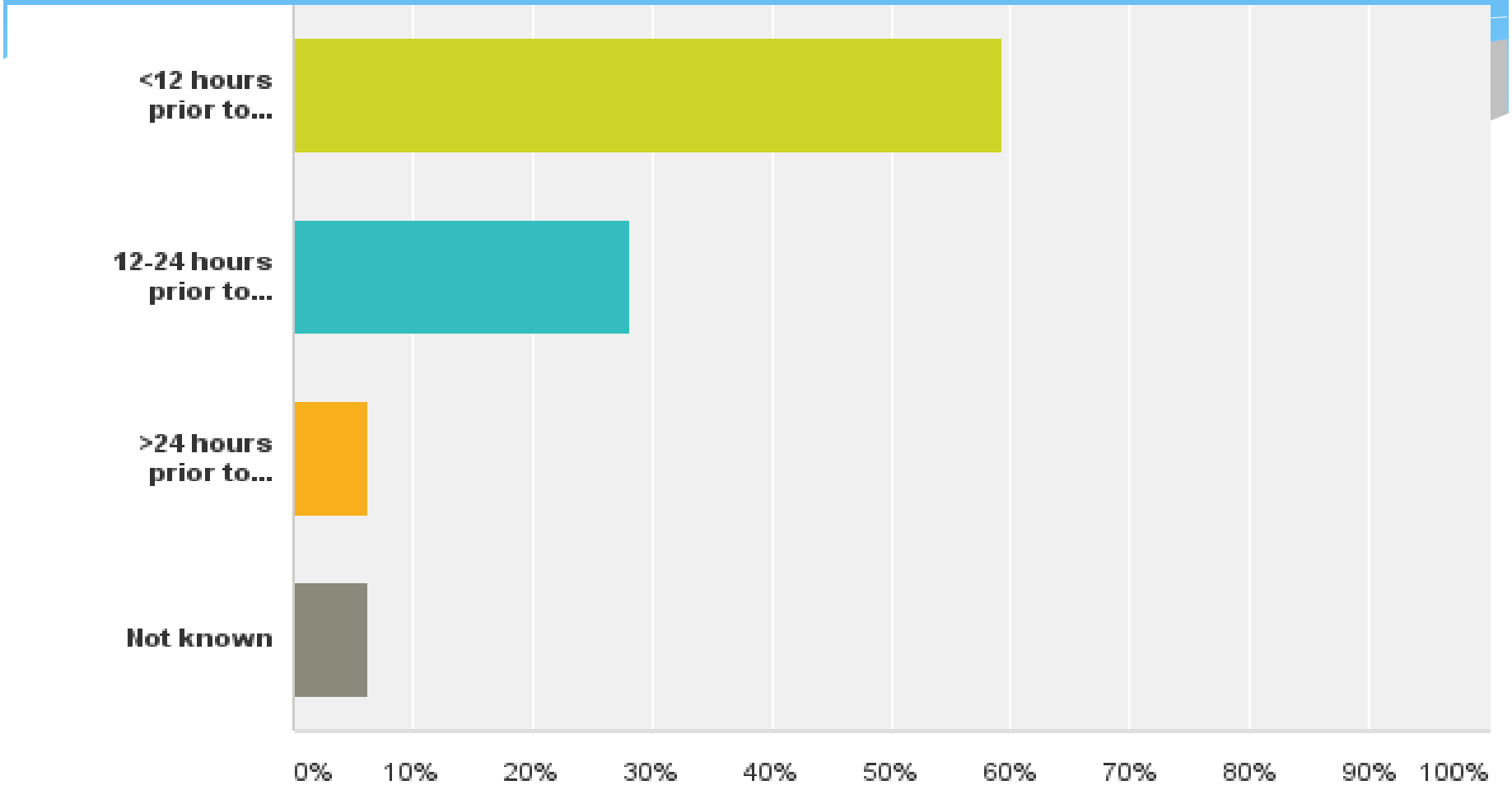
Q9: If Rivaroxaban - dose?



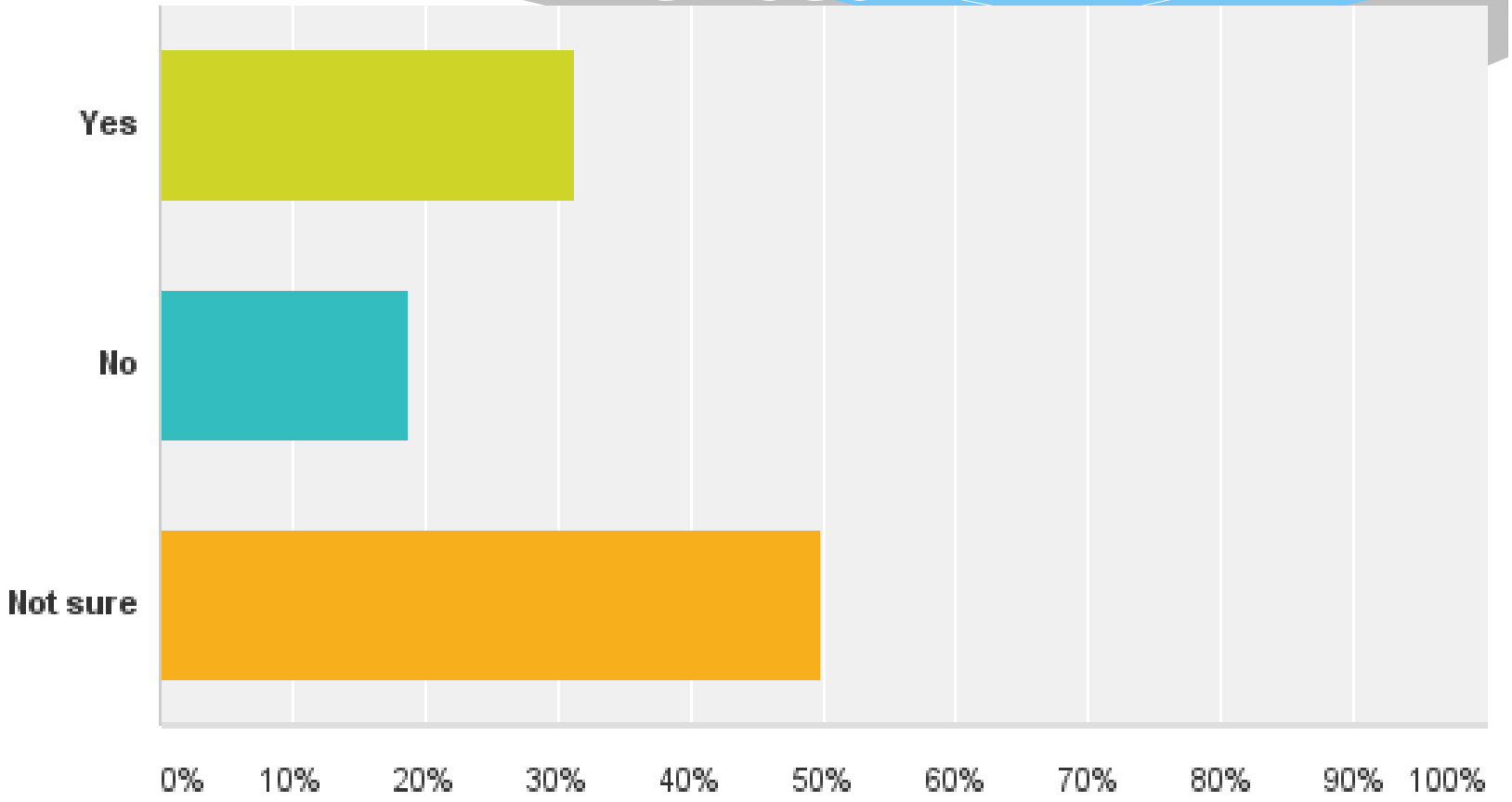
Q11: Indication



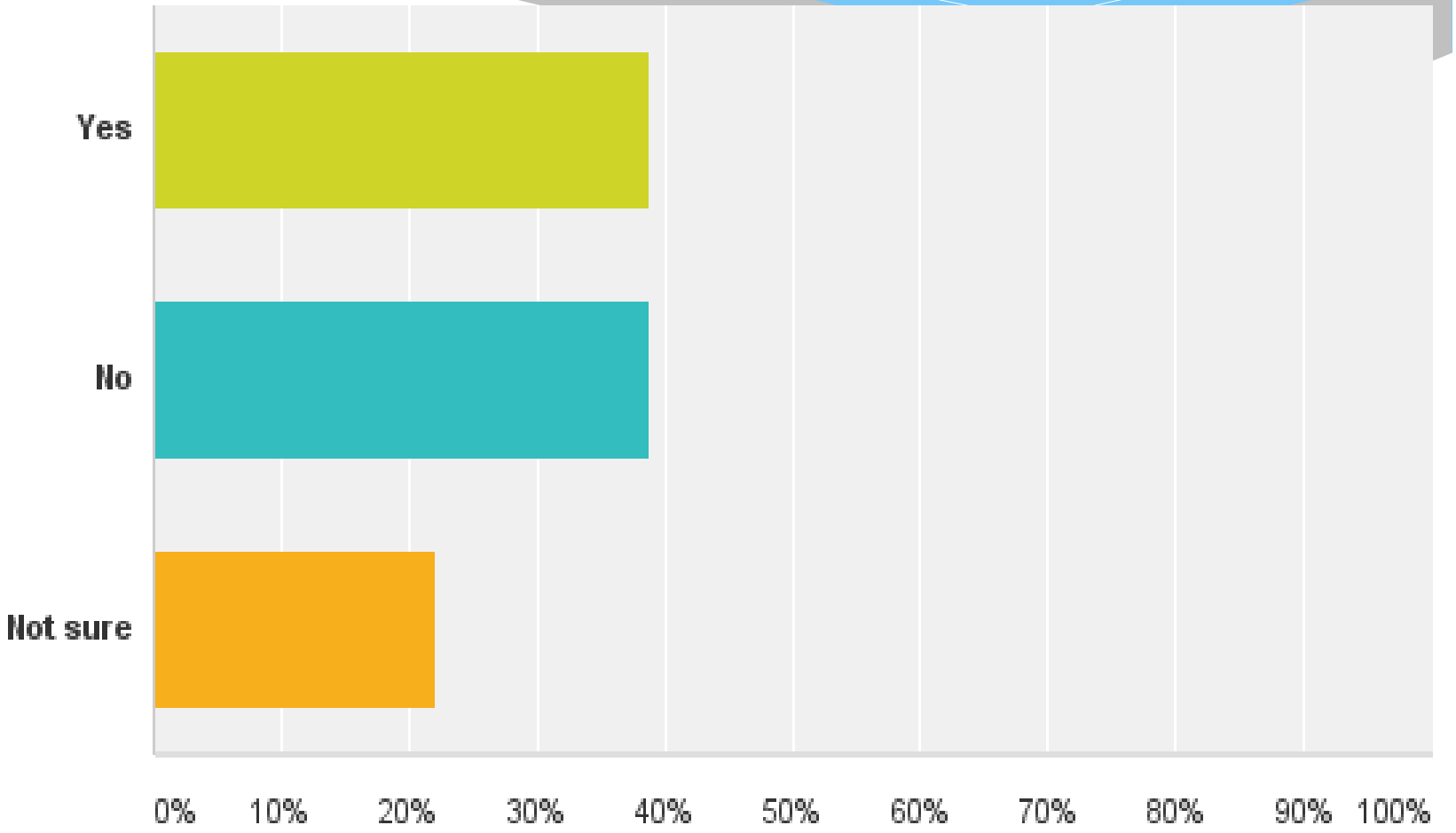
Q12: When was the last dose of anticoagulant taken?



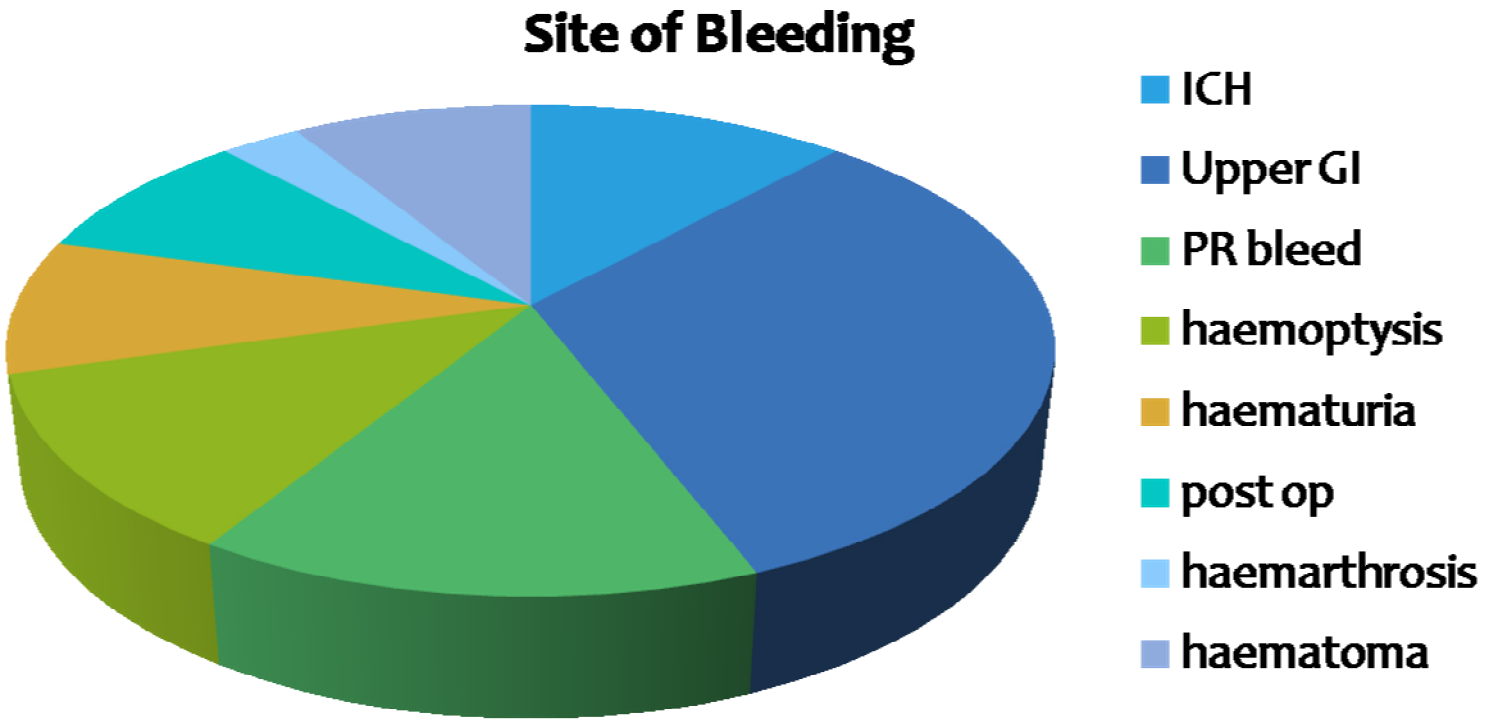
Q14: If renal failure - was this know when anticoagulant was commenced?



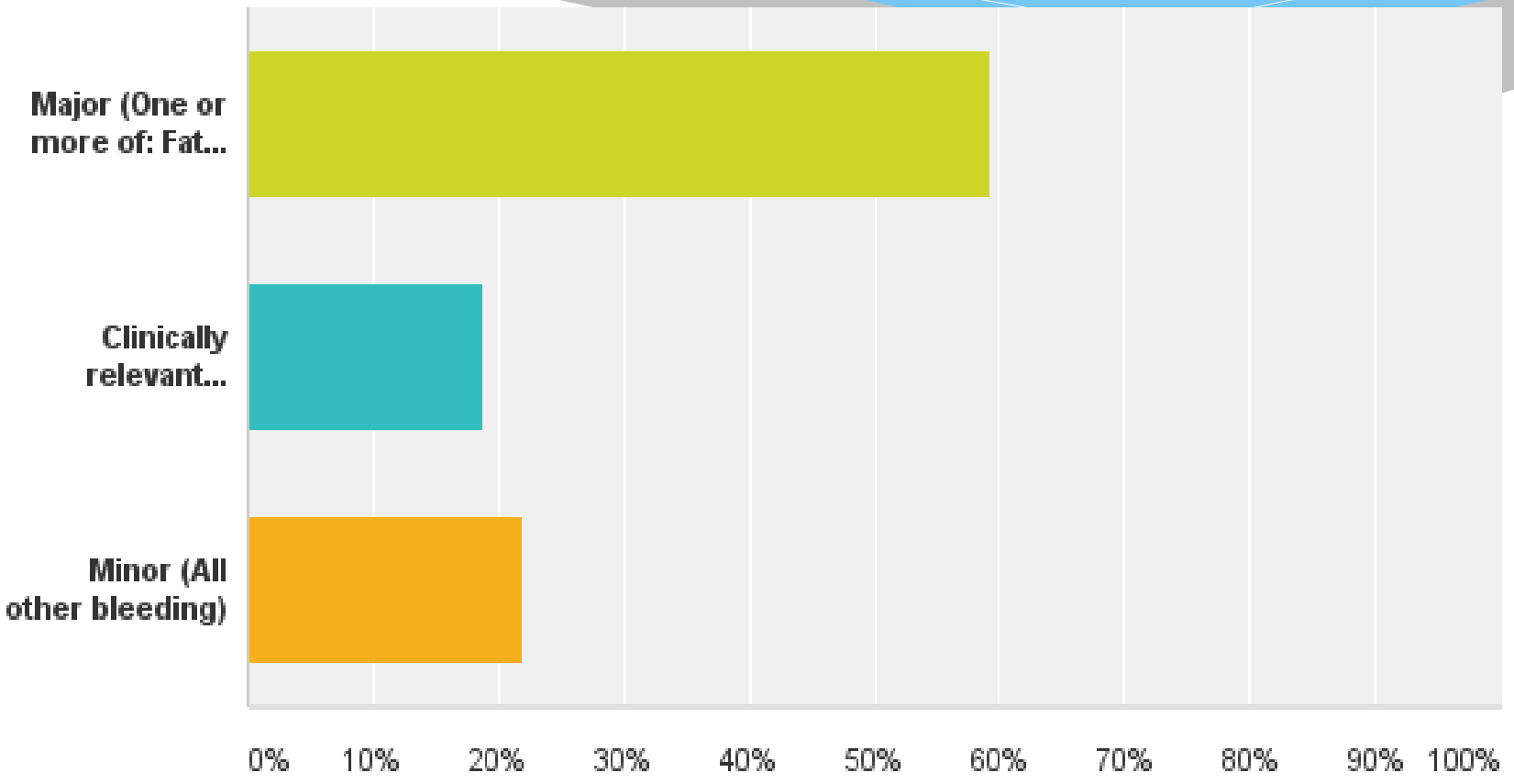
Q15: If renal failure- had renal function deteriorated prior to presentation?



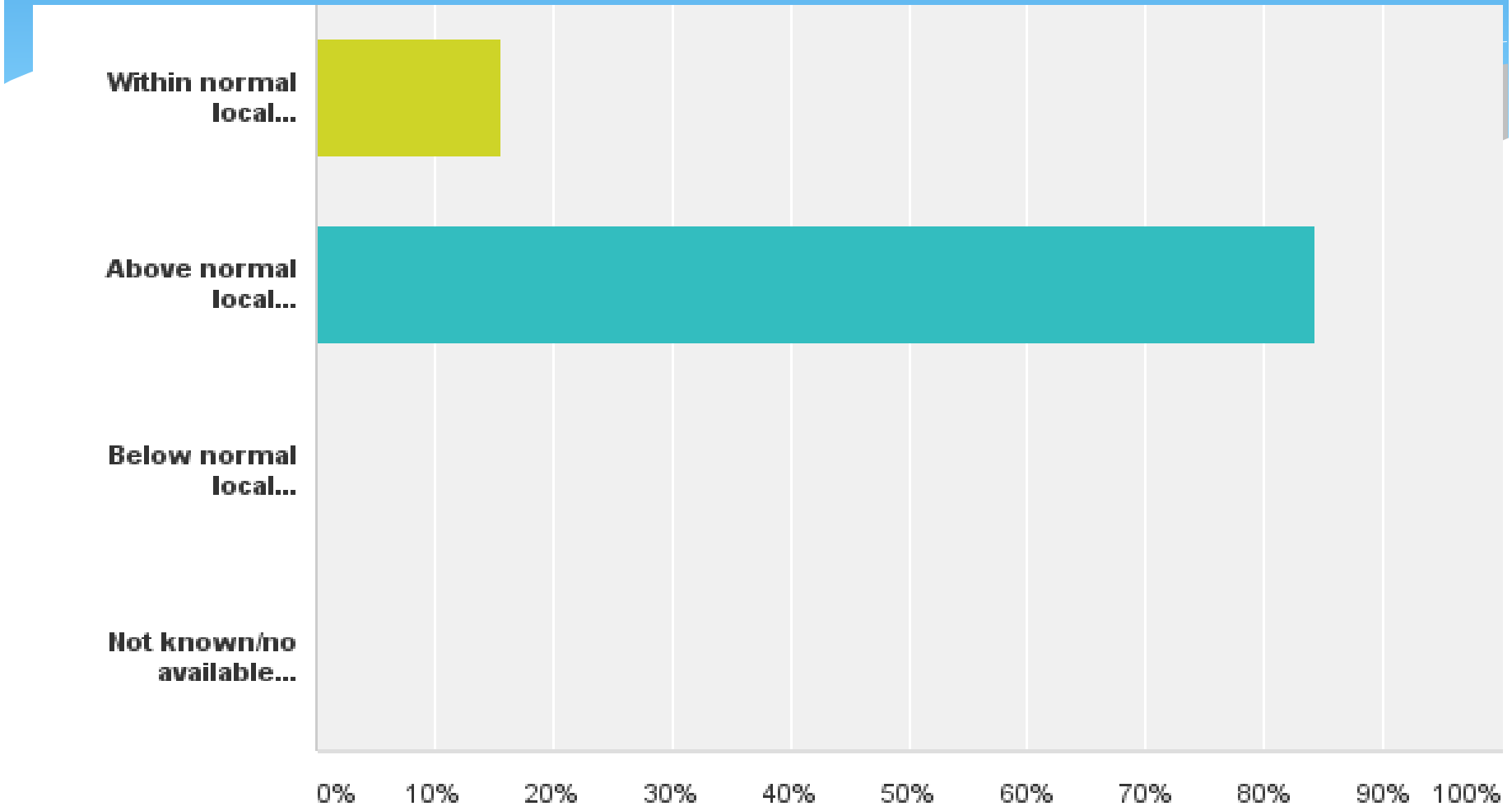
Site of bleeding



Q17: Severity of bleed (according to ISTH criteria)



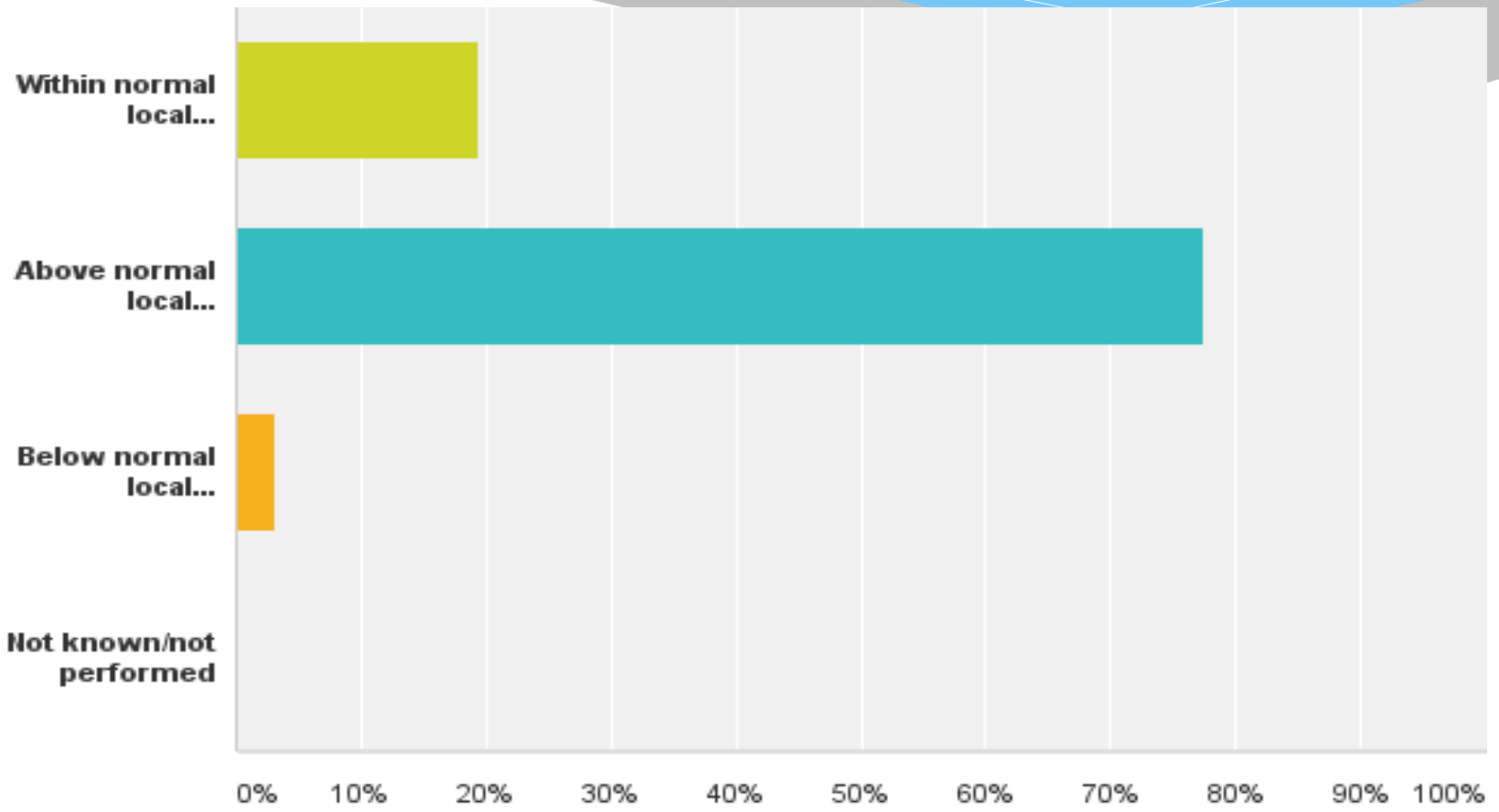
Q18: Prothrombin Time (PT)



* 15/17 cases (88%) of bleeding on Dabigatran - prolonged prothrombin time

* 11/15 cases-(73%)of bleeding on Rivoraxaban prolonged prothrombin time

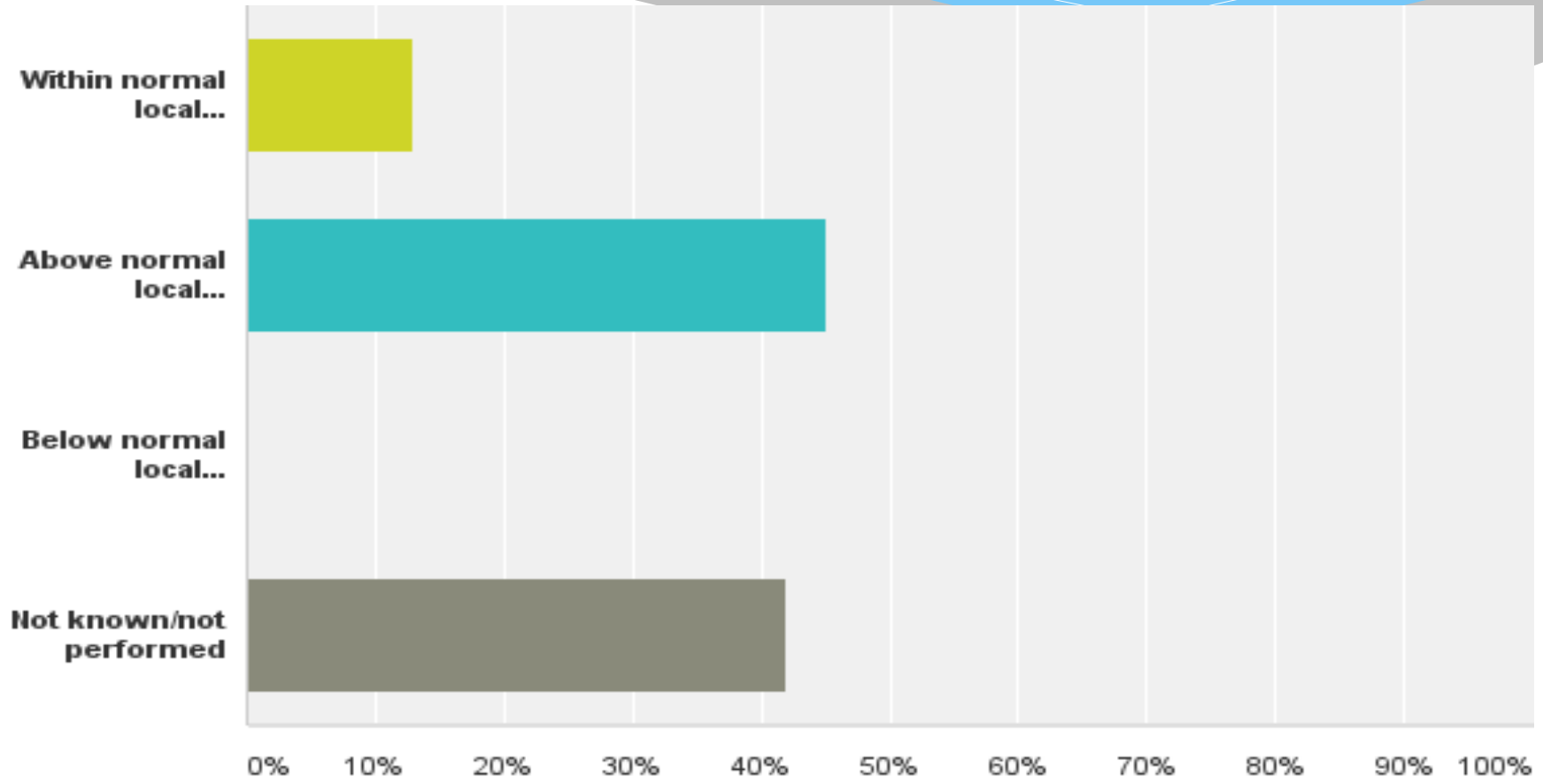
Q19: Activated Partial Thromboplastin Time (APTT)



* 15/17-cases (88%) –where bleeding on Dabigatran – prolonged APTT

* 9/15 cases (81.8%) – on Rivoraxaban – prolonged APTT

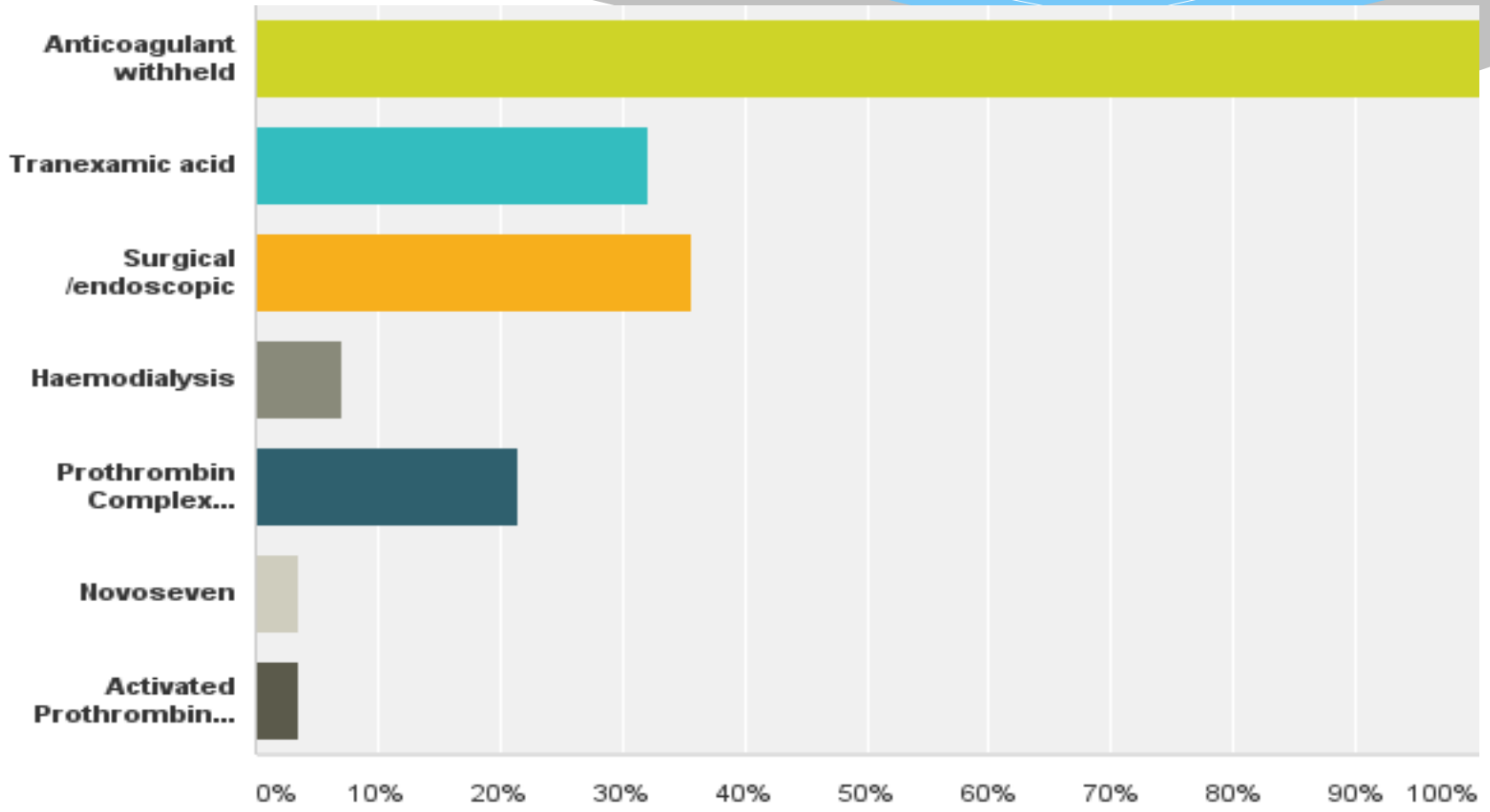
Q20: Thrombin Time



* Dabigatran –prolonged Thrombin Time – 13/17 (76.4%)

* Rivoraxaban- 0 cases recorded with prolonged Thrombin time

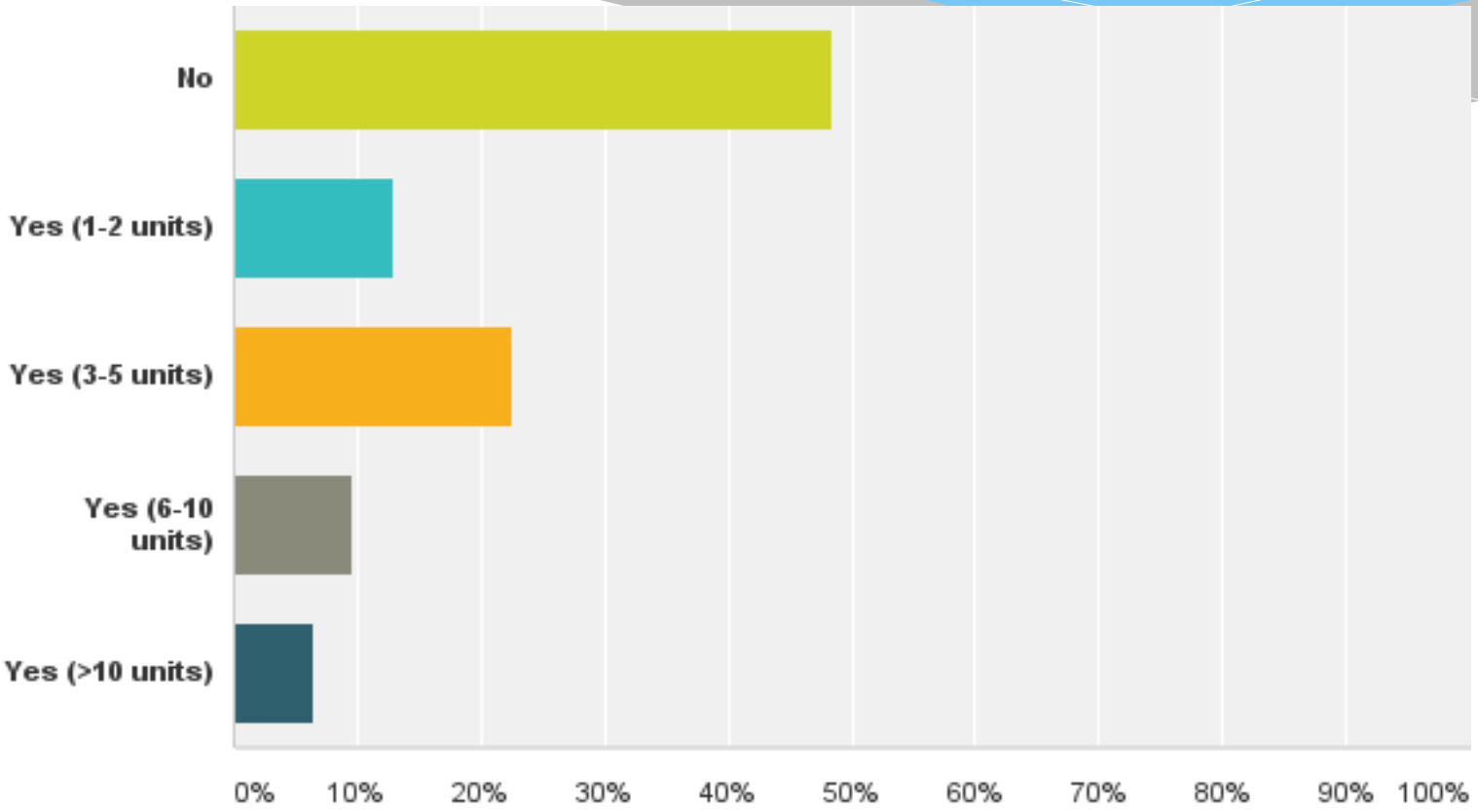
Q21: Management of bleed (mark all that apply)



Q21: Management of bleed (mark all that apply)

Answer Choices	Responses	
Anticoagulant withheld	**100.00%**	28
Tranexamic acid	**32.14%**	9
Surgical /endoscopic	**35.71%**	10
Haemodialysis	**7.14%**	2
Prothrombin Complex Concentrate (ie Beriplex)	**21.43%**	6
Novoseven	**3.57%**	1
Activated Prothrombin Complex Concentrate (ie FEIBA)	**3.57%**	1
Total Respondents: 28		

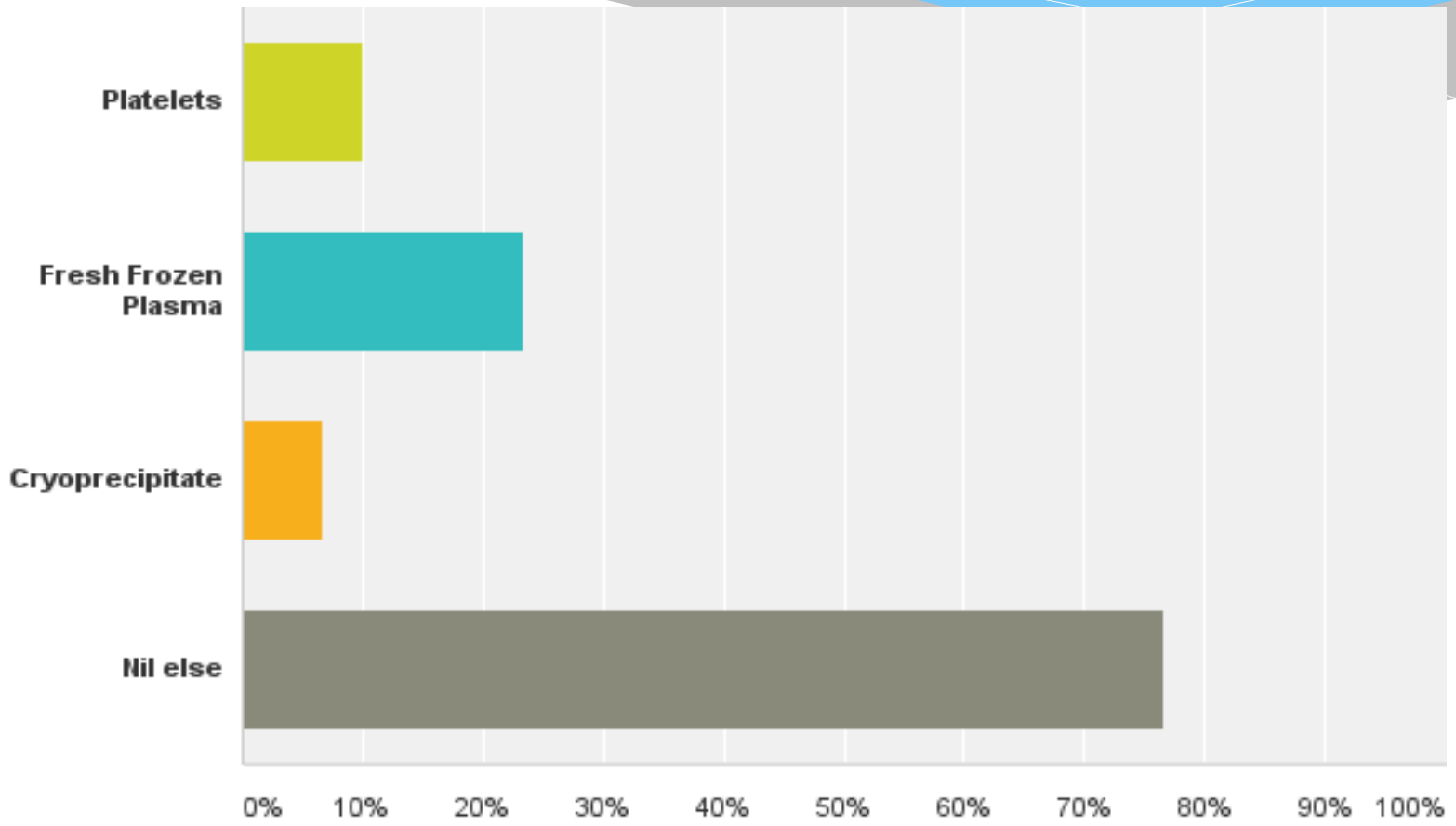
Q22: Were red cells tranfused?



Q22: Were red cells tranfused?

Answer Choices	Responses	
No	48.39%	15
Yes (1-2 units)	12.90%	4
Yes (3-5 units)	22.58%	7
Yes (6-10 units)	9.68%	3
Yes (>10 units)	6.45%	2
Total Respondents: 31		

Q23: Other blood components tranfused? (Mark all that apply)



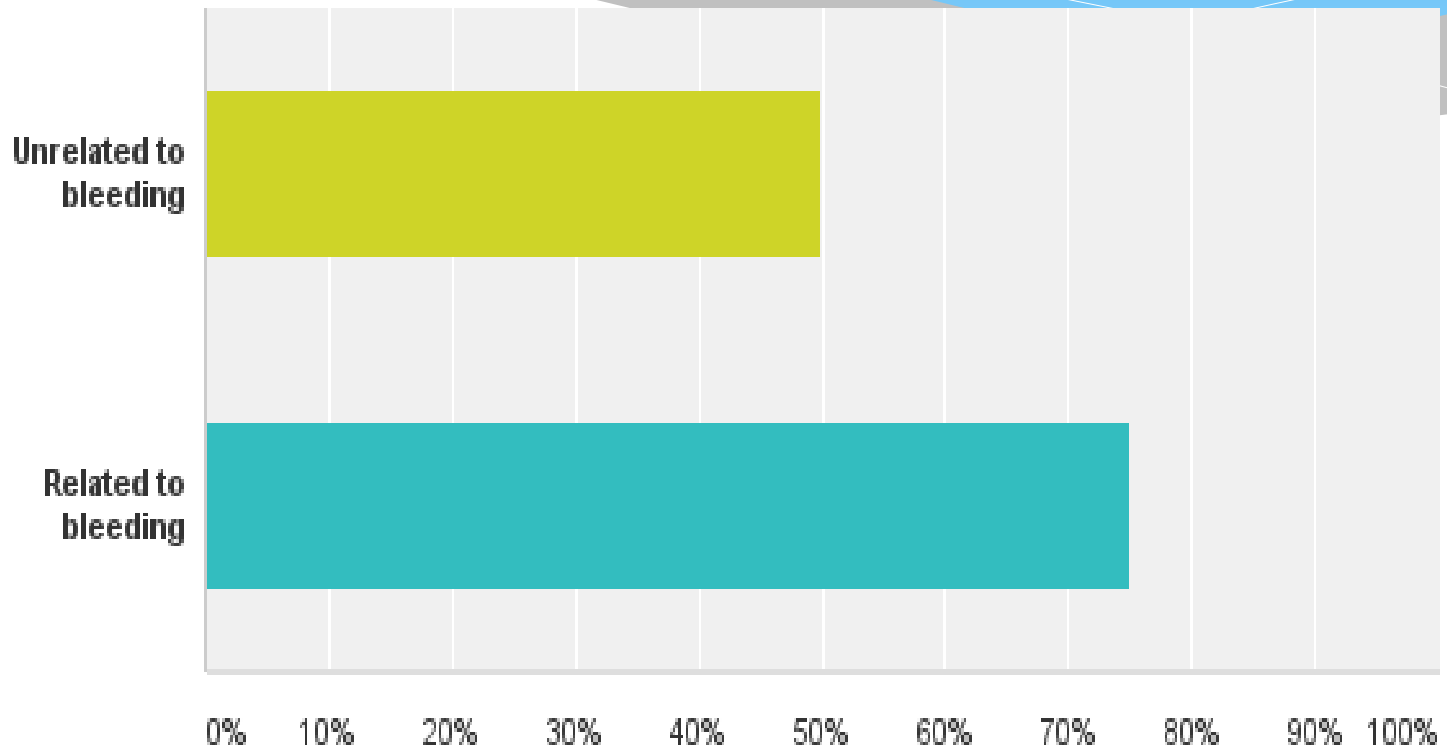
Q23: Other blood components tranfused? (Mark all that apply)

Answer Choices	Responses	
Platelets	10.00%	3
Fresh Frozen Plasma	23.33%	7
Cryoprecipitate	6.67%	2
Nil else	76.67%	23
Total Respondents: 30		

Q24: Outcome

Answer Choices	Responses	
Bleeding stopped - anticoagulation restarted	32.14%	9
Bleeding stopped - no further anticoagulation	57.14%	16
Death	14.29%	4
Total Respondents: 28		

Q25: If death as outcome?



* 5 cases were post fall/trauma
* 2 post operative – bleeding
* 1 case – undiagnosed Acquired Haemophilia – prolonged APTT one week after discontinuation of NOAC

* One case – DIC post Group A streptococcal infection – post op bleeding

* Given Beriplex (coagulation profile not correcting with blood products/vitamin K and ongoing major haemorrhage)

* but unaware at time of discussion /issue of PCC - that patient on Dabigatran - ?given Beriplex earlier if known

* initally prolonged PT/APTT/Thrombin time – then low fibrinogen

* 26 units RCCs/ 32 pools FFP/4 pools Cryoprecipitate/4 pools of platelets

* One case post operative bleeding– for emergency surgery for incarcerated hernia
* Case of major bleeding post trauma – to be discussed in afternoon session
* Several cases –where patients remained on NOACs despite bleeding (clinical staff unaware of action/relevance)

Discussion

* Limitations – response rate ?Due to infrequent bleeding episodes or low completion of survey
* Survey only open to haematologists – so may not have been aware of some bleeding episodes if not reported to them (ie - minor bleeding)
* Haematologists - more likely to be informed of major bleeding episodes

* However most discussion re NOACs and bleeding is about reversal in major bleeding

* Cannot assess bleeding rate on NOAC from this survey – would need data on numbers of patients on NOACs in the region (commenced in hospital and community)

* Sometimes lack of awareness that patients are even on NOACs

* Omissions –unable to find information /full coagulation profile not recorded

* ‘is the patient on an anticoagulant?’ – ‘No’ often filled on request information by clinical team

* Laboratory staff alerted to discrepancy by abnormal coagulation profile

* Bleeding on Dabigatran – majority - prolonged thrombin time

BCSH June 2014 guidelines - measurements of non coumarin anticoagulants and their effects on tests of haemostasis - normal thrombin time suggests level of dabigatran likely to be very low)

* Rivoraxaban – majority of cases had prolonged PT and APTT

* BCSH guidelines 2014 –PT and APTT can be used with most reagents for crude estimation of level of anticoagulation –PT more sensitive (but cannot be used to determine drug concentration)

* Some patients with therapeutic concentrations will have normal PT and APTT

* Individual labs will have their own reagents and coagulation ranges..

* Some patients had impaired renal function at commencement of treatment ?Coumarin anticoagulant more suitable

* Some bleeding episodes – deterioration of renal function ?Due to other factors ie AKI

* Majority of bleeding occurred when patient had NOAC <12 hrs before presentation

* Still variation re reversal agents used – PCC vs recombinant VIIa
* Only 2 patients underwent haemodialysis

* 'Antidote' still in production – availability and cost….

* Small survey –to gather local experience
* More data collection is needed –to establish bleeding rate, management protocols
* More education of doctors, nurses, students – re awareness of NOACs and their action – prescribing/advice to patients

* ?measuring of NOAC levels
* Aid in management of bleeding??

ORANGE STUDY

* **OR**al **AN**ticoagulant a**G**ent associated bleeding events reporting system study
* 3 year prospective observational study
* Collecting data on the management and outcomes of patients who develop major bleeding on oral anticoagulants across the UK
* Recruiting clinicians to take part in the study until 31st December 2016
* Sponsored by Queen Mary University London
* Funded by British Society of Haematology

* Thanks to Northern Region HTCs
* NRHG
* Haematology registrars
* Barry Logan – Sunderland Royal Hospital -