ROYAL COLLEGE of PHYSICIANS of EDINBURGH

Evening Medical Update: Haematology January 2023

Venous thrombosis: Investigation and management – Dr Andrew Page

What do you do with the common scenario... where a d-dimer is done before (by someone else...) and it comes back as raised... You weren't suspecting a DVT up to then?

I would try to assess the patient without taking this result into account. That said, if there is no other reason for the D-dimer to be raised (ie no evidence of infection etc) then the result is likely to have some impact on clinical impression and I don't think this is avoidable, even though it is not the "correct" diagnostic pathway. Also, very raised D-dimer results would raise concern of underlying malignancy etc and should prompt appropriate clinical assessment in this regard.

How does anticoagulation affect the d-dimer?

D-dimer levels tend to fall with time on anticoagulation. Generally, over a few days, this will not have a major effect but it can impact the diagnostic pathway for those with only marginally raised D-dimer levels at outset. Hence, checking them before empirical anticoagulation is started.

What's the likelihood of a patient having a mild chest infection AND a PE? Because they would also present with pleuritic chest pain, tachycardia, sob, d dimer will be raised.

Very difficult to say as we don't have really good data on this and it is likely to depend on the specific infection, severity etc. In the COVID era, we know that PE is significantly increased even in patients with non-hosptialised COVID and the risk is highest at / shortly after diagnosis with COVID although absolute risk of PE is low in a non-hospitalised patient. Looking at infective exacerbations of COPD, incidence of PE has been estimated to be as high as 10%. The best guidance on this is that PE and infection can (and not uncommonly do) coexist. If there is significant clinical concern regarding PE then the appropriate diagnostic pathway should be followed. D-dimer is still reasonable to use as a rule-out in an outpatient with low suspicion (based on Wells or other scoring system) of PE, but should only be checked if the patient would be planned to undergo CTPA if D-dimer is raised.

For a patient with background of AF (on a DOAC) and CKD, with a Wells Score for DVT of 3, how do we interpret a raised d-dimer and what should be our threshold for a scan?

This would qualify as a high likelihood of DVT (Wells = 3) so duplex USS would be needed regardless of the D-dimer result. The main issue with D-dimer interpretation in the context of anticoagulation is that values may be lower than they otherwise would have been, so D-dimer is not validated for ruling out VTE in the context of anticoagulation. A raised D-dimer would still be considered to increase the likelihood of DVT but arguably should not be checked as a low D-dimer cannot safely be assumed to rule out DVT in the low Wells score scenario.

For case 2, after starting apricavano was she discharged and have CTPA as OP or did she need admitted?

We would ambulate the large majority of low risk PE patients (in line with good quality clinical evidence that this is safe to do). Use of apixaban (or rivaroxaban) for empirical management of VTE prior to diagnostic imaging (instead of LMW heparins) is an area of some debate but NICE deemed it a potentially reasonable approach in their 2020 guidance, based on the clinical trials data of DOACs being used very shortly after diagnosis with VTE and after minimal pre-treatment with LMW heparin. Some hospitals have already introduced this approach owing to practical considerations and I am not aware of a concern of a large increase in treatment failure, but in an ideal world there would be better data to support this approach. It is also important to note that this is an off-label use of Apixaban as the diagnosis of VTE had not been confirmed.

Is there a preferred anticoagulant to use? Does the literature suggest certain anticoaguants are better for DVTs/PEs

There is not one best anticoagulant for all scenarios. Also, clinical trials have not compared the different DOACs head-to-head. Most of the data comes from comparison to warfarin. What we can say here is that only Apixaban and Rivaroxaban can be used without a lead in period of a parenteral anticoagulant, so there are practical considerations that favour these two agents. Rivaroxaban needs to be taken with food for optimal absorption, which is not the case for Apixaban, so this is arguably a point in favour of Apixaban. DOACs (where not contraindicated) appear to be at least as effective as warfarin / VKAs and appear to have a lower overall risk of major bleeding. GI bleeding is a little more uncertain for most DOACs, where there is a trend towards an increased incidence compared to warfarin. This is not the case for Apixaban, which appears to result in a lower rate of GI bleeding than warfarin but with a downside of a twice daily dosing. Therefore, whilst head-to-head data are not available to prove a “best” agent, my personal preference would be for Apixaban in most scenarios unless there is a strong preference for a once daily agent.

What about Patients with cancers...with likely high D.Dimers?

I am aware of studies which have tried to define normal ranges for different tumour types. However, these cannot be used in any validated pathway to rule out VTE as yet. It is reasonable to assess cancer patients via the established diagnostic pathways but they are very likely to end up needing imaging, both because of high likelihood of VTE in this context and likely raised D-dimers. Whether the clinical suspicion is high enough to go down the route of ?VTE is the key determinant of whether a scan will need to be done.

Who carries out catheter directed thrombolysis. Would this be urgent vascular referral?

This will vary from hospital to hospital but generally catheter directed thrombolysis would be performed by an interventional radiologist. In my hospital, they would generally expect the referral to interventional radiology to come from a vascular surgeon, so I would refer to vascular surgery who would refer on to interventional radiology.

In our ED dept, for patients suitable for outpatient pathway of PE treatment, we give a stat dose of LMWH subcut and then start apixaban BD from then. Is the heparin dose necessary? How long does apixaban take to load?

The clinical trials of Apixaban and Rivaroxaban (the only two DOACs that can be used without LMW heparin lead in) allowed for up to 48 hours / 2 doses of treatment with LMW heparin prior to

initiation of DOAC. The reality is that most patients almost certainly had at least one dose of LMW heparin prior to starting DOAC. That said, it is standard practice to wait 24 hours post a therapeutic dose of dalteparin to initiate Apixaban or Rivaroxaban, and this is frequently done after a single dose of LMW heparin. 24 hours after a dose of dalteparin, for example, there will be negligible residual drug effect (6-8 drug half-lives have passed) so this DOAC initiation period is routinely done in the absence of any covering anticoagulation and after only a single prior dose of LMW heparin. It is therefore a reasonable expectation that DOACs could be started without any prior LMW heparin treatment, but trials have not proven this as far as I am aware. NICE took the view that the approach of starting Apixaban or Rivaroxaban up front was reasonable but this is an off-label use of these medications.

A more practical consideration in my hospital is that the diagnosis is not usually made on the day of attendance and patients receive empirical anticoagulation prior to imaging. This is generally available the next day, so giving a single dose of LMW heparin in ED and sending a patient away to come back for imaging and then to be started on DOAC is easier than checking for drug interactions etc. and starting DOAC empirically prior to imaging being done.

IVC Filters recommended for intra abdominal/pelvic extension of DVT or only for those who are not eligible for those contraindicated for anticoagulation?

I think the only universally recognised indication for IVC filter insertion is when anticoagulation is contraindicated in the setting of acute VTE. For IVC thrombus, there might be a reduction in risk of PE but there has never been mortality benefit demonstrated with this and there is clear risk of filter complications. NICE and international guidance has tended to steer away from IVC filter placement even in the context of pelvic / IVC DVT, an exception being if intervention is planned for the DVT – some interventional approaches do come with a recommendation to consider a retrievable IVC filter.

How many additional DVTs do the repeat scans at one week pick up (in the high risk groups with positive d-dimer but initial scan negative)?

According to the Wells study, around 3% of these scans will be positive, which is around 5% of all DVTs diagnosed. Interestingly, none of the patients with a second negative scan were diagnosed with VTE in the 3 months after assessment, so the second scan at one week is an effective way to rule out DVT in this group.

Is there different eGFR cut off for Apixaban and Rivaroxaban?

For VTE, Apixaban should be used with caution if creatinine clearance is 15-30 ml/min, and is recommended against if creatine clearance is less than 15. Rivaroxaban comes with similar guidance but, after the first 3 weeks of treatment, consideration can be given to using the reduced dose of 15mg OD (rather than 20mg OD) for those with creatinine clearance 15-49 ml/ml if bleeding risk outweighs the risk of thrombosis.

I thought the latest NICE guidance recommends ORBIT?

ORBIT is recommended in atrial fibrillation guidance by NICE. ORBIT is not, as far as I am aware, validated in VTE. NICE 2020 guidance on VTE recommended consideration of HAS-BLED in this context (although this comes with significant caveats as discussed).

Would you recommend starting LMWH initially rather than DOAC in pts. who need more rapid treatment but not thrombolysis (e.g. submissive PE, large DVT) before switching to DOAC later? Would you advocate loading with IV heparin in these situations for speed of action (like in LMWH trials?)

If there is a concern about high risk PE, I would err on the side of using LMW heparin (or IV heparin if very high risk) primarily because there is more experience of using these agents with thrombolysis, which may turn out to be needed if the patient deteriorates. Simply for a large proximal DVT, I would be happy enough for a patient to start on DOAC provided there were no concerns regarding phlegmasia or a threatened limb. This would come down to clinical judgement, but if the patient is suitable to ambulate then they are likely to be suitable for treatment with a DOAC (with the usual provisos)

We do not load with IV heparin prior to LMW heparin in my hospital, as much as anything because simplicity in treatment pathways tends to lead to more rapid institution of appropriate management. In addition, I am not aware of any evidence that supports superior outcomes with this approach. That said, in a patient has a high likelihood of needing thrombolysis we would often use IV heparin infusion with appropriate bolus (although there are data to support systemic thrombolysis alongside LMW heparin being similarly safe and efficacious as thrombolysis plus IV heparin for anticoagulation).

Do you treat below knee DVT?

Yes, when symptomatic (although I would not advocate screening for asymptomatic below knee DVT in e.g. orthopaedic surgery patients). There is a Cochrane review on this topic which would support the approach of treating these patients in view of reduced recurrence risk. In addition, anticoagulation would reasonably be expected to give a better symptomatic outcome too.

For Apixaban dose is it affected by body weight or it should be given 10 mg BD One week then 5 mg BD regardless of weight?

In VTE, there is no dose adjustment of apixaban for body weight. As discussed, use outside the range 50-120 kg is somewhat controversial, but increasingly common. If given in this context, the standard dosing that you describe should be used. As I discussed, I would recommend checking a peak drug level on one occasion to ensure that it lies within the expected range, but guidance on this may well change over time as more data become available.

Is anticoagulation indicated for cerebral venous sinus thrombosis without any infarct/bleed in MRI also?

Yes. The trials evidence for use of anticoagulation in CVST is limited, but those trials included in the Cochrane analysis which favoured anticoagulation in this setting did not exclude patients without infarct or haemorrhage. From my perspective, I would have significant concerns about risk of progression of thrombosis with resultant infarct +/- haemorrhage if anticoagulation was not used in this context, although the evidence to answer this specific question is limited at best.

Thank you for this talk. Just wanted to ask why Dabigatran isn't used much in the UK? Is there any situation wherein it is preferred more here?

I think many NHS trusts / health boards have made choices on DOAC procurement based on financial considerations historically and I can only presume that these have favoured other agents than dabigatran for most NHS organisations. Now, NICE has come out with a positive recommendation for use of apixaban or rivaroxaban ahead of other DOACs in the context of acute VTE, based on the fact that dabigatran and edoxaban both need a lead in period with a parenteral anticoagulant. Whilst there is a lack of head-to-head trails for the different DOACs, comparisons to warfarin at least suggest that Apixaban may have a preferable risk-benefit profile to the other DOACs (accepting that indirect comparisons of this type are not really valid) so some clinicians at least favour this agent when given free choice.

Regarding specific scenarios where dabigatran might be favoured, other than prior treatment failure of a Xa inhibitor where other alternatives are not suitable, CVST is the one scenario that I have come across where some clinicians have actively chosen dabigatran ahead of other DOACs. This is because it is the only DOAC with RCT evidence for its use in the adult population for this indication to date.

What anticoagulation would you start for a patient with a new thromboembolic event who had a raised APTT at baseline, with no known APS prior to presentation?

If there is a concern of APS (even if just based on a prolonged APTT) I would suggest anticoagulation with LMW heparin pending clarification of the cause of the prolonged APTT (specifically whether this might be due to a lupus anticoagulant). An alternative explanation for a prolonged APTT could be a significant bleeding disorder, so consideration should be given to performing urgent intrinsic pathway coagulation factor assays in this context to ensure that anticoagulation can be given safely (this is what we would do in my hospital in this scenario, especially as our APTT reagent is lupus insensitive).

What modicum of dose adjustment of DOACs would you suggest in a patient with advanced cancer with history of critical site bleeding?

This would depend on context. In the setting of acute VTE, there is no established role for dose adjustment of DOACs. If a DOAC is to be used in someone with acute VTE with previous critical site bleeding, then it would generally be with standard doses.

Whether a DOAC would be used in this context would depend on the bleeding history (recent vs historic; tumour related vs not related to tumour etc; site of bleeding; traumatic vs atraumatic; clear reversible contributing factors to bleeding etc).

I would often use an agent where more titration is possible in the scenario of high bleeding risk and high thrombotic risk, with LMW heparins allowing for more dose titration (or in extreme scenarios, unfractionated heparin).

That said, patient choice would be the key to the final agent chosen, especially in the context of advance cancer and if an informed decision is made that a DOAC is preferable to SC injection despite risk of bleeding, patient wishes should be respected.

Sorry, I missed why a dimer was repeated for the first case and when an USS was repeated again... why did we do that?

D-dimer wasn't repeated. The case was structured this way to illustrate that, if treating with empirical anticoagulation before diagnostic imaging, the D-dimer sample should be taken before anticoagulation is initiated because D-dimer will tend to fall with time on anticoagulation, which could arguably result in a falsely reassuring (ie low) D-dimer result if taken once the diagnosis is made as the patient will have been anticoagulated for 24 hours by this time (the real impact of this is likely to be small).

The patient had a high Wells score so went for scan without the D-dimer being considered (appropriately) but the D-dimer result was reviewed when this initial scan was negative. At this point, the D-dimer result could be used to stratify the risk of a DVT having been missed (or, more likely, a distal DVT being present and subsequently extending to be proximal over the coming week).

In the scenario of a high Wells score, negative first scan but positive D-dimer, the risk of DVT on repeat scan after a week was 3% in the Wells trial. NICE deemed this risk sufficient to justify the second scan after a week.

Has critical site bleeding been defined in the context of use of DOACs in advanced cancer?

Not to the best of my knowledge.

That said, the ANNEXA-4 trial (which is the basis for the license of Andexanet alfa) defined acute major bleeding as follows:

One or more of the following features: potentially life-threatening acute overt bleeding with signs or symptoms of hemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained); acute overt bleeding associated with a decrease in hemoglobin of at least 2 g per deciliter or a hemoglobin level of 8 g per deciliter or less if no baseline hemoglobin level was available (or an investigator's opinion that the hemoglobin level would fall to 8 g per deciliter or less); or acute symptomatic bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, intracranial, or intramuscular with the compartment syndrome).

In this, the critical sites are basically those where either haematoma is likely to expand with little tamponade effect, resulting in potentially life-threatening bleeding (retroperitoneal) or where expansion of bleed will be very poorly tolerated. I am not aware of any specific adaptation of this to cancer patients.

Have you ever come across 'Cocktail Purpura'?

I think this question may have been meant for Dr Watts. That said, I have come across a case where quinine from tonic water (no gin involved) was the likely cause of severe thrombocytopenia with an ITP-type presentation. The patient had been treated with dexamethasone for a couple of days before I met her, but on reviewing the history this was stopped. Things were already improving at

this stage and she has not suffered any subsequent recurrence of which I am aware, so this probably was a case of quinine-induced immune thrombocytopenia.

Fortunately, I don't think I have seen a case of thrombotic microangiopathy associated with quinine.

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Tips and pitfalls in the investigation of anaemia – Dr Adam Forbes

It is common in inpatients to see drops in Hb without symptoms, how much of a drop would you start to consider investigating further, rather than putting to 'dilatational' effect (e.g. following IV fluids)?
Like every other lab test a haemoglobin level has a margin for error; I would not worry about drops of up to 10g within an inpatient episode. Most inpatients will have their FBC repeated at some point, particularly if there has been an odd result identified, so a dilutional effect from iv fluid is easy to identify, and if the trend continues down then I suggest you would start basic investigation (with clinical correlation!) even without symptoms.

Is Iron level more accurate for IDA

Iron level is not accurate for IDA. The only reason we measure serum iron is to establish the transferrin saturation. It is the TSAT that is most helpful in supporting an IDA diagnosis, that or the reticulocyte haemoglobin.

What are your thoughts on testing hepcidin for ruling out hereditary hemochromatosis?

Genetic diagnostic pathways for HH are so well established there may not be much of a role, particularly as the current hepcidin ELISA platforms are not yet approved for routine use. Hepcidin measurement will also not exclude the rarer HH subtypes where it is resistance rather than deficiency that causes the iron overload phenotype.

If transferrin is low, is the saturation valid to interpret?
No test for iron status is perfect, but the value of using TSAT is that as a ratio (rather than the individual measured indices) some of the variability is ironed out. Unless you are dealing with rare genetic hypotransferrinemias, the TSAT is valid. In conjunction with all of your other lab tests and the clinical correlation of course.

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Platelets – the highs and lows; when to worry? Dr Emily Watts

Thank you for the great talk. I am looking to apply to Haem ST3 training. Would you recommend the newcastle deanery?

Definitely. The Northern Deanery is consistently rated either top or among the top in the country for trainee satisfaction. It's a relatively large area, so you end up spending time in geographically relatively far apart places in comparison to smaller deaneries, but it is very friendly, and I would say the experience and training is excellent. As an ST3 in Haem you spend roughly 3 years between the RVI and Freeman (both tertiary centre teaching hospitals) which gives you experience in all aspects of malignant haem including CAR T (we were the first centre outside of London to do this) in addition to specialist bleeding disorder experience in the Haemophilia Centre at the RVI. Rotations are 4 monthly whilst in the Newcastle hospitals covering haem onc, transfusion, lab/liaison, ward SPR, H&T, Paeds and a split rotation between Newcastle and Wansbeck, which is a really lovely DGH in Northumberland. You get a year between Sunderland and Gateshead (Sunderland – big level 2 DGH so AML/intensive chemo etc and Gateshead level 1 so more general experience but lovely and v friendly) and a year at James Cook in Middlesbrough (also big level 2 DGH). All are commutable from Newcastle (I did for my year in JCUH), but some choose to move around to be closer to jobs. Would say the unique thing about the NE is that all of the haematologists throughout get on really well and work v well as a large team, which doesn't happen everywhere. The TPD Annette Nicolle is really trainee focused and puts in huge amounts of effort to make the training work for people- she's fantastic.

The NE in general is a great place to live and work. Lovely people, relatively affordable still, very friendly and great outdoor places such as the coast and Northumberland on the doorstep, which London 3hours on the train and an airport which flights to Dubai and other hubs daily. Newcastle a great city to live in.

Only area in which I would say our training is relatively lacking in comparison to somewhere like London is in Haemaglobinopathies and Sickle, purely as we don't have that many patients with the condition , but numbers are increasing as you do get experience. If you saw yourself as a hardcore red cell haematologist perhaps not the place to get experience but other than that all in all would highly recommend.

Come and join us!

If a patient is diagnosed with iron deficiency causing thrombocytosis without anaemia, would you still consider referral for GI investigations to look for a cause for iron deficiency?

Depends on the context- needs history and examination. Most women who menstruate are iron deficient if you look for it as a result, and therefore unless other symptoms of concern need no further investigation. A lot of these are those which are referred high plts ?cause. If anaemic also then definitely, if >60 and no dietary or other clear medical cause then yes investigations also.

Thrombocytopenia: please can I request that patients with low platelet counts should also be tested for HIV? I can't emphasize how this would save the life of an infected and undiagnosed patient. Thanks

Think you perhaps must have missed the slides in relation to this when it was mentioned and listed as a cause of low platelets. It was on the slide with the causes of thrombocytopenia for both consumptive thrombocytopenia and failed production thrombocytopenia. Absolutely and as I explained during the talk and mentioned in slides on 2 occasions in relation to thrombotyopenia this is a key tests in any cytopenia and a HIV defining illness – we test anyone with an unexplained cytopenia for HIV/HepB and C.

Sorry - question to Dr Watt - Is assessment of platelet function/dysfunction ever indicated in thrombocytosis?

Not really- if bleeding we would check VWS in first instance. Would need something else to go on to do PFTs. In conditions such as uraemia etc there is platelet dysfunction for example but not that can be tested for in PFTs.

How high could you expect platelets to be, due to smoking alone without another cause?

Smoking doesn't cause high platelets. It will give a neutrophilia commonly and occasionally a monocytosis, +/- high Hb/Hct if significant lung disease but should not give high platelets on it's own. That said, smokers often have other causes of reactive thrombocytosis e.g. lung disease/COPD with infection/inflammation, secondary polycythaemia as a result of smoking etc. In a smoker with normal inflammatory markers and high platelets would send Jak2/Cal-R/MPL screen if no obvious cause and persistent.

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Causes of thrombocytopenia - increased consumption

- Infection/sepsis
- DIC
- Liver disease/hypersplenism
- Autoimmune disorders - e.g. SLE, APS
- HIV/leishmaniasis/malaria/Hep B/Hep C
- Gestational thrombocytopenia
- Haemolysis
- Pre-eclampsia/HELLP/aHUS
- Heparin Induced Thrombocytopenia (HIT)
- Thrombotic Thrombocytopenic Purpura
- ITP

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Investigations

- Fbc and film
- Coag and clauss fibrinogen +/ - D Dimer
- U&E/LFT
- LDH/DAT/haptoglobin/reticulocyte count
- B12/folate/ferritin
- Inflammatory markers
- TSH
- HIV/Hep B/Hep C
- Pregnancy test in women of child bearing potential

In selected patients:

- Antiphospholipid antibodies/ANCAs/ANA/RF
- Serum electrophoresis and serum free light chains
- HIT screen
- PNH screen
- ADAMTS 13 level
- EBV serology
- USS/CXR/cross sectional imaging
- Bone marrow aspirate and trephine

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Causes of thrombocytopenia- failed production

- Medication
- Infections- HIV/Hep B/C/parvovirus/EBV
- ETOH misuse
- Thyroid dysfunction
- B12/folate deficiency
- Haematological cancers- MDS, AML/ALL/APL/lymphoma/myeloma
- Chemotherapy
- Metastatic solid organ cancers