Barking, Havering and Redbridge University Hospitals NHS Trust

Guideline for the Prescribing of Direct Oral Anticoagulants (DOACs) for Lower Limb Venous Thromboembolism (VTE) in non-pregnant Adult Patients in Primary Care

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1. Introduction

DOACs are licensed and approved by NICE for the treatment of acute VTE and the prevention of recurrence. Adult patients between 40 and 120kg with a new lower limb deep vein thrombosis (DVT) or pulmonary embolism (PE) can be considered for DOAC therapy as per Barking Havering and Redbridge Hospital Trust (BHRUT) guidelines. This guideline provides information on how to safely anticoagulate patients with a DOAC including monitoring and follow up. While all DOACs are available for prescribing at BHRUT in the context of treating VTE; rivaroxaban should be considered as the DOAC of choice unless there are patient specific factors that favour another DOAC. This guideline does not contain information on prescribing DOACs for alternate indications, if needed please consult the relevant Trust guideline on the intranet.

1.1 Aims

To offer patients the most appropriate treatment for suspected and confirmed lower limb VTE in primary care.

1.2 Background

Low molecular heparins (LMWH) and vitamin K antagonists (VKAs) have been the mainstay of VTE treatment for many years. Apixaban, dabigatran, edoxaban and rivaroxaban have all been licenced for the treatment and recurrence of lower limb DVTs and PEs.

2. Management

Patients diagnosed with an acute or who are being treated for a suspected VTE should be offered Apixaban or Rivaroxaban or alternative anticoagulation.

DOACs are not suitable if any of the following apply.

- Creatinine clearance less than 30mls/minute using actual bodyweight and the Cockroft & Gault equation.
- Massive PE requiring thrombolysis.
- Active cancer (discuss with haematology if a DOAC is the patients preferred choice).
- Active bleeding or in patients who are at high risk of bleeding (discuss with haematology):
    - Haemophilia of von Willebrand's disease.
    - Active peptic ulcer, oesophageal varices, aneurysm, proliferative retinopathy.
    - Recent organ biopsy.
    - Lesion or condition at risk of significant major bleed e.g. recent trauma or surgery to the head, eyes, orbits or spine.
    - Recent stroke(less than 4 weeks).
    - Confirmed intracranial or intraspinal bleed usually within the last 4 weeks.
    - Infective endocarditis.
    - Platelets $<75x10^9/L$
    - Systolic blood pressure greater than 180mmHg or diastolic blood pressure greater than 110mmHg.
    - APTT > 1.5 and/or INR>1.5 with no history of vitamin K antagonist use.
    - Liver enzymes (LFTs) greater than 2x upper limit of normal.
- Prosthetic or metal heart valves.
- Antiphospholipid Syndrome.
- The patient is already taking warfarin or other vitamin K antagonist.
- The patient is already taking a DOAC.
- The patient is already administering Low Molecular Weight Heparin (LMWH).
- The patient is being treated for a suspected or confirmed upper limb DVT (if a DOAC is the preferred option discuss with haematology).
- The patient weighs <40kg or >120kg (if a DOAC is preferred discuss with haematology).
- Contraindications to their use see individual product SPC for further information.

- The patient is taking any interacting medication(s) which may reduce or increase plasma levels of the DOAC. If unsure, please discuss with pharmacists or medicines information on ext 3354.
- Pregnant or breast-feeding NB women of child bearing age must be on adequate contraception (NB this may apply to many women of child bearing age presenting with a VTE whom may be advised to stop taking oral contraceptives. Adequate family planning advice is an important aspect of VTE management in young women).

If a DOAC is considered appropriate discuss the options with the patient and or carer. If they decide to be treated with a DOAC see below for dosing and monitoring.

3. Choice of DOAC

In the absence of direct head-to-head trials the DOAC with the lowest acquisition cost should be used as first line for the treatment of suspected or confirmed VTE, at the times of writing this is rivaroxaban.

Alternative DOACs are available in primary care for the treatment of confirmed or suspected VTE. These include apixaban, dabigatran & edoxaban. Caution should be exercised for the initial treatment of suspected or confirmed VTE if dabigatran or edoxaban are to be used as they can only be commenced after an initial 5 days of parental anticoagulation i.e. Low Molecular Weight Heparin (LMWH).

Dabigatran and Edoxaban are reserved for the treatment of VTE in secondary care only after a VTE has been confirmed.

3.1 Baseline Investigations

- Prior to commencing anticoagulation, all patients must have the following baseline investigations:
  - Full Blood Count
  - Creatinine, Urea and Electrolytes
  - Liver Function Test/Enzymes
  - Prothrombin time (PT) and activated partial thromboplastin time (APTT)

- All patients commencing DOACs must also be weighed and their weight recorded clearly in the patient's healthcare records and on the front of the drug chart.

- Patients commencing DOACs must have their Creatinine Clearance (CrCl) calculated using the Cockroft-Gault method rather than the estimated GFR (eGFR):

  CrCl **male** (mL/min) = $\frac{(140 - \text{age}) \times \text{Actual Body Weight (kg)} \times 1.23}{\text{serum creatinine}}$

  CrCl **female** (mL/min) = $\frac{(140 - \text{age}) \times \text{Actual Body Weight (kg)} \times 1.04}{\text{serum creatinine}}$

3.2 DOACs in Cancer

Patients with active cancer i.e. those patients receiving antimitotic treatment; or diagnosed within the past 6 months; or recurrent or metastatic; or inoperable. This definition excludes squamous skin cancer and basal cell carcinoma. Patients with cancer associated VTE should receive anticoagulation for a minimum of 3-6 months. After reviewing tumour site, bleeding risk, on-going risk factors, drug interactions (particularly if concurrent use of P-glycoprotein inhibitors) and patient preference consider extended therapy for the duration of active malignancy or whilst on anticancer therapy.

The standard of care in this patient group remains LMWH. The use of DOACs for the treatment of VTE in cancer is considered to be "off-label" but has been approved by NICE for use in this indication. Patients consent should be obtained before the initiation as per the Use of Unlicensed Medicines Policy. Clinical trials in the use of DOACs in patients with active cancer have shown equivalent efficacy for VTE prevention but with increased risk of bleeding, particularly in patients with gastro intestinal (GI) malignancy (gastric, oesophageal, hepatobiliary, pancreatic and colorectal).

Apixaban should be offered as the first line option for the treatment of suspected or confirmed VTE in patients with active cancer as a single RCT demonstrated non inferiority without increased risk in major bleeding, however further trials are required to validate this.

Avoid in patients with GI malignancy due to increased risk of bleeding. GI malignancies include pancreatic and liver cancers in addition to luminal cancers.

3.2.1 Avoid DOACs in following groups:

- GI malignancy (gastric, oesophageal, hepatobiliary, pancreatic and colorectal)
- Factors influencing drug absorption, e.g. mucositis, colitis, nausea and vomiting.
- Chronic kidney disease stage 4-5 (GFR <30mls/ml)

For such patients, LMWH remains preferred choice due to parenteral administration, superior safety data and ease of dose titration.

3.2.2 Use with caution in the following groups:

Patients in this group are likely to have higher bleeding risk with DOACs in the context of cancer and the patient should be consulted appropriately:

- Chronic Kidney disease stage 3a to 3b (30mls/min< GFR <60mls/min)
- Genitourinary cancer
- Brain metastases
- Recent surgery (within 2 weeks)
- Concurrent use of antiplatelets or bevacizumab (on-going or within 6 weeks)

4. Dosing in Extremes Bodyweight

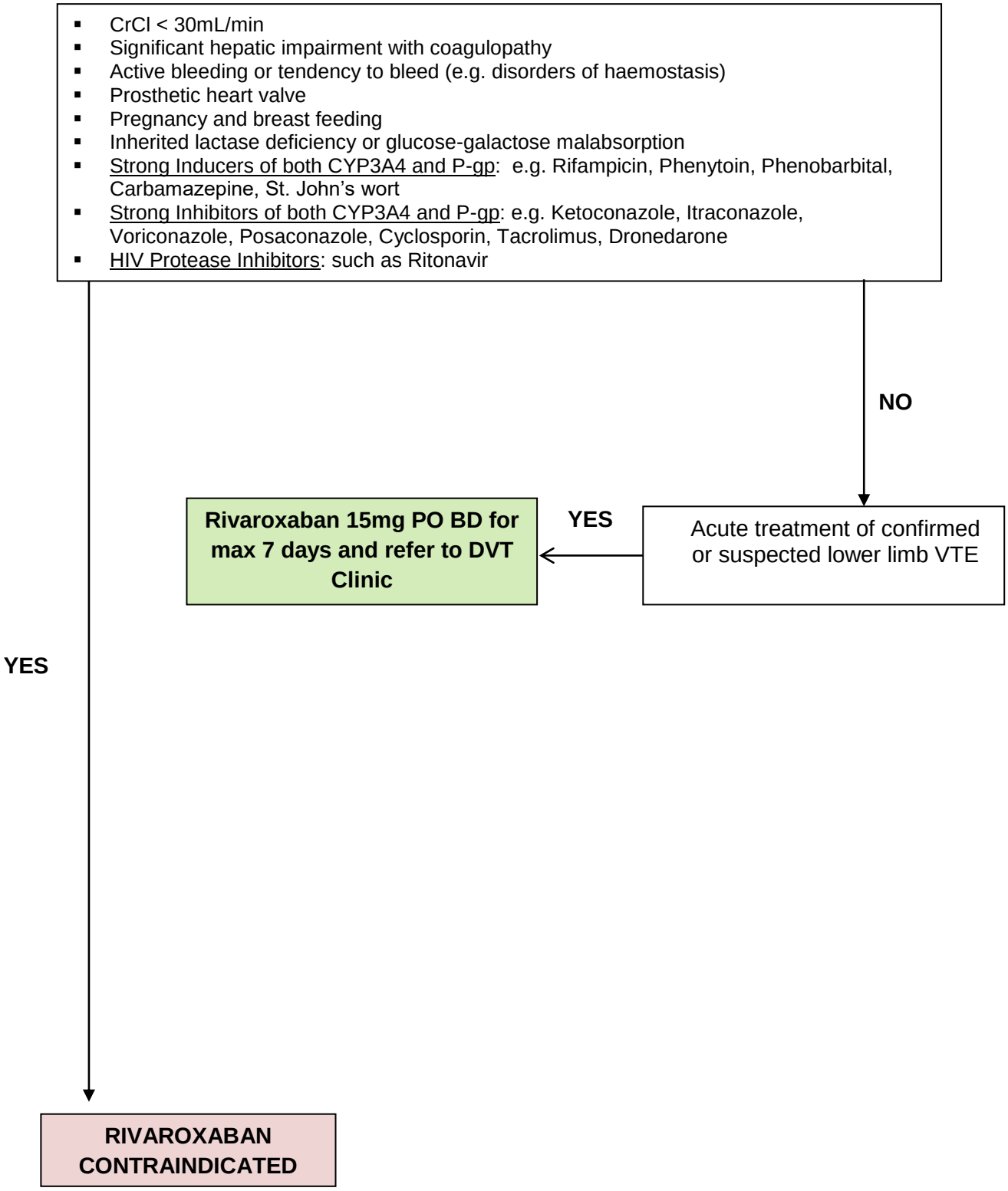
DOACs are characterised by a fixed dosing regimen. Dose adjustments for patients with high body mass index (BMI) are not recommended and data regarding the efficacy and safety of DOACS at extremes of bodyweight is limited.

1) Patients should be counselled regarding the relative uncertainty of efficacy of the DOACs in patients with a weight of less than 50kg or greater than 120 kg, compared to warfarin where

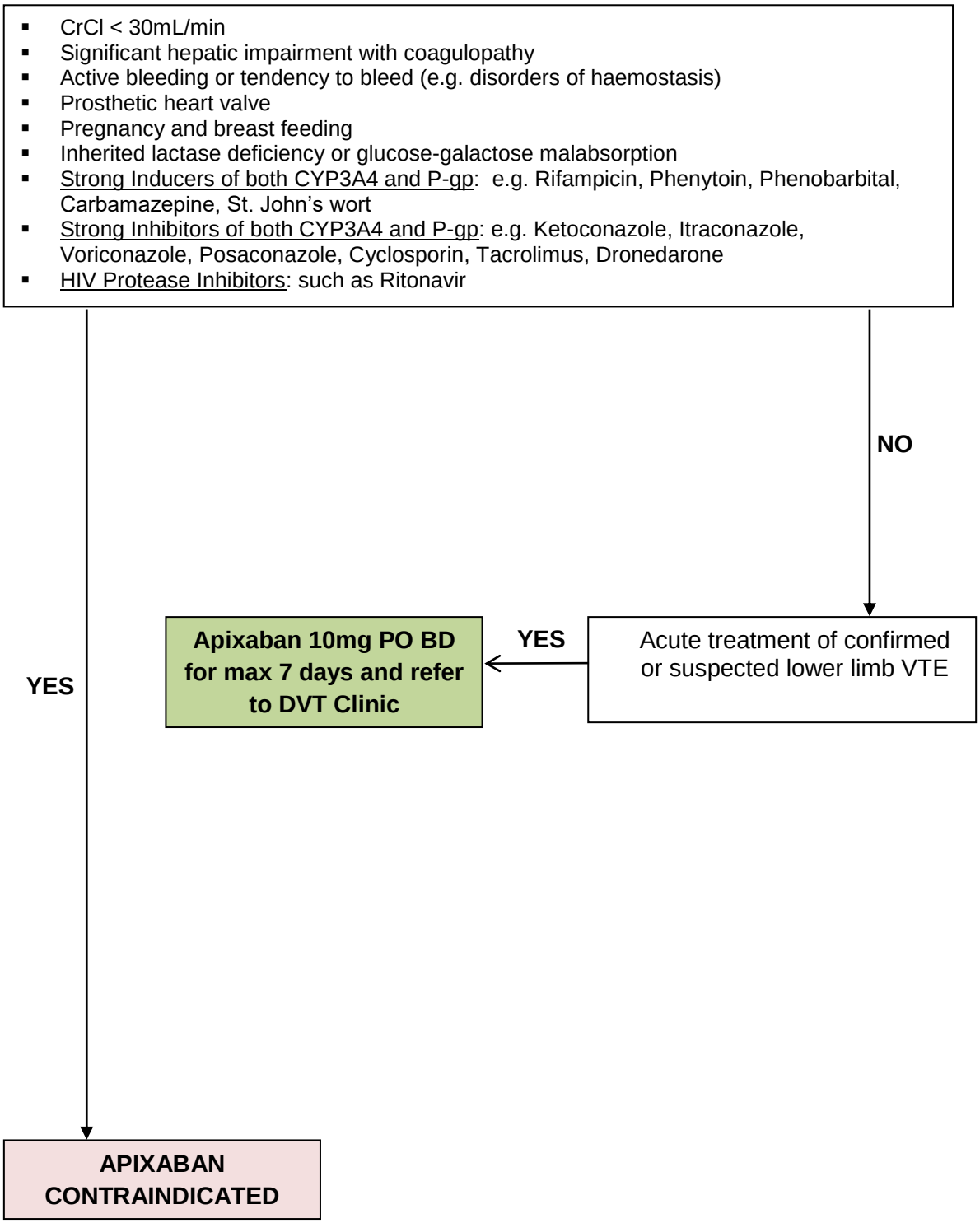
INR monitoring ensures dosing is therapeutic, or Low Molecular Weight Heparin (LMWH) where there is greater clinical experience in these patient cohorts.

2) A shared decision should be made between the prescriber and the patient to initiate a DOAC for the treatment of suspected lower limb VTE. Subsequently the patient requires treatment for confirmed DVT the decision of what agent will be decided by the patient in conjunction with a specialist nurse or haematologist.

5. Rivaroxaban Dosing



6. Apixaban Dosing



8. Counselling, Discharge and Referral Pathway for DOACS

8.1 Responsibility of prescribing clinician and referral pathway

- In the absence of direct head to head trials for the treatment of VTE it is recommended that the DOAC with the lowest acquisition cost and does not require 'bridging' with parental anticoagulant should be selected as initial therapy. At the time of writing this is rivaroxaban if initiated on presentation.
- The patient should be **supplied with an alert card** and **information booklet**.
- A patient **must** present to the DVT Clinic with a copy of an approved referral proforma (see Appendix A Deep Vein Thrombosis GP Referral Proforma and Appendix B Deep Vein Thrombosis BHRUT & Urgent Treatment Centre Referral Proforma)
- The prescribing clinician must **refer the patient to the anticoagulant clinic at Queens Hospital 0170843500 ext 6216 Monday to Friday 08:30 to 16:00 excluding Bank Holidays.**

9. Supply, Administration, Monitoring and Side Effects of DOACs

9.1 Supply

The patient should be supplied with a prescription or a pre-labelled DOAC, at the appropriate dose for the treatment of suspected lower limb VTE for a maximum of 7 days.

9.2 Administration

- **Apixaban** tablets can be taken **with or without food** at the same times twice daily. The tablets are suitable for use in pill boxes. For patients who are unable to swallow tablets, Apixaban can be crushed and mixed with water. The crushed tablet can also be administered in a small amount of water via an enteral feeding tube into the stomach.
- **Edoxaban** tablets can be **taken with or without food** at the same time each day. The tablets are suitable for pill boxes. For patients who are unable to swallow tablets, Edoxaban 60mg tablets can be crushed and mixed with a small amount of water or apple puree. The crushed tablet can also be administered in a small amount of water via an enteral feeding tube into the stomach. **There is currently no data available on crushing edoxaban 30mg tablets.**
- **Rivaroxaban** tablets must be taken **with food** at the same time each day. The tablets are suitable for use in pill boxes. For patients who are unable to swallow tablets, rivaroxaban can be crushed and mixed with water. The crushed tablet can also be administered in a small amount of water via an enteral feeding tube into the stomach.

9.3 Monitoring

- Routine monitoring of DOACs is not routinely needed for patients who are not at extremes of bodyweight.
- If there is any clinical need to assess anticoagulant effects of DOACs, this will be decided in anticoagulation clinic if VTE confirmed as per established BHRUT guidelines.

9.4 Side Effects

- As with any anticoagulant, patients need to be warned about potential bleeding complications, both minor and major. Patients should be educated to recognise signs of GI bleeding (e.g. black stools).

- Usually encountered side-effects of DOACs are listed in Table 1 below for an exhaustive list please refer to products SPC:

Table 1: DOAC Side Effects

Drug	Side-effect
Apixaban	Epistaxis, haematuria, easy bruising
Edoxaban	Epistaxis, nausea, haematuria, rash, pruritus, abnormal LFTs
Rivaroxaban	Headache, epistaxis, rash, oedema, abnormal LFTs

11. References

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4. EMC. *Rivaroxaban SPC. https://www.medicines.org.uk/emc/product/2793/smpc (accessed 13/08/2019).*
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6. EMC. *Edoxaban SPC. https://www.medicines.org.uk/emc/product/2878/smpc (accessed 13/08/2019)*

Appendix A Deep Vein Thrombosis GP Referral Proforma

DEEP VEIN THROMBOSIS
GP REFERRAL PROFORMA

Barking, Havering and Redbridge NHS University Hospitals NHS Trust

ALL SECTIONS MUST BE COMPLETED IN FULL
A COPY OF THIS PROFORMA MUST BE GIVEN TO THE PATIENT FOR THEM TO HAND TO THE DVT CLINIC NURSE #6216

Two-Level DVT Wells Score		
Clinical Feature	**Points**	**Score**
Active Cancer (treatment ongoing, within 6/12 or palliative).	1	
Paralysis, paresis or recent plaster immobilisation of the lower limb.	1	
Localised tenderness along the distribution of the deep vein system.	1	
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia.	1	
Entire leg swollen	1	
Calf swelling at least 3cms larger than asymptomatic leg.	1	
Pitting oedema confined to the symptomatic leg.	1	
Collateral/dilated superficial veins (non-varicose).	1	
Previously documented DVT.	1	
An alternative diagnosis is at least as likely as DVT.	-2	
Total Score		

Calf measurements	
Left	Cm
Right	Cm

DVT likely (2 points or more):

DVT unlikely (1 point or less):

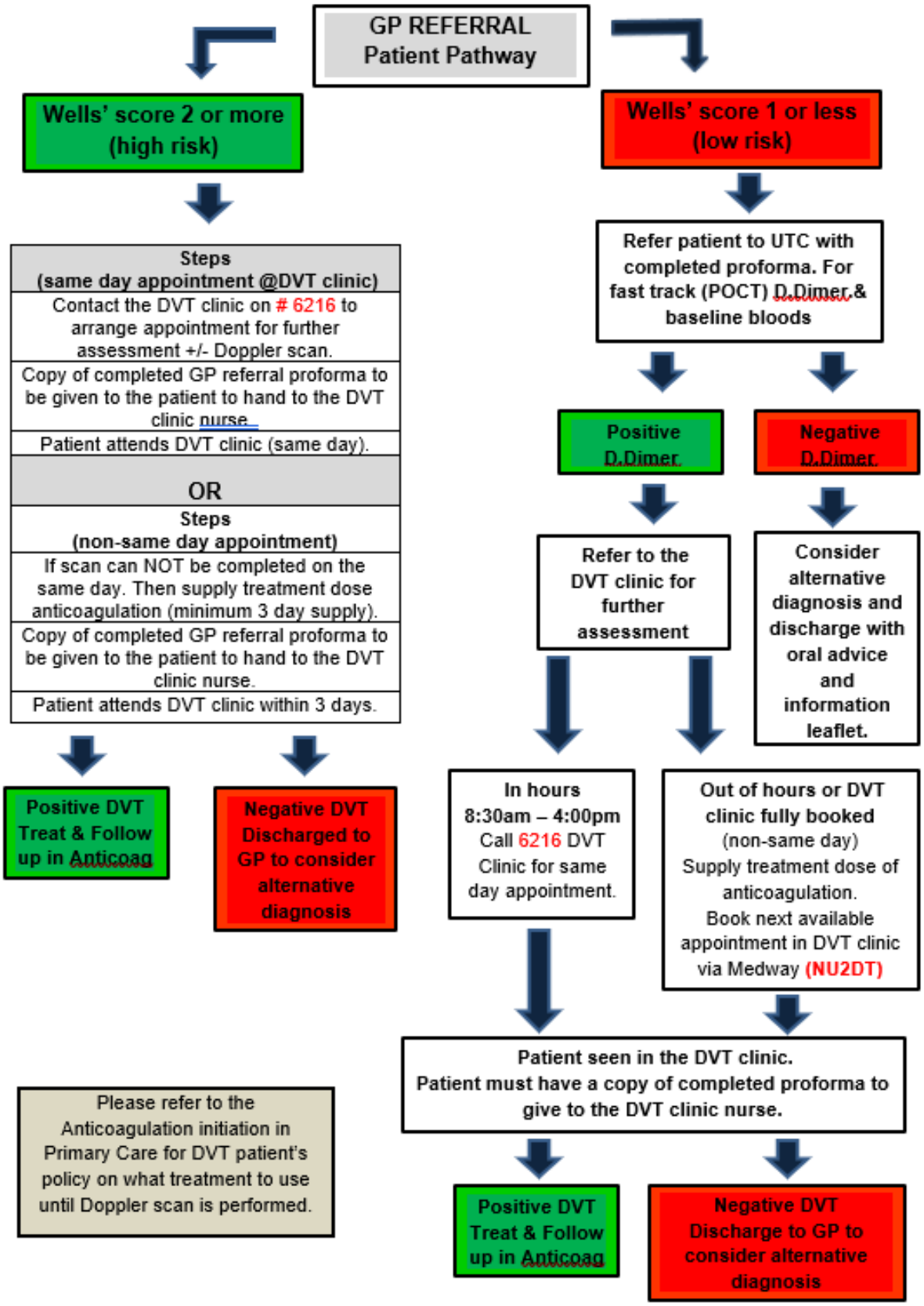
See over for pathway

Patient No:	**Date:**	**Time seen:**
Date of birth:	**Seen by – print name:**	
Name:	**Position:**	
Address:	**GMC/NMC Number:**	
Telephone No:	**Referring department:**	

Observations	
Temp	
Resps	
Pulse	
BP	/
O2 Sats%	
Weight	

Presenting Complaint:

Past medical history:


GP REFERRAL
Patient Pathway
Wells' score 2 or more (high risk)
Wells' score 1 or less (low risk)
Steps
(same day appointment @DVT clinic)
Contact the DVT clinic on # 6216 to arrange appointment for further assessment +/- Doppler scan.
Copy of completed GP referral proforma to be given to the patient to hand to the DVT clinic nurse.
Patient attends DVT clinic (same day).
OR
Steps
(non-same day appointment)
If scan can NOT be completed on the same day. Then supply treatment dose anticoagulation (minimum 3 day supply).
Copy of completed GP referral proforma to be given to the patient to hand to the DVT clinic nurse.
Patient attends DVT clinic within 3 days.
Positive DVT Treat & Follow up in Anticoag
Negative DVT Discharged to GP to consider alternative diagnosis
Refer patient to UTC with completed proforma. For fast track (POCT) D.Dimer & baseline bloods
Positive D.Dimer
Negative D.Dimer
Refer to the DVT clinic for further assessment
Consider alternative diagnosis and discharge with oral advice and information leaflet.
In hours
8:30am – 4:00pm
Call 6216 DVT Clinic for same day appointment.
Out of hours or DVT clinic fully booked
(non-same day)
Supply treatment dose of anticoagulation.
Book next available appointment in DVT clinic via Medway (NU2DT)
Patient seen in the DVT clinic.
Patient must have a copy of completed proforma to give to the DVT clinic nurse.
Please refer to the Anticoagulation initiation in Primary Care for DVT patient's policy on what treatment to use until Doppler scan is performed.
Positive DVT Treat & Follow up in Anticoag
Negative DVT Discharge to GP to consider alternative diagnosis

Appendix B Deep Vein Thrombosis BHRUT & Urgent Treatment Centre Referral Proforma

DEEP VEIN THROMBOSIS
PROFORMA – BHRUT & URGENT TREATMENT CENTRE

Barking, Havering and Redbridge NHS University Hospitals NHS Trust

ALL SECTIONS MUST BE COMPLETED IN FULL
A COPY OF THIS PROFORMA MUST BE GIVEN TO THE PATIENT FOR THEM TO HAND TO THE DVT CLINIC NURSE #6216

Two-Level DVT Wells Score		
Clinical Feature	**Points**	**Score**
Active Cancer (treatment ongoing, within 6/12 or palliative).	1	
Paralysis, paresis or recent plaster immobilisation of the lower limb.	1	
Localised tenderness along the distribution of the deep vein system.	1	
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia.	1	
Entire leg swollen	1	
Calf swelling at least 3cms larger than asymptomatic leg.	1	
Pitting oedema confined to the symptomatic leg.	1	
Collateral/dilated superficial veins (non-varicose).	1	
Previously documented DVT.	1	
An alternative diagnosis is at least as likely as DVT.	-2	
Total Score		

Calf measurements	
Left	Cm
Right	Cm

DVT likely (2 points or more):

DVT unlikely (1 point or less):

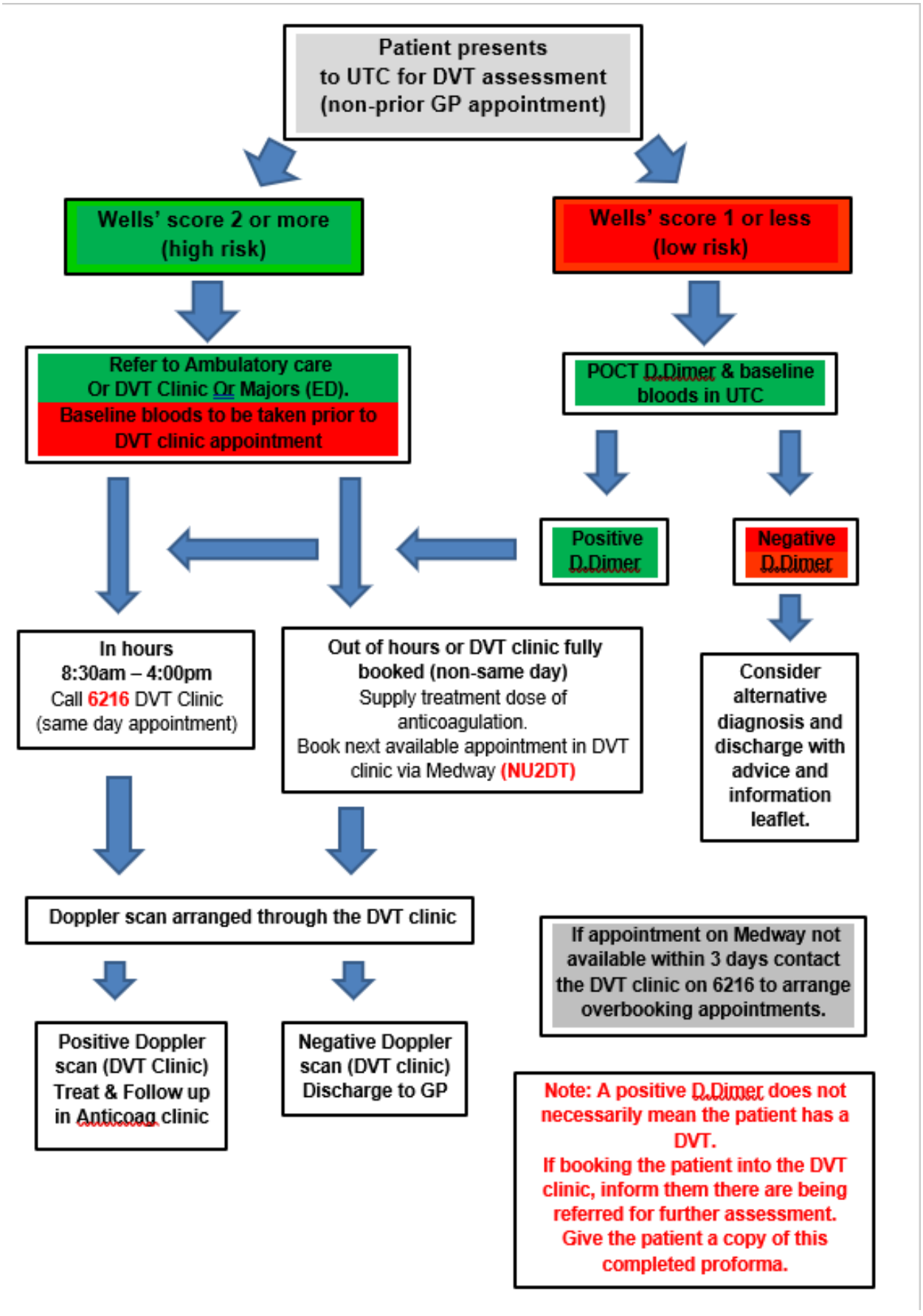
See over for pathway

Patient No:	**Date:**	**Time seen:**
Date of birth:	**Seen by – print name:**	
Name:	**Position:**	
Address:	**GMC/NMC Number:**	
Telephone No:	**Referring department:**	

Observations	
Temp	
Resps	
Pulse	
BP	/
O2 Sats%	
Weight	

Presenting Complaint:

Past medical history:


Patient presents
to UTC for DVT assessment
(non-prior GP appointment)
Wells' score 2 or more
(high risk)
Wells' score 1 or less
(low risk)
Refer to Ambulatory care
Or DVT Clinic Or Majors (ED).
Baseline bloods to be taken prior to
DVT clinic appointment
POCT D.Dimer & baseline
bloods in UTC
Positive
D.Dimer
Negative
D.Dimer
In hours
8:30am – 4:00pm
Call 6216 DVT Clinic
(same day appointment)
Out of hours or DVT clinic fully
booked (non-same day)
Supply treatment dose of
anticoagulation.
Book next available appointment in DVT
clinic via Medway (NU2DT)
Consider
alternative
diagnosis and
discharge with
advice and
information
leaflet.
Doppler scan arranged through the DVT clinic
If appointment on Medway not
available within 3 days contact
the DVT clinic on 6216 to arrange
overbooking appointments.
Positive Doppler
scan (DVT Clinic)
Treat & Follow up
in Anticoag clinic
Negative Doppler
scan (DVT clinic)
Discharge to GP
Note: A positive D.Dimer does not
necessarily mean the patient has a
DVT.
If booking the patient into the DVT
clinic, inform them there are being
referred for further assessment.
Give the patient a copy of this
completed proforma.