South West Essex NHS

Basildon and Thurrock University Hospitals NHS
NHS Foundation Trust

Dabigatran Shared Care Guideline (SCG)

Dabigatran SCG for the prevention of stroke and embolism in adult patients with nonvalvular atrial fibrillation

Introduction

Indication and Licensing

Dabigatran is the first of the novel oral anticoagulants (NOAC) to be licensed for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure (e.g. New York Heart Association (NYHA) Class 2 or above)
- Age > 75 years
- Age > 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

Dabigatran is a direct thrombin inhibitor and has been trialled in a large randomised controlled trial with 18,000 patients with non valvular AF and at least one additional risk factor for stroke (i.e. CHADS2score >2). The primary endpoint was a composite of prevention of stroke and systemic embolism; at a median two-year follow-up the lower dose of dabigatran (110 mg twice daily) was non-inferior to warfarin for the primary endpoint (1.54% per year vs. 1.71% per year respectively, $p < 0.001$), whilst the higher dose (150 mg twice daily) was found to be statistically superior (1.11% per year vs. 1.71% per year, $p < 0.001$). Due to its selective inhibition of one clotting factor, the anticoagulation effects are more predictable and as such there is no requirement for regular monitoring (unlike warfarin that requires regular INR checking).
Within the East of England, warfarin remains the drug of choice for individuals requiring anticoagulation in nonvalvular atrial fibrillation. Dabigatran can be prescribed for the management in non-valvular atrial fibrillation as outlined in flow chart in Appendix I and requires prior approval (Appendix II).

Patient Pathway

Clinical speciality	Prescribing initiated by	Prescribing continued by	Monitored by	Duration of treatment
Cardiology Haematology Stroke	Hospital consultant	GP following initiation by hospital	GP following initiation by hospital	Life long*

*temporary discontinuation for surgical procedures advised, see appendix III

Patients are to be initiated in the first instance via a consultant (cardiology, haematology, stroke). One month supply to be made by hospital when initiated.

Treatment should continue indefinitely on confirmation of nonvalvular atrial fibrillation that requires anticoagulation. Treatment should be reviewed (at least annually) and an assessment made for new contraindications to ongoing anticoagulation with dabigatran (e.g. temporary discontinuation for surgery, marked decline in renal function and increased bleeding risk (see

below for further advice on bleeding risk)). Where new contraindications are found, treatment is to be reviewed and anticoagulation therapy withdrawn if risks are deemed to outweigh benefits. If therapy is to be withdrawn, refer to specialist to assess and initiate suitable antithrombotic therapy.

Ongoing compliance should be reviewed on a regular basis, the duration and method of compliance assessment should be determined by the GP and patient characteristics.

NORMAL DOSE AND ADMINISTRATION
Dabigatran is available as 2 strengths for prevention of stroke and systemic embolism in atrial fibrillation. Both are hard capsules containing 110mg or 150mg.

Usual dose:
150mg capsule twice daily* to be swallowed whole with or without food.
Patients are **NOT** to open the capsule as this can lead to increased bioavailability and increases the risk of bleeding.
*Unless dose reduction indicated as below

Dose alterations:

Increased risk of bleed:
- If bleeding risk is initially assessed as high (in accordance with HAS-BLED score), patients are to be considered for 110 mg capsule twice daily or no anticoagulation (if no anticoagulation refer to specialist for antithrombotic of choice). Clear documentation should be made as to reason for dose reduction.
- For subjects with gastritis, oesophagitis, or gastroesophageal reflux, a dose of 110 mg capsule twice daily should be considered due to the increased risk of major gastro-intestinal bleeding (and where appropriate gastro protection prescribed concomitantly e.g. PPI)
- Individuals at low body weight (<50kg) may be more prone to bleeding and as such monitored closely and dose reduction (110mg twice daily) considered.
- Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia, more details below). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (as CHADS2 or CHADS2VASc score increases, the benefits of treatment with anticoagulation increase).
- A coagulation test (see below) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose 110 mg twice daily is recommended.
- If clinically relevant bleeding occurs, treatment should be interrupted and reviewed prior to re initiation.

Age:
- Patients between 75-80 years should be risk assessed for bleeding as above and dose reduced if deemed necessary.
- Patients aged 80 years or above should be given 110 mg capsule twice daily due to the increased risk of bleeding in this population.

Renal impairment:
- Renal function should be assessed by calculating creatinine clearance prior to initiation of treatment with dabigatran to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min).
- CrCl 50 to 80 mls/min; no adjustment
- CrCl 30 to 49mls/min; 150mg twice daily, for patient at increased risk of bleeding (see above), consider dose reduction
- CrCL <30 mls/min; contraindicated

Monitoring

Routine monitoring with coagulation test is generally not indicated unless the patient has fluctuating renal function or has bleeding symptoms

Parameter	Renal function (Creatine clearance - CrCl)
Target level	CrCl 50 to 80 mls/min; no adjustment required CrCl 30 to 49 mls/min; 150mg twice daily, but for patients with risk factors for bleeding, consider dose reduction to 110mg twice daily CrCl <30 mls/min; contraindicated, avoid use
Frequency of monitoring	Assess renal function prior to treatment to ensure appropriate starting dose then while on treatment renal function should be assessed at least once a year (or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate such as hypovolemia and dehydration).
Action	Dose reduction may be required based on initial renal function. If renal function declines rapidly may need to temporarily withhold therapy and review prior to restarting.

Parameter	Minor bleeding (or those at high risk of bleed on treatment)
Target level	The activated partial thromboplastin time (aPTT) test is widely available and provides an approximate indication of anticoagulation intensity achieved with dabigatran. Inpatients who are bleeding or at risk of bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution. If required and following haematology advice, a more sensitive quantitative tests such as calibrated diluted Thrombin Time (dTT) could be performed. If the dTT is used, dabigatran concentrations above 200 ng/ml, measured at trough after 150 mg twice daily dosing (10-16 hours after the previous dose), are associated with an increased risk of bleeding and may require a dose reduction to 110mg twice daily – If required, close liaison with haematology will be necessary prior to ordering and interpreting the results of these tests.
Frequency of monitoring	Only if excessive minor bleeding observed or patient at high risk of bleed and on 150mg twice daily, a raised APTT should prompt a dose reduction if clinically indicated
Action	Dose reduction if clinically indicated and / or liaison with haemotology

Parameter	Adherence
Target level	100%
Frequency of monitoring	Prior to initiation, likely compliance should be considered and discussed with the patient. Following initiation, compliance should be checked and reinforced at a minimum of annually although this is left at the discretion of the physician.
Action	If compliance likely to be low, consider alternative anticoagulation that can be monitored.

Key adverse effects and action

Adverse effects	Symptoms/ signs (specify what would prompt action	Actions
Minor bleeding	Self terminating minor bleeding from scratches, cuts, nose bleeds, gum bleeding etc. may be experienced. If these are frequent or patient / physician concerned - contact local haematology department for advice	The degree of bleeding will dictate action. If minor bleeding is infrequent and self terminates, patient can be reassured. If minor - self terminating episodes occur frequently, consider dose reduction to 110mg twice daily. If already on lower dose or concerns are raised - liaise with haematology for advice.
Moderate bleeding	Bleeding that does not stop with reasonable intervention should be referred to local A&E, if in doubt contact local haematology department for advice	The degree of bleeding will dictate the action. If bleeding stops spontaneously and patient taking 150mg twice daily, consider omitting a day's dose and reducing to 110mg twice daily. If already on lower dose or concerns are raised - liaise with haematology for advice. For bleeding that does not stop with intervention, send patient to local A&E.
Major bleeding	Major bleeding in the RELY trial was defined as a reduction in haemoglobin of at least 20g/L or leading to a transfusion of at least 2 units of blood. If bleeding presents as clinically significant send patient to local A&E or call 999	Immediate referral to secondary care, protocol in place to manage major bleeding available via A&Es
GI	Dyspepsia	Consider gastro protection in accordance with local guidance. If no further improvement, consider alternatives or referral to specialist

This only lists important ADRs - For comprehensive information on cautions, contra-indications and interactions, please refer to the current British National Formulary and Summary of Product Characteristics

Detail any important cautions

Results from the RELY study suggest that there may be an increased risk of myocardial infarction (MI) in patients taking dabigatran. Although the overall rate of MI was relatively small (0.82, 0.81, and 0.64 % per year for dabigatran 110 mg twice daily, 150 mg twice daily and warfarin respectively) the relative risk for dabigatran was 29 % and 27 % compared to warfarin. It is not clear whether this increase risk is due to dabigatran or loss of cardioprotective benefit of warfarin, for this reason, until further information is available, dabigatran is not to be used in patients with pre existing MI.

Drug interaction:
Strong P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels and as such patients at high risk of bleeding should have a reduced dose. Strong P-gp inducers (such as rifampicin, St. John`s wort, carbamazepine, or phenytoin) are expected to result in decreased dabigatran plasma concentrations, and should be avoided.

Pregnancy and breast feeding
The safety of dabigatran has not been established in pregnant or lactating women; as such use in these patients is to be avoided.

Shared care guideline
SCG is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Consultant
1. Ensure that the patient/carer is an informed recipient of dabigatran.
2. Ensure that patients understand dabigatran treatment and monitoring (e.g. renal function) or follow up that is required (using advocacy if appropriate).
3. Ensure baseline investigations are normal before commencing treatment. Give the patient a patient held anticoagulant card.
4. Initiate treatment and prescribe until the GP formally agrees to shared care. Supply the
1. first month of treatment
5. Send a letter to the GP requesting shared care for the patient following completing the prior approval form and receiving agreement from primary care prescribing team.
6. Send a letter/results notification to the GP after the clinic meeting confirming the current dose and most recent blood results.
7. Evaluation of any reported adverse effects by GP or patient.
8. Advise GP on review, duration or discontinuation of treatment where necessary.
9. Ensure that backup advice is available at all times.

General Practitioner
1. Reinforce the patient's understanding of the nature, effect and potential side effects of dabigatran before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate. Monitor patient's overall health and well-being.
2. Report any adverse events to the consultant, where appropriate.
3. Report any adverse events to the CSM, where appropriate.
4. Help in monitoring the progression of disease
5. Prescribe the drug treatment as described
6. Undertake monitoring outlined in monitoring section once shared care agreed

CCG
1. To provide feedback to trusts via Trust Medicines Committee.
2. To support GPs in decision making and facilitate appropriate use and monitoring of dabigatran.
3. To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment (dabigatran).
3. Report any changes in disease symptoms to GP and/or specialist
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease
5. Take/ administer dabigatran as prescribed

Contact details

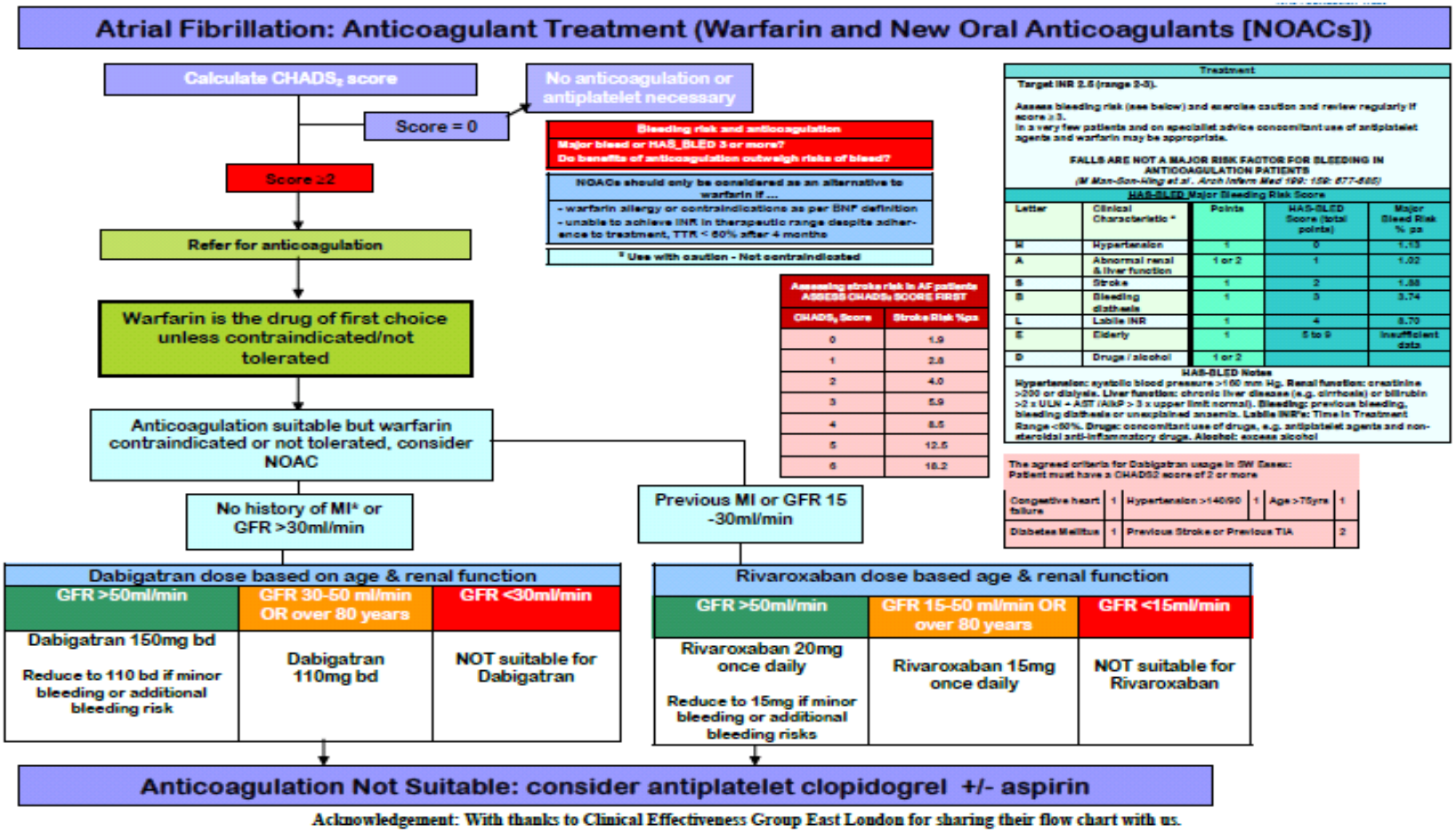
Initial contact should be made with the initiating consultant. Contact consultant haematologist if haematologist is the initiating consultant or on the advise of the initiating consultant.

Initiating consultant at BTUH Name (please print):	Please insert: Contact details:
CCG prescribing team	Contact details:

Acknowledgement:

These shared care guidelines are based on the shared care guidelines by NHS North East London Cardiovascular and Stroke Network

Appendix I



Acknowledgement: With thanks to Clinical Effectiveness Group East London for sharing their flow chart with us.

Appendix II

Approval Form for Dabigatran and Rivaroxaban Usage in Atrial Fibrillation Patients

Patient name: DOB:

Patient Hospital no: NHS no:

This form is for completion by **haematology, stroke and cardiac consultants ONLY**. Forms filled in by any other grade or speciality will be declined. Only patients meeting the agreed criteria will be supplied with NOACs (a prescription is also required).

The agreed criteria for Dabigatran usage in SW Essex are:

Patient must have a CHADS2 score of 2 or more

Congestive heart failure	1	Hypertension >140/90	1	Age >75yrs	1
Diabetes Mellitus	1	Previous Stroke or Previous TIA			2

**Please circle the relevant risk factors*

Plus the patient should have **one** of the following
**Please circle which apply*

Clinical contraindications to warfarin causing drug discontinuation

Yes	No	The C/Is are:

Allergy to warfarin

Yes	No	The allergy is:

Experience of substantial side effects with warfarin causing drug discontinuation

Yes	No	The S/Es are:

A further embolic event whilst on warfarin if eligible for 150 mg dabigatran

Yes	No

Time in therapeutic range for warfarin of less than 60% for 4 months i.e. poor control (Note: concordance issues must be fully explored and resolved before looking at poor control)

Yes	No

Patient requiring domiciliary phlebotomy

Yes	No

Please send completed form with the prescription to Fatemeh Leedham, pharmacy department

Consultant name: Signature: Date …../…../……

PCT advisor name: Signature Date …../…../……

Approved:

Yes	No

Fatemeh leedham Signature Date …../…../……

Please only dispense when all above signatures are complete and approval received from PCT

Appendix III

Guidelines for perioperative management of Dabigatran

Semi-acute or elective surgery

1. Assess the risk of bleeding against the risk of thrombosis when considering discontinuing anticoagulation
2. Minor procedures, dagibatran may not need to be discontinued
3. If dagibatran does need to be stopped, it is important to plan ahead as there is no treatment available to immediately reverse dagibatran
4. Dabigatran is primary renally excreted therefore discontinuation depends on renal patients renal function.

Renal function (CrCl, mL/min)	Half-life of Dabigatran (hours)	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk surgeries
GFR > 50	15 hours	24 hours	2-4 days
GFR 30 -50	18 hours	At least 48 hours before	4 days
GFR < 30	27 hours	2-5 days	> 5 days

- If there is risk of thrombosis, consider bridging anticoagulation therapy

Urgent surgery

1. Stop Dabigatran
2. Check FBC, electrolytes, renal function and coagulation screen (PT, APTT, fibrinogen)
3. Consider delaying surgery if appropriate until coagulation screen is normal
4. Where urgent life-saving surgery cannot be delayed, consult on-call haematologist for measures to control bleeding prior to or during surgery (eg: recombinant factor VIIa)

Restarting Dabigatran after surgery

1. The appropriate time to restart Dabigatran after surgery will be determined by the nature of the surgery, urgency for thromboprophylaxis and haemostatic state of the patient. Discussion with haematologist is appropriate to determine individual case management.
2. Elective situations with stable haemostatic Dabigatran can be restarted with a single capsule (110mg or 150mg depending on indication) 1-4 hours after surgery and the usual daily dose commenced the following day.

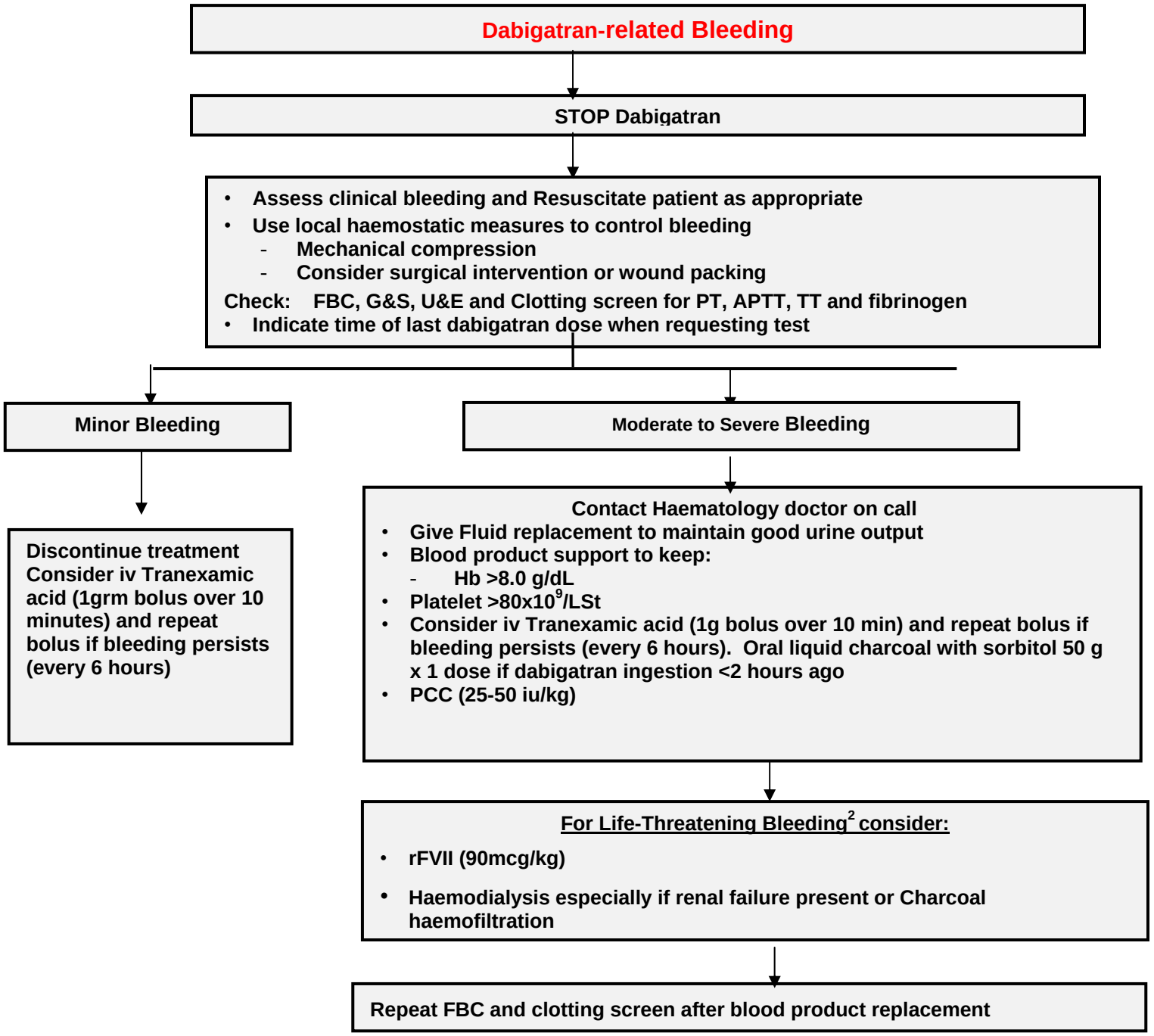
***High risk surgeries**

Cardiac surgery, neurosurgery, abdominal surgery or surgery involving major organ. Other procedures such as spinal anaesthesia or patients with high bleeding risk such as advancing age, multiple co-morbidities (eg. major cardiac, respiratory, liver disease) and concomitant use of anti-platelet therapy.

Appendix IV

Guidelines for management of bleeding with Dabigatran

- Dabigatran is an oral direct thrombin inhibitor that has a plasma half-life of 12-17 hours
- Dabigatran is mostly (80%) excreted by the kidneys and as such appropriate diuresis must be maintained in order to promote adequate drug clearance
- There is **NO REVERSAL** agent for dabigatran



[1]**Moderate to Severe bleeding: -** reduction in Hb ≥ 2gd/L, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area (i.e. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).
[2]**Life-threatening bleeding:** – symptomatic intracranial bleed, reduction in Hb ≥ 5gd/L, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

Appendix V

Shared care agreement letter

Name of Trust: Basildon and Thurrock University Hospital NHS FT
Dabigatran (Pradaxa ®)
Prevention of stroke and embolism in adult patients with nonvalvular atrial fibrillation

Name of GP ……..… Address …….
…….....
..……
..……
Dear GP

Re: Patient's Name……..……Date of Birth…….……
NHS Number……..
Hospital Number……..……

Indication for oral dabigatran 150 / 110 mg (delete as appropriate) twice daily for prevention of stoke and embolism in adult patients with nonvalvular atrial fibrillation.

Enclosed is a copy of the shared care guidelines for dabigatran to be retained in the patient's notes.
Should you agree to shared care, we will send a letter containing the details of the patient's treatment plan, the dose to be prescribed and all relevant blood results.

Please sign below and return this letter to the Hospital Specialist if you agree to the shared care arrangements for this patient.

Many thanks

Hospital Specialist	GP
Signature……...	Signature……...
Name ……..……...	Name ……...
Date……..	Date……..…..……...

If you are not taking on shared care for this patient please state the reason why and return this letter to the Hospital Specialist.
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