708FM.5 ANTIPLATELETS AND RIVAROXABAN 2.5 mg TABLETS FOR SECONDARY PREVENTION OF OCCLUSIVE VASCULAR EVENTS

Purpose/Scope

- This guideline covers the use of antiplatelets and rivaroxaban 2.5 mg tablets following an occlusive vascular event.
- It does NOT cover the use of these agents following an occlusive vascular event if the patient is anticoagulated for another indication.

Duration of dual antiplatelet therapy (DAPT) or single antiplatelet plus rivaroxaban 2.5 mg tablets

When these medicines are started in secondary care, VERY clear information about duration of treatment needs to be communicated to primary care so that a stop date can be put on EMIS for all repeat prescriptions. To achieve this:

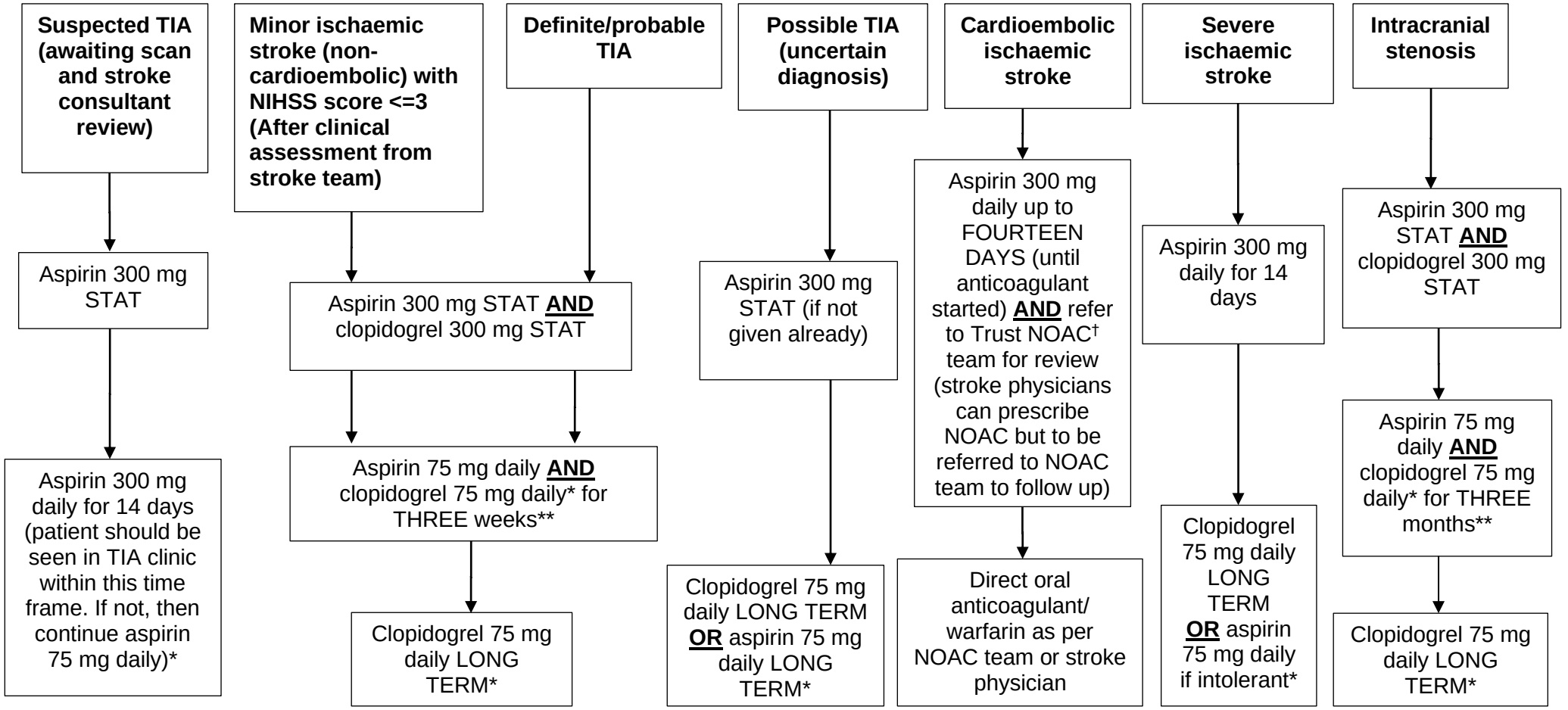
- The discharging clinician will clearly document the DURATION of treatment and STOP DATE on discharge letters and discharge prescriptions.
- The validating pharmacist will check that the DURATION and STOP DATE are recorded on discharge prescriptions and pharmacy staff will document this on hospital pharmacy medicine labels. It will be reinforced via counselling of patients.

Gastrointestinal (GI) bleeding risk assessment for DAPT:
Use appendix 1 to decide whether gastro protective medicine is needed.

Antiplatelet intolerance:
See algorithms 1 and 2 and their footnotes**.**

CONTENTS

ALGORITHM 1. Transient ischaemic attack (TIA), ischaemic stroke, intracranial stenosis: Immediate and long term management



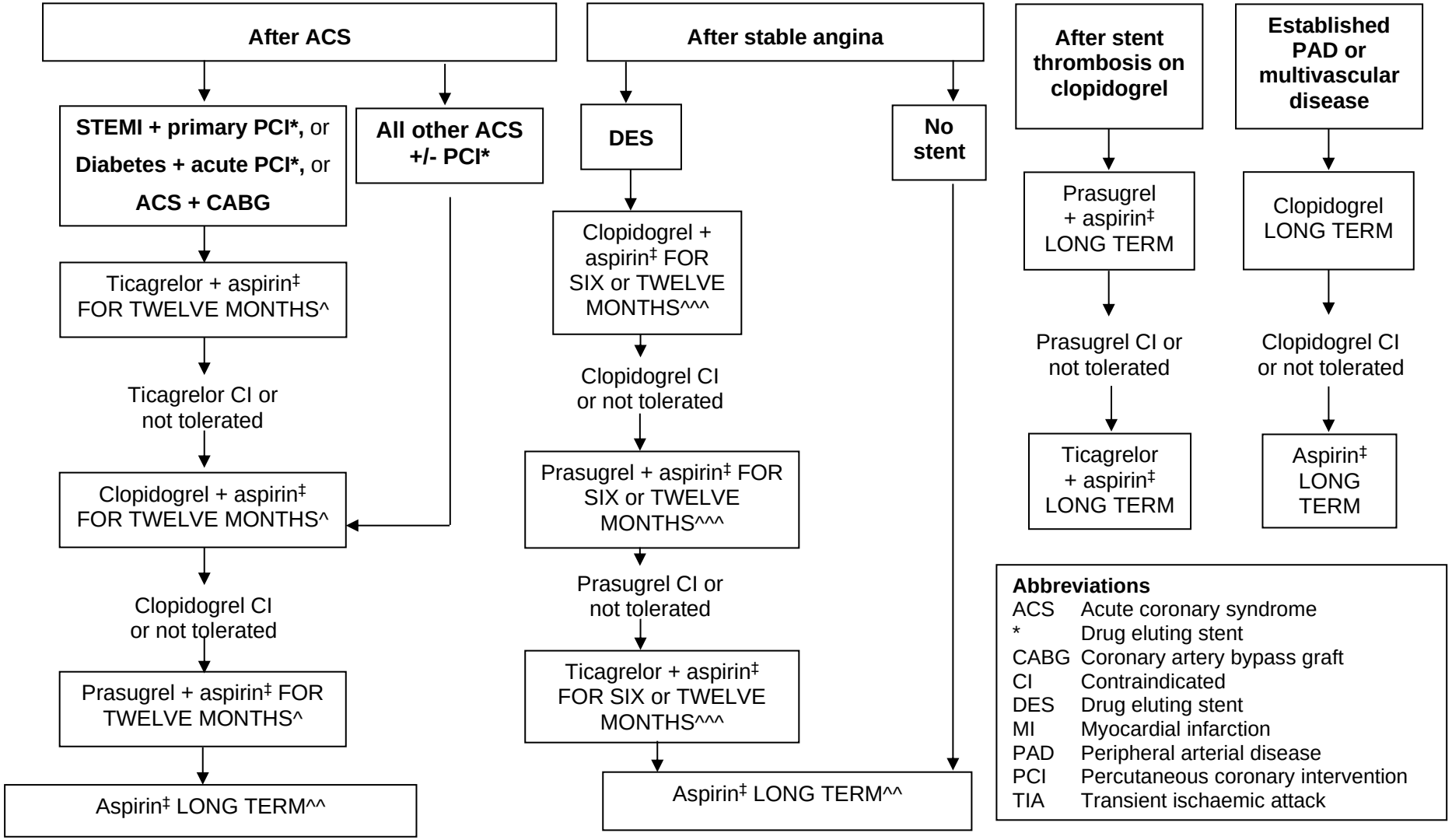
Note: Refer to Appendix 1 for assessment of gastrointestinal (GI) bleeding risk in patients prescribed dual antiplatelet therapy

* For true aspirin and/or clopidogrel intolerance, dipyridamole M/R can be continued in existing patients. For new patients, contact stroke physician on-call (SPOC)

** The discharge summary/letters and hospital Pharmacy medicine labels will record the stop date for DAPT and this will be reinforced via counselling of patients. Hospital to supply full course of aspirin (3 weeks for minor ischaemic stroke/TIA and 3 months for intracranial stenosis).

† NOAC = Novel oral anticoagulant

ALGORITHM 2. ACS, stable angina, stent thrombosis, vascular disease: Long term management (see Table 1 for doses)



^Some high risk MI patients may require ticagrelor 60 mg twice daily + aspirin 75 mg daily as extended prophylaxis for up to 3 years (NICE TA 420)
^^Some high risk MI patients may require rivaroxaban 2.5 mg twice daily + aspirin 75 mg daily as extended prophylaxis long term (NICE TA 607 and TA 335)
^^^Duration of antiplatelet therapy will be guided by the cardiologist based upon the ischaemic and bleeding risk.
‡ For true aspirin intolerance in stable angina with no stent, switch to clopidogrel 75 mg daily. For true aspirin intolerance in all other patients, seek specialist advice using ERS Advice and Guidance or by contacting the cardiologist on-call via switchboard.

TABLE 1. Doses for immediate and long term management of ACS, stable angina, stent thrombosis, and vascular disease (based upon first choice treatment). See also extended prophylaxis below.

After an occlusive vascular event	Immediate treatment in hospital	Followed by
STEMI + primary PCI OR ACS + diabetes + acute PCI	Ticagrelor 180 mg STAT (even if clopidogrel has been given in the ambulance or if the patient is taking clopidogrel regularly) and aspirin 300 mg STAT	Ticagrelor 90 mg twice daily and aspirin 75 mg daily FOR TWELVE MONTHS. **The duration of dual therapy is not affected by the type of stent used.** Then: Aspirin 75 mg daily LONG TERM
ACS + CABG (not suitable for PCI)	**Awaiting CABG** Ticagrelor 90 mg twice daily and aspirin 75 mg daily **Loading dose for CABG** Ticagrelor 180 mg STAT and aspirin 300 mg STAT	
ACS +/- PCI (drug eluting stent)	**NSTEMI/UA** Clopidogrel* 300 mg STAT and aspirin 300 mg STAT	Clopidogrel 75 mg daily and aspirin 75 mg daily FOR TWELVE MONTHS. **The duration of dual therapy is not affected by the type of stent used.** Then: Aspirin 75 mg daily LONG TERM
Stable angina + stent (drug eluting stent)	Clopidogrel* 300 mg STAT and aspirin 300 mg STAT	Clopidogrel 75 mg daily and aspirin 75 mg daily FOR SIX or TWELVE MONTHS followed by aspirin 75 mg daily LONG TERM
Stable angina – no stent	Aspirin 75 mg daily	Aspirin 75 mg daily LONG TERM
Stent thrombosis whilst taking clopidogrel	Prasugrel 60 mg STAT and aspirin 300 mg STAT	Prasugrel 10 mg daily** and aspirin 75 mg daily LONG TERM
Stent thrombosis whilst taking clopidogrel where prasugrel is CI or not tolerated	Ticagrelor 180 mg STAT and aspirin 300 mg STAT	Ticagrelor 90 mg twice daily and aspirin 75 mg daily LONG TERM

* Clopidogrel loading dose should be administered 24 hours after last dose of ticagrelor if the patient is already pre-loaded with ticagrelor.

** Prasugrel 10 mg daily for patients >60 kg and <75 years.
Prasugrel 5 mg daily for patients <60 kg or ≥75 years. Evidence for use of the 5 mg dose is not based on clinical data but on pharmacokinetic principles. To be initiated at the discretion of the consultant.

EXTENDED PROPHYLAXIS WITH MORE THAN ONE AGENT FOR HIGH RISK ISCHAEMIC PATIENTS

^ Extended prophylaxis with ticagrelor 60 mg twice daily + aspirin 75 mg daily (NICE TA 420)
The cardiologist will confirm the duration of extended prophylaxis at the time of the MI. This will be included on the discharge letter together with the name of the cardiology consultant responsible for the decision.

Eligibility for extended prophylaxis with ticagrelor 60 mg twice daily + aspirin 75 mg once daily:

- History of MI of at least one year and a maximum of two years and
- A risk factor; ≥65 years old, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel coronary artery disease or chronic non-end-stage renal dysfunction (CrCl <60 mL/min).

Ticagrelor 60 mg twice daily + aspirin 75 mg daily may be continued after the first 12 months of antiplatelet therapy for up to a maximum antiplatelet duration of 3 years. It can also be initiated within one year of stopping previous antiplatelet therapy. If a switch is needed, the first dose of ticagrelor 60 mg should be administered 24 hours following the last dose of the other antiplatelet.

^^ Extended prophylaxis with rivaroxaban 2.5 mg twice daily + aspirin 75 mg daily long term (NICE TA 607)

The cardiologist will confirm the need for the addition of rivaroxaban 2.5 mg tablets twice daily to aspirin 75 mg daily for patients with coronary artery disease. This will be at the discretion of the cardiologist in patients considered high risk of ischaemic events defined as:

- Aged 65 or over, or
- Atherosclerosis in at least 2 vascular territories (such as coronary, cerebrovascular, or peripheral arteries), or
- 2 or more of the following risk factors: Current smoking, diabetes, kidney dysfunction with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min (note that rivaroxaban is contraindicated if the eGFR is less than 15 mL/min), heart failure, previous non-lacunar ischaemic stroke.

^^ Extended prophylaxis with rivaroxaban 2.5 mg twice daily + aspirin 75 mg daily (NICE TA 335)

After an ACS, rivaroxaban 2.5 mg twice daily may be used in some high risk patients in combination with both aspirin 75 mg daily and clopidogrel 75 mg daily for a maximum of 12 months (NICE TA 335). After 12 months' treatment, clopidogrel should be stopped. The decision to continue or stop rivaroxaban 2.5 mg twice daily after 12 months will be made in advance, at the point of the ACS, by the cardiologist and documented on the discharge letter and/or Cath Lab report.

ADDITIONAL PRESCRIBING INFORMATION IN ACS

Ticagrelor

Contraindications

- Patients at high risk of bleeding - recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding or active peptic ulcer disease.
- Previous intracranial haemorrhage.
- Patients on long term warfarin **or other oral anticoagulant** therapy, as the risk of bleeding with triple therapy including ticagrelor will be significantly higher than with triple therapy involving clopidogrel.
- Severe hepatic impairment.

Cautions

- Patients presenting with 2° or 3° atrioventricular (AV) block, sick sinus syndrome or profound bradycardia in the Cath Lab – increased risk of bradycardia.
- Patients with chronic obstructive pulmonary disease (COPD) and asthma – ticagrelor may increase dyspnoea.
- Patients with gout – increased risk of hyperuricaemia.

Drug interactions

- Simvastatin – ticagrelor increases simvastatin levels – maximum dose 40 mg daily. The first line statin post ACS is atorvastatin, for which there is no clinically significant interaction.
- Clarithromycin and other strong CYP3A4 inhibitors (ketoconazole, nefazodone, ritonavir and atazanavir) – avoid concomitant use.
- CYP3A4 inducers including rifampicin, phenytoin, carbamazepine and phenobarbitone – avoid concomitant use as antiplatelet efficacy will be reduced.
- Verapamil – increases ticagrelor levels – avoid concomitant use.

Side effects

- Bradycardia – asymptomatic ventricular pauses were observed during clinical trials.
- Dyspnoea – incidence ≥1/10 patients.
- Increase in creatinine levels – mechanism unknown – to be monitored at one month in PCI follow-up clinic.
- Increased risk of bruising and bleeding.

Prasugrel

Contraindications

- Patients with a prior history of stroke or TIA.
- Patients at high risk of bleeding - recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding or active peptic ulcer disease.
- Patients on long term warfarin **or other oral anticoagulant therapy**, as the risk of bleeding with triple therapy including prasugrel will be significantly higher than with triple therapy involving clopidogrel.
- Severe hepatic impairment.

Cautions

- Patients ≥75 years old.
- Patients <60 kg.

In these patients, the 5 mg daily dose is used at the consultant's discretion.

Drug interactions

- Increased risk of bleeding in patients on warfarin, phenindione and nonsteroidal anti-inflammatory Drugs (NSAIDs).

Side effects

- Increased risk of bleeding and bruising.
- Anaemia, rash.

Clopidogrel is the antiplatelet agent of choice for cardiology indications when there are contraindications or intolerance to ticagrelor or prasugrel in:

- Patients on long term warfarin or other oral anticoagulant therapy.
- Patients at high risk of bleeding - recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding or active peptic ulcer disease.

Rivaroxaban

Contraindications

- Patients with a lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants.
- Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a TIA.
- Patients with previous haemorrhagic or lacunar stroke, or any stroke within a month.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Creatinine clearance <15 mL/min.
- Pregnancy and breastfeeding.

Cautions

- Patients with creatinine clearance 15 - 29 mL/min.
- Elderly patients e.g. ≥75 years of age.
- Other haemorrhagic risk factors e.g. congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease), vascular retinopathy, bronchiectasis or history of pulmonary bleeding.
- Patients with lower body weight (<60 kg).
- Patients with severe symptomatic heart failure as study data indicates that these patients may benefit less from treatment with rivaroxaban.

Notable drug interactions (refer to BNF and SPC)
Rivaroxaban is metabolised by cytochrome P450 and is also a substrate for P-glycoprotein.

Class	Drugs	Effect	Action
Strong P-gp inhibitors and CYP3A4 inhibitors	Dronedarone Ketoconazole Itraconazole Voriconazole Posaconazole HIV protease inhibitors, e.g. ritonavir	Levels of rivaroxaban increased by up to 160%	Contraindicated
Moderate CYP3A4 inhibitor	Fluconazole	Levels of rivaroxaban increased by 40%	Not considered clinically significant
Strong CYP3A4 and moderate P-gp inhibitor	Clarithromycin	Levels of rivaroxaban increased by 50%	Not considered clinically significant. No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
Moderate CYP3A4 and P-gp inhibitor	Erythromycin	Levels of erythromycin increased by 30%	Not considered clinically significant. No dose reduction required. Monitor closely. Consider use of azithromycin (safer alternative).
CYP3A4 inducer	Rifampicin Carbamazepine Phenobarbital Phenytoin St John's Wort	Reduces area under curve (AUC) of rivaroxaban by 50% causing a reduced anticoagulation effect	Contraindicated
Others	Aspirin Clopidogrel	Increased risk of bleeding	Combination not recommended unless indicated by specialist. Consider GI protection. Close monitoring for signs of bleeding.
	NSAIDs	Increased risk of bleeding	Combination not recommended
	SSRIs	Increased risk of bleeding	If combination is needed then consider GI protection if not already prescribed.
	Prasugrel Ticagrelor	Increased risk of bleeding	Avoid combination

General Points

1. All medicines in this guideline are administered orally as tablets/ capsules. Aspirin 300 mg is also available as a suppository for rectal administration in patients who are 'nil by mouth'.
2. **Stroke/TIA:** The Royal College of Physicians Stroke guideline 2016[5] and recent trial research results[14,15] recommend the use of dual antiplatelet therapy for non-cardioembolic minor acute ischaemic stroke, probable/definite TIA and intracranial stenosis.
3. **TIA:** Secondary prevention is an unlicensed indication for clopidogrel.
4. **PAD:** Clopidogrel is recommended for peripheral arterial disease (PAD) in NICE TA 210[4]. Although the NICE TA does not discuss product choice when clopidogrel is contraindicated or not tolerated, it seems sensible to offer aspirin as an alternative.

BACK-UP INFORMATION/ADVICE

Contact Details	Telephone no	Email
BHT Cardiology Advice	Cardiologist advice service via ERS Advice and Guidance Dr Piers Clifford Tel: 01494 425004	bht.cardiologysecswgh@nhs.net
BHT Stroke Service	Dr Matthew Burn Tel: 01494 426252 Dr Simmie Manchanda Dr Amulya Misra 01494 426311	bht.strokeadmin@nhs.net
Medicines Resource Centre	01494 425355 (urgent enquiries Monday to Friday, 9am to 5pm,)	bucks.medicinesresource@nhs.net

REFERENCES

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RELATED GUIDELINES:

Guideline 146FM Management of Acute Stroke
Guideline 314FM Acute Coronary Syndrome
Guideline 775FM Treatment of Atrial Fibrillation
Guideline 733FM Thomboprophylaxis in the hospital setting: reducing the risk of hospital acquired DVT or PE
BHT Pol 071 Medicines Policy Annexe 4: Unlicensed Medicines (BHT users only)

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APPENDIX 1: Assessment of gastrointestinal (GI) bleeding risk in patients prescribed dual antiplatelet therapy (DAPT)

ALL patients should have a risk assessment to ascertain the risk of GI bleeding with dual antiplatelet therapy. This includes patients already taking a proton pump inhibitor (PPI) or H_2 receptor antagonist as their therapy may need to be reviewed.

Risk Factors

- **Previous peptic ulcer**
- **Previous GI bleed**
- **Other anticoagulant drugs**
- **Concurrent corticosteroids**
- **Concurrent non-steroidal anti-inflammatory drugs (NSAIDs)**
- **Chronic renal failure**
- *Age >65*
- *Previous long term NSAID use*
- *Diabetes*
- *Baseline anaemia haemoglobin (Hb) <120 males; <110 female*
- *Alcohol excess >21 units/week male; >14 units/week female*

A PPI is recommended for ALL patients with at least one risk factor marked in **BOLD.**

A PPI should be *considered* for all other patients who have two or more of the risk factors marked in *italics*.

A PPI should be strongly considered for all patients on a single antiplatelet and an anticoagulant for the duration of combination therapy

Lansoprazole 30 mg OD is our first line PPI. It does not interact with clopidogrel.

Omeprazole should be avoided in combination with clopidogrel ***wherever possible*** due to a potential drug interaction which may result in reduced antiplatelet effect. However, if patients are admitted on high dose omeprazole and are known to the gastroenterology team, this should be continued.