

**North of Tyne and Gateshead guidelines for
anti-platelet treatment for prevention of
cardiovascular events in patients with, or at
risk of, vascular disease**

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Introduction

This guidance is intended to inform the use of anti-platelet treatment in patients with vascular disease and updates the previous guidance published July 2009, updated in November 2012. It has been developed jointly between primary and secondary care and has been informed by the recommendations in relevant NICE guidance, including TAG 210 (Vascular disease – clopidogrel and dipyridamole)¹, TAG 317 (Acute coronary syndrome – prasugrel)² and TAG 236 (Ticagrelor for acute coronary syndrome)³, a meta-analysis of aspirin in the primary and secondary prevention of vascular disease⁴ and advice from the MHRA⁵.

The guideline is presented as a summary and the relevant published literature should be referred to for further information. The cost impact has been considered and it is made explicit when this has a major impact on a particular recommendation.

Using the guideline

This guideline is intended to be used by clinicians in Newcastle, North Tyneside, North Cumbria, Northumberland and Gateshead who are responsible for managing patients with, or at risk of atheromatous vascular disease. The summary tables (which can be printed double sided on a single A4 page) are presented so they can be laminated for ease of reference, and is followed by further explanatory information thereafter.

It is assumed that clinicians will consider and consider any additional indications or contra-indications in individual patients and the BNF and the Local Formulary should be referred to as appropriate.

¹ Available at <http://guidance.nice.org.uk/TA210>

² Available at <http://guidance.nice.org.uk/TA317>

³ Available at <http://www.nice.org.uk/ta236>

⁴ Lancet 2009; 373:1849-60

⁵ <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087716>

⁶ http://www.rcplondon.ac.uk/sites/default/files/documents/stroke_key_recommendations_guide_web.pdf

Patients with Coronary Artery Disease – anti-platelet agents

Indication	Recommendation	Notes
Acute ST elevation MI These patients will be treated with Percutaneous Coronary Intervention (PCI)	Aspirin and either prasugrel or ticagrelor for 12 months and then review*, or as advised by a cardiologist. Clopidogrel (loading dose 600 mg once daily then 75 mg daily) is now reserved for those unable to tolerate ticagrelor or prasugrel, or if these are not available.	Aspirin (loading dose 300 mg ⁷ then 75 mg once daily), plus either ⁸ : Ticagrelor 180 mg loading dose then 90 mg bd, or Prasugrel loading dose 60 mg then 10mg once daily (5 mg once daily considered if weight < 60 kg and/or aged > 75 years).
Acute non-ST elevation MI / unstable angina Including patients managed medically or with PCI	Aspirin and ticagrelor for 12 months then review*, or as advised by the cardiologist. Clopidogrel (loading dose 600 mg once daily then 75 mg daily) is now reserved for those unable to tolerate ticagrelor, or if this is not available.	Aspirin (loading dose 300 mg then 75 mg once daily) plus ⁸ : Ticagrelor 180 mg loading dose then 90 mg bd (if either medical or invasive management), with reduction to 60 mg bd after a year if treatment is extended for longer (up to 3 years).
Stable patients with elective PCI Bare metal stent Drug eluting stent (3 rd generation)	 Aspirin 75mg once daily and clopidogrel 75mg once daily for 4 weeks (or up to 12 months if advised by cardiologist). Aspirin 75mg once daily and clopidogrel 75mg once daily for 6 months.	Patients for elective PCI will already be treated with aspirin and will be advised about clopidogrel loading at preadmission clinic (dose and timing) Prasugrel or ticagrelor may be substituted for clopidogrel in patients with previous stent thrombosis (individual patient management plan for duration).
Stable patients with previous MI and or angina, including those with prior coronary intervention Following any recommended period of dual anti-platelet treatment	Aspirin 75 mg once daily life long, unless patients have multivascular disease when clopidogrel 75 mg once daily lifelong is recommended. Rivaroxaban 2.5mg bd and Aspirin 75mg once daily for those at high risk of cardiovascular events ** and low bleeding risk	Clopidogrel may be substituted in patients with coronary disease, if aspirin is contra-indicated or not tolerated Patients planned for lifelong clopidogrel rather than aspirin, should start 75 mg once daily the day after stopping dual anti-platelets.

Additional notes (refer to the BNF / drug SPC as required)

- When planned stop/ review date of dual anti-platelet treatment with aspirin and clopidogrel/prasugrel/ticagrelor is reached, the patient should be reviewed and appropriate treatment stopped, unless there is good reason for continuation e.g. a subsequent cardiovascular event/intervention for which on-going dual anti-platelet is indicated or an extended period of treatment is recommended by the interventional cardiologist. **Dual anti-platelet treatment should not be interrupted earlier than planned without discussing with an interventional cardiologist first.**
- A longer duration of dual antiplatelet drug treatment may be recommended in patients at higher risk of ischaemic events, at the expense of an increase in bleeding events, at the discretion of the individual cardiologist. The NICE TAG for treatment with aspirin and ticagrelor (December 2016) recommends that this is for as long as clinically indicated and for a maximum of 3 years.
- * The review should normally be carried out by the clinician responsible for prescribing the anti-platelet agents (usually the GP) considering any specific advice from the cardiologist.
- Creatinine levels should be measured one month after starting ticagrelor
- For patients intolerant of ticagrelor, e.g. unexplained breathlessness or significant bradycardia with no other explanation: stop ticagrelor and give clopidogrel 300 mg loading dose, then 75 mg once daily. If suspected ticagrelor side effects persist > 2 weeks, symptoms are unlikely to be due to ticagrelor. In such case, stop clopidogrel and start ticagrelor with 180 mg loading dose then 90 mg bd. If previous stent thrombosis, or if doubt whether switching is appropriate, discuss with an interventional cardiologist first.
- Avoid co-prescription of strong CYP3A4 inhibitors with ticagrelor e.g. clarithromycin, ketoconazole, nefazodone, ritonavir, atazanavir, and in patients with a previous intracranial haemorrhage.
- Prasugrel should not be prescribed in patients with a previous stroke / intracranial haemorrhage
- **Combining Rivaroxaban 2.5mg bd and Aspirin is based on at high risk of cardiovascular event as defined by COMPASS⁹ criteria - Age ≥65, or Age <65 and documented atherosclerosis or revascularization involving at least 2 vascular beds, or at least 2 additional risk factors (current smoking, diabetes, chronic kidney disease, non-lacunar ischaemic stroke and heart failure). Regularly monitoring for bleeding (avoid in those with high bleeding risk – caution age >75, body weight <60kg).

7 Administered pre-hospital unless the patient presents direct to A&E

8 Agent used is dependent on individual patient characteristics, decided by the cardiologist.

9 <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.046048>

Cerebrovascular Disease and Peripheral Arterial Disease – anti-platelet agents

Indication	Recommendations	Notes
Ischaemic stroke / TIA	<p>Patients with acute ischaemic stroke: Aspirin 300 mg once daily for first 14 days, then clopidogrel 75 mg once daily long term.</p> <p>Patients with TIA: 300mg aspirin daily pending specialist review. After diagnosis is confirmed by a specialist, clopidogrel 75mg once daily should be commenced (see below)</p> <p>Selected patients with minor strokes (NIHSS 3 or less) and high risk TIAs (ABCD2 \geq 4) presenting within 24 hours of symptom onset: loading dose of aspirin 300 mg once daily and clopidogrel 300mg, then aspirin 75 mg once daily plus clopidogrel 75 mg once daily for 3 weeks, then clopidogrel 75 mg once daily alone.</p>	<p>If clopidogrel contra-indicated / not tolerated consider the following alternatives lifelong</p> <p>First line: Aspirin 75 mg plus dipyridamole MR 200 mg bd</p> <p>Second line: aspirin 75mg once daily</p> <p>Third line: dipyridamole MR 200 mg bd</p>
Carotid endarterectomy	Existing anti-platelet regime before procedure (see above) then clopidogrel 75 mg once daily after the procedure, lifelong.	Clopidogrel does not need to be stopped prior to carotid endarterectomy.
Carotid stenting	Existing anti-platelet regime before procedure (see above) then aspirin 75 mg once daily and clopidogrel 75 mg once daily for 1 month after procedure, then clopidogrel 75 mg once daily, lifelong.	Patients not currently treated with clopidogrel 75 mg once daily: clopidogrel loading with 300 mg the day prior to carotid stenting will be arranged at the preadmission clinic.
Peripheral arterial disease (PAD)	Clopidogrel 75 mg once daily lifelong.	Patients with a past history of PAD currently treated with aspirin alone should be considered for a switch to clopidogrel 75 mg once daily as above
PAD with drug eluting balloon angioplasty / drug eluting stent angioplasty	Aspirin 75 mg once daily (aspirin 300mg to load) and clopidogrel 75 mg once daily for 2 months, then clopidogrel 75 mg once daily alone, lifelong.	Patients will be taking clopidogrel 75mg once daily prior to the procedure and do not require additional clopidogrel loading.
Multi-vascular disease Following any recommended period of dual anti-platelet treatment	Clopidogrel 75 mg once daily lifelong	Patients with a past history of multivascular disease currently treated with aspirin alone should be considered for a switch to clopidogrel 75 mg once daily

Notes

When a planned stop / review date at the end of the planned duration of dual anti-platelet treatment with aspirin and clopidogrel is reached, the patient should be reviewed and the appropriate treatment stopped, unless there is good reason for continuing e.g. the patient has another cardiovascular event / intervention for which on-going dual anti-platelet is indicated.

Primary Prevention - anti-platelet agents

Indication	Recommendation	Notes
Primary prevention, including diabetes without established atheromatous vascular disease	Anti-platelet treatment is not routinely recommended.	

Notes

Primary prevention

There was a consensus that aspirin should not be routinely recommended for primary prevention and the advice from the MHRA¹⁰ was noted that “Aspirin is not licensed for the primary prevention of vascular events. If aspirin is used in primary prevention, the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease (including conditions such as diabetes) and the risk of gastrointestinal bleeding”. Some patients at highest risk might choose to take aspirin, but this should only be following a discussion with the patient about their risks and benefits of doing so. Other risk factors for which the evidence base for intervention and risk reduction is much clearer should be addressed in preference.

The risk of major upper GI bleeding with low dose aspirin is increased 2–3 fold (2–6 events per 1000 patient years, and of these 10% are fatal) and is higher in those who are frail, who have co-morbidities and in those treated with other drugs such as steroids and NSAIDs. If patients are treated with aspirin for primary prevention blood pressure should be controlled to less than 150/90, and if patients already treated develop sustained uncontrolled hypertension, aspirin should be temporarily withheld.

NICE do not recommend antiplatelet treatment for primary prevention in people with Type 1¹¹ or Type 2¹² diabetes without cardiovascular disease.

Dyspepsia taking aspirin

- Review and modify other contributory factors and medication which might be causing dyspeptic symptoms e.g. excess alcohol, other NSAIDs
- Consider if further investigation is required (refer to other guidelines for dyspepsia)
- Ensure aspirin is taken with food
- Use aspirin 75 mg once daily
- Combine aspirin with a PPI (Omeprazole can reduce the antiplatelet effect of clopidogrel, and concomitant use should be avoided)
- Enteric coated aspirin is NOT recommended and non-formulary

History of GI bleeding with aspirin or NSAIDs

Combine anti-platelet agent with PPI e.g. lansoprazole 15-30 mg once daily (preferred if treated with clopidogrel) or omeprazole 10 – 20 mg once daily.

Bleeding complications whilst treated with dual anti-platelet agents

Dual anti-platelet treatment should not be interrupted in primary care unless discussed with an interventional cardiologist, or other clinician initiating the treatment. If urgent advice is required, the on-call cardiology SpR or the vascular surgery SpR at the Freeman Hospital can be contacted (phone via Newcastle Hospitals switchboard) and are available 7 days per week. Major and life-threatening bleeding will be managed in secondary care with individual patient management plans.

10 MHRA Drug Safety Update Volume 3, Issue 3, October 2009

11 <https://www.nice.org.uk/donotdo/do-not-offer-aspirin-for-the-primary-prevention-of-cardiovascular-disease-to-adults-with-type-1-diabetes>

12 <https://www.nice.org.uk/guidance/ng28/>

Suspected intolerance to ticagrelor

Dyspnoea and bradycardia are reported side effects with ticagrelor. Other causes of dyspnoea (e.g. heart failure, bronchospasm) should be excluded before considering any change in treatment (see summary table). In the ticagrelor studies, most bradycardia was asymptomatic, but if the heart rate is less than 50 beats per minute an ECG is required. If changes to treatment are thought to be required, modifying other rate limiting drugs (e.g. beta blocker, rate limiting calcium channel blockers) should be considered first. If patients have had a previous stent thrombosis or there is any doubt if switching is appropriate, patient's management should be discussed with an interventional cardiologist first.

Surgery and invasive procedures in patients treated with anti-platelet agents

- The risk of bleeding complications is increased by anti-platelet agents, in particular clopidogrel, prasugrel and ticagrelor, and the risks and benefits of interrupting anti-platelet treatment prior to surgery and other invasive procedures needs to be considered.
- In general, clopidogrel / prasugrel / ticagrelor will be stopped for 10 days before and for the duration of elective procedures (although may depend on the nature of the procedure), even if aspirin is continued (refer to local Trust peri-operative guidelines).
- In patients treated with clopidogrel alone and who are more than 9 months following an acute event (i.e. acute ischaemic stroke or TIA), clopidogrel can be temporarily withheld with minimal risk. However, in ***all patients treated with dual anti-platelet agents*** (aspirin in combination with either clopidogrel, prasugrel or ticagrelor) any proposed modification to the anti-platelet regime should be discussed in advance with the cardiologist, vascular surgeon or other clinician who initiated the treatment.
- For emergency cases, if urgent advice is required, the on-call cardiology SpR or the vascular surgery SpR at the Freeman Hospital can be contacted (phone via Newcastle Hospitals switchboard) and are available 7 days per week.
- It is the responsibility of the medical staff undertaking the operation / biopsy to ensure any modification to the anti-platelet regime has been appropriately discussed and is undertaken safely. Local Trust guidelines should be referred to as appropriate (see above).

Use of anti-platelet agents with anti-coagulants

The combination of anti-platelet agents and anti-coagulants increases the risk of bleeding. Such combinations should only be used on the recommendation of hospital specialists, considering the risks and benefits. There should be appropriate arrangements for follow up and review of the indications to continue combination treatment.

Atrial fibrillation

Anti-platelet agents are not recommended for thrombo-embolic prophylaxis in patients with atrial fibrillation, and are not a substitute for oral anticoagulants¹³.

Updated March 2021 by

Alastair Green, Senior Clinical Pharmacist for Cardiology, Northumbria Healthcare NHS Trust

Andrew Mcleod, Consultant Cardiologist, Northumbria Healthcare NHS Trust

Mark Garside, Consultant Stroke Physician, Northumbria Healthcare NHS Trust

Sandip Nandra, Specialist Vascular Registrar ST8, The Newcastle upon Tyne Hospitals NHS Foundation Trust

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