

**ANTIPLATELETS, ANTICOAGULANTS AND BLEEDING RISK – WHICH AGENTS AND FOR HOW LONG? WHY USE PPIs?**

**KEY RECOMMENDATION**

- Patients taking anticoagulants or antiplatelet medicines at high bleed risk **should be considered for a Proton Pump Inhibitor (PPI). PPIs reduce bleeding risk by 70% or more.**
- Patients age 65 years or more on anticoagulants or antiplatelet agents are at increased risk because of their age and bleeding risk continues to rise exponentially at older ages.
- PPIs are recommended in patients on anticoagulants or antiplatelet agents:
  - At any age with previous GI bleeding
  - Age 75 years or older
  - 65 years or older with additional risk factors (see box below)
  - Interacting medication
- **Dual antiplatelet therapy (DAPT)** for cardiac conditions - typically aspirin + clopidogrel - is rarely justified for more than 1 year. Review use for more than one 1 year and in conjunction with the cardiologist consider whether this can revert to a single agent.
- **Dual-pathway therapy** for atrial fibrillation - both an anticoagulant and one or more antiplatelet agents- is also rarely justified for longer than 1 year. Consider anticoagulant alone with appropriate specialist advice.

**ADDITIONAL GI-BLEED RISK FACTORS**

Anaemia Hb <11g/L

Impaired renal function (eGFR<30)

Upper GI inflammation (and of course previous GI bleeding)

Liver disease

Interacting medicines (NSAIDs, SSRI/SNRIs, bisphosphonates, lithium, spironolactone, phenytoin, carbamazepine)

**WHAT DO WE MEAN BY ANTITHROMBOTICS?**

Antithrombotics reduce blood clot formation<sup>1</sup>. There are two main categories:

1. **Antiplatelet agent – inhibit platelet aggregation** e.g. Aspirin, Clopidogrel, Prasugrel, Dipyridamole, Prasugrel, Ticagrelor
2. **Anticoagulants – inhibit formation of the fibrin mesh:**
  - a. **Vitamin-K Antagonists (VKAs)** e.g. Warfarin, Acenocoumarol, Phenindione
  - b. **Direct oral anticoagulants (DOACs)** e.g. Apixaban, Dabigatran, Edoxaban, Rivaroxaban [also known as Non-VKA OACs (NOACs)]

There are also parenteral low-molecular weight heparins used for other indications.

**WHO SHOULD BE ON WHAT?**

This can be quite confusing and here we consider **secondary prevention** in the context of pre-existing cardiovascular (CVD) and/or Atrial Fibrillation only<sup>2-4</sup>:

1. People who have **ischaemic heart disease (IHD), peripheral arterial disease (PAD) or have had a stroke or a heart attack** should be on at least one antiplatelet agent
2. People who **have AF** should be on an anticoagulant
3. **Some people may be on more than one antithrombotic**; either two antiplatelets (i.e. dual-antiplatelet therapy (DAPT)) or an anticoagulant plus and antiplatelet treatment (known as dual-*pathway* therapy which can include triple-therapy (i.e. anticoagulant + 2 antiplatelets))

## WHO SHOULD BE ON DUAL ANTIPLATELET THERAPY? AND FOR HOW LONG?

Patients should be on DAPT if they have “recently” had an acute coronary syndrome (ACS) (whether treated interventionally or not) or if they have “recently” had an elective percutaneous coronary intervention (PCI). The recommended combination of antiplatelets depends on the indication and the question of how long is summarised in Table 1.

**Only a small number of patients with complex cardiac conditions should be on DAPT extending beyond 1 years’ duration. Review with cardiologist where appropriate, to consider reversion to a single agent after 1 year. Add PPI where appropriate.**

## WHO SHOULD BE ON DUAL-PATHWAY THERAPY AND FOR HOW LONG?

Recall that Dual-*pathway* therapy means the concurrent use of an anticoagulant and one or more antiplatelet agents.

Patients with AF on anticoagulants may also have an indication for additional antiplatelet treatment (e.g. AF patient requiring a coronary stent insertion) or patients on antiplatelet treatment can develop an indication for oral anticoagulation (e.g. AF).

Patients with AF after a myocardial infarction (MI) may be on *triple-therapy* - an anticoagulant plus two different antiplatelet agents - not usually exceeding 3 months. Dual-*pathway* treatment (OAC + antiplatelet) should be initiated in secondary care and should have a recorded duration of treatment.

Our local cardiology advice is that patients with AF should, after a new coronary event, be put on triple-therapy (OAC + two antiplatelet agents) for up to 3 months, on dual-agent therapy (OAC + one antiplatelet) for up to one year and anticoagulation only thereafter. The European Society for Cardiology guidelines give similar advice with treatment and treatment duration “titrated” to the balance of benefit versus bleeding risk<sup>3</sup>. Their summarized advice is reproduced in Figure 1.

**For any patients on dual-pathway therapy, PPI cover should be strongly considered particularly if aged 65 years or more. Triple-therapy beyond three months and any dual-therapy beyond 12 months should be carefully reviewed\*.**

## HOW EFFECTIVE ARE PPIs?

Gastrointestinal bleeding is the single greatest cause of hospital admission or death due to adverse drug reactions largely caused by prescribed antithrombotics<sup>5</sup>. Bleeding is not benign. In patients aged 75 years or older, major upper gastrointestinal bleeding was as likely to be disabling or fatal as recurrent ischaemic stroke<sup>6</sup>

Trials clearly demonstrate PPI effectiveness in reducing bleeding from antiplatelets. In addition, there are observational studies which show PPIs reduce major bleeding and hospital admission from both anticoagulants and antiplatelet agents. Currently there are no trials on PPIs to prevent bleeding from anticoagulation. In a meta-analysis of 10 trials in antiplatelet agents, PPIs reduced bleeding by 70% without any increase in CVD<sup>7</sup>. PPIs were superior to H2RA. In observational studies, PPIs reduced hospital admission for anticoagulant bleeding by 35%<sup>8</sup>.

Although PPIs reduce upper GI bleeding risk there may be instances at older ages where even with protection, bleeding risk outweighs CVD benefits and antithrombotic agents are not appropriate.

## BUT ARE PPIs SAFE? AND WHAT ABOUT THEIR SIDE EFFECTS?

PPIs are not without risk and are associated with increased risk of bone fractures (2/1000 person years at risk) and pneumonia (1/1000 person years at risk)<sup>9,10</sup>. There is also an association with Vitamin B deficiency and with *Clostridium difficile* infection in hospitalised patients. Hypomagnesaemia is a rare complication. Concerns that PPIs might be linked to dementia have not been supported by evidence<sup>11–13</sup>.

However, **these adverse events are ten-times less likely than anticoagulant or antiplatelet bleeding**. People aged 75 years or more with AF/CVD have a 20/1000 person years at risk of GI bleeding [<http://qbleed.org>] and the beneficial effects of PPIs in those at high bleeding risk substantially outweigh these relatively uncommon risks making a PPI highly worthwhile in this age group.

\* The recently published NICE Technology appraisal guidance TA607<sup>15</sup> considers long-term dual-pathway treatment with a low-dose DOAC (rivaroxaban 2.5mg BD) and aspirin for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

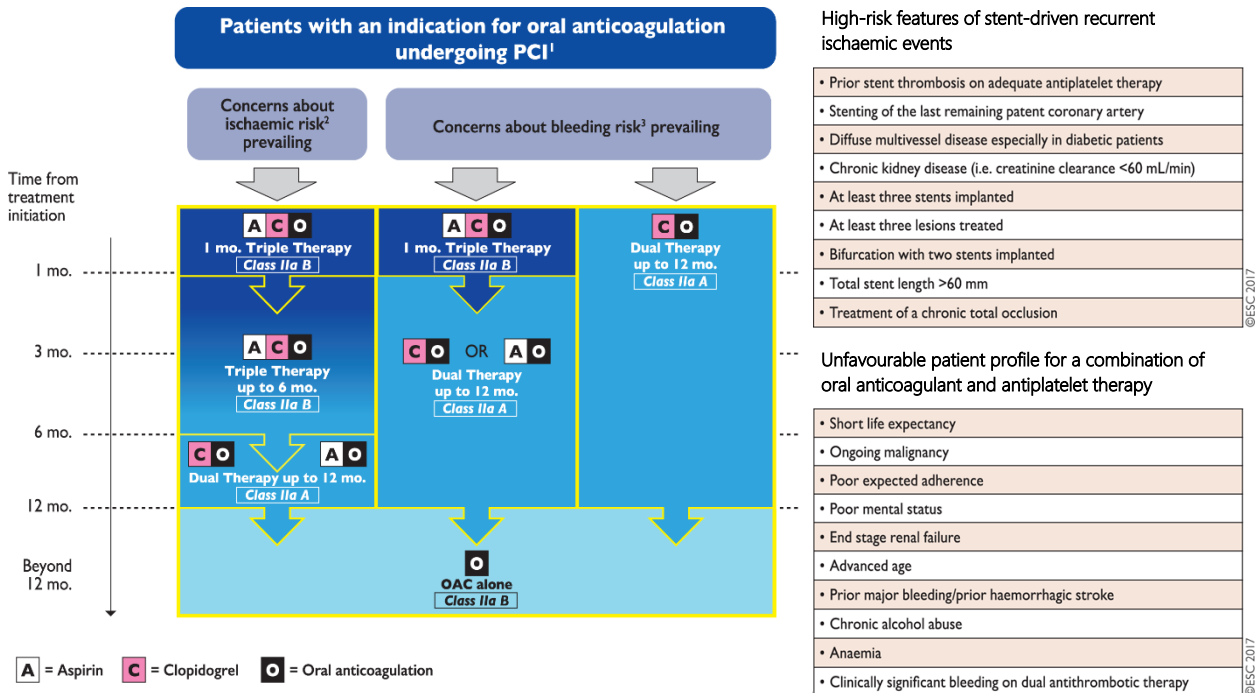
**Figure 1:** [Reproduced from ESC guidelines<sup>3</sup>] Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). Colour-coding refers to the number of concomitant antithrombotic medication(s). Triple therapy denotes treatment with DAPT plus oral anticoagulant (OAC). Dual therapy denotes treatment with a single antiplatelet agent (aspirin or clopidogrel) plus OAC.

ABC = age, biomarkers, clinical history; ACS = acute coronary syndrome; mo. = month(s); PCI = percutaneous coronary intervention.

1: Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy.

2: High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the risk for myocardial infarction.

3: Bleeding risk can be estimated by HAS-BLED or ABC score.



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| Condition   | Antiplatelet 1                                | Antiplatelet 2           | Typical duration | Comment   |
|---|---|--------------------------|------------------|---|
| Acute coronary syndrome (ACS) -- Medically managed  | Asprin 75mg OD                                | Ticagrelor 90 mg BD      | 12m              | <i>consider</i> extending DAPT up to 36m if high-risk CVD and no bleeding event (ticagrelor 90 BD -> 60mg BD)<br>Use clopidogrel 75mg OD if ticagrelor not tolerated and <i>consider</i> extending >12m if high-risk cardio and no bleeding event |
| Acute coronary syndrome (ACS) -- managed with PCI   | Asprin 75mg to 100mg OD                       | Ticagrelor 90 mg BD      | 12m              | If high risk of bleeding, avoid prasugrel and stop DAPT at 6m (continue aspirin alone)<br><i>consider</i> extend to 36m if well tolerated and no bleeding event (ideally ticagrelor 60mgBD)   |
| OR  | Asprin 75mg to 100mg OD                       | Prasugrel 10 mg OD       | 12m              |   |
| OR (if neither prasugrel or ticagrelor suitable)  | Asprin 75mg to 100mg OD                       | Clopidogrel 75mg OD      | 12m              |   |
| Angina (Stable)   | Asprin 75mg OD                                | NO DAPT                  | Lifelong         | <i>Consider treatment</i>   |
| Angina (Unstable)   | Asprin 75mg OD                                | NO DAPT                  | Lifelong         | <i>Offer treatment</i> ; alternative = clopidogrel 75mg OD  |
| Coronary artery bypass grafting (CABG) [secondary care decision]                              | DAPT; typically resume pre-existing (if any). |                          | Variable         | As per secondary care advice  |
| Peripheral arterial disease (PAD)   | Clopidogrel 75mg OD                           | NO DAPT                  | Lifelong         | or aspirin 75mg OD if clopidogrel not tolerated   |
| Stroke (ischaemic) or transient ischaemic attack (TIA) [long-term]                            | Clopidogrel 75mg OD                           | NO DAPT                  | Lifelong         | Clopidogrel is widely used post-TIA although it is only licensed for stroke prevention  |
| OR (clopidogrel unsuitable or not tolerated)  | Asprin 75mg OD                                | Dipyridamole MR 200mg BD | Lifelong         |   |
| OR (aspirin and dipyridamole unsuitable or not tolerated)                                     | Dipyridamole MR 200mg BD                      | NO DAPT                  | Lifelong         |   |
| OR (clopidogrel and dipyridamole unsuitable or not tolerated)                                 | Asprin 75mg OD                                | NO DAPT                  | Lifelong         |   |
| Stroke (minor, ischaemic) or high-risk transient ischaemic attack [Acute phase] <sup>14</sup> | Asprin 75mg OD                                | Clopidogrel 75mg OD      | <b>21 days</b>   | Minor stroke is National Institutes of Health Stroke Scale (NIHSS) ≤3 and high-risk TIA is ABCD2≥4  |
| Stable CAD managed with elective PCI  | Asprin 75mg OD                                | Clopidogrel 75mg OD      | 6m               | 6m majority patients (1m v. high bleed risk, 3m high bleed risk, if very high ischaemic risk, consider >6m)   |
| Secondary prevention of cardiovascular disease (post-MI; PAD)                                 | Asprin 75mg OD                                | NO DAPT                  | Lifelong         | or clopidogrel if aspirin not tolerated   |

**Table 1:** Antiplatelet therapy: Indications, recommended agent(s) and duration of treatment (sources: NICE guidelines<sup>2</sup>, European Society for Cardiology<sup>3</sup>, BMJ<sup>14</sup>)