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PRACTICE

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Indications for anticoagulant and antiplatelet combined therapy

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Antithrombotic medications reduce thromboembolic events by inhibiting platelet aggregation and coagulation. Antiplatelet drugs and oral anticoagulants are examples of antithrombotic medications and are among the most commonly prescribed drugs in both primary and secondary care.[1] Clinicians are familiar with their use, however antiplatelets and oral anticoagulants are the drug classes most commonly implicated in adverse drug reactions occurring both in the community and in hospital.[2 3] Increasing numbers of patients have an indication for combination antiplatelet and oral anticoagulant therapy. For example, more than one million people in the UK have atrial fibrillation, of whom approximately one third also have an indication for antiplatelet therapy as secondary prevention.[4] Despite the need to understand the balance between benefit and risk, there are limited randomised data investigating antithrombotic co-prescription. Current guidelines are therefore based on expert opinion and the extrapolation of non-randomised data.

Who might need co-prescription?

Patients can develop independent indications for antiplatelet and oral anticoagulant therapy, but in most cases the pathophysiology will intersect. The relationship between cardiovascular disease and atrial fibrillation is the typical example, where one fifth of patients presenting with atrial fibrillation will subsequently require coronary intervention, and up to one fifth of acute coronary syndrome (including ST elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina) presentations develop atrial fibrillation.[5 6] Similarly, patients with essential thrombocythaemia and polycythaemia vera can be prescribed aspirin for primary prevention of cardiovascular disease, but may also require oral anticoagulation due to the high lifetime prevalence for venous thrombosis.[7]

What are the risks of co-prescription?

Combination antithrombotic therapy increases the risk of fatal and non-fatal bleeding. In a Danish registry of patients with atrial fibrillation (n=82 854; mean follow-up over three years) the annual incidence of bleeding was less than 4% for aspirin or warfarin monotherapy, but rose to 15.7% for triple therapy comprising aspirin, clopidogrel, and warfarin.[8] The gastrointestinal tract is the most common site for bleeding, followed by upper airways.

Is the balance of benefit and risk quantifiable for an individual patient?

There are numerous scoring systems to prognosticate clinical outcomes (box 1), although none have been developed specifically in the context of combination antithrombotics. However, the patient cohort used to develop the CHA_2DS_2-VASc score was prescribed antiplatelet drugs in 74.0% of cases and so provides a reasonable estimation of annual stroke risk for patients already prescribed an antiplatelet drug.[9 10] In contrast, only 7.1% of the cohort used to develop the HAS-BLED score were co-prescribed an antiplatelet and oral anticoagulant, although subsequent investigation showed that HAS-BLED predicted bleeding events with moderate accuracy.[11 12] These two scoring systems are endorsed by European cardiovascular guidelines.[13]

Should everyone who has an indication for antiplatelet therapy plus oral anticoagulant be prescribed both?

The decision to co-prescribe antithrombotic medication must be based on the relative merit of each indication, the incremental risk of bleeding, and patient preference. Common clinical

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What you need to know

- Combination antithrombotic treatment increases the risk of bleeding, and this risk should be estimated and discussed with patients to guide treatment decisions (eg, using risk scores such as HAS-BLED)
- In most patients with independent indications for both antiplatelet and oral anticoagulant therapy the pathophysiology will intersect and combination antithrombotic treatment may not be necessary
- When co-prescribing, check that the patient is not prescribed medication that will increase bleeding risk further (eg, non-steroidal anti-inflammatory drugs) and consider the addition of an H_2 antagonist or proton pump inhibitor.

Box 1: Risk factors for stroke in atrial fibrillation (CHA_2DS_2-VASc) and for bleeding in patients on anticoagulation (HAS-BLED).

For details on calculation of these scores and how to use them to guide therapy, see https://www.nice.org.uk/guidance/cg180/chapter/key-priorities-for-implementation

CHA_2DS_2-VASc

- Congenital heart failure
- Hypertension
- Age 65-74, or ≥ 75 years
- Diabetes mellitus
- Stroke, transient ischaemic attack, or thromboembolism
- Vascular disease
- Female sex

HAS-BLED

- Hypertension
- Abnormal liver function
- Abnormal renal function
- Stroke
- Bleeding
- Labile international normalised ratios
- Age > 65 years
- Drugs which predispose to bleeding (ie, antiplatelet medications or non-steroidal anti-inflammatory drugs)
- Alcohol

scenarios discussing possible indications for combination therapy are discussed below (see infographic).

Primary prevention of cardiovascular disease

Antiplatelets are not recommended for the primary prevention of cardiovascular disease, although there is weak evidence that aspirin might confer some benefit in patients who are hypertensive and have impaired renal function or elevated risk for cardiovascular disease (10 year risk >20%).[14 15]

In patients who develop an indication for an oral anticoagulant, this should replace the antiplatelet agent for which evidence is weak.

Secondary prevention of cardiovascular disease

Antiplatelet therapy is recommended for the secondary prevention of cardiovascular disease.[16] In patients with stable coronary artery disease who have an additional indication for oral anticoagulation, it is recommended that they are prescribed oral anticoagulant monotherapy unless they are very high risk for coronary events. In these patients the addition of aspirin or clopidogrel might be considered.[13]

Non-valvular atrial fibrillation and treatment after acute coronary syndrome or percutaneous coronary intervention

In patients with non-valvular atrial fibrillation who have acute coronary syndrome and/or undergo percutaneous coronary intervention, the combination and duration of antithrombotic therapy depends on stroke risk (CHA_2DS_2-VASc score), bleeding risk (HAS-BLED score), and clinical setting (stable coronary artery disease versus acute coronary syndrome).[13]

In general, it is recommended that patients receive triple therapy for the initial phase (four weeks to six months after the event), followed by dual therapy (antiplatelet plus oral anticoagulant) to complete 12 months of treatment.[13]

In patients who are at high risk of bleeding, the use of bare metal stents in preference to drug eluting stents is recommended to shorten dual antiplatelet and anticoagulant therapy to four weeks.[13]

At 12 months after the event, treatment should be as per secondary prevention of cardiovascular disease (ie, antiplatelet only or oral anticoagulant if indicated).

Valvular heart disease

Oral anticoagulant therapy is recommended for all patients with native valvular heart disease and atrial fibrillation.[17] Choice of oral anticoagulant is limited to warfarin, as clinical trials for direct oral anticoagulants (DOACs) in valvular heart disease have not been undertaken.

The target international normalised ratio is determined by a combination of prosthesis thrombogenicity and patient related risk factors.[17]

The addition of an antiplatelet to oral anticoagulants reduces the risk of valve thrombosis and arterial thromboembolism but at an increased risk of major bleeding.[18]

Oral anticoagulants are recommended lifelong for patients with a mechanical prosthesis, with the possible addition of low-dose aspirin in patients with concomitant atherosclerotic disease.[17]

Bioprosthetic values might not require oral anticoagulants beyond three months after insertion unless there is another indication such as atrial fibrillation.

Venous thromboembolism

Acute deep vein thrombosis in patients prescribed antiplatelets should be treated with oral anticoagulants for a minimum of three months.[19] In patients with intermediate to high risk of bleeding, consider stopping any antiplatelet for the duration of the treatment unless there is an acute indication (eg, recent cardiac event).

On completion of treatment for a provoked deep vein thrombosis the patient should return to their pre-event antithrombotic regimen. Patients who have had an unprovoked deep vein thrombosis should be investigated and might continue long term oral anticoagulants in place of the pre-event antithrombotic regimen.[19 20]

Myeloproliferative disorders

Patients with essential thrombocytosis or polycythaemia vera are prescribed low-dose aspirin to mitigate their increased thrombotic risk. There is insufficient evidence to suggest that thromboembolism in this population should be treated differently to the regimen described above.[21]

Which antiplatelets and oral anticoagulants can be combined?

Aspirin should be prescribed as the first line antiplatelet agent unless the patient is intolerant or has a compelling contraindication. In patients receiving dual antiplatelet therapy, for example after percutaneous coronary intervention without an indication for an oral anticoagulant, then a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) is added. The novel $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) are reserved for patients with acute coronary syndrome as they inhibit platelet activity to a greater extent than clopidogrel and so increase the risk of bleeding.[22-24] The combination of novel $P2Y_{12}$ inhibitors with oral anticoagulants increases the risk of bleeding, and cannot currently be recommended. In patients with atrial fibrillation and coronary artery disease, the dose of warfarin should be carefully regulated to a target INR 2.0-2.5.[13] DOACs (apixaban, dabigatran, rivaroxaban) have been generally shown to be a safe alternative to warfarin for the management of both atrial fibrillation and venous thromboembolism, although there remains uncertainty with regards to real world risk:benefit.[25-27] Prescribe patients the lower licensed dose of a DOAC when combined with an antiplatelet. In patients on warfarin with a stable international normalised ratio there is no indication to switch to a DOAC.[13] Where prescribers choose to switch between oral anticoagulants, it is important that they check both the licensed indications and contraindications of the new medication, as these differ between oral anticoagulants.

What else needs to be considered when co-prescribing?

Pharmacology

Check that the patient is not prescribed medication that will increase bleeding risk further (eg, non-steroidal anti-inflammatory drugs).

Consider the addition of an H_2 antagonist or proton pump inhibitor to reduce the risk of gastrointestinal bleeding.

Patient factors

Discuss the risk:benefit of treatment with all patients, with specific emphasis on the required duration of treatment if they are undergoing any procedure that will necessitate co-prescription (eg, coronary stent insertion). Use the CHA_2DS_2-VASc and HAS-BLED scores to aid this discussion.

Risk stratification is a dynamic process, and is best performed at regular intervals (ie, on a yearly basis).[13] Consider the patient's ability to adhere to the medication regimen and take steps to assist as necessary (e.g. dosette box, care package).

Physician factors

Discharge patients on medications that are available for prescription on community formularies.

Ensure that suitable follow-up is arranged to review termination or continuation of antithrombotic treatment as appropriate.

How might recommendations change in the future?

There is emerging evidence that triple antithrombotic therapy results in no better cardiovascular outcome and an increase in bleeding when compared with clopidogrel plus oral anticoagulant.[28 29] Upcoming studies aim to report on whether aspirin provides any benefit when prescribed with novel $P2Y_{12}$ inhibitors, the optimum DOAC dose when combined with an antiplatelet, and the duration of antiplatelet therapy after acute coronary syndrome.

We have read and understood the BMJ policy on declaration of interests and declare the following interests: none

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Case studies

Case 1

A 63 year old, post-menopausal woman visits her general practitioner having noticed intermittent blood in her urine. These episodes have been associated with dysuria, but she denies increased frequency or vaginal discharge. She reports that her urine has been a light pink colour and that she first noticed this after commencing rivaroxaban 20 mg once daily five weeks ago for an unprovoked, below knee deep vein thrombosis. Her medical history includes stable ischaemic heart disease, for which she takes clopidogrel 75 mg once daily (she is intolerant of aspirin). Clinical examination is unremarkable. Her heart rate is 65 beats/min and blood pressure 145/76 mmHg. Urine is coloured pink; dipstick reveals 4+ blood and trace protein. Is it appropriate to attribute the haematuria to antithrombotic therapy? Should her antithrombotic therapy be stopped?

Discussion

Perform a full blood count and screening for renal function and coagulation as initial investigations. Don't attribute macroscopic haematuria to antiplatelet and/or anticoagulant therapy without urological investigation, and so refer the patient on a two week wait cancer pathway.[30 31] The rivaroxaban is required to prevent propagation of deep vein thrombosis and/or embolism and so should be continued unless bleeding is sufficient to require inpatient assessment. The clopidogrel is prescribed for secondary prevention and so short-term cessation is low risk.

Case 2

A 71 year old man undergoes an angiogram after acute coronary syndrome and receives two drug eluting stents in an uncomplicated percutaneous coronary intervention. His medical history includes non-valvular atrial fibrillation for which he takes warfarin. Prognostic scoring shows that he is high risk for stroke (CHA_2DS_2-VASc) and intermediate risk for bleeding (HAS-BLED). What is the optimum antithrombotic strategy?

Discussion

The patient should receive triple antithrombotic treatment for six months, at which point aspirin can be stopped. At 12 months after the percutaneous coronary intervention, switch the patient to oral anticoagulant monotherapy.[13]

Education into practice

To what extent do you review the indication for co-prescription of oral anticoagulants and antiplatelets in your patients? How do you monitor whether the indications continue to be clear and appropriate?

Does this article give you any ideas about how to approach a discussion with patients about the risk:benefit of prescribing oral anticoagulants and antiplatelets and how to encourage joint decision making?

What will you do differently as a result of reading this article?

How patients were involved in the creation of this article

We asked two patients to review the article, both of whom are prescribed antiplatelet medication for secondary prevention and involved in research governance. Feedback focused on the "partnership between patient and practitioner" when making prescribing decisions, and that, due to the stress that can be caused by excessive bleeding, "each case should be carefully considered with respect to the balance struck between the protection of a patient's medical welfare and their quality of life." In response we put greater emphasis on considering the risk:benefit balance throughout the article. The case studies in this article are hypothetical.

How this article was made

Guidelines produced by the National Institute for Health and Care Excellence and the European Society of Cardiology provided the basis for recommendations in this article. When information from guidelines was incomplete or inconclusive, *ad hoc* literature searches of Medline were performed.

of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;359:3155-79. doi:10.1093/eurheartj/ehu298 pmid:25154388.

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