NEW ORAL ANTIPLATELETS AND ANTICOAGULANTS IN GENERAL PRACTICE: PART 1

This series discusses two new antiplatelet and four new oral anticoagulant (OAC) medications that GPs are increasingly finding on routine repeat prescriptions

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In healthy individuals, a number of factors constantly balance thrombus formation and fibrinolysis. Classically, injury to endovascular cells causes a number of reactions, culminating in thrombus production. Endothelial vascular cells create thrombus by synthesising von Willebrand factor, tissue factor and by inhibiting fibrinolysis; the blood vessel contracts and the normally soluble clotting factors (F) are activated by a protein cleavage cascade to activate F10a. This acts to cleave prothrombin (F2) and produce thrombin (F2a), which cleaves fibrinogen to create insoluble fibrin (F1a). Platelets actively participate in the process, releasing a number of agents to encourage and to control thrombus production; they bind to fibrinogen and create a soft plug to stem the bleeding.

This physiology is exploited by the antiplatelets and oral anticoagulant (OAC) drugs to help people with thrombotic conditions. There is a prevalence of genetic differences in thrombotic and fibrinolytic factors in the normal population, predisposing to bleeding or coagulation tendencies, and individual normal genetic variations in the ability of the liver to metabolise medications which may influence outcomes in a normal population. GPs are well aware of risk factors for atheromatous and thrombotic diseases.

In 2013, cancers killed 29% of people in England and Wales, while coronary heart disease (CHD) and stroke (CVA) combined killed 28%.[1] Heart disease is the leading cause of death for men over 50 years of age and the single biggest killer in the UK. Secondary CHD prevention is usually with antiplatelet therapy.

Stroke is the third most common cause of death for people in England and is the leading cause of chronic disability for all ages.[1] Atrial fibrillation (AF) is the commonest cause of embolic stroke and it is estimated by NICE that 2% of the population are in AF.[2]

Estimated annual incidence rates of venous thromboembolism (VTE) as deep vein thrombosis (DVT) and/or pulmonary embolism (PE) among people of European descent range from 104-183 per 100,000 person years, rates similar to that of stroke (CVA).[3] A number of these events occur in medical inpatients, many of whom are elderly, immobile and may not be fully hydrated and also in patients post operatively, especially post knee and hip replacements. Once a day subcutaneous injections of low molecular weight (LMW) heparin is used for prophylaxis and early treatment, before warfarin has reached anticoagulant action in VTE. Once warfarin, an oral anticoagulant (OAC) has reached anticoagulant levels it is the main therapy for VTE. However, LMW heparin is recommended therapy for prevention and treatment of VTE in cancer patients, in preference to warfarin.

Aspirin is the most commonly used antiplatelet and warfarin, a vitamin K antagonist (VKA) that prevents the action of a number of clotting factors, is the most commonly used OAC. Both these drugs are in the top four medications implicated in hospital admissions in older people due to adverse medication events.[4] This series highlights the newer oral agents which GPs are becoming familiar with when signing prescriptions and the need to weigh up patient medication benefits and risks. All OACs and antiplatelet medications are contraindicated in patients with inherited or acquired coagulation tendencies, including liver problems, as they will aggravate their bleeding risks.

In general practice, the most common liver problem encountered is liver failure due to alcoholism. The failure of the liver to synthesise clotting factors, combined with the consequences of portal hypertension, results in a number of alcoholic patients dying from bleeding oesophageal varices. The bleeding

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TABLE 1

Numbers of prescriptions of oral antiplatelet agents dispensed in 2014[5] with class of action. Trade names, if no generic is available, are in brackets

Name	Number of prescriptions dispensed 2014 to nearest 50,000	Class of action
Aspirin	29,600,000	Antiplatelet COX inhibitor
Dipyramidole	850,000	Antiplatelet (cAMP action) and vasodilator
Dipyramidole plus aspirin	150,000	Antiplatelet and vasodilator
Clopidogrel	7,500,000	Antiplatelet inhibits P2 Y_{12} ADP receptors thienopyridine
Prasugrel (Efient)	100,000	Antiplatelet inhibits P2 Y_{12} ADP receptors thienopyridine
Ticagrelor (Brilique)	300,000	Antiplatelet inhibits P2 Y_{12} ADP receptors via novel action

is problematic but the inability to coagulate creates a desperate situation.

All antiplatelets and OACs are contraindicated in patients with active bleeding, previous haemorrhagic conditions such as haemorrhagic CVA, cerebral haemorrhage and are contraindicated in pregnancy and breast feeding. They are contraindicated post-operatively after recent ophthalmic, spinal and brain surgery. GPs need to look at the British National Formulary (BNF) to check interactions and unusual patient reported side-effects when co-prescribing. The BNF is available electronically for GPs who register at https://www.medicinescomplete.com to add to their desktops in clinics.

New oral antiplatelet drugs post acute coronary syndrome in general practice

The two traditional and most commonly prescribed antiplatelet drugs are aspirin and clopidogrel,[5] (see Table 1).

Aspirin (acetyl salicylic acid) acts by irreversibly inhibiting cyclo-oxygenase, an enzyme that activates and aggregates platelets via prostaglandins, prostacyclin and thromboxane. Aspirin acts for about 10 days, until platelets are replaced by the body. It is prescribed for the secondary prevention of CHD, post coronary artery bypass surgery (CABG), intermittent claudication (IC), angina, acute coronary syndrome (ACS), post coronary stents,[6,7] ischaemic stroke (iCVA) and transient ischaemic attacks (TIAs). ACS refers to unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation MI (STEMI), which may also include new onset left bundle branch block rather than ST elevation on the ECG. Aspirin is not recommended for primary prevention of CHD and is not recommended for treatment of AF.[2]

Clopidogrel is used with aspirin after ACS with percutaneous coronary intervention (PCI), usually with drug eluting stent placement. This is Dual Antiplatelet Therapy (DAPT), using aspirin 75mg daily with clopidogrel ec 75mg daily for four weeks post STEMI and 12 months post NSTEMI, after which time the patient is reviewed and the clopidogrel may be stopped. The timing of cessation of DAPT is related to the risk of late stent thrombosis versus the risk of bleeding for the patient, and cardiologists may individualise time of DAPT cessation related to perceived patient risk at the time of the procedure. Clopidogrel is also indicated long-term in patients who cannot tolerate aspirin, in patients with multiple atheromatous induced diseases, and in patients with IC.

The two new oral antiplatelet medications are prasugrel (Efient) and ticagrelor (Brilique) and can be used instead of clopidogrel with aspirin post-ACS. Each can be given in the hospital on presentation of ACS at a loading dose instead of clopidogrel and continued after discharge with aspirin. They are not licensed for use as a sole antiplatelet therapy at present. The advantage is that they have a more rapid onset of action than clopidogrel and ticagrelor has a more rapid cessation of action (seven-12 hours). Like clopidogrel, Prasugrel is metabolised through the cytochrome P450 enzyme complex at the liver. Some patients are slow responders to clopidogrel due to variance in liver activation. As clopidogrel is a pro-drug there are also high responders who may be at increased risk of bleeding. Prasugrel and ticagrelor have less variation in individual genetic metabolism than clopidogrel.

Prasugrel (Efient)

Prasugrel dose is usually 10mg once daily. It is an irreversible binder to platelet receptors and so inhibits platelet activation and aggregation, like clopidogrel, but

Aspirin (acetyl salicylic acid) acts by irreversibly inhibiting cyclo-oxygenase, an enzyme that activates and aggregates platelets via prostaglandins, prostacyclin and thromboxane

is about 10 times more potent.[8] Like clopidogrel it is a pro-drug and has a similar action, so hypersensitivity to clopidogrel is a contraindication to prasugrel. GPs will see patients discharged on prasugrel in conjunction with aspirin after STEMI post PCI for ACS for up to 12 months. It has a superior action to clopidogrel in this group, and an indication in diabetics post STEMI or NSTEMI, but risks of major and minor bleeding combined are slightly increased in the prasugrel group compared to clopidogrel.[8]

Prasugrel should be used with caution in renal and liver impairment. Rare side-effects are thrombocytopoenia and thrombotic thrombocytopoenia; usually occurring in the early months after starting therapy (clopidogrel is also a known cause). In lightweight <60kg patients or elderly patients >75 years old the dose is 5mg a day, while other patients can take 10mg a day.[9] It should be stopped seven days before surgery when normal coagulation is desired.

Ticagrelor (Brilique)

Ticagrelor is an oral antiplatelet taken as 90mg twice a day. It has a novel action in antagonising ADP receptors on platelets to prevent platelet aggregation, but not in the same way as prasugrel and clopidogrel. It is not a pro-drug and has a rapid onset and cessation of action.[10] It is indicated with low dose aspirin for up to 12 months for people with ACS.[6]

It has some unusual side-effects: it may cause bradycardia, sick sinus syndrome, second- or third-degree AV block. It may cause breathlessness but the mechanism of this is not understood. The BNF suggests caution in people with asthma or chronic obstructive pulmonary disease, as well as in patients with a history of gout. The BNF recommends that the eGFR is monitored a month after starting ticagrelor to ensure renal function has not deteriorated.[11] There are interactions with liver metabolised medications and serotonin substance reuptake inhibitors. Clarithromycin should be avoided and interactions occur with simvastatin and digoxin.

CASE STUDY

A fit lady of 76 years old with a history of hypertension controlled on therapy to normal levels, and with no other risk factors who develops AF has a CHA_2DS_2VASC score of 4. The web calculator this score predicts an iCVA risk of 4.8% per annum and a combined TIA, iCVA and systemic embolism risk of 9.3% per annum. Her HAS-BLED score is 1 giving her a 3.4% risk of major bleeding.[15]
HAS-BLED does not include fall frequency, polypharmacy interactions, diet, bowel function, risky activities like skiing or forgetfulness and it is the GP's role to individualise risk and discuss benefits and harms with their patients.

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NEXT ISSUE

New oral antiplatelets and anticoagulants in general practice: Part 2