Novel antithrombotic agents 1

Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments

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Antithrombotic drugs, which include antiplatelet and anticoagulant therapies, prevent and treat many cardiovascular disorders and, as such, are some of the most commonly prescribed drugs worldwide. The first drugs designed to inhibit platelets or coagulation factors, such as the antiplatelet clopidogrel and the anticoagulant warfarin, significantly reduced the risk of thrombotic events at the cost of increased bleeding in patients. However, both clopidogrel and warfarin have some pharmacological limitations including interpatient variability in antithrombotic effects in part due to the metabolism, interactions (eg, drug, environment, and genetic), or targets of the drugs. Increased knowledge of the pharmacology of antithrombotic drugs and the mechanisms underlying thrombosis has led to the development of newer drugs with faster onset of action, fewer interactions, and less interpatient variability in their antithrombotic effects than previous antithrombotic drugs. Treatment options now include the next-generation antiplatelet drugs prasugrel and ticagrelor, and, in terms of anticoagulants, inhibitors that directly target factor IIa (dabigatran) or Xa (rivaroxaban, apixaban, edoxaban) are available. In this Series paper we review the pharmacological properties of these most commonly used oral antithrombotic drugs, and explore the development of antiplatelet and anticoagulant therapies.

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This is the first in a Series of three papers about novel antithrombotic agents

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Introduction

Haemostasis consists of a complex interplay of the vascular endothelium, platelets, and coagulation factors. This process can lead to clot formation in the arteries or veins, which ultimately manifests as an acute coronary syndrome (ACS) or venous thromboembolism. As such, antithrombotic drugs, including antiplatelet therapies and anticoagulants, are frequently used in patients with cardiovascular disease. This Series paper focuses on the pharmacological properties of the most commonly used oral antithrombotic drugs.

Careful consideration of the efficacy to safety ratio is needed in design and selection of antithrombotic drugs. Additionally, several pharmacological factors can affect a drug's success: a high rate of absorption, an active parent drug rather than a prodrug that needs to be metabolised, minimum interactions, rapid action, linear pharmacokinetics with a dose-dependent drug effect, many modes of elimination, and a direct target. These features restrict drug resistance and reduce interpatient variability in the antithrombotic effect. The aim is now to develop antithrombotic drugs with these more favourable pharmacological properties, thereby reducing thrombotic events without generation of unacceptably high bleeding rates.

Oral antiplatelet treatments

Targeting of platelets

Platelets are integral to the development of the pathological thrombus responsible for cardiovascular disease.[1] Disruption of the endothelium exposes platelets to the adhesive proteins of the subendothelial matrix. Platelet adhesion is dependent on the interactions between the matrix proteins and platelet-receptor glycoproteins (figure 1). Activation of intracellular signalling pathways in the platelet results in the release of activators such as ADP, adrenaline, serotonin, thrombin, and thromboxane A2. These agonists bind to G-protein-coupled receptors, which further potentiate each other's actions. Finally, the glycoprotein IIb/IIIa complexes on platelets bind to fibrinogen, a process that results in platelet aggregation and can culminate in thrombus formation—especially during conditions of high shear stress in stenotic arteries. Thus, the adhesion, activation, and aggregation of platelets is a many stepped process and pharmacological targeting of platelet activating factors and their receptors has become a main strategy in antithrombotic drug development.

Aspirin

Aspirin (acetylsalicylic acid) is the most prescribed antiplatelet drug for prevention of cardiovascular disorders. Low doses of aspirin selectively inhibit cyclooxygenase (COX)-1, resulting in antiplatelet effects, whereas high doses of aspirin inhibit both COX-1 and COX-2 leading to anti-inflammatory and analgesic effects.[3] The inhibition of prostaglandin production by aspirin was first reported in three healthy individuals.[3]

Search strategy and selection criteria

We searched PubMed for relevant articles using the terms "antithrombotic", "antiplatelet", and "anticoagulant" in conjunction with the terms "pharmacology", "oral", "medications", "agents", and "therapies." Relevant articles were selected and we reviewed their references. We did not apply any date restrictions to our search.

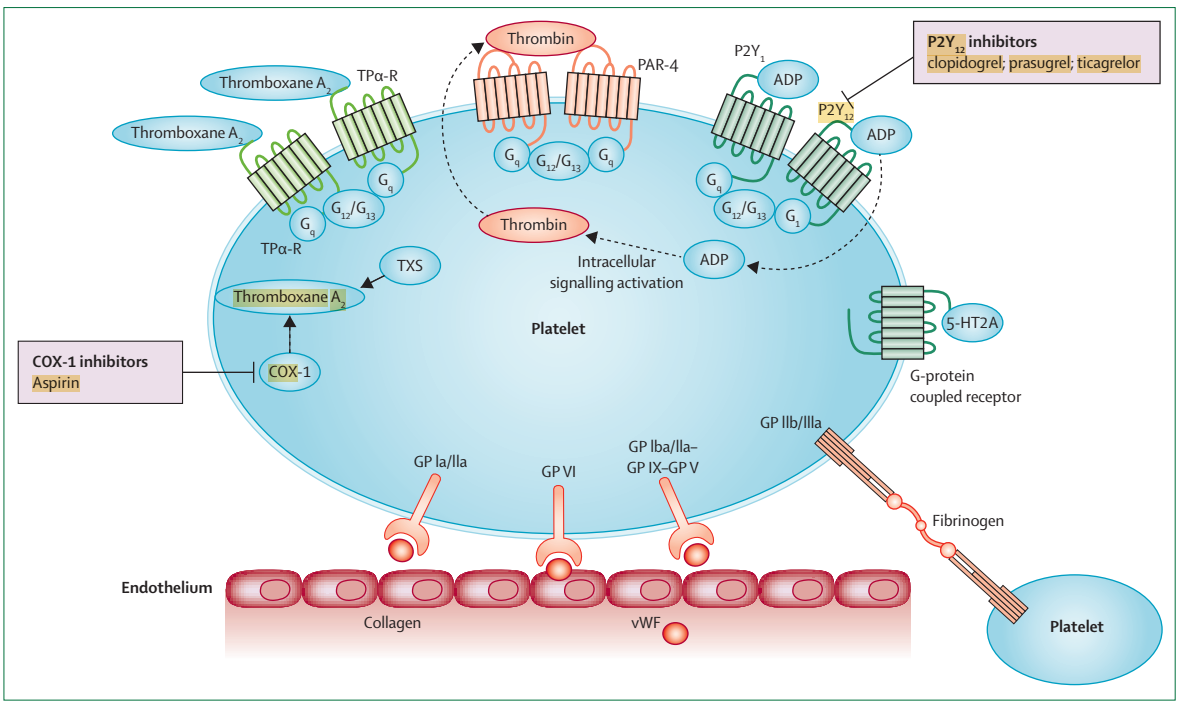

Figure 1: **Platelet pathways and commonly used oral antiplatelet treatments**
Disruption of the endothelium exposes adhesive proteins of the subendothelial matrix (collagen and von Willebrand factor [vWF]) that interact with platelet-receptor glycoproteins (GP). Intracellular signalling pathways result in the release of robust platelet activators such as ADP, adrenaline, serotonin, thrombin, and thromboxane A2. These agonists bind to G-protein-coupled receptors and further potentiate the process. Ultimately, GP IIb/IIIa binds to fibrinogen and results in platelet aggregation. 5-HT2A=serotonin receptor 2A. COX-1=cyclooxygenase 1. PAR=protease-activated receptor. TP-R=thromboxane prostanoid receptor. TXS=thromboxane A2 synthase. G=G-protein. Dotted arrows show movement of molecules. Adapted from Franchi and Angiolillo,[2] by permission of Nature Reviews Cardiology.

More than a decade later, Bengt Samuelsson was awarded the Nobel Prize for identifying thromboxane A2 and solidifying the mechanistic relation between platelet arachidonic acid metabolism and platelet aggregation.[5]

Aspirin blocks the access of arachidonic acid to its receptor and inhibits production of thromboxane A2 by acetylating a serine residue near the narrow catalytic site of the COX-1 channel.[6] Thromboxane A2 inhibition is cumulative with repeated low doses of aspirin because of the permanent and irreversible enzyme inactivation throughout the 7–10 day lifetime of anucleated platelets, which allows for aspirin to be given once daily and be effective despite its very short half-life (15–20 min). Although aspirin's effect on thromboxane A2 inhibition in part accounts for its antithrombotic properties, indirect properties of aspirin (including the reduction of inflammatory cytokines, oxygen radicals, and growth factors) are also relevant.[7]

Absorption of aspirin is rapid and mediated by passive diffusion through gastrointestinal membranes. Its systemic bioavailability is about 45–50% and remains at a similar level after single or repeated oral administration, but is much lower when given as the enteric-coated formulation. Peak plasma concentration of aspirin is obtained within 30 min after ingestion of regular aspirin and up to 4 h after ingestion of the enteric-coated formulation.[8] For patients with ACS, a recommended 150–325 mg of oral aspirin is chewed to achieve rapid inhibition of thromboxane A2.[9,10] Where approved, aspirin can also be given intravenously preferably at lower doses.[9] After a patient has had an ACS, no clear ischaemic advantage seems to be noted with higher versus lower doses of oral aspirin, but the lower doses (81–100 mg) result in relatively less bleeding than higher doses of aspirin.[11]

The recovery of platelet function after aspirin administration is related to the physiological turnover of platelets. With the daily generation of 10–12% new platelets from megakaryocytes, near normal haemostasis can be recovered within 2–3 days after the last aspirin dose in patients with a typical rate of platelet turnover; although, this time can vary.[12] A faster rate of platelet turnover and platelet hyper-reactivity reported in some proinflammatory settings (such as in patients with ACS or diabetes)[13] might explain, in part, the variability in inhibition of platelet thromboxane A2, so-called aspirin resistance.[14] Increases in the frequency of aspirin administration from once to twice daily reduce the recovery of platelet function and the drug responsiveness variability in patients with diabetes.[15,16] Whether this strategy could overcome the reduced efficacy of aspirin in patients with diabetes is yet to be proven.

P2Y12 receptor antagonists

Use of aspirin and a P2Y12 receptor antagonist, known as dual antiplatelet therapy, represents the basis of treatment in patients with ACS and those undergoing coronary stenting. The P2Y12 receptor antagonist ticlopidine reduces the risk of stent thrombosis compared with standard treatments.[17–21] Because of haematological side-effects, ticlopidine was quickly replaced with clopidogrel to reduce atherothrombotic events.[22–24] The complete clopidogrel pharmacokinetic and pharmacodynamic profile and its interindividual variability were extensively studied after it became authorised on the market, by contrast with the newer P2Y12 receptor antagonists prasugrel and ticagrelor, which were studied before being authorised.

Overall, improvements in knowledge of the mechanisms underlying arterial thrombosis and the pharmacology of antiplatelet drugs led to the development of prasugrel and ticagrelor with faster onset of action and less interpatient variability in platelet inhibition than with clopidogrel (table 1). In phase 3 clinical trials, both prasugrel[25] and ticagrelor[26] reduced cardiovascular adverse events compared with clopidogrel in patients with ACS, although they simultaneously increased major spontaneous bleeding.[25,26] No large-scale randomised study has yet compared the effects of prasugrel versus ticagrelor on patient outcomes. Discussions are also continuing about how early patients with ACS should be given P2Y12 receptor antagonists and the optimum duration of dual antiplatelet therapy in patients with cardiovascular disease.[27–31]

The thienopyridines clopidogrel and prasugrel are both prodrugs that need biotransformation to become active. These two drugs irreversibly inhibit the P2Y12 receptor.[32,33] After absorption, 85% of clopidogrel is hydrolysed by esterases into an inactive carboxylic acid. The remaining 15% of clopidogrel undergoes a two-step oxidation process via hepatic cytochrome P450 isoenzymes, mainly CYP2C19, which is associated with both steps, and to a lesser extent CYP1A2, CYP2B6, CYP3A4, and CYP3A5.[34] The transient active thiol-metabolite specifically and irreversibly binds the platelet P2Y12 receptor. By contrast, prasugrel, after rapid and extensive absorption, is hydrolysed by intestinal carboxylestarases to a thiolactone intermediate metabolite that undergoes a one-step oxidation mainly via CYP3A4 and CYP2B6, and to a lesser extent via CYP2C9 and CYP2C19,[33] to form the active metabolite.

Steady state inhibition of platelet function is noted after 5–7 days of clopidogrel maintenance dosing, accounting for the role of a loading dose to achieve more rapid inhibition. For clopidogrel, the recommended loading dose is 600 mg and maintenance dose is 75 mg.[9,10] Onset of clopidogrel antiplatelet action is reported at 2 h after a loading dose, compared with after 30 min for prasugrel (loading dose 60 mg and maintenance dose 10 mg), whereas both drugs have a slow offset of action of 7–10 days. The active metabolites for clopidogrel and prasugrel are equipotent. The faster and more predictable antiplatelet response with prasugrel than with clopidogrel is mainly due to its greater absorption and higher active metabolite bioavailability rather than due to differences between drug affinity for the P2Y12 receptor.[35,36]

	Clopidogrel	Prasugrel	Ticagrelor
Drug class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine
P2Y12 receptor blockade	Irreversible	Irreversible	Reversible
Route of administration	Oral	Oral	Oral
Frequency of administration	Once a day	Once a day	Twice a day
Prodrug	Yes	Yes	No
Percentage of active metabolite	15%	85%	90–100%
Onset of action	2–8 h	30 min–4 h	30 min–4 h
Offset of action	7–10 days	7–10 days	3–5 days
Interactions with CYP-targeted drugs	CYP2C19	No	CYP3A4 or CYP3A5
Possible interactions with P-gp transporter	Yes	No	Yes (weak inhibitor)

CYP=cytochrome P450. P-gp=permeability glycoprotein.

Table 1: **Properties of P2Y12 inhibitors**

The ischaemic benefit of prasugrel compared with clopidogrel in patients with ACS undergoing percutaneous coronary intervention was particularly evident in those with diabetes. Prasugrel should not be used in patients who previously had a stroke or transient ischaemic attack (TIA), nor those older than 75 years, because of an increased risk of bleeding—unless high-risk ischaemic features are present. In the TRILOGY trial,[37] prasugrel was not better than clopidogrel in reducing ischaemic events in patients with non-ST-segment elevation myocardial infarction who had not undergone revascularisation. Duration of treatment with prasugrel and additional antiplatelet drugs continues to be investigated. Findings from one study[38] showed 30 months' treatment with prasugrel reduced the frequency of ischaemic events in patients receiving a paclitaxel-eluting stent more than did 12 months' treatment. An increase in myocardial infarction after withdrawal from prasugrel after either treatment duration was also noted,[38] which might be related to the stent type, resumption of the underlying disease risk, or rebound in platelet reactivity.

Unlike prasugrel, clopidogrel has been shown to have a wide interindividual variability in inhibiting ADP-induced platelet function. The mechanisms causing this variability are multifactorial and include drug, environmental, and genetic interactions, in addition to clinical features such as diabetes and obesity. Many studies have emphasised the link between carriers of *CYP2C19* loss-of-function alleles, mainly *CYP2C19*2*, and a heightened risk of major cardiovascular events in patients being treated with clopidogrel with ACS or those who have stents.[39–42] From these data, a clopidogrel boxed warning was issued by the

US Food and Drug Administration (FDA) recommending the use of different treatments or treatment strategies in people who are poor metabolisers and have two copies of the *CYP2C19* loss-of-function alleles.[43] Findings from some studies have also suggested an increased risk of bleeding with clopidogrel in patients with *CYP2C19*17* gain-of-function alleles.[44] No study has shown the clinical efficacy of personalising the antiplatelet clopidogrel dose in accordance with genetic testing; however, point-of-care genetic testing can be done effectively[45] and trials in progress[46,47] are aiming to further address this topic. Notably, findings from studies suggest that increased doses of clopidogrel continue to affect the extent of platelet inhibition without a ceiling effect.[11,48–51]

Proton-pump inhibitors (PPIs), such as omeprazole and esomeprazole (both substrates and inhibitors of CYP2C19), are associated with decreased inhibition of platelet aggregation by clopidogrel (appendix).[52] However, this mechanism did not adversely affect clinical outcomes in most studies,[53,54] and it was not substantiated in a randomised trial.[55] In the PLATO trial,[56] PPI and non-PPI gastrointestinal treatments were associated with increased cardiovascular events (ie, cardiovascular death, myocardial infarction, or stroke) in both the clopidogrel and ticagrelor arms, which could be because of confounding; although, the possibility of a heightened risk in patients with two *CYP2C19* loss-of-function alleles cannot be formally excluded.[57] Thus, clopidogrel combined with a PPI with reduced CYP2C19 involvement, such as pantoprazole or rabeprazole, might theoretically be a better option for patients with cardiovascular disorders.

See Online for appendix

Drugs that interact with other CYP enzymes associated with clopidogrel metabolism might alter the antiplatelet effect. A faster onset of clopidogrel action with greater platelet inhibition has been noted in smokers compared with non-smokers.[58] This surprising finding (the so-called smoker paradox) could in part be due to the increased CYP1A2 activity or upregulation of CYP2B6 expression by nicotine.[59] However, in a study[60] of smokers and non-smokers randomly assigned to treatment with clopidogrel and prasugrel, the findings suggest that mechanisms in addition to clopidogrel-specific mechanisms might underlie this paradox. Inhibition of CYP3A4 by drugs, such as ketoconazole, or regular consumption of 600–800 mL of grapefruit juice reduce the area under the curve of the clopidogrel active metabolite and the inhibition of platelet aggregation.[61] The effect of these pharmacokinetic and pharmacodynamic interactions on clinical outcomes remain inconclusive.

Despite compliance with standard doses of clopidogrel treatment, variability in platelet inhibitory effects and high on-treatment platelet reactivity (HPR) were reported in up to 35% of patients.[62] Findings from some studies[63–65] showed a relationship between HPR and incidence of recurrent clinical events, particularly between stent thrombosis or major adverse cardiovascular events in stented patients with ACS, and an association between a high risk of bleeding with lowest platelet reactivity during treatment. Platelet function measurements are used in pharmacokinetic and pharmacodynamic studies as a phenotypic marker for the efficacy of antiplatelet drugs. As a result, in specific patients, such as those with a body mass lower than 60 kg, a dose of 5 mg prasugrel (instead of 10 mg) is recommended on the basis of data from pharmacokinetic and pharmacodynamic studies.[66,67] However, randomised trials[68–70] have, so far, not shown the effectiveness of personalising antiplatelet clinical response in accordance with platelet function measurements, and codifying the ideal treatment range for ischaemic and bleeding events is difficult.[63,71,72] Thus, although some factors might account for these results (ie, timing of sampling, type of assays, cutoff value for definition of HPR, target population, or drug intervention),[73] there is not enough evidence so far to recommend routine platelet function testing to guide antiplatelet therapy in clinical practice. Ongoing studies will provide useful data to inform care in the future.[74,75]

Ticagrelor is the first clinically available oral cyclopentyltriazolopyrimidine that inhibits the P2Y12 receptor, and provides low interindividual variability in antiplatelet response. Unlike thienopyridines, ticagrelor does not bind to the ADP-binding site and instead binds to a separate site of the P2Y12 receptor to inhibit G-protein activation and signalling.[76] The recommended loading and maintenance doses of ticagrelor are 180 mg once and 90 mg twice per day. Ticagrelor is not a prodrug and platelet inhibition happens directly with action of the parent drug and the active metabolite mediated by hepatic CYP3A4 or CYP3A5 and possibly by intestinal CYP3A4. Ticagrelor has a faster onset of action than clopidogrel, with inhibition of more than 40% of platelets in 30 min after dosing and a peak effect in 2 h.[77] Nonetheless, with both ticagrelor and prasugrel in the setting of ST-elevation myocardial infarction, at least 4 h are needed to achieve effective platelet inhibition in most patients,[78] raising interest in drugs such as cangrelor, a rapidly acting intravenous inhibitor of the P2Y12 receptor. Ticagrelor has a plasma half-life of 8–12 h and reaches steady state after 2–3 days. Because the binding of ticagrelor to the P2Y12 receptor is reversible, the offset of ticagrelor action is faster than with thienopyridines.[77] However, ticagrelor's mechanism of action also affects the approach to treatment for patients who are bleeding. With aspirin and thienopyridines, the effects can be offset with platelet transfusions, whereas thienopyridines need transfusion with a higher percentage of platelet mass.[79] By contrast, because circulating ticagrelor and its metabolite are likely to inhibit transfused platelets, studies[80,81] suggest that platelet transfusions might not reverse the drug's properties.

Because ticagrelor's metabolism is mediated by CYP3A4 or CYP3A45, the coadministration of ticagrelor with potent CYP3A4 inhibitors and inducers should be avoided. Ticagrelor is not only a substrate, but also a CYP3A4 inhibitor that can increase plasma concentrations

of simvastatin and lovastatin, which themselves are CYP3CA4 substrates. Thus, the coadministration of ticagrelor with simvastatin and lovastatin doses of more than 40 mg should be avoided. Drinking of grapefruit juice also increases ticagrelor peak plasma concentrations, area under the curve, and its effect on platelet inhibition.[82] Ticagrelor is a substrate and a weak inhibitor of permeability glycoprotein (P-gp), and might interact with other drug substrates of P-gp. Therefore, monitoring of the plasma concentrations of drugs in a narrow therapeutic window, such as with digoxin, is needed at the start or modification of ticagrelor treatment.

Unlike other P2Y12 antagonists, ticagrelor also has non-P2Y12 mediated effects. These effects are associated with blockage of the equilibrative nucleoside transporter, which results in increased plasma concentrations of adenosine.[83] Adenosine has several properties including coronary vasodilation, reduction of ischaemia and reperfusion injury, inhibition of inflammatory responses to stress conditions, negative dromotropic and chronotropic effects, reduction of glomerular filtration, and stimulation of pulmonary vagal C fibres that might induce dyspnoea. Although these effects deserve to be further studied, they might have contributed to the reduction of mortality in patients with ACS who were treated with ticagrelor in the PLATO trial, in addition to the increased incidence of ventricular pauses, increased serum concentrations of creatinine, and dyspnoea. Additionally in this trial[26] the known atherothrombotic benefit of ticagrelor versus clopidogrel was not noted in patients in north America, a finding that is thought to most likely be due to an interaction with aspirin maintenance dose or chance. Studies in progress will help to expand on all of these findings, as well as assess patients with a more remote history of myocardial infarction.[31]

Other targets

The combination of aspirin with a P2Y12 receptor antagonist leaves the thrombin-mediated pathway available for activation. Vorapaxar and atopaxar are thrombin receptor (protease-activated receptor-1) antagonists that inhibit thrombin-mediated and thrombin receptor agonist peptide (TRAP)-mediated platelet aggregation.[84] Vorapaxar can achieve 80% or more inhibition of TRAP-induced platelet aggregation within 1 week since initiation. Because of vorapaxar's long half-life (165–311 h), 50% inhibition of TRAP-induced platelet aggregation was recorded at 4 weeks after discontinuation. In patients with stable atherosclerosis, vorapaxar reduced the risk of cardiovascular events; although this drug increased moderate or severe bleeding.[85] As such, vorapaxar has been approved by the FDA for use in patients with a myocardial infarction or peripheral vascular disease. Vorapaxar should not be used in patients who have had a stroke, TIA, or intracranial haemorrhage. Compared with vorapaxar, atopaxar has a shorter plasma half-life (22–26 h); it has not been assessed in phase 3 studies.

Other available oral drugs that affect platelet function include cilostazol and dipyridamole. Cilostazol inhibits phosphodiesterase III and and increases levels of cyclic AMP, which leads to vasodilation, reduction of vascular smooth muscle proliferation, and inhibition of platelet aggregation. Cilostazol is suggested for symptomatic management of peripheral vascular disease and has been used after percutaneous coronary intervention and for secondary prevention of non-cardioembolic stroke or TIA. Dipyridamole blocks the uptake of adenosine, which acts on the platelet A_2-receptor to activate platelet adenylate cyclase, reducing platelet aggregation. Furthermore, dipyridamole inhibits phosphodiestase. This drug is used for prevention of postoperative thromboembolic complications associated with cardiac valve replacement and for prevention of secondary stroke. Investigations[2,86] are assessing several other compounds that target additional platelet activating factors and their associated receptors, such as the thromboxane prostanoid receptor.

Oral anticoagulant treatments

Targeting of the coagulation system

In 1964, the concept of the coagulation cascade of enzymatic steps was introduced.[87] Since then, there has been a change in the notion of the process, whereby complexes of vitamin K-dependent enzymes and non-enzyme cofactors interact. These complexes include extrinsic tenase, intrinsic tenase, and prothrombinase. Their interaction leads to the formation of thrombin (factor IIa) that further amplifies the coagulation system, converts soluble fibrinogen to insoluble fibrin, and activates platelets[88] (figure 2). This system is offset by a set of anticoagulant mechanisms, including fibrinolysis by plasmin.

Vitamin K antagonists

Vitamin K-dependent antagonists (VKAs), such as warfarin, are the most commonly used oral anticoagulants. The history of warfarin dates back to the 1920s; serious bleeding after minor procedures were noted in cattle who ingested spoiled hay made from sweet clover containing substances that decreased haemostatic factors. In 1940, the active compound was identified as 3,3 -methylenebis-(4-hydroxycoumarin). This discovery led to the initial use of warfarin as a rodenticide; subsequently, warfarin and other related compounds were used as anticoagulants in human beings.[89] By antagonising vitamin K, warfarin disrupts the formation of clotting proteins dependent on vitamin K including factors II, VII, IX, and X, and proteins C and S. Warfarin has a mean plasma half-life of 40 h and the complete anticoagulant effects emerge 48–72 h after its administration. Inactivation and metabolism of this drug occur via enzymes including CYP2C9, CYP1A2, and CYP3A4.[90] Reversal of anticoagulant effects of warfarin can be achieved by administration of vitamin K or infusion of clotting factors.

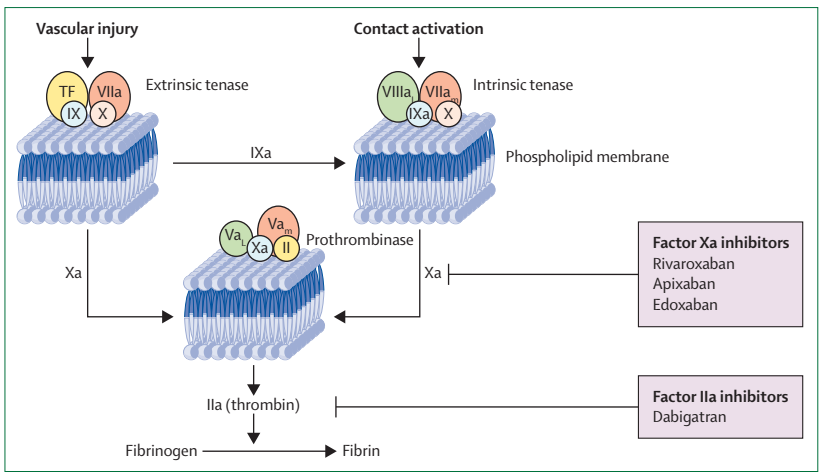

Figure 2: **Coagulation system and oral direct factor IIa and Xa inhibitors**
Vascular injury leads to the exposure of tissue factor (TF). TF binds to factor VIIa and forms extrinsic tenase, which activates factors IX and X. Factor IXa binds to factor VIIIa and forms intrinsic tenase (which can also be caused by contact activation), which activates factor X. Factor Xa binds to factor Va and forms prothrombinase, that converts factor II to IIa (thrombin). Factor IIa further amplifies the coagulation system, converting soluble fibrinogen to insoluble fibrin, and activates platelets. Non-vitamin K-dependent antagonist oral anticoagulants (NOACs) directly target factor IIa inhibitors (dabigatran) or Xa inhibitors (rivaroxaban, apixaban, edoxaban). Adapted from Weitz,[88] by permission of Elsevier Saunders.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Factor target	IIa (thrombin)	Xa	Xa	Xa
Prodrug	Yes	No	No	No
Route of administration	Oral	Oral	Oral	Oral
Bioavailability	3–7%	66% (~100% with food)	50%	62%
Hours to C_{max}	1–3	2–4	3–4	1–2
Half-life (h)	12–17	5–13	9–14	10–14
Renal clearance	80%	33%*	27%	50%
Liver metabolism: CYP3A4 involved	No	Yes (elimination)	Yes (elimination; minor CYP3A4 contribution)	Minimal
Absorption with H2B/PPI	–12% to 30%	No effect	No effect	No effect
Absorption with food	No effect	39%	No effect	6–22%
Dyspepsia	5–10%	No effect	No effect	No effect

C_{max}=maximum concentration. CYP=cytochrome P450. H2B=H2 blockers. PPI=proton pump inhibitor. *33% of rivaroxaban renally cleared, 33% excreted unchanged. Table is adapted from Heidbuchel and colleagues[101] and Grip and colleagues.[102]

Table 2: **Properties of non-vitamin K-dependent oral anticoagulants**

Although VKAs, such as warfarin, have been used clinically for more than 60 years, several challenges have been noted with these anticoagulants. Bleeding complications with warfarin are one of the main causes of severe adverse drug events.[91–93] Warfarin has a narrow therapeutic index and as a result its use is accompanied by routine blood testing to determine the appropriate dose for the relevant anticoagulant effect, which can vary by more than 20 times between patients.

This variability in patient response to warfarin is multifactorial. Consumption of foods containing vitamin K will attenuate warfarin's anticoagulant effect, whereas depletion of the body's vitamin K reserves (eg, antibiotics given to a patient that inhibit intestinal flora production of vitamin K) will potentiate it. Furthermore, inducers or inhibitors of particular CYP enzymes affect the properties of warfarin via altered metabolism. For example, an enhanced anticoagulant effect is reported when amiodarone and warfarin are coadministered, a finding that is attributed to CYP2C9 enzyme inhibition.[94] Likewise, drugs involving CYP1A2 and CYP3A4 can affect the anticoagulation ability of warfarin.

Genetic variants also alter the variability in warfarin dosing.[95] Polymorphisms in *CYP2C9* and *VKCOR1*, which encode the molecular target of warfarin, have been extensively studied. The FDA has noted that variants in these two genes can affect warfarin dosing and has recommended clinicians to consider a patient's genotype, if known, before prescription of the drug. The advantage of genetic testing in this setting continues to be debated, and trials[96–99] assessing the effects of genotype-guided warfarin dosing on anticoagulant parameters have reported mixed results. In the future, studies appropriately powered to assess clinical events will be helpful to further assess the use of warfarin-related genotypes.[100]

Non-VKA anticoagulants

Because of VKA's narrow therapeutic index, interactions, and need for blood monitoring of patients, different anticoagulants with more predictable pharmacological effects have been searched for. Alternatives to warfarin are now available and these non-VKA oral anticoagulants (NOACs) directly target factor IIa (dabigatran) or Xa (rivaroxaban, apixaban, and edoxaban; figure 2). As a group, NOACs have faster onset and offset of action than warfarin and routine blood monitoring is not necessary. Nonetheless, the pharmacokinetics of NOACs differ. Comedications and the comorbidities of every patient should be considered before use (table 2).

Dabigatran has the lowest bioavailability of present NOACs, and changes in absorption or elimination could have a greater effect on drug plasma concentrations.[103] Likewise, renal function should be monitored regularly in patients taking an NOAC. Chronic kidney disease affects the drug half-lives and plasma concentrations, with variable renal clearance in this drug group. As such, every NOAC has its own dose adjustment recommendations based on renal function; additionally, differences exist between NOACs regarding when to take the last dose of drug before an elective procedure. Trials of NOACs have included patients with mild or moderate chronic kidney disease, but have not extensively studied patients with more severe disease or those on dialysis. Thus, use of NOACs is generally avoided for patients on dialysis.[101]

NOACs involve the P-gp transporter system after intestinal absorption, and the P-gp transporter is also part of their renal clearance. As such, drugs for cardiovascular

disorders that are P-gp substrates (such as verapamil, dronedarone, and amiodarone) can increase NOAC plasma concentrations. Removal of rivaroxaban is CYP3A4-dependent, and strong inducers and inhibitors can alter plasma concentrations. With apixaban, hepatic clearance occurs mainly with the unchanged molecule; however, there is some CYP3A4-related metabolism. Thus, although the NOACs have generally fewer drug–drug interactions than warfarin, cotherapies should still be considered (appendix). Product labels and guidance documents provide practical information about contraindicated medications and indications for NOAC dose reductions.[101]

Appreciation that the appropriate dose of an NOAC is affected by the clinical indication and characteristics of the patient is increasing. For patients with venous thromboembolism or pulmonary embolism, the initial treatment typically consists of parenteral anticoagulation or a higher NOAC dose (based on the design of the clinical trial) followed by stable full dose anticoagulation; lower NOAC doses are used to prevent venous thromboembolic disease. The use of NOACs for stroke prevention in patients with atrial fibrillation particularly outlines differences in dosing strategies.[101] For example, in these patients, 150 mg (or 110 mg where available) of dabigatran is given twice per day, and in the USA a twice per day dose of 75 mg is approved for patients with a creatinine clearance of 15–30 mL/min, whereas the rivaroxaban dose is 20 mg once per day taken with the evening meal, and is 15 mg when the creatinine clearance in patients is 15–49 mL/min. For apixaban, the dose is 5 mg twice per day unless the creatinine clearance is 15–29 mL/min or a combination of risk factors are present. For edoxaban, in the USA, the dose is 30 mg if the creatinine clearance is 15–50 mL/min, 60 mg if 50–95 mL/min, and is not recommended for use in patients if the creatinine clearance is more than 95 mL/min.

Likewise, considered together the trials of atrial fibrillation highlight some important themes that emerge when directly targeting factor IIa or Xa versus using a vitamin K-dependent approach. In a meta-analysis[104] of phase 3 randomised trials[105–108] including 71 683 participants, the NOACs compared with warfarin reduced stroke or systemic embolic events by 19%, intracranial haemorrhage by 52%, and mortality by 10%. Although NOACs reduced intracranial bleeding, dabigatran, rivaroxaban, and edoxaban resulted in more people with gastrointestinal bleeding than did warfarin. A possible explanation is that warfarin is 95% absorbed and the remaining drug does not have anticoagulant effects; bleeding is related to systemic properties of warfarin. By contrast, with use of NOACs varying amounts of active drug remain in the gastrointestinal tract and could induce bleeding from susceptible lesions.[109] Efforts are underway, including by the FDA and its mini-sentinel programme, to continue to assess the efficacy to safety ratio of NOACs.

Dose selection of oral anticoagulants proved to be particularly relevant in patients stabilised after ACS, where dual antiplatelet therapy is also commonly used. In this setting, large phase 2 studies[110–112] were undertaken to assess many doses and dosing regimens for rivaroxaban, apixaban, and dabigatran. One subsequent phase 3 trial[113] tested twice per day doses of rivaroxaban at 2·5 mg or 5 mg, which are just a quarter and a half, respectively, of the total daily doses tested in trials of stroke prevention in atrial fibrillation. Results from this trial[113] showed that the twice per day dose of 2·5 mg reduced adverse cardiovascular events, mortality, and stent thrombosis compared with placebo, and this dose also had an improved bleeding safety profile than the 5 mg dose. As a result, the 2·5 mg dose of rivaroxaban given twice per day has been approved by the European Medicines Agency for patients with recent ACS and raised markers of cardiac necrosis.

In another phase 3 trial[114] that assessed NOACs in patients stabilised after ACS, apixaban was tested at the full anticoagulant dose versus placebo, which resulted in increased bleeding without increased efficacy. This study[114] included a particularly high-risk group of patients and patients who had previous stroke or TIA. In participants without previous stroke or a TIA,[114] findings showed a trend towards a reduction in cardiovascular death, myocardial infarction, or stroke with use of apixaban versus placebo. However, further conclusions are restricted because the trial was terminated early because of the overall reported safety and efficacy results and these are data from a subgroup. Thus, antithrombotic dose selection and the target population continue to be important, yet challenging, aspects in development of these drugs.

Although NOACs were designed to avoid the need for routine monitoring, in some instances measurements of the anticoagulant effect can be helpful. To make a qualitative assessment, the prothrombin time can be used in the case of factor Xa inhibitors, or the activated partial thromboplastin time can be used in the case of dabigatran.[88,115] Assays with more specific calibration are needed to provide quantitative information, but these are not necessarily accessible worldwide. Additionally, direct antidotes to NOACs are not available but are being investigated. Nonetheless, the relatively short half-life of NOACs versus warfarin is an advantage in terms of the associated side-effect of bleeding. Additionally, studies are underway to address NOACs in the setting of procedures, and in patients who are at advanced age. Furthermore, use of NOACs in conjunction with antiplatelet therapy in patients with atrial fibrillation and percutaneous coronary intervention is an area of great interest; the PIONEER AF-PCI trial testing rivaroxaban and REDUAL-PCI evaluating dabigatran will add data to this unresolved area.[116,117] Importantly, the acceptance of NOACs versus warfarin (which is generic) as cost effective for stroke prevention in atrial fibrillation

For the **US FDA's sponsored mini-sentinel programme** see http://mini-sentinel.org/

depends on several factors including drug pricing, anticoagulation control with warfarin, and cost of anticoagulation services.[118,119] Efforts are ongoing to improve characterisation of the cost effectiveness of NOACs in various medical settings.

Conclusions

Antithrombotic drugs have been developed to inhibit platelets or coagulation factors that can cause ACS or venous thromboembolism, and the initial oral antiplatelet and anticoagulant treatments successfully reduce thrombotic events. However, over time some limitations to these treatments were noted. As a result, clopidogrel has been joined by the next generation of P2Y12 inhibitors, prasugrel and ticagrelor. In terms of anticoagulants, options now include warfarin and the direct factor inhibitors dabigatran, rivaroxaban, apixaban, and edoxaban. Selection of the most appropriate drug for a patient needs an understanding of the pharmacology, clinical indication, comorbidities, and personal preferences of patients. Moving forward, new antithrombotic drugs will continue to be investigated with the hope to optimise their pharmacological properties and improve their benefit–risk profiles.

Contributors

JLM and TS were responsible for the literature search, first draft, and critical editing of the Series paper.

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Novel antithrombotic agents 2

Clinical evidence for oral antiplatelet therapy in acute coronary syndromes

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This is the second in a Series of three papers about novel antithrombotic agents

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Platelet-mediated thrombosis is a major pathophysiological mechanism that underlies acute coronary syndromes, and therefore, antiplatelet therapy is an important foundation in the treatment and prevention of recurrence of these syndromes. Nearly 30 years ago, aspirin was the first agent to show a benefit for acute coronary syndromes and is still a key therapeutic agent. The landmark CURE trial showed that the addition of a P2Y12 antagonist, clopidogrel, to aspirin was beneficial in the treatment of acute coronary syndromes. Despite substantial benefits with clopidogrel, limitations include the slow speed of onset, variable response, and a modest antiplatelet effect. Next-generation P2Y12 antagonists, prasugrel and ticagrelor, overcome these limitations and have been shown, in large-scale clinical trials for acute coronary syndromes, to reduce ischaemic events more than clopidogrel, at the expense of an increase in bleeding. Additional agents that target platelets by alternate mechanisms, including the protease-activated receptor-1 antagonist vorapaxar, have shown ischaemic benefit. These large-scale trials inform treatment decisions that need to balance ischaemic benefit and bleeding risk in patients with acute coronary syndromes. This Series paper describes major trial results, implications for clinical practice, and summarises continuing controversy.

Introduction

Acute coronary syndromes are a leading cause of mortality, morbidity, and loss of productivity. The major pathophysiological mechanism underlying unstable angina and myocardial infarction is atherosclerotic plaque rupture with resultant coronary thrombosis. Platelets adhere to ruptured plaques, aggregate, and release secondary messengers, which result in further thrombosis and vasoconstriction, and serve as a surface for activation of the clotting cascade. As a result, antiplatelet therapies have led to major advances in the treatment of acute coronary syndromes and the prevention of recurrent events. With key components of the thrombotic process targeted, obligate increases in bleeding exist. The past 25 years has seen the completion of various large-scale clinical trials that have investigated the efficacy and safety of several pharmaceutical agents, including aspirin and P2Y12 antagonists, alone or in combination (table 1). These trials provide evidence to guide patient management in balancing the efficacy and safety of pharmaceutical compounds, the pharmacology of which is described in detail in a companion Series paper.[8]

Aspirin

Historically, the first antiplatelet agent to show benefit in acute myocardial infarction was aspirin, which blocks the production of thromboxane A2. The first major trial,[1] ISIS-2, showed the additive benefits of thrombolysis and low-dose aspirin in patients with ST-segment elevation acute myocardial infarction. The Antithrombotic Trialists' collaboration summarised the evidence for the benefit of aspirin in vascular disease, and showed that low-dose aspirin reduced vascular events (6·7% *vs* 8·2% per year; p<0·001) and total stroke events (2·08% *vs* 2·54% per year; p=0·002).[13] Reductions were consistent in men and women. Since then, aspirin has been the foundation of antithrombotic therapy for all acute coronary syndromes. Even rare patients with a history of hypersensitivity to aspirin can be desensitised rapidly to tolerate chronic treatment with low-dose aspirin.[14] After an initial oral-loading dose of 150–300 mg, patients should receive a maintenance dose of 75–100 mg daily (table 2) since there is no evidence of a benefit from any higher aspirin doses, but a substantial reduction in gastrointestinal bleeds with the lower doses.[2]

Combination of clopidogrel with aspirin

The CURE trial[2] was the landmark trial that established the benefits of addition of the P2Y12 receptor blocker, clopidogrel, to aspirin in patients with non-ST-segment elevation acute coronary syndromes, showing a 20% reduction in the composite outcome of cardiovascular death, myocardial infarction, and stroke, compared with placebo over 9–12 months of therapy. No increase in TIMI major bleeding was noted with the combination of aspirin and clopidogrel, but a 38% increase in the trial primary endpoint of CURE major bleeding was reported. The benefits of clopidogrel were established early, well before angiography and percutaneous coronary intervention were done,[15] thereby lending support to the value of early therapy. The benefits of addition of clopidogrel (with a 300 mg loading dose and a 75 mg maintenance dose) to aspirin were also seen in patients with ST-segment elevation acute myocardial infarction (aged ≤75 years) who had been treated with thrombolysis in the CLARITY trial.[3] In this trial, the primary efficacy composite endpoint of an occluded infarct-related artery on angiography, or death or recurrent myocardial infarction before angiography, was reduced in absolute

	Population	Groups	Background therapy	Primary efficacy outcome	Primary efficacy results	Primary safety outcome	Primary safety results
ISIS-2 (1988)[1]	17 187 patients with suspected AMI	Streptokinase, aspirin, both, and placebo	None	Vascular mortality at 5 weeks	10·4%,* 10·7%,* 8·0%,*† 13·2%	Bleeding that needs transfusion	0·51%,* 0·16%, 0·56%,* 0·26%
CURE (2001)[2]	12 562 patients with NSTE-ACS	Clopidogrel 300 mg then 75 mg once a day and placebo	Aspirin	Cardiovascular death, MI, stroke at 12 months	9·3%, 11·4%, p<0·001	CURE major bleeding	3·7%, 2·7%, p=0·001
CLARITY–TIMI 28 (2005)[3]	3491 patients with STEMI	Clopidogrel 300 mg then 75 mg once a day and placebo	Aspirin (and heparin when appropriate)	Occluded infarct-related artery, death, myocardial infarction at 30 days	15·0%, 21·7%, p<0·001	TIMI major bleeding	1·3%, 1·1%, p=0·64
COMMIT (2005)[4]	45 852 patients with suspected AMI	Clopidogrel 75 mg/day and placebo	Aspirin	Death, reinfarction, stroke (all-cause death) at 28 days	9·2% (7·5%), 10·1% (8·1%), p=0·002 (p=0·03)	All fatal, transfused, or cerebral bleeding	0·58%, 0·55%, p=0·59
CURRENT–OASIS 7 (2010)[5]	25 086 patients with NSTE-ACS or STEMI	Clopidogrel 600 mg then 150 mg/day for 7 days then 75 mg/day, clopidogrel 300 mg then 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 30 days	4·2%, 4·4%, p=0·30	CURRENT major bleeding	2·5%, 2·0%, p=0·01
TRITON–TIMI 38 (2007)[6]	13 608 patients with NSTE-ACS or STEMI undergoing PCI	Prasugrel 60 mg then 10 mg/day, and clopidogrel 300 mg then 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 450 days	9·9%, 12·1%, p<0·001	Non-CABG-related TIMI major bleeding	2·4%, 1·8%, p=0·03
TRILOGY ACS (2012)[7]	7243 patients aged <75 years with STEMI or UA without revascularisation	Prasugrel 10 mg/day and clopidogrel 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 17 months	13·9%, 16·0%, p=0·21	GUSTO (TIMI) non-severe/life-threatening (major) bleeding	0·4% (1·1%), 0·4% (0·8%), p=0·87 (p=0·27)
PLATO (2009)[8]	18 624 patients with NSTE-ACS or STEMI	Ticagrelor 180 mg then 90 mg twice a day and clopidogrel 300–600 mg then 75 mg/day	Aspirin	Cardiovascular death, MI, stroke at 12 months	9·8%, 11·7%, p<0·001	PLATO major bleeding	11·6%, 11·2%, p=0·43
PEGASUS-TIMI 54 (2015)[9,10]	>21 000 patients with MI 1–3 years previously	Ticagrelor 90 mg twice a day, ticagrelor 60 mg twice a day and placebo	Aspirin	Cardiovascular death, MI, stroke	Pending	TIMI major bleeding	Pending
TRACER (2012)[11]	12 944 patients with NSTE-ACS	Vorapaxar 40 mg then 2·5 mg/day and placebo	Standard therapy	Cardiovascular death, MI, stroke, hospitalised recurrent ischaemia, urgent revascularisation at 2 years	18·5%, 19·9%, p=0·07	GUSTO moderate-severe bleeding	7·2%, 5·2%, p<0·001
TRA 2P–TIMI 50 (2012)[12]	26 449 patients with a history of MI, ischaemic stroke or PAD	Vorapaxar 2·5 mg/day and placebo	Aspirin	Cardiovascular death, MI, stroke at 3 years	9·3%, 10·5%, p<0·001	GUSTO moderate-severe bleeding	4·2%, 2·5%, p<0·001

ACS=acute coronary syndromes. AMI=acute myocardial infarction. NSTE=non-ST-segment elevation. MI=myocardial infarction. STEMI=ST-segment elevation myocardial infarction. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. UA=unstable angina. PAD=peripheral artery disease. *p<0·001 versus placebo. †p<0·001 versus single drug.

Table 1: **Large-scale clinical trials on the efficacy and safety of treatments in ACS**

terms by 6·7% with clopidogrel compared with placebo. Likewise, in the COMMIT trial,[4] in 45 852 Chinese participants with ST-segment elevation myocardial infarction, many of whom had not received thrombolysis, 75 mg/day of clopidogrel for 16 days or placebo added to aspirin reduced both coprimary endpoints. The COMMIT trial showed a reduction of 9% in the triple composite outcome of mortality recurrent myocardial infarction and stroke, and a reduction in all-cause mortality by 7% at 28 days.[4] A double-loading dose of 600 mg instead of 300 mg increased the speed of onset and the magnitude of the antiplatelet effect.[16] The large CURRENT-OASIS 7 double-blind trial,[5] subsequently compared a regimen of 600 mg loading followed by 150 mg clopidogrel for 1 week, with the conventional regimen of 300 mg loading followed by 75 mg for 1 week, in 25 086 patients with acute coronary syndromes and intended invasive management. The double dose did not reduce adverse cardiac outcomes overall,[5] but in a prespecified analysis of the 17 263 patients treated with percutaneous coronary intervention,[17] it reduced the primary outcome (3·9% *vs* 4·5%; adjusted hazard ratio [HR] 0·86, 95% CI 0·74–0·99; p=0·039) at the expense of an increase in major bleeding (1·6% *vs* 1·1%; adjusted HR 1·41, 95% CI 1·09–1·83; p=0·009).

Notably, the evidence for the benefits of the aspirin and clopidogrel combination in acute coronary syndromes somewhat predated the routine use of percutaneous coronary intervention in acute coronary syndromes. In parallel with acute coronary syndromes studies, clinical trials[18–20] established the key role of dual inhibition of cyclooxygenase-1 and the P2Y12 platelet receptor with the

	Indication	Loading dose (mg)	Maintenance dose (mg)	Duration of treatment (years)	Recommended delay between last dose and CABG surgery in stabilised patients (days)
Aspirin	All types of ACS	150–300	75–100 once a day	Indefinite	No interruption recommended
Prasugrel	ACS treated with PCI (including primary PCI) no previous history of stroke or TIA	60	10* once a day	1	7
Ticagrelor	STEMI treated with primary PCI	180	90 twice a day	1	3–5
Ticagrelor	NSTE-ACS regardless irrespective of management (invasive or conservative)	180	90 twice a day	1	3–5
Clopidogrel	STEMI treated with thrombolysis	300†	75 once a day	1	5
Clopidogrel	All types of ACS if little access to ticagrelor or prasugrel, or if high risk of bleeding (including chronic treatment with oral anticoagulants)	300–600	75 once a day	1	5
Vorapaxar	History of MI or PAD, no previous history of stroke or TIA	NA	2·5 once a day‡	3	No interruption recommended

ACS=acute coronary syndromes. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. TIA=transient ischaemic attack. STEMI=ST-segment elevation myocardial infarction. NSTE=non-ST-segment elevation. MI=myocardial infarction. PAD=peripheral artery disease. *5 mg, if bodyweight <60 kg or age ≥75 years. †No loading dose, if age 75 years or more. ‡Vorapaxar sulfate (equivalent to 2·08 mg vorapaxar).

Table 2: **Dosing and indications for the main oral antiplatelet drugs used during or after ACS**

combination of aspirin and either ticlopidine (at the time) or clopidogrel, in the striking reduction of the risk of stent thrombosis after percutaneous coronary intervention. Other randomised trials[21] also established primary percutaneous coronary intervention as the standard of care for reperfusion therapy in patients with ST-segment elevation myocardial infarction. Since then, ticlopidine use has been abandoned, with its rare but severe haematological side-effects, and the combination of aspirin and a P2Y12 inhibitor has become the standard of care for patients who receive stents. Although the data in ST-segment elevation myocardial infarction were restricted to the first month after the acute phase, guidelines universally endorsed the recommendation of aspirin and clopidogrel use for up to 12 months after acute coronary syndromes, with a loading dose of 300 mg at the start (which can be increased to 600 mg in patients managed with an invasive strategy) and a maintenance dose of 75 mg/day. In lytic-treated patients, no loading dose is to be used in those older than 75 years based on the designs of CLARITY[3] and COMMIT.[4]

Limitations of clopidogrel

Clopidogrel has substantial limitations in the management of acute coronary syndromes with a modest inhibition of platelet aggregation and a delayed onset and offset of action. Although no accepted test or specific target goal exists for platelet inhibition, variability in response to clopidogrel is substantial,[22,23] with estimations that 4–34% of patients have an inadequate response dependent on the method and cut point used. These patients are at high risk of subsequent clinical events including stent thrombosis, recurrent myocardial infarction, and death,[24–26] although evidence of the benefit of a platelet function-based treatment strategy has proven elusive.[27–29] High on-treatment platelet reactivity with clopidogrel is related to clinical (eg, acute coronary syndromes and diabetes), behavioural (eg, adherence), and genetic factors. Clopidogrel is a prodrug that needs to be transformed into an active metabolite; the transformation process relies on a multistep conversion by hepatic cytochrome P450 enzymes including CYP2C19, 3A4, 2B6, and 2C9,[8] whereas much of the parent molecule is inactivated and a proportion is metabolised to the key active metabolite. Reduced effectiveness of clopidogrel has been shown in carriers of reduced-function alleles of these enzymes, particularly in the common variant *CYP2C19*2*. Carriers of *CYP2C19*2* have worse clinical outcomes with clopidogrel treatment than patients without this variant,[30–32] but the restricted antiplatelet response to clopidogrel in carriers of the reduced-function alleles can, in part, be overcome with increased dosing of clopidogrel.[33] However, it has been difficult to show the ability to modulate clinical outcomes with a genetic-based strategy.[34] Finally, clopidogrel has a slow onset of action with a peak effect after 6–12 h, dependent on the dose, and a slow offset of action (3–5 days) because the active metabolite of clopidogrel irreversibly binds to the platelets, which could potentially limit the use of this drug in some clinical scenarios, such as when the need for surgery is uncertain before use. These limitations have led to the development of alternative P2Y12 antagonist strategies that are discussed in detail later in this Series paper.

Prasugrel

Prasugrel is a second-generation thienopyridine that, similarly to clopidogrel, needs conversion from an inactive form to an active metabolite by use of cytochromes.[35] Unlike clopidogrel, however, prasugrel is rapidly and more wholly metabolised to its active components. This metabolic difference allows prasugrel to have a more rapid onset, higher levels of platelet inhibition, and less interpatient response variability than clopidogrel.[36]

The major clinical outcomes trial of prasugrel, TRITON-TIMI 38 trial,[6] compared prasugrel (60 mg loading dose and 10 mg daily) with clopidogrel (300 mg

loading dose and 75 mg daily) in patients with acute coronary syndromes and treatment at the time of planned percutaneous coronary intervention. Prasugrel had a 19% reduction in relative risk compared with clopidogrel in the primary efficacy endpoints of cardiovascular death, myocardial infarction, or stroke (figure 1),[6] with a 24% reduction in myocardial infarction, a 52% reduction in stent thrombosis, and no differences in cardiovascular or overall mortality. Stent thrombosis and myocardial infarction reductions were recorded early after the procedure and throughout the 15-month follow-up.[37,38] Consistent with the increased inhibition of platelets, higher overall bleeding was noted with prasugrel than clopidogrel, including a 32% increase in TIMI major bleeding that was not associated with coronary artery bypass grafting (CABG), higher rates of fatal bleeding, and bleeding associated with CABG. No excess in intracranial haemorrhage was reported.[6]

In TRITON-TIMI 38, there were notable subgroups that have shaped the use of prasugrel in clinical practice. Patients with a reported history of stroke or transient ischaemic attack were at higher risk of serious bleeding complications, including intracranial haemorrhage, and showed lesser efficacy with prasugrel than the overall trial population. As a result, regulatory agencies worldwide (eg, US Food and Drug Administration and the European Medicines Agency) have recommended against the use of prasugrel in patients with previous stroke or transient ischaemic attack. In patients aged 75 years or more, or who weigh less than 60 kg, the balance of risk and benefit with prasugrel was less favourable than in the overall trial population, and caution is generally recommended for the use of this agent in such patients, with the exception of the use of a lower 5 mg maintenance dose.[39–41] By contrast, a better clinical benefit and risk profile of prasugrel compared with the overall trial population tended to be seen in patients with ST-segment elevation myocardial infarction or diabetes.[42,43]

The TRILOGY ACS trial[7] compared prasugrel with clopidogrel in 9326 patients with acute coronary syndromes managed medically without planned revascularisation. The primary endpoints of cardiovascular death, myocardial infarction, and stroke were not reduced and bleeding did not differ between groups.[7] Prasugrel had better results in the subset of patients with angiographically proven coronary artery disease.[44] However, because of the little reduction in the primary composite endpoint in the full trial cohort, prasugrel has not been approved or recommended for the treatment of acute coronary syndrome without percutaneous coronary intervention.

Ticagrelor

Ticagrelor is a direct-acting P2Y12 antagonist that does not need metabolic activation and is therefore not dependent on cytochrome P450 enzymes. The drug acts rapidly and has more potent and consistent antiplatelet effects than clopidogrel. Ticagrelor was compared with clopidogrel in patients with acute coronary syndromes in the PLATO trial,[45] which enrolled 18 624 patients with moderate to high risk of unstable angina, or non-ST-segment elevation myocardial infarction, or patients with ST-segment elevation myocardial infarction with planned primary percutaneous coronary intervention. Patients were randomly assigned, and treated as soon as possible, before percutaneous coronary intervention was attempted. Patients were given aspirin and could be clopidogrel naive or not. Ticagrelor was given with a loading dose of 180 mg and a maintenance dose of 90 mg twice daily, and clopidogrel with a loading dose of 300 mg (unless patients were previously on clopidogrel) and a maintenance dose of 75 mg daily. Physicians had the option to reload patients before percutaneous coronary intervention with an additional 300 mg. Ticagrelor reduced the primary outcome of cardiovascular death, myocardial infarction, and stroke by 16% compared with clopidogrel (HR 0·84, 95% CI 0·77–0·92; p=0·0003).[45] A prespecified hierarchical analysis of secondary outcomes showed that ticagrelor also reduced cardiovascular mortality (HR 0·79, 95% CI 0·69–0·91; p=0·001).[45] Ticagrelor reduced the occurrence of definite stent thrombosis by around 33%, irrespective of stent type, patient profiles, and cotherapies used.[46] The benefits of ticagrelor were consistent for invasive or conservative management strategies (figure 2).[47–49] Likewise, these benefits were consistent across subgroups defined by age,[50] risk factors, bodyweight, previous medical history (including transient ischaemic attack),[47] type of acute coronary syndrome,[51] and genotype.[52] A noteworthy interaction (p=0·045) was present between treatment effect and enrolment region of the trial, with no benefit from ticagrelor in patients enrolled in North America. This interaction might result from a negative interaction between ticagrelor and the higher doses of aspirin (more

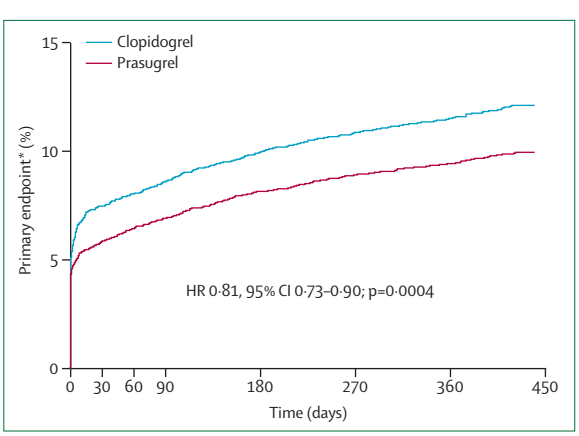

Figure 1: **Kaplan-Meier estimates of the primary endpoints for prasugrel and clopidogrel in the TRITON-TIMI 38 trial**
*Cardiovascular death, myocardial infarction, and stroke. Adapted with permission from Wiviott and colleagues.[31]

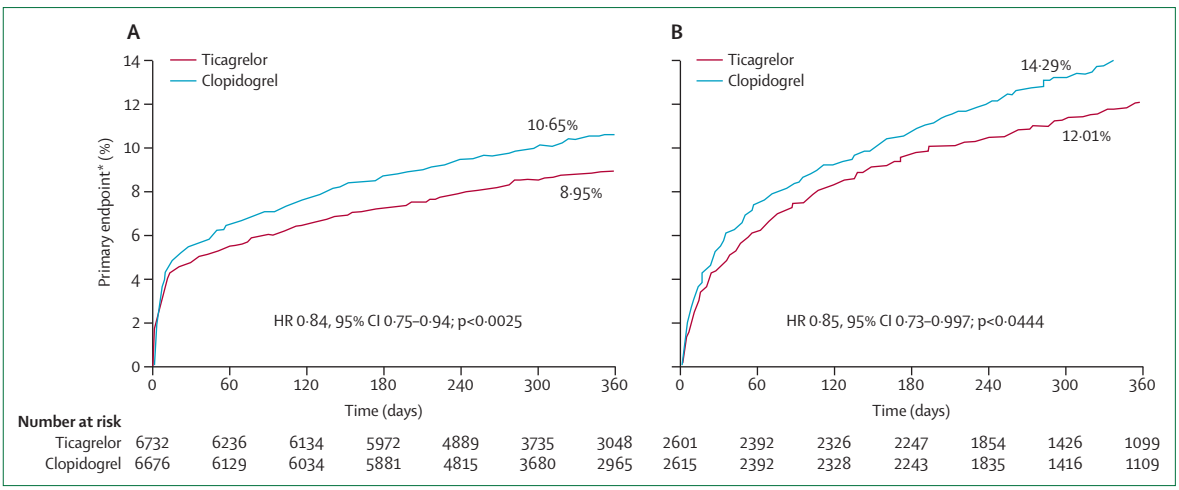

Figure 2: **Kaplan-Meier estimates of the primary endpoint for patients given ticagrelor or clopidogrel in PLATO in relation to the management strategy planned at the time of randomisation**

(A) Invasive strategy (72% of patients in PLATO). (B) Conservative strategy (28% of patients in PLATO). Adapted with permission from James and colleagues.[43] *Cardiovascular death, myocardial infarction, and stroke.

than 150 mg/day) often used in the USA compared with other regions, although a chance variation cannot be formally excluded. This has led to the recommendation to use ticagrelor with low-dose aspirin (up to 150 mg).[53] In PLATO,[45] ticagrelor did not increase major or fatal bleeding, although there was an increase in bleeding not related to CABG surgery (by around 20%) and a borderline increase in the proportion of intracranial bleeding (0·3 *vs* 0·2%, p=0·06). Combined major and minor PLATO bleeding rates increased by 11% (p=0·008), although TIMI major and minor bleeding rates did not increase. Dyspnoea was twice as frequent in patients given ticagrelor compared with patients given clopidogrel and led to treatment discontinuation in around 1% of patients. Dyspnoea was generally mild and transient, occurring early after therapy started, and was not associated with abnormalities on physical examination, chest radiograph, or lung-function tests.[54] Discussions on the risk of shortness of breath with patients before their discharge are important to avoid unplanned disruption of antiplatelet therapy.[55] The reduction in cardiovascular mortality seen in PLATO might be related to the fact that ticagrelor reduces ischaemic outcomes without an increase in fatal bleeding, or might stem from non-platelet mediated effects of ticagrelor (for which inhibition of adenosine reuptake in erythrocytes by ticagrelor has been postulated),[56,57] or could be a chance finding.

Vorapaxar

Vorapaxar is a competitive antagonist of the protease-activated receptor, which is a major thrombin receptor on human platelets. Vorapaxar has been studied in two major trials of patients with acute coronary syndromes: TRACER[11] and TRA 2P–TIMI 50.[12] TRACER enrolled 12 944 patients with non-ST-segment elevation acute coronary syndromes and compared vorapaxar with placebo, in addition to standard therapy, which included aspirin plus clopidogrel in 92% of patients. The combination primary endpoint of cardiovascular death, myocardial infarction, stroke, recurrent ischaemia, or urgent revascularisation tended to be lower (HR 0·92; p=0·07) than the placebo group but was not significant. The prespecified combination secondary endpoint of cardiovascular death, myocardial infarction, and stroke was marginally reduced (HR 0·89; p=0·02). GUSTO severe and TIMI major bleeding were significantly increased with vorapaxar. TRA 2P–TIMI 50[12] was a trial of 26 449 patients with a history of atherosclerotic vascular disease including myocardial infarction, stroke, or peripheral arterial disease within 2 weeks to 12 months of enrolment. The trial compared daily vorapaxar with placebo in addition to standard therapy. Use of dual antiplatelet therapy differed from 78% of patients with myocardial infarction to 37% of those with stroke. The stroke arm of the trial was stopped early because of an increased risk of intracranial haemorrhage. Overall, vorapaxar reduced the risk of the combined primary endpoint of cardiovascular death, myocardial infarction, and stroke by 13% (HR 0·87; p<0·001) compared with the placebo group, although non-CABG-related TIMI major bleeding increased (HR 1·48; p<0·001). Clinical events were fewer with vorapaxar in patients with previous-myocardial infarction and those with peripheral arterial disease. On the basis of these data, the US Food and Drug Administration approved vorapaxar for the secondary prevention of vascular events in patients with myocardial infarction, or peripheral arterial disease, but without previous stroke or transient ischaemic attack, but not for acute management of patients with acute coronary syndromes. The European

Medicines Agency also approved vorapaxar, but only in post-myocardial infarction patients. Importantly, vorapaxar has not been studied in combination with prasugrel or ticagrelor.

Cilostazol

Cilostazol is an orally available cyclic adenosine monophosphate phosphodiesterase III inhibitor that has vasodilatory and antiplatelet effects. This agent is predominantly used for the management of intermittent claudication associated with peripheral arterial disease. Cilostazol has been studied in small studies (predominantly in Asia) as a component of triple antiplatelet therapy with aspirin and clopidogrel. One meta-analysis[58] suggests that a strategy of cilostazol, in addition to standard dual antiplatelet therapy, could improve clinical outcomes, including cardiovascular events and stent thrombosis. These data are important but need confirmation in large-scale clinical trials before formal recommendation for use in acute coronary syndromes can be made.

Combined therapy with aspirin and either prasugrel or ticagrelor

Since both prasugrel and ticagrelor have shown superior outcomes to clopidogrel in pivotal trials, these novel agents are now preferred to clopidogrel as a first-line therapy in conjunction with aspirin, for most patients with acute coronary syndromes, as endorsed by both European and US guidelines.[39–41] Prasugrel is a preferred option for patients undergoing percutaneous coronary intervention (except for patients with a previous history of stroke or transient ischaemic attack, with a bodyweight less than 60 kg, or at an age of 75 years or more), while ticagrelor is a preferred option for moderate-to-high risk patients with acute coronary syndromes, irrespective of the management strategy.[39–41] Clopidogrel is now the preferred second-line therapy when there is a high risk of bleeding, in patients who have received thrombolysis, or in patients who need long-term oral anticoagulation (dependent on the availability of more data with prasugrel and ticagrelor), when the novel agents are unavailable, or when cost or specific patient issues exist.

Although the novel P2Y12 blockers are more effective than clopidogrel for most patients, they also have limitations: they increase the risk of bleeding; they do not abolish the residual ischaemic risk; their cost is substantially higher than clopidogrel (which is now available as a generic drug); and the rapidity of onset, although quicker than clopidogrel, could be insufficient in some settings such as ST-segment elevation myocardial infarction.[59] For patients with ST-segment elevation myocardial infarction, particularly those receiving morphine, the antiplatelet efficacy of ticagrelor and prasugrel could be delayed for several hours, leaving patients without adequate protection against platelet aggregation during the first crucial hours of treatment. In that setting, injectable agents with immediate efficacy, such as glycoprotein IIb and glycoprotein IIIa inhibitors[60] or, in the future, cangrelor,[61,62] could provide immediate efficacy (particularly as bail out therapy in patients with high-thrombus load or recurrent-thrombotic events during percutaneous coronary intervention), although this increases costs and, at least for glycoprotein IIb/IIIa inhibitors, the bleeding risk.

Personalised antiplatelet therapy

In view of the high cost and bleeding risk of the novel agents, and the availability of clopidogrel as a generic drug, it might seem important to identify patients with a poor clopidogrel response (based on platelet-function testing or genotyping) and give them either a high dose of clopidogrel or the novel agents, and use the standard dose of clopidogrel in good responders. However, this approach is currently not recommended in routine practice, by guidelines;[39,40] first, a large genotypic analysis from PLATO has shown that ticagrelor provides consistently better clinical outcomes compared with clopidogrel, irrespective of the presence, or absence, of loss-of-function alleles for genes encoding for clopidogrel metabolism.[52] Additionally, randomised trials testing a personalised antiplatelet strategy have so far not shown any clinical benefit of this approach compared with a conventional approach,[27,28,34] although trials so far have largely used high-dose clopidogrel rather than the novel P2Y12 inhibitors. To achieve the desired antiplatelet effect consistently in patients carrying loss-of-function alleles for clopidogrel metabolism, prasugrel or ticagrelor might be preferable to an increase in the dose of clopidogrel.[33]

When to start therapy with oral-antiplatelet agents

Substantial diagnostic uncertainty often exists in patients with suspected acute coronary syndromes in the early phases of management, and some patients might either eventually have other final diagnoses (including some contraindications to antiplatelet therapy, such as aortic dissection) or need urgent surgery (in which case, after the patients have received a potent oral antiplatelet agent, the risk of bleeding would be increased). The diagnostic uncertainty is greatest in patients with non-ST-segment elevation acute coronary syndromes and has prompted the administration of any antiplatelet agent other than aspirin to be delayed in some patients until a coronary angiogram has been done, and a decision to proceed with percutaneous coronary intervention can then be made. This is particularly true for prasugrel because its benefits were shown in PCI-treated patients with acute coronary syndromes in TRITON-TIMI 38, but not among medically managed patients in TRILOGY ACS. The ACCOAST randomised trial[63] showed no benefit of upstream loading with prasugrel compared with prasugrel given after angiography in patients with non-ST-segment elevation myocardial infarction, but did

show a substantial increase in bleeding risk. Note, however, that the time difference between treatment administration in the two strategies was only 4 h, which minimised any potential disparity between trial arms. By contrast, a meta-analysis[64] of clopidogrel trials has shown a reduction in cardiac events when clopidogrel was given before PCI in patients with acute coronary syndromes and, in the PLATO trial, treatment with ticagrelor was started at the time of diagnosis and always before PCI. Randomised trials of pretreatment with clopidogrel and ticagrelor are scarce. Overall, these findings suggest that in patients with suspected non-ST-segment elevation acute coronary syndromes, it is prudent to delay loading with oral-antiplatelet agents in case of diagnostic uncertainty or, if the P2Y12 receptor antagonist planned is prasugrel, until a decision to proceed to PCI is made (provided that angiography is planned within hours of presentation). If ticagrelor or clopidogrel are used, then treatment can be started as soon as a diagnosis is established, particularly if the expected delay to coronary angiography exceeds a few hours.

In patients with ST-segment elevation acute coronary syndromes, less diagnostic uncertainty exists and the risk of urgent surgery is low. Routine practice has often been to load these patients with aspirin and a P2Y12 agent as soon as possible, including clopidogrel, prasugrel, or ticagrelor. The ATLANTIC double-blind trial[65] randomly assigned patients with ST-segment elevation myocardial infarction, identified in the pre-hospital setting and triaged to primary PCI, to receive ticagrelor at the time of diagnosis. No differences were recorded between treatment arms in the two coprimary outcomes of the trial: ST-segment resolution and coronary flow in the infarct-related artery. However, there was a substantial reduction in definite stent thrombosis at 30 days (0·2 *vs* 1·2%; p=0·02), even though there was only a 31 min difference between the administration of ticagrelor in the two treatment arms. There was no increase to the risk of bleeding. These results lend support to the early loading of antiplatelet agents in the pre-hospital setting in patients with ST-segment elevation myocardial infarction triaged to primary PCI.

Optimum duration of therapy

Patients with acute coronary syndromes are at high risk of recurrence[66] and therefore should receive combined antiplatelet therapy for the initial post-acute coronary syndrome period and subsequently remain indefinitely on single antiplatelet therapy. In addition to the prevention of recurrences, combined antiplatelet therapy also contributes to the prevention of stent thrombosis in the large proportion of patients with acute coronary syndromes who have stents. There is, however, some uncertainty regarding the optimum duration of combined antiplatelet therapy. In view of the costs and ease of use of aspirin, this drug is generally advised for indefinite therapy as secondary prevention. With respect to P2Y12 antagonists, both American and European guidelines suggest the use of these drugs for a duration of 12 months after acute coronary syndromes.[39–41]

Although the CHARISMA trial[67] did not show an overall benefit for long-term clopidogrel for secondary prevention of events in patients with atherosclerosis (coronary artery disease, peripheral arterial disease, or cardiovascular disease), a reduction in recurrent events was observed in patients with a history of prior ischaemic events, such as myocardial infarction.[68]

In the DAPT trial of dual antiplatelet therapy (aspirin with clopidogrel or prasugrel),[69] patients with stents who were free of clinical events (myocardial infarction, stent thrombosis, or bleeding) 12 months after stent placement were randomly assigned to discontinue or remain on thienopyridine therapy for an additional 18 months. Overall, the occurrence of major adverse cardiac events was 29% lower and that of stent thrombosis was a remarkable 71% lower in patients who continued thienopyridine than in those who discontinued, although, major bleeding was also 61% higher.[69] A marginally higher rate of overall mortality was noted in the persistent dual antiplatelet therapy group than in the discontinuation group, driven predominantly by non-cardiovascular mortality, an effect not seen in a meta-analysis of the persistent dual antiplatelet therapy trials.[9] The risk of spontaneous (non-stent-related) myocardial infarction was reduced in the persistent therapy trials, suggesting a secondary preventive benefit, beyond stent protection. Overall, these results suggest that persistent antiplatelet therapy might be warranted in patients with acute coronary syndromes who have not had complications in the first year and who are not at high risk of bleeding. The PEGASUS trial[10] has tested long-term use of ticagrelor (at two doses 90 mg bid and 60 mg bid) in stable patients at high risk 1–3 years after acute myocardial infarction. Preliminary results show that both doses of ticagrelor reduced the primary outcome of cardiovascular death, myocardial infarction, or stroke, providing evidence of a continued benefit of the combined ticagrelor and aspirin after the initial 12 months.[70]

Patients needing oral anticoagulation

A subset of patients with acute coronary syndromes need permanent oral anticoagulation (eg, because of a prosthetic heart valve or atrial fibrillation). In these patients, the treatment of combined antiplatelet therapy and oral anticoagulation is complex. Typically, management of acute coronary syndromes will entail an initial period of triple therapy, combining aspirin, clopidogrel, and oral anticoagulation, which increases the risk of bleeding.[71,72] To minimise bleeding, it seems reasonable to avoid prasugrel or ticagrelor use, at least until prospective trials have established the best regimens and duration in this setting.[73,74] Therefore, clopidogrel is the antiplatelet agent of choice for these patients. Another consideration is to shorten the duration of triple therapy and stop use of one antiplatelet agent as soon as possible. The optimum

duration of antiplatelet therapy remains uncertain, although fairly complex recommendations based on expert consensus have been proposed.[75] One trial showed no difference in efficacy or safety between 6 weeks and 6 months of clopidogrel,[76] but was somewhat underpowered. The WOEST trial[77] suggested that it might be possible to use clopidogrel without aspirin in patients who are receiving oral anticoagulation and undergoing stent placement. This strategy reduced the risk of bleeding without an increase in the risk of ischaemic events.

Management of patients undergoing CABG

In patients with acute coronary syndromes, a few will need CABG surgery. Although it is recommended to continue aspirin throughout the perioperative period, it is desirable, in most patients, to withhold P2Y12 receptor blockers before and during surgery to minimise bleeding (unless patients are highly unstable). In very unstable patients or those with new stents, injectable reversible antiplatelet agents, such as glycoprotein IIb/IIIa receptor blockers or, in the future, cangrelor, might allow maintenance of platelet inhibition until surgery, although the exact clinical safety and efficacy of these bridging approaches has not been formally assessed. Surgery sooner than 5 days after stopping of clopidogrel, or 7 days after stopping of prasugrel, is associated with an increased bleeding risk. For ticagrelor, the recommendations on the label suggest a delay of 7 days, although in PLATO, discontinuation for 3–5 days before surgery was not associated with an increased bleeding risk. Therefore, in stabilised patients, it seems prudent to wait for this minimum amount of time before surgery. Long-term outcomes of patients with acute coronary syndromes who underwent CABG after having previously received ticagrelor or prasugrel showed substantially lower mortality compared with patients who had received clopidogrel.[78,79] Whether to restart P2Y12 receptor antagonists after surgery is uncertain, although it seems reasonable to judge whether therapy should resume once the risk of surgical bleeding has abated.

With respect to vorapaxar, in view of its very long half-life with residual platelet inhibition remaining up to 4 weeks after discontinuation, withholding for brief periods is not helpful for the management or prevention of bleeding. Results from TRACER suggest that patients with acute coronary syndromes undergoing CABG on vorapaxar had a substantial reduction in ischaemic events (HR 0·55, 95% CI 0·36–0·83; p=0·005 for the primary composite outcome of death, myocardial infarction, stroke, recurrent ischaemia with readmission to hospital, or urgent coronary revascularisation during index hospital admission) without a significant increase in major CABG-related bleeds.[80]

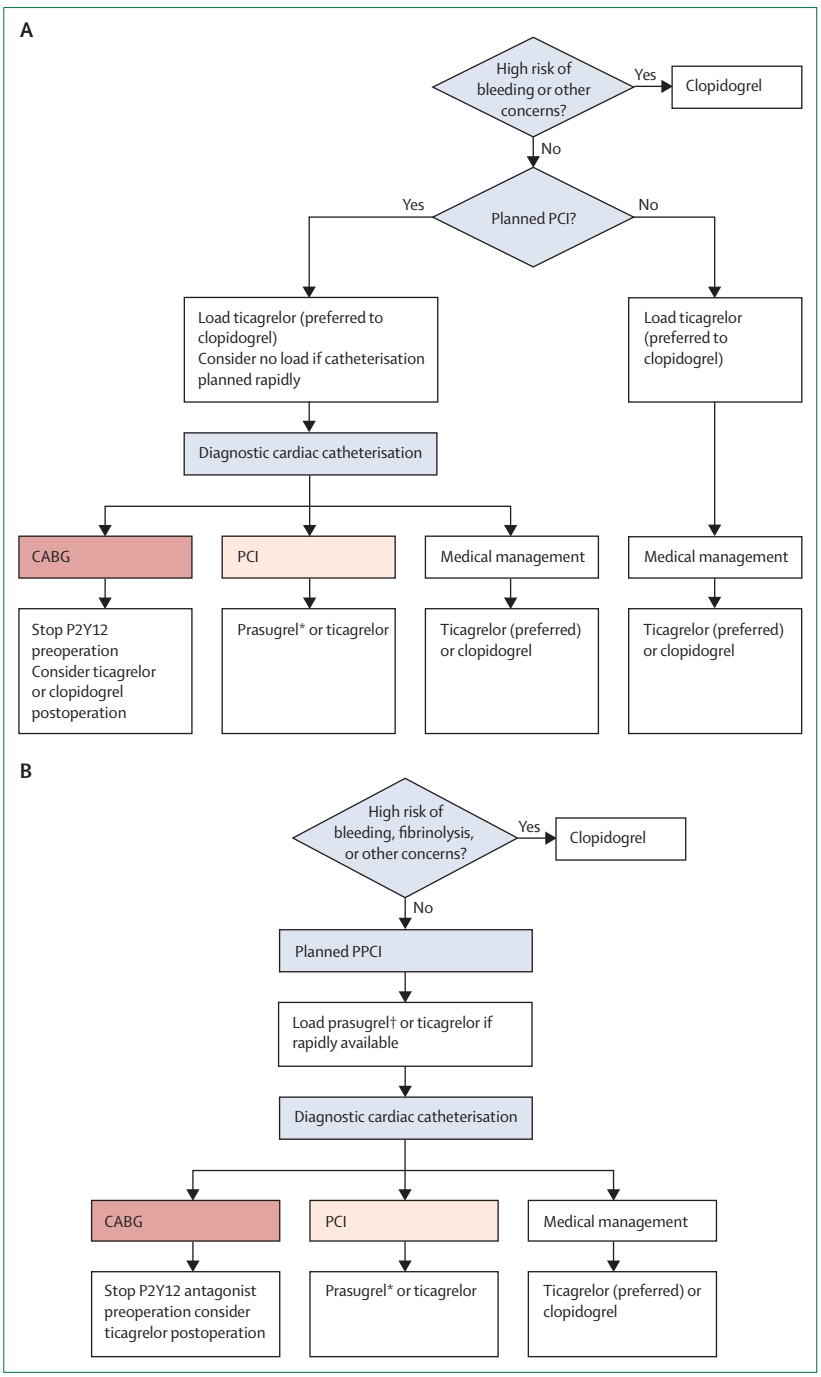

Figure 3: **Framework for choice of P2Y12 antagonist in acute coronary syndromes based on US and European Guidelines.**[34-36]
(A) Unstable angina or non-ST-segment elevation myocardial infarction. (B) ST-segment elevation myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. PPCI=primary percutaneous coronary intervention. *Without contraindication (stroke or transient ischaemic attack), if no preload. †Without contraindication (stroke or transient ischaemic attack).

Conclusions

Antiplatelet therapy improves cardiovascular outcomes after acute coronary syndromes. A broad and comprehensive dataset from large-scale trials allows for evidence-based decisions regarding these therapies (figure 3). The combination of aspirin with a potent inhibitor of the P2Y12 receptor (prasugrel or ticagrelor) is recommended in most patients with acute coronary syndromes, but patient factors and bleeding risk should

be considered in the choice of agents. Additional data from trials of novel agents, strategies, combinations of drugs, and for duration of therapy continue to emerge to help to refine recommendations. Personalised therapy based on genetics or platelet-function testing remains an elusive goal that needs additional research.

Contributors

SDW and PGS wrote the paper and are responsible for its content.

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Novel antithrombotic agents 3

Oral anticoagulants for stroke prevention in atrial fibrillation: current status, special situations, and unmet needs

Freek W A Verheugt, Christopher B Granger

In patients with non-valvular atrial fibrillation, oral anticoagulation with vitamin K antagonists reduces the risk of stroke by more than 60%. But vitamin K antagonists have limitations, including causing serious bleeding such as intracranial haemorrhage and the need for anticoagulation monitoring. In part related to these limitations, they are used in only about half of patients who should be treated according to guideline recommendations. In the past decade, oral agents have been developed that directly block the activity of thrombin (factor IIa), as well as drugs that directly inhibit activated factor X (Xa), which is the first protein in the final common pathway to the activation of thrombin. These novel non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be at least as good as warfarin for stroke prevention in atrial fibrillation and they have proved to have better safety profiles. Their net advantage is underscored by significantly lower all-cause mortality compared with warfarin in large clinical trials. Because of these features and their ease of use, they are recommended for stroke prevention in atrial fibrillation. They have also a fast onset and offset of action, but they currently lack specific antidotes. This paper addresses the role of anticoagulation for stroke prevention in atrial fibrillation in the era of NOACs, with a focus on special situations including management in the event of bleeding and around the time of procedures including cardioversion, catheter ablation, and device implantation. Also their use in patients with concomitant coronary artery disease, with advanced age, with chronic kidney disease, or with valvular heart disease will be discussed as well as the interaction of NOACs with other cardiac medication, and switching between anticoagulants.

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This is the third in a Series of three papers about novel antithrombotic agents

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Introduction

Oral anticoagulation is the cornerstone in the prevention of stroke in atrial fibrillation. Vitamin K antagonists (VKA) have been the traditional anticoagulants. These compounds block the vitamin K dependent liver production of the plasma coagulation factors II (prothrombin), VII, IX, and X. They have a relatively narrow therapeutic window, the clinical consequences of which are compounded by a variable dose-effect response both within and between patients. This is mainly related to unpredictable and variable metabolism due to genetic variation and food and drug interactions. Therefore, VKA need close monitoring: overdosing can result in life-threatening bleeding and underdosing in stroke. An international and uniform laboratory standard of the intensity of anticoagulation, the international normalised ratio (INR), is widely used, replacing the non-standardised prothrombin time. Patients on chronic VKA therapy spend less than two-thirds of the time within the therapeutic INR window of 2·0–3·0.[1] Time outside the therapeutic window is highly correlated with worse outcomes.[2] Of all patients with atrial fibrillation who should be on oral anticoagulation according to clinical practice guidelines,[3] only about half are currently being treated, even in high-income countries.[4]

In the past decade several oral direct inhibitors of thrombin (dabigatran) and of factor Xa (rivaroxaban, apixaban, edoxaban) have been developed and studied in large clinical trials of patients with atrial fibrillation (table 1). These non-VKA oral anticoagulants (NOACs) have predictable pharmacological effects and relatively few drug and food interactions compared with VKA. This feature has allowed the drugs to be developed using fixed doses without the need for routine anticoagulation monitoring. They have a fast onset of activity (2–3 h to peak effect) and a relatively short duration of action, which in case of bleeding or planned surgery is another advantage over VKA. On the other hand, despite similar half-lives of about 12 h for all four drugs, dabigatran and apixaban were developed with twice per day dosing versus once per day dosing (for atrial fibrillation) with rivaroxaban and edoxaban. The short half-life has advantages related to rapid recovery of haemostatic ability in the case of bleeding or need for procedures, but at the same time can be problematic in case of poor adherence.[9] Adherence to NOACs in atrial fibrillation (75% in the case of dabigatran[10]) does not seem to be different from that of warfarin.[11] But when NOACs are given once a day, one missed dose results in low trough drug concentrations. Thus, adherence might be more of a concern compared with VKA, since there is no routine measurement of whether the drugs are being taken and no monthly interaction with the health-care team regarding the treatment. Furthermore, an antidote for NOACs is not yet clinically available, although reversal agents are in phase 2 of clinical development (see below). This is by contrast with VKA, where for warfarin there is a well established reversal strategy with vitamin K and coagulation factor replacement, although this approach has not been shown to be effective at improving outcomes in patients with severe bleeding. Finally, with substantial renal clearance for each of the NOACs, and in particular for dabigatran, the drugs have not been clinically tested in patients with stage IV chronic kidney disease (estimated creatinine clearance <30 mL/min) and thus should not be used in this population, pending further study.

	RE-LY[5]	ROCKET-AF[6]	ARISTOTLE[7]	ENGAGE-AF[8]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Renal clearance	~80%	~35%	~25%	~50%
Drug dosing	150 mg twice a day; 110 mg twice a day	20 mg once a day (15 mg for creatinine clearance <50 mL/min)	5 mg twice a day (2·5 mg when two of three following criteria are met: age ≥80 years, weight ≤60 kg, creatinine ≥1·5 mg/dL [133 μmol/L])	60 mg once a day (30 mg for creatinine clearance 30–50 mL/min, weight ≤60 kg, or strong P-glycoprotein inhibitor
Drug metabolism	P-glycoprotein	P-glycoprotein and CYP3A4	P-glycoprotein and CYP3A4	P-glycoprotein
Mean CHADS score	2·1	3·5	2·1	2·8
Design	Open label (dabigatran *vs* warfarin)	Blinded	Blinded	Blinded

Table 1: **The four large trials comparing non-vitamin K antagonist oral anticoagulants with warfarin for stroke prevention in atrial fibrillation**

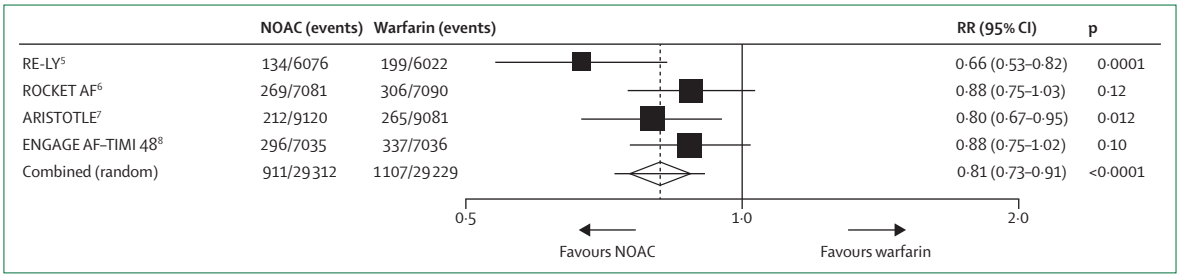

Figure 1: **Stroke or systemic embolism in the four trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin in patients with atrial fibrillation[12]**
RR=risk ratio. Reproduced from reference 12, by permission of Elsevier.

In atrial fibrillation NOACs have been at least as effective as warfarin in preventing stroke (and significantly better for higher dose [150 mg] dabigatran and for apixaban), with less life-threatening bleeding.[12] The safety advantage persists over time,[13] and is particularly notable for intracranial haemorrhage (see below).

In the past 5 years, NOACs have been found to be effective at preventing thrombotic events after acute coronary syndromes by comparison with placebo against a background of dual antiplatelet therapy (DAPT), at least in the case of rivaroxaban. But here bleeding was excessive in the context of adding the anticoagulant on top of DAPT, which is the standard of care.[14]

Because of their efficacy, safety, ease of administration, and lack of need for monitoring, NOACs are expected to replace VKA in most patients, as long as health-care systems and patients are willing and able to bear the extra cost, which appears to be justified from a cost-effectiveness perspective.[15] Whether any of these drugs will have a routine role after acute coronary syndromes remains uncertain, and the combination of oral anticoagulants and antiplatelet therapy for patients with an indication for both is a challenge.

NOACs for stroke prevention in atrial fibrillation

NOACs have been extensively tested for stroke prevention in patients with atrial fibrillation eligible for oral anticoagulation with VKA. More than 72 000 such patients have been tested in four large randomised trials[5–8] that have undergone meta-analysis.[12] The NOACs are at least as effective as warfarin at preventing stroke (figure 1) with advantages of less serious bleeding (figure 2) except for gastrointestinal bleeding, which occurs 25% more often than with warfarin. Also, a relative risk reduction in death of about 10% is observed. In particular, intracranial bleeding including haemorrhagic stroke, the most feared complication of oral anticoagulation, is more than halved by comparison with VKA,[16] although the absolute rate with warfarin is low at around 0·5% per year. The findings in the four trials have been supported by observational analyses from registries.[17,18]

Current guidelines do not provide uniform recommendations regarding which oral anticoagulant should be used in atrial fibrillation. In the guidelines issued by the European Society of Cardiology in 2012 the NOACs are preferred over VKA in atrial fibrillation,[3] whereas the 2014 American College of Cardiology/American Heart Association guidelines give NOACs and VKAs a similar level of recommendation.[19] Insurance coverage and cost[19] are important considerations since NOACs are more expensive than VKA. Practical guidance recommendations have been made as to which NOAC might be preferred for individual patients depending on the clinical scenario (table 2).[20,21]

Patients ineligible for VKA can derive a significant 28% reduction in stroke risk with DAPT consisting of aspirin and clopidogrel compared with aspirin alone, and with a similar risk of major bleeding as for VKA.[26] Therefore,

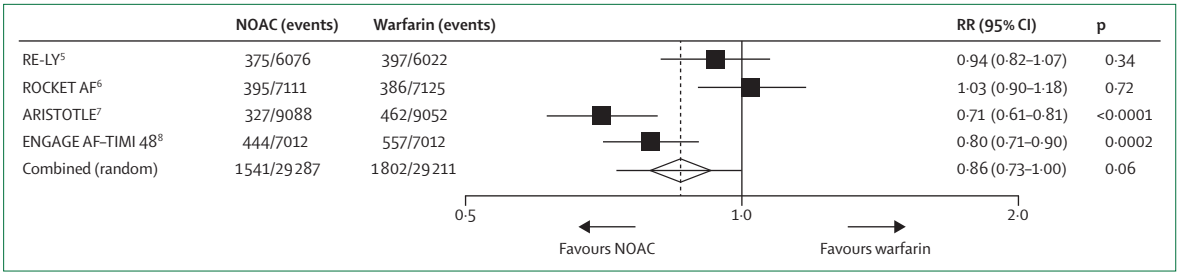

Figure 2: **Major bleeding in the four trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin in patients with atrial fibrillation[12]**
RR=risk ratio. Reproduced from reference 12, by permission of Elsevier.

	Drug	Considerations
Patients' preference		
Once per day dosing	Rivaroxaban, edoxaban	..
Patients' features		
Age ≥80 years	Dabigatran 110 mg Apixaban, rivaroxaban, edoxaban	Dabigatran 150 mg has been associated with excess bleeding in these patients[22] No particular safety issues with these drugs[8,23,24]
History of stroke	Apixaban, rivaroxaban	Apixaban has largest reduction compared with warfarin;[7] rivaroxaban has largest population with previous stroke[6]
Previous gastrointestinal bleeding	Apixaban	Only NOAC with reduction in gastrointestinal bleeding compared with warfarin[7]
High stroke risk, low bleeding risk	Dabigatran 150 mg	Dabigatran 150 mg has largest reduction in ischaemic stroke[5]
High stroke risk, high bleeding risk	Dabigatran 110 mg, apixaban, or edoxaban	Significantly safer than warfarin[5,7,8]
Concomitant coronary disease	Rivaroxaban	Only NOAC with mortality reduction after acute coronary syndromes[14]
Concomitant kidney disease	Apixaban, rivaroxaban, edoxaban	These drugs have only 25%, 35%, and 50% renal elimination, respectively
Intended electrocardioversion	Rivaroxaban	Only NOAC with prospective trial compared with warfarin[25]

Table 2: **Appropriate indications for use of non-vitamin K antagonist oral anticoagulants (NOACs) in different clinical scenarios of atrial fibrillation[20,21]**

aspirin monotherapy is discouraged for stroke prevention for atrial fibrillation.[3] A more effective option would be the use of the oral factor Xa-inhibitor apixaban that in the AVERROES trial with 5599 VKA-unsuitable patients reduced stroke or systemic embolism by 55% compared with aspirin (figure 3) and had a similar risk of major bleeding (1·4%/year with apixaban versus 1·2%/year with aspirin) including intracranial haemorrhage.[27]

Special situations with the use of NOACs in atrial fibrillation

Management of bleeding

Although large clinical trials have provided clear evidence of the effects of NOACs versus warfarin in the atrial fibrillation population, there are several practical clinical issues that have not been fully addressed by those trials. To use the NOACs safely, there are special situations with which clinicians should be familiar.[28]

One of the advantages of the NOACs includes the lack of the need for anticoagulation monitoring. However, in case of serious or life-threatening bleeding the ability to assess anticoagulation status might be important. Yet, few accurate tests are commonly available (table 3).[29] The activated partial thromboplastin time (aPTT) provides some information about the effect of dabigatran, such that a normal aPTT suggests relatively little dabigatran effect. The prothrombin time is usually elevated, at least slightly, in patients treated with rivaroxaban. A modified thrombin time is commercially available to quantitate the effect of dabigatran, and anti-factor Xa assays are available that can establish the effects of the direct Xa inhibitors, although these assays are not widely available as tests with rapid turnaround times needed to guide emergent care. Since NOACs have a half-life of around 12 h, knowledge of when the last dose was taken allows an estimate of how much anticoagulation effect might be present. With dabigatran plasma drug level and clinical outcome are significantly correlated, with higher levels associated with lower risk of stroke and with higher rates of major bleeding.[30]

To treat serious bleeding, antithrombotic therapy should be stopped. Identification of bleeding source and local measures to control bleeding are the same as for any bleeding patient. If the patient took the NOAC within 2–4 h, oral activated charcoal will reduce absorption. Reversal of other antithrombotics, such as aspirin with platelet transfusion, should be considered. Fluid resuscitation and blood transfusions might be indicated. Restoration of coagulation appears to be achieved, at least partly, by the administration of prothrombin complex concentrate[31] or even activated factor VII, although no reliable clinical data exist to guide when and how to use the treatments. When use of these agents is under consideration, prompt consultation with an anticoagulation expert, when available, is advised.

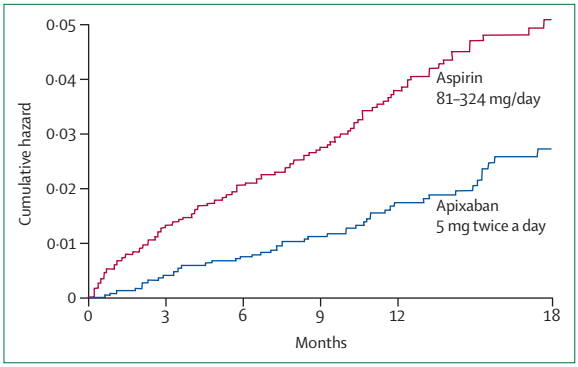

Figure 3: **Stroke or systemic embolism in the AVERROES trial comparing the oral direct factor Xa blocker apixaban with aspirin[27]**

	Class	Preferred test	Emergency scenario test
Dabigatran	Anti-IIa	Dilute thrombin time	Accelerated partial thromboplastin time
Rivaroxaban	Anti-Xa	Anti-Xa concentration	Prothrombin time
Apixaban	Anti-Xa	Anti-Xa concentration	Dilute prothrombin time
Edoxaban	Anti-Xa	Anti-Xa concentration	No data available

Table 3: **Laboratory test for monitoring of non-vitamin K antagonist oral anticoagulants in laboratory and emergency settings[29]**

	Molecule	Target
Idarucizumab[32]	Humanised monoclonal antibody	Dabigatran
Andexanet-alfa[33]	Decoy (inactivated) factor-Xa	Xa blockers
PER977[34]	Small synthetic molecule	All non-VKA oral anticoagulants

Table 4: **Antidotes to non-vitamin K antagonist (VKA) oral anticoagulants**

Needless to say, with reversal of the anticoagulant, patients will no longer be protected against stroke and systemic embolism.

Specific antidotes to NOACs are in development (table 4),[32–34] but as of early 2015 they are not yet available for clinical use. One is a humanised monoclonal antibody against dabigatran, one is a decoy (truncated) factor Xa molecule, that binds Xa blockers, and one binds non-specifically all NOACs. Whether the dabigatran antibody will be effective in patients with bleeding on dabigatran or patients needing emergent surgery who are on dabigatran is under investigation in a clinical trial (REVERSE-AD, NCT02104947).

Although relatively uncommon by comparison with VKA, intracranial bleeding occurs in patients on NOACs. Intracranial bleeding in association with any oral anticoagulant has a poor prognosis, and although reversal of the effects of the antithrombotic therapy is a priority, whether it improves outcome is not clear. The only very effective way to deal with intracranial haemorrhage is to prevent it from happening to begin with, thus supporting the role of NOACs.

One type of bleeding that is more common with NOACs, at least with dabigatran,[5] rivaroxaban,[6] and edoxaban[8] than with warfarin, is gastrointestinal bleeding. This is particularly important since the gastrointestinal tract is the most common site of bleeding in this population. Thus, for patients with previous gastrointestinal bleeding, protection with a proton-pump inhibitor should be considered, although no prospective studies have assessed this strategy. Non-steroidal anti-inflammatory and antiplatelet therapy, which is associated with a 75% higher rate of major bleeding,[35,36] should be avoided, unless clearly indicated.

Management around the time of surgery

Like any antithrombotic, NOACs can increase bleeding around the time of surgical procedures, and interruption of therapy will be needed for those procedures with substantial bleeding risk. Since NOACs are partly cleared by the kidney, especially dabigatran, which is about 80% renally excreted, renal function and the NOAC used are important factors determining how long the drug should be interrupted for before elective surgery—eg, dabigatran has a prolonged half-life of 18 h in a patient with a creatinine clearance of 30 mL/min. For procedures with moderate bleeding risk, holding the drugs for two to three half-lives is advised, whereas for procedures with high risk, five half-lives are needed for the drug effect to be completely resolved. When to resume the drug is also important and very different from VKA, when resuming immediately after the procedure can be reasonable since the full effect will take days. NOACs, which typically have peak effect 2–3 h after dosing, should not be resumed until haemostasis has occurred, usually the morning after a procedure that has bleeding risk. Unlike with VKA, there is no rationale for bridging with a parenteral anticoagulant when using NOACs that have a similar half-life as low molecular weight heparin, unless the patient cannot take oral medications.[28] In patients with atrial fibrillation undergoing implantation of a device, generally one or two doses of NOAC are held before the procedure, although studies are ongoing to define whether this is needed. In the situation of urgent surgery, monitoring of the NOAC might be helpful to anticipate how much haemostatic ability exists.[29] In those cases, the anticoagulation status can be estimated and specific measures can be taken if needed.

Cardioversion

Electric or pharmacological cardioversion is commonly used to restore sinus rhythm in patients with atrial fibrillation, and cardioversion can result in stroke if anticoagulation is inadequate. An important issue is how and when to use NOACs around the time of cardioversion. Typically, patients with atrial fibrillation lasting longer than 48 h (or lasting an uncertain period of time) should be given well managed oral anticoagulation for at least 3–4 weeks before cardioversion. Post-hoc analyses from

three of the major trials with NOACs versus VKA suggest acceptable safety with NOACs in patients undergoing cardioversion.[37–39] The first prospective trial of a NOAC versus VKA for cardioversion was done in 1502 patients who were randomly assigned 2:1 to rivaroxaban or VKA.[25] Event rates were low and similar with rivaroxaban and warfarin. This provides some reassurance that rivaroxaban can be used in this situation, although only ten thrombotic and ten major bleeding outcome events occurred and, thus, the study results were not definitive. An advantage in the rivaroxaban-treated patients was the reduced time to cardioversion (in patients not undergoing transoesophageal echocardiography and immediate cardioversion), since warfarin typically takes several weeks to have a stable therapeutic effect. Rivaroxaban becomes effective almost immediately, as long as patients are adherent. Similar studies with apixaban (EMANATE, NCT02100228) and with edoxaban (ENSURE, NCT02072434) are underway.

Catheter ablation

Invasive therapy of atrial flutter or fibrillation with radiofrequency ablation is common and the optimum periprocedural use of oral anticoagulation including NOACs is not well established. Generally, VKA are continued through the time of the procedure with a therapeutic or low therapeutic INR. The first medium-size study of 1584 patients showed that continuing VKA appeared to be safe and effective compared with discontinuation of VKA and bridging with parenteral anticoagulants.[40] NOACs have a short onset and offset of action and might also be attractive around the time of catheter ablation. Since NOACs lack an effective antidote, however, electrophysiologists have been reluctant to continue these agents through the time of the procedure. Cardiac tamponade, an uncommon but known complication of catheter ablation, can be more challenging to manage when patients are taking a NOAC. Two relatively large case-control studies found similar rates of adverse outcomes with continuing dabigatran compared with warfarin.[41,42] More trials are underway to define the role of dabigatran (DAPPAR AF [NCT01468155] and ODIn-AF [NCT02067182]) and rivaroxaban (VENTURE-AF [NCT01729871]) around the time of ablation procedures.

Concomitant coronary artery disease

Of patients with atrial fibrillation 20–40% have concomitant coronary artery disease.[43] In patients with acute coronary syndromes antiplatelet therapy is indicated and is often combined with anticoagulants, including with oral anticoagulants at the time of hospital discharge. This results in substantially increased bleeding. When aspirin and clopidogrel are used in combination with VKA, the bleeding risk appears to be two-fold higher compared with VKA alone.[35] Since VKA is effective in preventing coronary thrombotic events and combination of anticoagulation and antiplatelet therapy substantially increases bleeding, the European guidelines on the management of atrial fibrillation discourage the use of antiplatelet therapy for patients with stable coronary disease treated with oral anticoagulants.[3]

Percutaneous coronary intervention is often needed to relieve ischaemic symptoms in stable patients with coronary disease, including in patients with atrial fibrillation who receive anticoagulation for stroke prevention. During and after intervention, potent antiplatelet therapy is needed to prevent early and late thrombotic complications including stent thrombosis.[44] This form of triple therapy (VKA, and DAPT consisting of clopidogrel and aspirin) is believed to be even more important when the intervention is in the setting of acute coronary syndromes, in which DAPT is advised for at least 12 months after the intervention irrespective of the type of stent used.[42]

To reduce bleeding several options might be considered. A prospective randomised trial in 573 patients showed that omission of aspirin reduced bleeding by around 60% without an increase of ischaemic events.[45] The trial size was too small to be conclusive, and for that purpose a study of 10 000 patients would have been necessary. Another option could be to use NOACs in view of their proven safety, but data for their use with dual antiplatelet therapy is insufficient to know the relative safety and efficacy.[35,36] Therefore, at least two randomised trials have been initiated to evaluate the safety and efficacy of a NOAC versus VKA in atrial fibrillation patients undergoing coronary intervention for either stable coronary disease or acute coronary syndrome (table 5). Interestingly, each trial will also evaluate the withdrawal of aspirin from the triple therapy regimen.

Thus, so far little evidence exists to guide combinations of antithrombotic treatment in patients with atrial fibrillation and coronary disease. When antiplatelet therapy is combined with NOACs, both bleeding and thrombotic risk (both ischaemic stroke and stent thrombosis) should be taken into account. DAPT should be given for the shortest clinically acceptable duration[46] during which a lower dose of a NOAC might be attractive. The ongoing trials shown in table 5 will provide guidance for optimum treatment in this group of patients.

Elderly patients

The rates of stroke and major bleeding both rise sharply with advanced age in patients with atrial fibrillation. The CHA_2DS_2VASc risk score includes two points for age 75 years or older, such that all these patients with atrial fibrillation have an indication for oral anticoagulation.

	n	Groups	Follow-up	NCT number	Hypothesis
PIONEER AF-PCI	2100	3	12 months	01830543	Superiority on bleeding
RE-DUAL PCI	8500	3	12 months	02164864	Superiority on bleeding and efficacy

Table 5: **Current trials with non-vitamin K antagonist oral anticoagulants after percutaneous coronary intervention in patients with atrial fibrillation**

Older age is also a strong risk factor for bleeding. When NOACs are considered in elderly patients, one should bear in mind that adherence to NOACs is of major importance in view of their fast offset of action compared with VKAs. Each patient started on a NOAC must be informed about this. Elderly patients might have more adherence issues than younger patients, and thus inclusion of family members and caregivers in discussions regarding medications is important. In large randomised trials adherence to NOACs did not seem problematic,[12] but in general practice rates of adherence might be lower, leading to excess thromboembolism.

With dabigatran significant interaction was noted between risk of bleeding and age, such that older patients had a relatively greater risk of bleeding with dabigatran than warfarin compared with younger patients.[22] This was not the case with the oral Xa inhibitors, for which the relative risk of bleeding versus warfarin was quite similar in elderly patients by comparison with younger patients.[23,24] With apixaban, patients at least 75 years of age, and even at least 80 years of age, had consistently less bleeding than with warfarin.[23] The European Society of Cardiology recommends the lower dose of dabigatran (110 mg twice a day) for patients aged 80 years or older.[3]

Chronic kidney disease

NOACs are all cleared by the kidneys to some extent, and more so with dabigatran. Therefore, their dosing in the clinical trials, and in their approved labels, is determined in part by taking into account creatinine clearance. Dabigatran is recommended to be given at the lower dose of 110 mg twice a day when the creatinine clearance is less than 50 mL/min, and not used in case of a creatinine clearance less than 30 mL/min. Likewise, in patients with a creatinine clearance of less than 50 mL/min, rivaroxaban should be given at 15 mg once a day, 25% lower than the standard dose. With apixaban, if two of three criteria exist (age ≥80 years, bodyweight ≤60 kg, or serum creatinine ≥1·5 mg/dL [133 μmol/L]), then the 50% lower dose (which is 2·5 mg twice a day) should be used. The dose of edoxaban must be halved from the standard 60 mg once a day to 30 mg once a day in patients with a creatinine clearance between 50 mL/min and 30 mL/min. The clinical trials excluded patients with an estimated creatinine clearance less than 25 mL/min to 30 mL/min, so these patients should generally not be treated with NOACs. Finally, since creatinine clearance diminishes over time with ageing, regular kidney function checks should be done,[28] especially in elderly patients.

Valvular abnormalities and heart valve prosthesis

Patients with significant mitral stenosis were excluded from the four large atrial fibrillation trials comparing NOACs with VKA for stroke prevention, since patients with rheumatic mitral stenosis and the related high risk of stroke were excluded from the historic VKA versus control trials that established the basis for non-inferiority for the warfarin-controlled trials. Thus, evidence is lacking as to whether NOACs are effective in this high-risk group. Some of the trials included patients with other valvular abnormalities including mitral insufficiency and aortic valve disease, and these patients had similar benefits with the NOACs as the rest of the population.[47] Patients with mechanical prosthetic valves were excluded, since they had another reason for anticoagulation. In a subsequent randomised warfarin-controlled study, dabigatran was inferior in safety and efficacy in patients with mechanical artificial heart valves.[48] Patients with valvular bioprostheses were included in some of the atrial fibrillation trials of NOACs versus warfarin, because their only indication for anticoagulation was their atrial fibrillation. Although this group of patients was relatively small, they are likely to have the same benefits with NOACs as patients without previous valve surgery.

Interactions with food and commonly prescribed drugs in atrial fibrillation

Unlike with warfarin, with which variable amounts of vitamin K in food contributes to instability of effect, there are no dietary restrictions with NOACs. The only important issue with respect to food is that rivaroxaban has 40% more gastrointestinal absorption when taken with a high calorie meal than with a low calorie meal, thus it is generally recommended to be taken with dinner as the most consistent meal. Many patients with atrial fibrillation are on several drugs, and a substantial proportion of these interact with metabolic pathways of NOACs. CYP3A4 and P-glycoprotein inhibitors are the most important drugs that increase plasma concentrations of NOACs, although drug interactions are much less of an issue than with VKA. For example, even though amiodarone has some inhibition of P-glycoprotein pathway and effect on NOAC metabolism,[28] the benefits of NOACs appear to be at least as great in this subgroup of patients,[49] perhaps because the interactions are even greater with warfarin. In the ENGAGE trial the dose of edoxaban was reduced by 50% for patients on verapamil or quinidine, strong inhibitors of the P-glycoprotein pathway.[8] The doses of NOACs in the other trials were not reduced for patients taking these drugs, although this could be taken into account, especially for patients on the border of dose reduction based on other criteria such as renal function. Interactions and dose recommendations for concomitant use of the most commonly prescribed agents in patients with atrial fibrillation are summarised in the drug package insert and in the European Society of Cardiology practical guide document.[28]

Switching between oral anticoagulants

When the treating physician decides to switch an eligible patient with atrial fibrillation from VKA to a NOAC, the patients should be provided with information about the NOAC and how to safely transition from the VKA. The INR should be monitored, and when it has

dropped to around 2·0 or less, the NOAC should be started. The gap in therapeutic anticoagulation status must be as short as possible.

At the end of some clinical trials the switch from blinded NOAC to open-label VKA was associated with excess stroke,[6,50] but by a stringent scheme of INR checks this can be prevented.[51] In general, bridging with parenteral anticoagulation is not advised.

On occasion, patients might switch from a NOAC to VKA for various reasons such as deteriorating kidney function or the patients' preference related to cost. In view of the slow onset of action of VKA, the NOAC and VKA should be given concomitantly until the INR is around 2·0. Since the oral direct factor Xa blockers affect INR early after intake, INR should be checked immediately before the next NOAC intake during the concomitant administration period, and retested 24 h after the last NOAC dose to ensure that the patient is in therapeutic range on the VKA. After the transition is completed frequent INR checks should be made, as in any other patient being initiated on a VKA.

Conclusion

For patients with atrial fibrillation and risk of stroke, oral anticoagulation is highly effective at preventing stroke, but a substantial proportion of eligible patients are treated either suboptimally or not at all. The oral direct inhibitors of factors IIa or Xa provide important new approaches, since they are at least as effective as warfarin for stroke prevention in atrial fibrillation with a more favourable safety profile, especially concerning intracranial bleeding. Safe use of these drugs, however, needs understanding of when to reduce the dose, their metabolic pathways, their dosing around the time of procedures, how to manage related bleeding, and to avoid concomitant aspirin without a clear indication. Studies are underway to clarify many of the unanswered practical questions including their use in the context of acute coronary syndromes and coronary stenting. It is important to know when the agents should not be used, such as in patients with severe renal impairment and those with mechanical prosthetic valves. Although the availability of antidotes is eagerly awaited, the absence of an antidote has not led to worse bleeding outcomes compared with warfarin in randomised trials. Although cost effective, the high cost of the drugs is a barrier to their use, especially in cost-constrained environments. Without frequent monitoring of drug effect, other ways to measure and encourage adherence are needed.

Contributors

FWAV contributed to writing, data interpretation, and composing tables and figures. CBG contributed to writing, data interpretation, and English editing.

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