

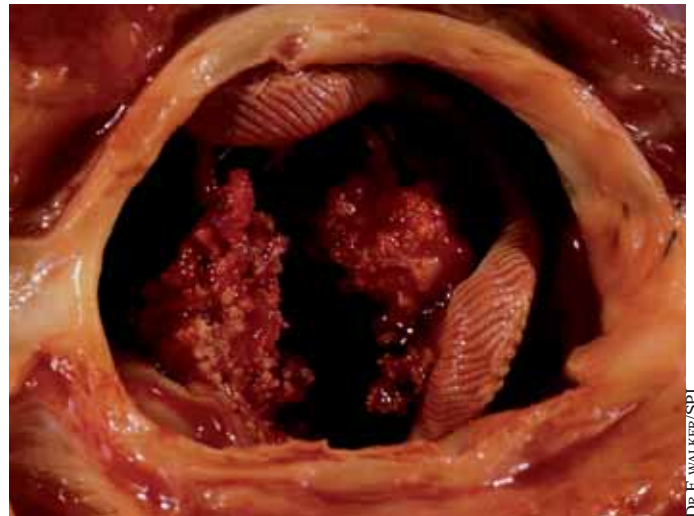
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Valvular heart disease

— preventing thrombosis and endocarditis

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Patients who have undergone heart valve replacement operations are at risk of thrombosis and endocarditis. This article, the second in a special feature on valvular heart disease, describes how these risks are managed



Bacterial endocarditis of an artificial heart valve (ribbed)

DR E. WALKER/SPL

Drug therapy in valvular heart disease (VHD) is used to delay surgical intervention, to stabilise the patient pre- and post-surgery, to control symptoms in those unsuitable for surgery and to treat comorbidities. The drugs commonly used in VHD are listed in Panel 1, and described in Panel 2 (p128).

Following valve replacement operations, patients are at risk of thrombosis and endocarditis. This article focuses on the prevention of these conditions.

It is estimated that anticoagulant-related bleeding or thrombosis accounts for 75 per cent of prosthetic valve complications.¹ Guidelines published by the European Society of Cardiology and joint guidelines from the American College of Cardiology and American Heart Association state that effective thromboprophylaxis requires careful use of anticoagulation and antiplatelet therapy, together with management of thrombosis risk factors such as atrial fibrillation (AF), left ventricular dysfunction and previous thromboembolism.^{1,2}

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Patients with mitral valve stenosis (see p121) and AF should be anticoagulated to reduce the risk of thromboembolism.

It is recommended that patients with mechanical valves, or with bioprostheses and additional risk factors, take oral anticoagulants for life.^{1,2} The ESC recommends that patients with bioprostheses and no additional risk factors receive oral anticoagulation for the first three months after their valve replacement operation (target INR 2.5), followed by life-long treatment with low dose aspirin (75–100mg daily). Patients with bioprostheses without other risk factors may not need any anticoagulation.^{1,2}

Anticoagulation therapy is guided by the type of replacement valve (mechanical or biological, see p121), the position of the implant, associated risk factors (eg, AF), bleeding risk and the patient's age.³ While a variety of vitamin K antagonists have been used for oral anticoagulation following valve replacement, the British Committee for Standards in Haematology recommends warfarin.⁴

Anticoagulation (usually with unfractionated heparin) should be started as soon as possible after the operation. Once the risk of bleeding falls below that of thrombosis, oral warfarin is introduced. The risk of thromboembolism and bleeding is greatest during the first month post valve replacement surgery, so the patient's INR must be frequently monitored. Previous practice was to provide a target INR range (eg, 2–2.5). Now

a precise target is set to reduce the time during which the patient is outside the optimal anticoagulation level.

Unfractionated heparin

Unfractionated heparin (UFH) has a “bridging” thromboprophylactic role. It is used post-operatively while the INR reaches target levels, and during any essential interruption to oral anticoagulation (eg, if major surgical intervention was required). It has a short half-life and its effects can be reversed rapidly if bleeding occurs.

It forms a complex with antithrombin which inactivates coagulation factors.⁵ UFH

Panel 1: Drugs commonly used in valvular heart disease

- Anticoagulants
- Antibiotics (for endocarditis prophylaxis)
- Angiotensin-converting enzyme inhibitors
- Dihydropyridine calcium channel blockers
- Beta-blockers
- Diuretics
- Nitroprusside
- Inotropic agents

Panel 2: Drugs used for valvular heart disease

Inotropic drugs

Inotropic sympathomimetic drugs (eg, dopamine and dobutamine) reduce hypotension by exerting a positive inotropic myocardial effect (increased contractility and output) through beta-1 adrenoceptors. There is little expected effect on heart rate, although tachycardia can occur. These drugs are used before emergency surgery in patients with poorly tolerated acute aortic regurgitation.¹ Noradrenaline (a catecholamine) and milrinone (a phosphodiesterase III inhibitor) are typically required post-operatively in intensive care to maintain controlled arterial pressures and organ perfusion. Cardiac output monitoring is required and arterial blood gases should be measured regularly to control the infusion rate.

Sodium nitroprusside

Sodium nitroprusside is a potent vasodilator given by intravenous infusion to control hypertensive crisis or hypertension following surgery. For patients with poorly tolerated acute aortic regurgitation (see p120), sodium nitroprusside can be used before surgery to stabilise the condition by reducing cardiac afterload and the regurgitant fraction.¹ A carefully monitored nitroprusside infusion can reduce pulmonary congestion and improve left ventricular (LV) performance in patients with aortic stenosis and acute pulmonary oedema.² The BNF warns of rapid severe hypotension and possible cyanide poisoning from excessive plasma concentrations of the cyanide metabolite, and it is recommended that the patient is treated in intensive care or in a high dependency unit.

Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors have antihypertensive and vasodilatory effects. ACE inhibitors are useful in controlling LV dysfunction and heart failure secondary to valve disease, and may be continued in those unsuitable for surgery.^{1,2} ACE inhibitors slow aortic root dilation in aortic regurgitation and may slow progression of aortic stenosis (see p119).^{1,2} They are also used to wean patients off milrinone inotropic support.

Dihydropyridine calcium channel blockers

Dihydropyridine calcium channel blockers (eg, amlodipine) predominantly reduce peripheral vascular smooth muscle resistance, increasing cardiac output and decreasing regurgitant volume. These effects should help preserve LV systolic function and reduce LV mass.² They are also used for treatment of comorbid hypertension.¹ However, the dose should not be increased excessively in an attempt to achieve a “normal” systolic blood pressure, because this is rarely possible in patients with VHD.²

Beta-blockers

Beta-blockers have antihypertensive, antiarrhythmic and antianginal effects — all essential in patients with LV dysfunction. Bisoprolol and carvedilol have been shown to reduce all-cause mortality in those with LV dysfunction.^{1,2} Beta-blockers exert a negative inotropic and chronotropic effect, reducing myocardial oxygen consumption and increasing the time for LV filling.^{1,2} They should be avoided in patients with aortic stenosis because they can cause the cardiac output across the valve to drop significantly.^{1,2}

Diuretics

Loop diuretics are important for VHD patients with heart failure and pulmonary congestion with symptoms of dyspnoea and orthopnoea. Reduction of central blood volume, cardiac workload and filling pressure helps reduce mitral regurgitation.² Careful monitoring is needed to avoid hypovolaemia and hypotension, since excessive preload reduction can reduce cardiac output.²

Panel 3: New NICE guidelines for endocarditis prophylaxis

The National Institute for Health and Clinical Excellence published new guidelines on endocarditis prophylaxis last month. The guidelines say that there is limited evidence to support routine antibiotic use in patients undergoing interventional procedures, and that the link between endocarditis and interventional procedures is less than clear. The new guidance is controversial and has been debated within the medical profession — some hospitals may wish to continue using local guidelines for the time being.

The guidelines say that people at particular risk of infective endocarditis include those with:

- Replacement valves
- Acquired valvular heart disease with stenosis or regurgitation
- Structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised)
- Hypertrophic cardiomyopathy
- A previous episode of infective endocarditis

The guidelines suggest offering people at risk clear and consistent information about prevention of endocarditis, including the benefits and risks of antibiotic prophylaxis, an explanation of why antibiotic prophylaxis is no longer routinely recommended, and the symptoms that may indicate infective endocarditis.

The guidelines suggest that antibiotic prophylaxis should not be offered to patients undergoing dental procedures, or procedures of the upper and lower gastrointestinal tract, genitourinary tract and upper and lower respiratory tract.

is heterogeneous, giving intra- and inter-patient variability in response.⁵

Cautions and contraindications UFH carries an intrinsic risk of causing haemorrhage and bleeding. An important but rare contraindication is heparin-induced thrombocytopenia (HIT), a cytotoxic, allergic reaction resulting in platelet aggregation and reduction in platelet number and function. This delayed, antibody-mediated hypersensitivity can take five to 10 days to develop. A thrombocyte count should be taken before treatment is initiated, and monitored throughout. If a patient's platelet count reduces by 50 per cent or if HIT is confirmed by assay, UFH should be discontinued immediately and an alternative anticoagulant such as danaparoid should be used.⁵

— Warfarin

Warfarin, a coumarin derivative, is the most well known oral anticoagulant.⁴ It has high bioavailability, is highly bound to plasma proteins and has a long half-life (36–42 hours).⁵

Once activated, vitamin K is a co-factor in the synthesis of clotting factors II, VII, IX and X and the natural anticoagulant proteins C and S. Coumarins exert an anticoagulant effect through antagonism of the hepatic enzyme required to convert vitamin K to its active form. This eventually leads to synthesised clotting factors with reduced coagulant activity. Because of active clotting factor

reserves, and because the response to warfarin is dose- and duration- dependent, three to four days of therapy may be required for a clinical response. The antithrombotic effect of warfarin is linked to a lowering of prothrombin levels.^{5–8}

The anticoagulant protein C has a shorter half-life than some clotting factors, so its levels are more rapidly depleted during warfarin loading. Therefore, there is a prothrombotic state during warfarin initiation, with a risk of coumarin-induced skin necrosis from extensive thrombosis of venules within the subcutaneous layer.⁶

Dose The dose of warfarin depends on factors such as the patient's age, comorbidities, and other medicines. Environmental and genetic factors can also influence the dose required.⁶ There are a number of warfarin induction schedules, but it is recommended not to use an initial dose of over 10mg, to reduce the risk of bleeding.^{4–6} Further doses are titrated according to response. Once the target INR has been maintained for two days, heparin can be stopped.

Monitoring Frequent INR monitoring is required during warfarin initiation, becoming less frequent once the INR is stable and a dose-response relationship has been established. Follow-up monitoring can be carried out through a pharmacist-led clinic, and some patients can self-monitor using home monitoring devices.⁶ These devices are not yet common in the UK (they are limited by cost) but may assist compliance.

Bleeding The risk of bleeding is closely associated with INR, increasing with INR values greater than 4 and rising sharply with values greater than 5. Patients with an INR above 6.5 should be admitted to hospital but should not be given intravenous vitamin K (phytomenadione) unless they are actively bleeding because rapid changes in INR can lead to valvular thrombosis. Oral vitamin K is often used and the INR is monitored frequently. An INR of 10 will require administration of fresh frozen plasma. Older patients, those with comorbid diseases (eg, renal disease, liver disease), patients taking medicines which interact with warfarin and those who misuse alcohol are at a greater risk of bleeding^{4,6,7} and dose adjustment is necessary in these groups.

Surgery Anticoagulation should not be interrupted in patients with mechanical valves because of the thrombosis risk. For patients who need to undergo minor procedures (eg, tooth extraction), warfarin should be continued at a lower dose, and the procedure can be performed if the INR is about 2 on the morning of the operation.⁹ Oral tranexamic acid mouthwash (4.8 per cent) can stop bleeding post dental extraction.

Patients requiring coronary angiography can safely undergo the operation with an INR of less than 2.^{1,2} If higher INRs are required, radial access is preferred. Patients requiring major surgery, including those undergoing endoscopy with biopsy, should be admitted to hospital four to five days before surgery. The warfarin should be stopped and the patient should be given intravenous UFH. A patient's INR should be less than 1.2 before

Panel 4: Procedures which may require antibiotic prophylaxis*

- Biopsy of urinary tract or prostate
- Bronchoscopy (with a rigid instrument)
- Cystoscopy during urinary tract infection
- Dental procedures with the risk of gingival or mucosal trauma
- Gynaecological procedures in the presence of infection
- Laproscopic probing of obstructed biliary tracts
- Lithotripsy
- Oesophageal dilation or sclerotherapy
- Tonsillectomy and adenoidectomy
- Transurethral resection of prostate
- Urethral instrumentation or dilation

*Before publication of the latest guidance from the National Institute for Health and Clinical Excellence, antibiotics were routinely given for these procedures

major surgery. Heparin should be stopped six hours before surgery and restarted six to 12 hours afterwards. Some centres use low molecular weight heparin although the evidence for its efficacy is lacking.

Cautions and contraindications Concurrent use of non-steroidal anti-inflammatory drugs with warfarin will increase the risk of bleeding, even in patients whose INR is stable.^{6,7} NSAIDs and aspirin also have a dose- and duration-dependent effect on the gastrointestinal mucosa, increasing the risk of erosion, ulceration and subsequent bleeding. Selective serotonin reuptake inhibitors also have an antiplatelet effect, since reducing platelet serotonin levels inhibits platelet aggregation.⁷ Patients should be warned about the risks of bleeding and observed carefully, and lower doses may be required. Warfarin is a teratogen and has noted embryopathy. Its use during pregnancy requires specialist advice. The ESC recommends warfarin therapy during the second and third trimesters until the 36th week.¹ Use of warfarin during labour is contraindicated because of risk of fetal cerebral bleeding.²

Interactions The identification, assessment and management of interactions with warfarin are critical to avoid serious bleeding or thrombosis.⁵⁻⁸ Warfarin is metabolised in the liver, so anything altering hepatic function or metabolism will affect warfarin levels and thus the INR. Changes in absorption will alter the bioavailability of warfarin, and changes in vitamin K intake alter intrinsic clotting reserve. The INR should be monitored when any changes are made to a patient's medicines, food or supplements (including herbal products) particularly in the two weeks following the change.⁸

Warfarin is metabolised by cytochrome P450 (CYP) enzymes. CYP inducers (eg, rifampicin and carbamazepine) reduce the anticoagulant effect, so higher doses of warfarin will be required. Enzyme induction and synthesis takes between one and two weeks.^{7,8} Similarly, CYP enzyme inhibitors reduce warfarin metabolism, potentiating the anticoagulant effect. Inhibition is seen more rapidly than induction, ranging from within 24 hours to one week.⁵ Examples of significant enzyme inhibitors are cimetidine, amiodarone, fluconazole, fluoxetine, erythromycin and metronidazole.^{7,8}

Patients should be advised to maintain a steady diet, and not to change their intake of vegetables rich in vitamin K (eg, broccoli, kale) once stabilised.⁶

Antibiotic courses can change vitamin K levels in the body by altering the intestinal microflora normally involved in vitamin K synthesis. The effect is variable and frequent INR monitoring is suggested during antibiotic use. Some antibiotics can also inhibit hepatic metabolism of warfarin (eg, erythromycin, ciprofloxacin).⁷

The role of the pharmacist

Pharmacists have an important role in ensuring the safe and effective use of medicines in patients with VHD, monitoring therapy, helping to prevent adverse effects, managing any interactions and promoting compliance with anticoagulation and antiplatelet therapy.

Educating patients about antibiotics for the prophylaxis of endocarditis and on the signs of suspected bleeding related to anticoagulation therapy is important.¹ Other warning symptoms include sudden dyspnoea in prosthetic valve patients, in which case obstructive valve thrombosis could be suspected.¹ Pharmacists can also suggest compliance aids to patients requiring life-long anticoagulation, and if appropriate, use of home INR monitoring.

On the wards, it is essential to alert other members of the multidisciplinary team to patients with prosthetic valve replacements, because these patients will need measures such as heparin infusions and antibiotic prophylaxis that may otherwise be forgotten. Pharmacists should also ensure that appropriate drug regimens are used and that doses are optimised. Drug interactions should also be recognised and managed.

Pharmacists should also recognise possible iatrogenic causes of VHD. As described in the first part of this feature (p124), people seeking weight loss treatments may use unlicensed preparations containing the appetite suppressants fenfluramine, dexfenfluramine and phentermine. These can cause VHD by activation of valve 5-HT_{2B} receptors.¹⁴ It would also be appropriate to counsel recreational users of methylenedioxymethamphetamine ("ecstasy") because this drug has been associated with valvulopathy.¹⁴ Pharmacists should ensure that patients with Parkinson's disease using dopamine agonists (cabergoline and pergolide) for periods longer than six months are monitored for clinically significant valvulopathy.¹⁴

— Antiplatelet therapy

It is argued that adding aspirin treatment to patients with mechanical valves who are on warfarin reduces mortality at the expense of an increased risk of bleeding.^{1,2} Antiplatelets do not alter the INR, and a thorough risk-benefit assessment and regular follow-up is required.⁵⁻⁸

In general, antiplatelet drugs should only be added to regimens containing warfarin in patients with concomitant vascular disease (coronary artery or other atherosclerotic disease), or in those who have thrombotic disease despite being at their target INR.^{1,8} Patients with drug eluting stents following myocardial infarction are often given warfarin and clopidogrel, without aspirin. This is advised by the ESC, but the evidence supporting the efficacy of this combination is limited.

Some clinicians use antiplatelet drugs as monotherapy after insertion of a biological valve, suggesting that there is no difference between low-dose aspirin and warfarin in the first three month period.¹⁰ A recent study

demonstrated that there was no difference in mortality or cerebral ischaemic events at 12 months in patients given only aspirin or no aspirin following biological aortic valve replacement without coronary artery bypass graft.¹⁰ However, this area remains controversial and decisions may be made on a case-by-case basis.

— Endocarditis prophylaxis

Infective endocarditis, a microbial infection of the intracardiac structures, has a high mortality rate despite the availability of good intravenous antibiotic therapy.^{11,12} New guidelines for endocarditis prophylaxis for patients with VHD and replaced valves have recently been published by the National Institute for Health and Clinical Excellence (see Panel 3, p130).

All patients with VHD and those with complex congenital heart disease are at high risk of this infection and must receive antibiotic prophylaxis if appropriate, according to the new guidelines. Patients with replaced valves, surgically created conduits or other foreign material such as grafts used to close ventricular or atrial septal defects are also at high risk of this infection.

The aim of antibiotic prophylaxis is to prevent bacteraemia which may allow bacteria to seed onto diseased endogenous valves or implanted material. Once seeded, the bacteria generate a protective layer (bio-layer) and will grow to form a destructive abscess which requires prolonged intravenous antibiotic therapy or, in the case of implanted material, surgery.¹²

The bacteria responsible for causing infection following dental, oral, respiratory

Suggestions for future special features

If you would like to suggest a topic for a future special feature in *Hospital Pharmacist*, or if you are a specialist clinical pharmacist interested in writing about your area of practice, please contact Hannah Pike (e-mail hannah.pike@pharmj.org.uk, telephone 020 7572 2425) or Gareth Malson (e-mail gareth.malson@pharmj.org.uk, telephone 020 7572 2419).

Panel 5: Antibiotic regimens for endocarditis prophylaxis in patients undergoing gastrointestinal/genitourinary tract procedures under general anaesthesia*

Age	Standard regimen	Regimen for patients allergic to penicillin†
over 10 years	Intravenous amoxicillin 1g and IV gentamicin 120mg at induction, followed by oral amoxicillin 500mg six hours post procedure	Teicoplanin 400mg (IV) and gentamicin 120mg (IV) at induction
5 to 10 years	Amoxicillin 500mg (IV) and gentamicin 2mg/kg (IV)	Teicoplanin 6mg/kg (IV) and gentamicin 2mg/kg (IV) (for children under 14 years)
under 5 years	Amoxicillin 250mg (IV) and gentamicin 2mg/kg (IV)	

*This panel has been put together considering the recently published NICE guidance for infective endocarditis prophylaxis in adults and children undergoing interventional procedures, and previous guidelines

†other regimens are listed in the BNF 54

and oesophageal procedures are usually *Streptococcus viridans* or HACEK organisms (a group of bacteria comprising *Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*). Gastrointestinal and genitourinary procedures principally risk infection with *Streptococcus bovis* and enterococci bacteraemia.

Invasive procedures can cause bacteraemia and if antibiotics are to be given, they should be given before the procedure. If not given in time, they may still help if given intravenously within two to three hours of the procedure.¹¹ Before publication of the latest NICE guidelines, antibiotics were routinely used in all of the procedures listed in Panel 4 (p130). During the transition phase to the new guidelines, many patients will still receive antibiotics as routine prophylaxis.

Single doses of antibiotics will achieve adequate serum levels. For dental and respiratory procedures, a broad-spectrum beta-lactam penicillin (amoxicillin) is usually indicated. Clindamycin is used for patients with penicillin allergy and azithromycin suspension (500mg in adults) is used for patients unable to swallow clindamycin capsules. For procedures involving general anaesthesia, and for bowel and genitourinary procedures, intravenous amoxicillin and gentamicin is preferred, given at the time of induction of anaesthesia. The combination of a penicillin and aminoglycoside allows cover for both enterococci and staphylococci.¹¹ Gentamicin alone has good efficacy against *Staphylococcus epidermidis*, a common agent of endocarditis on prosthetic valves.¹¹

The ESC recommends vancomycin in penicillin allergic patients rather than teicoplanin, however the latter has better tissue penetration.

The NICE guidance states that patients at risk of endocarditis (see Panel 3, p130) who are undergoing a gastrointestinal or genitourinary tract procedure at a site where infection is suspected, should receive appropriate antibacterial therapy that includes cover against organisms that cause endocarditis. Antibiotic regimens appropriate for such prophylaxis are shown in Panel 5 (adapted from Gould et al¹¹ and the BNF 54).

Recent research has suggested that dental procedures are less likely to cause endocarditis than previously thought and this remains a matter of controversy.¹¹ The recent AHA guidelines indicate that only an extremely small number of infective endocarditis cases might be prevented by antibiotic prophylaxis for dental procedures, even if such prophylactic therapy were 100 per cent effective.¹³ This would be balanced against the possibility of adverse effects related to antibiotic use, including allergic reactions.¹³ The NICE guidelines have considered this evidence and have suggested that routine prophylaxis during dental procedures is no longer necessary.

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Corrections

Patients undergoing minor surgical procedures, who are taking anticoagulants and have a stable INR between 2–4, do not need alter the dose of their anticoagulant.

In this Special feature, the attempt to emphasise the importance of not stopping oral anticoagulation for such procedures may have led readers to believe a dose adjustment is always necessary (*Hospital Pharmacist* 2008;15:130).