VALVE DISEASE

Anticoagulation in valvar heart disease: new aspects and management during non-cardiac surgery

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The indications for oral anticoagulant treatment have been extended over the last 10 years. The detection of new congenital thrombophilic risk factors, the studies on non-valvar atrial fibrillation, and the increase in valvar heart surgery have all led to a rise in the number of patients being treated. In 1997, 64 000 valve operations were performed across Europe; in two thirds of these operations mechanical prostheses were used, subsequently requiring lifelong oral anticoagulant treatment.^{w1}

New developments in anticoagulation

Several recent developments in the management of anticoagulation with vitamin K antagonists can potentially improve the efficacy and safety of this treatment.

- The introduction of the international normalised ratio (INR) as a measure of the intensity of anticoagulation has provided a reliable parameter for monitoring oral anticoagulant treatment, independent of the responsiveness of the thromboplastin used.^{1 w2 w3} All the expert committees have recommended the use of the INR instead of prothrombin time, although its acceptance has varied from country to country.
- The development of the concept of risk factor adjusted, prosthesis specific intensity of anticoagulation^{2 w4} has influenced the management of patients with mechanical valve prosthesis and valvar heart disease in general, allowing risk stratification and lower anticoagulation intensities in certain lower risk groups of patients.
- The results of prospective, randomised studies evaluating the effect of different intensities of anticoagulation on thromboembolic and haemorrhagic events allow a more targeted approach.^{3 4 w5 w6}
- The development of simple anticoagulation monitors has dramatically improved the quality of anticoagulation control.^{5 6}
- The guidelines developed by the working group on valvar heart disease of the European Society of Cardiology on the management of antithrombotic treatment in heart valve disease,² together with the guidelines of the British Society of Haematology¹ and the American Heart Association/American College of Cardiology (AHA/ACC),⁷ have provided the basis for the following discussion.

Indication for oral anticoagulant treatment

The indications for lifelong anticoagulation are listed in table 1. Anticoagulation is indicated for the first three months after valve replacement with bioprostheses, even when sinus rhythm is present. This also applies to mitral valve repair. Oral anticoagulation is indicated 3–4 weeks before and after cardioversion.

Concept of risk factor adjusted, prosthesis specific intensity of anticoagulation

The concept of risk factor adjusted, prosthesis specific intensity of anticoagulation was first proposed by Butchart^{w4} in regard to mechanical valve prosthesis, and was included in the recommendations by the working group on valvar heart disease.² Within certain limits the degree of reduction in thromboembolic events is higher with increasing intensity of anticoagulation, yet at the expense of an exponential rise in bleeding risk with increasing intensity.

There is only a narrow range of intensity of anticoagulation in which the reduction in thromboembolic events is as pronounced as possible and the bleeding risk is as low as possible. This optimal range of INR or target INR varies from patient to patient, and can be illustrated by comparing two patients at the extreme ends of thromboembolic risk:

- A young man with a valve prosthesis of low thrombogenicity such as the St Jude Medical valve or the Medtronic Hall valve in aortic position, in sinus rhythm, with normal left ventricular function and size, without heart failure and other risk factors, has a thromboembolic risk of about 1% a year with moderate anticoagulation intensity.^{1 3 8}
- A 70 year old patient with a first generation Starr-Edwards prosthesis in the mitral position, with atrial fibrillation, large left atrium, and congestive heart failure, has a thromboembolic risk of about 5% per year.⁸ ^{w4} Thus the intensity of anticoagulation used in this latter patient should be higher than in the former.

Three major groups of risk factors for thromboembolic events and strokes should be taken into account when defining the intensity of oral anticoagulant treatment in valvar heart disease. These risk factors are related to the

Table 1 Absolute indication for lifelong oral anticoagulation

All patients with:
• Mechanical prostheses
• Chronic or intermittent atrial fibrillation in the presence of
– native valve disease
– bioprostheses
– valve repair
– valvuloplasty
• Native valve disease and previous emboli
• Mitral valve stenosis, independent of rhythm, with
– high valve gradients
– thrombus in left atrium
– spontaneous echo contrast in left atrium
– large left atrium > 50 mm
– low cardiac output
– congestive heart failure

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general and cardiac status of the patient, to the prosthesis being used, and to the time interval from the operation.

Patient related risk factors

The incidence of stroke and systemic embolism rises with increasing age, smoking, hypertension, diabetes, hyperlipidaemia, increasing fibrinogen, and acquired or congenital abnormalities of the coagulation system.

The type and severity of the underlying valve disease are important risk factors. Patients with the highest risk for thromboembolism are patients with mitral stenosis, particularly those who develop atrial fibrillation. In these patients the risk of thromboembolism increases to 20% per year. Atrial fibrillation is a very potent risk factor for thromboembolic events, particularly in patients with heart valve disease and after valve replacement. Whereas atrial fibrillation without associated heart disease is associated with a minimal increase in thromboembolic risk to 0.5% per year, the association with other cardiovascular diseases such as hypertension increases the risk of stroke to about 4–6% per year. Atrial fibrillation associated with mitral valve disease leads to an 18 fold increase in embolic risk.

Decreased ventricular function, low cardiac output, and congestive heart failure, as well as left atrial enlargement, are risk factors for thromboembolic events; even loss of atrial contraction in the presence of electrophysiologically normal sinus rhythm carries an increased risk. The degree of mitral stenosis is an important determinant of embolic risk. Patients with severe mitral stenosis are prone to thromboembolism even in sinus rhythm. A history of previous peripheral emboli is associated with a 20% recurrence rate within the first year.

Prosthesis related risk factors

Prosthesis related risk factors are defined by the type and localisation of the prosthesis. While bioprostheses in general have a lower thromboembolic risk than mechanical prostheses, a further differentiation can be made on the basis of localisation and design. Prostheses in the aortic position have a lower thromboembolic risk than in the mitral position.

Furthermore, first generation prostheses like the Starr-Edwards, the older Björk-Shiley standard, and the Omniscience prostheses have a higher thromboembolic risk than the second generation prostheses such as the St Jude Medical or the Medtronic Hall valves.

With anticoagulation, generally most second generation prostheses have a thromboembolic risk of 0.5–2.2% per year in the aortic position and 2–3% per year in the mitral position.^{7–9}

Of further importance is the time interval from the operation. The thromboembolic rate is highest in the first three months following surgery. Twenty per cent of all thromboembolic complications occur during the first month,⁹ when a pronounced hypercoagulable state is present which decreases with time. The endothelialisation process of a newly implanted valve takes several weeks. The valve ring with the sutures are prone to platelet deposition and thrombus formation. This is the basis for the recommendation to anticoagulate patients with bioprostheses during the first three months after surgery.

Intensity of anticoagulation, therapeutic range of INR, target INR

Among the most recent recommendations for anticoagulation in patients with mechanical valves, opinions differ in regard to the desired intensity of anticoagulation.

On the basis of the concept of risk factor and prostheses adjusted oral anticoagulation, the European Society of Cardiology² recommends intense anticoagulation with an INR of 3.0–4.5 in patients with the older first generation prostheses such as the Starr-Edwards (table 2). However, the British Society of Haematology¹ considers a target INR of 3.5 to be sufficient for all mechanical valves, as does the AHA/ACC although the addition of aspirin 80–100 mg is suggested.⁷ Only for high risk patients who cannot tolerate additional aspirin does the AHA/ACC recommend an INR of 3.5–4.5.⁷

Whether an INR > 3.5 is indeed required in high risk patients with first generation mitral valves or other high risk patients has not been investigated prospectively. Such a decision

Table 2 Intensity of anticoagulation

	European Society of Cardiology 1995 ² INR range	British Society of Haematology ¹ target INR	AHA/ACC 1998 ⁷ INR range
Mechanical valve: first generation (eg. Starr-Edwards, Björk-Shiley standard); second generation (St Jude Medical, Medtronic Hall, BS Monostrut)	3.0–4.5	3.5 in all patients with mechanical prostheses	2.5–3.5
Aortic position	2.5–3.0		2.0–3.0*
Mitral position	3.0–3.5		2.5–3.5
Bioprostheses sinus rhythm			
Aortic position	2.5–3.0		Aspirin 80–100 mg
Mitral position	3.0–3.5	2.5	Aspirin 80–100 mg
	No AC after 3 months	No AC after 3 months	No AC after 3 months
Bioprostheses and atrial fibrillation	3.0–4.5	2.5	AVR + RF 2.0–3.0 MVR + RF 2.5–3.5
Rheumatic valvar heart disease and atrial fibrillation	3.0–4.5	2.5	
Patients with recurrent emboli under adequate anticoagulation	3.0–4.5 + 100 mg aspirin		
Non-valvar atrial fibrillation with risk factors	2.0–3.0	2.5	

*With RF 2.5–3.5; AC, anticoagulation; AVR, aortic valve replacement; MVR, mitral valve replacement; RF, risk factors

should be taken on an individual basis, particularly in view of the increased bleeding risk.

Patients with the St Jude Medical valve, the Medtronic Hall valve, and the Monostrut valve need less intense anticoagulation. The European guidelines² recommend a target INR of 3.0–3.5 in the mitral position and 2.5–3.0 in the aortic position. This may need to be adjusted if other underlying risk factors for thromboembolism and stroke are present.

The AREVA study³ compared two different intensities of oral anticoagulation (INR 2.0–3.0 *v* 3.0–4.5) in low risk patients with aortic valve replacement, mostly with the St Jude Medical valve. A mean INR of 2.7 was achieved in the first group and 3.2 in the second group. The moderate anticoagulation group with an INR of 2–3 had a significantly lower haemorrhagic event rate (11.2 per 100 patient years) than the group with an INR of 3–4.5 (20.5 per 100 patient years). This was not associated with an increased rate of thromboembolic events (3.1% *v* 2.4%). Since the median INR for each patient was between 2.5 and 3.5 in 72% of all patients, this study may not support an INR target level of < 2.5 in patients with low risk aortic valve prostheses.

A retrospective analysis revealed that if the INR falls below 2.5 in patients with mechanical heart valves a rather pronounced rise in the thromboembolic rate occurs.¹⁰

The importance of risk factors for determining the intensity of anticoagulation is also addressed in patients with bioprostheses. As long as patients remain in sinus rhythm, they only need anticoagulation for three months and none thereafter. In case of mitral bioprostheses the AHA/ACC guidelines recommend lifelong low dose aspirin.⁷ Whether this is necessary in patients without associated coronary artery disease and only aortic valve bioprosthesis is still undecided.

Yet when atrial fibrillation occurs, patients with bioprostheses also require anticoagulation. In the mitral position an INR of 3.0–4.5 is recommended by the European guidelines²; in the aortic position an INR of 2.5–3.5 is recommended. Generally, in those patients with atrial fibrillation as a risk factor for thromboembolic events, the intensity of anticoagulation should be adjusted according to the underlying pathological condition and the risk associated with it.

If atrial fibrillation occurs in patients with rheumatic mitral valve disease, particularly in severe mitral stenosis, the risk for stroke and other thromboembolic complications is high—at least 5% per year—thus an INR of 3.0–4.5 is recommended. In aortic valve disease the risk is less, thus an INR of 2.5–3.5 can be considered sufficient. In patients with non-valvar atrial fibrillation and risk factors, an even less intense anticoagulation with an INR of 2–3 is sufficient.

In patients with previous emboli despite adequate anticoagulation the risk of recurrent thromboembolism is higher. Therefore for these patients an INR of 3.0–4.5, in addition to aspirin 100 mg daily, is recommended if no other cause for the recurrent emboli can be

identified. Most of these patients with recurrent emboli have, however, inadequate anticoagulation. Furthermore, other risk factors for thromboembolic events—such as hyperlipidaemia, smoking, hypertension, diabetes—are frequently present which also need to be better controlled. Many studies have shown that lipid lowering in patients with coronary artery disease leads to a reduction in stroke rate by 30%.¹¹ Cardiologists have universally accepted that risk factor modification is an established part of the treatment of coronary patients. However, there are no studies in patients with valvar heart disease or mechanical prostheses. This concept can at least be applied to patients with valve disease and associated coronary artery disease. Because of the profound effects of atherosclerotic risk factors on the coagulation system, leading to a hypercoagulable state,^{w7} it seems logical to implement a strict risk factor modification programme for all patients with valvar heart disease or mechanical prostheses in order to reduce the likelihood of stroke and general thromboembolic events in these patients.

Modification of anticoagulant treatment for specific procedures

Patients receiving anticoagulant treatment require adjustments in their anticoagulation when undergoing different types of non-cardiac surgery or diagnostic procedures. This most commonly arises when patients undergo dental procedures, but anticoagulant adjustment is also required for ophthalmic and minor or major surgical procedures, either on an elective or emergency basis. Patients may need to undergo interventional cardiac procedures such as cardiac catheterisation, coronary angioplasty, and the implantation of pacemakers or defibrillators, which also necessitate alteration in anticoagulation. Adjustment is also needed in the event of conditions such as cerebral haemorrhage and certain gastrointestinal disorders such as bleeding ulcer. Randomised studies are not available for most of these situations,^{w8} and there are only a few prospective observational studies^{w9} to guide management. Much of the available information comes from retrospective analyses, and opinions differ over what is felt to be the safest level of anticoagulation for various procedures^{9 w10–12} and on the estimation of the thromboembolic risk that exists.^{w13}

In studies concerning non-cardiac surgery in patients with mechanical valves the incidence of thromboembolic events varied between 0–2% in patients with aortic valve replacement and 11–20% in patients with mitral valve replacement.^{7 8 12 w9 w14}

Thus the risk to be anticipated in case of interruption of anticoagulation during non-cardiac surgery may be appreciably higher than calculated, depending upon the individual risk factors for thromboembolic events, which are related to patients, prostheses, procedures, and pathology (table 3).

Table 3 Risk assessment for non-cardiac surgical procedures

According to risk factors related to:	Low risk	High risk
Patients		
Atrial fibrillation		+
Previous thromboembolism		+
Hypercoagulable congenital or acquired conditions		+
Left ventricular dysfunction		+
Heart failure		+
Prostheses design		
Ball valve		+
Tilting disk	+	
Bileaflet	+	
Prostheses position		
Aortic	+	
Mitral	+	
Procedures		
Dental, ophthalmic	+	
Skin	+	
Gastrointestinal		+
Pathology		
Tumour		+
Infection		+

Different management strategies have been suggested, including:

- discontinuation of oral anticoagulation until normalisation of the INR without heparin replacement;
- discontinuation of oral anticoagulation until normalisation of the INR with heparin replacement as soon as the INR is < 2.0 ;
- lowering the intensity of anticoagulation while oral anticoagulation is maintained;
- continuing a therapeutic level of anticoagulation.

The choice of which regimen should be followed should be based on the individual risk for thromboembolic events, the time interval required to be off or at low anticoagulation levels, and the risk of haemorrhage determined by the procedure.

Thus the concept of risk factor adjusted intensity of anticoagulation can also be used to determine the most appropriate and safest strategy.

Patient related risk factors (table 3) increase thromboembolic risk by a factor of 5–20. Also prosthesis design and position have to be taken into account. Discontinuation of anticoagulation for one week leads to a significant thromboembolic risk in patients with mitral valve replacement varying between 10–20%, whereas the incidence of thromboembolism in patients with aortic valve replacement is 0–2%.^{12 w9 w14}

The prothrombotic state of the surgical procedure itself may increase the risk for thromboembolic events.

All stages of haemostasis can be altered during and after surgery—with increased platelet aggregation and activation, conversion of fibrinogen to fibrin, and depressed fibrinolysis by decreased activators and increased inactivators—thus potentially increasing the thromboembolic risk of the prosthetic valve patient. The level of hypercoagulable changes correlates with the magnitude and duration of surgery, and postoperative changes and complications such as infection. The underlying disease which first led to the surgical procedure—such as a tumour—is a further risk

factor. In a large general surgical population 68% (11/16) of thromboembolic events occurred among patients who were operated on because of a tumour.¹²

The time interval necessary to discontinue anticoagulation before non-cardiac surgical procedures depends on: the half life of the oral anticoagulant used; the actual INR; the desired INR for the specific procedure; and the individual vitamin K pool.¹³

If warfarin is used, the guidelines of the AHA/ACC⁷ and the British Society of Haematology¹ suggest discontinuation for 72 hours before routine non-cardiac surgical procedures. The INR should be closely monitored, because the decrease in INR may vary greatly among different patients.

Dental surgery

Dental surgery is one of the procedures with the lowest risk for thromboembolic complications. A recent literature review¹⁴ covering 2014 dental surgical procedures and 1964 extractions showed that thromboembolic complications occurred in five (0.9%) of 493 patients in whom anticoagulation was discontinued. However, four of the five thromboembolic complications were lethal. In contrast, continuation of anticoagulation in 774 patients was not associated with any thromboembolic events. Bleeding complications occurred in 1.6% patients, and none were fatal. All bleedings occurred with an INR > 4.5 .¹⁴

Thus dental surgical procedures do not require major changes in the intensity of anticoagulation. Continuation of anticoagulation at an INR of 2.0–2.5 is the safest approach for dental surgery; even full mouth extractions have a low risk for bleeding, which can easily be treated with local measures (table 4).^{2 w15 w16} Heparin, as suggested by Peuten^{w17} is not necessary.

Interventional cardiac procedures

For left heart catheterisation by the brachial route, the INR should be < 2.5 , and by the femoral route it should be < 1.8 .^{2 w15}

Surgical procedures

Minor surgical procedures can be performed while the INR is just < 2 and oral anticoagulation can be resumed on the day of surgery. Robinson^{w10} and Bartley^{w11} suggested it was not necessary to discontinue oral anticoagulation before cataract extractions and other oculo-plastic surgical procedures, provided the INR was not above the therapeutic range.

Table 4 Anticoagulation before diagnostic and surgical procedures (European Society of Cardiology²)

	INR
Left heart catheterisation (Sones)	< 2.5
Left heart catheterisation (Judkins)	< 1.8
Tooth extraction	< 2.5
Minor surgical procedure	< 2.0
Major surgical procedure	< 1.5
Replace with heparin when INR:	< 2.5 in high risk patients
Replace with heparin when INR:	< 2.0 in average risk patients

Major surgical procedures require lowering of the INR to < 1.5 . In these cases anticoagulation needs to be maintained with heparin. Heparin should be started when the INR is < 2.5 in high risk patients (for example, in patients with mitral mechanical valves) and < 2.0 in patients with aortic mechanical valves. The activated partial thromboplastin time (aPTT) should be prolonged to 1.5–2.0 of the control value. Heparin should be continued until six hours before surgery and resumed 6–12 hours after surgery, when surgically feasible. It should be continued until INR is > 2 . Oral anticoagulation can be resumed 1–2 days after surgery.^{1 2 7}

Management before emergency surgery

In the event of emergency surgery, oral anticoagulation needs to be neutralised by infusion of prothrombin complex concentrate or fresh frozen plasma, the dose of which needs to be individualised. Additional repeat small doses of vitamin K may be given intravenously or orally.^{15 16} Complete reversal of oral anticoagulants with vitamin K in large doses may lead to prolonged resistance to oral anticoagulants and the possibility of valve thrombosis and thromboemboli.

Low molecular weight heparin

Recently it has been suggested that low molecular weight heparin (LMWH) can be used for the interim maintenance of anticoagulation. Although it is not approved for application in patients with mechanical prosthesis, and no studies are available for non-cardiac procedures, it is already used for this purpose in some countries. Montalescot¹⁷ reported the use of LMWH in the immediate postoperative period after valve surgery. In 102 patients there were two major bleedings and one thromboembolic event, which did not differ from the incidence of bleeding and thromboembolic events in a group of patients previously treated with unfractionated heparin. The study was not randomised and was conducted for only 14 days without further follow up or echocardiographic studies.

If follow up is short after discontinuation of anticoagulation, and echocardiographic studies are not performed routinely, significant thromboembolic events may be missed. Valve thrombosis may develop slowly and insidiously and may not be evident for 1–2 months.

No definite information on the safety and efficacy of LMWH is available at this time to guide its use. Because of the longer half life, requiring only 1–2 doses per day in randomised studies on unstable angina pectoris, LMWH appears to have a promising role in the perioperative management of non-cardiac surgery. Randomised studies, aimed at defining doses in different patient groups, are necessary.

The optimal management of anticoagulation during non-cardiac surgery requires careful risk assessment of patients and procedures. Self testing and self management of anticoagulation

Management of oral anticoagulant treatment can be improved by:

- Following the concept of risk factor adjusted indication for and intensity of oral anticoagulant treatment
- Use of the INR for monitoring the intensity of anticoagulation
- Intensive education of the patient about anticoagulation
- Implementing self testing by suitable patients
- Increasing the frequency of testing

The risks associated with interruption of oral anticoagulant treatment during non-cardiac surgery can be reduced by:

- Performing dental procedures at an INR between 2–2.5
- Using local measures to treat bleeding in the dental surgery
- Replacing oral anticoagulant treatment with heparin before major surgery, when INR is < 2.5 in high risk patients with mechanical mitral valves, and < 2.0 in patients with aortic valves, up to six hours before surgery
- Discontinuing warfarin 72 hours before surgery, but observing factors influencing the time interval required for reduction in INR
- Resuming heparin 6–12 hours postsurgery and maintaining until INR > 2.5

by the patient can facilitate management and reduce risks.

Outlook for better anticoagulation control

Physicians and patients should become more informed about anticoagulation control. Patients need verbal and written information about the purpose of their anticoagulation treatment and its effects, the desired INR range and target INR, side effects, drug interference, diet, and signs and symptoms of overdose (bleeding) and underdosing (valve thrombosis and thromboembolism), as well as other complications.

Self monitoring of anticoagulation by patients has improved their anticoagulation control⁵ and thus their quality of life. Modification of atherosclerotic risk factors is important for all patients with diseased native and prosthetic heart valves to reduce thromboembolic and stroke risk.

Future research should be directed towards evaluation of alternatives to conventional anti-

coagulation in non-cardiac surgery, such as LMWH.

Methods for improved risk assessment and risk stratification in different patient groups should be developed, including family history and laboratory studies for congenital or acquired risk factors for thromboembolic events.

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