Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends

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Over 4 million people worldwide have received a prosthetic heart valve, and an estimated 300 000 valves are being implanted every year. Prosthetic heart valves improve quality of life and survival of patients with severe valvular heart disease, but the need for antithrombotic therapy to prevent thrombotic complications in valve recipients poses challenges for clinicians and patients. Here, we review antithrombotic therapies for patients with prosthetic heart valves and management of thromboembolic complications. Advances in antithrombotic therapy and valve technologies are likely to improve the management of patients with prosthetic heart valves in developed countries, but the most important unmet need and potential for benefit from these new therapies is in developing countries where a massive and rapidly increasing burden of valvular heart disease exists.

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Introduction

Valvular heart disease affects more than 100 million people worldwide and is a growing problem because of the high incidence of rheumatic heart disease in developing countries and the increasing burden of degenerative valve disease in the ageing population.[1,2] About 4 million prosthetic heart valve replacements have been done over the past 50 years,[3] and this remains the only definitive treatment for most patients with severe valvular heart disease. 300 000 prosthetic heart valve replacements are done every year worldwide, 100 000 in North America;[4] the total number of replacements is projected to be 850 000 per year by 2050.[5]

Two major types of prosthetic heart valves exist: mechanical and bioprosthetic. Mechanical prosthetic heart valves are more durable but also more thrombogenic than bioprosthetic valves. The advantages of bioprosthetic over mechanical valves are that they provide more physiological haemodynamics and do not need long-term anticoagulation. Recent developments in the design of bioprosthetic heart valves have improved their durability and resistance to structural deterioration, and these valves are now increasingly being used in younger patients than in the past.[6,7]

In this review, we discuss different types of prosthetic heart valves and assess the antithrombotic management of patients with prosthetic heart valves and the management of valve-related thrombotic complications. We also review new developments and emerging technologies, including genotype-based warfarin dosing, self-monitoring of oral anticoagulant therapy, novel antithrombotic drugs, and the potential benefit of transcatheter valve replacement.

Prosthetic heart valves

Mechanical valves

Three main types of mechanical valves exist: caged-ball, single leaflet or tilting-disk, and bileaflet valves. Mechanical valves have three key components: occluder (closure mechanism), housing, and sewing ring.[8] All have some degree of regurgitant flow (washing jet) that prevents thrombus formation on the surfaces of the valve.

The first prosthetic heart valve was the Starr-Edwards caged-ball valve introduced in 1960.[9] The original version of the Starr-Edwards valve had a silicone rubber (silastic) ball or poppet that freely moved within the confines of a three-strut alloy cage (figure 1A). Subsequent models had a metal ball and a four-strut cage. The free-ball design theoretically prevents thrombus that forms on the sewing ring from extending onto the occluder.[10] However, the ball generates a wake of stagnant blood flow that might contribute to the high risk of thromboembolism reported with caged-ball valves.[11] The Starr-Edwards valve was the gold standard against which new mechanical valves were compared for more than 20 years,[12] and is still widely used in many developing countries because of its low cost.

Single-leaflet or tilting-disk valves consist of a major and a minor orifice. Because the tilting disk enables central flow of blood, the risk of thromboembolism is lower than that with caged-ball valves, which have circumferential blood flow. Tilting-disk valves seem to be associated with a slightly higher risk of thromboembolism

Search strategy and selection criteria

We searched Medline between 1966 and March, 2009, and the Cochrane electronic database (4th quarter 2008) for English-language articles that addressed the long-term management of patients with prosthetic heart valves, with the terms "heart valve prosthesis", "heart valve prosthesis implantation", "antithrombotic", "antiplatelet", "anticoagulation", "aspirin", "vitamin K antagonist", "warfarin", "acenocoumarol", "phenprocoumon", "thrombosis", "randomised controlled trial", "randomised", "controlled trial", and "meta-analysis". We reviewed reference lists of relevant papers identified by our electronic search. We focused on randomised controlled trials and meta-analyses of randomised controlled trials because they provide the least biased and most robust evidence for treatment. When randomised controlled trials were not available, we included observational studies and took into consideration expert opinion.

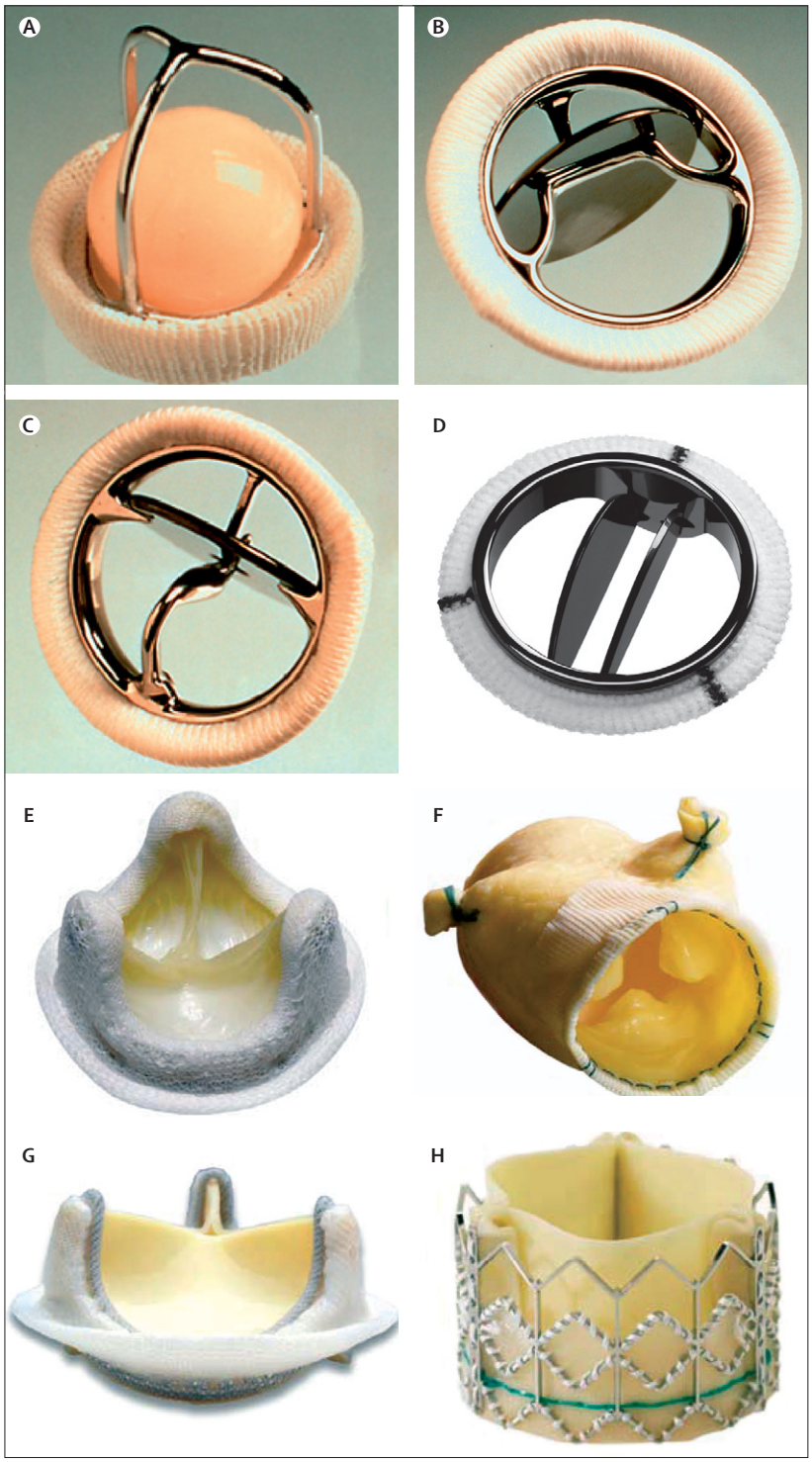

Figure 1: **Different models of prosthetic heart valves**
(A) Starr-Edwards caged-ball valve (courtesy of Edwards Lifesciences LLC, Irvine, CA, USA). (B) Bjork-Shiley tilting-disk valve (courtesy of Sorin Group of Canada Inc, Canada). (C) Medtronic Hall tilting-disk valve (with permission from Medtronic Inc, Canada). (D) St Jude Medical Regent bileaflet valve (courtesy of St Jude Medical Canada). (E) Medtronic HK II ultra porcine valve (with permission from Medtronic Inc). (F) Medtronic Freestyle porcine valve (with permission from Medtronic Inc). (G) Carpentier-Edwards Perimount bovine pericardial valve. (H) Edwards SAPIEN transcatheter pericardial aortic valve (courtesy of Edwards Lifesciences LLC, Irvine, CA, USA).

than bileaflet mechanical valves, possibly because they have a region of stagnant blood flow adjacent to the aorta, immediately downstream from the minor orifice, and because the regurgitant washing-jet volume is lower than that of bileaflet valves.[8]

The first successful tilting-disk valve was the Bjork-Shiley valve introduced in 1969,[13] which consists of a single leaflet of pyrolytic carbon held in place by large inflow and small outflow alloy struts encircled by a teflon sewing ring[8] (figure 1B). The Bjork-Shiley convexo-concave valve was withdrawn in 1986 because of several cases of strut fracture and embolisation of the disk.[8] The Medtronic-Hall tilting-disk valve was one of the most commonly implanted tilting-disk valves (figure 1C).

The St Jude Medical valve introduced in 1977[14] was the first bileaflet valve and is the single most commonly implanted mechanical valve to date. It is made of pyrolytic carbon coated with graphite and consists of two leaflets hinged on a ring (figure 1D). Encircling this structure is a sewing ring. Bileaflet valves provide symmetric, non-turbulent, central blood flow.[8] Numerous bileaflet valves modelled on the St Jude valve are commercially available. Bileaflet valves are currently the most commonly used mechanical valve.

Bioprosthetic valves

Most bioprosthetic valves are of porcine origin (an intact heart valve from a pig is sewn into the valve structure) or constructed from a sheet of bovine pericardium that is cut to form valve leaflets and sewn into the valve structure. Valves are preserved in glutaraldehyde and mounted on a frame or stent made of metal or plastic covered with fabric that acts as the sewing ring.[15] Bioprosthetic valves mimic native heart valves more closely than mechanical valves because they have unobstructed central flow, although both types of valves provide excellent haemodynamics. Bioprosthetic heart valves are less thrombogenic than mechanical valves and do not require long-term anticoagulant therapy. Porcine and pericardial (bovine) valves have similar thrombogenicity.

Porcine valves are the most widely used bioprosthetic valves.[10] The first commercial porcine valve was the Hancock valve introduced in 1970. An example of a porcine bioprosthetic valve is shown in figure 1E. Bovine pericardial valves have several theoretical advantages over porcine valves. Valve leaflets are larger, which accommodates shrinkage during the life of the valve; leaflet opening is more complete and symmetric, which improves valve haemodynamics; and the collagen content is higher, which improves valve durability. The Carpentier-Edwards Perimount valve (figure 1G) is the only pericardial valve widely available in North America. Pericardial valves seem to be at least as durable as contemporary porcine valves,[16,17] but it is unclear whether theoretical advantages of pericardial valves over porcine valves translate into improved outcomes for patients. Table 1 shows rates of valve deterioration according to

age of the recipient and to the position of the valve (ie, in the aortic or mitral position).[18]

Stentless bioprosthetic valves have no stent or frame as part of their structure. The aim of these valves is to provide a larger effective orifice area and lower postoperative transvalvular gradients than stented valves, thereby facilitating left ventricular mass regression in patients with severe aortic stenosis. Several randomised trials have compared stented with stentless valves, and a meta-analysis of these studies found that left ventricular mass regression was significantly greater at 6 months in patients receiving stentless valves than in those receiving stented valves.[19] By 12 months, however, left ventricular mass regression was equivalent in the two groups. Figure 1F shows a Medtronic freestyle valve consisting of a porcine valve housed within its native aorta. Other freestyle valves include the Sorin Freedom, Edwards Prima Plus, and St Jude Toronto.

Transcatheter valves

Two transcatheter aortic valves have been implanted in many patients in clinical trials: the Cribier-Edwards (now Edwards SAPIEN) (figure 1H) and the CoreValve System aortic valve prosthesis.[20] The original Cribier-Edwards valve consisted of equine tissue, but the SAPIEN consists of bovine pericardium and a steel stent, and the CoreValve of porcine pericardium and a nitinol stent. The effect of crimping to enable transcatheter placement and subsequent re-expansion of the valve on their long-term durability and thrombogenicity is unknown. Valve prototypes of different materials, some of which can be repositioned or retrieved, are in early stages of clinical assessment.[21]

Antithrombotic therapy

Figure 2 shows a suggested algorithm adapted from the 2006 American College of Cardiology (ACC) and American Heart Association (AHA),[22] and the 2008 American College of Chest Physicians (ACCP) guidelines[23] for the antithrombotic management of patients with prosthetic heart valves. These guidelines are mostly based on observational data because only a few randomised studies have been done.

Factors that contribute to the thrombogenicity of prosthetic heart valves include: altered blood flow and haemostatic activation caused by vessel-wall disruption during surgery or exposure of artificial surfaces (sutures, sewing ring, occluder, and valve housing) to the circulating blood.[24] Because almost all prosthetic valves are stented, they have a smaller effective orifice area than native valves, which results in a transvalvular flow gradient. Stagnant flow can be caused by the valve occluder or growth of endocardial tissue (pannus) into the leaflets or valve mechanism. Endothelialisation of the valve stent occurs over about 3 months after valve implantation, after which the risk of thrombosis decreases.[10,25]

	10 years	15 years
Aortic valve		
21–40	20%	70%
41–50	12%	46%
51–60	18%	42%
61–70	6%	33%
>70	2%	5%
Mitral valve		
21–40	36%	90%
41–50	37%	61% (at 12 years)
51–60	31%	47% (at 12 years)
61–70	31%	67%
>70	18%	34%

Data are based on 2943 patients (17 471 patient-years). *Data are from Jamieson and colleagues.[18] Valve failure=intrinsic abnormality of the valve, not due to endocarditis or thrombosis, leading to an increase in New York Heart Association (NYHA) class symptoms or reoperation.

Table 1: **Bioprosthetic valve failure at 10 and 15 years according to age (years) of patient and valve position at implantation***

Short-term parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparin is often used until therapeutic concentrations of an oral vitamin K antagonist are reached. Aspirin and vitamin K antagonists, alone or in combination, are used for long-term management of patients with prosthetic heart valves. Vitamin K antagonists are the only oral anticoagulants available for valve-implanted patients. Warfarin has a mean half-life of about 40 h and is the most widely used vitamin K antagonist in North America. Other antagonists commonly used in Europe include acenocoumarol (half-life 8–11 h), fluindione (half-life 30 h), and phenprocoumon (half-life 3–5 days).

Vitamin K antagonists are difficult to use in clinical practice because they have a slow onset and offset, narrow therapeutic window, and variable dose–response in individuals, and interact with several foods and drugs.[24] These antagonists need to be closely monitored for their anticoagulant effect, which is inconvenient for patients and costly for health-care systems. The international normalised ratio is a standardised method of reporting the intensity of anticoagulant therapy with vitamin K antagonists.[26,27]

Antithrombotic treatment for mechanical valves

Estimates of the risk of thromboembolism after mechanical prosthetic heart valve replacement in patients not treated with anticoagulants mainly come from small case-series of patients with a contraindication to vitamin K antagonists. A 1994 systematic review of these studies[28] showing 1225 patient-years of follow-up reported rates of valve thrombosis of 1·8 (95% CI 0·9–3·0) per 100 patient-years, major embolism of 4·0 (2·9–5·2) per 100 patient-years, and total embolism of 8·6 (7·0–10·4) per 100 patient-years. These data are mainly derived from

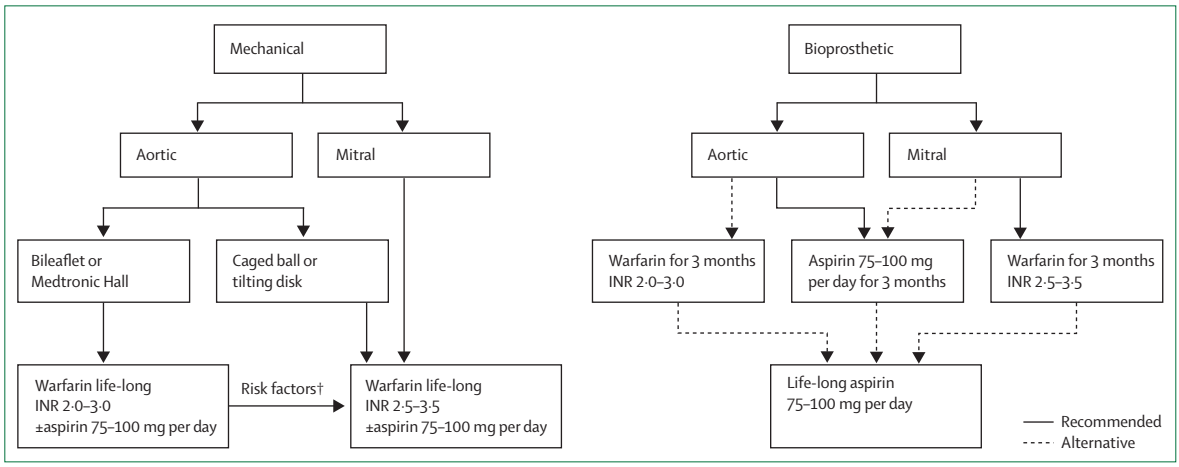

Figure 2: **Algorithm for antithrombotic therapy for prosthetic heart valves***
ACC=American College of Cardiology. ACCP=American College of Chest Physicians. AHA=American Heart Association. INR=international normalised ratio. *Based on the 2006 ACC/AHA guidelines[22] and the 2008 ACCP guidelines.[23] †Risk factors: atrial fibrillation, previous thromboembolism, left ventricular ejection fraction less than 35%, and hypercoagulable condition.

patients with caged-ball or tilting-disk valves in the aortic position; thromboembolism rates are 1·5 to 2 times higher for mechanical valves in the mitral position.[28] No reliable data exist for the risk of thromboembolism in patients with bileaflet mechanical valves who do not receive antithrombotic therapy.

No randomised trials have compared vitamin K antagonists alone with vitamin K antagonists with initial heparin (either unfractionated heparin or low-molecular-weight heparin) immediately after valve surgery. A 2006 systematic review of observational and randomised trials comparing outcomes in patients with mechanical valves treated immediately after surgery with different intensities of vitamin K antagonists reported an absolute rate of thromboembolism of 0·9% and bleeding of 3·3% during the first 30 days.[29] Patients—who also received a combination therapy with unfractionated heparin or low-molecular-weight heparin started 6–24 h after surgery and continued until a therapeutic international normalised ratio was achieved—had thromboembolism rates of 0·6–1·1% and bleeding rates of 4·8–7·2% during the first 30 days. An observational study has shown a reduction in the risk of valve thrombosis when low-molecular-weight heparin was added to oral anticoagulation until the international normalised ratio reached the target therapeutic range.[30] No randomised controlled trials have compared initial bridging therapy with unfractionated heparin versus low-molecular-weight heparin, but observational studies found no difference between them for either thromboembolism or bleeding.[31,32]

On the basis of the scarce data available, it is reasonable to start treatment with vitamin K antagonists after mechanical heart valve replacement as soon as haemostasis is secure, usually within 6–24 h after surgery. No high-quality data exist to guide decisions for the use of unfractionated or low-molecular-weight heparin immediately after mechanical heart valve replacement until the international normalised ratio is therapeutic on vitamin K antagonist therapy. The ACC/AHA and ACCP guidelines suggest that it is reasonable to start bridging therapy immediately after surgery if bleeding is not an issue.[22,23]

The rationale for long-term anticoagulation in patients with mechanical heart valves is based on their inherent thrombogenicity and the high rates of thromboembolism in the absence of anticoagulation. One randomised study[33] showed that antiplatelet therapy alone compared with oral anticoagulation was associated with a three-fold increase in thromboembolic events during 18–24 months of follow-up, although antiplatelet drugs caused less bleeding.

The optimum target international normalised ratio range for mechanical valves was analysed in a retrospective, observational study by Cannegieter and colleagues[34] involving patients with different types of mechanical prosthetic heart valves in the aortic, mitral, or both, position who received varying intensities of vitamin K antagonist therapy. The lowest rates of a combination of bleeding and thromboembolic events occurred when the international normalised ratio was between 2·5 and 4·9 (absolute rate of 2 events per 100 patient-years).[34] Rates of thromboembolism were higher for valves in the mitral compared with those in the aortic position (0·9 *vs* 0·5 per 100 patient-years). Caged-ball valves seemed to be the most thrombogenic (2·5 thromboembolic events per 100 patient-years), followed by tilting-disk valves (0·7 per 100 patient-years) and bileaflet valves (0·5 per 100 patient-years).

Two subsequent randomised studies[35,36] assessed whether targeting the low end of the international normalised ratio range would give adequate protection from thromboembolic events while reducing the risk of

bleeding. Results showed that mechanical bileaflet aortic valves can be anticoagulated to an international normalised ratio of 2·5 (range 2·0–3·0) instead of a higher international normalised ratio without an increased risk of thromboembolism and with a reduction in bleeding.[35,36] The number of patients with mechanical mitral valves in these randomised studies was small and, because mitral valves have a higher rate of thromboembolism than that of aortic valves, a target international normalised ratio of 3·0 (range 2·5–3·5) is recommended for mechanical mitral valves. For patients with caged-ball or tilting-disk valves in the aortic position, the same target ratio is recommended because these valves are more thrombogenic than bileaflet valves.

A Cochrane systematic review of 11 randomised controlled trials involving 2428 patients found that the addition of aspirin to oral anticoagulation reduced mortality and thromboembolic events compared with oral anticoagulation alone at the cost of increased bleeding.[37–39] The addition of low-dose aspirin (≤100 mg per day) to warfarin did not increase bleeding, but increased bleeding with this combination of drugs has been shown in other clinical settings.[40] The ACC/AHA guidelines[22] recommend the use of aspirin and warfarin for all patients with mechanical valves, whereas the ACCP guidelines[23] and the European Society of Cardiology (ESC) guidelines[41] recommend the addition of aspirin only for those who have additional thromboembolic risk factors or other indications for antiplatelet therapy, such as coronary or peripheral arterial disease.

No reliable evidence exists concerning the appropriate antithrombotic management of patients with mechanical heart valves who have other thromboembolic risk factors (eg, decreased left ventricular function [ejection fraction <35%], atrial fibrillation, previous thromboembolism, and hypercoagulable conditions[42,43]). A reasonable target international normalised ratio is 3·0 (range 2·5–3·5) in patients deemed to be at increased risk or to treat with low-dose aspirin therapy (75–100 mg per day), in addition to a vitamin K antagonist, but these recommendations are based only on expert opinion.

Antithrombotic treatment for bioprosthetic valves

The rate of thromboembolic events for patients with bioprosthetic valves seems to be highest during the first 3 months after surgery.[44] The largest reported groups of patients with bioprosthetic valves who were given no antithrombotic therapy during both the initial 3 months and long term consisted of only 156[45] and 136[46] patients with follow-up for 1 and 7 years, respectively. The rate of thromboembolism at 1 year was 1·3% (aortic valves only) and at 7 years was 1·5% and 1·7% per patient-year for aortic and mitral valves, respectively.

According to two small observational studies,[47,48] patients with bioprosthetic heart valves who received anticoagulation therapy for 3 months after surgery followed by no antithrombotic therapy had a thromboembolism rate of 1·5–5·2% per patient-year after 3–7 years of follow-up. 5·2% is likely to be an overestimation and has not been reproduced in other studies or case series.

Because of the perceived increase in thromboembolic risk during the first 3 months after surgery in patients with bioprosthetic heart valves, most studies have treated patients with a vitamin K antagonist for the first 3 months. The only published randomised study[49] that compared varying intensities of vitamin K antagonist therapy for the management of patients with bioprosthetic valves involved 108 patients (most of whom received an aortic bioprosthetic valve) and found no difference in major embolic events between vitamin K antagonist therapy that targeted international normalised ratio of 2·0–2·3 compared with that of 2·5–4·0 during the first 3 months after surgery (~2% in each group). However, the lower target group had 37% less bleeding than the higher target group. On the basis of this study, it seems reasonable to target an international normalised ratio of 2·5 (range 2·0–3·0) for patients with bioprosthetic valves in the aortic position. The target for patients with a bioprosthetic valve in the mitral position is 3·0 (range 2·5–3·5). Therapy with vitamin K antagonists is usually started immediately after surgery and continued for 3 months.

Two small randomised trials[50,51] and many small observational studies[52–57] have assessed whether treatment with vitamin K antagonists could be replaced with antiplatelet treatment as initial therapy for patients with a bioprosthetic aortic valve. None of the studies found a difference in thromboembolic or bleeding events in patients treated with vitamin K antagonists compared with those treated with aspirin, but studies were small and underpowered, and observational studies are subject to confounding factors.

Low-dose aspirin is regarded by the ACC/AHA[22] and the ACCP,[23] as an alternative to warfarin for the first 3 months after bioprosthetic aortic valve replacement. The ESC[41] recommends initial treatment with vitamin K antagonists over antiplatelet therapy. Two ongoing, prospective international, multicentre registries—ACTION[58] and ANSWER[59]—are following patients after bioprosthetic valve replacement to assess whether there is a difference in clinical outcomes for different postoperative antithrombotic regimens. On the basis of available evidence, low-dose aspirin is a reasonable alternative to warfarin during the first 3 months after surgery in patients with bioprosthetic aortic valves.

Because the risk of thromboembolism is low after 3 months,[44] risk of bleeding is likely to outweigh any benefit if vitamin K antagonist therapy is continued beyond 3 months. Irrespective of the choice of initial antithrombotic therapy, patients should be treated with life-long, low-dose aspirin (≤100 mg per day) after the first 3 months. An observational study of 215 patients[47] showed that those who received aspirin therapy had 75% fewer thromboembolic events than those receiving

no antithrombotic therapy at 36 months.

Antithrombotic treatment for valvuloplasty bands and rings

Annuloplasty bands and rings are used to repair mitral and tricuspid valves. They are sewn to the annulus to plicate it and prevent further dilatation. They consist of rubber covered in polytetrafluoroethylene similar to the stents of prosthetic valves.[15]

A systematic review[60] identified 12 small observational studies that reported outcomes in patients receiving antithrombotic therapy after valve repair. Most patients in these studies were treated with vitamin K antagonists for the first 2–3 months, and had low rates of thromboembolic events (0·4–3·0% per patient-year) and bleeding (0·3–0·8% per patient-year). A third of patients developed atrial fibrillation during the first 3 months. In the absence of high-quality data, use of the same antithrombotic treatment in patients with valvuloplasty bands and rings as in patients receiving bioprosthetic valves is recommended. The ACC/AHA and ACCP guidelines do not provide recommendations for the antithrombotic management of valvuloplasty rings and bands. The ESC guidelines[41] recommend the use of vitamin K antagonists for 3 months (target international normalised ratio 2·5, range 2·0–3·0), and the European Association for Cardiothoracic Surgery (EACTS) recommends either vitamin K antagonists for 3 months or antiplatelet therapy.[61]

Anticoagulation for dental procedures and surgery

Patients with bileaflet mechanical valves in the aortic position are at low risk (9% per patient-year[28]) of thromboembolic complications during temporary discontinuation of anticoagulation for procedures. Those with mechanical valves in the mitral position, or tilting-disk and caged-ball valves in any position, are at high risk (~1·5–2 times the thromboembolic rates of the low-risk group, or 13–18% per patient-year[28]) for thromboembolic events. Moderate-risk patients include those with mechanical aortic valves and at least one additional risk factor (eg, atrial fibrillation of previous thromboembolic event) for thromboembolism (9–13% per patient-year).[62] However, no randomised studies have been done to compare bridging anticoagulation to no anticoagulation, and thus management recommendations are based on observational studies or expert opinion. In patients with low-risk mechanical heart valves who require discontinuation of warfarin for a procedure, treatment should be interrupted 4–5 days before surgery and restarted within 24 h after surgery, if haemostasis is secure. 14 prospective cohort studies involving 1367 patients with a mechanical heart valve have shown that those in the moderate-risk and high-risk groups bridged with unfractionated or low-molecular-weight heparin, started 2–3 days before the procedure and recommenced the day after surgery in combination with vitamin K antagonists, have low rates of thromboembolism (0·8%) and major bleeding (0·1%).[62]

Management of thrombotic complications

The reported rate of prosthetic valve thrombosis from a large randomised trial and two large series done in developed countries with modern valves and routine oral therapy with vitamin K antagonists is 0·03–0·13% per patient-year (10–15-year follow-up).[63–65] The risk is highest during the first year after valve implantation and in patients with a mechanical tricuspid valve replacement.[66,67] The long-term rate of prosthetic valve thrombosis is similar in patients with bioprosthetic valves (with or without antiplatelet therapy) and in properly anticoagulated patients with mechanical valves, but most cases occur in patients with mechanical valves who are inadequately anticoagulated or have additional risk factors such as atrial fibrillation.[63]

Prosthetic valve thrombosis can be either obstructive or non-obstructive. Patients with obstructive thrombosis present with dyspnoea or acute pulmonary oedema, arrhythmia, cardiogenic shock, or systemic embolism. Heart sounds might be muffled or absent, especially in patients with mechanical valves, and a regurgitant murmur might be present. Patients with non-obstructive thrombosis are more likely to present with embolic events but almost 50% are asymptomatic. The clinical history can be helpful to distinguish prosthetic valve thrombosis from pannus (the two often occur concurrently) and from vegetation. Valve thrombosis is more likely in patients with a history of subtherapeutic anticoagulation, thromboembolic risk factors (prosthetic valve in the mitral or tricuspid position, atrial fibrillation, or hypercoagulable states), or soon after surgery. Fever can occur with both prosthetic valve thrombosis and endocarditis, and thus blood cultures should be done in febrile patients with suspected thrombosis to rule out endocarditis.[68] The diagnosis of prosthetic valve thrombosis can be confirmed 85% of the time by the combination of transthoracic echocardiography and fluoroscopy, but transoesophageal echocardiography remains the gold standard test.[69] Infective and other non-thrombotic causes (eg, pannus, tumour) should be excluded before making a diagnosis.[68]

Current recommendations for the management of prosthetic valve thrombosis, based on observational data from case series and cohort studies, favour the use of thrombolytic therapy as first-line treatment.[68,70] The reported success rate for thrombolytic therapy is 71–88%, with complication rates (thromboembolism or bleeding) of 15–25% and mortality rates of 3–12%.[71–74] Thrombolytic therapy is effective irrespective of valve type and position,[72,73,75] but success rates seem to be higher in patients with New York Heart Association (NYHA) class I or II symptoms than in those with more severe symptoms.[74,75] Bleeding and thromboembolic events after thrombolytic therapy are common in patients with NYHA

class III or IV symptoms and in those with haemodynamic instability, previous history of stroke, a thrombus area of 0·8 cm² or more, and rapid infusion of thrombolysis.[72,74] Observational data suggest that streptokinase is more effective than urokinase or tissue plasminogen activator.[74]

Patients with non-obstructive prosthetic valve thrombosis are frequently stable clinically but are at high risk of thromboembolic complications. Success of thrombolytic therapy depends on the size of the thrombus; in small case series, the reported success rate is 82% with thrombi smaller than 5 mm, with thromboembolism and death rates of 4% and 8%, respectively. For thrombi larger than 5 mm, the success rate drops to 61%, with thromboembolic and death rates of 23% and 38%, respectively.[68] Surgical mortality for prosthetic valve thrombosis ranges from 12% to 46%.[70,75,76] Figure 3 shows a proposed algorithm for the management of patients with prosthetic valve thrombosis.

Prosthetic valves carry a long-term thromboembolic risk of 0·5–1·7% per patient-year despite appropriate antithrombotic therapy. No good evidence exists on how to manage patients with prosthetic heart valves who experience cerebral embolisation during anticoagulant therapy. Our practice is to use imaging to confirm the absence or presence of intracerebral haemorrhage. In the absence of intracerebral hemorrhage, we continue treatment with vitamin K antagonists. In the presence of haemorrhage, we reverse anticoagulation with a combination of low-dose vitamin K and fresh frozen plasma. We generally restart treatment after 7–10 days if there is no recurrent bleeding. This approach is associated with a 5% rate of thromboembolism and 1% risk of rebleeding.[77] All patients with a prosthetic heart valve who have thromboembolic events must be examined with echocardiographic scans to rule out valve thrombosis or endocarditis.

Expert consensus guidelines[22] recommend that patients with a bioprosthetic valve who have a thromboembolic event while not receiving any antithrombotic therapy should commence therapy with vitamin K antagonists or low-dose aspirin (75–100 mg per day) if they are within 3 months of valve implantation, or low-dose aspirin if they are more than 3 months after implantation. A vitamin K antagonist can be added in a patient already receiving low-dose aspirin. In patients with a prosthetic heart valve already receiving oral anticoagulation, adequacy of therapy should be assessed at the time of the thromboembolic event. In patients not adequately treated at the time of the event, efforts should focus on improving anticoagulant control. Aspirin can be added to vitamin K antagonist therapy in a patient adequately treated with oral anticoagulation at the time of the event or, if the patient is already taking aspirin, the target international normalised ratio can be increased by 0·5.

Future developments

Vitamin K antagonist therapy is highly effective in reducing thromboembolic events in patients with prosthetic heart valves but increases the risk of bleeding even when the treatment is carefully monitored. The rate of bleeding is greatest during the initial weeks or months of starting warfarin therapy.[78] About 40% of a patient's variability to warfarin dose can be explained by cytochrome P450 2C9 and vitamin K epoxide reductase complex 1 genotypes.[79] Tables 2 and 3 show the effect of cytochrome P450 2C9 and vitamin K epoxide reductase complex 1 genotypes on warfarin metabolism and dose.

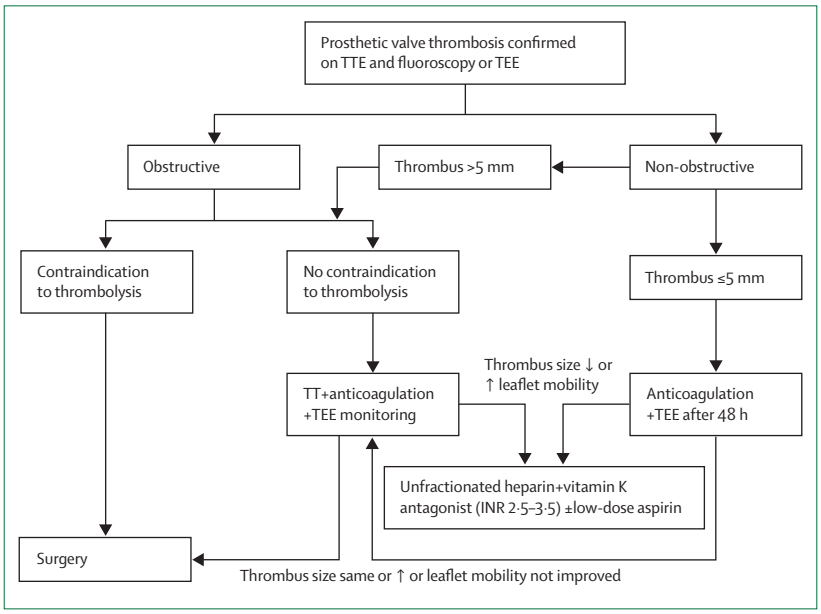

Figure 3: **Algorithm for the management of patients with prosthetic valve thrombosis***
SHVD=Society of Heart Valve Disease. INR=international normalised ratio. TEE=transoesophageal echography. TT=thrombolytic therapy. TTE= transthoracic echography. *Based on the 2005 SHVD guidelines.[68] Contraindications to thrombolysis: standard (active bleeding, history of haemorrhagic stroke, recent cranial trauma or neoplasm, or uncontrolled hypertension) and specific (left-sided thrombus ≥10 mm or 0·8 cm², large left atrial [non-appendage] thrombus, recent ischaemic stroke [6 weeks], or recent major surgery [<4 days]).

	Metabolism
*1/*1	Extensive, rapid, ultra-metaboliser
*1/*2	Intermediate
*1/*3, *2/*3, *2/*2	Poor, slow
*3/*3	Extremely slow

†Adapted from McClain and colleagues.[79]

Table 2: **Cytochrome P450 2C9 variants and their association with warfarin metabolism†**

	Enzyme production
AA	High (lower warfarin dose needed)
AB	Medium
BB	Low (higher warfarin dose needed)

*Adapted from McClain and colleagues.[79]

Table 3: **Vitamin K epoxide reductase complex 1 variants and their association with warfarin enzyme production***

	Developed countries (44 918 patient-years follow-up)	Developing countries (12 642 patient-years follow-up)
Thromboembolism	1·8% per patient-year	2·6% per patient-year
Prosthetic valve thrombosis	0·1% per patient-year	1·3% per patient-year
Bleeding	1·0% per patient-year	1·9% per patient-year

Table 4: **Rates of thromboembolic and bleeding events for patients with similar mechanical heart valves in developed and developing countries**[114-130]

The risk of major bleeding could be increased by two-fold to four-fold in patients with poor-metabolising cytochrome P450 2C9 genotypes.[78–82]

Genotype-based warfarin therapy has shown potential to reduce complications. A report from the American Enterprise Institute-Brookings Joint Center, with input from the US Food and Drug Administration, concluded that routine genotyping could prevent 85 000 serious bleeding events and 17 000 strokes every year in the USA. If these targets were achieved, corresponding health-care savings would be between US$100 million and $2 billion per year.[83] Small, randomised trials comparing standard with genotype-based dosing[84–86] have shown that genotype predicts the initial warfarin dose but with no evidence of improved clinical outcomes. The potential benefit of genotype-based therapy is substantial, but much research is needed before routine genotyping can be recommended to guide therapy.

Patients who self-monitor therapy with vitamin K antagonists at home rather than in a laboratory are more often in the therapeutic range and have a lower incidence of complications and hospital admissions than those who do not.[87–90] Meta-analyses of randomised trials have recently found that patient self-monitoring was associated with a 33% reduction of risk of death, a 55% reduction of risk of thromboembolism, and a slight decrease in major haemorrhage.[91,92] Self-monitoring was also associated with improved quality of life and satisfaction. The main obstacle to widespread use of patient self-monitoring is cost. In the UK National Health Service, the estimated cost of patient self-monitoring is £122 000 per quality-adjusted life year (QALY) over 5 years and £63 000 over 10 years.[91] This is not cost-effective considering the commonly accepted threshold of £30 000 per QALY. Costs are related to the portable international-normalised-ratio-monitoring device, test strips, and patient education programmes. The US Medicare programme has recently decided to cover the cost of patient self-monitoring.[93] Patients who can lead an independent and self-supporting life are candidates for its use.[94]

The oral direct thrombin inhibitor—dabigatran etexilate—and two oral direct factor Xa inhibitors—rivaroxaban and apixaban—are in advanced stages of clinical development and are expected to replace oral vitamin K antagonists for many indications.[95] Dabigatran etexilate and rivaroxaban have been approved in Europe and Canada for prevention of venous thromboembolism, and trials of these agents and of apixaban in patients with atrial fibrillation are almost completed.[96] The main advantages of these drugs compared with those of vitamin K antagonists include their predictable pharmacokinetics and pharmacodynamics, and reduced interactions with foods and drugs, which allows them to be administered in fixed doses without monitoring coagulation. None of these new agents have been studied in patients with prosthetic heart valves.

Another device—ThromboCheck (Cardosignal GmbH, Hamburg, Germany)—that enables patient self-monitoring of mechanical heart valve function has been tested in observational studies.[97] This device records the individual frequency spectrum of sounds created by a patient's valve. With each subsequent check, the recorded frequency is compared with the original one, and results are automatically sent to a medical centre. Changes in the measured sound frequency of the valve might indicate early onset of valve thrombosis, paravalvular leak, pannus formation, or endocarditis. An observational study[97] of more than 500 patients with a mechanical heart valve who used the device has recently shown that an alarm signal had positive predictive values and specificities of 97% and 100%, respectively, for valvular pathology subsequently diagnosed by echocardiography and fluoroscopy.

In 2000, Bonhoeffer and colleagues[98] did the first successful human transcatheter valve implantation in the pulmonic valve position, which was followed by Cribier and colleagues[99] in 2002 who implanted a valve in the aortic position. Inoperable patients with severe, symptomatic aortic stenosis can be given valves (Edwards SAPIEN and CoreValve) via a percutaneous (retrograde femoral artery) or transapical (mini thoracotomy and insertion through the left ventricular apex) approach. The percutaneous approach has given the following outcomes in clinical trials: successful implantation 78–86%, 30-day or in-hospital death 11–25%, stroke 0–10%, and major vascular complications 8–17%.[100–107] With the transapical approach, the data are: successful implantation 90–100%, 30-day or in-hospital death 8–22%, stroke 3–5%, and major vascular complications 2%.[108–110] Results are expected to improve as operators become increasingly more experienced and technology improves. The Placement of AoRTic TraNscathetER Valve Trial (PARTNER) is an international, multicentre trial that will randomly assign more than 1000 patients to open-heart aortic valve replacement, transcatheter aortic valve replacement (Edwards SAPIEN valve), or medical therapy (ClinicalTrials.gov identifier NCT00530894). Results are expected in 2014.

Although no standardised recommendations for antithrombotic therapy in patients with transcatheter aortic valves currently exist, commonly used approaches include life-long low-dose aspirin (Walther T, Leipzig University, Germany, personal communication), life-long low-dose aspirin in combination with clopidogrel

for 1 month (Webb JG, St Pauls Hospital, Vancouver, BC, Canada, personal communication), or life-long dual antiplatelet therapy with low-dose aspirin and clopidogrel (Svensson LG, Cleveland Clinic, Cleveland, OH, USA, personal communication).

Prosthetic valves: a global perspective and research priorities

Since prosthetic heart valves were first introduced in the 1950s and 1960s, great advances have been made to increase their durability, reduce their thrombogenicity, and improve the long-term care of patients who receive them. However, a huge unmet need remains in developing countries where the burden of valvular heart disease is greatest.

An international population-based study[2] estimated that there are currently 15–20 million people worldwide living with rheumatic heart disease, of whom more than three-quarters are in developing countries. There are an estimated 282 000 new cases of rheumatic heart disease every year worldwide, with 95% of these occurring in developing countries. Almost 500 000 people die every year from rheumatic heart disease, with most deaths occurring during childhood or early adulthood.[2]

Rheumatic valve disease is usually not amenable to surgical repair and requires replacement with a prosthetic heart valve.[111] Mechanical valves are preferred over bioprosthetic valves for the management of rheumatic heart disease because they are more durable and the disease most commonly affects children and young adults. However, most patients in developing countries do not have access to cardiac surgery.[112] For those who receive a mechanical heart valve, the need for long-term anticoagulation poses unique challenges because of illiteracy, poverty, remote distances, underfunded and underequipped medical facilities, and lack of drugs. A study done in Africa[113] found that patients with mechanical valves attended their anticoagulation clinic once every 59 days and could maintain therapeutic international normalised ratio levels only 18% of the time. Consequently, rates of thromboembolic events, prosthetic valve thrombosis, and bleeding in patients with mechanical valves are much higher in developing countries than in developed countries (table 4).[114–130] The development of durable valves that do not require anticoagulation and can be delivered safely with a catheter has the greatest potential to benefit developing countries, but patients are also least able to afford them.[131] The PROACT trial is randomly assigning low-risk patients undergoing a mechanical On-X bileaflet aortic valve replacement to receive either combination of aspirin and clopidogrel or vitamin K antagonist therapy (ClinicalTrials.gov identifier NCT00291525). This valve is composed of pure pyrolytic carbon (without silicon), which might reduce its thrombogenicity compared with that of other prosthetic valves.[8] Completion of this study is expected in 2015.

Asian people are more sensitive and African people less sensitive to warfarin than white populations.[132,133] Asia, being the most populous continent on earth, is where genotype-based warfarin dosing could prevent the greatest number of bleeding events by avoiding hyperanticoagulation when commencing therapy. Conversely, genotype-based dosing for patients of African descent could avoid delays in reaching therapeutic levels of anticoagulation, and thus prevent thromboembolic events.

Conclusions

Prosthetic heart valves have greatly improved survival of patients with severe valvular disease, and the number of valve implantations worldwide has steadily increased. Despite limited randomised studies, vitamin K antagonists are widely used and are highly effective for prevention of thromboembolic complications in patients with mechanical heart valves, if they are appropriately monitored. New developments and technologies have increased access to valve replacement and have improved the antithrombotic management of patients with prosthetic heart valves in developed countries, but the greatest unmet need is in developing countries, which have the greatest burden of valvular heart disease. Our future aims should ensure that improvements in valve technologies and antithrombotic therapies are applied globally to truly reduce the morbidity and mortality of patients with valvular heart disease.

Contributors

JCJS and JWE contributed to the design, literature review, data interpretation, and writing of the report. AL and MJD contributed to the literature review and writing of the report.

Conflicts of interest

JCJS has received research funding from Bristol-Myers Squibb and GlaxoSmithKline. JWE has received honoraria and/or research support from Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, McNeil, and Sanofi-Aventis. MJD is a consultant for Edwards Life Sciences and Medtronic Inc. AL declares that he has no conflicts of interest.

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