

Anticoagulants and the Björk-Shiley prosthesis

Experience of 390 patients

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SUMMARY From September 1972 to January 1975, 390 patients underwent valve replacement using the Björk-Shiley tilting disc prosthesis. For the group as a whole hospital mortality was 13.3 per cent and was lowest in those undergoing isolated mitral or aortic valve replacement (5.3 and 9.4%, respectively). Available for follow-up were 209 patients of whom 123 were maintained on dipyridamole and 96 on warfarin. Thromboembolic complications were significantly ($P < 0.01$) commoner in the dipyridamole (28 of 123, 22%) than warfarin (6 of 86, 7%) treated group. In the dipyridamole treated group the incidence of thromboembolic complications was similar whichever valve was replaced and thromboembolic complications were responsible for 14 of the 28 late deaths. In the warfarin treated group thromboembolic complications only occurred in patients with a mitral prosthesis. Anticoagulation is indicated for all patients with this prosthesis wherever inserted.

Although valve replacement with biological and mechanical prostheses has been in clinical use for many years (Starr and Edwards, 1961), the search for the ideal prosthesis has been pursued enthusiastically because of the high failure and complication rates from earlier forms of metal, plastic, and biological prostheses (Braunwald and Detmer, 1968). Such a prosthesis would combine durability and non-thrombogenicity as well as interfering minimally with cardiac function. With increasing experience of valve replacement operative mortality has fallen, but systemic thromboembolism has remained the major cause of late mortality and morbidity despite careful anticoagulant control. The most frequent site of thrombus formation is upon the prosthesis itself (Arrigoni *et al.*, 1973), secondary to platelet deposition on the struts and base-plate, and on exposed metal or cloth-covered sewing rings. With no cage, small struts, a low profile sewing ring, and a tilting disc instead of a central occluder, the Björk-Shiley valve seemed to meet the criteria for an ideal prosthesis. Gradients across the valve are small (Björk *et al.*, 1971), there is a large orifice to tissue diameter permitting a more laminar central flow, and there is a low incidence of thromboembolism in patients on anticoagulants (Björk, 1969). Our own investigations show that when the Björk-Shiley mitral prosthesis is assessed

in terms of left ventricular filling rate and filling time (determined echocardiographically), it is less obstructive than either the Starr-Edwards prosthesis or the Hancock xenograft (Sutton *et al.*, 1977). Because of these features we have used this prosthesis at the Brompton Hospital.

Although long-term anticoagulants have been strongly recommended in all patients with artificial valves (Gadboys *et al.*, 1967), comparable results have been obtained using dipyridamole and salicylates combined (Harker and Slichter, 1970). Dipyridamole has been shown to have antithrombotic and antiplatelet properties but there has been no previous clinical study using dipyridamole alone in patients with prosthetic valves. To assess its efficacy in preventing thromboembolism, it was used in over half of our patients undergoing valve replacement with a Björk-Shiley prosthesis. The incidence of thromboembolic complications in this group of patients is compared with that occurring in those who were anticoagulated with warfarin. We report our experience in a large series of 390 patients of whom 209 were available for long-term follow-up.

Subjects and methods

A total of 390 patients had Björk-Shiley prostheses inserted in the 2½-year period between September 1972 and January 1975.

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HOSPITAL MORTALITY

Hospital mortality was defined as death occurring before discharge from hospital or after discharge when death occurred from whatever cardiovascular cause within 6 weeks of valve replacement.

ANTICOAGULATION AND DIPYRIDAMOLE

The selection of patients for treatment with either warfarin or dipyridamole was not random in that patients who were returning overseas where there were no adequate facilities for careful anticoagulant control were treated with dipyridamole rather than risk the danger of overanticoagulation. The dosage of dipyridamole was 50 mg 3 times a day, which required no monitoring, treatment beginning on the third postoperative day. Warfarin was used in the dose necessary to maintain the prothrombin time within 26 to 36 seconds, with a ratio of patient to control of 2.0-2.5 : 1, and was also started on the third postoperative day. Estimates of prothrombin time and ratio were repeated at frequent intervals until the prothrombin time was in the therapeutic range, and thereafter estimates were repeated at 4 to 6 week intervals.

LATE DEATHS

The mean duration of follow-up for the 209 patients attending follow-up was 23.5 months, with a range of 12 to 41 months. Sixty-two per cent of the patients were followed up at the Brompton Hospital; patients from overseas returned at yearly intervals for medical review.

THROMBOEMBOLISM

Criteria for the diagnosis of thromboembolism were as follows:

- (1) Transient or permanent neurological symptoms (sensory or motor) including truncal ataxia from brain-stem platelet microemboli. Transient or permanent reduction in visual acuity or scotomata.
 - (2) Transient or permanent loss or reduction of peripheral pulses; skin manifestations of ischaemia, or muscle ischaemia.
 - (3) Valve obstruction detected clinically by reduction or loss of prosthetic opening or closing sounds, or echocardiographic evidence of reduced left ventricular filling rate or prolonged filling time indicative of mechanical obstruction to left ventricular inflow (Sutton *et al.*, 1977).
 - (4) Whenever possible, necropsy was performed on patients dying from any cause, who had undergone valve replacement, the valve being examined for any adherent thrombus.
- Any patient in the dipyridamole group who met

the above criteria for systemic thromboembolism was admitted to hospital for intravenous heparin therapy and anticoagulated with warfarin. From November 1974, all patients were treated with warfarin because of the unacceptably high incidence of thromboembolism in the dipyridamole treated group.

Results**HOSPITAL MORTALITY**

For isolated mitral and aortic valve replacement hospital mortality was 5.3 per cent (8 of 150) and 9.4 per cent (11 of 117), respectively. For combined mitral and aortic valve replacement hospital mortality was 17.5 per cent (10 of 57) and for mitral replacement with tricuspid repair 10 per cent (3 of 30). Finally of the 52 hospital deaths (13.3%), 20 occurred in patients who underwent either triple valve replacement or valve replacement combined with procedures such as major reconstruction of the ascending aorta, aneurysmectomy, or aortocoronary bypass grafting; the hospital mortality in this group was 55.5 per cent (20 of 36).

LATE DEATHS

Of the 338 early survivors, 129 were lost to follow-up leaving 209 in whom data are available on late mortality. There were 28 late deaths (13.3%) and of these half (14) were the result of thromboembolism. There was a further 9.1 per cent incidence of non-fatal thromboembolic complications. The other cause of late death was a paraprosthetic leak (9 patients) caused by infective endocarditis in all but 2 patients. There were 5 patients who died at home and in whom no necropsy was obtained.

ANTICOAGULANT VERSUS DIPYRIDAMOLE

Of the 209 patients attending follow-up, 86 were anticoagulated with warfarin and 123 were given oral dipyridamole. In the former group there was a 7 per cent incidence of thromboembolic complications of which 16.6 per cent were fatal, compared with the dipyridamole treated group in which the incidence of thromboembolism was 22 per cent of which 48 per cent were fatal (Table). These differences are significant ($P < 0.01$). There were, in addition, 5 late deaths occurring at home; no necropsy was performed, but 4 of these deaths were in the dipyridamole treated group and could have resulted from thromboembolism. There was a higher incidence of thromboembolic complications in the dipyridamole treated patients *whichever surgical procedure had been performed*. Conversely, the only thromboembolic complications seen in the

Table Thromboembolic complications in 209 patients

Maintenance drug therapy	No.	Fatal thromboembolism		Non-fatal thromboembolism		Total
Warfarin	86	1	1.2%	5	5.8%	6 (7.0%)
Dipyridamole	123	13	10.6%	14	11.4%	27 (22%)

warfarin treated group occurred in patients with a mitral prosthesis. Thrombotic obstruction of a mitral prosthesis occurred in 7 patients in the dipyridamole treated group (7 of 61 or 11% of those at risk) and in only one patient in the warfarin treated group (1 of 61 or 2% of those at risk). Thrombotic obstruction of an aortic prosthesis occurred in 3 patients in the dipyridamole treated group (3 of 73 or 4% of those at risk) and did not occur in the warfarin treated group though there were a smaller number (27) of patients at risk in this group.

Discussion

Our operative mortality for isolated mitral and aortic valve replacement is similar to that reported from most centres (Björk *et al.*, 1973; Bonchek and Starr, 1975a) but, despite meticulous anticoagulant control, late mortality and morbidity resulting from thromboembolic complications continue to cloud the prognosis of these patients. While some investigators find a much higher frequency of thromboembolism with no anticoagulant therapy (Gadboys *et al.*, 1967; Friedl *et al.*, 1971), others have failed to show a significant difference, and focus their attention on improvements in prosthetic valve design (Bonchek and Starr, 1975b).

There is general agreement that anticoagulants are useful in preventing venous thrombosis, but they have been considerably less effective in preventing arterial thrombosis. In venous thrombosis the cellular elements of the blood are distributed at random throughout the fibrin mesh, and anticoagulant drugs that prevent the formation of fibrin have been useful in preventing this type of thrombus (Weiss, 1974). In arterial thrombogenesis, the deposition of platelets and their subsequent aggregation at sites of blood vessel injury and on prosthetic valves plays a more important role (Arrigoni *et al.*, 1973) and fibrin formation occurs late.

Thus one way of reducing the incidence of arterial thromboembolism would be to select for clinical use agents that change platelet properties by reducing their adhesiveness, thus inhibiting platelet aggregation and deposition. Dipyridamole has been shown to reduce platelet adhesiveness and aggregation (Emmons *et al.*, 1965) and to

inhibit thrombus formation in injured arterial tissue (Didisheim, 1968). It has also been shown to reduce deposition of thrombus in indwelling arterial cannulae and extracorporeal shunts (Harker and Slichter, 1970; Cucuiana *et al.*, 1971). In conjunction with warfarin (Sullivan *et al.*, 1971) or acetylsalicylic acid (Harker and Slichter, 1970; Dale *et al.*, 1975) dipyridamole has been shown to reduce the incidence of thromboembolism in patients undergoing prosthetic valve replacement. It was our hope that to the haemodynamic advantages of the Björk-Shiley prosthesis could be added the practical realisation of the theoretical advantages of dipyridamole, while the high incidence of severe haemorrhagic complications of long-term anticoagulants could be reduced.

Our results in 209 patients followed up for a mean period of approximately 2 years show a high incidence of thromboembolic complications in the dipyridamole treated group significantly different ($P < 0.01$) from the incidence in warfarin treated patients. This is in agreement with Björk and Henze's recently published series (1975) which suggested that the frequency of thromboembolism in patients treated with dipyridamole was the same as in patients on no treatment at all. We freely admit that, as with much clinical experience, our study falls short of ideal requirements for a statistically acceptable investigation. In particular, allocation to the dipyridamole or warfarin groups was not randomised and the patients were not matched. Indeed the majority of the dipyridamole treated patients were from the Middle East, and racial and climatic differences might be held to be the cause of the increased incidence of thromboembolic complications in this group. There is, however, no evidence that arterial thromboembolism is more common in Middle Eastern countries and our experience is similar to that of Björk and Henze in Sweden. While a prospective randomised trial would be a better method of investigating the feasibility of using dipyridamole alone, our own experience has been so chastening that we no longer feel justified in withholding anticoagulant treatment from any patient with a Björk-Shiley prosthesis and feel that such an experience is worth reporting in case others might be tempted to initiate a similar method of management.

Thromboembolism was most frequent in patients

undergoing mitral valve replacement, and a high proportion (8 out of 13) of these presented with mitral valve obstruction. At operation or necropsy, thrombus appeared to arise from the struts on the atrial side, growing through the valve so as to obstruct the left ventricular inflow tract and render the tilting Delrin disc immobile. Similar valve encapsulation has been described by Björk and Henze (1973). Obstruction of a (mitral) prosthesis occurred in only one patient who was well anticoagulated with warfarin. Of the 8 patients presenting with mitral valve obstruction, 3 had major systemic emboli during the month before admission to hospital, but had not sought medical attention until they presented with severe pulmonary oedema. On clinical examination the cardinal diagnostic feature was that both prosthetic opening and closing sounds were indistinct or absent. Echocardiographic assessment of left ventricular filling showed it to be characteristically slow (Sutton *et al.*, 1977). Thrombectomy was successfully carried out in one patient. The other 7 died before or during reoperation.

Three patients presented with aortic prosthetic valve malfunction caused by thrombotic obstruction. In all deterioration was very rapid within 24 hours of admission, all presented with severe left ventricular failure and had absent valve sounds. All died, one during reoperation for thrombectomy.

The incidence of thromboembolic complications in the group of patients treated with warfarin was low, and was of the same order as that reported by Björk *et al.* (1973) and Bonchek and Starr (1975a), as was the incidence of paravalvular leaks.

Great significance should be placed on the presence of indistinct or absent prosthetic valve sounds in patients with aortic or mitral Björk-Shiley prostheses and either unexplained rapid onset of pulmonary oedema or a recent history of thromboembolism. In our experience, this physical sign was absolutely reliable and indicative of thrombotic encapsulation of the prosthesis. Echocardiography was of equal diagnostic assistance in recognising mitral prosthetic obstruction by reduction in left ventricular filling rate, and by the 'rounding off' of the normally sharp angular echoes of the Björk-Shiley disc. Significant paravalvular leaks were also identifiable echocardiographically by return of septal motion to normal and by a much increased left ventricular filling rate.

The increased incidence of thromboembolic complications in the dipyridamole treated group of patients was statistically significant by November 1974; from this time, all patients were anticoagulated with warfarin. Thus dipyridamole alone is ineffective in preventing thromboembolism, and anticoagulation with warfarin is indicated for all

patients with the Björk-Shiley prosthesis wherever it is inserted.

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