

Quattro Valve Trial at Mid-Term: December 1996 to November 2004

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Background and aim of the study: The Quattro valve is a stentless pericardial mitral bioprosthesis that is treated with a post-tanning aldehyde capping designed to reduce calcification. A prospective trial was started in December 1996; herein are reported the results of the three centers that performed the surgery and followed up patients in the majority of cases. Young patients were deliberately included in the trial.

Methods: Follow up data from 175 patients (mean age 46 years; range: 12-87 years) were collected and analyzed. Among patients, 44% were aged <40 years. Follow up was 91% complete; mean follow up was 3.4 years (range: 0-7.5 years); total follow up was 465 patient-years (pt-yr). Clinical outcome was assessed according to the AATS/STS guidelines, and results analyzed according to Kaplan-Meier product limit calculation and by FDA Optimal Performance Criteria (OPC).

Results: Early mortality was 1.7% (all non-valve related). At 60 months after surgery, mean overall survival was $84.8 \pm 3.6\%$, mean overall freedom from valve-

related death was $99.2 \pm 0.9\%$, and mean overall freedom from calcification, pannus and tears was $96.1 \pm 2.2\%$. FDA OPC values (data for mechanical valve, tissue valve, Quattro valve in patients aged <40 years and of all ages, respectively; expressed as %/pt-yr) were as follows: thromboembolism/stroke 3.0, 2.5, 0, 0.4; thrombosis 0.8, 0.2, 0, 0; major hemorrhage 1.5, 0.9, 0, 0.4; major perivalvular leak 0.6, 0.6, 0.4, 0.6; late endocarditis 1.2, 1.2, 1.8, 1.3; calcification/pannus 0, 0, 0.8, 0.6. Statistical analysis of these data showed there to be no difference between patients aged less or more than 40 years.

Conclusion: Overall mid-term results with the Quattro valve were acceptable. The lack of early calcification in young patients shows promise. More young patient-years of follow up will be needed to establish a secure indication for use in young, rheumatic patients where anticoagulation control is deficient.

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Worldwide, the most common form of valve disease is rheumatic, with the dominant proportion of this population being young, poor, and living under circumstances that make anticoagulant treatment difficult or sometimes impossible. Experience in young patients with the first generations of bioprostheses showed early calcification. Mechanical valves continue to show high rates of thromboembolic or hemorrhagic complications in societies without good anticoagulant control. The design goal of the Quattro valve was to

produce a durable bioprosthetic valve for use in patients of this category (1). The study aim was to determine whether this goal is being achieved.

Clinical material and methods

Valve design

The valve was made stentless in an effort to avoid the excessive flexion stresses seen in three-leaflet stented valves. To distribute stress, there was one large anterior leaflet and three posterior scallops. In order to lessen the effect of papillary displacement on leaflet coaptation and to simplify attachment of the chordal support to the papillary muscles, the chordae were brought together into two flaps designed to be stitched to the left and right papillary muscles. In the great majority of cases the anterior part of each papillary muscle which gives support to the anterior leaflet

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forms the bulkiest part of the muscle and, as such, provides a secure attachment for the two papillary flaps. Depth-measuring tools determine the distance from the trigones for the sutures which anchor the flaps. The sewing ring has three layers of pericardium, and is D-shaped.

The valve is constructed from bovine pericardium selected for its thickness, strength, flexibility, and collagen fiber direction. The design requires the collagen fibers to run from the papillary attachment to the annulus. The pericardium is first cross-linked with glutaraldehyde, after which the residual unlinked aldehyde groups are capped with propylene glycol. Preclinical testing followed Food and Drug Administration (FDA) and Communauté Européenne (CE) guidelines. Studies in juvenile rats showed minimal calcification, as well as reduced inflammatory and immunological responses compared to controls, while an initial study in juvenile sheep showed a marked anticalcification effect compared to controls. A subsequent repeat study performed six years later, using a different breed of sheep, failed to show the same effect. Fluid dynamic and wear tests were successfully accomplished with taut, normal and billowing chordal positions (2,3).

Clinical trial

The clinical trial was conducted according to FDA trial guidelines (4). Scheduled follow up was by clinic visit, in addition to annual echocardiography.

An initial pilot trial was commenced in December 1996 at Johannesburg Hospital, South Africa. Although other centers were subsequently recruited, at the present stage the trials in South Africa, Leipzig and Riyadh have recruited and followed by far the major proportion of the patients. For a variety of reasons, including institutional difficulties and changes of location of the investigators, the follow up was incomplete in 60 other patients in nine other institutions. Ethical committee approvals were obtained for all centers, with special approval being obtained in Johannesburg and Riyadh for patients aged under 20 years. As the trial has progressed, 24 relevant articles have been published; a small selection is listed in the bibliography (5-8).

All data presented in this report were entered into a custom-designed database in Microsoft Excel 200 (Microsoft, Redmond, WA, USA). These data were then imported into SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA) which was used for all statistical computations.

Patients were separated into two groups based on their age of <40 years or \geq 40 years. Kaplan-Meier curves were used to estimate the time-related probabilities of explantation and/or death due to a variety of causes (see Results). The log rank test was used to

compare results for the two groups. A p-value <0.05 was considered to be statistically significant.

Inclusions and exclusions

Patients who had undergone aortic valve replacement were excluded from the trial. Cases with coronary artery surgery, left atrial thrombectomy, left atrial reduction, left atrial ablation procedures for atrial fibrillation (AF) and tricuspid annuloplasty were all included.

All patients provided their informed consent in their own language. Any patient unwilling to return for follow up examinations was excluded. Many of the patients were poor; hence, in order not to bias the consent, patients were not informed that financial assistance for transportation to follow up visits would be available before they consented.

Patient population

Among the total patient population (n = 175; 126 females, 49 males), 49 were in Johannesburg, 55 in Leipzig, and 71 in Riyadh. The overall mean patient age at surgery was 46 years (range: 12 to 87 years); mean ages at Johannesburg, Riyadh and Leipzig were 33, 39 and 67 years, respectively. Seventy-seven (44%) of the patients were aged under 40 years, and 45 were aged between 40 and 60 years; hence, a total of 122 patients (70%) was aged under 60 years.

Clinical status at the time of surgery

At the time of surgery, 139 patients (79%) were in NYHA classes III (n = 110) or IV (n = 29), and dominant mitral regurgitation was present in 41%. The ejection fraction was <50% in 40% of patients, while AF was present in 32% of those patients aged <40 years and in 46% of those aged >40 years. The overall incidence of AF was 39%.

Valvular indications for surgery

Among the patients, 90% were rheumatic. Eighteen patients underwent surgery for failed previous valve replacements (16 calcified valves; two infected valves, one biological, one mechanical), and 21 for failed previous valve repairs. Bacterial endocarditis of the native valve was the indication in nine patients.

Surgery

Inevitably, there were differences between institutions in the manner in which surgery was conducted and the patients managed. In Leipzig, 33% of the operations were performed using a video-assisted minimally invasive approach, and 33% underwent atrial ablation procedures for AF. Two patients at other centers had atrial ablation. Tricuspid annuloplasty was performed in 58% of patients at Johannesburg, but in

only 5% of patients at the other centers. At discharge, warfarin anticoagulation was not used in the Johannesburg patients, even in the presence of AF. The inability of patients to follow an anticoagulation regimen was not regarded as a contraindication to the use of a biological valve for a patient in NYHA class III or IV. In Riyadh, 24% of the patients had undergone prior mitral valve replacement.

Concomitant procedures

Concomitant procedures included tricuspid annuloplasty (n = 43), atrial ablation ('minimize'; n = 21), left atrial reduction (n = 4), left atrial thrombectomy (n = 6), and coronary artery bypass grafting (n = 6).

Results

In-hospital death

There were three in-hospital deaths, though none was valve-related. The first patient had a perioperative stroke and died from multiorgan failure after 19 days. The second patient had an infective focus preoperatively, developed sternal sepsis, and died after two months from multiorgan failure. The third patient, an 87-year-old, underwent reoperation for severe bleeding from a left internal thoracic graft and died from multiorgan failure after 12 days.

Follow up

Scheduled follow up was by clinic visit, with annual echocardiography. This procedure has remained true for the majority of patients, though over the years some follow up contacts have been by telephone and/or via physicians or relatives. At the end of 2004, contact had been made within the past year with 91% of the live patients. The total follow up for all patients was 465 patient-years (pt-yr), and 222.5 pt-yr for those aged under 40 years. In total, 73 patients have been followed from 3.5 to 7.5 years (mean 4.9 years).

NYHA class

At follow up, 114 patients (88.7%) were in NYHA class I, 12 (9.3%) were in class II, and one patient (1%) was in each of classes III and IV.

Pregnancy

A total of nine patients became pregnant postoperatively, and achieved successful deliveries of healthy infants.

Endocarditis

The nine patients who underwent Quattro valve replacement of their infected native valve had no further infection. The one Quattro valve used to replace an infected porcine valve had to be replaced within

two weeks due to infection. However, six patients developed early endocarditis after replacement of uninfected native valves. (One of these patients had acidosis and pneumonia at the time of operation). Four of the early endocarditis patients were from the same institution, with three incidents occurring within a short time span; the infecting microorganism was *Staphylococcus epidermidis*. Two other patients had late endocarditis, one at three years (diphtheroid), and one at 15 months (infected pacemaker, *Streptococcus faecalis*).

Late mortality

The assignment of causes of death followed the Society for Thoracic Surgery/American Association of Thoracic Surgeons guidelines. There were 16 late deaths. Six patients died from non-cardiac and non-valve-related causes, while seven died from cardiac, non-valve-related causes. Most of the latter group had a normally functioning valve, but myocardial disease led to heart failure and death. Valve-related mortality occurred in three patients. One of these patients had a low ejection fraction and died suddenly; the valve appeared to be functioning normally, but no autopsy was performed. The second patient died one month after valve re-replacement due to structural failure. Finally, one patient died from endocarditis, with multiple organ failure after reoperation.

Reoperation with valve replacement

Reasons for explantation and replacement included bacterial endocarditis, paravalvar leak, structural failure, pannus/calcification and malinsertion/malfunction.

Bacterial endocarditis

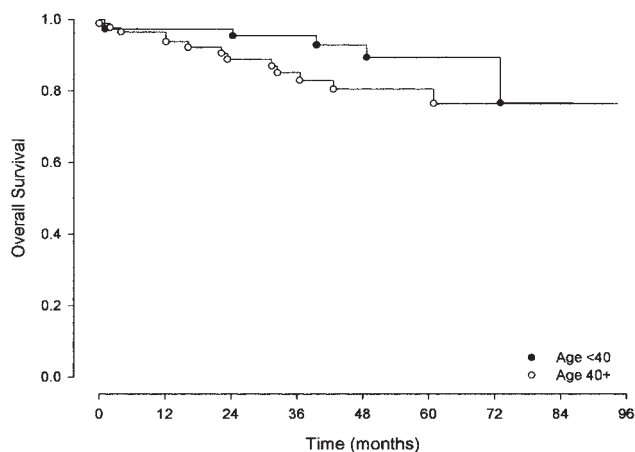
Eight cases have been detailed above; notably, six of the eight cases came from one institution.

Paravalvar leak

There were three cases of paravalvar leak (one was anterior, one posterior, and one medial). The original operation was minimally invasive in two of these patients.

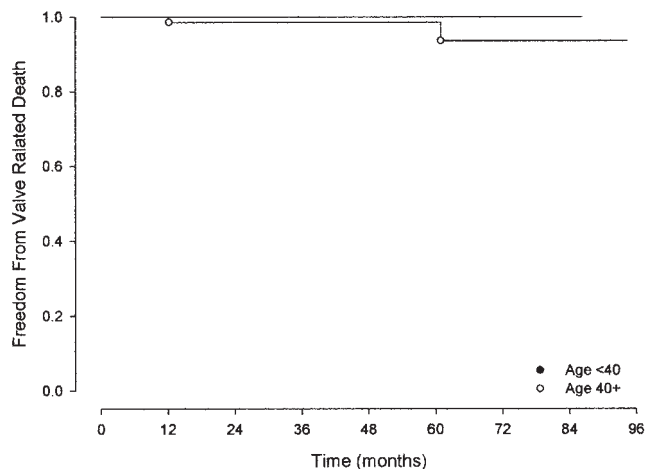
Pannus/calcification

There were three cases of pannus/calcification. One case occurred within four months in a patient with rheumatoid disease. One 24-year-old patient was reoperated on at 6.5 years; after four years the valve had remained thin, and multislice computed tomography (CT) did not reveal the presence of calcium. At explant, pannus had grown down from the annulus, mostly over the ventricular side of the posterior scallops, with some on the anterior leaflet. There were small nodules



<40 :	78	63	50	41	27	19	8	2
40+ :	89	70	52	41	33	20	6	2

Figure 1: Overall freedom from death due to all causes ($84.8 \pm 3.6\%$ at 60 months).



<40 :	78	63	50	41	27	19	8	2
40+ :	89	70	52	41	33	20	6	2

Figure 2: Overall freedom from valve-related death ($99.2 \pm 0.9\%$ at 60 months).

of intrinsic calcification in the anterior leaflet. Another 20-year-old male had a densely calcified rheumatic valve replaced. This patient did very well initially, but at five years thickening was noted on echocardiography and calcium was detected on multislice CT scanning. He slowly developed mitral stenosis, and the valve was replaced at seven years; at explant the calcium was seen to be confined to the anterior leaflet.

Malfunction/malinsertion

Seven patients were explanted due to malfunction/malinsertion, six for insufficiency and one for stenosis. The valve explanted for stenosis was a size 30 valve which appeared to have been grossly oversized, with redundant tissue causing the obstruction to flow. The remaining six valves were removed for insufficiency; three of these patients had undergone previous valve surgery, and three had early insufficiency with explantation within one year. These three valves all showed early billowing, and all had been implanted at the same center.

Structural failure

In 1999, routine repeat in-vitro testing revealed that some valves had been manufactured, contrary to specifications, with transverse orientation of fibers in the anterior leaflet. A correction was made in the manufacturing process to avoid this error. Later, two patients with valves made before the correction experienced rupture of some anterior chordae and came to reoperation at four and five years, respectively. The fiber orientation was shown to be transverse at the rupture sites. Since then, one 'post correction' valve had a similar incident at 3.5 years and was explanted.

A further refinement to determine fiber direction for tissue selection was developed and should prevent any future failures.

Calcification

Two explants have been described above. One other young patient showed multislice CT evidence of leaflet calcification, but has not undergone repeat surgery.

Thrombosis and embolism

Two patients aged 75 and 76 years at surgery (both had chronic AF, and one had also had a previous stroke) underwent Quattro valve insertion and atrial ablation. Both patients ultimately suffered fatal strokes: one at 23 months and one at 43 months post-operatively, shortly after normal echocardiograms had been recorded, with no evidence of atrial or valvular thrombus. Otherwise, there were no instances of thrombosis or embolism. It was notable that 32% of the patients with AF were not receiving warfarin.

Comparison of patients aged <40 and ≥ 40 years at the time of surgery

The major study objective was to design a device that could be used without anticoagulation in young patients, and which would not be subject to the early calcification that had plagued the first generation of bioprostheses used in young patients. Kaplan-Meier analyses were made for:

- Freedom from death due to the following causes: (i) all causes (Fig. 1); (ii) non-valve and non-cardiac; (iii) valve-related (Fig. 2); and (iv) cardiac non-valve-related.
- Freedom from occurrence of endocarditis.

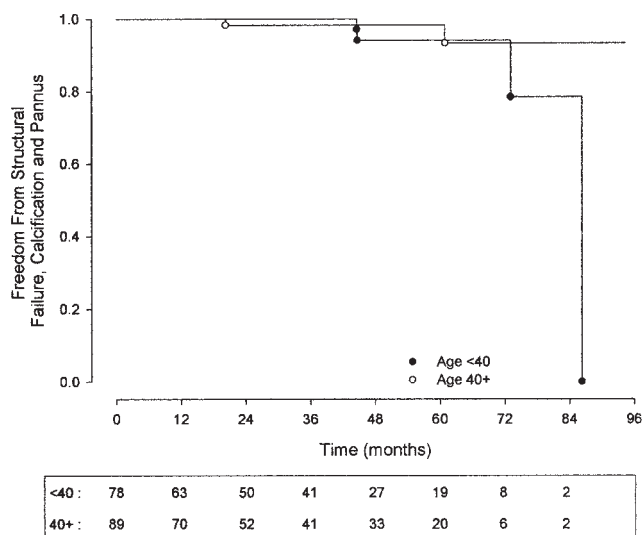


Figure 3: Overall freedom from calcification, pannus and tears (96.1 ± 2.2% at 60 months). The steep fall in the Kaplan-Meier curve between six and seven years relates to the two cases which developed calcification/pannus at 6.5 years.

- Freedom from explant due to: (i) all causes; (ii) endocarditis; (iii) structural failure (tears), calcification or pannus (Fig. 3); (iv) structural failure (tears) alone; (v) malinsertion/ malfunction; and (vi) a combination of (iii) and (v).

There was no statistical difference between those patients aged <40 years and those aged ≥40 years for any category. Freedom from death due to all causes at 60 months was 84.8 ± 3.6% (Fig. 1). Freedom from valve-related death at 60 months was 99.2 ± 0.9% (Fig. 2). Freedom from calcification, pannus and tears at 60 months was 96.1 ± 2.2% (Fig. 3). In the latter situation, the steep fall in the Kaplan-Meier curve between six and seven years was related to two patients who developed calcification/pannus at 6.5 years. The numbers at this part of the survival curve were too small for statistical analysis, but the curves have been presented

out to the 2004 end-point of the study, even though the numbers were insignificant, because they may represent the start of a trend which further follow up might disclose. It is important that, at four years, multislice CT scanning at the Johannesburg center revealed calcium in three cases, only two of which have since come to reoperation.

FDA Objective Performance Criteria

The FDA established Optimal Performance Criteria (OPC) which are published in ANSI/AAMI/ISO standard 5840-2005, Annex R, page 67. The published values in the standard may be used without further justification. The formal statistical test is that the observed rates must be significantly less than two-times the OPC rate. Rates of events (in %/pt-yr) between published rates in the standard valve and observed rates for the Quattro valve (in all patients and in only those aged <40 years) are compared in Table I. There is no OPC for calcification.

Discussion

These analyses have shown no difference in outcome following Quattro valve implant between patients aged <40 and ≥40 years. The fact that death from all causes showed no difference was surprising, because it might have been expected that the older population would have suffered more deaths from age-related diseases. Indeed, this was the case, but this situation was balanced by poverty-related deaths among the socially deprived African patients.

With regard to endocarditis, successful use of the Quattro valve in nine cases of native valve endocarditis suggests that the material is not especially susceptible to infection. It is equally clear that the valve is not especially resistant to infection, and the occurrence of a cluster of four cases during the first year at one center may imply a local causative factor.

The category of malinsertion/malfunction served as

Table I: FDA Optimal Performance Criteria (OPC): Comparison with Quattro valve for patients of all ages and those aged <40 years.*

OPC	Mechanical valve	Tissue valve	Quattro valve	
			<40 years	All ages
Thromboembolism/stroke	3.0	2.5	0	0.4
Thrombosis	0.8	0.2	0	0
Major hemorrhage	1.5	0.9	0	0.4
Major perivalvar leak	0.6	0.6	0.4	0.6
Late endocarditis	1.2	1.2	1.8	1.3
Calcification/pannus	-	-	0.8	0.6

*Values are % per pt-yr.

a reminder that the attachment to papillary muscles can be either too taut or too loose. The valve was designed to tolerate a degree of tethering and a degree of billowing. It remains possible for the valve to be inserted too taut or too loose, according to how close to the top or base of the papillary muscle the papillary flaps are sutured. Since the left and right papillary muscles are not at equal depths from the trigones, measurements must be made on both sides. Whilst it is possible to insert the valve, with perfect competence and without any measurements, it seems that consistent success is more likely when careful measurements are made on every occasion. Care must also be taken to achieve an even suturing of the ring, without crimps or gaps. The fact that three of these cases occurred in patients with previous valve replacement, emphasizes the extra difficulty of inserting chordally supported valves in patients whose native valves and chordae had been previously excised. In this respect, new and improved tools which mark the site of the papillary sutures have been developed.

Comparisons

The OPCs provided by the FDA were derived from the developed world, and from series in which the patients' ages reflected those in the developed world. The entire present series had a mean age of 46 years, which was significantly younger than has been seen in any series coming from the developed world. For an event with an annual rate of 1.2%, if the rate is two-thirds of the FDA's OPC, a sample size of 400 pt-yrs will furnish approximately 80% power for satisfying the formal statistical test (9). The number of patient-years for the present whole group was 465, such that for all but the category of endocarditis the results showed better than average comparative performance. Further observation will help to define whether factors intrinsic to the design, or institutional and social factors, account for the more than expected cases of infection after replacement of normal native valves. The satisfactory use for endocarditis in nine native valves was encouraging.

There has been a small contemporary series of valves with the same goal of providing a device to be used in young patients, without anticoagulants. Kumar et al.

(10), in New Delhi, concluded that mitral homografts used in 37 patients did not fulfill their expectations, with three deaths and eight reoperations during a mean follow up period of 26.6 months. Kabbani et al. (11), in Damascus, have been using an inverted pulmonary autograft in a Dacron conduit in the mitral position with the pulmonary valve being replaced with a homograft, an operation first described by Ross. This published series was too small for valid comparison, but good results were achieved in 34 of 43 patients with a mean follow up of 18 months, and further results are awaited.

For more valid comparisons, historical data must be examined. Two series were published from South Africa during the 1980s; the difficulty with these is that they were confined to children and so are not strictly comparable with the present study. The series of Antunes (12), in Johannesburg, included 135 patients all aged under 20 years, with a total follow up of 356 pt-yr. At the time of the study, there was an overall incidence of 80 patients with structural failure, 64 who had replacement, 11 who died without replacement, and five who were awaiting replacement. In 1986, Odell et al. (13) reported a series of 195 patients aged under 15 years, using porcine and bovine pericardial valves in the mitral position. At four years, valve survival without calcification was less than 20% (32.5% for porcine valves, 2.5% for pericardial valves).

Perhaps a better comparison would be the series of Magilligan et al., in Detroit (14). These authors compared results in patients aged <35 and >35 years. There was a statistically lower failure rate in patients aged >35 years, with failure being defined as the occurrence of calcification and/or tears leading to explant. Infections were specifically excluded. The first valve removals in patients aged <35 years began after three years, and by six years 20% of the valves had been explanted. In the present study, none of the Quattro valves had been explanted for calcification at six years. The first explants, in fact, occurred at 6.5 years, thereby confirming that, despite the 'anticalcification' treatment, when implanted in young people the Quattro valve can indeed calcify, and that the difference from past experiences may only be one of degree (see Table II).

Table II: Comparison of explants for calcification between previous bioprostheses and Quattro valve.

Reference	Year	No. of patients	Patient age (years)	Time to first explant	Explants at 6 years (%)
Magilligan et al.	1982	62	<35	3 years	20
Odell et al.	1984	195	<15	2 years	>80
Present study	2006	77	<40	6.5 years	0

In going beyond the distinction of age <40 and >40 years, it must be emphasized that the mean age for the entire series was 46 years (33 years for Johannesburg, and 39 for Riyadh). Clearly, the great majority of patients are at an average age that simply would not be considered for bioprosthetic insertion in North America, Europe, or Japan.

Study limitations

In the trial of a biological valve in young patients, the critical issue is the occurrence of time-related failure. The historical evidence quoted above indicated a significant start to calcification from three years, and clear evidence by five years that there was a serious problem. In order to be useful, a study must include a significant number of patients who have had sufficient time of follow up to reveal time-related events. A total of 800 pt-yr could be achieved by following 250 patients for one year, 150 for two years, or 90 for three years, though this would be useless for assessing the risk of tears and calcification. Although it is important that patients in the present study have been followed for a mean of 4.9 years (range: 3.5 to 7.5 years), a longer follow up is needed to confirm these findings.

In conclusion, the Quattro valve trial was unique in that it involved both old and young patient populations, yet no age-related difference in biological valve performance was evident. Indeed, comparison with FDA/ISO OPCs showed excellent performance, except for infective endocarditis. There was also a complete absence of thrombosis or embolism in young patients. Although explant for calcification/pannus was necessary in two young patients, it seemed to occur later and less often than in previous studies. In patients aged 40 to 65 years who, in the developed world, define the division between 'old' and 'young', there was no evidence of calcification. If this experience is continued, the Quattro valve may be seen as being useful either for populations of young patients in whom anticoagulation is difficult, or for individuals living under special circumstances that render anticoagulation difficult or dangerous. Additional observations were that: (i) the valve could be inserted using minimally invasive techniques; (ii) it could be used in patients who had had their native valve removed previously, though with a possibility of malinsertion; (iii) it can be used successfully for native valve endocarditis; and (iv) successful pregnancy is possible in women of child-bearing age. Despite the evidence presented, however, further follow up will be required to determine the full extent of the Quattro valve's benefits for young, rheumatic patients in the developing world.

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Meeting discussion

MR. J. PEPPER (London, UK): Is it possible to visualize the pannus with echocardiography? Pannus on mechanical valves is quite difficult to predict in vivo, but with your valve it may be easier.

DR. R.W.M. FRATER (Bronx, New York, USA): Yes, it probably is. What we see with the ring is invariably dense healing, and it is the same for the papillary muscles. In this particular case it can be seen tracking down the posterior and anterior leaflets from the ring - from the top down, immobilizing the leaflets. Inside the pannus you could see the leaflet, which had some intrinsic calcification. I suspect that the pannus may relate to the mechanics at the annulus, stimulating a vigorous response. With luck, the pannus continues to move and does not grow down. Occasionally, it can be seen on echo.

MR. PEPPER: May I ask you about gradients across this valve?

DR. FRATER: If you implant a size 26 valve, the gradients are generally 6, 7 or 8 mmHg, but not with a size 30 valve. If you force a large valve into a small annulus you can make it stenotic because it is so flexible. What is interesting is that there are gradients, but the clinical status is fine. Clearly, our goal is to get these patients back to work and leading a normal life. Yes, the gradient could be lower if we did more to make an orifice larger rather than try to make it less vulnerable to other consequences of a flexible valve, whether it be rupture or whatever.

DR. CHARLES YANKAH (Berlin, Germany): What type of biological phenomenon favors decreased calcification in these patients? Do you find any endothelial lining in the explant specimen, or how would you explain this favorable condition?

DR. FRATER: In sheep, dogs and baboons this material endothelializes very quickly, and spontaneously. Histologically, I have not seen endothelial cells in an explant, but we have not had many explants to examine - they are very often destroyed. To find endothelium in an autopsy specimen or an explant specimen you must treat it very gently so as not to rub it off. The only effect of the treatment is that you have reduced the toxicity of the residual aldehyde groups - but then half of the anticalcification treatments described at this meeting do that as part of their functions.