J VASC ENDOVASC SURG 2011;18:215-23

Prophylactic surgery of the aortic root in Marfan Syndrome: reconsideration of the decision making process in the era of customised external aortic root support

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Elective surgery is used to safeguard people whose aortic root is affected by Marfan syndrome from the consequences of aortic dissection. In making the decision about the choice of surgery there is a complex trade off of the ongoing risk of dissection if surgery is deferred versus the risk of the operation itself and of the ensuing lifetime consequences. These are re-explored to include the latest option: customised external aortic root support.

KEY WORDS: Marfan syndrome - Aorta - Dissection - Surgical procedures, operative.

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Aortic dissection originating in the sinuses of Valsalva is a characteristic cause of death in Marfan syndrome and there is a very high likelihood of death when it occurs. This risk is preventable by aortic root surgery.[1] Clinical practice in the management of patients with proximal aneurysmal dilatation of the ascending aorta is based on this premise. People with the Marfan phenotype or with a family history of Marfan syndrome should have echocardiographic imaging and measurement of the aortic root. If the aorta is found to be morphologically characteristic of Marfan syndrome, ongoing echo monitoring is usual in western medical practice and at some stage surgical intervention may be proposed.

Conflicts of interest: The Authors declare that Golesworthy T. is a shareholder and director of Exstent Ltd, which holds the intellectual property in the External Aortic Root Support project. TG was the first recipient of the external aortic root device.

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Following the description of total root replacement by Bentall [2] there was progressive refinement of the surgical techniques leading to a highly reproducible form of surgery.[3] By the mid 1980s surgical replacement of the ascending aorta along with the aortic valve became standard of practice with the intention of preventing ascending aortic dissection. There were further ongoing refinements in commercially available valved conduits.[3] In parallel, concerns about the life time risks of thromboembolism and anticoagulant related bleeding, led surgeons to seek to avoid mechanical valve replacement and to explore the use of tissue valves within the conduit,[4] homograft root replacement, and valve sparing forms of root replacement.[5-8]

With a more recent non-ablative approach the whole of the aortic root and valve are retained and are externally supported by a porous support, customised to the individual patient using computer aided design (Figure 1).[9-11] Here, at the outset we declare a special interest in that several of the present authors were innovators [12, 13] and continue as mem-

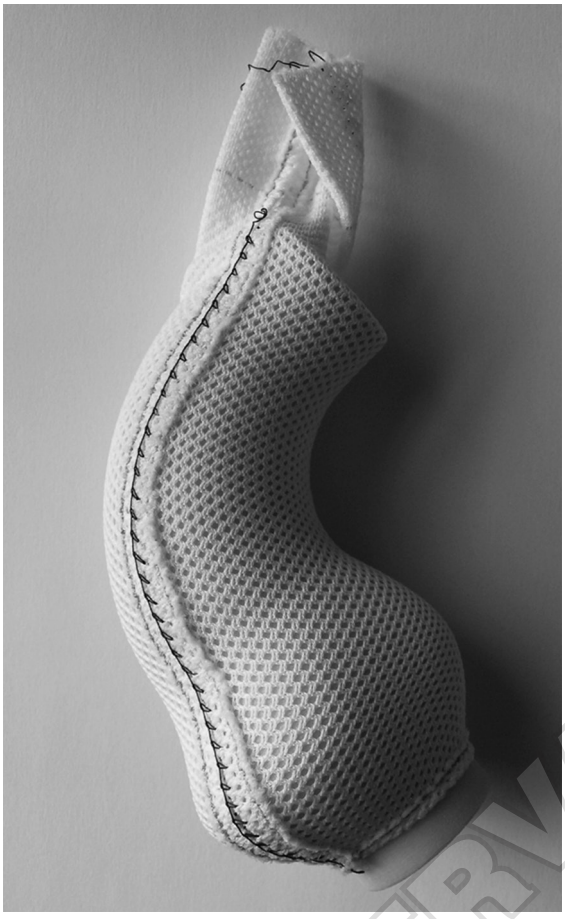

Figure 1.—The custom-made external support on the former derived by computer aided design from the patient's recent preoperative MRI. The aorta is dissected to the aortoventricular junction. The suture line at the front is released and the lower margin of the support is placed around the aorta proximal to coronary arteries to beyond the brachiocephalic artery. Incisions are made match the size and position of the origins of the coronary arteries. From Allen C *et al*.[11]

bers of the research team working on the External Aortic Root Support (EARS) project. Since EARS is a recent entry into the list of options for Marfan aortic root surgery, the number of patients operated upon and the time scale over which they have been followed,[10] are both small compared with more established form of surgery. Nevertheless, it is at this stage that we have to consider what are the reasonable comparisons that should be drawn from this initial experience and what forms of future evidence will we need to accumulate to establish the role of EARS in the modern era.[14]

The decision to offer surgery is based on the diameter of the aorta and whether it is enlarging, with the passage of time. The rate of change and the presence of a family history of dissection are known to make dissection more likely in the individual patient under consideration.[15-17] The advice given must include consideration of the adverse consequences of having aortic root surgery and the life time hazard associated with the specific operations (Figures 2, 3).[18, 19] Advice should also include considerations of other features of a patient's life, such as the anticipation of a having a normal pregnancy and continuing to enjoy sports and other physical pursuits.

Given that the wishes of the patient are paramount, quantitative analysis of the pros and cons of different clinical management options would be useful and the application of decision analysis seems appropriate.[17] However, it has to be said from the outset that this approach has inherent limitations in this context due to the lack of directly comparable evidence related to contemporary natural history and recent innovations in the field.

Included in any non-operative or preoperative strategy should be beta-blockade and in due course evidence from the Aortic Irbesartan Marfan Study (AIMS) may guide practice in medical strategies to reduce aortic dilatation.[20]

Survival prior to prophylactic aortic root surgery

If a claim is to be made for the benefit attributable to any intervention, it is essential to know what would have been the outcome of the disease process in the absence of any intervention. That is traditionally known as the "natural history" of the disease. The classical study of the natural history of Marfan syndrome is that from Murdoch *et al.* from Johns Hopkins Hospital, Baltimore, USA published in 1972 - nearly 40 years ago.[1] They had data on 74 deaths in people diagnosed as having Marfan syndrome. Their average age at death was 32 years and most could be directly attributed to the disease affecting the ascending aorta. At that time the authors estimated that for a 20 year-old there was a nearly 50% chance of death by the age of 46. Faced with these data it was evident that death at young age was the most likely outcome for people with Marfan syndrome. That surely remains the case but nature is not now allowed to run its course so we

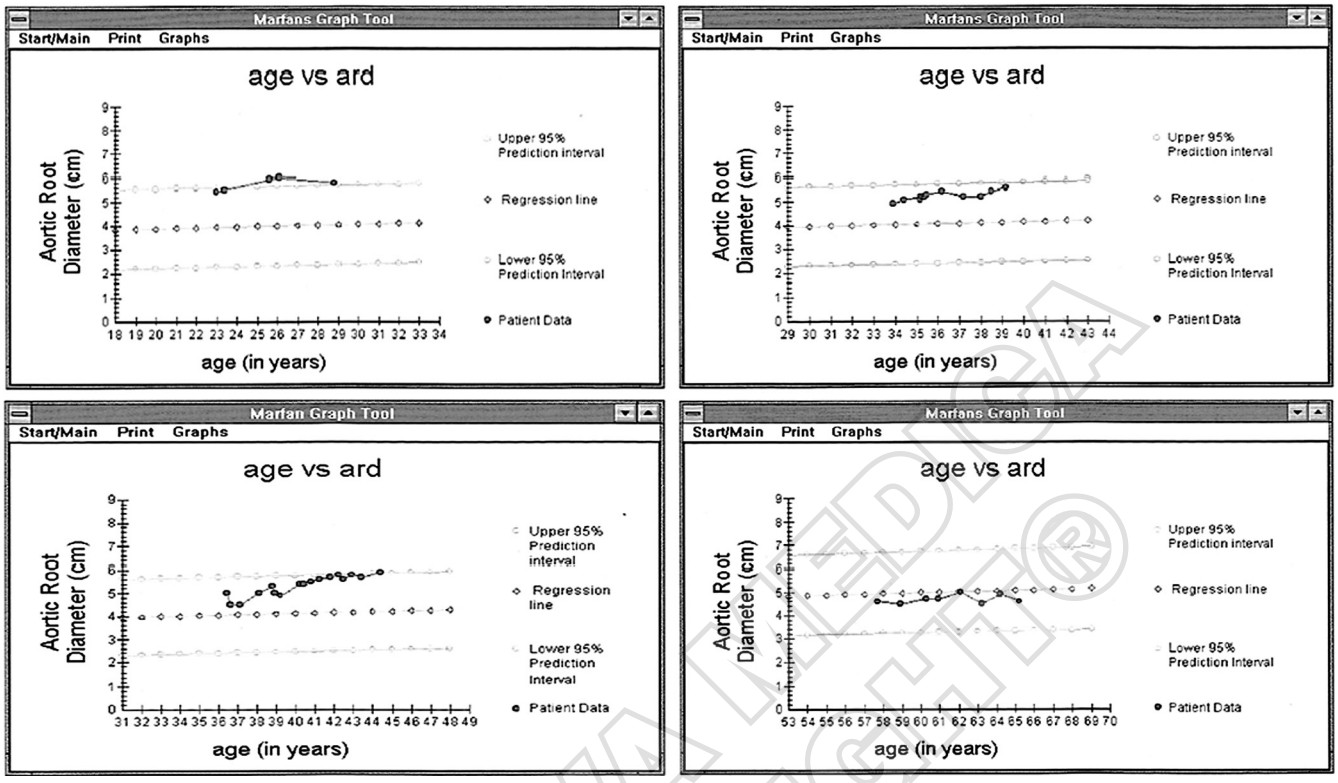

Figure 2.—From Treasure T *et al*.[25] The individual panels show screen shots of the output of a computer based decision aid for individual patients. These were all patients having elective aortic root replacement and the charts were constructed retrospectively in the development of the decision aid. In current practice we anticipate that the decision to operate would have been made earlier and would have curtailed the period of monitoring. In all cases the patient's echo measurements are superposed on a nomogram. The plot displays the expected diameter of the aortic diameter from regression analysis of age *versus* aortic diameter, with upper and lower prediction intervals, for patients of that age and height. A) A patient with an aortic diameter reaching 6 cm who had been followed without intervention from 23 to 29 years of age; B) a patient with increasing aortic diameter over five years from age 34 to 39 years; C) a patient whose aorta was increasing over eight years of monitoring. As can be seen here and subsequently confirmed in formal duplicate measurements of the aorta, there is considerable read-reread variation quite apart from technical and physiological variation in aortic measurement.

have to rely largely on data acquired in the presurgical era.

Early surgical experience

The advances in aortic surgery published by Cooley *et al.* in 1966 [21] and the case report of total root replacement in for Marfan syndrome in 1968 [2] offered an opportunity to change the outcome for these people. As operative risk reduced, the case for elective replacement was strong. Early recommendations suggested a threshold aneurysm diameter of 6 cm, above which operation was considered justified on the grounds that the risk of rupture appeared to rise abruptly beyond that size.[22] That decision threshold of 6 cm still appeared in Gott's series from Johns Hopkins reported in 2002.[23] It should be emphasised that this measurement relates to the diameter at the widest point in sinuses of Valsalva and more precisely, in recent work, to the diameter at the level of closure of the aortic cusps.[9] Our own observational data from an echocardiography database showed a strong statistical relationship between size and dissection [24] without an obvious threshold.

During the 1990s as echo measurement became routinely available, and surgery became safer, surgery for Marfan related aortic root aneurysms was offered at progressively lower aortic size. In a British Heart Journal editorial in 1993 the suggested thresh-

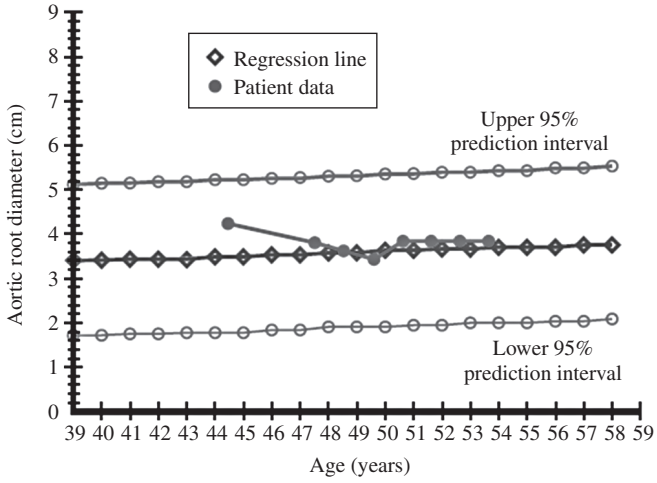

Figure 3.—Reproduced from Treasure T *et al*.[16] This patient with measurements taken from when he was 44 to when he was 54 had an aortic root diameter of about 40 mm without increase and did not reach our criteria at that time for aortic root replacement.

old on the ground of size alone was 5.5 cm [15] and in 2002 the question of replacing the root before it reached 5.0 cm was proposed.[16] It should be noted that that a number of European surgeons were performing elective replacement well below those sizes. Among other factors generally considered to be important are the rate of change in diameter and the presence of a family history of dissection.[15-17]

To aid discussion with patients a decision support tool was developed in which an individual's sequential aortic root diameters were superposed on a chart of age related change in Marfan aortic root diameter for patients of similar height (Figures 2, 3).[25, 26] It must be remembered that as root replacement has become widespread, and something of a matter of routine, the true natural history in the absence of surgery and in the era of modern monitoring, is no longer attainable.

Composite root replacement with a mechanical valve (TRR)

The original total root replacement as described by Bentall [2] and as practiced until the mid 1980s [3] required pre-clotting of unsealed graft material and incorporation of a valve hand sewn into the tube graft. This changed as presealed material became available followed by factory-made composite grafts during the late 1980s. In the early days an inclusion technique was used: the coronary orifices were sutured *en face* into the graft and the native aorta wrapped around the tube graft. Precise anastamosis of the coronary arteries with an aortic button obviated the need for an inclusion technique and the operation became standardised and highly reproducible. Criteria for elective root replacement were established.[15]

A recent systematic review and meta-analysis provides the most comprehensive summary of outcomes for total root replacement (TRR).[18] The review includes seven publications spanning 1971 to 2006 reporting a total of 972 patients whose average age was 35 years at the time of surgery. It is important to note that the authors were unable to extract data on the aortic root dimension prior to surgery. Also the rate of change, the degree of any aortic regurgitation, and family history of dissection were not retrievable from the data provided, all considerations in recommending such surgery.[15]

Mortality for elective cases in expert hands is low. In collected worldwide series of 455 elective operations 30 day mortality was 1.5% [27] and in the Johns Hopkins experience there were no deaths in 235 consecutive root replacement operations for Marfan syndrome.[23] In the meta-analysis calculated estimates of the thromboembolic hazards associated with a mechanical valve were 0.7% per year, endocarditis 0.3% per year, re-intervention 0.3% per year and composite valve related events 1.3% per year.[18] For a 20 year old this translates into a 65% probability of a valve related event in addition to a day in day out concern with treading a path between thrombosis and bleeding.

While excellent reproducible results are obtained with the "modern Bentall" operation, these young patients are committed to a life long risk of valve related thromboembolism and an accompanying fear of bleeding from the anticoagulation required to minimise that risk. Neither the authors of the meta-analysis [18] nor of the decision analysis [17] were able to estimate the impairment of health related quality of life attributable to these factors but ideally they are needed for the purposes of any future analysis and particularly for a thorough incremental cost-effectiveness evaluation.

Composite root replacement with a tissue valve

There is a review on this question but it does not relate directly to Marfan patients and is of-

fered as an option for older patients. The average age of patients in the largest series (N.=275, 74% of patients) was 69 years.[4] Follow-up was on average under three years which is insufficient to give any realistic impression of the lifetime requirement of Marfan patients. In this context the authors saw root replacement with a tissue valve as a means of avoiding the need for anticoagulation in older patients undergoing root replacement for degenerative disease. It does not appear to have useful place in Marfan syndrome.

Valve sparing root replacement (VSRR)

Yacoub [5, 7] and David [6, 8] pioneered means of conserving the aortic valve while excising the aortic root. These operations have been through numerous iterations, each seeking to correct the failings of an earlier version. Such experience is often described as a "steep learning curve". If what we are intended to visualise is the trajectory of curve depicting repeated experience towards a plateau of reliability, such learning curves might be better described as flat, or even faltering.

Valve sparing root replacement is a much more time consuming operation than standard composite root replacement with a manufactured composite graft, relying heavily on skill and judgement. Drawing an analogy from the writing of the late David Pye, a Professor of furniture design at the Royal College of Art [18-28] what had become in the modern Bentall close to "the workmanship of certainty" in which the quality of the result is mechanically predetermined and less in the control of the operator, valve sparing root replacement takes a step back to the "workmanship of risk" which relies heavily on skill and experience. This is a concern for many excellent surgeons who recognise that the certainty of the result is more important to the patient than their own creative flair.

The systematic review [18] includes data on a total of 413 patients of average age 33 patients having valve sparing surgery in six reports spanning 1993 to 2006. The patients are a little younger than others in the analysis and the clinical series start 20 years later. Both of these might bias the results in favour of VSRR and any direct comparison must be made cautiously.

The re-intervention rate, probably largely for valve failure, was 1.3% per year which, within the limits of the meta-analysis, was independent of follow up duration. This means that by 20 years more than a quarter of patients who have had valve sparing surgery might need further aortic valve surgery and at best only half of them are likely to complete their life span without another aortic root operation. The thromoembolic event rate was 0.3%/year and the endocarditis rate was 0.2%/year. These were lower but not significantly so compared with TRR and notably were not zero. The composite valve related event rate for VSRR was 1.9%/year, significantly greater than TRR. For a 20 year old hoping for a full life span this translates into a 95% probability of a valve related event.

External aortic root support (EARS)

The proposal for this innovation came from the floor at the annual meeting of the Marfan Association from an engineer (TG) with inherited Marfan syndrome.[13] He proposed that the quality of modern imaging should allow the manufacture of an exact replica of an individual's aorta by the process of computer aided design and that could be used to manufacture, by rapid prototyping, a physical model of the aorta. This model provides a former on which a support is then made of porous vascular graft material. This is all prepared before operation and the surgeon then embarks on a fully planned operation in the spirit of the "workmanship of certainty". The support is positioned around the aorta, from the aortoventricular junction proximally, to beyond the brachiocephalic artery distally.[9]

Data on EARS are limited.[10] The first operation was done in 2004 and there are now 25 patients. The median time since surgery is 44 months at the time of submission of this paper. At the time of writing, all patients are alive and well. Myocardial ischaemia and cardiopulmonary bypass are avoided. Perioperative use of blood products is largely eliminated (Treasure T, Crowe S, Chan K, Ranasinghe A, Attia R, Lees B *et al*. Aortic root replacement compared with external support of the ascending aorta in Marfan syndrome: differences in use of cardiopulmonary bypass, myocardial ischaemia and blood products. Submitted 2011). The valve and the blood endovascular interface are entirely undisturbed.

Choosing between the options

In the context of evidence based medicine, the standard answer to the question of how to choose between interventions is to run a randomised trial. Were they available, directly comparable outcomes for patients allocated at random might make the decision clear but such trials do not exist. Even if the obstacles to running a trial were to be surmounted, the primary outcome of interest, that is the relative death rates from dissection, would take many years to accrue. There are also many other variables. The timing of surgery may be dependent on which surgical option is to be used so it is difficult to construct a direct comparison. The complex interplay of the consequences of mechanical versus tissue preserving strategies [29] might make a like with like comparison never possible. Whatever is the eventual answer to the difficult conundrum [14, 30] we have to decide how to advise our patients in the meantime.

It must also be remembered that, as root replacement has become widespread and something of a matter of routine, and there have been advances in other fields such as medical management and modern monitoring, the true natural history in the absence of surgery cannot be assessed directly. Outcomes with surgery have improved both in terms of perioperative risks and postoperative complications. There is no longer a simple decision of opting for surgery or not, but a choice between three or four operative strategies. Patients can be informed of many issues associated with these different forms of surgery and what follows [18, 19] because that has been documented in follow-up studies. One thing they cannot be given is an accurate prediction of the chances of dissection, or the years for which they will be free of dissection if no operation is performed. In decision analytic terms, this is akin to knowing the returns from making a winning bet but not what the stake is.

The analysis of health benefits for therapeutic and prophylactic operations are very different. A simple way of considering this is the "number needed to treat" (NNT) statistic. In a young patient with an aneurysm of 7 cm and growing we might reasonably anticipate that death due to this cause approaches 100% and the number needed to treat to achieve benefit would be one. Most operations are not that effective and the natural history often uncertain. The number needed to treat becomes much greater when the strategy is prophylactic. So for example carotid endarterectomy is performed to prevent stroke. The NNT is 6 for 70-99% carotid stenosis and rises to 24 for 50-69% carotid stenosis.[31, 32] These data are based on randomised trials where we can be sure that like is compared with like at the time of randomisation and that thereafter outcomes are collected fastidiously in both arms. Often (and this is the case with root replacement for Marfan syndrome) we have to glean data from where we can.

There has been an attempt to carry out a formal decision analytic assessment based on threshold aortic dimension, and change within the last year, that triggers consideration of surgical intervention for patients with and without a family history.[17] This deserves attention in that addresses the options in a formal and explicit way. When the authors came to populating the model with data on the risk of aortic dissection or rupture without prophylactic aortic root surgery they found no literature available for this quantity – one that is central to the decision analysis. To be fair, echo measurement were not available in an earlier era and in contemporary times most root diameters above an ever lowering threshold would already have been acted upon, possibly well before dissection was a likelihood. Lacking these data, the authors constructed a questionnaire which was completed by five colleagues who were invited to estimate the probability of aortic dissection for a 20 year old patient with aortic diameter 3, 4, 5, 6 or 7 cm, increase in the preceding year of 0, 2, or 5 mm, with and without a family history. The respondents returned 30 estimates each for the probability of dissection within a year. The range of estimates is reported. The average of the five was used in the decision analysis. Estimated probabilities ranged from 0.1% for a 3 cm aorta, with no annual increase to 55% for a 7 cm aorta, increasing by 5 mm, with a family history of aortic dissection.

The summary recommendation is that early prophylactic surgery would be offered to any patient with an aortic root diameter of 3 cm or greater.[17] This recommendation pushes for even earlier prophylactic surgery than anything we are aware of to date and appear at odds with the outcomes from the model that led up to it. According to estimates of survival derived from the model the expectation of life was extended from 71.4 years to 73.8 which seems both an optimistic expectation the non-surgical outcome and a very modest gain, given that the Johns Hopkins pre-surgery data were that 50% died but mid forties.

The approach adopted by the authors is known to have its limitations [31] but that apart, the output of the model does not fit with clinical experience. We applaud the overall effort but would want to revisit the detail before relying on it.

Discussion

The first point for discussion is the threshold at which watchful waiting should be curtailed in favour of a surgical intervention to prevent dissection. The question has been revisited by decision analysis and the conclusion is to further reduce the aortic size at which surgery is recommended for those with Marfan aortic root morphology to 3 cm. It may be that a more applicable rule might now be that in a patient with a Marfan phenotype which includes a Marfan morphology of the aortic root, prophylactic surgery should be offered once adult size is attained.

As far as health economic evaluation is concerned the operative costs are broadly similar for all of these operations. The patients are typically young without significant comorbidity. NHS reference costs for complex valve surgery are of the order of £ 12000. Surgeons in other countries will need to use their own local costings. Amortised over the potential lifetime of a patient this is inexpensive for what is regarded as life saving surgery. An additional complication is that for both cost and health outcomes extending beyond one year it is standard practice to apply a discount rate (a weighting) on these deferred impacts. Discounting is a technique used to reflect the observation that people prefer to receive goods and services now rather than later. (And defer costs to later time periods). This is known as "time preference". Currently UK's National Institute for Health and Clinical Excellence (NICE) applies a 3.5% annual discount rate for both health benefits and costs.

However, if as the threshold for operation comes down, an increasing number of those operations would have proved to be unnecessary if we were able to capture the natural history in that aortic dissection would not have occurred during the life time of the patient. The number needed to treat will escalate and so the cost per added quality adjusted life year will rise. Also the ongoing costs of anticoagulation and further surgery, and the detrimental effects of stroke, bleeding and anticoagulant therapy, must all be calculated. An individual destined to never dissect is disadvantaged considerably by root replacement and particularly by loss of the aortic valve. If tissue valves are used in young patients there is an inevitability of tissue valve failure well within the expected life of the patient.[29, 33]

In considering the relative merits of mechanical valve replacement versus valve sparing surgery, there is very little difference in the objective data in the meta-analysis [18] while the decision analysis previously described offers results that appear to favour valve sparing.[17] As the authors concede, however this decision analytic model ignores the impact on health-related quality of life for both positive and negative health outcomes for all the alternatives considered. Nevertheless, if we take account of the burden of anxiety and disruption of life resulting from anticoagulation the balance would swing in favour of valve sparing. Neither is a perfect solution however and both leave the rest of the Marfan affected aorta as it was before and some of these patients will represent with dissection in the arch or the descending aorta. The need for anticoagulation certainly adds complexity but the coexistence of a failing aortic valve would also add complexity to the clinical problem.

Our own perspective is that external support achieves all that can realistically be expected of the ideal valve sparing operation, save for one thing: it leaves the diseased aortic tissue where it is. It is recognised that the proximal aorta and in particular the sinuses of Valsalva are the most prone to dissection and it has become generally accepted that the replacement of the aorta from the aortoventricular junction to beyond the sinotubular junction is an essential component of preventative surgery. What is rarely considered is that the operation reported in 1968 [2] was undertaken to replace the aortic valve for severe symptomatic and life threatening aortic regurgitation. The surgeon encountered "a large globular dilatation of the ascending aorta. Its bulging inelastic wall was so thin that blood could be seen eddying within." No size is given but on pathological examination the aortic wall was considered to be 1/10th of normal thickness. Replacement of the aorta was an intraoperative decision, undertaken because the surgeon could see no hope of suturing a tube graft distal to the coronary arteries as then advocated by De Bakey's group.[21] Bentall therefore took the innovative step of anchoring the tube graft to the robust sewing ring of a Starr Edwards prosthesis thus

showing that exclusion of all of the vulnerable part of the aorta could be achieved, including the tissue between the aorto-ventricular junction and the coronary orifices.

The surgery has been progressively refined and modified over the intervening forty years [3] but common to all the modifications through composite grafts with mechanical and then tissue valves and more recently valve sparing surgery, has been exclusion or eradication of the aortic wall. It remains uncertain whether the initiating lesion of aortic dissection is intramural haemorrhage into the diseased media or the transverse tear in the aortic intima, but it is characteristically in the area where the aortic dimensions have departed most from normal. While a small aorta can dissect and a remarkably large aorta remain undissected, the absolute size and the rate of change are the predictors clinically used [254, 26] as has been re-emphasised in the decision analysis. However, as aortic root surgery became safer in terms of the risk of perioperative death, it became appropriate that prophylactic surgery was advocated at smaller and smaller size.[15, 16] Indeed, it can be argued that as soon as the aorta displays the characteristic Marfan morphology, the patient should be protected from the risk of dissection, provided the operation carries very low early and late risks. Somewhat to our surprise that was the conclusion of the decision analysis for root replacement surgery if the decision point is as low as 3 cm.[17] Aortic root surgery in all the versions under consideration is therefore truly prophylactic: it is employed before the aortic disease is clinically manifest, the patient is asymptomatic as far as the cardiovascular system is concerned, and the purpose of the operation is the prevention of dilatation and dissection originating in the most vulnerable part of the aorta and aortic regurgitation.

For aortic root replacement in Marfan syndrome, low risk of perioperative death has been achieved but the trade off of all risks *versus* lifetime benefit is not straightforward. Every part of the calculation introduces uncertainty: the knowledge on which we base our estimates of the likelihood of fatal dissection are from over forty years ago, they were based on patients presenting with clinically evident disease, and in the decision analysis they were provided as opinion from five individuals.

We are now considering surgery in young asymptomatic people, many of whom are screened for the disease and who undergo an operation in the hope of a full and active life. How many would have had experienced dissection? How many who are saved from dissection in the most vulnerable area will have aortic dissection elsewhere? A contemporary teenager might expect a further 60-70 years of life. The time scale over which adverse events should ideally be counted (both in their health impacts and costs) is as long as the period during which we assume benefit. In this paper we have been unable to provide robust answers but have attempted to frame the salient questions.

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