Long-term follow-up of patients with the antibiotic-sterilized aortic homograft valve inserted freehand in the aortic position


ABSTRACT A series of 252 isolated aortic homograft valves in 248 patients have been followed for 9 to 16.5 years (mean 10.8). The valves were sterilized in antibiotic solution and stored in a nutrient medium at 4° C and were nonvital. There were 15 in-hospital deaths (6%) and a mortality of 2.7% in patients undergoing an elective first operation. Actuarial survival with the study valve in situ was 57% at 10 years and 38% at 14 years. Only 8.4% of the patients died late from homograft valve failure, chiefly because of failure to refer patients with endocarditis for reoperation or because reoperation was refused in elderly, frail subjects. Incompetence was the sole cause of valve failure and was due either to valve wear or endocarditis. Significant incompetence required reoperation. On actuarial analysis, freedom from significant incompetence for the entire group was 95% at 5 years, 78% at 10 years, and 42% at 14 years. Factors increasing the risk of significant incompetence due to valve wear on multivariate analysis were increasing donor valve age (&ge; 55 years), recipient age (< 15 years), and an aortic root diameter over 30 mm. Analysis of the patient group that excluded each of these variables (low-risk group), which comprised 61% of the study population, indicated freedom from significant incompetence due to valve wear of 98% at 5 years, 94% at 9 years, and 56% at 13 years. Circulation 75, No. 4, 768–777, 1987.

FREEHAND INSERTION of an aortic homograft valve in the subcoronary position was first performed in 1962.1,2 The earliest valves inserted at Green Lane Hospital were collected by sterile technique (untreated or fresh valves) but for logistic reasons sterile collection was soon replaced by chemical sterilization of valves removed at routine autopsy. Chemical sterilization was abandoned in August 1968 because of the high incidence of valve failure and was replaced with the antibiotic sterilized aortic homograft valve (ASAHV).3 The short- and midterm clinical results with the ASAHV were superior to those with chemical sterilization and similar to those with untreated homograft valves.4 The purpose of this report is to analyze the late follow-up results of the ASAHV, with particular reference to the incidence and causes of homograft valve failure.

Patients and methods

Between August 1968 and December 1974, a total of 506 isolated aortic valve replacements (prosthetic 113 [22%], homograft 393 [78%]) were undertaken. During this period the ASAHV was the valve of choice and was inserted in almost all patients regardless of aortic valve and root pathology by the two most experienced surgeons in the group of five who operated on these patients. Prosthetic valves were mostly used by the less experienced surgeons and in some of the repeat operations. The 248 patients who received ASAHVs and resided within 150 miles of Green Lane Hospital were selected for detailed review. This geographic area was chosen to improve the quality of the follow-up. The nine patients with stent-mounted ASAHVs were excluded, as were those who received surgical attention to either the mitral or tricuspid valves or a coronary artery bypass graft at the same operation. Patients who had had previous valvular surgery, including aortic valve surgery, were included.

The 248 patients received 252 ASAHVs; in four patients a second ASAHV was inserted during the study period and became a new study valve. There were 174 male and 74 female patients, aged 10 to 76 years (mean 51.1). At the time of operation, 65% were aged 50 years or older. The aortic valve lesion was pure or dominant stenosis in 128 instances, pure or dominant regurgitation in 108 instances, and combined aortic stenosis and regurgitation in 16. Thirteen patients (5%) were in NYHA class I, 131 (52%) class II, 18 (7%) class III, and 74 (29%) class IV. Sixteen patients (6%) were terminally ill (class V) and underwent emergency valve replacement. Seventy-two patients had angina, 108 had syncope or presyncope, and 47
(19%) had evidence of congestive heart failure. The electrocardiogram showed severe left ventricular hypertrophy in 200 patients, moderate hypertrophy in 34 patients, and less than moderate hypertrophy in the remainder.

Sixty-one (24%) had had previous operations on their aortic valves, which included homograft valve replacement (n = 55), prosthetic valve replacement (n = 2), valvotomy (n = 3), and Bahnson leaflets (n = 1). Associated lesions included proven coronary artery disease (n = 16), ventricular septal defect (n = 3), coarctation (n = 6), and patent ductus arteriosus (n = 1). Routine coronary arteriography was not undertaken over the period that these patients were operated on.

Surgical technique. The surgical technique for freehand insertion of the ASAHV has remained essentially unchanged throughout our experience and uses double continuous suture lines to approximate the upper and lower cut margins of the aortic wall remnant of the graft to the host aortic root plus vertical mattress sutures beneath the valve commissures to obliterate the major portion of dead space between graft and host. Aortic root tailoring, which involved excision of a wedge of the aortic root to allow a proper match with the available homograft valve when the root was excessively large (or occasionally when larger valves were unavailable) was done in 19 patients (7.5%). The myocardium was protected during the period of aortic cross-clamping by continuous perfusion of both coronary arteries with blood at 30°C. Every effort was made to keep the heart beating throughout the procedure.

Homograft valve preparation. The 252 aortic valves were obtained from 160 male and 71 female cadaver donors. Donor sex was not recorded in 21 instances. Donor age ranged from 11 to 73 years. In particular, seven donors were over 65 and 28 were 55 to 65 years old. The commonest causes of donor death were trauma (n = 147), malignancy (n = 24), and poisons or drugs (n = 20). Almost all causes of death were accepted other than septicemia and jaundice. The salvage time between death of the donor and autopsy was under 24 hr in 114, 24 to 48 hr in 88, and 49 to 75 hr in seven. Salvage time was not recorded in 43. The valves were sterilized and stored at 4°C, initially in Hanks’ balanced salt solution, to which was added 50 U of penicillin, 1 mg of streptomycin, 1 mg of kanamycin, and 25 U of amphotericin B per milliliter of solution, but after 7 days the valve was transferred to Hanks’ solution without antibiotics. About halfway through the study period, nutrient medium 199 was substituted for the Hanks’ solution. The valve was accepted for use when bacterial and fungal cultures showed it to be sterile and the donor serum was hepatitis antigen negative. The valves were used within as short a time as possible; storage time was 8 to 19 days in 86, 20 to 50 days in 128, and more than 50 days in 38. Most, if not all, were therefore nonvital at the time of insertion. Valves with significant abnormalities such as major leaflet fenestrations, naked eye calcification, or a congenital abnormality were rejected, but minor imperfections were accepted in 43 instances.

Follow-up protocol. All survivors have been reviewed periodically either by Green Lane Hospital cardiologists (59%) or by the patient’s own cardiologist or practitioner (39%). Only two patients (0.8%) had to be contacted by telephone and only two were lost to late follow-up after 19 and 48 months, respectively. Follow-up was considered to be complete at the time of reoperation and removal of the study valve, at late death with the study valve in situ, or at last follow-up in survivors with their study valves in situ. Death after removal of the study valve, however, has also been recorded in order to construct an actuarial survival curve regardless of whether the ASAHV remained in situ. All survivors with their study valves in situ were reviewed between July 1982 and December 1984 and had a minimum follow-up of 9 years and a maximum of 16.5 years (mean 10.8). The mean follow-up until the time of censoring in all 237 hospital survivors was 8.3 years.

Homograft valve failure was diagnosed when there was evidence of clinically significant (moderate or severe) homograft valve incompetence according to criteria previously reported. Thus an aortic early diastolic murmur alone was not considered indicative of valve failure unless it was associated with signs of a significant valve leak as judged by the pulse pressure and character of the pulse. The time of censoring for significant incompetence was the date of reoperation or late death from this cause, or last follow-up in the remainder. The two patients lost to late follow-up were censored at the date of their last review.

An attempt was made to identify the cause of valve failure in each patient with significant incompetence. Valves failed as a result of cusp rupture or a central leak (retraction or malposition or prolapse of cusps or cusp separation due to progressive aortic root dilatation) or peripheral suture line leak, or after endocarditis. In some patients with significant incompetence, the valve could not be examined and hence the cause was unknown. In this group most had the clinical features of cusp rupture. Significant incompetence due to cusp rupture or central leak or by unknown causes were all considered the result of cusp wear, i.e., primary failure of the homograft valve leaflet.

Patient survival and valve failure data were analyzed with contingency tables and Kaplan-Meier actuarial curves. In addition, multivariate analysis of the discrete and continuous variables that could have influenced valve function and failure due to valve wear was made with the Cox proportional hazards model. Variables relating to the recipient included age, sex, race, type of lesion, underlying etiology, aortic root size (and therefore donor valve size), need for aortic root tailoring, calcification, and previous aortic valve surgery. Variables relating to the donor valve included age, sex, cause of death, salvage time, storage time, type of storage solution (Hanks’ or nutrient medium), and presence of minor imperfections in the valve. The actuarial and multivariate analyses of valve failure due to cusp wear included, by definition, significant incompetence from cusp rupture, central leak, or unknown cause only. Significant incompetence known to be due to either late endocarditis or peripheral leak was excluded since these causes were not related to valve wear and are common to all valve replacement devices.

Results

Early mortality and morbidity (30 day). There were 15 hospital deaths (6%), eight in critically ill emergency patients (class V) and seven at a reoperation (five of which were also class V). The 30 day mortality in patients undergoing an elective first operation was 2.7% (five deaths in 183 operations). In contrast, the mortality when the operation at entry (i.e., between August 1968 and December 1974) was a reoperation was 13%, and that for a class V patient was 50%. Myocardial failure and cerebral damage accounted for the majority of deaths (table 1). The incidence and causes of significant in-hospital morbidity are shown in table 2.

Late results

Survival. There were 111 late deaths (47%) in patients with a study valve in situ. These occurred between 1 and 175 months (average 83) after surgery at an average patient age of 65.7 years. Actuarial survival in this
group, including in-hospital mortality, was 77% at 5 years, 57% at 10 years, and 38% at 14 years (figure 1)

When patients undergoing reoperation for significant incompetence were not censored at that time but rather at the time of subsequent death or last follow-up (December 1984), actuarial survival was identical at 5 and 10 years but increased to 41% at 14 years. The two curves were therefore not significantly different. The causes of late death, with the study valve in situ, are listed in table 3. Thirty-three patients underwent autopsy. Seventy-five (68%) of the 111 deaths were known to be cardiac in origin. Those dying from myocardial infarction were known to complain of angina, and those listed as dying suddenly were not. "Cardiomyopathy" was reserved for patients dying in heart failure with cardiomegaly in the absence of significant valvular disease. Nine patients died from a stroke (at the ages of 67 to 78, mean 72) and one from cerebral damage sustained perioperatively. In six instances, patients dying from one of the above causes had moderate homograft valve incompetence that was not life-threatening (table 3).

Only 8.4% of the study group died from homograft valve failure. Eight of these 20 patients had acute infective endocarditis. One death was caused by a candidal infection (Torulopsis glabrata) first recognized 12 months postoperatively and subsequently cured with antibiotics and reoperation. The patient died of heart failure 6 months after the second homograft valve was inserted, secondary to extensive embolic coronary artery occlusions and infarctions. At no time was there significant incompetence. Another patient with bacterial endocarditis died of embolic cerebral abscess, also without significant incompetence. None of the other six patients dying from active endocarditis and significant incompetence were referred for consideration of reoperation, and in only two was this management justified by the presence of severe cerebral complications. The seven patients who underwent reoperation for significant incompetence due to endocarditis (one still active and six subsequent to abolition of the infect-

TABLE 1
Causes of hospital death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>NYHA class</th>
<th>Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>II</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic aortic dissection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral damage</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multisystem failure</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

*a*Ruptured mycotic aneurysm in one, cause unknown in three.
*b*Five of seven in class V.

FIGURE 1. Actuarial survival curve for aortic valve replacement with an ASAHV with the study valve in situ. The bars represent 1 SE (70% confidence limits). The dashed line is survival of an age- and sex-matched population. The numbers at risk are noted.

TABLE 2
Causes of hospital morbidity

<table>
<thead>
<tr>
<th>Cause of morbidity</th>
<th>n</th>
<th>% of 252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postop. bleeding</td>
<td>17</td>
<td>6.7</td>
</tr>
<tr>
<td>Sternal dehiscence</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Other causes</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>Cerebral damage</td>
<td>16</td>
<td>6.3</td>
</tr>
<tr>
<td>Complete heart block</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Associated moderate homograft valve incompetence.
tion by antibiotic treatment) all survived. Seven patients dying from valve failure had cusp rupture and were not considered suitable for reoperation because of age (mean 77 years) and frailty or associated incurable disease. Five more patients (2.1%) died at reoperation for significant incompetence due to valve wear or peripheral leak.

Morbidity. At the time of censoring, significant incompetence was present in 76 (32%) of the hospital survivors. A further 89 (38%) had an aortic early diastolic murmur from trivial or mild aortic regurgitation, and 72 (30%) patients had no murmur. On actuarial analysis the incidence of freedom from significant incompetence from all causes was 95% at 5 years, 78% at 10 years, and 42% at 14 years (figure 2). The slope of the curve increased with time and indicated a valve failure rate of 1% per year for the first 5 years of follow-up, 3.4% in the second 5 years, and 8% in the final 4 years. Reoperation to replace the aortic homograft valve was carried out in 53 (22%) of the hospital survivors. Of these, 51 had significant incompetence. The other two had only mild aortic incompetence due in one to active endocarditis; in the other the major purpose of reoperation was to perform coronary artery bypass graft surgery. On actuarial analysis 93% were free of reoperation at 5 years, 79% at 10 years, and 54% at 14 years. Five patients died at reoperation (a 30 day mortality for reoperation of 9%). One of these deaths occurred elsewhere, while three of the four deaths at reoperation at our hospital occurred before 1974, giving a reoperation mortality from 1974 to 1984 of 2%. Significant obstruction of the aortic homograft valve was not recognized in any patient, although mild stenosis was noted in 28 (12%) at autopsy, reoperation for significant incompetence, or recatheterization. It was due either to patchy cauliflower-like leaflet calcification or to a subleaflet fibrous shelf caused by the insertion of a large valve in a smaller root.

Systemic embolism originating from the homograft valve was thought not to occur, since thrombi were never seen in relation to the valve at reoperation or postmortem examination, despite the fact that anticoagulation was not used routinely (15 patients did receive anticoagulants for deep vein thrombosis, atrial fibrillation, or transient ischemic attacks). However, 10 patients, eight of whom were over 60 years of age, had incidents that could have been embolic (excluding those with endocarditis). Two of these 10 patients had similar symptoms preoperatively and three were in atrial fibrillation. Most patients with minor strokes were thought to have internal carotid artery stenosis or vertebrobasilar insufficiency. Hemolysis was recognized in only one patient in association with cusp rupture.

Causes of valve failure. The frequency of the various categories of significant incompetence are listed in figure 3. On actuarial analysis the incidence of freedom from proven cusp rupture was 97% at 5 years, 86% at 10 years, and 64% at 14 years. Because incompetence from uncertain causes (unknown) was probably due almost entirely to rupture, a truer incidence combines these two and was 96% at 5 years, 81% at 10 years, and 46% at 14 years. Bacterial endocarditis was an uncommon cause of significant incompetence, 96% of patients being free of this complication at 5 years and 92% at 14 years. It was never associated with a
perivalvar leak, which, per se, was very rare (one patient), and it did not occur before 11 months postoperatively. Moreover, adequate antibiotic treatment usually cured the infection. The incidence of homograft valve endocarditis was similar with first, second, and third operations.

The actuarial analyses of the donor factors affecting the incidence of significant incompetence due to valve wear (excluding, therefore, bacterial endocarditis and peripheral leak) indicated no significant differences in donor sex, donor valve salvage time, or type of storage medium. Storage time was of borderline significance, with freedom from significant incompetence of 88% at 10 years when storage time was under 20 days and 65% when it exceeded 50 days (p = .06). The results were also less good when minor imperfections were present, with freedom from significant incompetence of 81% at 10 years when the donor valve was perfect compared with 59% when imperfections were present (figure 4), but this difference was not significant (p = .2). A highly significant factor was donor age (figure 5), with freedom from significant incompetence of 94% at 10 years when donor age was less than 20 years (representing only two examples of leaflet rupture at 106 and 113 months amongst 48 patients) and 62% when donor age was over 50 years.

Actuarial analysis of recipient factors affecting the development of significant incompetence indicated that a large aortic root became important (figure 6) when the diameter exceeded 30 mm (aortic root size being 2 mm larger than the internal diameter of the homograft valve). The diameters were those recorded after aortic root tailoring, which was performed in 19 patients. Significant incompetence due to valve wear (excluding endocarditis and peripheral leak) occurred in only three (18%) of the 17 survivors, indicating a satisfactory long-term result in this subset, particularly as the four patients alive with the study valve in situ at the time of censoring had either absent (n = 3) or only mild (n = 1) incompetence. Significant incompetence was more common in patients under 20 years of age, but the numbers in this group were small and the differences not significant on this type of analysis. Patients with aortic incompetence fared slightly worse than those with aortic stenosis or a combined lesion (p = .03). The degree of aortic root calcification, a previous aortic valve operation (almost all had been homograft procedures), or recipient sex or race did not influence the incidence of significant incompetence.

FIGURE 5. Actuarial incidence of freedom from significant incompetence in relation to age of donor providing the homograft valve. Same data set and format as in figure 4.

FIGURE 6. Actuarial incidence of freedom from significant incompetence in relation to aortic root diameter. Same data set and format as in figure 4.
On multivariate analysis the significant variables increasing the incidence of significant incompetence due to valve wear were donor age, aortic root size, and recipient age (table 4). Donor age was highly significant as a continuous variable (p = .004) and as a yes/no variable (> 50 years). However, the best split occurred at 55 years and older (p = .0002). Aortic root size was also significant as a continuous variable (p = .002), but the best split occurred at over 30 mm (corresponding to a homograft valve internal diameter of > 28 mm) (p = .0007). Recipient age was not significant as a continuous variable. It was of borderline significance when considered as a yes/no variable (< 20 years; p = .04) and only highly so when age was under 15 years. In fact, there were only five such patients (children), three of whom developed cusp rupture at 32, 59, and 118 months postoperatively. Leaflet calcification was not present. One of these had received a valve from a 60-year-old donor, presumably because a young valve was not available. In the total group, there was a weak relationship between patient age and donor age.

Those patients over 14 years of age who received a homograft valve from a donor under 50 years of age and with an internal diameter of 28 mm or less (aortic root diameter ≤ 30 mm) were grouped together as those least likely to develop significant incompetence due to valve wear (low-risk group). Twenty-six of these 144 patients, who composed 61% of the study group, developed significant incompetence at 44 to 181 months (mean 115) follow-up. The actuarial incidence of freedom from significant incompetence was 98% at 5 years, 87% at 10 years, and 62% at 13 years (figure 7). In this group of patients there was a sharp increase in the incidence of significant incompetence after 9 years, for at 9 years the incidence-free figure was a striking 94% (± 2.3). In contrast, the 93 patients who were either under 15 years of age or who received a homograft valve from a donor of at least 50 years of age or with an internal diameter over 28 mm (high-risk group) showed an actuarial incidence of freedom from significant incompetence of 90% at 5 years, 65% at 10 years, and 40% at 13 years. The difference between the two groups was highly significant (p = .0001). The total incidence of significant incompetence was obtained by adding that caused by bacterial endocarditis (and the single example of peripheral leak); in the low-risk group the total was 95% at 5 years and 90% at 9 years.

Discussion

In this series of patients receiving a nonvital antibiotic sterilized homograft valve, the unrestricted selection of patients for this procedure has made it possible to examine numerous factors that might influence the rate of degeneration, and thus the long-term homograft valve function, by standardized techniques of valve insertion and antibiotic sterilization. The long duration and the completeness of the follow-up, plus the fact that the assessment of valve function was based on clinical examination rather than patient interview by telephone, are favorable features. Moderate as well as severe homograft valve incompetence was considered significant since the former invariably progressed to the latter, although this often took many months and did not necessarily require reoperation during the period of review. Fortunately, the clinical differentiation between hemodynamically insignificant (trivial and mild) aortic incompetence and the more severe degrees is seldom incorrect. The fact that the time of censoring

TABLE 4
Significant variables (incremental risk factors) increasing the risk of significant homograft valve incompetence using the Cox proportional hazards model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age ≥55 yr</td>
<td>1.12 ± .30</td>
<td>.0002</td>
</tr>
<tr>
<td>Aortic root size &gt;30 mm</td>
<td>1.39 ± .41</td>
<td>.0007</td>
</tr>
<tr>
<td>Recipient age &lt;15 yr</td>
<td>2.03 ± .61</td>
<td>.0008</td>
</tr>
</tbody>
</table>

n = 228. A p value of < .05 was required for entry into the model. A better fit was obtained when these variables were categorized (rather than continuous). This process has exaggerated the p values, which should therefore be reduced somewhat, although they remain highly significant.
for significant homograft valve incompetence was re-
operation or death from this cause rather than its first
appearance means that most classed as moderate were
patients still alive without reoperation at last follow-
up. This is the main explanation for the differences
between the actuarial incidence of reoperation vs sig-
nificant incompetence in patients followed beyond 10
years.

The in-hospital mortality in this precardioplegic era
was low overall (6%) but high (50%) in the 16 emer-
gency procedures. For the entire set of homograft op-
erations (n = 393) for the time frame under considera-
tion (1968 to 1974) the mortality for emergency pro-
cedures (n = 26) was 38%. These figures can be
compared with the in-hospital mortality for the current
cardioplegic era (1980 to 1986, n = 348) of 1.7%
overall and 12.5% for emergency procedures (n = 16).
The slightly longer time taken to insert a homo-
graft valve when compared with a prosthetic device is
not considered to be a contraindication to its use in
emergency situations.

The late survival of patients with the study homo-
graft valve in situ (that is, censoring each patient hav-
ing a reoperation when this occurred) is very similar to
that reported for the Starr-Edwards valve, although
such comparisons are not valid unless patient selection
is similar. Of particular interest is the number of
patients dying from valve-related complications. In
contrast to a prosthetic valve, for which valve-related
deaths have a variety of causes (thromboembolism,
valve occlusion, hemorrhage from anticoagulants,
structural failure, and early and late endocarditis), the
only homograft valve complication leading to death (as
well as morbidity) is the appearance of significant in-
competence. Fortunately, when caused by valve wear,
this failure mode is benign, and late-appearing aortic
diastolic murmurs may be associated with mild incom-
petence for 2 or more years before progressing. Thus,
in contrast to the bioprosthetic porcine glutaraldehyde-
treated device, the late onset of a diastolic murmur is
not an indication for early reoperation, which should
be delayed until the leak is significant. Moreover, the
mortality of reoperation has been low in our hands
since 1974.

In this series, only 8.4% of the hospital survivors
died later from significant incompetence. It is of inter-
est that four of these 20 deaths were caused by late
endocarditis that was improperly managed, so that cur-
rently such deaths should be less frequent. Moreover,
six other deaths occurred in elderly patients in whom
reoperation for significant incompetence was not con-
sidered appropriate. This might be considered by some
as a contraindication to the selection of a homograft in
elderly patients rather than a more durable prosthesis.

It is thought to be justified not to attribute death from
stroke in these patients to thromboembolism for the
reason that thrombus has never been found in relation
to a homograft valve in this or other reported se-
sies. The figure of 3.8% late death from stroke in
an elderly group of patients is not untoward and sug-
gests that a similar percentage of stroke deaths occur-
ing in elderly patients with prosthetic valves may not
be thromboembolic in origin. This present series
would also suggest that late sudden death is not throm-
boembolic in origin but is due to arrhythmia, ischemia,
or some other mechanism.

Significant homograft valve stenosis has not occu-
pred in this series because the valve can be inserted
in small aortic roots without a gradient and because
leaflet calcification is uncommon and, when present,
occurs as discrete, small, bony, cauliflower-like spic-
ules that have only a minor effect on leaflet movement.
They predispose, however, to leaflet rupture, so that
the patient presents with incompetence rather than ste-
nosis. In contrast to the leaflets, the aortic wall rem-
nant of the valve graft often calcifies in egg-shell fash-
ion and this may make its removal at reoperation
difficult and tedious. Other authors have reported oc-
casional cases of severe stenosis in antibiotic-treated
homografts due to leaflet calcification. The exam-
pies from Thompson et al. occurred only in donors
over 65 years old, and the patient described by Lorch et
al. received a homograft valve from a 59-year-old
donor.

Homograft valve incompetence has a variety of
mechanisms. Rupture is a wear phenomenon occur-
ing at the sites of greatest stress and strain, i.e., the
leaflet belly and the commissures. It can be postulat-
ed that it is more likely to occur when the commissural
leaflet tissue is weakened by congenital fenestrations
and when the valve has been imperfectly placed by the
surgeon (the valve is twisted or too small for the root)
or the aortic root subsequently dilates so that the leaf-
lets are poorly supported centrally at the moment of
closure and tend to prolapse. Thus, although no at-
tempt has been made to assess this factor in this analy-
sis, it is highly likely that the valves that function
longest are those that are perfectly positioned. Incom-
petence has been categorized as due to a "central leak"
only when the leaflets remained intact despite the in-
creased stresses resulting from imperfect placement,
aortic root dilatation, or both. Others have included
central leak under the terms "prolapse" and "tech-
nical failure."
Bacterial endocarditis was the only other cause of leaflet incompetence. It is unrelated to leaflet wear or, in contrast to prosthetic devices, to the presence of a perivalvular leak (which is itself very rare) or to the number of previous aortic valve replacements. The most significant predisposing factor is a history of prior aortic valve endocarditis. The homograft valve appears to be highly resistant to perioperative bacterial endocarditis, for this did not occur before 11 months postoperatively despite the fact that 19 patients had recent endocarditis as the cause of their aortic incompetence. For this reason it is the valve of choice in patients with active endocarditis on either the native or a prosthetic valve. Fungal endocarditis, however, can occur earlier and is probably a contaminant on the donor valve, emphasizing the need for meticulous screening of all valves to avoid implanting any that are infected. In addition, and again in contrast to other devices, homograft valve endocarditis can usually be cured with antibiotic treatment, although in most instances the residual incompetence requires reoperation.

The actuarial incidence of significant incompetence in antibiotic-treated valves is significantly less than for those chemically treated (figure 8). Data reported elsewhere show that this is caused by the reduced incidence of cusp rupture with the antibiotic valve. It is apparent that the actuarial curve for significant incompetence in chemical valves is almost linear, whereas that for antibiotic valves reflects a reduced incidence of significant incompetence in the first 9 to 10 years of follow-up. Thereafter the curves are almost parallel.

The incidence of significant incompetence due to valve wear (rupture and central leak) is increased by factors related to both the donor valve and the recipient. The most important is donor age, a factor also emphasized by Virdi et al. Although the analysis indicates that the younger the donor the better the result and that the risk increases sharply at 55 years, for practical purposes a valve from a donor who is no older than 50 years would appear to be satisfactory. The increasing risk of significant incompetence with increasing donor age is presumably related to the structural changes in the leaflet that are known to occur with aging. Recipient age is much less important and was a risk factor only in those under 15 years. The small number of children, however, make the conclusions tentative. The reason for this group having a high risk is unclear. At present, the ASAHV remains our valve of choice in children.

This study confirms the importance of aortic root size, but we must emphasize that the risk of significant incompetence increases sharply only when the diameter exceeds 30 mm. It is therefore not necessary to restrict the use of homograft valves to patients with an aortic root diameter of less than 25 mm, as has been assumed in the reports from Southampton. There are several possible reasons for the deleterious effect of larger root sizes. A significant number of our patients in this category had frank aneurysms of the ascending aorta and/or sinuses of Valsalva, which are prone to progressive dilatation, particularly when the pathologic change is medionecrosis. When this occurs, the freehand homograft also enlarges until a central leak occurs, with or without cusp rupture. An alternative technique in such patients, not used in this series, is to replace the aortic valve and aneurysmal ascending aorta with a valved aortic homograft conduit. Another possible factor is that it is more difficult to size the root and position the valve accurately in large and distorted roots, in part because the range of large valve sizes is limited. It seems unlikely that the diameter of the donor valve is, per se, a risk factor.

This analysis confirms our contention that reduction of aortic root diameter by aortic root tailoring is a most useful maneuver when it achieves a root diameter of less than 30 mm, for in such patients the risk of significant incompetence is not increased. It has been performed virtually only in patients with healthy aortic root tissues that hold sutures well and consists of excision of a segment of aorta. The plication technique used by Virdi et al. has not given comparable results and is not recommended.

The results of our multivariate analysis are at variance with those reported by Penta et al., who fol-
lowed 142 patients for 10 to 13 years after isolated aortic valve replacement with an antibiotic-treated homograft valve and found that valve failure due to valve wear was increased by older patient age and female sex, longer valve salvage time, and diagnosis of aortic stenosis. It is probable that their analysis is misleading by virtue of their inappropriate use of logistic regression to assess a time-related factor.

O'Brien\textsuperscript{31} has recently reported superior results using viable homograft valves from young donors in a small, highly selected series of patients with smaller aortic roots. The valves were collected with sterile techniques, incubated at 37°C for 24 hr in an antibiotic solution containing penicillin, streptomycin, and amphotericin B, and then frozen and stored, using liquid nitrogen.\textsuperscript{32} Their 10 year valve failure rate is similar to that in our comparable low-risk group in which nonviable valves were used. Virdi et al.\textsuperscript{27} have recently reported their late follow-up of antibiotic-treated nonviable homograft valves stored in a nutrient medium at 4°C. One hundred eighty-five of the 193 valves were less than 25 mm in diameter and all were from donors under 50 years of age. Again, their 10 year valve failure rate was similar to that in our comparable low-risk group. Follow-up beyond 10 years is not available from either of these reports.

With a view toward further improving these long-term results, we have recently altered the composition of the antibiotic solution and have reduced the concentration of the antibiotics and their time in contact with the valve to 48 hr.\textsuperscript{33, 34} Currently, the valves so treated are then frozen with liquid nitrogen and stored until used. Cryopreservation is known to preserve fibroblast viability\textsuperscript{32} and avoids the graft wastage that occurs after longer periods of wet storage at 4°C. The new antibiotic solution, which consists of cefoxitin 240 µg/ml, lincomycin 120 µg/ml, polymyxin B 100 µg/ml, vancomycin 50 µg/ml, and amphotericin B 25 µg/ml, is capable of sterilizing 98% of valves collected cleanly at autopsy and in animal experiments provides a similar host reaction to the fresh, untreated viable grafts collected with sterile techniques.\textsuperscript{34} If confirmed, this could be an important step forward, since a technique that uses only grafts collected in a sterile manner severely limits graft availability.

In comparing the incidence of valve failure between the ASAHV inserted freehand and a stented porcine or pericardial tissue valve, several points need emphasis. First, the incidence of tissue failure with a bioprosthetic valve is inversely related to patient age at implantation, and within 10 years of operation has been estimated to be at least 30% at age 20 years, 15% at age 40, and 10% at age 60.\textsuperscript{35} In contrast, with a homograft, patient age is possibly a risk factor only in children. Second, follow-up studies of bioprostheses that report only a reoperation rate are misleading because they exclude patients dying without reoperation or awaiting reoperation. Thus, in this report 32% of patients were found to have valve failure (significant incompetence) from all causes, but only 22% underwent reoperation. Third, it is inappropriate when reporting valve failure with a bioprosthetic valve to exclude cases of perivalvular leak and endocarditis, since both are related to the presence of the stent and its cloth-covered sewing ring; for this reason alone, both are much more common with a bioprosthetic valve than with a freehand homograft valve.\textsuperscript{36, 37} The report by Gallo et al.\textsuperscript{38} provides a 5 year incidence of tissue failure in porcine valves of 4% and a 9 year incidence of 24% (63 instances in 794 patients). The incidence was similar for valves in the aortic and mitral positions. However, only 1.3% of the patients were under 20 years of age, and valve failure due to infection (n = 33) and perivalvular leak (n = 27) were excluded. The 5 year incidence of hemodynamically important degeneration in bioprostheses reported by Williams et al.\textsuperscript{39} was 18%. It is likely that the failure rate from all causes for bioprostheses is at least three times higher at 9 to 10 years than for the unstented homograft. Finally, when making these comparisons the absence of morbidity other than significant incompetence with a homograft valve is important, since a bioprosthetic valve without anticoagulants is likely to cause thromboembolism, and occasional thrombotic occlusion and hemolysis can be associated with a perivalvular leak. Moreover, a porcine aortic valve of less than 23 mm diameter has a significant gradient, which is not present with a homograft valve.\textsuperscript{4, 29}

Conclusions. The ASAHV is a satisfactory device for aortic valve replacement and in our clinic remains the valve of choice for almost all patients. Donor valve age should be less than 50 years and the aortic root size should be 30 mm or less (equivalent to a donor valve internal diameter of 28 mm or less). The valve should be free of any imperfections and should not be stored for longer than 50 days (when wet storage at 4°C is used). It is recommended particularly in women of childbearing age, and in other patients unsuitable for anticoagulants, and in those with a small aortic root. It is also the valve of choice in patients with active endocarditis on a native or a prosthetic valve. The significant contraindications to its use are the presence of aortic root aneurysm, diffuse mediocerebral dilatation, or aortic root dilatation from other causes that is unsuitable for or cannot be reduced by aortic root tailor-
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