Marfan Syndrome: Literature Review of Mortality Studies

Kenneth J. Krause, MD

Marfan syndrome is an autosomal dominant heritable disorder of fibrous connective tissue due to mutation in the fibrillin-1 gene, located on chromosome 15. Early mortality from Marfan syndrome results from aortic dilatation. The medical literature contains long-term follow-up series of patients with Marfan syndrome accrued at major medical centers that address overall survival following surgical intervention, and prognosis in relation to certain risk factors such as family history and aortic root diameter. Mortality analyses based on these data are presented in this paper. Advances in surgical and medical therapy have improved mortality of affected individuals over the past 2–3 decades. However, significant mortality occurs, peaking in the third and fourth decades of life. Although surgery is successful treatment of aortic dissection, one cannot conclude that surgical repair confers a mortality advantage. Emergency surgery and history of aortic complications in first-degree relatives are associated with a higher mortality. Chronic beta-blocker therapy may slow the rate of aortic dilatation and may be associated with more favorable prognosis. Clinical research evaluating beta-blockade, echo assessment of the aortic root diameter progression, and gene mutation analysis may provide tools useful for future mortality assessments.

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typic expression of Marfan disease is very variable. About one quarter of affected individuals may have new mutations.

Diagnosis is based on the presence of typical clinical features and a positive family history when available. In the absence of an unequivocally affected first-degree relative, the involvement of the skeleton and at least two other systems with a minimum of one major manifestation (lens subluxation, aortic dilation or dissection (or dural ectasia) is required (‘Berlin criteria’). Linkage analysis and sequencing of the fibrillin gene are research tools that may be used for confirmation in certain instances.

Early mortality from Marfan syndrome results from complications associated with aortic dilatation. Symmetric dilation of the sinuses of Valsalva is progressive throughout life and often detectable in infancy. There are 2 treatments used to manage the potential catastrophic consequences of aortic rupture in patients with Marfan syndrome. These are β blockade and surgery. Long-term β blockade has been shown to slow the rate of aortic dilatation and reduce the development of aortic complications in patients with Marfan syndrome in a randomized controlled trial. The positive effect may be due to a reduction in the impulse (rate of pressure change in the aortic root) of left ventricular ejection and heart rate. The size of the series (70 patients) and the number of deaths (2) is insufficient for conducting a mortality analysis. Unfortunately, additional longitudinal data have not been collected to extend this study (R. E. Peyritz, oral communication). β blockade is clinically accepted as a standard therapy, based on benefit in terms of morbidity outcomes.

Surgical repair, involving use of a composite aortic valve-ascending aortic graft, with coronary artery ostial reanastomosis to the graft, a procedure originally described by Bentall, is recommended for patients with aortic dilation of 5.5 cm or more or moderate aortic regurgitation. Clinical studies suggest that this procedure prevents the occurrence of catastrophic aortic rupture and improves survival of those with Marfan syndrome. Outcomes based on an initial assessment of aortic root diameter measured echocardiographically have suggested that this measurement identifies a group at lower risk. However, this study was small (N = 89), and the number of deaths was small (5). Further, the study has not been continued to accrue additional data (C. M. Otto, oral communication).

Details of surgical procedures involving the aorta in patients with Marfan syndrome have been described and illustrated in detail by Baumgartner et al. Composite graft repair of Marfan ascending aorta aneurysms can be performed with 5–10% operative mortality by experienced surgeons. The medical literature contains several long-term follow-up series of patients with Marfan syndrome accrued at major medical centers. These series have addressed overall survival of Marfan syndrome patients, as well as survival following surgical intervention and in relation to certain risk factors such as family history.

COMPREHENSIVE NATURAL HISTORY STUDY

Silverman et al. conducted a large contemporary analysis of life expectancy. This series consisted of 417 patients with a definite diagnosis of Marfan syndrome from the Marfan clinics of university medical centers in the United States and Scotland. Data were obtained retrospectively from each institution's databases and excluded patients who died before 1970. This date was chosen because of the existence of a prior study with experience up to 1972, published by Murdoch et al., and because of the introduction and success of the Bentall procedure, which coincides with this era. Both operated and unoperated patients are included in this series. Overall there were 47 deaths among 213 males and 204 females. The mean age of living patients was $33 \pm 16$, the mean age of those dying was $41 \pm 18$, and the mean duration of follow-up (to death or time of analysis) was $5.2 \pm 3.6$ years. The authors compared survival data in this series to that in the Murdoch et al. study and
KRAUSE—MARFAN SYNDROME

Table 1. Multicenter Study of Males With Marfan Syndrome: Retrospective Data of Patients Registered From 1970–95*

<table>
<thead>
<tr>
<th>Duration (Age)</th>
<th>( P )</th>
<th>( P' )†</th>
<th>Geo ( q_i )</th>
<th>Geo ( q'_i )</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 ( q_i/q'_i ))</th>
<th>Mortality Ratio (100 ( q_i/q'_i ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10 y</td>
<td>0.990</td>
<td>0.976</td>
<td>0.001</td>
<td>0.002</td>
<td>−1.9</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>10–20 y</td>
<td>0.995</td>
<td>0.968</td>
<td>0.036</td>
<td>0.001</td>
<td>2.8</td>
<td>436</td>
<td>431</td>
</tr>
<tr>
<td>20–30 y</td>
<td>0.860</td>
<td>0.948</td>
<td>0.010</td>
<td>0.002</td>
<td>8.3</td>
<td>499</td>
<td>1213</td>
</tr>
<tr>
<td>30–40 y</td>
<td>0.790</td>
<td>0.926</td>
<td>0.012</td>
<td>0.002</td>
<td>9.9</td>
<td>523</td>
<td>501</td>
</tr>
<tr>
<td>40–50 y</td>
<td>0.700</td>
<td>0.879</td>
<td>0.008</td>
<td>0.005</td>
<td>3.0</td>
<td>157</td>
<td>155</td>
</tr>
<tr>
<td>50–60 y</td>
<td>0.700</td>
<td>0.774</td>
<td>0.0</td>
<td>0.013</td>
<td>−12.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60–65 y</td>
<td>0.360</td>
<td>0.686</td>
<td>0.125</td>
<td>0.024</td>
<td>100.1</td>
<td>522</td>
<td>427</td>
</tr>
<tr>
<td>65–70 y</td>
<td>0.255</td>
<td>0.575</td>
<td>0.067</td>
<td>0.037</td>
<td>31.9</td>
<td>192</td>
<td>180</td>
</tr>
</tbody>
</table>

* From Silverman et al.8 Observed survival was derived by measurement/estimation method described by Pokorski10 using survival curves appearing in the referenced article. \( P \) indicates observed cumulative survival; \( P' \), expected cumulative survival; Geo \( q_i \), observed geometric average mortality; Geo \( q'_i \), expected geometric average mortality; excess death rate, 1000 (observed − expected geometric annual mortality); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted.

† \( P' \) for males from 1974 US Life Tables.

concluded that life expectancy had improved by more than 25% since that time. Developments in medical and surgical care were hypothesized as reasons for the improvement.

Overall survival curves for men and women are presented, allowing development of mortality data from survival curves for each of these groups. Table 1 displays mortality data for men, and Table 2 displays mortality data for women. These include all patients in the series, regardless of the type of treatment, if any, received.

RESULTS OF AORTIC SURGERY

In this same series of patients studied by Silverman et al8, 112 underwent cardiovascular surgery at least once during the follow-up period and 32 underwent more than one surgery. Surgical indications were not defined in the group, and the specific cardiovascular procedure performed was not known in all cases. The mean age at first operation was 31 ± 11 years, with a mean follow-up period of 6.2 ± 3.8 years. The ratio of men and women was not provided. Cumulative survival for all patients having surgery showed high initial postoperative mortality. The authors comment that survival of patients undergoing surgery after 1980 was markedly better than that of those undergoing surgery prior to 1980, though cumulative survival was depicted for the entire series. (Prior to 1980, 63% of patients undergoing surgery died, while 16% of patients undergoing surgery after 1980 had died). Mortality table data derived from this series are displayed in Table 3.

Additional series assessing the survival of patients with Marfan syndrome include those published by Finkbohner et al7 and Gott et al.11,12

Gott et al11 reported on 212 patients who underwent aortic root replacement between September 1976 and June 1995. Of these, 202 used composite grafts, 185 were elective, and 27 underwent urgent surgery. The outcomes for all procedures and surgical circumstances were combined in the reported results. The majority of these patients (73%) were male, with a mean age of 32.4 years (range, 4.4–73.3 years). Mortality data based on survival presented in this study are displayed in Table 4A.

Gott et al12 updated this series to include 675 patients who had undergone aortic root replacement at ten North American and Eu-
### Table 2. Multicenter Study of Females With Marfan Syndrome: Retrospective Data of Patients Registered From 1970–95*

<table>
<thead>
<tr>
<th>Duration (Age)</th>
<th>(P)</th>
<th>(P')†</th>
<th>Geo (q_i)</th>
<th>Geo (q'_i)</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10 y</td>
<td>0.998</td>
<td>0.982</td>
<td>0.0002</td>
<td>0.002</td>
<td>−1.6</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>10–20 y</td>
<td>0.991</td>
<td>0.978</td>
<td>0.007</td>
<td>0.0004</td>
<td>0.3</td>
<td>172</td>
<td>172</td>
</tr>
<tr>
<td>20–30 y</td>
<td>0.983</td>
<td>0.971</td>
<td>0.001</td>
<td>0.0007</td>
<td>0.1</td>
<td>112</td>
<td>198</td>
</tr>
<tr>
<td>30–40 y</td>
<td>0.918</td>
<td>0.959</td>
<td>0.007</td>
<td>0.001</td>
<td>5.6</td>
<td>548</td>
<td>535</td>
</tr>
<tr>
<td>40–50 y</td>
<td>0.856</td>
<td>0.932</td>
<td>0.007</td>
<td>0.002</td>
<td>4.1</td>
<td>244</td>
<td>25</td>
</tr>
<tr>
<td>50–60 y</td>
<td>0.689</td>
<td>0.873</td>
<td>0.021</td>
<td>0.006</td>
<td>15.0</td>
<td>329</td>
<td>308</td>
</tr>
<tr>
<td>60–65 y</td>
<td>0.671</td>
<td>0.823</td>
<td>0.005</td>
<td>0.012</td>
<td>−6.4</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>65–70 y</td>
<td>0.548</td>
<td>0.757</td>
<td>0.040</td>
<td>0.017</td>
<td>23.0</td>
<td>239</td>
<td>229</td>
</tr>
</tbody>
</table>

* From Silverman et al.8 Observed survival was derived by measurement/estimation method described by Pokorski10 using survival curves appearing in the referenced article. \(P\) indicates observed cumulative survival; \(P'\), expected cumulative survival; Geo \(q_i\), observed geometric average mortality; Geo \(q'_i\), expected geometric average mortality; excess death rate, 1000 (observed − expected geometric annual mortality); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted.

† \(P'\) for females from 1974 US Life Tables.

### Table 3. Multicenter Study of Survival Following Cardiovascular Surgery for Marfan Syndrome: Retrospective Data of Patients Registered From 1970–95*

<table>
<thead>
<tr>
<th>Duration (y Postoperative)</th>
<th>(P)</th>
<th>(P')</th>
<th>Geo (q_i)</th>
<th>Geo (q'_i)</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.880</td>
<td>0.999</td>
<td></td>
<td></td>
<td>8955</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.870</td>
<td>0.997</td>
<td></td>
<td></td>
<td>829</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.835</td>
<td>0.996</td>
<td></td>
<td></td>
<td>2833</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.825</td>
<td>0.994</td>
<td></td>
<td></td>
<td>798</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.820</td>
<td>0.993</td>
<td></td>
<td></td>
<td>381</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.805</td>
<td>0.991</td>
<td></td>
<td></td>
<td>1076</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.760</td>
<td>0.989</td>
<td></td>
<td></td>
<td>3054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.750</td>
<td>0.987</td>
<td></td>
<td></td>
<td>703</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.710</td>
<td>0.985</td>
<td></td>
<td></td>
<td>2503</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.700</td>
<td>0.984</td>
<td></td>
<td></td>
<td>667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>0.820</td>
<td>0.993</td>
<td>0.0275</td>
<td>0.0018</td>
<td>15</td>
<td>969</td>
<td>947</td>
</tr>
<tr>
<td>5–10</td>
<td>0.700</td>
<td>0.983</td>
<td>0.0311</td>
<td>0.0020</td>
<td>29</td>
<td>1581</td>
<td>1491</td>
</tr>
<tr>
<td>1–10</td>
<td>0.700</td>
<td>0.983</td>
<td>0.0251</td>
<td>0.0019</td>
<td>23</td>
<td>1324</td>
<td>1207</td>
</tr>
</tbody>
</table>

* From Silverman et al.8 Observed survival was derived by measurement/estimation method described by Pokorski10 using survival curves appearing in the referenced article. \(P\) indicates observed cumulative survival; \(P'\), expected cumulative survival; Geo \(q_i\), observed geometric average mortality; Geo \(q'_i\), expected geometric average mortality; excess death rate, 1000 (observed − expected geometric annual mortality); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted. Expected survival/mortality is based on 1979–81 US Life Tables.

† \(q'_i\) for population, starting age 31, advancing one year per year of postoperative follow-up (gender distribution not given).
Table 4A. Based on Survival Study of 212 Patients With Marfan Syndrome Undergoing Aortic Root Replacement at a Single Center (Johns Hopkins) Between 1976 and 1995 (From Gott\(^1\)^)*

<table>
<thead>
<tr>
<th>Duration (Y Post-operative)</th>
<th>(P)</th>
<th>(P')</th>
<th>Geo (q_i)</th>
<th>Geo (q_i)(,)</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 (q_i/q_i))</th>
<th>Mortality Ratio (100 (q_i/q_i))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>0.880</td>
<td>0.990</td>
<td>0.0131</td>
<td>0.0016</td>
<td>12</td>
<td>840</td>
<td>820</td>
</tr>
<tr>
<td>5–10</td>
<td>0.770</td>
<td>0.977</td>
<td>0.0265</td>
<td>0.0027</td>
<td>24</td>
<td>968</td>
<td>923</td>
</tr>
<tr>
<td>10–14</td>
<td>0.705</td>
<td>0.961</td>
<td>0.0218</td>
<td>0.0040</td>
<td>18</td>
<td>537</td>
<td>522</td>
</tr>
<tr>
<td>1–14</td>
<td>0.705</td>
<td>0.961</td>
<td>0.0203</td>
<td>0.0028</td>
<td>18</td>
<td>723</td>
<td>646</td>
</tr>
</tbody>
</table>

* Observed survival was derived by measurement/estimation method described by Pokorski\(^10\) using survival curves appearing in the referenced article. \(P\) indicates observed cumulative survival; \(P'\), expected cumulative survival; Geo \(q_i\), observed geometric average mortality; Geo \(q_i\), expected geometric average mortality; excess death rate, 1000 (observed − expected geometric annual mortality); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted. Expected survival/mortality is based on 1979–81 US Life Tables.

† \(q_i\) is weighted for gender distribution: 0.75 male, 0.25 female, starting age 33 to 34, advancing one year per year of postoperative follow-up.

European centers between October 1968 and March 1996. Survival was assessed based on the circumstances in which the surgery was performed. Elective repair occurred in 455 cases, urgent repair (within 7 days of a surgical consultation) occurred in 117, and emergency repair (within 24 hours of a surgical consultation) occurred in 103. The majority of these patients was also male (70%), with a mean age of 34 (range, 4–73 years). This study confirmed the expected difference in outcome between elective and emergent surgery for Marfan syndrome. For all circumstances, there was a high initial 60-day perioperative mortality. Overall there was a 59% 20-year survival rate. Mortality data based on survival data presented in this study are displayed in Table 4B.

Finkbohner et al\(^7\) retrospectively reviewed 192 patients with Marfan syndrome who had undergone aortic aneurysm surgery between 1966 and 1988. There were 114 men and 78 women. In this series, the first surgery involved the ascending aorta in 84%, and at aortic sites from the aortic arch to the abdomen in the remainder. The majority of patients had second surgeries to repair subsequent aneurysms or dissections at second sites (53%), with substantial numbers having third (35) and fourth (9) surgeries. The presence of dissection at the time of the first operation was a significant predictor of subsequent repeat operation. Of the 192 patients, 21 had mitral valve repair at some point. Mortality table data based on analysis of this study are displayed in Table 5.

FAMILY HISTORY OF SERIOUS CARDIOVASCULAR COMPLICATIONS

Silverman et al\(^13\) addressed the question of whether survival of an individual with Marfan syndrome was related to a family history of severe cardiovascular complications. One hundred eight affected patients from multi-generational families affected by Marfan syndrome were assessed for the presence of a history of a severe cardiovascular event in a first-degree relative. Severe cardiovascular event was defined as nonischemic cardiovascular death, history of aortic dissection, or history of cardiac surgery (non-coronary artery bypass graft). Of those with a positive family history (64), 31 were male and 33 female, with a mean age of 28 ± 16 years. Of those with a negative family history, 19 were male and 25 female, with a mean age of 32 ± 18 years. These investigators noted that patients with a family history of severe cardiovascular disease had a significantly greater
Table 4B. Based on Survival Study of 675 Patients With Marfan Syndrome Undergoing Aortic Root Replacement at 10 Experienced Centers Between 1968 and 1997, by Surgical Situation (From Gott et al12) *

<table>
<thead>
<tr>
<th>Duration (Y Postoperative)</th>
<th>$P$</th>
<th>$P'$</th>
<th>Geo $q_i$†</th>
<th>Geo $q_i$</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (1000 $q_i/q'_i$)</th>
<th>Mortality Ratio (100 $q_i/q'_i$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective (n = 455)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>0.926</td>
<td>0.992</td>
<td>0.0192</td>
<td>0.0019</td>
<td>17</td>
<td>1011</td>
<td>985</td>
</tr>
<tr>
<td>5–10</td>
<td>0.835</td>
<td>0.979</td>
<td>0.0203</td>
<td>0.0026</td>
<td>18</td>
<td>768</td>
<td>741</td>
</tr>
<tr>
<td>10–15</td>
<td>0.891</td>
<td>0.959</td>
<td>0.0038</td>
<td>0.0042</td>
<td>$-0.3$</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>15–20</td>
<td>0.765</td>
<td>0.927</td>
<td>0.0133</td>
<td>0.0067</td>
<td>7</td>
<td>199</td>
<td>197</td>
</tr>
<tr>
<td>1–15</td>
<td>0.819</td>
<td>0.964</td>
<td>0.0141</td>
<td>0.0026</td>
<td>12</td>
<td>540</td>
<td>502</td>
</tr>
<tr>
<td>1–20</td>
<td>0.765</td>
<td>0.927</td>
<td>0.0139</td>
<td>0.0040</td>
<td>10</td>
<td>352</td>
<td>323</td>
</tr>
<tr>
<td>Urgent (within 7 d, n = 117)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>0.898</td>
<td>0.992</td>
<td>0.0266</td>
<td>0.0019</td>
<td>25</td>
<td>1405</td>
<td>1353</td>
</tr>
<tr>
<td>5–10</td>
<td>0.818</td>
<td>0.979</td>
<td>0.1838</td>
<td>0.0026</td>
<td>16</td>
<td>693</td>
<td>671</td>
</tr>
<tr>
<td>10–15</td>
<td>0.670</td>
<td>0.959</td>
<td>0.3904</td>
<td>0.0042</td>
<td>35</td>
<td>938</td>
<td>874</td>
</tr>
<tr>
<td>15–20</td>
<td>0.534</td>
<td>0.927</td>
<td>0.0444</td>
<td>0.0067</td>
<td>38</td>
<td>664</td>
<td>615</td>
</tr>
<tr>
<td>1–15</td>
<td>0.723</td>
<td>0.964</td>
<td>0.0182</td>
<td>0.0026</td>
<td>16</td>
<td>696</td>
<td>630</td>
</tr>
<tr>
<td>1–20</td>
<td>0.534</td>
<td>0.927</td>
<td>0.0325</td>
<td>0.0040</td>
<td>29</td>
<td>820</td>
<td>642</td>
</tr>
<tr>
<td>Emergency (within 24 h, n = 103)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>0.0872</td>
<td>0.992</td>
<td>0.0336</td>
<td>0.0019</td>
<td>32</td>
<td>1776</td>
<td>1693</td>
</tr>
<tr>
<td>5–10</td>
<td>0.7326</td>
<td>0.979</td>
<td>0.0343</td>
<td>0.0026</td>
<td>32</td>
<td>1292</td>
<td>1213</td>
</tr>
<tr>
<td>10–15</td>
<td>0.5000</td>
<td>0.959</td>
<td>0.0735</td>
<td>0.0042</td>
<td>69</td>
<td>1767</td>
<td>1538</td>
</tr>
<tr>
<td>15–20</td>
<td>0.5000</td>
<td>0.927</td>
<td>0.0067</td>
<td>0.0040</td>
<td>$-7$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1–15</td>
<td>0.5000</td>
<td>0.964</td>
<td>0.0483</td>
<td>0.0026</td>
<td>44</td>
<td>1844</td>
<td>1386</td>
</tr>
<tr>
<td>1–20</td>
<td>0.5000</td>
<td>0.927</td>
<td>0.0358</td>
<td>0.0040</td>
<td>31</td>
<td>905</td>
<td>689</td>
</tr>
</tbody>
</table>

* Observed survival was derived by measurement/estimation method described by Pokorski10 using survival curves appearing in the referenced article. $P$ indicates observed cumulative survival; $P'$, expected cumulative survival; Geo $q_i$, observed geometric average mortality; Geo $q_i'$, expected geometric average mortality; excess death rate, 1000 (observed – expected geometric annual mortality); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted. Expected survival/mortality is based on 1979–81 US Life Tables.

† $q_i'$ is weighted for gender distribution: 0.70 male, 0.30 female, starting age 33 to 34, advancing one year per year of postoperative follow-up.

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observed/expected aortic diameter ratio than those without such a family history, or normals. Also, a significantly greater proportion of patients with a family history was taking β-blockers (41% versus 21%). Mortality table data based on analysis of survival presented in this study are displayed in Table 6 and Table 7.

COMMENTS

Silverman et al8 compiled one of the most comprehensive, contemporary series of patients with Marfan syndrome by including all patients in the registries of two major US and UK Marfan syndrome referral centers. This registry study excluded only patients whose death occurred prior to 1970. In this study, peak mortality was in the age group 20–40 in males and 30–40 in females. This corresponds with the age at which major aortic manifestations often appear, as illustrated by the mean surgical age in several of the studies reviewed here. There appears to be a relative mortality advantage for females in younger age groups (under age 30). The article's main clinical conclusion is that there was a 25% improvement in survival over that seen pre-
Table 5. Based on Survival of Patients With Marfan Syndrome Undergoing Aortic Aneurysm Surgery Replacement at a Single Center (University of Texas) Between 1966 and 1998 (From Finkbohner et al)\(^*\)

<table>
<thead>
<tr>
<th>Duration (Age)</th>
<th>(P)</th>
<th>(P')(^\dagger)</th>
<th>Geo (q_i)</th>
<th>Geo (q'_i)</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–20</td>
<td>0.985</td>
<td>0.977</td>
<td>0.0007</td>
<td>0.0012</td>
<td>−0.4</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>20–30</td>
<td>0.890</td>
<td>0.963</td>
<td>0.0100</td>
<td>0.0014</td>
<td>9</td>
<td>695</td>
<td>869</td>
</tr>
<tr>
<td>30–40</td>
<td>0.760</td>
<td>0.946</td>
<td>0.0157</td>
<td>0.0017</td>
<td>14</td>
<td>907</td>
<td>852</td>
</tr>
<tr>
<td>40–50</td>
<td>0.640</td>
<td>0.911</td>
<td>0.0170</td>
<td>0.0038</td>
<td>13</td>
<td>450</td>
<td>424</td>
</tr>
<tr>
<td>50–60</td>
<td>0.500</td>
<td>0.829</td>
<td>0.0244</td>
<td>0.0094</td>
<td>14</td>
<td>258</td>
<td>241</td>
</tr>
<tr>
<td>60–68</td>
<td>0.130</td>
<td>0.707</td>
<td>0.1550</td>
<td>0.0197</td>
<td>135</td>
<td>787</td>
<td>503</td>
</tr>
<tr>
<td>0–68</td>
<td>0.130</td>
<td>0.707</td>
<td>0.0296</td>
<td>0.0051</td>
<td>24</td>
<td>580</td>
<td>296</td>
</tr>
</tbody>
</table>

\(^*\) Observed survival was derived by measurement/estimation method described by Pokorski\(^10\) using survival curves appearing in the referenced article. \(P\) indicates observed cumulative survival; \(P'\), expected cumulative survival; Geo \(q_i\), observed geometric average mortality; Geo \(q'_i\), expected geometric average mortality; excess death rate, 1000 \((\text{observed} − \text{expected geometric annual mortality})\); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted. Expected survival/mortality is based on 1979–81 US Life Tables.

\(^\dagger\) \(P'\) is weighted for gender distribution: 0.58 male, 0.41 female.

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Table 6. Based on Survival Study of Patients With Marfan Syndrome From Multigenerational Families With Positive Family History of Severe Cardiovascular Complications in a First-Degree Relative (From Silverman et al)\(^*\)

<table>
<thead>
<tr>
<th>Duration (Age)</th>
<th>(P)</th>
<th>(P')(^\dagger)</th>
<th>Geo (q_i)</th>
<th>Geo (q'_i)</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
<th>Mortality Ratio (100 (q_i/q'_i))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>0.990</td>
<td>0.983</td>
<td>0.0010</td>
<td>0.0017</td>
<td>−0.7</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>10–20</td>
<td>0.970</td>
<td>0.977</td>
<td>0.0020</td>
<td>0.0006</td>
<td>1.0</td>
<td>333</td>
<td>330</td>
</tr>
<tr>
<td>20–30</td>
<td>0.919</td>
<td>0.965</td>
<td>0.0054</td>
<td>0.0012</td>
<td>4.0</td>
<td>436</td>
<td>861</td>
</tr>
<tr>
<td>30–35</td>
<td>0.874</td>
<td>0.958</td>
<td>0.0100</td>
<td>0.0014</td>
<td>8.0</td>
<td>686</td>
<td>675</td>
</tr>
<tr>
<td>35–40</td>
<td>0.863</td>
<td>0.949</td>
<td>0.0025</td>
<td>0.0019</td>
<td>0.6</td>
<td>134</td>
<td>30</td>
</tr>
<tr>
<td>40–45</td>
<td>0.815</td>
<td>0.936</td>
<td>0.0114</td>
<td>0.0027</td>
<td>9.0</td>
<td>413</td>
<td>406</td>
</tr>
<tr>
<td>45–50</td>
<td>0.736</td>
<td>0.915</td>
<td>0.0202</td>
<td>0.0045</td>
<td>16.0</td>
<td>445</td>
<td>432</td>
</tr>
<tr>
<td>50–55</td>
<td>0.675</td>
<td>0.883</td>
<td>0.0171</td>
<td>0.0071</td>
<td>10.0</td>
<td>241</td>
<td>236</td>
</tr>
<tr>
<td>55–60</td>
<td>0.460</td>
<td>0.837</td>
<td>0.0738</td>
<td>0.0106</td>
<td>63.0</td>
<td>693</td>
<td>611</td>
</tr>
<tr>
<td>60–65</td>
<td>0.460</td>
<td>0.771</td>
<td>0</td>
<td>0.0163</td>
<td>−16.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>65–70</td>
<td>0.332</td>
<td>0.682</td>
<td>0.0631</td>
<td>0.0242</td>
<td>39.0</td>
<td>260</td>
<td>291</td>
</tr>
<tr>
<td>0–70</td>
<td>0.332</td>
<td>0.682</td>
<td>0.0156</td>
<td>0.0054</td>
<td>10.0</td>
<td>286</td>
<td>210</td>
</tr>
</tbody>
</table>

\(^*\) Observed survival was derived by measurement/estimation method described by Pokorski\(^10\) using survival curves appearing in the referenced article. \(P\) indicates observed cumulative survival; \(P'\), expected cumulative survival; Geo \(q_i\), observed geometric average mortality; Geo \(q'_i\), expected geometric average mortality; excess death rate, 1000 \((\text{observed} − \text{expected geometric annual mortality})\); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted. Expected survival/mortality is based on 1979–81 US Life Tables.

\(^\dagger\) \(P'\) for population, no correction for gender distribution: 0.48 male, 0.52 female.
Table 7. Based on Survival Study of Patients With Marfan Syndrome From Multigenerational Families With Negative Family History of Severe Cardiovascular Complication in a First-Degree Relative (From Silverman et al13)*

<table>
<thead>
<tr>
<th>Duration (Age)</th>
<th>P</th>
<th>P'†</th>
<th>Geo q_i</th>
<th>Geo q'_i</th>
<th>Excess Death Rate</th>
<th>Mortality Ratio (100 q_i/q'_i)</th>
<th>Mortality Ratio (100 q_i/q'_i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>1.000</td>
<td>0.974</td>
<td>0</td>
<td>0.0026</td>
<td>-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10–20</td>
<td>0.976</td>
<td>0.968</td>
<td>0.0024</td>
<td>0.0006</td>
<td>2</td>
<td>424</td>
<td>421</td>
</tr>
<tr>
<td>20–30</td>
<td>0.976</td>
<td>0.956</td>
<td>0</td>
<td>0.0013</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30–35</td>
<td>0.976</td>
<td>0.950</td>
<td>0</td>
<td>0.0013</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35–40</td>
<td>0.976</td>
<td>0.942</td>
<td>0</td>
<td>0.0028</td>
<td>-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40–45</td>
<td>0.976</td>
<td>0.929</td>
<td>0</td>
<td>0.0026</td>
<td>-3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45–50</td>
<td>0.976</td>
<td>0.910</td>
<td>0</td>
<td>0.0042</td>
<td>-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50–55</td>
<td>0.948</td>
<td>0.879</td>
<td>0.0058</td>
<td>0.0068</td>
<td>-1</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>55–60</td>
<td>0.905</td>
<td>0.835</td>
<td>0.0092</td>
<td>0.0103</td>
<td>-1</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>60–65</td>
<td>0.905</td>
<td>0.771</td>
<td>0</td>
<td>0.0157</td>
<td>-16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>65–70</td>
<td>0.725</td>
<td>0.686</td>
<td>0.0433</td>
<td>0.0231</td>
<td>20</td>
<td>188</td>
<td>180</td>
</tr>
<tr>
<td>0–70</td>
<td>0.725</td>
<td>0.686</td>
<td>0.0046</td>
<td>0.0054</td>
<td>-1</td>
<td>85</td>
<td>88</td>
</tr>
</tbody>
</table>

* Observed survival was derived by measurement/estimation method described by Pokorski10 using survival curves appearing in the referenced article. \( P \) indicates observed cumulative survival; \( P' \), expected cumulative survival; Geo \( q_i \), observed geometric average mortality; Geo \( q'_i \), expected geometric average mortality; excess death rate, 1000 (observed − expected geometric annual mortality); mortality ratio, given as derived from geometric average observed and expected mortality, and interval observed and expected mortality as noted. Expected survival/mortality is based on 1979–81 US Life Tables.

† \( P' \) is weighted for gender distribution: 0.43 male, 0.57 female.

1972. Improved surgical technique, postoperative care, and more widespread use of \( \beta \) blockade in patients with Marfan syndrome are likely explanations. Improved clinical diagnosis and awareness may also have lead to an increase in the number of cases with milder manifestations.

Finkbohner et al7, Silverman et al8, and Gott et al11,12 present survival data for patients who have undergone aortic surgery because of manifestations of Marfan syndrome. Silverman et al8 covers a broad time range (death of patient, 1970–93) and includes data for patients undergoing any procedure on any segment of the aorta (the type of surgery was not known in 27 of 112 patients). Silverman et al8 includes a group of patients with high mortality that had surgery before 1980. (Patients were not separated into two groups based on this date.)

Finkbohner et al7 and Gott et al11 each published a series accumulated at US university medical centers during the same interval and probably represent similar groups. Mortality following surgery in these two series is somewhat better than mortality derived from the Silverman et al8 study. This improvement may reflect the era during which surgery was performed, particularly for the Gott et al11 study that began to accumulate patients in 1976. This Johns Hopkins series included a male majority with a preponderance of initial procedures performed as elective (185/212). The Finkbohner et al University of Texas series7 also had a (less pronounced) male majority; however, a majority of the patients in this series had a second (or more) surgery.

The updated series by Gott et al12 includes a broad time frame (1968–77) and a breadth of experience at multiple centers in North America and Europe (10). Though not stated, this series most likely includes patients that were counted in his previous series11 and other previously published series. The average age at operation, 34 years, corresponds to that seen in other series. Outcomes are tracked by
surgical circumstance: elective, urgent, and emergency. As expected, mortality rates are lower with elective repair than with urgent or emergency repair. Mortality during the middle years, 10–20 years following elective repair, appears to be quite favorable from this series. However, this finding should be viewed with caution, as relatively few individuals were at risk at years 10 (97) and 16 (17). This series also reflects various surgical techniques performed in different eras.

All of the postsurgical series appear to have a relative trend of worse mortality, compared to the Silverman et al\textsuperscript{8} inclusive series of all registered patients with Marfan syndrome. An explanation is that performance of aortic surgery identifies a more affected, higher risk population. Relative to the entire population with Marfan syndrome, one cannot conclude that surgical repair of the aorta offers a mortality equalization or advantage compared to unoperated on patients or that it eliminates the future risk of an aortic complication. However, as is evident from Gott et al,\textsuperscript{12} elective repair, prior to development of cardiovascular complications, is clearly an advantageous practice. Early institution of medical therapy\textsuperscript{14} and elective aorta repair at an earlier juncture than at the currently recommended\textsuperscript{4,12} aorta diameter criteria may be measures that further improve survival of patients with Marfan syndrome.

Silverman et al\textsuperscript{13} also compared survival of patients from multigenerational families affected by Marfan syndrome. In those with a positive family history of a first-degree relative having a serious cardiovascular manifestation, there was clear evidence of decreased survival and increased mortality. Diagnosis of Marfan syndrome was clinically based on the Berlin criteria.\textsuperscript{3} Differing expressivity of Marfan phenotype appears to be the explanation. The use of genetic testing to assess a possible relationship of severity from different mutations and to remove any diagnostic uncertainty would be useful in further developing the conclusions of this study.

Finally, clinical evidence suggests that the use of β-blockade significantly reduces morbidity events and reduces mortality. The quality of this evidence is strong.\textsuperscript{5,8,14} Unfortunately the scope and results of published studies available did not permit mortality analysis. Rossi-Fouldes et al\textsuperscript{14} recently demonstrated that medical treatment with β blockers or calcium channel antagonist (when medical condition or side effects prevented β blocker use) was associated with slower aortic growth, both absolute and corrected for body size, in a group of 53 children and adolescents with Marfan syndrome.

Aortic root diameter is a key parameter for use in research studies assessing risk of cardiovascular complications in patients with Marfan syndrome. Leggett et al\textsuperscript{6} and Silverman et al\textsuperscript{13} have concluded that assessment of an aortic ratio normalized for body surface area and aortic root diameter assessed echocardiographically, respectively, are significantly higher in individuals at greatest risk for aortic complications. The details of these measurements are reviewed in detail in the references.

REFERENCES

9. Murdoch JL, Walker BA, Halpern BL, Kuzma JW,


