Effect of Age on Mortality Experience in Patients with Hypertrophic Cardiomyopathy

Robert J. Pokorski

Abstract: Medical authors typically combine all patient groups to increase the amount of data available for analysis. Use of this statistical methodology generally conceals higher mortality ratios at younger ages and masks survival differences related to disease severity and comorbid impairments. This paper discusses the effects of age and clinical characteristics on mortality experience in patients with hypertrophic cardiomyopathy. Limited data suggest the mortality pattern associated with this impairment is similar to that observed with most disorders: excess mortality (compared to the general population) that is high at younger ages, intermediate in middle-aged people, and minimal in the very elderly. Optimism regarding generally favorable mortality at older ages must be tempered with caution since studies report much poorer experience in certain subgroups of elderly patients with this impairment.

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Introduction
The article addresses the relationship between age and mortality in patients with hypertrophic cardiomyopathy. It is based upon two key articles recently published in this journal.

The first article reported experience from Erasmus University, Rotterdam. This paper was a valuable addition to the insurance medicine literature because it highlighted the more favorable prognosis of patients with HC who are followed in out-patient clinics as compared to prior series comprised mainly of individuals hospitalized in large research institutions.

Kofflard et al provided additional detail regarding this cohort. Patients were divided into two groups: ages ≤30 years (n=43), and ages >30 years (n=70; 64 subjects aged 31-65 years, and 6 patients aged 66 years or older). Five deaths (all cardiac) occurred in age group ≤30 years during mean follow-up of 8 ± 5 years, and 8 deaths (6 cardiac, 2 noncardiac) were reported in age group >30 years during mean follow-up of 7 ± 6 years, leading the authors to conclude that "This study is the first to report a benign prognosis for a large, relatively nonselected population of patients with HC." They further observed that "No significant difference in risk of cardiac death was found in any subgroup [including ages ≤30 vs. >30 years]."

What do these data indicate from an insurance perspective? Since details were not provided regarding when deaths occurred in the two cohorts, the assumption was made that all 5 deaths in age group ≤30 years occurred during the mean 8-year follow-up. The 8-year
interval mortality rate would be .116 (5/43), yielding an interval survival rate of .884 (1-.116), a geometric average annual survival rate of .985 (8th root of .884), and a geometric average annual mortality rate of .015 (1-.985). Corresponding expected values were determined for ages ≤30 (Tables 1 and 2) using these assumptions: (1) mean age at the beginning of the study was 25 years (it is not necessary to know the exact mean age since mortality rates are very similar at young ages); (2) the age of the cohort advanced 1 year with the passage of each calendar year (mean age 25 in year 1, 26 in year 2, etc.); and (3) the same male/female distribution persisted during the 8-year mean follow-up. The same process was used to calculate observed and expected survival in age group >30 years (Tables III and IV), assuming the 8 observed deaths occurred during the mean follow-up of 7 years. Mean q' at the beginning of the study corresponded to a cohort age of 52 years (refer to methodology described by Pokorski).

Table V summarizes data for the two cohorts. Mortality experience was significantly different. Geometric average annual mortality ratios and excess death rates, respectively, were 2500% and 15 per mil (age group ≤30 years), and 260% and 11 per mil (age group >30 years).

Limitations in this analysis should be acknowledged. First, data were insufficient to determine when deaths occurred in the two age groups. The estimates chosen - 5 deaths in a mean follow-up of 8 years for ages ≤30 years, and 8 deaths during mean follow-up of 7 years in the cohort aged >30 years - appear reasonable given the wide variation in duration of follow-up (8 ± 5 years, and 7 ± 6, respectively), and the fact that very few patients were observed for long durations, e.g., only 51, 36, and 29 patients, respectively, were being followed at time periods 8, 10, and 12 years. Second, minimal data were available to estimate mean q' for the >30-year-old cohort. Third, confidence intervals for mortality ratios and excess death rates would be wide because of the small number of deaths.

The second article in this Journal concerning hypertrophic cardiomyopathy was an analysis of a paper from the Mayo Clinic by Cannan et al that reported the natural history of HC among residents of Olmsted County, Minnesota. Iacovino determined that mortality experience for each 2-year interval and for the entire 10-year follow-up period was better than expected, i.e., mortality ratios were less than 100% and excess death rates were negative. His thoughtful review discussed possible explanations for this unexpected finding. I would like to elaborate on other statistical and methodological factors that should be considered.

Cannan et al concluded “there was no significant difference in overall survival [in subjects with HC] compared with an age- and sex-matched population.” What was the nature of this age- and sex-matched population? In a word, elderly. Mean age of the cohort was 59 ± 20 years (range 1 week to 92 years). The mean age of 59 years is misleading, however, because of the large proportion of elderly patients; 41% (n=15) of subjects were aged 66 or older, and only 14% (n=5) were <40 years of age. (Markedly higher q' values in elderly compared to young or middle-aged subjects disproportionately weight mean q' towards older ages.) The authors stated that expected cumulative survival rates at 1 and 5 years, respectively, were 97% and 87%. These survival rates correspond to what would be expected in a group comprised of 69-year-old people (U.S. Population Table 1992, White Population, assuming the same sex distribution reported in the paper). Findings from this report might be re-worded as follows. “This was a very small study. Thirty-seven patients were observed for a median of 7.7 years (range: 45 days to 17.2 years), but only 17 patients were followed for
5 years or longer. Eight deaths occurred - 2 cardiac and 6 noncardiac. There was no significant difference in overall survival [in subjects with HC] compared with an age- and sex-matched population, i.e., compared with a population of subjects aged 69 years.” Thus, this paper suggests that elderly patients with HC - particularly subjects with minimal symptoms - may have a prognosis similar to that of 69-year-old people in the general population. Even this conclusion must be considered tentative. Patients in the study were divided into two groups: “pure” hypertrophic cardiomyopathy (discussed by Iacovino) and hypertensive hypertrophic cardiomyopathy (subjects meeting the echocardiographic criteria for HC who also had a history of hypertension requiring drug therapy). Survival in the latter group was much poorer than in the control population. It may be that HC in the elderly is a relatively benign condition in patients with no history of hypertension, and a significant impairment in those with long-standing hypertension requiring drug therapy.

An earlier report from the Mayo Clinic by Fay et al also observed a mixed prognosis in elderly patients with HC. Ninety-five patients initially diagnosed with HC at age ≥65 years were followed for a median duration of 4.2 years (range 6 days to 9.1 years). Participants were very elderly; mean age was 71.8 ± 5.1 years (range 65 to 90). Seventy-five percent of patients were symptomatic as defined by the presence of chest pain, dyspnea or syncope, and serious co-morbid impairments (e.g., coronary heart disease, diabetes mellitus, cancer) were common. Twenty-four deaths occurred - 11 cardiac, 10 noncardiac and 3 of unknown cause. The authors concluded that “patients presenting with hypertrophic cardiomyopathy at advanced age generally do well, with a survival rate no different from that of an age- and gender-matched control group [i.e., compared with a control group comprised of individuals aged 71.8 years].” However, they stressed that a benign clinical course was not universal. Subjects presenting with functional class I or II dyspnea had a survival rate no different from that of control subjects and only 18% progressed to functional class III or IV. The 1-year mortality rate (36%) of patients with class III dyspnea at the time of diagnosis was much higher than that of controls.

In support of the contention that excess mortality associated with HC varies with age, consider the experience of a group described by Hecht et al. This very small study from the National Heart, Lung, and Blood Institute reported the outcome of 31 middle-aged asymptomatic (New York Heart Association functional class I) patients with HC identified between 1979 and 1985. Average age of the cohort was 42 ± 5 years (range 35 to 55 years). Clinical course could be assessed for ≥2 years in 29 subjects. During mean follow-up of 8 years (range 2.1 to 11.5), 22 patients (76%) remained completely asymptomatic or had only minor and transient symptoms, 3 experienced increasing symptoms (1 to functional class II, and 2 to class III), and 4 patients died suddenly (after 25, 36, 131, and 136 months of follow-up).

The authors stated that the annual mortality rate was 1.7% (.017). How does this mortality rate compare with what would be expected in the general population? For an interval of 8 years, the geometric average annual mortality rate for an age- and sex-matched population would be .00384. This value was determined from U.S. Population Table 1992, White Population, using the following assumptions (1) the male/female distribution specified in the article; (2) the age of the cohort advanced 1 year with the passage of each calendar year; and (3) the initial mean q’ corresponded to what would be expected in a cohort comprised of 43-year-old people. (Except in instances with very narrow age ranges or studies heavily skewed to younger ages, mean q’ always corresponds to an age
### Table I.

Mean $q'$ Values for Age Group $\leq 30$ Years*

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>Mean Age</th>
<th>Tabular Male $q'$</th>
<th>Tabular Male $q'$ Adjusted For % Male</th>
<th>Tabular Female $q'$</th>
<th>Tabular Female $q'$ Adjusted For % Female</th>
<th>Mean $q'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1r</td>
<td>25</td>
<td>0.00075</td>
<td>0.00041</td>
<td>0.00035</td>
<td>0.00016</td>
<td>0.00057</td>
</tr>
<tr>
<td>1-2</td>
<td>26</td>
<td>0.00076</td>
<td>0.00041</td>
<td>0.00036</td>
<td>0.00017</td>
<td>0.00058</td>
</tr>
<tr>
<td>2-3</td>
<td>27</td>
<td>0.00076</td>
<td>0.00041</td>
<td>0.00038</td>
<td>0.00018</td>
<td>0.00059</td>
</tr>
<tr>
<td>3-4</td>
<td>28</td>
<td>0.00077</td>
<td>0.00041</td>
<td>0.00041</td>
<td>0.00019</td>
<td>0.00060</td>
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<tr>
<td>4-5</td>
<td>29</td>
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<td>0.00042</td>
<td>0.00043</td>
<td>0.00020</td>
<td>0.00062</td>
</tr>
<tr>
<td>5-6</td>
<td>30</td>
<td>0.00079</td>
<td>0.00043</td>
<td>0.00046</td>
<td>0.00021</td>
<td>0.00064</td>
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<td>31</td>
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<td>0.00044</td>
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<td>0.00067</td>
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<td>7-8</td>
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<td>0.00054</td>
<td>0.00025</td>
<td>0.00071</td>
</tr>
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</table>

*Netherlands Population Table 1985-1990

### Table II.

Expected Survival and Mortality Rates for Age Group $\leq 30$ Years

<table>
<thead>
<tr>
<th>Duration Cumulative (years)</th>
<th>Survival Rate</th>
<th>Mortality Rate</th>
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<tbody>
<tr>
<td></td>
<td>$P'$</td>
<td>$\tilde{p}'$</td>
</tr>
<tr>
<td>0-1</td>
<td>0.99943</td>
<td>0.99943</td>
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<tr>
<td>1-2</td>
<td>0.99886</td>
<td>0.99942</td>
</tr>
<tr>
<td>2-3</td>
<td>0.99827</td>
<td>0.99941</td>
</tr>
<tr>
<td>3-4</td>
<td>0.99767</td>
<td>0.99940</td>
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<tr>
<td>4-5</td>
<td>0.99706</td>
<td>0.99938</td>
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<td>5-6</td>
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<td>0.99936</td>
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<tr>
<td>6-7</td>
<td>0.99575</td>
<td>0.99933</td>
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<tr>
<td>7-8</td>
<td>0.99505</td>
<td>0.99929</td>
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<tr>
<td>0-8</td>
<td>0.99505</td>
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Table III.

Mean q' Values for Age Group >30 Years*

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>Mean Age</th>
<th>Tabular Male q'</th>
<th>Tabular Female q'</th>
<th>Tabular Male q' Adjusted For % Male</th>
<th>Tabular Female q' Adjusted For % Female</th>
<th>Mean q'</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>52</td>
<td>0.00603</td>
<td>0.00326</td>
<td>0.00328</td>
<td>0.00151</td>
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<td>53</td>
<td>0.00671</td>
<td>0.00362</td>
<td>0.00359</td>
<td>0.00165</td>
<td>0.00528</td>
</tr>
<tr>
<td>2-3</td>
<td>54</td>
<td>0.00746</td>
<td>0.00403</td>
<td>0.00394</td>
<td>0.00181</td>
<td>0.00584</td>
</tr>
<tr>
<td>3-4</td>
<td>55</td>
<td>0.00830</td>
<td>0.00448</td>
<td>0.00432</td>
<td>0.00199</td>
<td>0.00647</td>
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<tr>
<td>4-5</td>
<td>56</td>
<td>0.00922</td>
<td>0.00498</td>
<td>0.00473</td>
<td>0.00218</td>
<td>0.00715</td>
</tr>
<tr>
<td>5-6</td>
<td>57</td>
<td>0.01024</td>
<td>0.00553</td>
<td>0.00518</td>
<td>0.00238</td>
<td>0.00791</td>
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<tr>
<td>6-7</td>
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<td>0.00568</td>
<td>0.00261</td>
<td>0.00875</td>
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</tbody>
</table>

*Netherlands Population Table 1985-1990

Table IV.

Expected Survival and Mortality Rates for Age Group >30 Years

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>Cumulative Survival Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.99524 0.99524</td>
<td>—</td>
</tr>
<tr>
<td>1-2</td>
<td>0.98999 0.99472</td>
<td>—</td>
</tr>
<tr>
<td>2-3</td>
<td>0.98420 0.99416</td>
<td>—</td>
</tr>
<tr>
<td>3-4</td>
<td>0.97784 0.99353</td>
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</tr>
<tr>
<td>4-5</td>
<td>0.97084 0.99285</td>
<td>—</td>
</tr>
<tr>
<td>5-6</td>
<td>0.96316 0.99209</td>
<td>—</td>
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<tr>
<td>6-7</td>
<td>0.95473 0.99125</td>
<td>—</td>
</tr>
<tr>
<td>0-7</td>
<td>0.95473 0.95473</td>
<td>0.99340</td>
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</table>
### Table V.

Summary of Mortality Experience for Age Groups ≤30 and >30 Years

<table>
<thead>
<tr>
<th>Age Duration Interval (years)</th>
<th>Mortality Rate</th>
<th>Mortality Ratio</th>
<th>Excess Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-8</td>
<td>0.116, 0.00495, 0.015, 0.00062</td>
<td>2300, 2500</td>
<td>111, 15</td>
</tr>
<tr>
<td>0-7</td>
<td>0.114, 0.04527, 0.017, 0.00660</td>
<td>252, 260</td>
<td>69, 11</td>
</tr>
</tbody>
</table>

### Table VI.

Comparison of Mortality Experience, by Age

<table>
<thead>
<tr>
<th>Citation</th>
<th>Approximate Mean Age of Cohort</th>
<th>Geometric Average Annual Mortality Ratio</th>
<th>Geometric Average Annual Excess Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kofflard et al²</td>
<td>25</td>
<td>2500</td>
<td>15</td>
</tr>
<tr>
<td>Hecht et al⁷</td>
<td>43</td>
<td>443</td>
<td>13</td>
</tr>
<tr>
<td>Kofflard et al²</td>
<td>52</td>
<td>260</td>
<td>11</td>
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<tr>
<td>Cannan et al⁴</td>
<td>69</td>
<td>100</td>
<td>0</td>
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