Changing causes of heart valve disease mortality in New Zealand from 1988 to 2007

Sean Coffey, Brian Cox, Michael JA Williams

ABSTRACT

AIM: We wished to determine the mortality burden of valvular heart disease (VHD) in New Zealand, and how it changed prior to the introduction of transcatheter aortic valve replacement.

METHOD: Patient-level cause of death data from 1988 to 2007 were used to examine trends in VHD mortality rates over time. Our outcome measure was death, where the primary cause of death was valvular heart disease.

RESULTS: The annual number of VHD deaths increased 2.9% in New Zealand each year (p<0.001). The total VHD mortality rate increased with older age and male sex. There was little, if any, overall change in age- and sex-adjusted total VHD mortality rate over time (annual mortality rate ratio 0.998, p=0.21). The oldest age group, aged 85 years and above, which now contribute most to total VHD mortality, had an increase in mortality rate through the 1990s, which plateaued after the year 2000. The adjusted mortality rate for non-rheumatic aortic valve disease increased (p<0.001), while that for rheumatic heart disease and endocarditis decreased (p<0.001). Assuming VHD mortality rates remain stable, deaths due to VHD are projected to double over the next 25 years.

CONCLUSION: Adjusted VHD mortality rates showed no change over the two decades examined. Without a substantial reduction in mortality rates, the ageing population is likely to lead to an increase in VHD deaths in the future.

Valvular heart disease (VHD) is a common form of heart disease, and without treatment, end-stage VHD leads to heart failure and death. No medical therapy has proven successful in altering the progression of any form of VHD, so the mainstay of treatment is surgical valve repair or replacement.

VHD is strongly associated with older age. The ageing of the population in New Zealand, and other countries worldwide, suggests that VHD will become an increasing burden on healthcare systems. The development of transcatheter aortic valve replacement (TAVR) for use in patients with end-stage aortic stenosis (AS) at high or prohibitive surgical risk indicates an unmet need for treatment, especially in high-risk elderly patients. To estimate the burden of VHD in New Zealand and how it has changed over time, we examined mortality due to VHD prior to the introduction of TAVR.

Method

Classification of cause of death

This study focused on adult deaths where the primary cause of death was recorded as valvular heart disease. We confined our analysis to those aged 15 years or older to allow standard 5-year age groups to be constructed. To allow comparison of cause of death across two different International Classification of Diseases (ICD) coding eras, six disease groups were chosen, namely, non-rheumatic aortic valve disorders, non-rheumatic mitral valve disorders, endocarditis, mixed valve disease, rheumatic heart disease, and non-rheumatic right-sided valve disease. The corresponding ICD9 and ICD10 codes are listed in Table 1.

As the mixed valve disease code (396 in ICD9, I08 in ICD10) included both rheumatic and unspecified valve disease, this code was included for the analysis of total VHD, but excluded for analysis of rheumatic VHD. The
rheumatic heart disease analysis is therefore a conservative figure, but has been used to examine changes in RHD over time.

The first use of TAVR in New Zealand was in 2008, with heterogenous uptake of the new technology around the country. Given the uncertain impact that this would have on trends in mortality, we focused on data prior to this time point. Patient-level data was obtained from the New Zealand Ministry of Health Mortality Collection from 1 January 1988 to 21 December 2007, a total of 20 years. The cause of death was recorded using the 9th revision of the International Classification of Diseases (ICD9) until 1999, and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10) from the year 2000 onwards. To calculate age-specific mortality, historical population estimates from Statistics New Zealand were used. For mortality projections, given the minimal change in age-adjusted mortality rates over time and the uncertainties regarding changes in this rate due to new therapies, we applied the 2006 age-specific mortality rates to population projections, assuming medium fertility, medium mortality and medium net migration.

**Statistical analysis**

Linear regression was used to analyse changes in unadjusted mortality rates over time and one-way ANOVA to test differences between age-specific mortality rates. Poisson regression was used to analyse trends over time for mortality rates. Mortality rates were modelled by year, with age group and sex as indicator variables. Poisson regression for each age group and separately for each cause group was conducted, excluding right-sided VHD and those aged less than 20 years, due to infrequent deaths in this age group. The average percentage change in mortality rate was calculated by (mortality rate ratio – 1) x100%. Statistical tests were performed using Stata version 12.1 (Statacorp, College Station, Texas). We performed nonlinear least-squares estimation (Stata’s “nl” command) to detect changes in trends of age-specific mortality rates over time. If a knot was detected, we then constructed linear splines and performed piecewise negative binomial regression to determine both the trend in mortality rate ratio before and after the knot, and to test the statistical significance of the change in trend. As several analyses were conducted, p<0.01 was taken to represent statistically significant trends.

**Results**

**Unadjusted mortality**

There were 8,876 adults whose primary cause of death was coded as being due to valvular heart disease in New Zealand over the 20-year period from 1988 to 2007. The most common cause of VHD-related mortality was non-rheumatic aortic valve disease (AVD), which was responsible for 48.9% of all VHD deaths (Table 2 and Figure 1).

The mean age at death was 74.8 years (standard deviation 16.9). The age-specific mortality rate for total VHD increased with older age (one-way ANOVA p<0.001), from a mean over the 20-year period of 2.6 per 100,000 in the 15–59 year old group, to 303.3

<table>
<thead>
<tr>
<th>Table 1: Cause of death by group, with corresponding ICD9 and ICD10 codes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD9 codes</td>
</tr>
<tr>
<td>Nonrheumatic aortic valve disorders, including bicuspid aortic valve</td>
</tr>
<tr>
<td>Nonrheumatic mitral valve disorders</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Mixed valve disease, rheumatic or unspecified</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Nonrheumatic right sided disease</td>
</tr>
</tbody>
</table>
**Table 2:** Number of deaths due to valvular heart disease by age group and cause.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>15–54</th>
<th>55–64</th>
<th>65–74</th>
<th>75–84</th>
<th>≥ 85</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>895</td>
<td>725</td>
<td>1,468</td>
<td>3,049</td>
<td>2,739</td>
<td>8,876</td>
</tr>
<tr>
<td>Non-rheumatic aortic valve disease</td>
<td>145</td>
<td>211</td>
<td>577</td>
<td>1,678</td>
<td>1,730</td>
<td>4,341</td>
</tr>
<tr>
<td>Non-rheumatic mitral valve disease</td>
<td>87</td>
<td>95</td>
<td>249</td>
<td>419</td>
<td>333</td>
<td>1,183</td>
</tr>
<tr>
<td>Mixed valve disease</td>
<td>269</td>
<td>152</td>
<td>265</td>
<td>445</td>
<td>339</td>
<td>1,470</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>303</td>
<td>214</td>
<td>270</td>
<td>329</td>
<td>172</td>
<td>1,288</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>79</td>
<td>48</td>
<td>103</td>
<td>177</td>
<td>162</td>
<td>569</td>
</tr>
<tr>
<td>Right-sided valve disease</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

**Figure 1:** Mean age-specific mortality in New Zealand per 100,000 population over the period 1988–2007.

Total valvular heart disease is shown as well as its components. AVD: non-rheumatic aortic valve disease; MVD: non-rheumatic mitral valve disease; Mixed: mixed valve disease; Rheumatic: rheumatic heart disease.
**Figure 2:** Number of total valvular heart disease related deaths in New Zealand per year by age group.

**Figure 3:** Total number of deaths in New Zealand due to valvular heart disease (VHD) per year, with underlying category of VHD.

Abbreviations as for Figure 1.
per 100,000 in those 85 or more years of age (Figure 1). By 1993, the absolute number of deaths in the oldest age group (85 years and older) had increased to the point that this became the age group with the highest number of deaths (Figure 2).

The ICD10 coding allowed examination of the AVD deaths in more detail. There were 2,177 deaths due to AVD from the year 2000 onwards. The vast majority (85.8%) of these were due to aortic stenosis (1,867 deaths), 99 deaths (4.5%) due to aortic valve insufficiency, 83 deaths (3.8%) due to combined aortic valve stenosis and insufficiency, and 128 deaths (5.9%) due to other and unspecified aortic valve disorders.

### Trends in New Zealand mortality rates

The total annual number of deaths rose from 382 in 1988 to 539 in 2007 (Figure 3). Univariate unadjusted linear regression showed an overall increase of 2.9% per year for the 1988–2007 time period ($R^2=0.75$, $p<0.001$).

Overall age- and sex-adjusted mortality rates changed little over the 20 years examined (average decrease 0.2%, 95% confidence interval (95% CI) 0.6% decrease to 0.1% increase, $p=0.21$) (Table 3). Women had on average a 16.9% lower age-adjusted mortality rate compared to men (95% CI 13.3% to 20.3% lower, $p<0.001$). When individual age groups were examined, there was a significant overall annual increase of 3.56% in VHD mortality in the oldest age group aged 85 years or more (95% CI 2.85% to 4.28%, $p<0.001$), with stable or decreasing mortality rates in those aged less than 85 years (Figure 4). Given the non-linearity visible in Figure 4, we performed a piecewise regression analysis of the trend in age-specific mortality rates. Only the oldest age group had a statistically significant change in mortality rate ratio, from a 7.16% increase (95% CI 5.72% to 8.62%, $p<0.001$) before the year 2000, to 1.55% decrease subsequently (95% CI 3.21% decrease to 0.33% increase, $p=0.11$ for difference compared to no change in mortality rates, $p<0.001$ for change in trend before compared to after 2000). This confirms the visual appearance of an increase in mortality rate through the 1990s until a plateauing in the 2000s.

Differences in trends of adjusted mortality rates over time between the groups of causes of VHD are shown in Table 3. The age- and sex-adjusted AVD mortality rate increased overall by 1.4% per year (95% CI, 0.87% to 1.94%, $p<0.001$), and mixed valve disease increased by 4.3% per year (95% CI, 3.3% to 5.3%, $p<0.001$). The age- and sex-adjusted endocarditis and RHD mortality rates both decreased, by 6.8% per year (95% CI, 8.2% to 5.5%, $p<0.001$) and 6.6% per year (95% CI, 7.5% to 5.6%, $p<0.001$), respectively, while there was a smaller change in non-rheumatic mitral valve disease mortality (1.0% decrease per year, 95% CI, 2.0% decrease to 0.0%, $p=0.042$).

### Table 3: Changes in annual age- and sex-adjusted mortality rates from 1988 to 2007.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Average annual mortality rate ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>0.998 (0.994–1.001)</td>
<td>0.21</td>
</tr>
<tr>
<td>Non-rheumatic aortic valve disease</td>
<td>1.014 (1.009–1.019)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-rheumatic mitral valve disease</td>
<td>0.990 (0.980–1.000)</td>
<td>0.042</td>
</tr>
<tr>
<td>Mixed valve disease</td>
<td>1.043 (1.033–1.053)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>0.934 (0.925–0.944)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.932 (0.918–0.945)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note the average increase in annual mortality rate for non-rheumatic aortic valve disease and mixed valve disease, and an average decrease for rheumatic heart disease and endocarditis. Total valve disease and non-rheumatic mitral valve disease mortality rate did not show a statistically significant change at the pre-specified threshold of $p<0.01$. CI: confidence interval.
Figure 4: Annual age-specific mortality rate due to valvular heart disease from 1988 to 2007.

Figure 5: Projected absolute mortality due to all valvular heart disease in New Zealand from 2006 until 2041.
Projections

The increasing number of elderly people in the population leads to a large projected increase in the number of deaths due to VHD in New Zealand, with deaths per year due to approximately double by 2031 compared to 2006 figures (Figure 5).

Discussion

In this study, we have shown that there was minimal, if any, change in mortality rates due to VHD prior to the introduction of TAVR. The numbers of people dying due to VHD is largely driven by those dying of AVD, and AVD deaths have increased over the 20-year time period examined. Although there was a relatively even mix of VHD deaths in each age-category examined in 1988, more recently the highest number of deaths were in the very elderly (aged 85 years and over). Finally, we have also shown a lower age-adjusted VHD mortality rate in women compared to men. Overall, our findings are similar to those of another high-income country, the US.7

The Multi-Ethnic Study of Atherosclerosis (MESA) showed that older age and male sex increase the risk of both new aortic valve calcification and progression of existing calcification.8 Previous studies have shown that the prevalence of VHD markedly increases with increasing age, and that the majority of new diagnoses of moderate to severe VHD are in those aged over 74 years.3 The present study findings support these observations, and highlight that VHD is usually a disease of old age. In addition, age- and sex-adjusted total VHD mortality rates have been shown to change little over time, indicating that the changing population structure is primarily responsible for the increase in deaths due to VHD. The average life expectancy of men and women aged 80 in New Zealand is a further 8.5 and 8.8 years of life, respectively.9 The development of TAVR and, potentially, future treatments for VHD may improve the quality-of-life of some patients, even of relatively advanced age. How mortality due to calcific AVD will change due to TAVR or the improving mortality of coronary artery disease remains unclear.

We saw a decline in endocarditis-related mortality (Figure 3), which is contrary to the pattern seen in the US, where increasing endocarditis-related deaths and mortality rates have increased to the point that it is now the second leading cause of VHD death.7 A number of differences between the countries may explain this finding. The International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) recruited patients with endocarditis from 2000 to 2005,10 and found that Staphylococcus aureus, which is independently associated with higher mortality, was the causative organism in 24% of the New Zealand cohort. The vast majority (94%) of this was methicillin-sensitive. By contrast, S. aureus was the causative organism in 43% of the North American cohort,11 and 44% of the S. aureus isolates in the US were methicillin-resistant in an earlier report from ICE-PCS.12 There were also differing rates of endocarditis due to cardiac devices, accounting for 8% of cases in the North American cohort of ICE-PCS, but none in the New Zealand cohort.11 Finally, the reduction in endocarditis deaths closely follows the reduction seen in RHD deaths. Only 4% of the New Zealand cohort of ICE-PCS had underlying RHD, which, while direct comparisons are not available, is much lower than New Zealand figures reported prior to the study period examined.10 It is possible that the reduction in the burden of RHD, unaccompanied by an increase in high-risk endocarditis related to methicillin-resistant S. aureus, has combined to lead to the reduction in endocarditis mortality.

Overall, the reduction in annual RHD deaths and mortality rate mirrors findings worldwide, with a global survey showing a decline in both absolute numbers and age-standardised mortality due to RHD from 1990 to 2013.13 This global picture likely reflects a number of improvements over the preceding decades, such as the dramatic reduction in the incidence of acute rheumatic fever (ARF), which preceded the use of penicillin, as well as improved access to medical care.14-16 However Māori and Pacific groups in New Zealand are disproportionately burdened by acute rheumatic fever, and had an increasing incidence of ARF until very recently, despite decreasing incidence in the New Zealand European population.17 It is possible that this will translate into a higher RHD mortality burden in the future.
although the widespread use of secondary prophylaxis in New Zealand may reduce the degree of chronic valvulopathy, and therefore RHD mortality.\textsuperscript{18}

Although we wished to examine the mortality rates in different ethnic groups, ethnicity was not provided for mortality data prior to 1996. There are also other well described issues with coding of this information.\textsuperscript{19} However, the most important VHD associated with ethnicity is RHD, and this has been analysed recently,\textsuperscript{20} showing, as expected, higher mortality rates in Māori and Pacific people, with little change from 2000 to 2007. There was also a much lower mean age at death for Māori and Pacific groups, of less than 60 years, compared to 80 years for non-Māori/non-Pacific people. Our analysis similarly shows a more even distribution of deaths across the age-groups compared to other forms of VHD (Table 2 and Figure 1). The focus on mortality, which is relatively easy to quantify, therefore underestimates the disease burden of RHD, compared to measures such as loss of disability-adjusted life-years or economic productivity. Clearly, much work still remains in the control of RHD, especially in these high risk groups.

There are a number of limitations to the present study, especially the use of cause of death data. However, New Zealand is one of only 23 countries that have been classified by the World Health Organization as providing 'high-quality' cause of death data,\textsuperscript{21} and New Zealand has among the lowest rates of 'garbage' coding in the world.\textsuperscript{22} In addition, autopsy-based studies have shown that death certificates estimate relatively accurately or underestimate the number of deaths due to VHD.\textsuperscript{23-25} We examined only those deaths where the primary cause of death was recorded as VHD—the numbers with VHD as a contributory cause of death would be higher. The mortality rates described here are therefore likely to be conservative estimates.

The comparability of ICD9 and ICD10 codes is also an issue. In particular, the estimated comparability ratio for RHD is relatively low at 82%.\textsuperscript{26} However, both the decline in RHD deaths and the increase in AVD deaths (Figure 3) occurred in the 1990s before the introduction of the ICD10 coding. Finally, the dataset did not allow investigation of the contribution of confounders, such as concomitant coronary artery disease in patients with valvular heart disease.

In conclusion, the results of this study show VHD mortality has increased substantially over the two decades from 1988 to 2007. Due to the ageing of the population, the burden of VHD can be expected to increase for the foreseeable future. In addition to support from clinical trials of agents to modify the disease process, a sustainable health service response will be needed to deal with the expected increased demand on New Zealand's healthcare system.
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Competing interests: Nil

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