Technology Assessment Report No. 1

Lipid-Modifying Agents

Type: Detailed Cost-Utility Analysis
Author: Scott Metcalfe
Last Updated: June 1997
Cost-Utility Analysis

This paper describes a model which PHARMAC has developed to assess the costs and benefits of extending subsidy criteria for lipid-modifying agents (LMAs). The model assesses both need for and cost-effectiveness/benefits of these agents. Impact is in terms of costs and benefits, from two perspectives:

1. a financial perspective (costs and savings for pharmaceuticals), and
2. a health economic perspective (pharmaceuticals, plus other impact on health sector costs, mortality and quality of life). This relates to regional health authorities (RHAs), PHARMAC’s joint owners.

Neither of these perspectives include wider societal perspectives, such as economic productivity.

Programme effectiveness (apart from prevented hospitalisations, prevented non-LMA pharmaceutical usage, etc) comprise both death and illness/disability prevented. Health gains through prevented death and illness/disability can be combined as QALYs to give a single unit of benefit. This is where gains from death reductions are measured as whole life years gained, and non-death improvements are measured as quality-adjusted life years gained. Such unitary measures are regardless of the type of health status improvements.

Hence we have calculated for each subpopulation both:
- deaths and non-fatal CHD events prevented (effectiveness)
- net QALYs gained through these prevented deaths/non-fatal CHD events (benefits/utilities) over any particular time period.

Costs are compared against benefits of LMA programmes, according to a modification of Weinstein and Stason’s equation1:

\[
\text{(direct pharmaceutical costs of LMAs)} + \text{(other lipid-lowering programme costs)} + \text{(costs of drug side effects)} - \text{(costs of other pharmaceuticals associated with CHD and other atherosclerotic disease prevented or delayed)} - \text{[(hospitalisation and other non-drug morbidity-associated costs of CHD etc prevented)]} \\
\text{(years of life gained from premature deaths prevented)} + \text{(quality-adjusted years gained from illness prevented)} - \text{(quality-adjusted years lost from side-effects)}
\]

Establishing “need” is based on a combination of the NHF 1996 updated guidelines and the Pharmaceutical and Therapeutics Advisory Committee (PTAC) subcommittee on LMA’s suggested thresholds for LMA use. This has been described elsewhere.

We measured net programme benefits in quality-adjusted life years, comprising:
1. potential years of life saved (LYS) from net all-cause premature deaths prevented
2. QALY gains from non-fatal CHD events prevented
3. QALY losses from side effects/adverse effects of LMA pharmaceuticals and programmes2:

\[
\Delta Y_{SE} = \Delta Y + \Delta Y_{morb} - \Delta Y_{SE}
\]

where:
\[ \Delta E = \text{net quality-adjusted life year gains} \]
\[ \Delta Y = \text{LYS from all-cause deaths prevented (ie unadjusted life years)} \]
\[ \Delta Y_{\text{morb}} = \text{QALY (gains) from non-fatal CHD events prevented (ie improvements in quality of life years due to prevention of morbidity)} \]
\[ \Delta Y_{\text{SE}} = \text{QALY (losses) from side effects/adverse effects of LMA pharmaceuticals and programmes (ie treatment side effects)} \]

We calculated life years saved and QALYS by combining:
- absolute risk of cardiovascular events and total mortality (AR)
- relative risk reductions through LMA use (RRR)

\[(\text{where } AR \times RRR = ARR)\]
- life expectancy (LE)
- health state utility values (QALY scores) (q)

to produce net quality-adjusted life years saved (QALYS), where

\[ q_{\text{base}} = \text{utility value (QALY score) for baseline health state} \]
\[ q_{\text{CHD}} = \text{utility value (QALY score) for CHD (0.925 TTO)} \]
\[ q_{\text{death}} = \text{utility value (QALY score) for death (0.000)} \]
\[ q_{\text{RxSE}} = \text{utility values (QALY scores) for Rx side effects} \]

\[ \text{QALYS} = AR \cdot RRR \cdot LE \cdot (1-q) \]

\[ \text{ARR}_{\text{death}} = AR_{\text{death}} \cdot RRR_{\text{death}} \]
\[ \text{ARR}_{\text{morb}} = AR_{\text{morb}} \cdot RRR_{\text{morb}} \]

\[ \text{potential years of life lost, premature death (PYLL}_{\text{death}}) = \text{ARR}_{\text{death}} \cdot LE \cdot (1-q_{\text{death}}) \cdot q_{\text{base}} \]

\[ \text{potential years of life saved, premature death prevented (\Delta Y)} = \text{ARR}_{\text{death}} \cdot LE \cdot (1-q_{\text{death}}) \cdot q_{\text{base}} \]

\[ \text{years of quality-adjusted life lost, morbidity (QYLL}_{\text{morb}}) = \text{ARR}_{\text{morb}} \cdot LE \cdot (1-q_{\text{CHD}}) \cdot q_{\text{base}} \]

\[ \text{years of quality-adj life gained, morbidity (\Delta Y}_{\text{morb}}) = \text{ARR}_{\text{morb}} \cdot LE \cdot (1-q_{\text{CHD}}) \]

\[ \text{years of quality-adjusted life lost, Rx side effects (\Delta Y}_{\text{SE}}) = \text{duration of Rx use} \cdot (1-q_{\text{RxSE}}) \]

\[ \text{net quality-adjusted life year gains (\Delta E)} = \Delta Y + \Delta Y_{\text{morb}} - \Delta Y_{\text{SE}} \]

We then combined QALYS with cost data and prevalence data (age/sex/CHD status/recommended Rx class) to derive average costs/QALYS. QALYS and cost data comprised both
- direct pharmaceutical and net health sector costs, and
- ideal and actual QALYS (accounting for Rx discontinuations),
to derive four levels of cost/QALYS:

<table>
<thead>
<tr>
<th></th>
<th>direct pharmaceutical costs</th>
<th>net health sector costs (includes hospitalisation offsets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>potential QALYS (cf trial data)</td>
<td>direct cost/potential QALYS</td>
<td>net cost/potential QALYS</td>
</tr>
<tr>
<td>actual programme QALYS (includes Rx discontinuation)</td>
<td>direct cost/actual QALYS</td>
<td>net cost/actual QALYS</td>
</tr>
</tbody>
</table>

Most cost/QALYS reported are net cost/potential QALYS (ie potential QALYS (cf trial data) and net health sector costs (including hospitalisation offsets))
We based the model around four key variables, viz age, sex, CHD status, and class of LMA. These in turn contained 23 subvariables, which when combined formed 480 strata for analysis (10 x 2 x 8 x 3):

<table>
<thead>
<tr>
<th>age</th>
<th>sex</th>
<th>CHD status</th>
<th>LMA class</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-39</td>
<td>men</td>
<td>pre-existing CHD, cholesterol ≥7.5 mmol/l</td>
<td>fibrates</td>
</tr>
<tr>
<td>40-44</td>
<td>women</td>
<td>pre-existing CHD, cholesterol 6.5-7.4 mmol/l</td>
<td>statins</td>
</tr>
<tr>
<td>45-49</td>
<td></td>
<td>pre-existing CHD, cholesterol 5.5-6.4 mmol/l</td>
<td>combined fibrate/statin programme</td>
</tr>
<tr>
<td>50-54</td>
<td></td>
<td>pre-existing CHD, cholesterol &lt;5.5 mmol/l</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td></td>
<td>genetic lipoprotein disorders*</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td></td>
<td>“at risk” with &gt;20% 5-year risk of CVS events**</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td></td>
<td>“at risk” with 15-20% 5-year risk</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td></td>
<td>“at risk” with 10-15% 5-year risk</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aka familial xanthomas, viz familial hypercholesterolaemia, familial dysbetalipoproteinemia
**as estimated from the Framingham logistic equation

The model takes a 5-year perspective for costs and benefits, ie the benefits and costs of taking LMAs for 5 years. This is consistent with the NHF 1996 guidelines’ 5-year risk categories and 1-5 year reassessment schedules. The model hence assumes that a patient will be reviewed at least every 5 years, and that when reviewed they are effectively a different patient, with a new likelihood of benefit (because of new life expectancy and new absolute risk reduction). Hence, once started, patients will not necessarily remain on LMAs for the rest of their lives.

For summary purposes, we reported on QALYs etc for each CHD status/LMA class population by broad age groups, combining both sexes. These were derived by aggregating component 5-year age/sex QALYs etc, then direct standardising to the age/sex distributions of the Fletcher Challenge-University of Auckland Heart and Health Study (FCUAHHS) combined with “need” defined by the National Heart Foundation and PHARMAC’s PTAC subcommittee (described in Annex). Similarly, we derived fibrate/statin programme QALYS by direct standardising to the 5-year age/sex/LMA eligibility criteria distributions of the FCUAHHS prevalence data:

---

1 The Fletcher Challenge-University of Auckland Heart and Health Study (FCUAHHS) undertaken in 1993/94 was based on a random sample of 2,465 European urban Aucklanders drawn from the general electoral roll. These included 370 people with evidence of current or past coronary heart disease. The study measured inter alia the prevalence of total cholesterol levels and total:HDL cholesterol ratios according to age, sex, and past history and/or absolute risk of coronary heart disease (according to the Framingham equation) [Source of raw data: Rod Jackson and Roy Lay Yee, Auckland School of Medicine].

II need is determined by: absolute CHD risk; total cholesterol; total:HDL cholesterol ratio; impact of dietary and other modification of lipid and other risk factors; and class of LMA
Age distributions by CHD status (AHHH Study)

Likely prevalence of LMA need by age and CHD status/risk

LMA need

<table>
<thead>
<tr>
<th>Population characteristics</th>
<th>Need (Auckland H&amp;H Study prevalence data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD status</td>
<td>gender</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>total m&amp;f</td>
<td>35-69</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>past CHD m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>at risk m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>total m&amp;f</td>
<td>70-84</td>
</tr>
<tr>
<td>total, all ages 35-84 m&amp;f</td>
<td>25-84 m&amp;f</td>
</tr>
<tr>
<td>NHF risk groups, m&amp;f 35-69</td>
<td>4.2%</td>
</tr>
</tbody>
</table>
All-cause deaths (AR\textsubscript{death}) expected for eligible populations

To calculate baseline absolute risks of all-cause deaths in patients with pre-existing CHD (ie population 1), we combined longitudinal mortality rates for patients with CHD from the ARCOS register with GISSI-2\textsuperscript{3} and Framingham 30-year follow-up data\textsuperscript{4} for each 5-year age/sex-specific group:

We first obtained numbers of:
- CHD patients surviving more than 28 days of an initial CHD event
- numbers of patients who then died from an cause during a time period
- numbers of patients lost to follow-up during a time period
- numbers of patients surviving at the end of a time period
of registrants aged 35 to 64 years for the period 1986 to 1992 in the Auckland Regional Coronary Outcomes Study (ARCOS, the New Zealand centre of the WHO’s MONICA project) [Robert Beaglehole and Alistair Stewart, personal communication]. These data were stratified by age (5-year bands), sex, and time period (28 days to 6 months, 6 months to three years).

Numbers of ARCOS 28-day survivors (1980-92 Auckland region)

<table>
<thead>
<tr>
<th>gender</th>
<th>age-group</th>
<th>ARCOS 28-day survivors (surviving &lt;28 days)</th>
<th>surviving &gt;28 days</th>
<th>deaths 28d-6m</th>
<th>deaths 6m-3y</th>
<th>lost to FU 28d-6m</th>
<th>lost to FU 6m-3y</th>
<th>surviving at 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td>35-39</td>
<td>157</td>
<td>59</td>
<td>98</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>men</td>
<td>40-44</td>
<td>321</td>
<td>111</td>
<td>210</td>
<td>5</td>
<td>11</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>men</td>
<td>45-49</td>
<td>517</td>
<td>180</td>
<td>337</td>
<td>5</td>
<td>19</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>men</td>
<td>50-54</td>
<td>717</td>
<td>296</td>
<td>419</td>
<td>8</td>
<td>29</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>men</td>
<td>55-59</td>
<td>1055</td>
<td>487</td>
<td>568</td>
<td>11</td>
<td>39</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>men</td>
<td>60-64</td>
<td>1284</td>
<td>637</td>
<td>647</td>
<td>23</td>
<td>53</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>total men</td>
<td></td>
<td>4051</td>
<td>1772</td>
<td>2279</td>
<td>56</td>
<td>154</td>
<td>147</td>
<td>26</td>
</tr>
<tr>
<td>women</td>
<td>35-39</td>
<td>24</td>
<td>9</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>women</td>
<td>40-44</td>
<td>75</td>
<td>30</td>
<td>45</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>women</td>
<td>45-49</td>
<td>104</td>
<td>50</td>
<td>54</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>women</td>
<td>50-54</td>
<td>169</td>
<td>75</td>
<td>94</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>women</td>
<td>55-59</td>
<td>284</td>
<td>116</td>
<td>168</td>
<td>5</td>
<td>13</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>women</td>
<td>60-64</td>
<td>482</td>
<td>252</td>
<td>230</td>
<td>10</td>
<td>20</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>total women</td>
<td></td>
<td>1138</td>
<td>532</td>
<td>606</td>
<td>25</td>
<td>43</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>5189</td>
<td>2304</td>
<td>2885</td>
<td>81</td>
<td>197</td>
<td>184</td>
<td>30</td>
</tr>
</tbody>
</table>

We used these data to calculate 3-year mortality rates for each age/sex group, taking into account those lost from follow-up. Given inconsistencies in mortality rates with variability from low numbers of registrants in certain age/sex groups, we recalculated mortality by combining certain age-groups into 10- or 15-year cohorts, namely men 35-44, men 45-54, and women 35-49. We then estimated 5-year mortality rates by scaling the ARCOS 3-year mortality rates against the 3 year and 5 year survival rates for MI survivors in the Framingham 30-year follow-up:

![5-year all-cause mortality rates](image)

To estimate 5-year death rates for those CHD patients aged 65 and over, we then scaled the ARCOS 28-day survivors’ assumed 5-year mortality for those aged 60-64 against: GISSI-2 mortality between 28 days and 6 months, stratified by age (ages 65 to 84), and the all-cause death relative risks for ages 65-94 for the CHD cohort at 6 months and 5 years from the Framingham 30-year follow-up:

\[
\text{d}(as) = \text{d}_{\text{ARCOS 60-64}}(s) \times \frac{\text{d}_{\text{GISSI 2 28d-6m}}(as)}{\text{d}_{\text{GISSI 2 28d-6m (60-64)}}} \times \frac{\text{d}_{\text{Fram 5m}}(as)}{\text{d}_{\text{Fram 5m}}(as)}
\]
where:

- \( d_{\text{ARCOS}} \) = age/sex-specific 5-year all-cause mortality rate, estimated for ARCOS population ages 65-84
- \( d_{\text{ARCOS} 60-64} \) = age/sex-specific 5-year all-cause ARCOS mortality rate, aged 60-64 years
- \( d_{\text{GISSI-2} 28d-6m} \) = GISSI-2 age-specific 28-day to 6-month all-cause mortality rate, for ages 65-84
- \( d_{\text{GISSI-2} 28d-6m (60-64)} \) = GISSI-2 age-specific 28-day to 6-month all-cause mortality rate, aged 60-64
- \( d_{\text{Fram} 5y} \) = Framingham 30-year FU 5-year cumulative mortality rate, CHD men/women 35-64/65-94
- \( d_{\text{Fram} 5m} \) = Framingham 30-year FU 5-month cumulative mortality rate, CHD men/women 35-64/65-94

**Calculated 5-year all-cause mortality rates for CHD survivors**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Calculated Rates and Ratios</th>
<th>Rate Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARCONS + GISSI-2/FRAM</td>
<td>ARCONS + GISSI-2/FRAM</td>
</tr>
<tr>
<td></td>
<td>non-CHD, low</td>
<td>non-CHD, low</td>
</tr>
<tr>
<td></td>
<td>ARCOS/AKH&amp;H</td>
<td>ARCOS/AKH&amp;H</td>
</tr>
<tr>
<td></td>
<td>(of 4S)</td>
<td>(of 4S)</td>
</tr>
<tr>
<td>men</td>
<td>(estimated NZ</td>
<td>NZ all (life</td>
</tr>
<tr>
<td>35-39</td>
<td>16.6% 0.5% 11.3% 16.6%</td>
<td>table)</td>
</tr>
<tr>
<td>40-44</td>
<td>17.3% 0.8% 12.2% 17.3%</td>
<td>1.2% 0.7% 14.9 23.1</td>
</tr>
<tr>
<td>45-49</td>
<td>17.9% 0.5% 12.8% 17.9%</td>
<td>1.7% 0.6% 10.5 31.3</td>
</tr>
<tr>
<td>50-54</td>
<td>18.9% 1.9% 14.0% 18.8%</td>
<td>2.9% 1.8% 6.4 10.4</td>
</tr>
<tr>
<td>55-59</td>
<td>19.7% 3.1% 15.1% 19.7%</td>
<td>5.0% 3.2% 4.0 6.1</td>
</tr>
<tr>
<td>60-64</td>
<td>26.6% 5.9% 23.8% 26.6%</td>
<td>8.0% 5.8% 3.3 4.6</td>
</tr>
<tr>
<td>65-69</td>
<td>29.1% 6.6% 26.1% 29.1%</td>
<td>13.0% 6.3% 2.2 4.7</td>
</tr>
<tr>
<td>70-74</td>
<td>30.4% 17.0% 27.2% 30.4%</td>
<td>19.9% 14.4% 1.6 2.0</td>
</tr>
<tr>
<td>75-79</td>
<td>32.7% 28.0% 29.3% 32.7%</td>
<td>29.9% 28.4% 1.1 1.2</td>
</tr>
<tr>
<td>80-84</td>
<td>44.2% 41.8% 39.6% 44.2%</td>
<td>42.8% 42.3% 1.0 1.0</td>
</tr>
<tr>
<td>85-89</td>
<td><strong>66.4%</strong> 51.0% 64.7% 66.4%</td>
<td>57.8% 54.2% 1.1 1.2</td>
</tr>
<tr>
<td>90+</td>
<td><strong>100.0%</strong> 100.0% 100.0% 100.0%</td>
<td>100.0% 100.0% 1.0 1.0</td>
</tr>
<tr>
<td>women</td>
<td>(estimated NZ  low</td>
<td>NZ all (life</td>
</tr>
<tr>
<td>35-39</td>
<td>14.4% 0.4% 9.7% 14.4%</td>
<td>table)</td>
</tr>
<tr>
<td>40-44</td>
<td>15.7% 0.6% 11.3% 15.7%</td>
<td>0.8% 0.5% 20.0 33.0</td>
</tr>
<tr>
<td>45-49</td>
<td>17.0% 0.9% 13.0% 17.0%</td>
<td>1.2% 0.4% 14.0 39.1</td>
</tr>
<tr>
<td>50-54</td>
<td>18.3% 1.4% 14.7% 18.3%</td>
<td>2.9% 1.2% 8.9 14.7</td>
</tr>
<tr>
<td>55-59</td>
<td>18.7% 2.0% 15.6% 18.7%</td>
<td>3.2% 1.3% 5.9 14.6</td>
</tr>
<tr>
<td>60-64</td>
<td>22.4% 3.1% 15.6% 22.4%</td>
<td>5.0% 2.8% 4.5 8.0</td>
</tr>
<tr>
<td>65-69</td>
<td>24.5% 2.8% 17.0% 24.5%</td>
<td>7.4% 2.1% 3.3 11.8</td>
</tr>
<tr>
<td>70-74</td>
<td>25.6% 7.9% 17.8% 25.6%</td>
<td>15.9% 7.1% 2.2 3.6</td>
</tr>
<tr>
<td>75-79</td>
<td>27.6% 15.8% 19.2% 27.6%</td>
<td>18.8% 16.1% 1.5 1.7</td>
</tr>
<tr>
<td>80-84</td>
<td>37.2% 27.0% 25.9% 37.2%</td>
<td>30.2% 29.0% 1.2 1.3</td>
</tr>
<tr>
<td>85-89</td>
<td><strong>52.9%</strong> 43.0% 44.4% 52.9%</td>
<td>46.1% 43.9% 1.1 1.2</td>
</tr>
<tr>
<td>90+</td>
<td><strong>100.0%</strong> 100.0% 100.0% 100.0%</td>
<td>100.0% 100.0% 1.0 1.0</td>
</tr>
</tbody>
</table>
We next used UK cohort data for familial hyperlipidaemia⁷ to calculate population 2’s all-cause mortality rates, extrapolating from the total New Zealand life table experience for those aged 75 years and over. We adjusted these UK mortality rates to account for them being confounded by some patients being on lipid-lowering treatment, to calculate all-cause mortality for patients not using LMAs.iii

We estimated 5-year all-cause mortality for each level of absolute risk in population 3, firstly estimating 5-year mortality for the overall non-CHD population (populations 2 and 3) from prevalence data and the above population 1 and NZ life table mortality ratesiv, then linear scaling to calculate each risk levels’ 5-year all-cause mortalityv, using:

### iii calculations for population 2 5-year mortality rates:

\[
\begin{align*}
\text{d}_{as} &= \left(\frac{n}{py}\right) \times 5 \\
\text{adas} &= \frac{\text{d}_{as}}{(1 / (1+RR_a)) \times c} + (1 - c)
\end{align*}
\]

where:

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>d_{as}</td>
<td>5-year mortality rate for age/sex group</td>
</tr>
<tr>
<td>n</td>
<td>no. deaths (BMJ 1991)</td>
</tr>
<tr>
<td>py</td>
<td>person years on register (BMJ 1991)</td>
</tr>
<tr>
<td>ad_{as}</td>
<td>adjusted 5-year mortality rate for age/sex group</td>
</tr>
<tr>
<td>RR_a</td>
<td>4S age-specific relative risk of all-cause death for statin treatment</td>
</tr>
<tr>
<td>c</td>
<td>coverage/uptake of statins amongst population 2 UK cohort patients, assumed at 80%</td>
</tr>
</tbody>
</table>

### iv calculations for 5-year mortality for the overall non-CHD population (populations 2 and 3):

for any age/sex group, assuming:

- CHD 5-year mortality rate \(d_{(CHD)}\) = ARCOS, with GISSI-2/Framingham 30yFU extrapolation (65-84 years)
- CHD survivor prevalence \(\rho_{(CHD)}\) = FCUAHHS prevalence

and where:

\[
\begin{align*}
\text{n}_{(total)} &= \text{total number of NZ deaths (CHD + non-CHD)} \\
\text{n}_{(CHD)} &= \text{number of CHD deaths} \\
\text{n}_{(non-CHD)} &= \text{number of non-CHD deaths} \\
\text{P}_{(total)} &= \text{total NZ population (CHD + non-CHD)} \\
\text{P}_{(CHD)} &= \text{CHD population} \\
\text{P}_{(non-CHD)} &= \text{non-CHD population} \\
\rho_{(CHD)} &= \text{prevalence of CHD} \\
\rho_{(non-CHD)} &= \text{prevalence of non-CHD,} \\
\text{CHD survivor prevalence (\rho}_{(CHD)}\text{)} &= \text{FCUAHHS prevalence}
\end{align*}
\]

and if \(\text{n}_{(CHD)} + \text{n}_{(non-CHD)} = \text{n}_{(total)}\) then

\[
\begin{align*}
\frac{(d_{(CHD)} \times \rho_{(CHD)} \times P_{(total)}) + (d_{(non-CHD)} \times \rho_{(non-CHD)} \times P_{(total)})}{(1 - \rho_{(CHD)})} &= (d_{(total)} \times 100\% \times P_{(total)}) \\
\therefore d_{(non-CHD)} &= \frac{(d_{(total)} \times \rho_{(CHD)} \times P_{(total)})}{(1 - \rho_{(CHD)})}
\end{align*}
\]

### v Linear scaling for each risk levels’ 5-year all-cause mortality:

\[
\begin{align*}
\frac{d_{(CHD)} - d_{(non-CHD)}}{e_{(no CHD)} - e_{(CHD)}} &= \text{rate of excess deaths due to presence of CHD} \\
\frac{d_{(non-CHD, at risk level)}}{e_{(no CHD, at risk level)}} &= \text{expected 5-year event rate for CHD events for those with pre-existing CHD} \\
\frac{d_{(non-CHD, at risk level)}}{e_{(no CHD, at risk level)}} &= \text{average expected 5-year event rate for all CHD events for those without pre-existing CHD} \\
\frac{e_{(no CHD, at risk level)}}{e_{(CHD)}} &= \text{specific level of expected 5-year events, in patients without pre-existing CHD}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>d_{(CHD)}</td>
<td>CHD mortality rate</td>
</tr>
<tr>
<td>d_{(non-CHD)}</td>
<td>non-CHD mortality rate</td>
</tr>
<tr>
<td>d_{(non-CHD, at risk level)}</td>
<td>expected 5-year event rate for all CHD events for those with pre-existing CHD</td>
</tr>
<tr>
<td>e_{(no CHD)}</td>
<td>average expected 5-year event rate for all CHD events for those without pre-existing CHD</td>
</tr>
<tr>
<td>e_{(no CHD, at risk level)}</td>
<td>specific level of expected 5-year events, in patients without pre-existing CHD</td>
</tr>
</tbody>
</table>
the differences between CHD and non-CHD mortality rates (as the excess risk of dying due to the presence of CHD), and expected 5-year CHD event rates, using mainly the median values of the Framingham 5% bands\textsuperscript{vi}

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
"At risk" group (Framingham logistic function) & Median risk value \\
\hline
<5 % & 2.5% \\
5-10 % & 7.5% \\
10-15 % & 12.5% \\
15 - 20 % & 17.5% \\
\geq 20% & 22.5% \\
\hline
\end{tabular}
\end{table}

\textsuperscript{vi} 5-year CHD events rates used the mid-point of each of population 3’s 5% Framingham bands for total CHD events (fatal and non-fatal). This was except for notional 22.5% median values for those with 5-year absolute risks of 20% and above, and notional 2.5% median values for those with risks of below 5%.
To calculate 5-year all-cause mortality rates for the cholesterol subdivisions of population 1, we also linearly scaled using:
- average CHD mortality rates,
- expected 5-year CHD event rates for each subdivision, and
- the differences between average CHD and non-CHD mortality rates.

We quantified 5-year absolute CHD event rates (fatal plus non-fatal) for the subdivisions of population 1 by total cholesterol as follows:

- Framingham CHD age x cholesterol
- Framingham CHD sex x cholesterol
- Framingham CHD age/sex x chol
  - age/sex x chol rr, relative to lowest chol (<5.17 Framingham, 4.7 AkH&H)
- AkH&H mean chol x age/sex
  - age/sex x chol rr (rel to mean AkH&H levels' rates for each age/sex)
- age/sex overall CHD event rates
  - age/sex/chol event rates (with max and min levels)
Firstly, we combined Framingham 30-year follow-up CHD cohort age-specific and sex-specific event rates by total cholesterol, in order to extrapolate age/sex-specific relative risks by total cholesterol:

![Relative risk of events in patients with past MI, by age (Framingham data)](image1)

![Relative risk of events in patients with past MI, by sex (Framingham data)](image2)

![Relative risk of all-cause death in patients with past MI, calculated from Framingham Study for age-sex groups)](image3)

![Relative risk of reinfarction (fatal & non-fatal) in patients with past MI, calculated from Framingham Study for age-sex groups)](image4)

We next assumed a log-linear dose-response relationship between total cholesterol and 5-year event rates, using the relationship of on average a 25% increase in CHD incidence for every 0.6 mmol/l increase in total cholesterol. Using this assumption, we calculated age/sex-specific risks by total cholesterol relative to the lowest grouping of cholesterol (<5.17 mmol in the Framingham cohort, which equated to an average level of 4.7 mmol/l in FCUAHHS data), using the function $1.25^{[(\text{cholesterol level} - \text{mean cholesterol level for age/sex group})/0.6]}$.

We next estimated absolute 5-year CHD event rates, for each age/sex/cholesterol group:

- We firstly recalculated the above cholesterol-related relative risks, to account for how each age/sex group differs in it distribution of cholesterol levels (and how these affect where baseline risk is set). We did this by resetting each age/sex group’s baseline relative risk (ie RR = 1.0) from that of the 4.7 mmol/l lowest grouping of FCUAHHS (equating to <5.17 mmol/l used in the Framingham cohort), to each age/sex’s mean total cholesterol values found in FCUAHHS.
We then multiplied these new relative risks by the 5-year age/sex-specific rates for population 1 overall (see above), to obtain each age/sex/cholesterol 5-year risk. For each age/sex group in population 1,

$$e_{e}(as)(chol) = r(chol) \times e(as)$$

where

- $e_{e}(as)(chol)$ = 5-year risk of CHD events for a particular level of cholesterol (for the age/sex group)
- $r(chol)$ = reset relative risk of CHD events for that level of cholesterol, relative to risk at the (age/sex group’s) mean cholesterol level
- $e(as)$ = 5-year risk of CHD events overall (for the age/sex group)

The above calculations produced all-cause mortality rates for each subpopulation, taking into account the risks of suffering coronary events.
Calculated 5-year all-cause mortality, patients with pre-existing CHD

- cholesterol <5.5 mmol/l
- cholesterol 5.5-6.4 mmol/l
- cholesterol 6.5-7.4 mmol/l
- cholesterol >=7.5 mmol/l
- (all CHD)
- (non pCHD)
Non-fatal CHD events (AR$_{morb}$) expected for eligible populations

ARCOS data for further CHD events (fatal and non-fatal) in population 1 were not currently available. Hence, we applied Framingham event rates to the ARCOS mortality rates. We first estimated age/sex-specific non-fatal CHD:total mortality ratios from the Framingham 30-year follow-up mortality and non-fatal CHD event rates for those with recognised myocardial infarction by broad age-group by sex, using linear scaling for 5-year age-groups:

We then applied these age/sex non-fatal CHD:total mortality ratios to the estimated ARCOS 5-year all-cause mortality rates. In addition however, we modified the non-fatal CHD:total death ratios for men to reflect the lesser differential in secondary case fatality rates (ie fatal:total CHD events) between older and younger age-groups in the 4S placebo group$^{[viii]}$.

<table>
<thead>
<tr>
<th>4S, Framingham and ARCOS 5-year event rates</th>
<th>cumulative event rate at 5 years</th>
<th>ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>all-cause death</td>
<td>CHD death</td>
</tr>
<tr>
<td>45-59 (men)</td>
<td>7.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>60-69 (men)</td>
<td>13.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Framingham 30-year follow-up, men, recognised MI:</td>
<td>15.8%</td>
<td>2.9%</td>
</tr>
<tr>
<td>60-69 (men)</td>
<td>38.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Framingham ratios, adjusted for 4S experience</td>
<td>40%</td>
<td>2.07</td>
</tr>
<tr>
<td>ARCOS:</td>
<td>18.6%</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

$^{[viii]}$ In 4S, non-fatal CHD placebo 5-year rates were 18.4% and 16.7% for 35-59 year olds and 60-70 year olds respectively (mainly men in both age-groups). By contrast, in the Framingham 30-year follow-up the equivalent rates were 25% and 16% - a much sharper difference. Yet both 4S and Framingham showed no difference between old and younger age-groups for total CHD events. Given the recent declines in the incidence of fatal CHD in men over that of non-fatal MI events*, then 4S differentials in fatal:total and non-fatal:total CHD by age may be more realistic, ie secondary CHD fatality does not increase as much with age as occurred in Framingham.

*eg ARCOS 1980-92 4.3% and 3.4% annual declines in men’s age-standardized incidence of fatal and non-fatal CHD respectively [Beaglehole R, Jackson R, Stewart A, for the Auckland MONICA team. The WHO MONICA project and trends in Auckland. Presentation at Cardiovascular disease: from epidemiology to policy and practice, University of Auckland, 3-4 August 1995]
For non-fatal CHD event rates for both
- the cholesterol subdivisions of population 1, and
- each 5% Framingham risk band of population 3,
We applied each age/sex secondary case-survival rate based on ARCOS to the age/sex/cholesterol or risk-band’s total CHD risk (ie event rates, calculated above), ie

\[
\text{non-fatal CHD events}_{\text{age/sex/cholesterol or risk}} = \left(1 - \frac{\text{A fatal CHD events}_{\text{age/sex}}}{\text{A total CHD events}_{\text{age/sex}}}\right) \times \text{CHD risk}_{\text{age/sex/cholesterol or risk}}
\]

where

\[
\begin{align*}
\text{A fatal CHD events}_{\text{age/sex}} &= \text{ARCOS-based CHD deaths by age/sex, calculated above} \\
\text{A total CHD events}_{\text{age/sex}} &= \text{ARCOS-based total CHD events by age/sex, calculated above} \\
\text{A fatal CHD events}_{\text{age/sex}} &= \text{ARCOS-based case fatality rate}_{\text{age/sex}} \\
\text{A total CHD events}_{\text{age/sex}} &= \text{secondary case survival rate} = 1 - \text{case fatality rate} \\
&= 1 - \frac{\text{fatal CHD events}}{\text{total CHD events}}
\end{align*}
\]

We used British cohort data\textsuperscript{11} to calculate population 2’s total CHD event rates, then using
- the event rates for 60-69 year olds for those aged 70-84, and
- modified Framingham age/sex case-fatality rates
to calculate non-fatal CHD event rates.
Relative risk reductions (RRR) through LMA use by each subpopulation

To calculate RRRs for each age-group by each CHD status by each type of LMA for each major end-point (all-cause death or non-fatal CHD), we sequentially derived:

1. RRRs for all-cause death for statins, patients with pre-existing CHD, aged 35-69
2. RRRs for all-cause death for statins, patients with pre-existing CHD, all ages
3. RRRs for all-cause death for statins, all ages, all CHD groups (including population 3 i.e. "at risk"); and cholesterol subdivisions of population 1
4. RRRs for all-cause death, all ages, all CHD groups, for fibrates
5. RRRs for non-fatal CHD by age (all ages, all risk groups, all LMA types):

We based the model’s RRR parameters for people with pre-existing CHD aged 35-69 on age-related RRRs calculated from 4S\textsuperscript{12}, but modified for a less marked difference between older and younger patients evident from meta-analysis of statin RCTs (4S was the only reported to date designed with sufficient power to demonstrate statistically significant improvements in all-cause mortality, is consistency with the overall evidence for statin efficacy in secondary prevention, and its study population is most similar to proposed populations eligible for statins in terms of CHD risk and total cholesterol levels. However, CARE\textsuperscript{13} showed a markedly different age-related pattern from 4S, and 4S may have underestimated potential RRRs in older patients through its exclusion criteria.):
We started with the RRRs reported by 4S by age for total CHD events, viz 39% for ages 35-59 and 29% for ages 60-70. We then combined the three major statin age-related prospective RCTs reported to date (4S, WOSCOPS14 and CARE15) to derive age-related RRRs for total CHD events for statins, viz 34% for younger patients and 28% for older. Next we combined the meta-analysis pattern of RRR by age back to 4S, to derive adjusted 4S RRRs by age for total CHD events of 38% for ages 35-59 and 31% for ages 60-70.
2. For those in population 1 aged ≥70 years using statins, we scaled the adjusted 4S age-dependent RRRs for total CHD against the RRRs reported in the analysis by Law et al of cholesterol lowering upon the incidence of CHD (relative reductions in CHD from decreases in cholesterol, stratified by age)\(^\text{16}\), to obtain age-specific RRRs in CHD incidence.\(^\text{ix}\)

3. | total CHD events: (Law meta-analysis) | RRR: adjusted (combined, combined, average weighted) | WOSCOPS II adj total CHD | WOSCOPS adj total CHD | 4S actual total CHD | WOSCOPS II actual total CHD |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years) (Law meta-analysis)</td>
<td>4S/WOSCOPS/CARE</td>
<td>4S adj total CHD</td>
<td>4S adj total CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47.5</td>
<td>43%</td>
<td>35%</td>
<td>36%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>50.0</td>
<td>39%</td>
<td>33%</td>
<td>35%</td>
<td>39%</td>
<td>36%</td>
</tr>
<tr>
<td>50.5</td>
<td>38%</td>
<td>33%</td>
<td>34%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>51.0</td>
<td>38%</td>
<td>33%</td>
<td>34%</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>51.5</td>
<td>37%</td>
<td>33%</td>
<td>34%</td>
<td>38%</td>
<td>35%</td>
</tr>
<tr>
<td>52.5</td>
<td>36%</td>
<td>32%</td>
<td>33%</td>
<td>38%</td>
<td>34%</td>
</tr>
<tr>
<td>55.0</td>
<td>33%</td>
<td>31%</td>
<td>32%</td>
<td>36%</td>
<td>33%</td>
</tr>
<tr>
<td>57.5</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>35%</td>
<td>31%</td>
</tr>
<tr>
<td>60.0</td>
<td>28%</td>
<td>29%</td>
<td>29%</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td>62.5</td>
<td>25%</td>
<td>28%</td>
<td>28%</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>63.7</td>
<td>24%</td>
<td>28%</td>
<td>28%</td>
<td>32%</td>
<td>28%</td>
</tr>
<tr>
<td>64.3</td>
<td>24%</td>
<td>28%</td>
<td>27%</td>
<td>32%</td>
<td>28%</td>
</tr>
<tr>
<td>65.0</td>
<td>24%</td>
<td>27%</td>
<td>27%</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>65.5</td>
<td>23%</td>
<td>27%</td>
<td>27%</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>old:young ratio</td>
<td>0.79</td>
<td>0.75</td>
<td>0.76</td>
<td>0.74</td>
<td>0.70</td>
</tr>
<tr>
<td>slope young-old</td>
<td>-1.09%</td>
<td>-0.40%</td>
<td>-0.52%</td>
<td>-0.55%</td>
<td>-0.58%</td>
</tr>
<tr>
<td>overall RRR</td>
<td>29.7%</td>
<td>30.0%</td>
<td>34.0%</td>
<td>31.0%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

\(^{ix}\) Note we took the higher of 4S’s 35-59 or 60-69 year-old treatment:placebo relative risks as reference points for scaling.
4. For CHD RRRs for population 1 stratified by total cholesterol levels, we combined the patterns displayed by 4S\(^{17}\) and CARE according to baseline total cholesterol levels. (Both 4S and CARE showed remarkably consistent patterns in RRR for both baseline total cholesterol and baseline LDL-cholesterol):

5. For all-cause death RRRs for population 1, we then scaled the relevant 4S RRRs against the age-related RRRs for total CHD from both 4S itself and the above meta-analysis (where, at any age, RRR all-cause death = 4S RRR all-cause death \(*\) meta-analysis RRR CHD / 4S CHD RRR), then fitting the data to the above age-related patterns. We similarly derived age-related RRRs for population 1 for fatal and non-fatal CHD.
Relative risk reduction through LMA use for those with pre-existing CHD
(4S population extrapolated to those aged >70)

For all-cause death RRR using statins for both
• the cholesterol subdivisions of population 1, and
• the risk levels of populations 2 and 3,
We extrapolated from the relative risks reported by 4S and the West of Scotland Coronary Prevention Study (WOSCOPS) using linear scaling from median 5-year all-CHD risks:
Linear scaling for all-cause death RRRs for statins:

\[ r_x = r_{4S} + \left( (e_{4S} - e_{WOSCOPS}) \times \frac{(e_x - e_{WOSCOPS})}{(e_{4S} - e_{WOSCOPS})} \right) \]

where:

- \( r_x \) = relative risk reduction for a particular CHD status
- \( r_{4S} \) = 4S RRR
- \( r_{WOSCOPS} \) = WOSCOPS RRR
- \( e_{4S} \) = 4S 5-year event rate for all CHD events
- \( e_{WOSCOPS} \) = WOSCOPS 5-year event rate for all CHD events
- \( e_x \) = 5-year event rate for all CHD events for that particular CHD status

Note that 4S’s 5-year risks were used for population 1, with for example men (aged 35-70) having a 13% 5-year placebo mortality risk and a 33% RRR with statin use. WOSCOPS had a much lower risk population and a lesser risk reduction, with a 4% overall 5-year placebo mortality risk and a 22% RRR with statin use (men aged 45-64).
WOSCOPS dealt only with men age 45-65 years. Because of this, for scaling purposes we assumed the age/sex distribution for populations with WOSCOPS’s level of risks’ placebo event rates and treatment:placebo relative risks would be similar to those of 4S. Hence we applied the relative weightings of 4S placebo event rates and relative risks, calculated above, to the WOSCOPS data, to predict treatment:placebo relative risks for men >65 years and all women for the WOSCOPS level of risk:
For all-cause death RRRs for fibrates, we used a 5.3% RRR calculated from using a meta-analysis of cited secondary prevention fibrate trials applied to the 4S population (odds ratio 0.95, 95% confidence interval 0.78 to 1.16, n= 6466 patients with 1381 deaths in 7 studies, 19% vs 39% mortality).

viz the Stockholm Study (clofibrate+nicotinic acid)\(^1\), ancillary Helsinki Heart Study (gemfibrozil)\(^2\), Scottish Society (clofibrate)\(^3\), Acheson & Hutchinson (clofibrate)\(^4\), Newcastle (clofibrate)\(^5\), Coronary Drug Project (clofibrate)\(^6\), and BECAIT (bezafibrate)\(^7\):

\[
RRR_{\text{fibrates, total deaths}} = 1 - (RRR_{\text{fibrates, total deaths}} \times \frac{AR_{4S, CHD deaths}}{AR_{4S, total deaths}}) + (RRR_{\text{fibrates, non-CHD deaths}} \times \frac{AR_{4S, non-CHD deaths}}{AR_{4S, total deaths}})
\]

where:
- \(RRR_{\text{fibrates, total deaths}}\) = relative risk reduction for fibrates for total deaths, applied to 4S
- \(RRR_{\text{fibrates, CHD deaths}}\) = relative risk for fibrates for CHD deaths
- \(AR_{4S, CHD deaths}\) = CHD death rate in 4S (ie absolute risk)
- \(RRR_{\text{fibrates, non-CHD deaths}}\) = relative risk for fibrates for non-CHD deaths
- \(AR_{4S, non-CHD deaths}\) = non-CHD death rate in 4S
- \(AR_{4S, total deaths}\) = total death rate in 4S

\[\text{Fibrate secondary prevention trials}\]

To calculate fibrate RRRs for all-cause deaths to each age/sex/CHD group, we then applied this overall RRR for fibrates to
- the above age/sex/CHD group RRRs calculated for statins and
- an overall RRR for 4S/WOSCOPS/CARE applied to the 4S population of 25%\(^{11}\), ie:

\[
RRR_{\text{fibrates, all-cause death}} = (RRR_{\text{statins, all-cause death}}) \times \frac{RRR_{\text{fibrates, all-cause death}}}{RRR_{\text{statins, all-cause death}}}
\]

\(^{11}\) not a higher 7% RRR calculable form one-step analysis of fibrate secondary prevention trials (OR 0.93, 95% CI 0.81 to 1.06)

\(^{11}\) not the higher 30% RRR for 4S. 25% RRR derived by same method as for 5.3% RRR for fibrates
Relative risk reductions for all-cause mortality through using fibrate
(from linear scaling of WOSCOPS and 4S Study RRs for statins, incorporating Law et al. meta-
analysis for those aged >70 years and 4S statin vs Rossouw fibrate analysis overall RRs)

[Graph showing relative risk reduction across different age/sex groups and cholesterol levels]
For non-fatal events, we assumed for the purposes of the model that population 1’s overall age-related RRRs for statins applied equally to populations 2 and 3 and the cholesterol-level subpopulations of population 1, and to all patients using fibrates. This was given:

- the close similarities in statin non-fatal CHD risk reductions for the 4S and WOSCOPS trials (despite significant differences in baseline risk), and
- similar magnitudes of total CHD risk reduction in some fibrate trials to that of 4S and WOSCOPS. Note that for fibrates there is an overall 24% RRR for non-fatal CHD when the main Helsinki Heart Study (primary prevention with gemfibrozil) is combined with all published secondary prevention trials except the ancillary Helsinki Heart Study (OR 0.76, 95% CI 0.66-0.89, Peto one-step method); Helsinki itself showed a 37% RRR for non-fatal CHD (with 34% RRR for total CHD events):

Hence RRRs in the model for non-fatal events vary according to age and type of event, but not by underlying CHD status nor LMA class:

---

Relative risks for non-fatal coronary events:

- estimated 0.73 for men 35-59, 0.70 for men 60-70 years in 4S Study (where men comprised 85% and 78% of each respective age-group);
- 0.69 for non-fatal MI (definite), 0.73 for definite + suspect non-fatal MI in WOSCOPS Study (men aged 45-64);

the 24% RRR may underestimate RRRs realizable in the model for fibrates, since under the NHF/PTAC criteria fibrates are indicated at lower cholesterol levels for mixed dyslipidaemia than in the trials (which also covered higher cholesterol levels), and hence may be more effective than measured in the trials.
Effectiveness

To calculate the relative effectiveness of LMA programmes, we re-presented absolute risk reductions as:

- events prevented per 1000 eligible population, and
- numbers needed to treat (NNT) to prevent one event.

For each age/sex/CHD status group,

\[
\frac{e}{NNT} = \frac{ARR \times \frac{1000 \text{ people}}{1 \text{ person}} \times \frac{1 \text{ year}}{5 \text{ years}}}{e} \]

where

\[
\begin{align*}
e & = \text{events prevented per 1000 eligible population each year} \\
ARR & = \text{5-year absolute risk reduction/person} \\
NNT & = \text{numbers needed to treat (NNT) to prevent one event}
\end{align*}
\]
Life expectancy, and expected loss in life years (PYLL) for eligible populations

We calculated life expectancy and expected loss in life years from mortality rates and expected numbers of deaths:

- death rates:
  - pop 1 x chol
  - pops 2 & 3
- life expectancy:
  - pops 2 & 3
  - pop 1 x cholesterol

To calculate the expected loss in life years for each age/sex/CHD group, we firstly calculated each group’s average life expectancy for it’s individuals, using the above mortality rates and standard period-based life table methods.²⁶
We then calculated each individual’s potential loss in life years from premature death (PYLL\textsubscript{death}) from mortality rates and life expectancy (and accounting for baseline health state):

\[
\text{potential years of life lost, premature death (PYLL\textsubscript{death})} = AR\textsubscript{death} \cdot LE \cdot (1-q\textsubscript{death}) \cdot q\textsubscript{base}
\]

where:
- PYLL\textsubscript{death} = potential years of life lost, premature death
- AR\textsubscript{death} = total mortality rate
- q\textsubscript{death} = utility value (QALY score) for death (0.000), \therefore (1-q\textsubscript{death}) = 1
- q\textsubscript{base} = utility value (QALY score) for baseline health state
  (CHD = 0.925, no CHD = 1.000, genetic lipoprotein disorders = 0.950)

We also calculated the expected numbers of deaths for each age/sex/CHD status-specific subpopulation, by combining
1. the above specific all-cause mortality rates
2. current and projected populations for each subpopulation
3. age/sex-specific predictions of annual decline in all-cause mortality for New Zealand\textsuperscript{xiv xv}.

We then calculated potential life years lost by each subpopulation, by combining numbers of deaths with average life expectancies:

\[
\text{total life years lost} = \text{no. of deaths} \times \text{average life expectancy} \times \text{baseline health state}
\]

\[
= \text{PYLL/person} \times \text{population (no. of people)}
\]


\textsuperscript{xv} for each age/sex/CHD status group.

\[
n = d \cdot p \cdot \delta d
\]

where
- n = number of deaths
- d = all-cause mortality rate
- p = population (current and projected)
- \delta d = projected change in mortality, relative to current rates
QALY gains

We calculated net QALY gains from non-fatal CHD prevented QALY gains, all-cause death prevented QALY gains and QALY losses from side effects/adverse effects for each age/sex/CHD status subpopulation:

To help derive potential QALY gains for each event prevented by an LMA programme, we used QALY scores developed in Australia for the Quality of Life (QoL) substudy of the LIPID study (n = 1112). The LIPID QALY scores were 0.983 using the Rosser index and 0.925 using the time trade-off method (TTO):
QALY scores for post-MI dyspnea and angina

<table>
<thead>
<tr>
<th>NYHA category (dyspnoea):</th>
<th>AUS-TASK</th>
<th>LIPID QoL</th>
<th>Rosser index</th>
<th>QALYs</th>
<th>TTO index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOTAL %</td>
<td>TOTAL %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AUS-TASK</td>
<td>LIPID QoL</td>
<td></td>
<td>AUS-TASK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weighted</td>
<td>Weighted</td>
<td></td>
<td>Weighted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>average,</td>
<td>average,</td>
<td></td>
<td>average,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ind</td>
<td>ind</td>
<td></td>
<td>ind</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AUS-</td>
<td>AUS-TASK</td>
<td></td>
<td>AUS-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TASK non-response</td>
<td>non-response</td>
<td></td>
<td>TASK non-response</td>
</tr>
<tr>
<td>NYHA category (dyspnoea):</td>
<td>1340 100%</td>
<td>0.976</td>
<td>0.983</td>
<td>0.979</td>
<td>0.940</td>
</tr>
<tr>
<td>no SOB</td>
<td>629 47%</td>
<td>0.99</td>
<td>0.987</td>
<td>0.989</td>
<td>0.97</td>
</tr>
<tr>
<td>SOB on strenuous exertion</td>
<td>475 36%</td>
<td>0.98</td>
<td>0.986</td>
<td>0.988</td>
<td>0.94</td>
</tr>
<tr>
<td>SOB on normal exertion</td>
<td>142 11%</td>
<td>0.96</td>
<td>0.956</td>
<td>0.958</td>
<td>0.85</td>
</tr>
<tr>
<td>SOB on mild exertion</td>
<td>85 6%</td>
<td>0.91</td>
<td>-</td>
<td>0.910</td>
<td>0.85</td>
</tr>
<tr>
<td>SOB at rest</td>
<td>9 1%</td>
<td>0.36</td>
<td>-</td>
<td>0.360</td>
<td>0.67</td>
</tr>
<tr>
<td>Karnofsky category (angina):</td>
<td>0.979</td>
<td>0.943</td>
<td>0.979</td>
<td>0.943</td>
<td></td>
</tr>
<tr>
<td>no angina</td>
<td></td>
<td>1.00</td>
<td>na</td>
<td>1.00</td>
<td>na</td>
</tr>
<tr>
<td>A: normal activity</td>
<td>1043 78%</td>
<td>0.99</td>
<td>0.99</td>
<td>0.97</td>
<td>na</td>
</tr>
<tr>
<td>B: unable to work</td>
<td>287 21%</td>
<td>0.94</td>
<td>na</td>
<td>0.94</td>
<td>na</td>
</tr>
<tr>
<td>C: unable to care for self</td>
<td>8 1%</td>
<td>0.30</td>
<td>na</td>
<td>0.36</td>
<td>na</td>
</tr>
<tr>
<td>CCVS Angina grade (angina):</td>
<td>0.983</td>
<td>0.924</td>
<td>0.983</td>
<td>0.924</td>
<td></td>
</tr>
<tr>
<td>no angina</td>
<td></td>
<td>1</td>
<td>na</td>
<td>1.00</td>
<td>na</td>
</tr>
<tr>
<td>no limit to normal activity</td>
<td>na</td>
<td>0.982</td>
<td>na</td>
<td>0.982</td>
<td>na</td>
</tr>
<tr>
<td>slight limitation</td>
<td>na</td>
<td>0.966</td>
<td>na</td>
<td>0.966</td>
<td>na</td>
</tr>
<tr>
<td>marked limitation</td>
<td>na</td>
<td>0.956</td>
<td>na</td>
<td>0.956</td>
<td>na</td>
</tr>
<tr>
<td>unable to perform physical activity</td>
<td>na</td>
<td>0.737</td>
<td>na</td>
<td>0.775</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>1338 100%</td>
<td>1112 100%</td>
<td>0.983</td>
<td>0.925</td>
<td></td>
</tr>
</tbody>
</table>

To calculate QALY gains, we firstly subtracted TTO QALY scores from 1. This obtained disutility values and hence one-year QALY gains for each non-fatal event prevented:

\[
1 - q_{CHD} = 1 - 0.925 = 0.075
\]

where

\[q_{CHD} = \text{utility value (QALY score) for CHD from the LIPID QoL substudy (0.925 time tradeoff)}\]

For each age/sex/CHD status subpopulation, we then applied the QALY gain score (0.075) to the above numbers of non-fatal events prevented and to CHD life expectancy. This calculated quality-adjusted life year gains from non-fatal CHD averted (\(\Delta Y_{\text{MM}}\)):

\[
\Delta Y_{\text{MM}} = n_{nf} \times dLE_{\text{CHD}} \times (1 - q_{CHD})
\]

where

\(\Delta Y_{\text{MM}}\) = non-fatal CHD quality-adjusted life year gains
\(n_{nf}\) = numbers of non-fatal events prevented
\(dLE_{\text{CHD}}\) = average life expectancy for CHD (for age/sex group), discounted to present value
\((1 - q_{CHD})\) = one-year QALY gains for each non-fatal event prevented

For deaths prevented, we multiplied numbers of all-cause deaths prevented by the relevant life expectancy and by the utility value for baseline health state (CHD, genetic lipoprotein disorder, or “at risk”), to derive life-year gains (\(\Delta Y\))\(^{\text{xvi}}\):

\[
\Delta Y = n_{f} \times dLE \times (1 - q_{\text{death}}) \times q_{\text{base}}
\]

where

\(\Delta Y\) = all-cause death life year gains
\(n_{f}\) = numbers of deaths (all-cause fatalities) prevented
\(dLE\) = average life expectancy, discounted to present value
\(q_{\text{death}}\) = utility value (QALY score) for death (0.000)
\(q_{\text{base}}\) = utility value (QALY score) for baseline health state (CHD = 0.925, no CHD = 1.000, genetic lipoprotein disorders = 0.950)

Gross QALY gains were obtained by summing non-fatal CHD prevented QALY gains with all-cause death prevented QALY gains, ie \(\Delta Y + \Delta Y_{\text{MM}}\).

For QALY losses from side effects/adverse effects of LMA, we used a notional utility value of 0.98 for quality of life with fibrate side effects. We based this upon a slightly higher value than the midpoint of the 0.95 - 0.99 utility range given for side effects of hypertension treatment cited by Torrance\(^{28}\). We assumed statin side effects to have a

\(^{\text{xvi}}\) Note here that each life year gained through death prevented equates to one full QALY
utility of 1.00 (i.e. nil disutility value/loss in life quality), given statins’ relatively high continuation rates, reputation for being well-tolerated by patients, and 4S and WOSCOPS placebo groups suffering more side effects than the treatment groups.

Assuming that the medication regime was able to be continued, fully complied with and taken over the course of a full year, we finally calculated QALY losses from side effects/adverse effects ($\Delta Y_{SE}$) by subtracting utility values from 1 and multiplying by the time period of interest (viz 5 years, cf 5-year absolute risks used above to calculate fatal and non-fatal QALY gains):

$$\Delta Y_{SE} = (1 - q_{RxSE}) \times 5 \text{ years}$$

where

$q_{RxSE}$ = utility values (QALY scores) for Rx side effects (fibrates 0.98, statins 1.0)

We calculated net QALY gains by summing non-fatal CHD prevented QALY gains, all-cause death prevented QALY gains and QALY losses from side effects/adverse effects, i.e.

$$\Delta E = \Delta Y + \Delta Y_{Morb} - \Delta Y_{SE}$$
Events attributed to each subpopulation (attributable fractions)

To estimate the extent to which each age/sex/CHD status subpopulation accounted for overall CHD events, and hence hospitalisations (and hence the potential savings in hospitalisations through LMA use, affecting net LMA costs for cost-benefit analysis), we needed to predict the number of events each subpopulation might experience for each age/sex group over a 5-year period.

We predicted subpopulation event numbers by applying each subpopulation’s median 5-year risk of CHD events (above) to the corresponding Auckland Heart & Health Study prevalence data. This was to predict the number of events each subpopulation might experience over a 5-year period:

\[
\text{no. events (5 years)} = \text{median 5-year risk} \times \text{prevalence}
\]

We then estimated the extent to which each age/sex/CHD status subpopulation accounted for overall CHD events. To do this, we summed the above event numbers for each subpopulation, to obtain the total number of events expected for all subpopulations combined (i.e., total overall events):

\[
\text{ntotal} = \sum \text{n}(as)(\text{CHD})
\]

where

\[
\text{n}(as)(\text{CHD}) = \text{number of events for an age/sex/CHD status subpopulation}
\]

We then used these two event numbers to calculate the proportion of events attributable to each subpopulation, where

\[
\text{proportion of events attributable to a subpopulation} = \frac{\text{number of events for that subpopulation}}{\text{total number of events overall}}
\]
Events attributable to each CHD-status group (attributable fractions)

- past CHD
- at risk >=20%
- fam.xanthomas at risk 15-19%
- at risk 10-14%
- low risk <10%

% events in CHD group/total events

age/sex group
Hospital and other morbidity-associated costs and offset savings

Costs of CHD and other atherosclerotic disease to the health sector comprise:
1. inpatient costs of hospital admissions
2. non-inpatient costs associated with hospital admissions, viz of outpatient consultations, community health services, and ambulance costs
3. disability support service costs for treating patients with residual disabilities
4. primary health care costs relating to CHD and atherosclerotic morbidity

Savings are due to cases prevented by LMAs. These include:
1. inpatient and other hospital savings
2. non-LMA cardiovascular pharmaceutical savings (cardiovascular drugs no longer needed because LMAs have prevented new cases)
3. disability support service savings
4. primary health care savings

At this stage, analysis has centred on hospital costs and savings due to LMA use. This is since:
• there are few data quantifying potential savings from pharmaceuticals for atherosclerotic diseases but no longer required because of events/states prevented by LMA use (note the difficulties generated by multiple indications). Note that 4S found simvastatin did not significantly reduce the use of other cardiovascular medications.\textsuperscript{29}
• there are few data regarding disability support service costs for patients following coronary heart disease events specifically

The model instead assumes the majority of costs are likely to be for hospitalisations.

Note that other costs may in fact partly or fully cancel out each other, viz non-pharmaceutical + costs of adverse effects, versus savings from pharmaceuticals no longer needed.

To calculate both numbers and costs of hospitalisations expected and numbers and costs prevented in real life through LMA use, for each age/sex/CHD status-specific group, we combined RHA and national data with components’ attributable risk calculations, RRRs and programme coverage/Rx continuation rates:
• To derive relevant volume and price data, we firstly obtained 1993 DRG-based discharge volume and unit price information from the four regional health authorities for conditions relevant to LMA programmes. We used the volume and price data to derive volume-weighted New Zealand prices for each DRG.xvii

• We then aggregated the volume and price data into five major groupings of DRGs:
  1. coronary heart disease

xvii Note that the RHA contracted hospital prices combine both inpatient and non-inpatient components (e.g., outpatient services, community health services, hospital overheads). Prices exclude GST.
2. surgery relating to coronary heart disease
3. other cardiac conditions associated with coronary heart disease (cardiac arrhythmias, left ventricular failure, cardiogenic shock, etc)
4. stroke
5. other atherosclerotic cardiovascular disease (mainly peripheral vascular disease).

We mapped these volumes and prices to relevant ICD9-CM diagnostic and operation codes. We next used New Zealand 1992 hospital discharge data to calculate volumes for each of the major groupings by age and sex, for both public and private hospitals xviii.

- To account for probable continuing reductions in the incidence of (new) cardiovascular disease, we applied age/sex-specific estimates of the likely decline in coronary heart disease to the above discharge volumes over time, to derive age/sex numerical trends (see Annexe)

- We next estimated the likely numbers of hospitalisations which might be attributable to each subpopulation potentially eligible for LMAs, by combining the age/sex/major DRG grouping-specific volumes and prices with the above attributable fractions for each major group. This produced age/sex/major DRG grouping/cardiovascular status-specific volumes and prices.

- To calculate the extent of reductions in hospitalisations which might realistically be expected as a result of LMA programmes, we:
  ◊ predicted the potential numbers of hospitalisations which could be prevented through using LMAs in ideal circumstances (from above RRRs),
  ◊ applied Auckland Heart & Health Study prevalence data regarding the proportions of each subpopulation who would be eligible for LMAs according to possible criteria, and
  ◊ adjusted for incomplete programme coverage (ie not all eligible patients necessarily receive LMAs, due to the cumulative effects of: people not presenting for medical care and screening; medical practitioners not identifying dyslipidaemia and absolute CHD risk and/or managing dyslipidaemia and absolute CHD risk to the full extent of the NHF guidelines; effective dietary and other CHD risk factor interventions negating the need for LMAs; and patients not uplifting scripts from pharmacies)
  ◊ adjusted for patient non-adherence and discontinuation (described in “Cost:benefit ratios” below).

xviii To calculate discharge volumes etc for cardiovascular disease amenable LMAs (with the same outcomes as reported by 4S) for each age/sex group, we notionally attributed 25% of arrhythmia admissions and 50% of CHF admissions to coronary heart disease. For stroke, we derived age/sex attributable fractions by subtracting admissions for haemorrhagic stroke, transient ischaemic attacks (TIAs) and late effects of stroke.
Net programme costs
We calculated net programme by combining actual pharmaceutical costs, non-pharmaceutical programme costs, and hospital and other savings.

Cost:benefit ratios
We based cost-benefit ratios for each age/sex/CHD status/LMA class stratum around PHARMAC’s cost/QALY calculation of NZS26,553 for the 4S study applied to all those with pre-existing CHD in New Zealand (ie simvastatin use in those aged 35-70 with pre-existing CHD, simvastatin Rx costs minus hospitalisation offsets, 0.925 utility value for life years saved). This calculation discounted both costs and benefits at 11.4%. This means that when calculating discounted benefits, the 4S population’s estimated 16.6 year life expectancy discounts to 7.3 years. Note the $26,553 figure for population 1 is slightly higher than the $24,648 figure calculated by PHARMAC for 4S patients meeting that study’s exclusion criteria (ie 1.000 utility value for life years saved).30

We derived ideal (ie potential) costs/QALY for each age/sex group/CHD status/LMA class stratum by firstly calculating each age/sex/CHD group’s net potential costs and discounted one-year QALY value for statins, then scaling this against the 4S group’s $26,553 cost/QALY and 0.091 discounted one-year QALY value. This assumed population 1 had similar statin QALY gains as for the 4S trial. We then calculated individual LMA class costs and discounted QALYS within each age/sex/CHD group, scaling to derive individual cost:QALYS:

for any age/sex/CHD status/LMA class group,

<table>
<thead>
<tr>
<th>cost/QALY</th>
<th>=</th>
<th>4Snet</th>
<th>uN</th>
<th>x</th>
<th>uN</th>
<th>dQ</th>
</tr>
</thead>
</table>

where

4Snet = $24,648 net costs per QALY gained,
for simvastatin use in pre-existing CHD aged 35-70 with 11.4% discounting of both costs and benefits,
thus discounted net benefits at 0.091 QALYS/person/year’s treatment (from 0.203 undis
QALYS/p/yr)
uN = undiscounted net costs/person/year for any age/sex/CHD status/LMA class
uN0 = index case undiscounted net costs, ie for statins for pre-existing CHD aged 35-69
dQ = discounted net QALYS/person/year for any age/sex/CHD status/LMA class
dQ0 = index case discounted net QALYS, ie for statins for pre-existing CHD aged 35-69

To derive likely actual costs/QALYs (to account for incomplete patient continuation and adherence with LMAsxix), we adjusted the above ideal costs/QALYS by applying the relevant continuation/adherence rates to undiscounted QALYS, then discounting. We assumed 44% of patients with CHD or genetic lipid disorders (populations 1 and 2) continue to take fibrates after 1 year, with 67% for statins. These figures were composites from recent discontinuation data from the United States and Australia.31 32 We adjusted these rates for age, with those aged ≥70 years having notionally 5% higher compliance relative to 45-49 year olds, and those aged 35-39 years 2% lower. We also adjusted for CHD status, assuming patients in population 3 to have a notional 15% lower compliance relative to populations 1 and 2 above:

xix The theoretical costs/QALYS are derived from intention-to-treat results from clinical trials with reasonably high patient continuation/compliance rates. However, many patients in the community cannot or do not continue with their medication, despite Rx being prescribed and dispensed - and hence effectiveness and benefits are lower for each amount of drugs prescribed and costs. Although patients who discontinue etc do not gain the benefits of LMA treatment, pharmaceutical costs remain.
We used a discount rate of 11.4% for both costs and benefits, this being equal to the cost of finance from the New Zealand Crown to regional health authorities. Discounting of costs is inherent in using PHARMAC’s 4S cost/QALY value, whilst we discounted benefits using present value calculations on life expectancies.
Assumptions in the base case:

Key assumptions with the model are:

Benefits
1. those in the community with pre-existing CHD in the Auckland Heart & Health Study, and those in the New Zealand population, have the same risks of death and CHD events as calculated from ARCOS
2. attributable fractions for each population for coronary heart disease events apply in equal proportions to other cardiovascular disease events  [Comment: CHD accounts for most cardiovascular disease in the 35-70 year age-group]
3. absolute risks for patients with genetic lipoprotein disorders (population 2) are the same as those in published British cohort data
4. for population 3, “median” risk values are a surrogate for the average 5-year risk of CHD events for each age/sex/absolute risk subpopulation (where in most instances, median risk values are the mid-point of each of the 5% bands supplied); the mean risk for those with absolute risk ≥15% includes the assumption that all those with risk ≥20% have a notional risk of 22.5%; and a notional 2.5% median value for those with risks ≤5%.
5. ARCOS 28 day-3 year death rates, extrapolated by GISSI-2 and Framingham data, reasonably estimate age/sex-specific death rates
6. ARCOS 28 day-3 year death rates and Framingham non fatal CHD:total death ratios (modified for 4S experience by age) reasonably estimate non-fatal CHD event rates
7. for population 3, event rates can be derived by scaling population 1’s event rates against a combination of Framingham logistic equation risks and ARCOS mortality/(Framingham nonfatal CHD:total death ratios) 4S absolute risks.
8. all-cause mortality continues to decline at the same rates over time
9. (lesser) RRRs apply for those aged 70 years and over
10. statin RRRs reductions for all-cause mortality are linearly scaled from 4S and WOSCOPS mortality according to event rates
11. fibrate all-cause mortality RRR of 5.3% derived from meta-analysis applied to 4S population, including ancillary Helsinki Heart Study, applies to all fibrate use
12. 4S RRRs for non-fatal major CHD events apply across all CHD status groups (populations 1, 2 and 3), cholesterol levels (<5.5mmol/l to ≥7.5 mmol/l for population 1) and classes (statins and fibrates), and vary only by age
13. those in the community with pre-existing CHD in the Auckland Heart & Health Study, and those in the New Zealand population, have the same RRRs as in 4S. That is, 4S results apply to all CHD survivors, regardless of severity of CHD or other morbidity, not just those who avoid 4S’s exclusion criteria
14. 4S RRRs also apply to higher levels of cholesterol, ie above 8.0 mmol/l.
15. period-based life table methods derive valid life expectancies
16. LIPID study CHD utilities (QALY scores) apply to the New Zealand population eligible for LMAs.

17. Baseline health state utilities of 0.925 for population 1 (ie LIPID CHD TTO QALY score), 1.0 for population 3, and 0.95 for population 2.

18. Notional QALY values of 0.98 for quality of life with fibrate side effects and 1.00 for statin side effects.

Comments:

- The lesser RRRs for those aged ≥70 are conjectural, given the relative lack of trial data regarding the total mortality effectiveness of LMAs in older age-groups.

- 4S was conducted in Northern European countries with populations considered largely similar to European New Zealanders, similar population lipid levels and similar prevalence of CHD. The LIPID study includes New Zealand patients as well as Australian, and will be even more relevant to the New Zealand setting.

- 4S recruited patients aged 35-70 years with a history of angina or acute myocardial infarction. However, it excluded a large number of potential recruits, including:
  - those with recent MI (within 6 months previously),
  - those with planned coronary artery surgery/angioplasty,
  - those taking antiarrhythmic therapy,
  - those with congestive heart failure requiring certain treatments for congestive heart failure
  - history of completed stroke

This in effect excluded sicker patients. Because the PTAC criteria do not specify such exclusions, overall those in the community eligible for LMAs would have, on average, greater levels of illness and poorer outcomes than both groups in 4S. In terms of potential benefits, this in turn means both poorer life expectancies but potentially greater ARRs (since baseline absolute risk is greater).

- Relative risks of death for patients with CHD (population 1) are probably less for New Zealand now than what they were for the Framingham cohort. This would be because age/sex-specific CHD death rates have decreased more than all-cause rates, and improved case-fatality rates (thus survival) for those with CHD compared with the general population. However, it is difficult to verify this, let alone quantify any such changes to the relative risks.

- By using 4S and WOSCOPS data for all statin RRRs, the model implicitly assumes all statins drugs have similar therapeutic effects. Regarding secondary prevention, 4S’s overall 30% RRR for all-cause mortality (15% to 42% [95% CI]), n = 4444 patients, 8.2% versus 11.5% mortality over 5.4 years) does lie between that of
  ◊ CARE’s RRR of 7% (95% CI -2% to 16%, n = 4139 patients, 8.7% pravastatin versus 9.4% placebo mortality rate over 5 years) and
  ◊ reported meta-analyses of other published (smaller) secondary prevention trials of 44%33 (OR 0.56, 95% CI 0.33 - 0.96, n = 3465 from the 7 trials, 1.2% versus 2.1% mortality over 1.6 years on average).

Further meta-analyses of statin efficacy in all-cause mortality (Peto one-step method) show use of 4S alone for statin secondary prevention trial RRRs is reasonable, given:
  ◊ analysis of all statin secondary prevention trials, ie 4S, CARE, PLAC-I34, PLAC-II35, REGRESS36, CCAIT37, PMNSG38, MARS39 and MAAS40 trials, gives an overall RRR for all-cause deaths for statins of 23% (OR 0.77, 95% CI 0.67 - 0.88 , n = 12,048 from 9 trials, 6.3% versus 8.1% mortality over 4.2 years on
average). This reduction is less than 4S’, but includes one trial lasting less than two years (PMNSG) a number of patients with lower cholesterol levels (CARE). Analysis of all statin secondary prevention trials excluding both 4S, trials of less than 2 year’s duration (viz PMNSG, Sahni et al7) and those confounded by low cholesterol levels (CARE) gives an overall RRR for all-cause deaths for statins of 28% (OR 0.72, 95% CI 0.65 - 0.80 , n = 2,403 from 7 trials, 1.7% versus 2.8% mortality overall 2.8 years on average), which is similar to 4S’.

However, such meta-analyses presume all statin drugs have similar therapeutic effects, and analyses are potentially confounded if this is not so. Hence the model has retained simvastatin age-related RRRs.
• We did not attempt to stratify RRR by gender as well. This is given the inconsistent RCT results to date of statin effects on total mortality by gender, with
  ◦ 4S demonstrating RRR of -12% ie net harm but result not statistically significant because of small numbers (ie 52 deaths in 827 women over 5 years, RR 1.12 (0.85, 1.46)), and
  ◦ CARE showing significantly greater RRR for women taking statins than men for CHD events, but no data reported to date regarding sex-specific RRRs for all-cause mortality. Note that overall mortality in CARE decreased insignificantly by just 7% (RR 0.93, 95%CI 0.84 - 1.02), and there were excess cases of breast cancer in the treatment arm.

Hence the model stratifies statin all-cause mortality RRRs by age only.

• The model varies RRR for CHD events for the cholesterol-related subdivisions of population 1, using the baseline total cholesterol pattern of 4S and CARE. This is controversial, given the 4S investigators reported no change in RRR for CHD events according to baseline LDL-cholesterol levels. However, combining both 4S and CARE data appears to show a threshold effect for statins, below which RRR markedly reduces.

In 4S, the quartile of patients with the lowest baseline LDL levels had a 35% RRR (95% CI 15% to 50%), compared with a 34% RRR for the highest quartile (95% CI 19 to 49%). This absence of effect with baseline LDL levels was used as evidence of the effectiveness of statins with lower levels of cholesterol, and hence benefits for a wider patient population. However, 4S did show a threshold response for RRR according to baseline total cholesterol, where the lowest-quartile of total cholesterol had a RRR of only 24% (95% CI 3% to 41%), compared with 38% for the next quartile (95% CI 20% to 51%). These seemingly contradictory results are however difficult to interpret, given their wide confidence intervals (and hence imprecision).
Results from CARE are consistent with 4S’ over same cholesterol ranges, and thus add to 4S’ experience. CARE too showed a decrease in RRR with low LDL levels. For LDL levels of 3.0 to 3.3 mmol, the RRR for CHD events was -3%, ie an increase in events of 3% (95% CI -38% to +23%). However, RRRs rose to 26% (13%-38%) for LDLs of 3.3 to 3.9 mmol/l and 35% (17%-50%) for LDL 3.9-4.6 mmol/l. Remarkably, CARE’s 35% RRR for middle-range LDLs was exactly the same as occurred in 4S for the same LDL levels. And CARE showed a similar gradient in RRR by total cholesterol as occurred with 4S:

Again, the CARE results are difficult to interpret because of their wide confidence intervals. However, there may be a threshold of around 4 mmol/l at which constant statin RRRs for CHD according to baseline LDL-cholesterol levels no longer apply. Hence below 4 mmol/l (ie the lowest quartile of LDL), RRRs might be less than for higher quartiles, statins’ are less effective for lower cholesterol levels, and overall benefit less for patients in population 1 with low baseline LDL-cholesterol. Alternatively, there may be important but unexplained differences between simvastatin and pravastatin in their ability to reduce CHD events at lower LDL levels. To resolve which possibility applies would require head-to-head comparisons.

- Regarding the validity of QALY scores, the New Zealand population eligible for LMAs comprises both:
- those in the LIPID study population - ie with CHD who avoid the exclusion criteria, and
- those outside of the LIPID study population, - ie either those with CHD who would be excluded by the LIPID study, and those without CHD but with high absolute risk or genetic lipoprotein disorders.
Note the LIPID study has a similar patient profile as 4S, and the LIPID QALYs appear to correlate closely with other Australasian work with higher levels of patient morbidity, eg AUS-TASK.43

- The baseline health state QALY score of 0.95 for population 2 is a notional value set between CHD (0.925) and at-risk (1.0) populations’ QALY scores, and accounts for non-CHD (biliary etc) morbidity of genetic lipoprotein disorders.

- The notional QALY value of 0.98 for quality of life with fibrate side effects is based upon a slightly higher value than the midpoint of the 0.95 - 0.99 utility range given for side effects of hypertension treatment cited by Torrance44.

- The notional QALY score of 1.00 for statin side effects is based on:
  1. statins’ relatively high continuation rates,
  2. statins’ reputation for being well-tolerated by patients, and
  3. 4S and WOSCOPS placebo groups suffering more side effects than the treatment groups.

Hospital and other morbidity-associated costs and offset savings
1. private hospital DRG costs are commensurate with public hospital costs
2. DSS costs are minimal
3. 25% of arrhythmia admissions and 50% of CHF admissions relate to coronary heart disease (and are therefore preventable by LMAs)
4. for projections, the supply of hospital beds does not change
5. for projections, hospitalisations reflect the incidence of CHD (new cases)

Comment:

- This analysis concentrates upon hospital costs and savings, rather than non-hospital costs. Non-hospital costs, although substantial, will be a fraction of hospital costs. In addition, restricting the analysis to hospital expenses still gives relativities between each subpopulation; including non-hospital costs does not enhance relativities.

Pharmaceutical cost component of CBA
1. simvastatin/pravastatin combination represents all costs for HMG-coA reductase inhibitors (statins), and bezafibrate represents all costs for fibrates.
2. an average daily dose for simvastatin of 20mg/day, and xx mg/day for bezafibrate
3. annual costs per patient include 10% wholesale margins and 11.28% retail pharmacist margins (cumulative markups 22.4%), but exclude GST.
4. price and ADD are fixed at 1996 levels.
Net cost-benefits

1. NZ$24,648 for the 4S population, i.e., simvastatin use in those aged 35-70 with pre-existing CHD, Rx costs minus hospitalisation offsets, discounting both costs and benefits at 11.4%

2. Scaling net costs and discounted one-year QALY values against population 1’s $26,553 cost/QALY and 0.091 discounted one-year QALY value

3. Applying continuation/adherence rates to undiscounted QALYS, then discounting, to derive likely actual costs/QALYs

Comment:

- Weinstein and Stason’s equation accounts for the benefits of interventions by subtracting savings from events prevented to derive net programme costs. Equally valid however is to ascribe, if possible, these benefits as additional QALYS. This is especially in cases such as savings from hospitalisations prevented (and hence impact on health care costs), since such savings are never realised in real life (δ hospital wards will not close as a result of μ fewer CHD cases because of LMA programmes, because of other patients). Rather these are opportunity savings, e.g., because there are μ fewer cases of CHD resulting from LMA programmes, λ other alternative interventions can occur (e.g., elective CABG surgery) conferring ϕ QALYS on recipients through improved life from their treatment.

However, given the need to choose alternative interventions and then calculate ARRs and ascribe relevant utility values in order to derive additional opportunity savings’ QALYS, we have retained net costs (subtracting hospitalisation costs averted) to account for preventive effects. Note that if alternative interventions are on average more cost-effective than LMA Rx, then cost:benefit ratios using extra QALYS from substituting LMA-prevented admissions with alternative interventions are better than if net costs are used.

- Direct scaling from 4S net costs and QALYS to derive discounted costs/QALYS for other groups is possible because:
  - LMA spending occurs constantly over the period of interest (5 years),
  - 4S Kaplan-Meier probabilities of avoiding hospitalisations for acute cardiovascular disease or revascularisation procedure diverged by as early as 10 months (5.4 year RRR of 27%)\(^4\), with similar patterns in WOSCOPS and CARE
  - Undiscounted QALYS in the model are averages for the 5-year period (derived from average ARR over five years).
Sensitivity Analyses

Given the number of assumptions the model is forced to make, we examined the effects on the base case’s QALYS of varying some of these assumptions (sensitivity analysis), viz:

- varying absolute risk
- varying relative risk reduction
- varying utility values (ie QALY scores) for health states prevented or side effects
- varying drug costs
- varying benefits’ discount rates.

In detail, we varied the model by:

1. using lower CHD mortality rates for population 1, as the lower of:
   - estimated ARCOS 5-year mortality for Europeans surviving 6 months-3 years
     (similar to the 4S population, but excluding non-MI patients and including CHF etc)
     [Robert Beaglehole and Alistair Stewart, personal communication], and
   - NZ life table mortality for the general population

2. using higher CHD mortality rates,
   - with for population 1 as the higher of:
     ◊ estimated ARCOS 5-year mortality for all surviving 28 day-3 years (ie base case), and
     ◊ GISSI-2 28 day-6 month mortality for all ages (ie aged 35-84 years), adjusted by Framingham 30-year follow-up all-cause death relative risks by age (35-64, 65-94) for the CHD cohort at 6 months and 5 years,
   - and with population 1’s base case mortality experience for population 2.

3. varying RRR for precision of estimate, ie 95% confidence intervals around 4S, WOSCOPS and fibrate meta-analysis RRRs

<table>
<thead>
<tr>
<th></th>
<th>relative risk reduction</th>
<th>(95% confidence interval)</th>
<th>% variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>all-cause deaths:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>30%</td>
<td>( 15% - 42% )</td>
<td>50%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>30%</td>
<td>( 15% - 42% )</td>
<td>100%</td>
</tr>
<tr>
<td>fibrate meta-analysis</td>
<td>5.3%</td>
<td>(- 16% - 22% )</td>
<td>180%</td>
</tr>
<tr>
<td>non-fatal CHD:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>30%</td>
<td>( 25% - 34% )</td>
<td>15%</td>
</tr>
<tr>
<td>all CHD (fatal plus non-fatal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>34%</td>
<td>( 25% - 41% )</td>
<td>26%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>34%</td>
<td>( 25% - 41% )</td>
<td>45%</td>
</tr>
</tbody>
</table>
For all-cause death relative risk reduction 95% confidence limits for statins, we scaled using linear (multiplicative) methods, ie

\[
\text{RRR}_{\text{asCHD}} = 1 - (\text{RRR}_{\text{asCHD}} \times \pm 95\% \text{ CI overall RRR})
\]

where
- \(\text{RRR}_{\text{asCHD}}\) = lower or upper 95% confidence limit for a statin age/sex/CHD group’s RRR for all deaths
- \(\text{RRR}_{\text{asCHD}}\) = a statin age/sex/CHD group’s relative risk reduction for all deaths
- overall RRR = 25% lower limit, 34% upper limit
- overall RRR = the 4S overall statin RRR for all deaths

However, because fibrate all-cause death odds ratios straddled 1 (ie some RRRs within the confidence interval were less than 0%, hence increase in risk), we calculated 95% confidence limits for fibrate age/sex/CHD groups by additive scaling, ie

\[
\text{RRR}_{\text{asCHD}} = 1 - (\pm 95\% \text{ CI RR asCHD})
\]

\[
\text{RRR}_{\text{asCHD}} = \text{RR asCHD} + (\pm 95\% \text{ CI overall OR} - \text{overall OR})
\]

where
- \(\text{RRR}_{\text{asCHD}}\) = lower or upper 95% confidence limit for a fibrate age/sex/CHD group’s RRR for all deaths
- \(\text{RR asCHD}\) = lower or upper 95% confidence limit for a fibrate age/sex/CHD group’s relative risk for all deaths
- overall OR = 0.81 lower limit, 1.06 upper limit
- overall OR = the overall fibrate odds ratio for all deaths

4. using a constant RRR for CHD events for the cholesterol-related subdivisions of population 1.

5. varying RRR for all-cause deaths by age only (not also by underlying CHD status), or by age/sex only

6. no change in RRR for both all-cause deaths and non-fatal CHD, ie \(\text{RRR}_{\text{all-deaths}}\) and \(\text{RRR}_{\text{nfCHD}}\) are constant at 29% and 26% respectively (ie vary by neither CHD status nor age)

7. using a lower QALY disutility value for CHD, viz that of AUS-TASK (time trade-off QALY score of 0.940, hence disutility of 0.060)

8. using a high disutility value for CHD of 0.20 (notional)
9. using a higher disutility value for fibrate Rx side effects of 0.05

10. assuming fibrates to be equally effective at preventing all-cause mortality as statins, i.e., same RRR(all-deaths) as for statins. Hence overall fibrate effectiveness equals that of statins (i.e., for both all-cause mortality and non-fatal CHD)

11. assuming fibrates to have nil net effect on all-cause mortality - i.e., they prevent non-fatal and fatal CHD, but non-CHD death counteracts CHD mortality improvements. Hence fibrates are only net effective at preventing non-fatal CHD, and RRR(non-fatal CHD) equals that of statins

12. combining fibrate poor all-cause mortality effectiveness with high side effect disutilities

13. decreasing statin price by 33%

14. varying discount rates for costs and benefits, viz:
   - 5% (commonly used in economic analyses of preventive programmes)
   - 10% (previously used by NZ Treasury economic analyses), and
   - 15% (an upper limit scenario for future costs of finance to regional health authorities)
Annex One

Criteria for “need” (eligibility)
The National Heart Foundation has recently published updated guidelines for managing dyslipidaemia. These guidelines establish “need”, based on various combinations of:

- age
- absolute risk of CHD events
- serum total cholesterol
- total:HDL cholesterol ratios
- impact of dietary and other modification of lipid and other risk factors.

“Absolute risk of CHD events” in turn comprises patients with:

- manifest coronary heart disease
- genetic lipoprotein disorders
- diabetic nephropathy
- patients otherwise at risk of developing coronary heart disease (>20%, 15-20%, 10-15% and <10% 5-year absolute risks).

PHARMAC’s Pharmaceutical and Therapeutics Advisory Committee (PTAC) subcommittee on LMA’s has in turn recommended that, for patients meeting the NHF criteria, fibrates or statins be prescribed according to total cholesterol levels:

- statins for manifest CHD with total cholesterol >=6.5 mmol/l,
- fibrates for manifest CHD with total cholesterol <6.5 mmol/l,
- statins for familial hyperlipidaemias
- fibrates for familial dysbetalipoproteinaemia
- statins for established diabetic nephropathy
- statins for “at risk” patients with total cholesterol >= 8.0 mmol/l
- fibrates for “at risk” patients with total cholesterol <8.0 mmol/l

The NHF and PTAC subcommittee criteria combine to describe “need” according to: absolute CHD risk, total cholesterol, total:HDL cholesterol ratio, impact of dietary and other modification of lipid and other risk factors, and class of LMA:
Treatment criteria used for LMA investment model
(following 3-6 months intensive dietary treatment, other risk factor modification, then reassessment of lipids & absolute CVD risk)

<table>
<thead>
<tr>
<th>A1: Established cardiovasc disease (part of population 1)</th>
<th>A2: familial hyperlipidemias (part of population 2)</th>
<th>A2: familial dysbeta lipoproteinemia (part of population 2)</th>
<th>A3: Established diabetic nephropathy (part of population 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total cholesterol (mmol/l)</td>
<td>total HDL cholesterol (ratio)</td>
<td>total HDL cholesterol (ratio)</td>
<td>total HDL cholesterol (ratio)</td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>&lt;5.5</td>
<td>&lt;5.5</td>
<td>&lt;5.5</td>
</tr>
<tr>
<td>5.5-6.5</td>
<td>5.5-6.5</td>
<td>5.5-6.5</td>
<td>5.5-6.5</td>
</tr>
<tr>
<td>6.5-7.5</td>
<td>6.5-7.5</td>
<td>6.5-7.5</td>
<td>6.5-7.5</td>
</tr>
<tr>
<td>7.5-8.0</td>
<td>7.5-8.0</td>
<td>7.5-8.0</td>
<td>7.5-8.0</td>
</tr>
<tr>
<td>&lt;8.0</td>
<td>&lt;8.0</td>
<td>&lt;8.0</td>
<td>&lt;8.0</td>
</tr>
</tbody>
</table>

B: Very high risk (>20% 5-year CVD risk) (part of population 3)

C: High risk (15-20% 5-year CVD risk) (part of population 3)

D: Moderate risk (10-15% 5-yr CVD risk) (part of population 3)

E: Mild risk (<10% 5-year CVD risk) (part of population 3)
Annex Two

New Zealand life table data

NZ Mortality and Life Table Data

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pop 1993</th>
<th>mortality NZ 1992</th>
<th>NZ life tables (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. rate: 1000</td>
<td>No. rate: 1000</td>
<td>%</td>
</tr>
</tbody>
</table>
Coronary heart disease and all-cause mortality rates by age/sex, NZ 1992

Life expectancy by age/sex, NZ 1991-1993
Annex Three

Calculation of age/sex-specific likely decline in CHD, and effects upon future hospitalisations.

To account for probable continuing reductions in the incidence of (new) cardiovascular disease, we applied age/sex-specific estimates of the likely decline in coronary heart disease to the above discharge volumes over time. We derived these age/sex trends using similar methods to component 3. This involves firstly combining:

1. age/sex-specific predictions of annual decline in coronary heart disease mortality for New Zealand, with
2. secular trends in the age-standardised sex-specific incidence of non-fatal coronary heart disease

to impute changes in age/sex incidence of CHD (new cases):

This then combines with:
3. changes in underlying age/sex-specific source populations

to derive age/sex-specific changes in the incidence and volume of new cases, and, by implication, hospitalisations.
References


12 Scandinavian Simvastatin Survival Study Group, op cit.


15 Sacks et al, op cit.


22 Trial of clofibrate in the treatment of ischaemic heart disease: five-year study by a group of physicians of the Newcastle upon Tyne region. BMJ 1971;14:767-75.


27 Quality of Life - LIPID Trial, Technical Report 9502. Inhouse paper supplied by S Mulray, NHMRC Clinical Trials Centre.


30 PHARMAC inhouse calculations [Sharplin P. Derestricting access to simvastatin - is it a good investment? With reference to cost utility analysis on simvastatin in treatment of hyperlipidaemia in patients with previous coronary events. Report to PHARMAC Board of Directors, March 1996 (reviewed October 1996).]


38 The Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/l (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. Am J Cardiol 1993;72:1031-7.


44 Torrance, op cit.

45 Pedersen et al, op cit.