PHARMAC *॥॥*
Pharmaceutical Management Agency

Technology Assessment Report No. 1

Lipid-Modifying Agents

Type: Detailed Cost-Utility Analysis
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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 equation[1]:

(direct pharmaceutical costs of LMAs)
+ (other lipid-lowering programme costs)
+ (costs of drug side effects)
- (costs of other pharmaceuticals associated with CHD and other atherosclerotic disease prevented or delayed)
- [(hospitalisation and other non-drug morbidity-associated costs of CHD etc prevented)]

(years of life gained from premature deaths prevented)
+ (quality-adjusted years gained from illness prevented)
- (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 programmes[2]:

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net quality-adjusted life year gains (ΔE) $= \Delta Y + \Delta Y_{morb} - \Delta Y_{SE}$

where:

ΔE =   net quality-adjusted life year gains

ΔY =   LYS from all-cause deaths prevented (ie unadjusted life years)

ΔY_{Morb} =   QALY (gains) from non-fatal CHD events prevented (ie improvements in quality of life years due to prevention of morbidity)

ΔY_{SE} =   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)

(where AR x RRR = ARR)

- life expectancy (LE)
- health state utility values (QALY scores) (q)

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

q_{base}	=	utility value (QALY score) for baseline health state (CHD = 0.925, no CHD = 1.000, genetic lipoprotein disorders = 0.950)
q_{CHD}	=	utility value (QALY score) for CHD (0.925 TTO)
q_{death}	=	utility value (QALY score) for death (0.000)
q_{RxSE}	=	utility values (QALY scores) for Rx side effects
QALYS	=	AR . RRR . LE . (1-q)
ARR_{death}	=	AR_{death} . RRR_{death}
ARR_{morb}	=	AR_{morb} . RRR_{morb}

potential years of life lost, premature death ($PYLL_{death}$) = AR_{death} . LE . (1-q_{death}) . q_{base}

potential years of life saved, premature death prevented (ΔY) = ARR_{death} . LE . (1-q_{death}) . q_{base}

           = $PYLL_{death}$. RRR_{death}

years of quality-adjusted life lost, morbidity ($QYLL_{morb}$) = AR_{morb} . LE . (1-q_{CHD})

years of quality-adj life gained, morbidity (ΔY_{morb}) = ARR_{morb} . LE . (1-q_{CHD})

           = $QYLL_{morb}$. RRR_{morb}

years of quality-adjusted life lost, Rx side effects (ΔY_{SE}) = duration of Rx use . (1-q_{RxSE})

net quality-adjusted life year gains (ΔE) = ΔY + ΔY_{morb} - ΔY_{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:

	direct pharmaceutical costs	*net health sector costs (includes hospitalisation offsets)*
potential QALYS (cf trial data)	direct cost/potential QALYS	**net cost/potential QALYS**
actual programme QALYS (includes Rx discontinuation)	direct cost/actual QALYS	net cost/actual QALYS

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):

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

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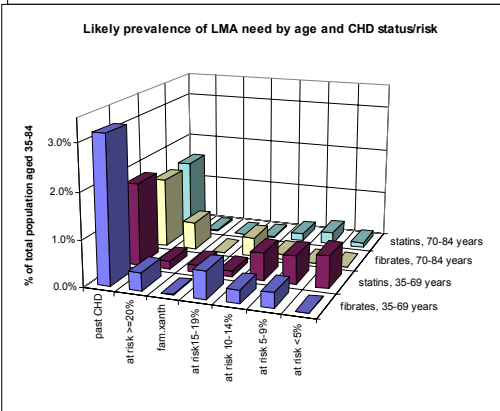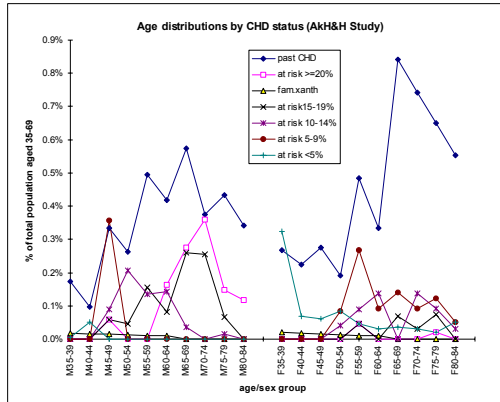**as estimated from the Framingham logistic equation

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)[i] combined with "need" defined by the National Heart Foundation and PHARMAC's PTAC subcommittee[ii] (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:

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[i] 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[i])[i] [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 (AkH&H Study)

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

LMA need

CHD status	gender	age-group	t.cholesterol, or 5-year risk/person	fibrates	statins	combined fibrate/statin programme
			population characteristics		need (Auckland H&H Study prevalence data)	
past CHD	m&f	35-69	>=7.5 mmol/l	0.0%	0.6%	0.6%
past CHD	m&f	35-69	6.5-7.4 mmol/l	0.0%	1.5%	1.5%
past CHD	m&f	35-69	5.5-6.4 mmol/l	3.2%	0.0%	3.2%
past CHD	m&f	35-69	<5.5 mmol/l	0.5%	0.0%	0.5%
past CHD	*m&f*	*35-69*	*all past CHD*	*3.8%*	*2.1%*	*5.9%*
at risk	m&f	35-69	at risk >=20%	0.5%	0.2%	0.6%
fam.xanth	m&f	35-69	fam.xanth			
at risk	m&f	35-69	at risk15-19%	0.7%	0.1%	0.8%
at risk	m&f	35-69	at risk 10-14%	0.3%	0.7%	1.0%
at risk	m&f	35-69	at risk 5-9%	0.4%	0.7%	1.1%
at risk	m&f	35-69	at risk <5%	0.0%	0.8%	0.8%
total	*m&f*	*35-69*		*5.7%*	*4.9%*	*10.5%*
past CHD	m&f	70-84	>=7.5 mmol/l	0.0%	3.0%	3.0%
past CHD	m&f	70-84	6.5-7.4 mmol/l	0.0%	7.1%	7.1%
past CHD	m&f	70-84	5.5-6.4 mmol/l	8.3%	0.0%	8.3%
past CHD	m&f	70-84	<5.5 mmol/l	1.6%	0.0%	1.6%
past CHD	*m&f*	*70-84*	*all past CHD*	*9.9%*	*10.2%*	*20.1%*
at risk	m&f	70-84	at risk >=20%	4.0%	0.2%	4.2%
fam.xanth	m&f	70-84	fam.xanth			
at risk	m&f	70-84	at risk15-19%	2.7%	0.1%	2.8%
at risk	m&f	70-84	at risk 10-14%	0.7%	1.0%	1.8%
at risk	m&f	70-84	at risk 5-9%	0.0%	1.7%	1.7%
at risk	m&f	70-84	at risk <5%	0.0%	0.7%	0.7%
total	*m&f*	*70-84*		*17.2%*	*13.9%*	*31.2%*
total, all ages		*35-84 m&f*		*7.5%*	*6.3%*	*13.7%*
NHF risk groups, m&f 35-69				*1.9%*	*2.6%*	*4.5%*
NHF groups A&B, m&f 35-69				**4.2%**	**2.5%**	**6.7%**

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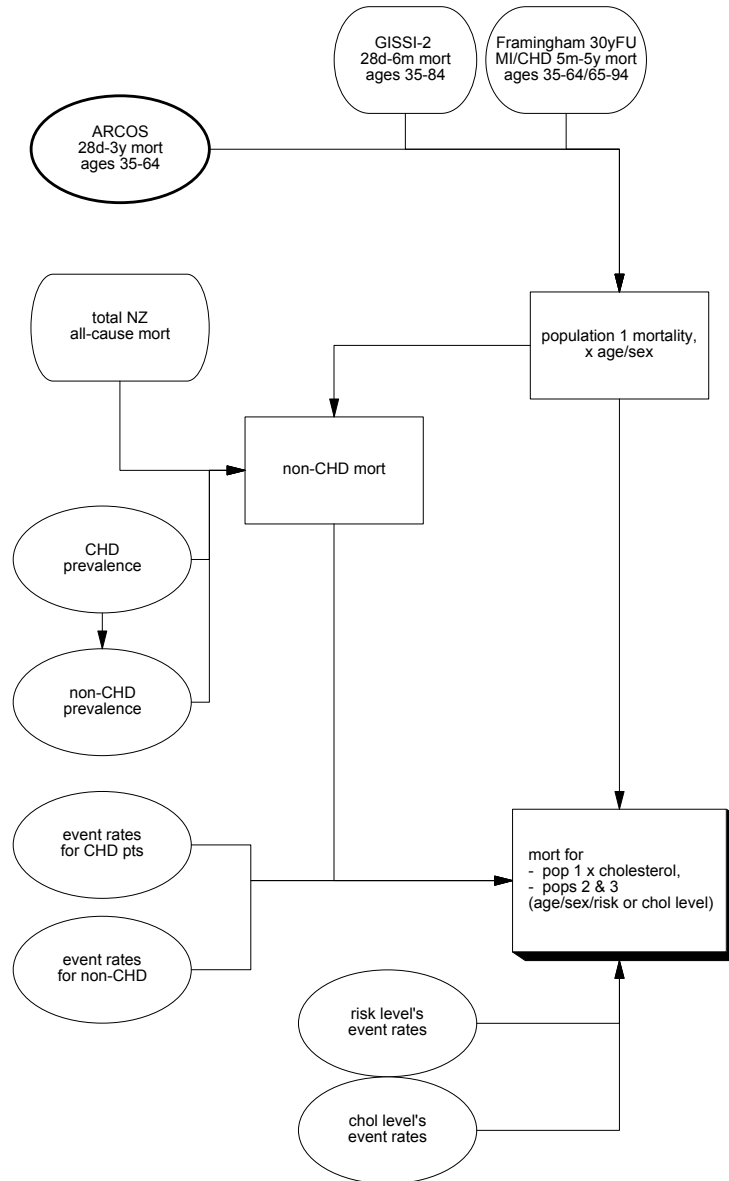
To calculate baseline absolute risks of all-cause deaths in patients with pre-existing CHD (ie population 1), we combined longitudinal mortality rates for patients with CHD from the ARCOS register with GISSI-2[3] and Framingham 30-year follow-up data[4] for each 5-year age/sex-specific group:

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)

gender	age-group	ARCOS registrants	(surviving <28 days)	surviving >28 days	deaths 28d-6m	deaths 6m- 3y	lost to FU 28d-6m	lost to FU 6m-3y	surviving at 3 years
men	35-39	157	59	98	4	3	6	0	85
men	40-44	321	111	210	5	11	15	3	176
men	45-49	517	180	337	5	19	26	5	282
men	50-54	717	298	419	8	29	26	7	349
men	55-59	1055	487	568	11	39	29	5	484
men	60-64	1284	637	647	23	53	45	6	520
total men		**4051**	**1772**	**2279**	**56**	**154**	**147**	**26**	**1896**
women	35-39	24	9	15	1	1	2	0	11
women	40-44	75	30	45	2	2	5	0	36
women	45-49	104	50	54	3	1	7	0	43
women	50-54	169	75	94	4	6	4	0	80
women	55-59	284	116	168	5	13	11	2	137
women	60-64	482	252	230	10	20	8	2	190
total women		**1138**	**532**	**606**	**25**	**43**	**37**	**4**	**497**
total		*5189*	*2304*	*2885*	*81*	*197*	*184*	*30*	*2393*

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:
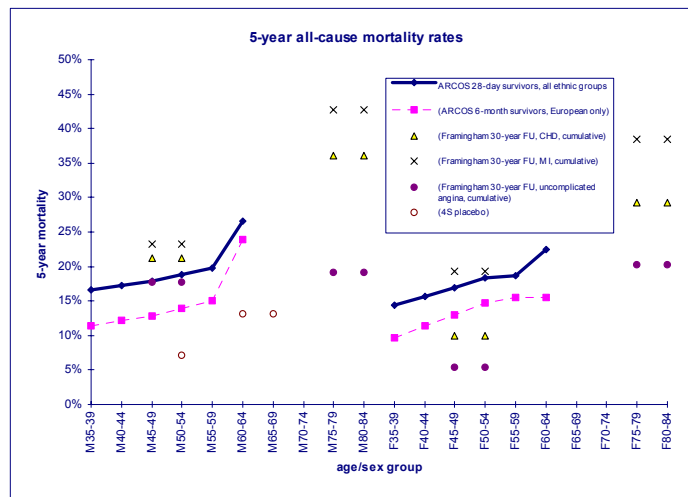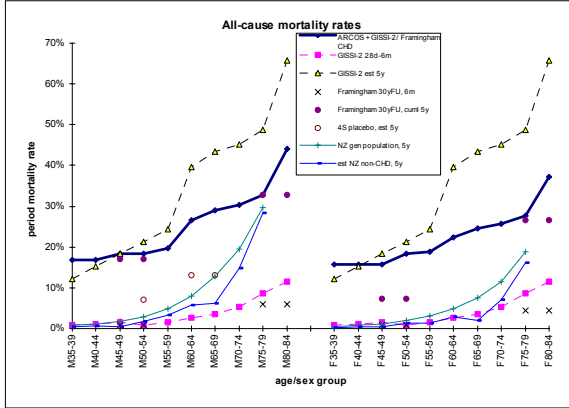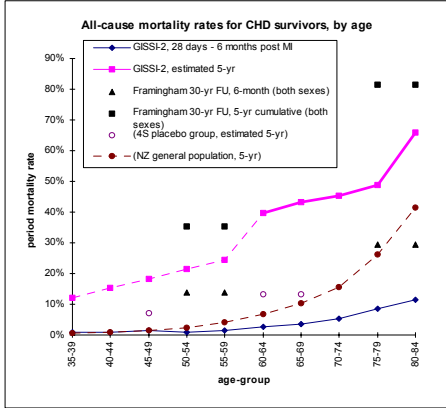

To estimate 5-year death rates for those CHD patients aged 65 and over, we then scaled the ARCOS 28-day survivors' assumed 5-year mortality for those aged 60-64 against: GISSI-2[5] mortality between 28 days and 6 months, stratified by age (ages 65 to 84), and the all-cause death relative risks for ages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

$$d_{(as)} \quad = \quad d_{ARCOS\ 60\text{-}64\ (s)} \quad \text{x} \quad \frac{d_{GISSI2\ 28d\text{-}6m\ (a)}}{d_{GISSI2\ 28d\text{-}6m\ (60\text{-}64)}} \quad \text{x} \quad \frac{d_{Fram\ 5y\ (as)}}{d_{Fram\ 5m\ (as)}}$$

where:

$d_{(as)}$ = age/sex-specific 5-year all-cause mortality rate, estimated for ARCOS population ages 65-84

$d_{ARCOS\ 60\text{-}64\ (s)}$ = age/sex-specific 5-year all-cause ARCOS mortality rate, aged 60-64 years

$d_{GISSI2\ 28d\text{-}6m\ (a)}$ = GISSI-2 age-specific 28-day to 6-month all-cause mortality rate, for ages 65-84

$d_{GISSI2\ 28d\text{-}6m\ (60\text{-}64)}$ = GISSI-2 age-specific 28-day to 6-month all-cause mortality rate, aged 60-64

$d_{Fram\ 5y\ (as)}$ = Framingham 30-year FU 5-year cumulative mortality rate, CHD men/women 35-64/65-94

$d_{Fram\ 5m\ (as)}$ = 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								
		mortality rates						rate ratios
		ARCOS + GISSI-2/ Framingham CHD	(estimated NZ non-CHD, low ARCOS/AkH&HS prvl)	ARCOS Eurp 6m survivors (cf 4S)	ARCOS + GISSI-2/ Framingham CHD	NZ all (life table)	(estimated NZ non-CHD, AkH&H	"ARCOS": NZ all	"ARCOS": NZ non-C
men	35-39	**16.6%**	0.5%	11.3%	**16.6%**	0.9%	0.5%	18.1	32.2
	40-44	**17.3%**	0.8%	12.2%	**17.3%**	1.2%	0.7%	14.9	23.1
	45-49	**17.9%**	0.5%	12.8%	**17.9%**	1.7%	0.6%	10.5	31.3
	50-54	**18.8%**	1.9%	14.0%	**18.8%**	2.9%	1.8%	6.4	10.4
	55-59	**19.7%**	3.1%	15.1%	**19.7%**	5.0%	3.2%	4.0	6.1
	60-64	**26.6%**	5.9%	23.8%	**26.6%**	8.0%	5.8%	3.3	4.6
	65-69	**29.1%**	8.6%	26.1%	**29.1%**	13.0%	6.3%	2.2	4.7
	70-74	**30.4%**	17.0%	27.2%	**30.4%**	19.5%	14.9%	1.6	2.0
	75-79	**32.7%**	28.0%	29.3%	**32.7%**	29.7%	28.4%	1.1	1.2
	80-84	**44.2%**	41.8%	39.6%	**44.2%**	42.8%	42.3%	1.0	1.0
	85-89	**66.4%**	51.0%	64.7%	**66.4%**	57.8%	54.2%	1.1	1.2
	90+	**100.0%**	100.0%	100.0%	**100.0%**	100.0%	100.0%	1.0	1.0
women	35-39	**14.4%**	0.4%	9.7%	**14.4%**	0.5%	0.2%	30.9	86.5
	40-44	**15.7%**	0.6%	11.3%	**15.7%**	0.8%	0.5%	20.0	33.0
	45-49	**17.0%**	0.9%	13.0%	**17.0%**	1.2%	0.4%	14.0	39.1
	50-54	**18.3%**	1.4%	14.7%	**18.3%**	2.0%	1.2%	8.9	14.7
	55-59	**18.7%**	2.0%	15.6%	**18.7%**	3.2%	1.3%	5.9	14.6
	60-64	**22.4%**	3.1%	15.6%	**22.4%**	5.0%	2.8%	4.5	8.0
	65-69	**24.5%**	2.8%	17.0%	**24.5%**	7.4%	2.1%	3.3	11.8
	70-74	**25.6%**	7.9%	17.8%	**25.6%**	11.5%	7.1%	2.2	3.6
	75-79	**27.6%**	15.8%	19.2%	**27.6%**	18.8%	16.1%	1.5	1.7
	80-84	**37.2%**	27.0%	25.9%	**37.2%**	30.2%	28.0%	1.2	1.3
	85-89	**52.9%**	43.0%	44.4%	**52.9%**	46.1%	43.9%	1.1	1.2
	90+	**100.0%**	100.0%	100.0%	**100.0%**	100.0%	100.0%	1.0	1.0

We next used UK cohort data for familial hyperlipidaemia[7] 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 rates[iv],

- then linear scaling to calculate each risk levels' 5-year all-cause mortality[v], using:

[iii] calculations for population 2 5-year mortality rates:

$$d_{as} = (n / py) * 5$$

$$ad_{as} = \frac{d_{as}}{((1 / (1+RR_a)) * c) + (1 - c)}$$

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

[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:

$n_{(total)}$	=	total number of NZ deaths (CHD + non-CHD)		$d_{(total)}$	=	total NZ mortality rate (CHD + non-CHD)
$n_{(CHD)}$	=	number of CHD deaths		$d_{(CHD)}$	=	CHD mortality rate
$n_{(non-CHD)}$	=	number of non-CHD deaths		$d_{(non-CHD)}$	=	non-CHD mortality rate
$P_{(total)}$	=	total NZ population (CHD + non-CHD)		$\rho_{(CHD)}$	=	prevalence of CHD
$P_{(CHD)}$	=	CHD population		$\rho_{(non-CHD)}$	=	prevalence of non-CHD,
$P_{(non-CHD)}$	=	non-CHD population			=	$(1 - \rho_{(CHD)})$

and if $n_{(CHD)} + n_{(non-CHD)} = n_{(total)}$,

then

$$(d_{(CHD)} \times \rho_{(CHD)} \times P_{(total)}) + (d_{(non-CHD)} \times \rho_{(non-CHD)} \times P_{(total)}) = (d_{(total)} \times 100\% \times P_{(total)})$$

$$\therefore d_{(non-CHD)} = \frac{d_{(total)} - (d_{(CHD)} \times \rho_{(CHD)})}{(1 - \rho_{(CHD)})}$$

[v] Linear scaling for each risk levels' 5-year all-cause mortality:

$$d_{(CHD)} - d_{(non-CHD)} = \text{rate of excess deaths due to presence of CHD}$$

$$d_{(non-CHD, at risk level)} = d_{(non-CHD)} + \frac{((e_{(no CHD)} - e_{(non-CHD, at risk level)}) \times (d_{(CHD)} - d_{(non-CHD)}))}{(e_{(no CHD)} - e_{(CHD)})}$$

where:
$d_{(CHD)}$	=	CHD mortality rate
$d_{(non-CHD)}$	=	non-CHD mortality rate
$d_{(non-CHD, at risk level)}$	=	non-CHD mortality rate for a particular 5-year risk of CHD events
$e_{(CHD)}$	=	expected 5-year event rate for all CHD events for those with pre-existing CHD
$e_{(non-CHD)}$	=	average expected 5-year event rate for all CHD events for those without pre-existing CHD
$e_{(non-CHD, at risk level)}$	=	specific level of expected 5-year events, in patients without pre-existing CHD

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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[vi]
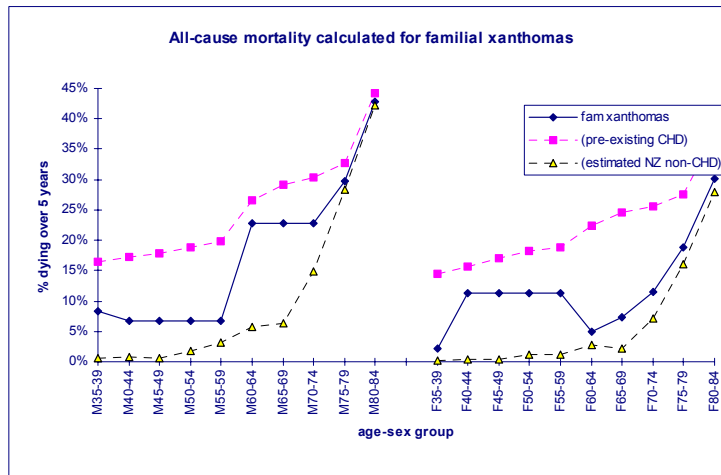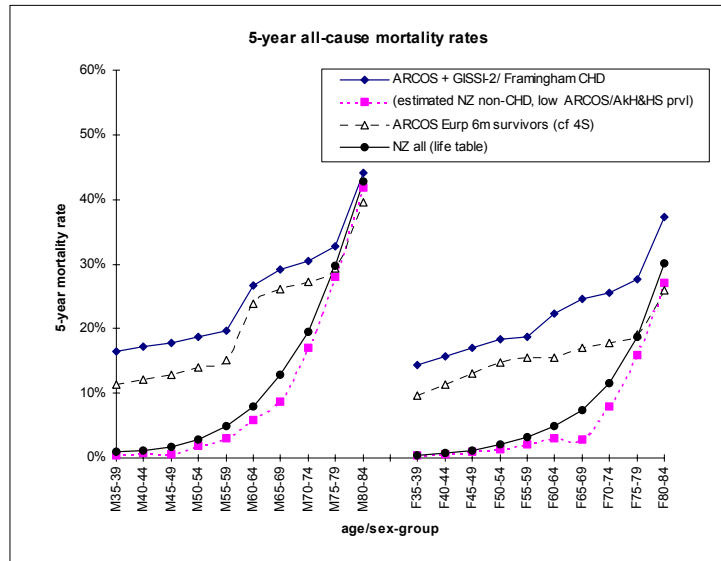
[vi] 5-year CHD events rates used the mid-point of each of population 3's 5% Framingham bands for total CHD events (fatal and non-fatal). This was except for notional 22.5% median values for those with 5-year absolute risks of 20% and above, and notional 2.5% median values for those with risks of below 5%:

| "At risk" group (Framingham logistic function)	Median risk value
<5 %	2.5%
5-10 %	7.5%
10-15 %	12.5%
15 - 20 %	17.5%
≥20%	22.5%
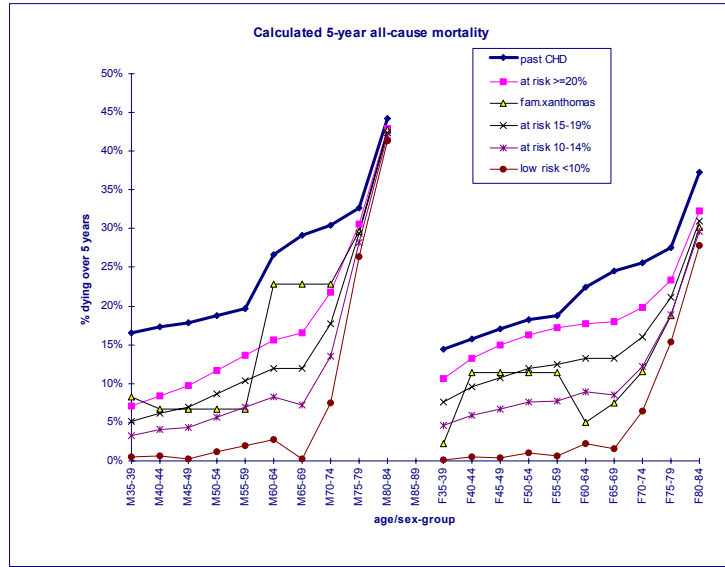
To calculate 5-year all-cause mortality rates for the cholesterol subdivisions of population 1, we also linear scaled using

- 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:
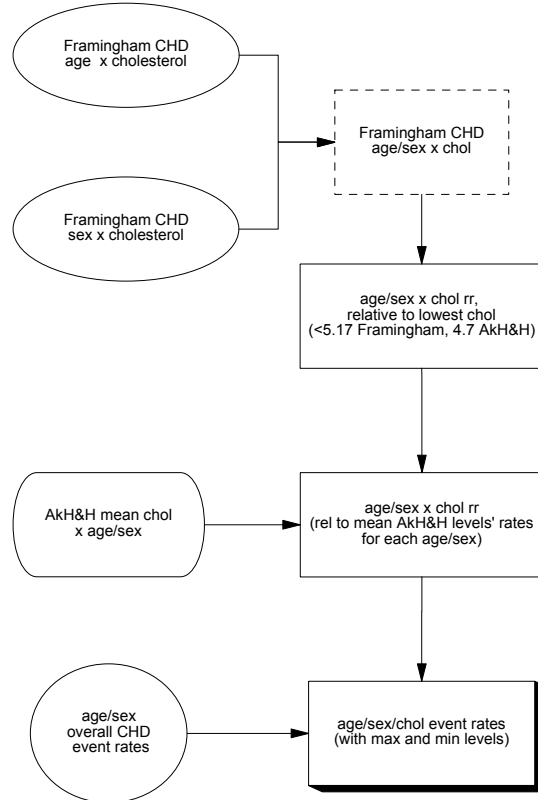
Firstly, we combined Framingham 30-year follow-up CHD cohort age-specific and sex-specific event rates by total cholesterol[8], in order to extrapolate age/sex-specific relative risks by total cholesterol:
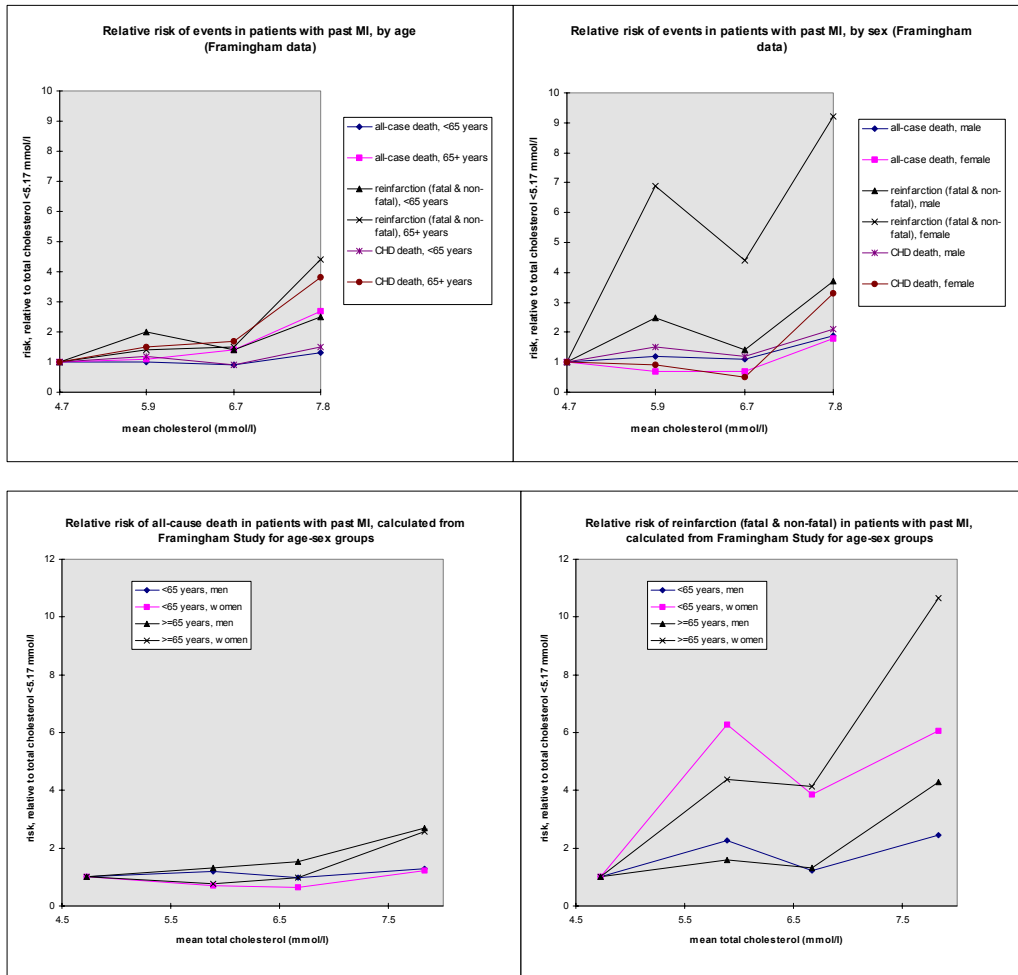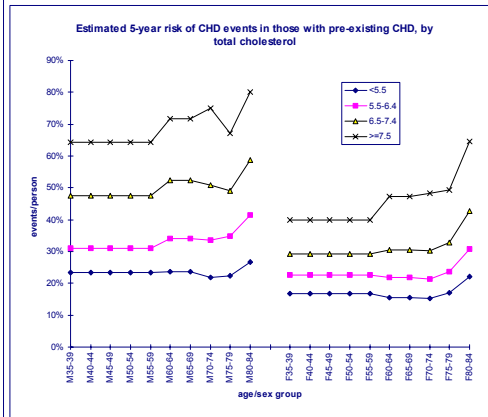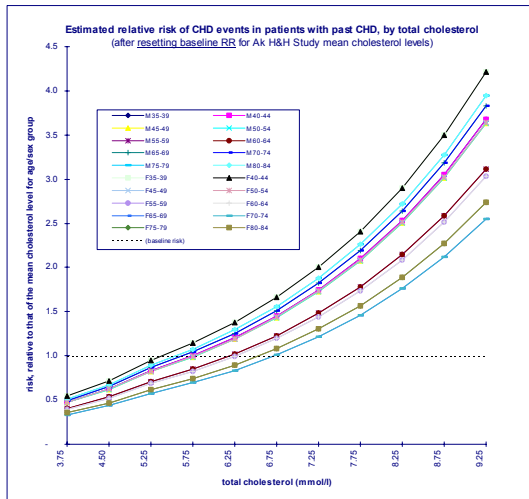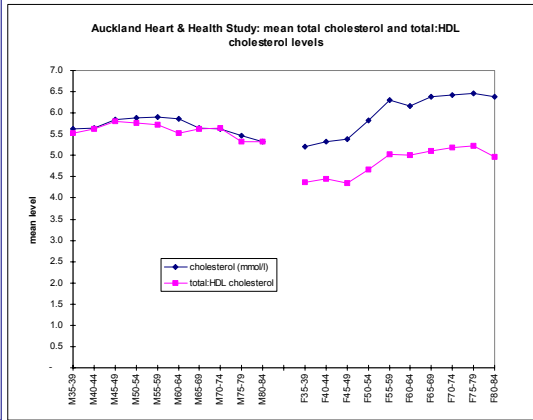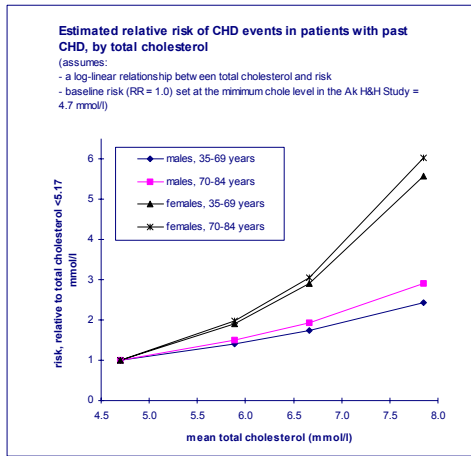

We next assumed a log-linear dose-response relationship between total cholesterol and 5-year event rates, using the relationship of on average a 25% increase in CHD incidence for every 0.6 mmol/l increase in total cholesterol[9]. Using this assumption, we calculated age/sex-specific risks by total cholesterol 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[vii].

Estimated relative risk of CHD events in patients with past CHD, by total cholesterol
(assumes:
- a log-linear relationship between total cholesterol and risk
- baseline risk (RR = 1.0) set at the minimum chole level in the Ak H&H Study = 4.7 mmol/l)

Auckland Heart & Health Study: mean total cholesterol and total:HDL cholesterol levels

Estimated relative risk of CHD events in patients with past CHD, by total cholesterol
(after resetting baseline RR for Ak H&H Study mean cholesterol levels)

Estimated 5-year risk of CHD events in those with pre-existing CHD, by total cholesterol

The above calculations produced all-cause mortality rates for each subpopulation, taking into account the risks of suffering coronary events:

[vii] for each age/sex group in population 1,

$$e_{(as)(chol)} = r_{(chol)} \times e_{(as)}$$

where

$e_{(as)(chol)}$ = 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)

Calculated 5-year all-cause mortality

Calculated 5-year all-cause mortality, patients with pre-existing CHD
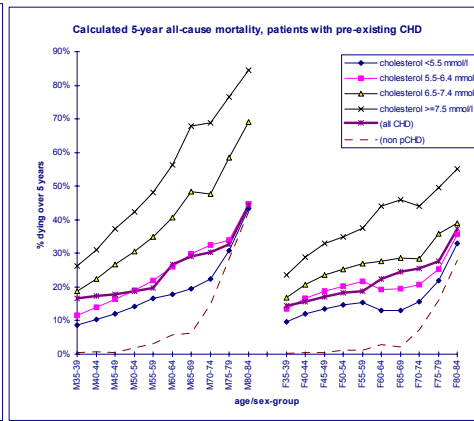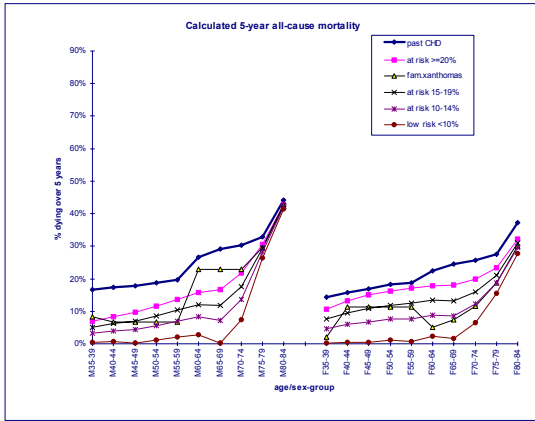
Non-fatal CHD events (AR$_{morb}$) expected for eligible populations

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:
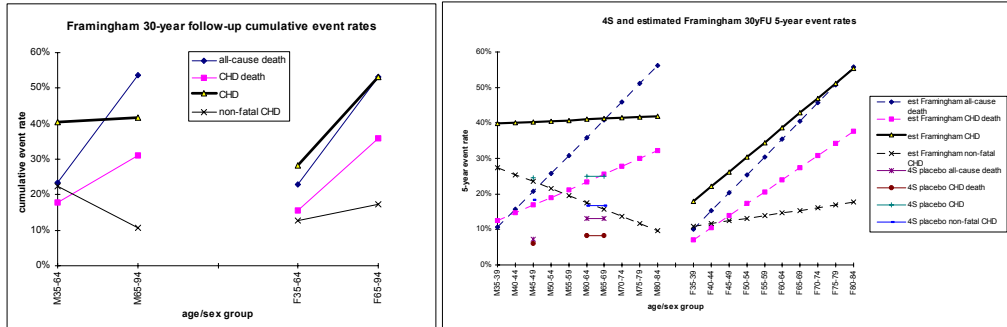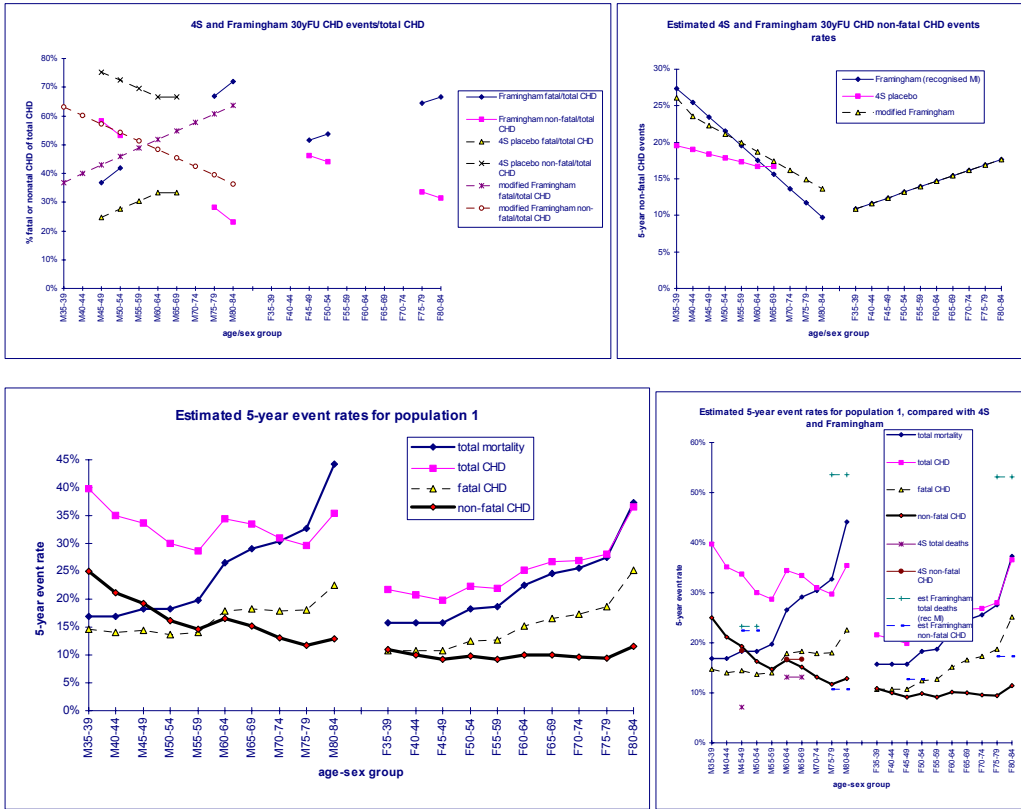

We then applied these age/sex non-fatal CHD:total mortality ratios to the estimated ARCOS 5-year all-cause mortality rates. In addition however, we modified the non-fatal CHD:total death ratios for men to reflect the lesser differential in secondary case fatality rates (ie fatal:total CHD events) between older and younger age-groups in the 4S placebo group[10viii]:

4S, Framingham and ARCOS 5-year event rates

	cumulative event rate at 5 years				ratios					Framingham ratios, adjusted for 4S experience			
	all-cause death	CHD death	CHD	non-fatal CHD	CHD/total deaths	CHD death/ total CHD	total CHD/ total dths	non-fatal/ total CHD	non-fatal CHD/total dths	CHD/total deaths	CHD death/ total CHD	total CHD/ total dths	non-fatal/ total CHD
4S placebo group (mainly men, mainly post MI but excl CHF etc):													
4S 35-59	7.2%	6.1%	24.5%	18.4%	84%	**25%**	3.4	75%	2.6				
4S 69-70	13.1%	8.4%	25.1%	16.7%	64%	**33%**	1.9	67%	1.3				
rr o/y	1.82	1.38	1.02	0.91	0.76	1.35	0.6	0.89	0.5				
Framingham 30-year follow-up, men, recognised MI:													
35-59 (est)	15.8%	14.6%	40.1%	25.4%	81%	37%	2.2	63%	1.2	83%	**40%**	2.07	60%
60-69 (est)	38.4%	24.5%	41.1%	16.6%	67%	59%	1.1	41%	0.6	65%	**53%**	1.22	47%
rr o/y	2.44	1.67	1.03	0.65	0.83	1.61	0.5	0.64	0.5	0.78	1.34	0.59	0.78
ARCOS:													
all 28d survivors (35-59 yo men)	18.6%	**15.4%**	**38.5%**	**23.2%**									
European 6m survivors (35-59 yo men)													

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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]

4S and Framingham 30yFU CHD events/total CHD

Estimated 4S and Framingham 30yFU CHD non-fatal CHD events rates

Estimated 5-year event rates for population 1

Estimated 5-year event rates for population 1, compared with 4S and Framingham

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

non-fatal CHD events $_{(age/sex/chol\ or\ risk)}$ $=$ $\left(\ 1 - \left(\dfrac{A\ fatal\ CHD\ events_{(age/sex)}}{A\ total\ CHD\ events_{(age/sex)}}\right)\ \right)$ x CHD risk$_{(age/sex/chol\ or\ risk)}$

where

A fatal CHD events$_{(age/sex)}$ $=$ ARCOS-based CHD deaths by age/sex, calculated above

A total CHD events$_{(age/sex)}$ $=$ ARCOS-based total CHD events by age/sex, calculated above

$\dfrac{A\ fatal\ CHD\ events_{(age/sex)}}{A\ total\ CHD\ events_{(age/sex)}}$ $=$ ARCOS-based case fatality rate$_{(age/sex)}$

secondary case survival rate $=$ $1 -$ case fatality rate

$=$ $1 - \left(\dfrac{fatal\ CHD\ events}{total\ CHD\ events}\right)$

We used British cohort data[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.

Non-fatal CHD event rates

Legend: past CHD; at risk >=20%; fam.xanth; at risk 15-19%; at risk 10-14%

Non-fatal CHD event rates, patients with pre-existing CHD

Legend: 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)
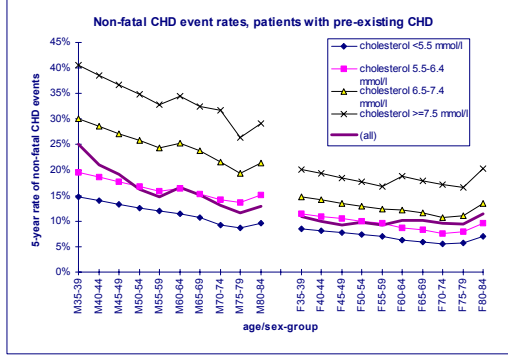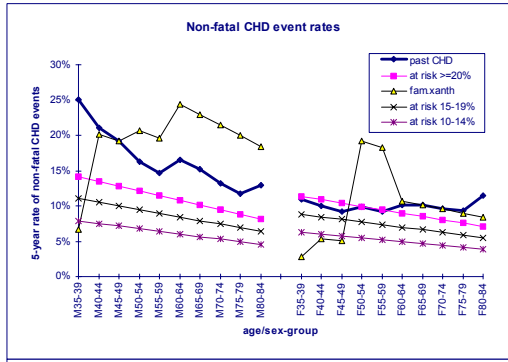
Relative risk reductions (RRR) through LMA use by each subpopulation

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 ie "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):
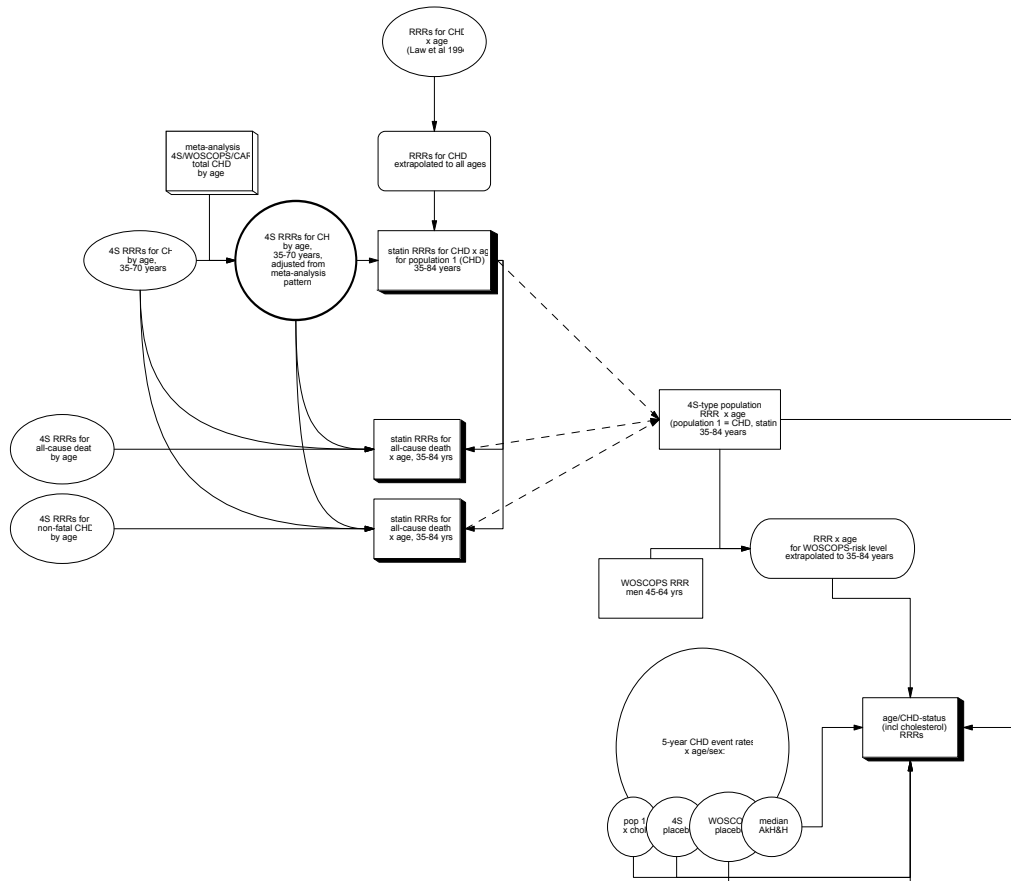
We based the model's RRR parameters for people with pre-existing CHD aged 35-69 on age-related RRRs calculated from 4S[12], but modified for a less marked difference between older and younger patients evident from meta-analysis of statin RCTs (4S was the only reported to date designed with sufficient 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 populaiton is most similar to proposed popualtions eligible for satins in tdrms of CHD risk and totaol choleterol levles. However, CARE[13] showed a markedly different age-related pattern from 4S, and 4S may have underestiamted potential RRRs in older patients through its exclusion criteria.):
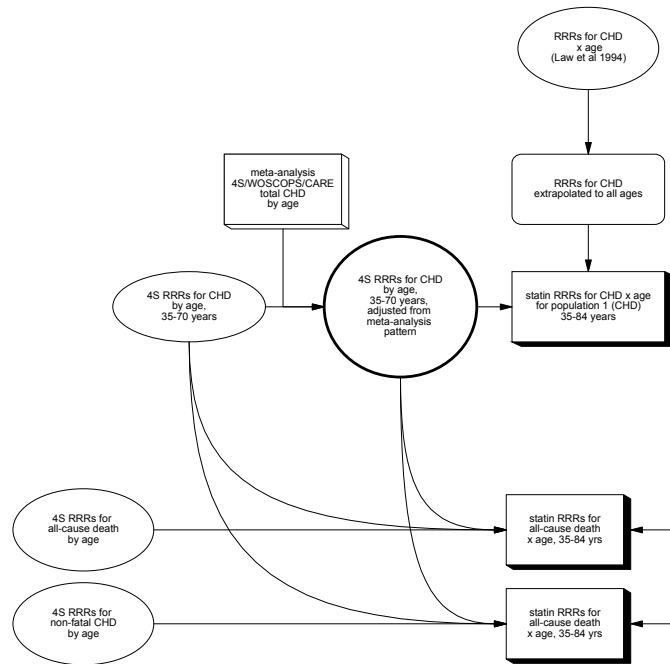
1. We started with the RRRs reported by 4S by age for total CHD events, viz 39% for ages 35-59 and 29% for ages 60-70. We then combined the three major statin age-related prospective RCTs reported to date (4S, WOSCOPS[14] and CARE[15]) to derive age-related RRRs for total CHD events for statins, viz 34% for younger patients and 28% for older. Next we combined the meta-analysis pattern of RRR by age back to $s, to derive adjusted 4S RRRs by age for total CHD events of 38% for ages 35-59 and 31% for ages 60-70.

CHD event rates in statin trials, stratifying by age:

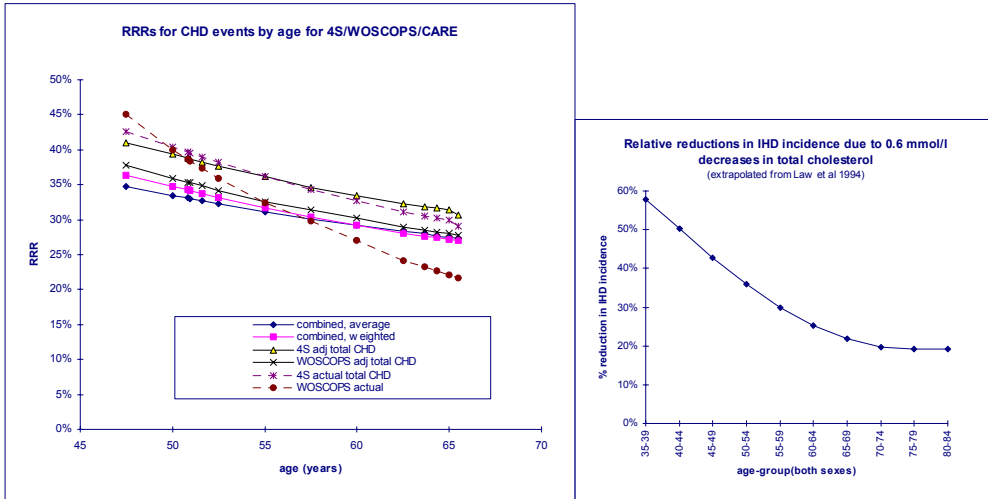| trial	no.	years duration (y)	patient type	5-year CHD risk	t.cholesterol range (mmol/l0)	age-range (years)	mid-age* (years)	RRR	no. placebo events** (e)	5-year AR for placebo group***	5-year ARR****	(no. CARE placebo "major coronary events")
aggregate data:												
4S	4,444	5.4	pCHD (79% MI)	25.9%	5.5-7.9	35-70	58.7	34%	622	25.9%	8.8%	
PLAC-I/II	586	3.0	pCHD	16.5%		35-64	58.5	48%	29	16.5%	7.9%	
CARE	4,159	5.0	pCHD (100% MI)	13.2%	<6.2	21-75	59.6	24%	274	13.2%	3.2%	549
WOSCOPS	6,595	4.9	at risk (5% angina)	7.7%	>6.5	45-64	55.1	31%	248	7.7%	2.4%	
combined (weighted RRs)	15,784	5.0		14.9%	>6.5	21-75	57.4	31%	1,173	14.9%	4.6%	
age-specific data and estimations (using ARCOS and FCUAHHS distributions):												
4S	2,162		younger	26.0%		35-59	51.6	39%	303	26.0%	10.1%	
	2,282		older	25.9%		60-70	65.5	29%	319	25.9%	7.5%	
PLAC-I/II	448		younger	13.4%		35-64	55.0	38%	18	13.4%	5.1%	
	138		older	26.6%		65-74	70.0	78%	11	26.6%	20.7%	
CARE	2,030		younger	12.7%		21-59	51.3	20%	129	12.7%	2.5%	258
	2,129		older	13.6%		60-75	67.5	27%	145	13.6%	3.7%	291
WOSCOPS	3,225		younger	6.1%		45-54	50.0	40%	96	6.1%	2.4%	
	3,370		older	9.2%		55-64	60.0	27%	152	9.2%	2.5%	
combined (weighted RRs)	7,865		younger	13.7%		21-64	51.1	34%	546	13.9%	4.8%	RRR 55-75/21-64:
	7,919		older	15.5%		55-75	63.8	28%	627	15.9%	4.5%	83%

* using ARCOS distributions, or assuming mid-point of age-range
** fatal CHD + non-fatal MI
*** AR=e/n*5/y
**** ARR=AR*RRR

trial	no.	years duration (y)	patient type	5-year CHD risk	t.cholesterol range (mmol/l0)	age-range (years)	mid-age* (years)	RRR	no. placebo events** (e)	5-year AR for placebo group***	5-year ARR****	(no. CARE placebo "major coronary events")
4S, CARE and PLAC-I/II	9,189	5.1	2ndry trials	19.6%		21-75	59.1	30.4%	925	19.9%	6.03%	
	4,640		younger	18.9%		21-64	51.8	30.6%	450	19.1%	5.85%	RRR 55-75/21-64:
	4,549		older	20.2%		60-75	66.6	29.6%	475	20.6%	6.09%	97%
4S, WOSCOPS and CARE	15,198	5.1	prospective trials	18.8%		21-75	57.4	30.0%	1,144	14.8%	4.45%	
	7,417		younger	8.6%		21-64	50.8	34.2%	528	14.0%	4.80%	RRR 55-75/21-64:
	7,781		older	5.8%		60-75	63.7	27.6%	616	15.6%	4.31%	81%
4S+CARE	8,603	5.2	2ndry prospective	19.8%		21-75	59.2	29.2%	896	20.0%	5.83%	
	4,192		younger	19.5%		21-64	51.5	29.8%	432	19.8%	5.89%	RRR 55-75/21-64:
	4,411		older	20.0%		60-75	66.5	28.0%	464	20.2%	5.67%	94%
4S+WOSCOPS	11,039	5.1	prospective t.chol>5.5	15.0%		35-70	56.6	32.2%	870	15.4%	4.98%	
	5,387		younger	14.1%		35-59	50.6	39.6%	399	14.5%	5.75%	RRR 55-75/21-64:
	5,652		older	15.9%		55-70	62.2	27.8%	471	16.3%	4.54%	70%
4S, WOSCOPS/CARE, avera	15,198	5.1	prospective trials	4.9%		21-75	57.8	29.7%	1,144	14.8%	4.38%	
	7,417		younger	14.9%		21-64	51.0	33.0%	528	14.0%	4.60%	RRR 55-75/21-64:
	7,781		older	16.2%		60-75	64.3	27.7%	616	15.5%	4.30%	84%
combined (one-step)	15,784	5.0		14.9%	>6.5	21-75	57.4	40%	1,173	14.9%	6.0%	
combined (crude)								34%			5.1%	
combined (one-step)	7,865	5.0		13.7%		21-64	51.1	37%	546	13.9%	5.1%	
combined (one-step)	7,919	5.0		15.5%		55-75	63.8	30%	627	15.9%	4.8%	
combined (crude)						21-64		33%			4.5%	
combined (crude)						55-75		25%			4.0%	

RRRs for major CHD events in major statin RCTs, by age

relative risk reduction

80%
70%
60%
50%
40%
30%
20%
10%
0%

45 50 55 60 65 70

age

(PLAC-I/II)

4S

WOSCOPS

CARE

combined
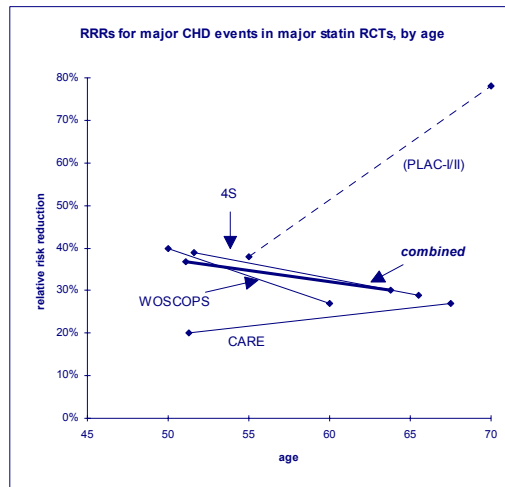
2. For those in population 1 aged ≥70 years using statins, we scaled the adjusted 4S age-dependent RRRs for total CHD against the RRRs reported in the analysis by Law et al of cholesterol lowering upon the incidence of CHD (relative reductions in CHD from decreases in cholesterol, stratified by age)[16], to obtain age-specific RRRs in CHD incidence.[ix]

3.

total CHD events:	(Law meta-analysis)	RRR 4S/WOSCOPS/CARE:		adjusted		actual	
age (years)	(Law meta-analysis)	combined, average	combined, weighted	4S adj total CHD	WOSCOPS adj total CHD	4S actual total CHD	WOSCOPS actual
47.5	43%	*35%*	*36%*	*41%*	*38%*	*43%*	*45%*
50.0	39%	33%	35%	39%	36%	40%	40%
50.8	38%	33%	34%	39%	35%	40%	39%
51.0	38%	33%	34%	39%	35%	40%	38%
51.6	37%	33%	34%	38%	35%	39%	37%
52.5	36%	32%	33%	38%	34%	38%	36%
55.0	33%	31%	32%	36%	33%	36%	32%
57.5	30%	30%	30%	35%	31%	34%	30%
60.0	28%	29%	29%	33%	30%	33%	27%
62.5	25%	28%	28%	32%	29%	31%	24%
63.7	24%	28%	28%	32%	28%	31%	23%
64.3	24%	28%	27%	32%	28%	30%	23%
65.0	24%	*27%*	*27%*	*31%*	*28%*	*30%*	*22%*
65.5	23%	27%	27%	31%	28%	29%	22%
old:young ratio		0.79	0.75	**0.76**	0.74	0.70	0.49
slope young-old	-1.09%	-0.40%	-0.52%	-0.55%	-0.58%	-0.72%	-1.30%
overall RRR		29.7%	30.0%	34.0%	31.0%	34.0%	31%

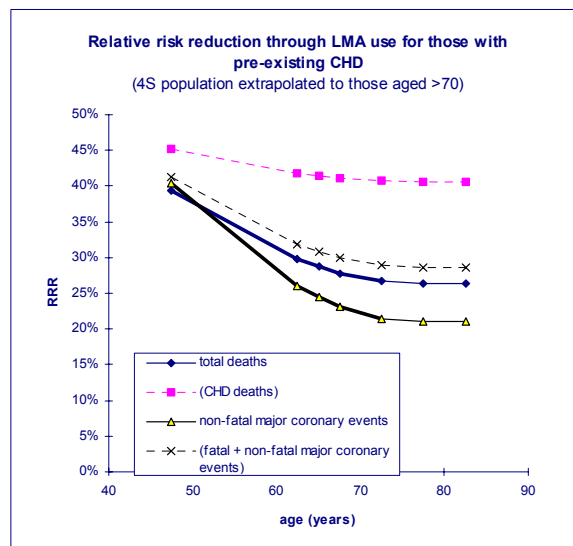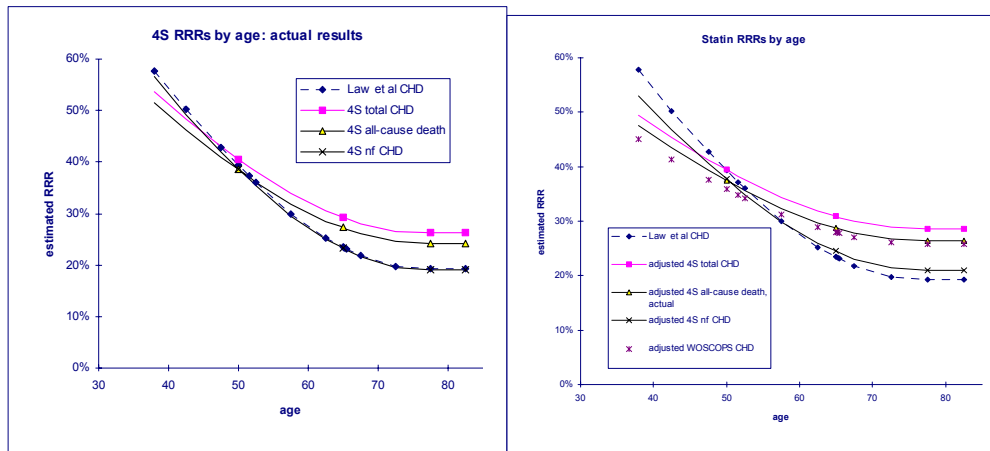[ix] Note we took the higher of 4S's 35-59 or 60-69 year-old treatment:placebo relative risks as reference points for scaling.

RRRs for CHD events by age for 4S/WOSCOPS/CARE

Relative reductions in IHD incidence due to 0.6 mmol/l decreases in total cholesterol
(extrapolated from Law et al 1994)

4. For CHD RRRs for population 1 <u>stratified by total cholesterol</u> 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):

Total CHD risk reductions

Statins' estimated relative risk reductions for total CHD events
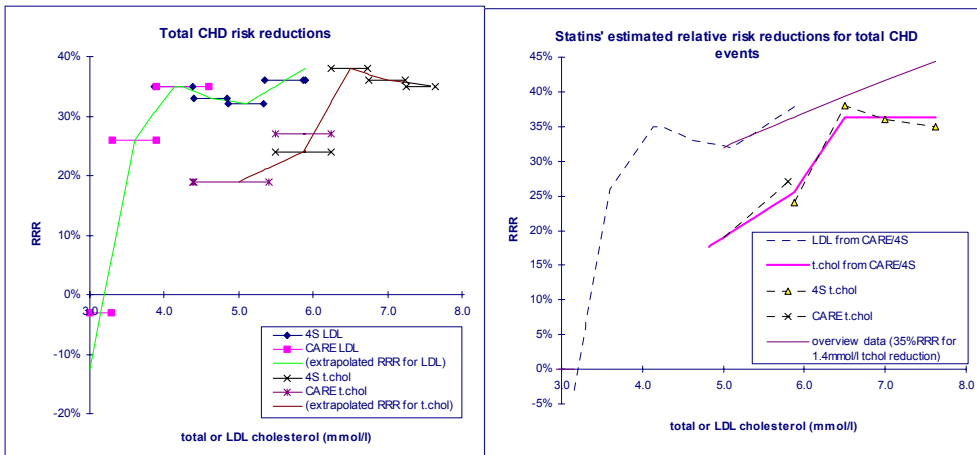
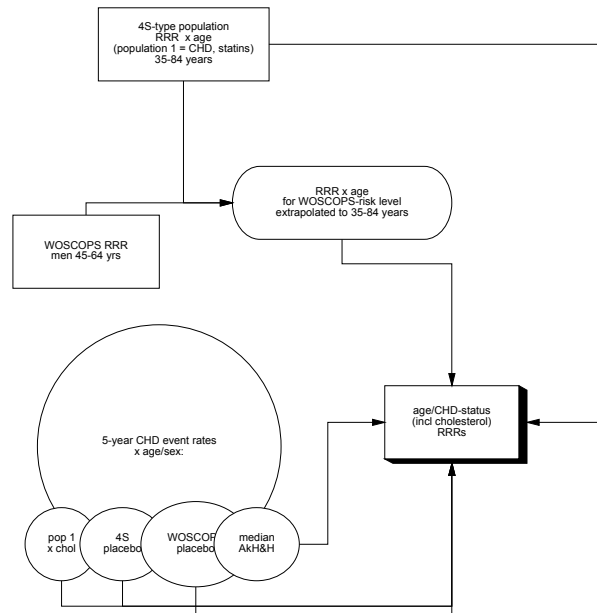5. For all-cause death RRRs for population 1, we then scaled the relevant 4S RRRs against the age-related RRRs for total CHD from both 4S itself and the above meta-analysis (where, at any age, RRR all-cause death = 4S RRR all-cause death * meta-analysis RRR CHD / 4S CHD RRR), then fitting the data to the above age-related patterns. We similarly derived age-related RRRs for population 1 for fatal and non-fatal CHD.

4S RRRs by age: actual results

estimated RRR

- Law et al CHD
- 4S total CHD
- 4S all-cause death
- 4S nf CHD

age

Statin RRRs by age

estimated RRR

- Law et al CHD
- adjusted 4S total CHD
- adjusted 4S all-cause death, actual
- adjusted 4S nf CHD
- adjusted WOSCOPS CHD

age

Relative risk reduction through LMA use for those with pre-existing CHD
(4S population extrapolated to those aged >70)

RRR

- total deaths
- - (CHD deaths)
- non-fatal major coronary events
- - (fatal + non-fatal major coronary events)

age (years)

For all-cause death RRR using statins for both
- the cholesterol subdivisions of population 1, and
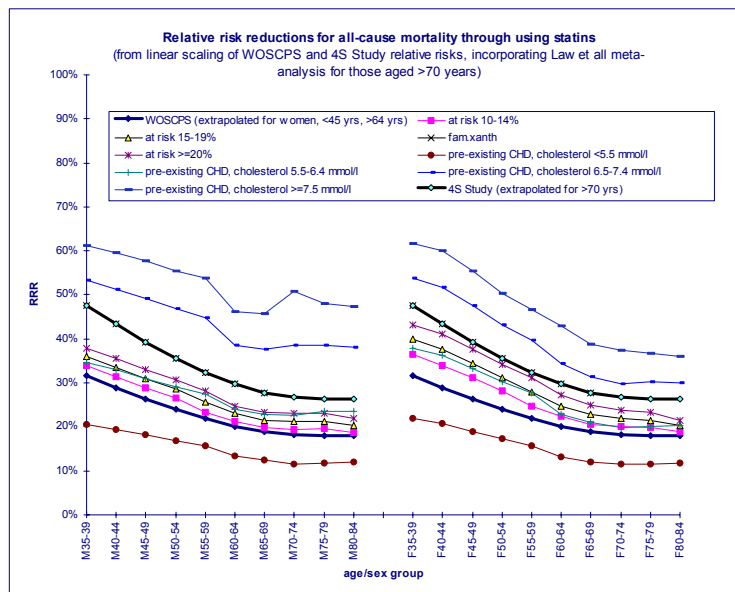- the risk levels of populations 2 and 3,

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:

4S-type population
RRR x age
(population 1 = CHD, statins)
35-84 years

RRR x age
for WOSCOPS-risk level
extrapolated to 35-84 years

WOSCOPS RRR
men 45-64 yrs

5-year CHD event rates
x age/sex:

pop 1
x chol

4S
placebo

WOSCOPS
placebo

median
AkH&H

age/CHD-status
(incl cholesterol)
RRRs

Linear scaling for all-cause death RRRs for statins:

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

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

Relative risk reductions for all-cause mortality through using statins
(from linear scaling of WOSCPS and 4S Study relative risks, incorporating Law et all meta-analysis for those aged >70 years)

Legend:
- WOSCPS (extrapolated for women, <45 yrs, >64 yrs)
- at risk 10-14%
- at risk 15-19%
- fam.xanth
- at risk >=20%
- pre-existing CHD, cholesterol <5.5 mmol/l
- pre-existing CHD, cholesterol 5.5-6.4 mmol/l
- pre-existing CHD, cholesterol 6.5-7.4 mmol/l
- pre-existing CHD, cholesterol >=7.5 mmol/l
- 4S Study (extrapolated for >70 yrs)

RRR (y-axis, 0% to 100%)

age/sex group (x-axis): M35-39, M40-44, M45-49, M50-54, M55-59, M60-64, M65-69, M70-74, M75-79, M80-84, F35-39, F40-44, F45-49, F50-54, F55-59, F60-64, F65-69, F70-74, F75-79, F80-84

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).

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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:
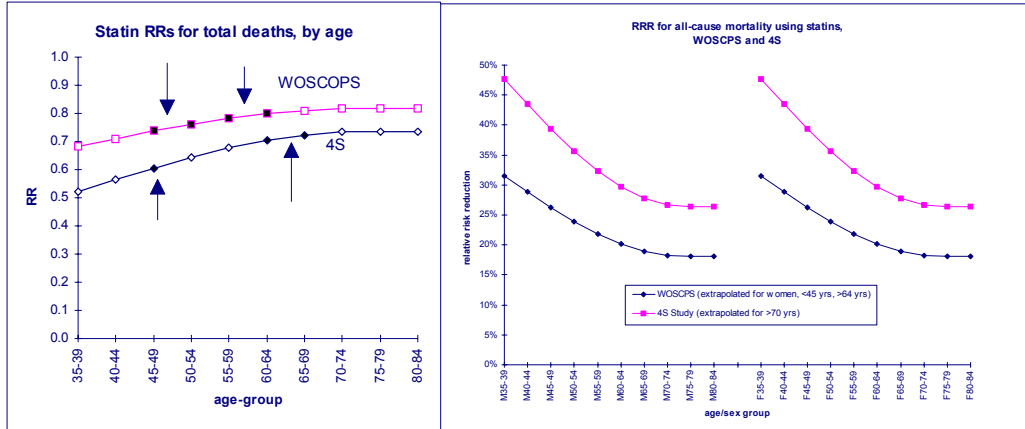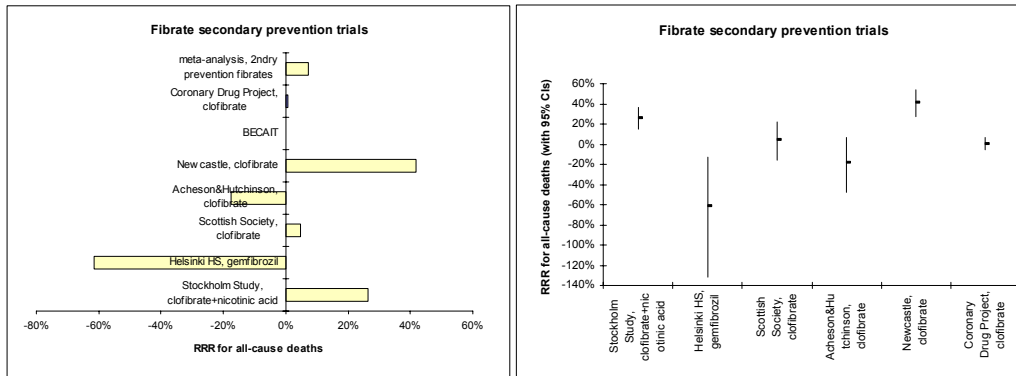
For all-cause death RRRs for <u>fibrates</u>, we used a 5.3% RRR calculated from using a meta-analysis of cited secondary prevention fibrate trials applied to the 4S population[x] (odds ratio 0.95, 95% confidence interval 0.78 to 1.16, n= 6466 patients with 1381 deaths in 7 studies, 19% vs 39% mortality),
 viz the Stockholm Study (clofibrate+nicotinic acid)[18], ancillary Helsinki Heart Study (gemfibrozil)[19], Scottish Society (clofibrate)[20], Acheson & Hutchinson (clofibrate)[21], Newcastle (clofibrate)[22], Coronary Drug Project (clofibrate)[23], and BECAIT (bezafibrate)[24]:

$$RRR_{fibrates,total\ deaths} = 1 - \frac{(RR_{fibrates,total\ deaths} * AR_{4S,CHD\ deaths}) + (RR_{fibrates,non\text{-}CHD\ deaths} * AR_{4S,non\text{-}CHD\ deaths})}{AR_{4S,total\ deaths}}$$

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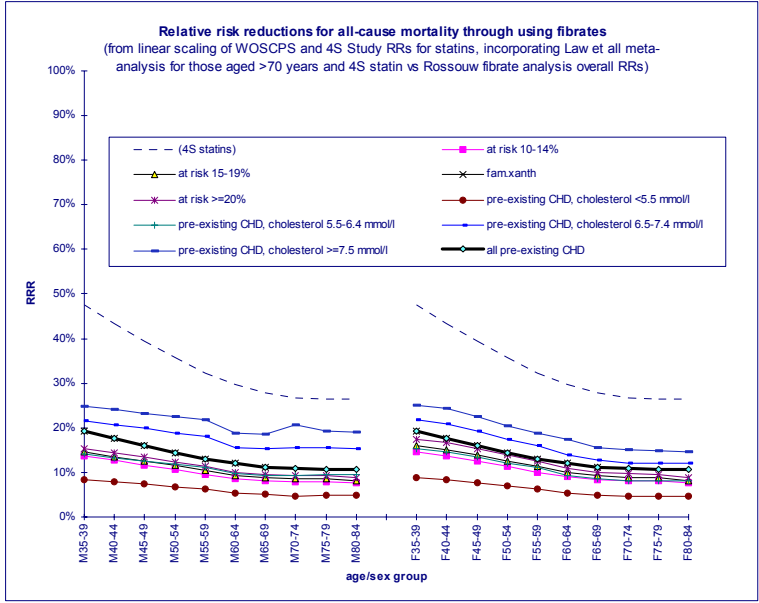$AR_{4S,total\ deaths}$ = total death rate in 4S

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%[xi], ie:

$$RRR_{fibrates,all\text{-}cause\ death} = (RRR_{statins,all\text{-}cause\ death}) \times \frac{RRR_{fibrate\ fibrates,all\text{-}cause\ death}}{RRR_{statin\ fibrates,all\text{-}cause\ death}}$$

---

[x] 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)

[xi] 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 fibrates
(from linear scaling of WOSCPS and 4S Study RRs for statins, incorporating Law et all meta-analysis for those aged >70 years and 4S statin vs Rossouw fibrate analysis overall RRs)

Legend:
- – – – (4S statins)
- at risk 10-14%
- at risk 15-19%
- fam.xanth
- at risk >=20%
- pre-existing CHD, cholesterol <5.5 mmol/l
- pre-existing CHD, cholesterol 5.5-6.4 mmol/l
- pre-existing CHD, cholesterol 6.5-7.4 mmol/l
- pre-existing CHD, cholesterol >=7.5 mmol/l
- all pre-existing CHD
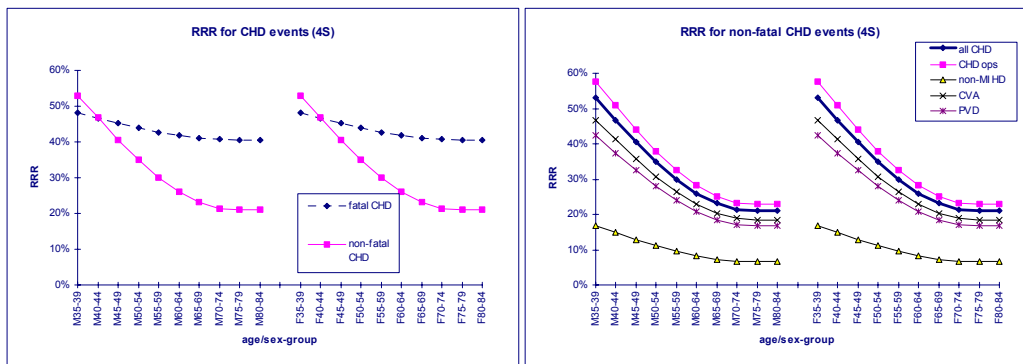
Y-axis: RRR
X-axis: age/sex group

For <u>non-fatal events</u>, 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)[xii], 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[25] (primary prevention with gemfibrozil) is combined with all published secondary prevention trials <u>except</u> the ancillary Helsinki Heart Study (OR 0.76, 95%CI 0.66-0.89, Peto one-step method)[xiii]; Helsinki itself showed a 37% RRR for non-fatal CHD (with 34% RRR fro total CHD events):
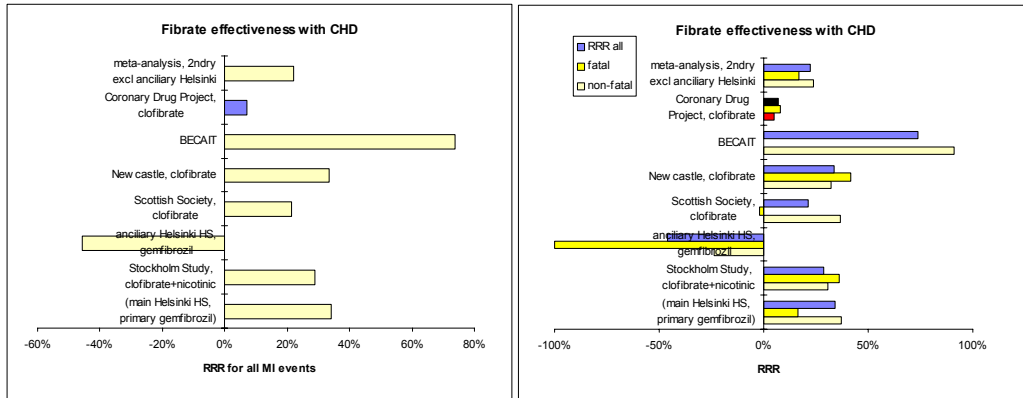
Hence RRRs in the model for non-fatal events vary according to age and type of event, but not by underlying CHD status nor LMA class:

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,

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

$$
NNT = \frac{1000}{e}
$$

where

e	=	events prevented per 1000 eligible population each year
ARR	=	5-year absolute risk reduction/person
NNT	=	numbers needed to treat (NNT) to prevent one event

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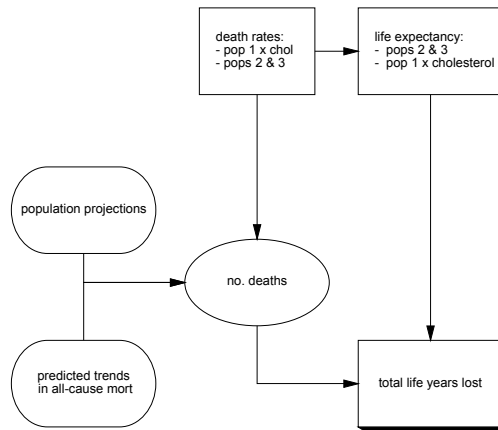
To calculate the expected loss in life years for each age/sex/CHD group, we firstly calculated each group's average life expectancy for it's individuals, using the above mortality rates and standard period-based life table methods. [26]
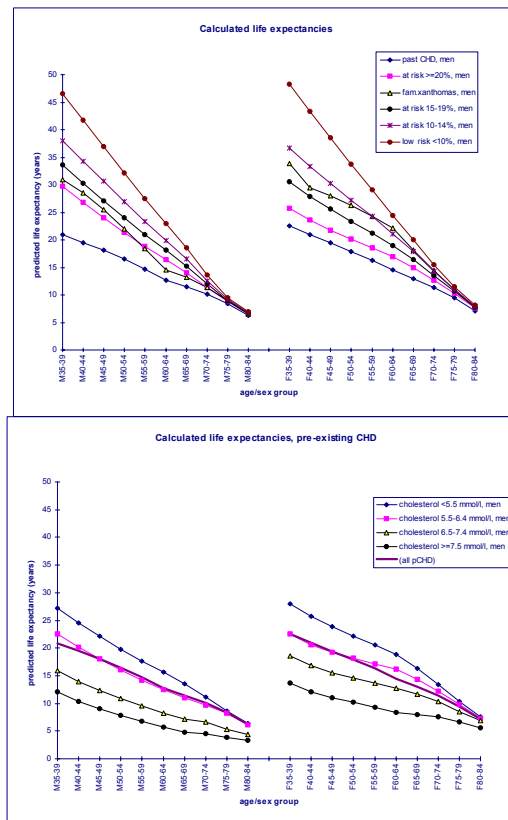
We then calculated each individual's potential loss in life years from premature death ($PYLL_{death}$) from mortality rates and life expectancy (and accounting for baseline health state):

potential years of life lost, premature death ($PYLL_{death}$)	=	AR_{death} . LE . $(1-q_{death})$. q_{base}

where:

| $PYLL_{death}$	=	potential years of life lost, premature death
AR_{death}	=	total mortality rate
q_{death}	=	utility value (QALY score) for death (0.000), $\therefore$ $(1-q_{death}) = 1$
q_{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[xiv] [xv]:

Projected incidence of all-cause mortality, relative to 1993
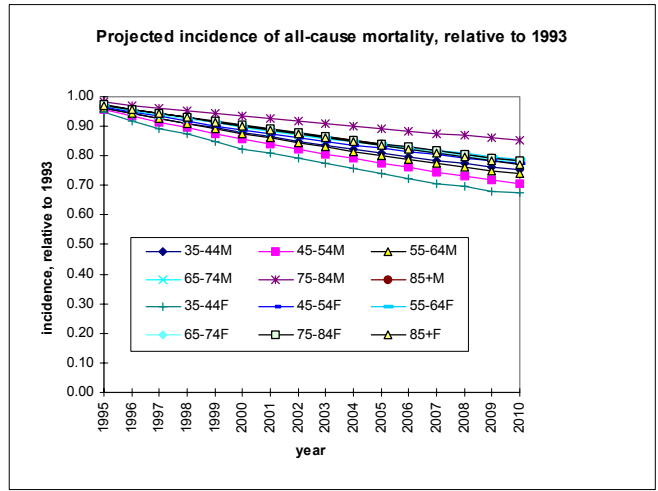
We then calculated potential life years lost by each <u>subpopulation</u>, by combining numbers of deaths with average life expectancies:

for each age/sex/CHD status group,

total life years lost state	=	no. of deaths	x	average life expectancy	x	baseline health
	=	PYLL/person	x	population (no. of people)		

[xiv] % change in total (all-cause) mortality 1970/2 to 1990/2 (source: Statistics NZ. Demographic Trends 1994. Wellington: Statistics NZ, 1995), combined with % change in CHD mortality 1970-1992 and projected incidence of CHD mortality

[xv] for each age/sex/CHD status group,

n	=	d . p . δd

where

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

QALY gains

We calculated <u>net QALY gains</u> 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:
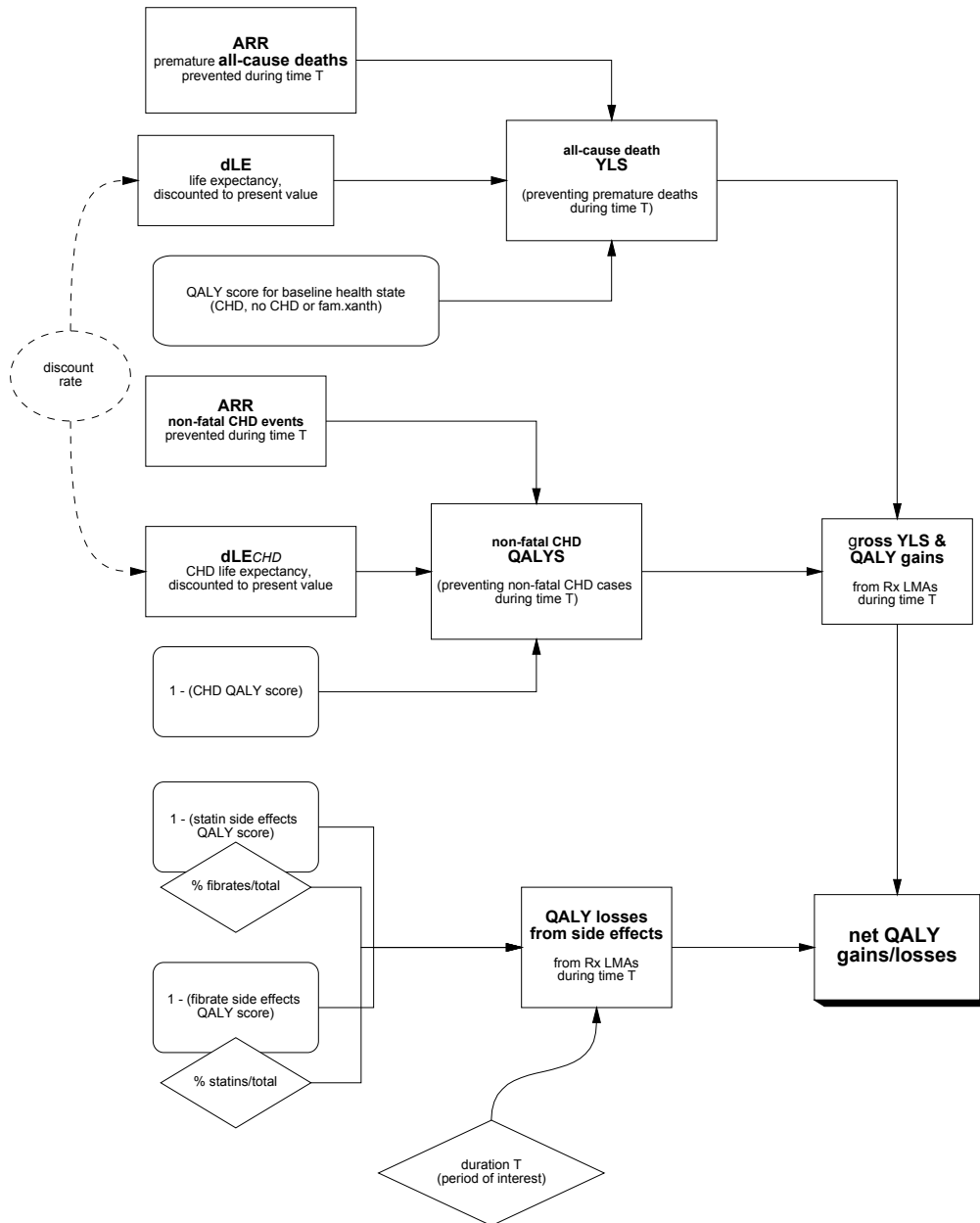
To help derive potential QALY gains for each event prevented by an LMA programme, we used QALY scores developed in Australia for the Quality of Life (QoL) substudy of the LIPID study (n = 1112).[27] The LIPID QALY scores were 0.983 using the Rosser index and **0.925** using the time trade-off method (TTO):

QALY scores for post-MI dyspnea and angina										
	no.				QALYs					
	AUS-TASK		LIPID QoL		Rosser index			TTO index		
	TOTAL	%	TOTAL	%	AUS-TASK	LIPID QoL	Weighted average, incl AUS-TASK non-response	AUS-TASK	LIPID QoL	Weighted average, incl AUS-TASK non-response
NYHA category (dyspnoea):	1340	100%			*0.976*	*0.983*	*0.979*	*0.940*	*0.923*	*0.932*
no SOB	629	47%	558	50%	0.99	0.987	0.989	0.97	0.943	0.957
SOB on strenuous exertion	475	36%	448	40%	0.98	0.985	0.982	0.94	0.923	0.932
SOB on normal exertion	142	11%	106	10%	0.96	0.956	0.958	0.85	0.822	0.838
SOB on mild exertion	85	6%	0	0%	0.91	-	0.910	0.85	-	0.850
SOB at rest	9	1%	0	0%	0.36	-	0.360	0.67	-	0.670
Karnofsky category (angina):					*0.979*			*0.943*		
no angina					1.00	na		1.00	na	
A: normal activity	1043	78%	na	na	0.99	na		0.97	na	
B: unable to work	287	21%	na	na	0.94	na		0.84	na	
C: unable to care for self	8	1%	na	na	0.30	na		0.36	na	
CCVS Angina grade (angina):						*0.983*			*0.924*	
no angina	na	na	743	67%	na	0.987		na	0.947	
no limit to normal activity	na	na	289	26%	na	0.982		na	0.895	
slight limitation	na	na	68	6%	na	0.966		na	0.822	
marked limitation	na	na	8	1%	na	0.956		na	0.725	
unable to perform physical activity	na	na	4	0%	na	0.737		na	0.775	
TOTAL	1338	100%	1112	100%			0.983			0.925

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} = 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 (ΔY_{Morb}):

$$\Delta Y_{Morb} = n_{nf} \times dLE_{CHD} \times (1 - q_{CHD})$$

where

ΔY_{Morb} = non-fatal CHD quality-adjusted life year gains
n_{nf} = numbers of non-fatal events prevented
dLE_{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
= 1 - utility value (QALY score) for CHD from the LIPID QoL substudy
= 0.075

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 (ΔY)[xvi]:

$$\Delta Y = n_f \times dLE \times (1 - q_{death}) \times q_{base}$$

where

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

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

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

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[xvi] Note here that each life year gained through death prevented equates to one full QALY

utility of 1.00 (ie 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 (ΔY_{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):

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

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, ie

$$\Delta E = \Delta Y + \Delta Y_{Morb} - \Delta Y_{SE}$$

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 <u>number of events</u> each <u>subpopulation</u> might experience over a 5-year period:

no. events (5 years)	=	median 5-year risk	x	prevalence
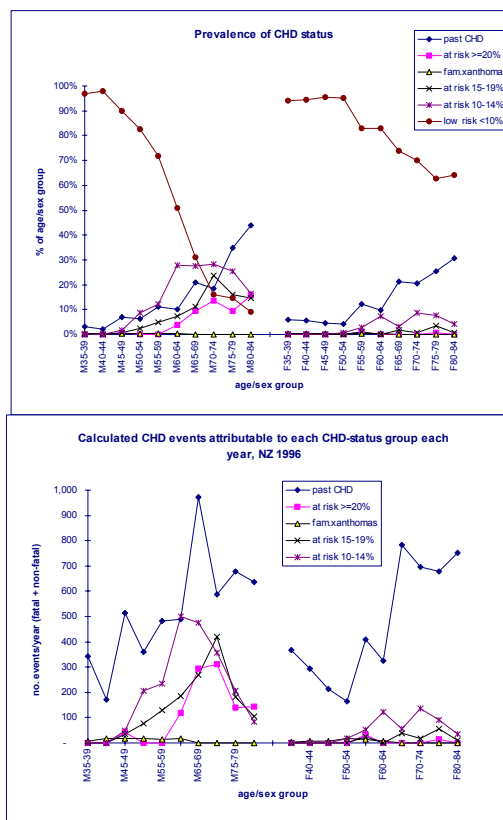
We then estimated the extent to which each age/sex/CHD status subpopulation accounted for overall CHD events. To do this, we summed the above event numbers for each subpopulation, to obtain the total number of events expected for all subpopulations combined (ie total overall events):

$$n_{total} = \sum n_{(as)(CHD)}$$

where

n_{total} = total number of events overall

$n_{(as)(CHD)}$ = 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

proportion of events attributable to a	<u>number of events for that</u>

subpopulation	subpopulation
	total overall number of events

Events attributable to each CHD-status group (attributable fractions)

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

Y-axis: % events in CHD group/total events

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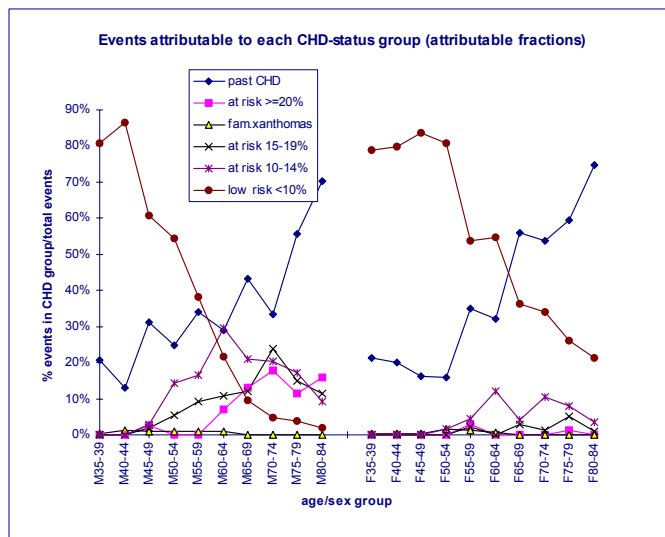
Hospital and other morbidity-associated costs and offset savings

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.[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:

DRG volumes

DRG prices

volume-weighted prices
for NZ,
each DRG

major DRG groupings
- volumes
- prices

hospital discharge data
x age/sex
- public hospitals
- private hospitals

major DRG groupings
x age/sex
- volumes
- prices

attributable
fractions

major DRG groupings
x age/sex
x CHD status
- volumes
- prices

RRRs

no. hospitalisations prevented,
ideal conditions

% eligible

% programme
coverage

no. hospitalisations prevented,
ideal conditions

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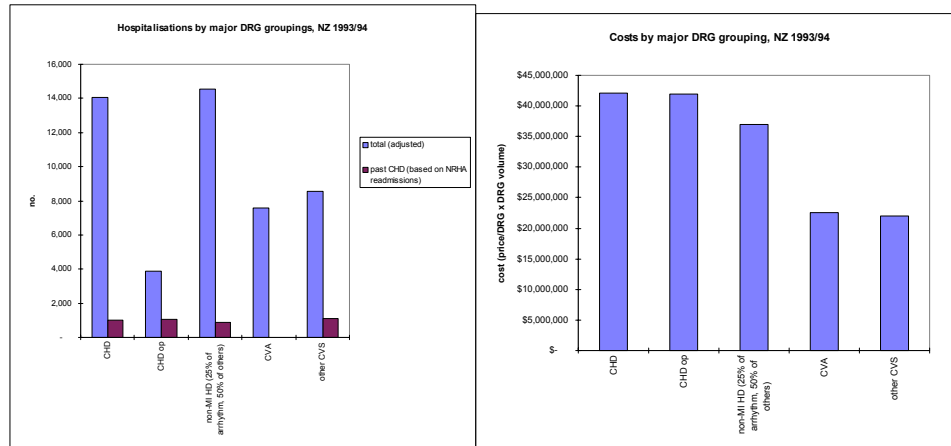
We mapped these volumes and prices to relevant ICD9-CM diagnostic and operation codes. We next used New Zealand 1992 hospital discharge data to calculate volumes for each of the major groupings by age and sex, for both public and private hospitals[xviii].

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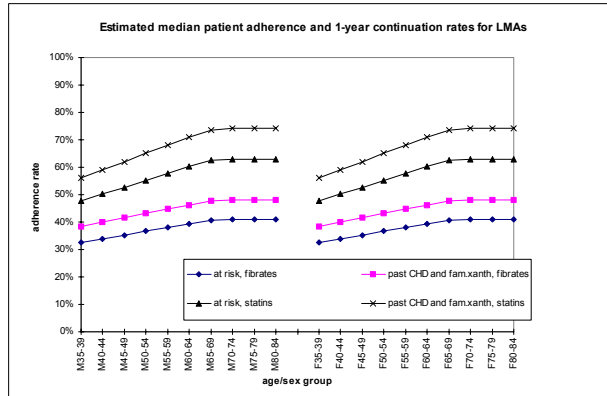y decline in coronary heart disease to the above discharge volumes over time, to derive age/sex numerical trends (see Annexe)

- 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 NZ$26,553 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,

$$\text{cost/QALY} \quad = \quad 4S_{NZ} \quad \frac{uN_i}{dQ_i} \quad \text{x} \quad \frac{uN}{dQ}$$

where

$4S_{NZ}$ = $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 undisc QALYS/p/yr)

uN = undiscounted net costs/person/year for any age/sex/CHD status/LMA class
uN_i = 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
dQ_i = 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 LMAs[xix]), 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.

Estimated median patient adherence and 1-year continuation rates for LMAs

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-I[34], PLAC-II[35], REGRESS[36], CCAIT[37], PMNSG[38], MARS[39] and MAAS[40] 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 <u>excluding both</u> 4S, trials of less than 2 year's duration (viz PMNSG, Sahni et al[41]) 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 over   2.8 years on average), which is similar to 4S':
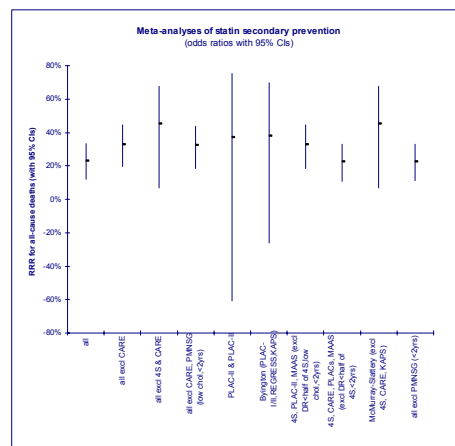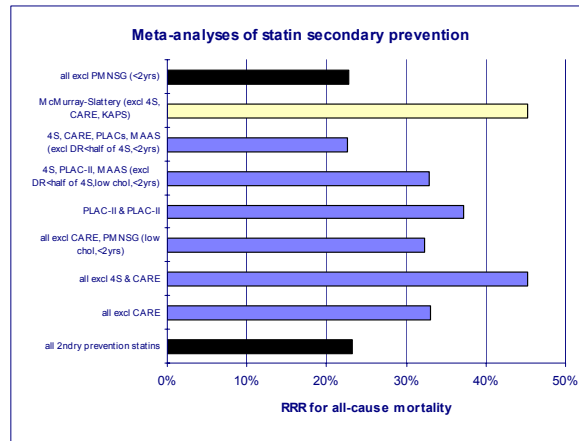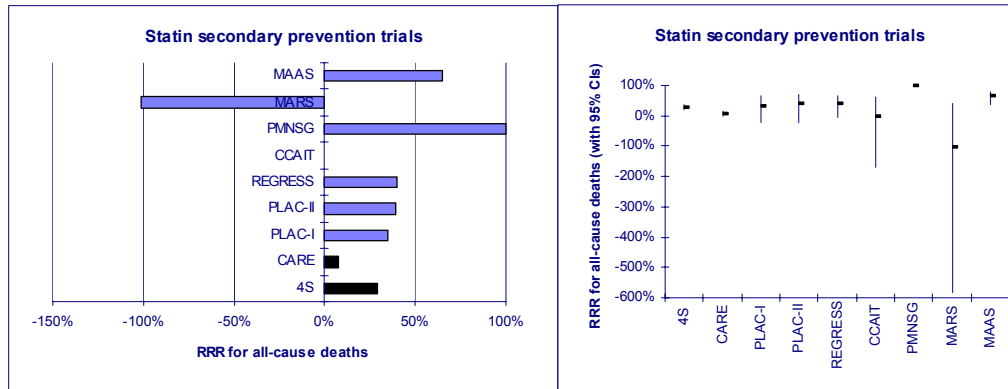

However, such meta-analyses presume all statin drugs have similar therapeutic effects, and analyses are potentially confounded if this is not so. Hence the model has retained simvastatin age-related RRRs.

- 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.[42] 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).

44

4S CHD RRRs, relative to quartile 1
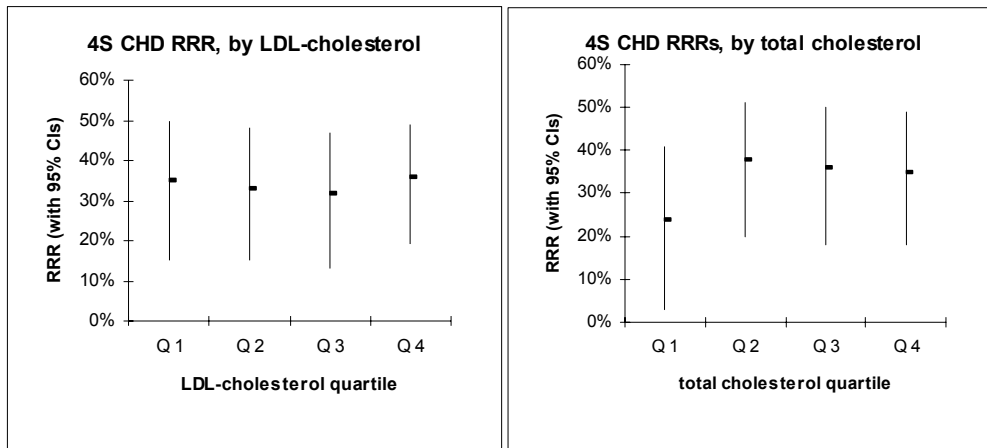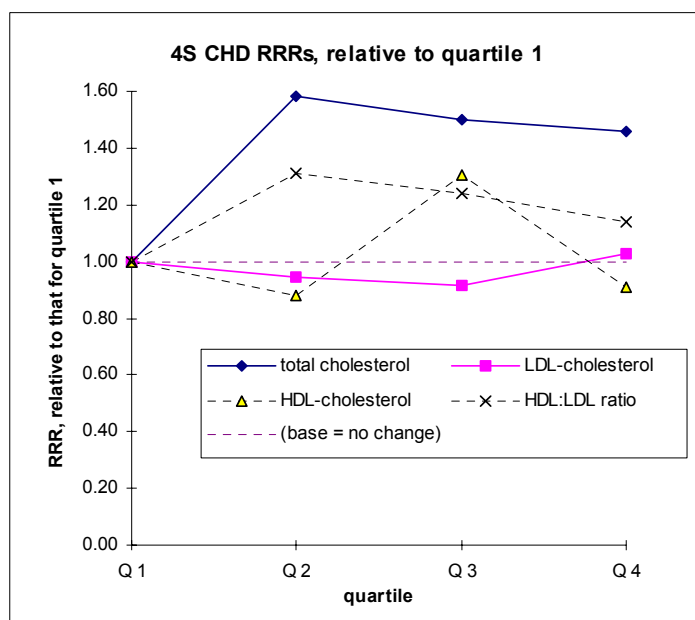
Results from CARE are consistent with 4S' over same cholesterol ranges, and thus add to 4S' experience. CARE too showed a decrease in RRR with low LDL levels. For LDL levels of 3.0 to 3.3 mmol, the RRR for CHD events was -3%, ie an <u>increase</u> in events of 3% (95% CI -38% to +23%). However, RRRs 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 occurrred in 4S for the same LDL levels. And CARE showed a similar gradient in RRR by total cholesterol as occurred with 4S:

CARE CHD RRRs, with 95% CIs

CHD RRRs for 4S and CARE
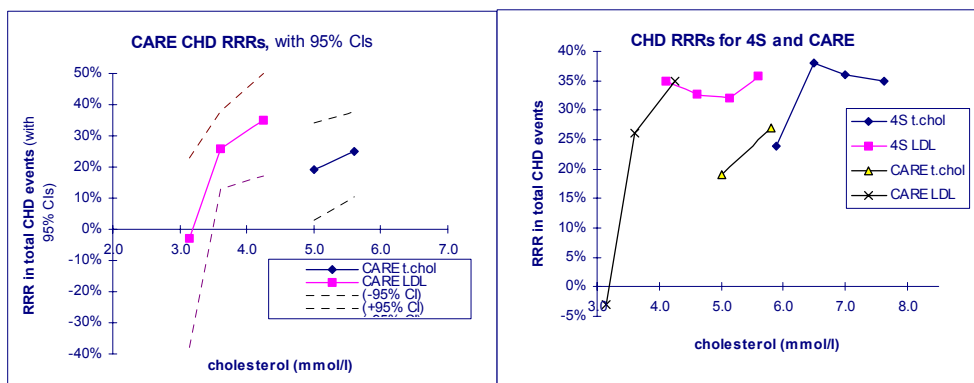
Again, the CARE results are difficult to interpret because of their wide confidence intervals. However, there may be a threshold of around 4 mmol/l at which constant statin RRRs for CHD according to baseline LDL-cholesterol levels no longer apply. Hence below 4 mmol/l (ie the lowest quartile of LDL), 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 Torrance[44].

- 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, ie 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 <u>net</u> 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, eg because there are μ fewer cases of CHD resulting from LMA programmes, λ other alternative interventions can occur (eg 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 revasularisation procedure diverged by as early as 10 months (5.4 year RRR of 27%)[45], with similar patterns in WOSCOPS and CARE
  ◊ undiscounted QALYS in the model are averages for the 5-year period (derived from <u>average</u> 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
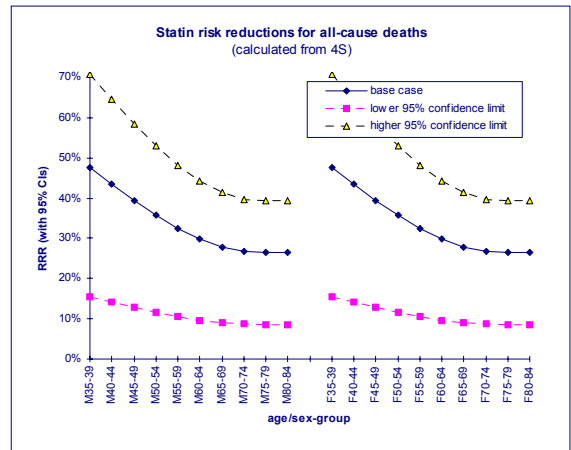- varying drug costs
- varying benefits' discount rates.

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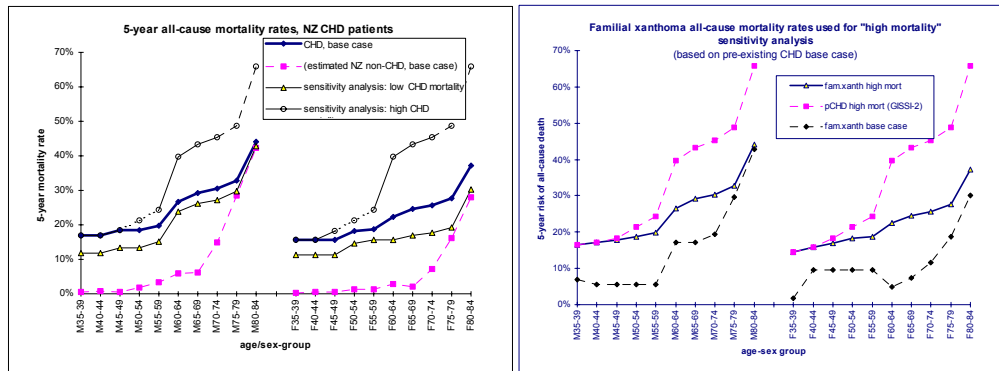
3. varying RRR for precision of estimate, ie 95% confidence intervals around 4S, WOSCOPS and fibrate meta-analysis RRRs

	relative risk reduction		(95% confidence interval)	% variation (lower CL vs point estimate)	
all-cause deaths:					
4S	30%		(15% - 42%)	50%	
WOSCOPS		22%	(0% - 40%)		100%
fibrate meta-analysis	5.3%		(- 16 % - 22%)	180%	
non-fatal CHD:					
4S	30%		(25% - 34%)	15%	
all CHD (fatal plus non-fatal)					
4S	34%		(25% - 41%)	26%	
WOSCOPS		31%	(17% - 43%)		45%

fibrate meta-analysis	13%	(2% - 23%)	84%

Statin risk reductions for all-cause deaths
(calculated from 4S)

For all-cause death relative risk reduction 95% confidence limits for statins, we scaled using linear (multiplicative) methods, ie

RRR_{asCHD} =	1	-	(RRR_{asCHD}	*	$\dfrac{\pm 95\%CL\ overall\ RRR}{overall\ RRR}$)

where
RRR_{asCHD} = lower or upper 95% confidence limit for a statin age/sex/CHD group's RRR for all deaths
RRR_{asCHD} = a statin age/sex/CHD group's relative risk reduction for all deaths
overall RRR = lower or upper 95% confidence limit for the 4S overall statin RRR for all deaths
  = 25% lower limit, 34% upper limit
overall RRR = the 4S overall statin RRR for all deaths
  = 29%

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

RRR_{asCHD}	=	1	-	$\pm 95\%CL\ RR_{asCHD}$		
RR_{asCHD}	=	RR_{asCHD}	+	($\pm 95\%CL\ overall\ OR$	-	overall OR)

where
RRR_{asCHD} = lower or upper 95% confidence limit for a fibrate age/sex/CHD group's RRR for all deaths
RR_{asCHD} = lower or upper 95% confidence limit for a fibrate age/sex/CHD group's relative risk all deaths
RR_{asCHD} = a fibrate age/sex/CHD group's relative risk for all deaths
overall OR = lower or upper 95% confidence limit for the overall fibrate odds ratio for all deaths
  = 0.81 lower limit, 1.06 upper limit
overall OR = the overall fibrate odds ratio for all deaths
  = 0.93

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 $RRR_{all-deaths}$ and RRR_{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 <u>all-cause</u> mortality as statins, ie same $RRR_{all\text{-}deaths}$ as for statins. Hence overall fibrate effectiveness equals that of statins (ie for both all-cause mortality and non-fatal CHD)

11. assuming fibrates to have nil <u>net</u> effect on <u>all-cause</u> mortality - ie 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 $RRR_{non\text{-}fatal\ CHD}$ 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.[46] 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
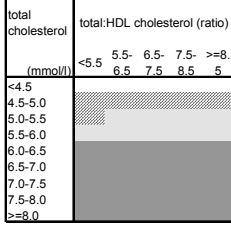- fibrates for "at risk" patients with total cholesterol <8.0 mmol/l

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:
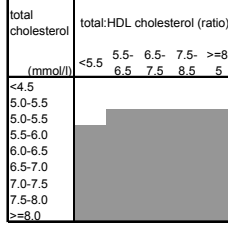
Treatment criteria used for LMA investment model

(following 3-6 months intensive dietary treatment, other risk factor modification, then reassessment of lipids & absolute CVD risk)
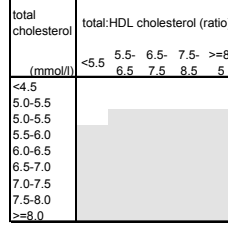
fibrates   statins

(fibrates, post CABG)   no LMA

A1: Established cardiovasc disease (population 1)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
4.5-5.0					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					

A2: familial hyperlipidemias (part of population 2)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					

A2: familial dysbetalipoproteinemia (part of population 2)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					

A3: Established diabetic nephropathy

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					
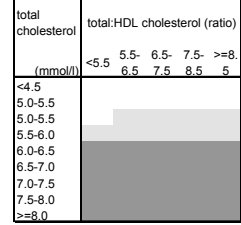
B: Very high risk (>20% 5-year CVD risk) (part of population 3)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					
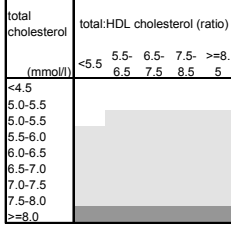
C: High risk (15-20% 5-year CVD risk) (part of population 3)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					
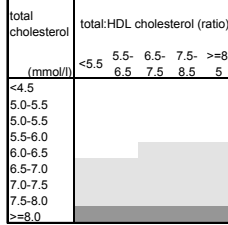
D: Moderate risk (10-15% 5-yr CVD risk) (part of population 3)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					
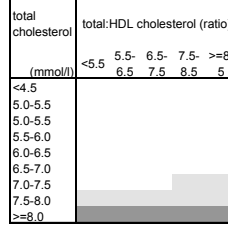
E: Mild risk (<10% 5-year CVD risk) (part of population 3)

total cholesterol (mmol/l)	total:HDL cholesterol (ratio)				
	<5.5	5.5-6.5	6.5-7.5	7.5-8.5	>=8.5
<4.5					
5.0-5.5					
5.0-5.5					
5.5-6.0					
6.0-6.5					
6.5-7.0					
7.0-7.5					
7.5-8.0					
>=8.0					
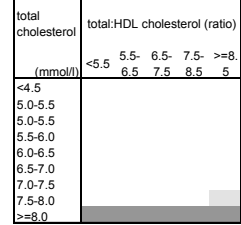
Annex Two

New Zealand life table data

NZ Mortality and Life Table Data

(source: NZ Health Information Service. Mortality and Demographic Data 1992. Wellington: Ministry of Health, 1994.
Statistics NZ. Demographic Trends 1994. Wellington: Statistics NZ, 1995.)

| | | pop1993 | mortality NZ 1992 | | | | chd vs all | NZ life tables (all) | | | |
| | | | coronary heart disease | | all cause | | | probability of survivors dying in age interval | probability of survivors surviving in age interval | proportion of age-group who survive a further 5 years | life expectancy at exact age (years) |
			no.	rate: 1000	no.	rate: 1000	%	qx	px	sx	ex
men	35-39	134,100	35	0.3	225	1.7	16%	0.9%	99.1%	99.0%	40.6
men	40-44	115,000	56	0.5	246	2.1	23%	1.2%	98.8%	98.6%	35.9
men	45-49	107,600	110	1.0	337	3.1	33%	1.7%	98.3%	97.7%	31.3
men	50-54	94,000	156	1.7	533	5.7	29%	2.9%	97.1%	96.1%	26.8
men	55-59	72,800	270	3.7	751	10.3	36%	5.0%	95.0%	93.6%	22.5
men	60-64	73,800	392	5.3	1,218	16.5	32%	8.0%	92.0%	89.6%	18.6
men	65-69	66,900	614	9.2	1,776	26.5	35%	13.0%	87.0%	84.0%	15.0
men	70-74	49,600	641	12.9	1,988	40.1	32%	19.5%	80.5%	76.0%	11.8
men	75-79	32,500	729	22.4	2,237	68.8	33%	29.7%	70.3%	64.9%	9.1
men	80-84	19,200	589	30.7	2,087	108.7	28%	42.8%	57.2%	51.7%	6.9
women	35-39	139,100	2	0.0	124	0.9	2%	0.5%	99.5%	99.4%	45.3
women	40-44	120,800	9	0.1	172	1.4	5%	0.8%	99.2%	99.0%	40.5
women	45-49	109,900	21	0.2	250	2.3	8%	1.2%	98.8%	98.4%	35.8
women	50-54	86,100	38	0.4	342	4.0	11%	2.0%	98.0%	97.4%	31.2
women	55-59	73,900	57	0.8	428	5.8	13%	3.2%	96.8%	95.9%	26.8
women	60-64	66,800	130	1.9	666	10.0	20%	5.0%	95.0%	93.8%	22.6
women	65-69	70,000	237	3.4	1,009	14.4	23%	7.4%	92.6%	90.6%	18.7
women	70-74	61,000	417	6.8	1,438	23.6	29%	11.5%	88.5%	85.0%	14.9
women	75-79	46,100	547	11.9	1,887	40.9	29%	18.8%	81.2%	76.1%	11.6
women	80-84	32,900	678	20.6	2,243	68.2	30%	30.2%	69.8%	63.3%	8.7

Coronary heart disease and all-cause mortality rates by age/sex, NZ 1992

Legend: coronary heart disease, all causes

y-axis: deaths per 1,000 (0 to 120)

x-axis: age/sex group (M35-39, M45-49, M55-59, M65-69, M75-79, F35-39, F45-49, F55-59, F65-69, F75-79)

Life expectancy by age/sex, NZ 1991-1993

Legend: men, women

y-axis: life expectancy (years) (- to 50)

x-axis: 5-year age-group (35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84)

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
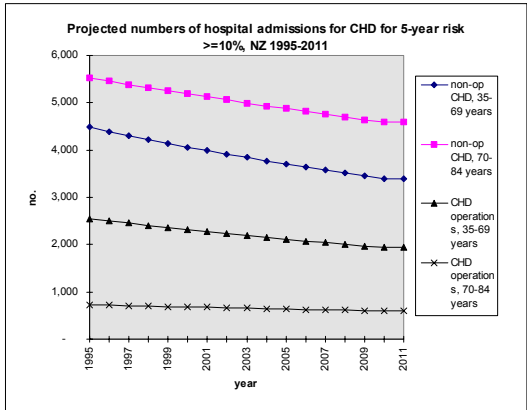
to impute changes in age/sex incidence of CHD (new cases):
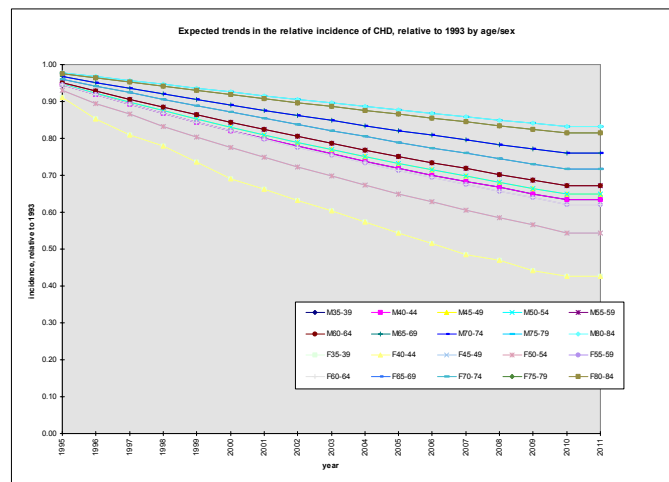
This then combines with:
3.   changes in underlying age/sex-specific source populations

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

Projected numbers of hospital admissions for CHD for 5-year risk >=10%, NZ 1995-2011

Expected numbers of hospitalisations for CHD for 5-year risk >10%, NZ 1995-2011 by age/sex
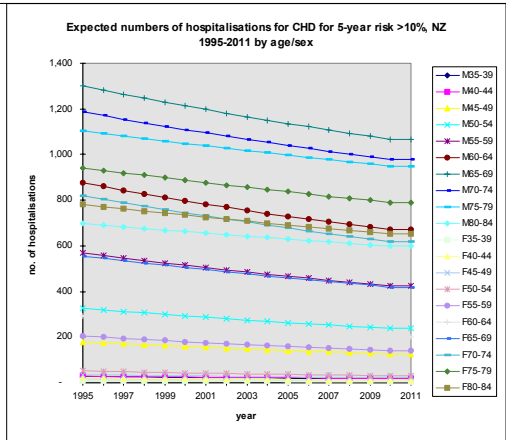
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