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Technology Assessment Report No. 2

Costs and Benefits of simvastatin 40 mg vs fluvastatin 80 mg for patients with familial hyperlipidaemia

Type: Detailed Cost-Utility Analysis
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Context

This paper examines the incremental benefits and costs of treating patients with familial hyperlipidaemia with simvastatin 40mg/day, over and above the net costs and benefits of treatment with fluvastatin 80mg/day.

The analysis assumes that for familial hyperlipidaemia that benefit is proportional to the degree of LDL-cholesterol lowering, given the lack of evidence for this condition.

Extent of Costs and Benefits

The below data and modelling give:

- A relatively unwell population, with 13.4% all-cause death rates and 23% total IHD event rates over 5 years for men aged 35-59 with FH, at average life expectancy of 20.8 years.

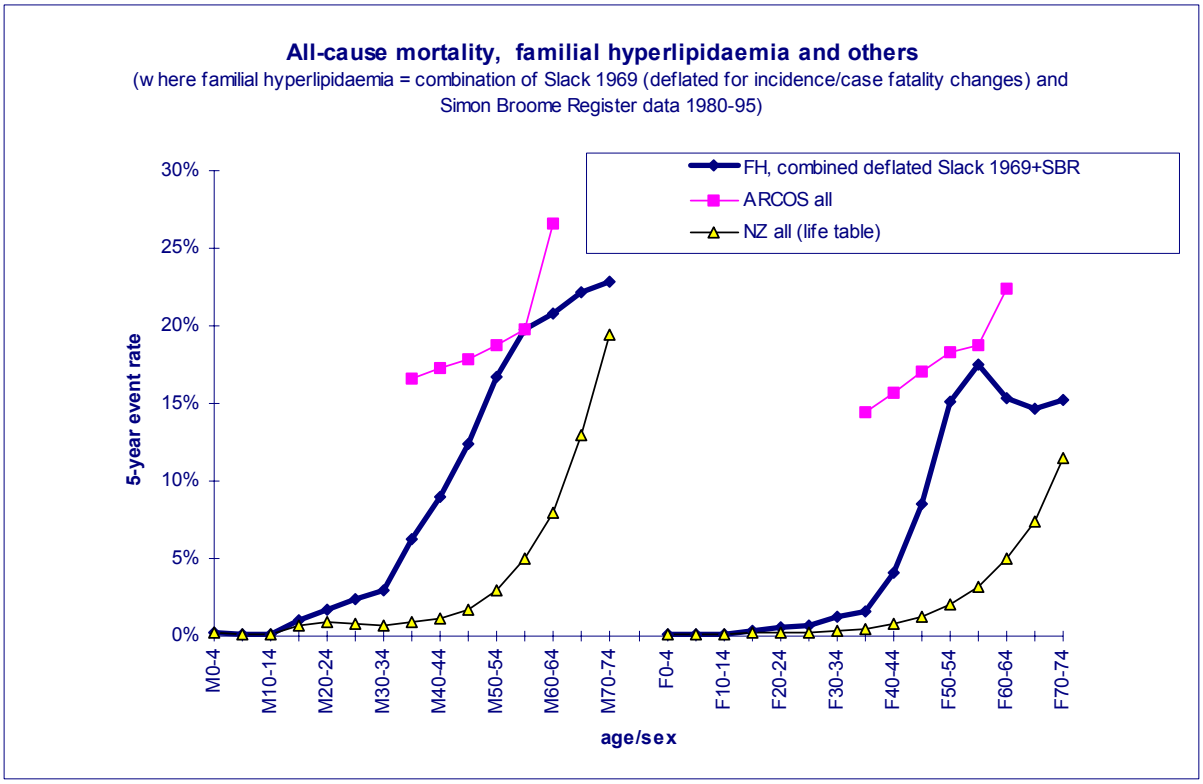
- The 13.4% mortality rate approaches the 18.6% 5-year all-cause death rate for 28-day post-myocardial infarction survivors in NZ men aged 35-59[1] (equivalent to NHF group A1:1), and is much higher than the 2.1% for the NZ general population of the same age/sex;

- Relative risk reductions for all-cause death for fluvastatin 80mg/day of 34% in men aged 35-59 with FH, versus 40% for simvastatin 40mg/day;

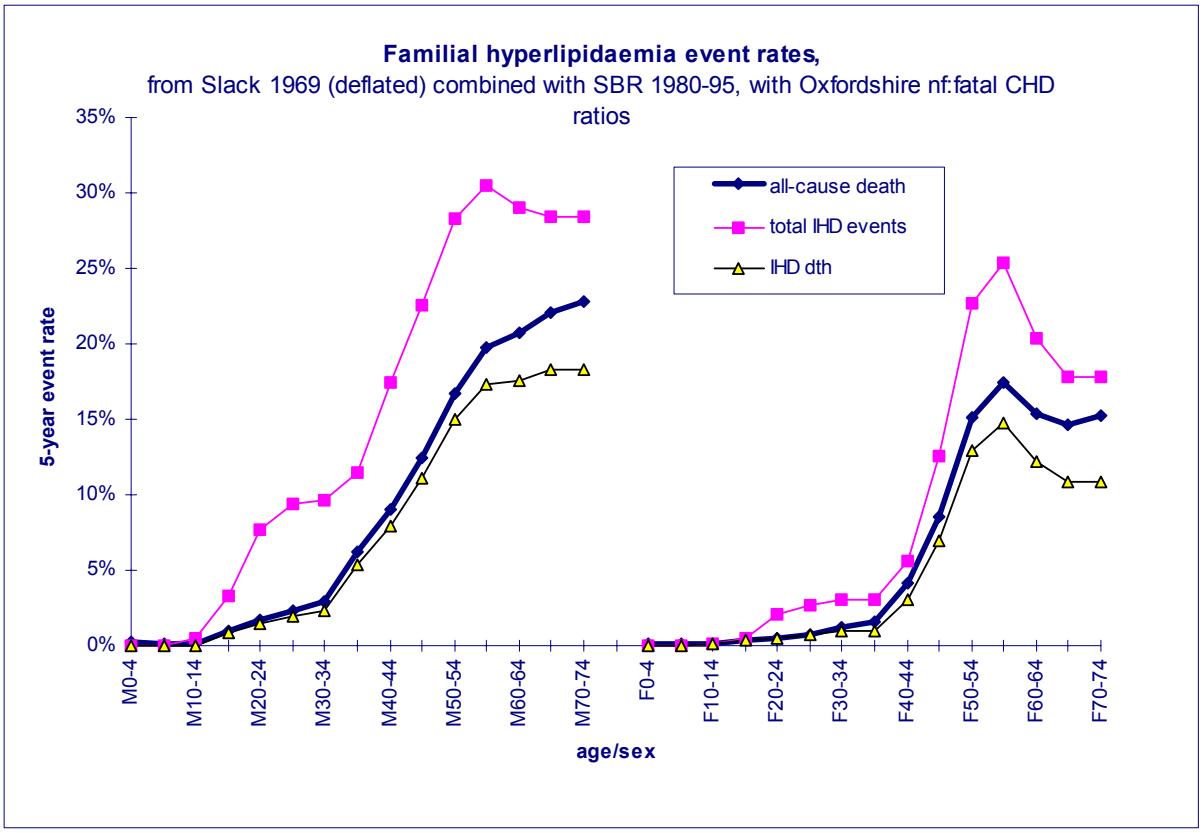
- 5-year undiscounted net QALYS for fluvastatin of 0.82 in men aged 35-59 with FH, versus 1.03 for simvastatin. These approach the 1.30 QALYS for men aged 35-69 with IHD (group A1:1-2) and 0.88 QALYS after discontinuations.

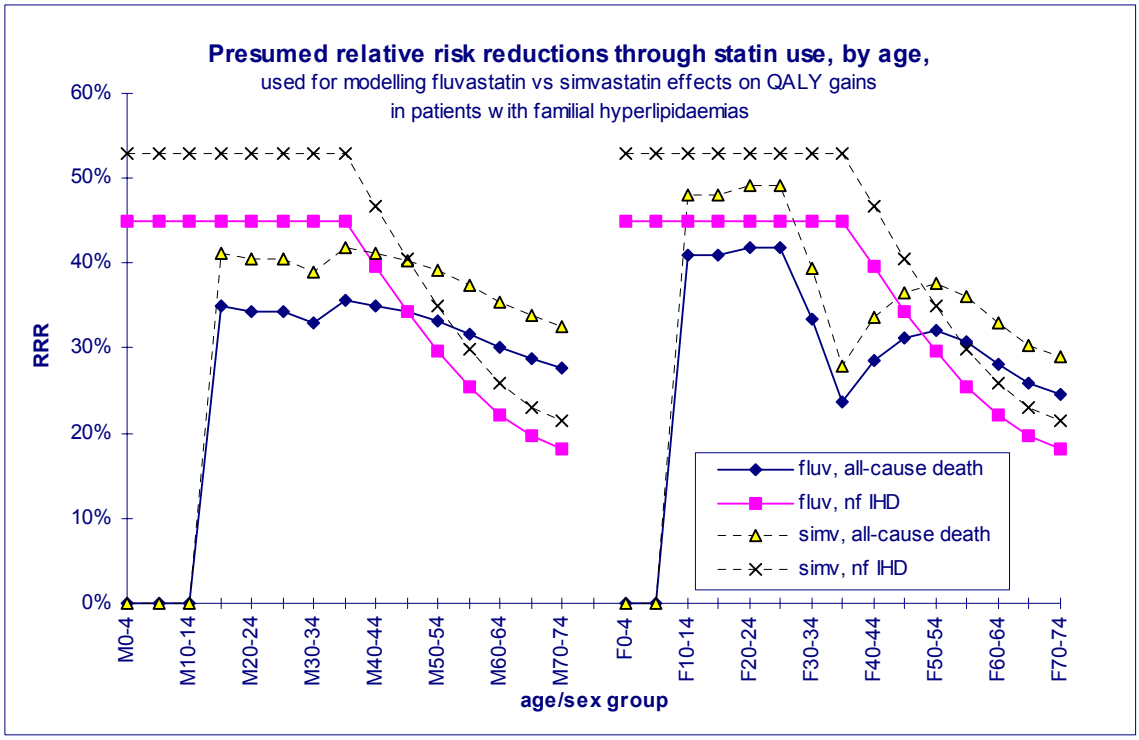
- After accounting for hospitalisation prevented, extra spending on simvastatin vs fluvastatin for every extra QALY gained (ie marginal cost/QALY) is $32,947 for men aged 35-59 with FH. Incremental cost/QALYS for FH patients range from $28,112 in men aged 55-59 to $77,000 in children.

These features can be seen in the following graphs:



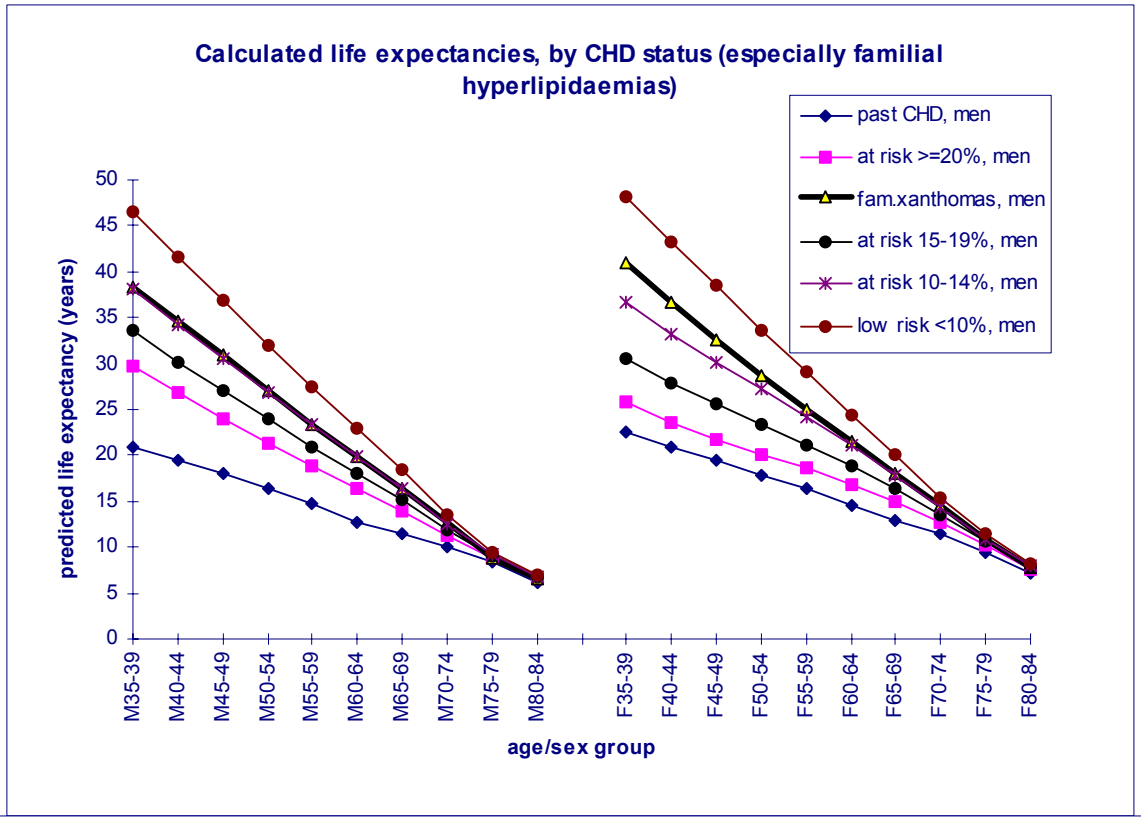
This graph shows FH all-cause mortality in adults rapidly increasing to reach that patients with previous myocardial infarction by age 50 (at around 20% 5-year mortality).

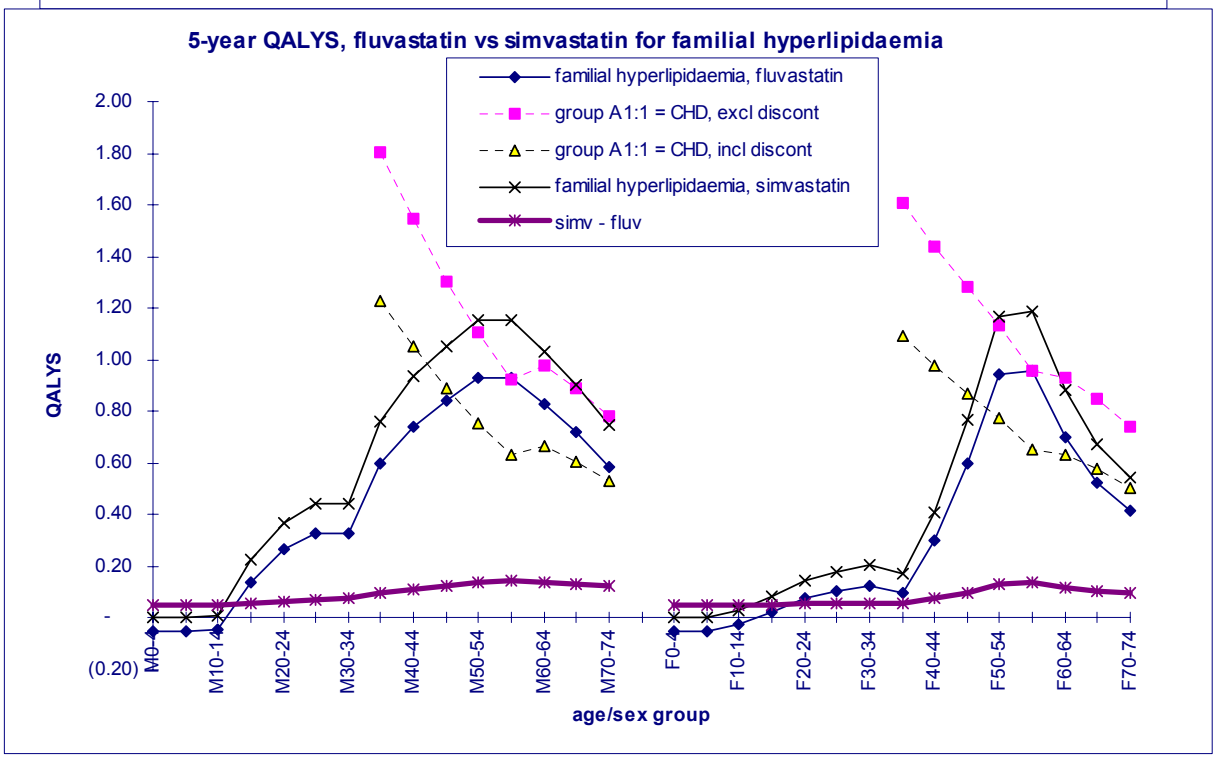




This graph shows:

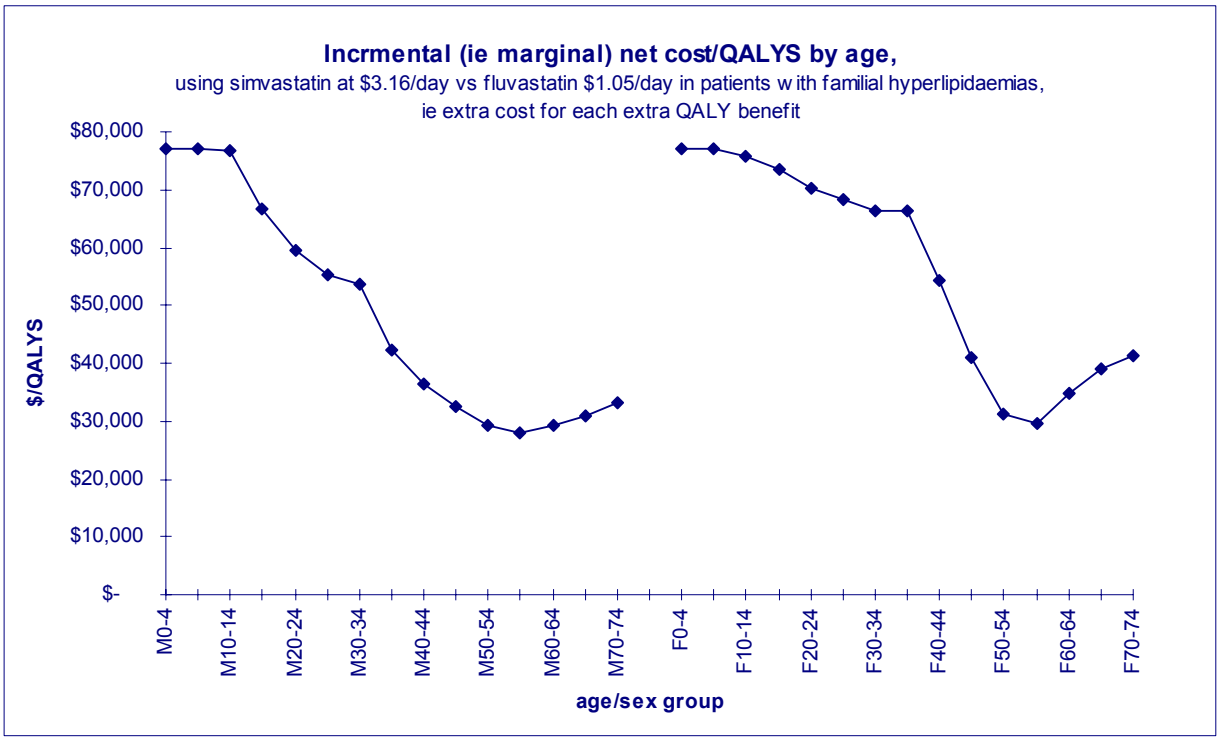
- Relative risk reductions of 30% for all-cause mortality and 26% for non-fatal IHD events for simvastatin for men aged 60, which was reported by or can be calculated from 4S[2].
- IHD RRRs for simvastatin at different ages follow the patterns predicted by 4S, assuming constant RRRs below the age of 35.
- Fluvastatin RRRs for IHD (which includes non-fatal events) are 85% that of simvastatin (= LDL-cholesterol lowering of 35/41.
- RRRs are assumed equal by sex.





This graph shows:

- Some lessening of benefit from using fluvastatin 80mg/day for FH patients when compared with simvastatin 40mg/day.
- Benefit for younger FH patients is less than for IHD patients, but is equal or greater than IHD patients for FH patients aged 40+.



This graph shows costs of around $32,000 per QALY gained if simvastatin 40mg is used for adult FH patients rather than fluvastatin 80mg. Cost-effectiveness improves with age, with comparatively poor value-for-money with you9nger age-groups.

Calculating Benefits

To calculate the extent of QALY gain benefits though using simvastatin 40mg/day over and above fluvastatin 80 mg/day in patients with familial hyperlipidaemia (FH), we used essentially the same methods as previously with cost utility analysis for the Lipid Review overall.[3] This involved six steps:

1. Calculating the absolute 5-year risks (ARs, ie event rates) for both all-cause deaths and non-fatal ischaemic heart disease (IHD) events occurring in those with FH, for each age/sex group (ages 0 to 79);

2. Applying age-specific relative risk reductions (RRRs) for statin treatment previously calculated for IHD patients (NHF group A1:1) from 4S and other sources for both all-cause death and non-fatal IHD events[4], in order to calculate age/sex-specific absolute risk reductions (ARRs) for FH patients using simvastatin (where ARR = AR * RRR);

3. Recalculating ARRs for fluvastatin use in FH patients, assuming fluvastatin is 85% as effective in reducing IHD events as simvastatin;

4. Calculating expected age/sex-specific life expectancies (LE) for FH patients, using all-cause mortality rates in step 1 above and standard life table techniques,

5. Calculating potential age/sex-specific QALYS for both simvastatin and fluvastatin treatment of FH for 5 years, from:
   - ARRs (from steps 2 and 3),
   - life expectancy (from step 4),

- the time trade-off utility score for IHD (U_{IHD}) of 0.925 used in previous PHARMAC analysis,
- disutility scores for side effects caused by fluvastatin (U_{SEf}) and simvastatin (U_{SEs}) of 0.01 and 0.00 respectively, and
- finally discounting to present value at PHARMAC's discount rate of 7.8%:

5-year QALYS = {QALY gains from preventing premature death}, plus {QALY gains from preventing morbidity caused by non-fatal events}, minus {QALY losses from treatment side effects}

$= [ARR_{\text{all-cause death}} * LE * U_{IHD}] + [ARR_{\text{non-fatal IHD}} * LE * (1 - U_{IHD})] + [5 * U_{SE}]$, discounted at 7.8%

6. Calculating actual QALYS realised in the community, accounting for discontinuation rates.

Estimating absolute risk of all-cause death and non-fatal IHD events (step 1):

- We identified relevant data from a Medline search based on the key words {familial combined} , {hyperlipidaemia}, {hypercholesterolaemia}, {mortality}, {coronary heart disease} and {ischemic heart disease}, and from relevant citations of identified articles. Studies with mortality and/or IHD event data comprised Jensen 1967[5], Slack 1969[6], Stone 1974[7], Heiberg 1977[8], Gagne 1979[9], Miettinen 1988[10], Kane 1990[11], and the Simon Broome Register Group 1991[12]. In addition, Professor Jim Mann supplied us with a draft copy of a paper awaiting publication describing Simon Broome Register mortality rates for 1980-95[13].

Prevalence and incidence of IHD in FH (ype II) patients, from earlier observational studies

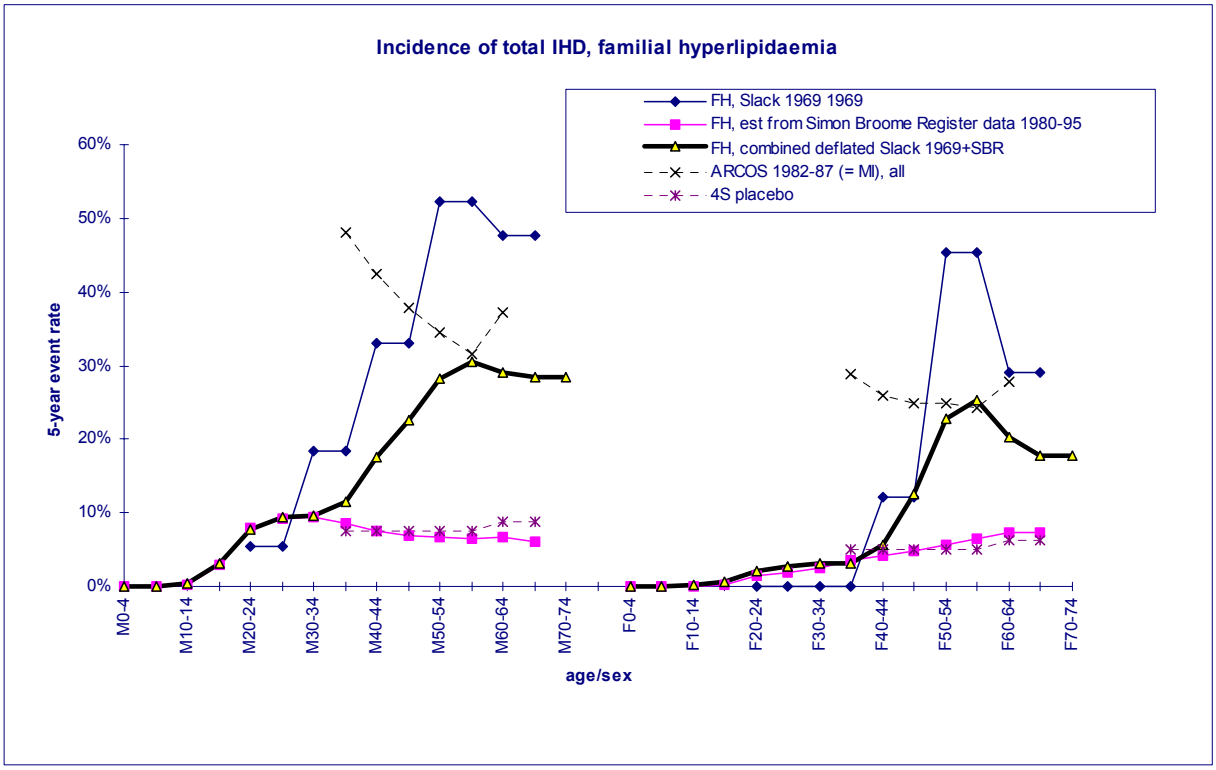
Study				Jensen et al 1967	Slack 1969	Stone et al 1974	Heiberg & Slack, 1977	Gagne et al 1979	Miettinen & Gylling 1988	*pooled data*	(Kane et al 1990)	Simon Broome Register Group 1991
no.				181	104	1,065	172	575	96	*2,193*	40	526
study type				families	adult index cases, relatives	index cases, relatives, deceased	families	index cases	index cases		(adults, RCT placebo group)	adult index cases
location, time period				Denmark 1944-64	London ?period	Maryland 1964-70	Norway & England ?period	Canada 1972-78	Finland 1968-95		San Francisco 1982-86	England 1980-89
pCHD prevalence		men			17.6%							23.0%
		women			26.4%							21.3%
		all		32.6%	22.1%	30.0%		21.6%		*27.3%*		22.2%
5-year incidence	IHD	men							24.4%			
		women							15.8%			
		all									5.8%	
	IHD death	men							14.6%			4.1%
		women							3.5%			2.6%
		all						2.1%				3.4%
	all-cause d	men							15.3%			5.9%
		women							5.6%			4.6%
		all										5.3%
cuml incidence	IHD	men	40	16.7%	23.7%	16.0%				*16.7%*		
			50	38.9%	51.4%	34.0%				*36.0%*		
			60		85.4%	52.0%				*55.0%*		
		women	40	13.0%	0.0%	9.0%				*41.9%*		
			50	39.1%	12.2%	19.5%				*21.6%*		
			60		57.5%	32.0%				*34.3%*		
	IHD death	men	40									5.7%
			50		23.4%							8.8%
			60									11.8%
		women	40									1.5%
			50		17.2%							6.0%
			60									10.4%
(mean age at event)	IHD death	men				42.0	50.0					
		women					62.9					

- Because we needed to calculate baseline (no treatment) absolute risks, we inflated both 1980-89 and 1990-95 Simon Broome Register series by factors of (1+16%) and (1+30%), reflecting RRR from treatment relevant to the periods when the data applied (viz 16% RRR in all-cause deaths from fibrates for 1991 series, 30% RRR for statins for 1998 series). We calculated 1990-95 mortality rates from the

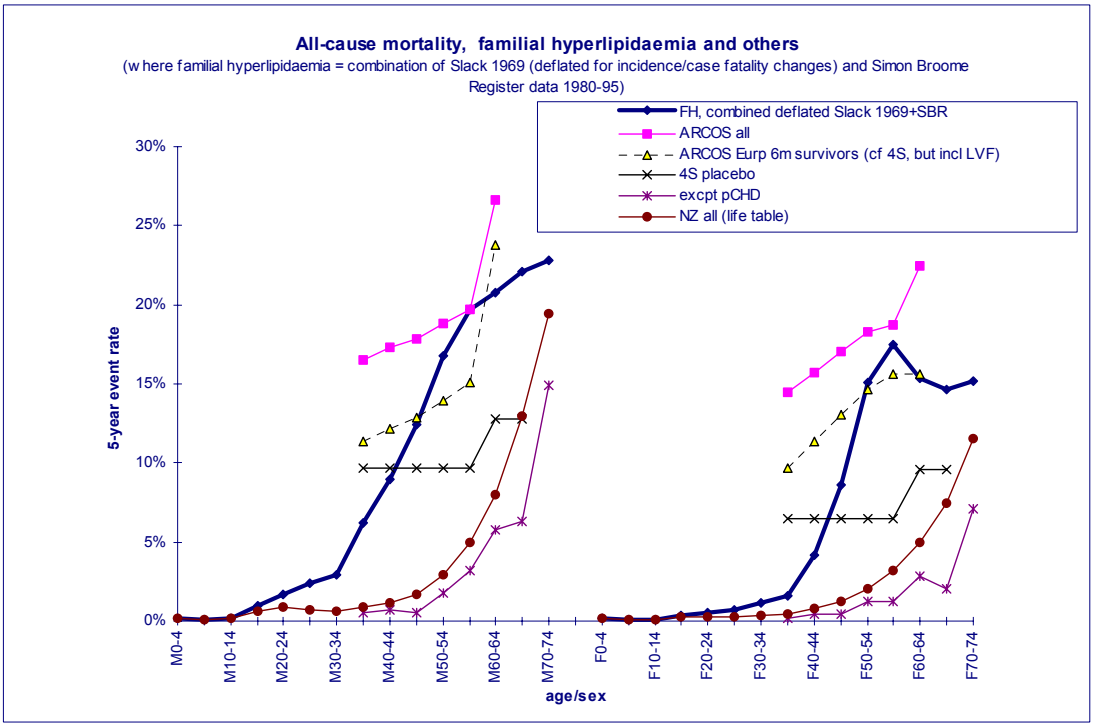
difference between the Simon Broome Register Group's two papers, ie deaths 1990-95/person-year equivalents 1990-95 = (deaths 1980-95 - deaths 1980-98) / (person-year equivalents 19800-95 - pye 1980-89). We calculated unadjusted and inflated event rates for the overall 1980-95 period as a person year-weighted average of the 1980-89 and 1990-95 rates. We finally fitted the FH mortality rates to those of NZ life tables, as a smoothing function.

- Note the IHD event rates reported by Slack in 1969 and other older papers appear excessive (at rates for example much higher than might be predicted from combining ARCOS all-cause mortality rates for 28-day survivors with Framingham total IHD/total death ratios[14] - see graph below). There also has been a general decline in IHD incidence, mortality and risk factors since the early 1980s, and both all-cause and IHD mortality rates in FH patients the Simon Broome Register declined between 1980-89 and 1990-95 (calculated from the two SB Register papers). In addition, rates derived from the Slack series are likely to be unstable, given the small numbers of patients in that cohort (n = 78). This compares with the much more stable and contemporary Simon Broome Register data, where 1,185 patients have now been followed over the last 16 years, equating to 8,770 person-years experience.

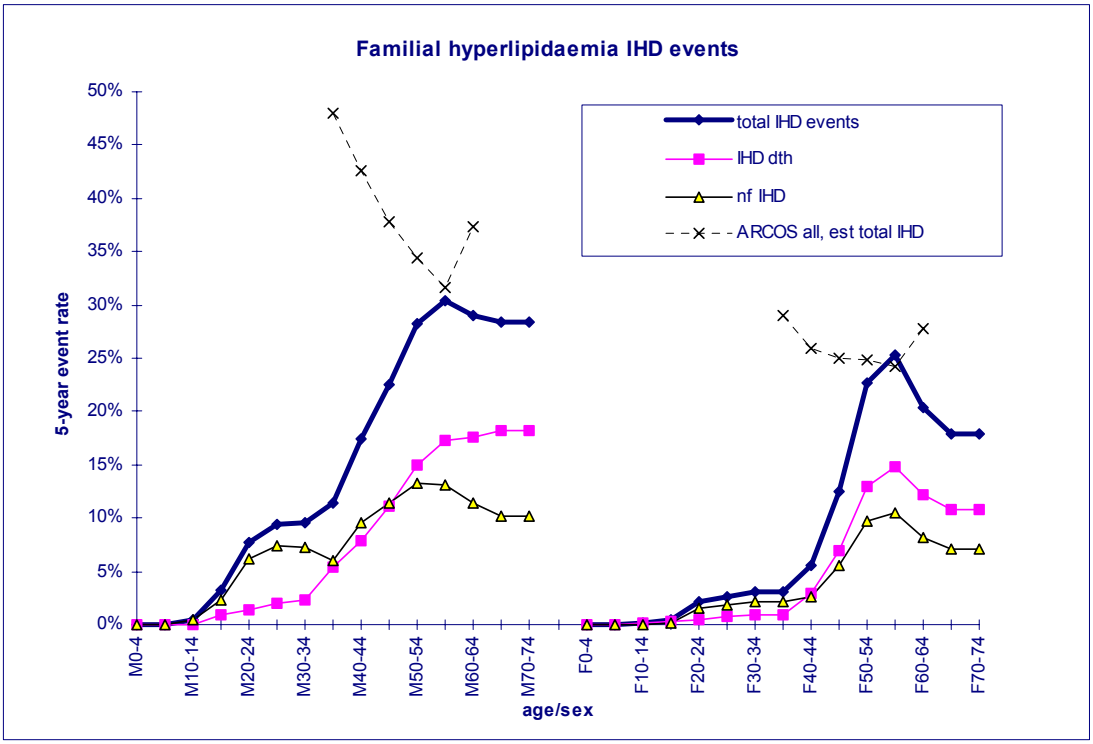
Because of these factors above, we decided not to rely on the older Slack etc data to determine total IHD event rates (and hence extrapolate to derive non-fatal IHD rates). Instead we decided to use the Simon Broome Registry combined data for 1980-95 for all-cause mortality rates, and to model total and non-fatal IHD mortality rates on Framingham and Oxfordshire IHD fatality rates[15]:



This graph shows the incidence of IHD in FH patients in Slack's 1969 paper was higher even than that predicted by ARCOS data for 28-day survivors of myocardial infarction.



This graph places FH patients' all-cause mortality rates in context with other groups. It shows FH patients have mortality rates similar to the 4S placebo group for those aged ≥ 50 years, but lower rates for younger patients.



This graph describes total, fatal and non-fatal IHD event rates for FH patients predicted from Simon Broome Register 1980-95 all-cause mortality data and from IHD event:all-cause mortality ratios described in the Framingham Study and impending Oxfordshire

total:non-fatal IHD ratios. Total IHD event rates are much lower than predicted from ARCOS for patients with past MI.

Estimating relative risk reductions (steps 2 and 3):

For step 2's relative risk reductions in IHD events (total, fatal and non-fatal) in FH patients through the use of simvastatin , we used the RRRs reported by 4S, scaled according to age (described previously) [16]. For all-cause death RRRs, we then calculated new simvastatin-related IHD death rates and then all-cause mortality rates, to derive age-specific all-cause death RRRs for FH patients using simvastatin:

simv AR IHD death = AR IHD dths * simv RR IHD dths

simv AR all-cause death = simv AR IHD death + (AR ac dths - AR IHD dths)

$$\text{simv RR all-cause death} = \frac{\text{simv AR all-cause death}}{\text{AR all-cause death}}$$

$$\text{simv RRR ac deaths} = 1 - \text{simv RR all-cause death}$$

$$= 1 - \frac{(\text{AR IHD dths} * \text{RR IHD dths}) + (\text{AR ac dths} - \text{AR IHD dths})}{\text{AR all-cause deaths}}$$

We assumed constant RRRs for those aged 0-34 equal to those calculated for 35-39 year olds.

The estimates in step 3 of comparative efficacy of fluvastatin vs simvastatin for preventing IHD events derive from PHARMAC analysis and Canadian Coordinating Office for Health Technology Assessment (CCOHTA)[17] and other data, where fluvastatin 80mg/day confers 35% LDL reduction and simvastatin 40mg/day confers 41%]. This analysis is not complete but gives a good indication. It is probably worth noting that the only published comparative trial shows little difference between the two drugs. [18]

We universally applied the 85% relative efficacy to the above age-specific RRRs with simvastatin for non-fatal IHD events, deriving fluvastatin non-fatal IHD RRRs. For all-cause death RRRs with fluvastatin, we similarly universally applied the 85% to the simvastatin IHD death RRRs to calculate fluvastatin IHD death RRRs (with the 42% overall RRR reported by 4S for IHD deaths with simvastatin becoming 36% with fluvastatin). We then calculated IHD death rates and all-cause mortality rates to derive fluvastatin all-cause death RRRs, using the same methods as above :

fluv RR IHD deaths = simv RR IHD deaths * 85% (ie 35%/41%)

fluv AR IHD death = AR IHD dths * fluv RR IHD dths (ie 85% of simv RR)

fluv AR all-cause death = fluv AR IHD death + (AR ac dths - AR IHD dths)

$$\text{fluv RR all-cause death} = \frac{\text{fluv AR all-cause death}}{\text{AR all-cause death}}$$

$$\text{fluv RRR ac deaths} = 1 - \text{fluv RR all-cause death}$$

$$= 1 - \frac{(\text{AR IHD dths} * \text{RR CHD dths} \mathbf{* 85\%}) + (\text{AR ac dths} - \text{AR IHD dths})}{\text{AR all-cause deaths}}$$

Other calculations

The -0.01 marginal disutility for fluvastatin side effects is notional. Note there are reports that fluvastatin 80mg is at least as well tolerated as simvastatin 40mg[19], which means if anything that the extra benefit for simvastatin in the model may be too high (and hence marginal cost/QALY should be even higher).

For actual QALYS rather than potential (step 6), we had previously applied continuation rates to undiscounted potential QALYS, then discounted. Previously for group A1:1 patients, this meant decreasing 5-year QALYS for 35-69 year old men by 32%, from 1.04 QALYS to 0.70. However, given the majority of FH patients are (or should be) treated in hospital specialist clinics, we assumed minimal benefit loss a over that modeled on the SB Registry data (specialist hospital clinics in the UK).

Calculating Costs

Estimated additional cost of simvastatin 40mg/day over fluvastatin 80mg/day is $771/patient/year (based on daily costs of $3.16 and $1.05 respectively). Note this cost difference is calculated on an ex manufacturer basis, due to changing pharmacy funding mechanisms for these agents. The differential costs to the THA would be greater than suggested here.

For hospital savings from IHD events prevented by FH patients using simvastatin, for each age-sex group we applied the ratio of (total IHD events in FH patients: total IHD events in CHF patientgs calculated previously[20]) to the proportion to hospitalisation savings/drug costs previously occurring in 4S (calculated using NZ hsopitalisation and drug costs). For fluvastatin we applied the 85% fluvastatin/simvastatin efficacy to the simvastatin-induced hospitalisation savings.

Calculating Cost/QALYS

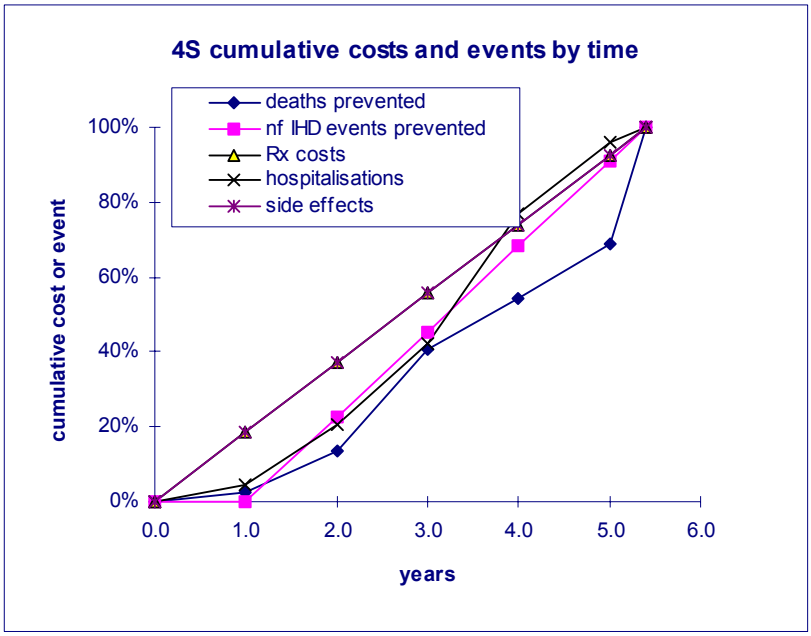
To calculate **marginal cost/QALYS** (of moving from fluvastatin 80mg to simvastatin 40mg, ie the additional costs vs additional hospitalisations prevented and the extra benefits gained from simvastatin over fluvastatin), we simply calculated the differences between the simvastatin and the fluvastatin costs, hospitalisation offsets and benefits for each age/sex group. We then discounted at 7.8% NPV according to the flows of:

- total deaths prevented in 4S (for the life years saved component of benefits),
- non-fatal IHD events prevented in 4S (for the QALY gains from non-fatal IHD events prevented component of benefits, and the hospitalisations prevented component of net costs) and
- net cost differences over five years (for the differences between drugs component of net costs):

$$\text{marginal cost/QALYS} = \frac{(\$Rx_s - \$Rx_f) - (\$h_s - \$h_f), \text{ discounted at 7.8\%}}{QALYS_s - QALYS_f, \text{ discounted at 7.8\%}}$$

where:

$\$Rx_s$	=	pharmaceutical costs of simvastatin
$\$Rx_f$	=	pharmaceutical costs of fluvastatin
$\$h_s$	=	hospitalisations prevented by using simvastatin, including discontinuations
$\$h_f$	=	hospitalisations prevented by using fluvastatin, including discontinuations
$QALYS_s$	=	net QALYs gained though using simvastatin, including discontinuations
$QALYS_f$	=	net QALYs gained though using fluvastatin, including discontinuations



[As in previous work, we based **average** cost-benefit ratios for each age/sex group (ie for each individual drug regime (fluvastatin 80mg, simvastatin 40mg)) around PHARMAC cost/QALY calculations for the 4S study applied to all those with pre-existing CHD (NHF group A1:1) in New Zealand for the two drug regimes:

- NZ$8,316 for $2.15 average daily costs for simvastatin at 4S' 27mg daily dose daily dose
- NZ$2,506 for $1.05 daily cost reference price for fluvastatin (regardless of daily dose), assuming fluvastatin has 85% efficacy as simvastatin at reducing total IHD (hence 86% for all-cause death)

These figures equate to statin use in those aged 35-70 with pre-existing CHD, Rx costs minus hospitalisation offsets, and 0.925 utility value for life years saved. These calculation discount both costs and benefits at 7.8%.

We derived ideal (ie potential) costs/QALY for each age/sex/statin drug 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 $8,316 or $2,146 cost/QALY and 0.091 discounted one-year QALY value. This assumed NHF group A1:1 has 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,

$$\text{cost/QALY} = \frac{\text{4SNZ}}{\text{dQi}} \div \frac{\text{uNi}}{\text{dQ}} \times \text{uN}$$

where

4SNZ = $8,316 or $2,146 net costs per QALY gained,

for simvastatin use in pre-existing CHD aged 35-70 with 7.8% 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

uNi = 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

dQi = index case discounted net QALYS, ie for statins for pre-existing CHD aged 35-69

References

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[16] Metcalfe, op cit.

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[18] Schulte KL, Beil S. Efficacy and tolerability of fluvastatin and simvastatin in hypercholesterolaemic patients. Clinical Drug Investigation 1996;12:119-126.

[19] Schulte and Beil, op cit.

[20] Metcalfe, op cit.