

Summary - cost utility analysis of the lipid modifying agents

Net benefits of LMAs

The benefits of LMAs can be measured in quality-adjusted life years saved (QALYS), which combine fatal with non-fatal events. Net quality-adjusted life years saved comprise:

1. QALY gains 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.

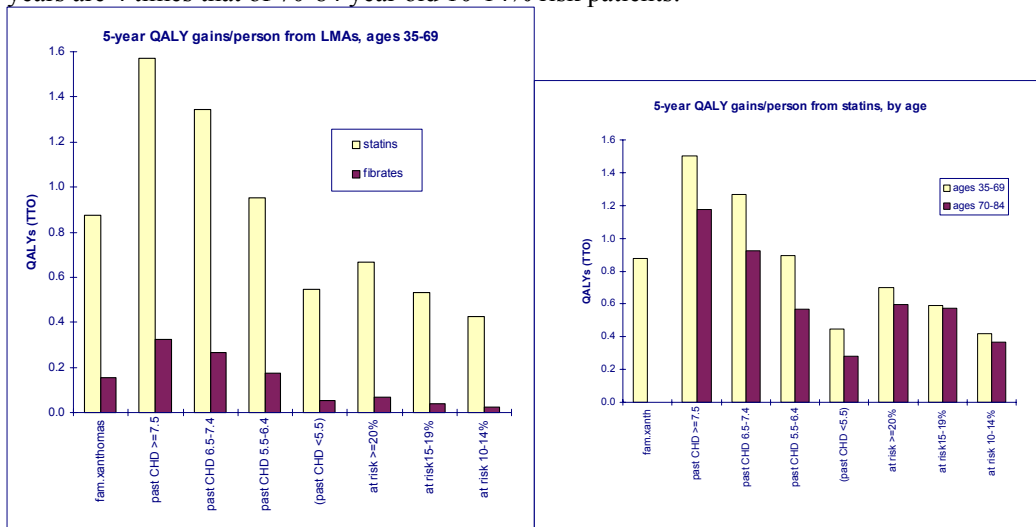
In general, variations in QALY gains due to LMAs between age/sex/CHD-status groups and LMA class reflect the interplay between:

- absolute risk (all-cause premature mortality and non-fatal CHD events),
- effectiveness (risk reduction) of LMAs (varying by class of LMA for all-cause deaths)
- life expectancy, and
- impact of side effects (particularly with 'fibrates').

The degree to which patients might benefit from LMA programmes varies considerably, according to age/gender, CHD status and LMA class. In general however, these follow a gradient, where relative youth, presence of pre-existing CHD with high baseline total cholesterol, and use of 'statins' confers the greatest potential health gain.

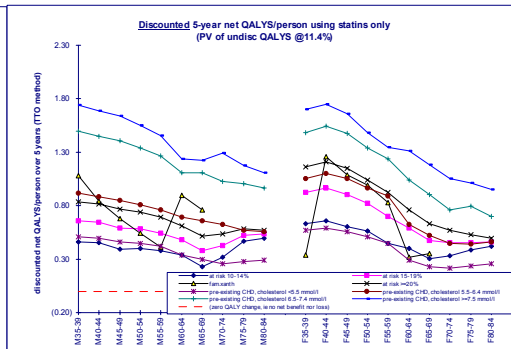
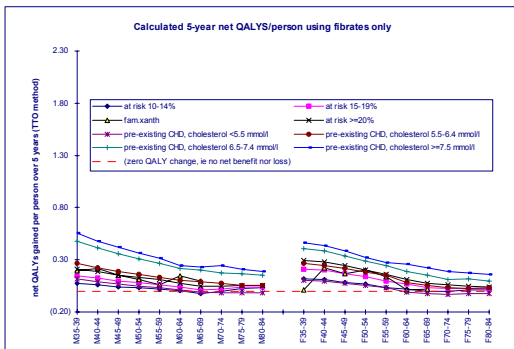
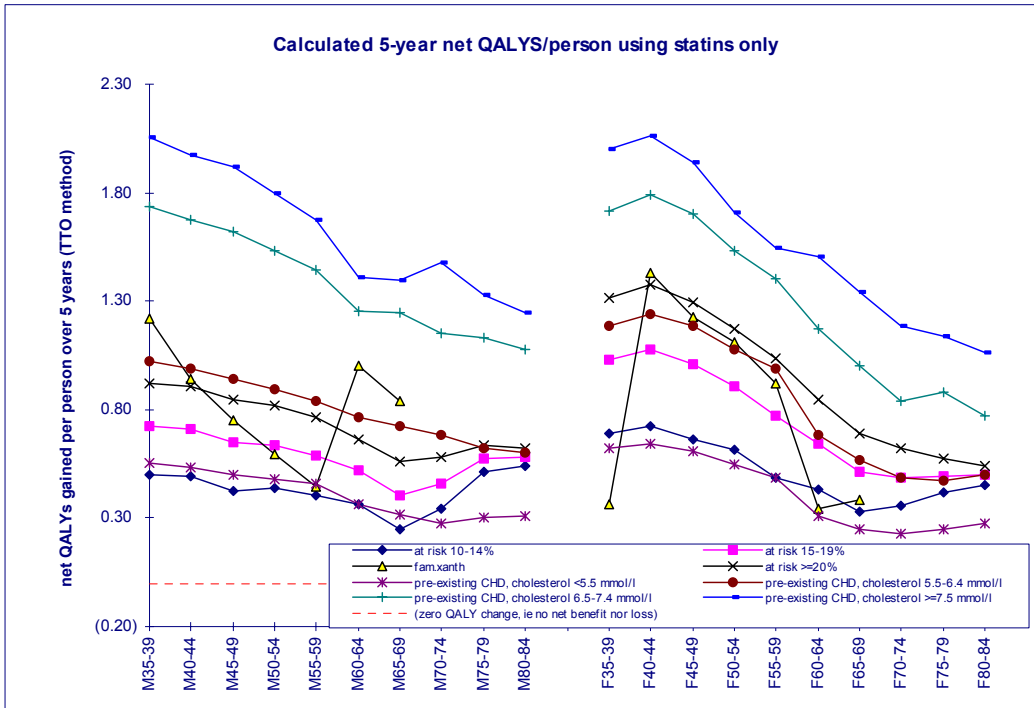
Unfortunately there are no trial data available to assess the extent of benefits from treating NHF groups A2, A3 and A1,3-4 (genetic lipoprotein disorders; diabetic nephropathy; non-CHD cardiovascular disease). Because these groups are similarly at high absolute risk of further cardiovascular events, many clinicians presume them to have benefits similar to patients with CHD. However, this assumes that lipid lowering agents are equally effective at preventing events in these groups as in trials using CHD patients - for which there are few supporting data..

For other groups (ie CHD patients, at-risk patients), overall LMA programme QALY gains in general increase with CHD risk. QALYS are highest for patients with pre-existing CHD with higher baseline total cholesterol. Statin QALYS in general are three times that of fibrates. Within statins, QALYS for those with CHD with total cholesterol ≥ 7.5 mmol/l aged 35-69 years are 4 times that of 70-84 year old 10-14% risk patients:



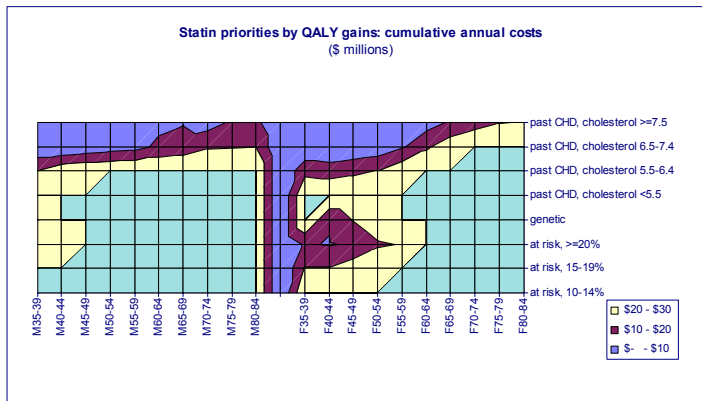
Men aged 35-39 with pre-existing CHD and total cholesterol ≥ 7.5 mmol/l have the highest undiscounted QALY gains, with 2.05 QALYs each for 5 year's treatment with statins, ie around two years extra quality life for each year treated. This is 8 times that of men aged 65-

69 “at risk” with 10-14% 5-year risk, who have 0.25 QALYs/person for the same treatment, ie three months. The same men treated with fibrates have -0.02 QALYS, ie a net loss of around 7 days quality-adjusted life for one year’s treatment.



Net benefits of LMAs: priority rankings

Age/sex/CHD subpopulations can be ranked according to QALY gains from LMA drugs and programmes. Given the sizes and likely Rx costs of treating these eligible subpopulations, patients are grouped according to QALY rankings and likely cumulative Rx costs. This shows a generalised “wave” pattern for which patient groups would gain most benefit for any level of spending:



Ignoring groups A2, A3, and A1,3-4 (genetic lipoprotein disorders, diabetic nephropathy, and non-CHD cardiovascular diseases), then at current spending levels and prices for statins (\$12.5 million/year, around \$1300/patient/year), best benefit is gained for

1. CHD and total cholesterol ≥ 7.5 mmol/l aged <70 years, and
2. CHD and total cholesterol ≥ 6.5 mmol/l aged <60 years.

This differs somewhat from current special authority criteria of CHD ≥ 7.0 mmol/l at any age.

For an extra \$25 million total spending (ie total \$37.5 million at current prices), or nil extra spending (ie current \$12.5 million) if prices were to decrease to one-third, best benefit would be gained for:

1. CHD and total cholesterol ≥ 7.0 mmol/l at any age (ie 35-84 years old), as currently authorised,

plus




2. CHD and total cholesterol 6.5-7.0 mmol/l at any age,
3. CHD and total cholesterol 5.5-6.5 mmol/l aged <65 years,
4. CHD and total cholesterol 5.5-6.4 mmol/l aged <60 years,
5. $>15\%$ 5-year risk (groups B and C) aged <45 years.

Again, **this differs from the proposed criteria** of CHD ≥ 6.0 mmol/l at any age (with specialist referral >75 years). However, estimates of benefit across age/CHD risk groups are reasonably uncertain, and it may be too impractical to juggle age as well as cholesterol and risk.

Note that including groups A2, A3, and A1,3-4 changes this pattern, since if statins were equally effective in these groups, they would have similar-sized benefits as CHD patients.

Priorities for statin Rx, based on QALY benefits







key:

-  first priority, ie if up to \$13.5m available at current statin prices
-  second priority, ie if up to \$24m available (current prices)
-  third priority, ie up to \$37.5m at current statin prices, \$13.5m at 1/3 of current price

age-group	CHD, cholesterol >=7.5	CHD, cholesterol 6.5-7.4	CHD, cholesterol 5.5-6.4	CHD, cholesterol <5.5	genetic	at risk, >=20%	at risk, 15-19%	at risk, 10-14%
35-39								
40-44								
45-49								
50-54								
55-59								
60-64								
65-69								
70-74								
75-79								
80-84								

Proposed priorities for statin Rx, compared with "ideal"

key:

-  current special authority criteria (any age)
-  additional from proposed SA criteria
-  additional from proposed SA criteria, with review >70 years and specialist referral >75
-  greatest benefit at current statins spending at current price (\$13.5m, \$1073/pt pa)
-  greatest benefit at proposed statins spending at current price (\$24m, \$1073/pt pa)
-  greatest benefit at current statin spending but 1/3 of current price

age-group	CHD, tc >=7.5	CHD, tc 7.0-7.4	CHD, tc 6.5-6.9	CHD, tc 6.0-6.4	CHD, tc 5.5-5.9	CHD, tc <5.5	genetic	at risk, >=20%	at risk, 15-19%	at risk, 10-14%
35-39										
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60-64										
65-69										
70-74										
75-79										
80-84										

Net benefits of LMAs: sensitivity analyses

"Base case" QALYS are sensitive to varying the various assumptions contained in the model.

These include:

- varying absolute risk
- varying relative risk reduction
- varying utility values (ie QALY scores) for health states prevented or side effects:

SENSITIVITY ANALYSES:		
NHF groups A&B 35-69 yrs with LMAs:	5-year QALYS per person	
	(TTO)	variation from base case
statins only	1.03	54%
fibrates only	0.21	-69%
base case (fibrates+statins)	0.67	
low total mortality	0.60	-10%
high total mortality	0.64	-4%
lower 95% CL for RRR	0.01	-99%
upper 95% CL for RRR	1.14	70%
RRR for pCHD constant by t.chol	0.41	-39%
RRR varies by age only	0.67	1%
RRR varies by age/sex only	0.48	-28%
constant RRR (from 4S)	0.59	-12%
low CHD QALY-gain value (AUS-TASK)	0.66	-1%
high CHD QALY-gain value (0.2)	0.70	5%
high fibrate SE QALY loss (0.05)	0.61	-9%
fibrates: max Rx effect	1.03	390%
fibrates: min Rx effect	-0.01	-107%
fibrates: min Rx effect + high SEs	-0.18	-187%
fibrates :high CHD QALY value	0.32	51%
statins: high CHD QALY value	1.23	20%
base discount rate (11.4%)	0.60	-10%
5% discount rate	0.63	-5%
10% discount rate	0.61	-9%
15% discount rate	0.58	-13%

Overall, there is reasonable uncertainty as to the size and precision of benefits from lipid-lowering agents. This is due to the magnitude and extent of the assumptions made, because of scarce information. For example, for NHF A&B aged 35-69, QALYS are -99% higher and 80% lower than the base case when upper or lower RRR confidence are combined with high or low CHD utility values and mortality estimates.

Out of all variables, the model is most sensitive to precisely how effective treatment is. Applying lower 95% confidence limits for RRRs causes NHF group A&B QALYS to decrease by -99%, whereas upper RRR 95% confidence limits cause a 70% increase. If RRRs for pre-existing CHD do not vary according to baseline total cholesterol, then CHD QALYS are more uniform with a narrower spread between levels of risk. Varying the assumptions about fibrate effectiveness on all-cause mortality significantly affect overall LMA QALYS, with benefits varying between nil and those of statins. Combining poor fibrate effectiveness with high side effect disutilities causes net QALY losses (ie side effects outweigh any benefits).

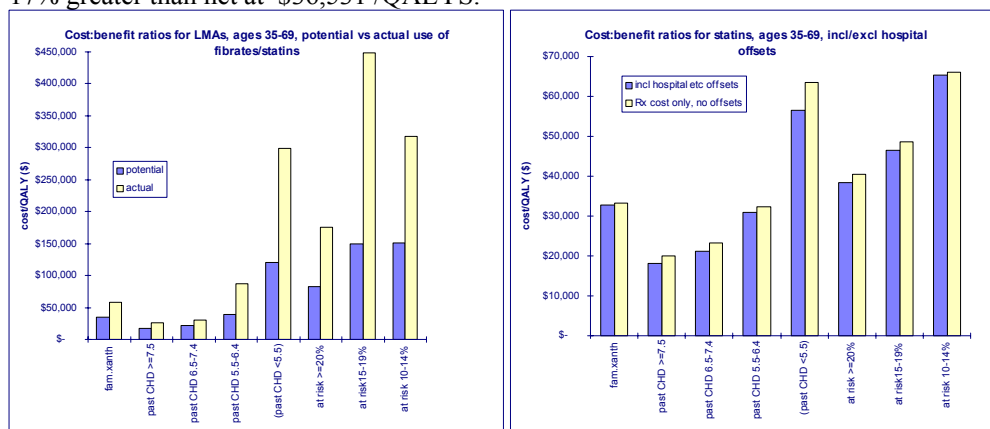
Cost-effectiveness

The model's cost-benefit ratios are based around PHARMAC's NZ\$24,648 per QALY calculated for the 4S population. This calculation discounted both costs and benefits at 11.4%, with life expectancy discounting to 7.0 years. Patterns of cost-effectiveness in general follow inversely those of benefits - apart from differences in overall LMA cost-effectiveness due to effects of differences between fibrates and statins.

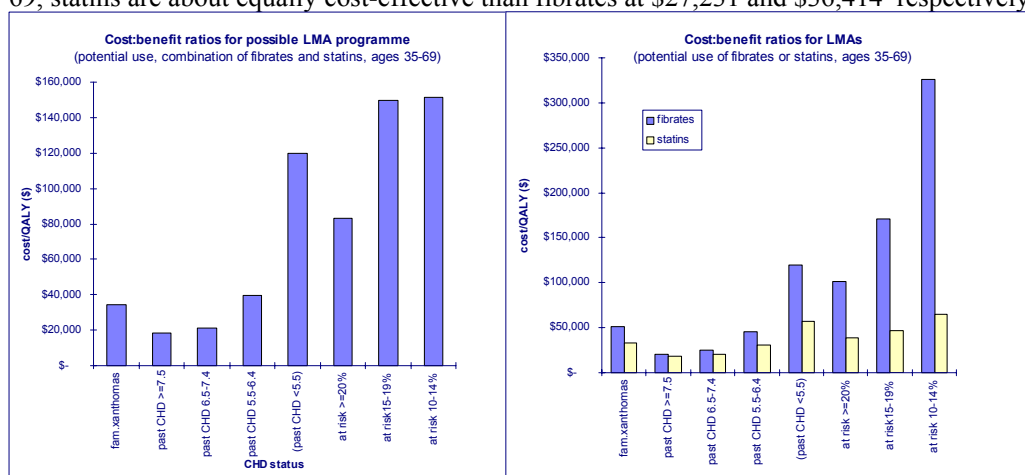
Cost-benefit ratios (ie costs per QALYS) increase with CHD risk. In theory it will cost \$31,194 /QALYS for patients for NHF groups A&B aged 35-69. In practice, these costs/QALYS rise substantially once Rx continuation rates are accounted for, e.g. rising 100% to \$62,345 /QALYS for NHF groups A&B.

The cost component in net theoretical costs/QALYS include opportunity savings (offsets) from hospitalisations prevented through CHD events no longer occurring, from effective LMA programmes. These net costs/QALYS are slightly below gross costs/QALYS (ie which

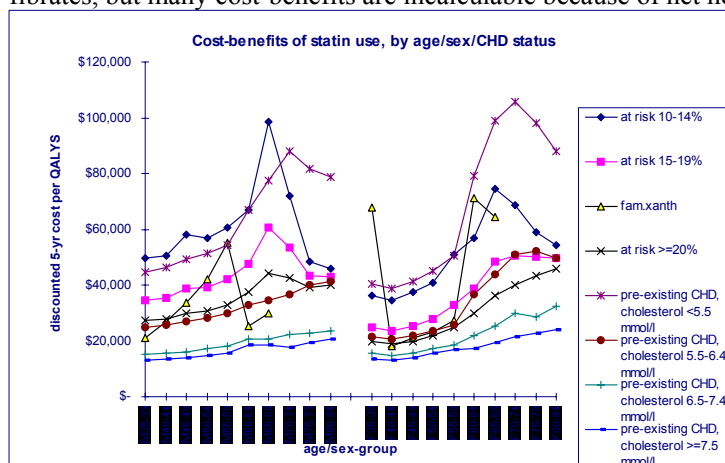
account for Rx spending only). For NHF groups A&B aged 35-69, gross cost/benefits are 17% greater than net at \$36,531 /QALYS.



As with QALY benefits, LMA cost/benefits vary considerably (by age/gender, CHD status and LMA class) but in general follow an age/CHD status gradient. Overall LMA programme cost-benefits in general increase with age and with CHD risk. For NHF groups A&B aged 35-69, statins are about equally cost-effective than fibrates at \$27,231 and \$36,414 respectively.



With statins (as an example), cost-benefits vary widely, from as low as \$14,542 / QALYS for men aged 35-39 with pre-existing CHD with total cholesterol >= 7.5 mmol/l, compared to \$78,152 for women aged 70-74 with 10-14% 5-year risk. Similar variation occurs with fibrates, but many cost-benefits are incalculable because of net negative benefits.

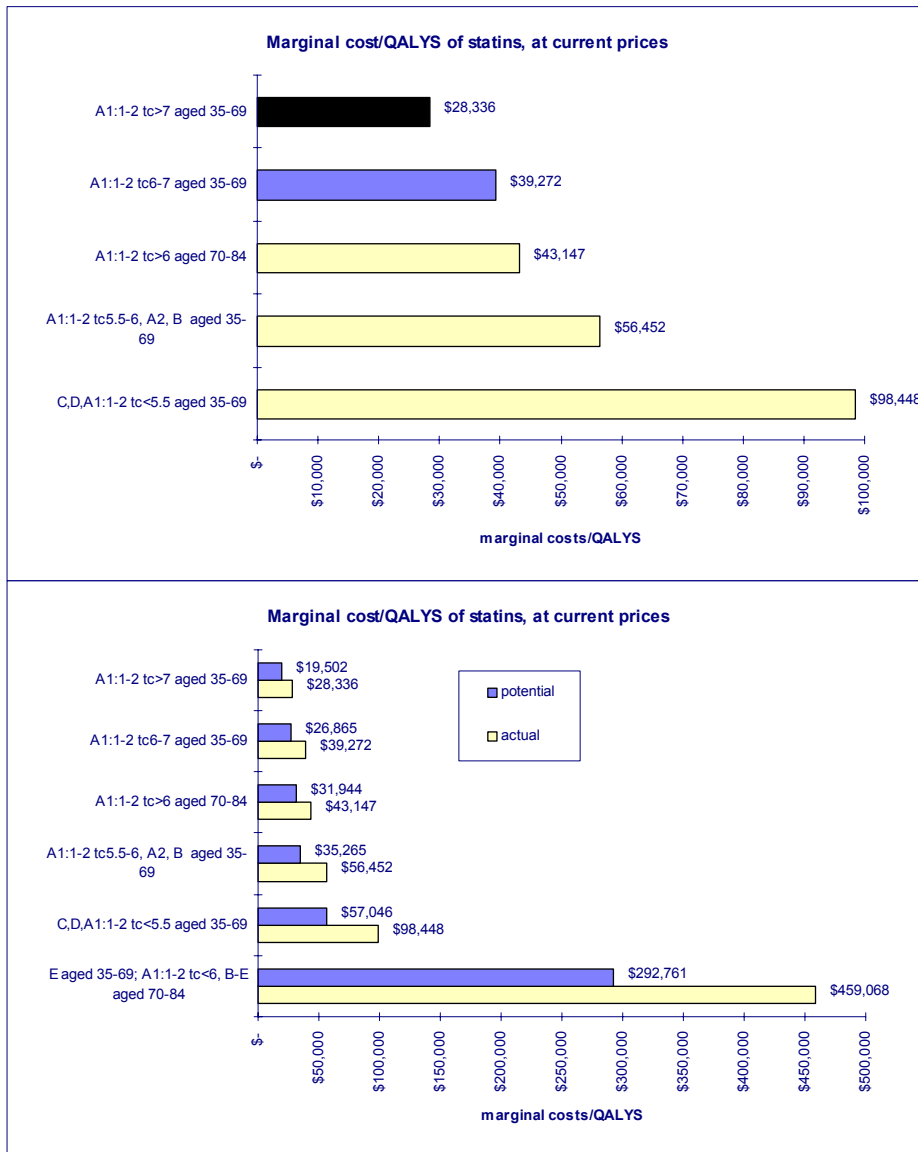


Marginal costs/QALYS of extending statin access show a similar pattern of decreasing value-for-money as CHD risk and benefits decrease:

- Treating all younger patients with CHD (group A1:1-2) currently eligible for statins (CHD with cholesterol ≥ 7.0 mmol/l, ages 35-69) potentially would gain 5,092 QALYS for \$19,198,546 costs (including mark-ups, excluding GST), at \$19,502 /potential QALY (compared with treating nobody).
- Widening access to CHD patients aged 35-69 with total cholesterol 6.0-7.0 mmol/l would potentially gain a further 6,408 QALYS for \$32,403,694 extra costs, at \$26,865 /potential QALY for each of the additional QALYs gained (compared with treating just CHD ages 35-69 cholesterol > 7.0 mmol/l).
- Extending access to patients with CHD (A1,1-2) with cholesterol > 6.0 mmol/l aged 70-84 would potentially gain a further 6,598 QALYS for \$39,608,844 extra costs, at \$31,944 /potential QALY for each of the additional QALYs gained (compared with treating just CHD cholesterol 6.0-7.0 mmol/l ages 35-69).
- Extending access to patients aged 35-69 with CHD and total cholesterol 5.5-6.0 mmol, or in groups A2 or B would potentially gain a further 838 QALYS for \$5,647,422 extra costs, at \$35,265 /potential QALY for each of the additional QALYs gained (compared with treating just CHD cholesterol > 6.0 mmol/l ages 70-84).
- Widening access to patients aged 35-69 in groups C and D or with CHD with cholesterol < 5.5 mmol/l would potentially gain a further 1,075 QALYS for \$12,631,916 extra costs, at \$57,046 /potential QALY for each of the additional QALYs gained (compared with treating just those aged 35-69 with CHD cholesterol 5.5-6.0 mmol/l or in groups A2 and B).
- Extending to all other NHF patients, ie group E aged 35-69 and those aged 70-84 in groups B to E or A1:1-2 with cholesterol < 6.0 mmol/l, would potentially gain a only further 44 QALYS for \$31,849,380 extra costs, at an expensive \$292,761 /potential QALY for each of the additional QALYs gained (compared with treating just those aged 35-69 in groups C and D or with CHD cholesterol < 5.5 mmol/l).

(Note that likely costs, will be lower, especially in year one, eg around \$10,438,026 (including mark-ups, excluding GST) for CHD patients aged 35-69 with total cholesterol 6.0-7.0 mmol/l)

Statin marginal costs and benefits, current prices							
	Rx costs (ex manuf)		potential benefits total undiscounted 1-year QALYS	costs/QALYS			
	potential need	likely demand, year 1		potential (0% discount)	actual (with 1-year discontinuations)		
			base (33% discount)		best (15% discount)	worst (65% discount)	
A1:1-2 tc>7 aged 35-69	\$19,198,546	\$10,438,026	5,092	\$19,502	\$28,336	\$21,772	\$52,874
A1:1-2 tc6-7 aged 35-69	\$32,403,694	\$17,621,084	6,408	\$26,865	\$39,272	\$28,733	\$69,779
A1:1-2 tc>6 aged 70-84	\$39,608,844	\$4,831,611	6,598	\$31,944	\$43,147	\$34,819	\$84,561
A1:1-2 tc5.5-6, A2, B aged 35-69	\$5,647,422	\$1,875,676	838	\$35,265	\$56,452	\$41,749	\$101,390
C,D,A1:1-2 tc<5.5 aged 35-69	\$12,631,916	\$404,134	1,075	\$57,046	\$98,448	\$74,569	\$181,097
E aged 35-69; A1:1-2 tc<6, B-E aged 70-84	\$31,849,380	\$483,887	44	\$292,761	\$459,068	\$274,882	\$667,570

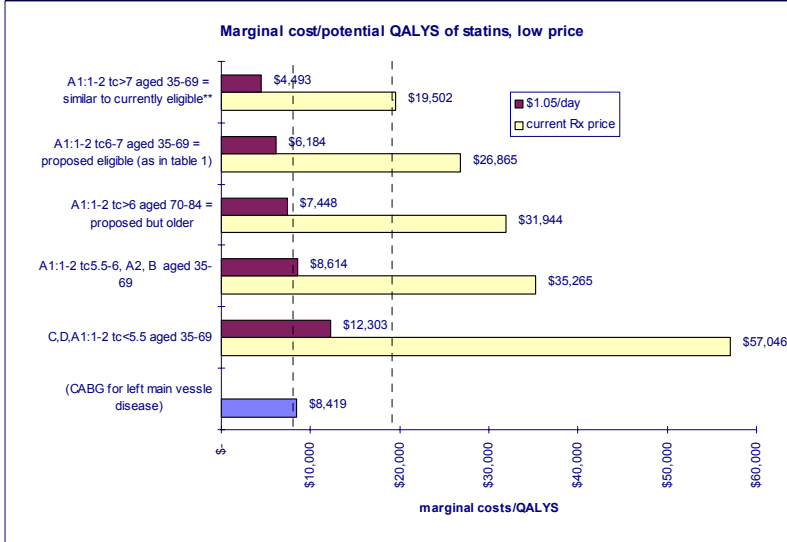


If statin prices were to decrease to one-third of current, ie \$1.05/day, then costs/QALYS would improve to extremely cost-beneficial levels:

- Low cost treatment of all younger patients with CHD (group A1:1-2) currently eligible for statins (CHD with cholesterol ≥ 7.0 mmol/l, ages 35-69) potentially would cost \$6,875,341 , at a mere \$4,493 /potential QALY (compared with treating nobody, and compared with \$26,865 /potential QALY for the same group at current statin costs).
- Low-cost widening access to CHD patients aged 35-69 with total cholesterol 6.0-7.0 mmol/l would potentially cost a further \$11,604,339 , at \$6,184 /potential QALY for each of the additional QALYs gained (compared with treating just CHD ages 35-69 cholesterol > 7.0 mmol/l, and compared with \$31,944 /potential QALY for the same group at current statin costs).
- etc.

These cost/QALYS compare favourably with other extremely cost-beneficial interventions, such as \$8,419 for coronary artery bypass surgery (CABG) for left main vessel disease.

	Rx costs (ex manuf)		potential benefits total undiscounted 1-year QALYS	costs/QALYS		(current statin prices)	
	potential need	likely demand, year 1		potential	actual (with 1- year discontinuations)	likely demand, year 1	cost/potential QALYS
A1:1-2 tc>7 aged 35-69 = current	\$6,875,341	\$3,738,043	5,092	\$4,493	\$6,529	\$10,438,026	\$19,502
A1:1-2 tc6-7 aged 35-69 = proposed	\$11,604,339	\$6,310,424	6,408	\$6,184	\$9,041	\$17,621,084	\$26,865
A1:1-2 tc>6 aged 70-84	\$14,184,632	\$1,730,286	6,598	\$7,448	\$10,060	\$4,831,611	\$31,944
A1:1-2 tc5.5-6, A2, B aged 35-69	\$2,022,442	\$671,713	838	\$8,614	\$13,789	\$1,875,676	\$35,265
C,D,A1:1-2 tc<5.5 aged 35-69	\$4,523,714	\$144,728	1,075	\$12,303	\$21,233	\$404,134	\$57,046
E aged 35-69; A1:1-2 tc<6, B-E aged 70-84	\$11,405,830	\$173,289	44	\$84,064	\$131,818	\$483,887	\$292,761



Again, the model is variably sensitive to a number of certain assumptions. Pharmaceutical price joins treatment effectiveness as important variables influencing results:

SENSITIVITY ANALYSES:					
NHF groups A&B 35-69 yrs with LMAs:	5-year QALYS/person (TTO)	discounted cost:benefit ratios			
		statins	fibrates	total	variation from base case
statins only	1.03	\$ -	\$ -	\$ 27,231	-12.7%
fibrates only	0.21	\$ -	\$ -	\$ 36,414	16.7%
base case (fibrates+statins)	0.67	\$ 27,231	\$ 36,414	\$ 31,194	0%
low total mortality	0.60			\$ 34,435	10%
high total mortality	0.64			\$ 32,596	4%
lower 95% CL for RRR	0.01			negl QALYS	
upper 95% CL for RRR	1.14			\$ 18,749	-40%
RRR for pCHD constant by t.chol	0.41			\$ 100,050	221%
RRR varies by age only	0.67			\$ 30,963	-1%
RRR varies by age/sex only	0.48			\$ 43,186	38%
constant RRR (from 4S)	0.59			\$ 35,156	13%
low CHD QALY-gain value (AUS-TASK)	0.66			\$ 31,387	1%
high CHD QALY-gain value (0.2)	0.70			\$ 29,677	-5%
high fibrate SE QALY loss (0.05)	0.61			\$ 34,285	10%
fibrates: max Rx effect	1.03			\$ 6,195	-83%
fibrates: min Rx effect	-0.01			net QALY loss	
fibrates: min Rx effect + high SEs	-0.18			net QALY loss	
fibrates: high CHD QALY value	0.32			\$ 21,694	-40%
statins: high CHD QALY value	1.23			\$ 23,346	-14%
low statin price	0.67	\$ 8,188	\$ 36,414	\$ 24,235	-22%
base discount rate (11.4%)	0.60				
5% discount rate	0.63			\$ 29,927	-4%
10% discount rate	0.61			\$ 31,257	0.2%
15% discount rate	0.58			\$ 32,588	4%

Decreasing statin prices by one-third decreases NHF group A&B aged 35-69 overall cost/QALYS by -22% to reach \$24,261 (comprising unchanged \$36,436 for fibrates but only \$8,188 for statins). A 5% discount rate decreases NHF A&B aged 35-69 costs/QALYS by -4% to reach \$29,927, whereas a 15% discount rate increases costs/QALYS by 4% to reach \$32,588.

