The University Of Sheffield.

Addendum to Technology Assessment Report 'Ezetimibe for the treatment of hypercholesterolaemia' 8th December 2006

Amendments to methodologies used to apply the effectiveness of ezetimibe co-administration

26th April 2007

This document replaces addendum issued 20th April 2007 and the document titled "Switching/titrating statins"

The clinical data and the methodology used to apply the results have been re-examined.

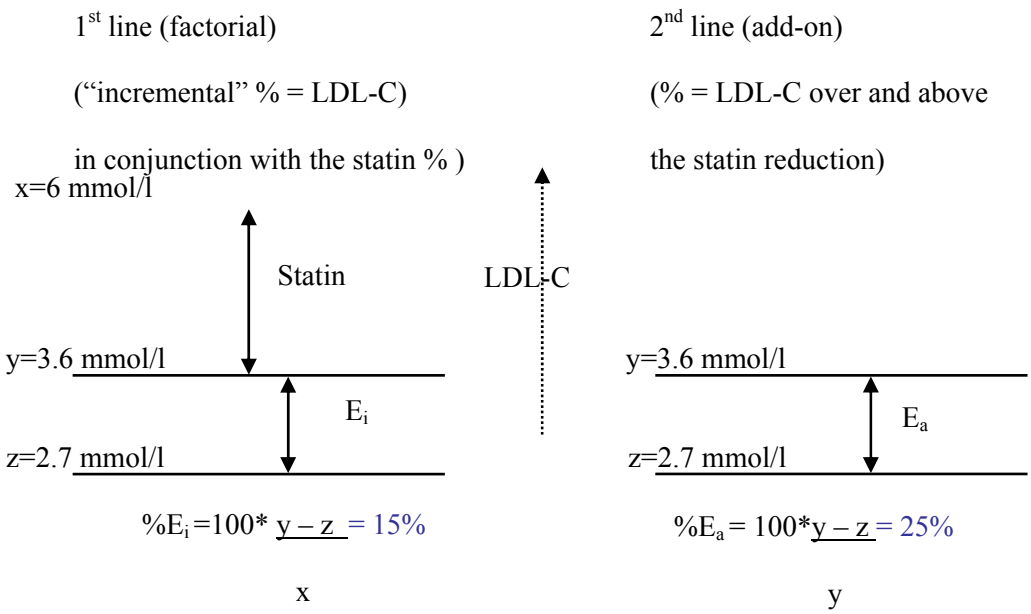
For the 12 week data, the individuals who had received statins prior to the start of the study had a wash-out period of up to 12 weeks. There is no information on pre-trial treatment history and previous treatment success. Hence it is not possible to determine if the study populations were inadequately controlled by statin monotherapy. Using the methodology proposed by the industry analysts, the results (Table 1) would suggest that a large proportion of the individuals in the RCTs would achieve lower than the absolute LDL-c NSF target (3.0 mmol/L) on statin monotherapy. The studies include a variety of treatment strategies with four of the studies comparing treatments including simvastatin, one comparing treatments including atorvastatin and the final comparing treatments including pravastatin. All studies also include a variety of doses in the arms ranging from pravastatin 10mg versus ezetimibe co-administered with pravastatin 10mg to atorvastatin 80mg compared with atorvastatin 80mg co-administered with ezetimibe treatment. As such it is not clear if either the patients in the studies or the treatment regimens being compared are indeed applicable to the definitions used in the ezetimibe appraisal protocol.

It is early in the evidence base to make conjectures about the effectiveness of ezetimibe in different patient groups, but it is quite likely that the effectiveness rates could be considerably different for individuals who cannot achieve targets on maximum tolerated statin doses.

While the 6 to 8 week studies do add ezetimibe onto ongoing statin treatment, again there is insufficient evidence to subgroup by patients who would be eligible for inclusion by the research question (adequately controlled by statin monotherapy) as described in the ezetimibe protocol. None of the studies used "not at target" on current statin or optimal statin as an inclusion criteria and although the studies include patients with hypercholesterolaemia, only one study explicitly included patients with primary hypercholesterolaemia. As brief summary table of the inclusion criteria used in these studies is provided in Appendix 1.

Re-examining the 12 week evidence using the hypothetical example:

Percentage Decrease in LDL-C With Ezetimibe in 1st vs. 2nd line: Hypothetical Example



Looking at the example above for the first line factorial study,

x = baseline LDL value after washout

y = LDL value for statin arm at end of RCT

z = LDL value for statin plus ezetimibe arm at end of RCT

%S = percentage reduction in the statin monotherapy arm

%ES = percentage reduction in the statin plus ezetimibe arm

$\%E_i$ = additional percentage reduction due to ezetimibe treatment

The 12 week RCT data is used to calculate the absolute values for y and z based on the observed percentage reductions in each arm of the trials as follows:

(1-%S) ; z = x_{es}(1-%ES); E_i= 1- z/y

Using the data from the Ballantyne study:

X_s = 4.65; X_{es} = 4.65, %S = 42.4%; %ES = 52.5%

$y = 4.65*(1-0.424) = 2.68$

$z = 4.65*(1-0.525) = 2.21$

Thus $E_i = 1- 2.21/2.68 = 17.5\%$

Table 1 summarises the incremental percentage reduction associated with adding Ezetimibe to ongoing statin treatment in the six 12 week studies.

Table 1: 12 week studies: observed LDL-c values and percentage reductions due to statin monotherapy and statin co-administered with ezetimibe, and estimated incremental percentage reduction due to adding ezetimibe onto statin treatment

	Statin monotherapy			Statin plus ezetimibe therapy			Percentage reduction		
	n	X_s	y	n	X_{es}	z	%S	%ES	%Ei
Ballantyne (atorva)	248	4.65	2.68	255	4.65	2.21	42%	53%	17.5%
Bays (simva)	612	4.62	2.82	604	4.58	2.15	39%	53%	23.6%
Davidson (simva)	263	4.64	2.96	274	4.58	2.29	36%	50%	22.6%
Goldberg (simva)	345	4.55	2.80	353	4.55	2.13	39%	53%	23.9%
Rodney (simva)	123	4.54	3.26	124	4.59	2.50	28%	46%	23.3%
Melani (prava)	302	4.60	3.48	204	4.6	2.87	24%	38%	17.7%

These results do suggest that if the baseline LDL-c is assumed to be in the region of 3.5 mmol/L, then the incremental percentage reduction of obtained from ezetimibe co-administered with statin is indeed higher than the results used (13.94%). A formal meta-analysis for Ei is outside the scope of this analysis, however, to give an indication of the likely impact of this revision the weighted average of the incremental percentage reduction is estimated at approximately 22.4%.

Using the data from the six ezetimibe studies in Table 1, the weighted mean reduction (%S) due to statin monotherapy is estimated to be 36.5%. Given a baseline LDL-c of 4.6 mmol/L using %S=36.5%, the mean value for y is estimated to be 2.92. If it is assumed that the additive value of a change in statin treatment is 6% (as per the Rule of 6) then the total percentage reduction from baseline (x) for the new statin treatment would be approximately 42.5% (36.5% + 6%). Using a 42.5% reduction on the baseline LDL-c (x), the absolute value for z for this arm would be 2.65mmol/L. The incremental percentage reduction due to the change in statin treatment would be 9.5% (9.5% = 1-2.65/2.92, difference due to rounding).

Based on the absolute reductions in the statin arms of the six studies, the baseline LDL-c for commencing ezetimibe co-administered with a statin would be 3.0 mmol/L with a range of 2.5 mmol/L to 3.5 mmol/L.

However, if the NSF target levels of 3 mmol/L are applied for ezetimibe co-administration, using the mean absolute LDL-c results for the individuals in the statin monotherapy arms, a large proportion of individuals in the majority of the 12 week RCTs (Ballantyne, Bays, Davidson, Goldberg) would achieve target levels without ezetimibe treatment.

Table 2: 6 week studies: observed LDL-c values and percentage reductions due to statin monotherapy and statin co-administered with ezetimibe

	Statin monotherapy			Statin plus ezetimibe therapy			Percentage reduction	
	n	x_s	z	n	x_{es}	z	%S	%ES
Gagne	390	3.59	3.46	379	3.57	2.68	3.7%	25.0%
Brohet	210	3.18	3.05	208	3.15	2.30	4.1%	27.1%
Cruz-Fernandez	224	3.13	3.00	219	3.14	2.19	4.2%	31.1%
Farnier	186	3.19	3.16	179	3.14	2.35	0.9%	25.2%
Pearson	968	3.34	3.25	1940	3.34	2.48	2.7%	25.8%

Using 22.4% to represent the effectiveness rate of adding ezetimibe onto ongoing statin treatment, and 9.5% to represent the effectiveness rate of changing the statin monotherapy, the results for scenarios 1, 3, 4 and 5 are provided below. The results for scenario 2 are unchanged from those presented in the Technology Assessment Report dated 8th December 2006.

Results for Scenario 1: ezetimibe plus current weighted statin versus current weighted statin titrated by one dose

The lifetime results for treatment Scenario 1 (Table 3) range from £24k per QALY to £42k per QALY for the secondary cohorts and from £24k per QALY for males aged 45 years with a baseline LDL-c of 3.5 mmol/L and no history of CVD to £62k per QALY for females aged 75 years with a baseline LDL-c of 2.5 mmol/L and no history of CVD.

Table 3: Scenario 1: discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	2.5	3.0	3.5	2.5	3.0	3.5
	20 year horizon					
Age	Male					
45	£71.5	£59.2	£50.5	£69.2	£57.4	£49.0
55	£59.7	£49.4	£42.1	£49.1	£40.7	£34.7
65	£49.6	£41.0	£34.9	£41.2	£34.2	£29.3
75	£59.2	£49.0	£41.8	£42.6	£35.5	£30.4
	Female					
45	£88.4	£73.2	£62.3	£75.3	£62.5	£53.4
55	£64.8	£53.5	£45.5	£50.2	£41.7	£35.6
65	£53.2	£43.9	£37.3	£42.0	£34.9	£29.9
75	£63.5	£52.5	£44.7	£41.4	£34.5	£29.5
	lifetime horizon					
Age	Male					
45	£34.7	£28.7	£24.4	£36.6	£30.4	£25.9
55	£37.4	£31.0	£26.4	£34.1	£28.3	£24.2
65	£41.3	£34.1	£29.0	£36.5	£30.4	£26.0
75	£57.4	£47.6	£40.5	£42.0	£35.0	£30.0
	Female					
45	£39.8	£32.9	£27.9	£38.0	£31.6	£27.0
55	£40.0	£33.1	£28.1	£34.5	£28.7	£24.6
65	£44.4	£36.7	£31.2	£37.1	£30.9	£26.4
75	£61.6	£51.0	£43.4	£40.8	£34.0	£29.1

Results for Scenario 3, ezetimibe plus generic simvastatin versus a more potent dose of atorvastatin (50% on 20mg and 50% on 40mg for each statin)

When varying the baseline LDL-c (Table 4), the ICERs for Scenario 3 are below £10k per QALY irrespective of time horizon (20 year or lifetime), age, gender or history of CVD.

Table 4: Scenario 3: discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	2.5	3.0	3.5	2.5	3.0	3.5
	20 year horizon					
Age	Male					
45	£5.0	£3.7	£2.8	£9.3	£7.5	£6.1
55	£4.0	£2.9	£2.1	£6.8	£5.5	£4.6
65	£3.2	£2.3	£1.6	£6.0	£4.9	£4.1
75	£4.1	£3.0	£2.2	£6.6	£5.5	£4.6
	Female					
45	£6.0	£4.3	£3.2	£10.3	£8.3	£6.9
55	£4.0	£2.8	£1.9	£7.0	£5.6	£4.7
65	£3.2	£2.2	£1.4	£6.3	£5.2	£4.4
75	£4.2	£2.9	£2.1	£6.3	£5.3	£4.5
	lifetime horizon					
Age	Male					
45	£2.8	£2.1	£1.6	£5.6	£4.6	£3.9
55	£2.9	£2.1	£1.6	£5.3	£4.4	£3.7
65	£2.9	£2.1	£1.5	£5.6	£4.6	£4.0
75	£4.1	£3.0	£2.2	£6.5	£5.4	£4.6
	Female					
45	£3.0	£2.2	£1.6	£5.9	£4.9	£4.2
55	£2.9	£2.1	£1.5	£5.4	£4.5	£3.9
65	£3.0	£2.1	£1.5	£5.9	£4.9	£4.2
75	£4.1	£2.9	£2.1	£6.3	£5.2	£4.5

Results for Scenario 4: Ezetimibe plus average weighted statin vs average weighted statin

When comparing the treatment regimen ezetimibe 10mg plus the weighted average statin versus the weighted average statin of the same doses (Table 5), the results for the lifetime horizon range from £18.7k per QALY for males aged 45 years with no history of CVD and a baseline LDL-c of 3.5 mmol/L to £47.3k per QALY for females aged 75 years with no history of CVD and a baseline LDL-c of 2.5 mmol/L.

Table 5: Scenario 4: discounted ICERs (£,000) when varying the baseline LDL-c value

Age	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	2.5	3.0	3.5	2.5	3.0	3.5
20 year horizon						
Age	Male					
45	£53.6	£44.2	£37.5	£56.7	£46.9	£39.9
55	£45.0	£37.1	£31.4	£40.9	£33.9	£28.8
65	£37.6	£30.9	£26.2	£35.4	£29.3	£25.0
75	£45.1	£37.2	£31.5	£38.4	£31.9	£27.2
	Female					
45	£66.3	£54.7	£46.4	£62.8	£52.0	£44.3
55	£49.0	£40.3	£34.1	£42.8	£35.4	£30.1
65	£40.5	£33.2	£28.1	£36.7	£30.4	£25.9
75	£48.6	£40.0	£33.8	£37.6	£31.2	£26.6
lifetime horizon						
Age	Male					
45	£26.9	£22.1	£18.7	£31.8	£26.3	£22.4
55	£28.8	£23.7	£20.1	£29.3	£24.3	£20.7
65	£31.5	£26.0	£22.0	£31.7	£26.3	£22.4
75	£43.8	£36.1	£30.6	£37.8	£31.4	£26.8
	Female					
45	£30.9	£25.4	£21.5	£33.6	£27.9	£23.8
55	£31.0	£25.5	£21.5	£30.2	£25.1	£21.4
65	£34.1	£28.0	£23.6	£32.7	£27.1	£23.2
75	£47.3	£38.9	£32.9	£37.1	£30.8	£26.2

Results for Scenario 5: Ezetimibe plus Rosuvastatin 40mg versus Rosuvastatin 40mg

As expected the results for Scenario 5 (Table 6) are the same as those for Scenario B and the lifetime ICERs for the secondary cohorts range from £21k to £38k per QALY. The lifetime ICERs for the primary cohorts range from £19.0k per QALY for males aged 45 years with a baseline LDL-c of 3.5 mmol/L to £48k per QALY for females aged 75 years with a baseline LDL-c of 2.5 mmol/L.

The results presented in Table 6 can be used to illustrate the cost-effectiveness of ezetimibe plus a statin compared with the same statin.

Table 6: Scenario 5: discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	2.5	3.0	3.5	2.5	3.0	3.5
	20 year horizon					
Age	Male					
45	£53.7	£44.4	£37.7	£56.9	£47.1	£40.1
55	£45.2	£37.3	£31.6	£41.2	£34.1	£29.1
65	£37.8	£31.2	£26.4	£35.7	£29.6	£25.3
75	£45.4	£37.4	£31.8	£38.8	£32.2	£27.5
	Female					
45	£66.4	£54.8	£46.5	£63.0	£52.2	£44.5
55	£49.2	£40.5	£34.3	£43.0	£35.6	£30.4
65	£40.7	£33.4	£28.3	£37.0	£30.7	£26.2
75	£48.9	£40.3	£34.1	£38.0	£31.6	£27.0
	lifetime horizon					
Age	Male					
45	£27.1	£22.3	£19.0	£32.1	£26.6	£22.7
55	£29.0	£23.9	£20.3	£29.6	£24.6	£21.0
65	£31.8	£26.2	£22.2	£32.0	£26.6	£22.7
75	£44.1	£36.4	£30.9	£38.2	£31.8	£27.2
	Female					
45	£31.1	£25.6	£21.7	£33.9	£28.2	£24.1
55	£31.2	£25.7	£21.8	£30.5	£25.4	£21.7
65	£34.3	£28.2	£23.9	£33.0	£27.5	£23.5
75	£47.5	£39.2	£33.2	£37.4	£31.1	£26.6

Results for ezetimibe co-administered with a statin compared with titrating to the same dose of a more potent statin

When switching to the same dose of a more potent statin there are 10 alternative treatment regimens (Table 7). The only difference in the 10 analyses is the incremental annual cost of the regimens being compared.

Table 7: Possible treatment regimens when switching to the same dose of a more potent statin and annual costs

	Treatment regimens[a]		Annual cost		Incremental annual cost
	combination therapy	monotherapy	combination therapy	monotherapy	
1	E10 + P10	S10	£368.00[b]	£23.59[b]	£344.40
2	E10 + A10	R10	£578.00	£235.03	£342.97
3	E10 + P20	S20	£366.56[b]	£30.50[b]	£336.06
4	E10 + A40	R40	£710.71	£387.03	£323.68
5	E10 + P40	S40	£375.17[b]	£55.14[b]	£320.03
6	E10 + A20	R20	£664.17	£387.03	£277.14
7	E10 + S10	A10	£366.56[b]	£235.03	£131.53
8	E10 + S80	A80	£453.25[b,c]	£367.74	£85.51
9	E10 + S20	A20	£373.47[b]	£321.20	£52.27
10	E10 + S40	A40	£398.11[b]	£367.74	£30.37

[a]A = atorvastatin, E = ezetimibe, P = pravastatin, R = rosuvastatin, S = simvastatin; combination therapy: E10+P10 = ezetimibe 10mg plus pravastatin 10mg; E10+A10 = ezetimibe 10mg plus atorvastatin 10mg etc; monotherapy: S10 = simvastatin 10mg; R10 = rosuvastatin 10mg etc. [b]costs are for generic pravastatin and generic simvastatin. [c]cost is for 2 x 40mg generic simvastatin.

Based on the results from the earlier analyses (Addendum dated 18th February, 2007); these can be split into 2 groups:

Group A: higher incremental annual treatment costs includes regimens 1 to 6

Group B: lower incremental annual treatment costs includes regimens 8 to 10

Results for regimen 1: ezetimibe co-administered with pravastatin 10mg versus simvastatin 10mg is used to represent the results for Group A (higher incremental annual treatment costs).

The lifetime ICERs for regimen 1 (Table 8) range from £31k per QALY to £54k per QALY for cohorts with a history of CVD. The ICERs for the cohorts who have no history of CVD range from £32k per QALY for males aged 45 years with a baseline LDL-c of 3.5 mmol/L to £81k per QALY for females aged 75 years with a baseline LDL-c of 2.5 mmol/L.

Table 8: Regimen 1: (E10+P10 v S10) discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	2.5	3.0	3.5	2.5	3.0	3.5
	20 year horizon					
Age	Male					
45	£94.1	£78.1	£66.6	£89.4	£74.2	£63.4
55	£78.6	£65.2	£55.6	£63.3	£52.5	£44.8
65	£65.3	£54.1	£46.1	£53.0	£44.0	£37.6
75	£77.7	£64.5	£55.1	£54.7	£45.5	£39.0
	Female					
45	£116.4	£96.5	£82.3	£97.3	£80.8	£69.1
55	£85.4	£70.7	£60.3	£64.7	£53.7	£45.9
65	£70.0	£58.0	£49.4	£53.9	£44.8	£38.3
75	£83.5	£69.2	£59.0	£53.1	£44.2	£37.8
	lifetime horizon					
Age	Male					
45	£45.4	£37.6	£32.0	£47.0	£38.9	£33.2
55	£49.0	£40.6	£34.6	£43.7	£36.3	£31.0
65	£54.1	£44.9	£38.2	£46.8	£38.9	£33.2
75	£75.4	£62.6	£53.4	£53.8	£44.8	£38.4
	Female					
45	£52.2	£43.2	£36.7	£48.7	£40.4	£34.5
55	£52.5	£43.5	£37.0	£44.2	£36.7	£31.4
65	£58.3	£48.3	£41.1	£47.4	£39.5	£33.8
75	£81.0	£67.1	£57.3	£52.2	£43.5	£37.2

Results for regimen 10: ezetimibe co-administered with simvastatin 40mg versus atorvastatin 40mg are used to represent the results for Group B (lower incremental annual treatment costs).

The ICERs for regimen 10 are all below £10k per QALY irrespective of horizon (20 year or lifetime) age, gender or CVD history.

Table 9: Regimen 10: (E10+S40 v A40) discounted ICERs (£,000) when varying the baseline LDL-c value

	Primary			Secondary		
	baseline LDL-c (mmol/L)					
	2.5	3.0	3.5	2.5	3.0	3.5
	20 year horizon					
Age	Male					
45	£1.8	£1.0	£0.5	£6.4	£5.1	£4.1
55	£1.3	£0.7	£0.2	£4.8	£3.8	£3.1
65	£1.0	£0.4	£0.0	£4.3	£3.5	£2.9
75	£1.5	£0.8	£0.3	£4.8	£4.0	£3.4
	Female					
45	£2.0	£1.0	£0.3	£7.1	£5.7	£4.6
55	£1.1	£0.3	c/s	£4.9	£3.9	£3.2
65	£0.8	£0.2	c.s	£4.6	£3.8	£3.2
75	£1.3	£0.6	£0.0	£4.7	£3.9	£3.3
	lifetime horizon					
Age	Male					
45	£1.2	£0.8	£0.5	£4.1	£3.4	£2.9
55	£1.2	£0.7	£0.4	£3.9	£3.2	£2.8
65	£1.1	£0.6	£0.2	£4.1	£3.4	£2.9
75	£1.5	£0.8	£0.3	£4.8	£4.0	£3.4
	Female					
45	£1.2	£0.7	£0.3	£4.4	£3.7	£3.1
55	£1.1	£0.6	£0.2	£4.0	£3.4	£2.9
65	£1.0	£0.4	£0.0	£4.4	£3.7	£3.2
75	£1.3	£0.6	£0.1	£4.7	£3.9	£3.3

c/s = cost saving

APPENDIX A

Table A1

	Inclusion criteria	Baseline	Run-in	Active period	Design	Statistics	Titration	Comment
Gagne et al, 2002	Patients with PHC at or above recommended NCEP ATP II target. LDL Targets (mmol/L). Primary population with: a) ≤1 risk factor: <4.14 b) ≥2 risk factors: <3.37 Secondary population: a) <2.59	Patients had to be on stable daily does of statin ≥6 weeks prior to randomisation	1 week	8 weeks	R,DB,PC (1:1 ratio)	ITT	Fixed	
Person et al, 2005	Patients at or above recommended NCEP ATP III target. LDL Targets (mmol/L). Primary population with: a) <2 risk factor: <4.14 b) ≥2 risk factors: <3.37 Secondary population: a) <2.59	Patients had to be on stable daily does of statin ≥6 weeks prior to randomisation	1 week	6 weeks	R,DB,PC (2:1 ratio)	Modified ITT	Fixed	
Cruz-Fernandez et al. 2005	Patients with documented CHD and following lipid targets (mmol/L): LDL: 2.6 to 4.2 TG: <4	Patients had to be on stable daily does of statin (ATORV: 10 or 20 mg/day) ≥6 weeks prior to randomisation	4 weeks	6 weeks	R,DB,PC (1:1 ratio)	Modified ITT	Fixed	1214 assessed for eligibility and 764 excluded – 92% failed to meet LDL-c entry criteria; 4% AE
Farnier et al, 2005	Patients with documented CHD and following lipid targets (mmol/L): LDL: 2.6 to 4.2 TG: <4	Patients had to be on stable daily does of statin (SIMVA: 10 or 20 mg/day) ≥6 weeks prior to randomisation	4 weeks	6 weeks	R,DB,PC	Modified ITT	Fixed	789 screened of which 417 excluded – 87.5% failed inclusion criteria; 2.2% clinical AE. Also approx. 67% randomised patients taking SIMVA 20mg/day
Brohet et al , 2005	Patients with documented CHD and	Patients had to be on	4	6 weeks	R,DB,PC (2:1 ratio)	Modified ITT	Fixed	

	following lipid targets (mmol/L): LDL: 2.6 to 4.2 TG: <4	stable daily does of statin (SIMVA: 10 or 20 mg/day) ≥6 weeks prior to randomisation						

General comments on 6 week studies

a) 3 of the 5 studies included patients with documented CHD 2 of them were mixed (primary/secondary) but we do not know the mix of primary/sec.

b) None of the patients in 3 studies were on maximum tolerated statin dose prior to randomisation. Of the other 2 studies we do not know proportions of patients on what dose/type of statin

c) All studies were fixed dose (no titration and no switching)

d) Of the 5 studies 4 of these were analysed using modified ITT and only 1 (not the largest one) was ITT

e) None of the studies used "not at target" on current statin or optimal statin as an inclusion criteria, although 2 studies included patients at or above recommended NCEP ATP LDL targets i.e. patients with <2 risk factor: <4.14 mmol/L; ≥2 risk factors: <3.37 mmol/L; Secondary population: <2.59 mmol/L

f) Although studies include patients with hypercholesterolaemia, only one study explicitly included patients with primary hypercholesterolaemia

Appendix B: The effectiveness of Switching/titrating statins

There are several reported relationships between statin dose and reductions in serum cholesterol:

- "Rule of 5" and "Rule of 7" {Roberts, 1997}
- "Rule of 6" {Knopp, 1999}
- "Rule of 8" {Jones, 2003}
- meta-analysis {Law, 2003}

Roberts, 1997, editorial

Includes atorva, simva, lova, prava, fluva

Rule of 7: "Doubling the dose of each statin lowers LDL-c by an additional 7%"

Rule of 5: "given patient is on a dose which achieves 22% reduction in Total-c, then doubling the dose after this lowers Total-c by an additional 5%"

Table B1: extract from table 1: comparative efficacy of the 5 currently available statin drugs {Roberts, 1997} - Lovastatin and fluvastatin not shown

statin drug (mg)			cholesterol			
Atorva	Simva	Prava	total	LDL	HDL	LE > 3x upper limit normal
			reduction		increase	
5	10	20	22%	27%	7%	0.25%
10	20	40	27%	34%		0.50%
20	40		32%	41%		1%
40	80		37%	48%		2%
80	160*		42%	55%		2%

*approval for use at this dose applied for to the FCA; LE: liver enzyme

- does not report the number of RCTs or the number of patients
- does not discuss either baseline LDL-c or change in % reduction achieved in relation to baseline LDL-c

Knopp, 1999, Review article

Includes prava, lova, fluva, simva, atorva, ceriva

Rule of 6: "In general, a doubling of the dose above the minimal effective dose decreases serum LDL cholesterol concentrations by an additional 6 percent."

"The response to increases in the dose is not proportional, because the dose response relation for all six statins is curvilinear."

- reported as pooled analyses
- does not discuss either baseline LDL-c or change in % reduction achieved in relation to baseline LDL-c

Jones, 2003, STELLAR RCT

N=2431; rosuvastatin 10, 20, 40, 80 mg; atorvastatin 10, 20, 40, 80 mg; simvastatin 10, 20, 40, 80 mg; or pravastatin 10, 20, 40 mg

"At 6 weeks, across-dose analyses showed that rosuvastatin 10 to 80 mg reduced LDL cholesterol by a mean of 8.2% more than atorvastatin 10 to 80 mg, 26% more than pravastatin 10 to 40 mg, and 12% to 18% more than simvastatin 10 to 80 mg (all $p < 0.001$)."

The approximate 8% additional reduction in LDL-c when switching to a more potent statin of the same dose gives the "rule of 8".

Law, 2003. review and meta-analysis of 154 placebo controlled RCTs

absolute reductions were greater in those with higher pre-treatment concentrations but percentage reductions were independent of pre-treatment LDL-c

Table B2: excerpt adapted from Table 2 in Law, 2003 Absolute reductions (mmol/L) and percentage reductions in LDL-c according to statin and daily dose

Statin	daily dose (mg)					estimated additional if titrate by 1 dose	estimated additional if switch statin
	5	10	20	40	80		
Prava	15%	20%	24%	29%	33%	5%	
Simva	23%	27%	32%	37%	42%	5%	
Atorva	31%	37%	43%	49%	55%	6%	
Rosuva	38%	43%	48%	53%	58%	5%	
Prava to Simva	8%	7%	8%	8%	9%		8%
Simva to Atorva	8%	10%	11%	12%	13%		11%
Atorva to Rosuva	7%	6%	5%	4%	3%		5%

Examples: estimated from table above:

titrate prava by 1 dose get approx 5% additional reduction

switch from prava to simva of same dose get approx 8% additional reduction

Edwards, 2003, dose-specific meta-analysis

"Reductions occurred irrespective of baseline total-c"

& "in general, trials with lower total-c (5.0-5.9 mmol/L) showed equivalent benefit to those with higher concentrations. The exceptions were the few trials in which patients had very high cholesterol levels (greater than 9.0 mmol/L)"

RCTs = 91. statins n=43,404 =; placebo n=25,081

ceriva n=2,314, fluva n=1,208, lovas n=8,561

Atorvastatin: n=1,334

For all doses combined, mean initial LDL-c =5.0 mmol/L; mean reduction =36%

Pravastatin: n=11,811

no evidence of a dose response with fixed doses or with titrated doses

For all doses combined, mean initial LDL-c = 4.5 mmol/L, mean reduction =27%

For prava 40mg, mean initial LDL-c = 4.4 mmol/L, mean reduction =28%

Rosuvastatin: n=1,006

For rosuva 5mg or 10mg mean initial LDL-c =4.8 mmol/L, mean reduction =46%

(mean reduction for rosuva 5mg = 44%; mean reduction for rosuva 10mg = 49%)

For pooled 5-80mg or 10-80mg mean initial LDL-c =4.8mmol/L, mean reduction =48%

Simvastatin: n=17,168

For all doses combined mean initial LDL-c =4.0 mmol/L mean reduction =34%

For 20mg (40mg) mean initial LDL-c = 4.8 (3.4) mmol/L, mean reduction =37% (34%)

Looking at the Ezetimibe data

There is insufficient detailed evidence to meta-analyse by individual statin and or dose but looking at data from individual studies:

Davidson provides data for 8 arms: simvastatin 10mg, 20mg, 40mg, 80mg arms (S10, S20, S40, S80) and ezetimibe plus simvastatin 10mg, 20mg, 40mg, 80mg arms (E+S10, E+S20, E+S40, E+S80)

Ballantyne provides data for 8 arms: atorvastatin 10mg, 20mg, 40mg, 80mg arms (A10, A20, A40, A80) and ezetimibe plus atorvastatin 10mg, 20mg, 40mg, 80mg arms (E+A10, E+A20, E+A40, E+A80)

Melani provides data for 6 arms: pravastatin 10mg, 20mg, 40mg arms (P10, P20, P40) and ezetimibe plus pravastatin 10mg, 20mg, 40mg arms (E+P10, E+P20, E+P40)

Table B3: showing the percentage reduction in LDL-c at the end of study for each of the statin monotherapy or statin plus ezetimibe combination therapy

Davidson				Ballantyne				Melani		
S10	S20	S40	S80	A10	A20	A40	A80	P10	P20	P40
n=61	n=53	n=60	n=63	n=248				n=205		
27%	36%	36%	44%	35%	40%	43%	51%	20%	24%	29%
E+S10	E+S20	E+S40	E+S80	E+A10	E+A20	E+A40	E+A80	E+P10	E+P20	E+P40
n=61	n=58	n=68	n=52	n=255				n=204		
44%	45%	53%	57%	50%	54%	54%	60%	34%	38%	41%

Table B4: data from table above used to estimate the additional percentage reduction when titrating by 1 dose or when switching to the same dose of a more potent statin

		daily dose				additional % reduction			
						titrate statin			estimated average
		10	20	40	80	10to20	20to40	40to80	
Melani	Prava	20%	24%	29%		4%	5%		5%
Davidson	Simva	27%	36%	36%	44%	9%	0%	8%	6%
Ballantyne	Atorva	35%	40%	43%	51%	5%	3%	8%	5%
Prava to Simva		7%	12%	7%					7%
Simva to Atorva		8%	4%	7%	7%				7%

- There is insufficient detail to establish if the percentage reductions differ according to baseline LDL-c

The baseline LDL-c values is approximately equal for all individuals

There is insufficient evidence in the RCTs reviewed to establish an incremental difference in the percentage reduction when titrating statin dose (or switching).

However, the incremental percentage reduction due to a switch or titration can be estimated by taking data from different studies (Davidson, Ballantyne, Melani). Baseline characteristics etc may differ.

Table B5: showing the baseline and calculated absolute LDL-c levels (based on reported % reduction) and the estimated incremental percentage reduction

	Absolute LDL-c			% reduction in LDL-c				
	base	statin 1	statin 2 or statin + Eze	%S1	% S2 or % S+E	%	abs diff in arms	mean diff
	x	y	z	=1-y/x	=1-z/x	=1-z/y		
COMPARING titrating the same statin by 1 dose								
E10+P10vP10	4.6	3.68	3.04	20%	34%	17.5%		
P20vsP10	4.6	3.68	3.50	20%	24%	5.0%	12.5%	
E10+P20vsP20	4.6	3.50	2.85	24%	38%	18.4%		
P40vsP20	4.6	3.50	3.27	24%	29%	6.6%	11.8%	
E+S10 vs S10	4.65	3.39	2.60	27%	44%	23.3%		
S20vsS10	4.65	3.39	2.98	27%	36%	12.3%	11.0%	
E+S20vsS20	4.65	2.98	2.56	36%	45%	14.1%		
S40vsS20	4.65	2.98	2.98	36%	36%	0.0%	14.1%	
E+S40vsS40	4.65	2.98	2.19	36%	53%	26.6%		
S80vsS40	4.65	2.98	2.60	36%	44%	12.5%	14.1%	
E+A10vsA10	4.65	3.02	2.33	35%	50%	23.1%		
A20vsA10	4.65	3.02	2.79	35%	40%	7.7%	15.4%	
E+A20vsA20	4.65	2.79	2.14	40%	54%	23.3%		
A40vsA20	4.65	2.79	2.65	40%	43%	5.0%	18.3%	
E+A40vsA40	4.65	2.65	2.14	43%	54%	19.3%		
A80vsA40	4.65	2.65	2.28	43%	51%	14.0%	5.3%	**13%**

COMPARING adding statin to ongoing statin versus switching to same dose of next potent statin								
E10+P10vsP10	4.6	3.68	3.07	20%	34%	16.6%		
S10vsP10	4.6	3.68	3.39	20%	27%	7.8%	8.8%	
E10+P20vP20	4.6	3.50	2.88	24%	38%	17.5%		
S20vsP20	4.6	3.50	2.98	24%	36%	14.9%	2.7%	
E10+P40vsP40	4.6	3.27	2.74	29%	41%	16.0%		
S40vsP40	4.6	3.27	2.98	29%	36%	8.9%	7.1%	
E+S10vsS10	4.65	3.39	2.60	27%	44%	23.3%		
A10vsS10	4.65	3.39	3.02	27%	35%	11.0%	12.3%	
E+S20vsS20	4.65	2.98	2.56	36%	45%	14.1%		
A20vsS20	4.65	2.98	2.79	36%	40%	6.3%	7.8%	
E+S40vsS40	4.65	2.98	2.19	36%	53%	26.6%		
A40vsS40	4.65	2.98	2.65	36%	43%	10.9%	15.6%	
E+S80vsS80	4.65	2.60	2.00	44%	57%	23.2%		
A80vsS80	4.65	2.60	2.28	44%	51%	12.5%	10.7%	**9%**

The estimated incremental additional benefits estimated are not considered to be robust.

There is insufficient evidence to adjust for any differences in baseline characteristics.

There is insufficient evidence to pool data from all the ezetimibe RCTs reviewed.

All individuals commence treatments with approximately the same baseline LDL-c value. The sample sizes are relatively small in comparison to the statin meta-analyses.

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