National Institute for Health and Care Excellence

Final

Cardiovascular disease: risk assessment and reduction, including lipid modification

Network meta-analysis of changes in LDL cholesterol and non-HDL cholesterol as a result of escalation of lipid-lowering treatment for secondary prevention of CVD

NICE guideline NG238

Network meta-analysis report

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Final

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Contents

1 Introduction

Network meta-analysis (NMA) is a statistical technique that allows simultaneous pooling of data for three or more interventions when the available evidence forms a connected network of intervention comparisons from RCTs. This enables both direct evidence and indirect evidence to be pooled. NMA combines all the available data simultaneously into a single set of treatment effects that provide a unique ordering of intervention effectiveness, whilst respecting the randomisation in the included RCTs. The resulting estimates are therefore easier to interpret than a series of pairwise comparisons, enables ranking of the interventions, and because both direct and indirect evidence is pooled treatment effects are more precisely estimated (have greater statistical power).

The analysis provides estimates of relative effects (with 95% credible intervals) for each intervention compared to a reference intervention (in this case the reference intervention was placebo, which included background statin treatment) as well as estimates of all pairwise comparisons. In addition, for a given assumed “baseline effect” on the reference intervention, we can obtain absolute effects for all interventions. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Having a single set of intervention effects that takes into account all the available evidence also facilitates cost effectiveness analysis.

The review for this guideline update (comparing adding ezetimibe, PCSK9 inhibitors or inclisiran to statins with statins alone) formed a connected network of RCT evidence and so an NMA was considered. This topic was considered a high clinical priority due to variations in practice and uncertainty about the most clinically and cost-effective strategy. It was also given the highest priority for new economic modelling as direct evidence on the relative effectiveness of different treatment options could not inform the optimal lipid level treatment target. Given this, the committee agreed that network meta-analysis was warranted to facilitate cost effectiveness analysis and help decision making in this area.

2 Study selection

A systematic review of RCTs comparing licenced doses of ezetimibe, inclisiran, alirocumab or evolocumab with each other, high or medium intensity stains, usual care or placebo in adults with CVD was undertaken for the guideline. Studies identified in this review were considered for inclusion in the NMA.

We performed NMAs that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence.

Further details of the evidence identified from the review can be found in the evidence review and the protocol, evidence tables and GRADE assessment appendices.

2.1 NMA model assumptions

2.1.1 Class effect models of evolocumab and alirocumab

Three different approaches to modelling dose and class effects for alirocumab and evolocumab were explored. Goodness of fit was assessed using the posterior mean of the residual deviance, where a well-fitting model would show total residual deviance equivalent to the number of data points. Different models of the class effect structure were compared on the basis of DIC, which is a measure of fit penalised for model complexity, residual deviance and estimates of heterogeneity (between-study and within-class standard deviation).

The simplest model to assume that all treatments and doses have the same relative effect compared with placebo; that there is a common class effect (sometimes called a fixed class effect model). Any differences would be captured as between study variability. The second model assumed that treatment and dose effects differ, so a mean effect across treatments and doses within class was estimated, with between treatment/dose variability (a random class effect model). The third model assumed a common (fixed) class effect for the two treatments but allowed for an effect of high and low dose for evolocumab. Of these three models, the common class effect (fixed class effect) model gave the best fit for each outcome and dataset, and so all results are reported using this model.

2.1.2 Network meta-regression on baseline lipid level

Network meta-regression was conducted using 2 different models to explore whether differences in mean lipid levels at baseline interacted with the relative treatment effects. The simplest was to assume that mean lipid levels moderated the effect of each active treatment in the same way relative to non-active treatments. This assumption was then relaxed to estimate a different covariate effect for each treatment class. There was very limited evidence with which to estimate the meta-regression models, and the effects are very uncertain, but there was no evidence of effect modification by baseline mean lipid levels in the studies. Specifically, the large credible intervals around the meta-regression term for baseline severity, and the fact that they include zero mean that it is not possible to infer an effect of baseline lipid level for these data. Therefore, in agreement with the committee, the results from this analysis were not used as the base case.

2.2 Outcome measures

Network models were fitted for the following outcomes:

- Percentage change from baseline in LDL cholesterol (%)
- Absolute change from baseline in LDL cholesterol (mmol/litre)

- Percentage change from baseline in non-HDL cholesterol (%)
- Absolute change from baseline in non-HDL cholesterol (mmol/litre)

Studies varied in whether they reported the outcomes as a percentage change from baseline or as an absolute outcome change from baseline, and some studies reported both. It is not possible to combine these two different outcome measure formats, and so we conducted NMA for both outcome formats separately.

3 Results

3.1 Imputed correlations and standard deviations

The correlation between lipid levels at baseline and follow-up was estimated to be 0.386 from 14 studies reporting mean LDL at baseline, follow-up and the change from baseline. This was used to estimate the standard error for mean change from baseline for studies that report baseline and follow-up means only. Imputed SD was specific to lipid type and outcome format (**Table 1**) and were used for studies which did not report a standard deviation or standard error.

Table 1: Values of imputed SD by data type

Dataset	Mean SD (imputed)
LDL, reported as percent change	24.87
LDL, reported in units of mmol/L	0.751
Non-HDL, reported as percent change	23.01
Non-HDL, reported in units of mmol/L	0.9574

3.2 Percentage change from baseline in LDL cholesterol

3.2.1 Network and data

Eighteen studies reported in 17 papers[1-4, 6, 7, 9-12, 16, 17, 21-23, 26, 28] were identified as reporting outcome data for percentage change from baseline in LDL cholesterol. Eight treatments were included in the network: placebo (including placebo and/or statin treatment), standard care, ezetimibe, inclisiran, alirocumab, evolocumab (mixed), evolocumab 140mg and evolocumab 420mg. Alirocumab and evolocumab were modelled as a single fixed class. The network can be seen in **Figure 1** and the trial data for each of the studies included in the NMA are presented in **Table 2**.

Figure 1: Network diagram for percentage change in LDL cholesterol

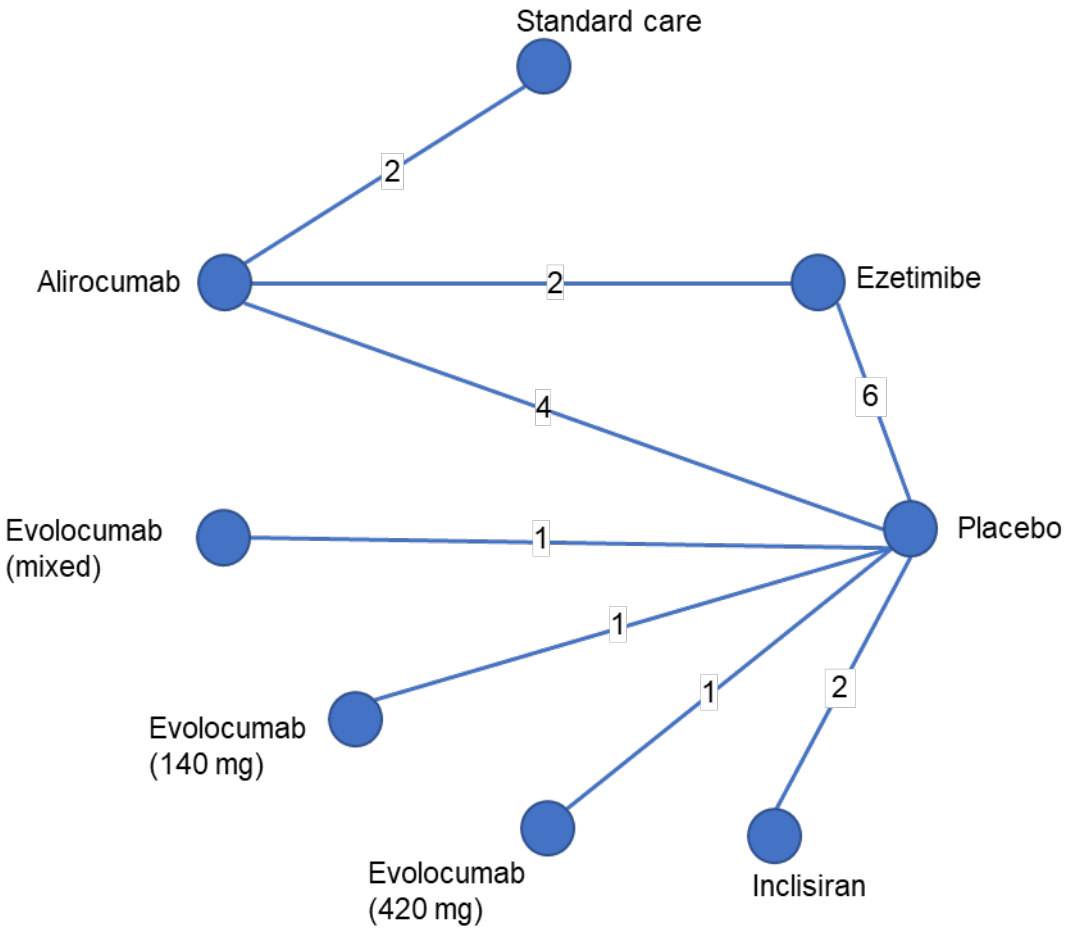


Table 2: Study data for percentage change in LDL cholesterol at 3-12 months included in the network meta-analysis

Study	Intervention	Comparison	% change LDL-C	
			Mean difference	SE
Cannon, 2015[3] IMPROVE-IT	Ezetimibe	Placebo	-24	0.423
Hougaard, 2017[9]	Ezetimibe	Placebo	-9.6	3.513
Joshi, 2017[10]	Ezetimibe	Placebo	-11.9	3.932
Masuda 2015[16]	Ezetimibe	Placebo	-19	5.984
Ran, 2017[21] NSTE-ACS	Ezetimibe	Placebo	-23.4	5.427
Tsujita, 2015[28] PRECISE-IVUS	Ezetimibe	Placebo	-11	2.981
Kereiakes, 2015[11] ODYSSEY COMBO I	Alirocumab	Placebo	-41	3.678
Koh, 2018[12] ODYSSEY KT	Alirocumab	Placebo	-63.4	4.173
McCullough, 2018[17]	Alirocumab	Placebo	-61.8	1.442

Study	Intervention	Comparison	% change LDL-C	
			Mean difference	SE
ODYSSEY-LONG TERM				
Ray, 2019[22] ODYSSEY DM-INSULIN	Alirocumab	Placebo	-48.5	4.4
Giugliano, 2012[6] LAPLACE-TIMI 57	Evolocumab low	Placebo	-66.1	2.759
Giugliano, 2012[6] LAPLACE-TIMI 57	Evolocumab high	Placebo	-50.3	2.886
Sabatine, 2017[26] FOURIER	Evolocumab	Placebo	-59	0.510
Ray, 2020[23] ORION-10	Inclisiran	Placebo	-49.2	1.224
Ray, 2020[23] ORION-11	Inclisiran	Placebo	-53.8	1.249
Ako, 2019[1] ODYSSEY J-IVUS	Alirocumab	Standard care	-50.5	2.758623
Ray, 2019[22] ODYSSEY DM-DYSLIPIDEMIA	Alirocumab	Standard care	-45.9	5.8
Cannon, 2015[4] ODYSSEY COMBO II	Alirocumab	Ezetimibe	-31.2	2.581
Han, 2020[7] ODYSSEY EAST	Alirocumab	Ezetimibe	-35.7	2.535

3.2.2 Results of network meta-analysis

Table 3 summarises the results of the pairwise meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA (this is from a random effects model, which was chosen on the basis of model fit), in terms of mean differences comparing each available treatment option with placebo/statin.

Table 3: Risk differences for percentage change in LDL cholesterol at 3-12 months; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise estimates - mean difference (95% confidence intervals)	NMA random effects model – mean difference (95% credible intervals)	
			Base case model	Model with meta-regression on baseline lipid levels
Standard care	Placebo/ statin	NA	-6.34 (-19.40, 6.98)	-5.27 (-19.63, 9.49)
Ezetimibe		-11.5 (-15.66, -7.33)[a]	-17.83 (-23.74, -11.89)	-26.29 (-57.75, 7.20)
Inclisiran		-51.45 (-53.17, -49.74)[b]	-51.27 (-61.88, -40.52)	-59.01 (-87.26, -28.88)
PCSK9i		-54.62 (-59.28, -49.97)[b]	-55.01 (-60.33, -49.39)	-61.37 (-90.66, -30.03)

(a) Fixed effects model
(b) Random effects model

3.2.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the studies. Moderate heterogeneity was observed for this outcome, with a large reduction in residual deviance and DIC seen in the RE NMA model, relative to the FE NMA model (**Table 4**). This, together with the moderate between-study SD supports choice of the RE model structure.

An inconsistency model was run and the model fit statistics were as seen in **Table 4**. The NMA model has a slightly smaller DIC suggesting that there is no evidence of inconsistency.

Table 4: Model fit statistics – percentage change in LDL cholesterol at 3-12 months

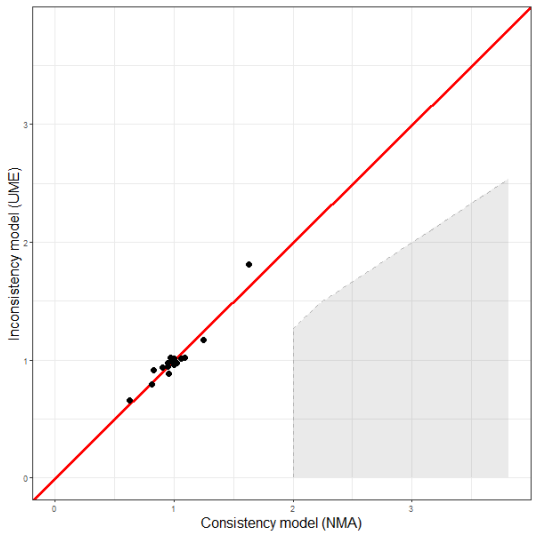
Relative effect models[(a)]	Between study SD (95% CrI)	Meta-regression covariate on baseline lipid level	Deviance information criterion (DIC)	Total residual deviance
NMA Fixed effects	-	-	181.9	108.2
NMA (Random effects)	7.23 (4.49, 11.40)	-	105.2	19.0
Unrelated mean-effects (Random effects)	7.30 (4.42, 11.79)	-	105.4	19.1
Meta-regression (Random effects)	7.55 (4.31, 12.75)	2.82 (-7.40, 12.40)	98.5	17.0

(a) Number of data points in the NMA and inconsistency models (n=19). Number of data points in the meta-regression model models (n=17).

The global check for inconsistency, modelling treatment effects independently of each other, indicates that there is little inconsistency in this dataset, with similar model fit in the RE NMA and RE UME models, and no evidence of local inconsistency. Figure 2 presents a dev-dev plot, which shows the contributions of each study datapoint to the residual deviance under the random effects UME and NMA models. There is no evidence of inconsistency, as there are no points notably below the line of equality, which would be indicative of data better predicted by the inconsistency model.

Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data.

Figure 2: Contribution of each study datapoint to the residual deviance under the random effects UME and NMA models – percentage change in LDL cholesterol at 3-12 months



3.2.4 Sensitivity analyses and subgroup analyses

Within the sensitivity analysis, including studies reporting baseline LDL, adding a meta-regression term on baseline LDL levels resulted in a model with good model fit (total residual deviance was 17, relative to 17 data points). However, the effect of baseline LDL was uncertain, 2.82 (95% credible interval (CrI): -7.40, 12.40), with the interval including zero. Between-study SD was higher in the meta-regression model, indicating greater differences between studies estimating the same treatment effect.

3.3 Absolute change from baseline in LDL cholesterol

3.3.1 Network and data

Thirty studies[1-6, 8-16, 18-21, 23-33] were identified as reporting outcome data for absolute change from baseline in LDL cholesterol. Eight treatments were included in the network: placebo (including placebo and/or statin treatment), standard care, ezetimibe, inclisiran, alirocumab, evolocumab (mixed), evolocumab 140mg and evolocumab 420mg. Alirocumab and evolocumab were modelled as a single fixed class. The network can be seen in Figure 3 and the trial data for each of the studies included in the NMA are presented in Table 5.

Figure 3: Network diagram for absolute change in LDL cholesterol

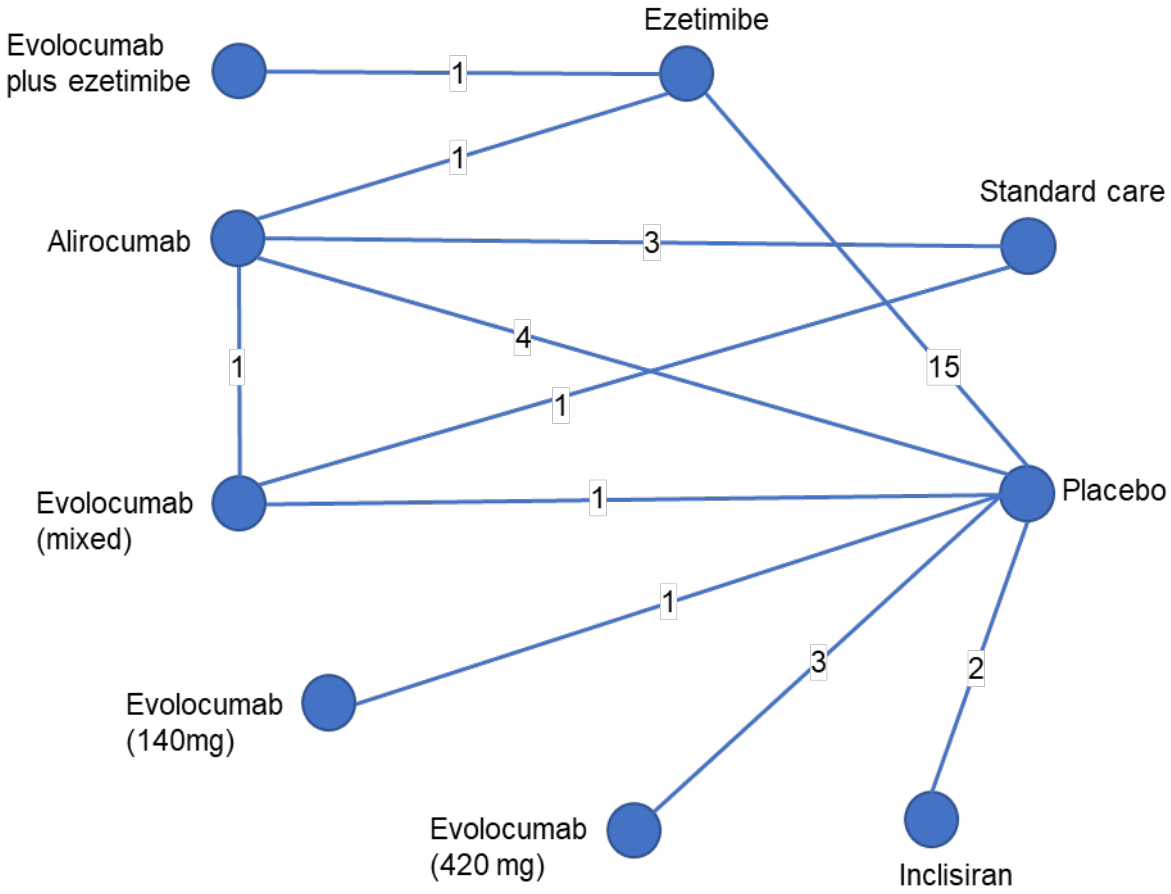


Table 5: Study data for absolute change in LDL cholesterol (mmol/litre) at 3-12 months included in the network meta-analysis

Study	Intervention	Comparison	Absolute change LDL-C (mmol/L)	
			Mean difference	SE
Arimura, 2012[2]	Ezetimibe	Placebo	-0.34	0.129
Cannon, 2015[3] IMPROVE-IT	Ezetimibe	Placebo	-0.43	0.034
Hougaard, 2017[9]	Ezetimibe	Placebo	-0.10	0.181
Joshi, 2017[10]	Ezetimibe	Placebo	-0.57	0.129
Kouvelos, 2013[13]	Ezetimibe	Placebo	-0.43	0.168
Luo 2014[14]	Ezetimibe	Placebo	-0.40	0.121
Luo 2016[15]	Ezetimibe	Placebo	-0.56	0.093
Masuda 2015[16]	Ezetimibe	Placebo	-0.69	0.217
Ran, 2017[21] NSTE-ACS	Ezetimibe	Placebo	-0.80	0.160
Ren, 2017[25]	Ezetimibe	Placebo	-0.37	0.183
Tsujita, 2015[28] PRECISE-IVUS	Ezetimibe	Placebo	-0.30	0.092
Ueda, 2017[29] ZIPANGU	Ezetimibe	Placebo	-0.36	0.128
Wang 2016[31]	Ezetimibe	Placebo	-0.62	0.238
Wang 2017[30]	Ezetimibe	Placebo	-0.45	0.154
West 2011/2011a[32, 33]	Ezetimibe	Placebo	-0.62	0.280
Kereiakes, 2015[11] ODYSSEY COMBO I	Alirocumab	Placebo	-1.10	0.093
Koh, 2018[12] ODYSSEY KT	Alirocumab	Placebo	-1.56	0.112
Raber, 2022[20] PACMAN-AMI	Alirocumab	Placebo	-1.41	0.116
Schwartz, 2018[27] ODYSSEY OUTCOMES	Alirocumab	Placebo	-1.24	0.013
Sabatine, 2017[26] FOURIER	Evolocumab	Placebo	-1.45	0.013
Giugliano, 2012[6] LAPLACE-TIMI 57a	Evolocumab 140mg	Placebo	-2.04	0.100
Giugliano, 2012[6] LAPLACE-TIMI 57	Evolocumab 420 mg	Placebo	-1.58	0.100
Nicholls, 2016[19] GLAGOV	Evolocumab 420 mg	Placebo	-1.46	0.059
Nicholls, 2022[18] HUYGENS	Evolocumab 420 mg	Placebo	-1.52	0.181
Ray, 2020[23] ORION-10	Inclisiran	Placebo	-1.38	0.033
Ray, 2020[23] ORION-11	Inclisiran	Placebo	-1.26	0.032
Ako, 2019[1]	Alirocumab	Standard care	-1.24	0.071

Study	Intervention	Comparison	Absolute change LDL-C (mmol/L)	
			Mean difference	SE
ODYSSEY J-IVUS				
Gao, 2021[5]	Alirocumab	Standard care	-0.76	0.141
Rehberger, 2022[24]	Alirocumab, evolocumab	Standard care	-1.50	0.206
Cannon, 2015[4] ODYSSEY COMBO II	Alirocumab	Ezetimibe	-0.90	0.073
Hao, 2022[8]	Evolocumab and ezetimibe	Ezetimibe	-0.71	0.095

3.3.2 Results of network meta-analysis

Table 6 summarises the results of the pairwise meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA (this is from a random effects model, which was chosen on the basis of model fit), in terms of mean differences comparing each available treatment option with placebo/statin.

Table 6: Risk differences for absolute change in LDL cholesterol at 3-12 months; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise estimates - mean difference (95% confidence intervals)	NMA random effects model – mean difference (95% credible intervals)	
			Base case model	Model with meta-regression on baseline lipid levels
Standard care	Placebo/ statin	NA	-0.30 (-0.59, -0.01)	-0.28 (-0.60, 0.03)
Ezetimibe		-0.41 (-0.47, -0.34)[a]	-0.46 (-0.58, -0.34)	-0.30 (-0.95, 0.34)
Inclisiran		-1.32 (-1.37, -1.28)[a]	-1.32 (-1.60, -1.05)	-1.17 (-1.78, -0.58)
Evolocumab plus ezetimibe		NA	-1.17 (-1.62, -0.74)	-1.01 (-1.80, -0.23)
PCSK9i		-1.51 (-1.65, -1.37)[b]	-1.46 (-1.60, -1.33)	-1.30 (-1.91, -0.72)

(a) Fixed effects model
(b) Random effects model

3.3.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the studies. Large heterogeneity was observed for this outcome, with a large reduction in residual deviance and DIC seen in the RE NMA model, relative to the FE NMA model. This, together with the moderate between-study SD (on the scale of the outcome) supports the choice of the RE model structure.

An inconsistency model was run and the model fit statistics were as seen in Table 7.

Table 7: Model fit statistics – absolute change in LDL cholesterol at 3-12 months

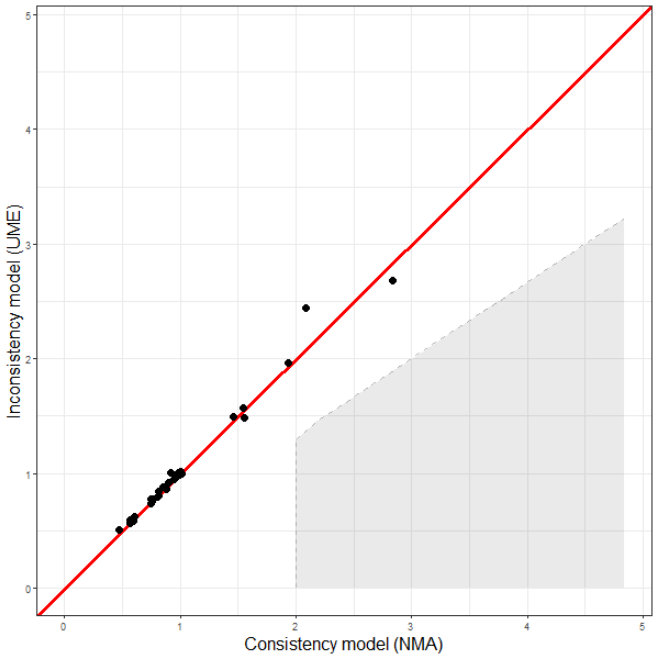
Relative effect models[(a)]	Between study SD (95% CrI)	Meta-regression covariate on baseline lipid level	Deviance information criterion (DIC)	Total residual deviance
NMA Fixed effects	-	-	156.2	239.9
NMA (Random effects)	0.19 (0.12, 0.27)	-	-33.4	31.7
Unrelated mean-effects (Random effects)	0.19 (0.12, 0.28)	-	-32.4	32.1
Meta-regression (Random effects)	0.20 (0.13, 0.30)	-0.06 (-0.25, 0.14)	-26.9	29.8

(a) Number of data points in the NMA and inconsistency models (n=31). Number of data points in the meta-regression model models (n=29).

The global check for inconsistency indicates that there is little inconsistency in this dataset, with similar model fit in the RE NMA and RE UME models, and no evidence of local inconsistency. Figure 4 presents a dev-dev plot, which shows the contributions of each study datapoint to the residual deviance under the random effects UME and NMA models. There is no evidence of inconsistency, as there are no points notably below the line of equality, which would be indicative of data better predicted by the inconsistency model.

Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data.

Figure 4: Contribution of each study datapoint to the residual deviance under the random effects UME and NMA models – absolute change in LDL cholesterol at 3-12 months



3.3.4 Sensitivity analyses and subgroup analyses

Within the sensitivity analysis, including studies reporting baseline LDL, adding a meta-regression term on baseline LDL levels gave a model with good statistical fit, but the effect of baseline LDL was uncertain, -0.06 (95% CrI: -0.25, 0.14), with the interval including zero.

3.4 Percentage change from baseline in non-HDL cholesterol

3.4.1 Network and data

Thirteen studies reported in 11 papers[1, 4, 6, 7{McCullough, 2018 #215, 11, 12, 16, 22, 23, 26] were identified as reporting outcome data for percentage change from baseline in non-HDL cholesterol. Eight treatments were included in the network: placebo (including placebo and/or statin treatment), standard care, ezetimibe, inclisiran, alirocumab, evolocumab (mixed), evolocumab 140mg and evolocumab 420mg. Alirocumab and evolocumab were modelled as a single fixed class. The network can be seen in Figure 5 and the trial data for each of the studies included in the NMA are presented in Table 8 and Table 2.

Figure 5: Network diagram for percentage change in non-HDL cholesterol

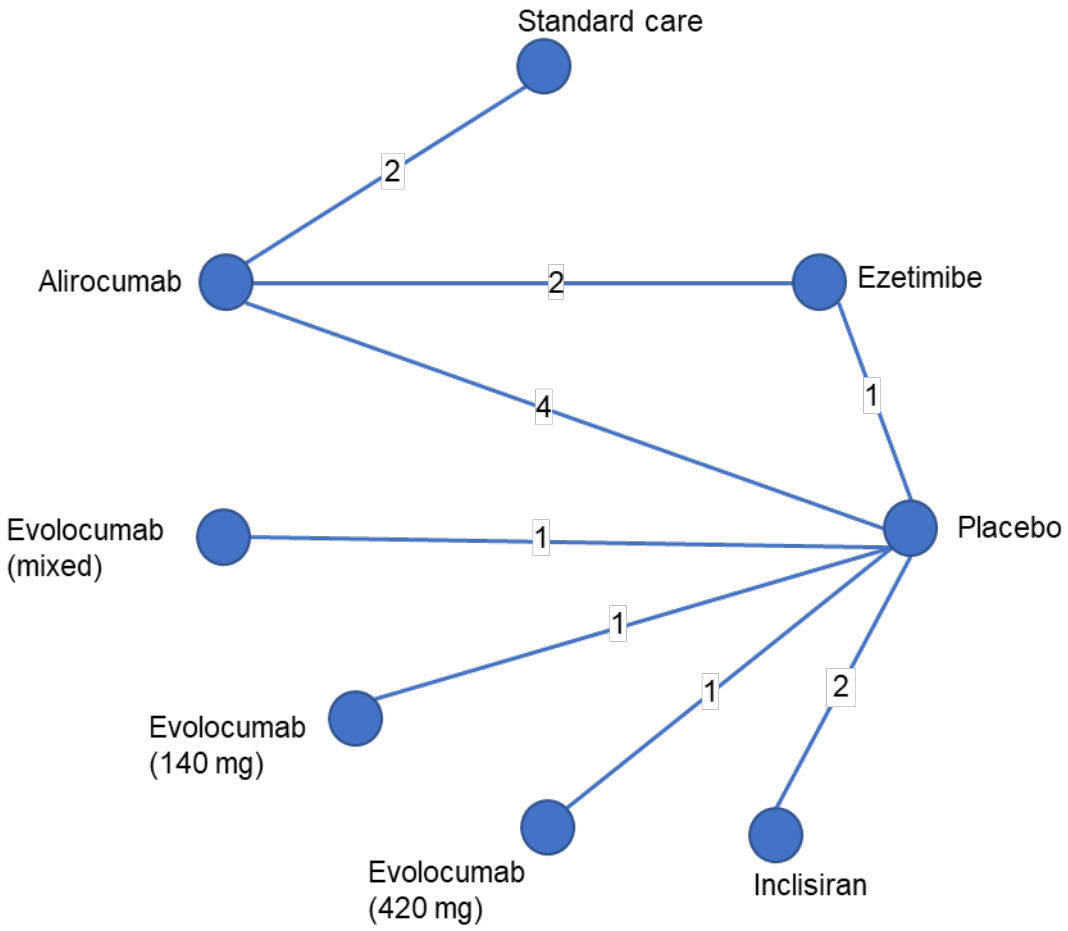


Table 8: Study data for percentage change in non-HDL cholesterol at 3-12 months included in the network meta-analysis

Study	Intervention	Comparison	% change LDL-C	
			Mean difference	SE
Masuda 2015[16]	Ezetimibe	Placebo	-15.5	5.67
Kereiakes, 2015[11]	Alirocumab	Placebo	-29.1	3.34

Study	Intervention	Comparison	% change LDL-C	
			Mean difference	SE
ODYSSEY COMBO I				
Koh, 2018[12] ODYSSEY KT	Alirocumab	Placebo	-51.5	3.46
McCullough, 2018[17] ODYSSEY-LONG TERM	Alirocumab	Placebo	-52.1	1.22
Ray, 2019[22] ODYSSEY DM-INSULIN	Alirocumab	Placebo	-37.4	3.90
Giugliano, 2012[6] LAPLACE-TIMI 57	Evolocumab low	Placebo	-61.4	2.50
Giugliano, 2012[6] LAPLACE-TIMI 57	Evolocumab high	Placebo	-47.6	2.60
Sabatine, 2017[26] FOURIER	Evolocumab	Placebo	-51.6	0.28
Ray, 2020[23] ORION-11	Inclisiran	Placebo	-47.3	1.16
Ray, 2020[23] ORION-10	Inclisiran	Placebo	-43.4	1.14
Ako, 2019[1] ODYSSEY J-IVUS	Alirocumab	Standard care	-40.4	2.40
Ray, 2019[22] ODYSSEY DM-DYSLIPIDEMIA	Alirocumab	Standard care	-31.1	4.30
Cannon, 2015[4] ODYSSEY COMBO II	Alirocumab	Ezetimibe	-22.9	2.08
Han, 2020[7] ODYSSEY EAST	Alirocumab	Ezetimibe	-27.6	2.08

3.4.2 Results of network meta-analysis

Table 9 summarises the results of the pairwise meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA (this is from a random effects model, which was chosen on the basis of model fit), in terms of mean differences comparing each available treatment option with placebo/statin.

Table 9: Risk differences for percentage change in non-HDL cholesterol at 3-12 months; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise estimates - mean difference (95% confidence intervals)	NMA random effects model – mean difference (95% credible intervals)	
			Base case model	Model with meta-regression on baseline lipid levels
Standard care	Placebo/ statin	NA	-10.83 (-26.95, 5.80)	-8.84 (-29.11, 11.76)
Ezetimibe		-15.5 (-26.61, -4.39)[a]	-20.02 (-33.05, -6.88)	-3.28 (-79.70, 77.44)
Inclisiran		NA	-45.14 (-58.62, -30.95)	-30.72 (-103.20, 46.14)

Intervention	Comparison	Pairwise estimates - mean difference (95% confidence intervals)	NMA random effects model – mean difference (95% credible intervals)	
			Base case model	Model with meta-regression on baseline lipid levels
Evolocumab plus ezetimibe		NA	NA	NA
PCSK9i		-42.47 (-48.45, -36.50)[b]	-46.99 (-54.26, -39.38)	-30.00 (-104.40, 48.65)

(a) Fixed effects model
(b) Random effects model

3.4.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the studies. Large heterogeneity was observed for this outcome, with a large reduction in residual deviance and DIC seen in the RE NMA model, relative to the FE NMA model. This, together with the moderate between-study SD supports choice of the RE model structure.

An inconsistency model was run and the model fit statistics were as seen in Table 10. The global check for inconsistency indicates that there is little inconsistency in this dataset, with similar model fit in the RE NMA and RE UME models, and no evidence of local inconsistency.

Table 10: Model fit statistics – percentage change in non-HDL cholesterol at 3-12 months

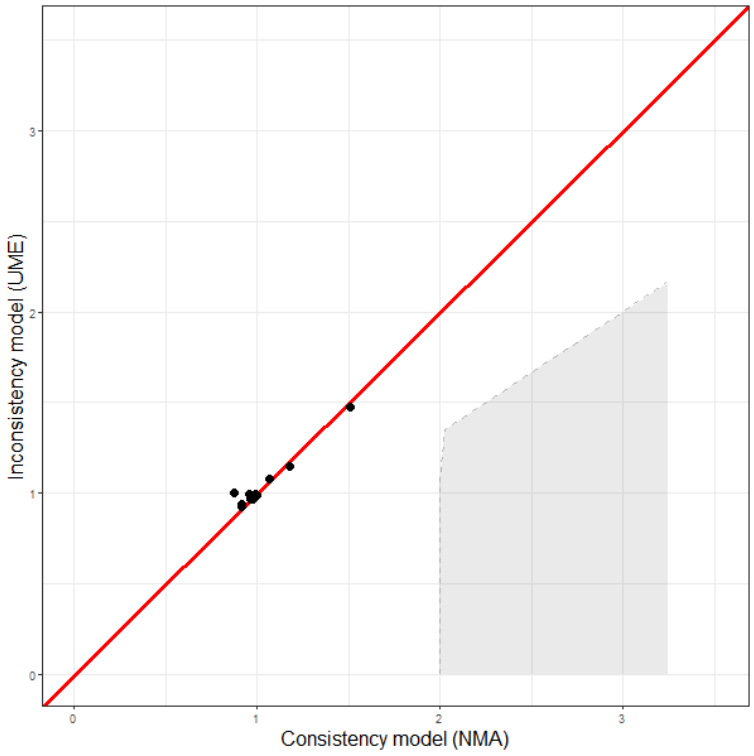
Relative effect models[(a)]	Between study SD (95% CrI)	Meta-regression covariate on baseline lipid level	Deviance information criterion (DIC)	Total residual deviance
NMA Fixed effects	-	-	146.1	95.6
NMA (Random effects)	9.44 (5.47, 16.36)	-	74.2	14.3
Unrelated mean-effects (Random effects)	9.92 (5.61, 17.71)	-	74.5	14.4
Meta-regression (Random effects)	11.35 (6.05, 21.43)	-4.14 (-25.56, 16.36)	68.6	12.1

(a) Number of data points in the NMA and inconsistency models (n=14). Number of data points in the meta-regression model models (n=12).

Figure 4 presents a dev-dev plot, which shows the contributions of each study datapoint to the residual deviance under the random effects UME and NMA models. There is no evidence of inconsistency, as there are no points notably below the line of equality, which would be indicative of data better predicted by the inconsistency model.

Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data.

Figure 6: Contribution of each study datapoint to the residual deviance under the random effects UME and NMA models – percentage change in non-HDL cholesterol at 3-12 months



3.4.4 Sensitivity analyses and subgroup analyses

Within the sensitivity analysis, including studies reporting baseline non-HDL, adding a meta-regression term on baseline non-HDL levels resulted in a model with good statistical fit, but the effect of baseline LDL was again uncertain, -4.14 (95% CrI: -25.56, 16.36), with the interval including zero.

3.5 Absolute change from baseline in non-HDL cholesterol

3.5.1 Network and data

Eight studies[1, 3, 11, 16, 18-21] were identified as reporting outcome data for absolute change from baseline in non-HDL cholesterol. Five treatments were included in the network: placebo (including placebo and/or statin treatment), standard care, ezetimibe, alirocumab, and evolocumab 420mg. Alirocumab and evolocumab 420 mg were modelled as a single fixed class. The network can be seen in Figure 3 and the trial data for each of the studies included in the NMA are presented in Table 11.

Figure 7: Network diagram for absolute change in non-HDL cholesterol

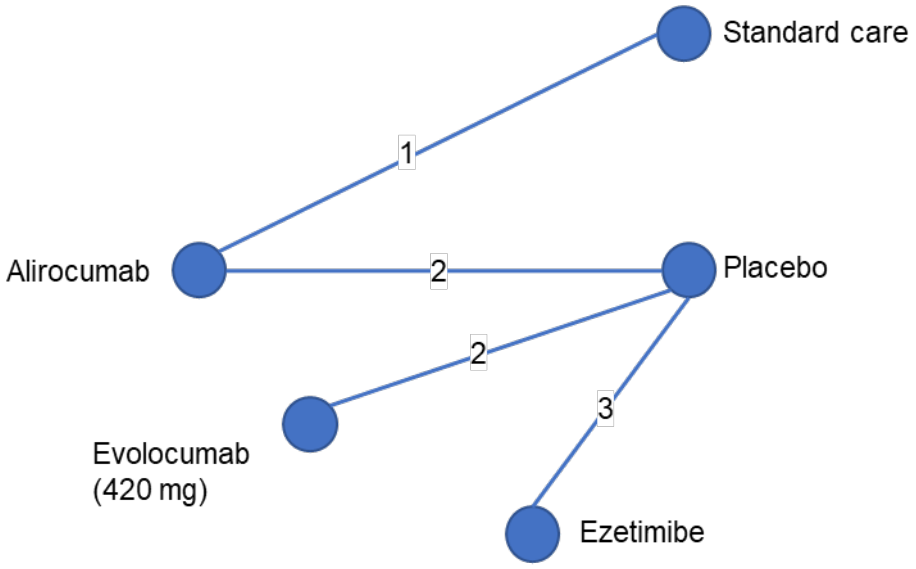


Table 11: Study data for absolute change in non-HDL cholesterol (mmol/litre) at 3-12 months included in the network meta-analysis

Study	Intervention	Comparison	Absolute change LDL-C (mmol/L)	
			Mean difference	SE
Cannon, 2015[3] IMPROVE-IT	Ezetimibe	Placebo	-0.52	0.043
Masuda 2015[16]	Ezetimibe	Placebo	-0.61	0.263
Ran, 2017[21] NSTE-ACS	Ezetimibe	Placebo	-1.06	0.189
Kereiakes, 2015[11] ODYSSEY COMBO I	Alirocumab	Placebo	-1.08	0.144
Raber, 2022[20] PACMAN-AMI	Alirocumab	Placebo	-1.58	0.119
Nicholls, 2016[19] GLAGOV	Evolocumab 420 mg	Placebo	-1.64	0.070
Nicholls, 2022[18] HUYGENS	Evolocumab 420 mg	Placebo	-1.70	0.189
Ako, 2019[1] ODYSSEY J-IVUS	Alirocumab	Standard care	-1.26	0.073

3.5.2 Results of network meta-analysis

Table 12 summarises the results of the pairwise meta-analyses in terms of mean differences generated from studies directly comparing different interventions, together with the results of the NMA (this is from a random effects model, which was chosen on the basis of model fit), in terms of mean differences comparing each available treatment option with placebo/statin.

Table 12: Risk differences for absolute change in non-HDL cholesterol at 3-12 months; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise estimates - mean difference (95% confidence intervals)	NMA random effects model – mean difference (95% credible intervals)	
			Base case model	Model with meta-regression on baseline lipid levels
Standard care	Placebo/ statin	NA	-0.24 (-1.17, 0.70)	-0.17 (-1.33, 1.01)
Ezetimibe		-0.67 (-1.00, -0.33)[a]	-0.71 (-1.23, -0.21)	0.11 (-3.16, 3.42)
Inclisiran		NA	NA	NA
Evolocumab plus ezetimibe		NA	NA	NA
PCSK9i		-1.45 (-1.67, -1.22)[a]	-1.50 (-1.93, -1.08)	-0.71 (-3.78, 2.41)

(a) Random effects model

3.5.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the studies. Moderate heterogeneity was observed for this outcome, with a substantial reduction in residual deviance and DIC seen in the RE NMA model, relative to the FE NMA model. This, together with the moderate between-study SD supports choice of the RE model structure.

An inconsistency model was run and the model fit statistics were as seen in Table 13. The global check for inconsistency, modelling treatment effects independently of each other, indicates that there is little inconsistency in this dataset, with similar residual deviance and DIC in the RE NMA and RE UME models, and no evidence of local inconsistency.

Table 13: Model fit statistics – absolute change in non-HDL cholesterol at 3-12 months

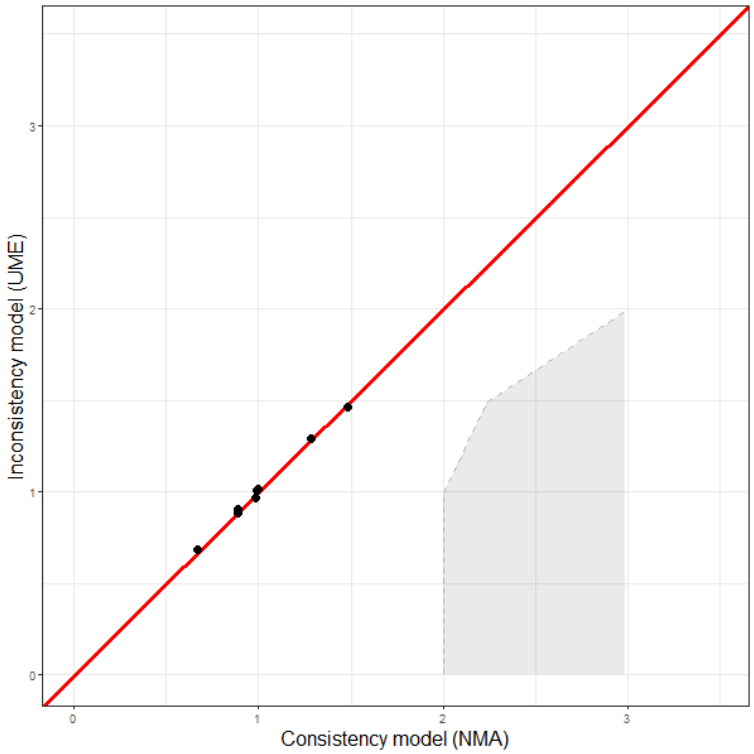
Relative effect models[(a)]	Between study SD (95% CrI)	Meta-regression covariate on baseline lipid level	Deviance information criterion (DIC)	Total residual deviance
NMA Fixed effects	-	-	7.3	24.0
NMA (Random effects)	0.35 (0.11, 0.89)	-	-4.2	8.2
Unrelated mean-effects (Random effects)	0.36 (0.11, 0.90)	-	-4.2	8.2
Meta-regression (Random effects)	0.42 (0.12, 1.22)	-0.22 (-1.10, 0.63)	-4.2	8.0

(a) Number of data points in all models (n=8).

Figure 8 presents a dev-dev plot, which shows the contributions of each study datapoint to the residual deviance under the random effects UME and NMA models. There is no evidence of inconsistency, as there are no points notably below the line of equality, which would be indicative of data better predicted by the inconsistency model.

Taken together, the model fit and dev-dev plots suggest there was little evidence of inconsistency in these data.

Figure 8: Contribution of each study datapoint to the residual deviance under the random effects UME and NMA models – absolute change in non-HDL cholesterol at 3-12 months



3.5.4 Sensitivity analyses and subgroup analyses

Within the sensitivity analysis, including studies reporting baseline non-HDL, adding a meta-regression term on baseline non-HDL levels resulted in a small reduction in total residual deviance, indicating improved model fit, but no change in DIC. The effect of baseline LDL was again both small and uncertain, -0.22 (95% CrI: -1.1, 0.63), with the interval including zero.

4 Risk of bias and indirectness

An overall risk of bias assessment was conducted for the studies and outcomes included in the NMA. Overall risk of bias for each study-outcome was determined by consideration of the independent domains of bias: selection bias, performance and detection bias, attrition bias, and outcome reporting bias. For each study, if there was no risk of bias in any domain, the risk of bias was given a rating of 'low risk of bias'. If there was risk of bias in just 1 domain, the risk of bias rated as 'some concerns', but if there was risk of bias in 2 or more domains the risk of bias was given a 'high risk of bias' rating.

As seen in Table 14, the majority of the relevant evidence for the NMAs had a low risk of bias. For studies where there were some concerns or high risk of bias, this was most frequently due to concerns about selection bias, for example, imbalance in baseline characteristics between groups, or insufficient information about randomisation procedures. Full risk of bias details can be found in the evidence tables and GRADE tables for the pairwise meta-analysis in evidence review D.

Table 14: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome

Study	% change LDL-C	Absolute change LDL-C	% change non-HDL-C	Absolute change non-HDL-C
Ako, 2019[1] ODYSSEY J-IVUS	Some concerns	Some concerns	Some concerns	Some concerns
Arimura, 2012[2]	-	Some concerns	-	-
Cannon, 2015[4] ODYSSEY COMBO II	Some concerns	Some concerns	-	Some concerns
Cannon, 2015[3] IMPROVE-IT	Low	Some concerns	Low	-
Gao, 2021[5]	-	Some concerns	-	-
Giugliano, 2012[6] LAPLACE-TIMI 57a	Low	Low	Low	-
Giugliano, 2012[6] LAPLACE-TIMI 57	Low	Low	Low	-
Han, 2020[7] ODYSSEY EAST	Low	-	Low	-
Hao, 2022[8]	-	High	-	-
Hougaard, 2017[9]	Low	Low	-	-
Joshi, 2017[10]	Some concerns	Some concerns	-	-
Kereiakes, 2015[11] ODYSSEY COMBO I	Low	Low	Low	Low
Koh, 2018[12] ODYSSEY KT	Low	Low	Low	-
Kouvelos, 2013[13]	-	Low	-	-
Luo 2014[14]	-	Some concerns	-	-
Luo 2016[15]	-	Some concerns	-	-
Masuda 2015[16]	High	High	High	High

Study	% change LDL-C	Absolute change LDL-C	% change non-HDL-C	Absolute change non-HDL-C
McCullough, 2018[17] ODYSSEY-LONG TERM	Some concerns	-	Some concerns	-
Nicholls, 2016[19] GLAGOV	-	Some concerns	-	Some concerns
Nicholls, 2022[18] HUYGENS	-	Low	-	Low
Raber, 2022[20] PACMAN-AMI	-	Low	-	Low
Ran, 2017[21] NSTE-ACS	Some concerns	Some concerns	-	Some concerns
Ray, 2019[22] ODYSSEY DM-DYSLIPIDEMIA	Some concerns	-	Some concerns	-
Ray, 2019[22] ODYSSEY DM-INSULIN	Low	-	Low	-
Ray, 2020[23] ORION-10	Low	Low	Some concerns	-
Ray, 2020[23] ORION-11	Low	Low	Some concerns	-
Rehberger, 2022[24]	-	High	-	-
Ren, 2017[25]	-	Some concerns	-	-
Sabatine, 2017[26] FOURIER	Low	Low	Low	-
Schwartz, 2018[27] ODYSSEY OUTCOMES	-	Some concerns	-	-
Tsujita, 2015[28] PRECISE-IVUS	Low	Low	-	-
Ueda, 2017[29] ZIPANGU	-	Some concerns	-	-
Wang 2016[31]	-	High	-	-
Wang 2017[30]	-	High	-	-
West 2011/2011a[32, 33]	-	Low	-	-

Key: colour shading represents level of risk (green = low; orange = some concerns; red = high).

An assessment of the directness of the evidence was also conducted for the studies and outcomes included in the NMA. Overall directness for each study-outcome was determined by consideration of how well the population, intervention, comparison, and outcomes matched the review protocol.

As seen in Table 15, the majority of the relevant evidence for the NMAs had no indirectness. For one study there was serious indirectness due to significant imbalance in the statin dose between the treatment groups, while some studies had minor indirectness due to using a weighted mean over a treatment period greater than the protocol specified 12 months. In other studies, insufficient details were provided to assess directness. Full details can be found in the evidence tables and GRADE tables for the pairwise meta-analysis.

Table 15: Pairwise meta-analysis indirectness assessment per NMA outcome

Study	% change LDL-C	Absolute change LDL-C	% change non-HDL-C	Absolute change non-HDL-C
Ako, 2019[1] ODYSSEY J-IVUS	No indirectness	No indirectness	No indirectness	No indirectness
Arimura, 2012[2]	-	No indirectness	-	-
Cannon, 2015[4] ODYSSEY COMBO II	Serious	Serious	-	Serious
Cannon, 2015[3] IMPROVE-IT	No indirectness	-	No indirectness	-
Gao, 2021[5]		No indirectness	-	-
Giugliano, 2012[6] LAPLACE-TIMI 57a	Unclear	Unclear	-	Unclear
Giugliano, 2012[6] LAPLACE-TIMI 57	Unclear	Unclear	-	Unclear
Han, 2020[7] ODYSSEY EAST	-	No indirectness	-	No indirectness
Hao, 2022[8]	-	No indirectness	-	-
Hougaard, 2017[9]	No indirectness	No indirectness	-	-
Joshi, 2017[10]	No indirectness	No indirectness	-	-
Kereiakes, 2015[11] ODYSSEY COMBO I	No indirectness	No indirectness	No indirectness	No indirectness
Koh, 2018[12] ODYSSEY KT	No indirectness	No indirectness	No indirectness	-
Kouvelos, 2013[13]	-	No indirectness	-	-
Luo 2014[14]	-	No indirectness	-	-
Luo 2016[15]	-	No indirectness	-	-
Masuda 2015[16]	No indirectness	No indirectness	No indirectness	No indirectness
McCullough, 2018[17] ODYSSEY-LONG TERM	No indirectness	-	No indirectness	-
Nicholls, 2016[19] GLAGOV	-	Minor indirectness	-	Minor indirectness
Nicholls, 2022[18] HUYGENS	-	Unclear	-	Unclear
Raber, 2022[20] PACMAN-AMI	-	No indirectness	-	No indirectness
Ran, 2017[21] NSTE-ACS	No indirectness	No indirectness	-	No indirectness
Ray, 2019[22] ODYSSEY DM-DYSLIPIDEMIA	No indirectness	-	No indirectness	-

Study	% change LDL-C	Absolute change LDL-C	% change non-HDL-C	Absolute change non-HDL-C
Ray, 2019[22] ODYSSEY DM-INSULIN	No indirectness	-	No indirectness	-
Ray, 2020[23] ORION-10	Minor indirectness	Minor indirectness	Minor indirectness	-
Ray, 2020[23] ORION-11	Minor indirectness	Minor indirectness	Minor indirectness	-
Rehberger, 2022[24]		Unclear		
Ren, 2017[25]	-	No indirectness	-	-
Sabatine, 2017[26] FOURIER	No indirectness	No indirectness	No indirectness	-
Schwartz, 2018[27] ODYSSEY OUTCOMES	No indirectness	No indirectness	-	-
Tsujita, 2015[28] PRECISE-IVUS	No indirectness	No indirectness	-	-
Ueda, 2017[29] ZIPANGU	-	Unclear	-	-
Wang 2016[31]	-	No indirectness	-	-
Wang 2017[30]	-	No indirectness	-	-
West 2011/2011a[32, 33]	-	No indirectness	-	-

Key: colour shading represents level of indirectness (green = none; yellow = minor indirectness; orange = serious indirectness; grey = unclear/could not be assessed).

5 Evidence summary

The order of efficacy for reducing cholesterol levels showed PCSK9i to achieve the largest reduction, with inclisiran achieving similar but slightly lower reductions, and ezetimibe achieving clinical important reductions that were considerably lower than that of the injectable therapies. This was true for all analysed outcomes, except percentage change in non-HDL because inclisiran was not present in this network.

The results for all outcomes were heterogeneous when using fixed-effects models, so the results were analysed using random effects models, which showed no inconsistency. The majority of the evidence was directly applicable to the review protocol.

In the percentage change in LDL-C and absolute change in non-HDL-C networks most of the evidence was at low risk of bias. However, in the absolute change in LDL-C and percentage change in non-HDL-C networks, the majority of the evidence was rated as having some concerns or high risk of bias.

For absolute and percentage change in LDL-C, there was little uncertainty for most of the estimates for active treatments compared to placebo, except for inclisiran in the percentage change network and evolocumab plus ezetimibe in the absolute change network. For absolute and percentage change in non-HDL-C there was uncertainty in the network for all interventions.

5.1 Modified GRADE assessments

Table 16: Modified GRADE table for NMA data on change from baseline in cholesterol

No. of studies	Study design	Sample size	Effect estimates	Risk of bias	Indirectness	Inconsistency	Quality[1]
Percentage change from baseline in LDL cholesterol							
18	RCT	49,429	See **Table 3**	No serious	No serious	No serious	High
Absolute change from baseline in LDL cholesterol							
30	RCT	68,262	See **Table 6Table 3**	Serious[2]	No serious	No serious	Moderate
Percentage change from baseline in non-HDL cholesterol							
13	RCT	35,190	See **Table 9**	No serious	No serious	No serious	High
Absolute change from baseline in non-HDL cholesterol							
8	RCT	14,744	See **Table 12**	Serious[2]	No serious	No serious	Moderate

[1] Imprecision was not included in ths GRADE assessment but was considered during committee discussions of the evidence, taking into account 95% confidence intervals around the point estimate of the effect, any relevant MIDs, committee expertise and the effect of a single intervention based on multiple outcomes.
[2] >50% of studies or participants in the NMA judged to have some concerns or high risk of bias. Quality downgraded 1 level.

6 Discussion

In the networks, the placebo group was acknowledged to involve statin use, and to include studies using statin as the comparator without a placebo control. Consideration was therefore given to pooling the placebo and standard care groups, as was done for the pairwise analyses. However, although we appear to be estimating an extra parameter in 'standard care', because the networks connect and the model fit is reasonable, this is justified statistically. These models can be viewed as estimating the effect of the treatment relative to a suitable reference, either placebo or standard care. Additionally, only two treatments, alirocumab and evolocumab, were compared with standard care in trials, in all datasets there was also trial evidence on their effect compared with placebo and inconsistency models indicated no inconsistency.

In considering whether to prefer the percentage or absolute change models to inform health economic modelling, these models support the use of the percentage change outcome. Although the absolute data allows more studies and one additional treatment to be included, the conclusions on treatments' relative effectiveness are unchanged. However, regarding heterogeneity, the between-study SD was 3.91 SD units (7.287/1.866), and 5.11 SD units (0.1892/0.03699) for the percentage and absolute models, respectively. This means that the percentage data were estimated to be more homogeneous than the absolute data and so are preferred.

Regarding the meta-regression analyses, the large credible intervals around the meta-regression term for baseline severity, and the fact that they include zero, mean that it is not possible to determine if there was an effect of baseline lipid level for these data. Given the size of the interval, what is estimated to be a negative effect of baseline severity for non-HDL could feasibly be a positive effect, so mean coefficients from these models could lead to unstable inferences. Furthermore, the projections extend beyond the data modelled – the highest baseline lipid levels reported and modelled were 4.2 mmol/litre, whilst the projection goes up to 6 mmol/litre.

For full discussion and conclusions see the committee's discussion of the evidence in the evidence review. For linked economic modelling see the separate economic analysis report.

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Appendices

Appendix A: WinBUGS Code

All codes are derived from Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011; last updated September 2016 (available from http://www.nicedsu.org.uk). This work should be cited whenever the code is used whether in its standard form or adapted.

A.1 NMA of contrast between arms, normal likelihood, FE on study, FE for treatment class

```
# Normal likelihood, identity link

# Trial-level data given as treatment differences

# Fixed effects model for multi-arm trials


## Updated with a class effect on d
model{                          # *** PROGRAM STARTS
for(i in 1:ns2) {                # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }


for(i in (ns2+1):(ns2+ns3)) {       # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
```

```
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                    }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }

for(i in 1:(ns2+ns3)){              #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {           #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]      # set precisions
      delta[i,k] <- d[t[i,k]] - d[t[i,1]]
    }
 }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment

## FIXED CLASS MODEL
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt){  d[k] <- classD }
classD ~ dnorm(0, 0.0001)

## Dummy vars
dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]
}                              # *** PROGRAM ENDS
```

A.2 NMA of contrast between arms, normal likelihood, RE on study, FE for treatment class

```
# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Random effects model for multi-arm trials
## Updated with a class effect on d
model{                         # *** PROGRAM STARTS
for(i in 1:ns2) {               # LOOP THROUGH 2-ARM STUDIES
```

```
    y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
    resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
    for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
        for (j in 1:(na[i]-1)) {
            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
         }
      }
    Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
    y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
    for (k in 1:(na[i]-1)){  # multiply vector & matrix
        ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                    }
    resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
for(i in 1:(ns2+ns3)){                    #   LOOP THROUGH ALL STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)   # calculate variances
        prec[i,k] <- 1/var[i,k]      # set precisions
      }
    for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of random effects distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of random effects distributions (with multi-arm trial correction)
```

```
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment

## FIXED CLASS MODEL
## (assuming that trts 2 to (nt-nclass) are not in a class
## and trts nclass to nt are the same class)
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt){  d[k] <- classD }
classD ~ dnorm(0, 0.0001)

sd ~ dunif(0,upperSD)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]

}                              # *** PROGRAM ENDS
```

A.3 NMA of contrast between arms, normal likelihood, FE on study, RE for treatment class

```
## Updated with a class effect on d

# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Fixed effects model for multi-arm trials
model{                         # *** PROGRAM STARTS
```

```
for(i in 1:ns2) {                    # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }

for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                    }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }

for(i in 1:(ns2+ns3)){               #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]      # set precisions
      delta[i,k] <- d[t[i,k]] - d[t[i,1]]
    }
 }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
```

```
## RE on CLASS MODEL
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt){  d[k] ~ dnorm(classD, tauD) }
classD ~ dnorm(0, 0.0001)
tauD <- pow(sdD,-2)
sdD ~ dunif(0,upperSD) # Vary limits if necessary

## Dummy vars
dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]
}                              # *** PROGRAM ENDS
```

A.4 NMA of contrast between arms, normal likelihood, RE on study, RE for treatment class

```
# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Random effects model for multi-arm trials
## Updated with a class effect on d (with RE)
model{                         # *** PROGRAM STARTS
for(i in 1:ns2) {               # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }
for(i in (ns2+1):(ns2+ns3)) {       # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
```

```
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                  }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }
for(i in 1:(ns2+ns3)){                  #   LOOP THROUGH ALL STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
   for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
    }
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of random effects distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of random effects distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
 }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment

## RE on CLASS MODEL
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt){  d[k] ~ dnorm(classD, tauD) }
```

```
classD ~ dnorm(0, 0.0001)
tauD <- pow(sdD,-2)
sdD ~ dunif(0,upperSD) # Vary limits if necessary

sd ~ dunif(0,upperSD)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]

}                              # *** PROGRAM ENDS
```

A.5 NMA of contrast between arms, normal likelihood, FE on study, FE treatment class with additional parameter for high-dose evolocumab (420mg)

```
## Updated with a class effect on d

# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Fixed effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns2) {                 # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }

for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
```

```
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                  }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }

for(i in 1:(ns2+ns3)){              #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)
      prec[i,k] <- 1/var[i,k]      # set precisions
      delta[i,k] <- d[t[i,k]] - d[t[i,1]]
    }
 }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment

## FIXED CLASS MODEL
## (assuming that trts 2 to (nt-nclass) are not in a class
## and trts nt-nclass to nt-1 are a class,
## with treat nt is high dose Evo)
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt-1){  d[k] <- classD }
d[nt]<- classD + evohigh
classD ~ dnorm(0, 0.0001)
evohigh ~ dnorm(0, 0.0001)

## Dummy vars
dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]
```

```
}                              # *** PROGRAM ENDS
```

A.6 NMA of contrast between arms, normal likelihood, RE on study, FE treatment class with additional parameter for high-dose evolocumab (420mg)

```
## Updated with a class effect on d


# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Random effects model for multi-arm trials
model{                         # *** PROGRAM STARTS
for(i in 1:ns2) {               # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }
for(i in (ns2+1):(ns2+ns3)) {       # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                  }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }
for(i in 1:(ns2+ns3)){                #   LOOP THROUGH ALL STUDIES
```

```
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
   for (k in 2:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
    }
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of random effects distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of random effects distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
 }
totresdev <- sum(resdev[])           #Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment

## FIXED CLASS MODEL
## (assuming that trts 2 to (nt-nclass) are not in a class
## and trts nt-nclass to nt-1 are a class,
## with treat nt is high dose Evo)
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt-1){  d[k] <- classD }
d[nt]<- classD + evohigh
classD ~ dnorm(0, 0.0001)
evohigh ~ dnorm(0, 0.0001)

sd ~ dunif(0,upperSD)     # vague prior for between-trial SD
```

```
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]

}                              # *** PROGRAM ENDS
```

A.7 NMA of contrast between arms, normal likelihood, RE on study, FE for treatment class with meta-regression on baseline lipid level

```
# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Random effects model for multi-arm trials
model{                         # *** PROGRAM STARTS

for(i in 1:ns2) {                  # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]

 }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
          #V[i] <- pow(se[i,1],2)
   for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
   y[i,2:3] ~ dmnorm(delta[i,2:3],Omega[i,1:2,1:2])
#Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
```

```
        ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                    }
    resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }

for(i in 1:(ns2+ns3)){                  #   LOOP THROUGH ALL STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
          #V[i] <- pow(se[i,1], 2)
#pooled baseline lipid
base[i]<- (base_m[i,1]+base_m[i,2])/2

for (k in 2:na[i]) {             #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)   # calculate variances WAS se[i,k]
        prec[i,k] <- 1/var[i,k]      # set precisions
      }
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of random effects distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + (beta[t[i,k]] - beta[t[i,1]])*base[i] + sw[i,k]
# precision of random effects distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - (d[t[i,k]] - d[t[i,1]] + (beta[t[i,k]] - beta[t[i,1]])*base[i]))
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }

  }
totresdev <- sum(resdev[])           #Total Residual Deviance
```

```
## Trt eff with class effect
d[1]<-0       # treatment effect is zero for reference treatment
sd ~ dunif(0,upperSD)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

## FIXED CLASS MODEL
## (assuming that trts 1-3 are not in a class and trts 4-7 are the same class)
for (k in 2:nt-nclass){  d[k] ~ dnorm(0,.0001) }
for (k in nt-nclass+1:nt){  d[k] <- classD }
classD ~ dnorm(0, 0.0001)

###Covariate Coefficients. All active equal.
beta[1]<-0
beta[2]<-0
for (k in 3:nt){  beta[k] <- B }
B ~ dnorm(0, 0.0001)

dv1 <- base_sd[1,1]
}                              # *** PROGRAM ENDS
```

A.8 Unrelated mean-effects (UME or inconsistency) model of contrast between arms, normal likelihood, RE on study

```
## UME

# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns2) {                 # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
```

```
  }
for(i in 1:(ns2+ns3)){                    #   LOOP THROUGH ALL STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    for (k in 2:na[i]) {             #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)   # calculate variances
        prec[i,k] <- 1/var[i,k]      # set precisions
      }

 for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific mean difference random effects distribution
        delta[i,k] ~ dnorm(d[tc[i,1],tc[i,k]] ,tau)
      }
  }
for(i in (ns2+1):(ns2+ns3)) {        # LOOP THROUGH THREE-ARM STUDIES
    for (k in 1:(na[i]-1)) {    # set variance-covariance matrix
        for (j in 1:(na[i]-1)) {
            Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
          }
      }
    Omega[i,1:2,1:2] <- inverse(Sigma[i,,])  #Precision matrix
# multivariate normal likelihood for 3-arm trials
    y[i,2:3] ~ dmnorm(delta[i,2:3],Omega[i,1:2,1:2])
#Deviance contribution for trial i
    for (k in 1:(na[i]-1)){  # multiply vector & matrix
        ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
        z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
                        }
    resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
  }
```

```
totresdev <- sum(resdev[])          #Total Residual Deviance

for(i in 1:(ns2+ns3)){
                    for (k in 1:na[i]) {  tc[i,k] <- class[t[i,k]]                    }
                    }

# treatment effect is zero for control arm
for (c in 1:nt) {           d[c,c] <- 0 }
# vague priors for treatment effects
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  {
                            d[c,k] ~ dnorm(0,.00001)
                            d[k,c] <- -d[c,k]
                            }
 }

sd ~ dunif(0,upperSD)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
dv1 <- base_m[1,1]
dv2 <- base_sd[1,1]
dv3 <- V[1]

for (n in 1:nt-nclass){
          class[n] <- n
          }
for (n in nt-nclass+1:nt){
          class[n] <- nt-nclass+1
          }



}                           # *** PROGRAM ENDS
```