Pharmacological Interventions for Familial Hypercholesterolaemia in Children and Adolescents: An Exploratory Evaluation Using Advanced Hierarchical Network Meta-Analysis Techniques

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Objectives

- To evaluate and compare the use of three network meta-analysis (NMA) techniques, using efficacy data from a systematic literature review (SLR) of pharmacological interventions for familial hypercholesterolaemia (FH) in children and adolescents:[1]
  1. Standard NMA
  2. Hierarchical NMA without dose constraints
  3. Hierarchical NMA with dose constraints

Introduction

- Hierarchical NMA is becoming increasingly popular and recognised by health technology assessment bodies. It is an extension of standard NMA, in which similar treatments can be grouped into classes, and assumed to be exchangeable.[2,3]

- Using this model, both treatment-level and class-level effects can be estimated and dose constraints can be applied to further reduce the uncertainty of the NMA output. In hierarchical models, within-class treatment equivalence is modelled by normally distributing each treatment around a class mean and standard deviation. Dose constraints are applied using indicator functions, so that higher doses of a drug must have equivalent or increased efficacy compared with lower doses of the same drug.

- To explore the utility of hierarchical NMA, we used the results of an SLR of randomised controlled trial (RCT) evidence for pharmacological interventions for FH in children and adolescents ≤18 years (see poster PCV16).[1]

- FH is a rare genetic disorder typically diagnosed in childhood and characterised by abnormally elevated levels of low-density lipoprotein cholesterol (LDL-C) and an increased risk of cardiovascular disease.

- Treatment of FH comprises a number of therapeutic classes including statins, bile acid sequestrants (BAS) and ezetimibe and aims to lower serum levels of LDL-C. Comparison of these treatments was therefore amenable to analysis using hierarchical NMA techniques.

Methods

- Full details of the SLR have been reported elsewhere.[1] Overall, 13 unique RCTs were identified which, between them, reported on all three classes of pharmacological intervention.

- A feasibility assessment was conducted to determine which studies adequately reported the outcomes of interest (percentage change from baseline in LDL-C and total cholesterol [TC]) and which studies were eligible for inclusion in the networks.

  – The outcomes of interest were adequately reported by seven studies, six of which could form a connected network containing the three treatment classes (Figure 1 and Figure 2).

  – To increase the available evidence base, multiple timepoints from the same study arm, which in some cases reported different treatment doses, were extracted from the included studies (Figure 1). The outcome timepoint in the network therefore ranged from 8 to 26 weeks.

- The standard NMA was conducted according to Decision Support Unit guidelines from the National Institute of Health and Care Excellence.[4] The hierarchical NMAs were conducted according to the methods described in Owen et al. 2015.[3]

- All three NMA methods were implemented in WinBUGS, and both fixed-effect (FE) and random-effects (RE) models were run. The R (version 3.3.0) package "coda" was used as a diagnostic tool to assess convergence and autocorrelation. Model fit was assessed using the deviance information criterion (DIC) and the total residual deviance.
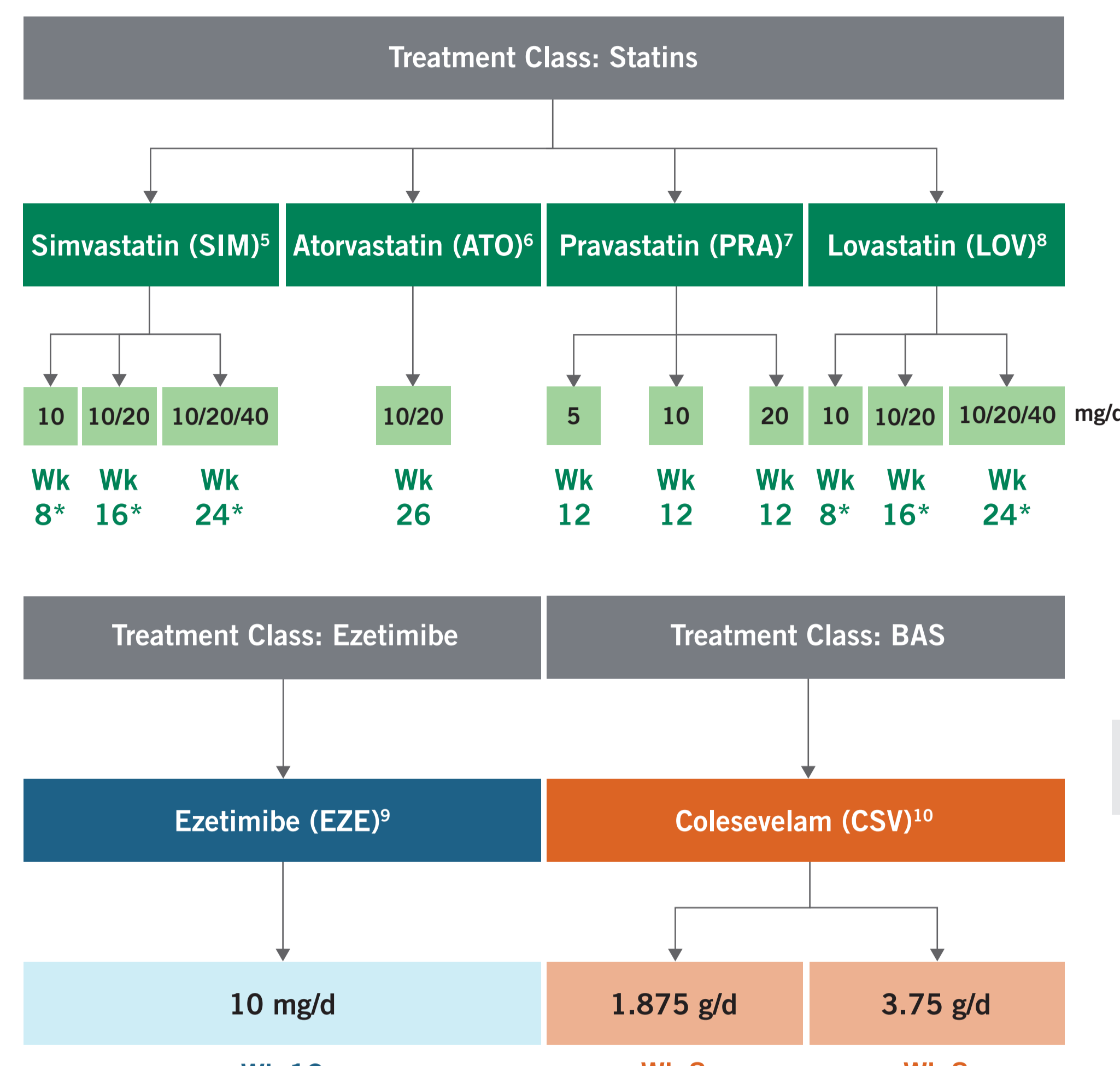
Results

- For both percentage change from baseline in LDL-C and TC, model fit was similar across each model type, as observed by the small range in DIC and total residual deviance (Table 1). The RE hierarchical NMA with dose constraints for percentage change from baseline in TC would not run due to high autocorrelation.

- For percentage change from baseline in LDL-C, all three NMA methods ranked atorvastatin as the most effective treatment. Placebo ranked the least effective treatment in all of the models for both outcomes. Both the hierarchical model with and without dose constraints ranked statins as the most effective class (data not shown).

- For percentage change from baseline in LDL-C, the point estimates for each treatment comparison versus placebo were relatively consistent across the three methods (Figure 3).

Discussion

- The results of the analyses were similar across all three methods. Class-level comparisons were also consistent across both hierarchical methodologies. Additionally, there was little difference in terms of model fit; for percentage change in LDL-C and TC, using hierarchical NMA with

or without dose constraints lowered the DIC but tended to marginally increase the total residual deviance compared to standard NMA.

- The main limitation of this analysis was the small evidence base. Only one study was available to inform each treatment comparison. Additionally, both the ezetimibe and BAS classes were informed by single studies. To increase the size of the network, multiple timepoints from the same study were extracted in several cases. This increased the evidence base but also increased the heterogeneity in terms of outcome timepoint.

- The majority of trials included were performed versus placebo, limiting network complexity. The benefits of using hierarchical NMA may have been more evident if the network was more complex; for example, if it included head-to-head trials between classes.

- Although dose constraints minimise the uncertainty of effect estimates, they should be used with caution. Applying dose constraints without sufficient clinical validation may lead to unrealistic results.

- Further work could focus on comparing these techniques in terms of network inconsistency and heterogeneity, which was not formally assessed here.

Figure 1 | Treatment class hierarchy

The first level of the model describes the class, the second level describes the individual treatments within each class and the third level describes the individual doses within each class. Wk: weeks.

*Multiple results extracted from a single study of simvastatin, and a single study of lovastatin. Patients started on 10 mg/day simvastatin or lovastatin up until Week 8. The dose was then raised to 20 mg/day until Week 16, and then up to 40 mg/day until Week 24.

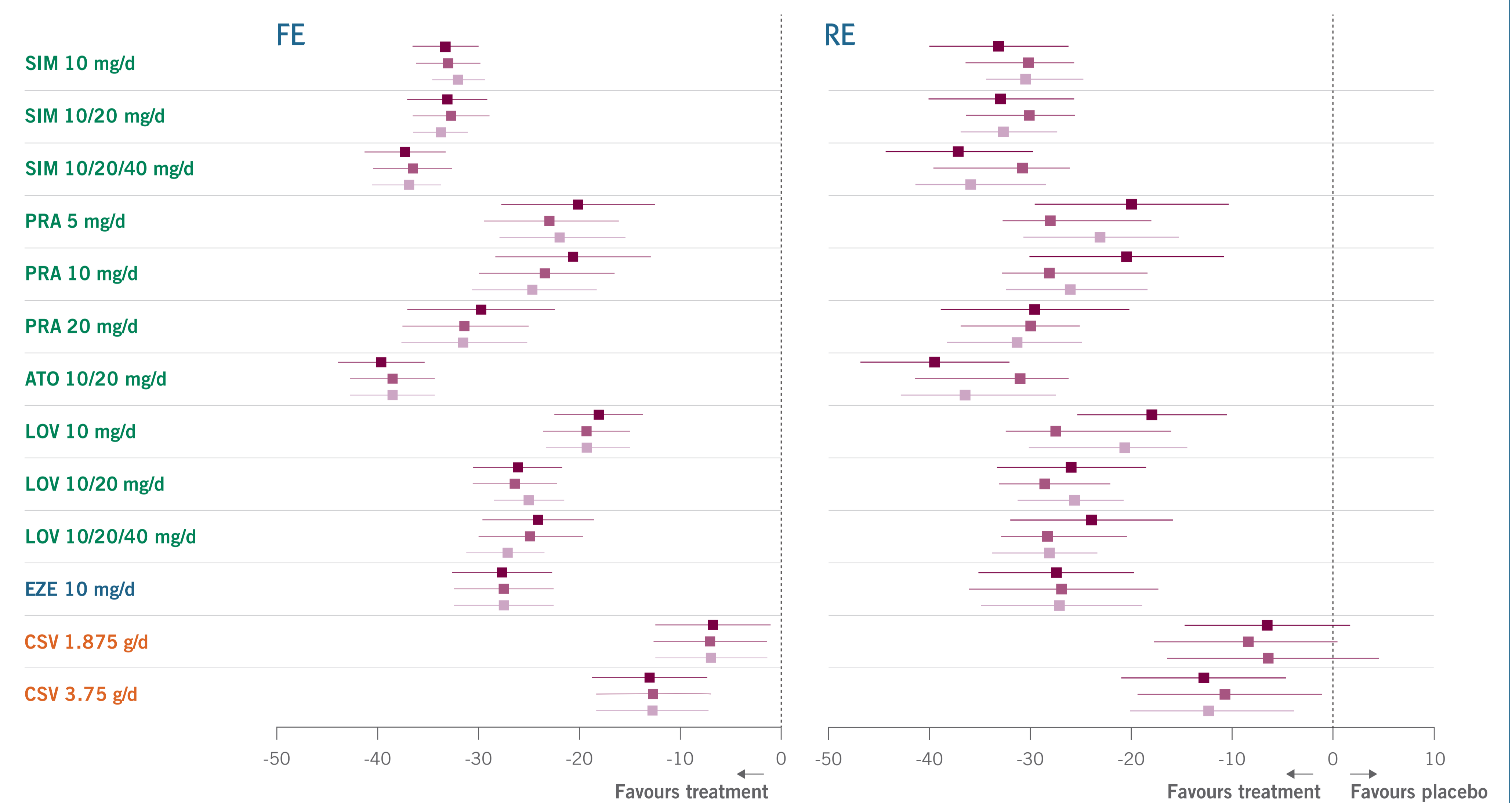### Figure 2 | Network diagram of included studies
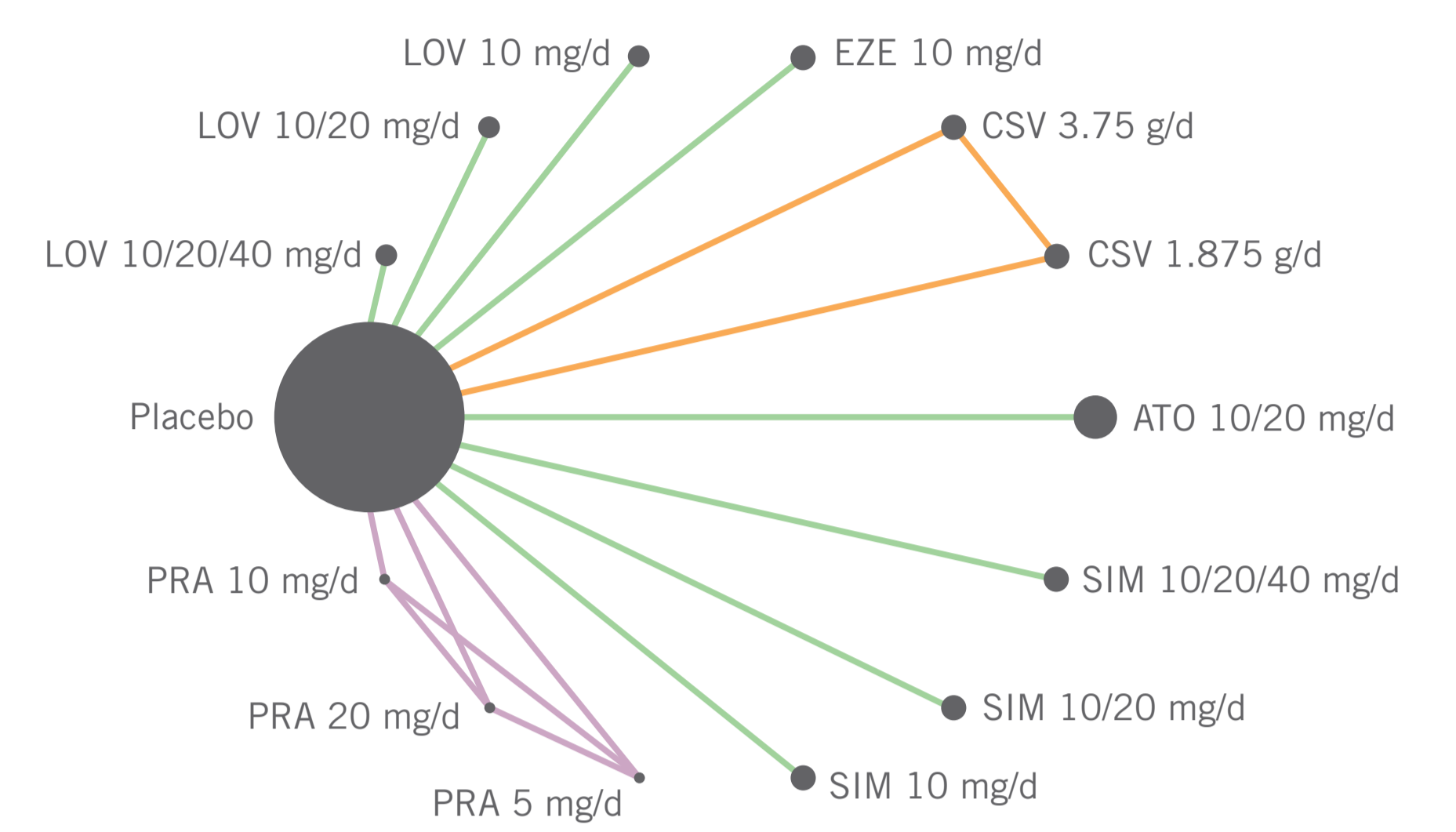
Node size represents total treatment population size. Line colours represent number of trial arms with green, orange and pink representing 2-, 3- and 4-arm trials, respectively.

Table 1 | Model fit diagnostics

NMA	Criteria	LDL-C		TC	
		FE	RE	FE	RE
Standard	Total residual deviance	22.96	22.98	22.97	22.98
	DIC	112.56	112.60	99.89	99.90
Hierarchical without dose constraints	Total residual deviance	23.42	24.57	23.57	23.74
	DIC	111.93	112.56	99.41	99.08
Hierarchical with dose constraints	Total residual deviance	23.32	22.91	24.58	NA
	DIC	109.52	112.11	97.71	NA

Total residual deviance values that lie close to the actual number of data points (in this analysis; 23) and lower DIC values are indicative of a better model fit.

Figure 3 | Forest plots of the difference in percentage change in LDL-C for individual treatments versus placebo

The results of the standard NMA, hierarchical NMA without dose constraints and hierarchical NMA with dose constraints are plotted sequentially for each individual treatment vs. placebo on the same plots.

Conclusions

- Hierarchical NMA can be used to make both treatment-level and class-level comparisons. This method is useful for a large evidence base, when treatments can be clearly categorised into several classes. When networks are small and contain limited data for each class, hierarchical NMA produces a model fit and treatment effect estimates that are very similar to that of a standard NMA.

References

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