**Comparative Effectiveness of Statins on Non-HDL Cholesterol by Type and Intensity in People with Diabetes and at Risk of Cardiovascular Disease: Systematic Review and Network Meta-Analysis**

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**What is already known on this topic**

* In people with diabetes, statins are the cornerstone of primary and secondary prevention of cardiovascular disease (CVD) by lowering plasma levels of low-density lipoprotein cholesterol (LDL-C); however evidence about the comparative effectiveness of statins on non–high-density lipoprotein cholesterol (non-HDL-C) is unknown.
* Non-HDL-C is thought to be more strongly associated with CVD risk than LDL-C in statin users, and therefore may be a better tool for cardiovascular risk and treatment assessments than LDL-C.
* The National Institute for Health and Care Excellence guidelines for adults with diabetes were updated in April 2021, and they now recommend that non-HDL-C replace LDL-C as the primary target for CVD risk reduction when using lipid-lowering treatment.

**What this study adds**

* This network meta-analysis of 42 trials randomizing 20,193 adults, evaluated the non-HDL-C reduction performance of seven statins, compared with placebo.
* Rosuvastatin administered at moderate and high intensity, and Simvastatin and Atorvastatin administered at high intensity were the most effective treatments in patients with diabetes, leading to between a 2.20 to 2.31 mmol/l reduction in non-HDL-C over 12 weeks.
* In patients at high-risk of major cardiovascular events (secondary prevention), Atorvastatin administered at high intensity showed greatest non-HDL-C lowering: ~2.0 mmol/L.
* Simvastatin and Rosuvastatin delivered at a high intensity were the most significant treatment options in lowering LDL-C with between 1.76 to 1.93 mmol/L reductions.
* These findings can guide clinicians’ decision making and supportpolicy guidelines for lipid management using non-HDL-C as a primary target in patients with diabetes.

**Abstract**

**Objective:** To compare the efficacy of different statin therapies by intensity for prevention of cardiovascular disease (CVD) in people with diabetes according to non-high-density lipoprotein cholesterol (non-HDL-C).

**Design:** Systematic review and network meta-analysis.

**Data Sources:** Searches in MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE until December 2021.

**Review Methods:** Randomised controlled trials comparing different type(s) and intensity of statins including placebo in adults with diabetes mellitus (type 1 or 2) were included.

**Main Outcome Measure:** Primary outcome was non-HDL-C, calculated using total cholesterol and high-density lipoprotein cholesterol measures. Secondary outcomes include low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), 3-point major cardiovascular events (MACE) (non-fatal stroke, non-fatal myocardial infarction, and cardiovascular related death) and discontinuations due to adverse events.

**Data Synthesis:** A Bayesian network meta-analysis of statin intensity (low, moderate, or high) using random-effects evaluated treatment effect on non-HDL-C through mean difference and 95% credible intervals. Subgroup analysis of patients at greater risk of MACE was compared with patients at low/moderate risk. The Confidence In Network Meta-Analysis (CINeMA) framework was applied to ensure the certainty of evidence.

**Results:** Forty-two trials randomizing 20,193 adults of which 11,698 were included in the meta-analysis. Compared to placebo, the greatest reductions in non-HDL-C were observed in Rosuvastatin at high (-2.31 mmol/L, 95% credible interval: -3.39 to -1.21) and moderate intensities (-2.27 mmol/L, -3.00 to -1.49), and Simvastatin (-2.26 mmol/L, -2.99 to -1.51) and Atorvastatin (-2.20 mmol/L, -2.69 to -1.70) at high intensity. Atorvastatin and Simvastatin at any intensity and Pravastatin at low intensity were also effective at reducing non-HDL-C. In 4,670 patients at greater risk of a MACE, Atorvastatin at high intensity was best ranked (-1.98 mmol/L, -4.16 to 0.26, surface under the cumulated ranking curve: 64%) in terms of non-HDL-C. Simvastatin (-1.93, -2.63 to -1.21 mmol/L) and Rosuvastatin (-1.76, -2.37 to -1.15 mmol/L) delivered at a high intensity level were the most significant treatment options for reducing LDL-C. Atorvastatin (-2.21, -2.62 to -1.74 mmol/L), Rosuvastatin (-2.18, -3.19 to -1.20 mmol/L) and Simvastatin (-2.20, -2.96 to -1.42 mmol/L) delivered at a high intensity level were the most significant treatment options for reducing TC. There was a significant reduction in non-fatal myocardial infarction for Atorvastatin delivered at moderate intensity when compared with placebo (RR=0.57, 95% CI: 0.43 to 0.76, n=4 studies). No significant differences were found for discontinuations, non-fatal stroke and cardiovascular deaths.

**Conclusions:** This network meta-analysis indicates that Rosuvastatin at moderate or high intensity and Simvastatin and Atorvastatin at high intensity were most effective at moderately lowering non-HDL-C in patients with diabetes. Given the potential improvement in accuracy in predicting CVD by means of the non-HDL-C target, our findings serve as a convenient guidance on which statin types and intensities are most effective by reducing non-HDL-C in patients with diabetes.

**Systematic Review Registration:** PROSPERO CRD42021258819.

**Introduction**

Type 2 diabetes is estimated to affect 380 million people worldwide by 2025 1 2, and patients with type 2 diabetes are at increased risk of cardiovascular diseases (CVDs), which are the leading cause of death globally, taking an estimate 17.9 million lives each year 3 4.

Lipid-modifying therapy such as statins are considered the cornerstone of primary and secondary prevention of CVD by helping to lower the level of low-density lipoprotein cholesterol (LDL-C) in the blood 5. They have been found to be the most effective agents in reducing the risk of coronary heart disease (CHD) in patients with diabetes, reducing the relative risk by one-third 6 7.

The National Cholesterol Education Program in the United States recommends that LDL-C values be used to estimate the lipoprotein-related risks for CVD in individuals 8. However, non–high-density lipoprotein cholesterol (HDL-C) may be more strongly associated with CVD risk than LDL-C in statin users 9, and it may be a better tool for cardiovascular risk and treatment assessments than LDL-C 10. The rationale for this recommendation is that non–HDL-C includes all potentially atherogenic cholesterol present in lipoprotein particles including LDL, lipoprotein(a), intermediate-density lipoprotein, and very-low-density lipoprotein remnants.

The National Institute for Health and Care Excellence (NICE) guidelines for adults with diabetes were updated in April 2021, and they now recommend that non-HDL-C replace LDL-C as the primary target for CVD risk reduction using lipid-lowering treatment 11. In contrast, other international guidelines do not have a non-HDL-C target. The European Society of Cardiology (ESC) uses LDL-C as their treatment goal 12. Similarly, the American College of Cardiology (ACC), American Heart Association (AHA) and National Lipid Association (NLA) target LDL-C reduction based on patient risk 13.

Despite the potential of non-HDL-C as a predictor of developing CVDs, no study has assessed the comparative effectiveness of different lipid lowering therapies on non-HDL-C in people with diabetes. Therefore, we aimed to carry out a systematic review and network meta-analysis to estimate the comparative effectiveness of seven statins on non-HDL-C level in patients with diabetes.

**Methods**

We undertook the systematic review and network meta-analysis according to a review protocol (PROSPERO, CRD42021258819) and results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) extension statement for network meta-analysis (see checklist in appendix 1) 14.

**Data sources and search strategies**

Searches were performed from inception to December 2021 in MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE. Screening was done by two independent blinded reviewers (AH, DT) using Covidence software, and disagreements were resolved by a third reviewer (MP). The full search strategy is available in appendix 2. Reference lists of included studies and relevant systematic reviews were screened for additional studies. Trial registries (ClinicalTrials.gov, ISCTRN, the WHO ICTRP portal, and OpenTrials.net) were also searched for unpublished or ongoing trials. Drug approval packages at the Food and Drug Administration and European Product Assessment Reports were also scanned for unpublished studies or relevant outcome data. We excluded studies not reported in English.

**Eligibility Criteria**

Studies of patients aged 18 years and over, diagnosed with type 1 or 2 diabetes were eligible. We also included patients at either primary (i.e., no diagnosis of CVD) or secondary (i.e., history of a CVD following the 3-point major adverse cardiovascular events (MACE) classification) prevention. The seven globally prescribed statins include Atorvastatin (brand name: Lipitor), Fluvastatin (Lescol), Lovastatin (Altoprev), Pitavastatin (Livalo, Zypitamag), Pravastatin (Pravachol), Rosuvastatin (Crestor, Ezallor) and Simvastatin (Zocor) at any dose. Comparator was either placebo or any of the seven statins. Primary outcome was non-HDL-C, but since this may not have been reported we included studies reporting both TC and HDL-C to enable calculation of non-HDL-C. Secondary outcomes include LDL-C, TC, classical 3-point MACE (defined as non-fatal stroke, non-fatal myocardial infarction, and cardiovascular related death) 15 and discontinuation due to adverse event. To limit potential bias, we included only randomised controlled trials.

**Data extraction**

We extracted data using a standardised form which was pilot tested beforehand. Data include *study characteristics*: country, placebo-controlled, duration of follow-up, number of patients and outcomes reported; *patient characteristics*: mean/median age in years, percentage of male patients, ethnicity classified according to the office for national statistics definition for ethnic group, national identity and region 16, baseline BMI (kg/m2), diabetes type (1 or 2), duration of diabetes, comorbidity, concomitant medication (other lipid lowering treatments) and risk of patients according to MACE; *intervention details*: statin agent, dose in mg’s and intensity based on the ACC/AHA 17, ESC 18 and NICE 19 guidelines. All data extractions were completed by two reviewers (AH, DT) and checked by another reviewer (MP).

**Categorisation of Statin Intensity**

Using the recommendations from ACC/AHA, ESC and NICE on CVD risk assessment and reduction, including lipid modification; statins were grouped into three different intensity categories according to the percentage reduction in LDL-C: a 20% to 30% reduction is low intensity; a 31% to 40% reduction is medium intensity; a reduction of more than 40% is high intensity 20. Table 1 shows the classification of the seven statins used in our analysis following the three dose intensity groups (low, moderate, or high) for the expected reduction in LDL-C. If the statin dose was positioned between the range of two intensity groups, we chose the nearest group to ensure an intensity was assigned.

**Quality Assessment of Evidence**

The quality of the individual studies was assessed independently by two reviewers using the Cochrane risk of bias tool 2.0 for randomised controlled trials. The overall risk of bias judgement was classified as follows: ‘low (1)’ – when a study was judged to be at low risk of bias for all domains with some concerns showing; ‘Some concerns (2)’ - when the study is judged to raise more domains with at least some concerns or high risk of bias in one domain; ‘High (3)’ - Study is judged to be at high risk of bias in at least one domain and/or to have some concerns for multiple domains in a way that substantially lowers confidence in the result 21. Additionally, we applied the CINeMA (confidence in Network Meta-Analysis) framework 22 23 to assess the certainty of evidence covering the six key domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.

**Data synthesis**

The primary outcome of changes in non-HDL-C, was calculated as the net difference between TC and HDL-C. Firstly, the mean and standard deviations of TC and HDL-C were converted from milligrams per decilitre (mg/DL) to millimoles per litre (mmol/L), the international standard measure for cholesterol modification. Variance for these calculated values were determined using previously developed procedures 24.

Net changes in non-HDL-C were calculated as the difference (statin – placebo/statin comparator) of the changes in these mean values in a network meta-analysis setting, which allowed for the simultaneous evaluation of the different statin intensities 25. To ensure transitivity within the network, we categorised all statin agents and intensity groups, and placebo into nodes and compared the distribution of clinical (TC, HDL-C) and methodological variables (age, sex and BMI) 26. We used a Bayesian, random effects network meta-analysis model with a normal likelihood. We accounted for the correlations induced by multi-group studies by using multivariate distributions. We considered the I2 statistic and the (heterogeneity) variance in the random effect’s distribution, (τ2) to measure the extent of the influence of variability across and within studies on treatment effects. I2 statistic and the 95% confidence interval was interpreted as 0-29%, 30-59%, 60-89% and above 89% indicating low, moderate, substantial and high heterogeneity, respectively, To rank the treatments by efficacy, we used the surface under the cumulative ranking curve (SUCRA) 27. We statistically evaluated consistency (that is, the agreement between direct and indirect evidence), by separating out direct evidence from indirect evidence using node splitting 28 29.

We fitted all models using the MBNMAdose (version 0.3.0) package 30 in R version 4.0.5 (R Foundation for Statistical Computing). Specifically, we used uninformative prior distributions for the treatment effects and a minimally informative prior distribution was used for common standard deviation parameter. Model convergence was ensured by visual inspection of three Markov Chain Monte Carlo chains after considering the Brooks-Gelman-Rubin diagnostic. Network graphs scaled by the number of studies and patients by each treatment node were presented in figures. The GeMTC package in R was used to produce some figures and to check results 31 32. The secondary outcomes LDL-C and TC was analysed in the same way as non-HDL-C. As the outcome discontinuations due to adverse events were reported with such low numbers, we analysed using Peto odds ratio method which is proven to be more suited for meta-analysing rare events 33. The 3-point MACE outcomes were analysed with DerSimonian and Laird ‘pairwise’ meta-analysis using relative risk 34.

We performed a subgroup network meta-analysis for non-HDL-C outcome that focused on high-risk patients, compared with low-to-medium risk patients 35. Using the inclusion/exclusion criteria and baseline data from the individual trial reports, the patient-risk was categorised into two groups: (i) ‘high risk (HR)’ patients involving those with a history of MACE outcomes (i.e., nonfatal stroke, nonfatal MI, CHD or CVD) 36, and (ii) ‘low-to-medium risk (LR)’ patients involving those that have never experienced a previous or current MACE at baseline.

A sensitivity analysis with the dose-specific network model was conducted, to examine the robustness of the findings from the analysis involving categorization by intensity. A network funnel plot was used to visually scrutinize the criterion of symmetry and potential presence for small-study effect bias 37.

**Patient and public involvement**

In designing this study, we held a patient and public involvement focus group with 24 adults who had diabetes and were using statins for prevention of CVD to help inform on the interpretation of our findings. These review results will be disseminated to the relevant patient communities.

**Results**

The search retrieved 2,906 references. After screening titles and abstracts of 1987 references, 1836 were excluded resulting in full-text screening of 151 reports. Forty-two randomised controlled trials (comprising 20,193 participants) met our inclusion criteria (Figure 1). The included studies are provided in Appendix 3.

**Characteristic of Included Studies**

The characteristics of the included studies are provided in Appendix 4. Fourteen (33%) of the studies were carried out in the EU, six (14%) in the US and four (10%) in the UK 6 38-40. The studies involved a median of 145 (Range: 52 to 390; IQR: 338) patients, with median age 60 years (Range: 58 to 62 years; IQR: 4). Eighteen (43%) studies involved 55% or more males, eleven (26%) involved 55% or more females, and eleven (26%) involved a mixture of both sexes. Patients were mostly overweight with the median BMI at baseline estimated as 29 kg/m2 (Range: 26 to 31; IQR: 5). Seventeen (40%) of the studies involved Asians (South Korean (n=6) 41-46, Japanese (n=3) 47-49, Taiwanese (n=3) 50-52, Arabic (n=2) 53 54, Chinese (n=1) 55, Indian (n=1) 56, Thai (n=1) 57), twelve (29%) studies involved patients of white (western or European) 6 58-68 ethnicity and one (2%) study involved patients of mixed ethnicity 69. In twelve of the studies (29%) ethnicity was not reported 38 40 70-79.

Thirty-five (83%) of the studies involved patients with a diagnosis of type 2 diabetes, five (12%) were diagnosed with either, type 1 or 2 diabetes 55 70 71 79 80, and two (5%) were only diagnosed with type 1 diabetes 63 74. Of the 22 (49%) studies that reported the average duration of diabetes diagnosis, the median was 8 years (Range 4 to 11; IQR 7). Most of the studies (n=32, 76%) involved the secondary prevention of CVD, however nine (21%) studies targeted primary prevention, and in one (2%) it was unclear 76. Other than the patients diagnosis of diabetes, common comorbidities included (stable hypercholesterolemia (n=12), CVD or cardiovascular risk factors (hypertension (n=6), coronary artery disease (n=3), coronary heart disease or peripheral vascular (n=3), acute myocardial infarction (n=3) or stable angina (n=2)), metabolic syndrome (n=1), retinopathy (n=1) and 11 studies did not report any other comorbidities other than their diabetes status). Other (concomitant) lipid lowering therapy was being used at enrolment in six of the studies, however of the remaining 36 studies most had a washout phase before recruitment or did not specify any use of lipid lowering therapy. Eighteen (43%) of the studies involved mostly low risk patients, twelve (29%) involved patients of moderate risk, and twelve (29%) involved patients of high risk with a current diagnosis of a CVD or a previous history of MACE.

Twenty-four (57%) of the studies were placebo-controlled, and the remaining eighteen studies (43%) involved only active statin therapies as their comparator. The median length of intervention period in the studies was 12 weeks ranging from 8 to 24 weeks.

**Assessment of Risk of Bias**

The quality of the studies varied as shown in appendix 5. Five (12%) studies revealed a high risk of bias for the randomisation process, six (14%) displayed a high risk for deviations from the intended intervention, five (12%) scored high risk for missing outcome data and eleven (26%) displayed a high risk for the measurement outcome domain. Selection reporting bias was present in seven (17%) of the studies. Overall, nineteen studies (48%) had a low risk of bias (overall bias score of 1), and twenty-two of the studies (52%) had a score above 1 indicating some concerns or high risk of bias.

**Network Meta-Analysis**

Figure 2 shows the network of eligible comparisons for the primary outcome non-HDL-C involving 36 of the trials with amenable data for including in the meta-analysis. The network of evidence included 15 interventions; 11,698 patients; 24 two-arm studies and 12 multi-arm studies. Twenty-one studies involved Atorvastatin (n=15 moderate intensity 6 42 46 49-53 58 59 67 71-73 75, n=10 high intensity 50 51 59 60 72 40 42 46 56 66, n=7 low intensity 50 58 46 51 57 72 76), three studies involved Fluvastatin (n=2 low intensity 47 68 and one moderate intensity 77), one study involved Pitavastatin at moderate intensity 52, eight studies involved Pravastatin (n=8 low intensity 41 44 49 58 63 70 73 79 and one moderate intensity 41), four studies involved Rosuvastatin (n=3 high intensity 45 56 58, n=2 moderate intensity 45 49 and one low intensity 45) and fourteen studies involved Simvastatin (n=10 moderate 43 44 50 53 54 58 65 69 74 76, n=5 low 43 71 73 76 57 and n=2 high intensity 43 65). The model fit statistics and the profile plots of treatment response by dose for the convergence model are provided in appendix 6.

**Inconsistency Analysis**

We found evidence of statistical inconsistency through node splitting analysis owing to one comparison of Atorvastatin at moderate intensity compared against Pravastatin at low intensity (P=0.071); this was because one study was at high risk of bias due to the measurement of the outcome in the Pravastatin treatment group showing a significant difference of both TC and HDL-C measures at baseline 73 (Appendix 7). One further inconsistency was found in the comparison between Pravastatin at low intensity compared to Simvastatin at moderate intensity (P=0.031). This was due to one study 44 which showed moderate risk of bias because of uncertainty with the randomisation process used and the high number of unexplained discontinuations. Because consistency (transitivity) is a central assumption of network meta-analysis, we removed both trials leaving 34 randomised controlled trials for the network on non-HDL-C.

**Performance on Non-HDL-C by Statin Intensity**

Figure 2 shows the network meta-analysis results for the primary outcome of all eligible trials after the inconstancy analysis. Both Rosuvastatin at high (-2.31, 95% CrI: -3.39 to -1.21 mmol/L) and moderate (-2.27, 95% CrI: -3.00 to -1.49 mmol/L), and Simvastatin (-2.26, 95% CrI: -2.99 to -1.51 mmol/L) and Atorvastatin (-2.20, 95% CrI -2.69 to -1.70 mmol/L) at high intensities respectively, lead to the largest reduction in non-HDL-C compared with placebo. All Atorvastatin and Simvastatin intensities and Pravastatin at low intensity were statistically significant showing a reduction in non-HDL-C. Whilst, the remaining statin agents (Fluvastatin low and moderate, Pitavastatin moderate, Pravastatin moderate, Rosuvastatin low intensities) did effectively reduce non-HDL-C when compared to placebo, the relative effects were not statistically significant. Heterogeneity was low in the network meta-analysis, with I2 = 0% (95% CI: 0 to 38%) (Appendix 8).

SUCRA scores, which provide an overall ranking of each treatment, provided additional insight. In terms of non-HDL-C reduction, Rosuvastatin at moderate intensity was ranked as the best statin treatment (SUCRA, 77.5%), with the second-best treatment being Rosuvastatin at high intensity (76.8%), third best being Simvastatin at high intensity (76.7%), followed by Atorvastatin at high intensity (76.3%). The treatment with the lowest SUCRA score (excluding placebo) was Fluvastatin at low intensity (8.5%) (Appendix 10).

The league table showing the results of the network meta-analysis comparing the effects of the different statin intensities (figure 3) showed that almost all statins were effective when compared against Fluvastatin and Pravastatin at low intensity. Rosuvastatin delivered at high intensity appeared to be the best performing statin when compared ‘head-to-head’ with the other statin intensities, but the difference in effect sizes were non-significant and revealed a small benefit when compared with the other top performers (i.e., Rosuvastatin moderate, Simvastatin high and Atorvastatin high intensity). To ensure the certainty of evidence, we incorporated the CINeMA judgments into figures 2 and 3. The evidence according to CINeMA was mostly moderate or high quality overall (Appendix 11), and there was no evidence of funnel plot asymmetry (appendix 12).

Sensitivity analyses of the network meta-analysis by specific statin dose showed similar results to the main statin intensity model, with Atorvastatin, Rosuvastatin and Simvastatin all resulting in a significant reduction of non-HDL-C (with the exception being Rosuvastatin 25mg) (Appendix 13).

**Secondary outcomes**

For the secondary outcome LDL-C reported among 29 studies (18 two-arm, 9 three-arm and 2 four-arm studies); Simvastatin (-1.93, 95% CrI: -2.63 to -1.21 mmol/L, SUCRA=93%) and Rosuvastatin (-1.76, 95% CrI: -2.37 to -1.15 mmol/L, SUCRA=89%) delivered at a high intensity level were the most significant treatment options for reducing LDL-C (figure 4). Heterogeneity was low in this network meta-analysis with I2 = 5% and no concerns of inconsistency were found (Appendix 7). For TC reported in 36 studies (23 two-arm, 8 three-arm, 4 four-arm, and 1 five-arm study); Atorvastatin (-2.21, 95% CrI: -2.62 to -1.74 mmol/L), Rosuvastatin (-2.18, 95% CrI: -3.19 to -1.20 mmol/L) and Simvastatin (-2.20, 95% CrI: -2.96 to -1.42 mmol/L) delivered at a high intensity level were the most significant treatment options for reducing TC. Of the twelve studies that reported discontinuations of treatment due to an adverse event, only four statin interventions (Pravastatin low, Atorvastatin moderate, Lovastatin low, Simvastatin moderate) were possible for meta-analyses. No significant associations were identified in these analysis, although there was high uncertainty around the estimates as expected. The full raw data for discontinuations due to adverse events are provided in appendix 9. Only five studies 6 39 55 59 64 reported at least one of the 3-point MACE outcomes and these were only studies involving Atorvastatin moderate and high intensity treatment groups. There was a significant reduction in non-fatal myocardial infarction for Atorvastatin delivered at moderate intensity when compared with placebo (RR=0.57, 95% CI: 0.43 to 0.76, n=4 studies). No significant results were found for non-fatal stroke or cardiovascular related death outcomes. All secondary outcome results are provided in appendix 9.

**Subgroup Analysis of Patient Risk for Non-HDL-C**

Figure 5 shows the subgroup network meta-analysis of 4,670 patients of high risk (10 studies) and 7,028 patients of low-to-medium risk (26 studies) of a MACE. The results showed that all statin agents and intensities except Fluvastatin, Pravastatin and Rosuvastatin administered at a low intensity led to statistically significant non-HDL-C reductions in patients at low-to-medium risk of a MACE. Atorvastatin at high intensity was the best (non-significant: -1.98, 95% CrI: -4.16 to 0.26 mmol/L; SUCRA: 64%) performer in the high-risk patients, and Fluvastatin at low intensity (0.56, 95% CrI: -2.17 to 3.37 mmol/L; SUCRA: 12%) was the worst. Two studies 50 79 with a high risk of bias score were removed from the network, but the results did not change (Appendix 14).

**Discussion**

**Principle findings**

This is the first network meta-analysis comparing the effectiveness of different statin agents at different intensities in adults with diabetes using non-HDL-C reduction as the primary lipid target. The findings derived from a population of 20,193 participants from randomised clinical trials show that Rosuvastatin administered at moderate and high intensities, and Simvastatin and Atorvastatin administered at high intensity, were the best performing statins at lowering non-HDL-C over an average treatment duration of 12 weeks when compared to placebo. The network model adjusting for patient-risk, showed that of the 4,670 adults (40% of total adults) at high-risk of MACE outcomes (secondary prevention), Atorvastatin administered at high intensity was the best performer. Rosuvastatin administered at moderate and high intensity, and Atorvastatin and simvastatin administered at high intensity was the most effective statin treatment option in the population of 7,028 adults at low-to-medium risk of MACE and possible primary prevention.

**Comparisons with similar research**

No prior meta-analysis has assessed the efficacy of statin intensity based on non-HDL-C. However, our findings align with a recent network meta-analysis 3 that assessed the primary efficacy endpoint of the same seven statins based on lipid management of LDL-C, HDL-C and TC in patients with dyslipidaemia, CVD, or diabetes disease status. That study concluded that Rosuvastatin was ranked as the best treatment for LDL-C reduction (-72.28 mg/dL ~ -1.87 mmol/L), which was close to our estimate of -1.76 mmol/L LDL-C reduction for Rosuvastatin delivered at a high intensity. However, as the authors highlighted the overall findings should be interpreted with some caution due to large variations in follow-up trial periods ranging between 14 weeks and 5 years, the intensity and doses of statins involved were not clearly unified, non-HDL-C was not used as an outcome, and several inconsistencies between direct and indirect evidence were identified, which would possibly cause bias within the network.

Current evidence suggests that some statins can cause more adverse events and administration at a more intensive level may actually be more harmful to the patient. For instance, a large meta-analysis of 246,955 patients to assess the tolerability and harms of individual statins 81 found that, when compared to other statins, higher doses of Atorvastatin and Rosuvastatin were associated with a higher risk of discontinuation, and higher doses of Atorvastatin, Fluvastatin, Simvastatin and Pravastatin were associated with greater risk of transaminase elevations. Our meta-analysis on discontinuations due to adverse events involved fewer studies and patients, and few events were reported with some studies reporting no events in both treatment arms. Meta-analysing rare events are problematic in this setting and often lead to spurious findings 82-84. Therefore, these results on discontinuations need to be interpreted with great caution. Reporting of discontinuations due to adverse events and other harm outcomes should be reported in the CONSORT flow diagram and within the study results 85. However, the primary reports for pharmacotherapy and device trials for chronic heart failure 86 and more specifically for statins 87, often do not provide these data. Practicing cardiologists need these data to help support clinical judgements when balancing the benefit-harms profile of the different statins.

**Implications for Policy and Practice**

The use of lipid or apolipoprotein parameters other than LDL-C as targets for statin therapy continues to be hotly debated. However, given that the clinical applicability of non-HDL-C and LDL-C are identical, and with the garnered evidence continually supporting the notion that non-HDL-C might be superior to LDL-C as a marker of cardiovascular risk 9 88-90, non-HDL-C levels are likely to be a more appropriate target for statin therapy than LDL-C in the future 9. Since the unveiling of non-HDL-C as a potential key lipid target, NICE have recommended that physicians use non-HDL-C as their primary target. They have set a target of reducing non-HDL-C by greater than 40% from baseline when using high-intensity statins. However, if the baseline value is not available, the Joint British Societies consensus recommends using the target non-HDL-C < 2.5 mmol/L (approximately equivalent to LDL-C < 1.8 mmol/L) 91. Further evidence from observational primary care data also suggests that at the time of diabetes diagnosis on average non-HDL-C level was found to be 4 mmol/L 92. However, many of the patients in this study were taking statins at the time and it should be expected that they would reach the < 2.5 mmol/L target over time.

**Strengths and limitations of the study**

Our review is the first to assess the efficacy of the most prescribed statin therapies at different intensities to observe reductions in non-HDL-C in patients with diabetes. Our analysis has used some of the most robust methods available including Bayesian meta-analysis and rigorous quality assessment through CINeMA.

However, these findings should be interpreted in light of several limitations. Patient risk classification cannot be considered exact since it was not confirmed at the individual participant level, therefore we made some assumptions based on the study inclusion/exclusion criteria and baseline characteristics to determine an appropriate risk category according to MACE definitions. Additionally, a flexible method for estimating the ‘effective sample size’ in indirect comparison meta-analysis and network meta-analysis 93 suggests that some of the pairwise comparisons in the high risk group were underpowered, meaning the results of the subgroup analysis should be interpreted with some caution. However, it is reassuring that our sensitivity analysis removing the high risk of bias studies resulted in no major differences compared to the main results.

There were only two studies 63 74 involving people with type 1 diabetes, thus limiting results to mostly patients with type 2 diabetes. The primary focus of our review and of the included studies was on surrogate outcome (lipid) measures and not CVD or MACE outcomes. Thus our results should primarily act mainly as a guidance as to whether or not individuals will reach the non-HDL-C, LDL-C, TC target with a specific statin therapy delivered at a certain intensity. Nevertheless, the 3-point MACE outcomes were analysed, but as only five studies 6 55 59 64 67 reported such outcomes the results were somewhat limited.

This is a (network) meta-analysis of aggregate data, and standard practice when dealing with aggregate data is to focus on the final score values, to obtain an effect estimate at the study-level. Thus, under this principle, our effect estimates did not adjust for baseline differences. A major constraint underpinning this type of adjustment is that the baseline data often are not reported within studies, which was the case involving the studies in this meta-analysis. Secondary, even if we had tried to include the studies that did provide the data it would have required a different methodological approach which would have led to a significantly reduced number of trials in our study pool94. Nevertheless, meta-analysing RCTs makes this feasible and defensible, since the underlying assumption (at least in large enough RCTs) is that the baseline levels are almost identical in the two (or more) treatment arms - which was also shown in the transitivity assessment part of CINeMA. With meta-analyses of aggregate data, little else can be done regarding the baseline scores, unfortunately, except perhaps a meta-regression where the association between baseline levels and effect sizes can be explored. However, this comes with considerable power limitations, even for large meta-analyses. Thus, the main avenue to investigate the role of baseline scores is usually through an individual patient data (IPD) meta-analysis. We tried contacting the authors for their baseline data, but only three responded 38 73 80. We recommend that these data are reported in future trials to allow for the adjusted baseline ‘change’ scores to be used instead of the final scores.

**Conclusions**

Rosuvastatin administered at moderate intensity and Rosuvastatin, Simvastatin and Atorvastatin administered at high intensity were the most effective treatments in patients with diabetes which led to modest reductions in non-HDL-C over 12 weeks when compared with placebo. Given the potential improvement in accuracy in predicting CVD by means of the non-HDL-C target, our findings serve as a timely analysis for informing policy on which statin types and intensities are most effective by reducing non-HDL-C in patients with diabetes and at risk of CVD.

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**Author Contributions**

AH, MP and EK had the initial research idea and obtained funding for this study. AH, MP and DT formulated the research questions and designed the study. AH and DT searched for published work, selected articles, and extracted data. AH performed all analysis and EK checked over. AH and DT drafted the protocol and the manuscript. MP helped in the searching of articles and data selection and extraction. MP contributed to designing the searches and the statistical analysis plan, writing of the manuscript, and interpreting the findings. MM, MR and EK contributed to the manuscript by providing review comments and edits. All authors have read and approved the final manuscript.

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**Conflicts of Interest Disclosures**

We declare that we have no conflicts of interest. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi\_disclosure.pdf and declare the funding support from the Evidence Synthesis Working Group (project

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**Ethical approval**

Not required.

**Data sharing**

AH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Dissemination to participants and related patient and public communities**

Dissemination of this research will be done at the World Heart Congress in October 2021 (https://heart.euroscicon.com/), and though a press release from the University of Manchester, social media and twitter, and charities including the British Heart Foundation and Heart Research Institute UK.

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