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META-ANALYSIS

Comparative safety and efficacy of statins for primary prevention in human immunodeficiency virus-positive patients: a systematic review and meta-analysis

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The efficacy and safety of different statins for human immunodeficiency virus (HIV)-positive patients in the primary prevention setting remain to be established. In the present meta-analysis, 18 studies with 736 HIV-positive patients receiving combination antiretroviral therapy (cART) and treated with statins in the primary prevention setting were included (21.0% women, median age 44.1 years old). The primary endpoint was the effect of statin therapy on total cholesterol (TC) levels. Rosuvastatin 10 mg and atorvastatin 10 mg provided the largest reduction in TC levels [mean −1.67, 95% confidence interval (CI) (−1.99, −1.35) mmol/L; and mean −1.44, 95% CI (−1.85, −1.02) mmol/L, respectively]. Atorvastatin 80 mg and simvastatin 20 mg provided the largest reduction in low-density lipoprotein (LDL) [mean −2.10, 95% CI (−3.39, −0.81) mmol/L; and mean −1.57, 95% CI (−2.67, −0.47) mmol/L, respectively]. Pravastatin 10–20 mg [mean 0.24, 95% CI (0.10, 0.38) mmol/L] and atorvastatin 10 mg [mean 0.15, 95% CI (0.007, 0.23) mmol/L] had the largest increase in high-density lipoprotein, whereas atorvastatin 80 mg [mean −0.60, 95% CI (−1.09, −0.11) mmol/L] and simvastatin 20 mg [mean −0.61, 95% CI (−1.14, −0.08) mmol/L] had the largest reduction in triglycerides. The mean discontinuation rate was 0.12 per 100 person-years [95% CI (0.05, 0.20)], and was higher with atorvastatin 10 mg [26.5 per 100 person-years, 95% CI (−13.4, 64.7)]. Meta-regression revealed that nucleoside reverse transcriptase inhibitors-sparing regimens were associated with reduced efficacy for statin's ability to lower TC. Statin therapy significantly lowers plasma TC and LDL levels in HIV-positive patients and is associated with low rates of adverse events. Statins are effective and safe when dose-adjusted for drug–drug interactions with cART.

Keywords HIV-positive patients • Cardiovascular risk • Statin therapy • Antiretroviral therapy • Dyslipidaemia

Introduction

Human immunodeficiency virus (HIV)-positive patients are exposed to a higher risk of cardiovascular (CV) adverse events, which represent the leading cause of death in this population, especially after the introduction of combination antiretroviral therapy (cART). The increased CV risk is related to the complex interaction between CV risk factors, the state of increased immune activation (even in patients who are virologically suppressed) and cART[1–3]

For HIV-positive patients, it is crucial to both assess and reduce CV risk, even more than it is for HIV-negative patients. Dyslipidaemia represents a frequent finding in this population and is driven by negative lifestyle habits, cART, and the virus itself.[4,5]

In the HIV setting, statins [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors][6] have become a crucial

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therapy for CV risk reduction and are widely used thanks to their efficacy to reduce cholesterol and to their pleiotropic effects regarding plaque stabilization and regression.[7]

Current evidence, however, is fraught by the absence of data on the most efficacious statin and the lack of definite data on the clinical relevance of the potential interactions with cART and on the rate of discontinuation due to side effects.[8] Consequently, we performed a systematic review and meta-analysis to offer physicians an accurate overview of the safety and efficacy of statin use in HIV-positive patients in the cART era.

Methods

To elaborate the present study, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), the amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement along with recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE). To perform the network meta-analysis, the National Institute for Health and Care Excellence Decision Supporting Unit (NICE DSU) guidelines were followed (http://www.nicedsu.org.uk/evidence-synthesis-tsd-series%282391675%29.htm).[9–13]

Search strategy

Two researchers (S.G. and F.D.A.) searched on MEDLINE/PubMed, Cochrane Library, Biomed Central, and Google Scholar for pertinent articles published in English according to the following strategy, with established methods and incorporating wild cards (identified by *) with the following terms: ((statin) OR (HMG-CoA reductase inhibitors) OR (atorvastatin) OR (rosuvastatin) OR (cerivastatin) OR (fluvastatin) OR (lovastatin) OR (mevastatin) OR (pitavastatin) OR (simvastatin)) AND (hiv OR aids OR (human AND immunodeficiency AND virus)) NOT (review[pt] OR editorial[pt] OR letter[pt]).

Study selection

All citations were discussed by two co-authors (S.G. and F.D.A.) at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were appraised as complete reports. Inclusion criteria were (all had to be present) (i) human studies, (ii) HIV-positive patients treated with statin in primary prevention, and (iii) $\geq$6-week follow-up. Exclusion criteria included (i) non-human setting, (ii) duplicate reporting (in which case the study reporting the largest sample of patients was included), and (iii) $<$75% of patients on cART.

Data extraction

For each paper, two co-authors (S.G. and F.D.A.) elaborated these clinical features: authors, journal, year of publication, location of the study group, baseline, CV and HIV features, and kind and dose of statin.

Absolute change of total cholesterol (TC) was the primary endpoint, while changes of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides and treatment discontinuation due to any adverse event the secondary ones.

Impacts of age, $CD4^+$ cell counts, body mass index (BMI), cART [divided by regimens including at least one protease inhibitor (PI-containing regimens, from now on), regimens including at least one non-nucleoside reverse transcriptase inhibitors (NNRTI-containing regimens, from now on), and regimens not including nucleoside reverse transcriptase inhibitors (NRTI-sparing regimens, from now on)], length of follow-up, time from HIV diagnosis, and cART exposure duration were tested at meta-regression analysis. Sensitivity analysis was performed for kind of statin, and after including also randomized controlled trials (RCTs).

Internal validity and quality appraisal

Two unblinded reviewers (S.G. and F.D.A.) evaluated the quality of the studies on pre-specified electronic forms, with divergences resolved after consensus. According to the MOOSE, we separately abstracted and appraised study design, setting, and data source, as well as (in keeping with the Cochrane Collaboration approach) the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, high risk of bias, or incomplete reporting leading to inability to ascertain the underlying risk of bias).

Data analysis and synthesis

Continuous variables are reported as mean [$\pm$ standard deviation (SD)] or as median [$\pm$ interquartile range (IQR) or minimum and maximum value] as appropriate. Values of TC, LDL, HDL, and triglycerides are expressed as millimoles per litre, where 1 mmol/L of TC, LDL, or HDL corresponds to 38.67 mg/dL and 1 mmol/L of triglycerides to 88.57 mg/dL.

Statistical pooling for incidence estimates was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CI) by using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Study bias was appraised by graphical inspection of funnel plots. Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and was based on the Cochran Q test, with I^2 values of 25, 50, and 75% representing mild, moderate, and extensive statistical inconsistency, respectively.

Network meta-analysis was performed with random-effect models (derived from NICE DSU statement, http://www.nicedsu.org.uk/evidence-synthesis-tsd-series%282391675%29.htm) with OPenBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Each analysis was based on non-informative priors for effect sizes. Convergence and lack of autocorrelation were checked and confirmed after a 100 000-simulation burn-in phase, and, finally, direct probability statements were based on an additional 500 000-simulation phase. Deviance and deviance information criterion (DIC) were used to appraise model fit. Results of network meta-analysis were reported as odds ratios (OR) with 95% CI for categorical variables and mean differences with 95% CI for continuous variables. Extent of small study effects/publication bias was assessed by visual inspection of funnel plots.

Meta-regression analysis was performed with Comprehensive Meta-Analysis, reporting results as Beta, i.e. regression coefficients.

Results

The systematic literature search produced 236 citations that were screened and evaluated at the abstract level (*Figure 1*). Of these, 37 were appraised as full text, among which 19 were excluded, as reported in Supplementary material online, *Table S1*. Finally, 18 studies were included, of which 2 utilized pravastatin 10–20 mg,[14,15] 9 pravastatin 40 mg,[16–24] 7 rosuvastatin 10 mg,[15,17,20,25–28] 2 atorvastatin 10 mg,[15,20] 1 atorvastatin 20–40 mg,[29] 1 atorvastatin 80 mg,[30] 1 fluvastatin 20–40 mg,[14] and 1 simvastatin 20 mg.[31]

A total of 736 patients were included (*Table 1*), of whom 21.0% were female, with a median age of 44.1 years [min–max (36.3, 56.0)] and a mean BMI of 23.9 [IQR (23.3, 25.1)]. At baseline (*Table 2*), median $CD4^+$ cell count was 521 cells/mm^3 [IQR (423, 552)], mean

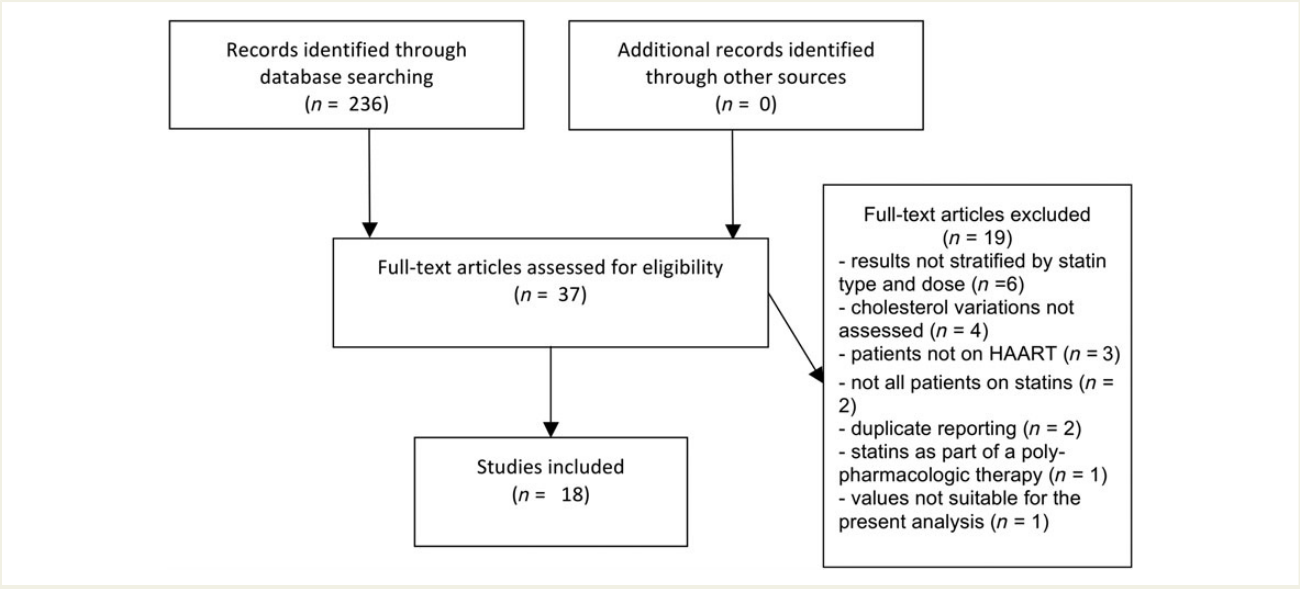

Figure 1 Systematic review's profile.

Table 1 Baseline features of enrolled patients

	Median	Interquartile range
Age (years, min–max value)	44.1	36.3–56.0
Female gender	21.0	13.2–25.5
Body mass index	23.9	23.3–25.1
Cuacasian ethnicity	91.0	84.5–96.5
Men having sex with men	41.1	33.8–47.7
Intravenous drug user (previous or current)	33.0	24.8–44.0
Hypertension	10.0	8.0–23.0
Smoke	46.5	45.0–52.3
Diabetes	0.0	0.0–0.0
HBV infection	3.6	2.9–4.2
HCV infection	21.4	17.9–21.9
Lenght of follow-up (weeks)	12	12–36
Total cholesterol (mmol/L)	6.8	6.3–7.1
LDL (mmol/L)	4.2	3.6–4.5
HDL (mmol/L)	1.2	1.1–1.3
Triglycerides (mmol/L)	3.0	2.6–3.3

Values are expressed as percentage unless specified.
HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2 HIV infection features of enrolled patients

	Median	Interquartile range
Baseline $CD4^+$ cells (cells/mm^3)	521	423–552
Patients with <50 copies/mL HIV-RNA	100.0	81.7–100.0
Time from HIV diagnosis (months)	106.0	74.4–115.0
Time on cART (months)	65.0	62.0–94.0
Patients on PI-containing regimens	100.0	53.8–100.0
Patients on NNRTI-containing regimens	16.7	0.0–44.4
Patients on NRTI-sparing regimens	0.0	0.0–4.4

Values are expressed as percentage unless specified.
cART, combination antiretroviral therapy; PI, protease inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors.

time from HIV diagnosis was 106.0 months [IQR (74.4, 115.0)], and average duration of cART exposure was 65.0 months [IQR (62.0, 94.0)]. The median follow-up was 12 weeks [IQR (12, 36)].

All patients were on cART: 76.5% on PI-containing regimens, 29.8% on NNRTI-containing regimens, and 16.2% on NRTI-sparing regimens.

Rosuvastatin 10 mg and atorvastatin 10 mg were the two statins associated with the largest reduction in TC levels [mean −1.67 mmol/L, 95% CI (−1.99, −1.35); and mean −1.44 mmol/L, 95% CI (−1.85, −1.02), respectively, *Figure 2*], while rosuvastatin 10 mg [mean −1.12, 95% CI (−1.40, −0.83)], atorvastatin 80 mg [mean −2.10, 95% CI (−3.39, −0.81)], and simvastatin 20 mg [mean −1.57, 95% CI (−2.67, −0.47)] reduced LDL cholesterol (*Figure 3*).

Larger increases in HDL cholesterol were observed in patients receiving pravastatin 10–20 mg [mean 0.24 mmol/L, 95% CI (0.10, 0.38)], rosuvastatin 10 mg [mean 0.10 mmol/L, 95% CI (0.04, 0.17)], and atorvastatin 10 mg [mean 0.15 mmol/L, 95% CI (0.07, 0.23), Supplementary material online, *Figure S1*].

Triglycerides values were significantly reduced (Supplementary material online, *Figure S2*) in patients treated with rosuvastatin 10 mg [mean −0.56, 95% CI (−0.70, −0.42)], atorvastatin 10 mg [mean −0.59, 95% CI (−0.81, −0.37)] and 80 mg [mean −0.60, 95% CI (−1.09, −0.11)], and simvastatin 20 mg [mean −0.61, 95% CI (−1.14, −0.08)].

Twenty-seven (3.0%) patients interrupted statin therapy due to adverse events, with a mean discontinuation rate of 0.12 [95% CI

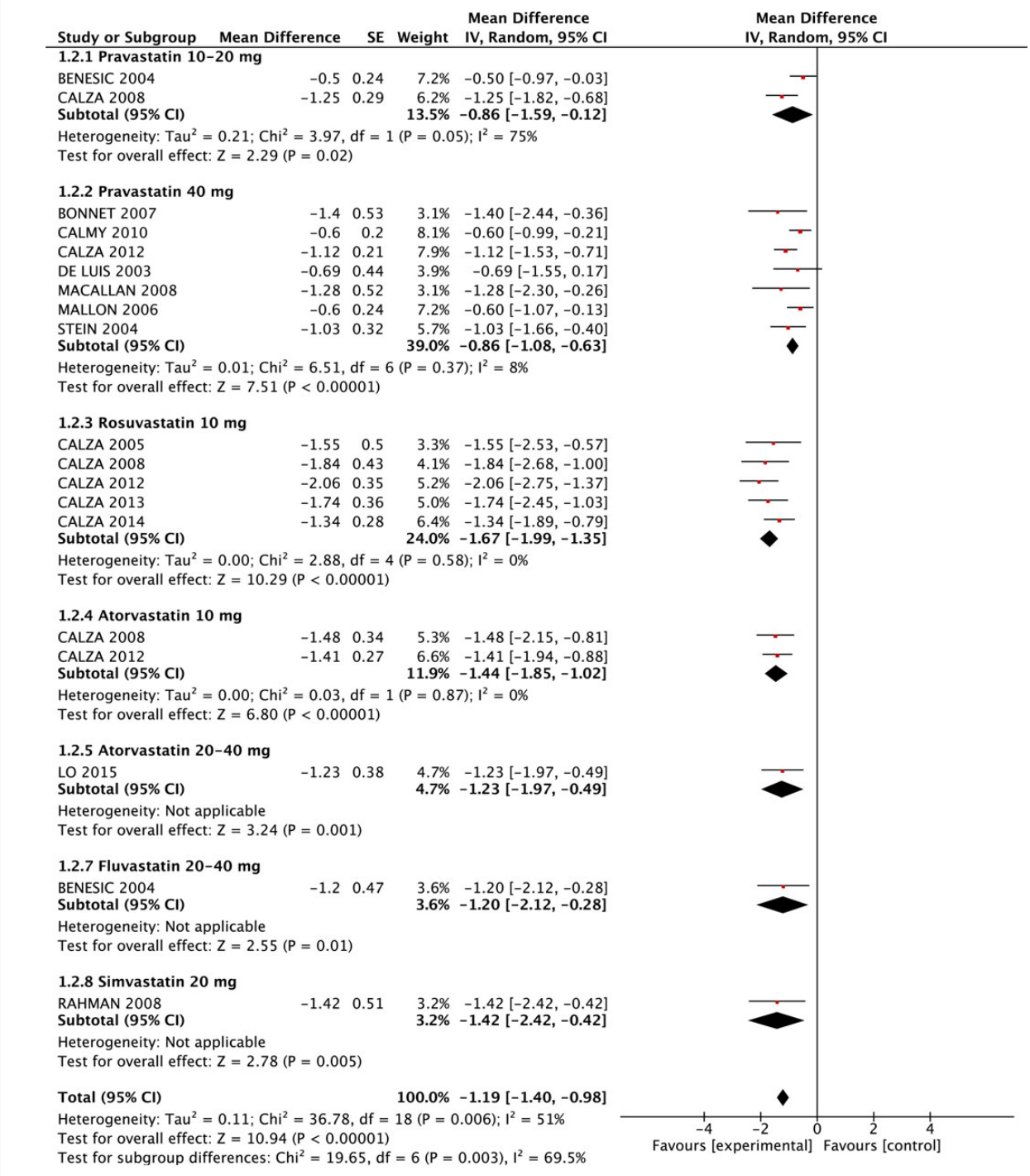

Figure 2 Total cholesterol reduction according to different statins and dosages; the mean reduction of 1.19 mmol/L corresponds to a decrease of 46.0 mg/dL.

(0.05, 0.20)] per 100 person-years overall. The higher incidence occurred with atorvastatin 10 mg [mean 26.5 per 100 person-years, 95% CI (−13.4, 64.7), *Figure 4*].

All results were consistent when including RCTs only; however, rosuvastatin 10 mg lost its significant correlation with HDL increase after this adjustment (data not shown).

Meta-regression analysis (Supplementary material online, *Table S2*) shows that NRTI-sparing regimens were associated with a smaller decrease in TC [Beta 0.007, 95% CI (0.001, 0.013), $P = 0.018$, *Figure 5*] and that HDL cholesterol increase was negatively affected by age [Beta −0.009, 95% CI (−0.016, −0.003), $P = 0.005$], NNRTI-containing regimens [Beta −0.002, 95% CI (−0.002,

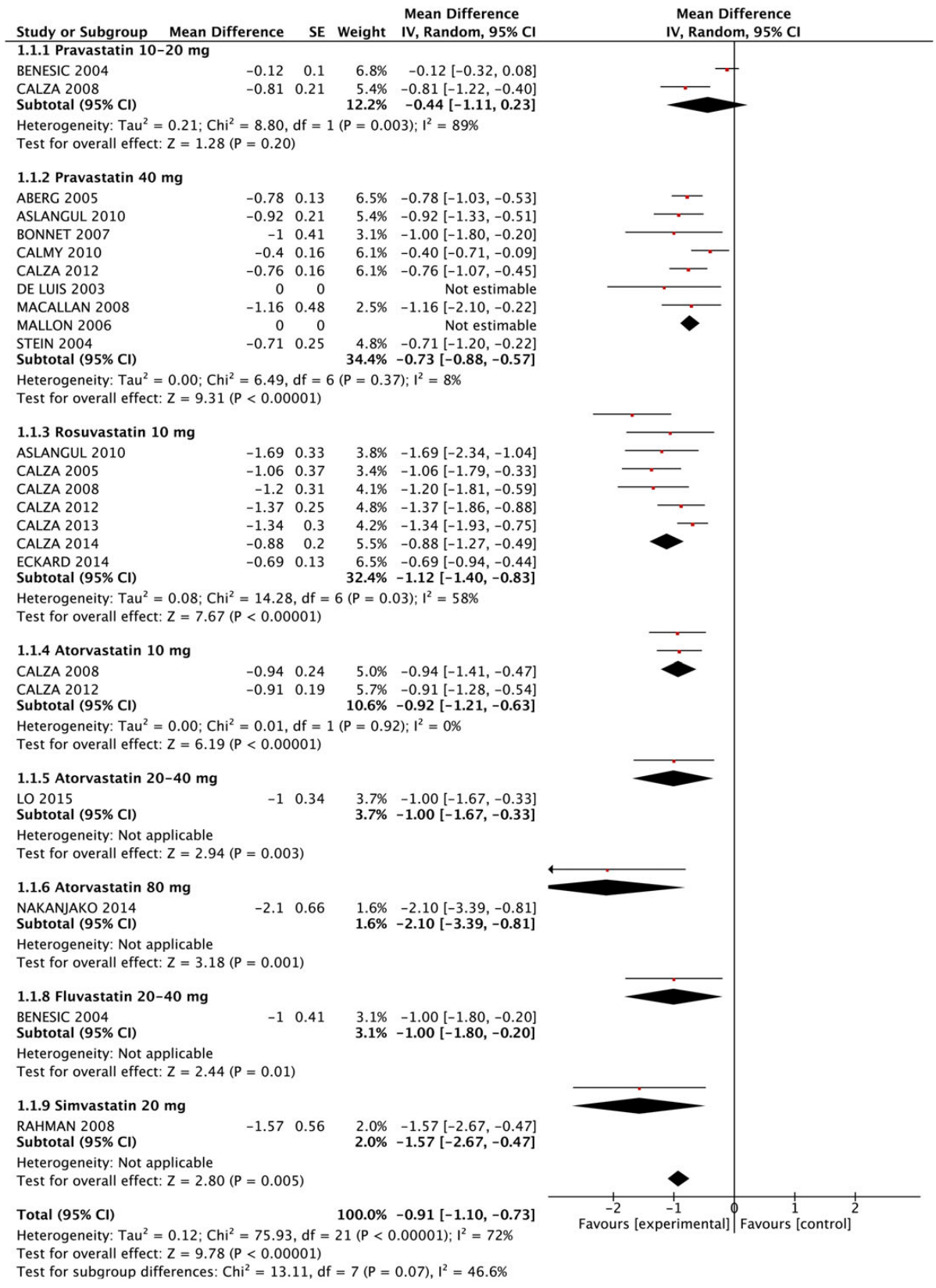

Figure 3 Low-density lipoprotein cholesterol reduction according to different statins and dosages; the mean reduction of 0.91 mmol/L corresponds to a decrease of 35.2 mg/dL.

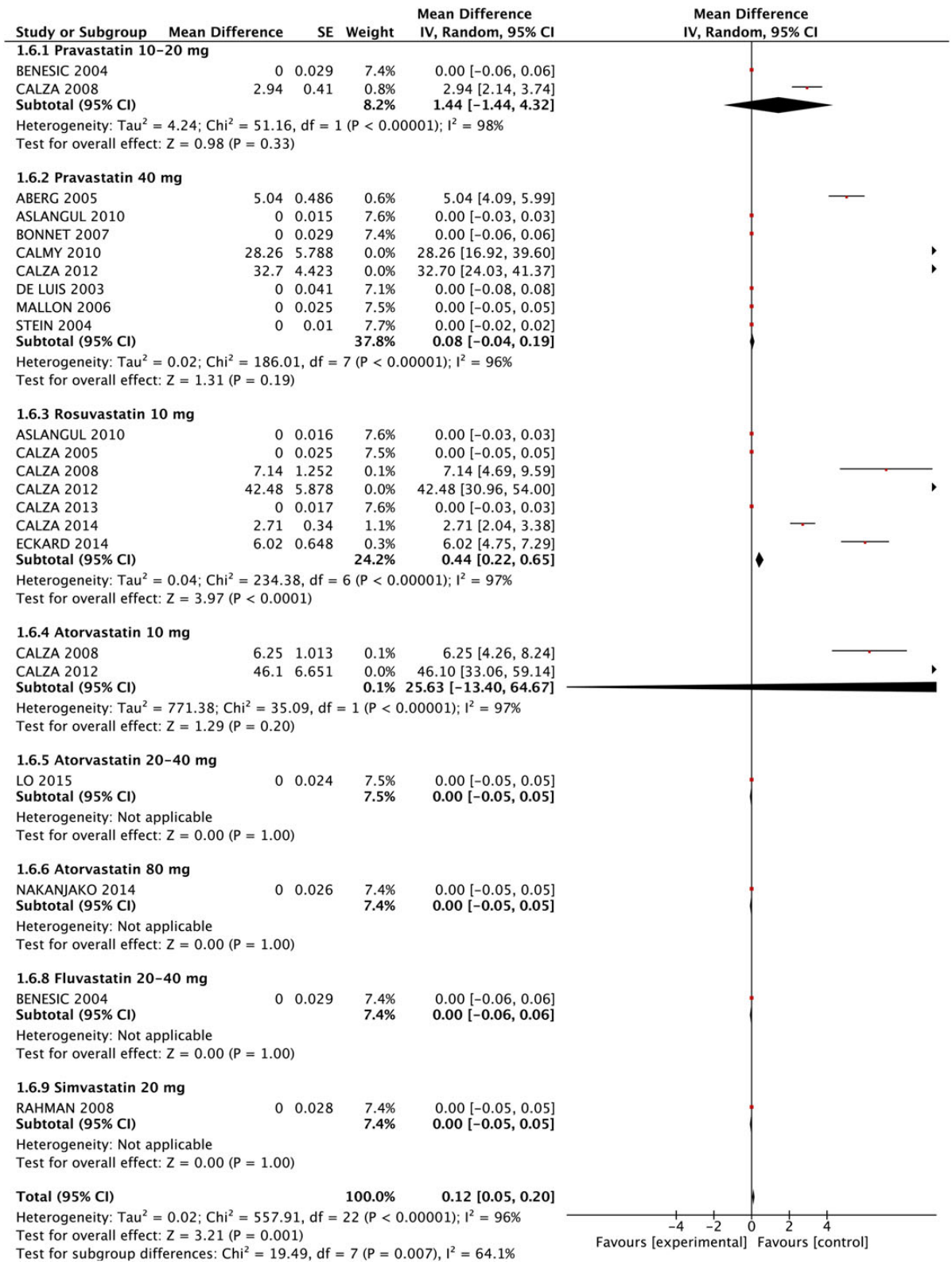

Figure 4 Statin discontinuation due to adverse events according to different statins and dosages; discontinuation rates are expressed as events/100 person-years.

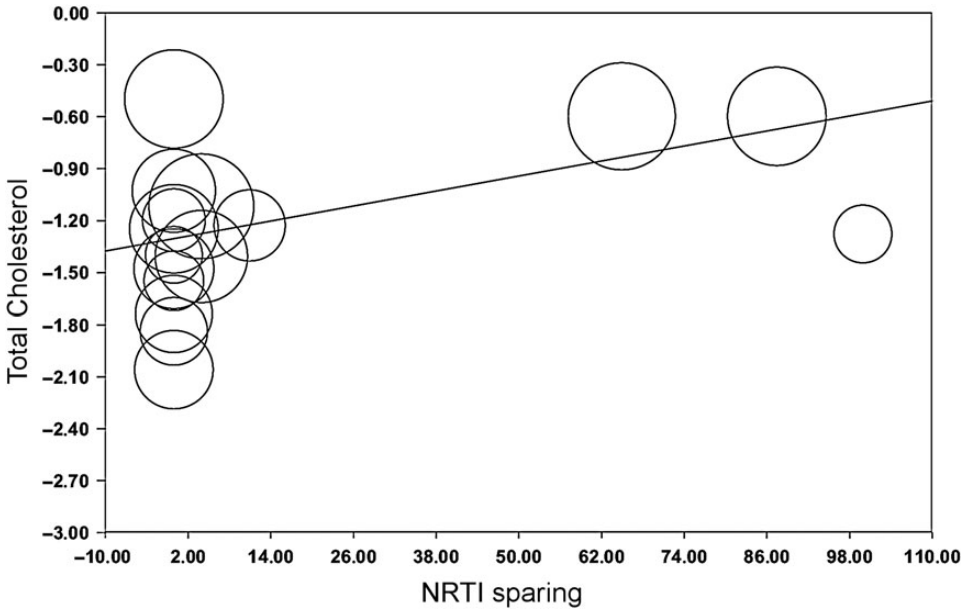

Figure 5 Meta-regression of total cholesterol reduction on percentage of patients on nucleoside reverse transcriptase inhibitors-sparing regimens (*x*-axis: percentage of patients on nucleoside reverse transcriptase inhibitors-sparing regimens; *y*-axis: mean cholesterol change in millimoles per litre). Area of circles is proportional to sample size.

−0.001), $P < 0.001$] and NRTI-sparing regimens [Beta −0.001, 95% CI (−0.002, −0.001), $P < 0.001$, Supplementary material online, *Figures S3–S5*]. Eventually, a smaller reduction of triglycerides was reported in older patients [Beta 0.030, 95% CI (0.002, 0.058), $P = 0.035$], in patients on NRTI-sparing regimens [Beta 0.006, 95% CI (0.002, 0.011), $P = 0.007$] and in those with a longer time from HIV diagnosis [Beta 0.005, 95% CI (0.003, 0.008), $P < 0.001$, Supplementary material online, *Figures S6–S8*], while no significant interactions were found for LDL and discontinuation relating to adverse events.

Network meta-analysis for TC did not show significant differences among treatments, but it was possibly limited by the inclusion of only four RCTs for TC and five for the other endpoints (Supplementary material online, *Table S3*).

The methodological assessment revealed an overall satisfactory quality of the included studies, the vast majority being prospective, a third multicentre, with low risk of bias; geographical origin of study was heterogeneous with the majority being performed in Europe (see Supplementary material online, *Figure S9* and *Table S4*).

Discussion

The main findings of the present analysis are as follows:

(1) Statins significantly reduce TC, LDL, and triglycerides in HIV-positive patients on cART.
(2) Statins have a limited efficacy for increasing HDL.
(3) Despite their risk of pharmacokinetic interactions (especially with PIs), statins and cART are safe and effective when concomitantly administered in this population.

Dyslipidaemia represents a major CV risk factor for HIV-positive patients, and it significantly contributes to increase the rate of CV events in this population.[32] Combination antiretroviral therapy, especially PIs and NNRTIs, may alter lipid metabolism and favour the development of pro-atherogenic lipid profiles, explaining the high prevalence of dyslipidaemia encountered in HIV-positive patients.[4]

Despite encouraging results for non-pharmacological interventions like diet and switching antiretroviral therapies,[6,33] statins represent a cornerstone for these patients. It has been estimated that statin therapy should be prescribed in anywhere from 19 to 26% of primary prevention patients, if treated according to current guidelines for general population.[34]

Our study is, to the best of our knowledge, the largest piece of evidence confirming the lipid-lowering effectiveness of statins in patients on cART, with all statins showing significant reductions in TC. Low-density lipoprotein and triglycerides were effectively reduced by almost all statins. High-density lipoprotein, as seen in HIV-negative patients, was only marginally influenced by statins and was the parameter with a higher number of interactions when meta-regression was performed, suggesting a weak relationship between its plasma levels changes and statin therapy. Statins also reduced non-HDL cholesterol, as can be inferred from the reduction of TC and the modest increase of HDL, and triglycerides, two strong, independent predictors of adverse CV events, which reduction may significantly improve CV prognosis.[35]

Based on our data, we can only postulate that the lipid-lowering effects of statins may lead to an improved CV outcome in HIV-positive patients; this hypothesis needs corroboration by means of adequately powered and designed studies. Statins have been shown to reduce inflammatory markers in HIV-positive patients by some

reports,[20,27] while others have failed to corroborate these findings.[28,36] More consistent positive effects have been shown for markers of atherosclerosis. Rosuvastatin decreased carotid intima-media thickness in 42 patients on NRTIs[26] and reduced monocyte activation (particularly in patients on PIs), as measured by soluble CD14, and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) in 147 patients randomized to rosuvastatin or placebo. Pravastatin showed a tendency to increase flow-mediated arterial vasodilation[24] and has been inconsistently associated with a reversion of lipodystrophy.[19,22,23] Atorvastatin reduced the atherosclerotic burden, assessed by coronary computed tomography, and Lp-PLA2, in 40 patients (95% on NRTIs).[29]

To appraise the overall effect of statin therapy in the HIV-positive population, we compared the changes in lipid values achieved in our study with those reported for the general population. As shown in Supplementary material online, *Table S5*, the main statins tested in our analysis reported a lower relative reduction of total and LDL cholesterol when compared with the values reported for general population.[37–39] Similar results emerged from three studies directly comparing statins in HIV-positive vs. HIV-negative patients,[31,40,41] and they are probably motivated by the complex interactions of cART with lipid metabolism and statins' pharmacokinetics.

Beyond effectiveness, the more critical aspect of statin therapy in HIV-positive patients is safety of their co-administration with cART, related to the numerous drug–drug interactions. Protease inhibitors variably inhibit CYP3A4 and may determine plasma accumulation of statins, especially simvastatin and lovastatin and, to a lesser extent, atorvastatin and rosuvastatin, increasing the risk of dose-related adverse events, while NNRTIs are inductors of CYP3A4 and may decrease plasma concentrations of those statins (http://www.hiv-druginteractions.org/data/ExtraPrintableCharts/ExtraPrintableChartID8.pdf). Discontinuation rate was generally low and comparable to those of the general population (3.0% in our study vs. 5.6% as reported from a pooled analysis of RCTs).[42] After assessment with meta-regression, cART did not show any significant interaction with statins concerning adverse events, confirming that statins, if appropriately dose-adjusted and monitored, may be safely prescribed regardless of the presence of these regimens. Only atorvastatin 10 mg showed a high discontinuation rate, even if no specific explanations can be provided for this finding, since, at meta-regression, no significant interactions emerged with cART, and no safety concerns were reported for higher dosages, highlighting the need of further data on this topic.

Concerning lipid-lowering effects on TC and LDL, the lone interaction with cART reported at meta-regression analysis was with NRTI-sparing regimens, which were associated with a reduced ability of statins to decrease TC. Nucleoside reverse transcriptase inhibitors have been inconsistently associated with increases in LDL and triglycerides, with the exception of tenofovir, which has been associated with lower values of TC.[43] Even if we can postulate a role of tenofovir on this result, we cannot estimate its relevance since studies included in our analysis did not provide complete reports on the specific drugs prescribed. Another possible explanation of this interaction may be that patients enrolled in the studies included in our meta-analysis with the higher prevalences ($\geq$65%) of NRTI-sparing regimens were treated with pravastatin, while in the other studies (14 studies, $\leq$20% of patients on NRTI-sparing regimens), rosuvastatin and atorvastatin were administered in 64.3% of cases. Furthermore, NRTI-sparing regimens are usually administered to more frail patients, i.e. with resistant variants (often after long treatment duration) or showing multiple co-morbidities.

No significant associations at meta-regression emerged between PIs and NNRTIs and statins, a partly unexpected finding considering the number of drug–drug interactions reported. A possible mechanism could be the fact that, as demonstrated in HIV-negative patients, lipid-lowering effect of statins may not relevantly resent of their plasma concentration, as it depends on expression and activity of hepatic uptake transporters, as organic anion transporter 1B1, which may be altered by drug–drug interactions in a scarcely predictable way.[44]

Limitations

Our study has some limitations. First, the present analysis includes both RCTs and observational studies, limiting the inferential strength of our data on one side, but increasing the applicability to real world on the other side.[45] Second, it is not a patient level meta-analysis. Third, for some classes of statins, only a few studies reported available data; however, we chose to focus on reports with statin and dose, in order to give a clear and concrete message. Fourth, results for rosuvastatin 10 mg are mainly based on the reports of a single study group (Calza *et al.*). In one of these studies,[26] it is unclear if patients enrolled were included in other studies from the same group[20,27]; after exclusion of this study,[26] analyses were repeated with no significant changes in the reported results, excepted for the discontinuation rate, which increased from 0.44 per 100 to 1.10 per 100 person-years. Moreover, conflicts of interest to exclude financial involvement with rosuvastatin producers were reported in only one out of the five studies by Calza *et al.* included.[26]

Conclusion

In HIV-positive patients on cART, statins prescribed for primary prevention presented a good safety profile and were effective for improving dyslipidaemia. Specifically, rosuvastatin 10 mg showed high reductions of TC, LDL, and triglycerides and significantly augmented HDL; pravastatin 40 mg mildly decreased TC, LDL, and triglycerides, but was unable to significantly increase HDL. Atorvastatin showed controversial safety results: pending further evidences its prescription should be carefully monitored. Simvastatin, despite proving to be safe and effective, should not be prescribed concomitantly with PIs due to pharmacokinetic interactions. Fluvastatin appeared to be safe and efficacious, even though results were based on a single study. The effectiveness of statins is apparently reduced in HIV-positive patients when compared with HIV-negative controls, probably as a consequence of the interactions of cART with lipid metabolism and with statins' pharmacokinetics. Combination antiretroviral therapy, despite the well-characterized drug–drug interactions, does not appear to affect the safety of dose-adjusted statins.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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