HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial

Paul M Ridker, Jacques Genest, S Matthijs Boekholdt, Peter Libby, Antonio M Gatto, Børge Nordestgaard, Samia Mora, Jean G MacFadyen, Robert J Glynn, John J P Kastelein, for the JUPITER Trial Study Group

Summary

Background HDL-cholesterol concentrations are inversely associated with occurrence of cardiovascular events. We addressed, using the JUPITER trial cohort, whether this association remains when LDL cholesterol concentrations are reduced to the very low ranges with high-dose statin treatment.

Methods Participants in the randomised placebo-controlled JUPITER trial, were adults without diabetes or previous cardiovascular disease, and baseline concentrations of LDL cholesterol of less than 3.37 mmol/L and high-sensitivity C-reactive protein of 2 mg/L or more. Participants were randomly allocated by a computer-generated sequence to receive rosvuastatin 20 mg per day or placebo, with participants and adjudicators masked to treatment assignment. In the present analysis, we divided the participants into quartiles of HDL-cholesterol or apolipoprotein A1 and sought evidence of association between these quartiles and the JUPITER primary endpoint of first non-fatal myocardial infarction or stroke, hospitalisation for unstable angina, arterial revascularisation, or cardiovascular death. This trial is registered with ClinicalTrials.gov, number NCT00239681.

Findings For 17 802 patients in the JUPITER trial, rosvuastatin 20 mg per day reduced the incidence of primary endpoint by 44% (p<0.0001). In 8901 (50%) patients given placebo (who had a median on treatment LDL-cholesterol concentration of 2.80 mmol/L [IQR 2.43–3.24]), HDL-cholesterol concentrations were inversely related to vascular risk both at baseline (top quartile vs bottom quartile hazard ratio [HR] 0.54, 95% CI 0.35–0.83, p=0.0039) and on-treatment (0.55, 0.35–0.87, p=0.0047). By contrast, among the 8900 (50%) patients given rosvuastatin 20 mg (who had a median on-treatment LDL-cholesterol concentration of 1.42 mmol/L [IQR 1.14–1.86]), no significant relationships were noted between quartiles of HDL-cholesterol concentration and vascular risk either at baseline (1.12, 0.62–2.03, p=0.82) or on-treatment (1.03, 0.57–1.87, p=0.97). Our analyses for apolipoprotein A1 showed an equivalent strong relation to frequency of primary outcomes in the placebo group but little association in the rosvuastatin group.

Interpretation Although measurement of HDL-cholesterol is useful as part of initial cardiovascular risk assessment, HDL-cholesterol concentrations are not predictive of residual vascular risk among patients treated with potent statin therapy who attain very low concentrations of LDL cholesterol.

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Introduction

Randomised trials of statin therapy consistently report large, significant reductions in myocardial infarction, stroke, and vascular death in both primary and secondary prevention.14 Statin therapy has been established as the pharmacological intervention of choice for patients with, or at-risk for, cardiovascular disease mainly on the basis of these trial results.

Nonetheless, a residual vascular risk remains in the active treatment arms of all statin trials. This residual risk might be explained in part because many patients have low concentrations of HDL cholesterol after statin therapy, suggesting that deficiency of HDL cholesterol could be a target for therapy. Data supporting this notion include the consistent finding7–12 that HDL-cholesterol concentrations are a strong inverse predictor of vascular events in the general population, and that on-treatment values correlated moderately with risk of future vascular events in early trials of pravastatin.13

However, analyses of the Treating to New Targets14 and PROVE-IT TIMI 22 trials, which analysed individuals with known cardiovascular disease, showed the relation between on-treatment HDL cholesterol and subsequent risk was attenuated and not significant in those allocated to receive atorvastatin 80 mg per day. One interpretation of these data is that low concentrations of HDL cholesterol might have less clinical relevance when patients are receiving high-dose statin therapy—which can reduce LDL cholesterol to very low concentrations—than when not on treatment. This possibility is especially important to assess for primary prevention, in which the cost of additional agents beyond statins will have a substantial economic burden. So far, no data about this issue are available.
In the JUPITER trial, the median on-treatment concentration of LDL cholesterol for patients allocated to receive rosuvastatin 20 mg per day was 1.42 mmol/L, and 25% achieved an LDL-cholesterol concentration of less than 1.14 mmol/L. After a median follow-up of 1.9 years (maximum 5 years), treatment with rosuvastatin was associated with a 54% reduction in myocardial infarction, a 48% reduction in stroke, a 46% reduction in revascularisation, a 43% reduction in venous thromboembolism, and a 20% reduction in total mortality. This analysis of the JUPITER trial cohort addressed, in a placebo-controlled, primary-prevention setting, whether residual risk after initiation of high-dose statin treatment was related to baseline or on-treatment concentrations of HDL cholesterol.

Methods

Patients and procedures

The study population was derived from JUPITER—a randomised, double-blind, placebo-controlled trial that was designed to investigate whether rosuvastatin 20 mg per day decreased the rate of first-ever cardiovascular events compared with placebo in 17 802 apparently healthy men and women with LDL cholesterol concentrations of less than 3.37 mmol/L and who were at high vascular risk due to concentrations of high-sensitivity C-reactive protein (hsCRP) of 2 mg/L or more. Patients with diabetes or previous cardiovascular disease were excluded from analysis. Full details of the trial protocol and CONSORT diagrams have been previously presented. Our analyses were done with the prespecified JUPITER trial primary endpoint of first occurrence of non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina, arterial revascularisation, or cardiovascular death.

JUPITER reported concentrations of LDL cholesterol, HDL cholesterol, apolipoprotein A1, triglycerides, and hsCRP for all patients at baseline (before randomisation), and once every year while on treatment. Methods used for lipid assessment followed reference Lipid Research Clinic protocols and for HDL cholesterol included use of the heparin–manganese chloride precipitation. Per protocol, and consistent with published analyses for on-treatment hsCRP, on-treatment LDL cholesterol, HDL cholesterol, and apolipoprotein A1 concentrations were prospectively defined as the values reported after the first year of treatment. Since statins have their greatest effect on LDL cholesterol, HDL cholesterol, and apolipoprotein A1 within 6–8 weeks, we decided a priori to include all postrandomisation events in our main analyses, rather than restrict the analysis to events that happened after a specific timepoint.

Randomisation and masking

JUPITER was a randomised, double-blind trial that assigned participants on a one-to-one basis to drug or placebo groups through an interactive voice-response system that generated the allocation sequence, enrolled participants to trial groups, and allocated treatment on the basis of a computer-generated list, stratified by centre, between March, 2003, and December, 2006. All endpoints were adjudicated by a committee with standardised diagnostic criteria and masked to rosuvastatin or placebo status.

Statistical analysis

The JUPITER trial enrolled 6801 women, and therefore we sought to avoid confounding of data due to sex effects caused by the higher concentrations of HDL cholesterol and lower vascular risk reported in women than in men. We divided the cohort into sex-specific quartiles of baseline and on-treatment HDL cholesterol and used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% CIs for first major cardiovascular events by HDL cholesterol concentration. Analyses were done separately for those randomly allocated to receive placebo and rosuvastatin. The analyses were repeated for baseline and on-treatment apolipoprotein A1 concentrations.

All regression analyses were adjusted for age, sex, smoking status, metabolic syndrome, family history of premature atherosclerosis, body-mass index, systolic blood pressure, fasting glucose, and estimated glomerular filtration rate. Analyses of baseline HDL cholesterol were also controlled for baseline concentrations of LDL cholesterol, triglyceride, and hsCRP; and analyses of on-treatment HDL cholesterol were also controlled for changes in concentrations of LDL cholesterol, triglyceride, and hsCRP. Reported p values are two-sided. Analyses were done with SAS version 9.1.

This trial is registered with ClinicalTrials.gov, number NCT00239681.

Role of the funding source

PMR designed and wrote the JUPITER trial protocol, which was approved by the local institutional review board at every participating centre. The trial data were analysed independently by the academic study statistician (RJG) and the academic programmer (JM) who, with the study chair (PMR), had full access to all study data. The trial was financially supported by AstraZeneca, who collected the trial data and monitored the study sites but had no role in the conduct of the analyses, in drafting this report, or in the decision to submit these analyses for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table I shows baseline characteristics from the JUPITER study population at study entry, which we divided into quartiles on the basis of HDL-cholesterol concentration. As anticipated, trial participants with high on-treatment HDL cholesterol concentrations had high concentrations...
Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | p value
--- | --- | --- | --- | ---
**Placebo**
Baseline
- n | 2308 | 2166 | 2306 | 2121
- HDL cholesterol in men (mmol/L) | 0·08 (0·0–0·98) | 1·09 (0·99–1·17) | 1·30 (1·18–1·42) | 1·63 (1·43–2·01)
- HDL cholesterol in women (mmol/L) | 1·04 (0·1–1·17) | 1·30 (1·18–1·40) | 1·55 (1·41–1·71) | 1·92 (1·71–2·12)
- Incidence (95% CI)* | 1·61 (1·32–2·01) | 1·36 (1·10–1·74) | 1·31 (1·06–1·67) | 1·15 (0·93–1·41)
- HR<sub>adj</sub> (95% CI) | 1·0 | 0·78 (0·54–1·13) | 0·69 (0·46–1·02) | 0·54 (0·35–0·83) | 0·0039
On treatment
- n | 2074 | 1995 | 1908 | 1888
- HDL cholesterol in men (mmol/L) | 0·88 (0·0–1·01) | 1·09 (1·02–1·17) | 1·32 (1·23–1·45) | 1·68 (1·46–1·92)
- HDL cholesterol in women (mmol/L) | 1·06 (0·1–1·19) | 1·32 (1·20–1·42) | 1·58 (1·43–1·74) | 1·94 (1·75–2·17)
- Incidence (95% CI)* | 1·47 (1·20–1·86) | 1·15 (0·92–1·52) | 0·90 (0·69–1·24) | 0·88 (0·66–1·22)
- HR<sub>adj</sub> (95% CI) | 1·0 | 0·87 (0·59–1·28) | 0·61 (0·39–0·95) | 0·55 (0·35–0·87) | 0·0047
**Rosuvastatin 20 mg**
Baseline
- n | 2389 | 2107 | 2244 | 2160
- HDL cholesterol in men (mmol/L) | 0·88 (0·0–0·98) | 1·09 (0·99–1·17) | 1·30 (1·18–1·42) | 1·66 (1·43–1·92)
- HDL cholesterol in women (mmol/L) | 1·04 (0·1–1·19) | 1·30 (1·20–1·40) | 1·53 (1·41–1·68) | 1·94 (1·69–2·21)
- Incidence (95% CI)* | 0·70 (0·53–0·98) | 0·85 (0·65–1·17) | 0·86 (0·66–1·17) | 0·64 (0·47–0·93)
- HR<sub>adj</sub> (95% CI) | 1·0 | 1·56 (0·95–2·56) | 1·53 (0·90–2·61) | 1·12 (0·62–2·03) | 0·82
On treatment
- n | 2128 | 1997 | 1920 | 1872
- HDL cholesterol in men (mmol/L) | 0·93 (0·0–1·06) | 1·14 (1·07–1·27) | 1·37 (1·28–1·52) | 1·76 (1·54–1·98)
- HDL cholesterol in women (mmol/L) | 1·09 (0·1–1·24) | 1·37 (1·25–1·50) | 1·63 (1·51–1·81) | 2·02 (1·82–2·25)
- Incidence (95% CI)* | 0·64 (0·47–0·91) | 0·70 (0·52–1·00) | 0·48 (0·33–0·74) | 0·62 (0·45–0·89)
- HR<sub>adj</sub> (95% CI) | 1·0 | 1·05 (0·62–1·80) | 0·86 (0·47–1·58) | 1·03 (0·57–1·87) | 0·97

Data are median (range) unless otherwise stated. Hazard ratios (HRs) and 95% CI adjusted as described in the methods. *Incidence per 100 person years.
of apolipoprotein A1 and low concentrations of triglycerides. For all baseline quartiles of HDL-cholesterol concentration, rosuvastatin significantly reduced vascular event rates, with a magnitude of effect similar to that seen in the JUPITER trial as a whole.

Random allocation to rosuvastatin in the JUPITER trial increased median on-treatment HDL cholesterol concentrations by 0.052 mmol/L (4%) compared with placebo (p=0.001). Webappendix p 1 shows baseline characteristics for patients allocated to receive placebo by quartile of on-treatment HDL cholesterol and webappendix p 2 shows data for rosuvastatin.

Consistent with studies of unselected populations, in this analysis the incidence of major cardiovascular events decreased sequentially across increasing quartiles of HDL cholesterol at baseline and on-treatment for those allocated to placebo (table 2). In fully adjusted models, the highest quartile of baseline HDL-cholesterol concentration in the placebo group had a 46% lower relative risk of vascular events at study entry than did the lowest (reference) quartile. Nearly identical inverse associations were reported in the group allocated to receive rosuvastatin (table 2). As previously reported for the JUPITER cohort, on-treatment concentrations of LDL cholesterol, apolipoprotein B, and hsCRP were associated with

By contrast with findings for patients allocated to receive placebo, the association between baseline or on-treatment HDL cholesterol concentrations and vascular risk were notably attenuated and no longer significant among those allocated to rosuvastatin (table 2). In fully adjusted models, the p value across quartiles was not significant for both groups.

As reported for HDL cholesterol, baseline and on-treatment apolipoprotein A1 concentrations were strongly inversely associated with risk of first vascular events in the placebo group (table 3). By contrast, these associations were attenuated and not statistically significant for patients allocated to receive rosuvastatin (table 3). Analyses based on percentage reduction in HDL cholesterol or apolipoprotein A1 were also null in the group given rosuvastatin (data not shown). The figure shows incidence per 100 person-years of exposure for the JUPITER primary outcome according to on-treatment concentrations of HDL cholesterol and apolipoprotein A1, stratified by random allocation to placebo or rosuvastatin groups.

Table 3: Relation between baseline and on-treatment concentrations of apolipoprotein A1 and subsequent cardiovascular disease in patients randomly allocated to receive placebo or rosuvastatin 20 mg

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
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<tr>
<td>Baseline n</td>
<td>2227</td>
<td>2263</td>
<td>2177</td>
<td>2189</td>
<td></td>
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<tr>
<td>Apolipoprotein A1 in men (g/L)</td>
<td>1.27 (0–1.38)</td>
<td>1.46 (1.39–1.54)</td>
<td>1.63 (1.55–1.73)</td>
<td>1.89 (1.74–1.97)</td>
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<tr>
<td>Apolipoprotein A1 in women (g/L)</td>
<td>1.45 (0–1.56)</td>
<td>1.66 (1.57–1.75)</td>
<td>1.84 (1.76–1.95)</td>
<td>2.12 (1.96–2.29)</td>
<td></td>
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<tr>
<td>Incidence (95% CI)*</td>
<td>1.69 (1.41–2.11)</td>
<td>1.35 (1.10–1.73)</td>
<td>1.37 (1.11–1.76)</td>
<td>0.98 (0.76–1.22)</td>
<td></td>
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<tr>
<td>HRadjusted (95% CI)</td>
<td>1.0</td>
<td>0.82 (0.58–1.14)</td>
<td>0.81 (0.57–1.14)</td>
<td>0.52 (0.35–0.77)</td>
<td>0.0018</td>
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<tr>
<td><strong>On treatment</strong></td>
<td></td>
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</tr>
<tr>
<td>n</td>
<td>2030</td>
<td>1927</td>
<td>1970</td>
<td>1906</td>
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<tr>
<td>Apolipoprotein A1 in men (g/L)</td>
<td>1.27 (0–1.38)</td>
<td>1.46 (1.39–1.54)</td>
<td>1.64 (1.55–1.74)</td>
<td>1.90 (1.75–2.06)</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1 in women (g/L)</td>
<td>1.40 (0–1.53)</td>
<td>1.61 (1.54–1.73)</td>
<td>1.82 (1.74–1.93)</td>
<td>2.10 (1.94–2.27)</td>
<td></td>
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<tr>
<td>Incidence (95% CI)*</td>
<td>1.47 (1.19–1.88)</td>
<td>1.34 (1.08–1.74)</td>
<td>0.79 (0.59–1.10)</td>
<td>0.83 (0.63–1.16)</td>
<td></td>
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<tr>
<td>HRadjusted (95% CI)</td>
<td>1.0</td>
<td>1.04 (0.72–1.50)</td>
<td>0.57 (0.37–0.88)</td>
<td>0.54 (0.35–0.85)</td>
<td>0.0012</td>
</tr>
</tbody>
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| **Rosuvastatin 20 mg** |            |            |            |            |         |
| Baseline n            | 2248       | 2248       | 2217       | 2150       |         |
| Apolipoprotein A1 in men (g/L) | 1.28 (0–1.38) | 1.47 (1.39–1.55) | 1.64 (1.56–1.75) | 1.91 (1.76–2.05) |         |
| Apolipoprotein A1 in women (g/L) | 1.46 (0–1.56) | 1.66 (1.57–1.75) | 1.85 (1.76–1.96) | 2.13 (1.97–2.30) |         |
| Incidence (95% CI)*       | 1.01 (0.80–1.33) | 0.70 (0.53–0.99) | 0.69 (0.51–0.98) | 0.65 (0.47–0.94) |         |
| HRadjusted (95% CI)       | 1.0         | 0.72 (0.46–1.14) | 0.74 (0.45–1.19) | 0.72 (0.44–1.19) | 0.20    |
| **On treatment**         |            |            |            |            |         |
| n                  | 1996       | 2017       | 1956       | 1904       |         |
| Apolipoprotein A1 in men (g/L) | 1.29 (0–1.40) | 1.49 (1.41–1.58) | 1.68 (1.59–1.80) | 1.97 (1.81–2.13) |         |
| Apolipoprotein A1 in women (g/L) | 1.43 (0–1.55) | 1.66 (1.56–1.76) | 1.87 (1.77–1.98) | 2.16 (1.99–2.33) |         |
| Incidence (95% CI)*       | 0.67 (0.49–0.97) | 0.75 (0.56–1.05) | 0.48 (0.33–0.73) | 0.47 (0.33–0.73) |         |
| HRadjusted (95% CI)       | 1.0         | 1.08 (0.64–1.83) | 0.73 (0.40–1.31) | 0.77 (0.42–1.42) | 0.25    |

Data are median (range) unless otherwise stated. Hazard ratios (HRs) and 95% CI adjusted as described in the methods. *Incidence per 100 person-years.
subsequent cardiovascular risk; thus, our study is adequately powered to show effects of lipids and other biomarkers on residual vascular risk. Other independent predictors of residual vascular risk on potent statin therapy in our fully adjusted analyses included age (p<0.00001), male sex (p=0·001), and present smoker status (p=0·0015).

Discussion
This analysis provides little evidence that residual risk after aggressive use of statin therapy is related to HDL cholesterol concentration. Although concentrations of HDL cholesterol inversely correlate with cardiovascular risk in the general population,\(^7\) whether HDL cholesterol concentrations remain an important biomarker of risk after residual vascular risk on potent statin therapy in our fully adjusted analyses included age (p<0.00001), male sex (p=0·001), and present smoker status (p=0·0015).

Our null data for HDL cholesterol and residual risk in a primary-prevention trial of rosuvastatin 20 mg are consistent with data from two secondary-prevention trials that assessed atorvastatin 80 mg per day. For secondary prevention patients enrolled in the Treating to New Targets trial,\(^14\) the inverse association between on-treatment HDL-cholesterol concentration and residual risk reported in patients given atorvastatin 10 mg per day was noticeably attenuated and no longer differed significantly in those patients given 80 mg per day. Similarly, in the PROVE-IT TIMI 22 trial of patients with acute coronary ischaemia, the relation between on-treatment HDL cholesterol and cardiovascular risk reported for patients given pravastatin 40 mg per day was not significant for those given atorvastatin 80 mg. Therefore, contemporary secondary prevention trials of high-dose statin treatment (with percentage LDL cholesterol reductions similar to rosuvastatin 20 mg per day) are consistent with our findings in a primary-prevention setting. Furthermore, investigators from a previous primary prevention lipid-lowering trial that selected participants on the basis of less than average HDL cholesterol, also showed that the relation between on-treatment HDL cholesterol and subsequent risk was null.\(^8\)

Our study has several strengths that increase validity of results. We controlled for effects of sex before analysis because women have both higher HDL cholesterol concentrations and lower vascular risk than do men, and thus analyses not done on a sex-specific basis could lead to a false finding of an inverse relation between on-

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**Figure:** Incidence rates per 100 person years of exposure for the JUPITER primary endpoint according to on-treatment concentrations of HDL cholesterol (A) and on-treatment concentrations of apolipoprotein A1 (B)

The JUPITER primary endpoint was defined as first non-fatal myocardial infarction or stroke, hospitalisation for unstable angina, arterial revascularisation, or cardiovascular death. (A) p value across HDL cholesterol quartiles was 0·0047 for placebo and 0·97 for rosuvastatin. (B) p value across apolipoprotein A1 quartiles was 0·0012 for placebo and 0·25 for rosuvastatin.
treatment HDL cholesterol concentrations and subsequent risk. Our ability to adjust for a wide range of covariates meant that any relations reported between HDL cholesterol and risk were unlikely to be attributable simply to the coincidence of low concentrations of HDL cholesterol with phenotypes typical of metabolic syndrome. Because our trial excluded participants with diabetes, residual confounding of relations between HDL cholesterol and risk on this basis was eliminated both in the placebo and rosuvastatin groups. As shown by analysis of our data, and in previously published analyses of on-treatment LDL cholesterol, apolipoprotein B, and hsCRP concentrations, we had adequate power to detect true patterns of residual risk in both treatment groups.

We used technically demanding reference Lipid Research Clinic-based heparin–manganese chloride procedures to assess concentrations of HDL cholesterol rather than more convenient, but potentially biased, direct measures that might have restricted previous investigations. Finally, our study is a primary-prevention trial in which on-treatment LDL cholesterol concentrations approach those typically reported in aboriginal populations, and thus provide valuable data for a large group of individuals with concentrations of LDL cholesterol reduced by statin therapy into the physiological range. In part, this effect is attributable to the required low LDL cholesterol concentrations for a large group of individuals with concentrations of LDL cholesterol reduced by statin therapy into the physiological range. In part, this effect is attributable to the required low LDL cholesterol concentrations for participant entry to the JUPITER trial (mean 2·71 mmol/L), which distinguish it from previous primary-prevention trials such as WOSCOPS, in which the mean entry LDL-cholesterol concentration was 4·97 mmol/L.

In our data, effects for the quartiles were similarly attenuated and non-significant for patients allocated to receive rosuvastatin 20 mg in analyses of apolipoprotein A1 rather than HDL cholesterol, although the qualitative degree of attenuation in our data seems lower for apolipoprotein A1 than for HDL cholesterol. Although this potential differential effect might be more apparent than real, our data do not prohibit the theory that elaborate measures of HDL cholesterol or HDL particles that more closely represent functionality rather than concentration might help to define residual risk. Future studies of HDL functionality are planned within the JUPITER cohort. Limitations of our study include that no diabetic patients were enrolled and that the primary-prevention JUPITER trial only included patients with LDL-cholesterol concentrations of less than 3·37 mmol/L and hsCRP concentrations of 2 mg/L or more. Thus, generalisation of our findings to other populations should be done with caution.

Our data should not reduce enthusiasm for measurement of HDL-cholesterol concentration as part of an initial cardiovascular risk assessment; as shown here among those allocated to placebo, HDLC was a powerful inverse risk predictor. However, these primary prevention data and recent secondary prevention data from the TNT and PROVE IT trials provide little evidence to support the hypotheses that HDLC levels predict risk of vascular events in the setting of high-dose statin therapy. So far, intervention trials in the statin era to test agents designed to increase HDL cholesterol concentrations have been disappointing in terms of reduction of cardiovascular disease events. However, the possibility remains that failure of published data for approaches such as inhibition of cholesterylester-transfer protein might be because of molecule-specific toxic effects rather than a failure of mechanism. Randomised trials of potent HDL cholesterol raising agents will be needed to definitively test this clinically important hypothesis.

Contributors PMR, the Principal Investigator and Trial Chairman of JUPITER, designed and undertook the trial, interpreted the data, and wrote this report. JPPK, JG, SMB, PL, and SM assisted in the design and interpretation of these analyses. RJG, the academic study statistician, along with JGM, managed the dataset and undertook the independent statistical analyses. JG, AMG, JPPK, PL, BGN, JS, and JTW are members of the JUPITER Steering Committee and assisted in many phases of the trial including participant recruitment, data collection, and data interpretation. All authors have seen and approved the final version of the report.

Conflicts of interest JUPITER was supported by AstraZeneca. During the period of this study, PMR reports having received investigator-initiated research grant support from the National Heart Lung and Blood Institute, the National Cancer Institute, the Donald W Reynolds Foundation, the Leducq Foundation, AstraZeneca, Novartis, Merck, Abbott, Roche, and Sanofi-Aventis; consulting fees and lecture fees from AstraZeneca, ISIS, Novartis, Merck-Schering Plough, Sanofi-Aventis, Seimens, and Vascular Biogenics; and is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. These patents have been licensed to several entities, including AstraZeneca. JG reports having received lecture fees from AstraZeneca, Novartis, Pfizer, Sanofi-Aventis, and Schering Plough; and consulting fees from AstraZeneca, Merck, Novartis, Sanofi-Aventis, Pfizer, and Schering-Plough. AMG reports having received consulting fees from Aegerion, Arisaph, Dupont, KOWA, Merck Schering Plough, Merck, Novartis, Pfizer, and Reliant. BGN reports receiving lecture fees from AstraZeneca, Pfizer, Merck, Sanofi-Aventis and Boehringer-Ingelheim; and consulting fees from AstraZeneca, Abbott, and Karo Bio. JPPK reports receiving research grant support from AstraZeneca, Pfizer, Roche, Novartis, Merck, and Merck Schering Plough. ISIS, Genzyme, and Sanofi-Aventis; lecture fees from AstraZeneca, Glaxo Smith Kline, Pfizer, Novartis, and Boehringer-Ingelheim; and consulting fees from AstraZeneca, Abbott, Pfizer, ISIS, Genzyme, Roche, Novartis, Merck, Merck Schering Plough, and Sanofi-Aventis. PL reports receiving lecture fees from Pfizer and lecture or consulting fees from AstraZeneca, Bristol Myers Squibb, Glaxo Smith Kline, Pfizer, Sanofi-Aventis, VIA Pharmaceutical, Interleukin Genetics, Kowa Research Institute, Novartis, and Merck Schering Plough. SM reports receiving research grant support from AstraZeneca and Merk. RJG reports receiving research grant support from AstraZeneca and Bristol Myers Squibb. All other authors reports no conflicts of interest.

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