Development of diabetes in trials of statins

An example of a systematic review and meta-analysis


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**Development of diabetes in trials of statins**

**Search strategy and selection criteria**

Large placebo and standard-care-controlled endpoint trials of statins.

Excluded:

- trials comparing statins or statin doses,
- unstable individuals, organ transplants, haemodialysis,
- only patients with diabetes,
- trials assessing change in surrogate markers of CVD,
- 1000 or fewer participants,
- mean follow-up of 1 year or less.
Search strategy and selection criteria
Trials needed to follow up patients in both treatment groups identically to avoid systematic error and resultant bias in diagnosis of incident diabetes.

Searched: Medline, Embase, and the Cochrane Central Register of Controlled Trials, from 1994 to 2009

Searched for randomised placebo and standard care-controlled endpoint trials of statins with the term “statin” as a title word and keyword, and with names of individual statins to identify reports of trials of adult patients.

Reports that were published in English between 1994 and 2009.

Identified 2841 reports.

Reviewed by two independent readers, with a third reviewer to settle any discrepancies.
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Data sources

Contacted investigators from nine trials about unpublished data for incident diabetes.

Received data from six of these trials.

Final: 13 trials, for which six had previously published data for incident diabetes and seven had not.

Because the effect estimates for incident diabetes were directly reported as hazard ratios (HRs) in only three of the six published trials, we adopted a standard approach across all trials, in which we calculated odds ratios (ORs) and their 95% CIs from the abstracted data for the number of patients who did not have diabetes at baseline and those developing incident diabetes.

Statistical analysis

Overall OR with a random-effects model meta-analysis, which assumes that the true underlying effect varies between trials.

Assessed statistical heterogeneity between trials with $I^2$ statistic (with 95% CIs), which provides a measure of the proportion of overall variation that is attributable to between-trial heterogeneity.

Used risk estimates obtained with random-effects meta-analysis instead of fixed-effects models, because this approach provides a more conservative assessment (ie, wide CIs) of the average effect size.
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Statistical analysis

Used meta-regression analyses to investigate potential sources of heterogeneity between trials.

Factors investigated were baseline age, baseline BMI, and percentage change in LDL-cholesterol concentrations, and these factors were decided before the meta-analysis was undertaken.

We analysed data with Stata version 10.1.

To test for publication bias, we formed a funnel plot and undertook the Egger test.

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<table>
<thead>
<tr>
<th>Trials</th>
<th>Statin and control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin 10 mg or placebo</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin 40 mg or placebo</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin 20 mg or placebo</td>
</tr>
<tr>
<td>WOSCOPS</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>MEGA</td>
<td>Pravastatin 10–20 mg or no treatment</td>
</tr>
<tr>
<td>AFCAPS TexCAPS</td>
<td>Lovastatin 20–40 mg or placebo</td>
</tr>
<tr>
<td>4S</td>
<td>Simvastatin 20–40 mg or placebo</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>Pravastatin 40 mg or no treatment</td>
</tr>
<tr>
<td>GISSI HF</td>
<td>Rosuvastatin 10 mg or placebo</td>
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<td>GISSI PREVENZIONE</td>
<td>Pravastatin 20 mg or no treatment</td>
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<table>
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<tr>
<th>Trials</th>
<th>Participant population</th>
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</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>Hypertension, CVD risk factors, no CHD</td>
</tr>
<tr>
<td>HPS</td>
<td>History of CVD</td>
</tr>
<tr>
<td>JUPITER</td>
<td>No CVD</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>No MI, raised cholesterol</td>
</tr>
<tr>
<td>LIPID</td>
<td>MI or unstable angina in previous 3 years</td>
</tr>
<tr>
<td>CORONA</td>
<td>Systolic heart failure (NYHA II-IV)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>Elderly people with CVD or at high risk</td>
</tr>
<tr>
<td>MEGA</td>
<td>No CVD, raised cholesterol, Japanese</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>No CVD</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>Previous MI or angina</td>
</tr>
<tr>
<td>GISSI HF</td>
<td>Chronic heart failure (NYHA II–IV)</td>
</tr>
<tr>
<td>GISSI PREVENZIONE</td>
<td>MI within past 6 months</td>
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- **Participant population**
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  - Chronic heart failure (NYHA II–IV)
  - MI within past 6 months

91,140 patients with no diabetes at baseline.
Rate = events per 1000 patient-years, random effects model.
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Meta-regression

On baseline age, baseline BMI, and on-treatment percentage reduction in LDL-cholesterol concentration

Age

\[ p = 0.019 \]

(note log vertical scale)
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Meta-regression

On baseline age, baseline BMI, and on-treatment percentage reduction in LDL-cholesterol concentration

The older the person is, the greater the increase is in the risk of diabetes when taking statins.

For younger people, aged 55 to 60, no increased risk, OR ≈ 1.00.
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Publication bias

Go to PDF file for funnel plot of the trials with published diabetes incidence data.
Funnel plot of the six statin trials which published data on incident diabetes with 95% confidence limits

Egger's test p-value = 0.144
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Publication bias

There is nothing to suggest publication bias in the funnel plot or Eggar test.

Combined estimates:
- all trials OR = 1.09
- published trials OR = 1.10

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