Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eTable 1: Trial-specific medians of five pre-specified predictors of diabetes

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>Age (years)</th>
<th>Body mass index (kg/m²)</th>
<th>Fasting plasma glucose (mg/dL)</th>
<th>HDL-cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>57</td>
<td>28.2</td>
<td>97</td>
<td>38</td>
<td>153</td>
</tr>
<tr>
<td>A to Z</td>
<td>60</td>
<td>*</td>
<td>*</td>
<td>39</td>
<td>146</td>
</tr>
<tr>
<td>TNT</td>
<td>61</td>
<td>27.6</td>
<td>97</td>
<td>46</td>
<td>131</td>
</tr>
<tr>
<td>IDEAL</td>
<td>61</td>
<td>26.6</td>
<td>97</td>
<td>46</td>
<td>131</td>
</tr>
<tr>
<td>SEARCH</td>
<td>65</td>
<td>27.4</td>
<td>*</td>
<td>39</td>
<td>143</td>
</tr>
</tbody>
</table>

* not available
eFigure 1. Standard data query sheet used for collection of data from trials

**Request for data from ________ trial:**

**Meta-analysis of incident diabetes in intensive vs. moderate dose statin trials**

1. Total number of non-DM subjects at baseline
   a. Intensive statin
   b. Low dose statin

2. Baseline characteristics of all non-DM participants at baseline, where available
   a. Mean age (SD) yrs
   b. Mean BMI (SD) kg/m²
   c. Mean fasting glucose (SD) mmol/L
   d. Mean fasting or random HDL-c (SD) mmol/L
   e. Mean fasting or random Natural log [trigs] (SD), log mmol/L
   f. Number of male _____ and female _____ non-DM at baseline
   g. Number of current smokers _____ and not current smokers at baseline

3. Mean LDL-cholesterol (SD) at:
   a. Baseline:
      i. Intensive statin
      ii. Low dose statin
   b. End of study or fixed time during study
      i. Intensive statin
      ii. Low dose statin

4. Methods of diagnosis of diabetes – which of the following were used?
   a. Physician reported (i.e. Adverse Event) **YES / NO**
   b. Commencement of oral medication or insulin **YES / NO**
   c. Biochemistry (2 fasting glucose ≥7.0mmol/L) **YES / NO**

5. Number developing diabetes in each group:
   a. Intensive statin
   b. Low dose statin
   c. Hazard ratio for developing diabetes [high vs. low dose] (95%CI) **(____)**

6. Number developing **CVD events** in each arm (where CVD events includes the following: CVD death, non-fatal MI, non-fatal stroke, coronary revascularisation [CABG, PCI])
   a. Intensive statin
   b. Standard/low dose statin
   c. Hazard ratio for CVD endpoints (high vs. low dose) [HR (95%CI)] **(____)**

7. Interactions for incident diabetes endpoint:
   a. Dichotomous: Nr developing DM / n
      i. Baseline BMI
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      ii. baseline fasting glucose (if available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      iii. baseline HDL-c (fasting or random as available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      iv. Baseline Triglycerides
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      v. baseline age
         1. > median high dose ___ / ___ low dose ___ / ___

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2. < median high dose ___ / ___ low dose ___ / ___

b. Hazard ratios (95%CI) for developing DM: high vs. low dose
   i. Baseline BMI
      1. > median
      2. < median
   
   ii. baseline fasting glucose (if available)
      1. > median
      2. < median
   
   iii. baseline HDL-c (fasting or random as available)
      1. > median
      2. < median
   
iv. Baseline Triglycerides
   1. > median
   2. < median
   
v. baseline age
   1. > median
   2. < median

8. Interactions for composite CVD endpoint (see point 6):
   a. Dichotomous: Nr developing composite CVD endpoint / n
      i. Baseline BMI
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      
      ii. baseline fasting glucose (if available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      
      iii. baseline HDL-c (fasting or random as available)
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      
      iv. baseline Triglycerides
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
      
      v. baseline age
         1. > median high dose ___ / ___ low dose ___ / ___
         2. < median high dose ___ / ___ low dose ___ / ___
   
b. Hazard ratios (95%CI) for developing CVD endpoint: high vs. low dose
      i. Baseline BMI
         1. > median
         2. < median
      
      ii. baseline fasting glucose (if available)
         1. > median
         2. < median
      
      iii. baseline HDL-c (fasting or random as available)
         1. > median
         2. < median
      
      iv. baseline Triglycerides
         1. > median
         2. < median
      
      v. baseline age
         1. > median
         2. < median
eFigure 2. Assessment of publication bias by funnel plot and Egger test

Incident diabetes

Incident CVD

Egger's test p-value = 0.536

Egger's test p-value = 0.696
eFigure 3. A comparison of new-onset diabetes and first major cardiovascular events in trials using atorvastatin 80mg and simvastatin 80mg as the respective intensive regimens

<table>
<thead>
<tr>
<th>Statin type</th>
<th>Intensive Cases / n (%)</th>
<th>Standard dose Cases / n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin 80 mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROVE IT-TIMI 22 (18)101/1707 (5.9%) 99/1688 (5.9%)</td>
<td>1.01 (0.76, 1.34)</td>
<td>315/1707 (18.4%) 355/1688 (21.0%)</td>
<td>0.85 (0.72, 1.01)</td>
</tr>
<tr>
<td>TNT (15) 418/3798 (11.0%)358/3797 (9.4%)</td>
<td>1.19 (1.02, 1.38)</td>
<td>647/3798 (17.0%) 830/3797 (21.9%)</td>
<td>0.73 (0.65, 0.82)</td>
</tr>
<tr>
<td>IDEAL (16) 240/3737 (6.4%) 209/3724 (5.6%)</td>
<td>1.15 (0.95, 1.40)</td>
<td>776/3737 (20.8%) 917/3724 (24.6%)</td>
<td>0.80 (0.72, 0.89)</td>
</tr>
<tr>
<td><strong>Simvastatin 80 mg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A to Z (17) 65/1768 (3.7%) 47/1736 (2.7%)</td>
<td>1.37 (0.94, 2.01)</td>
<td>212/1768 (12.0%) 234/1736 (13.5%)</td>
<td>0.87 (0.72, 1.07)</td>
</tr>
<tr>
<td>SEARCH (5) 625/5398 (11.6%)587/5399 (10.9%)</td>
<td>1.07 (0.95, 1.21)</td>
<td>1184/5398 (21.9%) 1214/5399 (22.5%)</td>
<td>0.97 (0.88, 1.06)</td>
</tr>
<tr>
<td><strong>Overall pooled odds ratio</strong></td>
<td>1.12 (1.04, 1.22)</td>
<td><strong>Overall pooled odds ratio</strong></td>
<td>0.84 (0.75, 0.94)</td>
</tr>
</tbody>
</table>

p-value for heterogeneity = 0.562

**Odds ratio (more vs. less intensive treatment)**
eFigure 4. A comparison of new-onset diabetes and first major cardiovascular events in trials of patients following a recent acute coronary syndrome and patients with stable coronary heart disease.
eFigure 5. A sensitivity analysis using hazard ratios for new-onset diabetes and first major cardiovascular events

<table>
<thead>
<tr>
<th>Outcome/study</th>
<th>Intensive Cases / N</th>
<th>Standard dose Cases / N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCIDENT DIABETES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNT (15)</td>
<td>418/3798</td>
<td>358/3797</td>
<td>1.18 (1.02, 1.36)</td>
</tr>
<tr>
<td>IDEAL (16)</td>
<td>240/3737</td>
<td>209/3724</td>
<td>1.16 (0.96, 1.39)</td>
</tr>
<tr>
<td>SEARCH (5)</td>
<td>625/5398</td>
<td>587/5399</td>
<td>1.07 (0.96, 1.20)</td>
</tr>
<tr>
<td><strong>Pooled hazard ratio</strong></td>
<td><strong>1283/12933</strong></td>
<td><strong>1154/12920</strong></td>
<td><strong>1.12 (1.03, 1.21)</strong></td>
</tr>
</tbody>
</table>

I² (95% CI) = 0% (0-83%), p = 0.535

| **INCIDENT CVD** |
| PROVE-IT TIMI 22 (18) | 315/1707 | 355/1688 | 0.88 (0.76, 1.02) |
| A to Z (17)            | 212/1768 | 234/1736 | 0.88 (0.73, 1.06) |
| TNT (15)               | 647/3798 | 830/3797 | 0.76 (0.68, 0.84) |
| IDEAL (16)             | 776/3737 | 917/3724 | 0.82 (0.75, 0.91) |
| SEARCH (5)             | 1184/5398| 1214/5399| 0.97 (0.89, 1.05) |
| **Pooled hazard ratio** | **3134/16408** | **3550/16344** | **0.86 (0.78, 0.95)** |

Subtotal (I-squared = 72.9%, p = 0.005)
eFigure 6. Meta-analysis of new-onset diabetes using non-standard diagnostic criteria in TNT and IDEAL

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive Cases / n</th>
<th>Standard dose Cases / n</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22 (18)</td>
<td>101/1707</td>
<td>99/1688</td>
<td>1.01 (0.76, 1.34)</td>
</tr>
<tr>
<td>A to Z (17)</td>
<td>65/1768</td>
<td>47/1736</td>
<td>1.37 (0.94, 2.01)</td>
</tr>
<tr>
<td>TNT (15)</td>
<td>351/3798</td>
<td>308/3797</td>
<td>1.15 (0.98, 1.35)</td>
</tr>
<tr>
<td>IDEAL (16)</td>
<td>239/3737</td>
<td>208/3724</td>
<td>1.15 (0.95, 1.40)</td>
</tr>
<tr>
<td>SEARCH (5)</td>
<td>625/5398</td>
<td>587/5399</td>
<td>1.07 (0.95, 1.21)</td>
</tr>
<tr>
<td><strong>Pooled odds ratio</strong></td>
<td><strong>1381/16408</strong></td>
<td><strong>1249/16344</strong></td>
<td><strong>1.11 (1.03, 1.21)</strong></td>
</tr>
</tbody>
</table>

\( I^2 = 0\% \) [95\% CI 0-64\%), \( p = 0.683 \)

_Footnote:_ use of non-standard criteria for TNT provided 117 fewer cases of new-onset diabetes and 2 fewer cases for IDEAL than in the primary analysis; the difference between TNT and IDEAL in the two analyses is explained by the differing protocols for frequency of FPG measurement in the two trials.