An Overview of CARDS (Collaborative Atorvastatin Diabetes Study): Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes

CARDS Overview 1
- A multi-center randomized placebo controlled trial to determine hard outcomes of atorvastatin 10mg vs. placebo in patients with Type 2 diabetes, & at least 1 additional cardiovascular risk factor (RF) *(63% had 1 RF, 30% had 2 RF, 6% had 3 RF & 1% had 4 RF)*, LDL ≤ 4.14 mmol/L, TG ≤ 6.78 mmol/L, and without a history of cardiovascular, cerebrovascular or peripheral vascular disease.
  * (Additional CV risk factors for inclusion were: hypertension 34%, retinopathy 40%, current smoking 23% or albuminuria 17%; in addition, the majority of patients were male, Caucasian and over 60 years of age)
- 2,838 high risk patients were followed for 4 years with the following baseline demographic characteristics:
  - age: 60-75 (Ave=62 yrs); sex: 68% male; white ethnic origin: 94%; LDL: 3.0 mmol/L; HDL: 1.4 mmol/L; TG: 1.7 mmol/L.
- Two treatment arms: **atorvastatin LIPI TOR 10mg daily** (n=1428) versus **placebo** (n=1410)

**Table 1: CARDS results - Atorvastatin 10mg daily vs placebo daily**

<table>
<thead>
<tr>
<th>Endpoints - (4 years)</th>
<th>Atorvastatin % (n=1428)</th>
<th>Placebo % (n=1410)</th>
<th>ARR %</th>
<th>RRR %</th>
<th>NNT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st time to 1st occurrence of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD death, non-fatal MI (including silent), hospitalized for unstable angina, resuscitated cardiac arrest, coronary revascularization or stroke</td>
<td>5.8 (83 events)</td>
<td>9.0 (127 events)</td>
<td>3.2</td>
<td>36</td>
<td><strong>32</strong></td>
<td>0.001</td>
</tr>
<tr>
<td>Acute Coronary Events</td>
<td>3.6</td>
<td>5.5</td>
<td>1.9</td>
<td>35</td>
<td>53</td>
<td>0.02</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1.7</td>
<td>2.4</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5</td>
<td>2.8</td>
<td>1.3</td>
<td>47</td>
<td>77</td>
<td>0.02</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>4.3</td>
<td>5.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.06</td>
</tr>
</tbody>
</table>

1 - primary outcome 2 - secondary outcome ARR = absolute risk reduction CV = cardiovascular CHD = coronary heart disease MI = myocardial infarction NNT = number needed to treat to benefit 1 patient RF = risk factor RRR = relative risk reduction

Of Note:
- **By intention to treat**: (an average of 9% of placebo group were taking a statin compared to 85% in treatment group)
- **LDL**: **initial 3.0mmol/L** (25% < 2.5mmol/L); at follow up (4yrs): placebo arm: 3.12 mmol/L; **atorvastatin arm**: **2.11 mmol/L**
- **SAFETY**: frequency of serious adverse events did not differ between groups (uncommon muscle and liver events reported in both groups)
- **Exclusion criteria** to ensure only carefully selected patients enrolled e.g. serum creatinine ≥ 150 μmol/L, creatine phosphokinase ≥ 3x normal, no concomitant drugs associated with rhabdomyolysis, fibrates or other interacting medications.
- **All-cause mortality**: trend for benefit in atorvastatin group however, it did not reach statistical significance; trial halted early.

What we knew and what these results add to that knowledge:
- Patients with Type 2 diabetes are at higher risk of stroke and cardiovascular events.
- Subgroup analysis of previous secondary prevention trials have shown reductions in major CV event rates with statins.
  - **HPS**: diabetes subgroup CHD or CVD (2) n=3051: Simvastatin 40mg/d NNT=18 over 4.8 yrs
  - **4S**: diabetes & FBG ≥ 7 mmol/L n=483: Simvastatin 20-40mg/d NNT = 7 over 5.4 yrs
  - **4S**: diabetes & IFG (FBG ≥ 6.0 mmol/L) n=678: Simvastatin 20-40mg/d NNT = 9 over 5.4 yrs
  - **CARE**: diabetes subgroup n=586: Pravastatin 40mg/d NNT = 13 over 5 yrs
- Diabetes subgroup analysis of previous primary prevention trials support possible benefit of statins.
  - **HPS**: diabetes subgroup CHD or CVD (1) n=2912: Simvastatin 40mg/d NNT = 24 over 4.8 yrs
  - **ASCOT**: diabetes subgroup n=2532: Atorvastatin 10mg/d Non-significant (Trend for benefit)
- **CARDS** is the first trial designed and powered to evaluate hard outcomes specifically in Type 2 diabetes patients with one or more cardiovascular risk factors. CARDS does not provide information on patients who are younger or without risk factors.
- **Magnitude of benefit (e.g. Number Needed to Treat)** in CARDS patients (Type 2 Diabetes & risk factors):
  - 1 less patient progressed towards a major CV event over 4 years for every 32 patients treated with atorvastatin 10mg/day.
- **CARDS** supports the findings of the HPS trial that it is cardiovascular risk and not necessarily elevated LDL that predicts beneficial outcomes in patients on statins. Similar beneficial outcomes were seen regardless of initial LDL and HDL levels.

**Questions Remaining:**
- **Would benefits be seen in younger/lower risk Type 2 diabetes patients and if so, would the numbers needed to treat justif)**
- **Is there an optimal LDL target for patients with Type 2 diabetes and if so, what is it?**
- **What effect would lipid lowering combinations (eg. statins + fibrates or ezetimibe) have on risks vs benefits?**
- **Are there any differences in risks and benefits of various statins in this population group?**
- **How do other lipid lowering drug classes compare to statins in patients with diabetes?**

**TAKE HOME:** Statin treatment (atorvastatin 10mg/d) in high risk Type 2 diabetes patients with at least 1 additional risk factor significantly reduces their risk of CV & stroke events even when initial LDL is already ≤ 3mmol/L.
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Atorvastatin benefits patients with type-2 diabetes at high risk for CVD. Benefits regardless of higher or lower initial LDL. Average atorvastatin patients achieved LDL ~ 2mmol/L

Atorvastatin 10mg/day vs Placebo in Type 2 Diabetes with 1 or more CVD risk factors, no hx of CV disease, LDLmmol/L ≤ 4.14 (Ave 3.0), TG ≤ 6.78 (Ave 1.7)

References:

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