Statins and New Onset Diabetes Mellitus

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Conflict of interest

None
Abbreviations

ADA = American Diabetes Association
ASCVD = atherosclerotic cardiovascular disease
ARR = absolute risk reduction
CHD = coronary heart disease
CHF = congestive heart failure
CVA = cerebrovascular accident
CVD = cardiovascular disease
DM = diabetes mellitus
FPG = fasting plasma glucose
GLUT4 = glucose transporter type 4
HFpEF = heart failure with preserved ejection fraction
HTN = hypertension
HDL = high-density lipoprotein
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
LDL = low-density lipoprotein
OGTT = oral glucose tolerance test
OR = odds ratio
PAD = peripheral artery disease
NNH = number needed to harm
NNT = number needed to treat
NODM = new onset diabetes mellitus
RCT = randomized control trials
RR = relative risk
RRR = relative risk reduction
SLC2A4 = solute carrier family 2 member 4
TG = triglycerides
TLC = therapeutic lifestyle changes
Lecture Objectives

1) Recognize the risk of diabetes associated with statin therapy in a population at high risk for diabetes

2) Compare and contrast statin benefit to risk when treating patients in a population at high risk for diabetes

3) Evaluate risk for diabetes as a result of statin therapy

4) Compare and contrast risk for new onset diabetes amongst individual statins
Flow

### Background
- Statin Guideline Review
- Statin benefit
- Pre-Diabetes identification and mgmt
- FDA advisory

### RCTs
- WOSCOPS, 1995
- JUPITER, 2008

### Meta-Analyses
- Rajpathk et al., 2009
- Sattar et al., 2010

### Statin Comparison
- Pitavastatin:
  - J-PREDICT, 2013
  - Vallejo-Vaz et al., 2015

### Conclusions
- Controversies
- NODM Risk Factors and Reviews
- Why does this happen?
- Other analyses and recap
Have you taken diabetes drugs? - Get justice for your suffering

If you have taken medicine for diabetes, you may qualify for compensation

Scholarly articles for Statins and diabetes

Statins and diabetes - Carmena - Cited by 34
Statins and diabetes - Maki - Cited by 9

American Diabetes Association Indications for Statins ... - Diabetes Care
care.diabetesjournals.org/content/32/suppl_2/S384
by R Eldor - 2009 - Cited by 38 - Related articles
We conclude that in this subset of individuals with diabetes, statin therapy should be based on the existing evidence and prescribed in a fixed-dose manner.

Statins Linked to Raised Risk of Type 2 Diabetes – WebMD
www.webmd.com › Diabetes › News
Mar 4, 2015 - Statins appear to increase the risk of type 2 diabetes in several ways, the researchers said. One is that the drugs can increase a person’s ...
### ADA: Testing for DM/pre-DM\(^1\)

- Adults any age who are overweight (BMI ≥ 25 kg/m\(^2\)*) + additional risk factors:

<table>
<thead>
<tr>
<th>Physical inactivity</th>
<th>Hypertension (≥140/90 mmHg or on therapy for HTN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk race/ethnicity: African American, Latino, Native American, Asian American..</td>
<td>HDL &lt; 35 mg/dL</td>
</tr>
<tr>
<td>A1C ≥ 5.7%, IGT, or IFG on previous testing</td>
<td>Other clinical conditions associated with insulin resistance (e.g., severe obesity, polycystic ovarian syndrome)</td>
</tr>
</tbody>
</table>

*Asian Americans with BMI ≥ 23 kg/m\(^2\)

Age > 45 years old
ADA: Pre-DM definitions and Management

Pre-diabetes or increased risk for diabetes

Definitions:
1. FPG 100-125 (IFG)
2. OGTT 140-199 (IGT)
3. A1c 5.7-6.4%

IFG and IGT should not be viewed as “clinical entities in their own right,” but as risk factors for DM & CVD

Management

<table>
<thead>
<tr>
<th>Management</th>
<th>A1c annually</th>
<th>150 min/week moderate activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive interventions and vigilant follow-up</td>
<td>7% weight loss</td>
<td></td>
</tr>
<tr>
<td>Treat other modifiable CVD risk factors</td>
<td>metformin* (BMI ≥35; age &lt;60; prior GDM)</td>
<td></td>
</tr>
</tbody>
</table>

*alpha-glucosidase inhibitors/orlistat/TZDs decrease incidence to various degrees (should consider cost/ADEs/lack of persistent effect with other meds)
ADA: ASCVD Risk reduction

Section 5. Prevention or Delay of T2DM
- “Increased vigilance” in the identification/treatment of modifiable CVD risk factors

Section 8. Cardiovascular disease/risk mgmt.
- ACC/AHA 10-year ASCVD risk calculator “may be a useful tool”
- Consider moderate intensity statin age 40-75 years and low-risk
- Consider high intensity statin in when high-risk (ASCVD risk factors*)
- Diabetes screening when on statin therapy

*ASCVD risk factors include: LDL ≥ 100 mg/dL, high blood pressure, smoking, CKD, albuminuria, family history premature ASCVD
Number needed to treat (NNT) x5 yrs, adjusted
- 1 case of all-cause mortality per 96 (64-244)* treated
- 1 CHD event (fatal/non-fatal) per 56 (46-75)* treated

Relative risk reduction (RRR) x5 yrs
- 25% RRR fatal/non-fatal CVD events
- 27% RRR fatal/non-fatal CHD events
- 22% RRR fatal/non-fatal CVA events
- 38% RRR revascularization (CABG, PCI)

*ranges represent 95% confidence intervals
FDA Drug Safety Communication

Increases in glycosylated hemoglobin (HbA1c) and fasting plasma glucose

2-28-2012

• Statin labels updated to reflect effect of statins on incident diabetes and increases in HbA1c and/or fasting plasma glucose

• Update was based on clinical trial, meta-analyses, and epidemiological data
Case 1

58 year old African American man is being seen for routine follow-up with PCP. Pt does not exercise, but does cook his own meals at home.

Problem list:
- Hypertension (x3 yr)
- Glaucoma (x1 yr)

Medications:
Amlodipine 10mg PO daily
Bimatoprost 0.03% i gtt OU QHS

Vitals (today):
BP: 138/79 mmHg
HR: 75 bpm
RR: 17 bpm
BMI: 31 kg/m²

Labs:

<table>
<thead>
<tr>
<th>Na⁺ 140</th>
<th>Cl⁻ 100</th>
<th>BUN 15</th>
<th>FPG 102</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ 4.5</td>
<td>HCO₃⁻ 26</td>
<td>SCr 1.1</td>
<td></td>
</tr>
</tbody>
</table>

A₁c (today) 5.9%
A₁c (1yr) 6.1%

CrCl: 103 mL/min

Fasting Lipid Panel

<table>
<thead>
<tr>
<th>TC 225</th>
<th>TG 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL 43</td>
<td>LDL 149</td>
</tr>
</tbody>
</table>

Family History:
Mother: deceased, CVA @ 68yo
Father: alive, glaucoma, HTN

Social History:
No EtOH / tobacco + cannabis, OMMP
Questions – Think Pair Share

1. What additional information is needed / wanted to assess ASCVD risk in this individual?

2. What is this person’s statin benefit group?

3. What are the **benefits** of statin therapy in understandable / layman’s terms?

4. What are the **risks** of statin therapy in understandable / layman’s terms?
1. What additional information is needed / wanted to assess ASCVD risk in this individual?
2. What is this person’s statin benefit group?
3. What are the **benefits** of statin therapy in understandable / layman’s terms?
4. What are the **risks** of statin therapy in understandable / layman’s terms?
• Statin Guideline Review
• Statin benefit
• Pre-Diabetes identification and mgmt
• FDA advisory

- WOSCOPS, 1995
- JUPITER, 2008
Randomized Control Trials: Primary Prevention

1. West of Scotland Coronary Prevention Study (WOSCOPS)
   - Primary Outcome: **Pravastatin** on incidence of MI, CHD-related death in men with **hypercholesterolemia**

2. Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)
   - Primary Outcome: **Rosuvastatin** on incidence of Major Adverse Cardiac Events in persons with **hsCRP > 2 without hyperlipidemia**
West of Scotland Coronary Prevention Study\textsuperscript{5} (and Sub-Study\textsuperscript{6}), 1995

- Sub-study Hypothesis: Pravastatin \textbf{delays} incident DM
  - \textit{WHY??} anti-inflammatory, “pleiotropic” effects of statins

- Sub-study Objective: Evaluate incidence of NODM with Pravastatin
- Total of \textbf{5,974} randomized with a 3.5 – 6.1 year follow-up

<table>
<thead>
<tr>
<th>Sub-study Included</th>
<th>Sub-Study Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 45-64 years old</td>
<td>Women</td>
</tr>
<tr>
<td>\textbf{&gt; 2 post-randomization BG readings} (checked every 6 months for duration of study)</td>
<td>\textbf{Self-reported DM} at baseline (N=76) \textbf{\textbullet} Impaired FPG (\textbf{\textgreater} 126 mg/dL) at baseline (N=72)</td>
</tr>
</tbody>
</table>
**Baseline Demographics**

*combined placebo and pravastatin groups

<table>
<thead>
<tr>
<th>Category, mean (SD)</th>
<th>Progression to DM was observed (N=139)</th>
<th>All Subjects (N=5974)</th>
</tr>
</thead>
</table>
| Age 55.6 (± 5.7) years | 55.2 | **NODM** was significantly associated with TG, BMI, FPG, pravastatin
| FPG 98.8 (± 12.4) mg/dL | 84.96 | Pravastatin reduced risk for NODM by 30% (HR 0.70 (0.50-0.99), p=0.042) |
| Systolic 138 (± 18) mmHg | 135 | |
| BMI 27.7 (± 3.6) kg/m² | 25.9 | |
| TG 193 (± 131) mg/dL | 148 | |
| Pravastatin 41% received | 50% | |

*Individuals progressing to DM on were less likely to have received pravastatin; higher average BMI, TG, BP, and FPG (unknown whether significantly different)
Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin

- Primary outcome: Incidence of Major Adverse Cardiac Events (MACE)
  - Secondary outcomes: individual components of MACE along with all-cause mortality, safety (i.e. DM)
- Randomized (1:1), prospective double-blinded, multicenter placebo-controlled trial
- Total of 17,802 randomized with median 2 year follow-up

<table>
<thead>
<tr>
<th>Included</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Men &gt; 50 y.o.</td>
<td>• Known CVD or DM</td>
</tr>
<tr>
<td>• Women &gt; 60 y.o.</td>
<td>• Uncontrolled hypertension:</td>
</tr>
<tr>
<td></td>
<td>• SBP &gt;190 or DBP &gt;100mmHg</td>
</tr>
<tr>
<td></td>
<td>• Any use of a lipid-lowering agent</td>
</tr>
<tr>
<td>• LDL &lt;130mg/dL</td>
<td>• Hepatic dysfunction (ALT &gt;2xULN)</td>
</tr>
<tr>
<td>• TG &lt;500mg/dL</td>
<td>• Creatine kinase &gt;3xULN</td>
</tr>
<tr>
<td>• hsCRP &gt;2.0mg/L</td>
<td>• Serum Creatinine &gt;2.0mg/dL</td>
</tr>
</tbody>
</table>
JUPITER\textsuperscript{7,8}

**Baseline Demographics (N= 17,802)**
*combined placebo and rosuvastatin groups*

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55.2 (± 5.5) years</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>61.8%</td>
</tr>
<tr>
<td>Race (Black or Hispanic)</td>
<td>16.6%</td>
</tr>
<tr>
<td>A1c (IQR)</td>
<td>5.7% (IQR 5.4-5.9%)</td>
</tr>
<tr>
<td>HTN</td>
<td>57%</td>
</tr>
<tr>
<td>FPG (IQR)</td>
<td>94 mg/dL (87-102)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>41.4%</td>
</tr>
</tbody>
</table>

**Incidence of New Onset DM**

<table>
<thead>
<tr>
<th>Hb-A1c (%) at 24-months</th>
<th>Physician-reported diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5.9% statin vs. 5.8% placebo; p=0.001</td>
<td>• 270 statin vs. 216 placebo; p=0.01</td>
</tr>
</tbody>
</table>

**Rosuvastatin increased risk** for NODM by \textbf{28\%}

(HR 1.28 (1.07-1.54), p=0.01)
Which of the following trials showed a protective effect from statins?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>West of Scotland Coronary Prevention Study (WOSCOPS)</td>
<td>Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)</td>
</tr>
<tr>
<td>Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)</td>
<td>Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN)</td>
</tr>
</tbody>
</table>
• Statin Guideline Review
• Statin benefit
• Pre-Diabetes identification and mgmt
• FDA advisory

• WOSCOPS, 1995
• JUPITER, 2008

• Rajpathk et al., 2009
• Sattar et al., 2010
Rajpathk et al., 2009⁹

Meta-analysis including 6 statin trials with 57,593 participants and mean follow-up x 2 years

First large meta-analysis to pool effects from multiple primary and secondary prevention trials

Used only published data
<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>SECONDARY PREVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>West of Scotland Coronary Prevention Study (WOSCOPS)</td>
<td>Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)</td>
</tr>
<tr>
<td>• RR (placebo) <strong>0.69 (0.49-0.96)</strong></td>
<td>• OR (placebo) <strong>0.95 (0.77-1.16)</strong></td>
</tr>
<tr>
<td>Anglo-Scandinavian Cardiac Outcomes Trial –Lipid Lowering Arm (ASCOT-LLA)</td>
<td>Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA)</td>
</tr>
<tr>
<td>• OR (placebo) <strong>1.14 (0.9 – 1.43)</strong></td>
<td>• OR (placebo) <strong>1.13 (0.86 – 1.49)</strong></td>
</tr>
<tr>
<td>Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)</td>
<td>Heart Protection Study (HPS)</td>
</tr>
<tr>
<td>• OR (placebo) <strong>1.25 (1.05 – 1.49)</strong></td>
<td>• OR (placebo) <strong>1.14 (0.98 – 1.33)</strong></td>
</tr>
</tbody>
</table>
Results

**Heterogeneity:** Low
**Publication bias:** None

**Trials included**

<table>
<thead>
<tr>
<th>Trials included</th>
<th>No. Statins / Total (%)</th>
<th>No. Placebo / Total (%)</th>
<th>Study Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
<td>335/7291 (4.6)</td>
<td>293/7252 (4.0)</td>
<td>1.14 (0.98, 1.33)</td>
</tr>
<tr>
<td>ASCOT</td>
<td>154/3910 (3.9)</td>
<td>134/3863 (3.5)</td>
<td>1.14 (0.90, 1.43)</td>
</tr>
<tr>
<td>LIPID</td>
<td>172/3970 (4.3)</td>
<td>181/3967 (4.6)</td>
<td>0.95 (0.77, 1.16)</td>
</tr>
<tr>
<td>CORONA</td>
<td>100/1771 (5.6)</td>
<td>88/1763 (5.0)</td>
<td>1.13 (0.86, 1.49)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>270/8901 (3.0)</td>
<td>216/8901 (2.4)</td>
<td>1.25 (1.05, 1.49)</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>1031/25843 (4.0)</td>
<td>912/25776 (3.5)</td>
<td>RR = 1.13 (1.03, 1.23) p = 0.008</td>
</tr>
</tbody>
</table>

**Excluding WOSCOPS (n = 5)**

**Statins increased risk for NODM by 13%**
(excluding WOSCOPS)
Sattar et al., 2010\textsuperscript{10}

Meta-analysis including 13 statin trials with 91,140 participants

– 6 trials with published data (included in Rajpathk analysis)
– 7 trials with unpublished DM data

New trials...
<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>SECONDARY/MIXED (1 &amp; 2) PREVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS)</td>
<td>Scandinavian Simvastatin Survival Study (4S)</td>
</tr>
<tr>
<td>• Primary Prevention</td>
<td>• Secondary Prevention</td>
</tr>
<tr>
<td>• OR (placebo) <strong>0.98 (0.70 – 1.38)</strong></td>
<td>• OR (placebo) <strong>1.03 (0.84-1.28)</strong></td>
</tr>
<tr>
<td>Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)</td>
<td>Effect of rosvastatin in patients with chronic heart failure (GISSI-HF)</td>
</tr>
<tr>
<td>• Primary prevention</td>
<td>• Primary and Secondary prevention in CHF</td>
</tr>
<tr>
<td>• OR (no treatment) <strong>1.07 (0.86-1.35)</strong></td>
<td>• OR (placebo) <strong>1.10 (0.89-1.35)</strong></td>
</tr>
<tr>
<td>Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction (GISSI-PREVENZIONE)</td>
<td></td>
</tr>
<tr>
<td>• Secondary Prevention</td>
<td></td>
</tr>
<tr>
<td>• OR (control) <strong>0.89 (0.67 – 1.20)</strong></td>
<td></td>
</tr>
<tr>
<td>Prospective study of pravastatin in the elderly at risk (PROSPER)</td>
<td></td>
</tr>
<tr>
<td>• Primary &amp; Secondary Prevention</td>
<td></td>
</tr>
<tr>
<td>• OR (placebo) <strong>1.32 (1.03-1.69)</strong></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT- LLT)</td>
<td></td>
</tr>
<tr>
<td>• Primary &gt; Secondary Prevention</td>
<td></td>
</tr>
<tr>
<td>• OR (control) <strong>1.15 (0.95-1.41)</strong></td>
<td></td>
</tr>
</tbody>
</table>

*All data are unpublished*
Results

9% increased risk for NODM (OR 1.09 (95%CI 1.02-1.17))

- NNH (statin x 4yrs) 255 (95% CI 150-852)
- ONE excess case per 1000 patient-years

Prevent FIVE (5) CV events per 1000 patient-years
Covariates associated with NODM

- Older age associated with higher incidence NODM
  - Pravastatin: 55 years WOSCOPS versus 75 years PROSPER

- No effect on outcome:
  - BMI
  - Change in LDL-C during treatment
  - Statin properties (i.e. hydrophilic versus lipophilic)

Statistical method: Meta-Regression
Conclusions *from meta-analyses*

- No evidence of a protective role from statins
- Small, but significant increase in risk for NODM
  - Attenuated with inclusion of all available evidence
- Clear CVD benefits outweigh risk for NODM
- Certain populations *(i.e. CHF in CORONA, GISSI HF)* did not see meaningful CVD benefit from statins…but still have increased risk for NODM
Results from meta-analyses characterize the risk for statin-induced NODM as:

<table>
<thead>
<tr>
<th>Non-statistically significant, but a relatively large risk</th>
<th>Statistically significant and a relatively large risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-statistically significant and a relatively small risk</td>
<td>Statistically significant, but a relatively small risk</td>
</tr>
</tbody>
</table>
Case 2

76 year old Caucasian woman is being seen for routine follow-up with PCP. The patient lives at home alone and prepares most meals for herself. She values her independence and feels she is healthy for her age.

Problem list:
- CKD Stage 3B (x5 yrs)
- Gout (x10 yrs)
- HFpEF (EF 55%)

Medications:
Allopurinol 100mg PO daily
Carvedilol 12.5mg PO BID

Social History:
No EtOH / tobacco or illicit substances

BMI: 23 kg/m²

Vitals (today):
BP: 118/69 mmHg
HR: 65 bpm
RR: 17 bpm

Family History:
Mother: unknown
Father: MI (84yo)

Labs:

<table>
<thead>
<tr>
<th>Na⁺ 140</th>
<th>Cl⁻ 100</th>
<th>BUN 15</th>
<th>FPG 102</th>
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<tr>
<td>K⁺ 4.5</td>
<td>HCO₃⁻ 26</td>
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<td></td>
</tr>
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A1c (today) 5.9%
A1c (1yr) 6.1%
CrCl: 43 mL/min
urine alb:creat: 10 mg/g

Fasting Lipid Panel

<table>
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<tr>
<th>TC 180</th>
<th>TG 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL 40</td>
<td>LDL 117</td>
</tr>
</tbody>
</table>

ACC/AHA 10-yr ASCVD risk: 13.7%
Questions – Think Pair Share

1. Is this patient indicated for statin therapy / what is her statin benefit group?

2. Is this patient at risk for new onset diabetes?
1. Is this patient indicated for statin therapy / what is her statin benefit group?
2. Is this patient at risk for new onset diabetes?
3. How does this change the risk/benefit discussion?
Flow

Background
- Statin Guideline Review
- Statin benefit
- Pre-Diabetes identification and mgmt
- FDA advisory

RCTs
- WOSCOPS, 1995
- JUPITER, 2008

Meta-Analyses
- Rajpathk et al., 2009
- Sattar et al., 2010
- Pitavastatin:
  - J-PREDICT, 2013
  - Vallejo-Vaz et al., 2015
- Other analyses and recap

Statin Comparison

Background Meta-Analyses
Statin Comparison

Rajpathk et al., 2009
Sattar et al., 2010
Pitavastatin:
  - J-PREDICT, 2013
  - Vallejo-Vaz et al., 2015
- Other analyses and recap
Risk differences between statins
Compare and Contrast: statins & goals

Preiss et al. (2011)^11
- Evaluated NODM risk based on statin-intensity
- **High vs. moderate-intensity** OR 1.12 (1.04 – 1.22)
  *No heterogeneity or publication bias

Navarese et al. (2013)^12
- Evaluated NODM risk of individual statins/doses
- **Pravastatin** 40mg/day vs. placebo OR 1.07 (0.86 – 1.30) *lowest risk*
- **Rosuvastatin** 20mg/day vs. placebo OR 1.25 (0.82 – 1.90) *highest risk*

Cai et al. (2014)^13
- Evaluated NODM risk based on **LDL goals** (< 70; 70-100; >100mg/dL goals)
- Pooled NODM target **LDL < 70 mg/dL** vs. control OR 1.33 (1.14 – 1.56)
- Pooled NODM target **LDL > 100 mg/dL** vs. control OR 1.01 (0.92 – 1.10)

More aggressive, higher-intensity therapies seem to confer higher risk
Priess et al., 2009

Favorable risk / benefit ratio when using high-intensity versus moderate-intensity statin for secondary prevention

NNT 155

CV events prevented

NODM cases

NNH 498

CV events prevented

NNT 155
Individual agents

Focus: pravastatin and pitavastatin
Pitavastatin (Livalo®) 1mg, 2mg, 4mg

FDA approved in 2009; Moderate-intensity statin

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Pitavastatin 2mg / day</th>
<th>Atorvastatin 10mg / day</th>
<th>Pitavastatin 4mg / day</th>
<th>Atorvastatin 20mg / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mean reduction, SD)</td>
<td>-37.9% (14)</td>
<td>-37.8% (15.6)</td>
<td>-44.6% (15)</td>
<td>-43.5% (16.2)</td>
</tr>
<tr>
<td>Non-HDL (mean reduction, SD)</td>
<td>-34.7% (13)</td>
<td>-35.2% (15.2)</td>
<td>-41.1% (14.2)</td>
<td>-40.6% (15.2)</td>
</tr>
<tr>
<td>HDL (mean increase, SD)</td>
<td>+4% (16.5)</td>
<td>+3% (16.9)</td>
<td>+5% (16.7)</td>
<td>+2.5% (13.7)</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov Identifier: NCT00249249

Pitavastatin 2-4mg ≈ Atorvastatin 10-20mg
Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT)\textsuperscript{15}

**Objective:** Evaluate the effect of pitavastatin on the incidence of diabetes using a prospective study design

**Primary outcome:** incidence of NODM
* determined by a 2-hr BG $\geq$ 200 mg/dl or a FPG $\geq$ 126 mg/dl measured at least once

**Design:** Multicenter, open-label, RCT (pitavastatin versus lifestyle modification) in persons with impaired glucose tolerance (IGT)

**Enrolled:** 1,269 participants
Incidence of Diabetes on Pitavastatin

- **Incidence:** 163 (pitavastatin) versus 186 (control) NODM cases per 1,000 person-years

**Cumulative HR for NODM**

**Hazard Ratio 0.82 (95% CI: 0.68-0.99)**

*p* = 0.041

18% decrease in NODM incidence with Pitavastatin compared to control.
Conclusions

- Limited conclusions can be made from a single study
- Might not be a class-effect

<table>
<thead>
<tr>
<th>Pitavastatin pros/cons assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
</tr>
<tr>
<td>Marginal reduction in risk for NODM in at-risk population</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Vallejo-Vaz et al., 2015

Meta-analysis including 15 trials with 4,815 non-diabetic participants taking pitavastatin or control*

- 4 trials with data provided by the investigators
- 11 trials provided by Kowa Pharmaceutical (mft.)

None of the other meta-analyses have included pitavastatin

*Control ranged from Placebo to active comparator (e.g. atorvastatin, simvastatin)
Pitavastatin effects on Hb-A1c

Correspondingly reduced NODM by 30% (not statistically significant)

Mean Difference (95%CI) -0.03 (-0.11, 0.05)

Heterogeneity: Moderate
Publication bias: None
Stratifying based on duration…

Effect on Hb-A1c is related to duration of therapy

### 1.9.1 Follow-up = 12 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>Hb-A1c Mean</th>
<th>Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPAGO-T</td>
<td>5.83</td>
<td>-0.03 [-0.19, 0.13]</td>
</tr>
<tr>
<td>PREVAIL-US</td>
<td>5.77</td>
<td>0.03 [-0.05, 0.11]</td>
</tr>
<tr>
<td>VISION</td>
<td>5.80</td>
<td>0.10 [-0.32, 0.52]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td><strong>0.02 [-0.05, 0.09]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity = 0%

### 1.9.2 Follow-up >12 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>Hb-A1c Mean</th>
<th>Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUTH</td>
<td>5.77</td>
<td>-0.20 [-0.63, 0.23]</td>
</tr>
<tr>
<td>COMPACT-CAD</td>
<td>5.55</td>
<td>-0.10 [-0.20, 0.00]</td>
</tr>
<tr>
<td>INTREPID</td>
<td>5.33</td>
<td>-0.13 [-0.21, -0.04]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td><strong>-0.13 [-0.21, -0.04]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity = 0%

**Effect on Hb-A1c**

- 12 week f/u
- >12 week f/u
Pravastatin
10-20mg = low-intensity ; 40-80mg = moderate intensity

• Previously reviewed:
  – West of Scotland Study (WOSCOPS)$^{5,6}$, although results are contested*
  – Meta-analyses indicating pravastatin has lower risk compared to other statins$^{12}$

• New:
  – Pravastatin has been shown to improve measures of insulin sensitivity compared to control$^{17}$
Take Home: Differences between statins

Most commonly used statins increase risk for NODM

More aggressive, higher-intensity therapies seem to confer higher risk

However…

Pitavastatin & Pravastatin consistently demonstrate a neutral (sometimes risk reducing) effect on NODM
Which statins are associated with neutral (sometimes lower) risk for NODM?

<table>
<thead>
<tr>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Pravastatin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rosuvastatin</th>
<th>Pitavastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Pravastatin</td>
</tr>
</tbody>
</table>
Case 3

48 year old Caucasian man is being seen for routine follow-up with PCP. He exercises 1-2 days/week and rarely eats out.

Problem list:
- T2DM (x10 yr)
- Hypertension (x15 yr)

Medications:
Lisinopril 10mg PO daily
Metformin 500mg (4) tabs PO daily
Aspirin 81mg PO daily

Social History:
No EtOH / tobacco or illicit substances

Family History:
Mother: alive, HTN
Father: alive, T2DM

Problems:

<table>
<thead>
<tr>
<th>Problem</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>x10 yr</td>
</tr>
<tr>
<td>Hypertension</td>
<td>x15 yr</td>
</tr>
</tbody>
</table>

Labs:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>140 mEq/L</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>100 mEq/L</td>
</tr>
<tr>
<td>BUN</td>
<td>15 mg/dL</td>
</tr>
<tr>
<td>FPG</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td>K⁺</td>
<td>4.0 mEq/L</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>26 mEq/L</td>
</tr>
<tr>
<td>SCr</td>
<td>1.1 mg/dL</td>
</tr>
</tbody>
</table>

| A₁c today     | 6.9%     |
| A₁c 3-months  | 8.1%     |

CrCl: 148 mL/min
urine alb:creat: 15 mg/g

Vitals (today):
BP: 139/89 mmHg
HR: 75 bpm
RR: 17 bpm
BMI: 41 kg/m²

ACC/AHA 10-year ASCVD risk: 14.7%

Fasting Lipid Panel:

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>250 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>300 mg/dL</td>
</tr>
<tr>
<td>HDL</td>
<td>35 mg/dL</td>
</tr>
<tr>
<td>LDL</td>
<td>155 mg/dL</td>
</tr>
</tbody>
</table>
Questions – Think Pair Share

1. What is this person’s statin benefit group?

2. Could statin therapy negatively impact glucose management efforts?

3. How does this change the risk/benefit conversation?
1. What is this person’s statin benefit group?
2. Could statin therapy negatively impact glucose management efforts?
3. How does this change the risk/benefit conversation?
### Flow

<table>
<thead>
<tr>
<th>Background</th>
<th>RCTs</th>
<th>Meta-Analyses</th>
<th>Statin Comparison</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin benefit</td>
<td>JUPITER, 2008</td>
<td>Sattar et al., 2010</td>
<td>Vallejo-Vaz et al., 2015</td>
<td>NODM Risk Factors and Reviews</td>
</tr>
<tr>
<td>Pre-Diabetes identification and mgmt</td>
<td>FDA advisory</td>
<td></td>
<td>Other analyses and recap</td>
<td>Why does this happen?</td>
</tr>
</tbody>
</table>

- **Statin Benefit**
- **Pre-Diabetes identification and mgmt**
- **FDA advisory**
- **WOSCOPS, 1995**
- **JUPITER, 2008**
- **Rajpathk et al., 2009**
- **Sattar et al., 2010**
- **Pitavastatin: J-PREDICT, 2013**
- **Vallejo-Vaz et al., 2015**
- **Other analyses and recap**
- **Controversies**
- **NODM Risk Factors and Reviews**
- **Why does this happen?**
Risk factors
Waters et al.\textsuperscript{18}  

Using data from secondary prevention trials (TNT & IDEAL)  

1. FPG $> 100$ mg/dL (IFG)  
2. Triglycerides $> 150$ mg/dL  
3. BMI $> 30$ kg/m$^2$ (Obese)  
4. History of HTN  

Effects of high-intensity Atorvastatin (80 mg/day)  
- 0 – 1 risk factors $\rightarrow$ no increased risk  
- 2 – 4 NODM risk factors $\rightarrow$ 24% higher risk
Navarese et al.\textsuperscript{19} recommends a “tailored” approach for statin therapy

1. Assess DM risk factors:
   - FPG > 100
   - HTN
   - BMI > 30kg/m\textsuperscript{2}
   - Triglycerides >150

2. Assess statin indication:
   - Primary versus secondary prevention

3. If primary prevention + 2-4 NODM risk factors
   $\rightarrow$ pravastatin 40mg/day + glycemic control

Conundrum: the risk for NODM is largest in patients who receive the largest benefit from statin therapy
What is the **best option** for someone who is indicated for high-intensity statin therapy, but is concerned about NODM?

<table>
<thead>
<tr>
<th>Atorvastatin 40-80mg</th>
<th>Avoid statins, recommend ezetimibe (Zetia) 10mg instead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin 40-80mg</td>
<td>Pravastatin 40-80mg + Additional lipid lowering agent (e.g. bile acid Sequestrant)</td>
</tr>
</tbody>
</table>
Discussing with patients
Risk vs. Benefit

- Patients who are Pre-DM and indicated for statins should still get them if they’re eligible
  - Benefit far outweighs risk

- Patients should be made aware of the risks for statin therapy, but should understand this risk in context
  - Some patients may be receptive to NNT / NNH explained in simple, understandable terms
  - Other patients may respond better to analogies: “Needing emergency treatment in the next year from injury by a can, glass bottle, or jar” has a 1 in 1000 risk (source: BMJ clinical evidence)

- Consider reviewing 10-yr ASCVD risk before and after statin therapy (using individualized risk factors)
Embrace the next paradigm

Discussing risks and benefits in absolute terms
NET ASCVD risk reduction benefit²⁰
Controversies

1. Differentiation among statins:
   - Risk tends to be higher using high-intensity statins / goals
2. Low CVD risk primary prevention / CHF groups
   - Does risk for NODM outweigh CV benefits ?

3. Changes in monitoring DM progression
   - National Lipid Association Safety Task Force recommend checking A1c before and within 1-yr after beginning statins in at-risk individuals (expert opinion)\(^2\)

4. Why does this occur
   - Many theories, very limited in vivo data

5. Statin trials fundamentally flawed for detecting NODM
Why does this happen?
Mechanism: HMG-CoA Reductase Inhibition

• Genetic studies have demonstrated that single nucleotide polymorphisms (SNPs) of HMGCoAR that are associated with *increased weight and T2DM*\(^2^2\)
  – SNPs selected as “proxies” of the HMG-CoAR inhibition activity of statins

• Statin mechanism is associated with NODM, but does not fully explain the phenomena

• Other analyses have found statistically significant increases in body weight \(+0.53 \text{ lbs}\) in statin treatment arms.\(^2^3\)
Nakata et al., 2006

- **SLC2A4 (GLUT4)**
  - Insulin-stimulated glucose uptake into adipose
  - Decreased expression → to insulin-resistance in T2DM
  - In vitro: atorvastatin inhibited adipocyte expression of SLC2A4

**In vivo:** Murine T2DM model showed **insulin resistance** with atorvastatin vs. control feed

- In vivo: T2DM patients receiving atorvastatin 10mg daily had a significantly higher A1c compared to baseline

**Graph:**

- **A1c (%)**
- **Total (N=78)**
- **BMI < 26**
- **BMI > 26**

**Images:**

[https://www.mnn.com](https://www.mnn.com)  [www.pachd.com](http://www.pachd.com)
### Other effects on glucose metabolism

<table>
<thead>
<tr>
<th>Effect on glucose metabolism</th>
<th>Statins associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased insulin secretion</td>
<td>Atorvastatin, Simvastatin</td>
</tr>
<tr>
<td>Decreased insulin sensitivity</td>
<td>Atorvastatin, Lovastatin, Simvastatin, Rosuvastatin</td>
</tr>
<tr>
<td>Increased insulin sensitivity</td>
<td>Atorvastatin, Pravastatin, Rosuvastatin</td>
</tr>
<tr>
<td>No effect on glucose metabolism</td>
<td>Pravastatin</td>
</tr>
</tbody>
</table>
Case 1: Redux

58 year old African American man is being seen for routine follow-up with PCP. Pt does not exercise, but does cook his own meals at home

Problem list:
- Hypertension (x3 yr)
- Glaucoma (x1 yr)

Medications:
Amlodipine 10mg PO daily
Bimatoprost 0.03% i gtt OU QHS

Vitals (today):
BP: 138/79 mmHg
HR: 75 bpm
RR: 17 bpm
BMI: 31 kg/m²

Labs:
<table>
<thead>
<tr>
<th>Na⁺ 140</th>
<th>Cl⁻ 100</th>
<th>BUN 15</th>
<th>FPG 102</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ 4.5</td>
<td>HCO₃⁻ 26</td>
<td>SCr 1.1</td>
<td></td>
</tr>
</tbody>
</table>

A₁c (today)  5.9%
A₁c (1yr)  6.1%
CrCl: 103 mL/min

Fasting Lipid Panel
<table>
<thead>
<tr>
<th>TC 225</th>
<th>TG 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL 43</td>
<td>LDL 149</td>
</tr>
</tbody>
</table>

Family History:
Mother: deceased, CVA @ 68yo
Father: alive, glaucoma, HTN

Social History:
No EtOH / tobacco + cannabis, OMMP
Questions – Think Pair Share

1. How many risk factors for NODM are present?

2. Does risk for NODM change initial thoughts about statin choice / dose?

3. What ongoing monitoring is recommended?
1. How many risk factors for NODM are present?
2. Does risk for NODM change initial thoughts about statin choice / dose?
3. What ongoing monitoring is recommended?
The decision is made to begin Atorvastatin 80mg PO daily.

High-intensity statin is contraindication based on 4 of the 4 risk factors for NODM

The therapy is inappropriate given the current 10-yr ASCVD risk

The addition of a statin may contribute a small risk of progression to DM

Statins have only been shown to worsen DM once a person has developed the disease

Which of the following is true in your evaluation of the chosen therapy?
References

Statins and New Onset Diabetes Mellitus

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St. Louis County Department of Public Health
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