Statin Benefits and Risks

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“The years between 50 and 70 are the hardest. You are always being asked to do things, and yet you are not decrepit enough to turn them down.”
-- T.S. Eliot, American-British writer

Outline

• Do statins work well?
• Do statins work well in patients with diabetes?
• How common is statin-induced “myopathy”?
• Do statins cause diabetes— if so how often?
• If so, can we identify risk-factors for statin-induced diabetes?
• What might be the mechanisms of statin-induced diabetes?
• What is the risk-benefit of statin use vis-a-vis diabetes?

Sequential steps in the LDL receptor pathway of mammalian cells

Joseph L. Goldstein, and Michael S. Brown

Where do Statins Work?

Brault M et al Metabolism 2014, 735-745

Nobel Prize in Physiology: Brown and Goldstein—October 15, 1985

Joseph L. Goldstein, and Michael S. Brown
Lipophilicity/Hydrophilicity of Statins

- Lipophilic:
  - Atorvastatin
  - Cerivastatin
  - Fluvastatin
  - Lovastatin
  - Pitavastatin
  - Simvastatin

- Hydrophilic:
  - Pravastatin
  - Rosuvastatin

CTT Collaboration: Lancet 2010; 376: 1670-81

HPS: Diabetes Subgroup (n=5963)


Atorvastatin for Primary CVD Prevention in Diabetes Mellitus (CARDs Trial)

Calhoun HM et al Lancet 2004

What About Randomized, Controlled Statin Trials in Type 1 Diabetes?
EDIC – Type 1 Diabetes and CV Events

Study Design

1,425 Type 1 Diabetics enrolled between 1983-1989 to achieve A1C < 6.5%

Intensive A1C Control
Conventional A1C Control

Double Blind
Observational

1375 DCCT patients continued into EDIC, all switched to intensive A1C control

Primary endpoint: CV events*, nonfatal MI, stroke and CV death
Secondary endpoints: Long-term microvascular and neurologic outcomes

Conclusions

First long-term study to show that early intensive control of A1C can reduce CV events relative to conventional control
- 42% risk reduction in all CV events
- 57% risk reduction in nonfatal MI, stroke and CV death

These risk reductions are greater than those seen in hypertension or lipid treatment studies to date
The beneficial CV results were mediated by reductions in A1C
Controlled A1C accounted for 97% of CV event reduction

Swedish National Diabetes Register

- N=24,230
- Observational
- Propensity-based
- Retrospective
- Type 1 diabetes
  - Rx insulin only
  - Less than 30 y.o.
- 22-44% risk redux
  - CVD
  - CV death

Statins and Muscle Pain: 10-15% of patients treated!!

Norata D et al. Pharmacological Res. Volume 88, October 2014, Pages 107-113
Review of Statins and Muscle Problems


STOMP: Atorvastatin Doubled Muscle Complaints


Gauss-3 and Muscle Symptoms


Proposed Mechanisms of Statin Side-Effects

Statins and Muscle Toxicity

Norata G et al. Pharmacological Res. Volume 88, October 2014, Pages 107–113

Statins and Diabetes

West of Scotland:
Development of diabetes mellitus according to (A) median BMI (B) Ln triglyceride (C) Baseline Glucose(D) placebo or pravastatin 40 mg/d.


Incidence rates of physician-diagnosed diabetes in the JUPITER trial

Ritler PM et al. Lancet 2012; 380: 565–71

Meta-analysis of Statins and Diabetes

Sattar N et al. The Lancet. 375(9716) 27 February–5 March 2010, Pages 735–742

KEY POINTS

- Only 30–50% of patients with self-reported statin myalgia actually experience muscle pain because of statins and not from other causes.
- There are likely to be multiple, interactive and potentially additive mechanisms underlying statin-associated muscle side-effects.
- More clinical trials on statin myalgia are critical to the field, as are resources for quantifying, predicting and reporting statin-associated muscle side-effects.
Risk of Statin-Induced Diabetes: Moderate vs Intensive Dose


Glycemic Effect of Statin Therapy in patients with Vascular Disease (from SMART study)

Van de Woestijne et al. Am J Cardiol. 2015 Feb 15;115(4):441-6

Risk Factors for Statin-Associated Diabetes


Risk Factors for Statin-induced Diabetes

Preiss D et al. JAMA. 2011 Jun 22;305(24):2556-64

Diabetes in New Statin Users: Ontario Drug Benefit (ODB) Database

Alesisa A Carter et al. BMJ 2013;346:b1630

South Korean Retrospective Study of Statins and New-Onset DM or IFG

Cho Y et al. Metabolism 2015; 482–488
Meta-analysis of Statin Trials and Type 2 Diabetes

Nat. Rev. Endocrinol. doi:10.1038/nrendo.2015.194

Diabetes in TNT, IDEAL and SPARCL according to number of risk factors and treatment

Waters DO et al JACC. 57(14), April 2011, pp 1535–1545

Predictors of New-Onset Diabetes in Patients Treated With Atorvastatin: Results From 3 Large Randomized Clinical Trials

Waters DO et al JACC. 57(14), April 2011, pp 1535–1545

Cardiovascular Event Reduction Versus New-Onset Diabetes During Atorvastatin Therapy: Effect of Baseline Risk Factors for Diabetes

Waters DO JACC Volume 61, Issue 2, 2013, 148–152

Do Statins Increase Microvascular Complications from Diabetes: 215,725 patient –year follow up


Statins: Benefits and Risks re: Diabetes

**Summary of Clinical Findings re: Statins and Diabetes**

- Statins are associated with ~10% increased risk of Type 2 diabetes over 4 years (but up to 46% in METSIM)
- Risk Factors
  - Age
  - Obesity
  - Inactivity
  - Lower HDL
  - Higher TG
  - Higher FPG
  - Higher 2 h PPG
  - Higher HbA1C
- 77?lipophilicity?? Is pravastatin preferable in high-risk patient??
- In patients with pre-existing diabetes, HbA1C rose 0.12-0.3%

**Statin Treatment is Associated with Both Impaired Insulin Sensitivity and Insulin Secretion**

Cederberg H et al Diabetologia (2015); 1109-1117

**Effect of Statin Dose on A1C and Insulin Levels**

Kwag KK et al JACC; 2010; 55(12) 1209–1216

**Effect of Statin Dose on Adiponectin and Insulin Resistance**

Kwag KK et al JACC; 2010; 55(12) 1209–1216

**Potential Effects of Statins on Insulin Action**

**Potential Effects of Statins on Beta Cell Function**

Potential Effects of Statins on Insulin Action

Brault M et al Metabolism 2014; 735-745

Association Between Familial Hypercholesterolemia and Prevalence of Type 2 Diabetes Mellitus

Besseling J et al JAMA 2015; 313(10):1029-1036

Sattar Meta-analysis

- 12-23 cases per 1000 patient-years with statin treatment and 11-25 cases per 1000 patient-years with control therapy
- Statin therapy was associated with a reduction in major coronary events of 5-4 events per 255 patients treated for 4 years compared with control therapy for a 1 mmol/L reduction in LDL-cholesterol concentration.
- In other words, NNT= 155 for CVD, and 498 for DM

Summary and Conclusions

- Do statins work well: YES
- Do statins work well in patients with diabetes: YES
- How common is statin-induced myopathy: RARE
- >20% vs placebo in patients with "statin-intolerance"
- Do statins cause diabetes: Probably. About 10% increased relative risk
- Can we identify risk factors for statin-associated diabetes: YES: the usual risk factors for diabetes, and statin dose; — ?Lipophilicity and potency?
- Mechanism of statin-associated diabetes: both impaired insulin secretion and insulin action
- What is the risk-benefit for statin-associated diabetes: Clearly in favor of treating when indicated—especially in patients with diabetes or patients without diabetes risk factors.

You always run a risk, but I think the positive outweighs the risks, ... Life itself is a risk. But I'm not worried about that. If I was concerned about that, I wouldn't be up here.