Statin Therapy An Update on Adverse Effects

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Introduction

- Statin use has been associated with many potential side effects.
- Statin intolerance rates are significantly high such that patient adherence should not be assumed.
- Statin side effects, both real and imagined, adversely affect patient health, their sense of well being, and can jeopardize the patient-physician relationship.

Overview

- Review the frequency of statin use and discontinuation rates.
- Review three potential adverse effects of statins and the data on their incidence.
- Discuss ways to approach patients with each side effect.

Statin Facts

- Statins are the most widely prescribed drugs worldwide.[1]
- According to IMS Health there were more than 300,000,000 prescriptions fo statins written between 2005 and 2011 alone.
- 25% of patients prescribed statins stop the medications within 6 months and up to 60% discontinue the medication within 2 years.[2]

1-Baigent C et al Efficacy and safety of cholesterol lowering treatment Lancet

Effects

Why use them?

- Statin use confers a clear benefit in reduction of risk of cardiovascular events for primary and secondary prevention.
- Statins lower the burden of atherogenic lipid particles, may stabilize vulnerable plaque, improve endothelial function, and potentially, in a subset of patients, lead to regression of atherosclerosis

3 Potential Side Effect of Statins

1. Myopathy
2. Memory and cognitive impairment
3. Diabetes mellitus

Statin Myopathy

- Myopathy-most common side effect but poorly defined (myalgias, arthralgias, fatigue, malaise). Occur more commonly in practice than in clinical trials. -incidence unknown but probably in range of 10-25%.
- Myositis-rare ≈.5% Elevated CK with or without muscle symptoms.
- Rhabdomyolysis-<.1%. CK > 10 times ULN with muscle symptoms.

Myopathy

- **Symptoms may include muscle pain, burning and weakness, particularly after exertion. Joint pains are also commonly described.**
- **There is no definitive test to diagnose statin myopathy.**
- **Often are not associated with an increase in creatine kinase (CK) levels.**
- **There are conditions or behaviors (thyroid disease, alcohol consumption, or excessive supplement use) that may increase the likelihood of statin myopathy.**

Statin Myopathy: The Data

- **Largest observational study was PRIMO-2005. 7900 hyperlipidemic patients. No control group.**
  - **10.5% of patients reported muscular symptoms. Median time to onset was 1 month.**
- **FDA Adverse Events Reporting System-2012 Higher potency≈higher reported rates of muscle complaints**
  - **Relative rank rosuvastatin 1.0> atorvastatin .55 >simvastatin .26>pravastatin .17>lovastatin .075**

statin myopathy

- **Our job is determine the likelihood that the symptoms are due to the statin vs. an alternative cause.**
  - **Did the symptoms start within a few weeks of initiation of the statin?**
  - **Is the discomfort more frequent or severe after physical activity? Is the discomfort symmetric?**
  - **Have the symptoms persisted for more than 2 weeks?**
  - **Do the symptoms resolve within 2 weeks of discontinuation of the statin?**

Differential diagnosis of statin myopathy

1. **Metabolic myopathy or peripheral neuropathy**
   - **Does the patient have a prior or family history of a neuromuscular disease?**
   - **Is there objective evidence of muscle weakness, fasciculations or abnormal reflexes?**
2. **Peripheral arterial disease-Dyslipidemia is a risk factor for PAD.**
   - **Asymmetric pain with diminished pulses and a pattern of exacerbation during (rather than after) activity and improves quickly with rest**

Statin Myopathy

- Strategies for addressing myopathy
  - Switching to a different statin.
  - Less frequent dosing or lowering the dose.
  - Accepting a less aggressive LDL target.
  - Coenzyme Q10-but no compelling clinical data and the supplement is expensive!

Cognitive Decline

- **Issues initially raised due to a 2003 post-marketing report of memory impairment and slowing of thought processing of higher functions.**
- **Flurry of press coverage this summer revisiting the issue following the release of the FDA summary on statin adverse effects.**

What does the data show?

- **Two large randomized studies**
  - **PROSPER-Prospective Study of Pravastatin in the Elderly at Risk for Vascular Disease-5800 subjects on 40 mg of pravastatin daily. Examined effect of drug on cognitive function with extensive tests every 9 months (mean f/u 42 months)**
    - **Findings-there was a general decline in cognitive function.**
    - **No difference though between pravastatin and placebo group in regard to cognitive function, memory loss or confusion.**
  - **HEART PROTECTION STUDY-20,536 patients on 40 mg of simvastatin**
    - **Assessed for change in cognitive function based on a single questionaire at end of study. Mean follow up just over 5 years.**
    - **No significant difference between simvastatin and placebo**

Cognitive Decline
What does the data show?

- Recent review of 9 observational studies revealed:
- 2 studies found evidence of an increased risk of cognitive impairment associated with statin use.
- 3 found no effect.
- 4 suggested a beneficial effect of statin use on cognitive performance.

- *Jukema et al J Am Coll Cardiol*. 2012;():. doi:10.1016/j.jacc.2012.07.007

safety label changes to cholesterol lowering statin drugs July, 2012

- **“Post marketing reports generally described individuals over the age of 50 who experienced notable, but ill defined memory loss or impairment that was reversible upon discontinuation of statin therapy.”**
- **“Data from observational studies and clinical trials did not suggest that cognitive changes with statin use are common or lead to clinically significant cognitive decline.”**

Statin use and Diabetes

Conflicting data from randomized trials

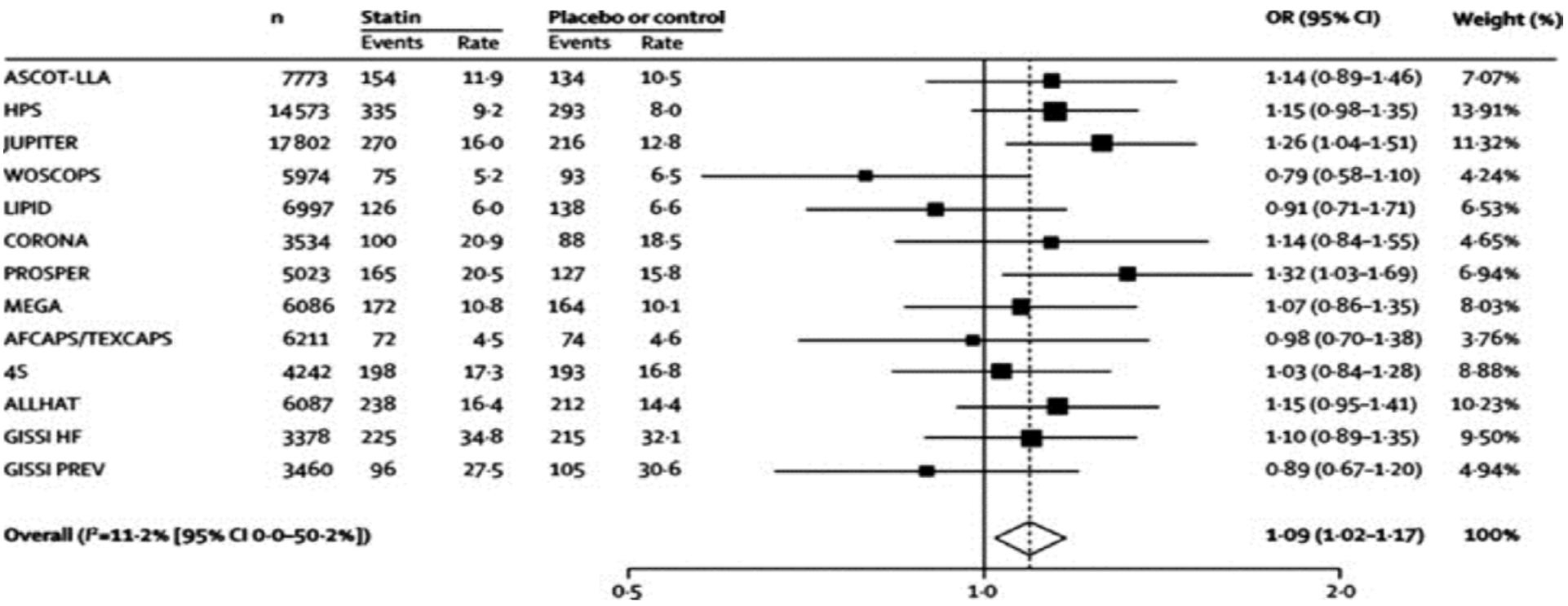
- **JUPITER-27% relative increased risk for developn diabetes after rosuvastatin therapy.**
- **WOSCOPS-reduced risk of diabetes following pravastatin therapy.**

Large meta-analysis in 2010 examined this question statin trials involving over 91,000 patients. Results:

- **Statin therapy associated with 9% increased risk f incident diabetes.**
- **Reduction in cardiovascular death risk, MI and CV**

Controversies of Statin Therapy: Title and subTitle BreakWeighing the Evidence

liol. 2012;():. doi:10.1016/j.jacc.2012.07.007



e Legend:

iation Between Statin Therapy and Incident Diabetes in 13 Major Cardiovascular Trials
s per 1,000 patient-years. Weights are from random-effects analysis. Figure was originally published in Sattar et al. (66); ssion for its use granted by the publisher. CI = confidence interval; OR = odds ratio.

Statin use and diabetes

- **FDA 2012 "increases in fasting serum glucose an glycosolated hemoglobin have been reported wit statin use."**
- **Update on JUPITER data-risk of developing diabetes generally confined to those with risk factors for the disease including: impaired fastin glucose, metabolic syndrome, obesity or raised hemoglobin A1c.[1]**
- **Follow HgbA1c or fasting glucose with lipid panels annually? Diet modification!**

Ridker et al. Cardiovascular benefits and

Statin Side Effects: The office visit

- **First--Remember to specifically ask about side effects!**
  - **Reassess risk-benefit of the medication and talks this over in detail with your patient.**
  - **Evaluate for objective evidence that the symptom is due to the statin.**
  - **Don’t overlook alternative diagnoses.**
  - **Spend time to reassure the patient and develop a mutually agreed upon strategy to minimize the side effect.**

Statin Side Effects Review

- Prevalence of statin use.
- Myopathy, cognitive decline and diabetes.
- Strategies for dealing with the patient who experiences these symptoms after taking a statin.