Current Issues and Controversies in the Management of Dyslipidemia

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Program Overview:
It was only around 30 years ago that the link between cholesterol and heart disease was established. The higher the cholesterol level, the higher the risk of getting heart disease. The lowering of cholesterol, on the other hand, was found to reduce the risk of getting the disease. However, disagreements in the management of dyslipidemia still exist. This knowledge-based program will identify current issues with treatment, outline the differing points of view, and offer potential changes in treatment based on findings from recent studies.

Objectives:
• Describe two current issues in the management of dyslipidemia.
• Compare and contrast the opposing viewpoints in at least one current controversy in the management of dyslipidemia.
• Identify at least one potential change in the management of dyslipidemia based on the findings of recent studies.

Speaker: Dr. Scott Stolte joined the faculty of the Bernard J. Dunn School of Pharmacy at Shenandoah University in 1998. Scott served as a faculty member and as Chair of the Department of Pharmacy Practice prior to assuming his position as Associate Dean for Academic Affairs. Dr. Stolte earned his Doctor of Pharmacy degree from Purdue University in West Lafayette, IN in 1997. After graduation, Dr. Stolte was the initial community pharmacy resident at FamilyPharmaCare Center, Inc. and Purdue University.

Speaker Disclosure: Dr. Stolte has no actual or potential conflicts of interest in relation to this program.

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Is LDL-cholesterol reduction with statins beneficial in individuals who do not have elevated LDL-cholesterol?

**Background**
- Previous studies suggest that CV risk decreases with LDL-C reduction by statins
  - Decrease is linear
  - Approximately 20% reduction in vascular events for 40 mg/dL reduction

**Meta-analysis**
- Patient-level data from 21 placebo-controlled trials
  - 130,000 patients
- ALSO, 5 trials comparing high-dose and low-dose statin therapy
  - 40,000 patients
- Average follow-up = 5 years
- All primary prevention

**Results**
- Placebo-controlled trials
  - 41 mg/dL greater decline in LDL-C
  - 22% fewer first major vascular events
    - (2.8% vs. 3.6% annually)
- High-dose vs. low-dose
  - High-dose patients had:
    - 20 mg/dL greater decline in LDL-C
    - 15% fewer first major vascular events
      - (4.5% vs. 5.3% annually)
**KEY FINDING**

- Both Trials
  - Relative risk reduction of 20% per 40 mg/dL decline in LDL-C
  - All patient subgroups
  - All baseline LDL-C levels
    - Including LDL-C <80 mg/dL
  - Rhabdomyolysis and myopathy dose-related but not frequent

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**Summary**

- LDL-C predictably and safely lowered CV risk regardless of baseline LDL-C concentrations
- Target-based treatments may not be optimal guidelines
- Risk reduction greater in patients with high CV risk vs. low CV risk
  - Priority should be given to high risk patients

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**References**


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**Do statins provide benefit to patients with elevated CRP with low CV risk?**
**Background**

- C-reactive protein is an acute-phase protein that rises in response to inflammation
- JUPITER trial
  - Patients had CRP ≥ 2 mg/dL
  - Patients were low risk
  - Trial suggests statins may benefit patients with high CRP who are low risk.

**Heart Protection Study**

- > 20,000 adults
  - High risk for vascular events
  - Received either for 5 years:
    - Simvastatin 40 mg po qd OR Placebo
  - Simvastatin patients:
    - 24% fewer first vascular events (MI, stroke, revascularization)
    - LDL-C and CRP available for 2727 patients

**CRP**

- Patients divided into six groups based on CRP
  - Lowest <1.25 mg/L
  - Highest >8.0 mg/L
- Vascular events lower for simvastatin patients than placebo at all levels
  - No relation to CRP concentrations
  - Simvastatin pts with low CRP and LDL-C had proportional reductions in vascular risk similar to those with high CRP and LDL-C

**Reference**

Overall Conclusions

- Statins produce proportional reductions in vascular events:
  ◦ Regardless of baseline LDL-C concentrations
  ◦ Regardless of baseline CRP levels in high risk patients

Should HDL-cholesterol be raised in healthy patients who have had LDL-cholesterol lowered substantially by statins?

Background

- After LDL-cholesterol has been lowered by statin therapy, some CV risk remains.
- Uncertain how much of this risk is based on remaining low HDL-cholesterol
- Some studies have shown residual low HDL-C is a risk

Initial Study

- JUPITER trial
  ◦ 17,802 patients
  ◦ Baseline LDL-C ≤130 mg/dL
  ◦ CRP ≥2 mg/dL
  ◦ No history of CV disease or DM
  ◦ Placed on rosuvastatin 20 mg or placebo
  ◦ After 2 years follow-up
    • Treatment group
      ◦ Median LDL-C = 54 mg/dL
      ◦ 50% fewer CV events
      ◦ 20% fewer deaths
**Post hoc Analysis**

- Placebo recipients with high baseline and on treatment HDL-C
  - Significantly fewer CV endpoints than those with low HDL-C
- Patients who received rosuvastatin
  - HDL-C concentration had no significant association with CV risk

**What does this mean?**

- In healthy patients receiving statins for primary prevention:
  - HDL-C is not an important residual CV risk factor
  - Somewhat conflicting findings from other studies

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**References**


**Why is the rate of fibrate prescribing increasing so rapidly in the US?**
Background

- Gemfibrozil (Lopid and generics), fenofibrate (Tricor and others), fenofibric acid (Trilipix) widely prescribed
- Effectiveness in preventing CV events is controversial
  - Especially in statin-treated patients

Study

- Examined US and Canada fibrate prescribing from 2002-2009
- During that time:
  - Rate flat in Canada
  - Rate doubled in US
- Brand name fenofibrate and fenofibric acid 80% of all fibrate prescriptions in 2009
- 2009 US sales of Tricor and Trilipix - $1.5 billion

Evidence

- Several large trials from 2005-2010 showed fenofibrate did not significantly improve CV outcomes in patients with Type 2 DM
  - JW Gen Med Feb 1 2006, p. 23
  - Lancet 2005; 366:1849
  - JW Gen Med Apr 15 2010, p. 61

Evidence

- Gemfibrozil did lower CV endpoint rate in older studies
  - Patients without DM
  - Studies completed before statin use
  - VA-HIT trial – JAMA 2001; 285:1585
- These patients would now receive statins as first-line therapy
Conclusions

- Expansion of prescribing is unwarranted
- Reasons for expansion of prescribing:
  - Aggressive marketing
  - Confusion among clinicians regarding evidence to support fibrates as add-on to statins

References

- http://www.drugs.com/top200.html

NIH Comparative Study

- AIM-HIGH
- 3414 patients with:
  - CV disease
  - Low HDL-C
  - High TGs
- All patients received statin therapy to LDL-C goal of 40-80 mg/dL
- Additionally, all patients received either:
  - Placebo OR
  - Extended-release niacin (Niaspan)

Does extended-release niacin, when added to statin therapy, benefit patients with CV disease?
Results

- Full study not yet published
- Trial stopped after average follow-up of three years – 1 year earlier than planned
- No evidence of benefit in extended-release niacin group
- Possible small increase in stroke risk in the extended-release niacin group

Conclusions

- Modifying risk factors does not always affect outcomes in predictable ways
- In patients with CV disease, adding extended release niacin does not lower risk, regardless of effect on HDL-C and TGs

Reference


What should we do about elevated cholesterol in children and young adults?
Study 1

Prospective US study of 3200 young adults (age range 18-30)
Underwent periodic lipid measurements for 2 decades after enrollment in 1985
After 15-20 years of follow-up, coronary calcium studies were performed

Results

13% of participants maintained LDL-C <100 mg/dL throughout young adulthood
LDL-C concentrations strongly predictive of coronary calcium two decades later
- Prevalence of coronary calcium with average LDL-C <70 mg/dL = 8%
- Prevalence of coronary calcium with average LDL-C ≥160 mg/dL = 44%
Weak relationship for HDL-C and coronary calcium
No relationship for TGs and coronary calcium

Findings

Adverse consequences of dyslipidemia occur early in life
Lifestyle modification should be emphasized throughout life

Reference

Study 2

- Stability of LDL-C of 6827 children studied
- Children’s LDL-C retested an average of 5 times from age 5 to 44
- Median interval between tests = 3 years

Results

- Overall, correlations between initial and subsequent LDL-C concentrations were moderate to high
- However, most children with initial LDL-C between 160 and 189 mg/dL (201) or ≥190 mg/dL (44) had lower concentrations at the next examination
- Only 34% and 39% had concentrations as high or higher on the next test

What does this mean?

- Important point – Data collection ended in 2002
- Obesity has worsened greatly since then
- Only 21% of children in this study were overweight or obese
- A minority of children who would qualify for drug therapy based on current AAP guidelines would still qualify on a subsequent test
- Recommendation may need to be revisited

Reference

Are there any new drug classes on the horizon for dyslipidemia?

**Cholesterol Ester Transfer Protein (CETP) Inhibitors**
- Anacetrapib
- Raises HDL-C
- Lowers LDL-C
- Inhibits the cholesterol ester transfer protein (CETP)
- CETP facilitates cholesterol ester and TG transfer between HDL and lipoproteins
- CETP activity elevated in dyslipidemia related to metabolic disease

**Study**
- 1623 patients with or at high risk for CHD
- At 24 weeks
  - LDL decreased significantly in treated patients (81 mg/dL to 45 mg/dL vs 82 mg/dL to 77 mg/dL)
  - HDL increased significantly in treated patients (41 mg/dL to 101 mg/dL vs 40 mg/dL to 46 mg/dL)
- Changes persisted through 76 weeks
- Adverse event rates similar
  - Important because another CETP inhibitor withdrawn because of adverse CV outcomes

**What does this mean?**
- Study not powered to address prevention of CV events
- Profound HDL-C raising effects
- Strong LDL-C lowering effects
- Large clinical outcomes trial to follow