Review of Lipid Management

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Sadly, No Disclosures or Conflicts of Interest


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"You know, if I do give you a heart, you'll have to start watching your cholesterol."

The Cleveland Clinic Dietary Research Project

"The average serum cholesterol levels in countries with low-fat consumption were 25% lower that in countries with high-fat consumption. It was evident that the incidence of coronary heart disease increased in those groups who migrated from a country that was relatively free of disease to one where it was prevalent. …..Of every thousand persons who were of disease at the beginning of the Framingham study, clinical signs of atherosclerosis developed within four years in only 42 persons with initial serum cholesterol levels less than 260mg per 100ml, in groups with higher than 260mg per 100ml there were three times as many cases. At the end of eight years these men had four times as much coronary disease as those with initial levels less than 200mg per 100ml"

Cleveland Clinic Journal, volume 29, April 1962

Basic Description of Lipids and Lipoproteins

- LDL
  - 60-70% of total serum cholesterol
  - Apo B
- HDL
  - 20-30% of total serum cholesterol
  - Apo A-I, apo A-II
- VLDL
  - Triglyceride rich
  - Apo B, apo Cs, apo E
- Chylomicrons
  - Apo B-48

Identify Clinical Atherosclerotic Disease (CHD) or (CHD equivalent)

- Clinical CAD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm
- Diabetes

Determine Presence of Major Risk Factors

- Cigarette smoking
- Hypertension
- Low HDL cholesterol
- Family history of premature CHD (male first degree relative < 55 years, women <65
- Age (men ≥ 45, women ≥ 55)

- HDL ≥60mg/dl counts as a “negative”

Calculate a Risk Score

- Framingham remains gold standard
  - >20%-CHD risk equivalent
  - 10-20% intermediate risk
  - <10% low risk

  Underestimates risk for younger men and women

Establish Goals of Therapy

- CHD or risk equivalents, 10 year risk >20%
  - LDL goal < **100, or <70mg/dl**
  - NHDL goal <130
- 2+ risk factors, 10 year risk 10-20%
  - LDL goal <**130mg/ml**
  - NHDL goal < 160
- 0-1 risk factor
  - LDL goal < **100mg/dl**
  - NHDL < 190

Identify the Metabolic Syndrome

- Abdominal obesity
  - Men waist > 40 inches
  - Women waist > 35
- Triglycerides
  - Greater than or equal to 150mg/dl
- HDL
  - Men < 40
  - Women < 50
- Blood Pressure
  - Greater than or equal to 130/85
- Fasting Glucose
  - Greater than or equal to 110 mg/dl

Treating the Metabolic Syndrome

- Nonatherogenic diet
  - Saturated fat < 7% of calories, cholesterol <200mg/day, viscous fiber 10-25mg/day and plant sterols
- Weight management
- Exercise
- Treat hypertension
- Use aspirin for CHD patients
- Consider triglyceride treatment after LDL at goal

Causes of Elevated Serum Triglycerides

- Obesity
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- Very high carbohydrate diet
- Other diseases (diabetes, hypothyroidism, renal failure, nephrotic syndrome)
- Medications (corticosteroids, protease inhibitors, diuretics, protease inhibitors, estrogens)
- Genetics

Serum Triglyceride Stratification

- Normal <150mg/dl
- Borderline high 150-199mg/dl
- High 200-499mg/dl
- Very high ≥500mg/dl

Emerging Risk Factors ? Predictive power

- Triglycerides
- Lipoprotein remnants
- Lp(a)
- Small LDL particles
- HDL subspecies
- Apo (B)
- Apo A-I
- Total cholesterol/HDL ratio
- Homocystein
- Thrombogenic factors
- Inflammatory markers
- Impaired fasting glucose
- Subclinical atherosclerosis

Statin Side Effects

- Muscle toxicity-myalgias 2-11%, myositis 0.1%, rhabdomyolysis 0.1%
  - Exclude drug interactions
  - Exclude hypothyroidism
  - Consider rechallenge with fluvastatin or Pravastatin
  - Niacin
  - Binding agents

Statin Side Effects

- Cognitive and behavioral change(pravastatin or resuvastatin)
- Neuropathy
- CKD (atorvastatin, fluvastatin)
- Chronic liver disease, not progressive (pravastatin)
- Drug interactions
  - CYP3A4 inhibitors (fluvastatin, pravastatin)
  - Cyclosporin (pravastatin)
  - Gemfibrozil (pravastatin and fluvastatin)
  - HIV proteinase inhibitors (pravastatin and fluvastatin)

Statin Side Effects Implications for Successful treatment

- Genetic/ethinc differences CYP2D6 absent in 7 percent of Caucasians and African-Americans (simvastatin)
- Asians have greater responses to low dose statins (rosuvastatin)
- Lipophilic statins may be associated with more adverse events, however, fluvastatin has least muscle side effects

Additional Drugs for Lipid Disorders

- Niacin
- Cholesterol Absorption Inhibitors
  - Zetia
  - Bile acid sequestrants
- Stanols and Sterols
- Omega 3 fatty acids
- Fibric acid derivatives
  - Gemfibrozil (Helsinki Heart Study)
  - Fenofibrate
  - Benzafibrate
  - Fenofibric Acid

Statin Intolerance

- Consider trying a different statin
- Consider every other day dosing or even once a week dosing

Red Yeast Rice

- F monacoinsermentation product of rice with Monascus purpureus
- Contains monocolins
- Monacolin K, mevinolin=lovastatin
- Some products contain citrin which is a mycotoxin that may cause renal failure
- More expensive than a statin

What Labs to Order and Monitor

- At age 20 or earlier if there is a family history of lipid disorders
- Fasting lipid panel, TSH, LFT's
- Check lipids 6 weeks later until at goal
- No longer recommended to monitor LFT's or lipid panel after

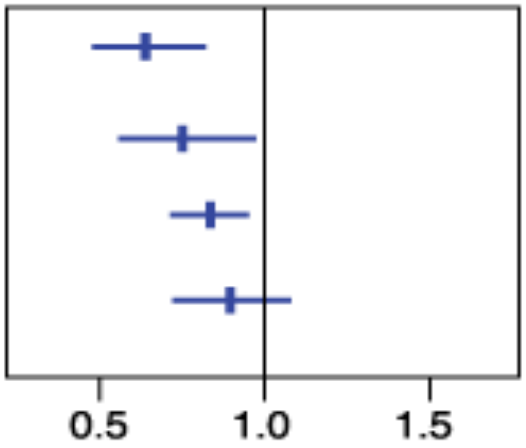
New Simvastatin Dosing

- 80mg dose limited to patients taking it for 12 months or more. Myopathy risk 0.9%
- Maximum dose of 10mg per day if taking amiodarone, diltiazem, or verapamil
- Maximum dose of 20mg per day if taking amlodipine or ranolazine
- If patient fails to achieve goal with this dosing then consider atorvastatin or rosvastatin

ASCOT Lipid Arm

Trial Design: ASCOT was a randomized, double blind factorial trial of treatment with atorvastatin (10 mg) (n=5168) or placebo (n=5137) in hypertensive patients with a total cholesterol <6.5 mmol/l who were also enrolled in the open-label anti-hypertensive arm of the ASCOT trial. The primary endpoint was non-fatal MI and fatal coronary disease by a median follow-up of 3.3 years.

Endpoint	HR	p-value
CV Death /MI	0.64	0.0005
Stroke	0.73	0.0236
CV events /procedures	0.79	0.0005
All-cause mortality	0.87	0.1649



Results

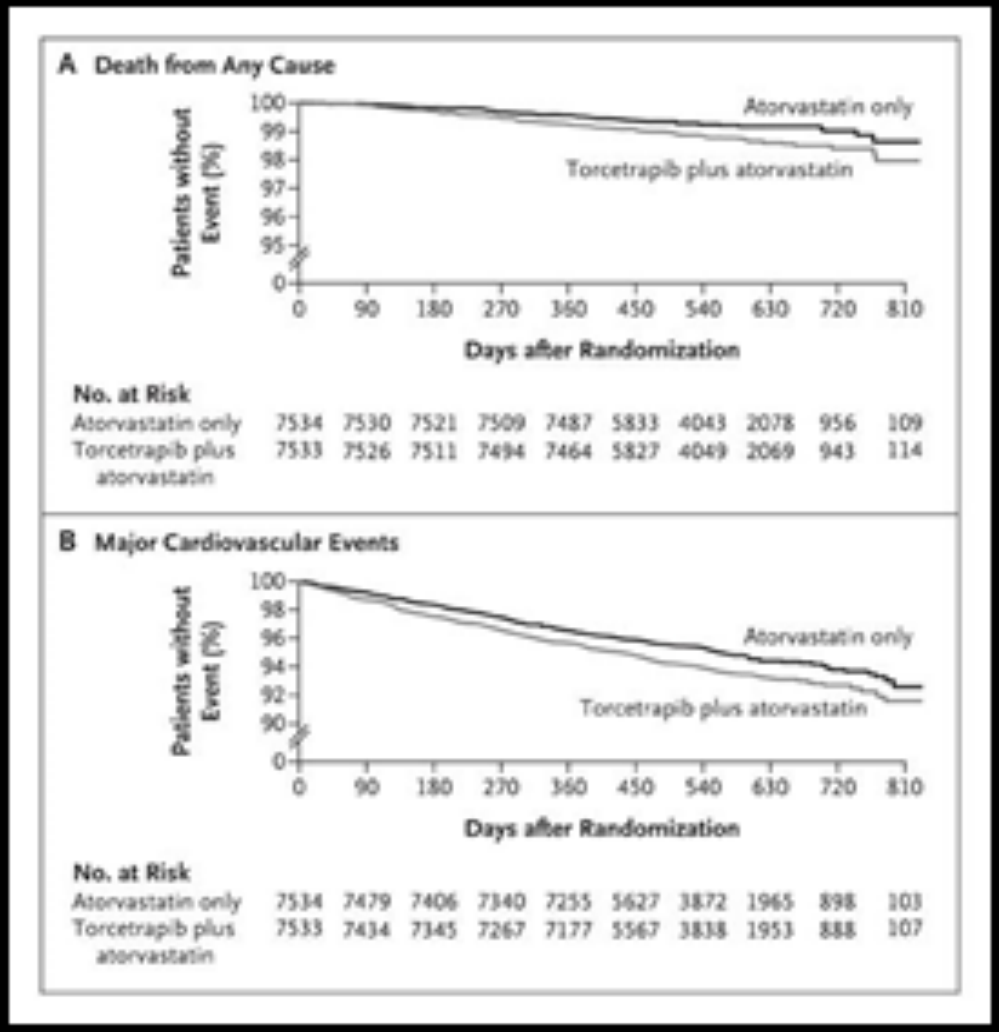
- Lipid-lowering limb of trial discontinued early due significant reduction in primary endpoint of non-fatal MI and fatal coronary disease
- Both total cholesterol and LDL-CH at 3 year follow-up were 1.0 mmol/L lower in the atorvastatin arm vs placebo
- All pre-specified subgroups favored atorvastatin arm with no heterogeneity in any subgroup

Conclusions

- Among patients with hypertension and relatively low cholesterol, treatment with atorvastatin was associated with ↓ non-fatal MI and fatal coronary disease at 3 year follow-up
- ASCOT results in line with other large statin trials such as 4S, CARE, LIPID, and PROSPER, all of which demonstrated a benefit in morbidity and/or mortality with statin therapy

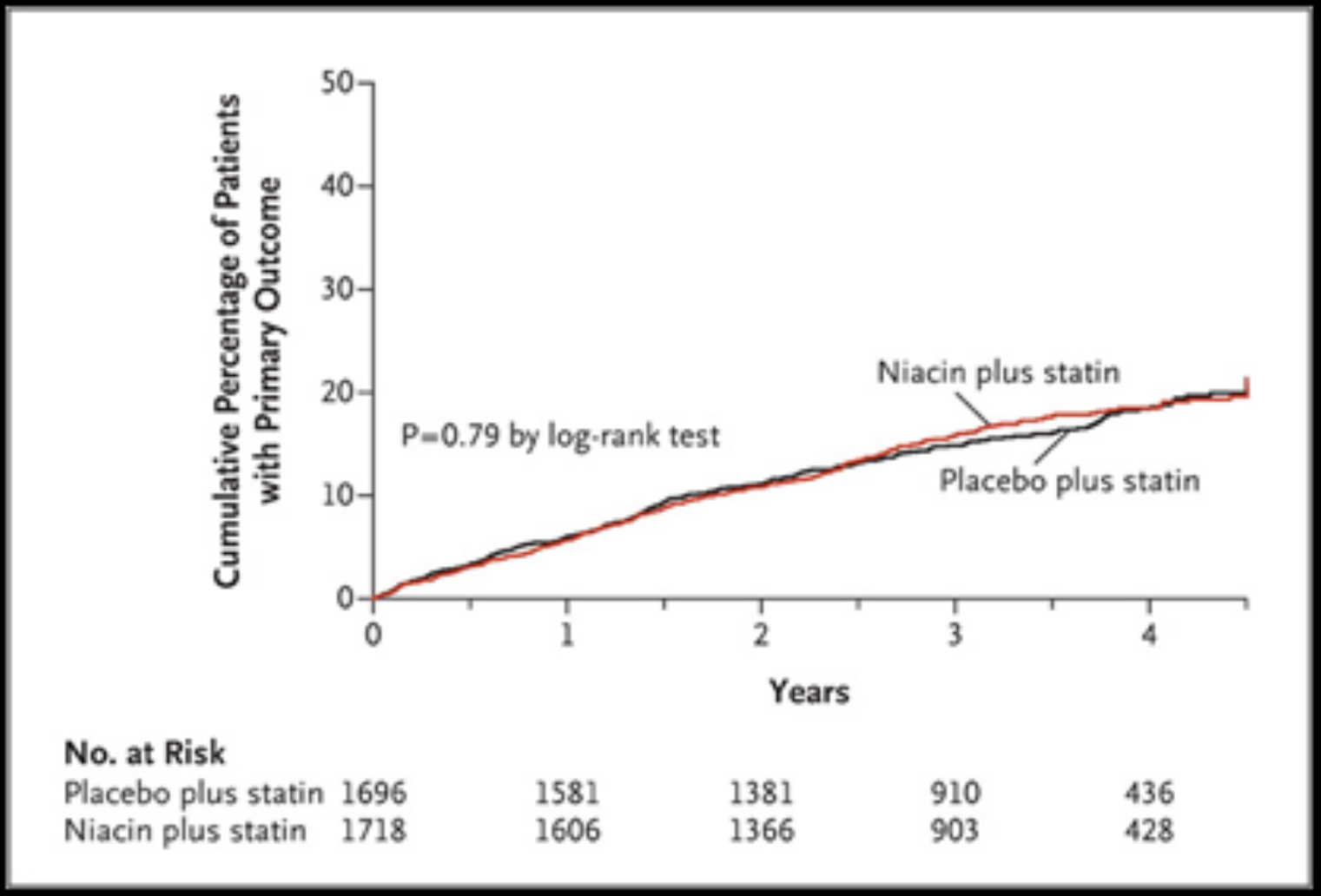
Lancet 2003;361:1149-58

Kaplan–Meier Curves for Death from Any Cause and for the Primary Composite Outcome.



Barter PJ et al. N Engl J Med 2007;357:2109-2122.

Kaplan–Meier Curve for the Primary End Point.



No. at Risk

Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

The AIM-HIGH Investigators. N Engl J Med 2011;365:2255-2267.

Drug Therapy for Homozygous Hypercholesterolemia

- Mipomersen-antisense oligonucleotide that binds the messenger sequence that encodes apolipoprotein (apoB is the principle lipoprotein of VLDL and LDL)

- Lomitapide-binds to and inhibits microsomal triglyceride transfer protein preventing the formation of apoB containing lipoproteins in the liver and intestine preventing synthesis of VLDL and LDL

Vascepa vs. Lovaza

- 95% icosapent-ethyl (the ethyl ester of EPA
- Reduces triglycerides by 45% without raising LDL
- Lovaza raises LDL-C by 31%

Pitavastatin

Unlike most new drugs, pitavastatin comes to the market with clinical trials comparing its efficacy in lowering serum lipid concentrations to that of other drugs in its class, but, unlike other statins, no data are available on its effects on mortality and morbidity from coronary artery disease.

The Medical Letter, volume 52, p57

Pitavastatin has not been shown to offer any advantage in cholesterol lowering over statins that are available generically.

The Medical Letter, volume 53, p61

ATP-IV

- CVD Risk Assessment
- More stringent targets versus a fixed dose strategy adjusting dose to risk
- Role of biomarkers
- Role of advanced lipoprotein testing
- Role of fibrates, niacin, ezetia
- Role of imaging of subclinical atherosclerosis