Novel Therapies and New Targets of Treatment for Familial Hypercholesterolemia

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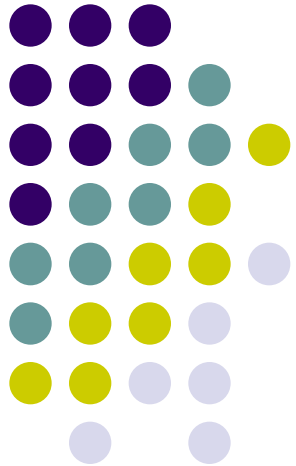
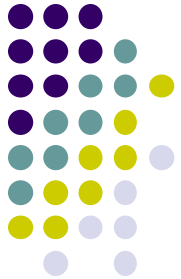


Why do we need more LDL-lowering therapies?



- For Familial Hypercholesterolemia
  - Homozygous patients cannot approach target levels on usual therapy
  - Heterozygous patients may still need further lowering even if they achieve 70% reduction with multiple drug combinations
  - Not all FH patients can tolerate current multi-drug combinations
  - LDL-apheresis is not available everywhere and has drawbacks

Potential therapies

- Apolipoprotein B Antisense
- Microsomal triglyceride transfer protein inhibitors
- Squalene synthase inhibitors
- Proprotein convertase subtilisin/kexin type 9 inhibitors
- Cholesterol absorption inhibitors

Stein EA. Other therapies for reducing low-density lipoprotein cholesterol: medications in development. Endocrinol Metab Clin North Am 2009;38:99-119.

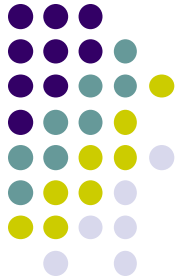
Davidson MH. Novel nonstatin strategies to lower low-density lipoprotein cholesterol. Curr Atheroscler Rep 2009;11:67-70.

Antisense oligonucleotides

- Single-stranded DNA corresponding to a specific mRNA sequence
- Bind to mRNA by Watson-Crick hybridization
- Induce selective degradation of mRNA
- Given as subcutaneous injections, have a long half-life and preferentially travel to liver and kidneys

Davidson MH. Novel nonstatin strategies to lower low-density lipoprotein cholesterol. Curr Atheroscler Rep 2009;11:67-70.

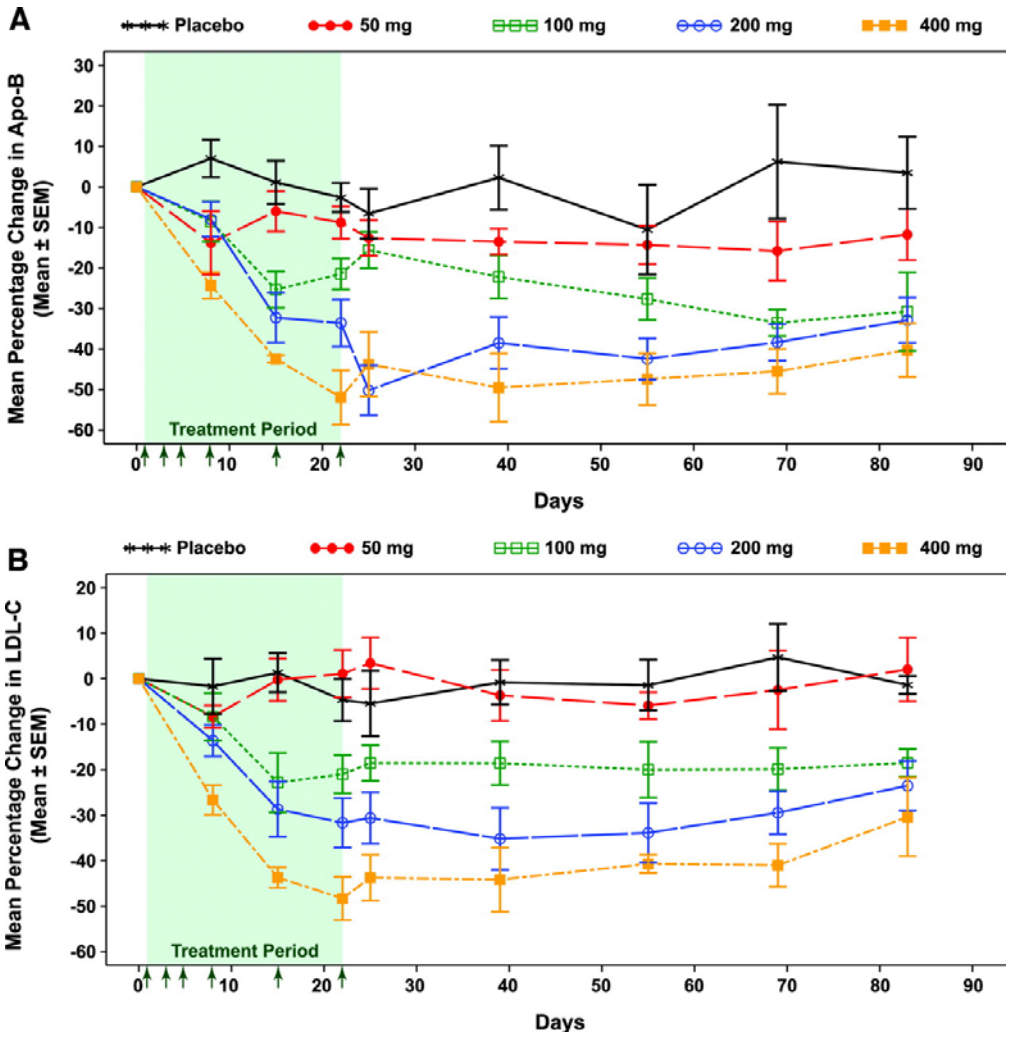
Antisense oligonucleotides: ApoB-100 (mipomersen)



- Second generation antisense oligonucleotide
- Apo B 100 production inhibited
- Decreased secretion of apo B containing lipoproteins from the liver
- Lowers apo B, LDL-cholesterol and lipoprotein (a) in humans

Stein EA. Endocrinol Metab Clin North Am 2009;38:99-119.

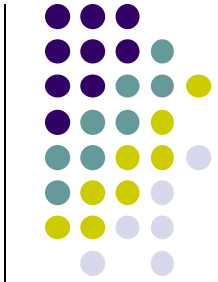
Dose-dependent effect of ISIS 301012 on (A) apoB and (B) LDL cholesterol levels, shown as mean % change from baseline



Kastelein, J. J.P. et al. Circulation 2006;114:1729-1735

Circulation

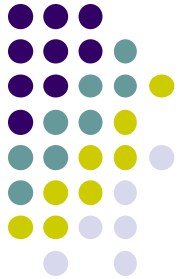
Mipomersen in patients with homozygous FH



- Multi-center study in 45 patients
- Baseline LDL-C on lipid drugs 11.4 mmol/L (440 mg/dL)
- Mipomersen 200 mg sc weekly or placebo for 26 weeks
- LDL-C decreased by 24.7% with mipomersen compared with -3.3% with placebo

Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet; 2010;375:998-1006.

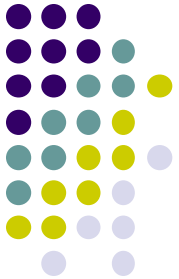
Mipomersen in heterozygous FH patients



- 26 week study in 124 patients randomized to mipomersen or placebo
- Mipomersen group 28% reduction of LDL-C
- Placebo group 5% increase LDL-C
- Of 83 on mipomersen, 73 completed and 9 discontinued due to adverse reactions
- Adverse reactions similar to previous
- Liver enzymes—none met Hy's law

http://ir.isispharm.com/phoenix.zhtml?c=222170&p=irol-newsArticle&ID=1385999&highlight Accessed 4/22/10

Mipomersen adverse effects



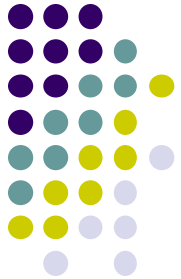
- Injection site reactions
- Flu-like symptoms
- Fatigue
- Pyrexia
- Increased ALT
- Increased liver fat

Liver fat

- Short term study using magnetic resonance spectroscopy
- 4 weeks and 15 weeks of treatment
- Trend toward increase in triglyceride accumulation in the liver of patients treated with mipomersen compared with placebo
  - 75% increase not statistically significant
  - 90% remained within normal range
- Need further data on long term use

Visser ME, Akdim F, Tribble DL, et al. Effect of apolipoprotein-B synthesis inhibition on liver triglyceride content in patients with familial hypercholesterolemia. J Lipid Res;2010;51:1057-62.
Feingold KR. Does inhibition of apolipoprotein B synthesis produce foie gras? J Lipid Res;2010;51:877-8.

Microsomal triglyceride transfer protein inhibitors



- MTP is a lipid transfer protein
- Localized in the endoplasmic reticulum of hepatocytes and enterocytes
- Critical role in lipoprotein lipidation of apoB
- Necessary for formation of chylomicrons, VLDL and downstream remnants
- MTP deficiency--abetalipoproteinemia

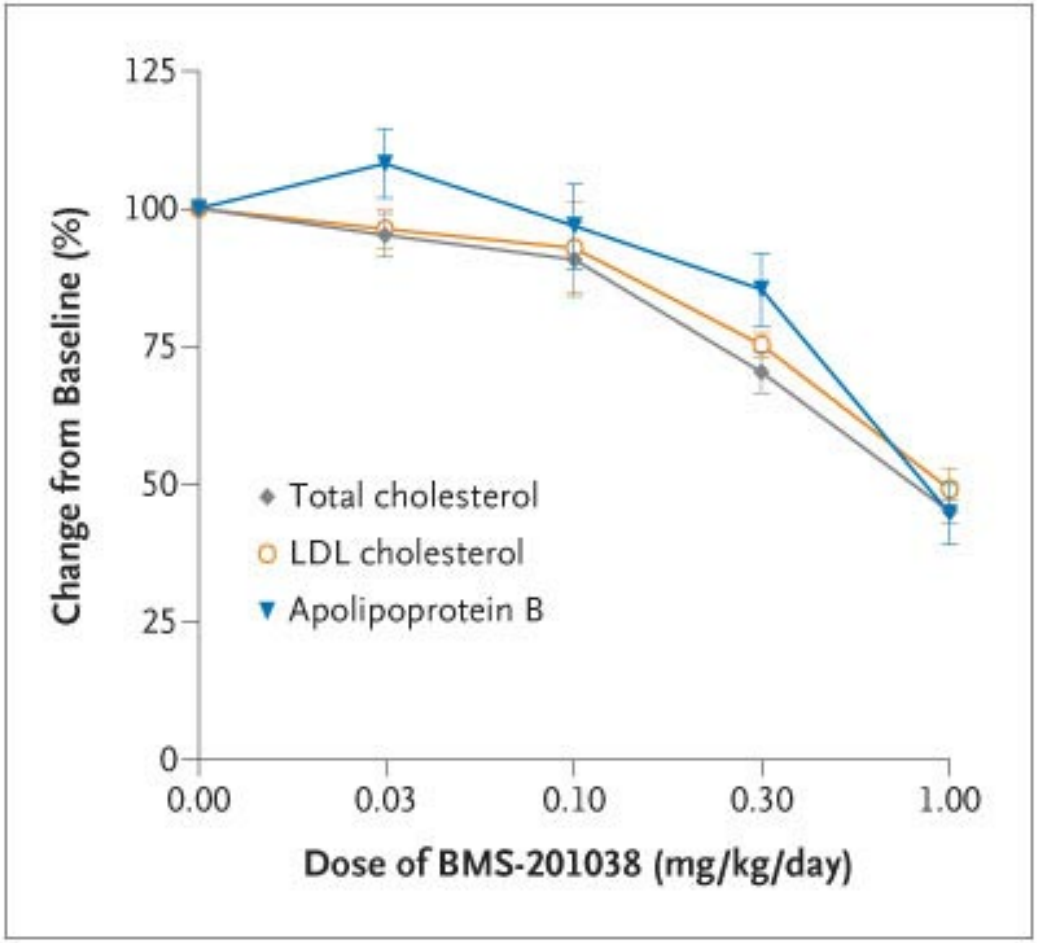
Stein EA. Endocrinol Metab Clin North Am 2009;38:99-119.

MTP inhibitor: homozygous FH

- 6 patients
- Four doses for 4 weeks each dose
- 0.03, 0.1, 0.3, and 1.0 mg per kilogram body weight
- At 1 mg/kg, LDL-C decreased by 50.9%
- Kinetic studies showed marked reduction in production of apo B
- GI side effects, increased transaminases and increased hepatic fat

Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med 2007;356:148-56.

Mean % Change from Baseline of Total Cholesterol, LDL-Chol, & ApoB after Receipt of 4 Doses of BMS-201038, Each for 4 Wks



Cuchel M et al. N Engl J Med 2007;356:148-156

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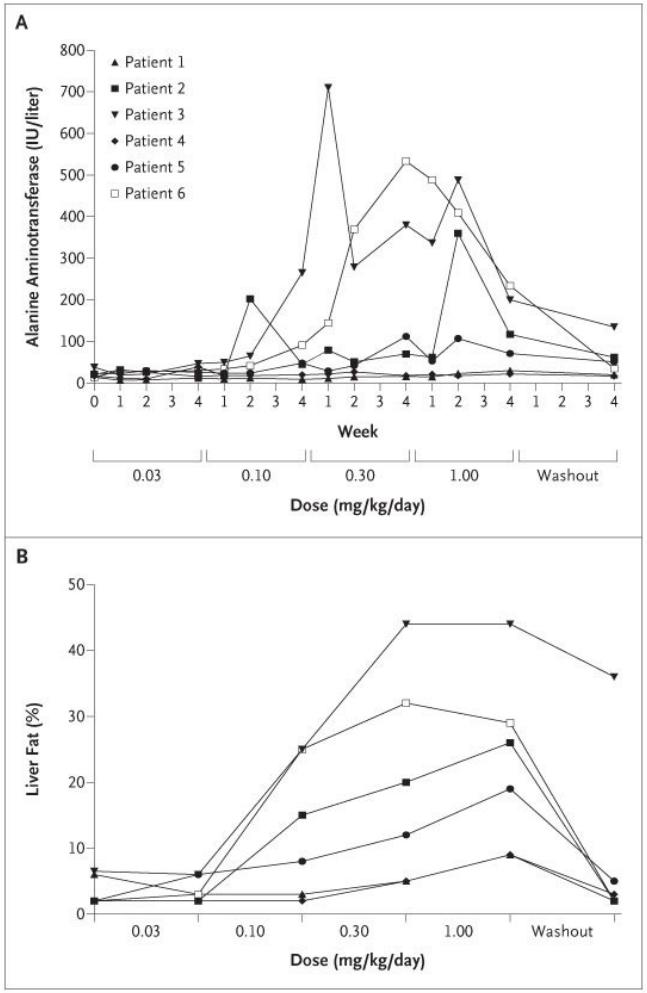
Serum Levels of Alanine Aminotransferase (Panel A) and Percentage of Fat in the Liver (Panel B), as Measured by MRI at Baseline, after Receipt of Four Doses of BMS-201038 and after the 4-Week Washout Period



Cuchel M et al. N Engl J Med 2007;356:148-156

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AEGR-733

- 12 week study, 84 patients
- Randomized, double-blind
  - Ezetimibe 10 mg (n = 29)
  - AEGR with up-titration: 4 weeks 5 mg, 4 weeks 7.5 mg, 4 weeks 10 mg (n = 28)
  - Ezetimibe plus AEGR (n = 28)
- LDL-C decreased
  - Ezetimibe 20%
  - AEGR 19, 26, 30%
  - Ezetimibe + AEGR 35, 38, 46%

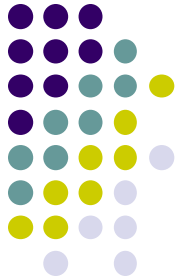
Samaha FF, McKenney J, Bloedon LT, Sasiela WJ, Rader DJ. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. Nat Clin Pract Cardiovasc Med 2008;5:497-505.

AEGR-733

- Adverse effects
  - Elevated transaminases: 9/56
  - Gastrointestinal symptoms: nausea, diarrhea
- Discontinuations mostly due to elevated transaminases
- Same compound as in Cuchel study but much lower doses
- Patients with baseline LDL-cholesterols160 mg/dl

Samaha FF et al. Nat Clin Pract Cardiovasc Med 2008;5:497-505.

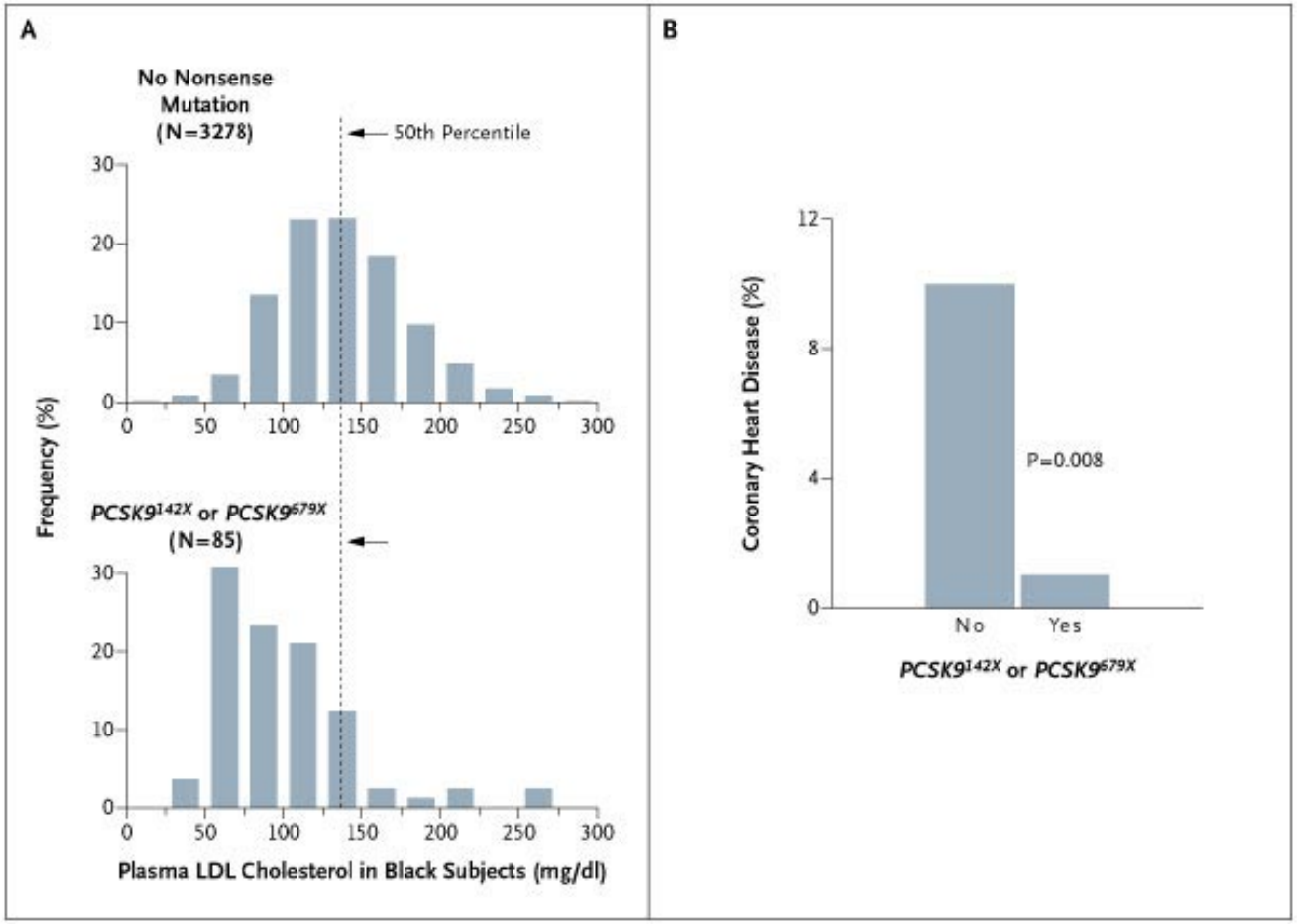
Proprotein convertase subtilisin/kexin type 9



- Member of the family of proteases involved in degradation of LDL-C receptor
- Mutations leading to loss of function are associated with lifelong low LDL-C levels and decreased risk of cardiovascular disease
- Inhibitors of PCSK9 are in development

Stein EA. Endocrinol Metab Clin North Am 2009;38:99-119.

Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a PCSK9142X or PCSK9679X Allele



PCSK9 (proprotein convertase subtilisin/kexin type 9 serine protease) gene

Cohen J et al. N Engl J Med 2006;354:1264-1272

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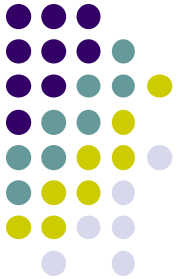
Squalene synthase inhibitors



- Squalene synthase is a late step in cholesterol biosynthesis
- Early inhibitors showed significant toxicity
- Lapaquistat reached phase 3 clinical trials but program was discontinued
  - Liver enzyme elevations in phase 2
  - Two cases of severe liver enzyme elevations in phase 3

Stein EA. Endocrinol Metab Clin North Am 2009;38:99-119.

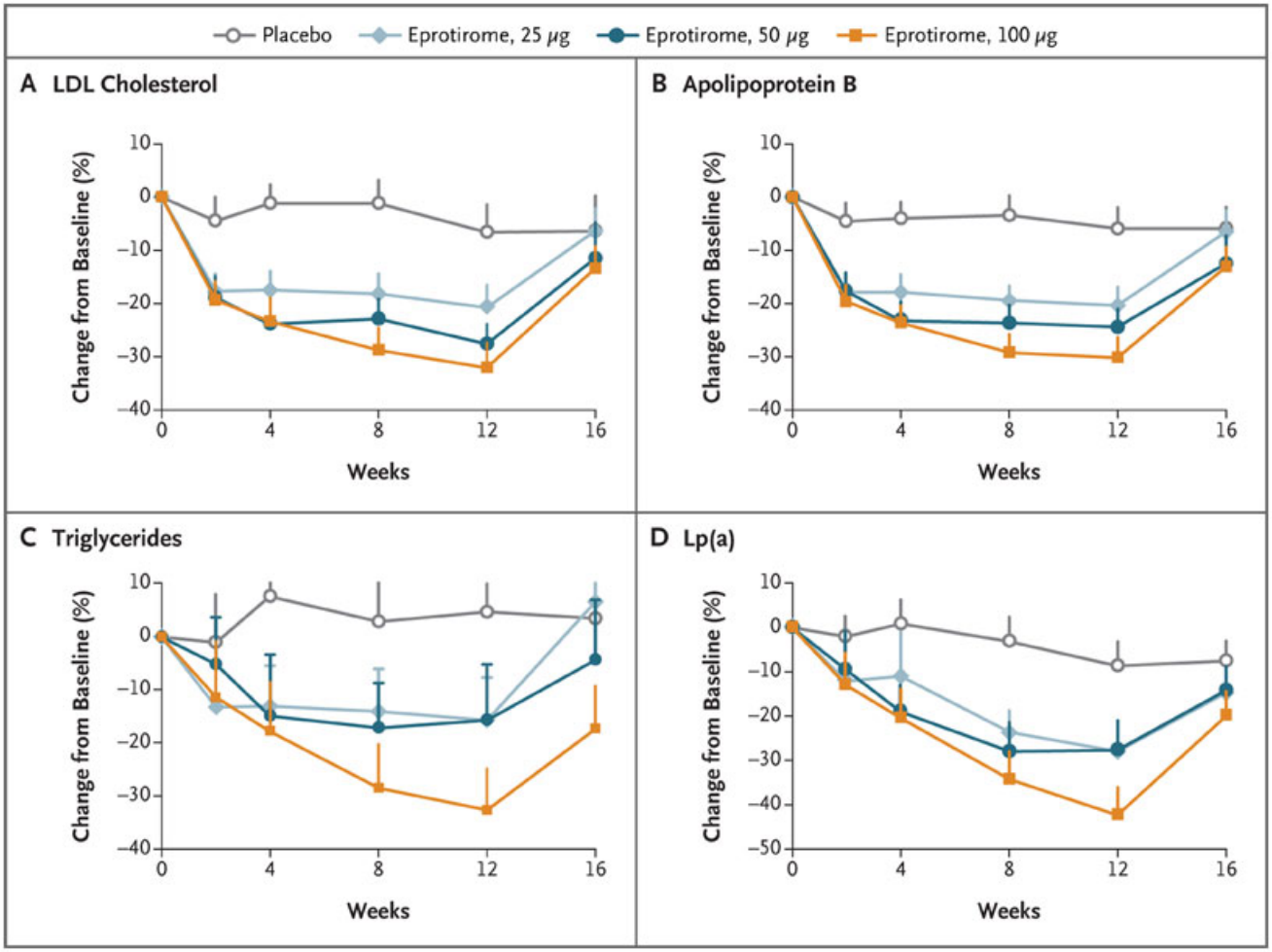
Davidson MH. Curr Atheroscler Rep 2009;11:67-70.

Thyroid hormone analogue

- Thyroid hormone lowers LDL-cholesterol
- Eprotirome –thyroid hormone analogue
- 12 week study
- Reduced LDL-cholesterol
- No change in TSH, thyroxine level decreased

Ladenson PW, Kristensen JD, Ridgway EC, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010; 362:906-916.

Effects of Eprotirome on Serum Levels of Cholesterol, Lipoproteins, and Triglycerides



Ladenson P et al. N Engl J Med 2010;362:906-916

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New Therapies for FH

- Several new types of therapy are in clinical trials
- It may be several years before any of these get to market
- Issues of long term safety and benefit on cardiovascular outcomes remain to be resolved