New Drugs for Lipid Management

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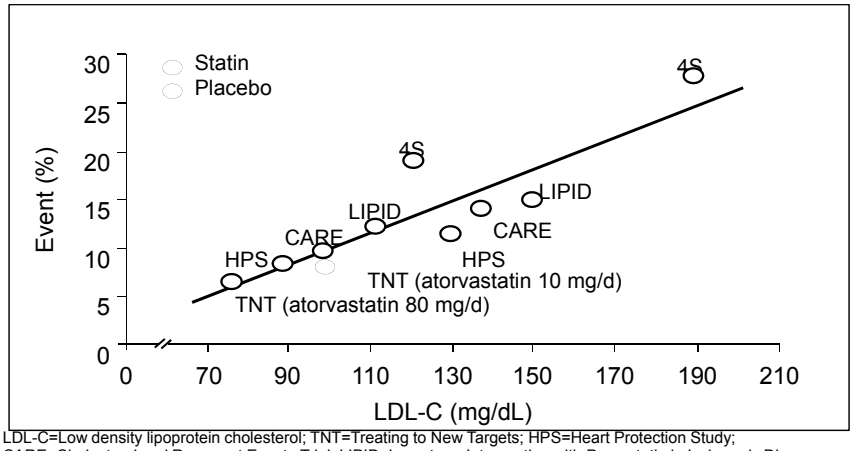
Disclosure

- **Site PI for the following clinical trials:**
- **Odyssey Outcomes, a study of Alirocumab in the prevention of coronary events, sponsored by Sanofi Aventis.**
- **Omthera Strength, sponsored by Omthera Pharmaceuticals**
- **CLEAR Serenity, sponsored by Esperion Therapeutics**

HMG-CoA Reductase Inhibitor: Secondary Prevention

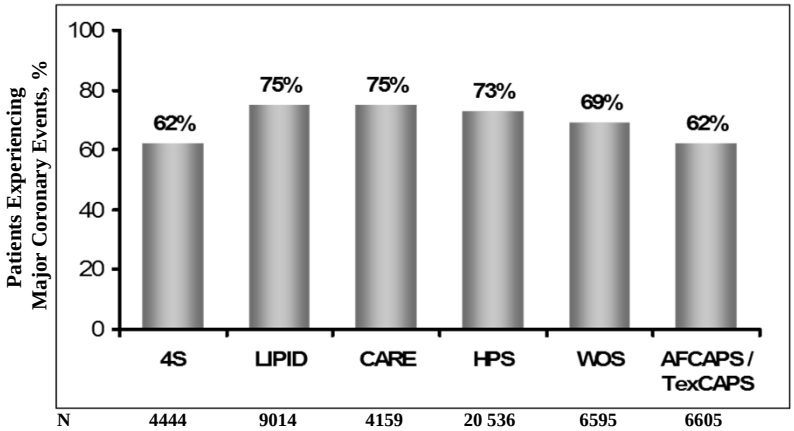
Relationship between LDL Levels and Event Rates in Secondary Prevention Trials of Patients with Stable CHD



LDL-C=Low density lipoprotein cholesterol; TNT=Treating to New Targets; HPS=Heart Protection Study; CARE=Cholesterol and Recurrent Events Trial; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; 4S=Scandinavian Simvastatin Survival Study.

LaRosa JC et al. *NEJM.* 2005;352:1425-1435

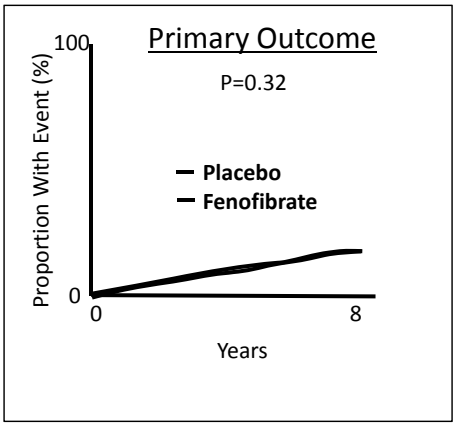
Residual Cardiovascular Risk in Major Statin Trials



	4S	LIPID	CARE	HPS	WOS	AFCAPS / TexCAPS
N	4444	9014	4159	20 536	6595	6605
ΔLDL	-36%	-25%	-28%	-29%	-26%	-27%
	Secondary			High Risk	Primary	

Libby PJ, et al. *J Am Coll Cardiol*, 2005:46:1225-1228.

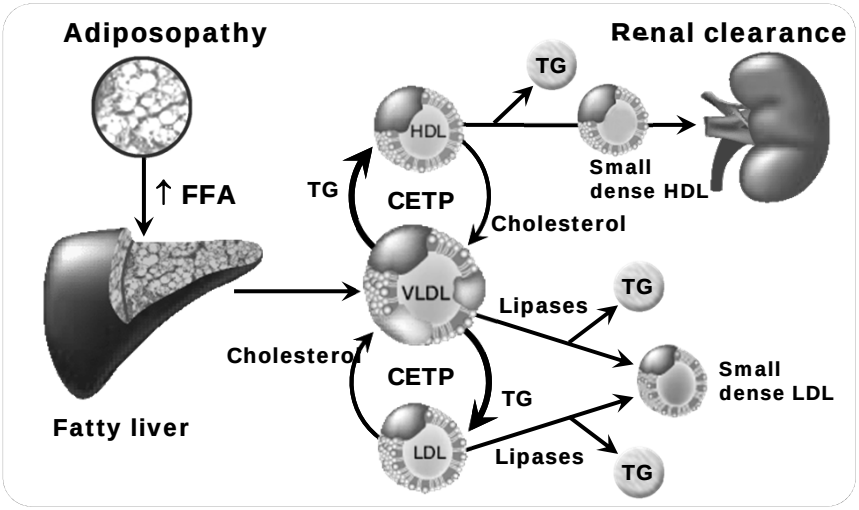
Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus: The ACCORD Study Group



- Primary outcome: P=0.32
- Expanded macrovascular outcome: P=0.30
- Death from any cause: P=0.33
- Death from cardiovascular causes: P=0.26

N Engl J Med Volume 362(17):1563-1574 April 29, 2010

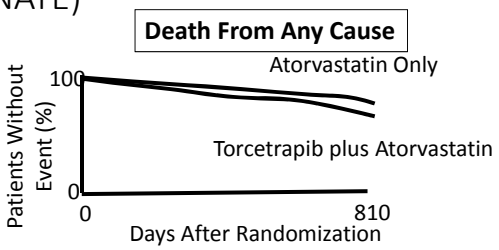
The Role of Cholesterol Ester Transfer Protein and the Dyslipidemia Found with Metabolic Syndrome

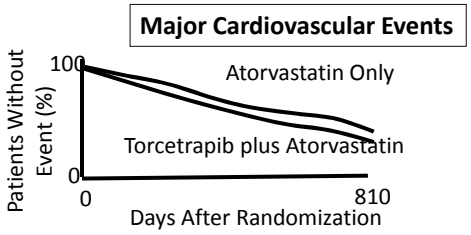


Bays H. *Expert Rev Cardiovasc Ther* 2004;2:89-105

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE)

- 15,000 patients on Atorvastatin with CAD or DM
- Increase of HDL cholesterol by 72.1% on torcetrapib
- Decrease of LDL cholesterol by 25% on torcetrapib
- Systolic BP increased by 6 mm Hg on torcetrapib

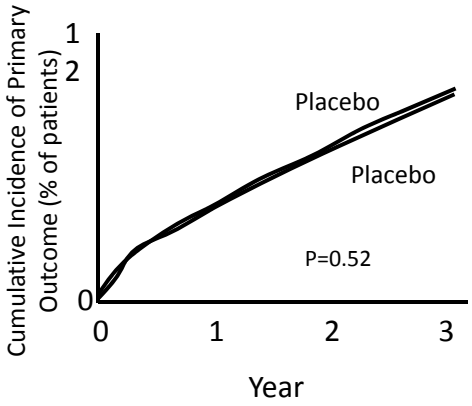




Barter PJ et al. N Engl J Med 2007;357:2109-2122.

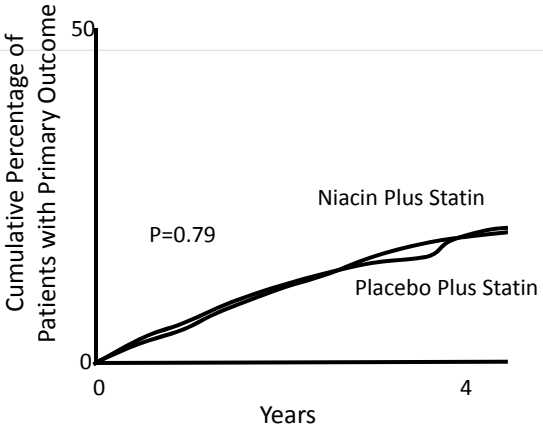
Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome: Dal-outcomes Trial

- 15,000 patients
- Mean HDL cholesterol level was 42 mg per deciliter
- Mean low-density lipoprotein (LDL) cholesterol level was 76 mg per deciliter
- HDL cholesterol levels increased from baseline by 4 to 11% in the placebo group and by 31 to 40% in the dalcetrapib group.



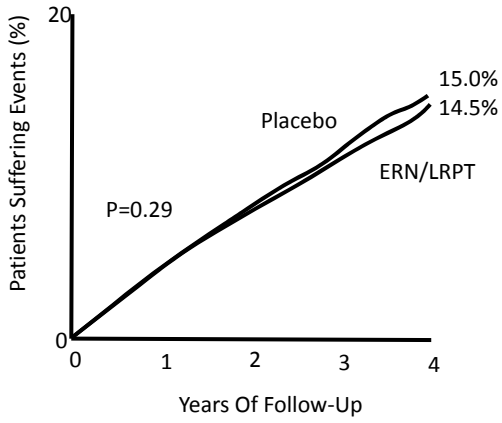
Schwartz GG et al. N Engl J Med 2012;367:2089-2099.

AIM-HIGH: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy.



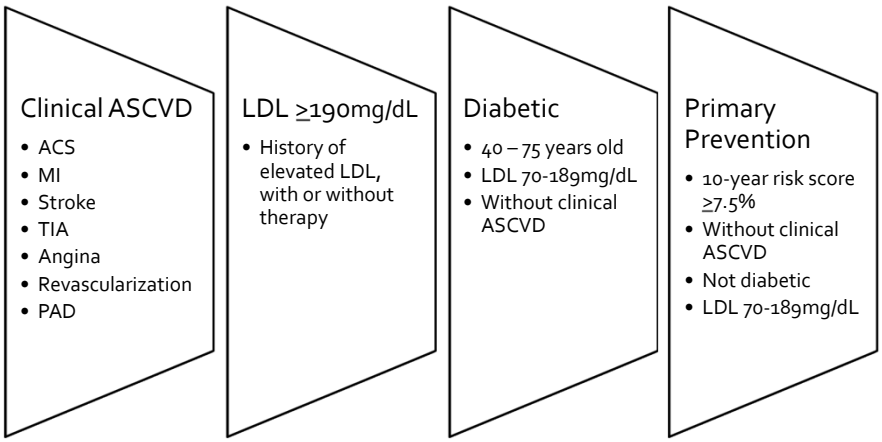
N Engl J Med 2011;365:2255–2267.

HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease



2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

4 Statin Benefit Groups



2013 ACC/AHA Blood Cholesterol Guidelines

Intensity of Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C by > 50%	Daily dose lowers LDL-C by 30-50%	Daily dose lowers LDL-C by < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

2013 ACC/AHA Blood Cholesterol Guidelines

2014 National Lipid Association Executive Summary

- When intervention beyond public health recommendations for long-term ASCVD risk reduction is employed, levels of atherogenic cholesterol (non-HDL-C and LDL-C) should be primary targets for therapies
- Non-HDL-C primary target (Except TG if TG ≥ 500mg/dL)

Risk Category	Non-HDL-C	LDL-C	Apo B*
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80

*Apo B is a secondary, optional target of treatment or LDL particle concentration

Journal of Clinical Lipidology, 2015

Case 1

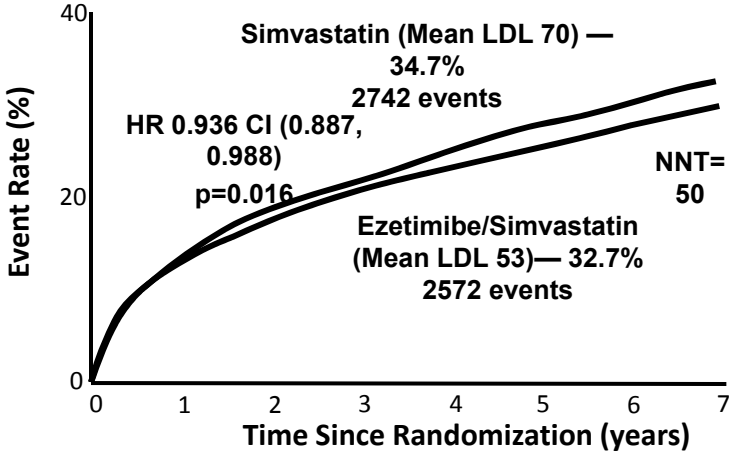
- 52 yo accountant presented with a non ST elevation MI. Cath revealed a 90% RCA stenosis. PCI with a drug eluting stent was performed.
- Lipid levels at the time of the event were:
  - Cholesterol 220
  - LDL 178
  - HDL 38
  - TG 70
- He is discharged on high dose statin therapy with Atorvastatin 80 mg once daily.

Case 1

- **In 3 months, repeat lipid levels reveal:**
  - **Cholesterol 149**
  - **LDL 99**
  - **HDL 39**
  - **TG 60**

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

Effect of the Addition of Ezetimibe to Simvastatin Compared to Simvastatin Monotherapy.



Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Cannon CP et al. N Engl J Med 2015;372:2387-2397

Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9)

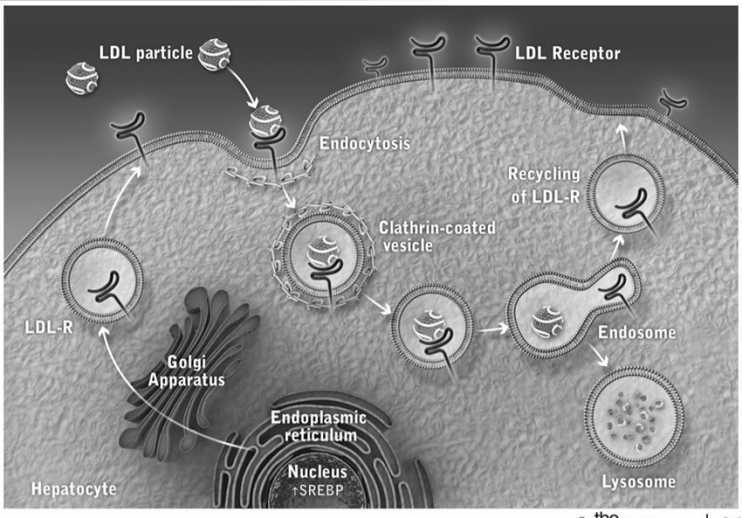
- In 2006, it was reported that a loss of function mutation in the gene encoding PCSK9 was associated with significantly lower long-term plasma levels of LDL cholesterol (1)
- A substantial (47 to 88%) lower risk of coronary heart disease was observed over a period of 15 years in middle-aged persons with such genetic polymorphisms.
- Additional genetic studies indicated that PCSK9 activity was a major determinant of plasma levels of LDL cholesterol in humans (2)
- Opened the door for drug development to synthesize inhibitors against PCSK9

(1) NEJM 2006;354:1264-72 (2) Am J Hum Genet 2006;78:410-22

PCSK9 inhibitors

- Monoclonal antibodies directed against PCSK9
- Alirocumab and Evolocumab are clinically available
- Many others are in varying stages of development
- Injectable agents
- Early clinical trials using in a variety of patient groups show an ~60% decrease in LDL cholesterol in the treatment groups, even those treated with statin therapy

LDLR Function and Life Cycle



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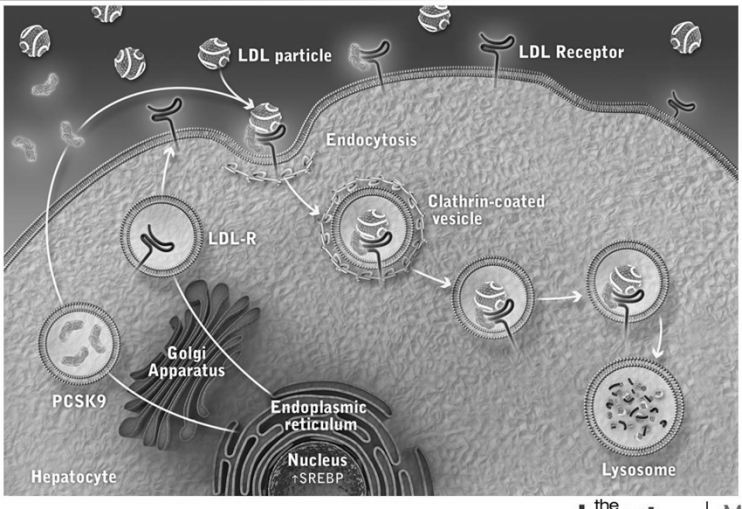
The Role of PCSK9 in the Regulation of LDLR Expression



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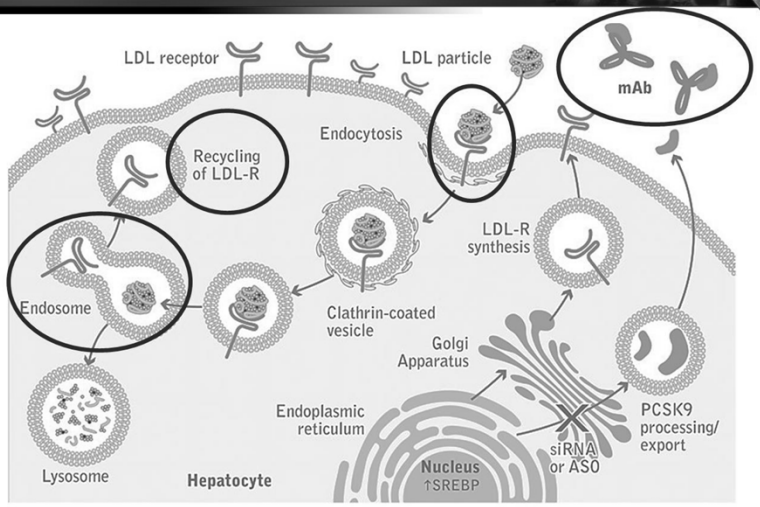
PCSK9 Inhibition Using Monoclonal Antibodies



Lambert G, et al. *J. Lipid Res*. 2012;53:2515-2524.[16]

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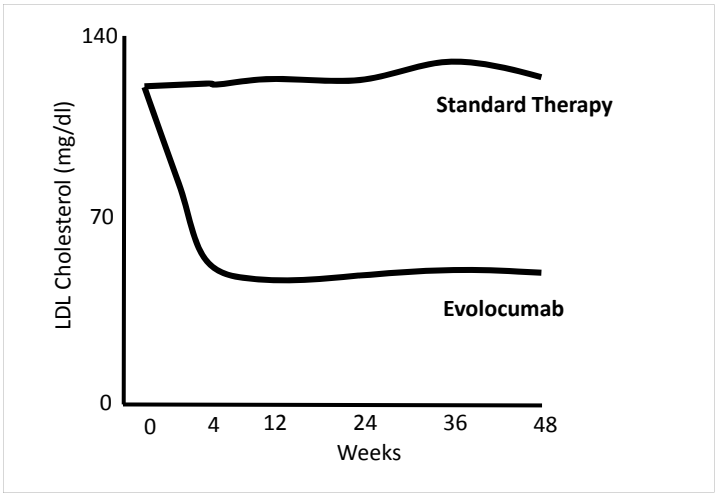
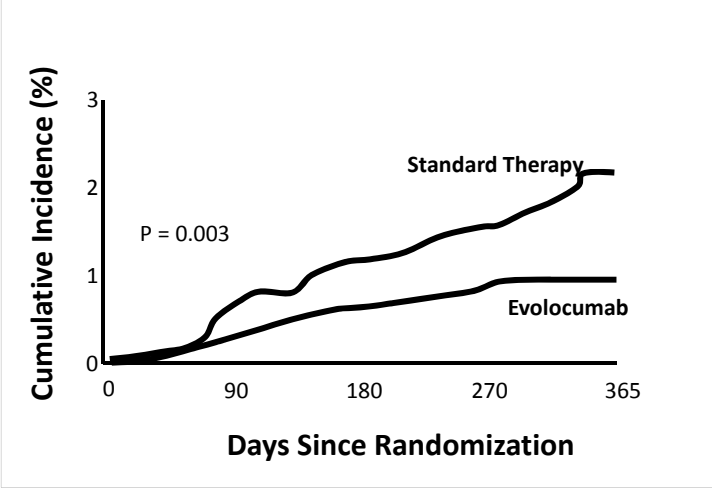
Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events



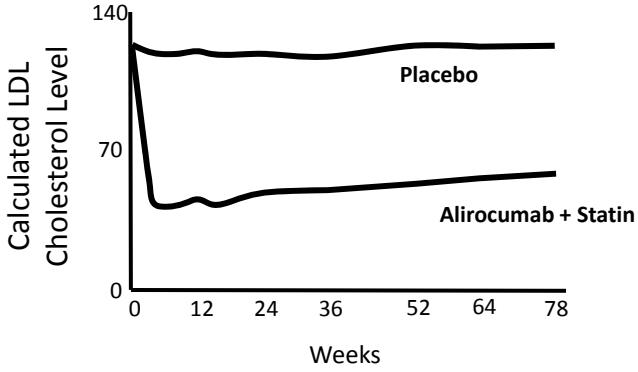
Osler Trial: Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events



Sabatine MS et al. N Engl J Med 2015;372:1500-1509

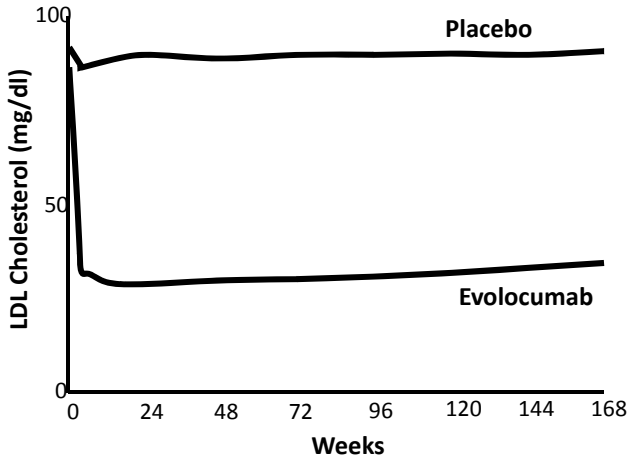
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events



Major adverse cardiovascular events were lower with alirocumab plus statin (1.7%) versus placebo plus statin (3.3%) in pre-specified post hoc analysis
(HR 0.52; 95% confidence interval, 0.31 to 0.90; nominal P = 0.02).

Robinson JG et al. N Engl J Med 2015;372:1489-1499

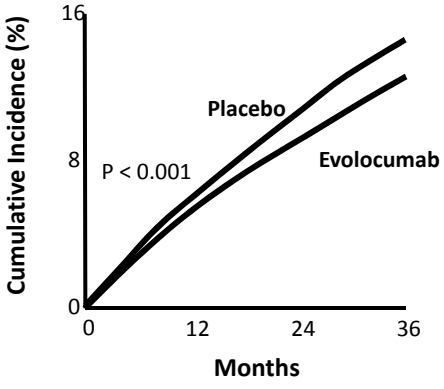
Low-Density Lipoprotein (LDL) Cholesterol Levels over Time



Sabatine MS et al. N Engl J Med 2017;376:1713-1722

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Cumulative Incidence of Cardiovascular Events



Sabatine MS et al. N Engl J Med 2017;376:1713-1722

Odyssey Outcomes:

- **Randomized controlled double blinded clinical trial comparing alirocumab versus placebo in patients treated with statin therapy whose LDL levels remains above 70.**
- **5 year outcome trial**
- **Results expected to be presented/published in March of 2018.**

PCSK9 inhibitors

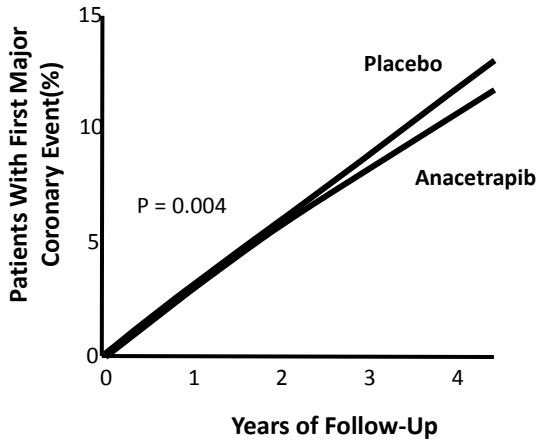
- **Alirocumab and Evolocumab are FDA approved for clinical use, indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C)**
- **Evolocumab also indicated for homozygous familial hypercholesterolemia**

Case 1

- **Decision made to add a PCSK9 inhibitor to the Atorvastatin**
- **3 months later:**
  - **Chol 102**
  - **LDL 46**
  - **HDL 40**
  - **TG 64**

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55-REVEAL Collaborative Group



N Engl J Med 2017; 377:1217-1227

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

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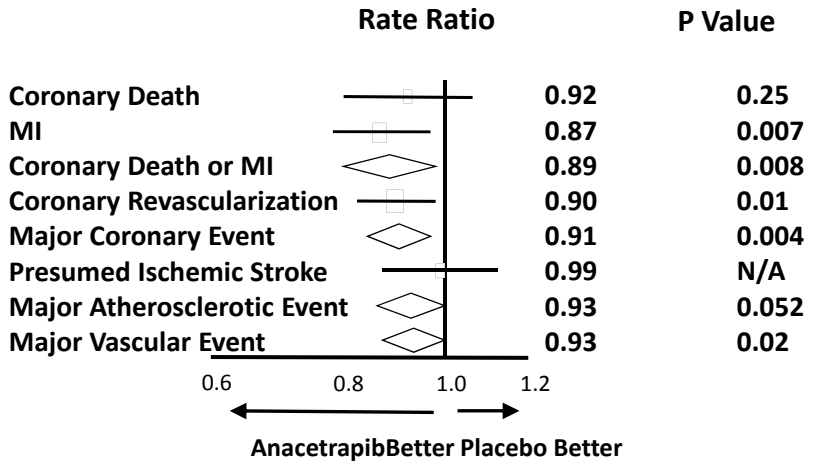

N Engl J Med 2017; 377:1217-1227

Summary

- **Diet, physical activity and for those at increased risk of cardiovascular events, statin therapy, remain the mainstay of lipid management**
- **For those patients who have LDL levels above NLA goal for non HDL cholesterol, secondary therapy may be considered**
- **Ezetimibe and the 2 PCSK9 inhibitors, Alirocumab and Evolocumab are clinically available**
- **Anacetrapib is a CETP inhibitor that may become available in the future**
- **New advances in lipid lowering improve the ability to reduce risk for cardiovascular events**

Lipid testing strategies

When to refer to a lipid specialist

New Drugs for Lipid Management

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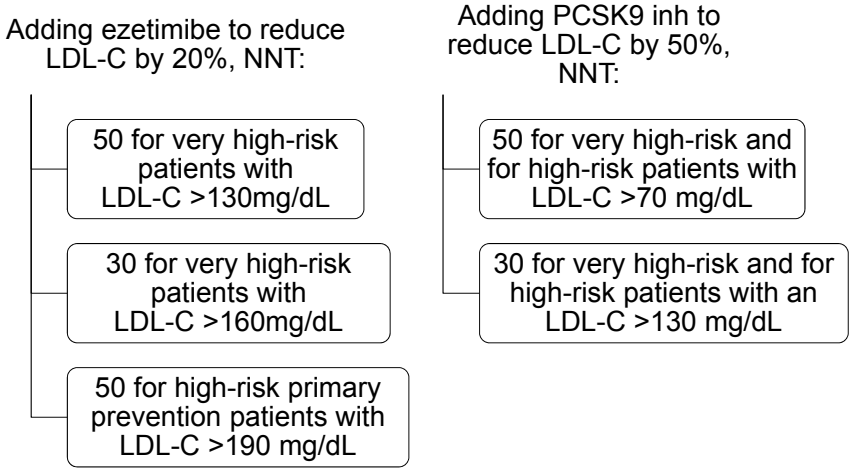
2017 ACC Focused Update of LDL Expert Consensus Decision Pathway



2017 ACC Focused Update of LDL Expert Consensus Decision Pathway

- **Clinical ASCVD w/ comorbidities**
  - **Ezetimibe**
    - **Factors with potential greater benefit:**
      - **CHF, HTN, age >75, DM, CVA, CABG, PAD, eGFR <60, smoking**
    - **Other specific considerations:**
      - **<25% additional LDL lowering needed**
      - **Recent ACS**
      - **Low cost burden**
      - **Ease of use preferred**
  - **PCSK9 inhibitor**
    - **Consider when >25% lowering of LDL is needed**
    - **Should NOT be considered for patients with a primary indication of diabetes or elevated 10 year risk**

Statin Benefit Group	Subgroup	Co-morbidities indicating higher risk	Initial Statin Intensity	Targets for Consideration	Initial Option	Secondary Option
Clinical ASCVD	No comorbidities	Age >65, ASCVD event within 3 months, ASCVD event while on statin, CKD, Current cigarette smoking, Diabetes, HDL <40 (M) or <50 (F), H/o non-MI related coronary revascularization, hs-CRP >2mg/dL, Lp(a) >30 mg/dL, Metabolic syndrome, Poor control of major risk factors, Prior MI/non-hemorrhagic stroke, Residual coronary artery disease (>40% stenosis in ≥2 large vessels), Symptomatic PAD	High	>50% LDL reduction LDL <70 Non-HDL <100	Ezetimibe	PCSK9 (add to or replace zetia)
	With Comorbidities (incl HF, dialysis, LDL >190)				Ezetimibe OR PCSK9i	Add other agent
LDL >190	Primary Prevention		High	>50% LDL reduction* LDL <100 Non-HDL <130	Ezetimibe OR PCSK9i	Add other agent

*If no high-risk co-morbidities, >50% LDL reduction alone may be sufficient. If patient has high-risk features or significant subclinical atherosclerosis, may be reasonable to target LDL <70 or non-HDL <100.

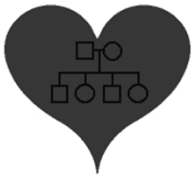
Statin Benefit Group	Subgroup	Co-morbidities indicating higher risk	Initial Statin Intensity	Targets for Consideration	Initial Option	Secondary Option
Diabetes	10 year risk <7.5% AND no high-risk features	Albuminuria (alb/cr >30 mg/g), CKD (eGFR <60), hs-CRP >2mg/dL, Lp(a) >30 mg/dL, Retinopathy, Subclinical atherosclerosis	Moderate	>30% LDL reduction LDL <100 Non-HDL <130	Titrate to high intensity	Add ezetimibe^ if LDL <50% decreased
	Risk >7.5% OR high-risk features		High	>50% LDL reduction LDL <100 Non-HDL <130	Ezetimibe	BAS
Age 40-75	Risk >7.5% and no high-risk markers	10 year risk >20%, Baseline LDL >160 mg/dL, Family h/o premature ASCVD, hs-CRP >2 mg/dL, Poor control of major risk factors, Subclinical atherosclerosis (eg CAC), "Other risk modifying conditions" including CKD, HIV, and chronic inflammatory disorders	Moderate	>30% LDL reduction LDL <100 Non-HDL <130	Titrate to high intensity	No further recommendations
	Risk >7.5% AND ≥1 high-risk markers				Titrate to high intensity	Add ezetimibe^ if LDL <50% decreased
	Risk 5-7.5%				Recommend against use of non-statins	

^Can consider BAS with inadequate response to ezetimibe or ezetimibe intolerance if TRG <300mg/dL

Familial Hyper-cholesterolemia

- **Familial hypercholesterolemia (FH) is a common genetic cause of premature coronary heart disease (CHD) due to lifelong elevated plasma low-density lipoprotein cholesterol (LDL-C) levels**
- **Prevalence**
  - **Heterozygous FH ~1:300-1:500**
  - **Homozygous FH ~1:1,000,000**
  - **~620,000 FH patients in US**
  - **Most common congenital metabolic disorder**
- **Group of genetic defects resulting in severe elevations of blood cholesterol levels**
  - **LDL receptor (LDLR)**
  - **Apolipoprotein B (Apo B)**
  - **Proprotein convertase subtilisin/kexin type 9 (PCSK9)**

Heterozygous FH (HeFH)



- If not treated:
  - 50% risk of CHD in men by age 50
  - 30% risk of CHD in women by age 60
- National Lipid Association Screening Recommendations[1]
  - FH should be suspected when untreated fasting LDL-C or non-HDL-c levels are at or above the following

Age	LDL (mg/dL)	Non-HDL (mg/dL)
≥ 20 years	≥ 190	≥ 220
< 20 years	≥ 160	≥ 190

  - For individuals with these levels, a family history of high cholesterol and heart disease should be collected

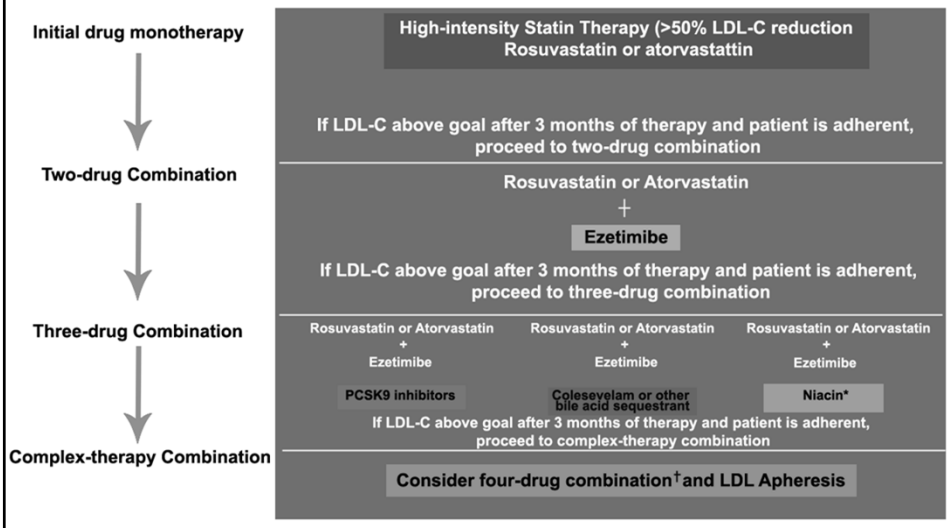
1. Goldberg et al. *J Clin Lipidol.* 2011; 5(3):133-140.

Diagnostic criteria

- Clinical diagnosis
  - Three validated sets of diagnostic criteria
  - All take into consideration a combination of the following:
    - Elevated, untreated LDL-C levels (cut points vary with age)
    - Family history (↑LDL-C; premature CHD)
    - Clinical history (premature CHD)
    - Physical examination (tendon xanthomas; corneal arcus <45y)
    - Functional mutation in *LDLR*, *APOB*, or *PCSK9*
- Genetic testing
  - ~$100 out of pocket for pt
  - Negative results do not rule out FH

Haase and Goldberg. *Curr Opin Lipidol* 2012, 23:282–289

2015 AHA Scientific Statement on FH



Gidding SS et al. Circulation 2015

Case #2

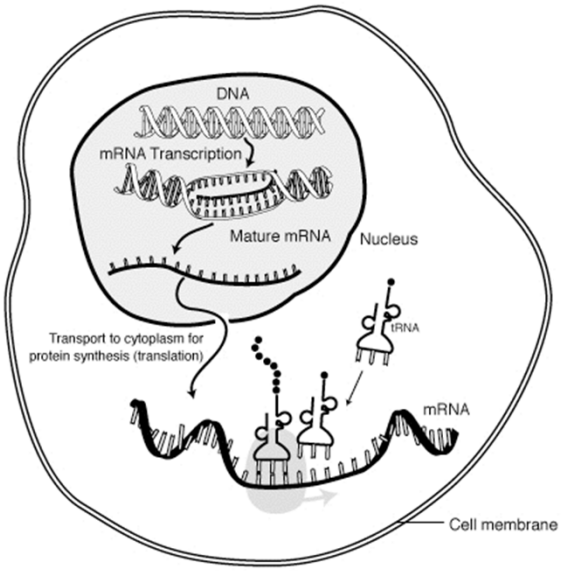
Case 2

- 24 yo white male
- Secondary prevention
- PMH:
  - Clinical HoFH diagnosed age 2 (highest TC 957)
    - Significant xanthomas on hands, elbows, achilles
  - Advanced CAD s/p mtp PCIs to LAD/Cx/RCA
    - Preserved LV systolic function
- Fam Hx:
  - Paternal GF CAD age 40. Father CAD age 46. Mother, brother, sister, father HLD
- Genetics: Compound heterozygous (both LDLR)

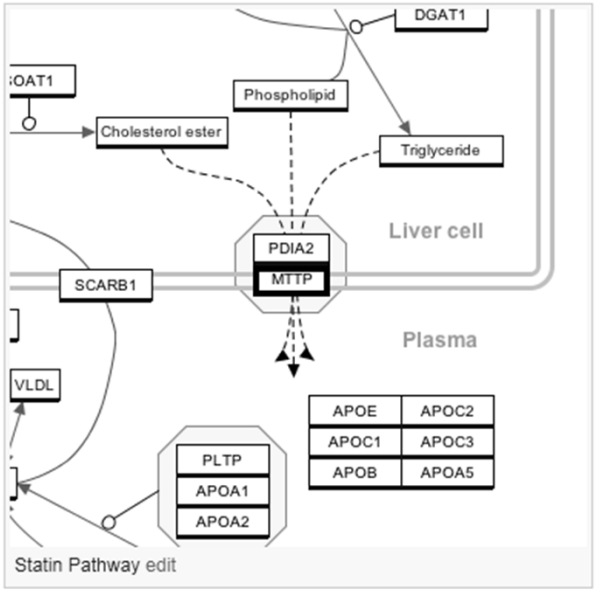
Case 2 Medications

- Atorvastatin 80mg daily
- Zetia 10mg daily
- Welchol 6 tabs daily
- Aspirin 81mg daily
- Plavix 75mg daily
- Metoprolol 25mg twice daily
- SL NTG prn
- Ferrous sulfate 324mg twice daily

Mipomersen (Kynamro®) – Apo B inhibitor



Lomitapide (Juxtapid®) – Microsomal TG Transfer Protein Inhibitor



HoFH agent comparison

	Mipomersen	Lomitapide
Mechanism	Apo-B synthesis inhibitor	MTP inhibitor
Efficacy	~25% LDL-C ↓	40-50% LDL-C ↓
Dose	Weekly injection	Oral tablet
Pt symptoms	Injection site rxn (76%), Flu-like symptoms (29%)	GI (75-90%) (n/v/d, abd discomfort)
Adverse reactions	LFT elevations (60%), Hepatic steatosis	LFT elevations (34%), Hepatic steatosis (8.6%)
REMS	Yes	Yes
Monthly Cost www.goodrx.com & www.drugs.com	~$28,000	~$30,000
Drug Interactions	Minimal	Many
LDL Apheresis	✖	✓

Prescribing information: Kynamro 2012 and Juxtapid 2012

Class	Primary MOA	↓ LDL-C HoFH	↓ LDL-C HeFH
Statins	Inhibition of HMG-CoA Reductase (↓Cholesterol synthesis ↑LDL clearance via LDL receptors)	Up to 28%	Up to 63%
Bile Acid Sequestrants	↓Bile acid re-absorption (↑LDLC update to make bile)	<10%	Up to 23%
Zetia	Intestinal Cholesterol absorption via NPC1L1 (↑LDL clearance via inhibiting absorption)	<10%	~25%
Stanol esters	Intestinal Cholesterol absorption (compete for absorption)	<10%	10-15%
Nicotinic acid	Inhibits lipolysis in adopocytes (↓VLDL/LDL synthesis; ↓HDL clearance)	<10%	14-40%
LDL apheresis	Removal of ApoB containing particles (↓VLDL, IDL, LDL, Lp(a))	20-40% 76% acutely	83% acutely
ApoB Inh	Inhibits ApoB containing particles (↓VLDL, IDL, LDL, TG, Non HDL, ApoB, Lp(a))	~25%	x
MTP Inh	Inhibits Microsomal TG Transport Protein (MTP) (↓VLDL, IDL, LDL, TG, Non HDL-C, ApoB)	~40%	x
PCSK9 Inh	Inhibits PCSK9 (↑LDL clearance via LDL receptors)	Up to 35%	~60%

Table adapted from Rader DJ, et al. J Clin Invest. 2003;111(12):1796-1803.

LDL Apheresis

What is it?

- FDA-approved process selectively removing Apo B-containing particles from bloodstream
- Extracorporeal precipitation with heparin
- Repeated every 1-2 wks
- Removes at least 60% Apo B-containing particles
- $$$$

Candidates for Apheresis

Patients on 6 months of maximal therapy who have not reached goal:

- HoFH w/ LDL ≥ 300
- HeFH w/ LDL ≥ 300
  - + 0-1 risk factor
- HeFH w/ LDL ≥ 200
  - + high risk (≥ 2 risk factors, Lp(a)≥50mg/dL)
- HeFH w/ LDL ≥ 160
  - + very high risk (CHD, CAD, or diabetes)

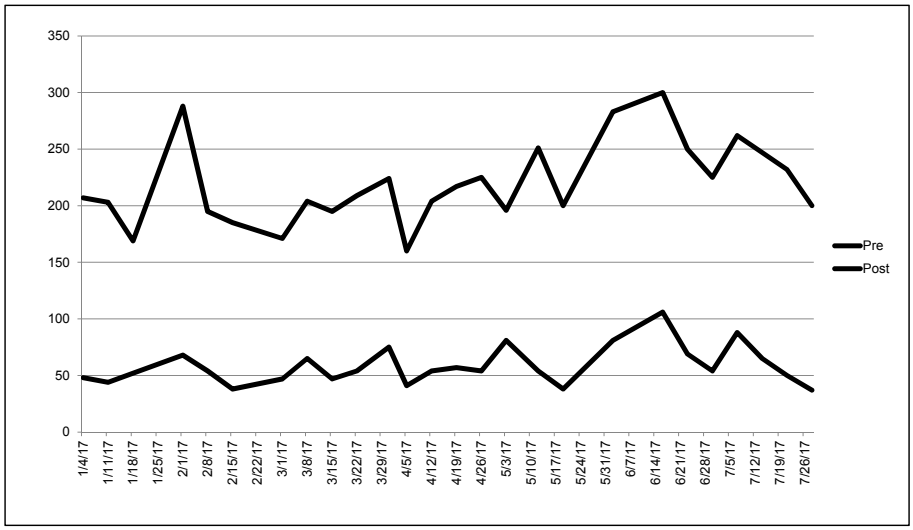
Ito. *J Clin Lipidol*. 2011;5(6).

Case 2 Current Medications

- Crestor 40mg daily
- Zetia 10mg daily
- Aspirin 81mg daily
- Plavix 75mg daily
- Metoprolol 25mg twice daily
- SL NTG prn
- Ferrous sulfate 324mg twice daily
- Weekly lipoprotein apheresis sessions

Case 2 Current labs

Average pre 219mg/dL
Average post 58mg/dL
Time averaged 138mg/dL



Statin intolerance

The true frequency of statin intolerance in the population is unknown

- May approach 10%

"Intolerance" if recurrent symptoms with rechallenge of 2-3 statins

- Metabolized by different pathways, different lipophilicities, and ≥ 1 at the lowest approved dose

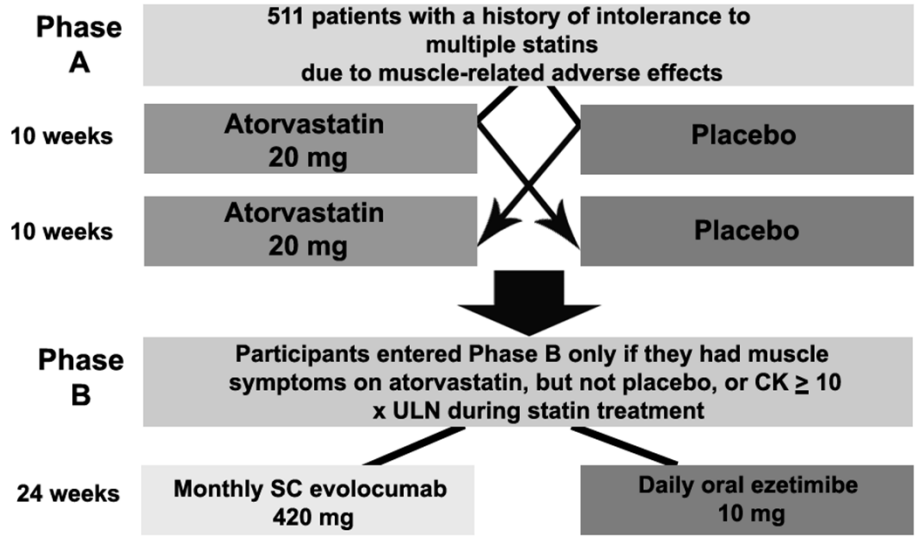
Real or perceived symptoms from statins may be underappreciated cause of non-adherence to therapy

- USAGE study - pt reported muscle symptoms may occur ~29%
- Effective and empathetic communication vital
- *"The secret of the care of the patient is in caring for the patient."* – Francis Peabody

2014 NLA Statin safety task force
Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. J Clin Lipidol. 2013;7(5):472–483.
Oglesby P. The Caring Physician: The Life of Dr. Francis W. Pea- body. Countway Library of Medicine; 1991.

GAUSS 3:
Evolocumab in statin intolerance

Two double-blind phases



Nissen SE, Stroes E, et al. JAMA 2016;315:1580-90

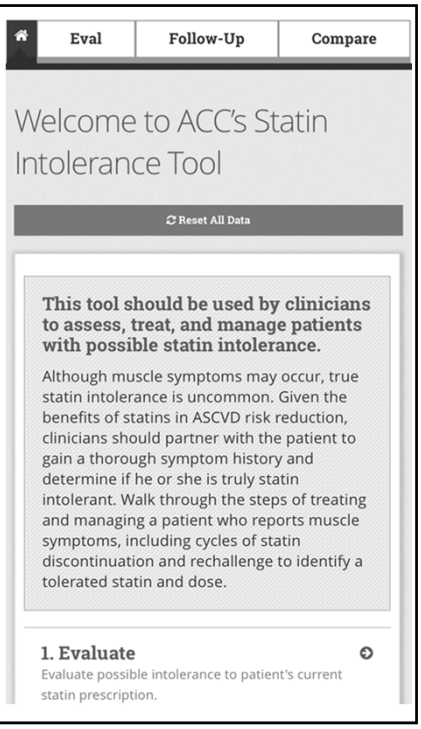
Phase A:
Study Drug Discontinuation Events

Intolerable Muscle Symptoms	**N=491**
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	20/511
Bypassed Phase A due to CK elevation ≥ 10 x ULN	**19 (3.9%)***

Nissen S, stroes E, et al JAMA 2016

Statin Intolerance

- **Drug Interactions**
  - **Risk of myopathy ↑ when statins coadministered w/ medications that inhibit their metabolism**
  - **Choosing a noninteracting medication or switching to a non-interacting statin may be the safest option**
- **Muscle safety**
  - **Algorithm exists for the evaluation and treatment of patients who may be intolerant to statins as the result of adverse muscle events**
- **Use ACC Statin intolerance app!**



Statin intolerance: Assess labs

Muscle symptom severity

- CK

Rhabdomyolysis

- Creatinine & Urinalysis

Risk factors / secondary causes

- Thyroid panel
- Electrolyte panel
- Renal panel
- Vitamin D 25-OH

Statin intolerance clinical pearls

Treat secondary causes
- Vit D
- Hypothyroid

Re-challenge and/or Reduce
- Ultra-low dose statin
- High potency, long half-life

Change
- Hydrophilic statin
- Non-statin

Internal data:
- ✓ ***75.9% of statin intolerant pts were able to tolerate statin therapy***
- ✓ ***43% achieved LDL-C goals***

Summary

- **Patient-centered, individualized clinical judgement is best**
  - **Lifestyle paramount to risk reduction**
- **Statins as first line pharmacotherapy,**
  - **Strongly consider non-statin add-on therapy for patients on max-tolerated statin with residual risk**
- **Familial hypercholesterolemia awareness is important and requires lifelong therapy**
  - **Response to lipid lowering therapies may vary**
- **Statin intolerance, while truly uncommon, can be overcome with various clinical strategies**
  - **Education, monitoring, and partnership with patients is vital**

OSUWMC Lipid Clinic

What we offer

- Comprehensive, personalized, high quality health care and patient education
- Ongoing assessment and therapeutic optimization for CAD risk reduction
- Application of current EBM and guidelines
- Quality monitoring and clinical outcomes

Staff

- Lipid specialists (ABCL & ACCL)
- Training in statin intolerance, complex drug regimens, ADE monitoring and management, various presentations of HLD

Partners

- Genetics Clinic
- Specialty pharmacy
- Smoking Cessation Clinic
- Apheresis Unit

Who to refer

- High risk ASCVD or FH with atherogenic cholesterol levels above treatment goals, on max tolerated statin
- Patient with multiple intolerance to recommended therapy
- Any patient seeking comprehensive cardiovascular risk reduction

How to refer

- Call for appointment to 614-293-0649
- Fax referral to 614-293-8260