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UNIVERSITY

Pharmacologic Therapies







Learning Objectives

1. Recognize the role of drug therapy in the management of dyslipidemia.
2. Review the mechanism of action, pharmacokinetics, and efficacy of available FDA approved drugs for the management of lipid disorders.
3. Assess the side effects of lipid-altering drugs to encourage their safe use in cardiovascular disease prevention.
4. Describe the appropriate use of lipid-altering drugs in special populations


Outline

- Lipid lowering pharmacotherapy:
 - Statins, Bile Acid Sequestrants, Cholesterol Absorption Inhibitor, PCSK9 Inhibitors, Niacin, Fibrates, Omega-3 Fatty Acids
- New Drugs
- Special Populations
- Combination Therapy
- Challenges

Drugs Affecting Lipoprotein Metabolism

	LDL-C	HDL-C	TG
 Statins	↓18-55%	↑5-15%	↓7-30%
 Bile acid sequestrants	↓15-30%	↑3-5%	↑0-10%
Nicotinic acid	↓5-25%	↑15-35%	↓20-50%
 Fibric Acids	↓5-↑20%	↑10-20%	↓20-50%
 Ezetimibe	↓13-20%	↑3-5%	↓5-11%
 Omega-3 fatty acids	↓6-↑25%	↓5-↑7%	↓19-44%
 PCSK9 inhibitors	↓40-72%	↑0-10%	↓0-17%

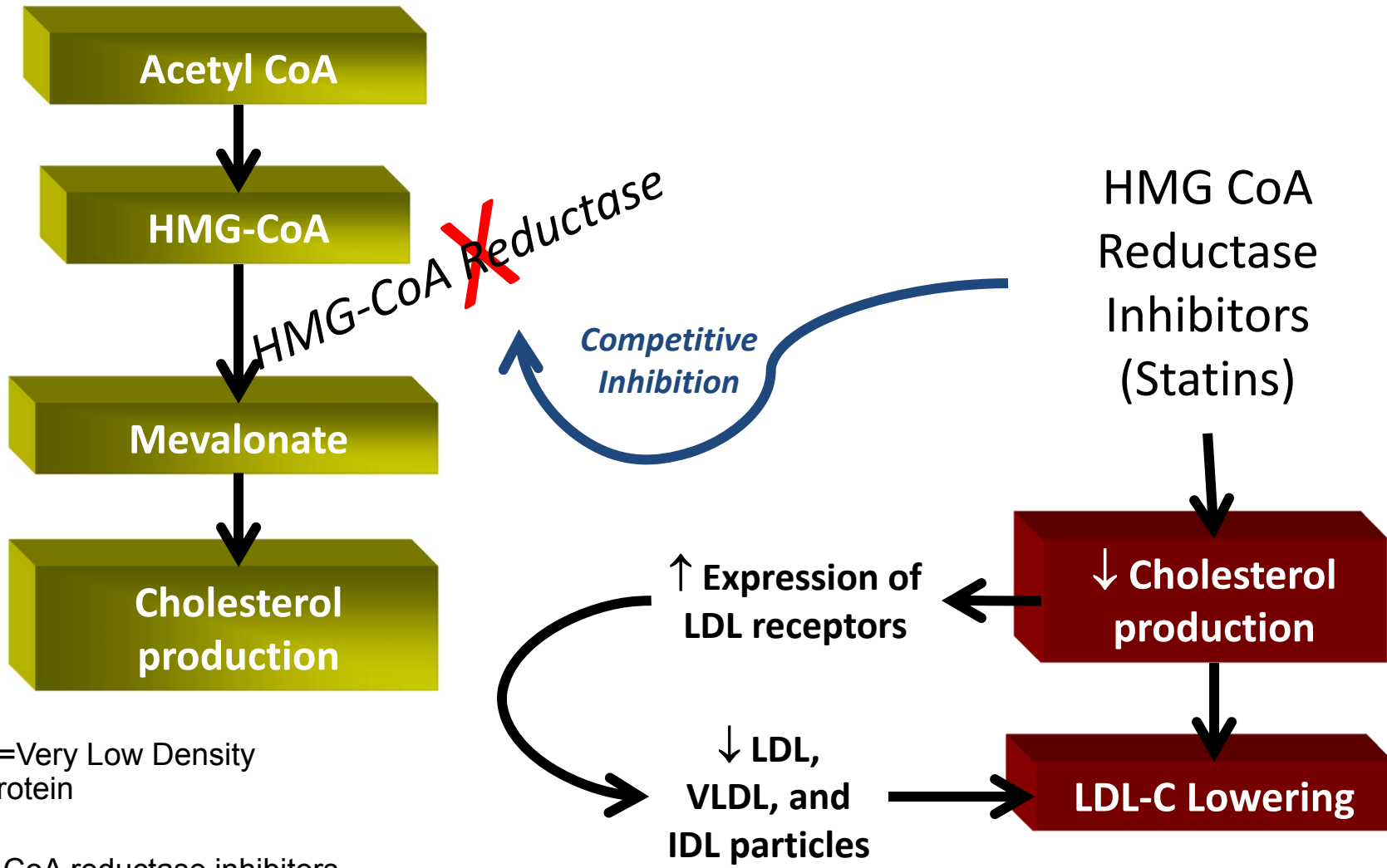
 For LDL-C lowering

 Primarily for hypertriglyceridemia

Jacobson TA et al. *J Clin Lipidol.* 2014; 8:473-88.

Shimada YJ and Cannon CP. *European Heart Journal* doi:10.1093/eurheartj/ehv174

Statins



VLDL=Very Low Density Lipoprotein
IDL
HMG-CoA reductase inhibitors

Statins: Role in Therapy

- First-line therapy for most patients
- Clinically proven to reduce mortality and recurrent cardiovascular events
- The most effective agents to lower LDL-C
- Stabilizing atherosclerotic plaques, reduces atherosclerotic plaque progression/possible regression
- Overall well tolerated

Statin Efficacy

	% Change		
	LDL-C ↓	HDL-C ↑	TG ↓
Lovastatin	21-31	5-6	8-19
Simvastatin	30-47	8-12	15-24
Pravastatin	22-37	2-12	11-24
Fluvastatin	22-35	3-7	12-19
Atorvastatin	39-60	8-9	19-37
Rosuvastatin	45-63	8-14	10-35
Pitavastatin	32-43	5-8	15-19

Listed in order of Food and Drug Administration approval

ACC/AHA 2013 Blood Cholesterol Guideline: Statin Intensity

High-Intensity	Moderate-Intensity	Low-Intensity
Daily dose lowers LDL-C on average, by ~ $\geq 50\%$	Daily dose lowers LDL-C on average, by ~ 30 to $<50\%$	Daily dose lowers LDL-C on average, 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 <i>Fluvastatin XL 80 mg</i> Fluvastatin 40 mg bid <i>Pitavastatin 2–4 mg</i>	<i>Simvastatin 10 mg</i> Pravastatin 10–20 mg Lovastatin 20 mg <i>Fluvastatin 20–40 mg</i> <i>Pitavastatin 1 mg</i>
<p>Specific statins and doses are noted in bold that were evaluated in randomized controlled trials. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in <i>italics</i>.</p>		

Stone NJ, et al. Circulation. 2013: published online before print November 12, 2013.

Statin Pharmacokinetics

	Bio-availability	Half-life (hr)	CYP450 Metabolism	Solubility
Lovastatin	<5%	2-3	3A4	Lipophilic
Simvastatin	<5%	2	3A4	Lipophilic
Pravastatin	17%	1.5-2	none	Hydrophilic
Fluvastatin	24%	1	2C9	Hydrophilic
Atorvastatin	12%	14	3A4	Lipophilic
Rosuvastatin	20%	20	2C9	Hydrophilic
Pitavastatin	43-51%	12	2C9, 2C8	Slightly Hydrophilic

Characteristics Predisposing Individuals to Statin Adverse Effects

- Multiple or serious comorbidities
- Previous statin intolerance or muscle disorders
- Unexplained ALT elevations >3 times ULN
- Patient characteristics or concomitant use of drugs affecting statin metabolism
- >75 years of age
- Additional characteristics:
 - History of hemorrhagic stroke and Asian ancestry

NLA Statin Muscle Safety Task Force

Spectrum of statin-associated muscle adverse events

Myalgia – unexplained muscle discomfort, often described as “flu-like” symptoms, with normal CK level. Spectrum of myalgia complaints includes: muscle aches, muscle soreness, muscle stiffness, muscle tenderness, and muscle cramps with or shortly after exercise (not nocturnal cramping)

Myopathy – muscle weakness (not attributed to pain and not necessarily associated with elevated CK)

Myositis – muscle inflammation

Myonecrosis – muscle enzyme elevation or hyperCKemia

- Mild >3-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race and sex.
- Moderate ≥ 10 -fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race and sex.
- Severe ≥ 50 -fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race and sex.

Myonecrosis with myoglobinuria or acute renal failure
(increase in S.Cr ≥ 0.5 mg/dL – clinical rhabdomyolysis)

NLA Statin Muscle Safety Task Force

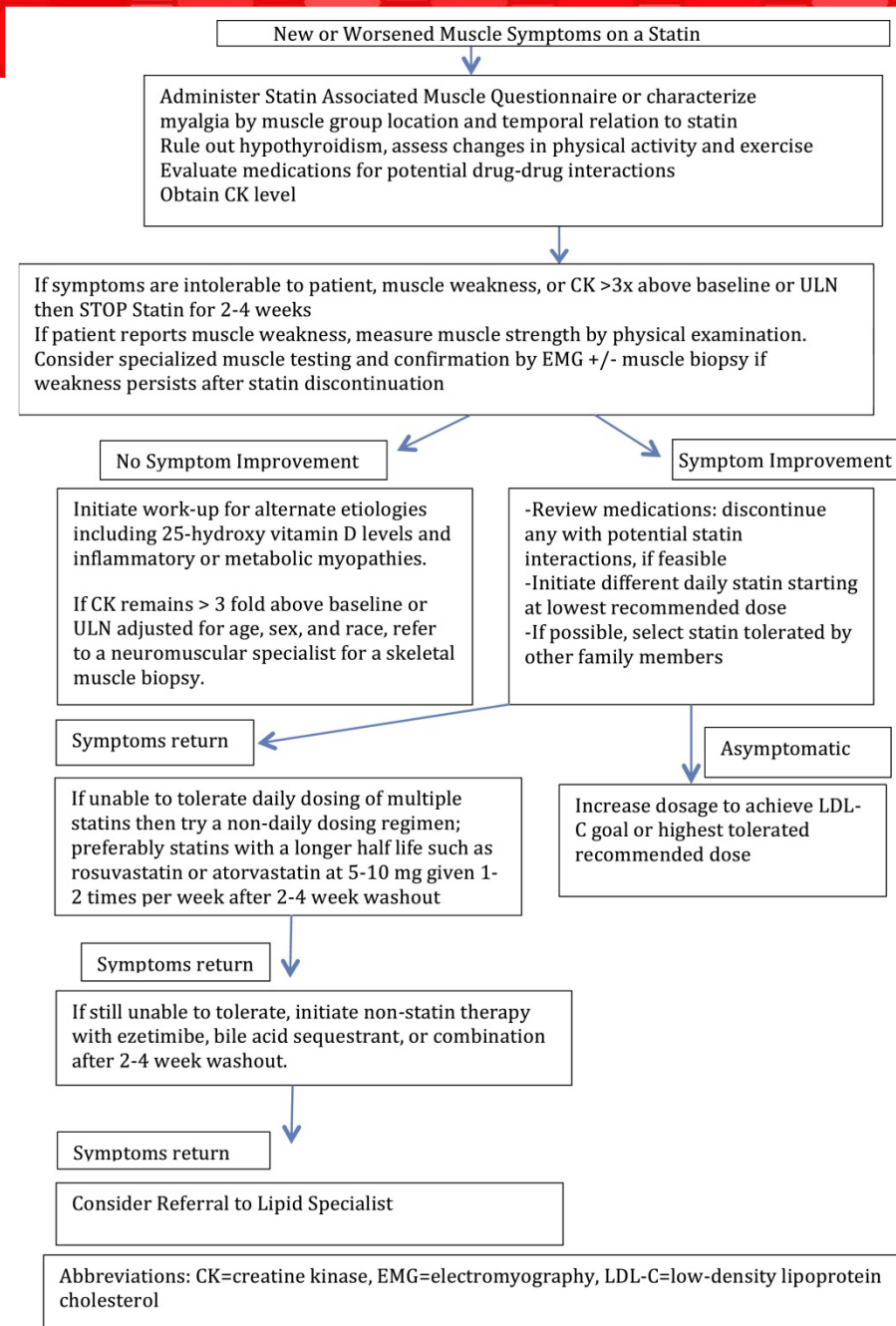
Proposed Statin Myalgia Clinical Index Score

Clinical Symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
– Symmetric hip flexors/thigh aches	3
– Symmetric calf aches	2
– Symmetric upper proximal aches	2
– Non-specific asymmetric, intermittent	1
Temporal pattern	
– Symptoms onset <4 weeks	3
– Symptoms onset 4-12 weeks	2
– Symptoms onset >12 weeks	1
De-challenge	
– Improves upon withdrawal (<2 weeks)	2
– Improves upon withdrawal (2-4 weeks)	1
Challenge	
– Same symptoms reoccur upon re-challenge <4 weeks	3
– Same symptoms reoccur upon re-challenge 4-12 weeks	1

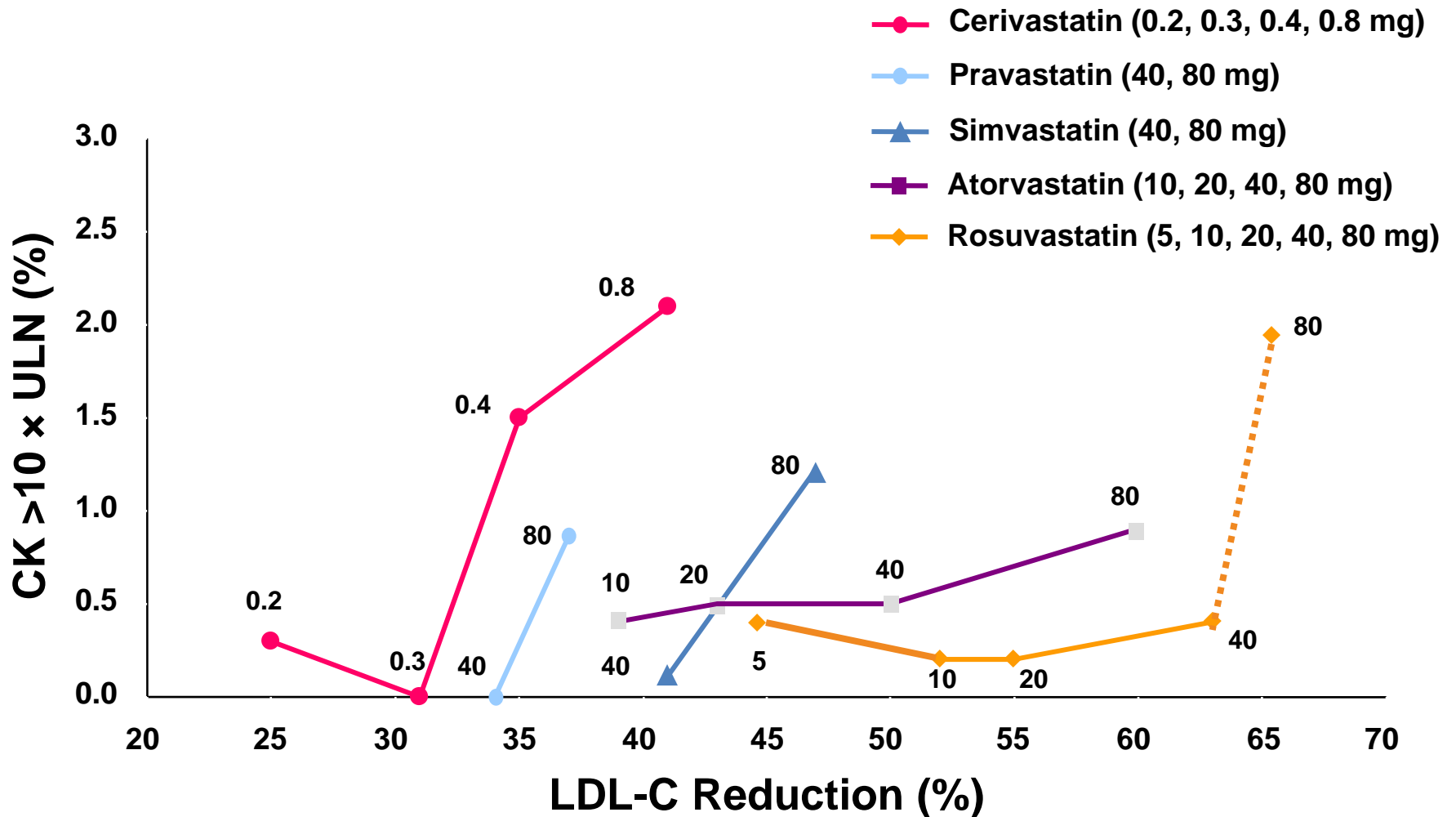
Statin myalgia clinical index score

- Probable 9-11
- Possible 7-8
- Unlikely <7

NLA Statin Muscle Safety Task Force



CK Elevations and LDL-C Reduction



NLA Statin Intolerance Expert Panel

Statin intolerance

- Clinical syndrome characterized by the inability to tolerate at least 2 statins, one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease)

NLA Statin Intolerance Expert Panel Recommendations to Clinicians

1. Statin intolerance is real, manifesting as an array of muscle-related symptoms including aching, stiffness, proximal motor weakness, fatigue, and back pain. Estimated frequency of muscle symptoms related to statin use is 1-10%. Severe myopathy with objective evidence is rare.
2. Cognitive difficulties while taking statins reported by a small number of patients, but objective documentation of impaired cognition is lacking. No evidence points toward progressive or permanent impairment of cognition. Frequency is unknown, but lower than that of muscle symptoms.
3. Increased serum hepatic transaminase levels (>3 times the ULN) in 0.3-3% of patients, dose-dependent Evidence does not support serious acute impairment or cumulative damage leading to chronic liver disease. Baseline liver function before statin initiation is recommended; regular monitoring is not recommended.
4. Associated increased risk for new-onset diabetes mellitus, especially with high doses. Magnitude of increased risk is small. CV Benefits outweighs risk.
5. The decision on statin intolerance is the patient's decision; best aided by evaluation and effective communication from the clinician

NLA Statin Intolerance Expert Panel Recommendations to Clinicians

6. Statin intolerance usually doesn't involve substantial risk for mortality or permanent disability. Distinguish statin intolerance from "drug allergy"
7. Maintain statin treatment in some form in almost every case of statin intolerance. Patients can be continued on statin treatment, commonly with doses and/or alternative statins that achieve a lower degree of LDL-C lowering. Atorvastatin or rosuvastatin at doses of 5–10 mg once or twice a week may reduce LDL-C by 16–26%.
8. Optionally pursue nonstatin treatments in statin-intolerant patients, with or without concomitant statin therapy. Options to be considered include bile acid sequestrants, niacin, ezetimibe, fibrates, plant sterol esters or stanol esters, viscous fiber, and substitution of mono- or polyunsaturated fats for trans unsaturated or saturated fats in the diet.
9. Specific recommendations for many issues of statin intolerance related to muscle, liver, cognition, and diabetes risk can be found in the reports of the Statin Safety Task Force Panels addressing those topics.

FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs

Safety Announcement [2-28-2012]

- **Monitoring Liver Enzymes**
 - Labels revised to remove the need for routine periodic monitoring of liver enzymes in patients taking statins
- **Adverse Event Information**
 - Potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.)
 - Reports of increased blood sugar and glycosylated hemoglobin (HbA1c) levels were been added

Statin and Risk of Incident Diabetes

- 2010 meta-analysis of 13 trials (n=91,140)
 - 4,278 developed diabetes (2,226 with statins vs. 2,052 with control) over a mean 4 yrs
 - 9% increased risk (OR 1.09 [1.02–1.17])
 - NNH was 255 patients
- 2011 meta-analysis of 5 trials (n=32,752)
 - 2,749 developed diabetes (1,449 with intensive-dose statin vs. 1,300 with moderate-dose statin) over a mean 1.9 yrs
 - 12% increased risk (OR 1.12 [1.04-1.22])
 - NNH was 498; but, NNT for CV events was 155

Benefits and Diabetes Risk in JUPITER

- 17,603 patients, randomized to placebo or rosuvastatin 20 mg for up to 5 years
 - Stratified based on presence of major risk factors for developing diabetes*

# of Diabetes Risk Factors*	Placebo vs. Rosuvastatin	
	# Primary CV Endpoints	# New Diabetes Cases
0 (n=6,095)	91 vs. 44 (p<0.0001)	12 vs. 12 (p=0.99)
	86 primary events avoided with no new cases of diabetes	
≥ 1 (n=11,508)	157 vs. 96 (p<0.0001)	204 vs. 258 (p=0.01)
	134 primary events avoided for every 54 new cases of diabetes	

*BMI ≥30 kg/m², metabolic syndrome, impaired fasting glucose, glycated haemoglobin A1c ≥6%

Lancet 2012; 380: 565–71.

Statin-Drug Drug Interactions

Primary Pathways:

1. Cytochrome P-450 interactions (esp. 3A4)
 2. Glycoprotein (P-gp)
 3. Organic Anion Transporting Polypeptide 1B1 (OATP)
- Subgroup analysis of the USAGE study:
 - concomitant use of medication(s) that inhibit statin metabolism associated with increased odds of new or worse muscle pain with statins and having previously stopped statin because of muscle symptoms

Inhibition of Metabolic Pathways

Medications	CYP450 3A4	P-gp	OATP1B1
Antimicrobials			
• Clarithromycin/Erythromycin	x	x	x
• Fluconazole	x		
• Itraconazole	x	x	
Cardiovascular			
• Amiodarone	x	x	
HIV			
• Delavirdine	x		
• Indinavir	x	x	x
• Nelfinavir	x	x	
• Ritonavir	x	x	x
• Saquinavir	x	x	x
Solid Organ Transplantation			
• Cyclosporine A	x	x	x

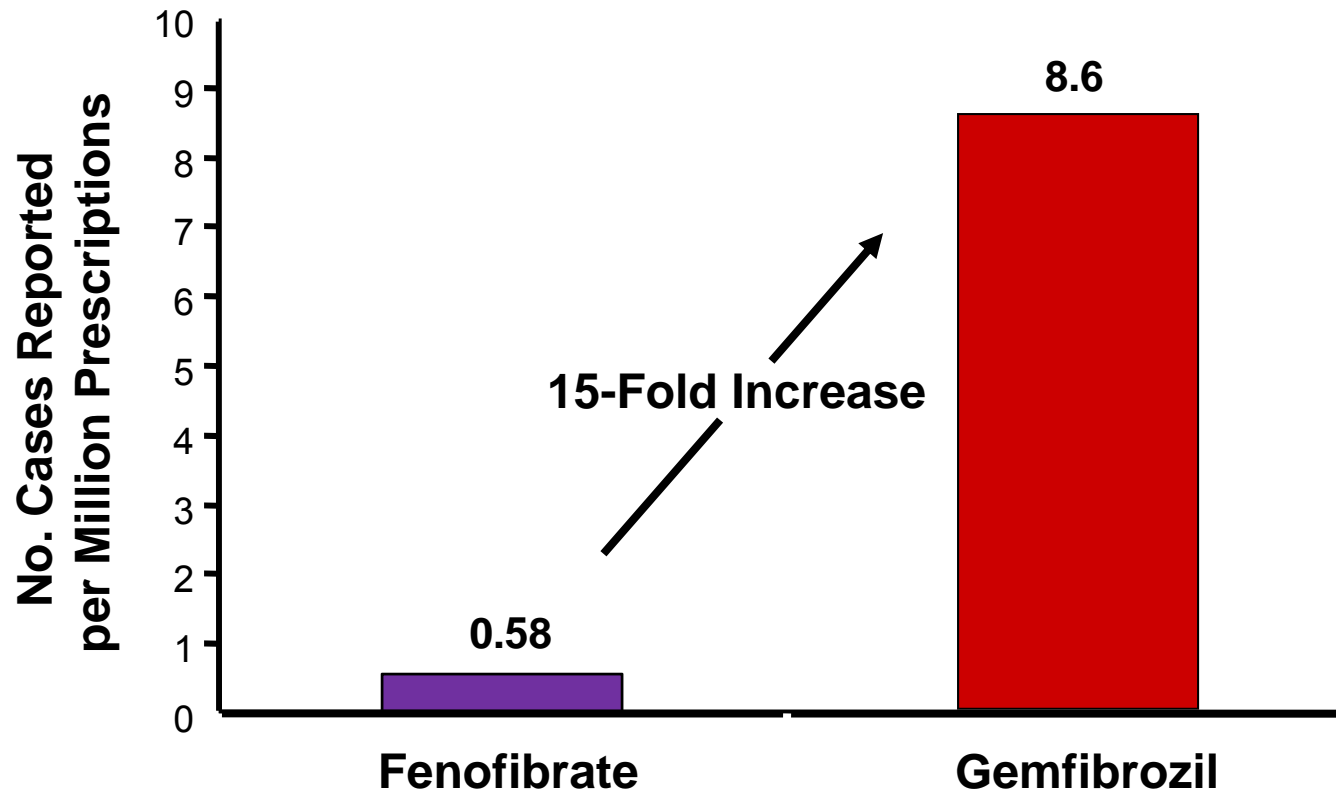
Certain Statin Drug-Drug Interactions

- Simvastatin & lovastatin - significant CYP3A4
 - Contraindicated with:
 - Azole antifungals (ketoconazole, itraconazole, fluconazole), erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, cyclosporine, gemfibrozil, and large quantities of grapefruit juice

Certain Statin Drug-Drug Interactions

- Some drugs have specific dose limitations with certain statins (partial list):
 - Amiodarone: Max simvastatin is 10 mg/day and lovastatin is 40 mg/day
 - Diltiazem, verapamil: Max simvastatin is 10 mg/day and lovastatin is 20 mg/day
 - Amlodipine: Max simvastatin is 20 mg/day
 - Ranolazine: Max simvastatin is 20 mg/day
 - Cyclosporine: Max rosuvastatin is 5 mg/day
 - Gemfibrozil: Max rosuvastatin is 10 mg/day

Rhabdomyolysis in Combination Therapy With Statins*



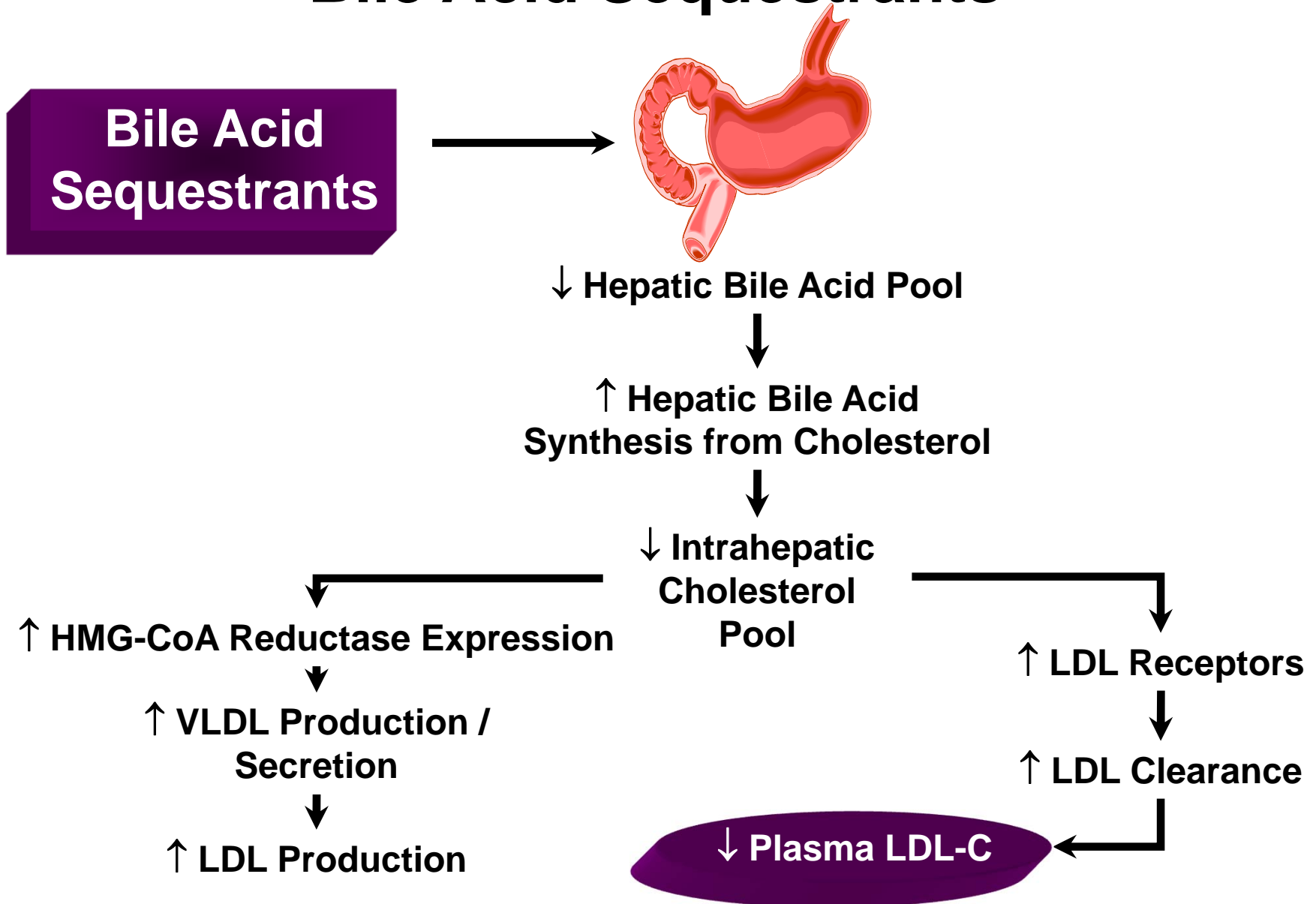
*Excludes cases involving cerivastatin

Jones PH et al. Am J Cardiol. 2005;95:120-122.

Statin/Fibrate Interaction

- Facts about gemfibrozil:
 - Known to ↑ risk of rhabdomyolysis with statins
 - Inhibits hepatic glucuronidation of certain statins
 - When used with certain statins:
 - Maximum rosuvastatin dose is 10 mg daily
 - Simvastatin is contraindicated
 - Lovastatin should be avoided
- Fenofibrate and fenofibric acid does not inhibit glucuronidation

Bile Acid Sequestrants



Bile Acid Sequestrants: Role in Therapy

- Combination with statin for additional LDL-C lowering (familial hypercholesterolemia)
- Alternative treatment in statin-resistant patients
- Non-cholesterol lowering use for lowering A1C (colesevelam) and other off-label uses
- CV Event Reduction:
 - LRC-Primary Prevention Trial (n=3086):
 - Cholestyramine reduced fatal CHD/non-fatal MI by 19% vs. placebo (p<0.05)

Bile Acid Sequestrants

- Tablet and powder formulations:
 - Powders must be mixed with water before use
- GI complaints are the most common side effects (constipation, abdominal discomfort, intestinal gas, indigestion, heartburn)
 - Constipation less with colesevelam
- Can bind other drugs and decrease absorption:
 - With colestipol and cholestyramine interacting drugs should be given 1 h before or 4 h after
 - Interaction risk is less problematic with colesevelam

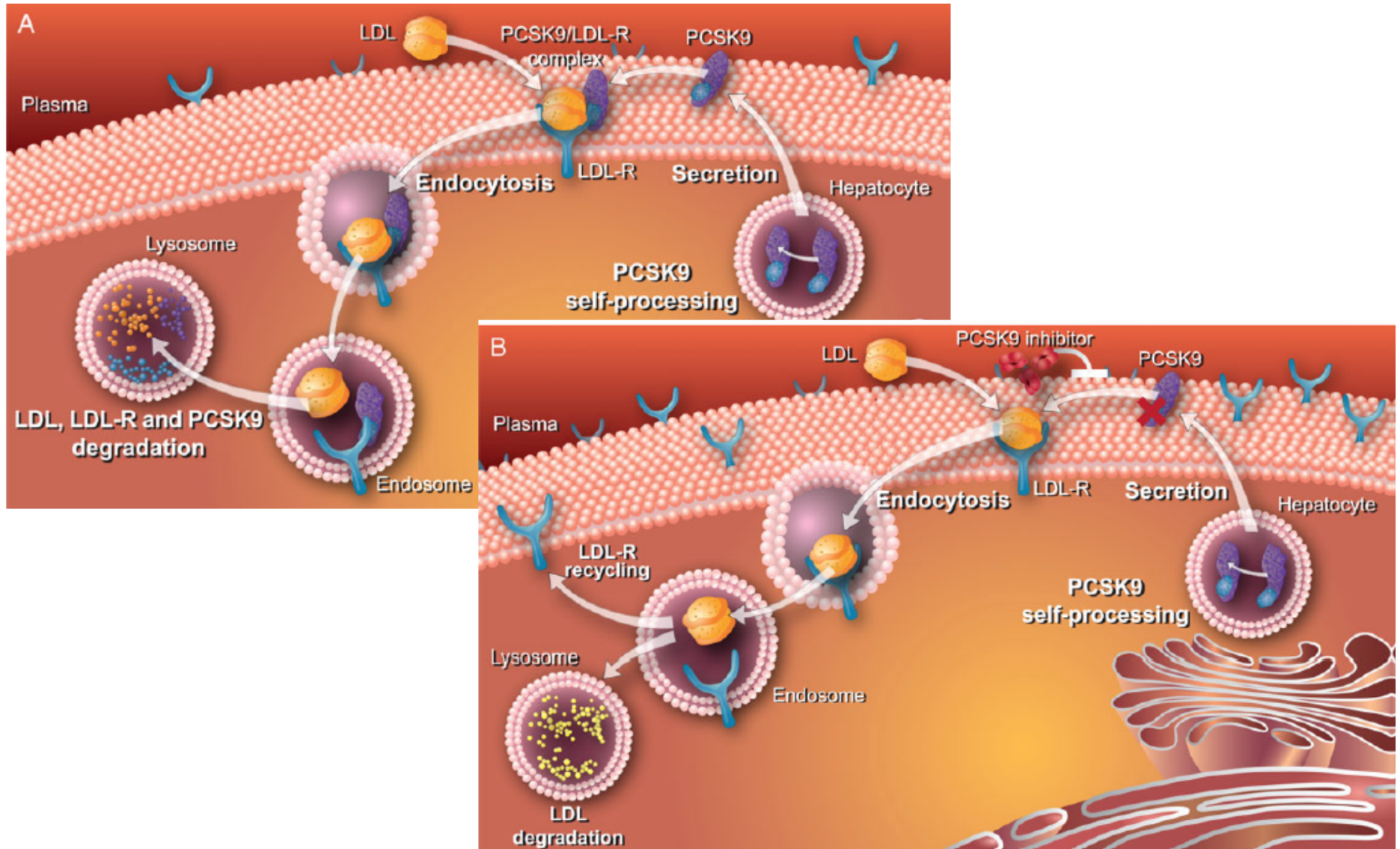
Cholesterol Absorption Inhibitor

- Mechanism of action:
 - After systemic absorption, reduces the small intestinal enterocyte uptake and absorption of cholesterol by binding to Niemann-Pick C1 Like 1 (NPC1L1), which keeps cholesterol in the intestinal lumen for excretion
 - May lead to increased LDL receptor expression in individuals with functional LDL receptors to also lowers plasma LDL-C

Cholesterol Absorption Inhibitor

- Combination with statin for additional LDL-C lowering (familial hypercholesterolemia)
- Alternative treatment in statin-resistant patients
- Ezetimibe is the only available agent
- Provides ~ 18% reduction in LDL-C
- Safe and well tolerated
- Outcomes data from IMPROVE-IT, though limited

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors



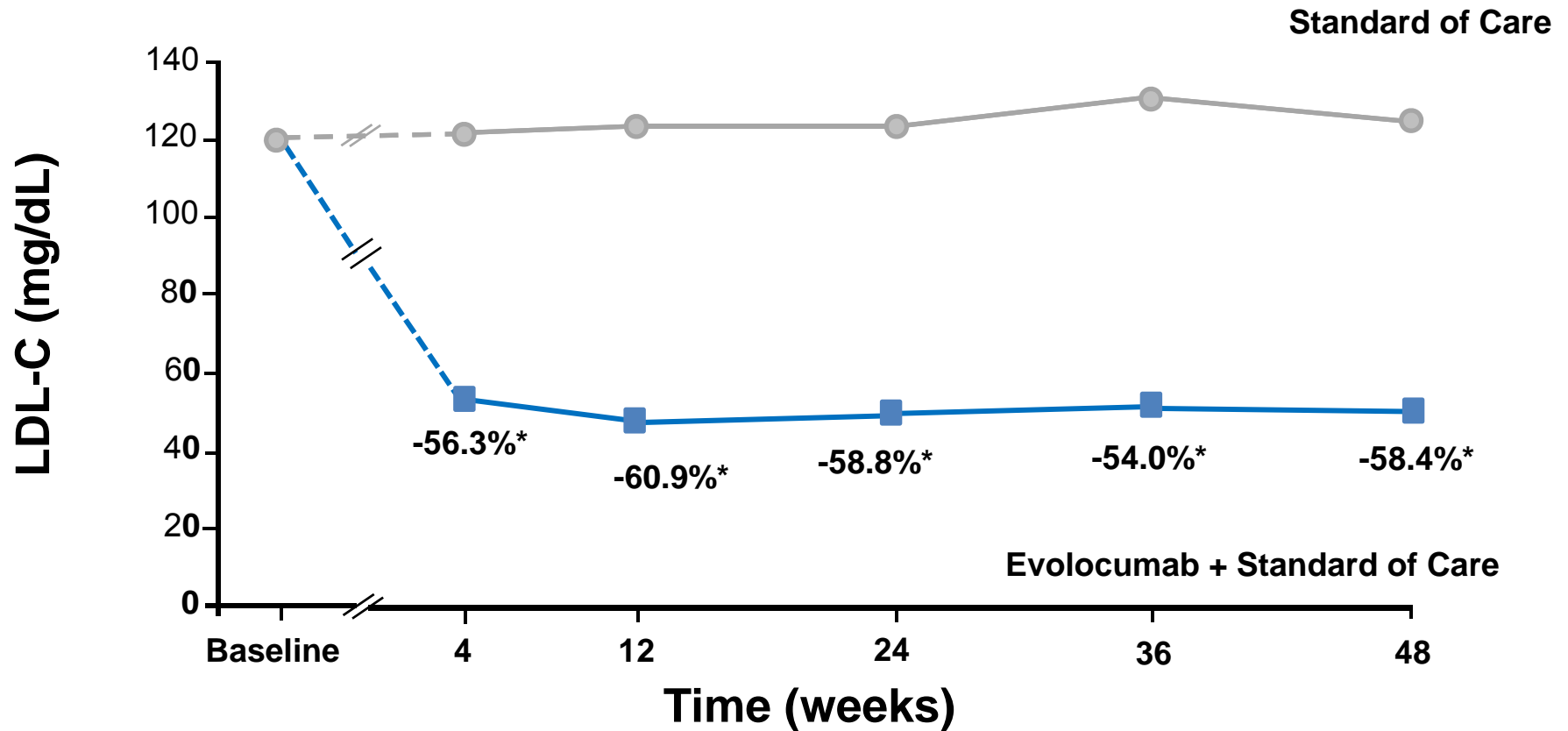
PCSK9 Inhibitors: Role in Therapy

- Alirocumab and Evolocumab FDA approval:
 - Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
 - Evolocumab also approved for homozygous FH

	Dosing
Alirocumab (Praluent)	75 – 150 mg sq every 2 weeks
Evolocumab (Repatha)	140 sq every 2 weeks or 420 mg once monthly in homozygous FH patients

- Use in statin intolerance is debated and evolving

Evolocumab (OSLER-1 and OSLER-2): LDL-C Levels Over Time



* All < 0.001

Sabatine MS, et al. *N Engl J Med.* 2015;372(16):1500-1509.

Alirocumab (ODYSSEY LONGTERM)

Summary of Adverse Events	Alirocumab (n = 1,550)	Placebo (n = 788)	P Value
Serious Adverse Events	290 (18.7%)	154 (19.5%)	0.66
• AE leading to discontinuation	111 (7.2%)	46 (5.8%)	0.26
• AE leading to death	8 (0.5%)	10 (1.3%)	0.08
General allergic reaction events	156 (0.1%)	75 (9.5%)	0.71
Local injection site reactions	91 (5.9%)	33 (4.2%)	0.10
Neurologic events	65 (4.2%)	35 (4.4%)	0.83
Neurocognitive events	18 (1.2%)	4 (0.5%)	0.17

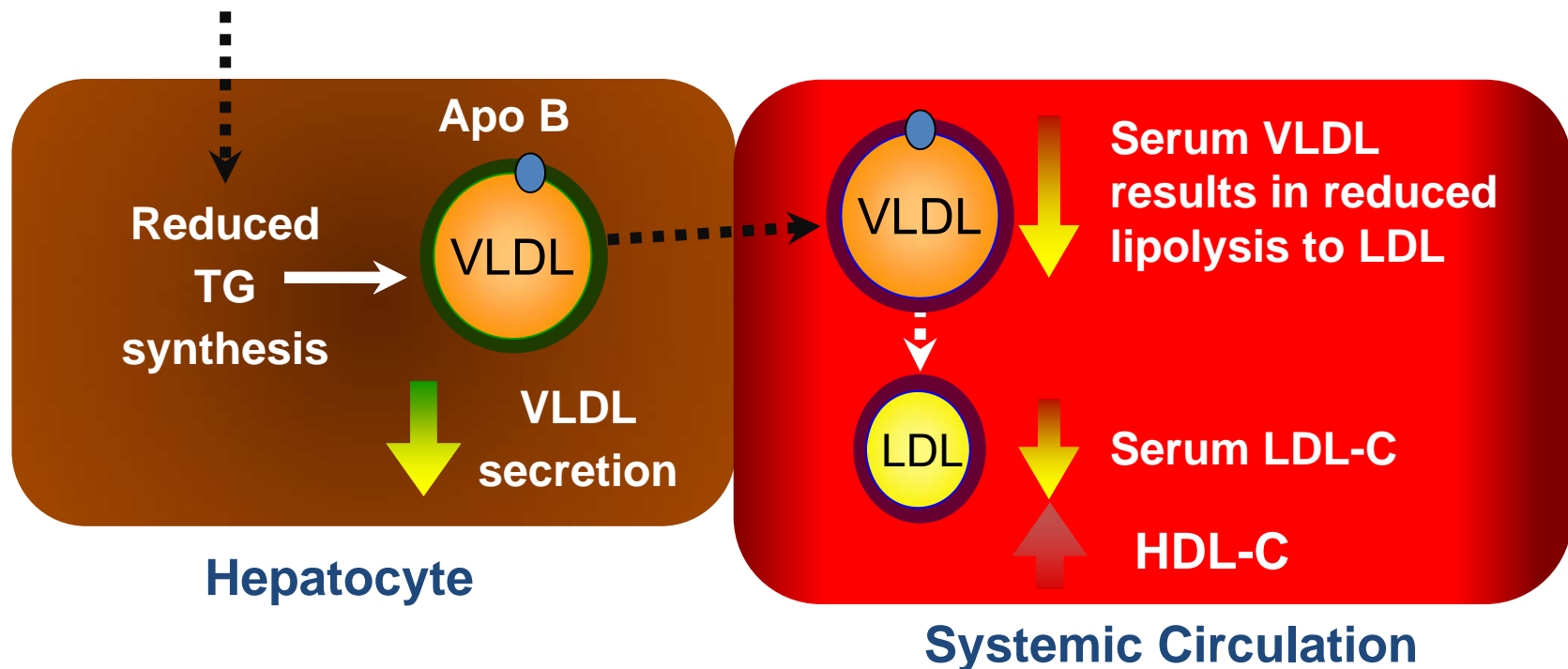
Among patients who received alirocumab, 575 (37.1%) had a calculated LDL-C level of < 25 mg/dL at 2 consecutive measurements. Rates of AEs were similar to those in the overall alirocumab group.

Outcomes Studies with PCSK9's

- Several pending large-scale outcome trials
- Preliminary Findings
 - Meta-analysis of 24 clinical trials (n=10,159)
 - Reduced MI
 - OR 0.49 (0.26-0.93)
 - Reduced all cause mortality
 - OR 0.45 (0.23-0.86)
 - No increase in serious adverse events

Niacin (a.k.a. Nicotinic Acid)

Inhibition of lipolytic release of fatty acids from adipose tissue resulting in reduced free fatty acid transport to liver



Overall decreased hepatic production of VLDL and Apo B

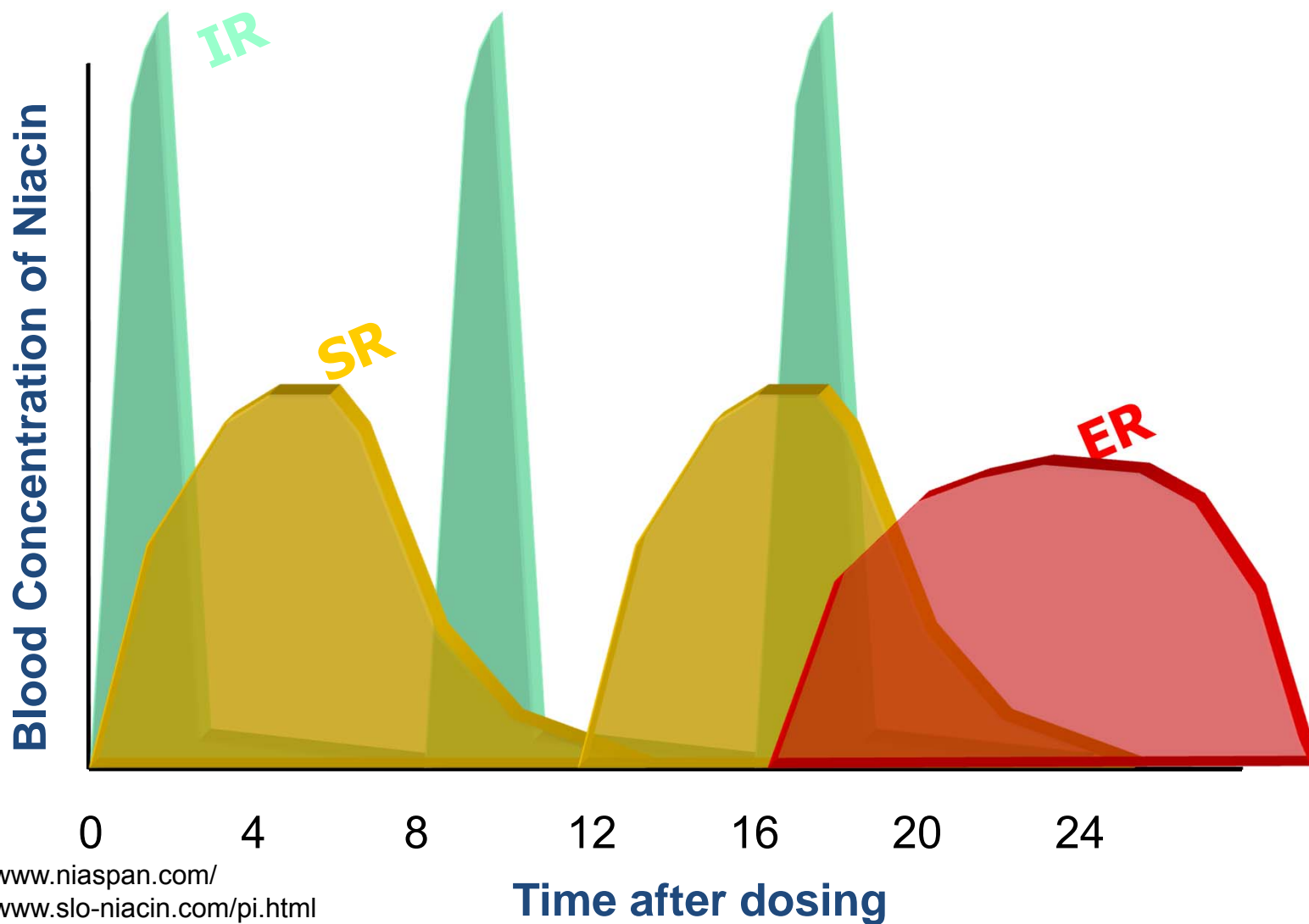
Niacin: Role in Therapy

- Treatment of hypertriglyceridemia
- Can raise HDL-C in isolated patients with low HDL-C
- Used in patients with mixed lipid disorders
- CV event reduction is unclear
 - Combination therapy with statin has not demonstrated reduced risk of CV events
- Several possible side effects:
 - Flushing, hepatotoxicity, hyperglycemia, hyperuricemia

Niacin Adverse Effects Among Products

- Three Different Products
 1. Immediate Release (IR)
 2. Slow Release (SR)
 3. Extended Release (ER)
- Adverse Effects per product:
 - Facial flushing: $IR \gg ER \ \& \ SR$
 - ER products are also enteric coated to minimize flushing
 - \uparrow hepatic transaminases: $SR > ER \ \& \ IR$
 - \uparrow glucose & \uparrow uric acid: same with all products

Pharmacokinetic Profiles

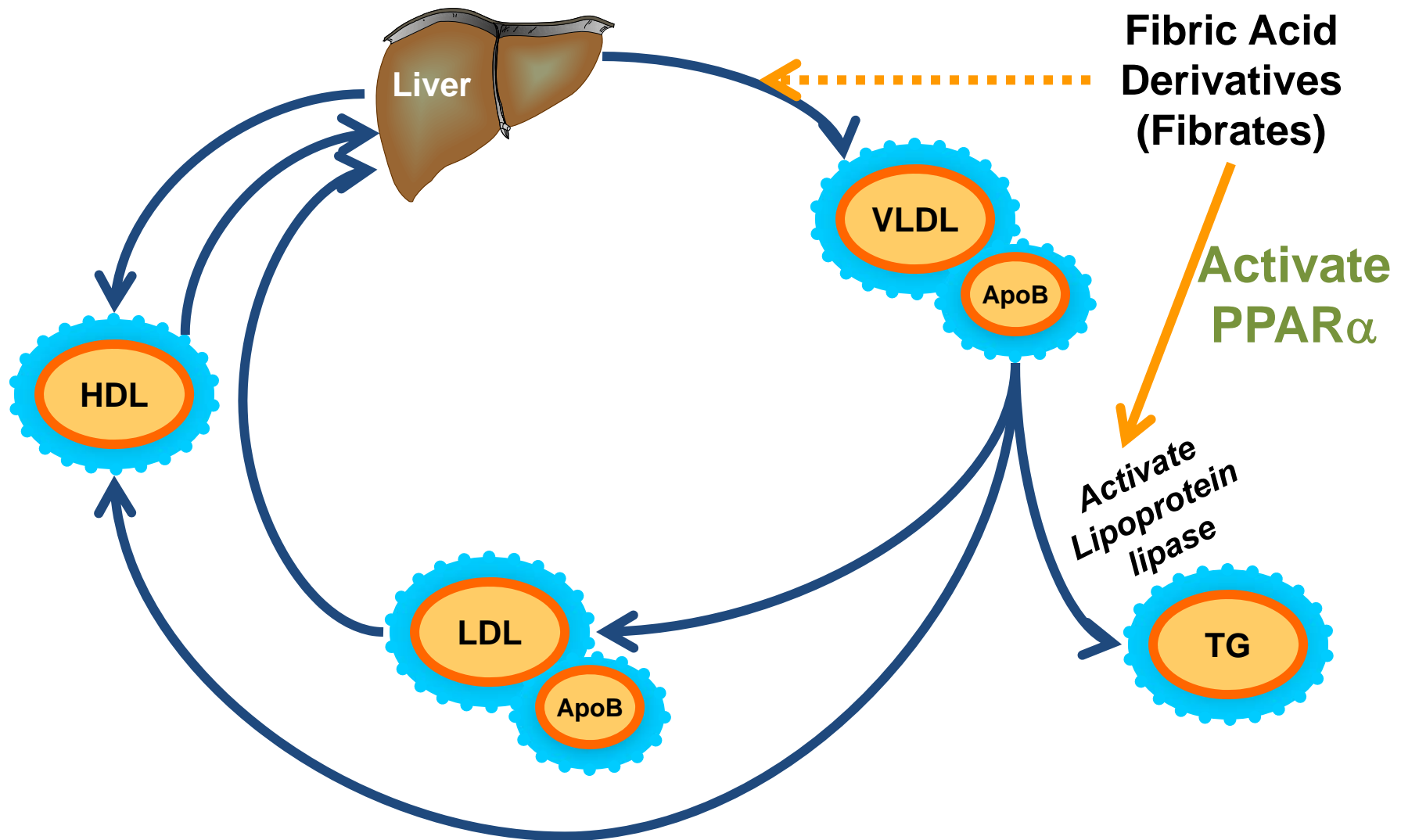


<http://www.niaspan.com/>
<http://www.slo-niacin.com/pi.html>

Flushing with Niacin

- Secondary to release of prostaglandin D2
- Frequency and intensity diminishes over weeks or months, but can be ameliorated by:
 - Starting with a low dose and titrating it up
 - Aspirin 325 mg or ibuprofen 200 mg 30-60 min prior
 - Dosing ER niacin at bedtime with a small snack
 - Failure of flushing rates to diminish, or reappearance of flushing, may be due to inconsistent dosing; A niacin-free interval of ≥ 3 days will often necessitate re-titration to avoid substantial flushing
 - Avoid alcohol, spicy foods, hot beverages, and hot baths or showers immediately before or after

Fibric Acid Derivatives



Fibrates: Role in Therapy

- Hypertriglyceridemia or mixed lipid disorders
- CV Event Reduction:
 - Helsinki Heart Study and VA-HIT trials demonstrated benefits with gemfibrozil
 - No CV Event Reduction in type 2 diabetes with fenofibrate in FIELD Trial and ACCORD
 - Meta-Analysis (18 trials, n=45,058)
 - 10% reduction in major CV events (p=0.048)

Frick MH et al. N Engl J Med. 1987;317:1237-1245.

Rubins HB et al. N Engl J Med. 1999;341:410-418.

Keech A et al. Lancet. 2005;366:1849–1861.

Accord Study Group. N Engl J Med. 2010;362,1563-1574.

Fibrates: Adverse Effects

- **Contraindications:**
 - Hepatic or severe renal impairment
 - Pre-existing gallbladder disease
- Minor increases in liver transaminases
- Myopathy, but most likely when gemfibrozil is used in combination with a statin
- May potentiate the action of warfarin
- May reversibly increase serum creatinine, but does not change glomerular filtration rate (GFR)

Fibrates: Renal Dosing (NLA and NKF)

Fibrate	Dose based on GFR (mL/min/1.73 m ²)			
	>90	60-90	15-59	<15
Fenofibrate	120-160 mg daily	80-108 mg daily	40-54 mg daily	AVOID
Micronized fenofibrate	130-200 mg daily	86-134 mg daily	43-67 mg daily	
Fenofibric Acid	135 mg daily	90 mg daily	45 mg daily	
Gemfibrozil	600 mg Twice daily	600 mg Twice daily	600 mg daily	

- Multiple fenofibrate formulations exist

Adapted from the National Kidney Foundation and National Lipid Association Recommendations, not product inserts

Omega-3 Fatty Acids (FA)

- Unclear mechanism; reduces hepatic VLDL-TG synthesis and/or secretion and enhances TG clearance from circulating VLDL
- Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower TGs; alpha-linoleic acid does not
- Role in therapy:
 - Prescription omega-3 FA products approved for severe hypertriglyceridemia (≥ 500 mg/dL)
 - Omega-3 Acid Ethyl Esters has both EPA and DHA
 - Icosapent Ethyl has EPA only
 - Omega-3-carboxylic acids has both EPA and DHA

Omega-3 Fatty Acid Products

	EPA	DHA	Dose	Take with Food
Omega-3 Acid Ethyl Esters	Yes	Yes	4 grams once daily or	needed
Icosapent Ethyl	Yes	No	2 grams twice daily	needed
Omega-3-carboxylic acids	Yes	Yes	2 or 4 grams once daily	not necessary

Omega-3 Fatty Acids vs. “Fish Oils”

- **Omega-3 fatty acids: Prescription agents**
 - Rigorous manufacturing purification processes
 - FDA regulated as a drug to treat a disease
- **“Fish Oils”: OTC nutritional supplements**
 - Content not necessarily equal to prescription agents
 - Not regulated products; USP verification is optional
 - Great variability among products regarding content
 - May cause fishy smelling belching/dyspepsia; minimized with enteric coating or freezing capsules

Lomitapide

Approved December 24, 2012

- Microsomal triglyceride transfer protein inhibitor that decreases lipoprotein production
- Approved as adjunct to diet and other lipid-lowering treatments to reduce LDL-C, TC, apo B, non-HDL-C in homozygous familial hypercholesterolemia (HoFM)
- Dosing: 5 mg daily titrated to a maximum of 60 mg daily
- Adverse effects: hepatic steatosis, elevated hepatic transaminases; GI adverse reactions (93%) could decreased absorption of vitamin E, alpha linoleic acid, linoleic acid, EPA, DHA (supplement recommended)
- Only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program

Mipomersen sodium

Approved January 30, 2013

- Antisense oligonucleotide that decreases secretion of apo B containing lipoproteins from the liver
- Approved as adjunct to lipid-lowering medications and diet to reduce LDL-C, apo B, TC, non-HDL-C in patients with homozygous familial hypercholesterolemia (HoFH)
- Dosing: 200 mg once weekly subcutaneous injection
- Adverse effects: injection site reactions (84%), flu-like symptoms (30%), elevated hepatic transaminases
- Only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program

Mean Additional Lipid-Lowering with “Standard” HoFH Therapy

Lomitapide

- LDL-C ↓ 40%
- TC ↓ 36%
- apoB ↓ 39%
- nonHDL-C ↓ 40%
- TG ↓ 45%
- HDL-C ↓ 7%

Mipomersen

- LDL-C ↓ 21%
- TC ↓ 24%
- apoB ↓ 19%
- nonHDL-C ↓ 22%
- TG ↓ 18%
- HDL-C ↑ 11%

Juxtapid Product Insert, Aegerion Pharmaceuticals, Inc. Cambridge, MA. December 2012.
Kynamro Product Insert, Genzyme Corporation. Cambridge, MA. January 2013.

Potential Agents on the Horizon

- Bococizumab
 - Another PCSK9 Monoclonal Antibody
- Anacetrapib, Evacetrapib
 - Inhibit cholesteryl ester transfer protein (CETP)
 - Note: Dalcatrapib and Torcetrapib have failed

Special Population Pharmacotherapy Considerations

Special Populations

- Elderly Patients
- Pediatrics
- Pregnancy and Lactation
- Solid Organ Transplantation and HIV
- Chronic Kidney Disease

Clinical Concerns in the Elderly

- Risk of CVD increases with age
- Pharmacologic response may be different
- Higher risk of potential drug-drug interactions

- Evidence:
 - Underrepresented in clinical trials, especially very elderly
 - Long term benefits sometimes extrapolated, especially in primary prevention

Clinical Trials of Lipid-Lowering Drug Therapy in the Elderly

Trial	Total Patients and Elderly (n)	Treatments	RRR in Primary Endpoint within the Elderly Subgroup
HPS	20,536; 5806 age \geq 70 yrs	Simvastatin 40 mg vs. placebo	18% (p<0.001)
LIPID	9014; 3514 age 65-75 yrs	Pravastatin 40 mg vs. placebo	24% (p=0.009)
4S	4444; 1021 age \geq 65 yrs	Simvastatin 20–40 mg vs. placebo	34% (p<0.05)
CARE	4159; 1283 age \geq 65 yrs	Pravastatin 40 mg vs. placebo	32% (p<0.001)
PROSPER	5804 all age 70–82 yrs	Pravastatin 40 mg vs. placebo	19% (p=0.006)
VA-HIT	2531; 1265 age 66-73 yrs	Gemfibrozil 1200 mg vs. placebo	26% (p=0.007)
JUPITER	17,802; 5695 age 70-97 yrs	Rosuvastatin 20 mg vs. placebo	39% (p<0.001)

RRR = Relative Risk Reduction

Statin Dosing Recommendations in Elderly Patients

Statin	Recommendation
Atorvastatin	<ul style="list-style-type: none"> • No dose adjustment recommendation • Greater sensitivity of some older adults cannot be ruled out
Fluvastatin	<ul style="list-style-type: none"> • No dose adjustment for geriatric patients
Lovastatin	<ul style="list-style-type: none"> • No dose adjustment based on age-related pharmacokinetic differences
Pitavastatin	<ul style="list-style-type: none"> • No dose adjustment recommendation • Greater sensitivity of some older adults cannot be ruled out
Pravastatin	<ul style="list-style-type: none"> • No dose adjustment
Rosuvastatin	<ul style="list-style-type: none"> • No dose adjustment recommendation • Greater sensitivity of some older adults cannot be ruled out
Simvastatin	<ul style="list-style-type: none"> • No dose adjustment recommendation • Greater sensitivity of some older adults cannot be ruled out

Recommendations are from product inserts

Clinical Concerns in Pediatric Patients

- Certain pediatric patients are higher risk for CVD (e.g., homozygous familial hypercholesterolemia), where coronary disease is evident in the first and second decades of life
- Lifestyles and behavior modification are primary risk reduction approaches
- Long term benefits of drug therapy are not clearly established

Approved Lipid-Lowering Drug Therapy in Pediatric Patients

Drug	Ages (yr)	Approved Daily Dose
Statins:		
• Atorvastatin	10–17	10 mg starting; 20 mg maximum
• Fluvastatin	10–16	20 mg starting; 80 mg maximum
• Lovastatin	10–17	10 mg starting; 20 mg maximum
• Pravastatin	8–13 14–18	20 mg starting; 20 mg maximum 40 mg starting; 40 mg maximum
• Pitavastatin	Safety and effectiveness have not been established	
• Simvastatin	10–17	10 mg starting; 40 mg maximum
• Rosuvastatin	10–17	5 mg starting; 20 mg maximum

Approved Lipid-Lowering Drug Therapy in Pediatric Patients

Drug	Ages (yr)	Approved Daily Dose
Ezetimibe	≥ 10	10 mg starting; 10 mg maximum
Bile Acid Sequestrants:		
• Colesevelam	10-17	3.75 g (powder preferred)
• Cholestyramine	n/a	240 mg/kg/day with 8 g maximum
• Colestipol	Safety and effectiveness not been established	
Fibric Acid Derivatives	Safety and effectiveness not established	
Omega-3 fatty acids	Safety and effectiveness not established	
Niacin	Safety and effectiveness of niacin therapy in pediatric patients (≤16 years) not established	
Lomitapide	Safety and effectiveness not established	

Recommendations are from product inserts

Lipid-lowering Therapies in Pregnancy and Lactation

Treatment	Used in Pregnancy	Pregnancy Category	Lactation Risk Category
All Statins	No	X	L3
Ezetimibe	-	C	L3
Colesevelam	±	B	L1
Cholestyramine	±	C	L1
Fenofibrate	—	C	L3
Gemfibrozil	±	C	L3
Niacin	No	C	
Omega-3 Fatty Acids	±	C	
Lomitapide	No	X	
Mipomersen	±	B	

Note: Empty areas reflect areas for which no data are available.

Lactation risk category: L1 = safest, L2 = safer, L3 = moderately safe, L4 = possible hazardous, L5 = contraindicated

Recommendations are from product inserts

Clinical Concerns in HIV or Solid Organ Transplantation

- Drug-Drug interactions are very common with several statins; many combinations are contraindicated or have maximum dose limits:
 - HIV protease inhibitors
 - Cyclosporine
- Drugs used to treat HIV or solid organ transplantation patients may cause lipid abnormalities and/or increase CV risk

Clinical Concerns in Patients with Chronic Kidney Disease (CKD)

- CKD is a risk factor for statin associated myalgia/myopathy
- Patients on long-term hemodialysis do not seem to achieve reduced risk of CV events with statin therapy
- Only one long-term study has demonstrated safety and efficacy (SHARP) with ezetimibe/simvastatin 10/20 mg daily

Recommendations for Dose Adjustments for Statins in CKD

Statin	Renal Elimination	Recommendations
Atorvastatin	<2%	Dose adjustment in renal impairment is not necessary
Fluvastatin	5%	Mild to moderate renal impairment dose adjustment is not necessary; has not been studied in doses > 40 mg in severe renal impairment
Lovastatin	10%	Severe renal insufficiency (CrCL < 30 mL/min) carefully consider doses > 20 mg daily
Pitavastatin	15%	Moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m ²) as well as end-stage renal disease on hemodialysis, 1 mg daily initial dose, 2 mg daily maximum dose
Pravastatin	20%	Significant renal impairment, 10 mg daily initial dose
Rosuvastatin	10%	Severe renal impairment (CrCL < 30 mL/min/1.73m ²) not on hemodialysis, 5 mg daily initial dose, 10 mg daily maximum dose
Simvastatin	13%	Mild to moderate renal impairment, dose adjustment is not necessary; severe renal impairment, 5 mg daily initial dose with close monitoring

Recommendations are from product inserts

Combination Therapy

Clinical Scenarios

Dyslipidemia	Monotherapy Options	Combination Therapies
Primary Target: Elevated LDL-C	<ul style="list-style-type: none"> • Statin • Niacin • Bile Acid Sequestrant • Ezetimibe 	<ul style="list-style-type: none"> • Statin + Bile Acid Sequestrant • Statin + Ezetimibe • Statin + Niacin • Others
Secondary Target: Elevated non-HDL-C	<ul style="list-style-type: none"> • Statin (high-dose) • Niacin 	<ul style="list-style-type: none"> • Statin + Fibrate • Statin + Niacin • Statin + Omega-3 Fatty Acids • Others
Other: Very high TG	<ul style="list-style-type: none"> • Fibrate • Omega-3 Fatty Acid • Niacin 	<ul style="list-style-type: none"> • Fibrate + Omega-3 Fatty Acids • Fibrate + Niacin • Niacin + Omega-3 Fatty Acids

Non-HDL-C Reduction

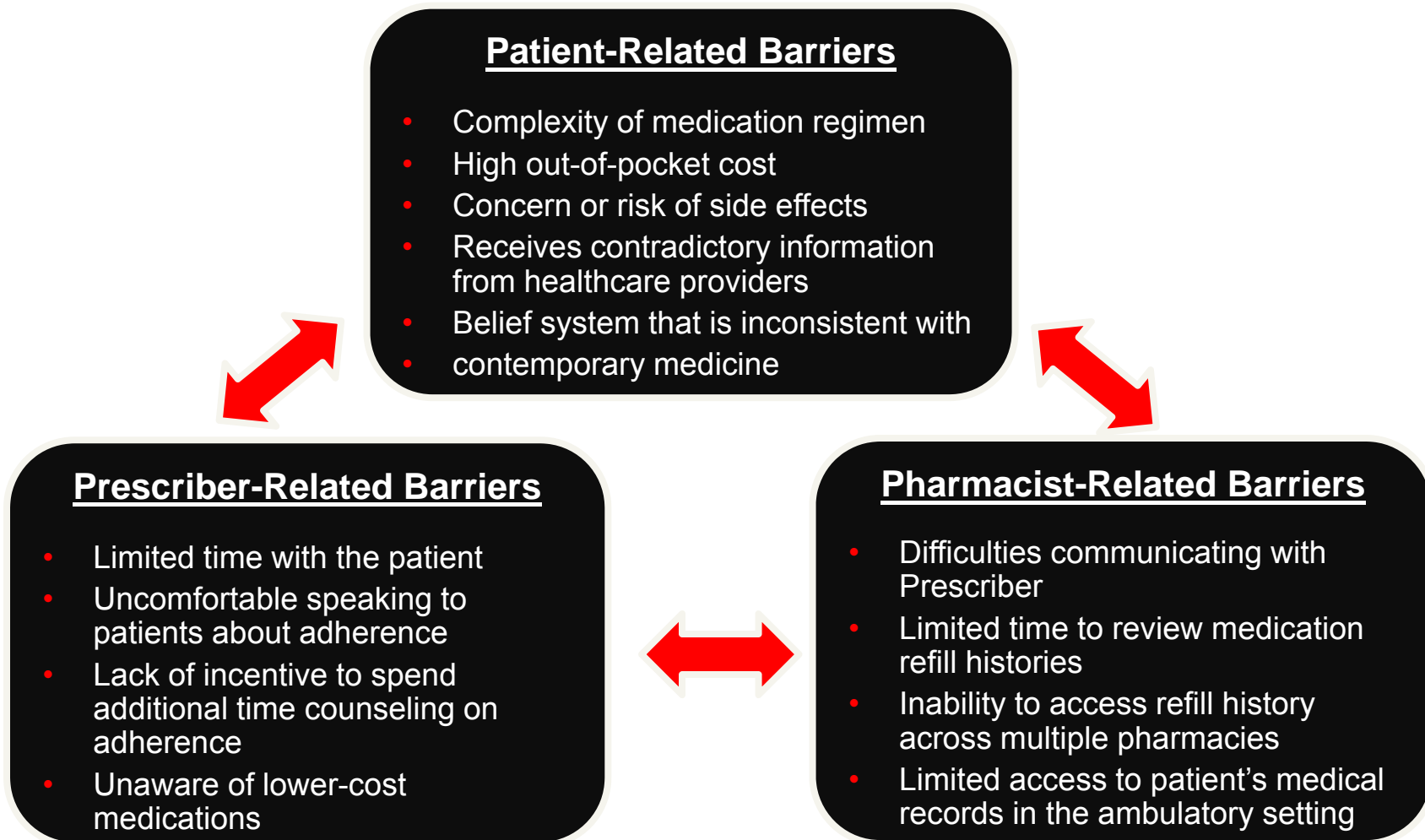
- Non-HDL-C = (Total Cholesterol) – (HDL-C)
- Target of therapy only after LDL-C is lowered and if triglycerides are 200 to 499 mg/dL
- **Options to reduce non-HDL-C can target:**
 - More intense LDL-C lowering
 - Lowering triglycerides
 - Raising HDL-C
 - A combination of LDL-C lowering, triglyceride lowering, and/or HDL-C raising

Challenges

"Drugs don't work in patients who don't take them."

- Former U.S. surgeon general C. Everett Koop

Barriers to Medication Adherence



Adapted from: Clinician's Toolkit: A Guide to Medication and Lifestyle Adherence. *National Lipid Association*. Available at: <https://www.lipid.org/practicetools/tools/adherence>.

Interventions to Improve Adherence

S	Simply the regimen	<ul style="list-style-type: none"> • Adjust timing, frequency, and dosage • Utilize once-daily medications whenever possible • Encourage the use of adherence aids (e.g., pillboxes, cell phone alarms) • Consider each patient's activities of daily living (e.g., swing shift workers)
I	Impart knowledge	<ul style="list-style-type: none"> • Patient-provider shared decision making • Provide clear instructions and expectations for all prescriptions • Involve relatives or caregivers when discussing medications • Recommend electronic education formats (e.g., video, websites)
M	Modify patient beliefs and human behavior	<ul style="list-style-type: none"> • Ask patient about their needs and what might help them adhere to therapy • Ensure patient understands consequences of non-adherence • Addressed perceived barriers of taking the medication • Provide rewards for adherence (e.g., praise, coupons, fewer clinic visits)
P	Provide communication and trust	<ul style="list-style-type: none"> • Practice to improve interviewing skills • Embrace active listening and provide emotional support • Elicit patient's input when discussing treatment options • Allow adequate time for the interaction and encourage patient to ask questions
L	Leave the bias	<ul style="list-style-type: none"> • Foster a greater understanding of health literacy and how it affects patients • Ensure communication style is patient-centered • Take extra time to understand and overcome cultural barriers • Tailor education to the patient's level of understanding
E	Evaluate adherence	<ul style="list-style-type: none"> • Ask patients simply and directly about adherence • Engage patients about adherence at every encounter • Measure drug levels or efficacy parameters, when applicable • Review medication containers, noting last fill date and remaining medicine

Adapted from: Clinician's Toolkit: A Guide to Medication and Lifestyle Adherence. *National Lipid Association*. Available at: <https://www.lipid.org/practicetools/tools/adherence>.

Evidence-Based Interventions Shown to Improve Adherence

- Telephone reminders
- Self-monitoring (medication diary)
- Fixed-dose combination products
- Unit-dose packaging
- Education counseling
- Case management by Pharmacists
- Automated refill reminders from pharmacy
- Waiving/reducing medication co-payments
- Rewards (money, gift cards)
- Pharmacist or Nurse-operated disease management clinics

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