How Low Can You Go?
Evaluating the Safety of Low Low-Density Lipoprotein

https://www.tctmd.com/news/ultra-low-ldl-levels-fourier-suggests-efficacy-evolocumab

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Learning Objectives:

1. Summarize current guidelines available for the treatment of dyslipidemia

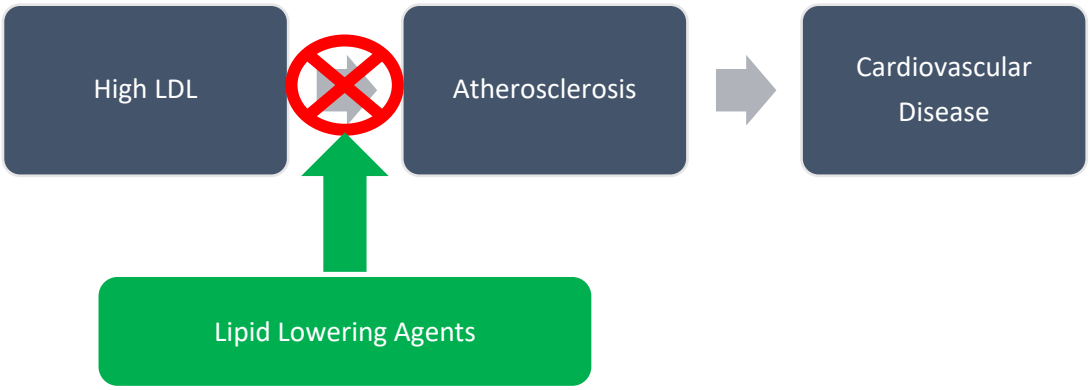
2. Identify the expected effect of lipid treatment options on low-density lipoprotein

3. Assess the evidence for the safety of low low-density lipoprotein

4. Using a patient case, formulate a treatment plan for a patient with low low-density lipoprotein

The Use of Lipid Lowering Agents

I. Why We Use Lipid Lowering Agents[1-3]



II. Goals of Lipid Lowering Therapy[3-7]

Table 1: Goals of Lipid Lowering Therapy	
Guideline	**Goals of therapy**
2017 AACE[4]	• Specific targets based on risk category (see Table 2)
2017 ACC Update[5]	• Refer to 2013 ACC/AHA goals of therapy • ≥ 50 % LDL reduction
2015 NLA Part 1[6]	• Specific targets based on risk category (see Table 3)
2014 VA/DoD[7]	• Do not support the of LDL-C or non-HDL-C goals
2013 ACC/AHA[3]	• No specific goal of LDL-C or non-HDL-C made • Do not recommend for or against the use of specific levels
Key: ACC: American College of Cardiology; AACE: The American Association of Clinical Endocrinologists; AHA; American Heart Association; NLA: National Lipid Association; VA/DOD: Veterans Association and Department of Defense	

Table 2: 2017 AACE LDL-C Treatment Goals[4]		
Risk Category	**Risk Factors/10-year risk**	**LDL – C goal**
Extreme Risk	• Progressive ASCVD including unstable angina in patients after achieving LDL-C < 70 mg/dL • Established clinical cardiovascular disease in patients with DM, CKD 3/4, or Heterozygous Familial Hypercholesterolemia (HeFH) • History of premature ASCVD (<55 male, <65 female)	< 55 mg/dL
Very High Risk	• Established or recent hospitalization for ASCVD, coronary, carotid or peripheral vascular disease, 10-year risk >20% • Diabetes or CKD 3/4 with 1 or more risk factor(s) • HeFH	< 70 mg/dL
High Risk	• ≥2 risk factors and 10-year risk 10-20% • Diabetes or CKD 3/4 with no other risk factors	< 100 mg/dL
Moderate Risk	≤2 risk factors and 10-year risk <10%	< 100 mg/dL
Low Risk	No risk factors	< 130 mg/dL

Table 3: 2015 National Lipid Association LDL-C Treatment Goals[6]		
Risk Category	**Criteria**	**LDL – C Treatment Goal**
Low	• 0 – 1 major ASCVD risk factors* • Consider other risk indicators, if known	< 100 mg/dL
Moderate	• 2 major ASCVD risk factors • Consider quantitative risk scoring (Framingham Risk Score) • Consider other risk indicators	< 100 mg/dL

High	• ≥ 3 major ASCVD risk factors
	• Diabetes mellitus (type 1 or 2)
	  • 0 – 1 other major ASCVD risk factors
	  • No evidence of end-organ damage
	• Chronic kidney disease stage 3B or 4
	• LDL-C of ≥ 190 mg/dL (severe hypercholesterolemia)
	• Quantitative risk score reaching the high-risk threshold (Framingham Risk Score)
		< 100 mg/dL

Very High	• ASCVD
	• Diabetes mellitus (type 1 or 2)
	  • ≥ 2 other major ASCVD risk factors
	  • Evidence of end-organ damage**
		< 70 mg/dL

*Risk Factors: Age (male ≥ 45 years old, female ≥ 55 years old); family history of early CHD (< 55 years of age in male 1st degree relative, < 65 years of age in female 1st degree relative); current cigarette smoker; high blood pressure (≥ 140/90 mmHg or on blood pressure medication); low HDL (Male < 40 mg/dL; Female < 50 mg/dL) **Increased albumin to creatinine ratio (≥ 30 mg/g), CKD (eGFR, < 60 mL/min/1.73 m^2), or retinopathy		

III. Effect of Lipid Lowering Agents on LDL[3,5]

Table 4: Lipid Lowering Agents Role in Therapy and Predicted Lipid Lowering Effect			
	Statins	Ezetimibe	PCSK-9 Inhibitors
Role in Therapy	1st line agent • Clinical ASCVD • LDL – C ≥ 190 mg/dL • Diabetes + LDL – C 70 to 189 mg/dL • Age 40 – 75 + ASCVD risk 5 to < 7.5 % • Age 40 – 75 + ASCVD risk ≥ 7.5 %	2nd line agent • Clinical ASCVD • LDL – C ≥ 190 mg/dL • Diabetes + LDL – C 70 to 189 mg/dL • Age 40 – 75 + ASCVD risk ≥ 7.5 %	2nd line agent • Clinical ASCVD • LDL – C ≥ 190 mg/dL
Expected % Reduction in LDL	• High: ≥ 50% • Moderate: 30 to < 50% • Low: < 30%	< 25 %	> 25 %

Clinical Controversy

I. Role of Cholesterol in the Body[8]
   a. Precursor for all steroids in the body
      I. Sex hormones
      II. Corticosteroids
      III. Vitamin D
      IV. Bile acids
   b. Essential structure of membranes allows for fluidity and permeability

II. Definition of Low LDL
   a. Currently no universally expected definition of low LDL
   b. 2013 ACC/AHA Guidelines[3]
      i. Consider reducing statin when LDL < 40 mg/dL on two consecutive occasions. (Weak recommendation)

III. Concerns of Low LDL[9]
   a. Neurocognitive Issues
      i. Dementia
      ii. Depression
   b. Retinal Disorders
      i. Cataracts
   c. Hemorrhage strokes
   d. Cancers

IV. Clinical Controversy
   a. What do we do with LDL levels < 40 mg/dL?
   b. What are the safety concerns for patients who reach low LDL levels?

Literature Review

Table 5: Wiviott SD, Cannon CP, Morrow DA et. al. Can Low – Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low, Low - Density Lipoprotein With Intensive Statin Therapy. A PROVE IT- TIMI 22 Substudy[10]

Objective	Evaluate the safety and efficacy of achieving very low LDL levels with intensive statin therapy
Methods	
Study Design	• Treatment groups of original trial: intensive statin therapy (atorvastatin 80 mg daily) vs. standard therapy (pravastatin 40 mg daily) • Post-hoc analysis that analyzed only patients who received atorvastatin 80 mg • Subgroups at 4 months: LDL 81-100 mg/dL, 61-80 mg/dL, 41-60 mg/dL, and ≤ 40 mg/dL • Very low LDL levels defined as LDL < 60 mg/dL
Patient Selection	**Inclusion:** • Within 10 days of ACS • Patients who achieved LDL < 100 mg/dL at 4 months • Treated with intensive statin therapy **Exclusion:** • Treated with standard therapy • Patients who did not achieve LDL < 100 mg/dL at 4 months
Outcomes	**Efficacy:** composite of death, myocardial infarction (MI), stroke, revascularization, and unstable angina requiring hospitalization **Safety:** hemorrhage stroke, liver-related events, muscle-related events, and retinal adverse events
Statistical Analysis	• 81-100 mg/dL reference group • Chi-square used for trends for safety, efficacy and baseline characteristics • Kaplan-Meier used for primary efficacy event rates • Multivariate analyses accounting for differences in baseline characteristics (age, gender, diabetes, prior history of myocardial infarction (MI), baseline LDL levels and smoking status)
Results	
Baseline Characteristics	• 1,756 patients met treatment goal of LDL < 100 mg/dL ▪ 81-100 mg/dL: 256 patients ▪ 61-80 mg/dL: 576 patients ▪ 41-60 mg/dL: 631 patients ▪ ≤ 40 mg/dL: 193 patients

Concomitant Medications	
Medication	**Percentage**
Aspirin	93
Warfarin	8
Clopidogrel or ticlodipine	72
Beta Blockers	85
ACE inhibitors	69
ARB	14

Selected Baseline Characteristics Based on Achieved LDL Level in (mg/dL)					
Characteristic	**81-100 (256)**	**61-80 (576)**	**41-60 (631)**	**≤ 40 (193)**	**p-value**
Age, median	55 (49, 63)	56 (50, 65)	58 (52, 66)	59 (51, 69)	0.0006
Female	24	24	17	16	0.008
Caucasian	89	93	93	89	0.11
Diabetes	16	16	15	25	0.04
Hypertension	52	50	49	49	0.88
Prior MI	25	16	15	17	0.008
Smoker	44	39	31	23	< 0.001
Prior statin	38	25	24	15	< 0.001
Total cholesterol, baseline median	190 (168, 213)	182 (161,209)	176 (158, 193)	162 (144,185)	0.0001
LDL, baseline median	115 (94, 137)	110 (93,131)	100 (85, 119)	89 (71, 106)	0.0001

<table>
<tr><td></td><td>
<table>
<tr><th colspan="2">Baseline Characteristics that Influence Achieving Lower LDL Levels</th></tr>
<tr><th>More likely to achieve</th><th>Less likely to achieve</th></tr>
<tr><td>• Older
• Male
• Diabetic
• Lower baseline total cholesterol and LDL levels</td><td>• Prior MI
• Prior coronary artery bypass graft
• Cigarette smoker
• Prior statin before study initiation</td></tr>
</table>
</td></tr>
<tr><td>Study Outcomes</td><td><u>Efficacy Outcomes:</u>
<table>
<tr><th colspan="3">Primary Composite Endpoint</th></tr>
<tr><th>LDL Level (mg/dL)</th><th>Hazard Ratio</th><th>95% Confidence Interval</th></tr>
<tr><td>61- 80</td><td>0.80</td><td>0.59 to 1.07</td></tr>
<tr><td>41-60</td><td>0.67</td><td>0.50 to 0.92</td></tr>
<tr><td>≤ 40</td><td>0.61</td><td>0.40 to 0.91</td></tr>
</table>
• Rate of MI was lower in patients with LDL < 80 mg/dL when compared to patients with LDL ≥ 80 mg/dL ($p < 0.01$)
<u>Safety Outcomes:</u>
• No significant difference in adverse events between LDL groups including muscle side effects, liver side effects, hemorrhagic stroke, retinal adverse effects, suicide/trauma death)</td></tr>
<tr><td>Author's Conclusion</td><td>• Not necessary to lower the dose of statin based on LDL levels
• No association between the achieved LDL level and adverse events of statins over a 2-year period.</td></tr>
<tr><td rowspan="2">Critique</td><td><u>Strengths:</u>
• Assessed efficacy and safety outcomes
• Variety of LDL levels evaluated
• Endpoints were adjudicated by an independent committee</td><td><u>Limitations:</u>
• Small number of patients experience side effects, lack of power to determine difference
• Applies to secondary prevention only
• Distribution of LDL in the LDL < 40 group
• Did not assess neurocognitive changes
• Post-hoc analysis – results only exploratory
• Only evaluated LDL levels 4 months post ACS</td></tr>
<tr><td colspan="2">Duration of follow-up is 2 years</td></tr>
<tr><td>Take away summary</td><td colspan="2">• No difference in safety or efficacy regardless of LDL level
• Additional efficacy does not appear to be present when comparing patients those who achieved a LDL of 41-60 mg/dL to those who achieved a LDL < 40 mg/dL</td></tr>
</table>

Table 6: Everett BM, Mora S, Glynn RJ, et al. Safety Profile of Subjects Treated to Very Low Low-Density Lipoprotei Cholesterol Levels (< 30 mg/dL) with Rosuvastatin 20 mg daily (from JUPITER)[11]

Objective	Evaluate the safety achieving very low LDL levels, either LDL – C < 30 mg/dL or ≥ 70% reduction in LDL-C, while on rosuvastatin 20 mg	
Methods		
Study Design	Post-hoc analysis, double-blind, placebo controlled	
Patient Selection	**Inclusion:** • Men ≥ 50 years and women ≥ 60 years • No history of diabetes • No history of cardiovascular disease • LDL-C < 130 mg/dL • C-reactive protein ≥ 2.0 mg/L	**Exclusion:** • Pre-existing diabetes • Previous use of lipid lowering medications • SBP > 180 mmHg or DBP > 100 mmHg • Cancer (except basal or squamous cell carcinoma of the skin) in the last 5 years • TSH > 1.5 x ULN or ALT > 2 x ULN, CK > 3 x ULN, Cr > 2.0 mg/dL • Recent alcohol or drug abuse • Inflammatory conditions • Use of immunosuppressants
Outcomes	Primary Outcome: Adverse reaction, hemorrhagic stroke was the only adverse drug reaction that was adjudicated.	
Statistical Analysis	Cox proportional hazard for propensity - adjusted analysis	
Results		
Baseline Characteristics	• 16, 304 participants	

Selected Baseline Characteristics

Characteristic	LDL < 30 mg/dL (N = 767)	LDL ≥ 30 mg /dL (N = 7387)	p value
Age	66 (61-72)	66 (60-71)	0.62
Women	32.2 %	38.9%	<0.001
Caucasian	69.6%	72.6%	0.001
BMI	29.3 (26.2-33.2)	28.2 (25.2-31.9)	<0.0001
Systolic BP	136 (125-148)	134 (124-145)	0.047
Metabolic Syndrome	51.6%	40.3%	<0.001
Impaired fasting glucose	36.3%	30.6%	0.001
Adherence to study medication	97.8%	89.0%	<0.0001
Total cholesterol	166 (146-186)	187 (171-201)	<0.0001
Triglycerides	134 (93-206)	118 (84-166)	<0.0001
HDL	46 (38-56)	49 (41-60)	<0.0001
LDL	86 (70-100)	109 (97-120)	<0.0001
Hemoglobin A1C	5.7 (5.4-5.9)	5.7 (5.4-5.9)	0.29

<table>
<tr><td></td><td>
<table>
<tr><th>Characteristics that Influence Achieving LDL < 30 mg/dL</th></tr>
<tr><td>• Men
• Black
• Have metabolic syndrome or its components
o Impaired fasting glucose
o Higher triglycerides
o Higher BMI
o Lower high-density lipoprotein (HDL) levels</td></tr>
</table>
</td></tr>
<tr><td>Study Outcomes</td><td>
• No difference in nervous system disorders (i.e. memory impairment, fatigue or hemorrhage stroke) and cancer when comparing those who achieved LDL < 30 mg/dL to those who achieved > 30 mg/dL
• No difference in adverse events when comparing patients who achieved ≥ 70 % reduction in LDL to those who achieved < 70 % reduction in LDL
<table>
<tr><th colspan="5">Selective Adjusted Adverse Events
LDL < 30 mg/dL compared to LDL ≥ 30 mg/dL</th></tr>
<tr><th>Adverse Event</th><th>LDL < 30 mg/dL
(N = 767)
N (Incidence Rate)</th><th>LDL ≥ 30 mg /dL
(N = 7387)
N (Incidence Rate)</th><th>Adjusted Relative Risk</th><th>p
value</th></tr>
<tr><td>Any</td><td>620 (103)</td><td>5930 (106.5)</td><td>1.10 (1.01-1.21)</td><td><0.05</td></tr>
<tr><td>Hepatobiliary Disorders</td><td>30 (1.7)</td><td>149 (0.9)</td><td>1.77 (1.15-2.73)</td><td><0.01</td></tr>
<tr><td>Psychiatric Disorders</td><td>69 (4.0)</td><td>534 (3.4)</td><td>1.40 (1.06-1.85)</td><td><0.01</td></tr>
<tr><td>Renal and urinary disorders</td><td>107 (6.4)</td><td>676 (4.3)</td><td>1.51 (1.21-1.90)</td><td><0.001</td></tr>
<tr><td>Physician- reported hematuria</td><td>34 (1.9)</td><td>175 (1.1)</td><td>2.10 (1.39-3.19)</td><td><0.001</td></tr>
<tr><td>Insomnia</td><td>27 (1.5)</td><td>195 (1.2)</td><td>1.59 (1.03-2.48)</td><td>< 0.05</td></tr>
<tr><td>Diabetes</td><td>47 (2.6)</td><td>209 (1.3)</td><td>1.56 (1.09-2.23)</td><td>< 0.05</td></tr>
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</td></tr>
<tr><td>Author's Conclusion</td><td>
• Suggests statin therapy overall is well tolerated at concentrations as low as 30 mg/dL
• Increased risk of diabetes in patients with LDL-C < 30 mg /dL compared to LDL-C > 30 mg /dL
• Question of whether very low levels of LDL puts patients at an increased risk of hematuria.
</td></tr>
<tr><td>Critique</td><td>
<table>
<tr><td><u>Strengths</u>
• Assessed cognitive function, hemorrhagic stroke and cancer
• Large sample size
• Patients without clinical ASCVD or diabetes</td><td><u>Limitations</u>
• Post- hoc analysis
• Did not assess incidence of cataracts
• Efficacy was not addressed in terms of LDL level
• Limited number of LDL levels evaluated
• Distribution of LDL levels achieved in each group not specified
• Large number of statistical tests preformed
• Only adjudicated 1 ADR endpoint</td></tr>
</table>
Duration of follow-up is 1.9 years
</td></tr>
<tr><td>Take away summary</td><td>
• Compared to adverse events of patients who achieved LDL levels > 30 mg/dL, those that achieved LDL levels < 30 mg/dL had more incidence of diabetes, insomnia and physician-reported hematuria. However, there was no difference seen in incidence rates of memory impairment and hemorrhagic stroke, which are potential safety concerned of achieving low levels of LDL.
• The safety concern is with the achieved LDL level rather than the percentage of LDL reduction.
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Table 7: Giugliano RP, Wiviott SD, Blazing MA et al. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol A Prespecified Analysis of the IMPROVE-IT Trial[12]

Objective	Evaluate the safety and efficacy of very low achieved LDL levels in patients receiving combination therapy with ezetimibe and simvastatin
	Methods
Study Design	• Randomized, double-bind, placebo controlled • Pre-specified safety analysis • Post-hoc analysis for incidence of cataracts • Intervention group: ezetimibe 10 mg daily plus simvastatin 40 mg daily • Comparator group: placebo plus simvastatin 40 mg daily • No medication adjustments made if patient's LDL was low • Patients with a LDL drawn at 1 month and who did not have an efficacy or prespecified safety event prior to the 1-month visit were included in the analysis • Pre-specified groups based on LDL: ≥ 70 mg/dL; 50 – 69 mg/dL; 30 – 49 mg/dL; < 30 mg/dL
Patient Selection	**Inclusion:** • ACS within the preceding 10 days • LDL level of 50 to 100 mg /dL (if taking a prior lipid lowering therapy) • LDL level of 50 to 125 mg/dL (if not on prior lipid lowering therapy) **Exclusion:** • CrCl < 30 mL/min • Active liver disease • Clinical instability • On other lipid lowering agents more potent than simvastatin 40 mg
Outcomes	• **Safety:** elevated liver enzymes, creatinine kinase levels, myopathy, rhabdomyolysis, adverse hepatobiliary events, cancer, adverse event leading to study drug discontinuation, heart failure leading to hospitalization, non-cardiovascular death, neurocognitive effects and a post-hoc analysis of cataract – related adverse event • **Efficacy**: composite of cardiovascular death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization after 30 days, stroke (hemorrhagic and ischemic) • Efficacy endpoints (except revascularization), muscle-related events and cancer were the only endpoints adjudicated by independent committee
Statistical Analysis	• Cox proportional hazard ratio to determine independent risk factors • Kaplan-Meier used for the rate of primary outcome at 7 years • Cochran-Armitage to trend independent risk factors among LDL groups
	Results
Baseline Characteristics	15,281 included in analysis

Concomitant Medications					
Medication	**< 30 (971)**	**30 – 49 (4780)**	**50 – 69 (5504)**	**≥ 70 (4026)**	**p value**
ACEi or ARB	437 (45.0)	1944 (40.7)	2210 (40.2)	1604 (39.9)	0.03
ASA	392 (40.4)	1910 (40.7)	2244 (40.8)	1830 (45.5)	< .001
β blocker	334 (34.4)	1550 (32.40)	1872 (34.0)	1497 (37.2)	< .001
Statin	217 (22.3)	1352 (28.3)	1958 (35.6)	1723 (42.8)	< .001

Selected Baseline Characteristics by Achieved LDL-C (mg/dL) Level at 1 month					
Characteristic	**< 30 (971)**	**30 – 49 (4780)**	**50 – 69 (5504)**	**≥ 70 (4026)**	**p value**
Ezetimibe	824 (84.9)	3433 (71.8)	2414 (43.9)	878 (21.8)	< .001
Age (IQR)	64.5 (57.9-71.5)	63.9 (57.9-71.5)	62.9 (57.4-71.7)	61.7 (55.8-69.3)	< .001
Male	773 (79.6)	3746 (78.4)	4190 (76.1)	2936 (72.9)	< .001
White	769 (79.2)	3980 (83.3)	4645 (84.4)	3431 (85.2)	< .001
BMI (IQR)	28.4 (25.8-32.0)	27.7 (25.0-31.2)	27.5 (24.8-30.8)	27.2 (24.7-30.5)	< .001
Comorbidities					
DM	403 (41.5)	1432 (30.0)	1327 (24.1)	940 (23.3)	< .001
HTN	642 (66.1)	2944 (61.6)	3251 (59.1)	2443 (60.7)	0.006
Current Smoker	272 (28.0)	1384 (29.0)	1799 (32.7)	1568 (39.0)	< .001
MI Hx	169 (17.5)	866 (18.1)	1137 (20.7)	979 (24.3)	< .001
PCI Hx	156 (16.1)	810 (16.9)	1055 (19.2)	928 (23.1)	< .001
CABG Hx	57 (5.9)	376 (7.9)	522 (9.5)	423 (10.5)	< .001
PAD Hx	45 (4.6)	243 (5.10	287 (5.2)	258 (6.4)	0.004
Baseline Lipid Panel					
TC	155 (136-174)	160 (141-178)	163 (145-181)	168 (151-186)	< .001
LDL	85 (70-100)	93 (77-108)	96 (80-112)	97 (85-113)	< .001
HDL	38 (32-46)	39 (33-48)	40 (33-49)	41 (34-50)	< .001
Triglycerides	141 (95-204)	120 (86-172)	117 (83-168)	122 (85-174)	0.002

Abbreviations: BMI, body mass index; DM, diabetes; HTN, hypertension; MI Hx, myocardial infarction history; PCI Hx, percutaneous coronary intervention; CABG Hx, coronary artery bypass surgery; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein

Characteristics that Influence Achieving LDL Levels < 30 mg/dL	
More likely to Achieve	**Less Likely to Achieve**
• Male • Non-white • Higher BMI • Pre-existing diabetes • Treated with statin prior to ACS	• Smoker • Have prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft

Study Outcomes

Selected Prespecified Safety Events by Achieved LDL Level (mg/dL) at 1 month				
Safety Endpoint HR (95% CI)	**< 30**	**30 – 49**	**50 – 69**	**p value (Trend)**
Neurocognitive events (all)	0.913 (0.545-1.529)	1.045 (0.772-1.414)	1.204 (0.92-1.574)	0.84
Hemorrhagic Stroke	0.36 (0.11-1.26)	1.05 (0.6-1.84)	0.58 (0.33-1.04)	0.69
Cancer	1.18 (0.91-1.53)	1.12 (0.95-1.33)	1.11 (0.96-1.29)	0.14

Rate of Primary Efficacy Endpoint at 7 years by Achieved LDL Level (mg/dL)	
LDL Level	**Rate**
< 30	31.9%
30 – 49	29.9%
50 – 69	30.8%
≥ 70	36%

Incidence of Cataract-Related Events by Achieved LDL Level (mg/dL) at 1 month		
LDL Level	**Odds Ratio**	**95 % Confidence Interval**
< 30	1.12	0.78-1.62
30 – 49	1.20	0.96-1.50
50 – 69	1.08	0.86-1.34

Time Weighted Mean LDL Levels	
1 - month LDL Level (mg/dL)	**LDL C Level 4-72 months (mg/dL)**
≥ 70	79.9
50-69	63.3
30-49	48.3
< 30	34.4

Author's Conclusion

- Patients with LDL level of < 30 mg/dL at one month had a similar safety profile over a median follow-up over 6 years when compared to patients who achieved a LDL > 30 mg/dL
- Overall patients who achieved LDL < 70 mg/dL had fewer efficacy outcomes
- Numerically the risk of an efficacy outcome was lowest in patients who achieved LDL < 30 mg/dL

Critique

Strengths

- Randomized
- Evaluated both safety and efficacy
- Safety endpoints of interest included (hemorrhagic stroke, cancer, cataracts, neurocognitive events)
- Large sample size
- Study duration longer than others
- Adjudication committee

Limitations

- Grouped based on LDL level at one month
- Included only secondary prevention patients
- Excluded patients on other lipid lowering agents
- Distribution of LDL < 30 mg/dL
- Mean LDL level in the < 30 mg/dL was 34.4 mg/dL
- Low event rate for some events therefore power was not met to determine difference
- Post-hoc analysis for incidence of cataracts
- Not all endpoints adjudicated (only efficacy outcomes, muscle-related events and cancer)

Duration of follow-up: median of 6 – years

Take away summary

- No significant difference in adverse events regardless of achieved LDL level
- When comparing efficacy of patients who achieved very low levels of LDL to LDL levels above 30 mg/dL but less than 70 mg/dL there was not a significant difference. This suggest that there is no benefit of achieving very low LDL levels compared to achieving levels < 70 mg/dL.

Table 8: Robinson JG, Rosenson RS, Farnier M et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels with Alirocumab Pooled Data from Randomized Trials[13]

Objective	Evaluate the safety of patients with LDL values < 25 mg/dL or < 15 mg/dL in the ODYSSEY program.
Methods	
Study Design	• Pooled data from 14 randomized, double blinded trials • Analysis of adverse events in patients who had 2 consecutive low LDL levels (defined in objective) • Consecutive levels defined as ≥ 21 days apart • Alirocumab dosing was 150 mg every 2 weeks in most trials. Some trials started with 75 mg every 2 weeks and increased to 150 mg every 2 weeks if desired LDL reduction was not achieved by week 8. • Intervention: alirocumab in addition to stable statin therapy (except ODYSSEY MONO) • Stable statin therapy: maximally tolerated (defined in 6 of the trials) • Comparator: placebo or ezetimibe
Patient Selection	**Inclusion:** • Heterozygous familial hypercholesteremia (HeFH) • High cardiovascular risk • LDL ≥ 70 mg/dL **Exclusion:** • Patients with recent ACS, stroke, or PVD intervention in the previous 3 months • Prior hemorrhage stroke • Hemoglobin A1C > 10% • Homozygous familial hypercholesteremia
Outcomes	Treatment-emergent adverse events (TEAEs) that occurred, worsened or became serious following the first LDL value < 25 mg/dL or < 15 mg/dL
Statistical Analysis	Cox proportional for propensity analysis
Results	
Baseline Characteristics	• 3,340 patients on alirocumab o 1,153 had low levels of LDL on 2 consecutive occasions ▪ LDL < 25 mg/dL: 839 (25.1%) ▪ LDL < 15 mg/dL: 314 (9.4%)

Selected Baseline Characteristics from Pooled Data of Patients with Low LDL level			
Characteristics (pooled from phase 2 and 3)	**≥ 25 (mg/dL) (2187)**	**< 25 (mg/dL) (839)**	**< 15 (mg/dL) (314)**
Age, yrs	58.6 ± 11.4	*61.9 ± 9.8*	61.8 ±9.9
Male	57.3 98 (1,434)	*75.0 (629)*	74.8 (235)
Race, white	88.5 (2,213)	91.1 (764)	89.8 (282)
BMI	30.1 ± 6.0	*29.7 ± 4.6*	29.8 ± 4.4
Calculated LDL	134.3 ± 48.9	100.3 ± 28.5	95.7 ± 28.3
HDL	51.1 ± 14.3	*46.6 ± 11.0*	45.1 ± 10.9
Fasting Triglycerides	122.0 (88.0-170.8)	*146.9 (108.8-206.2)*	168.0 (126.5-231.0)
Baseline HbA1C	5.98 ± 0.84	6.17 ± 0.98	6.22 ± 0.94
Medical History (pool of phase 3)			
CHD	60.6 (2,061)	76.9 (624)	73.4 (224)
CHD risk equivalents	29.9 (709)	40.45 (328)	45.9 (140)
Type 2 Diabetes	27.9 (662)	37.1 (301)	42.0 (128)
HeFH	33.5 (794)	10.2 (83)	9.5 (29)
High-intensity statin	55.9 (1,325)	53.0 (430)	49.5 (151)
Other lipid lowering therapy	30.6 (725)	23.6 (191)	23.3 (71)
Italics: p < 0.05 for comparison of LDL ≥ 25 mg/dL to < 25 mg/dL in the phase 3 studies			

	Factors Associated with LDL < 25 mg/dL • Lower baseline LDL • Higher triglycerides and lower HDL • Male, older, with a lower BMI • Did not have HeFH • Cardiovascular Disease • Type II Diabetes and higher hemoglobin A1C • Use of 150 mg every 2 weeks and baseline LDL < 160 mg/dL
Study Outcomes	**Selected Treatment Emergent Adverse Events** **Adverse Event** | **LDL ≥ 25 mg/dL (2,501)** | **LDL < 25 mg/dL (839)** | **LDL < 15 mg/dL (314)** **Neurocognitive disorders** | 1.0 (26), [0.8] | 0.6 (5), [0.5] | 0.3 (1), [0.3] ***Amnesia*** | 0.2 (5), [0.2] | 0.1 (1), [0.1] | 0 ***Aphasia*** | < 0.1 (1), [0.1] | 0.1 (1), [0.1] | 0 ***Confused state*** | 0.3 (7), [0.2] | 0.1 (1), [0.1] | 0 ***Dementia*** | 0 | 0.1 (1), [0.1] | 0 ***Frontotemporal Dementia*** | 0 | 0.1 (1), [0.1] | 0.3 (1), [0.3] **Ophthalmological** | 1.9 (47), [1.5] | 1.5 (13), [1.2] | 1.6 (5), [1.3] **Cataract** | 0.8 (19), [0.6] | 2.5 (21), [2.0] * | 2.9 (9), [2.3] Values reported in % (n) [rate per 100 patient years] *p=0.0018 when comparing LDL ≥ 25 mg/dL to < 25 mg/dL **Propensity Analysis of Selected Adverse Events in patients with Low LDL** **Adverse Event** | **LDL ≥ 25 mg/dL (2371)** | **LDL < 25 mg/dL (811)** | **Hazard Ratio** | **95 % Confidence Interval** **Neurocognitive disorders** | 1.1 (25) | 0.6 (5) | 0.38 | (0.13-1.09) **Ophthalmologic events** | 2.0 (47) | 1.6 (13) | 0.64 | (0.31-1.31) **Cataracts** | 0.8 (19) | 2.6 (21) | 3.4 | (1.58-7.35) * Values reported in % (n); *p=0.0018
Author's Conclusion	• Increased incidence of cataracts in patients with LDL < 25 mg/dL, however this may be due to confounding factors as the patients compared were not randomized. • Longer term safety of low LDL levels remains unknown, despite not finding a difference in TEAEs in this study.

<table>
<tr><td rowspan="2">Critique</td><td><u>Strengths</u>
Safety events of interest evaluated
Evaluated factors that increase risk of low LDL
Multiple patient populations assessed (primary prevention, secondary prevention, familial, etc.)
Multiple alirocumab doses
Various background therapies
Appropriate FLP draw (fasting and 6 weeks)
Verified that LDL was low with 2 readings
Used central lab
Data monitoring committee member and independent physician monitored patients
Propensity analysis to account for confounding factors</td><td><u>Limitations</u>
Limited LDL distribution
Efficacy not addressed
Post-hoc analysis</td></tr>
<tr><td colspan="2">Duration of follow-up: 26 months</td></tr>
<tr><td>Take away summary</td><td colspan="2">Although overall there was not a significant difference in adverse events regardless of LDL level, efficacy was not evaluated and therefore we do not know if it is efficacious. Thus, we do not know if the risk outweighs the benefits.</td></tr>
</table>

Table 5: Additional Studies				
Study	**Population (P)**	**Intervention (I)**	**Comparator (C)**	**Outcomes (O)**

Hsia 2011[14]	• Patient without clinical ASCVD or diabetes
	• Patient had LDL < 130 mg/dL
	• C-reactive protein ≥ 2.0 mg/L
	• Two LDL groups:
	  • > 50 mg/dL (n=4,000)
	  • < 50 mg/dL (n=4,154)
		rosuvastatin 20 mg daily	Placebo	• Significantly higher rate of any adverse drug events in the LDL < 50 mg/dL group compared to > 50 mg/dL group
				• Higher rate of memory impairment and depression in the LDL > 50 mg/dL compared to the < 50 mg/dL group
				• No difference in incidence of cancer or cataracts

Giugliano 2017[15]	• 40-85 years old with stable atherosclerotic disease
	• Five LDL groups:
	  • < 20 mg/dL (n=2,669)
	  • 20 to < 50 mg/dL (n=8,003)
	  • 50 to < 70 mg/dL (n=3,444)
	  • 70 to < 100 mg/dL (n=7,471)
	  • > 100 mg/dL (n=4,395)
		evolocumab 140 mg every 2 weeks or 420 mg once monthly + statin therapy	Placebo + statin therapy	No difference in adverse events including neurocognitive events, cataract related events, new or progressive malignancy and hemorrhagic stroke.

Giugliano 2017[16]	• 40-85 years old with stable atherosclerotic disease
	• Three LDL groups:
	  • < 25 mg/dL (n=?)
	  • 25 to 39 mg/dL (n=?)
	  • ≥ 40 mg/dL (n=?)
		evolocumab 140 mg every 2 weeks or 420 mg once monthly + statin therapy	Placebo + statin therapy	No difference in change of cognitive function when comparing different levels of achieved LDL.

LaRosa 2007[17]	• Patients with clinical atherosclerotic disease
	• Average age of 61
	• Five LDL groups:
	  • < 64 mg/dL (n=1,836)
	  • 64 to < 77 mg/dL (n=1,932)
	  • 77 to < 90 mg/dL (n=1,987)
	  • 90 to < 106 mg/dL (n=2,030)
	  • ≥ 106 mg/dL (n=1,984)
		atorvastatin 80 mg daily	atorvastatin 10 mg daily	No difference in adverse events including death from cancer and hemorrhagic stroke.
				
				*neurocognitive events and cataracts were not evaluated

Conclusions and Recommendations

I. Summary of Primary Literature

PROVE-IT TIMI 22 (2005)
• No difference in safety outcomes • Additional benefit is not apparent between achieving LDL of 41- 60 mg/dL versus < 40 mg/dL

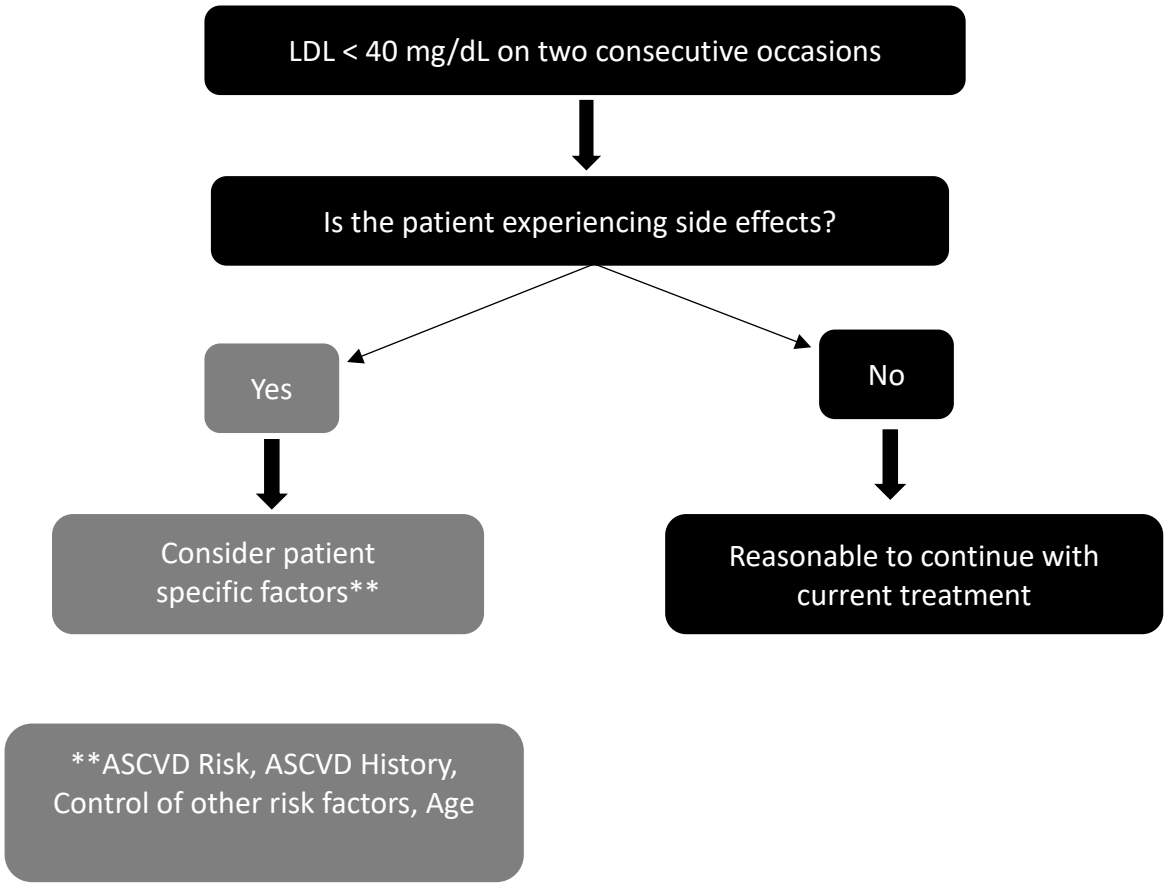
JUPITER (2014)
Increased incidence in diabetes, insomnia and hematuria in LDL < 30 mg/dL

IMPROVE-IT (2017)
• No difference in safety outcomes • No significant difference in efficacy between LDL < 30 vs. LDL 30 - 70 mg/dL

ALIROCUMAB POOLED TRIALS (2017)
• No difference in overall safety outcomes • Increase incidence of cataracts in patients with LDL < 25 mg/dL compared to > 25 mg/dL

Other Studies
No difference in safety outcomes with the exception of increased rates of memory impairment and depression in patients achieving LDL ≥ 50 mg/dL vs. < 50 mg/dL

II. Recommendations



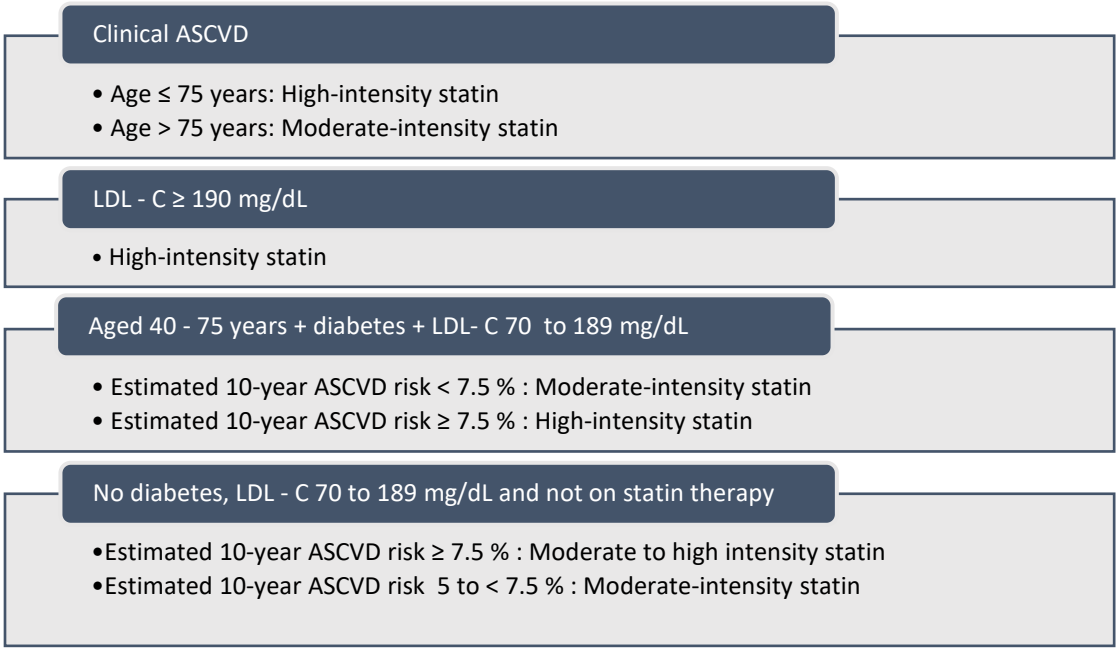
References:

1. Atherosclerosis. http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Atherosclerosis_UCM_305564_Article.jsp#.W42zydgzrq2 (accessed 2018 Sept 3)
2. Heart Disease. Centers for Disease Control. https://www.cdc.gov/nchs/fastats/heart-disease.htm (accessed 2018 Sept 3)
3. Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA Guideline on The Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013;129: S1–S45
4. Jellinger PS, Handelsman Y, Rosenblit PD et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract*. 2017;23: 1-87
5. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *Journal of The American College of Cardiology* 2017. 23976; DOI: 10.1016/j.jacc.2017.07.745
6. Jacobson TA, Ito MK, Maki KC et al National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1 Full Report. *Journal of Clinical Lipidology* 2015; 9: 129-169
7. VA/DoD Clinical Practice Guidelines for the Management of Dyslipidemia for Cardiovascular Risk Reduction. *Department of Veterans Affairs, Department of Defense*. 2014 (3): 1-112
8. Botham KM, Mayes PA. Cholesterol Synthesis, Transport, & Excretion. In: Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil P. eds. *Harper's Illustrated Biochemistry, 31e* New York, NY: McGraw-Hill; http://accesspharmacy.mhmedical.com.uiwtx.idm.oclc.org/content.aspx?bookid=2386&sectionid=187832435. Accessed August 13, 2018.
9. Bandyopadhyay D, Qureshi A, Ghosh S et al. Safety and Efficacy of Extremely Low LDL-Cholesterol Levels and Its Prospects in Hyperlipidemia Management. *Journal of Lipids.* 2017 (2018):1-8
10. Wiviott SD, Cannon CP, Morrow DA et. al. Can Low – Density Lipoprotein Be Too Low? The Safety and Efficacy of Achieving Very Low, Low - Density Lipoprotein with Intensive Statin Therapy. A PROVE IT- TIMI 22 Substudy. *Journal of American College of Cardiology*. 2005; 46 (8): 1411-1416
11. Everett BM, Mora S, Glynn RJ, et al. Safety Profile of Subjects Treated to Very Low Low-Density Lipoprotein Cholesterol Levels (< 30 mg/dL) with Rosuvastatin 20 mg daily (from JUPITER). *American Journal of Cardiology*. 2014; 114: 1682-1689
12. Giugliano RP, Wiviott SD, Blazing MA et al. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol a Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiology*. 2017; 2 (5):547-555
13. Robinson JG, Rosenson RS, Farnier M et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels with Alirocumab Pooled Data from Randomized Trials. *Journal of the American College of Cardiology*. 2017; 69 (5): 471-482
14. Jsai J, MacFadyen JG, Monyak J et al. Cardiovascular Event Reduction and Adverse Events Among Subjects Attaining Low-Density Lipoprotein Cholesterol < 50 mg/dL with Rosuvastatin. *Journal of American College of Cardiology.2011*; 57(16):1666-1675

15. Giugliano RP, Pedersen TR, Park JG et al. Clinical efficacy and safety of achieving very low LDL - cholesterol concentrations with PCSK9 inhibitor Evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017; 390: 1962-1971
16. Giugliano RP, Mach F, Zavitz K et al. Cognitive Function in a Randomized Trial of Evolocumab. *New England Journal of Medicine*. 2017; 377:633-643
17. LaRosa JC, Grundy SM, Kastelein JP et al. Safety and Efficacy of Atorvastatin-Induced Very Low-Density Lipoprotein Cholesterol Levels in Patients with Coronary Heart Disease (a Post Hoc Analysis of the Treating to New Target [TNT] Study. *American Journal of Cardiology*. 2007; 100:747-752

Appendices

A. 2013 ACC/AHA Cholesterol Guideline: Initiation of Statin Therapy[3]



B. 2017 ACC Focused Update: Initiation of Non-Statin Therapy[5]