PCSK9 Inhibitors: Changing the Landscape of Lipid-Lowering Therapy

http://parriscardio.theangelheartcenter.com/wp-content/uploads/2013/03/heart-disease-prevention.jpg

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Learning objectives:

1. Understand the epidemiology and pathophysiology of coronary heart disease and atherosclerosis
2. Review current guidelines for the management of dyslipidemia
3. Summarize literature regarding the efficacy of PCSK9 inhibitors
4. Examine the benefits of lower LDL cholesterol
5. Formulate recommendations on the use of PCSK9 inhibitor

1. Coronary Heart Disease (CHD)
    a. Epidemiology[1-3]
        i. An estimated 15.5 million or 6.2% of Americans ≥20 years of age have CHD
        ii. CHD was an underlying cause of about 1 of every 7 deaths in the United States in 2011
        iii. Ischemic heart disease is the leading cause of death worldwide, accounting for 7.4 million deaths in 2012
        iv. About 50% of all MIs and at least 70% of CHD deaths occur in patients with known CHD
        v. The estimated direct and indirect cost of heart disease was $204.4 billion in 2010
    b. Background[1,4-6]
        i. Includes angina pectoris, myocardial infarction, coronary death, and coronary revascularization
        ii. CHD results from the formation of atherosclerotic plaque within coronary arteries
        iii. Elevated LDL is the primary factor responsible for the pathogenesis of CHD
        iv. LDL has been identified as the key modifiable risk factor for cardiovascular disease
        v. Reductions in plasma LDL cholesterol have been strongly associated with a lower incidence of coronary events
    c. Pathophysiology[4,6,7]
        i. LDL transports about 65-70% of plasma cholesterol
        ii. Atherosclerotic plaques form when LDL particles penetrate through dysfunctional endothelium and accumulate in the arterial intima. LDL particles become oxidized and trigger the migration of macrophages. The macrophages internalize the lipoproteins and become cholesterol-laden foam cells. Inflammation triggers smooth muscle cells in the arterial intima to proliferate and produce collagen. The plaque enlarges and can eventually rupture, leading to the development of an atherosclerotic clinical event
        iii. Atherosclerosis begins early
        iv. Progressive process
    d. Risk factors[4,8,9]
        i. High LDL
        ii. Low HDL
        iii. Cigarette smoking
        iv. Hypertension
        v. Diabetes mellitus
        vi. Family history of premature CHD: male first-degree relative <55 years; female first-degree relative <65 years
        vii. Age: men ≥45; women ≥55 years

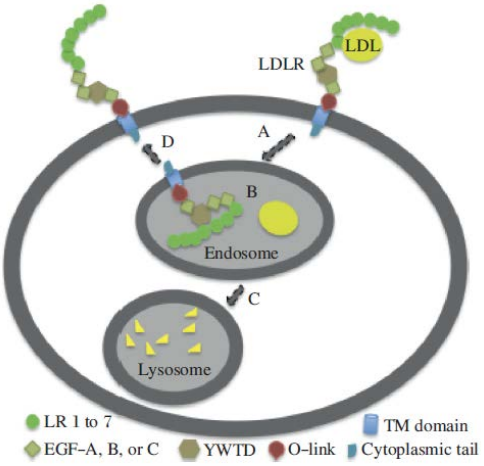
2. Guidelines
    a. 2012 American Association of Clinical Endocrinologists[8] (refer to Appendix A)
    b. 2014 National Lipid Association[9] (refer to Appendix B)
    c. 2013 American College of Cardiology/American Heart Association (ACC/AHA) blood cholesterol guideline[10]
        i. No randomized controlled trials were designed to achieve a prespecified LDL goal
        ii. Statins reduce atherosclerotic cardiovascular disease (ASCVD) events for primary and secondary prevention
        iii. Relative reduction in ASCVD risk from statin therapy is related to the degree of LDL-lowering
        iv. Level of statin LDL-lowering (refer to Appendix C)
        v. Four statin benefit groups (refer to Appendix D)
        vi. May consider decreasing the statin dose when two consecutive values of LDL are <40 mg/dL (class IIb, level C)

1. "However, no data was identified that suggests an excess of adverse events occurred when LDL-C levels were below this level"

vii. High-risk patients (those with ASCVD, LDL ≥190 mg/dL, or diabetes) who have a suboptimal therapeutic response to statins (class IIb, level C) or who are statin intolerant (class IIa, level B) may consider addition of a nonstatin therapy
   1. Preference should be given to cholesterol-lowering drugs shown to reduce ASCVD events

3. Pharmacotherapy
   a. Statins
      i. An analysis of a large managed care database in the US from 2004-2012[11]
         1. ¾ of patients with ASCVD did not meet LDL goal of <70 mg/dL
         2. Only about 25% of these patients were receiving high-potency statin therapy
   b. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
      i. Mechanism of action
         1. Normal pathway for LDL removal from plasma[12]
            a. LDL binds LDL receptors (LDLR) on the liver cell surface and is internalized by endocytosis
            b. LDL is delivered to lysosomes for degradation
            c. LDLR is recycled to the cell surface

Figure 1. Normal pathway for LDL removal from plasma[12]



         2. PCSK9 mechanism[5,12-14]
            a. PCSK9 is a protease that is primarily synthesized in the liver
            b. PCSK9 binds to hepatic LDL receptors and is internalized via endocytosis
            c. PCSK9 blocks recycling of the LDLR to the cell surface
            d. The LDLR is subsequently transported to the lysosome for degradation
               i. Decreased numbers of LDLR results in increased LDL levels
            e. PCSK9 inhibitors bind PCSK9 and inhibit it from binding to the LDLR, thereby preventing degradation of LDL receptors, which lowers LDL levels

Figure 2. PCSK9 mechanism[14]

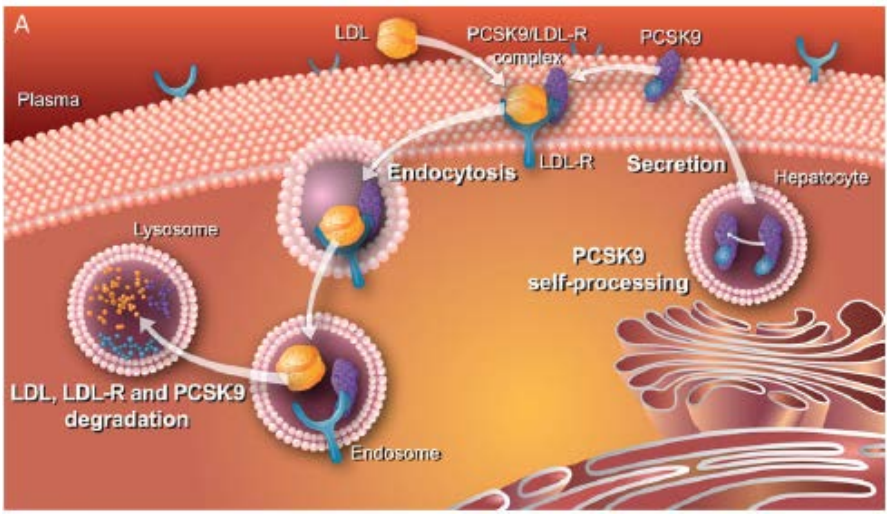
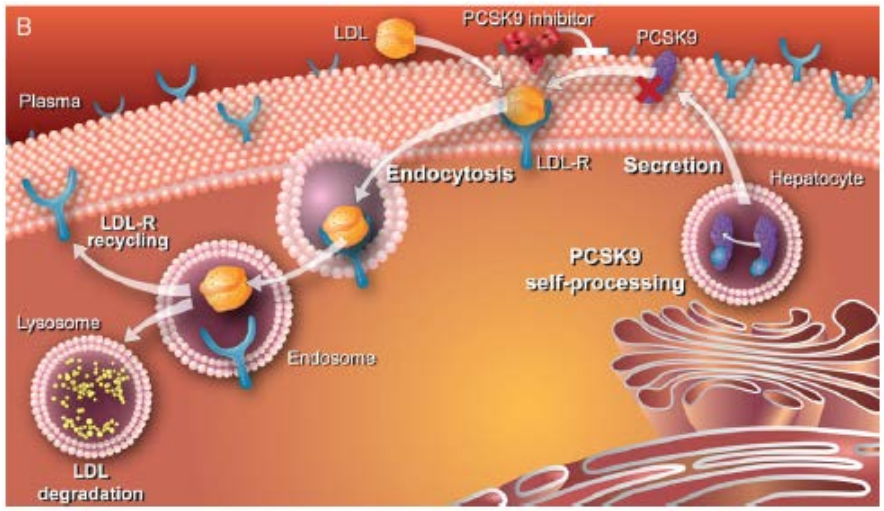


Figure 3. PCSK9 inhibitor mechanism[14]



ii. Agents
    1. Alirocumab (Praluent®) and evolocumab (Repatha®)
    2. Bococizumab is in phase 3 studies[14]

iii. FDA-approved indications[15,16]
    1. Primary hyperlipidemia
        a. Adjunct to diet and maximally tolerated statin therapy
        b. Treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL
    2. Homozygous familial hypercholesterolemia (evolocumab only)
        a. Adjunct to diet and other LDL-lowering therapies

iv. Pharmacology (refer to Appendices E and F)

4. Clinical question
    a. What is the efficacy of PCSK9 inhibitors in lowering LDL and what is their place in therapy for patients with ASCVD?

5. Literature review

Table 1. Cohen JC, Boerwinkle E, Mosley TH Jr, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006 Mar 23;354(12):1264-72.[5]	
Objective	Analyze the effects of PCSK9 sequence variations and lifelong low LDL on the risk of CHD
Study design	Prospective, longitudinal cohort study initiated in 1987
Inclusion criteria	• Self-identification as black or white race • Age 45-64 years at study initiation • Fasting lipoproteins at baseline and subsequent monitoring
Exclusion criteria	• Use of lipid-lowering drugs at baseline • Presence of symptomatic cardiovascular disease at baseline
Outcomes	Incidence of CHD (myocardial infarction, fatal CHD, or coronary revascularization)
Methods	• Incidence of CHD was determined by contacting subjects annually, identifying hospitalizations and deaths, surveying discharge lists from local hospitals and death certificates for potential CV events • Follow-up data included events up to January 1, 2003
Statistics	• Chi-square tests, t-tests, and Cox proportional-hazards modeling
Results	Nonsense mutations in PCSK9 alleles ($PCSK9^{142X}$ and $PCSK9^{679X}$) • 2.6% of the 3363 black subjects • 28% (38 mg/dL) lower mean LDL than noncarriers (**p<0.001**) • 1.2% of carriers vs 9.7% of noncarriers had a coronary event (**p=0.008**) • 88% reduction in the incidence of CHD (HR 0.11, 95% CI 0.02-0.81, **p=0.03**) • Mean carotid-artery intima-media thickness was significantly lower in carriers (0.70mm vs 0.73 mm) (**p=0.04**) PCSK9 sequence variation ($PCSK9^{46L}$) • 3.2% of the 9524 white subjects • 15% (21 mg/dL) LDL reduction compared to noncarriers (**p<0.001**) • 6.3% of carriers vs 11.8% of noncarriers had a coronary event • 47% reduction in CHD (HR 0.50, 95% CI 0.32-0.79, **p=0.003**) • Mean carotid-artery intima-media thickness was significantly lower in carriers (0.71 mm vs 0.73 mm) (**p=0.005**)
Authors' conclusions	PCSK9 sequence variations conferred protection against CHD. The reductions in CHD incidence were larger than those predicted from lipid-lowering trials despite a similar reduction in LDL. The results suggest that a single measurement of LDL does not reflect the effect of a lifetime of reduced plasma LDL on CHD. Lifelong reduction of LDL may confer greater benefit than a similar reduction later in life, even in populations with a high prevalence of cardiovascular risk factors.
Strengths	• Prevalence of all major CV risk factors were similar between carriers and noncarriers, except for significantly lower prevalence of hypertension in black carriers • 15 year follow-up • Large sample size • Prospective, longitudinal study • Clinically significant endpoint
Limitations	• May lose subjects to follow-up
Application	Earlier use of a lipid-lowering therapy may confer increased protection from CHD. Results are consistent with other studies that show a low incidence of coronary events in populations with lifelong low cholesterol levels; these suggest LDL lowering can prevent coronary events when the lowering is begun before the development of atherosclerotic plaques.[6]

Table 2. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015 Apr 16;372(16):1489-99.[17]	
Objective	Obtain long-term data on safety and reduction in LDL in patients receiving treatment with statins at the maximum tolerated dose with or without alirocumab
Study design	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multinational study

Inclusion criteria	• Adults ≥18 years with one of the following:
	  o heterozygous familial hypercholesterolemia
	  o CHD
	  o CHD risk equivalent, defined as any of the following
	  ▪ peripheral arterial disease
	  ▪ ischemic stroke
	  ▪ moderate chronic kidney disease
	  ▪ diabetes mellitus plus two or more additional risk factors
	  • hypertension
	  • ankle–brachial index of ≤0.90
	  • microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein
	  • preproliferative or proliferative retinopathy or laser treatment for retinopathy
	  • family history of premature coronary heart disease
	• LDL ≥70 mg/dL at the time of screening
	• Receiving high-dose statin or a statin at the maximum tolerated dose, with or without other lipid-lowering therapy, for ≥ 4 weeks prior to screening or ≥ 6 weeks if taking fenofibrate

Exclusion criteria	• Fasting serum triglycerides >400 mg/dL • Taking a statin other than simvastatin, atorvastatin, or rosuvastatin
Outcomes	• Primary end point: percentage change in LDL from baseline to week 24 • Secondary end point: percentage change in LDL at intervals throughout the study, and changes in other lipoprotein variables at weeks 12 and 24 • Safety end point: adverse events
Methods	• Patients were randomized in a 2:1 ratio to get alirocumab 150 mg q2 wks or placebo, in addition to their statin therapy ± other lipid-lowering therapy • 78-weeks study duration with follow-up safety assessment at week 86
Statistics	• Intention-to-treat analysis used to evaluate the primary end point • Cox proportional-hazards model used to compare rates of major adverse CV events • Descriptive analysis of safety data
Baseline characteristics	• 2341 patients: 1553 received alirocumab and 788 got placebo • Demographic characteristics and clinical history were balanced between the 2 study groups • Total of 68.9% of patients had a history of CHD • Total of 17.7% had heterozygous familial hypercholesterolemia • Total of 41.1% had a CHD risk equivalent • 46.8% of patients were receiving high-dose statin • 28.1% were also receiving other lipid-lowering therapy • Mean baseline LDL was 122.2 mg/dL

<table>
<tr><td>Results</td><td>
<table>
<tr><th>End point</th><th>Alirocumab</th><th>Placebo</th></tr>
<tr><td>Mean change in LDL from baseline to week 24 (p<0.001)</td><td>-61.0%
-56.3% in HeFH subgrp
-62.1% in non-HeFH grp</td><td>0.8%
2.4% in HeFH subgrp
-0.5% in non-HeFH grp</td></tr>
<tr><td>Mean LDL at week 24</td><td>48 mg/dL</td><td>119 mg/dL</td></tr>
<tr><td>% of patients with LDL <70 mg/dL at week 24 (p<0.001)</td><td>79.3%</td><td>8.0%</td></tr>
<tr><td>Mean change in LDL from baseline to week 78 (p<0.001)</td><td>-52.4%</td><td>3.6%</td></tr>
<tr><td colspan="3">Mean change from baseline to week 24 (p<0.001):</td></tr>
<tr><td>Non-HDL cholesterol</td><td>-51.6</td><td>0.7</td></tr>
<tr><td>Total cholesterol</td><td>-37.8</td><td>-0.3</td></tr>
<tr><td>Fasting triglycerides</td><td>-15.6</td><td>1.8</td></tr>
<tr><td>HDL cholesterol</td><td>4.0</td><td>-0.6</td></tr>
<tr><td>Lipoprotein(a)</td><td>-29.3</td><td>-3.7</td></tr>
<tr><td>Apolipoprotein B</td><td>-52.8</td><td>1.2</td></tr>
<tr><td>Any adverse event (p=0.40)</td><td>81.0%</td><td>82.5%</td></tr>
<tr><td>Injection-site reactions (p=0.10)</td><td>5.9%</td><td>4.2%</td></tr>
<tr><td>Myalgia (p=0.006)</td><td>5.4%</td><td>2.9%</td></tr>
<tr><td>Neurocognitive disorders (p=0.17)</td><td>1.2%</td><td>0.5%</td></tr>
<tr><td>Ophthalmologic events (p=0.65)</td><td>2.9%</td><td>1.9%</td></tr>
<tr><td>Cardiovascular events (p=0.68)</td><td>4.6%</td><td>5.1%</td></tr>
<tr><td>Nonfatal myocardial infarction (p=0.01)</td><td>0.9%</td><td>2.3%</td></tr>
</table>

Among patients receiving alirocumab, 37.1% had a calculated LDL <25 mg/dL at two consecutive measurements; rates of adverse events were similar to those among the overall alirocumab group
In a post hoc safety analysis, the rate of major adverse cardiovascular events was 1.7% in the alirocumab group vs 3.3% in the placebo group (HR = 0.52, 95% CI 0.31-0.90, p=0.02)

</td></tr>
<tr><td>Authors' conclusions</td><td>Alirocumab reduced LDL cholesterol by 62% at 24 weeks, with a consistent reduction over a treatment period of 78 weeks. A post hoc analysis demonstrated a reduction in cardiovascular events with alirocumab.</td></tr>
<tr><td>Strengths</td><td>Longer study period than most other trials of PCSK9 inhibitors
Large sample size
Baseline characteristics were well-matched between treatment and placebo groups
Placebo-controlled, double-blind study</td></tr>
<tr><td>Limitations</td><td>Duration of follow-up is relatively short for a treatment for chronic disease
Lack of formal neurocognitive testing limits the usefulness of the neurocognitive findings
Small number of cardiovascular events limits the confidence that they are not a chance finding
About 47% of patients were receiving high-dose statins
Multiple investigators receive consulting fees from Sanofi/ Regeneron Pharmaceuticals</td></tr>
<tr><td>Application</td><td>The study found significantly reduced levels of LDL when added to maximum-tolerated dose of a statin, and suggests that alirocumab may reduce cardiovascular outcomes.</td></tr>
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Table 3. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: A systematic review and meta-analysis. *Ann Intern Med*. 2015 Jul 7;163(1):40-51.[18]	
Objective	Investigate the safety and efficacy of treatment with PCSK9 inhibitors
Study design	Systematic review and meta-analysis of randomized controlled trials
Inclusion criteria	Phase 2 or 3 RCT comparing PCSK9 inhibitors to other therapy in adults with hypercholesterolemia

<table>
<tr><td>Exclusion criteria</td><td>Studies in which doses of PCSK9 inhibitors given were not used in phase 3 RCTs</td></tr>
<tr><td>Outcomes</td><td>• Primary: all-cause mortality, cardiovascular mortality, change in LDL and HDL from baseline
• Secondary: myocardial infarction, unstable angina, increased serum creatine kinase level, serious adverse events, changes in total cholesterol and lipoprotein(a) levels from baseline</td></tr>
<tr><td>Methods</td><td>Multiple databases were searched until April 4, 2015 for the following keywords: PCSK9 antibody, evolocumab, alirocumab, bococizumab, randomized controlled trial, and hypercholesterolemia</td></tr>
<tr><td>Statistics</td><td>• Intention-to-treat analysis
• Heterogeneity assessed using the Cochran Q test and the I^2 statistic
• Fixed-effects model used if <50% inconsistency found; random-effects model used otherwise</td></tr>
<tr><td>Results</td><td>• 24 studies with a total of 10,159 patients were included: 8 phase 2 trials, 16 phase 3 trials, 12 were of familial hypercholesterolemia, 9 were of nonfamilial or unspecified hypercholesterolemia, 1 was mixed, and 2 were statin-intolerant
• Control groups were treated with placebo or ezetimibe
<table>
<tr><th>Outcome</th><th>Incidence (PCSK9 inhibitor vs control)</th><th>OR (95% CI)</th><th>P value</th><th>I^2</th></tr>
<tr><td>All-cause mortality</td><td>0.31% vs 0.53%</td><td>0.45 (0.23-0.86)</td><td>0.015</td><td>0%</td></tr>
<tr><td>Cardiovascular mortality</td><td>0.19% vs 0.33%</td><td>0.50 (0.23-1.10)</td><td>0.084</td><td>0%</td></tr>
<tr><td>Myocardial infarction (MI)</td><td>0.58% vs 1.00%</td><td>0.49 (0.26-0.93)</td><td>0.030</td><td>0%</td></tr>
<tr><td>Unstable angina</td><td>0.04% vs 0.08%</td><td>0.61 (0.06-6.14)</td><td>0.676</td><td>0%</td></tr>
<tr><td>Increased creatine kinase</td><td>1.96% vs 2.31%</td><td>0.72 (0.54-0.96)</td><td>0.026</td><td>0%</td></tr>
<tr><td>Serious adverse events</td><td>9.26% vs 7.73%</td><td>1.01 (0.87-1.18)</td><td>0.879</td><td>0%</td></tr>
</table>
<table>
<tr><th>Efficacy end point (see Appendix G)</th><th>Mean difference with PCSK9 inhibitor vs control</th><th>P value</th></tr>
<tr><td>LDL</td><td>-47.49%</td><td><0.001</td></tr>
<tr><td>HDL</td><td>6.30%</td><td><0.001</td></tr>
<tr><td>Total cholesterol</td><td>-31.49%</td><td><0.001</td></tr>
<tr><td>Lipoprotein(a)</td><td>-26.45%</td><td><0.001</td></tr>
</table></td></tr>
<tr><td>Authors' conclusions</td><td>Use of PCSK9 inhibitors is associated with lower odds of all-cause mortality and myocardial infarction, a nonsignificant reduction in cardiovascular mortality, a reduction in atherogenic lipids, lower increase in serum creatine kinase levels, and no increase in serious adverse events. The magnitude of LDL reduction was greater than that with ezetimibe. Reduction in lipoprotein(a) may also contribute to the reduction in mortality and MI rates and suggests another possible long-term cardiovascular benefit of PCSK9 inhibitors. These agents seem to be a safe and effective treatment option for patients with dyslipidemia.</td></tr>
<tr><td>Strengths</td><td>• No publication bias suggested by funnel plots or the Egger regression test
• RCTs were similar in their risk of bias
• No signal for heterogeneity in the analysis of all-cause and CV mortality
• Included phase 2 and 3 RCTs</td></tr>
<tr><td>Limitations</td><td>• Results derived from study-level data rather than patient-level data
• A few of the studies were only reported in abstracts or meeting presentations
• A small number of cardiovascular events were used to derive the outcomes data so should be interpreted with caution
• Most of the studies had a short duration of follow-up (ranging from 2 months to 2 years)
• Combined studies with different subpopulations, and information was generalized to patients with dyslipidemia
• No RCT was powered to evaluate mortality and CV events</td></tr>
<tr><td>Application</td><td>PCSK9 inhibitors produce a significant reduction in LDL and lipoprotein(a). This analysis shows a benefit in all-cause mortality with PCSK9 inhibitors. However, the findings are preliminary and should be interpreted with caution. The study confirms the overall safety of the PCSK9 inhibitors. Ongoing studies will provide more data on safety and the effects on cardiovascular events.</td></tr>
</table>

6. Benefits to lower LDL
    a. A meta-analysis of 8 statin RCTs[19]
        i. LDL, non-HDL cholesterol, and apolipoprotein B were measured at baseline and at 1-year follow-up
        ii. Patients achieving an LDL <50 mg/dL had a statistically significantly lower risk for major cardiovascular events than patients achieving an LDL level between 75 and <100 mg/dL (adjusted HR 0.81, 95% CI 0.70 to 0.95) and LDL level ≥175 mg/dL (adjusted HR 0.44, 95% CI 0.35 to 0.55)
        iii. Patients with an LDL <50 mg/dL had a lower risk of major coronary events compared with an LDL ≥175 mg/dL (adjusted HR 0.47, 95% CI 0.36-0.61)
        iv. Risk of hemorrhagic stroke was higher among patients achieving very low levels of atherogenic lipoproteins, however, the number of hemorrhagic strokes was low and statistical power was insufficient to make definite conclusions
        v. >40% of patients taking a high-dose statin did not reach an LDL <70 mg/dL
        vi. Results suggest that achieving very low LDL levels lowers CVD risk
    b. IMPROVE-IT[20]
        i. 18,144 patients hospitalized for an acute coronary syndrome in the prior 10 days
        ii. Randomized to the combination of simvastatin and ezetimibe or simvastatin and placebo
        iii. Median follow-up of 6 years
        iv. Addition of ezetimibe lowered LDL by about 24%
        v. The CV event rate at 7 years was 32.7% in the ezetimibe group and 34.7% in the placebo group (p=0.016)
        vi. No difference in cardiovascular mortality or in rate of death from any cause
        vii. Supports the concept that lower LDL is better

7. Atherosclerosis regression[7]
    a. Animal and human observational studies suggest that atherosclerotic lesions can regress with intensive LDL-lowering, especially earlier in the atherosclerotic process
    b. Plaque regression relies on aggressive LDL-lowering, generally beyond that which is achievable with statin therapy alone
    c. Young adults with multiple risk factors may be potential targets of early, aggressive LDL-lowering with statin/PCSK9 inhibitor

8. Cost[21-24]
    a. Alirocumab is priced at $14,600 per year; annual cost for evolocumab is $14,100
    b. Cost effectiveness analysis
        i. Secondary prevention among patients with prior history of CVD and LDL ≥70 mg/dL on statin

	Total MACE averted	NNT_5	QALYs gained	Incremental drug costs (million $)	ICER ($/QALY)
Statin	Comparator				
Ezetimibe + statin	2,253,800	51	4,345,900	$673,155	$135,000
PCSK9 inhibitor + statin	5,621,800	21	10,573,800	$3,406,692	$302,000

        ii. If willing to pay $100,000/QALY, then the PCSK9 inhibitor would be cost effective at $5300 anually
        iii. Limitation: analysis based on short-term data
    c. Express Scripts expects to spend $750 million in 2016, less than industry forecasts
    d. Repatha™ Copay Card
        i. Eligible commercially-insured patients pay $5 for each prescription regardless of income
    e. MyPRALUENT™ Copay Card

i. Eligible patients with commercial insurance may pay $0 for their first 6 months
ii. After that, pay no more than $10 copay per month

9. Future direction
    a. ODYSSEY OUTCOMES[25]
        i. 18,000 subjects
        ii. Will evaluate effect of alirocumab on cardiovascular outcomes after an acute coronary syndrome
        iii. Treatment period of 64 months
        iv. Expected completion: December 2017
    b. FOURIER[26]
        i. 27,500 subjects
        ii. Will assess safety and efficacy of evolocumab in reducing cardiovascular events in patients with established cardiovascular disease
        iii. 5 year study duration
        iv. Expected completion: February 2018
    c. Small molecule inhibitors of PCSK9 are under development[12]

10. Conclusion
    a. PCSK9 inhibitors can further lower LDL by about 50-60% when added to statin therapy
    b. Overall, no significant differences in the rate of adverse effects compared to control
    c. Patients at high risk for cardiovascular events would benefit from intensive LDL lowering
    d. Preliminary data from post hoc analyses of phase III efficacy/safety RCTs suggest that PCSK9 inhibitors may further reduce ASCVD risk when added to statin therapy
    e. RCTs evaluating long-term ASCVD outcomes are ongoing and will provide more evidence on the potential for cardiovascular risk reduction and long-term safety data with PCSK9 inhibitors and low LDL levels

11. Clinical recommendations
    a. Statins should continue to be first line treatment
    b. PCSK9 inhibitors should be used with caution until the results of the major outcomes trials are available
    c. Patients who may benefit from a PCSK9 inhibitor:
        i. Patients with ASCVD who have an inadequate response to statins
        ii. Patients with familial hypercholesterolemia
        iii. Patients intolerant to statins

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Table 4. Abbreviations	
ACC/AHA	American College of Cardiology/American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease
FH	Familial hypercholesterolemia
HR	Hazard ratio
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HDL	High density lipoprotein cholesterol
ICER	Incremental cost effectiveness ratio
LDL	Low density lipoprotein cholesterol
LDLR	LDL receptor
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NNT_5	Number needed to treat for 5 years to avert one MACE
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SubQ	Subcutaneous

Appendix

Appendix A

2012 American Association of Clinical Endocrinologists[8]		
Risk Category	**Risk Factors/ 10-Year Risk**	**LDL Treatment Goal**
Very high risk	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease or diabetes plus 1 or more additional risk factor(s)	<70 mg/dL
High risk	≥2 risk factors and 10-year risk >20% or CHD risk equivalents*, including diabetes with no other risk factors	<100 mg/dL
Moderately high risk	≥2 risk factors and 10-year risk 10%-20%	<130 mg/dL
Moderate risk	≥2 risk factors and 10-year risk <10%	<130 mg/dL
Low risk	≤1 risk factor	<160 mg/dL

*includes diabetes, peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease

Appendix B

2014 National Lipid Association[9]			
Risk category	**Criteria**	**LDL Treatment goal**	**Consider drug therapy**
Low	• 0–1 major ASCVD risk factors • Consider other risk indicators, if known	<100 mg/dL	≥160 mg/dL
Moderate	• 2 major ASCVD risk factors • Consider quantitative risk scoring • Consider other risk indictors	<100 mg/dL	≥130 mg/dL

High	• ≥3 major ASCVD risk factors
	• Diabetes
	  o 0–1 other major ASCVD risk factor
	  o No evidence of end organ damage
	• CKD stage 3B or 4
	• LDL-C >190 mg/dL
	• Quantitative risk score reaching high risk threshold
		<100 mg/dL	≥100 mg/dL

Very high	• ASCVD
	• Diabetes
	  o ≥2 major risk factors or
	  o Evidence of end-organ damage
		<70 mg/dL	≥70 mg/dL

Appendix C

Classifying Statins[10]		
Low-intensity: *Lowers LDL < 30%*	**Moderate-intensity:** *Lowers LDL 30 to <50%*	**High-intensity:** *Lowers LDL ≥ 50%*
Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 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 BID Pitavastatin 2-4 mg	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

Appendix D

2013 ACC/AHA Statin Benefit Groups[10]		
Risk Category	**Age**	**Initial Drug Therapy**
Primary Prevention		
LDL ≥190 mg/dL	≥21 years	High-intensity statin
Type 1 or 2 diabetes and LDL 70-189 mg/dL	40-75 years	Moderate-intensity statin
Type 1 or 2 diabetes and LDL 70-189 mg/dL with an estimated 10-year ASCVD risk ≥7.5%	40-75 years	High-intensity statin
10-year ASCVD risk ≥7.5% and LDL 70 to 189 mg/dL	40-75 years	Moderate- to high-intensity statin
10-year ASCVD risk 5 to <7.5% and LDL 70 to 189 mg/dL	40-75 years	Moderate-intensity statin
Secondary Prevention		
Clinical ASCVD*	≤75 years	High-intensity statin
Clinical ASCVD*	>75 years	Moderate-intensity statin

*includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin

Appendix E

Alirocumab (Praluent®)[15]	
Indication	• Adjunct to diet and maximally tolerated statin for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional LDL lowering • Limitation of use: cardiovascular morbidity and mortality have not been determined
Dosing	• 75 mg subcutaneously once every 2 weeks, up to max dose of 150 mg every 2 weeks if inadequate LDL response • No dose adjustment needed for mild to moderate hepatic or renal impairment
Administration	• Use a single-dose prefilled pen or single-dose prefilled syringe to inject subcutaneously into the abdomen, thigh, or upper arm • Warm to room temperature 30-40 minutes prior to use; use as soon as possible after warming
Adverse reactions	Nasopharyngitis, Injection site reactions, Influenza Urinary tract infection, Diarrhea, Bronchitis Myalgia, Muscle spasms, Sinusitis Allergic reactions, Liver enzyme abnormalities, Cough Confusion or memory impairment
Pharmacokinetics	• Absorption: t_{max}= 3-7 days • Bioavailability: 85% • Distribution: primarily in the circulatory system (V= 0.04-0.05 L/kg) • Metabolism: degrades to peptides and amino acids; not affected by CYP P450 or P-gp • Half-life: 17-20 days
Drug interactions	• None reported
Monitoring	• Measure LDL within 4-8 weeks of initiation or dose titration to assess response
Storage	• Store in the refrigerator at 2°C to 8°C • Do not use if it exceeds 24 hours at room temperature • Do not shake

Appendix F

Evolocumab (Repatha®)[16]			
Indication	• Adjunct to diet and maximally tolerated statin for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional LDL lowering • Adjunct to diet and other LDL-lowering therapies for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional LDL lowering • Limitation of use: cardiovascular morbidity and mortality have not been determined		
Dosing	• HeFH, primary hyperlipidemia: 140 mg subQ every 2 weeks or 420 mg subQ once monthly • HoFH: 420 mg subQ once monthly • No dose adjustment needed for mild to moderate hepatic or renal impairment		
Administration	• To administer 420 mg dose, give 3 injections consecutively within 30 minutes • Use a single-use prefilled autoinjector or single-use prefilled syringe to inject subcutaneously into the abdomen, thigh, or upper arm • Warm to room temperature for at least 30 minutes prior to use		
Adverse reactions	Nasopharyngitis Urinary tract infection Myalgia Allergic reactions	Injection site reactions Gastroenteritis Back pain Cough	Influenza Upper resp. tract infection Sinusitis Neurocognitive events
Pharmacokinetics	• Absorption: t_{max}= 3-4 days • Bioavailability: 72% • Distribution: V=3.3 L • Metabolism: degrades to peptides and amino acids; not affected by CYP P450 or P-gp • Half-life: 11-17 days		
Drug interactions	• None reported		
Monitoring	• HoFH: measure LDL-C 4-8 weeks after initiation		
Storage	• Store refrigerated at 2°C to 8°C, or can store at room temperature if used within 30 days • Do not shake		

Appendix G

Comparison	Analysis		Efficacy Outcome: Mean Difference (95% CI), %			
			LDL-C	HDL-C	TC	Lp(a)
Placebo	MAb	Alirocumab 75 mg Q2W	-52.63 (-56.12 to -49.14)	-	-	-14.60 (-28.27 to -0.93)
		Alirocumab 150 mg Q2W	-56.15 (-58.29 to -54.00)	4.97 (3.67 to 6.27)	-38.87 (-43.58 to -34.16)	-25.60 (-37.80 to -13.40)
		Evolocumab 140 mg Q2W	-63.46 (-65.41 to -61.51)	6.65 (5.12 to 8.17)	-41.18 (-43.96 to -38.41)	-32.31 (-38.23 to -27.38)
		Evolocumab 420 mg Q4W	-57.26 (-58.97 to -55.54)	7.25 (5.71 to 8.78)	-36.96 (-39.67 to -34.29)	-26.03 (-30.58 to -21.48)
	Background statin	None	-53.65 (-59.51 to -47.78)	7.80 (5.20 to 10.40)	-33.05 (-38.40 to -27.70)	-23.56 (-31.19 to -15.92)
		Nonintensive	-65.24 (-70.46 to -60.02)	6.78 (4.53 to 9.04)	-40.62 (-43.81 to -37.43)	-29.05 (-35.57 to -22.52)
		Intensive	-57.93 (-60.95 to -54.91)	6.18 (5.01 to 7.35)	-39.22 (-41.41 to -37.02)	-28.90 (-33.23 to -24.57)
Ezetimibe	MAb	Alirocumab 75 mg Q2W	-31.67 (-34.45 to -28.90)	6.20 (0.87 to 11.53)	-22.20 (-26.65 to -17.76)	-5.40 (-20.79 to 9.99)
		Evolocumab 140 mg Q2W	-39.27 (-41.84 to -36.70)	7.39 (5.16 to 9.62)	-25.35 (-30.99 to -19.72)	-26.88 (-33.46 to -20.30)
		Evolocumab 420 mg Q4W	-37.49 (-39.74 to -35.25)	6.37 (4.30 to 8.45)	-23.96 (-27.33 to -20.59)	-24.84 (-31.26 to -18.42)
	Background statin	None	-36.23 (-39.24 to -33.26)	6.24 (3.87 to 8.60)	-22.20 (-26.65 to -17.76)	-15.39 (-21.02 to -9.76)
		Nonintensive	-37.49 (-40.81 to -34.16)	6.75 (4.47 to 9.03)	-25.29 (-29.10 to -21.48)	-26.12 (-30.54 to -21.71)
		Intensive	-34.42 (-39.06 to -29.79)	7.92 (4.70 to 11.14)	-23.00 (-27.46 to -18.55)	-33.66 (-40.05 to -27.28)

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); MAb = monoclonal antibody; TC = total cholesterol; Q2W = once every 2 weeks; Q4W = once every 4 weeks.