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EXPERT perspectives

From Clinical Trial to Clinical Practice: Demonstrating the Value of PCSK9 Inhibitors in Lipid Management Plans

A CME Activity

Overview

Leslie Cho, MD, and **Jennifer G. Robinson, MD, MPH,** provide their perspectives on issues related to the evolving role and value of PCSK9 inhibitors in the management of patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia. Drs. Cho and Robinson examine the impact of PCSK9 inhibitors on patients with elevated low-density lipoprotein cholesterol (LDL-C). They discuss the benefits and risks of lowering LDL-C below 25 mg/dL and the evidence regarding possible effects of PCSK9 inhibitors on cognition and antibody formation. Suggestions are offered for overcoming restrictions to PCSK9 inhibitor therapy implemented by payers.

Content Areas:

- Proprotein convertase subtilisin/kexin type 9 inhibitors
- Low-density lipoprotein cholesterol hypercholesterolemia
- Apolipoprotein B
- Safety
- Overcoming payer restrictions

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CE/CME Information

Target Audience
This activity was developed for cardiologists, cardiology fellows, nurses, nurse practitioners, physician assistants, pharmacists and other health care professionals who have an interest in lipid management.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Summarize the clinical implications of new data on PCSK9 inhibitors
- Apply evidence-based research into clinical practice as appropriate plans with appropriate therapeutic selection for optimal outcomes improvement

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Consultant	Amgen—Clinical area: Lipid lowering PCSK9

Jennifer G. Robinson, MD, MPH

	Clinical area: Lipid modifying and cardiovascular prevention for all companies listed below.
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Heather Marie Gibson, BSN, MSN (lead nurse planner)

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Question 1
Do the PCSK9 inhibitors affect cognition?

Answer:
As monoclonal antibodies, the PCSK9 inhibitors are too large to cross the intact blood-brain barrier. Although a meta-analysis of safety data from 6 trials (N=9581) published prior to March 2015 showed a significant increase in neurocognitive adverse events, the rates were low.[1] Adverse cognitive event rates were: 0.72% with PCSK9 inhibitor therapy compared with 0.28% with placebo (odds ratio [OR] 2.34; 95% confidence interval [CI] 1.11-4.93). In contrast, a more recent meta-analysis of 8 trials (N=10,656) suggested no difference in the incidence of neurocognitive adverse events.[2] Event rates were 0.8% with PCSK9 inhibitor therapy compared with 0.5% with no PCSK9 inhibitor therapy (OR 1.29; 95% CI 0.64-2.59). In this latter meta-analysis, the 2 outcome trials (N=6806) (ODYSSEY LONG-TERM with alirocumab and OSLER with evolocumab), showed an increased incidence of neurocognitive adverse events (OR 2.81; 95% CI 1.32-5.99).

These results are in contrast to a pooled analysis by Robinson, et al, of 14 phase 2 and 3 alirocumab trials up to 104 weeks in duration.[3] The rate of a neurocognitive disorder was the same in patients treated with alirocumab compared with placebo or ezetimibe (0.7 events/100 patient-years). Moreover, the rate declined with lower LDL-C level, occurring at a rate of 0.8 events/100 patient-years in patients with LDL-C ≥25 mg/dL vs 0.5 events/100 patient-years in patients with LDL-C <25 mg/dL and 0.3 events/100 patient-years in patients with LDL-C <15 mg/dL **(Table 1).**

Additional information about neurocognitive adverse events has recently been reported in the 27,500-patient Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial of evolocumab added to moderate- or high-intensity statin therapy for an average of 2.3 years. In FOURIER, there were similar rates of cognitive adverse events in the evolocumab and placebo groups.[4] A preplanned substudy of FOURIER, Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS), also found no increased risk of neurocognitive events with the PCSK9 inhibitor evolocumab.[5] In EBBINGHAUS, patients (N=1154) underwent a baseline cognitive function evaluation before treatment. No differences across the 5 groups of achieved LDL-C at 4 weeks were observed in the primary cognitive endpoint of spatial working memory strategy index of executive function, any of the 3 secondary endpoints (spatial working memory between errors, paired association learning, or reaction time 5-choice), or global composite score. Similarly, no differences across the 5 groups were observed for patient-reported changes in memory, except for divided attention and total score, which were significantly better with lower achieved LDL-C **(Table 2).** However, the absolute differences were small.

In conclusion, the risk of a neurocognitive adverse event with PCSK9 inhibitor therapy appears low, with a rate similar to placebo. Moreover, the rate is similar independent of achieved LDL-C after 4 weeks of PCSK9 treatment. Treatment with a PCSK9 inhibitor over several years is needed to confirm these findings, and open-label long-term follow-up of 5000 FOURIER participants is ongoing.

Table 1. Treatment-emergent adverse events in patients with ≥2 consecutive LDL-C values <25 mg/dL or <15 mg/dL

Events/100 patient-years	Pooled control (n=1894)	Overall alirocumab (n=3340)	LDL-C ≥25 mg/dL (n=2501)	LDL-C <25 mg/dL (n=839)	LDL-C <15 mg/dL (n=314)
Neurologic	3.1	3.1	3.4	1.9	2.3
Neurocognitive disorders	0.7	0.7	0.8	0.5	0.3
Ophthalmologic	1.1	1.4	1.5	1.2	1.3
Hepatic disorders	1.9	2.2	2.4	1.6	1.8
Cataract	0.9	1.0	0.6	2.0	2.3

Table 2. EBBINGHAUS Substudy (full study population)

Everyday Cognition Domain	LDL-cholesterol at 4 weeks					*P*trend
	<19 mg/dL (n=2669)	19 to <50 mg/dL (n=8003)	50 to <70 mg/dL (n=3444)	70 to <100 mg/dL (n=7471)	≥100 mg/dL* (n=4395)	
Memory	1.17 (0.38)	1.15 (0.36)	1.18 (0.41)	1.16 (0.37)	1.18 (0.40)	0.11
Executive Functioning, Total	1.12 (0.32)	1.10 (0.29)	1.13 (0.34)	1.11 (0.31)	1.13 (0.34)	0.12
Planning	1.11 (0.34)	1.08 (0.28)	1.12 (0.35)	1.09 (0.31)	1.12 (0.35)	0.27
Organization	1.10 (0.31)	1.09 (0.30)	1.12 (0.34)	1.09 (0.32)	1.12 (0.35)	0.98
Divided Attention	1.15 (0.40)	1.13 (0.36)	1.17 (0.42)	1.14 (0.38)	1.17 (0.42)	0.0374
Total Score	1.13 (0.32)	1.12 (0.29)	1.15 (0.35)	1.13 (0.31)	1.15 (0.35)	0.0168

*Reference group

Question 2
What steps can a provider take to overcome restrictions to PCSK9 inhibitor therapy implemented by payers?

Answer:
The US Food and Drug Administration (FDA) approved 2 PCSK9 inhibitors for patients with atherosclerotic cardiovascular disease or familial hypercholesterolemia who require additional LDL-C lowering despite lifestyle and maximal statin therapy.[6,7] However, denials by payers quickly became the rule rather than the exception, limiting patient access. A 2016 survey revealed an approximately 20% initial approval for PCSK9 therapy, with final approval after appeal of 27% by commercial payers and 61% by Medicare.[8] Another survey demonstrated an approval rate of 21% for PCSK9 inhibitor therapy.[9] These low approval rates primarily resulted from the use of 3 principal measures implemented by payers: prior authorization, step therapy, and an involved appeals process.

In 2016, the American Society for Preventive Cardiology convened 2 town hall meetings of multiple stakeholder organizations.[10] Their objective was to identify barriers to PCSK9 inhibitor therapy with viable solutions that could be implemented so that patients who meet the prescribing criteria established by the FDA can receive PCSK9 inhibitor therapy.

Among the recommendations for payers, many related to greater transparency and simplifying their approval and appeals process. To help providers over the prior authorization process, the panel developed a template prior authorization form. In addition to identifying essential information required by payers, the form also included definitions of ill-defined terms believed to often complicate the decision process. These terms include: maximally tolerated statin therapy, heterozygous and homozygous familial hypercholesterolemia, and atherosclerotic cardiovascular disease, as well as a description of patients who may require additional lowering of LDL-C. Given the high rate of denials and the need for appealing a payer's decision, the panel also developed an appeals template letter that provides guidance to both providers and payers to improve appeal success. The template prior authorization form and appeals letter may be found at: http://onlinelibrary.wiley.com/doi/10.1002/clc.22713/abstract;jsessionid=4348E67BB53D32F9E4445B2881A138B4.f04t04.

Question 3
Are there any benefits from lowering LDL-C below 25 mg/dL with PCSK9 inhibitors? Are there any risks?

Answer:
Cardiovascular benefits with progressive lowering of LDL-C have recently been reported from the FOURIER trial with the PCSK9 inhibitor evolocumb.[4] Following 48 weeks of treatment with evolocumab, the LDL-C was reduced from a median baseline level of 92 mg/dL to a median of 30 mg/dL. There was a 17% reduction in the risk of the key secondary endpoint (composite of cardiovascular death, myocardial infarction, or stroke) among patients with a median LDL-C of 126 mg/dL at baseline (43 mg/dL at 48 weeks) compared with a 22% reduction in patients with a median LDL-C of 73 mg/dL at baseline (22 mg/dL at 48 weeks).

The EBBINGHAUS substudy of FOURIER provided more detailed event rates by achieved LDL-C at 4 weeks **(Table 3).** Compared to patients with LDL-C ≥100 mg/dL at 4 weeks, there was a significant reduction with lower achieved LDL-C for the primary composite endpoint, as well as for the individual endpoints of myocardial infarction, stroke, and coronary revascularization. Patients in the LDL-C <19 mg/dL group had the lowest risk of a composite of cardiovascular death, myocardial infarction, or stroke, as well as the individual endpoint of coronary revascularization.

These results are consistent with the findings of the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial. The results of GLAGOV showed a linear relationship between LDL-C level after 18 months of treatment and change in percent atheroma volume **(Figure 3).**[11]

In terms of safety, the pooled analysis of 14 phase 2 and 3 trials of alirocumab up to 104 weeks in duration by Robinson, et al, showed a similar incidence of neurologic, ophthalmologic, and hepatic adverse events with alirocumab in patients with LDL-C <25 mg/dL compared with LDL-C ≥25 mg/dL **(Table 1 from question 1).**[3] The only exception was a significantly higher incidence of cataracts in patients with LDL-C <25 mg/dL vs LDL-C ≥25 mg/dL at treatment end (2.0% vs 0.6%, respectively; HR 3.40; 95% CI 1.58-7.35). The incidence of cataracts in patients with LDL-C <15 mg/dL at treatment end was 2.3%. Results of the ODYSSEY LONG TERM study showed no clinically meaningful differences with alirocumab in cortisol levels, gonadal hormones, or vitamins A, D, E, or K in patients who achieved LDL-C <15 mg/dL.[12]

Generally similar results were observed with evolocumab in the EBBINGHAUS substudy of FOURIER **(Table 4).**[5] No significant association was observed between achieved LDL-C and safety outcomes, either for all serious adverse events or any of the other 9 prespecified safety events. However, as with alirocumab, the only exception was a significantly greater risk of cataracts in patients with LDL-C <19 mg/dL compared with LDL-C ≥100 mg/dL (HR 1.54; 95% CI 1.03-2.31).

These results with PCSK9 inhibitors parallel results of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study. JUPITER demonstrated the benefit in cardiovascular risk reduction with progressive lowering of LDL-C to a mean of 44 mg/dL following 2.0 years of treatment with rosuvastatin.[13] Further support for the cardiovascular benefits of low LDL-C levels was demonstrated in a meta-analysis of 8 statin trials involving 38,153 patients.14 Over 1 year of follow-up, those who reached an LDL-C 75 to <100 mg/dL, 50 to <75 mg/dL, and <50 mg/dL, had adjusted hazard ratios for major cardiovascular events of 0.56 (95% CI 0.46-0.67), 0.51 (95% CI 0.42-0.62), and 0.44 (95% CI 0.35-0.55), respectively, compared to those who achieved an LDL-C >175 mg/dL.

Table 3. Cardiovascular event rates by achieved LDL-C at 4 weeks.

Endpoint	Adjusted Hazard Ratio (95% CI)					*P*trend
	LDL-cholesterol at 4 weeks					
	<19 mg/dL	19 to <50 mg/dL	50 to <70 mg/dL	70 to <100 mg/dL	≥100 mg/dL	
Primary composite*	0.76 (0.64-0.90)	0.85 (0.76-0.96)	0.94 (0.82-1.09)	0.97 (0.86-1.09)	1.0	<0.0001
CV death, MI, or stroke	0.69 (0.56-0.85)	0.75 (0.64-0.86)	0.87 (0.73-1.04)	0.90 (0.78-1.04)	1.0	<0.0001
CV death	0.99 (0.67-1.47)	1.07 (0.80-1.43)	0.99 (0.69-1.43)	1.14 (0.85-1.53)	1.0	0.83
MI	0.59 (0.45-0.78)	0.69 (0.57-0.84)	0.87 (0.69-1.09)	0.85 (0.71-1.03)	1.0	<0.0001
Stroke	0.81 (0.55-1.18)	0.63 (0.47-0.85)	0.81 (0.57-1.14)	0.90 (0.68-1.20)	1.0	0.0054
Coronary revascularization	0.63 (0.50-0.78)	0.78 (0.67-0.91)	0.91 (0.76-1.09)	0.91 (0.78-1.05)	1.0	<0.0001
Unstable angina	1.18 (0.80-1.74)	1.04 (0.78-1.39)	0.95 (0.66-1.37)	1.09 (0.82-1.47)	1.0	0.73
All-cause death	0.89 (0.66-1.20)	0.98 (0.79-1.23)	1.00 (0.77-1.31)	1.02 (0.82-1.27)	1.0	0.47

*Cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

Figure 3. Change in atheroma volume with evolocumab added to moderate-/high-intensity statin therapy over 18 months.

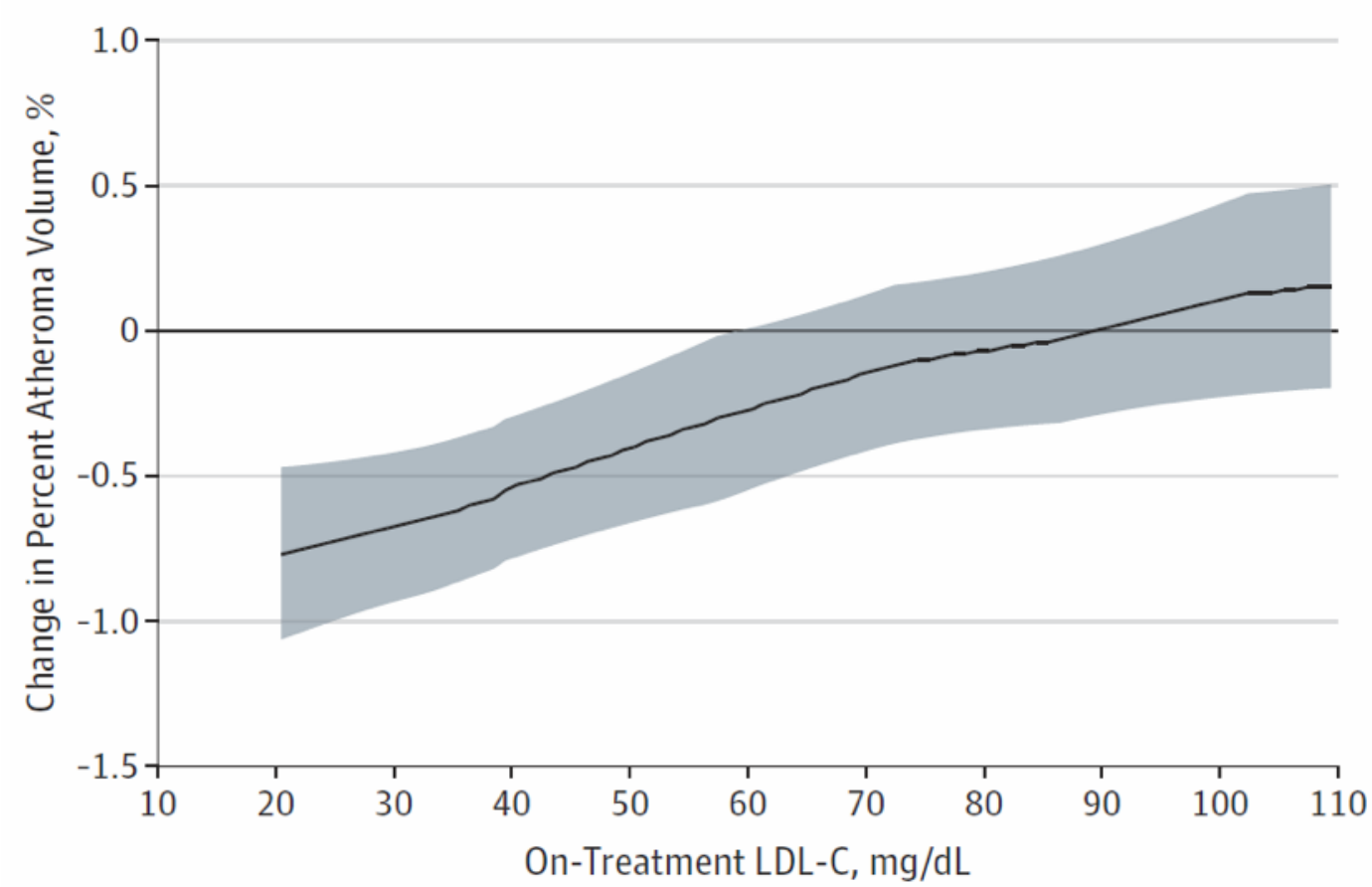


Table 4. Safety events by achieved LDL-C concentration at 4 weeks after randomization

Event	Adjusted Odds Ratio/Hazard Ratio (95% CI)					*P*trend
	LDL-cholesterol at 4 weeks					
	<19 mg/dL (n=2669)	19 to <50 mg/dL (n=8003)	50 to <70 mg/dL (n=3444)	70 to <100 mg/dL (n=7471)	≥100 mg/dL (n=4395)	
Serious AE	0.97 (0.86-1.10)	1.01 (0.92-1.11)	1.01 (0.90-1.13)	0.93 0.84-1.02)	1 (ref)	0.30
AEs leading to DC	1.08 (0.82-1.43)	1.07 (0.86-1.33)	1.07 (0.83-1.39)	0.91 (0.73-1.14)	1 (ref)	0.13
AST or ALT elevation (>3 times ULN)	0.96 (0.64-1.43)	0.87 (0.64-1.17)	1.25 (0.90-1.74)	0.91 (0.68-1.24)	1 (ref)	0.64
Creatinine kinase elevation (>5 times ULN)	1.02 (0.53-1.96)	1.07 (0.65-1.77)	0.88 (0.47-1.65)	1.23 (0.75-2.02)	1 (ref)	0.72
Neurocognitive events	1.28 (0.84-1.96)	1.10 (0.78-1.55)	1.10 (0.73-1.65)	0.97 (0.68-1.39)	1 (ref)	0.15
New onset diabetes mellitus	1.06 (0.83-1.35)	1.00 (0.83-1.20)	1.03 (0.83-1.30)	0.95 (0.78-1.14)	1 (ref)	0.48
Cataract-related	1.54 (1.03-2.31)	1.14 (0.82-1.60)	1.34 (0.91-1.98)	1.35 (0.96-1.89)	1 (ref)	0.43
New or progressive malignancy	0.90 (0.64-1.27)	1.01 (0.78-1.31)	1.04 (0.77-1.42)	0.88 (0.67-1.15)	1 (ref)	0.72
Hemorrhagic stroke	.71 (0.17-2.90)	1.55 (0.62-3.85)	1.39 (0.47-4.14)	1.57 (0.62-3.98)	1 (ref)	0.91
Non-cardiovascular death	0.89 (0.53-1.50)	1.06 (0.72-1.55)	1.03 (0.65-1.64)	0.89 (0.60-1.33)	1 (ref)	0.73

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Question 4

In addition to low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB) is also important as an atherogenic lipoprotein. What impact do alirocumab and evolocumab have on ApoB?

Answer:

The effects of PCSK9 inhibitors on various blood lipids and proteins, including ApoB, have been investigated in phase 3 clinical trials. The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG-TERM) involved 2341 patients with LDL-C ≥70 mg/dL despite maximally tolerated statin therapy, with or without other lipid-lowering therapy.[12] Patients were continued on baseline treatment and randomized to alirocumab 150 mg or placebo every 2 weeks for 78 weeks. From a mean of 102 mg/dL at baseline, the placebo-subtracted ApoB decreased 54% at week 24 with alirocumab. Other significant reductions are shown in Figure 1.

The efficacy of evolocumab in reducing ApoB was investigated in the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) over 52 weeks of treatment.[15] Patients (N=901) with LDL-C ≥75 mg/dL and triglyceride ≤400 mg/dL underwent a 4- to 12-week run-in phase wherein patients were randomized to background lipid-lowering therapy consisting of diet alone or diet plus atorvastatin 10 mg/day, atorvastatin 80 mg/day, or atorvastatin 80 mg/day plus ezetimibe 10 mg/day. At the end of the run-in, patients with an LDL-C ≥75 mg/dL were randomized to evolocumab 420 mg or placebo every 4 weeks. From a mean of 87 mg/dL at baseline, the placebo-adjusted ApoB level decreased 44% at week 52 with evolocumab. Other significant reductions were observed in levels of non-high-density lipoprotein cholesterol, lipoprotein(a), and triglycerides.

Figure 1. Efficacy of alirocumab in reducing blood lipids and proteins.

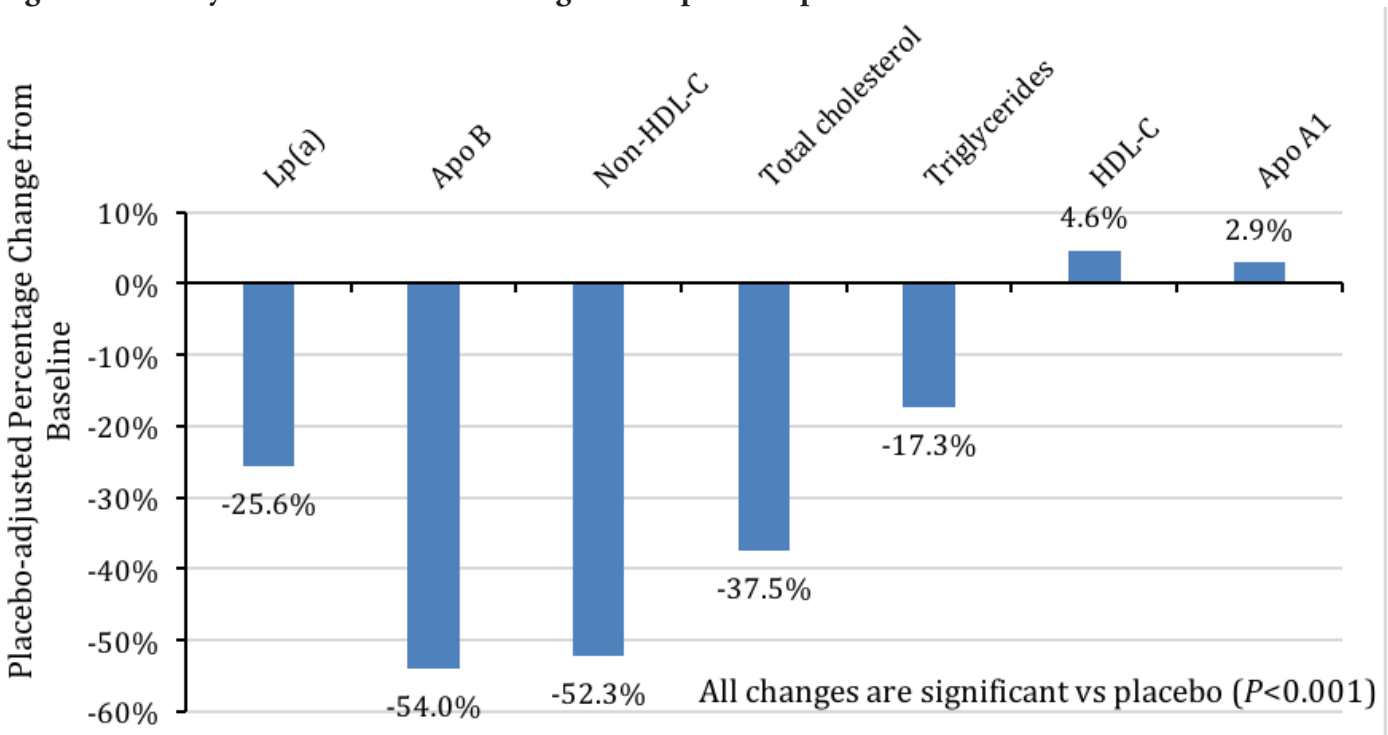
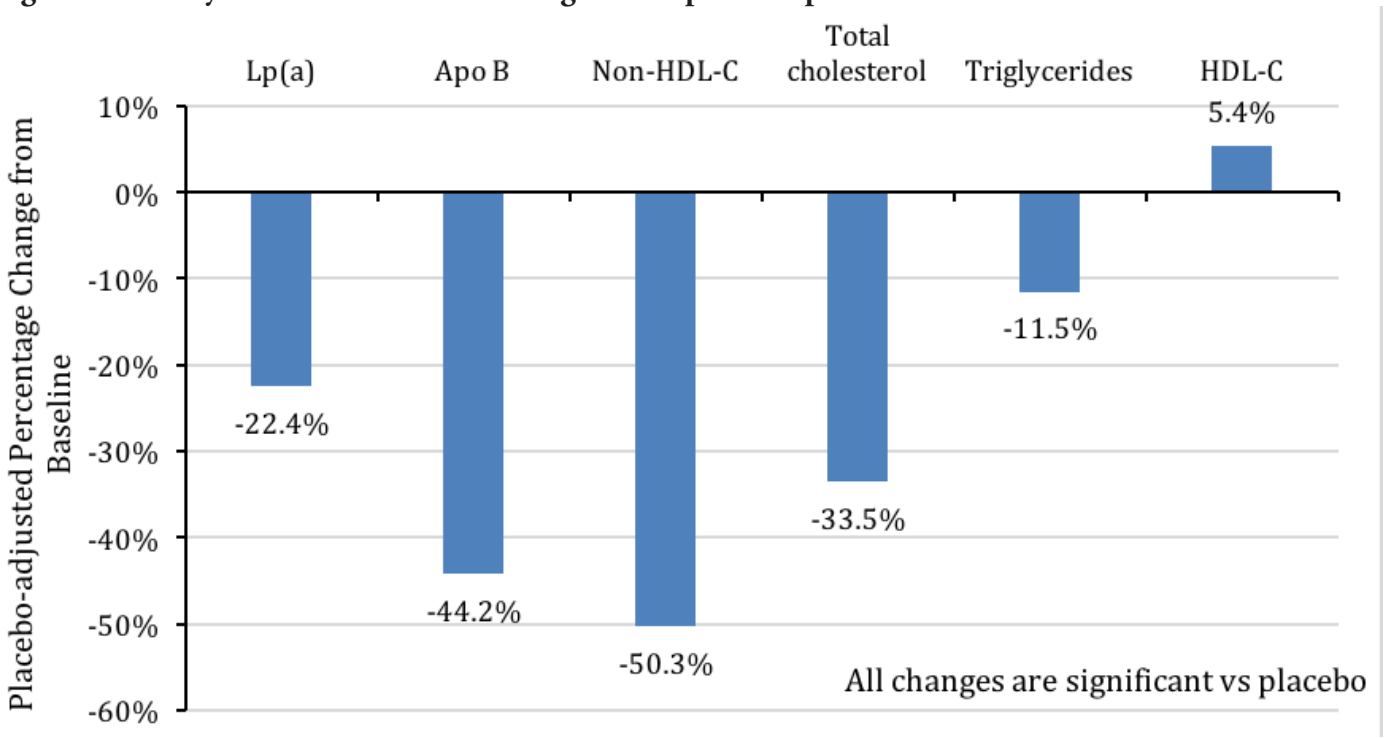


Figure 2. Efficacy of evolocumab in reducing blood lipids and proteins



Question 5
The development of the investigational PCSK9 inhibitor bococizumab was stopped because of antidrug antibody formation that attenuated LDL-C lowering. Is this observed with alirocumab and evolocumab?

Answer:
Treatment with monoclonal antibodies carries the possibility of causing unwanted immunogenicity, leading to minor complications such as injection site reactions or flu-like symptoms. Major complications may occur as well, such as anaphylaxis or loss of drug efficacy. Complications, including a markedly diminished magnitude and durability of LDL-C lowering, have been observed with the humanized PCSK9 monoclonal antibody bococizumab.[16,17] These effects led to termination of the development of bococizumab.

Antibody formation has been closely monitored during the clinical development of the 2 PCSK9 inhibitors currently available in the United States. Roth, et al, analyzed data from 10 placebo-controlled studies involving approximately 4700 patients.[18]

Antidrug antibodies were observed in 5.1% of patients treated with alirocumab compared with 1.0% of placebo patients. Alirocumab-treated patients experienced significant and enduring LDL-C reductions over the duration of the studies. No increase in adverse events associated with antidrug antibodies to alirocumab were observed with the exception of frequent, but mostly mild, injection site reactions.

In patients treated with evolocumab (N=13,784) in the FOURIER study, using a different assay, new binding antibodies developed in 0.3% of patients, while neutralizing antibodies did not occur in any patient treated with evolocumab.[4] The overall LDL-C-lowering effect of evolocumab continued without attenuation.

It seems likely that the observed differences between bococizumab and alirocumab and evolocumab in neutralizing antibody formation are due to the murine origin of the antibody in bococizumab, whereas alirocumab and evolocumab are fully human monoclonal antibodies.

Question 6

Case

LR is a 69-year-old woman with unstable angina. Her LDL-C is 104 mg/dL despite atorvastatin 80 mg/day. Her baseline LDL-C was 176 mg/dL. Beyond further lifestyle management, what change would you make to lower her LDL-C?

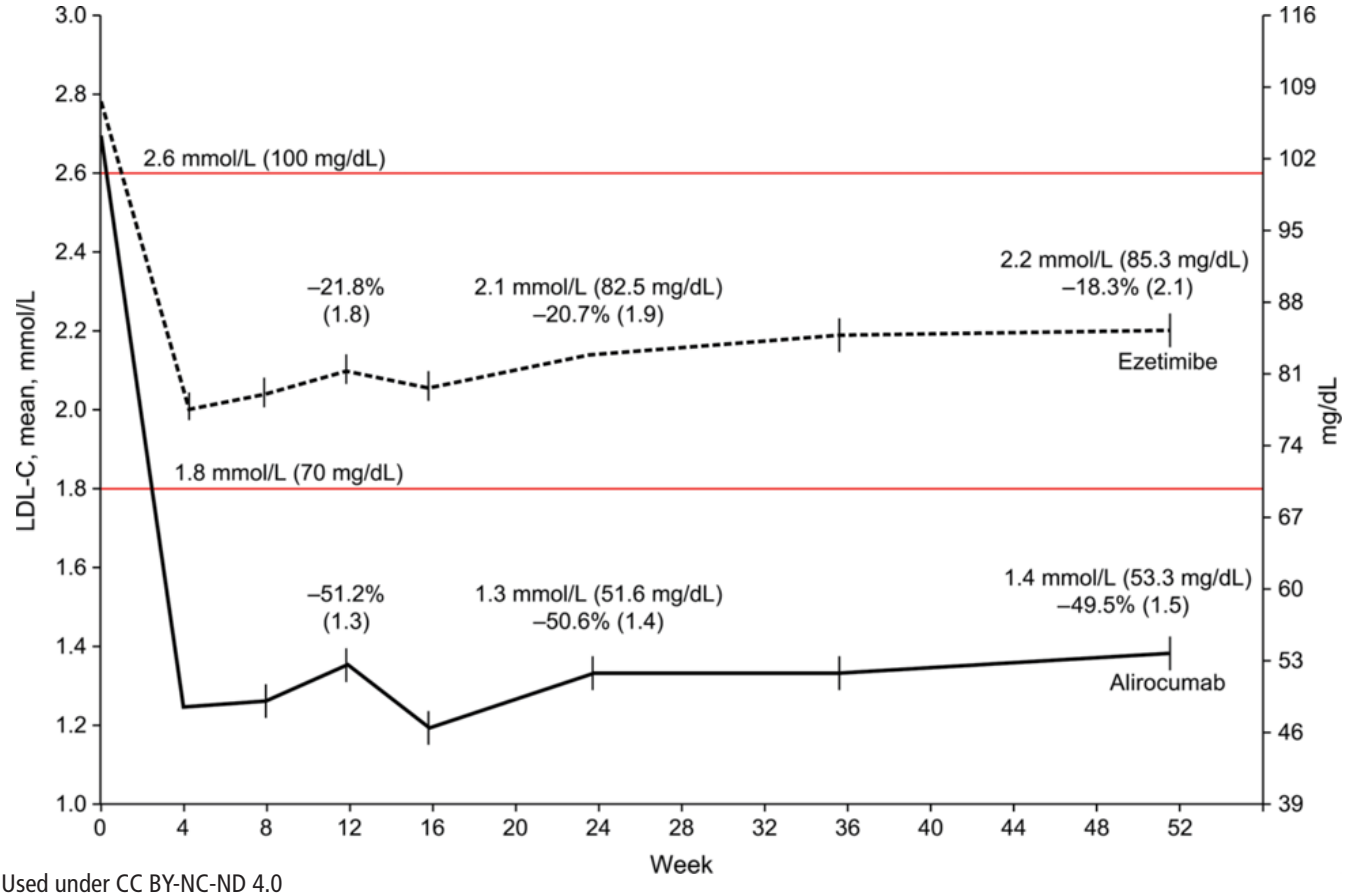
Answer:

High-intensity statin therapy is appropriate first-line treatment for primary prevention in this patient at high risk of a cardiovascular event.[19] Although she is close to the treatment goal of LDL-C <100 mg/dL,[20] her continuing symptoms of cardiovascular disease indicate that treatment intensification is needed. In addition, she has not achieved at least 50% reduction of her baseline LDL-C.[21] The 2016 American College of Cardiology Expert Consensus Decision Pathway recommends ezetimibe as second-line therapy; alternatively, a bile acid sequestrant can be used if the patient does not tolerate ezetimibe and has a triglyceride level <300 mg/dL.[21]

Treatment intensification with ezetimibe 10 mg/day would be expected to lower her LDL-C approximately 20% to approximately 85 mg/dL over 4 weeks or so **(Figure 4).**[22] If this LDL-C level is not achieved, or if the patient continues to have symptoms of unstable angina, further treatment intensification with a PCSK9 inhibitor would be appropriate.

A PCSK9 inhibitor would have been appropriate as second-line therapy instead of ezetimibe if the patient had type 2 diabetes mellitus since it is unlikely that ezetimibe would have lowered the LDL-C to the treatment goal of less than 70 mg/dL in patients with atherosclerotic cardiovascular disease and type 2 diabetes mellitus. Another reason to consider a PCSK9 inhibitor as second-line therapy is the ability to achieve even greater cardiovascular risk reduction (~mean 50%) than with the addition of ezetimibe to maximally tolerated statin therapy (see question #4).

Figure 4. LDL-C lowering with ezetimibe vs alirocumab: Achieved LDL-C over time on background of maximally tolerated statin



Question 7

Case

EF is a 78-year-old woman who underwent percutaneous coronary intervention 3 years ago for 90% occlusion of the left anterior descending coronary artery. Since that time, she has been managed with atorvastatin 40 mg/day, which is her maximally tolerated dose. Her current LDL-C is 82 mg/dL; her baseline LDL-C is unknown. She also has hypertension. How should her lipid management be modified?

Answer:

This patient is at high risk (20% to 29% 10-year ASCVD risk) for another cardiovascular event, but has stable ASCVD without comorbidities. The general goal is to reduce the LDL-C ≥50% from baseline (and may consider LDL-C <100 mg/dL). Since her baseline LDL-C is unknown, it is not possible to determine if she has achieved the ≥50% LDL-C reduction; however, her current LDL-C is 82 mg/dL.

To help identify patients who might benefit from the addition of a nonstatin to background statin therapy, Robinson, et al, performed a systematic review of subgroup analyses from randomized trials and observational studies with statin-treated subjects.[23] They used the relative risk reductions for the addition of a nonstatin to lower LDL-C to calculate the number needed to treat (NNT) to prevent 1 ASCVD event over 5 years for each risk group, and to allow comparisons with 5-year cost analyses. They estimated that the 10-year ASCVD risk is 20% to 29% (high risk) for patients with ASCVD without comorbidities or who have heterozygous familial hypercholesterolemia. They also included the results of the ODYSSEY COMBO II trial, indicating that the addition to maximally tolerated statin therapy of ezetimibe 10 mg/day lowers the LDL-C approximately 20% and alirocumab 75 to 150 mg every 2 weeks approximately 50%.[22] Based on these analyses, they calculated that adding ezetimibe to reduce LDL-C by 20% from baseline would provide a 5-year NNT ≤50 for high-risk patients with baseline LDL-C ≥190 mg/dL. Adding a PCSK9 inhibitor to lower LDL-C by at least 50% from baseline would provide a 5-year NNT ≤50 for high-risk patients with LDL-C ≥70 mg/dL and NNT ≤30 for high-risk patients with LDL-C ≥130 mg/dL.

Based upon this analysis, it can be concluded that EF would experience little benefit with the addition of ezetimibe. Moreover, it is probably not reasonable to consider the addition of a PCSK9 inhibitor.

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