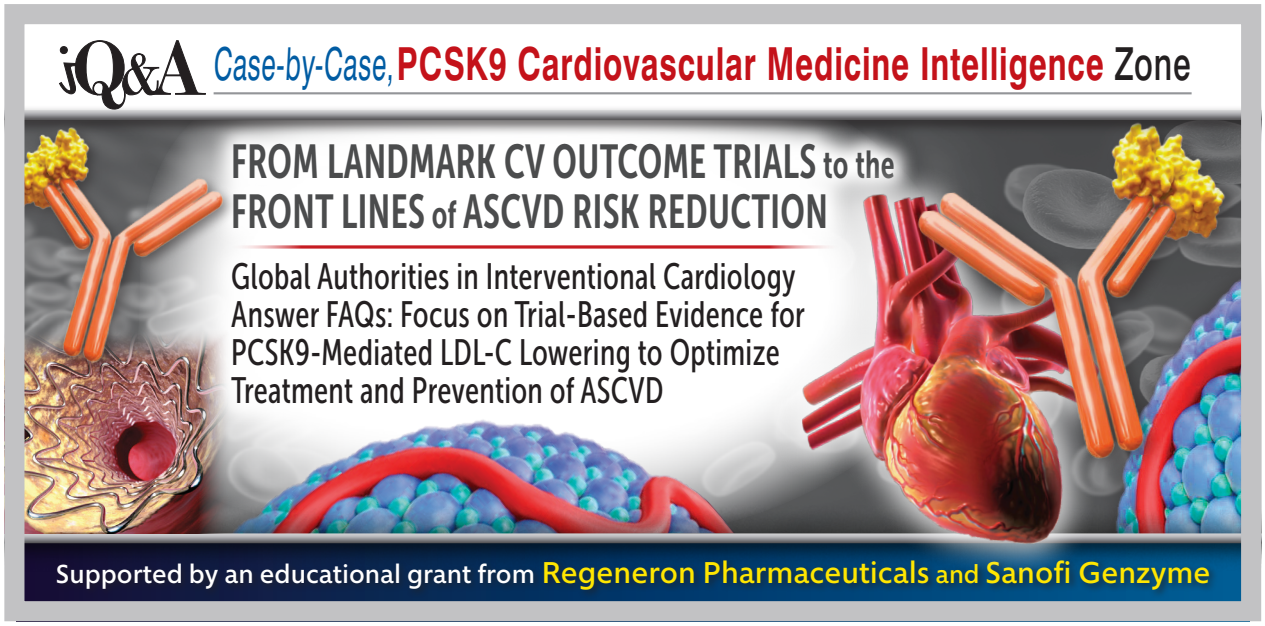
FROM LANDMARK CV OUTCOME TRIALS to the FRONT LINES of INTERVENTIONAL CARDIOLOGY

Global Authorities in **Interventional Cardiology** Answer FAQs: Focus on Trial-Based Evidence for PCSK9-Mediated LDL-C Lowering to Optimize Treatment and Prevention of ASCVD?

A Case-, Guidelines, and Outcomes-Based, Best Practice Roadmap for PCSK9 Inhibition and CV Risk Reduction at the Front Lines of Diabetes Specialty Care



Year 2019 Best Practice, Case-Based and Guideline-Driven Update for the Interventional Cardiologist

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QUESTION #1: Can you discuss the foundational importance of the two principal PSCK9 CV outcome trials—ODYSSEY Outcomes and FOURIER—and how they are similar and in what ways they are different? And what implications this has for the importance of LDL-C reduction the patient with T2D and ASCVD?

QUESTION #2: Can you discuss the specific reductions in MACE events that were reported in the PCSK9 CV outcome trials and how they are shaping the benefit/safety equation for the use of alirocumab and evolocumab in high-risk patients, including diabetics, for secondary prevention of ASCVD?

QUESTION #3: Based on the ODYSSEY Outcomes and FOURIER Trials, which patient populations, including individuals with T2D, do you believe should be targeted for PCSK9 inhibitors?

QUESTION #4: What should the ideal target LDL-C be in the Type 2 diabetes population? And what is the advantage of the treat-to-target strategy employed in ODYSSEY Outcomes and what did we learn about associated, all-cause mortality with alirocumab in that trial?

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QUESTION #5: What have we learned from the ODYSSEY Outcomes pharmacoeconomic analysis that you and Professor Deepak Bhatt reported at the AHA 2018 Meeting? And what are the implications for the clinician-cardiologist who is making the case to payors to support reimbursement for alirocumab in high-risk patients?

QUESTION #6: How exactly did you and your colleagues model the pharmacoeconomic effectiveness of alirocumab based on the actual results of the ODYSSEY Outcomes Trial? And at what price point did you determine that the acquisition cost of the drug would be highly cost-effective in terms of meeting the current accepted standard of QALY analysis? And was your analysis consistent with the ICER recommendations?

QUESTION #7: How have the 2016 Canadian Cardiovascular Society Guidelines for LDL-C reduction positioned their recommendations for LDL-C target goals, and how do you anticipate these might change in the future based on the ODYSSEY Outcomes and FOURIER Trials?

QUESTION #8: From a medical cardiologist's and ACS expert's perspective, can you identify which patients should undergo serious consideration for PCSK9-mediated LDL-C reduction and what kind of risk factors, statin-related treatment failures or side effects, vascular disease, procedures, and/or other co-morbid features should encourage CV specialists to overcome clinical inertia and pursue PCSK9-based therapies based on current trial-based evidence?

QUESTION #9: What LDL-C target goals should a consulting or treating medical cardiologist recommend for patients with Type 2 diabetes—with a known ACS event vs. diabetes alone as a risk factor?

QUESTION #10: What should the approach be in patients who have had a coronary event with an LDL-C level of 70 mg/dL? Do the outcome studies with PCSK9 inhibitors provide an evidentiary roadmap for this common situation?

QUESTION #11: What did ODYSSEY Outcomes and FOURIER teach us about high-risk patients with diabetes and the relative favorability of their responses to LDL-C lowering with PCSK9 inhibitors?

QUESTION #12: How do you approach the diabetic patient who also has a constellation of multiple high-risk features, above and beyond the underlay of diabetes? What is the relative and absolute benefit of employing PCSK9 inhibitors in this patient population?

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QUESTION #13: From your perspective as both an interventional cardiologist and lipid medicine specialist, in light of the recent results showing a reduction in associated all-cause mortality in the ODYSSEY Outcomes Trial, as well as the absence of a J-point curve as it relates to LDL-C lowering to levels as low as 25 mg/dL, which patient types deserve our greatest and most focused attention to optimize the translational impact of this study and PCSK9-based therapy?

QUESTION #14: Since both PCSK9 outcome trials, ODYSSEY Outcomes and FOURIER, demonstrated impressive safety when LDL-C levels are lowered into ranges much lower than 70 mg/dL, what should be the approach of both the interventional and medical cardiologist to achieving LDL-C levels in this range, which are easily achievable in a large percentage of patients treated with PCSK9 inhibitors? Does the subset analysis from ODYSSEY Outcomes give us an actionable roadmap for the degree of aggressiveness of LDL-C lowering that is desirable?

QUESTION #15: As an interventional cardiologist, you are seeing post-ACS/post-PCI patients whose atherosclerotic vascular disease burden is exceptional and, therefore, potentially amenable to PCSK9-mediayed CV risk reduction? Where then, is your specific focus for using these agents in your patient population? And much weight should cardiologists give to clinical signatures vs. metabolic biomarkers when triggering this therapy?

QUESTION #16: What has been your experience with respect to patient satisfaction, discontinuation rates and toleration of this injection-based approach to LDL-C management?

QUESTION #17: Although the AHA Guidelines emphasize the CV risk and mortality reductions observed with statins, ODYSSEY Outcomes provides comparable evidence for both CV risk and all associated, all-cause mortality reduction with the PCSK9 inhibitor, alirocumab. What is your reading of how compelling the evidence is for PCSK9 inhibition as a mediator of both CV risk and mortality reduction?

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QUESTION #18: How has our knowledge of the safety and efficacy of PCSCK9 inhibitors evolved over the past several months, and how has the ODYSSEY Outcomes "treat-to-target" trial with alirocumab, in particular, helped us translate these advances into the front lines of interventional cardiology practice?

QUESTION #19: What unique aspects, with respect to all-cause mortality outcomes and baseline LDL-C levels, were observed in the ODYSSEY Outcomes Trial and how would you translate these results into patient care?

QUESTION #20: Can you drill down into the specific results of the ODYSSEY Outcomes Trial that demonstrate unique, significant reductions in associated all-cause mortality and how these positive findings in the alirocumab treatment arm might be especially relevant to the interventional cardiologist, as well as other clinicians?

QUESTION #21: From the specific vantage point of the interventional cardiologist, based on the results of the ODYSSEY Outcomes Trial, which patients who have undergone procedural coronary interventions do you believe are the best candidates for PCSK9 therapy and LDL-C lowering with alirocumab, or PCSK9 inhibitors, in general?

QUESTION #22: Since both professional organizations such as ESC and ACC/AHA, as well as consensus update panels, are examining the role and value of establishing hard LDL-C targets for patients at risk for ASCVD, how do the results of the ODYSSEY Outcomes Trial help inform interventional and medical cardiologists about the rationale for PCSK9-mediated lowering to achieve ultra-low—new target—levels (i.e. <50 mg/dL) of LDL-C?

QUESTION #23: Can you help us de-convolute what is more important, (a) the absolute level of LDL-C level that was attained among patients in the ODYSSEY Outcomes Trial, or (b) the delta, i.e. the relative change from baseline LDL-C level at time of entry into the trial? What patients are getting the greatest "relative benefit" in CV risk reduction?

QUESTION #24: Based on the results of the ODYSSEY Outcomes Trial, as well as the FOURIER Trial, what are the clinical findings and/or biologic risk features—Lp(a), for example—in patients managed in an interventional cardiology setting that would make you advocate for the use of PCSK9 inhibitors and exploit their favorable benefit-to-risk profile?

QUESTION #25: In a high-risk patient who has undergone multiple stent procedures, what criteria do you prioritize for initiating a PCSK9 inhibitor in the setting of PCI, and what absolute LDL-C targets are in your cross-hairs based on the results of the ODYSSEY Outcomes Trial?

QUESTION #26: Although interventional cardiologists have a strong incentive to use PCSK9 inhibitors in a wide segment of the high-risk population they care for, and the ODYSSEY Outcomes Trial makes clear the excellent benefit-to-risk ratio for their deployment, real world factors such as cost can present barriers to optimizing CV risk prevention. Can you discuss this issue and its relevance to the IC?

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QUESTION #27: In your interventional cardiology practice, which markers of risk, in the patient who has undergone a PCI, do you focus on to promote consideration for using a PCSK9 inhibitor?

QUESTION #28: Based on ODYSSEY Outcomes, which patients in an interventional cardiology practice do you believe will benefit most from PCSK9 inhibition?

QUESTION #29: Can you discuss and compare the current ESC Guidelines for LDL-C targets and the recent AHA Guidelines designating a target threshold of 70 mg/DL? Is this low enough and what is your recommendation for PCSK9 inhibition in the high-risk patient who has had ACS and undergone PCI?

QUESTION #30: Within the context of both the ESC and U.S. guidelines for LDL-C reduction, which recommend 70 mg/dL as a threshold target, how should we view the cholesterol landscape between 20 mg/dL and 70 mg/dL in light of the results of the ODYSSEY Outcomes Trial?

QUESTION #31: With respect to patients with HeFH and homozygous FH who are challenged with lifelong CV disease risk burden due to genetic risk, what role do you believe PCSK9 inhibitors should play, especially in younger patient populations?

QUESTION #32: What has been your clinical experience with respect to the comparative toleration of statins vs. PCSK9 inhibitors?

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QUESTION #33: In the interventional cardiology setting, what percentage of your patients do not achieve the ESC Lipid Guideline goal of 70 mg/dL and, therefore, are suitable candidates for PCSK9 inhibition? Can you discuss your patient selection process for this therapy?

QUESTION #34: From an interventional cardiology perspective, in a patient who is post-PCI/post-stent insertion for ACS, when is the aggregated risk of the patient sufficiently alarming for you to consider intensive lowering of LDL-C to a level <50 mg/dL with a PCSK9 inhibitor? How have the results of the ODYSSEY Outcomes Trial and FOURIER helped support this strategy?

QUESTION #35: What do we know from the subanalyses of the ODYSSEY Outcomes Trial that looked specifically at patients who had achieved LDL-C levels below 50 mg/dL? Which of the patients in this group, based on their baseline LDL-C level at entry, derived disproportionate mortality reduction benefit from alirocumab?

QUESTION #36: Since the overwhelming majority of post-ACS patients in ODYSSEY Outcomes had PCI as part of their ACS management, what have we learned about the safety and efficacy of alirocumab in this unique, stent-rich population of high-risk patients? What is the translational message for the interventional cardiologist?

QUESTION #37: From an interventional cardiology perspective, what did ODYSSEY Outcomes teach us about the large subgroup of diabetic patients who had ACS plus stent insertions?

QUESTION #38: If someone is more than 12 months out after an ACS event and currently has a stent, would you still consider them to be eligible for PCSK9 therapy to lower LDL-C and residual CV risk?

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QUESTION #39: Professor Bhatt, you presented the landmark pharmacoeconomic/cost-effectiveness "in trial" analysis for alirocumab based on results from the ODYSSEY Outcomes Trial. Can you discuss the clinical implications of your analysis, and how the current reduced costs for alirocumab will affect interventional cardiology practice and deployment of this agent, especially in patients with and LDL-C>100 mg/dL?

QUESTION #40: From the vantage points of both an interventional cardiologist and a lipid medicine/atherosclerosis specialist, can you discuss what kind of LDL-C thresholds vs. clinical burden/clinical history thresholds and features you feel are most important for guiding CV specialists in patient selection for PCSK9-based CV risk reduction? Put simply, how do we derive maximal benefits for these patients?

QUESTION #41: Interventional cardiologists and lipid medicine specialists are both being challenged by maximizing CV risk burden reduction in unusually high-risk populations. How should clinicians approach the 70 mg/dL LDL-C target threshold identified in the AHA Guidelines, and when, in your practices, is the push to LDL-C territory in the 30 mg/dL – 70 mg/dL range even more desirable, based on the results—including reduction in all-cause mortality—of ODYSSEY Outcomes and related trials?

QUESTION #42: Representing the clinical landscapes of interventional cardiology and atherosclerosis prevention/lipid management, the two of you manage a broad spectrum of "clinical signatures" amenable to PCSK9-based intervention. Can you discuss the clinical axes that will help you identify the "progressing patients" with high CV risk in whom PCSK9 therapy represents a game-changing strategy?

QUESTION #43: What other markers, besides LDL-C levels, do you believe we should consider to refine CV risk stratification?