FROM LANDMARK CV OUTCOME TRIALS to the FRONT LINES of ASCVD RISK REDUCTION

Global Authorities in **Medical and Preventive Cardiology, Lipid Medicine and Atherosclerosis Prevention, and Diabetes Management** 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 Prevention and Treatment for ASCVD

Year 2019 Best Practice, Case-Based and Guideline-Driven Update for Medical and Preventive Cardiology, Lipid Medicine and Atherosclerosis Prevention, and Diabetes Management

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INTERVENTIONAL CARDIOLOGY

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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?

Shaun Goodman, MD, MSc, FRCPC, FACC, FESC, FAHA

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Professor, Department of Medicine
University of Toronto
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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?

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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?

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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?

J. Wouter Jukema, MD, PhD, FESC, FACC MC

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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?

Phillipe Gabriel Steg, MD

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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?

Ulf Landmesser MD, FESC

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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?

Professor Andreas Zeiher, MD

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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?

Deepak L. Bhatt, MD, MPH

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and

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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?

MEDICAL AND PREVENTIVE CARDIOLOGY

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QUESTION #44: In the setting of secondary post-ACS prevention, what is your trigger for moving beyond a statin/ezetimibe combination to a PCSK9 inhibitor?

QUESTION #45: Given the new AHA Guidelines and the anticipation of new ESC Guidelines in 2019, what is your view about LDL-C level target thresholds vs. degree of LDL-C reduction? What level do you consider optimal in high-risk patients with progressive ASCVD?

QUESTION #46: Does the presence of a stent in the setting of ACS color your approach to the degree of LDL-C reduction you would pursue?

QUESTION #47: Can you share with us a specific patient who has had an ACS event and is post-PCI, and how you optimize CV risk reduction in the age of PCSK9-mediated LDL-C risk reduction and aggressive LDL-C lowering?

QUESTION #48: What are the current challenges and protocols in Europe for making PCSK9 inhibitors an easily reimbursable, "mainstream" approach to managing patients with require secondary prevention for their high-risk ASCVD?

QUESTION #49: What is the current unmet need for CV risk reduction, in general, beyond LDL-C level lowering?

Christie M. Ballantyne, MD

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Methodist DeBakey Heart Center
Chief of the Section of Cardiovascular Research
Baylor College of Medicine
Director of Atherosclerosis Laboratory
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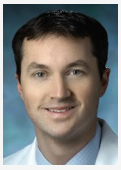
QUESTION #50: How should the most recent 2018 AHA Guidelines for LDL-C that specify specific target levels for high risk patients impact our approach to selecting therapies—including PCSK9 inhibitors—that have the potential to lower LDL-C to threshold levels far lower than those recommended by the Guidelines?

QUESTION #51: A confluence of important events—new AHA guidelines, trial reports, and publications (ODYSSEY Outcomes), and price reductions—has reshaped the accessibility, evidence basis, and actionability profile for PCSK9 inhibitors. As a lipidologist, ACS, and atherosclerosis specialist, how have these developments changed the equation and shaped your approach to CV risk reduction with these agents; and, importantly, identification of appropriate patients who stand to benefit for this therapeutic strategy?

QUESTION #52: Although the AHA Guidelines identify a 70 mg/dL threshold target for patients at high risk for recurrent ACS, do you believe this is merely a "starting point" identifying a minimal level of LDL-C goal attainment; and, that to really optimize outcomes, specialists should push to much lower LDL-C targets? How do the ODYSSEY Outcomes and FOURIER studies help us sort this out?

QUESTION #53: From a patient-centric, clinical profile perspective, which "high risk burden" patient populations do you, as an atherosclerosis specialist, single out for PCSK9-mediated LDL-C reduction?



Michael J. Blaha, MD, MPH

Director of Clinical Research
Ciccarone Center for the Prevention of Heart Disease
Associate Professor of Medicine
Johns Hopkins School of Medicine
Baltimore, MD

QUESTION #54: What should the "threshold" of 70 mg/dL identified in the AHA Guidelines mean to the medical or preventive cardiologist in his/her aspiration to optimize CV risk reduction in high-risk patients with a history of ACS or related high-risk features?

QUESTION #55: Which patients, in your view, based on the ODYSSEY Outcomes and FOURIER trials, do you want to drive below the LDL-C "threshold" of 70 mg/dL? What is your rationale and how do you select your patients and achieve your targets in the real world?

QUESTION #56: Given the new guidelines, price reductions with alirocumab and evolocumab, and the reduction in associated all-cause mortality reported with alirocumab in ODYSSEY Outcomes, which patients at the front lines of cardiology practice should now be embraced as plausible candidates for PCSK0-mediated CV risk reduction?

QUESTION #57: How do you approach younger patients with known, advanced subclinical atherosclerosis?

Michael H. Davidson, MD, FACC, FACP, FNLA

Clinical Professor
Director of Preventive Cardiology
The University of Chicago Hospitals and Clinic
Pritzker School of Medicine
Chicago, Illinois

QUESTION #58: With the exciting results of the ODYSSEY Outcomes Trial and the much more attractive pricing for PCSK9 inhibitors, including alirocumab and evolocumab, how do you now see the landscape for this therapy, especially in the context of the lipid medicine and atherosclerosis specialist and the preventive cardiology setting?

QUESTION #59: With the ODYSSEY Outcomes Trial's favorable pharmacoeconomic analysis now established—and a reduction in all-cause mortality with alirocumab—from the perspective of the lipid and atherosclerosis specialist, where do you see the evidence-based opportunities for these agents in your practice setting? Which patients at what LDL-C level?

QUESTION #60: As you point out, the PCSK9 trials have now confirmed (a) the absence of a J-point curve for LDL-C lowering and (b) continuing CV risk reduction, even when lowering LDL-C from, let's say, 100 mg/dL to 30 mg/dL. In light of this, how and in whom should the lipid specialist deploy a PCSK9 inhibitor, even though practice guidelines have not yet weighed in on this evidence for aggressive LDL-C lowering within the so-called "acceptable, guideline-consistent" target range?

QUESTION #61: You have introduced the concept of "progressive atherosclerotic burden" to characterize the multiplicity of biologic, metabolic, and clinical markers that inform a patient's global CV risk profile. How should your colleagues apply this concept of "aggregated risk" to their perspectives about patient selection for treatment with PCSK9 inhibitors?

QUESTION #62: From a lipid specialist's perspective, do the results from the ODYSSEY Outcomes Trial suggest the need to be more focused on achieving absolute target levels of LDL-C or relative percentage reductions in LDL-C levels, irrespective of the final absolute level?

Sergio Fazio, MD

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QUESTION #63: Given the reduction in both CV outcomes and associated, all-cause mortality, are the LDL-C thresholds currently recommended by the AHA and ESC low enough, and what are the implications for PCSK9-mediated CV risk reduction?

QUESTION #64: In your mind, as a Director of a Lipid Clinic and Preventive Cardiology Center, how do you apply the results of the ODYSSEY Outcomes and other trials in terms of the lack of safety signals when lowering LDL-C to levels < 50 mg/dL?

QUESTION #65: What is your personal experience deploying PCSK9 inhibitors in your preventive cardiology clinic, and what are the most reliable and actionable triggers for deploying this injectable program for CV risk reduction? And predictably achieving reimbursement and payor support for this therapy? What are your strategies for ensuring insurance coverage?

QUESTION #66: From a lipid medicine and preventive cardiovascular perspective, how do you triage the diabetic patient with ACS into a PCSK9-based treatment strategy for LDL-C reduction?

QUESTION #67: Do you use different LDL-C levels in persons with diabetes to justify initiation of PCSK9 inhibitors? Is the presence of ACS required or symptomatic ASCVD required to triage them into PCSK9-based treatment?

QUESTION #68: What does the pharmacoeconomic landscape currently look like for PCSK9 inhibition, especially in light of the recent price reductions for alirocumab and evolocumab?

Keith A.A. Fox, MBChB, FRCP, FMedSci

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QUESTION #69: As an interventional cardiologist in the UK, what do the results from the ODYSSEY Outcomes Trial and price reductions mean to the clinician at the front lines of cardiology care as far as access to and triggers for deploying a PCSK9 inhibitor?

QUESTION #70: Although 70 mg/dL is the target threshold identified by both ESC and AHA, should the interventionalist, in a patient who has just undergone a PCI and has an LDL-C of 69 mg/dL, be considered adequately CV risk-mitigated? Or is this a patient in whom a PCSK9 inhibitor or some other agent should be considered to provide additional lowering of LDL-C?

QUESTION #71: How should the fact that CV risk is not binary, but progressive, influence the decision to use a PCSK9 inhibitor?

Samuel Z. Goldhaber, MD

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Director, Thrombosis Research Group
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QUESTION #72: From a medical cardiologist's perspective with an expertise in both atherosclerotic heart disease and thrombosis medicine, why is the mandate to lower LDL-C level so foundationally important for reducing cardiovascular risk? And how low do recommend lowering the LDL-C level? Where do the PCSK9 inhibitors fit into the overall sequencing strategy?

QUESTION #73: At your institution, do you experience any significant barriers to having prescriptions authorized for either alirocumab or evolocumab? And how have the price reductions affected either your perception of, access to, and/or reimbursement for these agents?

QUESTION #74: The ODYSSEY Outcomes Trial has shown the potential of PCSK9 inhibitors to reduce associated all-cause mortality in high-risk patients, especially in those with elevated LDL-C levels, as well as to safely lower LDL-C levels to "ultra-low" levels <50 mg/dL, accompanied by progressive CV risk reduction. As a thrombosis specialist and cardiologist, how do respond to the recent AHA guidelines identifying <70 mg/dL as a threshold target for high-risk patients? Is this target a starting point or a stopping point for your LDL-C lowering goals?

QUESTION #75: Based on the results of ODYSSEY Outcomes and FOURIER, do you recommend that clinicians strive, in selected high-risk populations, to lower LDL-C significantly lower than 70 mg/dL? And how has the reduced cost of PCSK9 inhibitors affected your perception of their cost-effectiveness at the front lines of cardiology practice?

QUESTION #76: Can you provide some specific examples of patients in your general cardiology practice in whom you have prescribed PCSK9 inhibitors and your rationale and the evidentiary basis for doing so? When does statin intolerance play a role? How does a recurrent ACS event in a patient with a low LDL-C level influence your strategy? The presence of PAD?

J. Wouter Jukema, MD, PhD, FESC, FACC MC

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Shaun Goodman, MD, MSc, FRCPC, FACC, FESC, FAHA

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Stephen J. Nicholls, MD

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QUESTION #90: Now, with the publication of ODYSSEY Outcomes, which demonstrated an associated, all-cause mortality reduction benefit, how do you view the foundational role of PCSK9 inhibitors in the CV risk treatment plan for high-risk patient populations?

QUESTION #91: Given the results of outcome trials like ODYSSEY, FOURIER, and others, as a lipid/atherosclerosis specialist what is your take home about what the appetite should be for using PCSK9 inhibitors to lower LDL-C levels beyond ESC and AHA recommended thresholds of 70 mg/dL?

QUESTION #92: In which of your patients with FH do you feel PSCK9 inhibitors will become foundational agents, in conjunction with statins, when tolerated?

QUESTION #93: In your lipid practice, which patients with ASCVD—especially those with a clinical signature suggestive of progressive disease—do you prioritize for PCSK9-mediated lowering of LDL-C? Based on ODYSSEY Outcomes, what do we know about the subgroup of post-ACS patients who benefited most from alirocumab?

QUESTION #94: Considering that younger persons are vulnerable to carrying a lifelong atherosclerosis burden when their LDL-C levels are elevated, how to do approach them management-wise?

QUESTION #95: As a lead investigator for both FH and ASCVD-focused trials evaluating PCSK9 inhibitors, what is your interpretation of the data confirming excellent regimen adherence and compliance with these injectable agents? And your personal experience in the clinic?

QUESTION #96: What change in clinical practice, based on the all-cause mortality reduction reported in ODYSSEY Outcomes, do you believe is warranted, especially as these results might impact the level of LDL-C that should be targeted and the duration of therapy with PCSK9 inhibitors?

Paul Ridker, MD,

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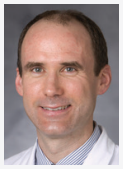
QUESTION #97: As a leading investigator and authority in the world of LDL-C-mediated CV risk reduction, can you provide us with your perspective on the evidence basis for PCSK9 inhibitors as a foundational approach for managing a broad spectrum of patients with high risk coronary heart disease? And how do the results of the ODYSSEY Outcomes Trial corroborate the efficacy and safety of this clinical strategy?

QUESTION #98: From your perspective as the Director of the Center for Cardiovascular Disease Prevention, what patient types and clinical signatures on the risk landscape of ASCVD do you believe deserve special attention because they are likely to be eligible candidates for PCSK9-mediated LDL-C reduction? Which patients—the "progressors," as you call them—should we worry about?

QUESTION #99: Based on the results of the ODYSSEY Outcomes Trial, which biological/metabolic risk markers—LDL-C > 100 mg/dL or elevated Lp(a), for example—in the setting of what kind of clinical features (recent ACS, recurrent events, diabetes, etc.) do you feel that medical cardiologists and atherosclerosis specialists should strive to achieve LDL-C levels that are even more aggressive than the thresholds identified in the recent AHA Guidelines?

QUESTION #100: You have identified the challenges of accessing PCSK9 inhibitors for patients whose CV risk is linked to genetic factors vs. those whose clinical course is characterized by progressive, recurrent vascular events. How do you approach each subset with respect to LDL-C management?



Matthew T. Roe, MD

Professor of Medicine
Duke Clinical Research Institute
Duke University School of Medicine
Durham, NC

QUESTION #101: How do you see the benefit/safety risk equation shaping up for PCSK9 inhibitors based on the FOURIER and, most recently, the ODYSSEY Outcomes Trial?

QUESTION #102: In your practice, how do you stratify your patients with known ASCVD to determine their eligibility for PCSK9 inhibitors, and are there some patients that you would characterize as ultra-high risk and, therefore, requiring LDL-C lowering to less than 70 mg/dL?

QUESTION #103: From a safety perspective how do you counsel your patients in whom you are beginning PCSK9 inhibitor therapy?

QUESTION #104: Are you finding it easier to get authorization for reimbursement and approval of PCSK9 inhibitors now that prices have come down and we have seen clear outcome benefits in both major trials, and reduction in associated, all-cause mortality in ODYSSEY Outcomes?

QUESTION #105: Do you have any safety concerns about driving LDL-C levels to less than 50 mg/dL with PCSK9 inhibitors?

Robert S. Rosenson, MD

Professor of Medicine (Cardiology)
Mount Sinai Icahn School of Medicine
Director, Cardiometabolics Unit
Mount Sinai Heart Institute
New York, NY

QUESTION #106: From a medical cardiologist's perspective, which patient subgroups in your practice do you feel represent ideal candidates for deployment of PCSK9 inhibitors to lower LDL-C levels, based on the results of the ODYSSEY Outcomes and FOURIER Trials?

QUESTION #107: Based on your analysis of the ODYSSEY Outcomes Trial, and specifically the low LDL-C levels that were achieved in this trial without adverse consequences, what target level of LDL-C do you recommend in medically managed patients with moderate-to-high risk features of ASCVD? As low as 50 mg/dL? On what evidentiary basis?

QUESTION #108: Within the context of a medical cardiology practice, especially navigating among patients with inadequate responses to ezetimibe and/or statin intolerance or resistance, how do you sequence PCSK9 inhibitors in your LDL-C lowering treatment plans, and how do apply the ICER recommendations given the new data and price reductions for PCSK9 inhibitors?

QUESTION #109: How do you interpret the favorable finding of the reduction in associated overall mortality seen with alirocumab in The ODYSSEY Outcome Trial as compared to the lack of such findings—at least at this point in the analysis, prior to reporting results for the planned extension phase in the FOURIER Trial—for the evolocumab trial?

QUESTION #110: Assuming optimization of patient outcomes, rather than cost, is the primary driver governing appropriate use of PCSK9 inhibitors, which patients in the context of a medical cardiology practice would you single out for this therapy, and to achieve what LDL-C target levels, based on the results of the ODYSSEY Outcomes Trial? Have the results of this trial—especially the "very low LDL-C analysis"—increased your appetite for lower LDL-C targets with alirocumab?

QUESTION #111: As shown in the ODYSSEY Outcomes Trial, alirocumab also lowers Lp(a). FOURIER also demonstrated similar results with evolocumab. What are the clinical implications of these findings and how do you translate the results into medical cardiology practice?

QUESTION #112: Assuming the community cardiologist is able to obtain reimbursement for PCSK9 inhibitors, in what segment of your patient population do you think this therapy is most under-utilized? What is your selection process? And how do the price reductions for these agents affect your approach?

QUESTION #113: How do you recommend managing the patient who has a major cardiovascular/thrombotic event—a recent MI—who is on a statin and has an LDL-C level of 60 -70 mg/dL? How does the ODYSSEY Outcome Trial and/or IVUS studies help you assess the role of a PCSK9 inhibitor in such post-ACS patients, and what would your therapeutic objectives be?

QUESTION #114: In the setting of a medical cardiology practice, to what extent is statin-induced muscle intolerance an important cause of poor statin adherence, increased healthcare costs, and increased cardiac event rates? You have studied this clinical problem in great depth, so what counsel can you offer to appropriately stratify and re-challenge these patients with alternative statins? And what is the role, evidence, and rationale for PCSK9 inhibitors in this significant population with statin muscle intolerance?

QUESTION #115: What percentage of patients have confirmed statin muscle intolerance based on the criteria and re-titration protocols you and your colleagues have developed? And why does there appear to be a disconnect between the significant prevalence of statin muscle intolerance in cardiology practice vs the results reported in major trials? Are PCSK9 inhibitors the answer to statin down-titration and the associated increase risk of MI?

QUESTION #116: Why is down-titration from a high-intensity statin dose potentially problematic, and what are the pragmatic implications as they relate to PCSK9 inhibitor use in patients who cannot achieve optimal CV reduction with statin therapy?

Christian Ruff, MD

Principal Investigator, ENGAGE-AF Trial
TIMI Group
Director, General Cardiology
Brigham and Women's Hospital
Assistant Professor of Medicine
Harvard Medical School

QUESTION #117: Although the ODYSSEY Outcomes Trial reports that post-ACS patients with starting LDL-C levels greater than 100 mg/dL benefited most, relatively speaking, from alirocumab-mediated LDL-C reduction, you and others have noted the importance of assessing "aggregate risk" when identifying triggers for PCSK9-based therapy? Can you discuss this and provide a clinical roadmap for the medical cardiologist?

QUESTION #118: In your framing of "aggregate ASCVD risk" as a stimulant to extremely aggressive LDL-C lowering, what clinical signature, in your view, should compel the general cardiologist to translate the results with alirocumab in ODYSSEY Outcomes to the front lines of practice?

QUESTION #119: You have noted that 70 mg/dL is the "AHA Guideline" threshold for the LDL-C level in high-risk patients, but when in your view is more aggressive lowering to levels such as those observed in the ODYSSEY Outcomes and FOURIER trials justified?

QUESTION #120: How have the trifecta of recent developments—associated, all-cause mortality reduction reported in ODYSSEY Outcomes, price reduction of PCSK9 inhibitors, and new AHA Guidelines—affected your approach to deploying these agents at the front lines of medical cardiology practice?

Freek W A Verheugt, MD, PhD

Professor of Cardiology
Chairman of the Department of Cardiology
Heartcenter of the University Medical Center
Nijmegen, The Netherlands

QUESTION #121: As the cost and institutional barriers to deploying PCSK9 inhibitors become less onerous, which patients in a medical cardiology practice represent the most attractive candidates for these agents and their profound LDL-C lowering effects?

QUESTION #122: Based on the ODYSSEY Outcomes Trial, which enrolled primarily patients with post-ACS, which subset of patients managed in a medical cardiology practice should be thoroughly evaluated for CV risk reduction benefits accruing to PCSK9 inhibitors?

QUESTION #123: From your perspective as a medical cardiologist, what impact should the reductions in associated overall mortality reported with alirocumab in the ODYSSEY Outcomes Trial have on selecting a PCSK9 inhibitor? And in what patient segment, particular, should we apply this evidence?

QUESTION #124: What would your approach be to a 57-year-old man with an LDL-C of 70 mg/dL who has recently had an ACS event and now develops recurrent ACS, or a new stent thrombosis? Does the ODYSSEY Outcomes Trial provide any evidence-based guidance?

QUESTION #125: How have the results of the ODYSSEY Outcomes Trial—especially as they relate to progressive CV risk reductions in patients with initially high LDL-C levels who achieve target levels of 50 mg/dL or less—support the "treat-to-target" approach to lipid management?

QUESTION #126: In the subpopulation of high-risk patients you described earlier—individuals with post-ACS, patients with diabetes, post-PCI and others—is there enough compelling evidence from the PCSK9 trials that the "LDL hypothesis" is a proven fact, and that we should therefore be lowering LDL-C levels to extremely low levels (< 50 mg/dL or lower) in selected patients?

R. Scott Wright, MD

Professor of Medicine
Department of Cardiovascular Medicine
Cardiovascular Division
Mayo Clinic

QUESTION #127: From a medical cardiologist's perspective, how do the threshold-setting targets of LDL-C levels of 70 mg/dL apply to PCSK9-based treatment for CV risk reduction? And did the guidelines emphasize sufficiently, the results of the CV outcome trials such as ODYSSEY Outcomes, IMPROVE-IT, and FOURIER?

QUESTION #128: Since ODYSSEY Outcomes demonstrated not only a reduction in adverse CV outcomes—as well as a decrease in associated, all-cause mortality—in post-ACS patients achieving LDL-C levels <70mg/dL, what is your view on treating with alirocumab—or other agents, including statin or ezetimibe—to push LDL-C levels to even lower levels than the 70 mg/dL threshold?

QUESTION #129: What are the risks of failing to lower LDL-C levels to AHA- or ESC Guideline-mandated thresholds?

QUESTION #130: As a medical cardiologist treating patients for secondary prevention of ASCVD, can you share with us the outcomes and disease course of patients you have managed with PCSK9 inhibitors? Has the cost reductions affected your appetite for these agents?

QUESTION #131: How do you view the lack of current safety signals encountered in CV outcome trials with PCSK9 inhibitors? What are the implications for lifelong use of these agents?

QUESTION #132: Have studies been done looking at PCSK9 inhibitors as monotherapy in post-ACS patients with elevated LDL-C levels?

QUESTION #133: How do you recommend that clinicians directly and immediately apply the results of the CV outcome trials with alirocumab and evolocumab directly to the front lines of medical cardiology practice?

QUESTION #134: As a program director with a broad mandate to improve quality of CV care in patients with ACS, diabetes, and lipid disorders, how do you see role of PCSK9 inhibitors in the four subspecialty groups—interventional cardiologists, medical/preventive cardiologists, lipidologists/ASCVD, and diabetes specialists—who manage high-risk patients requiring LDL-C lowering to optimize the CV risk profile? What specific LDL-C targets do you recommend?

QUESTION #135: How do you see the future of access, affordability, and general utilization of PCSK9 inhibitors as a result of the price reductions and results from CV outcome trials?

QUESTION #136: What is the true incidence of statin intolerance and how do you diagnose it? And what is your approach to re-challenge and titration with other statins? How many do you try? And where do alirocumab and evolocumab fit into the statin intolerance treatment plan?

LIPID MEDICINE AND ATHEROSCLEROSIS

Christie M. Ballantyne, MD

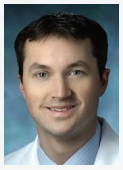
Director, Center for Cardiovascular Disease Prevention
Methodist DeBakey Heart Center
Chief of the Section of Cardiovascular Research
Baylor College of Medicine
Director of Atherosclerosis Laboratory
Professor of Medicine
Baylor College of Medicine
Houston, TX

QUESTION #137: How should the 2018 AHA Guidelines for LDL-C that specify target levels for high risk patients impact our approach to selecting therapies—including PCSK9 inhibitors—that have the potential to lower LDL-C to levels far lower than those recommended?

QUESTION #138: A confluence of events has reshaped the accessibility, evidence basis, and actionability profile for PCSK9 inhibitors. As an atherosclerosis specialist, how have these developments changed the equation and shaped your approach to CV risk reduction?

QUESTION #139: Although the AHA Guidelines identify a 70 mg/dL threshold target for patients at high risk for recurrent ACS, do you believe this is merely a "starting point" identifying a minimal level of LDL-C goal attainment?

QUESTION #140: From a patient-centric, clinical profile perspective, which "high risk burden" patient populations do you, as an atherosclerosis specialist, single out for PCSK9-mediated LDL-C reduction?



Michael J. Blaha, MD, MPH

Director of Clinical Research
Ciccarone Center for the Prevention of Heart Disease
Associate Professor of Medicine
Johns Hopkins School of Medicine
Baltimore, MD

QUESTION #141: What should the "threshold" of 70 mg/dL identified in the AHA Guidelines mean to the medical or preventive cardiologist in his/her aspiration to optimize CV risk reduction in high-risk patients with a history of ACS or related high-risk features?

QUESTION #142: Which patients, in your view, based on the ODYSSEY Outcomes and FOURIER trials, do you want to drive below the LDL-C "threshold" of 70 mg/dL? What is your rationale and how do you select your patients and achieve your targets in the real world?

QUESTION #143: Given the new guidelines, price reductions, and the reduction in associated all-cause mortality reported with alirocumab in ODYSSEY Outcomes, which patients should now be embraced as plausible candidates for PCSK9-mediated CV risk reduction?

QUESTION #144: How do you approach younger patients with known, advanced subclinical atherosclerosis?

Alberico Catapano, PhD

Full Professor of Pharmacology
University of Milano
Director, Laboratory for the Study of Lipoproteins and Atherosclerosis
Director, Center for the Study of Atherosclerosis of the Italian Society of Atherosclerosis
Bassini Hospital
Director, Center of Epidemiology and Preventive Pharmacology
University of Milano (SEFAP)
Immediate Past President, European Atherosclerosis Society (EAS)
Milan, Italy

QUESTION #145: How have recent PCSK9 trials affected your position on the role of intensifying LDL-C reductions to new target levels, and how are they likely to affect future global/ESC 2019 guidelines for LDL-mediated CV risk reduction?

QUESTION #146: In light of the effectiveness and safety in post-ACS patients of the "ultra-low" levels of LDL-C achieved in the ODYSSEY Outcomes and FOURIER Trials, how has that shaped your clinical perspective on the role of PCSK9 inhibitors in high-risk patients?

QUESTION #147: From the perspective of a lipid and atherosclerosis specialist, assuming that the barriers to PCSK9 inhibitors are reduced, which patients at risk for—or with confirmed—ASCVD represent the best, risk-directed candidates for LDL-C lowering?

QUESTION #148: Which patient subgroups that, based on the Odyssey Outcomes Trial, could benefit significantly from a PCSK9 inhibitor, in your observation, are not getting treatment consistently enough—i.e. are being "under-treated"—with these agents?

QUESTION #149: In patients requiring down-titration of their statins due to muscle discomfort/pain, what is the trigger point for moving beyond statins to consider PCSK9 inhibitors?

QUESTION #150: Can you cite specific patient types where you are strongly inclined to use a PCSK9 inhibitor because achieving both significant percentage-based reductions in LDL-C level as well as achieving an LDL-C level <70mg/dL are of critical importance?

QUESTION #151: Given what we know about the safety of PCSK9 inhibitors and the risk of recurrent events in patients who have experienced an ACS, are there any risk signatures that compel a lipid specialist to consider using a PCSK9 inhibitor early in the patient's course?

QUESTION #152: Where did the 70 mg/dL LDL-C target goal come from? Why wasn't it set lower in the guidelines from the outset for patients with ACS?

QUESTION #153: How are your 2019 ESC/EAS guidelines going to be influenced by recent RCTs, including ODYSSEY Outcomes and FOURIER?

QUESTION #154: What specific LDL-C-related endpoints are likely to undergo review and revisions based on the publication of two PCSK9-related trials, ODYSSEY Outcomes and FOURIER?

QUESTION #155: Should lipidologists consider other markers such as apoB as well as LDL-C for reducing CV risk in diabetes and hypertriglyceridemia?

QUESTION #156: From a lipid medicine and atherosclerosis expert's perspective, when you look at the ODYSSEY Outcomes and Fourier Trials, what consistent or comparative message do you take from these investigations into the safety and efficacy of PCSK9 inhibitors?

Michael H. Davidson, MD, FACC, FACP, FNLA

Clinical Professor
Director of Preventive Cardiology
The University of Chicago Hospitals and Clinic
Pritzker School of Medicine
Chicago, Illinois

QUESTION #157: With the results of ODYSSEY Outcomes and the more attractive pricing for PCSK9 inhibitors, how do you now see the landscape for this therapy, especially in the context of the lipid medicine/atherosclerosis specialist and the preventive cardiologist?

QUESTION #158: With the ODYSSEY Outcomes Trial's favorable pharmacoeconomic analysis now established—and a reduction in all-cause mortality with alirocumab— where do you see the evidence-based opportunities for these agents in your practice setting?

QUESTION #159: The PCSK9 trials have confirmed (a) the absence of a J-point curve for LDL-C lowering and (b) continuing CV risk reduction, even when lowering LDL-C from 100 mg/dL to 30 mg/dL. In light of this, how should the lipid specialist deploy PCSK9 inhibitors?

QUESTION #160: You have introduced the concept of "progressive atherosclerotic burden" to characterize the multiplicity of biologic, metabolic, and clinical markers in a CV risk profile. How do you apply this "aggregated risk" to patient selection for PCSK9 inhibitors?

QUESTION #161: From a lipid specialist's perspective, do the results from the ODYSSEY Outcomes Trial suggest the need to be more focused on achieving absolute target levels of LDL-C or relative percentage reductions in LDL-C levels?

Stefano Del Prato, MD PhD

Professor of Endocrinology and Metabolism
School of Medicine, University of Pisa
Chief of the Section of Diabetes
University of Pisa, Italy
Clinical Associate Professor of Medicine
University of Texas, San Antonio Health Science Center
San Antonio, TX

QUESTION #162: In the setting of secondary prevention for patients with diabetes, the role of LDL-C has special significance. How do you view the importance for the of PCSK9 inhibitors, therefore, specifically for reducing residual CV risk in the T2D population?

QUESTION #163: Given that ODYSSEY Outcomes has shown not only reduction in CV events, but also a reduction in associated, all-cause mortality, what is the role of PCSK9 inhibitors in diabetes patients with a prior ACS event?

QUESTION #164: In the Type 2 diabetes population that you manage in your, what percentage of patients do you estimate do not achieve risk-appropriate LDL-C for any number of reasons? Is it as high as 10%, as reported in by some diabetes experts?

QUESTION #165: Can you paint the profile of the post-ACS patient with T2D in whom the aggregate CV risk exceeds a threshold that supports a strategy of PCSK9-mediated LDL-C reduction in order to achieve levels of less than 70 mg/dL; or, even less than 50 mg/dL?

QUESTION #166: Do you see safety signals associated with ultra-aggressive LDL-C lowering and what is the role of PAD as a risk factor guiding LDL-C reduction?

Sergio Fazio, MD

Director, Center for Preventive Cardiology
Professor of Medicine
Division of Cardiovascular Medicine
School of Medicine
Oregon Health Sciences University (OHSU)
Portland, OR

QUESTION #167: Given the reduction in both CV outcomes and associated, all-cause mortality, are the LDL-C thresholds currently recommended by the AHA and ESC low enough, and what are the implications for PCSK9-mediated CV risk reduction?

QUESTION #168: In your mind, as a Director of a Lipid Clinic and Preventive Cardiology Center, how do you apply the results of the ODYSSEY Outcomes and other trials in terms of the lack of safety signals when lowering LDL-C to levels < 50 mg/dL?

QUESTION #169: What is your experience deploying PCSK9 inhibitors in the clinic, and what are the most reliable and actionable triggers for deploying this program for CV risk reduction? And predictably achieving reimbursement and payor support for this therapy?

QUESTION #170: From a lipid medicine and preventive cardiovascular perspective, how do you triage the diabetic patient with ACS into a PCSK9-based treatment strategy for LDL-C reduction?

QUESTION #171: Do you use different LDL-C levels in persons with diabetes to justify initiation of PCSK9 inhibitors? Is the presence of ACS required or symptomatic ASCVD required to triage them into PCSK9-based treatment?

QUESTION #172: What does the pharmacoeconomic landscape currently look like for PCSK9 inhibition, especially in light of the recent price reductions for alirocumab and evolocumab?

Keith A.A. Fox, MBChB, FRCP, FMedSci

Professor, University of Edinburgh
Department of Cardiovascular Medicine
Professor, University and Royal Infirmary
Edinburgh, United Kingdom

QUESTION #173: As an interventional cardiologist in the UK, what do the results from the ODYSSEY Outcomes Trial and price reductions mean to the clinician at the front lines of cardiology care as far as access to and triggers for deploying a PCSK9 inhibitor?

QUESTION #174: Although 70 mg/dL is the target threshold identified by both ESC and AHA, should the interventionalist, in a patient who has just undergone a PCI and has an LDL-C of 69 mg/dL, be considered adequately CV risk-mitigated?

QUESTION #175: How should the fact that CV risk is not binary, but progressive, influence the decision to use a PCSK9 inhibitor?

Anne C. Goldberg, MD, FNLA, FACP, FAHA

Professor of Medicine
Division of Endocrinology, Metabolism & Lipid Research
Washington University in St. Louis
St. Louis, MO

QUESTION #176: From the perspective of a lipid medicine specialist, how do the results of the now-published ODYSSEY Outcomes Trial, and related trials, help you select patients for PCSK9-mediated LDL-C reduction? And what targets do you advocate?

QUESTION #177: From a lipid specialist perspective, how do you navigate the risk territory of LDL-C levels <70 mg/dL?

QUESTION #178: From a lipid specialist perspective, how do you navigate the risk territory of LDL-C levels <70 mg/dL with PCSK9 inhibitors? And in which patient subgroups do these agents offer unique outcome-related benefits?

QUESTION #179: What are the specific patient types that you manage in your lipid-focused practice and which are referred to you for potential intervention with a PCSK9 inhibitor? Why are these patients being referred to you for PCSK9-mediated LDL-C reduction?

QUESTION #180: Why are patients who should clearly be on a PCSK9 inhibitor not being treated in the primary cardiology setting, but rather seeking and obtaining this treatment in the lipid clinic environment?

QUESTION #181: To what degree have you observed statin intolerance or resistance in patients with high risk CAD? What protocol do you employ to mitigate and/or manage statin intolerance? Where does the PCSK9 inhibitor fit into your sequencing strategy?

QUESTION #182: When is 70 mg/dL not good enough? Is this a threshold? What clinical factors suggest lower targets are better? What is happening at the vascular biology level?

QUESTION #183: In the lipid clinic setting, in patients you have treated with PCSK9 inhibitors, what are you finding as far as regimen adherence, toleration, and patient engagement/satisfaction with these injectable strategies?

QUESTION #184: Which patients, in your view, are not candidates for PCSK9 inhibition?

QUESTION #185: How should the lipid specialist approach the individual with diabetes who doesn't yet have ASCVD?

J. Wouter Jukema, MD, PhD, FESC, FACC MC

Professor of Cardiology
Netherlands Heart Foundation
Chairman, Leiden Vascular Medicine
Leiden University Medical Center (LUMC)
Leiden, Netherlands

QUESTION #186: From your perspective as an IC and lipid medicine specialist, in light of the results showing a reduction in associated all-cause mortality in ODYSSEY Outcomes, which patients deserve our attention to optimize the translational impact of this study?

QUESTION #187: Since both PCSK9 outcome trials demonstrated impressive safety when LDL-C levels are lowered into ranges much lower than 70 mg/dL, what should be the approach of the interventional and medical cardiologist to achieving LDL-C levels in this range?

QUESTION #188: As an IC, you are seeing post-ACS/post-PCI patients whose atherosclerotic disease burden is exceptional and potentially amenable to PCSK9-mediayed CV risk reduction. Where is your specific focus for using these agents in this population?

QUESTION #189: What has been your experience with respect to patient satisfaction, discontinuation rates and toleration of this injection-based approach to LDL-C management?

QUESTION #190: Although the AHA Guidelines emphasize CV risk and mortality reductions with statins, ODYSSEY Outcomes provides comparable evidence for alirocumab. How compelling is the evidence for PCSK9 inhibition as a mediator of CV risk and mortality reduction?

Lawrence A. Leiter, MD, FRCP(C), FACP

Head, Division of Endocrinology and Metabolism
Director, Lipid Clinic
Associate Director, Clinical Nutrition and Risk Factor Modification Centre
St. Michael's Hospital
Professor, Medicine and Nutritional Sciences
University of Toronto
Toronto, Ontario, Canada

QUESTION #191: What is the rationale for a new category called "extreme risk," introduced by AACE in which they designate a threshold LDL-C target of 55 mg/dL?

QUESTION #192: What is your analysis of the two major CV outcome trials and from a mortality end point perspective in what way do mortality outcome end points/results distinguish the ODYSSEY Outcomes Trial with alirocumab?

QUESTION #193: What is the profile of the diabetic patient in whom the diabetes specialist should strongly consider the LDL-C lowering and outcome-improving effects of PCSK9 inhibitors? How do we risk stratify populations for secondary prevention?

QUESTION #194: How large is the subgroup of diabetic patients who you feel are likely to appropriate candidates for PCSK9 inhibition to optimize CV risk reduction? And how does the lack of a safety signal influence your recommendations for this group?

Stephen J. Nicholls, MD

SAHMRI Deputy Director and Heart Foundation Heart Health Theme Leader
Professor of Cardiology
University of Adelaide
Consultant Cardiologist
Royal Adelaide Hospital
Adelaide, Australia

QUESTION #195: Now, with the publication of ODYSSEY Outcomes, which demonstrated an associated, all-cause mortality reduction benefit, how do you view the foundational role of PCSK9 inhibitors in the CV risk treatment plan for high-risk patient populations?

QUESTION #196: Given the results of ODYSSEY, FOURIER, and others, as a lipid/atherosclerosis specialist what is your take home about what the appetite should be for using PCSK9 inhibitors to lower LDL-C levels beyond ESC and AHA recommended thresholds of 70 mg/dL?

QUESTION #197: In which of your patients with FH do you feel PSCK9 inhibitors will become foundational agents, in conjunction with statins, when tolerated?

QUESTION #198: In your lipid practice, which patients with ASCVD do you prioritize for PCSK9-mediated lowering of LDL-C? Based on ODYSSEY Outcomes, what do we know about the subgroup of post-ACS patients who benefited most from alirocumab?

QUESTION #199: Considering that younger persons are vulnerable to carrying a lifelong atherosclerosis burden when their LDL-C levels are elevated, how to do approach them management-wise?

QUESTION #200: As a lead investigator for both FH and ASCVD-focused trials evaluating PCSK9 inhibitors, what is your interpretation of the data confirming regimen adherence and compliance with these injectable agents?

QUESTION #201: What change in practice, based on the all-cause mortality reduction reported in ODYSSEY Outcomes, do you believe is warranted, especially as these results might impact the LDL-C level that should be targeted and the duration of therapy?

Paul Ridker, MD,

Eugene Braunwald Professor
Harvard Medical School
Division of Cardiovascular Medicine
Director, Center for Cardiovascular Disease Prevention
Brigham and Women's Hospital
Boston, MA

QUESTION #202: As a leading authority in LDL-C-mediated CV risk reduction, can you provide us with your perspective on the evidence for PCSK9 inhibitors as a foundational approach for managing a broad spectrum of patients with high risk coronary heart disease?

QUESTION #203: As the Director of the Center for Cardiovascular Disease Prevention, what patient types on the risk landscape of ASCVD do you believe deserve special attention because they are likely to be eligible candidates for PCSK9-mediated LDL-C reduction?

QUESTION #204: Based on ODYSSEY Outcomes, for which biological/metabolic risk markers do you feel that cardiologists and atherosclerosis specialists should strive to achieve LDL-C levels even more aggressive than those identified in the AHA Guidelines?

QUESTION #205: You have identified the challenges of accessing PCSK9 inhibitors for patients whose CV risk is genetic vs. those whose clinical course is characterized by progressive vascular events. How do you approach each subset with respect to LDL-C management?

Eric Stroes, MD, PhD

Professor
Department of Vascular Medicine
Academic Medical Center
Amsterdam, The Netherlands

QUESTION #206: From the perspective of a lipid specialist, especially in light of the associated all-cause mortality reductions reported in ODYSSEY Outcomes, how should the clinician be thinking about PCSK9 inhibitors as a tool in their day-to-day practice?

QUESTION #207: How should the lipid and atherosclerosis disease specialist interpret the ESC and AHA Guideline threshold of 70 mg/dL LDL-C level and determine whether even lower levels are even better to mitigate residual CV risk?

QUESTION #208: Can you describe the actual clinical phenotypes—actual patients referred to you by interventional or medical cardiologists—in which PCSK9 inhibition would represent a foundational approach to reduction of residual CV risk burden?

QUESTION #209: From a lipid medicine specialist's perspective, what would your approach be to a post-ACS patient with two stents and triple-vessel disease whose LDL-C level is 70 mg/dL?

QUESTION #210: How vigorous should we be in trying to lower LDL-C in patients who have statin intolerance? What is the role of combined—so-called "backbone"—statin treatment plus PCSK9 inhibitor therapy?

DIABETES MANAGEMENT

Stefano Del Prato, MD PhD

Professor of Endocrinology and Metabolism
School of Medicine, University of Pisa
Chief of the Section of Diabetes
University of Pisa, Italy
Clinical Associate Professor of Medicine
University of Texas, San Antonio Health Science Center
San Antonio, TX

QUESTION #211: In the setting of secondary prevention of patients with diabetes, the role of LDL-C has special significance for the diabetes specialist. How do you view the importance for the diabetes specialist of PCSK9 inhibitors, therefore, specifically for reducing residual CV risk in the T2D population? What LDL-C targets do you recommend for your patients with diabetes?

QUESTION #212: Given that ODYSSEY Outcomes has shown not only reduction in CV events, but also a reduction in associated, all-cause mortality, what is the role of PCSK9 inhibitors in diabetes patients with a prior ACS event?

QUESTION #213: In the Type 2 diabetes population that you manage in your specialty clinic in Europe, what percentage of patients do you estimate do not achieve risk-appropriate LDL-C for any number of reasons? Is it as high as 10%, as reported in by some diabetes experts?

QUESTION #214: Can you paint the clinical profile of the post-ACS patient with T2D in whom the aggregate CV risk exceeds a threshold that you feel supports a strategy of PCSK9-mediated LDL-C reduction in order to achieve levels of less than 70 mg/dL; or, as you suggested, even less than 50 mg/dL?

QUESTION #215: Do you see safety signals associated with ultra-aggressive LDL-C lowering and what is the role of PAD as a risk factor guiding LDL-C reduction?

Vivian A. Fonseca, MD, FRCP

Professor of Medicine and Pharmacology
Tulis-Tulane Alumni Chair in Diabetes
Chief, Section of Endocrinology
Tulane University Health Sciences Center
New Orleans, LA
President, Science and Medicine (2012)
American Diabetes Association (ADA)

QUESTION #216: What is the unmet need for residual CV risk reduction in post-ACS patients with Type 2 diabetes? And In your role as a member of the LDL Guideline Group for AACE, what did you conclude were the implications of treating diabetic patients with so-called "extreme risk"?" And what LDL-C target goal do you recommend—70 mg/dL or 50 mg/dL—in these patients?

QUESTION #217: You have made the case for a call-to-action to treat LDL-C very aggressively in diabetic patients with known ASCVD? What is your rationale for this and how do the ODYSSEY Outcomes and FOURIER Trials support your recommendation to treat diabetics with ASCVD aggressively?

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QUESTION #218: From the perspective of a lipid medicine specialist, how do the results of the now-published ODYSSEY Outcomes Trial, and related trials, help you select patients for PCSK9-mediated LDL-C reduction? And what targets do you advocate?

QUESTION #219: From a lipid specialist perspective, how do you navigate the risk territory of LDL-C levels <70 mg/dL?

QUESTION #220: From a lipid specialist perspective, how do you navigate the risk territory of LDL-C levels <70 mg/dL with PCSK9 inhibitors? And in which patient subgroups do these agents offer unique outcome-related benefits?

QUESTION #221: What are the specific patient types that you tend to manage in your lipid-focused practice and which are referred to you for potential intervention with a PCSK9 inhibitor? Why are these patients, with clear manifestations, markers, and metrics of elevated CV risk, being referred to you for PCSK9-mediated LDL-C reduction?

QUESTION #222: Why are patients who should clearly be on a PCSK9 inhibitor not being treated in the primary cardiology setting, but rather seeking and obtaining this treatment in the lipid clinic environment?

QUESTION #223: To what degree have you, within the context of a lipid clinic setting, observed statin intolerance or resistance in patients with high risk CAD? And what protocol do you employ to mitigate and/or manage statin intolerance? Where does the PCSK9 inhibitor fit into your sequencing strategy?

QUESTION #224: When is 70 mg/dL not good enough? Is this a threshold? What clinical factors suggest lower targets are better? What is happening at the vascular biology level?

QUESTION #225: In the lipid clinic setting, in real world patients you have treated with PCSK9 inhibitors, what are you finding as far as regimen adherence, toleration, and patient engagement/satisfaction with these injectable strategies? How do you motivate patients to adhere to these agents?

QUESTION #226: Which patients, in your view, are not candidates for PCSK9 inhibition?

QUESTION #227: How should the lipid specialist approach the individual with diabetes who doesn't yet have ASCVD?

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QUESTION #228: What is the rationale for a new category called "extreme risk," introduced by AACE in which they designate a threshold LDL-C target of 55 mg/dL?

QUESTION #229: As a diabetes, endocrine, and lipid specialist what is your analysis of the two major CV outcome trials and from a mortality end point perspective in what way do mortality outcome end points/results distinguish the ODYSSEY Outcomes Trial with alirocumab? What did we learn about the subset of patients with diabetes evaluated in this study?

QUESTION #230: What is the profile of the diabetic patient in whom the diabetes specialist, lipidologist, and/or cardiologist should strongly consider the LDL-C lowering and outcome-improving effects of PCSK9 inhibitors? How do we risk stratify populations for secondary prevention?

QUESTION #231: How large is the subgroup of diabetic patients who you feel, for any one or more reasons, are likely to appropriate candidates for PCSK9 inhibition to optimize CV risk reduction? And how does the lack of a safety signal influence your recommendations for this group?

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QUESTION #232: What are the principal concerns related to CV risk reduction in patients with T2D and where does LDL-C lowering with PCSK9 inhibitors fit into the clinical strategy?

QUESTION #233: What did we learn specifically about the population of patients with post-ACS and T2D who were treated with alirocumab in the ODYSSEY Outcomes Trial?

QUESTION #234: Which diabetic patients, in particular, should be prioritized for PCSK9-mediated CV risk reduction?