Focus on the Role of Antisense Oligonucleotides (ASOs) and Emerging Novel Therapies to Achieve LDL Target Goals in FH

Twelve (12) FH Specialists, Cardiologists and Lipidologists Analyze, Answer and Discuss 73 FAQs Addressing Clinical Dilemmas and Therapeutic Advances for Patients with Familial Hypercholesterolemia

**Question # 1:**
What new changes on the treatment landscape for patients with heterozygous FH (HeFH), including antisense technology, should we be focusing on, and how might these novel strategies help achieve LDL level target goals in this difficult-to-manage patient population?

**Question # 2:**
At what LDL levels in a patient with HeFH, would you consider moving beyond statins and second tier adjunctive agents, and deploy a more intensive approach to LDL reduction? What are the triggers?

**Question # 3:**
What risk factors in patients with FH, beyond LDL level alone, indicate a level of risk or disease burden that would justify a more aggressive approach to LDL lowering?

**Question # 4:**
Based on clinical studies, what levels of LDL lowering can we expect with novel, emerging therapies, including the ASO, mipomersen; how it is used, and what is the side effect profile associated with this agent?

**Question # 5:**
What are the key clinical efficacy, mechanistic, and side effect features of mipomersen that the lipidologist and cardiologist should be aware of when managing patients with hyperlipidemia?

**Question # 6:**
What are the advantages of early detection and diagnosis of patients—and their relatives—with FH, and has early treatment been shown to have an impact on clinical outcomes? And what is the approach in children with FH?
Question # 7:
FH Patient Case Study #1: How would you optimize CV risk reduction in a patient with HeFH on maximal dose of atorvastatin who still has an LDL level of 170 mg/dl and IVUS demonstrating severe atherosclerosis?

Michael Davidson, MD, FACC, FNLA
Director of Preventive Cardiology
Clinical Professor of Medicine
University of Chicago Pritzker School of Medicine
Executive Medical Director, Radiant Research
Chicago, Illinois

Question # 8:
What changes on the treatment landscape for patients with heterozygous FH (HeFH), including antisense technology, should we be focusing on, and how might these novel strategies help achieve LDL level target goals in this difficult-to-manage patient population?

Question # 9:
When desired LDL target goals have not been achieved with initial therapy in patients with FH, what are the triggers to intensify therapy, and which agents should be considered to optimize LDL target goal attainment? Where do apheresis and mipomersen fall into the algorithm?

Question # 10:
What percentage of the estimated 500,000 patients in the U.S. with HeFH are able to achieve the desired LDL target goals, and therefore, what proportion of patients with FH are likely to be candidates for more aggressive therapies utilizing ASO, apheresis, and other strategies?

Question # 11:
Cost aside, based on purely the clinical necessity to optimize CV risk reduction in FH, at what LDL levels does deployment of ASO-based therapy make sense?

Question # 12:
Can you explain the Simon-Broome scoring criteria, which is used primarily in Europe, for diagnosing FH and what are the clinical implications?

Question # 13:
What criteria have been developed in the U.S. to screen for and confirm the diagnosis of FH? How do we detect these patients?

Question # 14:
Once the clinical diagnosis of FH is confirmed, what does the subsequent work-up consist of? Imaging? Lp(a)? And what are the clinical implications?

Question # 15:
What is the currently accepted approach to timing and sequencing therapy aimed at LDL level reduction in patients with FH? What are triggers for LDL apheresis? ASO-based therapy?

Question # 16:
Can you summarize the mechanism(s) of antisense technology and key results, including levels of LDL reduction and any side effect-related issues, emanating from the pivotal trials evaluating mipomersen, an ASO, in patients with FH?

Question # 17:
Which patients at this point in time, based on the science and evidence reported in clinical trials, do you believe will be the best candidates for mipomersen (ASO)-based therapy to achieve optimal LDL levels?

Question # 18:
FH Patient Case Study #1: How would you optimize CV risk reduction in a patient with HeFH on maximal dose of atorvastatin who still has an LDL level of 170 mg/dl and IVUS demonstrating severe atherosclerosis?

Question # 19:
FH Patient Case Study #2—How would you optimize CV risk reduction in a 21 year-old patient with HeFH who is intolerant of statin therapy? Apheresis? ASO?

Question # 20:
FH Patient Case Study # 3: How would you optimize management of a patient with FH who, after maximum statin dose therapy and apheresis, continued to have an LDL level of 165 mg/dl, and a previous history of MI? Apheresis? ASO?

Question # 21:
At what point after the suspicion or diagnosis of HeFH, based on an LDL level >200 mg/dl, should a patient be referred to a lipidologist and/or atherosclerosis expert?

Professor Erik Stroes, MD
Chair of the Department of Vascular Medicine
Academic Medical Center in Amsterdam
Amsterdam, The Netherlands

Question # 22:
What new developments on the treatment landscape for patients with heterozygous FH (HeFH), including antisense and monoclonal technology, should we be aware of?

Question # 23:
What are your LDL target goals for patients with FH, and what measures do you rely on to achieve these goals?

Question # 24:
What is the mechanism of action for mipomersen, and based on the current algorithm for treating FH, what would the likely trigger(s) be for antisense-based treatment with mipomersen, if this agent becomes available?

James de Lemos, MD
Professor of Medicine
Cardiovascular Division
Sweetheart Ball-Kern Wildenthal, M.D., Ph.D.
Distinguished Chair in Cardiology
UT Southwestern Medical Center
Dallas, Texas

Question # 25:
What changes on the treatment landscape for patients with heterozygous FH (HeFH), including antisense technology, should we be aware of as we look to the future of therapy in this area? What is your perspective?

Question # 26:
Which patient subsets with FH are likely to be the most appropriate for treatment with novel, emerging therapies aimed at lowering LDL levels in patients who have insufficient responses to statins and related agents?

Question # 27:
What would be current clinical triggers for deploying ASO-based therapy in patients with FH? And how are these triggers affected by lifetime disease burden?
Question # 28:
Based on clinical studies, what degrees of LDL reduction can be achieved with maximal statin and ezetimibe dosing regimens? Addition of mipomersen? Apheresis?

Question # 29:
What is the rationale for treating patients with FH early, and what other non-LDL markers, including imaging metrics and other biomarkers, would induce a more intensive approach, beyond statins, to LDL lowering?

Question # 30:
Which patients with FH are likely to be the most appropriate candidates for ASO-based therapy? What should the sequencing algorithm be? Will it replace LDL apheresis?

Question # 31:
FH Patient Case Study #1: How would you optimize CV risk reduction in a patient with HeFH on maximal dose of atorvastatin who still has an LDL level of 170 mg/dl and imaging studies demonstrating severe atherosclerosis?

Question # 32:
FH Patient Case Study #2: How would you optimize management of a patient with FH who, after maximum statin dose therapy and apheresis, continued to have an LDL level of 165 mg/dl, and a previous history of MI? Apheresis? ASO?

Question # 33:
How do we diagnose heterozygous FH early? What LDL levels should alert us to the diagnosis? What are the clinical and treatment implications of FH being characterized by lifetime disease burden?

Prof. Dr. Heribert Schunkert, MD
Professor of Internal Medicine and Cardiology
Director of Medizinische Klinik II
Universitätsklinikum Schleswig-Holstein
Campus Lübeck, Germany

Question # 34:
Is there genetic testing that is predictive of how patients with FH and elevated LDL will respond to specific pharmacologic therapies?

Question # 35:
Are there point-of-care genomic tests that facilitate the diagnosis of FH and/or are predictive of disease burden and lifetime CV risk?

Question # 36:
Once you have identified a patient with HeFH, what is the appropriate sequence of therapeutic interventions, and what are the triggers for intensifying treatment with adjunctive therapy?

Question # 37:
Based on published trials and expert opinion, how should patients with FH be treated and titrated with the medications available to reduce LDL levels? What emerging treatments should we be aware of to achieve target goals?

Question # 38:
What do we know about the relationship between genomic markers/loci and risk for lipid disorders and cardiovascular disease?

Question # 39:
Based on genome wide studies, what is the potential value of identifying genetic determinants of atherosclerotic heart disease and what is translational value of these discoveries as they relate to conditions such as FH and antisense technology?

Question # 40:
How do we diagnose patients with FH, how important is the disease burden of FH, and what is the current status of therapy for this increasingly important condition?

Question # 41:
What levels of LDL reduction do we see with conventional agents, what is the unmet need for additional LDL lowering, and what emerging therapies can help us get closer to LDL targets in patients with FH?

Question # 42:
In FH patients who have not achieved LDL goals with usual therapy, what might be the role for ASOs such as mipomersen and other LDL-lowering agents currently under evaluation?

Question # 43:
How do we risk stratify patients with FH? LDL particle number? Spectroscopy? Lp(a)?

William Boden, MD
Chief of Medicine, Professor of Medicine
Albany (NY) Stratton VA Medical Center
Albany Medical Center
Albany, New York

Question # 44:
What new changes on the treatment landscape for patients with heterozygous FH (HeFH), including antisense technology, should we be aware of as we look to the future of therapy in this area?

Question # 45:
How should lipidologists and CV specialists apply the results of trials evaluating ASO-based therapies when these strategies become available for patients with HeFH?

Question # 46:
What is the mechanism by which ASO-based therapy reduces LDL levels in patients with FH, and how might these agents be used in practice, if and when they become available for clinical use?

Question # 47:
What is the efficacy profile of antisense-based therapy with mipomersen, and what is the side effect profile of this agent? How do we weigh the benefits and risks of this novel approach to LDL reduction in FH?

Question # 48:
As far as sequencing LDL-targeted therapy in patients with FH, how do we sequence established and emerging therapies, including statins, apheresis, ASO-based strategies, and other options?

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, Texas

Question # 49:
What is the potential value of identifying genetic determinants of atherosclerotic heart disease and what is translational value of these discoveries as they relate to conditions such as FH and antisense technology?
Question # 49:
Can you characterize the key issues in managing patients with homozygous and heterozygous FH, and why this disease falls into the categories of “failure to assess” and “failure to prevent” syndrome?

Question # 50:
What is the unmet need for additional LDL reduction in patients with FH, and how do we get there? Where does antisense technology fit into this unmet need for patients with FH?

Question # 51:
What degree of LDL reductions can we expect in patients with FH using conventional therapy? New ASO-based therapies?

Question # 52:
What is the effect of mipomersen on Lp(a) and what are the clinical implications of these effects on this atherogenic lipoprotein?

Question # 53:
How do we confirm the diagnosis of HeFH and what are the initial approaches to patient evaluation, treatment, and CV risk assessment?

Question # 54:
Once maximal doses of statins have been employed to lower LDL in FH, what additional therapeutic measures, including antisense oligonucleotides (ASOs), should be considered?

Question # 55:
What additional degree of LDL level reduction is observed when an ASO such as mipomersen is used in FH patients who have been treated with maximal doses of statin therapy?

Question # 56:
What is the rationale for using ASO-based therapy for achieving additional reductions of LDL in patients with FH?

Question # 57:
Based on the most recent trials in patients with dyslipidemias, what have we learned about Lp(a)? What is the relationship of this marker to FH? And do we know what the effect of mipomersen is on Lp(a)?

Question # 58:
What makes Lp(a) an atherogenic risk factor? What is the mechanism for its pro-atherogenicity? At what level does atherogenic risk become evident?

Question # 59:
Is Lp(a) an independent risk factor? Independent of other risk factors that co-exist in patients with cardiometabolic disease?

Question # 60:
What effect does mipomersen have on Lp(a) levels? On LDL levels?

Question # 61:
How do you construct outcome studies looking at the effect of Lp(a) lowering on CV risk? Are there guidelines for Lp(a)?

Question # 62:
Do statins lower Lp(a)?

Question # 63:
If it becomes available, in your view what are the triggers for using the ASO mipomersen in a patient with FH?

Question # 64:
Can you provide an overview of familial heterozygous hypercholesterolemia (HeFH)?

Question # 65:
Once the diagnosis of FH has been made, what is the systematic approach to evaluating a patient’s cardiovascular risk?

Question # 66:
What is the role of vascular imaging, either as a primary test, or an adjunctive modality, for assessing risk patients with FH?

Question # 67:
How can the results of serial vascular imaging tests, including IMT and coronary calcium burden, help stratify patients, monitor therapy, and guide other interventions in FH?

Question # 68:
What are the primary treatment goals and initial approach to therapy in patients with FH?

Question # 69:
What is the role of calcium burden imaging and, moving forward, the role of CT angiography for screening and assessing patients with hyperlipidemia?

Question # 70:
What levels of LDL risk reduction in FH patients can be anticipated with statin therapy, and what level of residual risk is generally still present after maximal doses of statins?

Question # 71:
How does one screen for FH among family members, especially children and siblings, once an index case is identified?

Question # 72:
How do we know that early, LDL-targeted therapy is working, with respect to mortality and CV risk reduction, in patients with FH? What is the evidence?

Question # 73:
What are the indications for calcium burden scanning or IMT assessment in patients with FH or elevated LDL levels? And how do we interpret and apply the results of subclinical disease testing?