Management of FAMILIAL HYPERCHOLESTEROLEMIA

Focus on New Therapies Targeting LDL to Optimize Target Goal Attainment and CV Risk Reduction

Sixteen (16) FH Specialists, Cardiologists and Lipidologists Analyze, Answer and Discuss 128 FAQs Addressing Clinical Dilemmas and Therapeutic Advances for Patients with Familial Hypercholesterolemia

Question # 1:
What are the new advances in the treatment of FH and how have new guidelines responded to these developments?

Question # 2:
What are the various strategies for making the diagnosis of FH, and what do European guidelines advocate?

Question # 3:
What LDL targets do you recommend for patients with FHP? Is there some debate about achieving absolute versus relative degrees of reduction? Can you clarify?

Question # 4:
Given the fact that we have specific target goals for FH, what is the sequencing of therapy that you follow, including the role of antisense oligonucleotide-based therapies?

Question # 5:
What levels of LDL reduction can we expect with ASOs in FH patients already treated to maximal levels with statins?

Question # 6:
What is the role of apheresis for patients with FH in Europe?

Question # 7:
What percentage of patients do not achieve ESC target goals with statin therapy and therefore, do you feel, should be considered for more intensive therapy with antisense oligonucleotide-based or other LDL-targeted therapies?

Question # 8:
When ASO-based treatment is selected for FH, what side effects of therapy should clinicians be aware of and monitor?

Supported by an educational grant from Genzyme

Visit us at www.iQandA-CME.com
Question # 9: How do you recommend we apply data from recent trials evaluating new, ASO-based treatment strategies for LDL reduction in FH to the front lines of cardiovascular and lipid-based practice?

Question # 10: What are the indications for referring a patient with FH to a lipidologist or specialized lipid centers for more intensive therapy?

Question # 11: What should the “call-to-action” be for FH patients to ensure that risk reduction is extended to this high-risk population? And do ASOs have a role to optimize outcomes in these patients?

Question # 12: What advances in detection, grading scale and treatment of FH have we made in the past 12 months? And how have the European guidelines responded to these advances for CV risk reduction in FH?

Question # 13: Is it possible to determine a precise level of LDL at which adjunctive agents should be added to foundational statin therapy?

Question # 14: What is the optimal way to employ statin therapy in FH?

Question # 15: What degree of LDL reduction, beyond maximal statin therapy, can be achieved with ASOs such as mipomersen?

Question # 16: Given that patients with FH are a heterogeneous group, with different underlying genetic defects, is there a role for genetic testing to align LDL-targeted therapies with specific subgroups of patients with FH?

Question # 17: What percentage of patients with FH fail to achieve recommended LDL target goals and what are the therapeutic implications of this finding?

Question # 18: What degrees of LDL level reduction can we expect in patients—both de novo patients and those already on statins and other agents—with FH who are treated with the ASO mipomersen?

Question # 19: What other lipoprotein/lipid moieties are affected by ASOs, including Lp(a), and what clinical importance should we ascribe to this?

Question # 20: What side effects associated with ASOs should clinicians be aware of and what kind of monitoring do you recommend for FH patients on mipomersen?

Question # 21: Considering the lifetime burden of risk associated with FH, when should treatment begin and how aggressively should we treat from the outset?

Question # 22: What have you noted clinically in your patients with APO-B mutations? And what are the implications for treatment with mipomersen?

Question # 23: What have we learned from the Netherlands study about survival outcomes in FH patients who have been treated to LDL targets versus those who have not been treated with pharmacologic agents?

Question # 24: Which high risk patient subgroups with FH do you see as logical and appropriate populations for treatment with the ASO mipomersen?

Question # 25: How common is FH in the general population? And what is the call-to-action in these patients?

Question # 26: What challenges do we face when trying to reach acceptable LDL levels in patients with FH when using statins alone?

Question # 27: What do you envision might be the role of ASOs such as mipomersen in patients with FH who are not meeting LDL targets or who are intolerant of statins? Are the benefits limited to LDL reduction or should Lp(a) levels also be considered?

Question # 28: What do you envision might be the role of ASOs such as mipomersen in patients with FH who are not meeting LDL targets or who are intolerant of statins? Are the benefits limited to LDL reduction or should Lp(a) levels also be considered? (German)

Question # 29: What are the LDL thresholds in patients with FH that suggest the need for intensifying therapy with agents other than statins, including ASOs and other adjuncts to LDL lowering? What are the thresholds for using agents such a mipomersen?

Question # 30: Given that there exist multiple guidelines directing LDL-targeting interventions, which specific guidelines and targets do you employ; and what other clinical factors and biomarkers do you consider when treating FH patients?

Question # 31: What percentage of patients with FH fail to meet their target goals, and therefore, will require combination therapy in addition to statins?

Question # 32: You are the director of the PROCOM study, which evaluated risk factors for ASHD in 50,000 individuals, much like the Framingham Study. Can you tell us what you have learned from the PROCOM study as it relates to LDL and risk assessment?

Question # 33: What is the role of HDL as a risk factor for ASHD?

Question # 34: When does combination therapy that includes the addition of other agents, such as the ASO mipomersen, make sense in patients with FH and poorly controlled LDL? (German)
Question # 35: Why is LDL the pre-eminent biomarker for ASHD and CV risk? On what basis, including inborn errors of metabolism, has LDL's pivotal role in ASHD been confirmed? And what role might ASOs play?

Guy De Backer, MD, PhD, FACC
Professor Emeritus
Division of Cardiology
University of Ghent
Ghent, Belgium

Question # 36: What are the benefits of identifying FH patients early in the course of their disease, and what evidence do we have that early pharmacologic intervention can positively impact outcomes?

Question # 37: What are some of the critical points and recommendations contained in the European Society Guidelines for Familial Dyslipidemias that you would like clinicians to be aware of? What LDL targets should we strive for?

Question # 38: What therapeutic sequencing strategies are recommended for patients with FH and how do we deploy newer therapies in appropriate risk groups?

Question # 39: How do you evaluate total risk burden in a patient with FH?

Question # 40: What is the rationale for aggressive pharmacological management of patients with FH?

Question # 41: Can you give us a systematic approach to the laboratory-based diagnostic evaluation of FH?

Question # 42: How do you recommend that international experts on FH and lipid management develop a consensus for this condition?

Question # 43: What are the barriers to implementation of the ESC Guidelines for managing patients with familial dyslipidemias?

Philip Barter, MD, PhD
Director, The Heart Research Institute
Professor of Medicine
University of Sydney
Sydney, Australia

Question # 44: Can you delineate the relationship between LDL and cardiovascular disease, and explain the disconnect between traditional LDL target goals and more recent analysis suggesting we should strive for lower LDL levels in high-risk patients such as those with FH?

Question # 45: Are statins still the mainstay of therapy for patients with FH? How do you use them and which ones do you use? And, at what doses?

Question # 46: What do you recommend if target goals are not being met with statins in patients with FH?

Question # 47: What LDL reductions can we expect to see with ASOs in patients with FH?

Christian Weber, MD
Director, Institute for Cardiovascular Prevention
Chair in Vascular Medicine
Ludwig Maximilians University
Munich, Germany
Professor, Cardiovascular Research Institute
Maastricht Maastricht University

Question # 48: What side effects have been reported with ASOs and how should we monitor these?

Question # 49: Given the lifetime disease burden associated with FH, what is the rationale for early identification and assessing family members?

Question # 50: Why are patients with FH undertreated, considering the complications and natural history of their disease?

Question # 51: What is the near future of FH therapy?

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

Question # 52: What is the relationship between LDL, cytokines, and atheroinflammatory disease and why is this paradigm central to our understanding of FH and its treatment?

Question # 53: How does LDL trigger endothelial inflammation? What are the mechanisms by which elevated LDL levels trigger atherosclerosis?

Question # 54: What are the roles of the inflammasone and Interleukin 1-beta in the development of atherosclerosis?

Question # 55: What are the protective mechanisms that keep the atherosclerotic process in check?

Question # 56: What new developments on the treatment landscape for patients with heterozygous FH (HeFH), including antisense and monoclonal technology, should we be aware of?

Question # 57: What are your LDL target goals for patients with FH, and what measures do you rely on to achieve these goals?

Question # 58: 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?
Question # 59:
Why is there a need to develop, assess, and deploy new LDL-targeted agents to manage familial dyslipidemias, including FH?

Question # 60:
Do you use specific LDL target goals, and if so, what are your indications for employing agents other than statins to optimize CV risk reduction in FH?

Question # 61:
What clinical factors do you consider when determining a specific LDL target in patients with FH?

Question # 62:
In what patient populations with FH are more potent agents, including ASOs, likely to be necessary?

Question # 63:
How do you systematically evaluate and follow a patient with FH, and how do you sequentially introduce agents into the patient’s regimen?

Question # 64:
Can you discuss the mechanism of action and pharmacokinetics of mipomersen?

Question # 65:
How do you approach an FH patient who is intolerant of statin therapy?

Question # 66:
Are there any gender differences in how we should approach FH therapy?

Question # 67:
Is it necessary to delineate the underlying genetic, LDL-receptor-specific mutations that are observed in FH?

Question # 68:
What are the underlying metabolic errors that produce the clinical phenotypes of FH?

Question # 69:
What is the mechanism by which errors in metabolism of APO-B-100 cause ASHD? What is the role of LDL as a precipitating factor?

Question # 70:
What is the role of ASOs, such as mipomersen, for monotherapy or combination therapy in patients with FH? How do these agents work at the molecular level? What is the unmet medical need for LDL reduction in these patients?

Question # 71:
What is the mechanism of action for PCSK-9 inhibitors?

Question # 72:
Are there subgroups of patients with FH in whom therapy with statins is contraindicated?

Question # 73:
Where exactly does mipomersen fit into the road map, or sequencing strategy, for patients with FH? What subgroups of patients will derive the greatest benefit based on the trial evidence and clinical experience?

Question # 74:
How would you optimize CV risk reduction in a patient with HeFH who has been on a maximal dose of statins, and still has an LDL level of 170 mg/dL?

Question # 75:
What should the LDL targets be for patients with FH?

Question # 76:
How would you optimize CV risk reduction in a patient with FH who was intolerant to statin therapy? How do you evaluate such a patient, and what other options deserve consideration?

Question # 77:
Are there gender differences in the way FH patients respond to or require therapy?

Question # 78:
What does the landscape for LDL reduction currently look like beyond the foundational approach based on statin therapy?

Question # 79:
How do you suggest we align the established therapies such as statins and the newly available therapies, including the ASO mipomersen, with specific subgroups of patients with FH?

Question # 80:
Can you explain the molecular mechanisms by which the ASO mipomersen reduces LDL and why this approach represents an advance in CV risk reduction for patients with FH?

Question # 81:
What are the effects of the ASO that is currently available in Europe on triglyceride levels and on Lp(a)?

Question # 82:
Which patient populations with FH would be considered appropriate for combination therapy, i.e. with agents in addition to statins?

Question # 83:
What are the LDL targets we need to achieve in patients with FH?

Question # 84:
How does your work help illuminate the role of ASO in CV risk reduction in the setting of cardiometabolic disease?
Question # 85:
What is the role of diet in producing dyslipidemic states that increase CV risk? What dietary interventions have been shown to be useful?

Question # 86:
How do dietary sugars affect LDL, APO-B, and impaired insulin sensitivity? What might be the clinical implications?

Question # 87:
In your FH practice, what percentage of patients achieve an acceptable target goal for LDL and what is the unmet need for additional therapeutic options to lower LDL to optimize residual CV risk reduction in this population?

Question # 88:
What additional measures are necessary to optimize LDL reduction in FH patients?

Question # 89:
What levels of reduction do you see with ASOs and in which FH patients—homozygous and/or heterozygous FH—will ASO-based therapy for LDL reduction be appropriate and necessary?

Question # 90:
Is there a reason to delineate the type of LDL or APO-B mutation that is responsible for LDL elevations, or is it sufficient, from a clinical perspective to just treat elevated LDL levels to acceptable targets?

Question # 91:
In addition to LDL levels, what other clinical findings and biomarker findings suggest the need for more aggressive treatment?

Question # 92:
What side effects associated with the ASO mipomersen do we need to be most aware of?

Question # 93:
Do you know whether we can positively affect survival outcomes in patients with FH and elevated LDL levels?

Question # 94:
How do LDL levels compare in FH patients based on the kind of APO-B mutation versus LDL-receptor mutations?

Question # 95:
What other factors, other than genetically determined mechanisms, can affect LDL levels in FH patients?

Question # 96:
What is the rationale for cascade screening for FH and for treating patients who have been identified with this dyslipidemia as early as possible after detection?

Question # 97:
How do we screen family members with FH? What programs have been established in the Netherlands to identify these patients?

Question # 98:
Why don’t we measure APO-B as a biomarker in patients with FH? Should we be monitoring APO-B levels?

Question # 99:
Why do patients with FH continue to be a management problem even though statins produce significant reductions in LDL? And what will the new guidelines suggest as far as the need for combination therapy?

Question # 100:
What are the shortfalls in LDL target goal attainment and what are the implications for more aggressive therapy with adjunctive agents?

Question # 101:
What systematic approach to patient assessment do you use to determine the LDL target goals for an individual patient with FH?

Question # 102:
What are the limitations of the current pharmacologic armamentarium for LDL-lowering in FH?

Question # 103:
What are the more aggressive therapies that have the potential for getting FH patients to target goals?

Question # 104:
Which patient populations do you feel are most amenable to ASO-based therapies?

Question # 105:
What surrogate markers do you use to assess risk in patients in FH?

Question # 106:
How do you evaluate aortic valve disease in patients with AF, and what implications does this have for treatment?

Question # 107:
In what specific situations and at what LDL elevations does adjunctive therapy with an ASO deserve serious consideration?

Question # 108:
What is the rationale for newer agents such as ASOs and PCSK-9 inhibitors? Why are these agents needed in our toolkit?

Question # 109:
How do the various global guidelines—from NICE, NLA, and ESC and other organizations—compare as far as the recommendations for LDL target goals in patients with FH?

Question # 110:
What is your sequential approach for deploying LDL-lowering agents in patients with FH? What is the role of apheresis? How widely available and comfortable is this approach? Where do ASOs fit into this scheme?

Question # 111:
What are the indications for apheresis in patients with FH?

Question # 112:
What are the Simon-Broome criteria for diagnosing and risk-stratifying patients with FH?
Question # 113:
What are the differences in response rates in FH patients based on genetic mutations?

Question # 114:
What is your statin-based strategy in patients with FH, and what are your indications for combination therapy?

Question # 115:
What are the indications for using ASO-based therapy in patients with FH? Can we use ASOs to avoid apheresis?

Raul D. Santos, MD, PhD
Director, Lipid Clinic Heart Institute (InCor)
University of Sao Paulo Medical School Hospital
Sao Paulo, Brazil

Question # 116:
Can you provide a mechanistically rigorous overview of the ASO mipomersen and its role in managing LDL levels in patients with FH?

Question # 117:
How should we apply ASO-based technology to the front lines of care for patients with FH?

Question # 118:
Which patients with FH are most amenable and most appropriate for ASO-based therapy?

Question # 119:
Are there drug interactions one should be concerned about with ASOs?

Question # 120:
Are dose adjustments required for ASOs? What side effects should clinicians be aware of?

Stephen Daniels, MD, PhD
Pediatrician in Chief
Professor, University of Colorado
L. Joseph Butterfield Chair of Pediatrics
Chairman of Pediatrics
Children’s Hospital of Colorado

Question # 121:
How should lipid specialists balance the advantages of mipomersen in terms of LDL reduction against toleration issues? How should clinicians mitigate the tolerability dimension and educate their patients?

Question # 122:
Are there gender issues we should be concerned about when managing FH? And when should treatment for FH be started?

Question # 123:
What is the biggest driver of CV risk in FH patients?

Question # 124:
What clinical framework, biomarkers, and scoring tools do you recommend we use to assess risk for FH patients?

Question # 125:
What new therapies will help meet the unmet need for greater LDL reductions in patients with FH? And will event-focused, outcome studies be necessary in these patients? And where does mipomersen fit into this unmet need for LDL-targeted treatment?

Raul D. Santos, MD, PhD
Director, Lipid Clinic Heart Institute (InCor)
University of Sao Paulo Medical School Hospital
Sao Paulo, Brazil

Question # 126:
Can you summarize the recent NHLBI guidelines that require universal screening for FH in children?