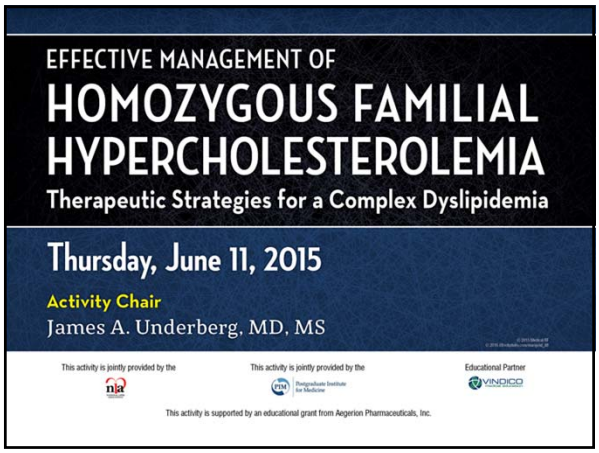

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Homozygous Familial Hypercholesterolemia: Current State of an Underdiagnosed and Undertreated Disease

Panel Discussion

Moderator:
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Topics for Discussion

- Diagnosis of homozygous familial hypercholesterolemia (HoFH)
- Currently approved therapies for the treatment of HoFH
- Emerging therapies for the treatment of HoFH

Diagnosis of HoFH

- Multiple definitions
- Genetic basis of initial description no longer fits current paradigm of phenotypic presentation
- Varying standards in different countries based on technology and insurance/cost

Criteria for the Clinical Diagnosis of Familial Hypercholesterolemia

US: MEDPED Criteria	Total Cholesterol (and LDL-C) Levels, mg/dL				Risk
Age (years)	First-degree Relative	Second-degree Relative	Third-degree Relative	General Population	
<18	220 (155)	230 (165)	240 (170)	270 (200)	98% specificity 87% sensitivity
20	240 (170)	250 (180)	260 (185)	290 (220)	
30	270 (190)	280 (200)	290 (210)	340 (240)	
40 +	290 (205)	300 (215)	310 (225)	360 (260)	

UK Simon Broome Criteria	Plus	Risk
Total cholesterol (and LDL-C) levels:	DNA mutation	Definite FH
	Tendon xanthomas in the patient or in first- or second-degree relative	Definite FH
Adults: 290 (190) mg/dL Children: 260 (155) mg/dL	Family history of MI at age <50 in second-degree relative, or at age <60 in first-degree relative or family history of TC >290 mg/dL in adult first-/second-degree relative, or 260 (155) mg/dL in a child/sibling aged <16 yrs	Possible FH

The Netherlands Dutch Lipid Clinic Criteria		Feature	Risk
Rating	1 point	First-degree relative with premature CVD or LDL-C >95th percentile, or Personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 mg/dL and 189 mg/dL	
	2 points	First-degree relative with tendinous xanthoma or corneal arcus, or First-degree relative child (<1 yrs) with LDL-C >95th percentile, or Personal history of CAD	
	3 points	LDL-C between 190 mg/dL and 249 mg/dL	Possible FH (3-5 points)
	4 points	Presence of corneal arcus in patients <45 yrs old	
	5 points	LDL-C between 250 mg/dL and 329 mg/dL	
	6 points	Presence of a tendon xanthoma	Probable FH (6-7 points)
	8 points	LDL-C >330 mg/dL, or Functional mutation in LDLR gene	Definite FH (≥8 points)

Diagnosis of HoFH

- Autosomal dominant inherited disorder (other than rare form of autosomal recessive *LDLRAP1*)
- Loss of function mutations in the LDLR (FH1), apoB (FH2) genes, and gain of function mutations in PCSK9 (FH3) gene
- Severe LDL-C elevations, premature aortic stenosis and premature atherosclerotic cardiovascular disease (ASCVD)
- Physical signs of cholesterol deposition – planar/tendon xanthoma, xanthelasmata, corneal arcus

Sjouke B, et al. *Curr Opin Lipidol*. 2015;26:200-209.

Diagnostic Criteria for HoFH from the Literature

Publication	Diagnostic Criteria for HoFH
Seftel, et al.	• Serum cholesterol concentration >550 mg/dL • Appearance of xanthomas during the first decade of life • Hypercholesterolemia or clinical signs of hypercholesterolemia in both parents
Moorjani, et al.	• Plasma cholesterol levels >550 mg/dL • Appearance of xanthomas at an early age • Detection of hypercholesterolemia in both parents
Haitas, et al.	• Hypercholesterolemia in both parents (when available) • Total serum cholesterol >500 mg/dL + presence of xanthomas in first decade of life
Raal, et al.	• Untreated serum LDL consistently >12 mmol/L • Appearance of xanthomas in first decade of life • Hypercholesterolemia, or its clinical features, documented in both parents • Confirmation by DNA analysis for LDLR mutations
Goldstein, et al.	• Unique yellow-orange cutaneous xanthomas (frequently present at birth) • Tendon xanthomas, corneal arcus, generalized atherosclerosis during childhood • Plasma cholesterol >650 mg/dL in non-jaundiced child
Cagne, et al.	2 mutant alleles at LDLR confirmed by genetic testing or • LDL-C ≥220 mg/dL while receiving lipid-lowering therapy at the highest tolerated dose (<15% response) • LDL-C >95th percentile in ≥2 first-degree relatives • Presence of tendinous xanthomas and/or manifestations of premature coronary heart disease or corneal arcus
Marais, et al.	• Childhood cutaneous or tendinous xanthomata • Total cholesterol >600 mg/dL • Both parents should have severe hypercholesterolemia (>300 mg/dL) or tendinous xanthomas • Family history of premature ischemic heart disease
Kolansky, et al.	• Total cholesterol >500 mg/dL • Xanthomas at an early age • Presence of hypercholesterolemia in proband's parents or other first-degree relative
Marais, et al.	Clinical criteria • Fasting LDL >500 mg/dL, TG <600 mg/dL • Either xanthomata before age 10 or FH in both parents Genetic criteria • Identification of 2 LDLR gene mutations Functional criteria • <30% uptake compared with normal of LDL and upregulated fibroblasts
Santos, et al.	Untreated LDL >500 mg/dL + at least 1 of the following: • Genetic testing confirmation of 2 mutated LDLR alleles • Tendinous and/or tuberous xanthoma prior to age 10 • Documented elevated LDL and both parents consistent with HeFH (LDL >200 mg/dL). If parent unavailable, history of CAD in first-degree relative
Raal, et al.	Untreated LDL-C >13 mmol/L and either appearance of xanthomas before age 10 or FH in both parents
Mabuchi, et al.	• Childhood cutaneous or tendinous xanthomata • Total cholesterol >600 mg/dL • Both parents should have severe hypercholesterolemia (>300 mg/dL) or tendinous xanthomas • Family history of premature ischemic heart disease

Raal FJ, Santos RD. *Atherosclerosis*. 2012;223:262-268.

? Accepted Diagnosis

- Untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥300 mg/dL (7.76 mmol/L) or treated non-HDL-C ≥330 mg/dL (8.5 mmol/L) + either
  - Cutaneous or tendinous xanthoma before age 10 years

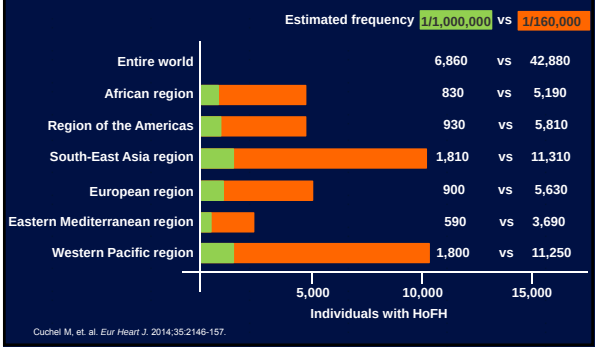
  or
  - Elevated LDL-C levels before lipid-lowering therapy consistent with HeFH in both parents (except in the case of ARH)

  OR
- Genetic confirmation of 2 mutant alleles at the LDLR, apoB, PCSK9, or ARH adaptor protein gene locus

- Genetic mutation alleles in same gene – true homozygotes
  - Same mutation in same gene – simple homozygotes
  - Different mutations in same gene – compound heterozygotes (cis or trans)
- Mutations in 2 different genes (1 usually LDLR) – double heterozygotes (cis or trans)

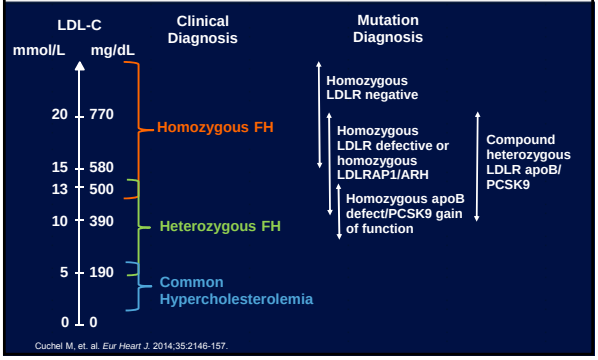
Raal FJ, Santos RD. *Atherosclerosis*. 2012;223:262-268; Cuchel M, et. al. *Eur Heart J*. 2014;35:2146-157.

Estimated Frequency of HoFH



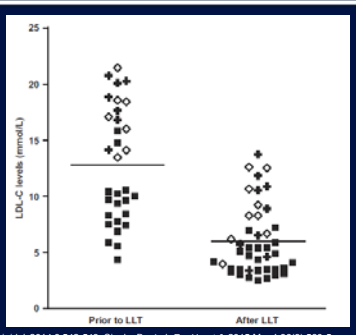
Cuchel M, et. al. *Eur Heart J*. 2014;35:2146-157.

LDL-C Levels in HoFH Patients



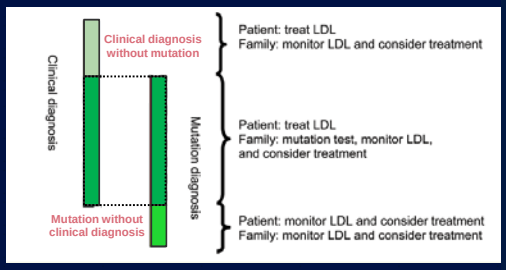
Cuchel M, et. al. *Eur Heart J*. 2014;35:2146-157.

LDL-C Levels in HoFH Patients



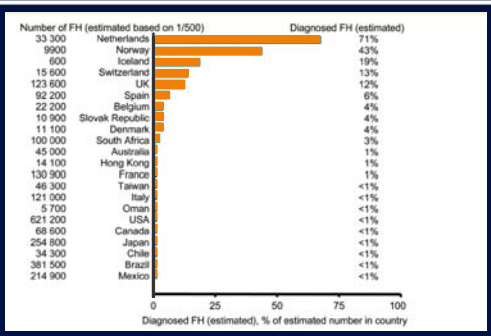
Baum SJ. *J Clin Lipidol*. 2014;8:542-549, Sjouke B, et al. *Eur Heart J*. 2015 Mar 1;36(9):560-5. doi:10.1093/eurheart/ehu058. Epub 2014 Feb 28.

Overlap of Clinical and Mutation Diagnosis of HeFH



Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-90a.

FH Diagnosis Rates Worldwide



Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-90a.

Discussion

Currently Approved Therapies for HoFH and HeFH

Class	Major Effect	LDL-lowering Response HoFH	HeFH
Low-cholesterol diet	↑LDLR activity	<10%	10%-25%
Statins	↑ LDLR activity	<10%	>25%
Resins	↑ LDLR activity	<10%	10%-25%
Ezetimibe	↓Cholesterol absorption + ↑LDLR activity	<10%	10%-25%
Stanol esters	↓Cholesterol absorption + ↑LDLR activity	<10%	10%-25%
Nicotinic acid	↓VLDL synthesis	<10%	>25%
LDL apheresis	Removes LDL	>25%	>25%

Rader DJ, et al. J *Clin Invest*. 2003;111:1795-1803.

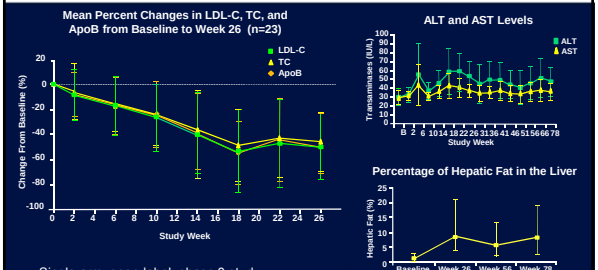
Recently Approved Therapies for HoFH

Class	Approval Date	Major Effect	LDL-lowering Response
Lomitapide	Dec. 2012	MTP activity	40%-50%
Mipomersen	Jan. 2013	Antisense ApoB	25%

Lomitapide and mipomersen are not approved for HeFH

Cuchel M, et al. *Curr Opin Lipidol*. 2013, 24:246-250; Plakogiannis R, et al. *Clin. Invest*. 2012;2:1033-1037.

Lomitapide in HoFH

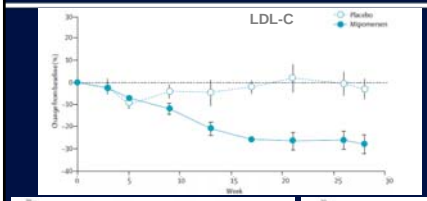


Single-arm, open-label, phase 3 study

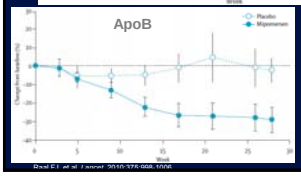
- LDL-C: 50% ↓ ApoB: 49% ↓ Lp(a): 15% ↓ TG : 45% ↓
- Mean hepatic fat measure by NMRS (n=20) from 1% at baseline to 8.6% at week 26, 5.8% at week 56, and 8.3% at week 78

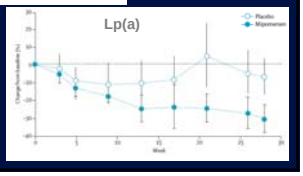
Cuchel M, et al. *Lancet*. 2013;381:40-46.

Mipomersen in HoFH



Randomized, double-blind, placebo-controlled, phase 2 study

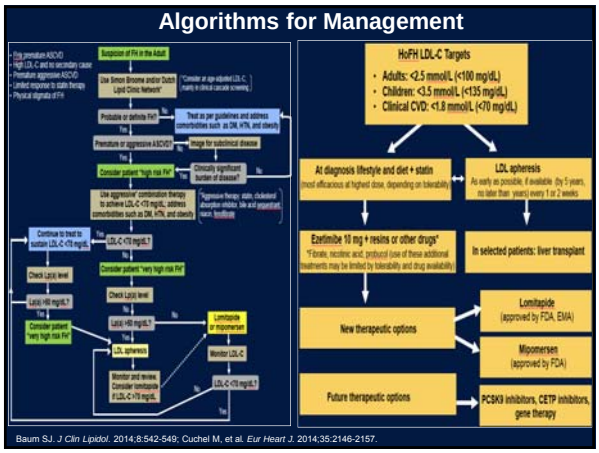


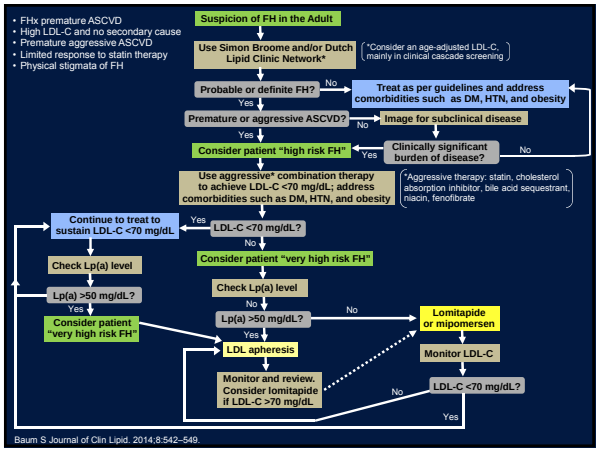


Effects of Lomitapide and Mipomersen on Atherogenic Lipoprotein Parameters in HoFH (Phase 3 Studies)

	Lomitapide* (n=29)	Mipomersen† (n=34)
LDL-C		
• Baseline, mg/dL	336	440
• Endpoint, mg/dL	190	324
• Mean change, %	-40	-25
Non-HDL-C		
• Baseline, mg/dL	386	463
• Mean change, %	-40	-25
Total cholesterol		
• Baseline, mg/dL	428	502
• Mean change, %	-36	-21
ApoB		
• Baseline, mg/dL	260	280
• Mean change, %	-39	-27
Lp(a)		
• Baseline, mg/dL	66	60
• Mean change, %	-13	-32

*Based on values at 26 weeks in all 29 subjects in an ITT analysis with the last observation carried forward. Change from baseline was statistically significant for all parameters
†Based on values obtained at the visit closest to 14 days after the last dose of study treatment. Change from baseline was significant for all parameters.
Rader DJ, Kastelein JJP. *Circulation*. 2014;129:1022-1032.





Discussion

Emerging Therapies for the Treatment of HoFH

- PCSK9 inhibition
  - Evolocumab
  - Alirocumab
- CETP inhibition
  - Anacetrapib
  - Evacetrapib
  - JTT-705
  - DEZ-001
- Gene therapy

Case Studies

Diagnosing Homozygous Familial Hypercholesterolemia

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38-Year-Old Jewish Man with Premature Atherosclerotic Cardiovascular Disease

- 38-year-old Jewish South African man with premature atherosclerotic cardiovascular disease (ASCVD)
- Family history
  - Father's family: hypercholesterolemia, died at young age from ASCVD
  - Mother's family: hypercholesterolemia, no ASCVD
  - 2 brothers: hypercholesterolemia; 1 of them experienced a MI at age 38
  - Teenage son: LDL-C >300 mg/dL

Cardiovascular History

- Age17: chest tightness and shortness of breath while playing basketball; rested for 30 min until symptoms resolved – did not seek medical attention
- Age 23: IMI
- Since then has required multiple coronary stents and a 5-vessel CABG
- Highest untreated LDL-C >400 mg/dL
- Highest total cholesterol >600 mg/dL

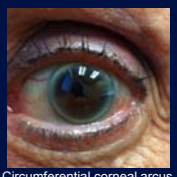
Lipid-Lowering Therapy

- Aggressively treated for hypercholesterolemia and ASCVD for the past 15 years
- Current lipid-lowering therapy
  - Rosuvastatin 20 mg QD
  - Ezetimibe 10 mg QD
  - Colesevelam 625 mg 6 tabs QD
  - Niacin-ER 500 mg QD
  - Lipoprotein apheresis

Physical Examination

- Height: 5'8"; weight: 172 lbs; BMI: 26.15 kg/m^2 → Slightly overweight
- Bilateral Achilles tendon xanthomas
- Superior corneal arcus

Superior corneal arcus



Circumferential corneal arcus

Lab Data on Multiple Lipid-Lowering Therapies, Including Lipoprotein Apheresis

- Total cholesterol: 215 mg/dL
- LDL-C: 174 mg/dL
- HDL-C: 36 mg/dL
- Triglycerides: 244 mg/dL
- Non-HDL-C: 179 mg/dL

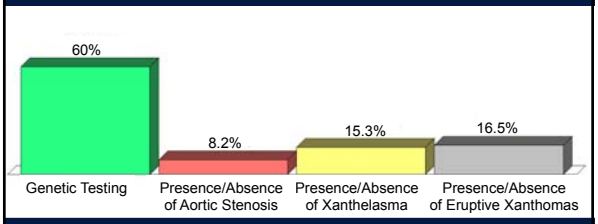
In considering therapeutic options for this patient, a diagnosis must first be made.

Does he have HoFH? What other data would help us make the diagnosis?

1) Genetic testing
2) Presence or absence of aortic stenosis
3) Presence or absence of xanthelasma
4) Presence or absence of eruptive xanthomas

Does he have HoFH? What other data would help us make the diagnosis?

Audience Response

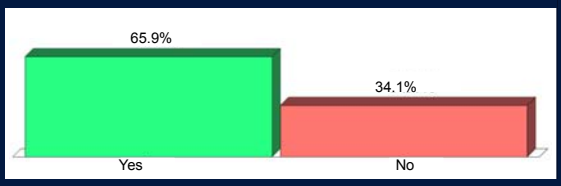


Are we certain of the diagnosis of HoFH?

1) Yes
2) No

Are we certain of the diagnosis of HoFH?

Audience Response

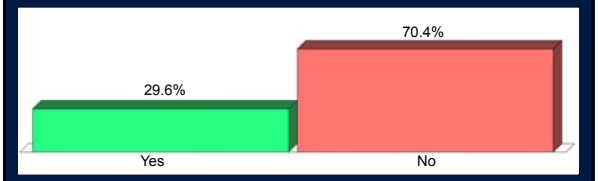


Could genetic testing rule out the diagnosis of HoFH?

1) Yes
2) No

Could genetic testing rule out the diagnosis of HoFH?

Audience Response

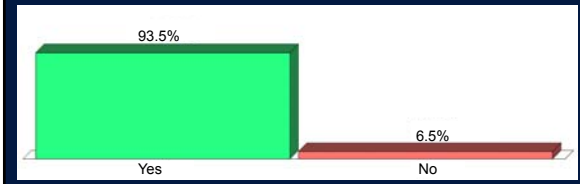


Could genetic testing rule in the diagnosis of HoFH?

1) Yes
2) No

Could genetic testing rule in the diagnosis of HoFH?

Audience Response



Treatment Decisions in the Management of Homozygous Familial Hypercholesterolemia

Sergio Fazio, MD, PhD
The William and Sonja Connor Chair of Preventive Cardiology
Professor of Medicine, Physiology and Pharmacology
Director, Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health and Science University
Portland, OR

Young Man with History of Severe Hypercholesterolemia

- 32-year-old Caucasian male, body builder
- Follows vegan meal plan
- Uses supplements, extracts, and anabolic agents
- History of severe hypercholesterolemia diagnosed at age 7
- No symptomatic CAD
- High CAC score
- No comorbidities or additional risk factors

Young Man with History of Severe Hypercholesterolemia

Family History

- Mother (55 years old): hypercholesterolemia; on statin therapy; no CAD
- Maternal uncle: hypercholesterolemia; CABG x3 at age 42; former smoker
- Maternal grandfather: hypercholesterolemia; died of cardiac causes at age 65; former smoker
- Older sister: milder hypercholesterolemia (untreated LDL-C: 180 mg/dL)
- Father's family history: unknown

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Young Man with History of Severe Hypercholesterolemia

- Normal TG/HDL-C
- Untreated LDL-C: 275 mg/dL-310 mg/dL
- BMI: 27.8 kg/m^2
- Recently, the patient was convinced by PCP to try atorvastatin 20 mg/day
  - LDL-C adjusted to 205 mg/dL
  - Discontinued after 3 months (fear of side effects)
  - Requested specialist referral – referred for genetic counselling

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Young Man with History of Severe Hypercholesterolemia

Fasting lipids at time of visit

- Total cholesterol: 383 mg/dL
- LDL-C: 298 mg/dL
- HDL-C: 65 mg/dL
- Triglycerides: 100 mg/dL
- Lp(a): 49 mg/dL

- Glucose: 88 mg/dL
- CAC score: 325 (99th percentile), with deposits in LM, LAD and LCX

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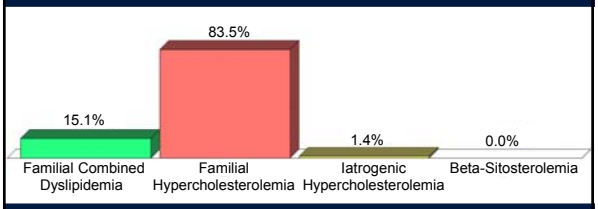
What is this patient's likely diagnosis?

1) Familial combined dyslipidemia
2) Familial hypercholesterolemia
3) Iatrogenic hypercholesterolemia (caused by diet and supplements)
4) Beta-sitosterolemia

What is this patient's likely diagnosis?

Audience Response

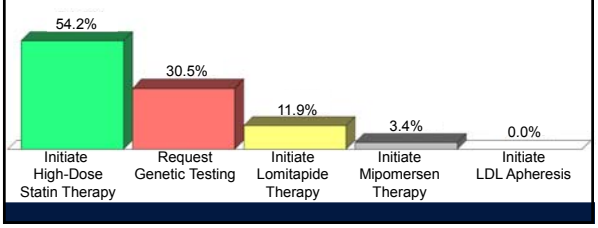


Considering the patient's history, current guideline recommendations, and available therapeutic options, you would recommend to:

1) Initiate high-dose statin therapy
2) Request genetic testing before determining therapeutic approach
3) Initiate lomitapide therapy
4) Initiate mipomersen therapy
5) Initiate LDL apheresis

Considering the patient's history, current guideline recommendations, and available therapeutic options, you would recommend to:

Audience Response



Young Man with History of Severe Hypercholesterolemia

- Genetic testing performed
  - Compound heterozygote for mutations partially inactivating LDLR
- Patient agrees to start rosuvastatin 20 mg/day and ezetimibe 10 mg/day
  - LDL-C adjusted to the 190 mg/dL range
- LDL apheresis denied by insurance

Young Man with History of Severe Hypercholesterolemia

- Lomitapide and mipomersen entry criteria: clinical/biochemical presentation compatible with diagnosis of HoFH
  - Patient elects to add lomitapide to rosuvastatin and ezetimibe regimen

Discussion

Question & Answer

EFFECTIVE MANAGEMENT OF
HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA
Therapeutic Strategies for a Complex Dyslipidemia

Thursday, June 11, 2015

Activity Chair
James A. Underberg, MD, MS

This activity is jointly provided by the

This activity is jointly provided by the

Educational Partner

This activity is supported by an educational grant from Aegerion Pharmaceuticals, Inc.