The Revolution in Cholesterol Management: PUTTING PCSK9 INHIBITORS INTO PRACTICE

ENDOCRINE SOCIETY PRESENTS

MONDAY, APRIL 3, 2017
6:00–8:00 AM
Hyatt Regency Orlando
Regency Ballroom R

CME CREDITS:
2 AMA PRA
Category 1 Credits™

This activity is supported by an educational grant from Amgen

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ENDOCRINE SOCIETY

CHAIR
Eliot A. Brinton, MD
Utah Foundation for Biomedical Research
Director, Atherometabolic Research
Salt Lake City, UT

AGENDA
PCSK9 and the LDL Receptor: Biological and Genetic Underpinnings of Heterozygous FH
Sergio Fazio, MD, PhD, Oregon Health and Science University

Patient Representative with Heterozygous FH
John R Guyton, MD, Duke University Medical Center

CVD Reduction with Non-Statins
Harold Edward Bays, MD, Louisville Metabolic and Atherosclerosis Research Center Inc

Management of Hypercholesterolemia in Diabetes: When to Treat and How
Eliot A. Brinton, MD, Utah Foundation for Biomedical Research
Director, Atherometabolic Research

LEARNING OBJECTIVES
Upon completing this activity, learners will be able to:
• Summarize the biology and genetic underpinnings of dyslipidemia as related to the LDL receptor and PCSK9
• Explain the results of IMPROVE-IT and FOURIER
• Assess the relative strengths and weaknesses of traditional vs newer cholesterol-lowering therapies to treat patients with familial hypercholesterolemia
• Evaluate strategies to optimize patient tolerance of and compliance to statin and ezetimibe treatment in FH and Diabetes Mellitus Type 2
• Incorporate PCSK9-I appropriately for further needed cholesterol lowering in high-risk patients
SYMPOSIUM AGENDA

The Revolution in Cholesterol Management: Putting PCSK9 Inhibitors into Practice
Monday, April 3, 2017

6:00 – 6:05 AM Welcome and Introduction
Eliot A. Brinton, MD

6:05 – 6:25 AM PCSK9 and the LDL Receptor: Biological and Genetic Underpinnings of Heterozygous FH
Sergio Fazio, MD, PhD

6:25 – 6:35 AM Patient Representative with Heterozygous FH
Michael Overstreet

6:35 – 6:55 AM Diagnosis of Heterozygous FH and Statin Treatment
John R. Guyton, MD

6:55 – 7:15 AM CVD Reduction with Non-Statins
Harold Edward Bays, MD

7:15 – 7:35 AM Management of Hypercholesterolemia in Diabetes: When to Treat and How
Eliot A. Brinton, MD

7:35 – 8:00 AM Roundtable Discussion and Q&A

FACULTY

Eliot A. Brinton, MD – Program Director
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
Salt Lake City, Utah

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

John R Guyton, MD
Professor of Medicine
Director, Duke Lipid Clinic
Duke University Medical Center
Durham, NC

Harold Edward Bays, MD, FTOS, FACC, FACE, FNLA
Medical Director / President
Louisville Metabolic and Atherosclerosis Research Center
Louisville KY
Eliot A. Brinton, MD – Program Director
Dr. Brinton is President, Utah Lipid Center and Director, Atherometabolic Research, Utah Foundation for Biomedical Research in Salt Lake City, UT. He is President, American Board of Clinical Lipidology and a fellow of the American Heart Association and National Lipid Association. Throughout his 30-year-plus career Dr. Brinton has been an investigator in research funded from many sources including grants from the National Institutes of Health (NIH), the Department of Veterans Affairs, the AHA, and industry. His primary research focus is on mechanisms of human high-density lipoprotein (HDL) metabolism, including the effects of diet, exercise, estrogen, and insulin resistance. He also has research interests in hypertriglyceridemia, hypercholesterolemia, diabetes, obesity, postmenopausal estrogen replacement, and insulin sensitivity.

His areas of clinical expertise include management of dyslipidemia, diabetes mellitus, obesity and insulin resistance, and prevention of atherosclerosis. At the Utah Lipid Center, he runs the only LDL-Apheresis center between Denver and the West Coast.

Dr. Brinton is Associate Editor of the Journal of Clinical Lipidology, Assistant Editor of the Journal of Obesity, and he has served as Editor of Lipids Online, and Section Editor of Current Atherosclerosis Reports. He is on the editorial boards of the Journal of Clinical Endocrinology and Metabolism, Journal of Managed Care Pharmacy, and Clinical Lipidology. Dr. Brinton is a peer reviewer for numerous journals including the American Journal of Cardiology, Archives of Family Medicine, Circulation, and Diabetes Care. He has authored of over 100 articles in peer-reviewed journals, including Science, the New England Journal of Medicine, JAMA, Circulation, and the Journal of Clinical Investigation. Dr. Brinton has received several scientific awards, including a Clinical Investigator Award from the NIH, a Merit Review Award from the Veterans Administration, and the Robert I. Levy Award of the Kinetics and Metabolism Society (co-recipient with Jan L. Breslow, MD of The Rockefeller University).
**Sergio Fazio, MD, PhD**
An MD graduate of the University of Rome, Italy, Dr. Fazio continued at the same institution with a fellowship in Metabolic Diseases. In 1985, he undertook a Ph.D. program in Experimental Medicine at the University of Siena, Italy, and completed it at the University of California, San Francisco (UCSF). In 1988 Dr. Fazio joined the Gladstone Institute of Cardiovascular Disease, UCSF, as a postdoc and then as an Instructor in Medicine.

In 1993 Dr. Fazio joined Vanderbilt University as an Assistant Professor in Endocrinology, where he co-founded the Lipid Clinic and became Director of the Lipid Laboratory. In 1998, he was promoted to Associate Professor. In 1999, he joined the Division of Cardiology to run the Atherosclerosis Research Unit. In 2002, he was promoted to Professor. In 2011 he was appointed the Cornelius Vanderbilt Chair of Cardiovascular Medicine and Chief of the section of Cardiovascular Disease Prevention. Since July 2014 he holds the William and Sonja Connor chair of Preventive Cardiology at the KCVI of OHSU.

His clinical interest is the management of dyslipidemic patients. Dr. Fazio’s NIH-supported research portfolio focuses on the pathogenesis of genetic dyslipidemias, the early cellular events in atherogenesis, and gene therapy approaches to atherosclerosis. He has been an Established Investigator of the American Heart Association and is PI and Co-PI on several NIH grants. He has published over 200 papers, including original articles, reviews, editorials, and book chapters. He was a charter member of the Study Section AICS of the NIH-NHLBI from 2006 to 2010. He is member of the American Society for Clinical Investigation and of the Association of American Physicians. He is on the editorial board of Arteriosclerosis, Thrombosis and Vascular Biology and of Circulation Research, and is an associate editor for the Journal of Clinical Lipidology.

**John R Guyton, MD**
Dr. John R. Guyton is Professor of Medicine, Endocrinology Division, and Director of the Lipid Clinic at Duke University Medical Center. Dr. Guyton received his undergraduate degree in Physics from the University of Mississippi and his M.D. from Harvard Medical School. He did his residency in internal medicine under Donald Seldin at University of Texas Southwestern Affiliated Hospitals in Dallas. He then completed a Research Fellowship in Pathology at Harvard Medical School with Morris Karnovsky, conducting research studies in atherosclerosis. Dr. Guyton moved to Baylor College of Medicine in Houston, where held a Research Career Development Award and two R01 grants from NIH for studies on lipid deposition in human atherosclerosis.

Dr. Guyton has published 135 articles on atherosclerosis and lipid disorders, as well as 24 book chapters. He was active in the founding of the Southeast Lipid Association, the National Lipid Association, and the American Board of Clinical Lipidology. He has served as President of each of these organizations. In the National Lipid Association, he has served on the Lipid Drug Safety Task Force in 2006-2007 and the Statin Intolerance Panel in 2014. He will begin a new position as editor of the Journal of Clinical Lipidology in September 2017.
Dr. Harold Bays is Board Certified in Endocrinology and Internal Medicine, Diplomate of the American Board of Clinical Lipidology, and Diplomate of the American Board of Obesity Medicine. He has served as an Investigator for over 450 Phase I - IV clinical trials regarding treatments for dyslipidemias, obesity, diabetes mellitus, hypertension, and other metabolic and hormonal disorders. As Medical Director and President of Louisville Metabolic and Atherosclerosis Research Center, Dr. Bays has written, or served as a contributing author to over 200 peer review scientific manuscripts and book chapters, as well as over 100 scientific abstracts presented at major scientific meetings. He is a Fellow of the National Lipid Association (FNLA), Fellow of The Obesity Society (FTOS), Fellow of the American College of Cardiology (FACC) and Fellow of the American Association of Clinical Endocrinologists (FACE).
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LEARNING OBJECTIVES

Upon completion of this educational activity, learners will be better able to:

- Summarize the biology and genetic underpinnings of dyslipidemia as related to the LDL receptor and PCSK9
- Explain the results of IMPROVE-IT and FOURIER
- Assess the relative strengths and weaknesses of traditional (statins and ezetimibe) vs newer (PCSK9-I) cholesterol-lowering therapies to treat patients with familial hypercholesterolemia (FH)
- Evaluate strategies to optimize patient tolerance of and compliance to statin and ezetimibe treatment in FH and Diabetes Mellitus Type 2 (DM2)
- Incorporate PCSK9-I appropriately for further needed cholesterol lowering in high-risk patients

TARGET AUDIENCE

This continuing medical education activity should be of substantial interest to endocrinologists and endocrine fellows, cardiologists, and other healthcare professionals caring for patients with lipid disorders including familial hypercholesterolemia.

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**Sergio Fazio, MD**: Ad Hoc Consultant, Amarin, Amgen, Sanofi, Kowa, Merck & Co.

**John R Guyton, MD**: Principal Investigator, Amarin, Amgen, Regeneron, Sanofi; Investigator, Regeneron; Speaker, Amgen

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**Connie Newman, MD**

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**Andrew Ahmann, MD**: Research Support, DexCom, Lexicon, Medtronic, Novo Nordisk; Consultant, Dexco, Novo Nordisk, Trividia Health

**Giuseppe Barbesino, MD**: Spouse, employee of Genzyme

**John Carmichael, MD**: Research Support, Novo Nordisk, Chiasma, Novartis, Pfizer, Strongbridge Biopharma; Speaker, Novartis; Advisory Board, Pfizer, Chiasma, Ionis Pharmaceuticals

**Natalie Cusano, MD**: Research Support, Shire; Speaker, Shire

**Joan Han, MD**: Research Support, Rhythm Pharmaceutical

**Alan Kelly, MD**: Speaker, Eli Lilly

**E Michael Lewiecki, MD**: Consultant, Amgen, Merck, Eli Lilly, Radius Health, Shire, Abbvie and Alexion; Speaker, Alexion, Shire; Research Grant Support, Amgen, Eli Lilly, Merck

**Lisa Nachtigall, MD**: Consultant, Ipsen, Novartis, Corcept; Grant Support/Investigator, Chiasma

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**ACKNOWLEDGEMENT OF COMMERCIAL SUPPORT**
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PCSK9 and the LDL Receptor:
Biological and Genetic Underpinnings
of Heterozygous FH

Sergio Fazio, MD, PhD
Familial Hypercholesterolemia (Classic Definition):
Genetically Inherited High LDL Due to Mutations in
1. LDL receptor (removes LDL from circulation)
2. ApoB (LDL protein ligand for the LDL receptor)

Familial Hypercholesterolemia (Expanded Definition):
Genetically Inherited High LDL Due to Mutations in
1. LDL receptor (removes LDL from circulation)
2. ApoB (LDL protein ligand for the LDL receptor)
3. PCSK9 GOF (binds and destroys LDL receptor)
4. LDLR-RAP (positions LDL receptor on apical surface)
Familial Hypercholesterolemia (Expanded Definition):
Genetically Inherited High LDL Due to Mutations in
1. LDL receptor (removes LDL from circulation)
2. ApoB (LDL protein ligand for the LDL receptor)
3. PCSK9 GOF (binds and destroys LDL receptor)
4. LDLR-RAP (positions LDL receptor on apical surface)
5. Some other genes...... or something

10 consecutive patients I sent to in-house clinical geneticist for genetic testing

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>JG</td>
<td>F</td>
<td>30</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>F</td>
<td>69</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>PK</td>
<td>M</td>
<td>54</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>TL</td>
<td>M</td>
<td>65</td>
<td>Cancelled</td>
<td>Patient cost too high</td>
</tr>
<tr>
<td>JC</td>
<td>M</td>
<td>52</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>JF</td>
<td>F</td>
<td>67</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>F</td>
<td>12</td>
<td>Positive</td>
<td>LDLR Ex8del</td>
</tr>
<tr>
<td>JL</td>
<td>M</td>
<td>45</td>
<td>Cancelled</td>
<td>Patient Unsure</td>
</tr>
<tr>
<td>RB</td>
<td>F</td>
<td>56</td>
<td>Positive</td>
<td>LDLR p.R595W</td>
</tr>
<tr>
<td>LB</td>
<td>M</td>
<td>66</td>
<td>Cancelled</td>
<td>Patient cost too high</td>
</tr>
</tbody>
</table>

Patient PK
54 year old male originally from Western Australia
Healthy, athletic, symptom free
His doctor told him it is time to get serious about his cholesterol
He admits he had known about his cholesterol problem since he was in high school
Never treated
A specialist told him that genetic testing is unnecessary because “You certainly have FH Morocco”
Mother affected by hypercholesterolemia, but no evidence of CAD/CVD
One sibling, in good health. Two children, healthy, not screened.
He will not take medications
Total cholesterol 368
Triglycerides 152
HDL 63
LDL 275
Lp(a) 84

Genetic testing negative

Patient RB
56 year old female
Healthy, symptom free, works as ED nurse
Long history of statin intolerance, now treated with natural therapies, willing to reconsider
Mother and two older siblings affected by hypercholesterolemia, but no evidence of CAD/CVD. Three children, healthy, not screened
Total cholesterol 456
Triglycerides 78
HDL 104
LDL 336
Lp(a) 14

Genetic testing positive

LDL-C Goal Attainment in FH

<table>
<thead>
<tr>
<th>Treated LDL-C &lt;100 mg/dL</th>
<th>Reduction in LDL-C 250%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>Percent</td>
</tr>
<tr>
<td>25</td>
<td>64</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

PCSK9: from Discovery to Clinic

NARC-1 = neural apoptosis-regulated convertase 1; POC = point of care
**Cardiovascular Outcomes Trials of PCSK9 Inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Sanofi/Regeneron</td>
<td>Amgen</td>
<td>Pfizer</td>
</tr>
<tr>
<td><strong>Trial</strong></td>
<td>ODYSSEY Outcomes</td>
<td>FOURIER</td>
<td>SPIRE I, SPIRE II</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>18,000</td>
<td>22,500</td>
<td>12,000, 6300</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>4-16 weeks post-ACS</td>
<td>MI, stroke, or PAD</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>Evidence-based Rx</td>
<td>Atorvastatin ≥20 mg or equivalent</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td>≥70 mg/dL</td>
<td>≥70 mg/dL</td>
<td>≥70-99 mg/dL, ≥100 mg/dL</td>
</tr>
<tr>
<td><strong>PCSK9i Dosing</strong></td>
<td>Every 2 weeks</td>
<td>Every 2 or Every 4 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>CHD death, MI, ischemic stroke, or UA hospitalization</td>
<td>Primary: CV death, MI, stroke, UA hospitalization or coronary revascularization Key Secondary: CV death, MI, or stroke</td>
<td>CV death, MI, stroke, or urgent revascularization</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>March 2018</td>
<td>December 2017</td>
<td>August 2017</td>
</tr>
</tbody>
</table>

**Nearly Half of Plasma PCSK9 Associates with LDL**

- Sun H et al. ATVB 2012.
Relative distribution of PCSK9 between LDL and Lp(a)

- Relative distribution between apoB-PCSK9 levels in LDL and Lp(a) was studied separately in each subject.

Conclusion

- Heterozygous FH is a relatively common inherited defect
- It is most commonly due to mutations in the LDL receptor (LDLR)
- Even in subjects with LDLR mutation, PCSK9 plays a critical role in regulating hepatic LDLR levels
- CVD risk is greatly enhanced in FH subjects due to their life-long exposure to severe hypercholesterolemia
- LDL goal attainment in FH subjects is difficult with inexpensive statins and other oral agents
- New PCSK9 agents reduce LDL by 50-65% but are expensive
- The biology of PCSK9 is not well understood, and discovery may lead to alternative approaches to blocking the action of this protein
Diagnosis of Heterozygous FH and Statin Treatment Sergio

John R. Guyton, MD
Clinical Points about Diagnosing Familial Hypercholesterolemia and Using Statin Medications

ENDO Satellite Meeting
April 3, 2017

John R. Guyton, M.D.
Duke University Medical Center

Disclosures

- Research grants: Amgen, Regeneron, Sanofi, Amarin
- Honorarium: Amgen

Learning Objectives

- Develop ability to diagnose familial hypercholesterolemia consistent with international norms.
- Cite and utilize current guidelines for moderate and intensive statin therapy.
- Recognize and respond to statin intolerance.
- Advise patients on expected benefits of statin and ezetimibe LDL-lowering therapy.

Case 117. Familial Hypercholesterolemia

Woman referred to Lipid Clinic in 1995 at age 51 for hypercholesterolemia. Occasional cigarette smoking. No hx of ASCVD events or symptoms. Did not “feel well” while taking simvastatin 40 mg/d. Achilles tendon xanthomas.

<table>
<thead>
<tr>
<th>Date</th>
<th>Chol</th>
<th>TG</th>
<th>HDLC</th>
<th>LDLC</th>
<th>Lp(a)</th>
<th>While taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>340</td>
<td>141</td>
<td>68</td>
<td>243</td>
<td></td>
<td>simvastatin 20 mg</td>
</tr>
<tr>
<td>1999</td>
<td>260</td>
<td>79</td>
<td>68</td>
<td>176</td>
<td>2</td>
<td>atorvastatin 10 mg, IR-niacin 500 mg bid</td>
</tr>
<tr>
<td>2001</td>
<td>258</td>
<td>73</td>
<td>76</td>
<td>167</td>
<td>2</td>
<td>atorvastatin 10 mg, IR-niacin 750 mg bid, colesevelam 4 tabs</td>
</tr>
<tr>
<td>2014</td>
<td>190</td>
<td>55</td>
<td>89</td>
<td>90</td>
<td></td>
<td>atorvastatin 10 mg, IR-niacin 1000 mg bid, ezetimibe 10 mg, colesevelam 6 tabs</td>
</tr>
</tbody>
</table>

Case 118. Familial Hypercholesterolemia

Daughter of previous patient. Lipid Clinic visit in 1996 at age 30 for hypercholesterolemia. No hx of ASCVD events or symptoms.

<table>
<thead>
<tr>
<th>Date</th>
<th>Chol</th>
<th>TG</th>
<th>HDLC</th>
<th>LDLC</th>
<th>Lp(a)</th>
<th>While taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>305</td>
<td>111</td>
<td>37</td>
<td>245</td>
<td></td>
<td>colestipol 1 g</td>
</tr>
</tbody>
</table>

July 2013. Enrolled in research study of monoclonal antibody to PCSK9.
**Familial Hypercholesterolemia**

- Original definition: Hypercholesterolemia due to defective LDL receptor function.
- Practical definition: Severe inherited hypercholesterolemia associated with tissue deposition of cholesterol and early ASCVD.

**Dx of FH: Dutch Lipid Clinic Network Criteria**

Definite > 8, Probable 6-8, Possible 3-5, Unlikely <3

1. LDL-C Points
   - >325 8
   - 251-325 5
   - 191-250 3
   - 155-190 1

2. Phys exam Points
   - Tendon xanthoma 6
   - Corneal arcus age <45 4

**Achilles Tendon Xanthoma**

**Corneal Arcus**
**Dx of FH: Dutch Lipid Clinic Network Criteria**

Definite > 8, Probable 6-8, Possible 3-5, Unlikely <3

3. **1st deg relative** | **Points**
--- | ---
Early CHD | 1
High LDL-C | 1-2
Xanth, arcus | 2

4. **ASCVD** | **Points**
--- | ---
Early CHD | 2
Early CerVD or PAD | 1

5. **Mutational analysis** | 8

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**Dx of FH: Simon Broome Register Criteria**

Definite FH: LDL-C > 190 in adult or >140 in child under age 16

**PLUS EITHER**

- Tendon xanthomas in patient, 1st degree relative, or 2nd degree relative (grandparent, uncle, aunt)
- OR
- DNA evidence of deleterious mutation.

Possible FH: LDL-C > 190, 140 and family hx MI male <50 y.o. female <60 y.o.

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**Dx of FH by Dutch Lipid Clinic Criteria in Copenhagen Population Study**

- Definite > 8 pts: 0.20%
- Probable 6-8 pts: 0.53%
- Possible 3-5 pts: 6.3%

*Benn M et al. JCEM 2012; 97:3956-64.*

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**DNA testing in CHD-free individuals with LDL-C > 190 mg/dl**

1.7% had a pathogenic FH mutation.

**Simon Broome “Possible FH”**

25-30% had a pathogenic FH mutation.

*Khera et al. JACC 2016;67:2578.*


---

**Distribution of Lipoprotein(a) Concentrations among FH Patients Who Did and Did Not Have CHD.**


---

**2013 AHA/ACC Four Statin Treatment Groups**

1. Clinical ASCVD | Age ≤ 75 high intensity*
--- | Age > 75 moderate intensity*

2. LDL-C > 190 mg/dl | Age ≥ 21 high intensity

3. Diabetes 40-75 years of age | Moderate intensity for most age

4. ASCVD risk† calculation ≥ 7.5% over 10 years | Moderate or high intensity

*High intensity – atorvastatin 80 or 40 mg, rosvustatin 20 or 40 mg. Moderate – several statins with LDLC lowering 40% to 49%.

†Also certain other situations, e.g., high coronary calcium score.
**2015 NLA Recommendations**

1. Non-HDL-C is the primary treatment target.
2. If very-high risk, begin with moderate- or high-intensity statin with non-HDL-C and LDL-C goals <100 and <70 mg/dl, respectively.
3. In other patients, count number of major risk factors and treat to goals for non-HDL-C <130 and LDL-C <100 mg/dl.

---

**2017 AACE Lipid Guidelines**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description of risk</th>
<th>LDL-C goal</th>
<th>Non-HDL-C goal</th>
<th>ApoB goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme risk</td>
<td>- Progressing ASCVD with LDL-C &lt;70</td>
<td>&lt;55</td>
<td>&lt;80</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>- Clinical ASCVD + DM, CKD3/4, HeFH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Premature ASCVD &lt;55 male, &lt;65 female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk</td>
<td>- Established ASCVD</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td></td>
<td>- Diabetes or CKD3/4 with 1+ risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HeFH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>- &gt; 2 risk factors &amp; 10 year risk 10-20%</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td></td>
<td>- Diabetes or CKD3/4 with 0 risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>± 2 risk factors &amp; 10 year risk &lt;10%</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Low risk</td>
<td>0 risk factors</td>
<td>&lt;130</td>
<td>&lt;160</td>
<td>NR</td>
</tr>
</tbody>
</table>

---

**Statin Intolerance**

- **Hierarchy of Evidence**

  1. N of 1 randomized trial
  2. Systematic reviews of randomized trials
  3. Single randomized trial
  4. Systematic review of observational studies addressing patient-important outcomes
  5. Single observational study addressing patient-important outcomes
  6. Physiologic studies
  7. Unsystematic clinical observations

- **Side Effects of Statins**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Transaminases</td>
<td>0.3-2.5%</td>
<td>Often fatty liver, other drugs ↑ ALT/AST rarely serious ↑ bilirubin rarely occurs</td>
</tr>
<tr>
<td>Myopathy (Sx + CK 10x ULN)</td>
<td>0.1%</td>
<td>Hypothyroid, drug interactions</td>
</tr>
<tr>
<td>Myalgia, stiffness weakness</td>
<td>1% - 5%?</td>
<td>Reported by 10-25% of patients</td>
</tr>
<tr>
<td>Cognitive issues</td>
<td>?</td>
<td>Reported by ~1% of patients</td>
</tr>
</tbody>
</table>

---

*“4 reasons why RCTs may not be helpful for determining whether a putative harmful agent truly has deleterious effects”*

1. Harm rarely a primary endpoint. Unethical to expose patients to harm without benefit.
2. Rare (less than 1%) and serious adverse events may occur over a period of years.
3. Late or legacy effects of treatment are difficult to ascertain (e.g., RAI for thyrotoxicosis).
4. RCT study reports often fail to provide adequate information on harm.

Statin Intolerance

1. Help the patient distinguish between intolerance and safety. Apart from mild promotion of diabetes mellitus, permanent organ damage from statins is very rare.

2. Shared decision-making, but the patient has the final say.

Statin Dosing after Statin-Induced Myalgia

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosing</th>
<th>LDL Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 MTh</td>
<td>-24%</td>
<td></td>
</tr>
<tr>
<td>5 MWF</td>
<td>-26%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-33%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>-38%</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 MTh</td>
<td>-25%</td>
<td></td>
</tr>
<tr>
<td>2.5 MWF</td>
<td>-28%</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>-35%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-40%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>-45%</td>
<td></td>
</tr>
</tbody>
</table>

What Insurance Companies Usually Require for anti-PCSK9 Prior Authorization

1. Trial of at least 2 statins, one of them at lowest recommended daily starting dose.

2. Addition of ezetimibe 10 mg daily. Sometimes bile acid sequestrant.

3. Anti-PCSK9 for patients who “require additional lowering of LDL cholesterol” – FDA prescribing information.

Anticipated Benefit of LDLC Lowering

1. Older estimate: For every 1% lowering of LDL-C, 1% lowering of occlusive vascular events.

2. Newer estimate: For every 1 mmol/L (38.7 mg/dl) lowering of LDL-C, 20% lowering of occlusive vascular events.

   Implication of #2: Residual risk will remain for some at very high initial risk even if LDL-C approaches zero.


Learning Objectives

- Develop ability to diagnose familial hypercholesterolemia consistent with international norms.
- Cite and utilize current guidelines for moderate and intensive statin therapy.
- Recognize and respond to statin intolerance.
- Advise patients on expected benefits of statin and ezetimibe LDL-lowering therapy.
CVD Risk Reduction with Non-Statins

Harold Bays MD, FTOS, FACC, FACE, FNLA
Disclosures

Dr. Harold Bays and his affiliated research center do not own pharmaceutical stocks or patents. In the past 12 months, Dr. Harold Bays’ research site has received research grants from Amarin, Amgen, Alere, Allergan, Arisaph, AstraZeneca, Bristol Meyers Squibb, Catabasis, Cymabay, Dr. Reddy, Eisai, Eli Lilly, Esperion, Ferrer/Chiltern, Genphere, Gilead, GSK, Janssen, Johnson and Johnson, Kowa, Merck, Necktar, Necitil, Novartis, Novonordisk, Oregaixen, Pfizer, Proven, Regeneron, Sanofi, Selecta, Takeda, and TIMI. In the past 12 months, Dr. Harold Bays has served as a consultant/advisor for Abylum, Akeea, Amgen, AstraZeneca, Eli Lilly, Esperion, Ionis (ISIS), Janssen, Johnson & Johnson, Merck, Moderna, Novartis, Proctor & Gamble, Regeneron, Sanofi, Teva, and Takeda. In the past 12 months, Dr. Harold Bays has served as a speaker for Amarin, Amgen, Astra Zeneca, Eisai, Oregaixen, Regeneron, Sanofi and Takeda.
**Post-hoc Analysis of AIM-HIGH: Niacin ER in Patients with HTG & Low HDL-C**

<table>
<thead>
<tr>
<th># Patients with CV Events</th>
<th>☐ ERN Better</th>
<th>☐ ERN Worse</th>
<th>☐ HR (95% CI)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo ERN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG ≥ 198 &amp; HDL &lt; 33</td>
<td>54 (22.4)</td>
<td>48 (17.0)</td>
<td>0.74 (0.50, 1.09)</td>
<td>0.073</td>
</tr>
<tr>
<td>No</td>
<td>220 (15.1)</td>
<td>234 (16.3)</td>
<td>1.09 (0.91, 1.31)</td>
<td></td>
</tr>
<tr>
<td>TG ≥ 200 &amp; HDL &lt; 32</td>
<td>50 (25.0)</td>
<td>40 (16.7)</td>
<td>0.63 (0.40, 0.98)</td>
<td>0.017</td>
</tr>
<tr>
<td>No</td>
<td>224 (15.0)</td>
<td>242 (16.2)</td>
<td>1.11 (0.93, 1.33)</td>
<td></td>
</tr>
</tbody>
</table>

Log HR and 95% CI


---

**Statin-Mediated CV Risk Reduction**

**Cholesterol Treatment Trialists’ (CTT) Meta-analysis**

![Graph showing cholesterol reduction](image)

1 mmol/L (39 mg/dL) LDL-C treatment group difference reduces risk 22% (CTT 2010)

---

**IMPROVE-IT Study Design**

Patients aged ≥ 50 years and stabilized post-ACS ≤ 10 days:

- LDL-C 50-125 mg/dL (or 50-100 mg/dL if prior lipid-lowering therapy)

N=18,144

**Primary Endpoint:** CV death, nonfatal MI, unstable angina (UA) requiring hospitalization, coronary revascularization (≥ 30 days), or nonfatal stroke

**Secondary Endpoints:**
- Death due to any cause
- CHD death
- nonfatal MI, or urgent coronary revascularization (PCI or CABG) occurring ≥ 30 days after randomization

Follow-up visit Day 30, every 4 months

Duration: Minimum 2½-year follow-up (at least 5250 events)

---

**IMPROVE-IT Key Baseline Characteristics**

<table>
<thead>
<tr>
<th>EZ/Simva N=9067</th>
<th>Simvastatin N=9077</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>63.6</td>
</tr>
<tr>
<td>Female,%</td>
<td>24.5</td>
</tr>
<tr>
<td>Diabetes,%</td>
<td>27.1</td>
</tr>
<tr>
<td>MpriortopriorACS,%</td>
<td>21.2</td>
</tr>
<tr>
<td>STEMI/NSTEMI-UA,%</td>
<td>28.5/47.4/24.0</td>
</tr>
<tr>
<td>Median=DaypostACStandind(IQR)</td>
<td>5(3,8)</td>
</tr>
<tr>
<td>Catheterization/PCIforACSevent,%</td>
<td>88.1/70.4</td>
</tr>
<tr>
<td>Priorlipid-loweringtherapy,%</td>
<td>35.6</td>
</tr>
<tr>
<td>MeanLDL-CatACSevent(mg/dL)</td>
<td>93.8</td>
</tr>
</tbody>
</table>

MI=myocardial infarction; ACS=acute coronary syndrome; NSTEMI=non-ST segment elevation myocardial infarction; UA=unstable angina; randomization; IQR=interquartile range; PCI=percutaneous coronary intervention.
**IMPROVE-IT LDL-C and Lipid Changes**

<table>
<thead>
<tr>
<th>Time Since Randomization (Months)</th>
<th>LDL-C</th>
<th>TG</th>
<th>HDL-C</th>
<th>Ho-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZ/simvastatin</td>
<td>53.2</td>
<td>128.4</td>
<td>48.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>56.9</td>
<td>145.1</td>
<td>37.1</td>
<td>48.1</td>
</tr>
</tbody>
</table>

Mean Time-Weighted Avg: 69.5 vs. 53.7 mg/dL

**IMPROVE-IT Primary Efficacy Endpoint**
CV Death, Nonfatal MI, UA Requiring Hospitalization, Coronary Revascularization (≥ 30 days), or Nonfatal Stroke (Protocol-Defined ITT Population)

Hazard ratio, 0.936 (95% CI, 0.887 – 0.988); p=0.016
NNT=50

**Similar Rates of Cancer AEs and Cancer Deaths**
Protocol-Defined ITT Population

**Currently Available PCSK9 Inhibitors**

<table>
<thead>
<tr>
<th>FDA approval</th>
<th>Indication</th>
<th>Dosing</th>
<th>How supplied</th>
<th>Side effects</th>
<th>Effect of alirocumab/evolocumab on CV mortality and morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jul 2015</td>
<td>Adjunct to diet and max tolerated statin for adults with HeFH, or clinical ASCVD, who require additional lowering of LDL-C</td>
<td>75 – 150 mg SC Q2W</td>
<td>Single-dose pre-filled pens and pre-filled glass syringes that deliver 75 mg/mL or 150 mg/mL solution</td>
<td>Nasopharyngitis, injection site reactions; hypersensitivity reactions</td>
<td>Has not been established.</td>
</tr>
</tbody>
</table>

**PCSK9 Inhibitors**

EPC SK9 Inhibitors

Efficacy and Safety of Combining Alirocumab With Atorvastatin or Rosuvastatin Versus Adding Ezetimibe, Doubling Statin Dose or Switching Statin Therapy in High Cardiovascular Risk Patients: ODYSSEY OPTIONS I and II

Harold Bays, Michel Farnier, Robert Weiss, Juan Lima Ruiz, Gerald F. Watts, Joanna Gouni-Berthold, Jennifer G. Robinson, Peter Jones, M. Colhoun, Jian Zhao, Yunling Du, Corinne Hanotin, Stephen Donahue
Alirocumab Significantly Reduced LDL-C in Patients on an Entry Statin of ATV 20 Or 40 mg or RSV 10 mg

<table>
<thead>
<tr>
<th>PCSK9 Inhibitor CV Outcomes Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evolocumab</strong> (AMG 145)</td>
</tr>
<tr>
<td>Sponsor</td>
</tr>
<tr>
<td>Trial</td>
</tr>
<tr>
<td>Sample size</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>LDL-C mg/dL (mmol/L)</td>
</tr>
<tr>
<td>PCSK9 inhibitor dosing</td>
</tr>
<tr>
<td>Endpoint</td>
</tr>
<tr>
<td>Completion</td>
</tr>
</tbody>
</table>

UA = unstable angina.

What About Costs?

- [PCSK9 INHIBITOR] is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

- The effect of [PCSK9 INHIBITOR] on cardiovascular morbidity and mortality has not been determined

* Evolocumab also indicated to treat homozygous FH.

**PCSK9 = proprotein convertase subtilisin/kexin type 9.**
Overall Conclusions of Non-Statins

- Resins (bile acid sequestrants) are used infrequently due to adverse effects, and potential drug interactions
- Niacin is used infrequently due to modest improvement in lipid levels, adverse effects, and lack of convincing CVD benefits when added to statins
- Cholesterol absorption inhibitors (e.g., ezetimibe) modestly lowers LDL-C and modestly reduces ASCVD risk (albeit without an approval to reduce ASCVD risk)
- PCSK9 inhibitors dramatically reduce LDL-C levels, with one study demonstrating moderate reduction in ASCVD (but not yet approved to reduce ASCVD risk)
Management of Hypercholesterolemia in Diabetes: When to Treat and How

Eliot A. Brinton, MD
Management of Hypercholesterolemia in Diabetes Mellitus: When and How to Treat?

ENDO 2017 Satellite Symposium
The Revolution in Cholesterol Management: Putting PCSK9 Inhibitors into Practice
April 3, 2017; Orlando, FL

Eliot A. Brinton, MD, FAHA, FNLA
Immediate Past-President, American Board of Clinical Lipidology
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
President, Utah Lipid Center
Salt Lake City
eliot.brinton@utah.edu

Duality of Interest

Dr. Brinton has received:
- **Research** funding: Amarin, Aurora Foundation, Kowa, National Institutes of Health
- Honoraria as **consultant/advisor**: Akcea, Alexion, Amarin, Amgen, Arazel, AriaSaph, AstraZeneca, Kastle, Kowa, Merck, PTS Diagnostics, Regeneron, Sanofi-Aventis
- Honoraria as **speaker**: Akcea, Alexion, Amarin, Amgen, Boehringer-Ingelheim, Janssen, Kastle, Kowa, Lilly, Merck, Novo-Nordisk, Regeneron, Sanofi-Aventis

Hypercholesterolemia in DM: Presentation Outline

- Prevalence and CVD impact of hypercholesterolemia in DM
- Glycemic effects and risk of new-onset DM2 with various statins and statin doses in patients with metabolic syndrome and DM2 and their clinical application
- Application of CVD outcome data with ezetimibe and PCSK9 inhibitors in the treatment algorithm for patients with dyslipidemia and diabetes

Hypercholesterolemia and ASCVD in Diabetes Mellitus

- “ASCVD...is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes.”
- DM2 lipids: LDL-C 101 mg/dL (1/3 > 112), Non–HDL-C 137 (~1/3 > 153), HDL-C 38 (1/3 < 34), TG 160 (1/3 ≥ 204)
- The most prevalent dyslipidemia in DM2 is: ↑ TG (even if "nl", <200), ↓ HDL-C (even if "nl", >40), with nl-to-↓ LDL-C, but ↓ LDL size (↑ atherogenic), ↑ Non–HDL-C & ↑ apo B
- HeFH associates with ↓ ↓ DM2 prevalence: odds ratio 0.62 (0.55-0.69)

Non–HDL-C (& Apo B) Include All Atherogenic Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>Very-low-density lipoprotein</td>
</tr>
<tr>
<td></td>
<td>Made in the liver</td>
</tr>
<tr>
<td></td>
<td>TG &gt;&gt; CE</td>
</tr>
<tr>
<td></td>
<td>Takes lipids from the liver to periphery</td>
</tr>
<tr>
<td>IDL</td>
<td>Intermediate-density lipoprotein</td>
</tr>
<tr>
<td></td>
<td>Formed from VLDL with loss of TG</td>
</tr>
<tr>
<td></td>
<td>TG = CE</td>
</tr>
<tr>
<td></td>
<td>Also known as a VLDL remnant</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td></td>
<td>Formed from IDL with loss of TG</td>
</tr>
<tr>
<td></td>
<td>CE &gt;&gt; TG</td>
</tr>
<tr>
<td></td>
<td>Main plasma cholesterol carrier</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Lipoprotein (a)</td>
</tr>
<tr>
<td></td>
<td>Formed from LDL plus Apo (a)</td>
</tr>
<tr>
<td></td>
<td>Very atherogenic/pro-oxidative</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td></td>
<td>Removes cholesterol from peripheral tissues</td>
</tr>
<tr>
<td></td>
<td>Other anti-athero effects</td>
</tr>
</tbody>
</table>

Non–HDL-C Is Stronger than LDL-C in Predicting CHD Risk

1. ADA Standards of Care, CVD & Risk Management, Diabetes Care 40, Supp 1, Jan 2017, S75-S87.
To Fast or Not to Fast?

Fasting Lipid Panel
- Better accuracy for TG
- TG cutoffs are based on fasting values
- Slightly better for LDL-C
- Easy to get before visit
- Allows fasting glucose test, best for Metabolic Synd.

Non-Fasting Lipid Panel
- Can get on any visit
- Accuracy: Non-HDL-C good, TG OK (but differs), LDL-C reasonable
- Good prediction of CVD (but direct comparison lacking)
- A1c OK for DM2 risk

Bottom line: fasting panel is generally better but non-fasting is generally easier

ASCVD Risk Assessment in DM1 & DM2

DM1
- Assume high ASCVD risk if > 40 y/o (women = men)
- Even higher risk if other risk factors: smoking, +FHx, ↑LDL-C, HTG, low HDL-C, central obesity, MetSynd

DM2
- Assume high lifetime ASCVD risk even before Dx (i.e. at onset of MetSynd), women = men
- Assume high 10-y risk if > 40 y/o
- Even higher risk if other risk factors: smoking, +FHx, ↑LDL-C, ↑Non-HDL-C, ↑ApoB, HTG, low HDL-C, central obesity, MetSynd

Statins Work Equally Well in Patients With or Without Diabetes

Patients with Diabetes Have High Residual CVD Risk Despite Statin Monotherapy (= non-DM w/o statin)

Degree of ↓CHD is by Degree and Duration LDL-C Lowering

Genetic Lifelong Lower LDL-C

Rx ~ 4-7 y Lower LDL-C

Degree of ↓CHD is by Degree and Duration LDL-C Lowering

Genetic Lifelong Lower LDL-C

3-4x benefit with lifelong vs short "Rx" is rationale for lifelong statins for DM2

Rx ~ 4-7 y Lower LDL-C
Statin Intolerance

New-Onset DM2 with Statin Therapy

Genetics of HMGCR & PCSK9 Suggest ↑ New DM is On-Target Effect (Mendelian Randomization)

Risk of New-Onset DM-2 w/ Statin by Age

Statin % Patients with muscle complaints (N=832)
Pravastatin 40 mg 10.9
Atorvastatin 40–80 mg 14.9
Simvastatin 40–80 mg 18.2
Fluvastatin XL 80 mg 5.1

Due to 1st-pass hepatic extraction, fluvastatin XL has ↓ systemic statin levels → ↓ muscle exposure

Fluva XL 80 may be worth trying in patients reporting total/near-total statin intolerance from muscle pain


Genetics of HMGCR & PCSK9 Suggest ↑ New DM is On-Target Effect (Mendelian Randomization)

A. Myocardial Infarction or Death from CHD

<table>
<thead>
<tr>
<th>Group</th>
<th>Difference in LDL Cholesterol vs. Both Scores below Median</th>
<th>Odds Ratio for Myocardial Infarction or Death from CHD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both scores above median</td>
<td>-7.2</td>
<td>0.88 (0.83–0.93)</td>
</tr>
<tr>
<td>PCSK9 score above median</td>
<td>-4.4</td>
<td>0.99 (0.90–0.98)</td>
</tr>
<tr>
<td>HMGCR score above median</td>
<td>-3.3</td>
<td>0.95 (0.91–0.99)</td>
</tr>
</tbody>
</table>

B. Diabetes

<table>
<thead>
<tr>
<th>Group</th>
<th>Difference in LDL Cholesterol vs. Both Scores below Median</th>
<th>Odds Ratio for Diabetes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both scores above median</td>
<td>-7.2</td>
<td>1.11 (1.05–1.16)</td>
</tr>
<tr>
<td>PCSK9 score above median</td>
<td>-4.4</td>
<td>1.07 (1.00–1.13)</td>
</tr>
<tr>
<td>HMGCR score above median</td>
<td>-3.3</td>
<td>1.06 (1.01–1.13)</td>
</tr>
</tbody>
</table>

Risk of New-Onset DM-2 w/ Statin by Age


P = 0.019
Additive Effect of Fasting Glucose & Statin Intensity on Risk of New-Onset DM2

Risk of New-Onset DM-2 by Statin

Pitavastatin Does Not Increase New-Onset DM2 (by OGGT)

Pitavastatin Has Neutral Glycemic Effect (3 mo-2y f/u; prava, < atorva, others)

Statins’ Effects on New-Onset DM-2: Summary

Overall and Special Cases
- ~9% ↑ DM risk
- ↑ Risk w/ ↑ age and/or MetSynd
- Little/no ↑ risk in patients w/ HeFH/HoFH*, NFG
- ↑ Risk w/ atorva, rosuva, simva, other (esp. high-dose)
- Little/no ↑ risk w/ pravastatin or pitavastatin (?)

Net Risk/Benefit Ratio Favorable
- NNH = 1 case of DM per 225 pts Rx’d x 4y
- NNT = 1 MACE per 31 pts Rx’d x 4y**
- 7:1 MACE prev/new DM (3:1 MACE/DM at high-dose)

Don’t avoid statin Rx in med- to high-risk pts (but DO prevent DM by diet, lifestyle and meds)

Waters, DD. J Am Coll Cardiol 2011;57:1535-1545.
Intestinally-Acting LDL-C Lowering Agents

- Bile-acid sequestrants
- Cholesterol absorption inhibitors (ezetimibe)

Major Pre-specified Subgroups

Ezetimibe Does Not Increase Risk of New-Onset DM2 (Despite further ↓ LDL-C)

Statin + Intestinally-Acting Agent (CAI or BAS) = 2 to 3 Statin Doublings

Intestinally Acting Lipid Meds
Summary/Overview

• Both BAS and CAI
  – ↑ LDL receptors (like statins)
  – ↓ LDL-C = 2-3 statin dose doublings

• CAI
  – Easy (one small pill, once daily, few side effects)
  – Proven ↓ ASCVD w/ statin
  – Greater benefit in DM2 (w/o)
  – Now generic, ↓ price soon

• BAS
  – Hard (many large pills vs gritty powder, 1-3 x daily, GI side effects, may ↓ drug absorption)
  – Contraindicated if TG >400 mg/dL
  – Proven ↓ ASCVD w/o statin (likely w/ statin)
  – ↓ Glucose in DM2 (DM2 prevention?)
  – Inexpensive generic

Phase 3, Placebo-Controlled Clinical Trial Program Included
3499 Randomized Patients: 100% on Maximally Tolerated Statins


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3499 Randomized Patients: 100% on Maximally Tolerated Statins

PCS-K-I mAbs Lower LDL-C Equally in Patients w/o or w/ DM2

DM2 alone (w/o HeFH or prior ASCVD)
~10% of patients studied but not an indication for PCSK9-I regardless of ASCVD risk!

N=312,175 (25% women) in 49 trials, 39,645 MVE, base LDL-C 122 mg/dL.
Can LDL-C be Too Low?

- Abetalipoproteinemia & HoHypobeta. (LDL-C <25 mg/dL)
  - Autosomal recessive Lo MTP, or apo B gene mutations
  - Apo B-cont. lipos (chylos, VLDL, LDL) very low/absent
  - Neurological/ophthalm sequelae Rx w/ fat-soluble vits/EFFA
  - Malabsorption 5x reduced by low fat diet + MCT oil
  - Hepatitis, hyperamylasemia, hep. fibrosis
- Heterozygous PCSK9 LoF (LDL-C ~60-100)—N=100s
  - PCSK9 ~1/2 nl
  - ↓↓ASCVD
- Homozygous PCSK9 LoF (LDL-C ~10-20)—N=3
  - PCSK9 absent
  - Normal neurological and reproductive function
- PCSK9-I mAb → LDL-C < 25: no evidence for harm

Clinical Pearls for PCSK9-I mAb Use

- Expensive, so use requires ↑↑ 10-y CVD risk
- Prescribe on-label (generally too hard to get approval for DM w/o HeFH or prior ASCVD!)
- Dx clinical ASCVD (↑↑ ↑↑ CAC??)
- Dx HeFH: LDL-C >190 (+ FHx, tendon xanth.)
- Document statin intolerance if < max. efficacy
- Ezetimibe (BAS, NA) good but optional?
- LDL-C > threshold, ~30 mg/dL (0-60) > goal
- Send Rx and clinic note to specialty pharmacy—they can and should get approval
- For co-pay help:
  - Commercial—manufacturer assistance programs
  - Medicare—foundation via spec pharm vs mfr. Assist
- If LDL-C ↓ to <25, don’t stop/↓ statin (d/c ezet)

Can LDL-C be Too Low?

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  - Autosomal recessive Lo MTP, or apo B gene mutations
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After Lee J, J Inherit Metab Dis 37:333, 2014; Cohen, JC. NEJM 2006;354:1264-72 and Sabatine MS.

Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at Which to Consider Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1 major ASCVD risk factors</td>
<td>Non-HDL-C mg/dL LDL-C mg/dL</td>
<td>≤130 ≥150</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors</td>
<td>≤130 ≥150</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥2 major ASCVD risk factors</td>
<td>≤100 ≥150</td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>ASCVD*</td>
<td>≤100 ≥70</td>
<td></td>
</tr>
</tbody>
</table>

*For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.
**2015 NLA Expert Panel Recommendations Specify PCSK9 Inhibitors as a Therapeutic Option in Appropriate Patients**

**PCSK9 inhibitors should be considered primarily in:**

- Patients with ASCVD who have LDL-C ≥100 mg/dL while on maximally tolerated statin (e.g., ezetimibe) therapy
- HfH patients without ASCVD who have LDL-C ≥130 mg/dL while on maximally tolerated statin (e.g., ezetimibe)

**PCSK9 inhibitors may also be considered in:**

- Selected high-risk patients with ASCVD (e.g., recurrent ASCVD events) who haveatherogenic cholesterol levels below the specified values, but above their treatment goals (i.e., LDL-C ≥70 mg/dL)

ASCVD: atherosclerotic cardiovascular disease; HfH: heterozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; NLA: National Lipid Association

*Such use should be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.


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**2016 ACC Expert Consensus Decision Pathway: PCSK9 Inhibitors are a Therapeutic Option in Appropriate Patients**

**Adding a PCSK9 inhibitor may be considered to lower LDL-C in patients:**

**With stable clinical ASCVD without comorbidities**

- If <50% LDL-C reduction or LDL-C ≥100 mg/dL on maximally tolerated statins + ezetimibe

**With clinical ASCVD with comorbidities**

- If <50% LDL-C reduction or LDL-C ≥70 mg/dL on maximally tolerated statins + ezetimibe

**With clinical ASCVD and baseline LDL-C ≥190 mg/dL (HeFH)**

- If <50% LDL-C reduction or LDL-C ≥70 mg/dL on maximally tolerated statins

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**2017 AACE Lipid Guidelines**

**Table 9: Atherosclerotic Cardiovascular Disease Risk Categories and Low-Density Lipoprotein Treatment Goals**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors*/10-year risk †</th>
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<th>Non-HDL-C (mg/dL)</th>
<th>Apo B (mg/dL)</th>
</tr>
</thead>
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<tr>
<td>Extensive Risk</td>
<td>Progressive atherosclerotic disease in patients with ASCVD</td>
<td>&lt;55</td>
<td>&lt;80</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>Established clinical cardiovascular disease in patients with ASCVD, coronary, carotid or peripheral vascular disease, 10-year risk ≥20%</td>
<td>&lt;50</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>High Risk</td>
<td>Diabetes or CVD 3/4 with 1 or more risk factors†</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
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<tr>
<td>Moderate Risk</td>
<td>Diabetes or CVD 3/4 with no other risk factors</td>
<td>&lt;100</td>
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<tr>
<td>Low Risk</td>
<td>52 risk factors and 10-year risk &lt;10%</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>None Risk</td>
<td>0 risk factors</td>
<td>&lt;130</td>
<td>&lt;160</td>
<td>NR</td>
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Risk factors include: age, family history, diabetes mellitus, hypertension, smoking, metabolic syndrome, obesity, metabolic syndrome, hyperlipidemia, and diabetes mellitus.

*All risk factors are elevated.
†If ≥10-year risk ≥20%, high-risk.

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**Summary: ASCVD Risk Management by Cholesterol Lowering in DM1 & DM2**

**DM1**

- Statins in most/all if > 40 y/o (women = men)
- Consider statin adjuncts (ezet & PCSK9-I) if LDL-C/Non-HDL-C above goal:
  - 2° prev: <70/100
  - 1° prev: <100/130

**DM2**

- Statins in most/all at any age (female = male, even children/adolescents) due to lifetime CVD risk vs efficacy, safety & cost of statins
- Consider statin adjuncts (ezet & PCSK9-I) if LDL-C/Non-HDL-C at or above goal:
  - 2° prev: <70/100
  - 1° prev: <100/130

**DM1 or DM2**

- Extra-aggressive Rx needed if DM + FH

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**Consider PCSK9-I for CVD pt goal or HeFH**

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  - 1° prev: <100/130

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