Emerging Challenges in Primary Care: 2017

New Agents, New Options, and Expanded Potential In Lipid Management: Integrating The Data Into Practice
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Disclosures

- **Jan Basile, MD** serves on the speakers bureau for Amgen, Arbor, and Janssen. Dr. Basile also serves as a consultant for Novartis, Medtronic, and Up-to-date.

- **Mahfouz El Shahawy, MD, MS, FACP** has no relevant financial relationships to disclose.

- **Keith C. Ferdinand, MD, FACC, FAHA, FNLA, FASH** serves as a consultant for Amgen, Novartis, Sanofi, and Quantum Genomics. Dr. Ferdinand also serves as a consultant/researcher for Boehringer-Ingelheim and as a researcher for Eli Lilly.

- **Barbara Hutchinson, MD, PhD, FACC** serves on the cardiovascular writing committee for ABIM.

- **Peter P. Toth, MD, PhD, FCCP, FAHA, FESC, FACC** serves on the speakers bureau for Amgen, Amarin, Kowa, Merck, Regeneron, and Sanofi.

- **Karol E. Watson, MD, PhD** serves as a consultant for Amarin and Amgen. Dr. Watson also serves as a consultant/speakers bureau member for Boehringer Ingleheim.
Please rate your confidence in your ability to treat hypercholesterolemia in patients who are not achieving optimal goals or are refractory to statin therapy:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2

A patient with no history of cardiovascular disease and an atherosclerotic cardiovascular disease (ASCVD) risk of 9.1%, starts atorvastatin 10 mg daily. On follow up, LDL-C is 40 mg/dL. She is tolerating therapy well. What is the most appropriate next step?

1. Switch to ezetimibe
2. Decrease the statin dose
3. Continue current statin dose
4. Switch to a less potent statin
5. Hold statin until LDL-C rises above 50 mg/dL
A patient with recent NSTEMI starts rosuvastatin 20 mg daily. On follow up he complains of disabling muscle pain. What is the most appropriate next step?

1. Switch to ezetimibe
2. Cut statin dose in half
3. Continue statin and add Coenzyme Q-10
4. Continue statin while you check CPK level
5. Hold the statin while you evaluate the muscular complaints
A patient with hypercholesterolemia is taking atorvastatin 80 mg and ezetimibe 10 mg daily. Lipid profile at follow up shows:

- LDL-C 185 mg/dL
- HDL-C 45 mg/dL
- Triglycerides 330 mg/dL
- She is tolerating therapy well

What is the most appropriate next step?

1. Add niacin
2. Add fish oil
3. Add fibrate
4. Add colesevelam
5. Add PCSK9 inhibitor
Pre-test ARS Question 5

All of the following patient types are included in the CMS Quality Measure for cholesterol management, EXCEPT:

1. Adults with ASCVD
2. Adults with LDL-C \( \geq 190 \) mg/dL
3. Adults age 40-75 years with diabetes, any LDL-C
4. Aged \( \geq 21 \) years with familial hypercholesterolemia
A 65-year-old African American man with a history of dyslipidemia, hypertension, and obesity presents 2 years post NSTEMI. He reports no symptoms or side effects of medical therapy.

BP 132/76 mmHg, eGFR 54 mL/min/1.73m², LDL-C 78 mg/dL, HDL-C 40 mg/dL, Triglycerides 152 mg/dL, and Total-C 148 mg/dL

Current medications include valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding ezetimibe 10 mg qd.

1. Yes, it is consistent

2. No, it is not consistent
65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m², LDL-C 78 mg/dL, HDL-C 40 mg/dL, Triglycerides 152 mg/dL, and Total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

If ezetimibe 10 mg qd is started and LDL-C remains >70 mg/dL at follow up, consider PCSK-9 inhibitor.

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 8

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m2, LDL-C 78 mg/dL, HDL-C 40 mg/dL, Triglycerides 152 mg/dL, and Total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding niacin.

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 9

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m2, LDL-C 78 mg/dL, HDL-C 40 mg/dL, Triglycerides 152 mg/dL, and Total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding fibrate.

1. Yes, it is consistent
2. No, it is not consistent
Pre-test ARS Question 10

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m², LDL-C 78 mg/dL, HDL-C 40 mg/dL, Triglycerides 152 mg/dL, and Total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding PCSK-9 inhibitor.

1. Yes, it is consistent
2. No, it is not consistent
Learning Objectives

▪ Employ evidence based treatment strategies for primary and secondary prevention of cardiovascular disease in high-risk patient populations

▪ Discuss ACC recommendations on the role of non-statin therapies in the management of atherosclerotic cardiovascular disease

▪ Explain the role of anti-PCSK9 monoclonal antibody therapy in LDL-C reduction to achieve cardiovascular risk reduction

▪ List 2017 Quality Measures for the use of statin therapy for the prevention and treatment of cardiovascular disease
Burden of Atherosclerotic Cardiovascular Disease

- Annual rates in US
  - Myocardial infarction – 1.1 million
  - Strokes - 795,000
  - CVD Mortality – 1,344,185 (every 30 seconds a death)
  - Cardiac catheterization – 1.0 million
  - Percutaneous revascularization – 492,000
  - Surgical revascularization – 291,000

- Annual cost – >$315 billion

63 year old woman with the Metabolic Syndrome

- 63 year old woman
- Cardiac risk factors include hypertension, obesity and pre-diabetes

Current medications:
Lisinopril 10 mg daily

Pertinent physical exam findings:
BP-135/82 mmHg BMI-31

Pertinent lab findings:
LDL-C – 145, HDL-C– 45, FBS – 115mg/dL
Statin effects on major vascular events

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4·4)</td>
<td>2769 (6·2)</td>
<td>0·74 (0·70 – 0·79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3·4)</td>
<td>1960 (4·4)</td>
<td>0·81 (0·75 – 0·87)</td>
</tr>
<tr>
<td><strong>Any major coronary event</strong></td>
<td>3337 (7·4)</td>
<td>4420 (9·8)</td>
<td>0·77 (0·74 – 0·80)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (3·3)</td>
<td>1006 (4·7)</td>
<td>0·75 (0·69 – 0·82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (2·4)</td>
<td>658 (3·1)</td>
<td>0·79 (0·69 – 0·90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3·1)</td>
<td>1770 (3·9)</td>
<td>0·76 (0·69 – 0·84)</td>
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<tr>
<td><strong>Any coronary revascularisation</strong></td>
<td>2620 (5·8)</td>
<td>3434 (7·6)</td>
<td>0·76 (0·73 – 0·80)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>105 (0·2)</td>
<td>99 (0·2)</td>
<td>1·05 (0·78 – 1·41)</td>
</tr>
<tr>
<td>Presumed ischaemic stroke</td>
<td>1235 (2·8)</td>
<td>1518 (3·4)</td>
<td>0·81 (0·74 – 0·89)</td>
</tr>
<tr>
<td><strong>Any stroke</strong></td>
<td>1340 (3·0)</td>
<td>1617 (3·7)</td>
<td>0·83 (0·78 – 0·88)</td>
</tr>
<tr>
<td><strong>Any major vascular event</strong></td>
<td>6354 (14·1)</td>
<td>7994 (17·8)</td>
<td>0·79 (0·77 – 0·81)</td>
</tr>
</tbody>
</table>
### Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High Intensity Statin Therapy</th>
<th>Moderate Intensity Statin Therapy</th>
<th>Low Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)-80 mg Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong> <strong>Rosuvastatin (5) 10 mg</strong> <strong>Simvastatin 20-40 mg‡</strong> <strong>Pravastatin 40 (80) mg</strong> <strong>Lovastatin 40 mg</strong> <strong>Fluvastatin XL 80 mg</strong> <strong>Fluvastatin 40 mg bid</strong> <strong>Pitavastatin 2-4 mg</strong></td>
<td><strong>Simvastatin 10 mg</strong> <strong>Pravastatin 10-20 mg</strong> <strong>Lovastatin 20 mg</strong> <strong>Fluvastatin 20-40 mg</strong> <strong>Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>
### ACC/AHA Statin Benefit Groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical ASCVD</td>
<td>• Age ≤ 75: High-intensity statin</td>
</tr>
<tr>
<td></td>
<td>• Age &gt; 75: Moderate-intensity statin</td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C ≥ 190 mg/dL</td>
<td>• High-intensity statin</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td></td>
</tr>
<tr>
<td>Age 40–75 with diabetes</td>
<td>• Low risk (10-yr risk &lt; 7.5%):</td>
</tr>
<tr>
<td>and LDL 70–189 mg/dL,</td>
<td>Moderate-intensity statin</td>
</tr>
<tr>
<td></td>
<td>• High risk (10-yr risk ≥ 7.5%):</td>
</tr>
<tr>
<td></td>
<td>High-intensity statin</td>
</tr>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>Age 40–75, ≥ 7.5% 10-yr</td>
<td>• Consider moderate or high</td>
</tr>
<tr>
<td>ASCVD risk</td>
<td>intensity statin</td>
</tr>
</tbody>
</table>

ASCVD Risk Estimator

- Gender
- Age
- Race
- Total Cholesterol
- HDL Cholesterol
- Systolic BP
- Treatment for BP?
- Diabetes
- Smoking

http://www.apple.com/itunes/affiliates/download/?id=808875968

Or just google: “ASCVD risk calculator”
ARS Question

Which parameter has the greatest influence on estimated ASCVD risk?

1. Blood pressure
2. Cholesterol level
3. Diabetes
4. Age
5. Gender
You’re fifty-seven years old. I’d like to get that down a bit.
Age provides an integrated estimate of lifetime exposure to risk factors
63 year old woman with the Metabolic Syndrome

- 63 year old woman
- Cardiac risk factors include hypertension, obesity and pre-diabetes

We begin rosuvastatin 20 mg daily and her LDL-C falls to 105 mg/dL

Have we improved her outcomes?
12,705 intermediate risk patients (average ASCVD risk ~ 10%) randomized to receive either rosvastatin 10 mg daily (moderate intensity statin) or placebo

- No entry lipid criteria
- No routine monitoring
- No dose titration
HOPE 3: CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure

HR (95% CI) = 0.75 (0.64-0.88)

63 year old woman with the Metabolic Syndrome

- 63 year old woman
- Cardiac risk factors include hypertension, obesity and pre-diabetes

We begin rosuvastatin 20 mg daily and her LDL-C falls from 145 to 105 mg/dL

Is her LDL-C low enough?

Why isn’t it lower?
Inter-individual Variability in Response to Statins

The graph below shows dramatic inter-individual variability in response to atorvastatin 10 mg daily. This has also been observed with other statins.

Poor response to statins increases cardiovascular event rates

- The Jupiter trial found that rosuvastatin 20 mg daily improved outcomes of patients with average LDL-C levels (LDL<135 mg/dl) but elevated hs-CRP (> 2)

- Although rosuvastatin 20 mg daily is expected to yield ~40-50% LDL reduction, they found wide variability in the % change in LDL-C in Jupiter

- Those who had less LDL-C reduction had increased cardiovascular event rates.

Paul M Ridker et al. Eur Heart J 2016;eurheartj.ehw046
63 year old woman with the Metabolic Syndrome

- 63 year old woman
- Cardiac risk factors include hypertension, obesity and pre-diabetes

We increase her rosuvastatin to 40 mg daily and her LDL-C falls to 95 mg/dL
67 year old man, 2 years S/P NSTEMI who complains of muscle aches

- 67 year old male
- Begun on guideline directed medical therapy post MI, including a statin
- Doing well, but has begun complaining of muscle aches
- Has tried several different statins at several doses over the past 2 years but he states “I ache all over”
Which of the following statements is true regarding statin intolerance?

1. Patients with statin intolerance have higher cardiovascular event rates
2. Patients with statin intolerance have lower cholesterol levels
3. In patients with statin intolerance, a secondary cause is usually found
4. In patients with statin intolerance, switching to a different statin usually alleviates the problem
5. Patients with statin intolerance are faking
Patients who are statin intolerant have higher cardiovascular event rates

105,329 Medicare beneficiaries who began a moderate- or high-intensity statin after hospitalization for MI (2007-2013)

Serban et al. JACC 60: 11 March 2017
Statin Intolerance

- An estimated 5–20% cannot tolerate statin treatment
- Statin intolerance (most commonly muscle pain, aching, and weakness) commonly leads to discontinuation
- Most statin-intolerant patients can be successfully re-challenged
  - Intolerance may be the result of perception or expectation
  - Hold statin and evaluate muscle symptoms first to rule out rhabdomyolysis
  - Muscle adverse events without significant elevation of creatine kinase levels are unlikely to be related to statin
- There is a subset of patients who are truly statin intolerant

Strategies to overcome statin intolerance

- Switching to a different statin
- Lowering statin dose
  - most side effects are dose related
- Changing statin dosing interval
  - every other day
  - twice weekly
  - once a week
- Adding non-statin medications to maximally tolerated statin
  - But what drug, and when?
Learning Objectives

- Employ evidence based treatment strategies for primary and secondary prevention of cardiovascular disease in high-risk patient populations

- Discuss ACC recommendations on the role of non-statin therapies in the management of atherosclerotic cardiovascular disease

- Explain the role of anti-PCSK9 monoclonal antibody therapy in LDL-C reduction to achieve cardiovascular risk reduction

- List 2017 Quality Measures for the use of statin therapy for the prevention and treatment of cardiovascular disease
Which of the following medications has been shown to improve cardiovascular outcomes when added to statin therapy?

1. Niacin
2. Ezetimibe
3. Bile Acid Sequestrant
4. All of the above
The 2013 ACC-AHA cholesterol guidelines were intentionally vague on the use of non-statin therapy.

To offer clinicians more guidance, the American College of Cardiology convened an Expert Panel to offer guidance:

- In what **patients** should non-statin therapy be considered?
- In what **situations** should non-statin therapy be considered?
- If non-statins are used, **which agents** and in **what order**?
2016 ACC Expert Consensus: “Thresholds” at which to consider adding a non-statin

- Familial Hypercholesterolemia (or LDL > 190 mg/dL)
  - If LDL-c ≥100 mg/dL or < 30-50% LDL-c reduction

- Diabetes
  - If LDL-c ≥100 mg/dL (or Non-HDL-c ≥130 mg/dL) OR if < 30-50% LDL-c reduction

- Uncomplicated ASCVD
  - If LDL-c ≥100 mg/dL

- Complicated ASCVD (ASCVD + DM or FH, recent ACS or stroke, ASCVD event while on a statin)
  - If LDL-c ≥70 mg/dL or < 50% LDL-c reduction

2017 ACC Expert Consensus*

- For adults with clinical ASCVD (with LDL of 70–189 mg/dL) who are taking statins, consider addition of a non-statin medication if:
  - < 50% LDL lowering was achieved
  - LDL remains > 70 mg/dL or
  - non-HDL remains > 100 mg/dL

- Clinicians may now consider an LDL of less than 70 mg/dL or a non-HDL level of less than 100 mg/dL for all patients, regardless of comorbidity.

- Clinicians may consider prescribing either ezetimibe or a PCSK9 inhibitor.

*Endorsed by the National Lipid Association

IMPROVE-IT Study Design

Patients < 10 days post ACS; LDL < 125mg/dL

ASA plus standard medical therapy

Simvastatin 40 mg

Eze/Simva 10/40mg

Duration: Minimum 2 ½ year follow up (5250 events)

Primary Endpoint: CV death, MI, Hospital Admission for Unstable angina, revascularization, or stroke

Cannon CP AHJ 2008;156:826-32
Primary Endpoint

CV death, MI, unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988) p=0.016

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

6% RRR

CV Death, Non-fatal MI, or Non-fatal Stroke

HR 0.90 CI (0.84, 0.97)
p=0.003
NNT= 56

Simva — 22.2%
1704 events

EZ/Simva — 20.4%
1544 events

10 % RRR

67 year old man, 2 years S/P NSTEMI who complains of muscle aches

- Has tried several different statins at different doses but still aches
- We decrease his statin dose to the maximum dose tolerated
- We decrease his dosing interval to every other day and his LDL falls to 110 mg/dL
- We then add ezetimibe 10 mg daily and his LDL is 76 mg/dL
2016 ACC Expert Consensus: “Thresholds” at which to consider adding a non-statin

- **Familial Hypercholesterolemia (or LDL > 190 mg/dL)**
  - If LDL-C $\geq$100 mg/dL or $< 30$-$50\%$ LDL-C reduction

- **Diabetes**
  - If LDL-C $\geq$100 mg/dL (or Non-HDL-C $\geq$130 mg/dL) OR if $< 30$-$50\%$ LDL-C reduction

- **Uncomplicated ASCVD**
  - If LDL-C $\geq$100 mg/dL

- **Complicated ASCVD (ASCVD + DM or FH, recent ACS or stroke, ASCVD event while on a statin)**
  - If LDL-C $\geq$70 mg/dL or $< 50\%$ LDL-C reduction

Educational Objectives

- Employ evidence based treatment strategies for primary and secondary prevention of cardiovascular disease in high-risk patient populations
- Discuss ACC recommendations on the role of non-statin therapies in the management of atherosclerotic cardiovascular disease
- Explain the role of anti-PCSK9 monoclonal antibody therapy in LDL-C reduction to achieve cardiovascular risk reduction
- List 2017 Quality Measures for the use of statin therapy for the prevention and treatment of cardiovascular disease
68 year old man with recurrent atherosclerotic events

- 68 year old man with history of recurrent atherosclerotic events (NSTEMI, TIA, UA)
- Currently on 80 mg atorvastatin and ezetimibe 10 mg daily with an LDL-C of 92 mg/dL
- While on this therapy, he suffers another NSTEMI
- What else can we do?
2016 ACC Expert Consensus: “Thresholds” at which to consider adding a non-statin

- **Familial Hypercholesterolemia (or LDL > 190 mg/dL)**
  - If LDL-C $\geq 100$ mg/dL or $< 30$-$50\%$ LDL-C reduction

- **Diabetes**
  - If LDL-C $\geq 100$ mg/dL (or Non-HDL-C $\geq 130$ mg/dL) OR if $< 30$-$50\%$ LDL-C reduction

- **Uncomplicated ASCVD**
  - If LDL-C $\geq 100$ mg/dL

- **Complicated ASCVD (ASCVD + DM or FH, recent ACS or stroke, ASCVD event while on a statin)**
  - If LDL-C $\geq 70$ mg/dL or $< 50\%$ LDL-C reduction

We haven’t yet seen the floor of LDL-C lowering benefit.
PCSK9
(Proprotein convertase subtilisin/kexin type 9)

- A secreted protein which targets the LDL receptor for degradation
- Gain of function mutations cause high LDL-C
- Loss of function mutations cause low LDL-C
- Inhibition of PCSK9 lowers LDL-C levels
How is cholesterol removed from blood?

Circulating LDL particles (which contain a large ApoB protein) are “grabbed” by an LDL receptor.
How is cholesterol removed from blood?

The entire complex is then internalized into the hepatocyte for LDL destruction.
How is cholesterol removed from blood?

Before the LDL particle is destroyed, the LDL receptor migrates back to the hepatocyte cell surface so that it can grab more LDL molecules.

Then the LDL particle is destroyed.
How is cholesterol removed from blood?

When PCSK9 is present, however, the LDL receptor gets “stuck” and cannot migrate back to the surface. It therefore gets destroyed along with the LDL. And surface LDL receptors are depleted from the cell surface.
The theory behind PCSK9 inhibitors

If PCSK9 is inhibited, the LDL receptor can migrate back to the cell surface.

And surface LDL receptors will be restored which will lower serum cholesterol.
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>Fully human IgG1 mAb</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Fully human IgG1 mAb</td>
</tr>
</tbody>
</table>
FOURIER Trial - Evolocumab

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Fourier Trial lipid results

Placebo

59% mean reduction (95% CI 58-60), P < 0.00001

Absolute reduction: 56 mg/dl (95% CI 55-57)

Evolocumab
(median 30 mg/dl, IQR 19-46 mg/dl)

LDL Cholesterol (mg/dl)

Weeks

Fourier Trial: MI/Stroke/CV Death

Hazard ratio 0.80 (95% CI, 0.73-0.88)  
P<0.00001

20% RRR

Placebo 7.9%
Evolocumab 9.9%

The PCSK9 inhibitor Evolocumab

- ↓ LDL-C by 59%
  - Mean LDL-C achieved 30 mg/dL (interquartile range 19-46 mg/dL)

- ↓ cardiovascular events in patients already on statin
  - 15% ↓ in primary endpoint (MI, stroke, CV death, UA, revascularization)
  - 20% ↓ in CV death, MI or stroke

- Was safe and well tolerated

But is it worth the price?

Kazi DS et al. JAMA. 2016; 316(7):743-753.
**Alirocumab: ODYSSEY LONGTERM Study Design**

- **Double-blind treatment (18 months)**
  - Patients with HeFH or high CV risk - on maximally tolerated statin - LDL-C > 70 mg/dL
  - Alirocumab 150 mg SC Q2W
  - Placebo SC Q2W

Alirocumab (ODYSSEY LONGTERM)
LDL-Cholesterol Levels Over Time (ITT)

Least-Squares Mean Calculated LDL-C Level (mg/dL)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo + statin therapy at maximum tolerated dose +/- LLT</th>
<th>Alirocumab + statin therapy at maximum tolerated dose +/- LLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>120</td>
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-52.4%*
-61.0%*

Post hoc Analysis of a Subgroup of Major Adverse Cardiovascular Events

Cox model analysis
HR = 0.52 (95% CI 0.31 to 0.90)
Nominal P-value = <0.01


No. at Risk
Placebo  788  776  731  700  670  653  644  597
Alirocumab  1550  1533  1445  1392  1342  1306  1266  1170

Placebo + statin therapy at maximum tolerated dose +/- LLT
Alirocumab + statin therapy at maximum tolerated dose +/- LLT
68 year old man with recurrent atherosclerotic events

- 68 year old man with history of recurrent atherosclerotic events (NSTEMI, TIA, UA*)
- Currently on 80 mg atorvastatin and ezetimibe 10 mg daily with an LDL-C of 92 mg/dL
- We add PCSK9 inhibitor to his regimen. His LDL falls to 38 mg/dL

*NSTEMI – Non ST Elevation MI, TIA – Transient Ischemic Attack, UA – Unstable Angina
ARS Question

Is this patient’s LDL-C level of 38 mg/dL safe?

1. No

2. Yes

3. Insufficient evidence to know
Primary Endpoint
Spatial Working Memory Strategy Index of Executive Function

Giugliano, RP et al for the Ebbinghaus Investigators. Adapted from Figure 1A. NEJM 2017;377:633-43.
Evolocumab had no effect on Cognitive Function (Stratified by Lowest Achieved LDL-C)

*CANTAB – Cambridge Neuropsychological Test Automated battery

Mean \( \Delta -Z \) score

Composite Global Score Change from Baseline

Giugliano, RP et al for the Ebbinghaus Investigators. Adapted from Table 2 NEJM 2017;377:633-43.
Cognition and Cholesterol

The brain synthesizes cholesterol locally

Educational Objectives

- Employ evidence based treatment strategies for primary and secondary prevention of cardiovascular disease in high-risk patient populations

- Discuss ACC recommendations on the role of non-statin therapies in the management of atherosclerotic cardiovascular disease

- Explain the role of anti-PCSK9 monoclonal antibody therapy in LDL-C reduction to achieve cardiovascular risk reduction

- List 2017 Quality Measures for the use of statin therapy for the prevention and treatment of cardiovascular disease
Hyperlipidemia 2017 Quality Measures (QMs)

- QMs are intended to reduce variability and increase standardized use of evidence-based interventions

- Defined by CMS and may impact reimbursement

Hyperlipidemia 2017 Quality Measures (QMs)

CMS Quality Measures for the use of statin therapy:

大多数人高风险患者被开治疗高胆固醇的药物

- 成年人 aged ≥21 years with ASCVD
- 成年人 aged ≥21 years with LDL-C ≥190 mg/dL or
  with familial or pure hypercholesterolemic; and
- 成年人 aged 40-75 years with diabetes and LDL-C 70-189 mg/dL

Quality Measures

Despite these QMs, statin therapy is widely underused in clinical practice\textsuperscript{1-7}

- <50% high-risk patients take statins, including those with a history of CHD, stroke, or diabetes
- According to the CDC, only 29.5% adults with high LDL-C levels are treated to target\textsuperscript{3}

Utilization of evidence based therapies varies by gender, ethnicity, and risk group. In MESA study:\textsuperscript{8}

- Men less likely than women to be treated and controlled
- Black and Hispanic less likely to be treated and controlled
- Control less common in high- and intermediate-risk patients than in low-risk patients
Take Home Points

- Despite improvements in cardiovascular care, coronary heart disease rates remain unacceptably high.
- Modification of risk factors is one of the most important strategies against heart disease and dyslipidemia is one of the most important risk factors.
- New therapies and new recommendations are emerging for treatment of dyslipidemia.
- Quality measures exist to ensure appropriate management of dyslipidemia.


POST-TEST QUESTIONS
Post-test ARS Question 1

Please rate your confidence in your ability to treat hypercholesterolemia in patients who are not achieving optimal goals or are refractory to statin therapy:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Post-test ARS Question 2

A patient with no history of cardiovascular disease and atherosclerotic cardiovascular disease (ASCVD) risk of 9.1% starts atorvastatin 10 mg daily. On follow up, LDL-C is 40 mg/dL. She is tolerating therapy well. What is the most appropriate next step?

1. Switch to ezetimibe
2. Decrease the statin dose
3. Continue current statin dose
4. Switch to a less potent statin
5. Hold statin until LDL-C rises above 50 mg/dL
A patient with recent NSTEMI starts rosuvastatin 20 mg daily. On follow up he complains of disabling muscle pain. What is the most appropriate next step?

1. Switch to ezetimibe
2. Cut statin dose in half
3. Continue statin and add Coenzyme Q-10
4. Continue statin while you check CPK level
5. Hold the statin while you evaluate the muscular complaints
A patient with hypercholesterolemia is taking atorvastatin 80 mg and ezetimibe 10 mg daily. Lipid profile at follow up shows:

- LDL-C 185 mg/dL
- HDL-C 45 mg/dL
- Triglycerides 330 mg/dL
- She is tolerating therapy well

What is the most appropriate next step?

1. Add niacin
2. Add fish oil
3. Add fibrate
4. Add colesevelam
5. Add PCSK9 inhibitor
All of the following patient types are included in the CMS Quality Measure for cholesterol management, EXCEPT:

1. Adults with ASCVD
2. Adults with LDL-C ≥190 mg/dL
3. Adults age 40-75 years with diabetes, any LDL-C
4. Aged ≥21 years with familial hypercholesterolemia
A 65-year-old African American man with a history of dyslipidemia, hypertension, and obesity presents 2 years post NSTEMI. He reports no symptoms or side effects of medical therapy.

BP 132/76 mmHg, eGFR 54 mL/min/1.73m², LDL-C 78 mg/dL, HDL-C 40 mg/dL, triglycerides 152 mg/dL, and total-C 148 mg/dL

Current medications include valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding ezetimibe 10 mg qd.

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 7

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m², LDL-C 78 mg/dL, HDL-C 40 mg/dL, triglycerides 152 mg/dL, and total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

If ezetimibe 10 mg qd is started and LDL-C remains >70 mg/dL at follow up, consider PCSK-9 inhibitor.

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 8

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m2, LDL-C 78 mg/dL, HDL-C 40 mg/dL, triglycerides 152 mg/dL, and total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as **consistent** with or **not consistent** with best clinical practice for ASCVD risk management:

**Consider adding niacin.**

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 9

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m2, LDL-C 78 mg/dL, HDL-C 40 mg/dL, triglycerides 152 mg/dL, and total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding fibrate.

1. Yes, it is consistent
2. No, it is not consistent
Post-test ARS Question 10

65 y/o asymptomatic AA man, dyslipidemia, HTN, obesity, 2 yrs s/p NSTEMI

BP 132/76 mmHg, eGFR 54 mL/min/1.73m², LDL-C 78 mg/dL, HDL-C 40 mg/dL, triglycerides 152 mg/dL, and total-C 148 mg/dL

Meds: valsartan/hydrochlorothiazide 320/25 mg qd, atorvastatin 80 mg qd, metoprolol XL 50 mg qd, and aspirin 81 mg qd.

After reviewing the brief scenario above, please rate each of the statements as consistent with or not consistent with best clinical practice for ASCVD risk management:

Consider adding PCSK-9 inhibitor.

1. Yes, it is consistent
2. No, it is not consistent