Target Audience
This educational activity is intended for an international audience of non-US cardiologists, diabetologists & endocrinologists, and neurologists.

Goal
The goal of this activity is to improve clinicians’ ability to recognize and treat patients with high-risk dyslipidemia.

Learning Objectives
Upon completion of this activity, participants will:

• Have increased knowledge regarding the
  – Screening and identification of patients with high-risk dyslipidemia
  – Latest clinical data for new lipid-lowering therapies, including proprotein convertase subtilisin/kexin type 9 inhibitors, in high-risk dyslipidemia

• Have increased competence regarding the
  – Selection of optimal lipid-lowering treatments for patients with dyslipidemia based on patient and disease characteristics
Disclosures

Host
Khung Keong Yeo, MBBS
Adjunct Associate Professor, National Heart Centre Singapore, Singapore, Thailand

Disclosure: Khung Keong Yeo, MBBS has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Boston Scientific

Served as a speaker or a member of a speakers bureau for: Abbott Cardiovascular Systems, Inc., Amgen Inc., Menarini Group

Received grants for clinical research from: Amgen Inc., Medtronic, Inc

Faculty
Sanjay Kalra, MD
Consultant Endocrinologist, Bharti Hospital, Bharti Research Institute of Diabetes & Endocrinology (BRIDE), Karnal, India

Disclosure: Sanjay Kalra, MD, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: Amgen

Masahiro Koseki, MD, PhD
Assistant Professor, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Disclosure: Masahiro Koseki, MD, PhD has disclosed the following relevant financial relationships:


Kian Keong Poh, MD, FRCP
Associate Professor, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Disclosure: Kian Keong Poh, MD, FRCP has disclosed no relevant financial relationships.

Editor
Anne M. Sendaydiego, PharmD
Scientific Director, WebMD Global, LLC

Disclosure: Anne M. Sendaydiego, PharmD, has disclosed no relevant financial relationships.

Content Reviewer
Nafeez Zawahir, MD
CME Clinical Director

Disclosure: Nafeez Zawahir, MD, has disclosed no relevant financial relationships.
Khung Keong Yeo, MBBS: Hello, I am Khung Keong Yeo. I am a Senior Consultant Cardiologist at the National Heart Center Singapore, in Singapore. Welcome to this program in collaboration with the Asian Pacific Society of Cardiology, titled “Management of Patients with High Risk Dyslipidemia: Case Studies”.

High-Risk Dyslipidemia in Asia[1-4]
Dyslipidemia is an important risk factor for cardiovascular disease (CVD) around the world and in Asia; it often remains untreated. These patients are frequently at high cardiovascular (CV) risk and include patients with prior acute coronary syndromes or stroke. There are also patients with familial hypercholesterolemia (FH), who are untreated. The first-line treatment for these patients is statins, however many patients do not achieve target low-density lipoprotein-cholesterol (LDL-C) levels, or do not tolerate statin treatment secondary to myalgia or other side effects. The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a new class of drugs, which have demonstrated consistent and highly effective reduction of LDL-C in patients who are already taking maximally tolerated statins.
Agenda
In this program 3 case studies will be reviewed: 1 on FH, 1 on the management of patients who are intolerant to statins, and 1 on the management of high-risk patients with atherosclerosis. The program will conclude with a review of the updates of recent data on management of patients with high-risk dyslipidemia looking at, in particular, studies out of the European Society of Cardiology and American Heart Association Meetings in 2017.

Thank You
Segment 2: Management of Familial Hypercholesterolemia

Masahiro Koseki, MD, PhD: Hello, I am Masahiro Koseki from the Osaka University in Japan. Welcome to this presentation titled, “Management of Familial Hypercholesterolemia”.

Stratification of CAD Risk in High-Risk Patients for Secondary Prevention

This year, the Japanese Atherosclerosis Guidelines were updated. The major point of the update was to define high-risk patients for secondary prevention. Patients with familial hypercholesterolemia, acute coronary syndrome, and diabetes mellitus with complications were defined as high-risk patients for secondary prevention. The LDL-C levels for these patients should be less than 70 mg/dL.
Diagnostic Criteria for Heterozygous FH in Adults

There are diagnostic criteria for heterozygous FH in adults, including LDL-C more than 180 mg/dL without any medication; xanthoma or skin nodular xanthoma; and a family history of FH or premature coronary artery disease (CAD). If a patient has 2 or more of these criteria, they are diagnosed with FH.

Treatment of Heterozygous and Homozygous FH in Adults

There is an algorithm for the treatment of FH in the new Japanese guidelines. One major point is that PCSK9 inhibitors were added to the algorithm.
Case 1: 48-Year-Old Man With Untreated Dyslipidemia

Two typical cases on the management of patients with FH will be reviewed. The first patient is a 48-year-old man. His untreated LDL-C is 312 mg/dL; he does not have chest pain. His height is 174 cm; his body weight is 65 kg. He does not have any other risk factor, including hypertension, diabetes or smoking. He has family history of CAD; his father suffered a myocardial infarction (MI) at 54 years of age.

Case 1: LDL-C Concentration Over Time With Treatment

This patient was treated with pitavastatin first; the dose was increased from 2 to 4 mg per day. Then, ezetimibe was added and his LDL-C level decreased to approximately 160 mg/dL. A reduction of almost 50% in the LDL-C level was achieved.
The cumulative CV risk and LDL-C level over time must be considered.

**Cumulative LDL-C and MI Risk: Threshold = 6000 mg/dL·y**

I have estimated that the threshold for the risk for an MI is approximately 6000 mg/dL-years; that is LDL-C level times years of exposure to the patient. For example, if a patient has a LDL-C level of 100 mg/dL and he suffered a MI at 80 years old, his cumulative LDL-C level becomes 6000 mg/dL-years at the age of 80 years. If a patient has a metabolic syndrome and this patient has a LDL-C level of 150 mg/dL, I hypothesize that this patient will have a MI at the age of 60. If a patient is heterozygous FH and undiagnosed and the patient’s LDL-C level is 400 mg/dL, then the cumulative LDL-C becomes 6000 at the age of 35. For the same patient, if I diagnose this patient as FH at the age of 30 and the patient receives medication to get a 50% reduction of LDL-C, the MI risk is delayed until age 40. However, if the patients is treated with a PCSK9 inhibitor and the LDL-C level is reduced to 50 mg/dL, the risk of MI is further delayed until the age of 70 years old.
Case 1: LDL-C Concentration Over Time With Treatment (cont)
In the first case, because he was not treated until 48 years old at all, his cumulative LDL-C level is extremely high. The patient was then treated with evolocumab and the LDL-C was reduce to approximately 50 mg/dL.

Metabolic Syndrome in Patients With FH
- Visceral fat area is correlated with coronary stenosis
  - Independent of age, BMI, and SC fat area

Metabolic Syndrome in Patients With FH[7]
If a patient has metabolic syndrome, that patient is very high risk for an adverse CV event. In fact, visceral fat area is correlated with coronary stenosis.
High Prevalence of CAD in Patients Who Have FH With Midband Pattern

In addition, patients with FH that have a midband pattern, are at high risk for CAD and are usually associated with glucose intolerance.

Case 2: 47-Year-Old Man With Dyslipidemia Who Is Receiving Treatment

- Height, 165 cm; body weight, 97 kg (BMI: 35.6 kg/m²)
- Past medical history significant for HTN and DM
  - History of smoking
  - Low HDL-C
- Patient was being treated with fluvastatin 20 mg/d and probucol 750 mg/d
- Patient reports chest pain

Case 2: 47-Year-Old Man With Dyslipidemia Who Is Receiving Treatment

The patient was a 47 year old man receiving treatment for his dyslipidemia. His height is 165 cm and body weight 97 kg; his body mass index (BMI is 35.6 kg/m2). He has hypertension, a low high-density lipoprotein-cholesterol (HDL-C) level, and smokes. He was treated with fluvastatin and probucol. When he had chest pain, he came to me.
Case 2: LDL-C Concentration Over Time With Treatment
He had been treated with fluvastatin, but unfortunately his LDL-C level is approximately 200 mg/dL, so not at goal.

Case 2: LDL-C Concentration Over Time With Treatment (cont)
The fluvastatin was stopped and replaced with a higher-intensity statin, rosuvastatin, then the dose of rosuvastatin was increased. Ezetimibe was added. Finally, evolocumab was added. His LDL-C level decreased to approximately 60 mg/dL with this treatment.
Take-Home Messages

In summary, diagnose FH patient as early as possible to start treatment early. FH with metabolic syndrome and FH with midband pattern are high-risk clinical scenarios. Consider the cumulative LDL-C to help guide treatment decisions.
Sanjay Kalra, MD: Hello. I am Sanjay Kalra from the Bharti Research Institute of Diabetes & Endocrinology located in Kamal, India. Welcome to this presentation, “Management of Patients with Dyslipidemia and Atherosclerotic Cardiovascular Disease”.

Case: 50-Year-Old Man Presenting With Stroke
The patient is a 50-year-old man that presents with stroke to our hospital. He smokes 4 cigarettes a day, does not exercise. He is of normal build and weight. He is normotensive and euglycemic. His LDL-C is 130 mg/dL. An older brother experienced a MI at the age of 50. In addition, he has a 55-year-old sister, who has type 2 diabetes and has come to receive him upon discharge from the hospital. She asks us what she can to do reduce her CV risk.
Management of Dyslipidemia: The 7T Approach
We use the 7D approach to manage such patients.

Management of Dyslipidemia: The 7T Approach (cont)
The first two steps are triage and 2-way communication.
How Is ASCVD Risk Assessed?[^9]

The 10-year risk of a coronary event should be determined by routine assessment. There are several tools available to assess atherosclerotic cardiovascular disease (ASCVD).

Major ASCVD Risk Factors[^9]

The major ASCVD risk factors include advancing age, dyslipidemia, diabetes, hypertension, stage 3 or 4 CKD, and smoking. Family history of ASCVD, polycystic ovary syndrome are also traditional risk factors.
ASCVD Risk Categories

In the case, there is a strong family history of ASCVD, in addition to other CVD risk factors. The risk for ASCVD can be classified as extreme risk, very high risk, or high risk of ASCVD. In the case, the patient would be classified as having extreme ASCVD risk.

Indications for Statin Pharmacotherapy

There is a simple algorithm from the Canadian Cardiovascular Society, which identifies patients that are indicated for statin therapy, including those with any evidence of clinical atherosclerosis, abdominal aortic aneurysm, diabetes, chronic kidney disease, or a very high LDL-C.
Management of Dyslipidemia: The 7T Approach (cont)

The next step in the process is target setting.

ASCVD Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme risk</td>
<td>≤ 55 mg/dL</td>
</tr>
<tr>
<td>Very high risk</td>
<td>≤ 70 mg/dL</td>
</tr>
<tr>
<td>High risk</td>
<td>≤ 100 mg/dL</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>≤ 100 mg/dL</td>
</tr>
<tr>
<td>Low risk</td>
<td>≤ 130 mg/dL</td>
</tr>
</tbody>
</table>

ASCVD Risk Categories and LDL-C Treatment Goals

For patients at extreme risk of ASCVD, the target LDL-C is less than 55 mg/dL. For those at very high risk, the target LDL-C is less than 70 mg/dL, and for all others, the target LDL-C is 100 mg/dL to 130 mg/dL. For LDL-C concentration, the lower the better. There doesn’t appear to be any significant adverse events with a very low LDL-C concentration. The lower the LDL-C level, the greater the reduction in ASCVD risk.
Management of Dyslipidemia: The 7T Approach (cont)

The next step in the process is determining the therapeutic strategy, including both pharmacologic and nonpharmacologic strategies.

Nonpharmacologic Dyslipidemia Treatments

Nonpharmacological strategies include increasing physical activity, medical nutrition therapy, and cessation of tobacco in every form.
Pharmacologic Dyslipidemia Treatments\(^9\)
The cornerstone of dyslipidemia management is statins. Fibrates can also be used for severe hypertriglyceridemia.

Pharmacologic Dyslipidemia Treatments (cont)\(^9\)
In select situations, bile acid sequestrants and omega-3 fish oil can be used.
Pharmacologic Dyslipidemia Treatments (cont)[9]
Other options include PCSK9 inhibitors and cholesterol absorption inhibitors.

Metabolic Pathways: Statins and PCSK9 Inhibitors[11]
PCSK9 is a newly discovered protein that degrades LDL-C receptors in the liver. When statins are used, LDL-C is reduced. However, as the LDL-C levels come down with statin therapy, PCSK9 expression is up-regulated. PCSK9 degrades the LDL-C receptors in the liver, and it prevents statins from working upon these receptors. Thus, there is a limit to which statins can be used to reduce cholesterol. When the PCKS9 protein is inhibited, degradation of the LDL-C receptors is prevented and LDL-C can be further reduced.

PCSK9 inhibitors are antibodies, which act upon PCKS9 and prevent it from working, prevent it from degrading LDL-C receptors and thus, allow a lowering of LDL-C.
Phase 3 and Long-Term Extension Studies with PCSK9 Inhibitors

PCSK9 inhibitors have demonstrated efficacy and safety in multiple clinical settings
- Monotherapy
- In combination with statins
- In addition to diet alone, statin, or statin + ezetimibe
- Statin intolerance
- Heterozygous FH
- Homozygous FH

PCSK9 inhibitors can be used in combination with statin therapy, in patients with FH. They can also be used in individuals with clinical CVD, who are unable to reach LDL-C or non-LDL-C goals, even with maximally targeted statin therapy.

Management of Dyslipidemia: The 7T Approach (cont)

- Triage: risk stratification
- Two-way communication
- Target setting
- Therapeutic strategy: nonpharmacologic and pharmacologic options
- Tool choice
- Timely monitoring
- Tailoring and tuning, as required

The next step in the process is determining which tools to use and when.
Questions When Considering PCSK9 Inhibition

In a patient who is at high risk of CVD, it is important to first reduce the risk factors. Then, behavioral modification and other nonpharmacologic therapy is started and statins are initiated. If, however, the patient is not able to achieve the target LDL-C goal with maximally-tolerated statins, other options have to be considered. Two options are available, ezetimibe or PCSK9 inhibitors.

Available PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Considerations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Require SC self-injection; refrigeration generally needed</td>
</tr>
<tr>
<td>Overall levels of adverse reactions and discontinuation very low</td>
</tr>
<tr>
<td>The most common adverse reactions with similar rates for drug vs placebo:</td>
</tr>
<tr>
<td>- Alirocumab: local injection site reactions, URI, pruritus</td>
</tr>
<tr>
<td>- Evolocumab: nasopharyngitis, back pain, and URI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Recommended Starting Daily Dosage</th>
<th>Dosage Range</th>
<th>Method of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>75 mg every 2 wk</td>
<td>75-150 mg every 2 wk</td>
<td>SC</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>140 mg every 2 wk or 420 mg</td>
<td>Not applicable</td>
<td>SC</td>
</tr>
</tbody>
</table>

Available PCSK9 Inhibitors$^{13,14}$

PCSK-9 inhibitors have been approved in several countries and they are quite easy to use. Evolocumab, is available as a subcutaneous injection, which can be administered either every 2 weeks or every month, depending upon the patient’s choice.
2016 ACC Expert Consensus Role of Nonstatin Therapies in Lowering LDL-C

The American College of Cardiology has provided specific guidance regarding the use of nonstatin therapies in the management of patients with elevated LDL-C. For example, in a patient with stable, clinical, ASCVD, without any comorbidities, who is on statin therapy for secondary prevention, if the LDL-C goal is not achieved with statins, consider treatment with ezetimibe first, and if the goal is still not achieved, consider adding a PCSK9 inhibitor or replacing ezetimibe with a PCSK9 inhibitor.

2016 ACC Expert Consensus Role of Nonstatin Therapies in Lowering LDL-C (cont)

In a patient with clinical ASCVD and comorbidities, again there is a choice between using ezetimibe or a PCSK9 inhibitor, if the LDL-C goal is not attained with statin therapy. PCSK9 inhibitors should be used along with lifestyle modification and with maximally tolerated statins.
There may be some patients with clinical ASCVD and a very high baseline LDL-C level. If the LDL-C is more than 190 mg/dL and the patient is taking a statin for secondary CVD prevention, then either ezetimibe or a PCSK9 inhibitor can be started. A PCSK9 inhibitor can be started along with the statin since it is unlikely that treatment with the statin alone will be able to achieve the goal LDL-C.

**Summary: The 7T Approach**

In summary, the first stop of the 7T approach is triage, or risk stratification. There is a difference between high risk and extreme risk. It is not enough to only do a triage, the risk must be communicated to the patient. Once the risk of CVD is determined and communicated, the target LDL-C goal is determined. Tactics, tools, and strategies are decided upon. The tools can be statins. The tool can be ezetimibe. The tools can also be PCSK9 inhibitors, such as evolocumab. Whatever tools are chosen, regular patient monitoring must occur. If the patient is not achieving the goal LDL-C, intensifying dyslipidemia therapy must occur. Tailoring and tuning therapy to the individual patient is important. If this dynamic approach is followed, a reduction in the risk of CVD, including stroke, for patients will occur.

Thank You
Segment 4: Management of Patients Intolerant to Statins

Kian Keong Poh, MD, FRCP: Hello, I am Professor Kian Keong Poh from the National University Heart Center Singapore. Welcome to this presentation titled, “Management of Patients Intolerant to Statins”.

Case: 70-Year-Old Woman With ACS
Let us start with a clinical case. The patient is a 70-year-old woman with a history of acute coronary syndrome (ACS). Her LDL-C before treatment was 170 mg/dL (4.4 mmol/L). Statin was started: atorvastatin 40 mg/d. LDL-C decreased with statin treatment to 95 mg/dL (2.5 mmol/L). Patient experienced muscle symptoms; CK > 3 × ULN. Statin was discontinued; after 4 wk, CK returned to normal.
Case: 70-Year-Old Woman With ACS (cont)

The patient was started on the same statin, but at a lower dose of 20 mg/day. However, even on that lower dose, she developed muscular symptoms. After a washout period, she was switched to rosuvastatin 5 mg/day. She continued to have muscular symptoms after the washout period while she was on rosuvastatin.

Definition of Statin Intolerance

- **SAMS**[^a]:
  - Muscle ache, weakness, soreness, stiffness, cramping, tenderness, or general fatigue
- Statin intolerance is the inability to tolerate ≥2 statins because of unexplained SAMS[^b]


**Definition of Statin Intolerance**[^16,17]

Statin-associated muscle symptoms (SAMS) are multiple and include muscle ache, weakness, soreness, stiffness, cramping, tenderness, or general fatigue. Statin intolerance is an inability to tolerate ≥2 statins because of unexplained symptoms.
Management of Patients With High-Risk Dyslipidemia: Case Studies

**Risk Factors for Statin-Induced Myopathy**[18]
There are multiple risk factors for statin induced myopathy, including demographics, medications, genetic predisposition, and comorbidities. In this case, being elderly, female, of Asian ethnicity, and with small muscle mass are risk factors. Other comorbidities include hypothyroidism, vitamin D deficiency, systemic muscular disease, alcohol abuse, and major surgery.

**Patients With Statin Intolerance Are at Increased Risk for CV Events and Mortality**[19]
Patients with statin-induced intolerance are at high CV risk.
Case: 70-Year-Old Woman With ACS (cont)

In our clinical case, the statin was completely discontinued and the patient was started on ezetimibe monotherapy. The LDL-C was reduced to 140 mg/dL. However, this patient is at very high risk of having another CV event; the goal LDL-C is less than 70 mg/dL, or, in Singapore, less than 80 mg/dL. Discussion of new therapeutics options for her occurred. She was started on a PCSK9 inhibitor and her LDL-C was reduced to 68 mg/dL and she did not experience any additional muscle symptoms.

GAUSS-3: Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance

- LDL-C < 100 mg/dL: 64.1% on evolocumab vs 1.8% on ezetimibe, P < .001

Gauss-3: Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance

The LDL-C target (<100 mg/dL) was achieved in 64% of the patients on evolocumab and 1.8% of patients on ezetimibe. This difference was highly significant (P<.001).
**ODYSSEY ALTERNATIVE: Alirocumab vs Ezetimibe in Statin-Intolerant Patients**

The ODYSSEY ALTERNATIVE study, compared the safety and efficacy of alirocumab vs ezetimibe in patients with statin intolerance.

**A Simplified Algorithm for Statin-Induced Myopathy**

A simplified algorithm for statin-induced myopathy is available from the Canadian Cardiovascular Society. In patients with normal CK, but with significant muscular symptoms, statins should be stopped and then restarted when the symptoms have resolved; reassess CK 6 to 12 weeks later or if the symptoms recur. In patients with CK less than 10 times the upper limit of normal, the statin should be stopped, consider precipitating factors, and follow-up until the CK is normal. The statin can be restarted at a lower dose or another statin with less muscular effects, such as rosvastatin or fluvastatin can be used. Review the enzymes in about 3 to 6 weeks' time. In the setting where the CK is more than or equal to 10 times upper limit of normal, one should stop the statin, consider precipitating factors, check renal function, including urine for myoglobin, and hydrate the patient. Consider then referring to specialist to weigh the risks and benefits of restarting statins.
Concluding Remarks

In conclusion, statin intolerance is associated with a higher CV risk profile. In patients with statin intolerance, PCSK9 inhibitors may be indicated to achieve a greater LDL-C reduction. For the primary care physician, these patients should be referred to a specialist.

Thank you
Segment 4: Pivotal CV Studies: Consequences for Asia

Khung Keong Yeo, MBBS: Hello, I am Khung Keong Yeo. I am from the National Heart Center Singapore, in Singapore. Welcome to this presentation titled, “Updates on Pivotal Studies and What Are the Consequences for Asia”.

Introduction

- Statins reduce CV events and mortality in patients with CAD\(^[a,b]\).
- Despite increased statin dose and addition of ezetimibe, many patients are not optimally controlled\(^[c]\).
  - There is a need for therapies to achieve the LDL-C targets
- The results of several clinical trials have recently been reported, which will likely have important clinical implications for patient management


Introduction\(^{[22-24]}\)

Statins reduce CV events and mortality in patients with CAD. Despite increasing the dose of statins and even with the addition of ezetimibe, many patients do not achieve appropriate LDL-C goals. Thus, there is a need for therapies that can help patient achieve target LDL-C levels. The year 2017 has been very rich in terms of results of trials that relate to the control of lipid levels in these patients, particularly in terms of trials with PCSK9 inhibitors.
In the FOURIER trial, treatment with evolocumab reduced mean LDL-C to 56 mg/dL, a reduction of 59%.

Similarly, the ODYSSEY LONG-TERM trial reduced mean LDL-C by 52%. The ODYSSEY Outcomes trial has not been released, but we hope to hear about the results soon.
FOURIER Trial: Evolocumab Associated With a Significant Reduction in MACE

Treatment with evolocumab in the FOURIER trial was associated with a cumulative reduction in major adverse cardiovascular events (MACE) and a composite outcome for CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The hazard ratio is 0.85, which is significant.

FOURIER Trial: Reduction in Secondary Endpoints With Evolocumab

In terms of secondary endpoints, there were reductions in the incidence of MI, stroke, and coronary revascularization with evolocumab treatment.
**ODYSSEY LONG TERM Trial: AEs of Interest and Laboratory Values: Safety Analysis**[26]

In the ODYSSEY LONG-TERM trial, treatment with alirocumab was associated with a reduction in nonfatal MI. However, this was a small trial and not powered to detect a difference in CV outcomes. The results of the ODYSSEY Outcomes study are not yet available.

**ODYSSEY Outcomes: Phase 3 CVOT in Patients Post-ACS**[27]

The ODYSSEY Outcomes study will include 18,000 patients.
FOURIER Trial: Lower LDL-C Reductions Associated With Better Outcomes

Very low LDL-C reductions were associated with favorable outcomes. There was a significant reduction in the risk for CV Death, MI, stroke, unstable angina, or coronary revascularization in patients with an LDL-C was less than 0.5 mmol/L. This is important because for patients at high CV risk, lower LDL-C concentrations are associated with superior outcomes.

FOURIER Trial: Very Low LDL-C Concentrations Are Well Tolerated

Very low LDL-C levels are not associated with increases in adverse events. The rate of serious adverse events was similar for placebo- and evolocumab-treated patients. Only about 3.4% of patients in either groups required drug discontinuation because of the adverse events, a very low percentage.
REAL-CAD: High-Intensity Statin Therapy Reduces CV Events in Japanese Patients With CAD

In the REAL-CAD trial, the safety and efficacy of high-dose statin therapy (pitavastatin 4 mg/d, n = 6526) was compared with low-dose statin therapy (pitavastatin 1 mg/d, n = 6528) in Japanese patients with stable CAD. High-dose statin therapy reduced the composite primary outcome of CV death, MI, ischemic stroke, and unstable angina compared with low-dose statin; the absolute risk reduction was 1.1% with a number needed to treat of 63. Pitavastatin 4 mg/d was also associated with a reduction in total mortality. In the past, there has been a concern that higher doses of statins may not be well tolerated in Asians. This trial demonstrated that higher dose of pitavastatin are safe, well tolerated, and beneficial, and supports the idea that intensive LDL-C lowering with high dose statins should be a strategy in Asian patients.

FOURIER Trial: Efficacy of Evolocumab in Patients with PAD

A subgroup analysis from the FOURIER trial was conducted in patients with peripheral arterial disease (PAD) and no MI or stroke. Treatment with evolocumab resulted in a 4.8% absolute risk reduction with a number needed to treat of 21 in terms of the composite outcome. This is important because, even in a group of patients with no prior MI or stroke, and just PAD, the drug has substantial benefit with a hazard ratio of 0.57.
FOURIER Trial: Benefit of Evolocumab Based on Time From Qualifying MI

In another analysis of the FOURIER trial, the benefit of evolocumab was determined based on the time from qualifying MI. In patients with a qualifying MI <2 years ago, as well as in patients with a qualifying MI ≥2 years ago, treatment with evolocumab was associated with a significant benefit.

Available Guidelines: Treatment Targets for LDL-C ECS/EAS-2016/AACE-2017

The European Society of Cardiology has indicated a Class 1 recommendation for aggressive treatment of LDL-C to less than 70 mg/ dl in patients with high risk. The American Association of Clinical Endocrinology has a similar recommendation for very high-risk patients.
Conclusions

In conclusion, it is clear that statins remain the drug of choice for the treatment of dyslipidemia in patients with CVD. In clinical trials, the PCSK9 inhibitors have demonstrated a strong reduction in LDL-C levels. In the FOURIER study, treatment with evolocumab demonstrated a significant reduction in CV events. In addition, evolocumab treatment has demonstrated beneficial effects in patients with PAD and in patients with a recent MI. The ongoing ODYSSEY Outcome study will give us more information about CV effects of PCSK9 inhibitors. PCSK9 inhibitors may be recommended to treat appropriate high-risk patients, if not well controlled by their current regimen.

Thank You

On behalf of the Asian Pacific Society of Cardiology, I want to thank all of the faculty involved in this program, and I want to thank you for participating in this activity.
References


