Healthy Heart

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Honorary Editor :
Dr. Urmil Shah

From the Desk of Hon. Editor:

Dear Friends,

Elevated LDL cholesterol remains an important driver of atherosclerotic vascular disease, a primary cause of premature cardiovascular mortality and morbidity. Many randomised, controlled trials have proven the utility of statins in reducing LDL cholesterol and cardiovascular disease during the last 25 years, but we need to go beyond the limitations of statins. The next generation of treatments to control elevated LDL cholesterol must address the substantial residual cardiovascular risk remaining after even intensive statin-based therapy, the unpredictability of the response to a statin in an individual patient, and the frequent occurrence of statin intolerance. An exciting new treatment for marked reduction of LDL cholesterol levels is now on the horizon: the PCSK9 inhibitors, a new class of biologics. This article seeks to summarize the rationale, current evidence base supporting the use and current status of PCSK9 inhibition for the improvement of long-term cardiovascular outcomes.

- Dr. Urmil Shah

PCSK9 INHIBITION : New Therapies in Cardiovascular Risk Reduction

LDL cholesterol remains the key target of lipidmodifying therapy

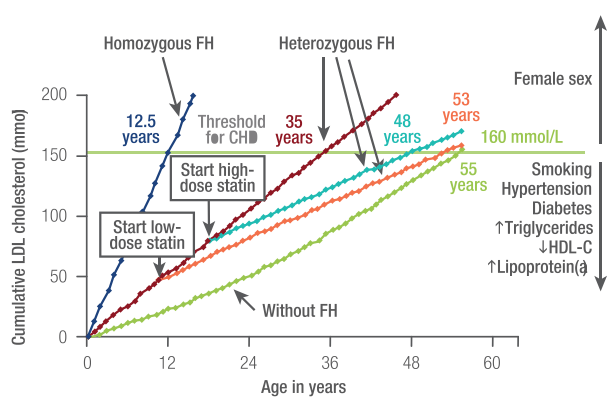
European and US guidelines continue to identify LDL-C as the main target for lipid-modifying therapy, with the aim of improving long-term cardiovascular prognosis.

The concept of the lifetime burden of elevated LDL cholesterol accounts for the early development of cardiovascular disease. The severity and duration of hypercholesterolaemia act together with additional cardiovascular risk factors such as other lipid abnormalities, smoking and diabetes, with a substantial risk of CHD occurring once the patient has reached a cumulative exposure to 160 mmol of LDL cholesterol.

Treatment with a statin delays the age at which CHD presents, by reducing the circulating level of LDL cholesterol and thus reducing exposure to LDL cholesterol over time. It is clear from Figure-1 that it is better to intervene earlier, rather than later, to address elevated LDL cholesterol, especially in a patient at severely elevated cardiovascular risk due to familial hypercholesterolaemia.

Familial hypercholesterolaemia is the most common genetic condition known to medical science, with a population prevalence that may be as high as about 1:200 - 99 % of which are not diagnosed. Patients with familial hypercholesterolaemia have severely elevated LDL cholesterol levels from early in life. They typically develop atherosclerotic vascular disease in childhood followed by clinical CHD by their twenties (homozygous familial

Figure-1 : Clinical importance of the concept of a lifetime burden of elevated LDL cholesterol



Female sex increases the cumulative threshold of LDL cholesterol for CHD, while cardiovascular risk factors (smoking etc.) decrease it so that CHD appears at an earlier age.

hypercholesterolaemia) or before middle age (heterozygous familial hypercholesterolaemia). Achieving treatment goals with statins in patients with familial hypercholesterolaemia is challenging, even when they are diagnosed and treated. All patients with familial hypercholesterolaemia should receive a statin, but 79% of patients with heterozygous familial hypercholesterolaemia in The Netherlands did not achieve their goal for LDL cholesterol (<2.5 mmol/L [100 mg/dL]), despite 96% receiving a statin.

Limitation of Statin Therapy

Many patients with elevated LDL cholesterol do not achieve LDL cholesterol goals with current treatments. A survey of 9,950 high-risk patients with CHD showed that more than half did not achieve LDL cholesterol <1.8 mmol/L (70 mg/dL) either with a statin alone, or with a statin combined with other lipid modifying agents (Figure 2).

Poor adherence to statin therapy is common (the majority of patients stop taking their statin within a year) and this is an important cause of the variable therapeutic response which is predictor of subsequent cardiac event.

The incidence of adverse events attributable to statins in randomised clinical trials is low. However, side-effects in muscle occurred in up to 29% of statin-treated patients in observational studies, presenting a potential barrier to treatment.

Though the introduction of statins has revolutionised the management of patients at increased cardiovascular risk due to elevated LDL cholesterol. As described above, these agents provide marked (if variable) reductions in LDL cholesterol and clinically significant reductions in cardiovascular event rates in patients at high cardiovascular risk. Nevertheless, most patients do not achieve their goal LDL cholesterol on these agents, particularly people with the severe hypercholesterolaemia associated with familial hypercholesterolaemia. Also, statins reduce the risk of a cardiovascular event by only up to about 50% at most, leaving a substantial burden of cardiovascular morbidity and mortality even after treatment. There remains a need for a consistently effective, well-tolerated treatment that will provide reductions in LDL cholesterol beyond those available with a statin, with reductions in other atherogenic lipoproteins, including VLDL cholesterol, lipoprotein remnants and lipoprotein(a) that will address the residual risk after treatment with a statin.

Lipid Metabolism and Mechanism of Lipid Lowering Agent

Figure-3 provides a simplified overview of the main sources of plasma LDL cholesterol. 75 % of circulating LDL cholesterol is synthesised in the liver, by HMG-CoA reductase and the principal means of removal of LDL cholesterol from the circulation is via a family of hepatic LDL receptors. Current therapies are targeted at reducing the rate of cholesterol biosynthesis (the main effect

Figure-2 : Low rates of LDL cholesterol goal achievement in patients with coronary artery disease on lipid-modifying therapy

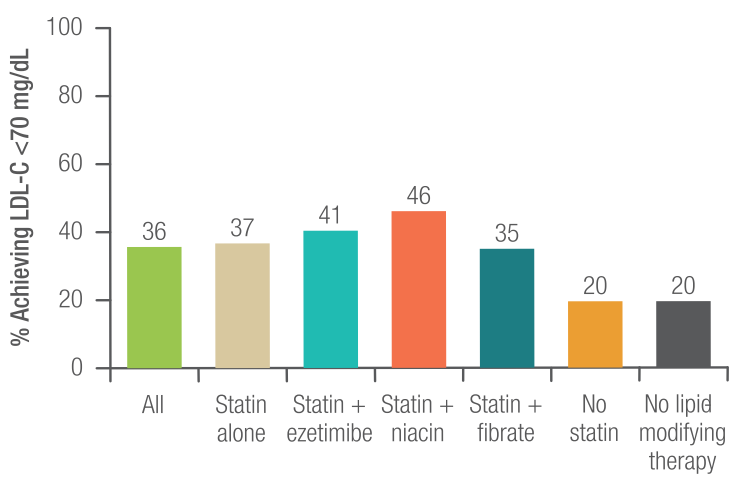
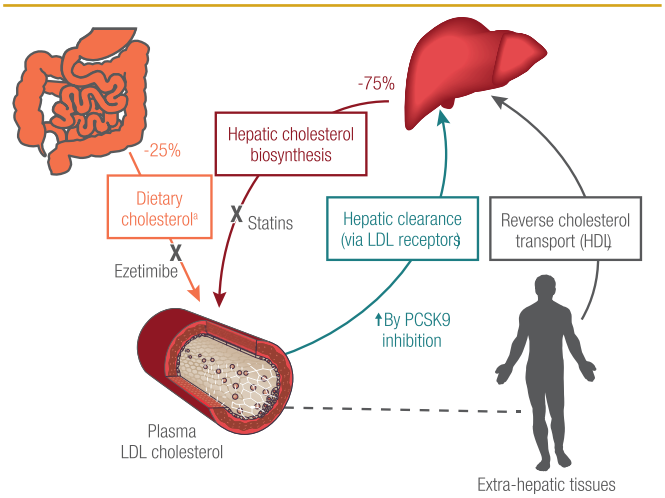
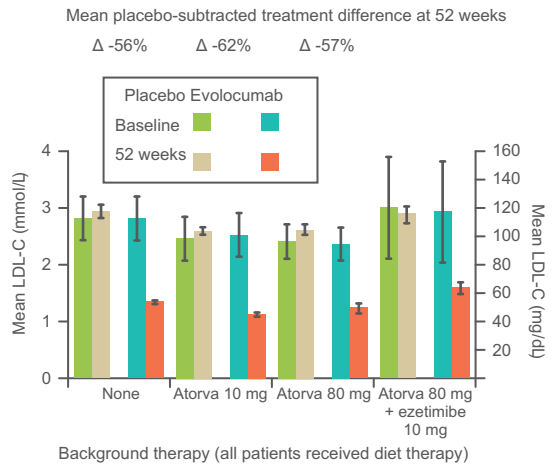


Figure-3 : Overview of cholesterol metabolism and transport



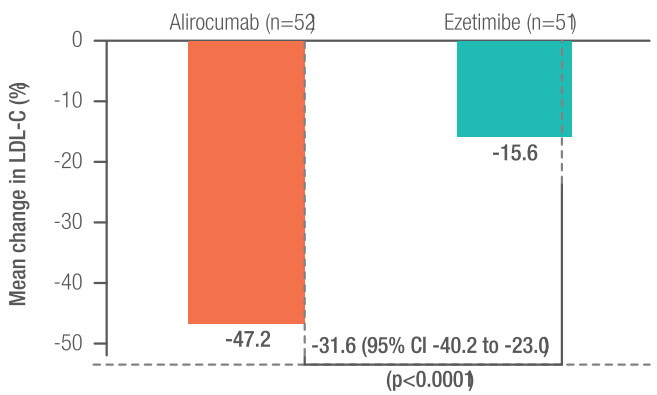
PCSK9: proprotein convertase subtilisin/kexin type 9.

Figure-4 : Substantial reductions in LDL-C with evolocumab irrespective of background intensity of lipid-modifying therapy



Δ: mean treatment difference vs. placebo. Atorva: atorvastatin.

Figure-5 : Effects of 24 weeks of treatment with alirocumab vs. ezetimibe on LDL cholesterol in patients with hypercholesterolaemia



2 Doses given were 75 mg s.c. Q2W for alirocumab and 10 mg QD for ezetimibe.

of statins) or reducing the rate of absorption of cholesterol into the circulation (ezetimibe, bile acid sequestrants or plant sterols/stanols) derived from food and/or from bile.

The hepatic LDL receptor is the most important mechanism of removal of LDL cholesterol from the circulation. Reducing the activity or expression of PCSK9 increases the number of LDL receptors, which reduces circulating LDL cholesterol. People with mutations of the PCSK9 gene that decrease its activity have lifelong low LDL cholesterol and a lower risk of cardiovascular events than the general population. Mutations of the PCSK9 gene that increase its activity can give rise to the familial hypercholesterolaemia phenotype.

PCSK9 inhibitor

A number of PCSK9 inhibitors are currently in clinical development. All these agents are monoclonal antibodies which must be given by injection; they have a long duration of action requiring infrequent administration compared with current therapies.

Evolocumab (Amgen)

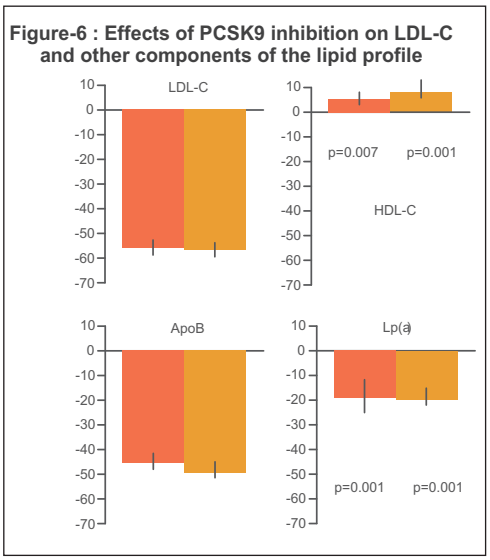
This agent has been evaluated using 2-weekly (140 mg dose) or monthly (420 mg dose) administration schedules in Phase III trials (the PROFICIO programme).

Alirocumab (Sanofi/Regeneron)

Phase III studies have generally involved administration of 75–150 mg of this agent at 2-weekly intervals (the ODYSSEY programme).

Bococizumab (Pfizer) is in Phase III clinical evaluation (the SPIRE trial programme).

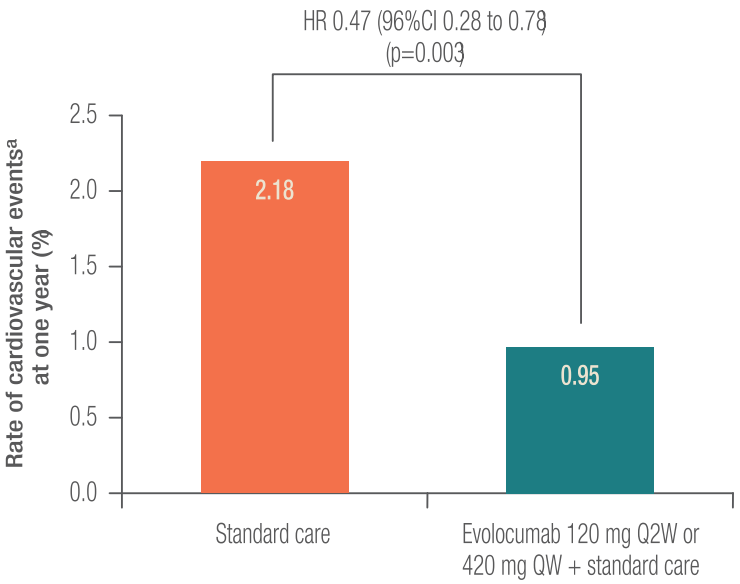
Figure-6 : Effects of PCSK9 inhibition on LDL-C and other components of the lipid profile



A one-year evaluation of evolocumab demonstrates the marked reductions in LDL-C that result from PCSK9 inhibition, irrespective of the nature of background lipid-modifying therapy (Figure 4). Mean reductions from baseline in LDL-C approaching 50%, or greater, were seen in patients on background diet therapy, low- or high-intensity statin treatment, or high-intensity statin plus ezetimibe. A reduction in LDL cholesterol of comparable magnitude was seen in a Phase III study in which alirocumab was compared with ezetimibe in patients with hypercholesterolaemia (Figure 5).

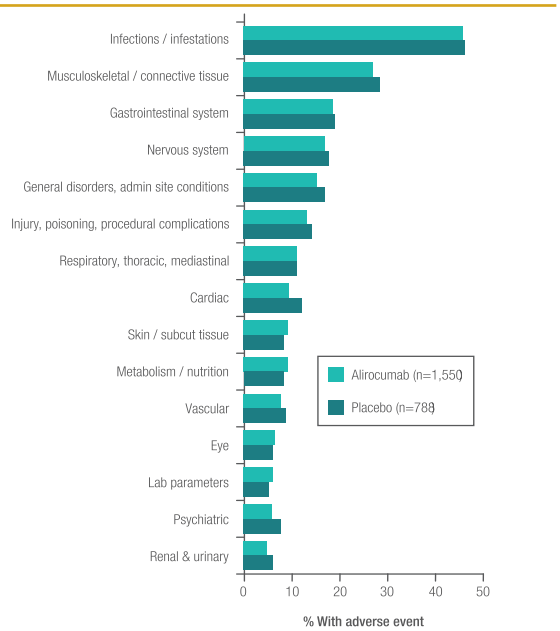
Lipoprotein(a) [Lp(a)] is an atherogenic lipoprotein that is closely associated with increased risk of cardiovascular disease independently of levels of LDL cholesterol or non–HDL cholesterol. Lp(a) should be controlled to below the 80th percentile of the population, which is about 50 mg/dL. The MENDEL-2 study also showed that PCSK9 inhibition was effective in reducing LPa significantly (Figure-6).

Figure-7 : Effect of evolocumab on cardiovascular outcomes in a pooled analysis of the OSLER-1 and OSLER-2 trials



Composite of death, myocardial infarction, hospitalisation for unstable angina, coronary revascularisation, stroke, transient ischaemic attack, or hospitalisation for heart failure.

Figure-8 : Tolerability profile of a PCSK9 inhibitor over one year of treatment from the preliminary analysis of the ODYSSEY LONG TERM outcomes trial



Adverse events occurring in at least 5% of either treatment group are shown.

An exploratory analysis (pooled analysis of the randomised OSLER-1 and OSLER-2 trials) showed significant beneficiary effect of Evolocumab for reduction of cardiovascular outcomes (Figure-7). Preliminary data from the ODYSSEY long term outcome study suggest a reduced frequency of adverse cardiovascular outcomes associated with a PCSK9 inhibitor - alirocumab in patients with hypercholesterolaemia.

PCSK9 inhibitors have been generally well tolerated in clinical trials (Figure-8). The main side-effects associated with these agents are injection site reactions, which is unsurprising for an injectable treatment. The tolerability and safety profiles of these agents so far support long-term administration for lifelong conditions such as hyper-cholesterolaemia.

Treatment with a statin, however intensive, leaves unaddressed a high level of residual cardiovascular risk. While improvements in the management of cardiovascular risk have reduced the burden of cardiovascular disease to some extent, future progress will depend on the implementation of new treatment strategies that are able to make inroads into this residual risk. PCSK9 inhibitor reduces LDL by improving the hepatic clearance of LDL (via LDL receptor) is new promising way of reducing LDL. Looking at large long term trials and beneficial effect on cardiovascular end point. USFDA approved alirocumab as lipid lowering therapy recently for following indication :

- People with familial hyper-cholesterolaemia who are likely to have lifelong exposure to very high levels of LDL cholesterol and other atherogenic lipoproteins, such as Lp(a), causes early onset of cardiovascular disease and low likelihood of achieving optimal control of LDL cholesterol on current therapies.
- People with statin intolerance especially with higher dose with problem of low adherence to LDL cholesterol-lowering therapy among this population
- People at high residual cardiovascular risk who are not at their LDL cholesterol goal for secondary prevention inspite of statin.

CIMS Learning Center

Advanced Echocardiography Training-Certification Course

Course Directors : Prof. Navin Nanda (USA) / Dr. Satya Gupta
Dr. Milan Chag / Dr. Vineet Sankhla

Date : September 1-2, 2015 (Tuesday & Wednesday) &
January 6-7, 2016 (Wednesday & Thursday)

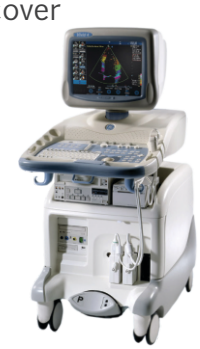
Duration : 2 days

Number of seats : 25

Venue : CIMS Auditorium

Program Overview:

The advanced echocardiography workshop is aimed at cardiologists, physicians and cardiac technicians with existing experience in echocardiography. The workshop will cover a wide range of lectures and live case demonstration of advanced echocardiography techniques keeping abreast with advances in modern cardiac ultrasound.



Program Highlights:

- Contrast echocardiography
- Stress echocardiography
- Strains & strain imagining echocardiography
- Transesophageal echocardiography
- 3-D echocardiography

*** Prof. Navin Nanda "Father of Echocardiography" will direct this course.**

American College of Cardiology (ACC) International Centers of Excellence

Registration Fees	: ₹ 25,000/- (Up to one month before course date)
Registration Fees	: ₹ 30,000/- **(Within 30 days before course date)**
Spot Registration Fees	: ₹ 35,000/-

* Hotel Registration: Separate

> Certificate of attendance will be given at the end of the course

Online Registration is compulsory

Visit www.cims.me/clc for online registration

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CIMS Learning Center (CLC) Android Application
www.cims.me/clc.apk

For more details about course detail contact on +91-90990 66527, +91-90990 66528, +91-94268 80247

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CIMS Learning Center

Use of IT and Electronics in Healthcare Web Based Practice of Medicine-Certification Course

Course Directors : Dr. Vineet Sankhla / Dr. Keyur Parikh
Dr. Dhaval Naik / Dr. Anish Chandarana

Date : September 13, 2015 (Sunday) /January 2016 (Tentative)

Duration : Three quarter day

Number of seats : 100

Venue : CIMS Auditorium

Program Overview:

- To educate and provide high-quality evidence-based medical care to patients, our health system and our physicians must keep up with the latest knowledge and skills.
- Continuing professional development initiatives using conventional and innovative electronic information technologies to meet physicians educational needs and translate exemplars of care into routine health practices, this program aims to educate medical professionals about various availablity of electronic gadgets and applications that can help change their clinical practice.

Program Highlights:

- Driving a Massive Shift in the Doctor - Patient Relationship
- Stuck in the Past: Why Doctors are Still Using Stethoscope & Manila Folder
- How Internet & Web based Resources Have Changed Practice of Medicine
- Smartphones in Medicine - The Future lies in our pocket & its not our wallet.....!
- Benchmarking in Health Care
- Smart Phone & Devices in OPD Based Practice
- Variable Devices & Wireless Monitoring in Medicine
- Smart Phones & Devices in Pediatric Medicine
- Use of Smart Phone & Devices: A Surgeon Perspective
- Use of Smart Phone & Devices in ICU Practice
- Importance of Database for Doctors
- E - Prescribing & Electronic Medical Record in Hospitals
- Smart Phones Use By General Public for Improving Healthcare
- Pitfalls of Technology in Medicine
- Android Vs iPhone Vs Blackbberry Vs Windows.. The Debate in Smartphone OS Continues ?Apple Watch Demonstration & Queries Related to Smart Phone

Registration Fees	: ₹ 1,000/- (Up to three weeks before course date)
Registration Fees	: ₹ 1,500/- **(Within 7 days before course date)**
Spot Registration Fees	: ₹ 2,000/-

Online Registration is compulsory

Visit www.cims.me/clc for online registration

› Certificate of attendance will be given at the end of the course

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