Dyslipidaemia: A major risk factor for coronary artery diseases and new strategy of its management
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Abstract
Dyslipidaemia is a major risk factor for coronary artery diseases, not only in the USA and most European countries but also in the developing country like Bangladesh. The results of recently reported clinical trials concluded with the recommendations for modifications of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) lipid-lowering guidelines. On the basis of evidence produced by the above trials and other clinical trial data, the NCEP has proposed changes to the ATP III guideline (table 2). For patients at very high risk, based on risk assessment, an LDL-C goal of <70 mg/dL (1.8 mmol/L) is considered a therapeutic option. In high-risk patients, initiation of drug therapy is recommended at LDL-C levels =100 mg/dL (2.6 mmol/L); initiation of drug treatment at an initial LDL-C of <100 mg/dL with a target of <70 mg/dL is also considered an option in patients at very high risk. For patients at moderately high risk, LDL-C<100 mg/dL is considered an optional treatment goal, and initiation of drug treatment at LDL-C levels of 100-129 mg/dL is now considered an option. The modifications also recommend that treatment in such patients be initiated with a lipid lowering agent at a dose sufficient to produce a reduction in LDL-C of at least 30-40%.

Introduction
Dyslipidaemia is a major risk factor for coronary artery diseases, the most common cause of death in the USA and most European countries. In future it will be the number one killer of developing country like Bangladesh also. More than 50% of the patients with unstable angina are dyslipidaemic1. The results of recently reported clinical trials have provided persuasive evidence that low-density lipoprotein (LDL-C) targets and initiation cut points in lipid-lowering therapy have been set too high in individuals at high or moderately high risk of coronary heart disease (CHD). The evidence has resulted in recommendations for modifications of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) lipid-lowering guidelines.

History
Atherosclerosis has been with us for at least 3500 years, but it appears to have been rare until industrialization. The onset of industrialization marks the first time in human history that several conditions conductive to the disease, including the mass cultivation of tobacco, were present at the same time, and under these conditions it did not take long before atherosclerotic diseases were common2. There are few data available on the beginning of epidemic, yet a picture of its growth can be sketched from coded data from death certificates available in the United States since around 19003 and from a data on a large Dutch kindred with familial hypercholesterolaemia (FH) available from 18504. Data suggest that individuals with FH, who are more susceptible to early and aggressive atherosclerotic disease due to mutation of LDL receptor gene, served much as miners'canaries, dying off earlier and at greater rates as industrialization and urbanization wrought their pro-atherogenic changes on society.

Classification of dyslipidaemia
Dyslipidaemia has numerous forms, from hypercholesterolemia to
hypoalphalipoproteinemia. The term itself refers to an abnormal metabolism of plasma lipids. Genetic, dietary or secondary disease factors can cause this abnormal metabolism. The major classes of plasma lipids are cholesterol, cholesterol esters, triglyceride and phospholipid. Although lipids are vital components of many of the body tissue, they are insoluble in water. So to reach those tissues, lipid must be transported in the blood stream by complex, water soluble molecule called lipoproteins.

These lipoproteins are divided into five classes according to their density on ultracentrifugation and by their mobility on agarose gel electrophoresis and size:

1. Chylomicrons
2. Very low density lipoproteins (VLDL)
3. Intermediate density lipoprotein (IDL)
4. Low density lipoproteins (LDL)
5. High density lipoproteins (HDL)

According to the Helsinki Heart Study patients in whom the greatest drop in CAD mortality was seen those with type IIb HLP (Hypolipoproteins), a condition manifested by elevated LDL and triglyceride level and depressed HDL levels. Patients with greater concentration of small dense LDL has been reported to have three time greater risk for acute MI. High density lipoprotein particles are thought to participate in the reverse transport of free cholesterol from peripheral tissues by way of a HDL receptor. This receptor mediated reverse transport could explain why patients with elevated HDL concentration are less prone to CAD. Several genetic, epidemiological and clinical studies have linked elevated triglyceride to an increased CAD risk.

**Pathophysiology of coronary artery diseases**
Coronary artery diseases are nearly always caused by atherosclerosis. Other causes of atherosclerosis are rare. Atherosclerosis development is a complex process influenced by a myriad of risk factors, although the LDL level is among the most important. In an atherogenic milieu, oxidized LDL infiltrates the intima where it stimulates inflammation, endothelial dysfunction, damaged endothelium are scavenged by macrophages which become foam cells. At the same time vascular smooth muscle cells migrate from the media into intima where they hypertrophy, proliferate and synthesized an extra cellular matrix of connective tissue. Extra cellular cholesterol accumulates within the matrix which is covered by a fibro muscular cap consisting of smooth muscle cells, collagen and a single layer of endothelial cells. The final lesion is the atherosclerotic plaque which is the pathological hallmark of coronary artery disease and is responsible directly or indirectly for all its manifestations.

**Relation of LDL cholesterol to CHD risk**
Although it is true that very high LDL levels (>200 mg/dl) are strongly associated with CHD risk, atherosclerosis is not uncommon even in those with relatively normal LDL levels (90 to 130 mg/dl). Moreover, the 10% of the population with the high LDL levels account for only 20% of the CHD events. Thus, focusing treatment only on those with very high cholesterol levels will ignore 80% of the people destined to suffer a CHD event. The mega-trials using statin therapy have demonstrated remarkable reductions in CHD events and in all-cause mortality among patients with base line LDL levels generally from 120 to 180 mg/dl and on treatment values between 100 and 140 mg/dl. Whereas cardiovascular events were reduced by 25% in these studies, approximately three out of four CHD events occurred despite the statin therapy. This 25% reduction in LDL represents only partial treatment, and more robust reductions appear to provide more impressive improvements in prognosis.

**Management of dyslipideamia**
Management of dyslipideamia involves the Therapeutic Lifestyle Change (TLC) program and if needed, drug therapy.
TLC program includes:
1. Diet:
   - Decrease saturated fat, trans fat, and cholesterol.
   - Add plant stanols and sterols and increase soluble fibre.
2. Physical activity.
3. Weight management.

Drug therapy
The major types of cholesterol-lowering drugs are: Statins (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and rosvastatin), Ezetimibe, Bile acid resins, Nicotinic acid (Niacin) and Fibrates.

The identification of an elevated LDL cholesterol as the primary target of lipid-lowering therapy is based on a wealth of information from basic research, animal studies, epidemiological studies, genetic forms of hypercholesterolemia, and controlled clinical trials. Recent clinical trials add support for the NCEP priority on high serum LDL cholesterol. Four new trials (HPS - Heart Protection Study, PROSPER study - Prospective Study of Pravastatin in the Elderly at Risk, ASCOT-LLA - Anglo-Scandinavian Cardiac Outcomes Trial - Lipid-Lowering Arm and PROVE IT - Thrombolysis in Myocardial Infarction) demonstrate that effective LDL cholesterol reduction substantially reduces risk for CHD.

The national Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines for reducing coronary heart disease (CHD) risk published in 2001 contained a number of important changes from prior lipid lowering guidelines. These included an increase focus on global risk in risk assessment and in determining intensity of therapy; attention to risk factors other than LDL cholesterol, including non-high-density lipoprotein cholesterol (non-HDL cholesterol) as a secondary target of therapy in individuals with elevated triglycerides; identification of the metabolic syndrome as a secondary target of therapy; and a new definition of the highest risk category to include CHD risk equivalents, such as diabetes, other atherosclerotic disease, and a 10-year CHD risk >20% conferred by the presence of multiple risk factors. This later high risk category was assigned a treatment goal of LDL-C < 100 mg/dl (2.6 mmol/L), representing a significant change from the prior goal of = 100 mg/dl (table 1). In essence, this change was an acknowledgement that simply reaching a level of 100 mg/dl was not enough, and that additional risk reduction was to be gained with further LDL-C reduction.

<table>
<thead>
<tr>
<th>Risk category</th>
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<tbody>
<tr>
<td>Consider drug therapy - 2001 guidelines</td>
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<tr>
<td>High risk: CHD or CHD risk equivalents, 10 year risk &gt;20%</td>
</tr>
<tr>
<td>Drug optional at 100-129 mg/dL (2.6 - 3.3 mmol/L)</td>
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<tr>
<td>Moderately high risk: 2+ risk factors, 10 year risk 10-20%</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors, 10-year risk &lt;10%</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
</tr>
<tr>
<td>Drug optional at 160-189 mg/dL (4.1-4.8 mmol/L)</td>
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Adapted from NCEP ATP III (2001 guidelines).

Table -1: NCEP ATP III LDL-C goals and cut-points for lipid-lowering drug therapy according to risk category - 2001 guidelines.
On the basis of evidence produced by the above trials and other clinical trial data, the NCEP has proposed changes to the ATP III guideline (table 2)\textsuperscript{20}. For patients at very high risk, based on risk assessment, an LDL-C goal of <70 mg/dL (1.8 mmol/L) is considered a therapeutic option. Patients with very high risk can be considered to be those with established atherosclerotic cardiovascular disease who have multiple risk factors (especially diabetes), severe and poorly controlled risk factors (e.g., ongoing cigarette smoking), of acute coronary syndromes. In high-risk patients, initiation of drug therapy is recommended at LDL-C levels =100 mg/dL (2.6 mmol/L); initiation of drug treatment at an initial LDL-C of <100 mg/dL with a target of <70 mg/dL is also considered an option in patients at very high risk. For patients at moderately high risk (two or more risk factors conferring a 10-20% 10-year risk), LDL-C<100 mg/dL is considered an optional treatment goal, and initiation of drug treatment at LDL-C levels of 100-129 mg/dL is now considered an option. It should be noted that the ATP III non-HDL-C goals in patients with elevated triglycerides after achieving target LDL-C, set at 30 mg/dL, the target non-HDL-C is <100 mg/dL. The guideline modifications also recommend that when lipid-lowering therapy is to be employed in high risk or moderately high risk patients, intensity of therapy should be sufficient to achieve at least a 30-40% reduction in LDL-C.

**Conclusion**

The evidence from the recently reported clinical trials of statin therapy has resulted in recommendations for modifications of the National Cholesterol Education Program (NCEP) Adults Treatment Panel III (ATP III) Lipid lowering guidelines. The recommendations include an optional LDL-C target of <70 mg/dl (1.8 mmol/L) and an optional treatment initiation cut point of <100 mg/dl (2.6 mmol/L) in high-risk patients, especially those considered to be at very high risk, and an optional target of <100 mg/dl (2.6 mmol/L) and a treatment initiation cut point of <130 mg/dl (3.4 mmol/L) in patients at moderately high risk. The modifications also recommend that treatment in such patients be initiated at a dose sufficient to produce a reduction in LDL-C of at least 30-40%.

**References**