Data from epidemiological studies indicate an adverse relation between HDL cholesterol (HDL-C) and coronary artery disease (CAD)\(^1,2\). Low levels of HDL cholesterol are associated with increased risk of CAD\(^3\). Genetic syndromes of high HDL resulting from increase production of apoA-I (the major HDL protein)\(^4\) are associated with decreased incidence of CAD and increased longevity\(^5\). There is an inverse relationship between HDL-C and triglycerides (TG). Low HDL-C is frequently associated with increased TG and reduction of TG usually results in some increase in HDL-C. However there are certain exceptions. Regular use of alcohol and oral oestrogen replacement raises TG levels but also raises HDL-C. Thus alcohol and oestrogen are likely to have direct effects on HDL metabolism independent of their effect on TG metabolism. Patients with low HDL-C and normal TG is labeled as isolated low HDL-C or primary hypoalphalipoproteinemia. The various causes of low HDL-C are in Table 1.

NCEP guide lines\(^6\) recommends screening all adults older than 20 year for both total cholesterol as well as HDL cholesterol. HDL exerts powerful anti-atherogenic effects (Table 2).

Management Strategies
The various modalities to elevate HDL are outlined in Table 3.

1. Identification and Correction of Secondary Cause
   The secondary causes of low HDL mentioned in Table 1 should be identified and corrected.

2. Life Style Modification
   Smoking cessation is usually associated with elevation of HDL-C. Weight loss is also associated with significant increase in HDL. Reduction of fat in diet does not increase HDL but may reduce it. Diet can be useful as an adjunct, particularly if weight loss is achieved. Exercise is limited in its ability to raise HDL but when accompanied by weight loss can have a substantial effect. Alcohol although it raises HDL-C, is not prescribed as HDL raising drug.

3. Drugs
   In patients with low HDL-C, first the LDL and non HDL cholesterol targets should be achieved
Table 1: Causes of Low HDL Cholesterol

1. Primary hypoalphalipoproteinemia

2. Secondary
   a. Genetic: Mutation in apoA-I and lecithin cholesterol acyl transferase (LCAT)
   b. Life style related causes:
      i) Cigarette smoking
      ii) Physical inactivity
      iii) Obesity
      iv) Very low fat diet.
   c. Type II diabetes mellitus.
   d. End stage renal disease.
   e. Chronic inflammatory disorders: Rheumatoid arthritis.
   f. Drugs: Betablockers
      Thiazides
      Androgens Progestins
      Probufol

Table 2: Beneficial effects of HDL cholesterol

1. Reverse cholesterol transport
2. Antioxidant
3. Anti complement
4. Pro fibrinolytic
5. Antiplatelet
6. Improves endothelial function.

Table 3: Modalities to Increase HDL

1. Identification and correction of any secondary cause.
2. Life style modification
   a. Cessation of smoking
   b. Weight loss
   c. Exercise
   d. Cessation alcohol
3. Drugs
   1. Nicotinic acid
   2. Fibrates
   3. Estrogen replacement (Not recommended)
4. Modulations of enzymes, transfer proteins, transporter, and scavenger receptors.
   a. Lecithin cholesterol acyl transferase (LCAT)
   b. Cholesteryl ester transfer protein (CETP)
   c. Phospholipid transfer protein (PLTP)
   d. ABC A1 transporter
   e. Scavenger receptor BI (SR-B1)
5. IV infusion of synthetic HDL preparations.

and then HDL-C can be targeted. In patients with CAD or at high risk of development, the issue is whether drugs should be used to elevated it? Data in humans are limited but a variety of evidence in animals indicates that increase in plasma HDL-C or Apo A-1 is associated with reduced atherosclerosis.

Nicotinic acid is the most potent agent available for elevating isolated low HDL-C. Fibrates are more effective in raising HDL if there is hypertriglyceridemia than in patients with isolated low HDL-C. In patients with combined dyslipidemia with controlled LDL levels but with low HDL cholesterol, the additions of nicotinic and or fibrate can be utilized to elevate HDL levels.
Trials

1. The Coronary Drug Project\textsuperscript{12}This used niacin in hypercholesterolemic patients with established CAD and found that after 15 years mortality was reduced in the treatment group but independent contribution of raising HDL is uncertain.

2. Helsinki Heart Study\textsuperscript{13}This study used gemfibrozil in hyperlipidemic patients without CAD and found a 34\% decrease in coronary events, a portion of which may have been related to an increase in HDL cholesterol levels.

3. HDL Atherosclerosis Treatment Study (HATS)\textsuperscript{14}This trial showed better results with Simvastatin along with niacin and the addition of anti–oxidants vitamins diminished the benefits achieved with simvastatin and niacin combination both on anatomic progression of coronary lesions and clinical outcome.

4. BenzafibrateInfarctionPrevention(BIP)\textsuperscript{15}and Veterans Affairs High Density Lipoproteins Cholesterol Intervention Trial (VA- HIT)\textsuperscript{16}The BIP trial indicated a benefit of benzafibrate only in subgroup with TG levels greater than 200 mg/dl. The VA-HIT trial indicated beneficial effect of gemfibrozil (which raised HDL cholesterol, reduced TG but did not change LDL cholesterol levels) in men with CAD and low HDL cholesterol levels. However in both the above trials fibrate treatment also significantly reduced TG.

4. Newer up Coming Modalities of Treatment\textsuperscript{17-21}

a. LCAT over activityThis enzyme directly acts on the HDL. It has a crucial role in maturation of small HDL particles formed in the first steps of RCT by esterifying the free cholesterol of these particles. Stimulation of LCAT activity by drugs or genetic over expression of enzyme may raise HDL-C and enhance RCT. In cholesterol fed, atherosclerotic rabbits, LCAT over activity induced by transgenic techniques was shown to result in a dramatic reduction of atherosclerosis.

b. Modulation of CETPThe CETP mediated transfer of cholesterol ester from HDL to TG rich lipoproteins is another pathway for movement of cholesterol ester out of HDL. This is another target for future treatment of low HDL cholesterol.

c. PLTPThis not only transfer phospholipids and cholesterol from HDL but also modulates the size of this lipoprotein. The clinical applications of PLTP are scarce at present state of time but this protein may be another area which may be considered in future for treatment of low levels of HDL-C.

d. ABC A1, TransporterThe ABC A1 transporter system will be evaluated in future for treatment of low HDL-C and stimulation of RCT. Decreased activity of this transporter system leads to intracellular accumulation of cholesterol and a reduced supply of cholesterol for the production of HDL.
e. SR-BI

The scavenger receptor–BI is a receptor for selective uptake of cholesterol esters from HDL by the liver. The regulatory role of SR-BI for the levels of HDL–C in humans is unknown. The receptor may be a futuristic target to stimulate RCT by increasing flux of cholesterol form HDL to the liver.

5. I.V. Infusions of Synthetic HDL Preparations

Synthetic HDL particles have been prepared from recombinant human pro-Apo A-1 combined with phospholipids. Short term infusion of 2-4 gms of this cholesterol free preparation to patients with dyslipidemia have resulted in a increase of HDL–C and have at the same time increased elimination of cholesterol from the body suggesting stimulation of RCT by synthetic HDL particles. Studies on the effect of infusion of HDL on existing atherosclerotic lesions are awaited with great interest by the medical fraternity.

Thus the future of elevating HDL-C seems to be bright and besides the upcoming modalities mentioned above, there are many promising but as yet unexplored avenues.

References