Chapter (4)

Low HDL-C as A Cardiovascular Risk Factor

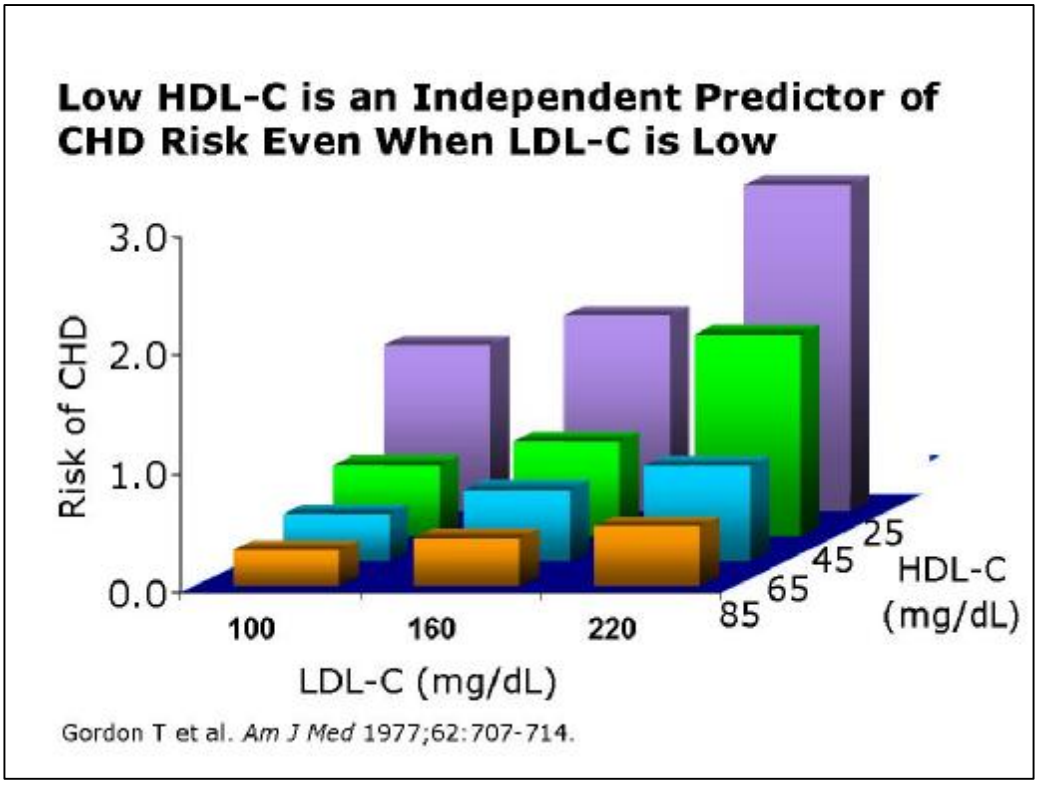
INTRODUCTION

Decades of information from large clinical studies have established that a low level of HDL-C is a risk factor for atherosclerotic cardiovascular disease. Furthermore, biochemical and pharmacological studies indicated that HDL had a variety of activities that may be responsible for its cardiovascular protective effects.

EPIDEMIOLOGICAL EVIDENCE

- Data from the Framingham investigators showed that the inverse relationship between HDL-C levels and CHD is evident in both men and women across various age groups.
- Amongst the various lipid parameters evaluated in the Framingham study, HDL-C appeared to have the strongest relationship to CHD.
- That relationship persisted after controlling for several factors known to influence the incidence of CHD, including age, blood pressure, body mass index and alcohol consumption.
- Importantly the inverse relationship between HDL-C and CHD persisted after controlling for known confounders of low plasma HDL-C, such as diabetes mellitus, obesity and hypertriglyceridemia. Taken together, these findings indicate that low HDL-C is a strong and independent risk factor for CHD. (Figure 4-1).

Figure (4-1)



- This inverse relationship between HDL-C and CHD risk was also demonstrated in the PROCAM study, in which men with HDL-C levels <35 mg/dl had a four-fold increased risk of CHD over a 6-year period, compared with men with HDL-C levels >35 mg/dl. A significant association between low HDL-C and increased risk of CHD remained even after adjustment for other risk factors.
- Meta-analysis of four prospective studies (Framingham study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial and Multiple Risk Factor Intervention Trial) confirmed these findings and consistently showed that for every 1 mg/dl decrease in plasma levels of HDL-C there was s 2%-3% increase in the risk of CHD, independent of other risk factors, including plasma LDL-C.
- The strength of the relationship between low HDL-C and increased risk of CHD may be greater in women than men.
- Recent data indicate that the association between HDL-C and CHD mortality is valid even in elderly patients aged at least 85 years.

ANGIOGRAPHIC AND ULTRASOUND EVIDENCE

- Angiographic and ultrasound studies provide additional support for the importance of low HDL-C as a risk factor for CHD.
- Low plasma levels of HDL-C have been associated with increased severity of CHD, as indicated by an increase in the number and extent of coronary vessel involvement.
- Evaluation of intima-media thickness in the carotid arteries of individuals with primary hypo-alphalipoproteinemia has revealed increased thickening comparable with that in primary hypercholesterolemia.

EVIDENCE FROM CLINICAL TRIALS

- Several clinical trials have demonstrated that HDL level is an independent risk factor for cardiovascular disease.
- The Prospective Pravastatin Pooling Project was a pooled analysis of 3 large randomized Pravastatin trials including 19,768 patients. As expected there was a significant inverse relationship between baseline HDL-C level and follow-up CHD event rates in patients not receiving a statin.
- In patients treated with Pravastatin, the relationship between HDL-C and CHD events was strikingly similar. In the group not treated with Pravastatin patients in the highest HDL-C quintile had 27% less CHD events compared to those in the lowest HDL-C quintile.

- In post-hoc analysis of the Scandinavian Simvastatin Survival Study, subgroups defined by HDL-C and triglyceride quartiles were compared to examine the influence of HDL-C and triglyceride on CHD events and response to therapy. Patients in the lowest HDL-C (<39 mg/dl) and highest triglyceride (>159 mg/dl) quartiles had increased proportions of the other features of the metabolic syndrome(increased body mass index, hypertension and diabetes), had increased risk for CHD events on placebo (35.9% at 5 years) and received greater benefit with Simvastatin therapy.

SUMMARY

- An inverse relationship exists between HDL-C levels and coronary heart disease (CHD).
- Low HDL-C is a strong and independent risk factor for CHD.
- This relationship is evident in both men and women and across various age groups.
- For every 1 mg/dl decrease in plasma levels of HDL-C there is a 2%-3% increase in the risk of CHD.
- Low levels of plasma HDL-C have been associated with increased severity of CHD, as indicated by an increase in the number and extent of angiographic coronary vessel involvement.
- Apart from epidemiologic data, several major clinical trials confirmed the inverse relationship between baseline HDL-C levels and follow-up CHD event rates.
- Other major clinical trials have revealed that raising HDL-C protected against cardiovascular disease.