LDL VS non HDL cholesterol where do we stand ?

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INTODUCTION

- **LDL-cholesterol (LDL-C), a measure of the cholesterol content within LDL, became the primary goal of therapy for historic reasons**

- **However , there continue to be numerous patients who succeed in meeting their target in LDL c goal , but still develop complications from atherosclerotic vascular disease and suffer from cardiovascular events .**

- Those patients bear the burden of having residual risks not identified using traditional metabolic and cardiovascular markers .

- There was considerable evidence that the triglyceride-rich very low-density lipoprotein(VLDL) and the remnant lipoproteins are also atherogenic

In the field of lipidology , there is a currentlly debate regarding the clinical utility of advanced lipoprotien analysis i.e. apoliprotien B100 (apo B) or low density lipoprotien particle number

LDL – P in clinical practice .

The American Diabetes Association / American Collegue of Cardiology Consensus Statement on Lipoprotien and Cardiometabolic Risk , and the National Lipid Association Expert Panel on Biomarkers and Lipoprotien analysis .. <u>Supported measure of : apo B (B 100) , or LDL – P   in certain clinical settings or patients population for further enhancement of cardiovasular risk prediction</u>

Classification of Lipoproteins

<u>There are five main classes of lipoproteins:</u>

- Chylomicrons
- Very Low Density Lipoproteins (VLDL)
- Intermediate Density Lipoproteins (IDL)
- Low Density Lipoproteins (LDL)
- High Density Lipoproteins (HDL)

Relative Sizes of Lipoproteins

Chylomicron   VLDL   IDL   LDL   HDL
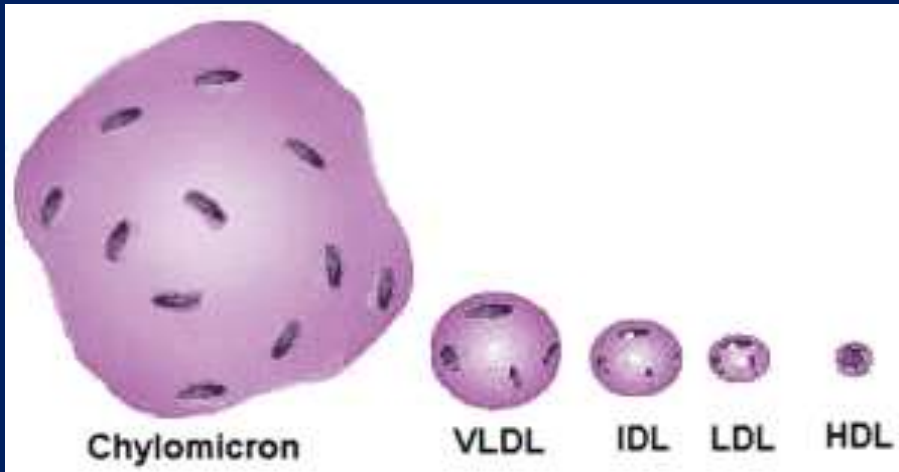
Chylomicrons

- **Chylomicrons are the <u>largest and least dense</u> of the lipoproteins. Their function is to transport dietary triglycerides and cholesterol absorbed by the intestinal epithelial cells.**

  <u>Chylomicrons contain about :</u>

- **1-2% protein,**
- **85-88% triglycerides,**
- **~8% phospholipids,**
- **~3% cholesteryl esters and**
- **~1% cholesterol.**

Very Low Density Lipoproteins (VLDL)

VLDL contains :

- 5-12% protein,
- 50-55% triglycerides,
- 18-20% phospholipids,
- 12-15% cholesteryl esters and
- 8-10% cholesterol.

- VLDL also acquires several apolipoproteins from plasma HDL and is a source of triglycerides for the cells.

Intermediate Density Lipoproteins (IDL)

- IDLs are derived from VLDL by triglyceride depletion and therefore contain the same apolipoproteins as VLDL.

- IDL becomes LDL as its triglycerides are transferred to the cells

Intermediate Density Lipoproteins (IDL) …..

They are composed of :

- 10-12% protein,
- 24-30% triglycerides,
- 25-27% phospholipids,
- 32-35% cholesteryl esters and
- 8-10% cholesterol.

Low Density Lipoproteins (LDL) - "Bad" Cholesterol

- **LDL contains :**

- 20-22% protein,
- 10-15% triglycerides,
- 20-28% phospholipids,
- 37-48% cholesteryl esters, and
- 8-10% cholesterol.

- One of the protein components of LDL is apolipoprotein B100 which serves to bind the lipoprotein particles to LDL-specific receptors on the surface of many cells.
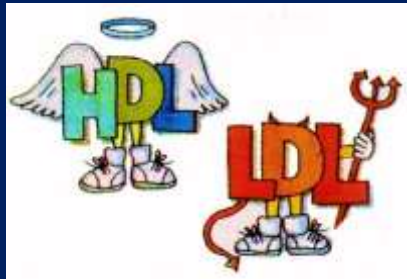
High Density Lipoproteins (HDL) - "Good" Cholesterol

- **High density lipoproteins are the smallest of the lipoproteins.**
  - **<u>HDL contains approximately :</u>**
- **55% protein,**
- **3-15% triglycerides,**
- **26-46% phospholipids,**
- **15-30% cholesteryl esters, and**
- **2-10% cholesterol.**

High Density Lipoproteins (HDL) ..

- **HDL contains a large number of different proteins including apolipoproteins such as : apo-AI (apolipoprotein A1), apo-CI, apo-CII, apo-D, and apo-E.**
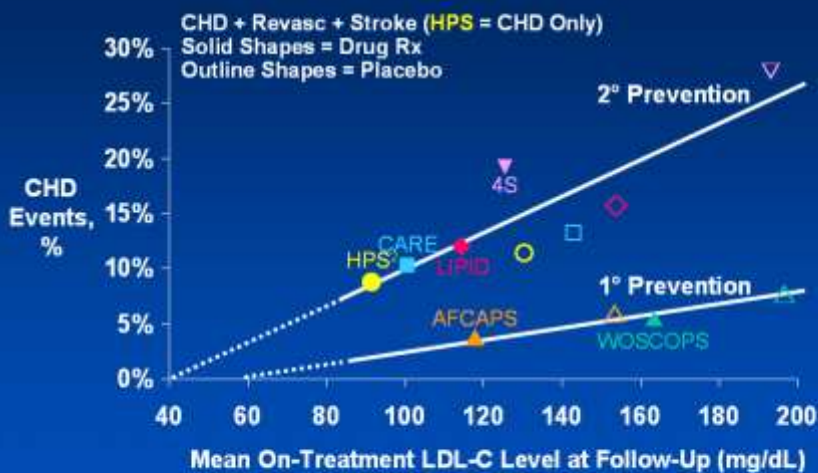
GOOD and BAD CHOLESTEROL

HDL c & LDLc

- **High Density Lipoproteins (HDL) particles is the good cholesterol , it is involved in clearing and removing cholesterol from arteries and atherosclerotic plaques , it appear to protect against cardiovascular diseases.**

- **Low Density Lipoproteins (LDL), the bad cholesterol , are associated with coronary atherosclerosis**

Clinical Background

Low-density lipoprotein cholesterol (LDL-C) is widely recognized as an established cardiovascular risk marker predicated on results from numerous clinical trials that demonstrate the ability of LDL-C to independently predict development and progression of coronary heart disease.

LDL-C Is Closely Related to CHD Events[1]

CHD + Revasc + Stroke (HPS = CHD Only)
Solid Shapes = Drug Rx
Outline Shapes = Placebo

2° Prevention

4S

CARE

HPS²   LIPID

1° Prevention

AFCAPS

WOSCOPS

CHD Events, %

30%
25%
20%
15%
10%
5%
0%

40 60 80 100 120 140 160 180 200

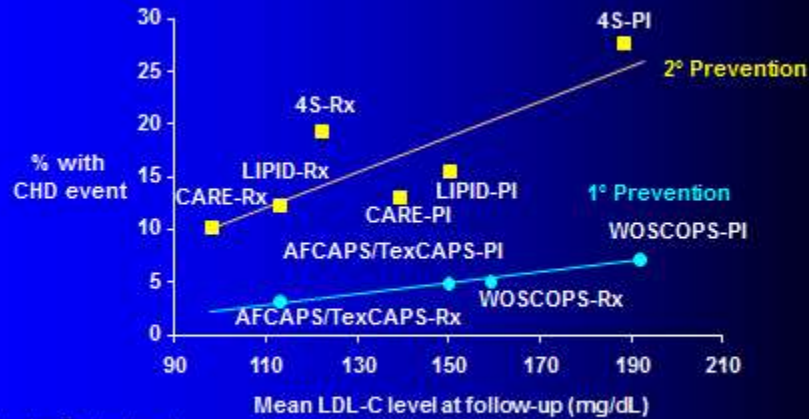**Mean On-Treatment LDL-C Level at Follow-Up (mg/dL)**

1. Adapted from Ballantyne CM. Low-density lipoproteins and risk for coronary artery disease.
   Am J Cardiol. 1998;82:3Q–12Q, with permission from Excerpta Medica.
2. Heart Protection Study Collaborative Group. Lancet. 2002;360:7–22

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Lipid profile measurements

- **A standard lipid profile measures total cholesterol, triglycerides, and HDL-C.**

- **These numbers are then used to calculate low-density lipoprotein cholesterol (LDL-C), according to the so-called Friedwald equation. <u>However, calculation of LDL-C has several limitations</u>.**

Limitations of LDL Cholesterol

- Recommendations regarding diet and drug therapy to lower cholesterol are most often based on the LDL-C number.

- However, LDL is not the only lipoprotein involved in atherosclerotic heart disease.

- Triglyceride-rich very low-density lipoprotein (VLDL) and the so-called remnant lipoproteins are also atherogenic.

Relying on LDL-C alone may be misleading.

- For example, individuals with abdominal obesity, metabolic syndrome or diabetic lipid disorders often have elevated triglycerides, low HDL-C, and relatively normal calculated LDL-C.

- Despite their normal LDL-C, these patients produce highly atherogenic lipoproteins such as VLDL and IDL (intermediate density lipoprotein) as well as small dense LDL particles.

- A patient with low LDL-C and high non-HDL-C is an example of a patient with increased risk who may slip through the cracks because we only look at LDL-C.

- These patients are also likely to have high LDL particle number (LDL-P) as well as high ApoB levels.

Therefore. ....

- There is a need for a lipid parameter that better reflects the amount of cholesterol within all atherogenic particles.

- This is of particular importance when triglyceride levels are high which is quite common, for example among people with abdominal obesity or metabolic syndrome.

What Is Non-HDL Cholesterol and Why Is It Important?

- HDL and LDL particles seem to play very different roles in the pathogenesis of atherosclerosis.

- Therefore, measuring the amount of cholesterol within these particles tells two different stories.

- While high levels of LDL-C are associated with increased risk of heart disease, high levels of HDL-C are associated with lower risk.

- HDL particles appear to be involved in clearing and removing cholesterol from arteries and atherosclerotic plaques while LDL-particles seem to be directly involved in the atherosclerotic process itself.

- Of course, it is the same cholesterol; the difference lies within the lipoproteins that carry it.

- Measuring total cholesterol provides limited information about risk because the number includes both HDL-C and LDL-C

- If we, however, subtract HDL-C from the total cholesterol we will have a measure of the amount of cholesterol carried by all lipoproteins except HDL.

- Doing this simple math will give us the amount of cholesterol carried within all lipoproteins that are atherogenic.

- In other words; a measure of cholesterol carried within all the "bad" lipoproteins but not the "good" ones (which is only HDL).

This measure is termed :
non-HDL cholesterol (non-HDL-C).

Definition

- Non-high-density lipoprotein cholesterol (non-HDL-C) is simply :

  the difference between the total cholesterol concentration and the HDL cholesterol concentration, providing an estimate of cholesterol in the atherogenic particles including IDL, VLDL, Lp(a), and LDL

How to Calculate Non-HDL Cholesterol

- An advantage of using non-HDL-C is that there is no need for fasting blood sample.

- Non-HDL cholesterol is total cholesterol minus HDL cholesterol

- This is the formula:

    Non-HDL Cholesterol = Total Cholesterol – HDL cholesterol

- The Friedewald equation calculates LDL-C by subtracting the HDL-C and VLDL-C (or TG/5) from the total cholesterol (LDL-C = TC-HDL-TG/5)

- So if Total Cholesterol is 220 mg/dL (5.7 mmol/L) and HDL cholesterol is 50 mg/dL (1.3 mmol/L);

- Non-HDL Cholesterol is 170 mg/dL (4.4 mmol/L

Clinical Implications

Non-HDL-C is not a novel concept and was recommended as a secondary target by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines in 2001 for patients with triglycerides greater than 200 mg/dL.

- Recent evidence suggests that non-HDL-C shows a better correlation with small dense LDL particles than do other lipid parameters including LDL-C.

- Non-HDL-C has been shown to be a better marker of risk in both primary and secondary prevention studies.

- In a recent analysis of data combined from 68 studies, non-HDL-C was the best risk predictor of all cholesterol measures, both for CAD events and for strokes.

- The CARE (Cholesterol and Recurrent Events) study found that VLDL-C, apo B, and apo C-IIIare potent predictors of events.

- The CHICAGO (Carotid IntimaMedia Thickness in Atherosclerosis Using Pioglitazone) study found that : triglyceride-rich lipoprotein cholesterol showed the greatest association with coronary calcium .

- A recent large meta analysis with 60,000 patients in statin trials found that when LDL-C was low (LDL-C 100 mg/dl), but non– HDL-C was elevated (non–HDL-C 130 mg/dl) , there was an increase in cardiovascular events compared with those with both elevated LDL-C and non–HDL-C .

What Is a Desirable Level of Non-HDL Cholesterol

- The treatment goal for non-HDL-C is usually 30 mg/dL above the LDL-C treatment target.

- For example, if the LDL-C treatment goal is <70 mg/dL, the non-HDL-C treatment target would be <100 mg/dL.

non-HDL-C levels are at in terms of risk:

- above 220 mg/dL (5.7 mmol/L) is considered very high
- 190 – 219 mg/dL (4.9 – 5.6 mmol/L) is considered high
- 160– 189 mg/dL (4.1 – 4.8 mmol/L) is considered borderline high
- 130 – 159 mg/dL (3.4 – 4.0 mmol/L) is considered near ideal
- below 130 mg/dL (below 3.4 mmol/L) is considered ideal for people at risk of heart disease
- below 100 mg/dL (below 2.6 mmol/L) is considered ideal for people at very high risk of heart disease

The non-HDL-C goal is less than 100 mg/dL for patients who meet 1 of the following criteria:

- (1) established cardiovascular disease plus diabetes,
- (2) established cardiovascular disease plus multiple poorly controlled risk factors,
- (3) multiple risk factors of the metabolic syndrome, or
- (4) patients with acute coronary syndrome and/or coronary heart disease .

Should non–HDL-C replace LDL-C as the main target of therapy?

The advantages appear clear: non–HDL-C is a better risk predictor

CONCLUSION

- Recently, non-HDL cholesterol (non-HDL-C) has become a commonly used marker for a blood lipid pattern associated with increased risk of heart disease.

- To calculate non-HDL-C, you only need to know the numbers for total cholesterol and high-density lipoprotein cholesterol (HDL-C).

- Several known limitations make LDL-C a less accurate marker of cardiovascular risk than either non-high-density lipoprotein cholesterol (non-HDL-C), LDL particle number, or apolipoprotein B (apoB).

- Furthermore, other triglyceride-rich lipoproteins also are atherogenic, including very-low-density lipoprotein (VLDL) remnants and intermediate-density lipoproteins (IDL).

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