National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Triglycerides & HDL-C

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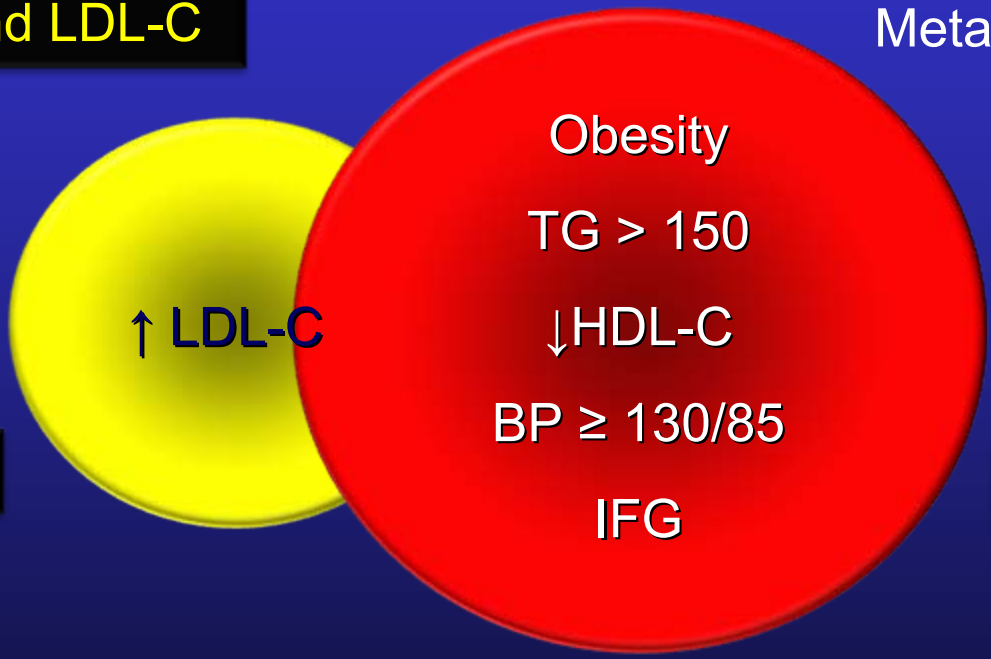
Global Risk Assessment

Going Beyond LDL-C

Metabolic Syndrome



ATPII

ATPIII

Normalize LDL-C

Normalize apoB or Non HDL-C

Circulation 2004;110:227-239

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Risk Factors That Modify LDL-C Goal

- Cigarette smoking
- Hypertension (≥ 140/90 or on Rx)
- Low level of HDL-C (≤ 40 mg/dL)
- Family History of Premature CHD
- Age (Female ≥ 55, male ≥ 45

High risk, defined as a net of two or more CHD risk factors, leads to more vigorous intervention in primary prevention.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

NCEP ATP-III Triglyceride Statements

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Lipid Risk Classification

Elevated serum triglycerides are associated with increased risk for CHD. In addition, elevated triglycerides are commonly associated with other lipid risk factors and **non-lipid risk factors**.

Remnant lipoproteins
Impaired RCT
Small LDL particles

Hypertension
Insulin resistance
Glucose intolerance
Prothrombotic states

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Risk of Triglycerides

- Several causes underlie elevated Triglycerides in the general population
  - Overweight and obesity
  - Physical inactivity
  - Cigarette smoking
  - Excess alcohol intake
  - Very high carbohydrate diets (>60% of energy)
  - Other disease (diabetes, renal failure, nephrosis)
  - Drugs: steroids, protease inhibitors, estrogen, etc
  - Genetic factors

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Elevations of Triglycerides

In persons with none of these factors, serum triglyceride levels typically are less than 100 mg/dL.

- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- Very high carbohydrate diets (>60% of energy)
- Other disease (diabetes, renal failure, nephrosis)
- Drugs: steroids, protease inhibitors, estrogen, etc
- Genetic factors

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Risk Classification of Triglycerides

As some of these triglyceride-raising factors develop, levels commonly rise into the range of 150 to 199 mg/dL.

Normal	<150 mg/dL
Borderline high	150–199 mg/dL

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Risk Classification of Triglycerides

Normal	<150 mg/dL
Borderline high	150–199 mg/dL

Although several factors can elevate triglycerides most common are overweight/obesity and physical inactivity

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Risk Classification of Triglycerides

When triglyceride rise to ≥200 mg/dL, genetic influences play an increasing role as well.

High Risk ≥ 200 - 499 mg/dL

Very High Risk > 500 mg/dL

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Risk of Triglycerides

Risk Classification of Serum Triglycerides

Normal <150 mg/dL

Borderline high 150–199 mg/dL

High 200–499 mg/dL

Very high ≥500 mg/dL

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Risk of Triglycerides: Lipoprotein Remnants

Renewed interest in the importance of elevated triglycerides has been stimulated by the publication of meta-analyses that found that raised triglycerides are in fact an ***independent risk factor*** for CHD.

This independence suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

The most likely candidates for atherogenic TGRLP are remnant lipoproteins. These lipoproteins include small very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). They are cholesterol enriched particles and have many of the properties of LDL.

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Elevated Triglycerides

Evidence statement

Some species of triglyceride-rich lipoproteins, notably, cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose to CHD.

Recommendation: In persons with high serum triglycerides, elevated remnant lipoproteins should be reduced in addition to lowering of LDL cholesterol.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

National Cholesterol Education Program Adult Treatment Panel III NCEP-ATP III Risk of Triglycerides

When **triglyceride levels are ≥200 mg/dL**, the presence of increased quantities of atherogenic remnant lipoproteins can heighten CHD risk **substantially** beyond that predicted by LDL cholesterol alone.

For these reasons, **ATP III modified the triglyceride classification** to give more attention to moderate elevations.

NCEP ATP III Chapter II Circulation December 2002 pp3169

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Goals of Therapy

- **Normalize LDL-C**
  - 130 mg/dl in moderate risk patients (10-20% 10 year risk)
  - <100 mg/dl in high risk patients (>20% 10 year risk)

- **Hypertriglyceridemia**

NCEP ATP III Chapter VI pp25-26

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Treatment of Triglycerides

- If triglycerides are very high **(≥500 mg/dL),** attention turns first to prevention of acute pancreatitis, which is more likely to occur when triglycerides are >1000 mg/dL.
- Triglyceride-lowering drugs (fibrate or nicotinic acid) **become first line therapy**; although statins can be used to lower LDL cholesterol to reach the LDL goal, in these patients

NCEP ATPIII. Chapter IV ***Circulation December 2002 pp 3247***

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III)
Non-HDL Cholesterol

- Non-HDL-C represents an acceptable surrogate marker for **apolipoprotein B** in routine clinical practice
- Non-HDL-C can be used for initial testing or for monitoring or response in the nonfasting state;
  - The measure is reliable in nonfasting serum, whereas calculated LDL-C can be erroneous in presence of postprandial hypertriglyceridemia

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Treatment of Triglycerides

What is the NCEP ATP III goal for TG therapy, if baseline TG is 200-500 mg/dL?

1) Normalize LDL-C
2) Normalize the non HDL-C value

} ↓ ApoB

TG are surrogates for apoB

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Adult Treatment Panel III NCEP-ATP III

Goals of Therapy

- **Normalize LDL-C**
  - 130 mg/dl in moderate risk patients (10-20% 10 year risk)
  - <100 mg/dl in high risk patients (>20% 10 year risk)

- If TG > 200 mg/dl, **normalize Non HDL-C**
  - <160 mg/dl in moderate risk patients
  - <130 mg/dl in high risk patients
  - < 100 mg/dL in very high risk patients

Circulation 2004;110:227-239

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

NCEP ATP-III
HDL-C Statements

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Risk of Low HDL-C

Evidence statement

A low HDL cholesterol level is strongly and inversely associated with risk for CHD

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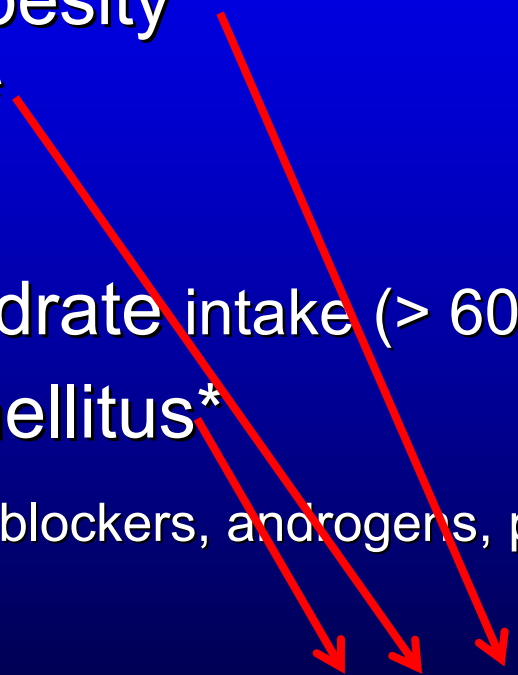
Causes of Low HDL-C

- **Elevated serum triglycerides**
- Overweight and obesity*
- Physical inactivity*
- Cigarette smoking
- Very high carbohydrate intake (> 60% of total energy)
- Type 2 diabetes mellitus*
- Certain drugs (beta-blockers, androgens, progestational agents)
- Genetic factors*



*Exert their effects on HDL cholesterol levels in part through insulin resistance and commonly through higher triglyceride levels.

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Isolated Low HDL-C

- When triglyceride levels are greater than 150 mg/dL, HDL-cholesterol concentrations frequently are <40 mg/dL in men (or <50 mg/dL in women).
- Thus, the term *isolated low HDL can* be reserved for HDL-cholesterol levels <40 mg/dL in the presence of serum triglycerides <150 mg/dL.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Risk of Low HDL-C

- Epidemiologic studies consistently show **low HDL-C** to be an independent risk factor for CHD
- In prospective studies HDL usually proves to be the lipid risk actor most highly correlated with CHD risk

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Risk of Low HDL-C

- Although there are conflicting data, multiple lines of evidence strongly intimate that HDL plays a direct role in the atherogenic process. If so, it is **potential target for therapy**
  - In genetically modified animals, high levels of HDL appear to protect against atherogenesis.
  - In vitro, HDL promotes efflux of cholesterol from foam cells in atherosclerotic lesions (reverse cholesterol transport).
  - Recent studies indicate that the antioxidant and anti-inflammatory properties of HDL also inhibit atherogenesis.

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Genetically Low HDL-C

- Some genetic forms of HDL deficiency are accompanied by increased risk for CHD; others appear not to be. This latter finding raises the possibility that some subspecies of HDL affect atherogenesis whereas others do not

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Associations of Low HDL-C

- The direct role of HDL in atherogenesis probably cannot fully account for the strong predictive power of HDL in epidemiological studies.
- Because of the association of low HDL with other atherogenic factors **(some of which are not included among standard risk factors),** a low HDL cholesterol is not as strongly *independent* in its prediction of CHD as suggested by usual multivariate analysis
- Its independence is partially confounded by some risk factors that are not routinely measured

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Risk of Low HDL-C

- This confounding raises the possibility that therapeutic raising of HDL-cholesterol levels **will not reduce CHD risk** as much as might be predicted from prospective epidemiological studies

- **High Risk HDL-C defined as <40 mg/dL** :No specific goal defined for raising HDL-C

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TC/HDL-C Ratio

- Many studies show that the **total cholesterol/HDL cholesterol ratio** (TC/HDL-C) is a powerful predictor of CHD risk.
- This ratio reflects two powerful components of risk.
  - A high total cholesterol is a marker for atherogenic lipoproteins
  - A low HDL cholesterol correlates with the multiple risk factors of the metabolic syndrome and probably imparts some independent risk.
- The TC/HDL-C ratio ratio is subsumed in the Framingham global risk equations that are the basis of the 10-year risk assessment used in ATP III.
- In this way, ATP III incorporates cholesterol ratios into risk assessment. If risk assessment is done using Framingham risk factors as continuous variables, then the ratio is incorporated.

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Treatment of Low HDL-C

- **Low HDL-C: <40 mg/dL** :No specific goal defined for raising HDL-C
- Targets of therapy:
  - All persons with low HDL-C: **achieve LDL-C goal**; then if metabolic syndrome is present: ↓ weight, ↑ physical activity
  - Those with TG 200–499 mg/dL: achieve **non–HDL-C goal** as secondary priority
  - those with TG <200 mg/dL: **consider drugs** for raising HDL-C (fibrates, nicotinic acid)

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HDL Cholesterol

HDL Cholesterol levels are inversely correlated with risk for CHD. Some evidence indicates that HDL protects against the development of atherosclerosis, although a **low HDL level** often reflects the presence of other atherogenic factors.

Beta-lipoproteins:
VLDL and IDL remnants,
Small LDL

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HDL Cholesterol

Since currently available drugs have multiple actions, it is difficult to dissect fully the benefit of HDL raising from that of **reducing atherogenic lipoproteins.**

It remains uncertain whether raising **HDL-C levels** per se, independent of other changes in lipid and/or nonlipid risk factors, will reduce risk for CHD.

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HDL Cholesterol

►**Whether raising HDL per se will reduce risk for CHD has not been resolved.**

►Nonetheless, HDL levels are raised to varying degrees with lipid-modifying drugs, e.g., nicotinic acid, fibrates, and statins. Furthermore clinical trials with nicotinic acid and fibrates provide suggestive evidence that HDL raising provides one component of risk reduction **with these drugs**.

►Whether the small rise in HDL-cholesterol levels accompanying statin therapy accounts for any of the risk reduction from these drugs is uncertain.

►Since currently available drugs have multiple actions, it is difficult to dissect fully the benefit of HDL raising from that of reducing atherogenic lipoproteins. Regardless, use of drugs that favorably modify multiple inter-related lipid risk factors appears to reduce risk for CHD

Final Report Circulation 2002;106:3143-3421

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HDL Cholesterol

Recommendation: A specific HDL-cholesterol goal level to reach with HDL-raising therapy is not identified.

However, nondrug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and nonlipid risk factors should be encouraged.

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TC/HDL Cholesterol Ratio

- ATP III **does not define** the total cholesterol/HDL-cholesterol ratio as a specified lipid target of therapy.
- Instead, LDL cholesterol is retained as the primary target of lipid-lowering therapy.
- **Nor** is the total cholesterol/HDL-cholesterol ratio recommended as a secondary target of therapy.
- Treatment of ratios will divert priority from specific lipoprotein fractions as targets of therapy.

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Adult Treatment Panel III NCEP-ATP III Treatment of Low HDL-C

- **Low HDL-C: is defined as <40 mg/dL**
  No specific goal defined for raising HDL-C

- Targets of therapy:
  - Normalize LDL-C in all
  - Those with TG 200–499 mg/dL: achieve **non–HDL-C goal** as secondary priority

↓ **ApoB**

JAMA 2001;285 :2331-2338

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Adult Treatment Panel III NCEP-ATP III Addendum

Low HDL-Cholesterol

Although the potential benefit of HDL-raising therapy has evoked considerable interest, current documentation of risk reduction through controlled clinical trials **is not sufficient** to warrant setting a specific goal value for raising HDL-C.

Recent lipid-lowering drug trials provide **no new evidence** in this regard.

Circulation 2004;110:227-239

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Treatment of Isolated Low HDL-C

- **Low HDL-C: <40 mg/dL with a TG < 150 mg/dL**

  No specific goal defined for raising HDL-C

- The combined use of an LDL-lowering drug with either a fibrate or nicotinic acid is attractive for high risk persons with isolated low HDL to improve the whole lipoprotein profile

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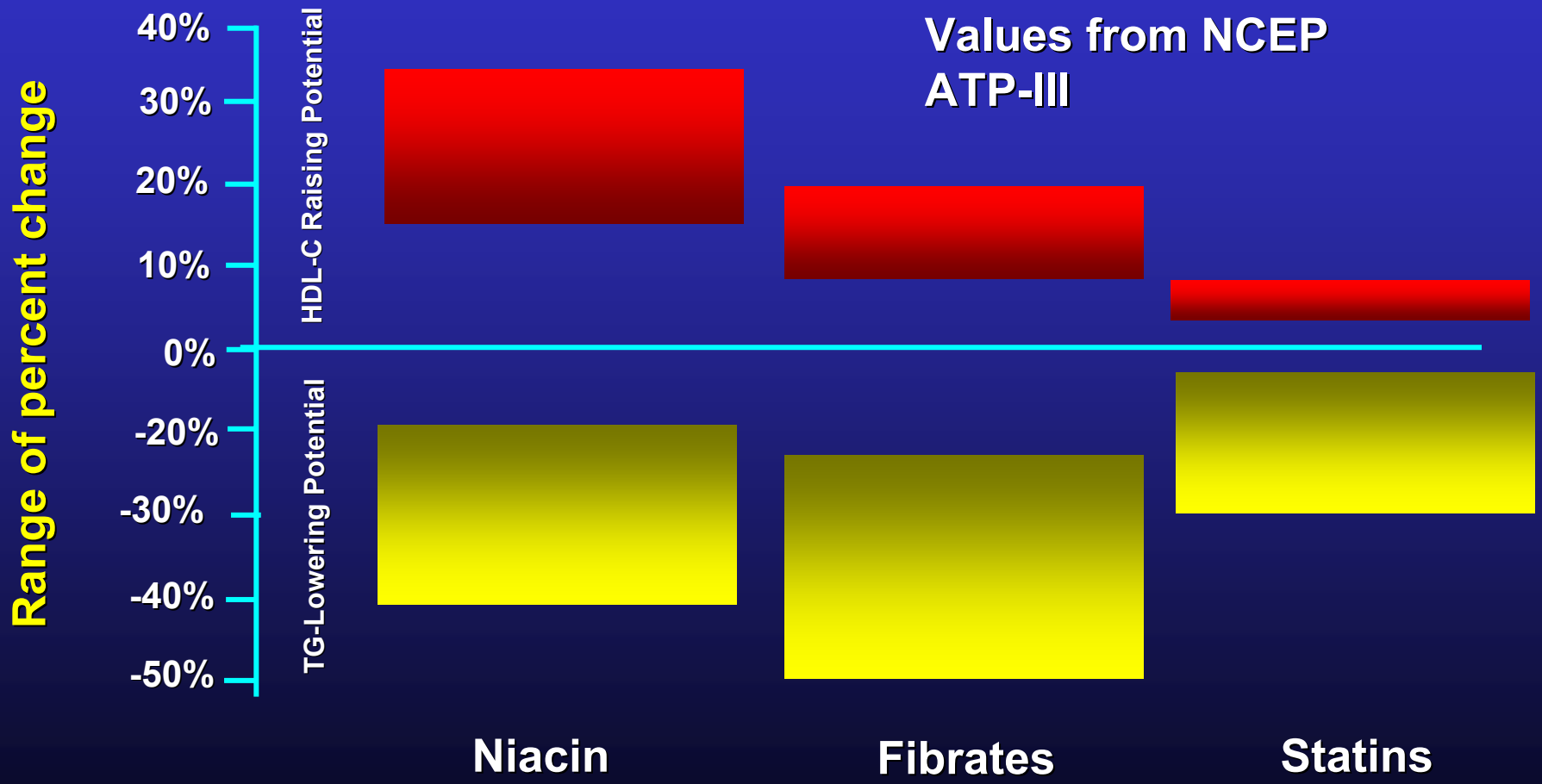
Effect of Drug Therapy on HDL-C and TG



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