

Egyptian Society of
CARDIOLOGY






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 45th Annual International Congress of the
EGYPTIAN SOCIETY OF CARDIOLOGY
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Low HDL: diagnostic and prognostic value

Haytham Soliman, MD
 Lecturer of cardiovascular medicine
 Fayoum University


HDL metabolism




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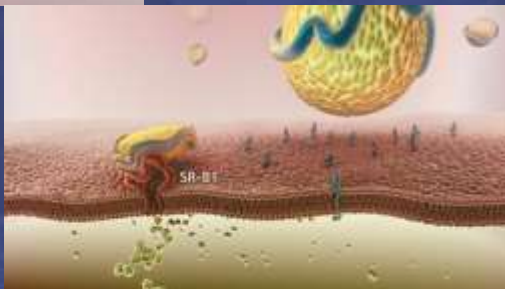
INDIRECT PATHWAY




HDL
CETP-MEDIATED

Indirect pathway
Esterification of cholesterol in HDL by **CETP** in exchange with **TG**

Direct transport of cholesterol via LDL receptors in liver





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ApoB Lipoproteins (Non HDL)

Intestine → Chylomicron → LPL → FA → Chylomicron Remnant

Intestine → VLDL → LPL → FA → IDL → LDL

Liver → VLDL

Cells → HDL₂ → CETP → HDL₃ → Nascent HDL → LCAT → HDL₂

ApoA-I Lipoproteins (HDL)

Liver → HDL₂ → LCAT → HDL₃ → Nascent HDL → LCAT → HDL₂

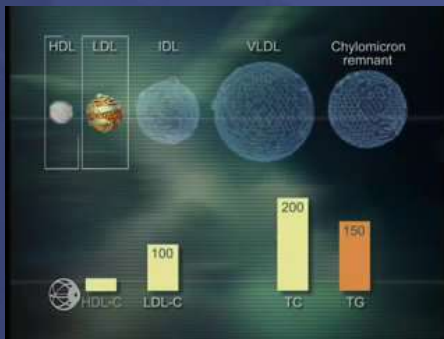
Cells → HDL₂ → LCAT → HDL₃ → Nascent HDL → LCAT → HDL₂



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Switching concept of measurements



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Types of low HDL (Hypoalphalipoproteinemia)

Familial or primary causes

- Familial apo A-I deficiency
- Familial lecithin-cholesterol acetyltransferase (LCAT) deficiency
- Tangier disease

Secondary causes

- obesity Physical inactivity
- Type 2 diabetes Cigarette smoking
- End-stage renal disease
- Hypertriglyceridemia
- Probucol, Androgens, Progestins
- High-dose thiazide diuretics
- High-dose beta blockers
- Very low-fat diet
- Severe liver disease
- Malabsorption
- Malnutrition
- Severe inflammatory disease



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Primary causes

- A genetic defect in Apo A LP synthesis
- Low HDL and some times low LDL
- Most of them are not accompanied with CHD
- HDL functions is also altered
- Usually has corneal opacities in young age



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Primary causes

- **Tangier disease:**
 - mutation in ATP cassette transporter 1
 - Low HDL up to 5md/dl and low LDL
 - apo A-I levels are low
 - Cholesterol ester deposition in reticuloendothelial system
 - Accelerated HDL catabolism
 - Orange tonsils, peripheral neuropathy
 - **Premature CHD**



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If primary causes are suspected

- Evaluation of HDL subfractions
- Measurement of the LCAT enzymatic activity
- Apo A-I, apo A-II, and HDL subfractions

Secondary causes

- **Metabolic syndrome** is the top of the list
- **Cigarette smoking** is an important cause
- **Low fat diet** results is ↓HDL but also ↓ CHD as the whole cholesterol contents is decreased
- **High TG** is accompanied with ↓HDL
- **Drugs:** high BB and thiazide diuretics

Clinical presentation

- Tendon xanthomas
- Cutaneous xanthomas
- Findings of ischemic coronary heart disease
- Signs of congestive heart failure
- Arrhythmias
- Corneal opacification



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Quality and not quantity

- A rare type of HDL with an apo A-I Milano was found
- Carriers express more CV protection even at lower HDL levels
- Pilot trials with infusion of apo A-I Milano showed regression of plaque by IVUS over 5 weeks
- Larger trials showed no significant effects of this infusion
- RCT are needed to verify its clinical significance

Nissen et al, Milano Pilot study
HDL/ApoA-1 infusion and ApoA-1 gene therapy in atherosclerosis
front Pharmacol. 2015; 6: 187.



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What's the significance of low HDL

- Low HDL-C can act synergistically with other lipid risk factors to increase ASCVD risk
- T Chol/HDL or LDL /HDL is a potentially sensitive marker of ASCVD risk
- (TNT) trial found that both ratios were highly predictive of major cardiovascular event risk
- HDL level of Below 40mg/dl in men and 50 mg/dl in women is a marker of ASCVD risk



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- a clinical study of 258 normotensive, nondiabetic individuals with overweight determined that a TG to HDL-C ratio 2.4 or higher was predictive of the presence of insulin resistance

McLaughlin T, et al Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med. 2003;139:802-809

- low HDL-C was a significant predictor of cardiovascular risk in all groups, including individuals with the lowest (<70 mg/dL) LDL-C levels
- In fact, a normal apo A level with low HDL-C may be an indication of less risk suggesting the presence of an adequate number of HDL-C particles that contain less cholesterol

Barter P, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular risk. N Engl J Med. 2005;352:1664-1671

Rubenstein M et al Treatment strategies for management of serum lipids Prog Cardiovasc Dis.1998;41:95-116. [EL 4; NE]



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Significance of High HDL levels

- HDL-C \geq 60 mg/dL is an independent negative risk factor in both sexes
- At 60 mg/dL, 1 risk factor can be subtracted from an individual's overall risk profile
- 1 mg/dL increase in HDL-C is associated with a decrease in ASCVD risk of 2% in men and 3% in women

Gordon DJ, et al. Highdensity lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989;79:8-15

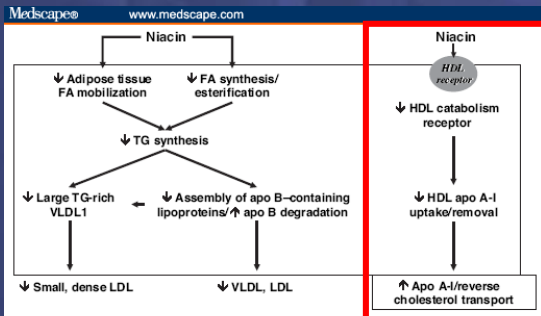


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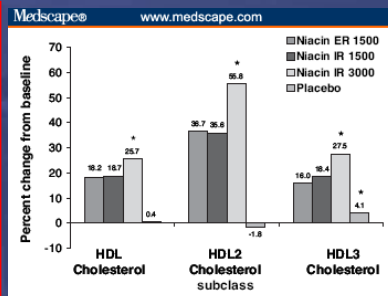
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So let's rise HDL (clinical trials)

- Niacin



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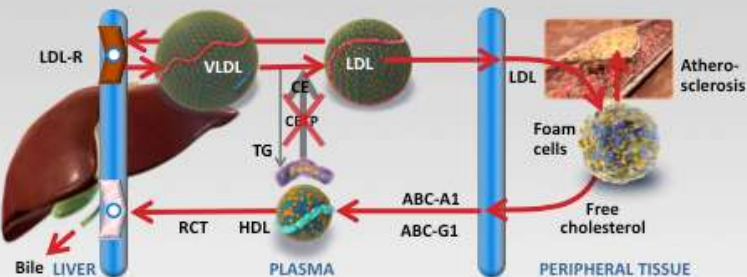
- AIM-HIGH: the addition of niacin to statin therapy did not provide any clear benefit to patients with cardiovascular disease and low HDL levels
- larger HPS2-THRIVE study (N=25,673) confirmed these findings
- Additionally, adding niacin to statins increased risk for serious adverse events

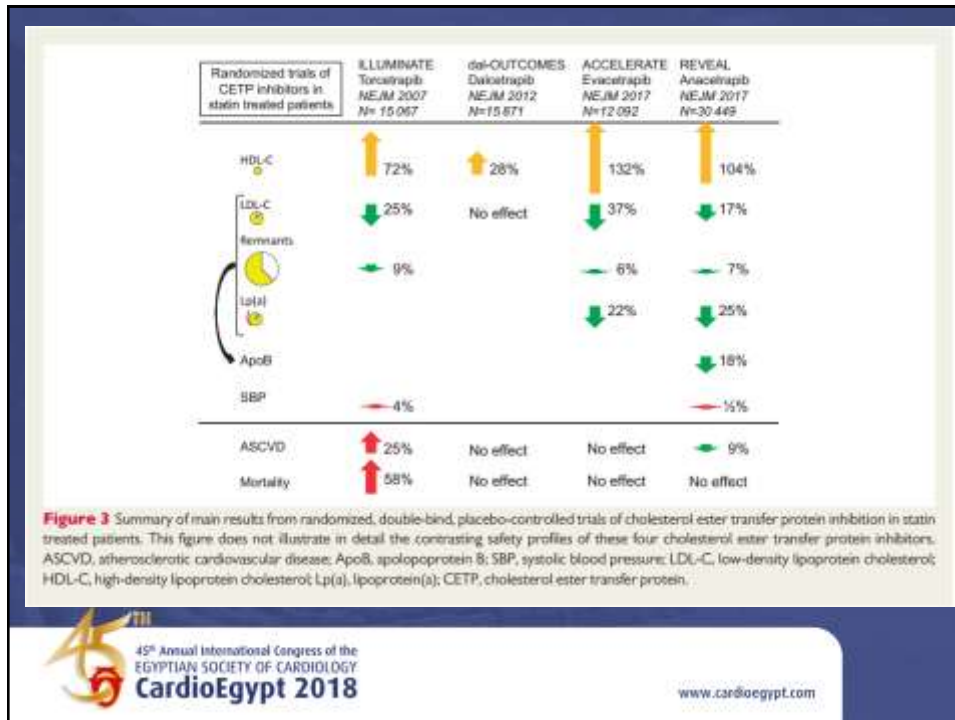
Drug treatments of low high-density lipoprotein-cholesterol is considered

Recommendations	Class	Level
Statin and fibrates raise HDL-C with similar magnitude and these drugs may be considered.	IIb	B
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B

Let's try CETP inhibitors

Role of CETP Inhibition in Atherosclerosis



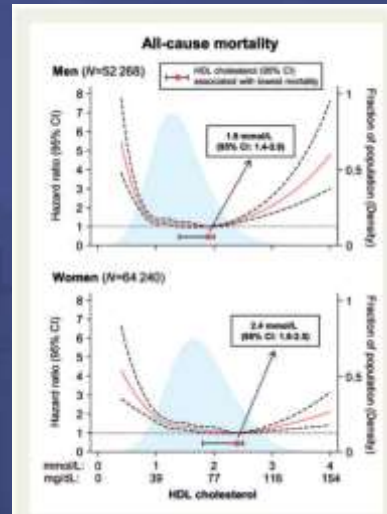


High HDL in CKD patients?

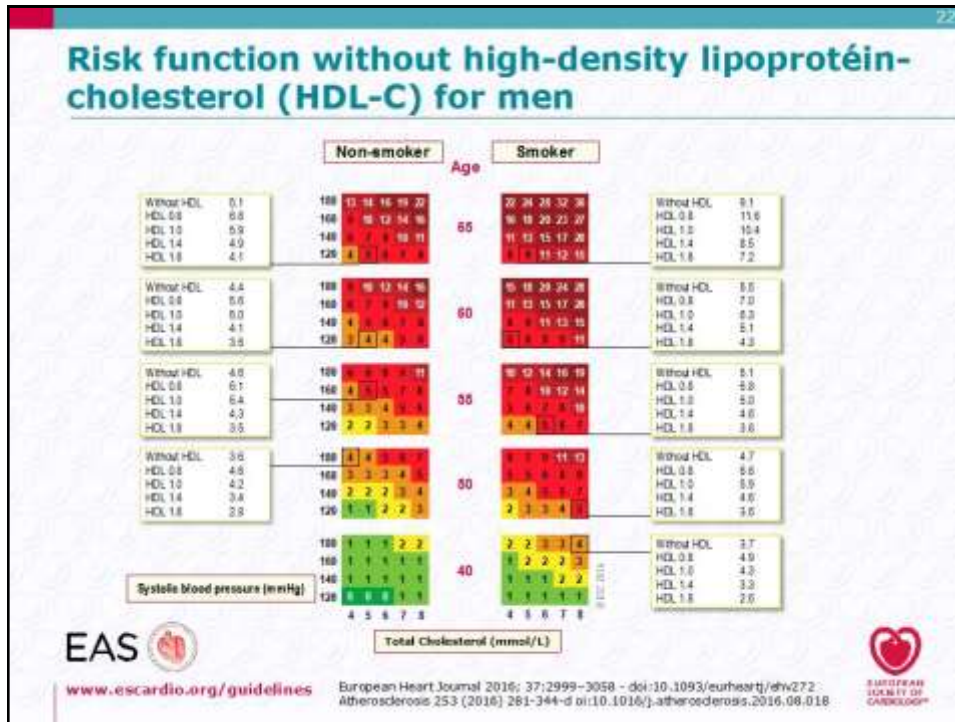
- Protective effects of HDL are altered in patients with ASCVD and chronic kidney disease
- Alterations of the protein cargo and small molecules such as **symetric dimethylarginine**
- In these patients increased HDL cholesterol is associated with adverse cardiovascular outcomes

Speer T et al, Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor- 2. *Immunity* 2013;38:754–768.

- two Copenhagen prospective population-based studies, extreme high HDL cholesterol paradoxically have high all-cause mortality
- Certainly, at high HDL cholesterol concentrations the HDL particle may not be functioning properly



So what's the benefit of
HDL value?



Lipid analyses

Recommendations	Class	Level
LDL-C has to be used as the primary lipid analysis.	I	C
HDL-C is recommended to be analysed before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
When available, apoB should be an alternative to non-HDL-C.	IIa	C
Lp(a) should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD.	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C







EAS **EUROPEAN SOCIETY OF CARDIOLOGY**

www.escardio.org/guidelines European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 261–344-d oi:10.1016/j.atherosclerosis.2016.06.018


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Risk estimation

Recommendations	Class	Level
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	I	C
TG adds information to risk and is indicated for risk estimation.	I	C
Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	I	C
ApoB should be considered as an alternative risk marker whenever available, especially in subjects with high TG.	IIa	C
Lp(a) should be considered in selected cases at high-risk, in patients with a family history of premature CVD, and for reclassification in subjects with borderline risk.	IIa	C
The ratio apoB/apoA1 may be considered as an alternative analysis for risk estimation.	IIb	C
The ratio non-HDL-C/HDL-C may be considered as an alternative but HDL-C used in HeartScore gives a better risk estimation.	IIb	C

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www.escardio.org/guidelines European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281–344-d oi:10.1016/j.atherosclerosis.2016.06.018

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To do or not to do lipid guidelines (2)

Recommendations	Class	Level
Lipid analyses for characterization of dyslipidaemias before treatment		
LDL-C has to be used as the primary lipid analysis.	I	C
HDL-C is recommended to be analysed before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
Lipid analyses as treatment targets in the prevention of cardiovascular disease		
LDL-C is recommended as the primary target for treatment.	I	A
HDL-C is not recommended as a target for treatment.	III	A
The ratios apoB/apoA1 or non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B
Treatment goals for low-density lipoprotein-cholesterol		
In patients at VERY HIGH CV risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL), or a reduction of at least 50% if the baseline LDL-Ce is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B

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www.escardio.org/guidelines European Heart Journal 2016; 37:2999–3058 - doi:10.1093/eurheartj/ehv272
Atherosclerosis 253 (2016) 281–344-d oi:10.1016/j.atherosclerosis.2016.06.018

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In conclusion

- Low HDL has many primary and secondary causes
- It's an important marker for increase CV risk
- HDL function is more important than it's level
- Aims to increase HDL failed to be of benefit
- Till present time HDL levels may reflect positive or negative risk factor
- But its not a target to treat



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Thank you



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