HMG-CoA Reductase Inhibitors in Lipid Metabolism.Discovery and Development

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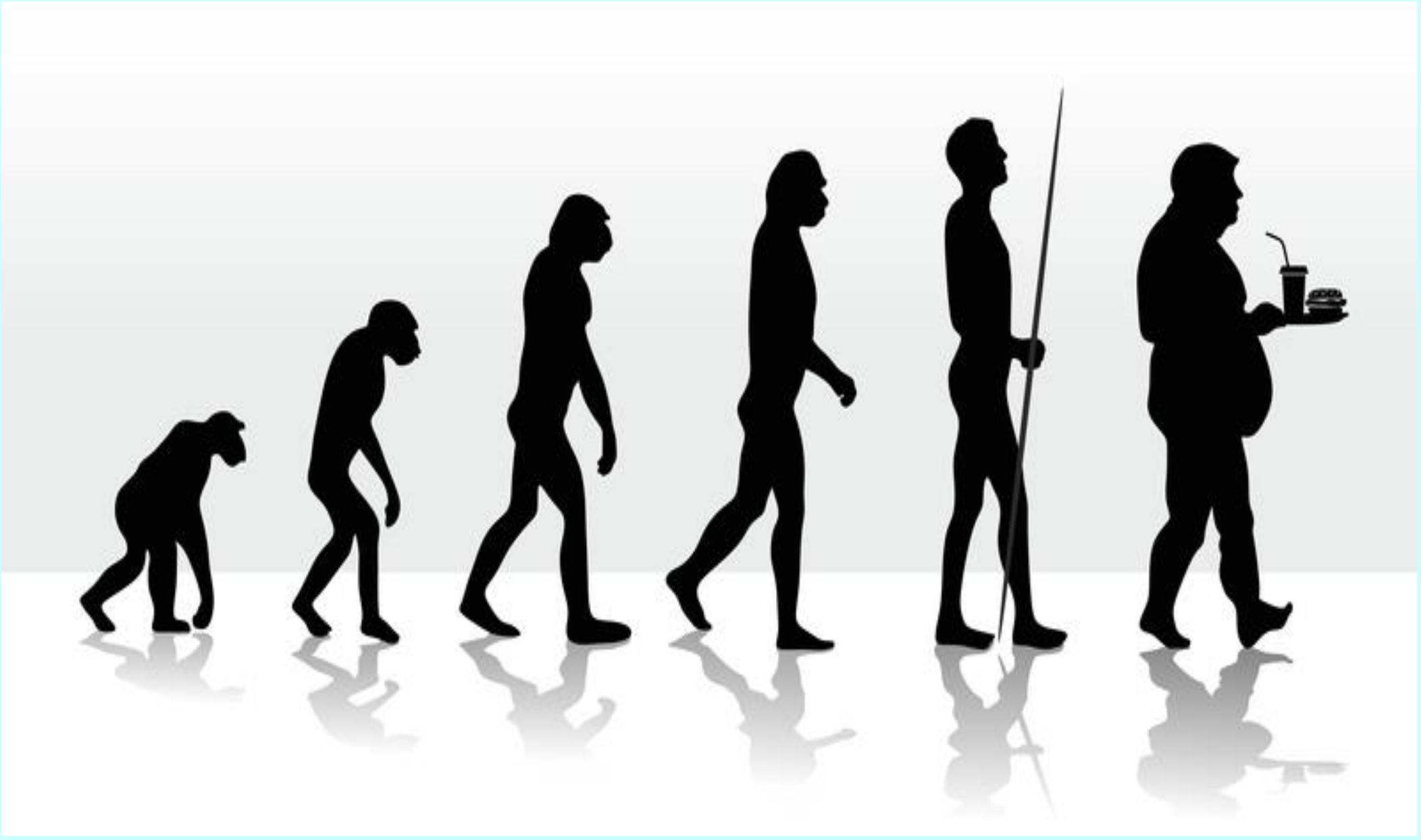
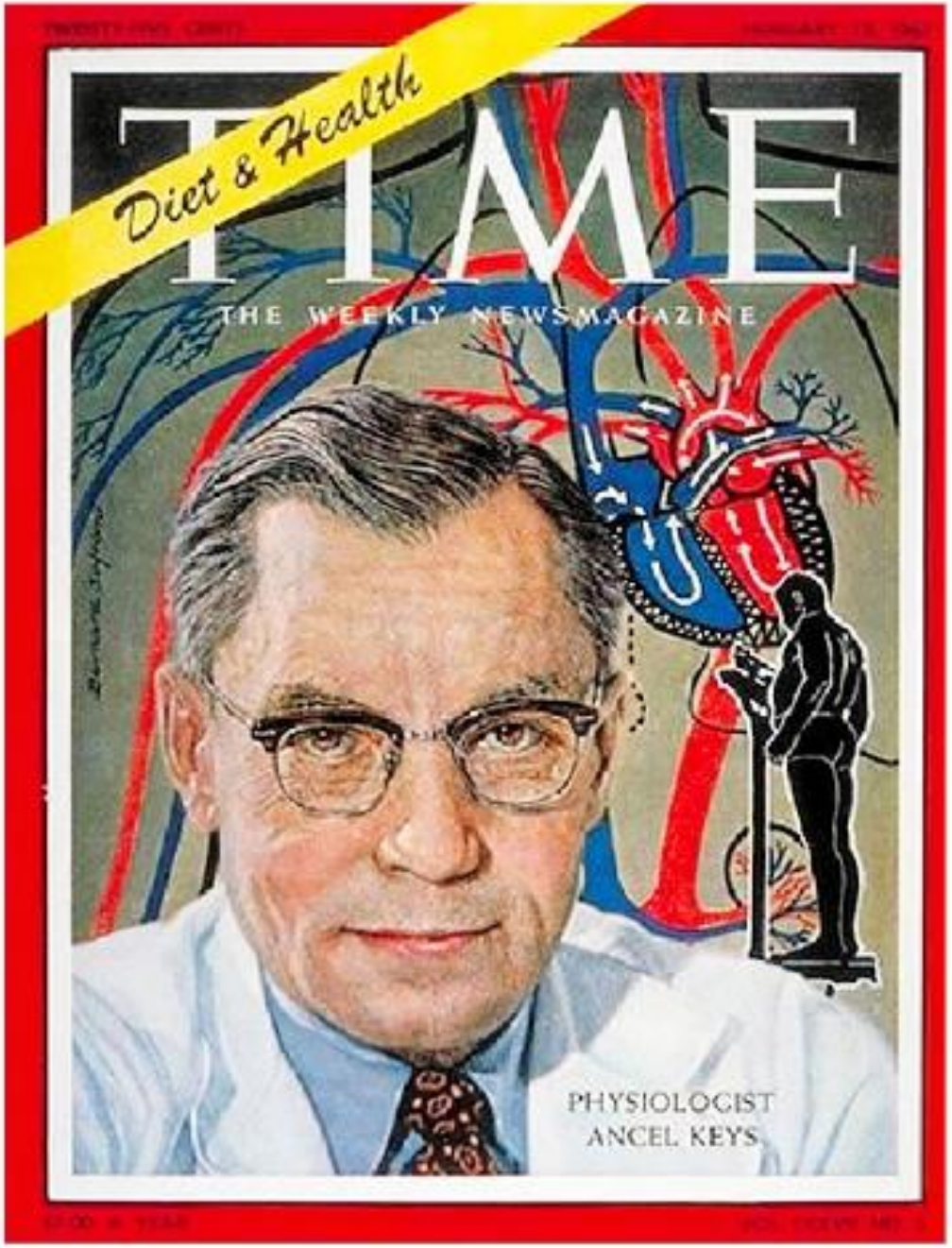
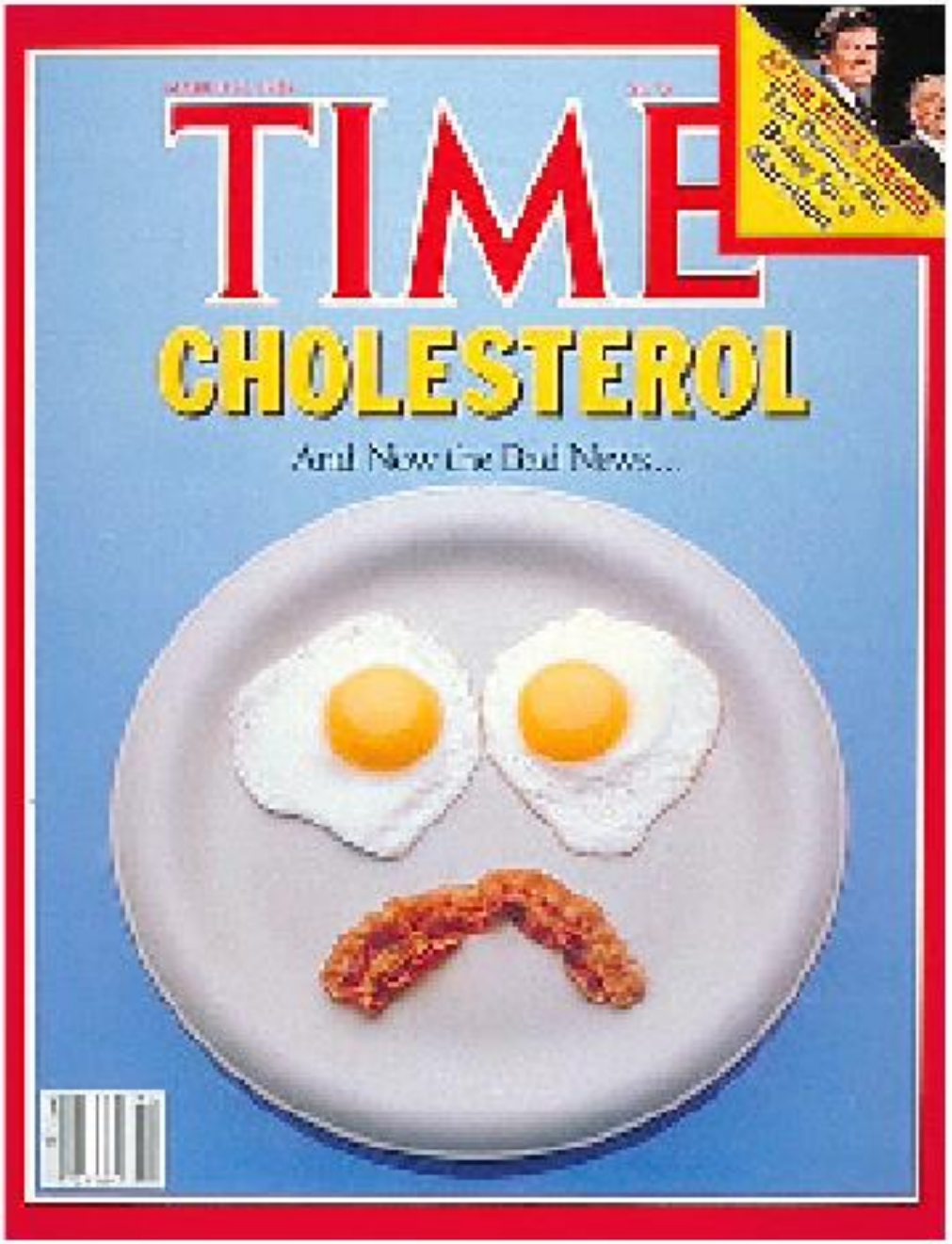
Clinical Chemist PhD

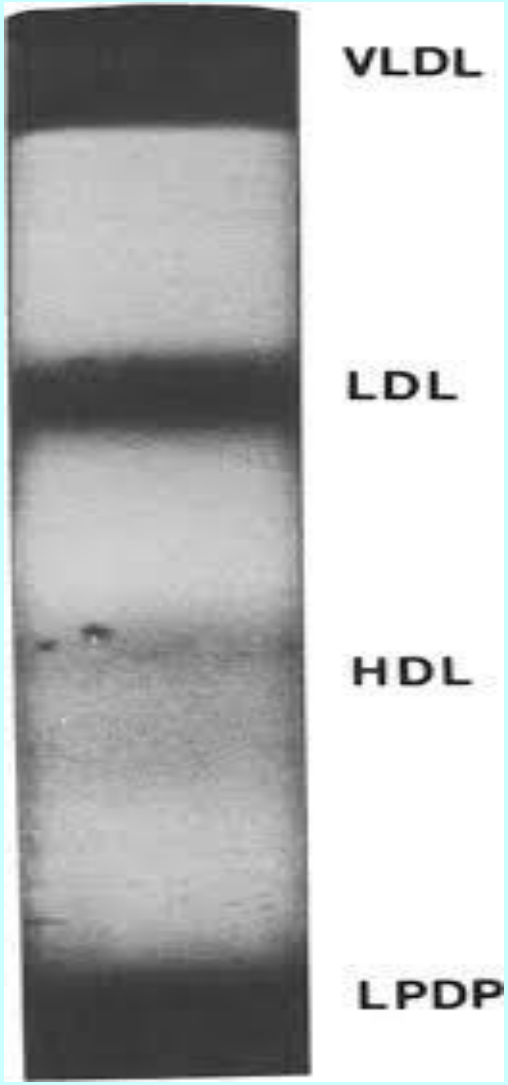
Economic Growth and Atherosclerosis

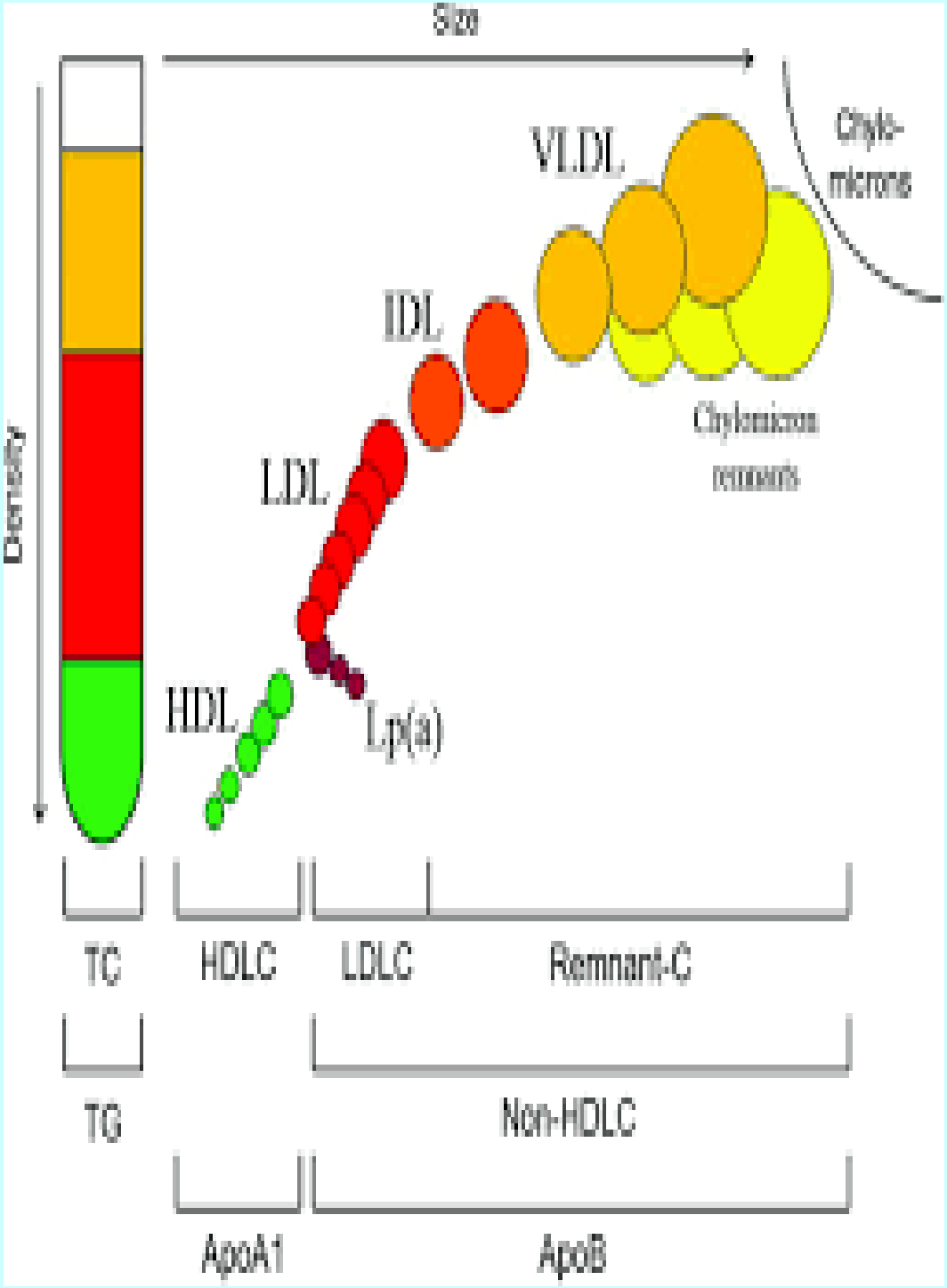




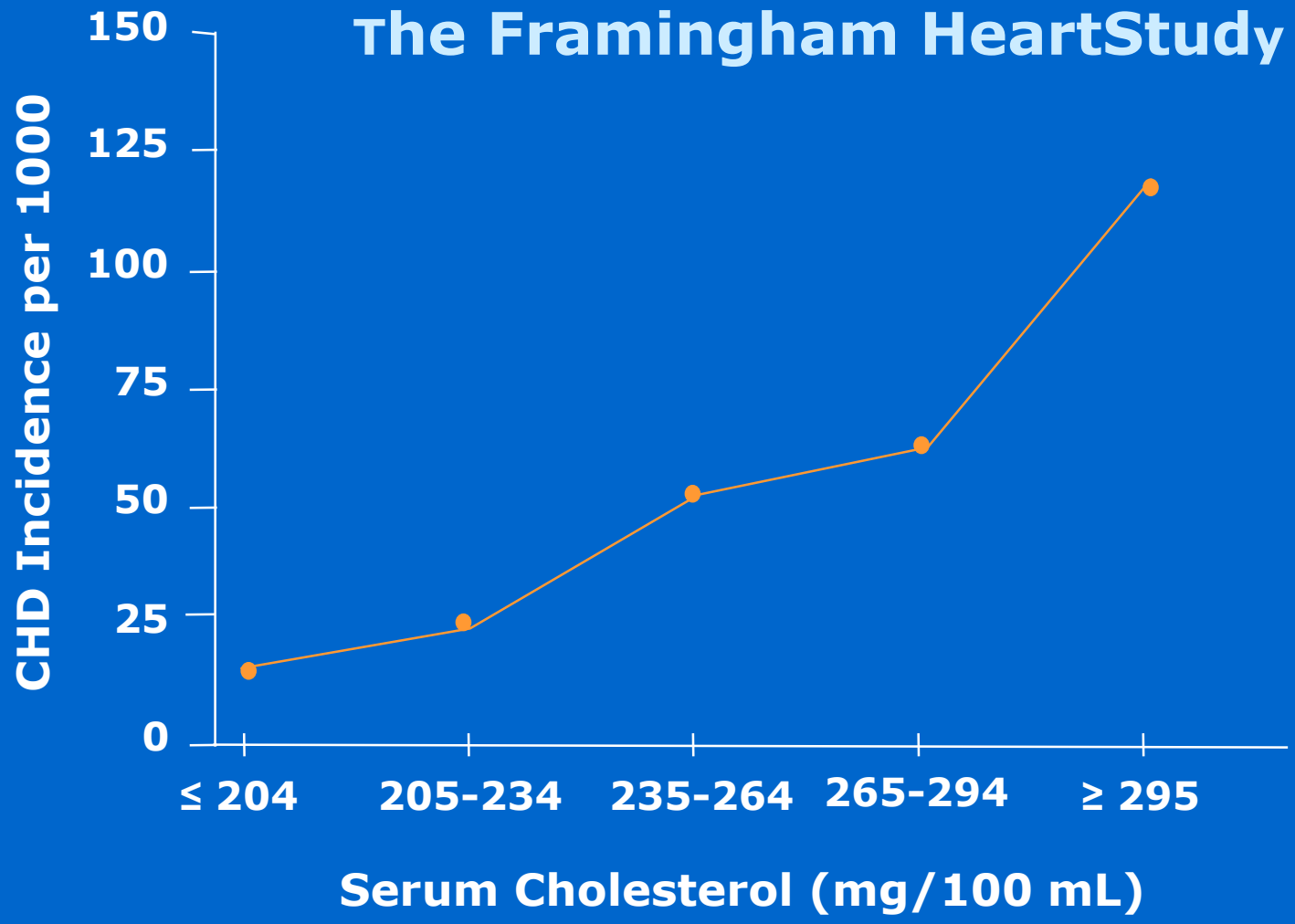


Two of many Time magazine covers since the 1950s that promoted physiologist Ancel Keys's alleged link between fat, cholesterol and heart disease.


VLDL
LDL
HDL
LPDP


Size
Density
VLDL
Chylo-microns
IDL
Chylomicron remnants
LDL
HDL
Lp(a)
TC
HDLC
LDLC
Remnant-C
TG
Non-HDLC
ApoA1
ApoB

Lower Cholesterol Levels Associated with Lower CHD Risk

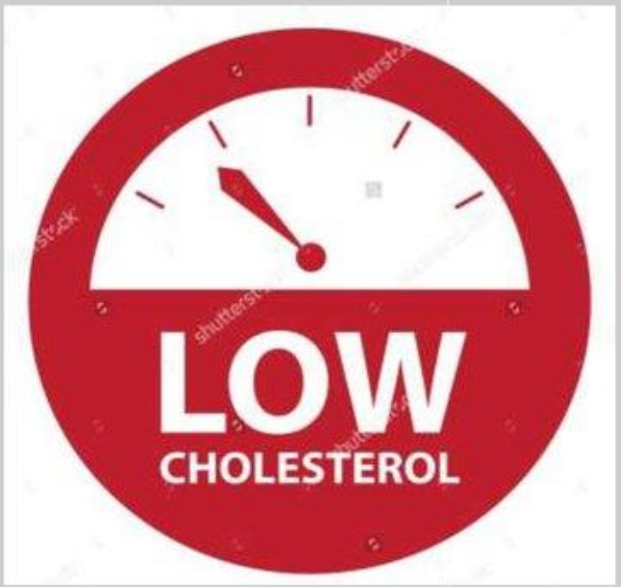


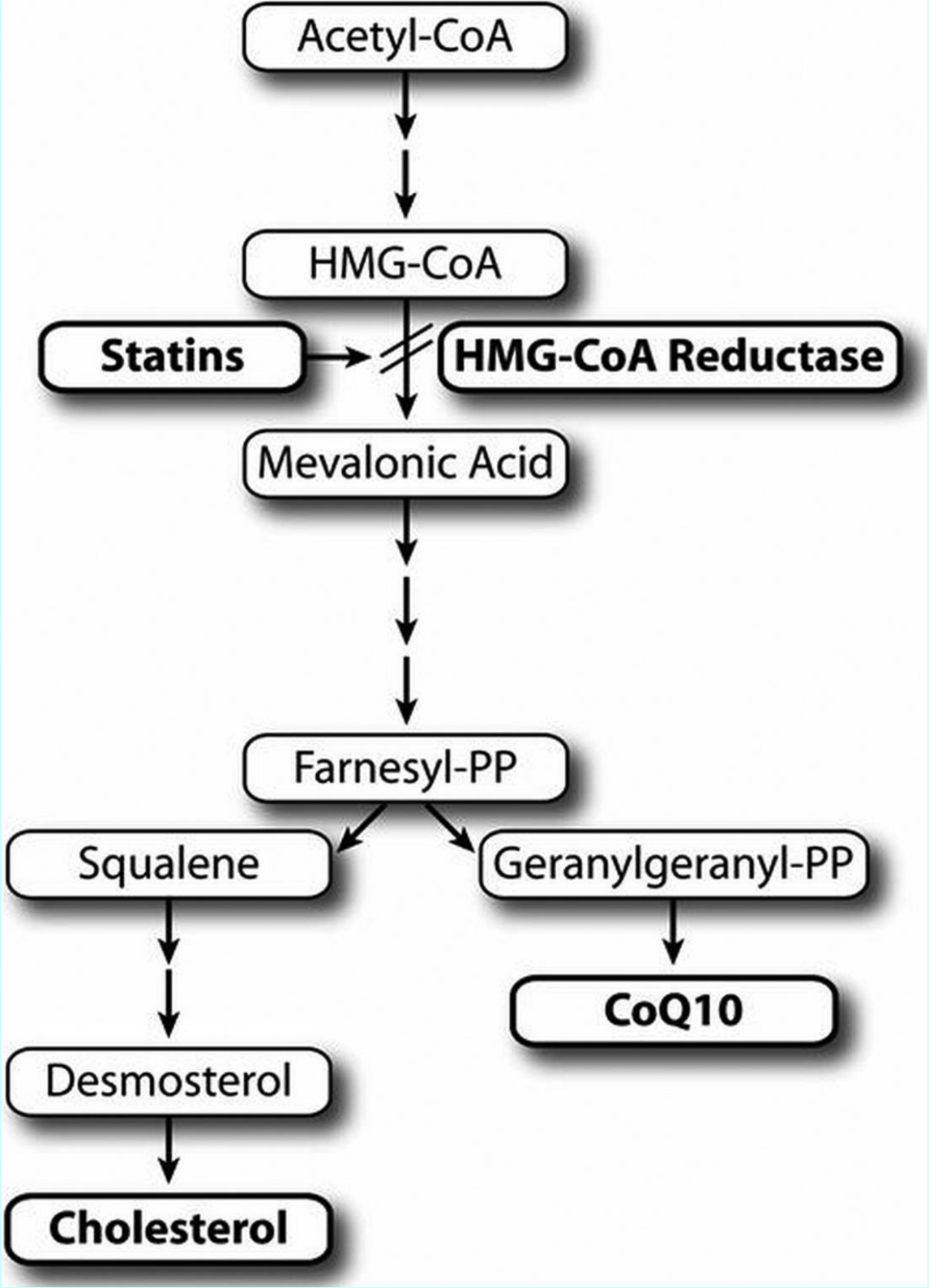
Castelli WP. *Am J Med*. 1984;76:4-12.

Controversy for Cholesterol

III. The Insanity of Lowering Cholesterol

- Conventional medicine misses the boat entirely when they dangerously recommend that lowering cholesterol with drugs is the way to reduce your risk of heart attacks, because what is actually needed is to address whatever is causing your body damage -- and leading to increased inflammation and then increased cholesterol.




Acetyl-CoA
HMG-CoA
Statins
HMG-CoA Reductase
Mevalonic Acid
Farnesyl-PP
Squalene
Geranylgeranyl-PP
CoQ10
Desmosterol
Cholesterol

3-hydroxy-3-methylglutaryl-CoA
(HMG-CoA)

HMG-CoA reductase ← STATINS

Mevalonate

ntyl-5-pyrophosphate

Geranyl PP

Farnesyl-PP → COENZYME Q10

HEME A

Squalene

Lanosterol

Lanosterol 14α-demethylase ← AZOLES

ERGOSTEROL

Endo's successful hypothesis

Fungi *defence from parasitic organisms, stopped ergosterol synthesis.*

(1971) 6192 compounds studied in 2 yrs

-Compactin inhibited the HMG-CoA reductase

Misfortunes in Compactin Project

- Compactin not effective in rats (1976)
- *“Toxic”* microcrystalline structures in rats hepatocytes
- Lymphoma noticed in dogs with 100x regular dose
- Sankyo Co. stopped Compactin's project

(Merck took over)

-**1978** an 18-yr old girl with FH first to be treated

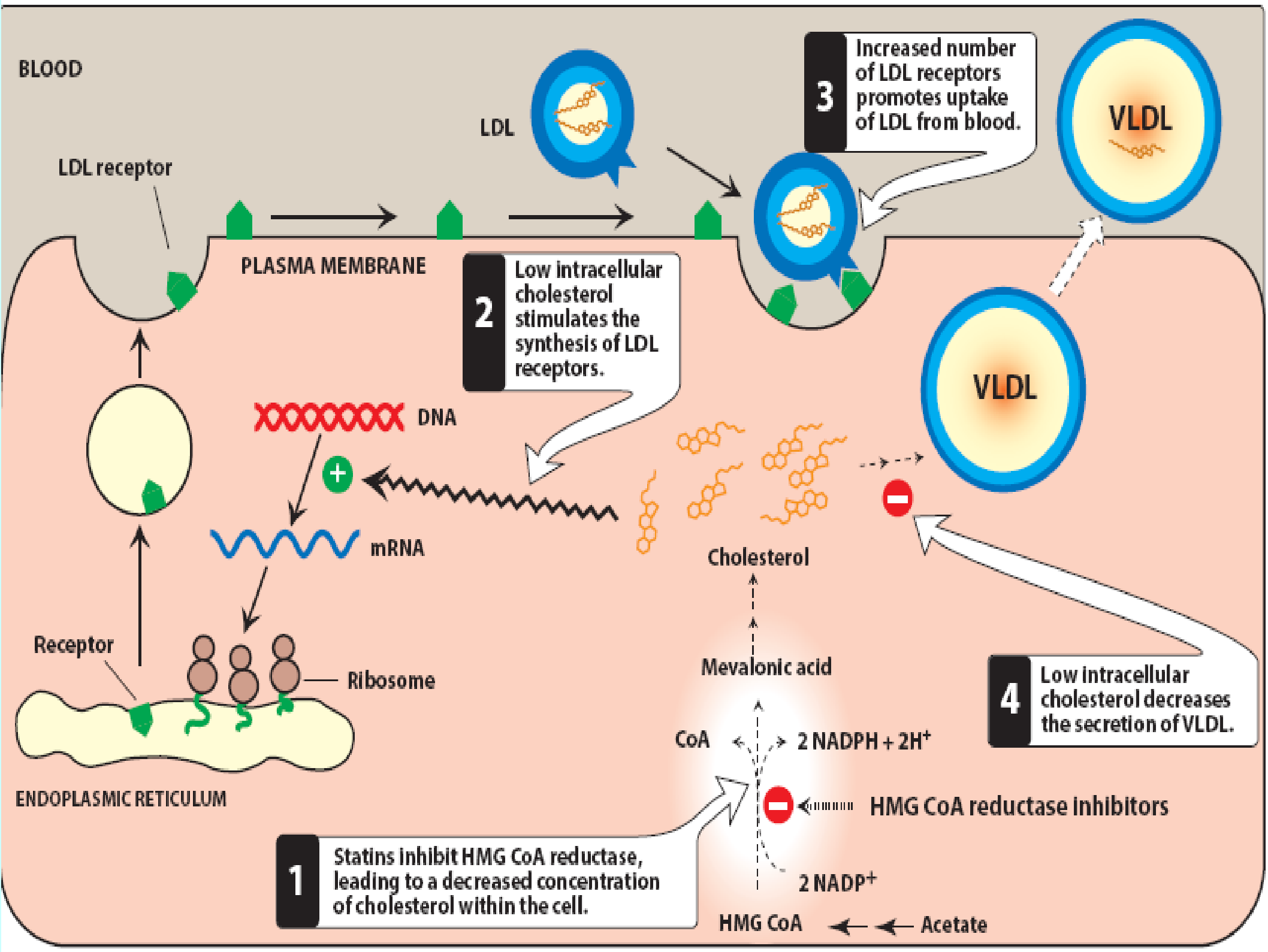
-**1979** Merck isolated lovastatin from Aspergillus terreus

-Sept **1980** Merck stopped (cancer in dogs)

-Impressive results, support from Clinicians

-Continuation

-**1987 FDA approval**


BLOOD
LDL
LDL receptor
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
PLASMA MEMBRANE
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Statins

- Atorvastatin
- Fluvastatin
- Lovastatin
- Pravastatin
- Rosuvastatin
- Simvastatin
- Pitavastatin

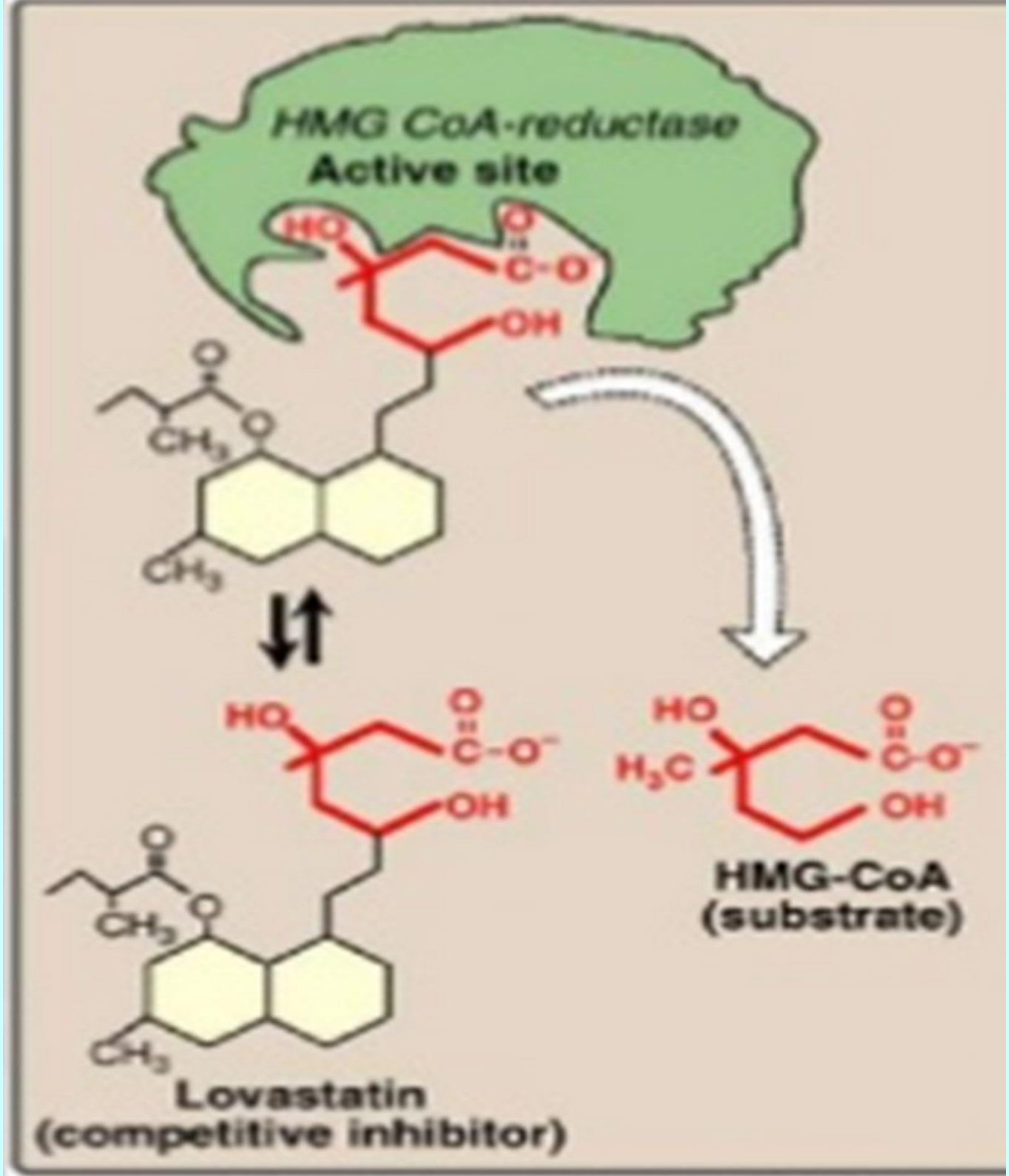
Statins tested in at least 27 major studies, with more than 170,000 adults followed for 5 years.

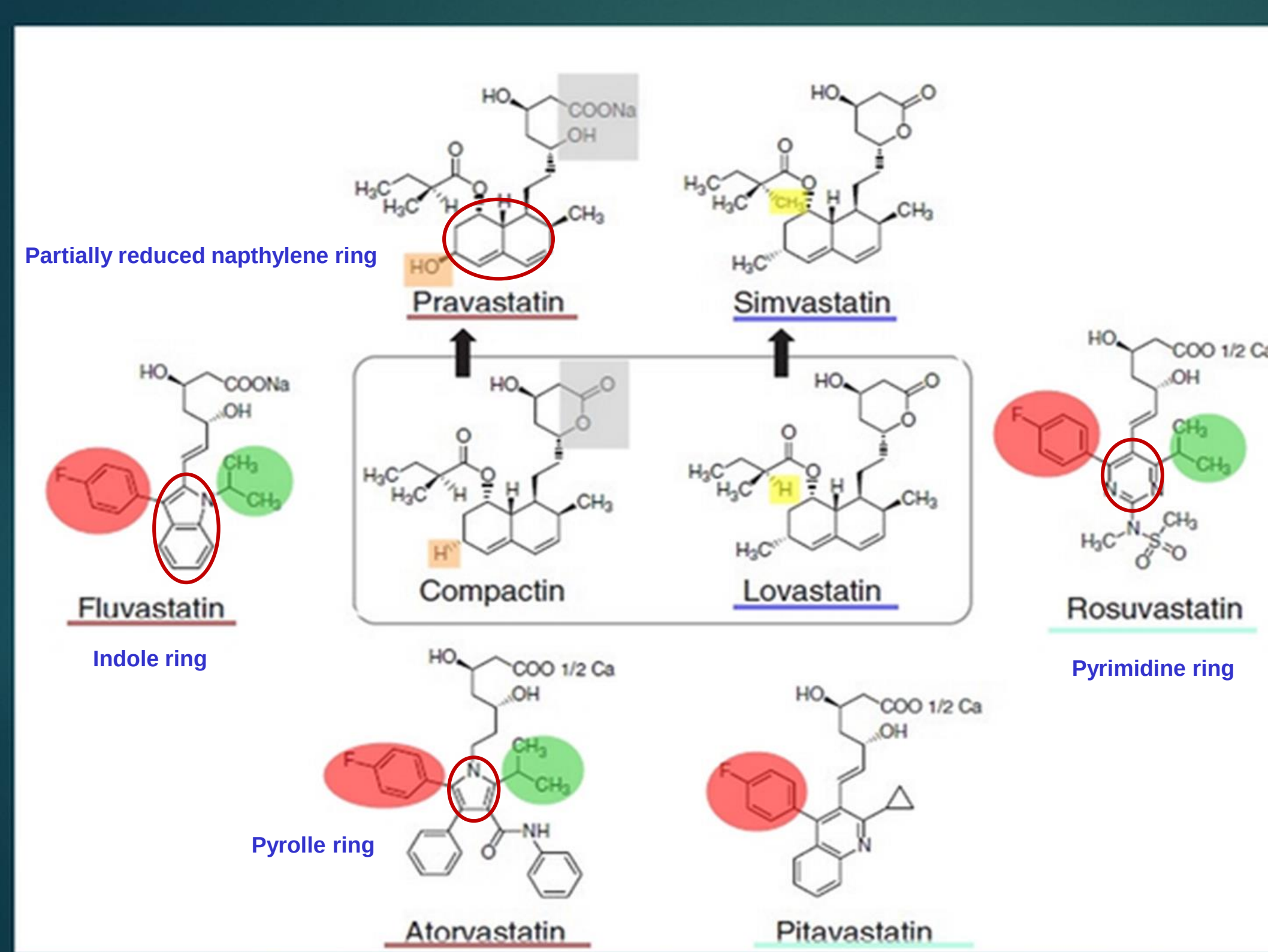
The results remarkably consistent:

-Statins lower LDL 30%.

-Reduce heart attacks by 30%, and extend life.

-30 million people worldwide take statins every day.


HMG CoA-reductase
Active site
HO
O
C-O
OH
CH3
CH3
HO
O
C-O⁻
OH
HO
H3C
O
C-O⁻
OH
HMG-CoA
(substrate)
Lovastatin
(competitive inhibitor)


Partially reduced napthylene ring
Pravastatin
Simvastatin
Fluvastatin
Compactin
Lovastatin
Rosuvastatin
Indole ring
Pyrimidine ring
Pyrolle ring
Atorvastatin
Pitavastatin

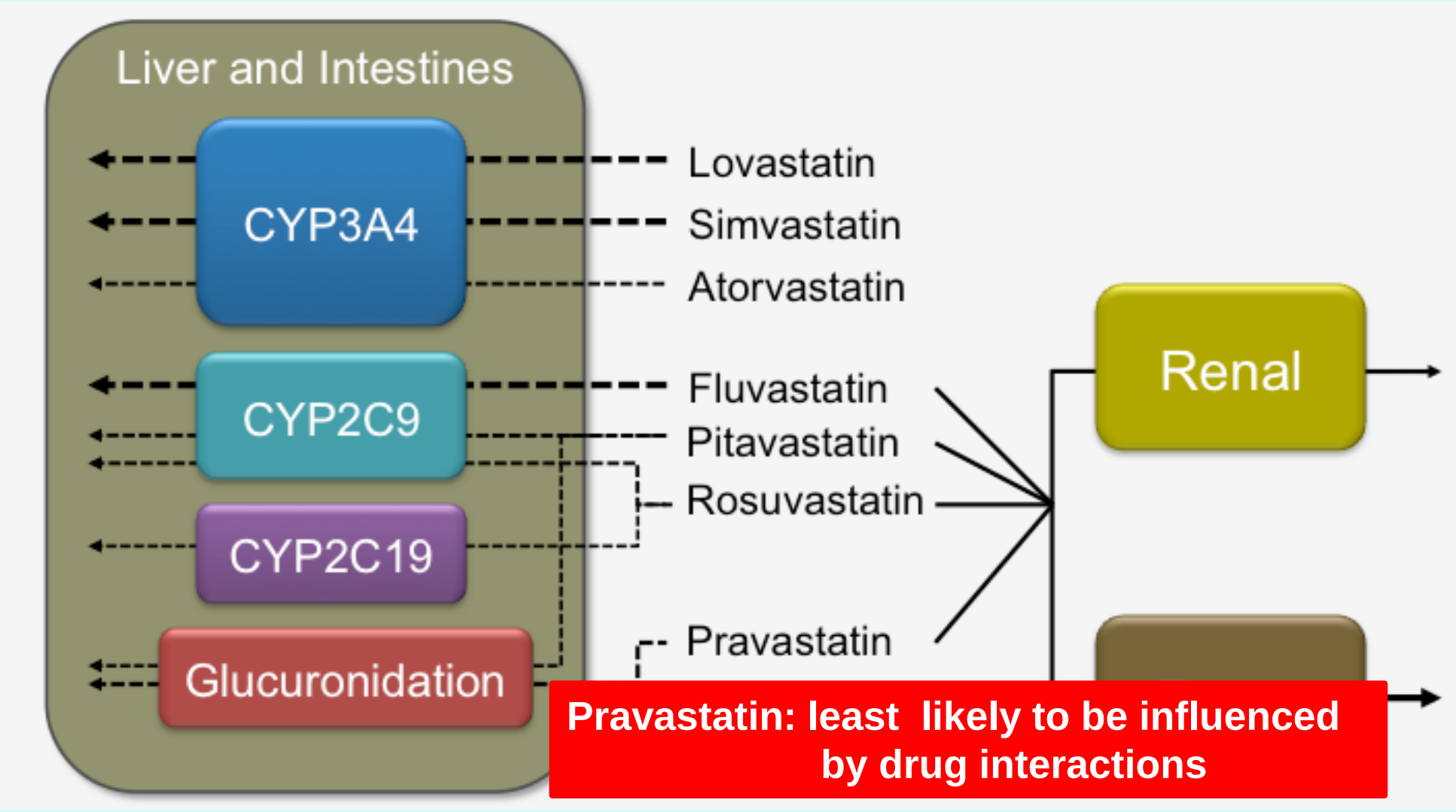
Classification of statins

1)How they are obtained

2) **Liver metabolism**

3) Physico-chemical properties

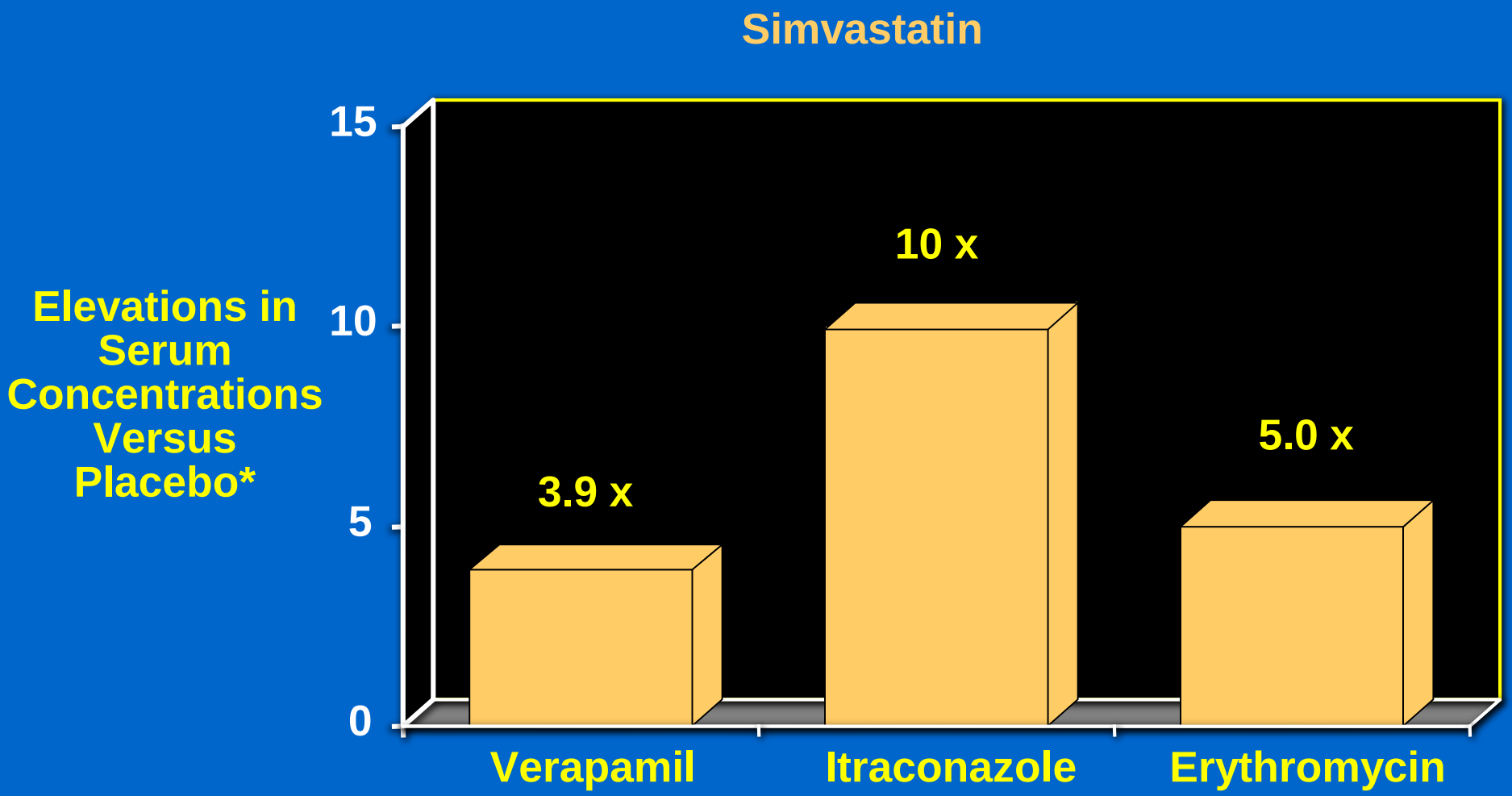
4) Specific activity


Liver and Intestines
CYP3A4
CYP2C9
CYP2C19
Glucuronidation
Lovastatin
Simvastatin
Atorvastatin
Fluvastatin
Pitavastatin
Rosuvastatin
Pravastatin
Renal
Pravastatin: least likely to be influenced by drug interactions

Significant Inhibitors of CYP3A4: Potential for interaction with statins

Antibiotics	clarithromycin*	erythromycin*	metronidazole
Antifungals	ketoconazole*	itraconazole*	miconazole
Protease Inhibitors	indinivir	ritonavir	nelfinivir
CCB's	mibefradil**		
Immunosuppressant	cyclosporin A*		
H2 Blockers	cimetidine		
Antidepressants	fluoxetine	fluvoxamine	
Food	grapefruit	**grapefruit juice**	

Effects of CYP 3A4 Inhibitors on Statin Serum Concentrations



* Area under the concentration-time curve (AUC) of active simvastatin acid

Classification of statins

1) How they are obtained

2) Liver metabolism

3) Physico-chemical properties

Hydrophilic –*pravastatin, rosuvastatin,*

Lipophilic- *Atorvastatin, lovastatin, pitavastatin, fluvastatin and simvastatin*

4) Specific activity

- **OATP1 (organic anion-transporting polypeptide) transports the statin from the plasma into the hepatocyte (Hydrophilic statins)**

- **Lipophilic statins diffuse passively and non-selectively into both hepatocytes and non-hepatocytes**

- **Hepatoselectivity is related with reduced risk of adverse effects**

- **Several drugs inhibit OATP1 (eg, clarithromycin, cyclosporine, erythromycin, several protease inhibitors, rifampin)**

Statin Effects

- **STATINS – Lipid-mediated effects**
- **STATINS -- Pleiotropic effects**

Pleiotropic effects of statins
(Cholesterol-indepedent effects)

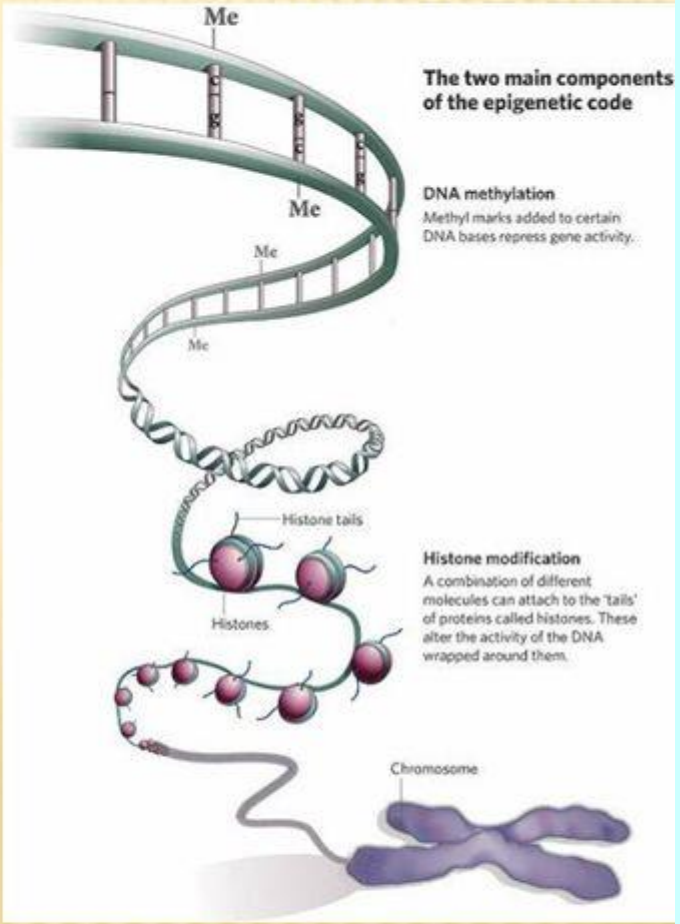
- Improve endothelial function ↑ **NO**
- Modulate inflammatory response ↓ **protein prenylation**
- *Anti-oxidant function* **-lipid peroxidation ↓**
- *Antithrombotic effects* **PAI-1 ↑**
- Maintain plaque stability

Epigenetics

genes can be turned on (expressed) or turned off (silenced)

Drugs that are known to cause epigenetic changes include :

- **statin cholesterol-lowering drugs,**
- **antidepressants,**
- **beta blockers**
- **Diuretics**
- **tamoxifen**
- **methotrexate,**
- **anti-inflammatories**
- **even anesthetics,**
- **oral contraceptives**
- **antibiotics.**



Permanent changes in the epigenome

Researchers are most concerned that drugs may produce defects in subsequent generations. They speculate that the current diabesity epidemic may be hastened by drugs.

[*Metabolism Clinical and Experimental* 57: (2008) S16–S23]

Statins and Epigenetic Modifications

Pleiotropic and adverse effects

-In vitro and animal studies statins can increase histone acetylation and demethylate histone residues and DNA.

-Changes alter expression of various genes including tumor suppressor genes and genes with anti-atherosclerotic actions.

-Statins influence the expression of numerous microRNAs that suppress the translation of proteins involved in tumorigenesis and vascular function.

Meta-analyses of controlled clinical trials have failed to find any effect on cancer rates


STATINS KEY TO A LONGER LIFE
HOW STATINS BEAT CANCER
STATINS CAN BE RISK TO HEALTH
But drug is still a life saver
Statins 'have no side effects'
STATINS IN NEW HEALTH ALERT
DOCTORS BAN ON STATINS
Medics at war over drug advice
STATIN IS NEW WONDER DRUG

BEWARE OF THE WONDER DRUG!

Statin Pharmacogenetics

❖ Variants of *HMGCR, CETP, ApoE* studied for their role in statin res

Polymorphisms in *HMGCR* can result in significantly diminished response to statin pharmacotherapy

❖ Genomic markers, *KIF6* and *SLCO1B1* affect statin the

- **Carriers of the *KIF6 2155T>C* allele display reduced response to simv, ator, rosu ⟹ increase dose**
- **Altered transport of statins - *SLCO1B1* 521C homozygous carriers were approximately three times more likely to be statin intolerant**

❖ C

atc 60% of those required by wild type

❖ Statin-associated muscle symptoms occur in ~10% of patients (clinical trials↓)

<u>Genetic association studies with statins are difficult</u>

Pharmacokinetic properties of Statins

Parameter	Rosuva	Atorva	Fluva	Lova	Prava	Simva
Absolute bioavailability, %	20	12	10-35	<5	18	>5
Food effect on bioavailability	None	↓13%	↓15-25%	↑50%	↓ 30%	None
Protein binding, %	90	>98	>99	95	48	95
Hepatic extraction, % dose	90	>70	68	>70	50	78-87
Metabolic enzyme (S, substrate; I, inhibitor)	(none) 2C9,2C19	3A4(S)	2C9(I)	3A4(S)	Sulfation (none)	3A4(S)
Half-life, h	20	14	<1	3-4	1.8	3
Elimination, % Urine Feces	 10 90	 2 96	 5 95	 10 70	 20 70	 13 80

Thomas N. Riley, PhD & Jack DeRuiter, PhD (2004)

Critical Issues

- Awareness of the possible interactions
- Underlying reasons for therapeutic failure
- Statin intolerance – side effects

(Co-medication, polymorphic expression of CYP450s, transporters, HMGCR, CETP)

Address to a TDM-Pharmacogenomic Lab

Graditude for Akira Endo

Apart from the recognition, Endo never derived financial benefit from his discovery, despite the fact that statins are amongst the most widely prescribed medications.

"The millions of people whose lives will be extended through statin therapy owe it all to Akira Endo"

Michael Brown and Joseph Goldstein

Nobel Prize for LDL Receptors.

THANK YOU

Andros Island