

Progress in Molecular Cardiovascular Medicine: Lipidomics, Proteomics & MicroRNAs

Manuel MAYR, MD, PhD

BHF Professor of Cardiovascular Proteomics

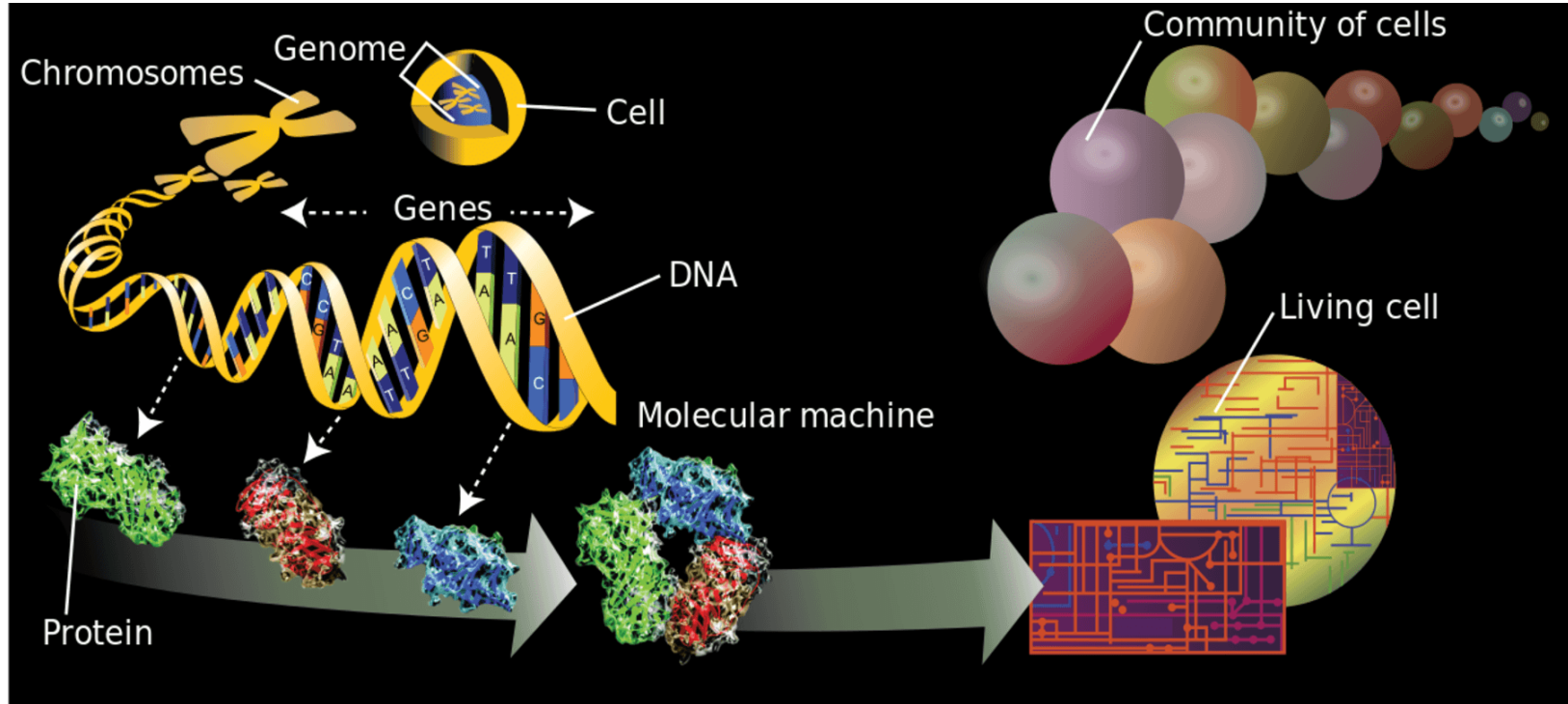
King's College London, UK

Icahn School of Medicine at Mount Sinai, NY

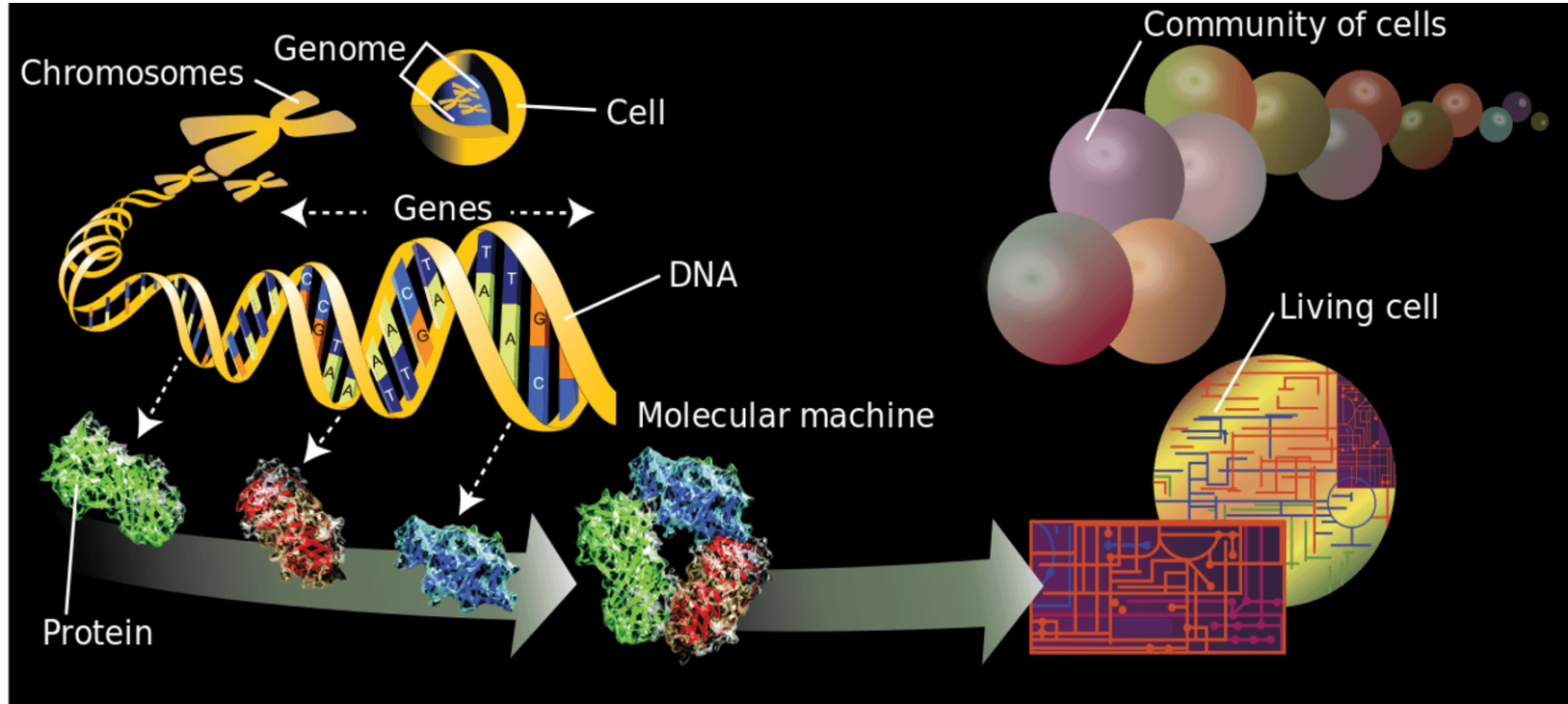


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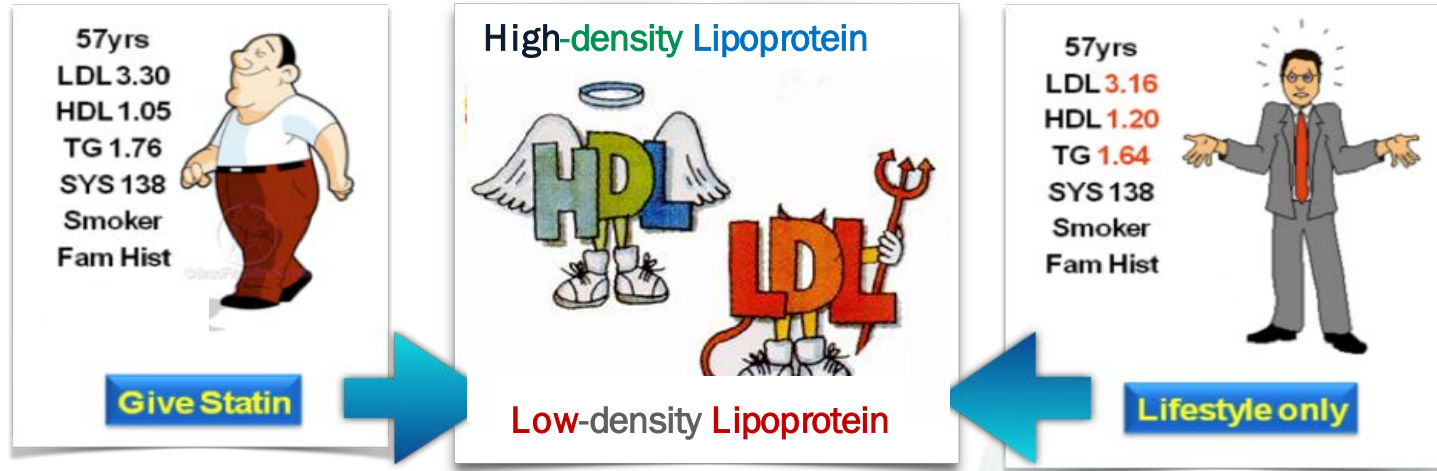
From Genes to Gene Products



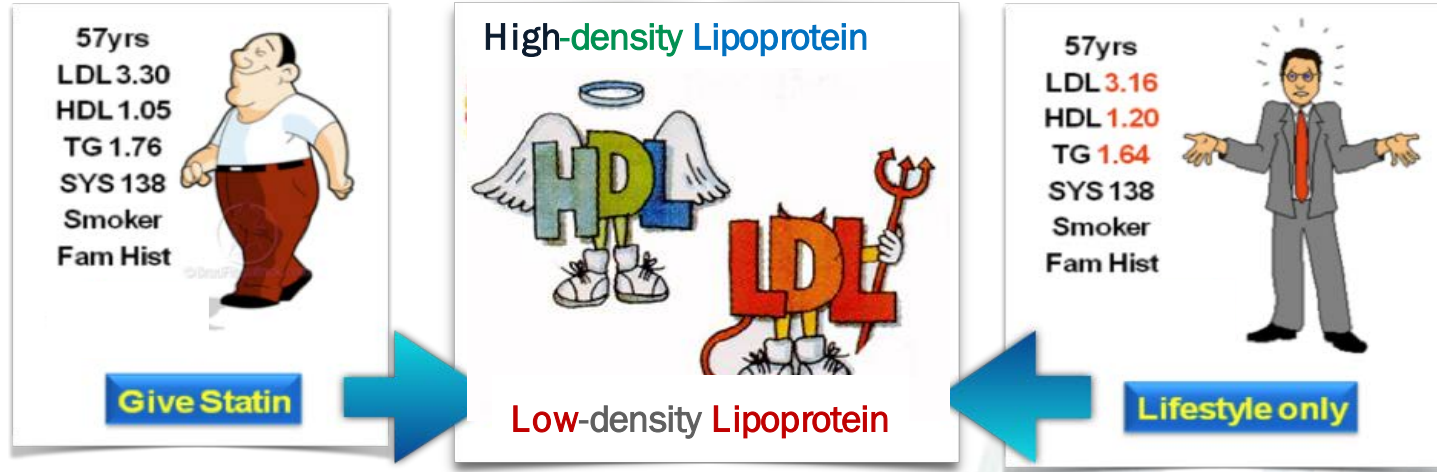
Lipidomics



Most Events in Patient at Intermediate Risk

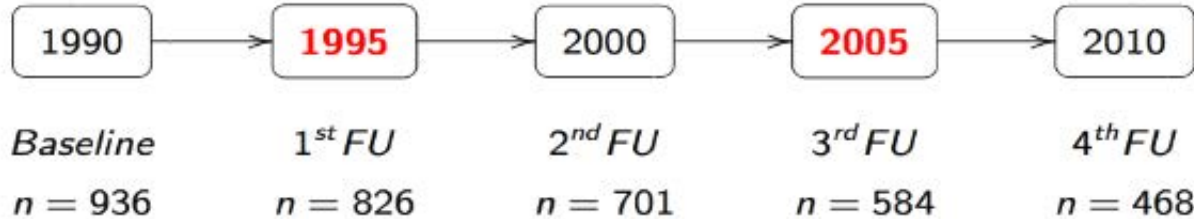


Most Events in Patient at Intermediate Risk

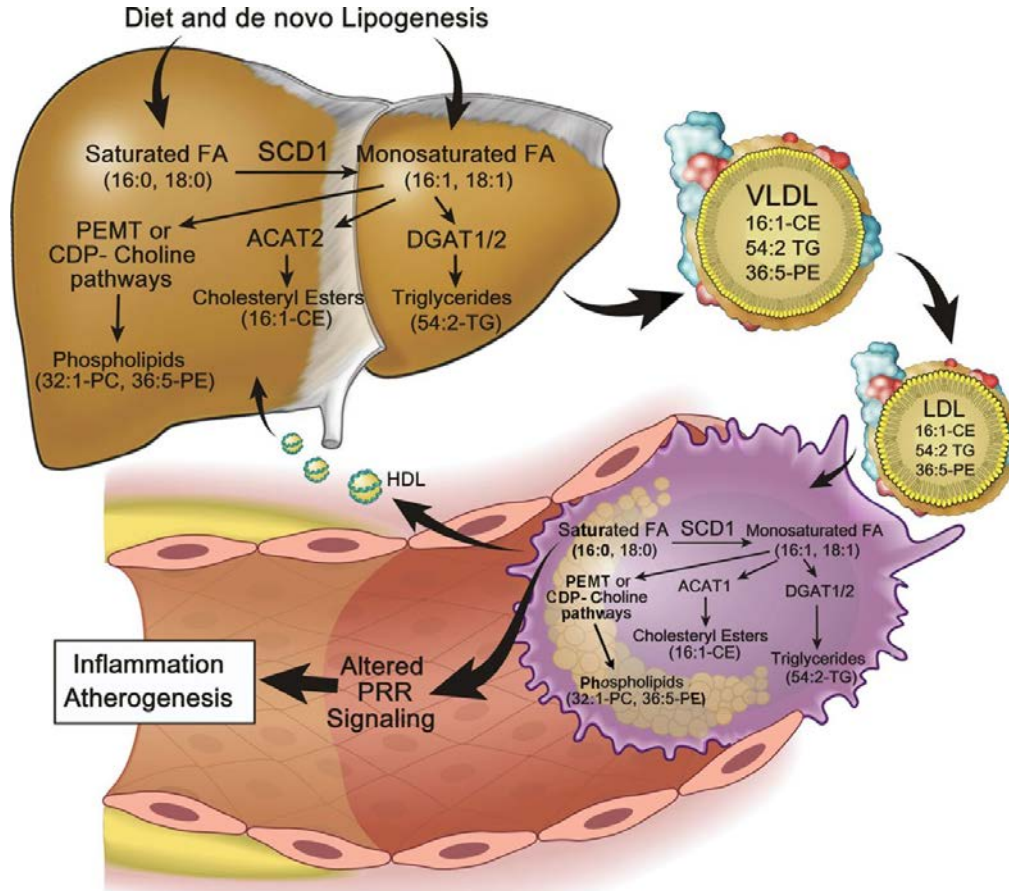


Routine lipid parameters have not changed over the last 50 years.

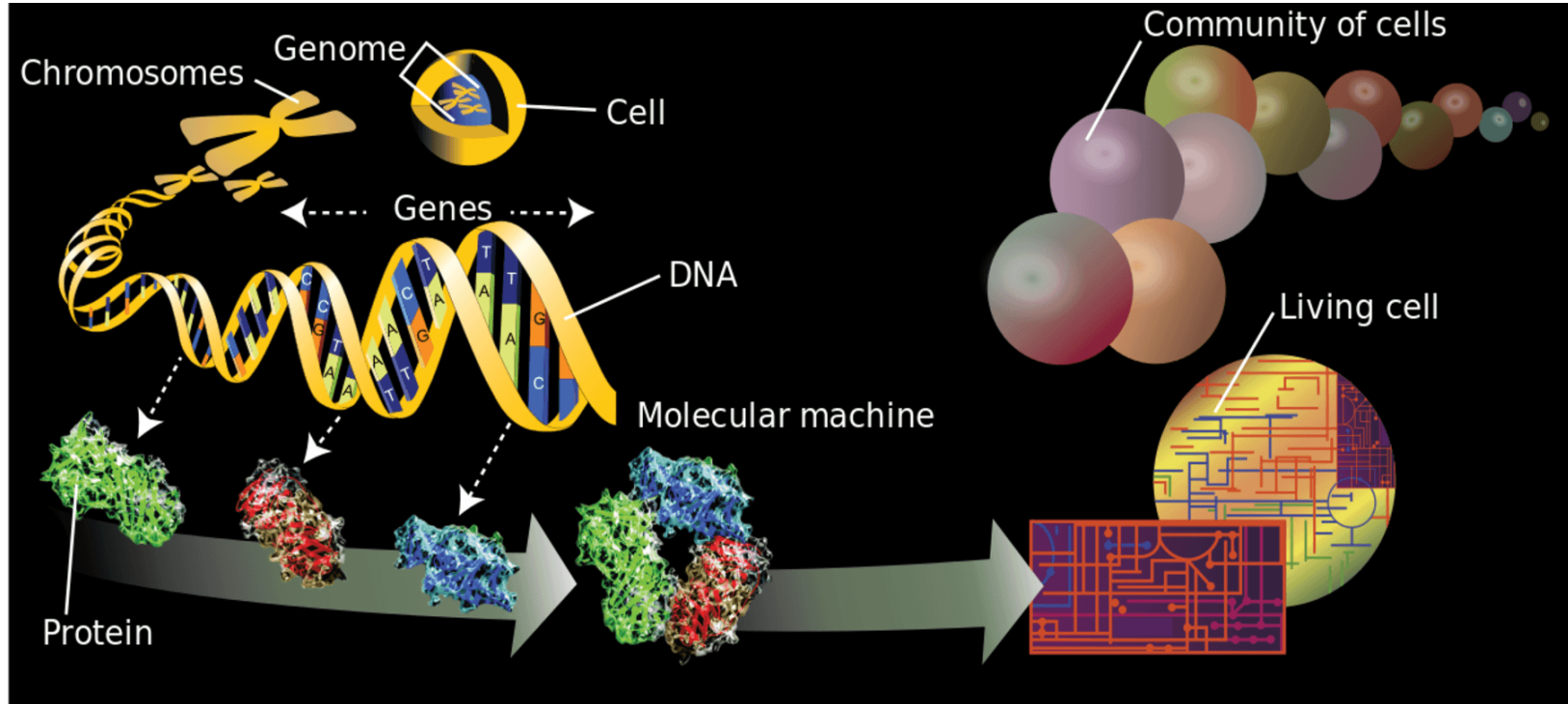
Bruneck Study on Cardiovascular Disease



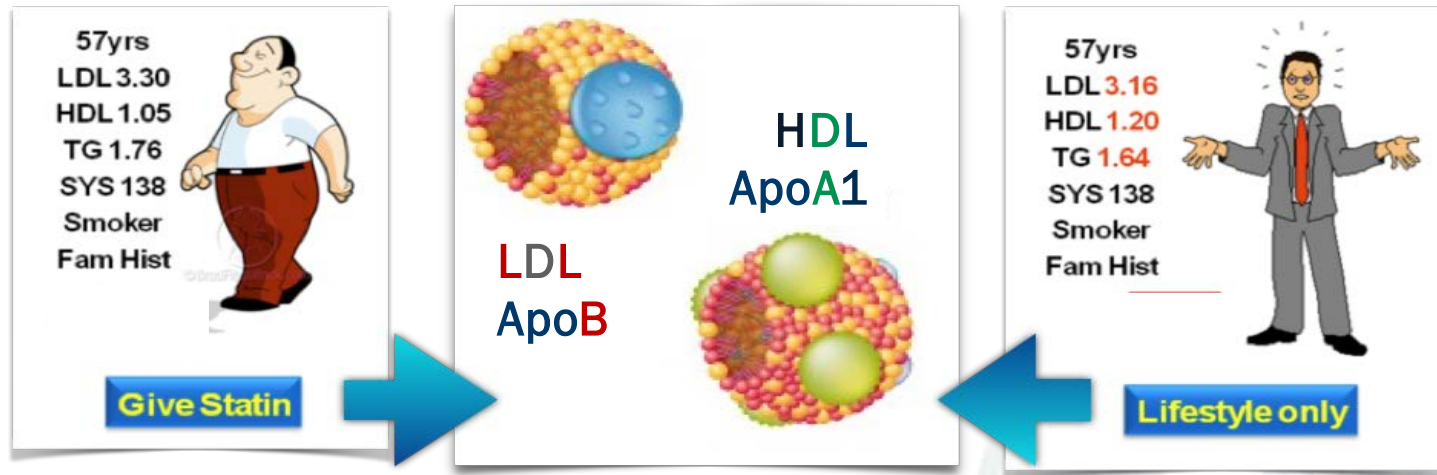
Lipidomics and Cardiovascular Risk



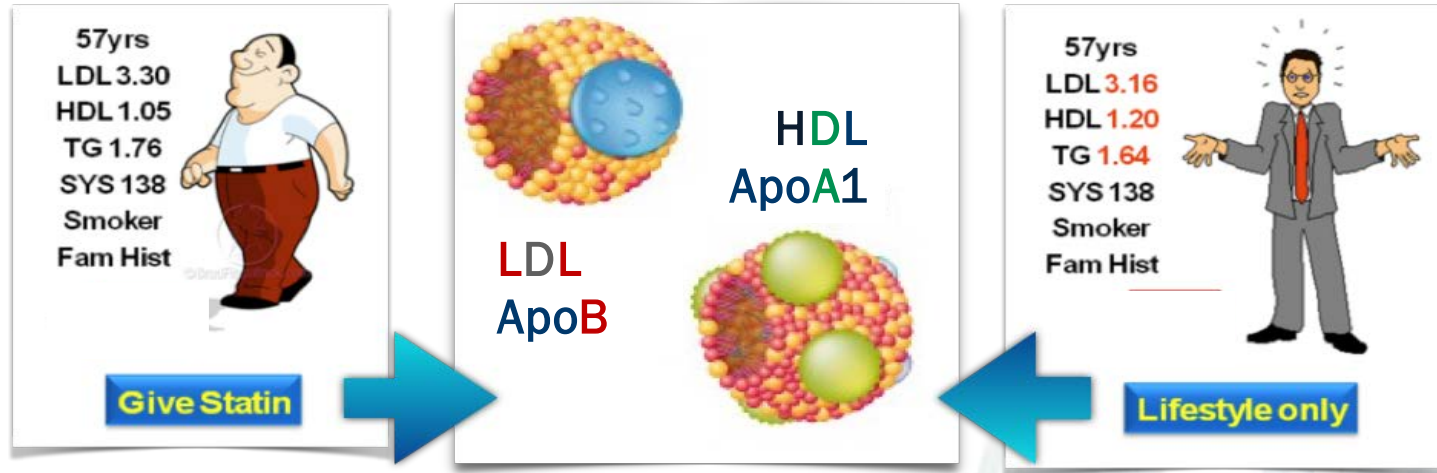
Proteomics



Most Events in Patient at Intermediate Risk

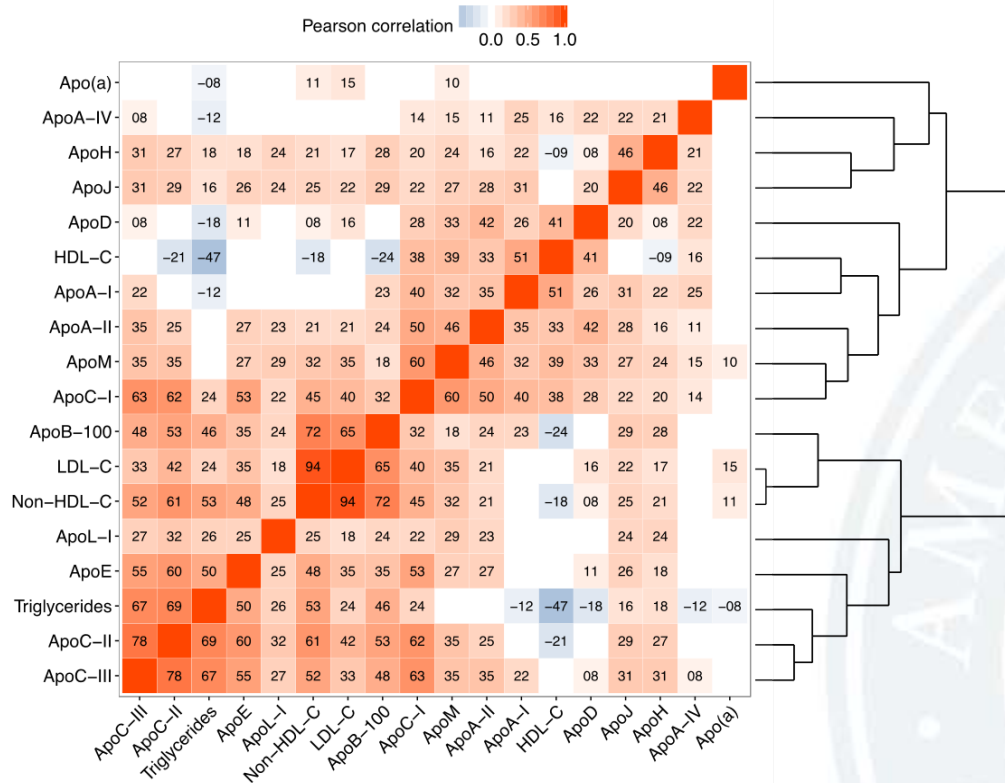


Most Events in Patient at Intermediate Risk



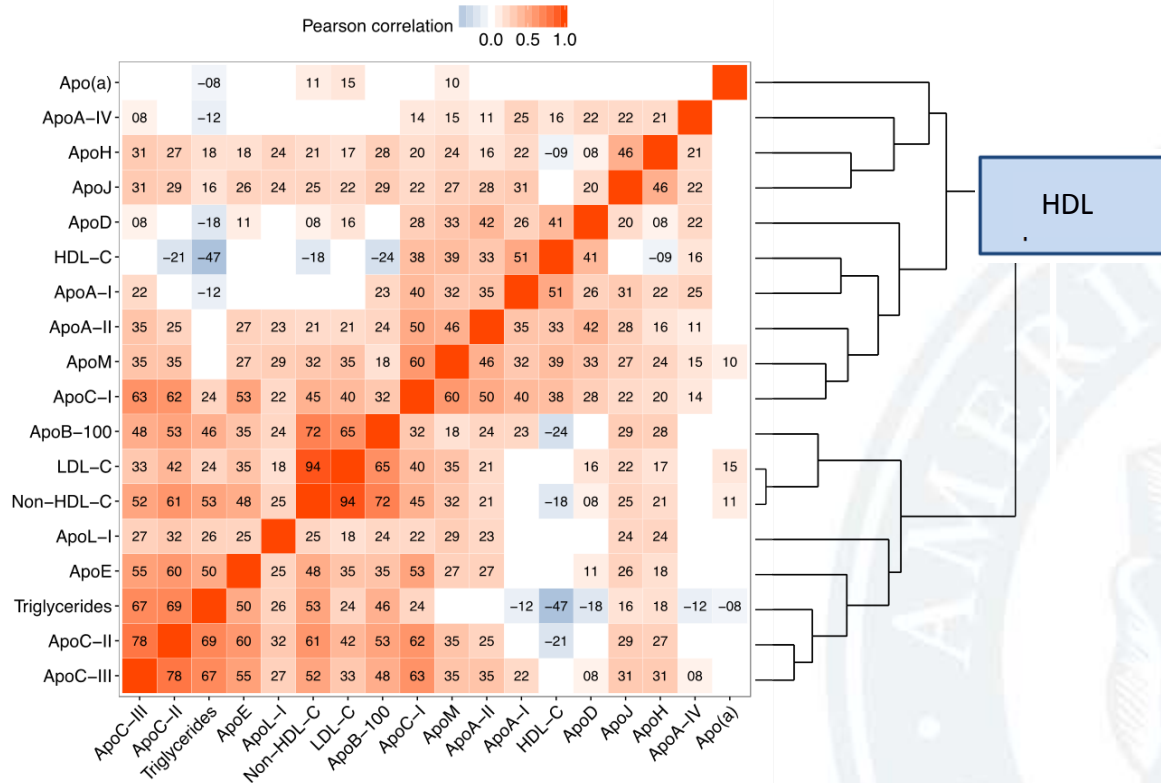
No direct comparison of the different apolipoproteins thus far.

Towards a Less Imprecise Medicine

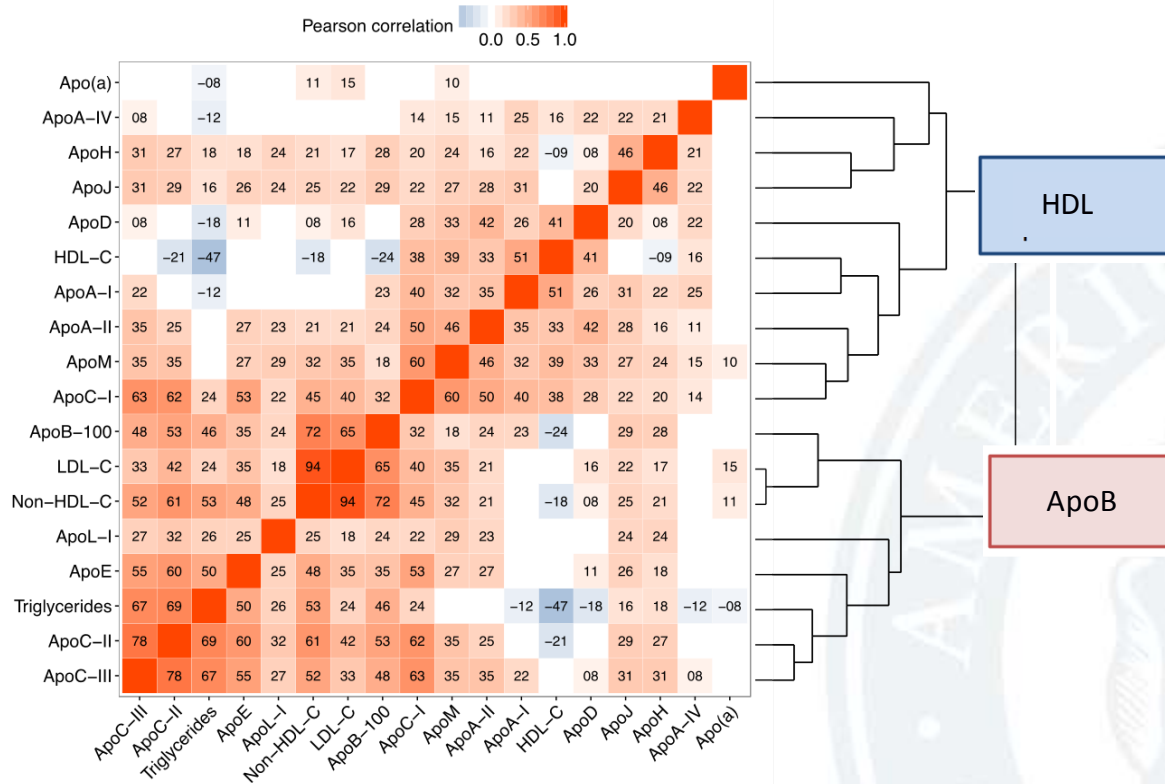


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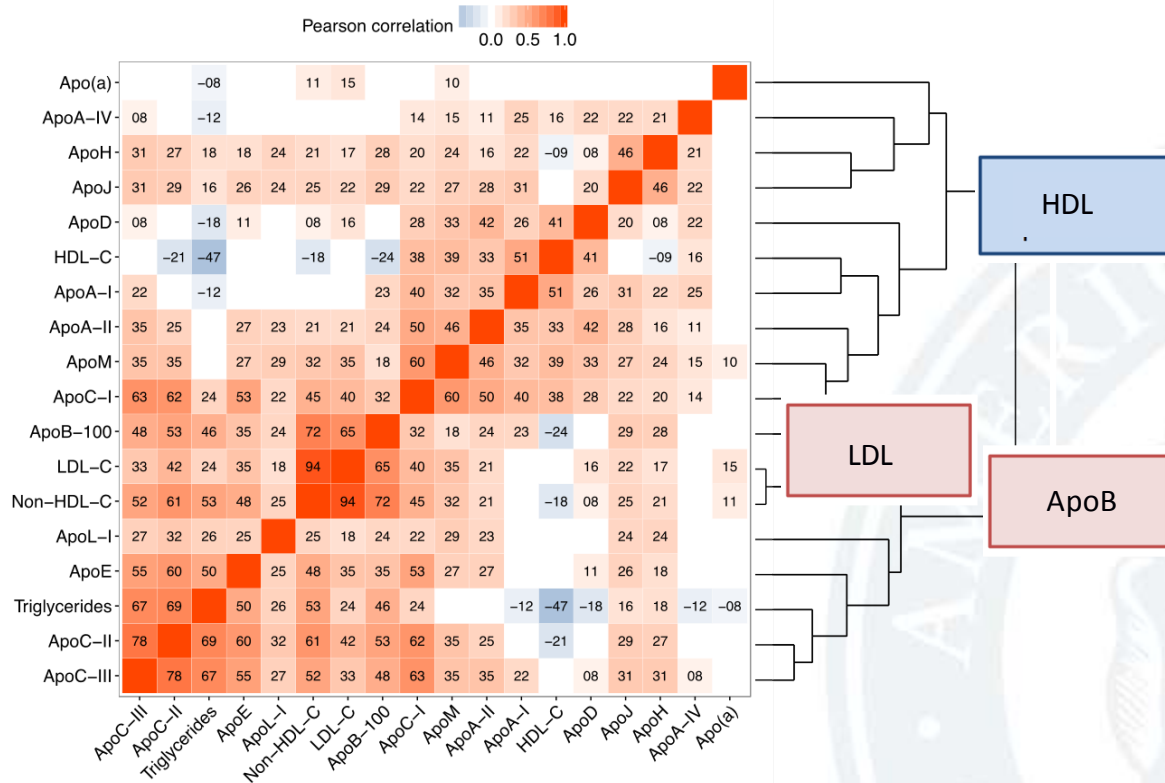
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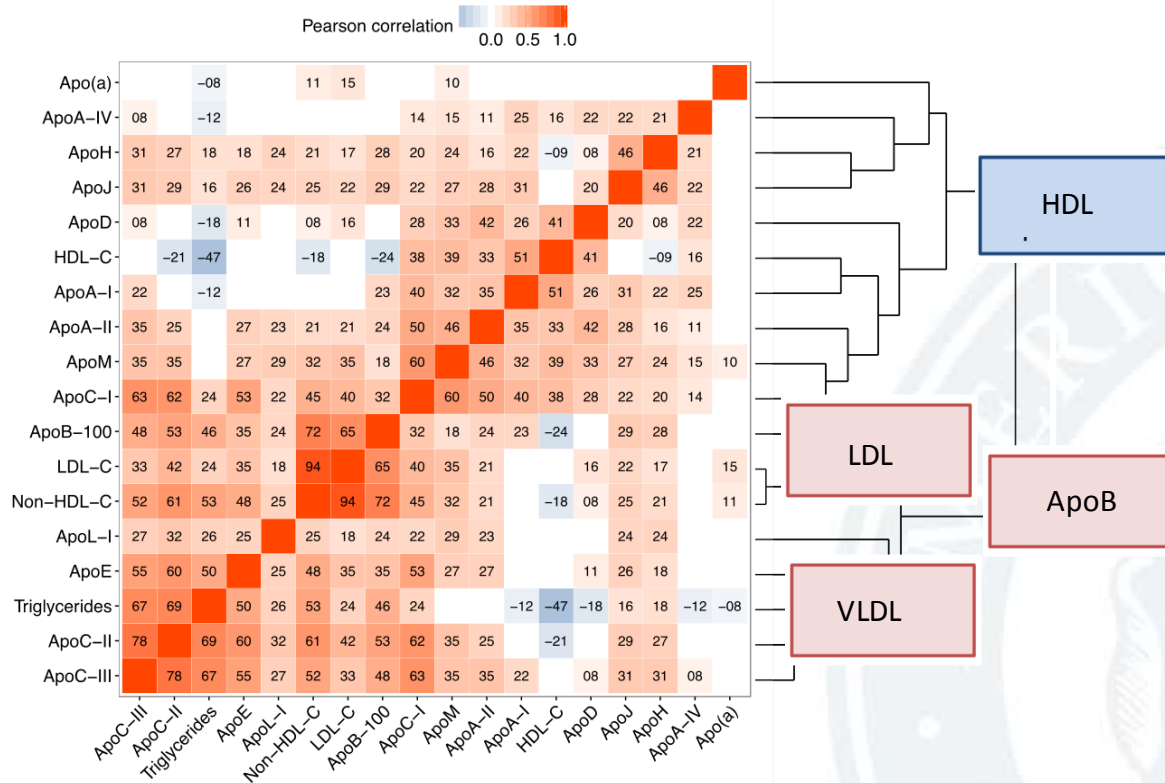
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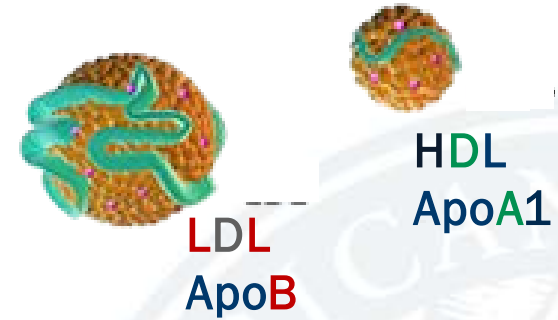
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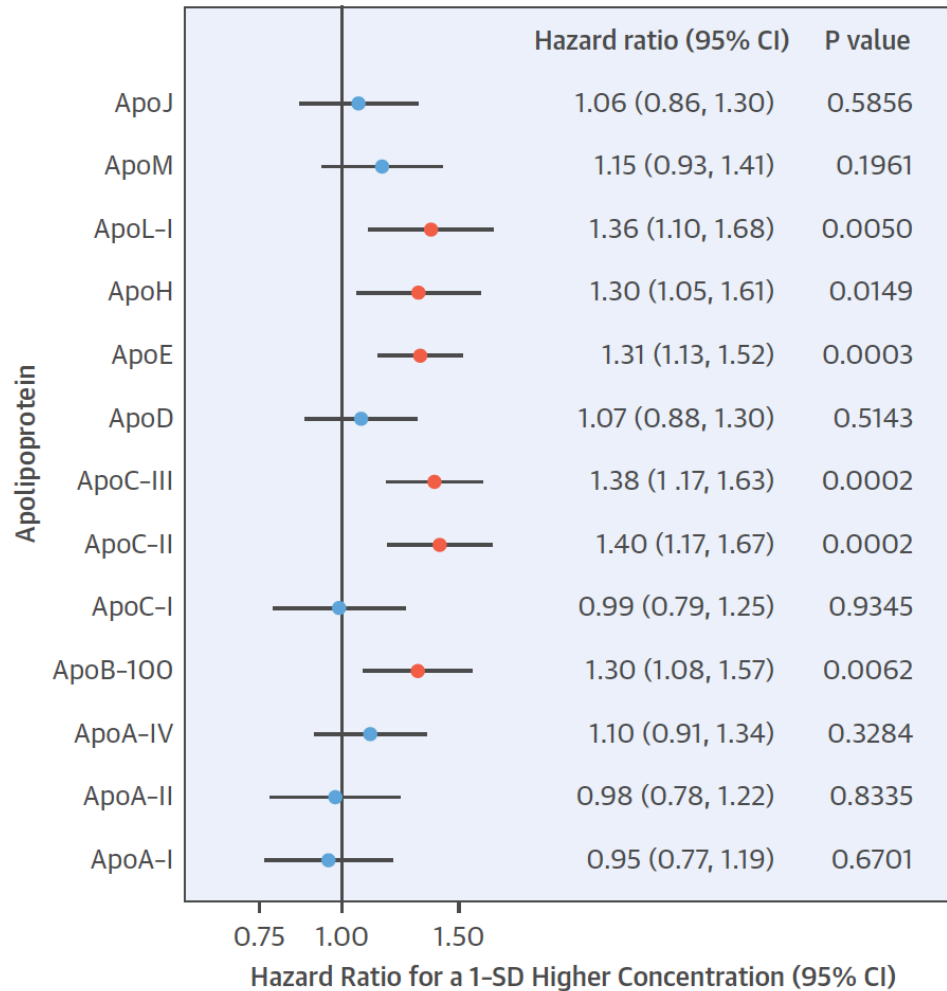
Towards a Less Imprecise Medicine



Cardiovascular Risk Beyond LDL Cholesterol?

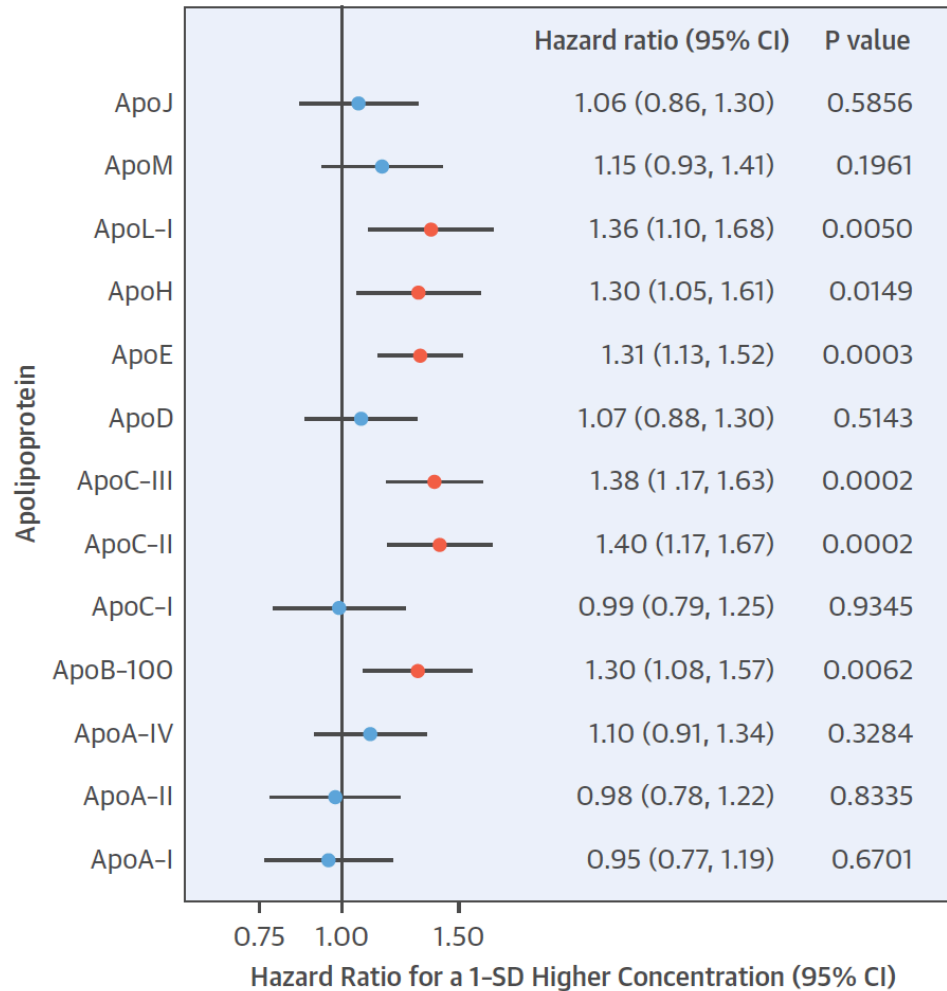


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+30%



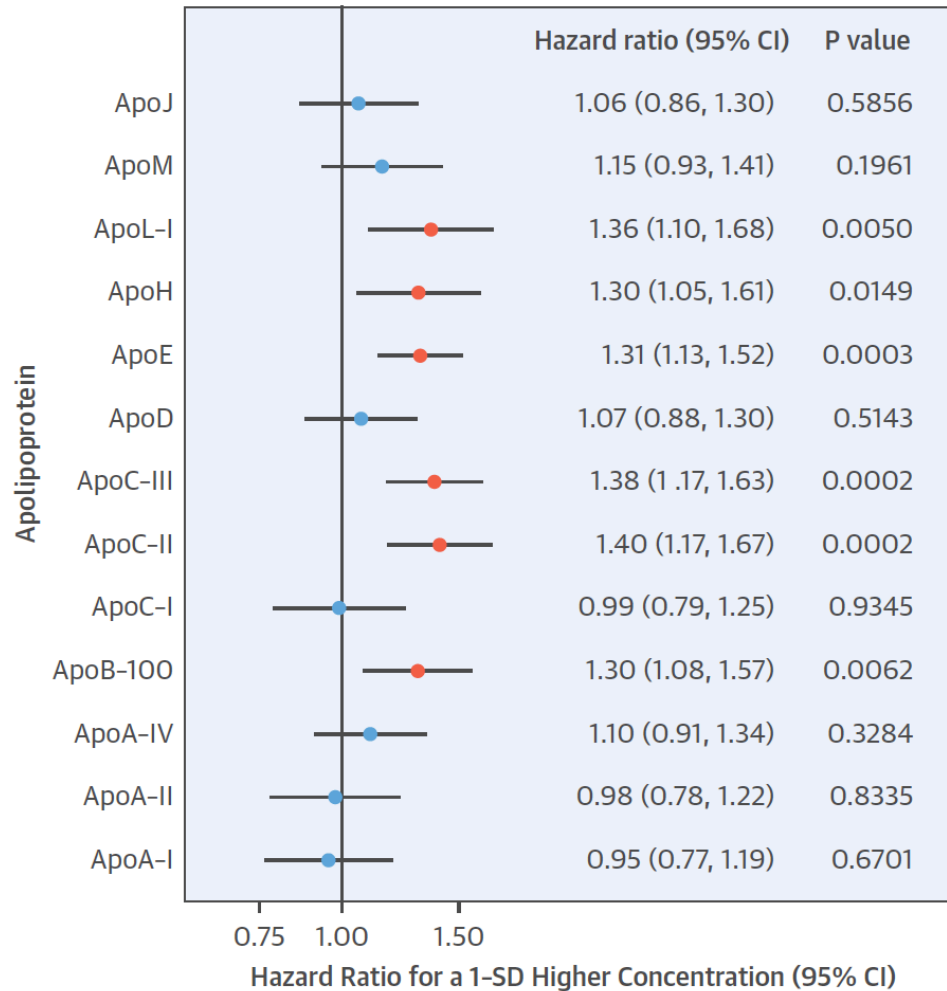
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+31%

+38%

+40%

+30%

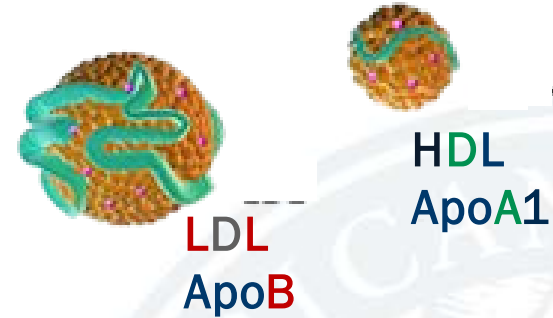


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Cardiovascular Risk Beyond LDL Cholesterol?

Very **Low**-Density
Lipoprotein

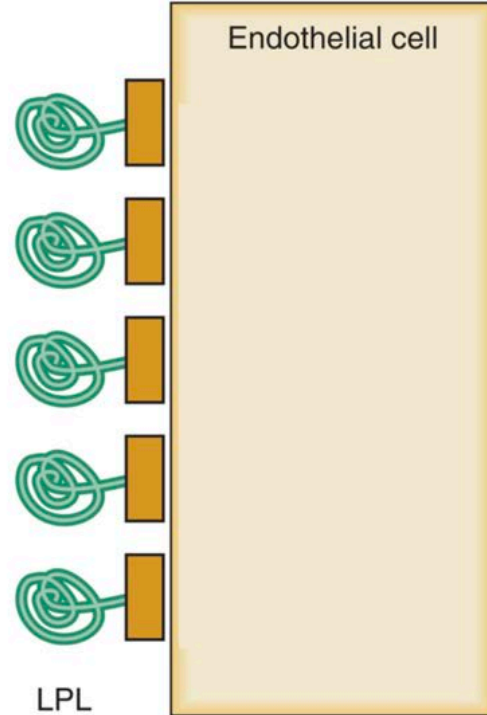
VLDL
Apo**B**
ApoC2
Apo**C3**
Apo**E**



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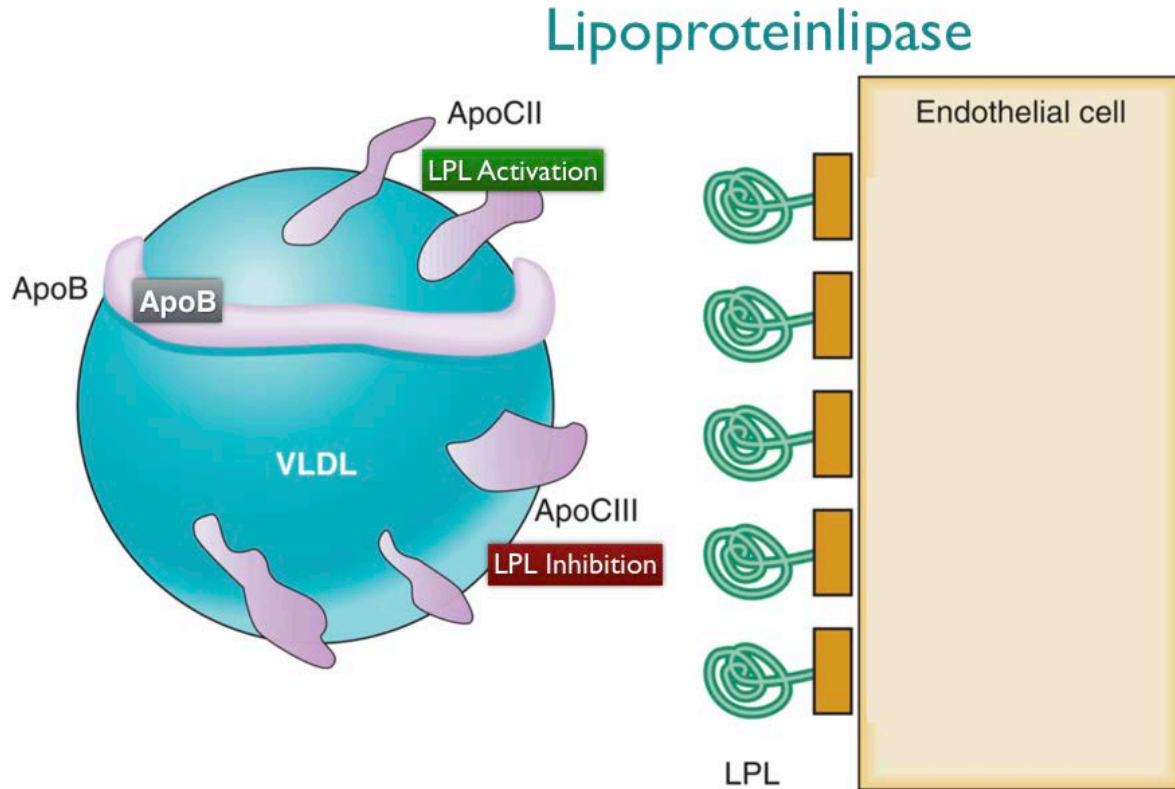
Function of ApoC2 and ApoC3

Lipoproteinlipase



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Function of ApoC2 and ApoC3



ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc.,
Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.



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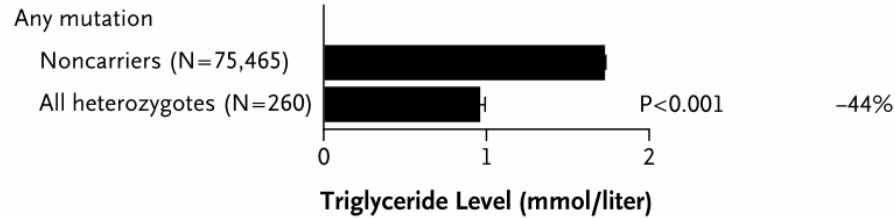
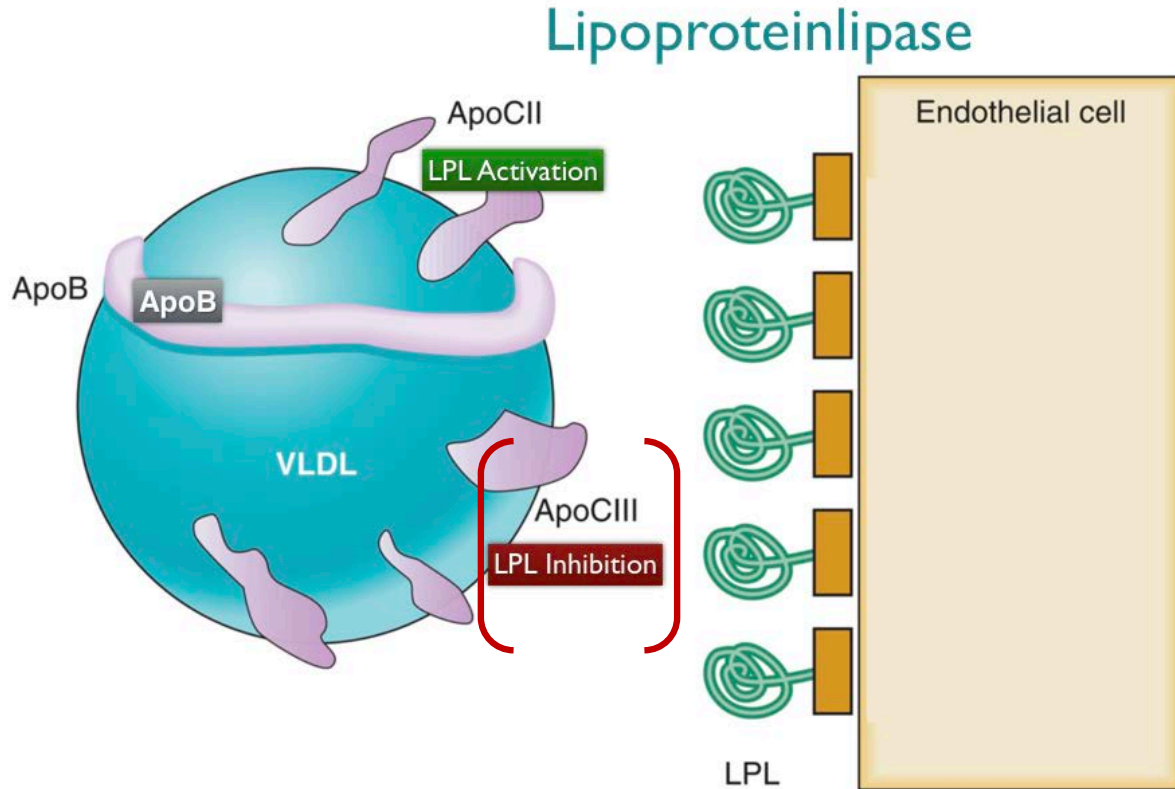


Figure 2. Mean Plasma Levels of Nonfasting Triglycerides as a Function

Faster Triglyceride Clearance



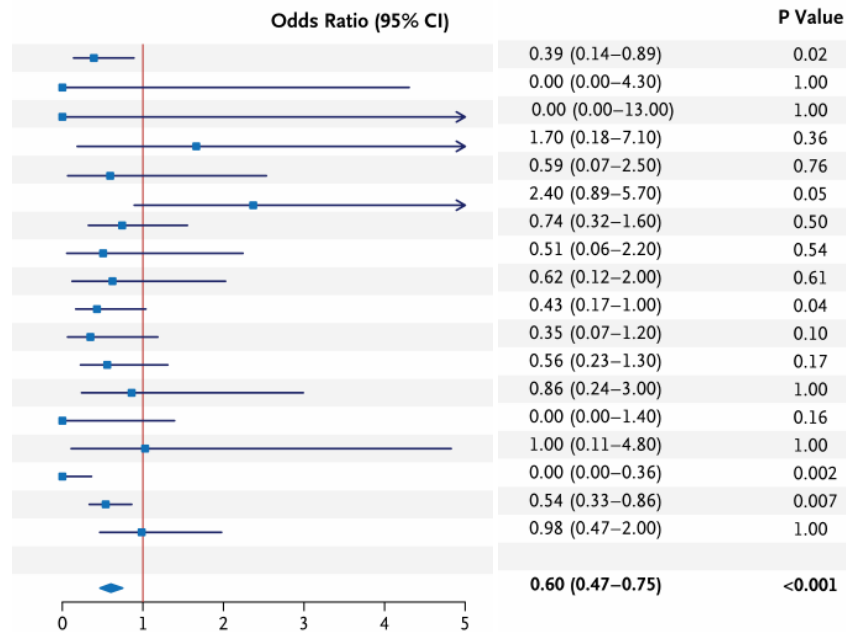
Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project,
National Heart, Lung, and Blood Institute*



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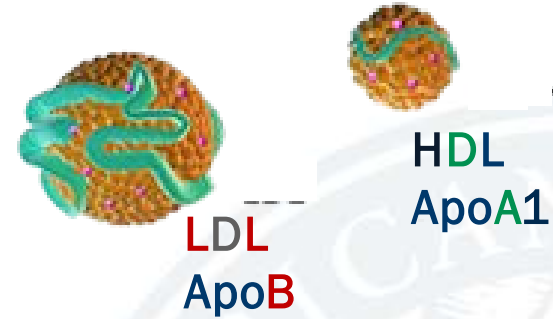
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Lipoprotein

VLDL
ApoB
ApoC2
(ApoC3)
ApoE



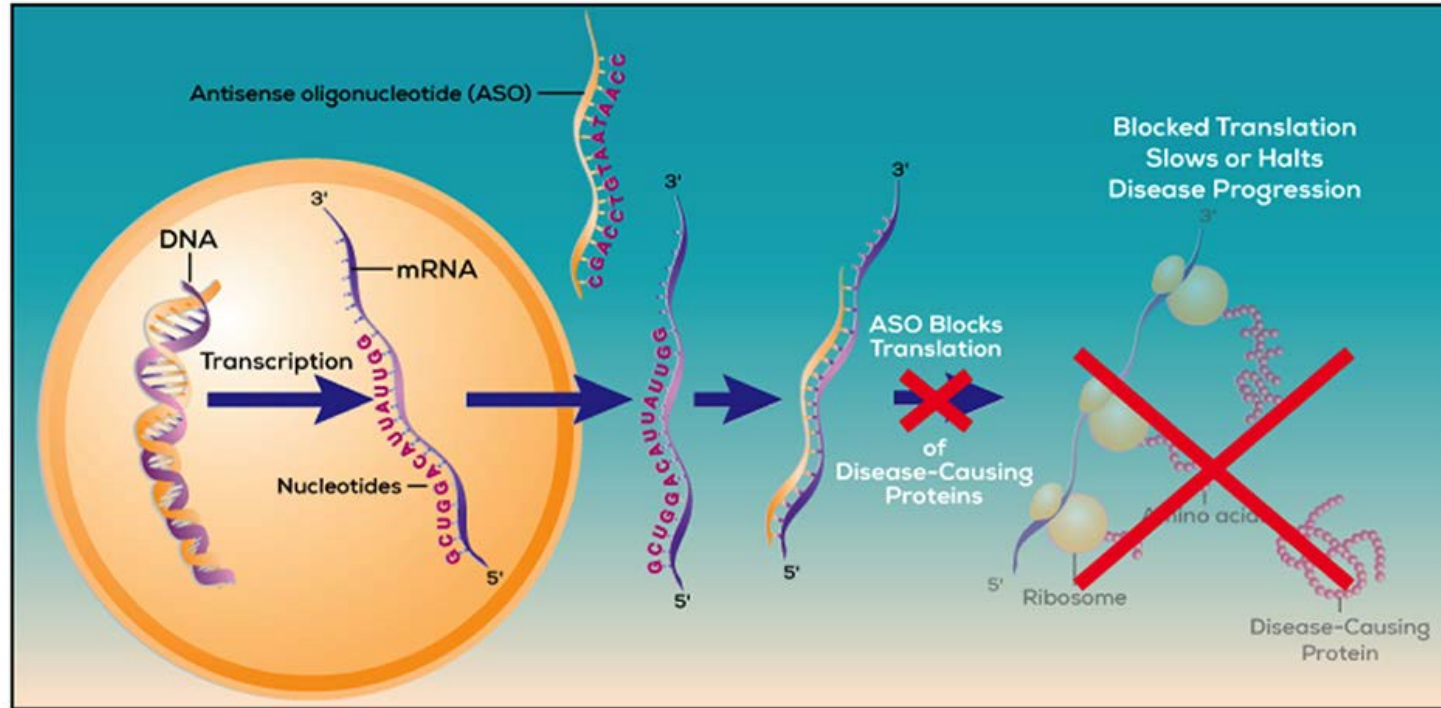
LDL
ApoB

HDL
ApoA1



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Antisense Therapy Targeting ApoC3



Management of Very High Triglycerides

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Targeting APOC3 in the Familial Chylomicronemia Syndrome

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D.,
Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S.,
Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S.,
Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.

NEJM 2014
IONIS 1 (n=3)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

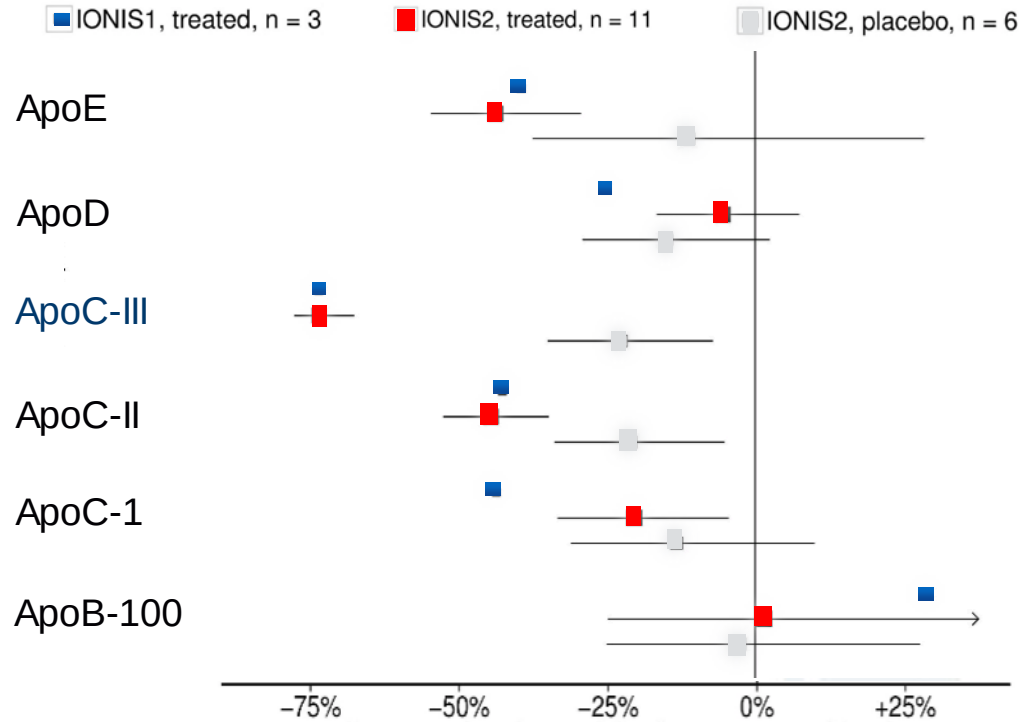
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John D. Brunzell, M.D.,* and John J.P. Kastelein, M.D., Ph.D.

NEJM 2015
IONIS 2 (treated n=11, placebo n=6)



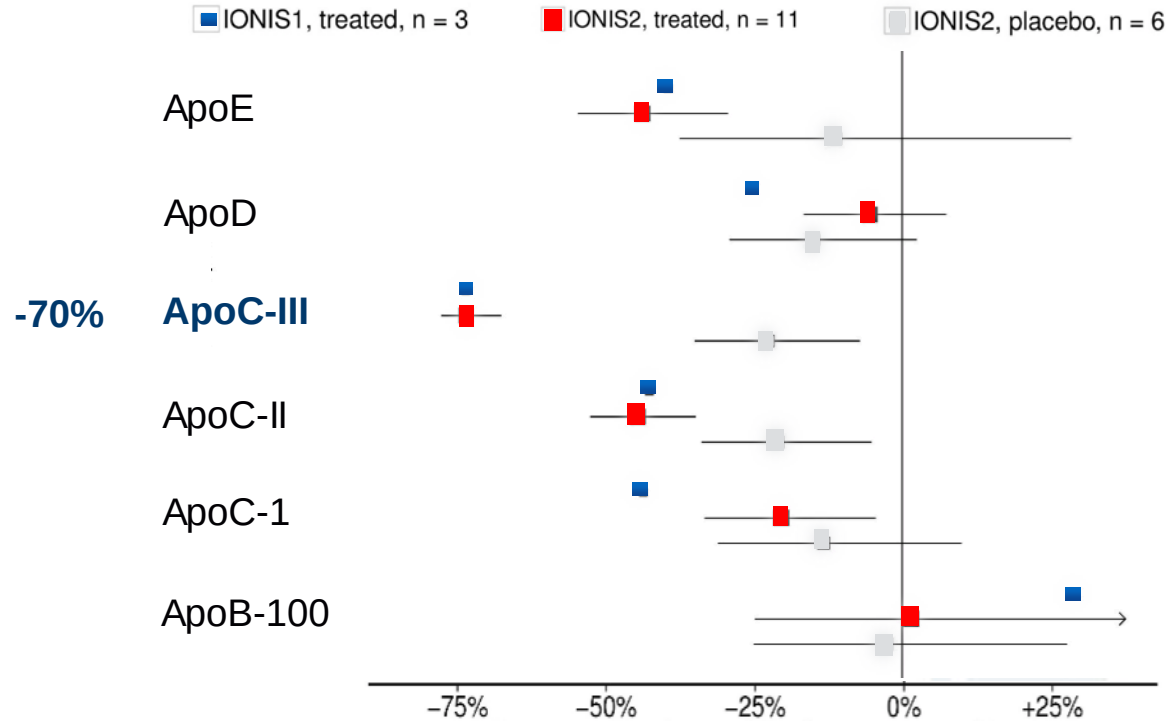
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Effect of ApoC3 Antisense



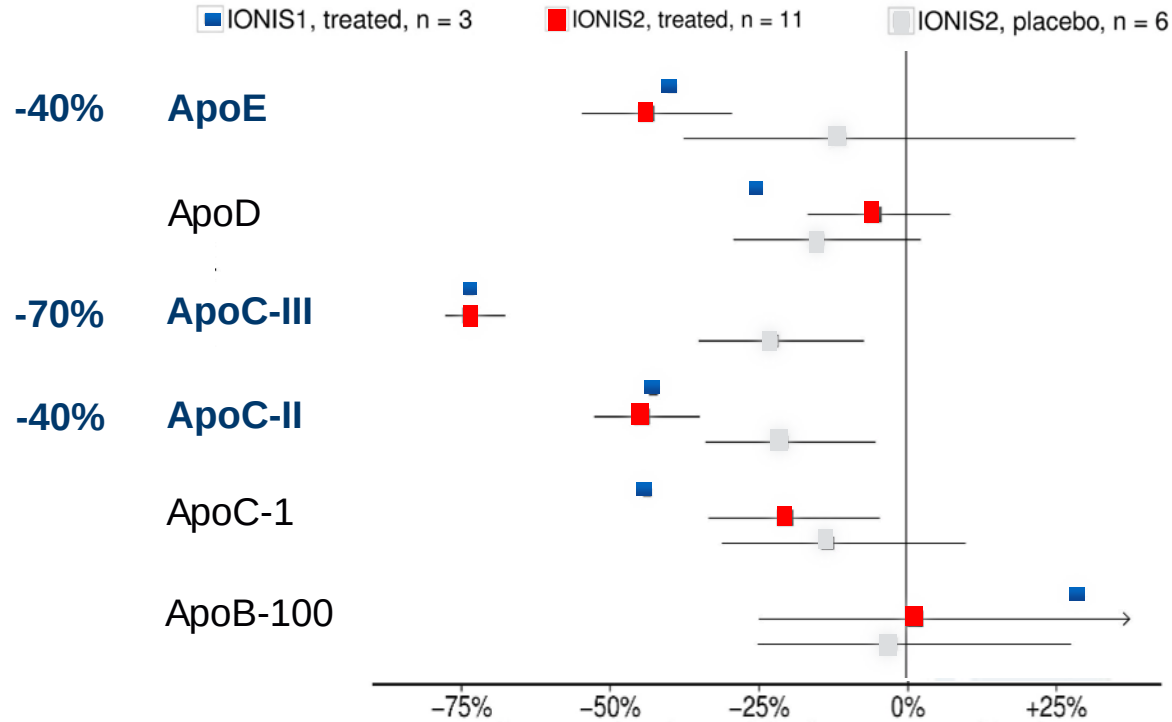
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Effect of ApoC3 Antisense



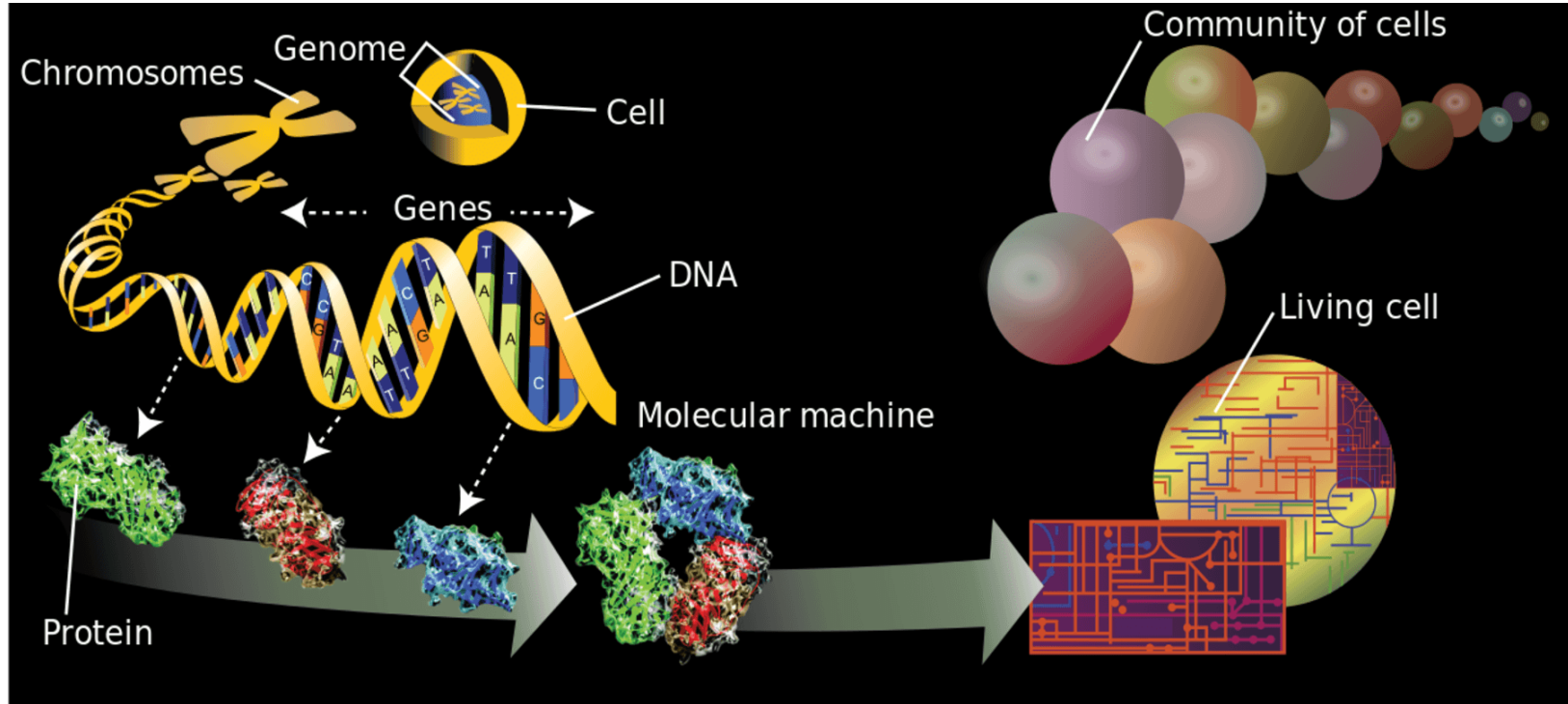
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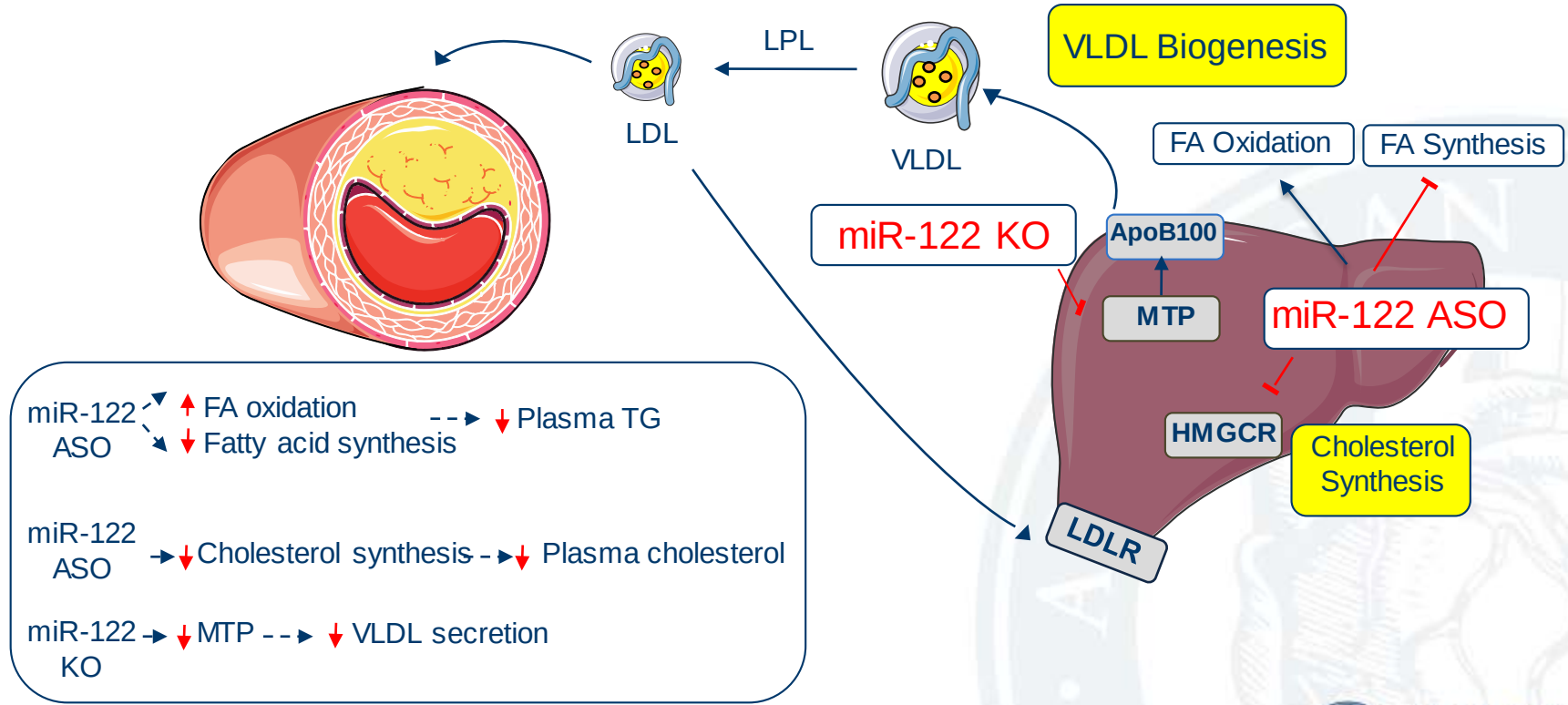


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MicroRNAs: Small Non-coding RNAs

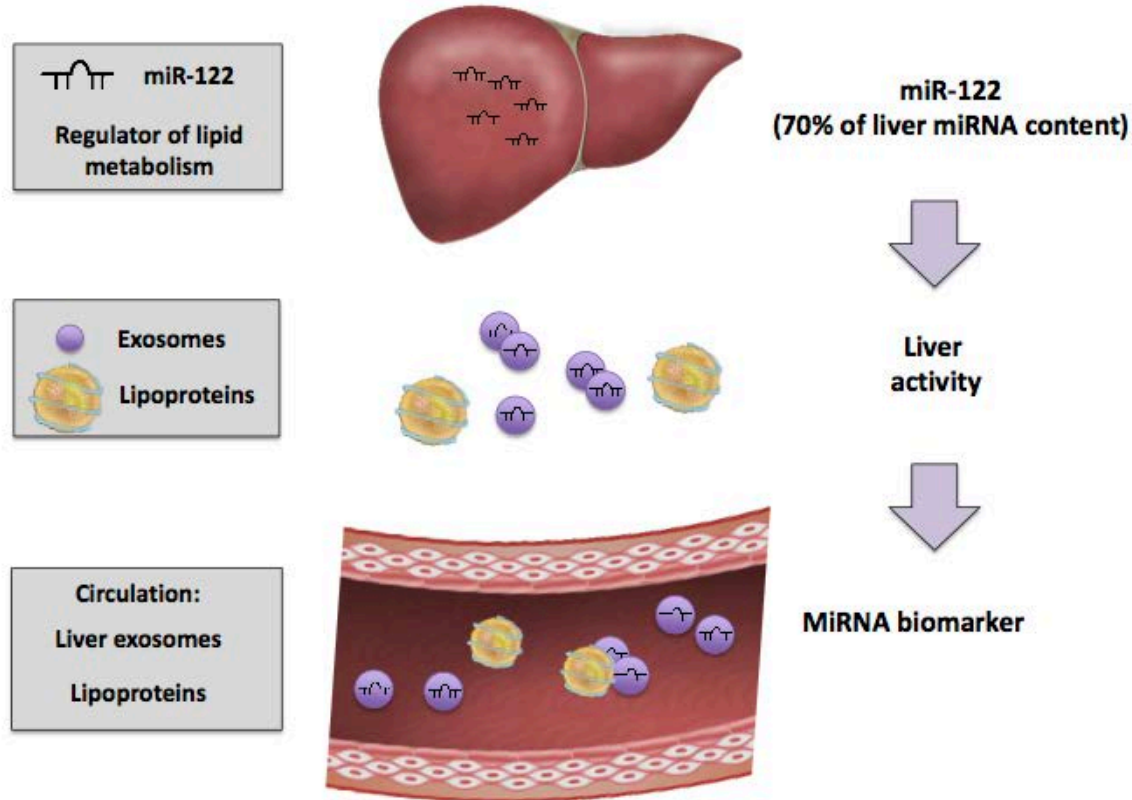


MicroRNA-122 & Lipid Metabolism



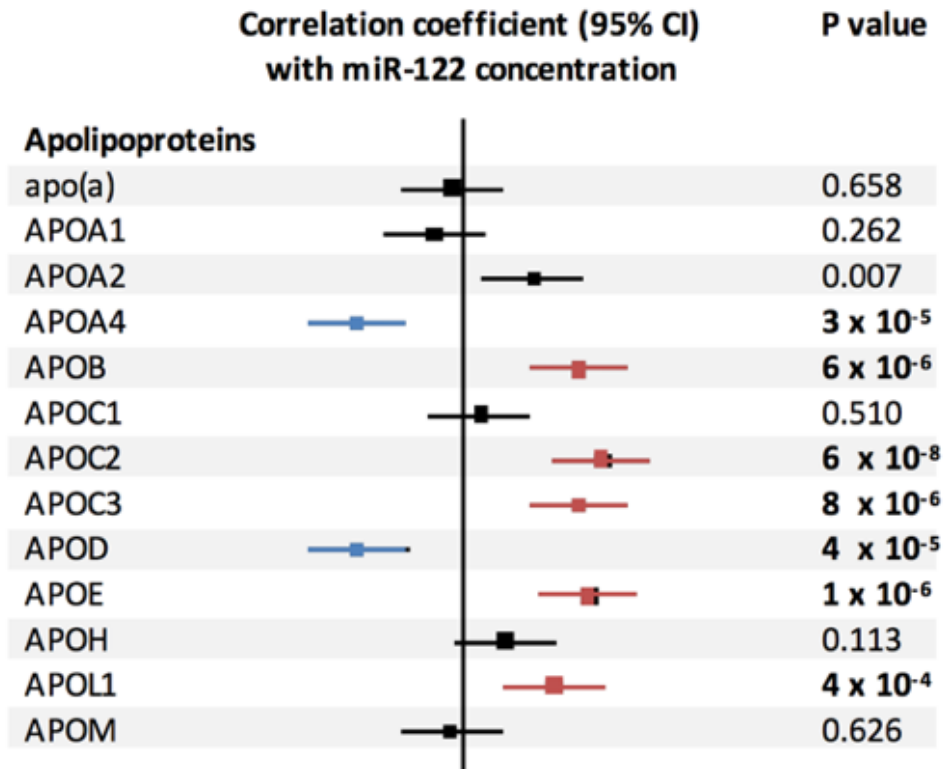
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MicroRNA-122 in Circulation



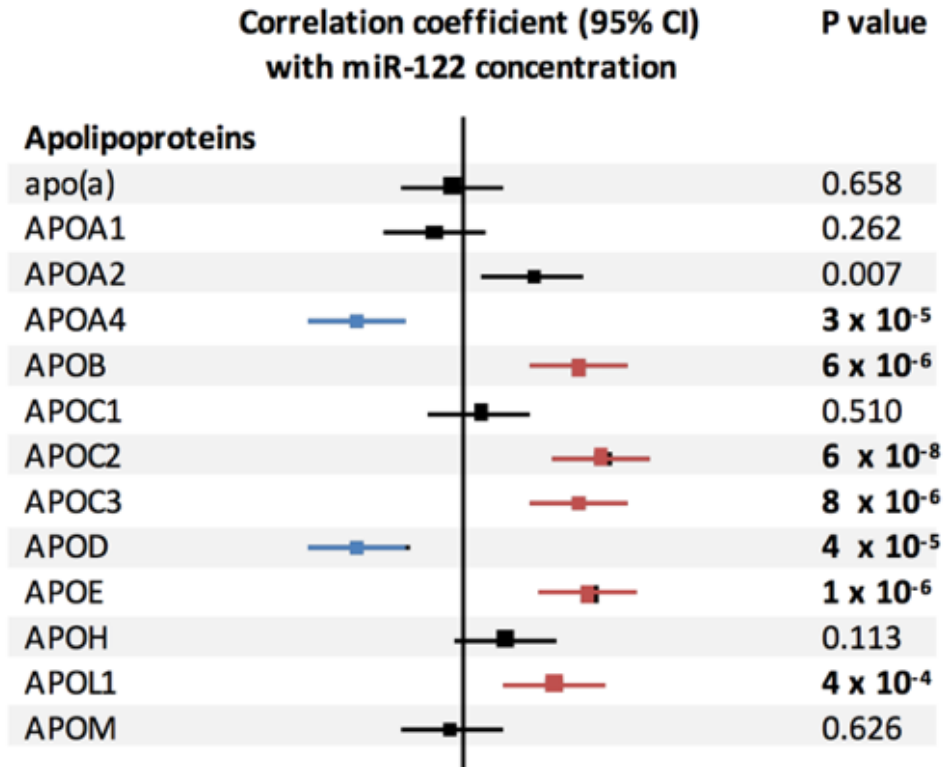
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MicroRNA-122 & Apolipoproteins



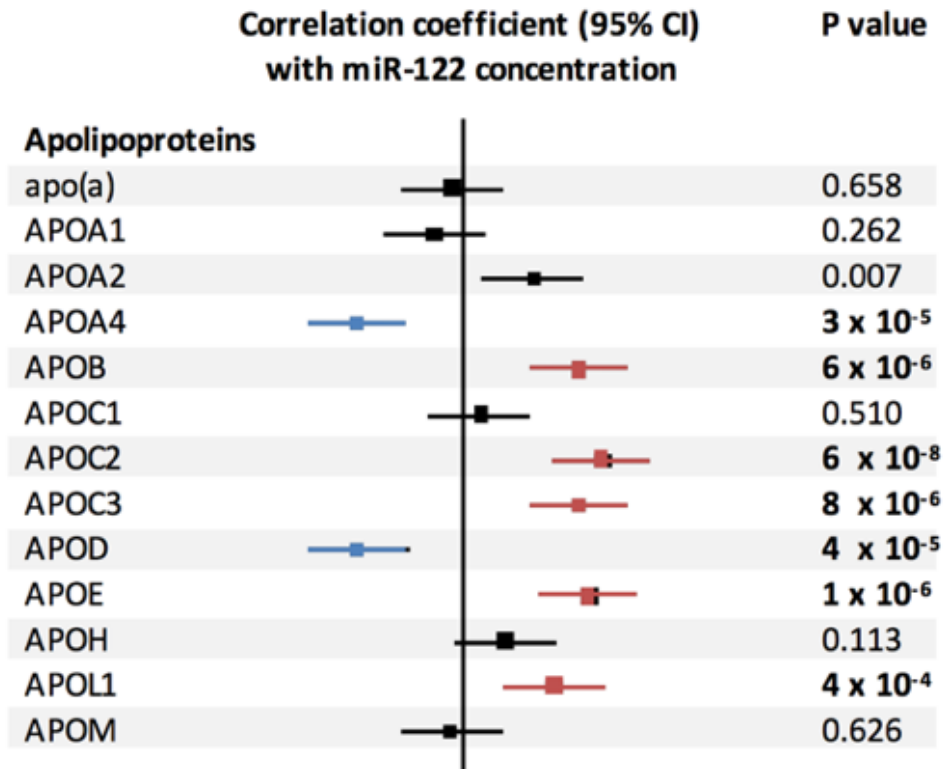
MicroRNA-122 & Apolipoproteins

HDL/CM
particles



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MicroRNA-122 & Apolipoproteins



HDL/CM
particles

VLDL
particle



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MicroRNA-122: Risk of Metabolic Syndrome

Outcome/ Level of adjustment	Top vs. bottom third of circulating miR-122	
	RR (95% CI)	P value
Metabolic syndrome (136 outcomes)		
Adjusted for age and sex	2.85 (1.78, 4.56)	<0.001

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	RR (95% CI)	P value
Metabolic syndrome (136 outcomes)		
Adjusted for age and sex	2.85 (1.78, 4.56)	<0.001
Multivariable model*	2.81 (1.76, 4.50)	<0.001
+ BMI + WHR	2.44 (1.48, 4.02)	<0.001
+ ln(HOMA-IR)	2.47 (1.53, 3.99)	<0.001

Conclusions

- Currently, we just monitor lipid classes (total cholesterol, total triglycerides) as well as HDL and LDL cholesterol. The focus is on “**quantity**” rather than “**molecular composition**”.



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- The strong associations of certain **triglyceride species and VLDL-associated apolipoproteins with incident CVD** in the general community provide support to the concept of targeting triglyceride-rich lipoproteins to further reduce risk of CVD in the statin era.



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- Currently, we just monitor lipid classes (total cholesterol, total triglycerides) as well as HDL and LDL cholesterol. The focus is on “**quantity**” rather than “**molecular composition**”.
- The strong associations of certain **triglyceride species and VLDL-associated apolipoproteins with incident CVD** in the general community provide support to the concept of targeting triglyceride-rich lipoproteins to further reduce risk of CVD in the statin era.
- Circulating levels of **liver-derived miRNA-122** positively correlate to **VLDL-associated apolipoproteins** and are a strong **predictor of metabolic syndrome**.



Acknowledgements



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Mr. Sean Burnap

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UCSD:

Prof. Sam Tsimikas
Prof. Joe Witztum



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