BRIGHAM AND WOMEN'S HOSPITAL

# High-resolution lipoprotein phenotypes and clinical outcomes

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

# Disclosures

BRIGHAM AND WOMEN'S HOSPITAL

- Dr. Mora has received institutional research support from the NIH (NHLBI/NCI/Common Fund/NIDDK), American Heart Association, and Atherotech Diagnostics.
- Quest Diagnostics and LabCorp measured the JUPITER ion mobility and NMR lipoproteins, respectively, at no additional cost to the study.

# High-resolution lipoprotein phenotypes and clinical outcomes

Topics

- Is LDL-C the best lipid measure?
- Are there other relevant lipid measures
- Monitoring and targets of therapy?

# *Case 1.*
# *Is this patient at high risk due to LDL?*

| | mg/dL | Population Percentile |
|---|---|---|
| TC | 187 | |
| TG | 69 | |
| LDL-C | 113 | 50th% |
| HDL-C | 42 | |
| Non-HDL-C | 145 | 55th% |

# *2. Is this patient at high risk due to LDL?*

**69 y.o. woman no prior CVD or DM, no smk,**
**BP 142/68, BMI 28.3, hsCRP 9.4 mg/L**
**ASCVD risk score 12.6%**
(Reynolds risk score 13.5%; FRS score 5%)

| Lipids | mg/dL |
|---|---|
| TC | 193 |
| TG | 289 |
| LDL-C | 89 |
| HDL-C | 46 |

# High-resolution lipoprotein phenotypes and clinical outcomes

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# LDL-c levels have been decreasing

**Table. NHANES Mean Estimates for Specific Lipid Levels and Frequency of Use of Lipid-Lowering Medications at Various Surveys[2,3]**

| | | | Calendar Years | | | | | |
|---|---|---|---|---|---|---|---|---|
| Item | Group | Age Range, y | 1960–1962 | 1971–1974 | 1976–1980 | 1988–1994 | 1999–2002 | 2007-2010 |
| Total cholesterol, mg/dL | Men | 20–74 | 220 | 215 | 213 | 204 | 202 | 194 |
| | Women | 20–74 | 225 | 217 | 216 | 207 | 204 | 198 |
| LDL-C, mg/dL | Men | 20–74 | No data | No data | No data | 131 | 126 | 116 |
| | Women | 20–74 | No data | No data | No data | 126 | 120 | 115 |
| Lipid medication use, % | Men | 20–74 | No data | No data | No data | 3.10 | 10.70 | 16.8 |
| | | 20–29 | No data | No data | No data | 0.40 | 1.50 | 1.8 |
| | | >70 | No data | No data | No data | 6.70 | 23.60 | 42.0 |
| | Women | 20–74 | No data | No data | No data | 3.50 | 8.10 | 14.4 |
| | | 20–29 | No data | No data | No data | 0.20 | 0.50 | 2.0 |
| | | >70 | No data | No data | No data | 8.70 | 22.80 | 38.3 |

*Farzadfar Lancet* 2011; Carroll *JAMA* 2012; Wilson *Circulation* 2016

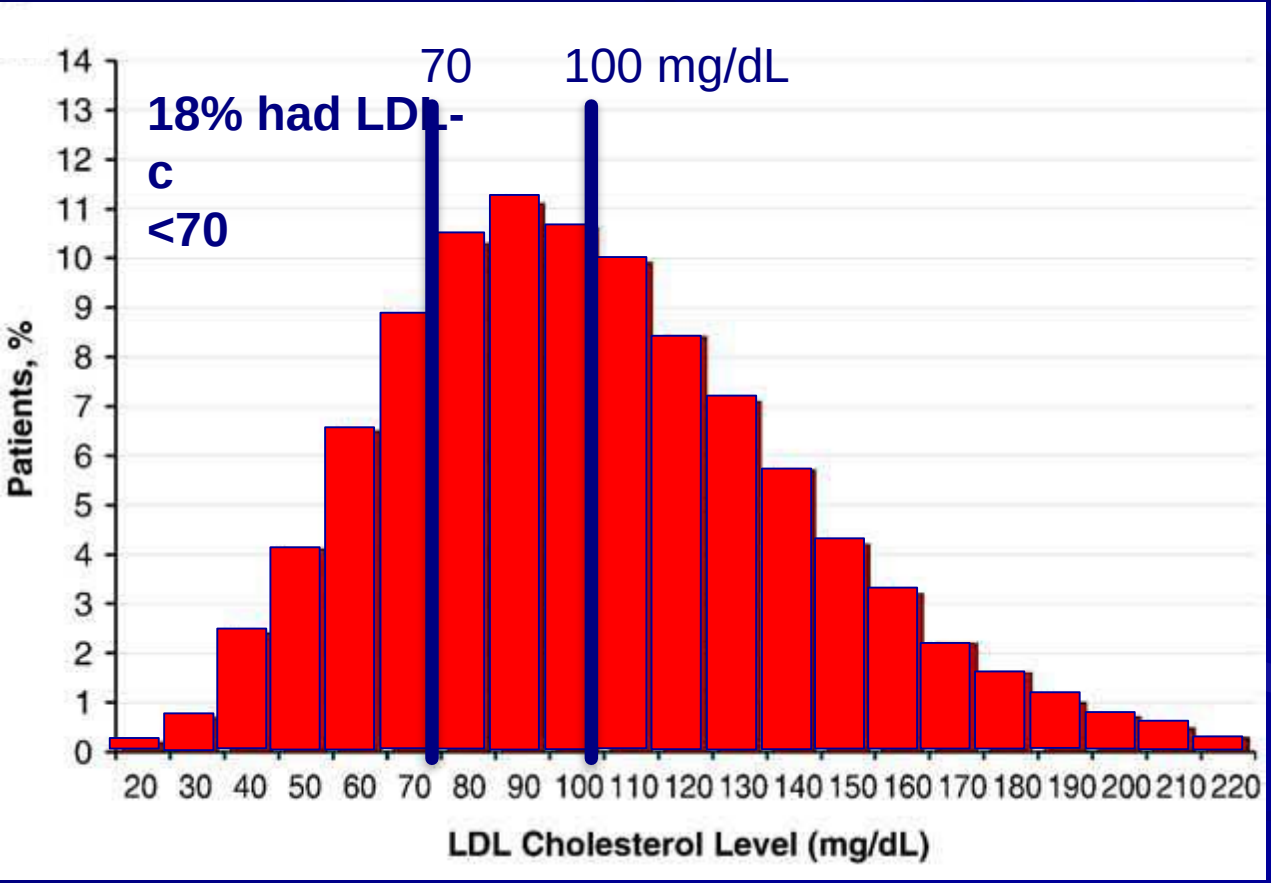
# CVD events occur despite low or normal levels of LDL-c

- Increasingly prevalent in era of statin-based primary and secondary prevention, and with increasing rates of obesity and diabetes
- Importantly, LDL-c does not account for all of the risk conferred by circulating atherogenic lipoproteins

**Baigent *et al. Lancet* 2005; Sniderman *Circ* CQO 2011; Boekholdt *JAMA* 2012**

# Approximately 50% of patients with a CHD event have LDL-c<100 mg/dL

LDL-c levels in 136,905 patients hospitalized with CHD




Sachdeva. et al, *AHJ* 2009;157: 111

# What should we measure?

# High-resolution lipoprotein phenotypes and clinical outcomes

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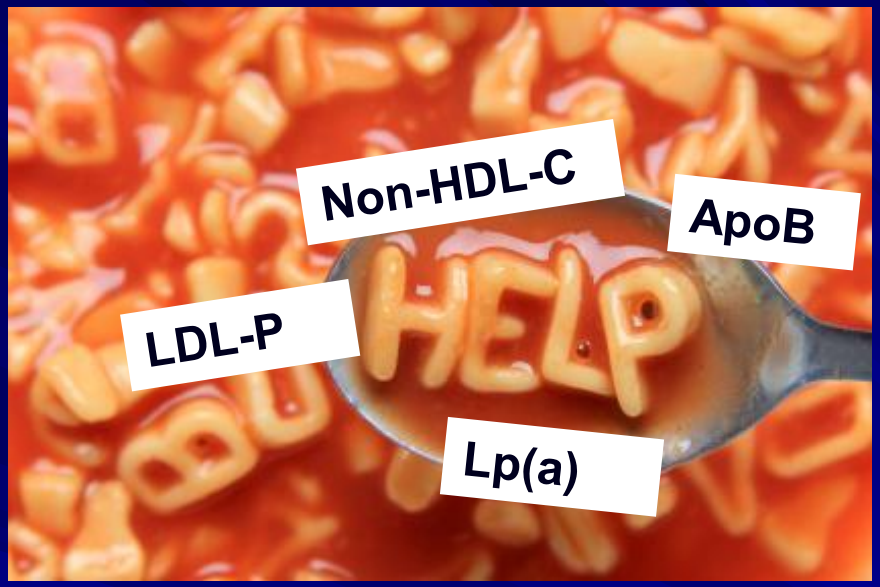
# What should we measure?




- To date, key “lipid” measures:
  - Better calculated LDL-C
  - Non-HDL cholesterol
  - Apolipoprotein B (ApoB) or LDL particle number (LDL-P)
  - Lipoprotein(a) (Lpa)

Harada P et al 2014
http://ldl.cardiosource.org/Hot-Topics/2014/08/Advanced-Lipoprotein-Testing.aspx

# ApoB

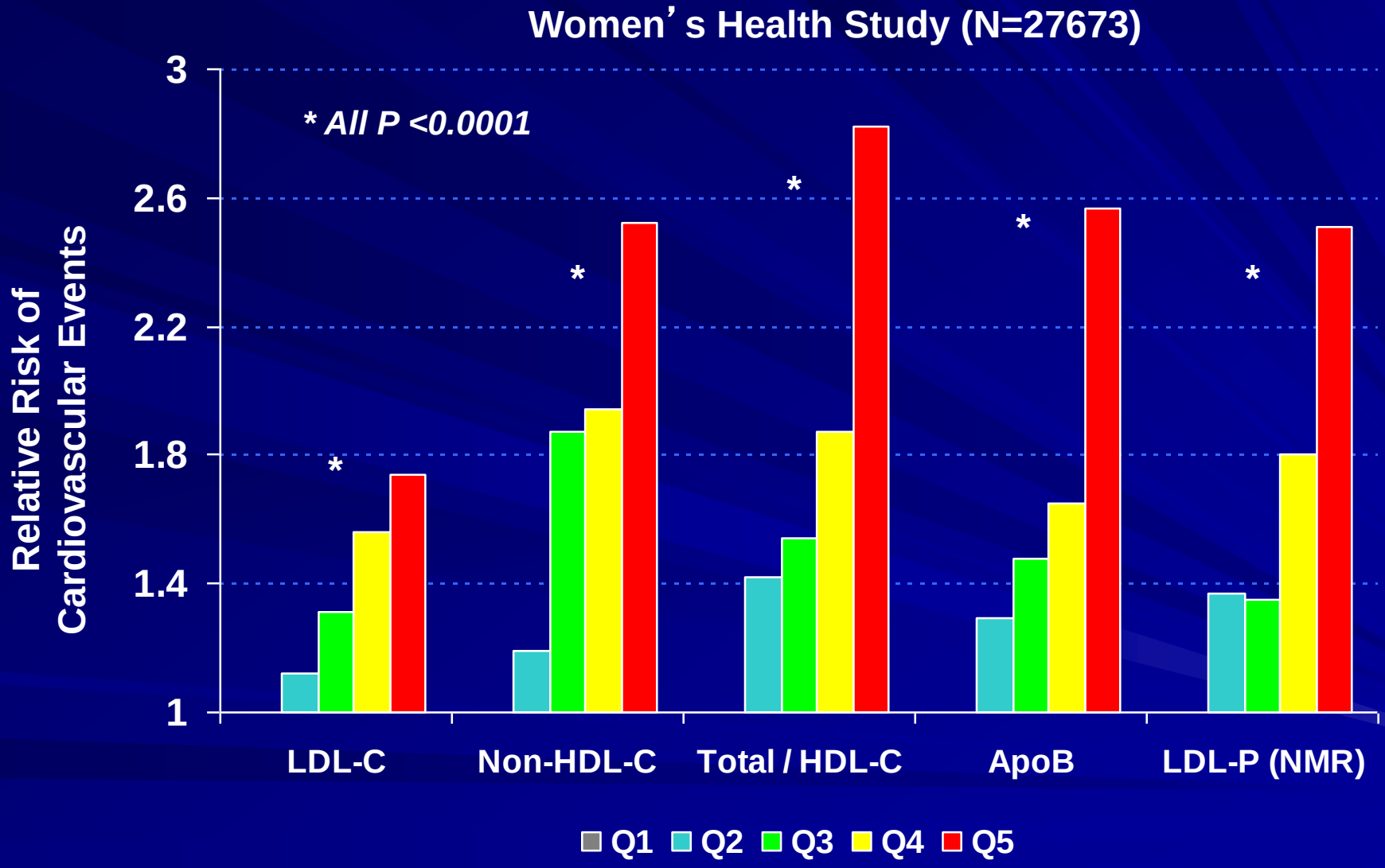
- Each VLDL, LDL, IDL, and Lp(a) carry one apoB
- ApoB is the total number of these atherogenic particles
- >90% of apoB is in LDL particles, hence ApoB ~ LDL particle number (LDL-P)

McPherson et al, Can J Cardiol 2006;22:913-27

LDL-C, nonHDL-C, apoB (LDL-P) are highly correlated (r ≥0.7), so most of the time they agree with each other…

*…. but what about when they don't agree, which is right?*

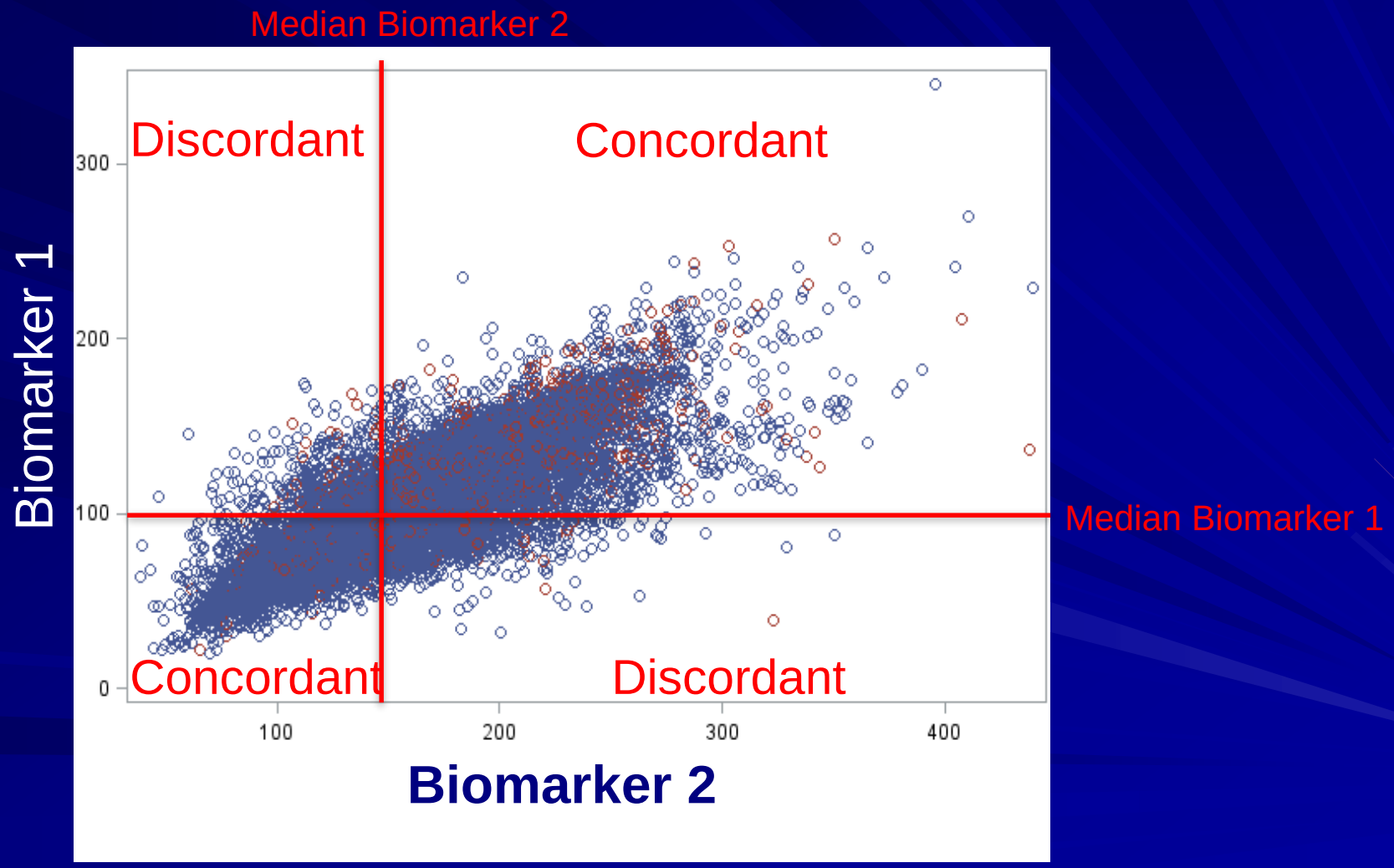
# ApoB and LDL-$P_{NMR}$ similar to Total/HDL-C or Non-HDL-C




Relative risk adjusted for age, smk, menopause, hormone use, BP, BMI, diabetes

Mora et al, *Circulation* 2009;119:931

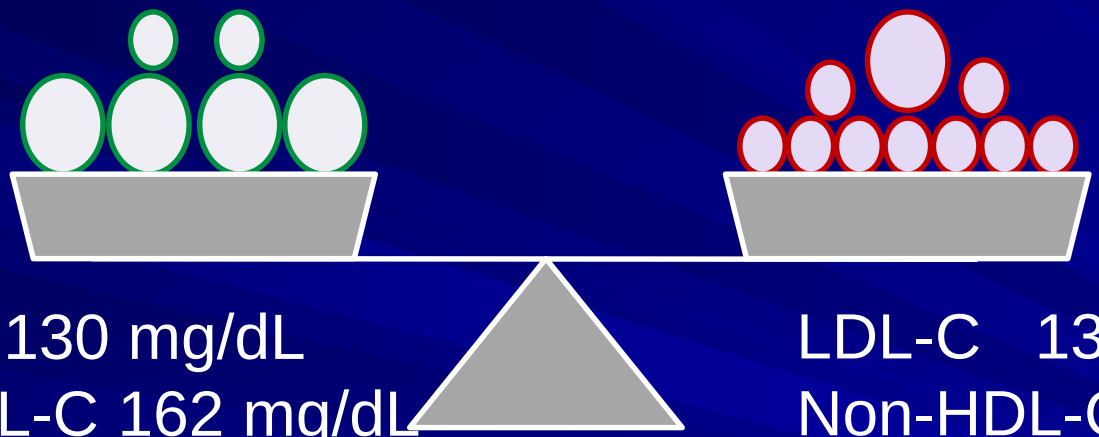
# Defining Discordance



# Which woman is at higher risk?

Fewer LDL Particles
Lower Risk

More LDL Particles
Higher Risk



LDL-C 130 mg/dL
Non-HDL-C 162 mg/dL
LDL-P 1011 nmol/L
ApoB 106 mg/dL

LDL-C 130 mg/dL
Non-HDL-C 181 mg/dL ↑
LDL-P 1723 nmol/L ↑
ApoB 127 mg/dL ↑

Mora S, Circulation 2009;119:2396-2403

# Which woman is at higher risk?

# Discordant high LDLP or apoB

Fewer LDL Particles
Lower Risk

More LDL Particles
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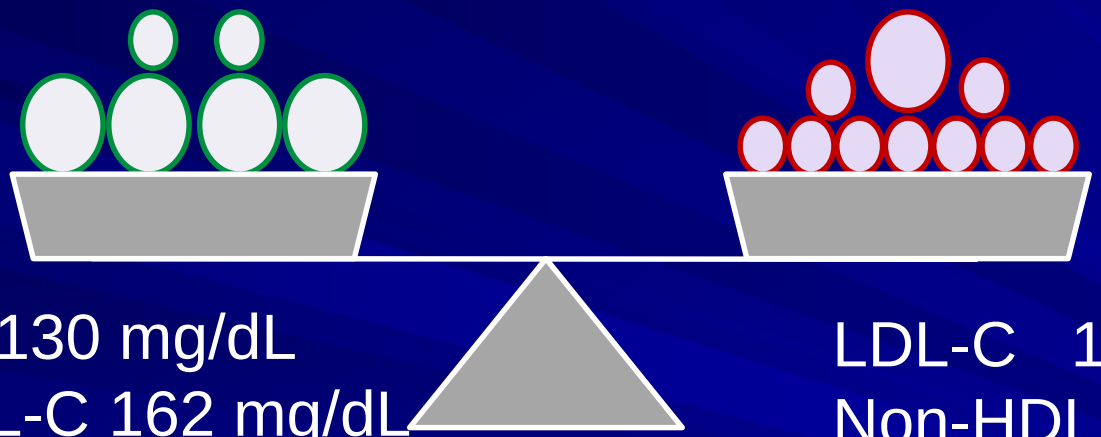

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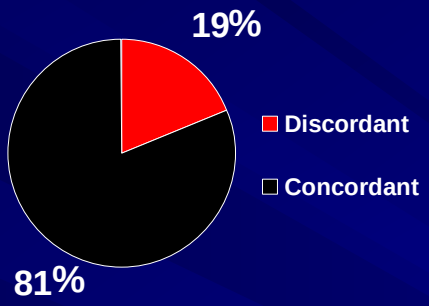
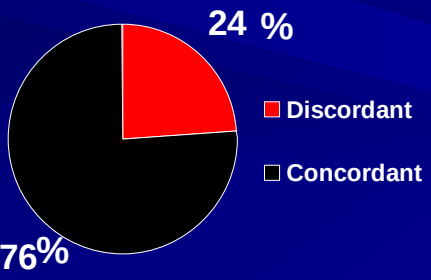
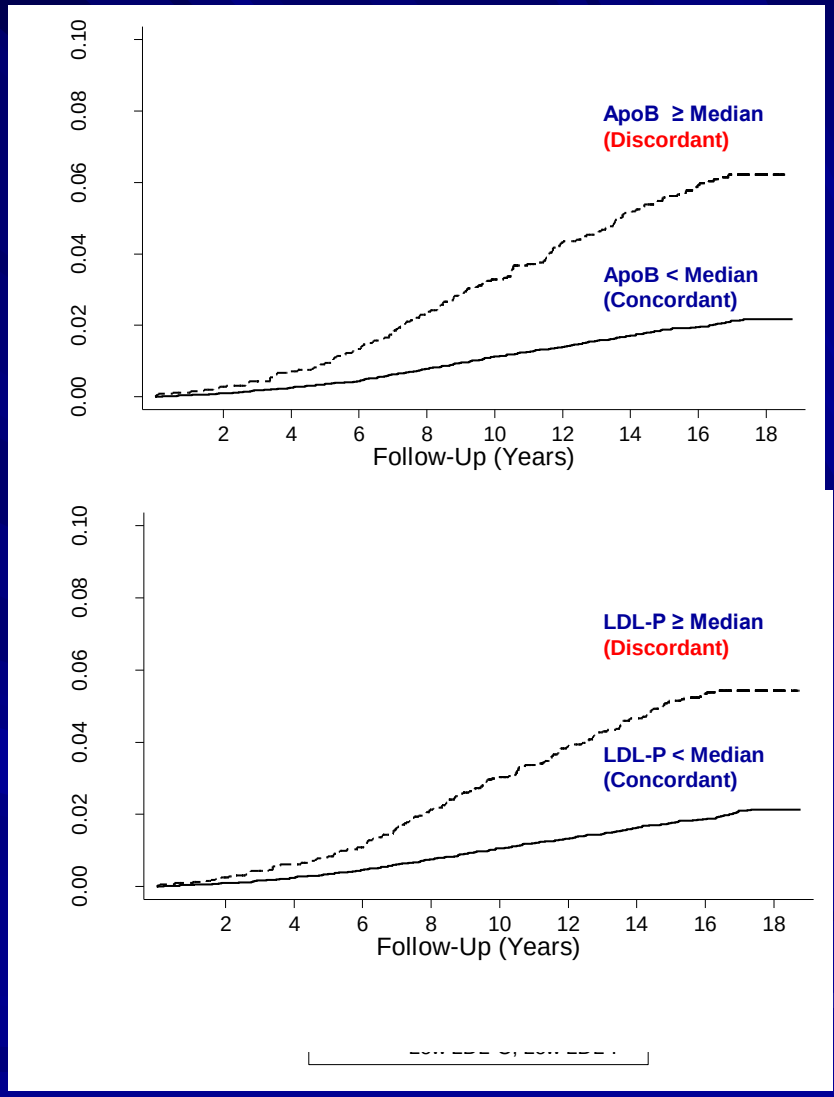
# Risk tracks with discordant LDL or apoB *particle* measures (more than LDL cholesterol)

**LDL-C and ApoB**



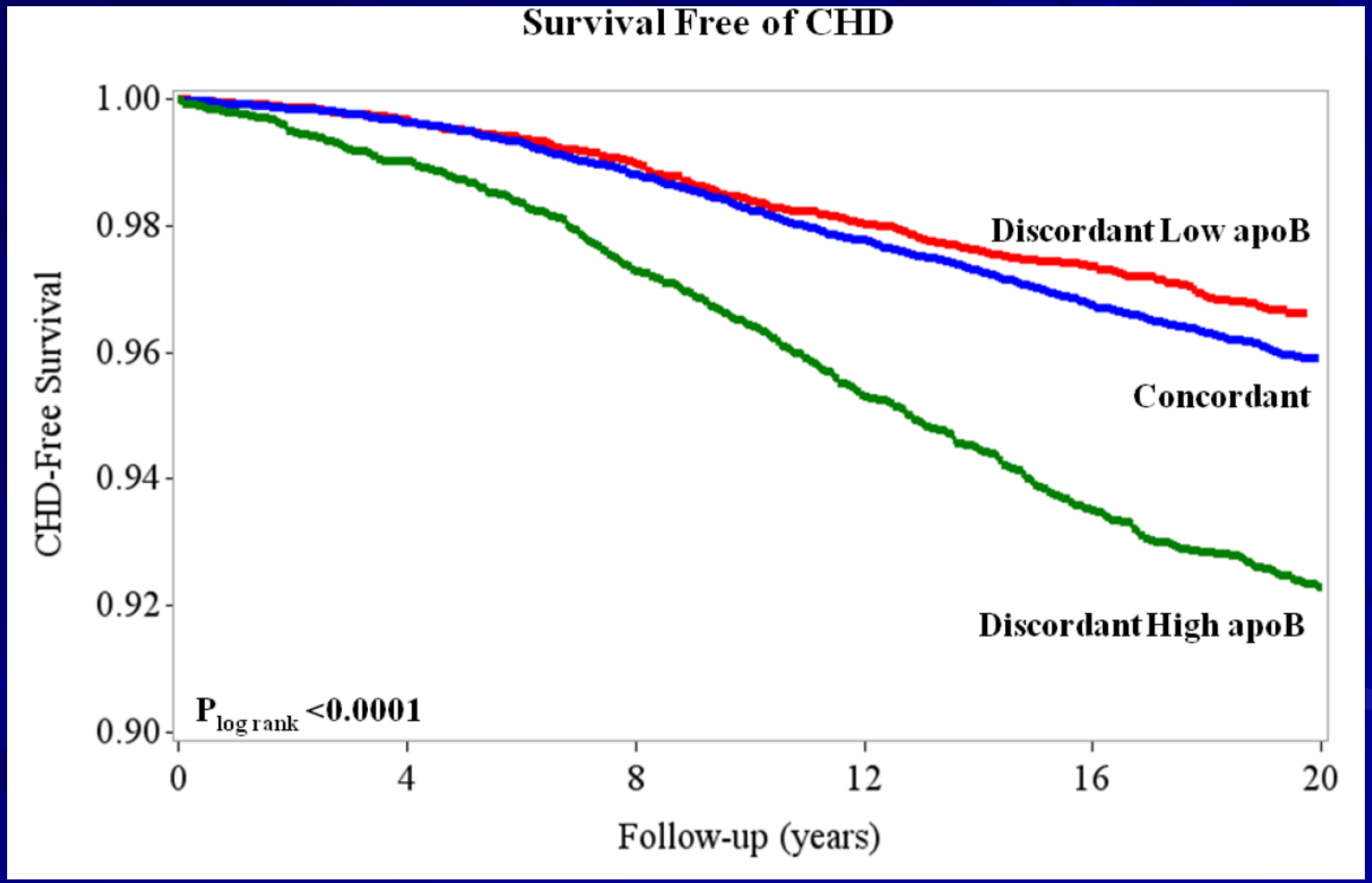

**LDL-C and LDL-P**




Mora et al, Circulation 2014; 129:583

# Long-term risk tracks with discordant LDL or apoB *particle* measures (more than nonHDLc)




Lawler et al *Clinical Chemistry* 2017 63:870-9

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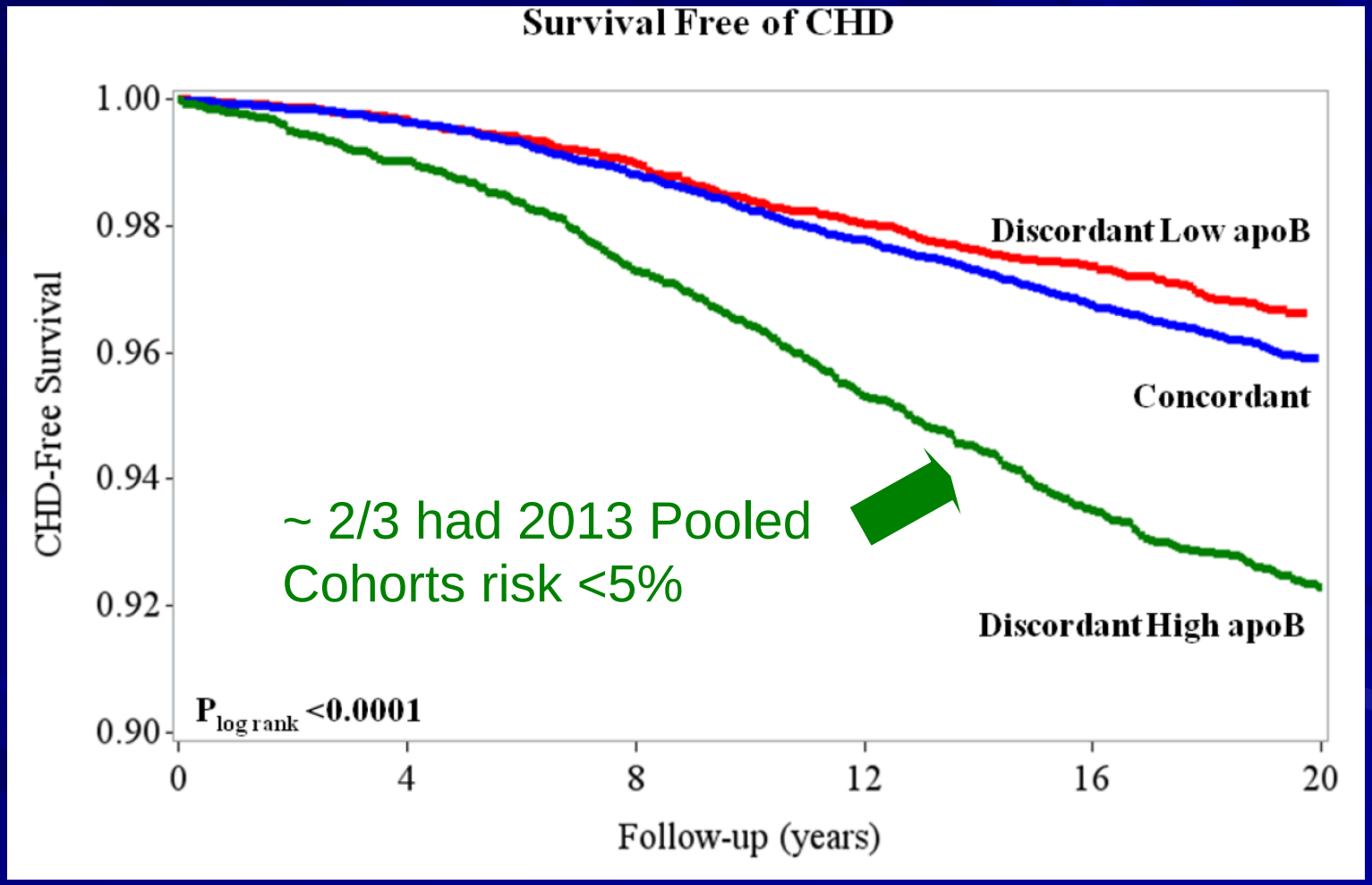
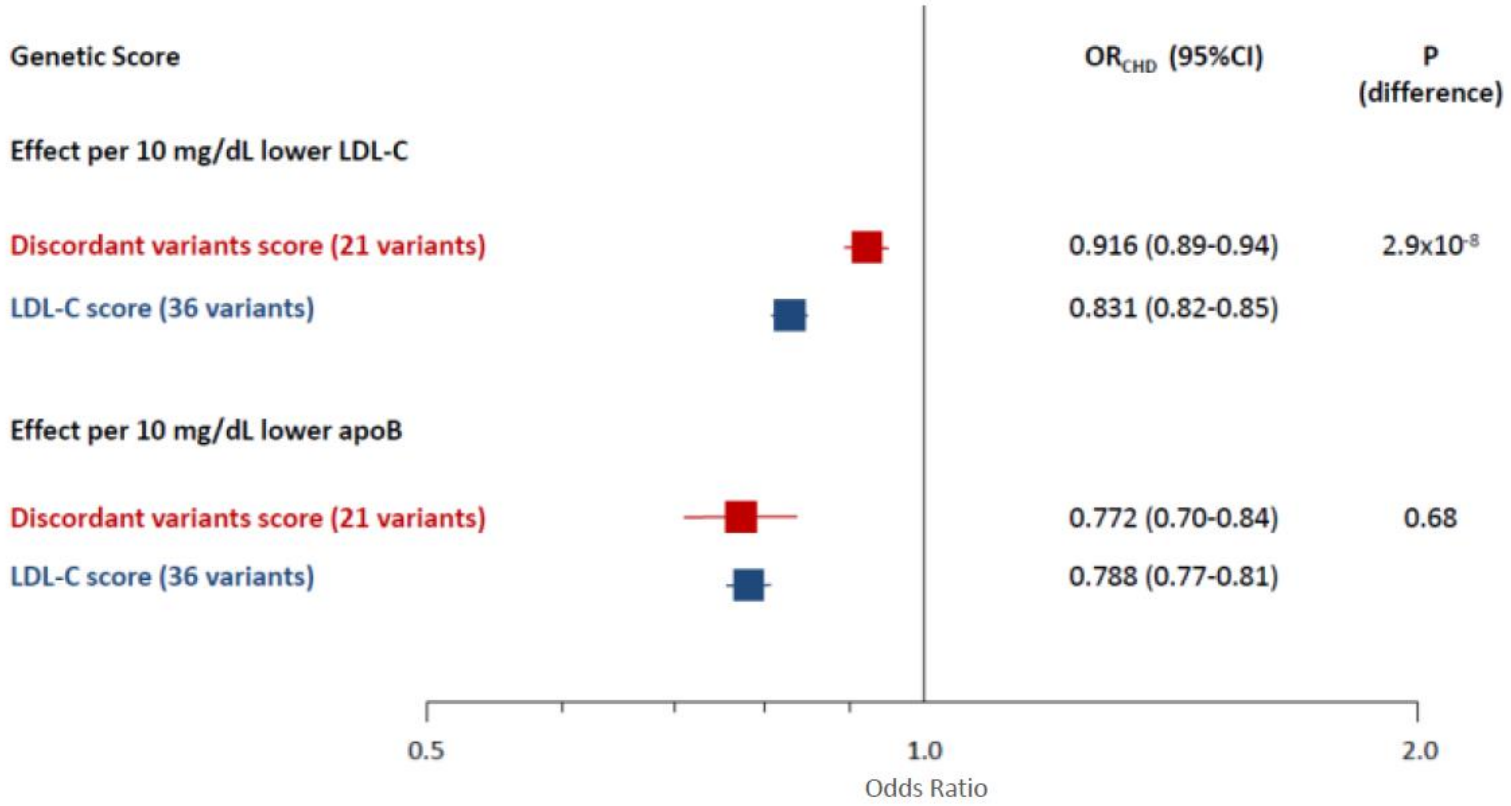



Lawler et al *Clinical Chemistry* 2017 63:870-9

# Genetic variants mimicking discordance between apoB (LDL particle number) and LDL-C: Risk tracked with apo B (LDL-P) more than with LDL-C

- 21 genetic variants with naturally occurring discordance between LDL-C and apoB similar in magnitude to what occurs when *CETP* & *HMGCR* inhibition are combined




Ference et al: JAMA 2017 Epub ahead of print August 28 2017

# Discordance of cholesterol and particle number

- Present in up to 20-25% of the population, more common among those with metabolic syndrome or diabetes
- When discordance is present, risk is more strongly associated with particle concentration than cholesterol
- Favor apoB or LDLP over LDLC or nonHDLC as a measure for atherogenic risk related to lipoproteins, in particular at low LDL-c levels or high TGs

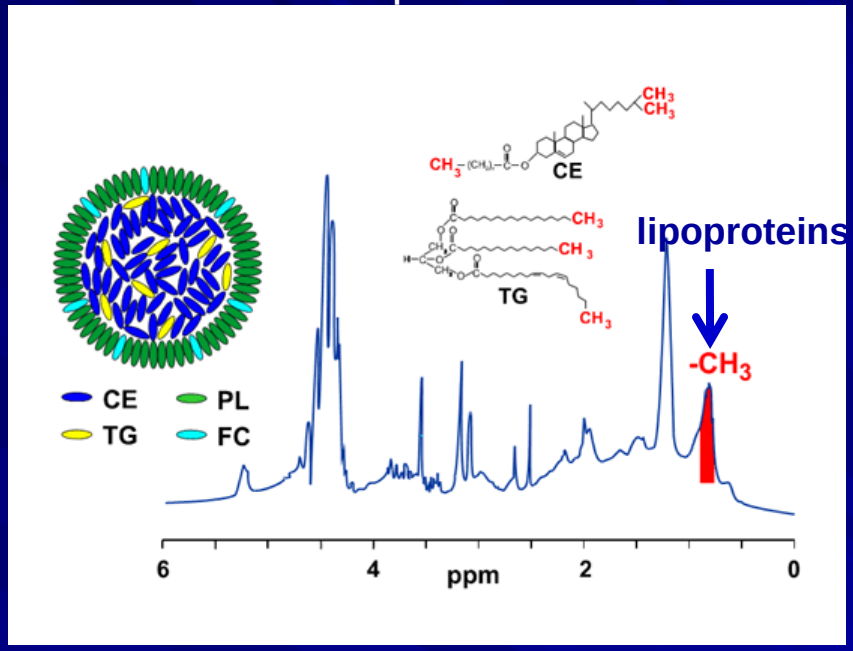
Mora *Circulation.* 2014; Pencina *Eur J Prev Cardiol.* 2015; Lawler *Clin Chem* 2016

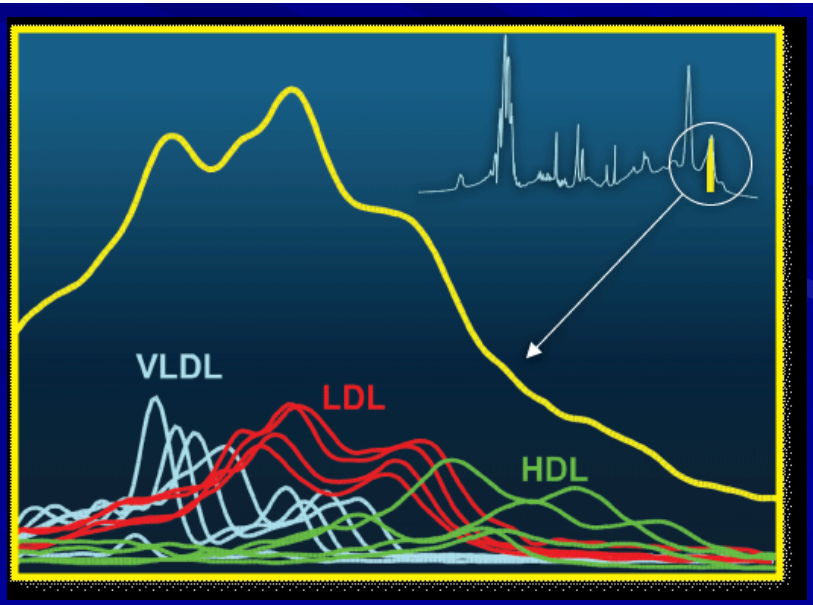
# Nuclear Magentic Resonance (NMR)

NMR spectroscopy measures the **concentration** (number) and **size** of lipoproteins:

LDL, IDL, VLDL, HDL

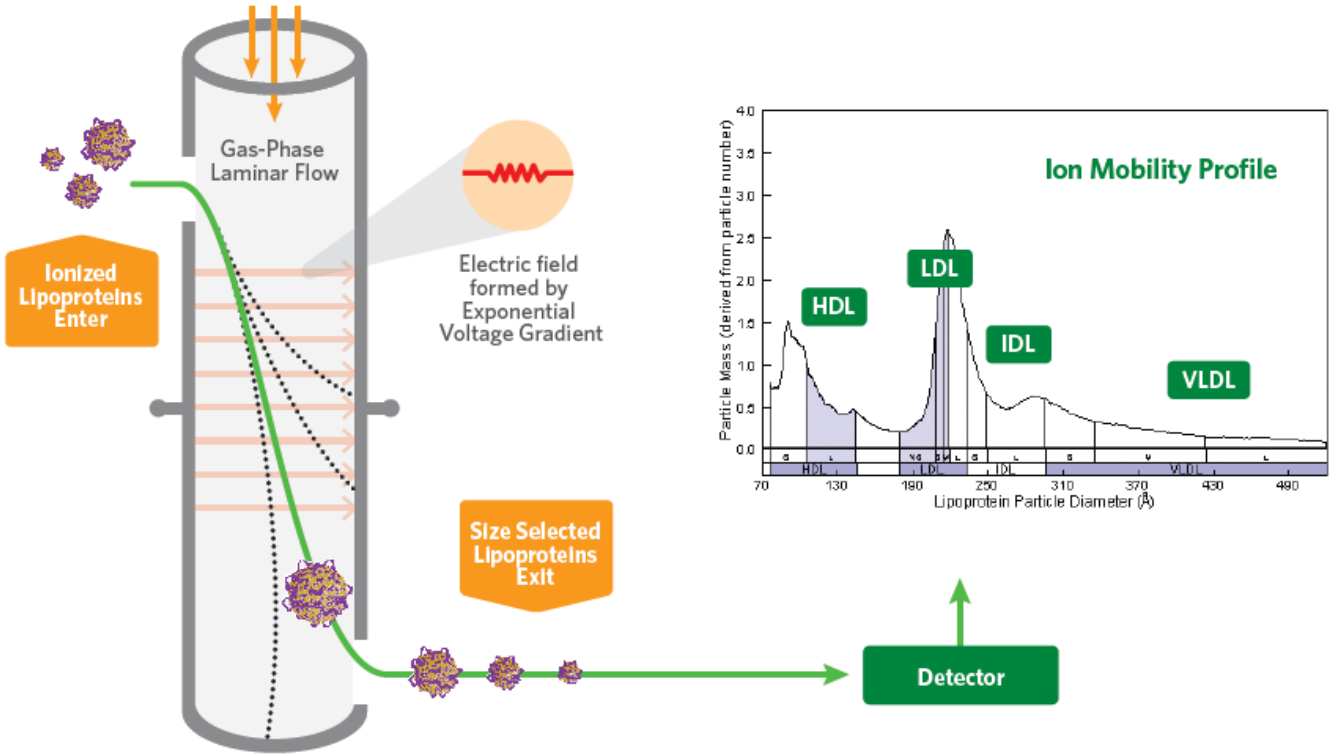
Proton NMR Spectrum of Plasma




www.liposcience.com

# Ion Mobility – Gas-Phase Electrophoresis




Ionized lipoproteins migrate across a laminar gas phase flow, based on size and electrical field. Only a single size of lipoprotein will exit the field and be isolated (green line) at any point during the voltage gradient; larger and smaller lipoproteins (dotted black) are not collected. As the voltage ramps across the gradient, all of the lipoproteins are captured.

Caulfield *Clin Chem* 2008; Musunuru *ATVB* 2009

Mora et al, *Circulation* 2015

Michael Caulfield, PhD, Quest Diagnostics

# High-resolution lipoprotein phenotypes and clinical outcomes

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- Is LDL-C the best lipid measure?
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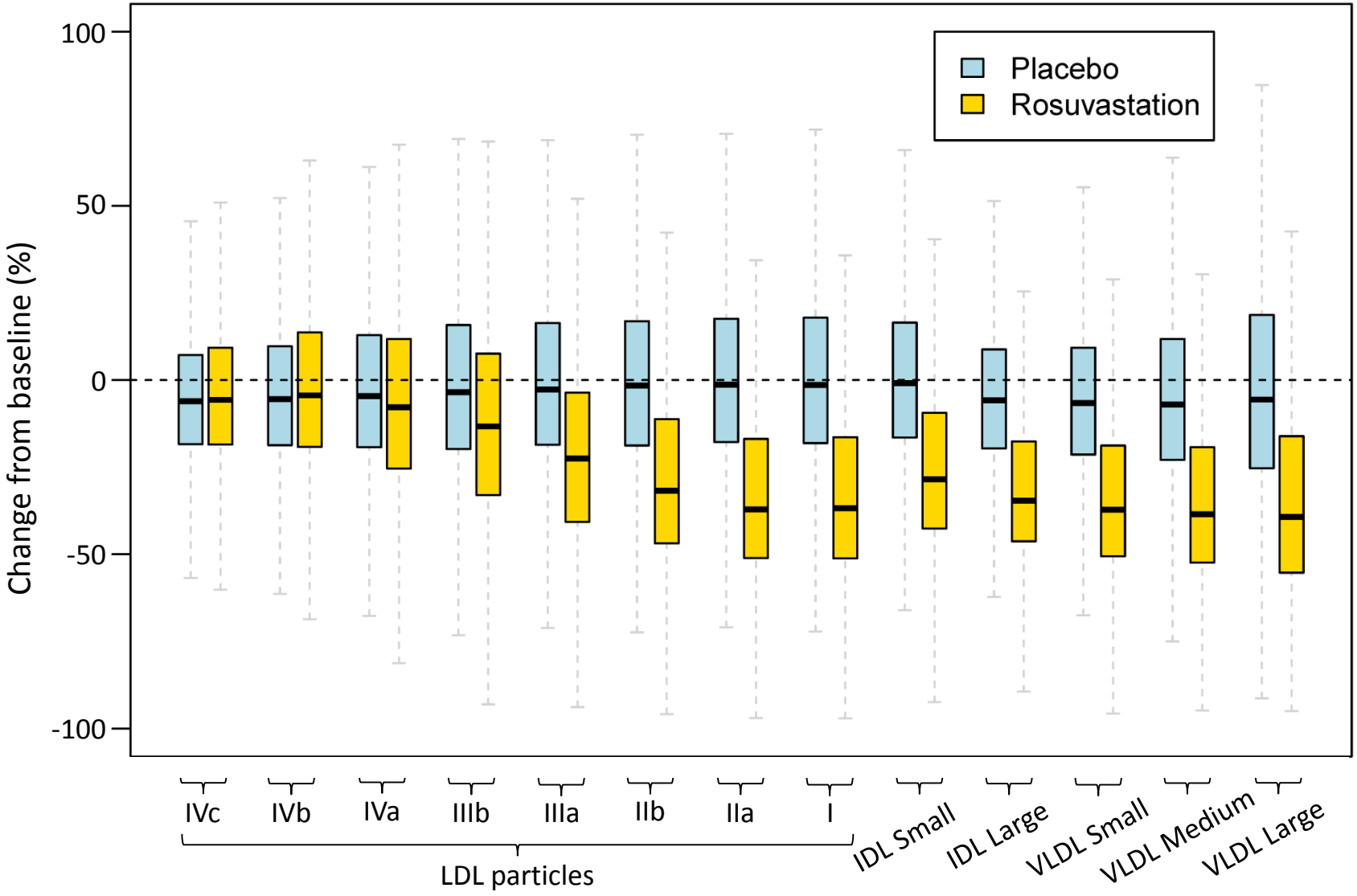
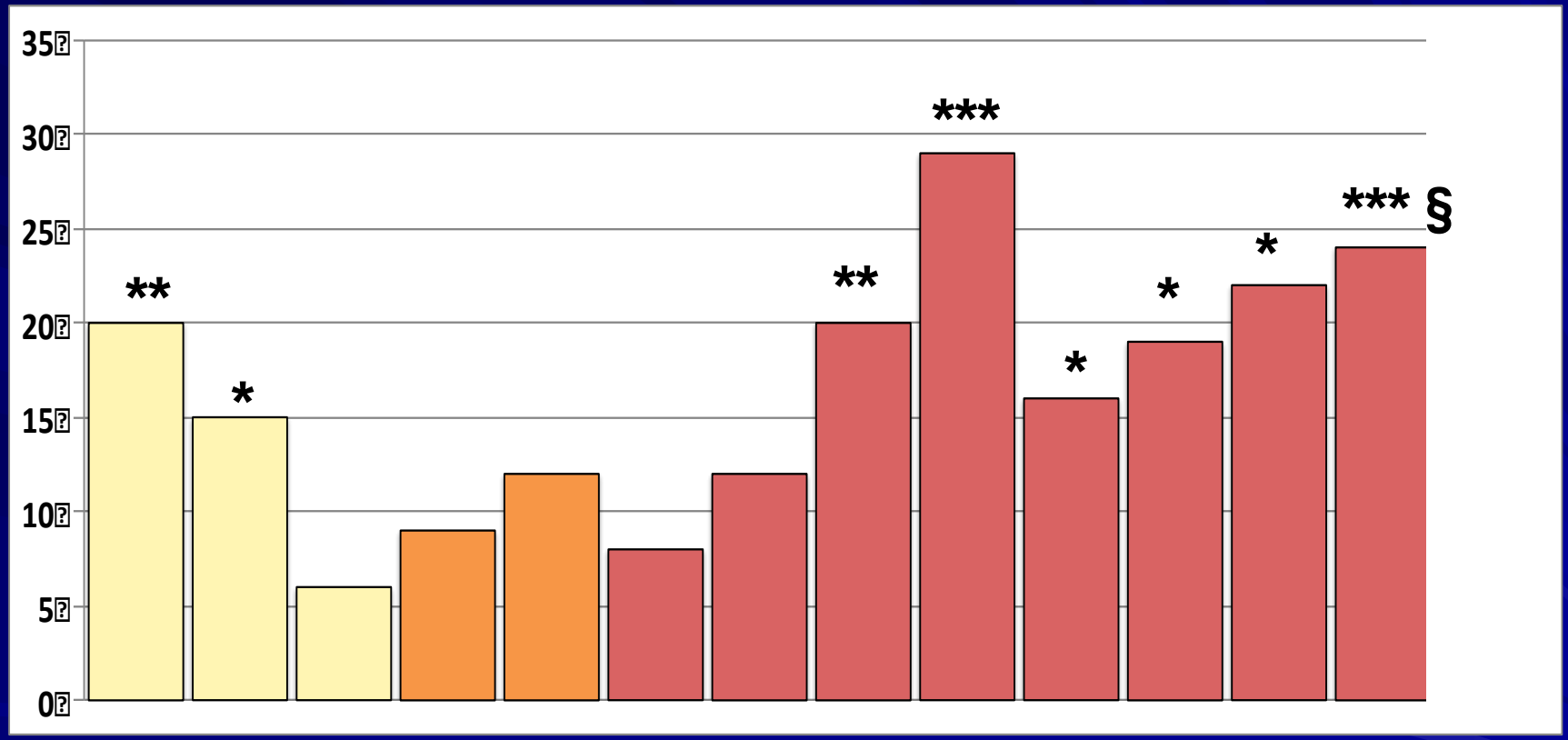
# JUPITER (N=9,548)

## Rosuvastatin had greatest effect on reducing larger LDL, IDL, and VLDL particles measured by ion mobility




Mora et al, *Circulation* 2015;132: 2220-9

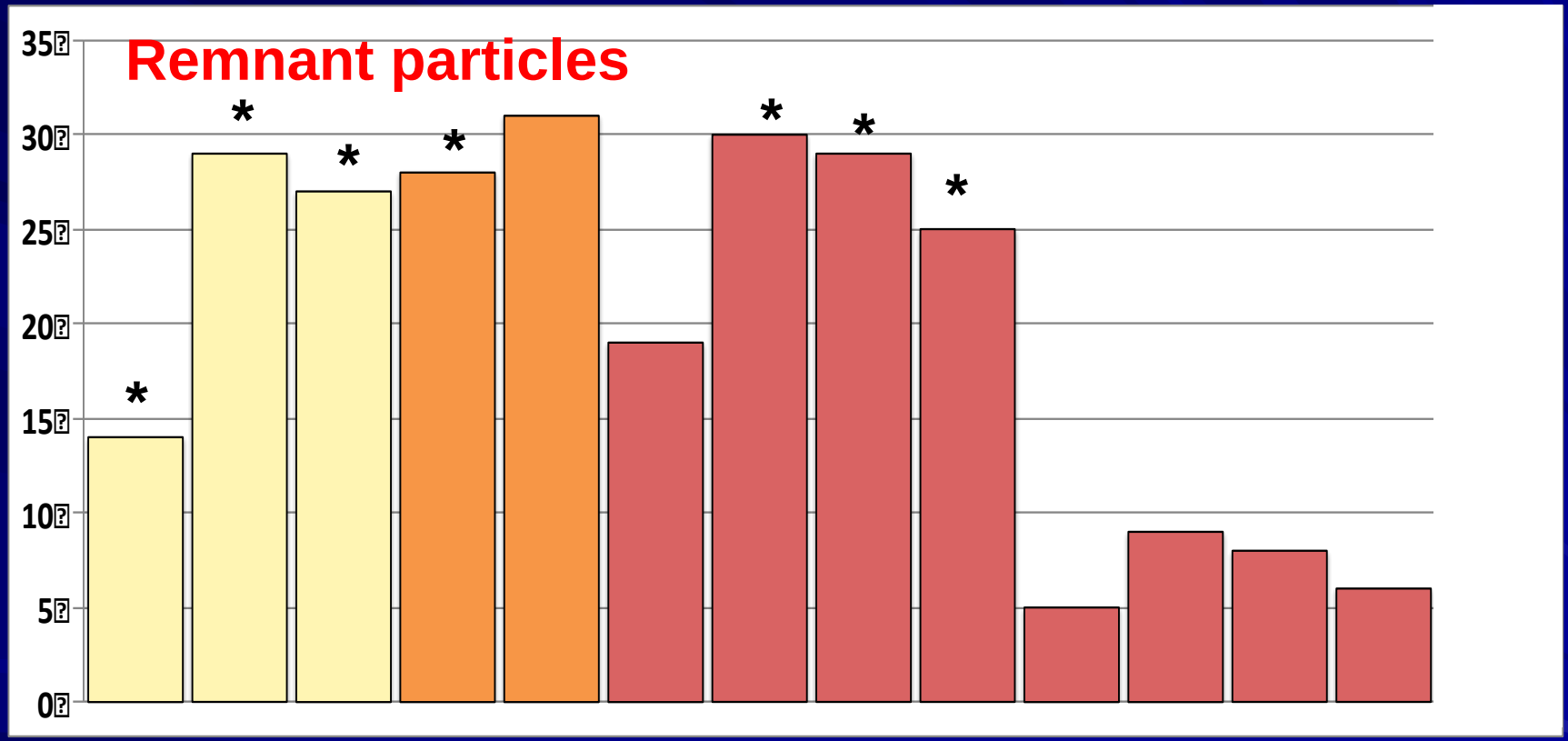
# Large VLDL-P and med-small LDL-P are associated with CVD in JUPITER placebo




*p < 0.05; ** p<0.01; ***p≤0.001;
§ adj. for standard lipids

*Mora et al. Circulation 132:2220, 2015*

# On statin therapy in JUPITER, particles spanning the VLDL remnant size range and extending across medium-small LDL are associated with risk ("residual risk")

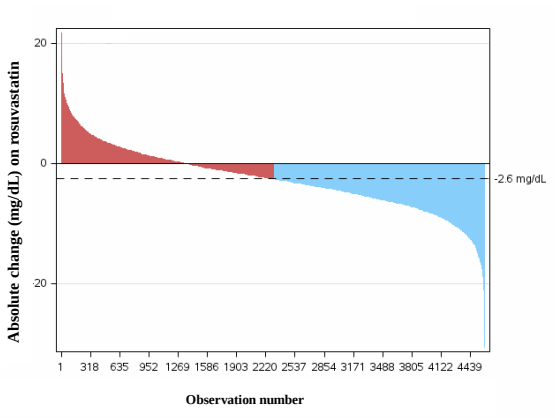


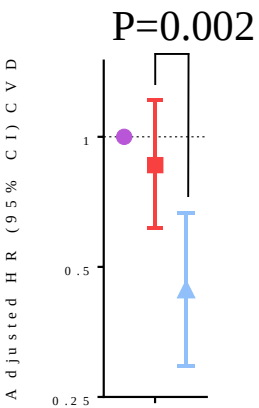

* P < 0.05

*Mora et al. Circulation 132:2220, 2015*

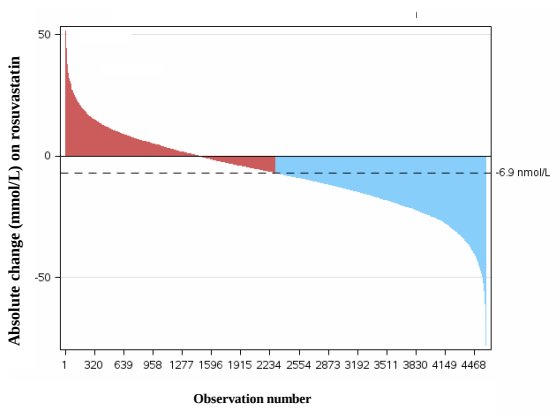
# Smaller VLDL lipoproteins and associated cholesterol could be potential therapeutic targets or risk markers after LDL-c lowering

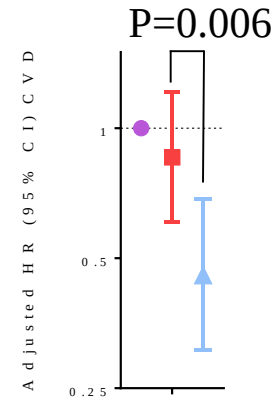
## VLDL-c



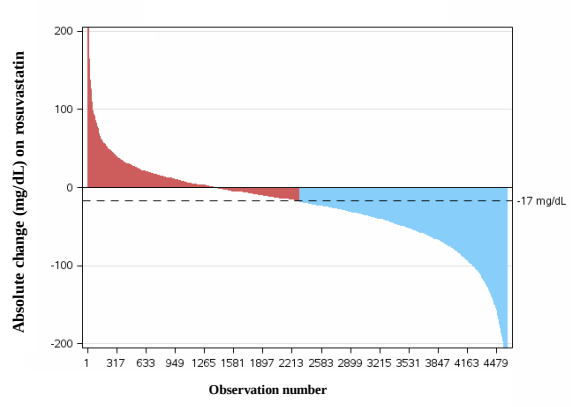



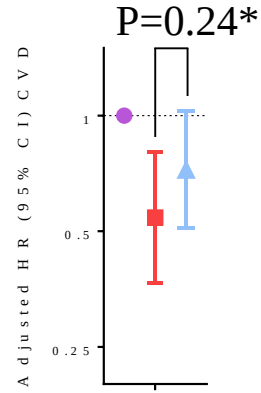

## Small VLDL-p (NMR)



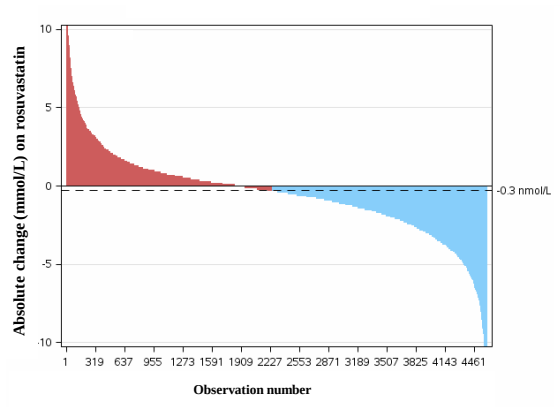



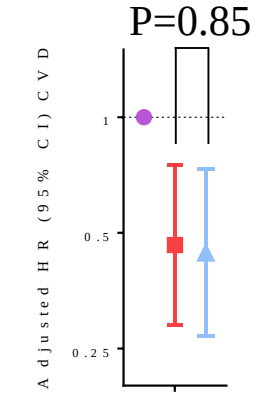

## Triglycerides



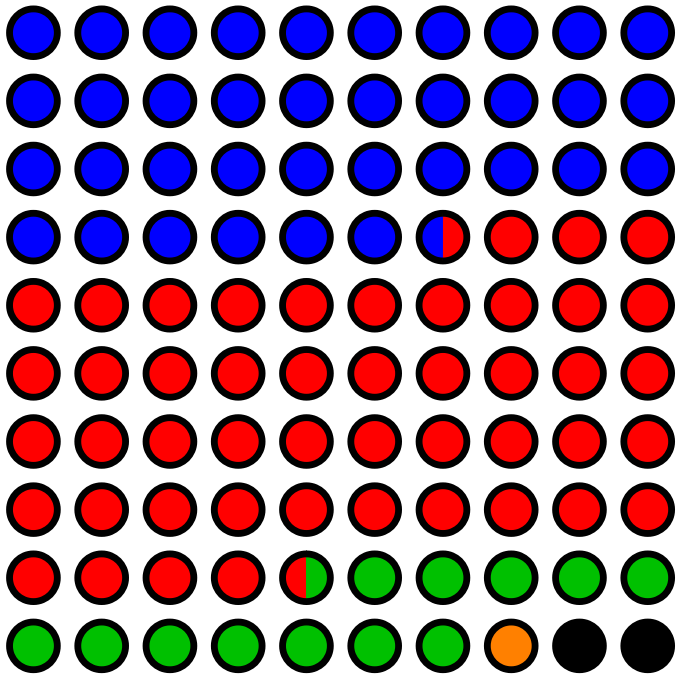

## Large VLDL-p (NMR)

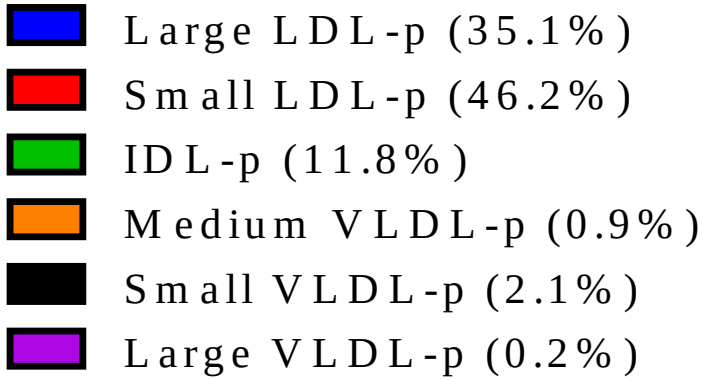



Lawler et al, JAHA 2017 Dec 9;6(12). pii: e007402. doi: 10.1161/JAHA.117.007402

# Baseline Atherogenic Lipoprotein Subclass Distribution NMR Spectroscopy (JUPITER)



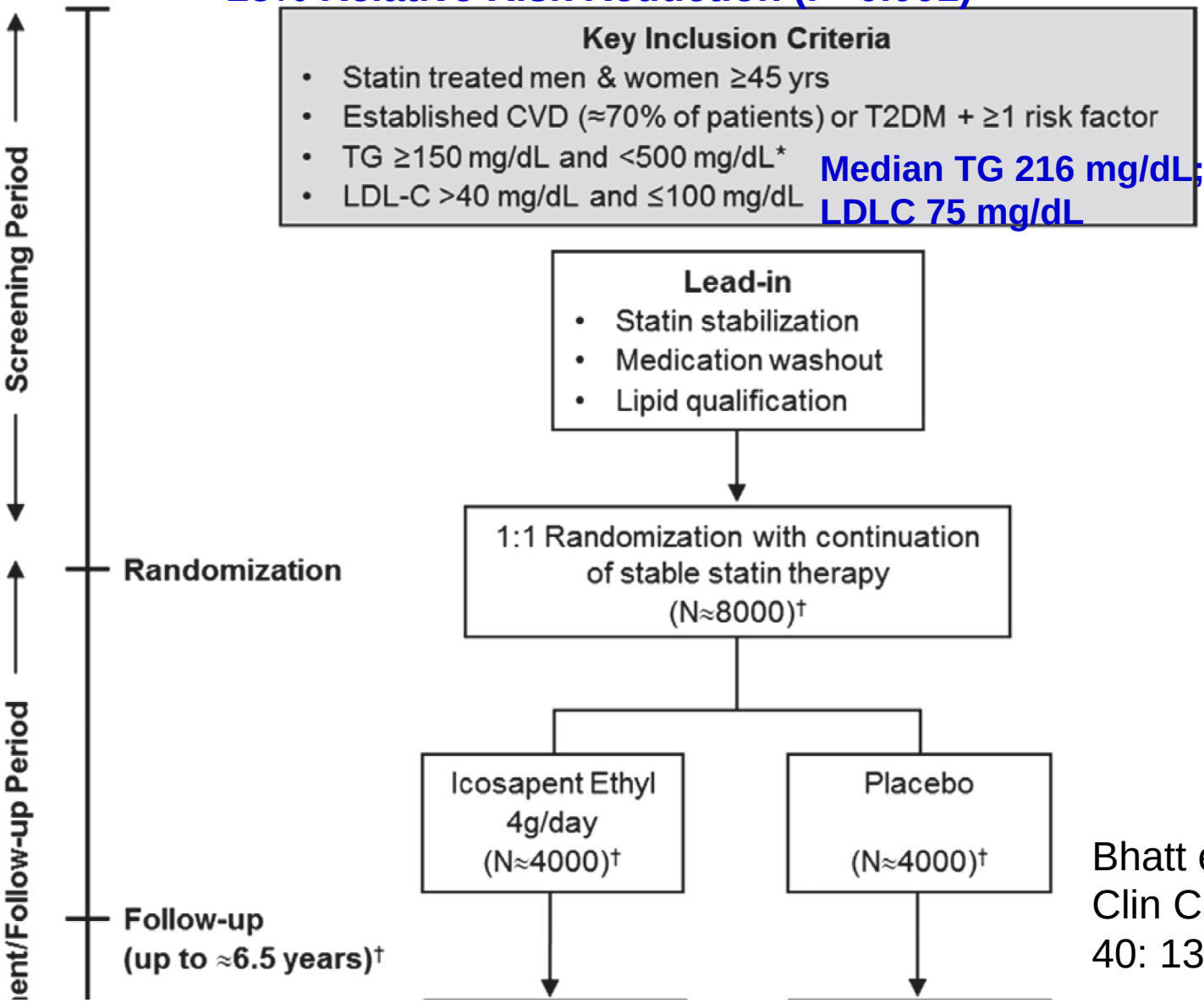



**Median Proportion of Atherogenic Lipoprotein Subclasses**
**(median subclass particle number/median total LDL + VLDL particles)**

# REDUCE IT (N=8,179)

## REDUCE-IT Cardiovascular Outcomes Study of Icosapent Ethyl (Vascepa®) Capsules Met Primary CVD Endpoint

## 25% Relative Risk Reduction (P<0.001)




Bhatt et al,
Clin Cardiol 2017
40: 138

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| ApoB | 122 | 90th% |
| $LDL\text{-}P_{IM}$ | 1450 nmol/L | 90th% |
| $LDL\text{-}P_{NMR}$ | 1800 nmol/L | 90th% |

LDL P IM LDL particle number measured by ion mobility (Quest Diagnostics)

LDLP NMR LDL particle number measured by nuclear magnetic resonance (LabCorp)

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| ApoB | 140 | >95th% |
| $LDL\text{-}P_{IM}$ | >1900 nmol/L | >95th% |
| $LDL\text{-}P_{NMR}$ | >1900 nmol/L | >95th% |

LDL P IM LDL particle number measured by ion mobility (Quest Diagnostics)

LDLP NMR LDL particle number measured by nuclear magnetic resonance (LabCorp)

# Summary

- Changing epidemiology of CVD → changing natural history/biology

- ApoB-carrying particles (LDL-P and triglyceride-rich lipoproteins) as mediators of CVD risk in patients with normal or low LDL-C (discordance)

# Summary

- Residual risk remains high, new approaches are required
- More precision lipid/lipoprotein phenotyping to better define risk pathways

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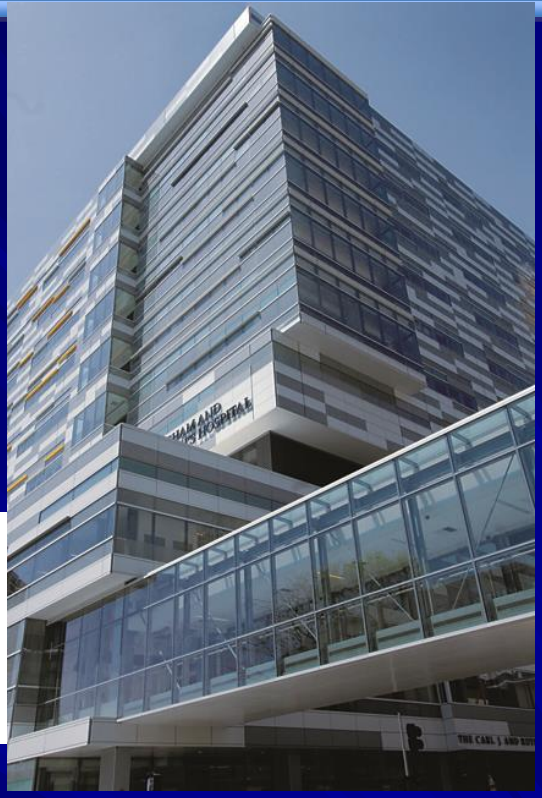
Akintunde Akinkuolie, MBBS

Nuria Amigo, PhD

Paulo Harada, MD



BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

## *Thank You*


Samia Mora, MD, MHS

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Patrick Lawler, MD

Amit V. Khera, MD

Sagar Dugani, MD PhD

Khendi White, MD

**Life. Giving. Breakthroughs.**

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