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Lipids

Post ADA / Post Endo Symposium

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22nd PostADA / PostENDO - Symposium

August 31st, 2023

Kursaal Berne

Agenda: LIPIDS

- LDL-Cholesterol - and what else?
- Tools for Risk Stratification
- Where are we going in the future?

LDL-Cholesterol: the lower the better!

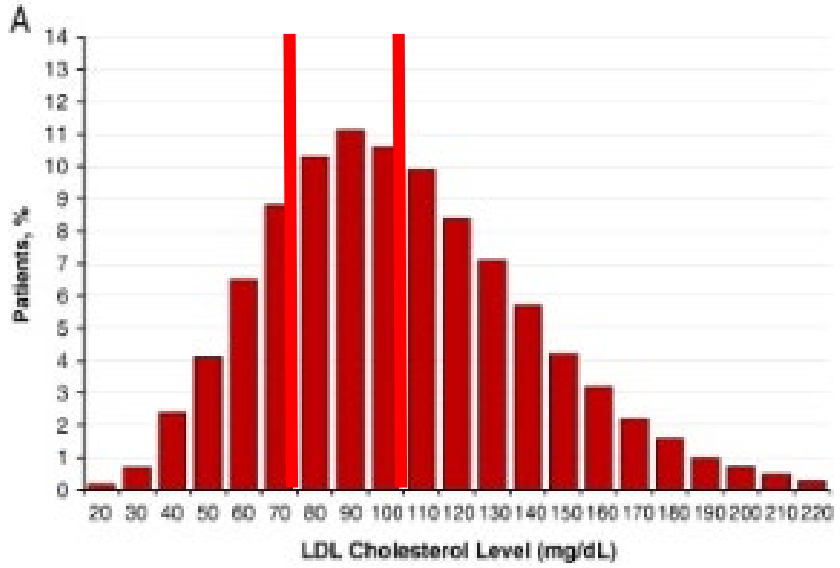
BUT …

Approximately 50% of patients with CHD event have LDL < 2.59 mmol/l

136‘905 patients hospitalized with CHD (541 hospitals from all census regions of US)

Approx. 20% had LDL-C < 1.81 mmol/l

➡ CHD event (first or recurrent) despite normal or slightly elevated LDL-C



Sachdeva et al. *AHJ.* 2009

Approximately 50% of patients with CHD event have HDL < 1.03 mmol/l

136‘905 patients hospitalized with CHD (541 hospitals from all census regions of US)

Only < 8% had HDL ≥ 1.81 mmol/l

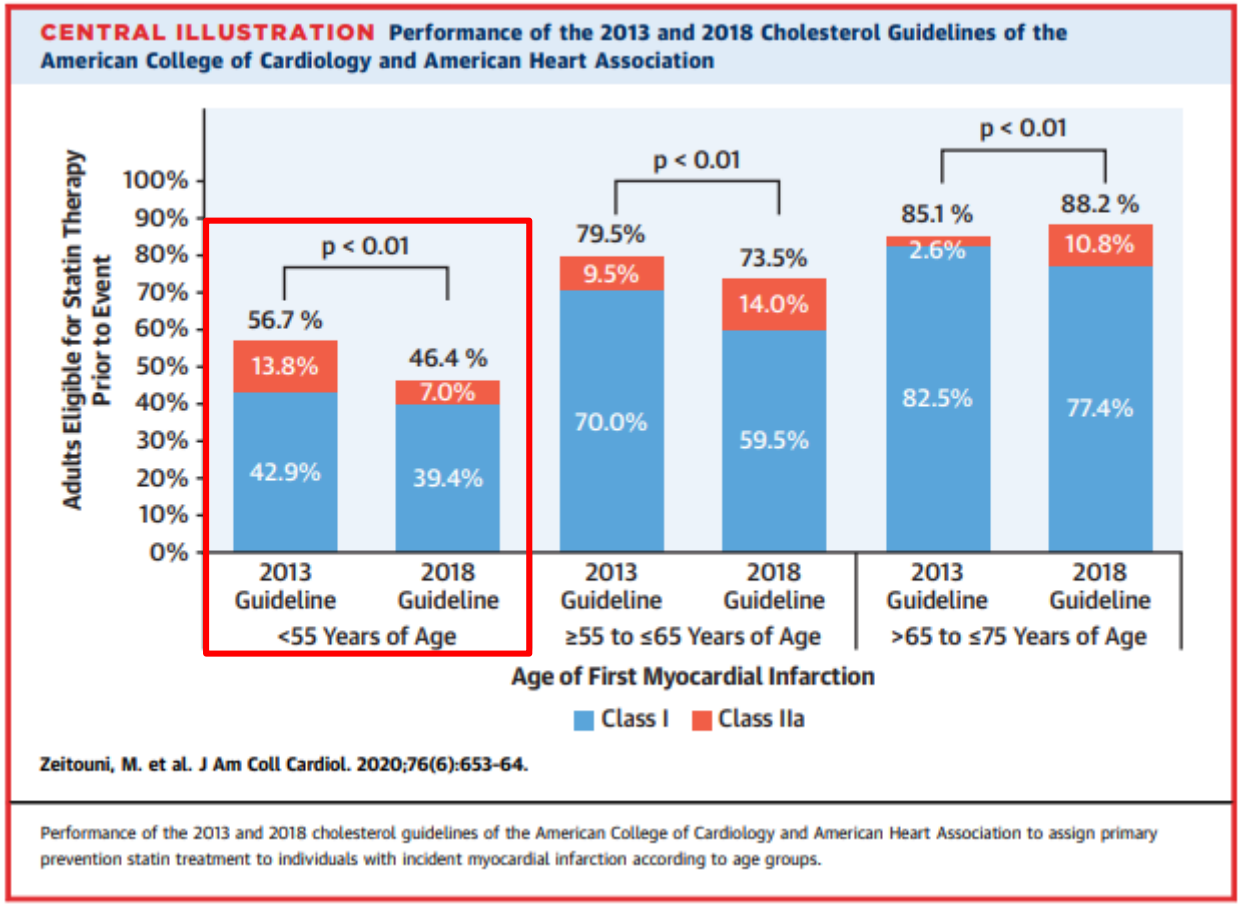
Ideal levels with LDL < 1.81 mmol/l and HDL ≥ 1.55 mmol/l in only 1.4 %

➡ For further reduction in cardiovaskular risk it may be necessary to identify and implement therapies that target other than LDL-goals and increase antiatherogenic HDL, respectively

Sachdeva et al. *AHJ.* 2009

2018 AHA/ACC Guideline identifies fewer younger adults eligible for statin therapy at the time of first MI

even though these young patients have a higher prevalence of cardiovascular risk factors (smoking, obesity, high LDL, low HDL) compared with their older counterparts

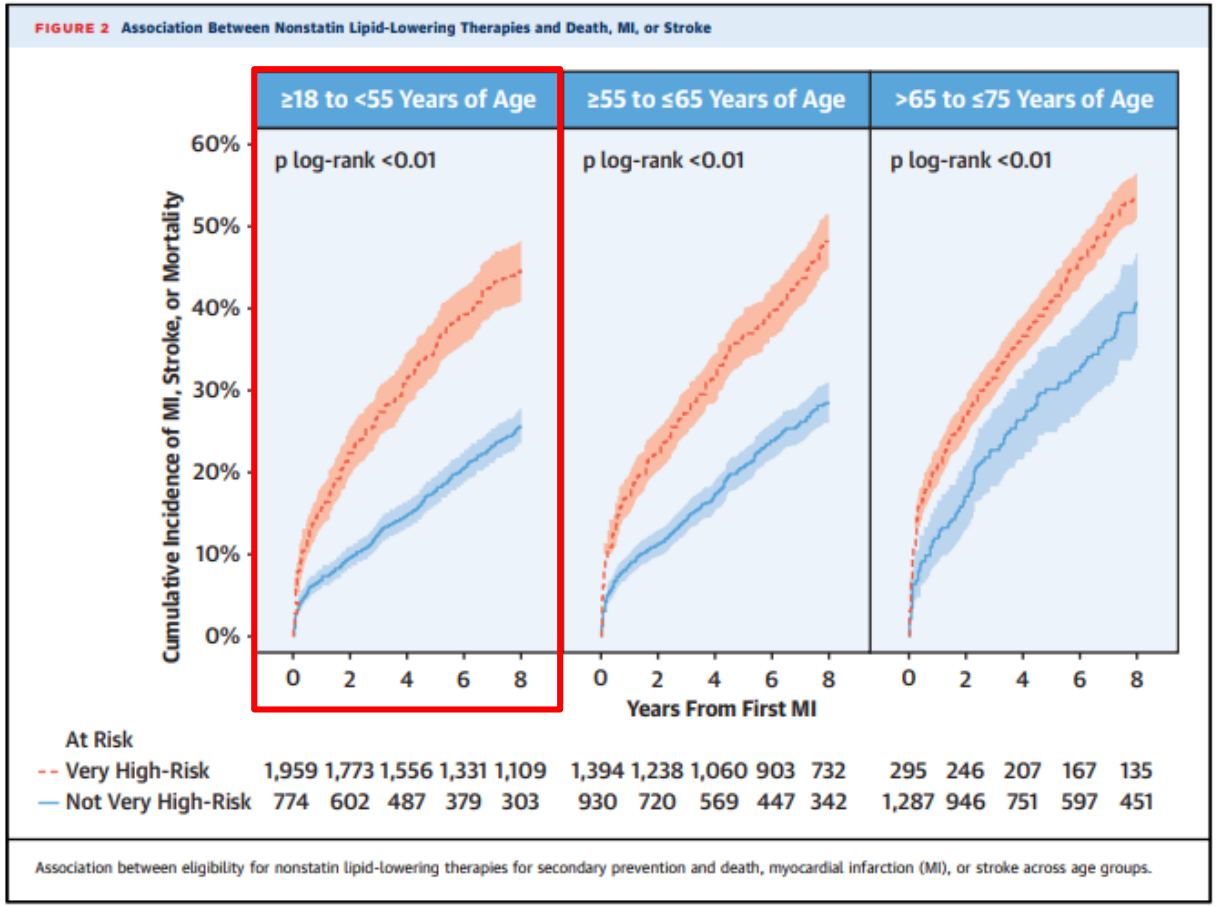


Zeitouni et al. *JACC*. 2020

Increased risk of major adverse cardiovascular events in individuals < 55 years

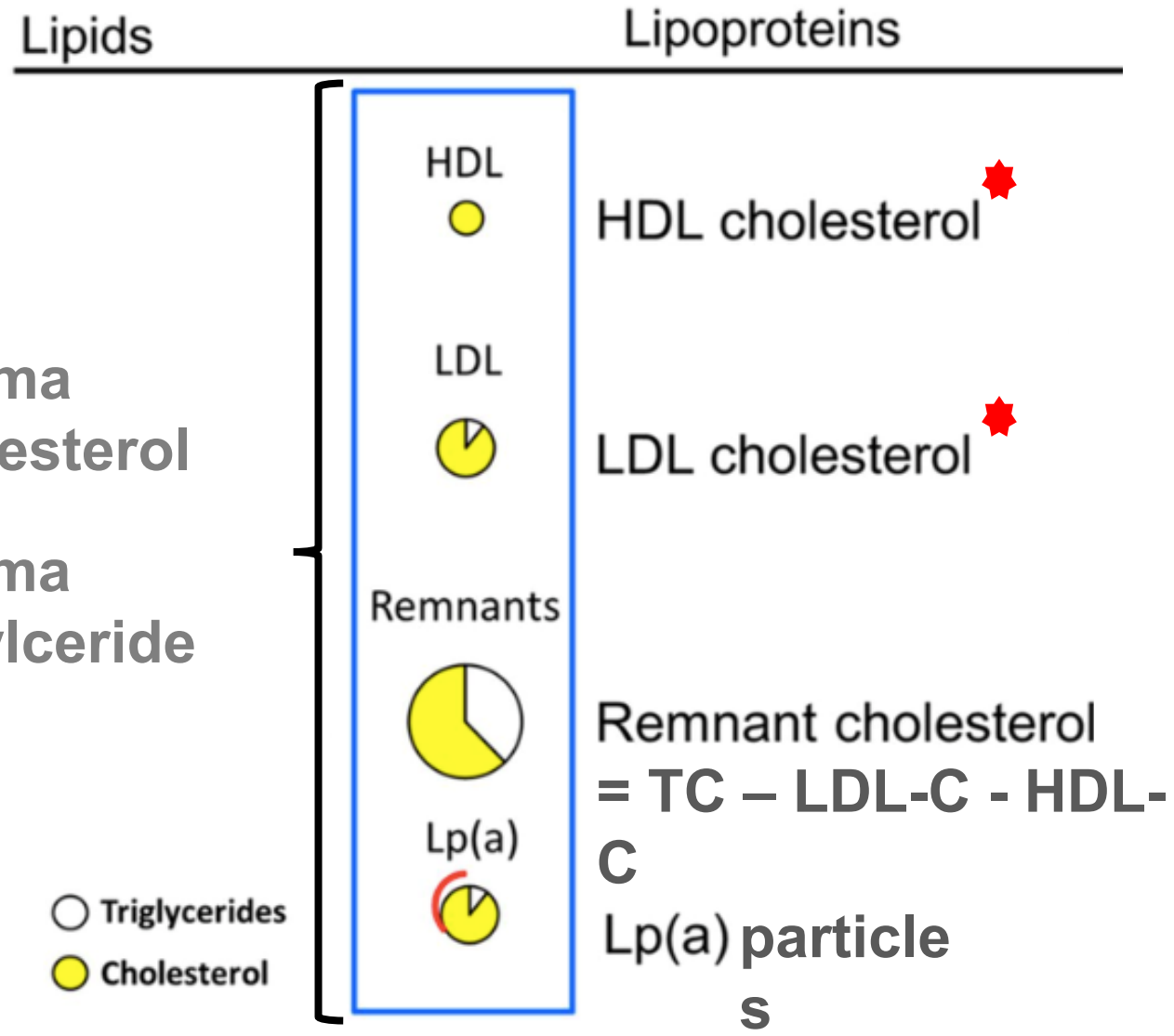
median follow-up of 8 years:

Younger patients with very high-risk criteria were at higher risk of all-cause death, MI, or stroke compared with patients without these criteria (44.6% vs. 25.9%; HR: 2.09, p < 0.001)



Zeitouni et al. *JACC* 2020

What do we measure?



Plasma Cholesterol

Plasma Triglycerides

HDL cholesterol

LDL cholesterol

Remnant cholesterol = TC – LDL-C - HDL-C

Lp(a) particles

Non-HDL-Cholesterol or ApoB

Standard lipid profile

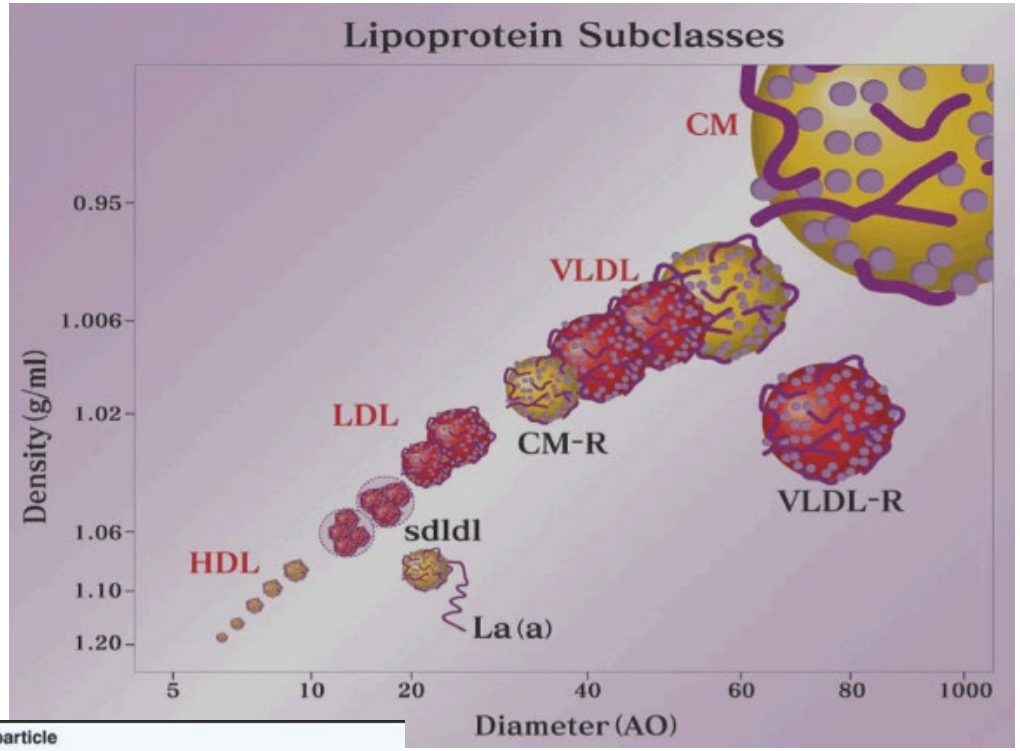
Nordestgaard et al. *Eur Heart Journal* 2016

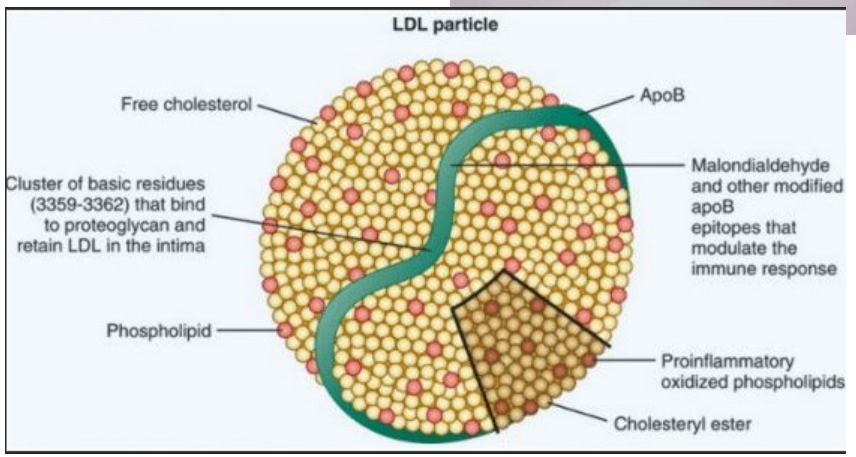
What else can we measure?

Lipoprotein and there subclasses

- Cholesterol in TG are carried by particles = lipoproteins

- **Non-HDL Cholesterol**
- **ApoB or LDL particle number**
- **Lipoprotein(a)**
- Lipoprotein Insulin Resistance (LPIR)



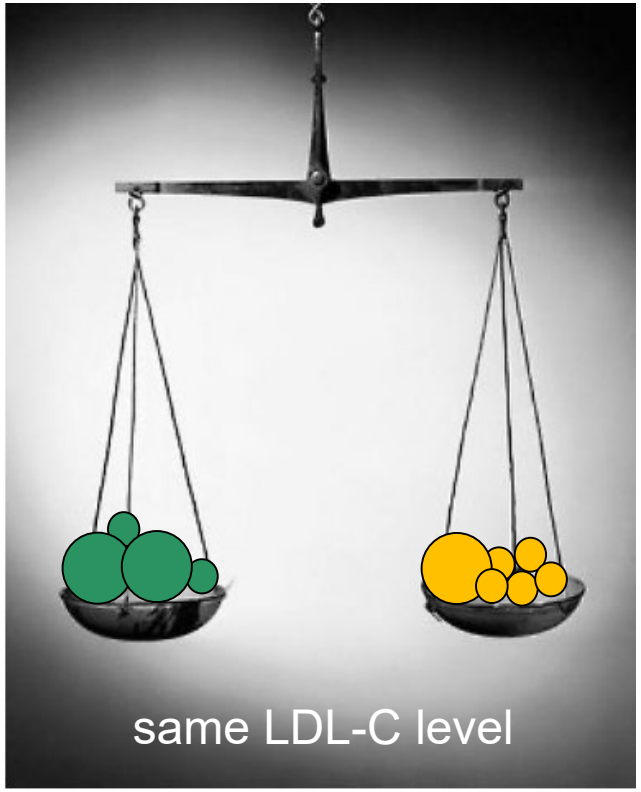


LDL-Cholesterol can be misleading: phenotyping!

- eg. in patients with metabolic syndrome (visceral adiposity, insulin resistance)

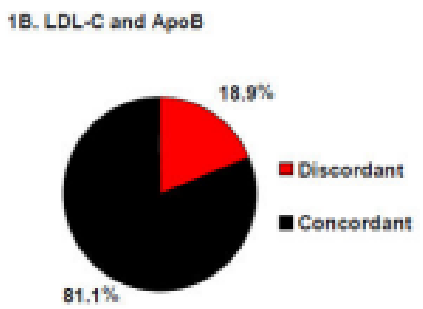
- Fewer bigger LDL particles = lower risk
- Many smaller LDL particles = higher risk

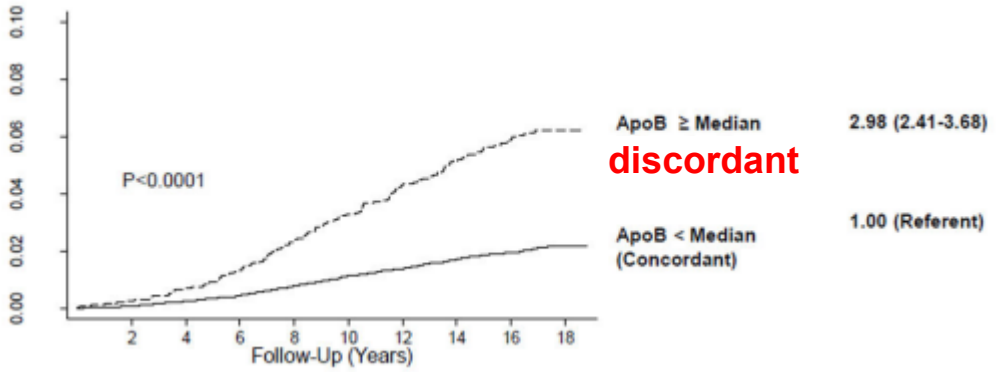
➡ Detection of discordance by measuring the atherogenic particles
= phenotype assessment



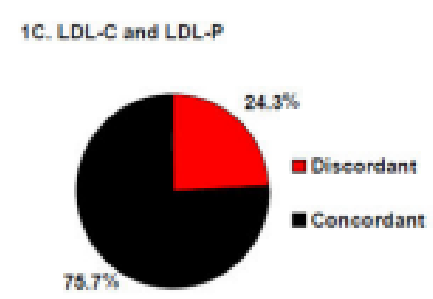
CHD events according to phenotypes

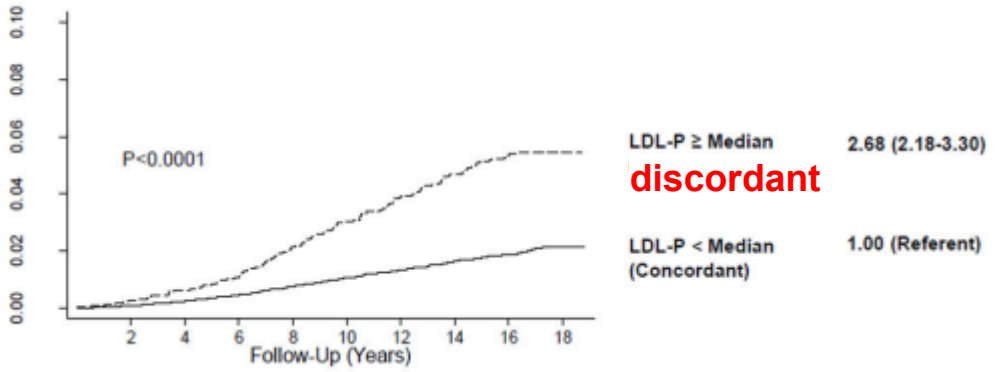
Discordant phenotype in up to 25% of general population





---- low LDL High ApoB
— low LDL, low ApoB





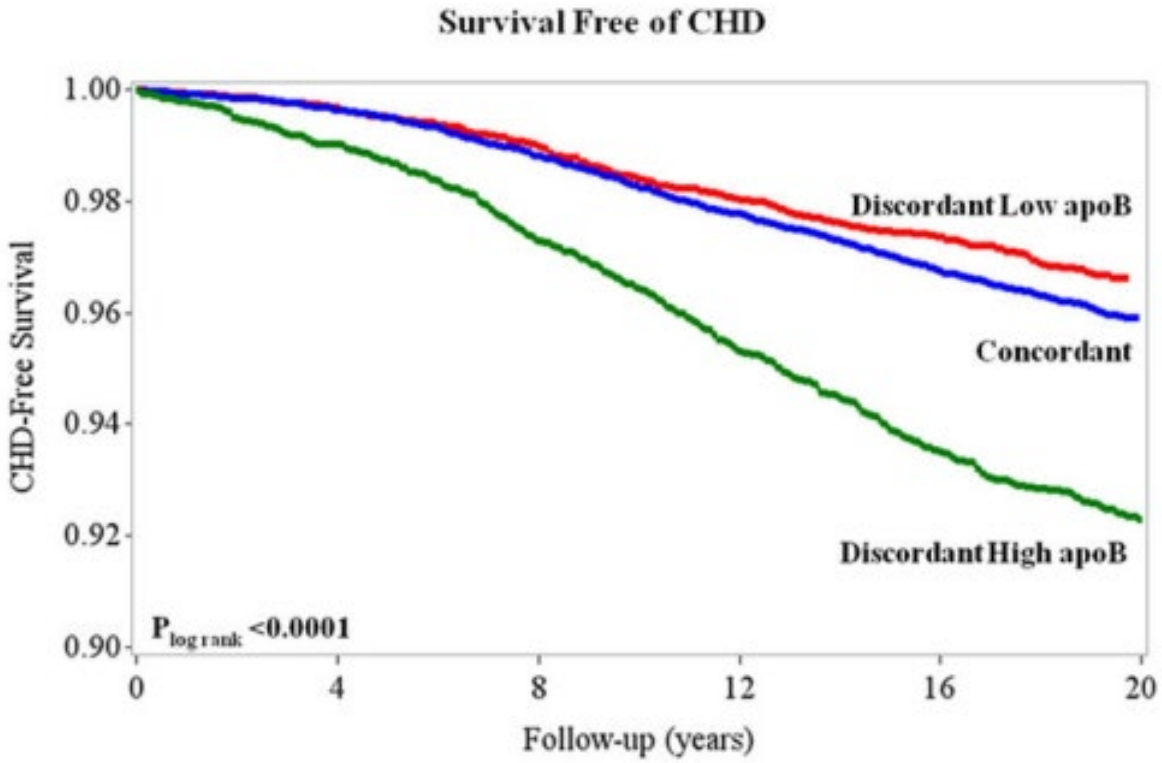
---- low LDL, High LPL-P
— low LDL, low LPL-P

Mora et al. *Circulation* 2014

CVD risk according to phenotypes

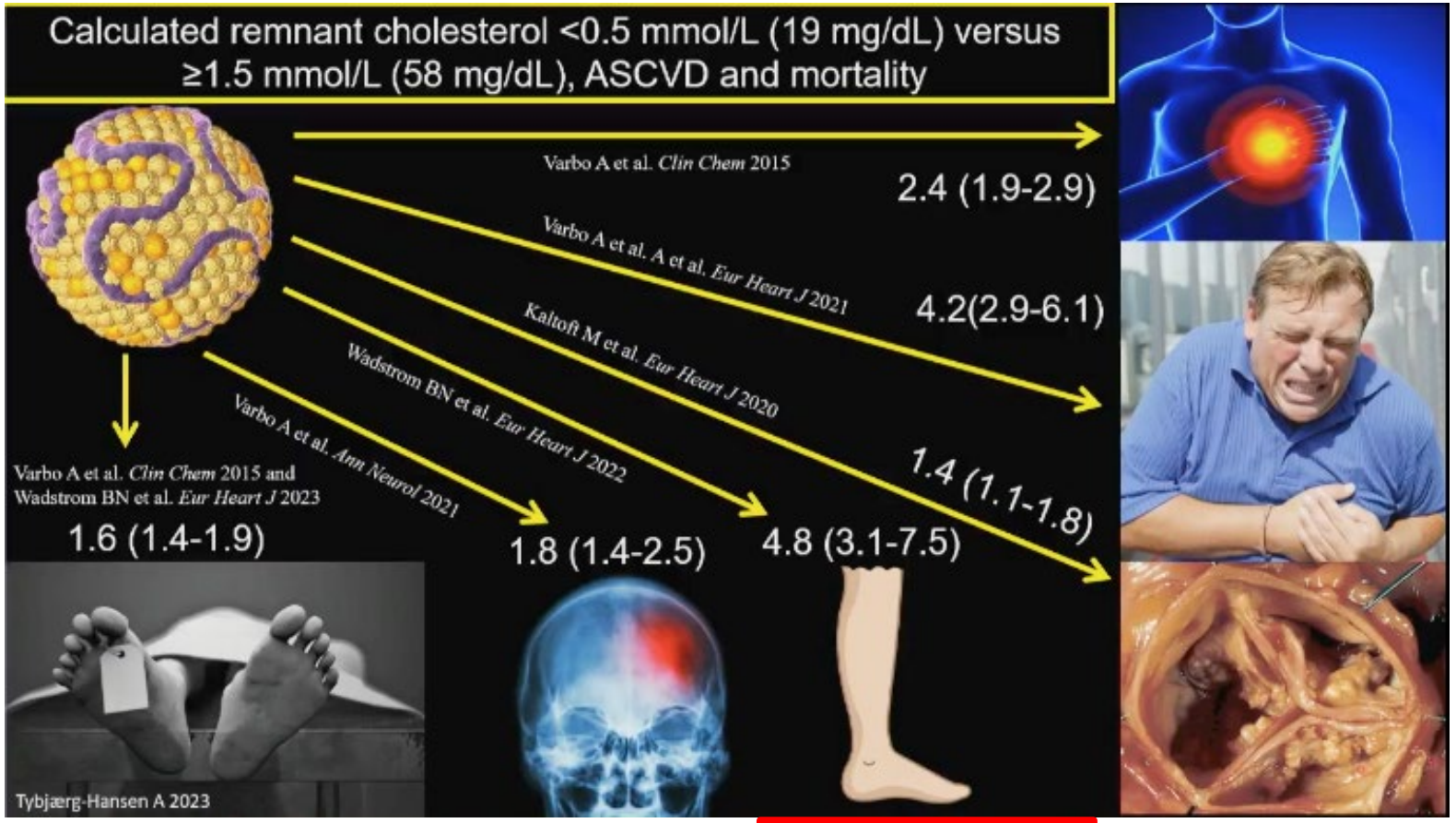
- among women with discordant concentrations of Non-HDL and apoB or LDL-P, CHD risk is more strongly associated with lipoprotein particle concentration (particularly apoB)

➡ CHD risk may be more closely related to the concentration of atherogenic lipoprotein particles rather than to the mass of cholesterol carried by them



Lawler et al. *Clinical Chemistry* 2017

Remnant Cholesterol is associated with ASCVD and mortality



Ischemic heart disease

Myocardial infarction

Aortic valve stenosis

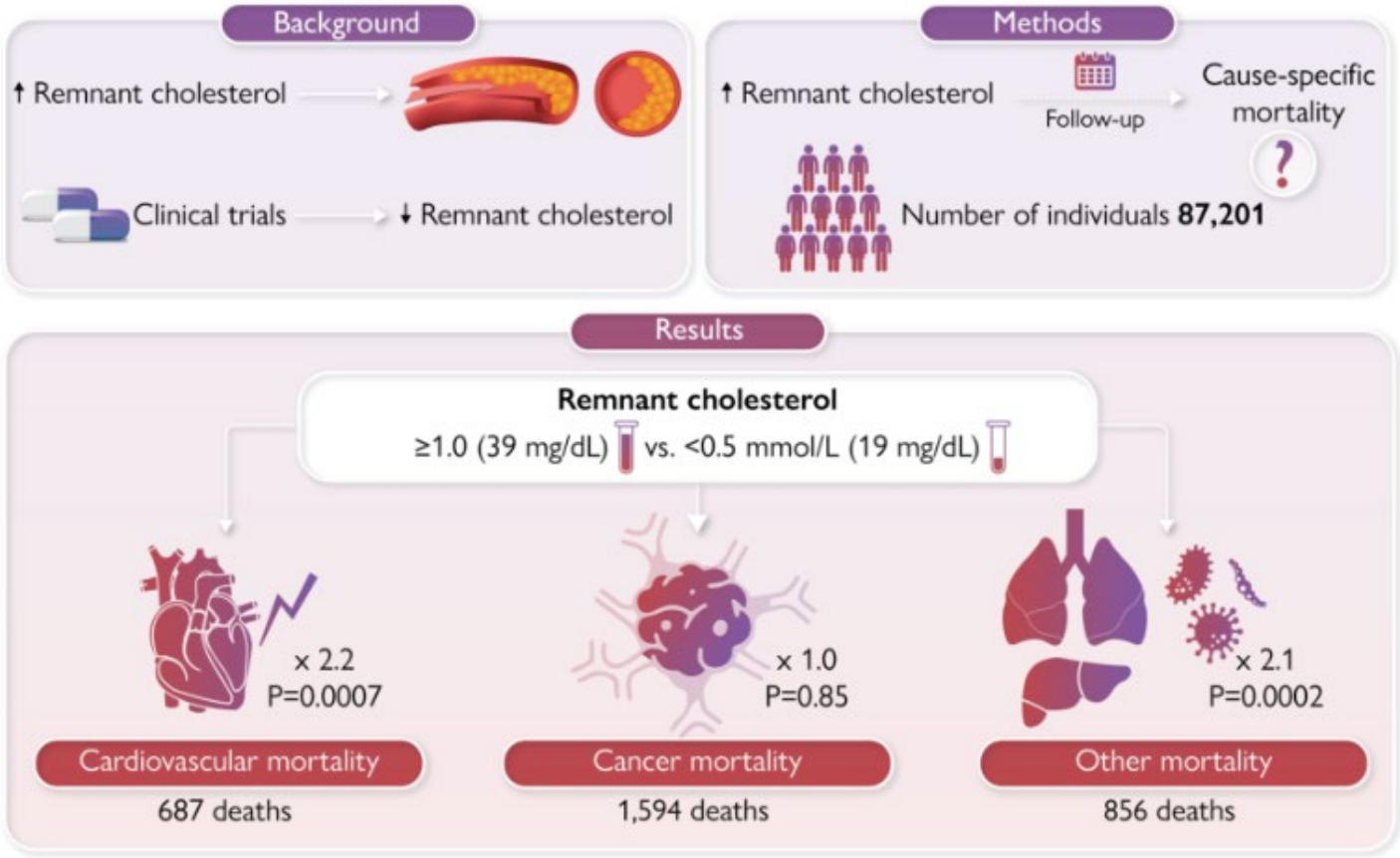
Total mortality

Ischemic stroke

Peripheral arterial disease

Slide from ADA 2023, „Do Triglycerides Contribute to Residual Cardiovascular Disease Risk in Diabetes?“, Anne Tybjaerg-Hansen

Remnant Cholesterol and Plasma Triglycerides are associated with 2-fold increased mortality from cardiovascular and other causes

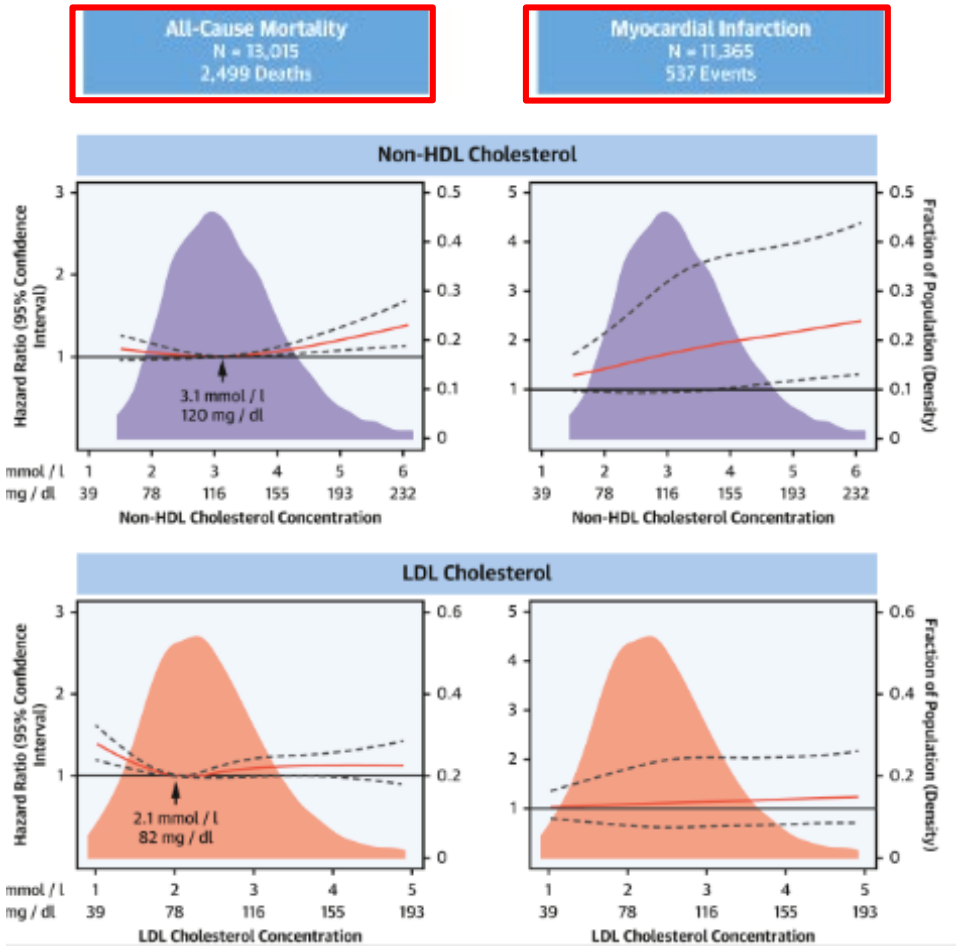


Remnant cholesterol ≥ 1 mmol/l in 22%

Plasma triglycerides ≥ 2 mmol/l in 28%

Wadström et al. *Eur Heart J* 2023

Remnant Cholesterol add to the risk of all-cause mortality and myocardial infarction in statin-treated individuals



Johannesen et al. *J Am Coll Cardiol* 2021

Even more evidence…

- Remnant Cholesterol as an independent risk factor for cardiovascular outcomes in primary prevention
- Castaner et al. *J Am Coll Cardiol.* 2020.
  (HR 2.69, p = 0.01, for remnant-C >0.8 mmol/l and LDL ≤2.6 mmol/l)
- Quispe et al. *Eur Heart J.* 2021.
  (HR 1.43, for remnant-C >0.6 mmol/l and LDL ≤3.3 mmol/l)

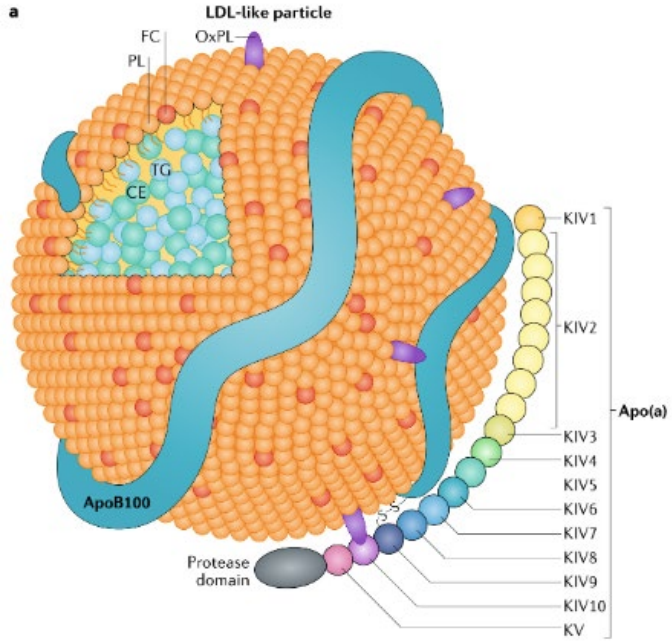
What about Lipoprotein(a)?

- LDL-like Lipoprotein with covalently bound Apo(a)

- Pro-atherogenic characteristics
  - Upregulation of cytokines and chemokines in monocytes/macrophages
  - Endothelial dysfunction
  - Smooth muscle cell migration and proliferation

- Promotion of valvular interstitial cell calcification

- Hereditary CVD risk factor (~ 90% genetically determined)
  - Lp(a) appears to modify ASCVD risk independent of race (Aniruddh et al. *Arterioscler Thromb Vasc Biol.* 2022.)

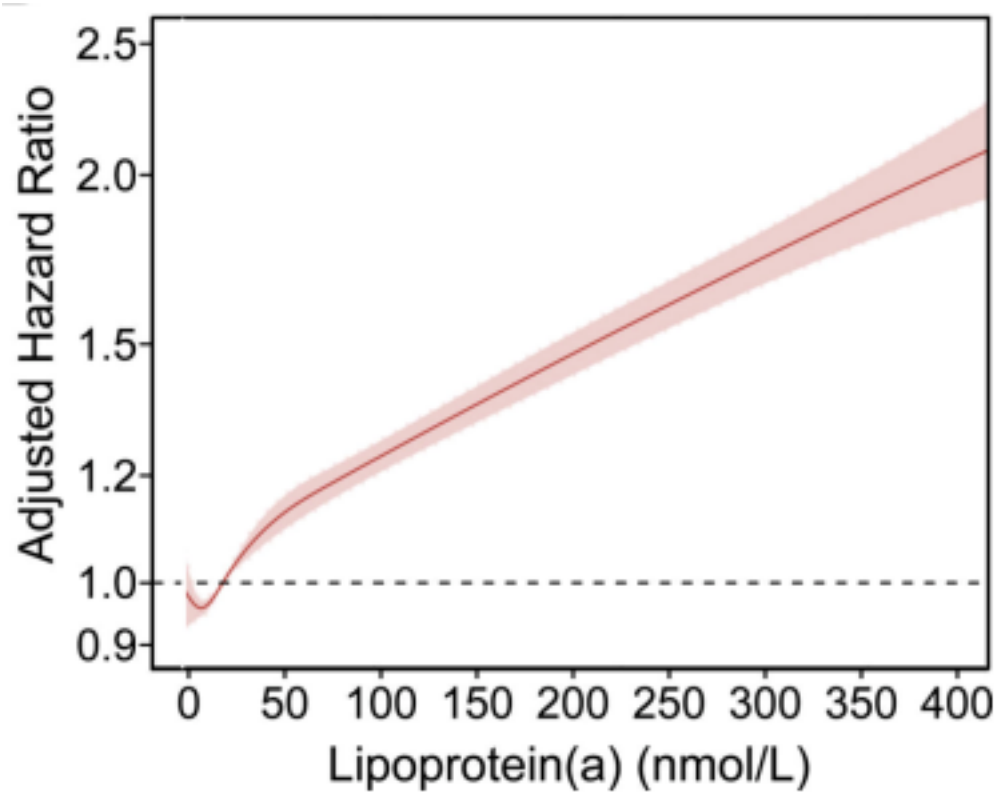


Boffa et al. *Nat Rev Cardiol* 2019

Lipoprotein(a) concentrations predict incident ASCVD

- 11% higher ASCVD risk per 50 nmol/l increment in lipoprotein(a) concentration

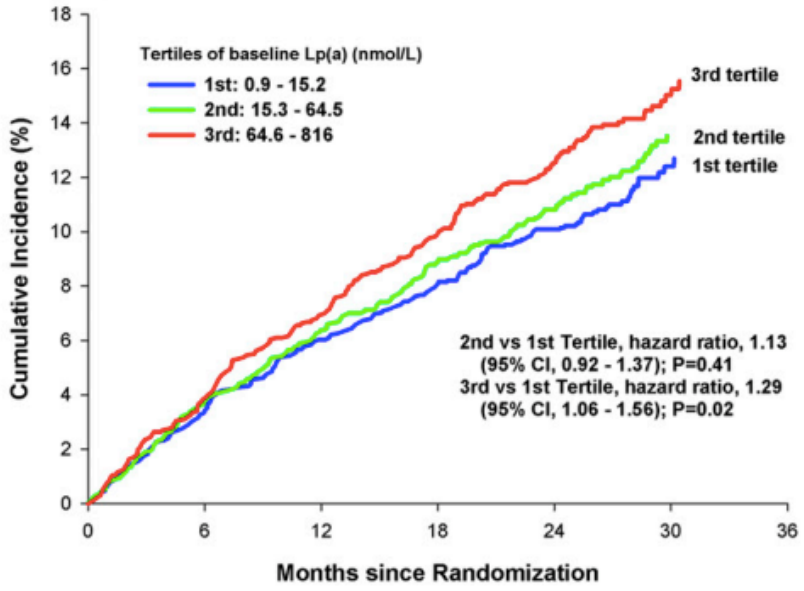
- minimal attenuation of risk when additionally adjusting for: hypertension, diabetes, smoking, total cholesterol and history of prior cardiovascular disease



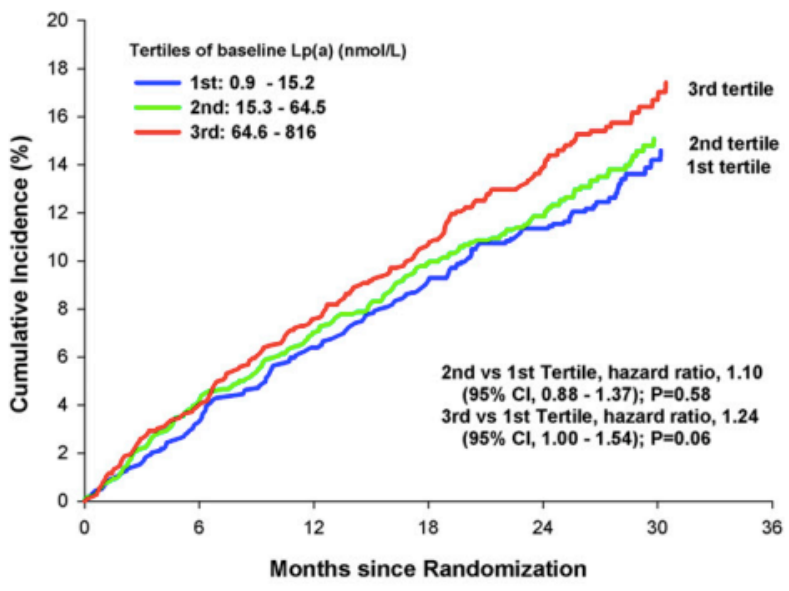
Aniruddh et al. *Arterioscler Thromb Vasc Biol* 2022

Post Hoc Analysis of ACCELERATE

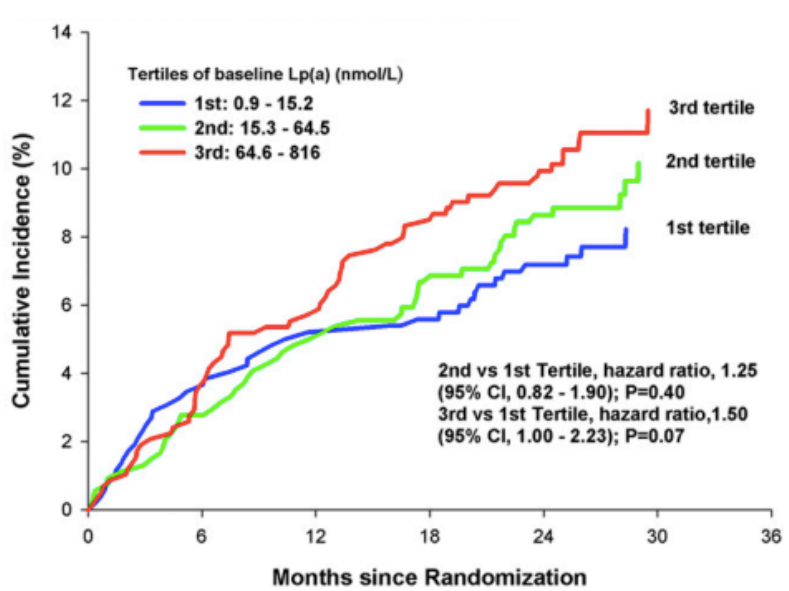
Overall population
N = 5121



Diabetics
N = 3482



Non-Diabetics
N = 1639



- Lp(a) is an independent risk factor with higher levels predicting ASCVD risk in both diabetics and non-diabetics (with established ASCVD)

Nishant et al. *Diabetes care* 2020

Whom should we screen for phenotype discordance?

- Diabetes
- Metabolic Syndrome
- Visceral obesity
- Higher hsCRP
- Higher Triglycerides
- Lower LDL-C
- Higher age
- Statin treatment

Wilkins et al. *J Am Coll Cardiol*. 2016

Discordance is present in up to 20-25% of the population and when present, risk is more strongly associated with particle concentration than cholesterol

Mora et al. *Circulation* 2014

Primary ASCVD prevention: Tools for risk stratification

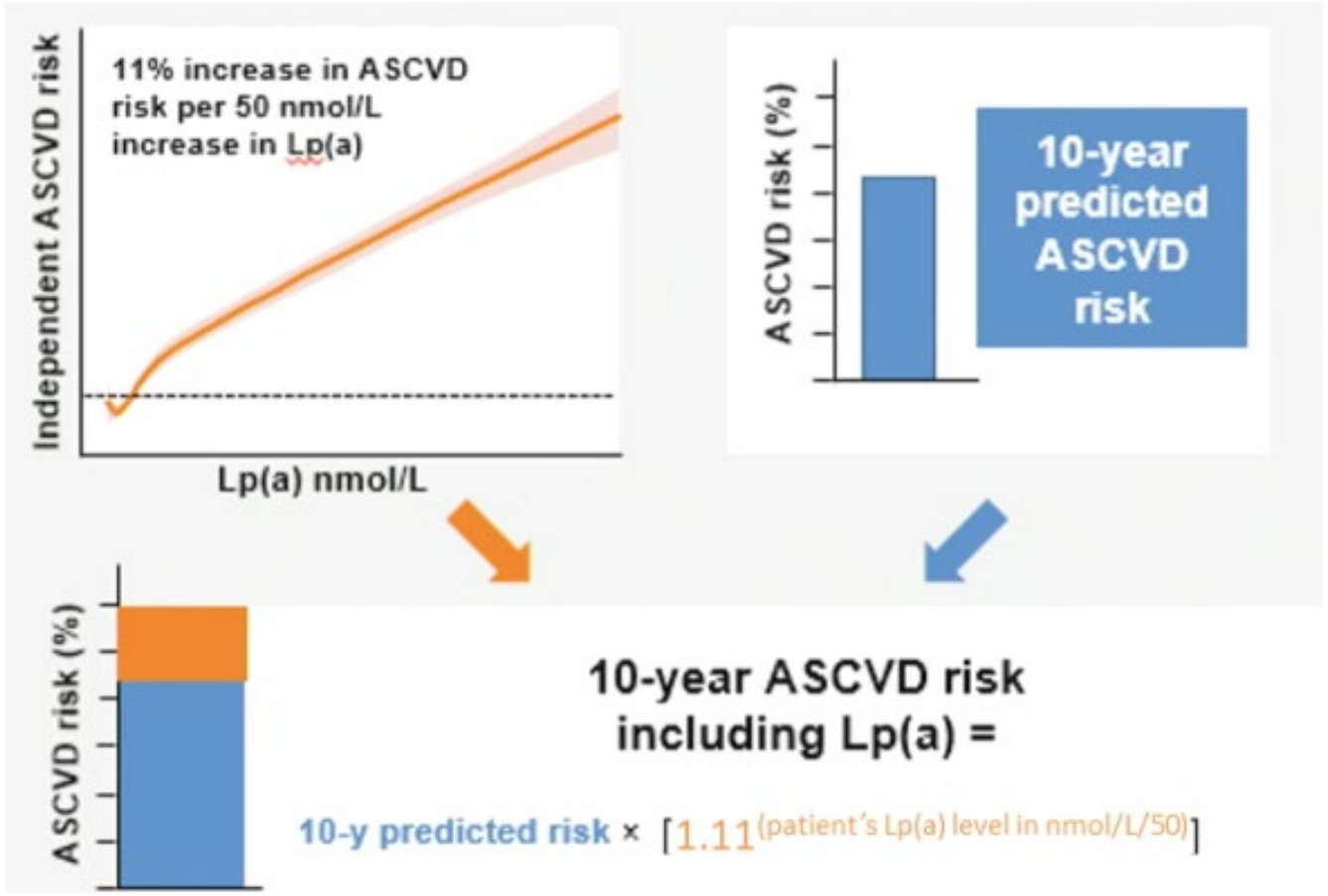
- **Lipoprotein Insulin Resistance (LPIR) Score**
  - not yet in the guidelines
  - phenotype that represents the atherogenic dyslipoproteinemia
  - LPIR improved T2D risk classification and may guide early and targeted prevention strategies

- **Coronary Artery Calcium (CAC)-Score**
  - reclassification of ASCVD risk in diabetics with absence of Coronary Calcium (CAC-Score = 0)?
  - But: diabetics as high(er) risk individuals

- **Lipoprotein(a)**

- **ApoB**

Comprehensive ASCVD risk assessment with Lipoprotein(a) as a risk modifier



Reyes-Soffer et al. *AHA* 2022

Guidelines: Lipoprotein(a)

„once in a lifetime“

Should We Test for Lp(a) in Diabetics?

	AHA/ACC	ESC	NLA	AACE	CCS	EAS
	2018	2019	2019	2020	2021	2022
All individuals to identify those at high CVD risk		X			X	X
Family/personal history of premature ASCVD	X	X	X	X	X	X
Specific Indications			To aid in decision making for statins in those with intermediate ASCVD risk. To identify a possible cause for less than anticipated pharmacologic LDL-C lowering. To identify those at risk for progressive aortic stenosis.	Individuals with South Asian or African ancestry, Individuals with a 10 year ASCVD risk ≥ 10%, Patients with statin resistance. Patients with a personal or family history of aortic stenosis		Youth with a history of ischemic stroke and no other identifiable risk factors.

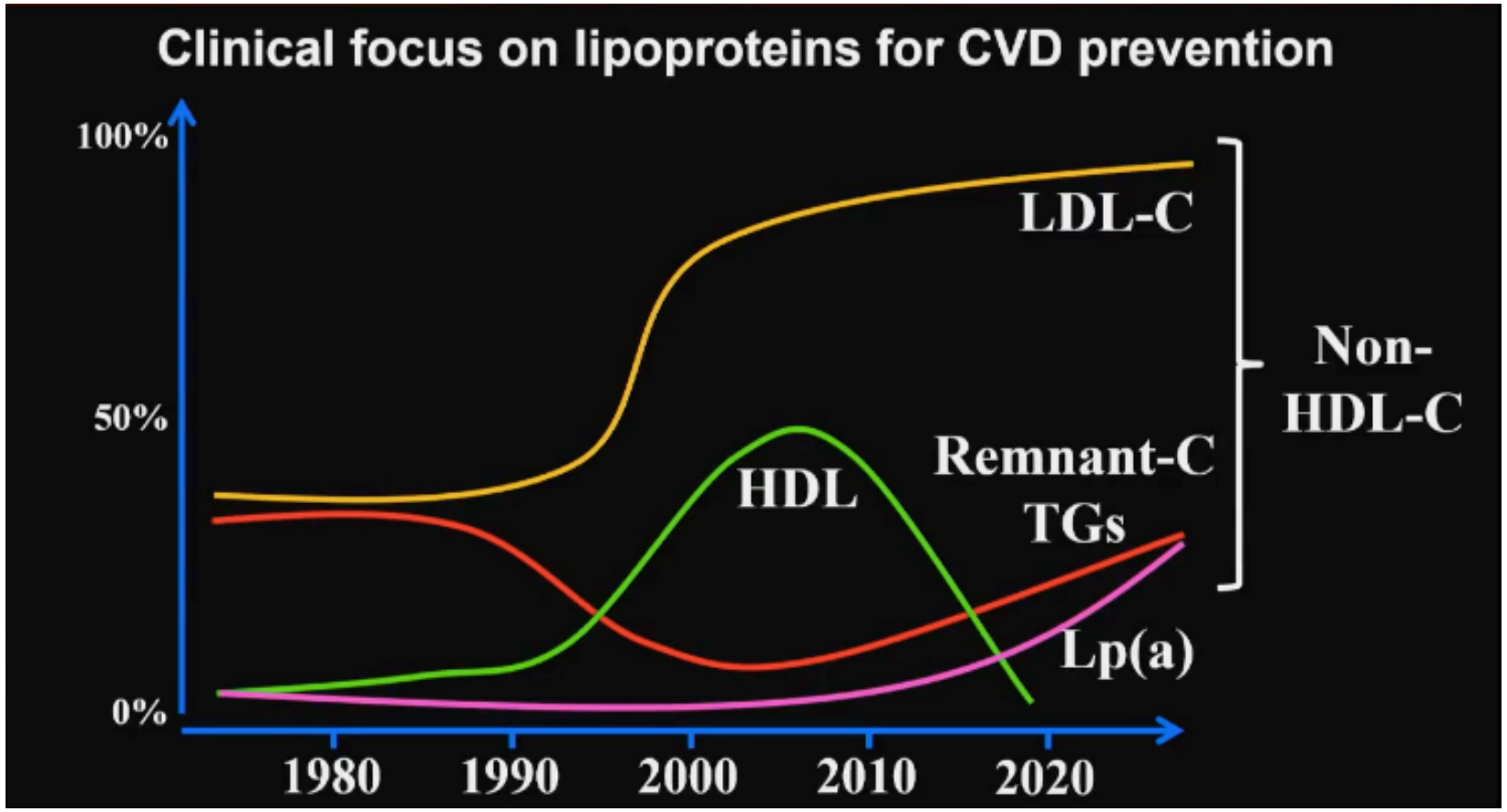
Slide from ADA 2023, „What is the Evidence That Lp(a) Is Significant in Diabetes Risk Assessment?“, Calvin Yeang

EAS/ESC Guidelines: Recommendation for ApoB measurement in combined hyperlipidemias

Upgrades	
2016	**2019**
Lipid analyses for CVD risk estimation	**Lipid analyses for CVD risk estimation**
ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG.	ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.

ESC/EAS Guidelines, *Eur Heart Journal* 2019

Where are we going in the future?



Nordestgaard et al. *Circ Res* 2016

Take Home Messages

- Lipids: Screen and treat early
- LDL-Cholesterol: The lower the better
  - Lowering total atherogenic particles is even better, diabetic dyslipidemia
- LDL-Cholesterol can be misleading (Discordance)
  - Measurement of ApoB (or LDL particle) in patients with normal or low LDL-cholesterol
- Lp(a) and remnant cholesterol as an independent risk factor for ASCVD risk in diabetics
- Tools for ASCVD risk stratification (LPIR Score, CAC Score, Risk Calculator)
- Growing number of treatment options: Statins, bempedoic acid, icosapent-ethyl, PCSK9-inhibitor, ANGPTL3, APOC3…


Thank you!

Questions?