How the new guidelines are approaching the RR

Speaker: Abdullah Shehab (UAE)

Moderator: Wael Al Mahmeed (UAE)

Educational objective: Recall guideline recommendations on cholesterol reduction and management of other drivers of residual risk

2020 MIDDLE EAST SUMMIT ON RESIDUAL CARDIOVASCULAR RISK

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Which of the following statements accurately reflects guideline recommendations on RR reduction?

Select all that apply

A. Statin-based therapy should be provided to all patients at risk of ASCVD
B. Statins should be prescribed at the lowest possible dose and titrated upwards
C. If statins are insufficient to achieve target LDL-C, it should be discontinued and replaced with ezetimibe and a PCSK9 inhibitor
D. If targets are not achieved with statins at a maximally tolerated dose, consider adding ezetimibe and a PCSK9 inhibitor in a stepwise approach until target is reached

Disclosures

Abdullah Shehab

- None

Wael Al Mahmeed

- None

A 55 yo male with HTN, DM II, and CAD follow up visit

- Two admissions for NSTEMI over the last 14 months and DES 3 months ago for second time

- Off statin for several months at the time of his last admission

Lipid panel during last admission and 3 months after

- Total Cholesterol: 205
- Triglycerides: 145
- HDL: 33
- LDL-C 120

Discharge medications:

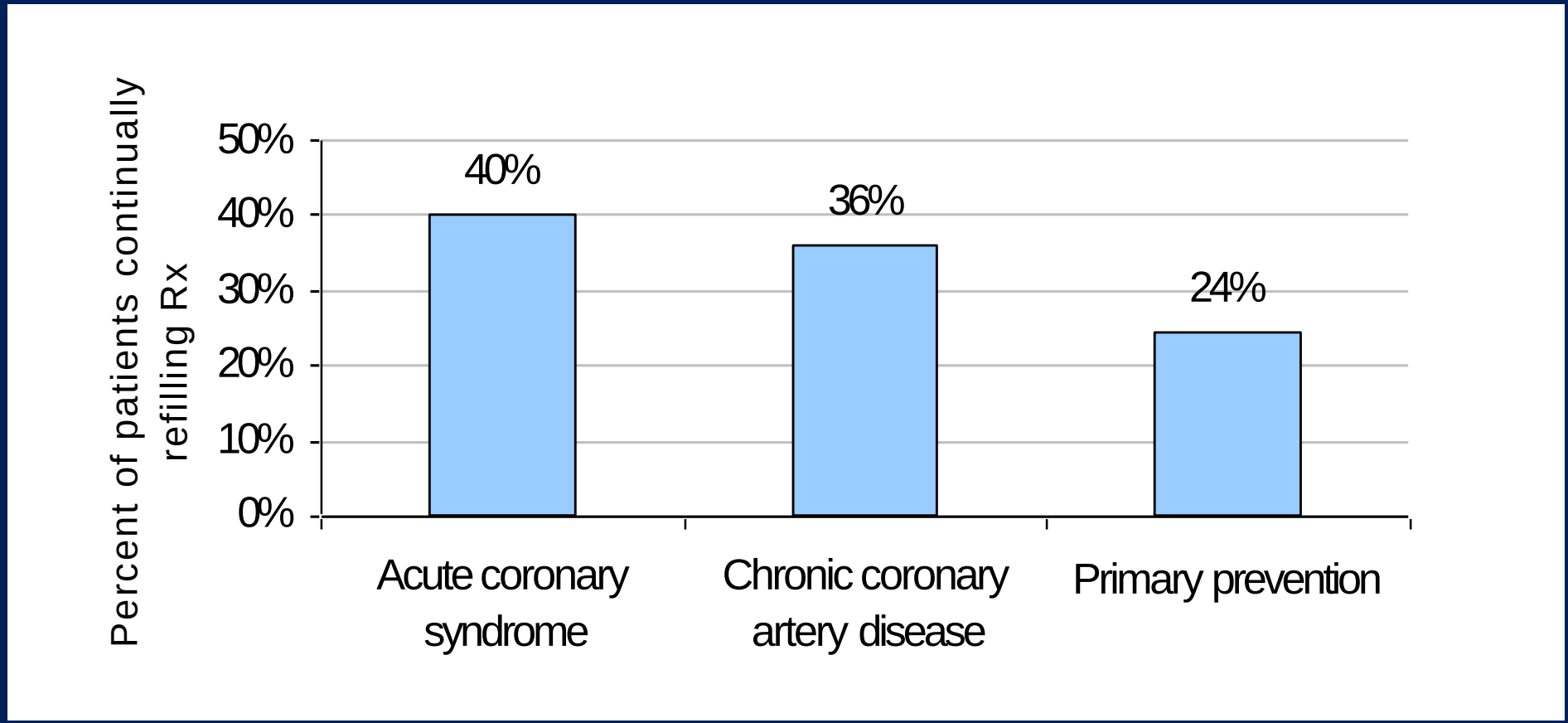
- Aspirin 81 mg daily, ticagrelor 90 mg twice daily
- Lisinopril 10 mg daily, Bisoprolol 2.5 mg daily
- Atorvastatin 80 mg daily or combination
- SGLT2 inhibitor and Metformin

- A 65 year man with HTN and DM had PPCI 2 years. Since then, Has been adherent to high-intensity statin, low-dose aspirin,Bisorolol, lisinopril and metformin/SGLT2 inhibitor

- His BP, LDL-C and HBA1c were controlled to goal levels. HDL-C of 35 mg/dL and triglycerides of 220 mg/dL

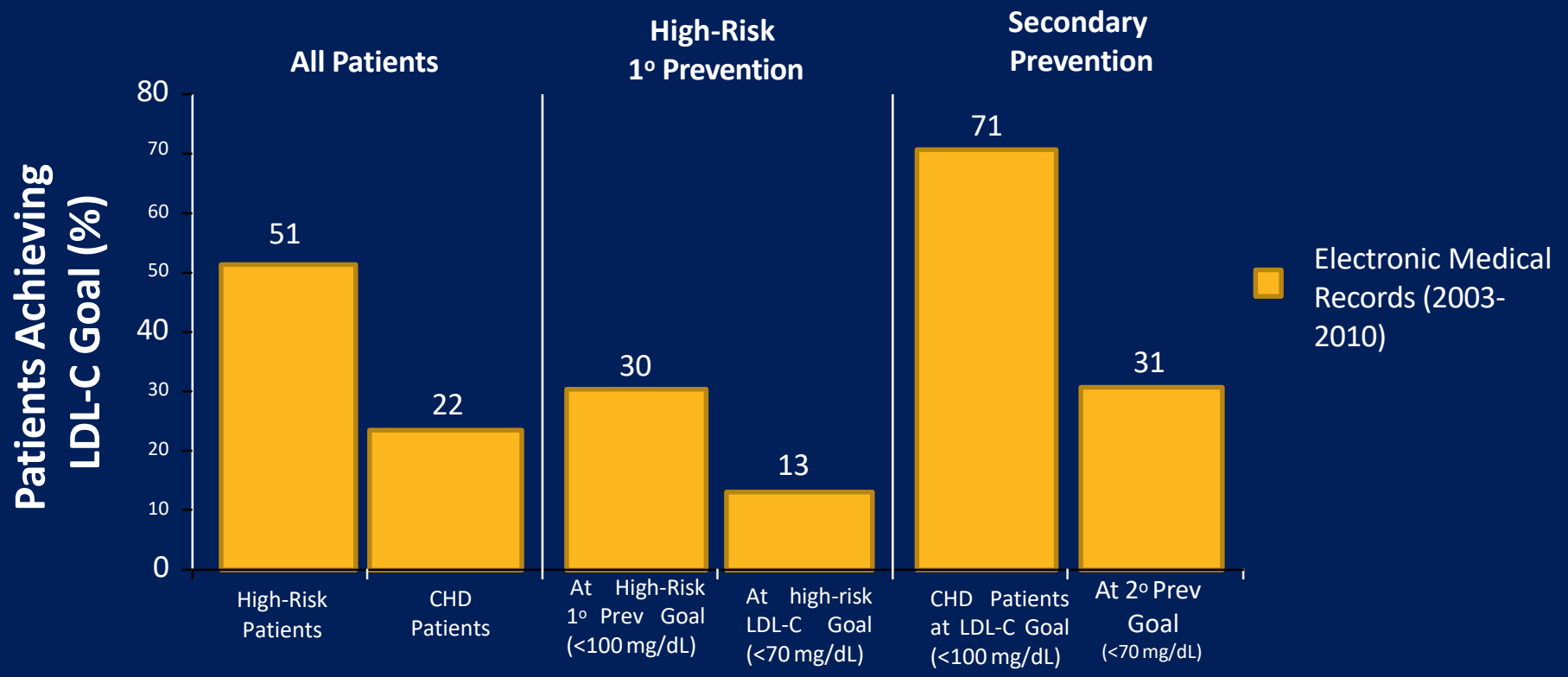
- After sustaining a recurrent MI one month ago, he sees you in clinic and asks how he can prevent yet another cardiovascular event

Adherence to statins after two years, by condition



Jackeviscius CA et al. JAMA 2002;288:462-467

Only about 1/3 of statin-treated patients achieve LDL-C goal



Similar data were obtained from administrative claims data, and NHANES

Jones PH et al. *J Am Heart Assoc.* 2012; doi 10.1161/JAHA.112.001800

28-36% of Guideline-recommended patients not on statins: ACC NCDR PINNACLE registry (Maddox et al., JACC 2014)

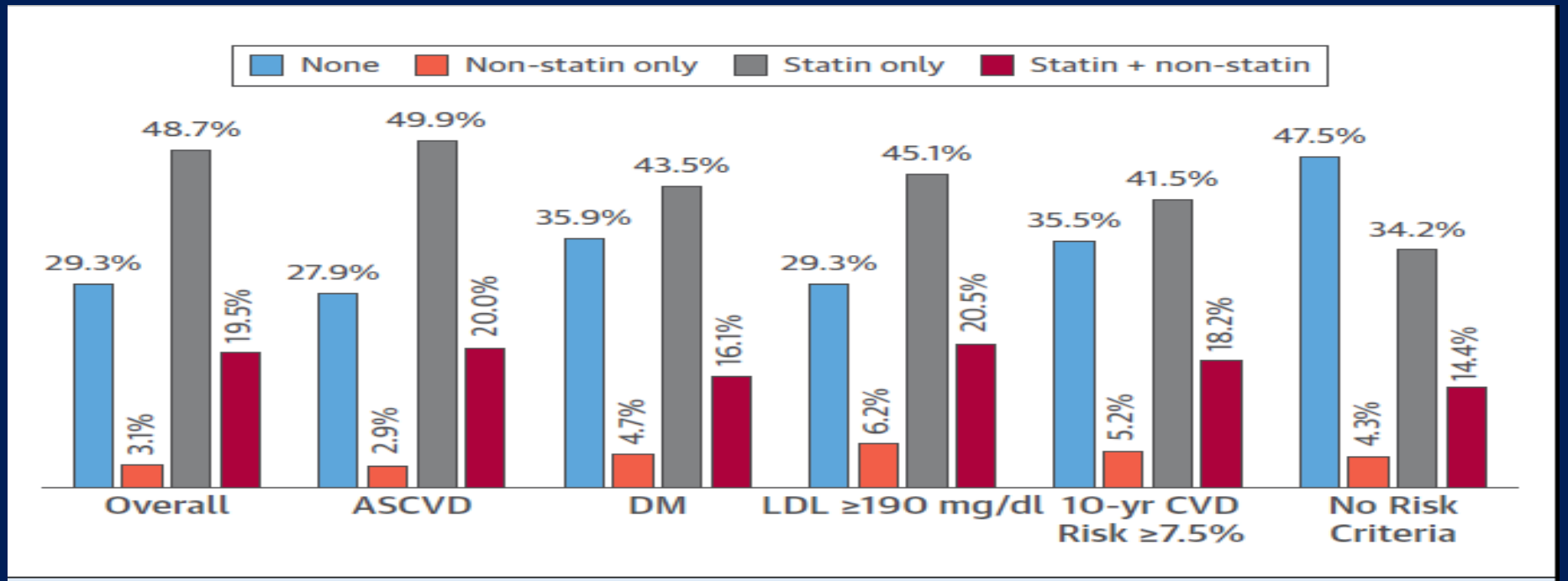


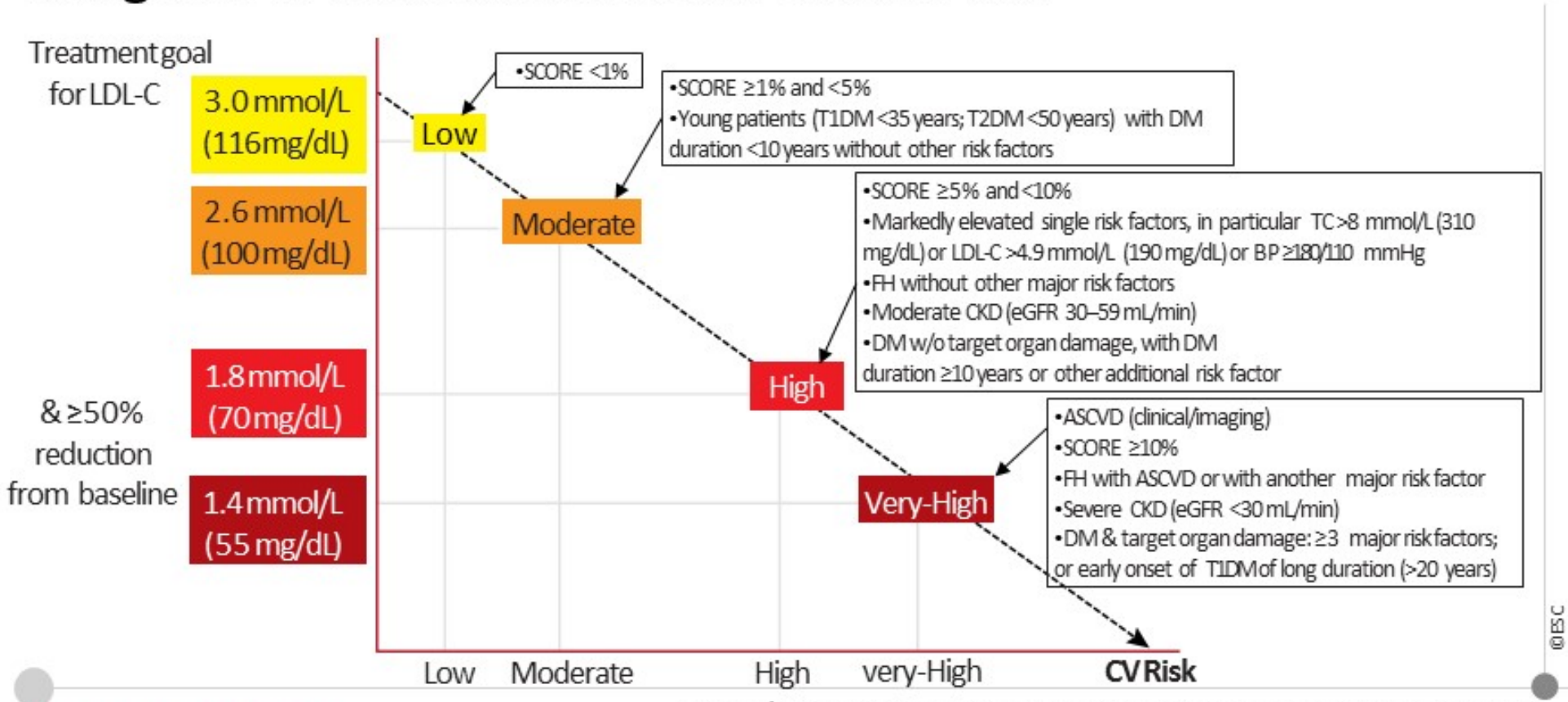
FIGURE 2 **Lipid-Lowering Therapies, Overall and by Patient Risk Group**

Display of lipid-lowering therapies by patient risk group. Percentages total >100% due to differing contraindication number per group. Refer to the methods section for further details. ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DM = diabetes mellitus; LDL = low-density lipoprotein.

Very high risk?

Central Illustration Upper panel Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

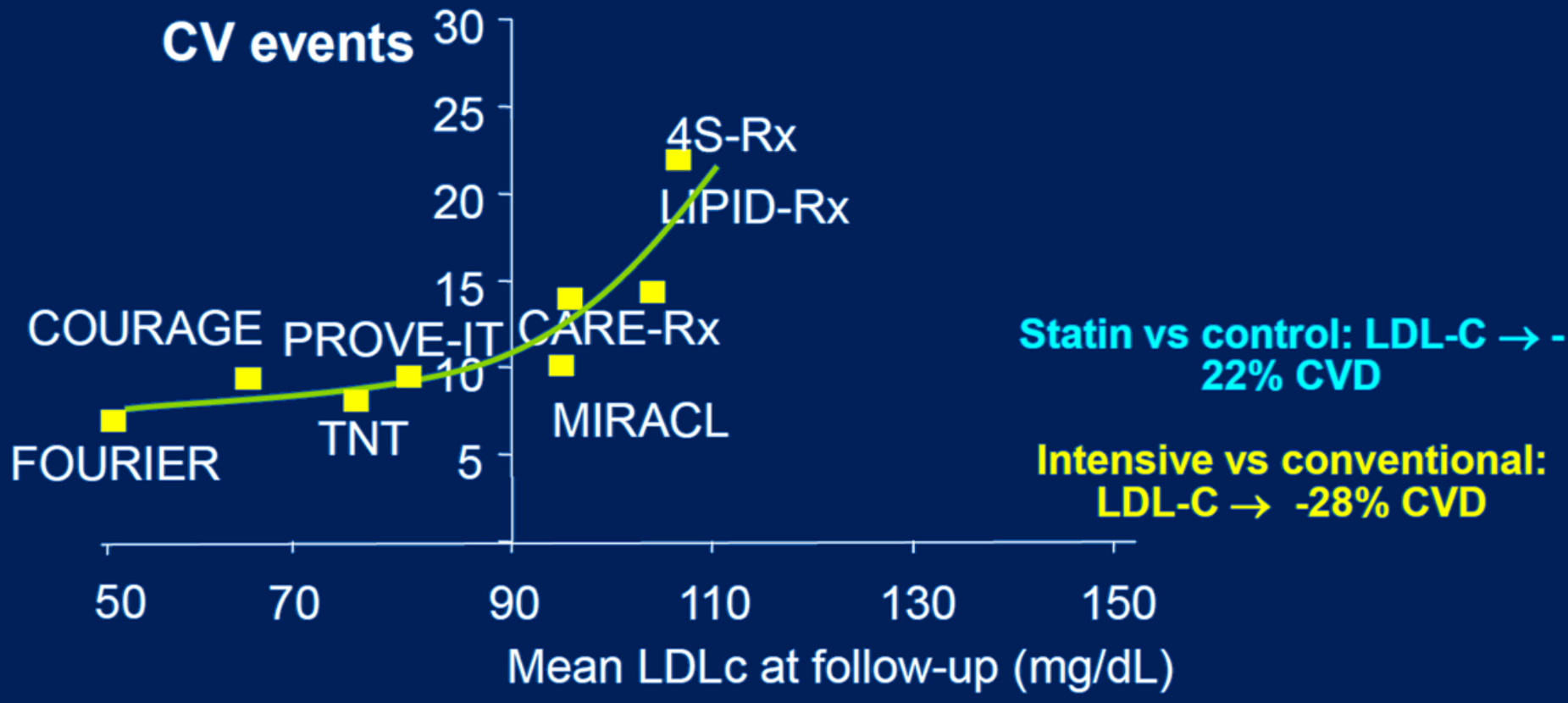
EAS ESC European Society of Cardiology



www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Plateau effect on the reduction of CVD events with LDL-C reduction



Statin vs control: LDL-C → -22% CVD

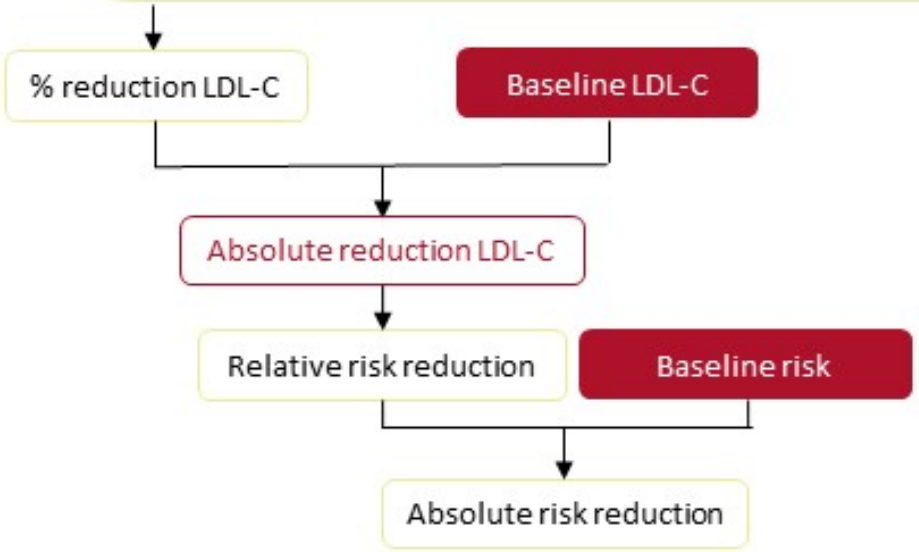
Intensive vs conventional: LDL-C → -28% CVD

Shepherd J et al. *N Engl J Med.* 1995;333:1301-1307. 4S Study Group. *Lancet.* 1995;345:1274-1275. Sacks FM et al. *N Engl J Med.* 1996;335:1001-1009. Downs JR et al. *JAMA.* 1998;279:1615-1622. Tonkin A. Presented at AHA Scientific Sessions, 1997. Sabatine MS et al. FOURIER Study. NEJM 2017

Expected clinical benefit of low-density lipoprotein cholesterol lowering therapies

Intensity of lipid lowering treatment

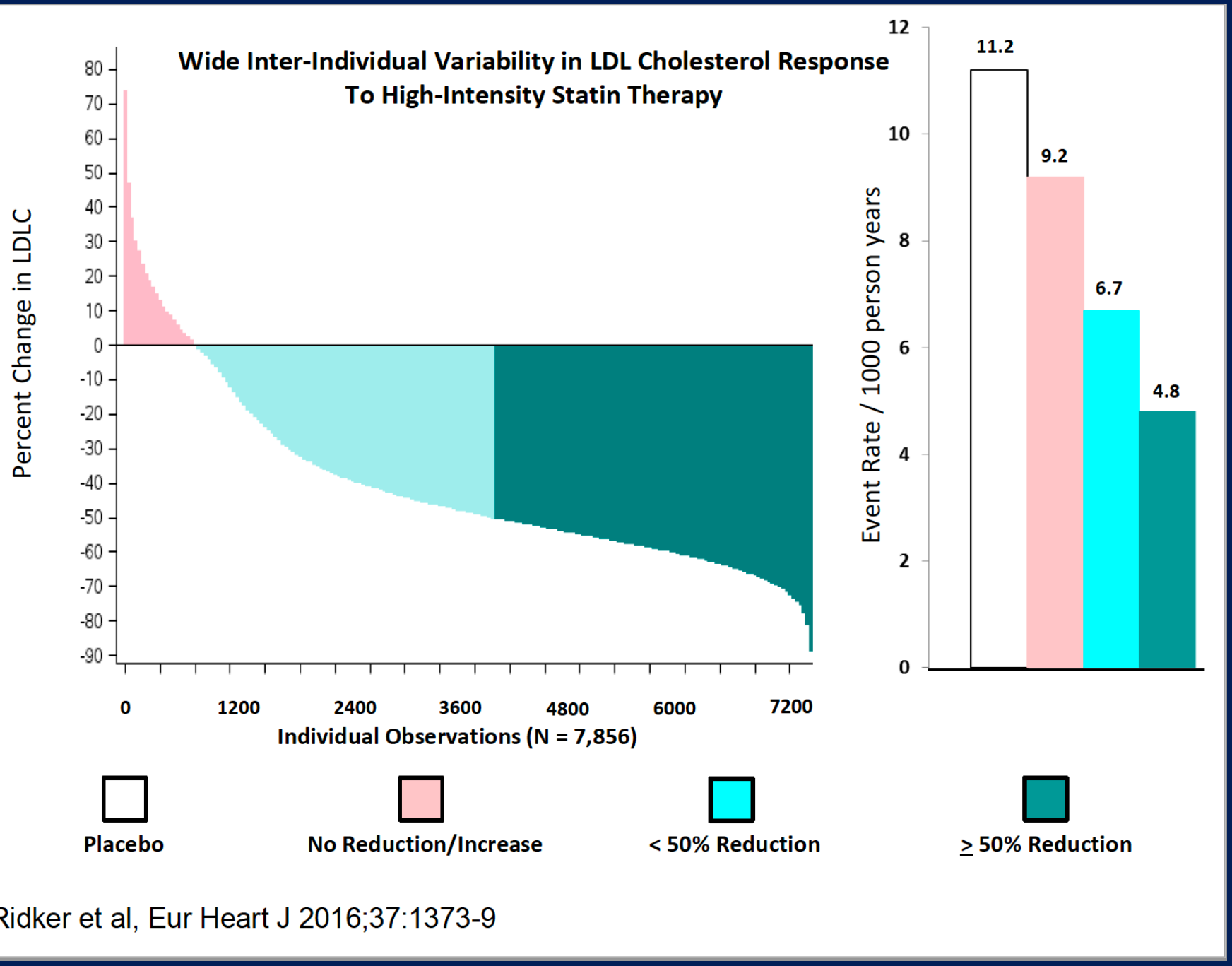
Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%



LDL-C = low-density lipoprotein cholesterol;
PCSK9 = proprotein convertase subtilisin/kexin type 9.

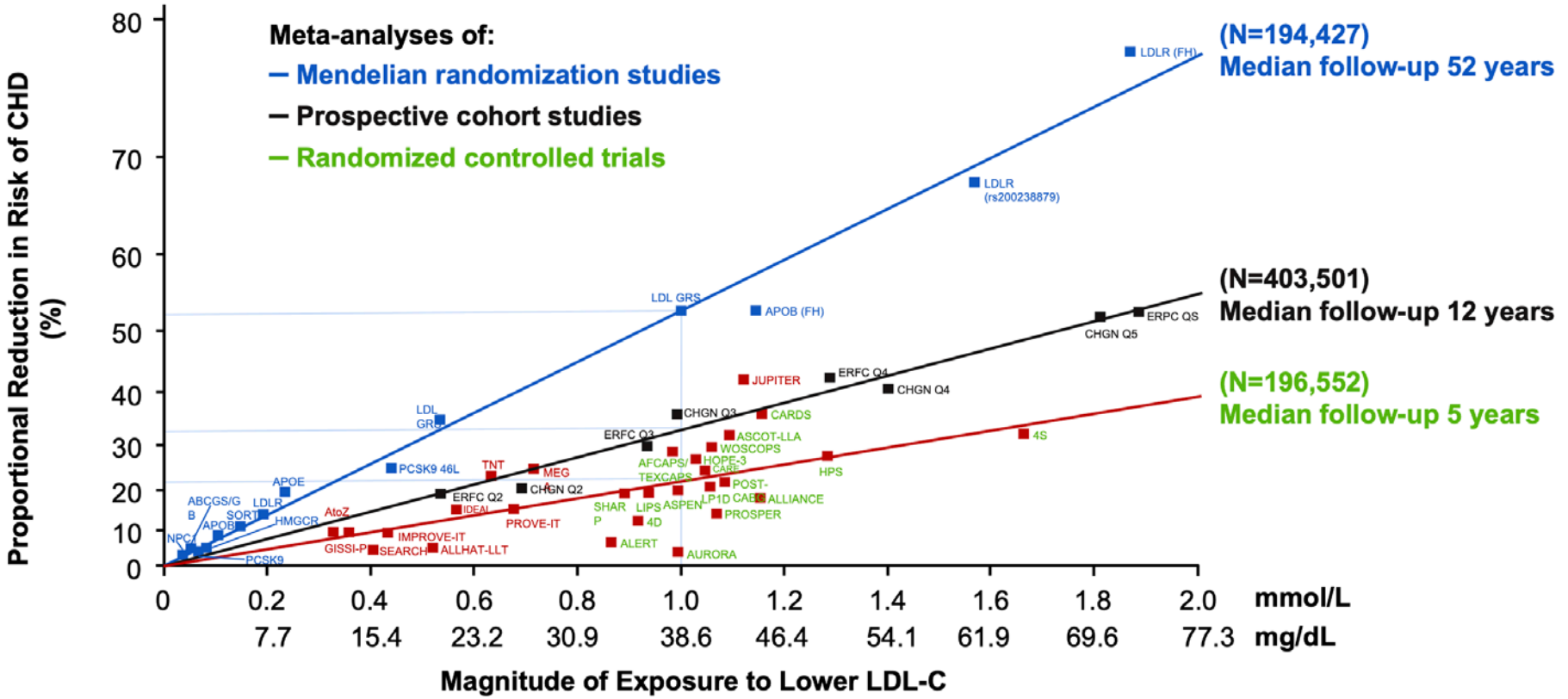
www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)



Ridker et al, Eur Heart J 2016;37:1373-9

Doesn't matter how you go low: What matters is how much and for how long



AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; ERFC, Emerging Risk Factors Collaboration; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; ; SHARP, Study of Heart and Renal Protection; TNT, Treating to New Targets; ; CHGN, Community Health Global Network; 4D Deutsche Diabetes Dialyse Studies; HOPE, HOPE, Heart Outcomes Prevention Evaluation Study; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus; HPS, Heart Protection Study

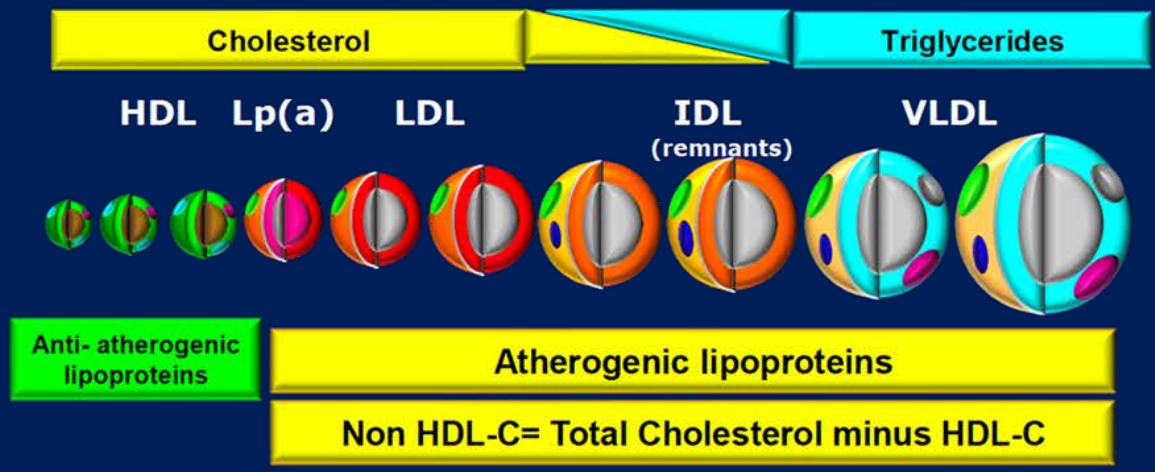
Ference BA *et al*. EAS Consensus Statement on LDL Causality. *Eur Heart J.* 2017;38(32):2459-2472.

- Even by aggressive LDL-C lowering treatment, patients still present a significant residual risk of MACE.

- Since non-HDL-C appears to be superior for risk prediction beyond LDL-C, current guidelines have emphasize the importance of non-HDL-C for guiding cardiovascular prevention strategies and have flagged non-HDL-C as a co-primary therapeutic target.

- The goals of non-HDL-C were recommended as 30 mg/dl higher than the corresponding LDL-C goals, but the value seemed inappropriate

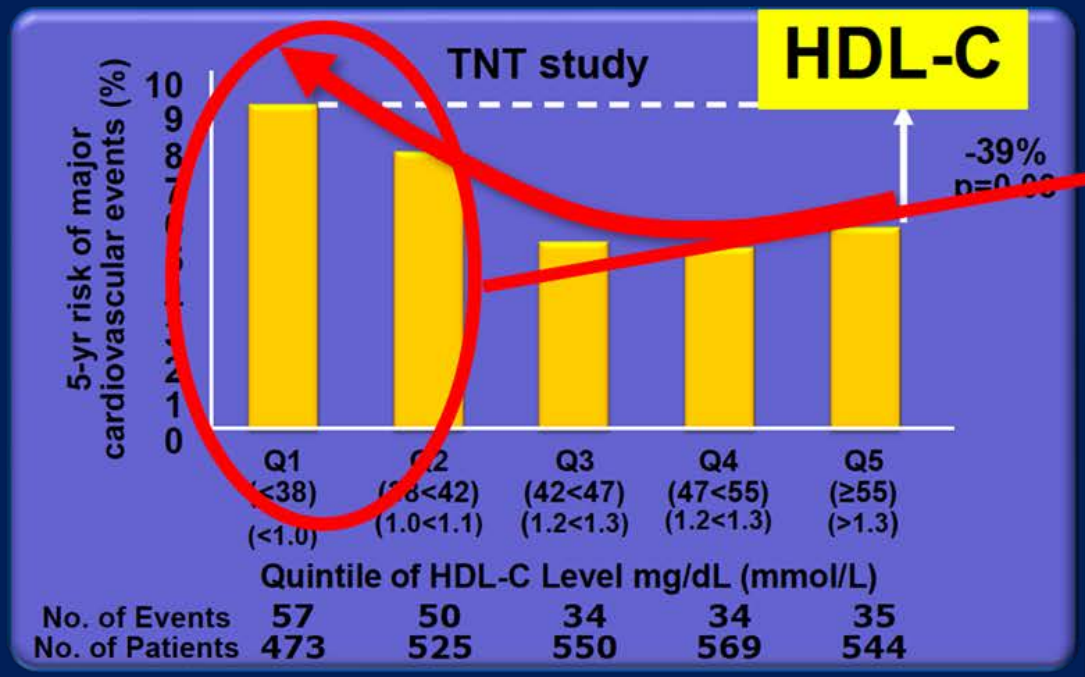
Non-HDL cholesterol: Emerging target for the treatment of (residual) CV risk



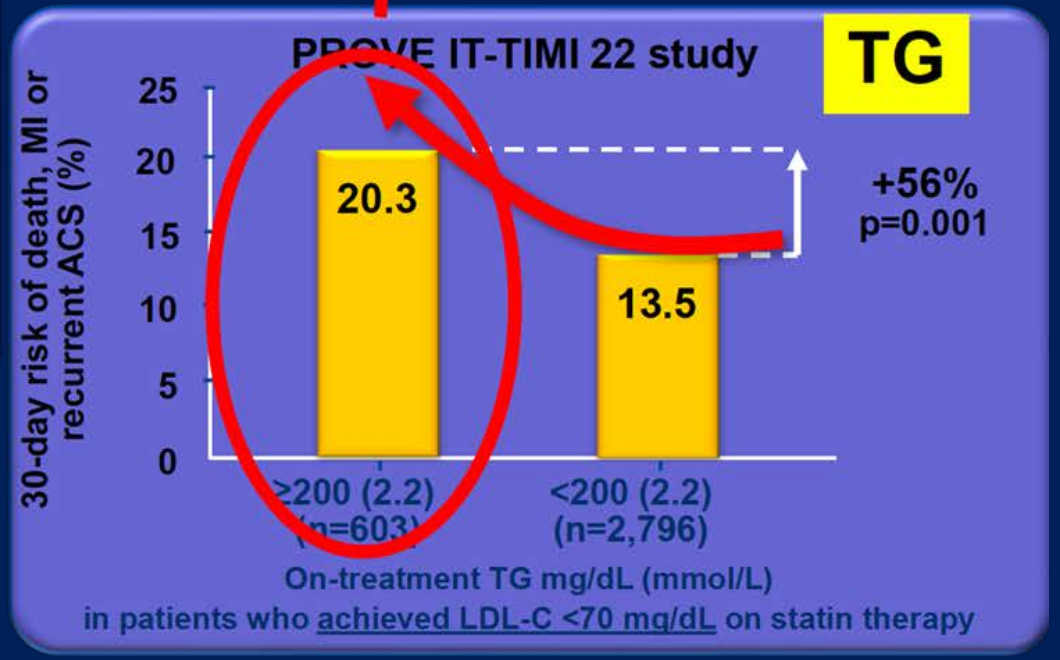
- ✓ **Accounts for all atherogenic lipoproteins;** improved estimate of CV risk in patients with diabetes, metabolic syndrome or chronic kidney disease
- ✓ **Fasting Not Required**
- ✓ Recommended as **secondary target** by national/international guidelines
- ✓ Target levels= **LDL-C goal + 30 mg/dl** (0.8 mmol/L)
- ✓ **Easy to calculate**: Total cholesterol minus HDL-C

European Heart Journal Advance Access online published August 27, 2016

Residual risk is associated with low HDL-C and high TG levels even when LDL-C70 mg/dl (1.8 mmol/L)

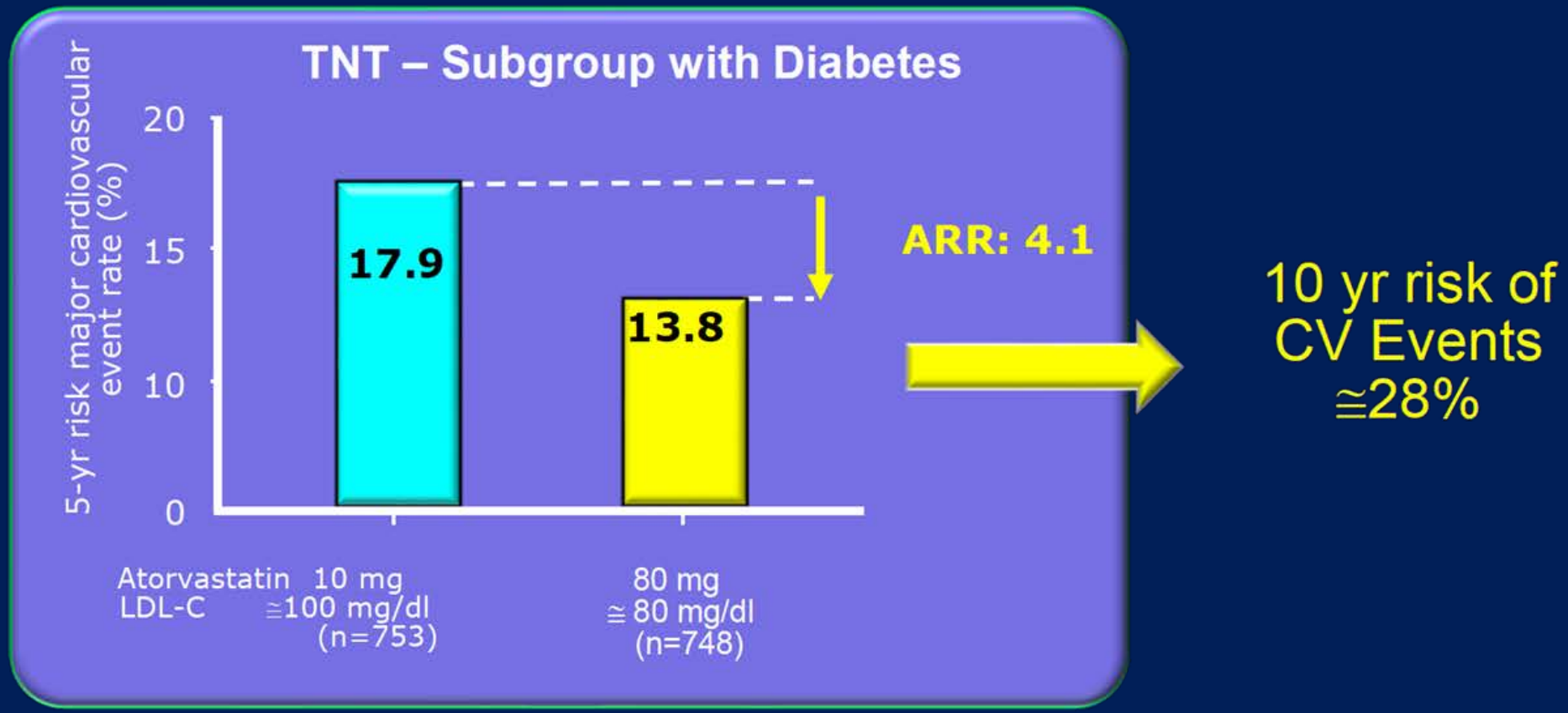


High non-HDLc



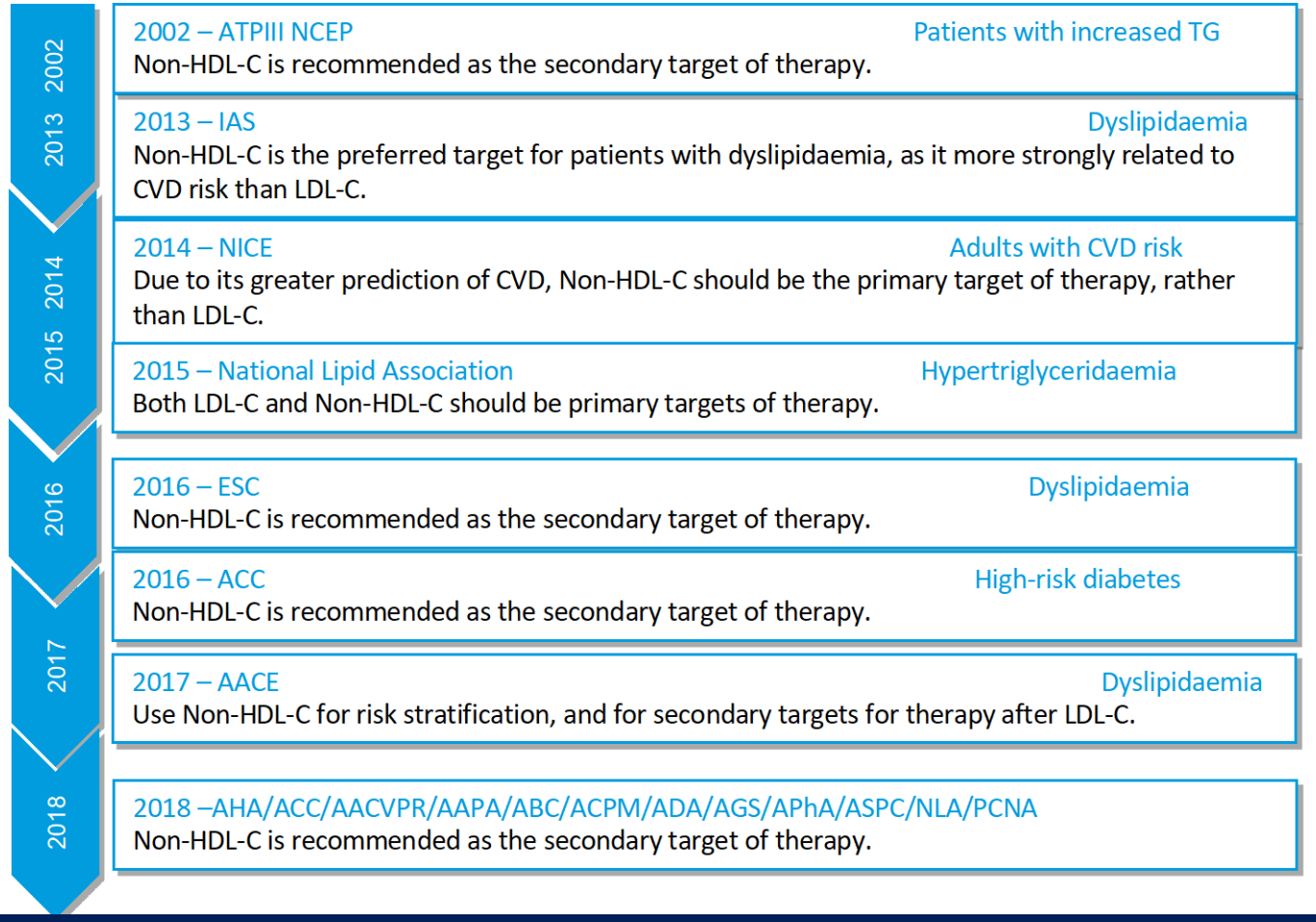
Barter P et al. *N Engl J Med.* 2007; 357:1301-10.
Miller M et al. *J Am Coll Cardiol.* 2008;51:724-30.

Aggressive LDL-C lowering with maximal doses of statins in type 2 diabetes and atherogenic dyslipidemia



LaRosa et al., N Engl J Med 2005;352:1425–35

Guidelines: Summary



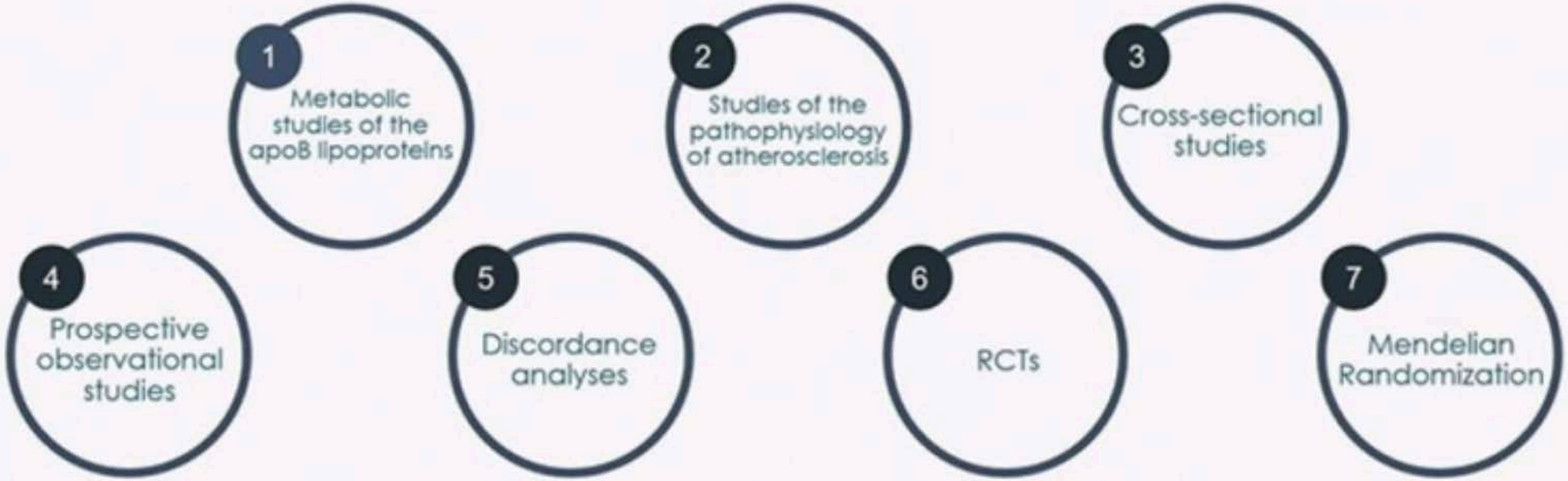
European guidelines: Recommended for risk assessment

Recommendations for lipid analyses for cardiovascular disease risk estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. 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 levels, DM, obesity, or very low LDL-C levels.	I	C

EVIDENCE THAT

ApoB > non-HDL-C > LDL-C



ESC/EAS guidelines 2019

- “Because ApoB provides an accurate estimate of the total concentration of atherogenic particles under all circumstances, it is the preferred measurement to further refine the estimate of ASCVD risk that is modifiable by lipid-lowering therapy”

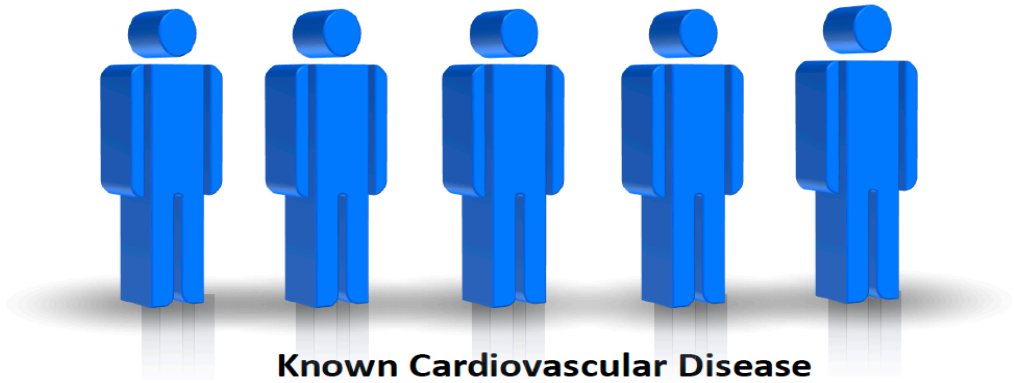
Is this 50-year-old woman at increased risk of CVD due to trapping of apoB particles?

TC	183 mg/dl	
Non-HDL C	131 mg/dl	43rd
LDL-C	110 mg/	45th
HDL C	52 mg/dl	
TG	106 mg/dl	
apoB	110 mg/dl	80th

A 60-year-old man with CVD on rosuvastatin 40 mg qd. Ezetimbe?

Non-HDL C	90 mg/dl
LDL-C	65 mg/dl
apoB	80 mg/dl

Ridker PM.
JACC 2018;72:3320-31



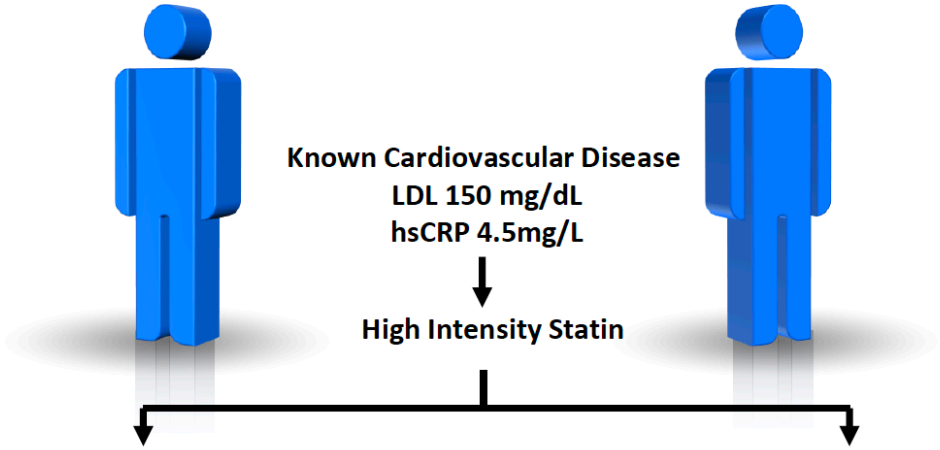
Known Cardiovascular Disease

High Intensity Statin

Biologic Issue	Residual Cholesterol Risk
Critical Biomarker	LDL-C >100mg/dL
Potential Intervention	Targeted LDL / Apo B Reduction
Randomized Trial Evidence	IMPROVE-IT FOURIER, SPIRE ODDYSEY

Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Eur Heart J 2016;37:1720-22



"Residual Cholesterol Risk"

LDL 110 mg/dL
hsCRP 1.8 mg/L

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe
FOURIER/SPIRE/ODYSSEY:
PCSK9 Inhibition q2 weeks

"Residual Inflammatory Risk"

LDL 70 mg/dL
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

CANTOS
Canakinumab 150mg SC q 3 months
COLCOT colchicine 0.5 mg qd

- A 57-year-old woman with history of diabetes, hypertension and DLP. She does not have any history of cardiovascular disease. Denies smoking

- Current medications: Atorvastatin/Ezetimibe 20/10, mg daily, metformin 1000 mg BID and SGLT2i, ARB/CCB

- BP: 127/84, HR: 73, BMI 26 kg/m^2
- Lipid profile: TC 143 mg/dL, TG 162 mg/dL
- HDL-C 38mg/dL, LDL-C 74 mg/dL

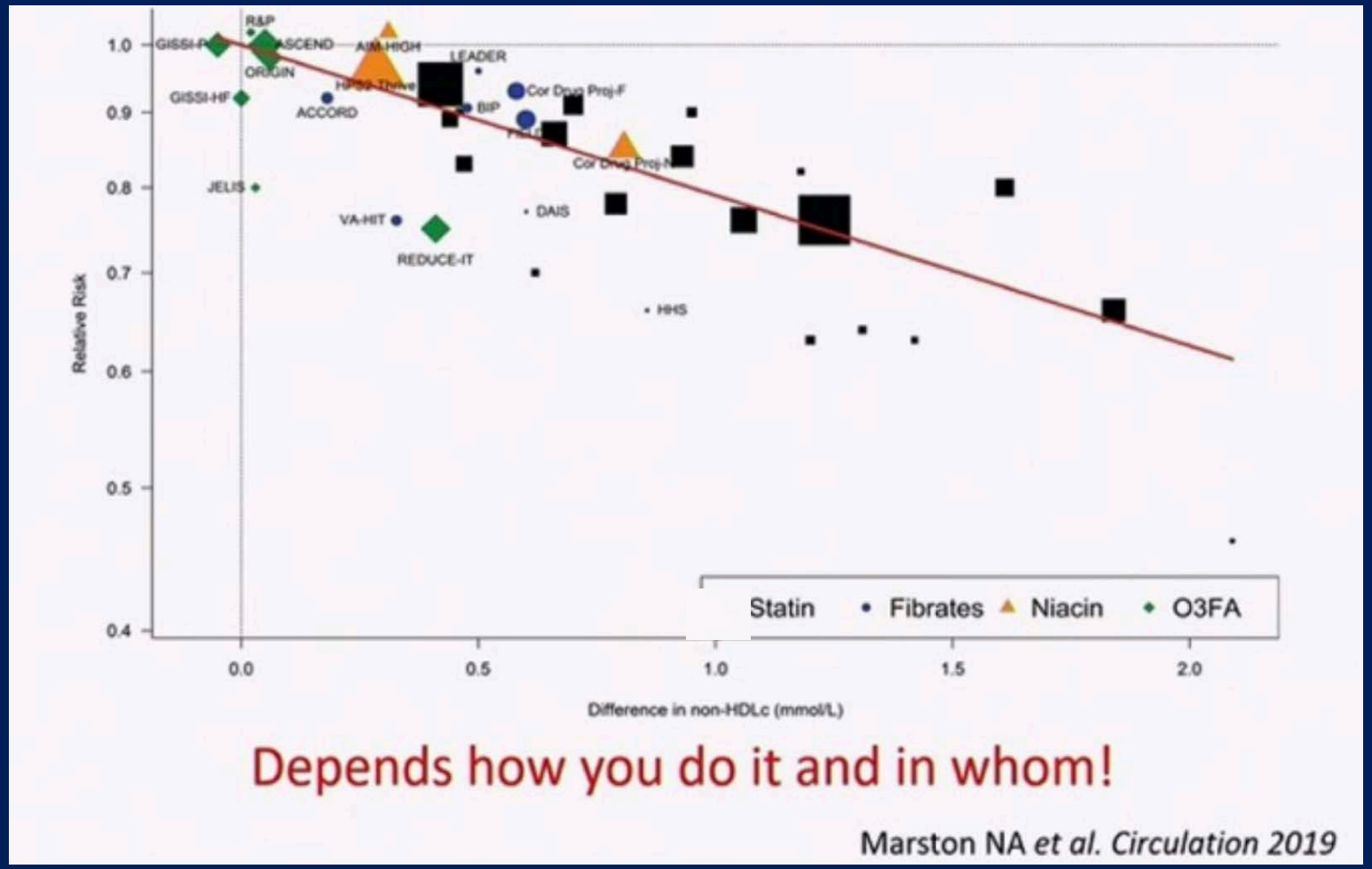
VLSL in hypertriglyceridemia

- VLDL normally represents 10% of apoB
- In mild-moderate hyperTG (1.5-3.0 mmol/L)
  - 16% of total apoB
- In marked hyperTG (>3.0 mmol/L)
  - 26% of total apoB

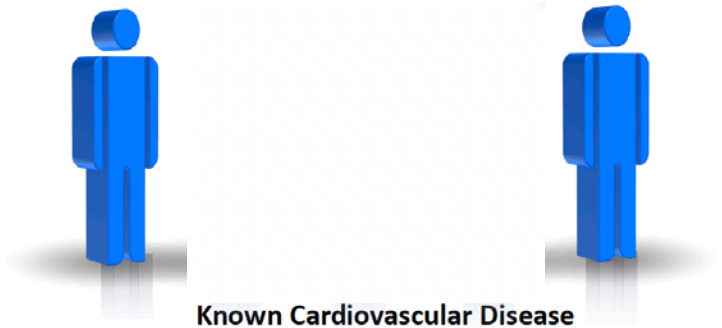
GREATER VLDL = GREATER CV RISK

Sniderman *et al. JLR 2018*

Does lowering TG reduce risk?



Ridker PM.
JACC 2018;72:3320-31



Known Cardiovascular Disease

High Intensity Statin

Residual ombotic Risk	Residual Triglyceride Risk
No simple biomarker	TG >200mg/dL HDL <40mg/dL
Targeted ntithrombotic Reduction	Targeted Triglyceride Reduction
COMPASS DAPT	REDUCE-IT STRENGTH PROMINENT

- Triglycerides and triglyceride-rich lipoproteins have also been identified as important contributors to residual risk

- In the REDUCE-IT trial, 4 g of EPA daily was found to be beneficial in a established ASCVD or diabetes with other risk factors with elevated triglycerides (135-499 mg/dL) and well controlled LDL-C (41-100 mg/dL)

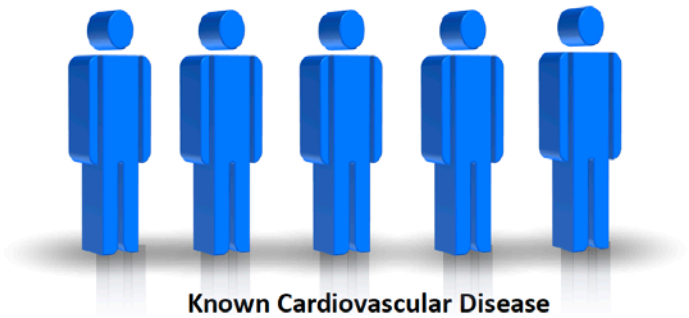
Conclusions

- Compared with placebo, icosapent ethyl 4 g/day significantly reduced total cardiovascular events by 30% including:
  - 25% reduction in first cardiovascular events
  - 32% reduction in second cardiovascular events
  - 31% reduction in third cardiovascular events
  - 48% reduction in fourth or more cardiovascular events
- Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019. Bhatt DL. ACC 2019, New Orleans.

- Up to 9% (about one third) of the proportional benefit in REDUCE- IT is explainable by lipid differences
- Up to 10% (about one third) of the benefit could be due to anti-thrombotic effects
- Up to 5% could be due to blood pressure lowering
- Other possible mechanisms include:
  - Anti-arrhythmic effects (causing reductions in cardiac death)
  - Anti-inflammatory deaths (no convincing evidence on measured cytokines

Ridker PM.
JACC 2018;72:3320-31



Known Cardiovascular Disease

High Intensity Statin

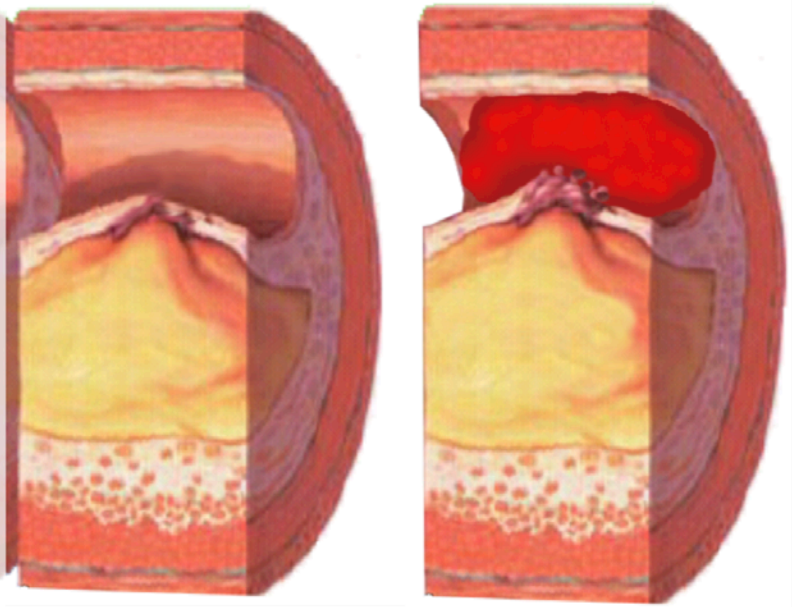
Biologic Issue	Residual Thrombotic Risk
Critical Biomarker	No simple biomarker
Potential Intervention	Targeted Antithrombotic Reduction
Randomized Trial Evidence	COMPASS DAPT

What can we learn from COMPASS

- large trial
- CAD/PAD pts
- well-treated
- careful registration of RF at baseline
- info on (different) antithrombotic strategies

- **>27 000** participants
- CAD/PAD pts
- 70% ACEi, 90% LLT
- full data on **6 major RF, including physical activity**
- randomization according to antithrombotic therapy

CV risk factors in secondary prevention?



reduce atherosclerosis

RF control

drugs + lifestyle

prevent thrombosis

antithrombotics

New guidelines recommend a second antithrombotic for selected patients with chronic coronary syndromes

- 2019 guidelines for the management of CCS

High ischaemic risk defined as:

- Diffuse multivessel CAD with **at least 1** of the following:
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - CKD with eGFR 15–59 ml/min/1.73 m^2

Moderate ischaemic risk defined as:

- **At least 1** of the following:
  - Multivessel/diffuse CAD
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - HF
  - CKD with eGFR 15–59 ml/min/1.73 m^2

Recommendations	Class	Evidence level
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention should be considered in patients with a **high risk of ischaemic events** and without high bleeding risk	IIa	A
Adding a **second antithrombotic drug** to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk of ischaemic events** and without high bleeding risk	IIb	A

Knuuti J *et al, Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz42

New guidelines recommend a second antithrombotic for selected patients with chronic coronary syndromes

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Recommendations	Class	Evidence level
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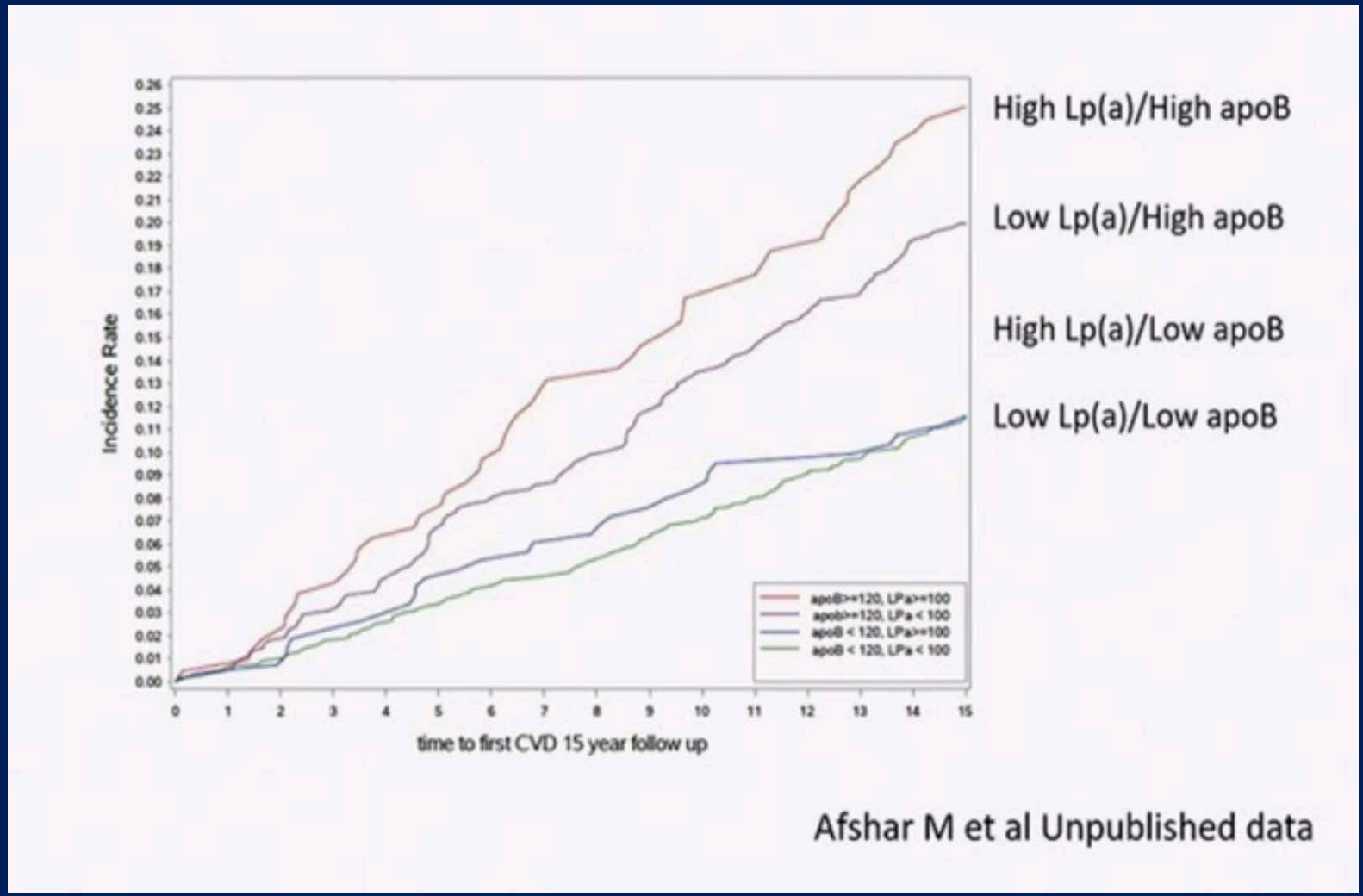
  - Recurrent MI
  - PAD
  - HF
  - CKD with eGFR 15–59 ml/min/1.73 m^2

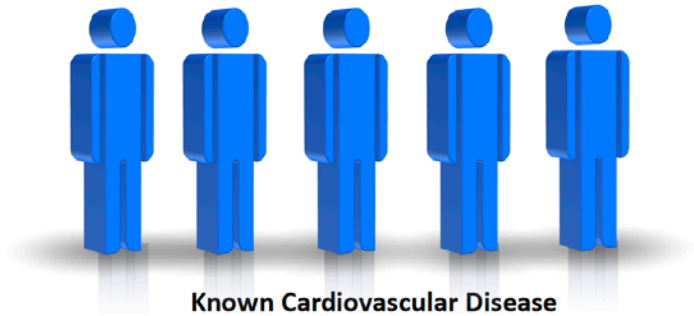
More Lp(a) = higher burden of atherogenic particles



What is Lp(a)?

- ApoB+apo(a) = Lp(a)
- Lp(a) levels are almost entirely mediated by genetics
- Highly atherogenic, pro-calcific
- Most common genetic dyslipidemia
  - 6 million Canadians high high Lp(a)

Ridker PM.
JACC 2018;72:3320-31



Known Cardiovascular Disease

↓

High Intensity Statin

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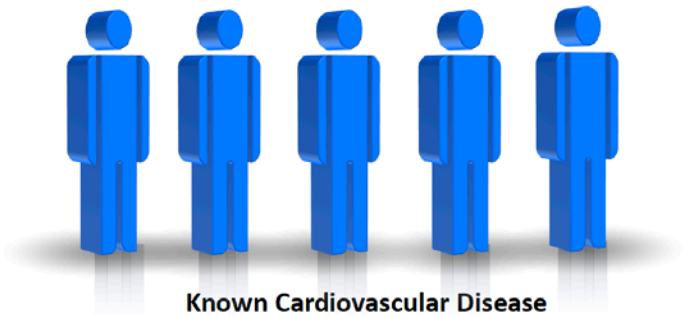
Residual Lp(a) Risk

Lp(a) >50mg/dL

Targeted Lp(a) Reduction

Planned

Ridker PM.
JACC 2018;72:3320-31



Known Cardiovascular Disease

High Intensity Statin

Biologic Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk
Critical Biomarker	LDL-C >100mg/dL	hsCRP >2mg/L	No simple biomarker	TG >200mg/dL HDL <40mg/dL	Lp(a) >50mg/dL
Potential Intervention	Targeted LDL / Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction
Randomized Trial Evidence	IMPROVE-IT FOURIER, SPIRE ODDYSEY	CANTOS COLCOT	COMPASS DAPT	REDUCE-IT STRENGTH PROMINENT	Planned

Which of the following statements accurately reflects guideline recommendations on RR reduction?

Select all that apply

A. Statin-based therapy should be provided to all patients at risk of ASCVD
B. Statins should be prescribed at the lowest possible dose and titrated upwards
C. If statins are insufficient to achieve target LDL-C, it should be discontinued and replaced with ezetimibe and a PCSK9 inhibitor
D. If targets are not achieved with statins at a maximally tolerated dose, consider adding ezetimibe and a PCSK9 inhibitor in a stepwise approach until target is reached