FROM SUSTAINABLE LIPID MANAGEMENT TO LIFE-SAVING CV PROTECTION FOR ACS PATIENTS

ASAN MEDICAL CENTER

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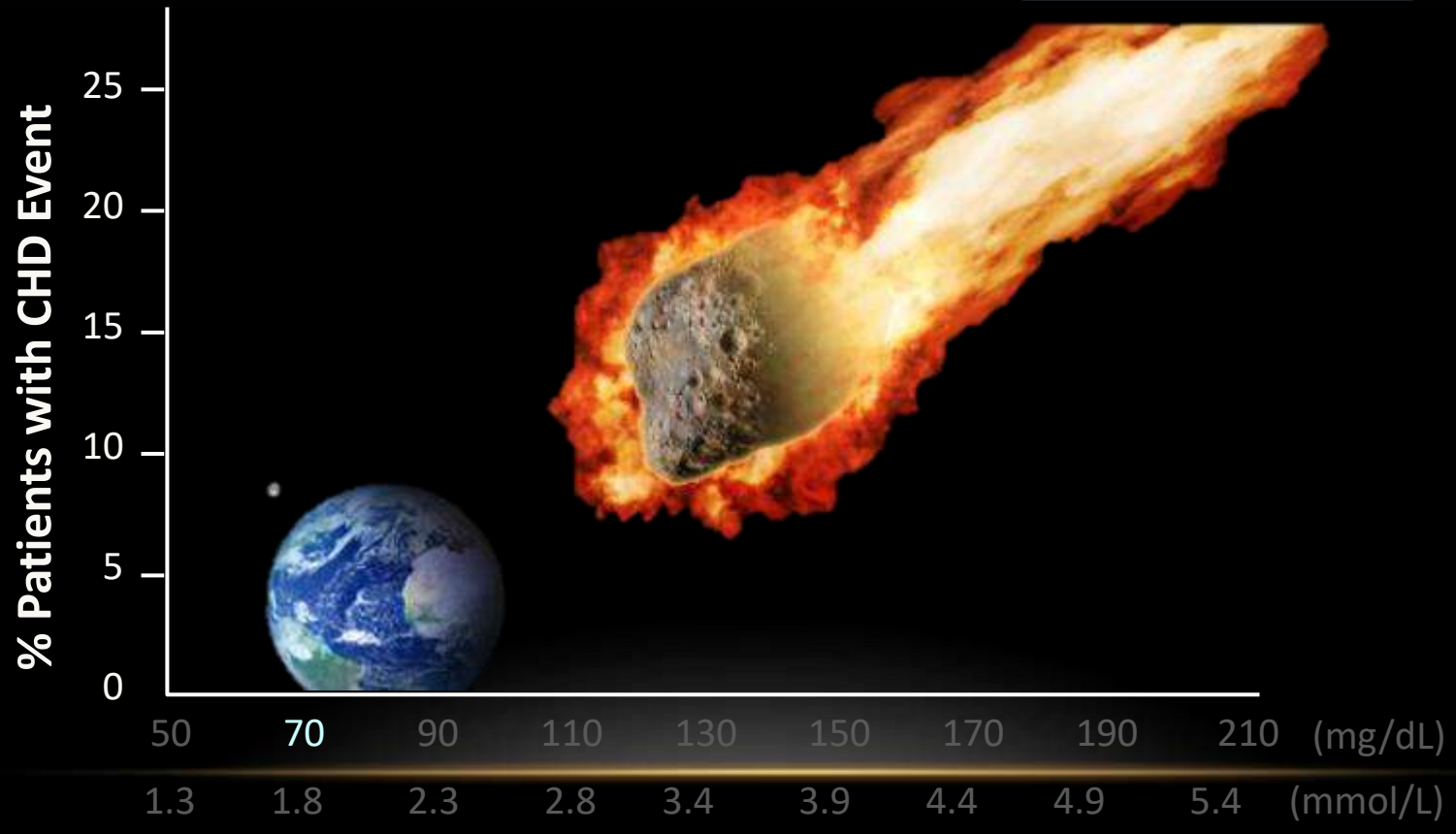
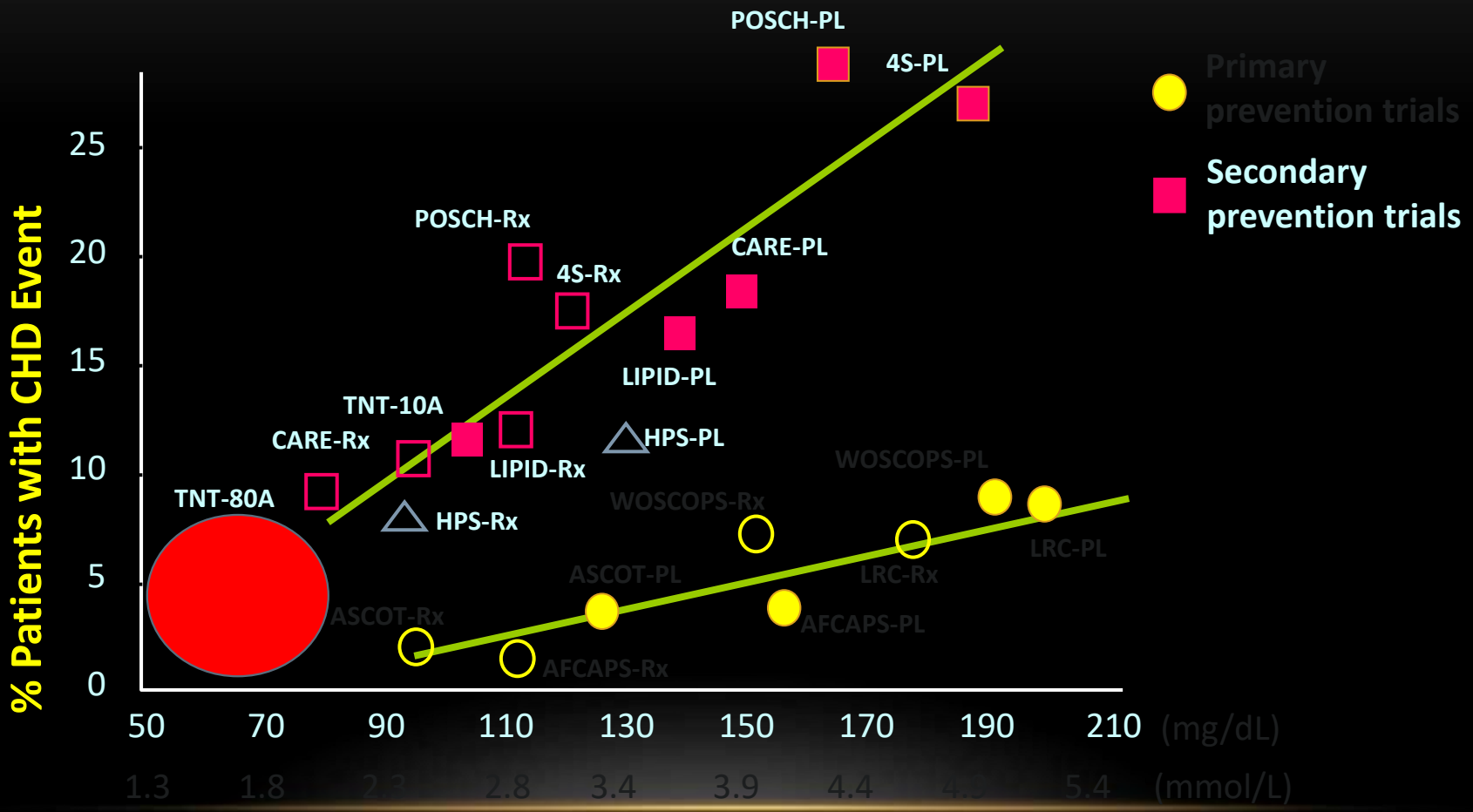
LDL-C ‘ACHIEVED LEVEL’ ; LOWER IS BETTER

“ Lower is better “ continues !

forever



LDL-C 'ACHIEVED' LEVEL ; LOWER IS BETTER



LIPID MANAGEMENT IN ACS PATIENTS

- Focused upon " **LDLc** " management.
- Intervention of TG or HDLc level is not proved to be effective.
- As **ASCVD** risk is higher, the **achieved LDLc** level should be lowered. ;; " **LDLc ; the LOWER, the BETTER** "

Achieved LDLc

LDL-C level (mg/dl)	Percentage with cardiovascular events	Adjusted hazard ratio
<50	4.4	0.44 (0.35–0.55)
50–75	11.4	0.51 (0.42–0.62)
75–100	16.5	0.56 (0.46–0.67)
100–125	16.5	0.58 (0.48–0.69)
125–150	17.8	0.64 (0.53–0.79)
150–175	22.0	0.71 (0.56–0.89)
>175	32.8	1.00 (ref)

Baseline LDLc

Baseline LDL-cholesterol (mg/dl)	Relative risk per 39 mg/dl reduction in LDL-cholesterol
<78	0.78
78–98	0.77
98–117	0.77
117–137	0.76
>137	0.80

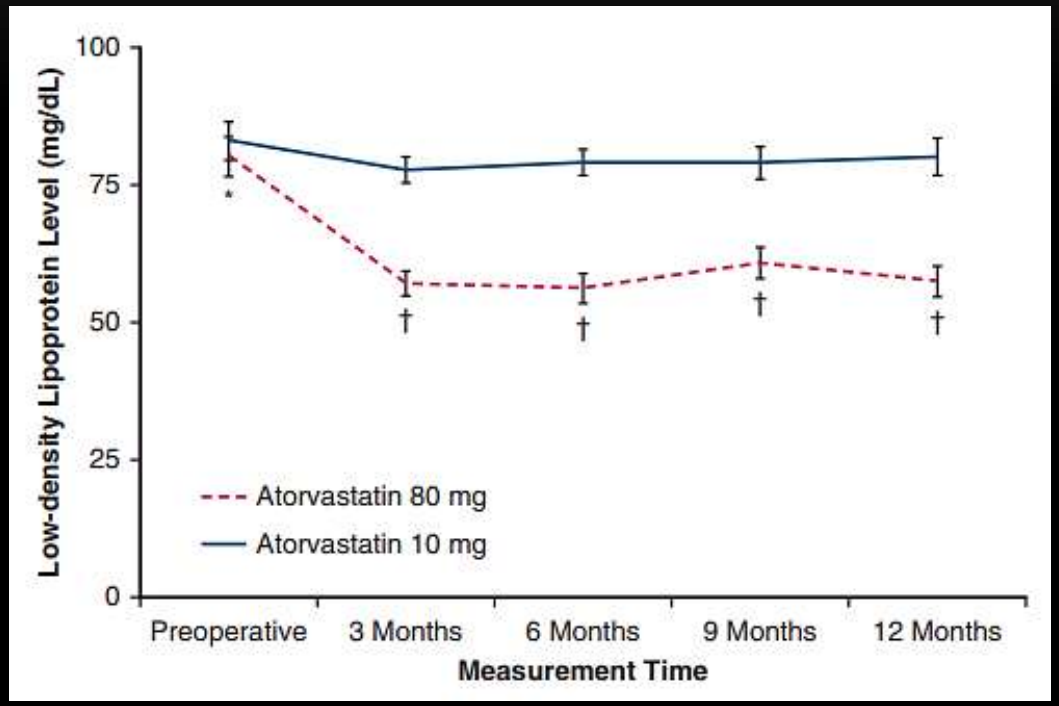
Gain-of-benefits according to CVD risk

	Absolute risk reduction (95% CI)
Timing of qualifying MI (years)	
<2	3.4 (1.4–5.3)
>2	0.8 (−1.1 to 2.7)
Number of prior MIs	
2 or more	3.7 (0.8–6.6)
1	1.3 (−0.2 to 2.7)
Residual multivessel CAD	
Present	3.6 (0.7–6.4)
Absent	1.2 (−0.3 to 2.7)

5-year event risk (%)	Relative risk (CI) per 39 mg/dl reduction in LDL-cholesterol	Absolute decrease in events per annum[a] (%)
<10	0.68 (0.62–0.74)	0.3
10–20	0.79 (0.75–0.84)	0.5
20–30	0.81 (0.78–0.85	1.1
>30	0.79 (0.75–0.83	2.2

Feingold KR. Maximizing the benefits of cholesterol-lowering drugs. *Curr Opin Lipidol.* 2019;30:388-394.

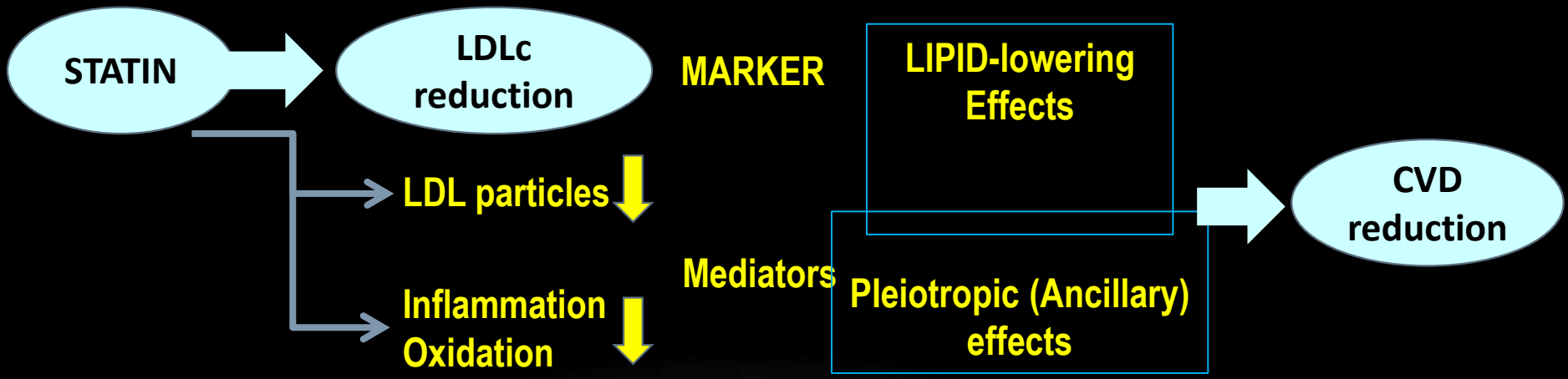
STATIN REACHES TO THE LIMIT ?
TNT TRIAL ; ATORVA 80 VS. 10 MG/DAY



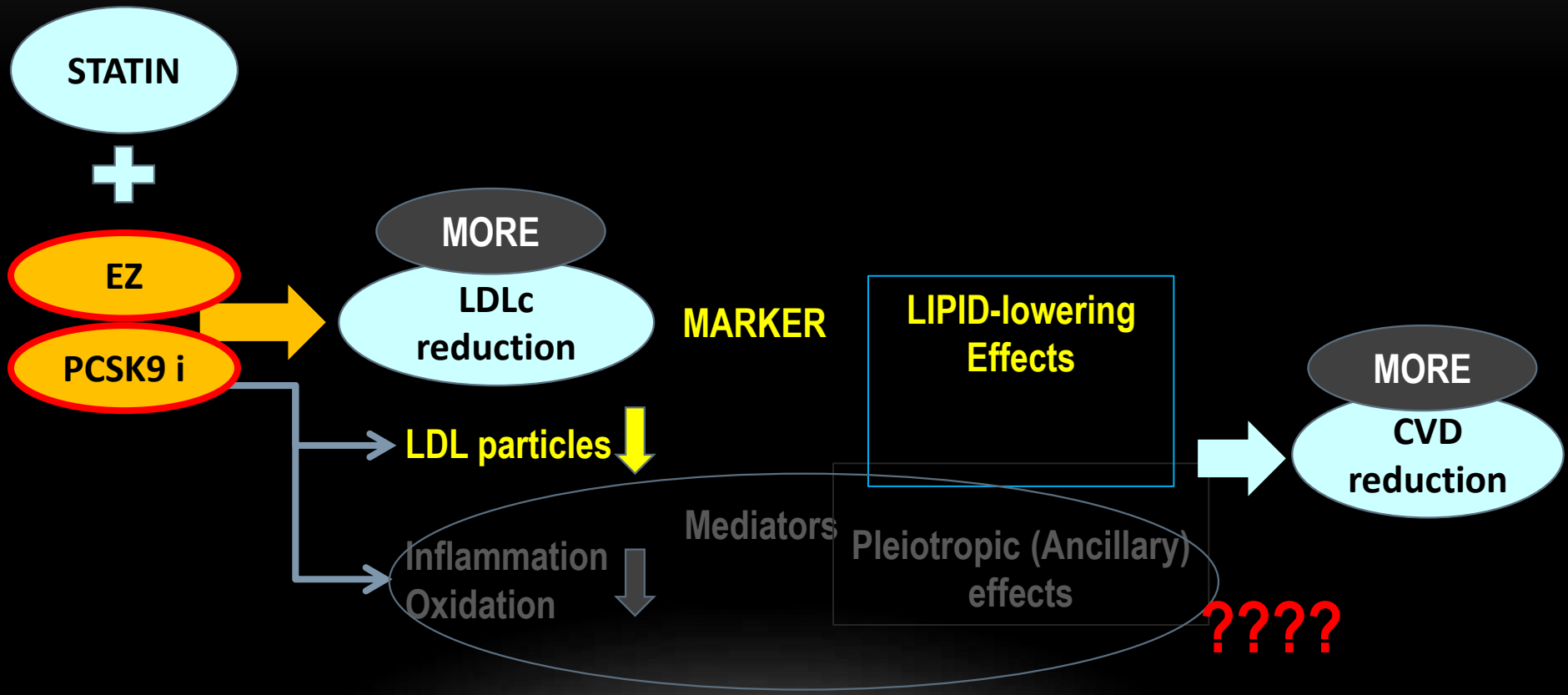
- It is hard to reach LDLc < 55 mg/dl with statin ONLY.

‘LDL-C’ MANAGEMENT IN ACS PATIENTS

- **ONLY statin** had been tried in RCT until 2010.
- Is the benefit d/t the reduction of LDLc or statin itself ?

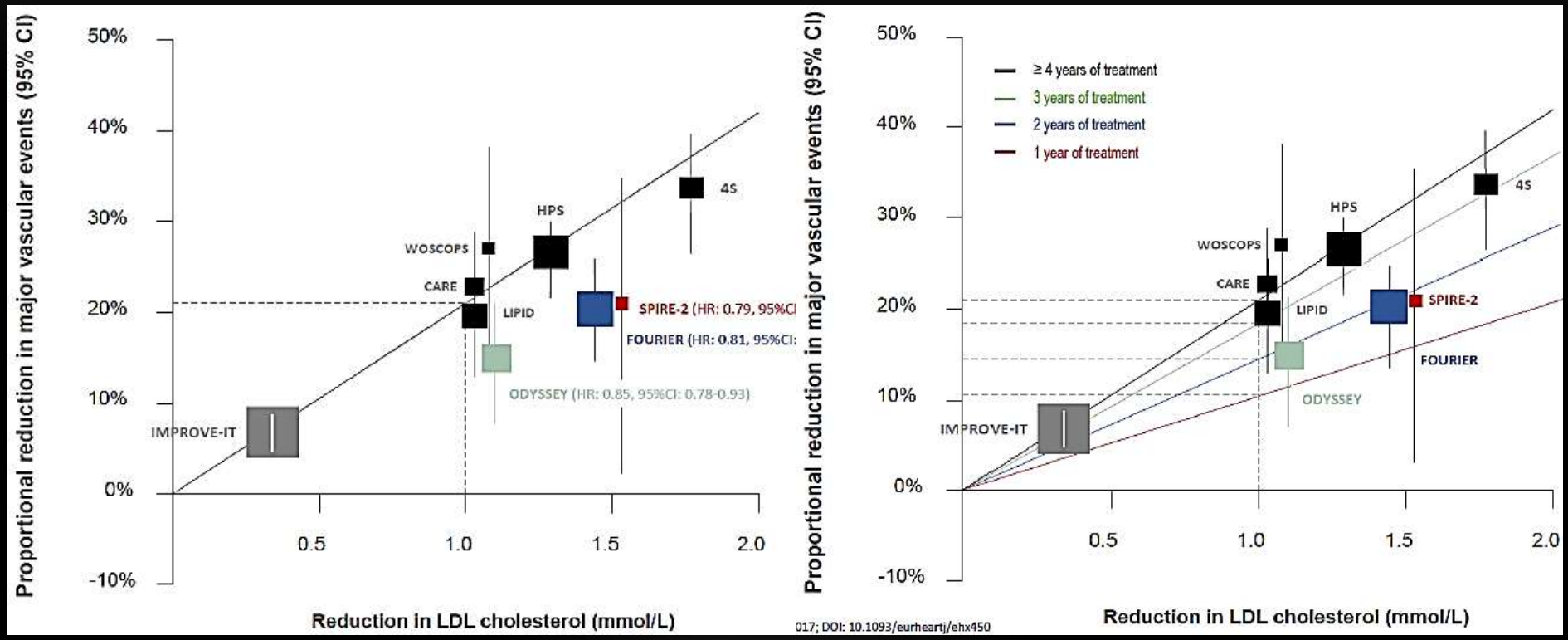


RECENT TRIALS WITH STATIN + NON-STATINS

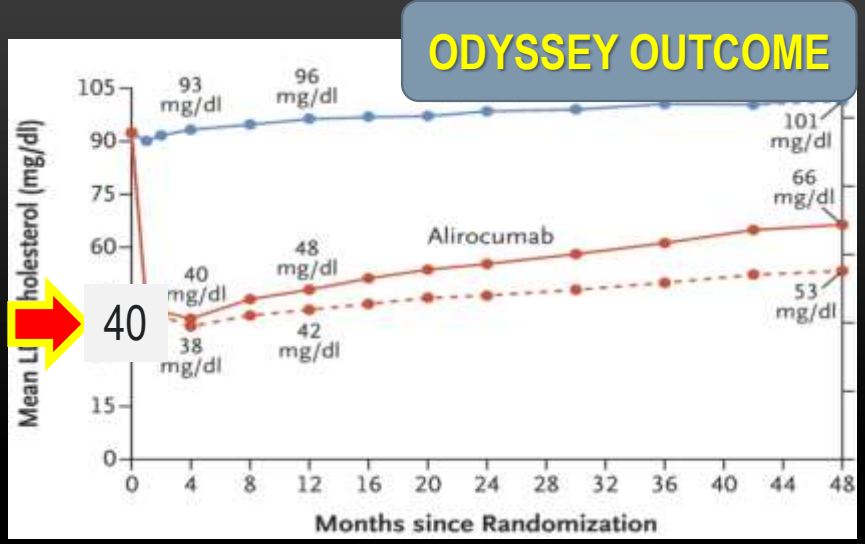


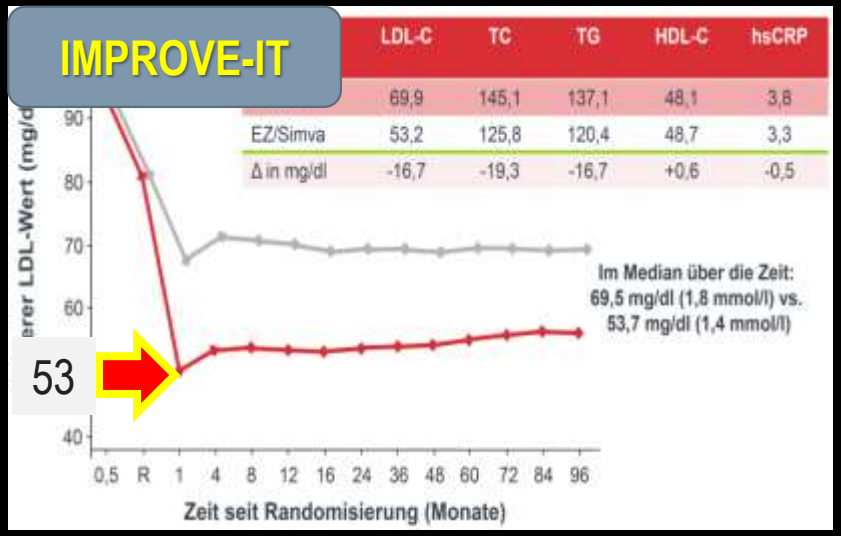
STATIN + Ezetimibe ; IMPROVE-IT
STATIN + PCSK9 inhibitor ; FOURIER and ODYSSEY OUTCOME

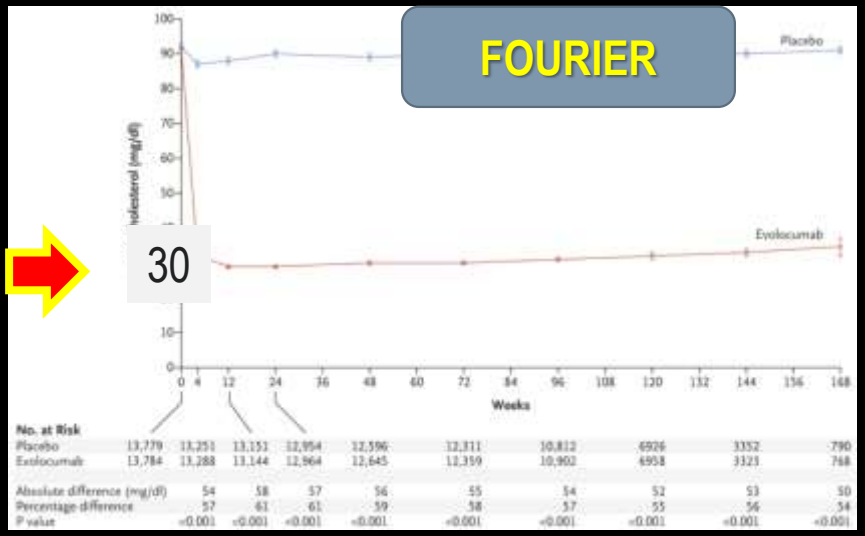
LDL-C ; “LOWER IS BETTER” CONTINUES WITH NON-STATINS !



- IMPROVE-IT ; ezetimibe
- ODYSSEY OUTCOME ; alirocumab
- FOURIER ; evolocumab







LDL-C < 55 MG/DL IS POSSIBLE WITH NON-STATIN !

TRENDS OF LIPID MANAGEMENT GUIDELINE TO ACS PATIENTS

- **2011 ESC ;**
  - LDLc must be **< 70 mg/dL OR > 50 % reduction**
- **2013 AHA** ;
  - **MAXIMAL TOLERABLE DOSE OF STATINS** rather than LDLc intervention.
  - If LDLc < 40 mg/dL, reduce or discontinue statins.
- **2018 AHA** ;
  - Should initiate/upgrade LDLc intervention when LDLc > 70 mg/dL in ACS patients
- **2019 ESC** ;
  - LDLc must be **< 55 mg/dL AND > 50 % reduction**.
  - LDLc must be **< 40 mg/dL AND > 50 % reduction,** if experienced **RECENT ASCVD events** within 2 years.

WHAT IS “VERY-HIGH RISK” ?

Table 4. Very High-Risk* of Future ASCVD Events

2013/2018 AHA GUIDELINE

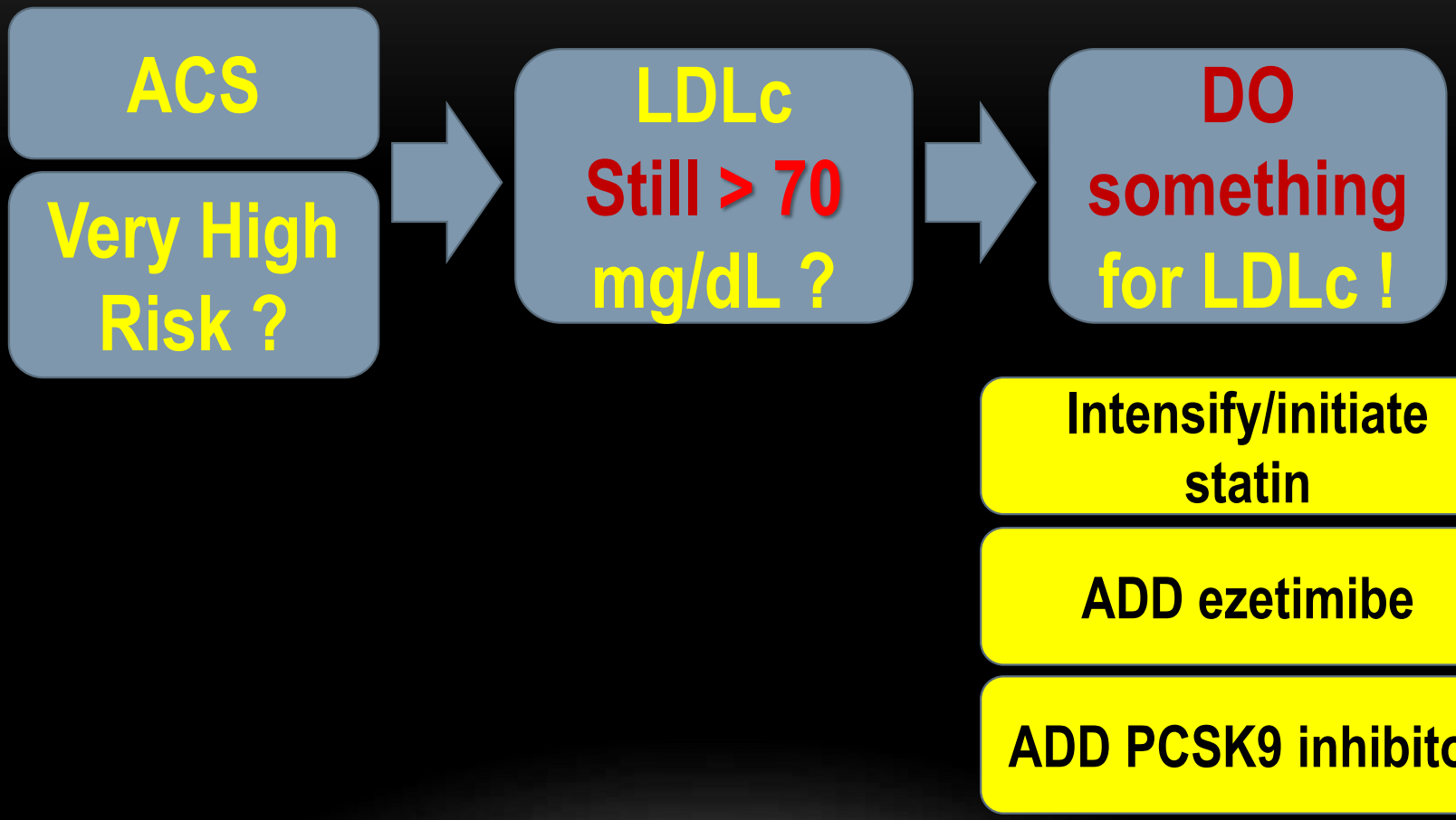
Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL, low-density lipoprotein cholesterol; and MI, myocardial infarction.

VERY HIGH RISK ; 2019 ESC

Documented ASCVD ;	previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease.
Unequivocally Documented ASCVD ;	significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. CAC score >100 Agatston units, ABI <0.9 or >1.40, Carotidfemoral pulse wave velocity >10 m/s, or the presence of plaques at carotid or femoral USG
Diabetes	with target organ damage, or at least three major risk factors, or early onset of T1DM or long duration T2DM (>20 years).
Severe CKD	eGFR <30 mL/min/1.73 m2.
SCORE≥10%	A calculated SCORE ≥10%.
FH	with ASCVD or with another major risk factor.


ACS
Very High Risk ?
LDLc Still > 70 mg/dL ?
DO something for LDLc !
Intensify/initiate statin
ADD ezetimibe
ADD PCSK9 inhibitor

TWO POSSIBLE STRATEGIES TO ACHIEVE LDL-C GOALS FOR ACS PATIENTS

- STEPWISE -

Initially

- " Maximal Tolerable Dose " of STATIN should be initiated

At F/U

- Do something more when LDLc level is > 70 (2013 AHA) or > 55 (2019 ESC) mg/dL.
- If LDLc level is > 40 (2019 ESC) mg/dL and experienced RECENT ASCVD within 2 years, additional LDLc intervention should be considered.

- FIRE & FORGET -

If LDLc level is > 55 or > 40 mg/dL (with history of recent ASCVD), START ;

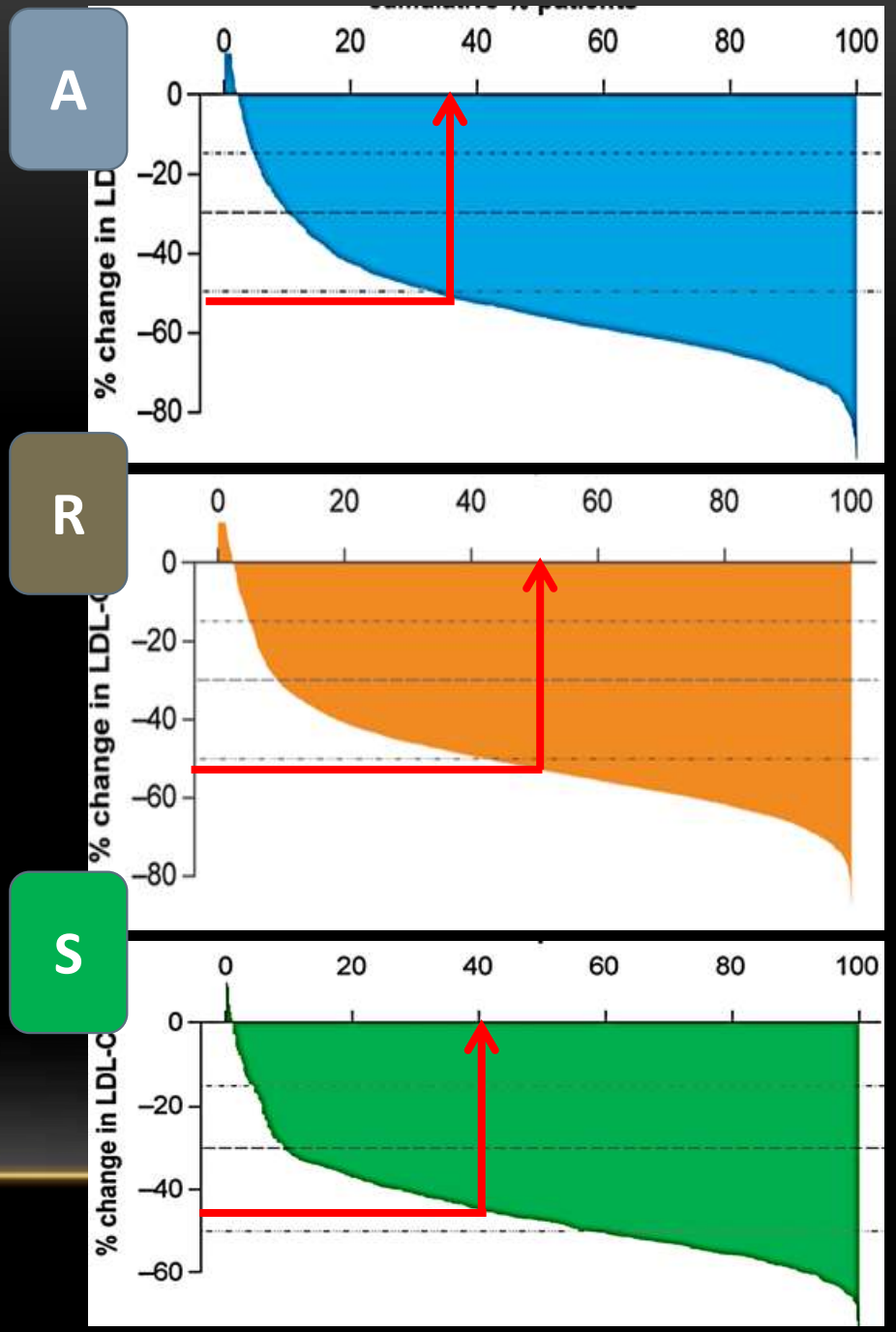
- " Maximal Tolerable Dose " of STATIN
- **Ezetimibe** 10 mg/day
- **PCSK9 inhibitor**

‘STEPWISE’ APPROACH

- Statin response is highly variable.

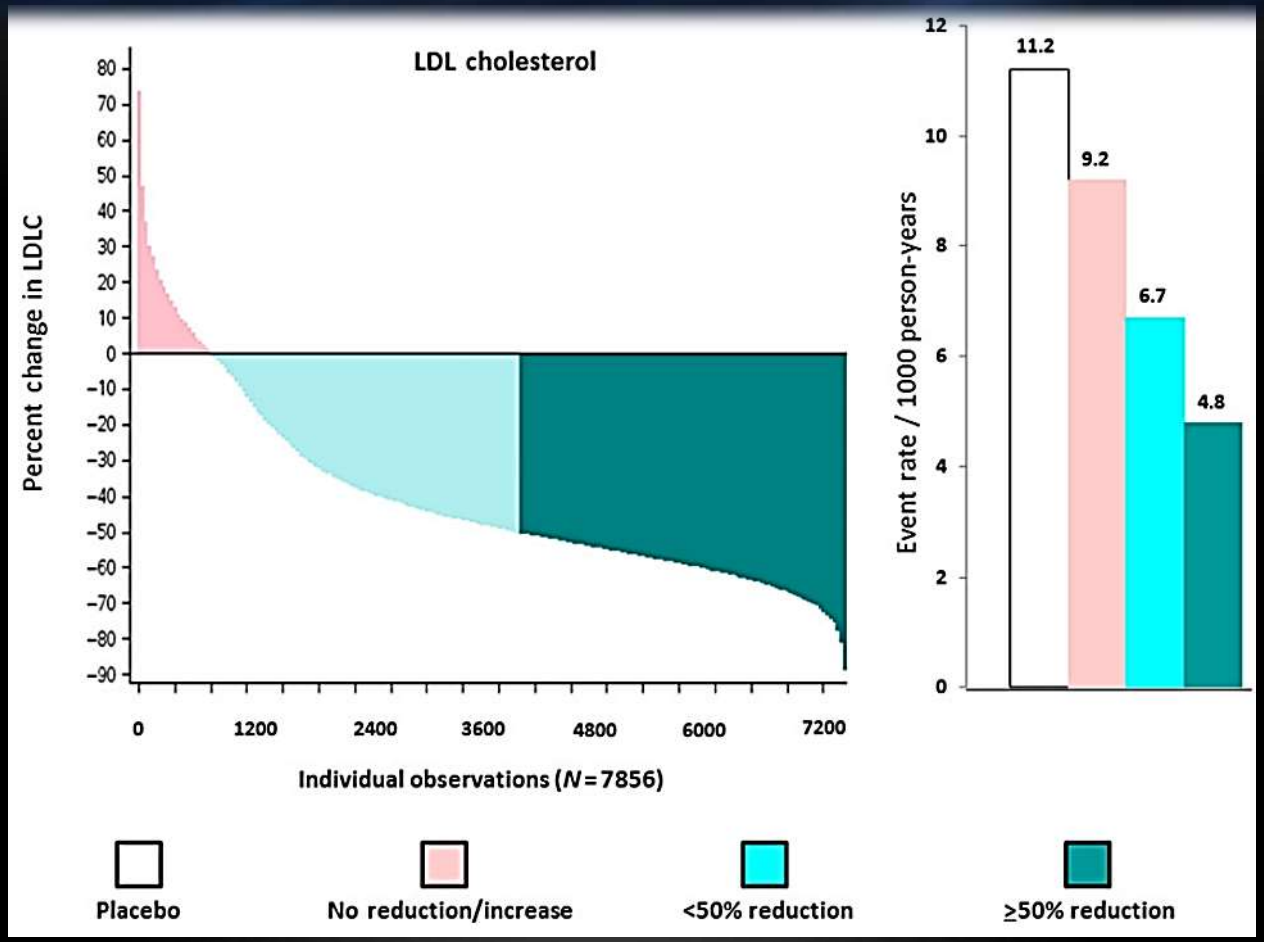
	n	LDL-C reduction (%)	
		Mean (SD)	Median (IQR)
Atorvastatin			
10 mg	7804	−35.7 (16.0)	−38.3 (−46.1, −28.8)
20 mg	3896	−43.1 (14.5)	−45.5 (−52.0, −37.2)
40 mg	1324	−47.9 (13.8)	−49.6 (−56.1, −42.4)
80 mg	2070	−49.2 (17.3)	−52.6 (−59.7, −43.4)
Rosuvastatin			
5 mg	668	−41.4 (12.8)	−43.6 (−49.5, −35.3)
10 mg	11 650	−43.5 (17.9)	−47.0 (−55.3, −36.1)
20 mg	3551	−49.4 (17.5)	−52.5 (−59.8, −43.4)
40 mg	2981	−55.5 (14.8)	−58.1 (−64.8, −49.6)
Simvastatin			
10 mg	165	−28.4 (13.8)	−29.4 (−37.6, −22.5)
20 mg	2923	−33.5 (15.8)	−35.8 (−43.9, −26.1)
40 mg	542	−40.3 (13.0)	−42.3 (−49.0, −33.2)
80 mg	478	−45.7 (13.1)	−47.6 (−54.7, −39.6)

IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.



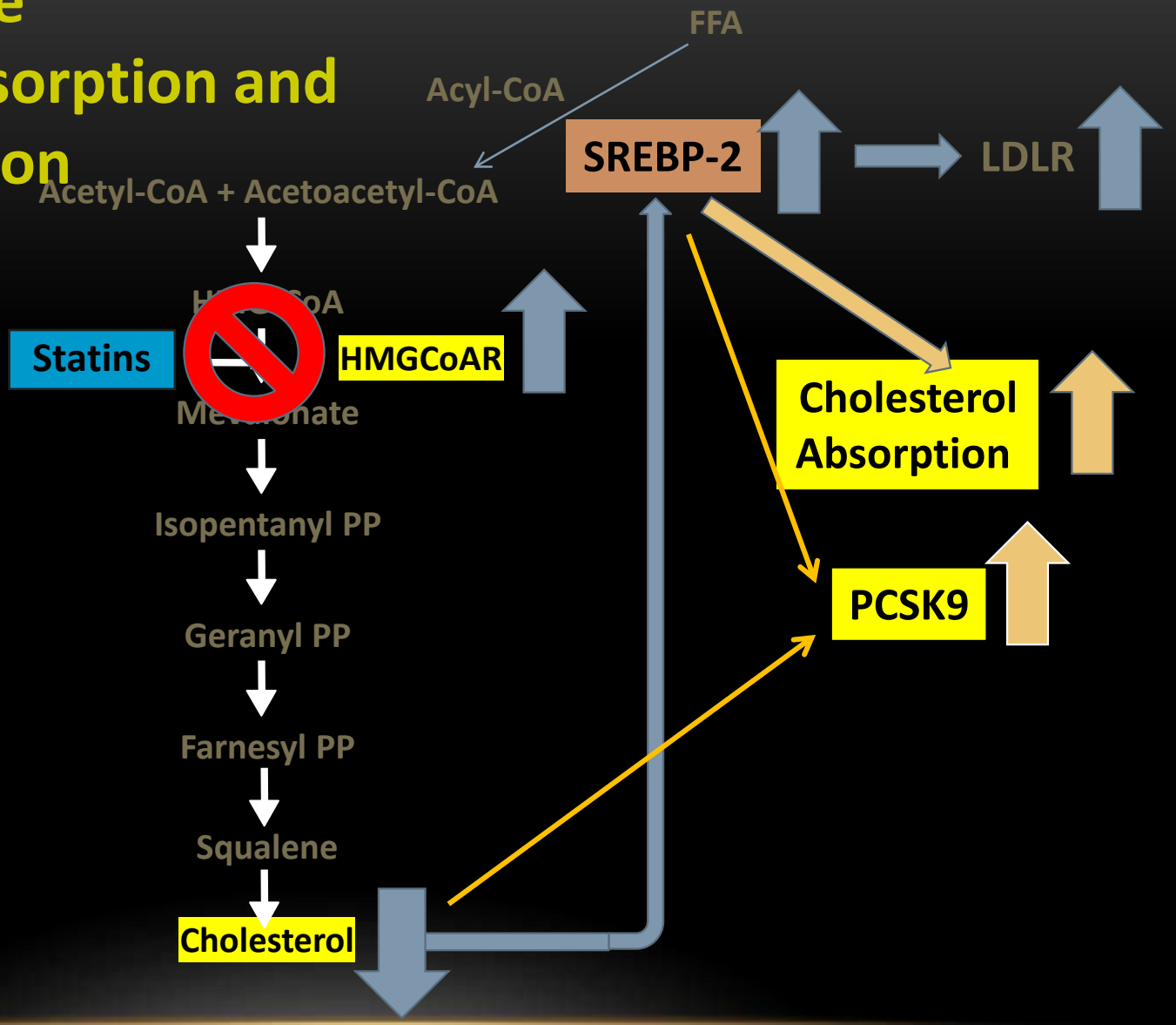
European Heart Journal – Cardiovascular Pharmacotherapy (2016) 2, 212–217

LESSONS FROM JUPITER TRIAL (20MG/D ROSU)



European Heart Journal (2016) 37, 1373–1379

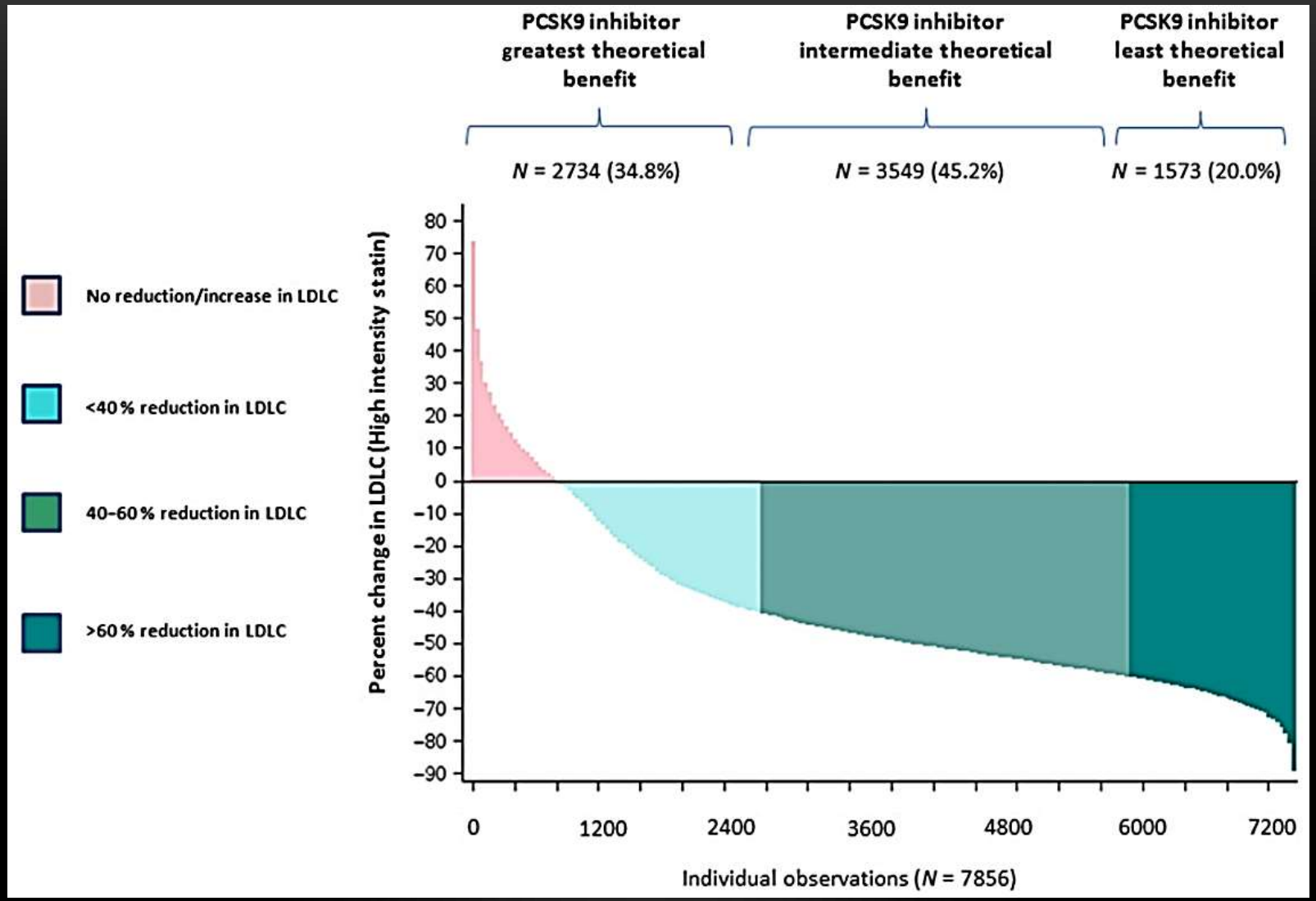
Statins enhance Cholesterol absorption and PCSK9 expression



PP = pyrophosphate.

Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.



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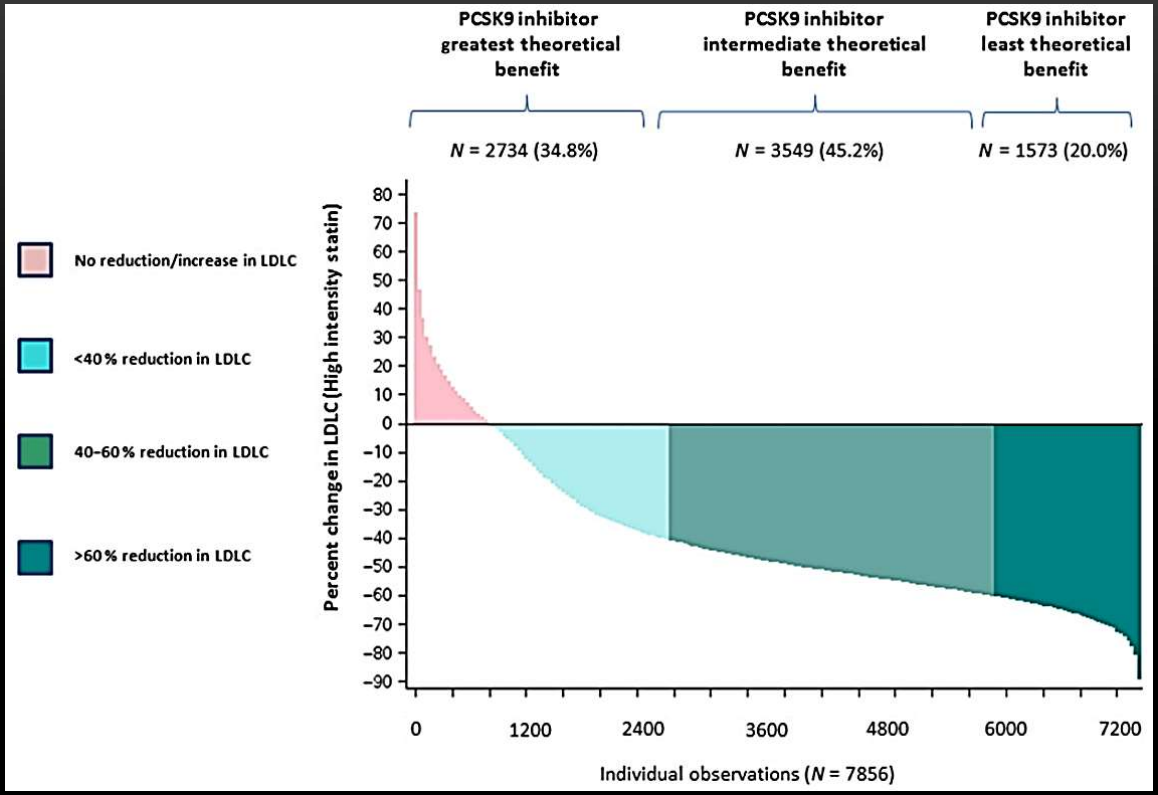
STEPWISE APPROACH

- Statin response is variable.
- Statin non-responder may response to PCSK9 inhibitors or/and ezetimibe better.
- May be cost effective.
- In case of statin intolerant group, statin dose can be reduced and minimize statin-induced adverse events.

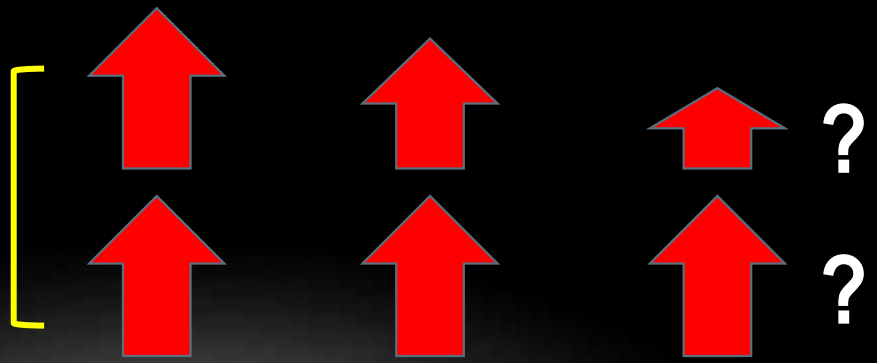
- However, TIME and EFFORT consuming process.

FIRE & FORGET APPROACH

- Simple and Straight-forward.



LDLc-lowering Capacity of PCSK9 inhibitor ?



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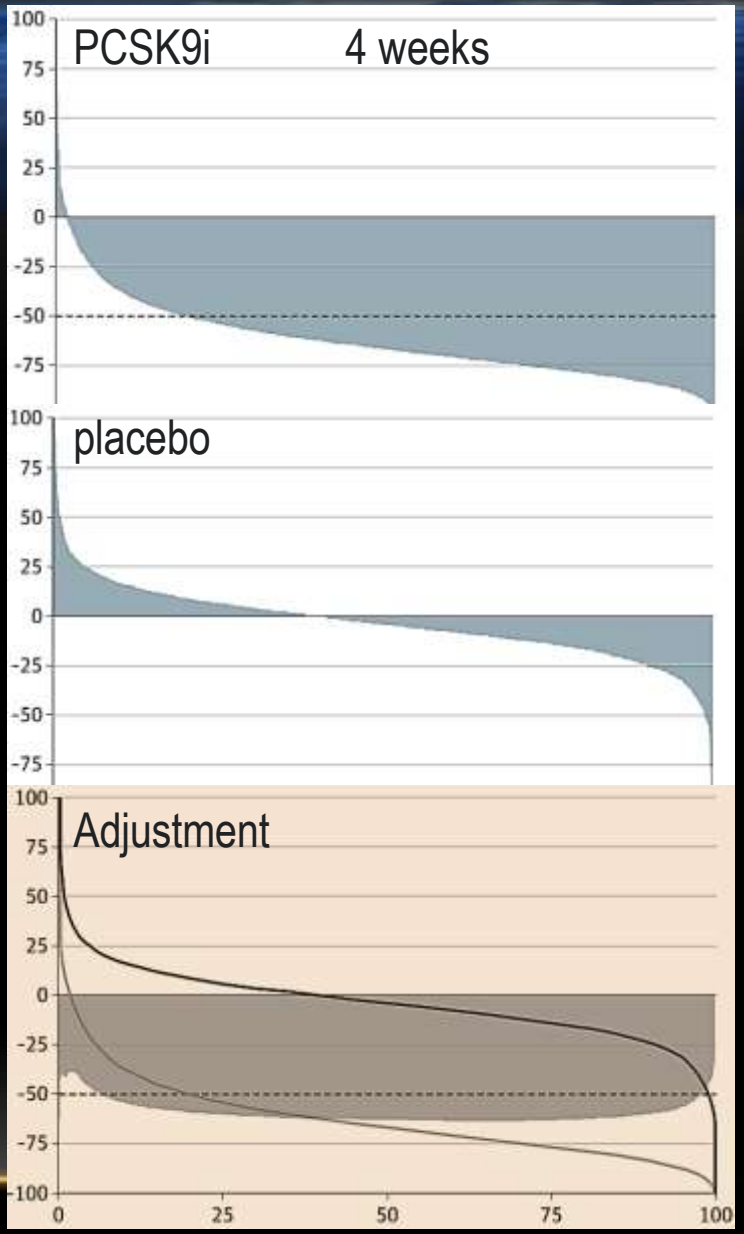
JAMA Cardiology | Brief Report

Interindividual Variation in Low-Density Lipoprotein Cholesterol Level Reduction With Evolocumab

An Analysis of FOURIER Trial Data

PCSK9 inhibitor little shows individual variability

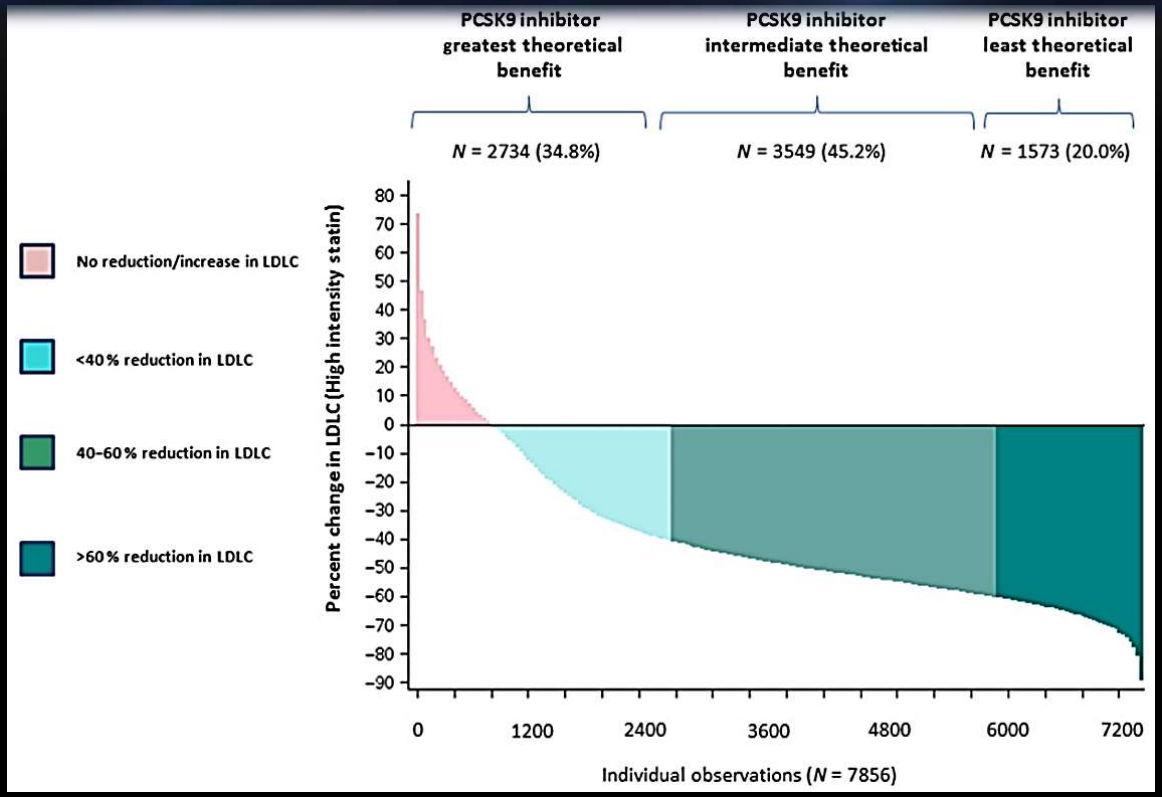
The addition of evolocumab to statin therapy lowered LDL-C levels by 50% or greater in more than 90% of patients and by 30% or greater in more than 99% of patients !



JAMA Cardiol. 2019;4(1):59-63

FIRE & FORGET APPROACH

European Heart Journal (2016) 37, 1373–1379



LDLc-lowering Capacity of PCSK9 inhibitor

ASCVD prevention

Minimal-effective Benefit

Maximal Benefit

!!

SUMMARY

- RCTs consistently show that CVD events are lower when maintained LDLc levels are lower.
- These findings were mostly from statin medication, therefore, such preventive effects may result from non-lipid (pleiotropic) statin effects, too.
- Recent trials testing add-on treatment with non-statins on the top of statin were successful and showed additional CVD prevention and further LDLc lowering, suggesting LDLc lowering itself can reduce future CVD events.
- LDLc goals are much lowered <55 and < 40 mg/dL to ACS patients and in order to achieve the goal, the addition of either/both ezetimibe or/and PCSK9 inhibitors to statins are required.
- There are two possible strategies i.e. stepwise or fire-and-forget approach.
- Unlike statins, there exists little cases intolerant to **PCSK9 inhibitors**, which can maximize CVD prevention effects to ACS patients.