LIPID LOWERING THERAPIES AND STRATEGIES IN 2022-23

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Managing Lipid targets is like Driving on a Difficult Terrain ?

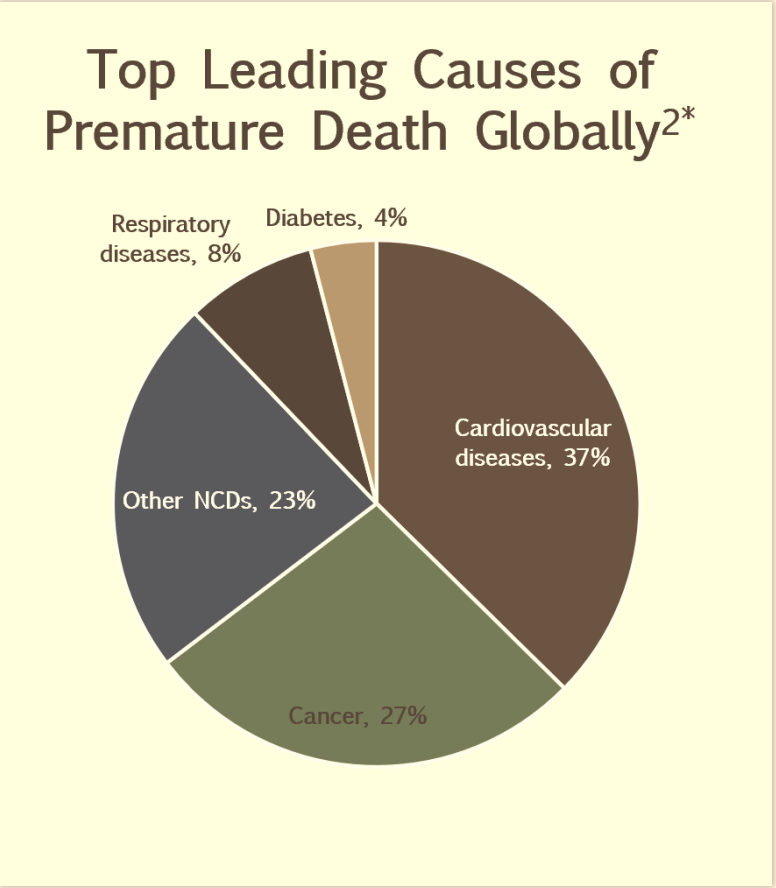
Lipid Lowering in ASCVD

Why Lipid Lowering ?

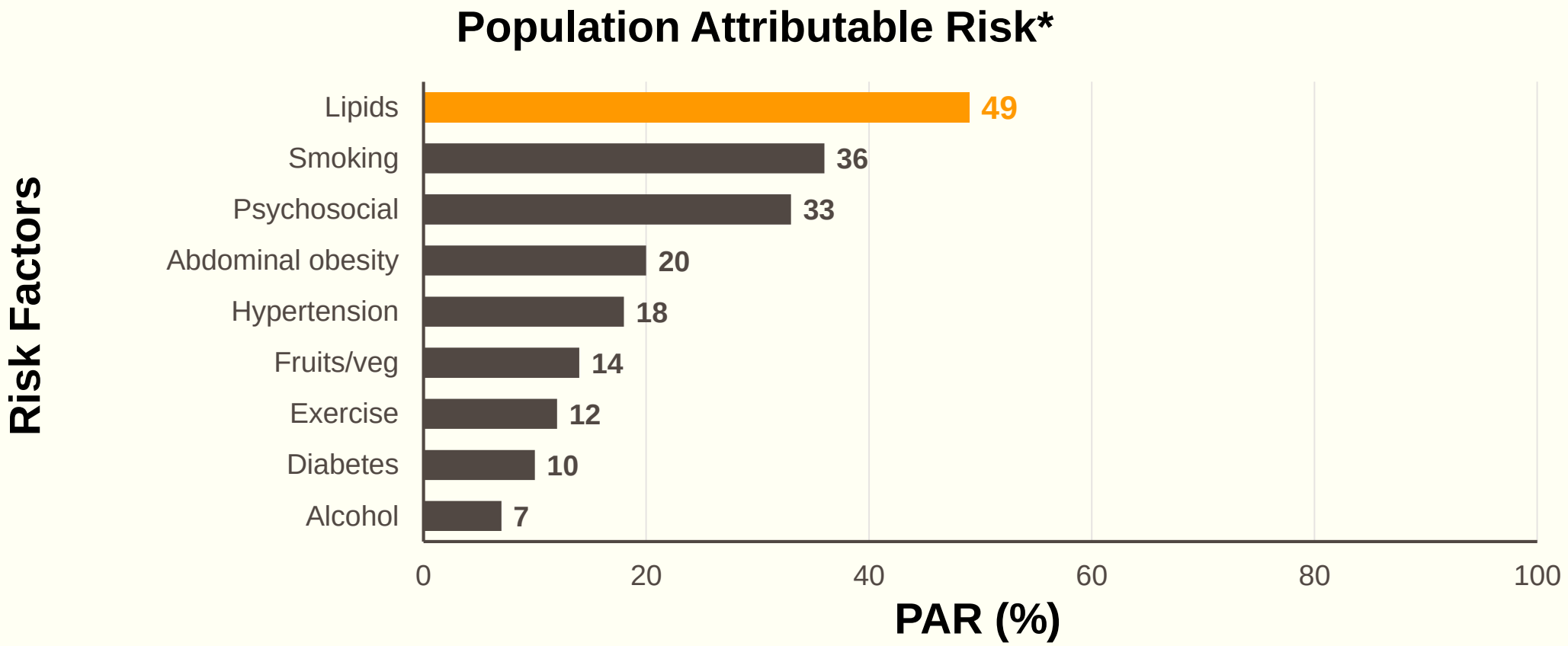
- **33% of STEMI die within 24 hours of index event**
- **15% of Unstable Angina die within 30 days**
- **LDL-C is a known modifiable risk factor:**

  reduces cardiovascular morbidity and mortality

  in patients with ASCVD including ACS

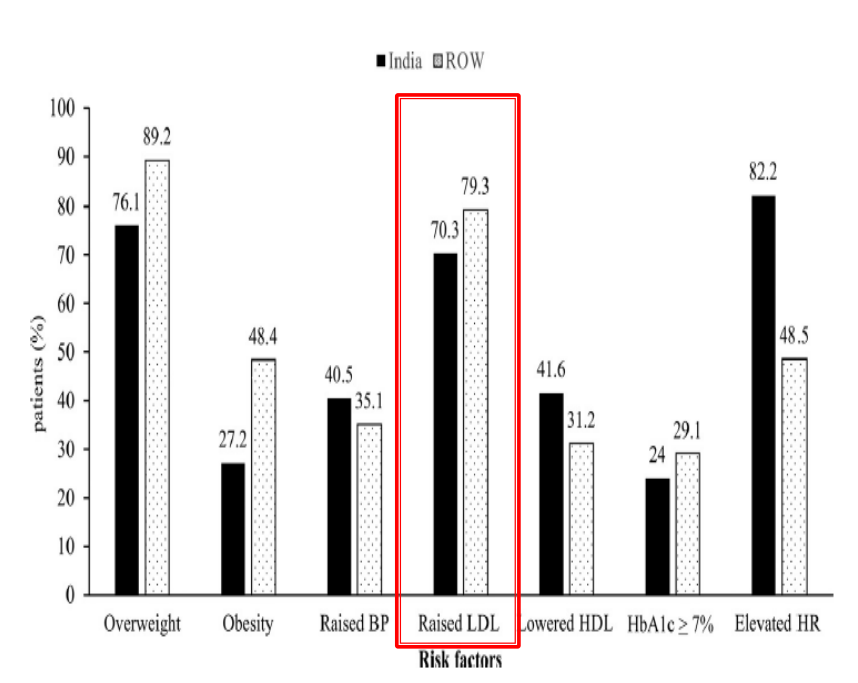


Lipids ARE One of the Most Critical Modifiable CV Risk Factor for Acute MI

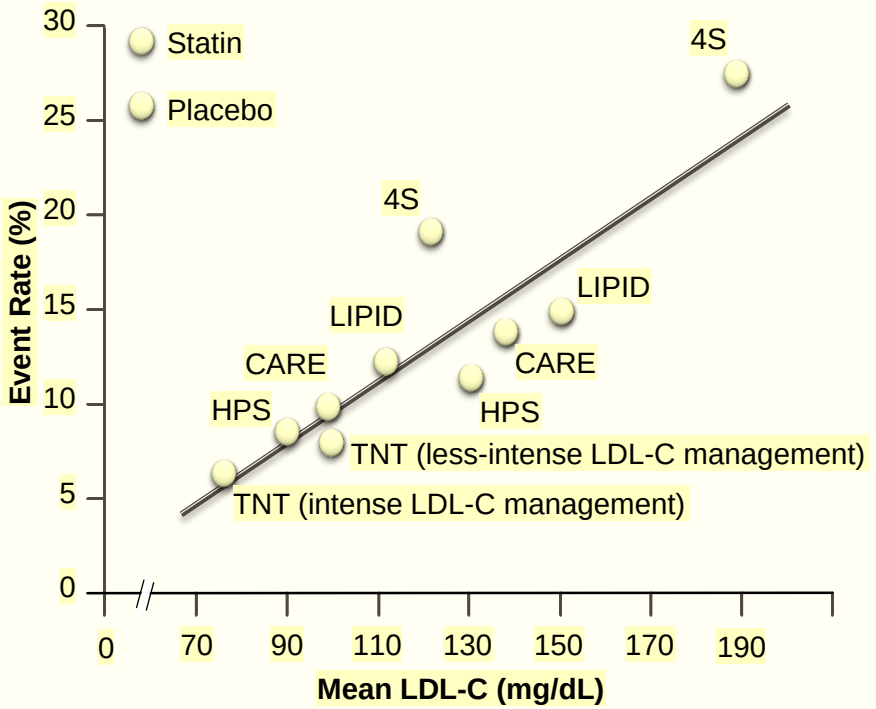


PAR = population attributable risk, adjusted for all risk factors.
INTERHEART: 9 modifiable factors account for 90% of first-MI risk worldwide, N = 15,152 patients and 14,820 controls in 52 countries.[1]
*Proportional reduction in population disease that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario (eg. no tobacco use).[2]
Yusuf S, et al. *Lancet.* 2004:364;937-952. 2. World Health Organization. https://www.who.int/healthinfo/global_burden_disease/metrics_paf/en/. Accessed February 1, 2019

LDL reduction in India: Fact File



Raised LDL (≥70 mg/dl) observed in upto 70% of CAD patients in India - CLARIFY Registry



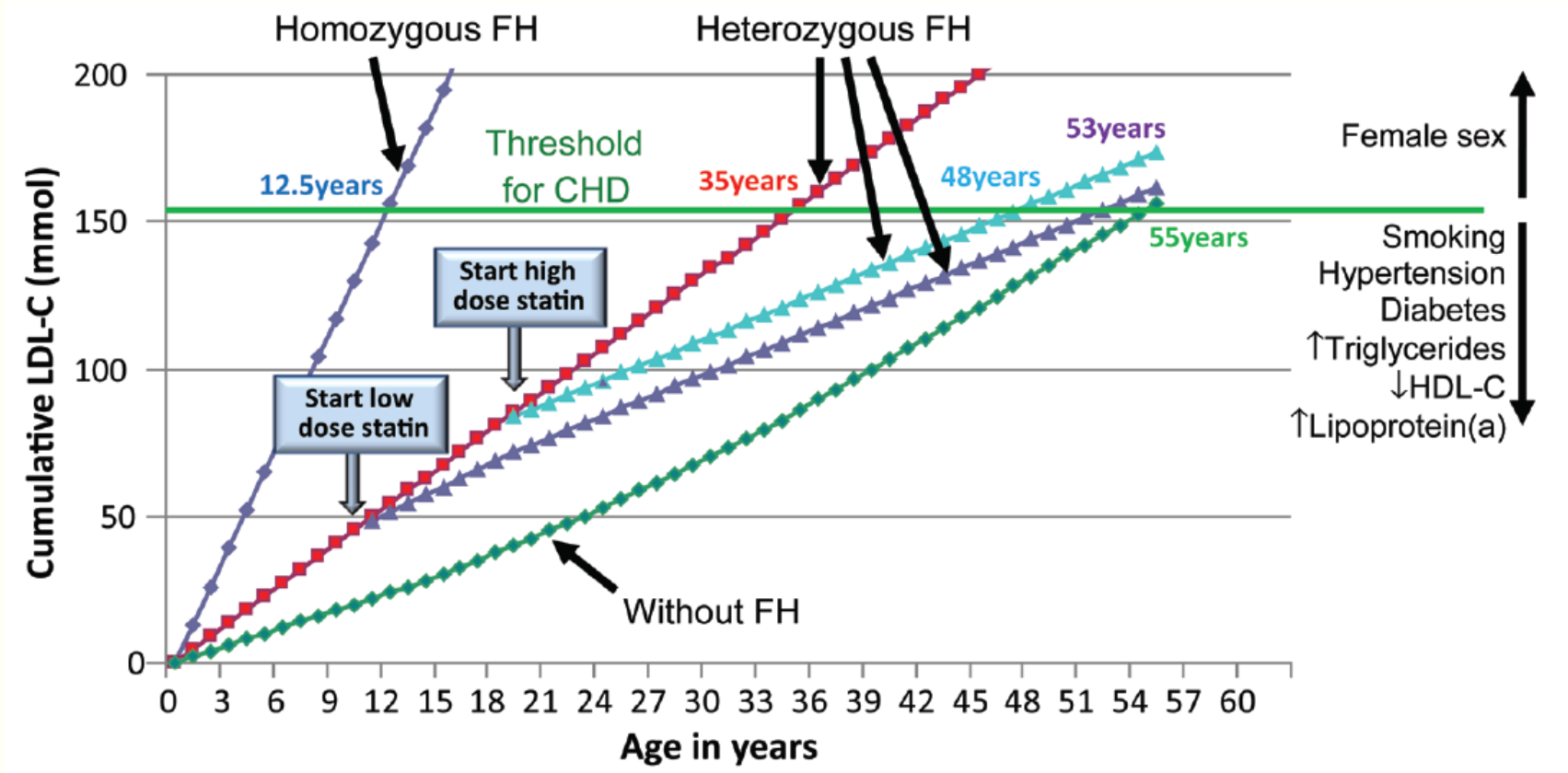
DYSIS II Study : Only 1/3rd of Asian CAD patients achieve LDL-C target with current therapy

Every 40 mg/dL decrease in LDL-C decreases relative risk for CV events by 20-25%

1. Kaul U, et al. Indian Heart Journal 2017;69:447–452; 2. New Targets.LaRosa JC, et al. N Engl J Med 2005;352:1425–35. 3. Sawhney JPS, *et al*. ESC 2015, London, UK. Poster P1684

The risk effect of LDL-C is cumulative over time

Cumulative LDL-C burden in individuals with or without FH as a function of their age at initiation of statin therapy



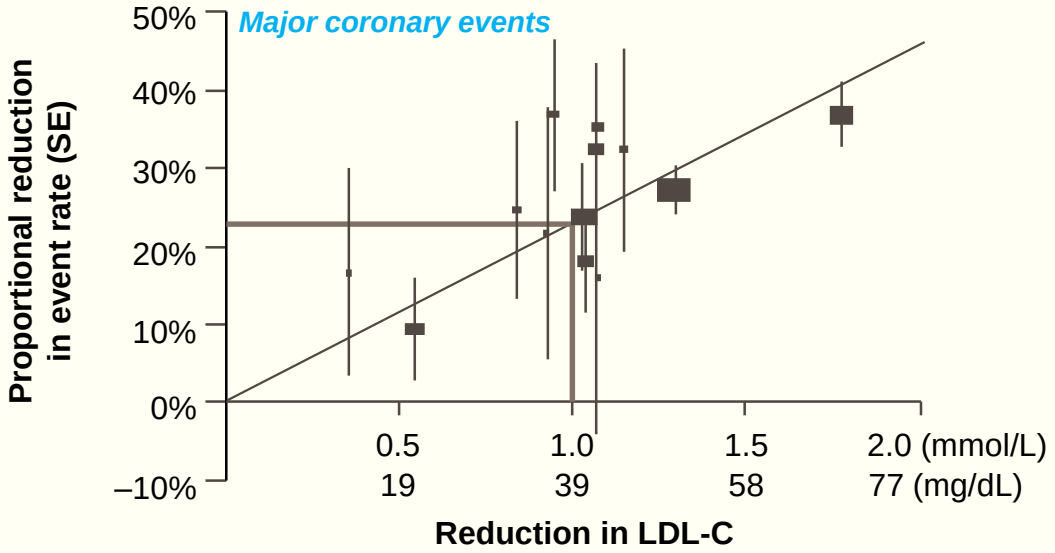
This figure uses modelled data.
CHD, coronary heart disease; CV, cardiovascular; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Nordestgaard BG, et al. Eur Heart J 2013;34:3478–90.

Absolute LDL-C Lowering is Correlated With Relative Risk Reduction in CV Events

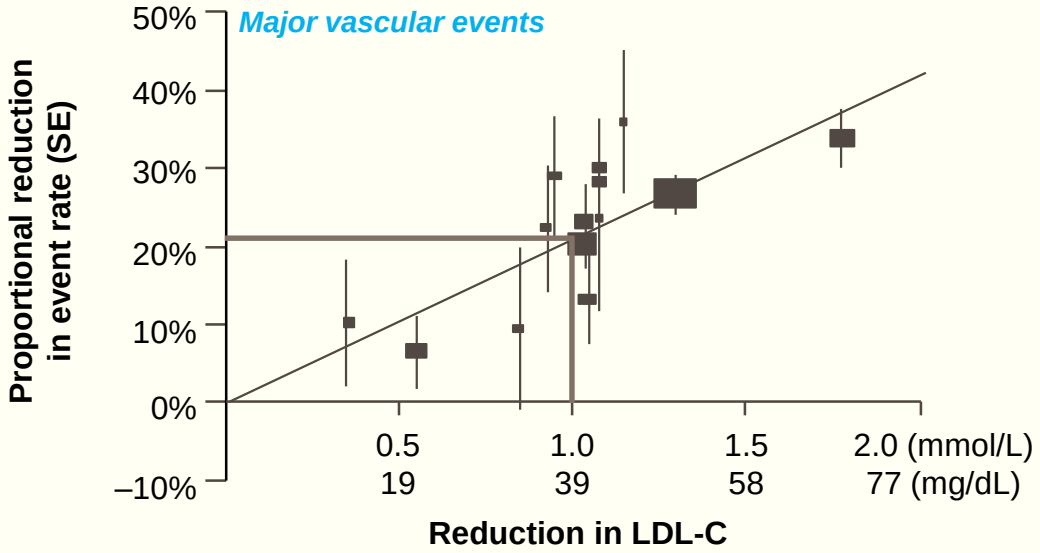
Mean absolute LDL-C reduction is linearly related to reduction in incidence of major coronary and vascular events (Meta-analysis of 14 Trials, 2005, N = 90,056)

1 mmol/L (39 mg/dL) reduction in LDL-C was associated over 5 years with:

23% reduction in major coronary events



21% reduction in major vascular events

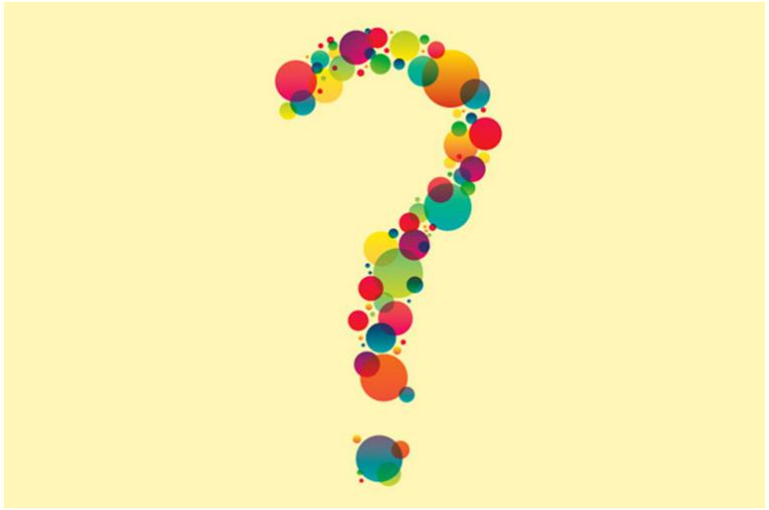


Absolute reduction in LDL-C levels is the primary predictor of relative risk reduction

Major coronary events = non-fatal myocardial infarction or CHD death. Major vascular events = the combined outcome of major coronary event, non-fatal or fatal stroke, or coronary revascularization. Square represents a single trial plotted against mean absolute LDL-C reduction, with vertical lines above and below corresponding to one SE of unweighted event rate reduction. Trials are plotted in order of magnitude of difference in LDL-C. For each outcome, regression line (which is forced to pass through the origin) represents weighted event rate reduction per mmol/L LDL-C reduction.

Baigent C, et al. *Lancet*. 2005;366:1267-1278.

Aggressive Lipid Reduction is MUST !!



How do we Risk Stratify ?

How do we risk stratify ASCVD patients currently ?

Updated Risk Stratification Approach Recommended by Lipid Association of India 2020

Risk factors/markers

Major ASCVD risk factors

1. Age ≥45 years in males and ≥55 years in females
2. Family history of premature ASCVD
3. Current cigarette smoking or tobacco use
4. High blood pressure
5. Low HDL-C

Other high-risk features

1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage
2. CKD stage 3B or 4
3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia)
4. Extreme of a single risk factor
5. Coronary calcium score >300 HU
6. Non-stenotic carotid plaque
7. Lipoprotein (a) ≥50 mg/dL

Moderate risk non-conventional risk factors

1. Coronary calcium score 100-299 HU
2. Increased carotid IMT
3. Lipoprotein (a) 20-49 mg/dL
4. Impaired fasting glucose*
5. Increased waist circumference**
6. Apolipoprotein B ≥110 mg/dL
7. hsCRP ≥2 mg/L***

Risk Group

Low risk	Moderate risk	High risk	Very High risk	Extreme Risk	
0-1 major ASCVD risk factor And Life-time CVD risk <30 %	• 2 major ASCVD risk factors • Low risk group with ≥1 moderate risk non- conventional risk factor • Life-time CVD risk ≥30%	• ≥3 major ASCVD risk factors • 2 major ASCVD risk factors with ≥I moderate risk non-conventional risk factor • ≥1 other high-risk features	• Pre existing ASCVD • Diabetics with ≥2 other major ASCVD risk factors or evidence of target organ damage • Familial homozygous hypercholesterolemia	**Category A** ↓ CAD with ≥1 feature of ***high risk group***	**Category B** ↓ CAD with ≥1 feature of ***very high risk group*** or recurrent ACS (within one year) despite LDL-C <50 mg/dL or polyvascular decease

Clinical judgment to be used if the patient has atherosclerotic peripheral arterial disease instead of coronary artery disease; *A fasting blood sugar level from 100 to 125 mg/dl. It should be confirmed by repeat testing; **Waist circumference is to be measured at the superior border of the iliac crest just after expiration. Increased waist circumference is defined as >90 cm in men and >80 cm in women. If increased waist circumference is the only risk factor, it should again be measured after 6 months after initiating heart healthy lifestyle measures; ***On two occasions at least 2

Risk Stratify your patient Properly !!

What are the current Goals of LDL-C in very High risk and Extreme Risk groups ?

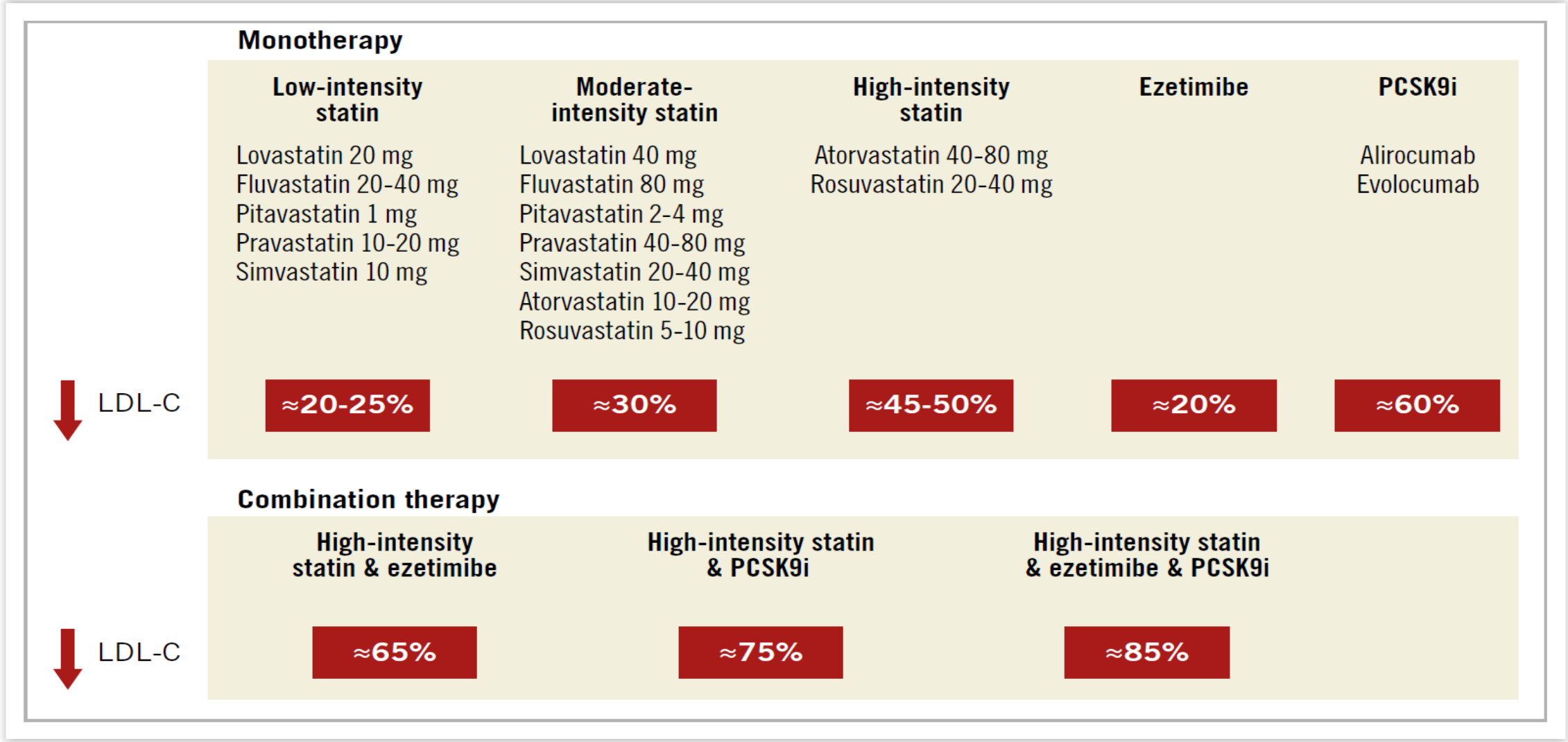
Table 1 Proposed LDL-C goals in very high risk and extreme risk group patients by the Lipid Association of India.[1,4,39]

Risk group		
Very High Risk group(VHRG)	Extreme Risk group Category A	Category B
LDL-C goal LDL-C goal of <50 mg/dl	LDL-C goal of <50 mg/dl (recommended) LDL-C goal of ≤30 mg/dl (optional) $^{\Delta}$	LDL-C goal of ≤30 mg/dl$^{\Delta}$
High-risk conditions Any one of following: ASCVD (CAD/PAD/TIA or stroke) Homozygous familial hypercholesterolemia Diabetes with ≥2 major ASCVD risk factors*/target organ damage	CAD with ≥1 of following: Diabetes without target organ damage/≤1 major ASCVD risk factors Familial hypercholesterolemia ≥3 major ASCVD risk factors CKD stage 3B and 4 ≥2 major ASCVD risk factors with ≥1 moderate non-conventional risk factor# Lp(a) ≥50 mg/dl Coronary calcium score ≥300 HU Extreme of a single risk factor PAD H/o TIA or stroke Non-stenotic carotid plaque	CAD with ≥1 of following: Diabetes + polyvascular disease/≥2 major ASCVD risk factors*/target organ damage Recurrent ACS (within 12 months) despite on LDL-C goal Homozygous familial hypercholesterolemia

What are the Goals ? ESC 2019

- **Reduction of LDL-C levels by at least 50% and the achievement of an LDL-C goal <1.4 mmol/L (<55 mg/dL) for all patients with ASCVD – i.e., including those who present with ACS or undergo PCI.**
- **For patients who experience a second vascular event within two years while taking maximally tolerated statin-based therapy, an even lower LDL-C goal <1.0 mmol/L (<40 mg/dL) may be considered (IIb/B recommendation)**
- **High intensity statin (IA) f/b adjunctive treatment with ezetimibe if LDL-C goals are not achieved. (IB)**
- **If LDL-C goals are still not achieved by 4-6 weeks: add PCSK-9 inhibitors (I)**

What is the reduction with different monotherapies and combination therapies ?



Choose the Target and identify the Bullet !!

Evolution of Lipid Lowering Therapies:

Statins* → Oral combination → MoAb → ASO → siRNA → Vaccination → Gene editing

Ezetimibe*
Icosapent ethyl*
Bempedoic acid
Fibrate

Daily

Alirocumab*
Evolocumab*
Evinocumab

Monthly
Bimonthly

Volanesorsen
Vupanorsen
Pelacarsen

Weekly
Monthly

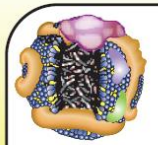
Inclisiran
Olpasiran

Bianually

Annual?

For life?

LDL-C
Main target

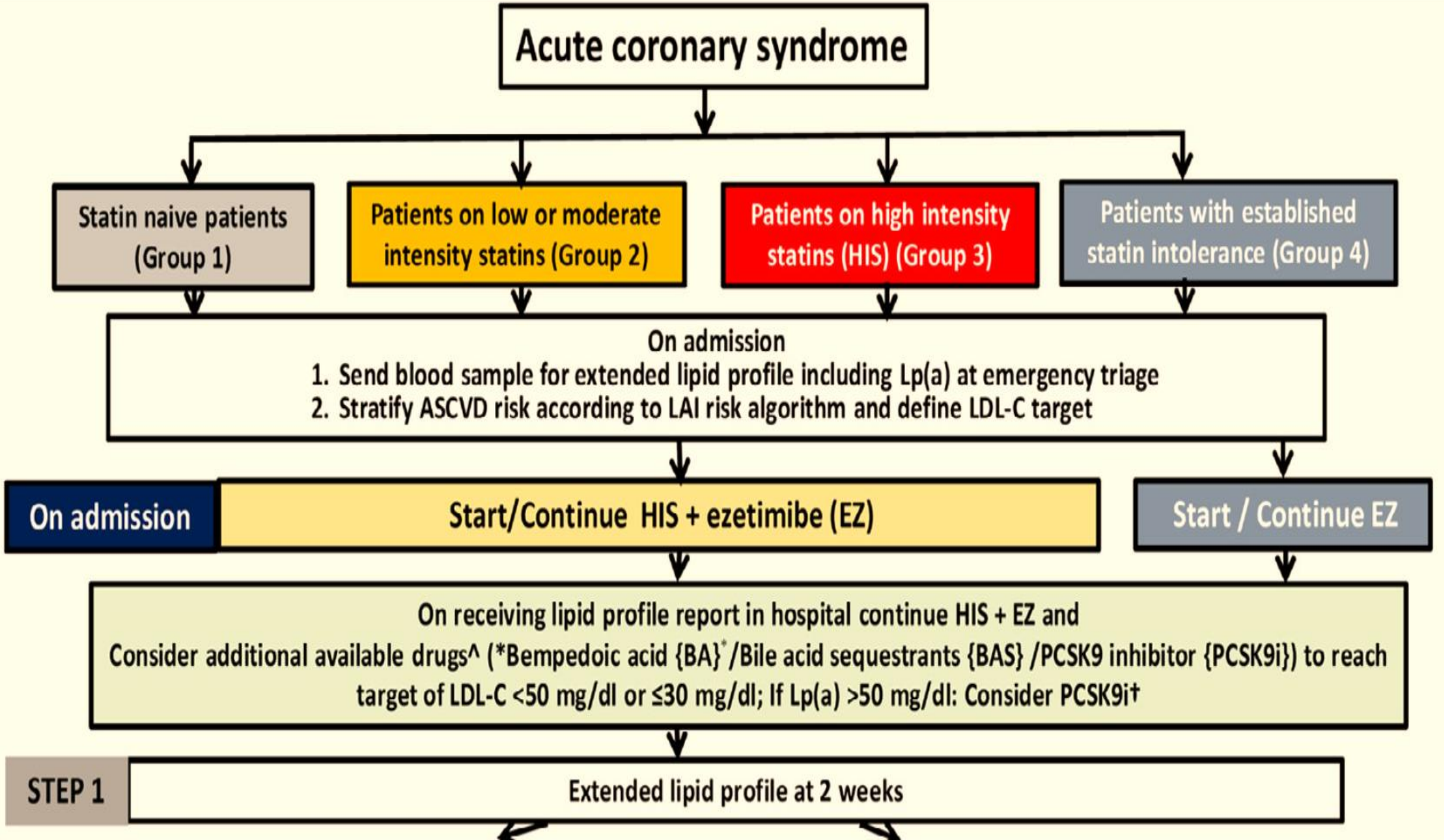


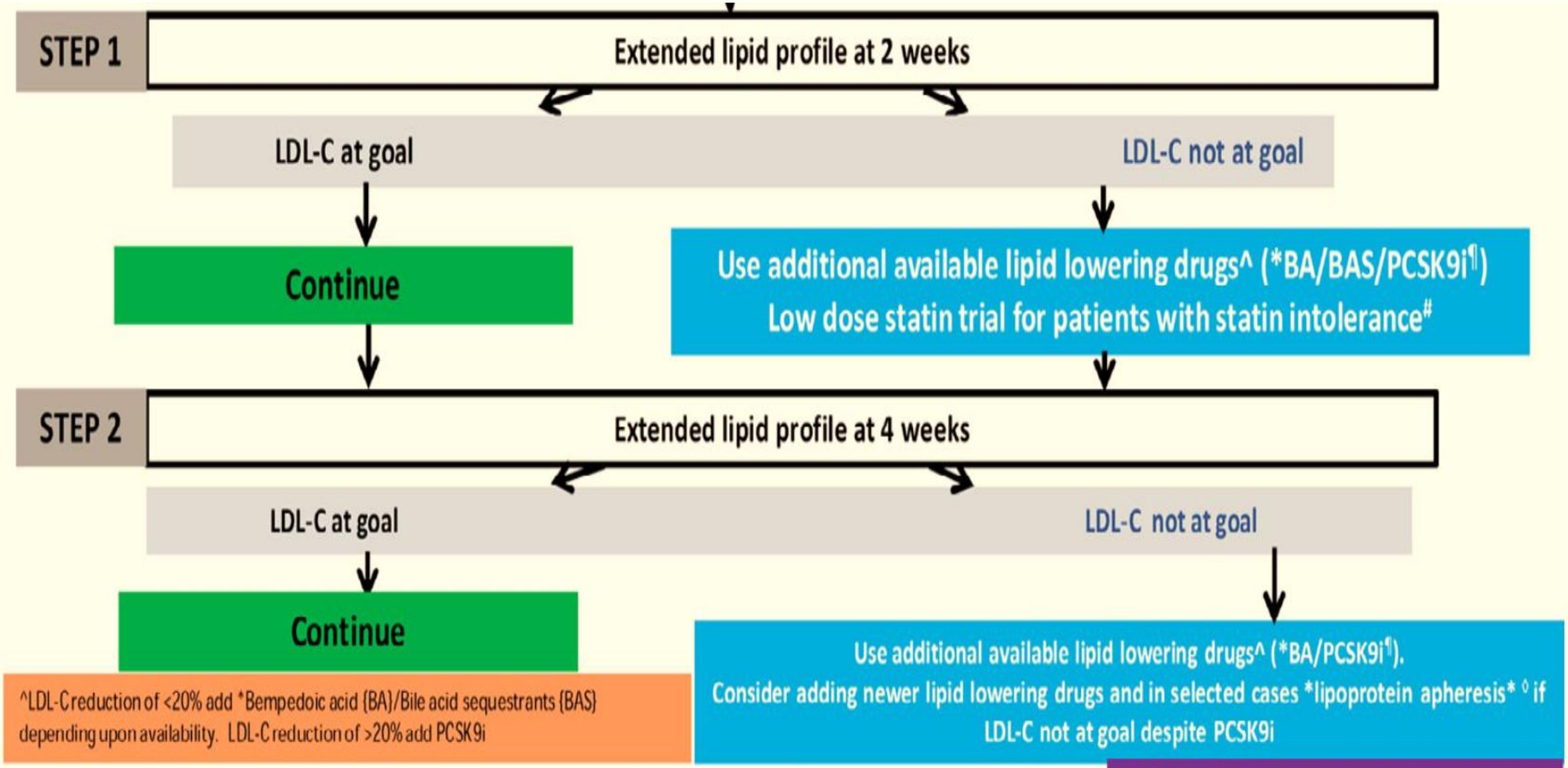
Non-HDL (including remnants)
Secondary target

Lp (a)
New target

*Therapies shown to decrease CV events

What should be the protocol of Lipid Management ?


Acute coronary syndrome
Statin naive patients (Group 1)
Patients on low or moderate intensity statins (Group 2)
Patients on high intensity statins (HIS) (Group 3)
Patients with established statin intolerance (Group 4)
On admission
1. Send blood sample for extended lipid profile including Lp(a) at emergency triage
2. Stratify ASCVD risk according to LAI risk algorithm and define LDL-C target
On admission
Start/Continue HIS + ezetimibe (EZ)
Start / Continue EZ
On receiving lipid profile report in hospital continue HIS + EZ and
Consider additional available drugs^ (*Bempedoic acid {BA}* /Bile acid sequestrants {BAS} /PCSK9 inhibitor {PCSK9i}) to reach target of LDL-C <50 mg/dl or ≤30 mg/dl; If Lp(a) >50 mg/dl: Consider PCSK9i†
STEP 1
Extended lipid profile at 2 weeks



*Approved for LDL-C lowering in ASCVD by FDA. Outcome trial pending. ¶shared decision, #Individualized clinical judgment, ◊see text, ˙not approved in India, †More aggressive LDL-C lowering therapy may be considered in individuals with high Lp(a) levels ≥50 mg/dl, which is recognized as high risk feature (LAI)/risk enhancing factor (ACC 2018).

Guideline Directed Medical Treatment for ACS to be continued. Emphasis on aggressive risk factor modification is essential.

Statin Therapy:

- **Pooled data from 26 RCTs with 170,000 individuals in primary and secondary prevention**
  - **lowering of LDL-C by 1.0 mmol/L reduces the risk of major CV events by 22% and lowers all-cause mortality by 10%.**
- **Studies:**
  - **MIRACL: 80 mg Atorva vs. placebo : within 24-96 hours in 3086 ACS pts.**
    - **16% MACE reduction at 16 weeks of FU.**
  - **PROVE-IT: 80 mg A vs. 40 mg P: 4162 ACS stabilized pts: within 10 days of index event**
    - **16% MACE reduction at 2 months FU.**
    - **Benefit appears as early as 30 days.**
- **Euro Heart survey: benefit starts within 24 hours.**

Is loading and Reloading of statins beneficial ?

- **ARMYDA- ACS: Pre-treatment with high intensity Atorvastatin 80 mg:**
  - **88% MACE reduction at 30 days**
- **13 RCTs metanalysis including 3,341 patients undergoing PCI:**
  - **Pre-treatment with high-dose statin (for statin-naïve patients) or loading of a high-dose statin (for patients already on statin therapy) reduced the risk of periprocedural MI and 30-day adverse CV events by 44%**
- **SECURE-PCI: 80 mg Atorvastatin: 2 doses: before and 24 hours after PCI: At 30 days: the EP didn't differ but was better in those undergoing PCI benefitted.**
- **Routine Pre-treatment/loading with high dose statin is recommended in patients undergoing PCI for an ACS or elective PCI (IIA: ESC)**

Ezetimibe: as an addition to Statin therapy !

IMPROVE-IT trial: 18,144 patients of ACS < 7 days from index event: simvastatin 40 mg vs. combination: Significant reduction of MACE with 7 years of FU. (Class I is statin alone is not able to achieve the target))

Statin and Ezetimibe remain first line therapy !!

Existing Therapy – Limitations and Challenges

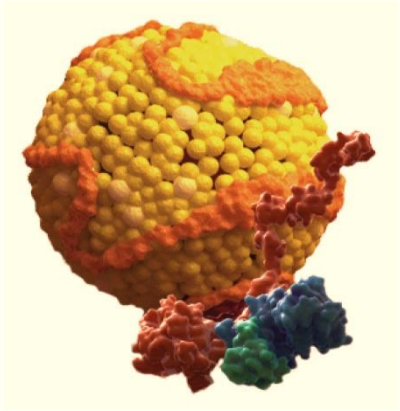
- **Statin therapy** is the cornerstone for prevention and treatment of CVD
- In real world setting, **7–29% of patients complain of statin associated muscle symptoms leading to poor adherence & discontinuation of therapy**

- There is unmet medical need for a potent, effective, non-statin agent that will lower LDL-C and reduce cardiovascular risk in
  - **High-risk patients unable to achieve optimally low LDL-C**
  - **Patients with heterozygous FH**
  - **Patients unable to tolerate/cannot be prescribed desired dose of statins due to tolerability issues**

1. Stroes ES, et al. European Heart Journal 2015;36:1012–1022

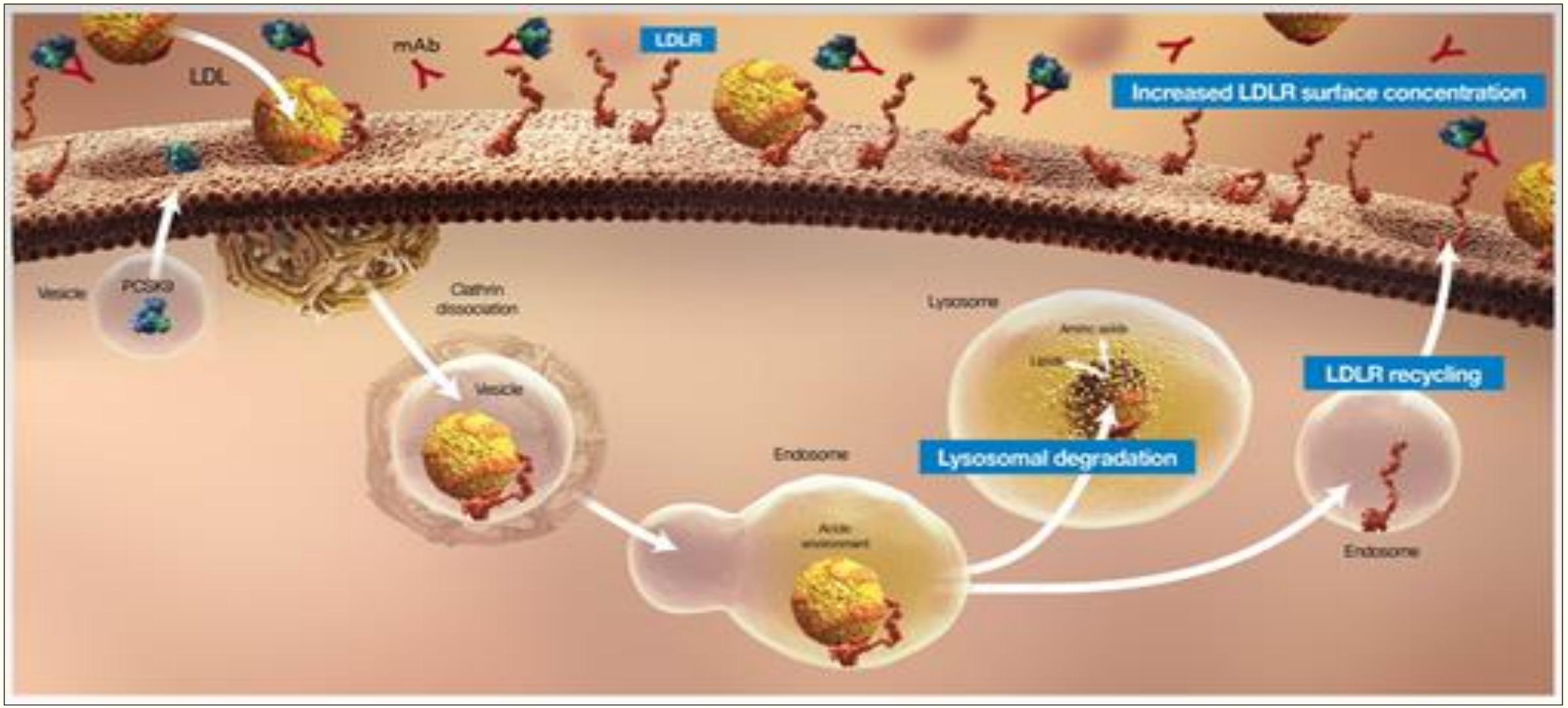
PCSK9 Inhibitors

PCSK9 is a regulator of LDL metabolism



- Proprotein convertase subtilisin/kexin type 9[1]
- Secreted by liver into plasma
- Binds LDL receptor on surface of hepatocyte
- Targets LDL receptor for degradation

PCSK9 inhibitors- Mechanism of Action



1. Abifadel M, et al. *Hum Mutat.* 2009;30:520-529. 2. Seidah NG, et al. *Circ Res.* 2014;114:1022-1036. 3. Steinberg D, Witztum JL. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

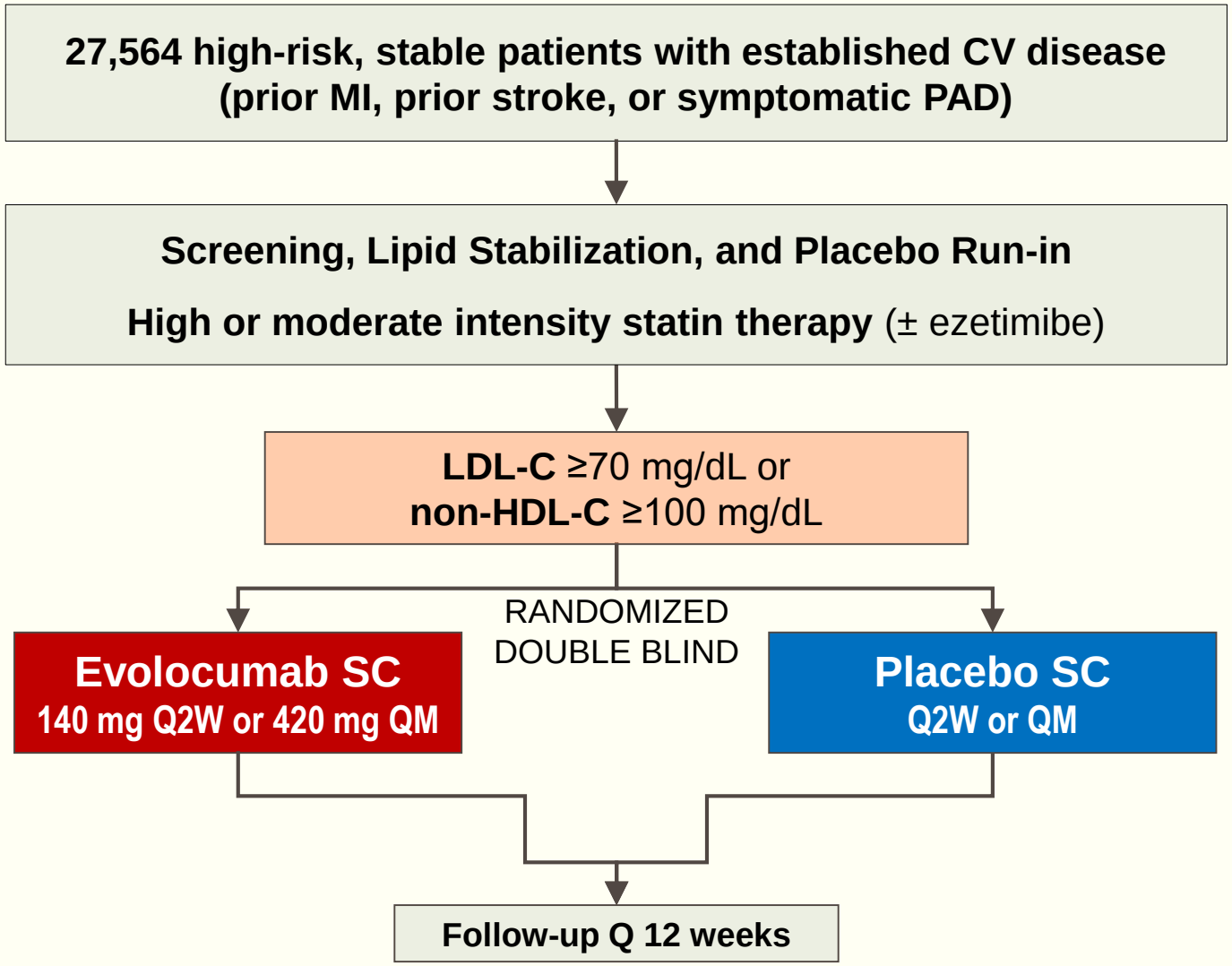
Pharmacokinetics

	Alirocumab	Evolocumab
Bioavailability	85%	72%
C max	8.18 mg/L with 75 mg in abdomen	130 µg/ml with 140mg; 46.0µg/ml
Time to C max	3-7 days (median)	3-4days (median)
Time to steady state	4-6 weeks	12 weeks
Volume of distribution	0.04 - 0.05 L/kg	3.3l
Half life	17-20 days (12 days with statin co-administration)	11-17 days

Generic (Brand)	FDA-Approved Indications	Initial Dose	FDA Max Dose
Alirocumab (Praluent®)	1) Familial hypercholesterolemia (FH) 2) Primary HLD 3) Secondary prevention of CV events	75mg every 2 weeks OR 300mg every 4 weeks	150mg every 2 weeks
Evolocumab (Repatha®)		420mg monthly (subQ) Off-label: 420mg every 2 weeks	420mg monthly
		140mg every 2 weeks OR 420mg once monthly	

FDA = Food and Drug Administration; HLD = hyperlipidemia; CV = cardiovascular; SubQ = subcutaneous

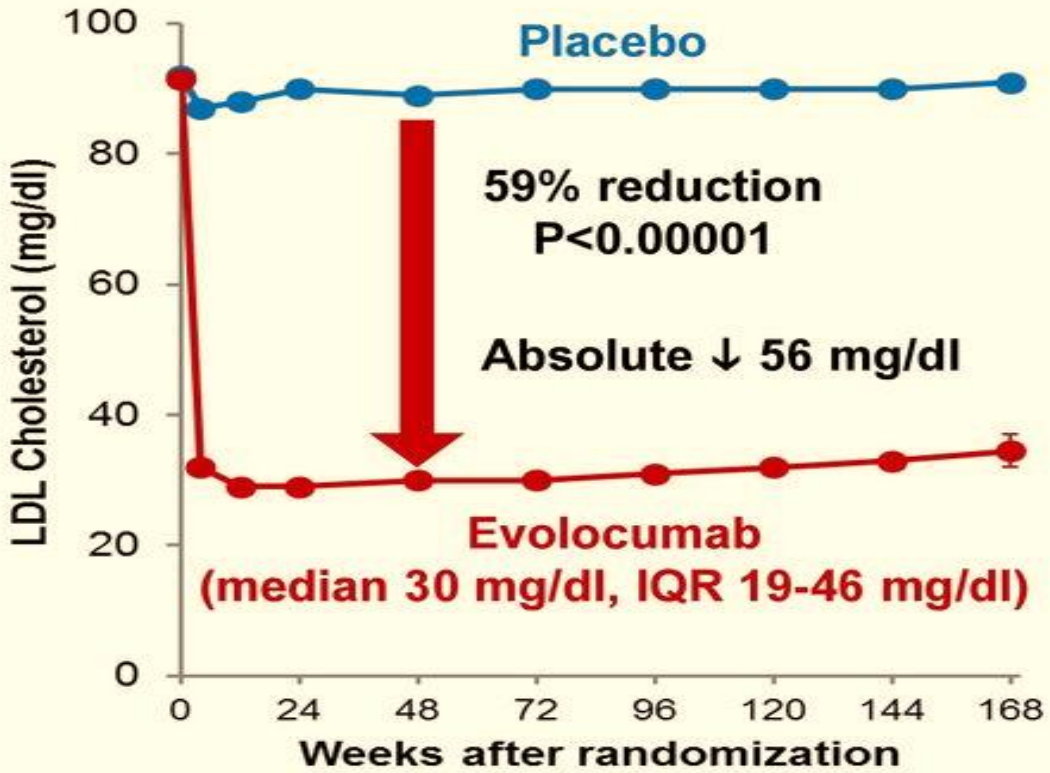
FOURIER Trial Design

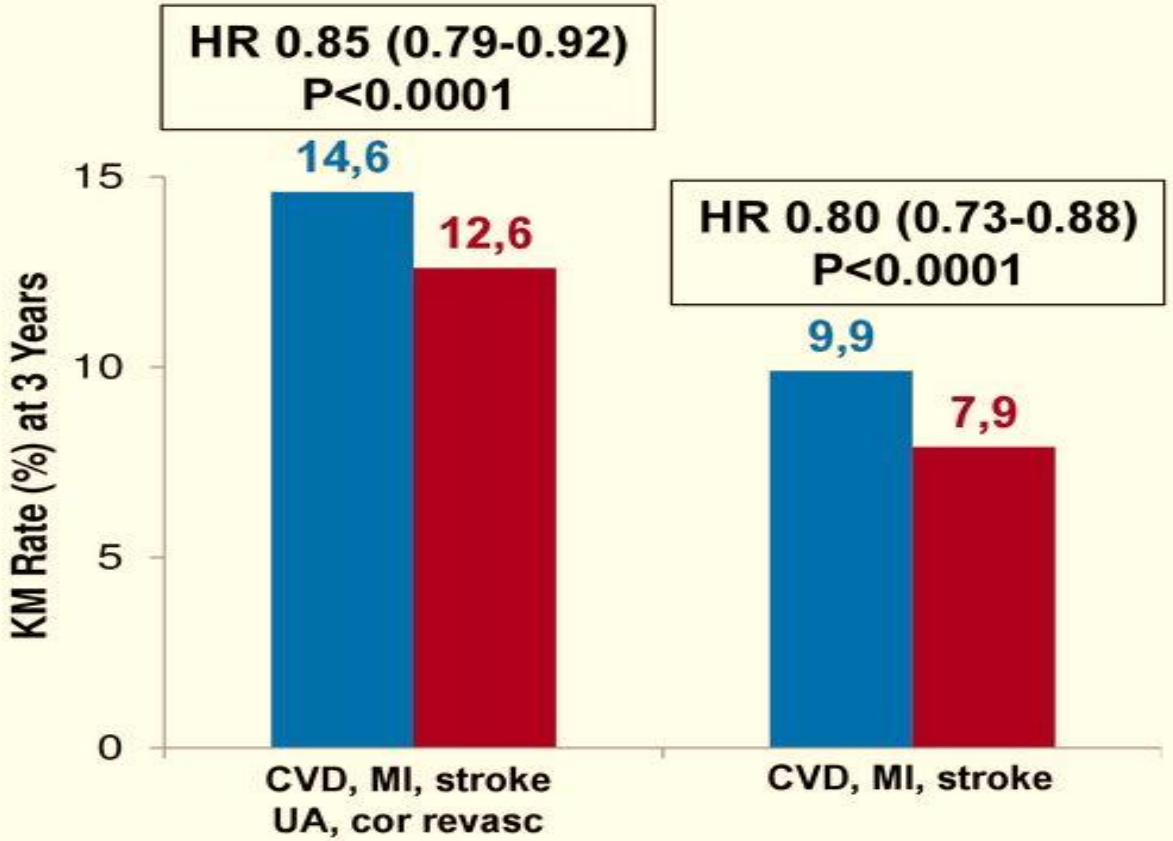


Sabatine MS et al. *Am Heart J* 2016;173:94-101

Summary of Effects of PCSK9i Evolocumab

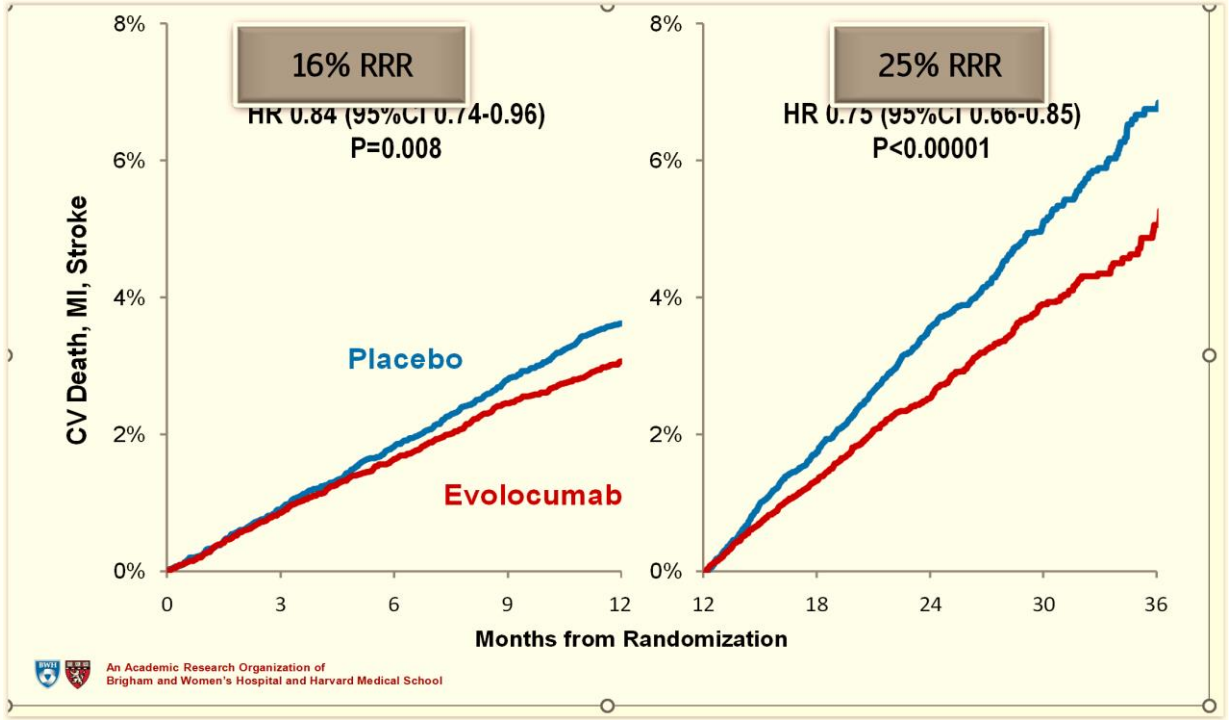
- ↓ LDL-C by 59%
- ↓ First CV outcomes in patients on statin
- Safe and well-tolerated





An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Sabatine MS et al. *NEJM* 2017;376:1713-22

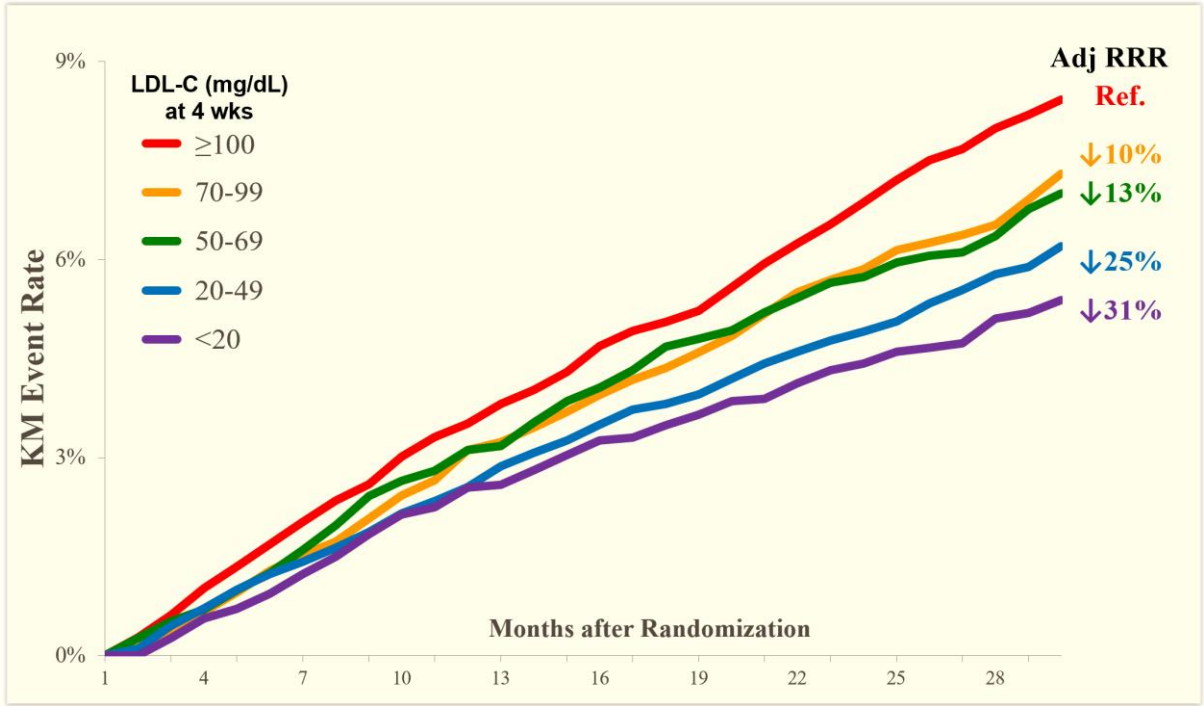


Highest reduction in second year

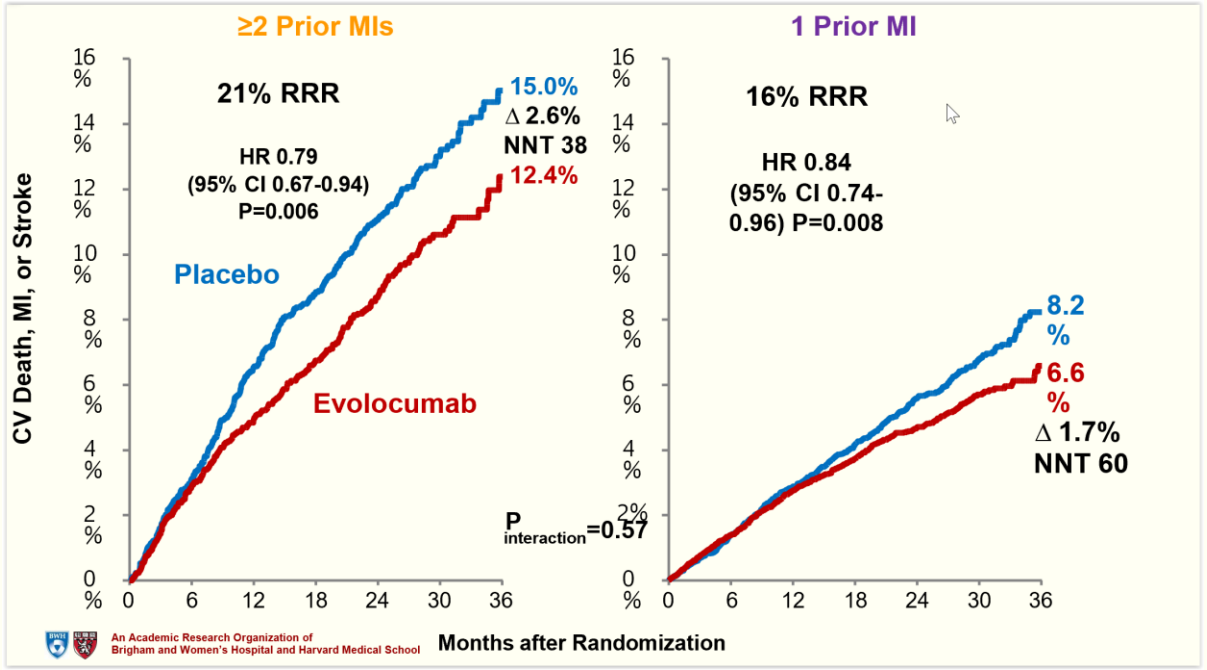
CV Death, MI or Stroke by Achieved LDL-C at Month

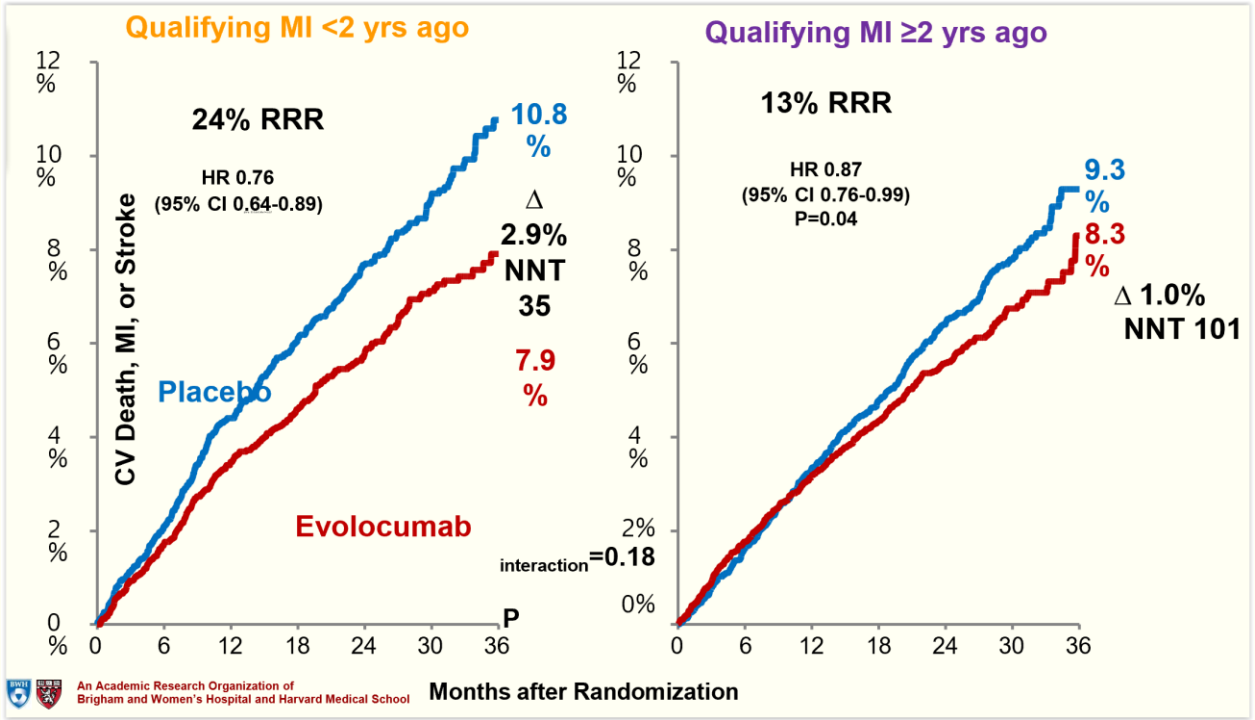
1

BENEFITS START EARLY !!



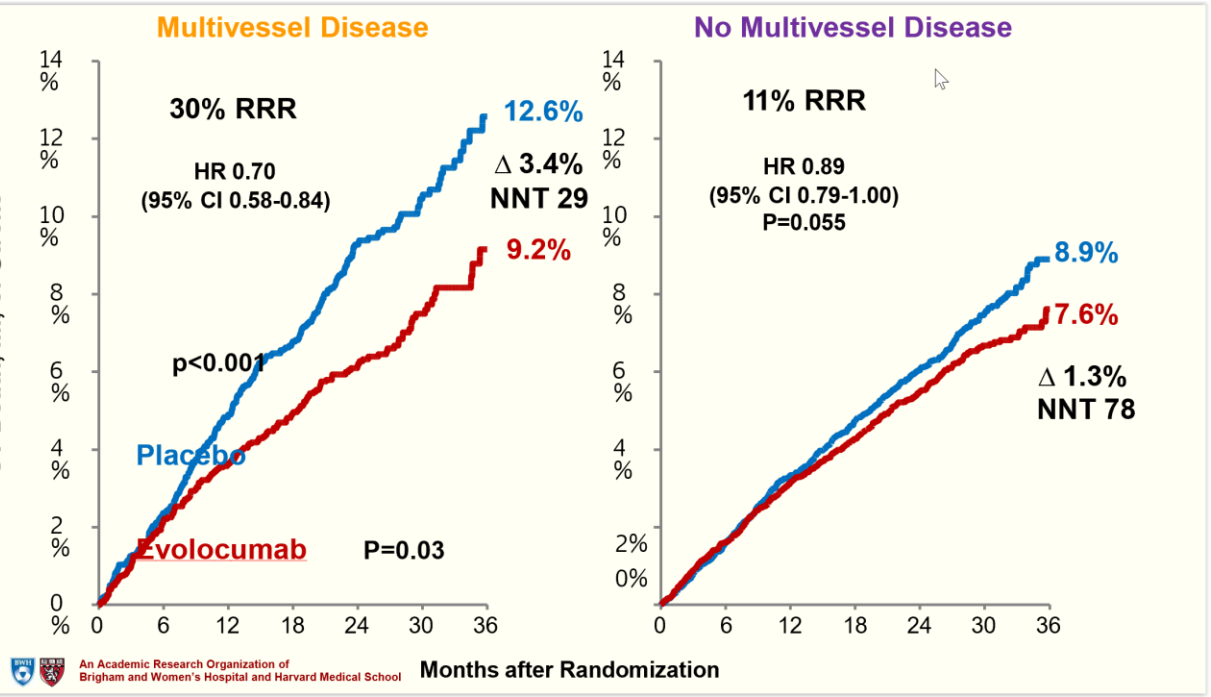
Higher risk reduction in >2 prior MI's

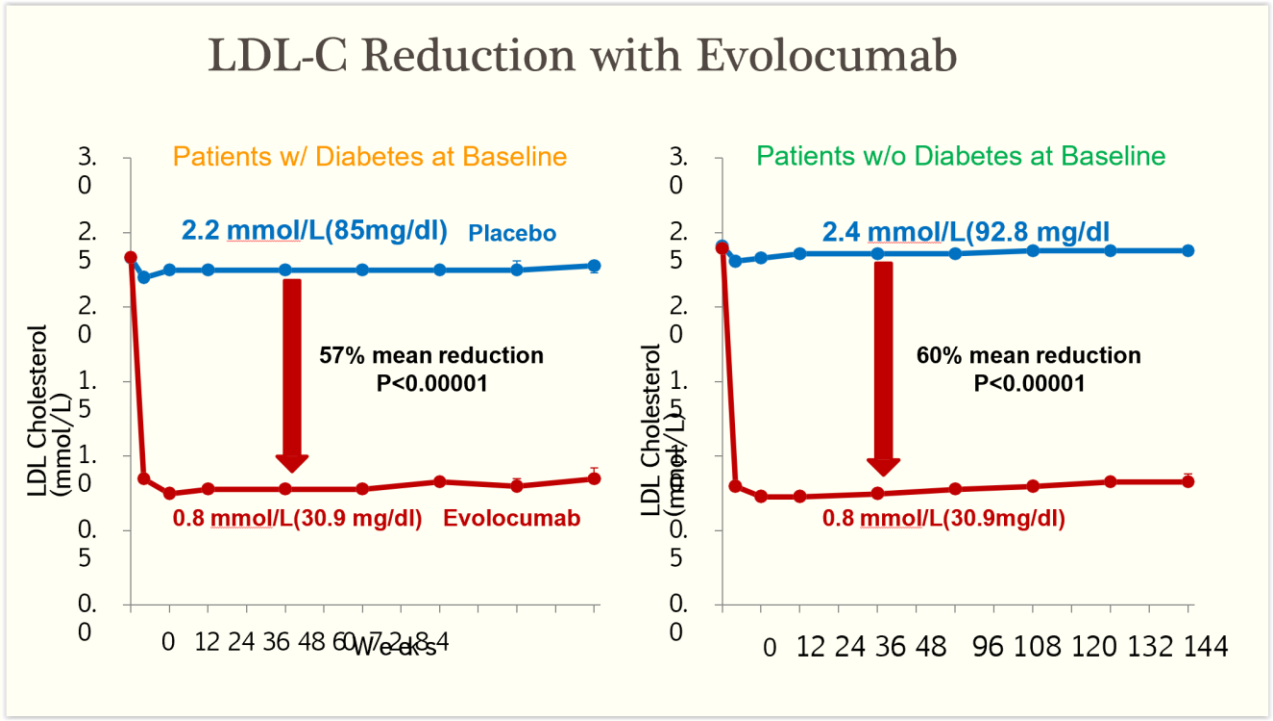




Higher risk reduction in MI < 2 years

Similar LDL reduction in people with or without diabetes



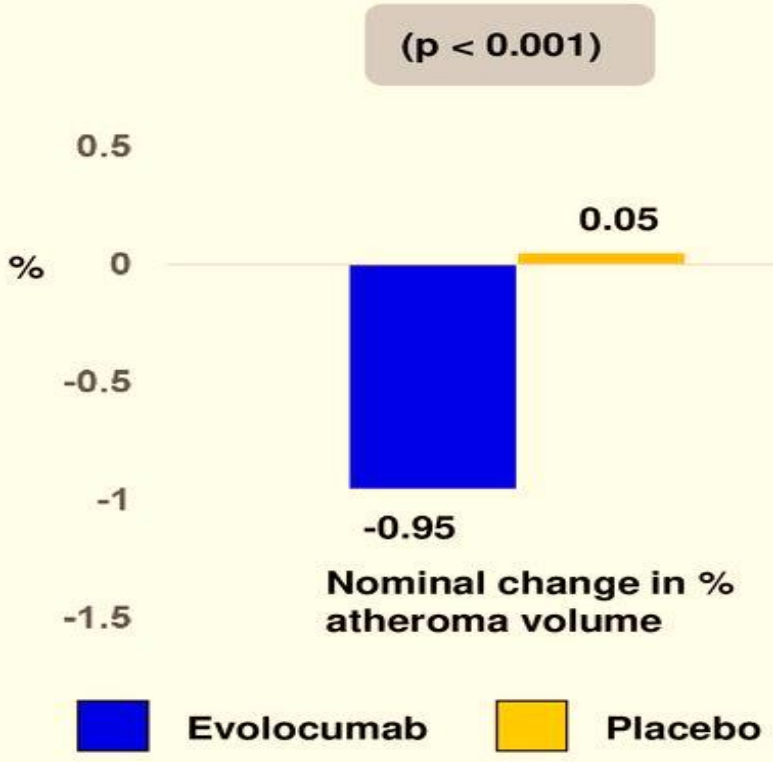


Higher risk reduction in multi-vessel disease

Can PCSK9 inhibitors change Plaque Volume ?

GLAGOV

Trial design: Patients with CAD and elevated LDL cholesterol on statin therapy were randomized to subcutaneous evolocumab (n = 484) vs. subcutaneous placebo (n = 486).



Results

- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group (p < 0.001 for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo (p < 0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

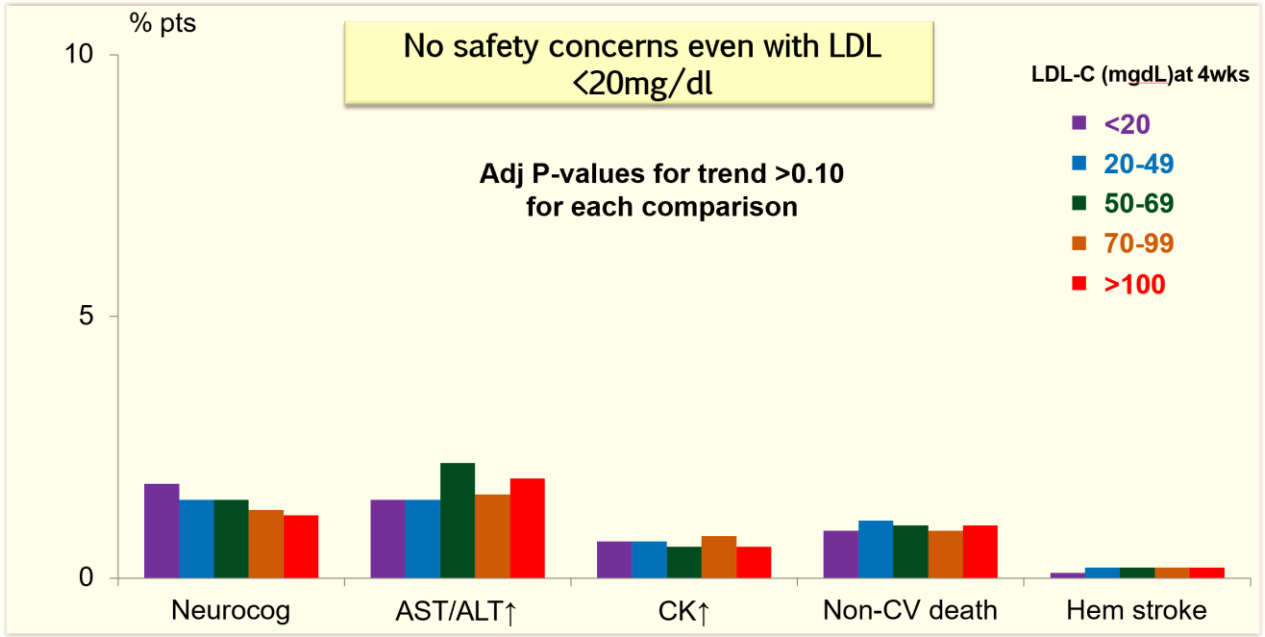
Conclusions

- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression

Nicholls SJ, et al. JAMA 2016;316:2373-84

FOURIER: Safety Data

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	77.4	77.4
Serious	24.8	24.7
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Treatment-related and led to d/c of study drug	1.6	1.5
Muscle-related	5.0	4.8
Cataract	1.7	1.8
Diabetes (new-onset)	8.1	7.7
Neurocognitive	1.6	1.5
Laboratory results (%)		
Binding Ab	0.3	n/a
Neutralizing Ab	*none*	n/a



Highest risk-Highest benefit strategy

- **‘Highest risk’ - those with the highest baseline event rate**
- **‘Highest benefit’- patients with the highest starting LDL-C will achieve the greatest absolute reduction in LDL-C and hence the greatest RRR on the drugs.**
- **Because-**
  - **RRR is proportionate to the absolute decrease in LDL-C level in mmol/L,**
  - **Magnitude of percent LDL-C reduction with PCSK9 inhibitor therapy appears similar across baseline LDL-C subgroups**

Lieven Annemans, et al. *Euro H Jour*, 39 (27), 2018, 2546–50

Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab - ODYSSEY OUTCOMES Trial

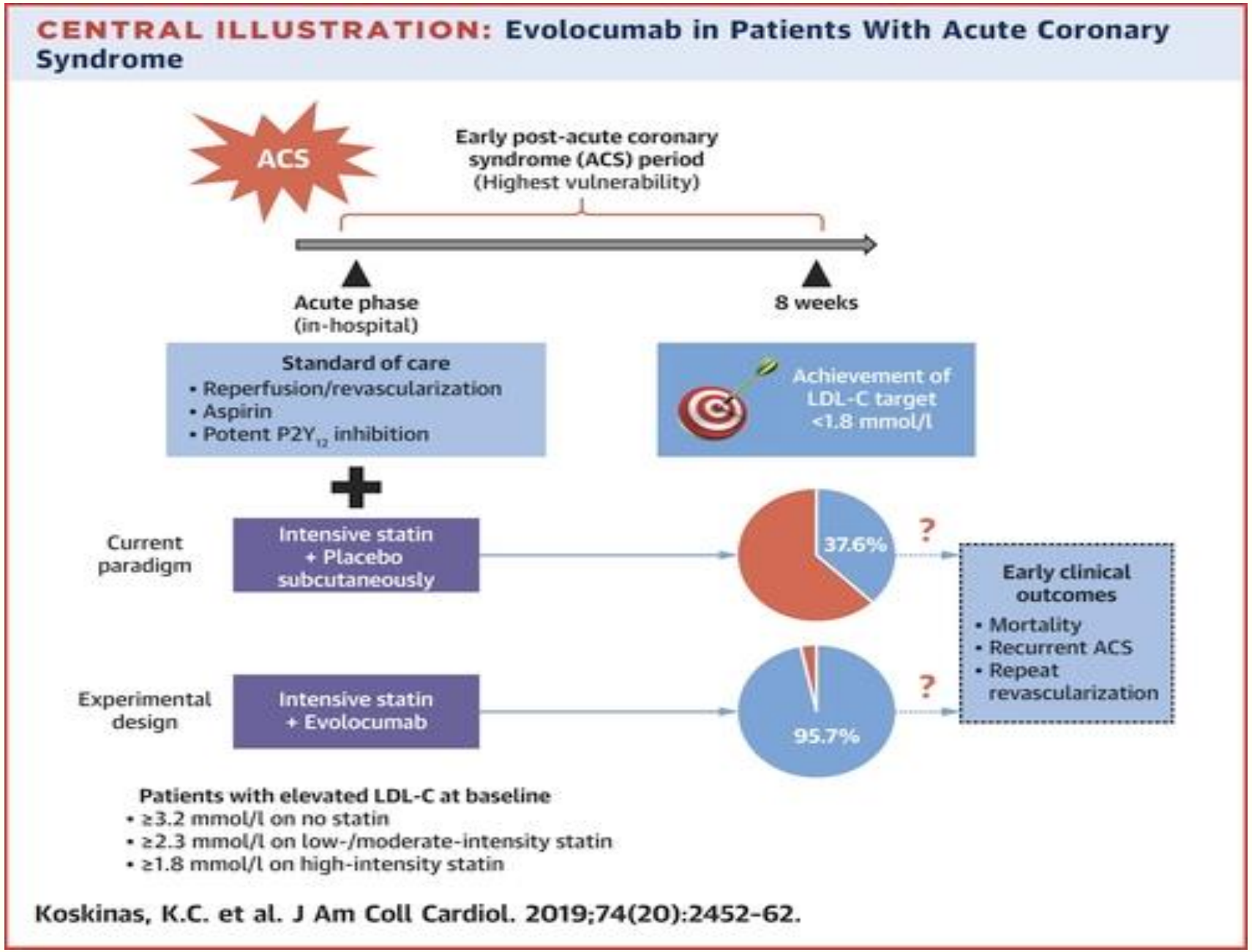
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY

>40y, ACS history withing past 1-12 months, on high dose statin, Inadequate control of lipids.

Alirocumab		Placebo
Dose titrated between 75 and 150 mg Goal: LDL-C 25-50 mg/dl, but above 15 mg/dl.		Dosed accordingly to studydrug 
N = 9462		N = 9462
9.5%	MAJOR ADVERSE CARDIAC EVENTS (MACE) HR 0.85 (0.78-0.93), p = 0.0003.	11.1%
6.6%	MYOCARDIAL INFARCTION 0.86 (0.77, 0.96) $P = 0.006$	7.6%
1.2%	ISCHEMIC STROKE 0.73 (0.57, 0.93) $P = 0.01$	1.6%
3.5%	ALL-CAUSE MORTALITY 0.85 (0.73, 0.98) $P = 0.026$	4.1%
37.6 MG/DL	LDL-C REDUCTION AT 4 MONTHS 62.7% reduction	93.3 MG/DL

Use of biweekly alirocumab significantly reduces cardiovasculat events, including all-cause mortality and MI, among patients with an ACS event within the preceding 1-12 months

EVOPACS: Evolocumab immediately after ACS



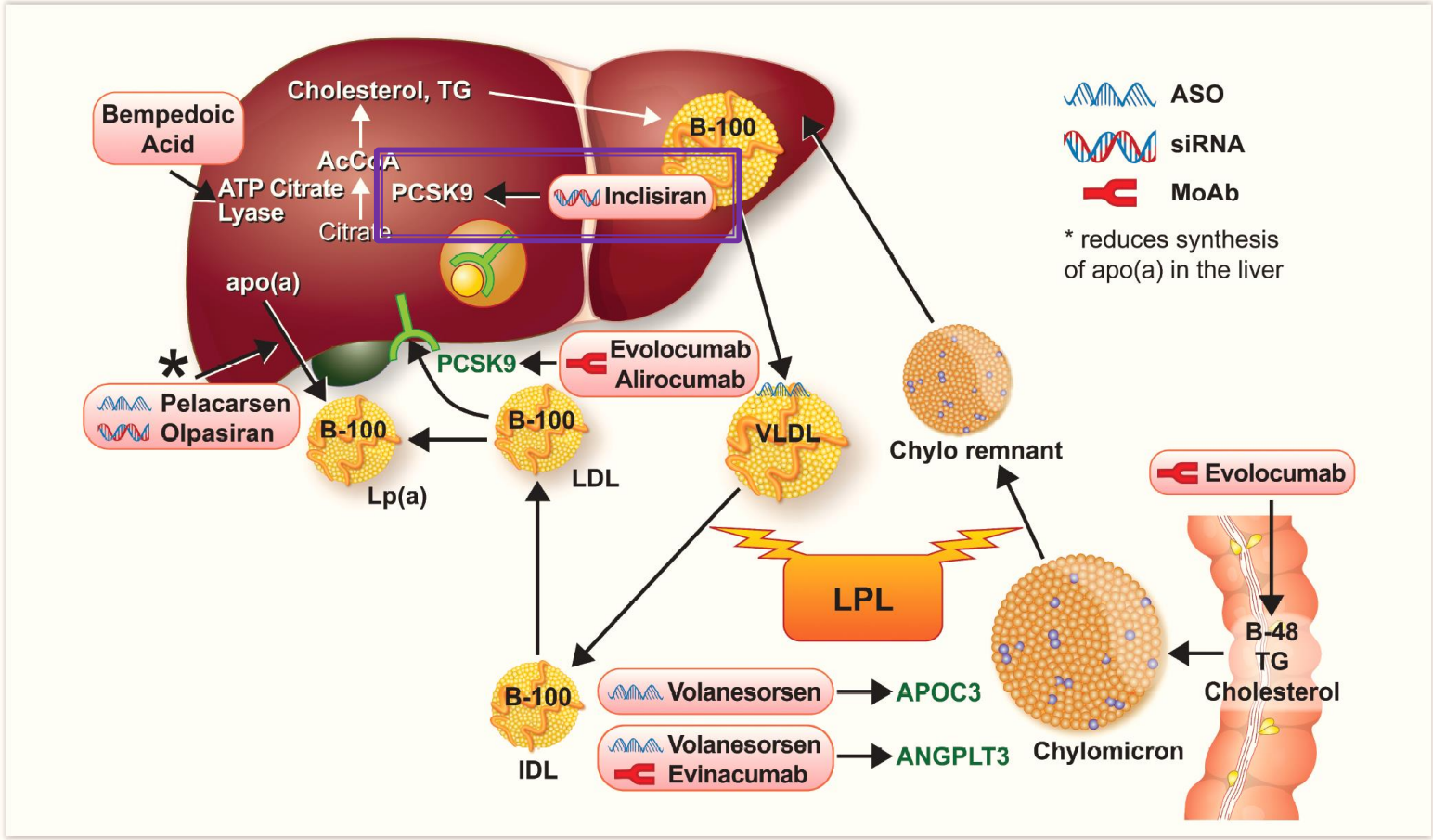
PCSK9 inhibitors are a very powerful tool and safe tool in Lipid lowering. They should be added judiciously at appropriate time.

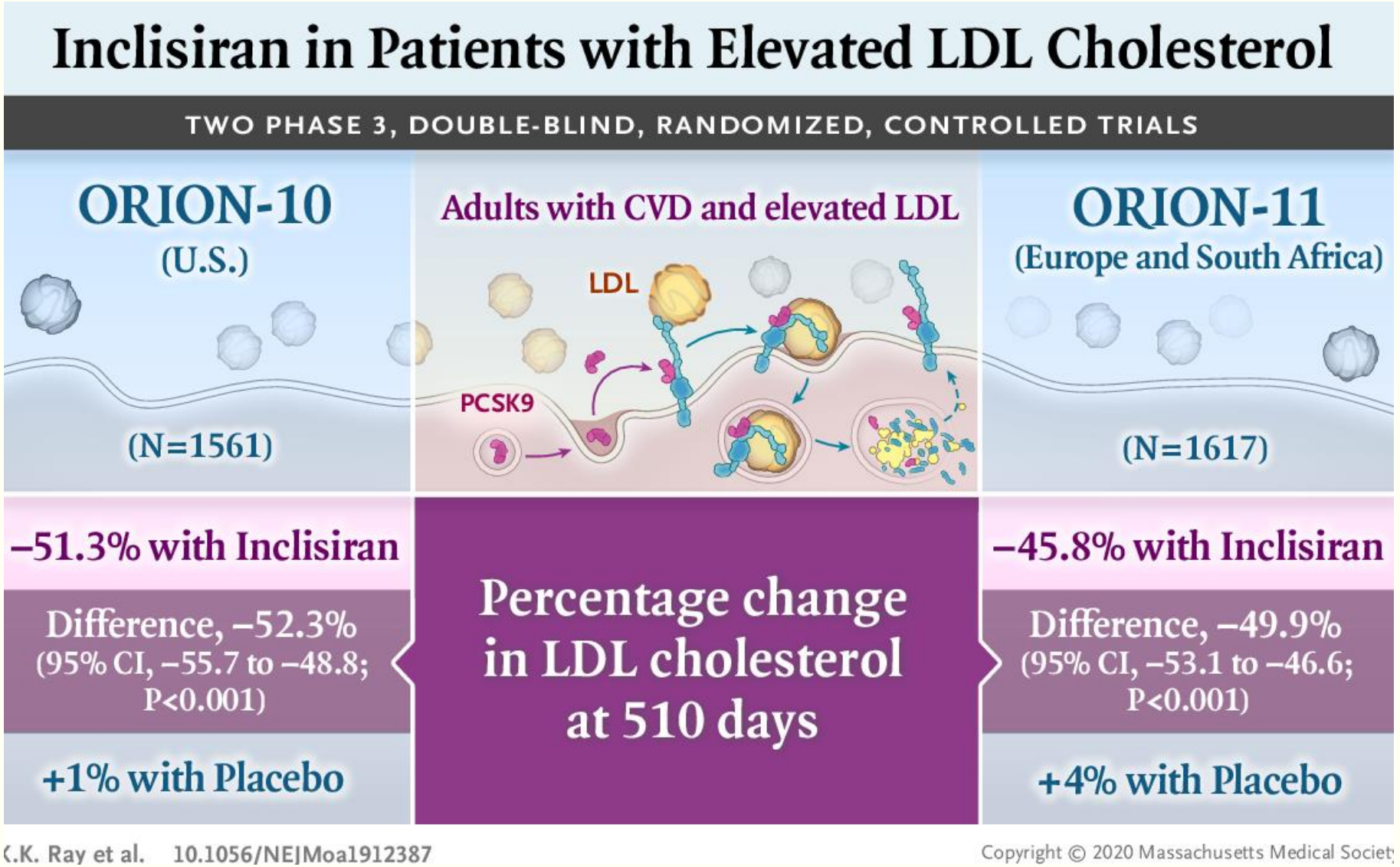
What are the newer Lipid lowering Drugs ?

Inclisiran

Inclisiran : Small Interfering RNA

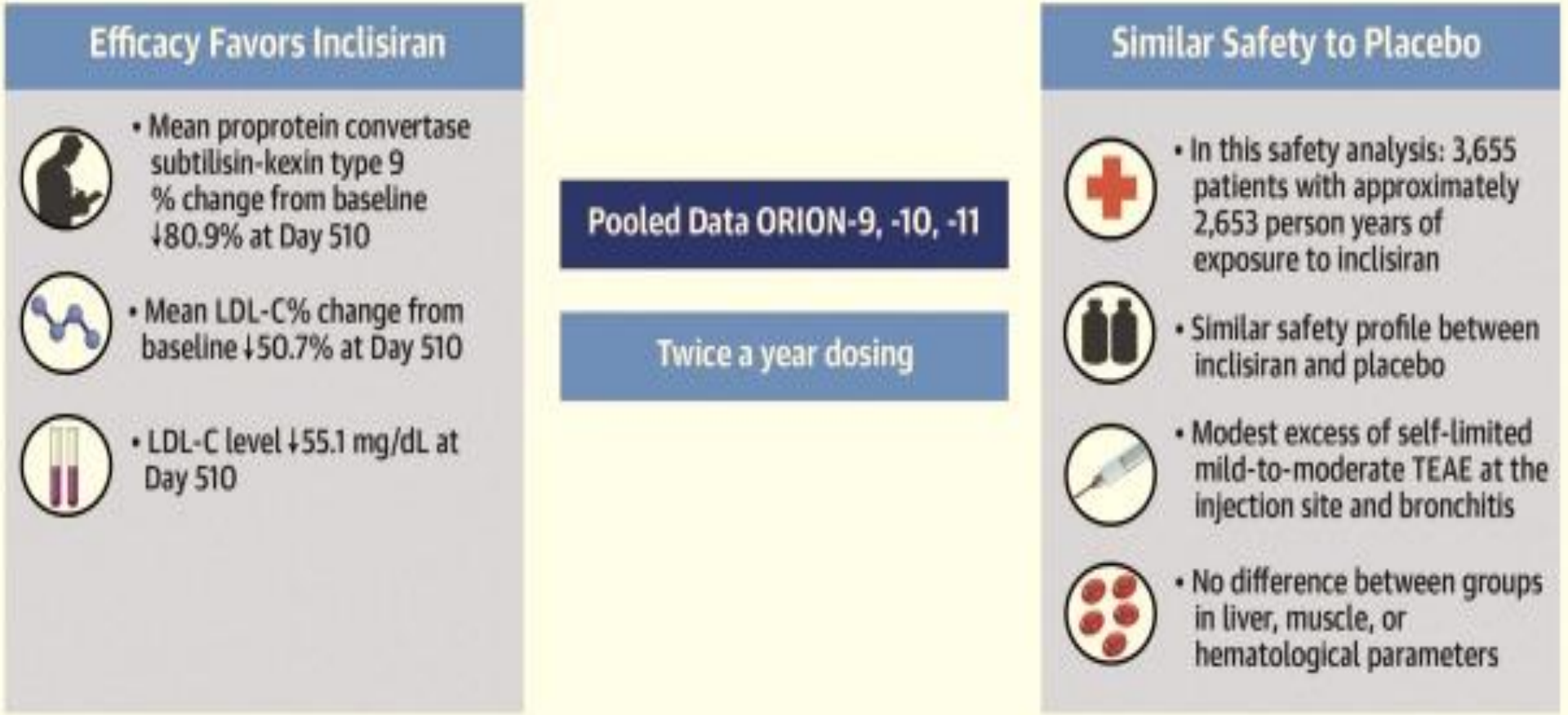
- **Reduces the hepatic synthesis of PCSK9 and durable effect of 3–6months when administered s/c.**
- **ORION-1, inclisiran reduced LDL-C levels up to 53% at 6months in subjects on the maximum dose of a statin with or without additional lipid-lowering therapy.**



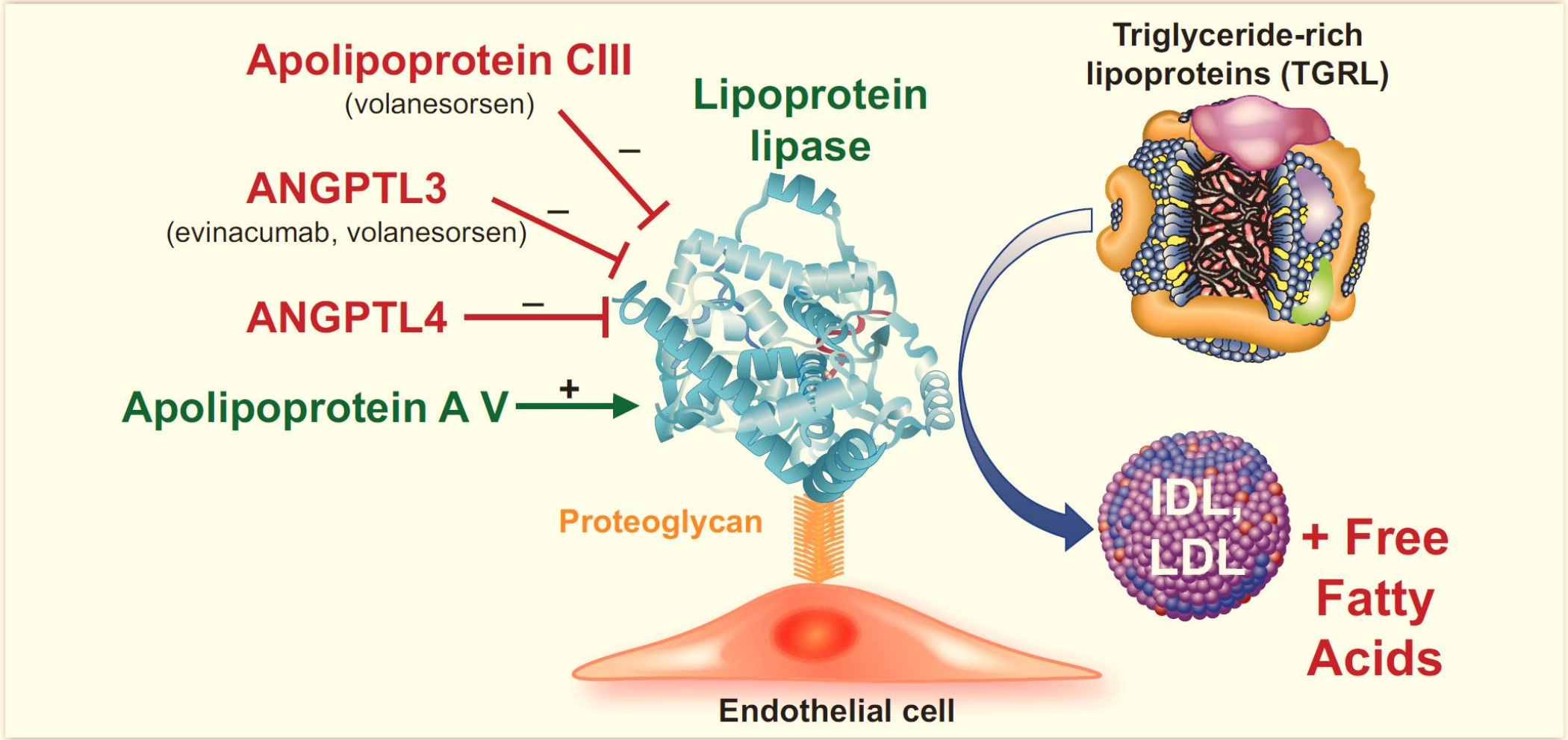


Inclisiran, administered s/c every 6months, reduced LDL-C by 50% and lowered non- HDL-C, apoB, triglycerides, and lipoprotein(a) [Lp(a)] significantly. Antidotes can reverse siRNA-mediated gene silencing

CENTRAL ILLUSTRATION: Inclisiran With Summary About Safety and Efficacy

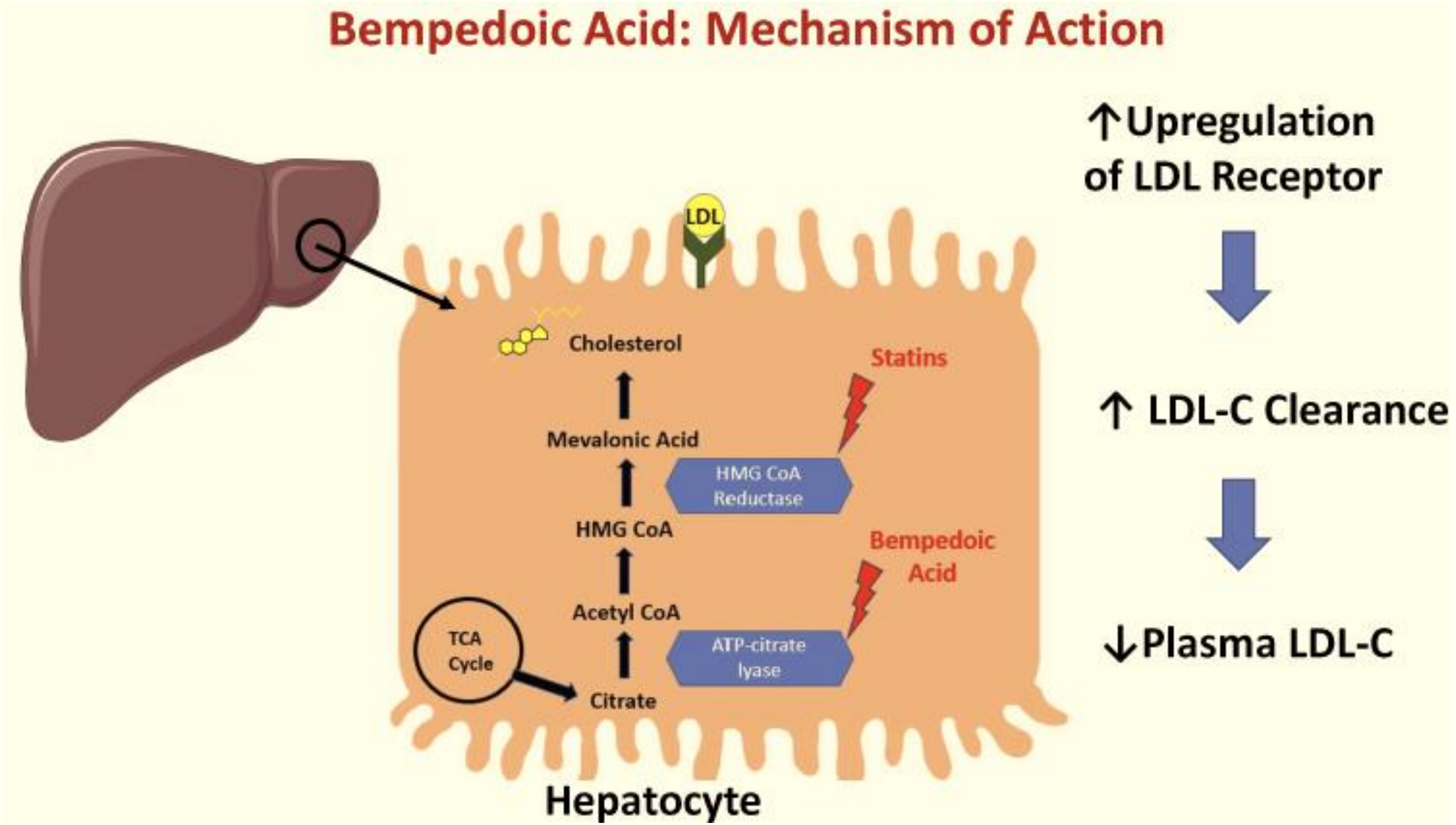


Wright, R.S. et al. J Am Coll Cardiol. 2021;77(9):1182-93.



- **Lipoprotein lipase-mediated hydrolysis yields free fatty acids and low-density lipoprotein and intermediate-density lipoproteins.**
- **The novel inhibitors inhibit these inhibitors and reduce Tg rich lipoproteins**

Bempedoic Acid



Administration	Oral once daily
Adsorption	Concomitant food administration had no effect on the oral bioavailability
T_{max} (180 mg)	3.5 h
Distribution volume	18 L
Binding to plasma proteins	99%
Pro-drug	Yes
Active metabolite	ESP15228
Metabolism	Glucuronide (UGT2B7 mediated)
Transporter-mediated drug interactions	OATP1B1/3, OAT2, OAT3
Half-life	15–24 h
Drug–drug interactions	1. Simvastatin dose should be limited to 20 mg daily 2. Bempedoic acid and its glucuronide weakly inhibit OATP1B1 and OATP1B3 at clinically relevant concentrations, raising simvastatin blood levels 3. Bempedoic acid may raise serum uric acid levels due to inhibition of renal tubular OAT2

The safety and efficacy of the long-term use of bempedoic acid have been addressed in the CLEAR (Cholesterol Lowering via BEmpedoic Acid, an ACL-inhibiting Regimen) program comprising the following four phase 3 trials:

1. CLEAR Tranquility (in statin intolerant patients) [30]
2. CLEAR Harmony (patients with LDL-C $\geq$ 70 mg/dL despite maximally tolerated statin therapy) [34]
3. CLEAR Wisdom (patients with ASCVD, HeFH or both, on optimal statin treatment) [35]
4. CLEAR Serenity (statin intolerant patients with ASCVD and inadequately controlled LDL-C) [36].

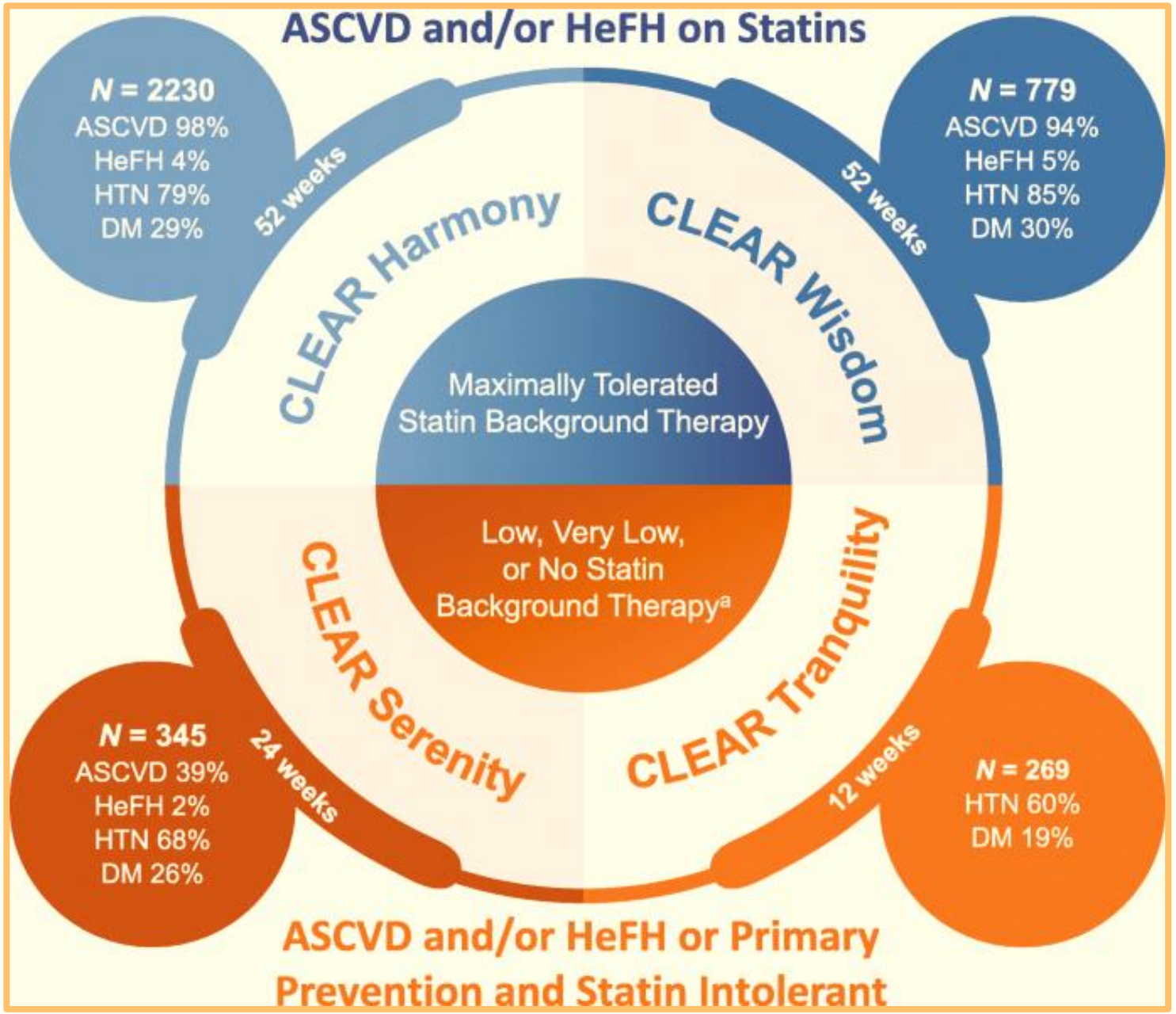

ASCVD and/or HeFH on Statins
N = 2230
ASCVD 98%
HeFH 4%
HTN 79%
DM 29%
52 weeks
CLEAR Harmony
N = 779
ASCVD 94%
HeFH 5%
HTN 85%
DM 30%
52 weeks
CLEAR Wisdom
Maximally Tolerated
Statin Background Therapy
Low, Very Low,
or No Statin
Background Therapy[a]
CLEAR Serenity
N = 345
ASCVD 39%
HeFH 2%
HTN 68%
DM 26%
24 weeks
CLEAR Tranquility
N = 269
HTN 60%
DM 19%
12 weeks
ASCVD and/or HeFH or Primary
Prevention and Statin Intolerant

Table 2 Changes in LDL-C levels in phase 3 CLEAR trials

Study	Duration	Population	Results at 12 weeks
CLEAR Wisdom	52 weeks	Patients with ASCVD and/or HeFH and LDL-C > 70 mg/dL while receiving maximally tolerated statin (with or without other LLT)	Bempedoic acid added to maximally tolerated statin (with or without other LLT) reduced LDL-C by 17.4% (95% CI, – 21.0, – 13.9) more than placebo ($P < .001$)
CLEAR Harmony	52 weeks		Bempedoic acid added to different intensities of background statin treatment (low, moderate or high) with or without additional LLT reduced LDL-C from baseline (difference vs placebo. – 18.1% (95% CI, – 20.0%, – 16.1%): $P < .001$
CLEAR Tranquility	12 weeks	Patients with hypercholesterolemia and a history of statin intolerance who required additional LDL-C lowering	Bempedoic acid added to stable LLT, including ezetimibe, reduces LDL-C up to 28.5% (95% CI, – 34.4, – 22.5) more than placebo ($P < .001$)
CLEAR Serenity	24 weeks		Treatment with bempedoic acid reduced LDL-C 21.4% (95% CI, – 25.1, – 17.7) more than placebo ($P < .001$)

CLEAR Wisdom, Evaluation of Long-Term Efficacy of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia at High Cardiovascular Risk; CLEAR Harmony, Evaluation of Long-Term Safety and Tolerability of ETC-1002 in High-Risk Patients With Hyperlipidemia and High CV Risk; CLEAR Tranquility, Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC-1002) as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C; CLEAR Serenity, Evaluation of the Efficacy and Safety of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia and Statin Intolerant. (Reproduced with permission of JAMA Network [14].)

ASCVD atherosclerotic cardiovascular disease, *HeFH* heterozygous familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol, *LLT* lipid lowering therapy

CLEAR Outcomes Trial (N=14,032)

- **Age 18 - 85 years**
- **History of ASCVD (CAD, symptomatic PAD, CVD disease, or at high risk for a CV event**
- **Statin intolerance (intolerant ≥2 statins, one at low dose)**
- **LDL ≥ 100 mg/dL**

Exclusion criteria:

- **Fasting TGs >500 mg/dL**
- **Major CV events, TIA, or unstable or symptomatic arrhythmia < 90 days**
- **History of severe HF**
- **Uncontrolled HTN or DM**

Randomized 1:1 Double Blinded

Bempedoic acid 180 mg po QD (N ≈ 7000)

Placebo po QD (N ≈ 7000)

Estimated average treatment duration: 3.75 years

CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

Start: November 18, 2016
Enrollment end: Sep 5, 2019
Completion: Q4 of 2022

Esperion Announces CLEAR Cardiovascular Outcomes Trial of NEXLETOL® (bempedoic acid) Meets Primary Endpoint

December 7, 2022

– Demonstrates statistically significant and clinically meaningful results –

– Bempedoic acid becomes the first ATP citrate lyase inhibitor and first oral non-statin to meet the major adverse cardiovascular events (*MACE-4) primary endpoint –*

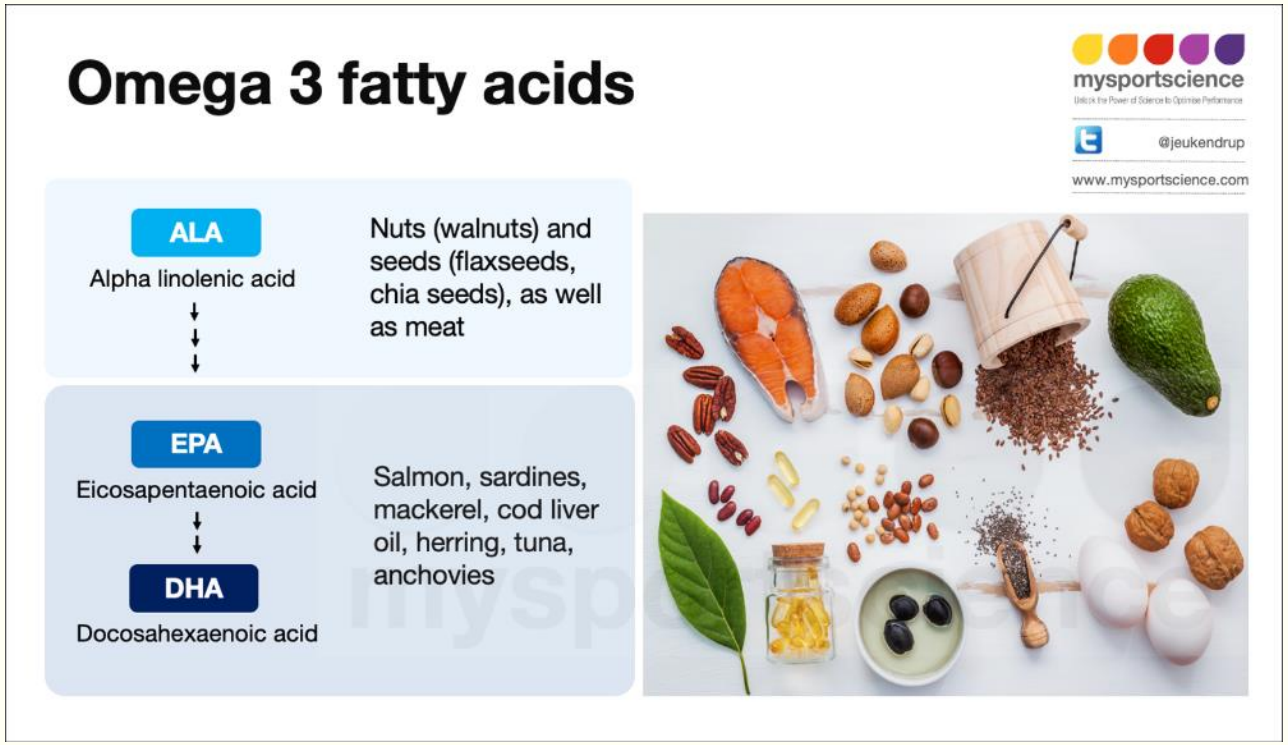
– Presentation of comprehensive data at a key medical conference in the first quarter of 2023 –

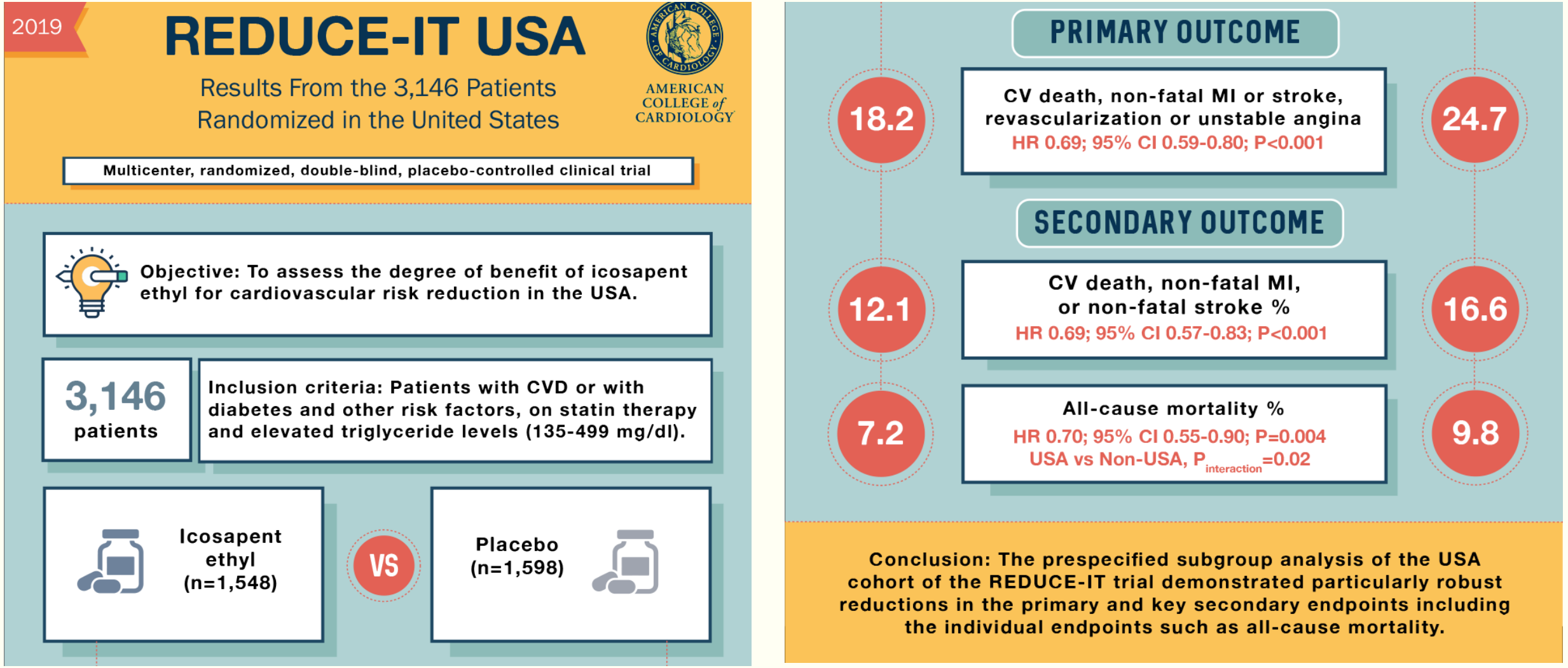
ANN ARBOR, Mich., Dec. 07, 2022 (GLOBE NEWSWIRE) -- Esperion (NASDAQ: ESPR) today announced that the landmark Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial met its primary endpoint, demonstrating statistically significant risk reduction in MACE-4 in patients treated with 180 mg/day NEXLETOL compared to placebo.

Bempedoic acid was approved in February 2020 by the US Food and Drug Administration, both as monotherapy and in combination with ezetimibe (which together provides LDL-C reductions of about 35%) for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional lowering of LDL-C.[47] While cardiovascular outcomes data are still pending, bempedoic acid is an option for providing further LDL-C lowering beyond maximally tolerated statin therapy, including for those with ACS who do not tolerate a high intensity statin.

Omega-3 Fatty Acids for Tg Reduction

- GISSI– Prevenzione study suggested a slight benefit of omega-3 fatty acid supplementation on heart failure
- The non-blinded JELIS study in Japanese individuals,which used a higher dose than most other studies [1.5 g/day of purified eicosapentaenoic acid (EPA)], did show a significant reduction in the primary endpoint outcomes.





The absolute risk reduction was 4% in patients with diabetes without CV disease, and 6% in patients with CV disease without diabetes. The highest benefit with a 10% absolute risk reduction was seen in patients with diabetes and established CV disease

EPA only vs EPA/DHA Omega-3 Fatty Acid Trials

STRENGTH		REDUCE-IT
EPA + DHA carboxylic acids	**Omega-3 preparation**	Icosapent ethyl
Corn oil	**Placebo used**	Mineral oil
49.9%	**High-intensity statin**	30%
55.9%	**% with ASCVD**	70.7%
70.1%	**% with diabetes**	58.5%
239 mg/dL	**Baseline triglycerides**	216 mg/dL
3.2 years	**Median follow-up**	4.9 years
HR (95% CI)	**RESULTS**	HR (95% CI)
0.99 (0.90-1.09)	**Overall**	0.75 (0.68-0.83)
1.16 (0.95-1.41)	**Primary prevention**	0.88 (0.70-1.10)
0.94 (0.84-1.05)	**Secondary prevention**	0.73 (0.65-0.81)
0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5		0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5
EPA+DHA Better / Placebo Better		EPA Better / Placebo Better

ASCEND was olive oil, STRENGTH used corn oil, while REDUCE-IT used mineral oil

What do Guidelines Say ?

2019 ESC/EAS Guidelines: Recommendations for pharmacological LDL-C lowering

Recommendations	Class*	Level†
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk	I	A
If the goals‡ are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended	I	B
For **secondary prevention, patients at very-high risk** not achieving their goal‡ on a maximum tolerated dose of a statin and ezetimibe, **a combination with a PCSK9 inhibitor is recommended**	I	A
For **very-high-risk FH patients** (that is, with ASCVD or with another major risk factor) who do not achieve their goal[c] on a maximum tolerated dose of a statin and ezetimibe, **a combination with a PCSK9 inhibitor is recommended**	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered	IIa	C
If a **statin-based regimen is not tolerated at any dosage** (even after rechallenge), **a PCSK9 inhibitor added to ezetimibe may also be considered**	IIb	C
If the goal‡ is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C
For **primary prevention patients at very-high risk**, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, **a combination with a PCSK9 inhibitor may be considered**	IIb	C

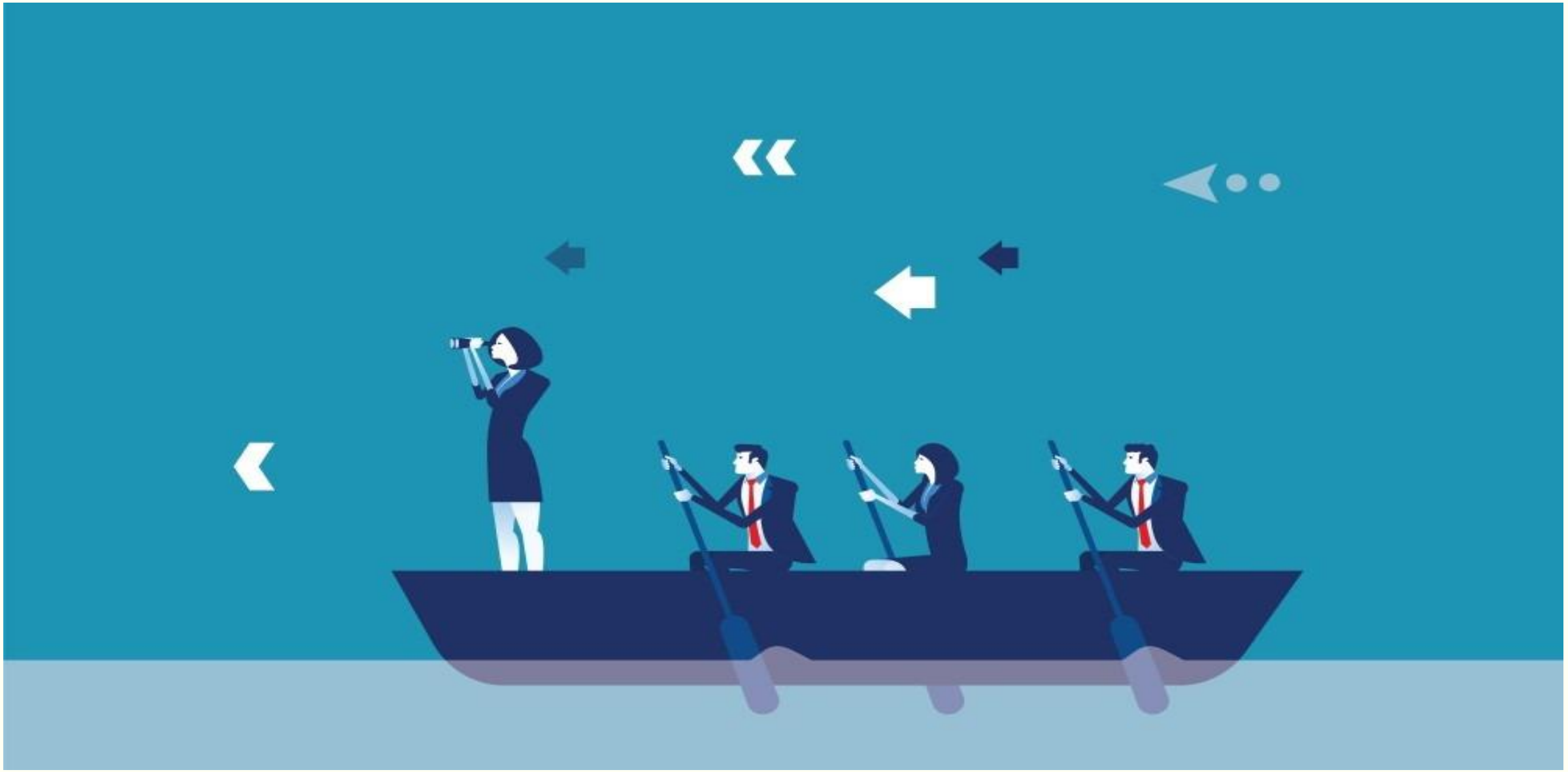
ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/ kexin type 9.
* Class of recommendation.
† Level of evidence.
‡ For definitions see Table 7.
Mach F, et al. *Eur Heart J.* 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

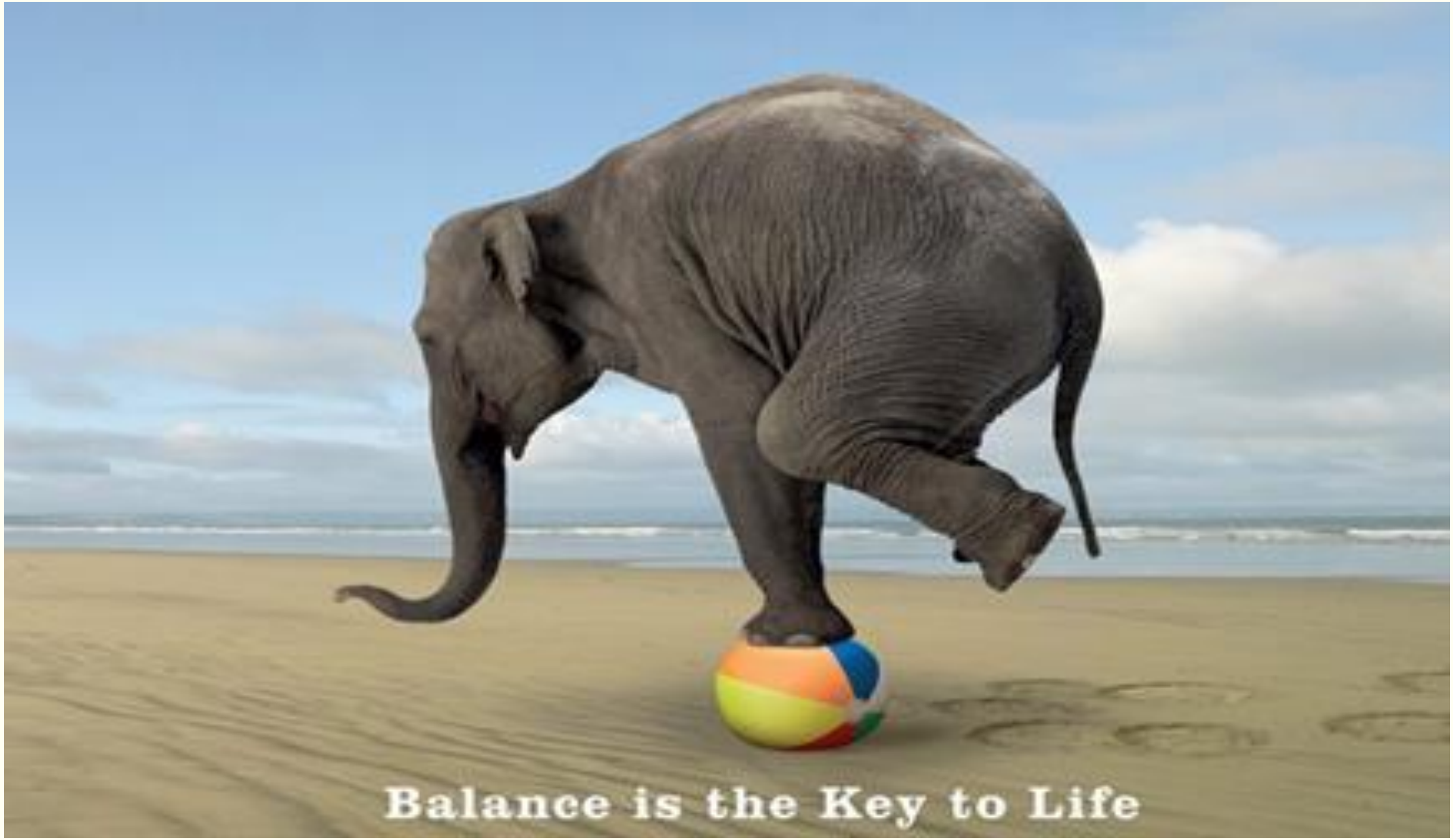
2019 ESC/EAS Guidelines: Recommendations For very high-risk patients **with ACS**

Recommendations	Class*	Level†
In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.	I	A
Lipid levels should be re-evaluated 4-6 weeks after ACS to determine whether a reduction of ≥ 50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	IIa	C
If the LDL-C goal is not achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the **LDL-C goal is not achieved after 4-6 weeks** despite maximal tolerated statin therapy and ezetimibe, **the addition of a PCSK9 inhibitor is recommended**	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contraindicated, ezetimibe should be considered.	IIa	C
For patients who present with an ACS and whose LDL-C levels are not at goal, despite already taking a maximally tolerated statin dose and ezetimibe, the **addition of a PCSK9 inhibitor early after the event (during hospitalization for the ACS event if possible) should be considered**	IIa	C

ACS
* Cla
† Le
Mac

Where have we Reached ?




Balance is the Key to Life

Conclusions

- **Systematic and aggressive approach to Lipid lowering is the Key.**
- **Statins, Ezetimibe, PCSK9-Inhibitors, Bempedoic acid have shown great results.**
- **One size does not fit all: Individualized therapy is important.**
- **Novel therapies are emerging: Small interfering RNA's.**
- **Indians need aggressive lipid lowering: due to aggressive ASCVD.**

All modalities should be used wisely along with clinical experience

A FOOL WITH A TOOL IS STILL A FOOL


That's all Folks!