LDL THE ACHILLES HEEL

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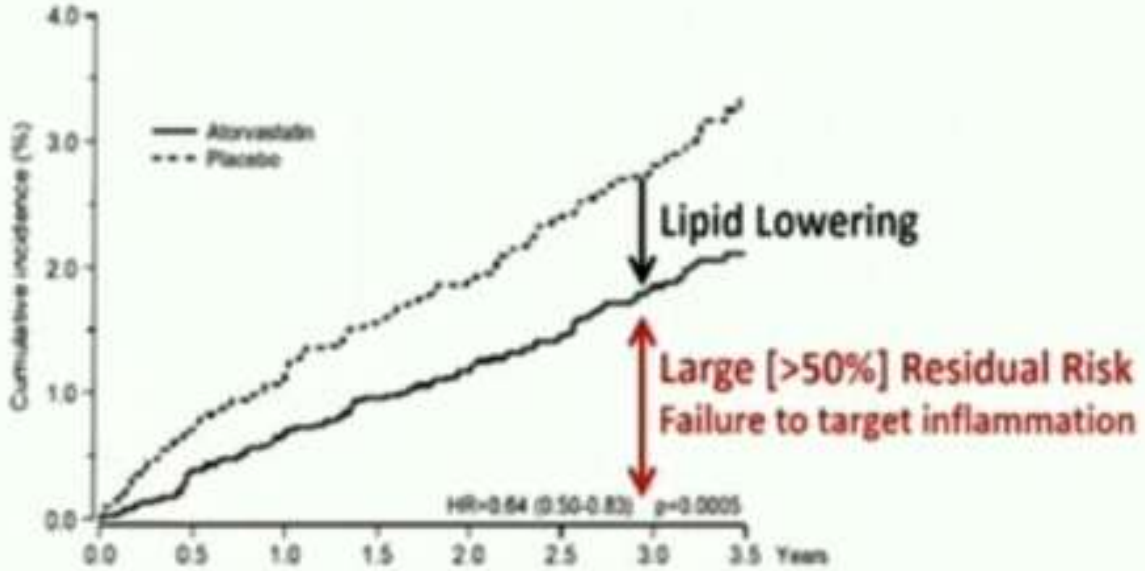
MEERUT.

Atherosclerosis Never Sleeps

Patients face a life-long risk

CV death, MI, IS and repeated interventions



Journal Pre-proof

There Is Urgent Need to Treat Atherosclerotic Cardiovascular Disease Risk Earlier, More Intensively, and with Greater Precision. A Review of Current Practice and Recommendations for Improved Effectiveness.

Michael E. Makover , Michael D. Shapiro , Peter P. Toth

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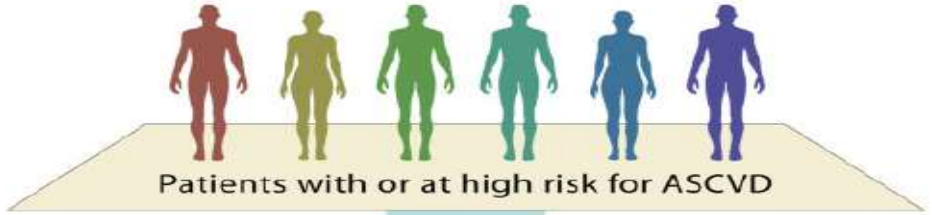
A CHILDHOOD DISEASE

Atherosclerosis begins in earliest childhood, sometimes even during gestation, presenting as yellow streaks in arterial walls (98-102). It is a chronic disease: absent intervention, it slowly progresses throughout life, unevenly, sometimes rapidly (16), but inevitably worsening over time (18,103-108). It has been shown that the progression can be halted, and even reversed to some degree with depletion of the lipid core, if plaque is not extensively fibrotic or calcified (18,109,110). Previously believed to just be part of normal aging, **atherosclerosis is actually a pediatric disease that progresses into adulthood (111-115).**



Patients with or at high risk for ASCVD

Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

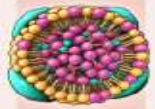
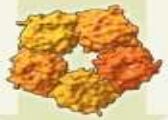
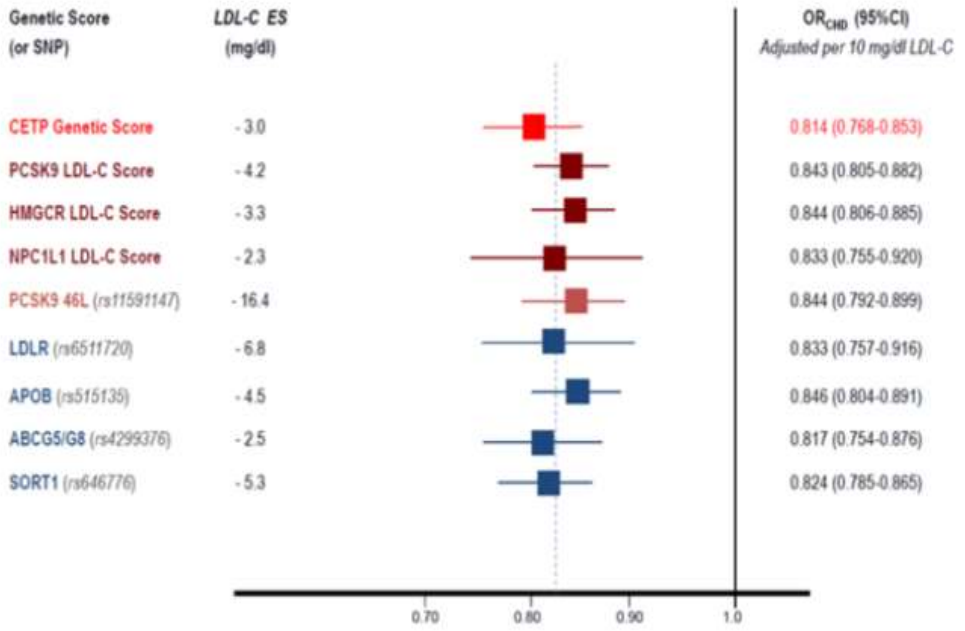
Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
						
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

Figure 2 Key contemporary residual risk pathways in secondary prevention. *In addition to standard evidence-based therapies, more aggressive blood pressure targets may be considered.

Clinical: Does it matter how LDL-C is lowered?

The answer is no!



Ference BA, et al. JAMA. 2017; 318(10):947-956

COCEPTUAL MODEL OF ATHEROSCLEROSIS

Lipoproteins and Atherosclerotic Plaque

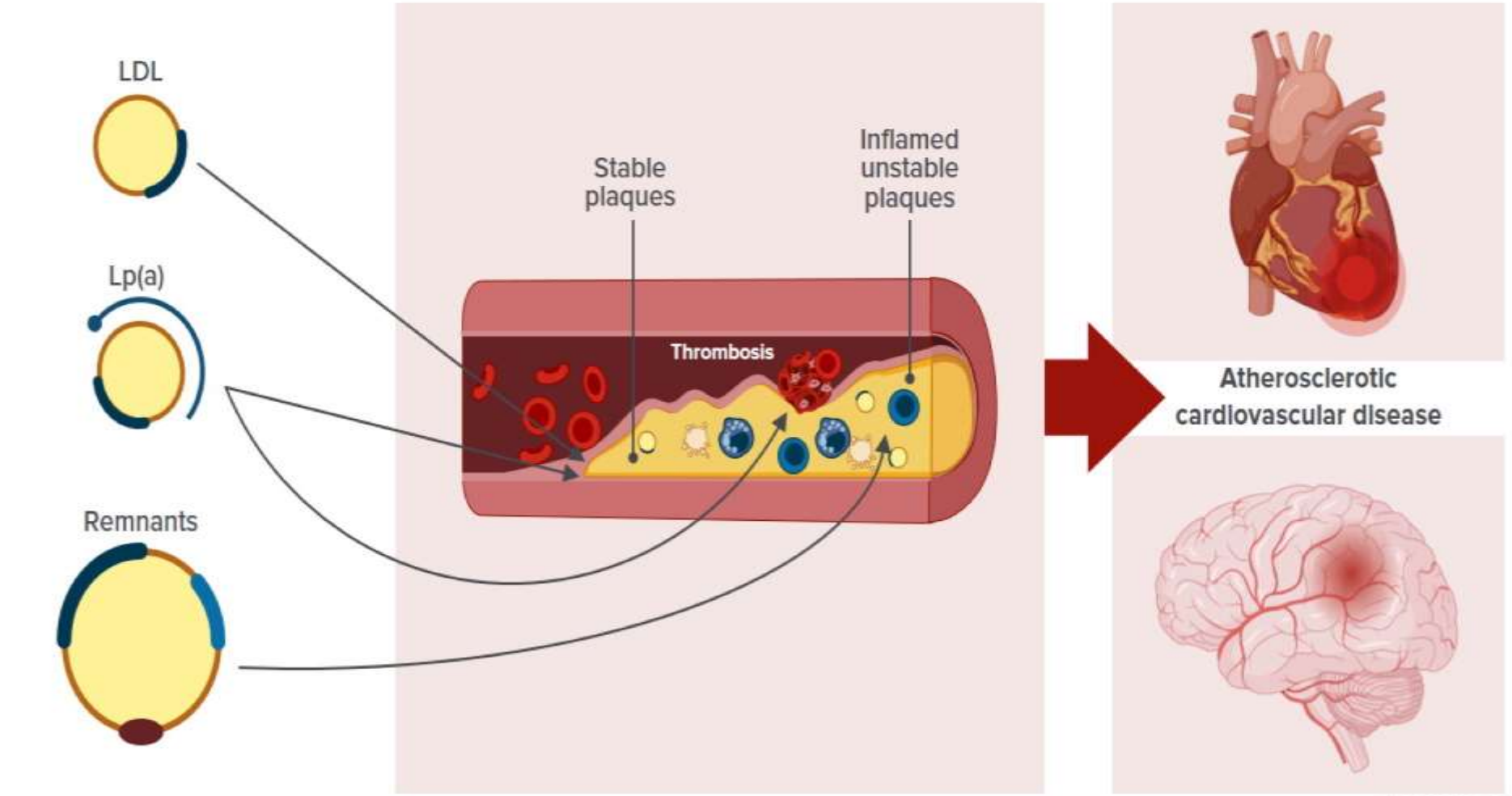
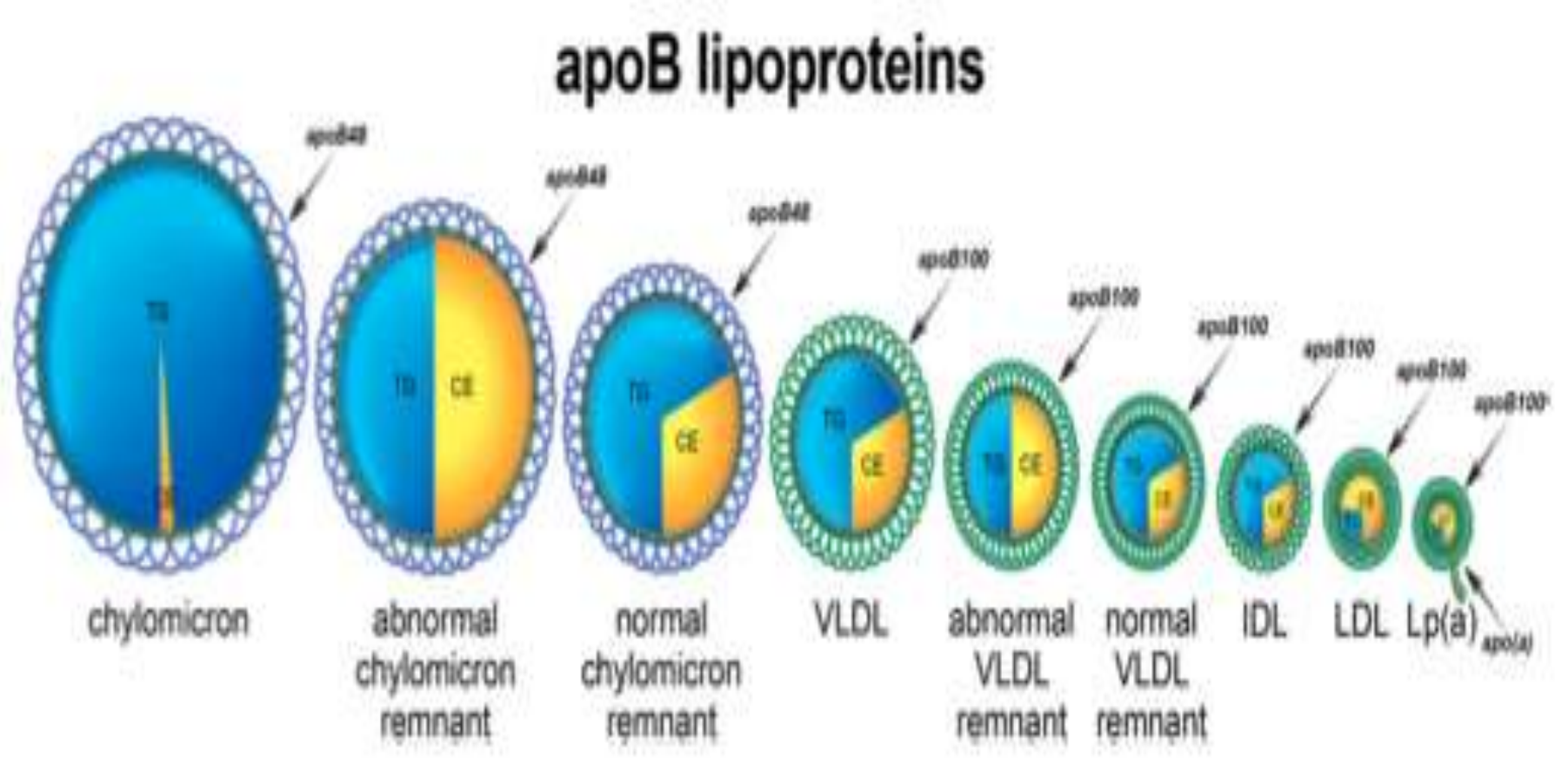


Image courtesy of Børge Nordestgaard, MD, DMSc.

The apoB family of lipoproteins: Due to plasma residence times, > 90-95% of the apoB particles are LDLs, meaning measuring apoB is basically measuring LDL-P. As atherogenic as they may be - chylo-P, VLDL-P, IDL-P, remnant-P, have no CLINICALLY MEANINGFUL impact on apoB levels

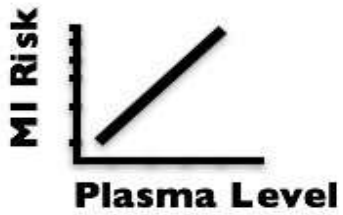


WHAT WE HAVE LEARNED SOOO FAR

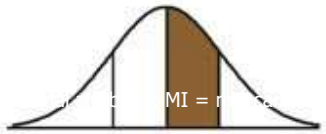
SUPPORT FOR LDL CAUSALITY IN ASCVD

LDL is main driver for atherosclerosis: 4 compelling lines of evidence

Epidemiology



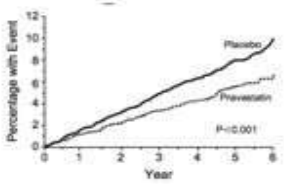
Human Genetics



Change in MI risk

Experimental

Therapy



Statins,
Ezetimibe
PCSK9 mAb

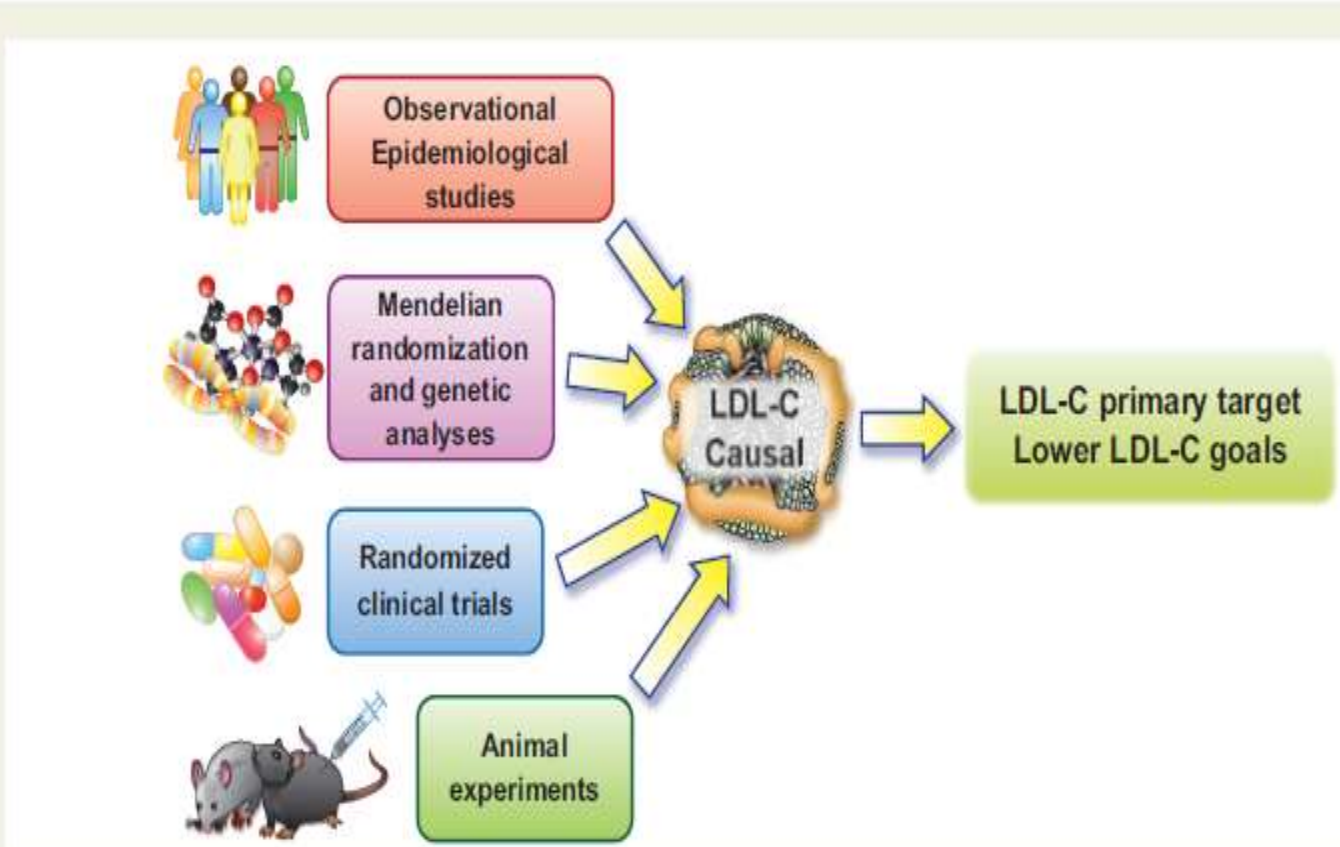


Figure 2 Multiple lines of evidence showing low-density lipoprotein cholesterol is causal for cardiovascular disease. Data that have accrued from observational data, human genetic analyses, randomized clinical trial results, and animal experimentation in multiple species, all concordantly support a causal contribution of low-density lipoprotein to atherosclerosis.

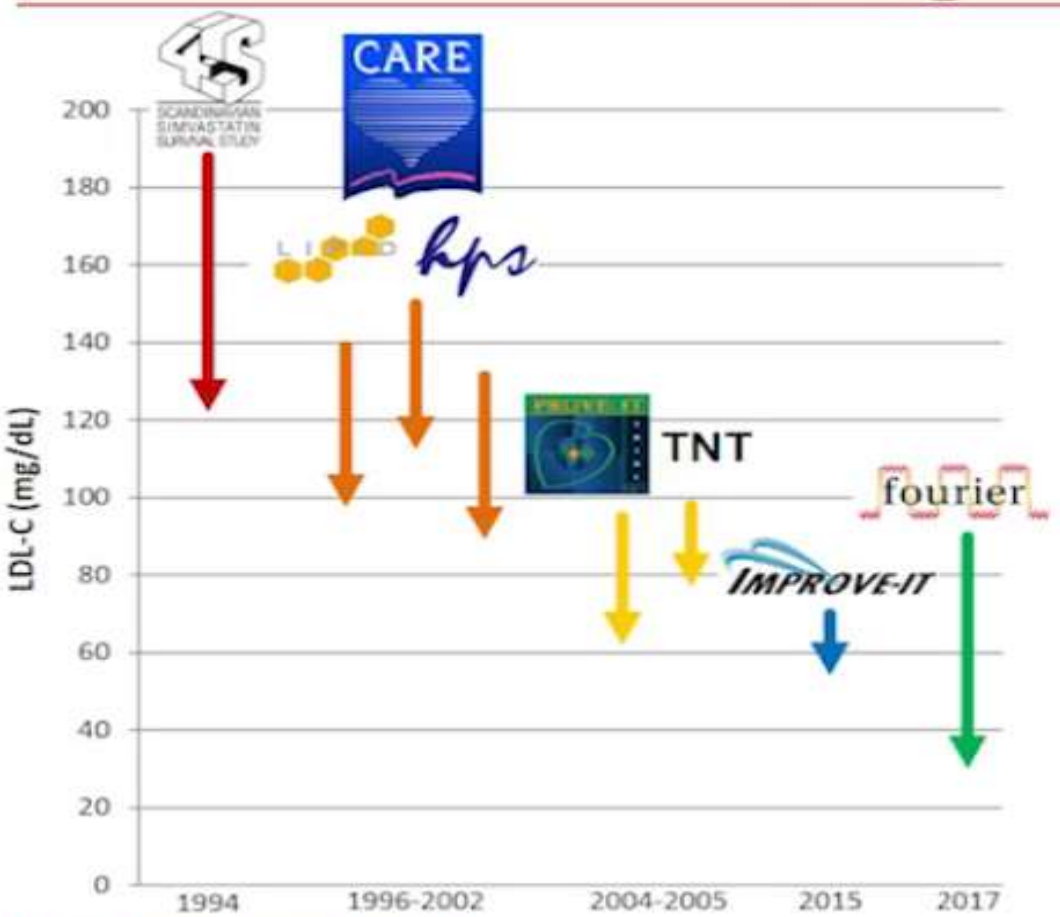
CTT Collaborators Meta-analysis Results

- 12% reduction in all-cause mortality (*P*<.0001)
- 19% reduction in coronary mortality (*P*<.0001)
- 23% reduction in MI or coronary death (*P*<.0001)
- 24% reduction in coronary revascularization (*P*<.0001)
- 17% reduction in fatal/nonfatal stroke (*P*<.0001)

  21% reduction in combination of above vascular events (*P*<.0001)
- No change in non-CVD mortality or cancer incidence
- Benefit of statins related to absolute reductions in LDL-C
- Statins safely reduce MCE 21% per 1 mmol/L reduction in LDL-C, regardless of baseline lipids, risk, age, gender

CVD = cardiovascular disease; MCE = major cardiovascular events.

A Quarter of a Century of Treating LDL-C



High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

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

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–3
doi:10.1093/eurheartj/ehab446
CARDIOPULSE

Braunwald's Corner

Cholesterol: the race to the bottom

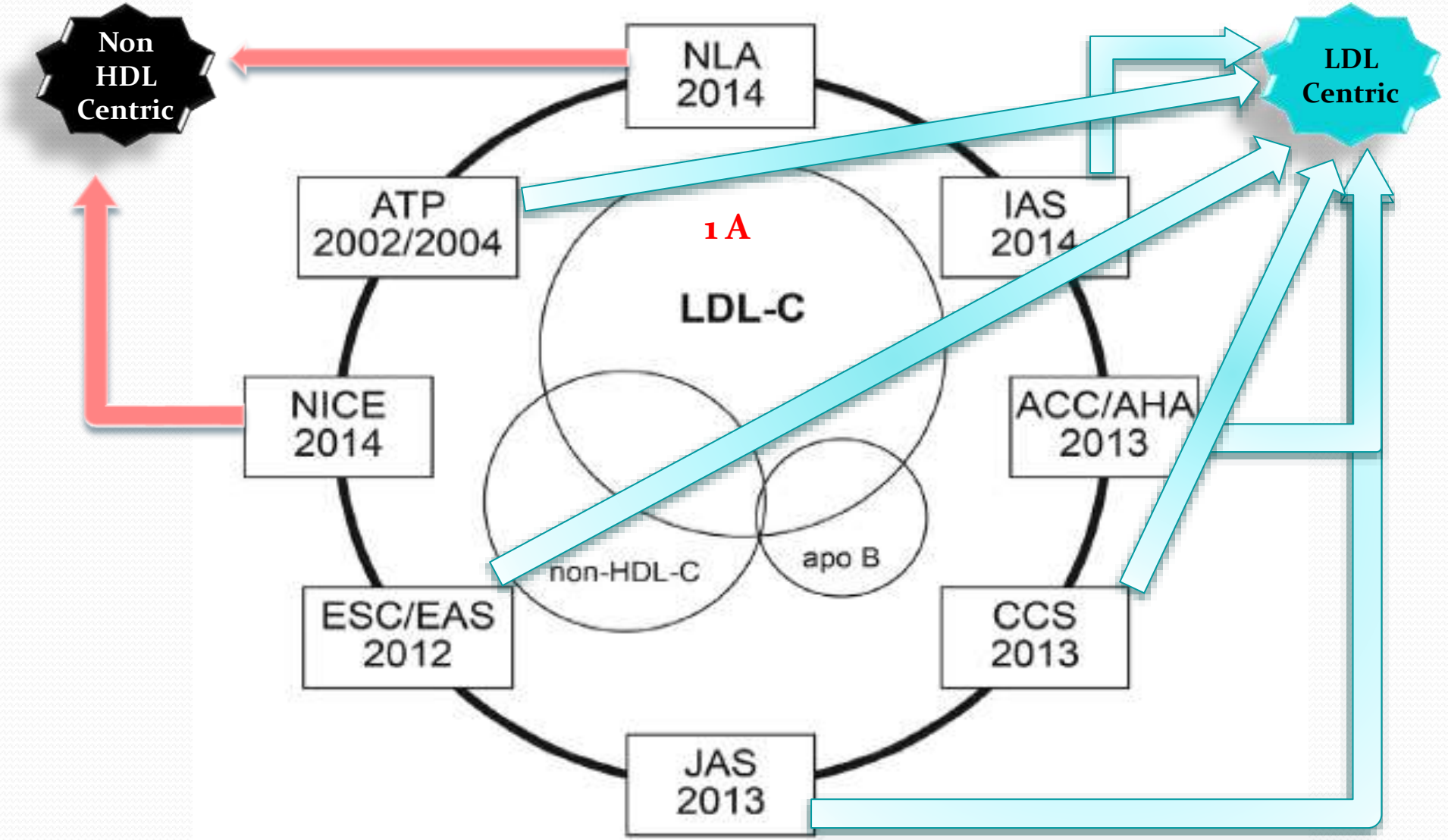
Eugene Braunwald *

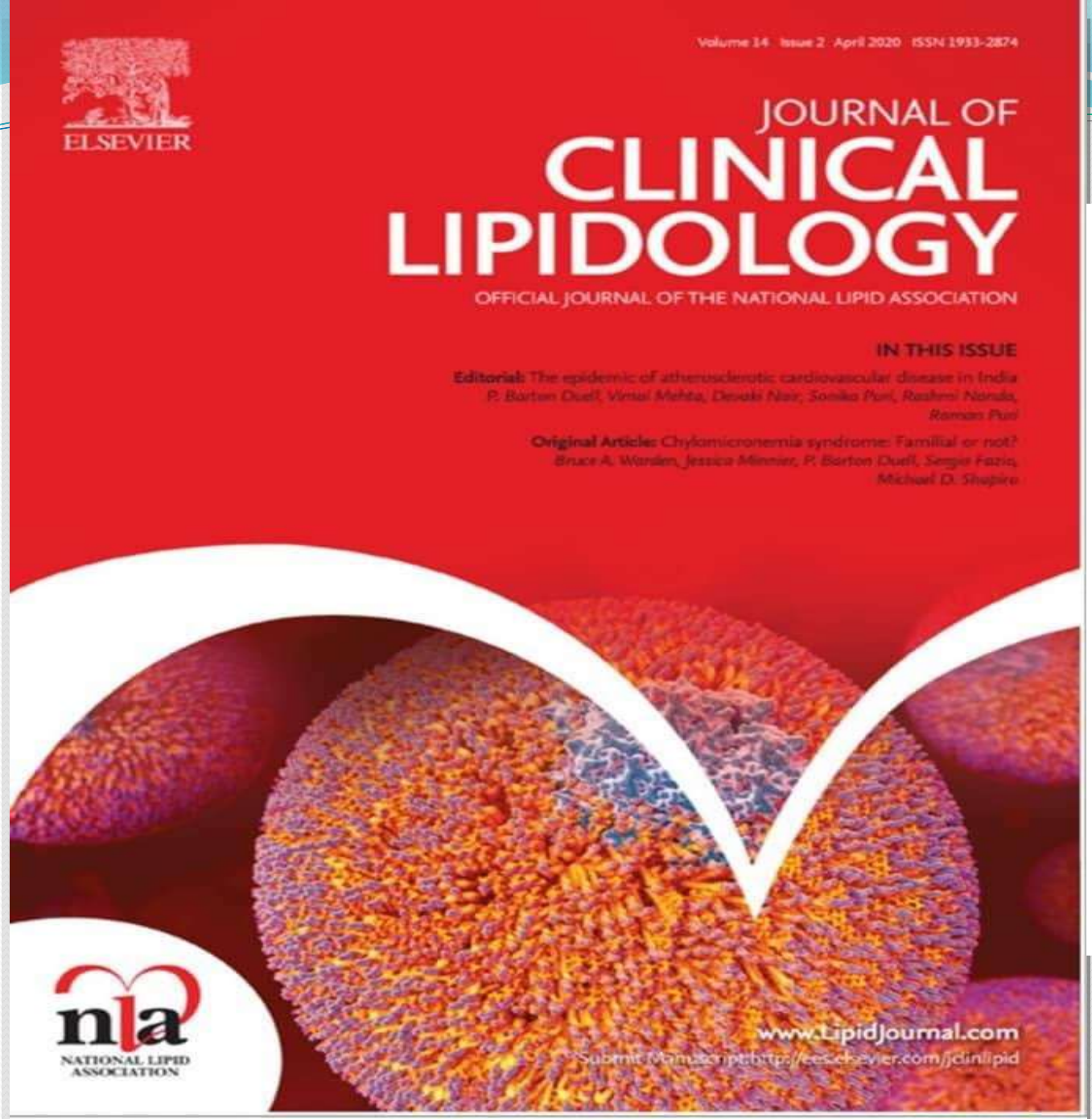
Conclusions

(1) There is substantial evidence that low levels of LDL-C (<0.5 mmol/L) and even ultra-low levels (<0.3 mmol/L) are well tolerated and safe.
(2) In secondary prevention trials, these low levels might be more effective in reducing MACE than the common guideline target levels of 1.8 and 1.4 mmol/L for high-risk and very high-risk patients, respectively.[18]
(3) It would be desirable and safe to conduct a prospective randomized trial to compare clinical effectiveness at three target levels: 1.4, 0.9, and 0.4 mmol/L.

WHAT GUIDELINES TELL

Current Guidelines in Perspective





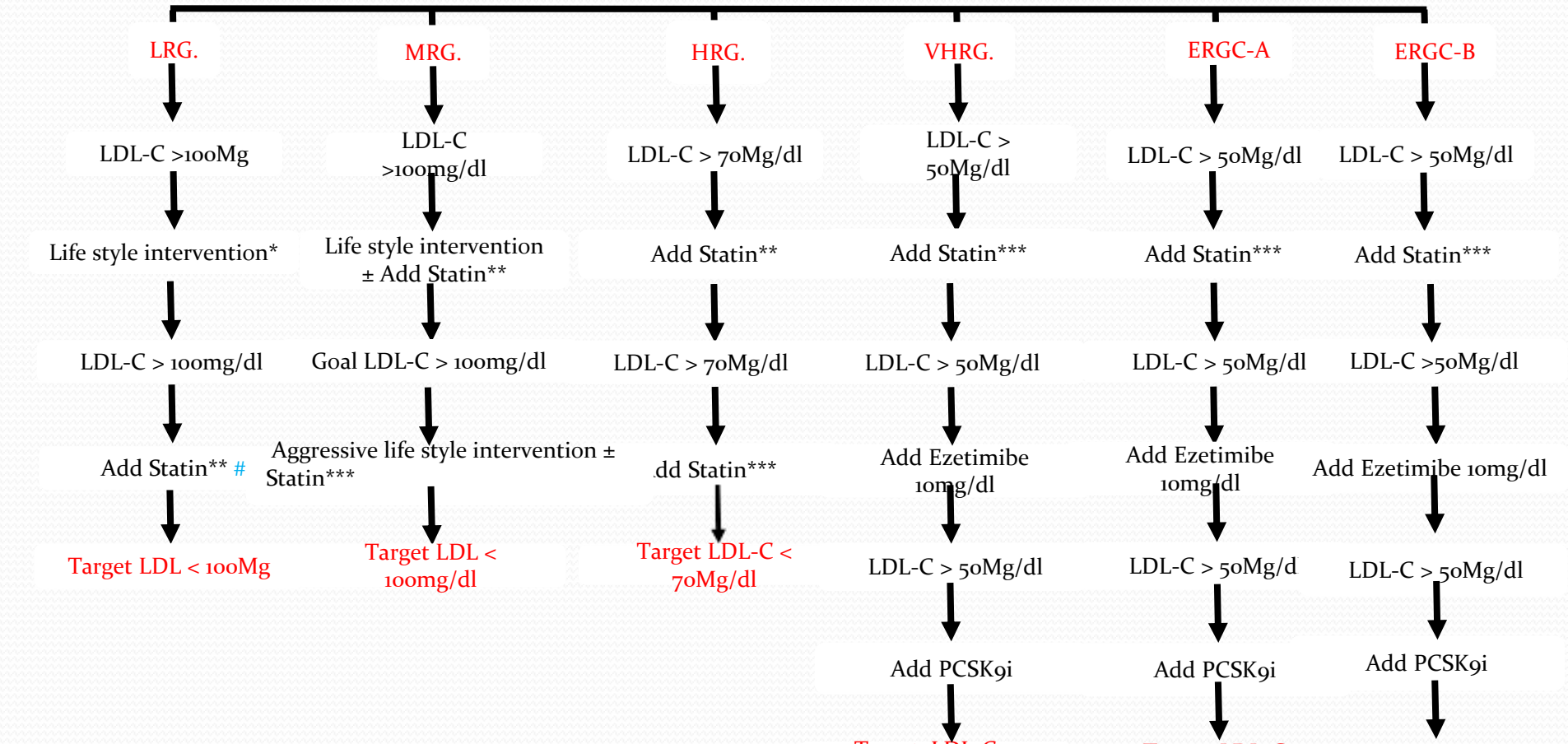
Journal of Clinical Lipidology

Proposed low-density lipoprotein cholesterol goals for secondary prevention and familial hypercholesterolemia in India with focus on PCSK9 inhibitor monoclonal antibodies: Expert consensus statement from Lipid Association of India

Raman Puri, MD, DM*, Vimal Mehta, MD, DNB, DM, FACC, P. Barton Duell, MD, FAHA, Devaki Nair, MD, Jagdish Chander Mohan, MD, DM, Jamal Yusuf, MD, DM, Jamshed J. Dalal, MD, DM, Sundeep Mishra, MD, DM, Ravi R. Kasliwal, MD, DM, Rajeev Agarwal, MD, DM, Saibal Mukhopadhyay, MD, DM, Harsh Wardhan, MD, DM, Narendra Nath Khanna, MD, DM, Akshaya Pradhan, MD, DM, Rahul Mehrotra, MD, DM, Amit Kumar, MD, Sonika Puri, MD, Arumugam Muruganathan, MD, Gururaj Balvantrao Sattur, MD, Madhur Yadav, MD, Harinder Pal Singh, MD, Rajesh Kumar Agarwal, MD, Rashmi Nanda, MD

*Indraprastha Apollo Hospitals, New Delhi, India (Dr Puri); G. B. Pant Institute of Postgraduate Medical Education and Research, New Delhi, India (Drs Mehta, Yusuf, and Mukhopadhyay); Knight Cardiovascular Institute and Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University, Portland, OR, USA (Dr Duell); Clinical Lead for Lipids and CVD Prevention, Royal Free NHS Foundation Trust Hospital, London, UK (Dr Nair); Fortis Hospital, New Delhi, India (Dr Mohan); Kokilaben Dhirubhai Ambani Hospital, Director-Centre for Cardiac Sciences, Mumbai, Maharashtra, India (Dr Dalal); AIIMS, New Delhi, India (Dr Mishra); Division of Clinical and Preventive Cardiology, Medanta Hospital, Gurugram, Haryana, India (Dr Kasliwal); Jaswant Rai Speciality Hospital, Meerut, Uttar Pradesh, India (Dr Agarwal); Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India (Dr Wardhan); Department of Cardiology, Indraprastha Apollo Hospitals, New Delhi, India (Dr Khanna); Department of Cardiology King George's Medical University, Lucknow, Uttar Pradesh, India (Dr Pradhan); Max Superspeciality Hospital, Saket, New Delhi, India (Dr Mehrotra); Mariampur Hospital, Kanpur, Uttar Pradesh, India (Dr Kumar); Department of Nephrology/Transplant, Rutgers Robertwood Johnson University Hospital, New Brunswick, NJ, USA (Dr Puri); AG Hospital, Tirupur, Tamil Nadu, India (Dr Muruganathan); Sattur Medical Care, Hubli, Karnataka, India (Dr Sattur); Lady Harding Medical College, New Delhi, India (Dr Yadav); Fortis Escorts Hospital, Amritsar, Punjab, India (Dr Singh); Department of Cardiology, Ruban Memorial Hospital, Patna, Bihar, India (Dr Agarwal); and Cardiac Care Centre, South Extension, Part-2, New Delhi, India (Dr Nanda)

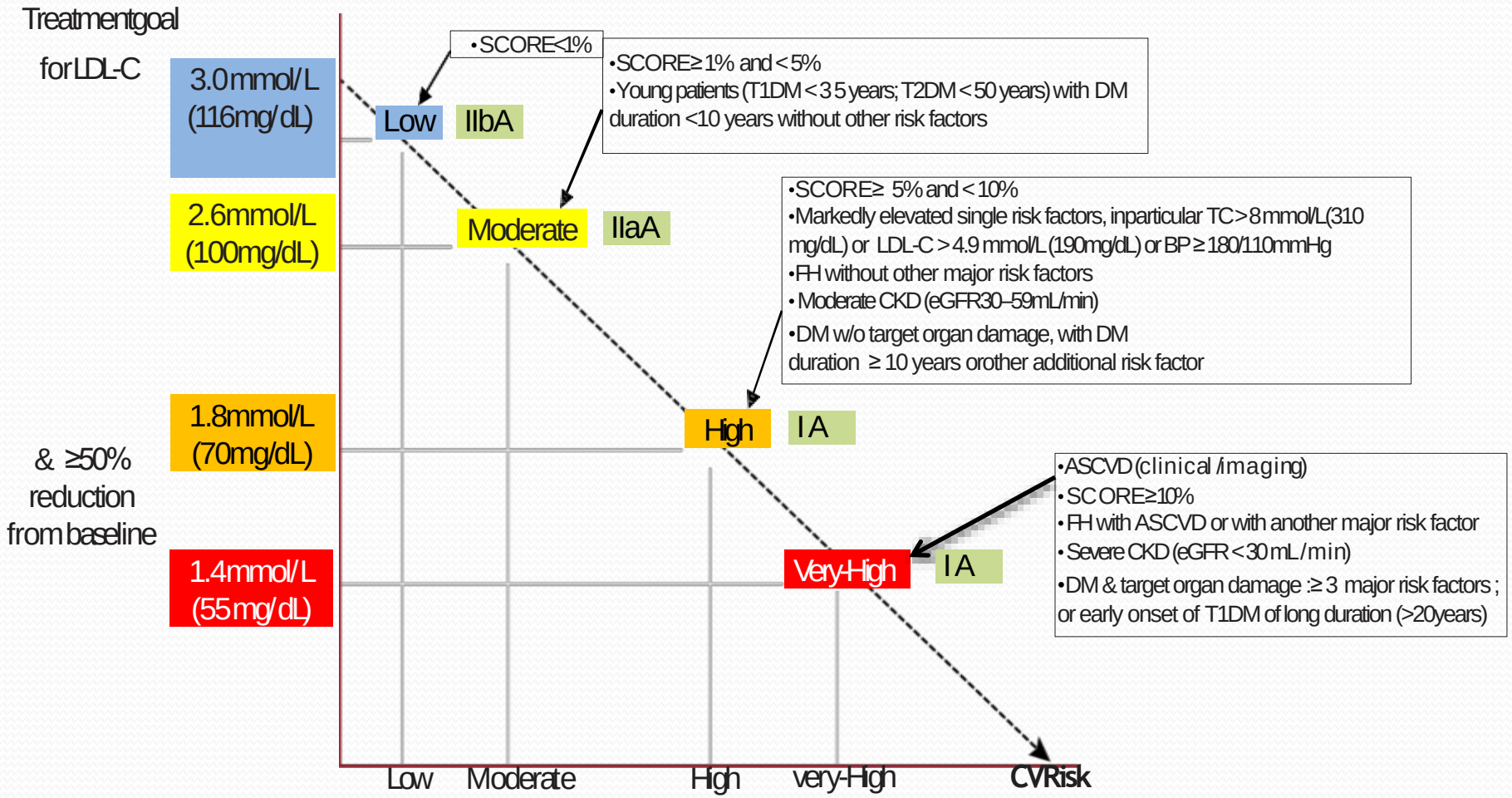
ASCVD Risk specification & LDL-C targets in prevention of ASCVD in Indians 2020
Expert consensus statement by Lipid Association of India



- *Life style intervention for at least 3 months
- ** Low to moderate intensity statin, need clinical judgement
- *** High intensity statin
- # Shared Decision

LRG Low Risk Group
MRG Moderate Risk Group
HRG High Risl Group
VHRG Very High Risk Group
ERGC-A Extreme Risk Group Category A
LRGC-B Extreme Risk Group Category B

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



Recommendations for treatment goals for low-density lipoprotein cholesterol

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

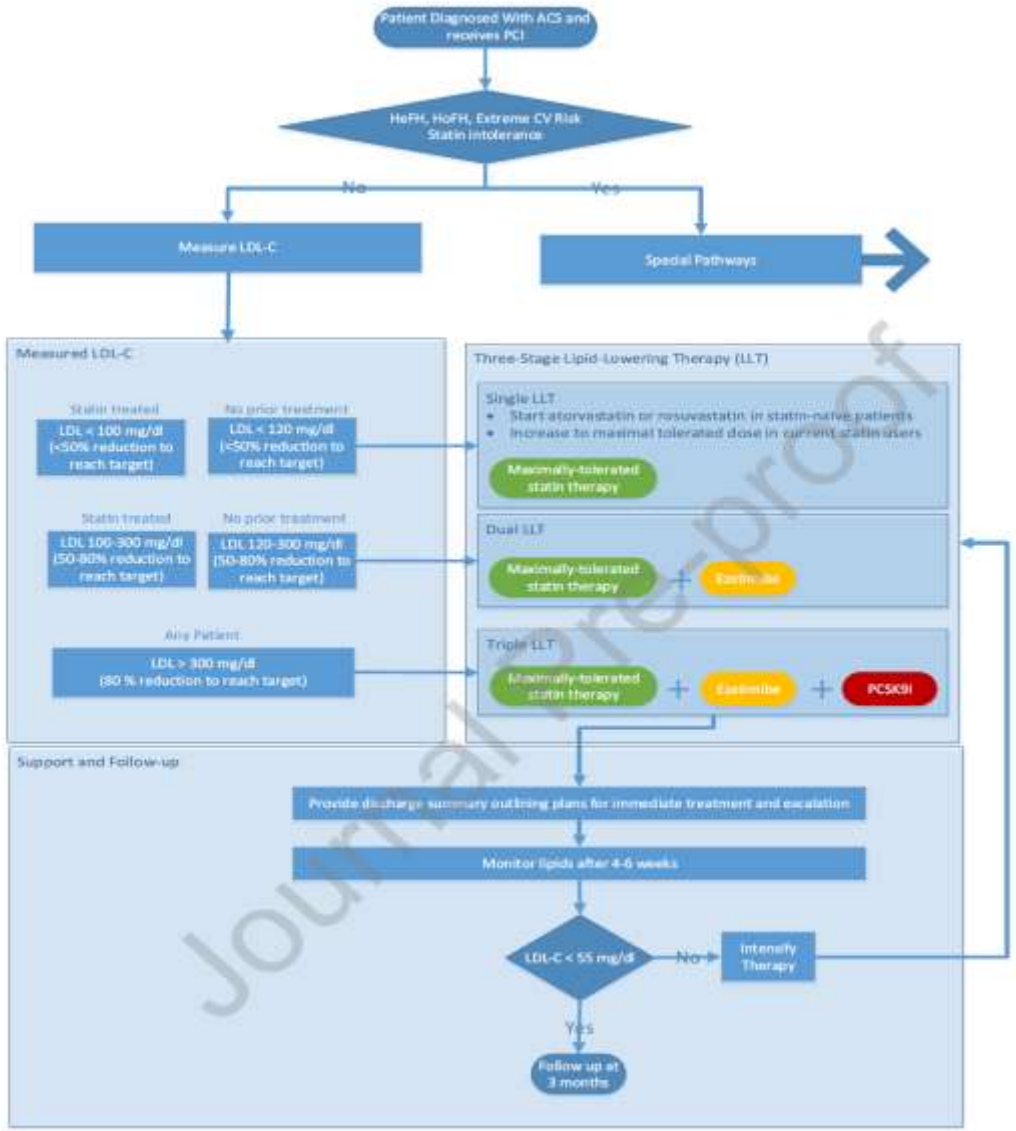
OPTIMAL USE OF LIPID-LOWERING THERAPY AFTER ACUTE CORONARY SYNDROMES:

A Position Paper endorsed by *the International Lipid Expert Panel (ILEP)*

Maciej Banach[1-3*#], Peter E. Penson[4,5#], Michal Vrablik[6], Matjaz Bunc[5], Krzysztof Dyrbus[6], Jan Fedacko[7], Dan Gaita[8], Marek Gierlotka[9], Zoltan Jarai[10], Stefania Lucia Magda[11], Eduard Margetic[12], Roman Margoczy[13], Azra Durak-Nalbantic[14], Petr Ostadal[15], Daniel Pella[16], Matias Trbusic[17], Cristian Alexandru Udroiu[11], Charalambos Vlachopoulos[18], Dusko Vulic[19], Zlatko Fras[20,21], Dariusz Dudek[22,23], Željko Reiner[24*] for *the ACS EuroPath Central & South European Countries Project.*

PII:	S1043-6618(21)00083-9
DOI:	https://doi.org/10.1016/j.phrs.2021.105499
Reference:	YPHRS105499

Graphical Abstract



Key words: combination therapy, effectiveness, ezetimibe, PCSK9 inhibitors, safety, statins.

FROM LDL REDUCTION TO LDL ERADICATION

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The Zero-LDL Hypothesis. Towards Extremely Low LDL Concentrations

La hipótesis del LDL cero. Hacia concentraciones de LDL extremadamente bajas

Recent clinical data show that very low low-density lipoprotein (LDL) cholesterol (LDL-C) levels are associated with an even lower incidence of arteriosclerosis-related diseases. The Cholesterol Treatment Trialists' Collaboration meta-analyses have shown a continuous linear correlation between LDL reduction and cardiovascular benefit.1 The IMPROVE-IT trial provided scientific evidence of incremental benefits down to an LDL-C concentration of 1.3 mmol/L (50 mg/dL).2 Proprotein convertase subtilisin kexin type 9 inhibitors have quickly been adopted in this field and have provided physicians with new scenarios. Patients with LDL-C values < 0.4 mmol/L (15 mg/dL) are occasionally seen, while concentrations below 1.3 mmol/L (50 mg/dL) are common. The LDL-C concentrations < 0.4 mmol/L (15 mg/dL) show no concerns in safety analyses; on the contrary, these concentrations are associated with even higher cardiovascular benefit. The recently reported GLAGOV trial data confirm a benefit to atherosclerotic plaque level by lowering LDL concentrations closer to 0.52 mmol/L (20 mg/dL).3 Can we live with these extremely low LDL-C levels? In other

Optimal Physiologic LDL-C?

A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

The LDL-receptor studies lend experimental support to the epidemiologists' suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (*9*). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (*28*). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (*118*). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (*119*). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might indeed be physiologic for human beings.

Adapted from Nobel Prize Lecture, Stockholm, Sweden, 1985.
Science 1986;232:34.

BIOMEDICINE

Lowering LDL—Not Only How Low, But How Long?

Michael S. Brown and Joseph L. Goldstein

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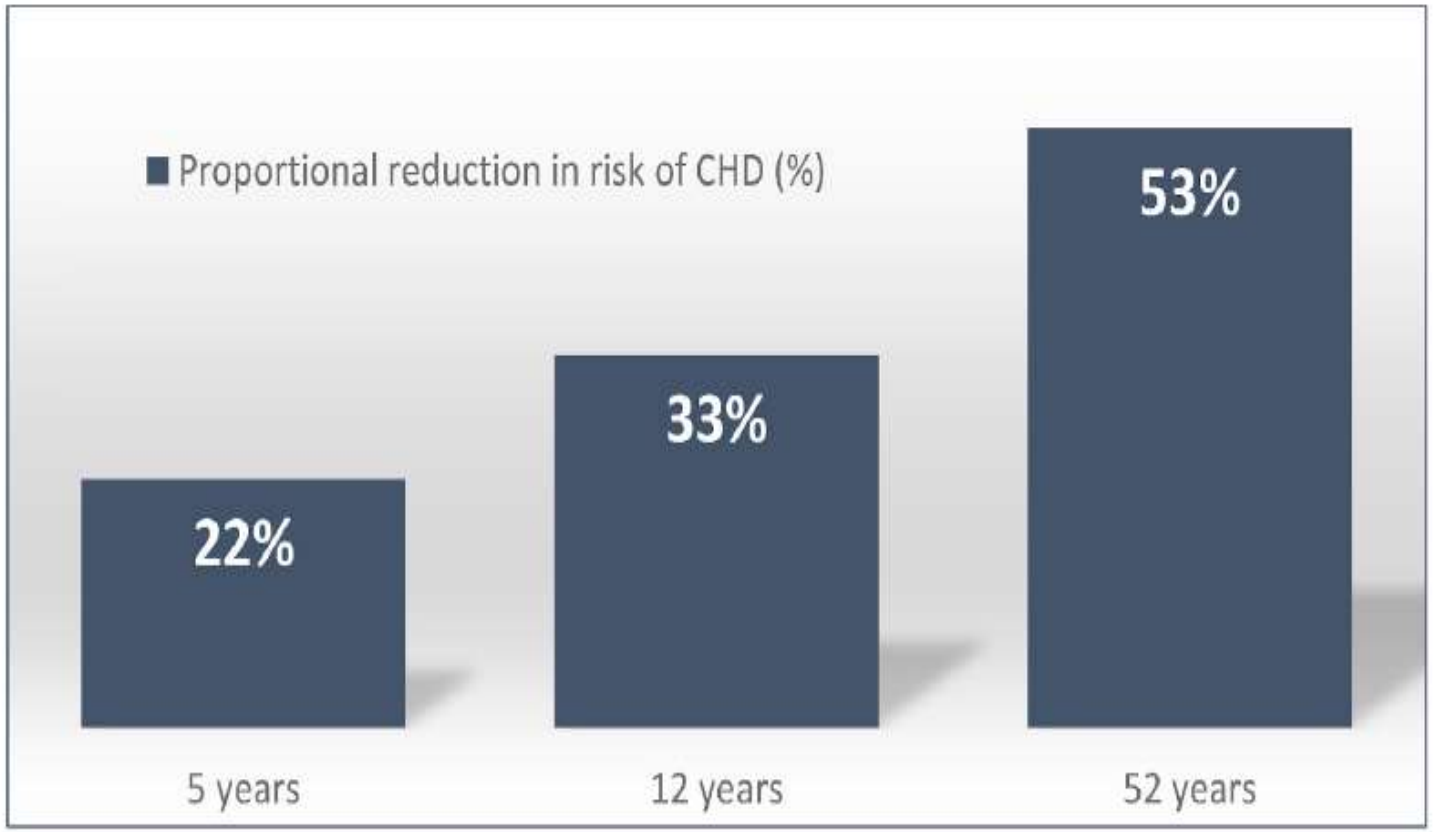


Fig. 1. Effect of duration of exposure to a 1 mmol/L reduction in LDL-C on CHD risk [64].
CHD, coronary heart disease; LDL-c, low-density lipoprotein cholesterol.

10.1161/CIRCULATIONAHA.122.061620

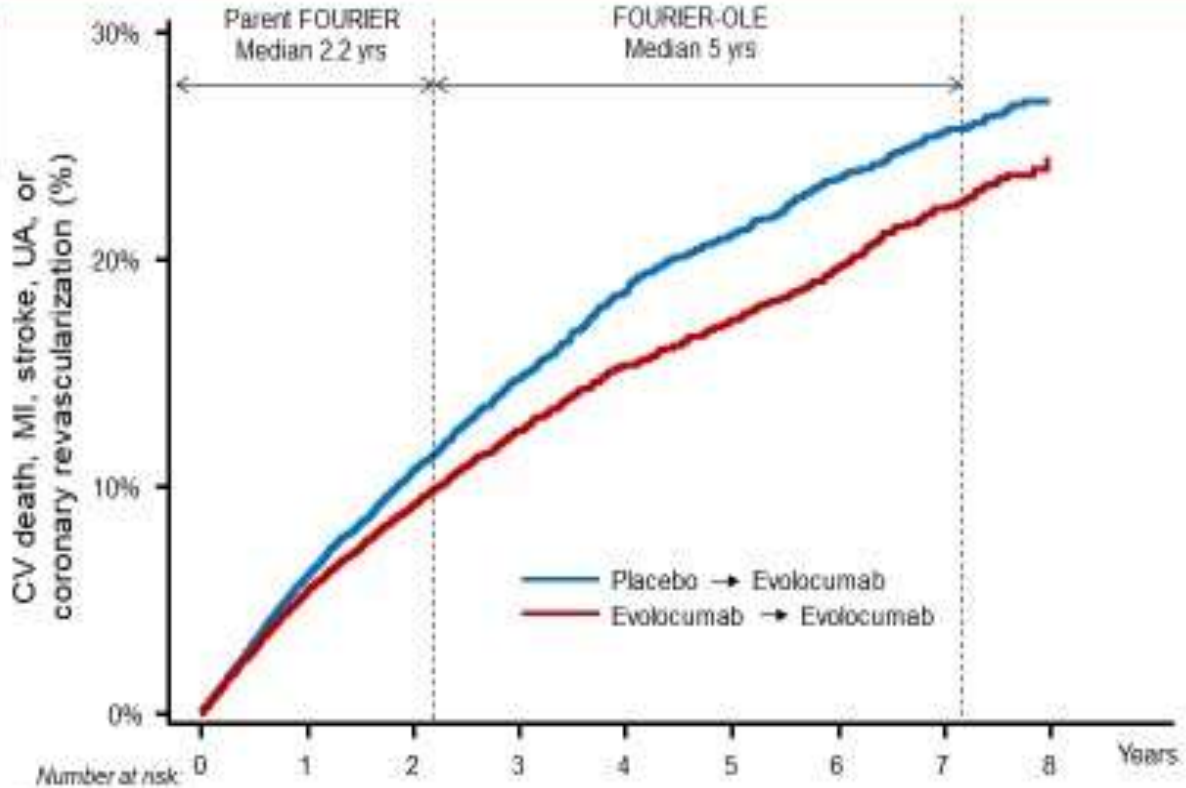
Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease

Running Title: *O'Donoghue et al.; Long-term evolocumab in cardiovascular disease*

Michelle L. O'Donoghue MD MPH[1]; Robert P. Giugliano MD SM[1]; Stephen D. Wiviott MD[1]; Dan Atar MD[2,3]; Anthony Keech MBBS[4]; Julia F. Kuder MA[1]; KyungAh Im PhD[1]; Sabina A. Murphy MPH[1]; Jose H. Flores-Arredondo MD[5]; J. Antonio G. López MD[5]; Mary Elliott-Davey MSc[6]; Bei Wang PhD[5]; Maria Laura Monsalvo MD[5]; Siddique Abbasi MD[5]; Marc S. Sabatine MD MPH[1]

Efficacy during FOURIER & FOURIER-OLE

FOURIER Primary Endpoint



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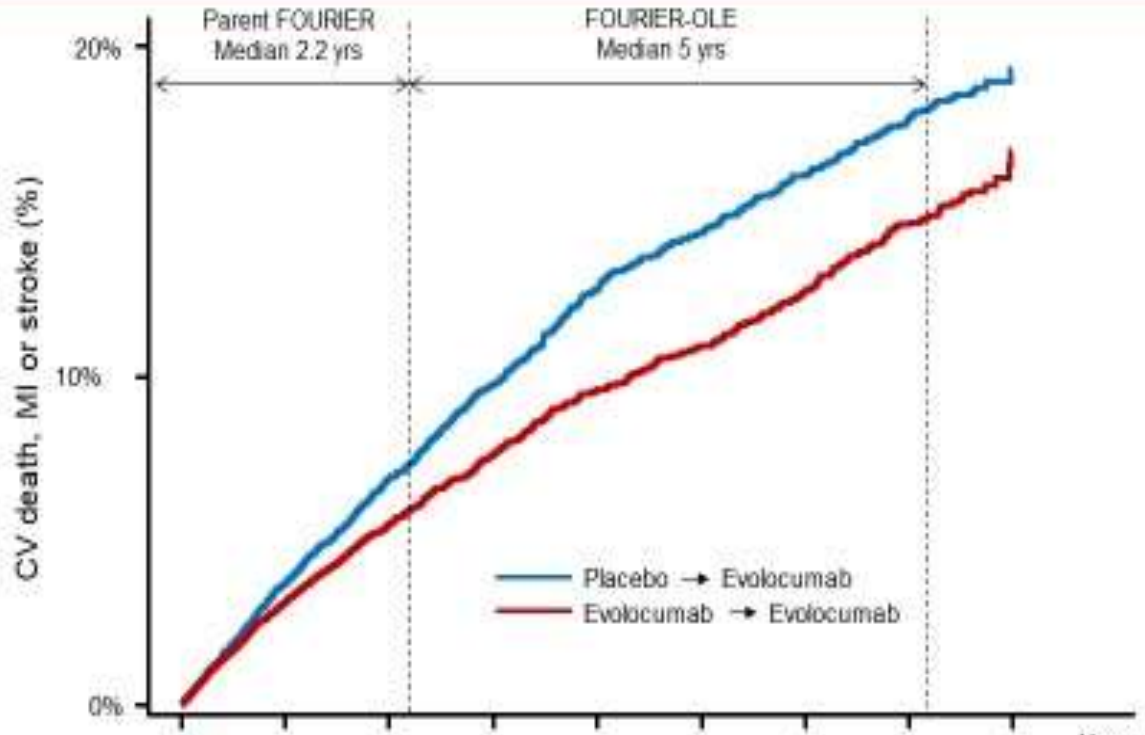
Brigham and Women's Hospital and Harvard Medical School

Efficacy during FOURIER & FOURIER-OLE

FOURIER Key Secondary Endpoint



Number at risk:	0	1	2	3	4	5	6	7	8
Placebo-Evolocumab	13780	13140	8848	3470	2861	2757	2621	1684	216
Evolocumab-Evolocumab	13784	13240	9051	3617	3046	2946	2810	1746	185

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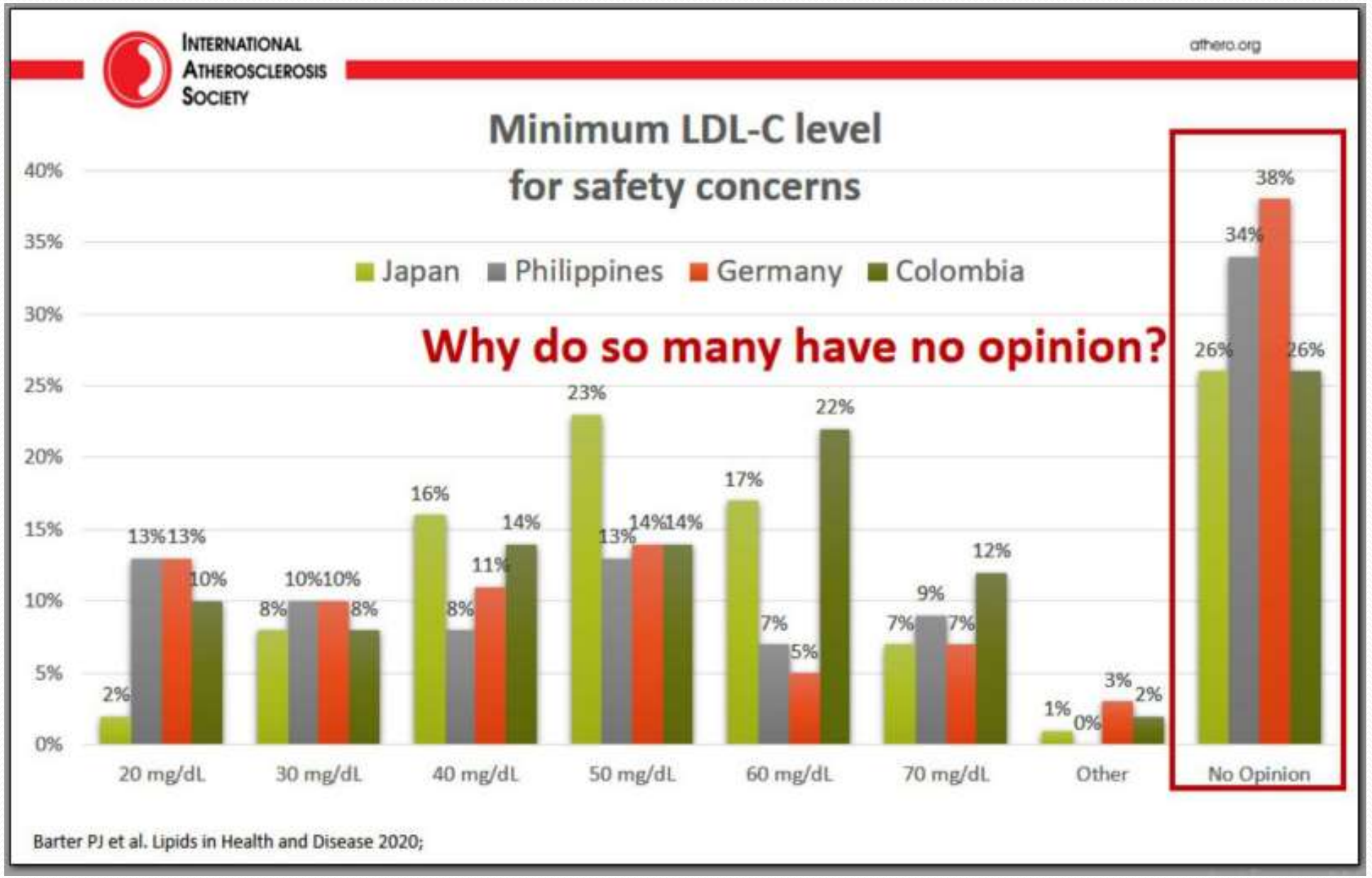
Brigham and Women's Hospital and Harvard Medical School


INTERNATIONAL ATHEROSCLEROSIS SOCIETY
athero.org
Minimum LDL-C level for safety concerns
Japan
Philippines
Germany
Colombia
Why do so many have no opinion?
40%
35%
30%
25%
20%
15%
10%
5%
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2%
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12%
1%
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3%
2%
26%
34%
38%
26%
20 mg/dL
30 mg/dL
40 mg/dL
50 mg/dL
60 mg/dL
70 mg/dL
Other
No Opinion
Barter PJ et al. Lipids in Health and Disease 2020;


IN 2019
1 IN 5
PATIENTS
WITH VERY HIGH CARDIOVASCULAR RISK ACHIEVED THE CHOLESTEROL TARGETS RECOMMENDED BY GUIDELINES
IN EUROPE, VERY HIGH RISK PATIENTS
10%
RECEIVE SOME FORM OF COMBINATION THERAPY
9%
RECEIVE COMBINATION THERAPY WITH EZETIMIBE
1%
RECEIVE COMBINATION THERAPY WITH PCSK9 INHIBITORS

HOW TO ACHIEVE

Current Cardiology Reports (2020) 22: 66
https://doi.org/10.1007/s11886-020-01326-w

LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (SECTION EDITORS)

Check for updates

Reasons Why Combination Therapy Should Be the New Standard of Care to Achieve the LDL-Cholesterol Targets

Lipid-lowering combination therapy

Lluís Masana[1,2] · Daiana Ibarretxe[1,2] · Núria Plana[1,2]

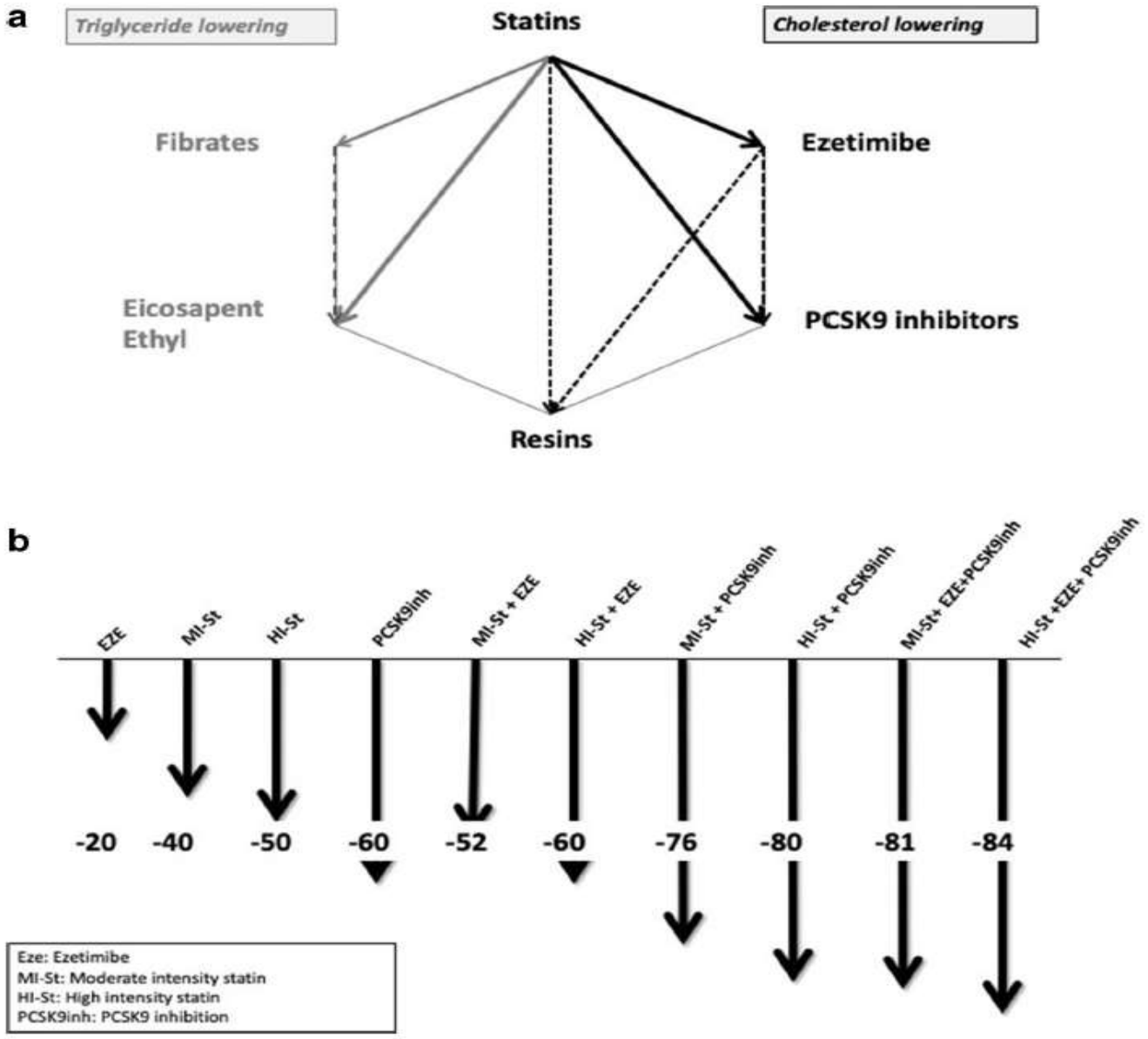
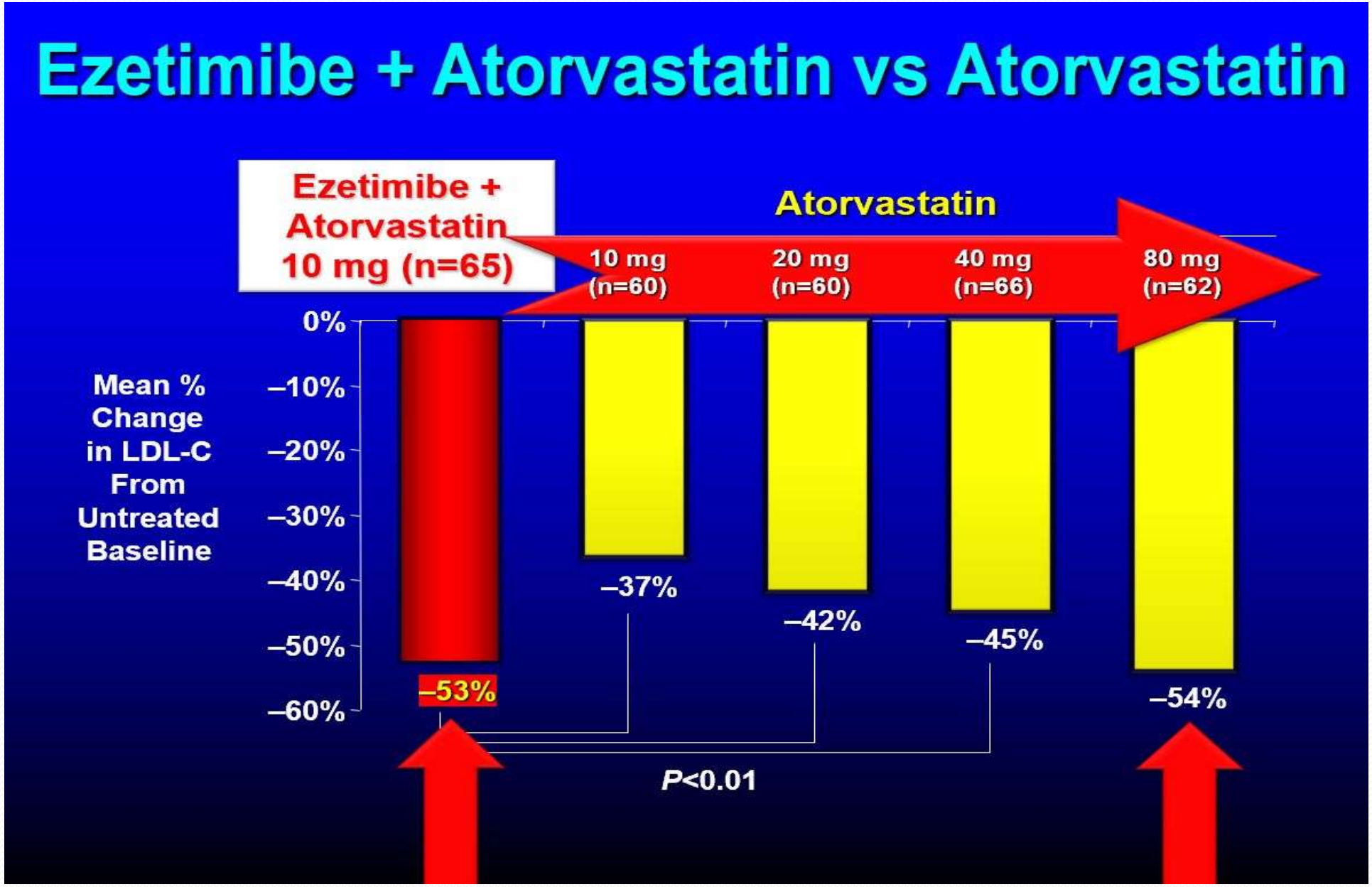
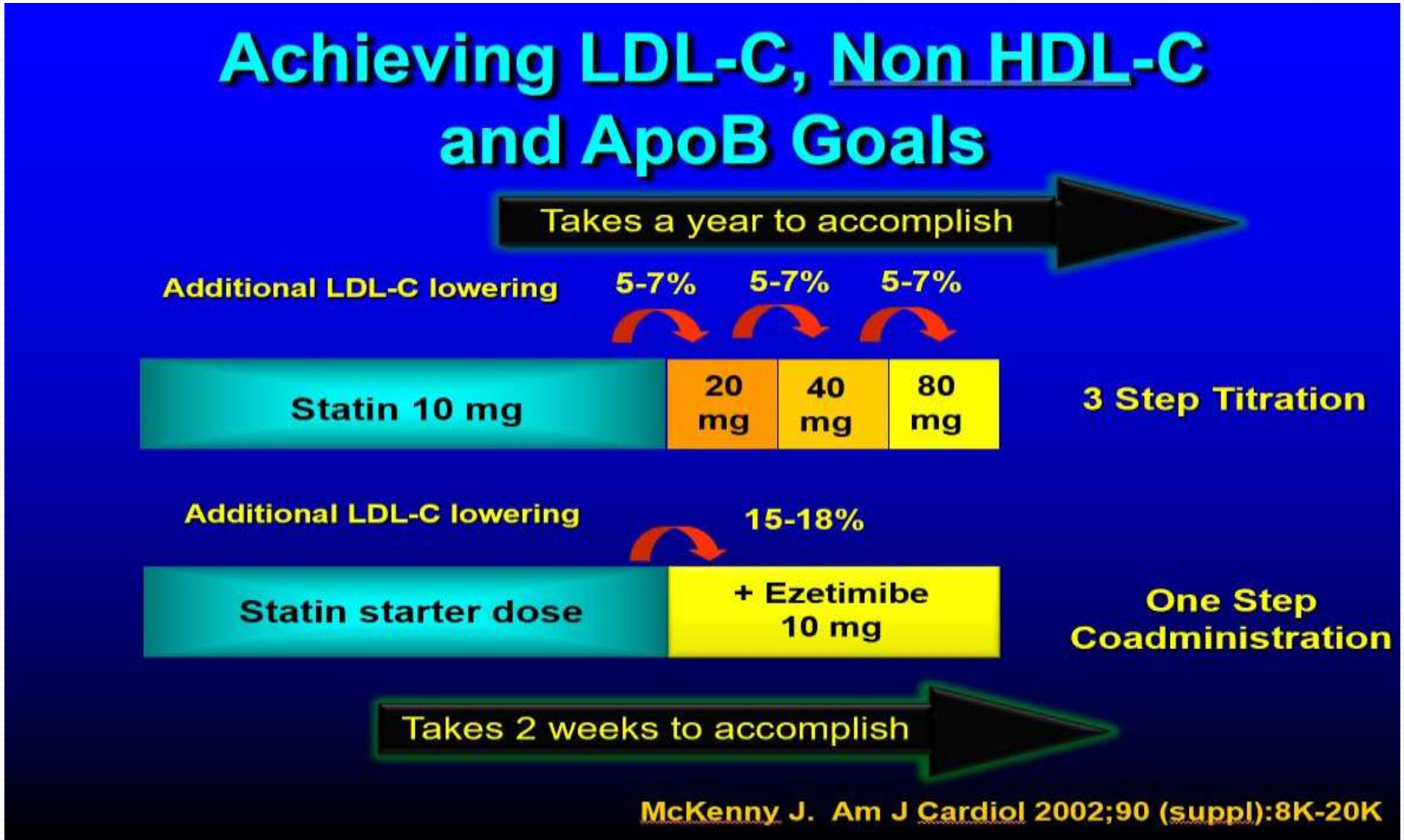


Fig. 1 Recommended lipid lowering therapy combinations and its efficacy. **a** Appropriated lipid-lowering combination therapies according scientific evidence. Thicker continuous lines indicate that at least one RCT supports the association. Thinner continuous lines indicate that combination is supported by subgroup analyses. Discontinuous lines indicate that combination potentiates lipid lowering therapy. Triglyceride lowering square indicates that drugs below could be combined with statins in patients with hypertriglyceridemia. Cholesterol-lowering square indicates that drugs below could be combined with statins to reduce LDL-cholesterol. **b** Theoretical percentage reduction on LDL cholesterol concentrations (Fig. 1b created with data from [34])

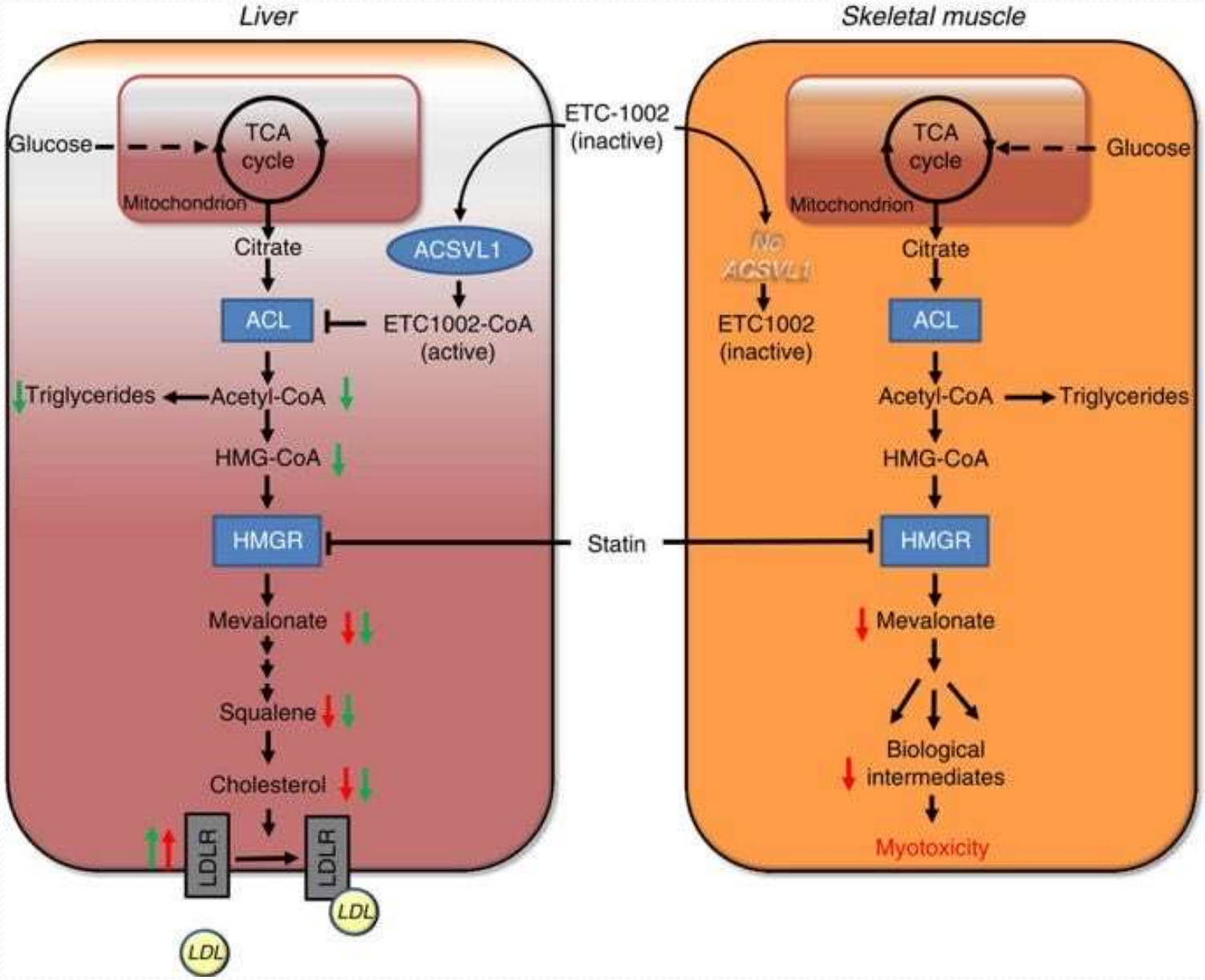

Ezetimibe + Atorvastatin vs Atorvastatin
Ezetimibe + Atorvastatin 10 mg (n=65)
Atorvastatin
10 mg (n=60)
20 mg (n=60)
40 mg (n=66)
80 mg (n=62)
Mean % Change in LDL-C From Untreated Baseline
0%
–10%
–20%
–30%
–40%
–50%
–60%
–53%
–37%
–42%
–45%
–54%
P<0.01

My thoughts: Considering the current apoB goals in high-risk patients, not starting dual therapy is just giving ⬆ apoB particles more time to invade artery. Statin monotherapy does not come close to statin + eze, statin + BA or for sure statin + PCSK9i on apoB lowering

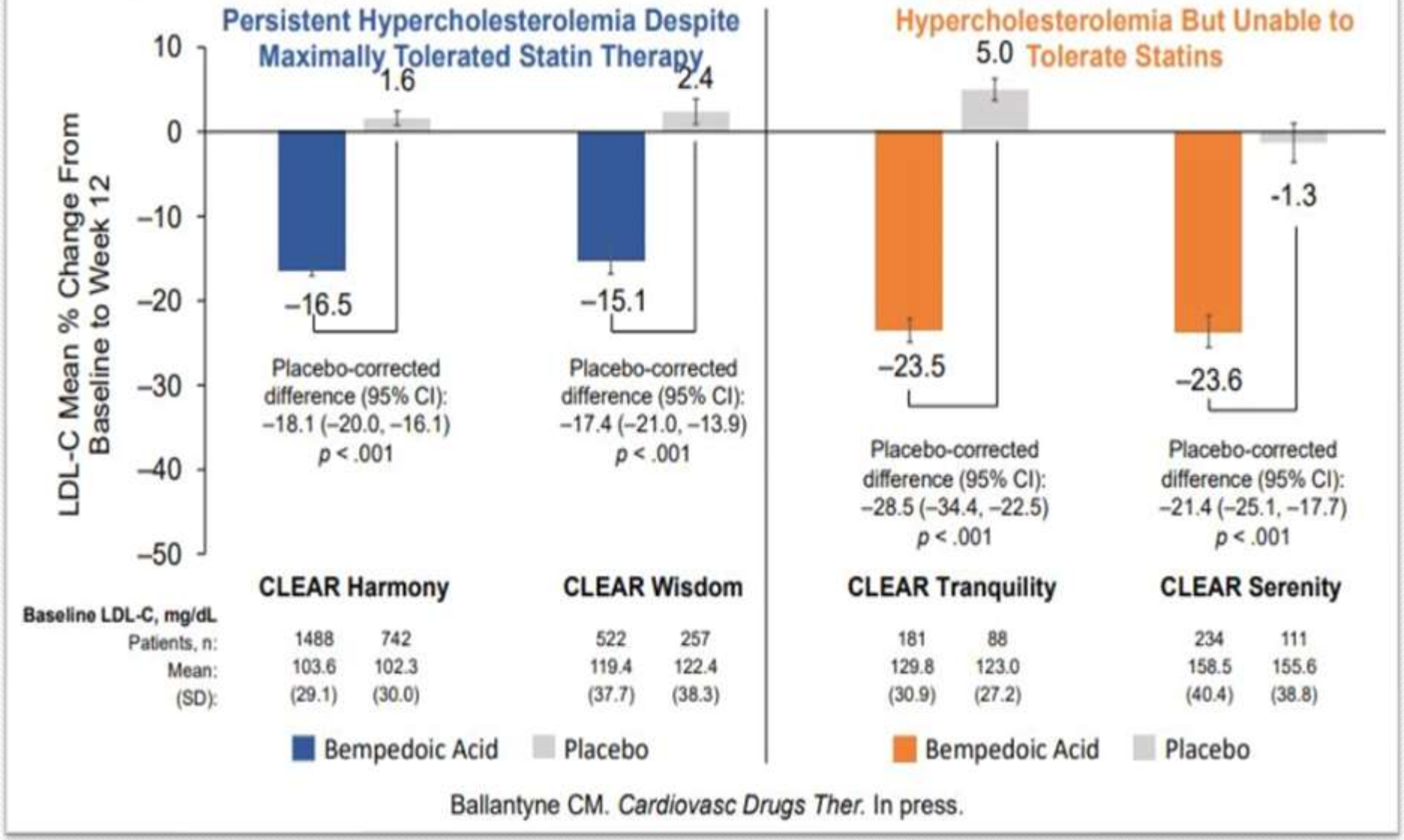


BEMOEDOIC ACID

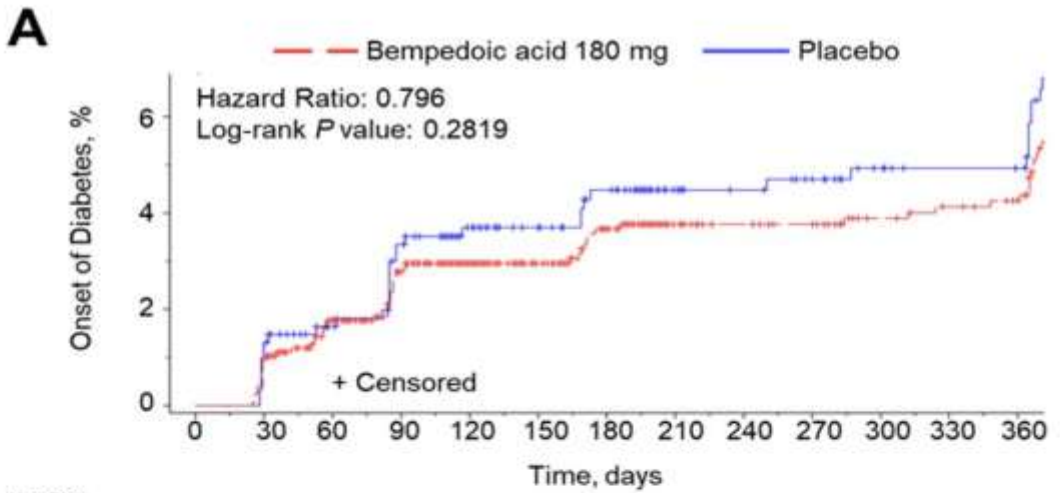
#BA : not available on the French market. Why ? #FDA approval. Ongoing #RCVOT no warning signal on safety. Useful for (real) statin's intolerance #lipids



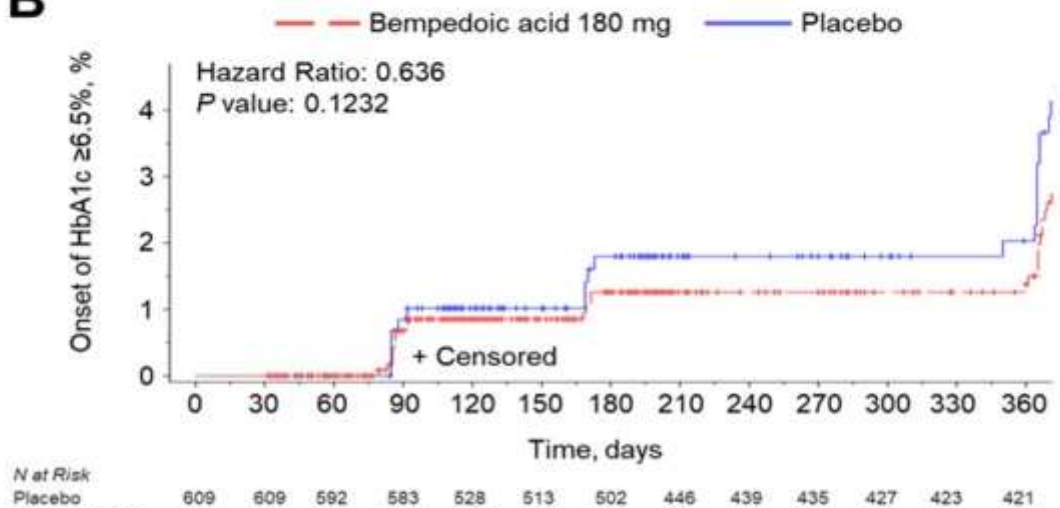
Effect of bempedoic acid on LDL-C after 12 weeks of treatment



Ballantyne CM. *Cardiovasc Drugs Ther.* In press.



N at Risk													
Placebo	609	603	585	571	515	498	488	433	428	420	412	408	407
Bempedoic acid	1259	1254	1187	1138	1013	967	941	831	818	813	795	789	783
Events													
Placebo	0	8	9	19	21	21	25	25	25	26	27	27	27
Bempedoic acid	0	12	21	33	35	35	42	43	43	43	44	46	47



N at Risk													
Placebo	609	609	592	583	528	513	502	446	439	435	427	423	421
Bempedoic acid	1259	1259	1208	1163	1036	988	966	854	841	837	819	814	810
Events													
Placebo	0	0	0	5	6	6	10	10	10	10	10	10	11
Bempedoic acid	0	0	0	8	10	10	14	14	14	14	14	14	15

Orion Constellation

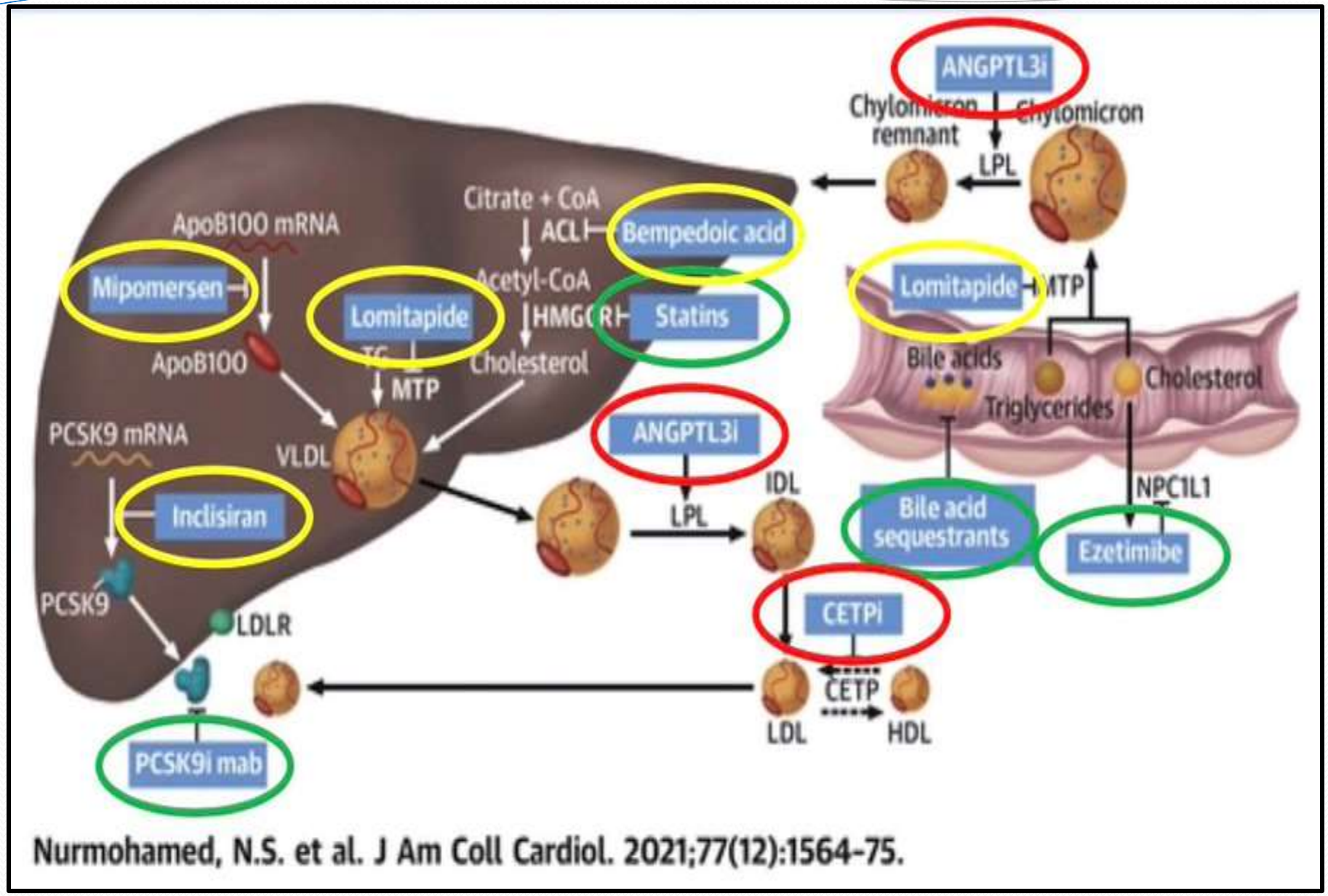
One of the most recognizable constellations – lies along the celestial equator and contains 2 of the 10 brightest stars in the sky. Named after Orion, a hunter in Greek mythology

Pivotal Phase 3 Trials of Inclisiran to Support LDL-C Lowering

- **ORION-9:** LDL-C lowering in patients with HeFH with LDL-C ≥100 mg/dL
- **ORION-10:** LDL-C lowering in ASCVD patients with LDL-C ≥70 mg/dL (US)
- **ORION-11:** LDL-C lowering in patients with ASCVD and LDL-C ≥70 mg/dL, or ASCVD risk equivalents and LDL-C ≥100 mg/dL (Europe and South Africa)

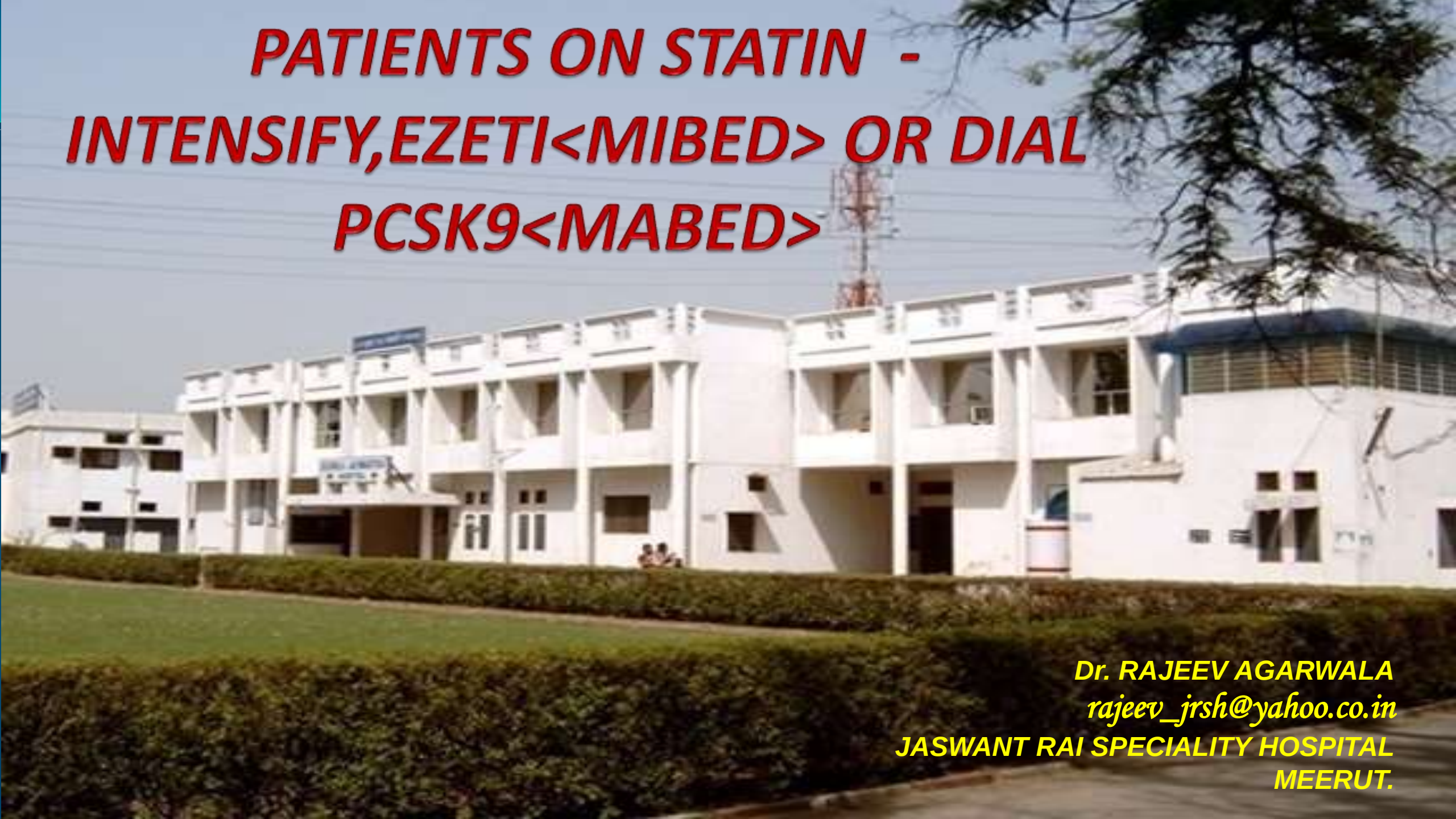
Raal FJ, et al. *N Engl J Med*. 2020;382:1520-1530; Ray KK, et al. *N Engl J Med*. 2020;382:1507-1519.

Working Mechanisms of LDLc Lowering Therapies



Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564-75.

PATIENTS ON STATIN - INTENSIFY,EZETI<MIBED> OR DIAL PCSK9<MABED>



Dr. RAJEEV AGARWALA
rajeev_jrsh@yahoo.co.in
JASWANT RAI SPECIALITY HOSPITAL
MEERUT.

EVIDENCES

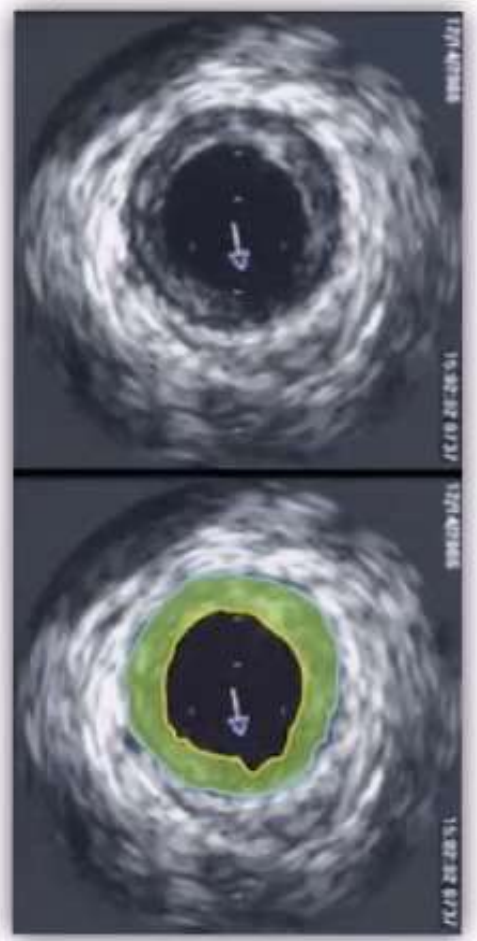
JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

The GLAGOV Randomized Clinical Trial

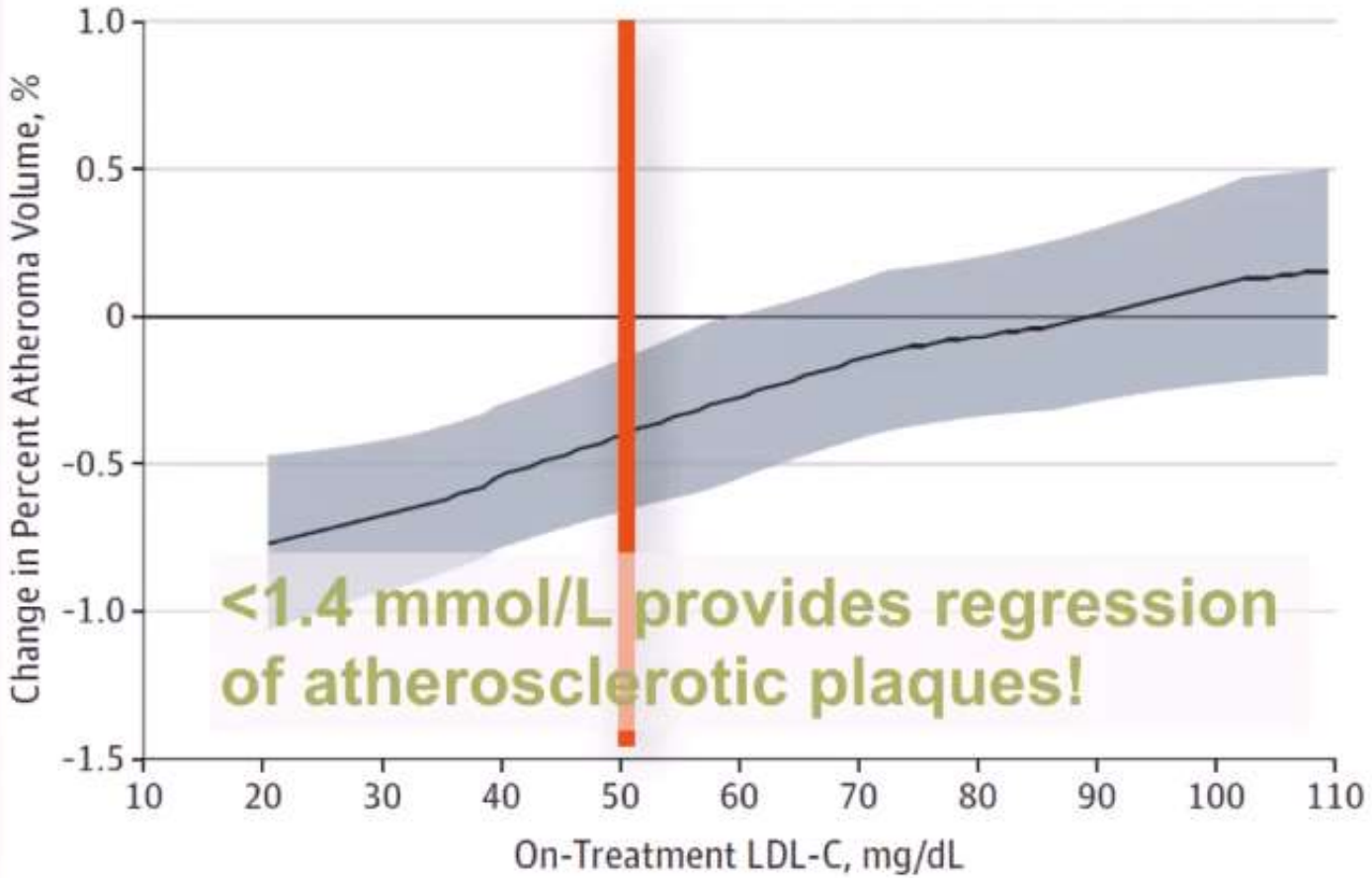
Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helios Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Daniel

Figure 2. Mean Absolut



Evolocumab 48

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



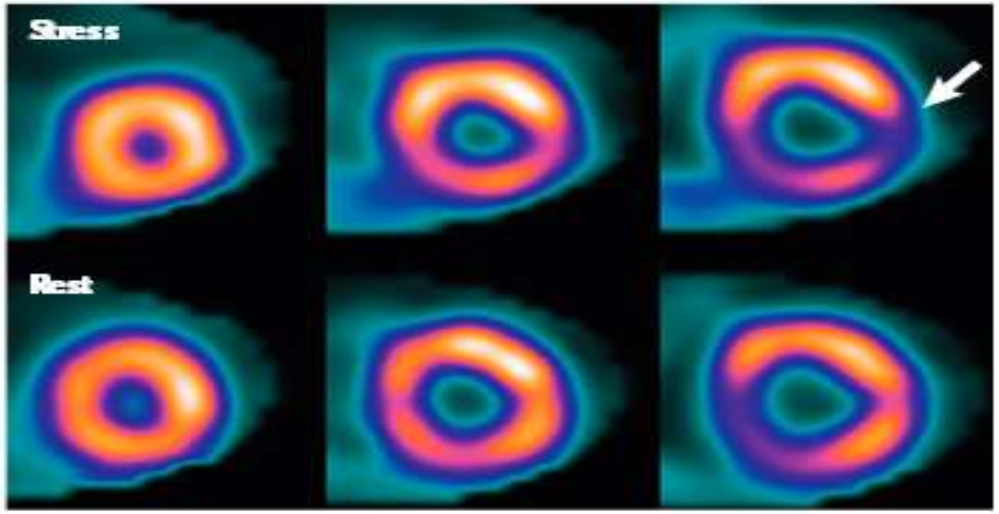
The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

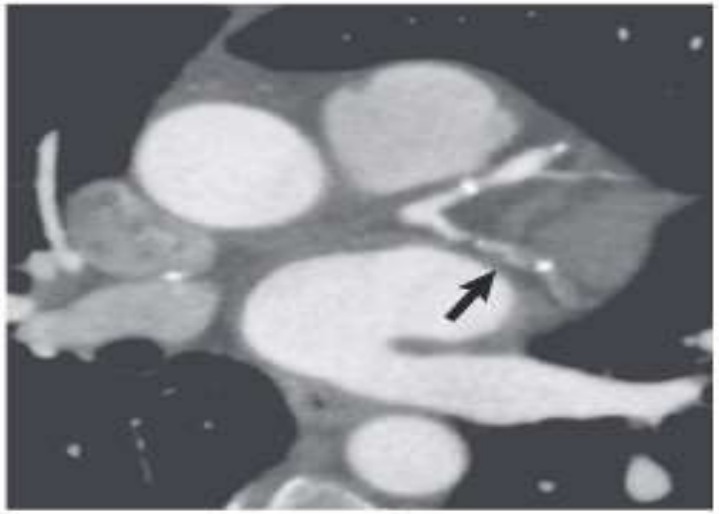
Chana A. Sacks, M.D., *Editor*

Regression of Coronary Atherosclerosis with Medical Therapy

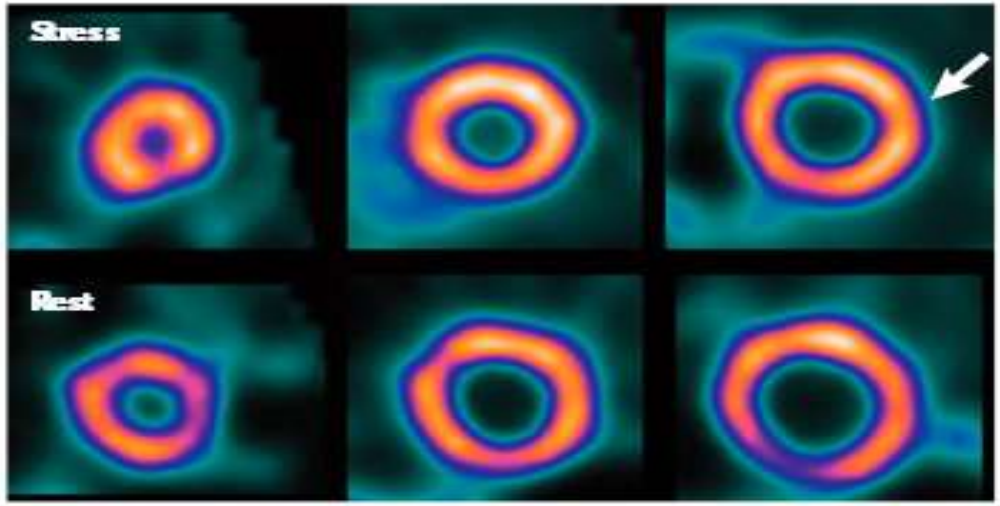
A Before Therapy, Moderate Ischemia on Perfusion Imaging



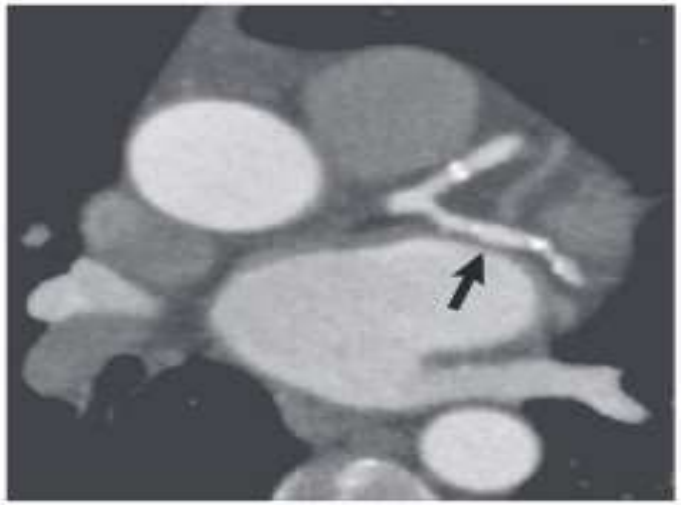
B Severe Stenosis on Coronary CTA



C After Therapy, No Visible Ischemia



D Reduction in Plaque on Coronary CTA



ESC European Society of Cardiology
European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytaa569

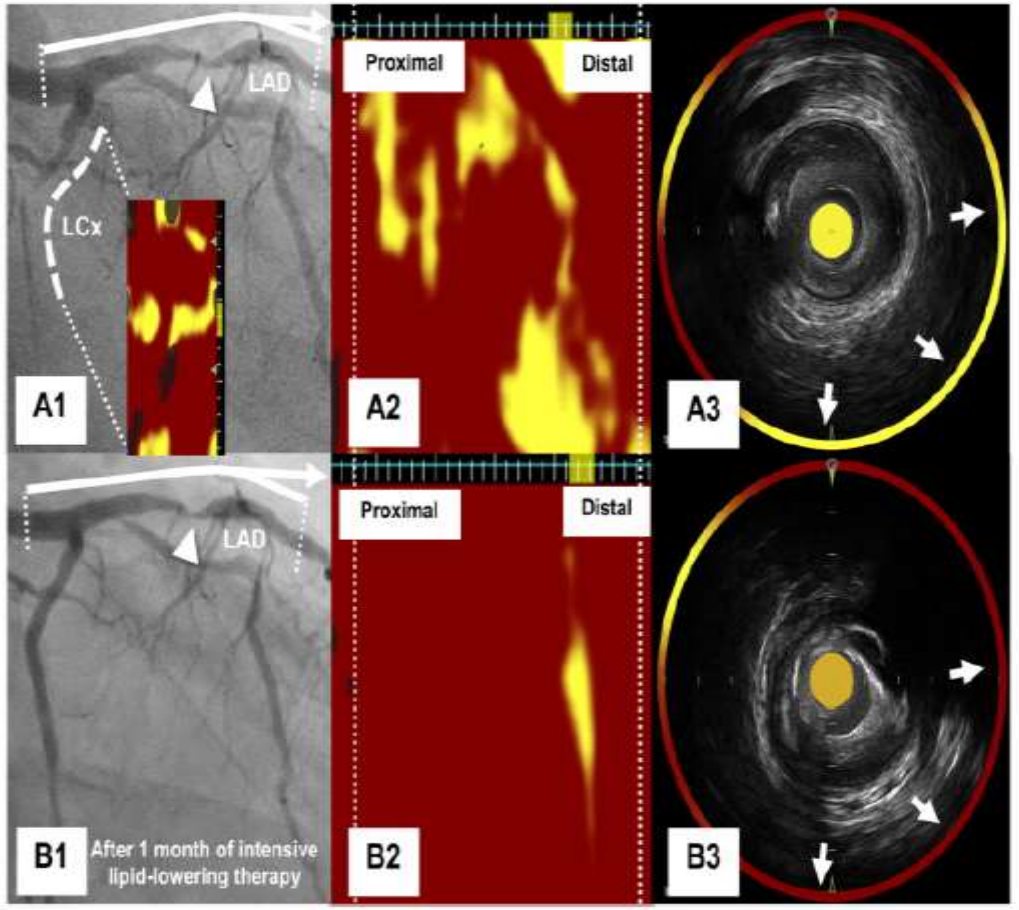
FLASHLIGHTS
Coronary heart disease

Impact of 1 month of intensive lipid-lowering therapy on plaque composition evaluated using near-infrared spectroscopy

Kensaku Nishihira*, Nehiro Kuriyama, and Yoshisato Shibata

Department of Cardiology, Miyazaki Medical Association Hospital, 1173 Arita, Miyazaki 880-2102, Japan

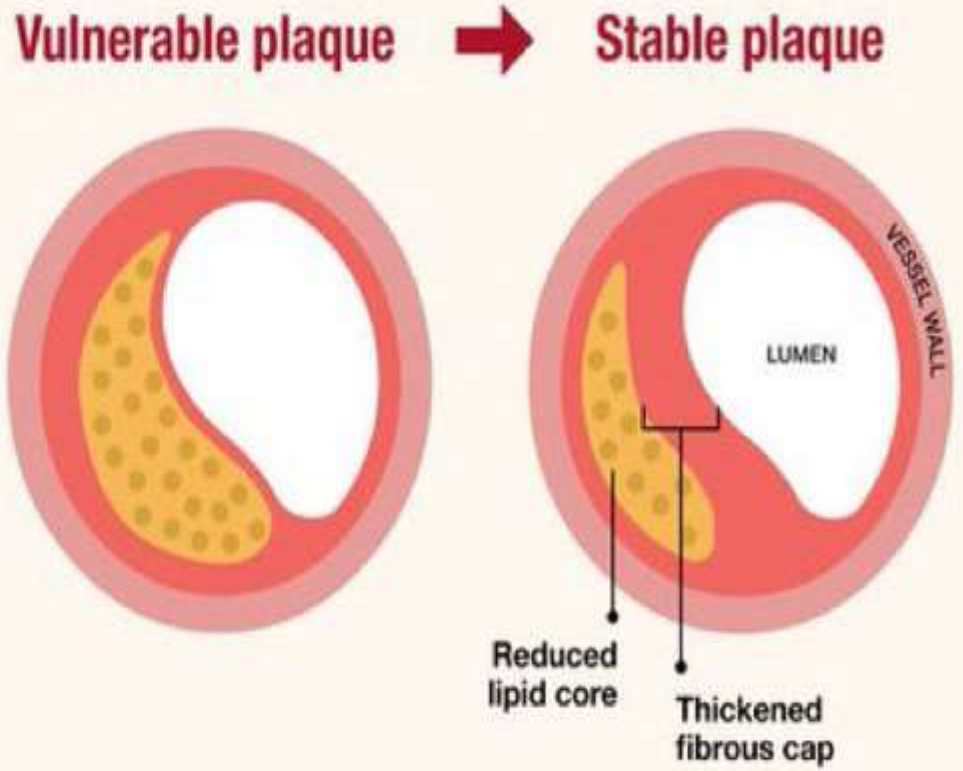
Received 19 November 2020; first decision 25 November 2020; accepted 18 December 2020



ESC
European Society of Cardiology

HUYGENS

Evolocumab and changes in plaque composition on OCT



Original Investigation

ONLINE FIRST FREE

April 3, 2022

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction

The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD[1]; Yasushi Ueki, MD, PhD[1]; Tatsuhiko Otsuka, MD[1]; et al

» Author Affiliations | Article Information

JAMA. Published online April 3, 2022. doi:10.1001/jama.2022.5218

Conclusions and Relevance Among patients with acute myocardial infarction, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non–infarct-related arteries after 52 weeks. Further research is needed to understand whether alirocumab improves clinical outcomes in this population.

JACC: CARDIOVASCULAR IMAGING VOL. 15, NO. 7, 2022

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Shining a Light on Plaque Vulnerability and Treatment*

Gregg W. Stone, MD, Jagat Narula, MD, PhD

https://doi.org/10.1016/j.jcmg.2022.04.019

ESC European Society of Cardiology

European Heart Journal Open (2021) **00**, 1–13
https://doi.org/10.1093/ehjopen/oeab039

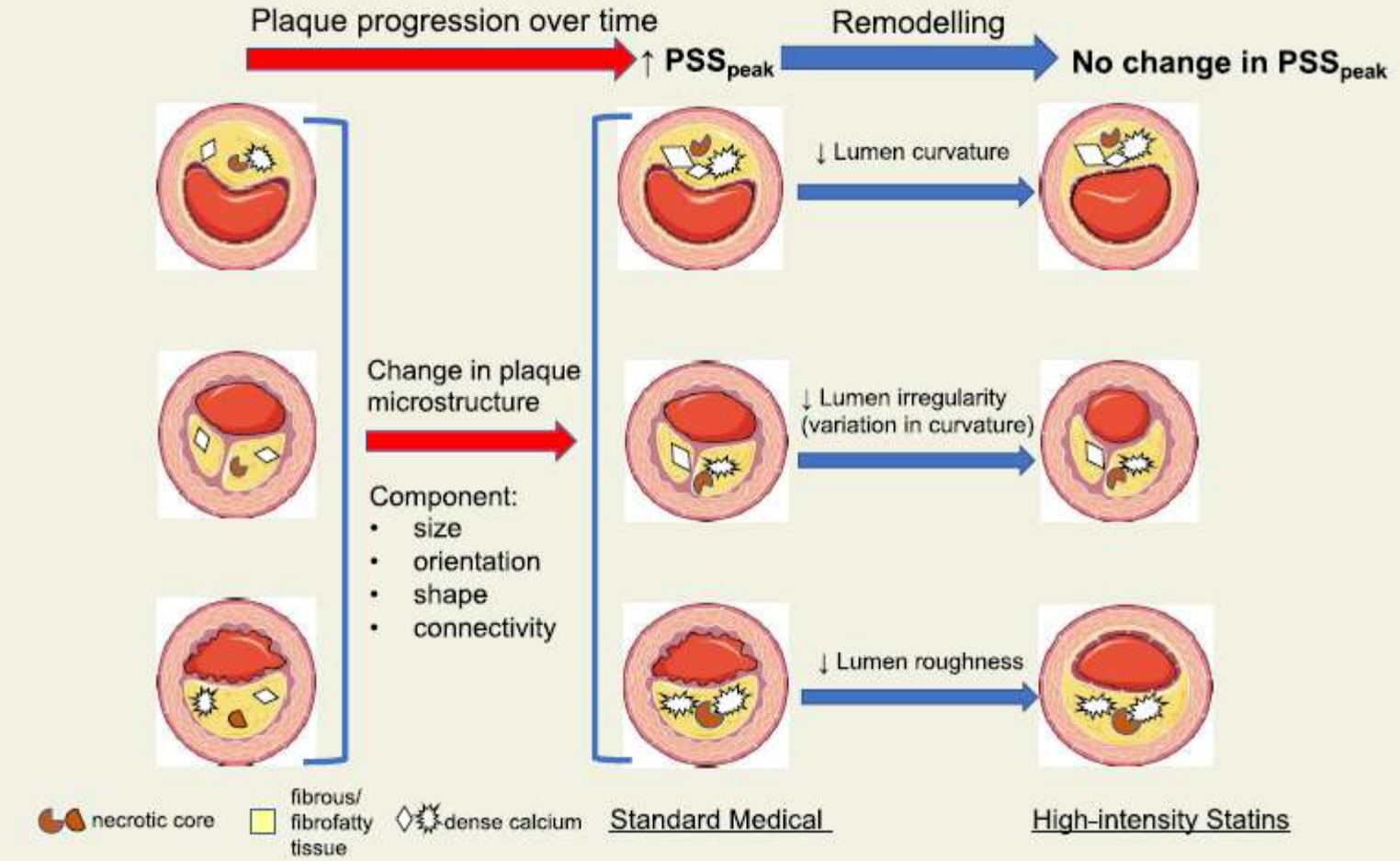
ORIGINAL ARTICLE
Coronary artery disease

High-intensity statin treatment is associated with reduced plaque structural stress and remodelling of artery geometry and plaque architecture

Sophie Z. Gu[1], Charis Costopoulos[2], Yuan Huang[3,4], Christos Bourantas[5,6], Adam Woolf[1], Chang Sun[4], Zhongzhao Teng[4,7], Sylvain Losdat[8], Lorenz Räber[9], Habib Samady[10], and Martin R. Bennett [1,*]

Conclusion Our observational study shows that PSS_{peak} changes over time were associated with baseline disease severity and treatment. The PSS_{peak} increase seen in advanced lesions with standard treatment was associated with remodelling artery geometry and plaque architecture, but this was not seen after HIS treatment. Smoothing plaques by reducing plaque/lumen roughness, irregularity, and curvature represents a novel mechanism whereby HIS may reduce PSS and, thus may protect against plaque rupture and MACE.

Graphical Abstract



Plaques progress over time with standard medical treatment due to changes in plaque microstructure, resulting in increased peak PSS. High-intensity statins remodel the lumen/plaque interface, reducing lumen curvature, irregularity and roughness, and preventing the increase in peak PSS seen with standard medical treatment. Smoothing plaques and reducing lumen curvature represent novel mechanisms whereby high-intensity statins may protect against plaque rupture. PSS, plaque structural stress.

European Heart Journal (2015) **36**, 472–474
doi:10.1093/eurheartj/ehu510

EDITORIAL

How does lipid lowering prevent coronary events? New insights from human imaging trials

Peter Libby*

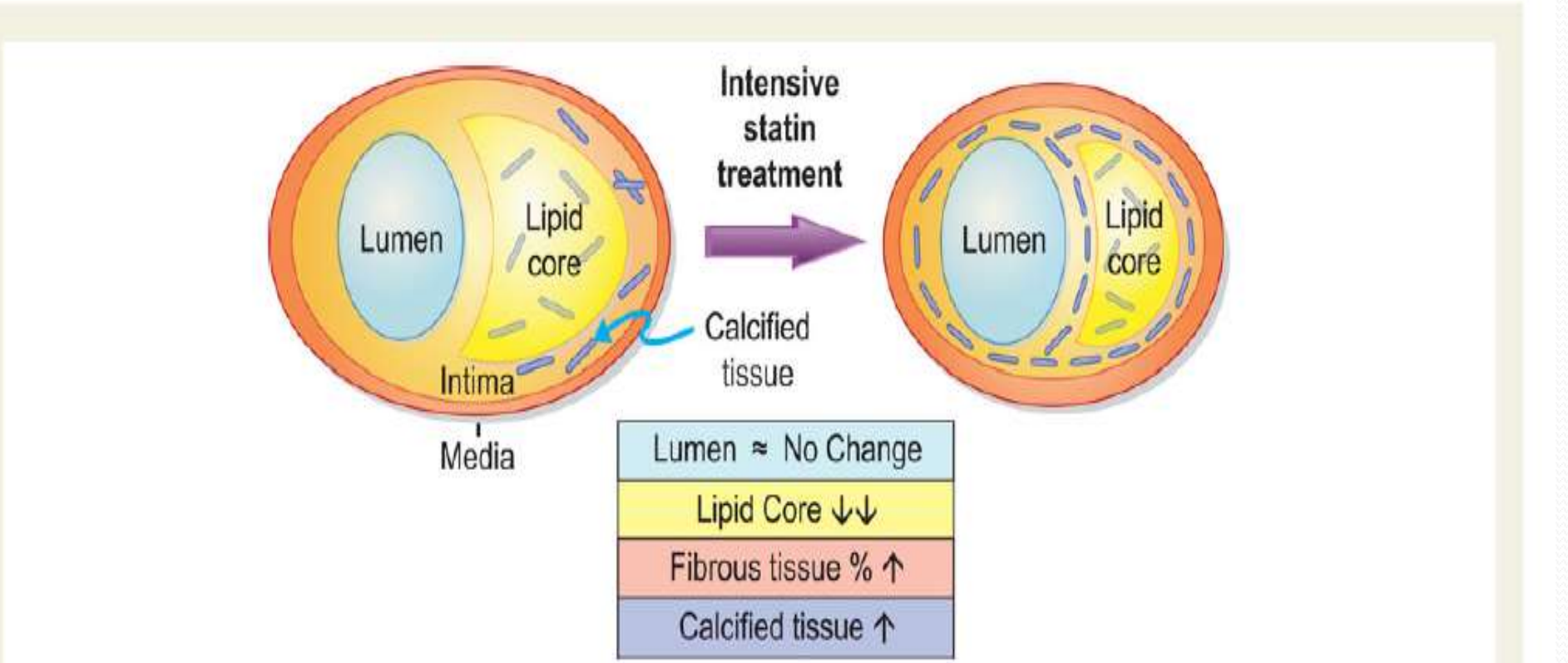
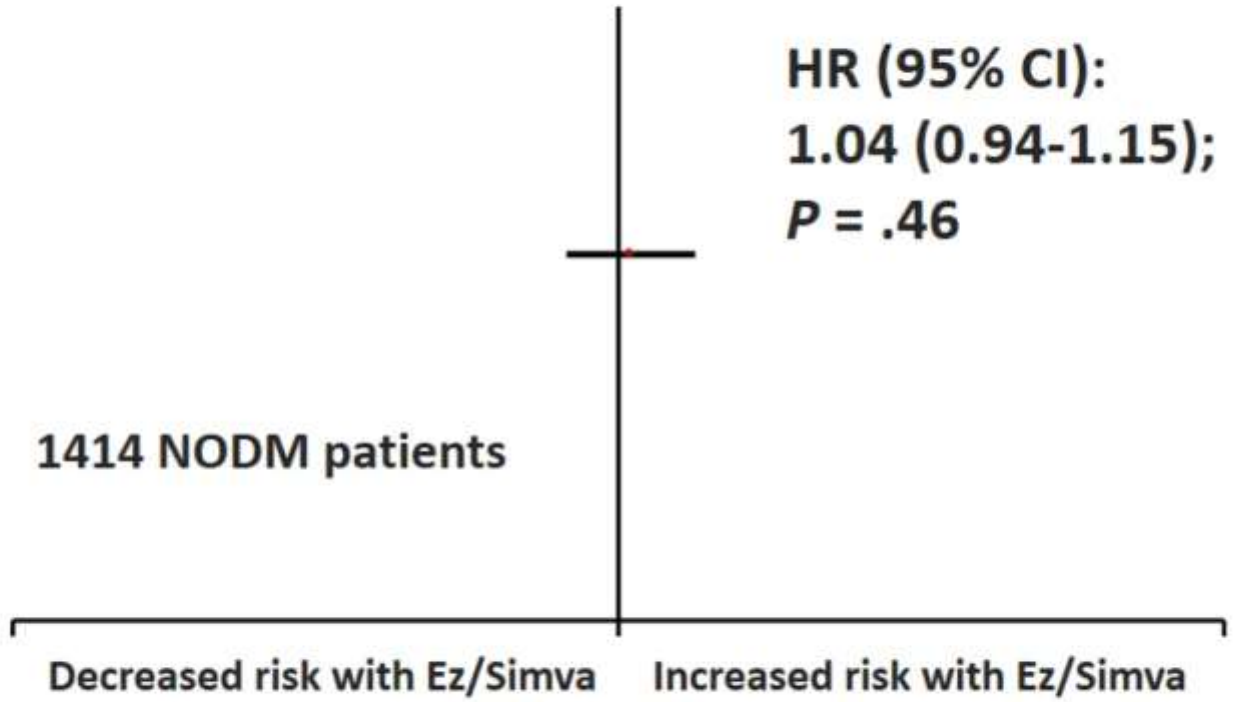


Figure 1 An integrated depiction of the effects of aggressive lipid lowering on human coronary plaques as revealed by 'virtual histology' and other cross-sectional imaging studies. The lumen remains largely unchanged, the lipid core shrinks, the amount of fibrous tissue may increase as a proportion of the intima, but modestly decrease in absolute terms, while the content of calcified tissue actually rises with lipid lowering.

SIDE EFFECTS

New Onset Diabetes Mellitus (NODM) in IMPROVE-IT



NODM = Initiation of antihyperglycemic medication; or 2 consecutive fasting glucose ≥7mmol/L.

Blazing MA, et al. ESC 2015. FP Number: 5774.

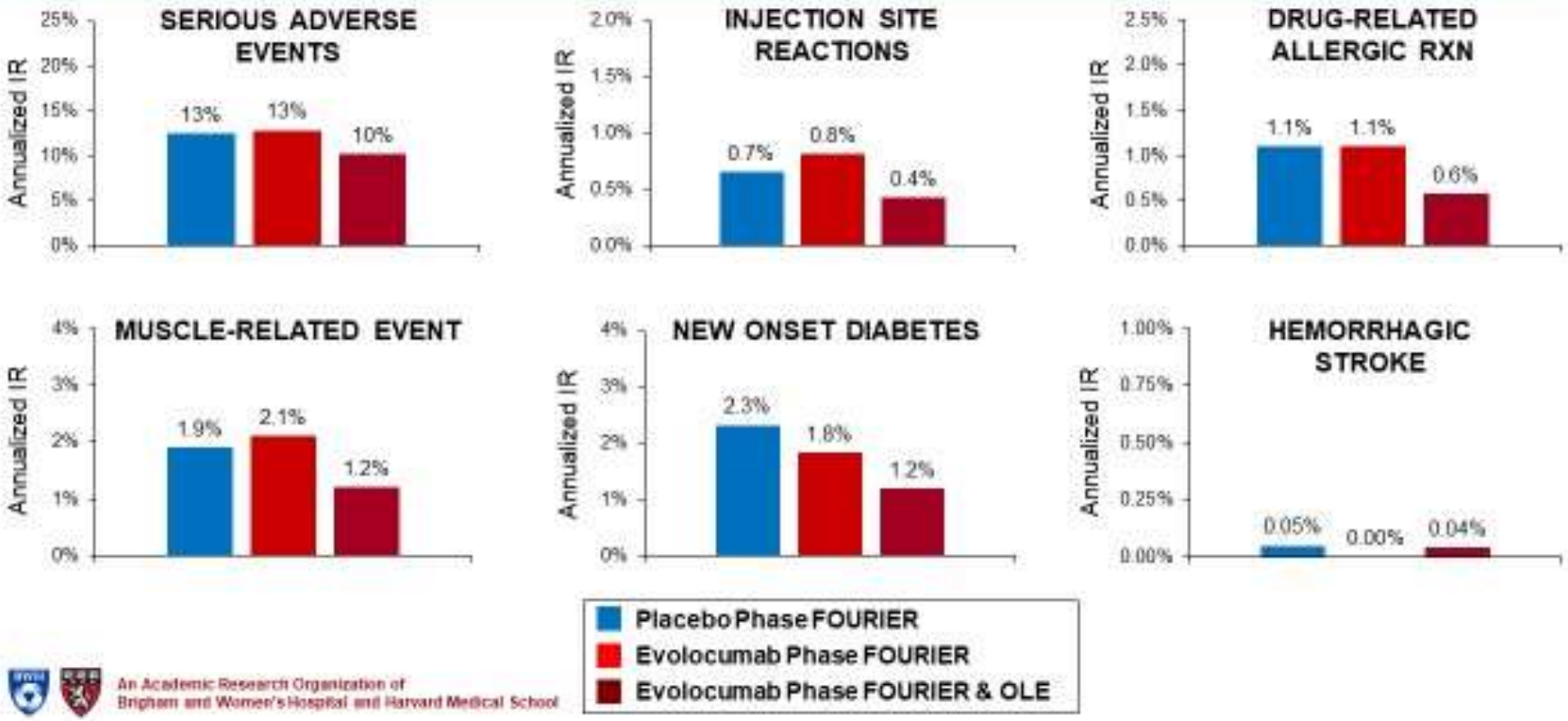
10.1161/CIRCULATIONAHA.122.061620

Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease

Running Title: *O'Donoghue et al.; Long-term evolocumab in cardiovascular disease*

Michelle L. O'Donoghue MD MPH[1]; Robert P. Giugliano MD SM[1]; Stephen D. Wiviott MD[1]; Dan Atar MD[2,3]; Anthony Keech MBBS[4]; Julia F. Kuder MA[1]; KyungAh Im PhD[1]; Sabina A. Murphy MPH[1]; Jose H. Flores-Arredondo MD[5]; J. Antonio G. López MD[5]; Mary Elliott-Davey MSc[6]; Bei Wang PhD[5]; Maria Laura Monsalvo MD[5]; Siddique Abbasi MD[5]; Marc S. Sabatine MD MPH[1]

Long-Term Safety



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

Published in final edited form as:
Lancet. 2012 August 11; 380(9841): 565–571. doi:10.1016/S0140-6736(12)61190-8.

Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention

Paul M Ridker, MD, **Aruna Pradhan, MD**, **Jean G. MacFadyen, BA**, **Peter Libby, MD**, and **Robert J Glynn, ScD**
Center for Cardiovascular Disease Prevention (PMR, AD, JM, GJG) and the Division of Cardiovascular Medicine (PMR, PL), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Interpretation—In the JUPITER primary prevention trial, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including among those at higher risk for developing diabetes

What's my risk of statin induced diabetes? JUPITER trial: in those with no risk factors for diabetes (BMI < 30, A1C <6, no metabolic syndrome, normal fasting glucose) (N=6,095), no increase in diabetes compared to placebo (HR 0.99, P= 0.99)

ncbi.nlm.nih.gov/pmc/articles/P...

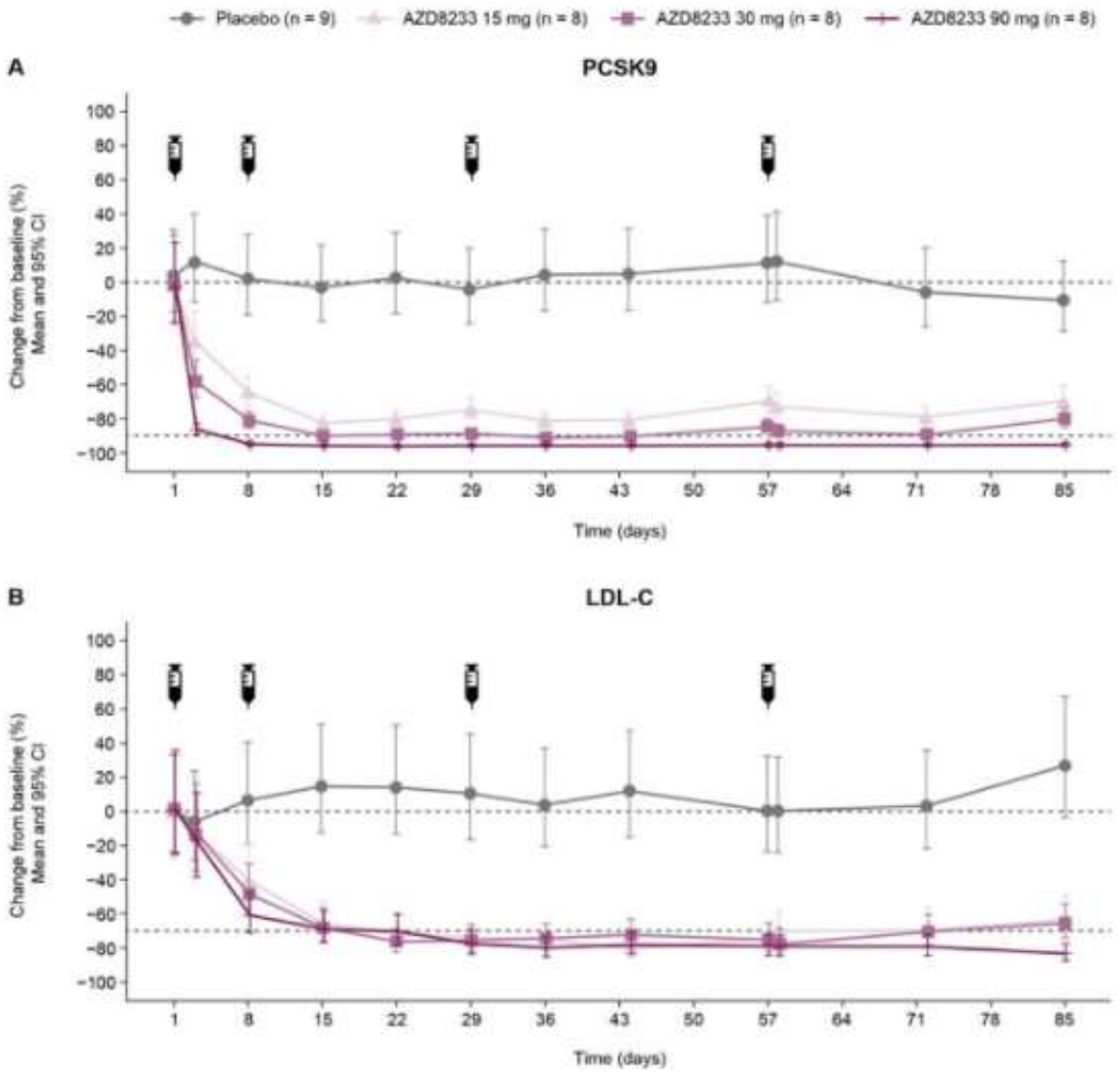
TOUGH TARGETS INNOVATIVE PATHS

Daily Oral PCSK9 Inhibitor Encouraging in Phase 1 Trials

Steve Stiles

November 23, 2021

Figure. Percent change from baseline in PCSK9 (A) and LDL-C (B) levels over time



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

CETP inhibitor reduces LDL-c on top of high-intensity statin

NEWS - MAY 24, 2022

Obicetrapib lowers LDL-c in patients on high-intensity statins: Results from the ROSE trial

Presented at the EAS congres 2022 by: **Kausik Ray, MD** - London, UK.

ESC
European Society of Cardiology

Cardiovascular Research (2021) **00**, 1–13
https://doi.org/10.1093/cvr/cvab350

REVIEW

Cholesteryl ester transfer protein inhibitors: from high-density lipoprotein cholesterol to low-density lipoprotein cholesterol lowering agents?

Nick S. Nurmohamed [1,2], Marc Ditmarsch [3], and John J.P. Kastelein [1]*

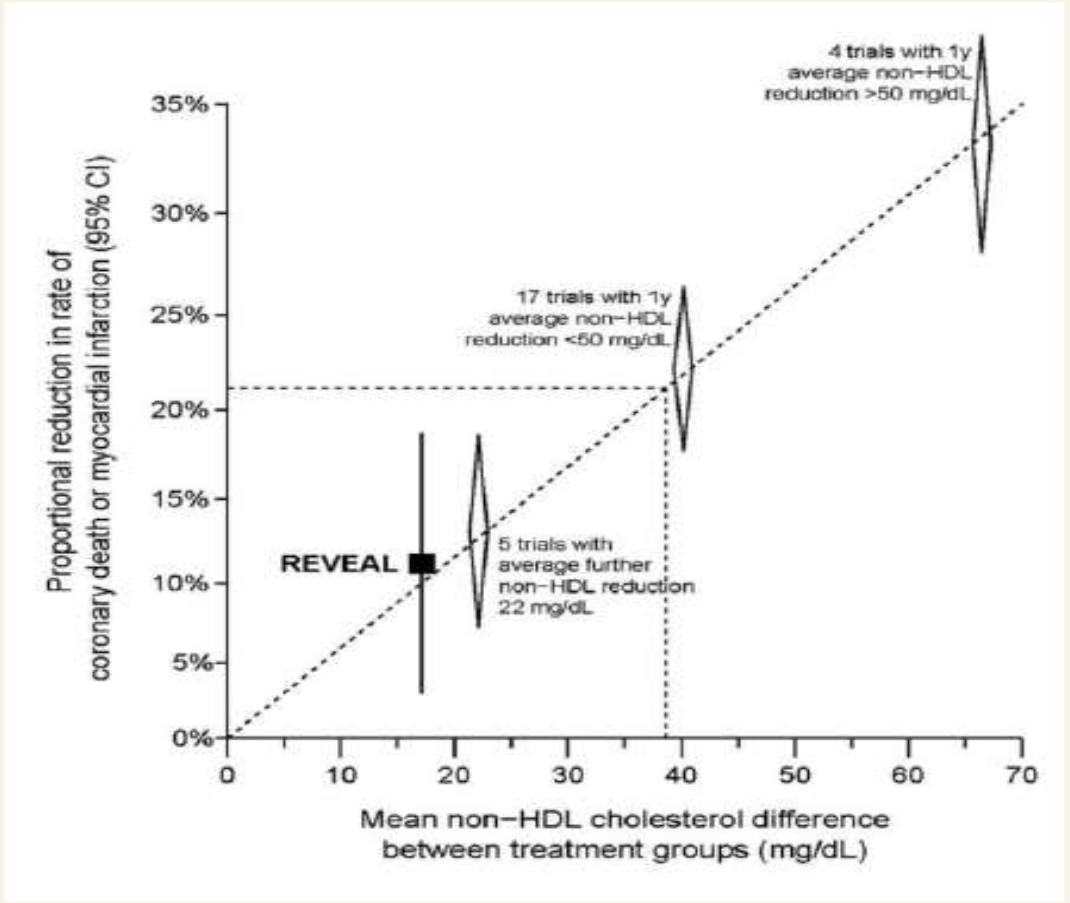


Figure 3 REVEAL trial and statins in the CTT meta-analysis. Reduction in rate of coronary death or myocardial infarction from the REVEAL trial, compared reduction in statin trials from the CTT, plotted according to the size of the absolute reduction in non-HDL cholesterol. Adapted from Bowman *et al.*,[58] Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from REVEAL, Randomized EValuation of the Effects of Anacetrapib through Lipid-modification. CTT, Cholesterol Treatment Trialists'; HDL, high-density lipoprotein.

Table I Per cent changes from baseline for LDL-C and HDL-C as conferred by CETP inhibitors

CETP inhibitor	Dose (mg)	LDL-C (mmol/L) % change from baseline	HDL-C (mmol/L) % change from baseline	Years	References
Torcetrapib	60	−15.7	33.1	2006	71
Dalcetrapib	600	−5.4	26.4	2009	86
Anacetrapib	100	−23.4	138.1	2010	1,79
Evacetrapib	100	−22.3	94.6	2011	87
Obicetrapib	5	−45.3	157.1	2015	44

Shown is the change in LDL-C and HDL-C levels of the different CETP inhibitors.
CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

ALICE IN WONDERLAND

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

Kiran Musunuru, Alexandra C. Chadwick, [...]Sekar Kathiresan


CRISPR/Cas9 gene editing scissors

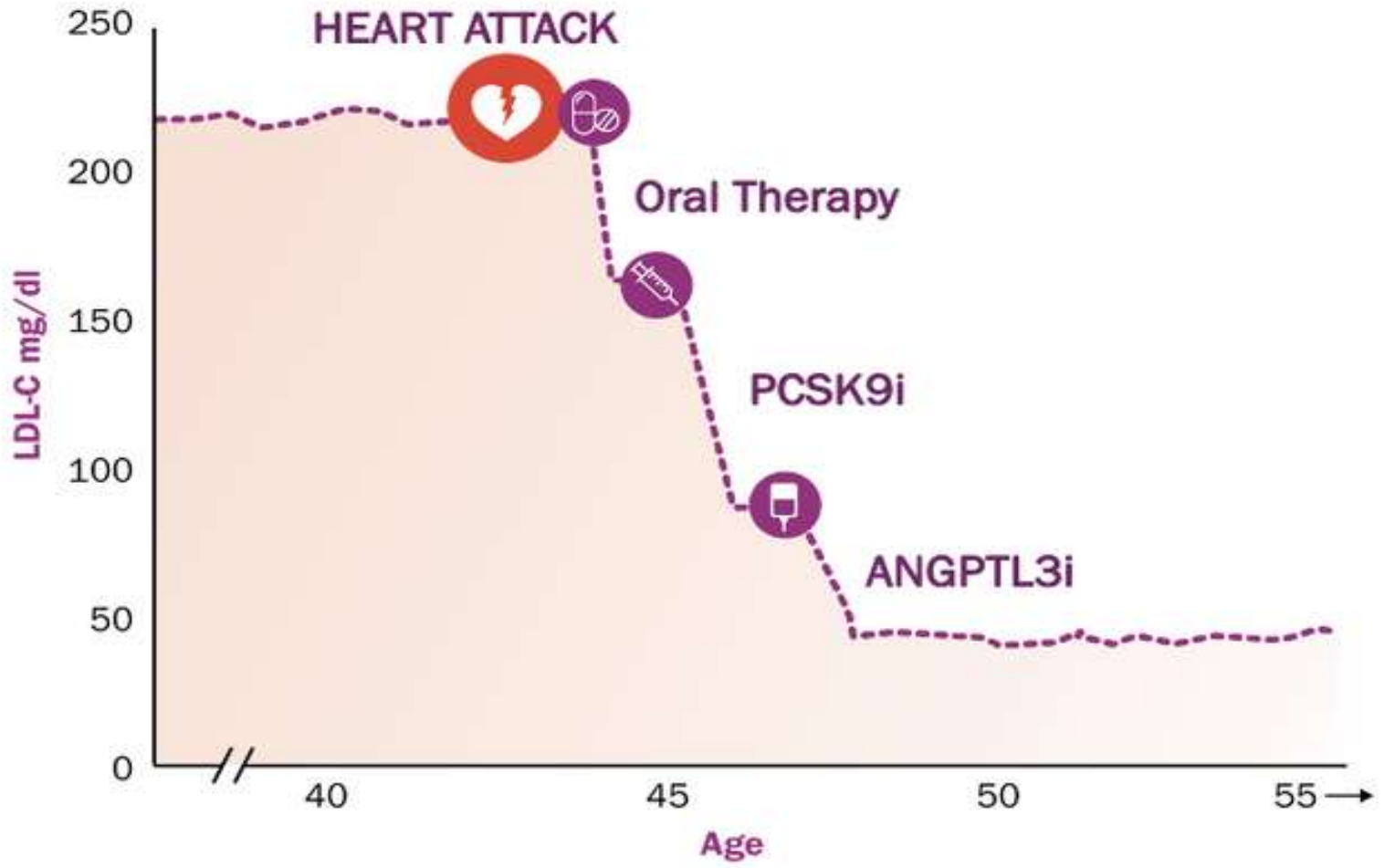
Some patients with very high LDL-C who have already suffered a heart attack:

*may need both the PCSK9 and the ANGTPL3 pathways inactivated

*can we accomplish this with gene editing -

the switching off of two genes in the liver in the same individual?

#ACC22 @VerveTx $VERV

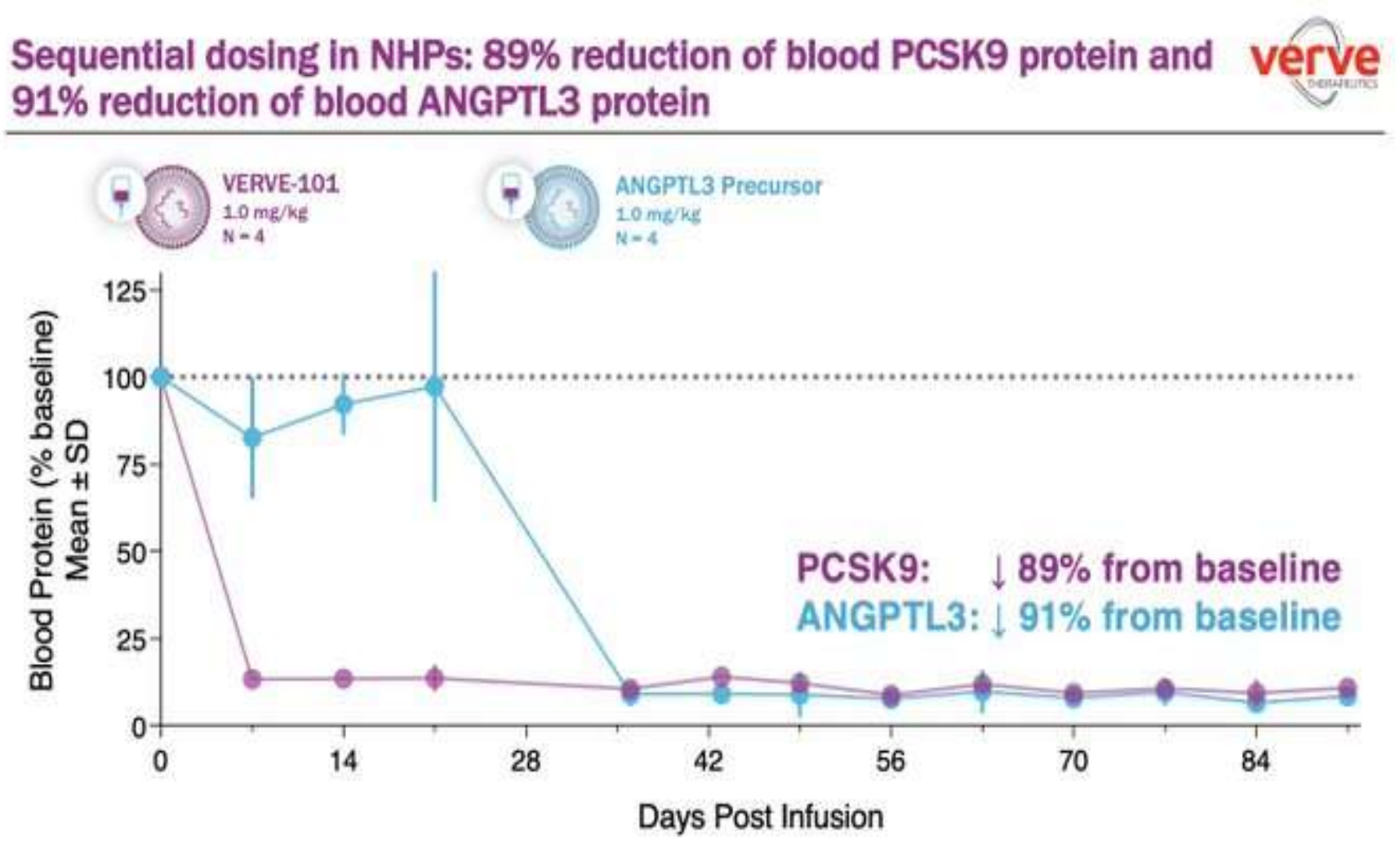


Illustrative graphic of a hypothetical patient with ASCVD and hypercholesterolemia treated with serial addition of lipid-lowering therapies to achieve goal LDL-C after suffering a heart attack at age 44.

Day 0 - VERVE 101 Rx,
blood PCSK9 level plummets

Day 30 - ANGPTL3 base editor Rx,
blood ANGPTL3 level plummets

This will likely be durable for lifetime animal (person)!



ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–2
doi:10.1093/eurheartj/ehab478

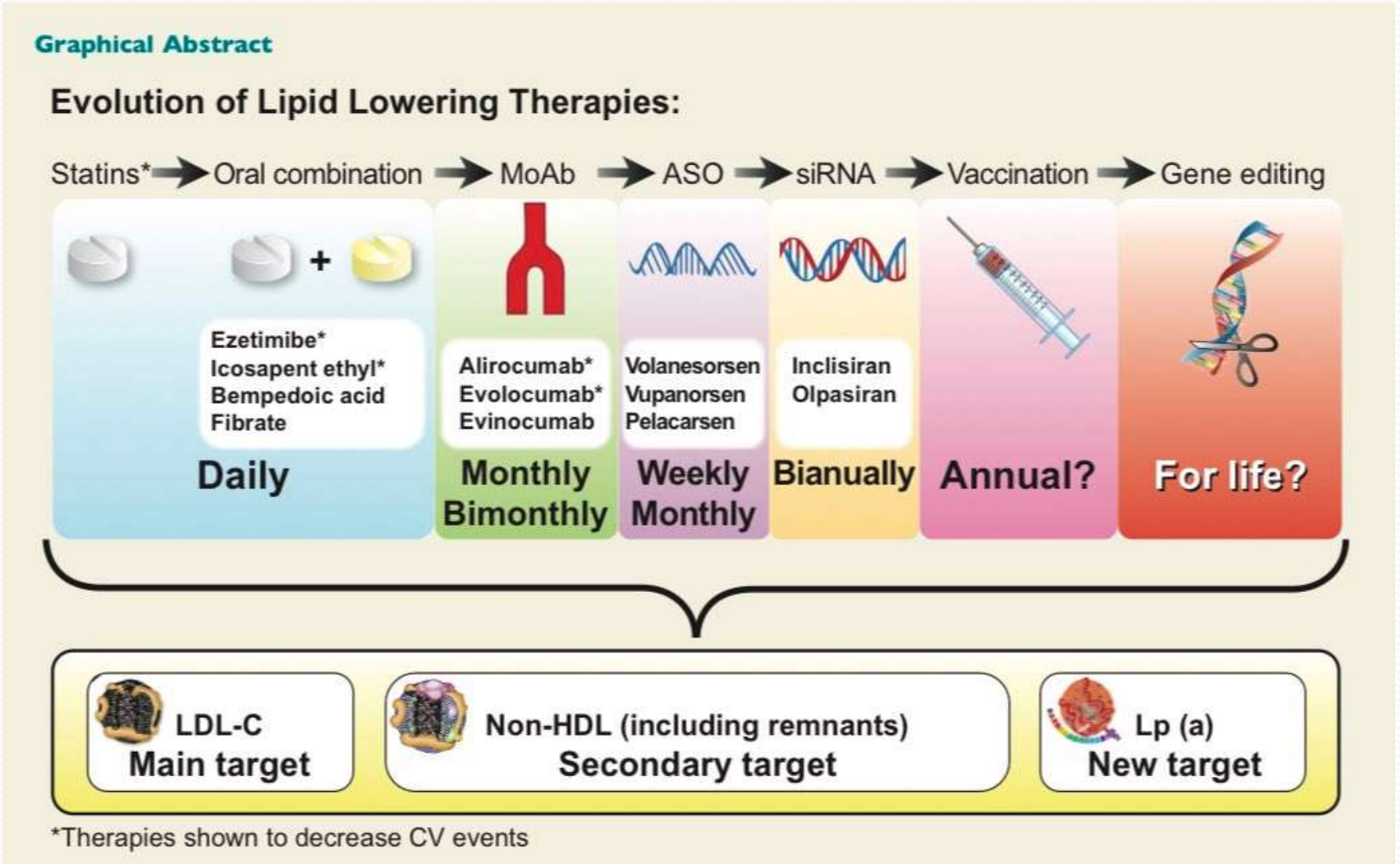
CARDIOPULSE

Weekly Journal Scan

A 'Once-and-Done' Approach to the Lifelong Reduction of Elevated Cholesterol

Francesco Paneni [1]* and **Massimo Volpe** [2]*

State of the art review via @ESC_Journals
The dawn of a new era of targeted lipid-lowering therapies
academic.oup.com/eurheartj/arti...
@DrMarthaGulati @drpablocorral @EstebanDL

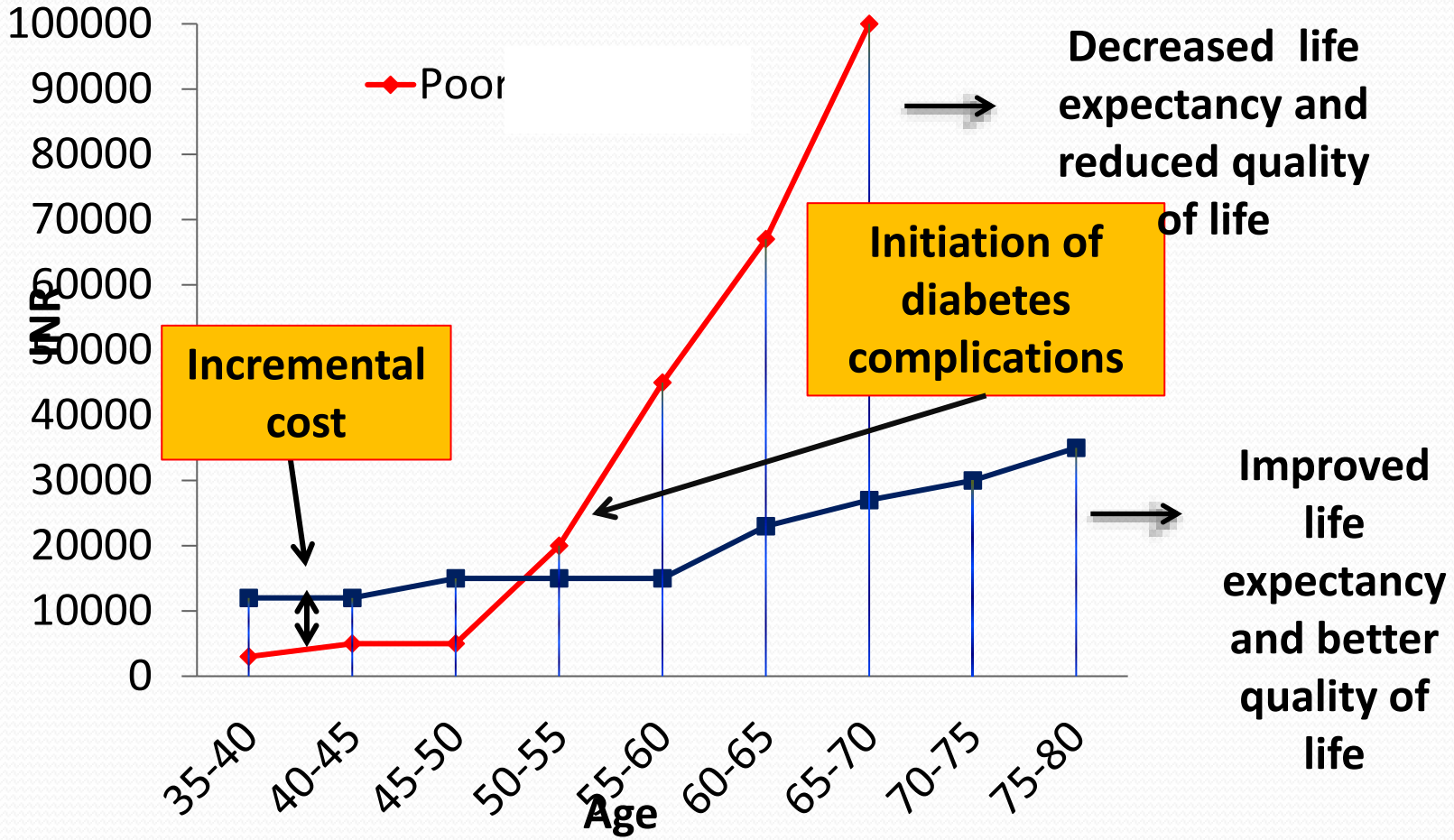


CONCLUSIONS

KOCHS POSTULATES FOR LDL HYPOTHESIS

- Ldl causes athersclerosis.
- Ldl can be effectively reduced
- Ldl reduction causes regression of athersclerosis and mortality reductions

Good glycemia control delays onset of complications and decreases overall cost of diabetes management



* Hypothetical graph /Ramachandran et al, IDRF (Indian Diabetes Research Foundation); Diabetes Care 2007 Feb;30(2):252-256.


Artery
1 HOUR
CLEANERS

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–2
doi:10.1093/eurheartj/ehab532

CARDIOPULSE

Braunwald's Corner

How to live to 100 before developing clinical coronary artery disease: a suggestion

Eugene Braunwald [1,2]*

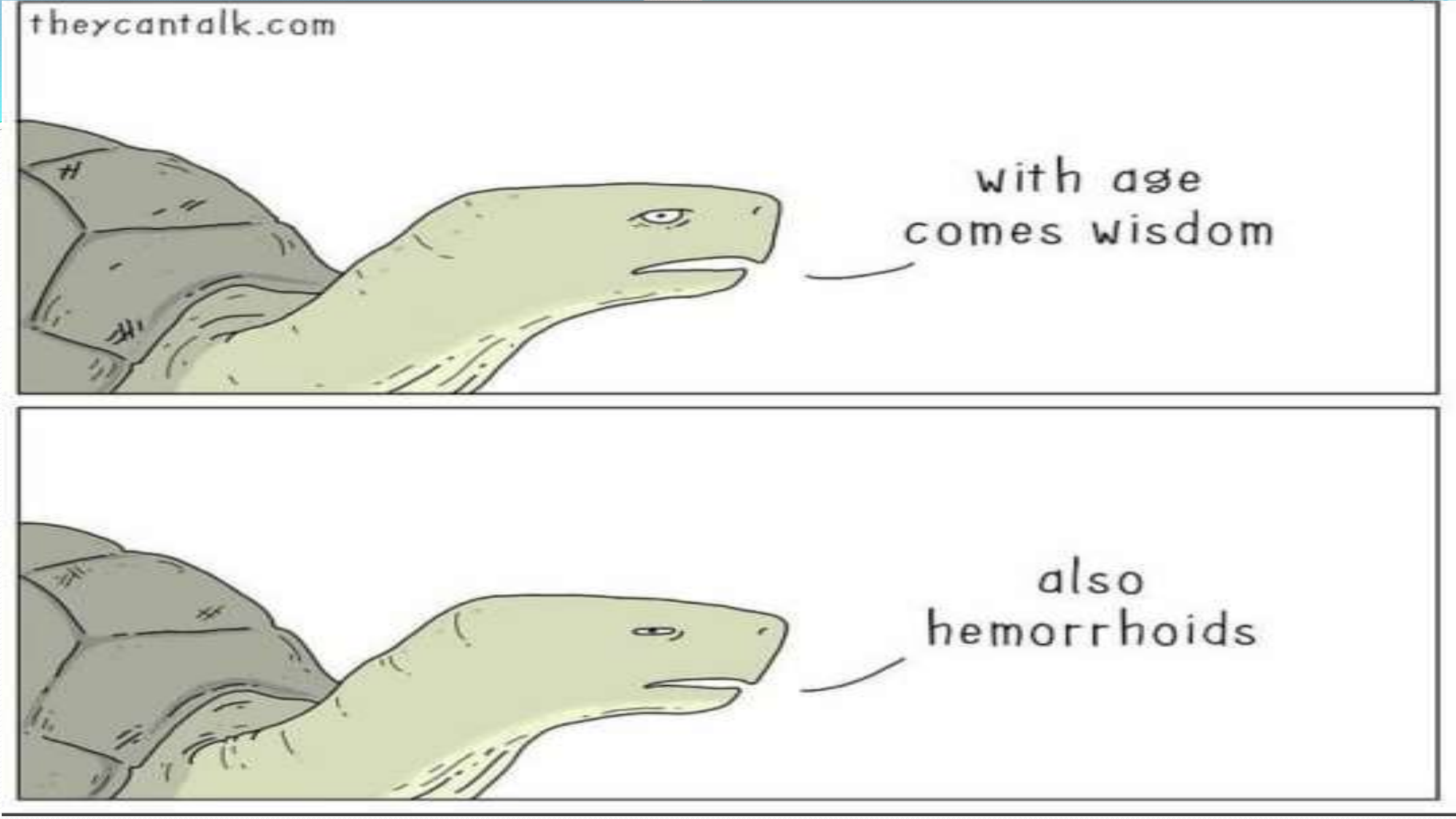
[1]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and [2]Department of Medicine, Harvard Medical School, Boston, MA, USA

The good physician treats the disease;
the great physician treats the patient.

-William Osler

The good physician treats stenoses;
the great physician treats the Atherosclerosis

LOW HANGING FRUITS


theycantalk.com
with age comes wisdom
also hemorrhoids

A fact is information minus emotion. An opinion is information plus experience. Ignorance is an opinion lacking information. And, stupidity is an opinion that ignores a fact.

IHJ
Indian Heart Journal

May-Jun 2018 | Article 1 of 31

Have we reached the bottom of the bottomless pit- lessons from the recent lipid-lowering trials?

Manish Bansal

DOI: https://doi.org/10.1016/j.ihj.2018.06.010

Open access funded by Cardiological Society of India.

+ Article Info

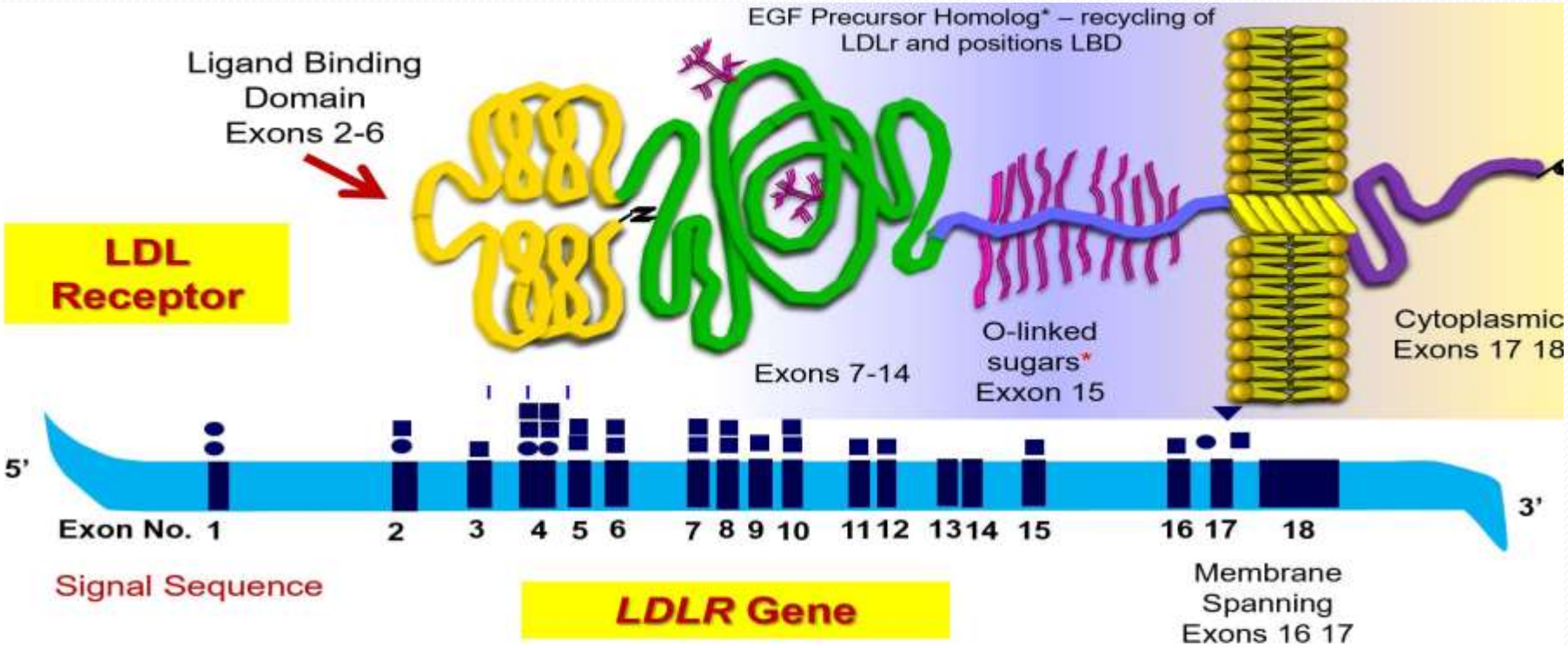
Rajeev Agarwala

+ Author Affiliations & Information

Open Access

Check for updates

A-2 One cause of ⬆️ LDL-C is related to the liver's ability to produce/maintain FUNCTIONAL LDL receptors (LDLR) which normally bind to & clear (remove) circulating in plasma LDLs that carry cholesterol. Abnormal genes can results in defective LDLR #KnowFH



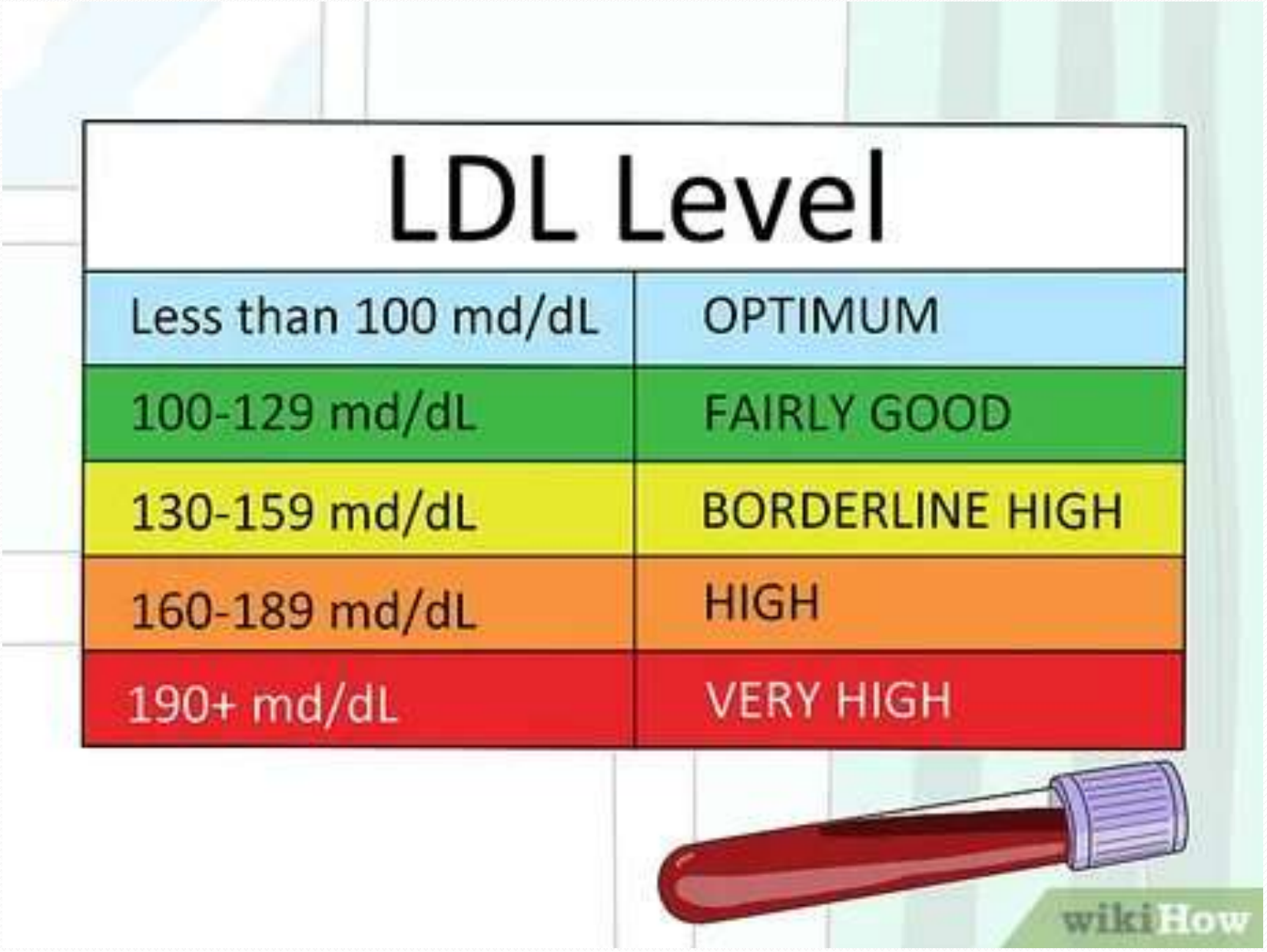
Extracellular domain is responsible for apo-B-100/apo-E binding

Intracellular domain is responsible for clustering of LDL receptors into coated pit region of plasma membrane

*EGF = Human epidermal growth factor gene

* **Oligosaccharides** of glycoprotein are roughly divided into two groups, O-linked and N-linked types. In the case of the O-linked type, small oligosaccharide attaches to the alcohol of serine or threonine by an N -acetyl-α- d -galactosaminyl linkage

A1: A healthy LDL cholesterol number is less than 100 mg/dL however someone with known plaque deposits #HeartDisease should have a lower number, at least < 70 mg/dL. Lower is always better. #KnowFH @TheFHFoundation



JAMA Clinical Evidence Synopsis

Aspirin Plus Clopidogrel vs Aspirin Alone for Preventing Cardiovascular Events Among Patients at High Risk for Cardiovascular Events

Marco P. Donadini, MD, PhD; Marta Bellesini, MD; Alessandro Squizzato, MD, PhD

Table. Aspirin Plus Clopidogrel Compared With Aspirin Alone for Preventing Cardiovascular Events Among Patients at High Risk of Cardiovascular Events

Event	No. of RCTs	No. of Participants	Estimated Absolute Risk per 1000 Participants (95% CI) for Aspirin Plus Clopidogrel[a]	Estimated Absolute Risk per 1000 Participants for Aspirin Alone[b]	Relative Risk (95% CI)	*P* Value
Cardiovascular mortality	7	31 903	37 (33-41)	37	0.98 (0.88-1.10)	.77
All-cause mortality	9	32 908	56 (46-66)	53	1.05 (0.87-1.25)	.62
Myocardial infarction[c]	6	16 175	45 (40-52)	58	0.78 (0.69-0.90)	<.01
Ischemic stroke[c]	5	4006	63 (51-78)	86	0.73 (0.59-0.91)	<.01
Major bleeding	10	33 300	30 (26-34)	21	1.44 (1.25-1.64)	<.01

Abbreviation: RCT, randomized clinical trial.

[a] The risk of having a cardiovascular event in the aspirin plus clopidogrel group is based on the assumed risk of having a cardiovascular event in the aspirin alone group and the relative risk of having a cardiovascular event in the aspirin plus clopidogrel group.

[b] The 95% CIs are not included because this column contains the reference values.

[c] Fatal or nonfatal.

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INVITED EDITORIAL

Linear reverse risk of HDL-C levels for predicting cardiovascular disease: it is not that straightforward!

Ragavendra R. Baliga[1]*, Eric H. Yang [2], and Eduardo Bossone [3]

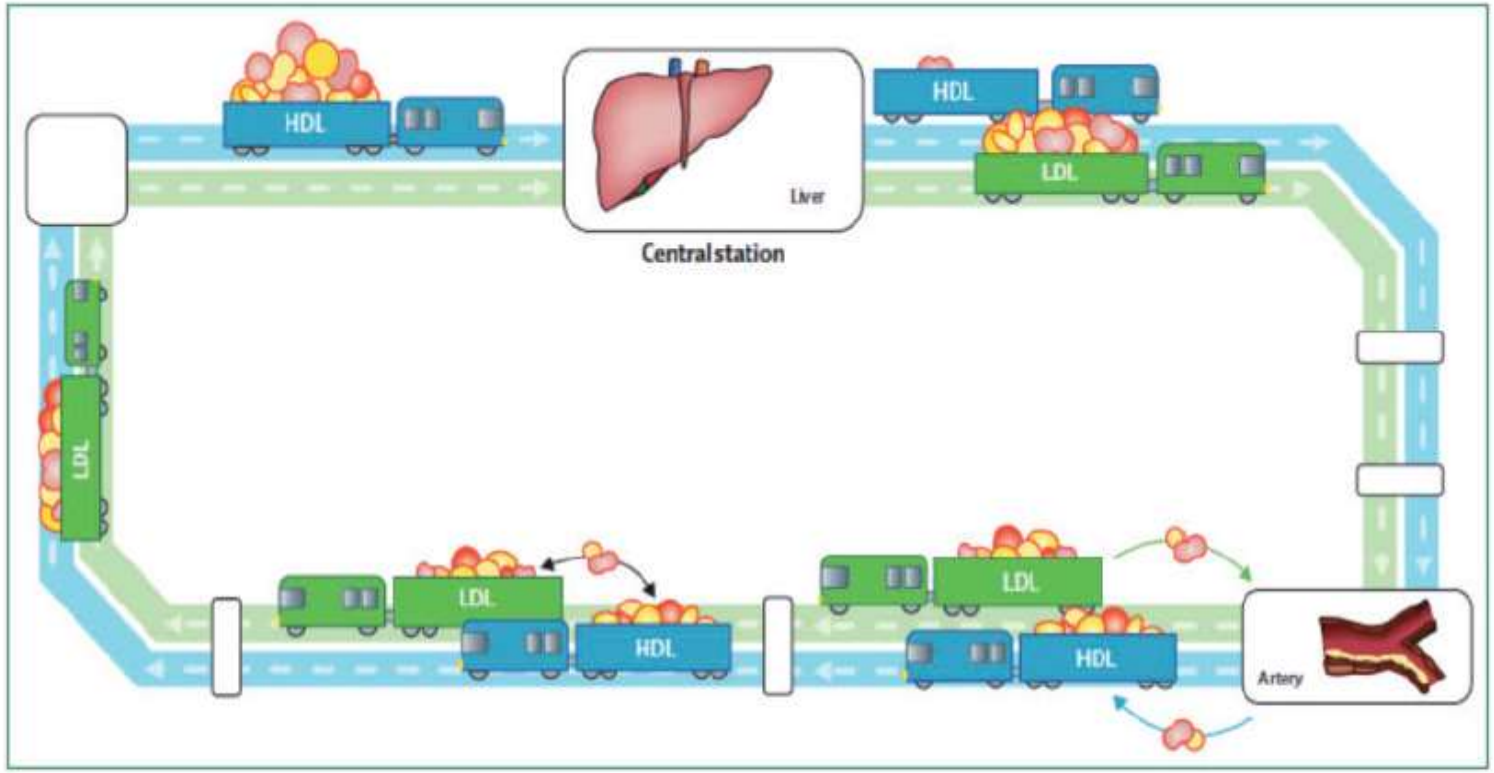
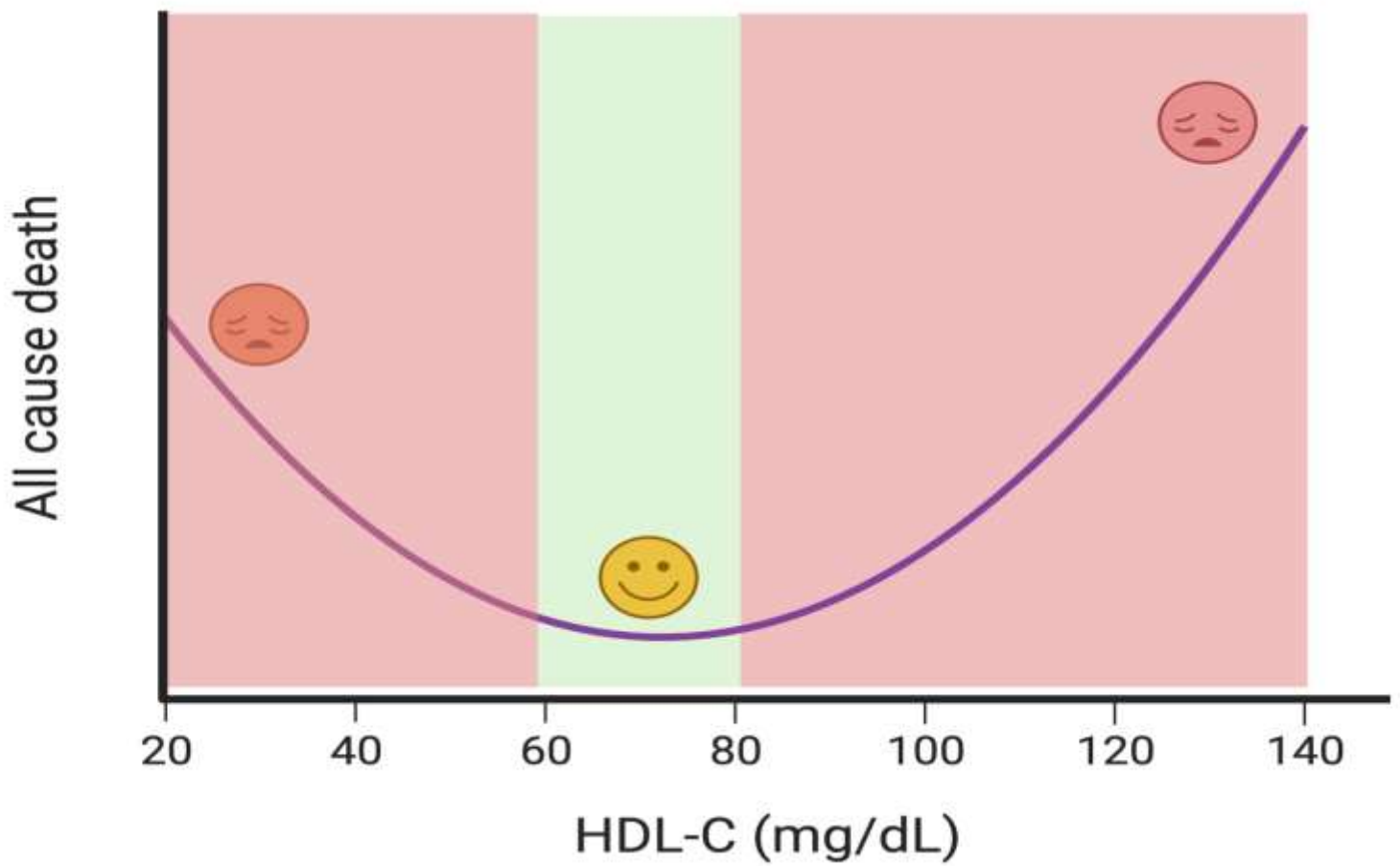


Figure 1 Schematic representation of lipid transport as a metro system. The HDL transport system (blue line) can be likened to a series of heterogeneous protein trains carrying a diverse group of lipid passengers (different lipid species indicated by various shapes and colours of passengers) through the circulatory system. As HDL trains travel through the circulatory system, lipid passengers embark and disembark at various stations [peripheral tissues (white rectangles and square)]. Lipid passengers can also move between circulating cells and lipoproteins [including LDLs (on the green line) and very low density lipoprotein (VLDLs) (not shown)]. The net direction of lipid movement associated with HDL is uptake from peripheral tissues and transport to the liver, which in arteries prevents proatherogenic lipid accumulation. In this analogy, the liver is the central station, where most lipid passengers disembark and previously lipid-laden HDL trains can be recycled and recirculated. The liver is also a hub of HDL production, forming nascent HDL particles that are lipid-poor and avid acceptors of peripheral lipids.[24]

Increased HDL-C Values and Mortality: Revolutionizing a Historical Paradigm? 🤔🤔thieme-connect.com/products/ejour… @MarcoMetra @MRMehraMD @DrMarthaGulati @gbiondizoccai @FlavioDascenzi @paolo_emilio @ThijsEijsvogels @LipidLover1030 @nationallipid @a_l_bailey @DBelardoMD @ErinMichos



Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Network Meta-Analysis of Randomized Trials Evaluating the Comparative Efficacy of Lipid-Lowering Therapies Added to Maximally Tolerated Statins for the Reduction of Low-Density Lipoprotein Cholesterol

Peter P. Toth, MD, PhD; Sarah Bray, PhD; Guillermo Villa, PhD; Tamara Palagashvili, PharmD*; Naveed Sattar, MD, PhD; Erik S. G. Stroes, MD, PhD; Gavin M. Worth, PhD*

CONCLUSIONS: Evolocumab, 140 mg Q2W/420 mg once a month, and alirocumab, 150 mg Q2W, were consistently the most efficacious nonstatin regimens when added to maximally tolerated statins to lower LDL-C, non–high-density lipoprotein cholesterol, and apolipoprotein B levels and facilitate attainment of guideline-recommended risk-stratified lipoprotein levels.

DOI: 10.1161/JAHA.122.025551

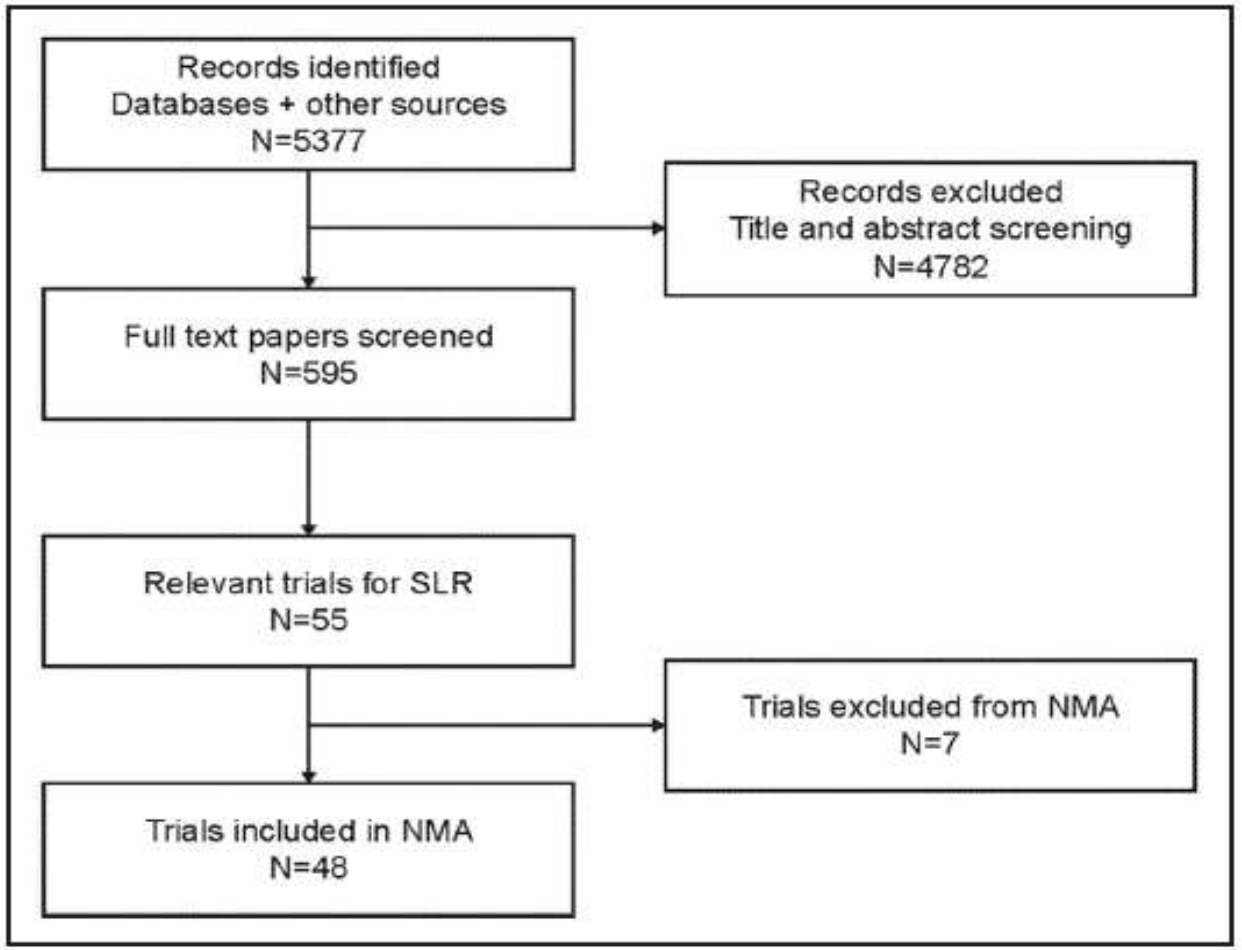


Figure 1. Study flow diagram of the systematic review.
Trials included in the network meta-analysis (NMA) included those with patients either receiving background statin treatment or who were statin intolerant. SLR indicates systematic literature review.

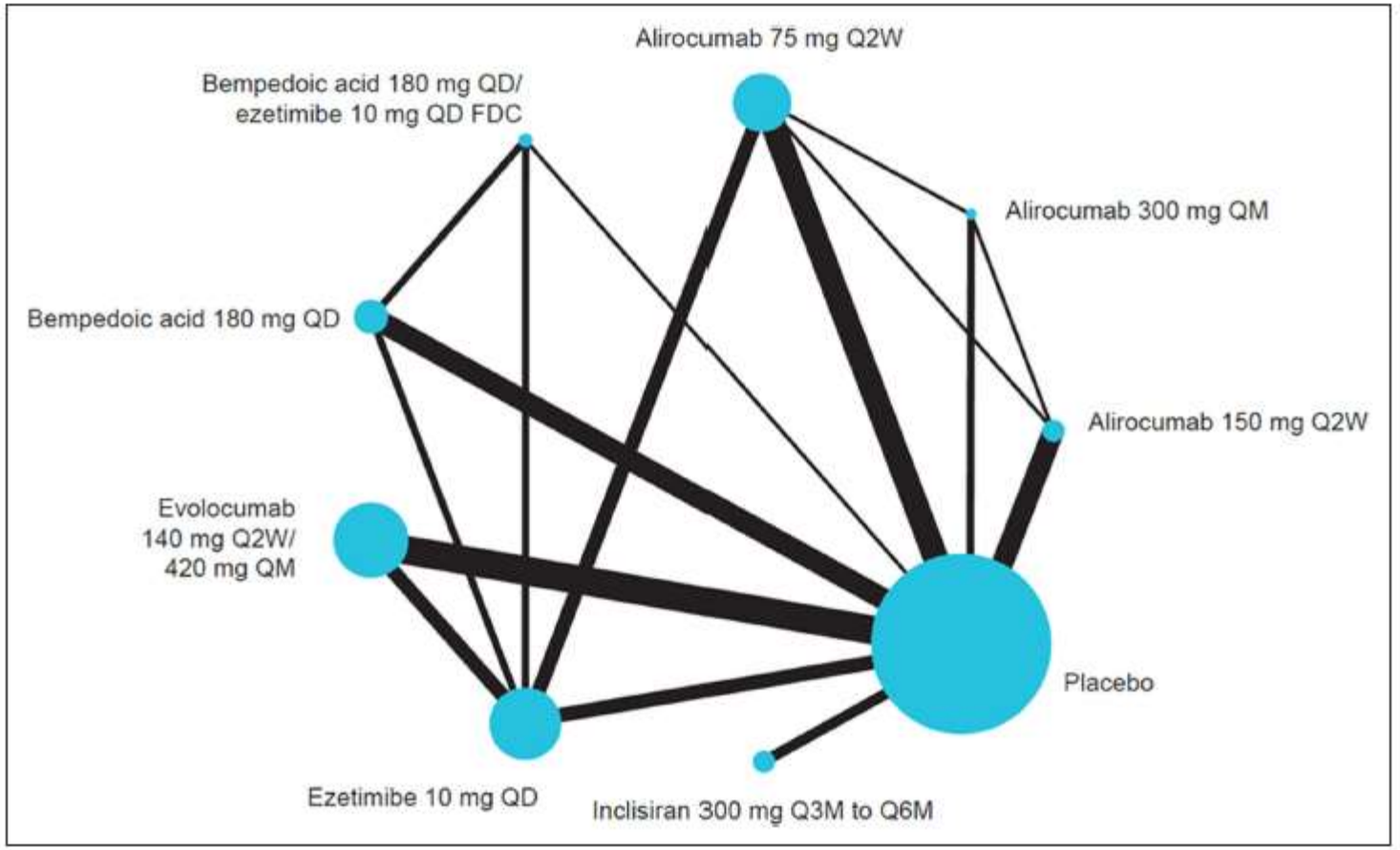


Figure 2. Primary network: connection of eligible randomized controlled trials reporting percentage change in low-density lipoprotein cholesterol from baseline to week 12.
The diameter of each circle represents the proportional total weight of all trials in the network that investigated that intervention. The thickness of each line connecting 2 interventions is proportional to the number of trials that investigated that pair of interventions. FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; QM, once a month; and RCT, randomized controlled trial.

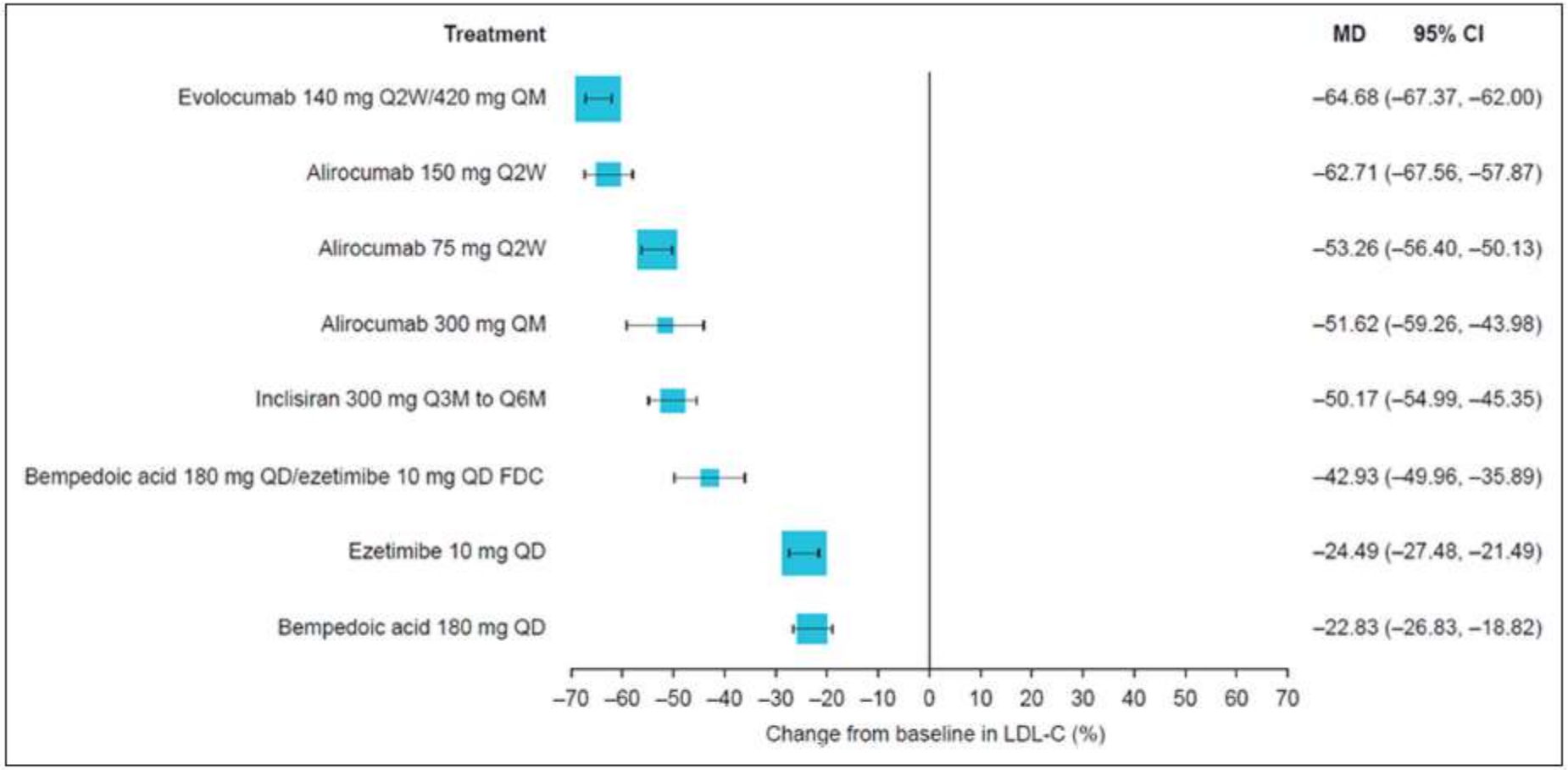


Figure 3. The mean difference (MD) in percentage change in low-density lipoprotein cholesterol (LDL-C) in response to lipid-lowering therapy relative to placebo at week 12.

FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

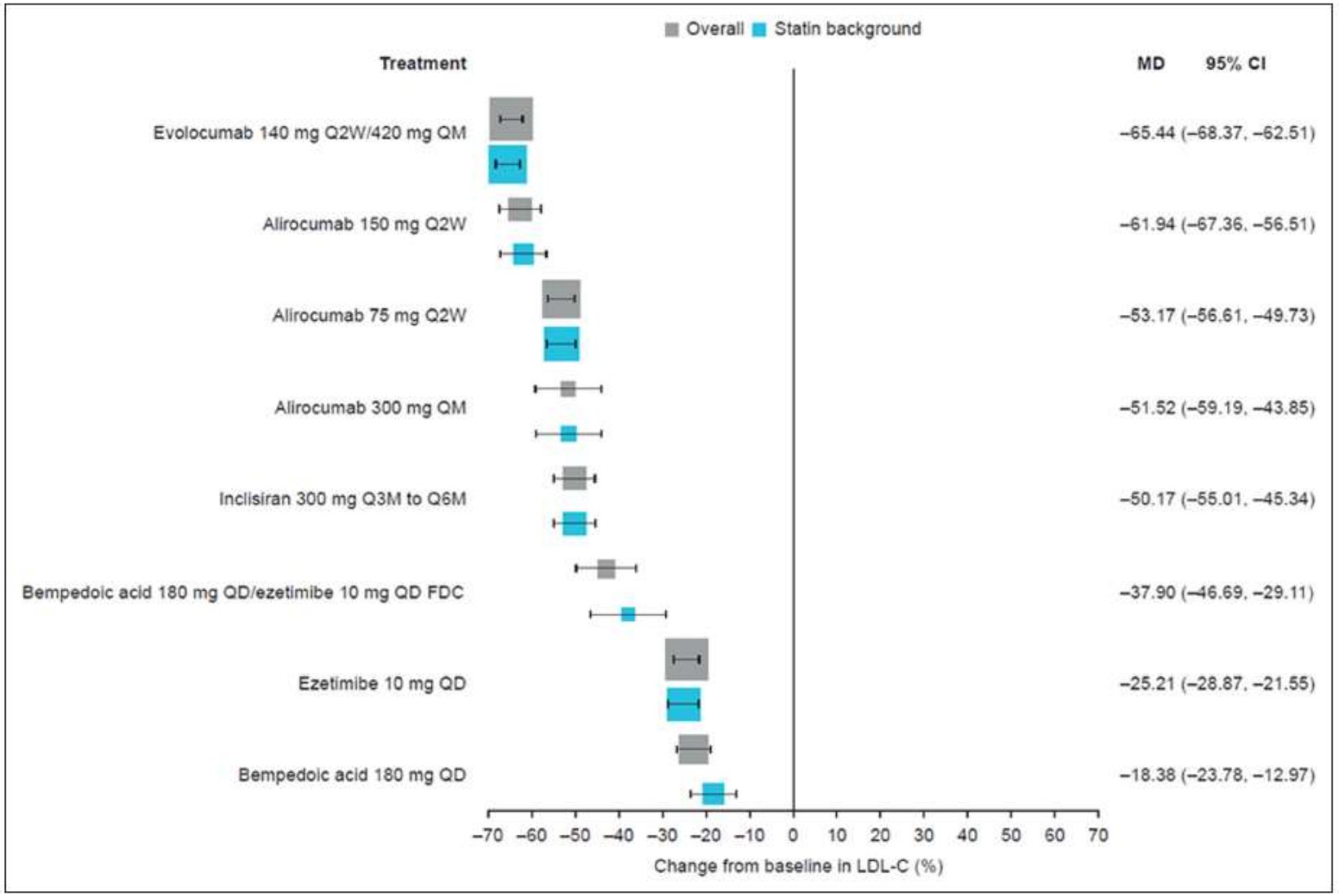


Figure 4. Subgroup analysis: the mean difference (MD) in percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline in response to lipid-lowering therapy relative to placebo at week 12 in patients receiving statin background therapy (moderate-high intensity) (blue), with the primary analysis data plotted for comparison (gray).
FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

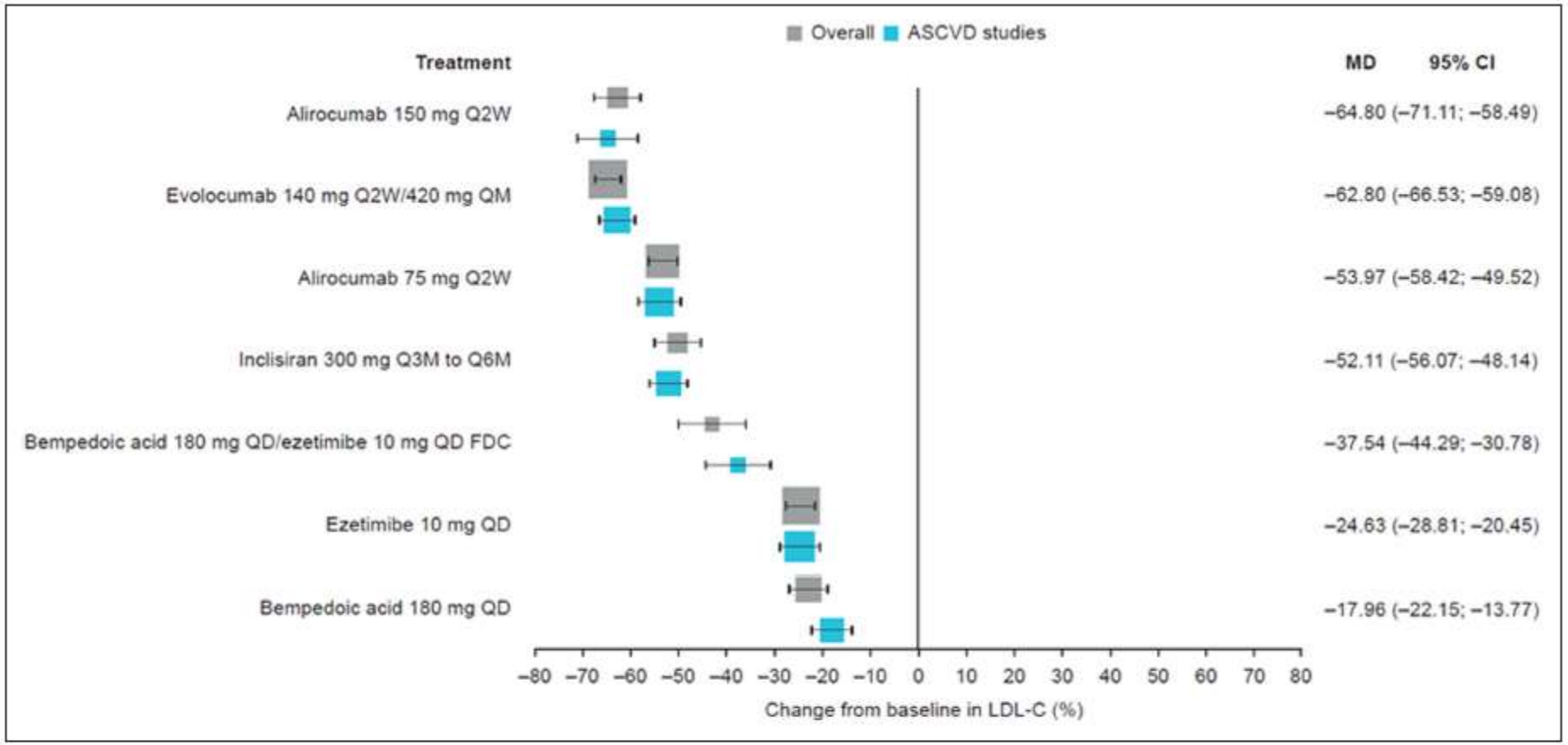


Figure 5. Subgroup analysis: the mean difference (MD) in percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline in response to lipid-lowering therapy relative to placebo at week 12 in predominantly populations with atherosclerotic cardiovascular disease (ASCVD) (blue), with the primary analysis data plotted for comparison (gray).
FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

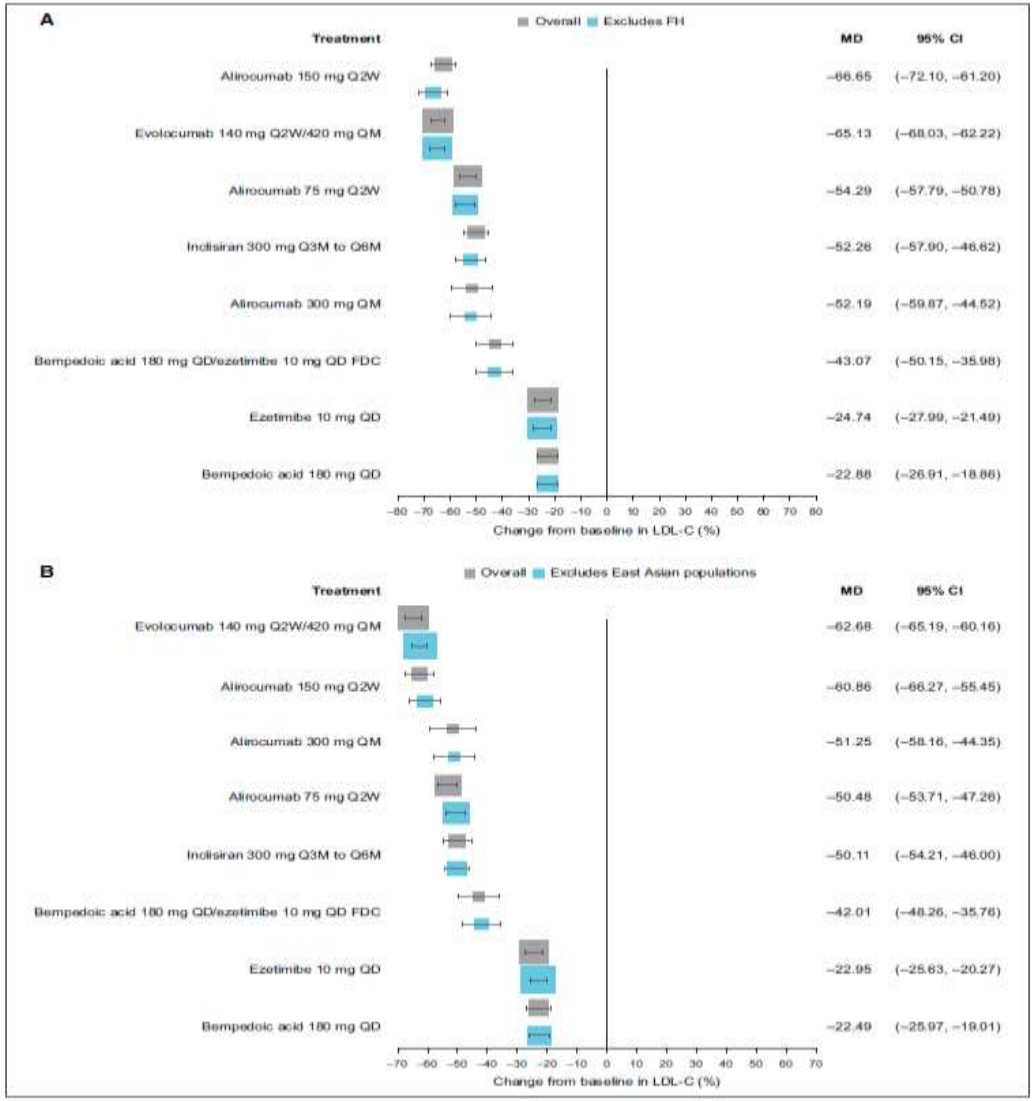


Figure 6. Sensitivity analyses: treatment difference in percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline in response to lipid-lowering therapy relative to placebo at week 12, excluding trials featuring familial hypercholesterolemia (FH) (A) or East Asian populations (B) (blue), with the primary analysis data plotted for comparison (gray).
FDC indicates fixed-dose combination; MD, mean difference; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

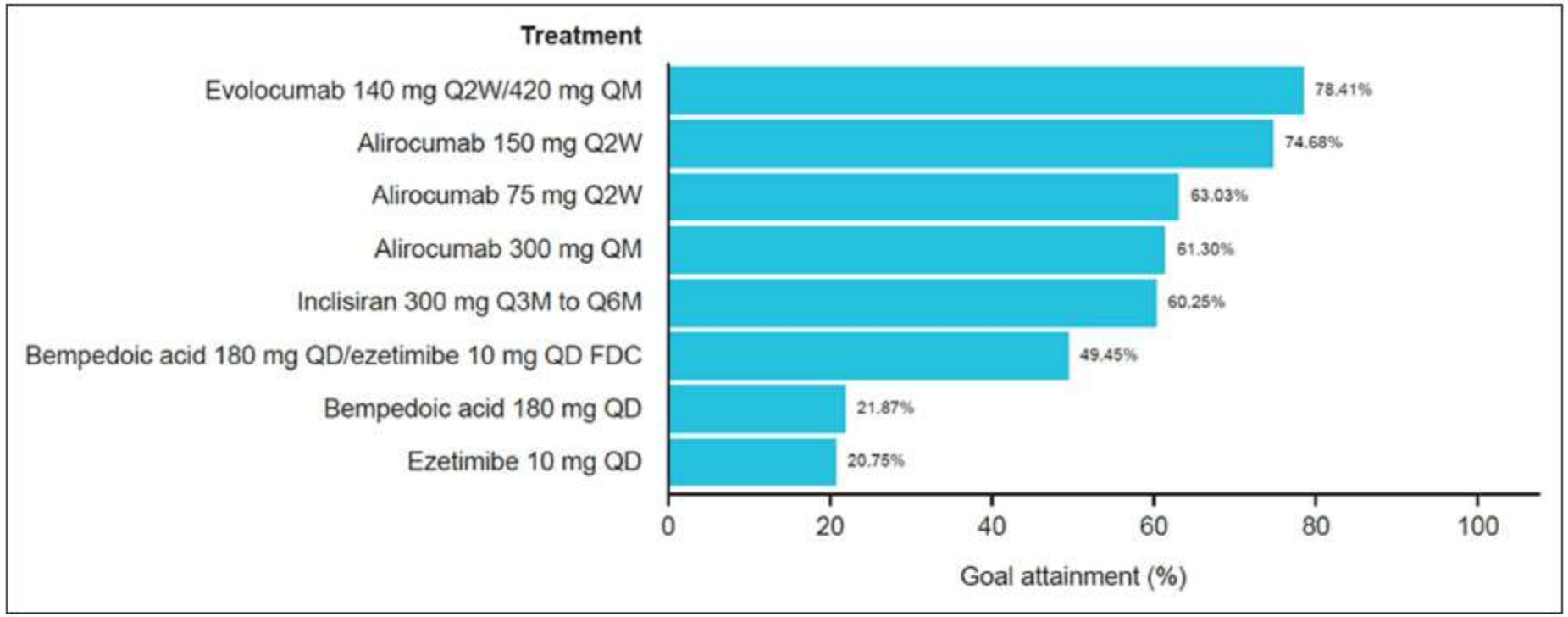


Figure 7. The proportion of simulated values that achieved a low-density lipoprotein cholesterol (LDL-C) level of <55 mg/dL (<1.4 mmol/L) following treatment with each intervention.

The simulation values represent a hypothetical population with atherosclerotic cardiovascular disease, and the <55-mg/dL value is the 2019 European Society of Cardiology/European Atherosclerosis Society guideline-recommended LDL-C level goal for very high-risk patients. FDC indicates fixed-dose combination; Q2W, every 2 weeks; Q3M, every 3 months; Q6M, every 6 months; QD, once a day; and QM, once a month.

Elevated plasma triglyceride concentration and risk of adverse clinical outcomes in 1.5 million people: a CALIBER linked electronic health record study

Conclusion:

Over the follow-up period, 84,874 (5.5%) patients had a MI. Patients with mild (1.7–4.5 mmol/L) and moderate (4.5–10 mmol/L) hypertriglyceridaemia had a modest albeit significant increase in risk for MI (7% and 17%, respectively) compared with those with triglyceride levels <1.7 mmol/L. The authors concluded that their findings from a real-world cohort support routine measurement of triglycerides for cardiovascular risk management.

Cholesterol remnants and acute coronary syndrome

Significantly higher levels of remnants were observed in patients with diabetes, current smokers, BMI >30 kg/m^2, absence of previous cardiovascular disease (CVD) or premature ACS. Remnant levels decreased with age (r:-0.29)and increased with BMI (r:0.44). At any age, the risk of having cholesterol remnants ≥30 mg/dl increased with higher BMI.

In-hospital mortality was 3.75% (280 patients) but, after adjustment for age, gender, previous CVD and GRACE score, remnant cholesterol was not associated with higher in-hospital mortality risk (OR: 0.89 95% CI 0.64-1.10; p=0.21).

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ENTRIGUE: pegozafermin shows promise in severe hypertriglyceridaemia

A Phase 3 trial is planned using the higher weekly doses of pegozafermin for a longer duration. Pegozafermin is also under development for the treatment of non-alcoholic steatohepatitis, including the Phase 2 ENliven study.

ESC European Society of Cardiology

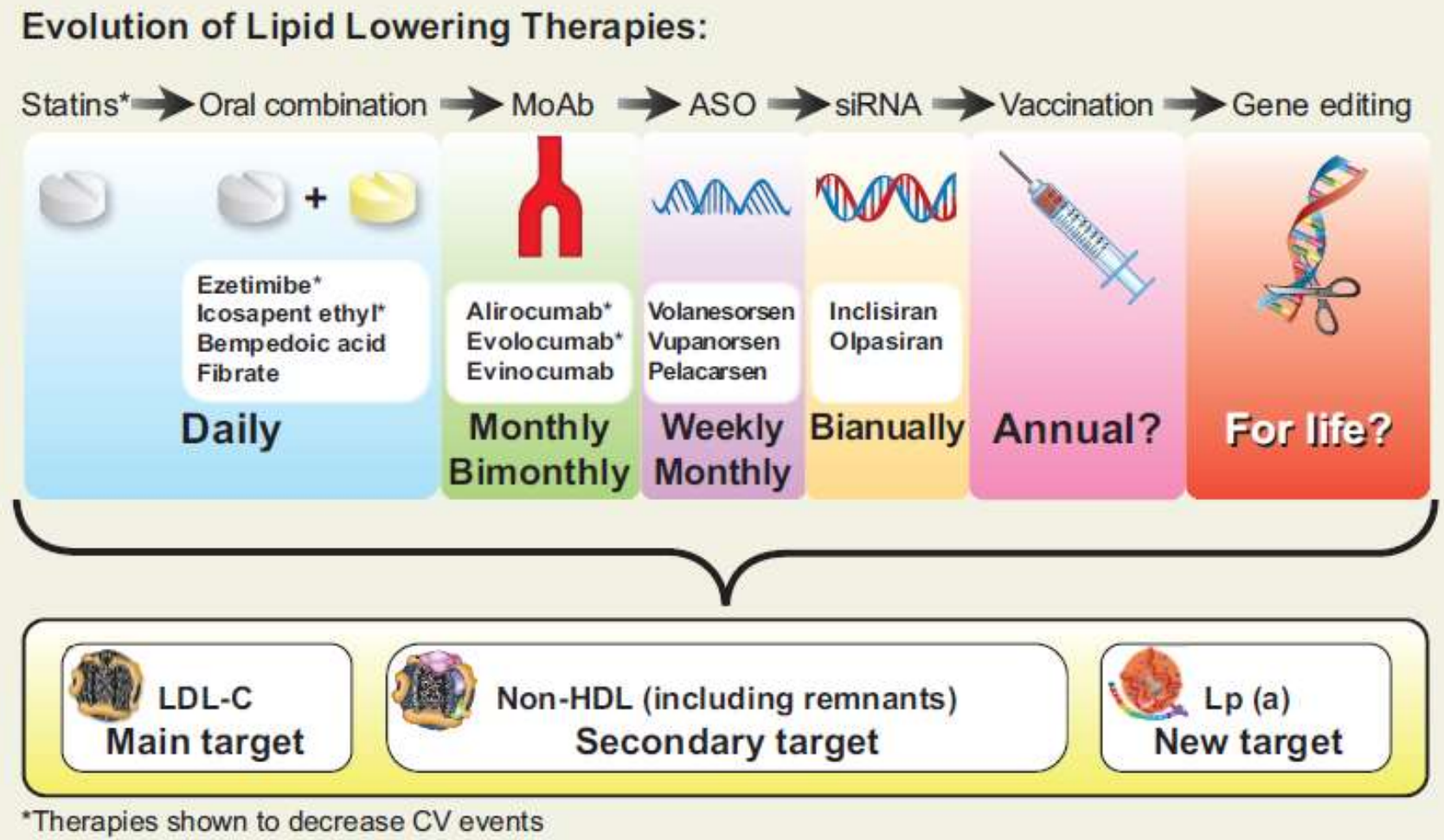
European Heart Journal (2022) **43**, 3198–3208
https://doi.org/10.1093/eurheartj/ehab841

STATE OF THE ART REVIEW
Dyslipidaemias

The dawn of a new era of targeted lipid-lowering therapies

Lale Tokgözoğlu[1] and Peter Libby[2]*

Graphical Abstract



The future evolution of lipid-lowering therapies. The quest for new lipid-lowering therapies enabling less frequent administration is continuing. Outcome trials to show cardiovascular event reduction will determine their clinical application. ASO, antisense oligonucleotide; CV, cardiovascular; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MoAb, monoclonal antibodies; siRNA, small-interfering RNA.

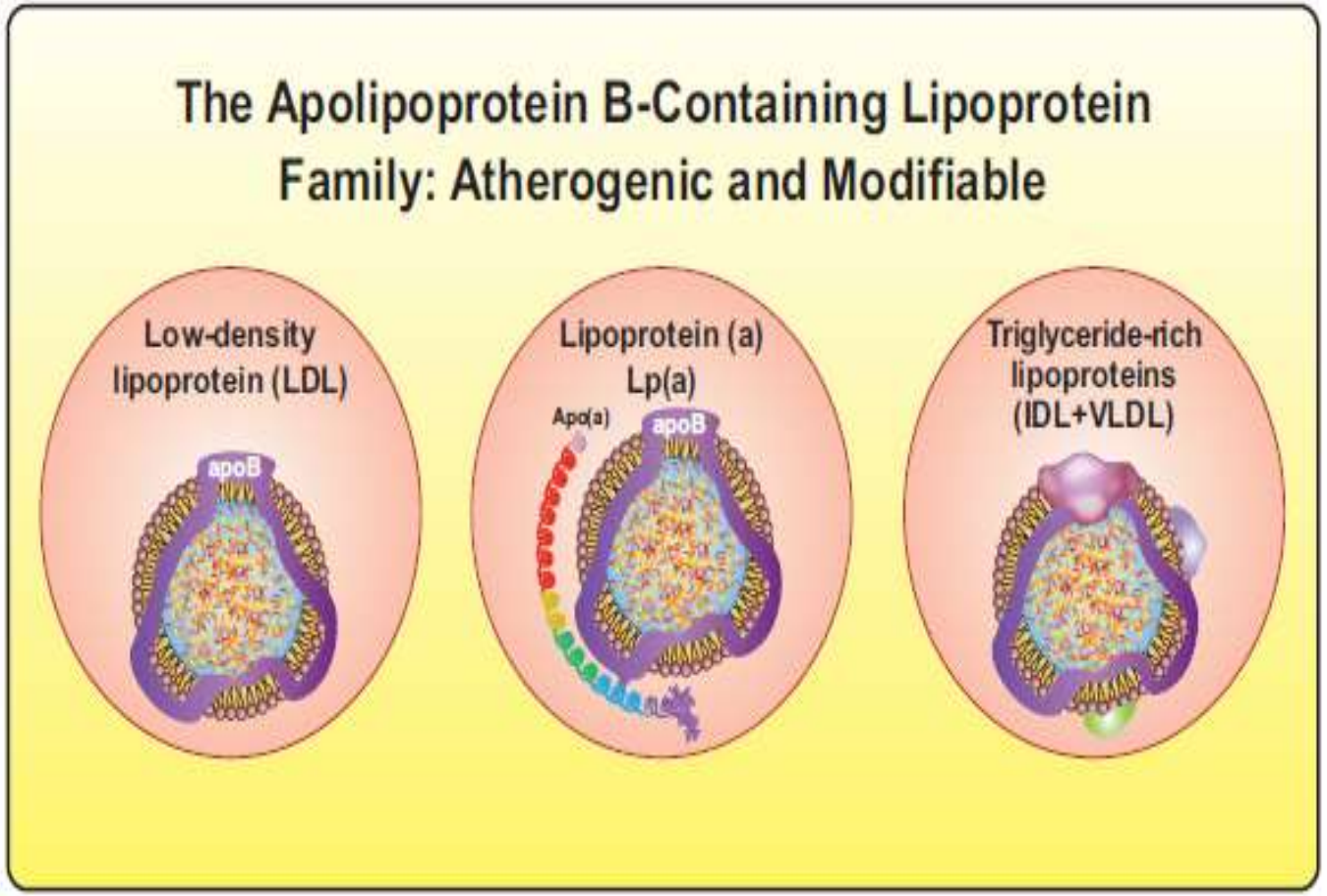


Figure 1 New targets for lipid-lowering therapies. Beyond low-density lipoprotein, lipoprotein(a) and triglyceride-rich lipoproteins or remnant lipoproteins have become actionable targets in lipid management. IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

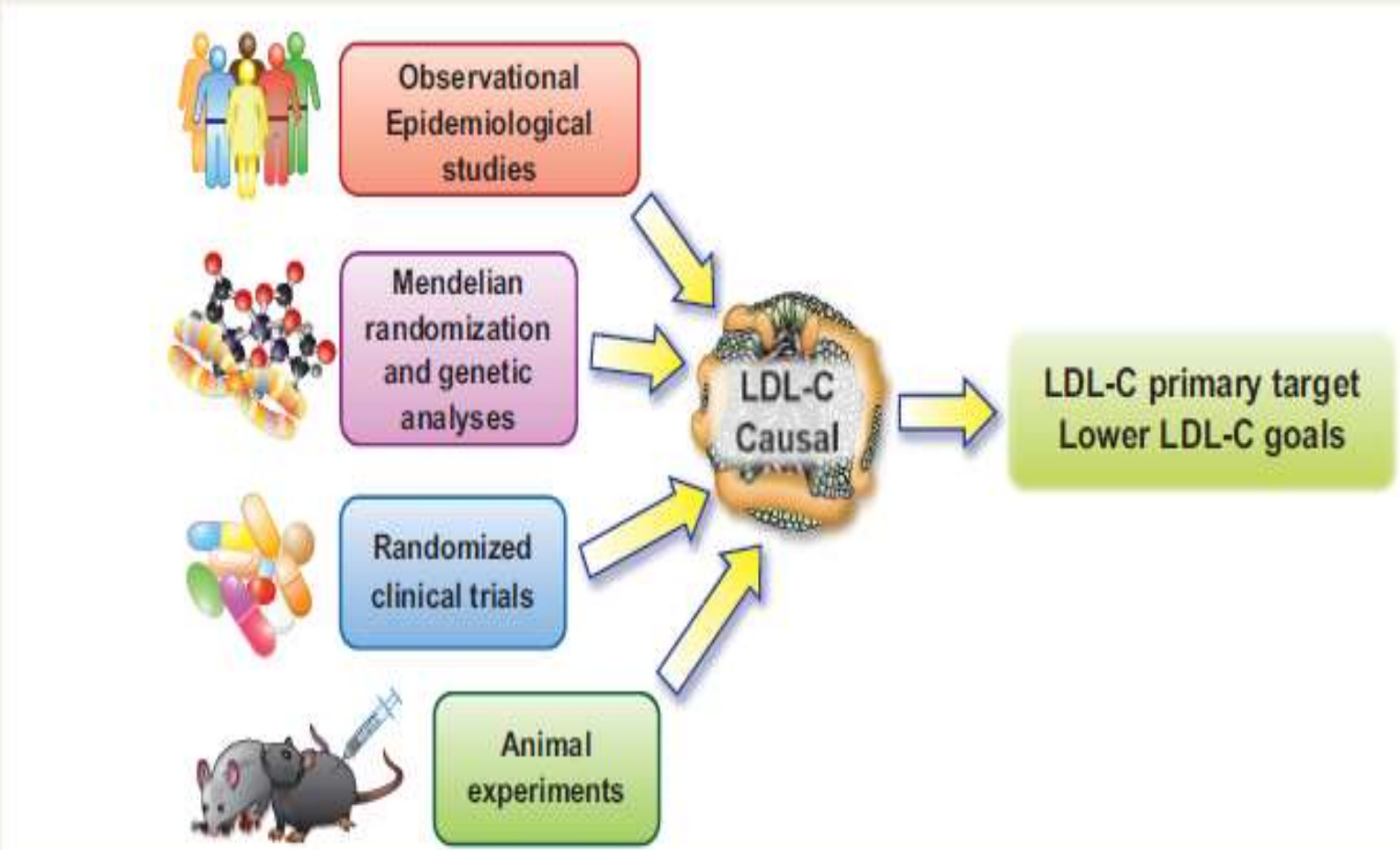


Figure 2 Multiple lines of evidence showing low-density lipoprotein cholesterol is causal for cardiovascular disease. Data that have accrued from observational data, human genetic analyses, randomized clinical trial results, and animal experimentation in multiple species, all concordantly support a causal contribution of low-density lipoprotein to atherosclerosis.

Selected mechanisms of targeted lipid therapies

Molecular target	Approach examples	Application examples
DNA 	Gene and base editing (e.g. CRISPR)	PCSK9 etc.
mRNA 	Antisense oligonucleotide Small interfering RNA	Lp(a) apoCIII
Protein 	Antibodies Small molecules	HMG Co-A reductase NPC1L1 ATP citrate lyase

Figure 3 Selected mechanisms of targeted lipid therapies. Current approaches to interventions that modify lipid metabolism include targeting genomic DNA, messenger RNA, or proteins. The strategies available include various strategies ranging from traditional small-molecule medicinal chemistry approaches through biological agents such as monoclonal antibodies, RNA therapeutics, and, on the horizon, gene editing. ApoC-III, apolipoprotein C-III; Lp(a), lipoprotein(a); HMG-CoA, hydroxymethylglutaryl coenzyme A; PCSK9, proprotein convertase subtilisin/kexin type 9.

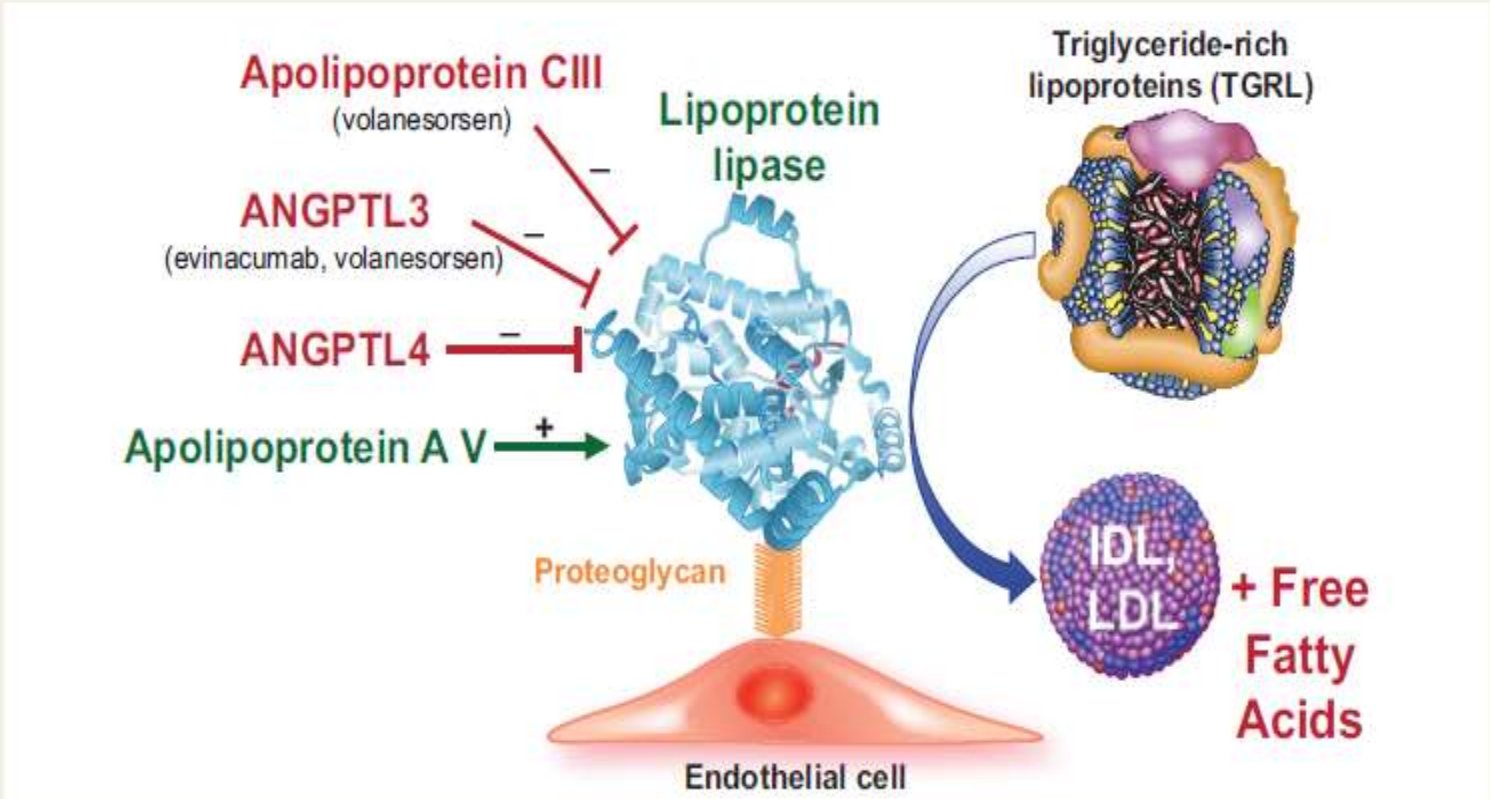


Figure 4 Lipoprotein lipase modifiers. The enzyme lipoprotein lipase (depicted by the ribbon structure) associates with the surface of endothelial cells by binding to proteoglycans. This enzyme trims triglyceride from triglyceride-rich lipoproteins which include remnants of chylomicrons produced by intestinal cells from dietary lipid and very low-density lipoproteins synthesized endogenously by the liver. Lipoprotein lipase-mediated hydrolysis yields free fatty acids and low-density lipoprotein and intermediate-density lipoproteins. The proteins named in red inhibit lipoprotein lipase, and thus raise blood triglyceride-rich lipoprotein concentrations by limiting triglyceride-rich lipoprotein catabolism. The novel therapeutic agents listed inhibit these inhibitors and thus lower triglyceride-rich lipoprotein levels. Apolipoprotein AV activates lipoprotein lipase (shown in green.) Very strong human genetic evidence support the causality of each of the modulatory proteins depicted in regulating triglyceride-rich lipoproteins. ANGPTL, angiopoietin-like protein.

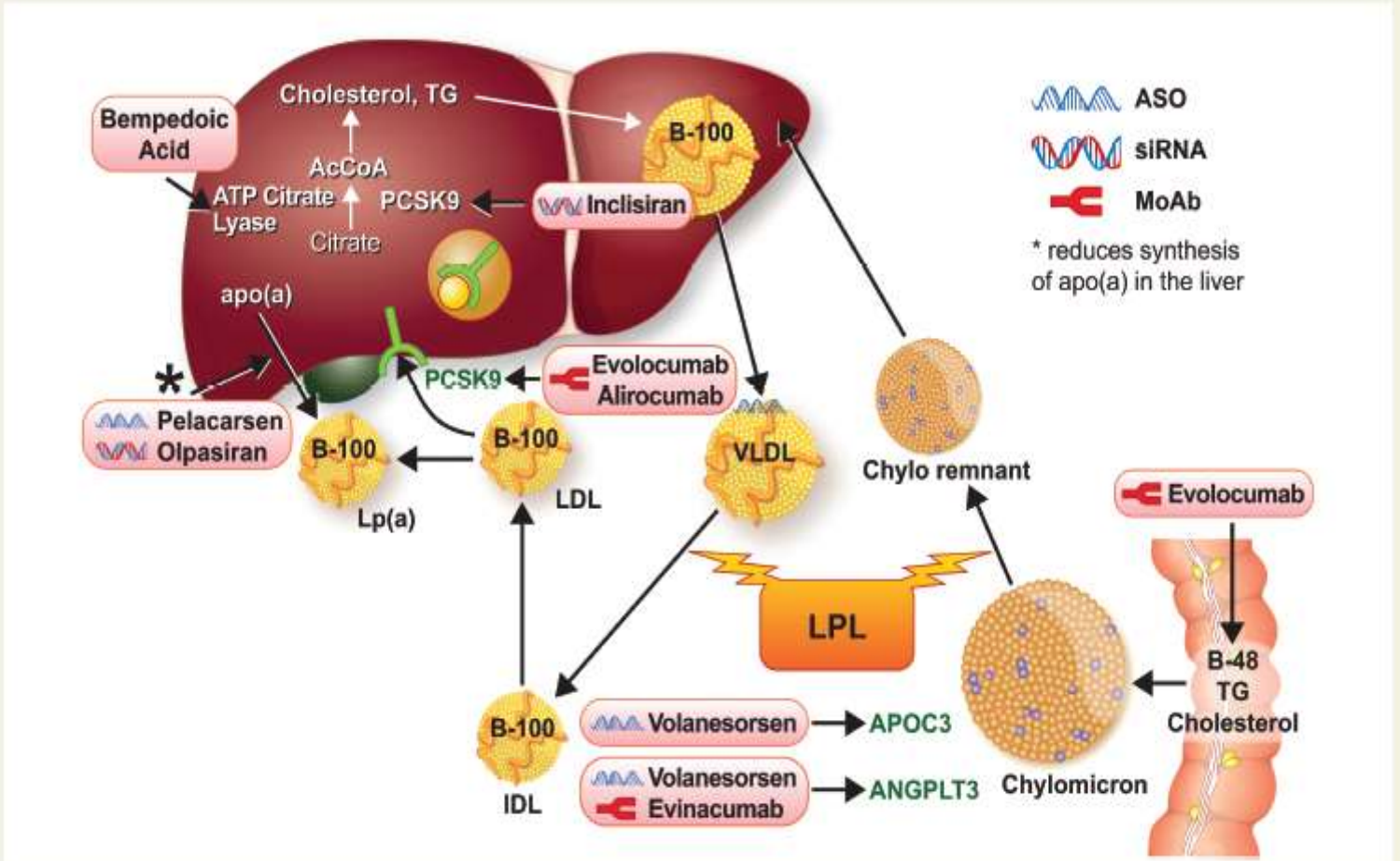


Figure 5 Newer and emerging lipid-lowering therapies target different aspects of lipid metabolism. The statins target hydroxymethylglutaryl coenzyme A reductase. The newer and emerging agents target other aspects of lipid metabolism as shown here. B48 refers to the shorter form of apolipoprotein B produced by RNA editing in the intestine. B100 refers to the longer form produced in the liver. See the list for explanations of other abbreviations.

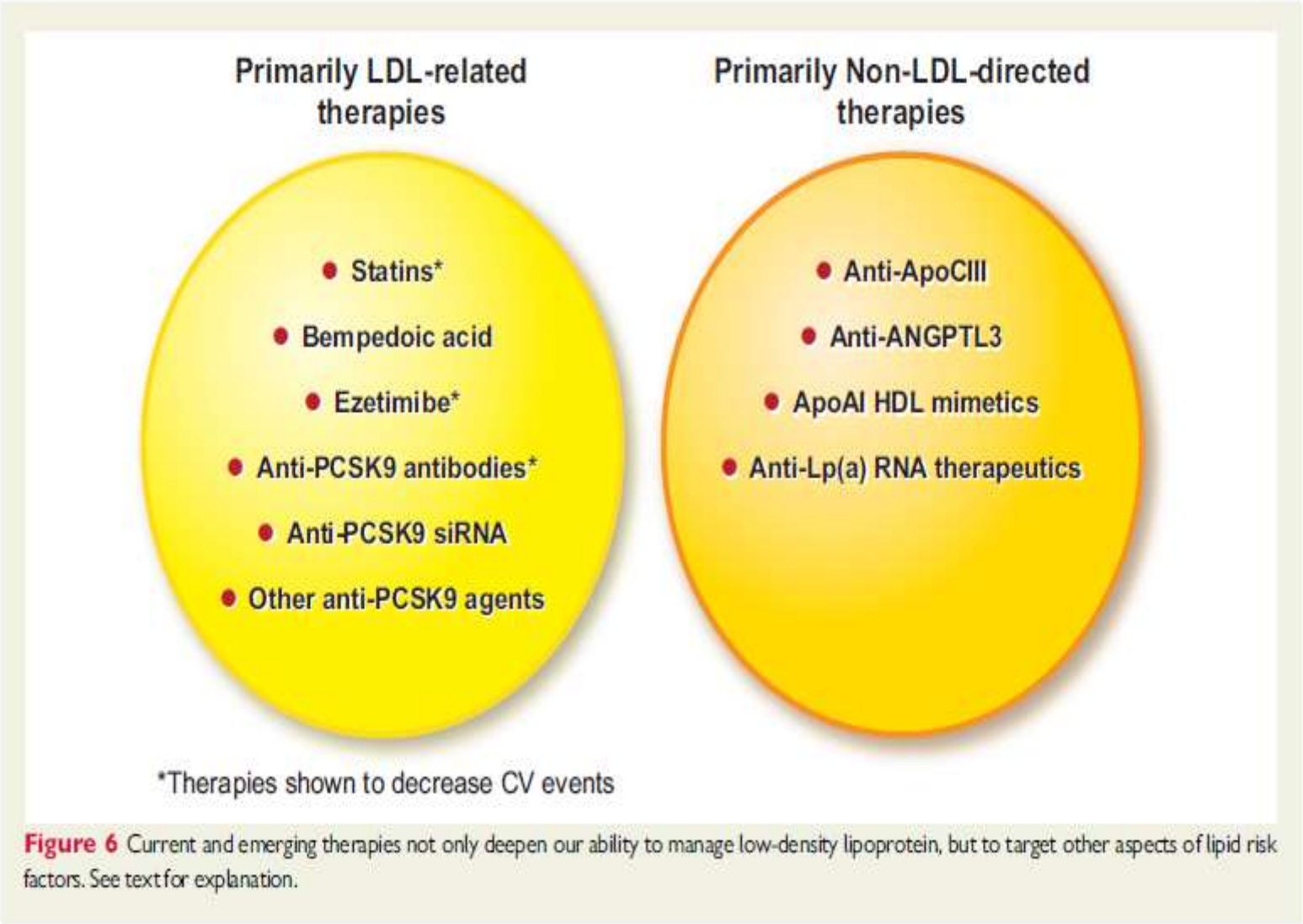


Figure 6 Current and emerging therapies not only deepen our ability to manage low-density lipoprotein, but to target other aspects of lipid risk factors. See text for explanation.