# Best of ACC.22: Advanced Lipid Management

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# DISCLOSURES

- Consulting
  - Genentech
- Medical Advisory Board
  - Clocktree
  - Measure Labs
- Research Funding
  - Amgen
  - Microsoft Research

# ACKNOWLEDGEMENTS


- Special thanks to Dr. Nihar Desai from Yale University School of Medicine for providing slides used for this presentation

# OUTLINE

- Review current blood cholesterol guideline recommendations (ACC/AHA and LAI)
- Discuss new lipid lowering therapies
- Take Home Points

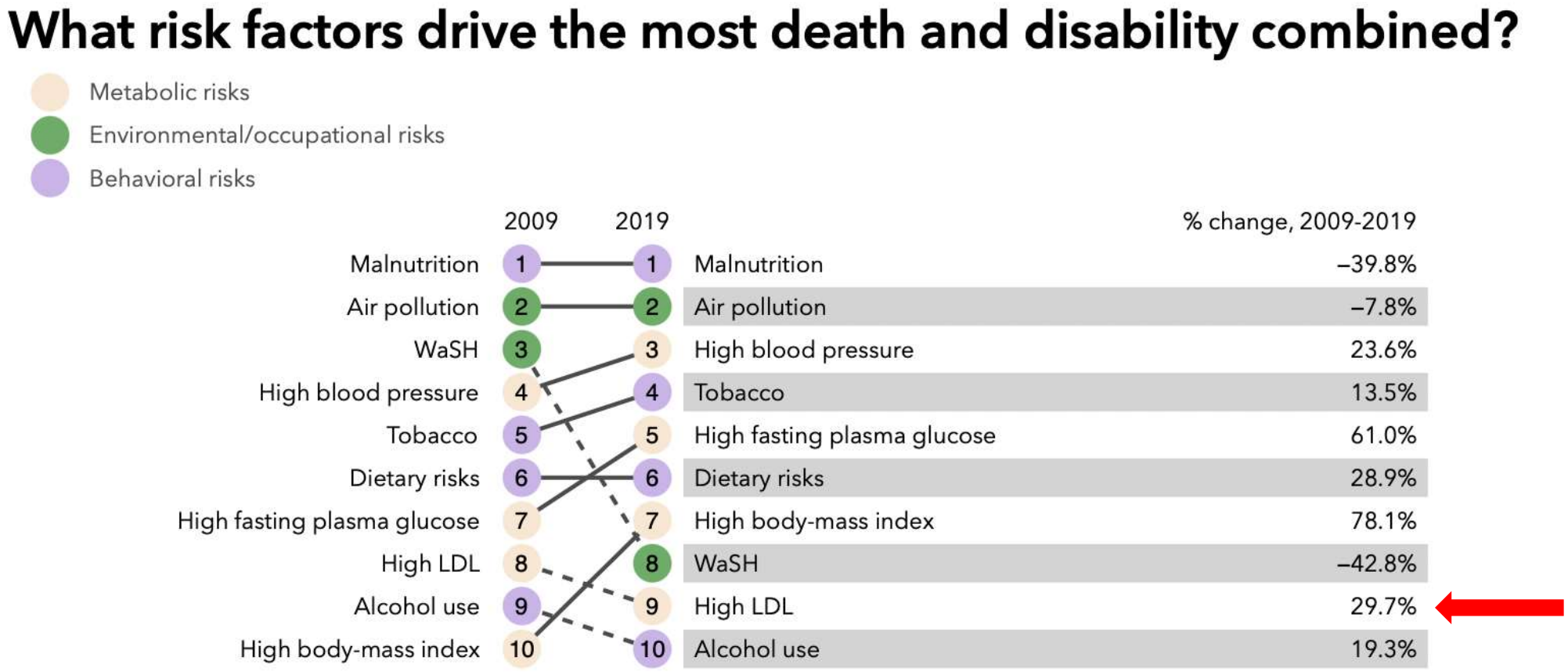
# CARDIOVASCULAR DISEASE IN INDIA– PUBLIC HEALTH EMERGENCY

- Leading cause of death (~28% of all deaths)

- Cardiovascular disease (CVD) occurs earlier (10 years) compared to Western populations
  - In Western countries, only 23% of CVD deaths occur before the age of 70; in India, it is **52%**

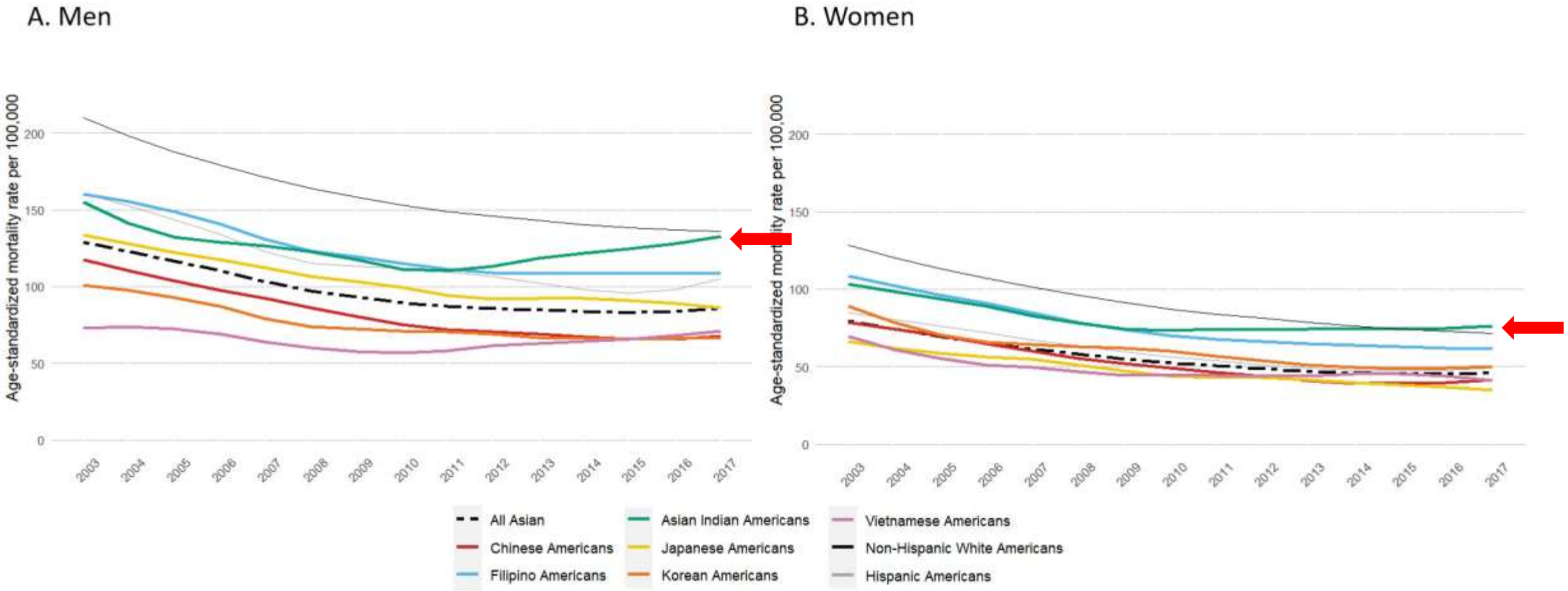
- It is predicted that India will have the highest number of CVD deaths in the world by 2030

# HIGH LDL CHOLESTEROL IS A LEADING CAUSE OF DEATH AND DISABILITY IN INDIA




Lancet 2020;396:1204–22.

# US CV MORTALITY RATES: ASIAN INDIANS HIGHEST!



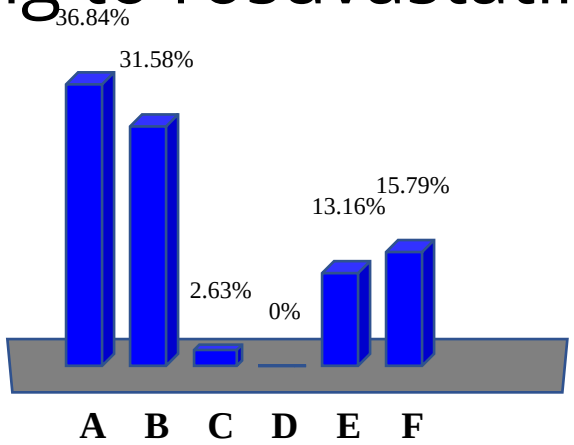

Shah NS et al. Circ Cardiovasc Qual Outcomes 2022.

# CASE PRESENTATION

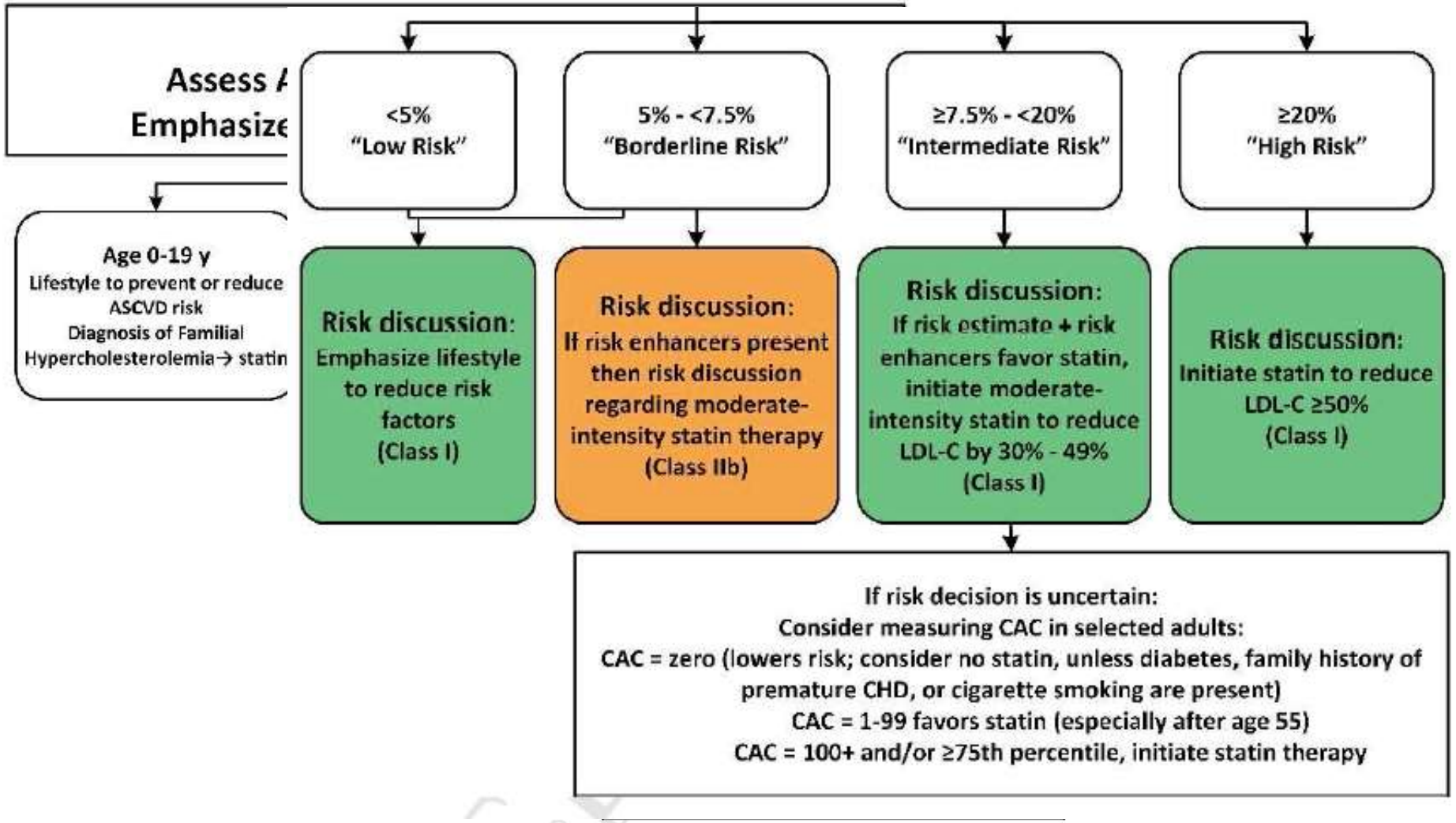
- 64 year old Indian man with history of CAD (PCI 5 years ago), hypertension, hyperlipidemia, and diabetes mellitus who presents for follow-up.
- Exam:
  - BP 132/78; HR 72 (sinus); 98% RA; RR 14; BMI 35.1 $kg/m^2$
  - JVP 6cm, lungs clear, 2/6 holosystolic ejection murmur, no edema
- Medications: Aspirin 81 mg, atorvastatin 80 mg, HCTZ 25 mg, lisinopril 40 mg, metformin 1 g twice daily, empagliflozin 10 mg daily
- Labs:
  - Total cholesterol: 145 mg/dL
  - LDL-C: 60 mg/dL
  - HDL: 50 mg/dL
  - TG: 185 mg/dL
  - HbA1c: 6.1%

# CASE PRESENTATION– WHAT DO YOU DO NEXT?

A. No changes, lipids look good!
B. Add ezetimibe
C. Add fenofibrate
D. Add icosapent ethyl
E. Switch from atorvastatin 80 mg to rosuvastatin 40 mg daily
F. Add PCSK9 inhibitor



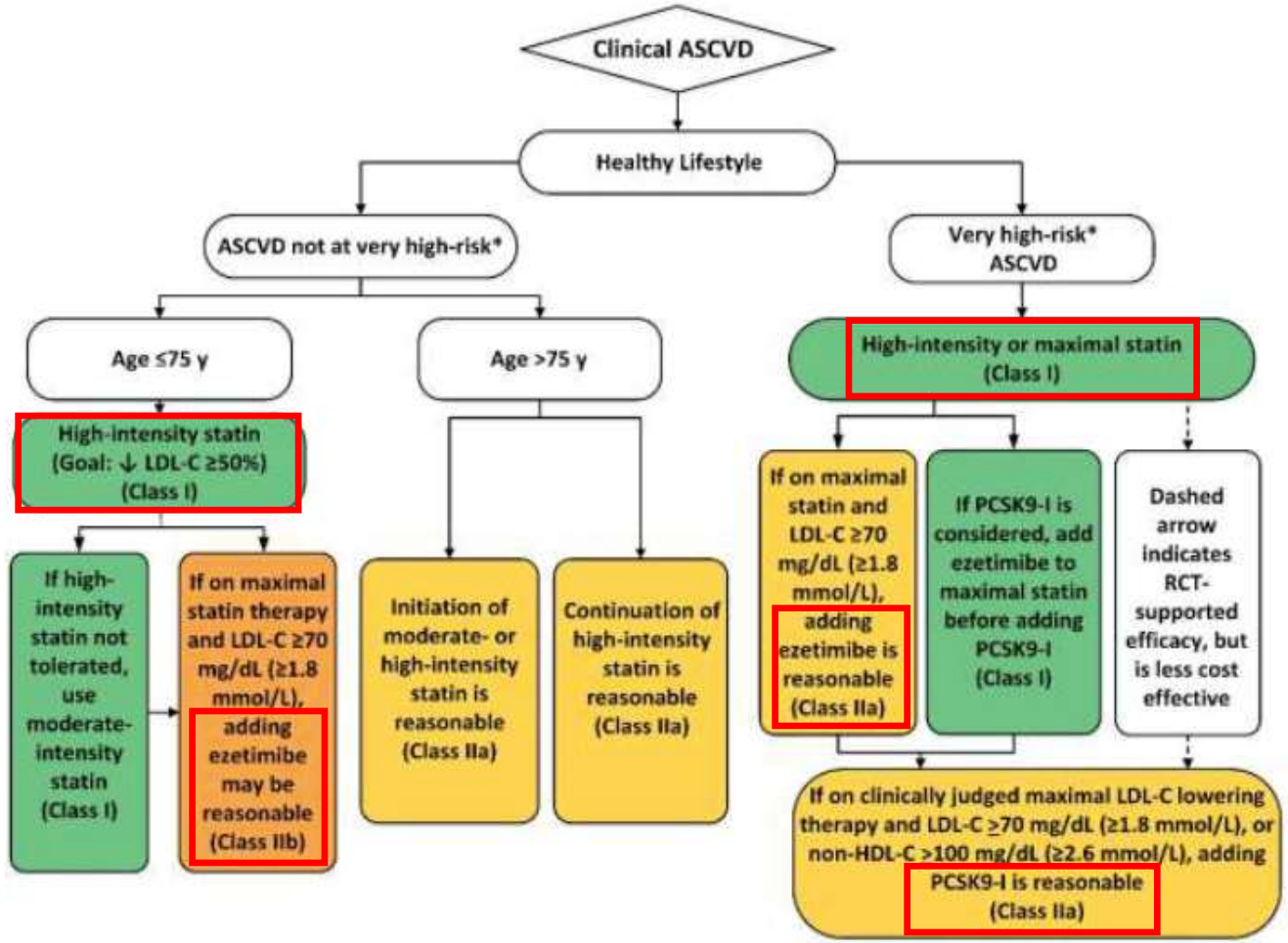
# 2018 ACC/AHA BLOOD CHOLESTEROL GUIDELINE




Arnett et al. JACC 2019.

# 2018 ACC/AHA BLOOD CHOLESTEROL GUIDELINE

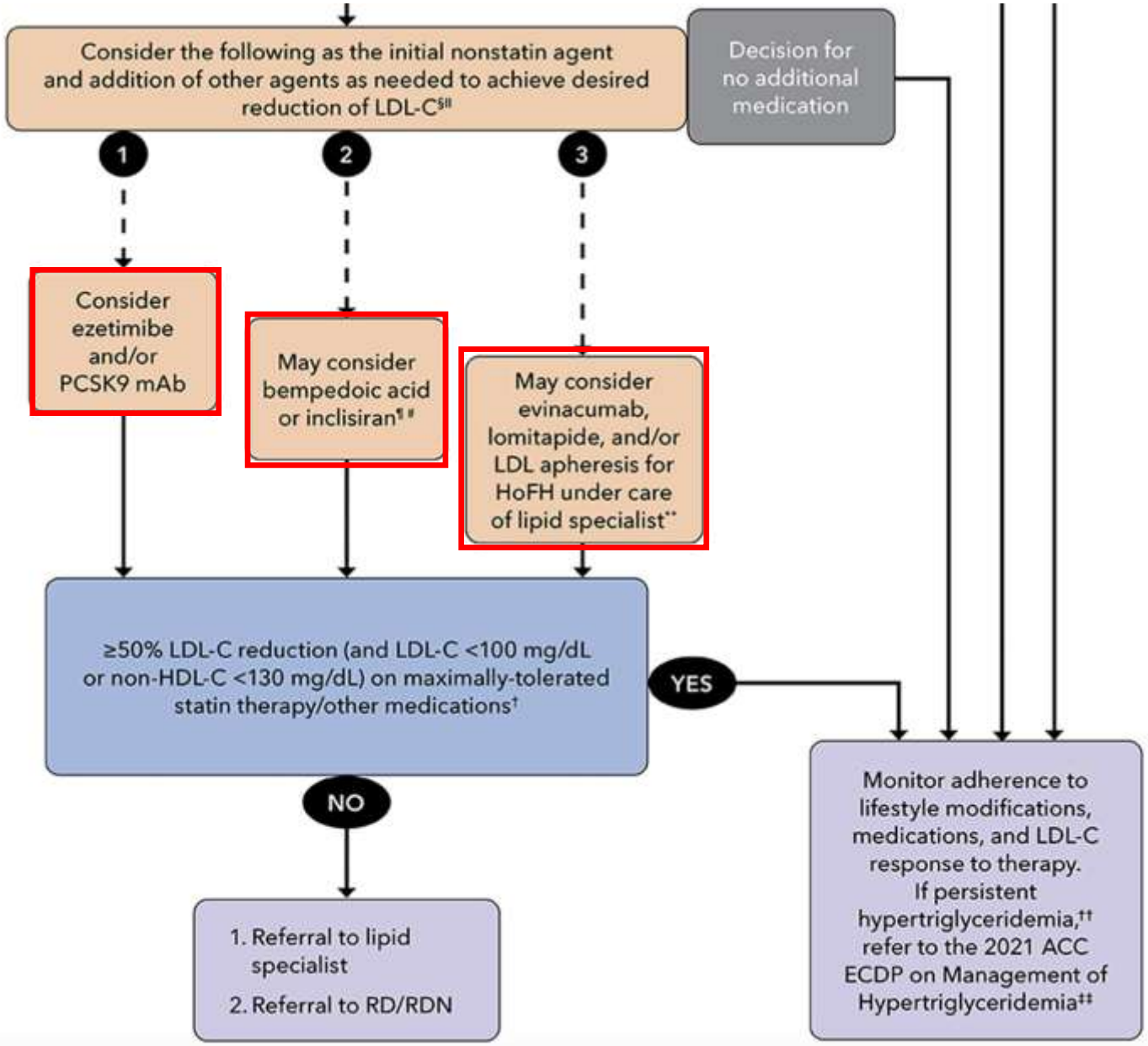
**Figure 1. Secondary Prevention in Patients With Clinical ASCVD**




Arnett et al. JACC 2019.

# 2022 A
# STATIN

# NON-




https://doi.org/10.1016/j.jacc.2022.07.006

# CURRENT LIPID LOWERING GUIDELINE RECOMMENDATIONS

**TABLE 4 ACC/AHA and ESC ASCVD Risk Categories and LDL-C Treatment Targets**

| Risk Category (10-y ASCVD risk) | ESC | ACC/AHA |
|---|---|---|
| Very high risk<br>ESC: ≥7.5% to ≥15% depending on age without established ASCVD | LDL-C reduction of ≥50% from baseline or <55 mg/dL (<1.4 mmol/L) | N/A |
| High risk<br>ACC/AHA: ≥20%<br>ESC: 2.5% to <15% depending on age | LDL-C reduction of ≥50% from baseline or <70 mg/dL (<1.8 mmol/L) | LDL-C reduction of ≥50% from baseline |
| Intermediate risk<br>ACC/AHA (7.5% to <20%) | N/A | If statin therapy is indicated, reduction of LDL-C 30%-49%[a] |
| Borderline risk<br>ACC/AHA (5% to <7.5%) | N/A | If risk enhancers present, consider moderate-intensity statin |
| Low risk<br>ACC/AHA (<5%) | N/A | Lifestyle |
| LDL-C ≥190 mg/dL (≥4.9 mmol/L) | Evaluation for FH (genetic testing or Dutch Lipid Clinic Network score) | High-intensity statin therapy |
| Diabetes mellitus<br>40-75 y without established ASCVD | Evaluation, stepwise approach | Moderate or high-intensity statin therapy |
| Chronic kidney disease (stage 3-5), nondialysis patients | Statin therapy | Utilize as risk enhancer |

[a]Calculation of ASCVD risk score, evaluation of enhancing risk factors, clinician-patient-risk discussion. If risk decision is uncertain, consider CAC measurement.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; N/A = not applicable. Other abbreviations as in Table 1.

J Am Coll Cardiol 2022;79:1304–1313.

# 2022 LIPID ASSOCIATION OF INDIA GUIDELINES

**Updated Risk Stratification Approach Recommended by Lipid Association of India**

**Risk factors/markers**

| Major ASCVD risk factors | Other high-risk features | Moderate risk non-conventional risk factors |
|---|---|---|
| 1. Age ≥45 years in males and ≥55 years in females<br>2. Family history of premature ASCVD<br>3. Current cigarette smoking or tobacco use<br>4. High blood pressure<br>5. Low HDL-C | 1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage<br>2. CKD stage 3B or 4<br>3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia)<br>4. Extreme of a single risk factor<br>5. Coronary calcium score >300 HU<br>6. Non-stenotic carotid plaque<br>7. Lipoprotein (a) ≥50 mg/dL | 1. Coronary calcium score 100–299 HU<br>2. Increased carotid IMT<br>3. Lipoprotein (a) 20–49 mg/dL<br>4. Impaired fasting glucose*<br>5. Increased waist circumference**<br>6. Apolipoprotein B≥110 mg/dL<br>7. hsCRP ≥2 mg/L*** |

**Risk group**

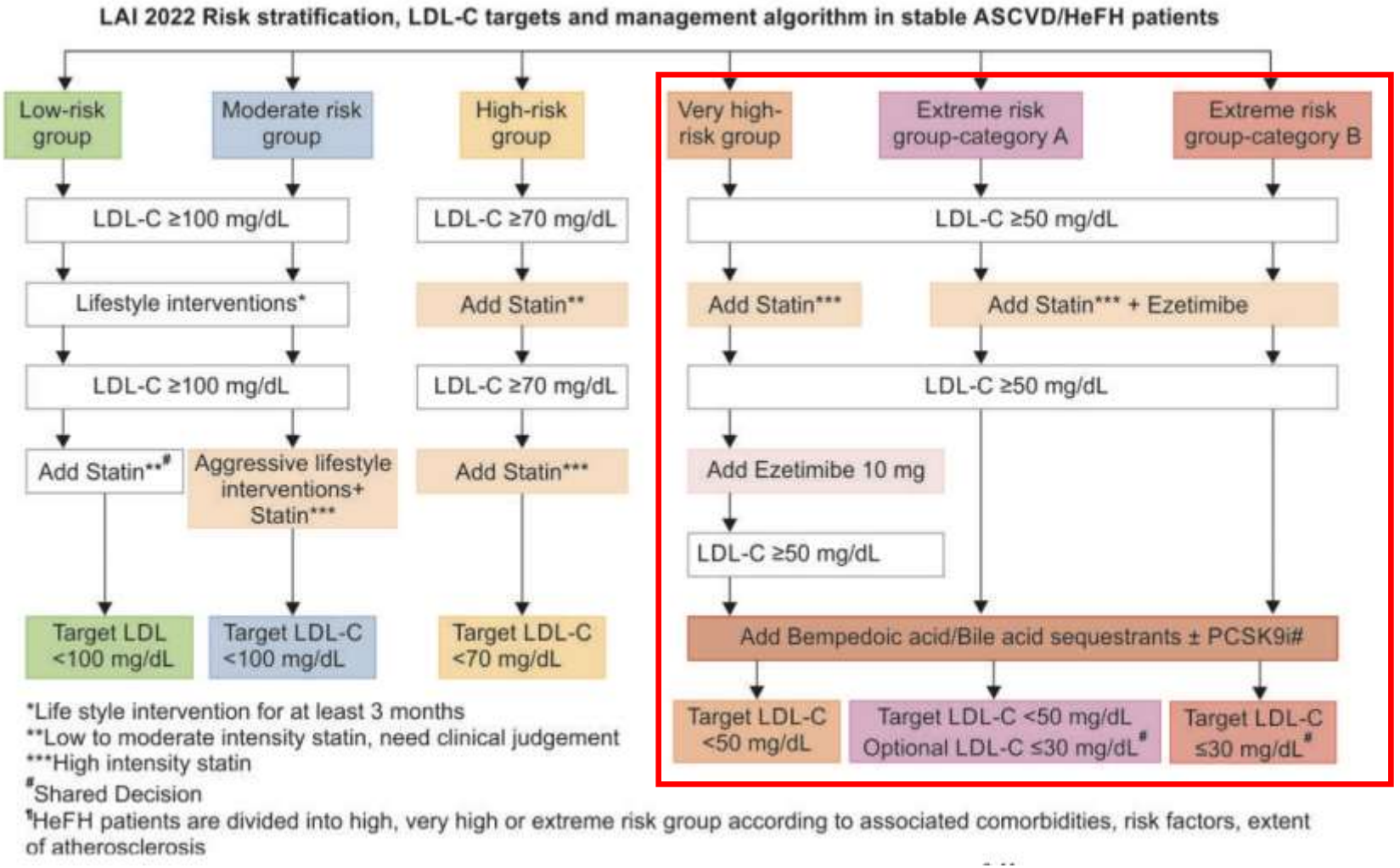
| Low-risk | Moderate risk | High-risk | Very high-risk | Extreme risk | |
|---|---|---|---|---|---|
| | | | | Category A | Category B |
| 0-1 major ASCVD risk factor and life-time CVD risk <30% | • 2 major ASCVD risk factors<br>• Low risk group with ≥1 moderate risk non-conventional risk factor<br>•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

Clinical judgment to be used if 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 weeks apart. For reclassifying moderate risk group only.

**Fig. 1:** Risk stratification algorithm recommended by the LAI[10,11]

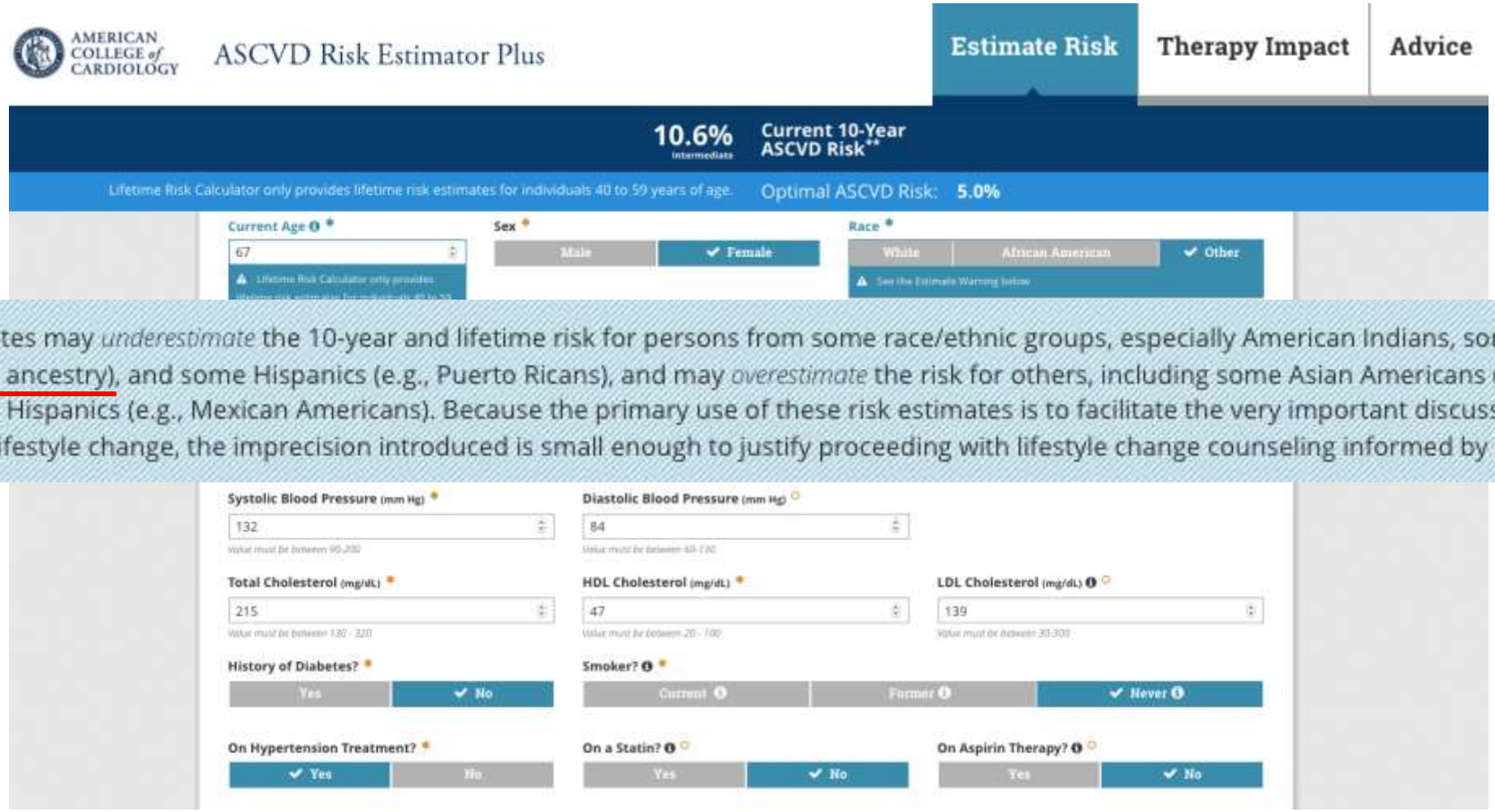
J Assoc Physicians India 2022;70:67–75.

# 2022 LIPID ASSOCIATION OF INDIA GUIDELINES

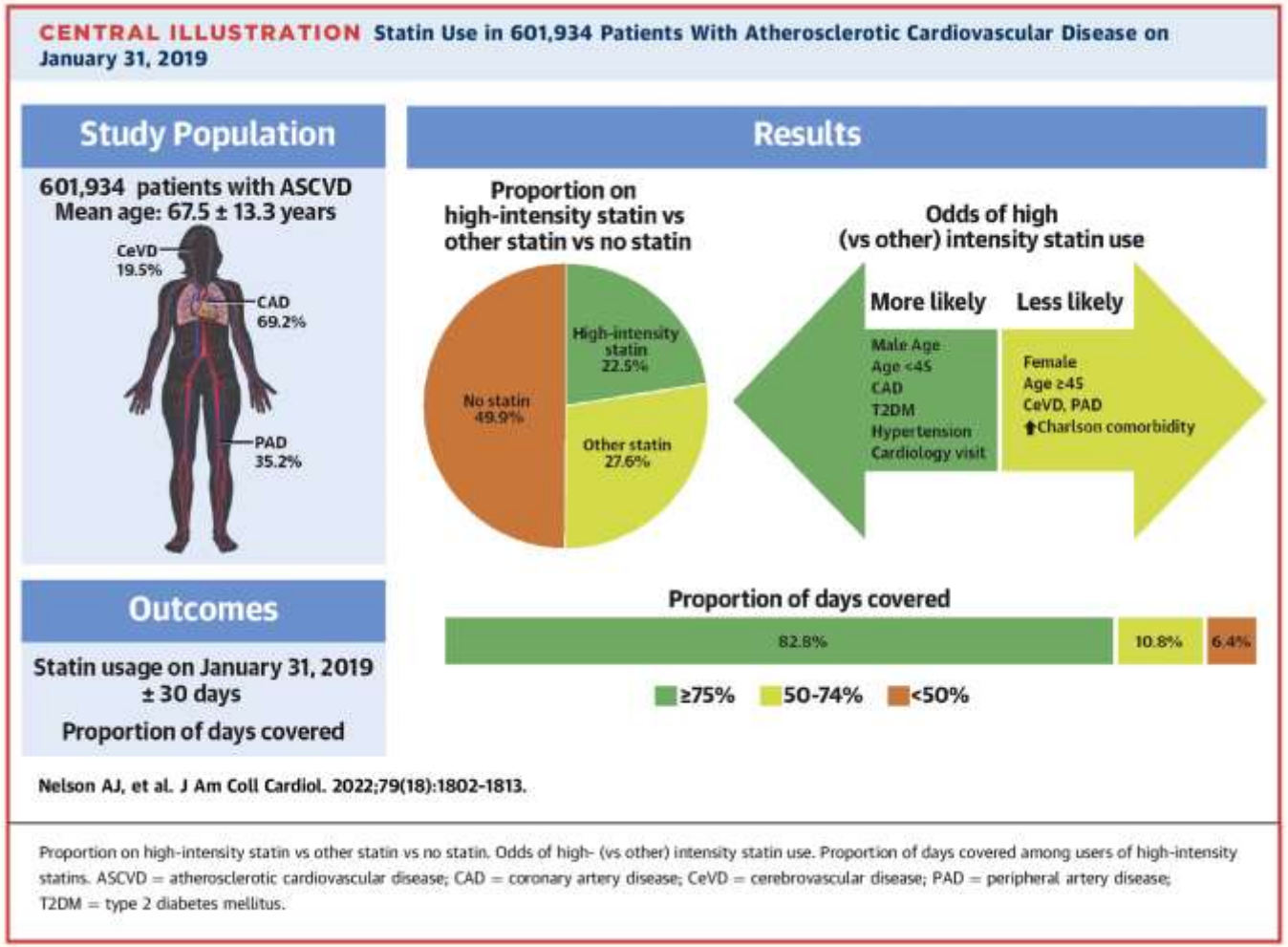



J Assoc Physicians India 2022;70:67–75.

# NO ASCVD RISK CALCULATOR FOR ASIANS

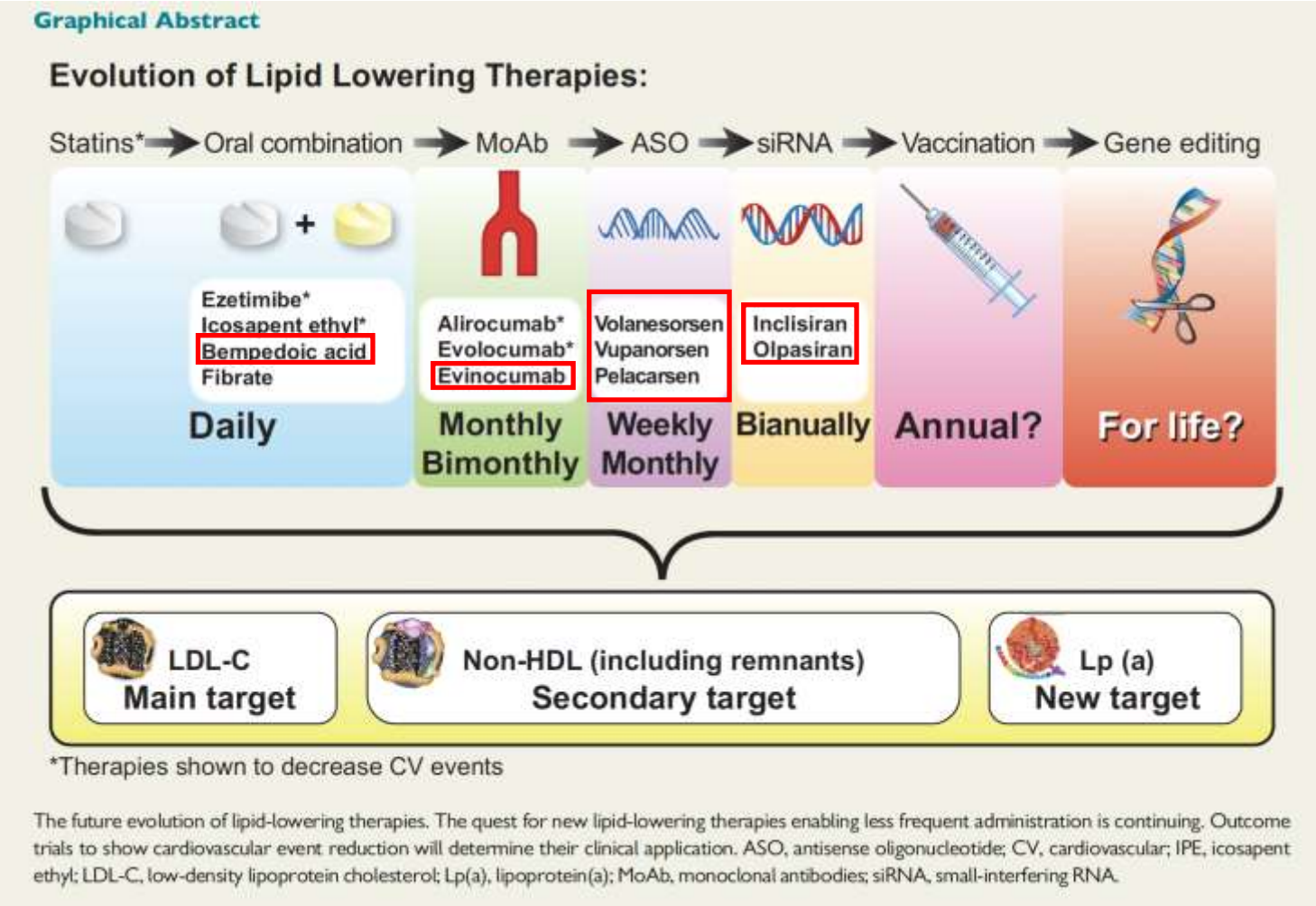


# USE OF STATIN THERAPY IS LOW: <50%!




J Am Coll Cardiol. 2022;79(18):1802–1813.

# NEW LIPID LOWERING THERAPIES




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.

*European Heart Journal*, 2022;, ehab841, https://doi.org/10.1093/eurheartj/ehab841

# NEW TARGETS FOR LIPID LOWERING THERAPIES

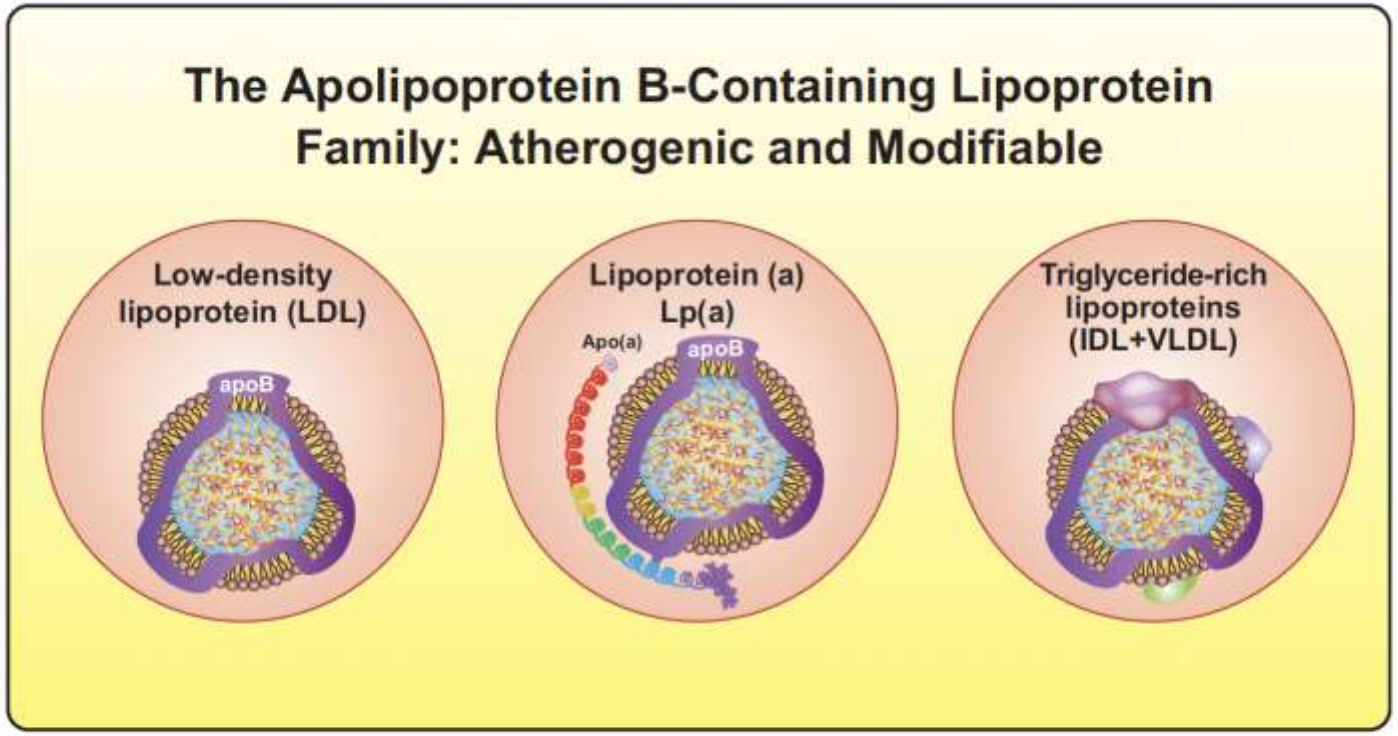



**Figure 1** New targets for lipid-lowering therapies. Beyond low-density lipoprotein, lipoprotein(a) and triglyceride-rich lipoproteins or remnant lipoproteins have become actionable targets in lipid management. IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

*European Heart Journal*, 2022;, ehab841, https://doi.org/10.1093/eurheartj/ehab841

# CAUSAL EVIDENCE FOR LIPID PATHWAYS AND CV DISEASE

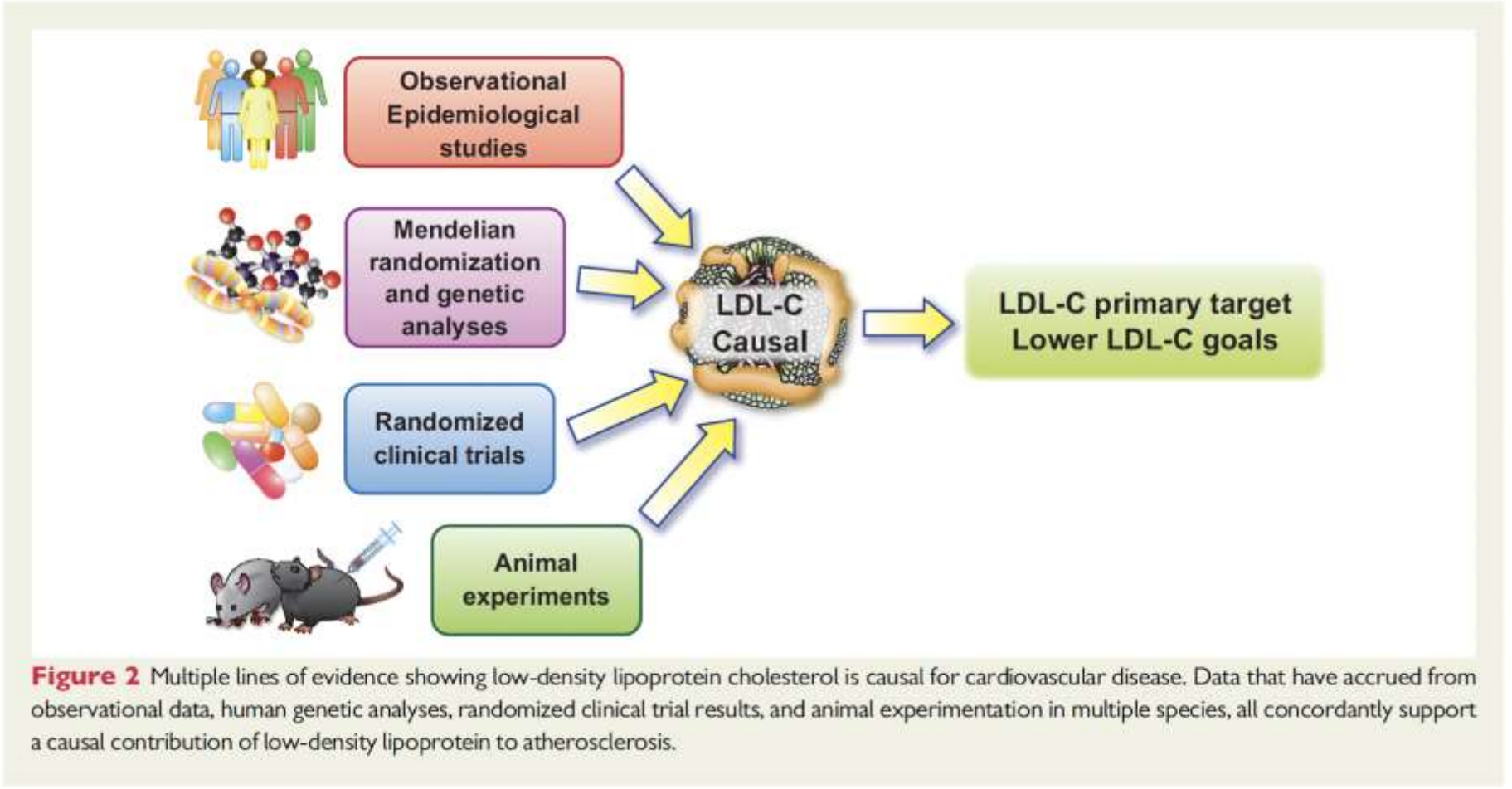



**Figure 2** Multiple lines of evidence showing low-density lipoprotein cholesterol is causal for cardiovascular disease. Data that have accrued from observational data, human genetic analyses, randomized clinical trial results, and animal experimentation in multiple species, all concordantly support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

*European Heart Journal*, 2022;, ehab841, https://doi.org/10.1093/eurheartj/ehab841

# NEW TARGETED DELIVERY MECHANISMS

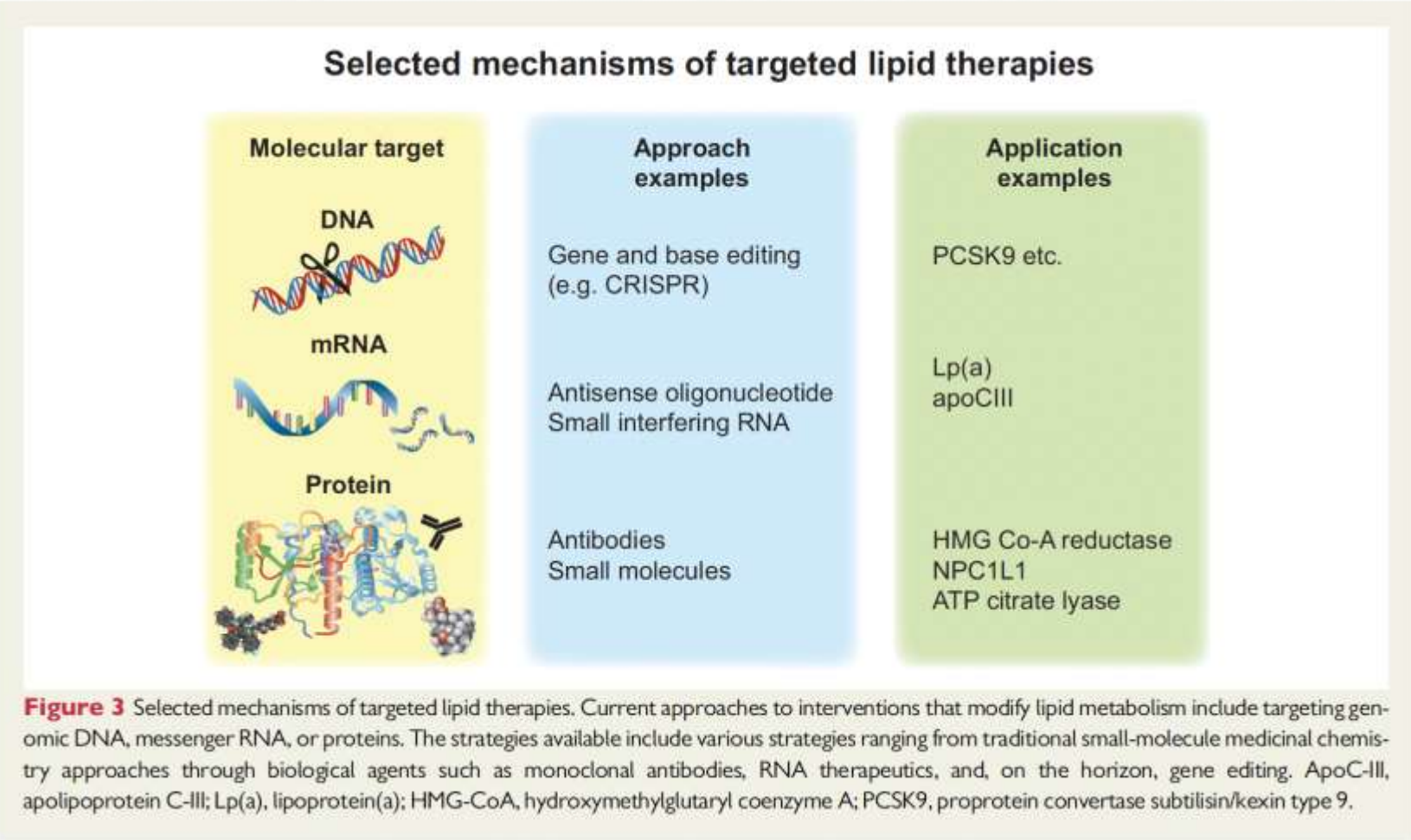



**Figure 3** Selected mechanisms of targeted lipid therapies. Current approaches to interventions that modify lipid metabolism include targeting genomic DNA, messenger RNA, or proteins. The strategies available include various strategies ranging from traditional small-molecule medicinal chemistry approaches 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.

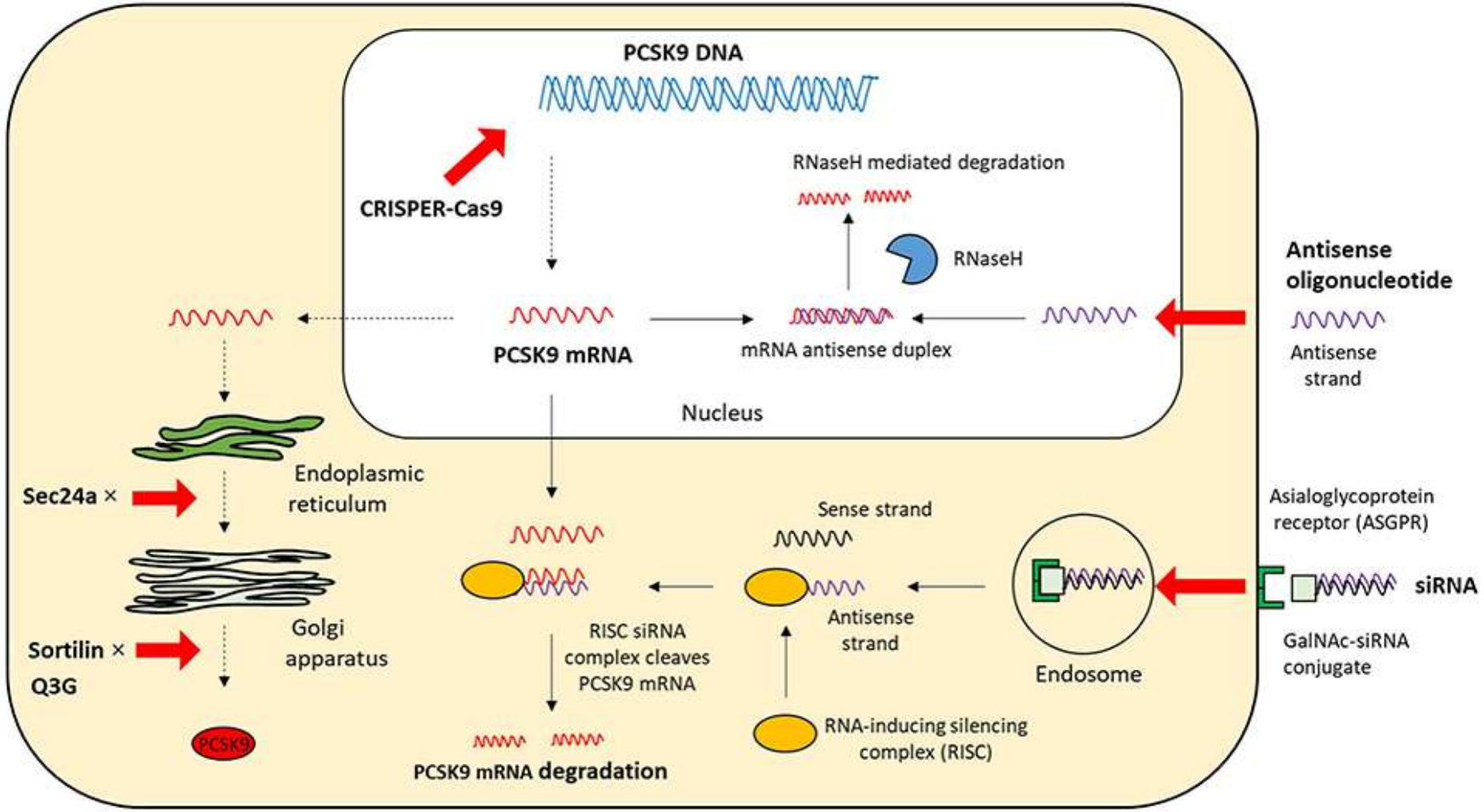
*European Heart Journal*, 2022;, ehab841, https://doi.org/10.1093/eurheartj/ehab841

# BEMPEDOIC ACID

- Approved in the US as adjunct to maximally-tolerated statin therapy for HeFH or established ASCVD patients
  - Inhibits ATP citrate lyase (upstream of HMG-CoA reductase)
  - Lowers LDL-C by 17-25%
  - Available in combination with ezetimibe (lowers LDL-C up to 38%)
  - More liver-specific than statins- Pro-drug converted to active form in hepatocytes
  - No outcome study yet! (CLEAR OUTCOMES)

- Warnings/Precautions
  - Hyperuricemia: higher risk in those with history of gout (consider monitoring uric acid levels)
  - Tendon rupture: avoid if prior history
  - Avoid with simvastatin dose >20 mg and pravastatin dose >40 mg

# NEW TARGETED PCSK9 INHIBITOR THERAPIES




Michos ED et al. N Engl J Med 2019; 381:1557-1567.

# INCLISIRAN

- Anti-PCSK9 si-RNA recently approved in the US as adjunct to statin therapy for:
  - Adults with heterozygous familial hypercholesterolemia (HeFH)
  - Overt atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low- density lipoprotein cholesterol (LDL-C)

- Reduces LDL-C ~50% with twice yearly SC injections
  - Injection site reactions ~5%

- Awaiting results of ORION-4 (secondary prevention trial)

# PCSK9 INHIBITORS- GENE EDITING

Molecular Medicine

## Permanent Alteration of PCSK9 With In Vivo CRISPR-Cas9 Genome Editing

Qiurong Ding, Alanna Strong, Kevin M. Patel, Sze-Ling Ng, Bridget S. Gosis, Stephanie N. Regan, Chad A. Cowan, Daniel J. Rader, Kiran Musunuru

***Rationale:*** **Individuals with naturally occurring loss-of-function proprotein convertase subtilisin/kexin type 9 (*PCSK9*) mutations experience reduced low-density lipoprotein cholesterol levels and protection against cardiovascular disease.**

***Objective:*** **The goal of this study was to assess whether genome editing using a clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated system can efficiently introduce loss-of-function mutations into the endogenous *PCSK9* gene in vivo.**

***Methods and Results:*** **We used adenovirus to express CRISPR-associated 9 and a CRISPR guide RNA targeting *Pcsk9* in mouse liver, where the gene is specifically expressed. We found that <3 to 4 days of administration of the virus, the mutagenesis rate of *Pcsk9* in the liver was as high as >50%. This resulted in decreased plasma PCSK9 levels, increased hepatic low-density lipoprotein receptor levels, and decreased plasma cholesterol levels (by 35–40%). No off-target mutagenesis was detected in 10 selected sites.**

***Conclusions:*** **Genome editing with the CRISPR–CRISPR-associated 9 system disrupts the *Pcsk9* gene in vivo with high efficiency and reduces blood cholesterol levels in mice. This approach may have therapeutic potential for the prevention of cardiovascular disease in humans. (*Circ Res*. 2014;115:488-492.)**

**Key Words:** coronary disease ■ genetic therapy ■ lipoproteins ■ molecular biology ■ prevention and control

Article | Published: 19 May 2021

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

Kiran Musunuru, Alexandra C. Chadwick, ... Sekar Kathiresan + Show authors

*Nature* **593**, 429–434 (2021) | Cite this article

**28k** Accesses | **76** Citations | **989** Altmetric | Metrics

### Abstract

Gene-editing technologies, which include the CRISPR–Cas nucleases[1,2,3] and CRISPR base editors[4,5], have the potential to permanently modify disease-causing genes in patients[6]. The demonstration of durable editing in target organs of nonhuman primates is a key step before in vivo administration of gene editors to patients in clinical trials. Here we demonstrate that CRISPR base editors that are delivered in vivo using lipid nanoparticles can efficiently and precisely modify disease-related genes in living cynomolgus monkeys (*Macaca fascicularis*). We observed a near-complete knockdown of *PCSK9* in the liver after a single infusion of lipid nanoparticles, with concomitant reductions in blood levels of PCSK9 and low-density lipoprotein cholesterol of approximately 90% and about 60%, respectively; all of these changes remained stable for at least 8 months after a single-dose treatment. In addition to supporting a 'once-and-done' approach to the reduction of low-density lipoprotein cholesterol and the treatment of atherosclerotic cardiovascular disease (the leading cause of death worldwide[7]), our results provide a proof-of-concept for how CRISPR base editors can be productively applied to make precise single-nucleotide changes in therapeutic target genes in the liver, and potentially in other organs.

# TRIGLYCERIDE RICH LIPOPROTEINS– A NEW TARGET

- Triglyceride-rich lipoproteins include remnant lipoproteins- chylomicron remnants, VLDL, and IDL
  - Atherogenicity due to delivery of cholesterol to foam cells?
  - Pro-inflammatory effect of remnant particles

- Lipoprotein lipase (LPL) is a key regulator of triglyceride levels
  - Releases free fatty acids from triglycerides reducing triglyceride concentrations
  - Genetic variants that lower LPL activity increase triglyceride-rich lipoproteins and are associated with increased CV events
    - Apolipoprotein C-III, ANGPTL3 and 4

*European Heart Journal*, 2022;, ehab841, https://doi.org/10.1093/eurheartj/ehab841

# TRIGLYCERIDE RICH LIPOPROTEINS– A NEW TARGET

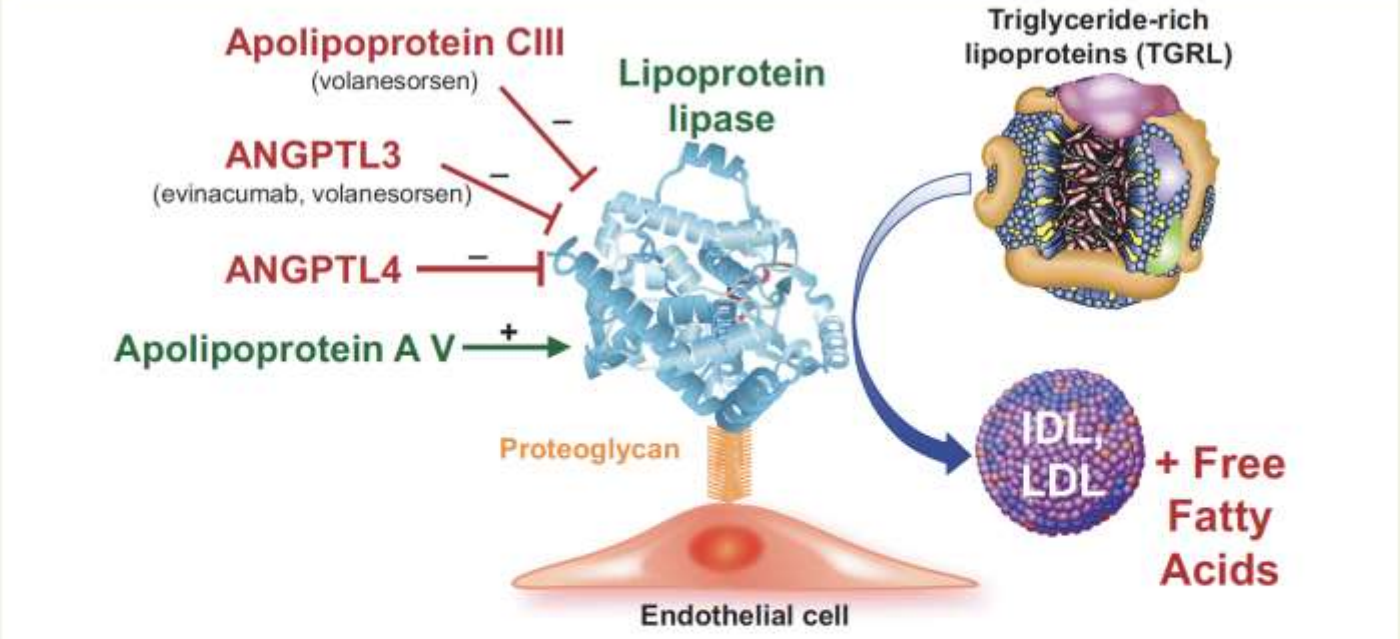



**Figure 4** Lipoprotein lipase modifiers. The enzyme lipoprotein lipase (depicted by the ribbon structure) associates with the surface of endothelial cells by binding to proteoglycans. This enzyme trims triglyceride from triglyceride-rich lipoproteins which include remnants of chylomicrons produced 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.

*European Heart Journal*, 2022;, ehab841, https://doi.org/10.1093/eurheartj/ehab841

# EVINACUMAB

- Monoclonal antibody directed again ANGPTL3
  - In patients with Ho-FH (ELIPSE-HoFH study), lowered LDL-C by 49% (LDL-receptor independent pathway), triglycerides by 55%
  - Approved in US for LDL-C lowering for Ho-FH patients
  - IV infusion every 4 weeks
  - **Cost- $450,000/year (US dollars)**

N Engl J Med 2020; 383:711-720.

# VUPANORSEN

- Anti-sense oligonucleotide directed against ANGPTL3
  - Blocks hepatic synthesis

- Drug development halted January, 2022 due to safety signal, poor results

- **TRANSLATE-70 Trial presented as LBCT at ACC.22**
  - Small-modest reductions in non-HDL-C (22-27%) and LDL-C levels (7.9-16%)
  - Significant increase in liver fat fraction (76%) and 3x LFT elevations


Circulation. 2022;145:1377–1386.

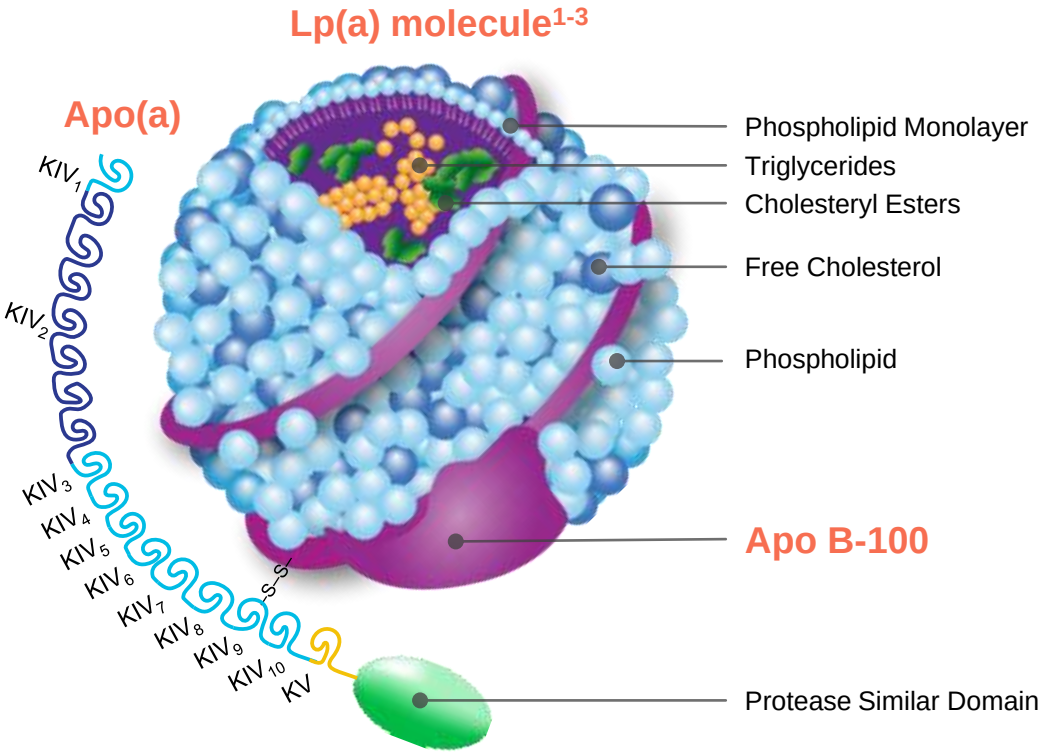
# VOLANESORSEN

- Antisense oligonucleotide targeting apolipoprotein C-III
- Approved by EMA for treatment of familial chylomicronaemia syndrome (FCS)
- In patients with hyperchylomicronaemia, lowered triglycerides by >70%
  - Caused injection-site reactions in almost a quarter of patients

# LIPOPROTEIN (a)– AN OLD BUT NEW THERAPEUTIC TARGET

- A unique form of LDL where Apo(a) binds to ApoB surrounding LDL particles
- Genome wide association studies (GWAS) and Mendelian randomization studies demonstrate causality of Lp(a) in ASCVD and calcific aortic valve disease
- *Statins do not lower Lp(a)*
- PCSK9i and niacin can lower Lp(a) ~30%

# Lp(a): Nuts and Bolts




- Lp(a) is produced in the liver and has two main components joined by a covalent disulfide bond[1,2]
  - A lipid core moiety that is an LDL-like particle containing apolipoprotein B-100, which is proatherosclerotic[1,2]

    and
  - A single molecule of apolipoprotein(a)[1-3]

**Lp(a) differs from LDL in that Lp(a) contains a molecule of apo(a)[1,2]**

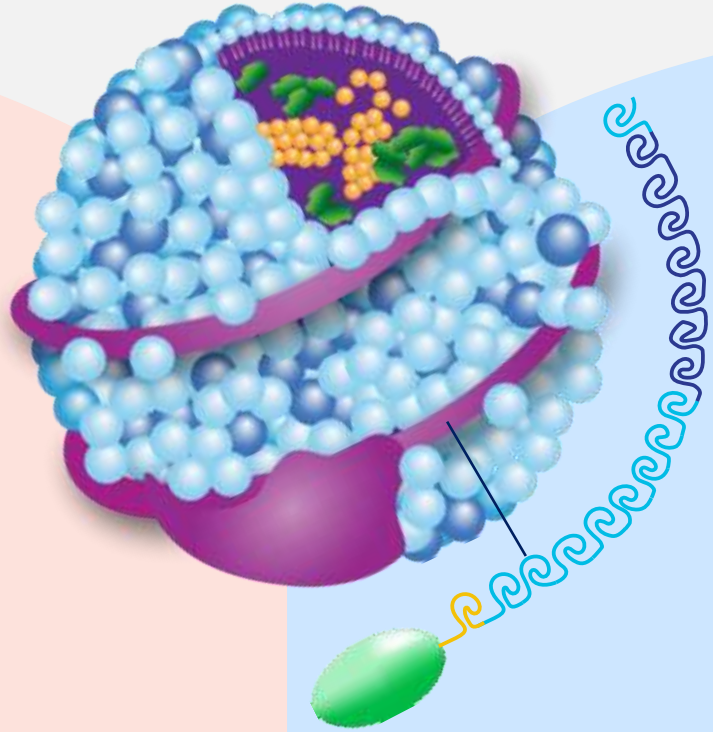
apo, apoprotein; KI, kringle type I; KII, kringle type II; KIII, kringle type III; KIV, kringle type IV; KV, kringle type V; Lp(a), lipoprotein (a).

1. Cai A, et al. *Dis Markers*. 2013;35(5):551-559. 2. Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711. 3. Jawi MM, et al. *J Lipids*.2020:1-26. doi.org /10.1155/2020/3491764.

# Lp(a) Has Several Pathogenic Mechanisms that may Affect CV Risk

## Pro-inflammatory

- ↑ Macrophage IL-8 expression
- ↑ Monocyte cytokine release
- ↑ Oxidized Phospholipids
- ↑ Monocyte chemotaxis/transmigration
- Carries MCP-1



## Proatherogenic

- ↑ EC binding
- ↑ Upregulation of adhesion molecules
- ↑ SMC proliferation
- ↑ Proteoglycan matrix binding
- ↑ Foam/cell formation
- ↑ Necrotic core formation
- ↑ Lesion calcification

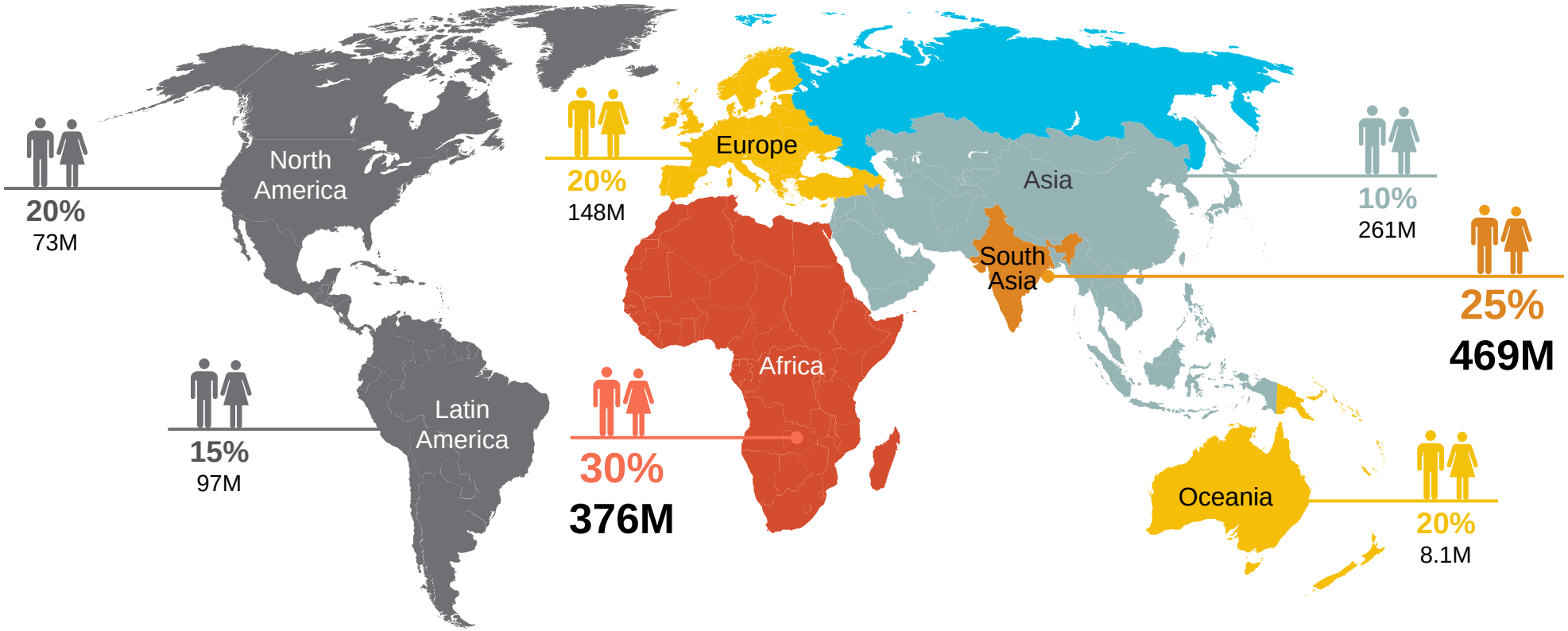
## Prothrombotic

- ↓ Plasminogen activation
- ↓ Fibrin degradation
- ↑ EC PAI-1 expression
- ↑ TFPI activity
- ↑ Platelet responsiveness

EC, endothelial cell; IL, interleukin; Lp(a), lipoprotein(a); MCP, monocyte chemoattractant protein; PAI, plasminogen activator inhibitor; SMC, smooth muscle cell; TFPI, tissue factor pathway inhibitor.

Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711.

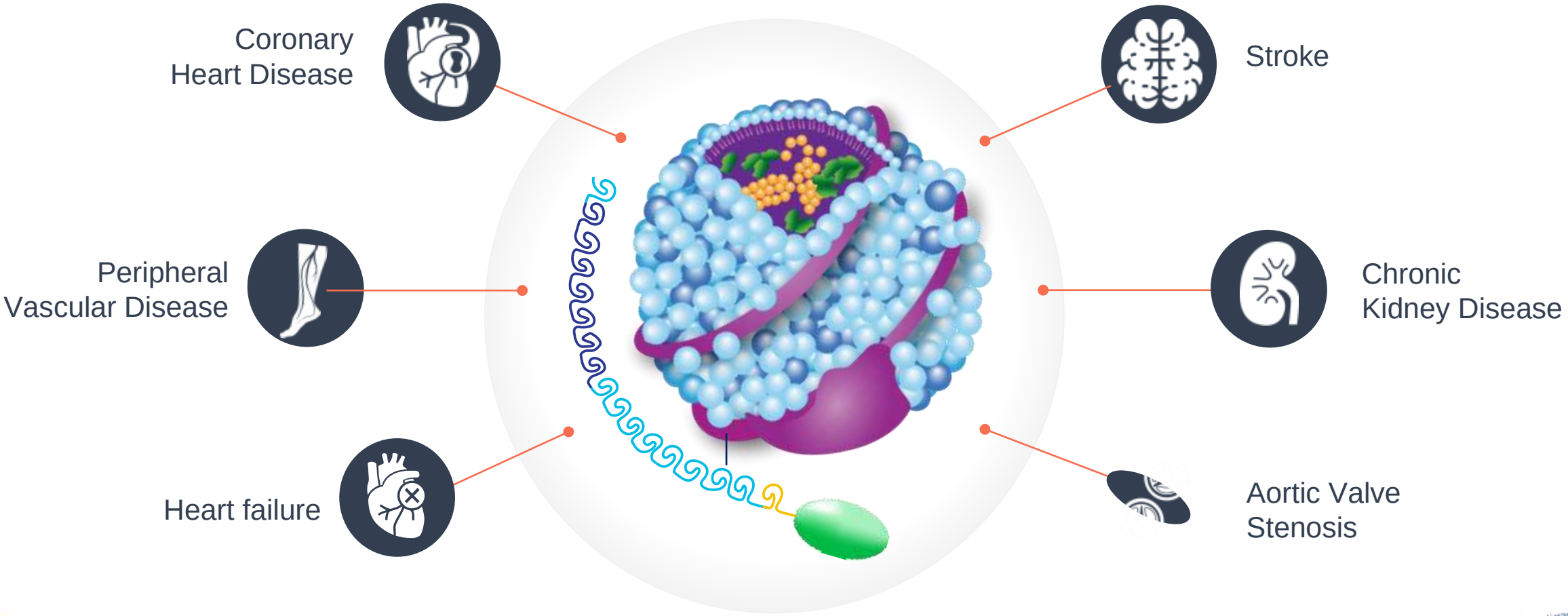
# ~1.4 Billion People Globally Have Elevated Lp(a) Levels > 50 mg/dL




African and South Asian individuals generally have higher levels of Lp(a)

Lp(a), lipoprotein(a); M, millions.
AHA, American Heart Association; ACC, American College of Cardiology; M, millions
Tsimikas S. *J Am Coll Cardiol*. 2018;71:177-192.

# Elevated Lp(a) is Associated with Various Disease States




Disease associations were determined using logistic regression data from UK Biobank, adjusted for age, sex, and 10 other key components, with the exception of chronic kidney disease, which was determined using statistics from CKDGen
Lp(a), lipoprotein(a)
Emdin CA, et al. *J Am Coll Cardiol*. 2016;68:2761-2772.

# PELACARSEN

- Anti-sense oligonucleotide directed against apolipoprotein(a) and lowers Lp(a) by 60-80%
  - No significant safety signal in early studies

- Lp(a) HORIZON Trial is a secondary prevention study currently enrolling patients with history of prior MI, stroke, PAD

# OLPASIRAN

- si-RNA directed against apolipoprotein(a) and lowers Lp(a) up to 80% at 113 days in Phase 1 clinical trial
  - No significant safety concerns

- Phase 2 dose finding study ongoing


Circulation. 2020;142:A13951

# SLN360- APOLLO TRIAL

- si-RNA directed against apolipoprotein(a) and lowers Lp(a) up to 81% at 5 months

- **Phase 1 APOLLO Trial presented at ACC.22**
  - Single ascending dose study with SC injection
  - No safety signal

# CASE PRESENTATION

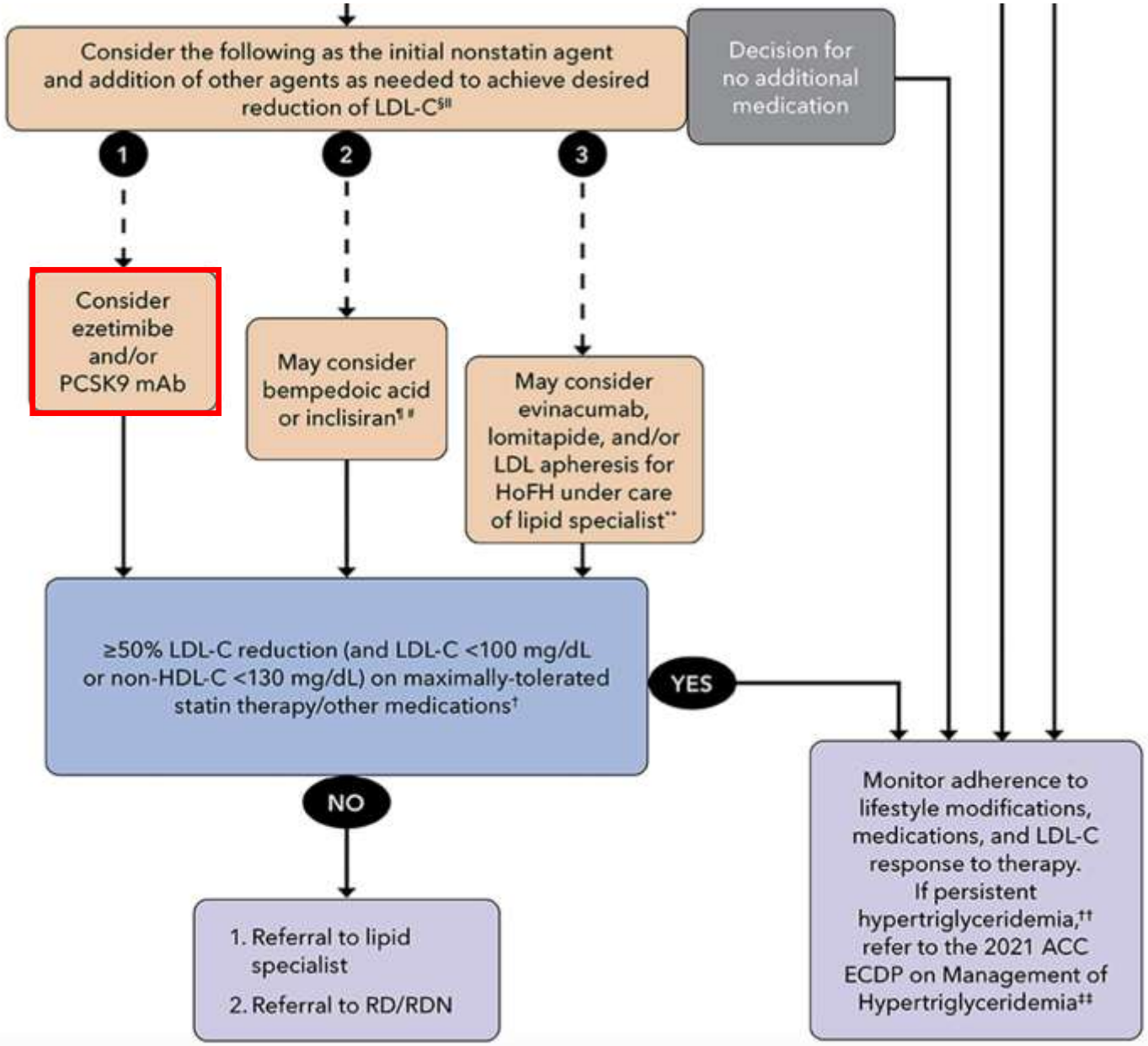
- 64 year old Indian man with history of CAD (PCI 5 years ago), hypertension, hyperlipidemia, and diabetes mellitus who presents for follow-up.
- Exam:
  - BP 132/78; HR 72 (sinus); 98% RA; RR 14; BMI 35.1 kg/m$^2$
  - JVP 6cm, lungs clear, 2/6 holosystolic ejection murmur, no edema
- Medications: Aspirin 81 mg, atorvastatin 80 mg, HCTZ 25 mg, lisinopril 40 mg, metformin 1 g twice daily, empagliflozin 10 mg daily
- Labs:
  - Total cholesterol: 145 mg/dL
  - LDL-C: 60 mg/dL
  - HDL: 50 mg/dL
  - TG: 185 mg/dL
  - HbA1c: 6.1%

# CASE PRESENTATION– WHAT DO YOU DO NEXT?

A. No changes, lipids look good!
B. Add ezetimibe
C. Add fenofibrate
D. Add icosapent ethyl
E. Switch from atorvastatin 80 mg to rosuvastatin 40 mg daily
F. Add PCSK9 inhibitor

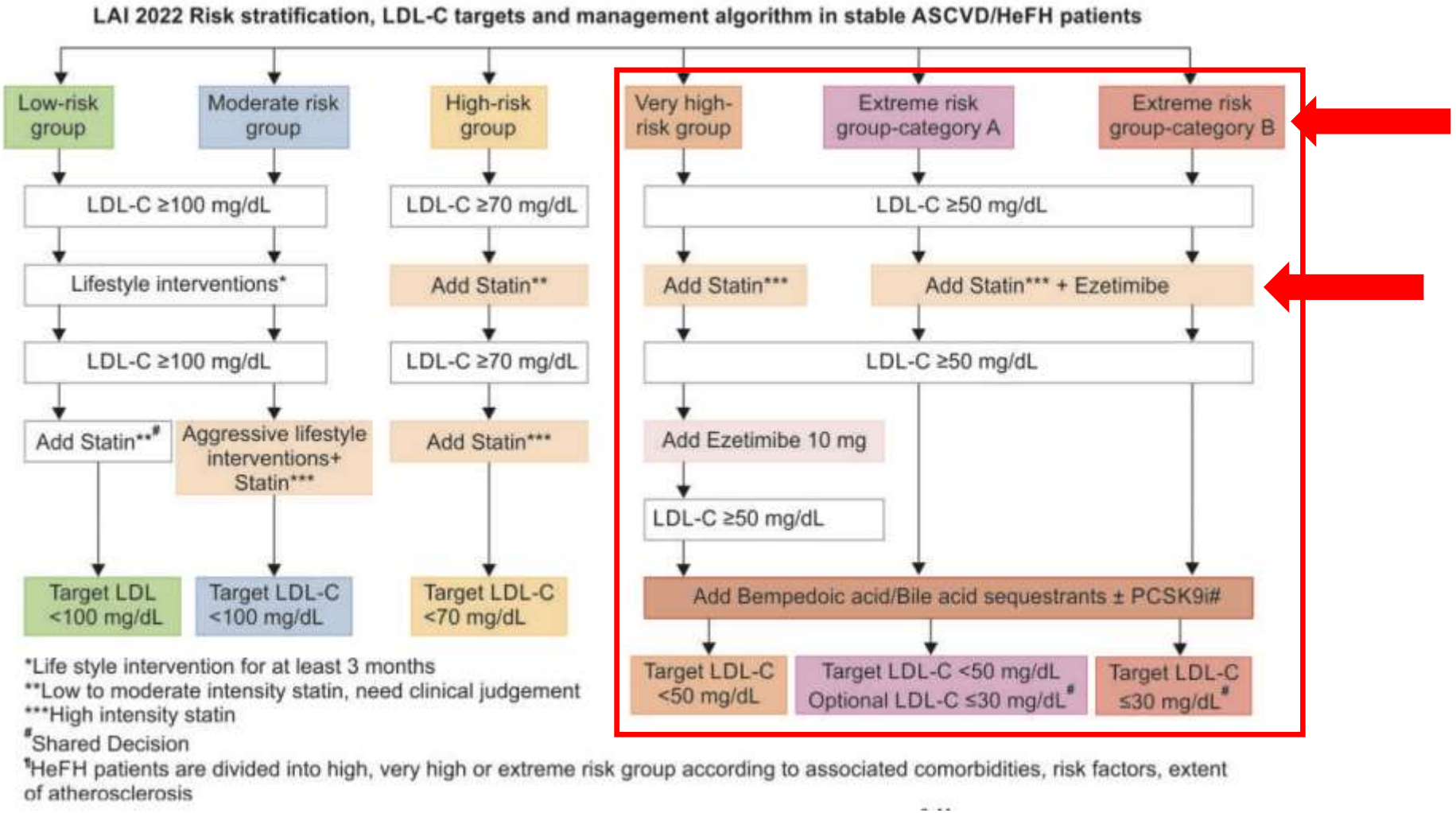
# 2022 A
# STATIN

# NON-




https://doi.org/10.1016/j.jacc.2022.07.006

# 2022 LIPID ASSOCIATION OF INDIA GUIDELINES




J Assoc Physicians India 2022;70:67–75.

# TAKE HOME POINTS

- Cardiovascular disease is the leading cause of death worldwide

- Major blood cholesterol guidelines recommend statin therapy as the primary treatment to reduced ASCVD risk
  - Statins are cheap but underutilized!

- Ezetimibe and PCKS9i (alirocumab and evolocumab) reduce ASCVD events in high risk patients
  - Should be considered 2$^{nd}$ and 3$^{rd}$ line treatments to achieve LDL targets

# TAKE HOME POINTS

- Bempedoic acid (approved in India) and inclisiran are approved in the US to achieve LDL-C targets in high risk populations, but no outcome data are available

- New targeted therapies against triglyceride-rich lipoproteins and lipoprotein(a), including anti-sense oligonucleotides and si-RNAs, are in various stages of development
  - Cost and access to therapies will be key challenges

- Vaccines and gene-editing technologies are in development

# THANKS!

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