The Role of Non Statin Therapy for Patient's with Atherosclerotic Cardiovascular Disease

D. Matt Wilkett DO FACOI, FACC

Oklahoma State University Center for Health Sciences

Department of Internal Medicine

Division of Cardiovascular Medicine

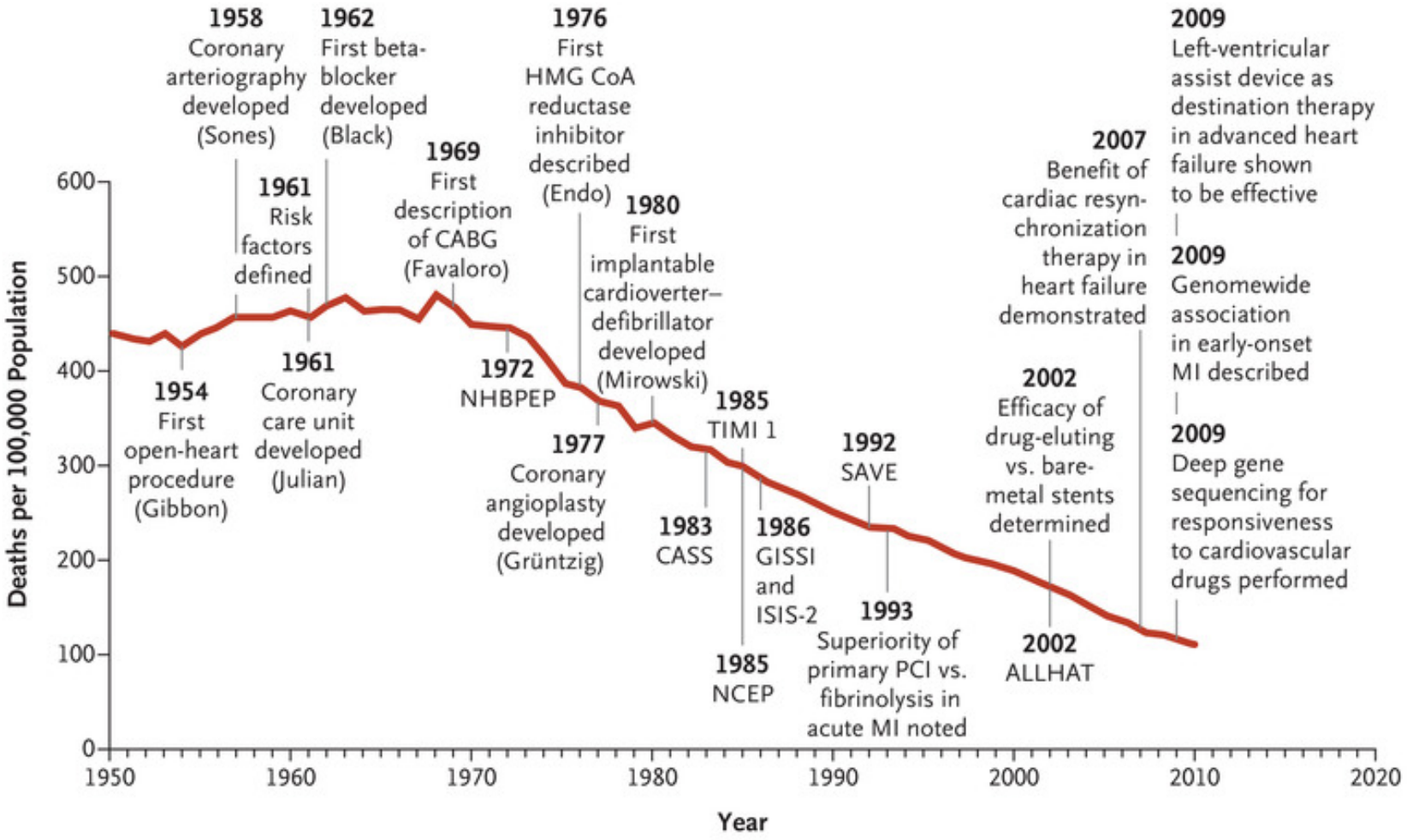
Conflict of Interest

- There are no Conflict of Interest

Objective

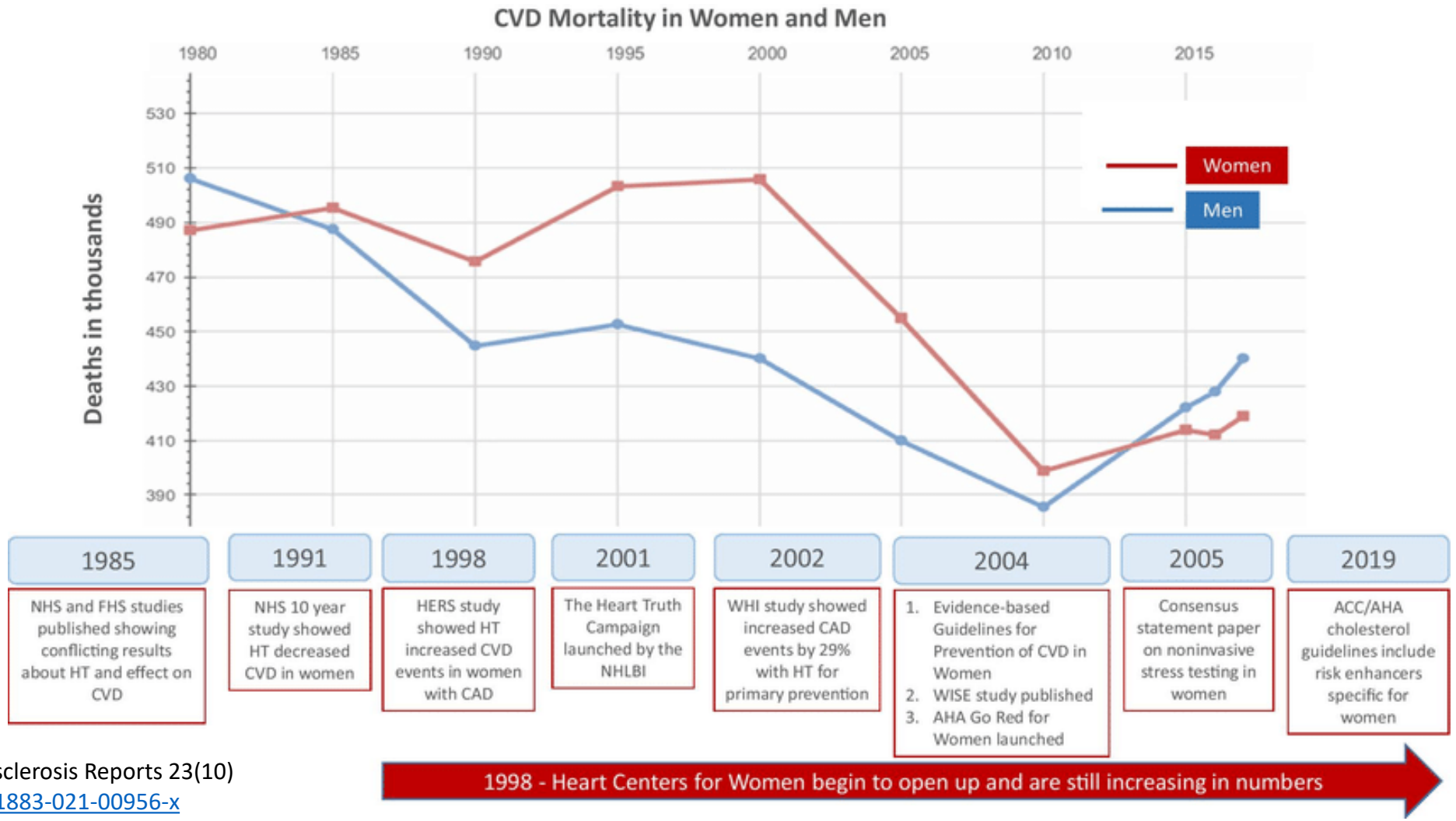
- Burden of Cardiovascular Disease
- Identifying Patients and assessing risk of Cardiovascular events
- Understanding non statin medications in the patient with ASCVD.
- Understanding the Pathway of the use of Non Statin therapies in the ASCVD patient.

Cardiovascular Burden



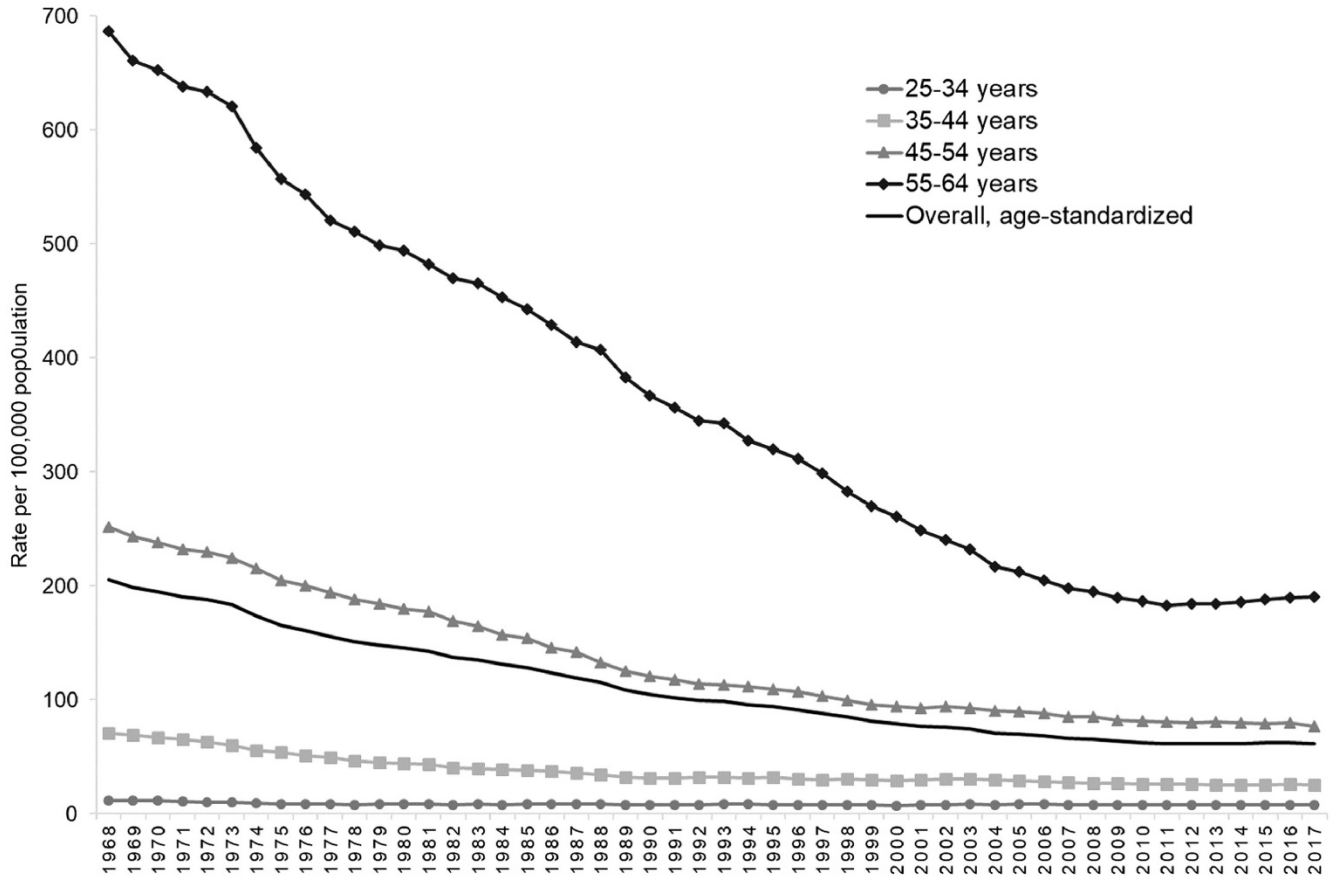
N Engl J Med 2012; 366:54-63
DOI: 10.1056/NEJMra1112570

Cardiovascular Burden



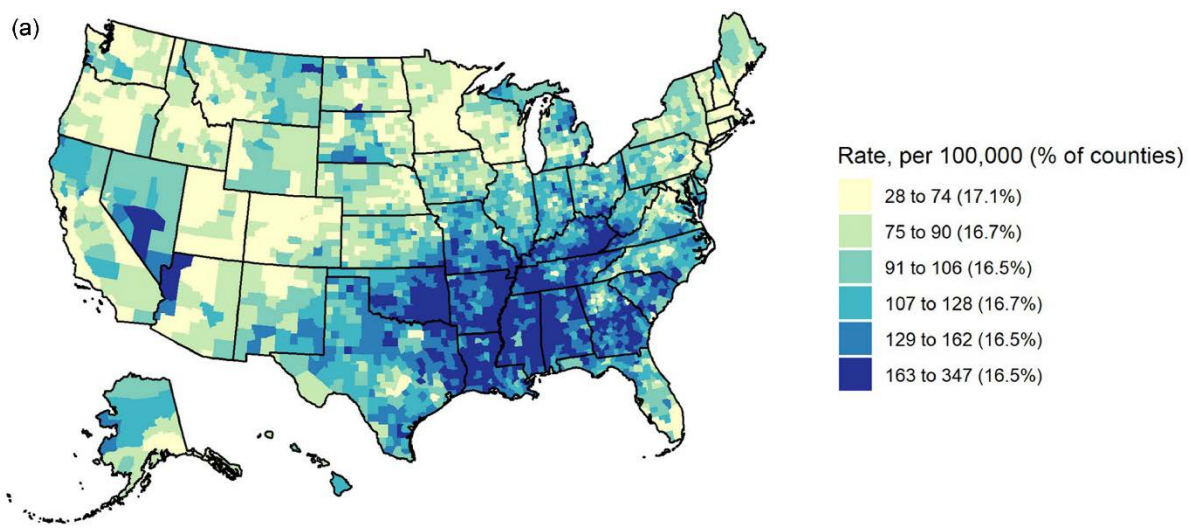
•October 2021
•Current Atherosclerosis Reports 23(10)
DOI:10.1007/s11883-021-00956-x

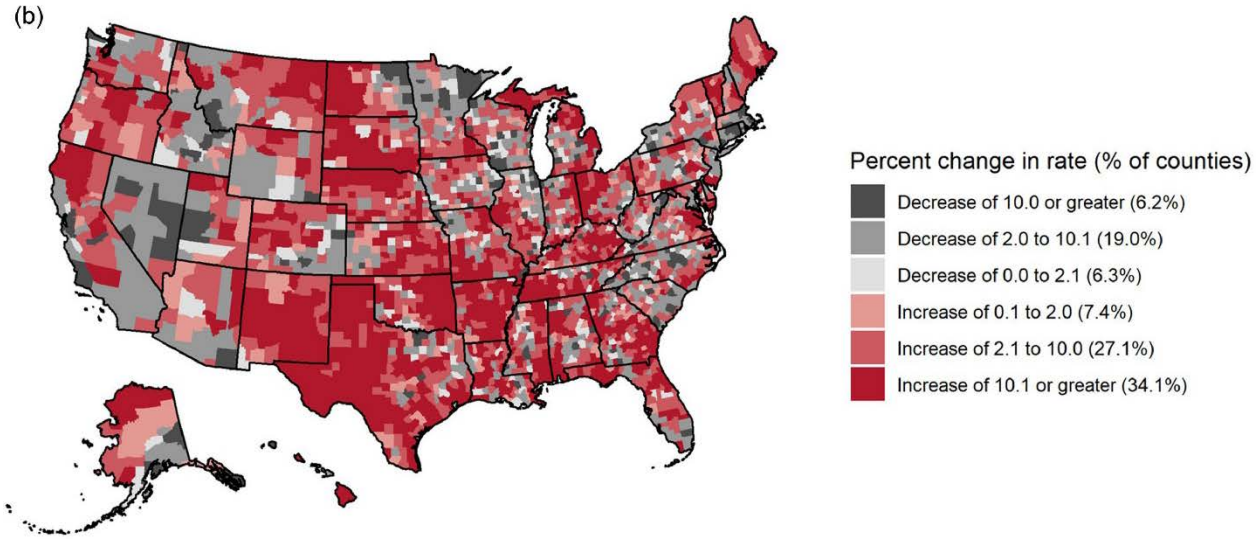
Age-standardized overall and age-specific premature heart disease mortality rates* among adults aged 25–64 years, 1968–2017.



Trends in Cardiovascular Medicine
Volume 30, Issue 6, August 2020, Pages 364-374

County-level heart disease mortality rates in 2017 (a) and percent change in heart disease mortality rates from 2010 to 2017 (b) among US adults aged 35 to 64 years.





Ann Epidemiol, 27 (12) (2017), pp. 796-800

ANALYSIS OF

Heart Disease

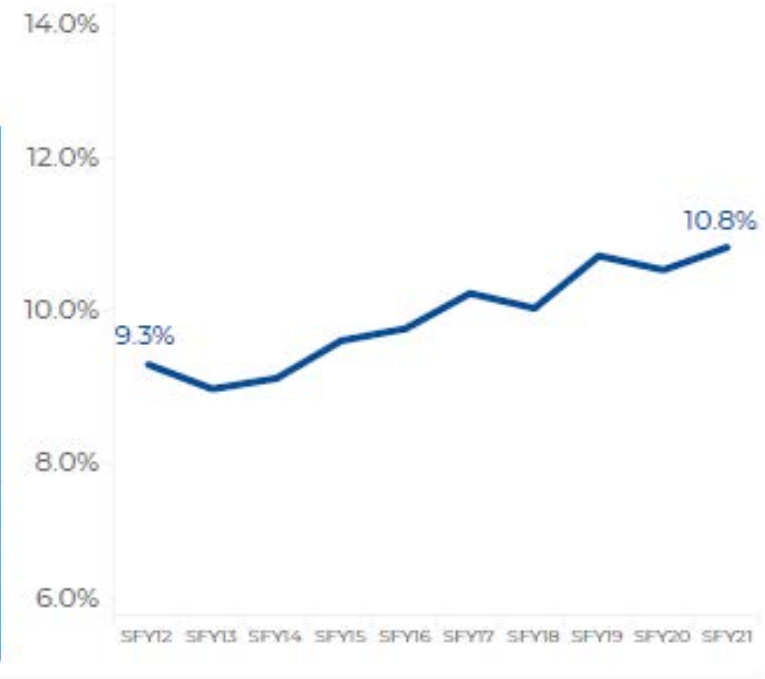
in Oklahoma's SoonerCare Program

OKLAHOMA Health Care Authority

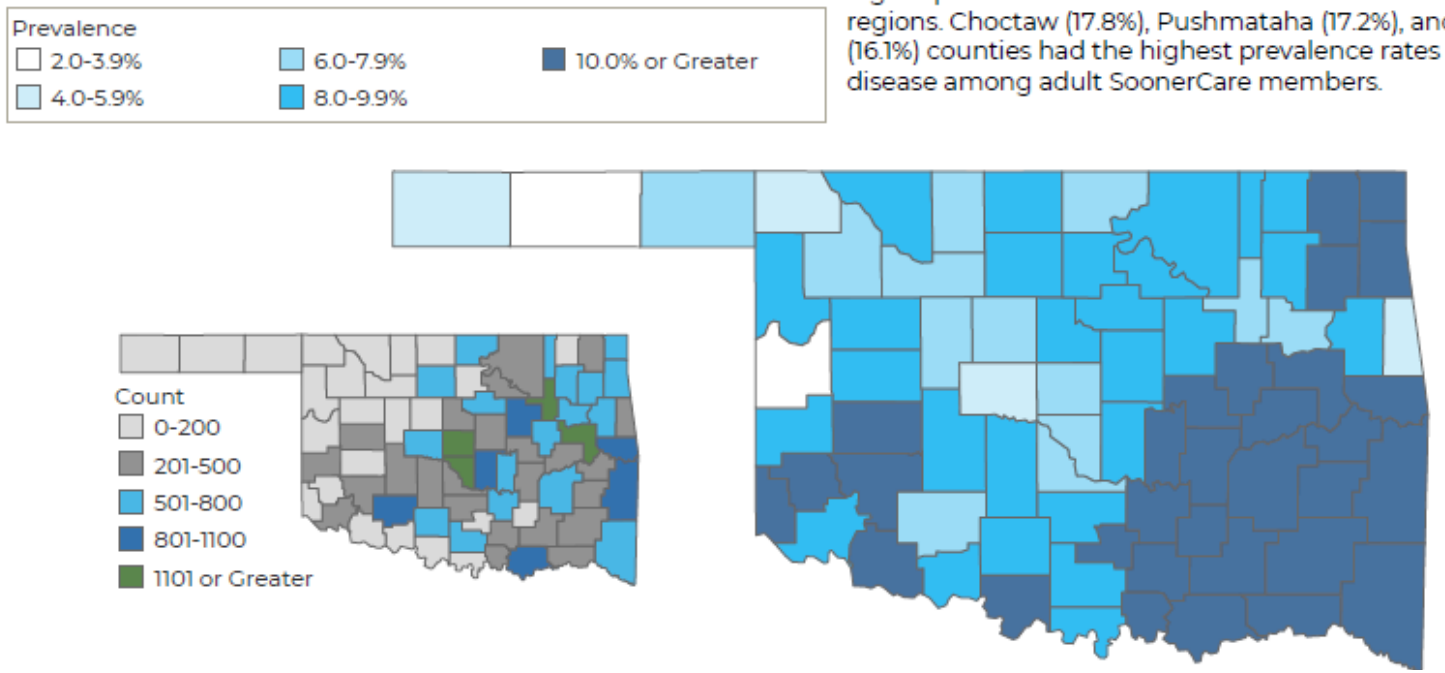
In SFY2021 there were

43,718 adult members with heart disease, or 10.8% of all adult members

Prevalence Rates of Heart Disease Among Adults
SFY2012 - SFY2021



Prevalence Rates



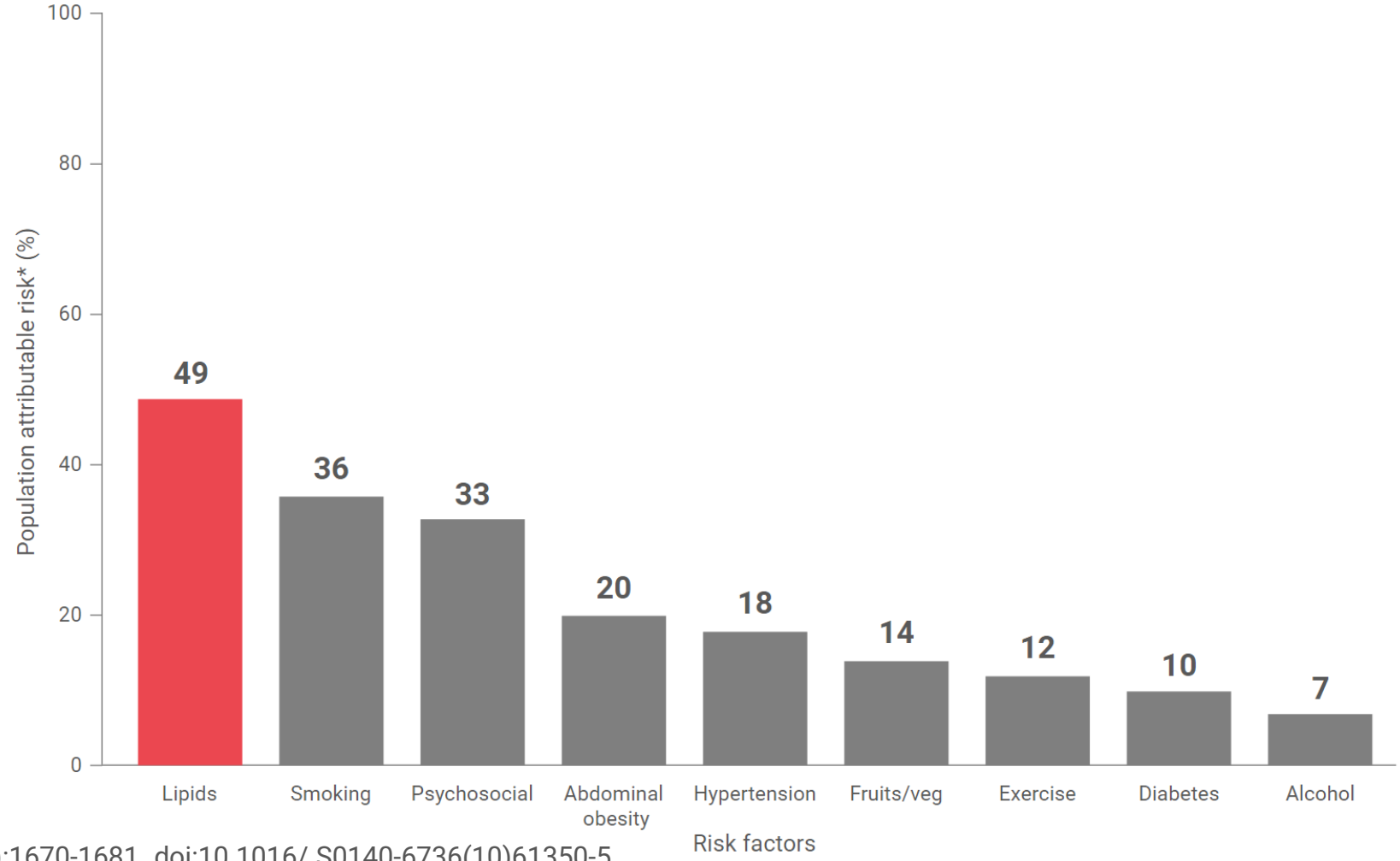
Counties in the southeastern region of the state had higher prevalence rates of heart disease than other regions. Choctaw (17.8%), Pushmataha (17.2%), and Kiowa (16.1%) counties had the highest prevalence rates of heart disease among adult SoonerCare members.

https://oklahoma.gov/content/dam/ok/en/okhca/docs/research/chronic-condition-executive-summaries/2023/22-11-16%20-%20Heart%20Disease%20Fully%20Branded.pdf

Highlights of Cardiovascular Disease Burden

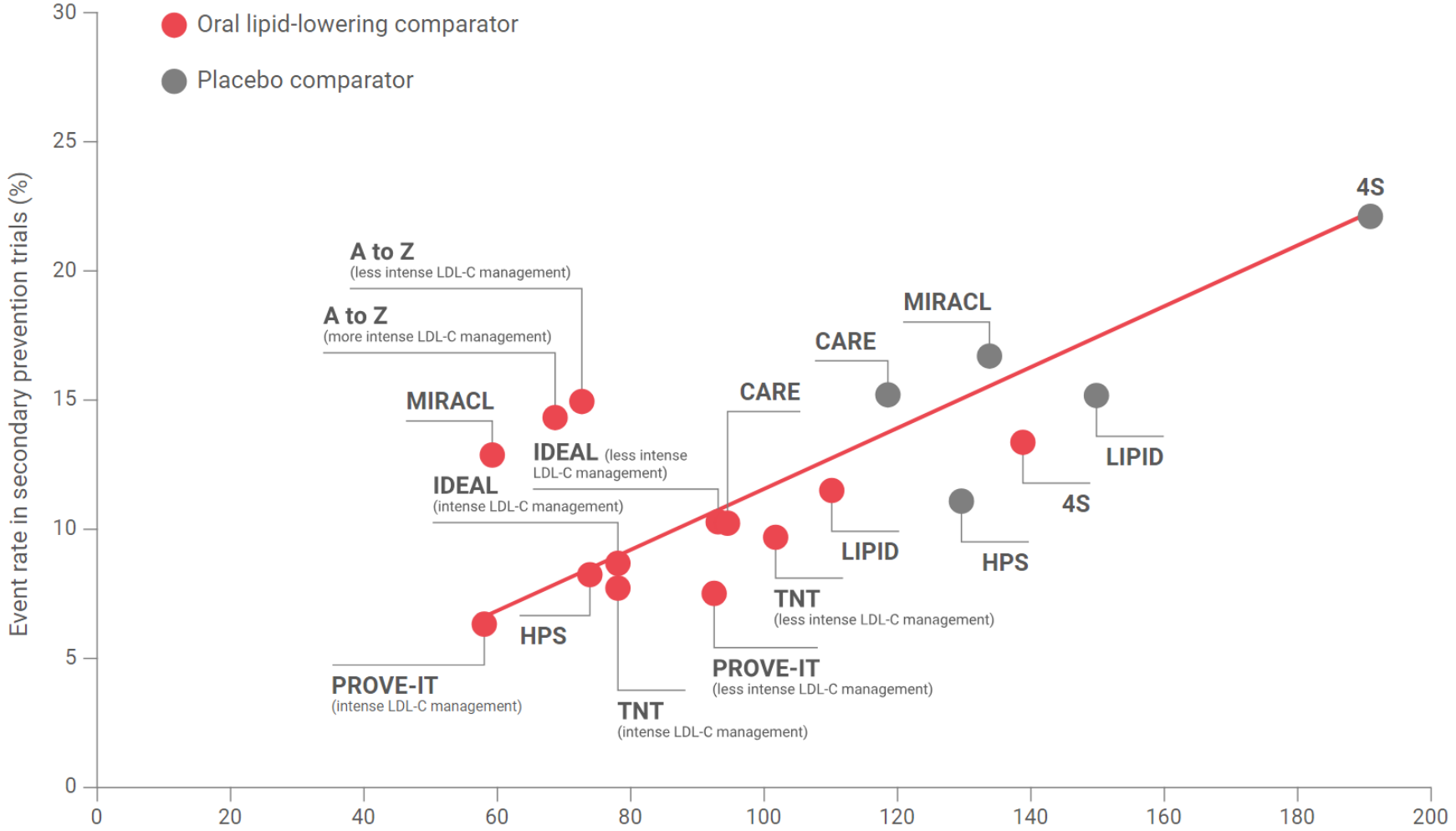
- ASCVD in general population has improved since 1960's but has flattened or risen over the last several years.
- There is a difference in ASCVD burden in Male Population with regards to the Female Population with regards to recognition of event rates and death.
- Oklahoma's ASCVD burden continues to be high and is presence in at least 10% of the Sooner Care population. Predominately in the rural Oklahoma.

Cardiovascular Risk factors and Population Attributable Risk



Lancet. 2010;376(9753):1670-1681. doi:10.1016/ S0140-6736(10)61350-5.

LDL lowering with proportion to reduction in CHD Risk



Am Heart J. 2001; **141**: 711-721

Inflammatory Markers and Associated Event rates for participants in the Fourier Trial

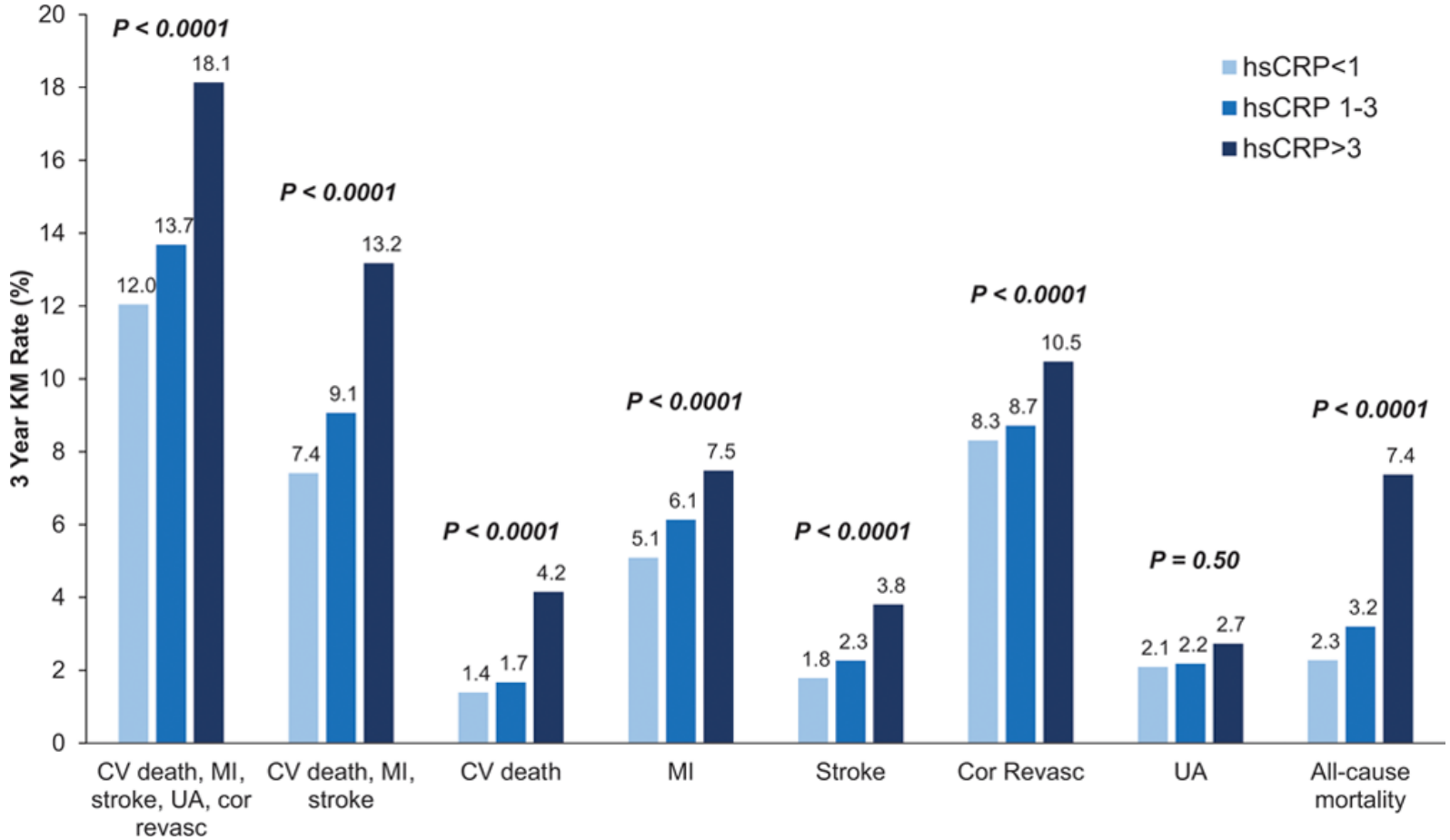
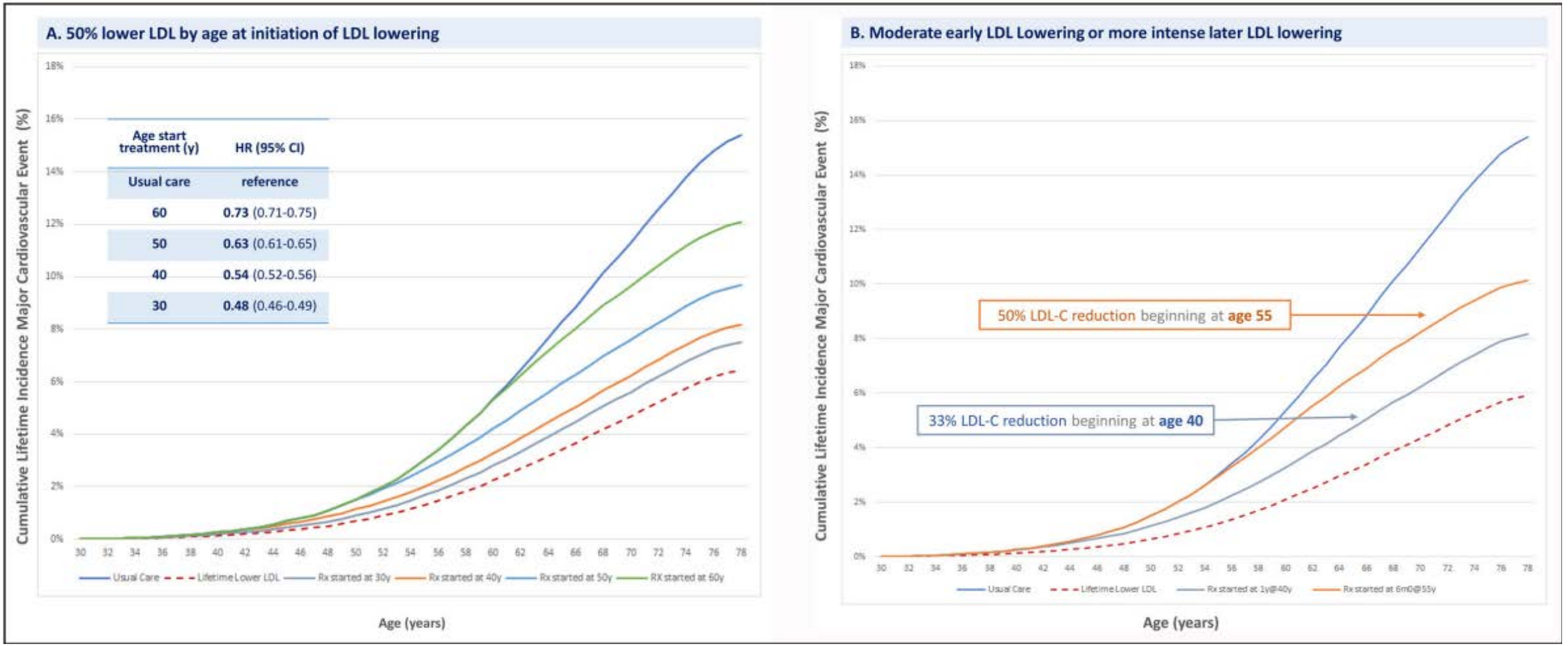


Figure 1. Gradient of cardiovascular risk by baseline hsCRP in the placebo arm. Three-year Kaplan-Meier event rates stratified by low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L) baseline hsCRP in subjects randomly assigned to placebo. The *P* value for trend across hsCRP subgroups is shown. Cor Revasc indicates coronary revascularization; CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; KM, Kaplan-Meier; MI, myocardial infarction; and UA, hospitalization for unstable angina.

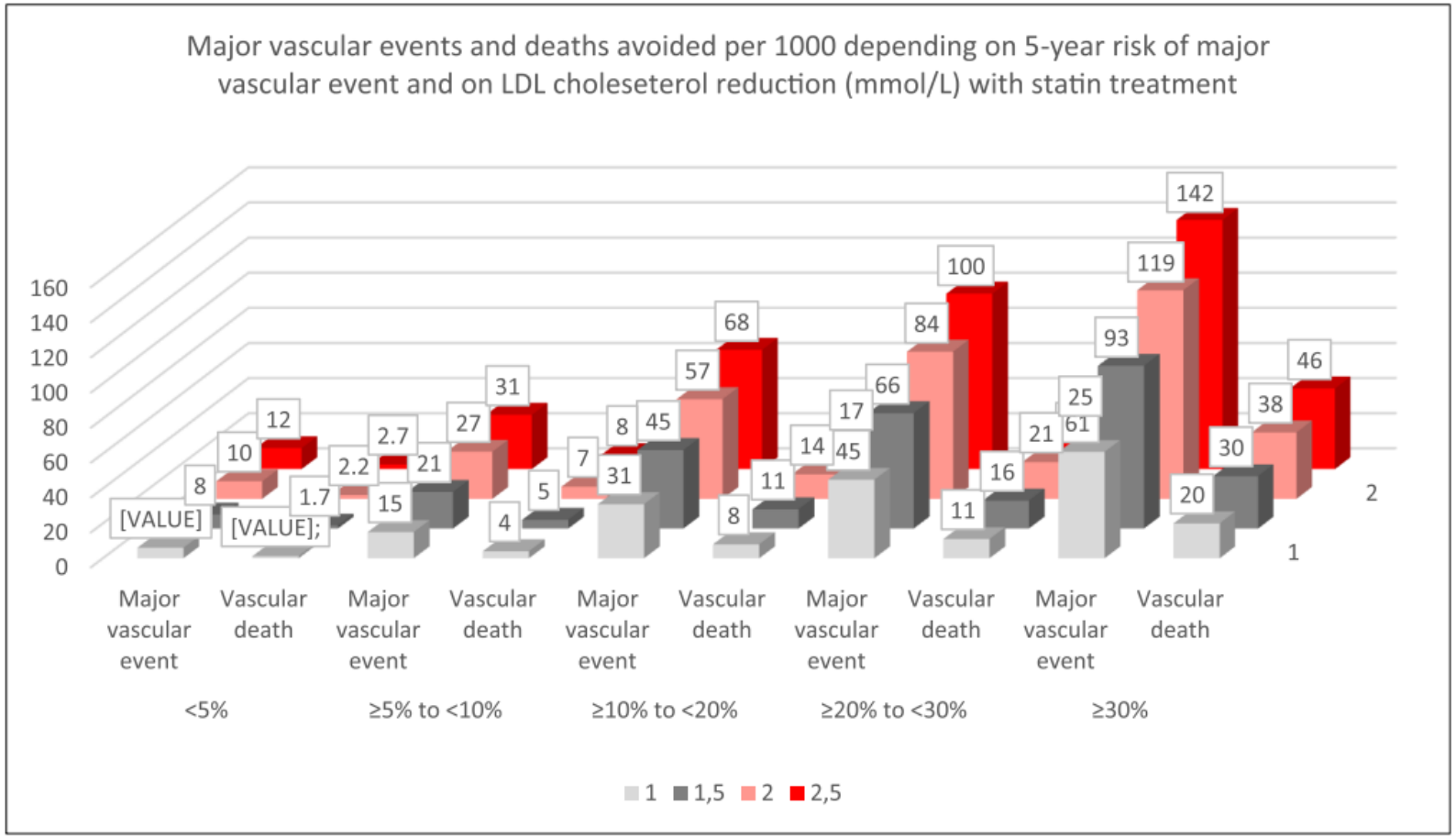
Circulation. 2018;138:131–140



Benefit of reducing cumulative exposure to LDL on the lifetime risk of atherosclerotic cardiovascular disease. Panel A shows the effect of reducing LDL by 50% from a population median of 3.5 mmol/L (135 mg/dl) resulting in an absolute difference of 1.75 mmol/L (67.7 mg/dL) on the lifetime risk of experiencing a major atherosclerotic cardiovascular event (defined as fatal or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or coronary revascularization) if LDL lowering is started at ages 30, 40, 50 or 60 years and continued up to age 80 years as compared to either no LDL reduction of lifelong exposure to the same magnitude of lower LDL. Panel B shows the effect on the lifetime risk of experiencing a major atherosclerotic cardiovascular event up to age 80 years from reducing LDL by 33% beginning at age 40 years, or by 50% beginning at age 55 years. Greater benefits are observed if LDL-C lowering is begun at an earlier age.

•October 2022
•Global Heart 17(1):75
DOI:10.5334/gh.1154

Major CV Events and Deaths avoided per 1000 depending of 5 year risk and on LDL reduction with statin therapy.



•October 2022
•Global Heart 17(1):75
DOI:10.5334/gh.1154

Events avoided based on baseline absolute risk and absolute lowering of LDL-C (Duality of risk and LDL-C lowering as determinants of benefit from lipid lowering therapies).

Criteria for a Very High Risk of Future ASCVD Events

Very High Risk of Future ASCVD Events

Major ASCVD Events
Recent ACS (within past 12 months)
History of MI (other than recent ACS)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior CABG or PCI outside of the major ASCVD event
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
History of congestive heart failure

ABI, ankle-brachial index; ACS, acute coronary syndrome;
ASCVD, atherosclerotic cardiovascular disease;
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate;
MI, myocardial infarction; PAD, peripheral artery disease.

https://www.acc.org/latest-in-cardiology/articles/2018/12/10/14/42/new-acc-aha-cholesterol-guideline-personalized-patient-centered-care-new-treatment-options

Continuum of Atherosclerotic Cardiovascular Disease Risk

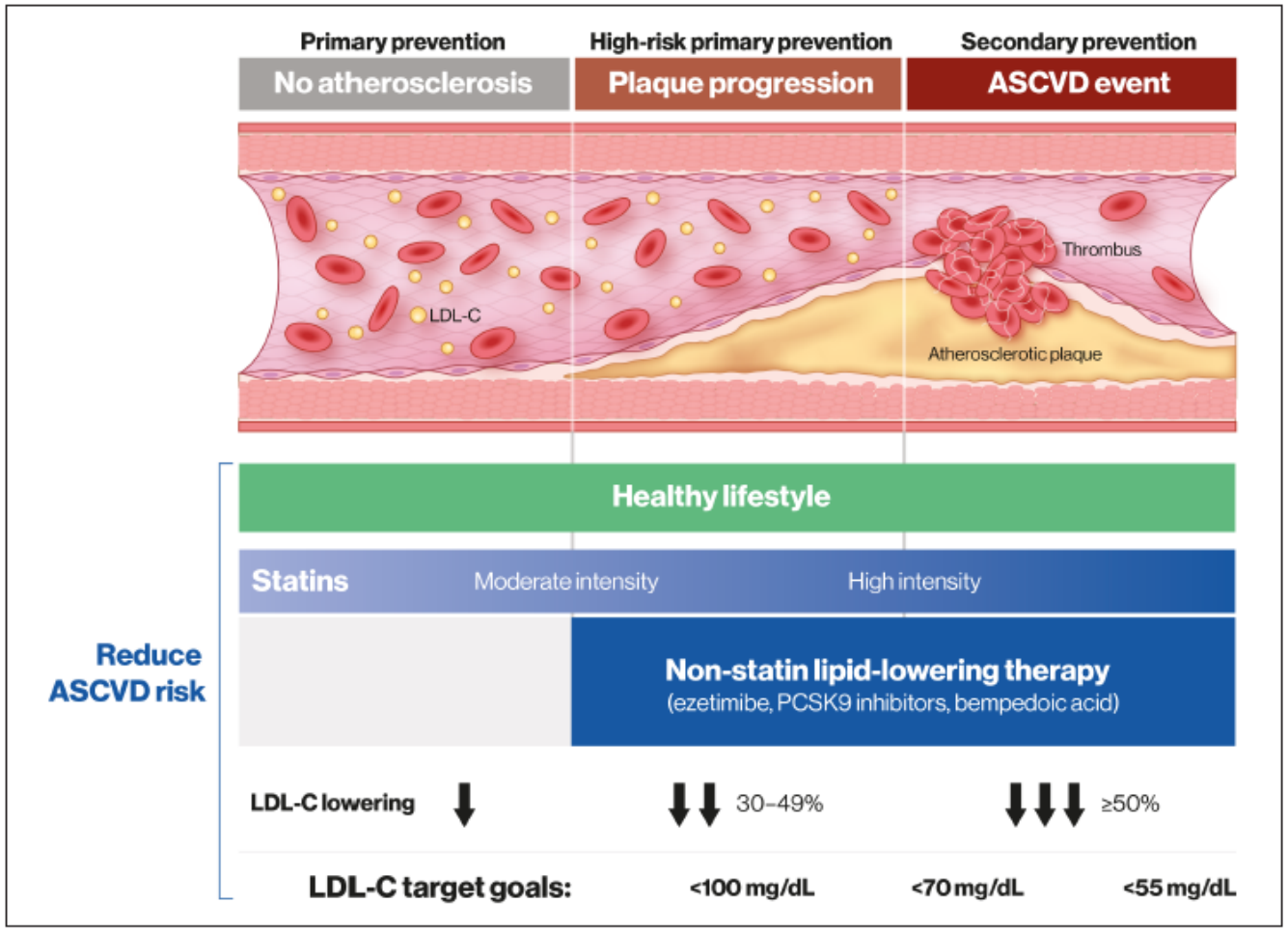


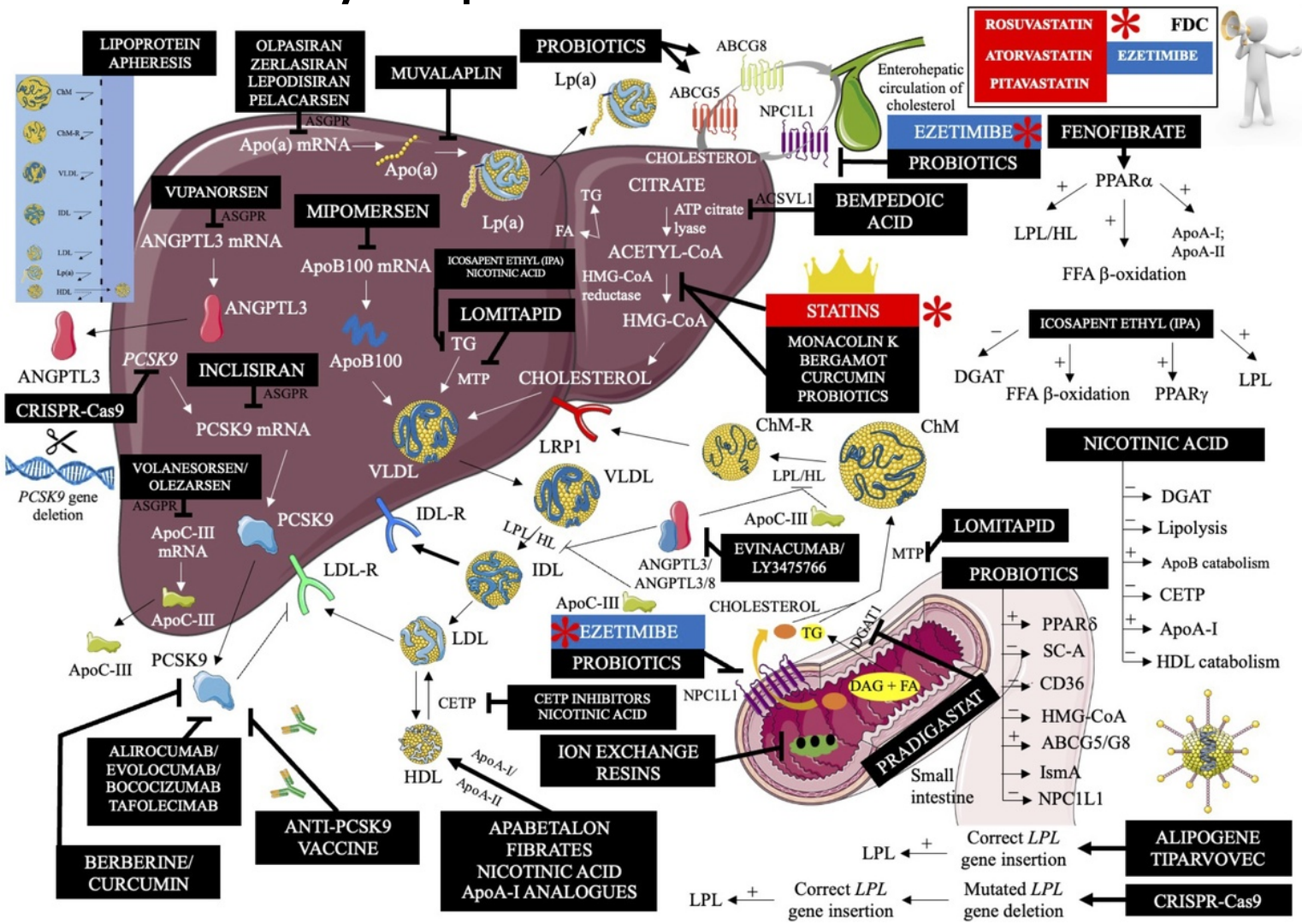
Figure 4. The continuum of atherosclerotic cardiovascular disease (ASCVD) risk.
Management of low-density lipoprotein cholesterol (LDL-C) levels across the continuum of ASCVD risk to prevent first and subsequent cardiovascular events. PCSK9 indicates proprotein convertase subtilisin/kexin type 9.

J Am Heart Assoc. 2023;12:eJAHA/2022/028892. DOI: 10.1161/JAHA.122.028892

Summary of Patient with ASCVD

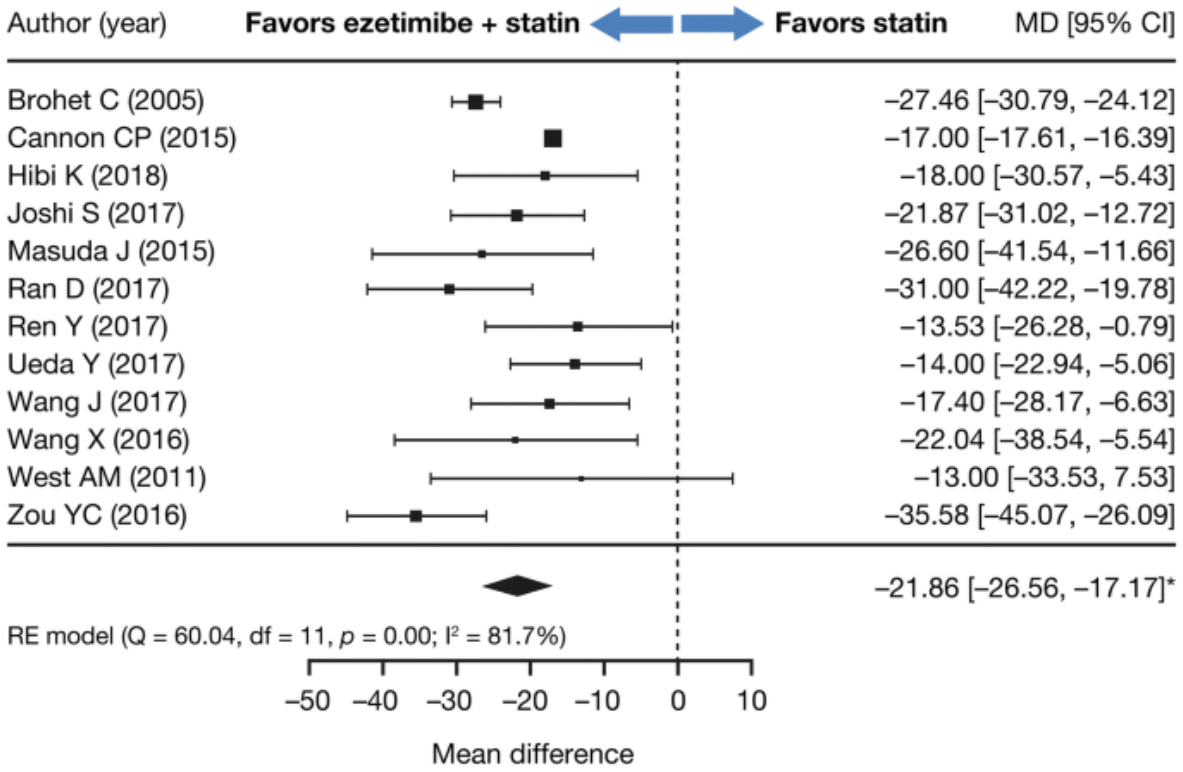
- Stay on statin if possible for reduction of coronary inflammation
- Patient with ASCVD or elevated LDL enjoy better outcomes with early LDL intervention.
- Higher the risk for future events enjoys better outcomes with aggressive LDL lowering therapy
- Understand the criteria for a very high risk ASCVD Patient
- Where is your patient on the Continuum of ASCVD disease. This will delineate a decision pathway and aggressiveness of LDL reduction

Treatment of Dyslipidemia

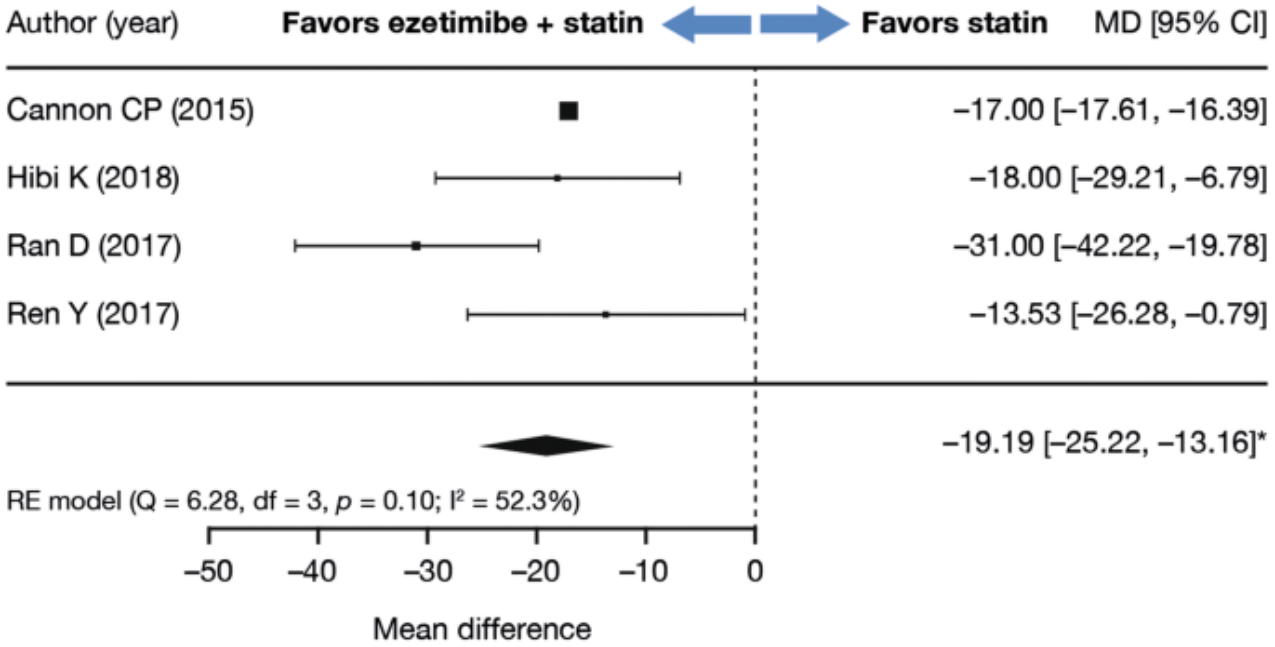


https://doi.org/10.5114/aoms/174743

Lipid-Lowering Efficacy of Ezetimibe in Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analyses



Treatment difference in mean LDL-C change (mg/dL) from baseline between combination ezetimibe plus statin therapy and statin monotherapy comparator at 6 months or at the reported timepoint closest to 6 months. [a]Meta-analysis included 19,404 participants from 12 studies, who received treatment (ezetimibe + statin vs. statin) for a mean duration of 11.56 months. *$p < 0.0001$. *CI* confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects



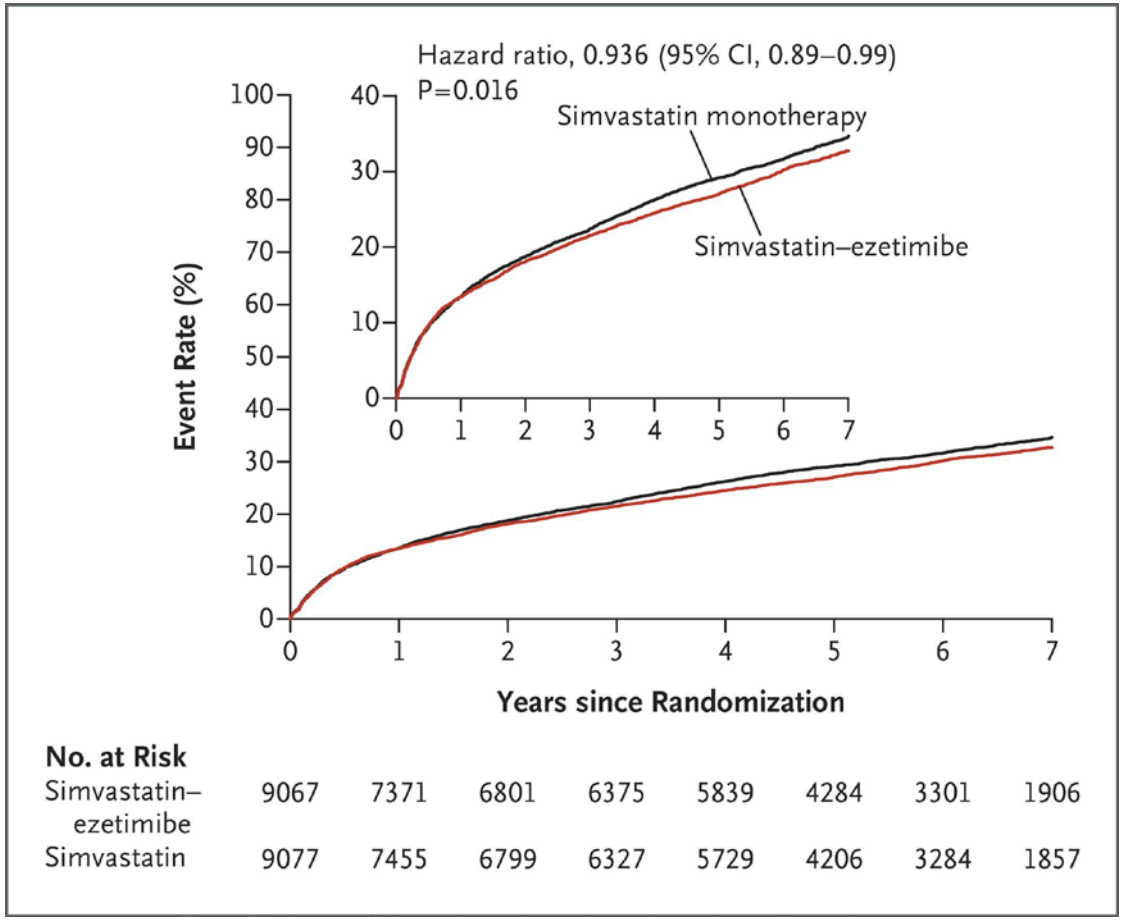
Subgroup analysis: LDL-C change (mg/dL) from baseline at 6 months, or at the reported timepoint closest to 6 months, limited to studies including patients with recent acute (< 1 year) coronary syndrome (Meta-analysis included 18,436 participants from four studies, who received treatment [ezetimibe plus statin vs. statin] for a mean duration of 11.90 months). *$p < 0.0001$. *CI* confidence interval, *LDL-C* low-density lipoprotein cholesterol, *MD* mean difference, *RE* random effects

https://doi.org/10.1007/s40256-019-00379-9

Ezetimibe Added to Statin Therapy after Acute Coronary Syndrome (IMPROVE-IT)

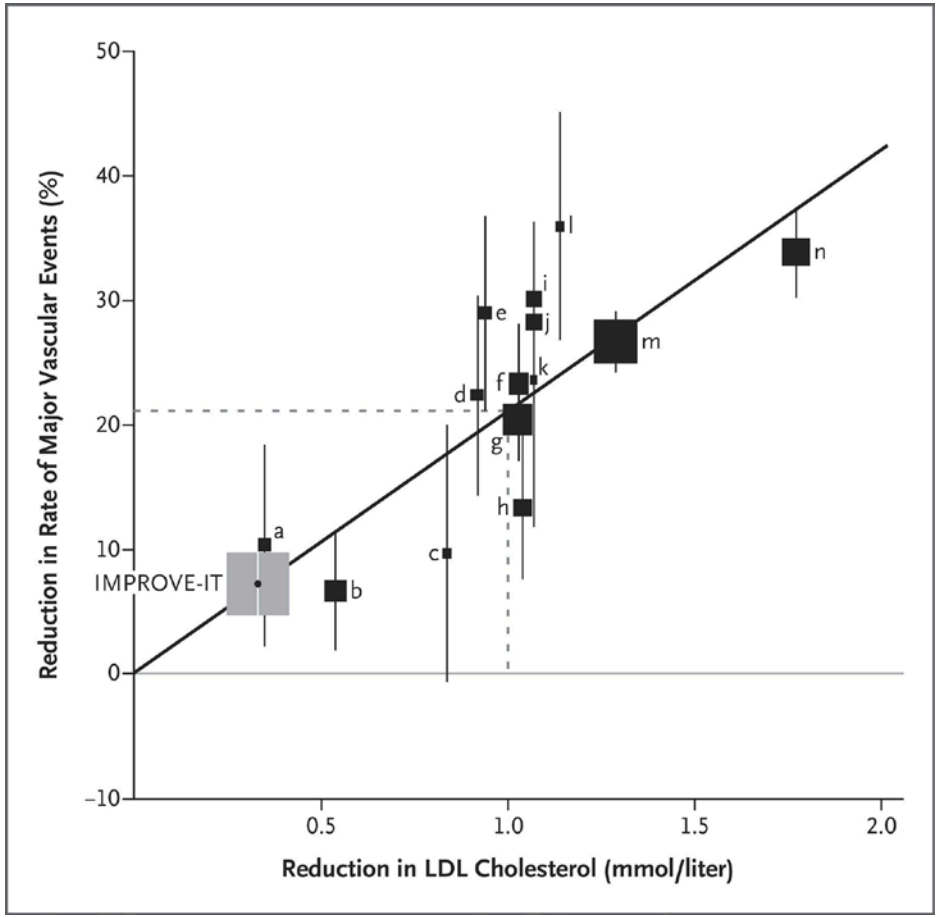
- In this trial, patients with an acute coronary syndrome within the previous 10 days were randomly assigned to simvastatin plus either ezetimibe or placebo.
- At a median of 6 years, the rate of cardiovascular events was modestly but significantly lower with simvastatin–ezetimibe.

Kaplan–Meier Curves for the Primary Efficacy End Point



Cannon CP et al. N Engl J Med 2015;372:2387-2397

Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.



Cannon CP et al. N Engl J Med 2015;372:2387-2397

Table 1. Baseline Characteristics.*

Variable	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)
Demographic characteristic		
Age — yr	63.6±9.8	63.6±9.7
Male — no. (%)	6886 (75.9)	6842 (75.5)
White race — no. (%)†	7624 (84.0)	7578 (83.6)
Weight — kg	83.0±17.4	82.9±17.4
Body-mass index‡	28.3±5.2	28.3±5.2
Region — no. (%)		
North America	3487 (38.4)	3486 (38.4)
Western Europe	3641 (40.1)	3633 (40.1)
Eastern Europe	707 (7.8)	709 (7.8)
Asia Pacific	448 (4.9)	448 (4.9)
South America	794 (8.7)	791 (8.7)
Coexisting conditions — no./total no. (%)		
Diabetes	2474/9077 (27.3)	2459/9067 (27.1)
Hypertension	5557/9072 (61.3)	5580/9063 (61.6)
Congestive heart failure	371/9077 (4.1)	419/9067 (4.6)
Peripheral arterial disease	518/9077 (5.7)	487/9067 (5.4)
Current smoker — no./total no. (%)	3035/9072 (33.5)	2943/9067 (32.5)
Previous MI — no./total no. (%)	1881/9077 (20.7)	1925/9054 (21.3)
Previous PCI — no. (%)	1796 (19.8)	1766 (19.5)
Previous CABG — no. (%)	842 (9.3)	842 (9.3)
Before index ACS		
Medications — no./total no. (%)		
Lipid-lowering agent	3207/9063 (35.4)	3227/9067 (35.6)
Statin	3111/9077 (34.3)	3135/9067 (34.6)
Aspirin	3855/9077 (42.5)	3799/9067 (41.9)
Creatinine clearance — ml/min		
Median	84.7	84.4
Interquartile range	65.8–107.4	65.8–106.5
At index event		
Type of event — no./total no. (%)		
MI with ST-segment elevation	2606/9077 (28.7)	2584/9067 (28.5)
MI without ST-segment elevation	4253/9077 (46.9)	4302/9061 (47.5)
Unstable angina	2211/9077 (24.4)	2175/9067 (24.0)
Diagnostic catheterization — no./total no. (%)	7936/9069 (87.5)	7988/9059 (88.2)
Prerandomization PCI — no./total no. (%)	6321/9071 (69.7)	6385/9061 (70.5)
Mean LDL cholesterol — mg/dl§	93.8	93.8
Time from ACS to randomization — days		
Median	5.0	5.0
Interquartile range	3.0–8.0	3.0–8.0
Medications at time of randomization — no./total no. (%)		
Aspirin	8794/9077 (96.9)	8798/9063 (97.1)
Thienopyridine	7813/9077 (86.1)	7869/9067 (86.8)
Beta-blocker	7879/9077 (86.8)	7912/9067 (87.3)
ACE inhibitor or ARB	6878/9077 (75.8)	6822/9063 (75.3)

* Plus–minus values are means ±SD. No significant differences were noted between the groups. ACE denotes angiotensin-converting enzyme, ACS acute coronary syndrome, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, LDL low-density lipoprotein, MI myocardial infarction, and PCI percutaneous coronary intervention.
† Race was determined by the investigators.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data on baseline levels were available for 9009 participants in the simvastatin-monotherapy group and for 8990 participants in the simvastatin–ezetimibe group; data on 1-year levels were available for 6939 participants in the simvastatin-monotherapy group and for 6864 participants in the simvastatin–ezetimibe group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Prespecified Safety End Points

Table 3. Prespecified Safety End Points.*

End Point	Simvastatin Monotherapy (N = 9077)	Simvastatin–Ezetimibe (N = 9067)	P Value
	no. of patients (%)		
ALT, AST, or both ≥3× ULN	208 (2.3)	224 (2.5)	0.43
Cholecystectomy	134 (1.5)	133 (1.5)	0.96
Gallbladder-related adverse events	321 (3.5)	281 (3.1)	0.10
Rhabdomyolysis	18 (0.2)	13 (0.1)	0.37
Myopathy	10 (0.1)	15 (0.2)	0.32
Rhabdomyolysis or myopathy	28 (0.3)	27 (0.3)	0.90
Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5× ULN	58 (0.6)	53 (0.6)	0.64
Cancer†	732 (10.2)	748 (10.2)	0.57
Death from cancer†	272 (3.6)	280 (3.8)	0.71

* Adverse events were assessed in the intention-to-treat population. The database for the analysis presented here was locked on October 21, 2014. All muscle and cancer events were adjudicated by a clinical events committee, whose members were unaware of the study-group assignments. Detailed definitions of the adverse events are provided in the Supplementary Appendix. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† Percentages for cancer are 7-year Kaplan–Meier estimates. Cancer includes any new, relapsing, or progressing cancer, excluding nonmelanoma skin cancer. Death from cancer includes death from nonmelanoma skin cancer.

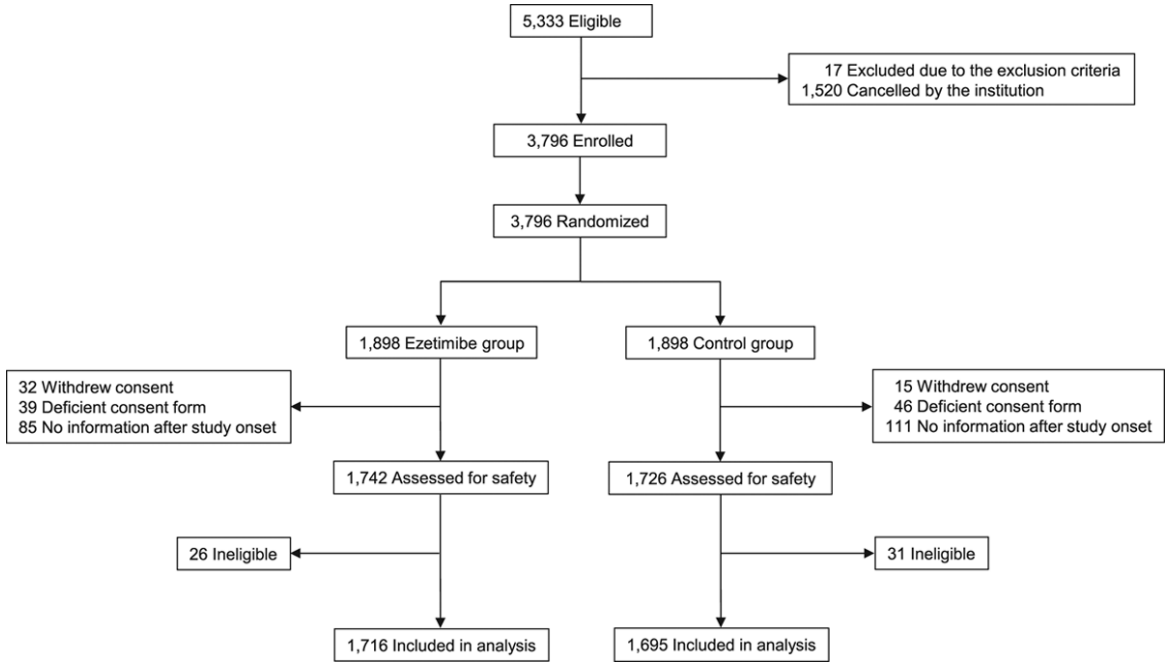
Cannon CP et al. N Engl J Med 2015;372:2387-2397

Conclusions

- When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes.
- Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit.

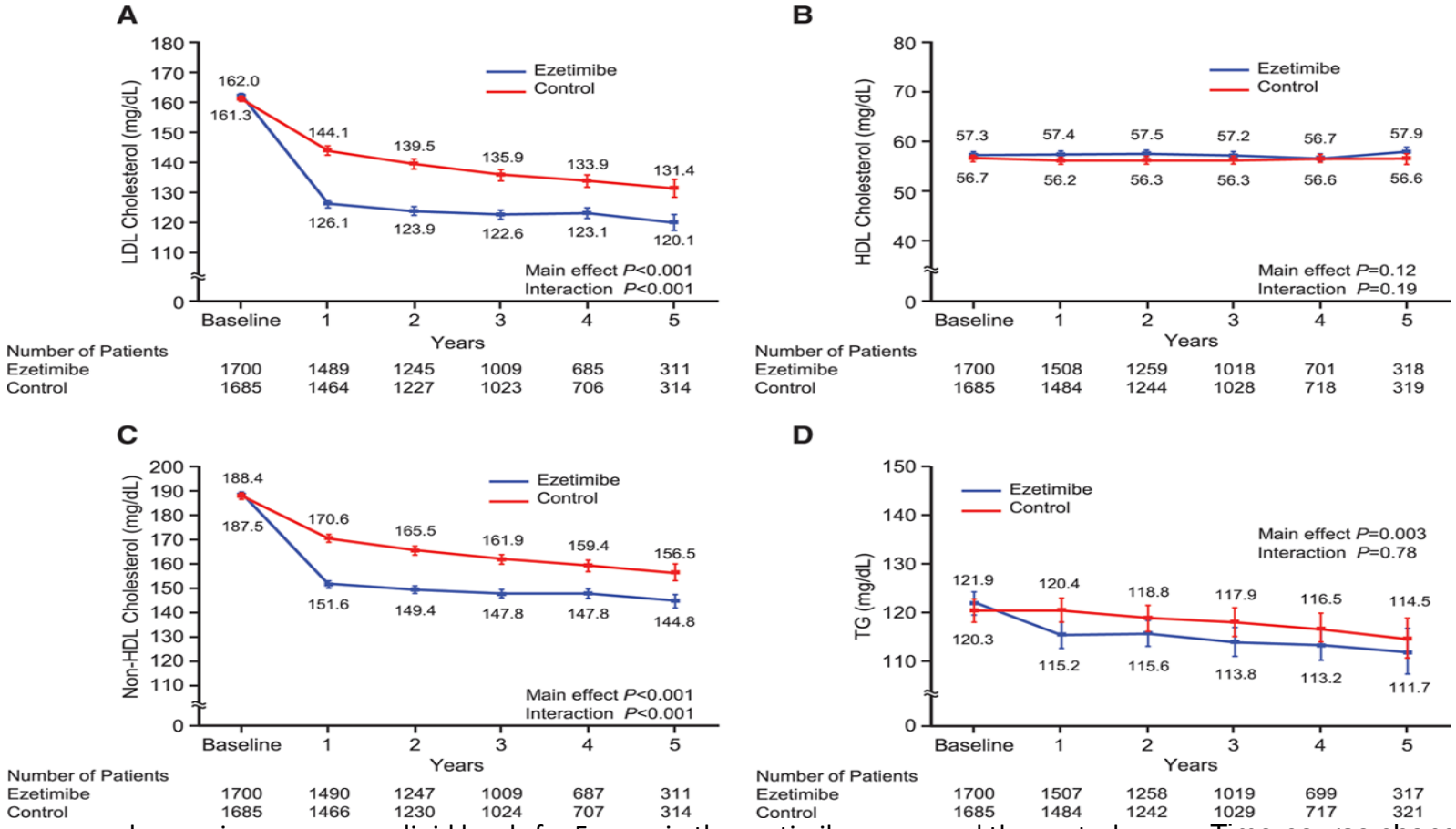
Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75)

- Multicenter, prospective, randomized, open-label, blinded end-point evaluation conducted at 363 medical institutions in Japan examined the preventive efficacy of ezetimibe for patients aged ≥75 years, with elevated LDL-C without history of coronary artery disease
- The primary outcome was a composite of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke.



https://doi.org/10.1161/CIRCULATIONAHA.118.039415

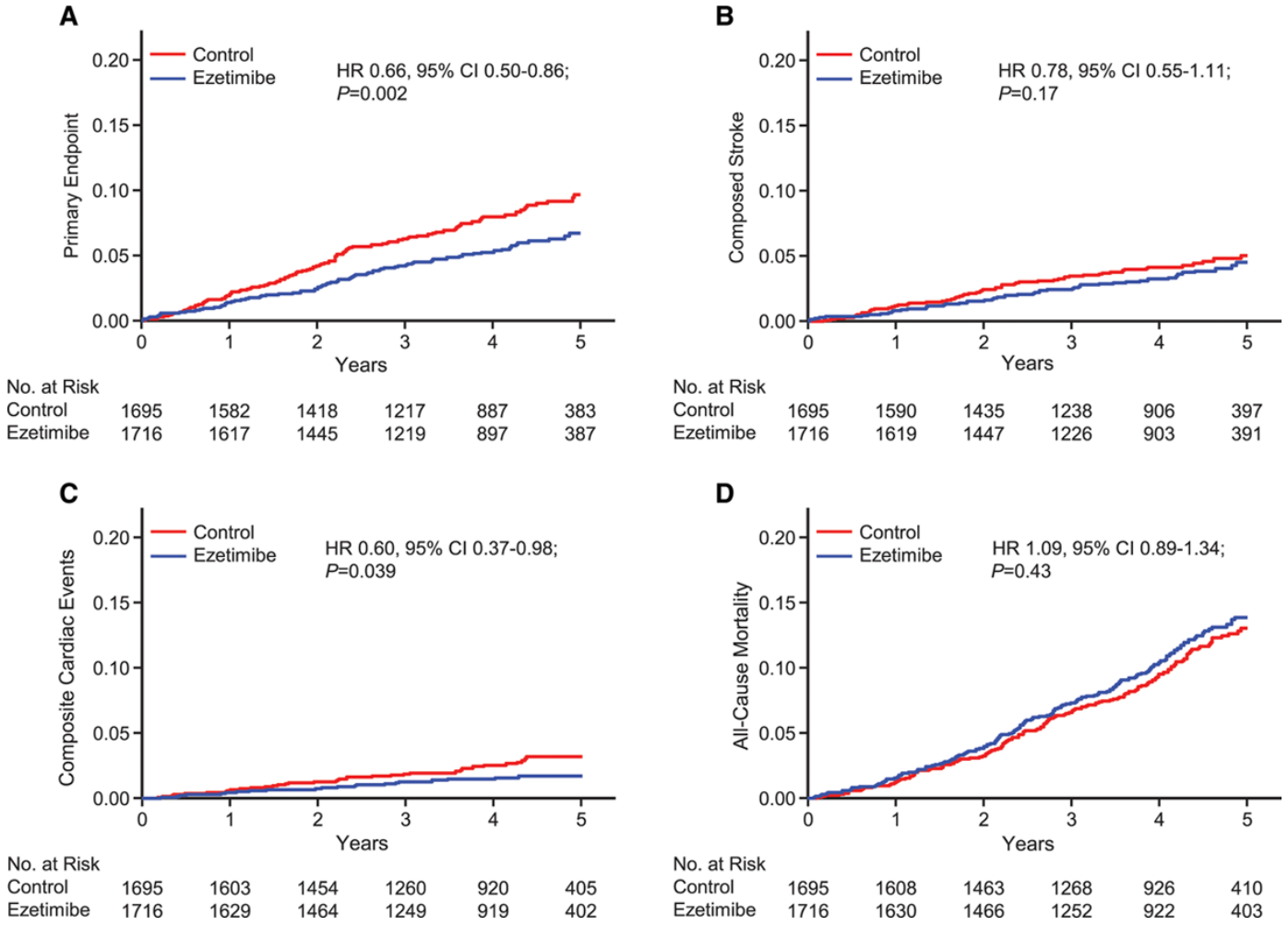
Time Course changes in mean serum lipid level for 5 years in the ezetimibe group and the control group.



https://doi.org/10.1161/CIRCULATIONAHA.118.039415

Time-course changes in mean serum lipid levels for 5 years in the ezetimibe group and the control group. Time-course changes in the serum levels of low-density lipoprotein cholesterol (LDL-C; A), high-density lipoprotein cholesterol (HDL-C; B), non–HDL-C (C), and triglycerides (TG; D) for 5 years after randomization in the ezetimibe group and the control group. LDL-C was calculated according to the Friedewald's formula: LDL-C=TC – (HDL-C + TG/5), and non–HDL-C as total cholesterol minus HDL-C.

Kaplan–Meier estimates of the incidences of outcome events in the ezetimibe group and the control group. A, **Primary outcome.** B, **Composed stroke.** C, **Composite cardiac events.** D, **All-cause mortality.**



https://doi.org/10.1161/CIRCULATIONAHA.118.039415

Conclusion of Ezetimibe

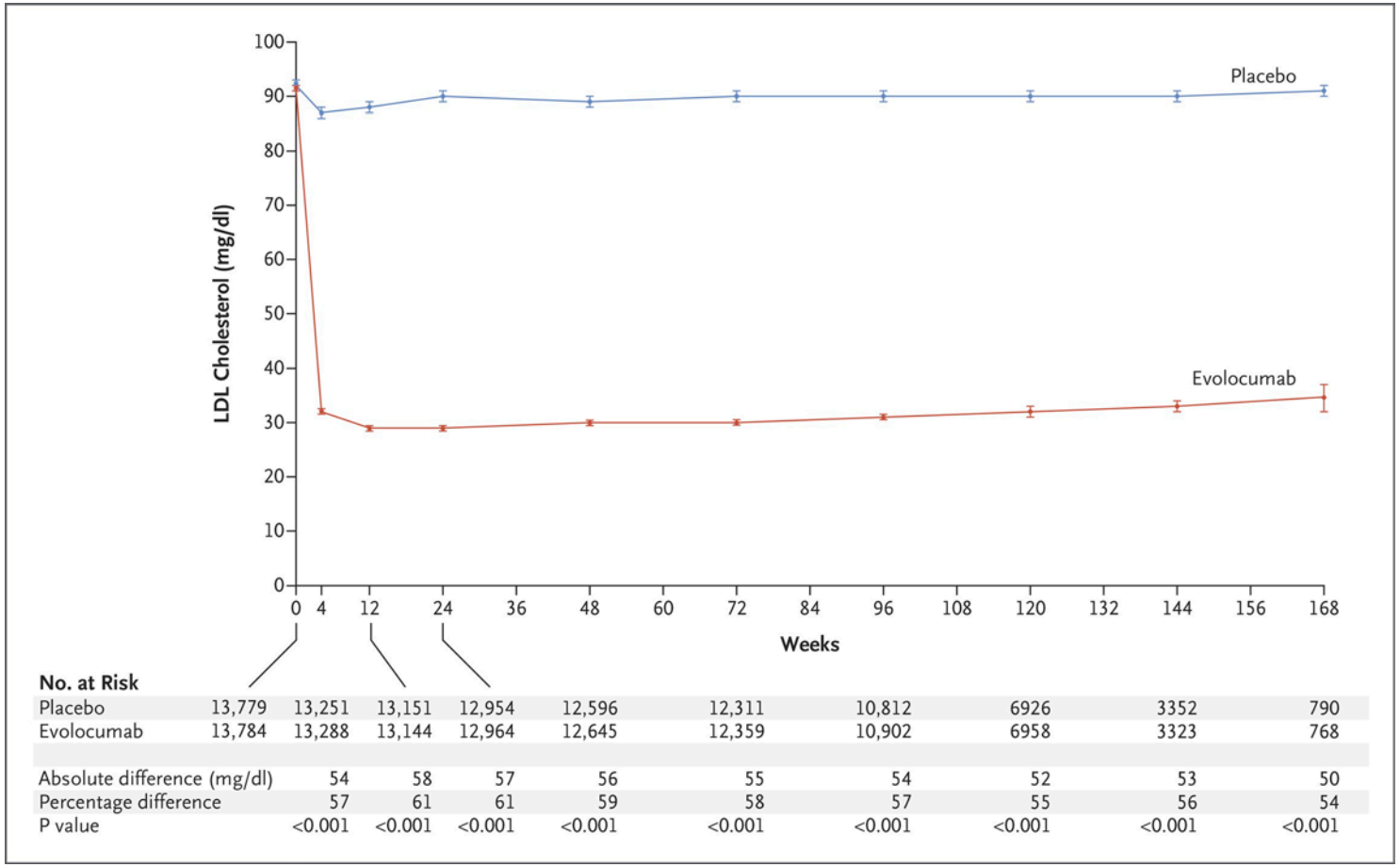
- Ezetimibe lowers LDL-C
- IMPROVE IT trial did show modest improvement in LDL–C reduction and vascular events.
- Ezetimibe has been shown to prevent cardiovascular events in individuals 75 years old and older with elevated LDL-C without history of coronary artery disease.
- No difference in adverse events with statin monotherapy and statin + Ezetimibe therapy.

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease Fourier Trial

- In this trial, 27,564 patients with cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter or higher on statin therapy were assigned to either evolocumab or placebo.
- At 2.2 years, the evolocumab group had a significantly lower rate of major adverse cardiovascular events.

Sabatine MS et al. N Engl J Med ;376:1713-1722

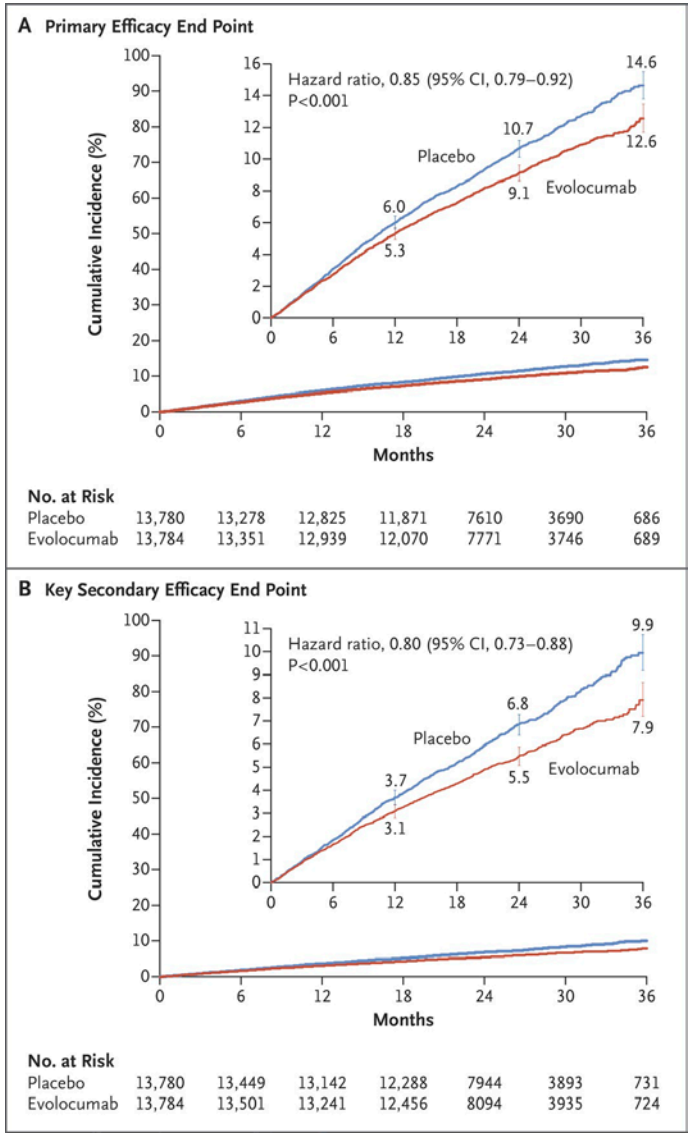
Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.



No. at Risk									
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Sabatine MS et al. N Engl J Med ;376:1713-1722

Cumulative Incidence of Cardiovascular Events.



Sabatine MS et al. N Engl J Med ;376:1713-1722

Characteristics of the Patients at Baseline.

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N=13,784)	Placebo (N=13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	85.0±17.3	85.5±17.4
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

* There were no nominally significant differences between the two groups in baseline characteristics with the exception of weight (P=0.01) and the use of aspirin, a $P2Y_{12}$ inhibitor, or both (P=0.03). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.
† Race was reported by the patients.
‡ Patients could have more than one type of atherosclerosis.
§ Statin intensity was categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.[12]

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Primary and Secondary End Points

Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N=13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
Cardiovascular death	251 (1.8)	240 (1.7)	1.05 (0.88–1.25)	0.62
Due to acute myocardial infarction	25 (0.18)	30 (0.22)	0.84 (0.49–1.42)	
Due to stroke	31 (0.22)	33 (0.24)	0.94 (0.58–1.54)	
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 (0.90–1.35)	
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91–1.19)	0.54
Myocardial infarction	468 (3.4)	639 (4.6)	0.73 (0.65–0.82)	<0.001
Hospitalization for unstable angina	236 (1.7)	239 (1.7)	0.99 (0.82–1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
Hemorrhagic	29 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
Unknown	13 (0.09)	14 (0.10)	0.93 (0.44–1.97)	
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71–0.86)	<0.001
Urgent	403 (2.9)	547 (4.0)	0.73 (0.64–0.83)	
Elective	420 (3.0)	504 (3.7)	0.83 (0.73–0.95)	
Cardiovascular death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 (0.86–1.13)	0.82
Ischemic stroke or transient ischemic attack	229 (1.7)	295 (2.1)	0.77 (0.65–0.92)	0.003
CTTC composite end point†	1271 (9.2)	1512 (11.0)	0.83 (0.77–0.90)	<0.001

* Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary end points should be considered significant, whereas all other P values should be considered exploratory.

† The Cholesterol Treatment Trialists Collaboration (CTTC) composite end point consists of coronary heart death, nonfatal myocardial infarction, stroke, or coronary revascularization.

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Adverse Events and Laboratory Test Results.

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

* The between-group difference was nominally significant ($P<0.001$).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

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Conclusions

- Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events.
- These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets.

Sabatine MS et al. N Engl J Med ;376:1713-1722

Original Article

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., P. Gabriel Steg, M.D., Michael Szarek, Ph.D., Deepak L. Bhatt, M.D., M.P.H., Vera A. Bittner, M.D., M.S.P.H., Rafael Diaz, M.D., Jay M. Edelberg, M.D., Ph.D., Shaun G. Goodman, M.D., Corinne Hanotin, M.D., Robert A. Harrington, M.D., J. Wouter Jukema, M.D., Ph.D., Guillaume Lecorps, M.Sc., Kenneth W. Mahaffey, M.D., Angèle Moryusef, M.D., Robert Pordy, M.D., Kirby Quintero, R.N., Matthew T. Roe, M.D., M.H.S., William J. Sasiela, Ph.D., Jean-François Tamby, M.D., Pierluigi Tricoci, M.D., M.H.S., Ph.D., Harvey D. White, D.Sc., Andreas M. Zeiher, M.D., for the **ODYSSEY OUTCOMES** Committees and Investigators

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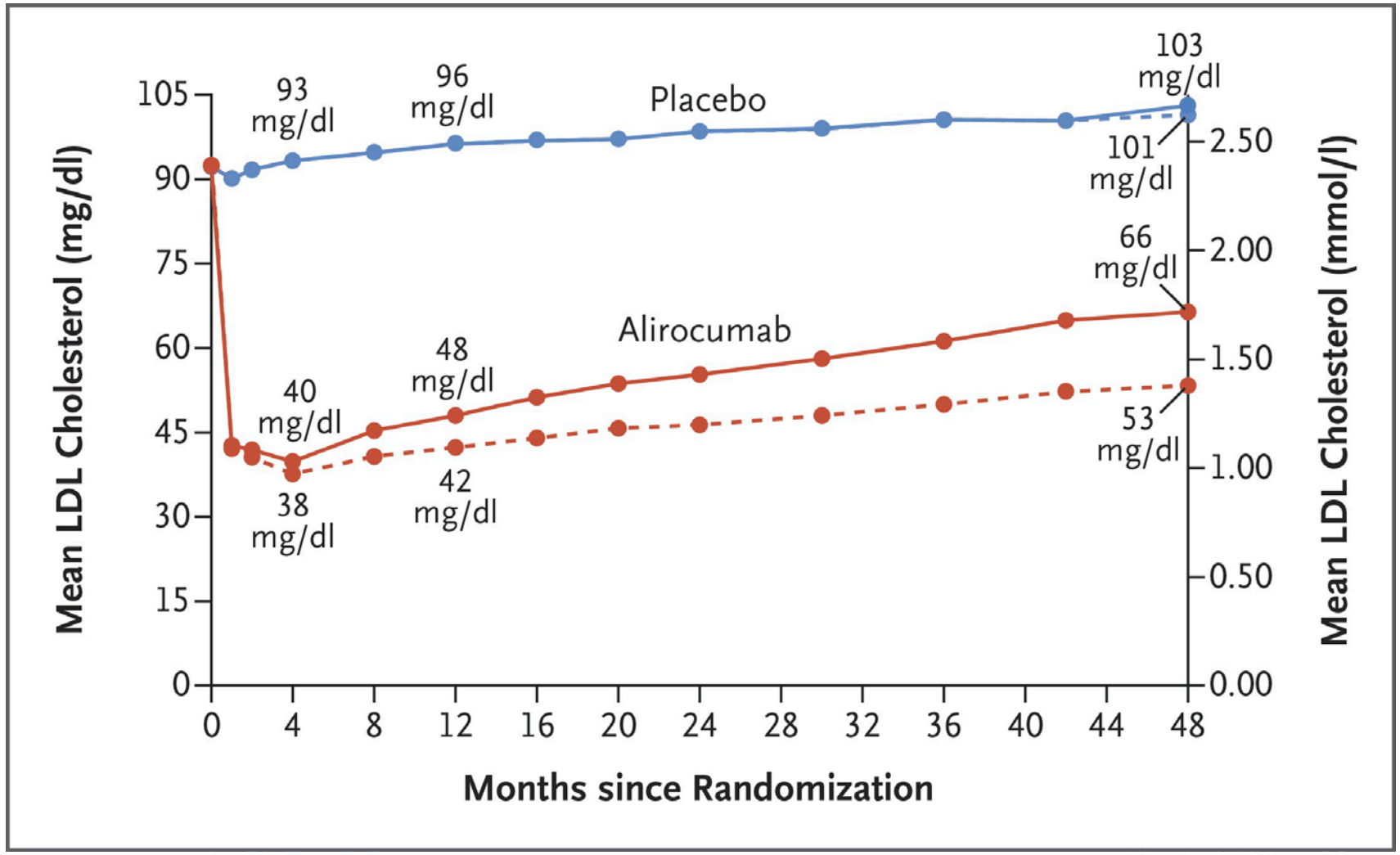
Study Overview

- Among patients who had had an acute coronary syndrome, the risk of death from coronary heart disease, nonfatal myocardial infarction, stroke, or unstable angina requiring hospitalization at 2.8 years was lower among those randomly assigned to alirocumab than among those assigned to placebo.

Schwartz GG et al. N Engl J Med 2018;379:2097-2107

LDL Cholesterol Levels during the Trial



Schwartz GG et al. N Engl J Med 2018;379:2097-2107

Demographic and Baseline Characteristics of the Patients.

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age — yr	58.5±9.3	58.6±9.4
Female sex — no. (%)	2390 (25.3)	2372 (25.1)
Race — no. (%)†		
White	7500 (79.3)	7524 (79.5)
Asian	1251 (13.2)	1247 (13.2)
Black	235 (2.5)	238 (2.5)
Other	475 (5.0)	451 (4.8)
Region of enrollment — no. (%)		
Central and Eastern Europe	2719 (28.7)	2718 (28.7)
Western Europe	2084 (22.0)	2091 (22.1)
Canada or United States	1435 (15.2)	1436 (15.2)
Latin America	1293 (13.7)	1295 (13.7)
Asia	1150 (12.2)	1143 (12.1)
Rest of world	781 (8.3)	779 (8.2)
Medical history before index acute coronary syndrome — no. (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Family history of premature coronary heart disease	3408 (36.0)	3365 (35.6)
Myocardial infarction	1790 (18.9)	1843 (19.5)
Percutaneous coronary intervention	1626 (17.2)	1615 (17.1)
Coronary-artery bypass grafting	521 (5.5)	526 (5.6)
Stroke	306 (3.2)	305 (3.2)
Peripheral artery disease	373 (3.9)	386 (4.1)
Congestive heart failure	1365 (14.4)	1449 (15.3)
Index acute coronary syndrome — no. (%)		
ST-segment elevation myocardial infarction	3301 (34.9)	3235 (34.2)
Non–ST-segment elevation myocardial infarction	4574 (48.3)	4601 (48.6)
Unstable angina	1568 (16.6)	1614 (17.1)
Missing data	19 (<0.1)	12 (<0.1)
Percutaneous coronary intervention or coronary-artery bypass grafting for index acute coronary syndrome — no. (%)	6798 (71.8)	6878 (72.7)
Median time from index acute coronary syndrome to randomization (IQR) — mo	2.6 (1.7–4.4)	2.6 (1.7–4.3)
Body-mass index‡	28.5±4.9	28.5±4.8

* Plus–minus values are means ±SD. There were no significant differences between the two groups in demographic or baseline characteristics. Additional baseline characteristics are listed in Table S2 in the Supplementary Appendix. Percentages may not sum to 100 because of rounding. IQR denotes interquartile range.
† Race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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Composite Primary End Point and Secondary End Points (Intention-to-Treat Population).

Table 2. Composite Primary End Point and Secondary End Points (Intention-to-Treat Population).

End Point	Alirocumab (N=9462)	Placebo (N=9462)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary end point: composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization	903 (9.5)	1052 (11.1)	0.85 (0.78–0.93)	<0.001
Major secondary end points, in order of hierarchical testing				
Any coronary heart disease event*	1199 (12.7)	1349 (14.3)	0.88 (0.81–0.95)	0.001
Major coronary heart disease event†	793 (8.4)	899 (9.5)	0.88 (0.80–0.96)	0.006
Any cardiovascular event‡	1301 (13.7)	1474 (15.6)	0.87 (0.81–0.94)	<0.001
Composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke§	973 (10.3)	1126 (11.9)	0.86 (0.79–0.93)	<0.001
Death from coronary heart disease	205 (2.2)	222 (2.3)	0.92 (0.76–1.11)	0.38¶
Death from cardiovascular causes	240 (2.5)	271 (2.9)	0.88 (0.74–1.05)	
Death from any cause	334 (3.5)	392 (4.1)	0.85 (0.73–0.98)	
Other end points‖				
Nonfatal myocardial infarction	626 (6.6)	722 (7.6)	0.86 (0.77–0.96)	
Fatal or nonfatal ischemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57–0.93)	
Unstable angina requiring hospitalization	37 (0.4)	60 (0.6)	0.61 (0.41–0.92)	
Ischemia-driven coronary revascularization procedure	731 (7.7)	828 (8.8)	0.88 (0.79–0.97)	
Hospitalization for congestive heart failure	176 (1.9)	179 (1.9)	0.98 (0.79–1.20)	

* This end point includes death from coronary heart disease, nonfatal myocardial infarction, unstable angina requiring hospitalization, and an ischemia-driven coronary revascularization procedure (definitions can be found in the Supplementary Appendix).
† This end point includes death from coronary heart disease and nonfatal myocardial infarction.
‡ This end point includes any death from cardiovascular causes, nonfatal myocardial infarction, unstable angina requiring hospitalization, an ischemia-driven coronary revascularization procedure, or nonfatal ischemic stroke.
§ The widths of the confidence intervals for the secondary end points were not adjusted for multiplicity, so the intervals for the outcomes listed below this outcome should not be used to infer definitive treatment effects.
¶ The hierarchical analysis was stopped after the first nonsignificant P value was observed, in accordance with the hierarchical testing plan.
‖ The analysis for other end points was not adjusted for multiplicity; therefore, no P values are reported.

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Adverse Events and Laboratory Abnormalities.

Table 3. Adverse Events and Laboratory Abnormalities.

Variable	Alirocumab (N=9451)	Placebo (N=9443)
Adverse events — no. (%)		
Any adverse event	7165 (75.8)	7282 (77.1)
Serious adverse event	2202 (23.3)	2350 (24.9)
Adverse event that led to death	181 (1.9)	222 (2.4)
Adverse event that led to discontinuation of the trial regimen	343 (3.6)	324 (3.4)
Local injection-site reaction	360 (3.8)	203 (2.1)
General allergic reaction	748 (7.9)	736 (7.8)
Diabetes worsening or diabetic complication among patients with diabetes at baseline — no./total no. (%)	506/2688 (18.8)	583/2747 (21.2)
New-onset diabetes among patients without diabetes at baseline — no./total no. (%)*	648/6763 (9.6)	676/6696 (10.1)
Neurocognitive disorder	143 (1.5)	167 (1.8)
Hepatic disorder	500 (5.3)	534 (5.7)
Cataracts	120 (1.3)	134 (1.4)
Hemorrhagic stroke, adjudicated	9 (<0.1)	16 (0.2)
Laboratory abnormalities at any time — no./total no. (%)		
Alanine aminotransferase >3 times upper limit of normal range	212/9369 (2.3)	228/9341 (2.4)
Aspartate aminotransferase >3 times upper limit of normal range	160/9367 (1.7)	166/9338 (1.8)
Total bilirubin >2 times upper limit of normal range	61/9368 (0.7)	78/9341 (0.8)
Creatine kinase >10 times upper limit of normal range	46/9369 (0.5)	48/9338 (0.5)
Antidrug antibodies†	67/9091 (0.7)	32/9097 (0.4)
Neutralizing antidrug antibodies	43/9091 (0.5)	6/9097 (<0.1)

* New-onset diabetes was defined according to the presence of one or more of the following, with confirmation of the diagnosis by blinded external review by experts in the field of diabetes: an adverse-event report, a new prescription for diabetes medication, a glycated hemoglobin level of at least 6.5% on two occasions (and a baseline level of <6.5%), or a fasting serum glucose level of at least 126 mg per deciliter (7.0 mmol per liter) on two occasions (and a baseline level of <126 mg per deciliter).

† Antidrug antibodies were defined by the presence of positive responses detected after the start of administration of the trial regimen in at least two consecutive postbaseline serum samples, separated by at least a 16-week period.

Schwartz GG et al. N Engl J Med 2018;379:2097-2107

Conclusions

- Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo.

Schwartz GG et al. N Engl J Med 2018;379:2097-2107

Original Article

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Steven E. Nissen, M.D., A. Michael Lincoff, M.D., Danielle Brennan, M.S., Kausik K. Ray, M.D., Denise Mason, B.S.N., John J.P. Kastelein, M.D., Paul D. Thompson, M.D., Peter Libby, M.D., Leslie Cho, M.D., Jorge Plutzky, M.D., Harold E. Bays, M.D., Patrick M. Moriarty, M.D., Venu Menon, M.D., Diederick E. Grobbee, M.D., Ph.D., Michael J. Louie, M.D., M.P.H., Chien-Feng Chen, Ph.D., Na Li, Ph.D., LeAnne Bloedon, M.S., Paula Robinson, M.S., Maggie Horner, M.B.A., William J. Sasiela, Ph.D., Jackie McCluskey, R.N., Deborah Davey, R.N., Pedro Fajardo-Campos, M.D., Predrag Petrovic, M.D., Jan Fedacko, M.D., Ph.D., Witold Zmuda, M.D., Ph.D., Yury Lukyanov, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., for the **CLEAR Outcomes** Investigators

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Study Overview

- In this randomized trial, statin-intolerant patients with, or at high risk for, CVD received bempedoic acid or placebo.
- Bempedoic acid reduced LDL cholesterol and the risk of cardiovascular events.

Nissen SE et al. N Engl J Med2023;388:1353-1364

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen SE et al. DOI: 10.1056/NEJMoa2215024

CLINICAL PROBLEM

Bempedoic acid is an ATP citrate lyase inhibitor that reduces low-density lipoprotein (LDL) cholesterol levels without the elevated risk of musculoskeletal adverse effects associated with statins. Although the goal of reducing LDL cholesterol levels is to prevent adverse cardiovascular events, studies of the effects of bempedoic acid on cardiovascular events are lacking.

CLINICAL TRIAL

Design: An international, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of bempedoic acid for the prevention of adverse cardiovascular events in statin-intolerant patients.

Intervention: 13,970 patients 18 to 85 years of age at increased cardiovascular risk who were unable or unwilling to take guideline-recommended doses of statins were assigned to receive 180 mg of oral bempedoic acid or placebo daily. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

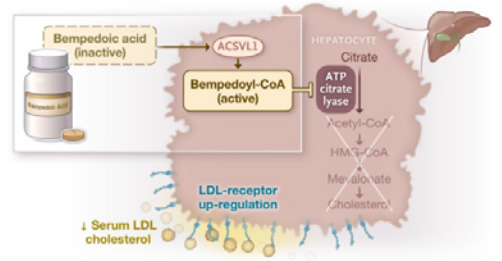
Efficacy: After a median follow-up of 40.6 months, the incidence of major adverse cardiovascular events was significantly lower in the bempedoic acid group than in the placebo group.

Safety: The incidences of adverse events were similar in the two groups overall; however, the bempedoic acid group had higher incidences of elevated hepatic enzymes, renal impairment, hyperuricemia, gout, and cholelithiasis.

LIMITATIONS AND REMAINING QUESTIONS

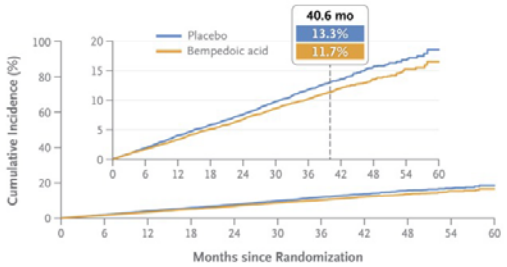
- The trial included only patients who were unable or unwilling to take statins, and therefore the mean LDL cholesterol level was high at baseline. The findings cannot be generalized to populations with lower LDL cholesterol levels.

Links: Full Article | NEJM Quick Take | Editorial | Science behind the Study



Four-Component Composite of Major Adverse Cardiovascular Events

HR, 0.87 (95% CI, 0.79–0.96); P=0.004



Adverse Events

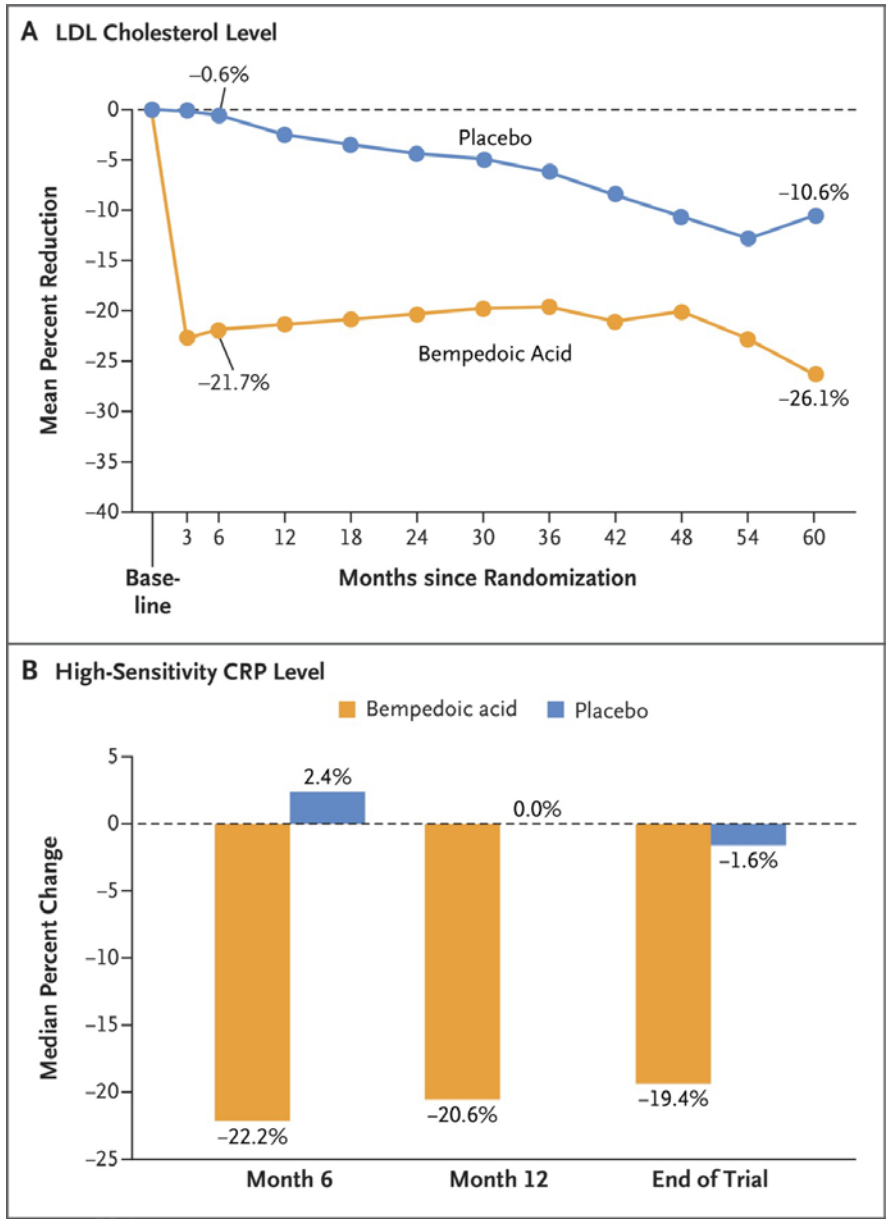
	Bempedoic acid (N=7001)	Placebo (N=6964)
	no. of patients (%)	
Any adverse event	6040 (86.3)	5919 (85.0)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

CONCLUSIONS

Among patients at increased cardiovascular risk who were unable or unwilling to take statins, treatment with bempedoic acid significantly reduced the risk of major adverse cardiovascular events.

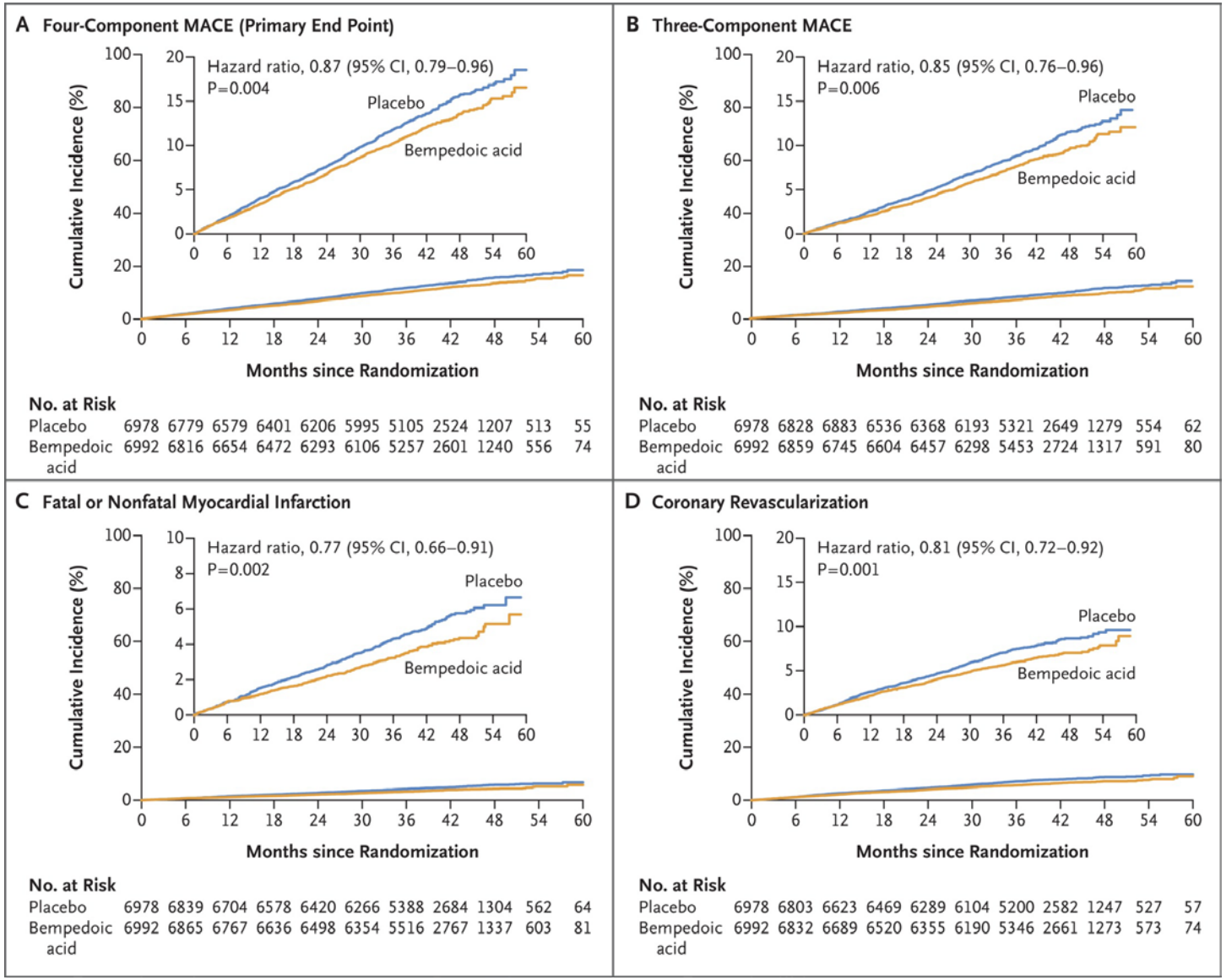
Nissen SE et al. N Engl J Med2023;388:1353-1364

Changes in LDL Cholesterol and High-Sensitivity CRP Levels over Time



Nissen SE et al. N Engl J Med2023;388:1353-1364

Cumulative Incidence of Cardiovascular Events



Nissen SE et al. N Engl J Med2023;388:1353-1364

Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population

Table 1. Demographic and Baseline Patient Characteristics in the Intention-to-Treat Population.*

Characteristic	Bempedoic Acid (N=6992)	Placebo (N=6978)
Age		
Mean — yr	65.5±9.0	65.5±8.9
Distribution — no. (%)		
<65 yr	2859 (40.9)	2907 (41.7)
≥65 to <75 yr	3070 (43.9)	3027 (43.4)
≥75 yr	1063 (15.2)	1044 (15.0)
Female sex — no. (%)	3361 (48.1)	3379 (48.4)
White race — no. (%)†	6397 (91.5)	6335 (90.8)
Hispanic or Latinx — no. (%)†	1190 (17.0)	1143 (16.4)
Body-mass index‡	29.9±5.2	30.0±5.2
LDL cholesterol		
Mean value — mg/dl	139.0±34.9	139.0±35.2
Distribution — no. (%)		
<130 mg/dl	3074 (44.0)	3089 (44.3)
≥130 to <160 mg/dl	2213 (31.7)	2250 (32.2)
≥160 mg/dl	1705 (24.4)	1639 (23.5)
HDL cholesterol — mg/dl	49.6±13.3	49.4±13.3
Non-HDL cholesterol — mg/dl	173.8±39.5	173.9±40.2
Total cholesterol — mg/dl	223.5±40.6	223.3±41.1
Median triglycerides (IQR) — mg/dl	159.5 (118.0–216.5)	158.5 (118.0–215.0)
Median high-sensitivity CRP (IQR) — mg/liter	2.3 (1.2–4.5)	2.3 (1.2–4.5)
Estimated GFR — no. (%)		
≥90 ml/min/1.73 m^2	1216 (17.4)	1233 (17.7)
≥60 to <90 ml/min/1.73 m^2	4322 (61.8)	4282 (61.4)
≥30 to <60 ml/min/1.73 m^2	1437 (20.6)	1444 (20.7)
Cardiovascular risk category — no. (%)		
Primary prevention	2100 (30.0)	2106 (30.2)
Secondary prevention	4892 (70.0)	4872 (69.8)
Coronary artery disease	3574 (51.1)	3536 (50.7)
Peripheral arterial disease	794 (11.4)	830 (11.9)
Cerebrovascular atherosclerotic disease	1027 (14.7)	1040 (14.9)
Glycemic status — no. (%)		
Diabetes§	3144 (45.0)	3229 (46.3)
Inadequately controlled diabetes¶	1356 (19.4)	1369 (19.6)
Statin use — no. (%)	1601 (22.9)	1573 (22.5)
Ezetimibe use — no. (%)	803 (11.5)	809 (11.6)

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. CRP denotes C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.

† Race and Hispanic or Latinx ethnic group were reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ At baseline, diabetes was defined as a medical history of type 2 diabetes, previous use of glucose-lowering medication, a glycated hemoglobin measurement of 6.5% or greater, or two or more fasting glucose measurements of 126 mg per deciliter (7.0 mmol per liter) or greater at baseline.

¶ Inadequately controlled diabetes was defined as diabetes and a glycated hemoglobin level of 7.0% or greater at baseline.

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Efficacy End Points in the Intention-to-Treat Population.

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

Outcome	Bempedoic Acid (N=6992)	Placebo (N=6978)	Difference (95% CI)*	P Value†
Primary efficacy end point				
Four-component MACE — no. (%)‡	819 (11.7)	927 (13.3)	0.87 (0.79 to 0.96)	0.004
Key secondary efficacy end points				
Three-component MACE — no. (%)§	575 (8.2)	663 (9.5)	0.85 (0.76 to 0.96)	0.006
Fatal or nonfatal myocardial infarction — no. (%)	261 (3.7)	334 (4.8)	0.77 (0.66 to 0.91)	0.002
Coronary revascularization — no. (%)	435 (6.2)	529 (7.6)	0.81 (0.72 to 0.92)	0.001
Fatal or nonfatal stroke — no. (%)	135 (1.9)	158 (2.3)	0.85 (0.67 to 1.07)	0.16
Death from cardiovascular causes — no. (%)	269 (3.8)	257 (3.7)	1.04 (0.88 to 1.24)	
Death from any cause — no. (%)	434 (6.2)	420 (6.0)	1.03 (0.90 to 1.18)	
Additional secondary end points				
Death from any cause, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization — no. (%)	962 (13.8)	1062 (15.2)	0.89 (0.82 to 0.97)	
Five-component MACE — no. (%)¶	831 (11.9)	952 (13.6)	0.86 (0.78 to 0.94)	
Hospitalization for unstable angina — no. (%)	91 (1.3)	137 (2.0)	0.66 (0.50 to 0.86)	
New-onset type 2 diabetes mellitus — no./total no. (%)‖	429/3848 (11.1)	433/3749 (11.5)	0.95 (0.83 to 1.09)	
Change from baseline in secondary lipid and biomarker efficacy end points				
Mean percent change in mean LDL cholesterol level at 6 mo (95% CI)**	−21.1 (−21.6 to −20.5)	−0.8 (−1.4 to −0.2)	−20.3 (−21.1 to −19.5)	
Median percent change in high-sensitivity CRP level at 6 mo (95% CI)	−22.2 (−23.5 to −20.8)	2.4 (0.0 to 4.2)	−21.6 (−23.7 to −19.6)	
Mean percentage-point change in glycated hemoglobin level at 12 mo in patients with inadequately controlled type 2 diabetes mellitus (95% CI)**††	−0.04 (−0.12 to 0.03)	−0.01 (−0.09 to 0.06)	−0.03 (−0.14 to 0.08)	

* The patients were followed for a median of 40.6 months. Differences are given as the hazard ratio for the primary efficacy end point, the key secondary efficacy end points, and the additional secondary end points and as the percentage-point difference for the changes from baseline in secondary lipid and biomarker efficacy end points.

† As prespecified in the hierarchical testing procedure, all P values after the first nonsignificant P value are not presented.

‡ The primary efficacy end point was a four-component composite of adjudicated major adverse cardiovascular events (MACE), defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization, as assessed in a time-to-first-event analysis.

§ The first key secondary end point was a three-component MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

¶ The five-component MACE was defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina.

‖ New-onset type 2 diabetes mellitus was defined as a glycated hemoglobin level of 6.5% or greater or two or more fasting glucose measurements of 126 mg per deciliter (7.0 mmol per liter) or greater in patients with a baseline glycemic status of no diabetes.

** Results were adjusted for baseline LDL cholesterol or glycated hemoglobin levels with the use of a pattern-mixture model for missing data.

†† Inadequately controlled type 2 diabetes was defined as type 2 diabetes and a glycated hemoglobin level of 7% or greater at baseline.

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Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.

Table 3. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.*

Event	Bempedoic Acid (N = 7001)	Placebo (N = 6964)
Any adverse event that started or worsened after the first dose of a trial agent — no. (%)	6040 (86.3)	5919 (85.0)
Serious adverse event that started or worsened after the first dose of a trial agent — no. (%)	1767 (25.2)	1733 (24.9)
Adverse event leading to discontinuation of the trial regimen — no. (%)	759 (10.8)	722 (10.4)
Prespecified adverse events of special interest		
Myalgia — no. (%)	393 (5.6)	471 (6.8)
Discontinuation of the trial regimen because of myalgia — no. (%)	124 (1.8)	129 (1.9)
New-onset diabetes in patients without diabetes at baseline — no./total no. (%)	621/3856 (16.1)	640/3740 (17.1)
New-onset diabetes in patients with prediabetes at baseline — no./total no. (%)†	569/2918 (19.5)	586/2877 (20.4)
New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%)†	52/938 (5.5)	54/863 (6.3)
Worsening hyperglycemia — no./total no. (%)‡	713/3145 (22.7)	746/3224 (23.1)
Hypoglycemia — no. (%)	304 (4.3)	267 (3.8)
Metabolic acidosis — no. (%)	13 (0.2)	11 (0.2)
Elevated hepatic-enzyme level — no. (%)	317 (4.5)	209 (3.0)
Renal impairment — no. (%)	802 (11.5)	599 (8.6)
Neurocognitive disorders — no. (%)	58 (0.8)	69 (1.0)
Atrial fibrillation — no. (%)	229 (3.3)	246 (3.5)
Adjudicated tendon rupture — no. (%)	86 (1.2)	66 (0.9)
Tendinopathies — no. (%)	118 (1.7)	128 (1.8)
Malignant conditions — no. (%)	321 (4.6)	341 (4.9)
Other adverse events — no. (%)		
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)
Laboratory results after 6 mo — mg/dl		
Change from baseline in uric acid level	0.76±1.2	−0.03±1.0
Change from baseline in creatinine level	0.05±0.2	0.01±0.2
Laboratory results after 12 mo		
Change from baseline in glycated hemoglobin level — %§	0.04±0.74	0.06±0.70
Abnormal enzyme level at any visit — no. (%)		
Creatine kinase level >5× ULN, single occurrence	45 (0.6)	40 (0.6)
Creatine kinase level >5× ULN, repeated and confirmed	8 (0.1)	8 (0.1)
Creatine kinase level >10× ULN, single occurrence	18 (0.3)	15 (0.2)
Creatine kinase level >10× ULN, repeated and confirmed	2 (<0.1)	4 (0.1)
Alanine aminotransferase level >3× ULN¶	83 (1.2)	53 (0.8)
Aspartate aminotransferase level >3× ULN¶	80 (1.1)	43 (0.6)

* Plus–minus values are means ±SD. The safety population included all patients who underwent randomization and received at least one dose of bempedoic acid or placebo; patients who received any dose of double-blind bempedoic acid were placed in the bempedoic acid group in the safety analyses. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for uric acid to micromoles per liter, multiply by 59.48. ULN denotes upper limit of the normal range.

† Prediabetes at baseline was defined as no medical history of diabetes plus a glycated hemoglobin level of 5.7 to less than 6.5% or one or more fasting glucose measurements of 100 mg per deciliter (5.6 mmol per liter) or greater but not more than one fasting glucose measurement of 126 mg per deciliter (7.0 mmol per liter) or greater. Patients with normoglycemia at baseline did not meet the criteria for prediabetes.

‡ Worsening hyperglycemia was assessed in patients with diabetes at baseline.

§ Change from baseline in the glycated hemoglobin level was not a prespecified safety measure.

¶ Measurements were repeated and elevations confirmed.

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Conclusions

- Among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization).

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Original Article

Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., John J.P. Kastelein, M.D., Ph.D., for the **ORION-10 and ORION-11** Investigators

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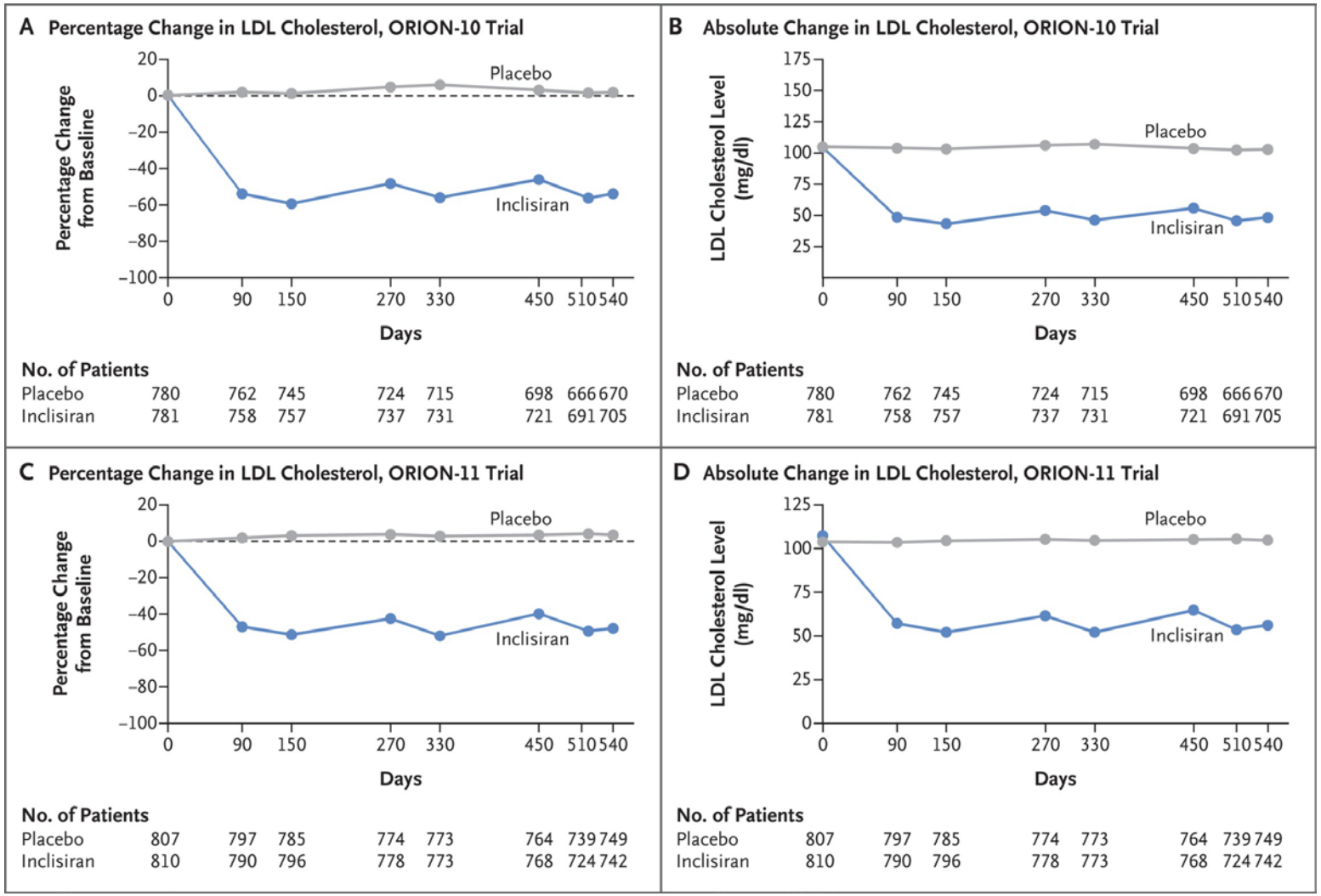
Study Overview

- Inclisiran, a small interfering RNA therapeutic, reduces hepatic synthesis of PCSK9.
- In two separate randomized trials, subcutaneous injections of inclisiran on day 1, day 90, and then every 6 months reduced LDL cholesterol levels by approximately 50% at month 17, with a modest excess of injection-site adverse events.

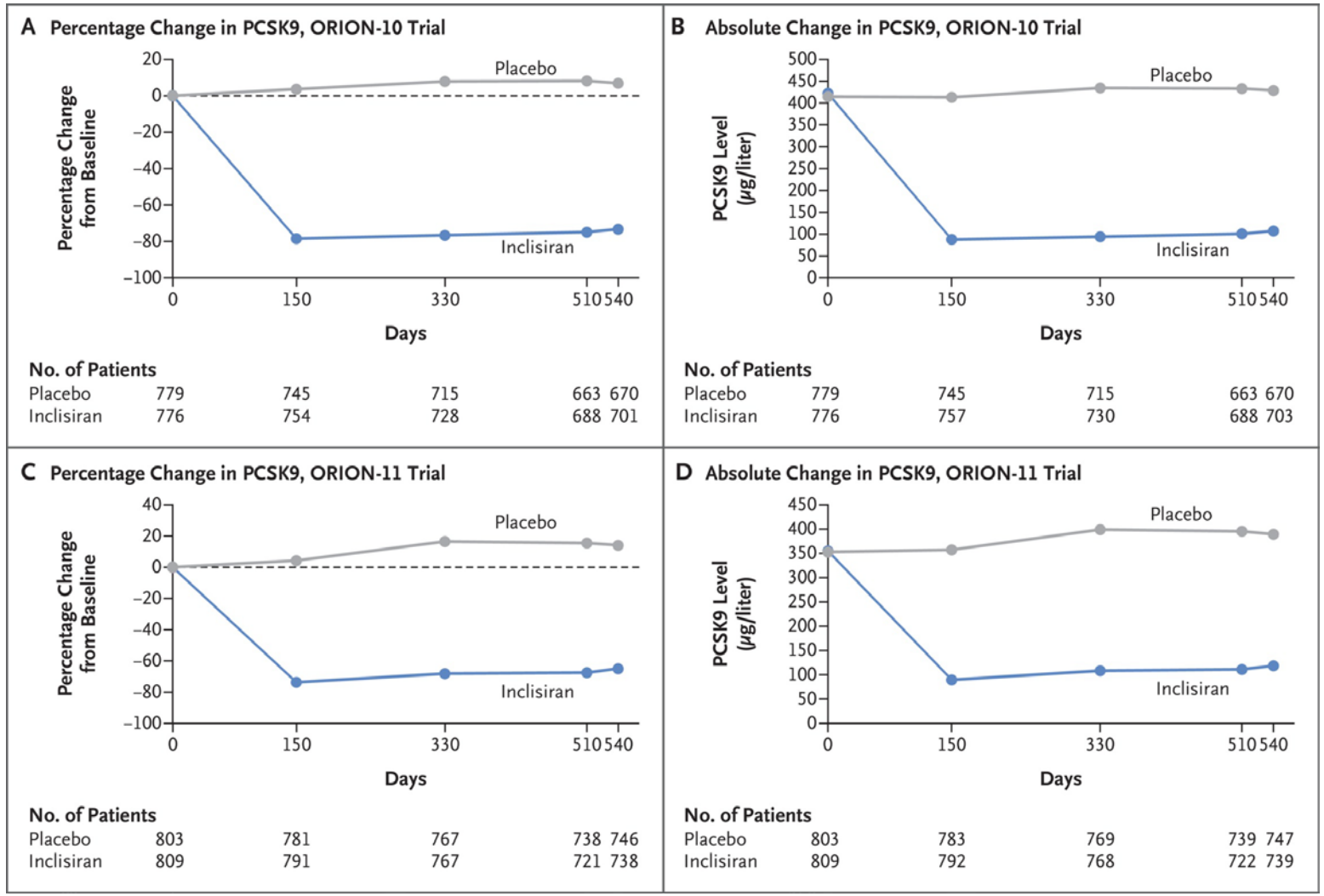
N Engl J Med 2020; 382:1507-1519

Efficacy of Inclisiran or Placebo in Lowering LDL Cholesterol over the 540-Day Trial Period (Intention-to-Treat Population).



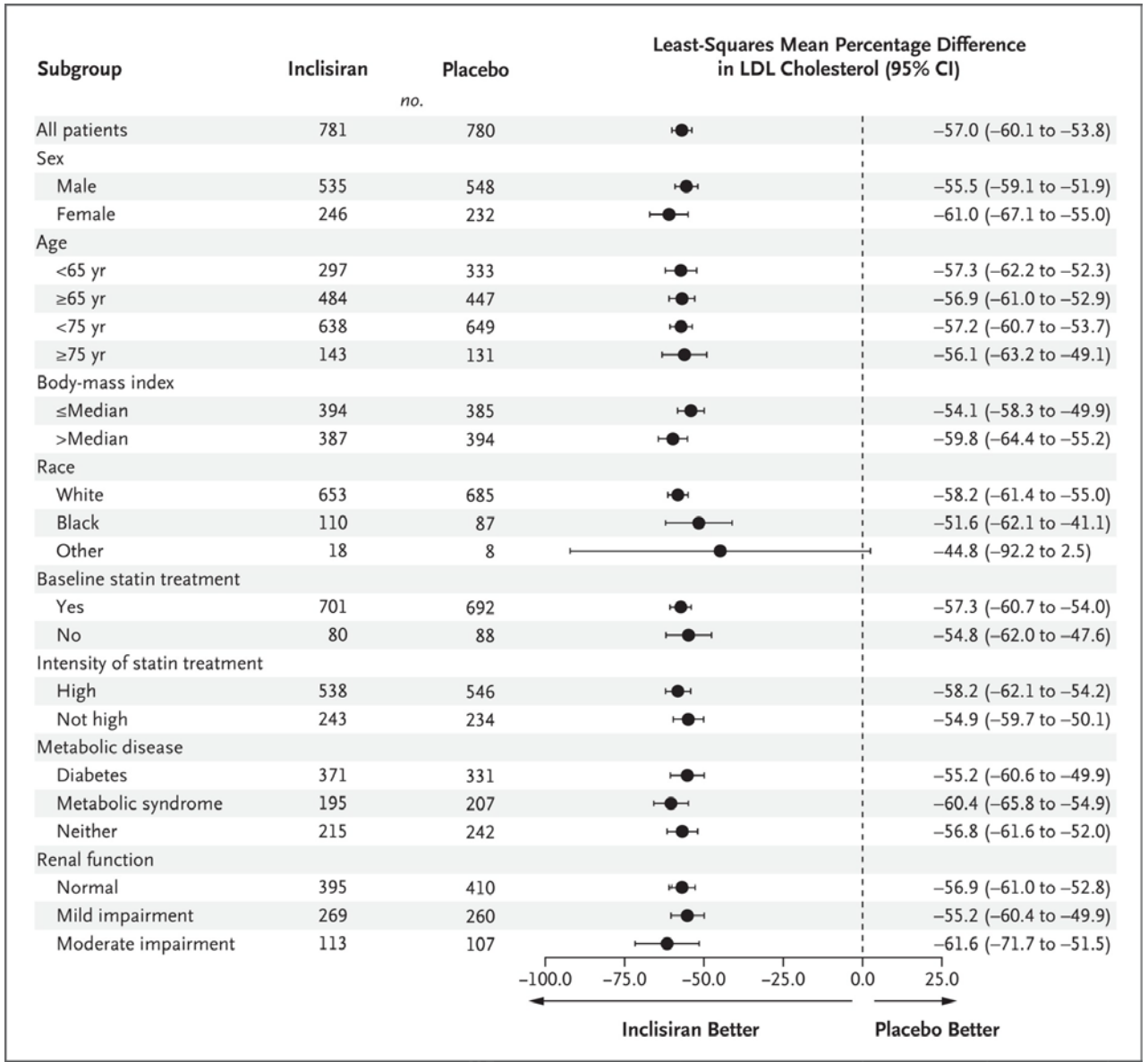
N Engl J Med 2020; 382:1507-1519

Efficacy of Inclisiran or Placebo in Lowering PCSK9 Levels over the 540-Day Trial Period (Intention-to-Treat Population).



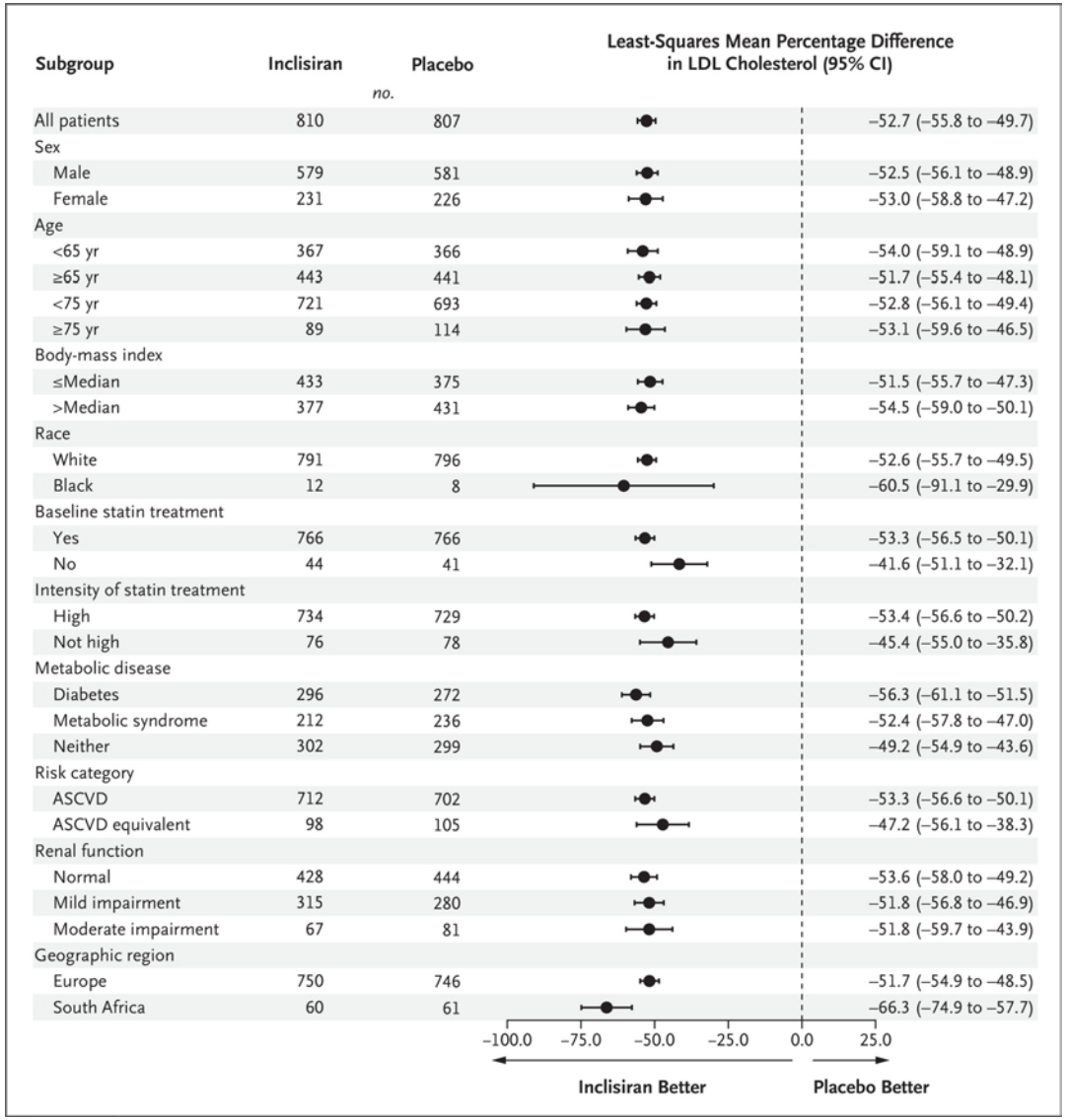
N Engl J Med 2020; 382:1507-1519

Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-10 Trial (Intention-to-Treat Population).



N Engl J Med 2020; 382:1507-1519

Subgroup Analysis of Placebo-Corrected Percentage Change in LDL Cholesterol from Baseline to Day 510 with Inclisiran in the ORION-11 Trial (Intention-to-Treat Population).



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Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	ORION-10 Trial		ORION-11 Trial	
	Inclisiran (N=781)	Placebo (N=780)	Inclisiran (N=810)	Placebo (N=807)
Age — yr	66.4±8.9	65.7±8.9	64.8±8.3	64.8±8.7
Male sex — no. (%)	535 (68.5)	548 (70.3)	579 (71.5)	581 (72.0)
White race — no. (%)†	653 (83.6)	685 (87.8)	791 (97.7)	796 (98.6)
Cardiovascular risk factors — no. (%)				
ASCVD	781 (100)	780 (100)	712 (87.9)	702 (87.0)
ASCVD risk equivalent‡	0	0	98 (12.1)	105 (13.0)
Current smoker§	123 (15.7)	111 (14.2)	160 (19.8)	132 (16.4)
Hypertension§	714 (91.4)	701 (89.9)	640 (79.0)	661 (81.9)
Diabetes§	371 (47.5)	331 (42.4)	296 (36.5)	272 (33.7)
Heterozygous familial hypercholesterolemia§	8 (1.0)	12 (1.5)	14 (1.7)	14 (1.7)
Concomitant lipid-modifying therapy — no. (%)				
Statin	701 (89.8)	692 (88.7)	766 (94.6)	766 (94.9)
High-intensity statin	525 (67.2)	537 (68.8)	640 (79.0)	631 (78.2)
Ezetimibe	80 (10.2)	74 (9.5)	52 (6.3)	62 (7.7)
Lipid measures — mg/dl				
LDL cholesterol	104.5±39.6	104.8±37.0	107.2±41.8	103.7±36.4
Total cholesterol	180.6±46.1	180.6±43.6	187.3±48.2	183.3±42.8
Non-HDL cholesterol	134.0±44.5	134.7±43.5	137.6±46.9	133.9±41.0
HDL cholesterol	46.6±14.3	45.9±14.4	49.7±15.5	49.3±13.8
Apolipoprotein B	94.1±25.6	94.6±25.1	97.1±28.0	95.1±5.2
Lipoprotein(a) — nmol/liter				
Median	57	56	42	35
IQR	18–181	20–189	18–178	18–181
Triglycerides — mg/dl				
Median	127	129	135	135
IQR	92–181	96–182	99–181	102–185
PCSK9 — μg/liter	422.1±176.9	414.9±145.7	355±98.9	353±97.4

* Plus–minus values are means ±SD. For the levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, triglycerides, and total cholesterol, the baseline value was defined as the mean of the values at screening and before receipt of the dose of inclisiran or placebo on day 1; for other variables, the baseline value was defined as the last value before the first dose of inclisiran or placebo. In a post hoc analysis to provide descriptive statistical comparisons, there were no significant differences between the two groups in the baseline characteristics. To convert values for cholesterol and apolipoprotein B to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ASCVD denotes atherosclerotic cardiovascular disease, IQR interquartile range, and PCSK9 proprotein convertase subtilisin–kexin type 9.
† Race was reported by the patient.
‡ Patients in this category had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.
§ Percentages are reported as a proportion of the overall cohort, including patients in the risk-equivalent category.

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Adverse Events and Key Safety Laboratory Findings

Table 2. Adverse Events and Key Safety Laboratory Findings.*

Variable	ORION-10 Trial			ORION-11 Trial		
	Inclisiran (N=781)	Placebo (N=778)	Risk Ratio (95% CI)	Inclisiran (N=811)	Placebo (N=804)	Risk Ratio (95% CI)
	no. of patients (%)			*no. of patients (%)*		
Adverse events						
≥1 Adverse event	574 (73.5)	582 (74.8)	1.0 (0.9–1.0)	671 (82.7)	655 (81.5)	1.0 (0.9–1.1)
≥1 Event leading to discontinuation of inclisiran or placebo	19 (2.4)	17 (2.2)	1.1 (0.6–2.1)	23 (2.8)	18 (2.2)	1.3 (0.7–2.3)
Serious adverse events						
≥1 Serious adverse event	175 (22.4)	205 (26.3)	0.9 (0.7–1.0)	181 (22.3)	181 (22.5)	1.0 (0.8–1.2)
Death	12 (1.5)	11 (1.4)	1.1 (0.5–2.4)	14 (1.7)	15 (1.9)	0.9 (0.4–1.9)
Death from cardiovascular causes	7 (0.9)	5 (0.6)	1.4 (0.4–4.4)	9 (1.1)	10 (1.2)	0.9 (0.4–2.2)
Cancer-related death	1 (0.1)	3 (0.4)	0.3 (0.0–3.2)	3 (0.4)	3 (0.4)	1.0 (0.2–4.9)
New, worsening, or recurrent cancer	26 (3.3)	26 (3.3)	1.0 (0.6–1.7)	16 (2.0)	20 (2.5)	0.8 (0.1–1.5)
Other cardiovascular adverse events						
Prespecified exploratory cardiovascular end point†	58 (7.4)	79 (10.2)	0.7 (0.5–1.0)	63 (7.8)	83 (10.3)	0.8 (0.6–1.0)
Fatal or nonfatal myocardial infarction	20 (2.6)	18 (2.3)	1.1 (0.6–2.1)	10 (1.2)	22 (2.7)	0.5 (0.2–0.9)
Fatal or nonfatal stroke	11 (1.4)	7 (0.9)	1.6 (0.6–4.0)	2 (0.2)	8 (1.0)	0.2 (0.1–1.2)
Injection-site adverse events‡						
Any reaction	20 (2.6)	7 (0.9)	2.9 (1.2–6.7)	38 (4.7)	4 (0.5)	9.4 (3.4–26.3)
Mild	13 (1.7)	7 (0.9)	1.9 (0.7–4.6)	23 (2.8)	3 (0.4)	7.6 (2.3–25.2)
Moderate	7 (0.9)	0	—	15 (1.8)	1 (0.1)	14.9 (2.0–112.3)
Severe	0	0	—	0	0	—
Persistent	0	0	—	0	0	—
Frequent adverse events§						
Diabetes mellitus	120 (15.4)	108 (13.9)	1.1 (0.9–1.4)	88 (10.9)	94 (11.7)	0.9 (0.7–1.2)
Nasopharyngitis	—	—	—	91 (11.2)	90 (11.2)	1.0 (0.8–1.3)
Bronchitis	46 (5.9)	30 (3.9)	1.5 (1.0–2.4)	—	—	—
Dyspnea	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	—	—	—
Hypertension	42 (5.4)	42 (5.4)	1.0 (0.7–1.5)	53 (6.5)	54 (6.7)	1.0 (0.7–1.4)
Upper respiratory tract infection	39 (5.0)	33 (4.2)	1.2 (0.7–1.9)	52 (6.4)	49 (6.1)	1.1 (0.7–1.5)
Arthralgia	—	—	—	47 (5.8)	32 (4.0)	1.5 (0.9–2.3)
Osteoarthritis	—	—	—	32 (3.9)	40 (5.0)	0.8 (0.5–1.2)
Back pain	39 (5.0)	39 (5.0)	1.0 (0.6–1.5)	—	—	—
Laboratory results						
Liver function						
Alanine aminotransferase >3× ULN	2 (0.3)	2 (0.3)	1.0 (0.1–7.1)	4 (0.5)	4 (0.5)	1.0 (0.2–4.0)
Aspartate aminotransferase >3× ULN	4 (0.5)	5 (0.6)	0.8 (0.2–3.0)	2 (0.2)	4 (0.5)	0.5 (0.1–2.7)
Alkaline phosphatase >3× ULN	5 (0.6)	3 (0.4)	1.7(0.4–6.9)	1 (0.1)	2 (0.2)	0.5 (0.0–5.5)
Bilirubin >2× ULN	4 (0.5)	3 (0.4)	1.3 (0.3–5.9)	6 (0.7)	8 (1.0)	0.7 (0.3–2.1)
Kidney function: creatinine >2 mg/dl	30 (3.8)	30 (3.9)	1.0 (0.6–1.6)	5 (0.6)	11 (1.4)	0.5 (0.2–1.3)
Muscle: creatine kinase >5× ULN	10 (1.3)	8 (1.0)	1.2 (0.5–3.1)	10 (1.2)	9 (1.1)	1.1 (0.5–2.7)
Hematology: platelet count <75×10^9/liter	1 (0.1)	0	—	0	1 (0.1)	—

* The safety population included all the patients who received at least one dose of inclisiran or placebo. Adverse events were recorded over the trial period of 540 days. ULN denotes the upper limit of the normal range.

† The exploratory cardiovascular end point comprised a *Medical Dictionary for Regulatory Activities*–defined cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke.

‡ Injection-site adverse events included the preferred terms injection-site erythema, injection-site hypersensitivity, injection-site pruritus, injection-site rash, and injection-site reaction.

§ Shown are events occurring with a frequency of 5% or more in either the inclisiran group or the placebo group in each trial. Some events occurred with a frequency of less than 5% in one trial but not the other; a dash indicates that the frequency was less than 5% in that trial.

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Conclusions

- Reductions in LDL cholesterol levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months.
- More injection-site adverse events occurred with inclisiran than with placebo.

Case

- 59 year old American Indian female on maximum dose Lipitor with CVRF's of HTN, Dyslipidemia, Tobacco use for 35 years and Family Hx of premature CAD.
- Ca Score 6057
- ASA 81 mg po q daily, Atorvastatin 80 mg po q hs, Lisinopril 20 mg po q hs
- LDL 302 mg/dl
- Walks every day for 3 miles without any angina or Dyspnea of exertion complaints.

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EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

Writing Committee

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Pamela B. Morris, MD, FACC, *Vice Chair*

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Kim K. Birtcher, PharmD, MS, FACC
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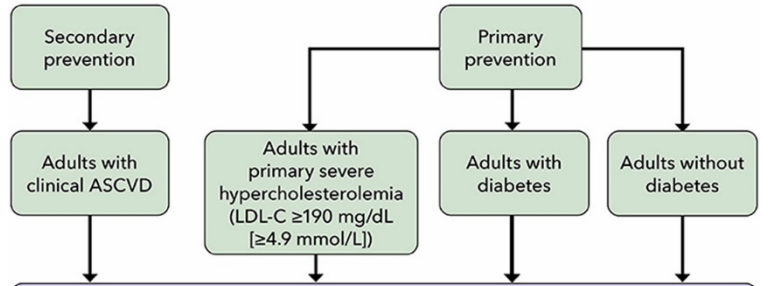
PATIENT MANAGEMENT GROUPS

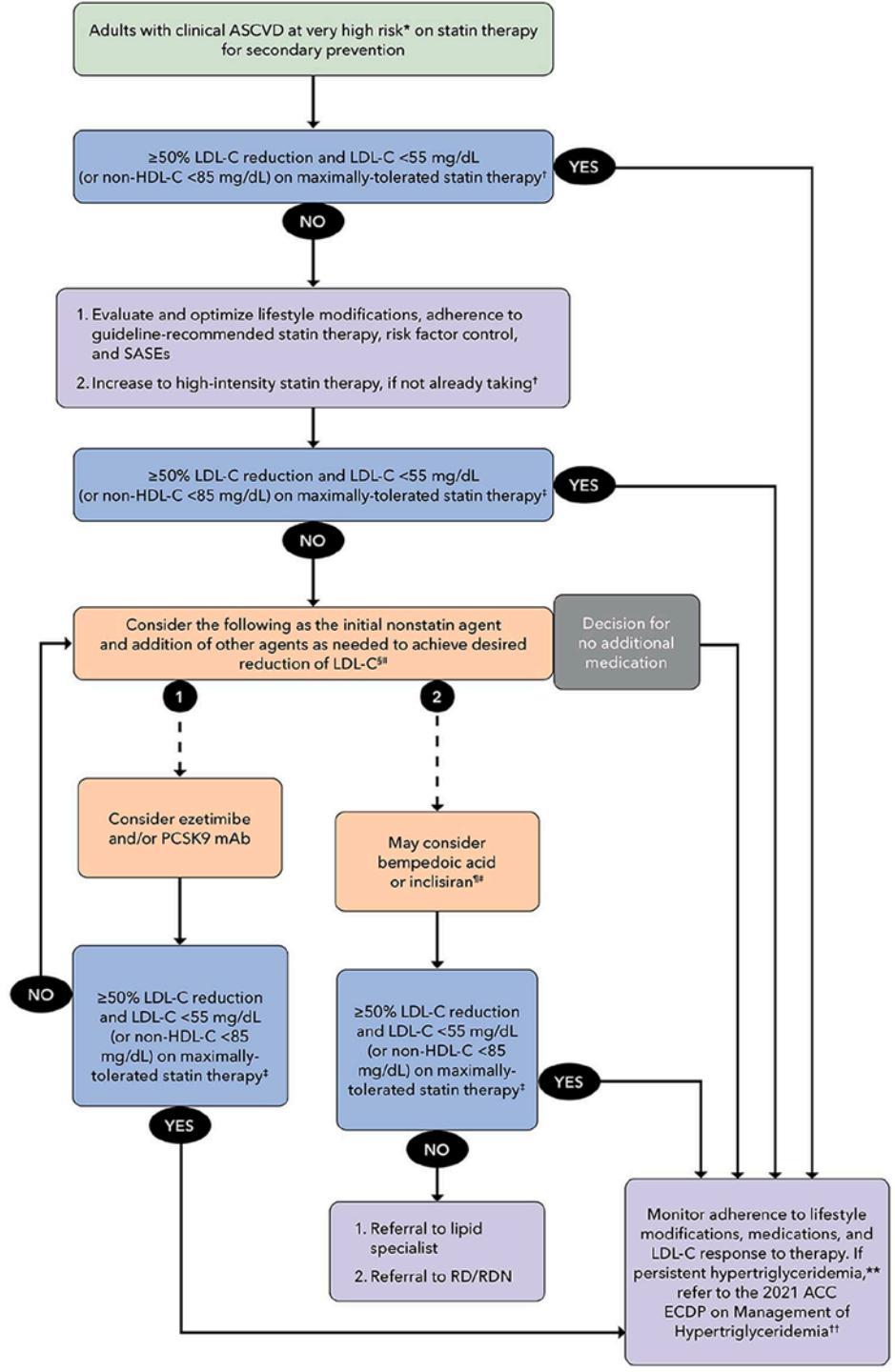


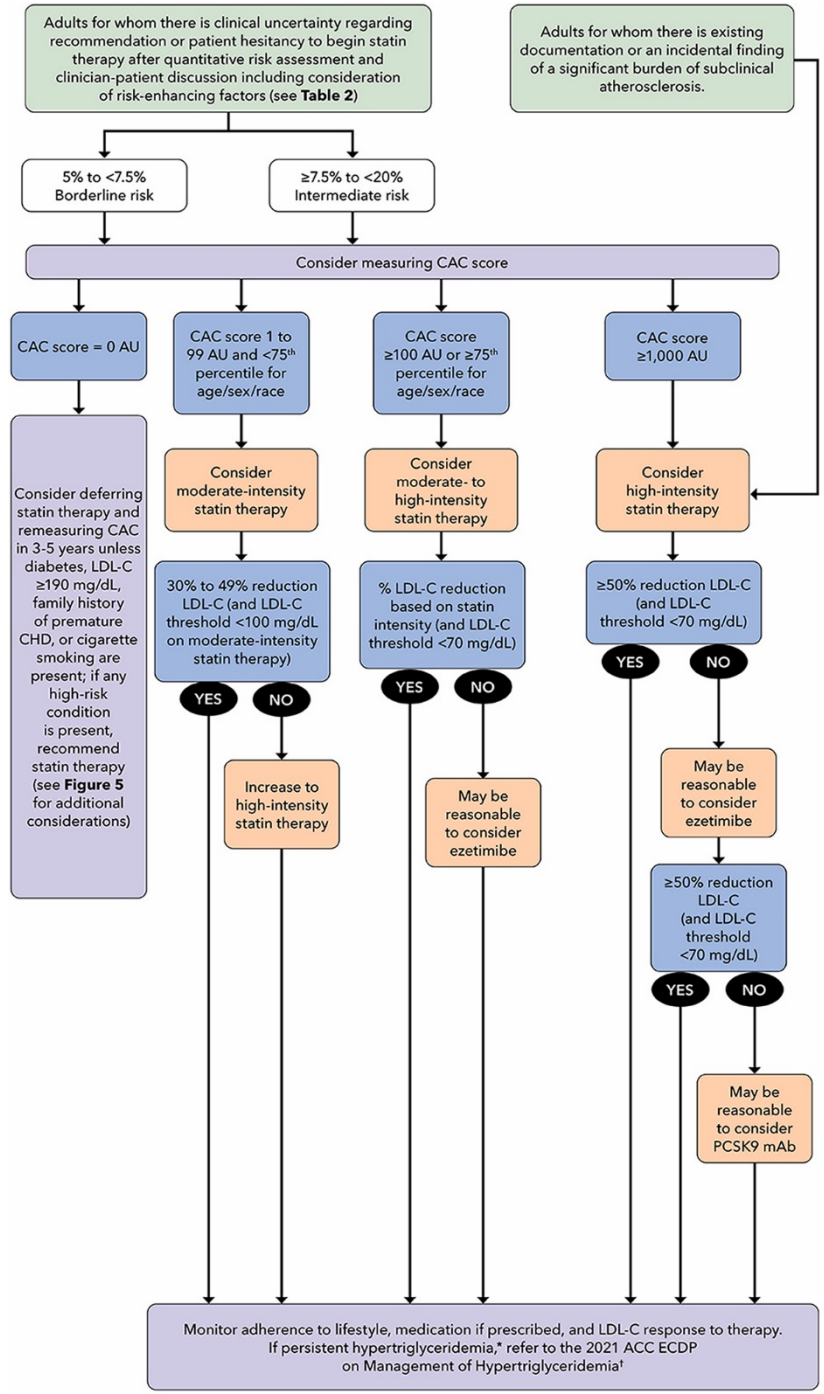
FACTORS TO CONSIDER:

- Adherence to lifestyle modifications and adherence to evidence-based, guideline-recommended statin therapy
- Patient on guideline-recommended statin therapy
- Risk-enhancing factors
- Control of other risk factors
- Clinician-patient decision about the potential benefits, potential harms, and patients preferences with regard to the addition of nonstatin therapies
- Percentage LDL-C reduction and absolute LDL-C or non-HDL-C level achieved
- Monitoring of response to lifestyle modifications, adherence, and therapy
- Cost of therapy
- Statin-associated side effects
- Persistent hypertriglyceridemia

OPTIONAL INTERVENTIONS TO CONSIDER IN APPROPRIATE PATIENT GROUPS:

- Referral to a lipid specialist and registered dietitian/registered dietitian nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 mAbs*
- Bempedoic acid
- Inclisiran
- LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia
- Lomitapide (only in HoFH)
- Evinacumab (only in HoFH)


Adults with clinical ASCVD at very high risk* on statin therapy for secondary prevention
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy†
YES
NO
1. Evaluate and optimize lifestyle modifications, adherence to guideline-recommended statin therapy, risk factor control, and SASEs
2. Increase to high-intensity statin therapy, if not already taking†
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy‡
YES
NO
Consider the following as the initial nonstatin agent and addition of other agents as needed to achieve desired reduction of LDL-C§‖
Decision for no additional medication
1
2
Consider ezetimibe and/or PCSK9 mAb
May consider bempedoic acid or inclisiran¶#
NO
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy‡
YES
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy‡
YES
NO
1. Referral to lipid specialist
2. Referral to RD/RDN
Monitor adherence to lifestyle modifications, medications, and LDL-C response to therapy. If persistent hypertriglyceridemia,** refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia††


Adults for whom there is clinical uncertainty regarding recommendation or patient hesitancy to begin statin therapy after quantitative risk assessment and clinician-patient discussion including consideration of risk-enhancing factors (see **Table 2**)
Adults for whom there is existing documentation or an incidental finding of a significant burden of subclinical atherosclerosis.
5% to <7.5% Borderline risk
≥7.5% to <20% Intermediate risk
Consider measuring CAC score
CAC score = 0 AU
CAC score 1 to 99 AU and <75th percentile for age/sex/race
CAC score ≥100 AU or ≥75th percentile for age/sex/race
CAC score ≥1,000 AU
Consider deferring statin therapy and remeasuring CAC in 3-5 years unless diabetes, LDL-C ≥190 mg/dL, family history of premature CHD, or cigarette smoking are present; if any high-risk condition is present, recommend statin therapy (see **Figure 5** for additional considerations)
Consider moderate-intensity statin therapy
Consider moderate- to high-intensity statin therapy
Consider high-intensity statin therapy
30% to 49% reduction LDL-C (and LDL-C threshold <100 mg/dL on moderate-intensity statin therapy)
% LDL-C reduction based on statin intensity (and LDL-C threshold <70 mg/dL)
≥50% reduction LDL-C (and LDL-C threshold <70 mg/dL)
YES
NO
YES
NO
YES
NO
Increase to high-intensity statin therapy
May be reasonable to consider ezetimibe
May be reasonable to consider ezetimibe
≥50% reduction LDL-C (and LDL-C threshold <70 mg/dL)
YES
NO
May be reasonable to consider PCSK9 mAb
Monitor adherence to lifestyle, medication if prescribed, and LDL-C response to therapy.
If persistent hypertriglyceridemia,* refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia†

Back to Case

- Encourage Compliance
- Tobacco cessation
- Continue exercise
- Started Evolocumab SubQ q 14 days Added NTG SL prn Chest pain
- Repeated Lipid Panel
- Education on anginal clinical signs and Diet education
- Repeat lipids panel in 8 weeks.

Follow up

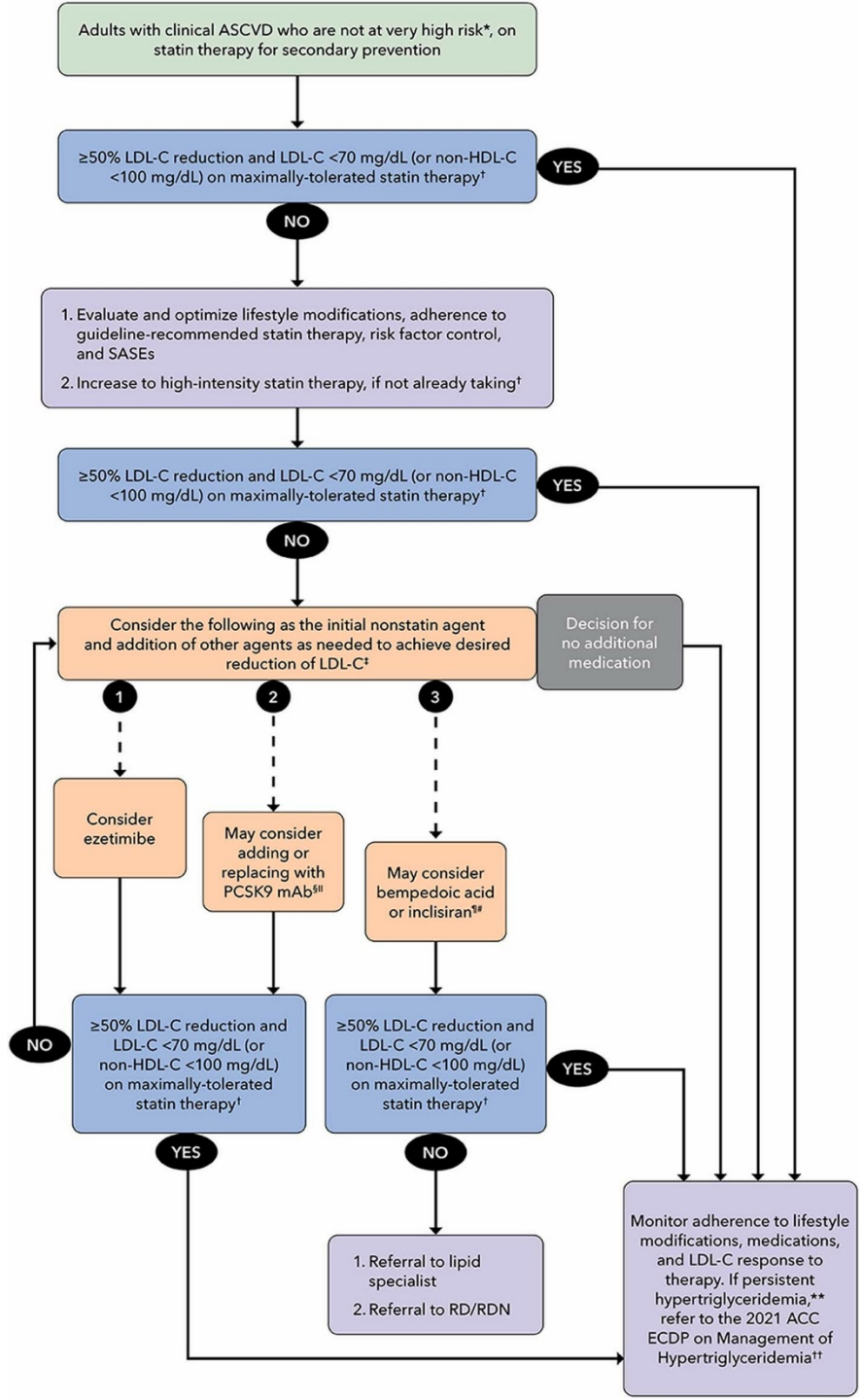
- Complete Tobacco cessation
- Continue to exercise
- Compliance with Atorvastatin and Evolocumab
- Repeat LDL was 41 mg/dl
- Aggressive CV Risk Factor Assessment and Modification

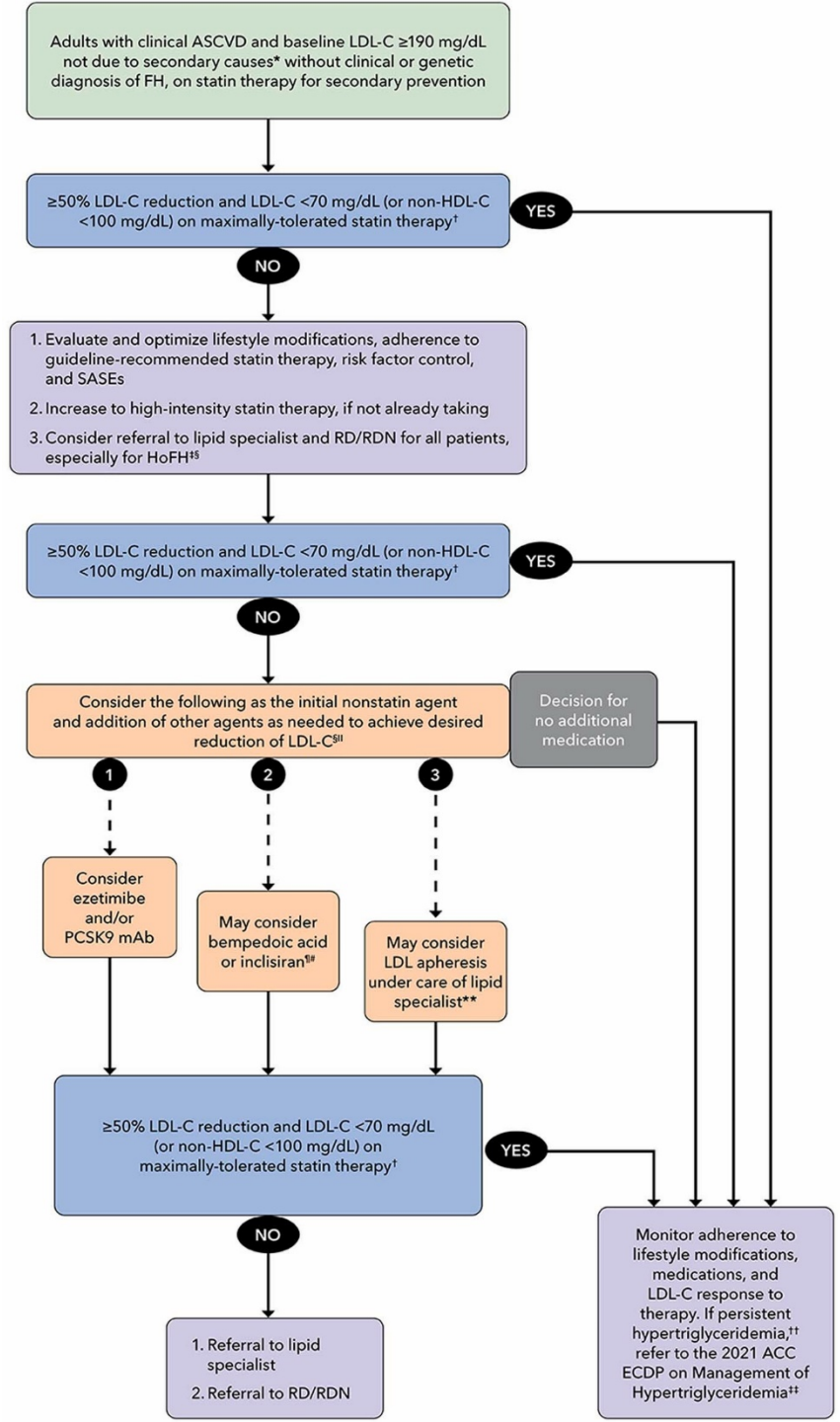
Highlights

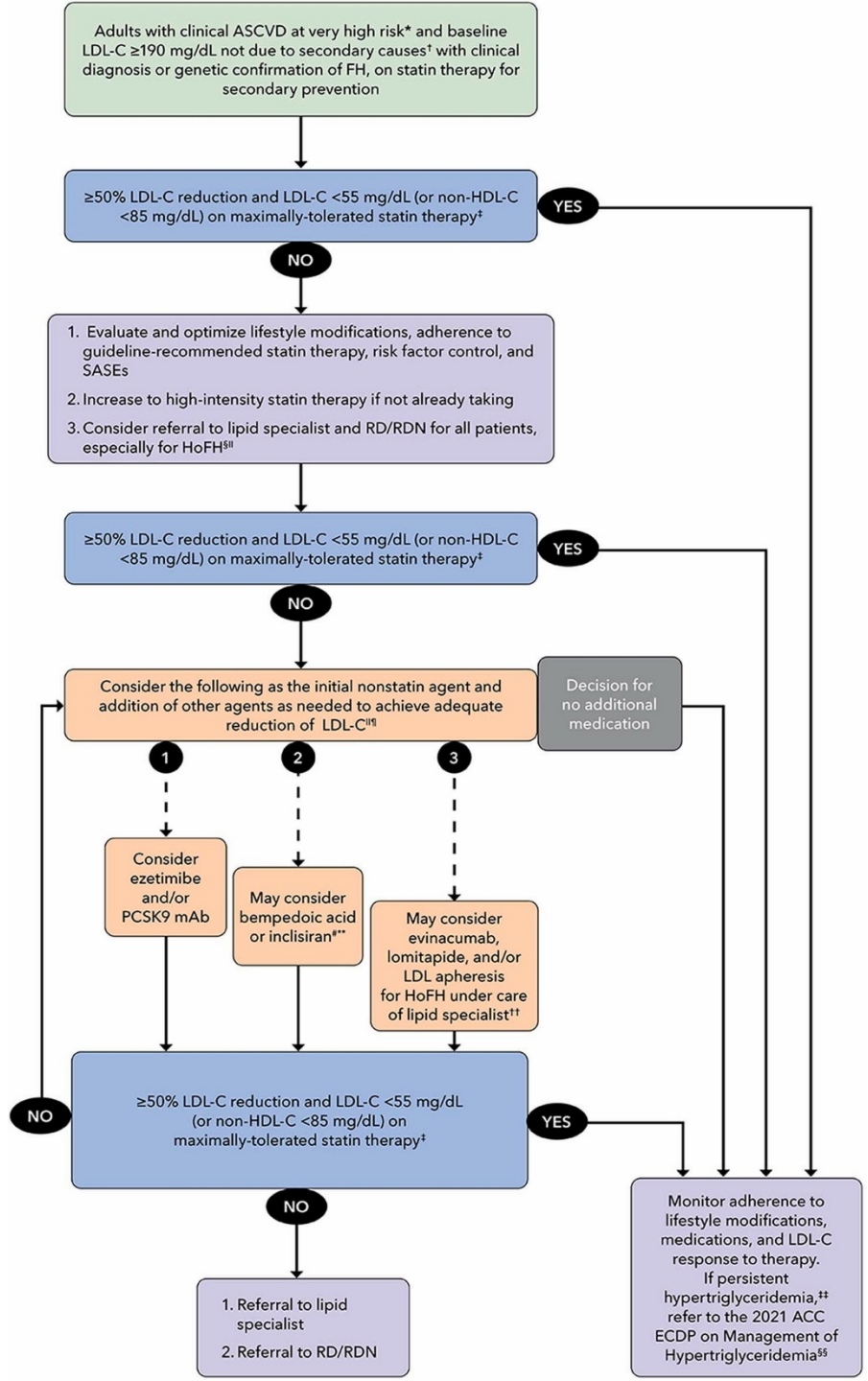
- Assess patient’s continuum of disease
- Assess 10 Year CV risk but understand lifetime Risk
- Knowing risk dictates treatment goals.
- Higher risk CV Patients have more to gain in benefits from therapy
- Earlier Combination treatment goals
- Education lowers barriers to lifestyle modifications and Medical therapy compliance. Spend time with your patients.
- Decreasing LDL exposure earlier equals decrease CV events, disability and death.

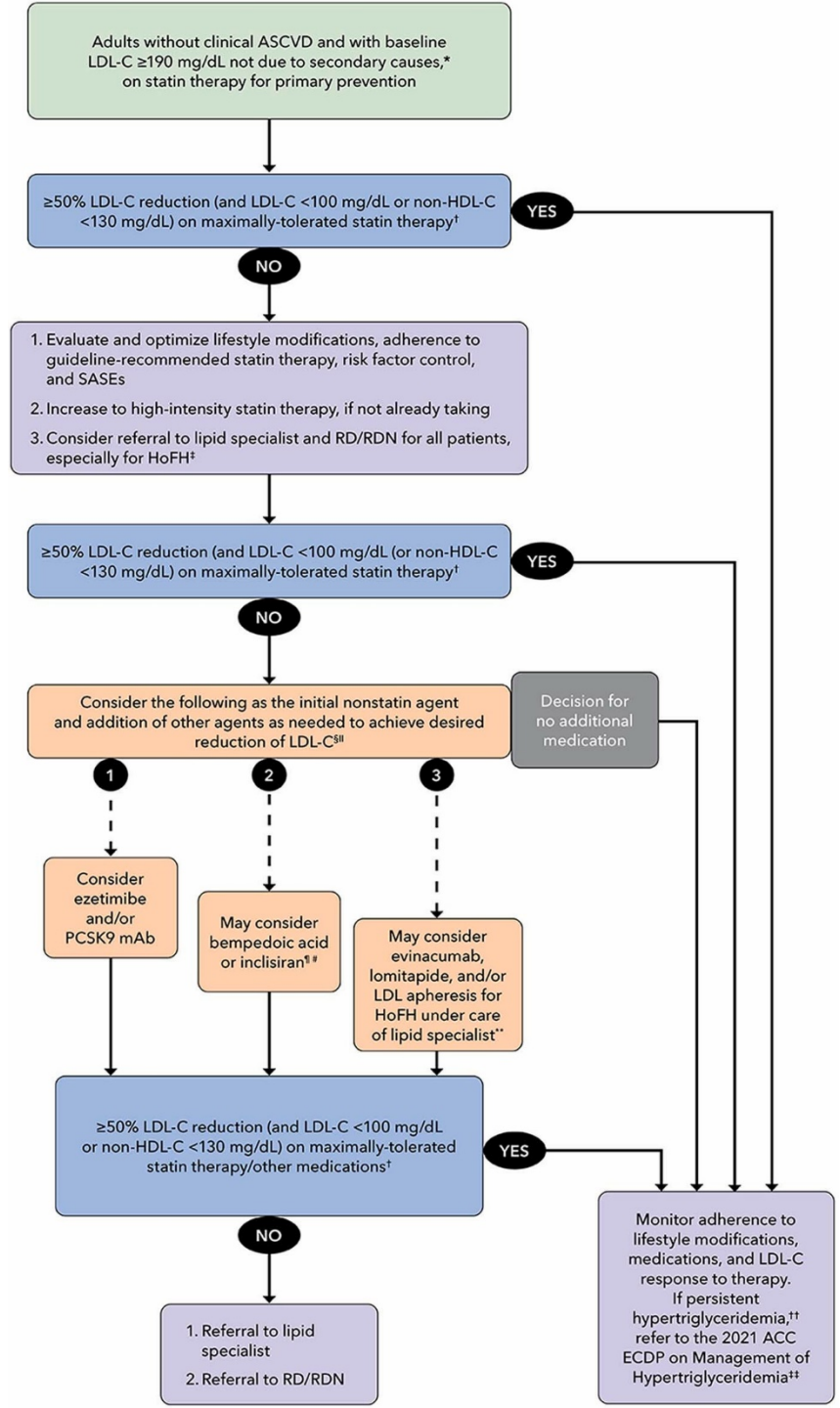
Thank you!

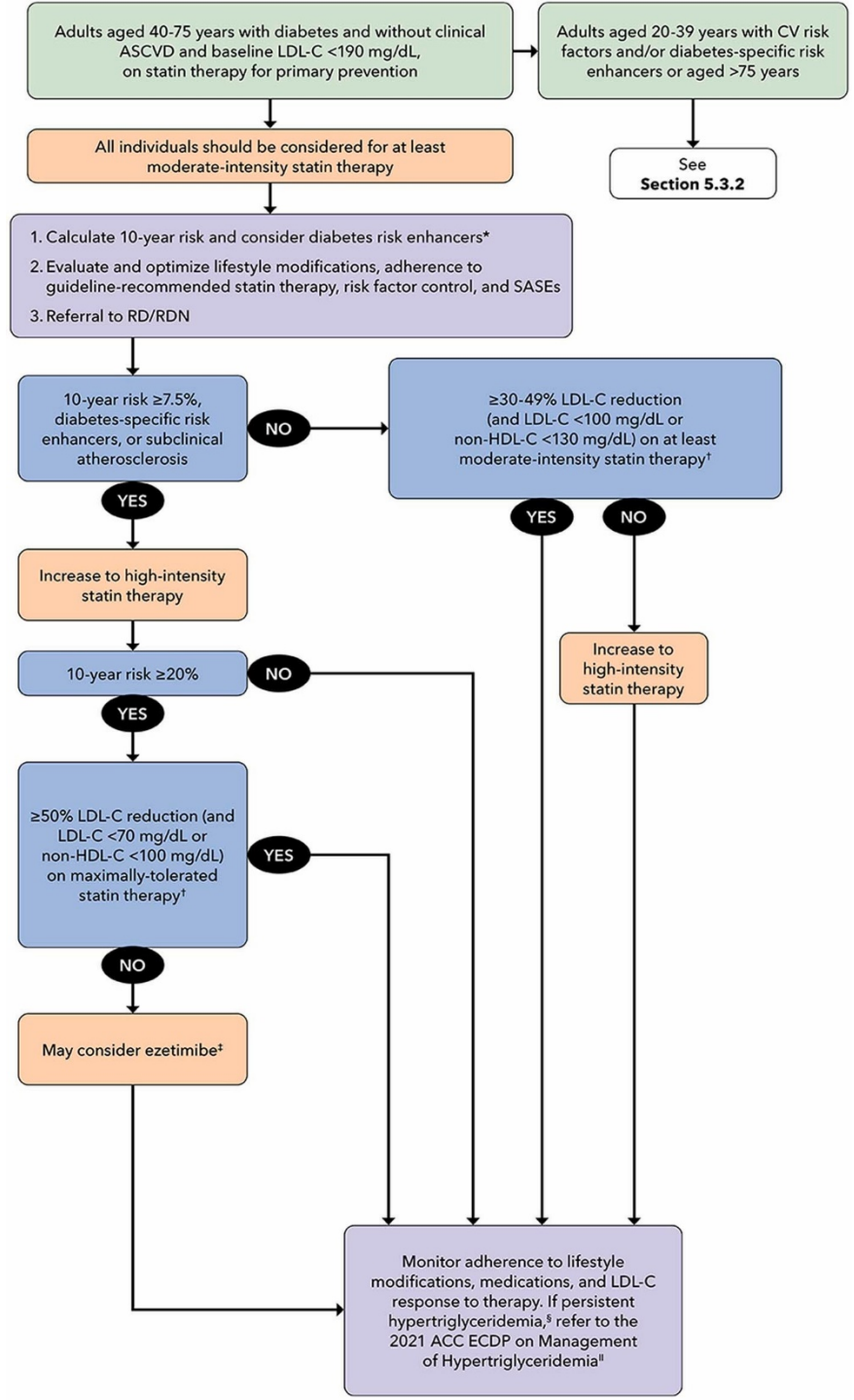
- Questions

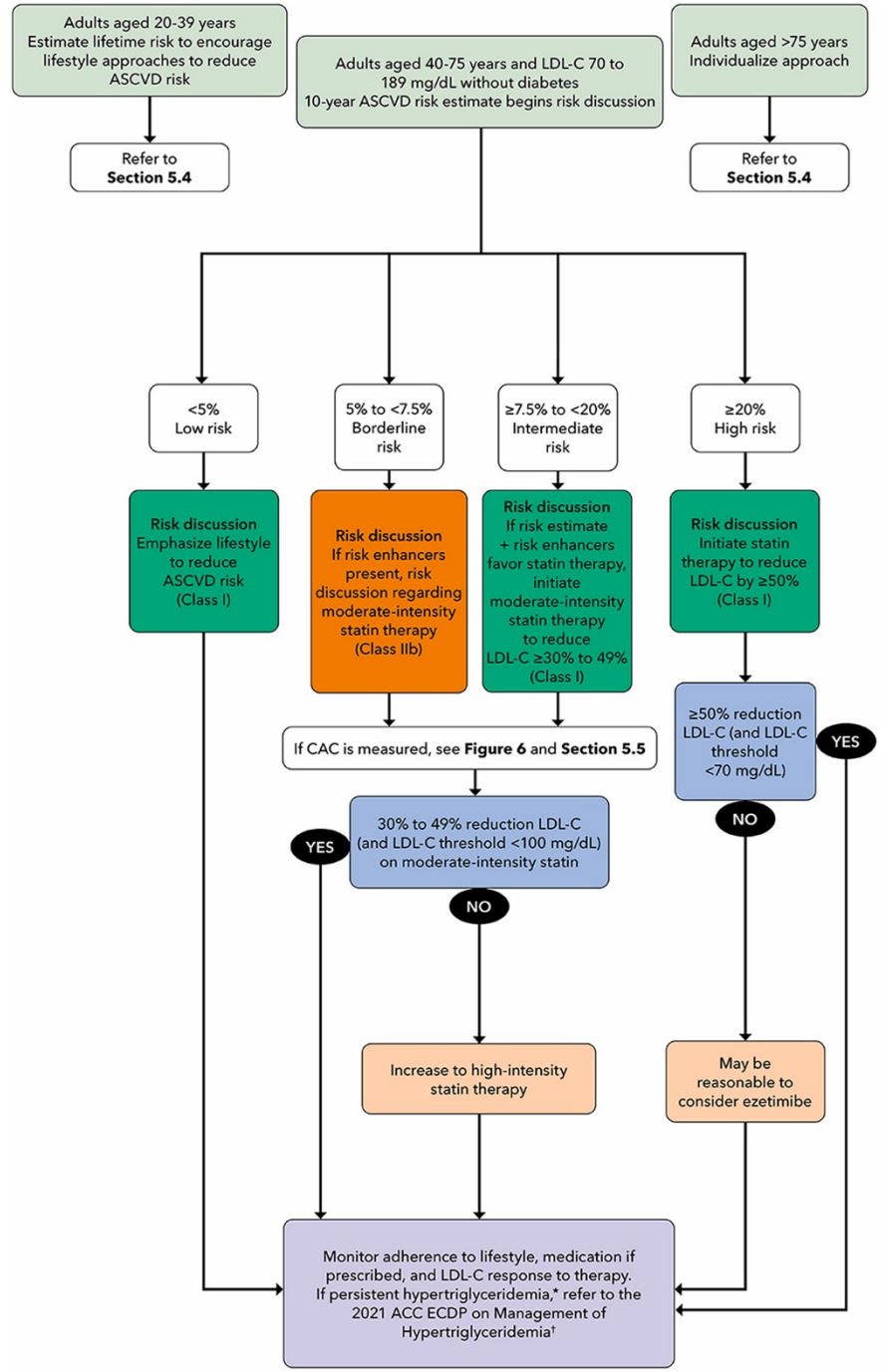

Adults with clinical ASCVD who are not at very high risk*, on statin therapy for secondary prevention
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
NO
1. Evaluate and optimize lifestyle modifications, adherence to guideline-recommended statin therapy, risk factor control, and SASEs
2. Increase to high-intensity statin therapy, if not already taking†
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
NO
Consider the following as the initial nonstatin agent and addition of other agents as needed to achieve desired reduction of LDL-C‡
Decision for no additional medication
1
2
3
Consider ezetimibe
May consider adding or replacing with PCSK9 mAb§||
May consider bempedoic acid or inclisiran¶#
NO
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
YES
NO
1. Referral to lipid specialist
2. Referral to RD/RDN
Monitor adherence to lifestyle modifications, medications, and LDL-C response to therapy. If persistent hypertriglyceridemia,** refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia††

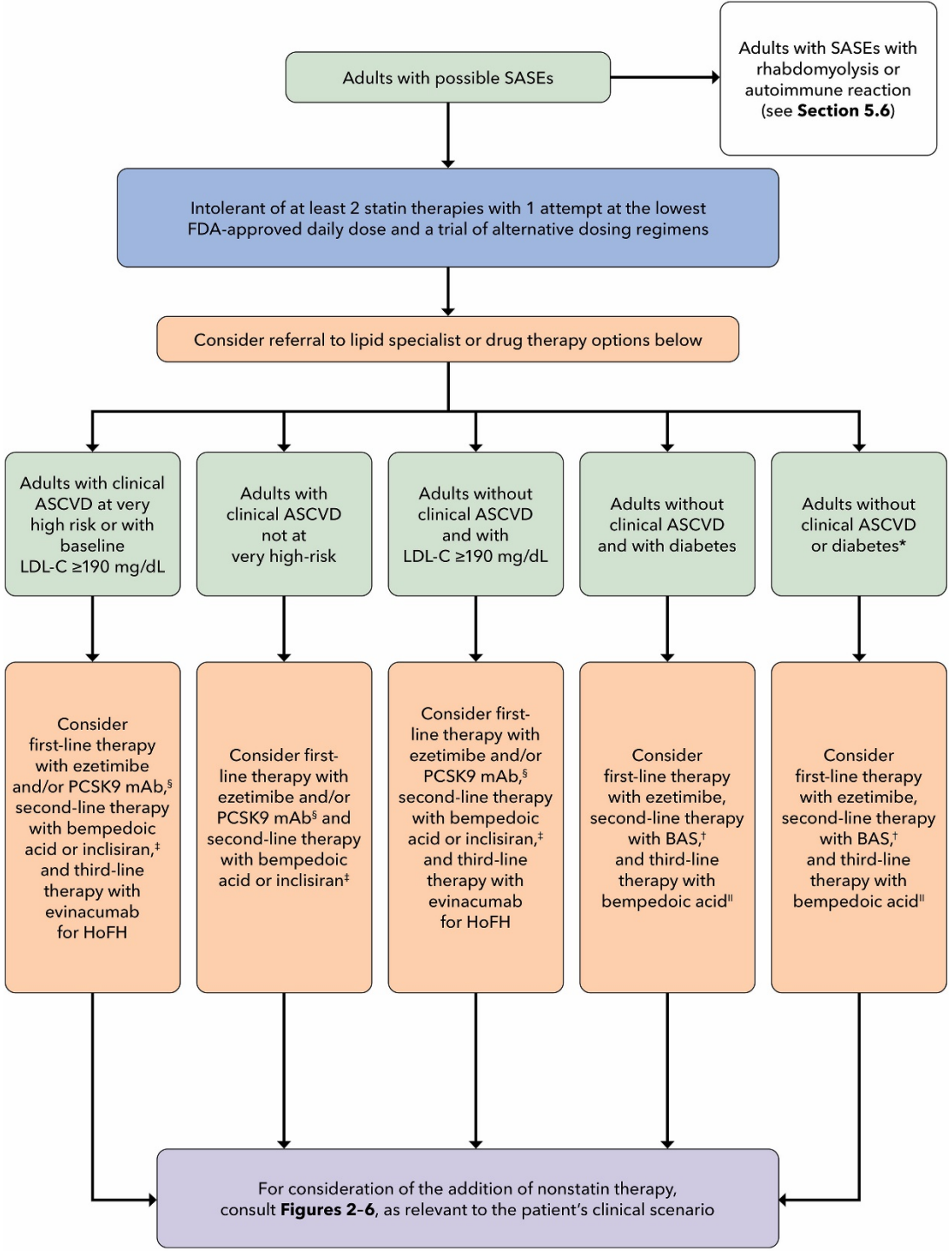

Adults with clinical ASCVD and baseline LDL-C ≥190 mg/dL not due to secondary causes* without clinical or genetic diagnosis of FH, on statin therapy for secondary prevention
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
NO
1. Evaluate and optimize lifestyle modifications, adherence to guideline-recommended statin therapy, risk factor control, and SASEs
2. Increase to high-intensity statin therapy, if not already taking
3. Consider referral to lipid specialist and RD/RDN for all patients, especially for HoFH‡§
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
NO
Consider the following as the initial nonstatin agent and addition of other agents as needed to achieve desired reduction of LDL-C§‖
Decision for no additional medication
1
2
3
Consider ezetimibe and/or PCSK9 mAb
May consider bempedoic acid or inclisiran‖#
May consider LDL apheresis under care of lipid specialist**
≥50% LDL-C reduction and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
NO
1. Referral to lipid specialist
2. Referral to RD/RDN
Monitor adherence to lifestyle modifications, medications, and LDL-C response to therapy. If persistent hypertriglyceridemia,†† refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia‡‡


Adults with clinical ASCVD at very high risk* and baseline LDL-C ≥190 mg/dL not due to secondary causes† with clinical diagnosis or genetic confirmation of FH, on statin therapy for secondary prevention
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy‡
YES
NO
1. Evaluate and optimize lifestyle modifications, adherence to guideline-recommended statin therapy, risk factor control, and SASEs
2. Increase to high-intensity statin therapy if not already taking
3. Consider referral to lipid specialist and RD/RDN for all patients, especially for HoFH§||
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy‡
YES
NO
Consider the following as the initial nonstatin agent and addition of other agents as needed to achieve adequate reduction of LDL-C||¶
Decision for no additional medication
1
2
3
Consider ezetimibe and/or PCSK9 mAb
May consider bempedoic acid or inclisiran#**
May consider evinacumab, lomitapide, and/or LDL apheresis for HoFH under care of lipid specialist††
NO
≥50% LDL-C reduction and LDL-C <55 mg/dL (or non-HDL-C <85 mg/dL) on maximally-tolerated statin therapy‡
YES
NO
1. Referral to lipid specialist
2. Referral to RD/RDN
Monitor adherence to lifestyle modifications, medications, and LDL-C response to therapy. If persistent hypertriglyceridemia,‡‡ refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia§§


Adults without clinical ASCVD and with baseline LDL-C ≥190 mg/dL not due to secondary causes,* on statin therapy for primary prevention
≥50% LDL-C reduction (and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally-tolerated statin therapy†
YES
NO
1. Evaluate and optimize lifestyle modifications, adherence to guideline-recommended statin therapy, risk factor control, and SASEs
2. Increase to high-intensity statin therapy, if not already taking
3. Consider referral to lipid specialist and RD/RDN for all patients, especially for HoFH‡
≥50% LDL-C reduction (and LDL-C <100 mg/dL (or non-HDL-C <130 mg/dL) on maximally-tolerated statin therapy†
YES
NO
Consider the following as the initial nonstatin agent and addition of other agents as needed to achieve desired reduction of LDL-C§‖
Decision for no additional medication
1
2
3
Consider ezetimibe and/or PCSK9 mAb
May consider bempedoic acid or inclisiran¶#
May consider evinacumab, lomitapide, and/or LDL apheresis for HoFH under care of lipid specialist**
≥50% LDL-C reduction (and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally-tolerated statin therapy/other medications†
YES
NO
1. Referral to lipid specialist
2. Referral to RD/RDN
Monitor adherence to lifestyle modifications, medications, and LDL-C response to therapy. If persistent hypertriglyceridemia,†† refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia‡‡


Adults aged 40-75 years with diabetes and without clinical ASCVD and baseline LDL-C <190 mg/dL, on statin therapy for primary prevention
Adults aged 20-39 years with CV risk factors and/or diabetes-specific risk enhancers or aged >75 years
See Section 5.3.2
All individuals should be considered for at least moderate-intensity statin therapy
1. Calculate 10-year risk and consider diabetes risk enhancers*
2. Evaluate and optimize lifestyle modifications, adherence to guideline-recommended statin therapy, risk factor control, and SASEs
3. Referral to RD/RDN
10-year risk ≥7.5%, diabetes-specific risk enhancers, or subclinical atherosclerosis
NO
≥30-49% LDL-C reduction (and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on at least moderate-intensity statin therapy†
YES
YES
NO
Increase to high-intensity statin therapy
Increase to high-intensity statin therapy
10-year risk ≥20%
NO
YES
≥50% LDL-C reduction (and LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally-tolerated statin therapy†
YES
NO
May consider ezetimibe‡
Monitor adherence to lifestyle modifications, medications, and LDL-C response to therapy. If persistent hypertriglyceridemia,§ refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia‖


Adults aged 20-39 years
Estimate lifetime risk to encourage lifestyle approaches to reduce ASCVD risk
Refer to Section 5.4
Adults aged 40-75 years and LDL-C 70 to 189 mg/dL without diabetes
10-year ASCVD risk estimate begins risk discussion
Adults aged >75 years
Individualize approach
Refer to Section 5.4
<5% Low risk
5% to <7.5% Borderline risk
≥7.5% to <20% Intermediate risk
≥20% High risk
Risk discussion Emphasize lifestyle to reduce ASCVD risk (Class I)
Risk discussion If risk enhancers present, risk discussion regarding moderate-intensity statin therapy (Class IIb)
Risk discussion If risk estimate + risk enhancers favor statin therapy, initiate moderate-intensity statin therapy to reduce LDL-C ≥30% to 49% (Class I)
Risk discussion Initiate statin therapy to reduce LDL-C by ≥50% (Class I)
If CAC is measured, see Figure 6 and Section 5.5
≥50% reduction LDL-C (and LDL-C threshold <70 mg/dL)
YES
NO
30% to 49% reduction LDL-C (and LDL-C threshold <100 mg/dL) on moderate-intensity statin
YES
NO
Increase to high-intensity statin therapy
May be reasonable to consider ezetimibe
Monitor adherence to lifestyle, medication if prescribed, and LDL-C response to therapy.
If persistent hypertriglyceridemia,* refer to the 2021 ACC ECDP on Management of Hypertriglyceridemia†


Adults with possible SASEs
Adults with SASEs with rhabdomyolysis or autoimmune reaction (see **Section 5.6**)
Intolerant of at least 2 statin therapies with 1 attempt at the lowest FDA-approved daily dose and a trial of alternative dosing regimens
Consider referral to lipid specialist or drug therapy options below
Adults with clinical ASCVD at very high risk or with baseline LDL-C ≥190 mg/dL
Adults with clinical ASCVD not at very high-risk
Adults without clinical ASCVD and with LDL-C ≥190 mg/dL
Adults without clinical ASCVD and with diabetes
Adults without clinical ASCVD or diabetes*
Consider first-line therapy with ezetimibe and/or PCSK9 mAb,§ second-line therapy with bempedoic acid or inclisiran,‡ and third-line therapy with evinacumab for HoFH
Consider first-line therapy with ezetimibe and/or PCSK9 mAb§ and second-line therapy with bempedoic acid or inclisiran‡
Consider first-line therapy with ezetimibe and/or PCSK9 mAb,§ second-line therapy with bempedoic acid or inclisiran,‡ and third-line therapy with evinacumab for HoFH
Consider first-line therapy with ezetimibe, second-line therapy with BAS,† and third-line therapy with bempedoic acid‖
Consider first-line therapy with ezetimibe, second-line therapy with BAS,† and third-line therapy with bempedoic acid‖
For consideration of the addition of nonstatin therapy, consult **Figures 2–6**, as relevant to the patient's clinical scenario