A Comparative Analysis of Current Lipid Guidelines

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Kaiser Permanente 18th Annual COAST Conference

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Outline

- Comparison of Guidelines
- Role of PCSK 9 Inhibitors

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7 Main Guidelines

- 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline
- 2016 Canadian Cardiovascular Society (CCS)
- 2016 European Society for Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines
- 2014 National Institute for Health and Care Excellence (NICE)
- 2017 Kaiser Permanente Cardiovascular Risk and Dyslipidemia Management guidelines (KP)
- 2016 U.S. Preventive Services Task Force (USPSTF) report
- 2014 U.S. Department of Veteran Affairs–U.S. Department of Defense (VA-DoD)

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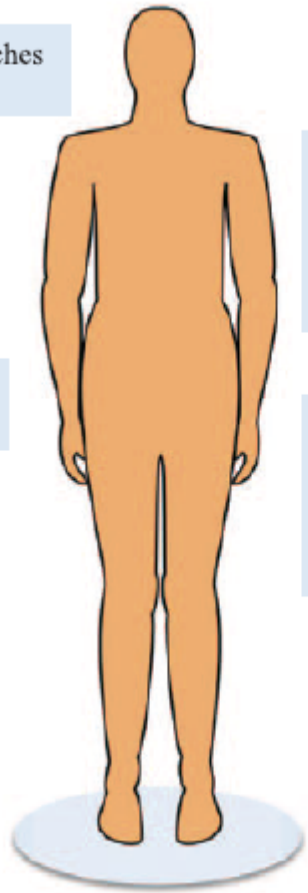
60 year old white man

Height: 69 inches
(175 cm)



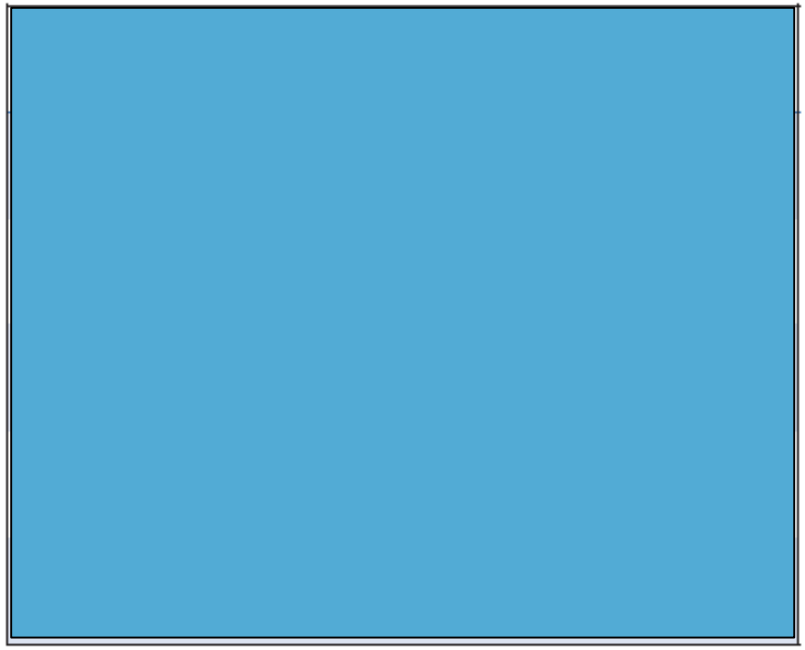
BP: 144/86
mm Hg

Medical History
No medications
Non-smoker
No CVD
No family history of CVD

Fasting Lipid Panel
Total cholesterol: 195 mg/dL
LDL-C: 125 mg/dL
HDL-C: 50 mg/dL
Triglycerides: 100 mg/dL

Weight: 180 pounds (81.6 kg)
Body mass index: 26.6 kg/m^2

Recommendations According to Different Guidelines



***Circulation*. 2016;133:1795-1806.**

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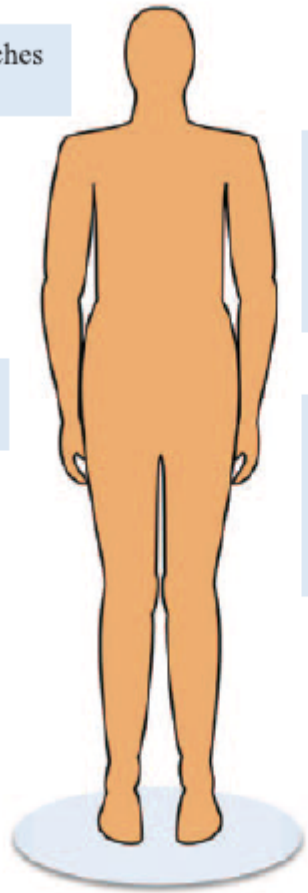

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Recommendations According to Different Guidelines

Guideline	10-year Global Risk Assessment (outcome)	Statin Recommended
2013 ACC/AHA	10.3% (ASCVD)	Yes
ATP III	10% (CHD)	No
2011 ESC/EAS	3-5% (CVD mortality)	Yes
2014 NICE	10.4% (CVD)	Yes
2012 CCS	16.6% (CVD)	No

***Circulation*. 2016;133:1795-1806.**

BACKGROUND

- The 2013 ACC/AHA guideline for cholesterol treatment made several notable changes to the older ATP III guidelines.

  1. Introduced the Pooled Cohort equations as the preferred risk assessment tool

  2. lowered the risk threshold for considering statin in primary prevention settings to a 10-year absolute ASCVD risk of 7.5%
  3. Removed cholesterol treatment targets.

A. Primary Prevention

Circulation. 2016;133:1795-1806.

J Am Coll Cardiol 2018;71:794-9)

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1. Risk Estimators and Risk Predictors

	ACC/AHA	CCS	ESC/EAS	NICE	KP
Recommended risk estimator	Pooled cohort risk equations	Framingham Risk Score	SCORE risk tool	QRISK 2	Pooled cohort risk equations

2. Outcomes and Thresholds

	ACC/AHA	CCS	ESC/EAS	NICE	KP
10-yr risk of	Hard ASCVD event (CHD death, nonfatal MI, or stroke)				
Threshold to **recommend** treatment	≥7.5% risk for age 40-75 years LDL-C ≥ 190 mg/dl for age ≥ 21 yrs				
Threshold to **consider** treatment	5%-7.5%				

3. Treatment recommendations

	ACC/AHA	CCS	ESC/EAS	NICE	KP
	Lifestyle				
	• ≥7.5% risk: moderate or high intensity statin • 5%–7.5% risk: moderate intensity • <5% or age <40 or >75 yrs and LDL-C <190 mg/dl: consider in select patients • Clinician-patient risk discussion prior to statin initiation				

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B. Secondary Prevention

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Treatment recommendations

	ACC/AHA	CCS	ESC/EAS	NICE	KPNC
	Lifestyle	Lifestyle	Lifestyle	Lifestyle	Lifestyle
	• ≤ 75 yrs : high-intensity statin • >75 yrs : moderate-intensity statin	• Target ≥50% reduction in LDL-C OR LDL-C <77 mg/dl • If LDL-C ≥193 mg/dl, target ≥50% reduction in LDL-C	Maximally tolerated dose of statin to achieve target treatment goal < 70 mg/dl	High intensity statin	Same as ACC/AHA

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Risk Categories per ESC

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

Elderly patients (age >75 yrs or life expectancy <5 yrs)

	ACC/AHA	CCS	ESC/EAS	NICE	KP
	Continue statin if already tolerating 1 prevention: recommend not starting statins for primary prevention. Statin therapy may be considered in selected individuals. 2 prevention: start moderate-intensity statin	If considered HIGH risk, recommend patient and physician discussion to initiate statin therapy	1 prevention: if risk factors for ASCVD, consider starting statin 2 prevention: treatment same as younger patients, but start at lower dose	QRISK2 is calibrated to age < 84 yrs	No special comment

End-stage renal disease

	ACC/AHA	CCS	ESC/EAS	NICE	KP
	Maintenance dialysis: no recommendation for or against use of statins	Not to initiate therapy in dialysis-dependent patients Continue therapy in those ALREADY receiving it at time of dialysis initiation	No recommendations	Treat as high risk	No special comment

Diabetes mellitus

	ACC/AHA	CCS	ESC/EAS	NICE	KP
	Continue or start statin for: • LDL-C 70-189 mg/dl for age 40-75 yrs • 10-yr ASCVD risk ≥7.5%, a high intensity statin is reasonable				

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Cardiovascular Risk and Dyslipidemia Management

Clinician Guide

SEPTEMBER 2017

Introduction

This Clinician Guide is based on the 2017 KP National Cardiovascular Risk and Dyslipidemia Guideline. It was developed to assist primary care physicians and other clinicians in the outpatient management of cholesterol for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). The KP National Cardiovascular Risk and Dyslipidemia Guideline adopted the 2013 recommendations developed by the American College of Cardiology Foundation (ACC)/American Heart Association (AHA), with minor modifications. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners.

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Kaiser Permanente Atherosclerotic Cardiovascular Disease (ASCVD) Prevention Tool

Age	60 years	**Atherosclerotic CVD** (?)	No ASCVD
African American	○ Yes ◉ No	**Diabetes**	○ Yes ◉ No
Gender	○ Female ◉ Male	**LDL Cholesterol**	125 mg/dL
Total Cholesterol	195 mg/dL	**On Statins** (?)	High Intensity
HDL Cholesterol	50 mg/dL	**On Aspirin RX**	○ Yes ◉ No
Systolic Blood Pressure	144 mm/Hg	**Statin Allergy / Intolerance / Contraindication**	○ Yes ◉ No
Diastolic Blood Pressure	86 mm/Hg	**Aspirin Allergy / Intolerance / Contraindication**	○ Yes ◉ No
On BP Medications	◉ Yes ○ No	**Child Bearing Potential**	○ Yes ○ No
Smoker	○ Yes ◉ No		

Check items in red before calculating.

Calculate Reset

10-Year ASCVD Risk: 12%	
Statin:	**Continue moderate intensity statin (atorvastatin 10-20 mg or simvastatin 20-40 mg daily), consider high intensity statin (atorvastatin 40-80 mg daily).**
Aspirin:	**Consider aspirin 81 mg daily.**

Note: 10-year ASCVD risk estimate generated using the 2013 AHA/ACC risk calculator. Statin recommendations generated using KP National Dyslipidemia Guideline (adapted from the 2013 AHA/ACC Guideline) and aspirin recommendations generated using the KP National Aspirin Recommendations (adapted from the 2016 USPSTF Aspirin Guideline). This is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners.

* **Clinical atherosclerotic cardiovascular disease (ASCVD)** includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, carotid stenosis ≥ 50%, or symptomatic peripheral arterial disease presumed to be of atherosclerotic origin.

Subclinical ASCVD includes asymptomatic coronary artery disease or peripheral artery disease, e.g., aortic atherosclerosis, or abnormal ankle brachial index (ABI) detected on screening.

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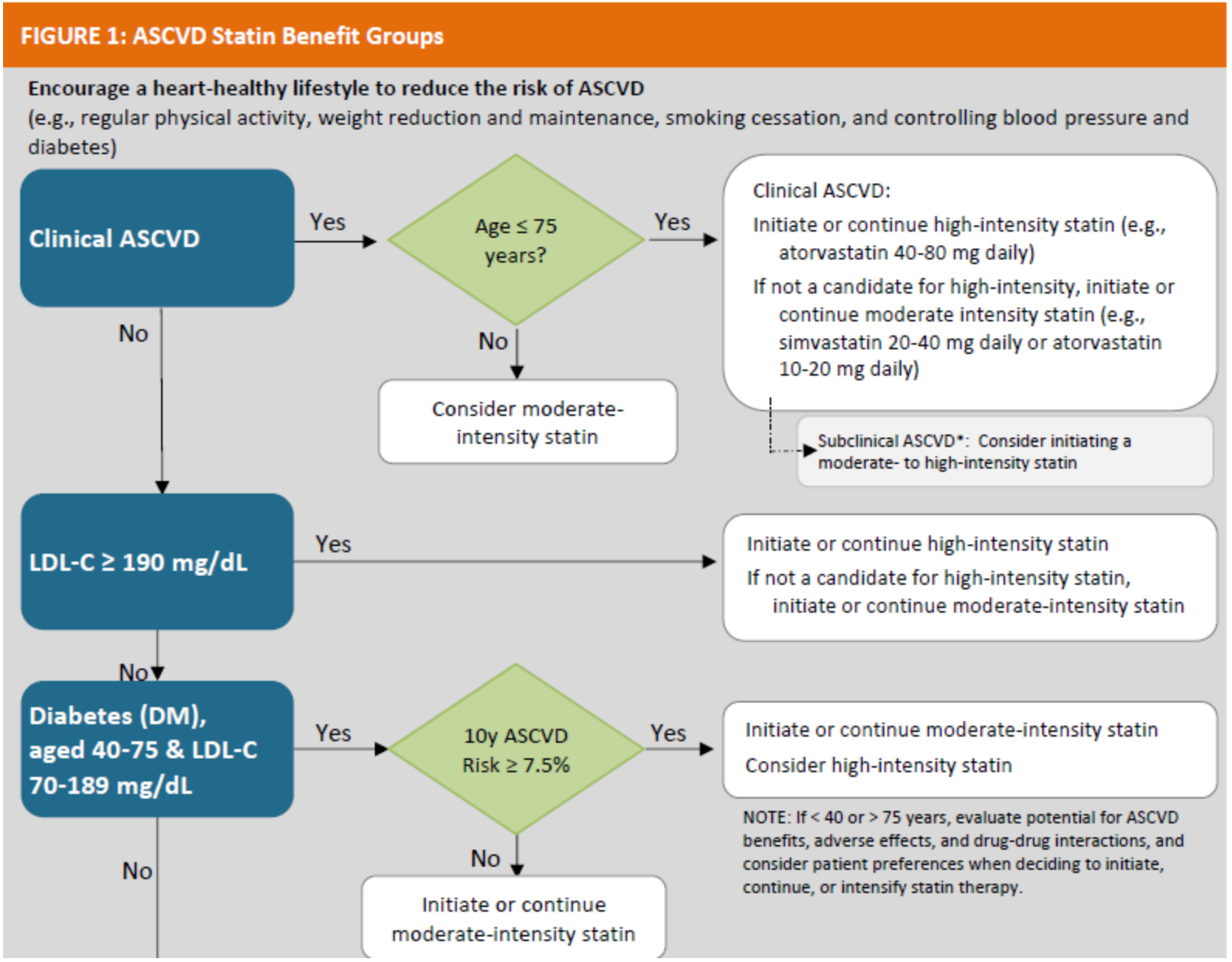
FIGURE 1: ASCVD Statin Benefit Groups



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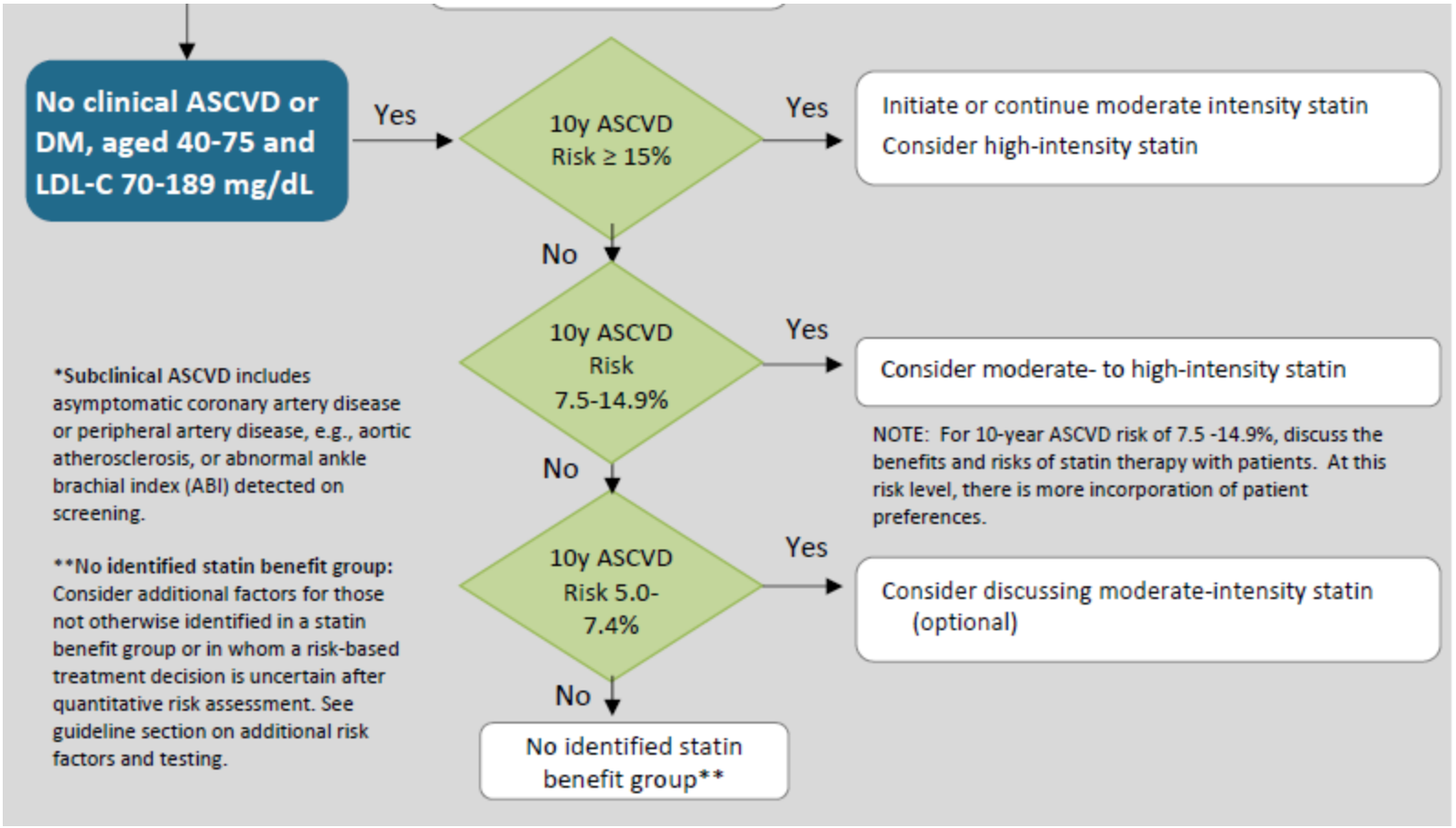

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Insufficient Response to Statin Therapy

Ezetimibe

- Focus on treatment of blood cholesterol to reduce ASCVD risk in adults.
- In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy:
  - Reinforce medication adherence;
  - Reinforce adherence to intensive lifestyle changes; and
  - Exclude secondary causes of hyperlipidemia.
- Consider using the following indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring:
  - High-intensity statin therapy generally results in an average LDL–C reduction of ≥ 50% from the untreated baseline.
  - Moderate-intensity statin therapy generally results in an average LDL–C reduction of 30-50% from the untreated baseline.
  - LDL–C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.
- In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, consider adding a nonstatin cholesterol-lowering drug(s) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
  Higher-risk individuals include:
  - Those with clinical ASCVD ≤ 75 years of age.
  - Those with baseline LDL–C ≥ 190 mg/dL.
  - Those aged 40-75 years with diabetes mellitus.
- In individuals who are candidates for statin treatment but are completely statin intolerant, consider using nonstatin cholesterol lowering drugs that have been shown to reduce ASCVD events in RCTs (i.e., ezetimibe) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
- Give preference to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs (i.e., ezetimibe).
- In individuals with clinical ASCVD on maximum tolerated oral lipid-lowering therapy (statin, ezetimibe, +/- bile acid sequestrant) and with persistently elevated lipids (e.g., LDL ≥ 130 mg/dL), consider discussing adding PCSK9 inhibitor with a lipid specialist (i.e., designated lipid specialist, cardiologist, or endocrinologist).

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In Summary

- Emphasize statins for primary/secondary prevention.
- Joint decision-making with a clinician-patient discussion.
- Utilization of differing risk estimators requires an understanding of compounding comorbidities and their influence on pre-test probability of ASCVD.
- New high-quality data could help resolve some of these differences.

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FEBRUARY 20, 2018:794–9

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) INHIBITORS

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PCSK9 Background

- Genetic studies identified *gain* of function (GOF) PCSK9 mutations causative gene for familial hypercholesterolemia (FH), which prompted extensive investigations into its relationship with LDL-R

- Individuals with PCSK9 *loss* of function (LOF) mutations were found to have lifelong low LDL cholesterol (LDL-C) levels, reduced ASCVD risk, and were otherwise healthy.

- These discoveries led to the development of PCSK9 inhibitors as a therapy to lower LDL-C.

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

The Evolving Future of PCSK9 Inhibitors

Robert S. Rosenson, MD,[a] Robert A. Hegele, MD,[b] Sergio Fazio, MD, PhD,[c]
Christopher P. Cannon, MD[d]

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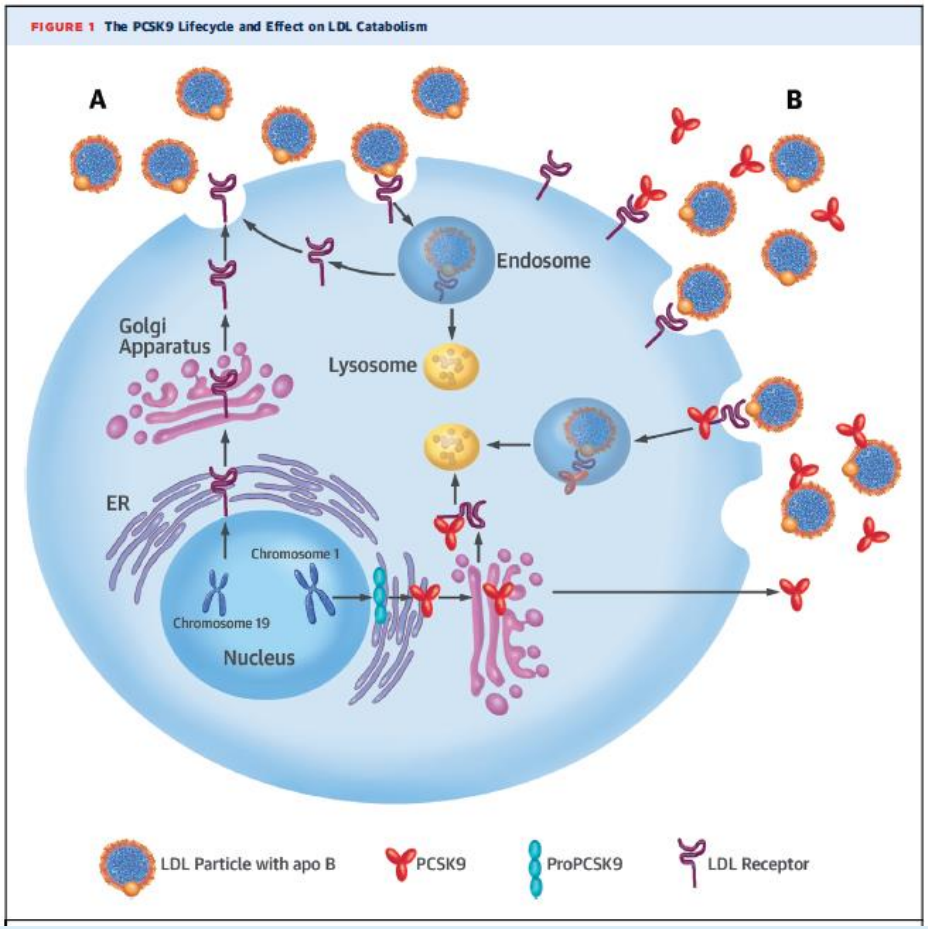

PCSK9 inhibits LDLR recycling. The binding of PCSK9 to the LDLR targets LDLR to the lysosome for degradation, preventing LDLR from returning to the surface of the hepatocyte to bind to additional LDL particles. antibodies against PCSK9 Upon binding to PCSK9, PCSK9 is unable to bind to LDLR and cause its degradation. The ultimate result is an accumulation of LDLR on hepatocytes, leading to accelerated clearance of LDL particles, and large decreases in LDL-C levels.

Alirocumab

- 75 mg / 150 mg - subcutaneous q 2 weeks or 300 mg per month.
- 75 mg ⇩ LCL-C 45% - 48%; 150 mg ⇩ LCL-C decrease 60%.
- Heterozygous FH (FDA-approved indication), LDL-C reduction 61%
- Lower TG by 10%- 15%, raise HDL cholesterol by 5% -10%, and lower lipoprotein (a) by 25%-30%.

Evolocumab

- 140 mg – q 2 weeks or 420 mg monthly.
- Both doses lower LDL-C approximately 60%.
- Heterozygous FH (FDA-approved indication), LDL-C reduction 51%
- Lower TG by 10%- 15%, raise HDL cholesterol by 5% -10%, and lower lipoprotein (a) by 25%-30%.

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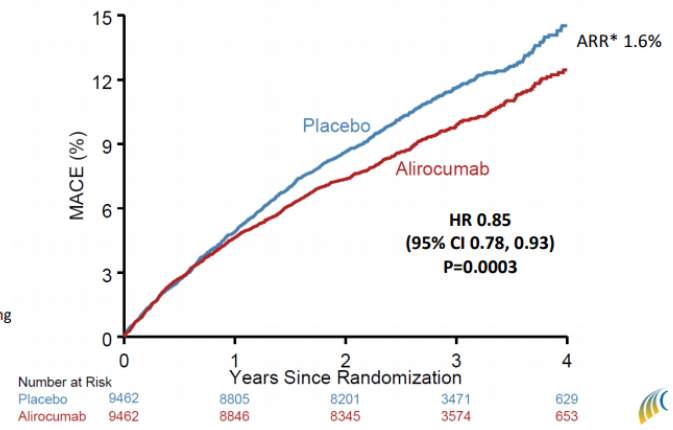
Alirocumab

- ODYSSEY OUTCOMES trial: 18,924 patients after ACS treated with maximally tolerated statin.
- 75 mg of alirocumab every 2 weeks, dose increased to 150 mg every 2 weeks if the LDL-C did not decrease to <50 mg/dl.
- > 3 yr Follow up, composite endpoint (CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization) 9.5% vs 11.1%
- The secondary endpoints of major CHD event, CV event, MI, or ischemic stroke were significantly reduced.

Evolocumab

- FOURIER trial: 27,564 patients with prior ASCVD with an additional high-risk feature treated with max tolerated statin therapy, but had LDL-C >70 mg/dl or a non-HDL-C >100 mg/dl.
- Evolocumab (either 140 mg every 2 weeks or 420 mg every month, based on patient preference) or placebo.
- 2 years of follow-up, composite endpoint (CV death, MI, stroke, hospitalization for angina, or revascularization) 9.8% versus 11.3%.
- CV death, MI, or stroke was reduced from 7.4% to 5.9% ($p < 0.001$).

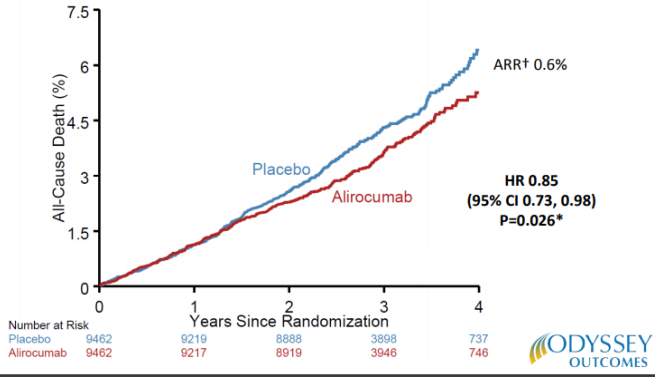
Alirocumab



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

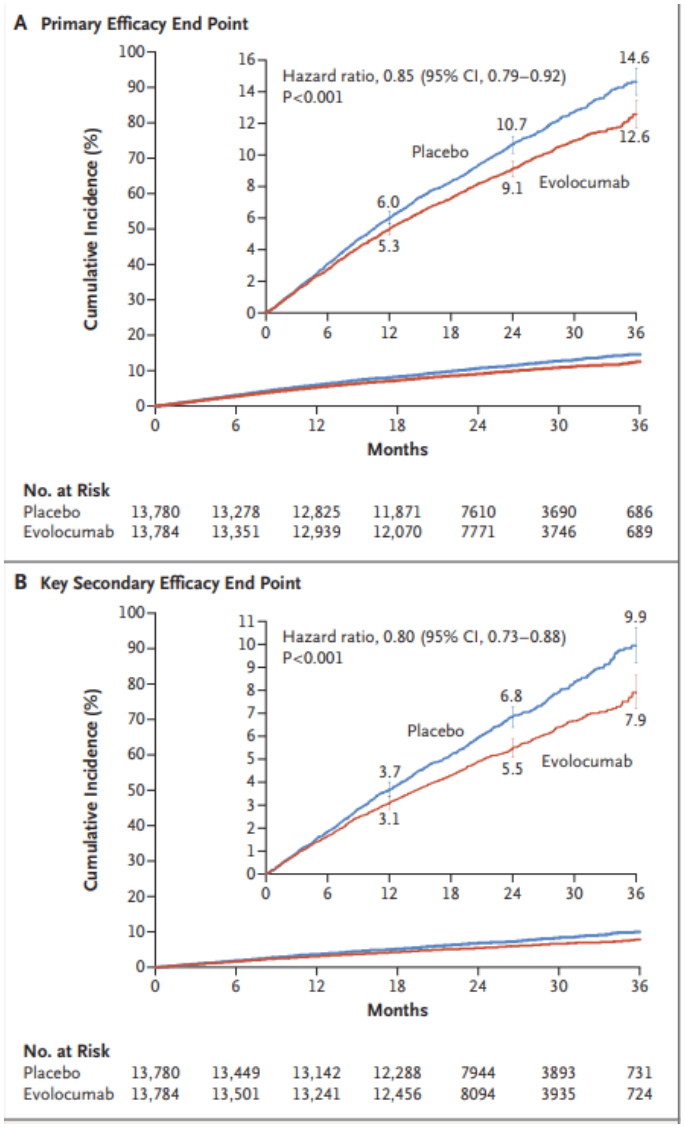
All-Cause Death



†-value cumulative incidence

ODYSSEY OUTCOMES

Evolocumab



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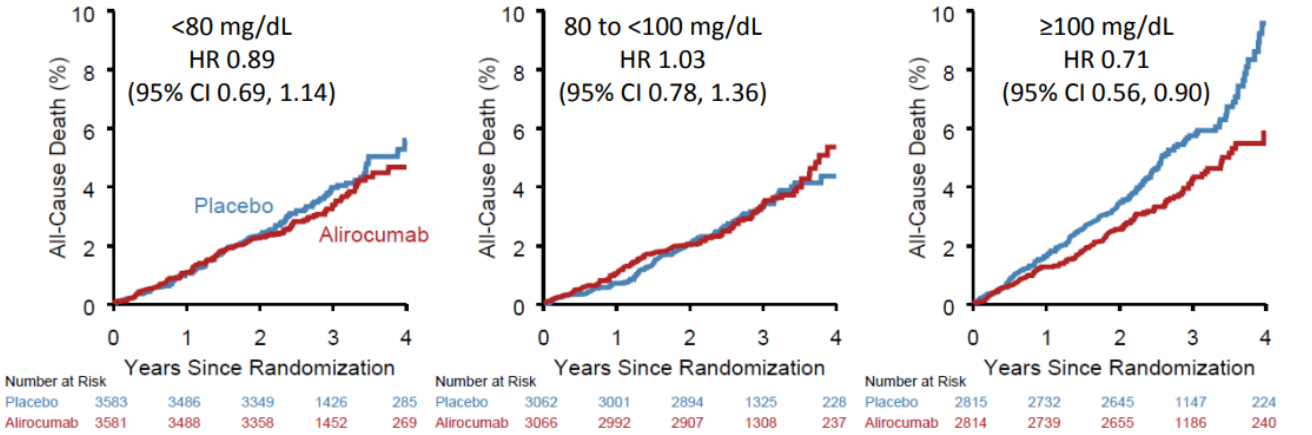
Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR* 1.7% $P_{interaction}$=0.12



sed on cumulative incidence

ODYSSEY OUTCOMES

Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo

- These are the patients who may benefit most from treatment

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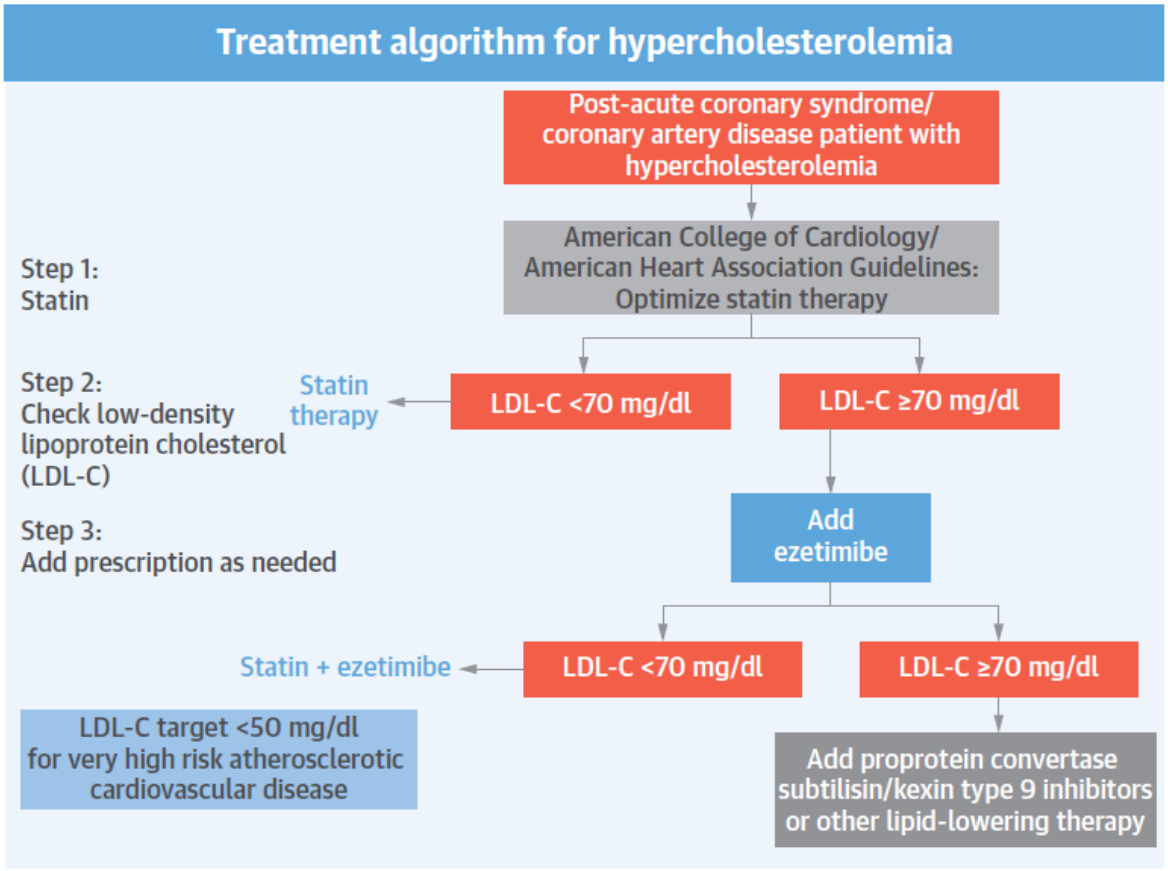
Opinions

- Main difference FOURIER and ODYSSEY Outcomes -- latter showed a statistically significant reduction all-cause mortality, which the investigators cautiously interpreted as a nominally significant result.

- Relative risk reduction was 15% in both trials.

- Expected the difference in all-cause mortality to be driven by the fact that the ACS population of ODYSSEY Outcomes should have been higher risk (FOURIER had a post-ACS population of 20%) with longer follow-up.



Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314–29.

Stepwise approach to managing low-density lipoprotein cholesterol (LDL-C) begins with therapeutic lifestyle changes (Step 1). Statin therapy (Step 2) is recommended in the 4 statin benefit groups, which include patients with atherosclerotic cardiovascular disease (ASCVD), LDL-C >190 mg/dl, or diabetes mellitus, as well as primary prevention patients with an ASCVD risk score of >7.5%. If the LDL-C target is not reached, ezetimibe is added (Step 3), and if the LDL-C target is not attained, proprotein convertase subtilisin/kexin type 9 inhibitor is added (Step 4).

Economic Impact

- Institute for Clinical and Economic Review (ICER) performed cost-effectiveness analyses to establish value-based price benchmarks for alirocumab.
  - $2,300-$3,400 per year would be cost-effective if used to treat all patients who meet trial eligibility criteria.
  - Alirocumab cost of $4,500-$8,000 per year would be cost-effective if used in the patients with LDL-C ≥100 mg/dl, with a slightly better relative risk reduction.

Institute for Clinical and Economic Review. Alirocumab for High Cholesterol – Preliminary New Evidence Update. March 10, 2018.

What about Kaiser Permanente ?

Alirocumab

- PRALUENT - $ 11-14 K

Evolocumab

- REPATHA - $ 14 K → KP < $ 5 K

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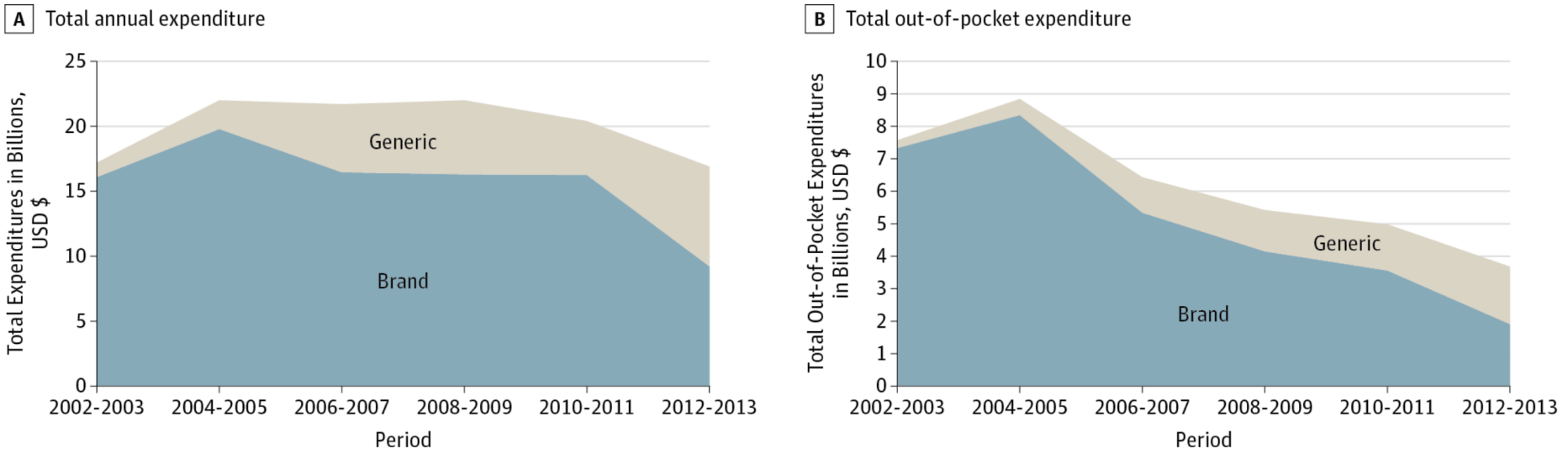
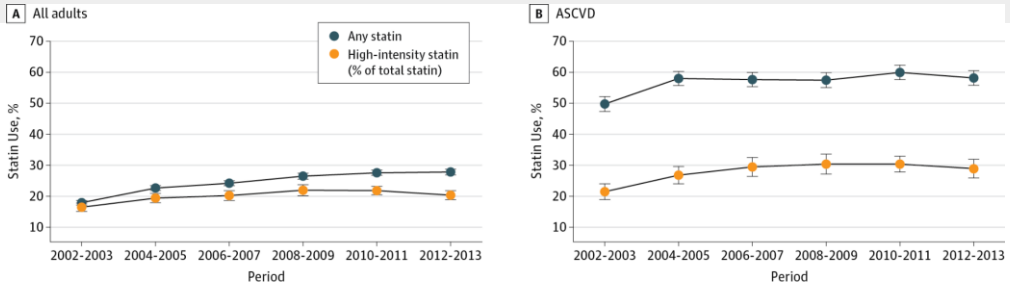
National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013Insights From the Medical Expenditure Panel Survey

Salami JA, Rana JS, Nasir K et al. JAMA Cardiol. 2017;2(1):56-65.

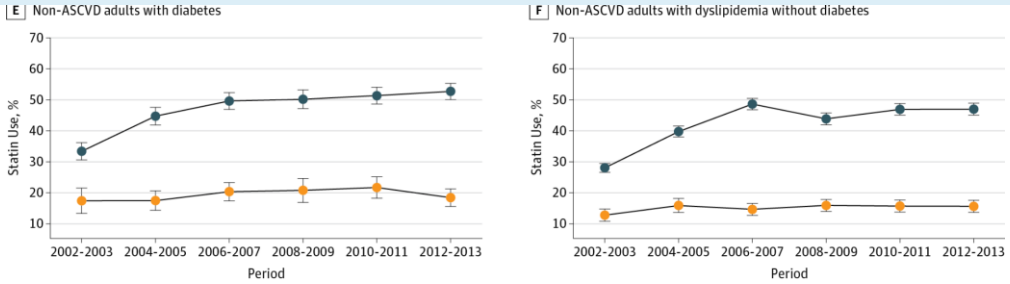


Trends in Statin Expenditures in the General Adult Population, Medical Expenditure Panel Survey 2002-2013The graphs show the (A) total annual expenditures on statins and (B) total out-of-pocket expenditures on statins in the general US adult population.

From: **National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013Insights From the Medical Expenditure Panel Survey**



Among those with established ASCVD, statin use was 49.8% and 58.1% in 2002-2003 and 2012-2013, respectively, and less than one-third were prescribed as a high-intensity dose.



CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Improved Cardiovascular Risk Factors Control Associated with a Large-Scale Population Management Program Among Diabetes Patients

Jamal S. Rana, MD, PhD,[a,b,c] Andrew J. Karter, PhD,[c,d] Jennifer Y. Liu, MPH,[c] Howard H. Moffet, MPH,[c] Marc G. Jaffe, MD[e]

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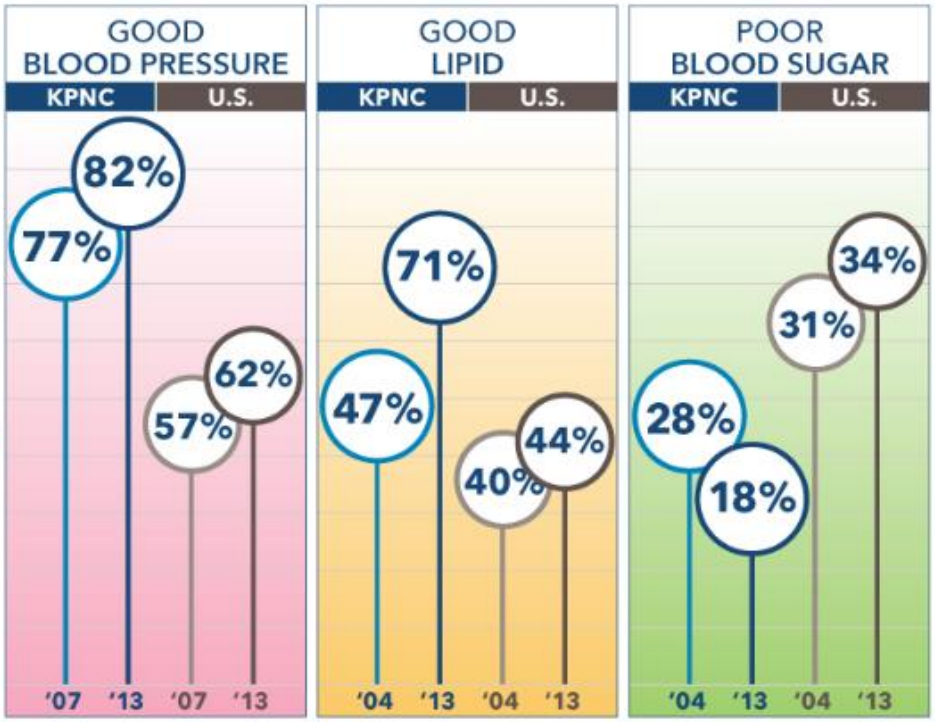
Kaiser Permanente's PHASE program **outperforms nation** on **controlling** **3** CARDIOVASCULAR risk factors for **diabetes patients***



*Rana et al. Am J Med 2018

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THANK YOU

KAISER PERMANENTE®