PACE

Pharmaceutical Assistance Contract for the Elderly

Alosa Health

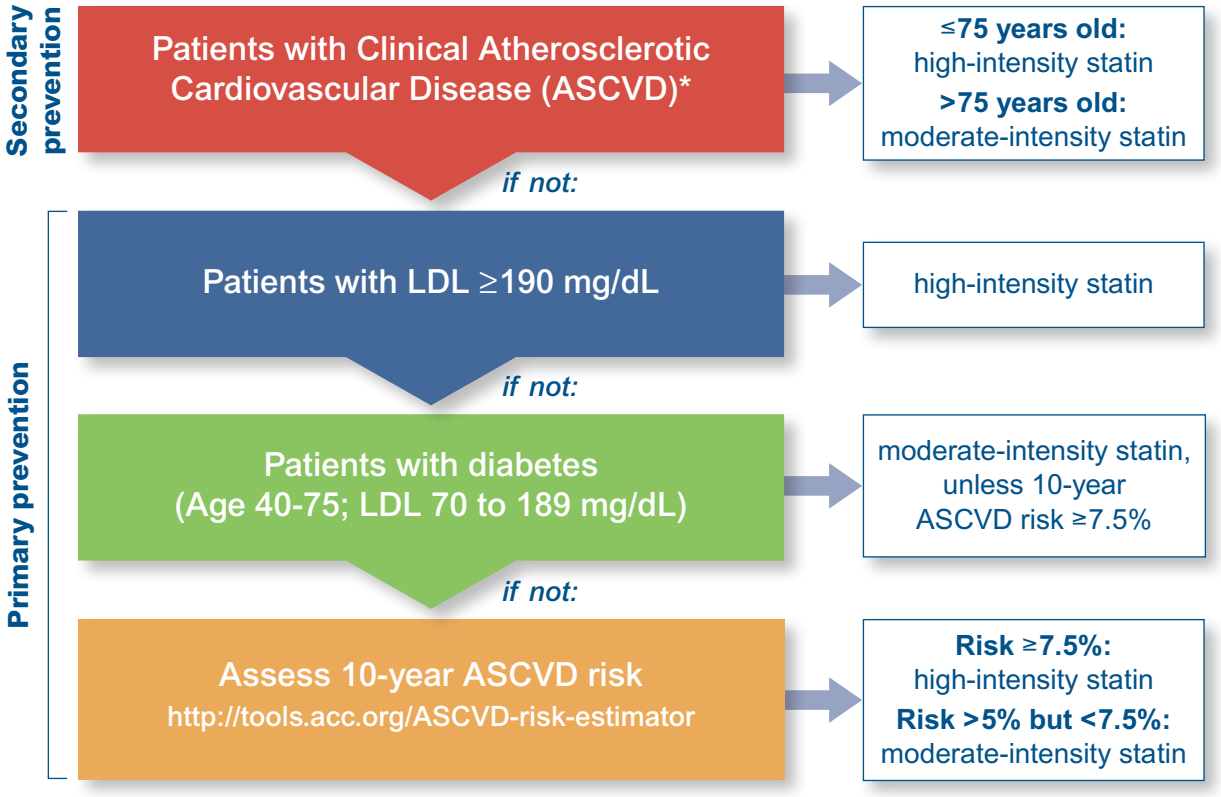
Balanced information for better care

Managing lipids to prevent cardiovascular events:

Integrating the current guidelines into practice

Statins save lives. But guidelines have evolved: focus is now on risk groups, not LDL targets

FIGURE 1. The 2013 American College of Cardiology and American Heart Association (ACC/AHA) Guidelines define four risk groups for treatment.[1]



*Clinical ASCVD: acute coronary syndrome (ACS), myocardial infarction (MI), angina, revascularization, stroke, TIA, or peripheral arterial disease.

TABLE 1. Select statin intensity based on patient risk factors. Each intensity grouping has an expected LDL response that can be used to assess adherence.[1]

High-intensity Lowers LDL by ≥50%	Moderate-intensity Lowers LDL 30-50%
atorvastatin 40-80mg	atorvastatin 10-20mg
rosuvastatin 20-40mg	rosuvastatin 5-10mg
If the patient cannot tolerate a high-intensity statin regimen, prescribe the highest tolerated dose.	simvastatin 20-40mg
	pravastatin 40-80mg

Then and now: comparing the guidelines and selecting treatment

TABLE 2. A comparison of the older Adult Treatment Panel III (ATP III) guidelines and the more recent ACC/AHA guidelines.[1,2]

	ATP-III (2004)	ACC/AHA Guidelines (2013)
Whom to treat	use coronary heart disease (CHD) risk factors and baseline LDL level	one of four ASCVD risk groups
What to treat with	a statin and/or other cholesterol lowering drugs	a statin only
How to choose a statin dose	based on LDL level	based on risk group and age
Role of LDL in follow-up	to set treatment goal and guide medical titration	to assess adherence

The newer guidelines base recommendations on preventing the cardiovascular (CV) outcomes studied in clinical trials, while previous guidelines focused on reaching specific LDL levels.

Lifestyle modification is still a key part of managing cholesterol.

Diet: Eat more fruits, vegetables, and fiber.
DASH or Mediterranean diets are best.
Visit **AlosaHealth.org/modules/lipids** for more information.

Exercise: Moderate aerobic activity 3-4 times a week, for at least 40 minutes each time.

Smoking: Quitting is vitally important.
Help is available at 1-800-QUITNOW.

Secondary prevention: prescribe a high-intensity statin for patients with ASCVD

For patients over 75, the best data are for moderate-intensity statins.

FIGURE 2. Patients under 65 benefitted from high-intensity statins in PROVE-IT.[3]

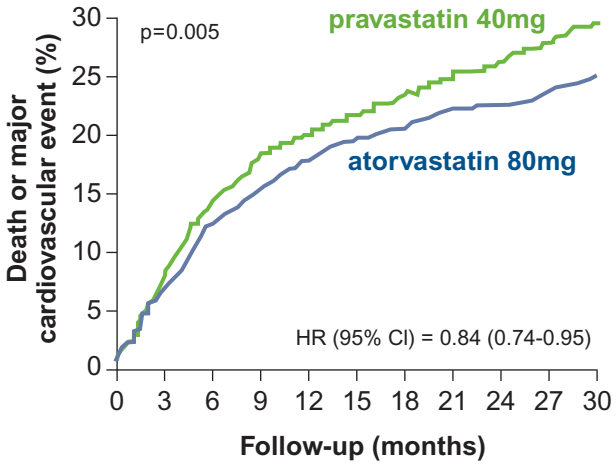
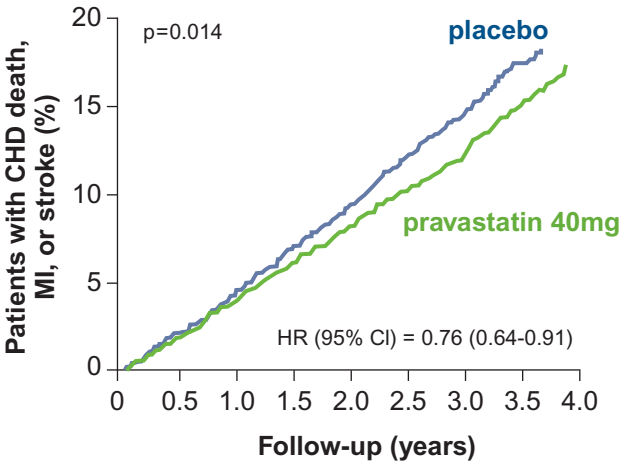
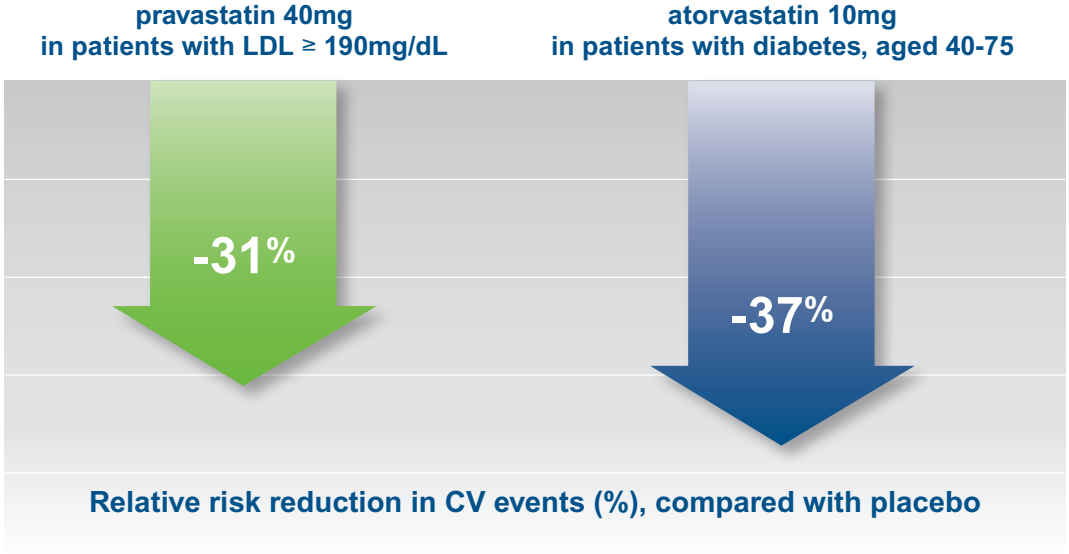


FIGURE 3. Patients over 70 had reduced risk of CV events with moderate-intensity statins in PROSPER.[4]



Primary prevention

FIGURE 4. In patients with high cholesterol, pravastatin 40mg reduced the risk of CHD death or MI by 31%.[5] For patients with diabetes aged 40-75, atorvastatin 10mg reduced CHD, stroke, and revascularization by over a third.[6]



Primary prevention: assessing the 10-year risk of an ASCVD event

Statins provide a clear net benefit in patients with a 10-year ASCVD risk ≥7.5%; reduction in cardiovascular events outweighs the risk of side effects, for most patients.

FIGURE 5. But for patients with a lower 10-year ASCVD risk (e.g. 5%), the decision to prescribe a statin requires balancing risks, benefits, and patient preference.[1]

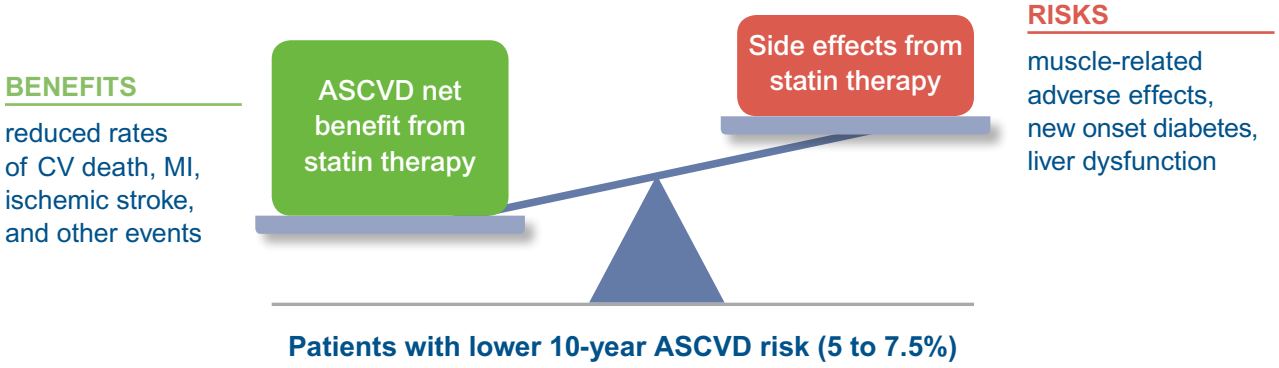
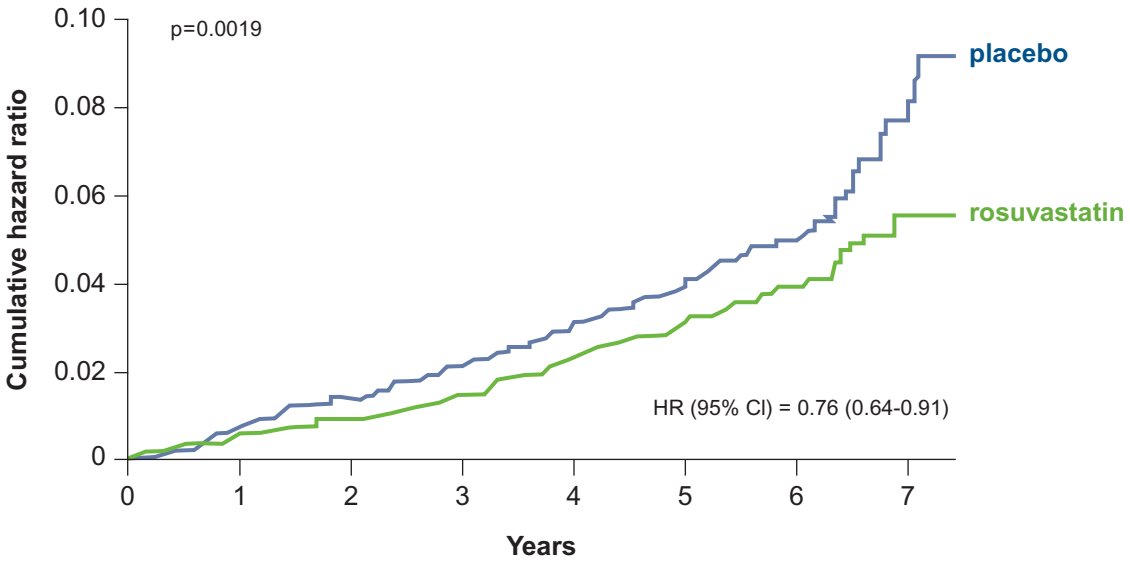


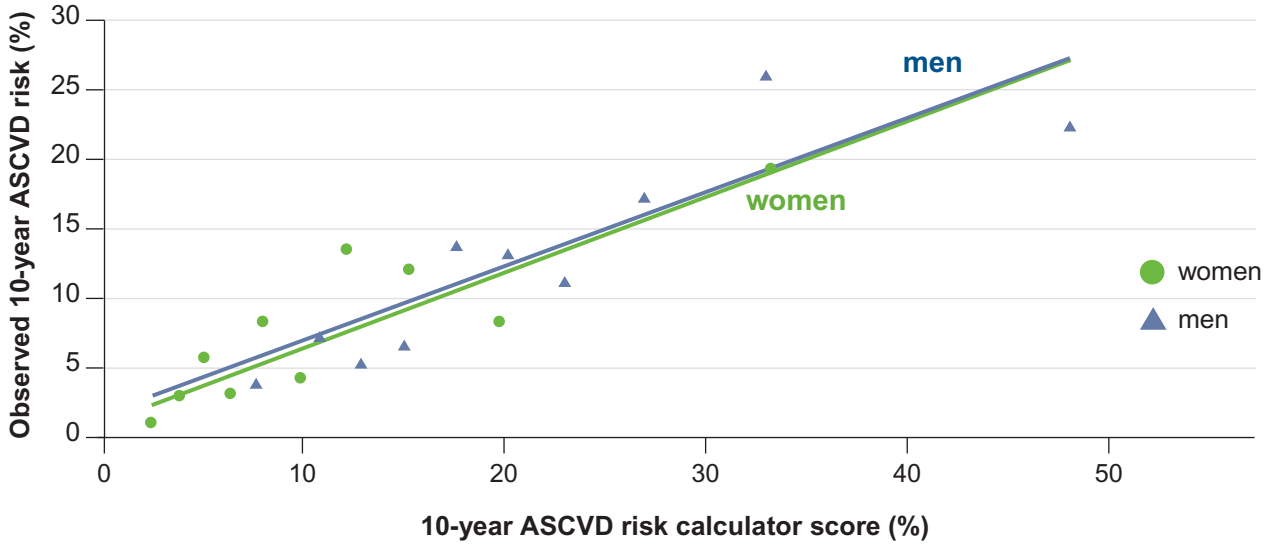
FIGURE 6. The HOPE-3 investigators recently reported a 24% relative reduction in CV death, MI, and stroke in patients with low to intermediate risk of ASCVD treated with rosuvastatin 10mg vs. placebo.[7]



Calculating risk: how best to estimate the likelihood of an ASCVD event?

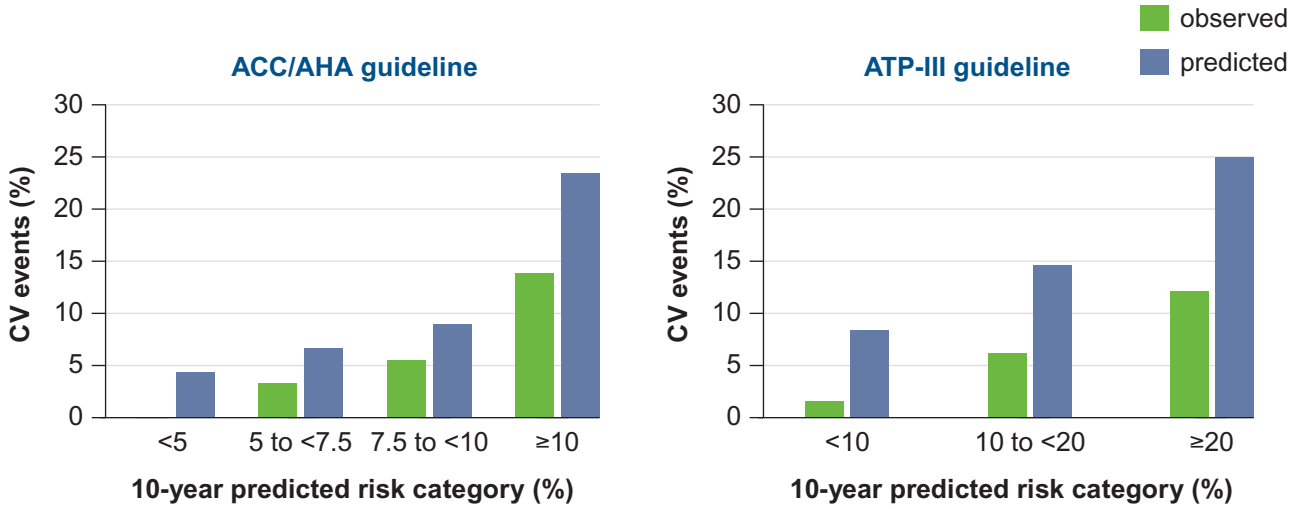
The 10-year ASCVD risk calculator recommended in the ACC/AHA guidelines includes two new factors: race and diabetes.

FIGURE 7. The risk of ASCVD events increases with higher 10-year ASCVD risk calculator score.[8]



Both current and prior calculators overestimate risk.

FIGURE 8. Both the newer "pooled-cohort equations risk calculator" and the older Framingham risk calculator overestimate risk.[8] Both risk calculators do appropriately predict a rise in risk with increasing score.*

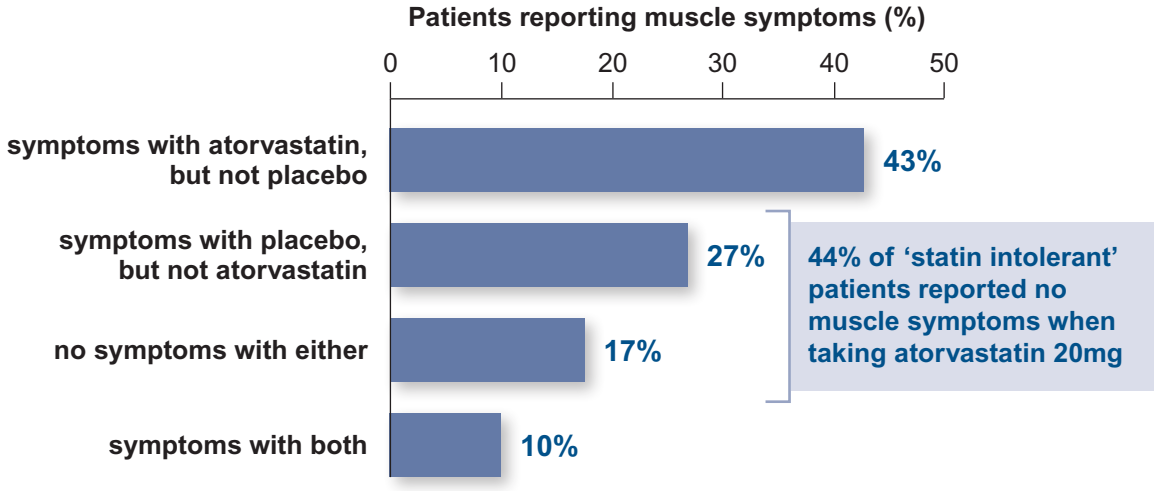


* Observed and predicted estimates represented are for men.

Evaluating statin-associated muscle symptoms

A patient who has muscle symptoms with one statin will not necessarily have symptoms with other statins.

FIGURE 9. In GAUSS-3, patients who reported intolerance to multiple statins were randomly switched between atorvastatin 20mg and placebo. Many reported symptoms with placebo but not with atorvastatin.[9]



Note: 3% of patients did not complete both the placebo and atorvastatin periods.

Most patients with statin-associated muscle symptoms should be given a trial of another statin, especially if they do not have CK abnormalities.

Checklist for most patients with statin-associated muscle symptoms[10]

- ❑ Assess whether the patient requires a statin.
- ❑ Was creatine kinase (CK) elevated?
  - —If CK elevation ≤4x upper limit of normal (ULN), rechallenge.
  - —If CK elevation >4x ULN, refer to a lipid specialist.
- ❑ Check for drug-drug interactions (e.g. fibrates, colchicine, cyclosporine, telapravir).
- ❑ Withhold statin therapy for 2-4 weeks, or until symptoms resolve.
- ❑ If symptoms do not resolve, consider alternate causes of muscle symptoms and rechallenge.
- ❑ If symptoms improve after stopping statin, rechallenge with a second statin.
- ❑ If the patient develops muscle symptoms on second statin, hold statins, then rechallenge with a third statin at low dose or an alternate dosing schedule (e.g. every other day).

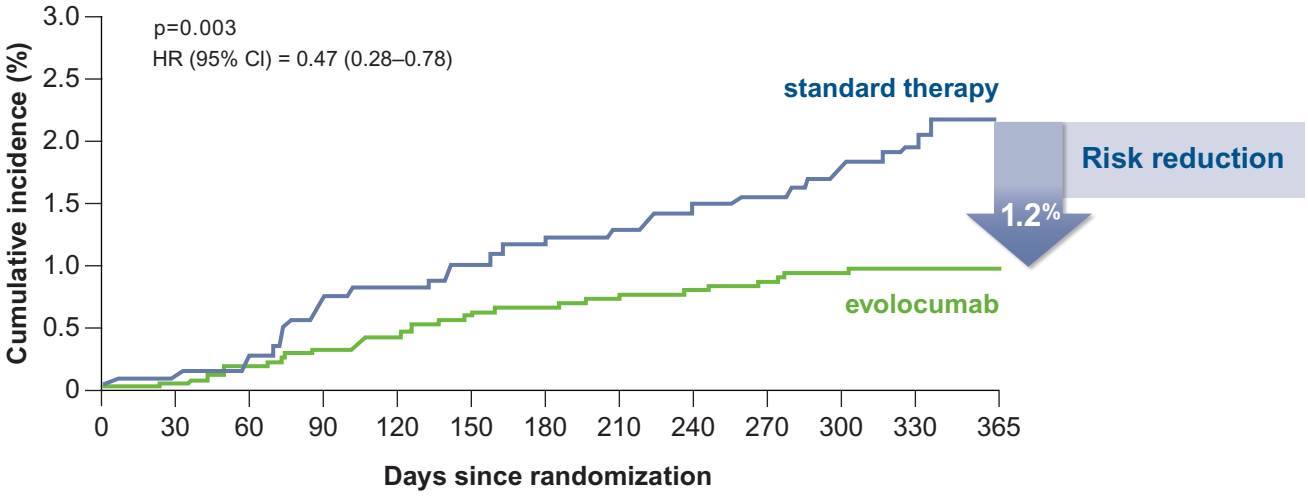
A new class of lipid-lowering drugs: PCSK9 inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, the newest FDA-approved LDL-lowering drugs.

TABLE 3. Alirocumab (Praluent)[11] and evolocumab (Repatha)[12] study characteristics

	alirocumab	evolocumab
Statin use at baseline	100%	70%
Baseline LDL (mg/dl)	122	120
Treatment	alirocumab: 150mg every 2 weeks	evolocumab: 140mg every 2 weeks, or 420mg monthly
LDL-lowering effect at 24 weeks (relative to controls)	62%	59%

FIGURE 10. Preliminary data suggest that evolocumab may also reduce CV events by 1.2%.[12] Longer term, more definitive studies are in progress.

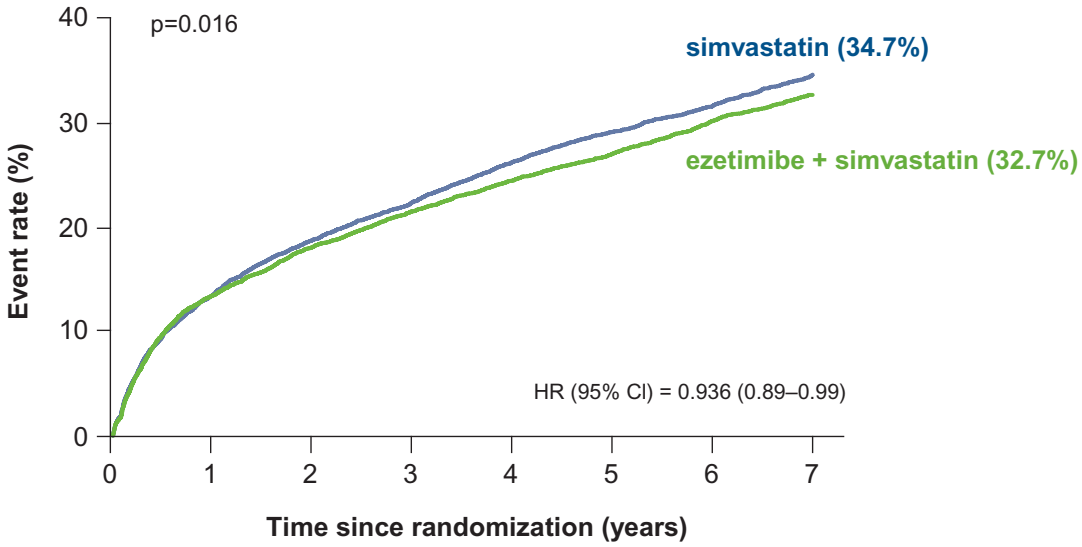


Side effects reported in clinical trials include: nasopharyngitis, myalgias, and injection site reactions.

Ezetimibe and PCSK9s have limited roles in cholesterol management for most patients

Ezetimibe, in combination with simvastatin, reduced CV events modestly in patients with acute coronary syndrome (ACS).

FIGURE 11. In IMPROVE-IT, ezetimibe plus simvastatin had a modest relative risk reduction of 6% for cardiovascular events in patients recently hospitalized for ACS, compared to simvastatin alone.[13]



When to use non-statin therapies?

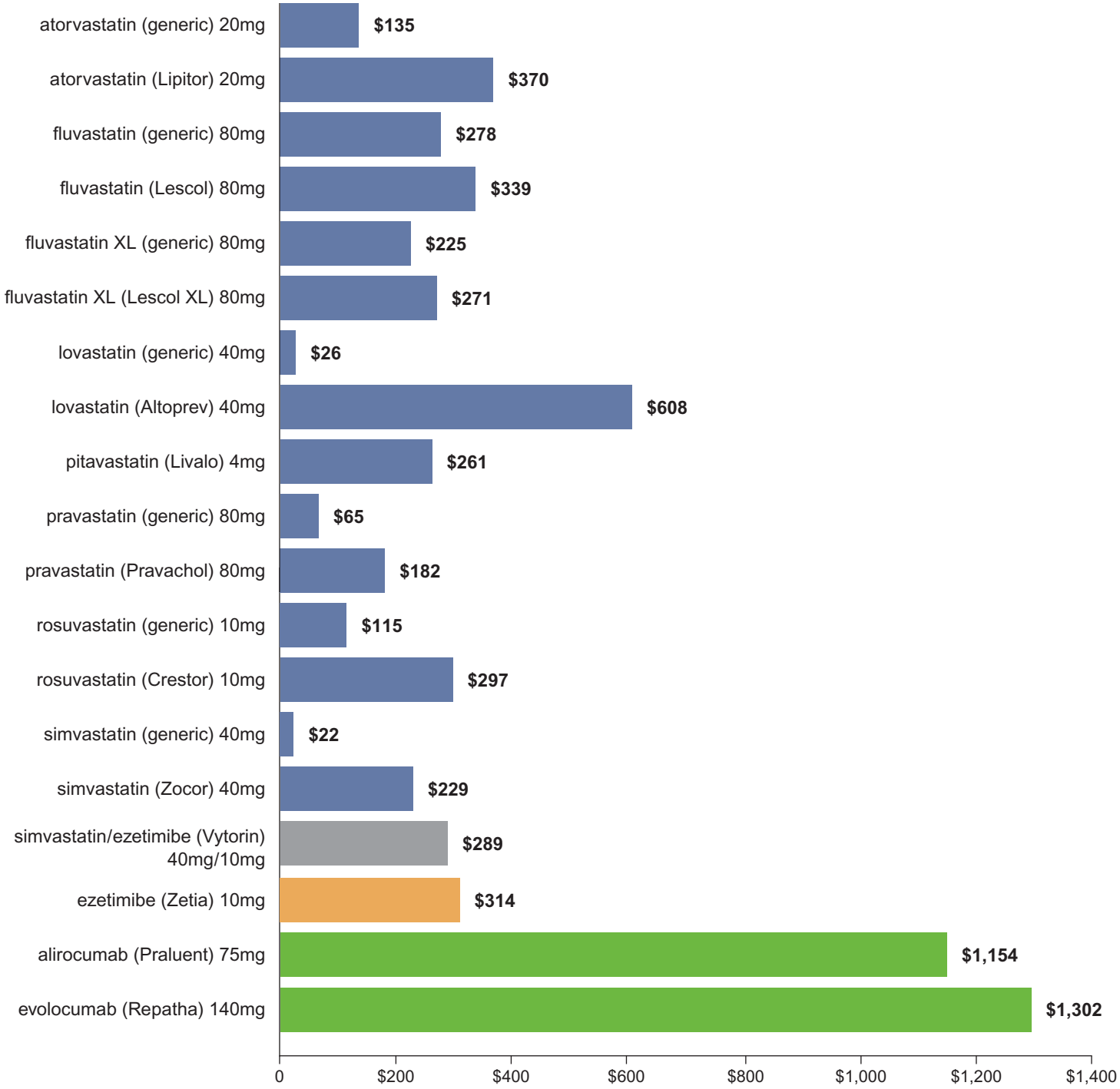
TABLE 4. Recent guidance from ACC recommends roles for non-statin therapies for patients who fail to respond to statins, despite good adherence.[14]

	PCSK9 inhibitors	ezetimibe
GOOD evidence of effectiveness for:	• high-risk patients with ASCVD	• patients with ACS
WEAK evidence of effectiveness for:	• patients unable to tolerate several statins	• high-risk patients with ASCVD • patients with diabetes for primary prevention • patients unable to tolerate several statins

There is little or no role for fibrates, niacin, or fish oil to prevent cardiovascular events in most patients.

Costs

FIGURE 12. Price for a 30-day supply of LDL-lowering medications



Prices are from goodrx.com as of April 2016. Statin doses used are moderate-intensity. PCSK9 inhibitor doses are the recommended starting doses.

Key messages

- Use current guidelines to identify patients requiring LDL-lowering therapy.
- Initiate treatment with lifestyle modification and a statin, selecting statin intensity based on patient factors.
- Ask about and address the common problem of non-adherence.
- Assess statin intolerance and how to manage patients with statin-associated muscle symptoms.
- PCSK-9 inhibitors can be useful for a small fraction of high-risk patients, but are not at present standard therapy.

Visit AlosaHealth.org/modules/lipids
for links to tools for prescribers, materials for patients, and a longer evidence document.

References:

(1) Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;129(25 Suppl 2):S1-45. **(2)** Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106(25):3143. **(3)** Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495-1504. **(4)** Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360(9346):1623-1630. **(5)** Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333(20):1301-1307. **(6)** Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364(9435):685-696. **(7)** Yusuf S, Bosch J, Dagenais G, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med.* 2016;374(21):2021-2031. **(8)** Kavousi M, Leening MJ, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA.* 2014;311(14):1416-1423. **(9)** Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *JAMA.* 2016;315(15):1580-1590. **(10)** Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* 2015;36(17):1012-1022. **(11)** Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372(16):1489-1499. **(12)** Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372(16):1500-1509. **(13)** Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372(25):2387-2397. **(14)** Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* 2016.

About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition. More detailed information on this topic is provided in a longer evidence document at AlosaHealth.org.

The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

This material is provided by **Alosa Health**, a nonprofit organization which is not affiliated with any pharmaceutical company. IDIS is a program of Alosa Health.

This material was produced by Jing Luo, M.D., M.P.H., Instructor in Medicine; Niteesh K. Choudhry, M.D., Ph.D., Associate Professor of Medicine (principal editor); Jerry Avorn, M.D., Professor of Medicine; Michael A. Fischer, M.D., M.S., Associate Professor of Medicine; Dae Kim, M.D., M.P.H., Sc.D., Assistant Professor of Medicine; all at Harvard Medical School; Jennifer Lewey, Research Fellow at Brigham and Women's Hospital, and Ellen Dancel, PharmD, MPH, Director of Clinical Material Development, Alosa Health. Drs. Avorn, Choudhry, Fischer, and Luo are physicians at the Brigham and Women's Hospital, and Dr. Kim practices at the Beth Israel Hospital, both in Boston. Dr. Lewey practices cardiology at the Columbia University Medical Center in New York. None of the authors accepts any personal compensation from any drug company.

Medical writer: Stephen Braun.

PDA pennsylvania DEPARTMENT OF AGING

PACE Pharmaceutical Assistance Contract for the Elderly