PHARMACY VISION 2020

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

When statins aren't enough: appropriate use of non-statin lipid-lowering agents to reduce cardiovascular events among high-risk patients

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DISCLOSURE

- No potential conflicts of interest

Learning Objectives

- Evaluate patients' risk of cardiovascular events and identify the presence of additional cardiovascular risk factors.
- Determine appropriate indication and use of non-statin agents to reduce cardiovascular risk.
- Apply data from sub-group analyses to current guideline recommendations for appropriate use of non-statin lipid-lowering medications.
- Develop a patient-specific pharmacotherapy plan for the use of statin and non-statin lipid-lowering agents to reduce patients' cardiovascular risk.

TEST QUESTIONS

A 68-year-old male with history of NSTEMI (2016), HTN, T2DM, CKD3, and PAD.

Recent lipids while receiving high-intensity statin therapy:

TC: 189 mg/dL TG: 166 mg/dL HDL-C: 42 mg/dL LDL-C: 108 mg/dL

1. **Based on the 2018 ACC/AHA Cholesterol Guideline, how would you classify this patient's risk for future ASCVD?**
   a) **Low risk**
   b) **Intermediate risk**
   c) **High risk**
   d) **Very-high risk**

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2. What risk-factors does this patient have that place him at increased ASCVD risk?

a) HTN

b) Low HDL-C

c) PAD

d) Male gender

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Recent lipids while receiving high-intensity statin therapy:

TC: 189 mg/dL TG: 166 mg/dL HDL-C: 42 mg/dL LDL-C: 108 mg/dL

3. Which modification to his current lipid-lowering therapy is most appropriate?

a) No change necessary, treated with high-intensity statin

b) Add ezetimibe 10 mg/day

c) Add evolocumab 140 mg every 2 weeks

d) Add icosapent ethyl 4 grams daily

TEST QUESTIONS

A 65-year-old patient with history of cardiovascular disease presents for lipid management; treated with maximally tolerated statin.

Recent lipid panel : TC: 167 mg/dL TG: 228 mg/dL
HDL-C: 39 mg/dL LDL-C: 72 mg/dL

4. **Which of the following would be the most appropriate add on therapy to lower triglycerides and reduce their risk of cardiovascular events?**
   a) **Icosapent ethyl 4g/day**
   b) **Ezetimibe 10 mg/day**
   c) **Alirocumab 75mg every 2 weeks**
   d) **Colesevelam 3.75 g/day**

OUTLINE

- Overview of current recommendations for use of non-statin lipid-lowering medications to reduce atherosclerotic cardiovascular disease (ASCVD)

- Review sub-group analyses exploring ASCVD reduction with non-statin agents

- Use presented information to identify patients most likely to benefit from the addition of non-statin lipid-lowering medications.

ABBREVIATIONS

PATIENT CASE #1

72 year old male with history of coronary stenting (2016) and recent ACS event, while receiving high-intensity statin

Lipid panel on high-intensity statin therapy:

TC: 166 mg/dL TG: 113 mg/dL HDL-C: 40 mg/dL LDL-C: 98 mg/dL

What, if any, changes would you make to his lipid-lowering therapy?

CVD IS #1 CAUSE OF MORTALITY

In the U.S., coronary heart disease (42.6%) and stroke (17%) are the leading causes of cardiovascular death[1]

Major risk factors for cardiovascular disease[2]

- Age
- Cigarette smoking
- Hypertension
- Elevated blood glucose
- Elevated serum cholesterol → atherosclerotic cardiovascular disease (ASCVD)

1. *Circulation*. 2020 Mar 3;141(9):e139-e596.

2. *Circulation*. 2019;139(25):e1082-e1143.

TREATMENTS TO LOWER ASCVD RISK[2]

Lifestyle Therapies

- Diet & weight control
- Physical activity

Lipid-lowering medications

- **Statins**
- LDL-C lowering non-statins
- Triglyceride-lowering agents

Statin intensity	Expected LDL-C lowering
Low	<30%
Moderate	30-49%
High	≥50%

2. *Circulation*. 2019;139(25):e1082-e1143.

STATINS + LIFESTYLE ARE KEY TO ASCVD REDUCTION

Statin therapy has shown to reduce risk of major cardiovascular events by up to 44%[3]

Greater LDL-C lowering is associated with greater ASCVD risk reduction[2]

Residual risk remains, despite "low" LDL-C

- PROVE-IT[4]: 22.4% event rate in patients treated with atorvastatin 80 mg
- Median LDL-C of 62 mg/dL

2. *Circulation*. 2019;139(25):e1082-e1143 .
3. *N Engl J Med*. 2008;359:2195-207.
4. *N Engl J Med*. 2004;350:1495-5104.

NON-STATINS TO REDUCE CARDIOVASCULAR EVENTS

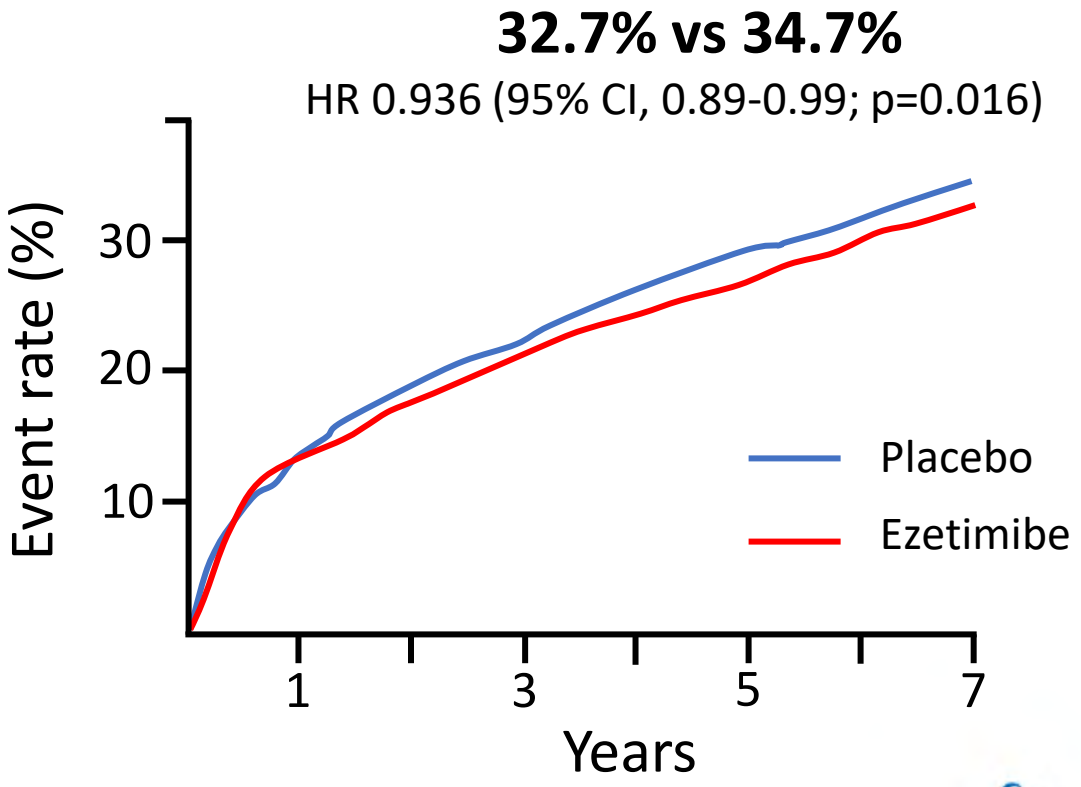
IMPROVE-IT trial[5] (n=18,144)

Post-ACS patients; LDL-C 50-125 mg/dL

- Placebo + simvastatin 40 mg
- Ezetimibe 10 mg + simvastatin 40 mg

Composite CV endpoint over 6 years

- CV death, non-fatal MI/stroke
- Unstable angina, revascularization



5. *N Engl J Med*. 2015; 372:2387-2397

NON-STATINS TO REDUCE CARDIOVASCULAR EVENTS

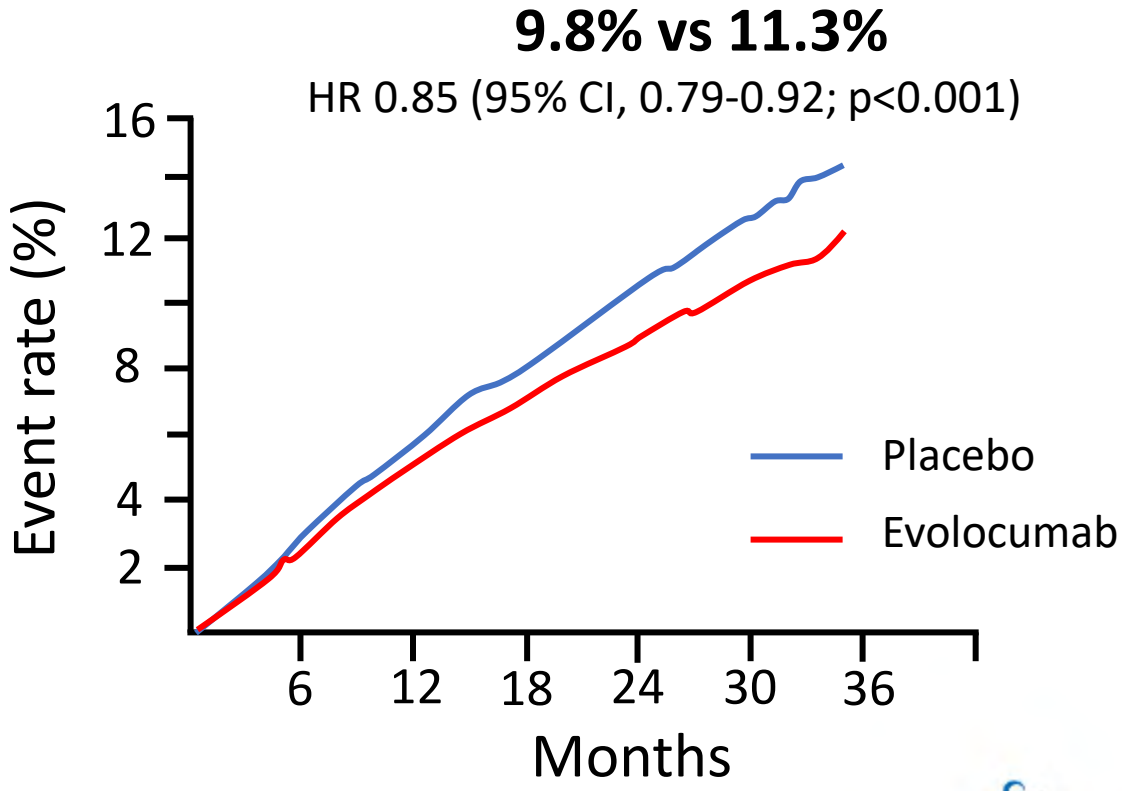
FOURIER[6] (n=27,564)

ASCVD on statin therapy; LDL-C ≥70 mg/dL

- Evolocumab
- Placebo

Composite CV endpoint over 2.2 years

- CV death, non-fatal MI/stroke
- Unstable angina, revascularization



6. *N Engl J Med*. 2017; 376:1713-1722

NON-STATINS TO REDUCE CARDIOVASCULAR EVENTS

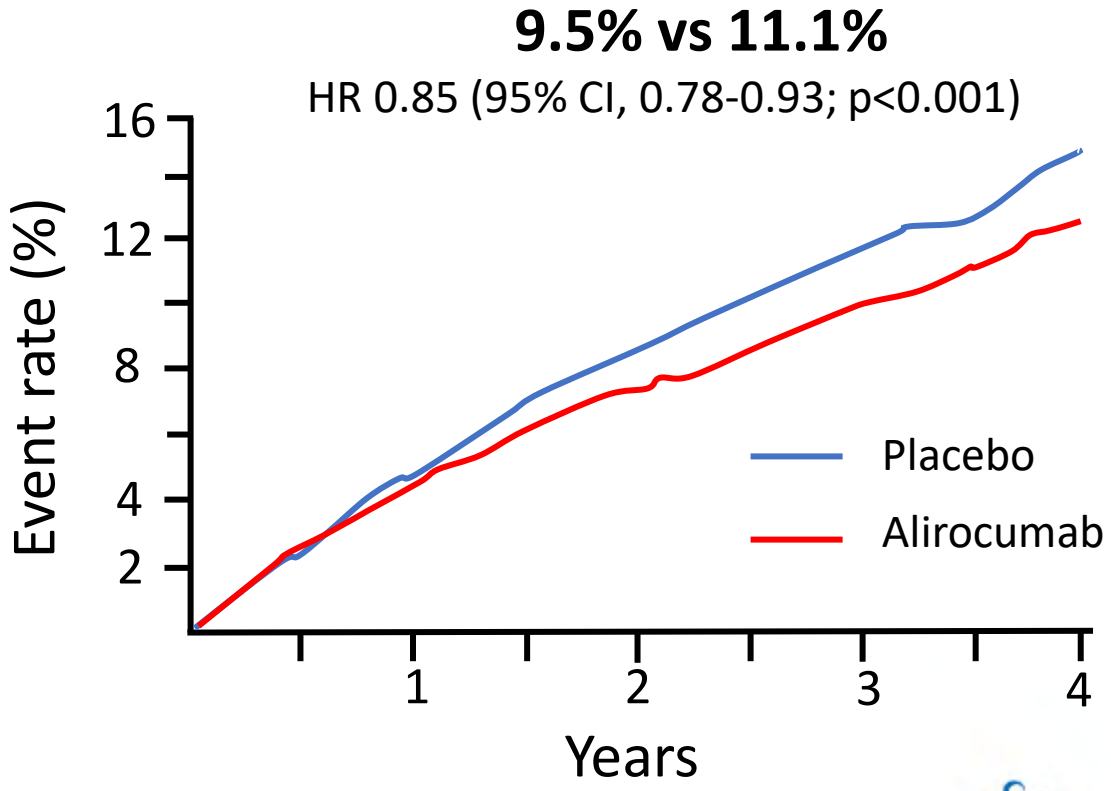
ODYSSEY OUTCOMES[7] (n=18,924)

ACS event ≤12 months; LDL-C ≥70 mg/dL

- Alirocumab + statin
- Placebo + statin

Composite CV endpoint over 2.8 years

- CV death, non-fatal MI/stroke
- Unstable angina



7. *N Engl J Med*. 2018; 379:2097-2107

RECOMMENDATIONS FOR NON-STATIN USE

True or False:

"Patients with ASCVD have an LDL-C goal of <70 mg/dL"

RECOMMENDATIONS FOR NON-STATIN USE

True or False:

*"All patients with ASCVD should receive maximally tolerated statin **plus** additional LDL-C lowering drugs"*

RECOMMENDATIONS FOR NON-STATIN USE

Not all patients with ASCVD have the same risk for future events

A

58 year-old, recent ischemic stroke
Moderate-intensity statin
LDL-C = 88 mg/dL

B

68 year-old, CKD, PAD, HTN
High-intensity statin
LDL-C = 113 mg/dL

C

62 year-old, T2DM, smoker, recent ACS
High-intensity statin
LDL-C = 68 mg/dL

D

72 year-old, previous PCI, CHF, recent MI
High-intensity statin
LDL-C = 83 mg/dL

RECOMMENDATIONS FOR NON-STATIN USE

2018 Guideline on the Management of Blood Cholesterol[2]

COR	LOE	Recommendation
I	A	In patients ≤75 years with clinical ASCVD, **high-intensity statin therapy** should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C
IIa	B	In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at **very-high risk** and have an LDL-C level ≥70 mg/dL it is **reasonable to add ezetimibe**
I	B	In patients with clinical ASCVD who are judged to be **very-high risk** and considered for PCSK9 inhibitor therapy, **maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe**
IIa	A	In patients with clinical ASCVD who are judged to be **very-high risk** and who are on maximally tolerated LDL-C lowering therapy with LDL-C ≥70 mg/dL (or non–HDL-C level ≥100 mg/dL), it is **reasonable to add a PCSK9 inhibitor**

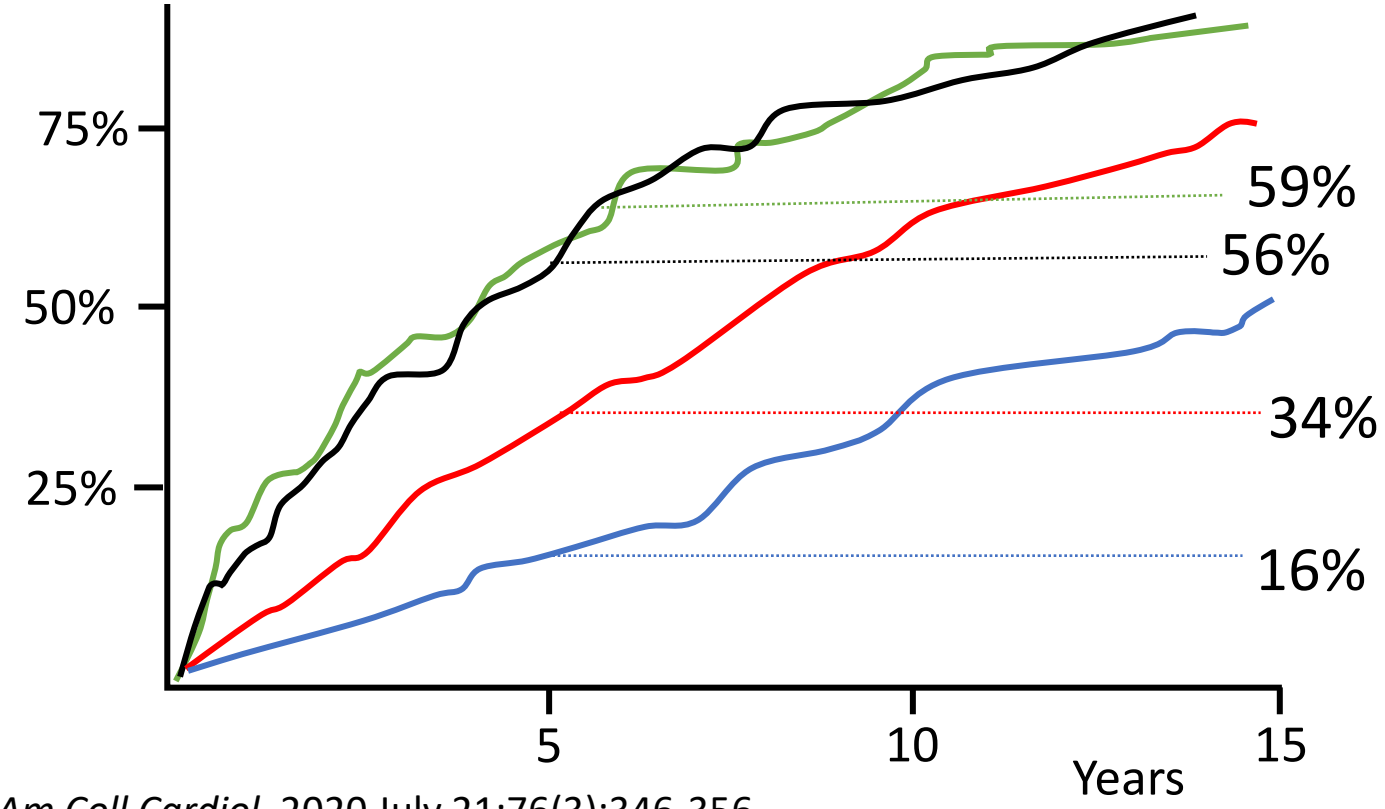
2. *Circulation*. 2019;139(25):e1082-e1143.

Very-high ASCVD risk[2]	
Multiple major ASCVD events	**Single ASCVD event + multiple high-risk conditions**
• Recent ACS event in past 12 months • Previous MI or ischemic stroke • Symptomatic PAD or previous revascularization or amputation (due to PAD)	• Age 65 years or older • Diabetes mellitus • Hypertension • CKD (eGFR 15-59 ml/min/1.73m^2) • Prior CABG or PCI event • Current smoking • Persistent LDL-C ≥100 mg/dL (despite statin ± ezetimibe) • Congestive heart failure • Heterozygous familial hypercholesterolemia (HeFH)

2. *Circulation*. 2019;139(25):e1082-e1143.

5-YEAR ASCVD EVENTS BY RISK GROUP

Cumulative incidence rate (all-cause mortality, MI, stroke, HF)



- ≥2 ASCVD
- ASCVD + ≥4 HRC
- ASCVD + 2-3 HRC
- High-risk

HRC= high-risk condition

8. *J Am Coll Cardiol*. 2020 July 21;76(3):346-356

NON-STATIN BENEFITS THOSE AT HIGHEST RISK

Sub-group analyses of non-statin cardiovascular outcomes trials reported greater ASCVD risk-reduction among select populations:

- Polyvascular ASCVD[9-11]
- Diabetes mellitus[12,13]
- Chronic kidney disease[14]

Knowing which patients derive greater benefit with additional LDL-C lowering ensures appropriate use of non-statin therapies

EVENT RATES BY CORONARY DISEASE SEVERITY

Event rates for primary composite endpoint among 22,351 patients with previous MI:

	Evolocumab	Placebo	ARR
MI ≥ 2 years	13.3%	14.0%	0.7%
MI < 2 years	13.5%	16.9%	**3.4%**
1 previous MI	11.5%	12.8%	1.3%
≥2 previous MI	18.7%	22.4%	**3.7%**
No residual multi-vessel CAD	12.4%	13.6%	1.2%
Residual multi-vessel CAD	15.8%	19.4%	**3.6%**

9. *Circulation*. 2018;138:756–766

PATIENTS WITH POLYVASCULAR DISEASE

Event rates for primary composite endpoint:

	Alirocumab	Placebo	ARR
Overall	9.5%	11.1%	1.6%
1 Coronary disease only	8.5%	10.0%	1.4%
Coronary + CeVD	18.5%	21.1%	2.6%
2 Coronary + PAD	22.8%	23.7%	0.9%
3 Coronary + CeVD + PAD	26.8%	39.7%	13%

ARR= absolute risk reduction; CeVD= cerebrovascular disease; PAD= peripheral artery disease

10. *J Am Coll Cardiol*. 2019;774:1167–1176

Patients with Peripheral Arterial Disease (PAD)

Subgroup analysis of FOURIER

- 27,564 patients with ASCVD
- 3,642 included based on PAD (no prior MI/stroke)

Event rates for primary composite endpoint (2.2 years):

	Evolocumab	Placebo	ARR
No PAD (n=23,922)	10.5%	12.1%	1.6%
PAD (n=3,642)	13.3%	16.8%	**3.5%**

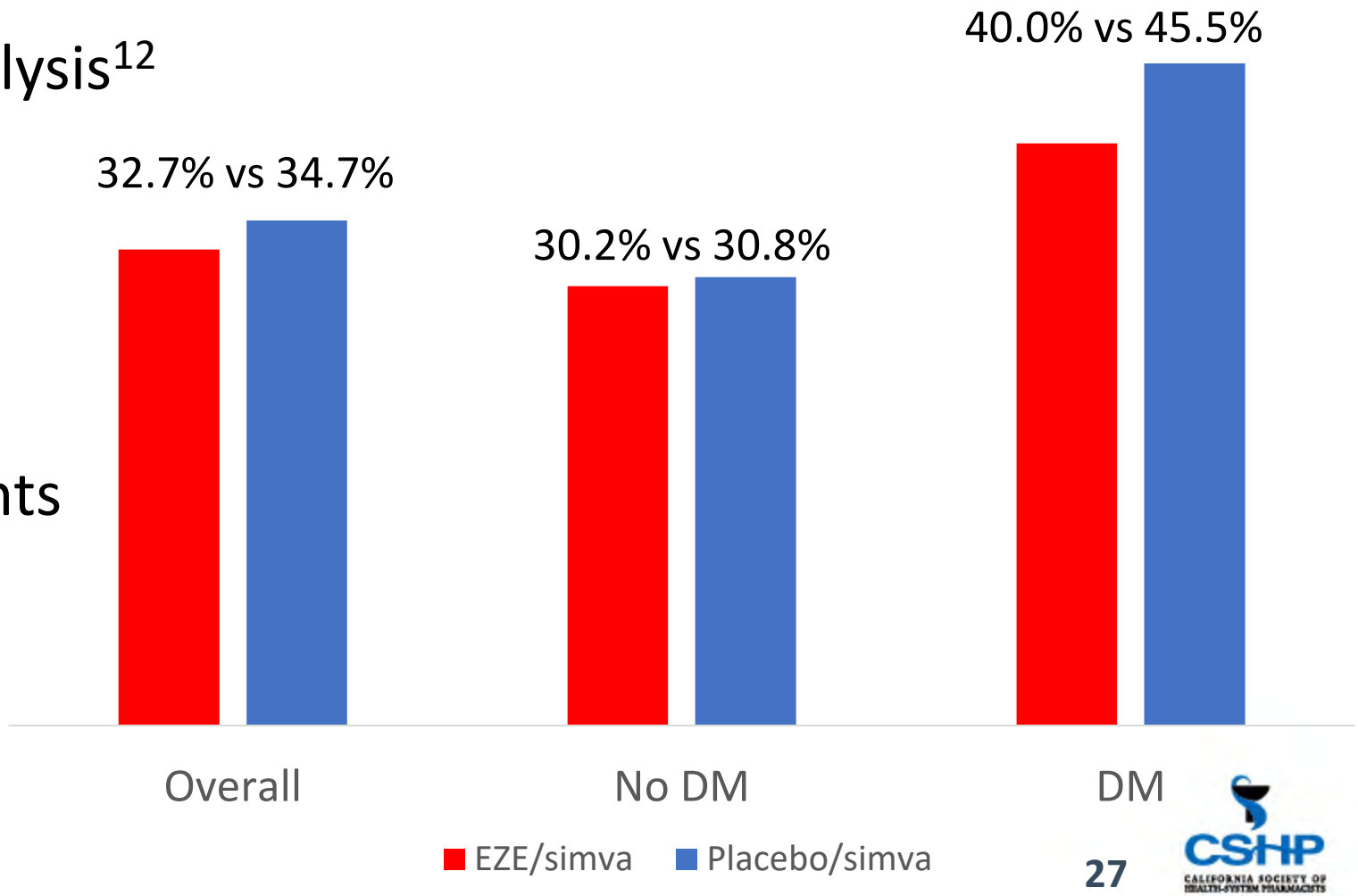
11. Circulation. 2018;137:338–350

PATIENTS WITH DIABETES MELLITUS (DM)

IMPROVE-IT sub-group analysis[12]

- ARR: 2% (overall)
- ARR: 0.6% (no DM)
- ARR: 5.5% (DM)

NNT over 7-years for patients with DM = 19



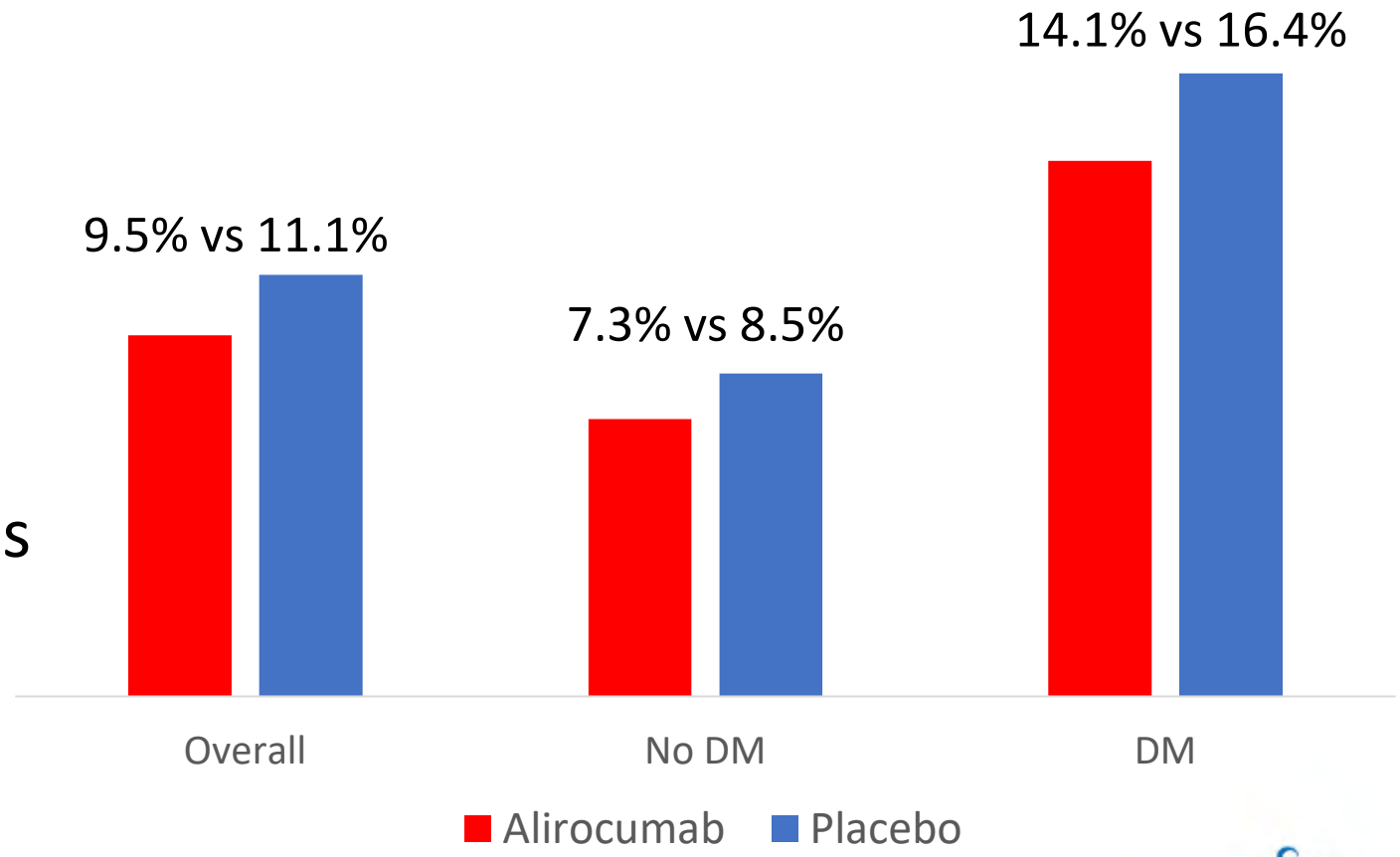
12. *Circulation*. 2018;137:1571–1582

PATIENTS WITH DIABETES MELLITUS (DM)

ODYSSEY sub-group analysis[13]

- ARR: 1.6% (overall)
- ARR: 1.2% (no DM)
- ARR: 2.3% (DM)

NNT over 2.8-years for patients with DM = 44



13. *Lancet Diabetes Endocrinol.* 2019; 7(8): 618–628

PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)

Key secondary endpoint: CV death, MI, or stroke

(evolocumab vs placebo)

- Preserved function (n=8,077)
  - 5.4% vs 7.1%
- Stage 2 CKD (n=15,034)
  - 6.2% vs 7.7%
- Stage ≥3 CKD (n=4,443)
  - 10.3% vs 12.8%

Absolute Risk Reduction	
Preserved:	-1.7%
CKD 2:	-1.5%
CKD ≥3:	**-2.5%**

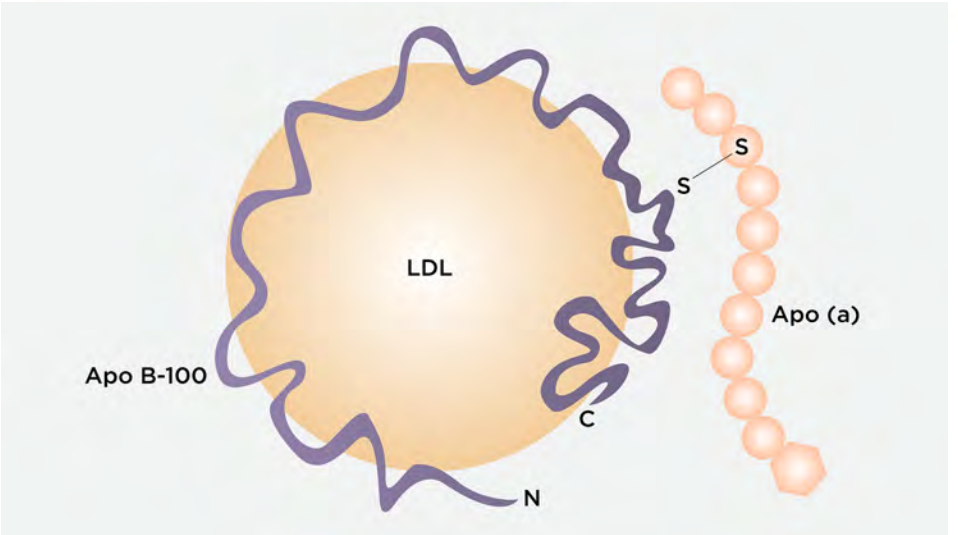
14. *J Am Coll Cardiol*. 2019;73:2961–2970

AGE AS A RISK FACTOR

	Event rate over 7-years			
Age cohort (years)	**Simva/placebo**	**Simva/Eze**	**HR (95% CI)**	**ARR**
<65	30.8%	29.9%	0.97 (0.90-1.05)	0.9%
65-74	35.9%	35.1%	0.96 (0.87-1.06)	0.8%
>75	47.6%	38.9%	0.80 (0.70-0.90)	8.7%

15. *JAMA Cardiol*. 2019;4(9):846-854

LIPOPROTEIN(A)



- Lp(a) is an LDL-like particle + apo(a)
- 80-90% hereditary
- Adverse effects
  - Atherogenic (cardiovascular disease, ischemic stroke, PAD)
  - Thrombotic
  - Inflammatory
- Lp(a) >125 nmol/L is a risk-enhancing factor
- PCSK9 inhibitors associated with 20-30% reduction

16. *N Engl J Med*. 2020;382(3):244-255.

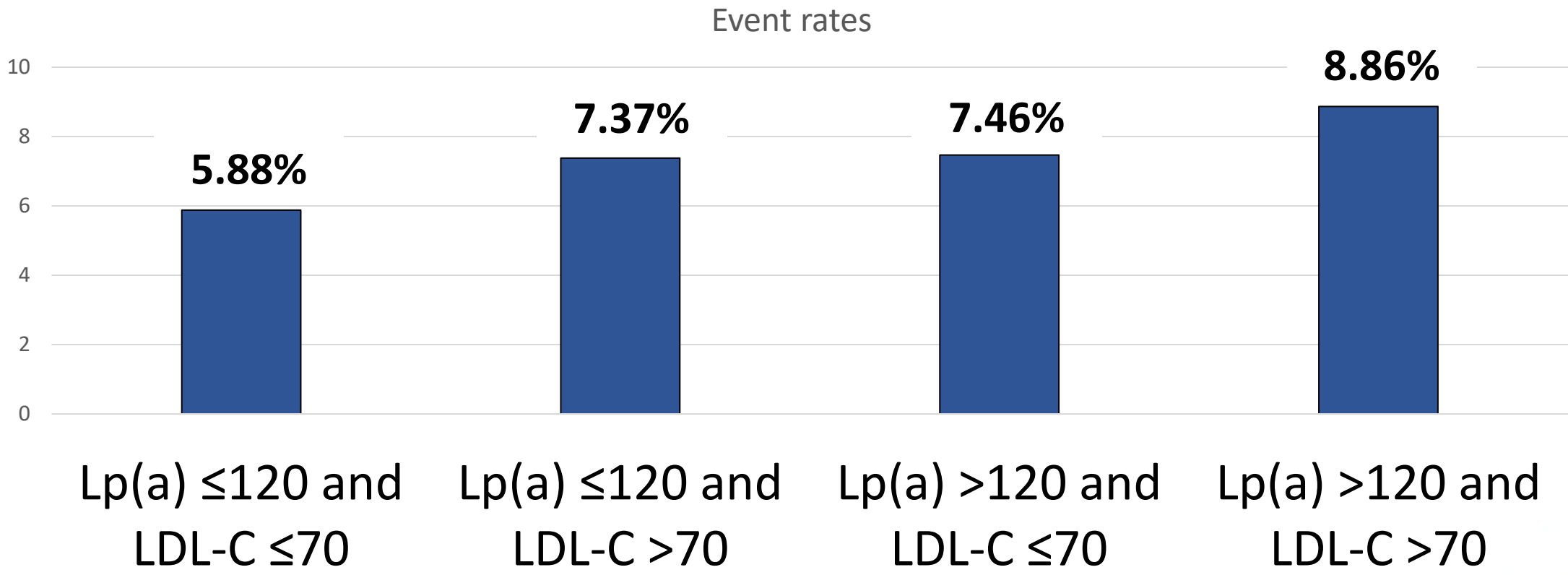
CARDIOVASCULAR RISK BY LP(A)

- Subgroup analysis from FOURIER (evolocumab vs placebo)[17]
- Stratified by baseline Lp(a) value

	3-year incidence rate of primary cardiovascular outcome		
Lp(a) at baseline	**Placebo**	**Evolocumab**	**HR (95% CI)**
≤120 nmol/L	8.15%	6.74%	0.89 (0.79-1.01)
>120 nmol/L	9.91%	7.50%	0.75 (0.64-0.88)

17. *Circulation*. 2019;139:1483–1492.

EVENTS BY ACHIEVED LP(A) & LDL-C



17. *Circulation*. 2019;139:1483–1492.

SUMMARY

Risk of future ASCVD events increased with patient risk-factors

- Multiple ASCVD events and ASCVD with multiple high-risk conditions have highest risk for additional cardiovascular events

Identify these *very* very-high risk patients

- Ensure maximally tolerated statin therapy
- PCSK9 inhibitors in polyvascular disease or ↑ Lp(a)
- Monitor LDL-C to ensure adherence

PATIENT CASE #2

64 year old female with history of coronary artery bypass (2015) and T2DM.

Lipid panel on high-intensity statin therapy:

TC: 178 mg/dL TG: 211 mg/dL HDL-C: 43 mg/dL LDL-C: 72 mg/dL

What, if any, changes would you make to her lipid-lowering therapy?

PREVALENCE OF ELEVATED TRIGLYCERIDES

Elevated triglycerides (TG) associated with ASCVD risk[18]

2007-2014 NHANES data (representing 219 million US adults)

- 56.9 million (25.9%) had TG ≥150 mg/dL
- 12.3 million statin-treated patients (31.6%) had TG ≥150 mg/dL

Use of TG-lowering agents with statins not shown to reduce ASCVD risk

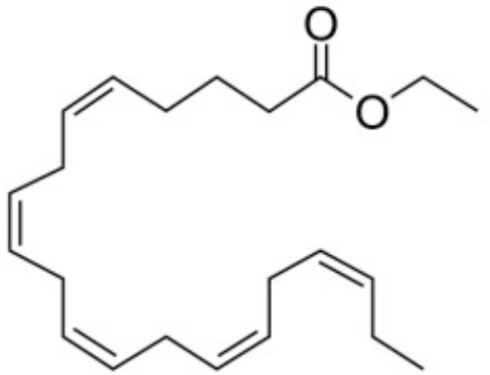
18. *Cardiol Ther*. 2020; 9:207–213.

ICOSAPENT ETHYL

- Prescription omega-3 fatty acid indicated for treatment of hypertriglyceridemia

- Triglyceride-lowering effects of omega-3 fatty acids due to
  - Eicosapentaenoic acid (EPA)
  - Docosahexaenoic acid (DHA)

- Icosapent ethyl is highly purified EPA



19. Vascepa [package insert]. Bridgewater, NJ: Amarin Pharma INC; 2020

TG-LOWERING IN STATIN TREATED PATIENTS

REDUCE-IT[20] (n=8,179)

1° and 2° prevention patients receiving statin therapy (LDL-C <100 mg/dL), with TG 135-499 mg/dL

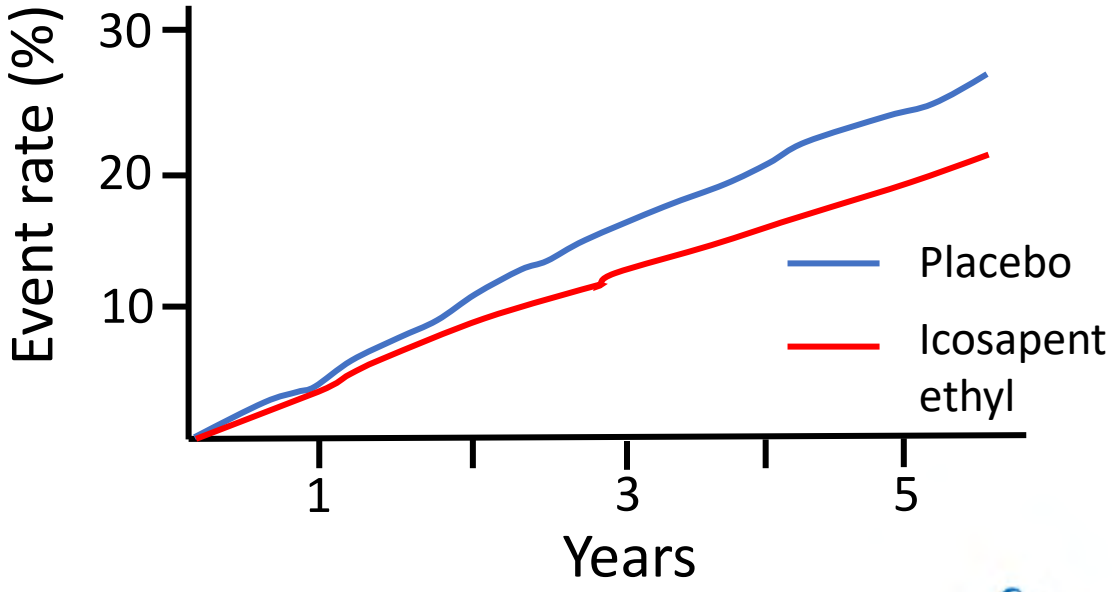
- Icosapent ethyl 4g/d
- Placebo

Composite CV outcome over 4.9 years

- CV death, non-fatal MI/stroke
- Unstable angina, revascularization

17.2% vs 22.0%

HR 0.75 (95% CI, 0.68-0.83; p<0.001)



20. N Engl J Med. 2019; 380:11-22

REDUCE-IT: SECONDARY OUTCOMES

- Key secondary endpoint (CV death or non-fatal MI/stroke) **↓ 26%** 0.74 (0.65–0.83)
- Fatal or non-fatal MI **↓ 31%** 0.69 (0.58–0.81)
- Cardiovascular death **↓ 20%** 0.80 (0.66–0.98)
- All-cause mortality ↓ 13% 0.87 (0.74–1.02)

20. N Engl J Med. 2019; 380:11-22

ICOSAPENT ETHYL

Indication: as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglycerides (≥ 150 mg/dL) and:

- Established cardiovascular disease or
- Diabetes mellitus and ≥2 additional risk factors for CV disease

19. Vascepa [package insert]. Bridgewater, NJ: Amarin Pharma INC; 2020

SUMMARY

- Icosapent ethyl significantly reduces cardiovascular events in patients with elevated TG, despite statin therapy
- Benefits occurred regardless of achieved triglyceride levels
- Icosapent ethyl ≠ prescription omega-3 ≠ OTC fish oil

Key Points to Consider

- Which patients are the best candidates for additional non-statin meds?
  - Count risk factors
  - Multiple ASCVD events
- Is residual risk related to LDL-C or triglycerides?
  - PCSK9 inhibitors for *very* very-high risk
  - Icosapent ethyl for elevated triglycerides

- **Ensure optimal statin therapy and adherence**

TEST QUESTIONS

A 68-year-old male with history of NSTEMI (2016), HTN, T2DM, CKD3, and PAD.

Recent lipids while receiving high-intensity statin therapy:

TC: 189 mg/dL TG: 166 mg/dL HDL-C: 42 mg/dL LDL-C: 108 mg/dL

1. **Based on the 2018 ACC/AHA Cholesterol Guideline, how would you classify this patient's risk for future ASCVD?**
   a) **Low risk**
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b) Low HDL-C

c) PAD

d) Male gender

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   a) **No change necessary, treated with high-intensity statin**
   b) **Add ezetimibe 10 mg/day**
   c) **Add evolocumab 140 mg every 2 weeks**
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TEST QUESTIONS

A 65-year-old patient with history of cardiovascular disease presents for lipid management; treated with maximally tolerated statin.

Recent lipid panel : TC: 167 mg/dL TG: 228 mg/dL
HDL-C: 39 mg/dL LDL-C: 72 mg/dL

4. Which of the following would be the most appropriate add on therapy to lower triglycerides and reduce their risk of cardiovascular events?

a) Icosapent ethyl 4g/day

b) Ezetimibe 10 mg/day

c) Alirocumab 75mg every 2 weeks

d) Colesevelam 3.75 g/day

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