Case 3

Frank

ASCVD with Multiple CV Risk Factors

ASCVD: atherosclerotic cardiovascular disease

Learning Objectives

Upon completion of this case based session, participants will be able to:

01	Identify patients with ASCVD and with multiple CV risk factors and those who have especially high risk features (eg: PAD)
02	Prioritize treatment options in alignment with patient priorities
03	Identify circumstances requiring use of statin-add-on therapies to achieve goal
04	Review safety and efficacy of PCSK9 inhibitors in specific high risk populations
05	Discuss safety and CV risk reduction benefits of very low LDL-C goals

Canadian Heart Research Centre

ASCVD: atherosclerotic cardiovascular disease

Case 3

Frank
65 years old

Frank's History

- Used to be a heavy smoker and drinker
- Had aortofemoral bypass surgery for peripheral vascular disease in 2007
- CVA with full recovery in 2011 while on ASA
- Recent nuclear scan for atypical chest pain shows area of fixed defect and mild area of distal anterior wall ischemia

Physical Exam

- Weight 159 kg
- Height 1.88 m
- BMI 45 kg/m^2
- BP 140/88 mmHg
- HR 70 regular
- Popliteal and pedal pulses full

Case 3

Frank
65 years old

Medications

- Clopidogrel 75 mg OD
- Rosuvastatin 20 mg OD
- Metoprolol 25 mg am and 50 mg pm
- 7 mg of perindopril and 5 mg of amlodipine

Labs

- A1C 6.3%
- eGFR 65 ml/min
- LDL-C 2.2 mmol/L
- 12 lead EKG, Q waves leads V1 to V3

Case 3

Frank
65 years old

Frank decides that he wants to try to be more active, watch his diet and try to lose weight.

So you make no changes to his medications and ask him to return in 6-8 weeks.

Case 3
Follow-Up Visit – 8 weeks

Frank
65 years old

Physical Exam

- Weight 157 kg (lost 2 kg since last visit)
- BP 132/82 mmHg (140/88 mmHg previous visit)

Labs

- A1C 6.3% (no change)
- eGFR 65 ml/min (no change)
- LDL-C 2.2 mmol/L (no change)

Case 3

Frank
65 years old

Frank indicates that it was more difficult than he anticipated to lose the 2 kg and is disappointed that his blood pressure and blood tests have not changed dramatically. He is most concerned about having another stroke.

Case 3

Frank
65 years old

Frank is reluctant to take more BP medications or anticoagulants and is convinced that he does not have diabetes because he avoids sugar.

2016 CCS Lipid Guidelines Recommend: Targeting Lower LDL-C to Lower the Risk for CV Events

Canadian Cardiovascular Society

TREATMENT TARGETS:

- LDL-C consistently <2.0 mmol/L or >50% reduction
- Consider <1.8 mmol/L in patients with clinical atherosclerosis
- Apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L can be considered as alternative treatment targets

STATIN INDICATED CONDITIONS

(those who will benefit the most):

- Clinical atherosclerosis*
- Abdominal aortic aneurysm
- Most diabetes mellitus
- CKD (age >50 years)
- LDL-C ≥5.0 mmol/L

*Clinical atherosclerosis, i.e., previous MI, or coronary revascularization by PCI or CABG surgery, other arterial revascularization procedures, angina pectoris, cerebrovascular disease including TIA, or peripheral arterial disease (claudication and/or ABI <0.9)
ABI, ankle brachial index; Apo B, apolipoprotein B; CABG, coronary artery bypass graft surgery; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Anderson TJ et al. 2016;32:1263-1282

What are your options for lowering Frank's LDL-C

Frank is currently taking rosuvastin 20 mg OD

Please select from one of the available options

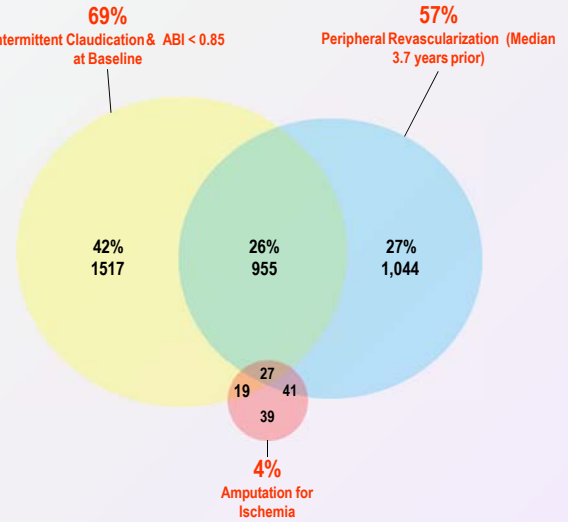
1. Use maximum dose rosuvastatin 40 mg
2. Add ezetimibe 10 mg to rosuvastatin 20 mg
3. Add ezetimibe 10 mg and increase rosuvastatin to 40 mg
4. Add a PCSK9 inhibitor

What LDL-C lowering expectations would you describe to Frank for each scenario?

1. Using a maximum dose rosuvastatin 40 mg?
   → "rule of 6%" suggests that LDL-C, on average, may fall insufficiently to meet LDL-C target
2. Adding ezetimibe 10 mg to rosuvastatin 20 mg?
   → this may provide a 15 – 20% lowering of LDL-C (perhaps to about 1.8 mmol/L)
3. Adding ezetimibe 10 mg and increasing rosuvastatin to 40 mg?
   → on average a 20 – 25% fall is expected (perhaps to 1.7 mmol/L)
4. Adding a PCSK9 inhibitor?
   → on average, a 50-60% or more reduction would be expected (perhaps to 1.1 mmol or less)

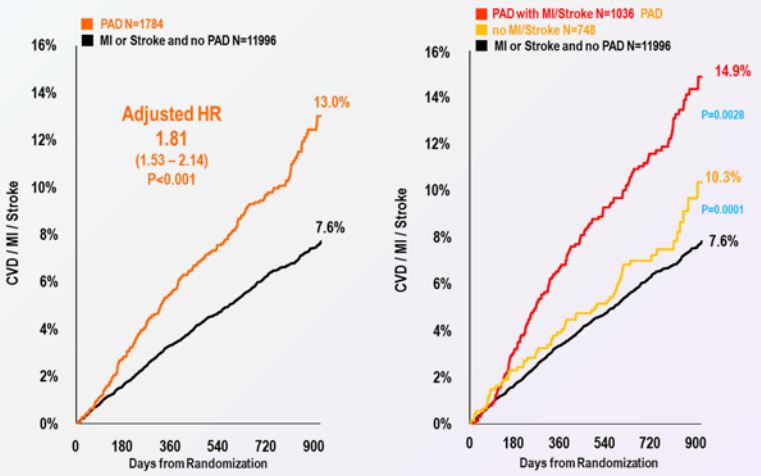
FOURIER
Patients with Peripheral Artery Disease

27,564
Patients with
Atherosclerosis
Randomized
↓
3,642
Patients with
Symptomatic Lower
Extremity Peripheral
Artery Disease
↓
1,505
Patients with Symptomatic
Lower Extremity
Peripheral Artery Disease
and no prior MI or Stroke



Bonaca MP et al; Circulation. 2018 Jan 23;137(4):338-350.

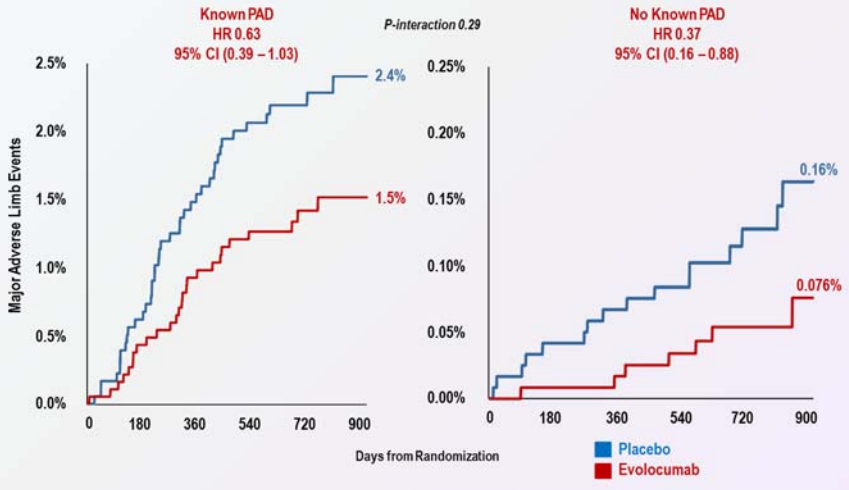
FOURIER
Peripheral Artery Disease and Risk in Placebo Patients



adjusted age, sex, race, BMI, diabetes, hypertension, smoking, eGFR, CHF, prior MI,

Bonaca MP et al; Circulation. 2018 Jan 23;137(4):338-350.

FOURIER
Major Adverse Limb Events in Patients with and without Known PAD

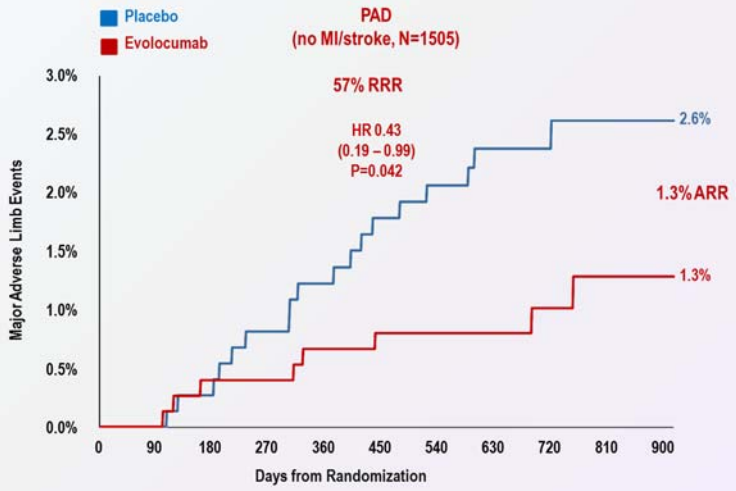


Note different scale of the 2 figures

Bonaca MP et al; Circulation. 2018 Jan 23;137(4):338-350.

FOURIER

Major Adverse Limb Events in Patients with PAD and no MI or Stroke



Bonaca MP et al; Circulation. 2018 Jan 23;137(4):338-350.

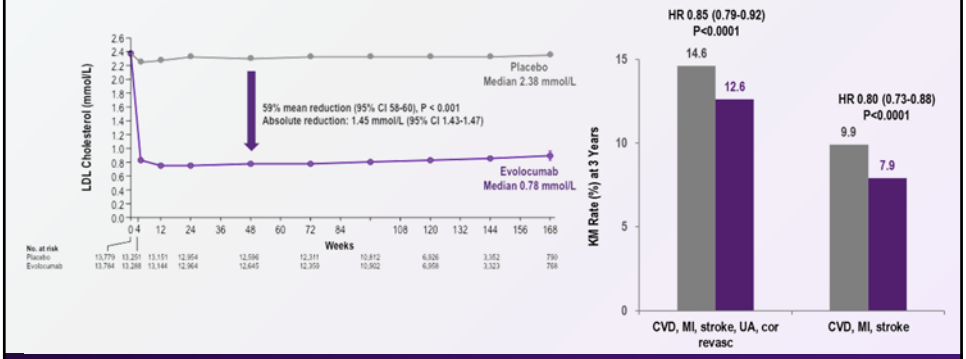
Summary

- Patients with PAD are at heightened risk of MACE and MALE
- LDL-C lowering with evolocumab in patients with PAD:
  - Reduces major adverse CV events with robust ARR
  - Reduces major adverse limb events
- Benefits extend to PAD without prior MI or stroke with an ARR for MACE or MALE of 6.3% (NNT 16) at 2.5 years
- **LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of MI or stroke, to reduce the risk of MACE and MALE**

Bonaca MP et al; Circulation. 2018 Jan 23;137(4):338-350.

FOURIER
Median LDL-C Levels Over Time

- LDL-C was significantly reduced in the evolocumab group (median: 0.78 mmol/L) including 42% who achieved levels ≤ 0.65 mmol/L vs < 0.1% in the placebo group, nearly all of whom were on background statin therapy
- ↓ CV outcomes
- Safe and well-tolerated

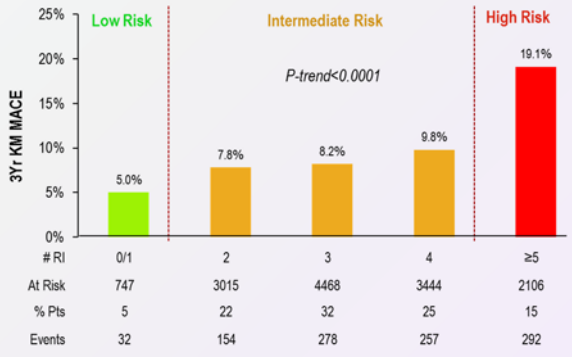


Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . N Engl J Med 2017; 376:1713-1722

FOURIER
Risk Stratification for MACE with Placebo

TIMI Risk Score for Secondary Prevention (TRS 2ºP)

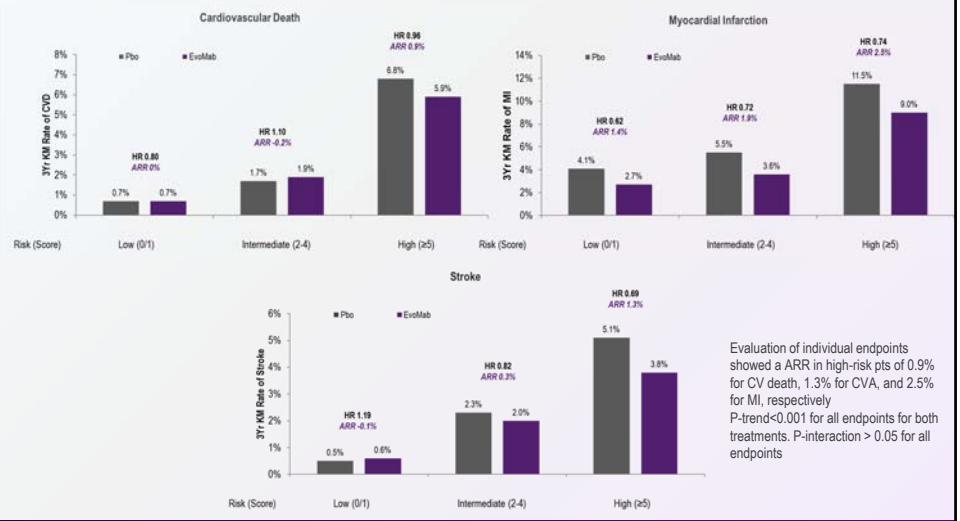
Risk Indicators	Points
CHF	1
HTN	1
Age ≥ 75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR < 60	1
Current Smoking	1
Prior MI	1
Max Possible	10



- The integer-based scheme showed a strong, graded relationship with the rate of CV death, MI or CVA and the components at 3 yrs in both treatment arms (p-trend < 0.0001 for all endpoints; c-statistic = 0.61 [0.67 in prior validation set]).

Bohula EA et al, Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER, AHA 2017 Poster

FOURIER
Individual Outcomes by Risk Category & Randomized Treatment
TIMI Risk Score for Secondary Prevention (TRS 2ºP)



Evaluation of individual endpoints showed a ARR in high-risk pts of 0.9% for CV death, 1.3% for CVA, and 2.5% for MI, respectively
P-trend<0.001 for all endpoints for both treatments. P-interaction > 0.05 for all endpoints

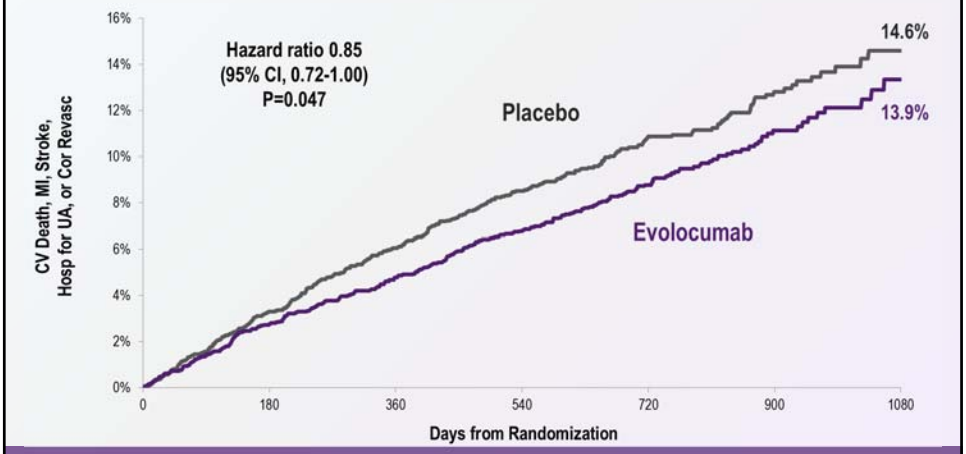
Bohula EA et al, Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER, AHA 2017 Poster

Summary

- In FOURIER, the TIMI Risk Score for Secondary Prevention (TRS 2ºP):
  - Predicted a gradient of risk for major adverse CV events
  - Identified high-risk pts w/ ASCVD who demonstrate a pattern of ***greater ARR*** in major CV events with evolocumab, with an **NNT_{3Yr} ~ 25** in the highest risk.
- This strategy may prove useful to personalize the intensification of secondary preventative therapies.

Bohula EA et al, Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER, AHA 2017 Poster

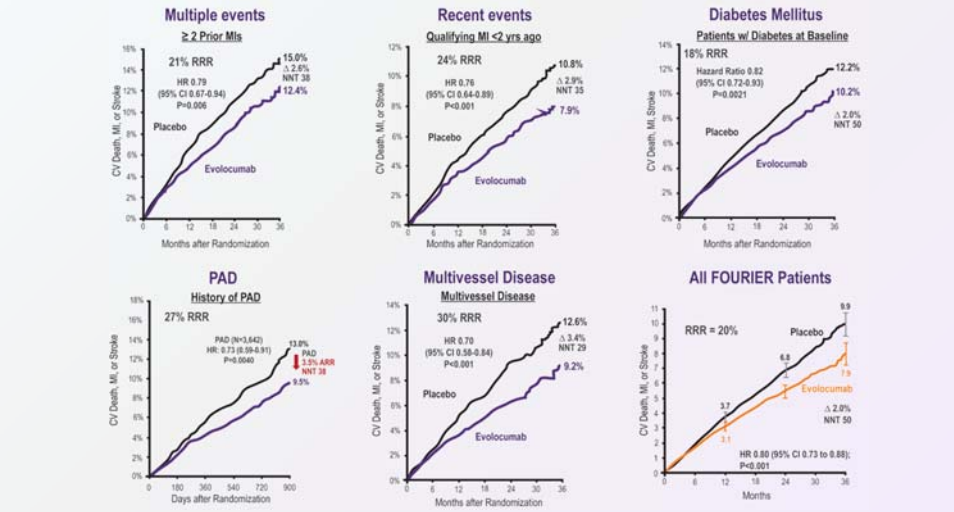
FOURIER
History of Stroke Cohort - Primary Endpoint



Patients with previous history of stroke:
Effect of evolocumab is similar to that for patients with other cardiovascular disease

Pedersen TR et al; presented at ESC 2017

FOURIER
Multiple High-Risk Patient Population Sub-Analysis



Sabatine MS, et al . AHA 2017 Poster

ODYSSEY Outcomes Study Design

Post-ACS (4-52 weeks) patients[1] age ≥40 yrs (n~18,000)
with *LDL-C ≥1.81 mmol/L, or ApoB ≥ 0.8 g/L, or Non-HDL-C ≥ 2.59 mmol/L*
despite high-intensity (or maximally tolerated) statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg/daily) x ≥2 wks ± other lipid-modifying therapy (e.g., ezetimibe, fenofibrate)[2]

Randomization[3]

Alirocumab 75 mg SC Q2wks x 2 months → 150 mg SC Q2wks based upon Month 1
LDL-C ≥ 1.3 mmol/L[4] with dose titrated to maintain LDL-C in the 0.6-1.3 mmol/L target range

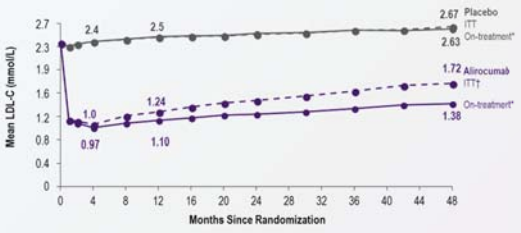
Placebo SC Q2wks

Primary Endpoint: Time to first CHD death/non-fatal MI/fatal and non-fatal ischemic stroke/unstable angina requiring hospitalization
Follow-Up: Minimum 24 months or target number of events (~1600) → estimated 11.4% rate at 4 yrs, 15% risk reduction; 90% power, 1-sided p=0.025, 1% lost

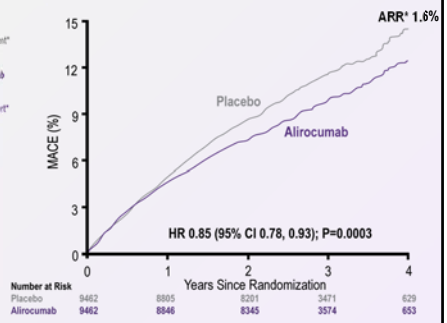
[1] Elevated troponin or CK-MB or resting ECG changes + obstructive coronary disease (new/presumed new ischemia/infarction by perfusion imaging, regional wall motion abnormality, coronary stenosis ≥70% by angiography)
[2] Key exclusion criteria: Uncontrolled hypertension; NYHA III-IV or LVEF<25%; prior hemorrhagic stroke; TG>4.52 mmol/L; hepatitis; eGFR<30 ml/min
[2] Following ≥2 wk (+ 5 days) run-in period with placebo (1 mL volume in an autoinjector) SC Q2wks
[3] Titration downwards for very low LDL

Schwartz et al Am Heart J 2014;168:682-689.e1

ODYSSEY Outcomes
LDL-C: ITT and On-Treatment Analyses & MACE



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



*Based on cumulative incidence

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

Steg G. et al; On behalf of the ODYSSEY OUTCOMES Investigators and Committees - American College of Cardiology – 67th Scientific Sessions - March 10, 2018

ODYSSEY Outcomes
Primary Efficacy Endpoint and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

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ODYSSEY Outcomes
Main Secondary Efficacy Endpoints - Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
CV death	**240 (2.5)**	**271 (2.9)**	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

***Nominal P-value**

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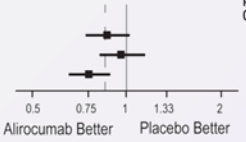
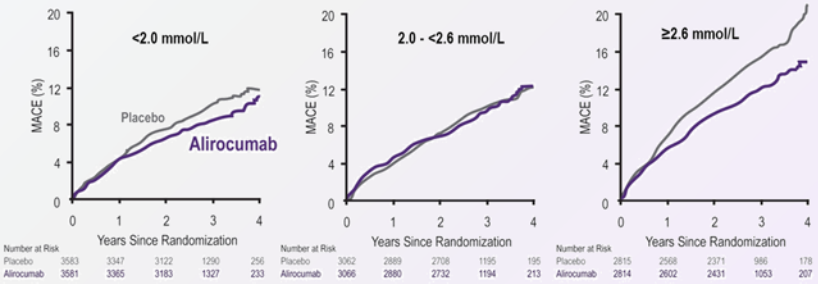
ODYSSEY Outcomes
Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
2.0	7164	8.3	9.5	0.86 (0.74, 1.01)	
2.0 - <2.6	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥2.6	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction



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ODYSSEY Outcomes
Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 0.6-1.3 mmol/L, and allowing levels as low as 0.4 mmol/L:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

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Case 3

Frank
65 years old

Frank has insurance and is interested in the PCSK9 inhibitor but is anxious to get on with therapy.
He reluctantly agrees to augment his rosuvastatin to 40 mg and to start ezetimibe while waiting for the paperwork approves his prescription of a PCSK9 inhibitor.
You see him after his 4th, q2wk injection.
LDL-C is 0.6 mmol/L and he is asymptomatic.

Case 3

Frank
65 years old

Frank decides to stop ezetimibe, continue full dose rosuvastatin and PCSK9 inhibitor.

Follow-up visit shows LDL-C 0.8 mmol/L.

Summary

- Patients with ASCVD have high CV risk
- Patients with ASCVD are at high CV risk and this risk varies greatly and is increased by patient specific features (eg: PAD)
- In addition to best efforts to optimize diet, weight and activity, other modifiable risk factors must be addressed aggressively and with patient priorities in mind
- Adjuncts to statin monotherapy, including PCSK9 inhibitors, are important adjuncts that will help achieve LDL-C goals
- Evidence is emerging that very low LDL-C levels can now be achieved and substantially lower LDL-C can significantly lower residual risk