Case Panel for the Lipidologist

Dyslipidemia Cases

FELLOWS

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Case 1

A 66-year-old woman presents for management of cardiovascular risk. Three years ago, she experienced a NSTEMI with coronary stent placement. At that time, she was started on atorvastatin 80 mg daily, metoprolol, aspirin, levothyroxine and omeprazole. Currently she reports feels well. She follows a heart-healthy dietary pattern, does moderate intensity exercise 45 minutes per day. She does not have a history of smoke. Denies symptoms of ischemia or heart failure.

On physical examination, her blood pressure is 134/82 mm Hg. Her height is 66 in and her weight is 161 lb (BMI of 26 kg/m^2).

Case 1

Laboratory test results (drawn fasting state):

Total Cholesterol: 205 mg/dL

Triglycerides: 225 mg/dL

LDL-C: 123 mg/dL

HDL: 37 mg/dL

Non-HDL-C: 168 mg/dL

In addition to emphasizing on comprehensive lifestyle interventions, which of the following is the best next step in the patient's management?

a) Add ezetimibe
b) Add PCSK9 inhibitor
c) Lp (a)
d) apoB
e) Add Icosapent Ethyl

Case 1

1) How reliable is the calculated LDL-C in hypertriglyceridemia?

Friedewald equation	**LDL-C = (TC) –(triglycerides/5) – (HDL-C)**

Martin-Hopkins equation	**LDL-C = (TC) – (HDL-C) – (triglycerides/adjustable factor*)**
	***Adjustable factor = strata-specific median TG:VLDL-C ratios**

Case 1

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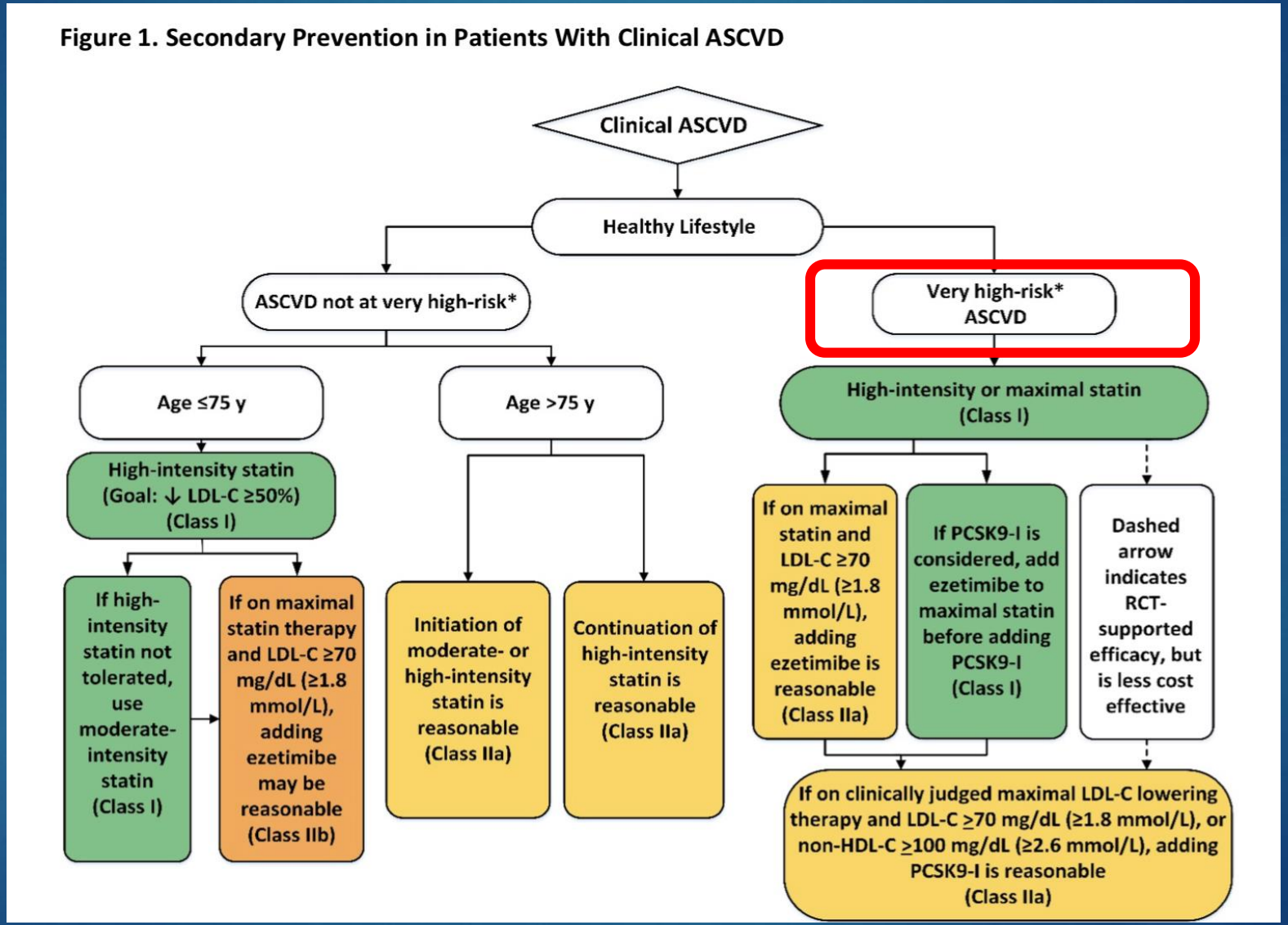
In addition to emphasizing on comprehensive lifestyle interventions, which of the following is the best next step in the patient's management?

a) Add ezetimibe
b) Add PCSK9 inhibitor
c) Lp (a)
d) apoB
e) Add Icosapent Ethyl

2) How would this patient be classified according to his ASCVD risk?



Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines

Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))

* Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high- risk conditions.

Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines

Table 4. Continued

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

* Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high- risk conditions

Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines

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Non-HDL-C: 168 mg/dL

3) Would it be reasonable to measure Lp (a) in this patient?

Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

A Scientific Statement from the National Lipid Association

Wilson et al. Lipoprotein (a) 2019

II. Lipoprotein(a) testing in clinical practice			
1. Adults (aged ≥20 y)			
a. Measurement of Lp(a) is reasonable to refine risk assessment for ASCVD events in:			
1) Individuals with a family history of first-degree relatives with premature ASCVD (males aged <55 y; females aged <65 y)	IIa	C-LD	Rallidis, 2018
2) Individuals with premature ASCVD (men aged <55 y and women aged <65 y), particularly in the absence of traditional risk factors.	IIa	B NR	Erqou, 2009; Kamstrup, 2013; Clarke 2009; CARDIoGRAMplus C4D Consortium, 2013; Genest, 1992
3) Individuals with primary severe hypercholesterolemia (LDL ≥190 mg/dL) or suspected FH.	IIa	B-NR	Pérez de Isla, 2017; Ellis, 2016; Langsted 2016; Ellis, 2019
4) Individuals at very-high-risk** of ASCVD to better define those who are more likely to benefit from PCSK9 inhibitor therapy	IIa	B-NR	O'Donoghue,2018; Bittner, 2018

II. Lipoprotein(a) testing in clinical practice			
b. Measurement of Lp(a) may be reasonable for individuals with:			
1) Intermediate (7.5%–19.9%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIa	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
2) Borderline (5%–7.4%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIb	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
3) Less-than-anticipated LDL-C lowering, despite good adherence to LDL-C lowering therapy.	IIb	C-LD	Yeang 2016; CARDIoGRAMplus C4D Consortium 2013; Langstead 2016
4) A family history of elevated Lp(a).	IIb	C-LD	Clarke 2009; CARDIoGRAMplus C4D Consortium 2013; Langsted 2016
5) Calcific valvular aortic stenosis.	IIb	C-LD	Thanassoulis 2013; Kamstrup 2014; Arsenault 2014; Vongpromek 2015; Capoulade 2015
6) Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy.	IIb	C-LD	Albers 2013; Khera 2014; Nestel 2013;

Lp(a) and Secondary Prevention: Summary

- Be aware of Lp(a)-associated increased risk for recurrent events
- Continue to follow Guideline based therapies, as most lipid-related risk is still attributable to LDL-C
- Consider more aggressive LDL-C lowering for ASCVD patients with increased Lp(a)
- Consider earlier use of PCSK9 inhibitors in ASCVD patients with elevated Lp(a)

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HDL: 37 mg/dL

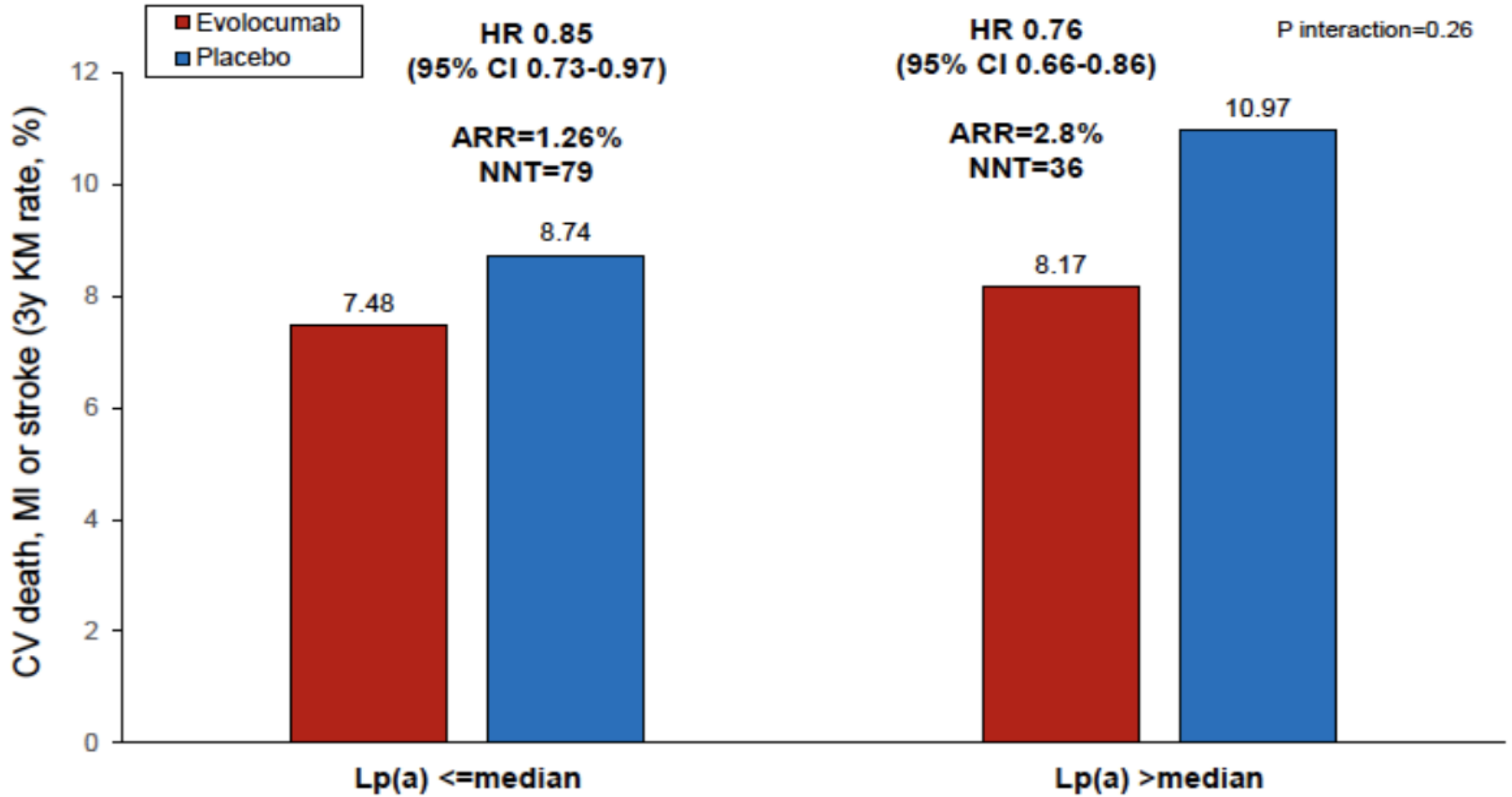
Non-HDL-C: 168 mg/dL

3) Would it be reasonable to measure Lp (a) in this patient?

Lp(a) 110 mg/dL

III. Treatment			
1. In adults aged 40–75 y with a 10-y ASCVD risk of 7.5%–19.9%, the finding of an Lp(a) ≥50 mg/dL or ≥100 nmol/L[§] is reasonable to be used as a risk-enhancing factor to favor initiation of a moderate- or high-intensity statin in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).	IIa	B-NR	Emerging Risk Factors Collaboration JAMA 2009; Clarke R et al. N Engl J Med 2009; Kamstrup PR et al. JAMA 2009
2. In high-risk* or very-high-risk** patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], it is reasonable to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.	IIa	A	Willeit, 2018); Khera, 2014; Baigent, 2000
3. In very-high-risk** patients, taking a maximally tolerated statin with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], the addition of ezetimibe is reasonable in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).	IIa	B-R	Cannon, 2015
4. In high-risk* patients taking a maximally tolerated statin, with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], the addition of ezetimibe may be reasonable in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).	IIb	B-R	Cannon, 2015
5. In very-high-risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL) and an Lp(a) of ≥50 mg/dL or ≥100 nmol/L[§], the addition of a PCSK9 inhibitor is reasonable.	IIa	B-R	O'Donoghue,2018; Bittner, 2018; Sabatine, 2017; Schwartz, 2018
6. Niacin, which lowers Lp(a) concentration, is not recommended to reduce ASCVD risk in patients receiving moderate- to high-intensity statins +/− ezetimibe and an on-treatment LDL-C <80 mg/dL	III (harm)	A	Albers, 2013J; Parish, 2018
7. HRT with estrogen and progesterone, which lowers Lp(a) concentration, is not recommended in perimenopausal/ postmenopausal women to reduce ASCVD risk.	III (harm)	B-R	Hulley, 1998; Shlipak 2000; Writing Group for the WHI Investigators, 2002

Efficacy by Baseline Lp(a)



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3) Would it be reasonable to measure Lp (a) in this patient?

Lp(a) 110 mg/dL
PCSK9 Inhibitor √

Needs > 20 % LDL Reduction

Case 1

Total Cholesterol: 205 mg/dL

Triglycerides: 225 mg/dL

LDL-C: 62 mg/dL * **calculated by Martin-Hopkin's equation** √

HDL: 37 mg/dL

Non-HDL-C: 168 mg/dL

4) Would you consider additional management in this patient with LDL-C in the optimal range in order to decrease residual ASCVD risk?

reduce-it

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD,

Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD,

Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD,

Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Christie M. Ballantyne, MD,

on Behalf of the REDUCE-IT Investigators

BWH

REDUCE-IT Population

Double-blind parallel group trial; median follow-up 4.9 years

- Statin treated men and women (aged ≥45 years)
- Well controlled LDL-C (41-100 mg/dL) (median baseline 75mg/dL)

8179 Patients

At High Risk for CV Events Due To:

- TG 150-499 mg/dL (median baseline 216 mg/dL), and
- Established CVD

OR

- Diabetes mellitus + aged ≥50 years + ≥1 risk factor for CVD

Randomization 1:1

Stable Statin + icosapent ethyl (Vascepa) 4g/d

Stable Statin + Placebo

PRIMARY COMPOSITE (MACE) ENDPOINT

CV Death
Nonfatal MI
Coronary Revascularization
Nonfatal Stroke
Unstable Angina requiring hospitalization

https://www.healio.com/cardiology/chd-prevention/news/online/%7Bdfc9db36-4c3e-4653-b454-d51862cc5b4c%7D/reduce-it-topline-results-announced-icosapent-ethyl-reduces-cv-events. Accessed October 22, 2018.

Inclusion Criteria for Secondary Prevention Cohort

One or more of the following:

1. Documented coronary artery disease
   - Multi vessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries – with or without antecedent revascularization
   - Prior MI
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity
2. Documented cerebrovascular or carotid disease
   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization
3. Documented peripheral artery disease
   - Ankle-brachial index <0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral artery intervention

Adapted with permission* from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148. [*https://creativecommons.org/licenses/by-nc/4.0/]

Inclusion Criteria for Primary Prevention Cohort

1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND
3. ≥1 additional risk factor for CVD
   - Men ≥55 years and women ≥65 years
   - Cigarette smoker or stopped smoking within 3 months
   - Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
   - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
   - hsCRP >3.0 mg/L
   - Renal dysfunction: Creatinine clearance >30 and <60 mL/min
   - Retinopathy
   - Micro- or macroalbuminuria
   - ABI <0.9 without symptoms of intermittent claudication

Patients with diabetes and CVD are counted under Secondary Prevention Cohort

Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Severe liver disease
3. History of pancreatitis
4. Hypersensitivity to fish and/or shellfish

Adapted with permission* from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148. [*https://creativecommons.org/licenses/by-nc/4.0/]

Effects on Biomarkers from Baseline to Year 1

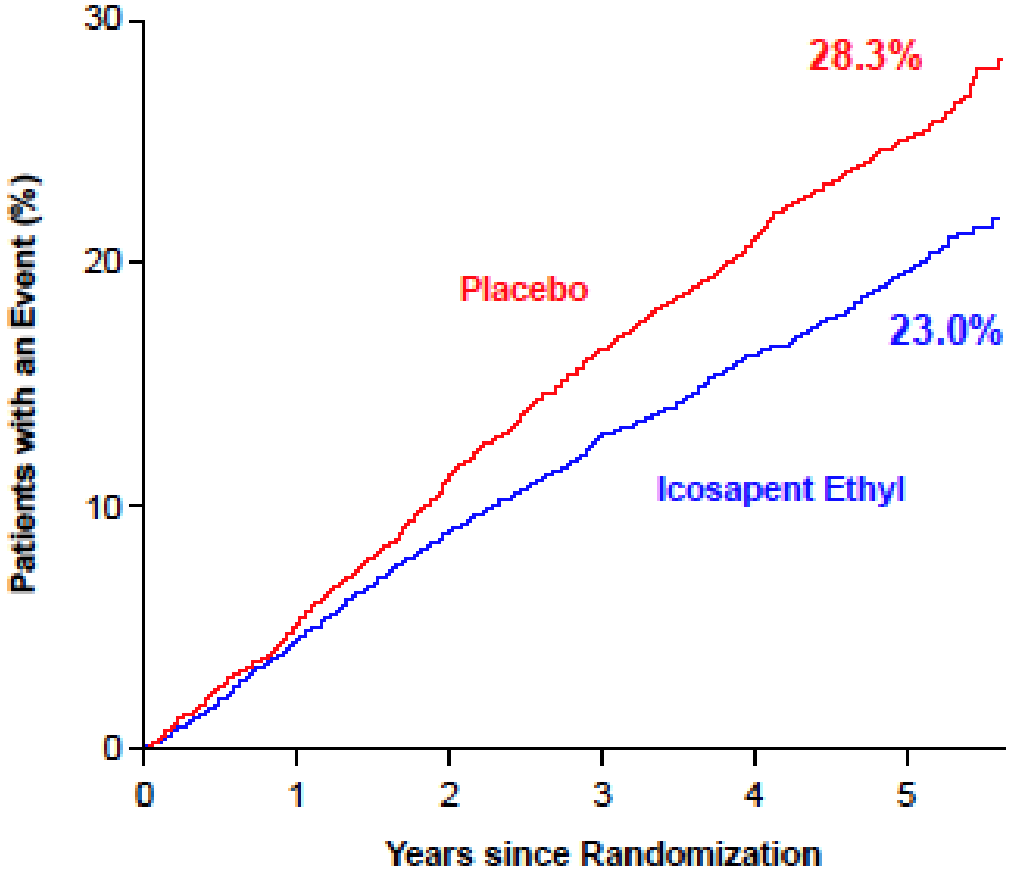
	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

Primary End Point:

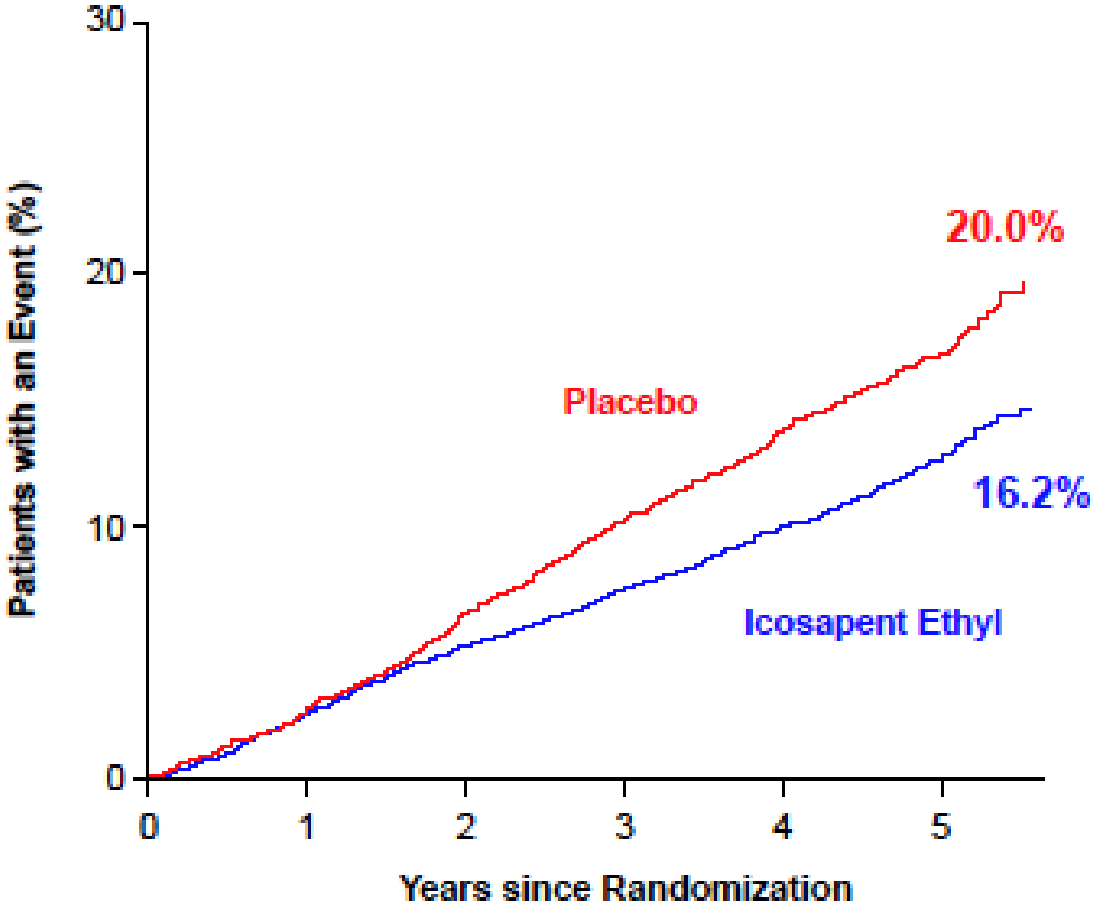
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

REDUCE-IT

Key Secondary Endpoint Subgroup Analysis

Icosapent ethyl was favored:*

- Primary and secondary prevention cohorts
- Men and women
- US and non-US populations
- With or without diabetes at baseline
- Baseline TG
  - < 200 or ≥ 200 mg/dL
  - < 150 or ≥ 150 mg/dL

**P* values were not statistically significant.

Bhatt DL, et al. *N Engl J Med*. 2018. [Epub ahead of print]

REDUCE-IT Implications

Study Limitations[a]

- 6.4% patients on ezetimibe in each group
- No concomitant PCSK9 inhibitor use
- ~5 mg/dL difference in LDL between groups
  - Cannot tell if due to drug or placebo
  - Would not account for 25% RRR
  - Consistent benefit in patients with elevated LDL vs not elevated
  - JELIS trial had 19% RRR in open-label design, no placebo[b]

Conclusion

- Compared with placebo, icosapent ethyl 4 g/day significantly reduced important CV events by 25%:
  - -20% for death due to CV causes
  - -31% for MI
  - -28% for nonfatal stroke
- Low rate of adverse effects:
  - Small but significant increase in Afib/flutter
  - Increase in serious bleeding (NS)
- Consistent efficacy across multiple subgroups:
  - Including baseline TG from 135-500 mg/dL
  - Including secondary and primary prevention cohorts

a. Bhatt DL, et al. *N Engl J Med*. 2018. [Epub ahead of print]; b. Yokoyama M, et al. *Lancet.* 2007;369:1090-1098.

Updated ADA SOC March 27 2019 on Lipid management for CV Risk Reduction

- Based on the outcome of Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT),
  The *Standards of Care* now include a recommendation that icosapent ethyl be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled LDL-C, but with elevated triglycerides (135-499) to reduce cardiovascular risk.

American Diabetes Association®

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American Diabetes Association®

ESC
European Society of Cardiology

In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B

NATIONAL LIPID ASSOCIATION

NLA Position on the Use of Icosapent Ethyl in High and Very-high-risk Patients

- For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with type 2 diabetes requiring medication and ≥1 additional risk factor*, and fasting triglycerides 135-499 mg/dL on maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD risk reduction. (I B-R)

CLASS I (STRONG) Benefit >>> Risk
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial

LEVEL B-R (Randomized)
• Moderate-quality evidence from 1 or more RCTs • Meta-analysis of moderate-quality RCTS

*
- Age: men ≥55 years and women ≥65 years
- Cigarette smoker or stopped smoking within 3 months
- Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication
- HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
- hs-CRP >3.0 mg/L
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4) Would you consider additional management in this patient with LDL-C in the optimal range in order to decrease residual ASCVD risk?

ADD ICOSAPENT ETHYL 2 GRAMS PO BID
BASED ON REDUCE IT

Case 2

- HPI
  - Case of a 55y/o male with medical history of DM, HTN, s/p CABG 6 months ago who was referred to endocrinology clinics for glycemic and metabolic control.

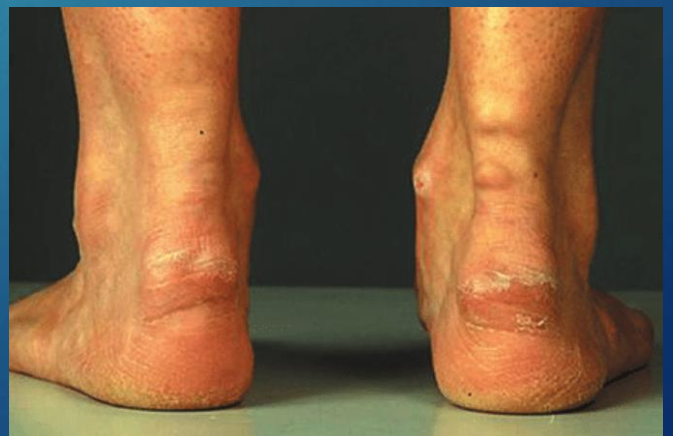
Case 2

- PMHx: CAD, HTN, DM, severe claudication
- Sx: s/p CABG 6 months ago
- Family Hx: Mother: CABG 60y/o, T2DM, HTN
- Toxic habits: Denied

- Meds:
  - Rosuvastatin 40mg po d
  - Lisinopril 20mg po bid
  - Carvedilol 6.25mg po q 12hrs
  - Empagliflozin/metfomin 12.5mg/1000mg po bid
  - ASA 81mg po d
  - Brillinta 90mg po BID

Case 2

- **Physical Exam**
  - VS: 145/85 mmHg HR: 65 bpm BMI: 35kg/m2 WC: 43”
  - Cardiovascular exam: Grade 3 SEM
  - Extremities: shiny skin lower extremities, Achilles tendon xanthoma



Case 2

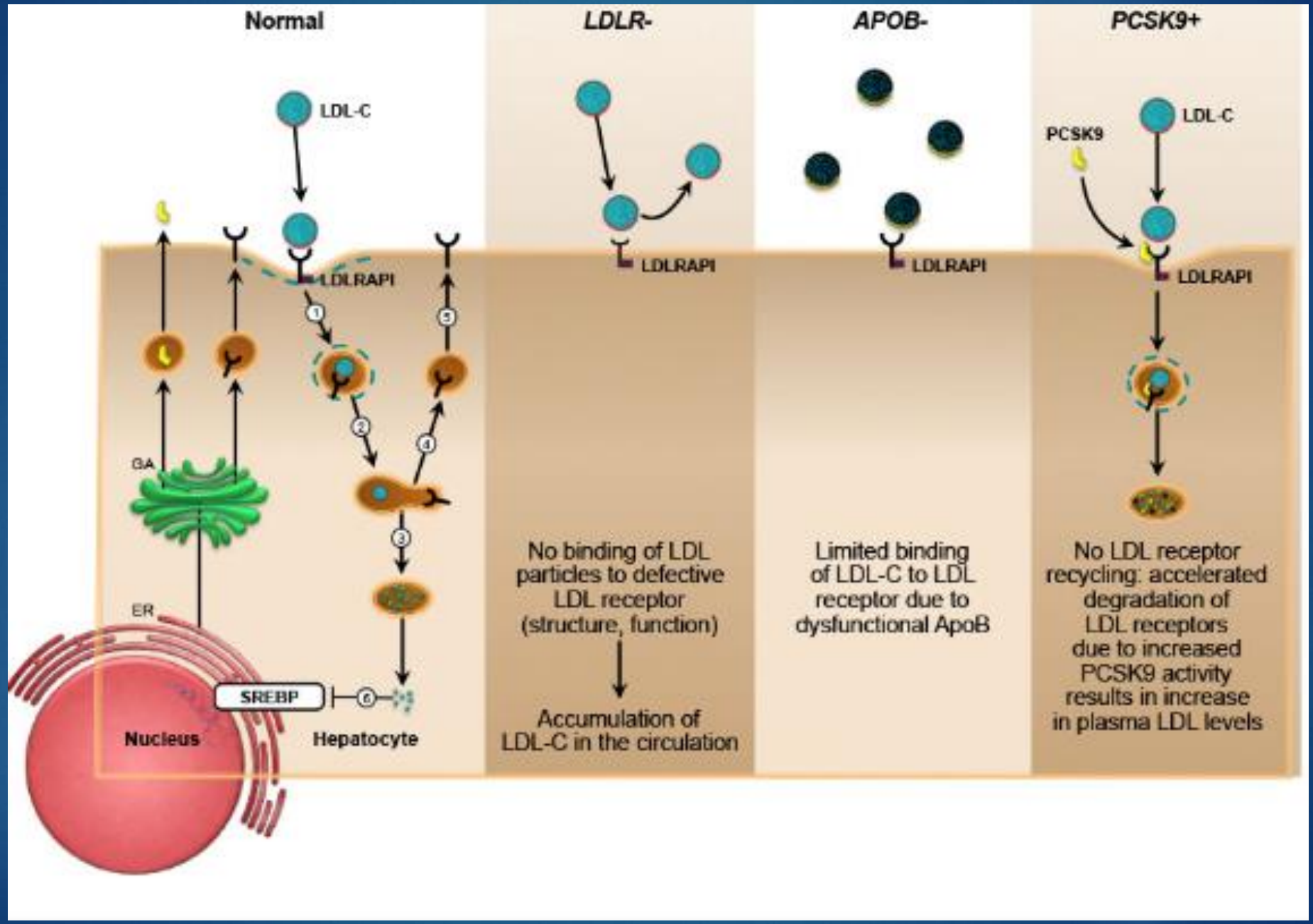
- **Laboratories:**
  - TC: 181 mg/dL
  - LDL:110 mg/dL
  - HDL: 40 mg/dL
  - TG's: 155 mg/dL,
  - Non-HDL: 141 mg/dL
  - Lp(a): 116 mg/dl
  - 10-year ASCVD risk: 15.8%

- With on-treatment LDL level in 110 mg/dl, would you diagnose this patient with familial hypercholesterolemia?

FH: Simon-Broome Criteria

TABLE 1
Simon Broome criteria for diagnostics of familial hypercholesterolemia

Criteria	Description
a	Total cholesterol concentration above 7.5 mmol/L in adults or a total cholesterol concentration above 6.7 mmol/L in children aged less than 16 years, or low-density lipoprotein cholesterol concentration above 4.9 mmol/L in adults or above 4.0mmol/L in children
b	Tendinous xanthomata in the patient or a first-degree relative
c	DNA-based evidence of mutation in the *LDLR* or *APOB* gene
d	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first degree relative
e	Family history of raised total cholesterol concentration above 7.5 mmol/L in a first- or second-degree relative
Diagnosis	
A 'definite' FH diagnosis requires either criteria *a* and *b* or criterion *c* A 'probable' FH diagnosis requires criteria *a* and *d* or criteria *a* and *e*	


Normal
LDL-C
LDLRAPI
GA
ER
SREBP
Nucleus
Hepatocyte
LDLR-
LDLRAPI
No binding of LDL particles to defective LDL receptor (structure, function)
Accumulation of LDL-C in the circulation
APOB-
LDLRAPI
Limited binding of LDL-C to LDL receptor due to dysfunctional ApoB
PCSK9+
PCSK9
LDL-C
LDLRAPI
No LDL receptor recycling: accelerated degradation of LDL receptors due to increased PCSK9 activity results in increase in plasma LDL levels

- How this patient should be classified regarding risk stratification? High, very high or extreme risk? Is it reasonable an LDL target of <55 mg/dl?

FIGURE 1 Secondary Prevention in Patients With Clinical ASCVD

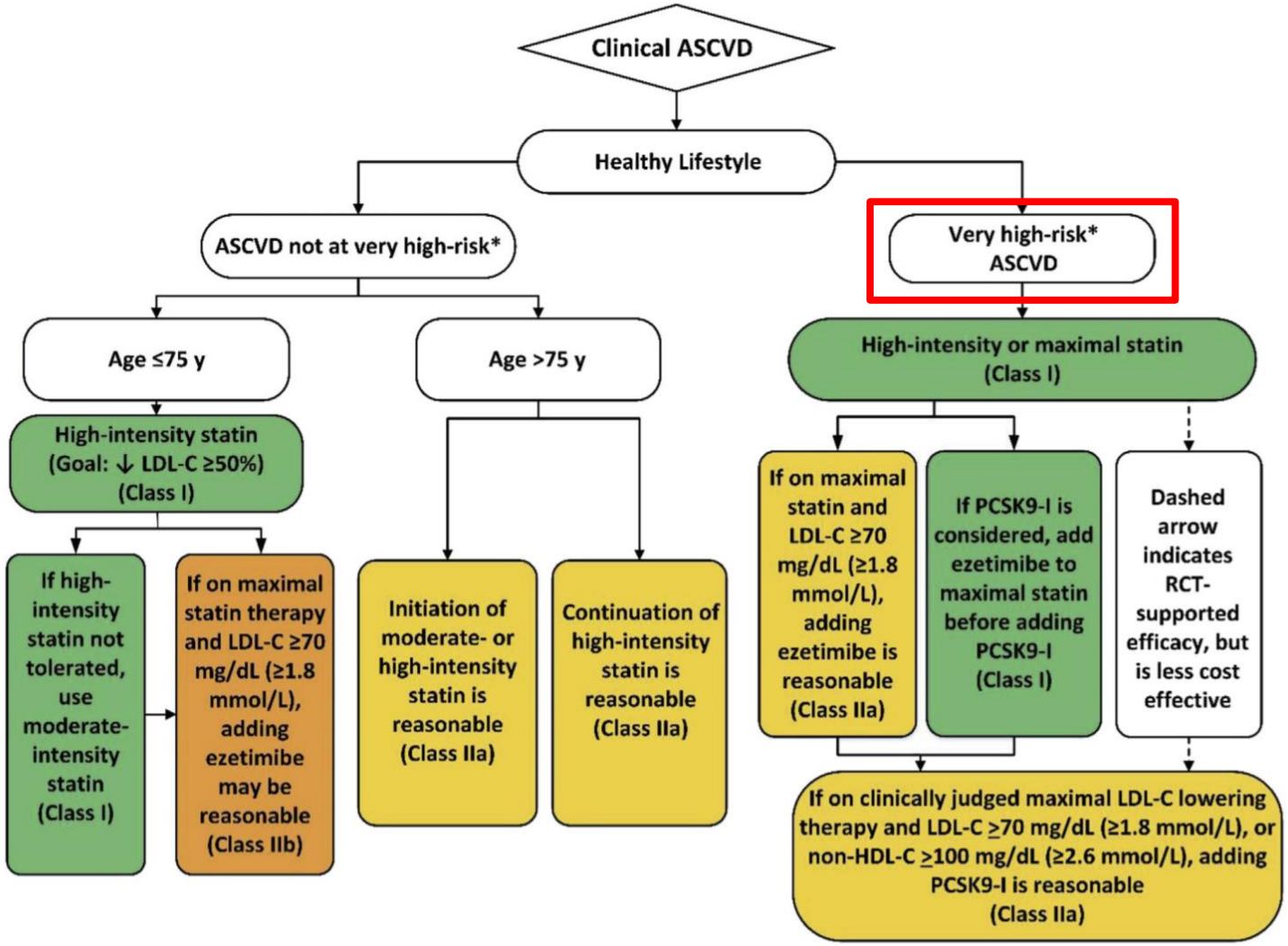


Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not recommended; UKPDS = United Kingdom Prospective Diabetes Study.

[a] Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

[b] Framingham risk scoring is applied to determine 10-year risk.

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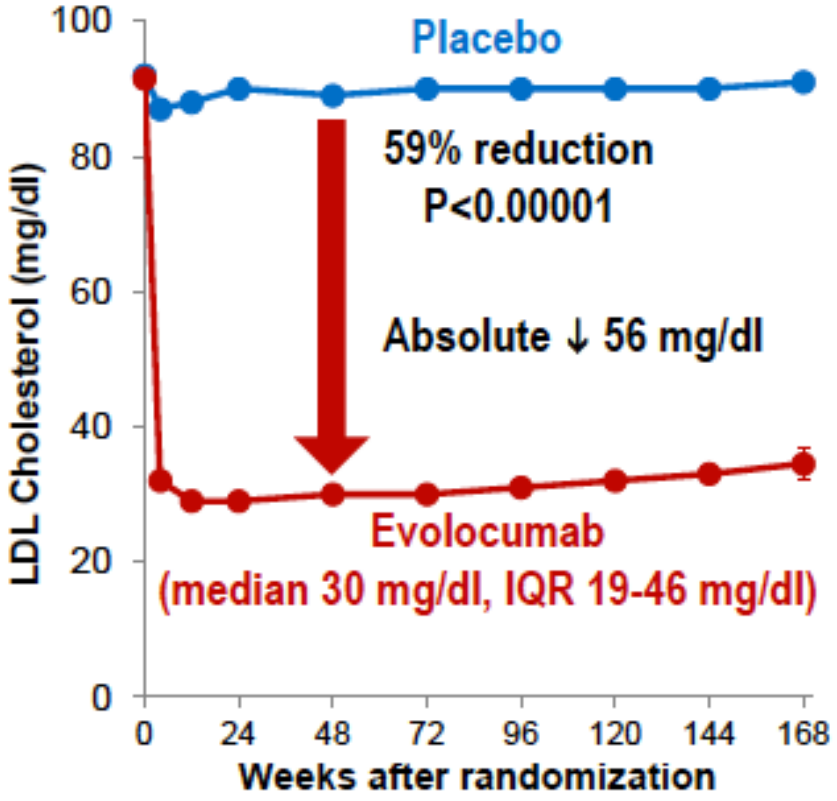
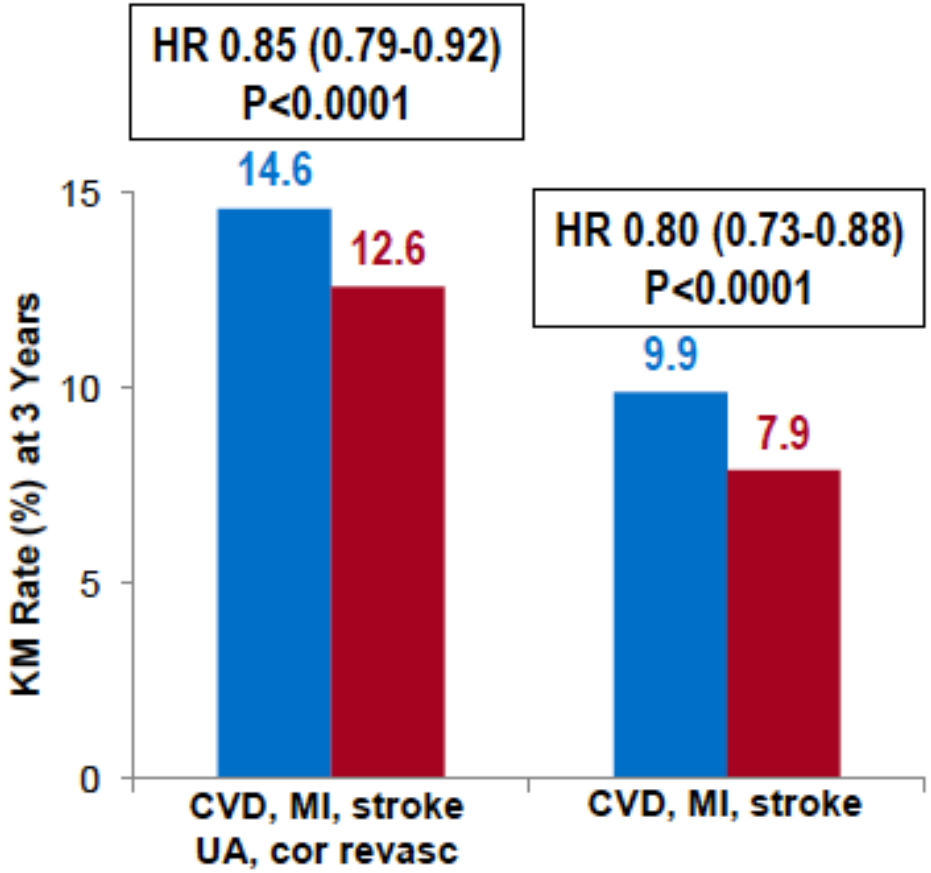
- Would you consider further intensification of lipid lowering therapy? Ezetimibe? PCSK9 inhibitor?
- Would you consider targeting a Lp (a) reduction in the management of this patient?

Summary of Effects of PCSK9i Evolocumab

- 27,564 pts w/ stable ASCVD & LDL-C ≥70mg/dL on a statin
- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





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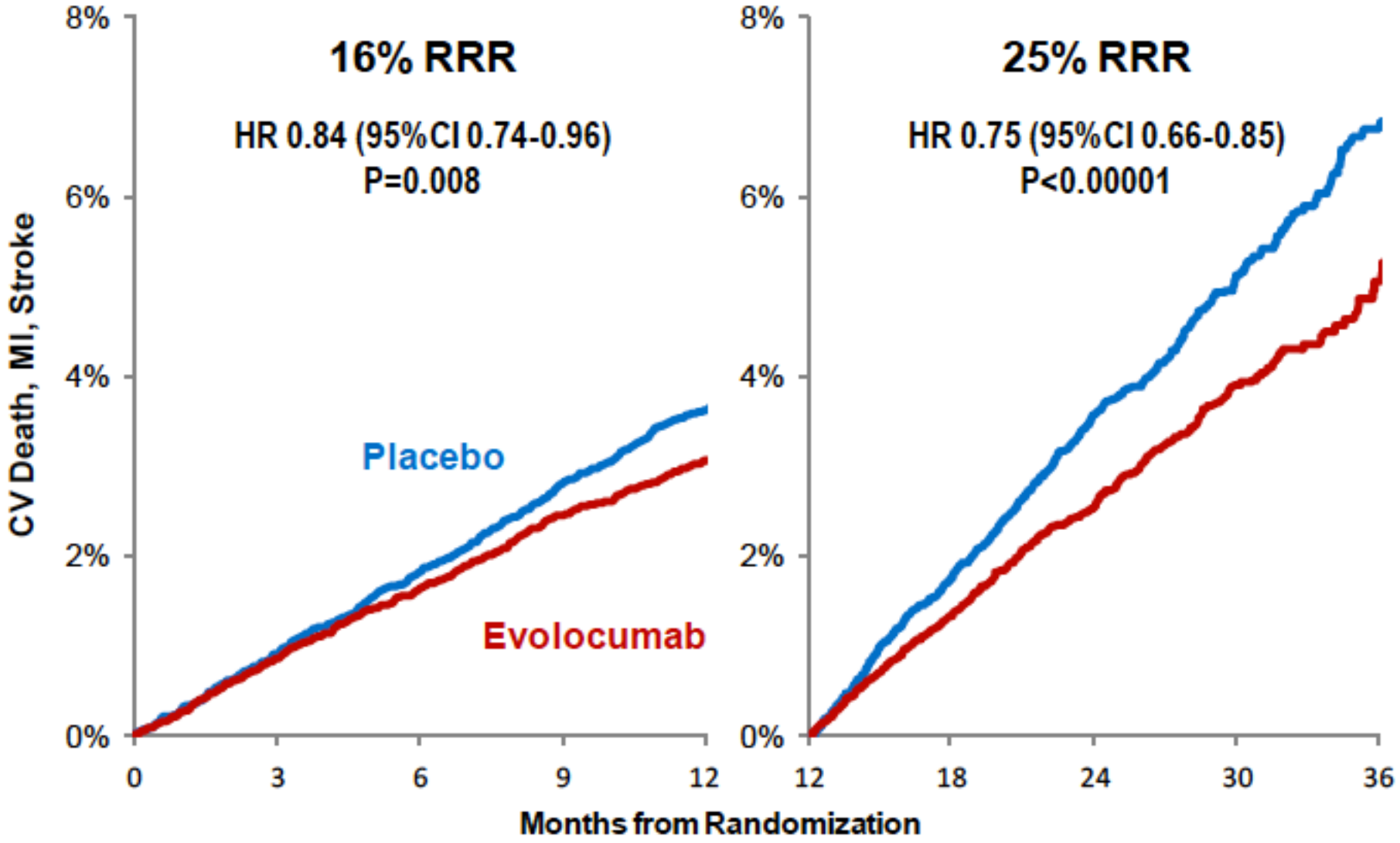
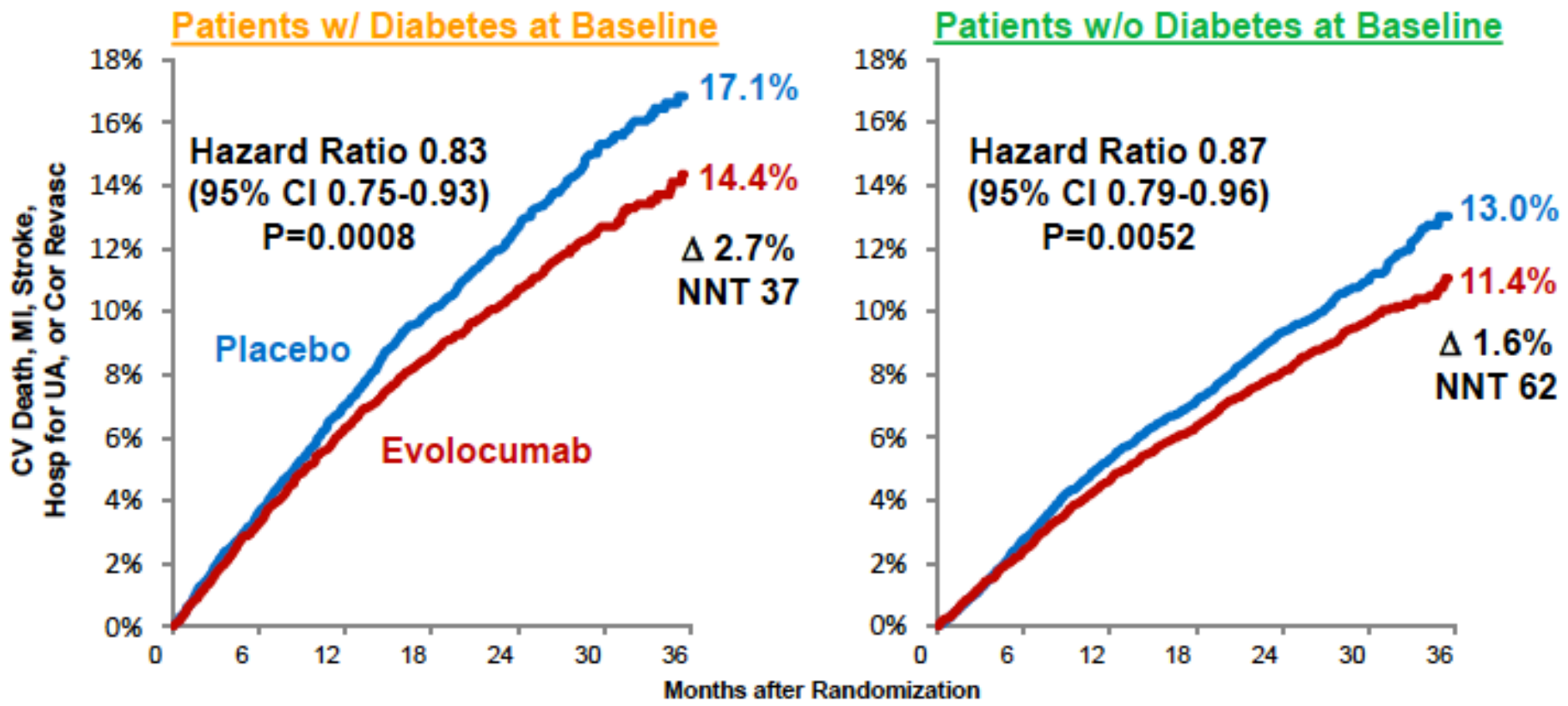
Sabatine MS et al. *NEJM* 2017;376:1713-22

Landmark Analysis



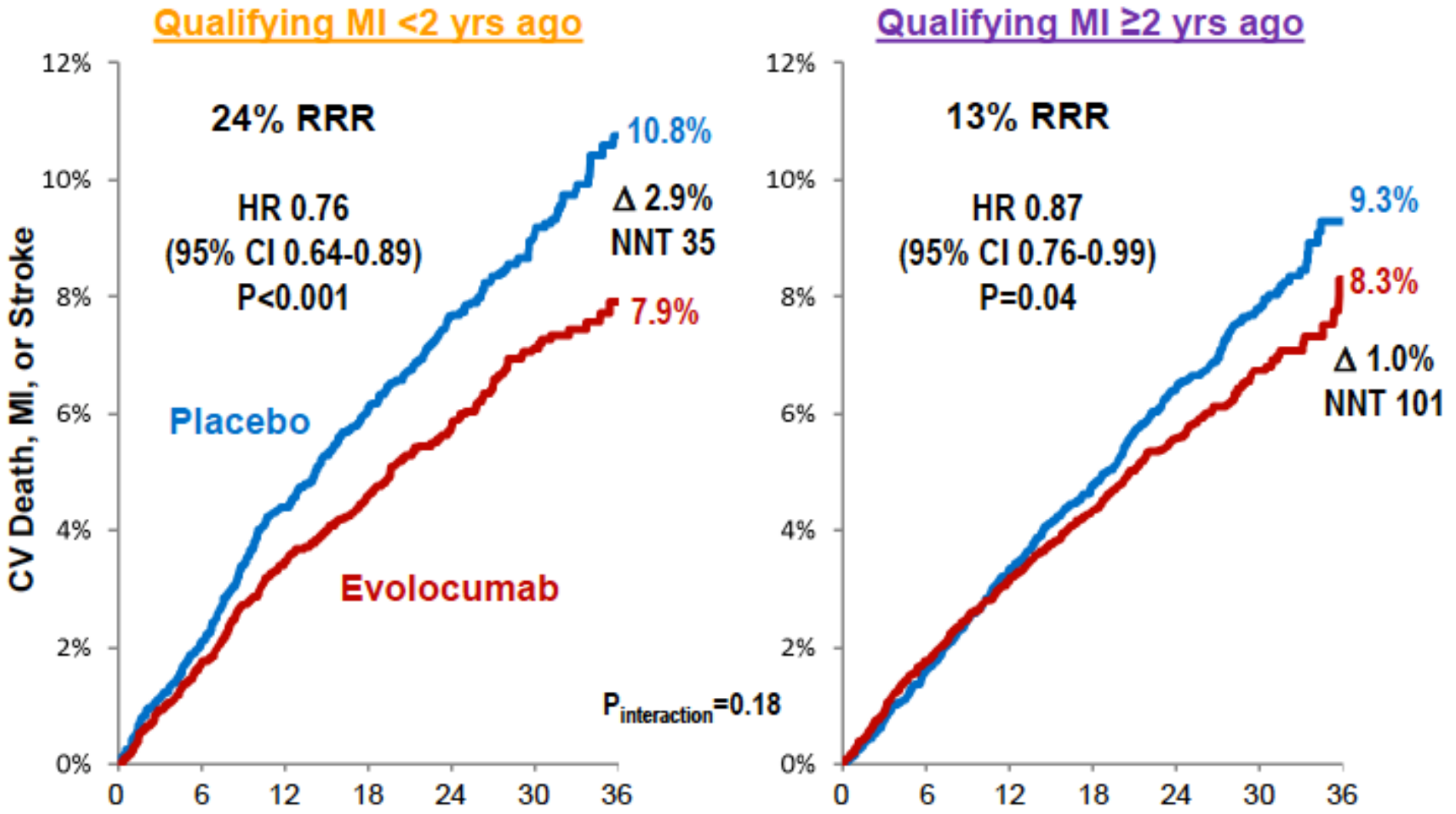
Sabatine MS et al. *NEJM* 2017;376:1713-22

Clinical Efficacy by Diabetes Status



Sabatine MS, Leiter LA et al. *Lancet Diab & Endo* 2017;5;941-50

Benefit of EvoMab Based on Time from Qualifying MI



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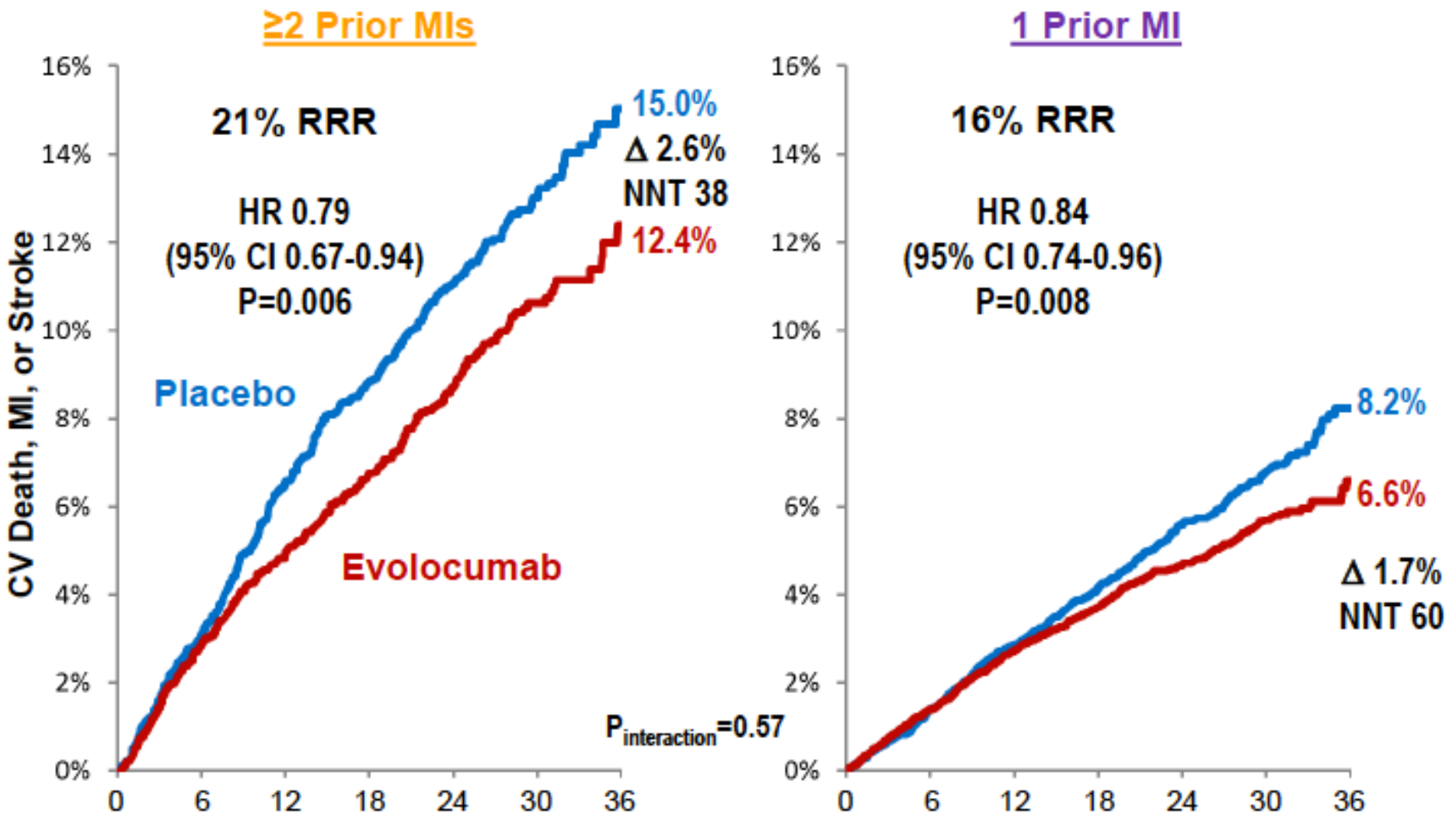
Sabatine MS et al. *Circulation* 2018;epub ahead of print

Benefit of EvoMab Based on # of Prior MIs



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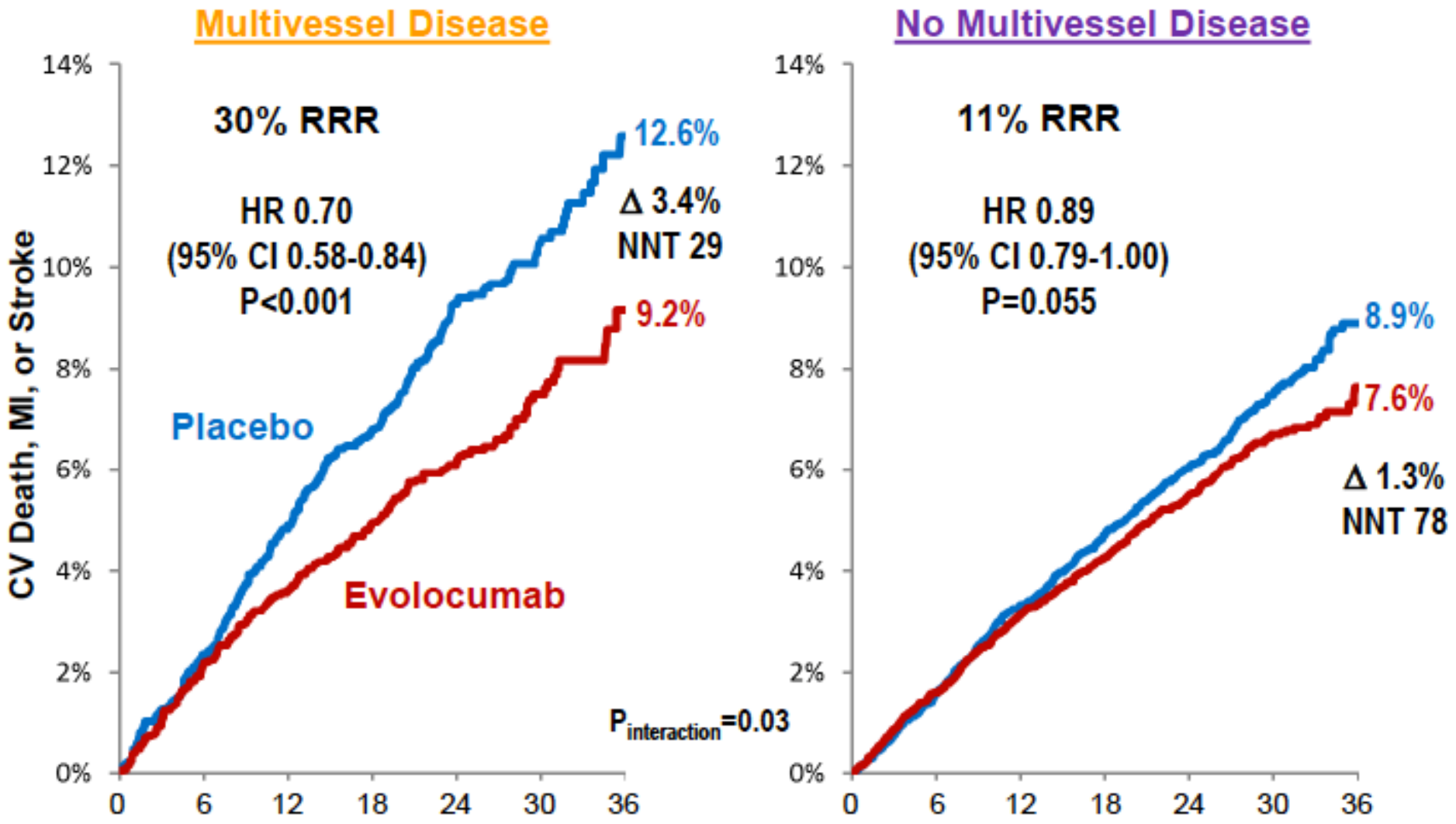
Sabatine MS et al. *Circulation* 2018;epub ahead of print

Benefit of EvoMab Based on Multivessel Disease



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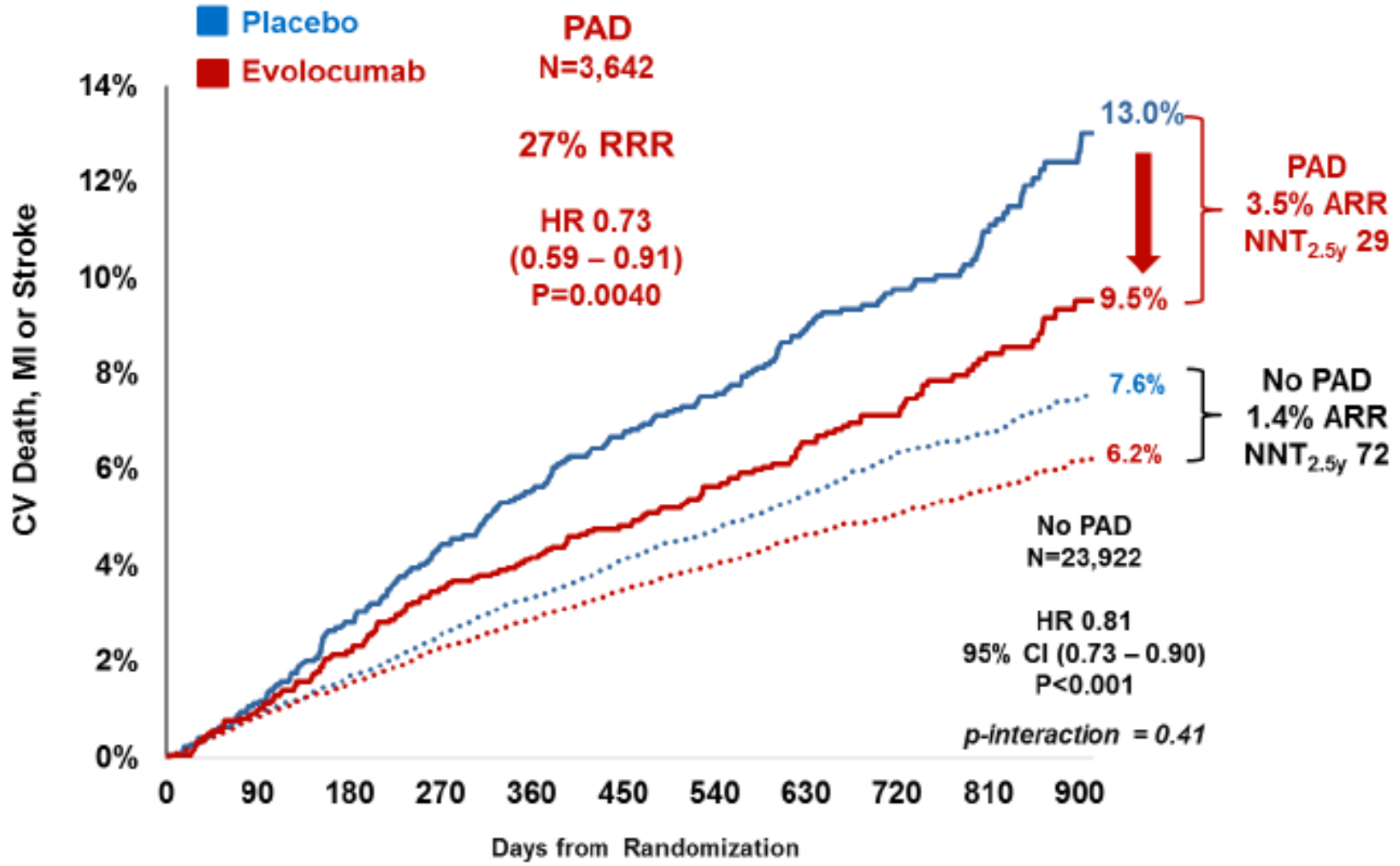
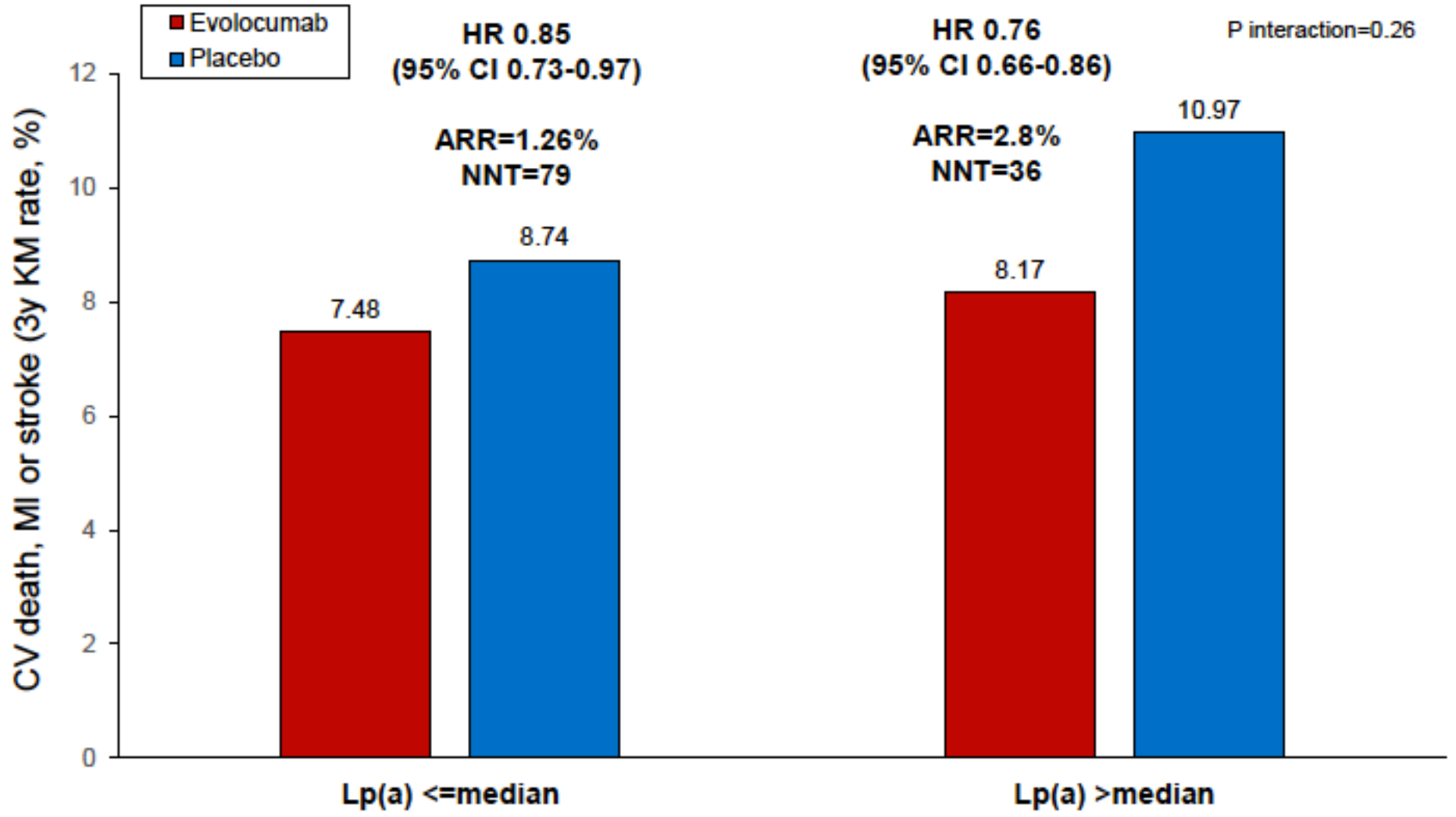
Sabatine. *Circulation* 2018; epub ahead of print

CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease



Bonaca MP et al. & Sabatine MS. *Circulation* 2018;137:338-50

Efficacy by Baseline Lp(a)

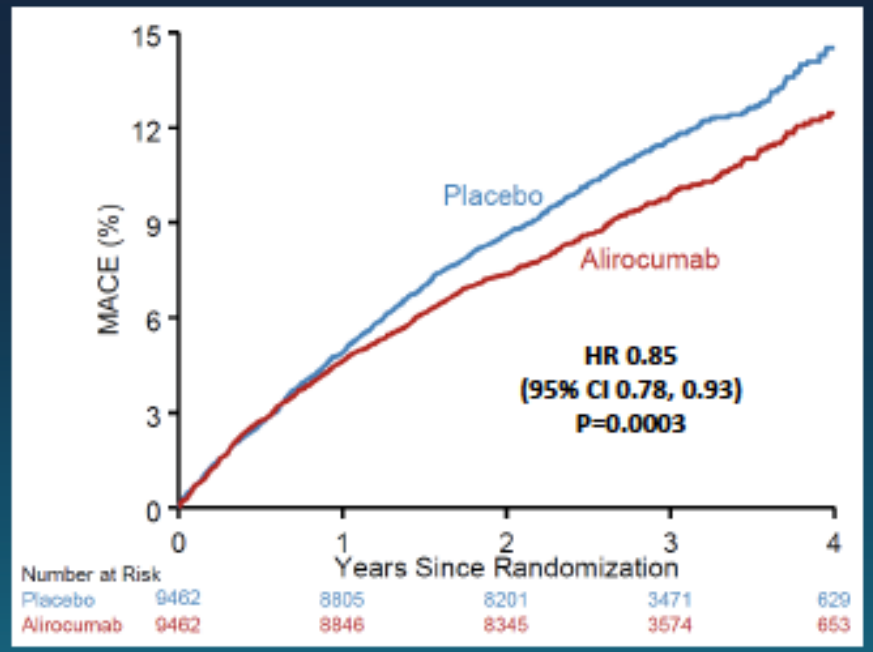


Impact of PCSK9 Inhibition Among Patients with Recent ACS

ODYSSEY Outcomes Trial

18,924 high-risk patients with an ACS within the preceding 1-12 months and an LDL-C ≥70 mg/dL on background high-intensity statin therapy randomized to alirocumab or placebo for a median of 2.8 years

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



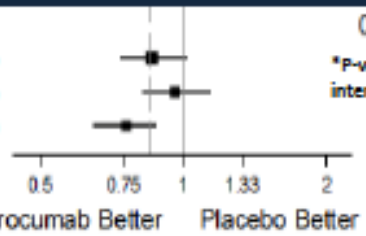
ARR 1.6%

(based on cumulative incidence)

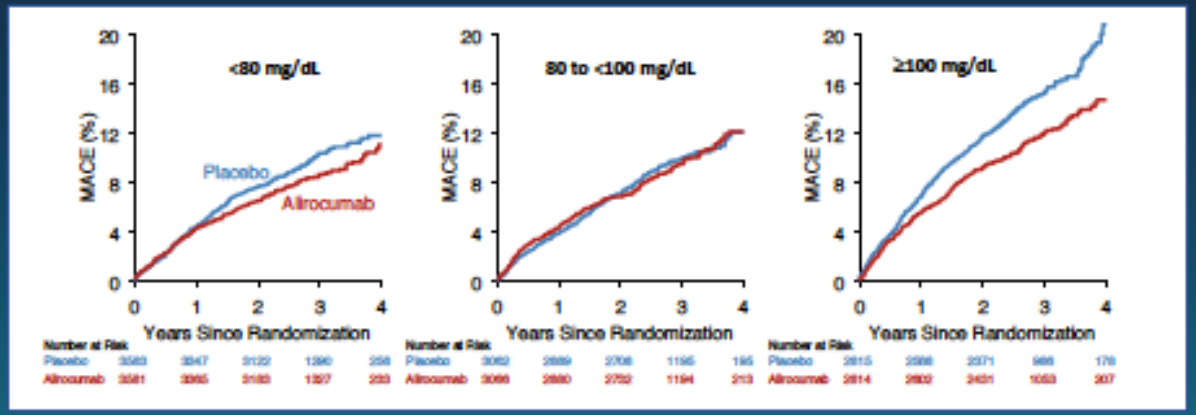
Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

Primary Efficacy Endpoint (MACE) in Prespecified Baseline LDL-C Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	

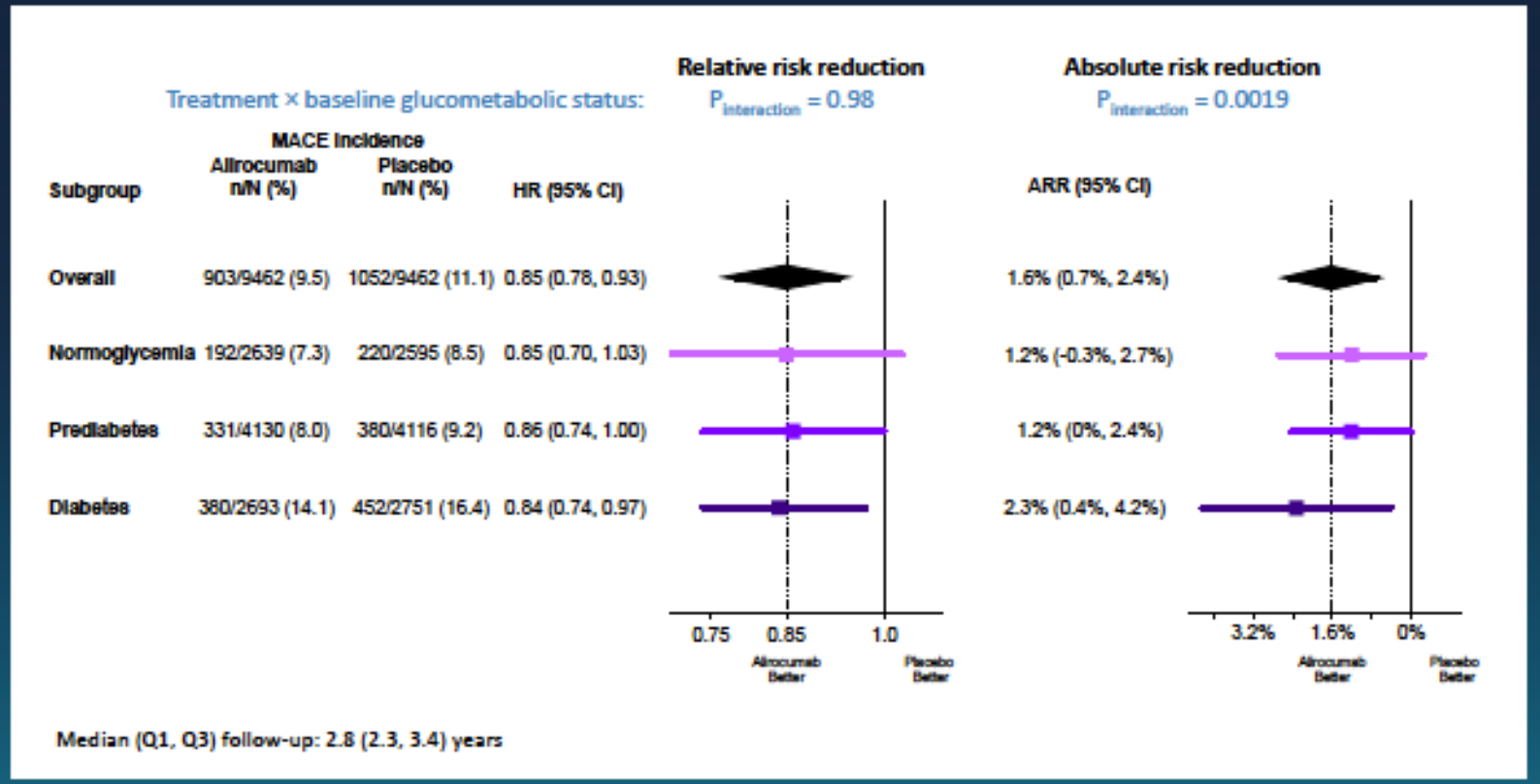


*P-values for interaction



Steg PG, et al. Presented at: ACC.18 Scientific Sessions; March 10, 2018; Orlando, FL.

Relative and Absolute Risk Reduction By Glucometabolic Status

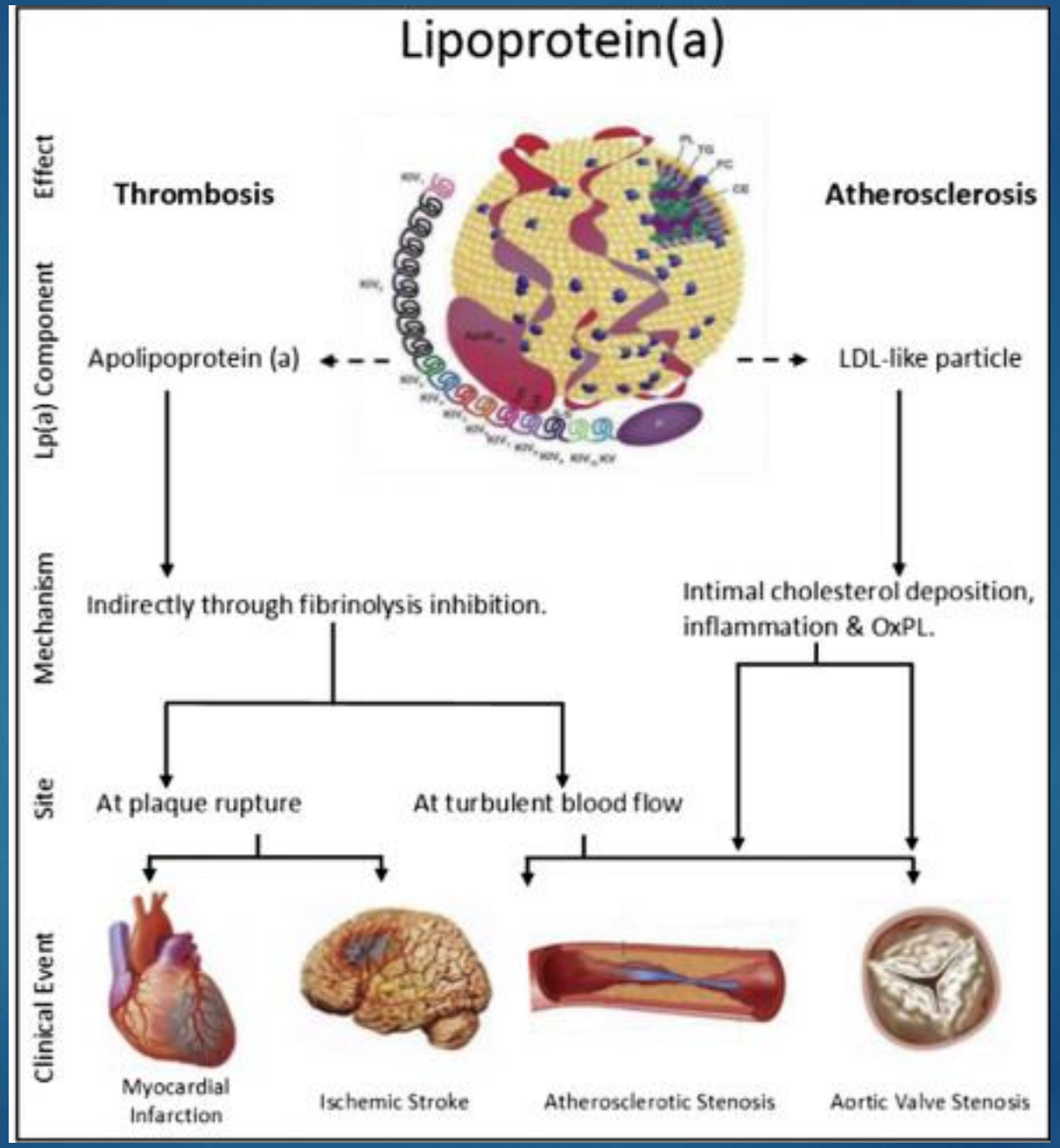


Ray K, et al. Presented at: ADA 2018; June 2018; Orlando, FL

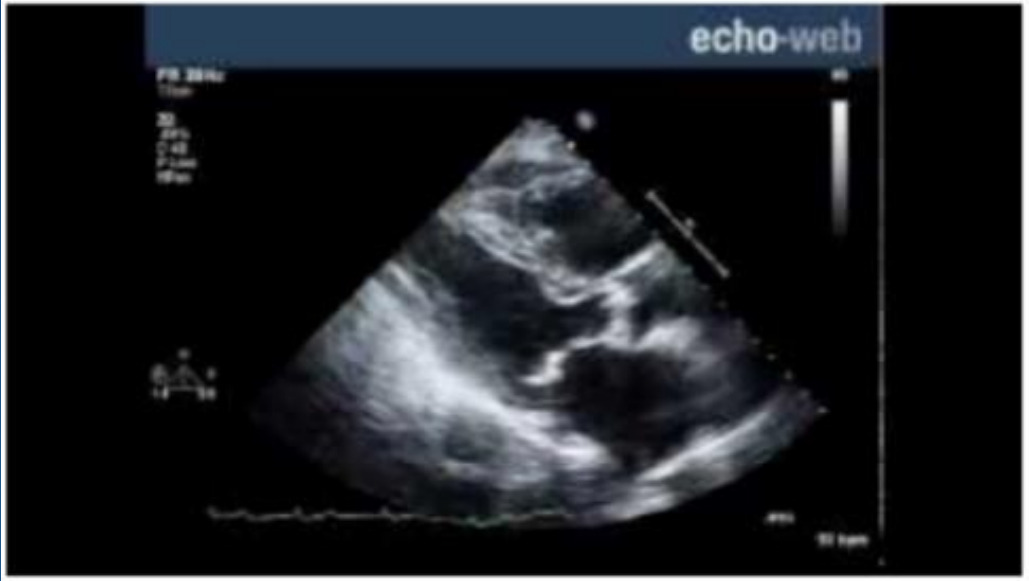
Case 2

- Follow up
  - Started on SC injection PCSK9i Q2W on top of high intensity statin
  - After 3 months:
    - LDL-C 52 mg/dL (>50% reduction)
    - nonHDL-C 64 mg/dL (>50% reduction)

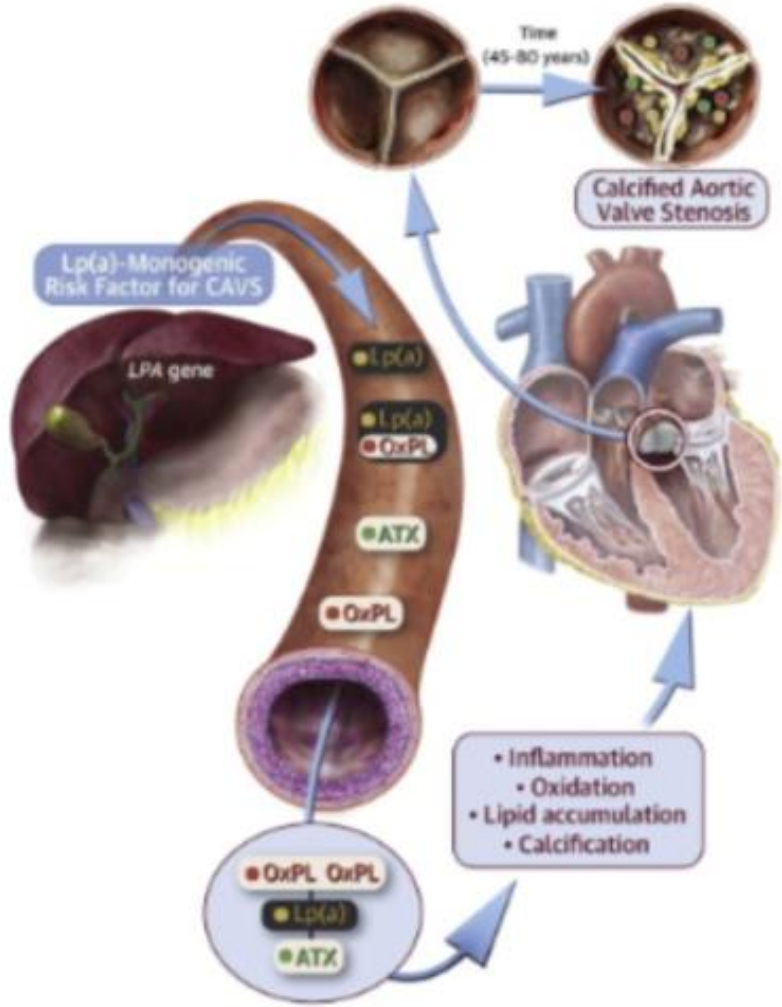
- Besides his lipids, blood pressure and metabolic care, what other condition you should look for in this patient?


Lipoprotein(a)
Effect
Lp(a) Component
Mechanism
Site
Clinical Event
Thrombosis
Atherosclerosis
Apolipoprotein (a)
LDL-like particle
Indirectly through fibrinolysis inhibition.
Intimal cholesterol deposition, inflammation & OxPL.
At plaque rupture
At turbulent blood flow
Myocardial Infarction
Ischemic Stroke
Atherosclerotic Stenosis
Aortic Valve Stenosis

Aortic Stenosis and it's severity is directly associated with Lp(a) levels



REMEMBER: Use Your Stethoscope



Torzewski, M. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(3):229-41.