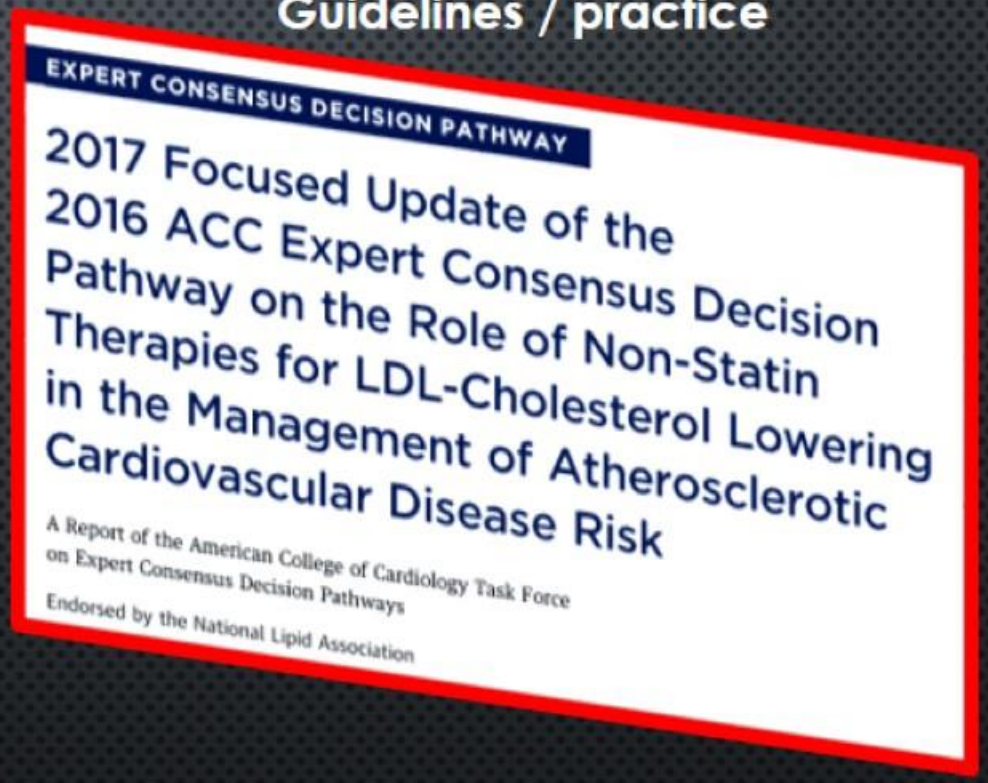
GOAL-DIRECTED THERAPY IN LIPID MANAGEMENT

Research evidence

Quality trials

≠

Guidelines / practice



Robert Chilton
Professor of Medicine
University of Texas Health Science Center
Director of Cardiac Catheterization labs
Director of clinical proteomics

JACC 2017;70:1785 guidelines

Which target?

Lifestyle wins: but no interest
Long term

Plaque stabilization

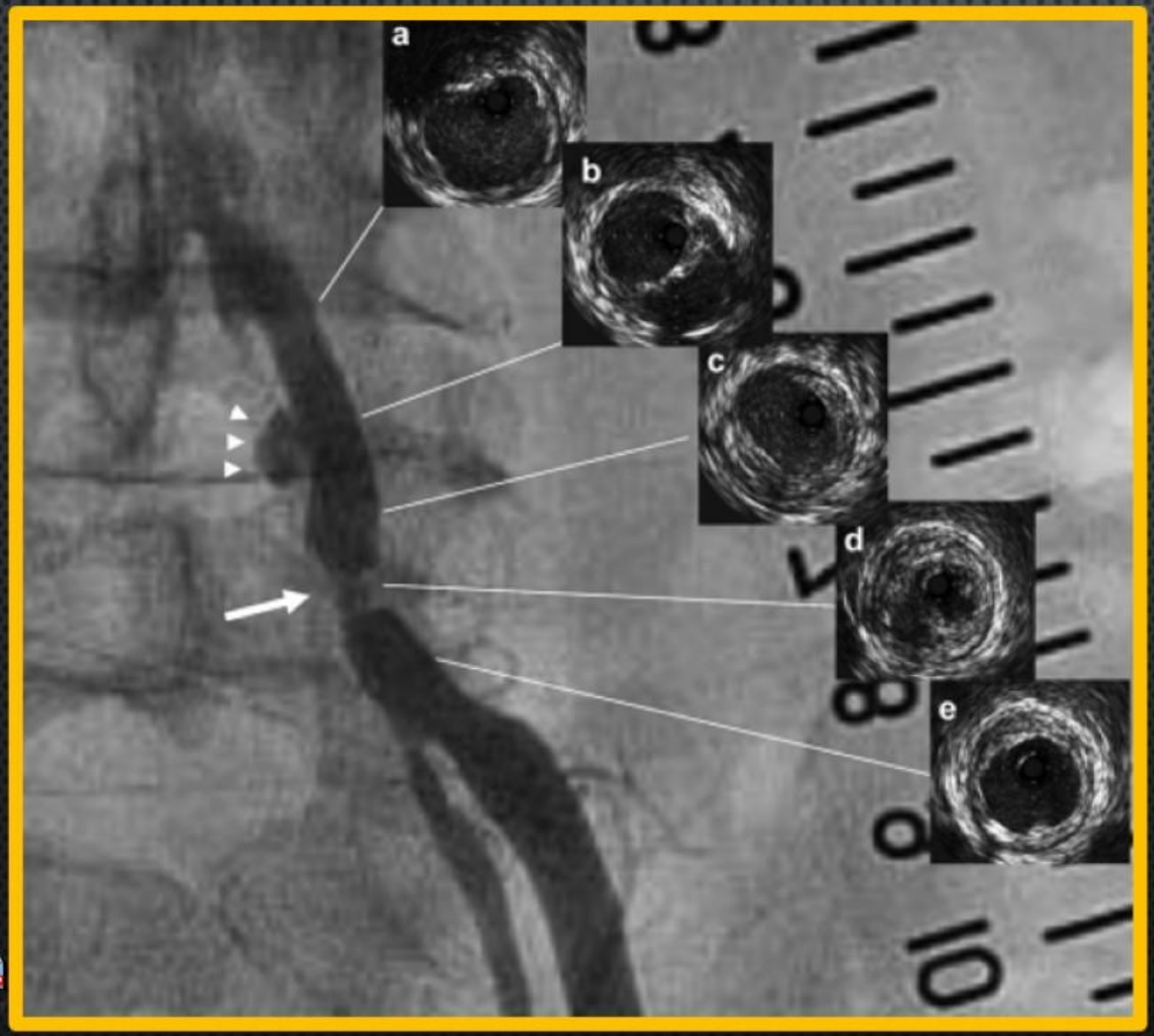
Acute coronary syndrome

Unstable plaque in body

Plaque regression

Regression of atherosclerosis

Multiple plaque ruptures from a patient with left common iliac artery stenosis



N=101

42% of patients with PAD have ruptures

ACS more common in PAD rupture p<0.01)

Male sex more common p<0.01

Circ Cardiovasc Interv. 2010;3:63-70

Statins Have a Dose-Dependent Effect on Amputation and Survival in Peripheral Artery Disease Patients….lower is better for target

155,647 VA patients with incident PAD

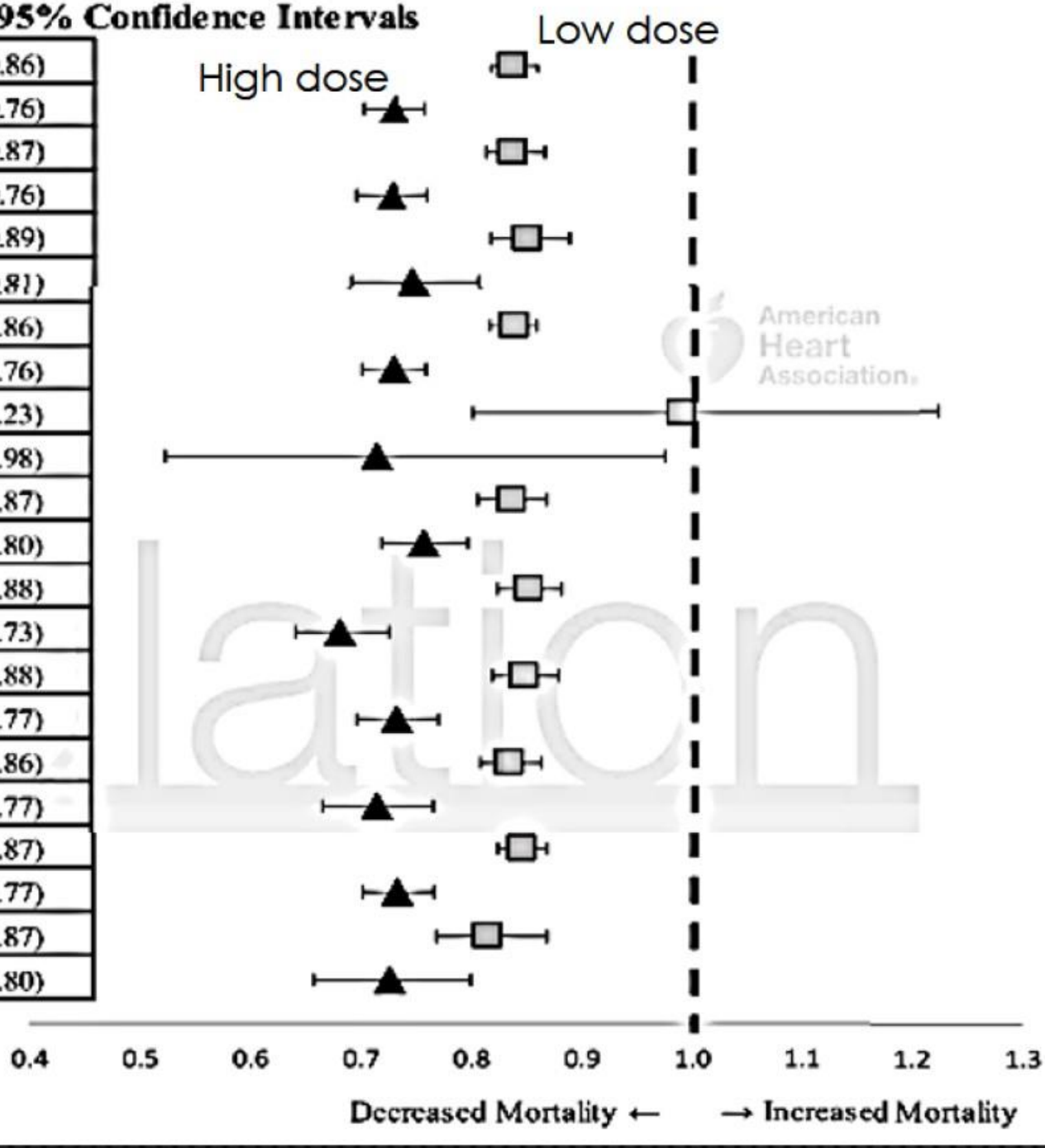
	Mortality HR (95% CI)	Amputation HR (95% CI)
3-level Propensity Score Matched Analysis (N= 30,780)		
Propensity Score Matched Model, Crude		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.83 (0.79 , 0.88)	0.84 (0.75 , 0.93)
High intensity statin	0.72 (0.68 , 0.76)	0.69 (0.61 , 0.76)
Propensity Score Matched Model, Adjusted		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.80 (0.75 , 0.85)	0.80 (0.70 , 0.91)
High intensity statin	0.70 (0.66 , 0.75)	0.60 (0.52 , 0.69)
2-level propensity matched analysis (N=30,418)		
Propensity Score Matched Model, Crude		
Low-Moderate intensity statin	Ref.	Ref.
High intensity statin	0.86 (0.82 , 0.91)	0.82 (0.74 , 0.90)
Propensity Score Matched Model, Adjusted		
Low-Moderate intensity statin	Ref.	Ref.
High intensity statin	0.85 (0.80 , 0.90)	0.78 (0.68 , 0.89)

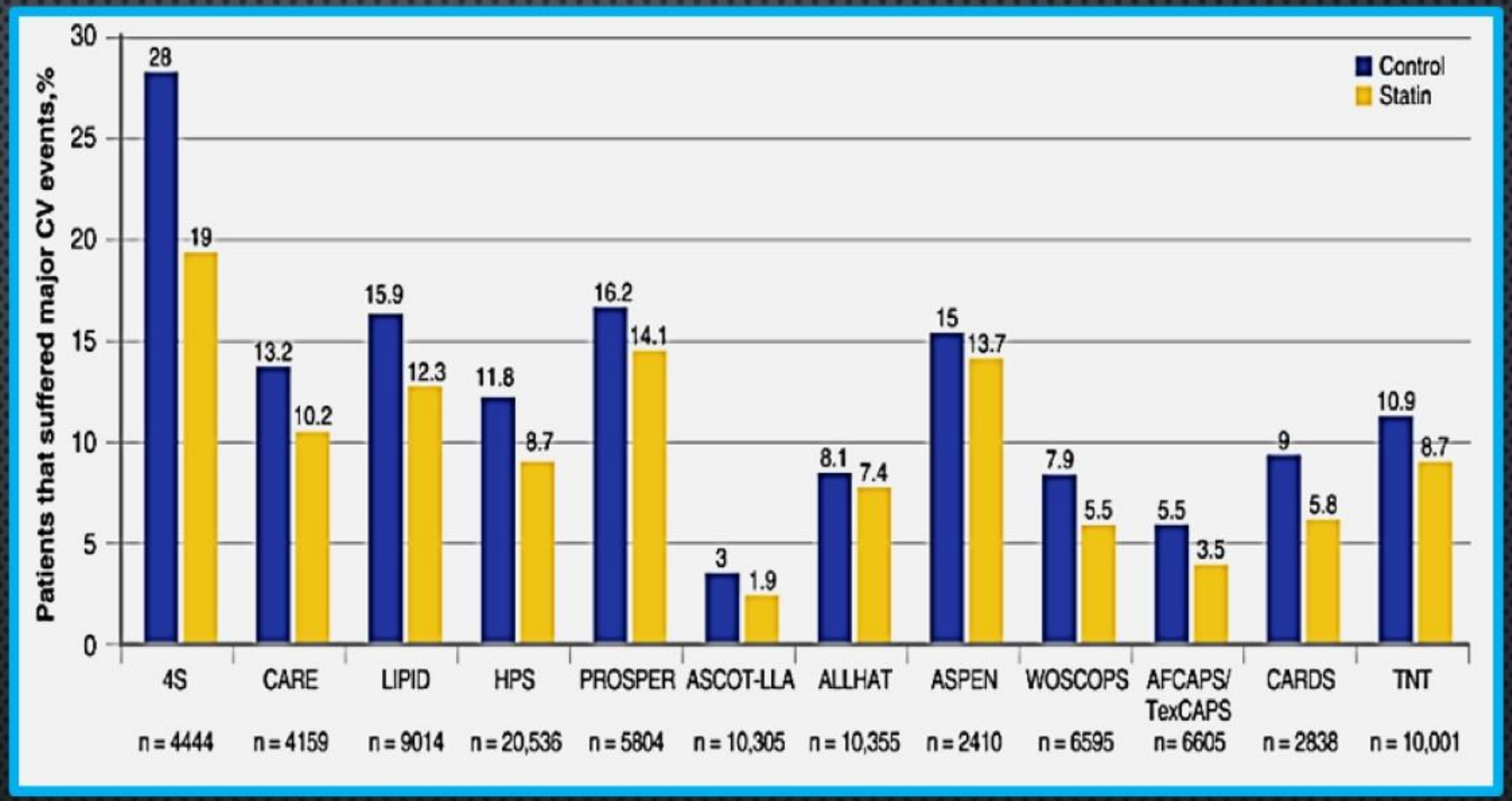
High intensity statins decrease risk of amputation and death in PAD patients

10.1161/CIRCULATIONAHA.117.032361

Mortality HR and 95% Confidence Intervals

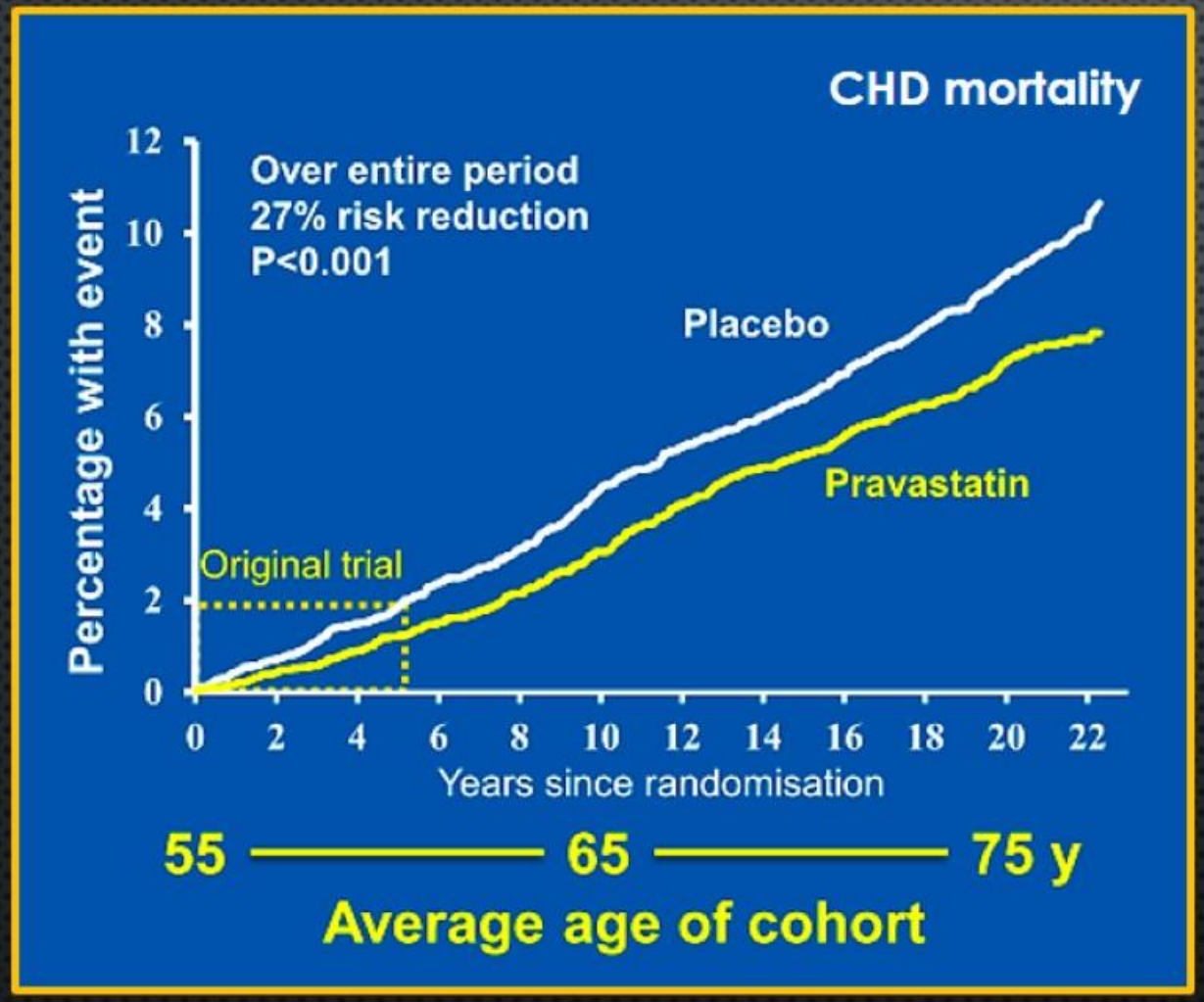
All (N=90,257)	Low-Medium vs. None	0.84 (0.82, 0.86)
	High vs. None	0.73 (0.70, 0.76)
<75 years (N=71,327)	Low-Medium vs. None	0.84 (0.82, 0.87)
	High vs. None	0.73 (0.70, 0.76)
>= 75 years (N=18,930)	Low-Medium vs. None	0.85 (0.82, 0.89)
	High vs. None	*0.75 (0.69, 0.81)*
Male (N=88,458)	Low-Medium vs. None	0.84 (0.82, 0.86)
	High vs. None	0.73 (0.70, 0.76)
Female (N=1,799)	Low-Medium vs. None	0.99 (0.80, 1.23)
	High vs. None	0.72 (0.53, 0.98)
DM (N=41,652)	Low-Medium vs. None	0.84 (0.81, 0.87)
	High vs. None	0.76 (0.72, 0.80)
No DM (N=48,605)	Low-Medium vs. None	0.85 (0.82, 0.88)
	High vs. None	0.68 (0.64, 0.73)
CAD (N=42,743)	Low-Medium vs. None	0.85 (0.82, 0.88)
	High vs. None	0.73 (0.70, 0.77)
No CAD (N=47,514)	Low-Medium vs. None	0.84 (0.81, 0.86)
	High vs. None	0.72 (0.67, 0.77)
Whites (N=74,883)	Low-Medium vs. None	0.85 (0.82, 0.87)
	High vs. None	0.73 (0.70, 0.77)
Blacks (N=14,279)	Low-Medium vs. None	0.82 (0.77, 0.87)
	High vs. None	0.73 (0.66, 0.80)

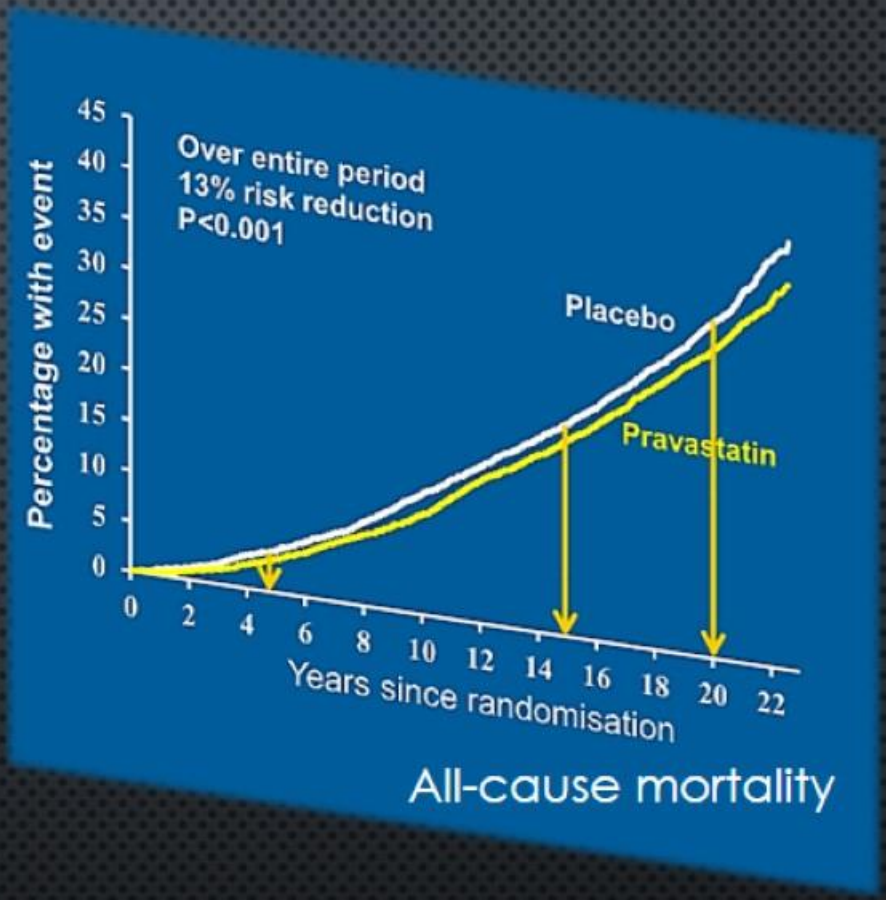




Cardiovascular events : MACE

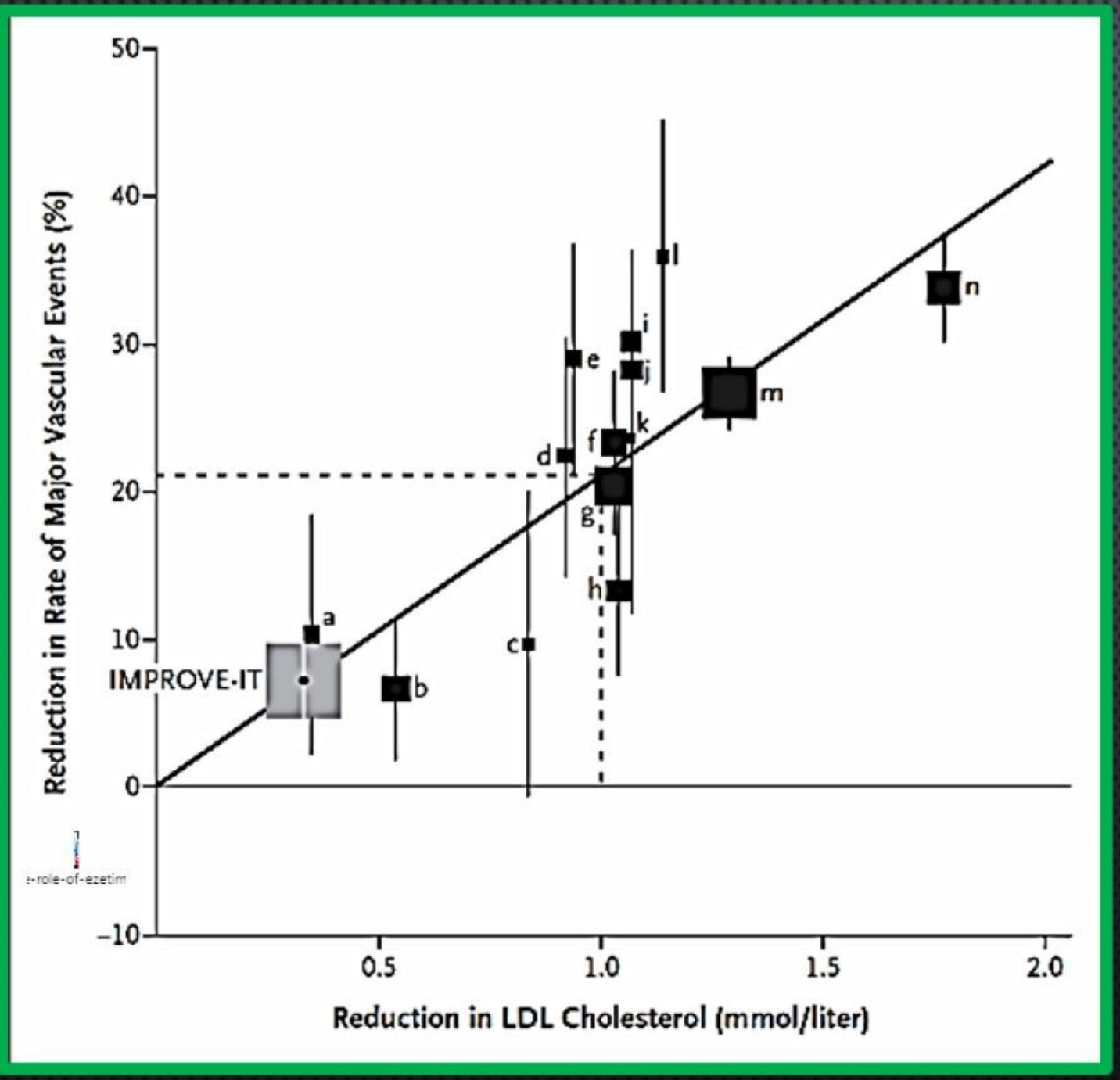
Long term benefits of keeping LDL low





Circulation. (2016); 133:1073-80

WOSCOPS 20-year follow up

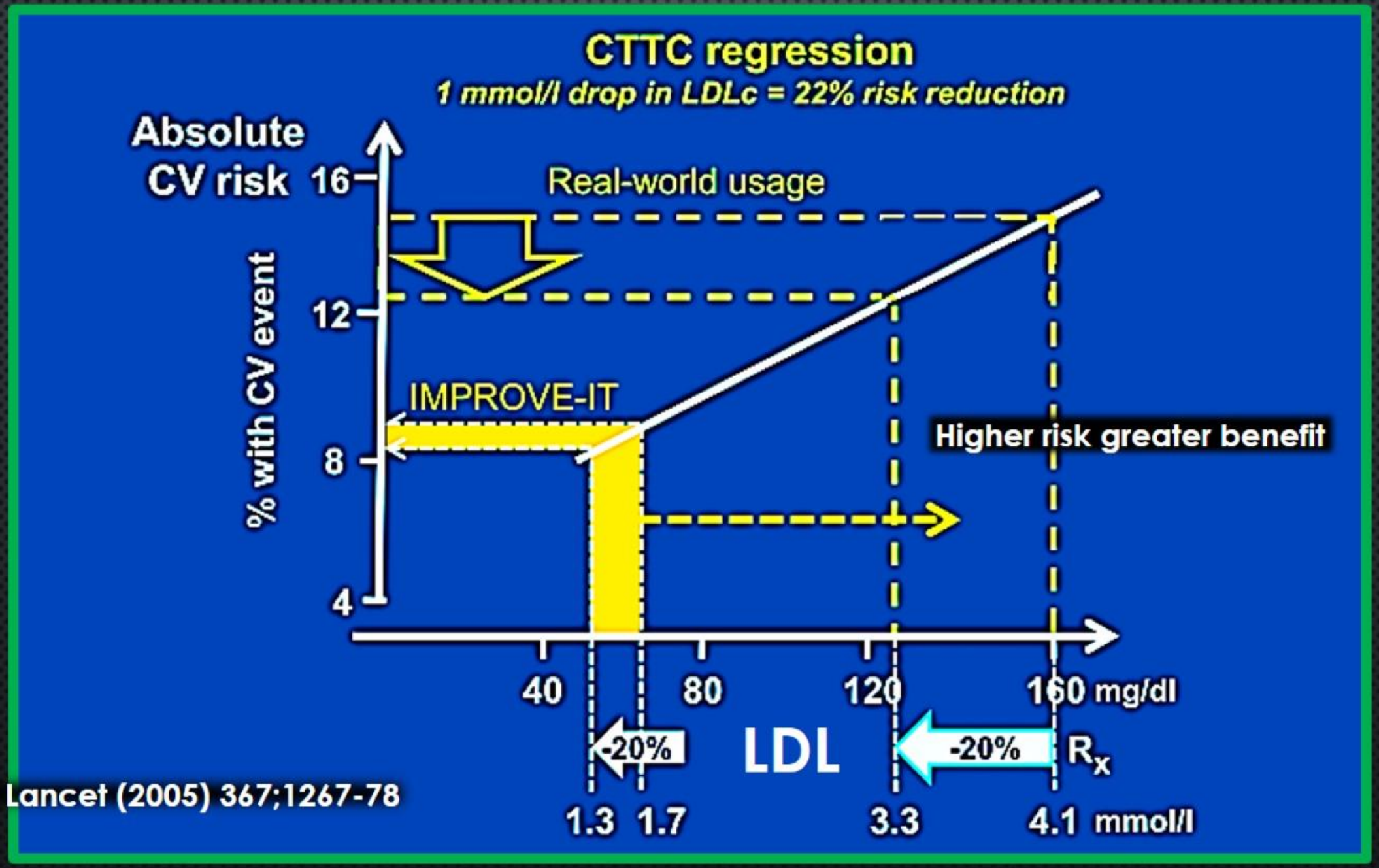


Lower LDL less major vascular events

"target lower is better"

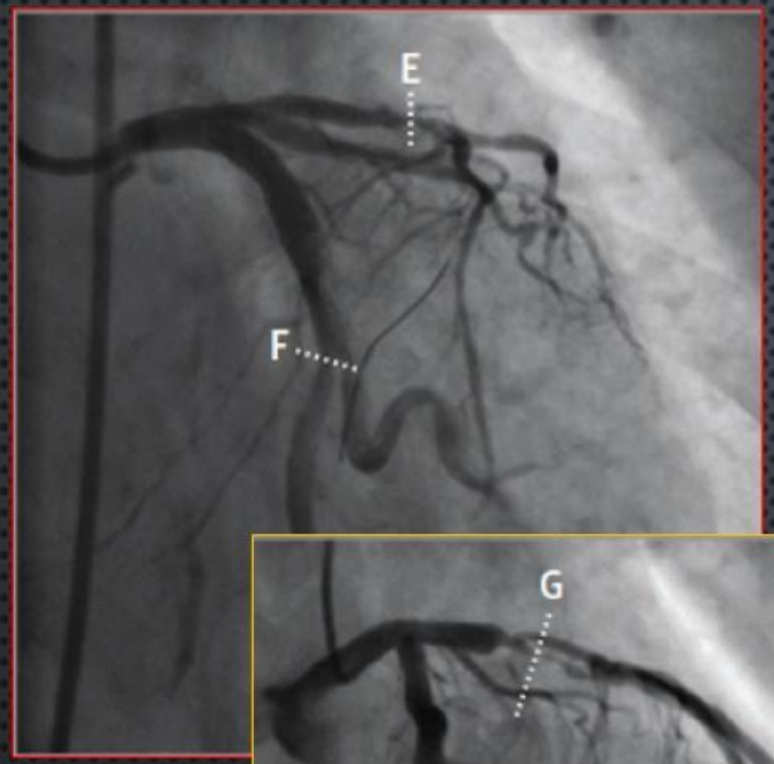
Cannon et al. N Engl J Med. (2015) 372:2387-97

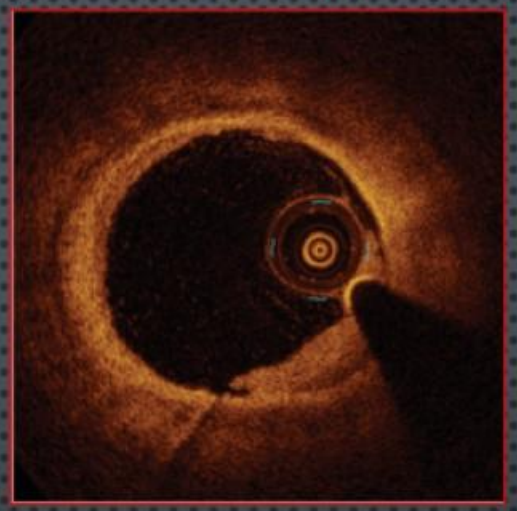
CTTC Lancet (2005) 367;1267-78



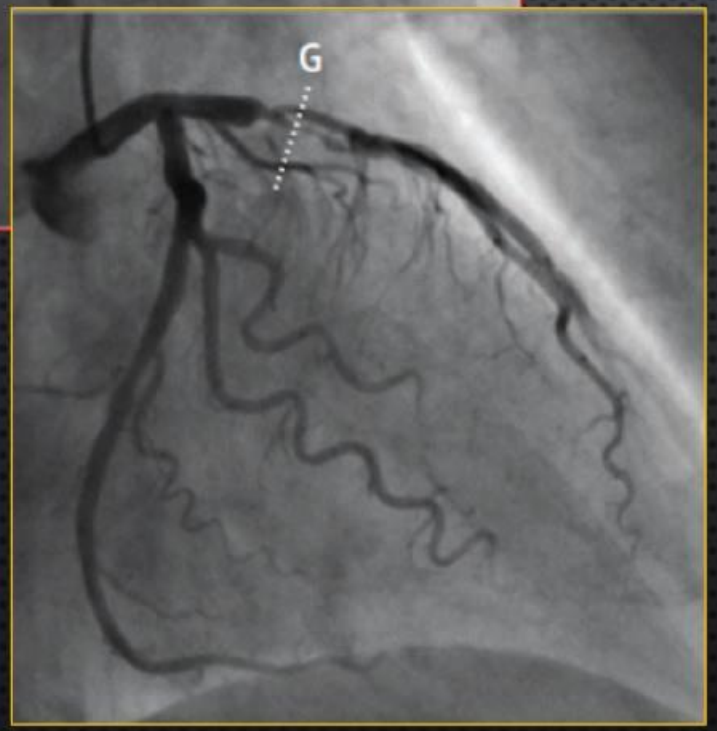
CTTC Lancet (2005) 367;1267-78

E-Erosion

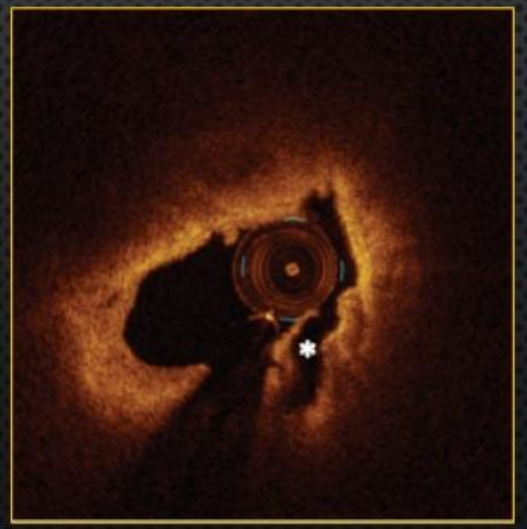




White thrombus overlying an intact plaque



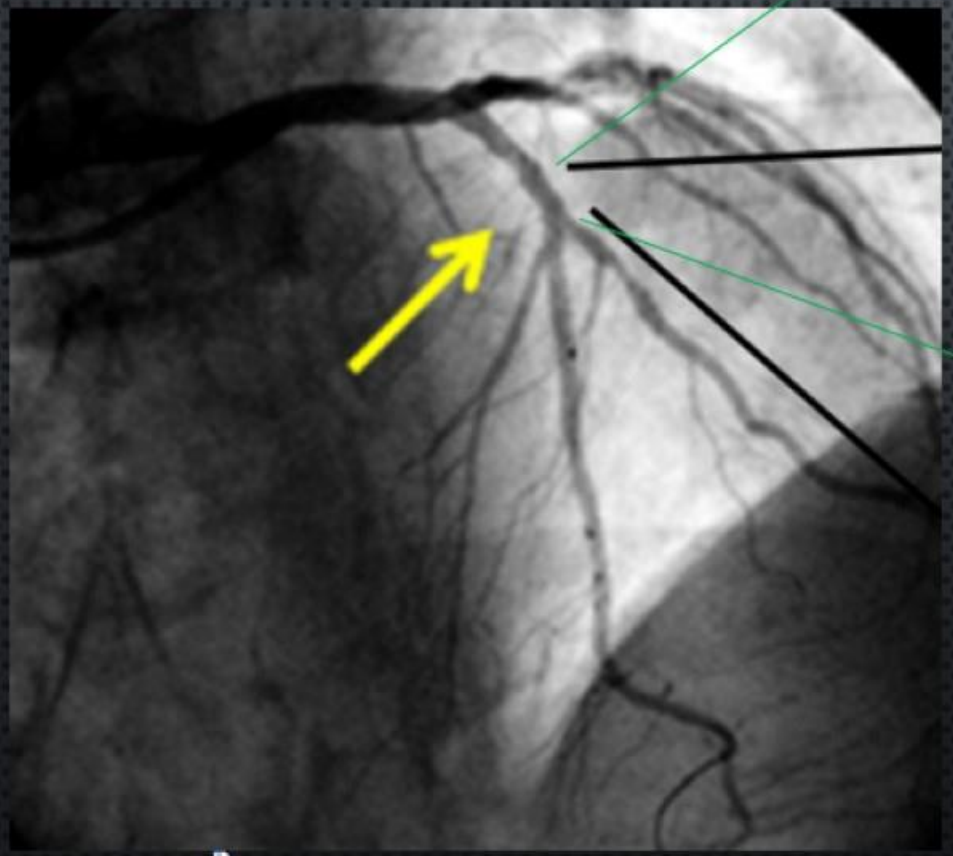
G-Culprit plaque **rupture**

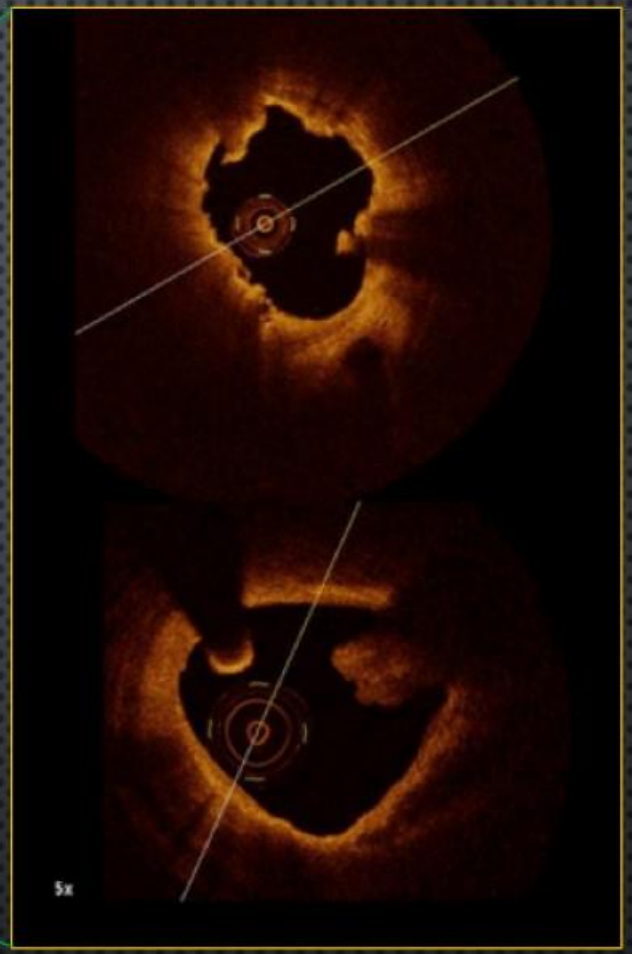


Culprit plaque shows fibrous cap discontinuity with cavity formation

JAMA Cardiol. 2018;3(3):207-214

Simvastatin treatment in rats accelerates re-endothelialization of the mechanically injured artery, in part as a result of increased mobilization of bone marrow–derived endothelial progenitor cells





Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 93, 1354–1363 (1996).

TRANSLATIONAL BIOLOGY

	Plaque rupture	Macrophages	Microvessels	Spotty calcium
Erosion	0	29%	21%	5%
Rupture	8%	53%	42%	22%
P value	0.001	0.01	0.003	0.006

Rupture: More macrophages and microvessels—inflammation/instability

Plaque rupture have **elevated levels of systemic matrix metalloproteinase–9**

from **macrophages and foam cells**, indicating active **proinflammatory** response and **degradation of extracellular matrix** leading to plaque instability

JAMA Cardiol. 2018;3(3):207-214

TRANSLATIONAL BIOLOGY: EROSION

Detachment of endothelial cells and **exposure of collagen** initiate platelet activation and aggregation as well as recruitment of polymorphonuclear leucocytes.

Recruited neutrophils mediate the formation of **neutrophil extracellular traps** and amplification of thrombosis and local inflammation.

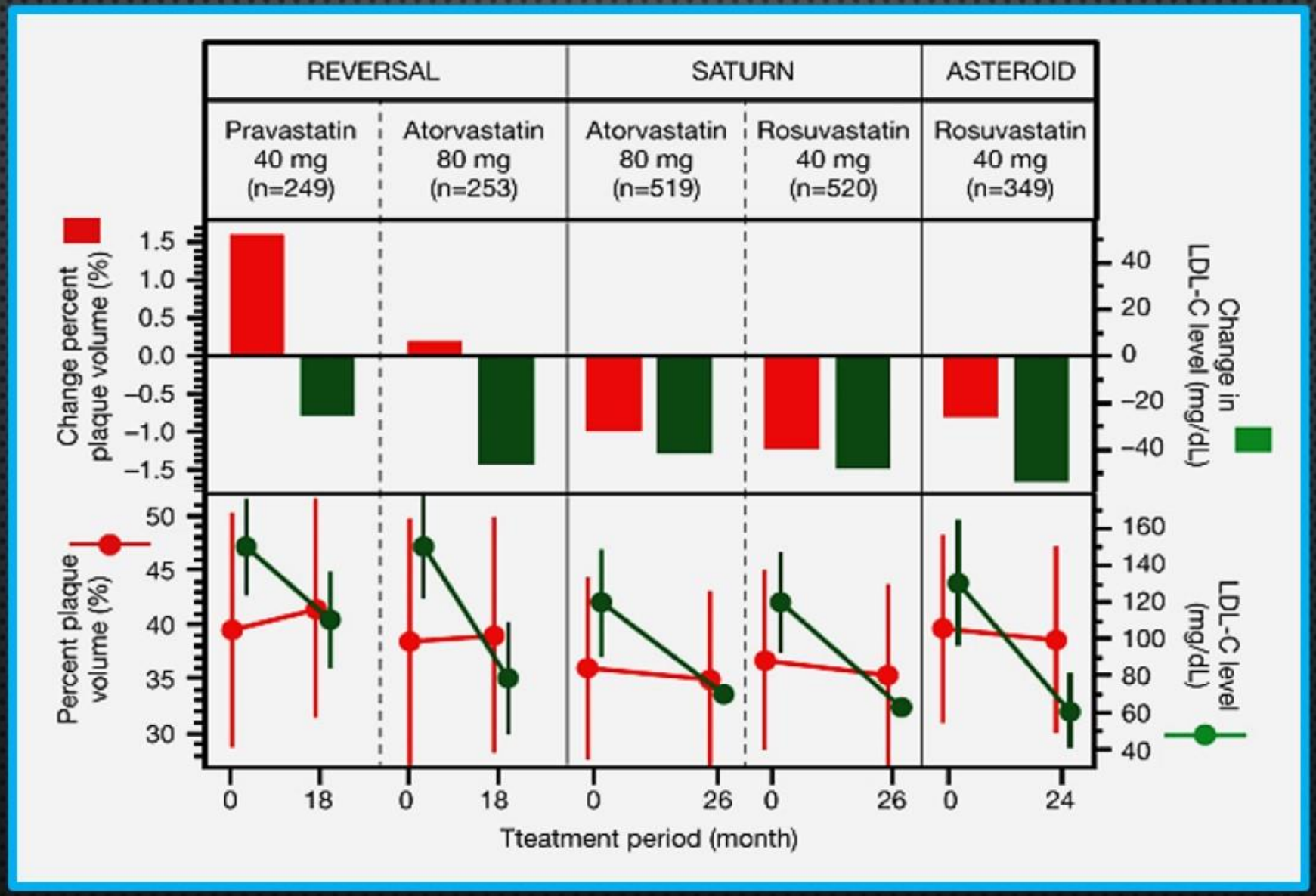
Neutrophils accumulate abundantly in eroded culprit plaques and elevated levels of markers of neutrophil extracellular trap formation are associated with this plaque morphology.

OCT study demonstrated the association between the presence of **plaque erosion** and **elevated levels of serum myeloperoxidase, a marker of neutrophil activation.**

These data imply that **local endothelial damage rather than widespread** coronary arterial inflammation initiates ACS owing to plaque erosion

JAMA Cardiol. 2018;3(3):207-214

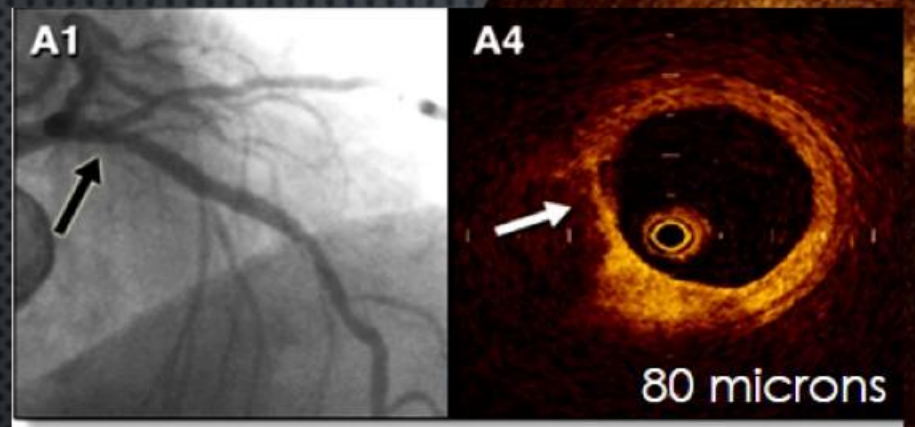
Lower the LDL the less plaque volume: less events



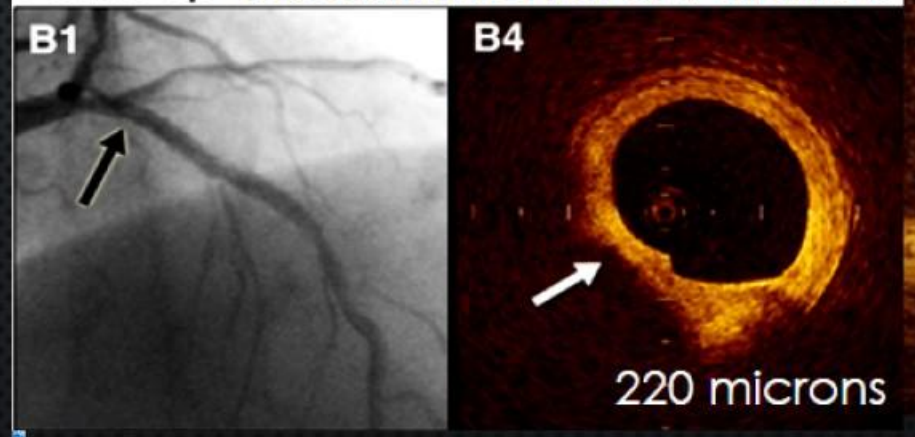
Cardiovasc Diagn Ther 2016;6(4):304-321

Do statins really change the cap thickness in real patients?

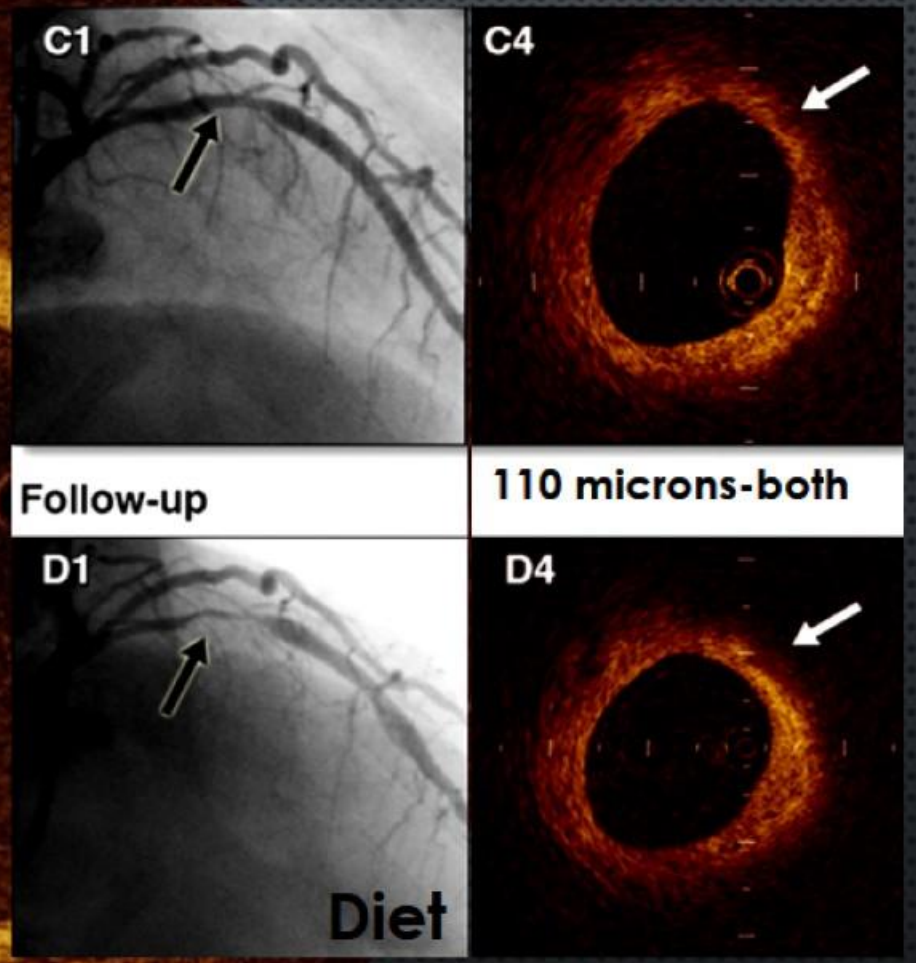
1. Yes
2. NO



Follow-up- **median interval of 9 months**



LDL 134 to 89 mg/dl on FU-statin



LDL 122 to 121 mg/dl on diet

JACC imag 2012;5:169-77

Newer trials

FOURIER

FURTHER CARDIOVASCULAR OUTCOMES RESEARCH WITH PCSK9 INHIBITION IN SUBJECTS WITH ELEVATED RISK

MS SABATINE, RP GIUGLIANO, AC KEECH, N HONARPOUR,
SM WASSERMAN, PS SEVER, AND TR PEDERSEN,
FOR THE FOURIER STEERING COMMITTEE & INVESTIGATORS

AMERICAN COLLEGE OF CARDIOLOGY – 66TH ANNUAL SCIENTIFIC SESSION

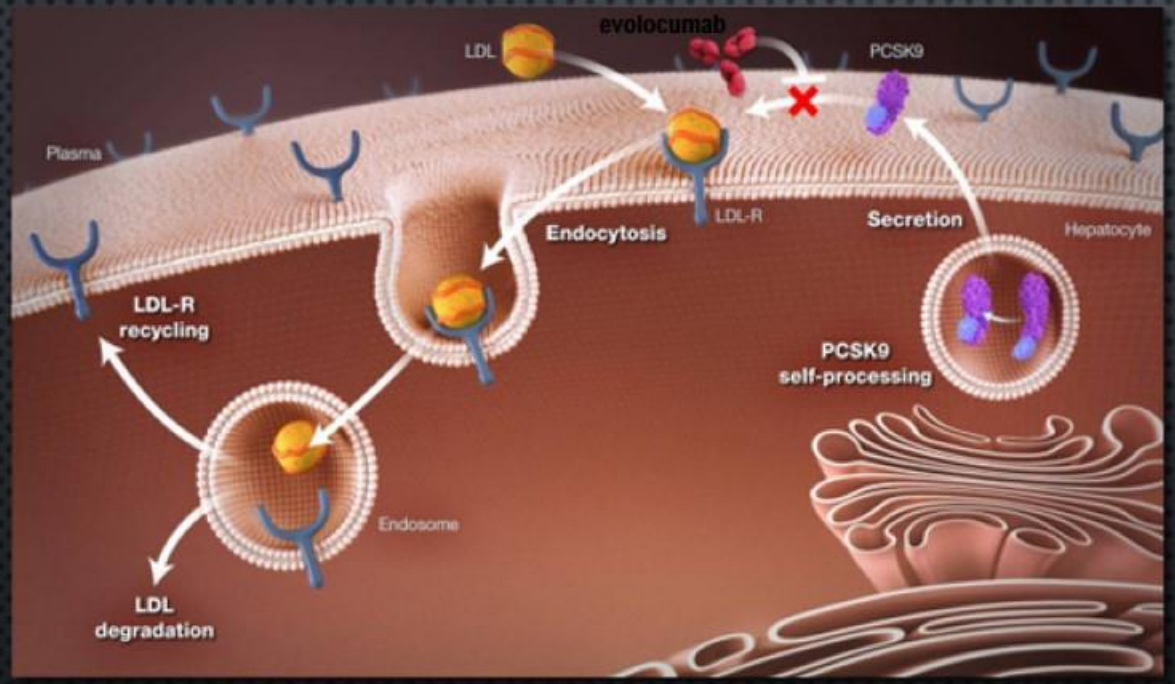
LATE-BREAKING CLINICAL TRIAL

MARCH 17, 2017

BACKGROUND

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI

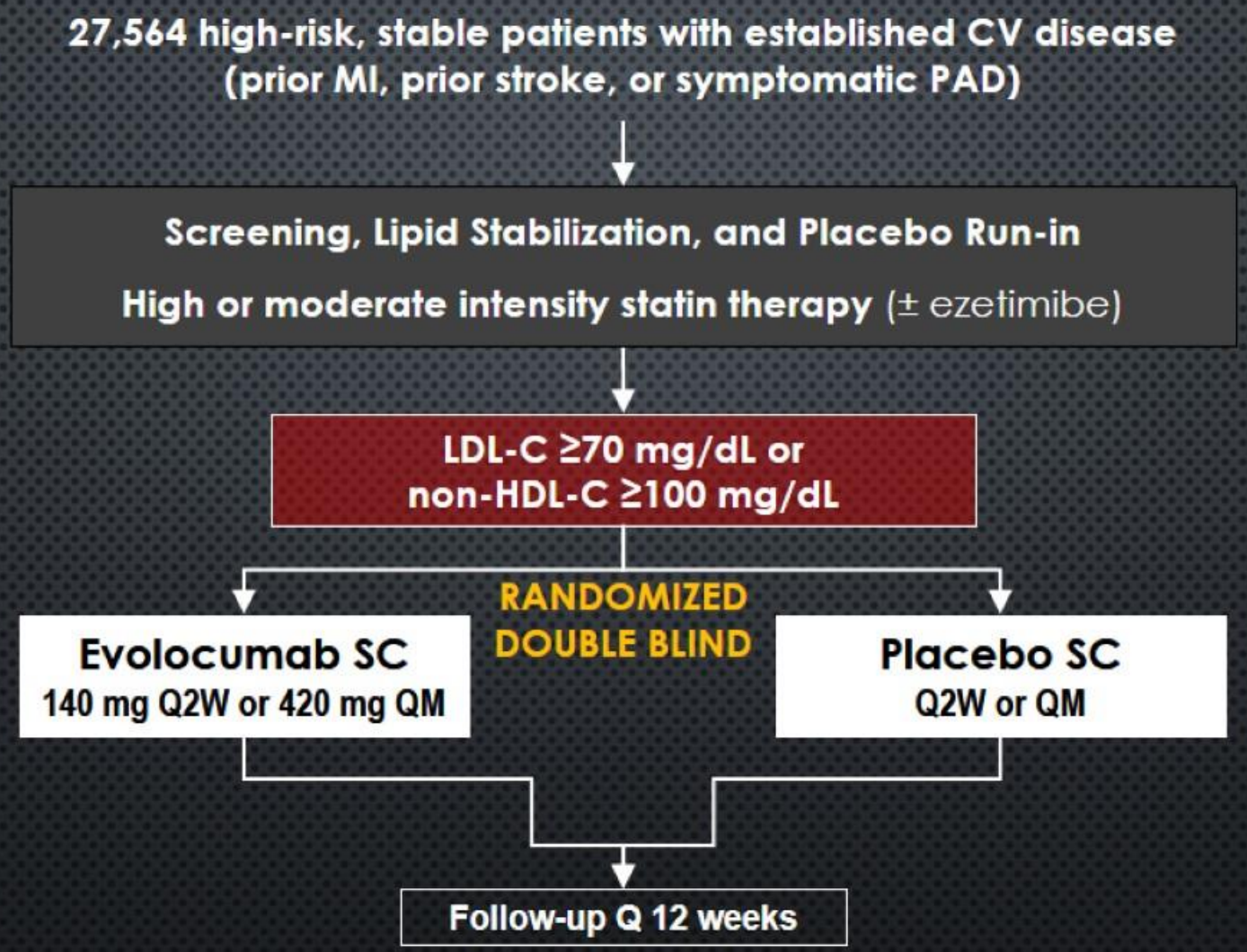


Evolocumab

- **Fully human anti-PCSK9 mAb**
- ~60% ↓ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested ↓ CV events

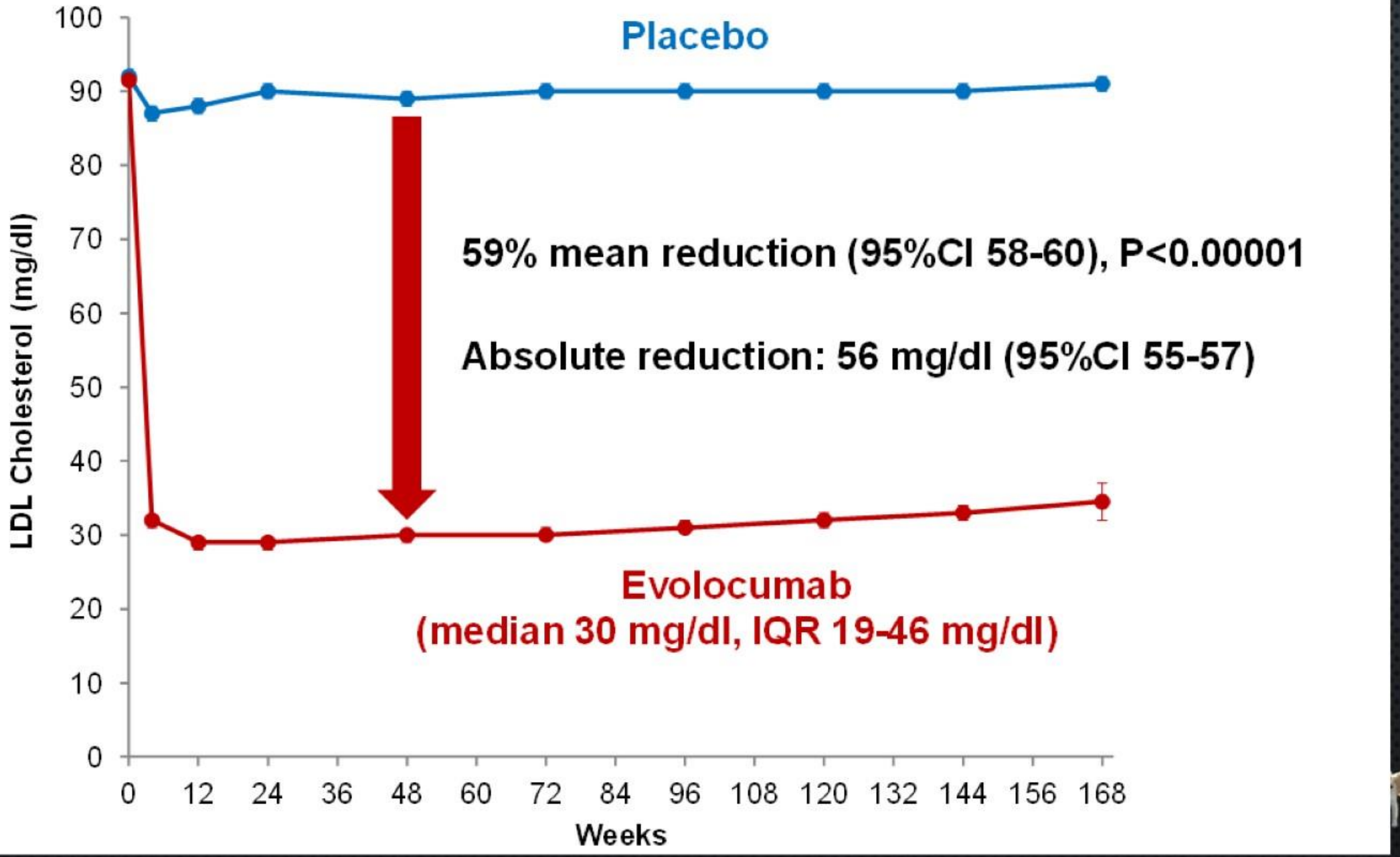
Sever P & Mackay J. *Br J Cardiol* 2014;21:91-3
Giugliano RP, et al. *Lancet* 2012;380:2007-17
Sabatine MS, et al. *NEJM* 2015;372:1500-9

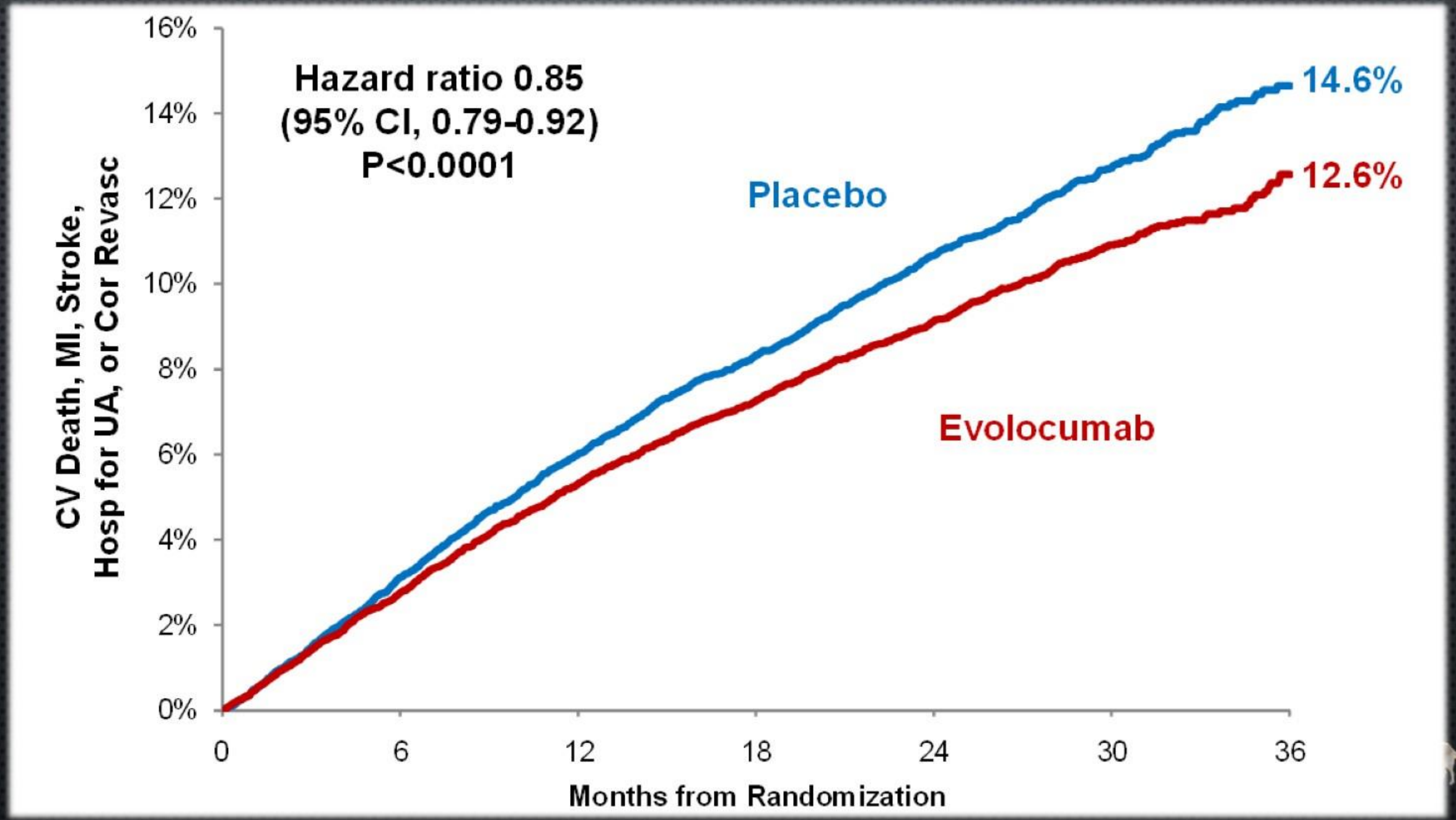
TRIAL DESIGN

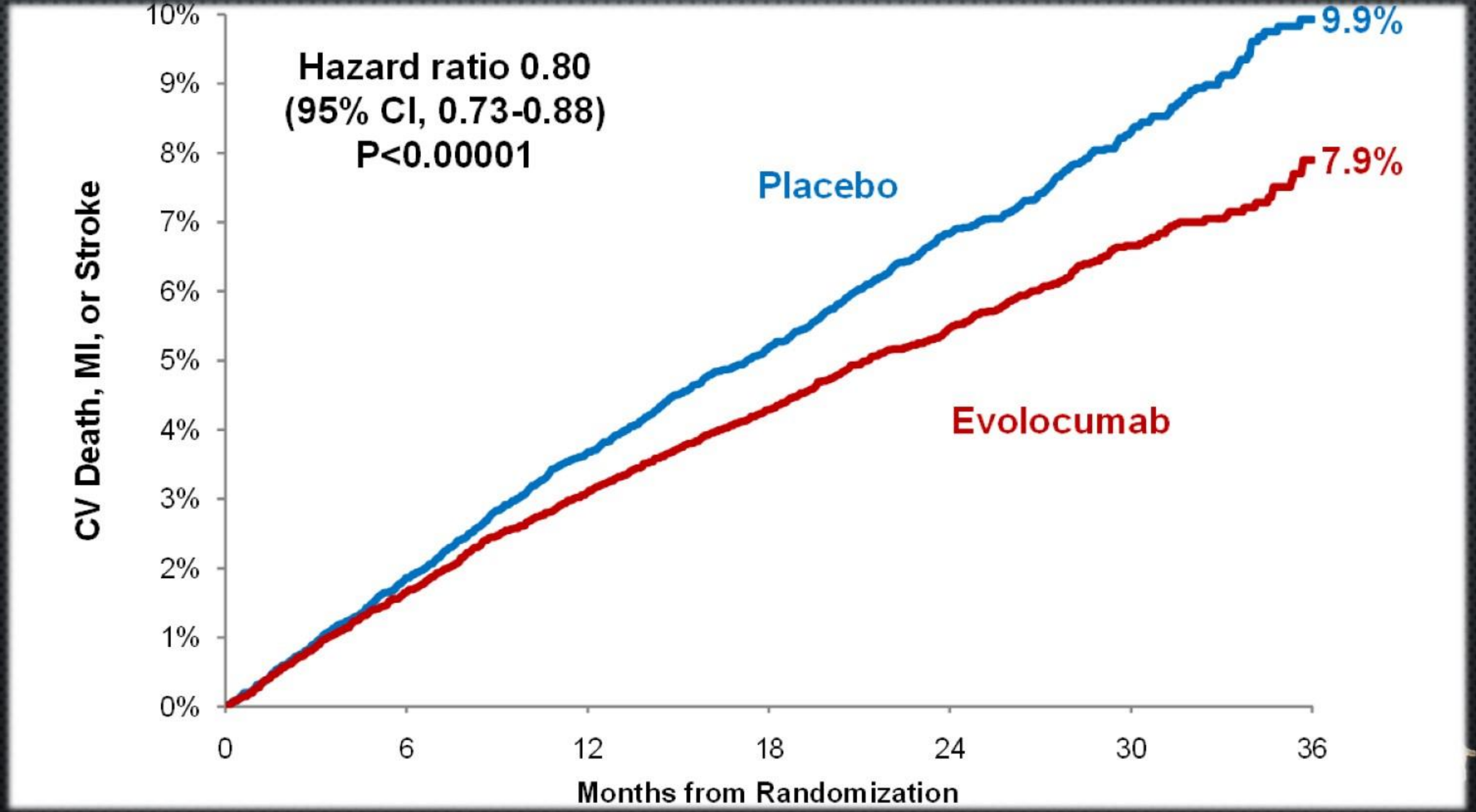


fourier

Sabatine MS et al. *Am Heart J* 2016;173:94-101


Placebo
59% mean reduction (95%CI 58-60), P<0.00001
Absolute reduction: 56 mg/dl (95%CI 55-57)
Evolocumab
(median 30 mg/dl, IQR 19-46 mg/dl)
LDL Cholesterol (mg/dl)
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Weeks


Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001
Placebo
Evolocumab
14.6%
12.6%
CV Death, MI, Stroke,
Hosp for UA, or Cor Revasc
16%
14%
12%
10%
8%
6%
4%
2%
0%
0
6
12
18
24
30
36
Months from Randomization

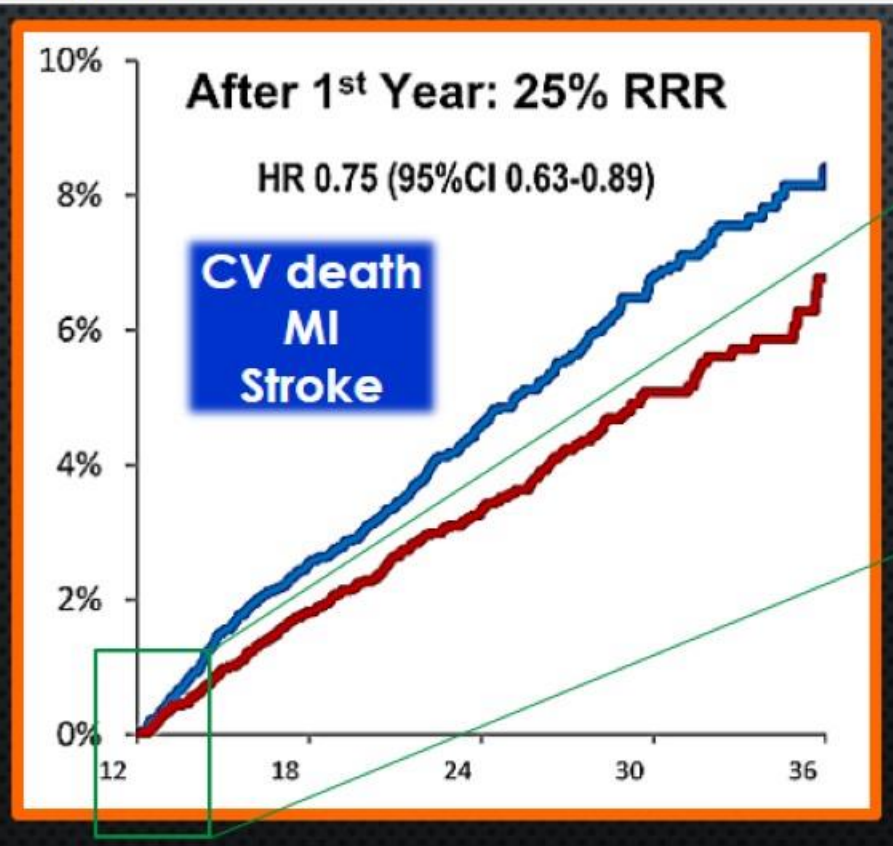

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P<0.00001
Placebo
Evolocumab
9.9%
7.9%
CV Death, MI, or Stroke
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
0
6
12
18
24
30
36
Months from Randomization

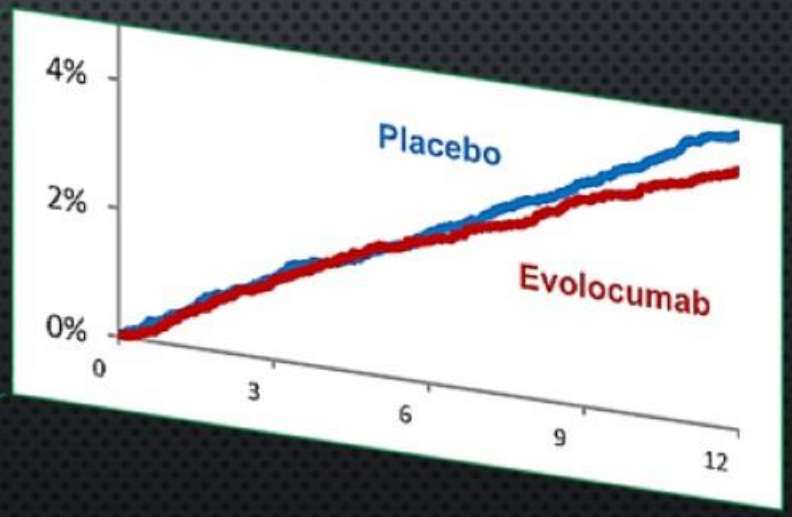
CV OUTCOMES

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
CV death, MI, or stroke	**7.9**	**9.9**	**0.80 (0.73-0.88)**
Cardiovascular death	**2.5**	**2.4**	**1.05 (0.88-1.25)**
Death due to acute MI	0.26	0.32	0.84 (0.49-1.42)
Death due to stroke	0.29	0.30	0.94 (0.58-1.54)
Other CV death	1.9	1.8	1.10 (0.90-1.35)
MI	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**2.2**	**2.6**	**0.79 (0.66-0.95)**

DIABETES: CV INDIVIDUAL OUTCOMES

Endpoint	Diabetes-EvoMab	DM-Placebo	HR (95%)
CV death	3.6%	3.5%	1.05(0.83-1.34)
MI	**5.5**	**7.5**	**0.77(0.65-0.92)**
Stroke **(diabetes only)**	2.9	3.2	0.79(0.62-1.01)
Coronary revasc	**7.4**	**10**	**0.77(0.66-0.88)**





EASD: September 15, 2017

GLAGOV

968 high risk patients with symptomatic CAD and 20-50% stenosis by invasive coronary angiography in a “target vessel”

Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features

Intravascular ultrasound at baseline

Statin Monotherapy (n=484)

18 months treatment

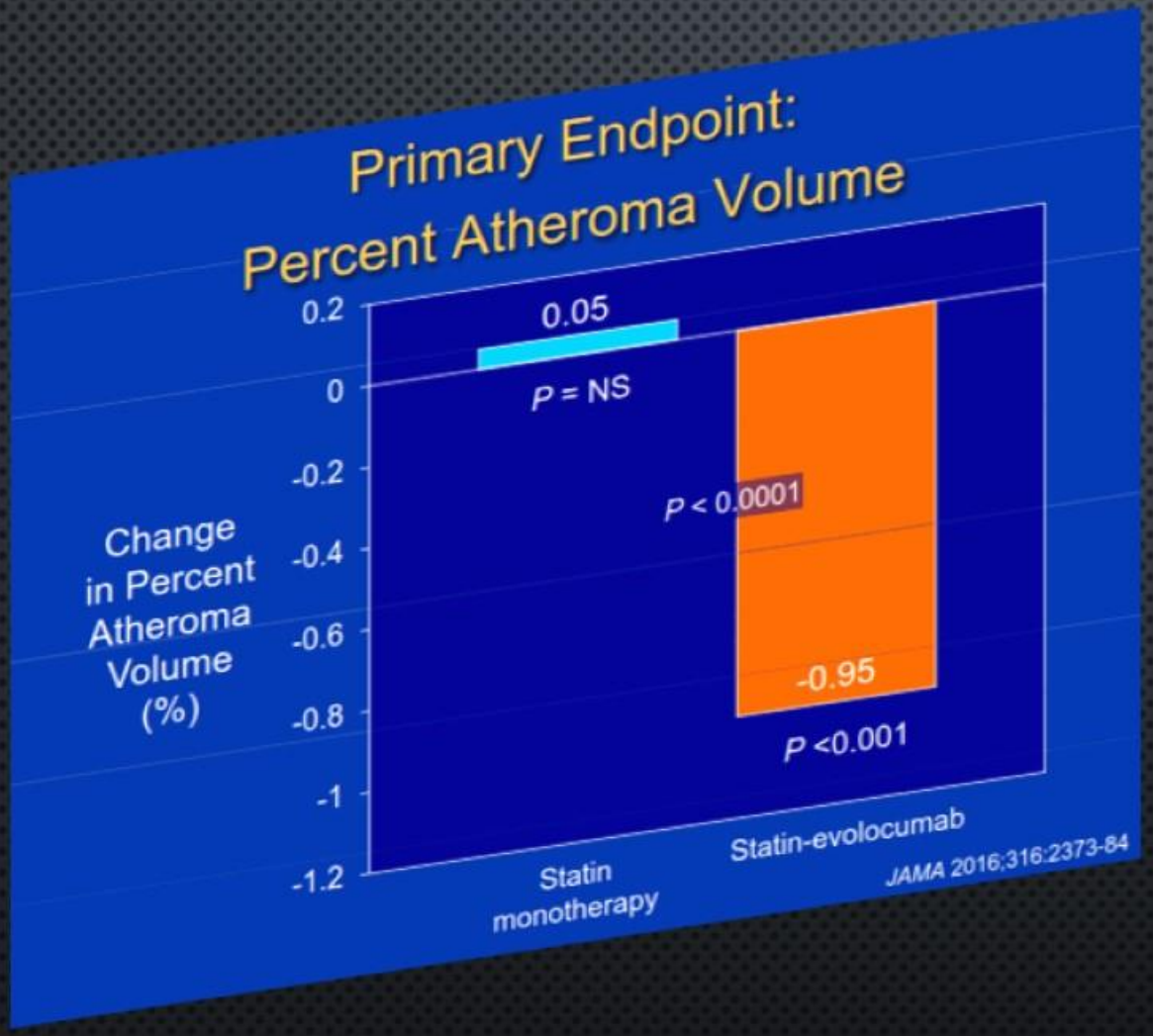
Statin plus evolocumab 420 mg QM (n=484)

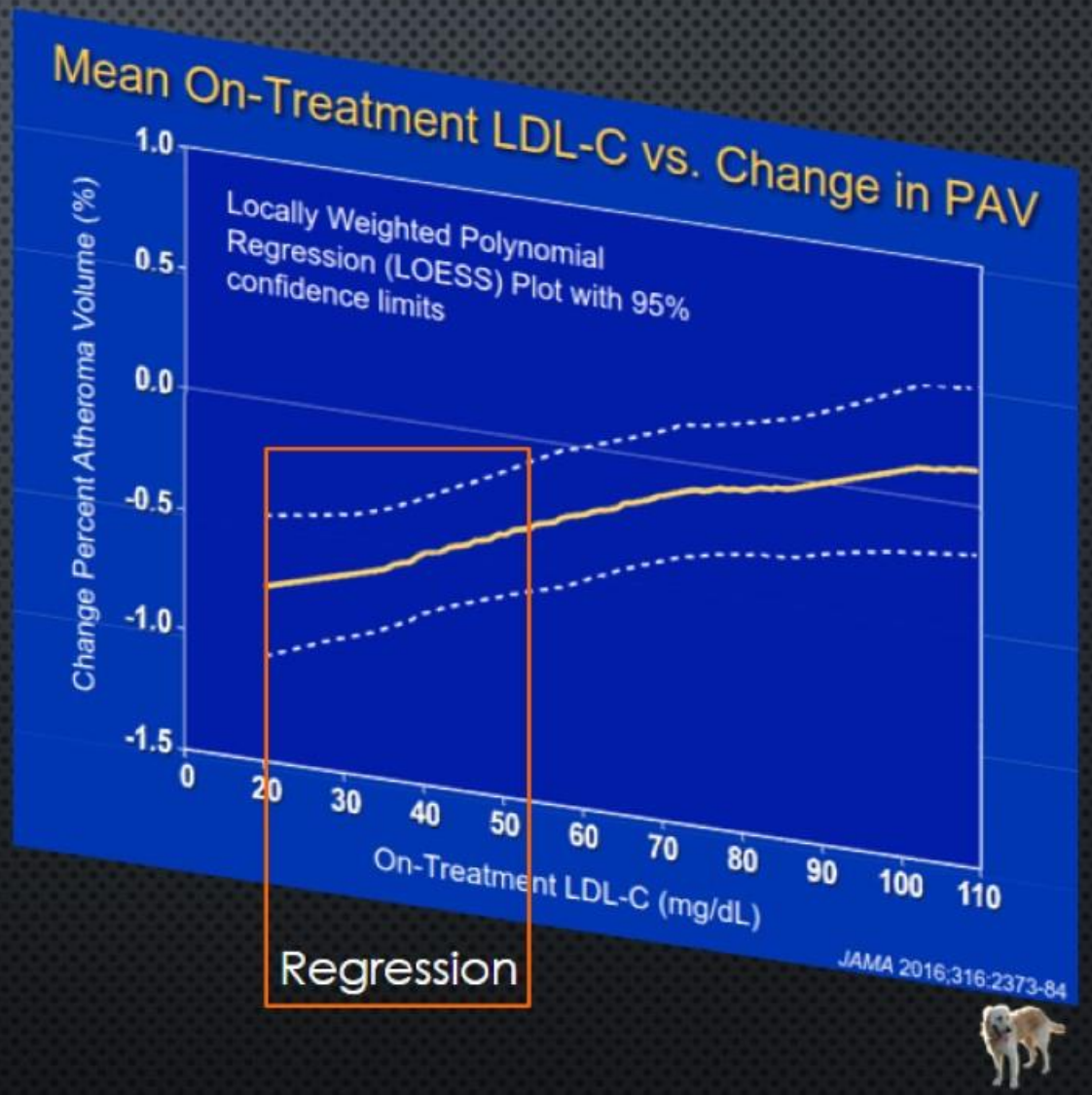
423 statin completers

423 evolocumab completers

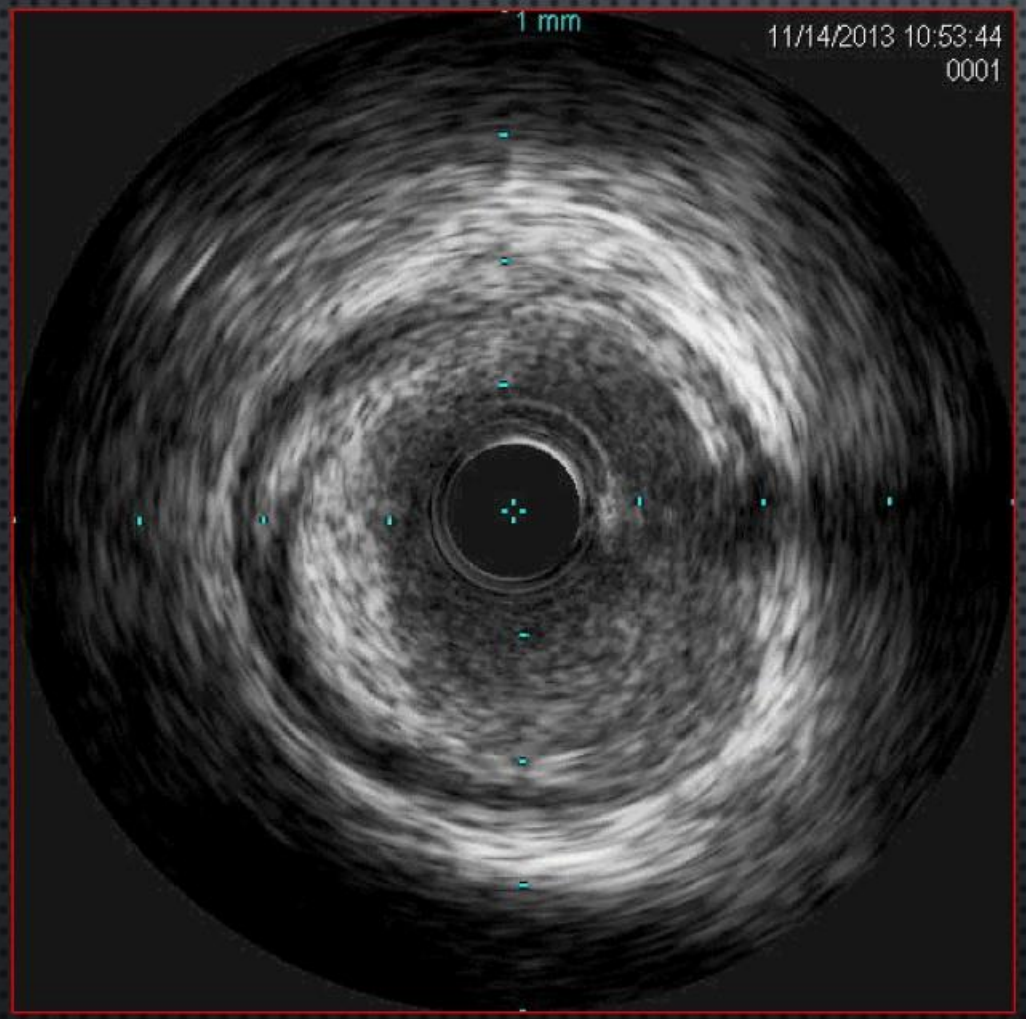
Follow-up IVUS of originally imaged “target” vessel (n=846)

ATHEROMA REGRESSION

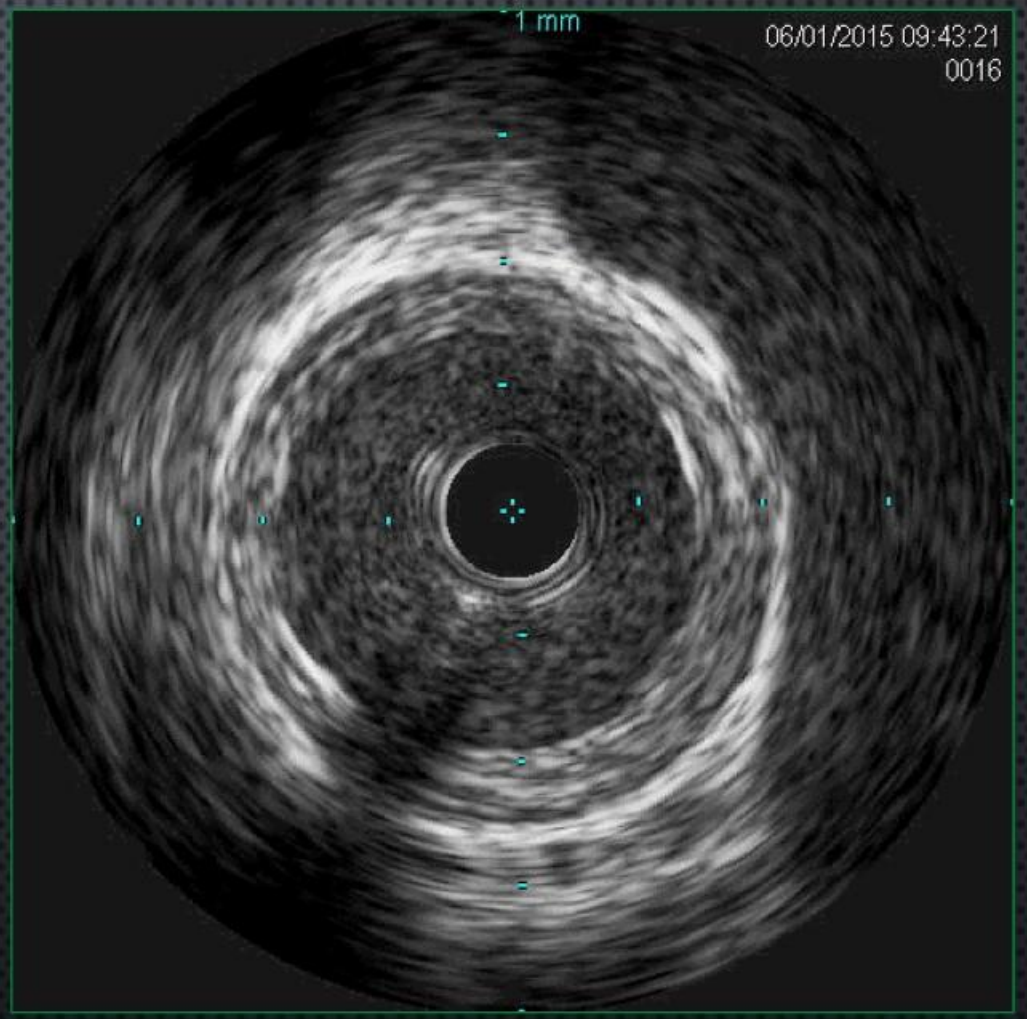




LDL-105



LDL-10



Glagov

AACE 2017 Guidelines

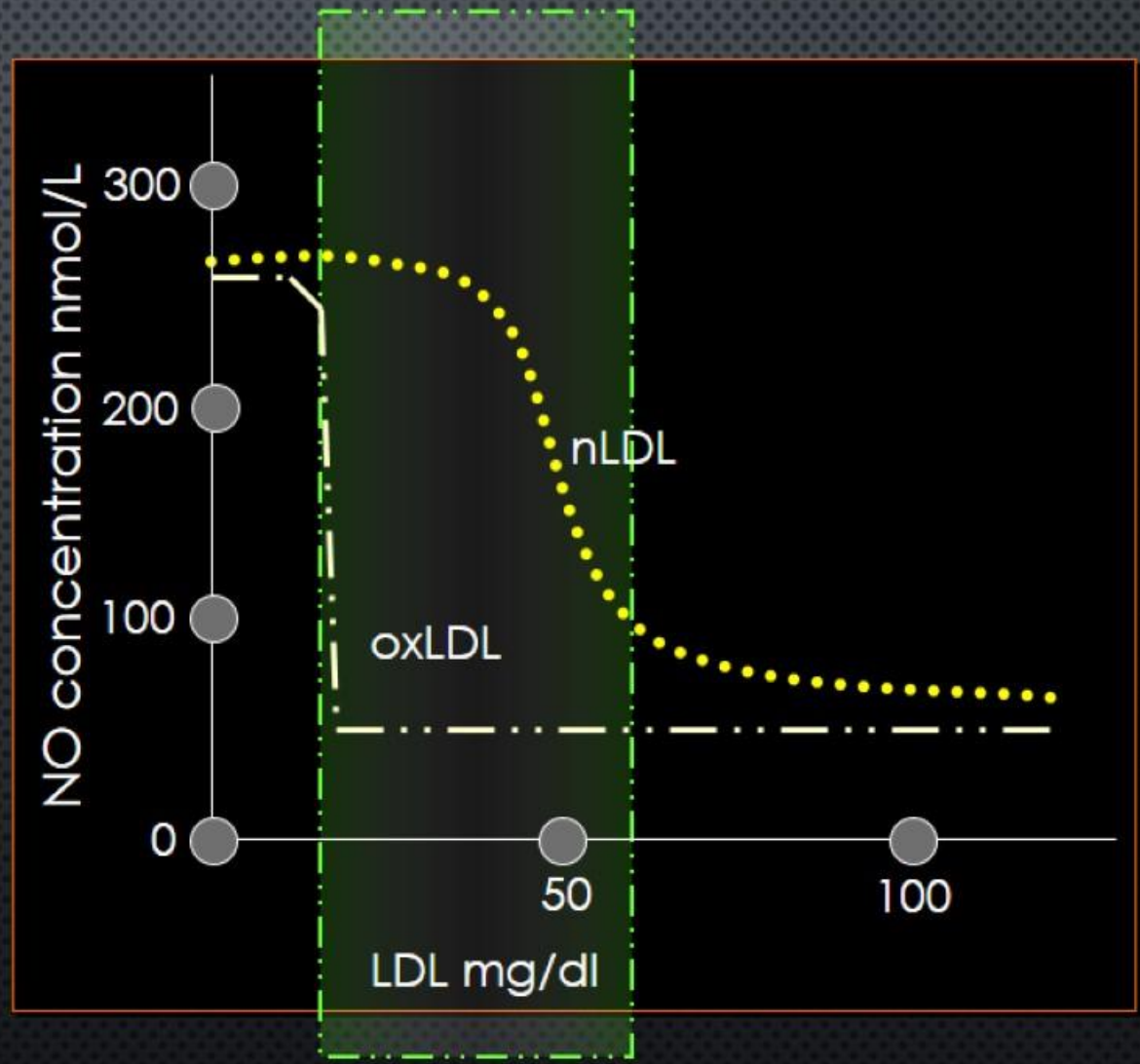
Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

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

Lipids / inflammation

EFFECT OF NATIVE AND OXIDIZED LOW-DENSITY LIPOPROTEIN ON ENDOTHELIAL NITRIC OXIDE

- DIRECT ASSESSMENT BY MICROSENSOR
- BOVINE EC
- EXPOSED 1 HR TO ↑ LDL



10,001 patients
Stable CAD
Baseline LDL<130 mg/dl

A-80

1º EP-↓ CV Death/CVA

Humans-TNT…77 LDL

Circulation March 21, 2000;101:1261-1266

Goal directed yes….lower is better…55 looks good LDL

Plaque regression

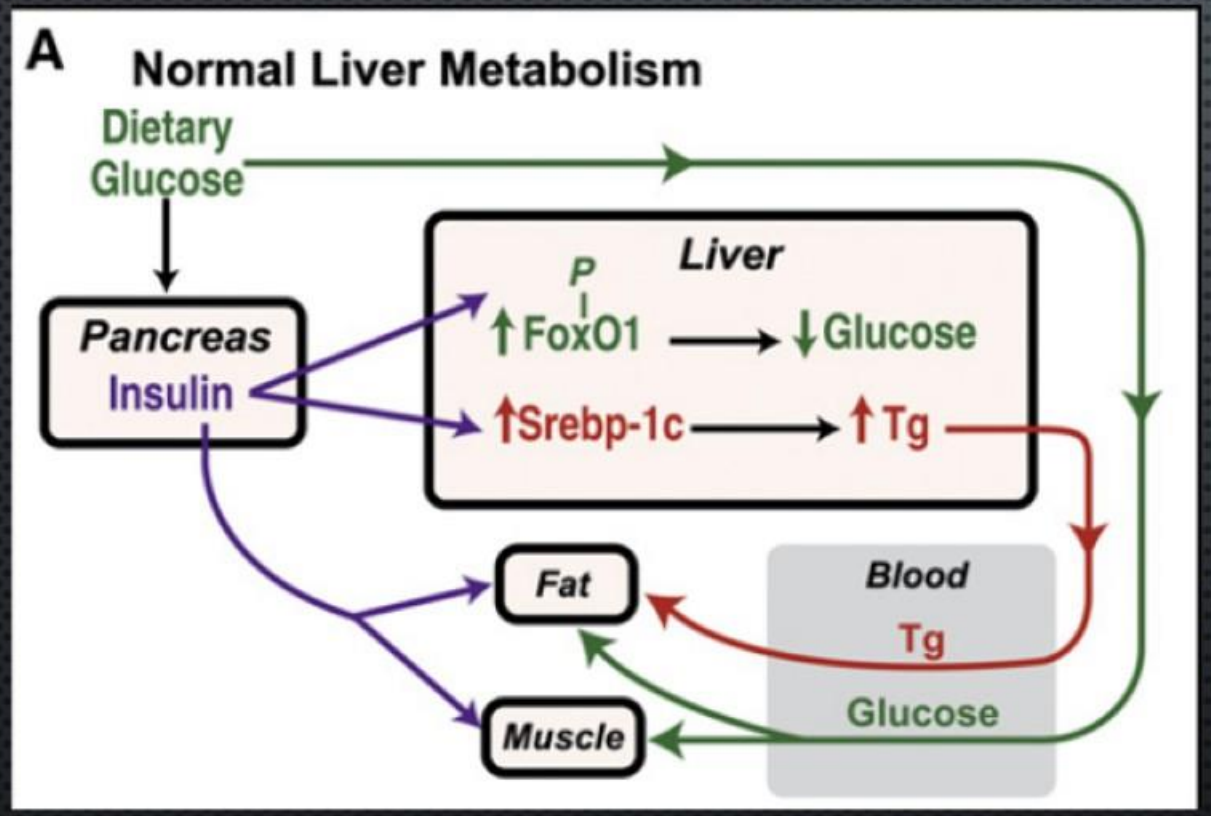
IVUS: lower is better

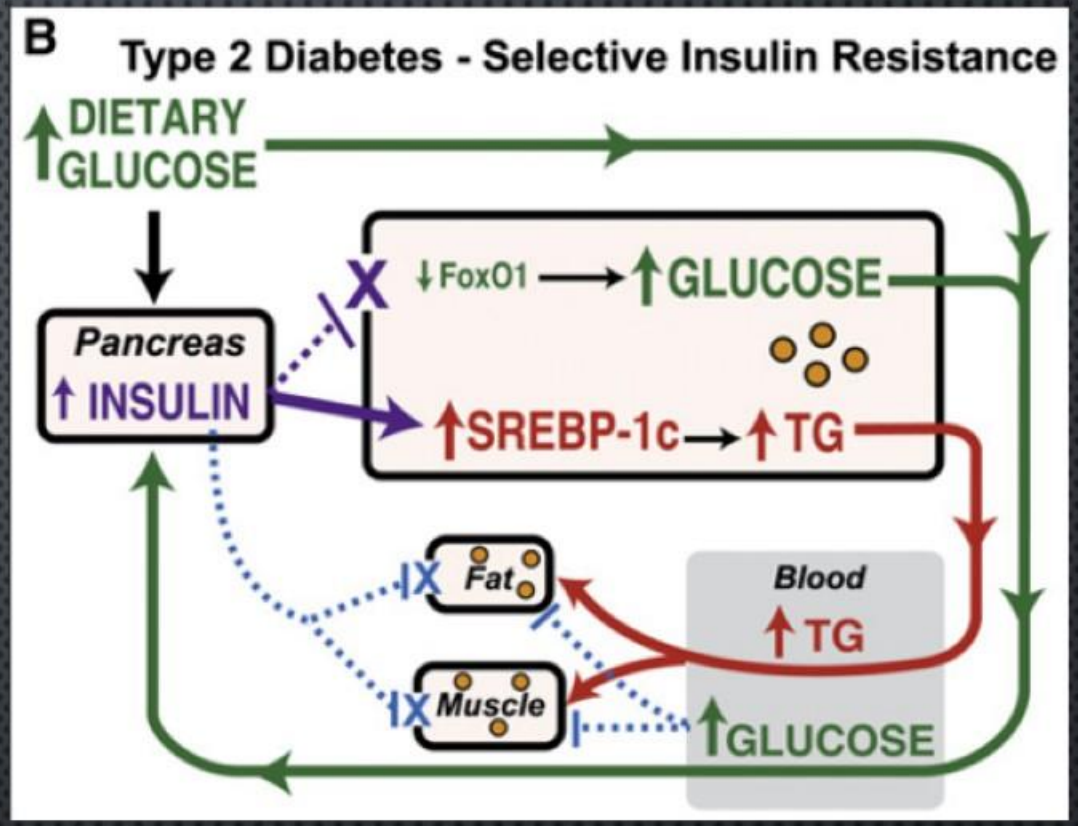
Plaque stabilization

Lower is better from trials

Thank you

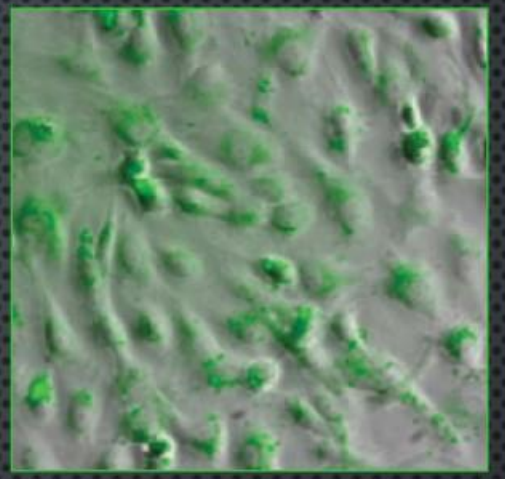
TARGETING METABOLICS





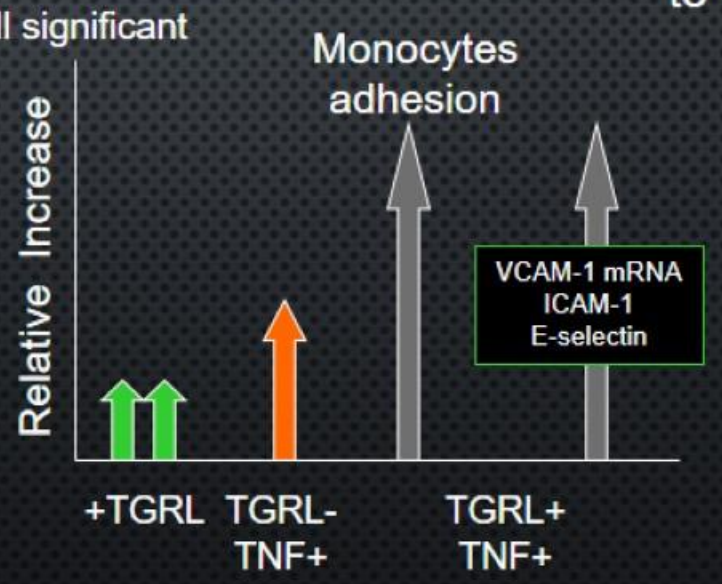
Selective insulin resistance in liver of mice with type 2 diabetes. Insulin fails to decrease gluconeogenesis, but it continues to stimulate synthesis of fatty acids and Tg. This produces the deadly combination of hyperglycemia and hypertriglyceridemia

PRIMING VASCULAR ENDOTHELIAL CELLS FOR ENHANCED INFLAMMATORY RESPONSE



TGRL electron transfer-based fluorescence bound to HAECs treated for 2hrs

- TGRL ALONE NO INFLAMMATION IN HAEC
- TGRL ENHANCED INFLAMMATORY RESPONSE 10X TO CYTOKINE STIMULATION



HAECs were repetitively incubated with dietary levels of freshly isolated TGRL for 2 hours per day for 1 to 3 days to mimic postprandial lipidemia.

Ting et al Circ Res Feb 2007;100:000

US GUIDELINES-2017 (NON STATIN OR ADDITIONAL LOWERING)

IMPROVE-IT (EZETIMIDE)

Patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months

Cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age >75 years, diabetes, stroke, CABG, PAD, eGFR <60 ml/min/1.73 m2, and smoking.

JACC 2017;70:1785 guidelines

US GUIDELINES-2017 (NON STATIN OR ADDITIONAL LOWERING)

PCSK-9 inhibitor

Clinical ASCVD and comorbidities require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent.

The….
clinician–patient discussion should consider the extent of available scientific evidence for net ASCVD risk- reduction benefit, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements **(refrigeration).**

JACC 2017;70:1785 guidelines

ADULTS >21 YEARS OF AGE WITH ***CLINICAL ASCVD***, ON STATIN FOR ***SECONDARY PREVENTION***

- **STABLE ASCVD**

NONE OF THESE

Diabetes,
Recent (<3 months) ASCVD event
ASCVD event while already taking a statin
Poorly controlled other major ASCVD risk factors
Elevated Lp(a), CKD, symptomatic heart failure

Baseline LDL-C >190 mg/dL not due to secondary causes
Hemodialysis
Prior MI, stroke, CABG
Currently smoking
Symptomatic PAD

Cath >40% stenosis in >2 vessels
HDL <40
hsCRP >2
Metabolic syndrome

1

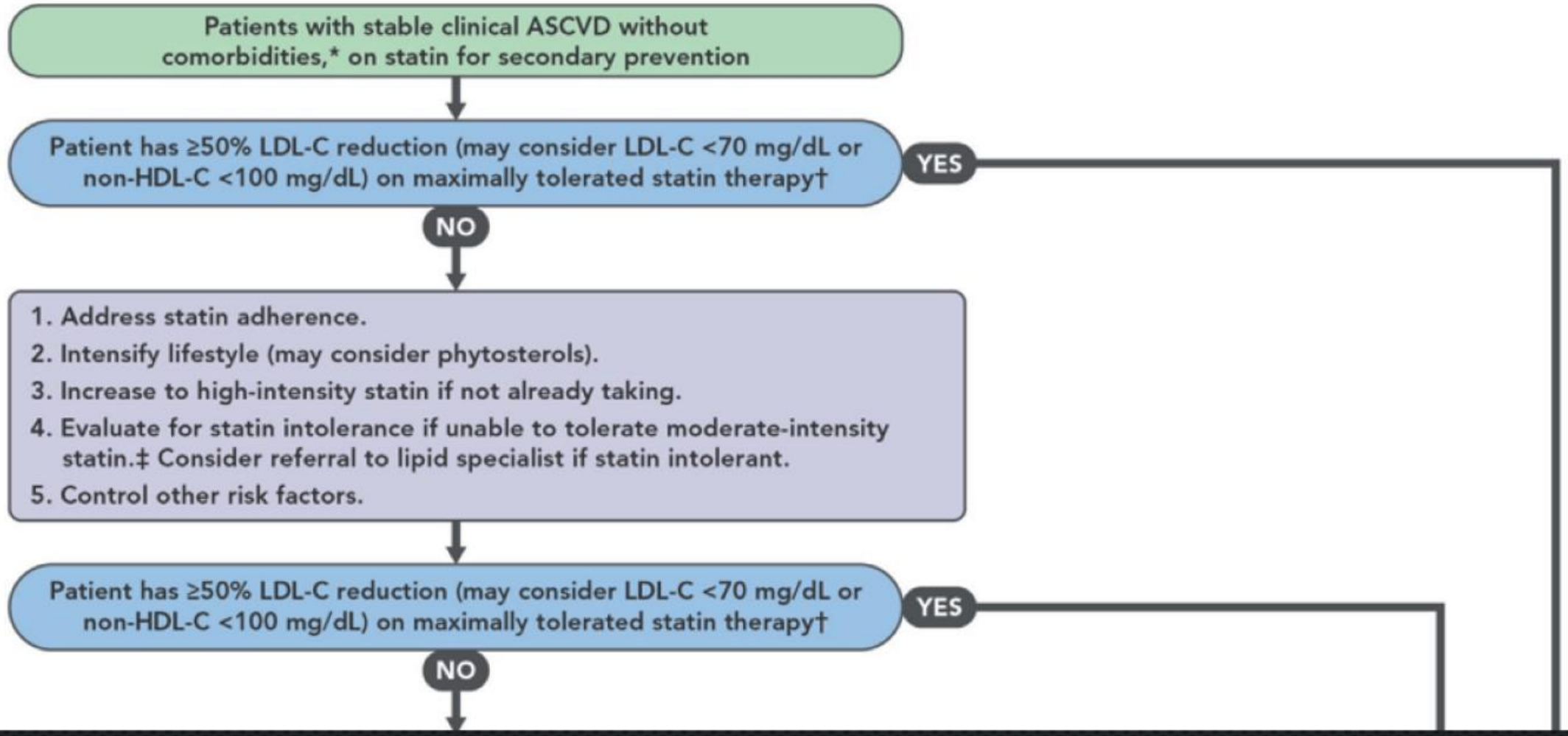
These patients should be treated first with maximally tolerated statin intensity.

If patients have a >50% reduction in LDL-C from baseline (and may consider LDL-C <70 mg/dL or non–HDL-C <100 mg/dL)

Continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy.

1

Patients who are unable to tolerate even a moderate-intensity statin should be evaluated for statin intolerance and considered for referral to a lipid specialist.



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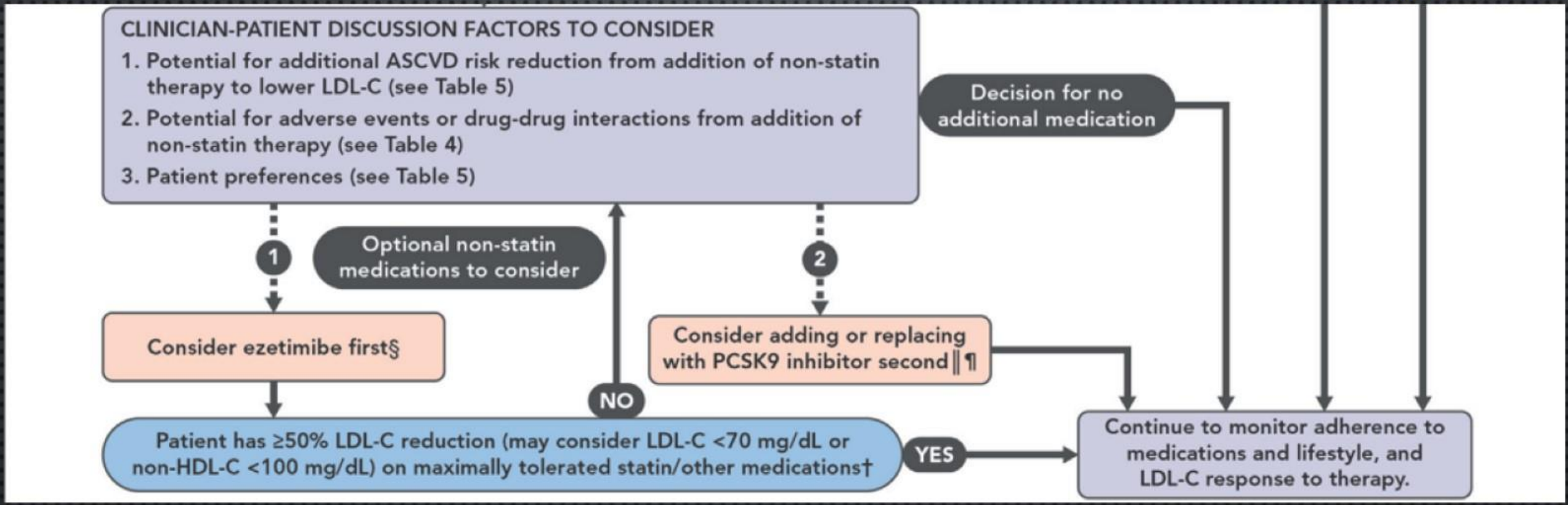
JACC 2017;70:1785 guidelines

YES met goal



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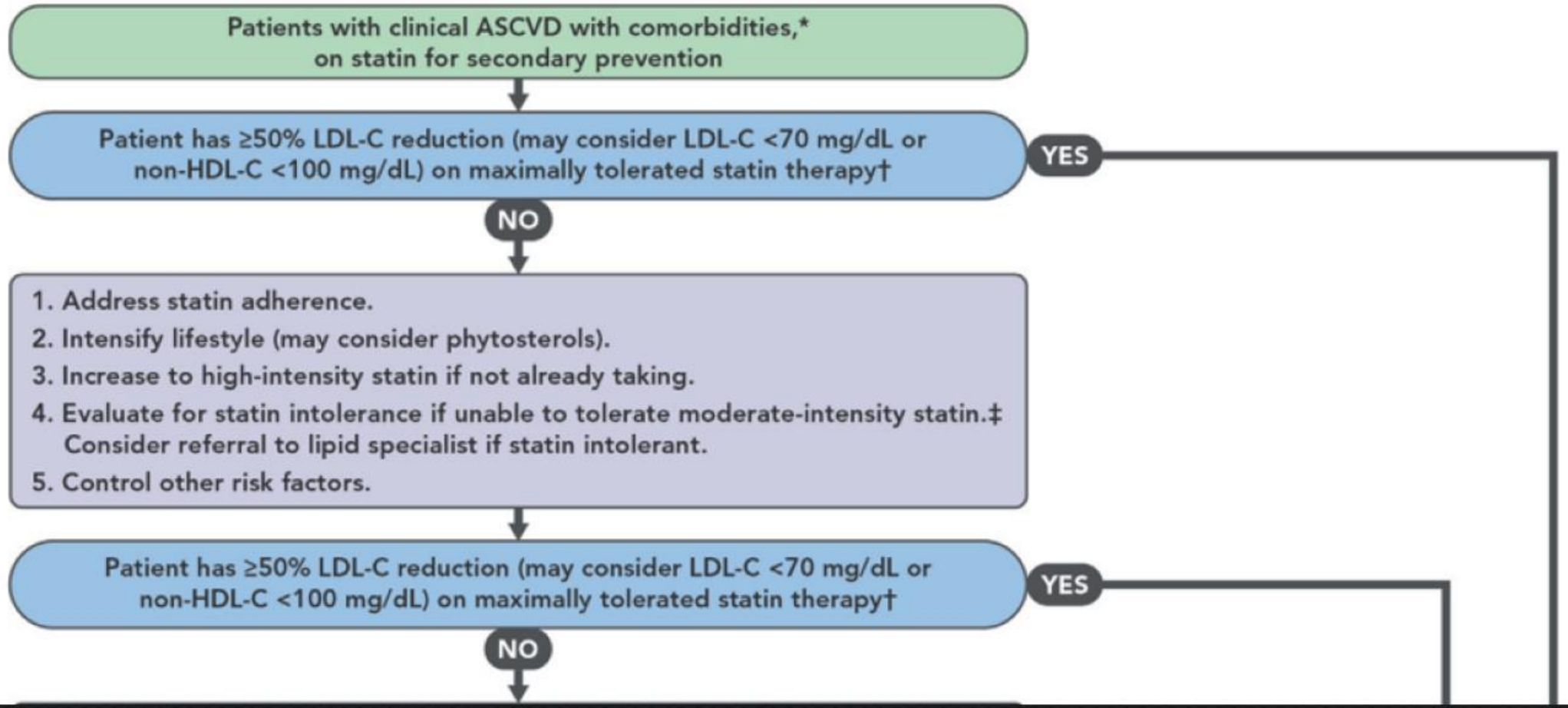
JACC 2017;70:1785 guidelines

FIGURE 2B Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention



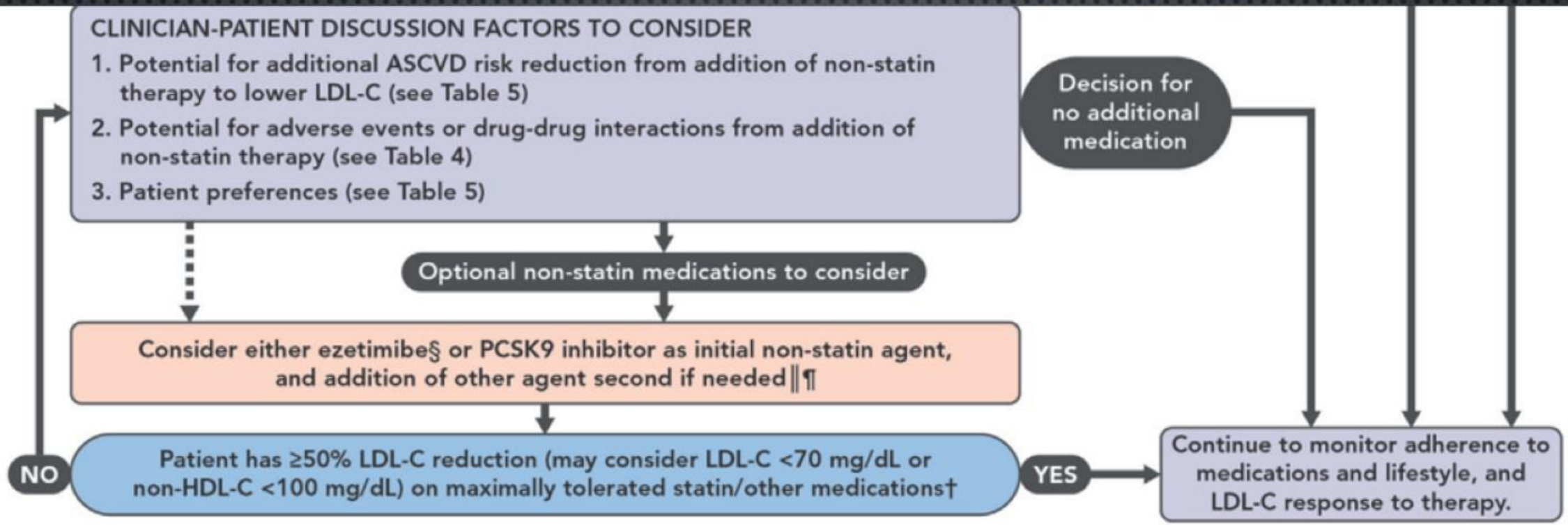
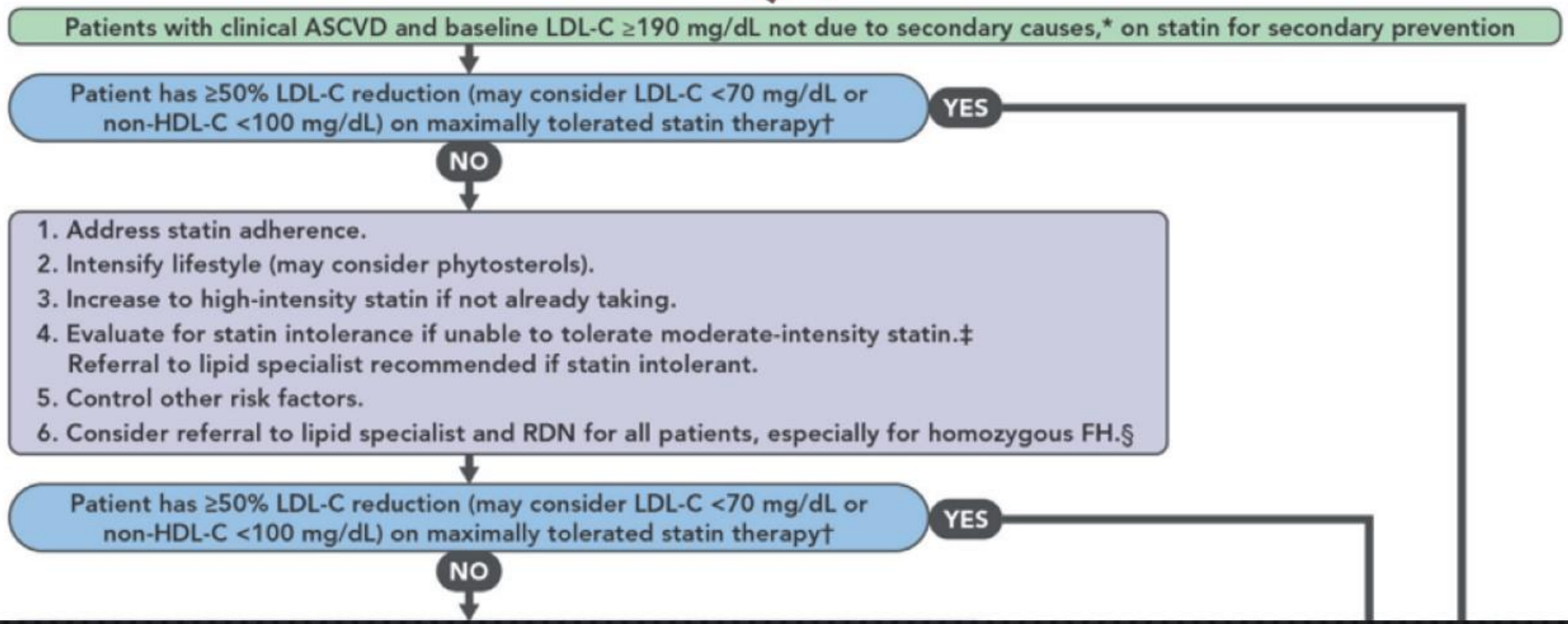

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)
Decision for no additional medication
Optional non-statin medications to consider
Consider either ezetimibe§ or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed‖¶
NO
Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†
YES
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

FIGURE 2C Patients ≥21 Years of Age with Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention



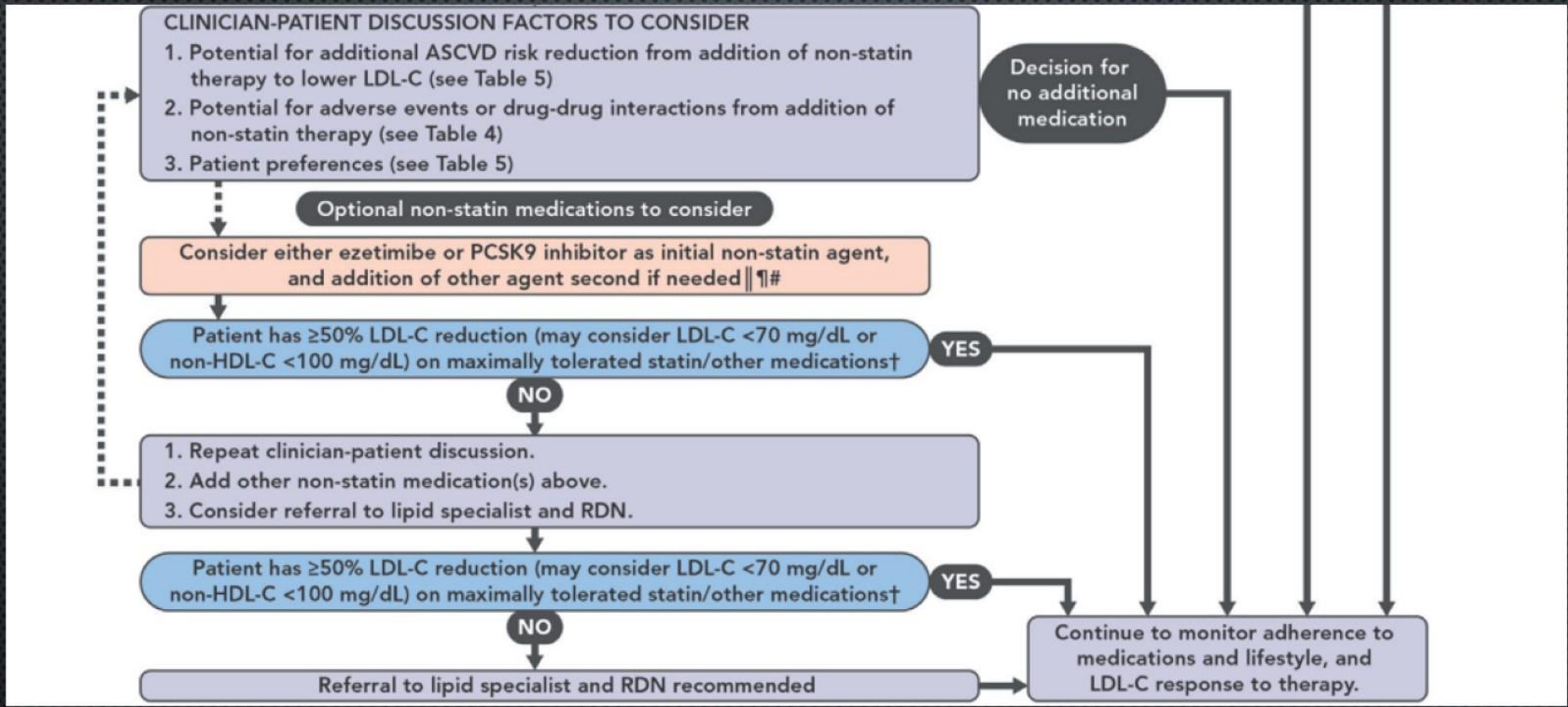
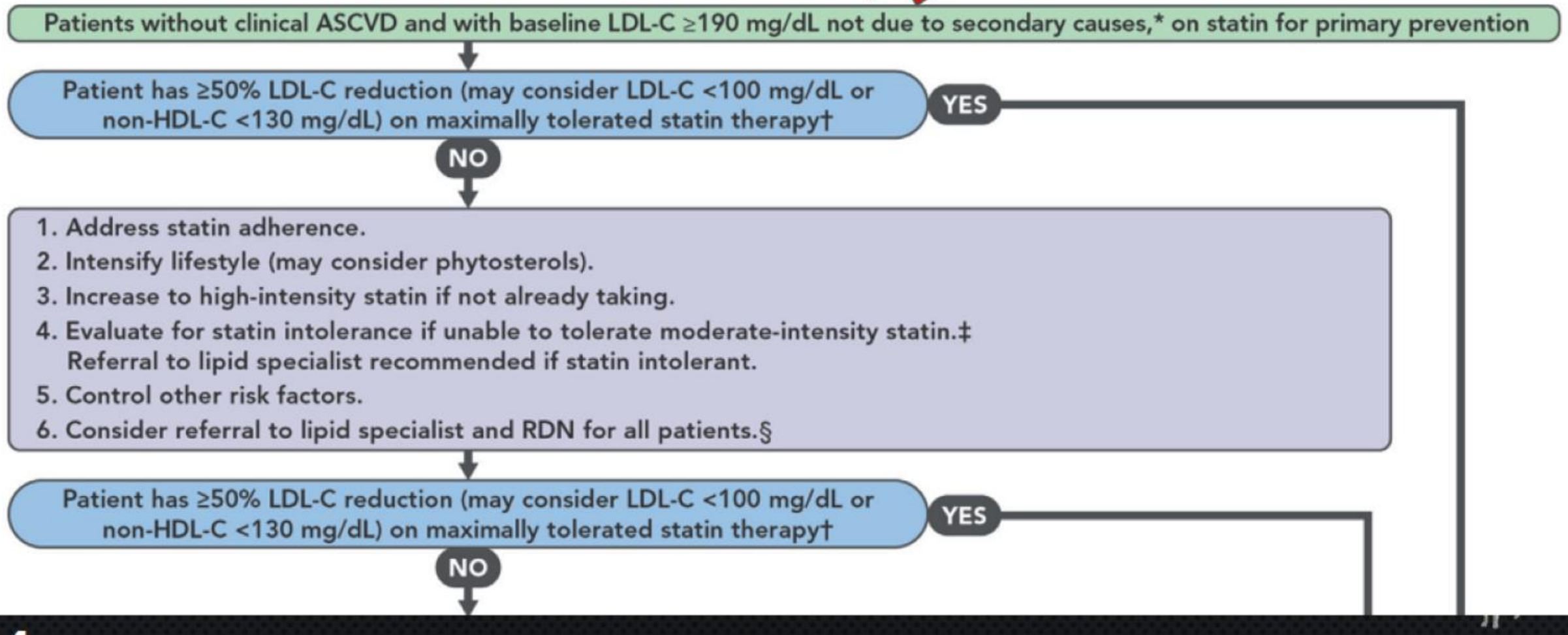

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)
Decision for no additional medication
Optional non-statin medications to consider
Consider either ezetimibe or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed‖¶#
Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†
YES
NO
1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.
Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†
YES
NO
Referral to lipid specialist and RDN recommended
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

FIGURE 3 Patients ≥21 Years of Age without Clinical ASCVD and with Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Primary Prevention



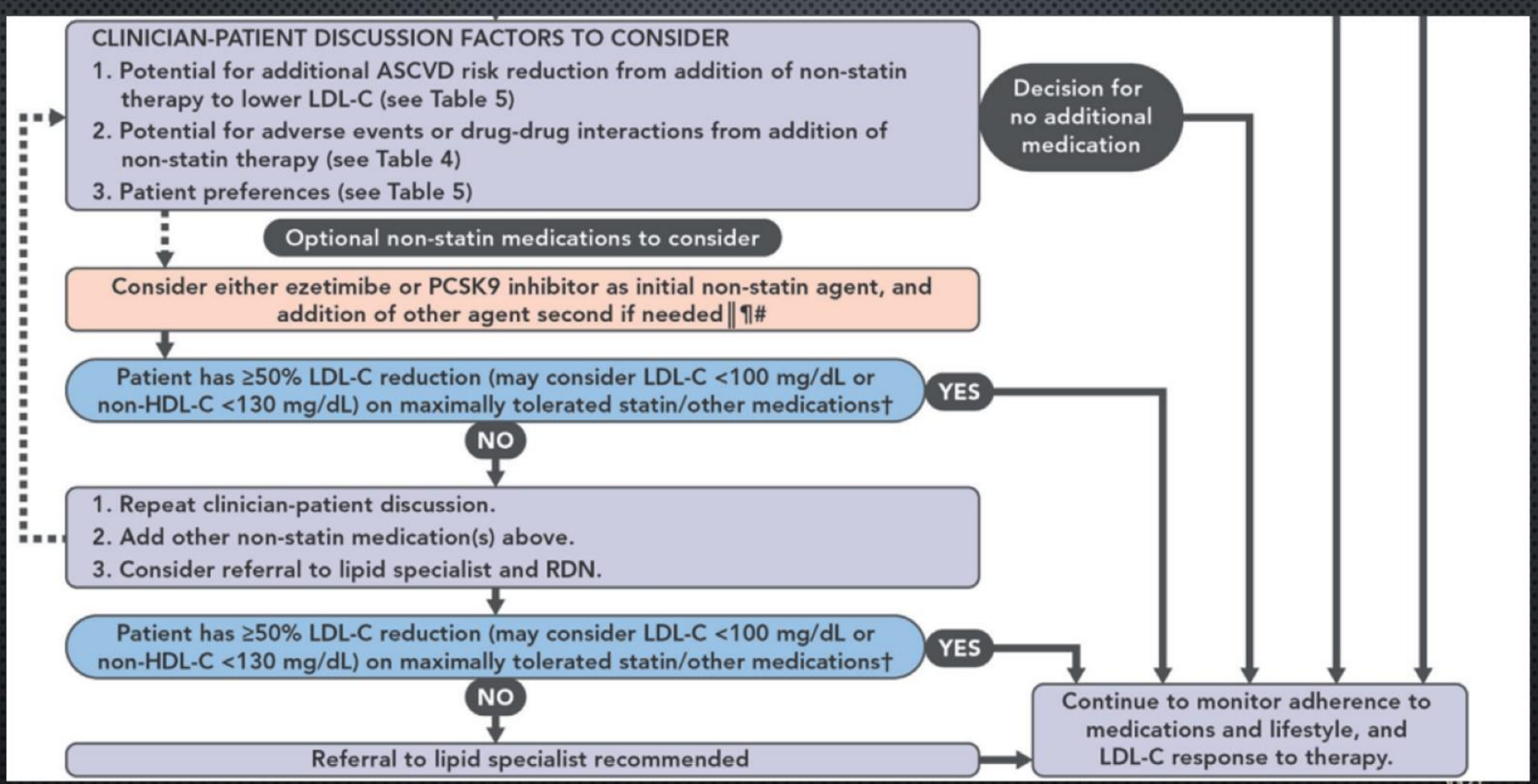
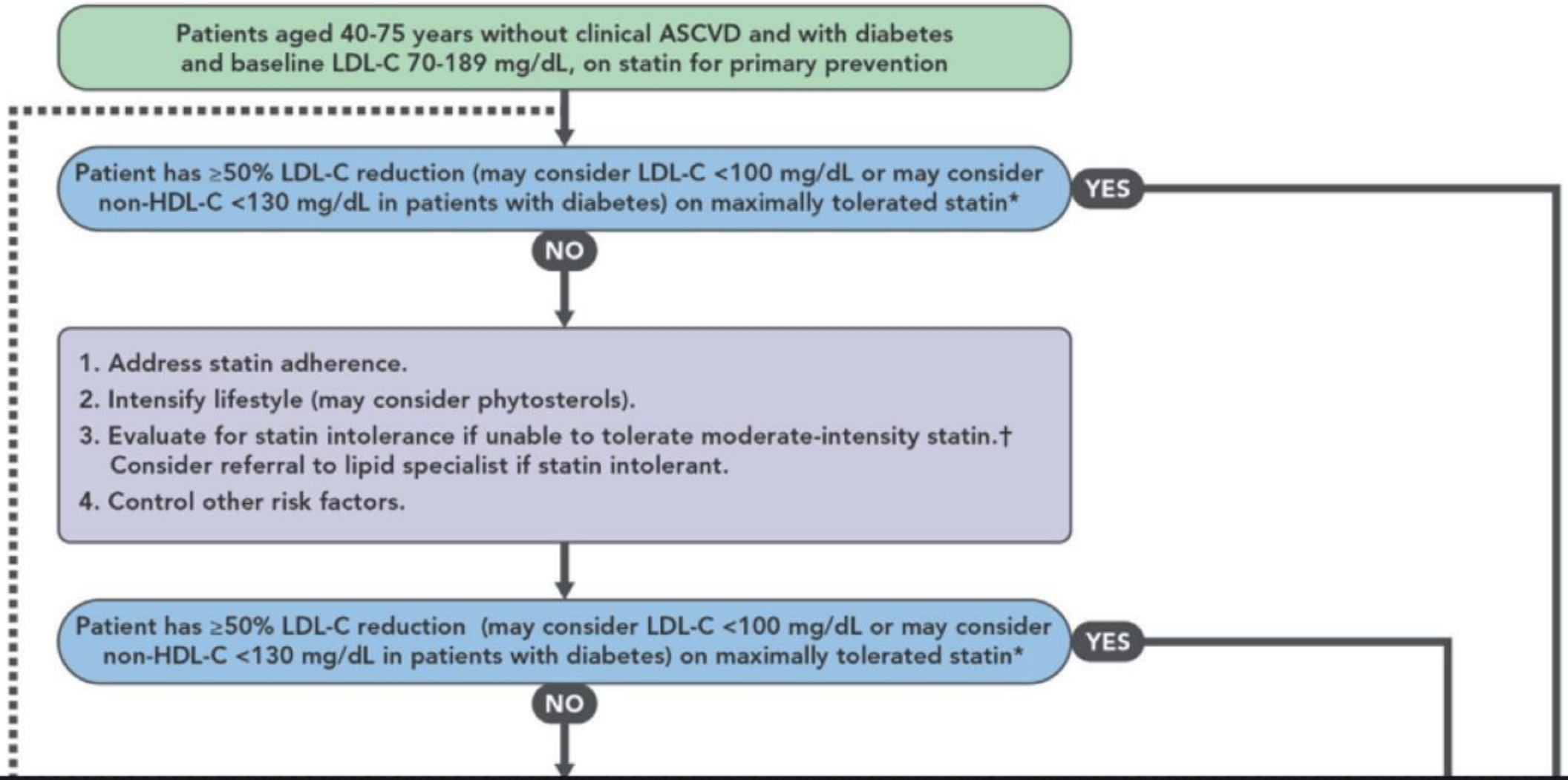

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)
Decision for no additional medication
Optional non-statin medications to consider
Consider either ezetimibe or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed‖¶#
Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin/other medications†
YES
NO
1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.
Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin/other medications†
YES
NO
Referral to lipid specialist recommended
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

FIGURE 4 Patients Aged 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention



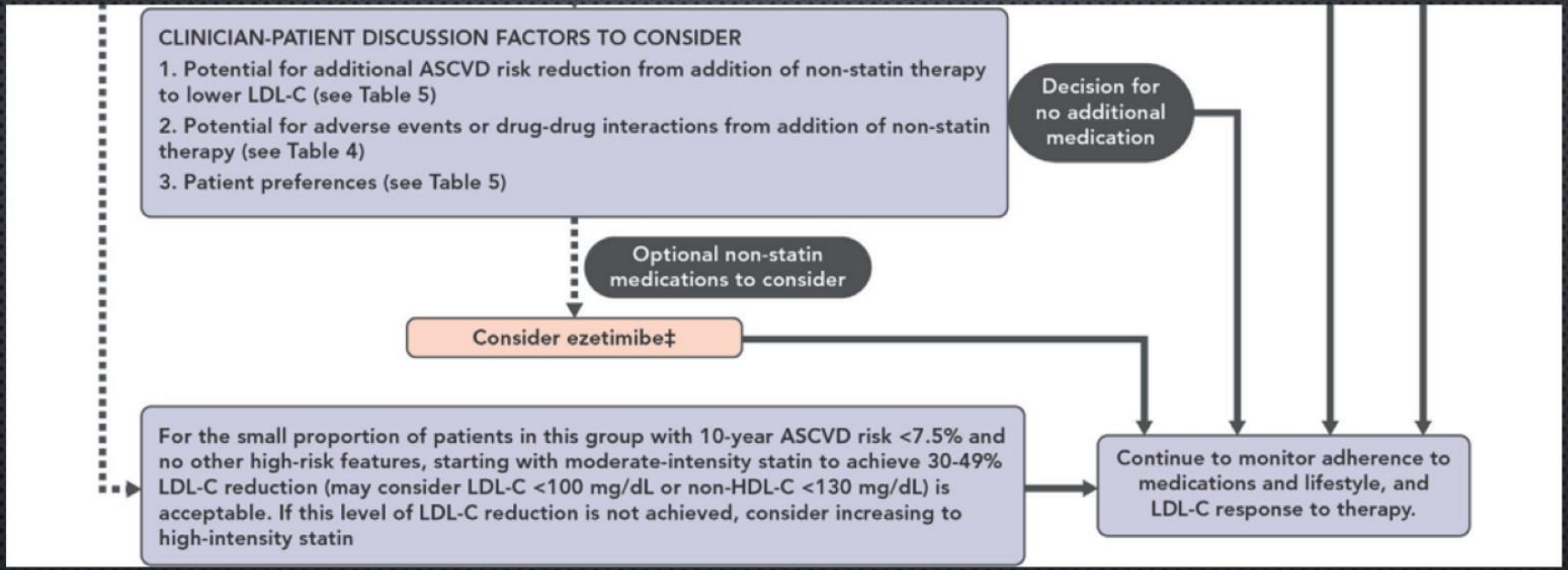
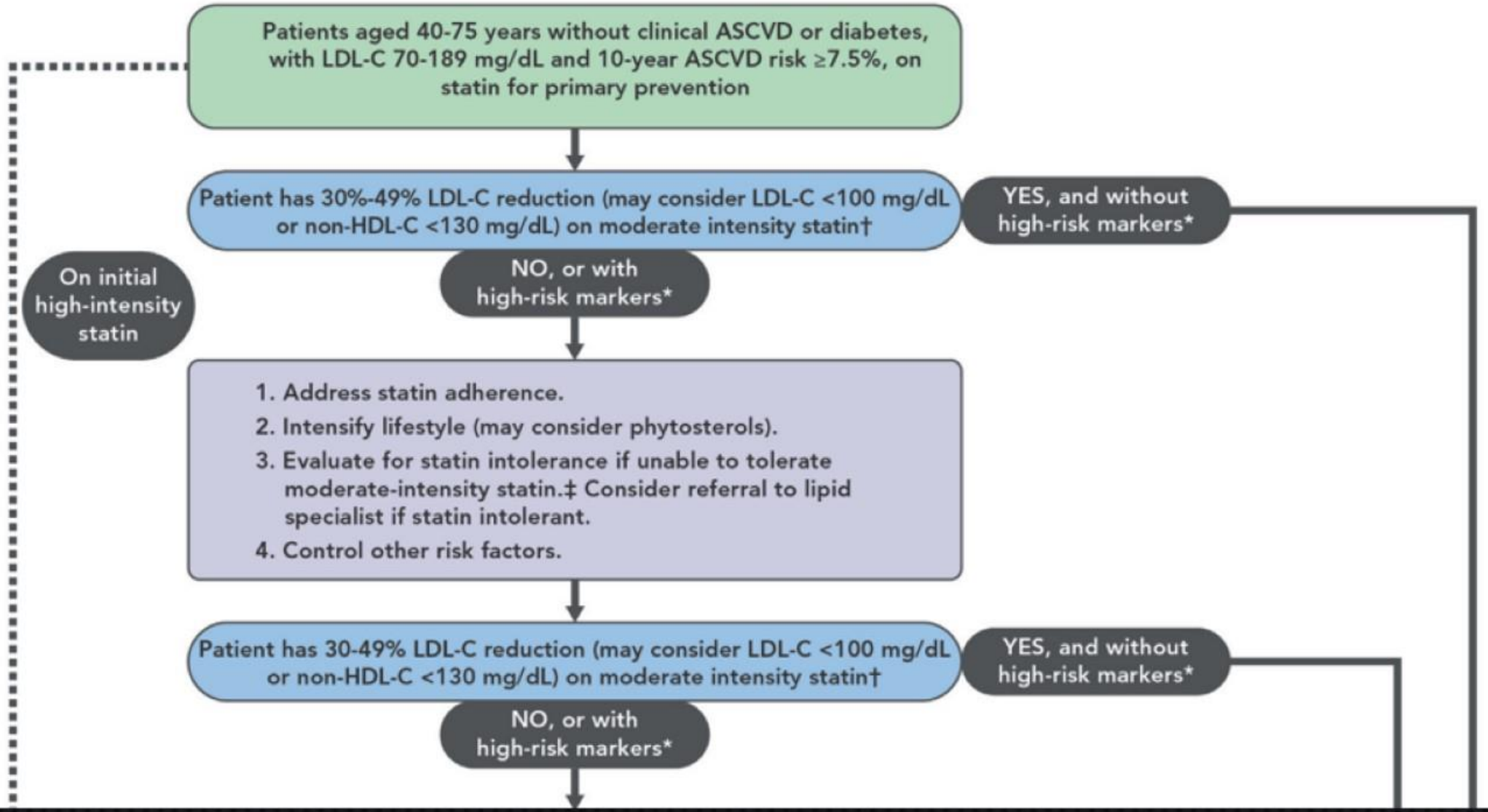
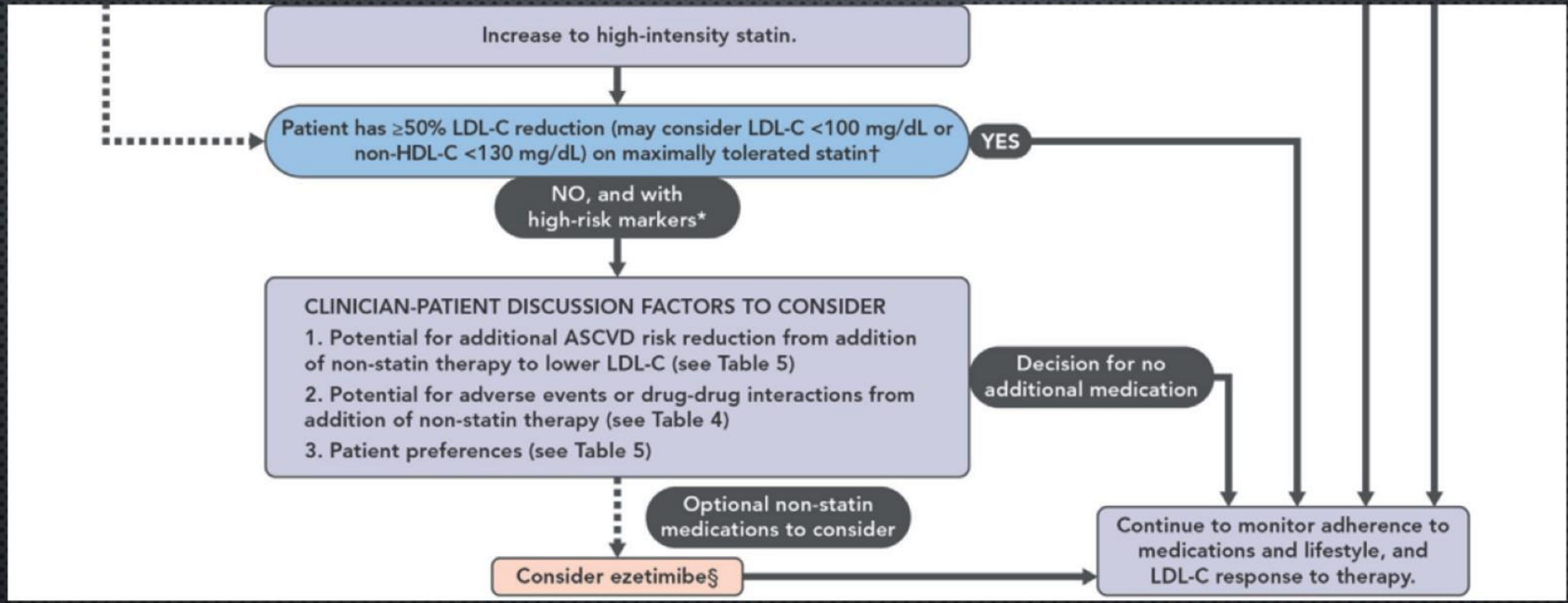

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)
Decision for no additional medication
Optional non-statin medications to consider
Consider ezetimibe‡
For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

FIGURE 5 Patients Aged 40-75 years without Clinical ASCVD or Diabetes, with LDL-C 70-189 mg/dL and 10-Year ASCVD Risk ≥7.5%, on Statin for Primary Prevention




Increase to high-intensity statin.
Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin†
YES
NO, and with high-risk markers*
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)
Decision for no additional medication
Optional non-statin medications to consider
Consider ezetimibe§
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

EZETIMIBE

Mechanism of action: Inhibits Niemann-Pick C1 like 1 (NPC1L1) protein; reduces cholesterol absorption in small intestine

Adverse effects: Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea.

Drug–drug interactions: cyclosporine, fibrates, BAS

EZETIMIBE--MAIN TRIALS

IMPROVE-IT -- (The addition of ezetimibe to moderate-intensity statin in patients with recent **ACS** resulted in incremental lowering of LDL-C and reduced primary composite endpoint of CV death, nonfatal MI, UA requiring re-hospitalization, coronary revascularization [$30 days after randomization], or nonfatal stroke. The median follow-up was 6 years.)

SHARP --(Simvastatin plus ezetimibe reduced LDL-C and reduced primary endpoint of first major ASCVD event [nonfatal MI or CHD death, non-hemorrhagic stroke, or any arterial revascularization procedure] compared to placebo over a median f/u of 4.9 years).

PCSK9 INHIBITORS

Mechanism of action: Human monoclonal antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL

Adverse effects: Alirocumab—nasopharyngitis, injection site reactions, influenza. Evolocumab—nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

No evidence of increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS