Cardiovascular Risk Assesment and Management in Diabetics for the Practicing Physician

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Diplomate of the American Board of Clinical Lipidology

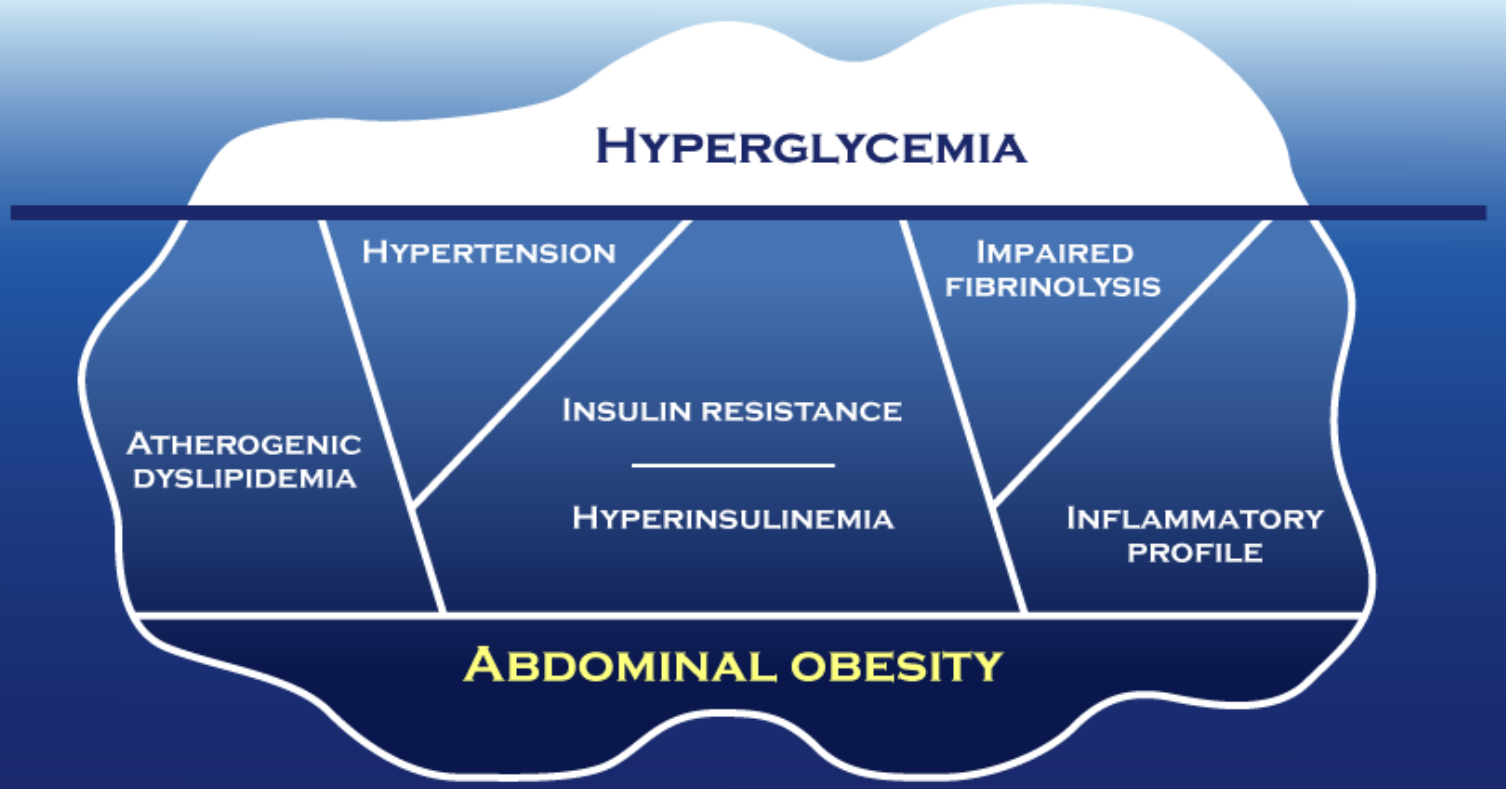
Disclosure

- Dr. Jose M. Garcia Mateo, endocrinologist, declares that he serves as a speaker and consultant for the following pharmaceutical companies: ***Eli Lilly, Astra Zeneca, Sanofi , Amgen, Boehringer Ingelheim, Janseen and Merck.***

Objectives

- Briefly discuss the multifactorial pathophysiology of ASCVD in diabetes and the contribution of dyslipidemia.
- Present current guidelines for the management of dyslipidemia in patients with diabetes and reduction of ASCVD from recognized medical societies.
- Case discussion to apply guidelines, technology and clinical knowledge for effective management.
- Discuss the importance of recognizing ASCVD, additional risk factors and Familial Hypercholesterolemia in diabetics.
- Is there room for nonstatin therapies in the clinical management of dyslipidemia in diabetic patients. A view at 2016 ACC Expert Consensus Decision Pathway of Non Statin Therapies in ASCVD Management.

Elevated CHD risk in type 2 diabetic patients: Beyond glycemia



HYPERGLYCEMIA: THE TIP OF THE METABOLIC SYNDROME ICEBERG

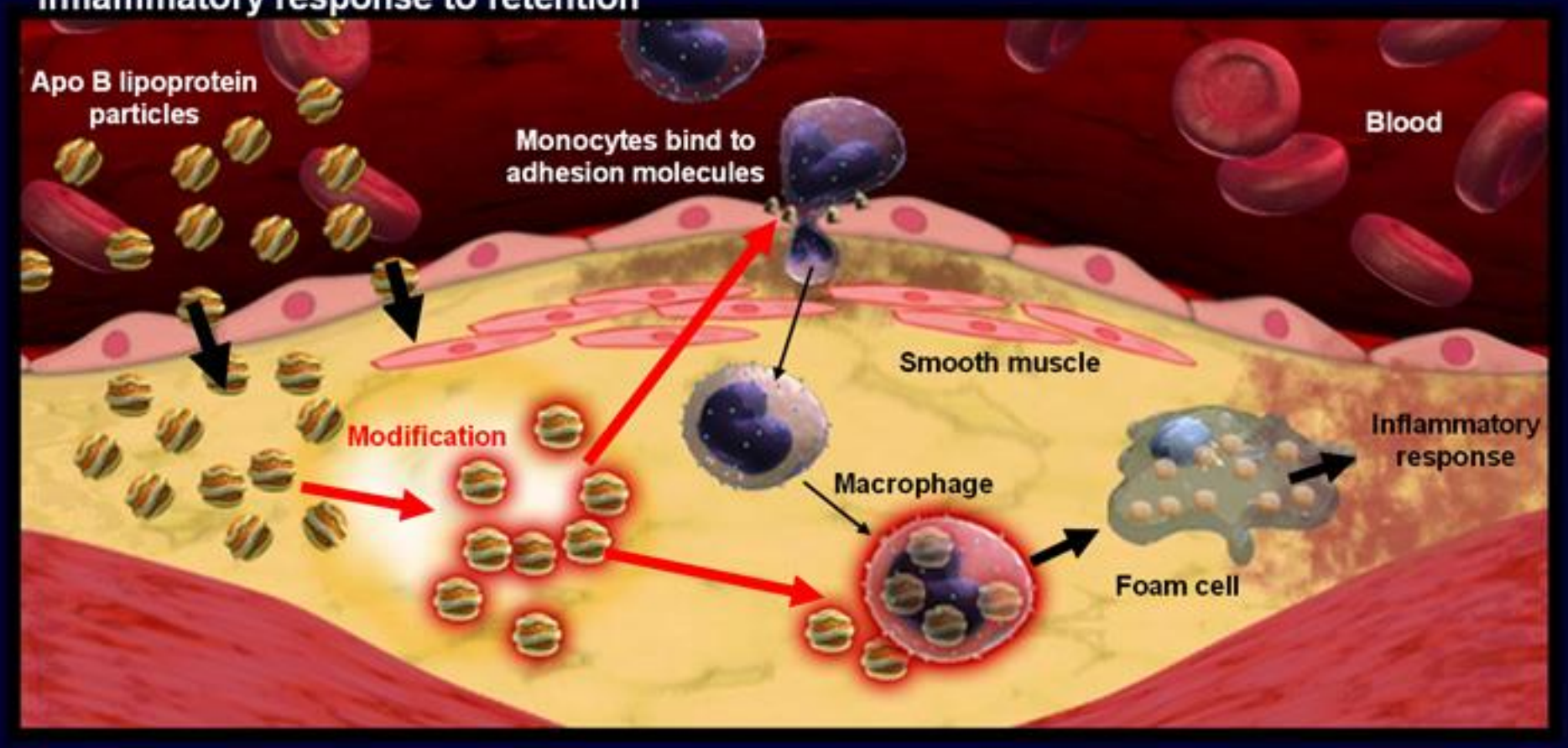
The Metabolic Syndrome Institute

Risk Factors for Macrovascular Disease

- Not modifiable
  - Genetic factors
  - Family history
- Modifiable
  - Hyperglycemia
  - Hypertension
  - **DYSLIPIDEMIA**
  - Smoking
  - Obesity
  - Physical inactivity

Apo B Lipoprotein Retention and its Ensuing Inflammatory Response is Cetral to Atheroma Formation

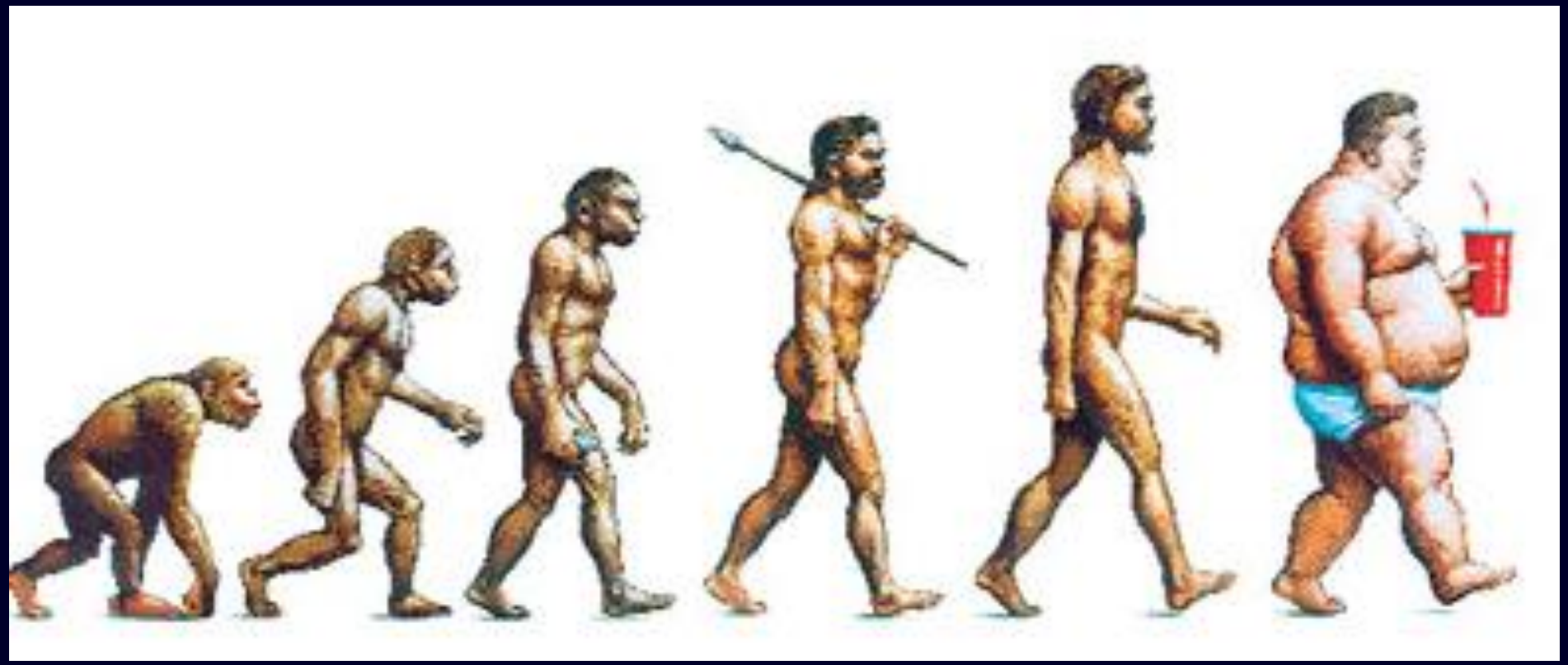
Rationale for therapeutic lowering of Apo B lipoproteins: decrease the probability of inflammatory response to retention



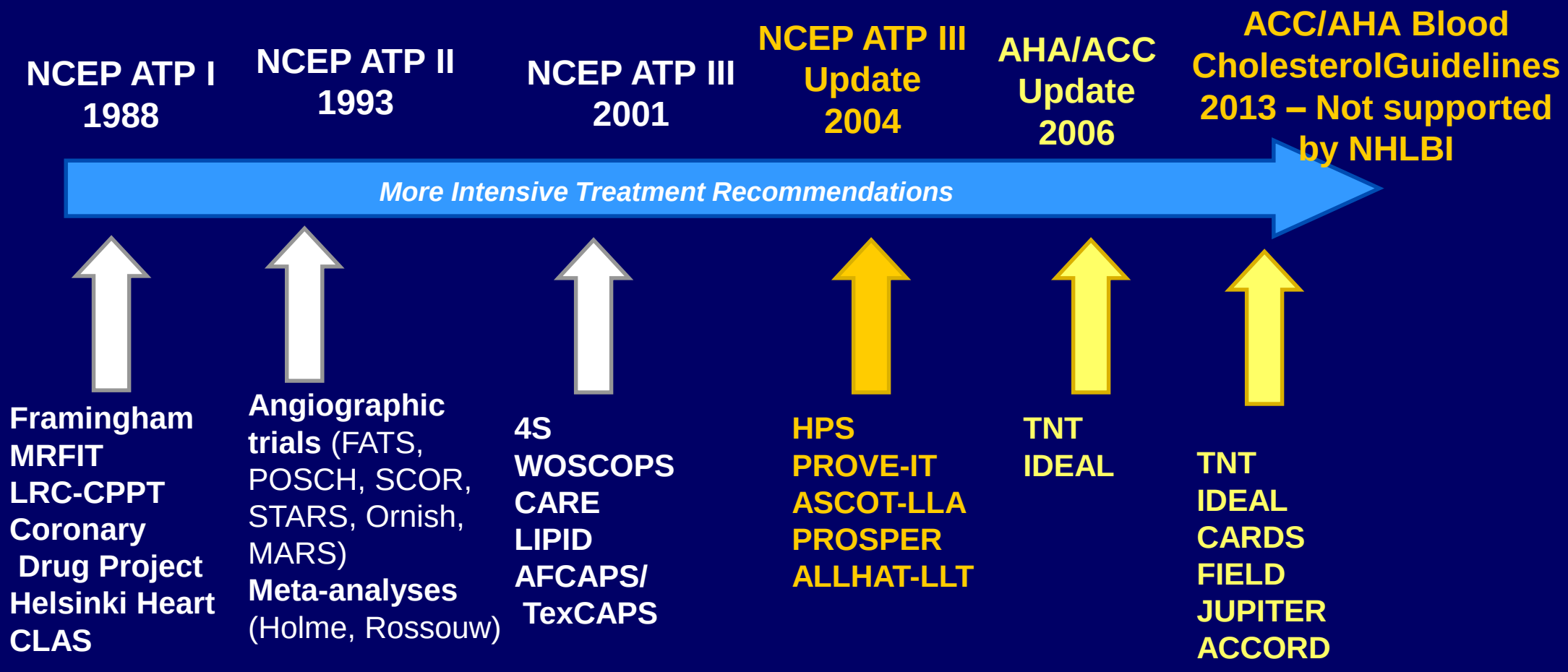
Tabas I et al. *Circulation.* 2007;116(16):1832–1844. Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 1995;15(5):551–561. Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 2005;25(8):1536–1540. Hoshiga M et al. *Circ Res.* 1995;77(6):1129–1135. Merrilees MJ et al. *J Vasc Res.* 1993;30(5):293–302. Nakata A et al. *Circulation.* 1996;94(11):2778–2786. Steinberg D et al. *N Engl J Med.* 1989;320(14):915–924.

Atherogenic Dyslipidaemia

The Metabolic Syndrome Institute



Evolution of NHLBI Supported Guidelines



NHLBI = National Heart, Lung, and Blood Institute.
NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel.
AHA = American Heart Association.
ACC = American College of Cardiology.


New ACC/AHA Prevention Guidelines Address Blood Cholesterol, Obesity, Healthy Living and Risk Assessment
Click Here to Learn More


NDC 0591-3777-19
Atorvastatin Calcium
Tablets
80 mg*
Watson.
90 Tablets Rx only


American Heart Association.
AMERICAN COLLEGE of CARDIOLOGY
2013 Prevention Guidelines Tools
CV RISK CALCULATOR
The American Heart Association and the American College of Cardiology are excited to provide a series of new cardiovascular prevention guidelines for the assessment of cardiovascular risk, lifestyle modifications that reduce risk, management of elevated blood cholesterol, and management of increased body weight in adults. To support the implementation of these guidelines, the new Pooled Cohort Equations CV Risk Calculator and additional Prevention Guideline Tools are available below. Others may be developed and available in the near future.
DOWNLOAD CV RISK CALCULATOR


2013 Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk
Click Here to Learn More


Taking Action to
Get Healthy

4 Statin Benefit Groups

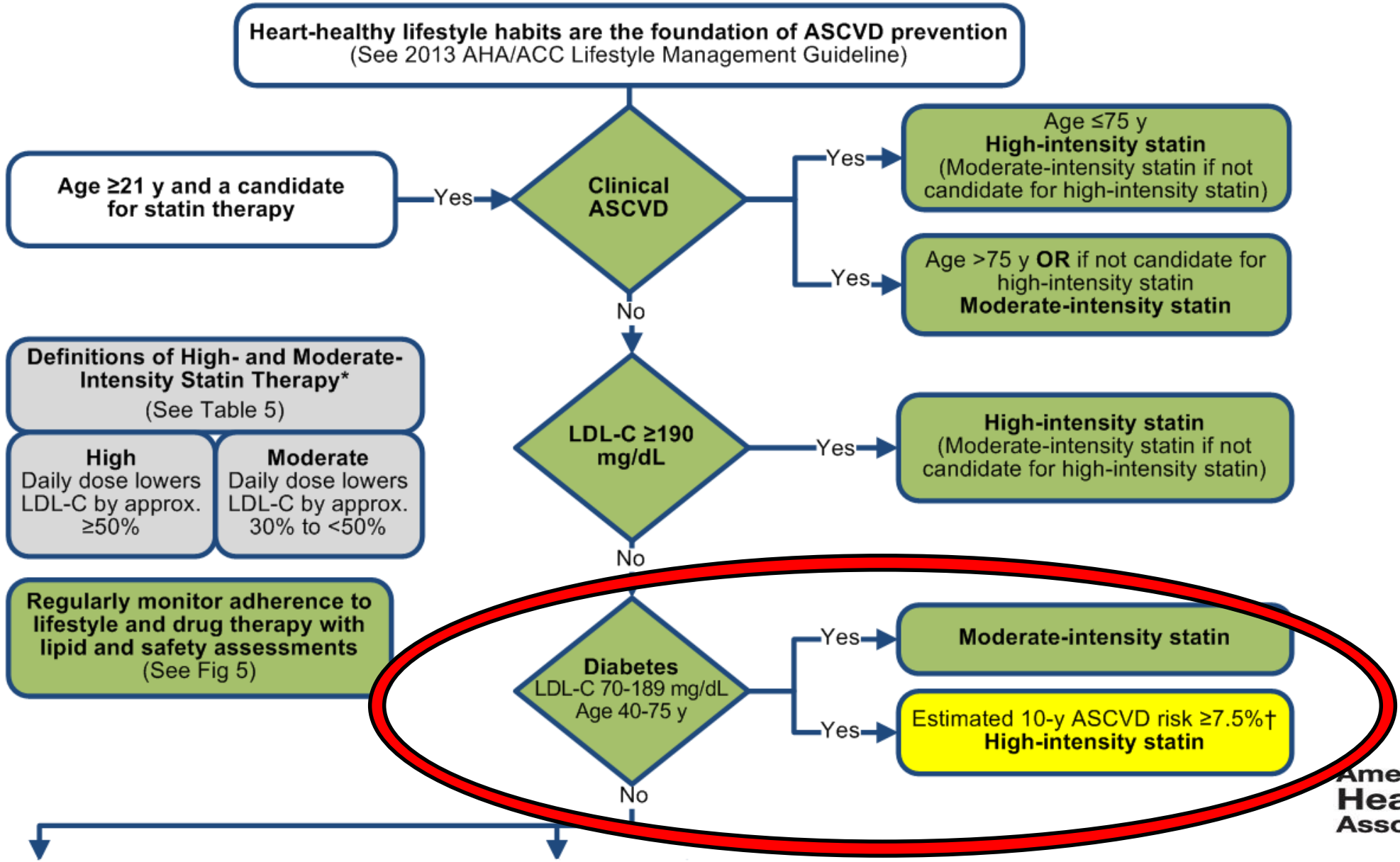
- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

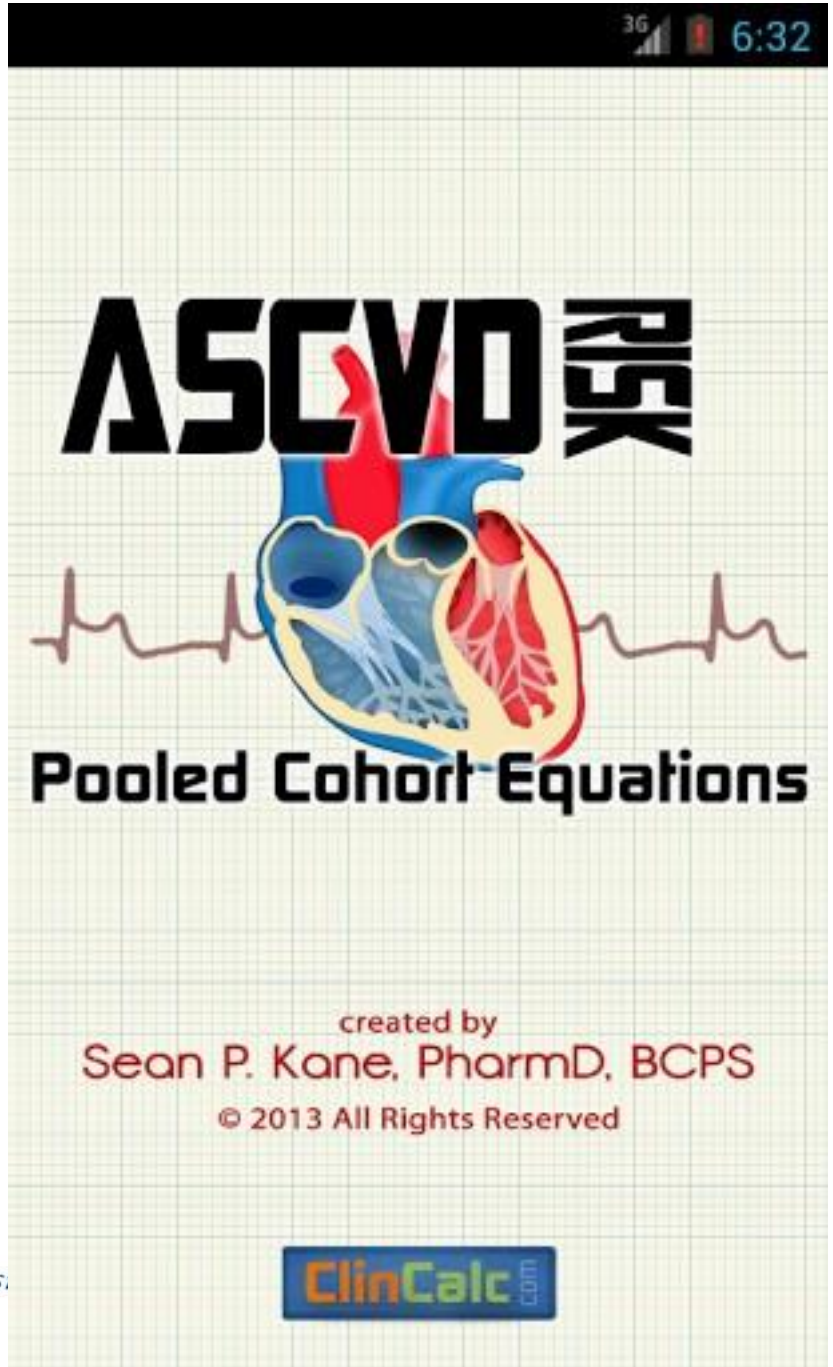
*Atherosclerotic cardiovascular disease

†Requires risk discussion between clinician and patient before statin initiation

‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)





Intensity of Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20 *(40)* mg**	**Atorvastatin 10 *(20)* mg** **Rosuvastatin (5) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 *(80)* mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

National Lipid Association

Statement on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

- *We ultimately felt that the document presented--although important and constructive--does not go far enough to address gaps in clinical care and therefore* ***decided not to endorse them as guidelines.***

NATIONAL LIPID ASSOCIATION

NLA Recommendations for Patient-Centered Management of Dyslipidemia

Part 1 -- Final

Treatment Goals and Levels to Consider Drug Therapy According to Risk Category

Risk Category	Treatment Goal	Consider Drug Therapy
	Non-HDL-C mg/dL LDL-C mg/dL	
Low	<130 <100	≥190 ≥160
Moderate	<130 <100	≥160 ≥130
High	<130 <100	≥130 ≥100
Very High	<100 < 70	≥100 ≥ 70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Intensity of Statin Therapy*

High Intensity Daily dose ↓ LDL-C ≥50%	Moderate Intensity Daily dose ↓ LDL-C 30 to <50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Fluvastatin 40 mg bid
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2-4 mg
	Pravastatin 40-80 mg
	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg

*Individual responses to statin therapy should be expected to vary in clinical practice. Moderate or high intensity statin therapy is preferred unless not tolerated.

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH: DM but no other major risk and/or age <40	VERY HIGH: DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking) or ASCVD*
	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70
Non-HDL-C (mg/dL)	<130	<100
TG (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
Apo B (mg/dL)	<90	<80
LDL-P (nmol/L)	<1200	<1000

IF NOT AT DESIRABLE LEVELS: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

TO LOWER LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
TO LOWER Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
TO LOWER Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
TO LOWER LDL-C in FH:**	Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:
DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

American Diabetes Association®

Standards of Medical Care in Diabetes — 2016

Recommendations for Statin Treatment in People with Diabetes

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL >50 who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL >50 who can't tolerate high dose statin	Moderate + ezetimibe

* In addition to lifestyle therapy. ** ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

American Diabetes Association®

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Case Study 1 : 55-Year-Old Man

Patient: ARG

- Hx of DM2 and CAD
- SP CABG x 3
- Poor compliant with diet
- No smoking
- Occasional exercise
- Currently on simvastatin 20 mg, ACEI, BB, ASA, metformin 2g /day

Selected Lab Measurements

Total-C	178 mg/dL
LDL-C	105 mg/dL
HDL-C	37 mg/dL
Non–HDL-C	141 mg/dL
TG	180 mg/dL
FBS	79 mg/dL
A1C	6.8%

Physical Examination

BP	140/88 mmHg
BMI	34
Waist circumference	40”

Possible treatment options:

ACC/AHA 2013

- Is there benefit from change statin therapy?
- What intensity?

NLA 2014 – 2015

- What risk category
- LDL optimal levels
- Non HDL optimal levels
- Patient may have residual CV risk

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*Atherosclerotic cardiovascular disease

†Requires risk discussion between clinician and patient before statin initiation

‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

Criteria for ASCVD Risk Categories

Risk Category	Criteria
Low	▪ 0-1 major ASCVD risk factors ▪ Consider other risk indicators, if known
Moderate	▪ 2 major ASCVD risk factors ▪ Consider quantitative risk scoring ▪ Consider other risk indicators

High	▪ ≥3 major ASCVD risk factors
	▪ Diabetes mellitus (type 1 or 2)
	  ▪ 0-1 other major ASCVD risk factors, and
	  ▪ No evidence of end organ damage
	▪ Chronic kidney disease Stage 3B or 4
	▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)
	▪ Quantitative risk score reaching the high risk threshold

Very High	▪ ASCVD
	▪ Diabetes mellitus (type 1 or 2)
	  ▪ ≥2 other major ASCVD risk factors or
	  ▪ Evidence of end organ damage

Treatment Goals and Levels to Consider Drug Therapy According to Risk Category

Risk Category	Treatment Goal	Consider Drug Therapy
	Non-HDL-C mg/dL LDL-C mg/dL	
Low	<130 <100	≥190 ≥160
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High	<130 <100	≥130 ≥100
Very High	<100 < 70	≥100 ≥ 70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Case Study 1: Which is the best treatment option?

- Lifestyle intervention
- Lifestyle intervention and moderate intensity statin
- Lifestyle intervention and discuss with patient the benefits and risks of statin therapy and reach the best clinical decission
- Lifestyle intervention and high intensity statin

Recommendations for Statin Treatment in People with Diabetes

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL >50 who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL >50 who can't tolerate high dose statin	Moderate + ezetimibe

* In addition to lifestyle therapy. ** ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

American Diabetes Association®

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71

Intensity of Statin Therapy*

High Intensity Daily dose ↓ LDL-C ≥50%	Moderate Intensity Daily dose ↓ LDL-C 30 to <50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Fluvastatin 40 mg bid
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2-4 mg
	Pravastatin 40-80 mg
	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg

*Individual responses to statin therapy should be expected to vary in clinical practice. Moderate or high intensity statin therapy is preferred unless not tolerated.

EBM Tools for Practice:

Guideline Fusion: A Reasonable Approach to Lipid Management

TERRANCE J. MORAN, MD, FACC, FAHA
Director, Advance Lipid Management Program
Tyler Heart Institute, Community Hospital of the Monterey Peninsula
Monterey, CA

Diplomate, American Board of Clinical Lipidology

Guideline Fusion

Clinical ASCVD. The LDL-C goal is >50 percent drop or <70mg/dL, whichever is lower. This fuses multiple recommendations.

Diabetics with LDL-C 70-189 and no clinical ASCVD.

Eliminate risk calculators.

- < 40 y/o with no major ASCVD risk factors and LDLC<100mg/dL, reasonable to defer pharmacotherapy until risk is considered higher (> 40 years old).
- Otherwise, treat everyone.

  > 40 y/o and no RF, LDL-C<100 or a 30 to 49 % drop.

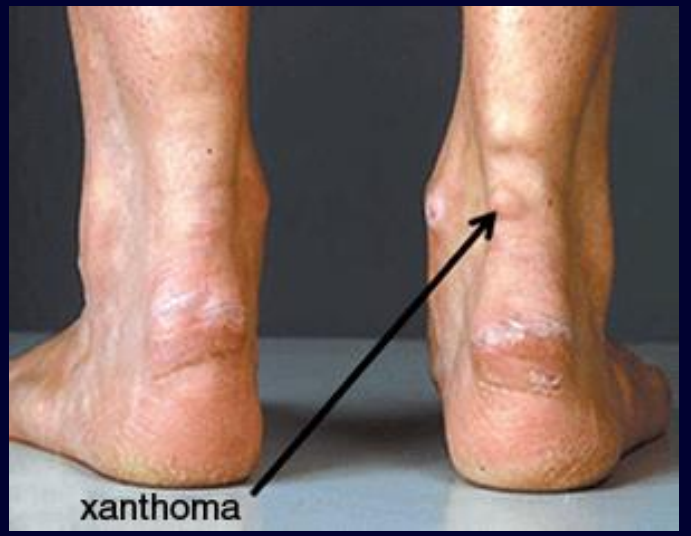
  If RF, EOD, or overt CVD, no matter age, aim for an LDL-C <70 or a >50 %. It's a fusion of multiple recommendations.

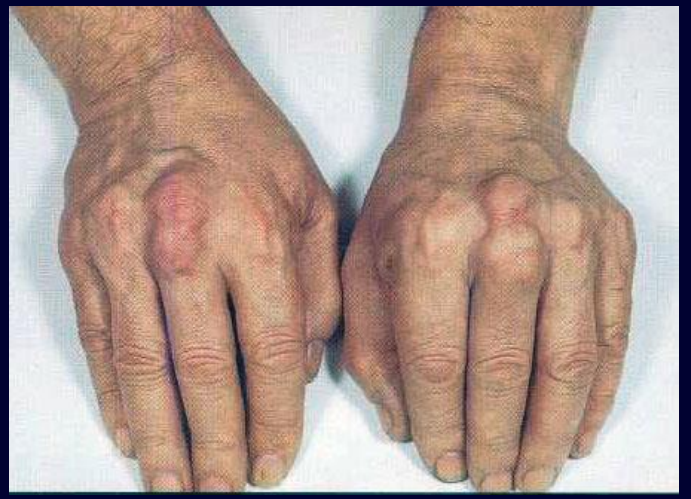
Case Study 2

- 52 y/o hispanic male came for a routine evaluation.
- He walks 45 min every day and follows a diabetic diet under nutritionist recommendations. Occasionally went to latin food restaurants where he breaks his diet.
- + Hx of HBP and DM2. Past smoker (quit 7 years ago)
- AMI 2 years ago. Upon cardiac cath 3 vessel disease and had uneventful CABG on same admission.
- Positive Fam Hx of early ASCVD in a 1st degree
- Rx: metformin 1g bid, glargine 25 units HS, losartan HCT 100/25mg QD, ASA 81 mg, clopidrogel 75mg, atenolol 50 mg QD, rosuvastatin 40 mg QD.

Case Study 2

- Physical Examination: BMI 32kg/m^2; waist 44”; BP142/85mmHg
- Healed DSW and rt leg saphenous wound, trophic skin changes in distal LE bilaterally. Tendon Xanthomas in achiles area and knuckles.
- T.Chol:191mg/dL; TG:155mg/dL; HDL:32mg/dL; LDL: 128 mg/dL; nonHDL: 159 mg/dL.
- FBS 127 mg/dL, creat 1.2 mg/dL, GFR 64 ml/min by EPI-CKD, LFT’s normal, A1C 7.5%.





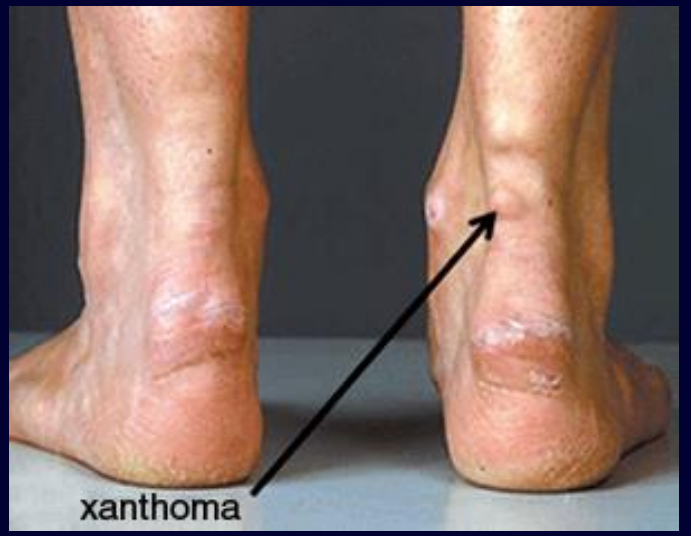
Cholesterol Calculator App

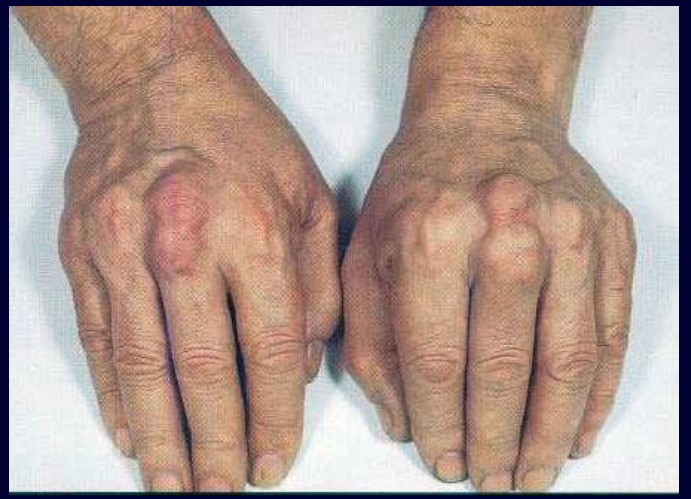
Includes:

- ***Current LDL-C***
- ***Current statin Rx***
- ***Current non statin Rx (if available)***

Case Study 2

- Physical Examination: BMI 32kg/m^2; waist 44”; BP142/85mmHg
- Healed DSW and rt leg saphenous wound, trophic skin changes in distal LE bilaterally. Tendon Xanthomas in achiles area and knuckles.
- T.Chol:191mg/dL; TG:155mg/dL; HDL:32mg/dL; LDL: 128 mg/dL; nonHDL: 159 mg/dL.
- Baseline untreated estimated LDL 269 mg/dL (not a 50% decrease from baseline with current therapy)
- FBS 127 mg/dL, creat 1.2 mg/dL, GFR 64 ml/min by EPI-CKD, LFT’s normal, A1C 7.5%.

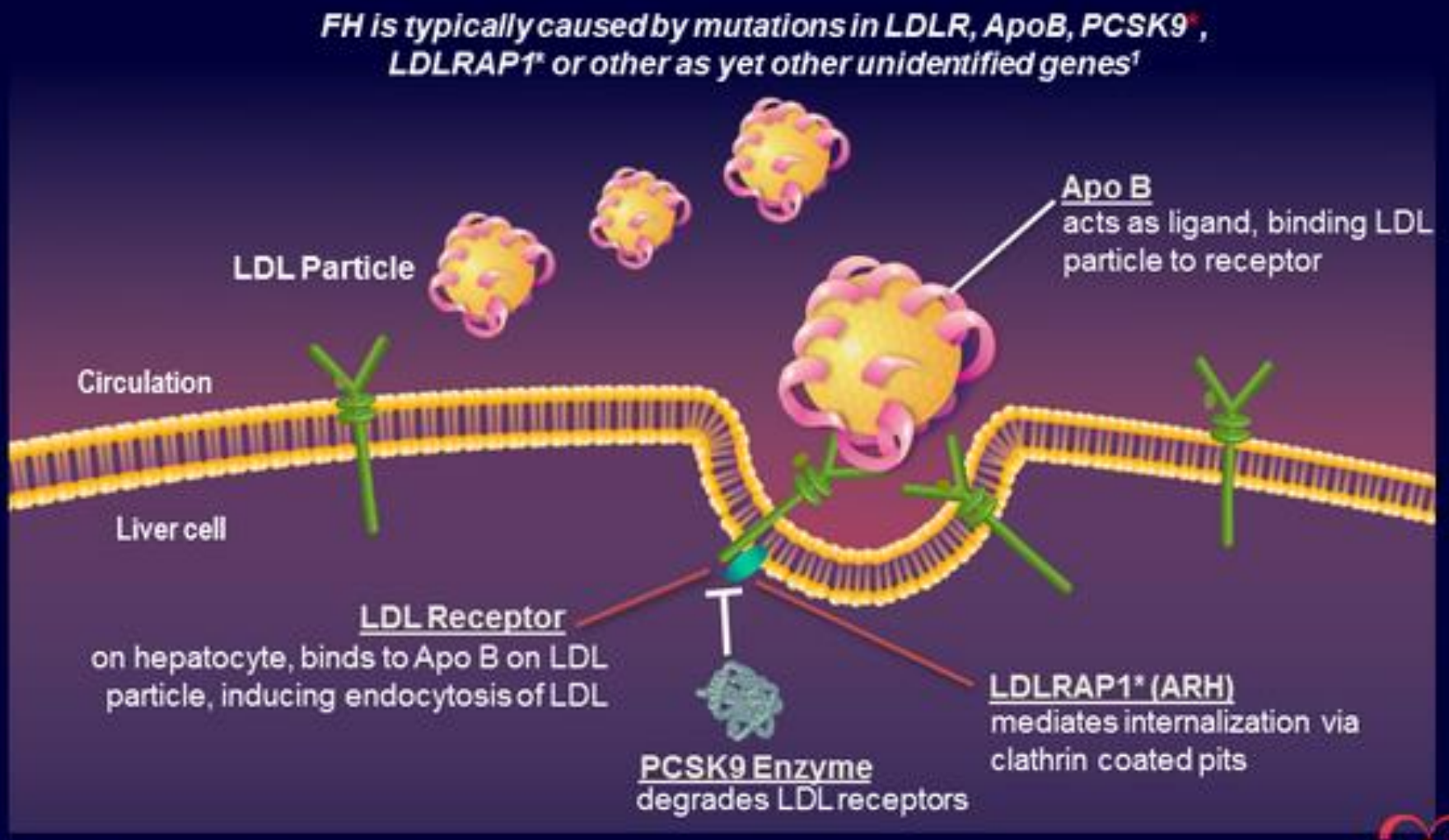




Case Study 2: What's your clinical approach?

- This patient's desirable atherogenic cholesterol levels are Non HDL < 130 mg/dL, LDL < 100 mg/dL.
- This patient may have Familia Hypercholesterolemia
- This patient has decreased LDL > 50% from baseline with high intensity statin. Will reinforce adherence and monitor.
- Further LDL lowering is not possible

FH can be caused by mutations in 4 known genes



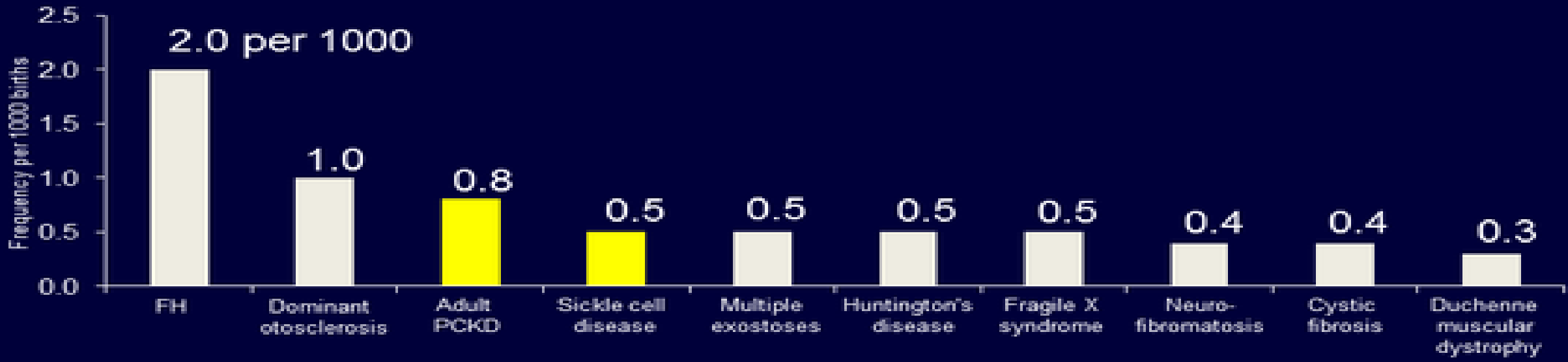
* LDLRAP1= LDL receptor adaptor protein 1.
* PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9

De Castro-Oros I, et al. *Appl Clin Genet.* 2010;3:53-64.

www.lipid.org

FH is a common inherited disorder

- The prevalence of HeFH is ~1:500[1-3]
- The prevalence of HoFH is ~1:1,000,000[2,3]



PCKD, polycystic kidney disease.

Figure adapted from Genetic Alliance UK. Available at http://www.geneticalliance.org.uk/education3.htm.

1. Citkowitz E. Familial Hypercholesterolemia. http://emedicine.medscape.com/article/121298-overview#a0199.
2. Vella A, et al. *Mayo Clin Proc*. 2001;76(10):1039-1046.
3. Austin MA, et al. *Am J Epidemiol*. 2004;160(5):407-420.

FH "Scoring Methods" for Clinical Diagnosis Require LDL Levels and Family History

Comparison of FH Clinical Diagnostic Criteria by Method

Simon Broome Register[1]	MEDPED[2]	Dutch Lipid Clinic Network[1]
Definite FH • TC or LDL levels • Tendon xanthoma in patient or relative Probable FH • TC or LDL levels • Family history of early MI or high TC/LDL	• TC or LDL levels based on family history and age (eg, age <20 y, with an FH relative)	• Score based on : ▪ Family history of premature CHD, high LDL, or xanthoma ▪ Clinical history of premature CAD or vascular disease ▪ Presence of xanthoma or arcus cornealis ▪ LDL panel

1. As summarized in: Marks D, et al. *Atherosclerosis*. 2003;168:1-14.
2. As summarized in: Civiera F, et al. *Circulation.* 2004;173:55-68.

Case Study 3

DEFINITE FAMILIAL HYPERCHOLESTEROLEMIA

Treatment Goals and Levels to Consider Drug Therapy According to Risk Category

Risk Category	Treatment Goal	Consider Drug Therapy
	Non-HDL-C mg/dL LDL-C mg/dL	
Low	<130 <100	≥190 ≥160
Moderate	<130 <100	≥160 ≥130
High	<130 <100	≥130 ≥100
Very High	<100 < 70	≥100 ≥ 70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Case Study 2: What's your next step?

- Encourage lifestyle modifications with increase fiber and plant stanol and sterol consumption.
- Order genetic testing to determine which mutation is causing HeFH.
- Add ezetimibe
- Add colesevelam
- Add PCSK9 inhibitor
- Add ER Niacin

Statin-Treated Individuals
Nonstatin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a nonstatin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - *Clinical* ASCVD <75 years of age
    - Baseline LDL-C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred

Drug Therapies – Important Considerations (continued)

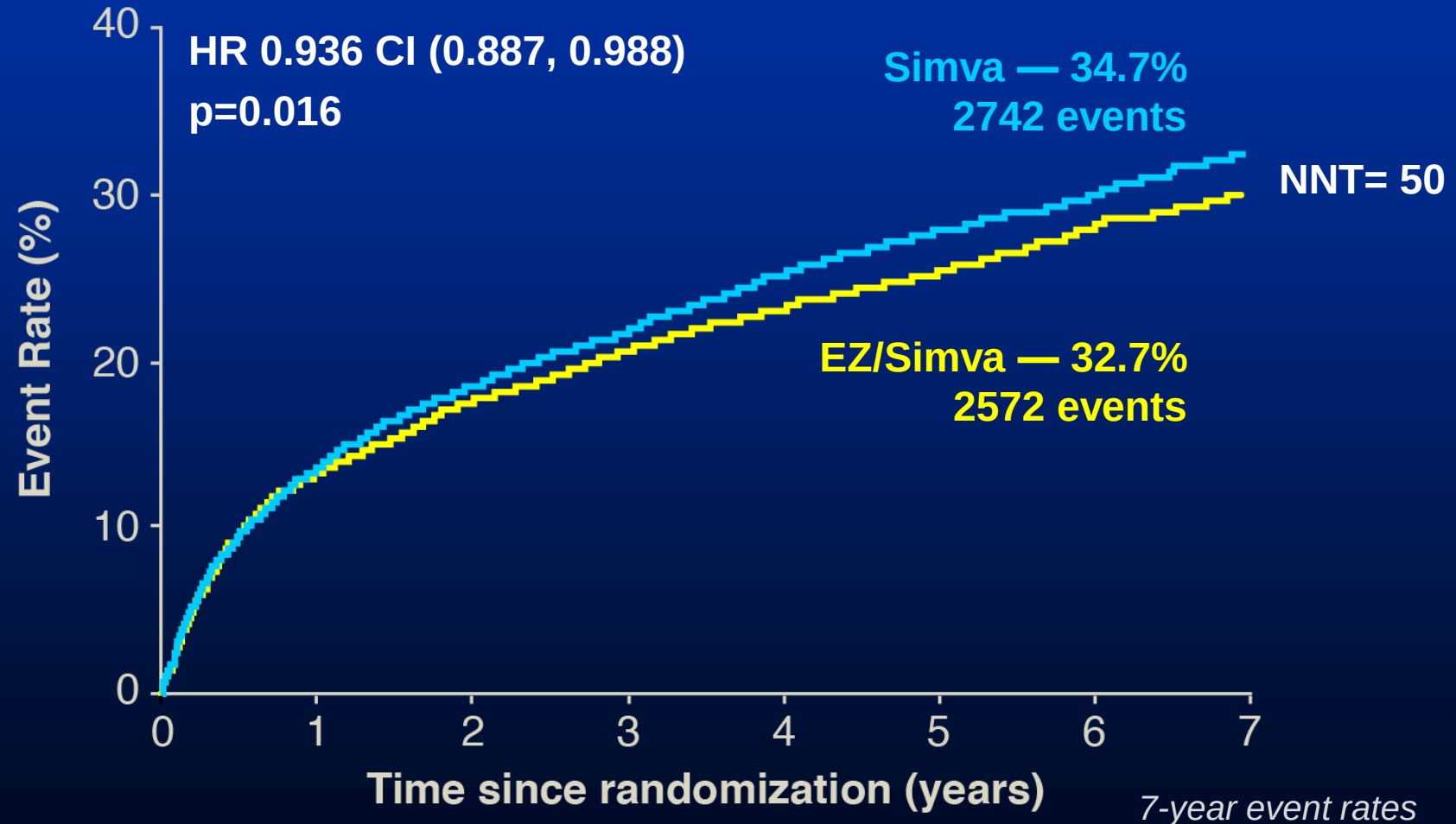
- Combination therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in those at high and very high risk. Generally, the maximally tolerated statin dose should be used before add-on therapy is considered.
- For patients with statin intolerance, reducing the dose of statin, switching to a different statin, and alternate regimens such as every other day statin dosing may be considered.
- For patients who cannot tolerate a statin using the above strategies, alternate agents alone or in combination may be considered.

FDA Pulls Approval of Niacin, Fibrate in Combo with Statins

- Based on several large cardiovascular outcome trials including AIM-HIGH, ACCORD, and HPS2-THRIVE, the FDA decided that "scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-cholesterol levels in statin-treated patients results in a reduction in the risk of cardiovascular events.
- “the FDA has determined that the benefits of niacin ER tablets and fenofibric-acid [delayed-release] capsules for coadministration with statins no longer outweigh the risks, and the approvals for this indication should be withdrawn,"

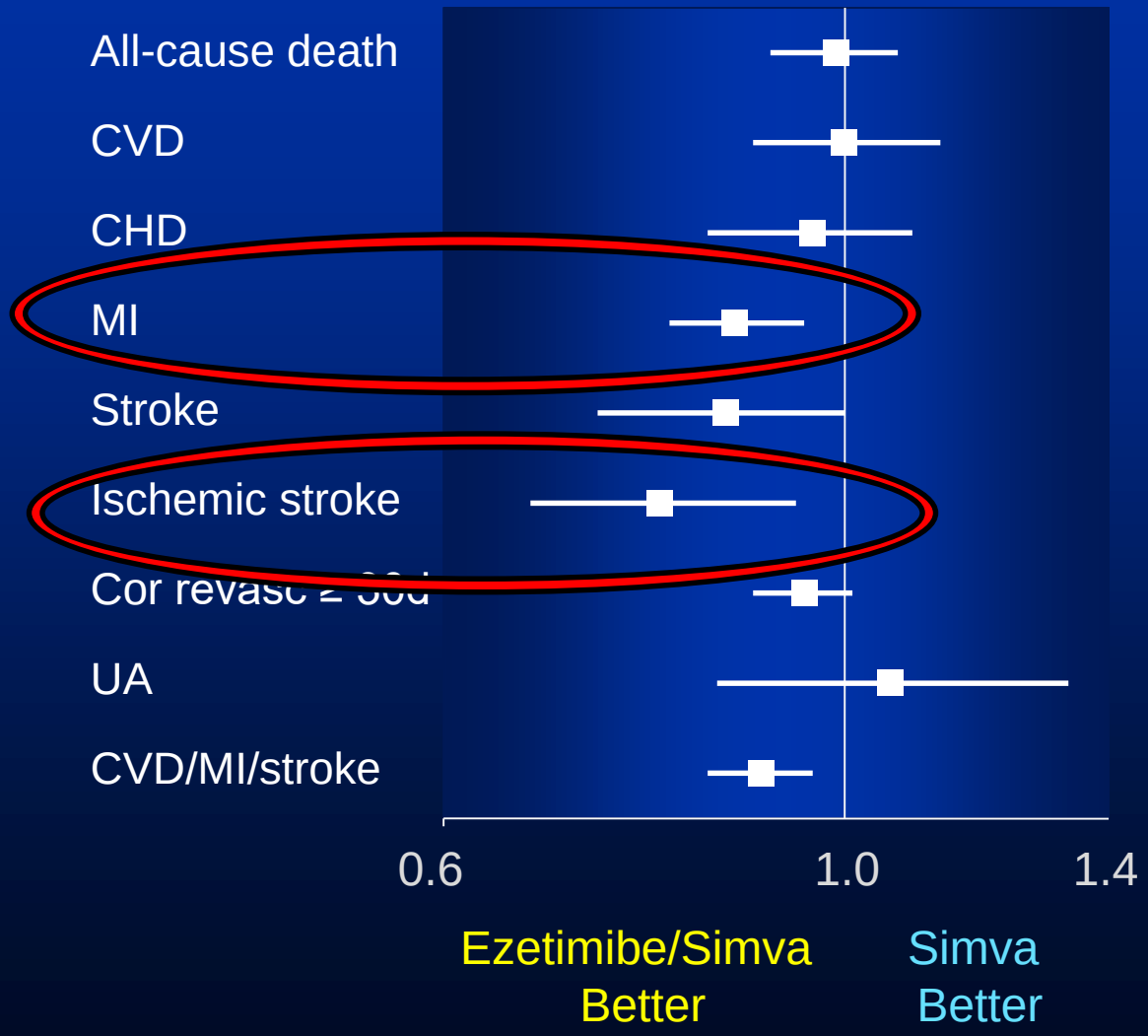
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

Individual Cardiovascular Endpoints and CVD/MI/Stroke



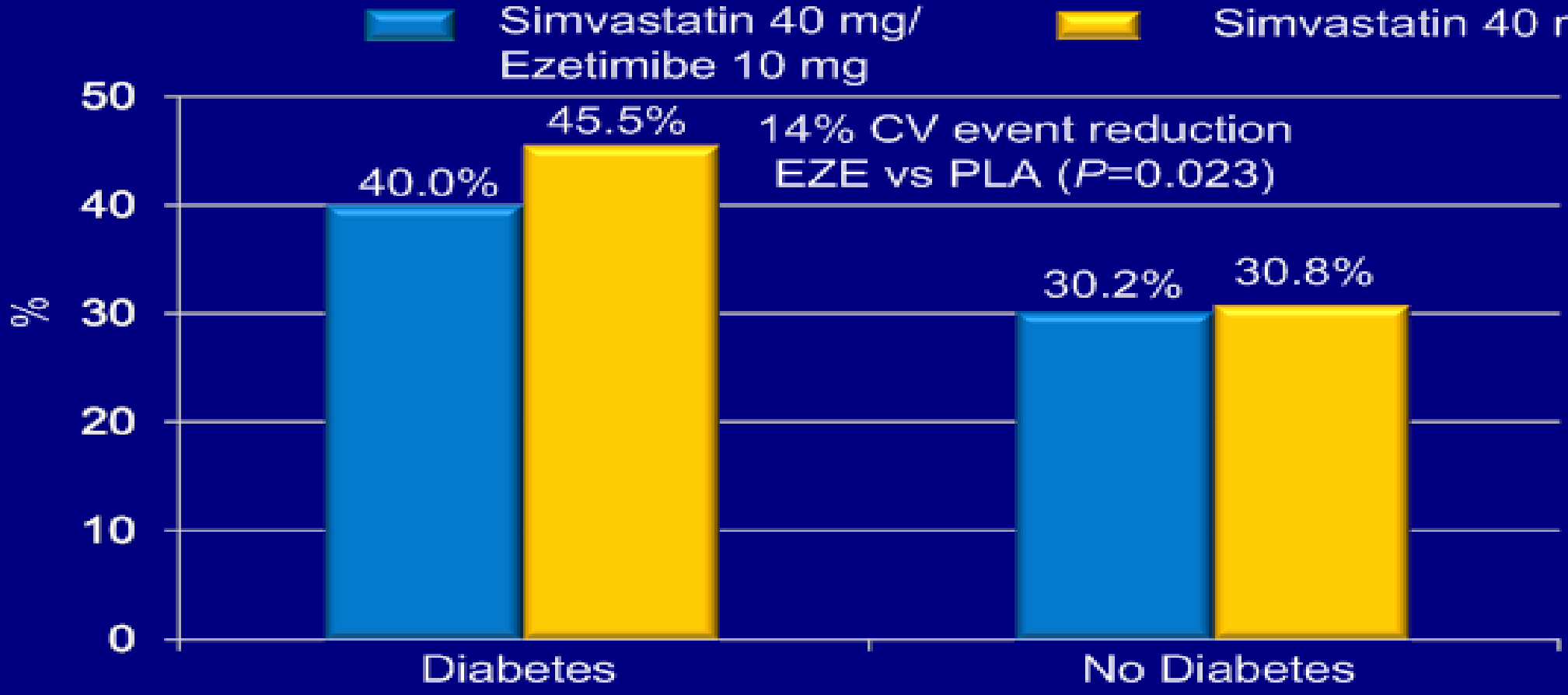
	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

**7-year event rates (%)*

IMPROVE-IT Substudy: Greater CV Event Reduction With Combo Ezetimibe Simvastatin in Diabetic Subjects

ESC Congress 2015

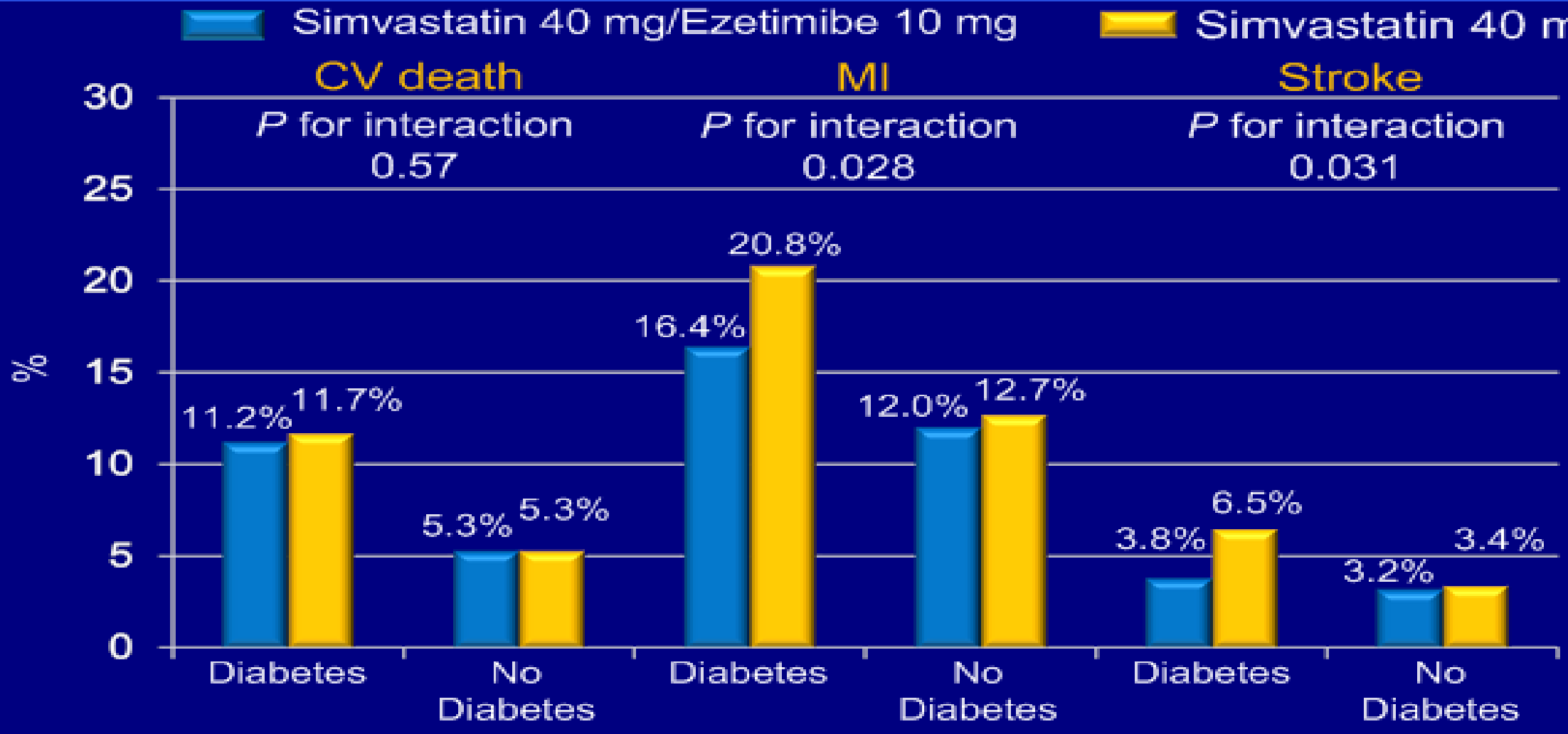
Primary endpoint: CV death, MI unstable angina requiring hospitalization, coronary revascularization*, or stroke



*After 1 month of treatment
CV=cardiovascular; MI=myocardial infarction

Giugliano RP, et al; for the IMPROVE-IT Investigators. Presented at ESC Congress 2015. London, England, UK. Abstract 1947.

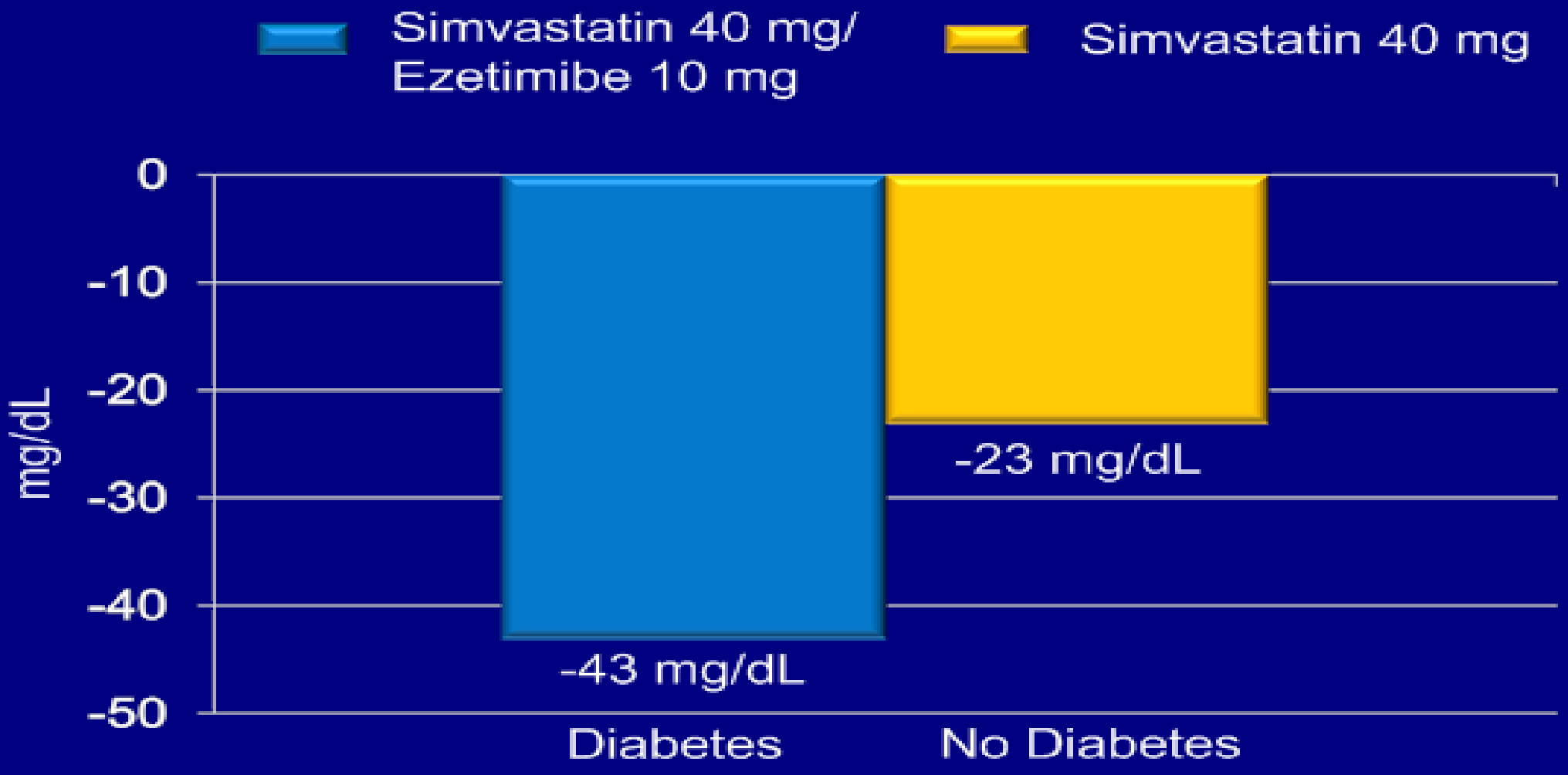
IMPROVE-IT Substudy: Greater MI & Stroke Reduction With Ezetimibe/Simvastatin in Diabetic Patients



CV=cardiovascular; MI=myocardial infarction

Giugliano RP, et al; for the IMPROVE-IT Investigators. Presented at ESC Congress 2015. London, England, UK. Abstract 1947.

IMPROVE-IT Substudy: LDL-C Reductions With Ezetimibe/Simvastatin at 1 Year



Giugliano RP, et al; for the IMPROVE-IT Investigators. Presented at ESC Congress 2015. London, England, UK. Abstract 1947.

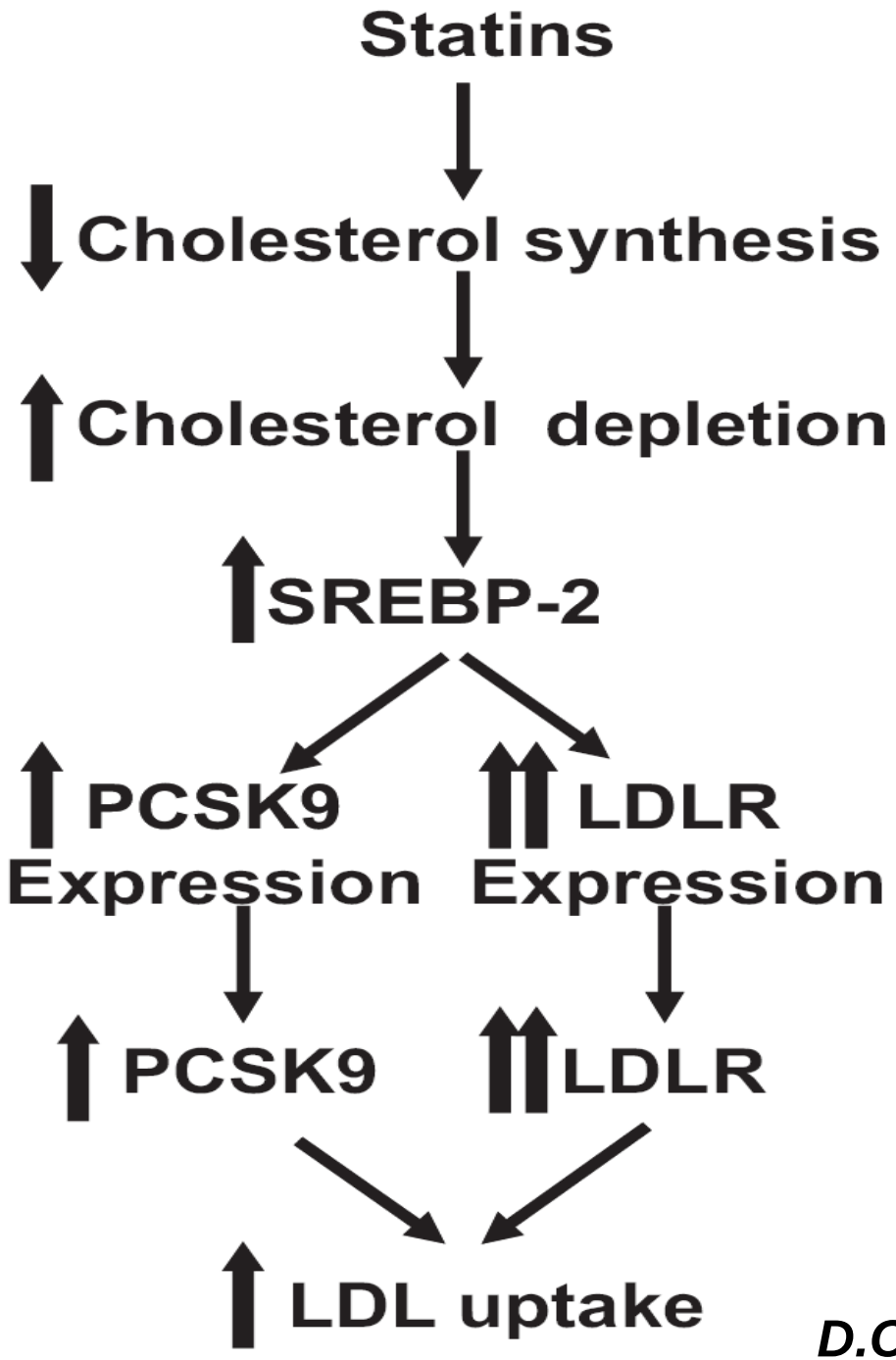
FDA Says No to Ezetimibe Secondary-Prevention Indication

- The FDA decision follows a December, 2015 vote by its Endocrinologic and Metabolic Drugs Advisory Committee ***not to recommend*** approval of the expanded indication—reduction of cardiovascular events in patients with established coronary heart disease—after reviewing the results of the IMPROVE-IT trial.

Case Study 2: What further LDL lowering?

- Encourage lifestyle modifications with increase fiber and plant stanol and sterol consumption ↓ **10%**
- Add ezetimibe ↓ **20%**
- Add colesevelam ↓ **16%**
- Add ER Niacin ↓ **17%**

PATIENT NEEDS ABOUT 46% further decrease in LDL on top of high intensity statin to reach optimal levels



Regulation of Proprotein Convertase Subtilisin/Kexin type 9

D.C. Chan/Atherosclerosis, 2011, in press

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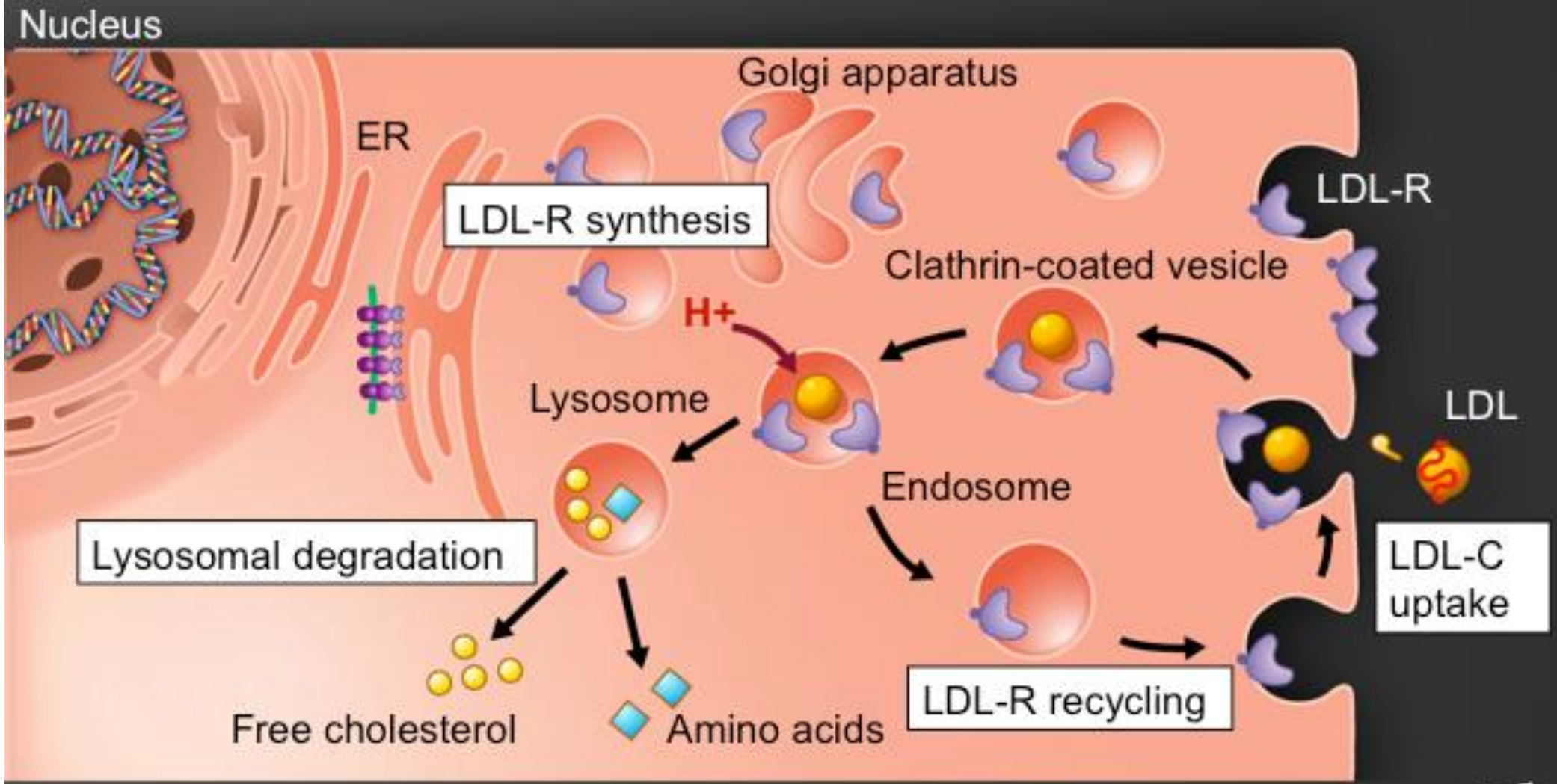
LDL-C is removed from the circulation via the LDL-R



Adapted from Jeon H & Blacklow SC, *Ann Rev Biochem* 2005;74:535-62

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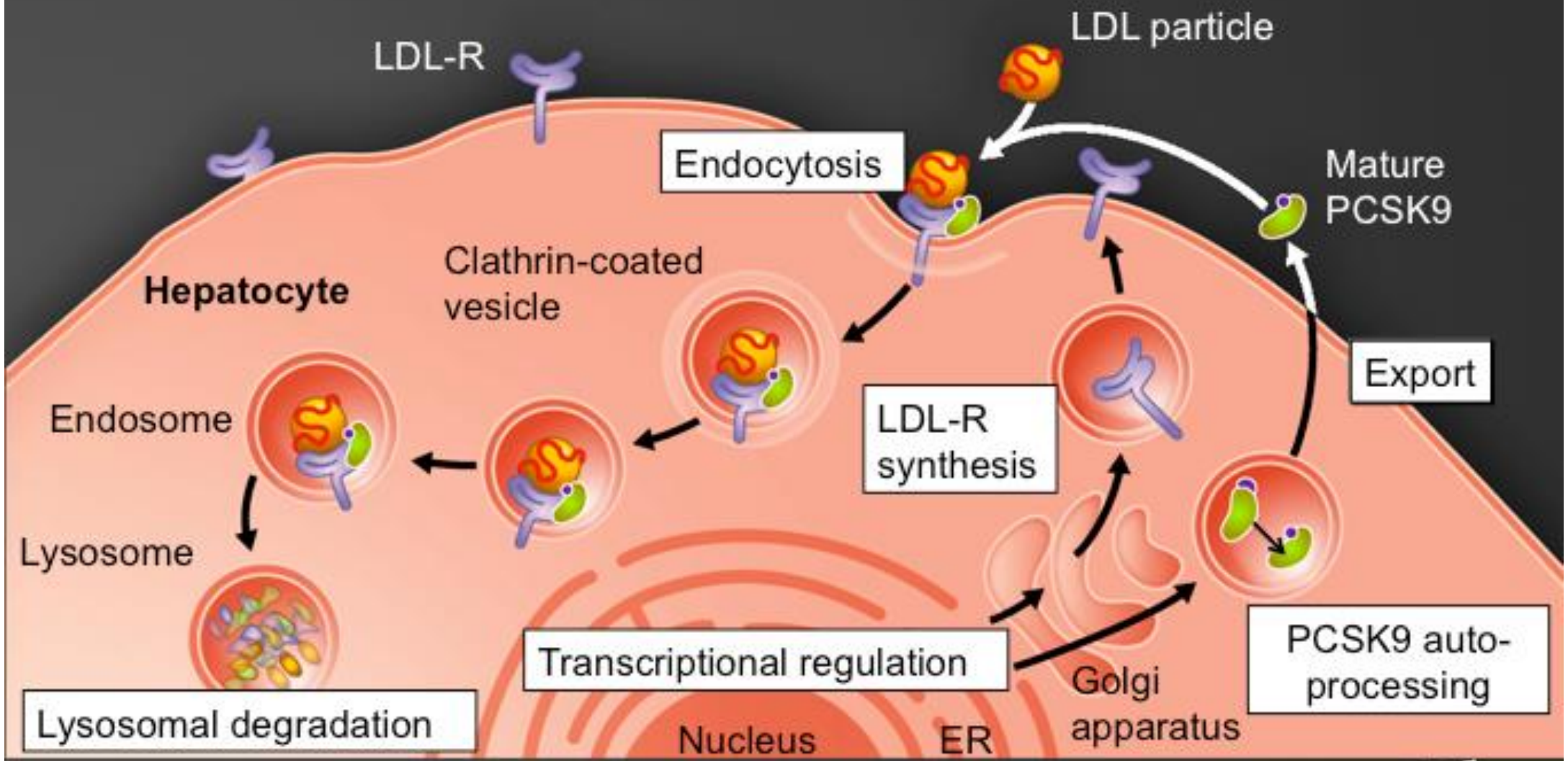
PCSK9: A natural promoter of LDL-R degradation



Adapted from Lambert G, *et al. J Lipid Res.* 2012; 53:2515-24

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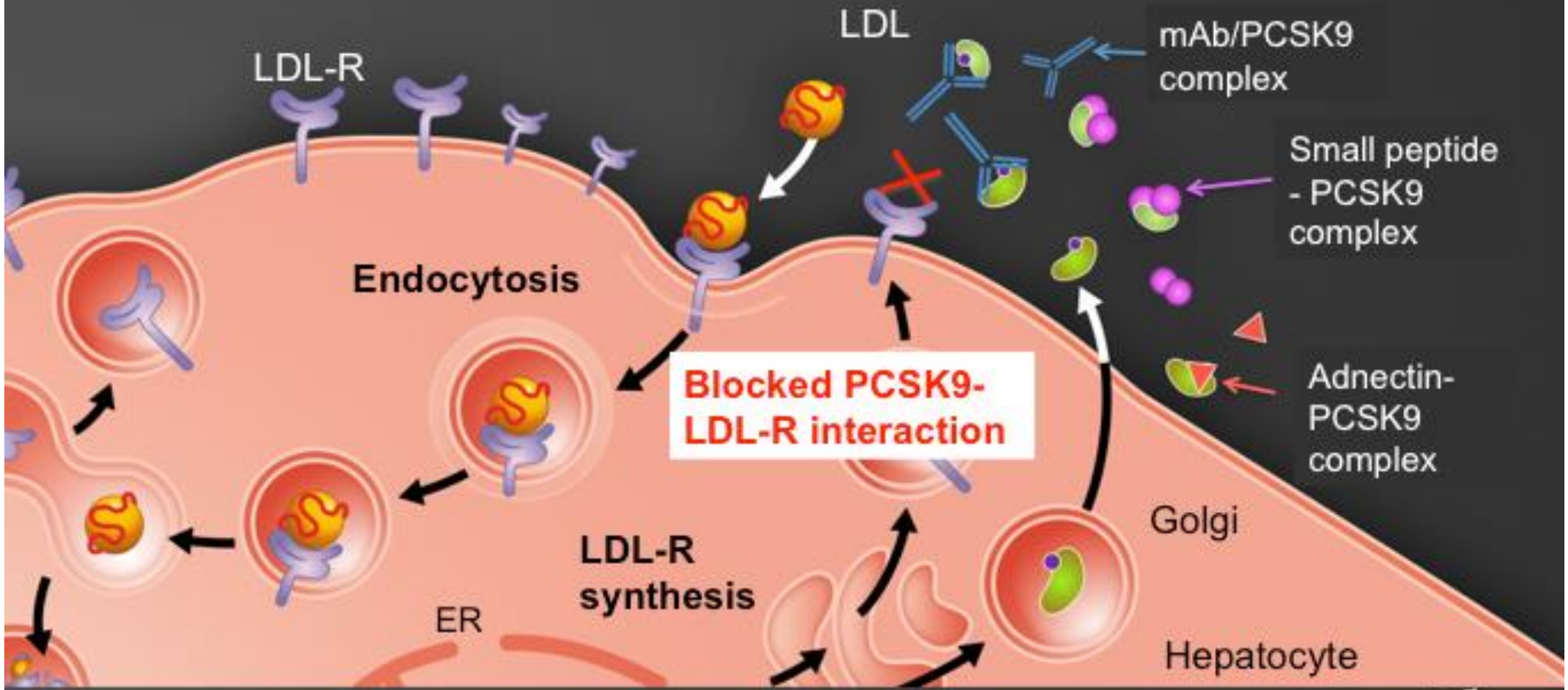
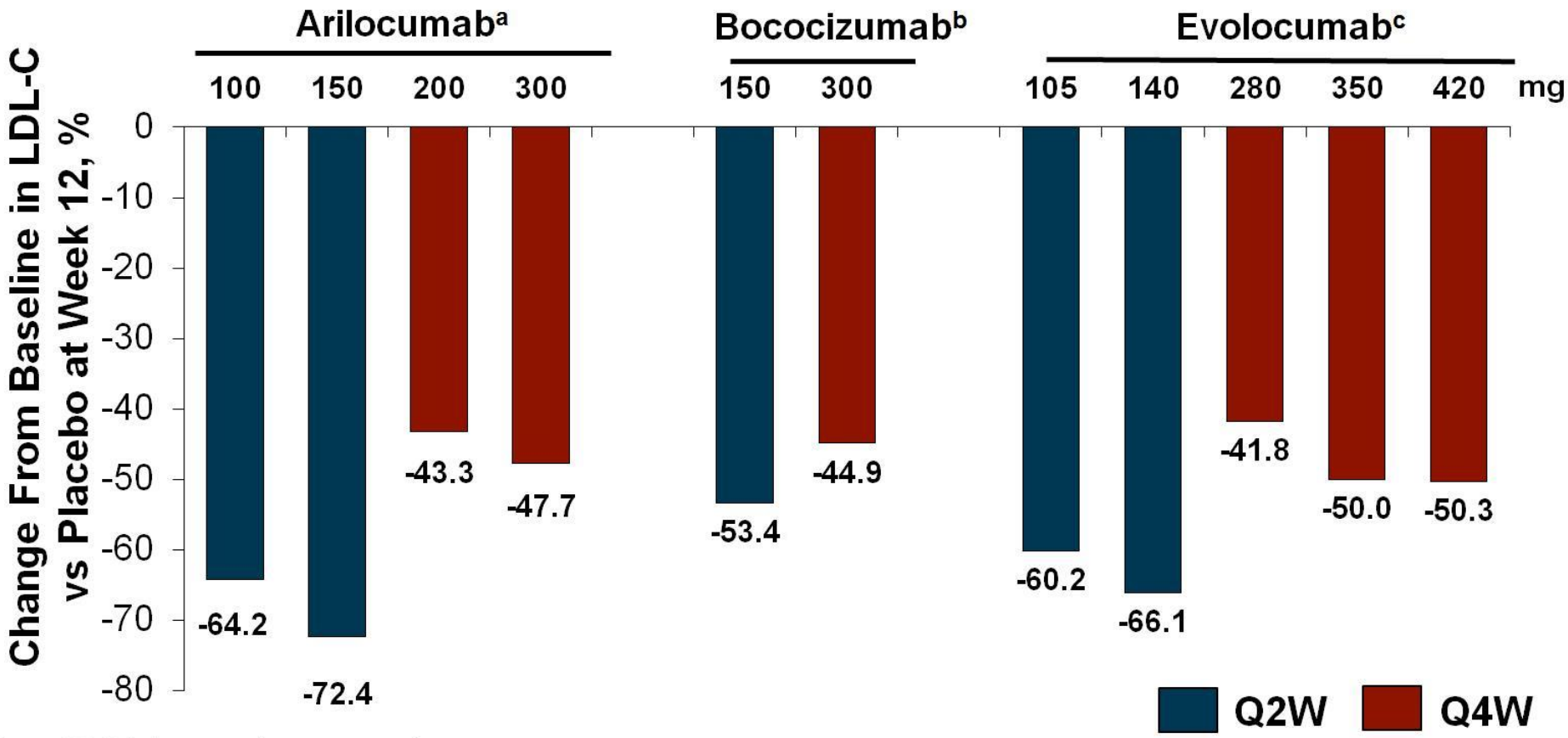
Inhibiting PCSK9/LDL-R interactions: Mimetic small peptides, mAbs and adnectins



Adapted from Lambert G, *et al. J Lipid Res.* 2012; 53:2515-24
Seidah NG, *et al. Nature Review Drug Discov.* 2012:367-83

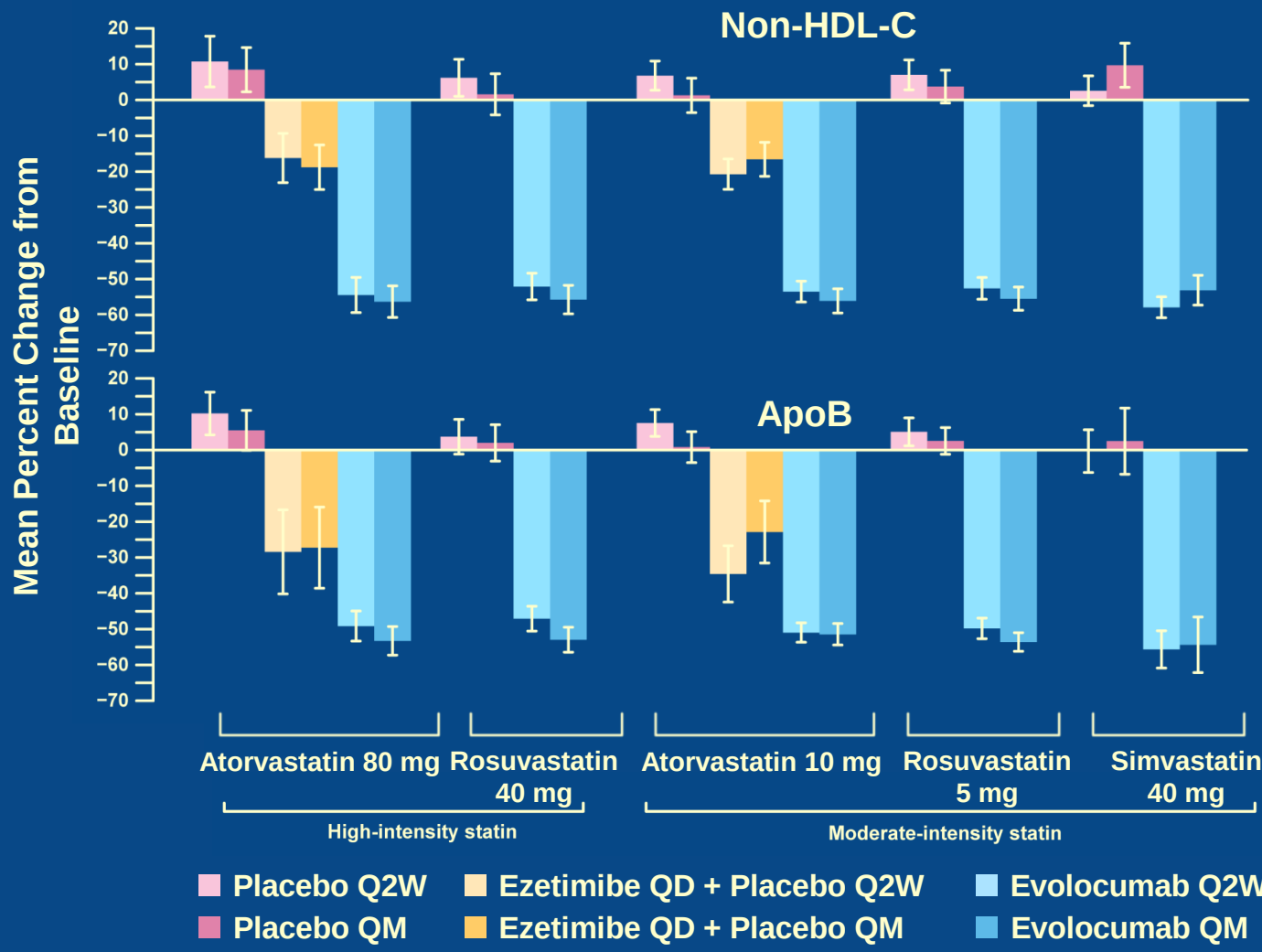
PCSK9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy



P < .0001 for each comparison.

a. McKenney JM, et al. *J Am Coll Cardiol*. 2012;59:2344-2353[9] b. Ballantyne CM, et al. *J Am Coll Cardiol*. 2014;63:A1374[10]; c. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017.[11]

LAPLACE-2: Other Lipids at Mean Weeks 10/12



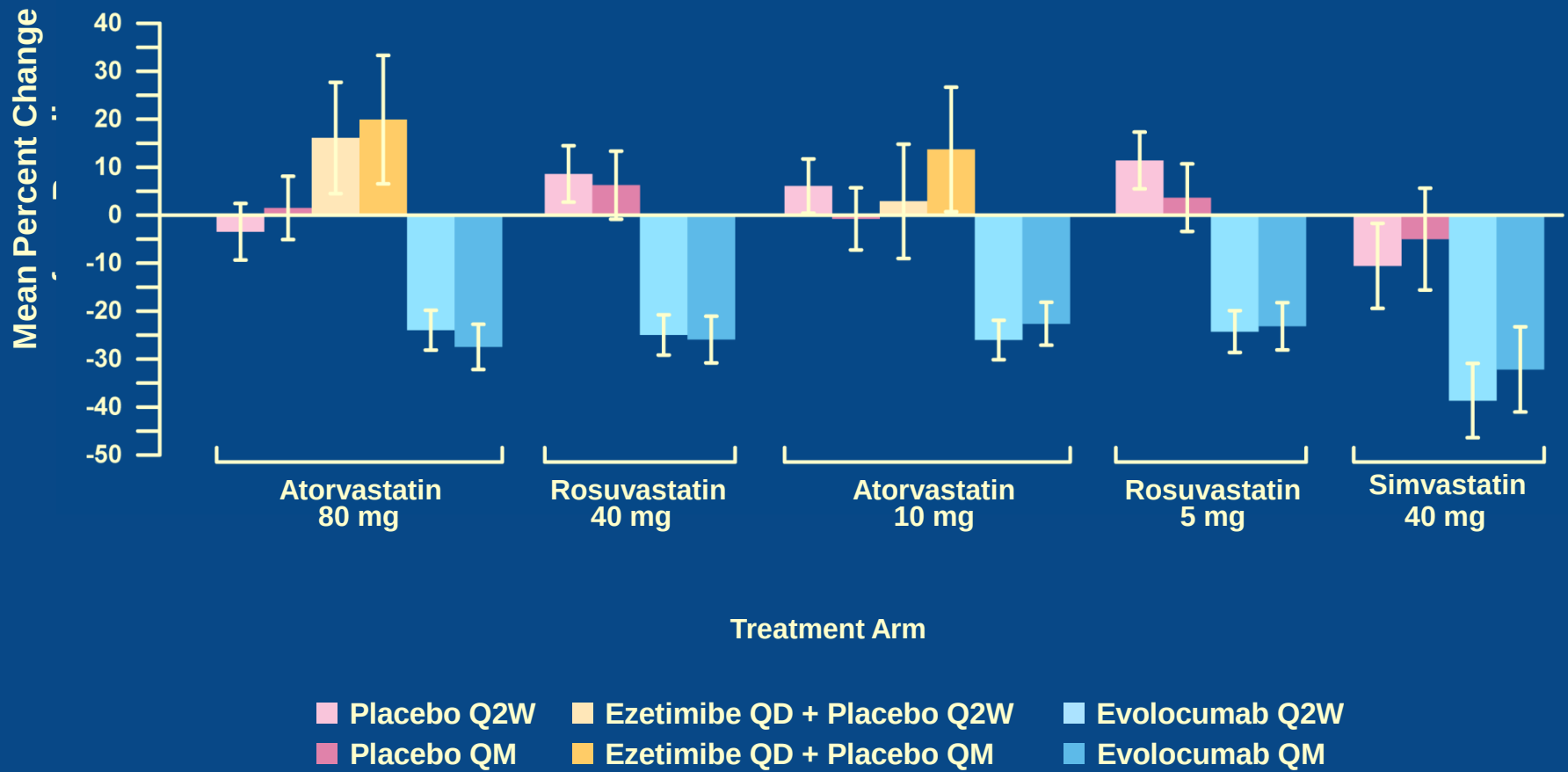
Q2W **–58 to –65%** vs placebo

Q2W **–51 to –59%** vs placebo

All treatment differences vs placebo and ezetimibe were statistically significant (P<0.05). Vertical lines represent 95% CIs.
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone. Non-HDL-C, non high-density lipoprotein cholesterol; ApoB, apolipoprotein B; Q2W, biweekly; QM, monthly.

LAPLACE-2: Other Lipids at Mean Weeks 10/12

Lipoprotein (a) Q2W **–21 to –36%** vs placebo



All treatment differences vs placebo and ezetimibe were statistically significant (P<0.05).
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.
Vertical lines represent 95% CIs. Q2W, biweekly; QM, monthly.

LAPLACE-2: Safety and Tolerability

n (%)	Any Statin + Placebo (N = 558)	Atorvastatin + Ezetimibe (N = 221)	Any Statin + Evolocumab (N = 1117)
Treatment-emergent AEs	219 (39)	89 (40)	406 (36)
Most common AEs[a]			
Back pain	14 (3)	7 (3)	20 (2)
Arthralgia	9 (2)	4 (2)	19 (2)
Headache	15 (3)	5 (2)	19 (2)
Muscle spasms	6 (1)	6 (3)	17 (2)
Pain in extremity	7 (1)	3 (1)	17 (2)
Serious AEs	13 (2)	2 (1)	23 (2)
AEs leading to study drug discontinuation	12 (2)	4 (2)	21 (2)
Deaths	1 (0.2)	0 (0)[b]	0 (0)
CK > 5 x ULN	2 (0.4)	0 (0)	1 (0.1)
ALT or AST > 3 x ULN	6 (1)	3 (1)	4 (0.4)
Potential injection site reactions[c]	8 (1)	2 (1)	15 (1)
Neurocognitive AEs			
Cognitive deterioration	0 (0)	1 (0.5)	0 (0)
Disorientation	0 (0)	1 (0.5)	0 (0)
Post-baseline binding antibodies	NA	NA	1 (0.1)[d]

[a] Top 5 in evolocumab treatment group. [b] One subject died after the end of study. [c] Reported using high-level term groupings which included injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria.
[d] Binding antibody was present at baseline and at the end of study. No neutralizing antibodies were detected.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2

Until cardiovascular outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered primarily in:

- 1) patients with ASCVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy
- 2) heterozygous FH patients without ASCVD who have LDLC ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy.

Strenght of Recommendation B ; Moderate Quality of Evidence

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2

- In addition, PCSK9 inhibitor use may be considered for selected high risk patients with ASCVD (e.g., recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]).
- Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.

Strenght of Recommendation C ; Low Quality of Evidence

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2

- PCSK9 inhibitor use may also be considered in selected high or very high risk patients who meet the definition of statin intolerance and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies. Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.

Strenght of Recommendation C ; Low Quality of Evidence

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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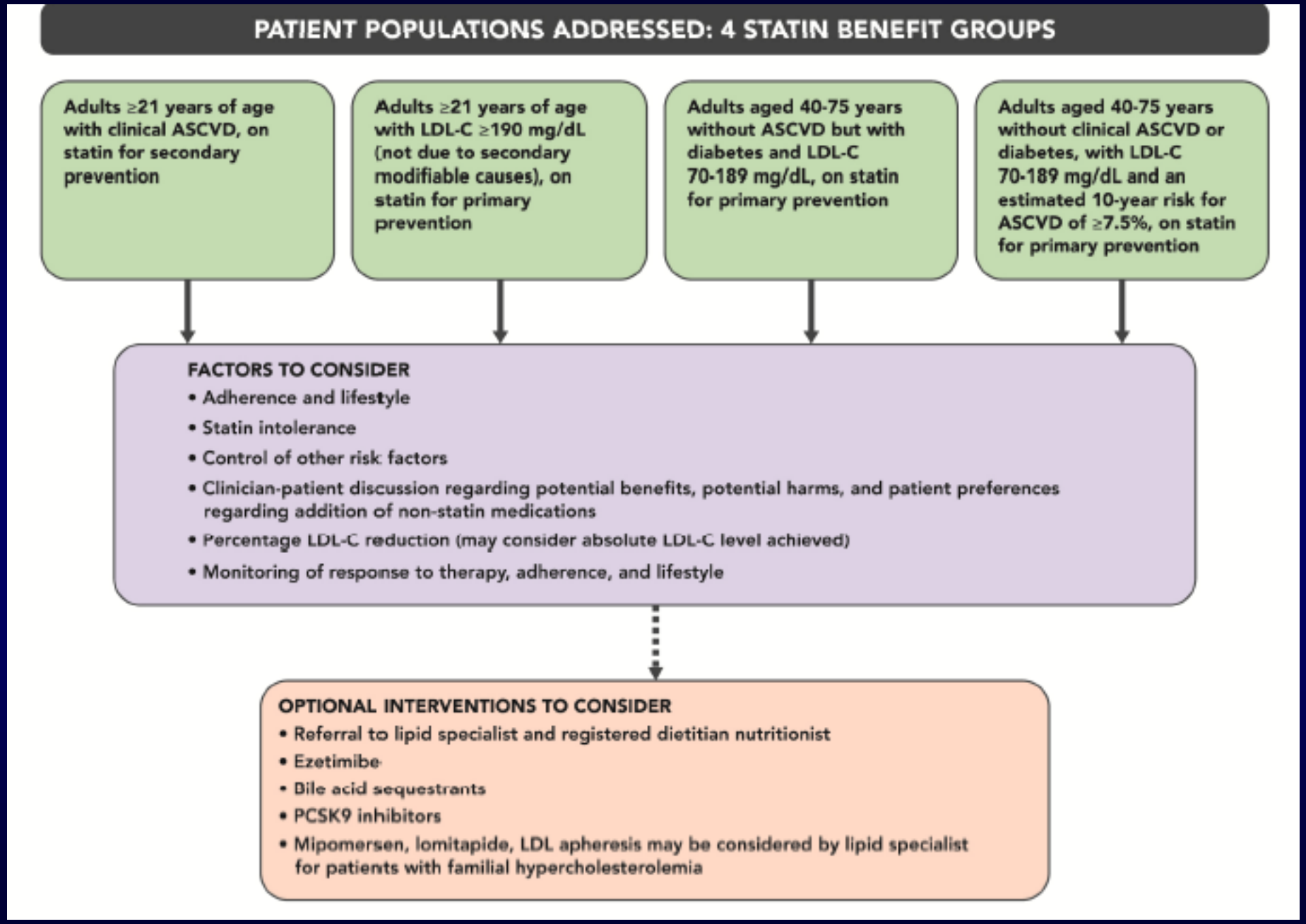
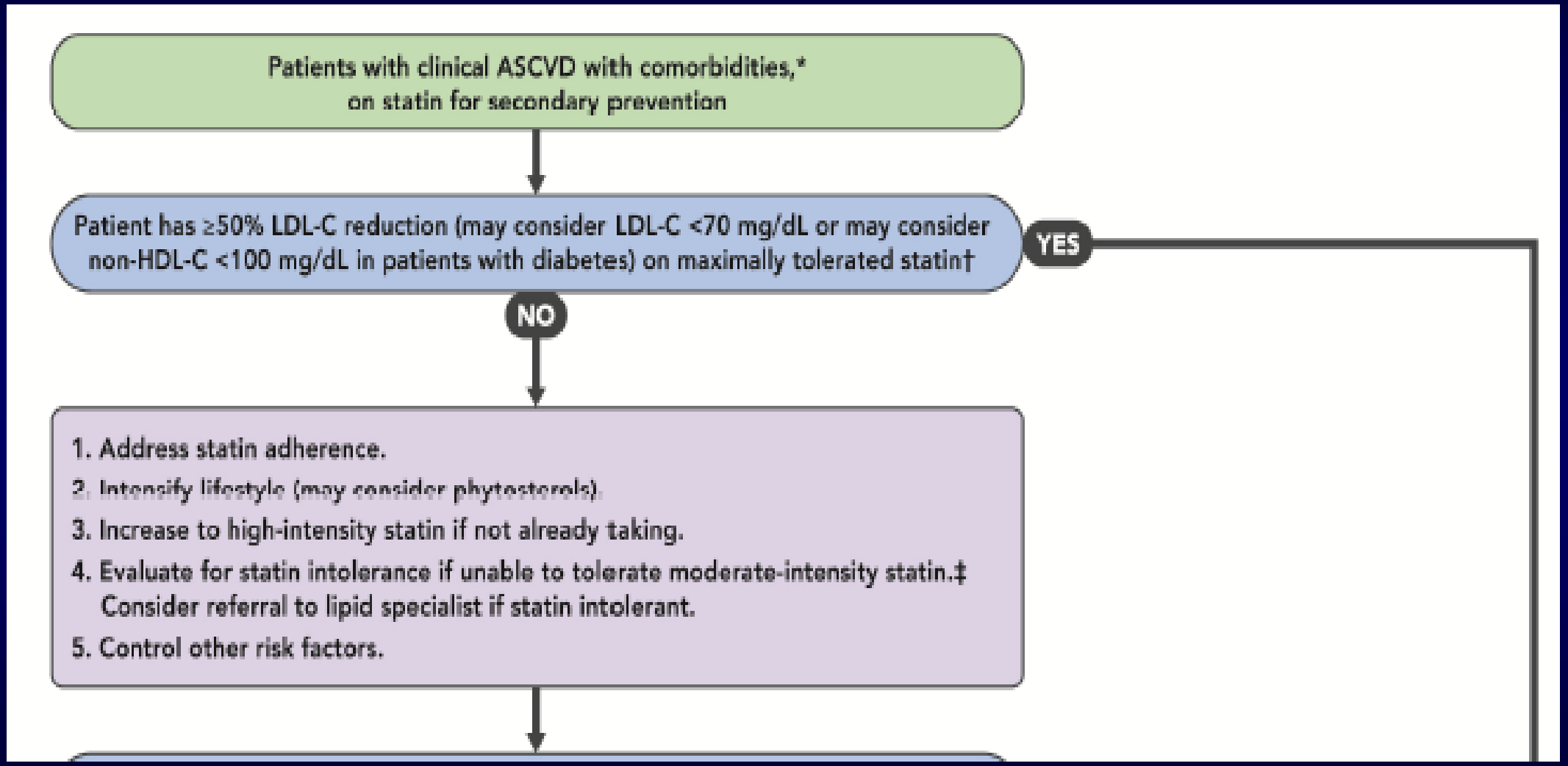
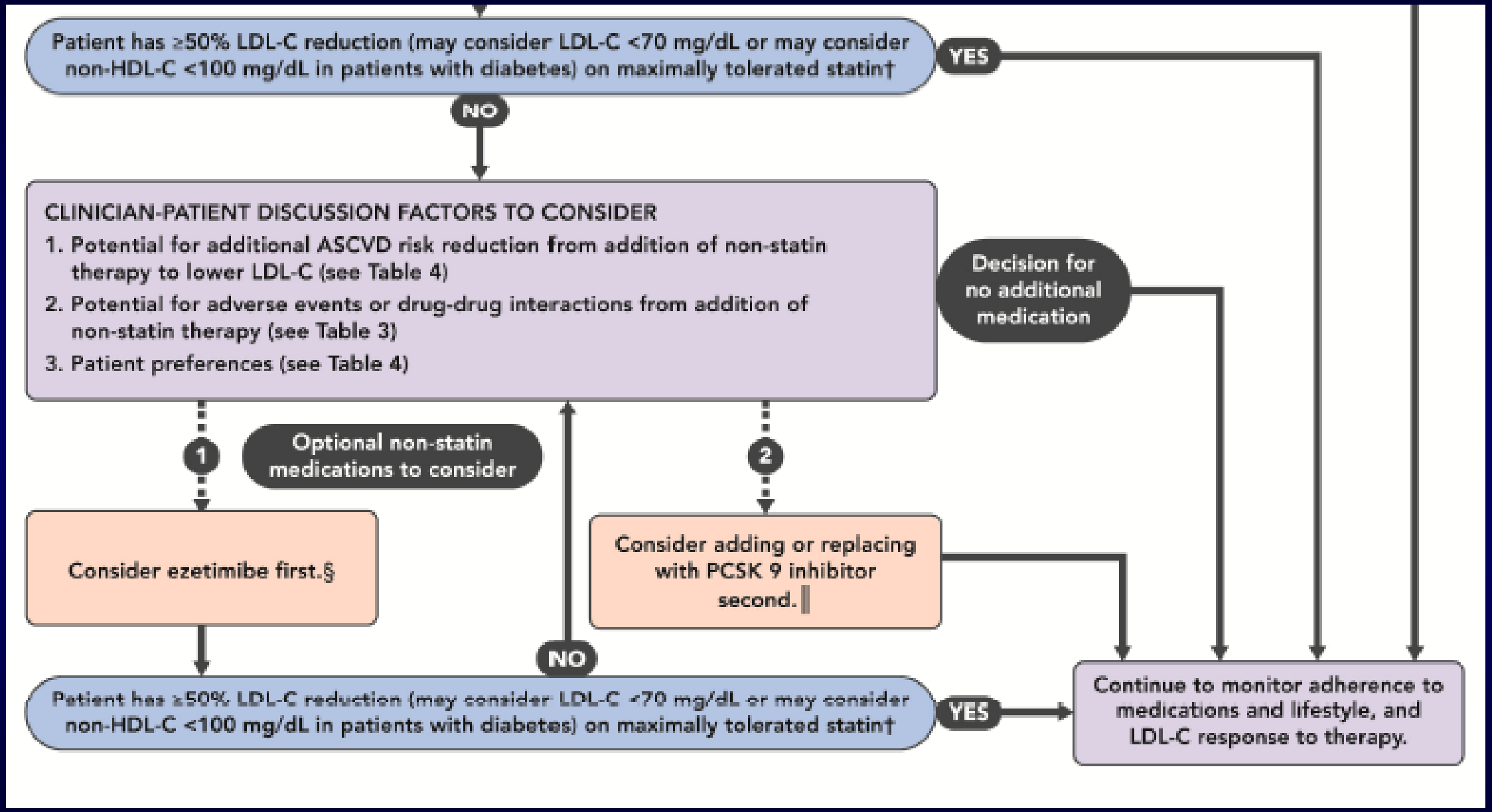
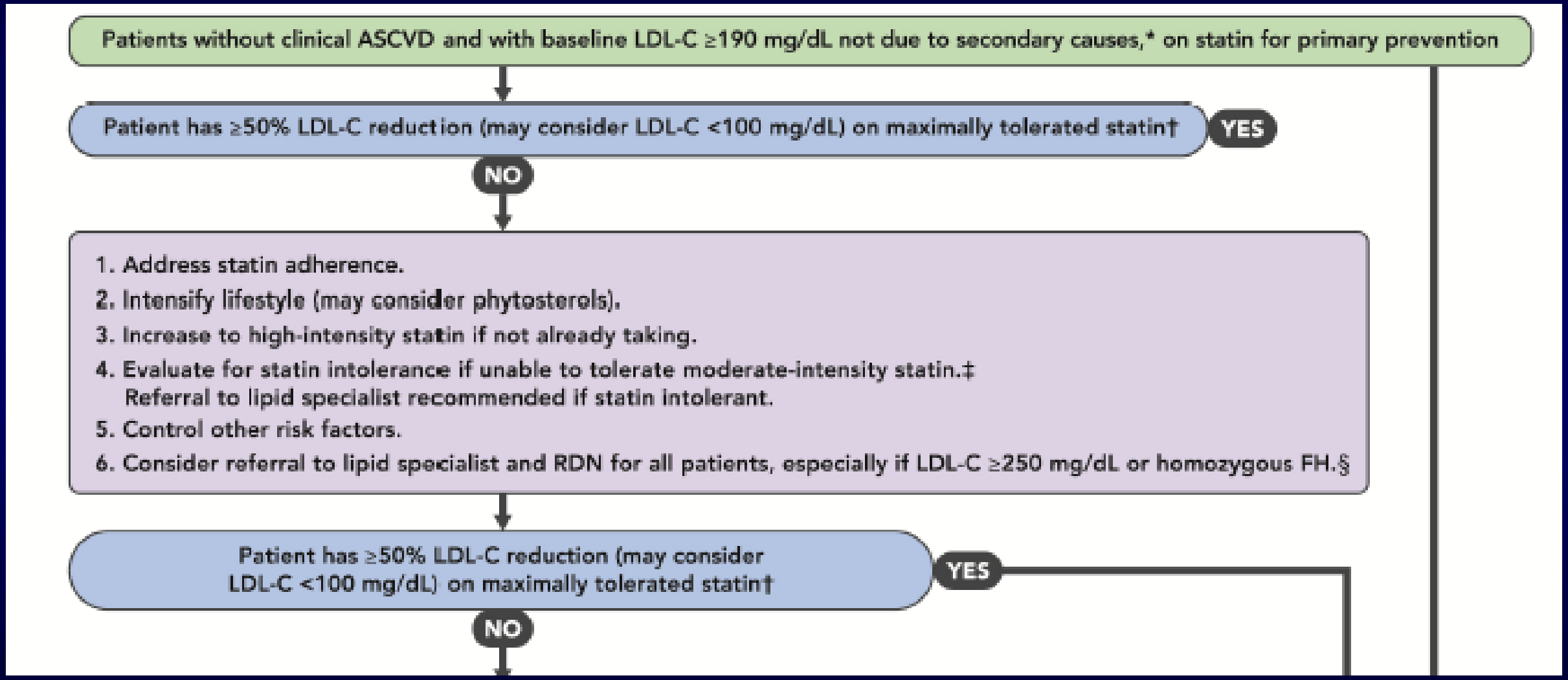

PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS
Adults ≥21 years of age with clinical ASCVD, on statin for secondary prevention
Adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention
Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention
Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention
FACTORS TO CONSIDER
• Adherence and lifestyle
• Statin intolerance
• Control of other risk factors
• Clinician-patient discussion regarding potential benefits, potential harms, and patient preferences regarding addition of non-statin medications
• Percentage LDL-C reduction (may consider absolute LDL-C level achieved)
• Monitoring of response to therapy, adherence, and lifestyle
OPTIONAL INTERVENTIONS TO CONSIDER
• Referral to lipid specialist and registered dietitian nutritionist
• Ezetimibe
• Bile acid sequestrants
• PCSK9 inhibitors
• Mipomersen, lomitapide, LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia

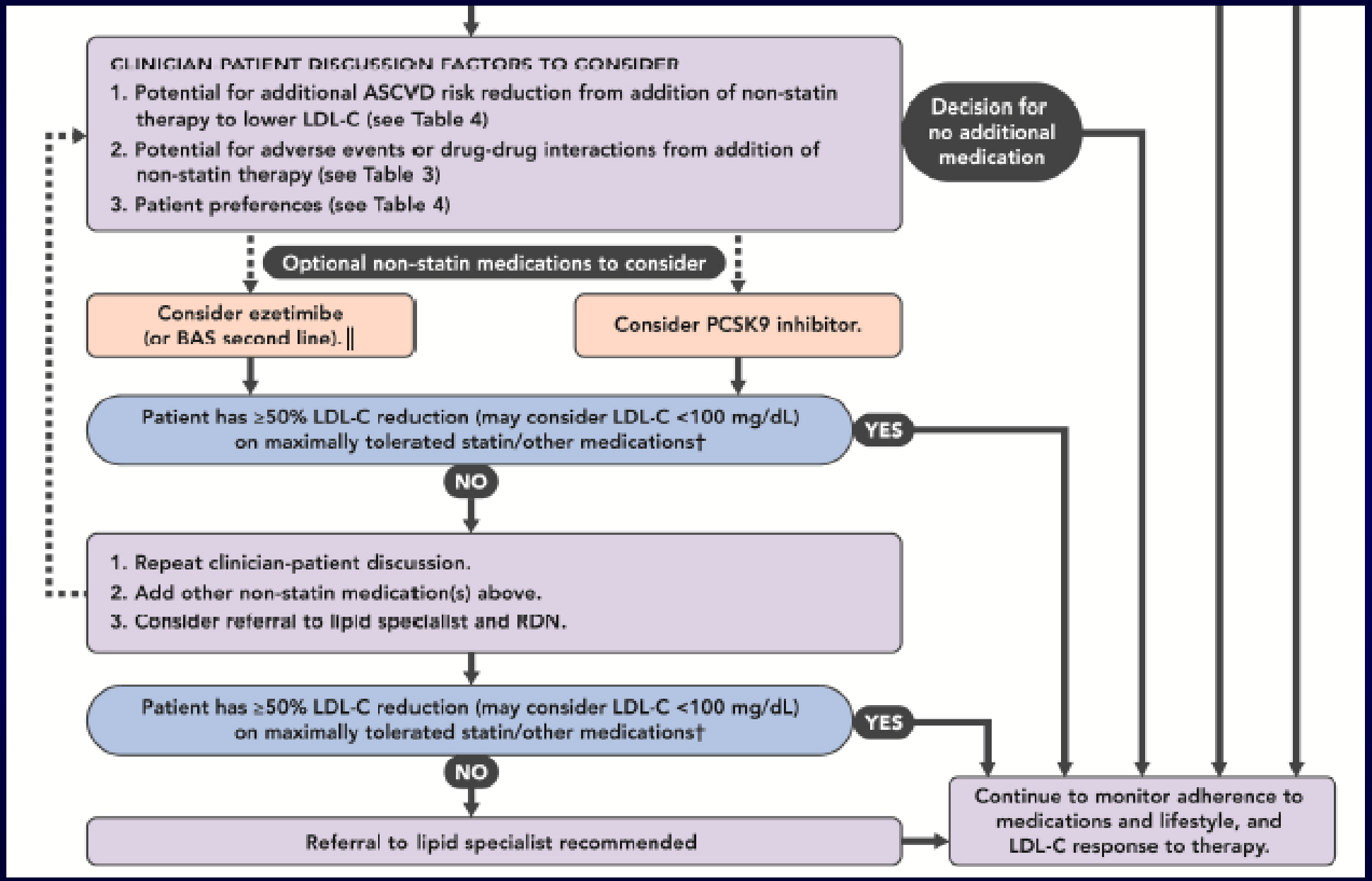
ASCVD with comorbidities on statin 2ry prevention



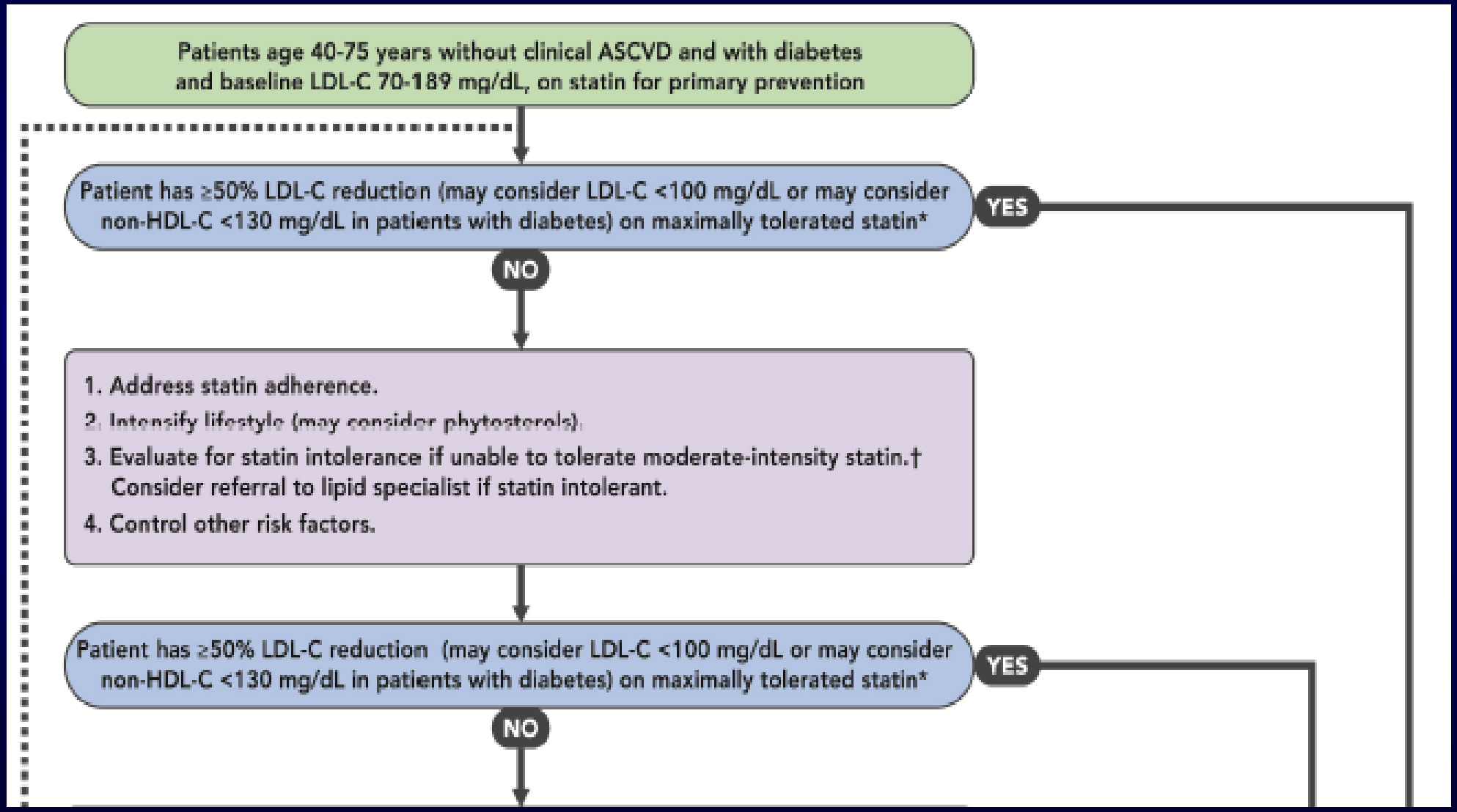

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†
YES
NO
CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)
Decision for no additional medication
1
Optional non-statin medications to consider
2
Consider ezetimibe first.§
Consider adding or replacing with PCSK 9 inhibitor second.‖
NO
Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†
YES
Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

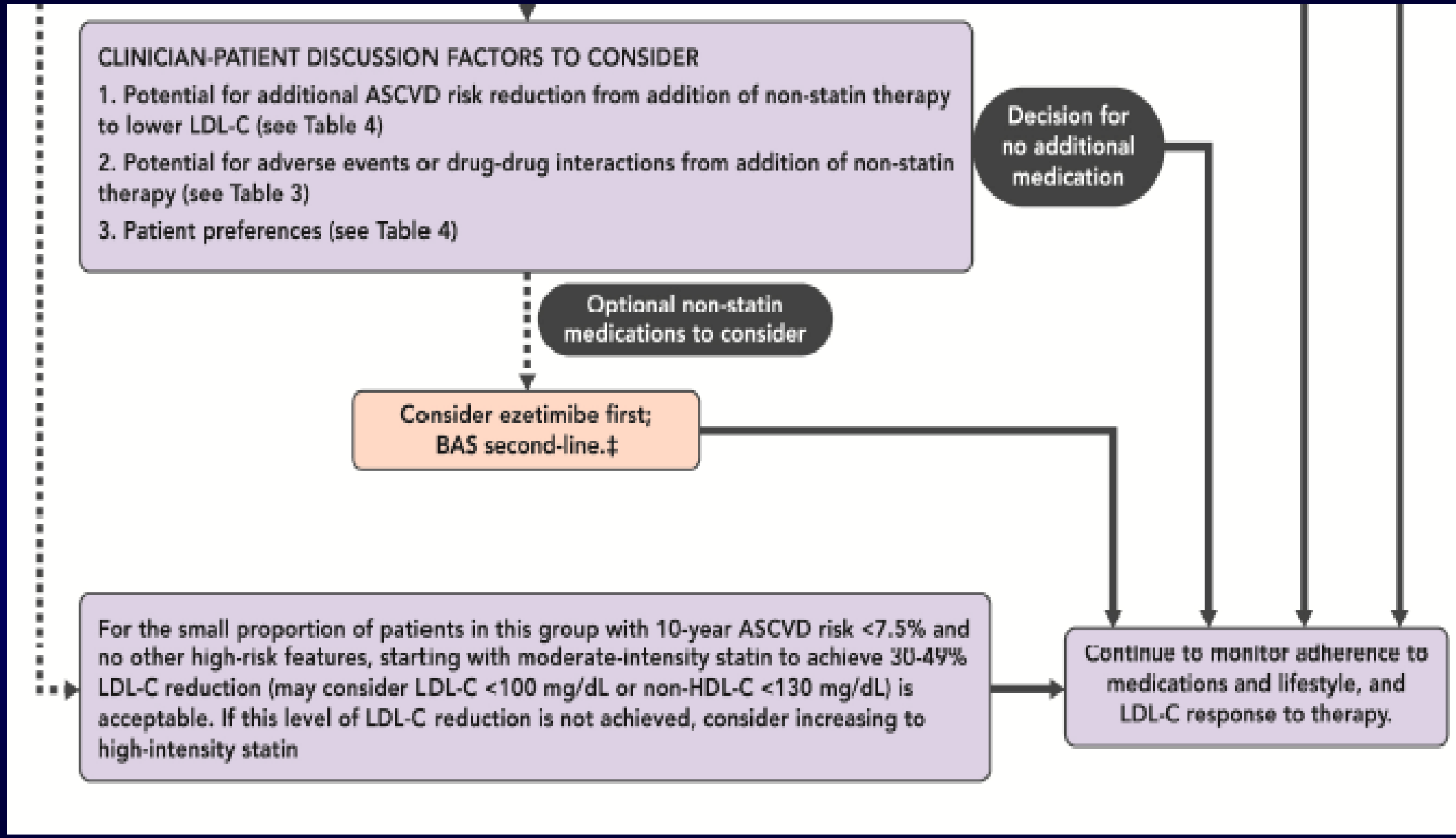
No ASCVD, LDL > 190 (w/o 2ry causes) on statin 1ry prevention




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 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)
Decision for no additional medication
Optional non-statin medications to consider
Consider ezetimibe (or BAS second line).‖
Consider PCSK9 inhibitor.
Patient has ≥50% LDL-C reduction (may consider LDL-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 <100 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.

40 -75 y/o, no ASCVD, with DM, LDL 70-189 on statin 1ry 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 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)
Decision for no additional medication
Optional non-statin medications to consider
Consider ezetimibe first; BAS second-line.‡
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.

Case Study 2: What's your next step?

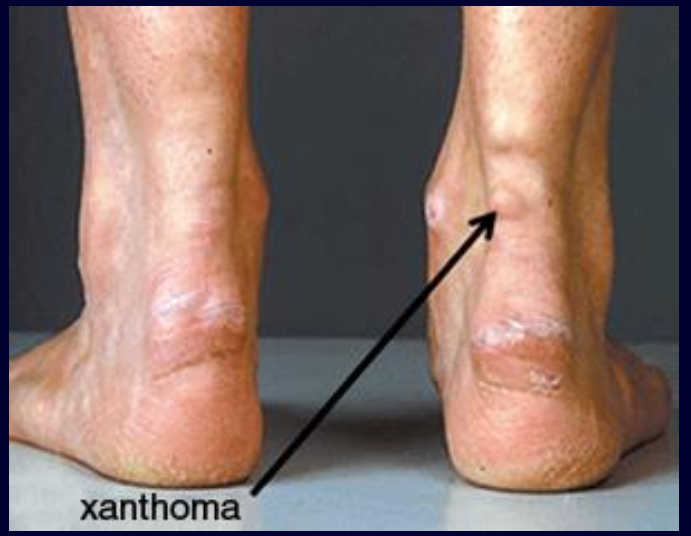
- Encourage lifestyle modifications with increase fiber and plant stanol and sterol consumption.
- Order genetic testing to determine which mutation is causing HeFH.
- Add ezetimibe
- Add colesevelam
- Add PCSK9 inhibitor
- Add ER Niacin

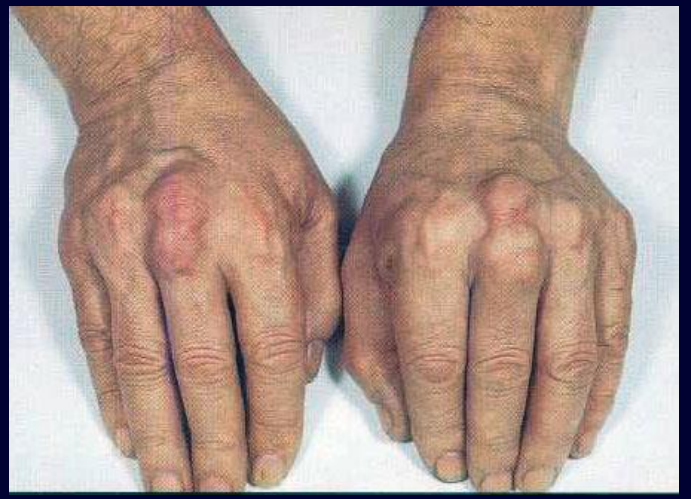
Case Study 2: Treatment

- Started on SC injection of PCSK9i Q2W on top of high intensity statin. TLC's encouraged.
- After 3 months:

  LDL-C 62 mg/dL (50%reduction)

  nonHDL-C 64 mg/dL (60% reduction)





Conclusions

- The use of high intensity statin therapy should be encouraged in the setting of ASCVD as stated in the new guidelines including diabetes. This approach was adapted on new ADA recommendations but not AACE.
- Despite lack of data from RCT about lipoprotein goals, atherogenic lipoprotein (LDL-C and non HDL-C) levels serve as a guide for patients and physicians to make sure that cholesterol is maintained low to decrease the ASCVD process. So they should not be ignored in primary and secondary prevention as stated on NLA and AACE recommendations.

Conclusions

- Risk calculation can be ignored in diabetics as they’re a risk equivalent to ASCVD.
- Certain diabetic groups are at higher ASCVD risk: multiple risk factors, older age, subclinical ASCVD, documented ASCVD and FH.
- Non statin therapies including the recently approved PCSK9 inhibitors have a place in clinical practice mostly in those where optimal atherogenic lipoprotein levels are difficult to obtain with high intensity statin therapy and statin intolerant individuals.
- Data from IMPROVE-IT, specially in diabetes sub analysis maintain the concept “lower the better”.

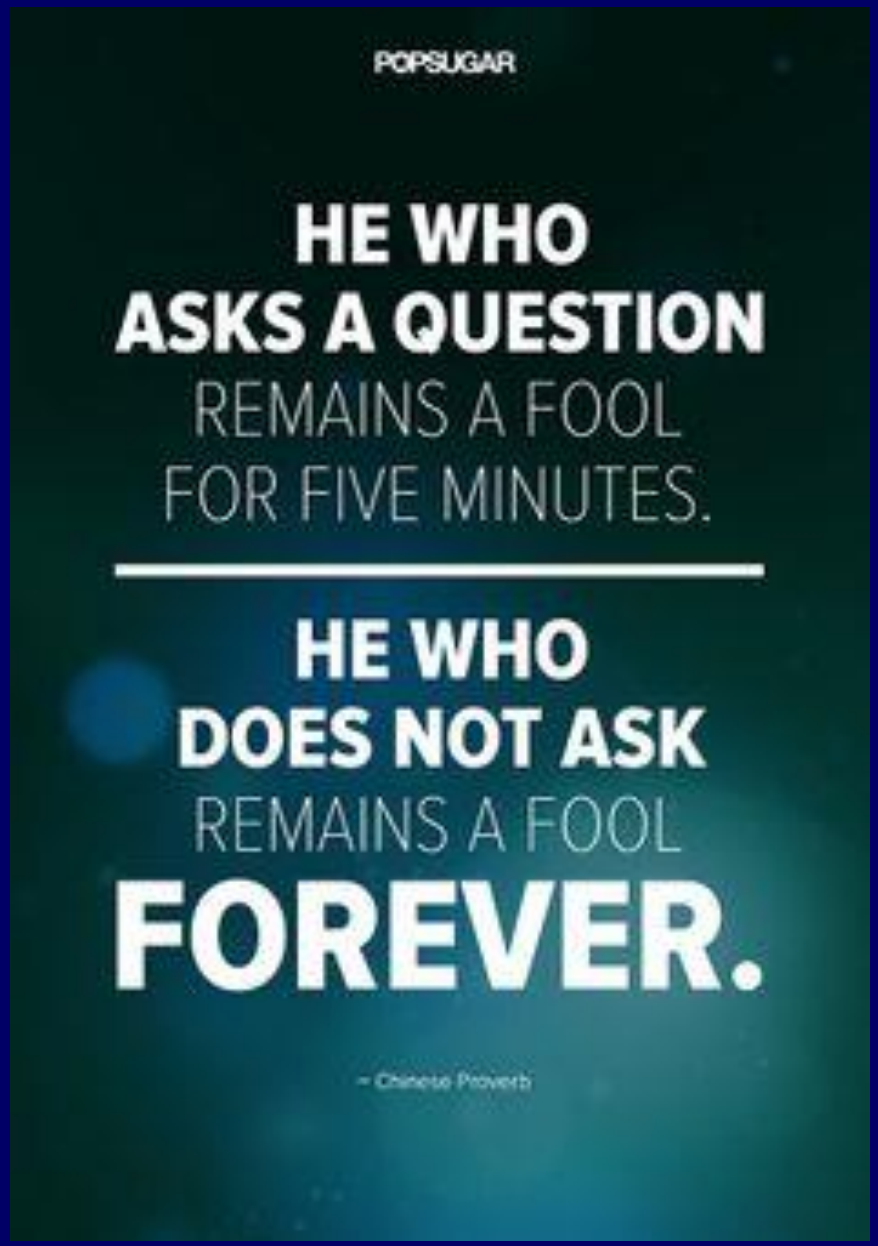
Conclusions

- 2014 and 2015 Recommendations for Dyslipidemia from the NLA seems to be a “happy medium” between past ATP guidelines and new ACC/AHA Blood Cholesterol Guidelines.
- A revision of ACC/AHA guidelines may be on the way mostly if data with new agents as PCSK9i came positive for CV outcomes.

Changes can be accepted,

BUT IN A WISE MANNER

THANKS


POPSUGAR
HE WHO
ASKS A QUESTION
REMAINS A FOOL
FOR FIVE MINUTES.
HE WHO
DOES NOT ASK
REMAINS A FOOL
FOREVER.
– Chinese Proverb