بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

PCSK9I Treatment

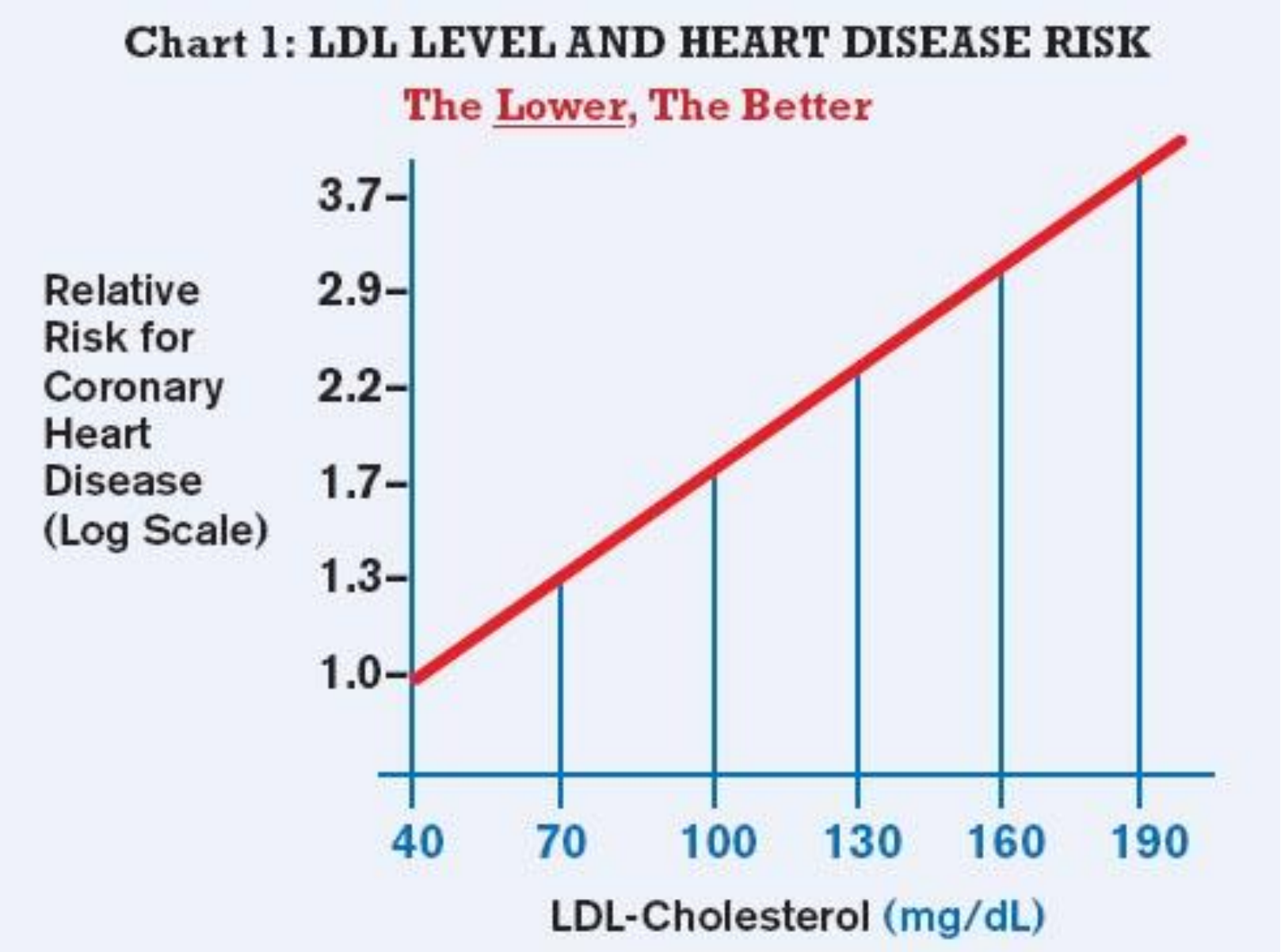
دکتر طوبـــی کاظمی –جنرال کاردیولوژیست

دکتر شیما جعفری– فارماکوتراپیست

دانشگاه علوم پزشکی بیرجند

۳۱ مرداد ماه ۱۴۰۱

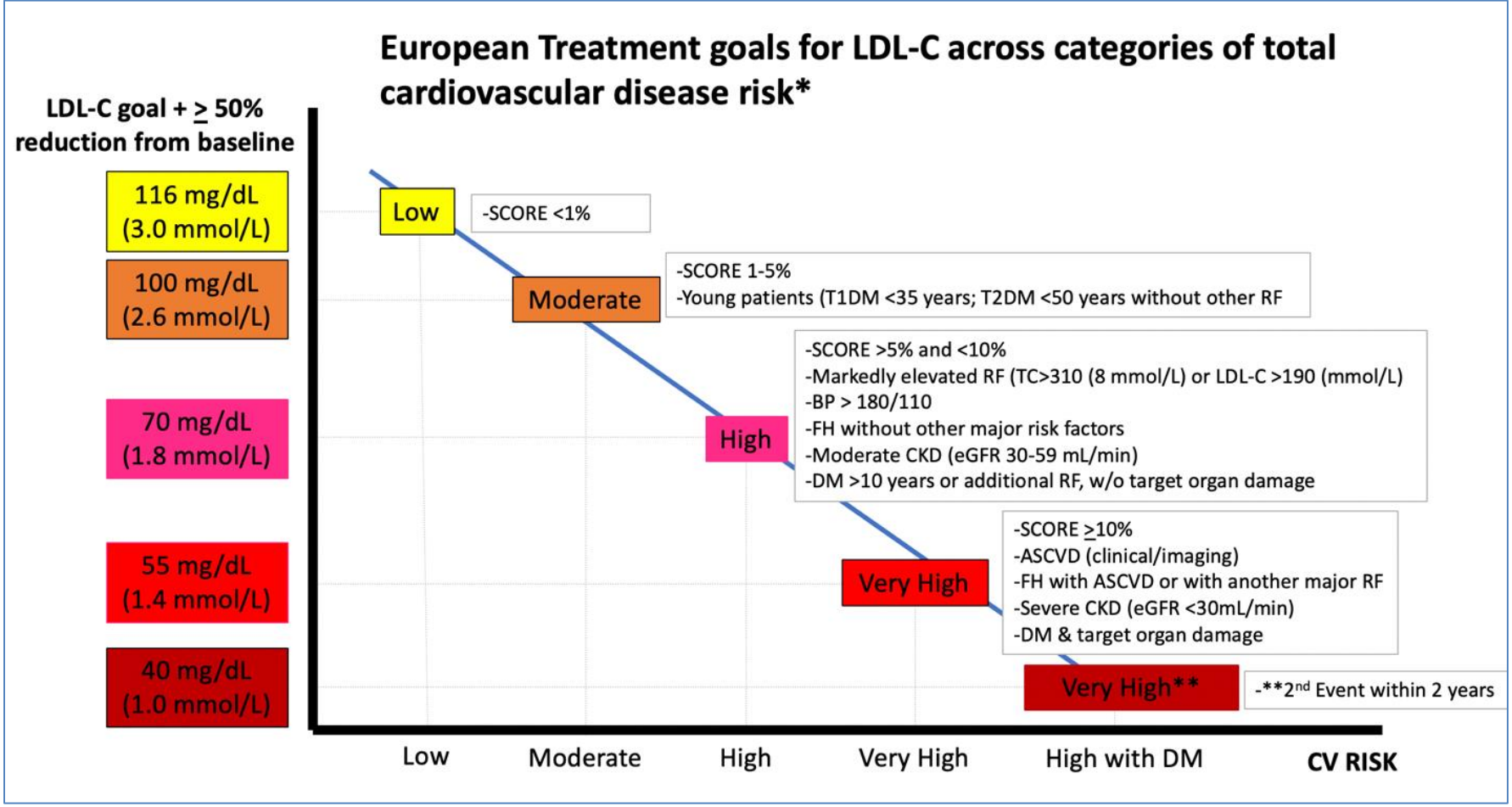
Importance of Dyslipidemia



Serum Lipid Level and CVD

Lipid level	CAD risk
Each **1 mg/dL increase** in **LDL**	**1% increase** in the risk of CHD in women and men
Each 1 mg/dL increase in Non-HDL-C	**1%** increase in the risk of CHD in women and men
Each **89 mg/dL** **increase** in **TG**	**37% increase** in the risk of CVD in women **14% increased** risk in men
Each **1 mg/dL** **increase** in **HDL-C**	**2% decrease** in CVD death in men **3% decrease** in CVD death in women

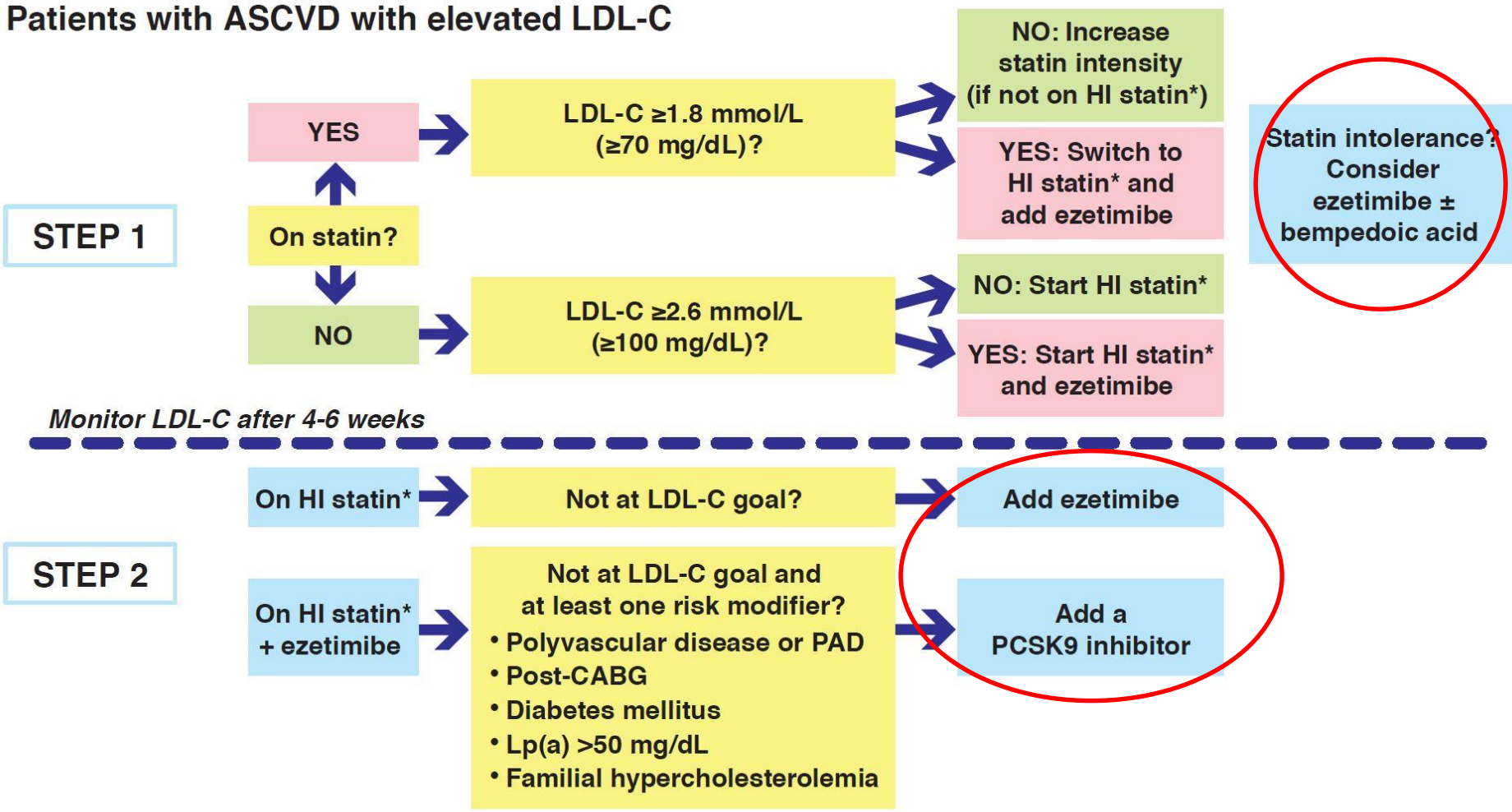
2019 ESC/EAC Guidelines for the management of dyslipidemia : lipid modification to reduce cardiovascular risk



2019 ESC/EAC Guidelines for the management of dyslipidemia : lipid modification to reduce cardiovascular risk

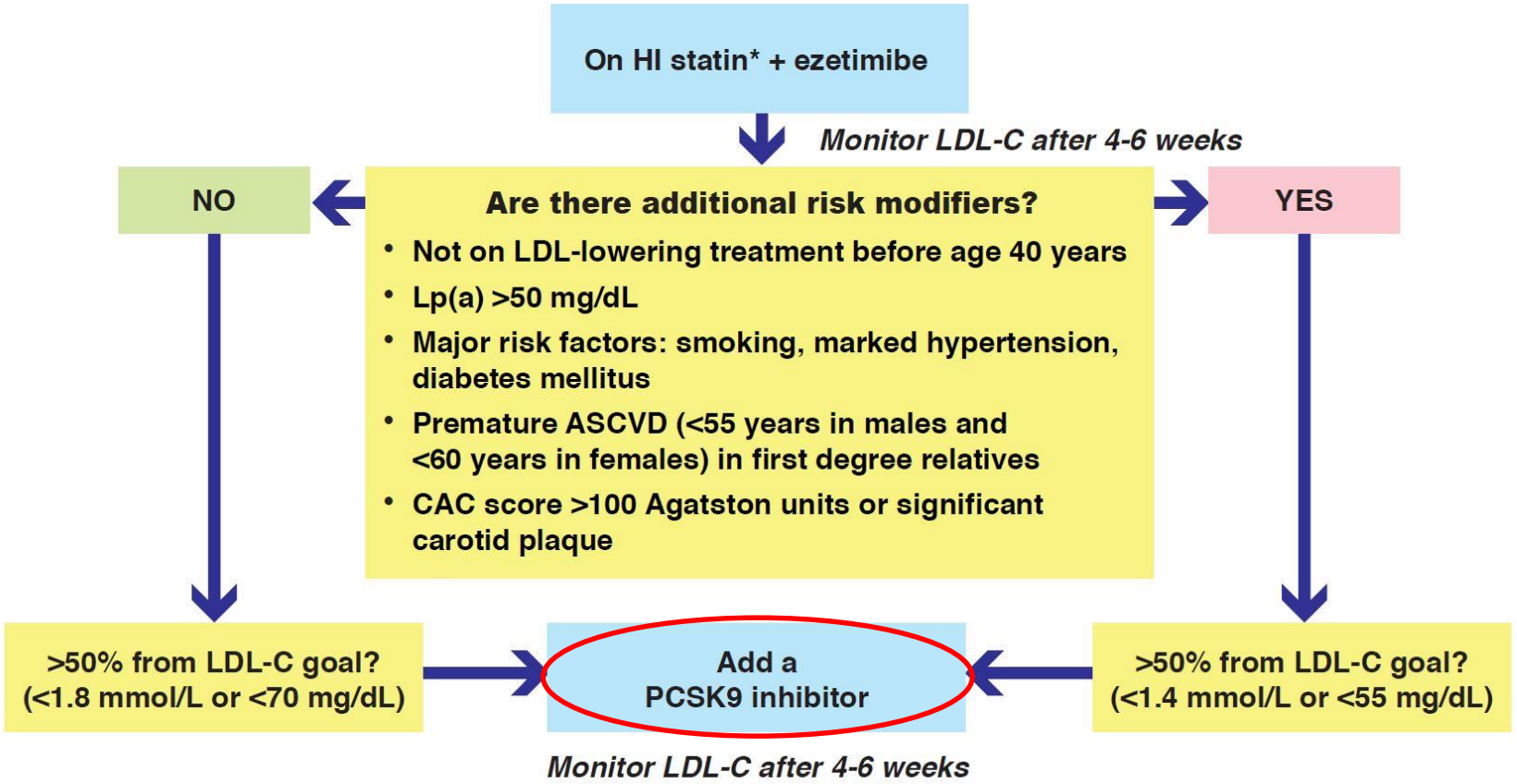
https://www.heartscore.org/en_GB

Risk group	Risk group Definition	LDL Goal mg/dl	Statin Dose
Very Very High	▪ ASCVD 2th Event during 2 years	< 40	High
Very High	▪ Score ≥ 10% ▪ ASCVD ▪ Familial Hyperchol with ASCVD or other RF ▪ Severe CKD (GFR <30 cc/min) ▪ DM + TOD	<55	High
High	▪ 5% <Score >10% ▪ LDL > 190 mg/dl or Chol > 310 mg/dl ▪ BP > 180/110 ▪ Familial Hyperchol . W/O other RF ▪ Moderate CKD (GFR 30-59 ml/min) ▪ DM > 10yr / with other RF /without TOD	<70	High
Moderate	▪ Score : 1-5% ▪ Young Patients (T1DM <35 yrs ;T2DM <50 yrs)without other RF	<100	moderate
Low	▪ Score <1%	<116	low



class of recommendation I, LOE A

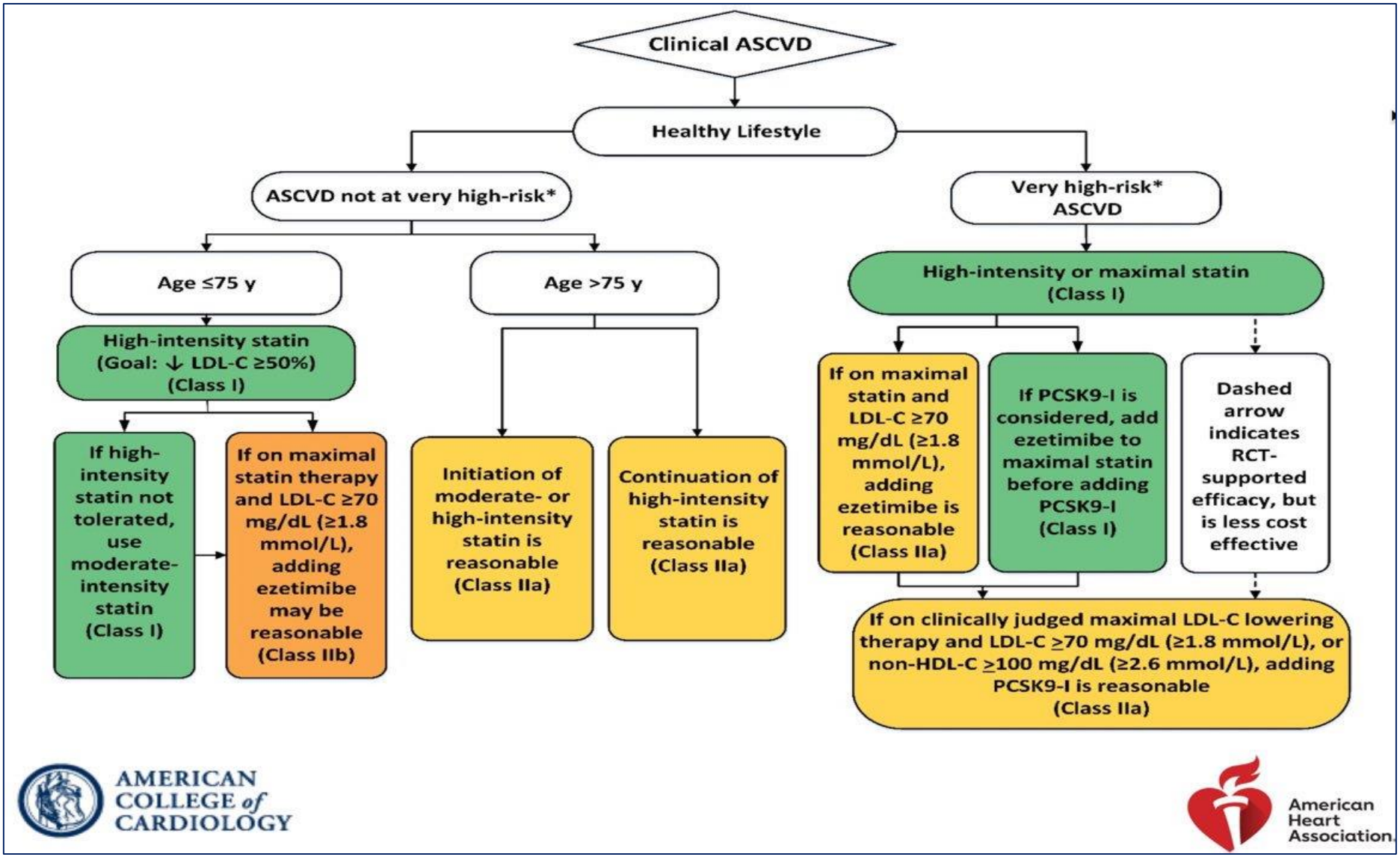
Primary prevention adult patients with familial hypercholesterolemia



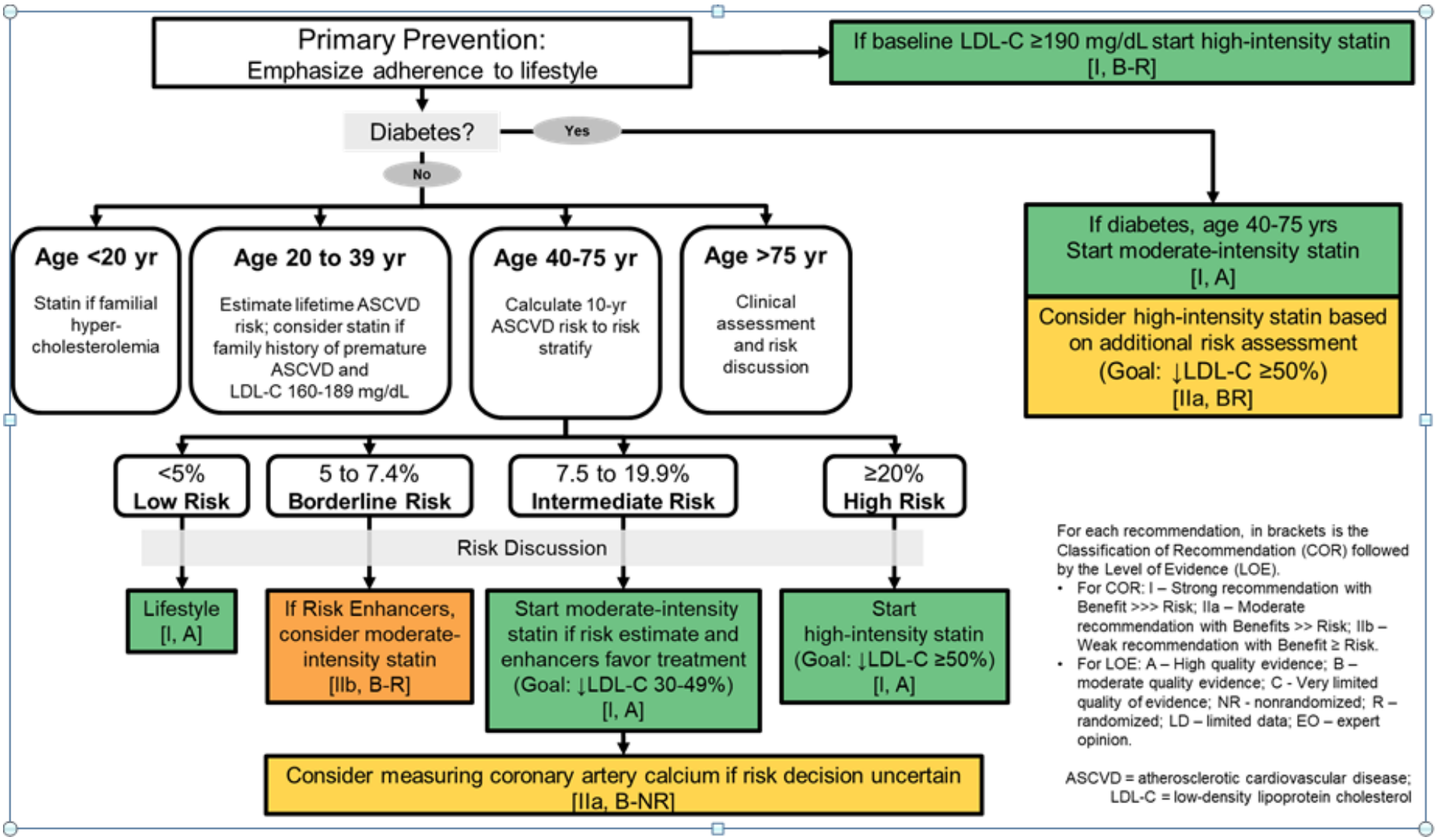
* HI statin: high-intensity statin or maximally tolerated statin

class of recommendation II b, LOE C

2018 AHA/…. Guideline on the Management of Blood Cholesterol

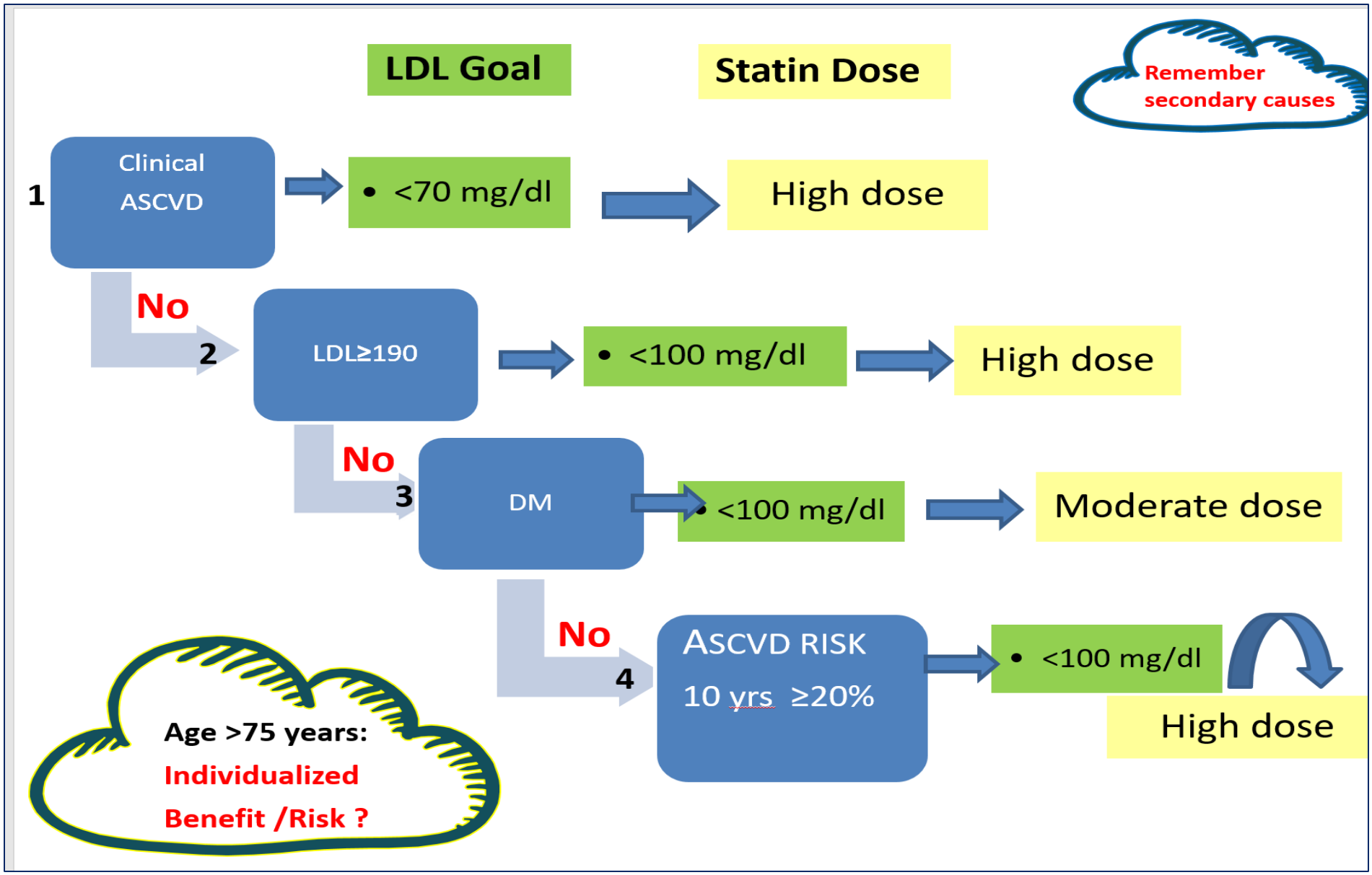


2018 AHA/…. Guideline on the Management of Blood Cholesterol

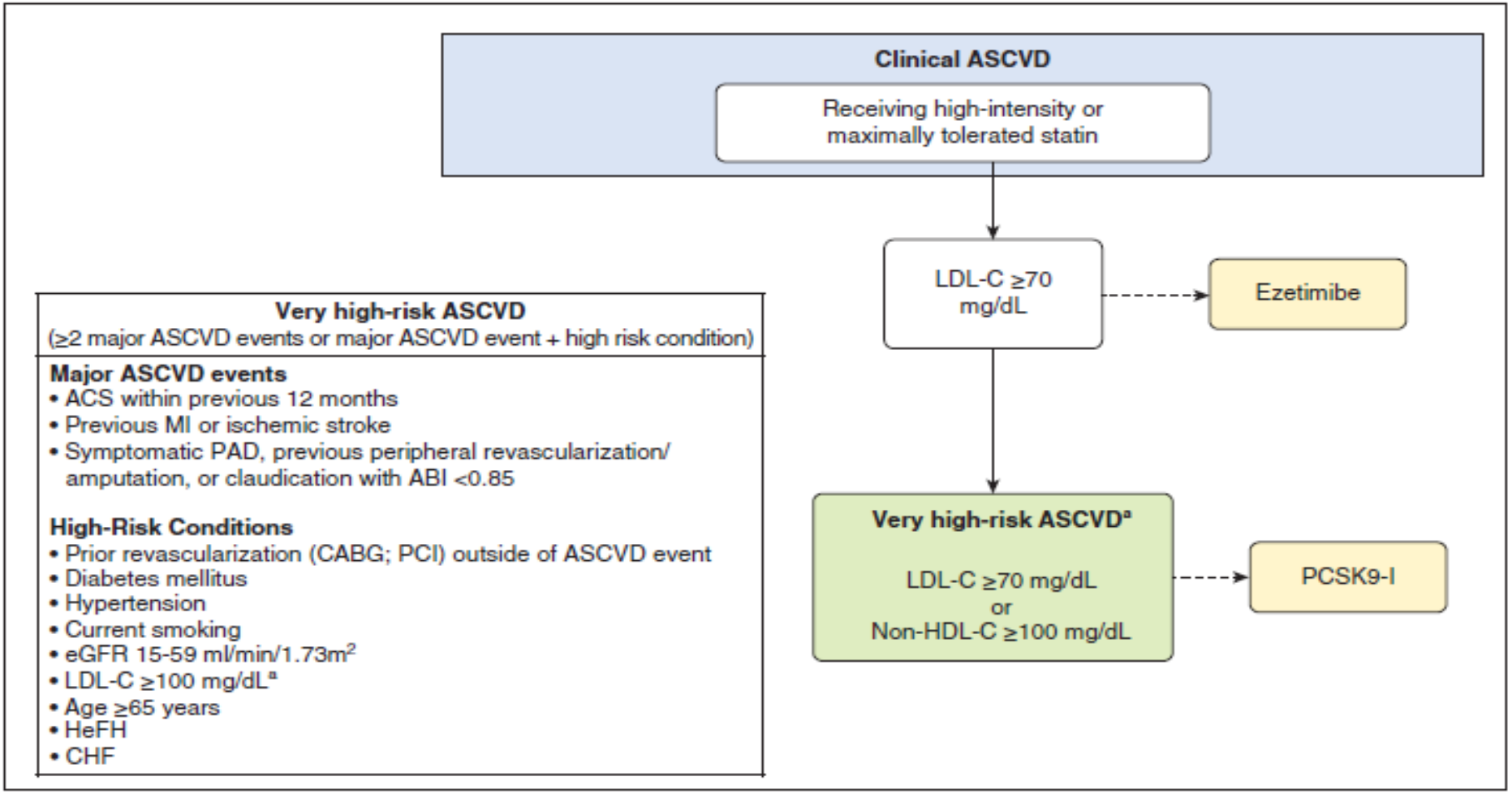


2018 AHA/…. Guideline on the Management of Blood Cholesterol

Approach LDL Treatment : Step by step



Step 1



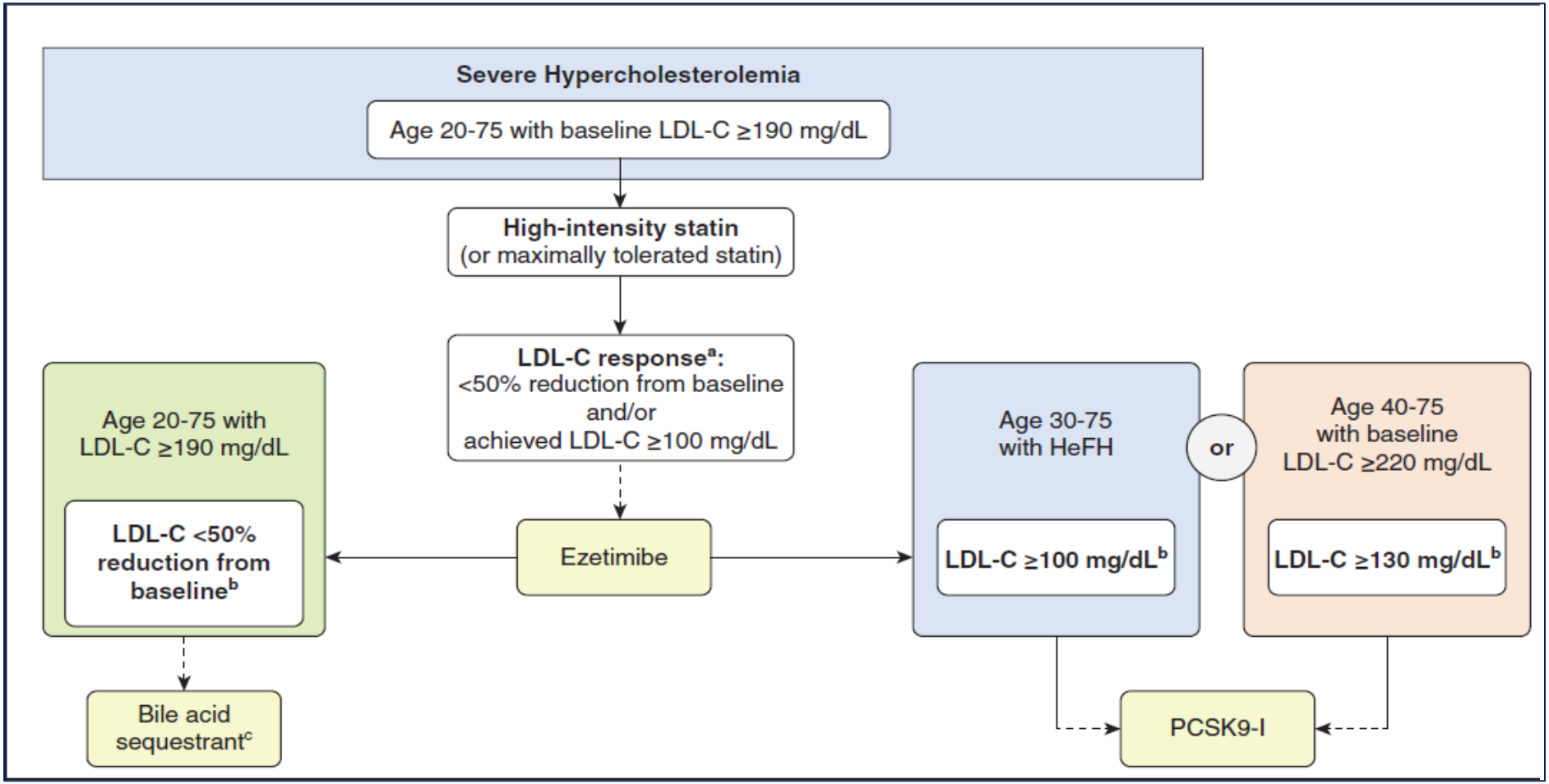
Clinical ASCVD

ACS (AMI ,UA)
CABG ,PCI
PAD
Carotid Disease
Chronic Stable Angina
Stroke ,TIA
Aortic Aneurysm
Revascularization of other Arteries

LDL Goal
<70 mg/dl

High dose Statin

Step 2



Severe Hypercholesterolemia

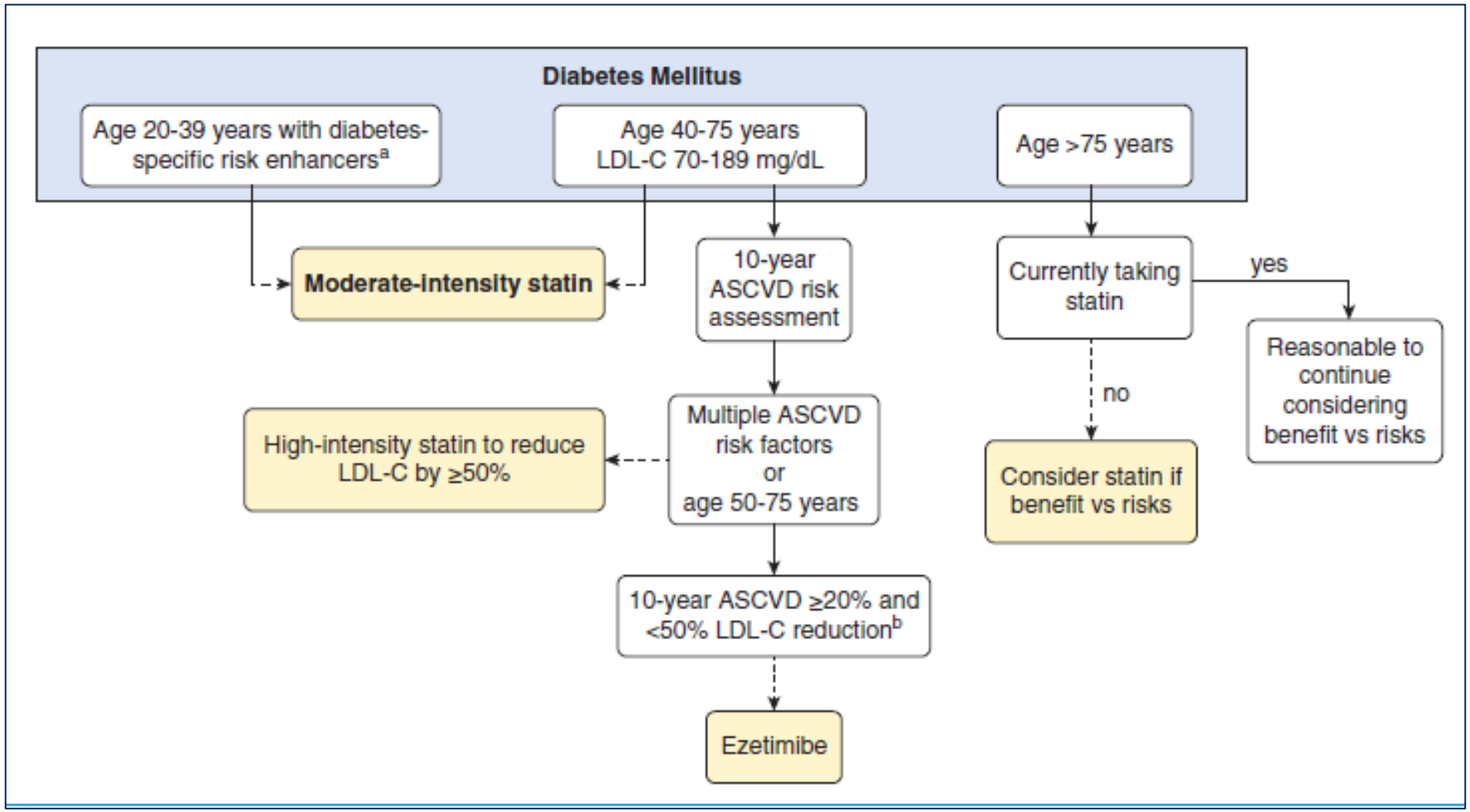
LDL ≥ 190

LDL Goal

<100 mg/dl

High dose Statin

Step 3



Hx of DM

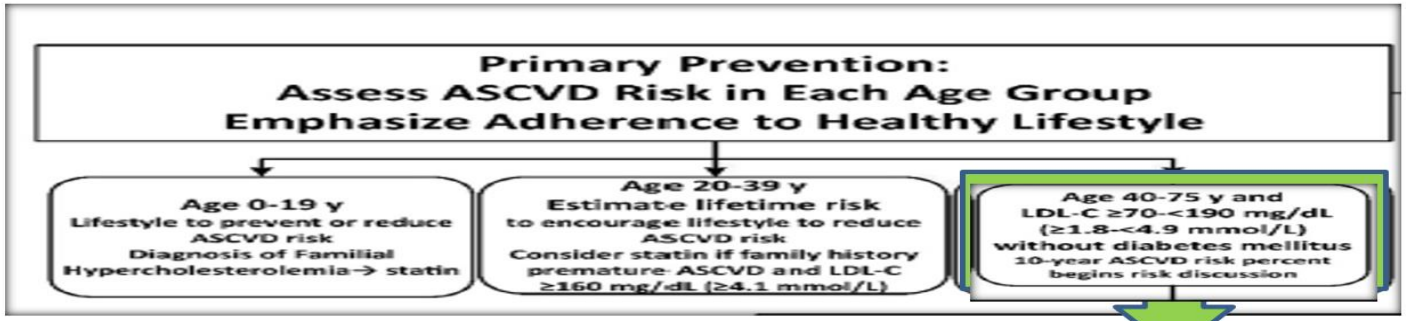
LDL Goal

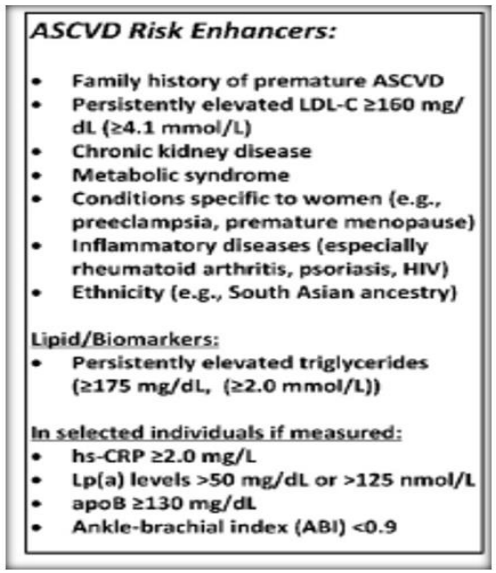
<100 mg/dl

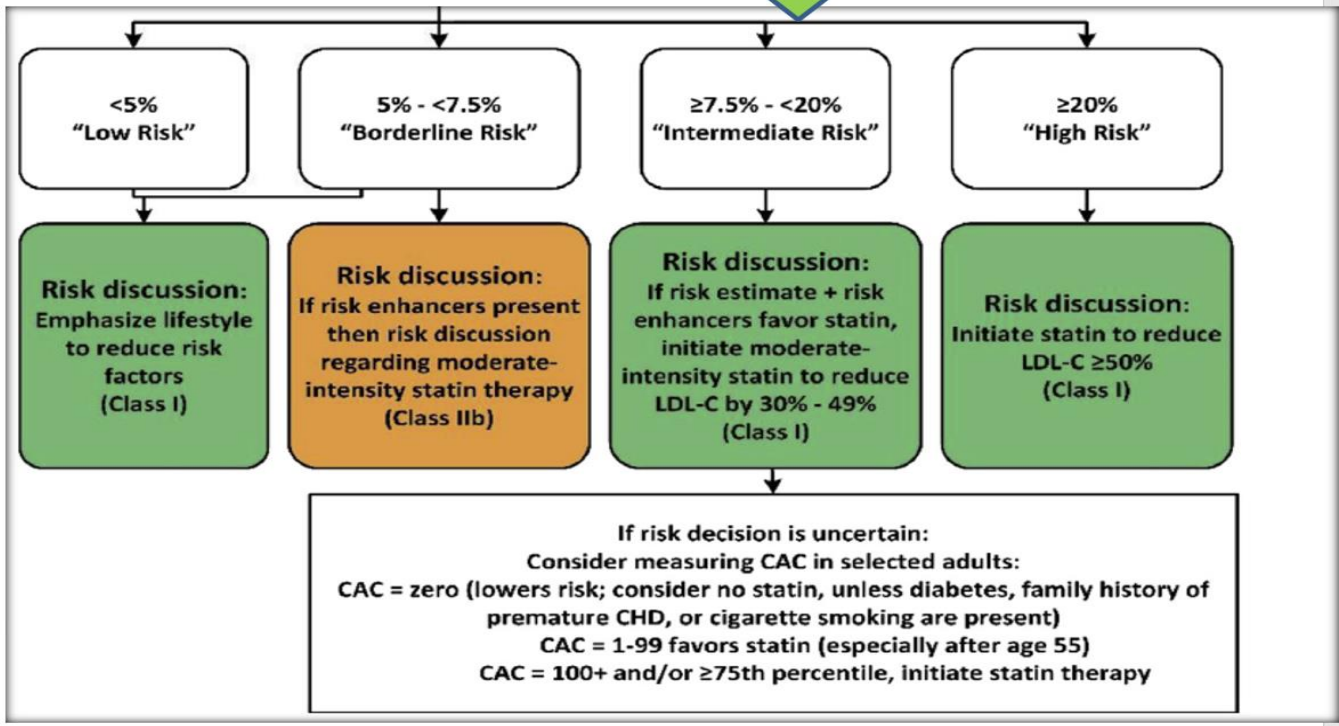
Moderate dose Statin

If ASCVD risk 10 y ≥ 20%: **High Dose**

Step 4







ASCVD risk 10 y: ≥ 20 %

LDL Goal
<100 mg/dl

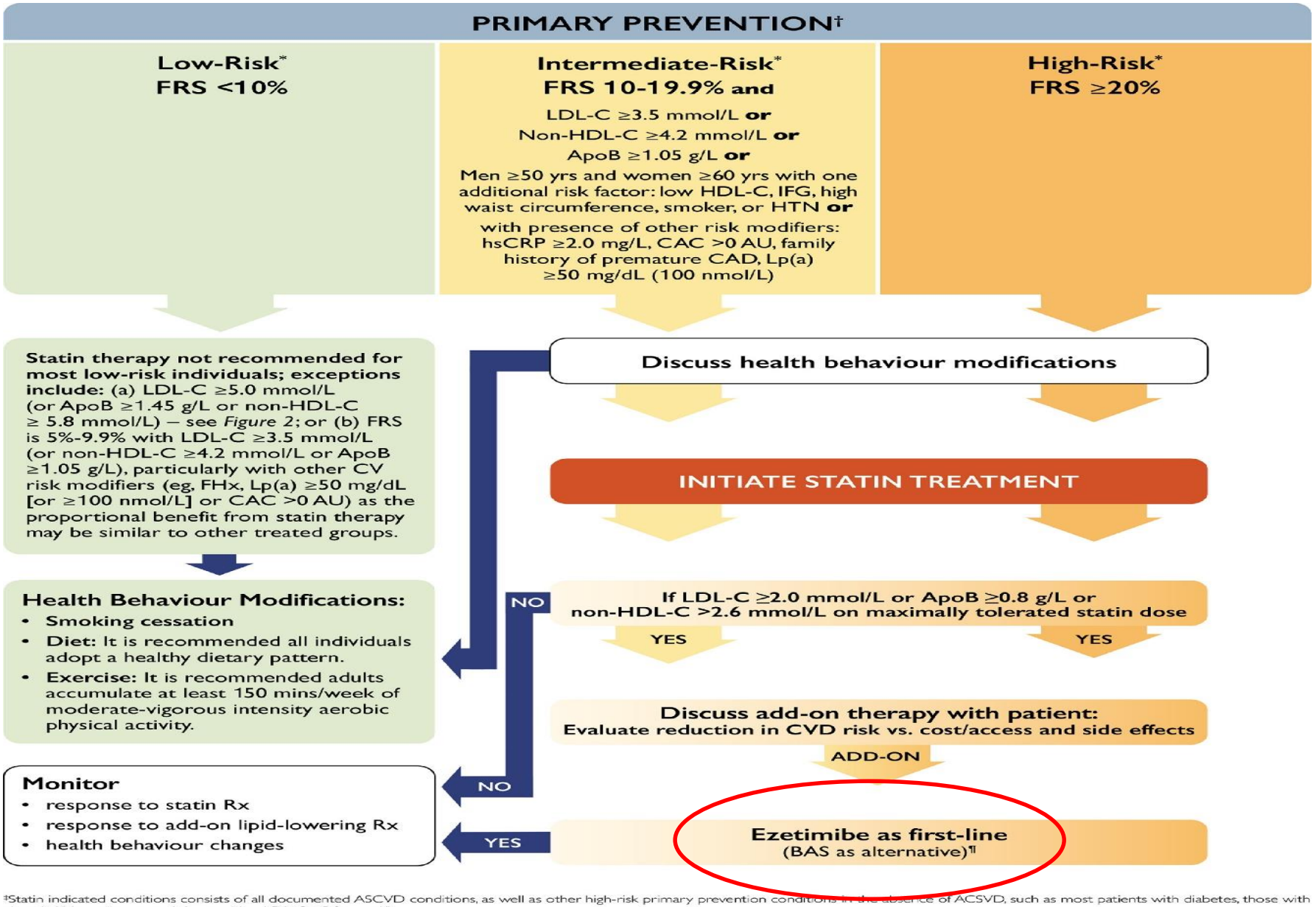
High dose Statin

ASCVD risk 10 y: 7.5-20%
And risk enhancers

LDL Goal
????

Moderate dose Statin

Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult 2021



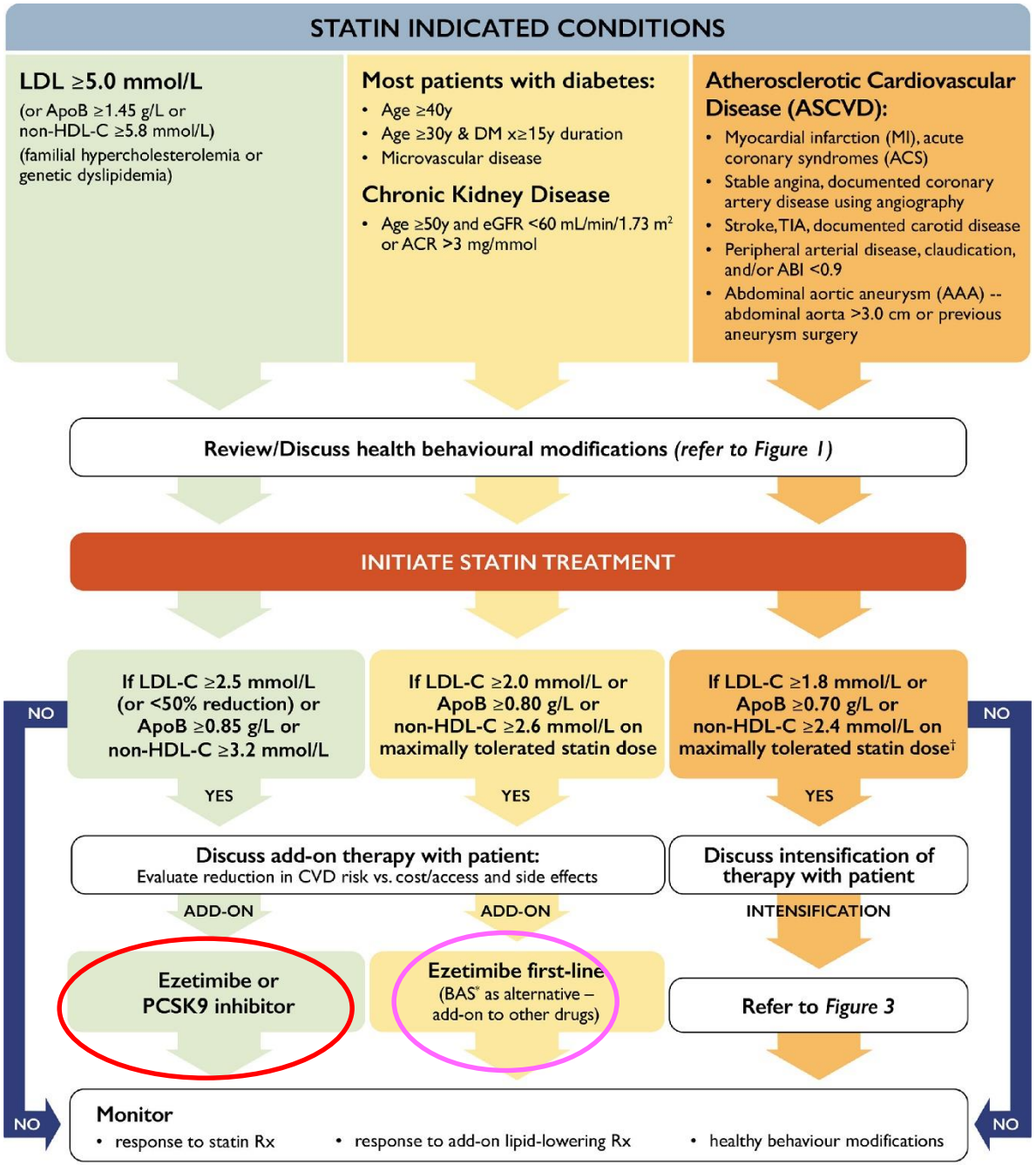
‡Statin indicated conditions consists of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ACSVD, such as most patients with diabetes, those with chronic kidney disease and those with a LDL-C ≥5.0 mmol/L.

†Calculate risk using the Framingham Risk Score (FRS) – refer to the iCCS available on the App Store or on Google Play

*Screening should be repeated every 5 years for men and women aged 40 to 75 years using the modified FRS or CLEM to guide therapy to reduce major CV events. A risk assessment might also be completed whenever a patient's expected risk status changes.

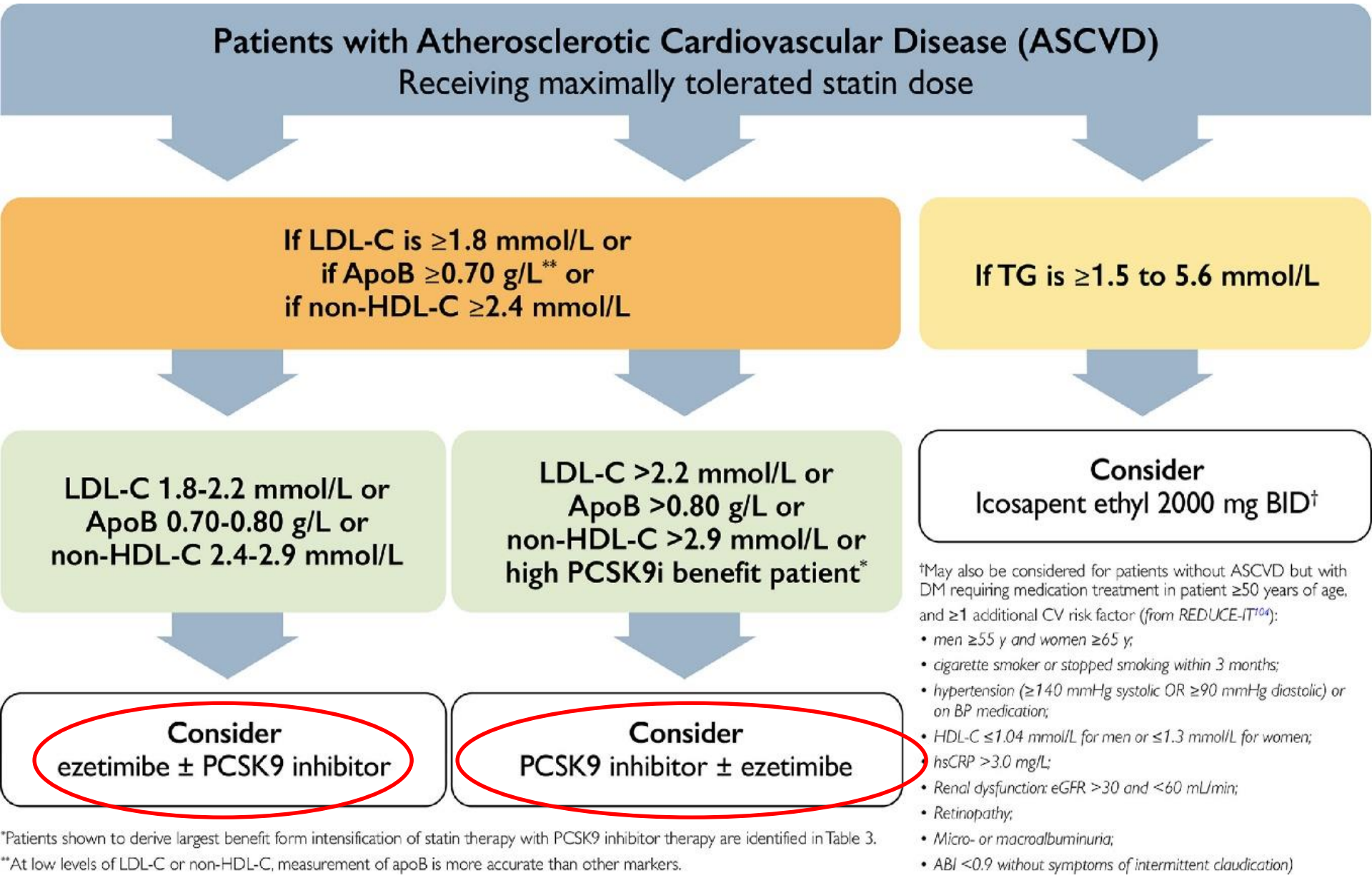
¶ studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

FRS = Framingham risk score; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoB = apolipoprotein B; IFG = impaired fasting glucose; HTN = hypertension; hsCRP = high-sensitivity C-reactive protein; CAC = coronary artery calcium; AU – Agatston unit; Rx = prescription; BAS = bile acid sequestrant



eGFR = estimated glomerular filtration rate; ACR = albumin-to-creatinine; TIA = transient ischemic attack; ABI = ankle-brachial index.

†‡LDL-C threshold selected on the basis of the PCSK9-inhibitor clinical trials lipid inclusion parameters (references 91 and 92) with percentile equivalents used for ApoB and non-HDL-C (see supplement).



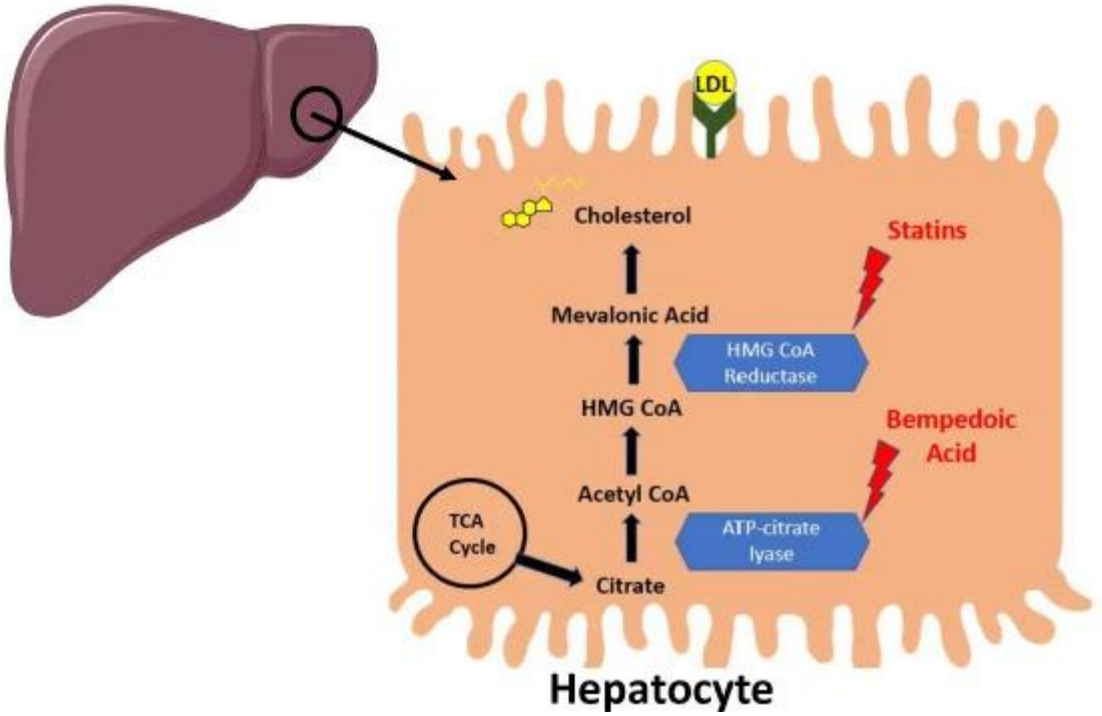
*Patients shown to derive largest benefit form intensification of statin therapy with PCSK9 inhibitor therapy are identified in Table 3.

**At low levels of LDL-C or non-HDL-C, measurement of apoB is more accurate than other markers.

†May also be considered for patients without ASCVD but with DM requiring medication treatment in patient ≥50 years of age, and ≥1 additional CV risk factor (*from REDUCE-IT*[104]):

- *men ≥55 y and women ≥65 y;*
- *cigarette smoker or stopped smoking within 3 months;*
- *hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on BP medication;*
- *HDL-C ≤1.04 mmol/L for men or ≤1.3 mmol/L for women;*
- *hsCRP >3.0 mg/L;*
- *Renal dysfunction: eGFR >30 and <60 mL/min;*
- *Retinopathy;*
- *Micro- or macroalbuminuria;*
- *ABI <0.9 without symptoms of intermittent claudication)*

Bempedoic Acid: Mechanism of Action



↑Upregulation of LDL Receptor

↓

↑ LDL-C Clearance

↓

↓Plasma LDL-C

NHS England Lipids Management Pathway 2021

Secondary Prevention: Medicines optimisation for Lipid Management

NHS South East London Clinical Commissioning Group

1) **Check baseline bloods** (non-fasting lipid profile, LFTs, HbA1c, thyroid and renal function)

2) **Offer high dose high intensity statin** therapy atorvastatin 40-80mg (or rosuvastatin 20-40mg)* to adults with CVD: this includes acute coronary syndromes (ACS), angina, previous myocardial infarction (MI), revascularisation, stroke or transient ischaemic attack (TIA), symptomatic peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA)

3) **Support the self-management** (*see page 6*) of modifiable risk factors eg. smoking, diet, obesity, alcohol intake, physical activity, blood pressure and glycaemic control (HbA1c)

In primary care check: **Is patient on high dose, high intensity statin?** atorvastatin 40-80mg (or rosuvastatin 20mg-40mg)*(*dose adjustments may be required for eGFR<30ml/min, drug interactions, intolerance*)

Yes ← **Has non-HDL-C reduced by 40% or more from baseline at 3 months?** NICE[6] (if no baseline value: consider a target of non-HDL-C < 2.5mmol/L or LDL-C <2.0mmo/L: JBS) → No

Discuss with patient statin choice: reinforce lifestyle and dietary measures-check adherence to medication and lifestyle (*for statin intolerance pathway see page 5*)
- After 3 months check non-fasting lipid profile (TC, TG, HDL, LDL-C); LFTs

Yes ← **Has non-HDL-C reduced by 40% or more from baseline at 3 months?** NICE[6] (if no baseline value: consider a target of non-HDL-C < 2.5mmol/L or LDL-C <2.0mmol/L). Check adherence to statin and lifestyle measures (*for statin intolerance see page 5*) → No

Consider adding Ezetimibe 10mg daily SPC

After 3 months, check non-fasting lipid profile (TC, TG, HDL, LDL-C); LFTs

Yes ← **Has non-HDL-C reduced by 40% or more from baseline at 3 months?** (if no baseline value: consider a target non-HDL-C < 2.5mmol/L or LDL-C <2.0mmo/L) → No

Following a review of adherence/adverse effects/intolerance/hesitancy and lifestyle interventions. **Refer to lipid clinic**

If LDL-C >4mmol/L (or LDL-C >3.5mmol/L with recurrent CVD event or multivascular disease) lipid clinic will consider PCSK9i (*see page 7: PCSK9i pathway and contact details for SEL lipid clinics*)

If statin intolerance and/or not achieving targets, lipid clinic will consider addition of bempedoic acid ▼to ezetimibe therapy (*see page 5*)

Review annually for adherence to medications, support for diet and lifestyle measures, and check required bloods eg lipid profile, LFTs if indicated

***Please note** that for rosuvastatin 40mg specialist supervision is recommended when this dose is initiated (see SPC)

Primary Prevention: Medicines Optimisation for Lipid Management

NHS South East London Clinical Commissioning Group

Lifestyle change and dietary measures are key to CVD event reduction together with drug therapy

In primary care check: bloods (non-fasting lipid profile: TC, TG, HDL-C, LDL-C, non-HDL-C) liver function (LFTs), HbA1c (manage/review diabetes mellitus (DM) if ≥48mmol/mol) thyroid & renal function, blood pressure (BP), weight, smoking status and calculate QRisk2 score using EMIS template (www.qrisk.org)

Please note **QRisk2 does not apply in the following conditions**: familial hypercholesterolaemia (FH), type 1 diabetes mellitus (T1DM)- *may be applied to QRisk3 calculations*, chronic kidney disease CKD (*QRisk3 has updated to eGFR <30ml/min; NICE states eGFR <60ml/min*) and/or albuminuria- **these patients are high CVD risk and require consideration for a high intensity (HI) statin**

Consider additional CVD risk factors, if present, together with with QRisk score: Severe obesity (BMI >40kg/m^2), socio-economic status, human immunodeficiency virus (HIV) treatment, severe mental illness, medications that may cause dyslipidaemia (eg. antipsychotics, corticosteroids, immunosuppressants), autoimmune disorders eg. systemic lupus erythematosus (SLE), impaired fasting glycaemia, significant hypertriglyceridaemia (*see page 9*), recent change in risk factors eg change to smoking status, BP and lipid management

Consider options with shared decision making (*see page 6*), education and lifestyle interventions to **modify CVD risk.**
For all patients consider the risk:benefit of therapy holistically: for example in patients aged ≥ 85years consider frailty, life expectancy and co-morbidities

Optimise management of BP and other co-morbidities. **Support** lifestyle interventions and medicines adherence.

If QRisk ≥10%: after addressing modifiable risk factors and following a shared decision: consider initiating or optimising statin therapy with a **moderate dose** of a **high intensity drug**: atorvastatin 20mg daily (or rosuvastatin 10mg daily) -*see page 6 for high intensity statin comparison table*- consider drug interactions that may affect dosing (see BNF)

After 3 months, has non-HDL cholesterol fallen by ≥ 40% from baseline?
Check adherence to medication, timing of dose, statin adverse effects/intolerance/hesitancy & diet/lifestyle interventions

Yes

No

Step 1 in primary care: Consider up-titration of statin to a maximum dose: atorvastatin 80mg (or rosuvastatin 20mg to 40mg*)- *see HI statin table page 6*

Step 2 in primary care: If intolerant to higher dose of statin, consider adding ezetimibe 10mg daily (SPC- check contra-indications) to maximal tolerated statin

Step 3 in primary care with secondary care support: If intolerant to any statin, start ezetimibe 10mg daily, **and refer to lipid clinic** to consider adding bempedoic acid 180mg daily ▼ (SPC) (*see statin intolerance pathway on page 5 for further information*)

Yes

After 3 months, has non-HDL cholesterol fallen by ≥ 40% from baseline? Check adherence to medication, adverse effects/intolerance/hesitancy and lifestyle interventions

No

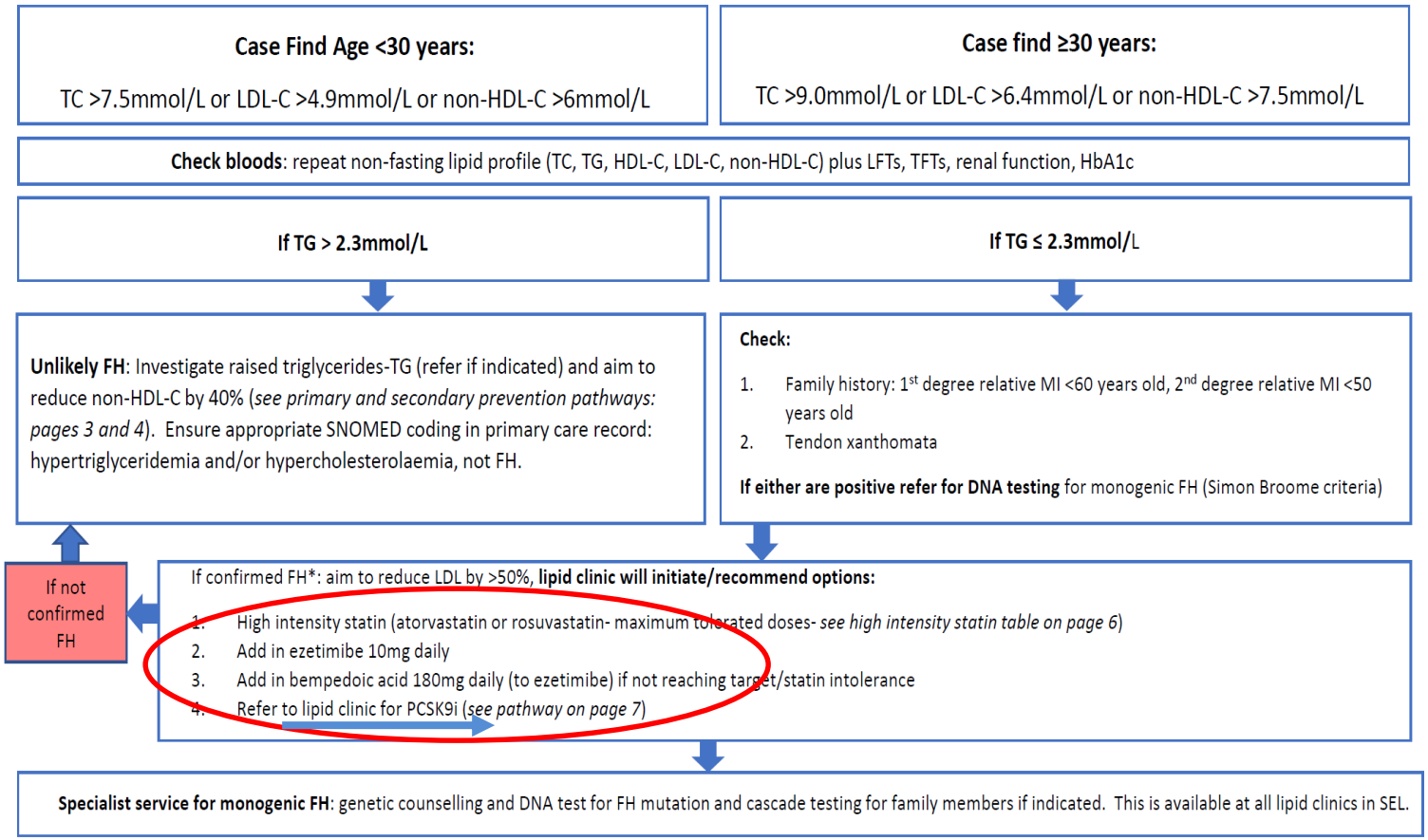
Review annually for adherence to medications, diet and lifestyle, check required bloods eg lipids. Refer for support as required from specialist teams.

Refer to lipid clinic (*see page 7 for SEL contact details*)

***Please note** that for rosuvastatin 40mg specialist supervision is recommended when this dose is initiated (see SPC)

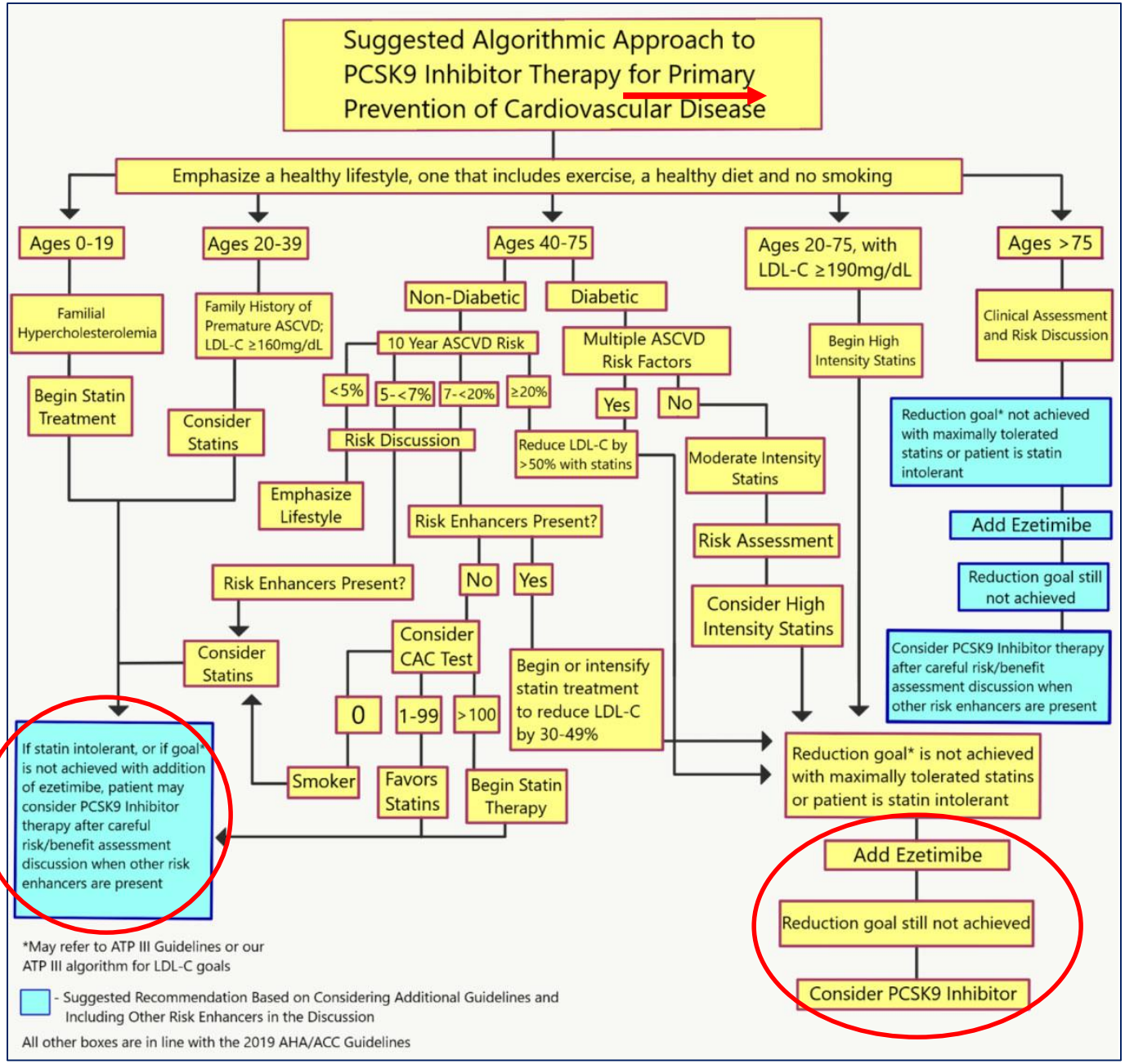
Familial Hypercholesterolaemia (FH) Pathway

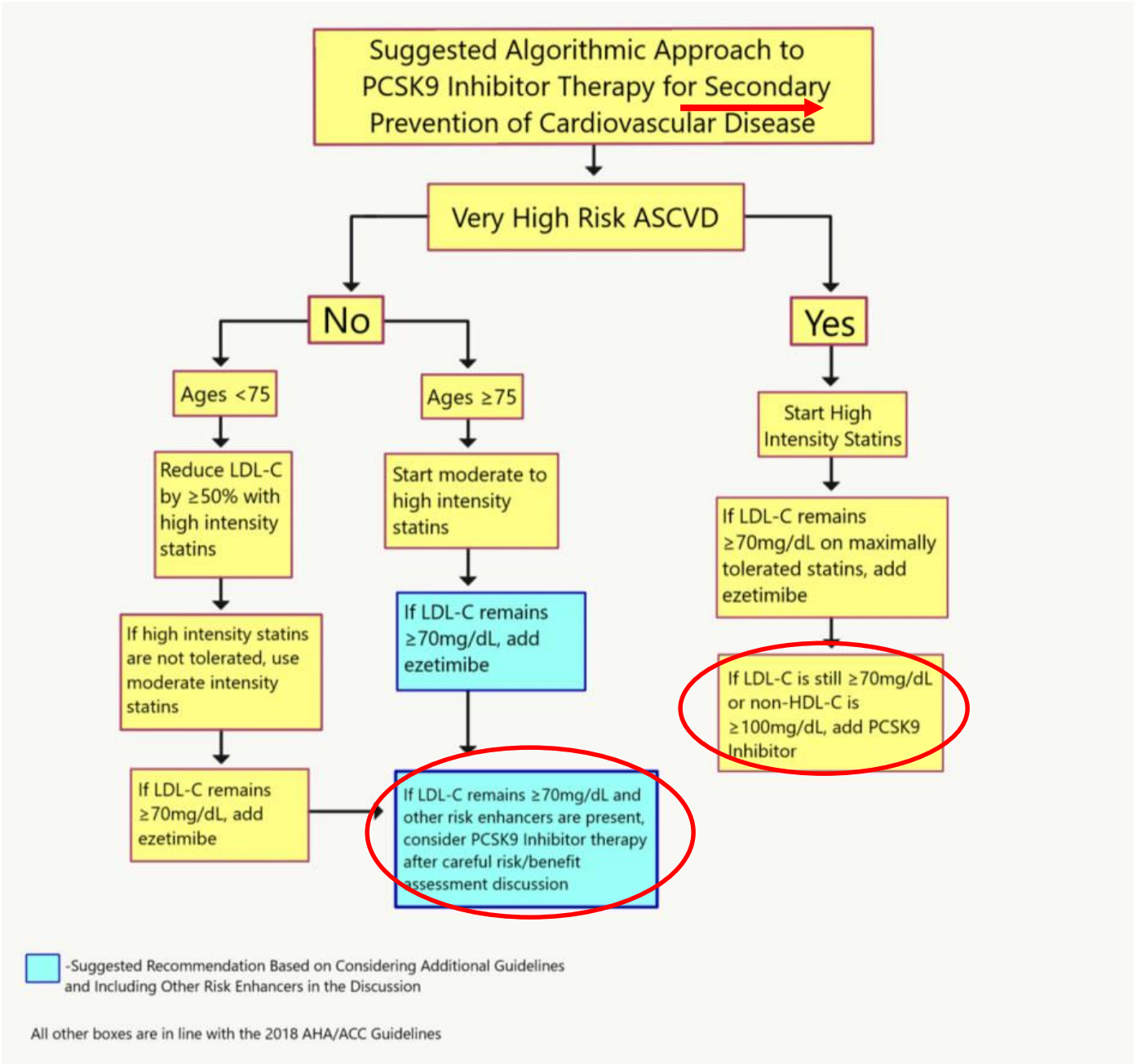
NHS South East London Clinical Commissioning Group

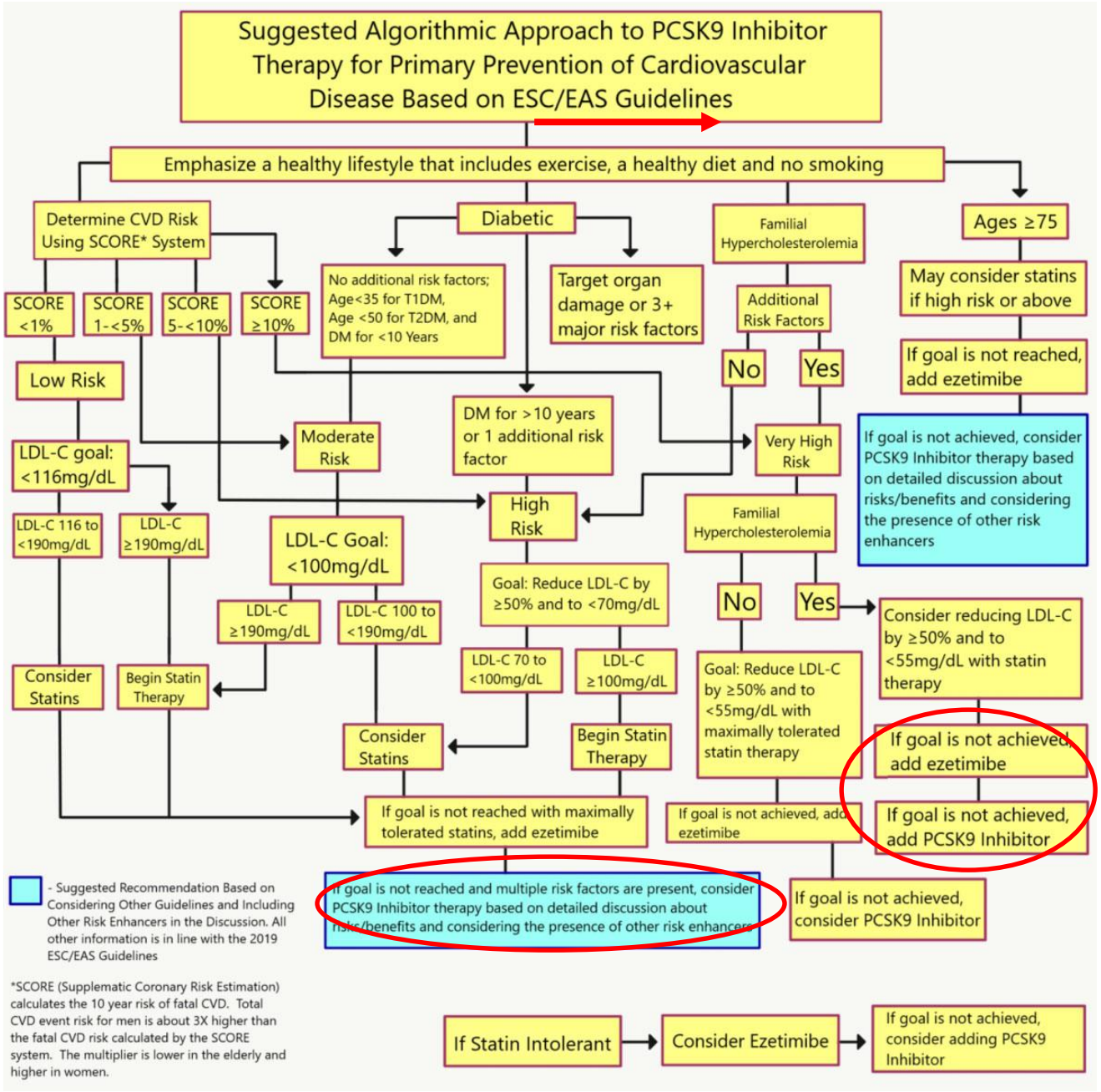


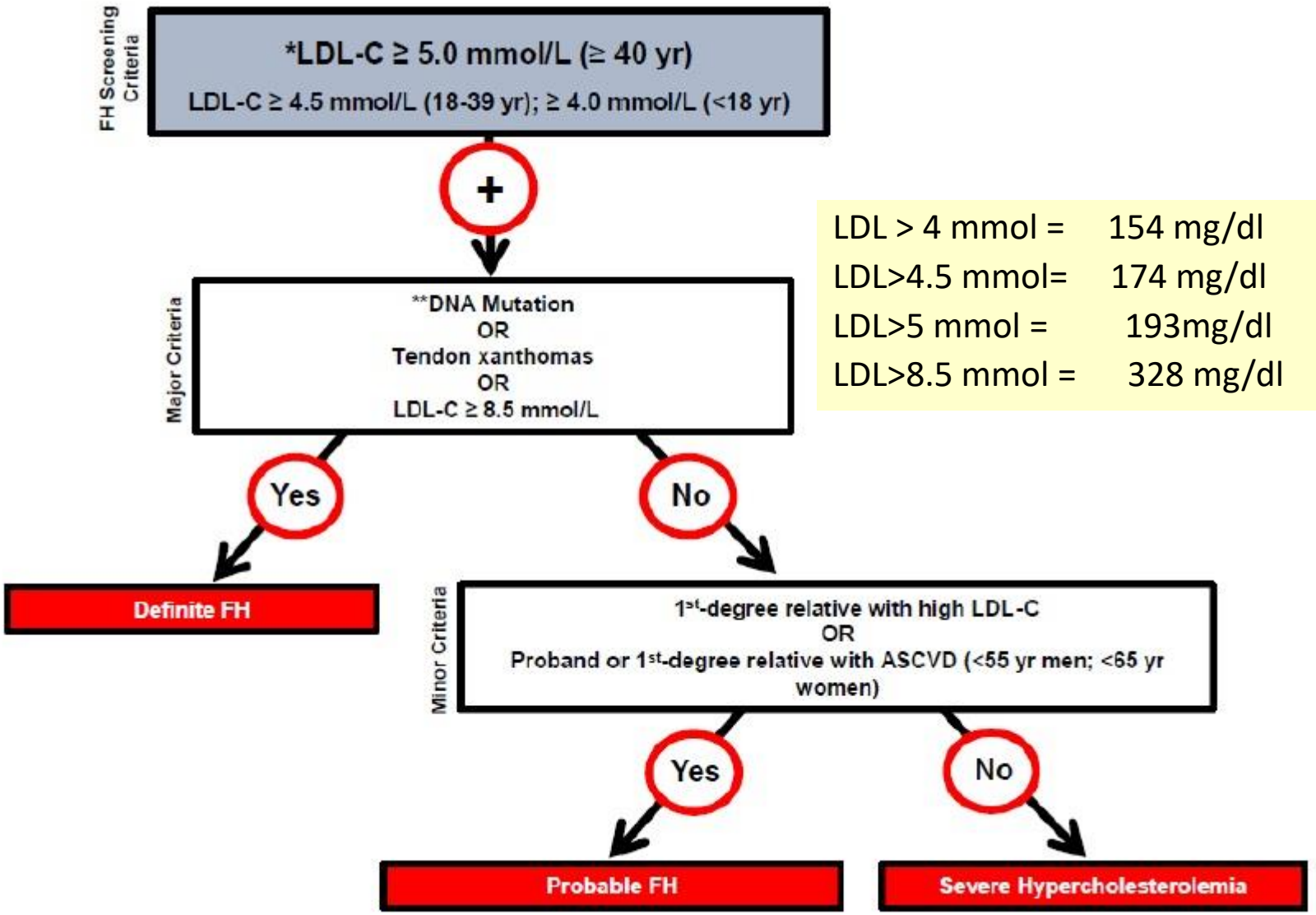
*Ensure correct coding in primary care record for confirmed FH. SNOMED: familial hypercholesterolaemia: 398036000, homozygous FH 238078005, heterozygous FH 23807900

Coppinger C, Movahed MR, Azemawah V, Peyton L, Gregory J, Hashemzadeh M. A Comprehensive Review of PCSK9 Inhibitors**. J Cardiovasc Pharmacol Ther. 2022** Jan-Dec


Suggested Algorithmic Approach to PCSK9 Inhibitor Therapy for Primary Prevention of Cardiovascular Disease
Emphasize a healthy lifestyle, one that includes exercise, a healthy diet and no smoking
Ages 0-19
Familial Hypercholesterolemia
Begin Statin Treatment
Ages 20-39
Family History of Premature ASCVD; LDL-C ≥160mg/dL
Consider Statins
Ages 40-75
Non-Diabetic
10 Year ASCVD Risk
<5%
5-<7%
7-<20%
≥20%
Risk Discussion
Emphasize Lifestyle
Risk Enhancers Present?
Consider Statins
Risk Enhancers Present?
No
Yes
Consider CAC Test
0
1-99
>100
Smoker
Favors Statins
Begin Statin Therapy
Diabetic
Multiple ASCVD Risk Factors
Yes
No
Reduce LDL-C by >50% with statins
Begin or intensify statin treatment to reduce LDL-C by 30-49%
Ages 20-75, with LDL-C ≥190mg/dL
Begin High Intensity Statins
Moderate Intensity Statins
Risk Assessment
Consider High Intensity Statins
Ages >75
Clinical Assessment and Risk Discussion
Reduction goal* not achieved with maximally tolerated statins or patient is statin intolerant
Add Ezetimibe
Reduction goal still not achieved
Consider PCSK9 Inhibitor therapy after careful risk/benefit assessment discussion when other risk enhancers are present
If statin intolerant, or if goal* is not achieved with addition of ezetimibe, patient may consider PCSK9 Inhibitor therapy after careful risk/benefit assessment discussion when other risk enhancers are present
Reduction goal* is not achieved with maximally tolerated statins or patient is statin intolerant
Add Ezetimibe
Reduction goal still not achieved
Consider PCSK9 Inhibitor
*May refer to ATP III Guidelines or our ATP III algorithm for LDL-C goals
- Suggested Recommendation Based on Considering Additional Guidelines and Including Other Risk Enhancers in the Discussion
All other boxes are in line with the 2019 AHA/ACC Guidelines


Suggested Algorithmic Approach to PCSK9 Inhibitor Therapy for Secondary Prevention of Cardiovascular Disease
Very High Risk ASCVD
No
Yes
Ages <75
Ages ≥75
Start High Intensity Statins
Reduce LDL-C by ≥50% with high intensity statins
Start moderate to high intensity statins
If LDL-C remains ≥70mg/dL on maximally tolerated statins, add ezetimibe
If high intensity statins are not tolerated, use moderate intensity statins
If LDL-C remains ≥70mg/dL, add ezetimibe
If LDL-C is still ≥70mg/dL or non-HDL-C is ≥100mg/dL, add PCSK9 Inhibitor
If LDL-C remains ≥70mg/dL, add ezetimibe
If LDL-C remains ≥70mg/dL and other risk enhancers are present, consider PCSK9 Inhibitor therapy after careful risk/benefit assessment discussion
-Suggested Recommendation Based on Considering Additional Guidelines and Including Other Risk Enhancers in the Discussion
All other boxes are in line with the 2018 AHA/ACC Guidelines


Suggested Algorithmic Approach to PCSK9 Inhibitor Therapy for Primary Prevention of Cardiovascular Disease Based on ESC/EAS Guidelines
Emphasize a healthy lifestyle that includes exercise, a healthy diet and no smoking
Determine CVD Risk Using SCORE* System
SCORE <1%
SCORE 1-<5%
SCORE 5-<10%
SCORE ≥10%
Low Risk
LDL-C goal: <116mg/dL
LDL-C 116 to <190mg/dL
LDL-C ≥190mg/dL
Consider Statins
Begin Statin Therapy
Moderate Risk
LDL-C Goal: <100mg/dL
LDL-C ≥190mg/dL
LDL-C 100 to <190mg/dL
Consider Statins
Diabetic
No additional risk factors; Age<35 for T1DM, Age <50 for T2DM, and DM for <10 Years
Target organ damage or 3+ major risk factors
DM for >10 years or 1 additional risk factor
High Risk
Goal: Reduce LDL-C by ≥50% and to <70mg/dL
LDL-C 70 to <100mg/dL
LDL-C ≥100mg/dL
Consider Statins
Begin Statin Therapy
Familial Hypercholesterolemia
Additional Risk Factors
No
Yes
Very High Risk
Familial Hypercholesterolemia
No
Yes
Goal: Reduce LDL-C by ≥50% and to <55mg/dL with maximally tolerated statin therapy
If goal is not achieved, add ezetimibe
Ages ≥75
May consider statins if high risk or above
If goal is not reached, add ezetimibe
If goal is not achieved, consider PCSK9 Inhibitor therapy based on detailed discussion about risks/benefits and considering the presence of other risk enhancers
Consider reducing LDL-C by ≥50% and to <55mg/dL with statin therapy
If goal is not achieved, add ezetimibe
If goal is not achieved, add PCSK9 Inhibitor
If goal is not reached with maximally tolerated statins, add ezetimibe
If goal is not reached and multiple risk factors are present, consider PCSK9 Inhibitor therapy based on detailed discussion about risks/benefits and considering the presence of other risk enhancers
If goal is not achieved, consider PCSK9 Inhibitor
- Suggested Recommendation Based on Considering Other Guidelines and Including Other Risk Enhancers in the Discussion. All other information is in line with the 2019 ESC/EAS Guidelines
*SCORE (Supplematic Coronary Risk Estimation) calculates the 10 year risk of fatal CVD. Total CVD event risk for men is about 3X higher than the fatal CVD risk calculated by the SCORE system. The multiplier is lower in the elderly and higher in women.
If Statin Intolerant
Consider Ezetimibe
If goal is not achieved, consider adding PCSK9 Inhibitor



LDL > 4 mmol = 154 mg/dl
LDL>4.5 mmol= 174 mg/dl
LDL>5 mmol = 193mg/dl
LDL>8.5 mmol = 328 mg/dl

HoFH: Definition according to the EAS Consensus Panel Statement

Box 1 Criteria for the diagnosis of homozygous familial hypercholesterolaemia

- Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus

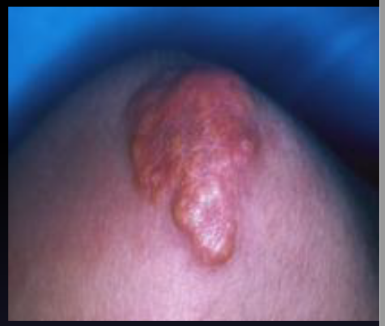
OR

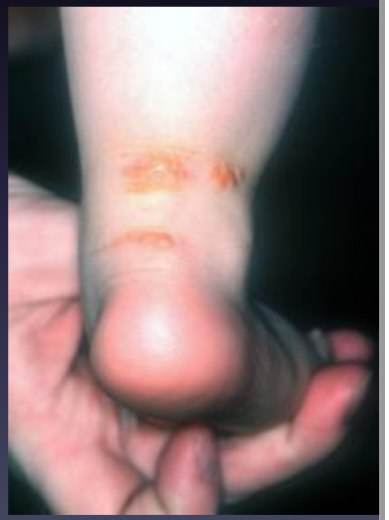
- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years

or

  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH





Cuchel M, Bruckert E, Ginsberg H et al. Eur Heart Journal 2014

Case presentation

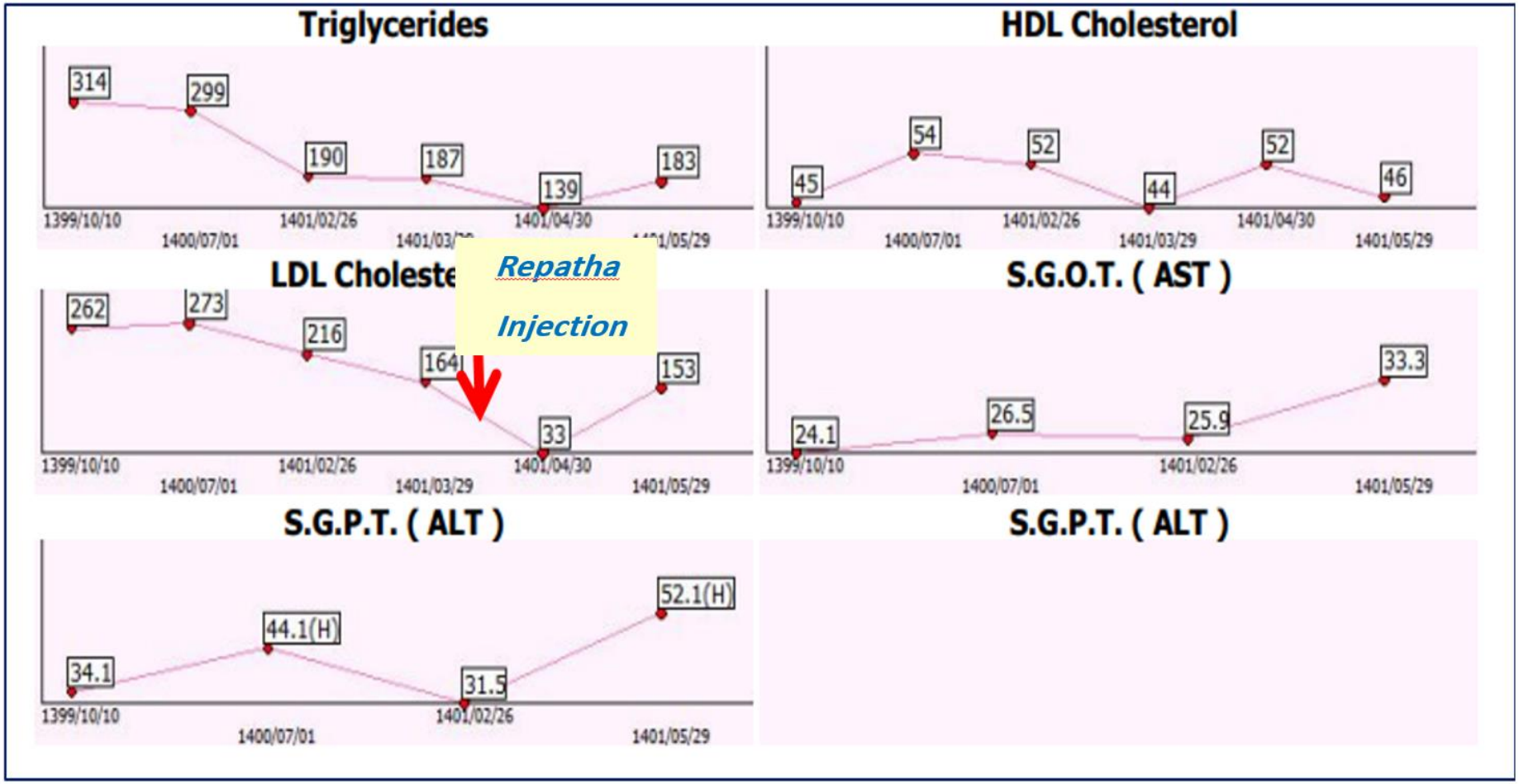
Case CAD & DLP

- ✓ A male 62 years
- ✓ Hx PCI 10 years age
- ✓ Familial Dyslipidemia
- ✓ DM , HTN
- ✓ Lipid drugs : Rosuvastatin 40 mg/d , Ezetimibe 10mg/d
- ✓ LDL= 164 mg/dl

Case CAD & DLP -continue

- ✓ Repatha (Evolocumab) 140mg q 2 wks SC
- ✓ significant reduction in LDL
- ✓ LDL 164mg/dl $\xrightarrow{\text{1 month}}$ 33 mg/dl
- ✓ Stop Repatha injection
- ✓ LDL 33mg/dl $\xrightarrow{\text{1 month}}$ 153 mg/dl

Our case -Lipid profile




Thank you