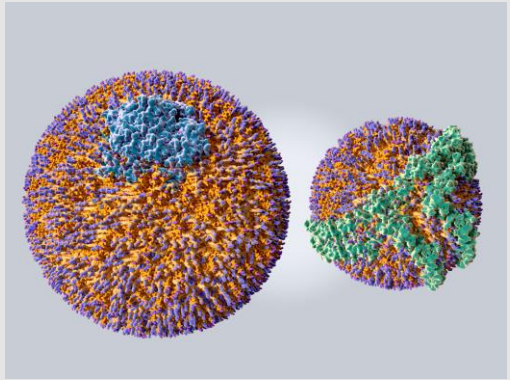
Critical Review of Current Lipid Management Guidelines ACC/AHA/AACE/ESC



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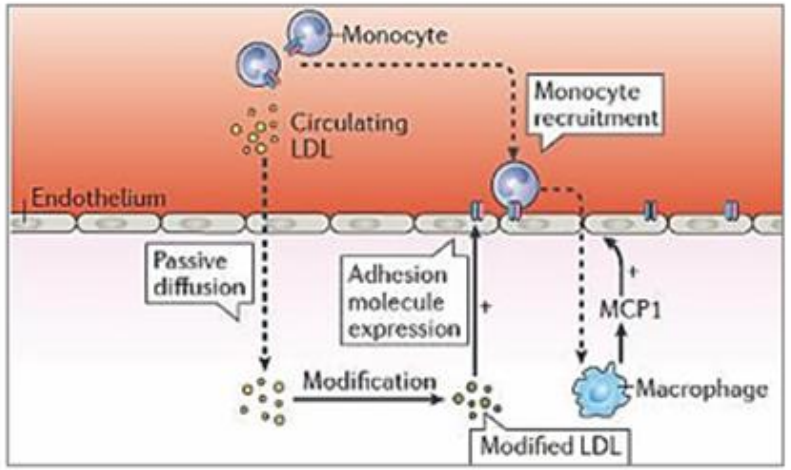
Financial Disclosures

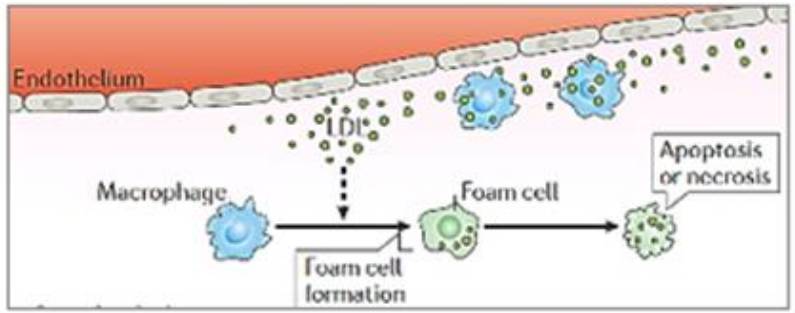
- Lecture Fees:
  - Boehringer Ingelheim
  - Merck
  - Sanofi
  - Amgen
  - Janssen
  - Pfizer

Role of Lipoproteins In the Stages of Atherosclerosis

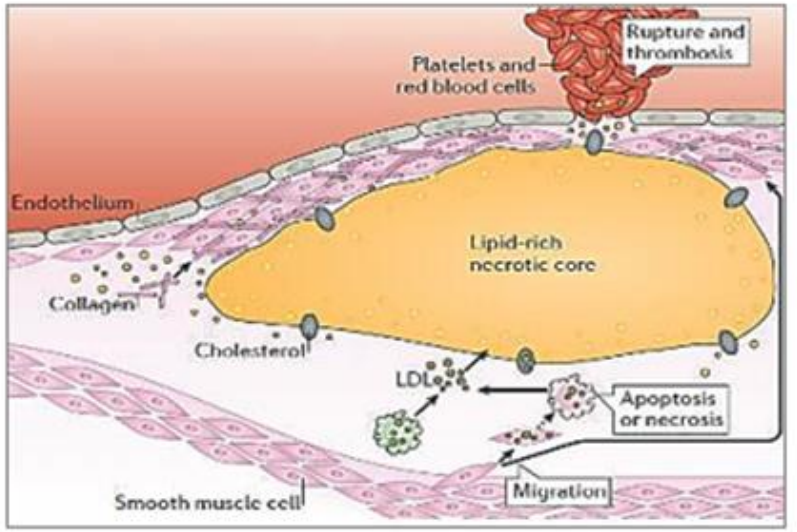
a. Initial Trigger



b. Fatty Streak



c. Complex Lesion



Evidence of **LDL-c** as a target of Therapy

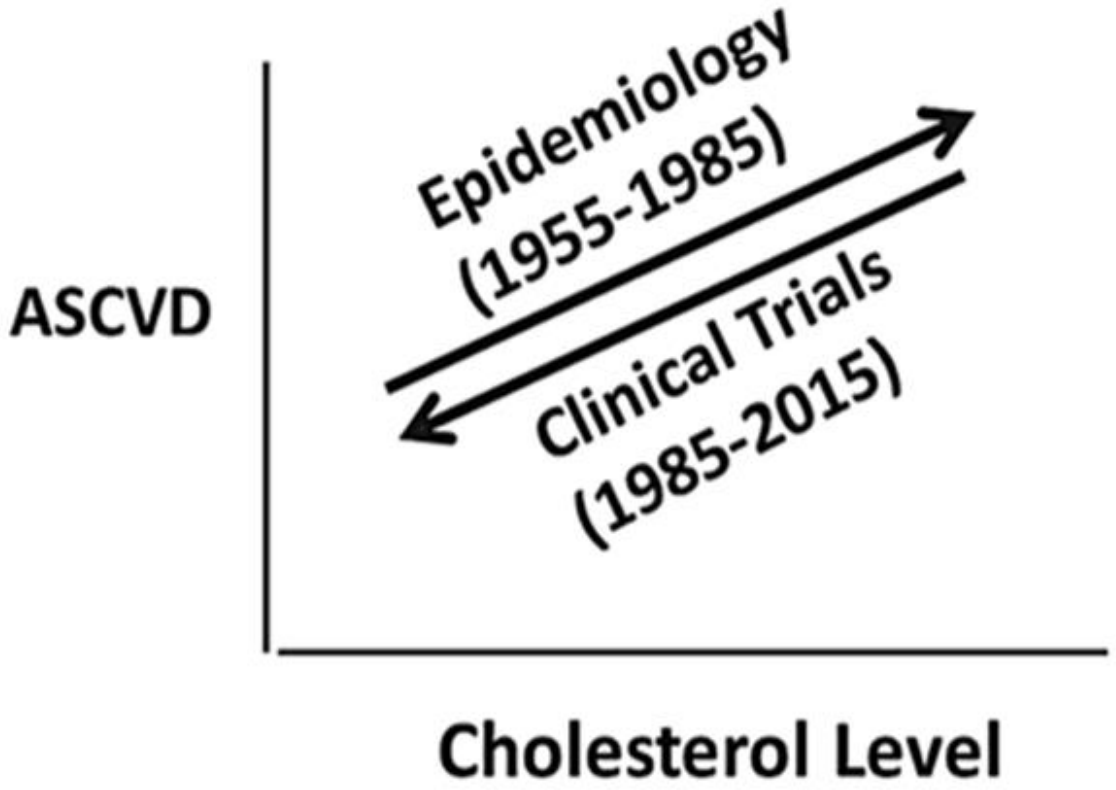
- **LDL –C comprises 75 % of the cholesterol carried** by circulating apo-B containing lipoproteins
- **LDL-C meets multiple criteria for causality related to ASCVD**, specificity, consistency, and proportional reduction in risk with intervention
- **LDL-C is the most studied lipid parameter in RTCs** and the primary target of lipid lowering therapy

Evidence for **Non-HDL-C** as a target of therapy

- **Non- HDL-C = Total cholesterol -HDL-C** Measures the cholesterol in all atherogenic particles (LDL, IDL, VLDL, remananets, Lpa), at no added cost
- **Non-HDL-C correlates more with Apo-B and LDL particle number** than those LDL-C when TGs are elevated, and is superior to LDL-C predicting ASCV risk
- **Non- HDL has limited appearance in U.S. guidelines due to underuse in RCTs,** but is a secondary target in NLA and non-U.S. guidelines

Summary of the Lipid Treatment Science Base

Bi-Directional Link between Cholesterol and ASCVD



Population Studies
Genetic Studies of FH

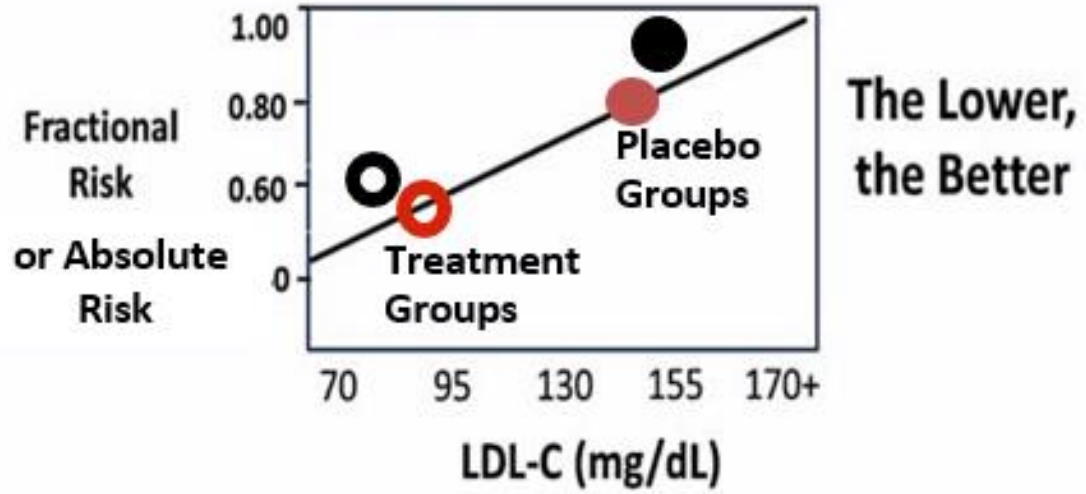
Mendelian Randomization

Angiographic RCTs
Clinical RCTs

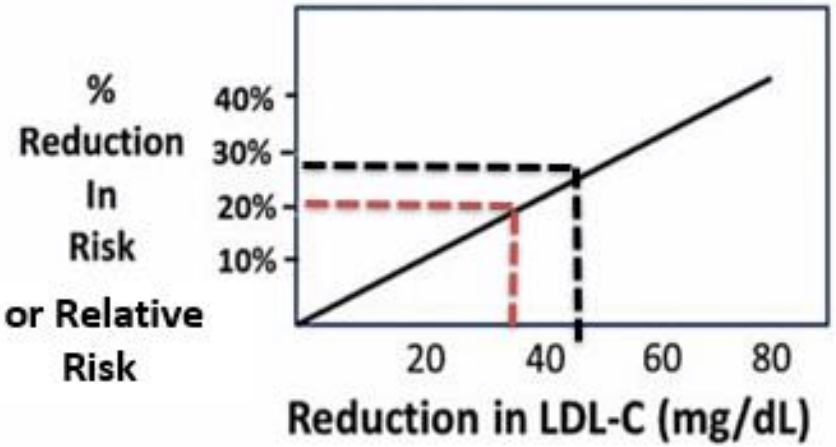
RCTs = randomized clinical trials

Interpreting Clinical Trials of Lipid Lowering

Two Interpretations of the Evidence



The Lower, the Better



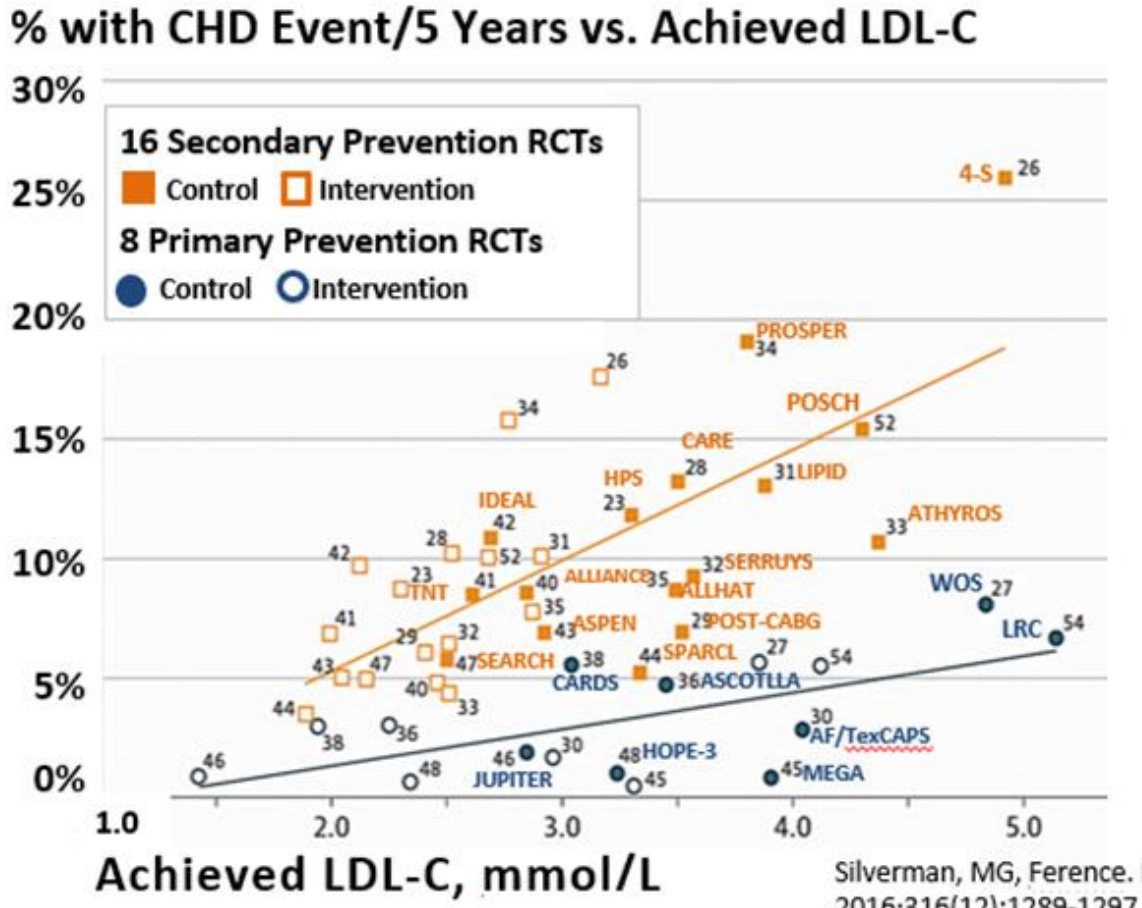
The More, the Better

Modified from:
Grundy S.
https://www.ncbi.nlm.nih.gov/ks/NBK305897/

nla
NATIONAL LIPID ASSOCIATION

Evidence that a *Lower Achieved LDL* is Better

Linear Relationship to *Absolute* CV Risk in 24 RCTs

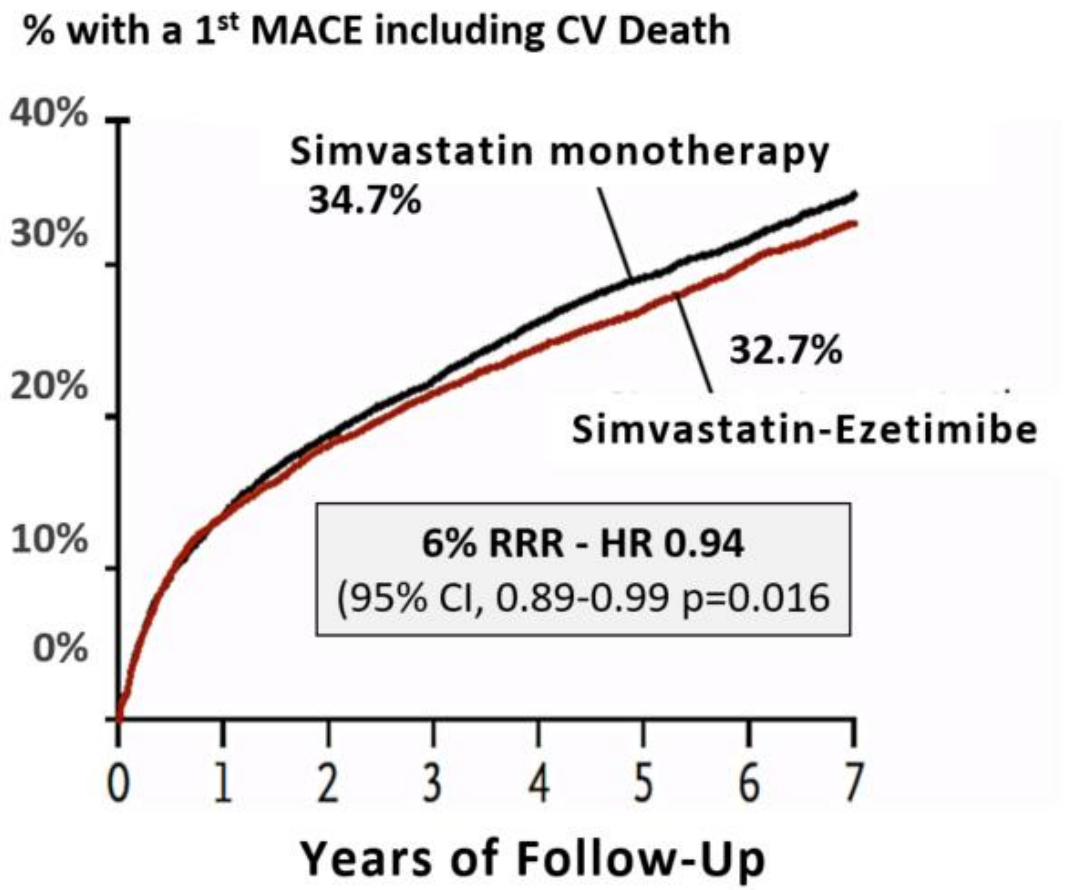


In a meta-analysis of 24 RCTs, each 1 mmol/L lower achieved LDL-C reduces absolute risk of CHD events 4.6% in secondary prevention, and 1.5% in primary prevention

Silverman, MG, Ference. BA et al. JAMA 2016;316(12):1289-1297

New Evidence that Lower Is Better

IMPROVE-IT – Statin + Ezetimibe Post-ACS if LDL ≥70 mg/dL



IMPROVE IT Design

N = 18,144 post-ACS
Age ≥ 50 + High risk
LDL ≥ 70 (Median 94 mg/dL)
Randomized to
- Simvastatin 40 mg + EZ
- Simva 40 mg + Placebo

Endpoint – MACE
Median F/U - 6 years

Results in Treatment Arm

Median LDL = **53 mg/dL**
HR for 1st MACE 0.94
HR for recurrent MI 0.88

Cannon CP et al. N NEJM. 2015;372(25):2387–2397. Murphy, S, Cannon, CP et al.JACC 2016;67:353-61.

New Evidence that Even Lower is Even Better

FOURIER - PCSK9-Inhibition in Stable CAD when LDL ≥70 mg/dL

FOURIER Design

N = 27,564 with stable ASCVD

LDL-C ≥70 or non-HDL-C ≥100

On high intensity statin (90%)

Randomized to

- Evolocumab 140 mg q 2 wks
- Placebo

Endpoint – MACE

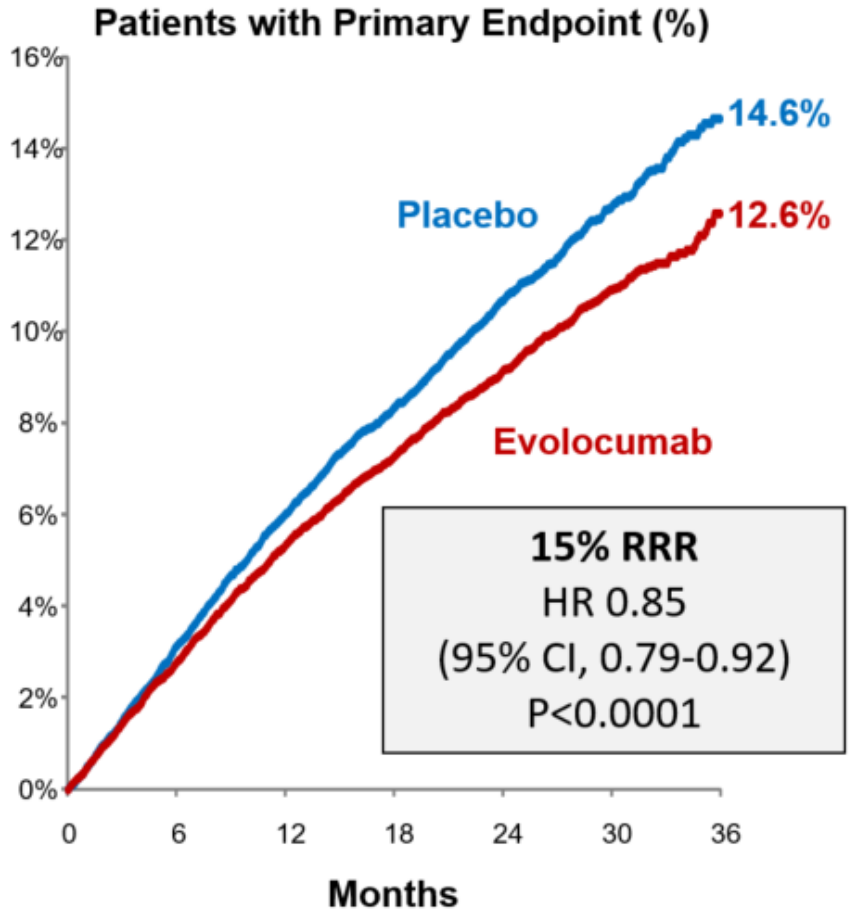
Median F/U - 26 months

Results in Treatment Arm

Median LDL = **30 mg/dL**

HR for MACE = 0.85

AE's - injection site reactions



Sabatine MS et al. N Engl J Med 2017;376:1713-22.

More Evidence that Even Lower is Better

ODYSSEY Outcomes - PCSK9i Post-ACS when LDL ≥70 mg/dL

ODYSSEY Design

N = 18,924 w/ recent ACS

LDL ≥70 non-HDL-C ≥100 or ApoB ≥80

On maximal statin therapy

Randomized to

- Alirocumab 75-150 q 2 weeks
- Placebo

Endpoint – MACE

Follow up - 2.8 years

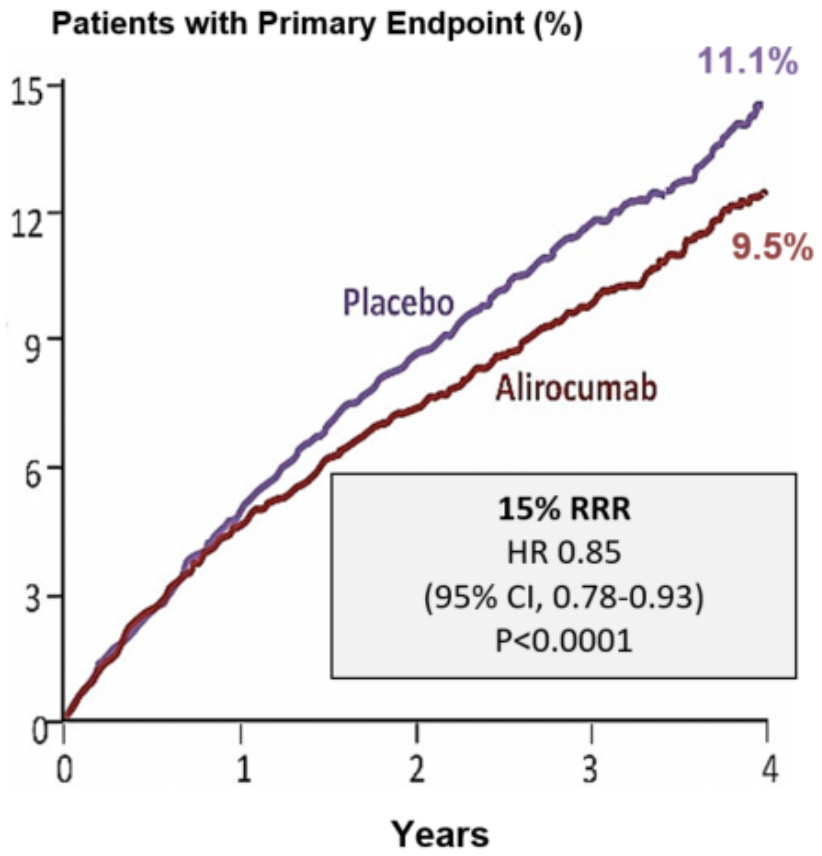
Results in Treatment Arm

Median LDL @ 48 mos **53 mg/dL**

Median LDL @ 4 mos **38 mg/dL**

HR for MACE = 0.85

AEs – Injection site reactions



Schwarts GG, et al. N Engl J Med 2018;379:2097-107.

Objectives

- 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol
- 2019 ESC/EAS Guidelines for the management of dyslipidemias
- AACE 2017 Guidelines

Circulation

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

2018 AHA/ACC Multi-society Cholesterol Guidelines

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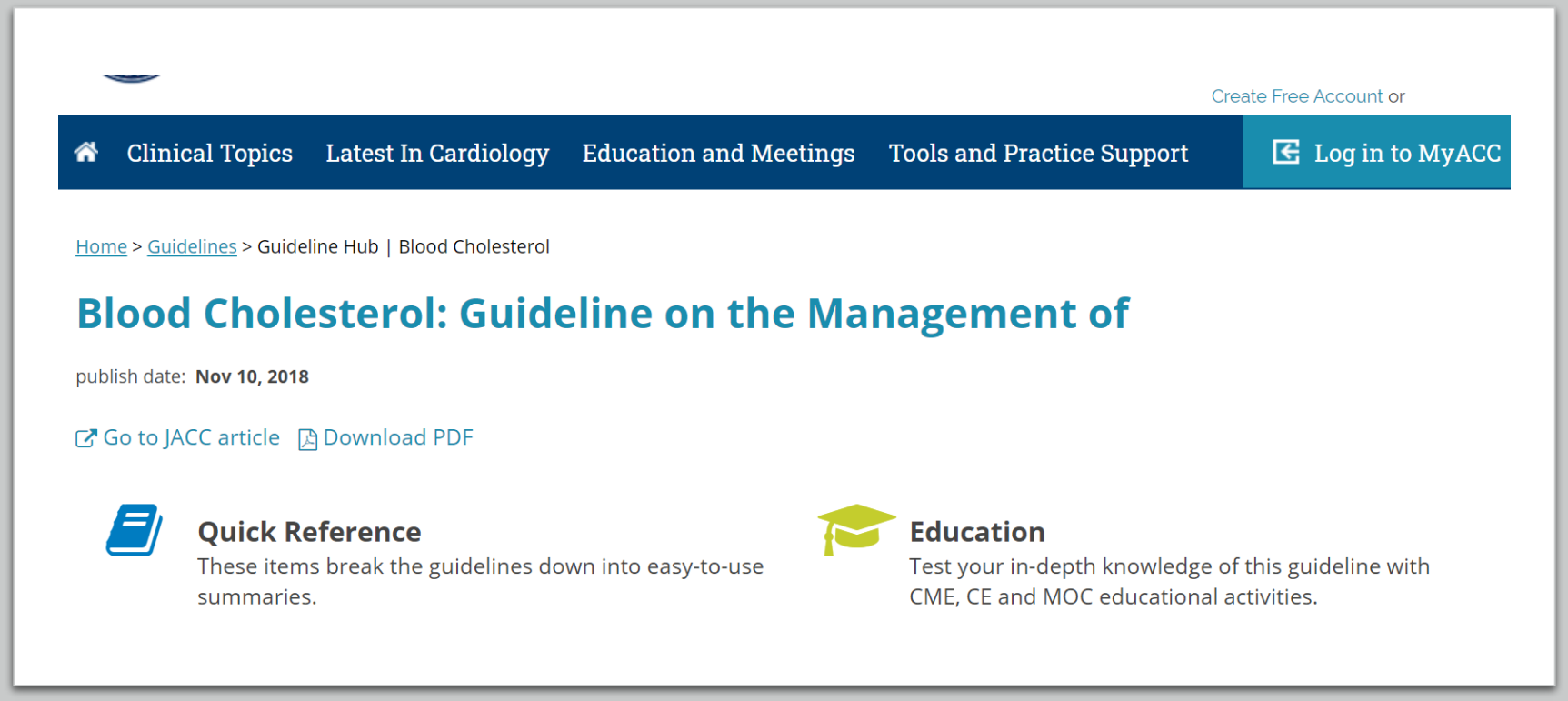


Google:
"Hub Cholesterol"

- Calculator Note: No separate PCE is available for Hispanic/Latino; use PCE for non-Hispanic whites. If African American ancestry is also present, then use PCE for blacks.
- Risk of MACE in 10 years

LEVEL (QUALITY) OF EVIDENCE

LEVEL A

- High-quality evidence from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)

- Moderate-quality evidence from 1 or more RCTs
- Meta-analysis of moderate-quality RCTS

LEVEL B-NR (Nonrandomized)

- Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

- Consensus of expert opinion based on clinical experience

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG)
Benefit >>> Risk

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administrated/other
- Comparative-Effectiveness Phrases:
  - Treatment / strategy A is recommended / indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE)
Benefit >> Risk

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases:
  - Treatment/strategy A is probably recommended/indicted in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK)
Benefit ≥ Risk

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered

Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE)
Benefit = Risk

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG)
Risk > Benefit

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

Top 10 Take-Home Messages for the 2018 Cholesterol Guidelines

Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

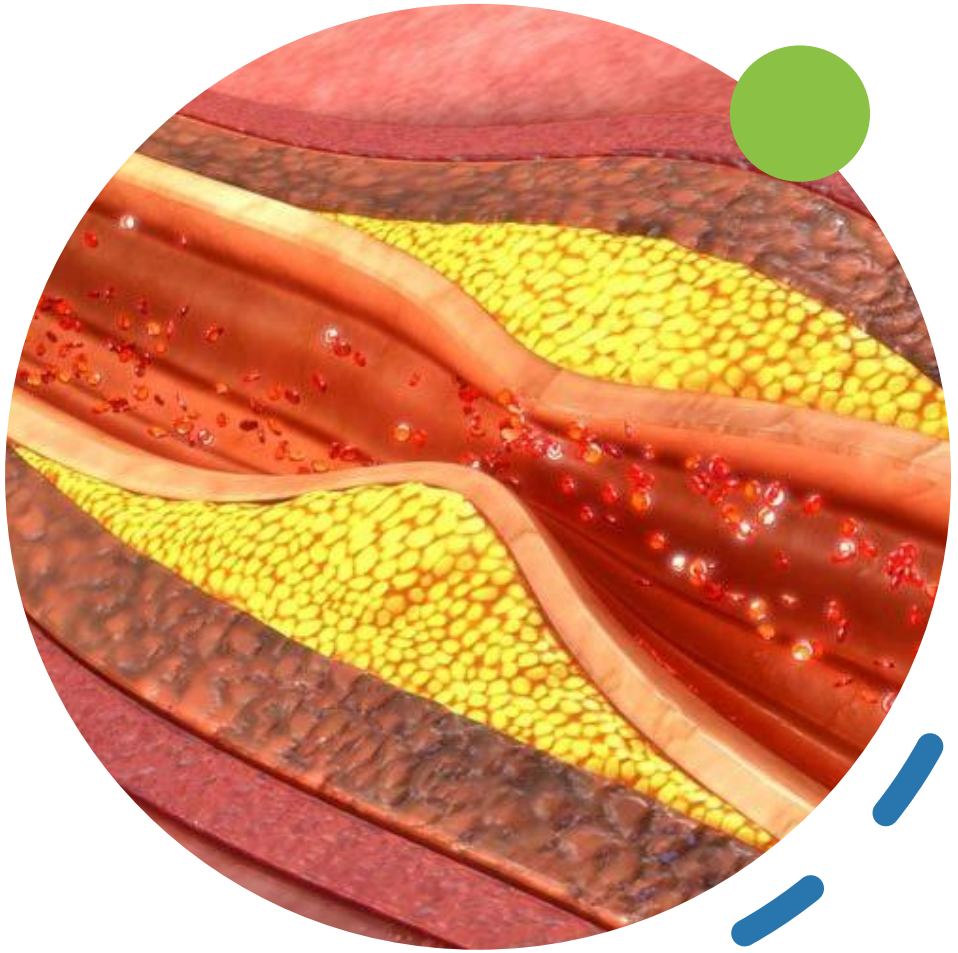
In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Top 10 Take Home Messages

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.



Statin intensity

- **Every decrease in LDL of 40 mg/dl (1.0 mmol/L) → 20-25% relative reduction in risk**

	Low intensity (↓ LDL < 30%)	Moderate intensity (↓ LDL 30-49%)	High intensity (↓ LDL ≥ 50%)
Atorvastatin		10 - 20 mg	40 - 80 mg
Fluvastatin	20 - 40 mg	40 - 80 mg	
Lovastatin	20 mg	40 - 80 mg	
Pitavastatin		1 - 4 mg	
Pravastatin	10 - 20 mg	40 - 80 mg	
Rosuvastatin		5 - 10 mg	20 - 40 mg
Simvastatin	10 mg	20 - 40 mg	

Top 10 Take Home Messages

3. In very high-risk ASCVD, use an LDL-C threshold of 70 m/dL to consider addition of non-statins to statin therapy.

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable

Very High Risk of Future ASCVD Events

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

Major ASCVD Events

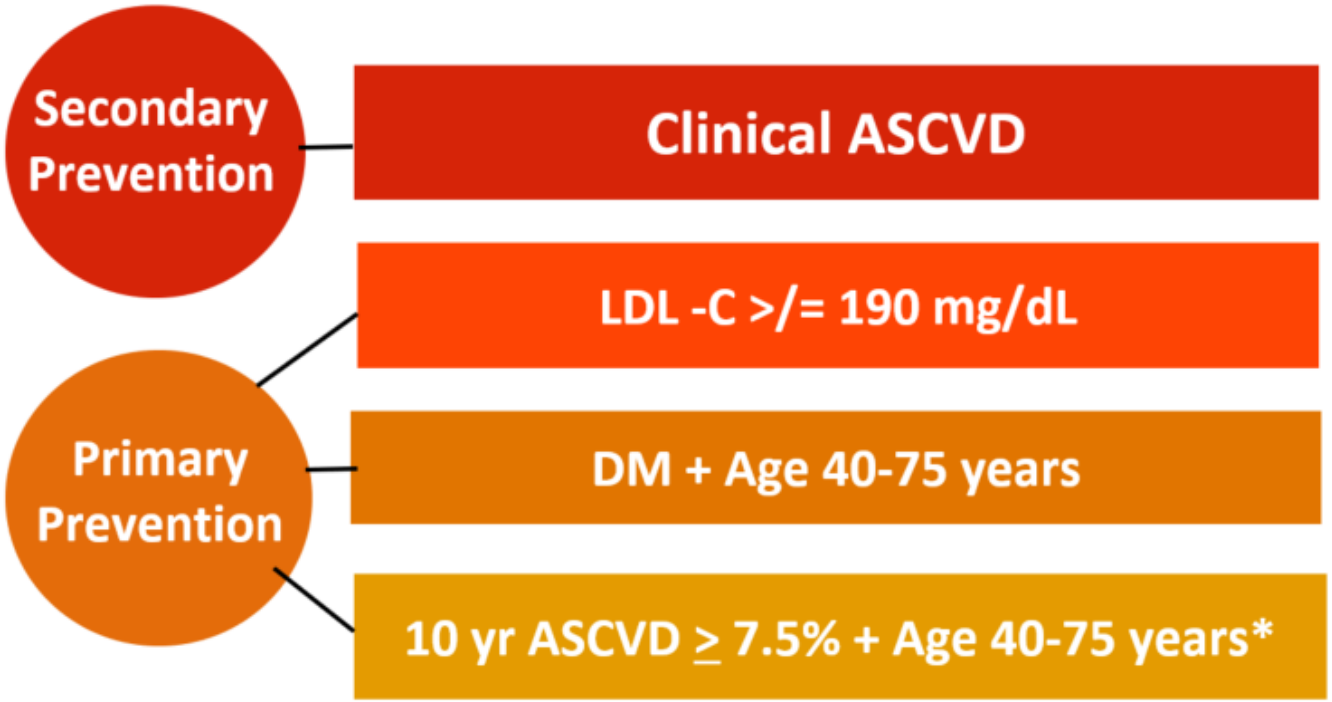
- -Recent ACS (within the past 12 months)
- -History of MI (other than recent ACS event listed above)
- -History of ischemic stroke
- -Symptomatic peripheral arterial disease (history of claudication with ABI <0.85 or previous revascularization or amputation

High Risk Conditions

- -Age ≥ 65 y
- -Diabetes Mellitus
- -Hypertension
- -Current smoking
- -Chronic Kidney Disease (eGFR 15-59 ml/min/1.73m^2)
- -Heterozygous familial hypercholesterolemia
- -Persistently elevated LDL-C (LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe
- -History of congestive HF

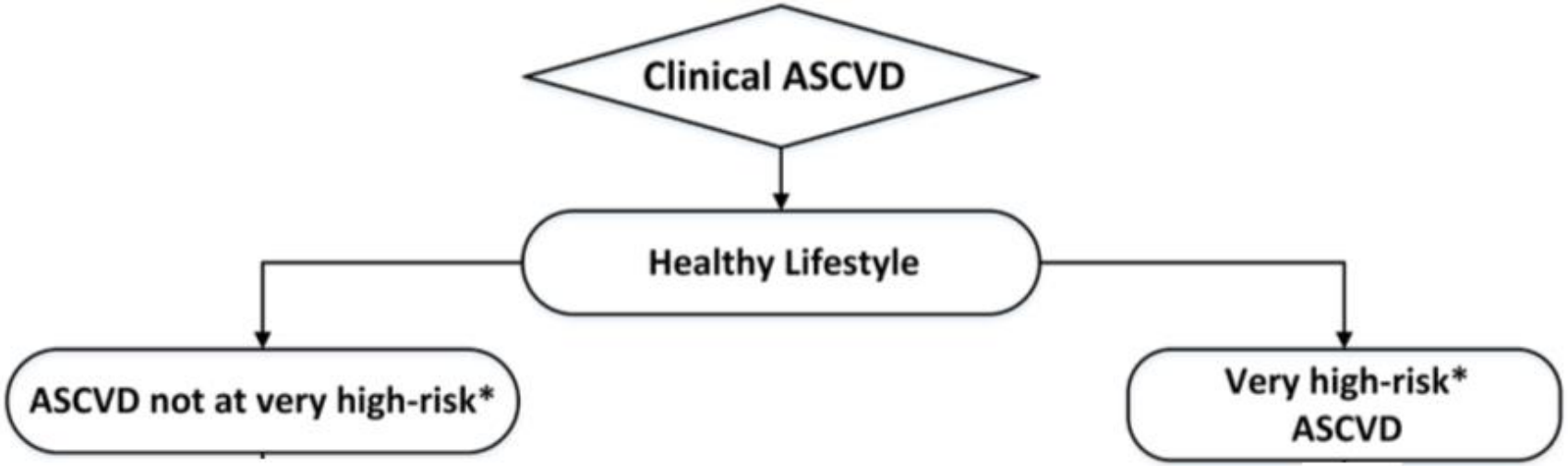
4 Statin Benefit Groups

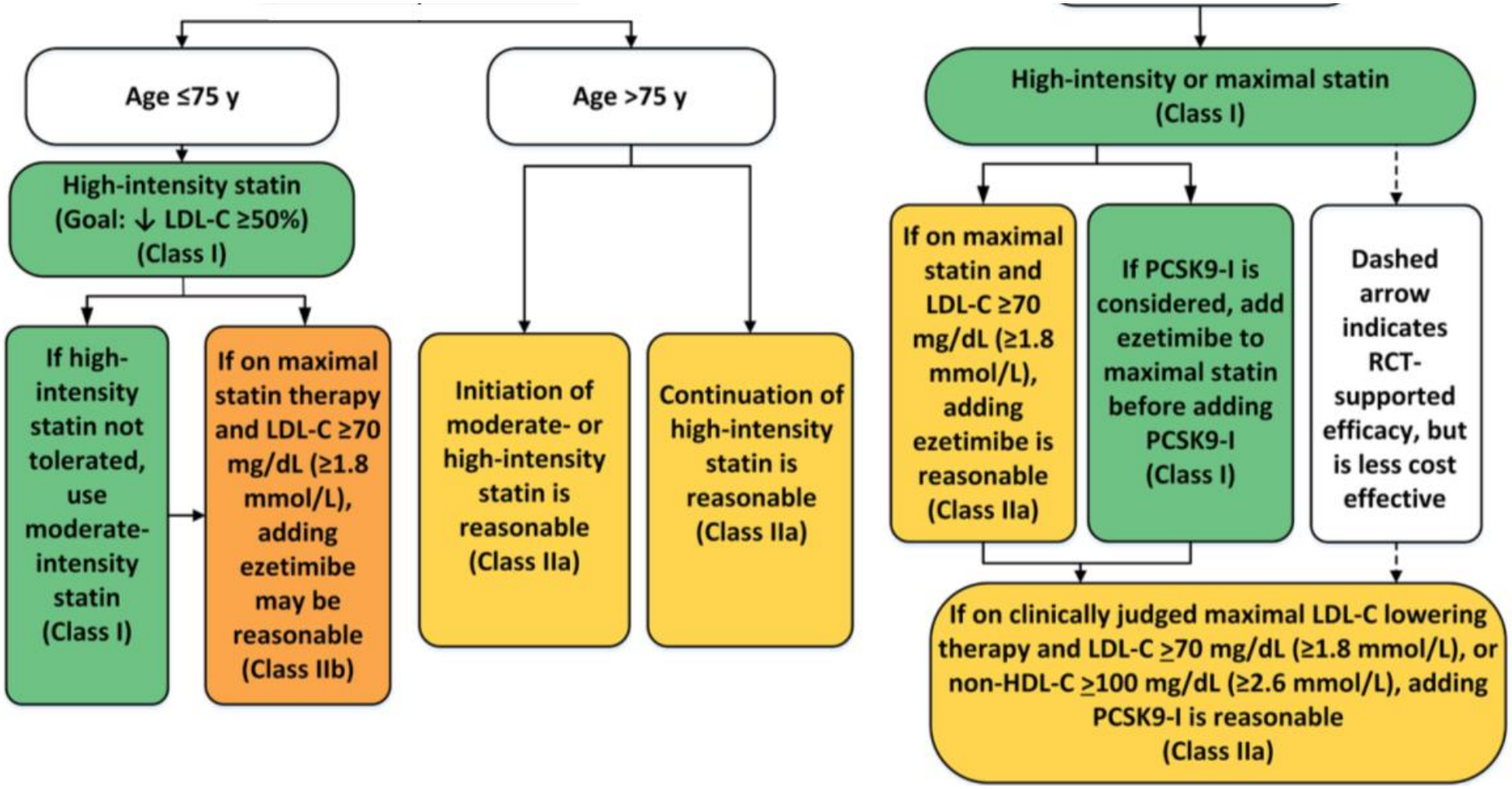
Groups In Whom Benefits Outweigh Risks

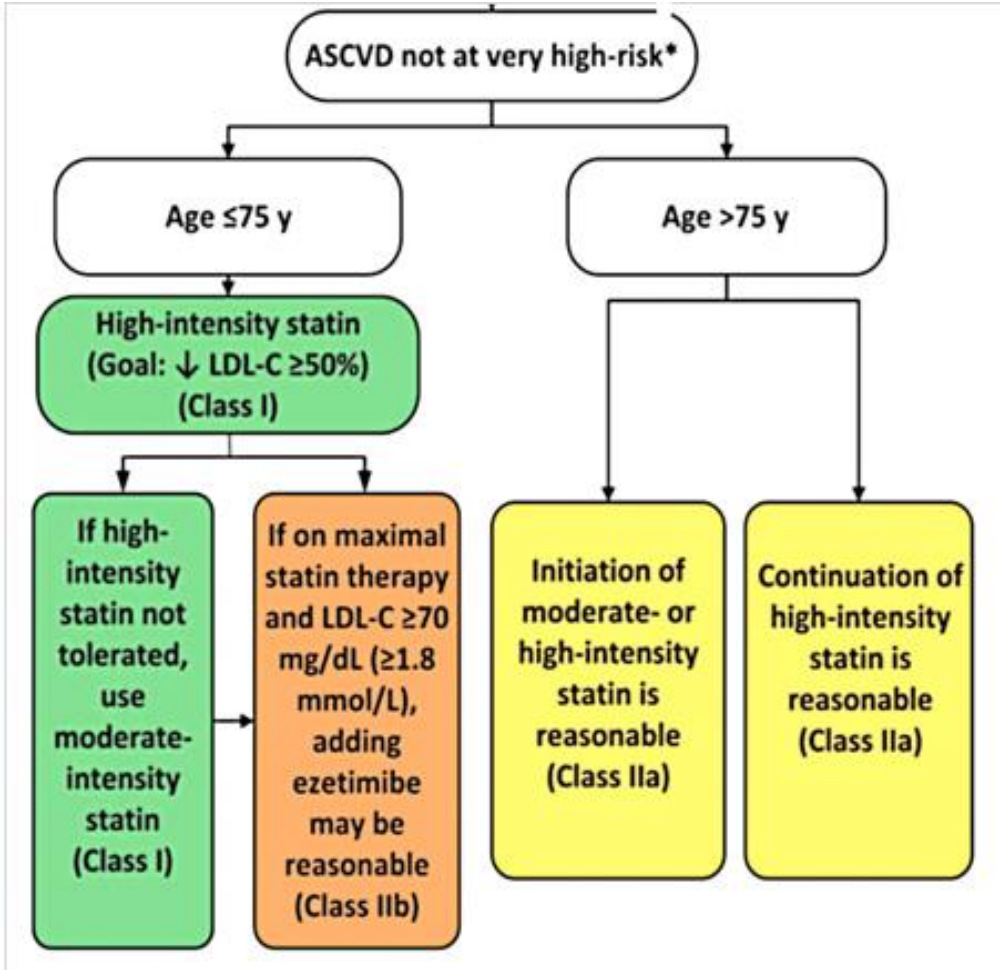


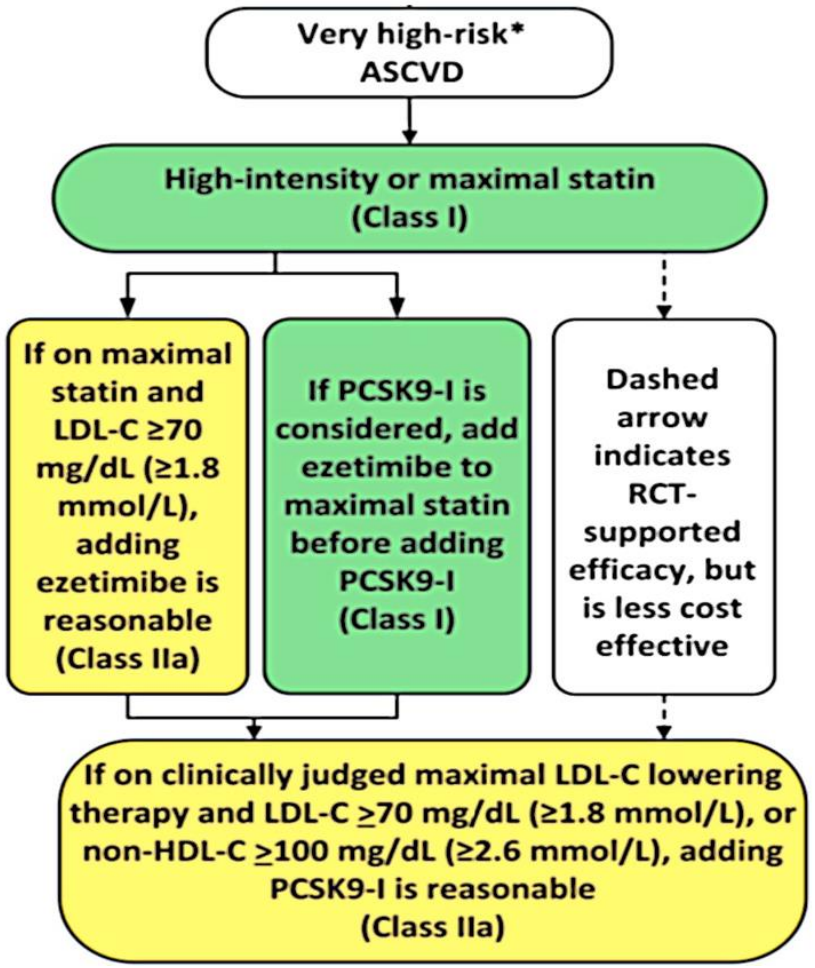
* where evidence has demonstrated benefit

Stone NJ, et al, J Amer Coll Card 2013, doi10.1016/jacc2013.11.002


Clinical ASCVD
Healthy Lifestyle
ASCVD not at very high-risk*
Very high-risk* ASCVD


Age ≤75 y
Age >75 y
High-intensity statin
(Goal: ↓ LDL-C ≥50%)
(Class I)
If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)
High-intensity or maximal statin
(Class I)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)
If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)
Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable
(Class IIa)


ASCVD not at very high-risk*
Age ≤75 y
Age >75 y
High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)
If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)

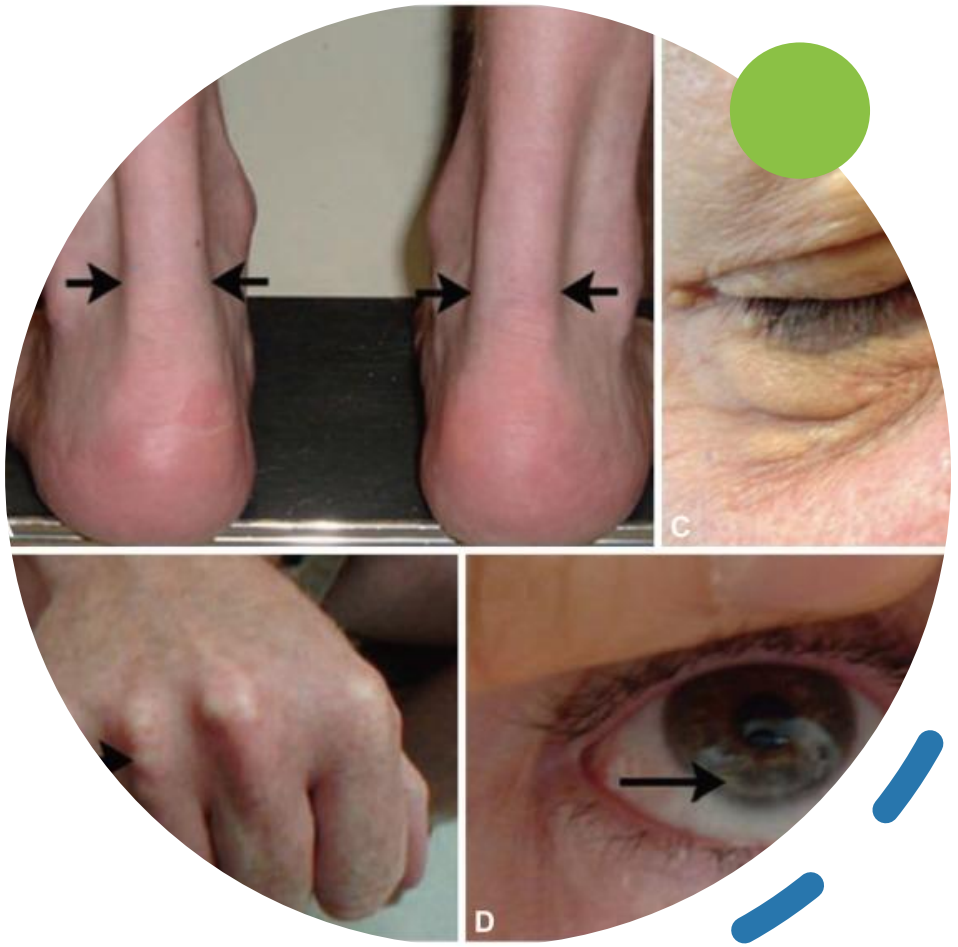

Very high-risk* ASCVD
High-intensity or maximal statin (Class I)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)
If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)
Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

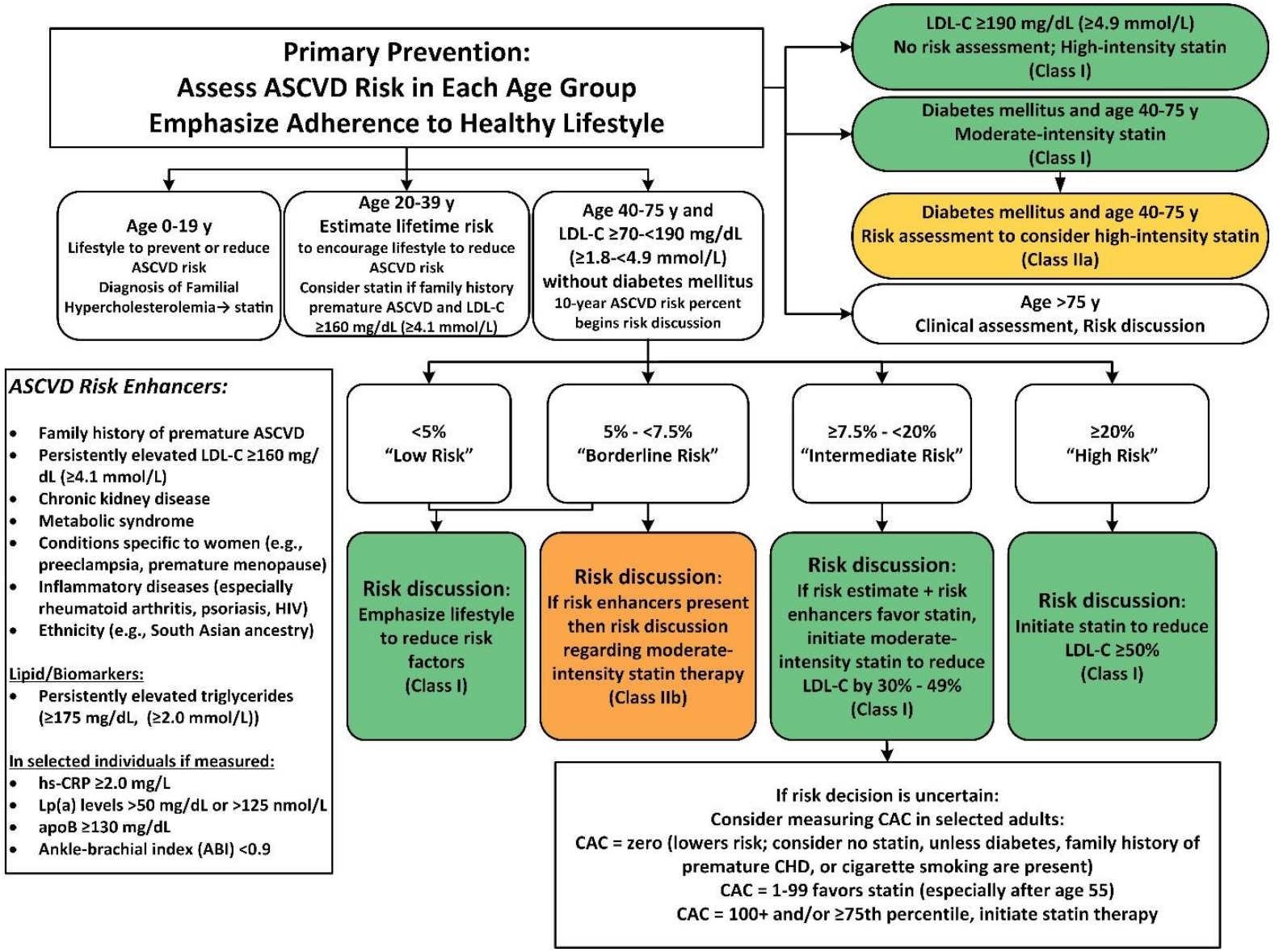
Top 10 Take Home Messages

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. (Any age)

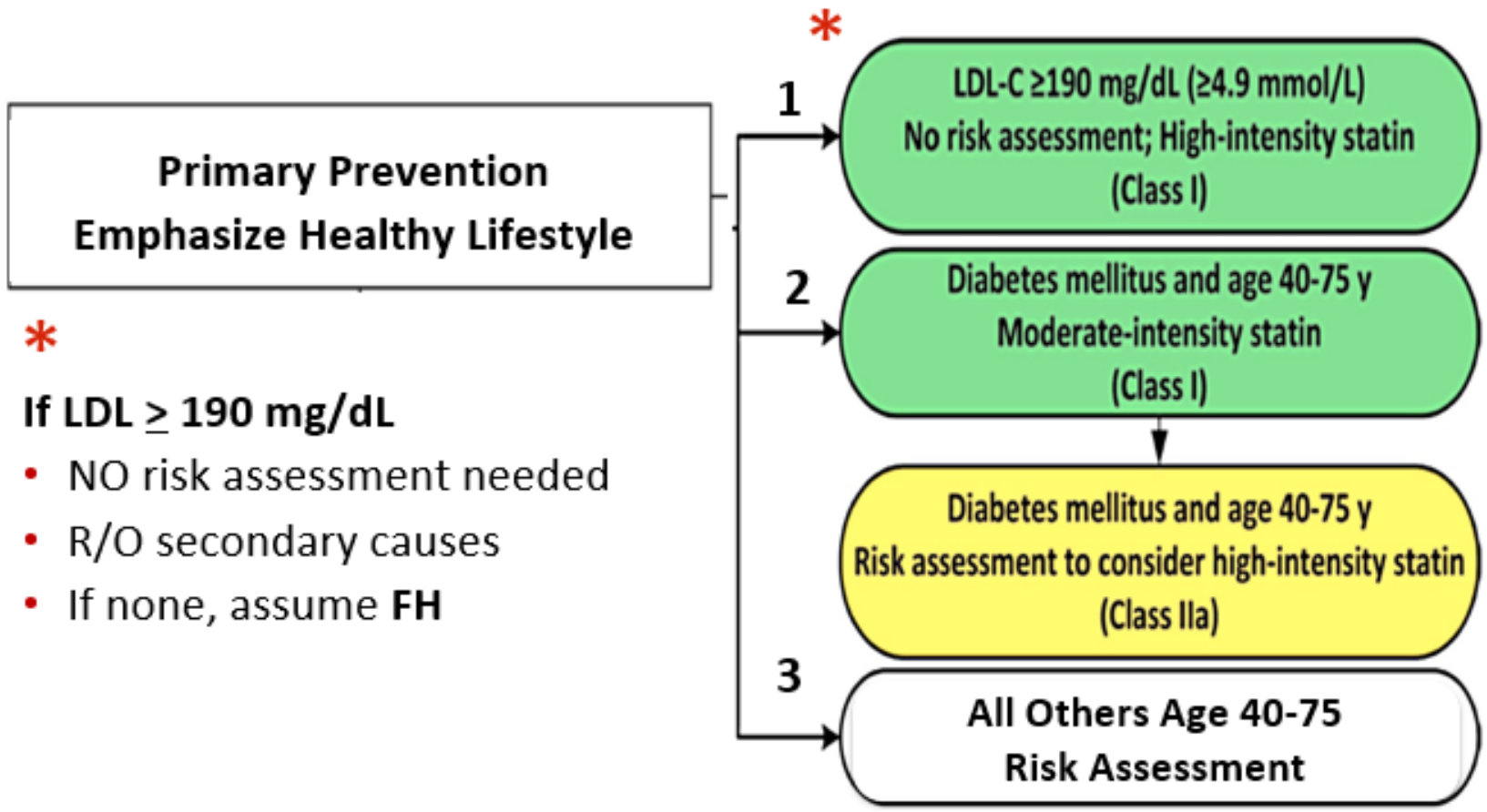
- If the LDL-C level remains ≥100 mg/dL adding **ezetimibe** is reasonable

- If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL & the patient has multiple factors that increase subsequent risk of ASCVD events, a **PCSK9 inhibitor** may be considered




Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and
LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)
without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Primary Prevention - LDL ≥ 190 mg/dL



Grundy SM, et al. Circulation 2019;139(25):e1082-e1143

Top 10 Take Home Messages

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

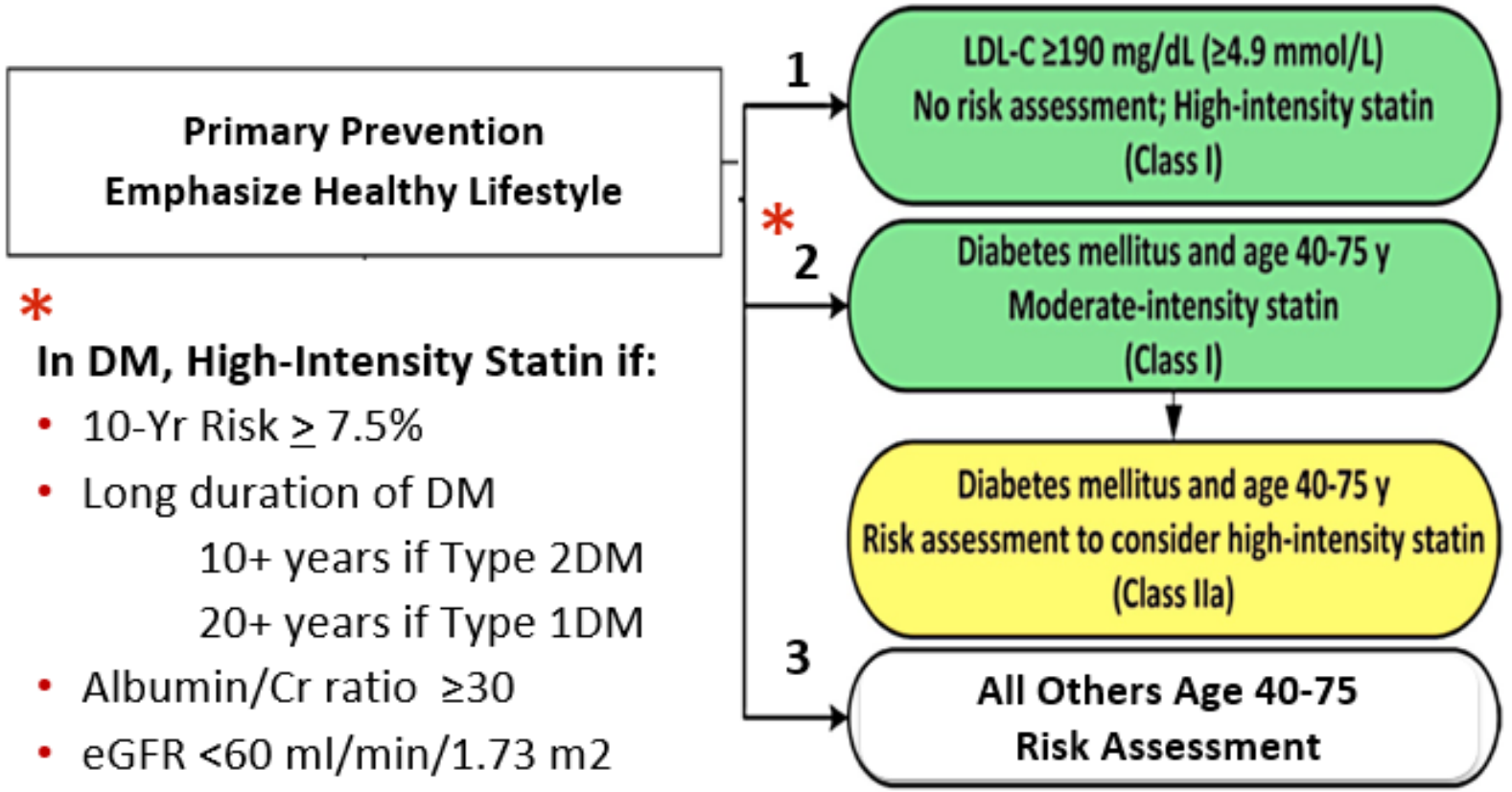
In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

Diabetes (DM); no ASCVD
In adults 40-75 years; LDL-C 70-189 mg/dL

- *Diabetes* present: No initial risk assessment
  - **Start moderate intensity statin**
  - Use high intensity statin in if high risk features

- **Changed from the 2013 Guideline for diabetes**
  - **10-year ASCVD risk 7.5%**

Primary Prevention – DM 40 – 75 Years



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In DM, High-Intensity Statin if:

- 10-Yr Risk ≥ 7.5%
- Long duration of DM
  - 10+ years if Type 2DM
  - 20+ years if Type 1DM
- Albumin/Cr ratio ≥30
- eGFR <60 ml/min/1.73 m2
- Retinopathy
- Neuropathy
- ABI <0.9

Grundy SM, et al. Circulation 2019;139(25):e1082-e1143

Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
• Long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus) • Albuminuria ≥30 mcg of albumin/mg creatinine • eGFR <60 mL/min/1.73 m^2 • Retinopathy • Neuropathy • ABI <0.9

Top 10 Take Home Messages

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

The presence of risk-enhancing factors

The potential benefits of lifestyle and statin therapies
The potential for adverse effects / interactions

The consideration of costs of statin therapy
The patient preferences & values in shared decision-making

Top 10 Take Home Messages

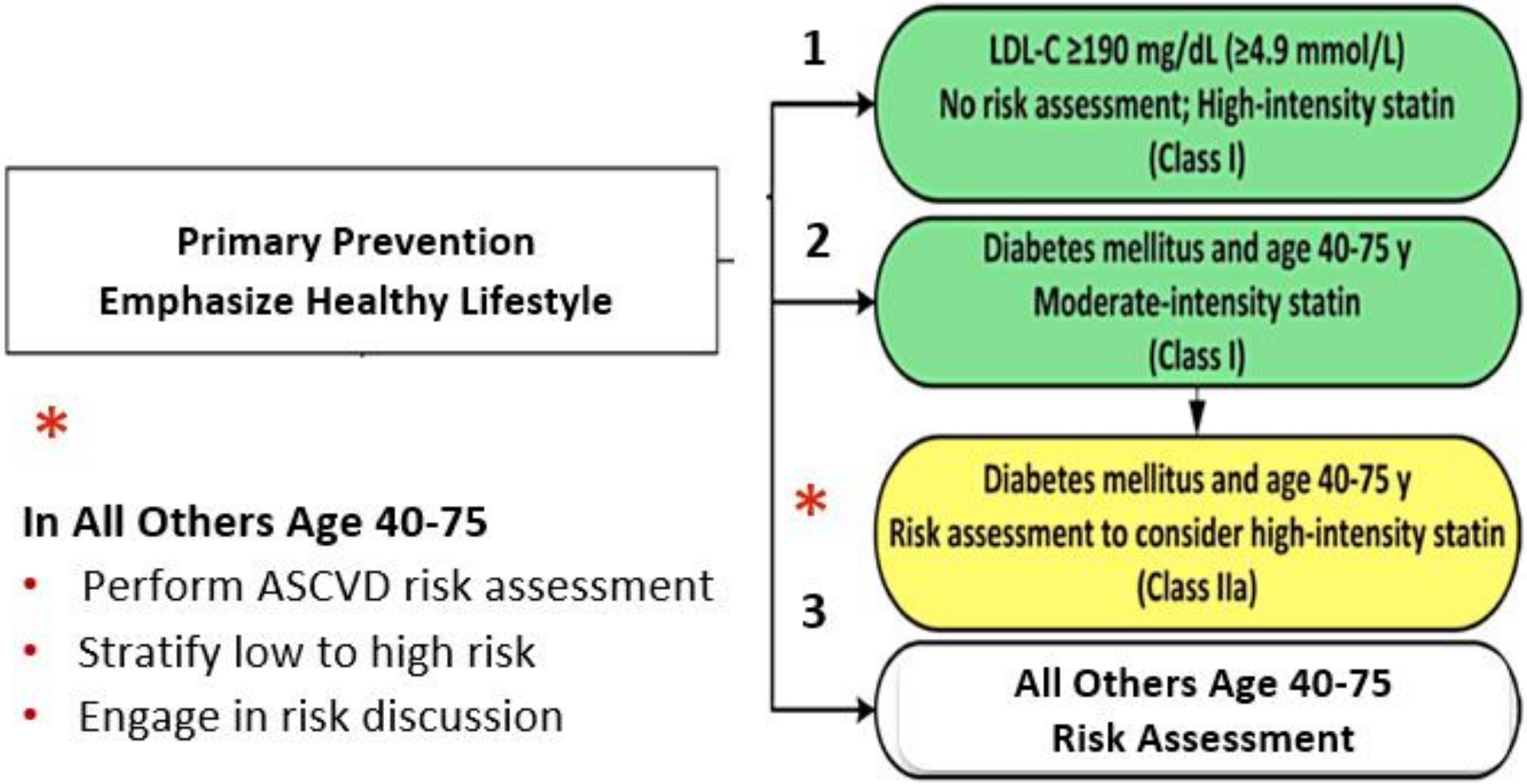
:TOOLS TO ACCOMPLISH THIS

-CALCULATE 10 YEAR AND LIFETIME ASCVD RISK SCORES

-PERSONALIZE WITH RISK ENHANCING FACTORS

-RECLASSIFY RISK IF RISK DECISION UNCERTAIN WITH CORONARY ARTERY CALCIUM SCORE

Primary Prevention – All Others



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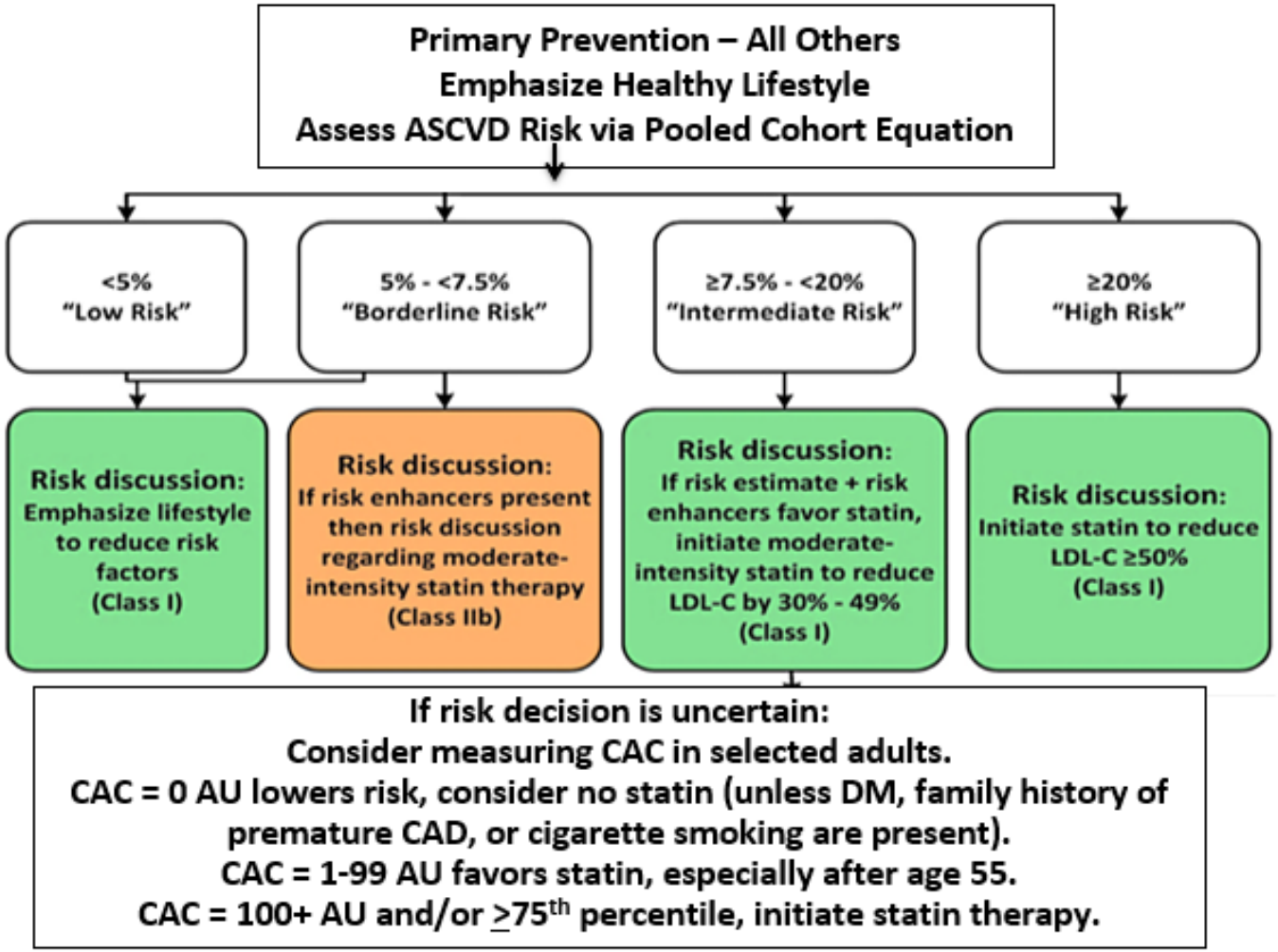
In All Others Age 40-75

- Perform ASCVD risk assessment
- Stratify low to high risk
- Engage in risk discussion

All Other Primary Prevention – Assess Risk



Risk Enhancing Factors

Consider in Intermediate or Borderline-Risk Patients

- **Family History** of premature ASCVD
- **Metabolic Syndrome** based on standard criteria
- **Chronic Kidney Disease**
  - eGFR 15–59 mL/min/1.73 m2 +/-albuminuria
  - Not on dialysis
- **Chronic Inflammatory Conditions**
  - Rheumatoid Arthritis, Systemic Lupus, HIV
- **Female-Specific Risk Factors**
  - History of pre-eclampsia OR early menopause before age 40
- **Ethnicity**
  - South Asian ancestry

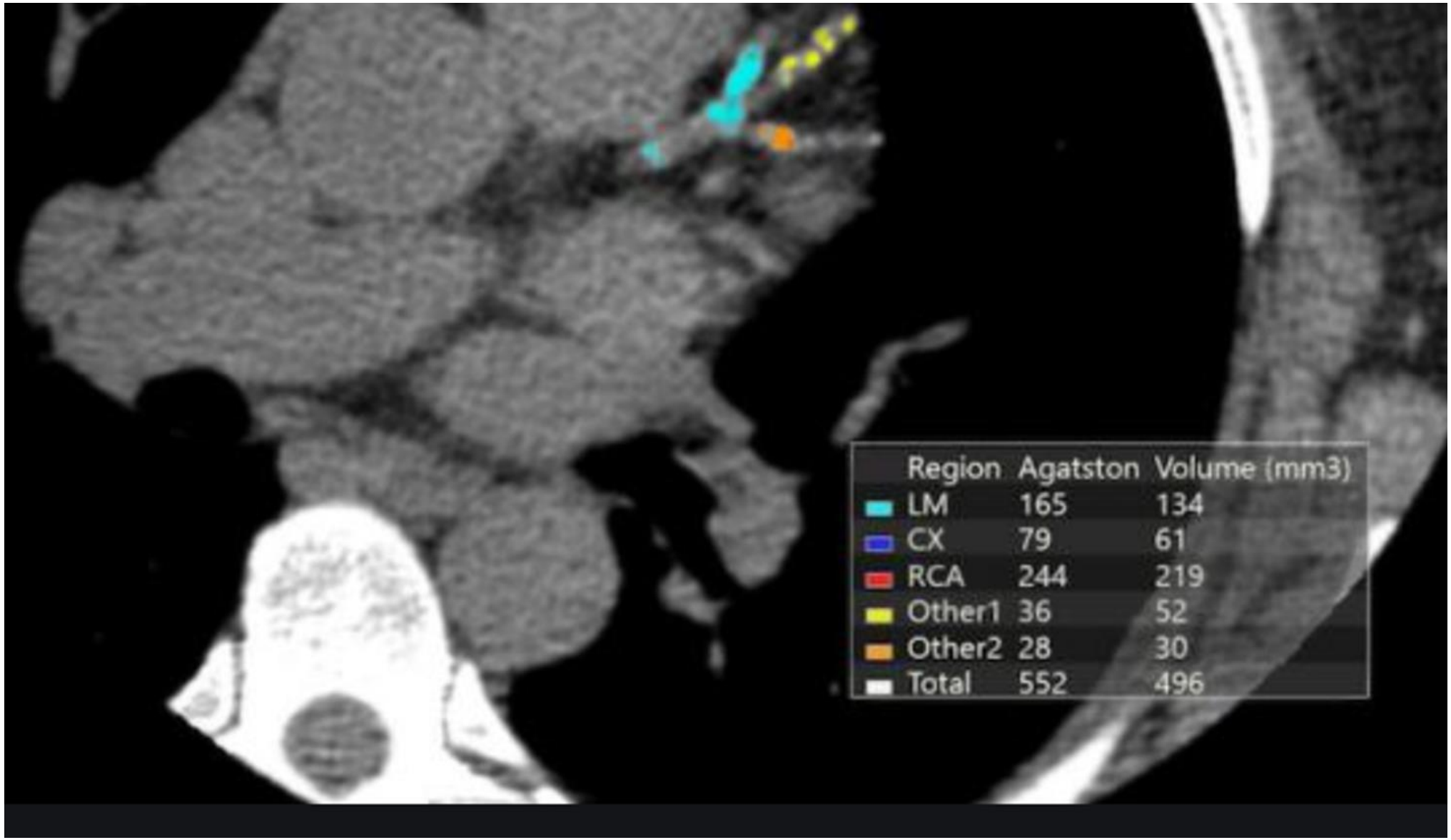
Grundy SM, et al. Circulation 2019;139(25):e1082-e1143

Risk Enhancing Factors-cont'd

Consider in Intermediate or Borderline-Risk Patients

- **Lipid/Risk Biomarkers**
  - Persistent LDL 160-189 mg/dL
  - Persistent primary TG elevation ≥ 175 mg/dL
  - High-sensitivity C-reactive protein ≥ 2.0 mg/dL
  - Apo B ≥ 130 mg/dL
  - Ankle brachial index <0.9
  - Lipoprotein(a) ≥125 nmol/L (≥ 50 mg/dL)

Grundy SM, et al. Circulation 2019;139(25):e1082-e1143


Region Agatston Volume (mm3)
LM 165 134
CX 79 61
RCA 244 219
Other1 36 52
Other2 28 30
Total 552 496

Top 10 Take Home Messages

7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity. If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

Top 10 Take Home Messages

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy

Top 10 Take Home Messages

9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

An Evidence-Based Schema for Use of CAC

Can Reclassify ASCVD Risk Between 7.5 – 19.9%

Using 10-year ASCVD risk estimate plus coronary artery calcium (CAC) score to guide statin therapy				
Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate	<5%	5-7.5%	>7.5-19.9%	>20%
Using ASCVD Risk Estimate alone	Statin not recommended	Consider Statin in select groups*	Recommend Statin*	Recommend Statin*
Using ASCVD Risk Estimate + CAC				
If CAC score = 0	Statin not recommended	Statin not recommended	Statin not recommended	Recommend statin
If CAC score > 0	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Does CAC score modify treatment plan ?	✗ CAC not effective for this population	✓ CAC can reclassify risk up or down	✓ CAC can reclassify risk up or down	✗ CAC not effective for this population

Modified from: Greenland, P et al. JACC 2018:72(4):434-47

* After risk discussion

Primary Prevention Summary

- Any age with FH / persistent severe hypercholesterolemic (LDL > 190 mg/dL); treat with statin
- Age 20-39 y/o with family history and LDL ≥ 160 mg/dL; consider statin
- Age 40-75 y/o and diabetes, treat statin
- Age 40-75y/o, nondiabetic => calculate 10-yr ASCVD risk
  - If > 20%, treat with a statin
  - Between 7.5-20%: assess risk enhancers, obtain CAC score and consider a statin
  - If < 7.5 %: assess risk enhancers, consider a statin
  - If <5 %: lifestyle therapy

Top 10 Take Home Messages

10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL on maximal statin therapy

2018 brough back LDL measurement to assess efficacy and adherence !!

Measurements of LDL-C and Non-HDL-C

Recommendations for Measurements of LDL-C and Non-HDL-C		
COR	**LOE**	**Recommendations**
I	**B-NR**	**In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C.**
I	**B-NR**	**In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C.**

What's changed?

- In secondary prevention a threshold of 70 mg/dl for treatment decision regarding further LDL-C lowering beyond maximal statin therapy with ezetimibe or PCSK9 inhibitors
- In severe primary hypercholesterolemia, a threshold of 100 mg/dl for the treatment decision regarding further LDL-C lowering beyond maximal statin therapy
- In primary prevention, risk groups now include:
  - <5%; 5-7.4%; 7.5-19.9%, 20%
- For borderline and intermediate risk groups, enhancing factors recommended to personalize the risk decision

What's changed?

- For borderline and intermediate risk groups, coronary artery calcium (CAC) score recommended if a risk decision uncertain.
- CAC = 0 may indicate selected individuals whose risk is reclassified to below that of a statin benefit group
  - (not for those with DM, cigarette smoking or family history of premature ASCVD)
- Non-fasting now recommended for screening
- Sections on pediatric considerations, hypertriglyceridemia, older adults >75 years, chronic kidney disease, women, safety and cost-effectiveness considerations.

Other High-Risk Groups Race Ethnicity Considerations

- South Asians have heightened risk for ASCVD c/w otht groups, risk calculator may underestimate risk
- East Asians may have increased sensitivity to statins, not need high intensity statins
- Blacks may have increased prevalence of hypertensio1
- Black women have increased ASCVD risk c/w white women
- Native American/ Alaskan natives have higher rates of ASCVD risk factors c/w whites

Other High-Risk Groups

- If TG are 175-499 mg/Dl look for and address secondary causes
  - Obesity, diabetes, metabolic syndrome
  - Hypothyroidism
  - Medications
- In those with **ASCVD risk** 7.5% high TG may indicate higher risk and may be treated (esp if TG $\geq$ 1000 mg/dL)

CKD

- CKD is a risk enhancing factor
- Statin therapy in CKD stages 1-4 is efficacious and safe
- Continuation of statin therapy with progression to ESRD may be protective
- Initiation of statin in ESRD has not been shown to benefit

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

2019 ESC/EAS Guidelines

- **LDL-C (and ApoB-contaning LP) are key elements in atherogenesis.**
  - *Mendelian randomization studies have confirmed that LDL-C is causally related to ASCVD.*
  - *Raising HDL-C with available therapies do not reduce the ASCVD risk.*
- **The addition of ezetimibe or PCSK9 monoclonal antibodies provides further benefit:**
  - *Further reduction in LDL-C further reduction in ASCVD.*
- **The lower LDL-C levels, the better:**
  - No J-curve effect , apparent safety of low LDL-C values (<1.4 mmol / L - 55 mg/ dL).

NEW CONCEPTS AND RECOMMENDATIONS:

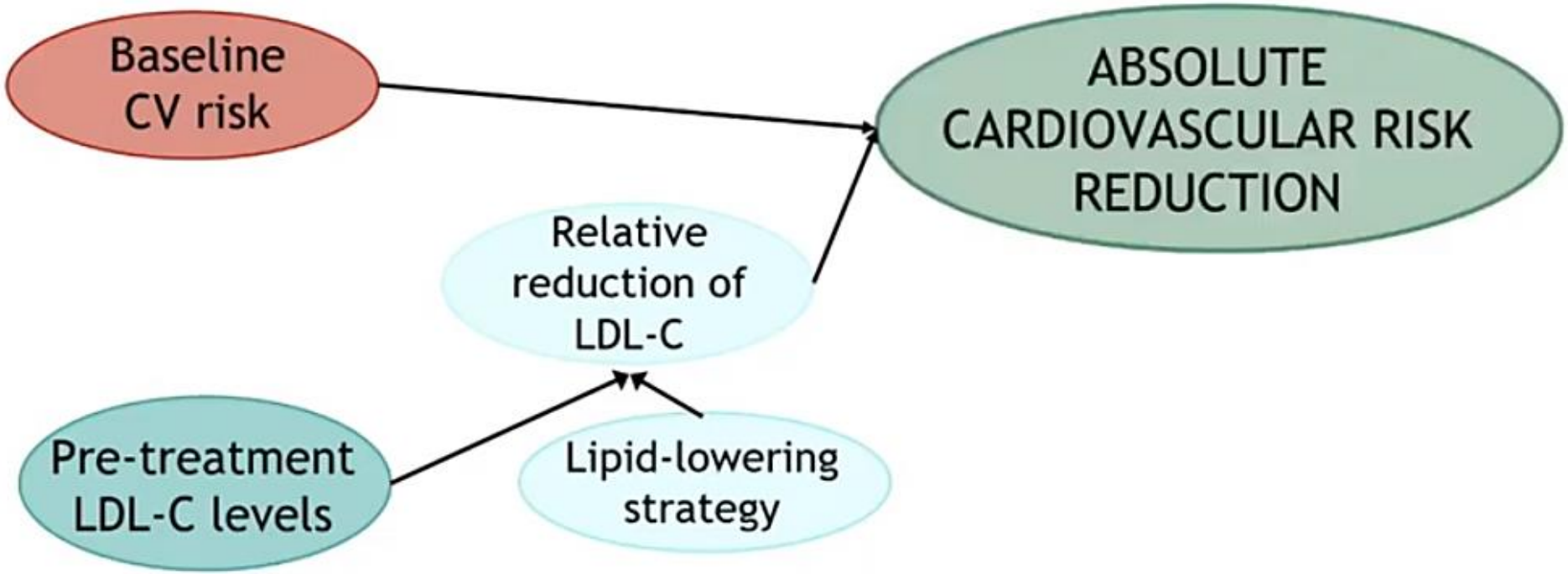
- RISK STRATIFICATION:
  - CV imaging for assessment of ASCVD risk:
    - **Arterial** (carotid/femoral) **plaque burden** (US)
    - **CAC score** assessment (CT)

} *Risk modifiers in low/moderate risk patients*

- SPECIAL POPULATIONS:
- > 65 years, DM, FH, hypertriglyceridaemia, ACS, CHF, PCI, CKD, prior stroke.

NEW CONCEPTS AND RECOMMENDATIONS:

- Assessment of predicted benefit:



RISK CATEGORIES:

	Very high risk	High risk	Moderate risk	Low risk
Documented ASCVD	Always	-	-	-
DM	• Target organ damage, • > 20 years	• No target organ damage • > 10 years	• No other RF • < 10 years	-
FH	+ ASCVD	Without RF	-	-
CKD	eGFR < 30	30-60	-	-
SCORE (10y-risk)	≥ 10	5-10	1-5	<1

RECOMMENDED STRATEGIES:

1 Baseline CV risk

2 Pre-treatment LDL-C levels

	Total CV risk (SCORE) %	Untreated LDL-C levels <1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary prevention	Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention

SCORE Risk Charts
The European cardiovascular disease risk assessment model

- Systematic COronary Risk Evaluation: High & Low cardiovascular Risk Charts based on gender, age, total cholesterol, systolic blood pressure and smoking status, with relative risk chart, qualifiers and instructions

NEW CONCEPTS AND RECOMMENDATIONS:

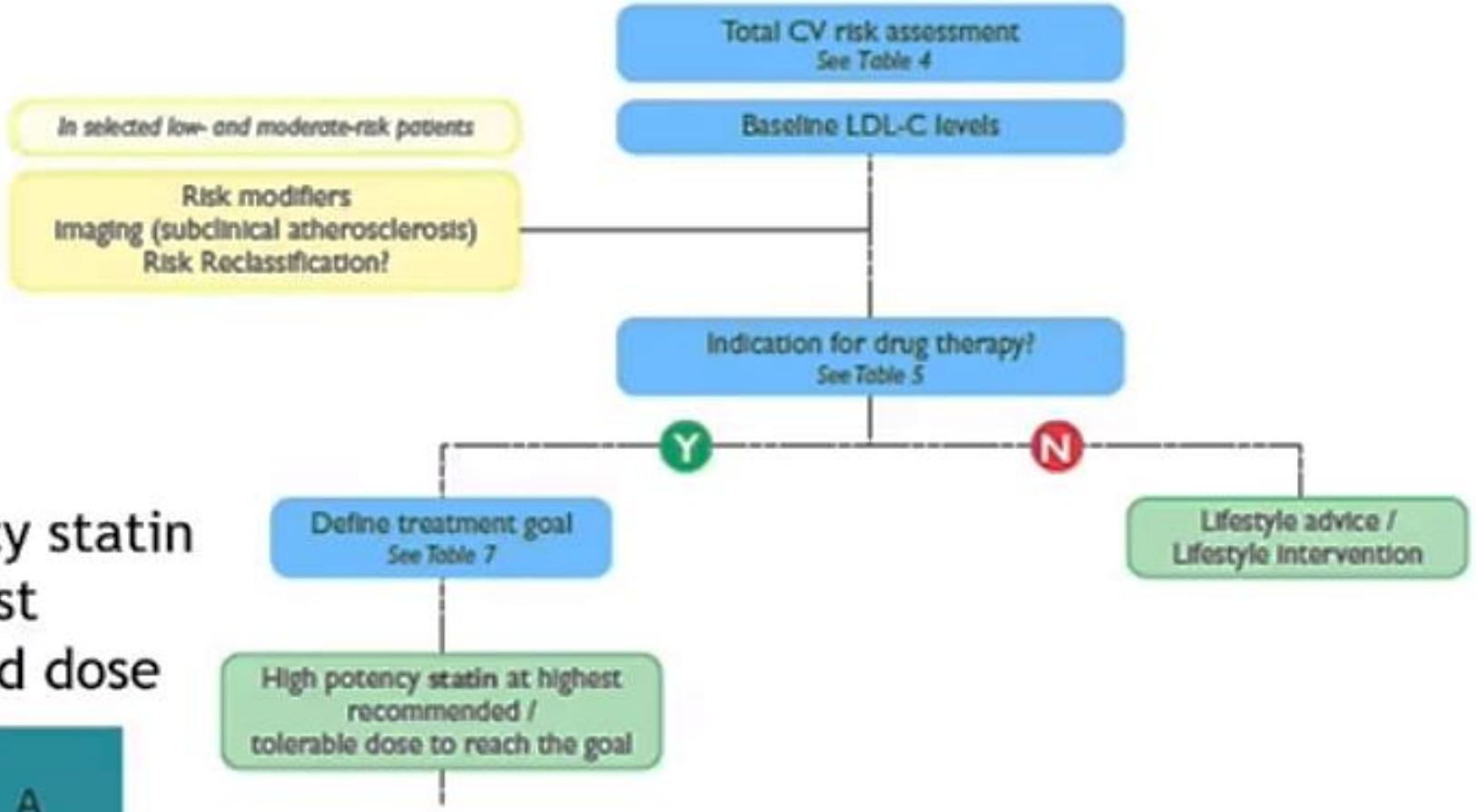
- LDL-C goals:

Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

CTT meta-analysis (Lancet 2010,
IMPROVE-IT (NEJM 2015)
FOURIER (NEJM 2017)
ODYSSEY (NEJM 2018)

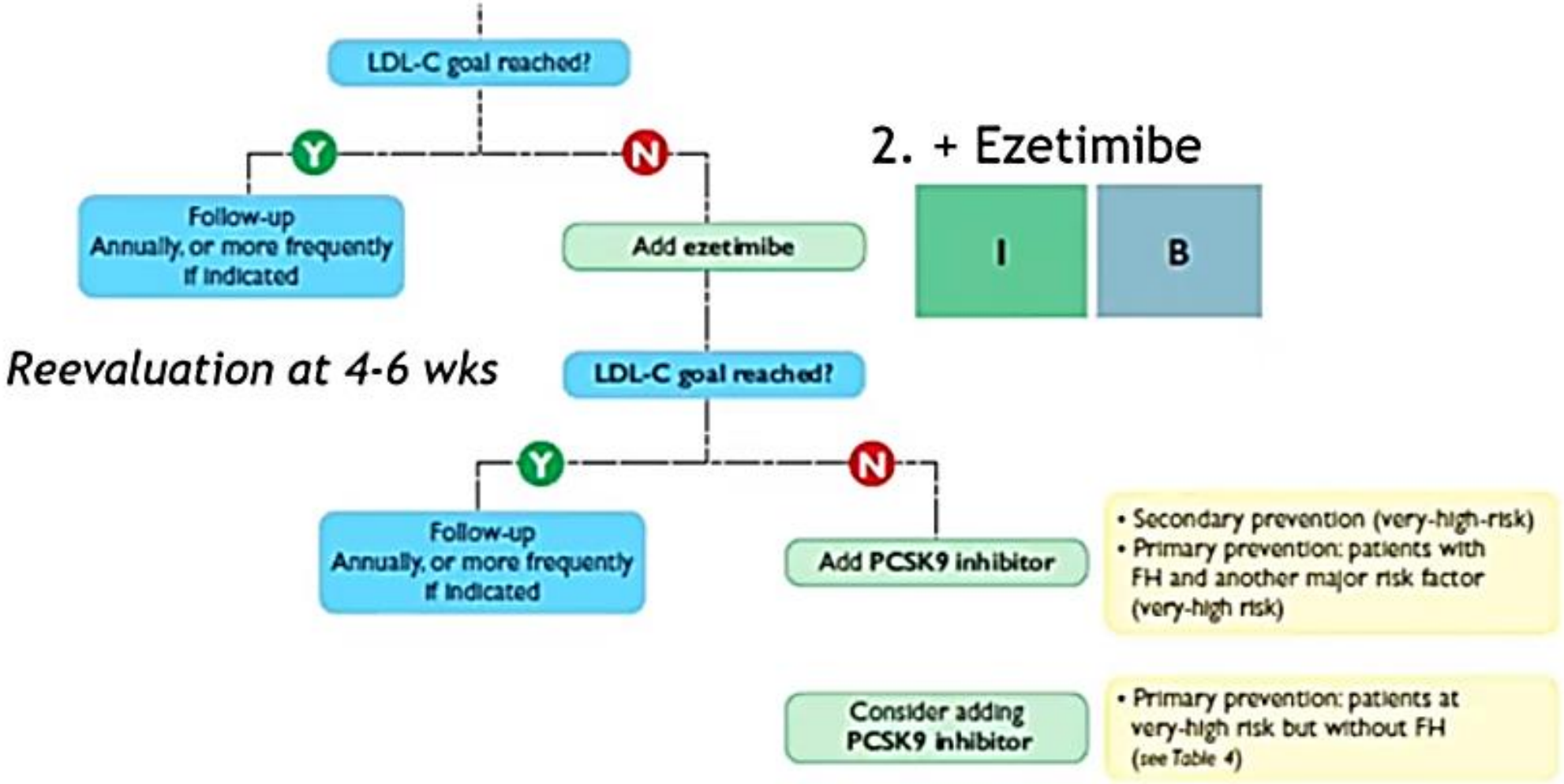
ALGORYTHM OF PHARMACOLOGICAL LDL-C LOWERING (I):



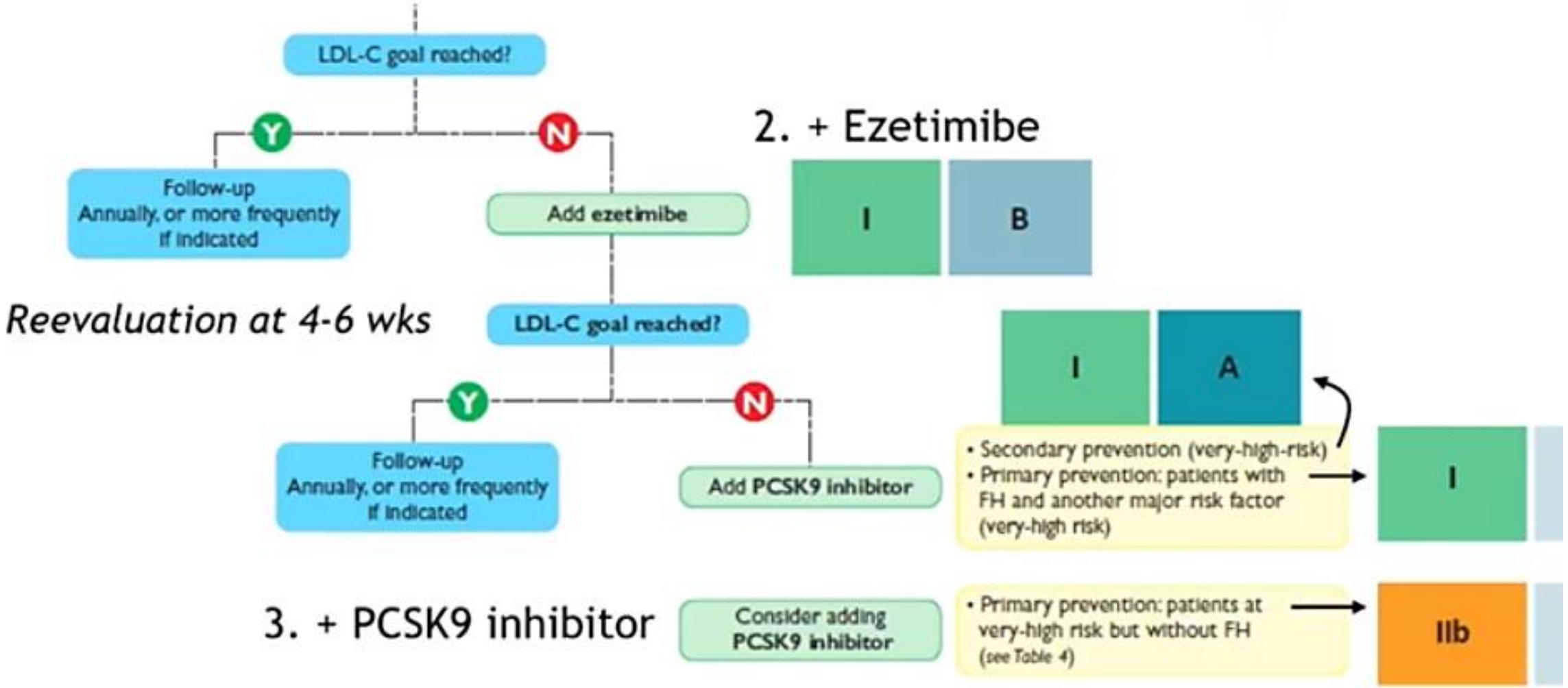
1. High potency statin at highest recommended dose

I A

ALGORYTHM OF PHARMACOLOGICAL LDL-C LOWERING (I):



ALGORYTHM OF PHARMACOLOGICAL LDL-C LOWERING (I):



CONCLUSIONES:

- El manejo del perfil lipídico para mejorar el riesgo CV viene condicionado por:
  1) Riesgo CV basal
  2) Niveles de LDL-C basales
- Además de hábitos de vida saludables, se recomienda inicio farmacológico para reducir los niveles de LDLD-C en:

	Considerar	Iniciar	Objetivo
Prev. secundaria	Cualquier LDL-C	LDL-C ≥ 55	↓ 50% + < 55
Prev. primaria - VHR	LDL-C ≥ 55	LDL-C ≥ 70	↓ 50% + < 55
Prev. primaria - HR	LDL-C ≥ 70	LDL-C ≥ 100	↓ 50% + < 70
Prev. primaria - MR	LDL-C ≥ 100	LDL-C ≥ 190	< 100
Prev. primaria - LR	LDL-C ≥ 116	LDL-C ≥ 190	< 116

CONCLUSIONES:

- El tratamiento hipolipemiante debe realizarse de forma escalonada:

Estatinas de alta potencia: primera elección — I A

↓

Aumentar estatinas a máxima dosis tolerada — I A

↓

Añadir Ezetimibe — I B

↓

Añadir inhibidores de PCSK9

(en prev. secundaria y prev. primaria + HF o prev. primaria - VHR)

I A

I C

IIb C

AACE 2017 Guidelines

GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

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

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

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

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

Reproduced with permission from Garber et al. *Endocr Pract*. 2017;23:207-238.

How is risk assessed?

The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using one or more of the following tools:

- Framingham Risk Assessment Tool
- MESA 10-year ASCVD Risk with Coronary Artery Calcification Calculator
- Reynolds Risk Score, which includes hsCRP and family history of premature ASCVD
- UKPDS risk engine to calculate ASCVD risk in individuals with T2DM

When the HDL-C concentration is greater than 60 mg/dL, one risk factor should be subtracted from an individual's overall risk profile

A classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity CRP; MESA, Multi-Ethnic Study of Atherosclerosis; T2DM, type 2 diabetes mellitus; TG, triglycerides. Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Key Cardiovascular Risk Scoring Tools: Framingham, MESA, Reynolds, and UKPDS

Framingham Global Risk Risk factors included/questions	Risk group/ Framingham Global Risk (10-year absolute ASCVD risk)	Clinical examples
Risk assessment tool for calculating 10-year risk of having a heart attack for adults 20 and older who do not have heart disease or diabetes (using data from the Framingham Heart Study): Age: ☐ years Sex: ◯ Female ◯ Male Total cholesterol: ☐ mg/dL HDL cholesterol: ☐ mg/dL Smoker (in last month): ◯ No ◯ Yes Systolic blood pressure: ☐ mm Hg Are you currently on any medication to treat high blood pressure: ◯ No ◯ Yes Calculate	High >20%	• Established coronary artery disease • Cerebrovascular disease • Peripheral arterial disease • Abdominal aortic aneurysm • Diabetes mellitus • Chronic kidney disease
	Intermediate 10-20%	• Subclinical coronary artery disease • MetS • Multiple risk factors[a] • Markedly elevated levels of a single risk factor[b] • First-degree relative(s) with early onset coronary artery disease
	Lower <10%	• May include women with multiple risk factors, MetS, or 1 or no risk factors
	Optimal <10%	• Optimal levels of risk factors and heart-healthy lifestyle

- **High risk:** A greater than 20% risk that you will develop a heart attack or die from coronary disease in the next 10 years.
- **Intermediate risk:** A 10-20% risk that you will develop a heart attack or die from coronary disease in the next 10 years.
- **Low risk:** Less than 10% risk that you will develop a heart attack or die from coronary disease in the next 10 years.

[a] Patients with multiple risk factors can fall into any of the 3 categories by Framingham scoring.
[b] Most women with a single, severe risk factor will have a 10-year risk ≤10%.

Multi-Ethnic Study of Atherosclerosis (MESA) Risk factors included/questions	Risk calculation outcomes
MESA 10-Year ASCVD risk with coronary artery calcification: Sex: Male ◯ Female ◯ Age (45-85 years): ☐ years Coronary artery calcification: ☐ Agatston Race/ethnicity (choose one): ◯ Caucasian ◯ Chinese ◯ African American ◯ Hispanic Diabetes: Yes ◯ No ◯ Currently smoke: Yes ◯ No ◯ Family history of heart attack: Yes ◯ No ◯ Total cholesterol: ☐ mg/dL HDL cholesterol: ☐ mg/dL Systolic blood pressure: ☐ mm Hg Lipid-lowering medication: Yes ◯ No ◯ Hypertension medication: Yes ◯ No ◯ Calculate 10-year ASCVD risk	• External validation provided evidence of very good discrimination and calibration • Harrell's C-statistic ranged from 0.779 to 0.816 in validation against existing studies • The difference in estimated 10-year risk between events and nonevents was approximately 8-9%, indicating excellent discrimination • Mean calibration found average predicted 10-year risk within 1/2 of a percent of the observed event rate • The test predicts 10-year risk of a ASCVD event

Multi-Ethnic Study of Atherosclerosis (MESA) Risk factors included/questions	Risk calculation outcomes
MESA 10-Year ASCVD risk with coronary artery calcification: Sex: Male ◯ Female ◯ Age (45-85 years): ☐ years Coronary artery calcification: ☐ Agatston Race/ethnicity (choose one): ◯ Caucasian ◯ Chinese ◯ African American ◯ Hispanic Diabetes: Yes ◯ No ◯ Currently smoke: Yes ◯ No ◯ Family history of heart attack: Yes ◯ No ◯ Total cholesterol: ☐ mg/dL HDL cholesterol: ☐ mg/dL Systolic blood pressure: ☐ mm Hg Lipid-lowering medication: Yes ◯ No ◯ Hypertension medication: Yes ◯ No ◯ Calculate 10-year ASCVD risk	• External validation provided evidence of very good discrimination and calibration • Harrell's C-statistic ranged from 0.779 to 0.816 in validation against existing studies • The difference in estimated 10-year risk between events and nonevents was approximately 8-9%, indicating excellent discrimination • Mean calibration found average predicted 10-year risk within 1/2 of a percent of the observed event rate • The test predicts 10-year risk of a ASCVD event

UKDPS Risk Score Risk factors included/questions	Risk calculation outcomes
UKPDS risk engine is a model for estimating risk of ASCVD in persons with T2DM (this risk is up to 3x greater than for the general population) Age ☐ years Weight ☐ kg Height ☐ cm Sex ◯ Male ◯ Female HDL cholesterol ☐ mmol/L Total cholesterol ☐ mg/L Systolic blood pressure ☐ mm Hg Smoker ◯ Yes ◯ No Afro-Caribbean ethnicity? ◯ Yes ◯ No A1C ☐ % Time period (duration of diabetes) ☐ years: (4, 5, 6, 7, 8, 9, 10, 15, 20) Regular exercise per week: ☐ # of times (1, 2, 3, 4, >5) Calculate risk	• Survival rates predicted by UKPDS Risk Score model were similar to rates observed in the UKPDS trial, well within non-parametric confidence intervals • Predicted survival rates adjust for A1C, blood pressure, and lipid risk factors • The UKPDS Risk Engine provides risk estimates and 95% confidence intervals in individuals with T2DM not known to have heart disease for: - Nonfatal and fatal coronary heart disease - Fatal coronary heart disease - Nonfatal and fatal CVA - Fatal CVA

Abbreviations: A1C = hemoglobin A1C; ATP III = Adult Treatment Panel III; ASCVD = atherosclerotic cardiovascular disease; A1C = glycated hemoglobin; CVA = cerebrovascular accident; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; ln = natural logarithm; MetS = metabolic syndrome; MI = myocardial infarction; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study.

For patients with diabetes, what risk categories does AACE recommend?

Based on epidemiologic studies, individuals with T2DM should be considered as high, very high, or extreme risk for ACSVD

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Additional Screening Tests

Coronary artery calcification

- Coronary artery calcification measurement has been shown to be of high predictive value and is useful in refining risk stratification to determine the need for more aggressive treatment strategies

hsCRP

- Use hsCRP to stratify ASCVD risk in individuals with a standard risk assessment that is borderline, or in those with an intermediate or higher risk with an LDL-C concentration less than 130 mg/dL

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Additional Screening Tests

Lp-PLA_2

- Measure lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of hsCRP elevations

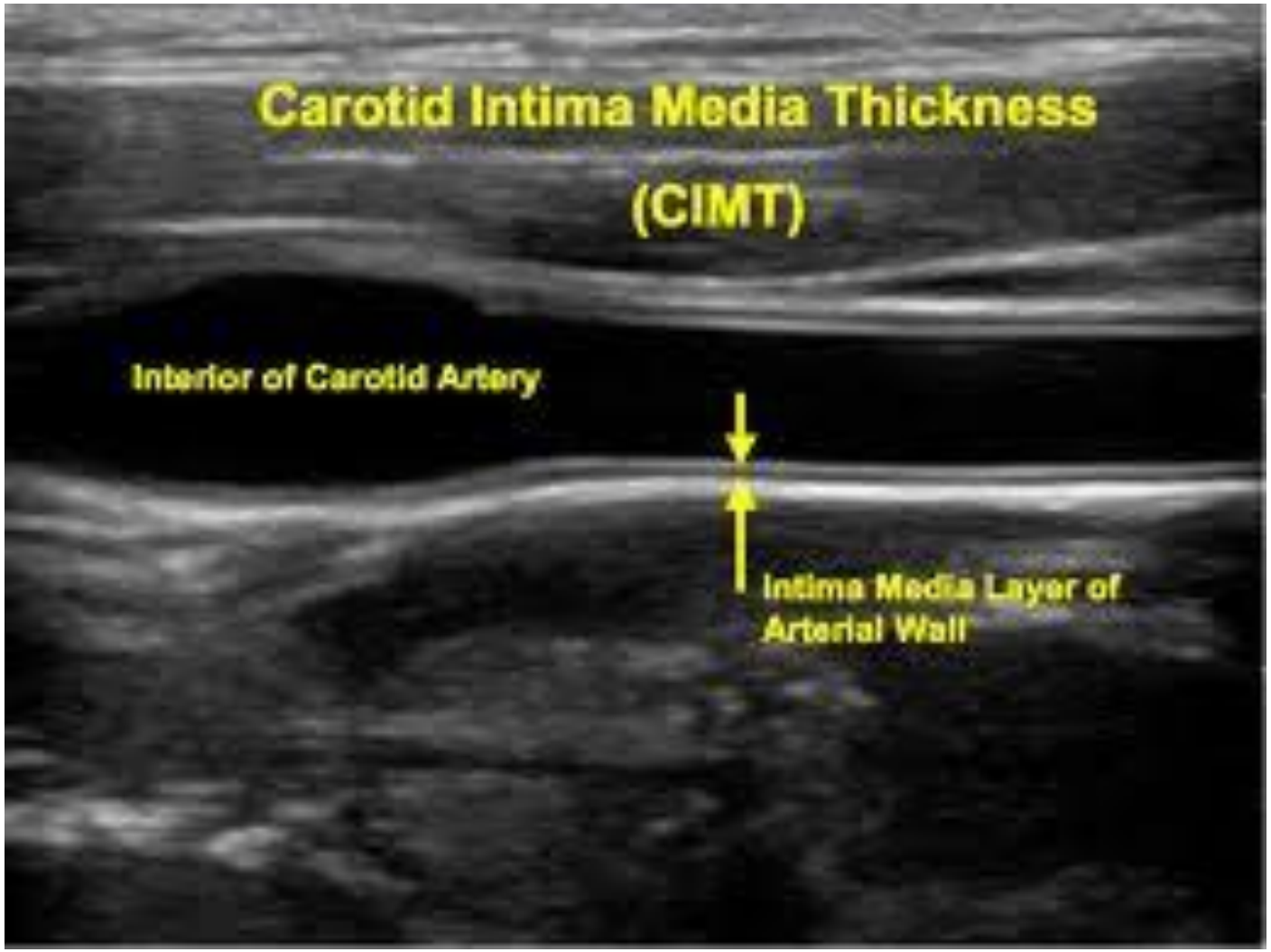
Homocysteine

- The routine measurement of homocysteine, uric acid, plasminogen activator inhibitor-1, or other inflammatory markers **is not** recommended because the benefit of doing so is not sufficiently proven

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Additional Screening Tests

- Carotid intima media thickness
  - Carotid intima media thickness may be considered to refine risk stratification to determine the need for more aggressive ASCVD preventive strategies



Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Question: What treatments are available for dyslipidemia?

Treatment categories for dyslipidemia:

- **Lifestyle changes**
  - Physical activity
  - Medical nutrition therapy
  - Smoking cessation
- **Pharmacologic therapy**
  - Statins
  - Fibrates
  - Omega-3 fish oil
  - Niacin
  - Bile acid sequestrants
  - Cholesterol absorption inhibitors
  - PCSK9 inhibitors
  - MTP inhibitor
  - Antisense apo B oligonucleotide
  - Combination therapies

A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using lifestyle and patient education with pharmacotherapy as needed to achieve evidence-based targets

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Question: How are different drugs used to treat dyslipidemia?

PCSK9 Inhibitors

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH

- PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals

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How should treatment be monitored?

- Reassess individuals' lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved
- While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals
- While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment

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Question: How are different drugs used to treat dyslipidemia?

- **Cholesterol Absorption Inhibitors**
  - Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals
  - Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk

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South African dyslipidaemia guideline consensus statement: 2018 update

A joint statement from the South African Heart Association (SA Heart) and the Lipid and Atherosclerosis Society of Southern Africa (LASSA)

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General Principles of Guidelines Unchanged

- Guidelines are not set in stone
- They evolve based on new scientific evidence
- Guidelines inform clinical practice, they don't replace clinical judgement
- Guidelines should help clinicians combine best scientific evidence formally graded for quality with clinical expertise.
- The goal is improved outcomes for heart attack/stroke

Thank You!

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