DISSECTING THE ACC/AHA LIPID GUIDELINES: WHERE DO WE STAND IN 2019?

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Disclosures

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ADVISORY BOARD		AVENTYN BAYLOR RESEARCH INSTITUTE LIFE 365 CARDIORENAL SOCIETY OF AMERICA NATIONAL LIPID ASSOCIATION
GRANTS/RESEARCH SUPPORT		NONE
ROYALTIES		NONE
SALARY/CONTRACTS		TENET LEGACY HEART CARE
SPEAKER'S BUREAU		NOVARTIS BOEHRINGER INGELHEIM/Lily AMGEN ASTRA ZENECA NOVO NORDISC Pfizer Amarin

Outline

Introduction	High TG
LDL Measurement	Women
Very High-Risk definition	CKD
FH	SAMS
Diabetes	Cost effectiveness of PCSK9 antibody
Risk Enhancers	Top 10 messages
Shared Decision	Caveats and common sense
Who should get a CAC score	Future

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Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care

(Updated August 2015)

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CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/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/indicated 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**

(Generally, LOE A or B use only)

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

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-analyses 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

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

High Blood Cholesterol and ASCVD

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.

Very High-Risk of Future ASCVD Events

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

Very High Risk (continued)

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

Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])		
COR	**LOE**	**Recommendations**
I	B-R	In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.
IIa	B-R	In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable.

Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])		
COR	**LOE**	**Recommendations**
IIb	B-R	In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL (≤3.4 mmol/L). while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.
IIb	B-R	In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.

Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus		
COR	**LOE**	**Recommendations**
I	A	In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.
IIa	B-NR	In adults 40 to 75 years of age with diabetes mellitus and an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it is reasonable to assess the 10-year risk of a first ASCVD event by using the race and sex-specific PCE to help stratify ASCVD risk.

Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus		
COR	**LOE**	**Recommendations**
IIa	B-R	In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.
IIa	B-NR	In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.
IIb	C-LD	In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more.

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

Diabetes Specific Risk Enhancers

- Long duration (≥10 years for type 2 diabetes mellitus (S.4.3-20) 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

Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry)

Risk Enhancers (continued)

Risk-Enhancing Factors

- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
    - **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - **ABI** <0.9

Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

Checklist Item	Recommendation
ASCVD risk assessment	• Assign to statin treatment group; use ASCVD Risk Estimator Plus.* o In lower-risk primary-prevention adults 40-75 y of age with LDL-C ≥70 mg/dL (≥1.8 mmol/L). o Not needed in secondary prevention, in those with LDL-C ≥190 mg/dL (≥4.9 mmol/L), or in those 40-75 y of age with diabetes mellitus. • Assess other patient characteristics that influence risk. See Risk-Enhancing Factors (Section 4.4.1.3. and Table 6) • Assess CAC (Section 4.4.1.4.) if risk decision is uncertain and additional information is needed to clarify ASCVD risk. o Use decision tools to explain risk (e.g., ASCVD Risk Estimator Plus,* Mayo Clinic Statin Choice Decision Aid).
Lifestyle modifications	• Review lifestyle habits (e.g., diet, physical activity, weight or body mass index, and tobacco use). • Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart, AHA Life's Simple 7, NLA Patient Tear Sheets, PCNA Clinicians' Lifestyle Modification Toolbox, cardiac rehabilitation, dietitian, smoking cessation program).

Shared Decision (continued)

Checklist Item	Recommendation
Potential net clinical benefit of pharmacotherapy	• Recommend statins as first-line therapy. • Consider the combination of statin and nonstatin therapy in selected patients. • Discuss potential risk reduction from lipid-lowering therapy. • Discuss the potential for adverse effects or drug–drug interactions.

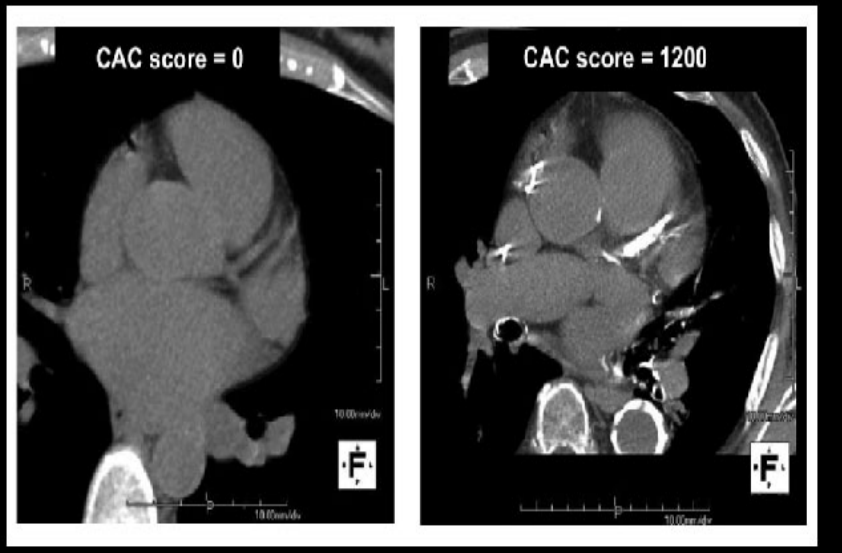
Shared Decision (continued)

Checklist Item	Recommendation
Cost considerations	• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment).
Shared decision-making	• Encourage the patient to verbalize what was heard (e.g., patient's personal ASCVD risk, available options, and risks/benefits). • Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications. • Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions. • Collaborate with the patient to determine therapy and follow-up plan.

Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero

- Patients reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely
- Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms
- Older patients (men, 55-80 y of age; women, 60-80 y of age) with low burden of risk factors who question whether they would benefit from statin therapy
- Middle-aged adults (40-55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group



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Hypertriglyceridemia

COR	LOE	Recommendations
I	B-NR	In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.
IIa	B-R	In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).

Hypertriglyceridemia

COR	LOE	Recommendations
IIa	B-R	In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy.
IIa	B-NR	In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.

Issues Specific to Women

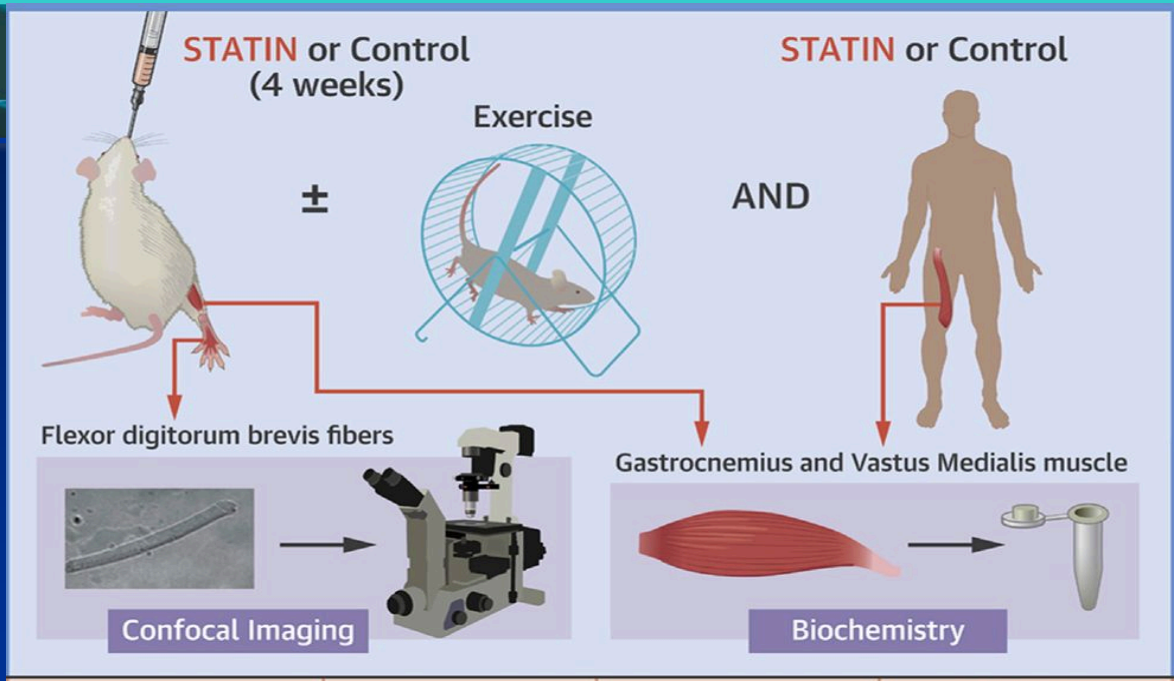
Recommendations for Issues Specific to Women		
COR	**LOE**	**Recommendations**
I	B-NR	Clinicians should consider conditions specific to women, such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and the potential for benefit of statin therapy.
I	C-LD	Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception.
I	C-LD	Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered.

Adults With Chronic Kidney Disease

Recommendations for Adults With CKD		
COR	**LOE**	**Recommendations**
IIa	B-R	In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who are at 10-year ASCVD risk of 7.5% or higher, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a moderate-intensity statin or moderate-intensity statins combined with ezetimibe can be useful.
IIb	C-LD	In adults with advanced kidney disease that requires dialysis treatment who are currently on LDL-lowering therapy with a statin, it may be reasonable to continue the statin.
III: No Benefit	B-R	In adults with advanced kidney disease who require dialysis treatment, initiation of a statin is not recommended.

2018 Cholesterol Guideline

Statin Safety and Statin-Associated Side Effects



	Control	STATIN	STATIN + Moderate Exercise
RyR1 Complex	FKBP RyR1		
Sarcoplasmic Reticulum Ca^{2+} Leak		Ca^{2+}	
Apoptosis			

Lotteau, S. et al. J Am Coll Cardiol Basic Trans Science. 2019;4(4):509-23.

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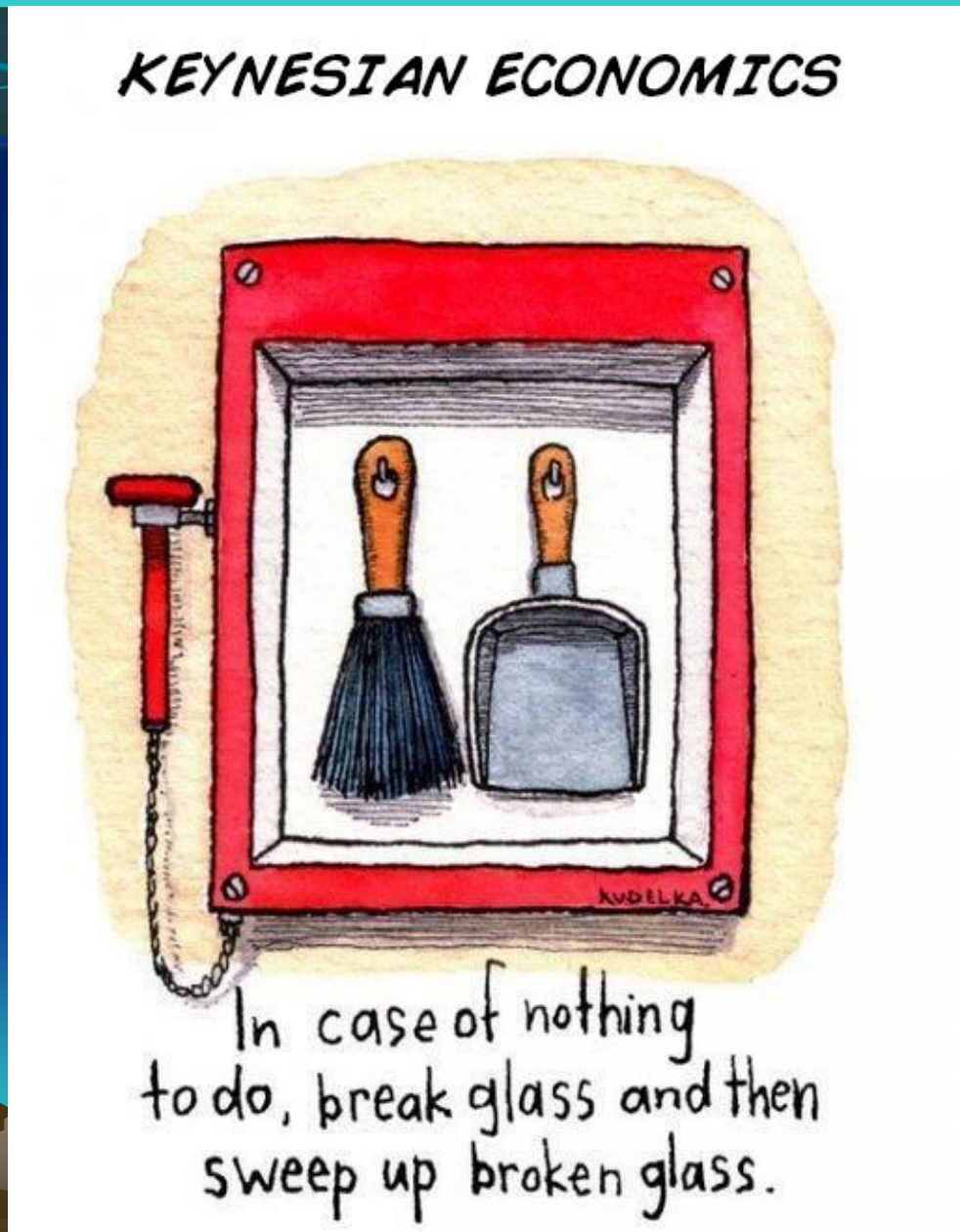
Statin Safety and Statin-Associated Side Effects

Recommendations for Statin Safety and Statin-Associated Side Effects		
COR	LOE	Recommendations
I	A	A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully.
I	A	In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors.

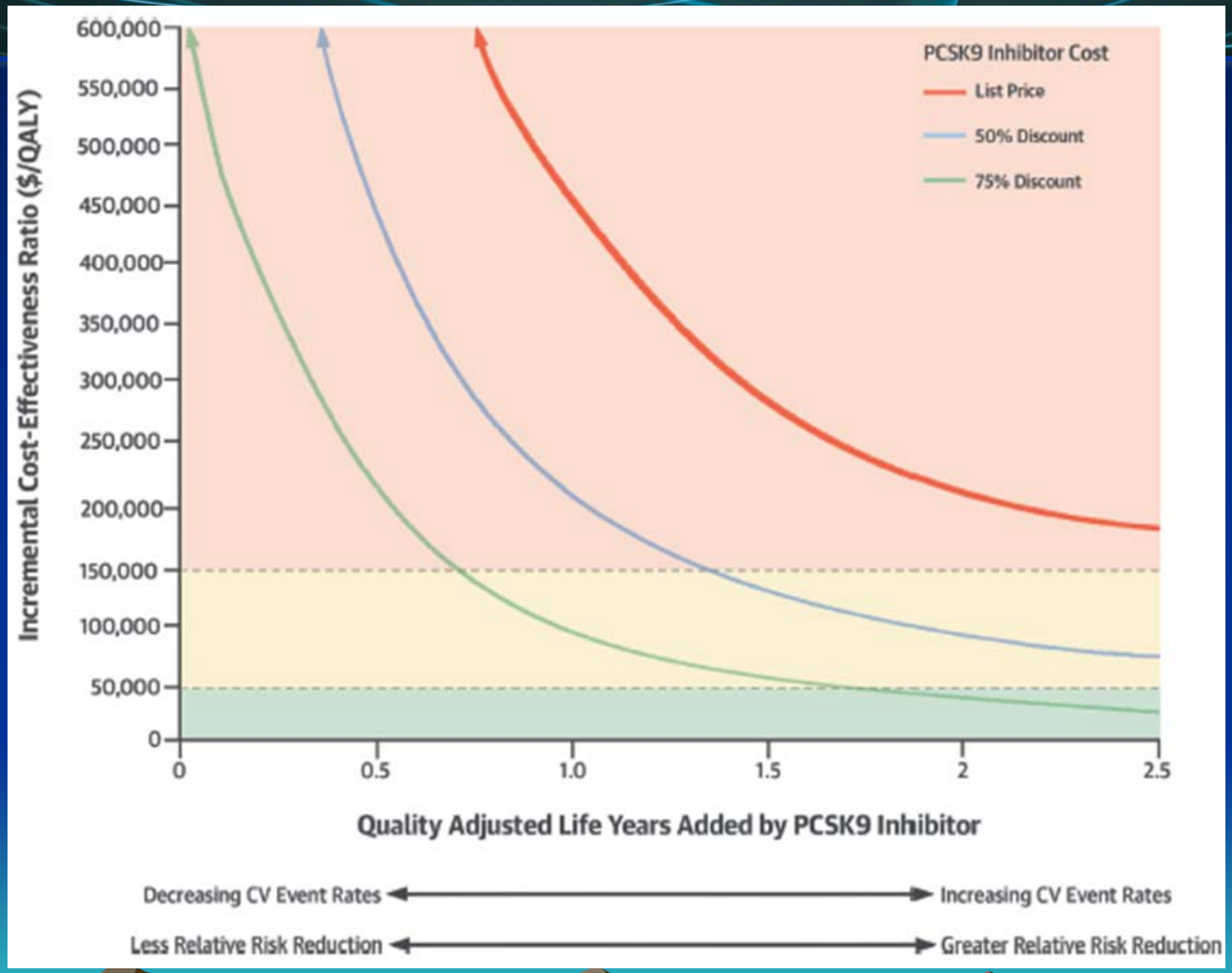
Cost and Value Considerations



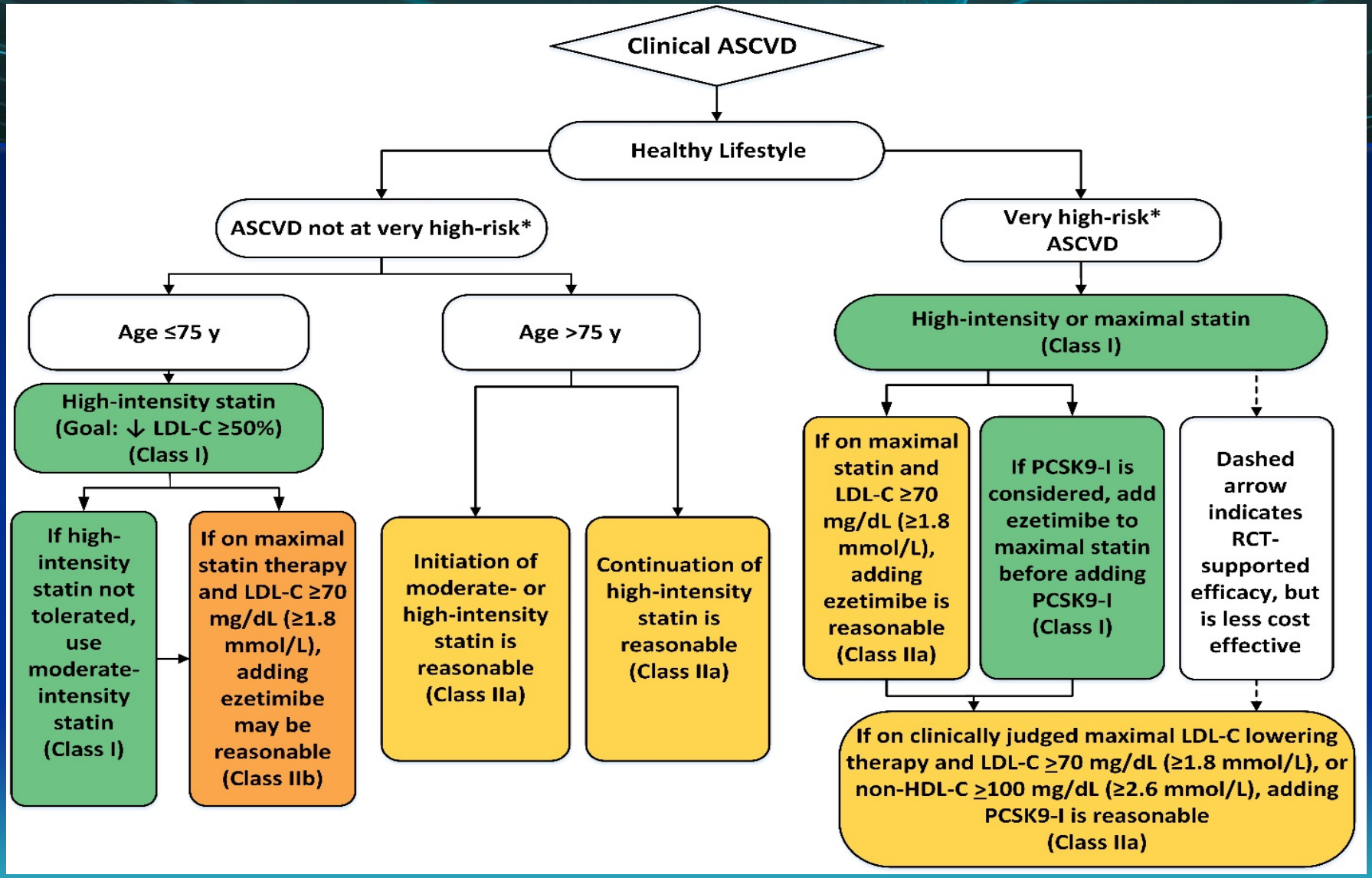
Proposed Integration of Level of Value Into Clinical Guideline Recommendations*

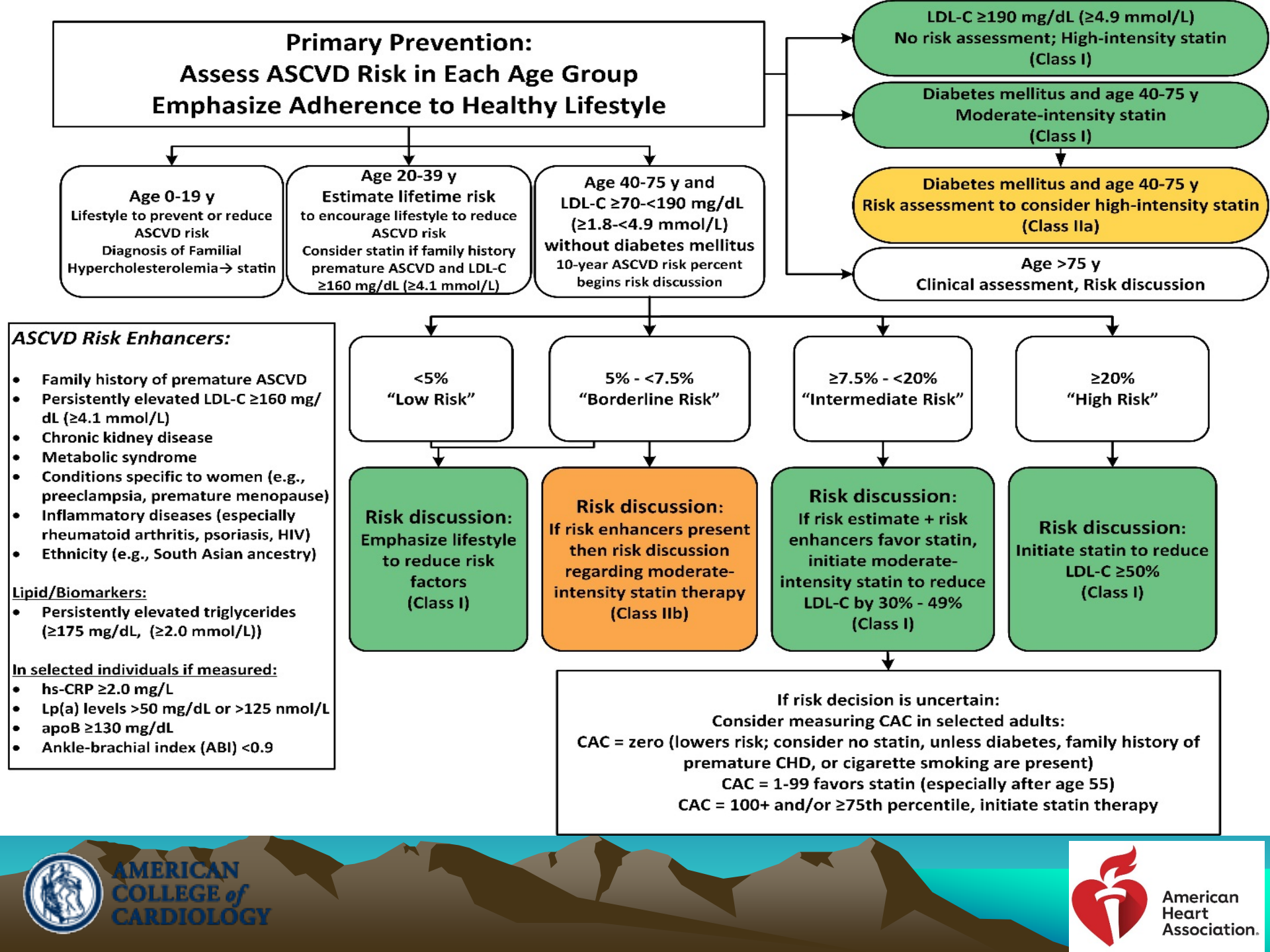
Level of Value
Level of Value
High value: Better outcomes at lower cost or ICER <$50,000 per QALY gained **Intermediate value:** $50,000 to <$150,000 per QALY gained **Low value:** ≥$150,000 per QALY gained **Uncertain value:** Value examined, but data are insufficient to draw a conclusion because of absence of studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant **Not assessed:** Value not assessed by the writing committee
Proposed abbreviations for each value recommendation: Level of value: H to indicate high value; I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed.

Cost-Effectiveness Analysis for PCSK9 Inhibitors



Secondary Prevention





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Top 10 Take-Home Messages

2018 Cholesterol Guidelines

Top 10 Take Home Messages Number 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 (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Top 10: Number 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%.

Top 10: Number 3

In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins 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 (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable ; 2019 prices make it more cost effective now

Top 10: Number 4

In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

•If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable

• If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered,

Top 10: Number 5

- **In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), 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%.

Top 10: Number 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 (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions; • the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.

Top 10: Number 7

In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). 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: Number 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 . Risk-enhancing factors include**

  • family history of premature ASCVD;
  • persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
  • metabolic syndrome;
  • chronic kidney disease;
- h/o preeclampsia or premature menopause (age <40 yrs.)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals
  • apolipoprotein B ≥130 mg/dL
  • high-sensitivity C-reactive protein ≥2.0 mg/L
  • ankle-brachial index <0.9 and l
  • lipoprotein (a) ≥50 mg/dL or 125 nmol/L

Top 10: Number 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.

Top 10: Number 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 non-statin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

Caveats, Common sense and Comfort zone

- Test children > 10 years of age: statins safe
- % LDL C reduction vs treating to target number
- PCE may underestimate risk in certain population
- High TG may be a higher risk: data from REDUCE IT for TG > 135 , Rx with EPA seems to reduce recurrent events.
- EPA may be more beneficial than statin in CKD and ESRD
- In NOD, NNH is 250 and NNT to prevent 1 CV event is 39
- HDL functionality being studied

Future

- LDL apheresis: Approved in US for LDL > 160 and very high risk not responding to other maximally tolerated measures
- In UK and Germany, approved for use for high Lp(a): > 60mg/dL
- Bempedoic Acid
- Nascent HDL
- Anti Apo C III
- Antisense Oligo nucleotides for Lp(a)
- Pemafibrate
- Evinacumab (ANGPTL3)
- Inclisiran (siRNA)
- Whither are we bound with Lomitapide and Mepomersan

The OVER-ARCHING MESSAGE

If you want to build a ship, don't drum up people to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea.

Antoine de Saint-Exupery