Prevention of Cardiovascular Disease

Presented by:

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Roger Bannister
May 6, 1954
First Sub-4-Minute Mile

Prevention of Cardiovascular Disease

- Overview of ASCVD Prevention
- Guidelines
- Estimation of Risk and Risk Scores
- Risk Enhancers, Inflammation, Coronary Artery Calcium
- Major risk factors: Dyslipidemia, Hypertension, Smoking and Tobacco Use
- Physical Activity, Diet and Weight Management, Mental Health

- Recent advances in medical therapeutics now allow us to stop a heart attack in progress.

- At the same time, we have also more knowledge in preventing disease from occurring or reoccurring. We now understand how diet, exercise, and other life-style changes, along with medication, can help prevent cardiovascular disease.

ASCVD in the United States

Heart Disease and Stroke Statistics—2023 Update:

A Report From the American Heart Association

Ischemic heart disease was the #1 cause of years of life lost to premature mortality and overall cause of death in 1990 and in 2019, this was ahead of cancers and COPD.

Among the 15 leading risk factors for years of life lived with disability are high body mass index, smoking, high systolic blood pressure, high LDL-C, and high fasting plasma glucose

Framingham Heart Study

- 1945—President Franklin D. Roosevelt dies prematurely from cerebral hemorrhage felt due to long standing severe hypertension
- The rates of cardiovascular disease (CVD) had been increasing since the 1940s and were felt to be unavoidable
- 1948– President Harry Truman signed the National Heart Act creating the National Heart Institute (now NHLBI) and dedicated funds to study CVD
- Adults aged 30-62 years without known CVD were recruited from Framingham MA, a Boston suburb for a longitudinal cohort study.
- Objective: identify the common factors that contribute to CVD
- Participants had regular physical examinations and blood tests. The original cohort was followed with several subsequent offspring cohorts and the Omni cohort with diverse ethnic and racial participants
- In 1959, cigarette smoking was linked to coronary heart disease with high blood pressure and high cholesterol linked in 1961
- The term “risk factor” was first coined by in 1961 by Dr. William Kannel, who was the 2nd Director of the Framingham Heart Study
- 1976—Kannel publishes paper on cardiovascular “risk profile” and in 1998 the Framingham Risk Score to predict 10-year risk is published.
- The Framingham Heart Study celebrated its 75th anniversary in 2023

Association of Physical Activity and Cardiovascular Disease

Jerry N. Morris, et al. *"Coronary Heart-disease and Physical Activity of Work“ Lancet. November 21, 1953*

Sedentary bus drivers of London’s double-decker buses had higher rates of cardiovascular disease than the conductors who climbed the stairs

Guidelines

- The establishment of a guideline is a complex undertaking. Guidelines influence who will receive medication and who will be labeled “sick” and how our health care dollars are spent as well as insurance coverage

- There are guidelines for the prevention of cardiovascular disease in general

- There are guidelines for management of cardiovascular risk factors such as hypertension and dyslipidemia

Guidelines: Prevention of Cardiovascular Disease

- 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

- 2021 European Society Cardiology Guidelines on Cardiovascular Disease Prevention in Clinical Practice

Risk Estimation

- Risk scores and algorithms are used to determine intensity of therapy to prevent manifest disease. They have been used extensively for CVD in particular to establish targets for therapy such as LDL-C and use of medications

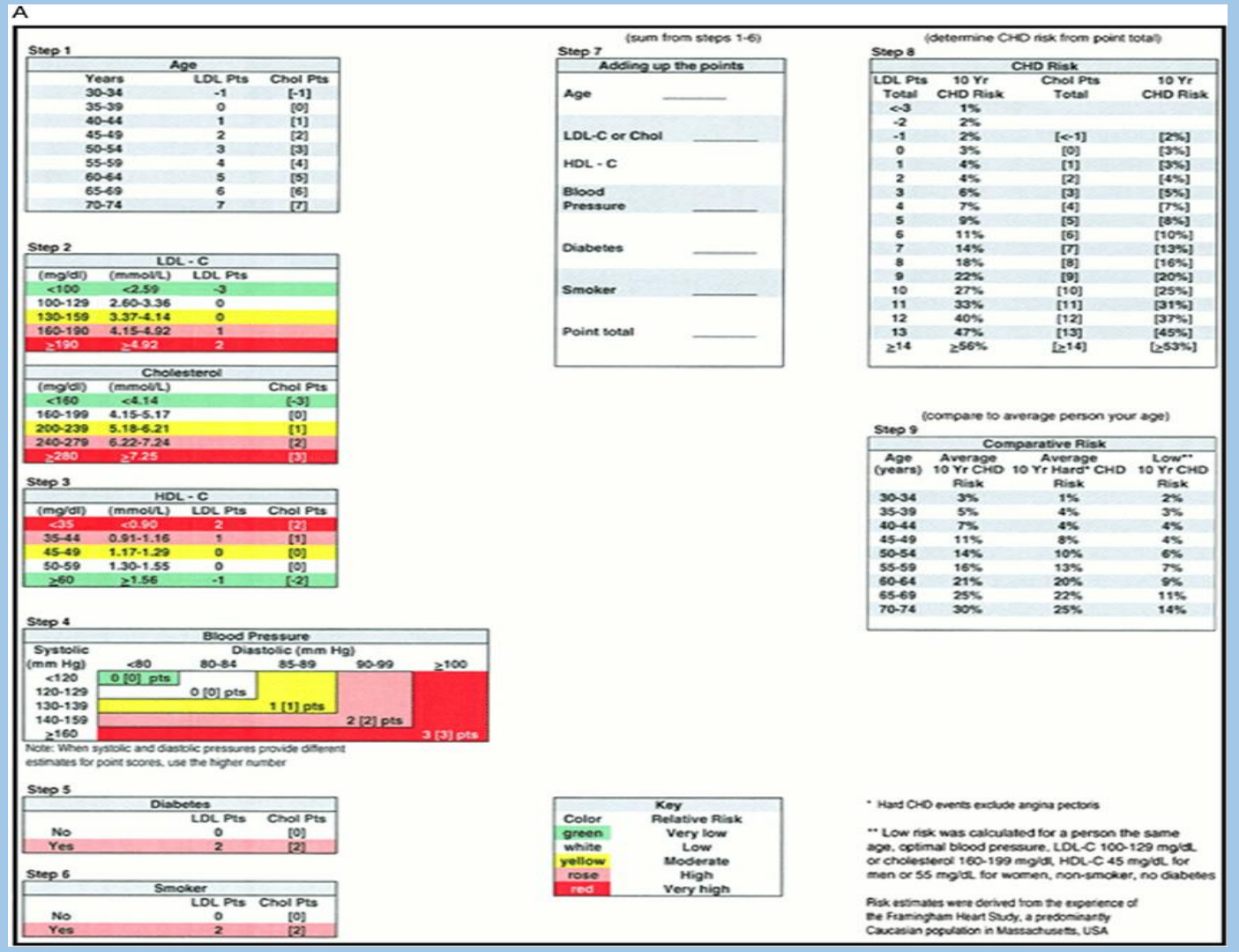
- Risk prediction is an evolving science because emerging risk factors and measures must be considered as well as different populations who have not been considered in existing risk scoring systems.

- Risk prediction schemes must also be easily employed and discriminate correctly

- 10-year risk score: determines who will be likely to benefit from drug therapy, most commonly lipid medication, in the near-term, thus improving cost-effectiveness and safety of therapy. Limitations include age being the most heavily weighted and not addressing long-term risk for younger persons

Risk Estimation: Framingham Risk Score

Age, LDL, total cholesterol, HDL, systolic blood pressure, diabetes, smoking



A

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-1	[-1]
35-39	0	[0]
40-44	1	[1]
45-49	2	[2]
50-54	3	[3]
55-59	4	[4]
60-64	5	[5]
65-69	6	[6]
70-74	7	[7]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-1	[-2]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	0 [0] pts				
120-129		0 [0] pts			
130-139			1 [1] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
<-3	1%		
-2	2%		
-1	2%	[<-1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥14	≥56%	[≥14]	[≥53%]

(compare to average person your age)

Step 9

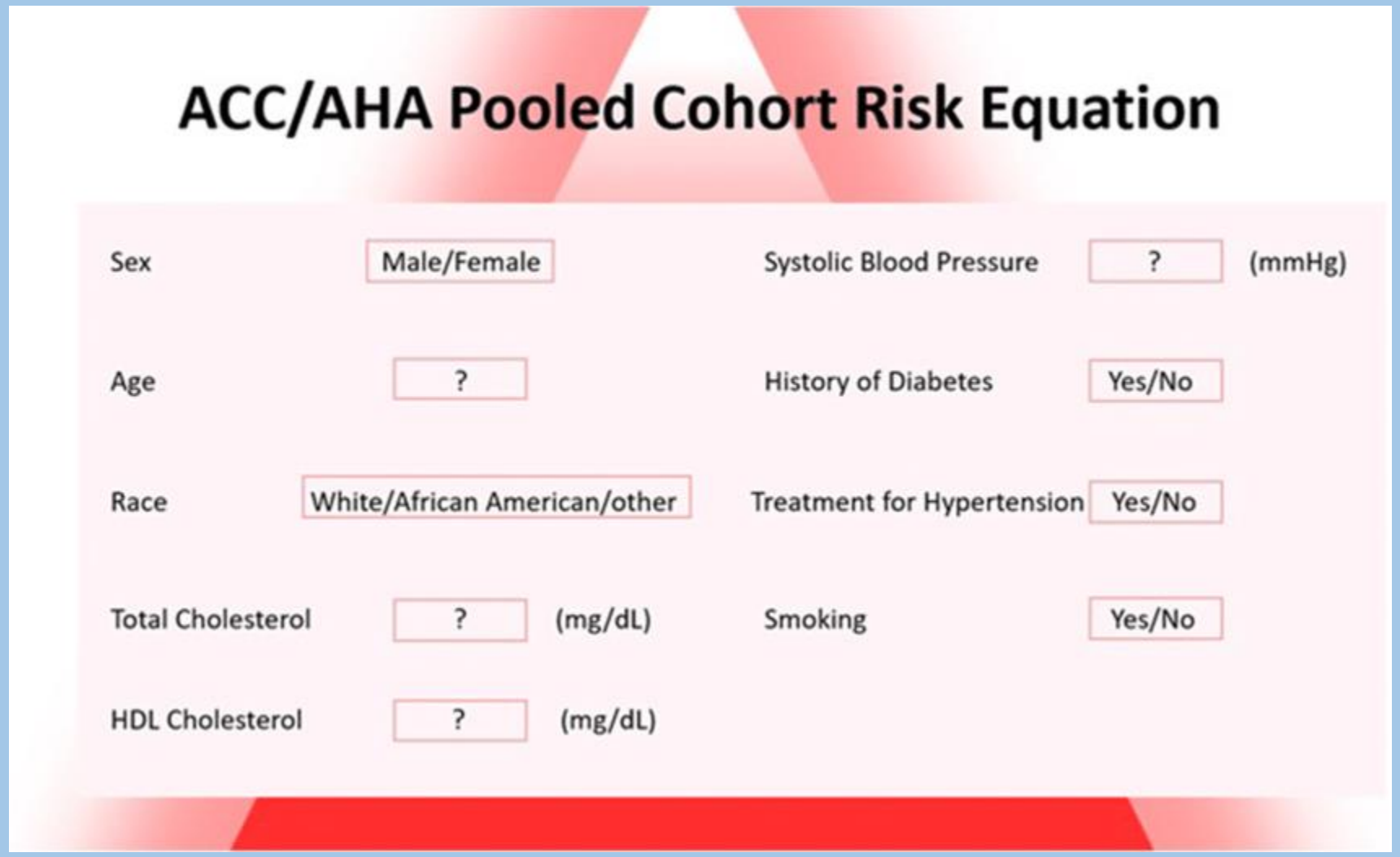
Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Risk Estimation 2013

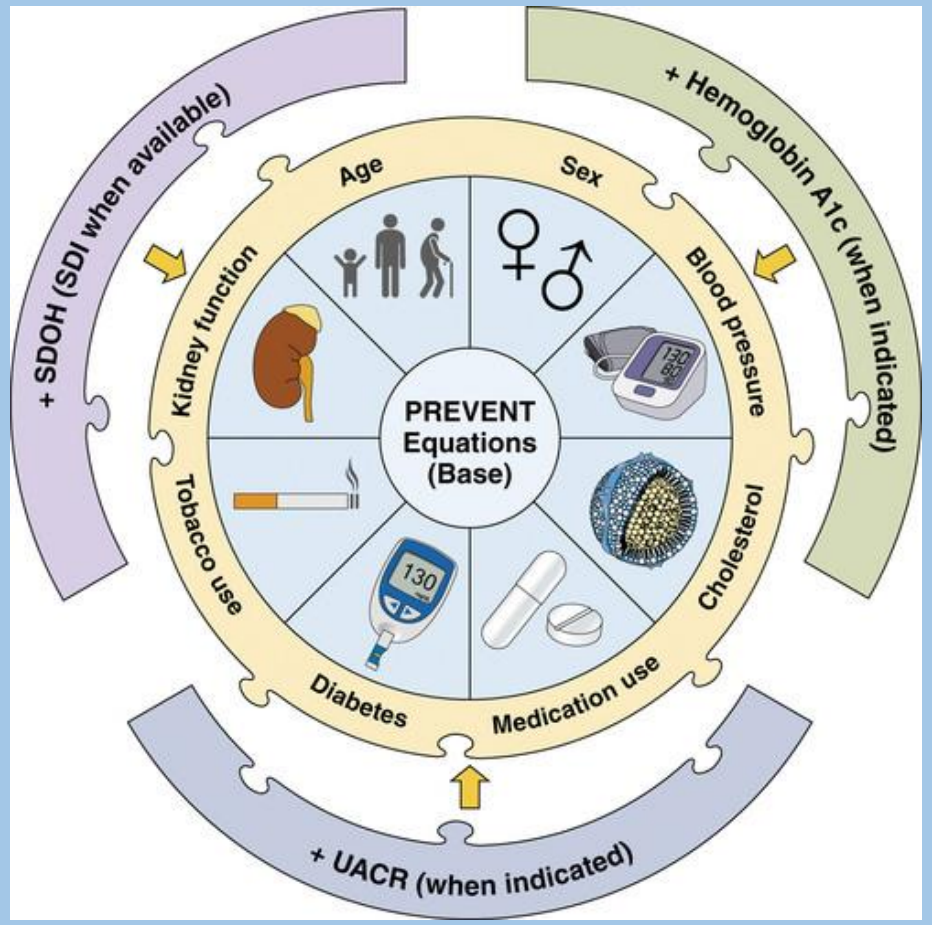


Risk Estimation 2023

AHA PREVENT Risk Calculator

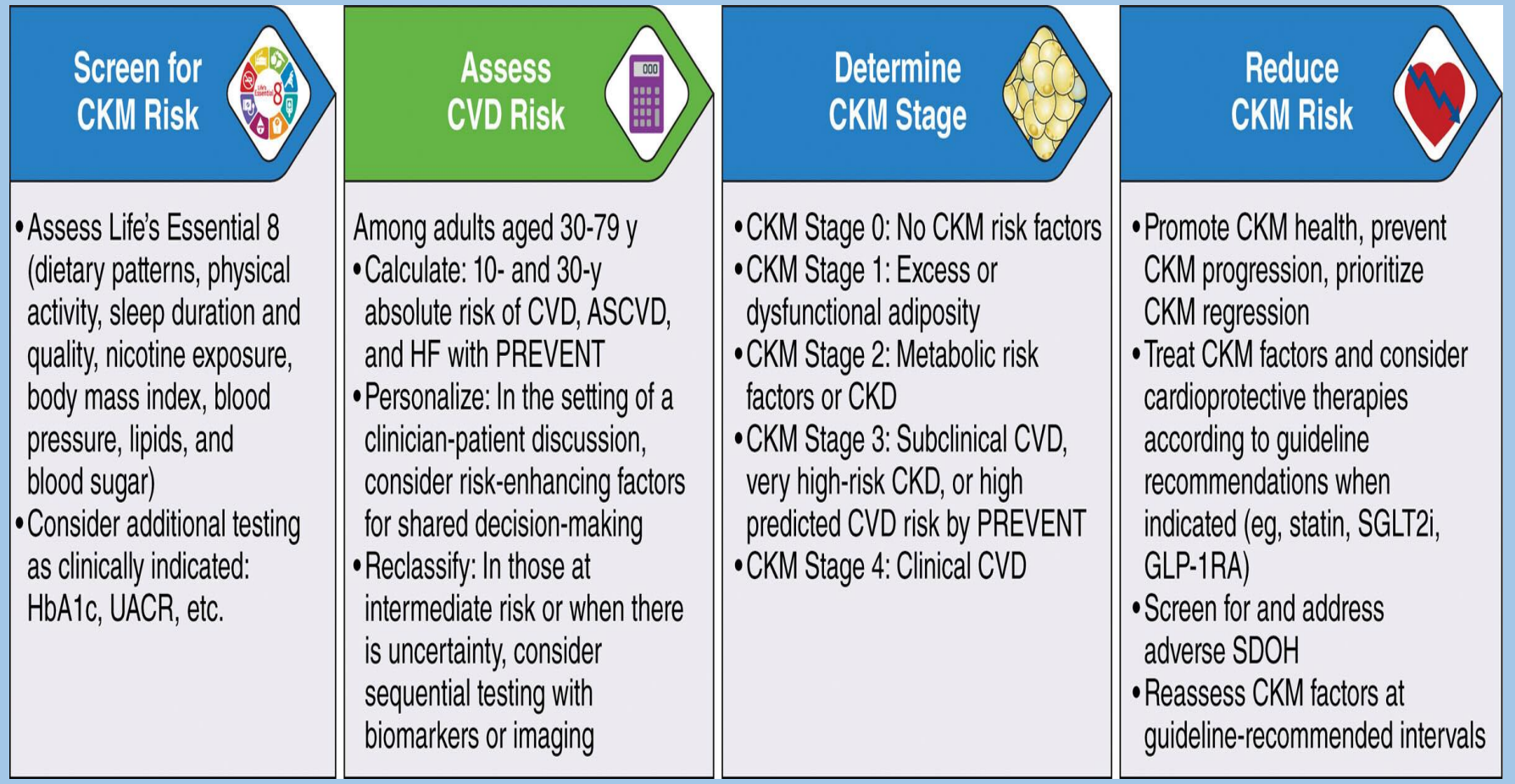
- Estimates 10- and 30- year risk of heart attack, stroke, and heart failure for those 30- 79 years of age
- Measures of kidney function
- Measure of metabolic health (HbA1c)
- Age, sex, blood pressure, cholesterol, tobacco use, medications

Risk Estimation: 2023 AHA PREVENT Risk Calculator



Risk Estimation: 2023 AHA PREVENT Risk Calculator

cardiovascular-kidney-metabolic = CKM



Risk Enhancers

- Metabolic syndrome
- Chronic kidney disease (eGFR 15-59 ml/min/1.73 m2)
- Chronic inflammatory conditions (psoriasis, rheumatoid arthritis, lupus)
- History of pregnancy-associated conditions such as pre-eclampsia
- Elevated high-sensitivity CRP (≥ 2.0 mg/L)
- Elevated Lipoprotein (a) (≥ 50 mg/dL or ≥ 125 nmol/L)
- Ankle-Brachial index < 0.9
- Polycystic Ovary Syndrome (2020 Consensus Statement, Clinical Endocrinologists and American College of Endocrinology)

Coronary Artery Calcium

Coronary artery calcium is a surrogate for coronary artery atherosclerosis burden. Amount is associated with burden of atheroma.

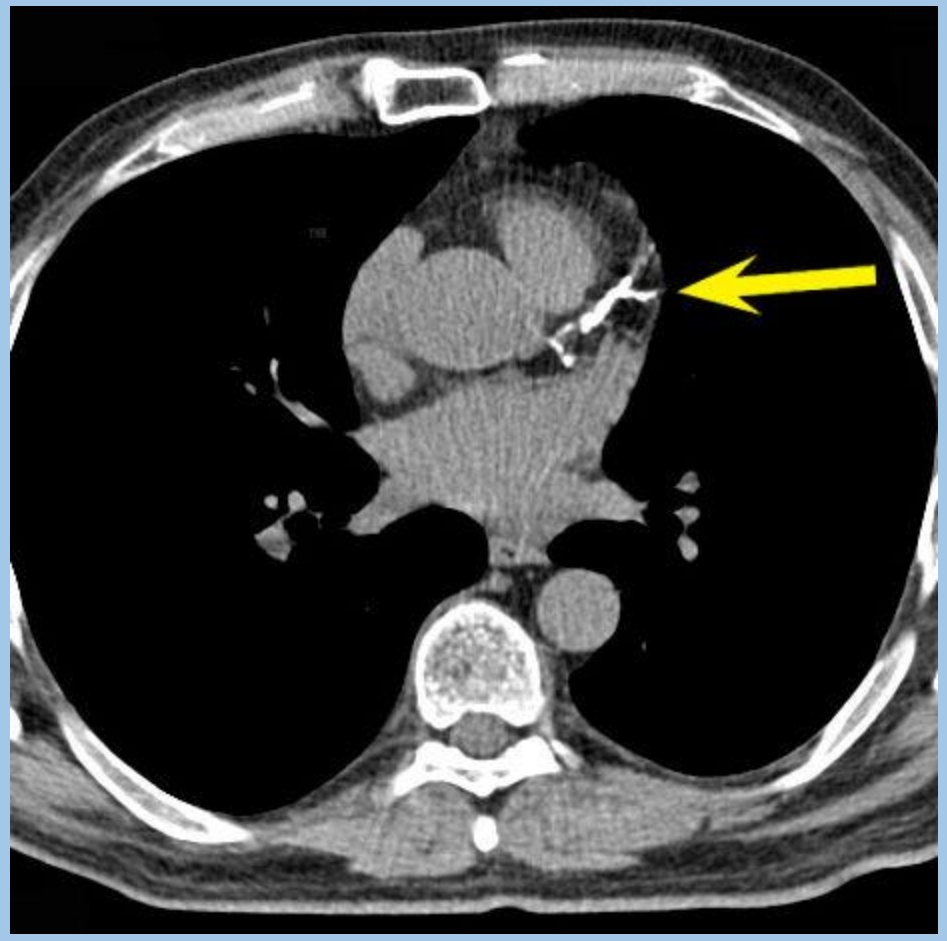
The exact mechanism of calcium deposition in atherosclerotic plaque and the process of coronary arterial calcification is not fully understood.

Budoff MJ, et al. When Does a Calcium Score Equate to Secondary Prevention?

J Am Coll Cardiol Img. 2023;16:1181

- Cohort study of 4,949 comparing event rates in those with ASCVD to rates in those with no history of ASCVD and known CAC score
- Patients with CAC scores > 300 but no known ASCVD are at equivalent risk of MACE as those with established ASCVD

Coronary Artery Calcium



Coronary Artery Calcium

- The density is measured in Hounsfield units and score of 1 for 130–199 HU, 2 for 200–299 HU, 3 for 300–399 HU, and 4 for 400 HU and greater. This weighted score is then multiplied by the area (in square millimeters) of the coronary calcification. For example, a "speck" of coronary calcification in the left anterior descending artery measures 4 square millimeters and has a peak density of 270 HU. The score is therefore 8 (4 square millimeters × weighted score of 2).
- The tomographic slices of the heart are 3 millimeters thick and average about 50–60 slices from the coronary artery ostia to the inferior wall of the heart. The calcium score of every calcification in each coronary artery for all of the tomographic slices is then summed up to give the total coronary artery calcium score (CAC score).
- The score, also called an Agatston score, is also converted to a percentile rank based on age and gender

Coronary Artery Calcium

2020 National Lipid Association Scientific Statement on Coronary Artery Calcium Scoring to Guide Preventive Strategies for ASCVD Risk Reduction

<u>Who to test?</u>

- Adults 40-75 years of age with LDL-C 70-189 mg/dL and a 10-year ASCVD risk of 5 -19.9%:

  CAC useful to decide on the need for and intensity of preventive therapies

- Adults ≥ 40 years with LDL-C 70-189 mg/dL and ASCVD risk < 5%:

  CAC reasonable in those with family history of premature ASCVD to decide on need for intensity or preventive therapies

- Adults with clinical ASCVD: CAC scoring is not recommended

- In selected individuals < 40 years old with multiple ASCVD risk factors or family history of premature ASCVD, it is reasonable to used CAC > 0 as a factor favoring intensification of lifestyle therapy and, if necessary, initiation of statin therapy

Coronary Artery Calcium

2020 National Lipid Association Scientific Statement on Coronary Artery Calcium Scoring to Guide Preventive Strategies for ASCVD Risk Reduction

Interpretation

- For a given CAC score, a diffuse distribution suggests higher risk vs. more localized distribution
- Left main coronary artery with > 25% of total score suggests higher risk
- No evidence to support stress testing or invasive coronary angiography in asymptomatic individuals with high scores

CAC ≥ 100: associated with > 7.5% 10-year ASCVD risk and the guideline-based threshold of statin benefit in primary prevention

CAC ≥ 300: associated with higher ASCVD risk suggesting benefit from greater LDL-lowering

CAC ≥ 1000: reasonable to use high-intensity statin therapy, optimal LDL-C goal < 70 mg/dL

Coronary Artery Calcium

2020 National Lipid Association Scientific Statement on Coronary Artery Calcium Scoring to Guide Preventive Strategies for ASCVD Risk Reduction

<u>CAC score = Zero</u>

- Adults aged 40-75 years with LDL-C 70-89 mg/dL and no diabetes, cigarette smoking, family history of premature ASCVD, it is reasonable to defer initiation of statin
- Adults aged 76-80 years in whom the decision about initiation of statin therapy is uncertain, it is reasonable to use this as a factor in avoidance of statin therapy

Coronary Artery Calcium

Hussain A, et al. *Circulation* 2020;142:917

- A zero calcium score is desirable, but is it enough to defer therapy given that up to one-third of events will occur in this group?
- Calcified plaque (detected as CAC on CT imaging) represents a small proportion of total plaque burden. Hence, there is a disconnection between zero calcium and zero atherosclerosis, which raises concerns about what age a zero CAC starts to be meaningful.

Coronary Artery Calcium

2020 National Lipid Association Scientific Statement on Coronary Artery Calcium Scoring to Guide Preventive Strategies for ASCVD Risk Reduction

<u>Repeat testing</u>

- CAC = 0: low risk (5-7 years), borderline – intermediate risk (3-5 years) high risk or diabetes (3 years)
- CAC 1 -99: 3-5 years if results might change treatment decisions
- CAC ≥ 100 and LDL ≥ 70 mg/dL: repeat in 3 years

Coronary Artery Calcium

2020 National Lipid Association Scientific Statement on Coronary Artery Calcium Scoring to Guide Preventive Strategies for ASCVD Risk Reduction

Incidental Findings on Chest CT

- Coronary artery calcium noted on thoracic CT, qualitative indication of severity:
  - mild: dedicated CAC scoring is useful
  - moderate or severe: generally correlates with CAC ≥ 100 and indication for statin benefit
- Pulmonary nodule found on CAC scoring exam: follow up and testing as indicated

Radiation

A single scan will expose a patient to about 2.3 millisieverts of radiation, equivalent to 23 chest x-rays (front and side views). Using modern equipment and protocols, a 1 millisievert exposure is possible.

Coronary Artery Calcium

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Who to test:

For those at intermediate ASCVD risk (≥ 7.5% - < 20% 10-year risk) and if risk decision is uncertain, consider measuring CAC in selected adults

Interpretation

CAC = zero

lowers risk and 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

Inflammation

Inflammation is now recognized as a key component in all phases of arterial atherosclerotic development. The pathways by which inflammation contributes to atherosclerosis and ASCVD are complex and involve cells in the arterial wall including smooth muscle cells, macrophages, and neutrophils.

Ridker PM, et al. Inflammation and Cholesterol as Predictors of CV Events Among Patients Receiving Statin Therapy. Lancet. 2023;401:1293

- Evaluate the relative importance of hsCRP and LDL-C as determinants of risk for major cardiac events, CV death, all-cause death among patients receiving statins.
- Collaborative analysis of patients with or at high risk of ASCVD and receiving statins in three multi-national trials
- Conclusion: inflammation assessed by hsCRP was a stronger predictor for risk of future CV events and death than cholesterol assessed by LDL-C among patients receiving statins
- Targeting LDL-C alone may not completely mitigate atherosclerotic risk. Anti-inflammatory pathways may provide incremental CV benefits

Inflammation

Nidorf SM, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383:1838.

- Randomized, controlled, double-blind trial
- Patients with chronic CAD randomized to 0.5 mg colchicine or placebo daily
- N = 5522, mean duration of follow up 28.6 months
- Primary endpoint: cardiovascular death, spontaneous MI, ischemic stroke, ischemia-driven coronary revascularization
- Primary endpoint: colchicine group: 6.8% (N = 187) placebo: 9.6% (N = 264) $p < 0.001$

Inflammation

Colchicine (Lodoco, Agrepha Pharma)

June 2023 FDA approval for colchicine 0.5 mg to reduce risk of MI, stroke, coronary revascularization, and cardiovascular death in adults with known ASCVD or multiple risk factors.

Colchicine has been used at 0.6 mg for treatment of gout flares. Colchicine interferes with neutrophil function and activation of interleukin 1-β in the inflammatory process.

C-Reactive Protein

CRP (hs)

- Acute-phase reactant protein
- Produced primarily by the liver during acute inflammatory processes and other diseases
- Functionally analogous to immunoglobulin G but it is not antigen specific
- Used to diagnose bacterial infections and inflammatory disorders, tissue necrosis, may/may not rise with viral infections
- Positive test indicates presence, but not cause of disease
- CRP is non-specific

C-Reactive Protein

- More sensitive and rapidly responding than esr
- Responds to anti-inflammatory agents, salicylates, or steroids
- Individual variability—therefore two separate measurements needed to classify a person’s risk level
- Elevation can occur with hypertension, elevated BMI, metabolic syndrome/diabetes, chronic infection (gingivitis), arthritis, cigarette smoking
- Elevated levels seen with arthritis, collagen vascular disease, tissue infection, bacterial infection (UTI), malignancy

Major Risk Factors

- Age
- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Chronic Kidney Disease
- Family History of premature ASCVD (males age < 55 and females < 65)

Lipids—A Bit of History

1929

Michel Macheboeuf of the Pasteur Institute first described plasma lipoproteins

1949

John Gofman at UC Berkeley used the newly developed ultracentrifuge to separate plasma lipoproteins by flotation. He observed that the fraction corresponding to LDL was associated with increased risk for cardiovascular disease

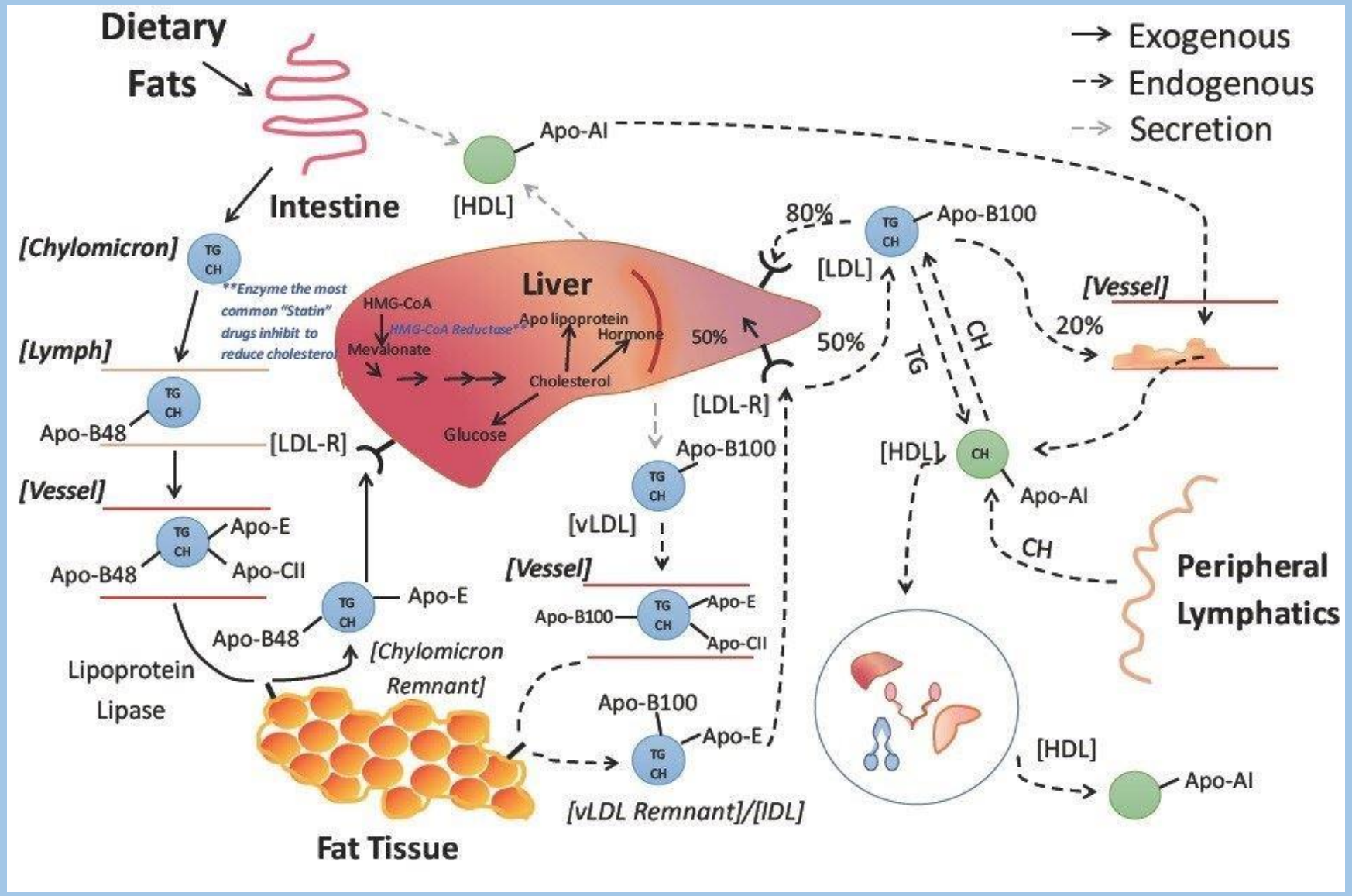
Lipids—A Bit of History

Joseph L. Rabinowitz– early 1950s discovered HMG-CoA with his team of researchers

Cholestyramine—bile acid sequestrant developed at Merck in the late 1950s

Niacin—shown to reduce lipid accumulation in rabbit aorta in 1955

HMG CoA Reductase inhibitor discovered in 1970s, Lovastatin was FDA approved in 1987

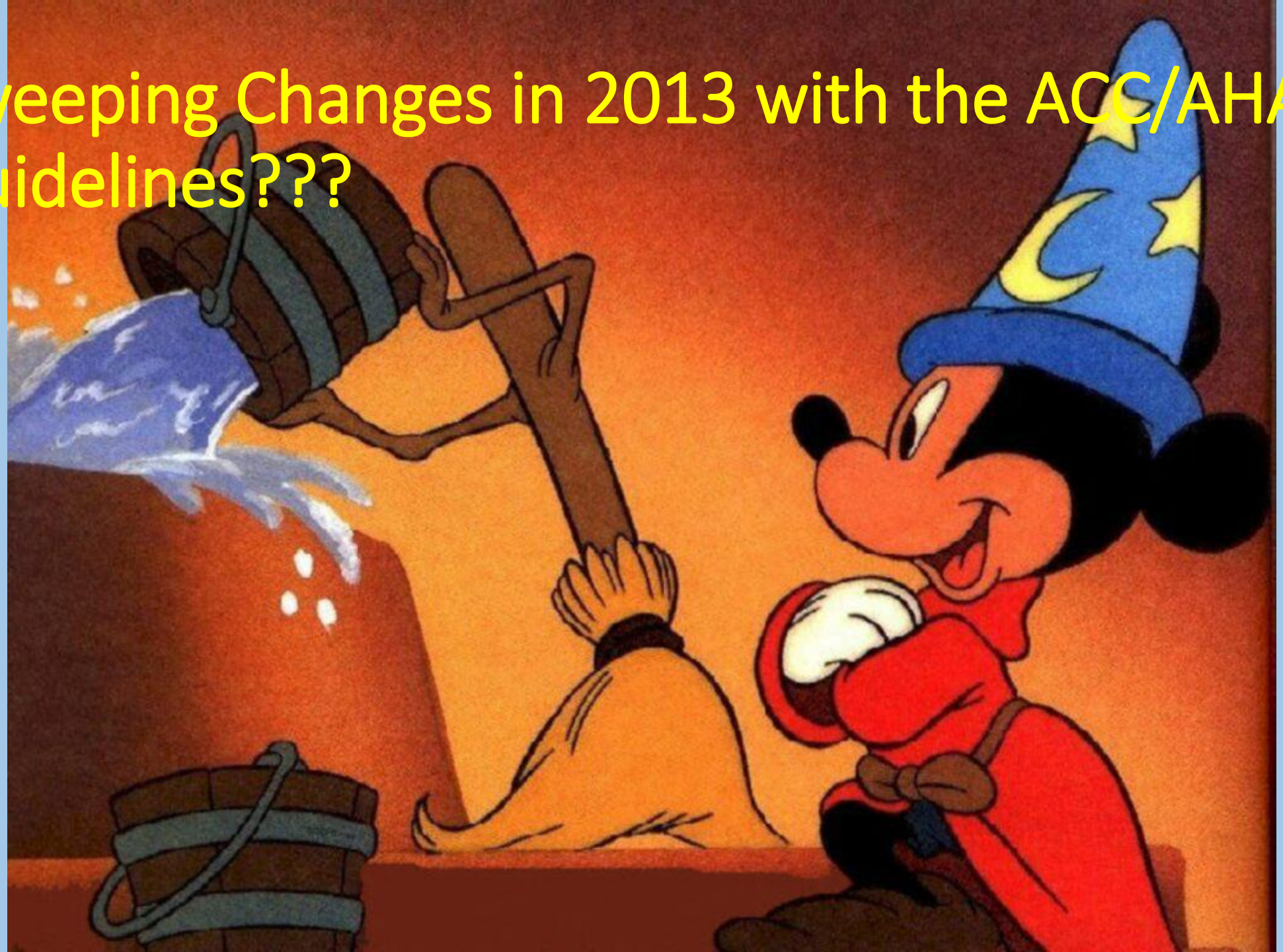

Dietary
Fats
Intestine
Exogenous
Endogenous
Secretion
Apo-AI
[HDL]
[Chylomicron]
TG
CH
**Enzyme the most common "Statin" drugs inhibit to reduce cholesterol
Liver
HMG-CoA
HMG-CoA Reductase**
Mevalonate
Apo lipoprotein
Hormone
Cholesterol
Glucose
50%
80%
Apo-B100
[LDL]
[Vessel]
20%
[Lymph]
Apo-B48
[LDL-R]
50%
TG
CH
[LDL-R]
Apo-B100
[HDL]
CH
Apo-AI
[vLDL]
[Vessel]
Apo-E
Apo-CII
Apo-B48
Apo-E
Apo-B48
[Chylomicron Remnant]
Lipoprotein
Lipase
Apo-B100
Apo-E
Apo-CII
CH
Peripheral
Lymphatics
Apo-B100
Apo-E
[HDL]
Apo-AI
[vLDL Remnant]/[IDL]
Fat Tissue

Lipids & The Evolution of the Guidelines

National Heart, Lung, and Blood Institute's National Cholesterol Education Program, Adult Treatment Panel

NCEP ATP I	1988
NCEP ATP II	1993
NCEP ATP III	2001
NCEP ATP IV	
ACC/AHA Guideline	2013

Sweeping Changes in 2013 with the ACC/AHA Guidelines???



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

- **4 groups treat with moderate to high dose statins**
  - Those with history atherosclerotic CV events
  - Those with LDLC $\geq$ 190 age 20 - 75
  - Those with diabetes 1 or 2 age 40 – 75
  - Those with 10 yr risk ASCVD > 7.5%

  - Depending on risk, simply add moderate or high dose statins, no evidence for using the LDL-C goals

Other Guidelines

2015 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia

2018 AHA/ACC Multi-society Guideline on the Management of Blood Cholesterol

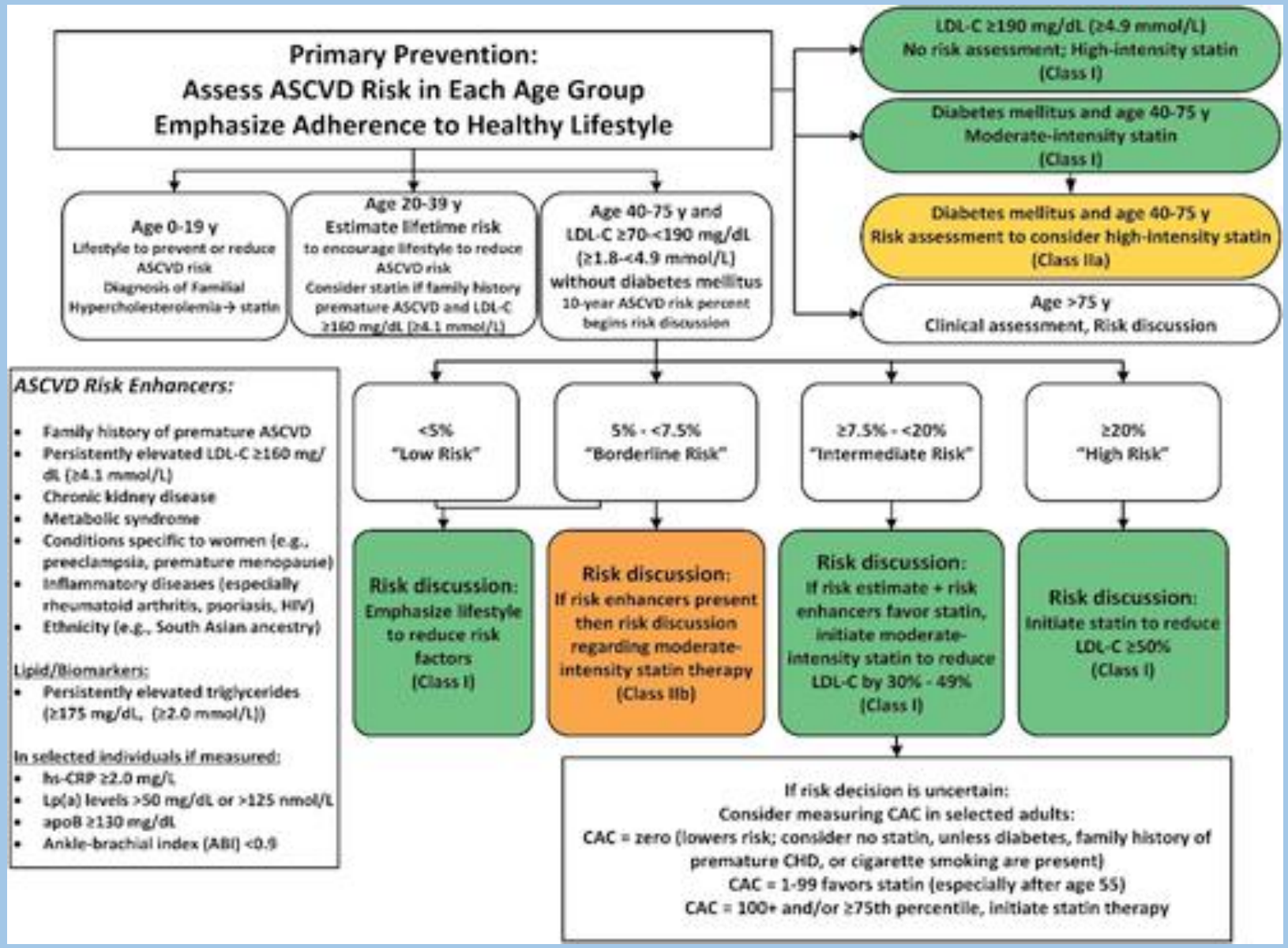
2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias

2020 Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular disease

- Used risk scoring schemes based on Framingham with tradition risk factors and “risk-enhancing” factors
- Kept lipid targets and goals
- Endorsed use of non-statin as well as statin therapy
- Used evidence from randomized clinical trials as well as observational and genetic studies

2018 ACC/AHA Mult-Society Guideline



LDL-C as a target of therapy with set goals

- The National Lipid Association and the American Society for the Preventive Cardiology recommend to reinstate routine monitoring of LDL-C as a quality metric (vs. prescribing statin) for the National Committee on Quality Insurance.*
- The 2013 ACC/AHA Guideline recommended high intensity statin treatment but did not endorse LDL as a target with goals depending on risk level
- The authors state that targets and goals are evidence-based.

*Vriani SS, et al. J Clin Lipidol. 2023;17:208-218

LDL-C and Apolipoprotein B as targets of therapy and goals

2020

American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease

Risk Category	LDL-Cholesterol	Apolipoprotein B
Extreme risk -progressive ASCVD -ASCVD + DM or CKD≥3 or familial hypercholesterol -premature ASCVD (male < 55 or female < 65	< 55	< 70
Very high risk -ASCVD -10-year risk > 20% -DM + ≥ 1 risk factor -CKD ≥ 3 + albuminuria -familial hypercholesterol	< 70	< 80
High risk -≥ 2 risk factors + 10-year risk 10-20% -DM or CKD ≥ 3	<100	< 90
Moderate risk < 2 risk factors + 10 yr risk < 10%	<100	<90
Low risk -no risk factors	<130	Not recommended

LDL: How Low to Go?

PCSK9 Inhibitors have shown safety and efficacy of very low LDL-cholesterol

- GLAGLOV Trial (Evolocumab) mean LDL 36.6
- FOURIER Trial (Evolocumab) mean LDL median 30
- OSLER Study (Evolocumab) LDL to < 15 (N = 1)
- ODYSSEY Outcomes Trial LDL to < 25 (N = 2)

Apolipoprotein B

LDL Cholesterol
What are we “Measuring”?

Report from your Lab:

Total Cholesterol	155
Triglycerides	108
LDL-C calculated	87
HDL-C	46

Friedewald Formula*

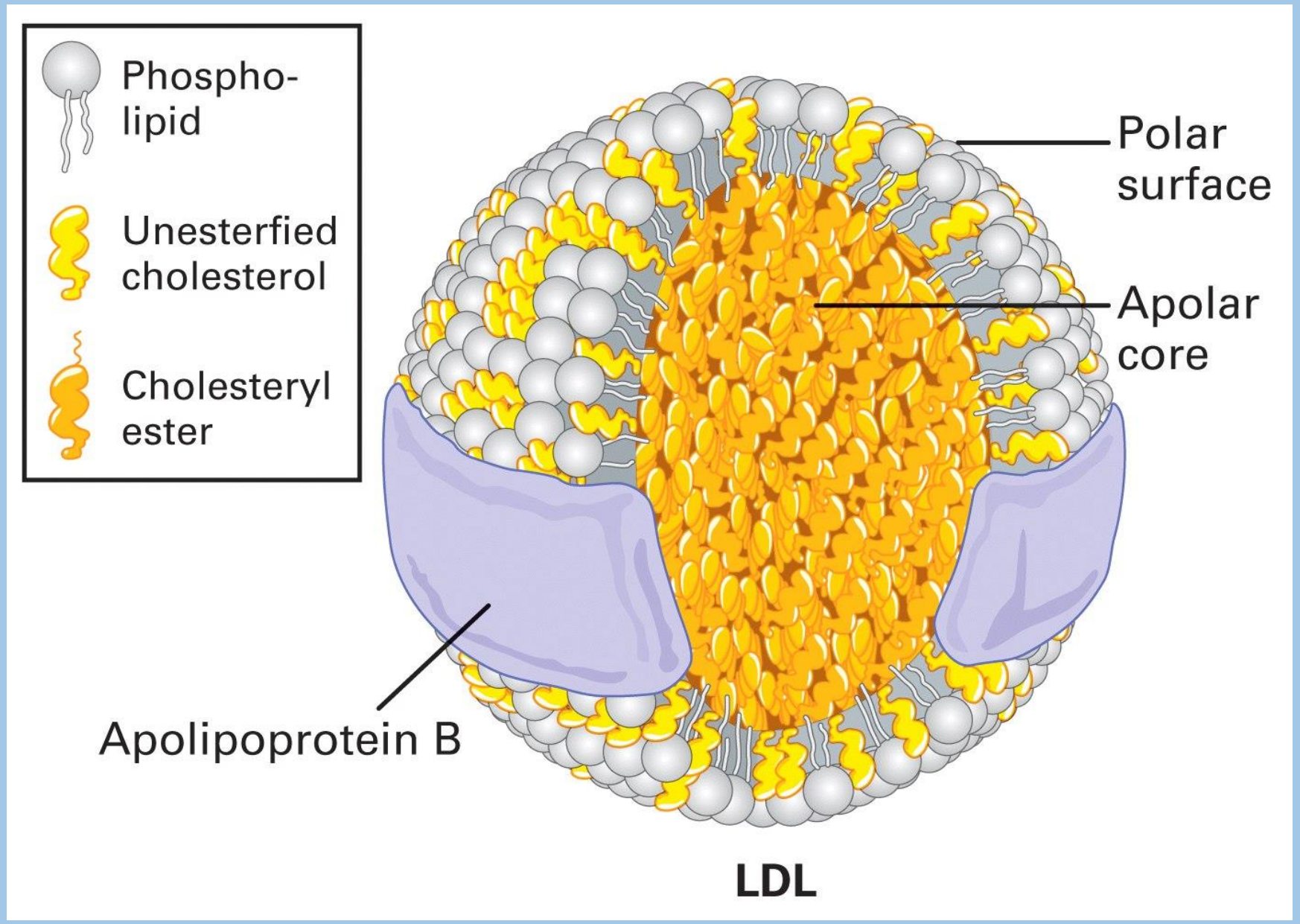
LDL-C = TC – HDL – TG/5

Reported: calculation of the cholesterol portion of the LDL particle

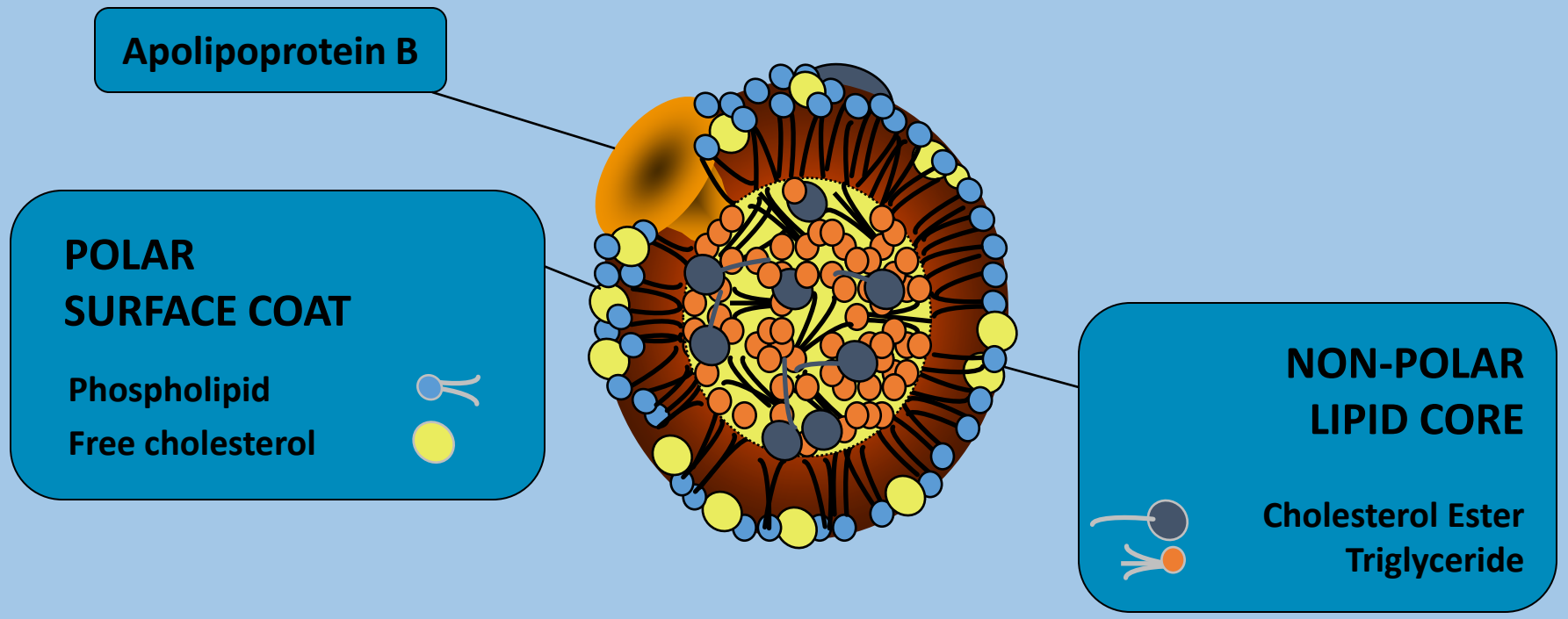
** Not accurate at higher TG values, can’t use if TG > 400*

Apolipoprotein B

Apo B-100 is the major apolipoprotein in LDL, IDL, VLDL, and Lp(a); each particle contains one molecule of apo B. Concentration of apo B = total number of atherogenic particles


Phospho-
lipid
Unesterfied
cholesterol
Cholesteryl
ester
Polar
surface
Apolar
core
Apolipoprotein B
LDL

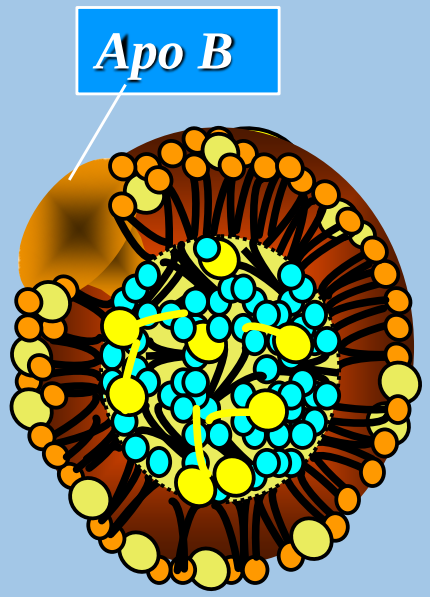
Low-Density Lipoprotein Particles (LDL)



LipoScience 2007

Lipids vs. Lipoproteins

This is an LDL Particle



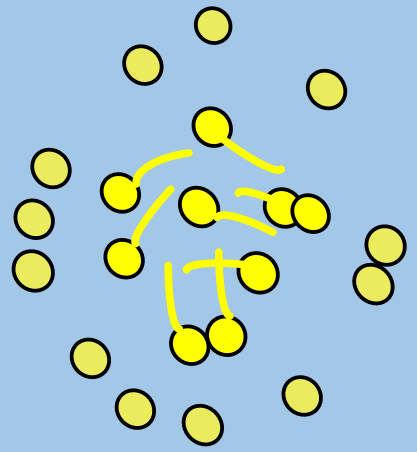
POLAR SURFACE COAT

Phospholipid
Free cholesterol

NONPOLAR LIPID CORE

Cholesterol Ester
Triglyceride

This is LDL Cholesterol



A convenient analytic surrogate of LDL since 1972

Apolipoprotein B

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III):

LDL-cholesterol levels do not completely measure the total atherogenic particles and components (VLDL, Lp(a), LDL) all of which have an Apolipoprotein B

While patients are risk stratified to match an LDL goal, there may be “residual risk” that remains after LDL goal is achieved.

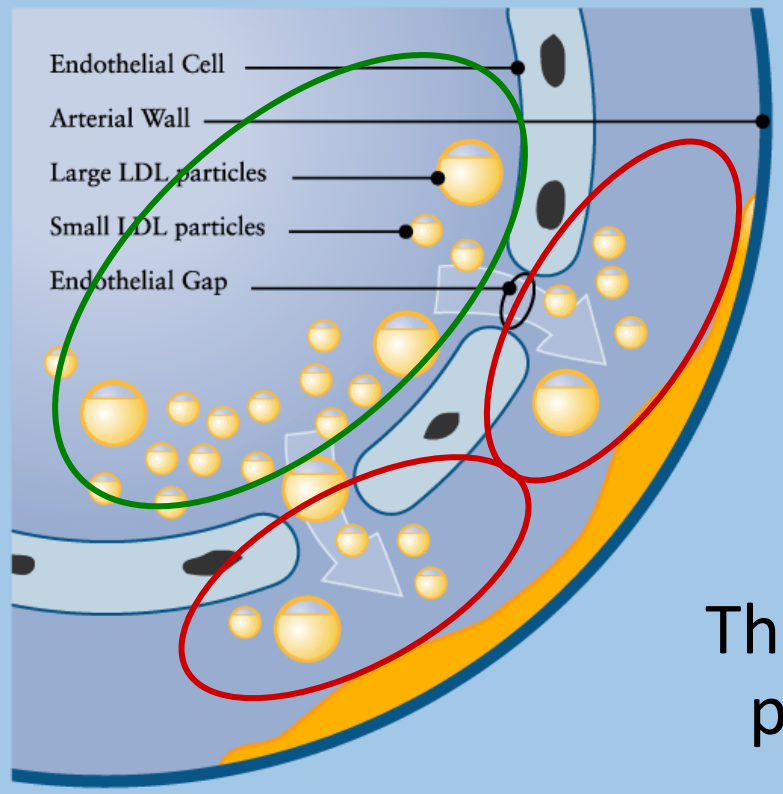
Non-HDL Cholesterol

- **Total cholesterol – HDL**
- NCEP ATP III Guidelines: secondary goal if TG are >/= 200 after LDL goal reached
- Goal is 30 mg/dL greater than LDL goal
- Non-HDL cholesterol is calculated, not directly measured and may reflect error in the measurement of total cholesterol or LDL
- ApoB has been shown to better predict risk

Apolipoprotein B
on every “atherogenic” particle

- The particle is the vehicle, the cholesterol is the passenger.
- LDL cholesterol has served as a useful surrogate for LDL-related risk but does not reflect the total atherosclerotic burden
- Apo B/LDL particles move into the arterial intima through a gradient-driven process; the rate is increased when the number of particles is increased.

LDL particle number is the most important driver of atherogenic plaque formation



Gradient driven process…LDL Particles invade the arterial wall

- **Oxidative Modification**
- **Foam Cell Formation**
- **Atherosclerosis**

The higher the number of LDL particles (LDL-P), the greater the risk for CHD.

Fredrickson et al. NEJM 1967; 276: 148

[redacted]

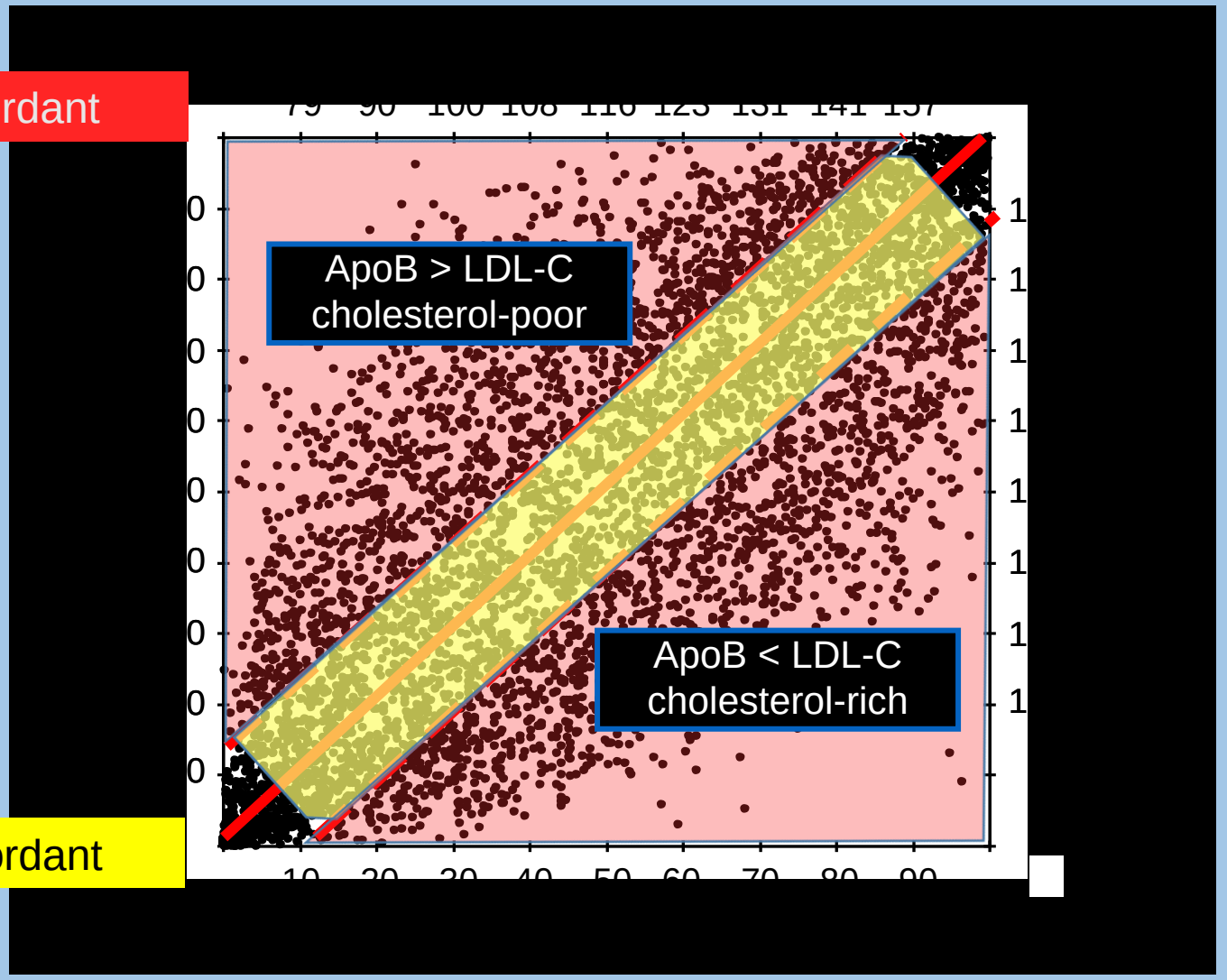
Outcome Associations or ApoB versus LDL Cholesterol (LDL-C)

1. Even in high TG patients, more than 90% of total plasma apoB is associated with LDL particles, except in type III hyperlipidemia [1,2]
2. LDL particle number (ApoB) is a superior predictor of CHD risk versus **LDL-C** in:
   - Prospective epidemiologic trials [3-12]
   - In assessing residual risk on statin or fibrate therapy in intervention trials [13-17].
3. LDL particle number (ApoB) is a superior predictor of CHD risk versus **non HDL-C**:
   - Prospective epidemiologic trials [8,11,18]
   - In assessing residual risk on statin or fibrate therapy in intervention trials [13-15,].

1. *Atherosclerosis.* 1991;89:109-16.
2. *Clin Chem Acta.* 1978;82:151-60.
3. *Circulation.* 1996;94:273-8.
4. *Circulation.* 1999;99:2517-22.
5. *Lancet.* 2001;358:2026-33.
6. *Arterioscler Thromb Vasc Biol.* 2002;22: 1918-23.
7. *AJC.* 2005;997-1001.
8. *Diabetologica.* 2006;49:937-944.
9. *Arterioscler Thromb Vasc Biol.* 2007;27:661-670.
10. *JAMA.* 2005;294:326-33.
11. *J Lipid Res.* 2007;48:2499-2505.
12. *JAMA.* 2007;298:776-785.
13. *Circulation.* 2000;101:477-84.
14. *Circulation.* 2002;105:1162-9.
15. *Arterioscler Thromb Vasc Biol.* 2000;20: 2408-2413.
16. *JACC.* 1998;32:1648-1656.
17. *Circulation.* 2003;107:1733-1737.
18. *Lancet.* 2003;361:777-780.

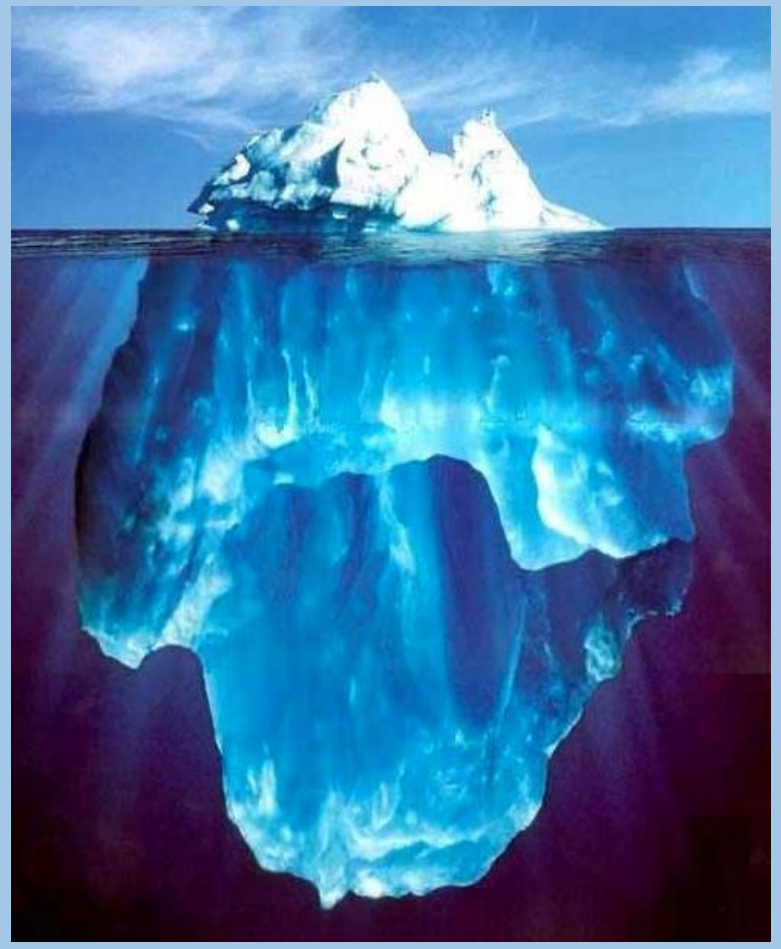
Discordance Between LDL-C and LDL-P in MESA

"Discordance" was defined as a difference of ≥12 percentile, to make 50% of subjects discordant



Otvos et al. J Clin Lipidol 2011;5:105-13

Oftentimes clinicians enjoy an unjustified sense of comfort with a “normal” LDL-Cholesterol value



Weight of LDL-C

Weight of ApoB (Atherogenic particles and residual risk)

What about directly measured LDL-C?

- DHMC Lab: has “reflex” direct measurement of LDL if Triglycerides > 400
- BUT—direct measurement of LDL-C and calculated LDL-C are very different and may vary up to 20 mg/dL
- The assay for direct measurement is not standardized
- Decades of research, guidelines, targets and goals based on calculated LDL-C
- We have established goals for calculated LDL-C, non-HDL-C, apoB, LDL-particle number
- **would not use “Directly Measured LDL-C, use ApoB”

LDL Particle Size

- Lipoprotein particles vary in size and lipid content

- Small, dense LDL particles (pattern B) are more atherogenic vs large, buoyant (pattern A) particles as they are bound and cleared less by LDL receptors and enter the arterial wall more easily and more likely to undergo oxidation

LDL Particle Size

While LDL particle size is a strong risk marker, the association with CVD and ability to predict risk is attenuated after adjustment for LDL particle number (MESA, Framingham, VA-HIT, Women's Health Study)

Treatment of Elevated LDL & ApoB

- Shared decision making
- Pharmacotherapy
- Lifestyle: exercise, diet
- Multi-disciplinary team: clinical pharmacist, dietician, exercise counselor
- National Lipid Association: patient tear sheets

Treatment of Elevated LDL & ApoB

Statins

- Remain first-line treatment
- Lowers LDL-C up to 60% and ApoB
- Pleiotropic effects: anti-inflammatory
- Limited by side effects, in particular muscle symptoms

Bile Acid Sequestrants

- 15-20% LDL-lowering
- May interfere with absorption of other medications
- Should not be used if elevated Triglycerides

Intestine Absorption Inhibitors

- 20-25% lowering

Treatment of Elevated LDL/ApoB

Bempedoic Acid
- small molecule inhibitor of ATP-citrate lyase and blocks cholesterol synthesis upstream of HMG Co-A reductase
- 35-40% LDL-lowering

PCSK9 Inhibitor
- Injectable
- Up to 60% LDL-lowering
- Lowers Lp(a)

Inclisiran
- Injectable, dosing every 6 months after initial doses
- Small interfering RNA preventing synthesis of PCSK9

Niacin
- 5-25% LDL-lowering
- Side effects limit use (flushing)

HDL

High Density Lipoprotein

- HDL is the “good” cholesterol
- Reverse cholesterol transport
- The higher the better?

HDL

ILLUMINATE Study

Enrolled approximately 15,000 patients at high risk for CHD who were randomized to treatment with Torcetrapib + atorvastatin vs. atorvastatin. Torcetrapib is a cholesterol ester transport protein (CETP) inhibitor. Mutations that inhibit CETP are associated with higher HDL levels

Barter PJ, et al. *N Engl J Med.* 2007;357:2109-22

HDL-C went up!

BUT,

- Excess of deaths in the torcetrapib/atovastatin group (82 vs 51)
- increases in heart failure, blood pressure, angina, revascularization procedures

HDL

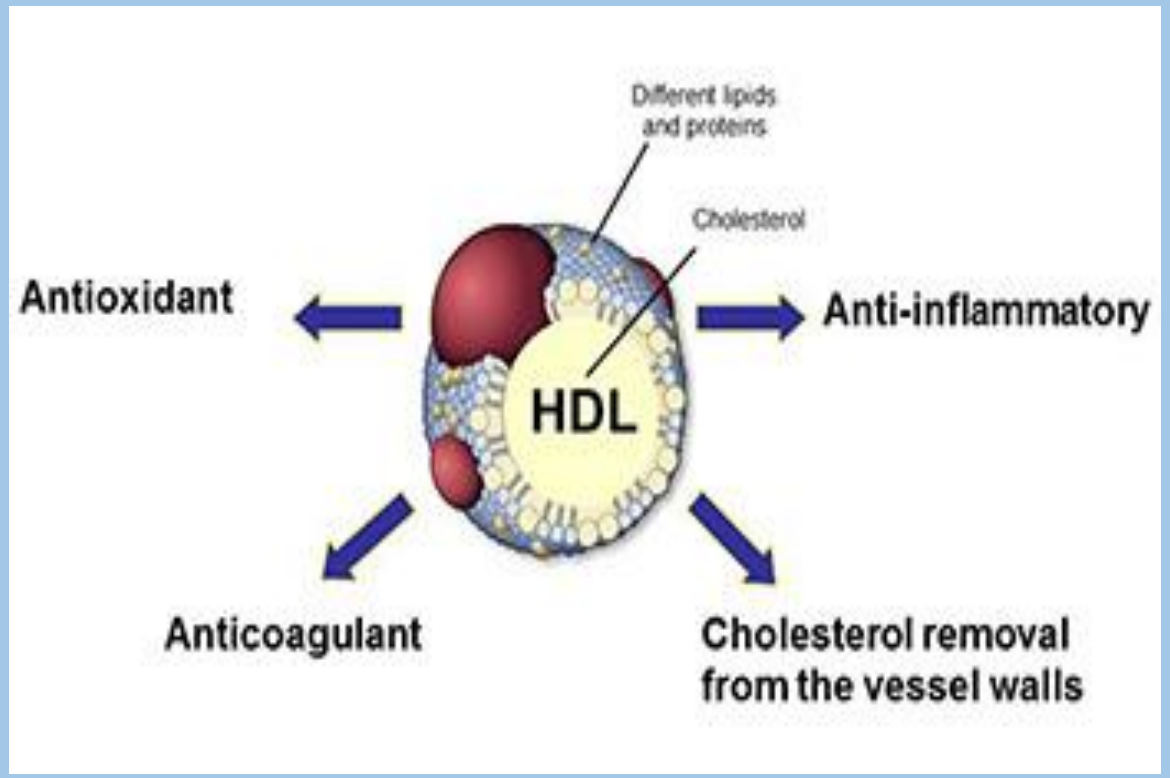
What Happened???

- Off-target adverse effects
- Maybe it is not the HDL-C (cholesterol content of the HDL particle) *but* the *function* of the HDL particle that was not improved

HDL function:
to remove (efflux) bad cholesterol from the body

A key property of HDL is its ability to promote cholesterol efflux from macrophage foam cells in atherosclerotic lesions.

So, is it the level of HDL-C or the function (efflux ability) of the HDL particle that we care about?


Different lipids
and proteins
Cholesterol
Antioxidant
Anti-inflammatory
HDL
Anticoagulant
Cholesterol removal
from the vessel walls

HDL

Current: measure the cholesterol portion of the HDL particle

Future: measure efflux potential?

To assess efflux, donor cells, such as hepatoma cells, fibroblasts or macrophages are incubated with 3H-cholesterol. Incubation with a medium containing an "acceptor" is carried out and scintigraphy used to show the amount of label released into the medium.

- Expensive and not available for clinical use

HDL Cholesterol
not currently target of treatment

Toth PP, et al. High Density Lipoproteins: A Consensus Statement from the National Lipid Association. Journal of Clinical Lipidology. 2013;7:484-525

- **The Panel concludes that, although low HDL-C identifies patients at elevated risk, and much investigation suggests that HDL may play a variety of antiatherogenic roles, HDL-C is not a therapeutic target at the present time.**

- The development of novel drugs designed to modulate the serum levels and functionality of HDL particles should continue.

Triglycerides

Triglycerides

Guidelines: Goals for Triglycerides

	1984	1993	2001
Desirable	< 250	< 200	< 150

2017 Endocrine Guidelines: Triglycerides < 150

Triglycerides

The independent relationship of TG to CVD risk?

- Large inter- and intra-individual variation
- Post prandial levels may be more important
- TG or the company it keeps? TG are closely aligned with metabolic syndrome, insulin resistance and diabetes
- Note: there are varied etiologies of elevated TG

Triglycerides
and cardiometabolic abnormalities

Insulin resistance and hyperinsulinemia are associated with lipid abnormalities: high TG, low HDL, small/dense LDL

When adipose tissue is resistant to insulin:

Inhibition of lipolysis → increased FFA flux to liver → increased VLDL secretion → increased TG→ CETP activated → more TG goes to LDL and HDL which is then hydrolyzed and → small, dense LDL and lower HDL

Triglyceride Treatment

Lifestyle Modification

- Key component for management
- Diet: restricted intake of simple carbohydrates, fat, and alcohol
- Weight loss
- Physical activity/exercise

Medication

- Fibrates
- Omega-3 fatty acids (~4000 grams/day)

Metabolic Syndrome

Some experts have questioned the clustering together of individual components and the definition is still in flux.

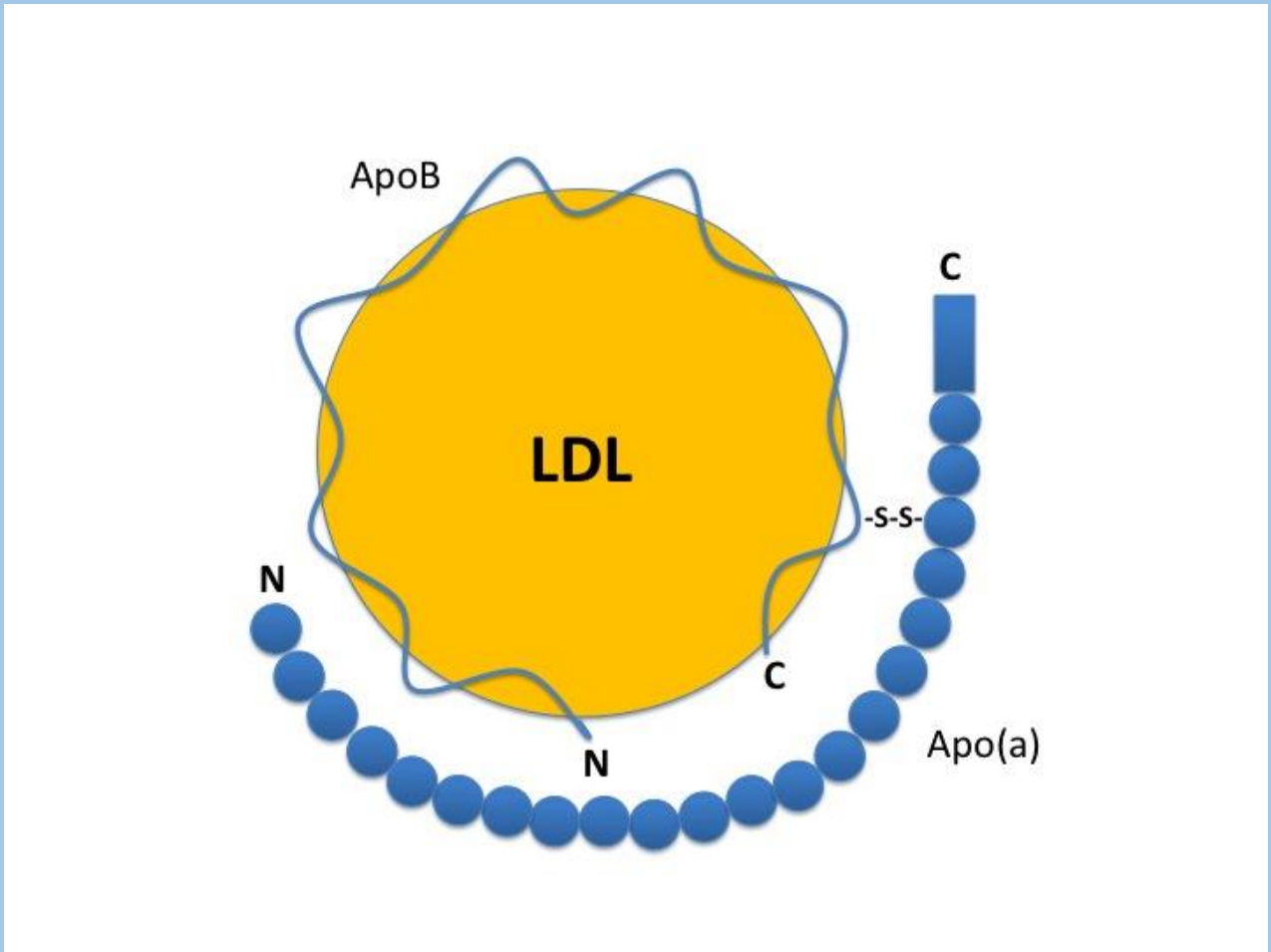
- Visceral adiposity
- Low HDL-C
- Elevated TG
- Hypertension
- Insulin resistance

NCEP ATP III required 3/5, international criteria: obesity + two other components

Lipoprotein (a)

- Complex protein particle comprised of a single copy of apo B-100 linked to a single copy of apo (a); many polymorphisms
- Apo (a) has a close homology to plasminogen and may compete with plasminogen for binding to fibrin (may inhibit thrombolysis)
- Heavily influenced by genetics, Not influenced by lifestyle (diet, exercise).
- Independently associated with CVD risk

Lipoprotein (a)



Lp(a) Measurement

Levels are conveyed as either the mass of the entire Lp(a) particle in mg/dL or as particle number of apo(a) in nmol/L.

Lp(a) may also be expressed as Lp(a) cholesterol in mg/dL. There is a lack of standardization of Lp(a) assays.

At this time, best to use assays that report results in nmol/L

Lp(a): When to Measure?

European Atherosclerosis Society Consensus Statement 2022

- Should be measured at least once in adults
- Patient with premature ASCVD w/o apparent risk factors
- Patient with strong family history of premature ASCVD
- Screening in youth with a family history of premature ASCVD or high Lp(a)

Lp(a) Treatment

- Lifestyle modification (diet, exercise) will not lower Lp(a)
- High dose niacin, estrogen will lower levels
- PCSK9 inhibitors will lower ~15 -30%
- Lipid Apheresis
- Pelacarsen (IONIS/Novartis): Phase III trials. Small interfering RNA (targets the LPA gene)
- Olpasiran (Amgen) Phase II trials. Small interfering RNA

Hypertension

Hypertension

2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Category	Range (Systolic, Diastolic)	Comments
Normal	<120 and <80 mmHg	
Elevated	120-129 and <80 mmHg	Non-pharmacological therapy Reassess in 3-6 months
Stage I	130-139 or 80-89 mmHg	10-year ASCVD risk ≥ 10% →pharmacologic Rx
Stage 2	≥ 140 or ≥ 90 mmHg	Pharmacological therapy

Hypertension

2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

- Proper measurement
- White coat hypertension: office readings high (consistently ≥ 140/90), home readings at goal. →continue home monitoring or ambulatory BP monitor
- Screen for secondary hypertension
  - -abrupt onset, exacerbation of previously controlled BP
  - -drug-induced: estrogen oral contraceptives, NSAIDS
  - -renal artery stenosis
  - -obstructive sleep apnea
- Resistant hypertension: ≥ 140/90 on optimal doses of 3 or more medications including one diuretic

Hypertension

Management

Lifestyle

- Weight loss
- Physical activity and exercise
- Diet: DASH dietary pattern

    -fruits, vegetables, whole grains, reduced saturated and total fat, low-fat dairy

    -low salt

Pharmacological

- First line agents: thiazide diuretics, calcium channel blockers (dihydropyridine), ARB (preferable vs. ACEI)
- Beta blockers if other reason to use this class of medications

Hypertension

Renal Artery Denervation

- The U.S. Food and Drug Administration (FDA) approved the Medtronic Symplicity Spyral™ renal denervation system for use in the United States. November 17, 2023
- The system, which carries the FDA's Breakthrough Device designation, uses radio frequency to disrupt overactive nerves in the kidneys and help lower blood pressure.
- In November, an advisory panel voted 6-7 against the device's benefit-risk profile, raising questions about whether the FDA would approve the device. A competing device made by Otsuka-backed Recor Medical received a positive advisory vote. The FDA often follows its advisers' recommendations, although it is not required.

Hypertension

Postural hypotension

- Common in older patients
- Worsened by diuretics, diabetes, venodilators, psychiatric medications
- Initiate medications at lower doses, titrate cautiously
- May limit ability to reach goal in some patients
- Keep well hydrated

Isolated diastolic hypertension

- Measurement less accurate
- Lifestyle modification can help

Smoking and Tobacco Use

Smoking and Tobacco Use

Pathway for Smoking Cessation Treatment

- Ask tobacco use status (cigarettes, vaping, chewing)
- Offer treatment options
    - behavior counseling
    - pharmacotherapy
        - nicotine replacement (gum, lozenge, patch, inhaler, nasal spray
        - Varenicline
        - buproprion
- Refer to outpatient smoking cessation clinic
- If inpatient, provide counseling (with certified counselor, if available) as this is “educable moment”

Smoking and Tobacco Use: E-Cigarettes

Rose, JJ, et al. Cardiopulmonary Impact of Electronic Cigarettes and Vaping Products: A Scientific Statement From the American Heart Association. 2023

- Combustible tobacco product: aerosol condensate generated has known toxicities
- Nicotine-delivery product
- Has not been shown to be a path toward smoking cessation
- Wide use among youth

Smoking and Tobacco Use: Reimbursement for Cessation Services

Medicare Coverage

- Medicare Part B covers up to 8 smoking and tobacco-use cessation counseling sessions in a 12-month period

- Medicare reimbursement

99407 ≥ 10 minutes of counseling is $28.96

99406 3-10 minutes of counseling is $15.70

These are national reimbursement amounts, local Medicare payments may vary.

Future: reimbursement for nurses, clinical pharmacists, medical assistants to provide counseling

Mental Health: Chronic Stress, Anxiety, Depression

Link between mental health and cardiovascular disease is both direct and indirect

Management

- Screen for psychological health issues
- Offer counseling if indicated: social worker, support groups, psychotherapy
- Offer pharmacotherapy in a shared-decision discussion

Pre-Diabetes and Diabetes

Pre-Diabetes

- Screen for prediabetes, especially those with metabolic syndrome

  American Diabetes Association 2023 diagnostic criteria:

fasting plasma glucose	100-125 mg/dL
2-hr post-load plasma glucose	140-199 mg/dL
hemoglobin A1c	5.7 – 6.4

- Treatment and prevention of progression to Type II diabetes

  lifestyle modification: diet, weight loss, exercise

  Pharmacologic: consider metformin, esp for those at higher risk of developing type II Diabetes, there is evidence for effectiveness with GLP-1 receptor agonists

Pre-Diabetes and Diabetes

Diabetes 2023 American Diabetes Association Standards of Care in Diabetes

- Glycemic Targets

A1c goal	< 7%
Stringent A1c goal	lower if can be achieved safely
Less stringent A1c goal	< 8% to reduce risk of hypoglycemia or other harms of treatment

- Multi-disciplinary care team including diabetes educator, dietician, clinical pharmacist
- Pharmacologic therapy
- Lifestyle modification
- Aggressive management of CVD risk factors

Physical Activity


5
CHAPLIN
180
2014 • WINSTON-SALEM, NC
ATLANTA
CLUB
COMPETITIVE TEAM
FOX
345
2014 • WINSTON-SALEM, NC

Physical Activity: Definitions

- Sedentary Behavior: any waking behavior characterized by energy expenditure of ≤ 1.5 METS
- Physical Activity: any bodily movement produced by skeletal muscle contraction that requires energy expenditure above basal levels
- Exercise: differentiated from physical activity in that it is typically planned, repetitive, and structured with the main objective of improving health and fitness
- Physical Fitness: a state of good health and strength achieved through physical activity and exercise. Includes cardiorespiratory fitness + muscular strength and muscular fitness

Fletcher, GF. J Am Coll Cardiol. 2018;72:1622-1639

Definitions

Cardiorespiratory Fitness:
the integrated ability to transport O_2 from the atmosphere → mitochondria to perform physical work.

This reflects the functional capacity of an individual and is dependent on a linked chain of processes that include pulmonary ventilation and diffusion, right and left ventricular function (both systolic and diastolic), ventricular-arterial coupling, the ability of the vasculature to accommodate and efficiently transport blood from the heart to precisely match O_2 requirement, and the ability of the muscle cells to receive and use the O_2 and nutrients delivered by the blood.

Exercise Prescription

Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise

Garber CE, et al. American College of Sports Medicine 2011

Cardiorespiratory (Aerobic) Fitness

- ≥ 5 days/week of moderate-intensity exercise, ≥ 3 days/week vigorous (or combination of the two for ≥ 3-5 days/week)
- 30-60 minutes/day of moderate (150 minutes/week), 20-60 minutes/day of vigorous (75 minutes/week)
- Regular exercise that involves major muscle groups and is rhythmic in nature
- Progression: gradual by adjusting the duration, frequency, and/or intensity until desired target reached

Moderate = 3 – 5.9 METS Vigorous = ≥ 6 METS

Exercise Prescription

Determining a “Training-Sensitive Zone” for aerobic exercise

Age	Lower-limit target HR	Upper-limit target HR
< 60 years	60-70% maximum HR	90% maximum HR
> 60 years	60% maximum HR	75% maximum HR

Maximum HR = 220 – age (years)

Example: 62-year old woman

220 – 62 = 158 HR_{max}

.60 X 158 = 95 beats/minute lower limit

.75 X 158 = 118 beats/minute upper limit

Source: McArdle, Katch, Katch. Exercise Physiology. Wolters Kluwer 2015

Exercise Prescription Real Life

Patient: 58 year-old woman, active but no regular exercise

Maximum HR 220 – 58 = 162

Lower-limit HR (.65 X 162) = 105 bpm

Upper limit HR (.90 X 162) = 145 bpm

Stretch	5 minutes before walking
Walk	2-3 miles at 3 mph, 5 days a week with HR approximately 115 bpm
Strength	5 minutes of pushups (modified), situps, toe raises

Exercise Prescription Real Life

Clinic note documentation of exercise counseling:

Patient currently not doing formal exercise which she states is related to time. We discuss the following as a way to meet goals for physical activity:

1. Work: Use stairs rather than the elevator, park the car further from her office building, try to walk during lunch
2. Home: she has two small children and she will aim to take a 10-15 minute walk with them when she gets home from work before she starts with dinner and household chores. She feels guilty about not spending enough time with them.
3. Family outings: one weekend day plan activity that requires walking: visiting a zoo, park, museum

Credit: Joyce Ross, MSN, CRNP and past president, National Lipid Association

Note: counseling billed on face-to-face time


DREHER
DREHER
DREHER
DREHER
RS

Diet and Weight Management

Diet: General Guidelines

Lichtenstein AH, et al. 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation. 2021;144

- Eat plenty of fruits and vegetables, choose a wide variety
- Choose foods made with whole grains rather than refined grains
- Choose health sources of protein: mostly from plants (legumes and nuts)

  2-3 servings of fish per week, low-fat or fat-free dairy products,

  if meat or poultry desired, choose lean cuts and avoid processed forms
- Use liquid plant oils rather than tropical oils, animal fats, and partially hydrogenated fats
- Choose minimally processed foods instead of ultra-processed foods
- Minimize intake of beverages and foods with added sugars
- Choose and prepare foods with little or no salt
- If you choose to drink alcohol, limit intake (1 drink/day for women and 2/day for men)

Diets

The Mediterranean Diet

- distinct for its large amounts of fruits, vegetables, nuts, legumes, fish, whole grains, and extra virgin olive oil; moderate intake of red wine; and low amounts of dairy products, red and processed meat
- The positive physiologic effects are attributed to the large amounts of antioxidative and anti-inflammatory nutrients found in the diet

The Dietary Approaches to Stop Hypertension (DASH) Diet

- mostly plant based with low fat dairy and lean animal proteins to be eaten in small amounts daily
- Daily sodium is limited to 1500 mg and alcohol is not recommended.
- The diet is specific in terms of daily servings of each food group making it an easy dietary pattern to follow.

Vegan and Vegetarian Diets

- Careful planning to ensure adequate protein, vitamins, minerals

Cautionary Diets

Ketogenic and carbohydrate-restricted diets

- Carbohydrate-restricted diets are helpful for patients with diabetes however there is no evidence that very low (< 10% of total daily energy (TDE)) carbohydrate is needed or helpful
- When very low carbohydrate diet is combined with high fat (> 30% of TDE) content ("Ketogenic Diet") there is generally considerable weight loss. However, studies have shown that this dietary pattern is associated with marked elevation in LDL-cholesterol, and increases risk for atherosclerotic cardiovascular events and cardiovascular mortality, and is not easily sustained

Intermittent fasting

- Intermittent fasting with daily time-restricted feeding such as 16-24 hours of fasting or 2-4 days a week of full-day fasting has been used for weight loss
- Current research on long-term consequences and overall benefits and risks are not fully understood
- Adverse effects include nutritional needs not being met, problems with needing to take certain medications with food, and hypoglycemia in patients with diabetes

Medical Nutrition Therapy

Medical nutrition therapy by trained dietitians is an integral part of a multidisciplinary health care team

Components of an MNT Evaluation

- The dietitian first assesses the patient's clinical status, goals of care, current dietary pattern and specific food preferences
- Potential limitations are identified such as access to healthy food choices and problems with adherence.
- Next, the dietitian develops a specific eating plan according to clinical practice guidelines for diabetes care or weight loss incorporating lifestyle modification into the plan.

Medicare Reimbursement:

- 3 hours of counseling in the first year; two hours in second year
- Reimbursement ranges from $17-$36 per session
- Only for those with diabetes or renal disease: YOU ALREADY HAVE TO BE SICK!

Weight Loss Drugs

- FDA approval: adults with body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 and at least one weight-related comorbidity who have not achieved ≥ 5% weight loss with lifestyle modification.
- Drugs such as Orlistat (Alli), Phentermine/Topiramate (Qsymia), and Naltrexone/Bupropion (Contrave) have not shown the same impressive results as the GLP-1 receptor agonists (GLP-1 RA)
- GLP-1 RA

Are incretin mimetics. Incretins are gut-derived peptide hormones that are secreted in response to food ingestion. They were initially developed for the treatment of diabetes as they stimulate pancreatic β-cells to secrete insulin, thereby lowering serum glucose. The GLP-1 receptor agonists also stimulate hypothalamic neurons that induce satiety, a process that is called “gut-brain signaling.”

Semaglutide (Wegovy), Tirzepatide (Zepbound), Liraglutide (Saxenda)

high cost and lack of reimbursement (Medicare)

must be taken indefinitely

long-term safety of these formulations unknown, in particular the multi-agonist formulations

Prevention of Cardiovascular Disease

- Overview of ASCVD Prevention
- Guidelines
- Estimation of Risk and Risk Scores
- Risk Enhancers, Inflammation, Coronary Artery Calcium
- Major risk factors: Dyslipidemia, Hypertension, Smoking and Tobacco Use
- Physical Activity, Diet and Weight Management, Mental Health


5
6