Lipid Update 2021

Top 10 Tips for Treating Lipids

James H. Stein, M.D.
Professor of Medicine, Cardiovascular Medicine
Director, Preventive Cardiology Program
UW School of Medicine and Public Health

CME Disclosures

- I disclose the following relevant financial relationships
  - Chair of Data and Safety Monitoring Committees
    - Lilly, Inc. (Chair, DSMCs)
    - Silence Therapeutics, Inc. (Chair, DSMC)

Outline

- Top 10 take home tips for treating lipids to prevent ASCVD
- Statin myalgias

“I have good news and bad news. Your cholesterol has stayed the same, but the guidelines have changed.

Cholesterol Screening to Prevent ASCVD

- Screen at age ≥20 years
  - Fasting or non-fasting lipid profile
  - Prefer fasting if family history of premature ASCVD or genetic hyperlipidemia
  - Avoid if high fat meal in past 8 hours
  - If non-fasting TG ≥400 mg/dL, repeat fasting

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

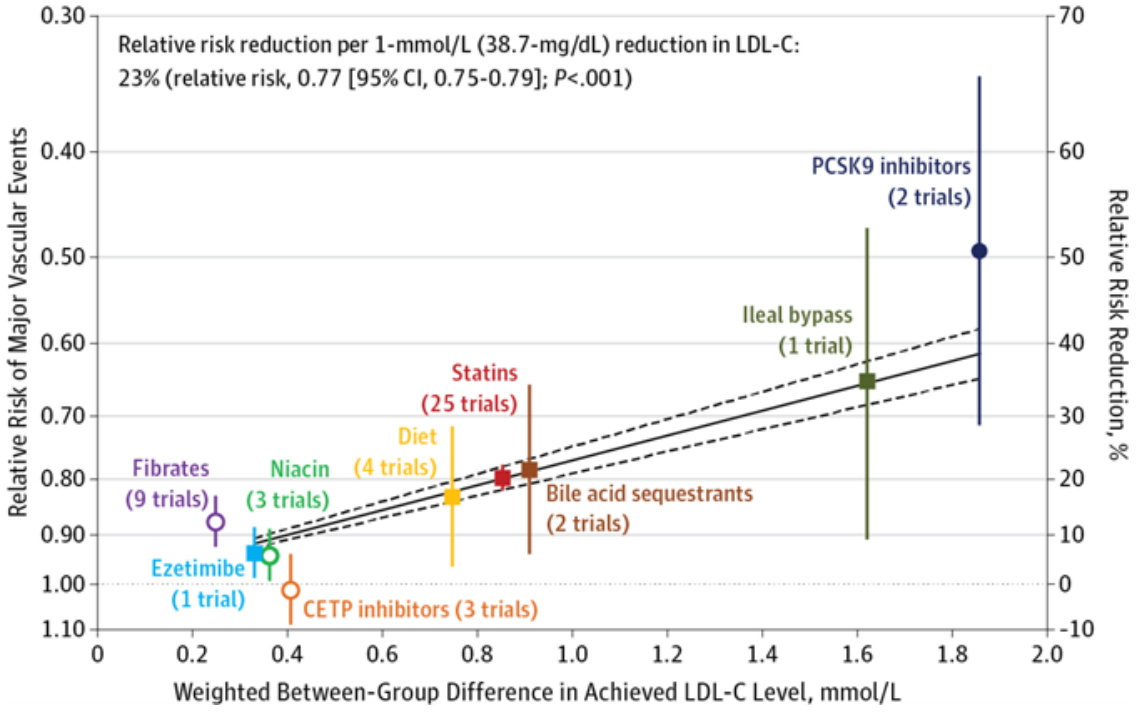
AHA-ACC Guidelines on Blood Cholesterol: Top 10 Take-Home Tips

1. In **all** individuals, emphasize a **heart-healthy lifestyle** across the life course.
   - A healthy lifestyle reduces ASCVD risk at all ages.
   - In younger people, healthy lifestyle can reduce development of RFs.
   - In young adults 20-39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion & emphasizes intensive lifestyle efforts.
   - In all age groups, lifestyle therapy is the primary intervention for Metabolic Syndrome.

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

Statins

- Strongest data for ASCVD events, but non-statins have similar efficacy: ~20-25% ASCVD reduction/39 mg/dL reduction/year.



Silverman MG, et al. JAMA 2016; 316

Statin Dosing

	High Intensity	Mod. Intensity	Low Intensity
LDL-C ↓	≥50%	30-50%	≤30%
Daily doses (mg)	Atorva 40-80 Rosuva 20-40	Atorva 10-20 Rosuva 5-10 Simva 20-40 Prava 40-80 Lova 40 Fluva 80 Pitava 2-4	Simva 10 Prava 10-20 Lovastatin 20 Fluva 20-40 Pitava 1

Individual responses to statin therapy varied in RCTs → expected to vary in clinical practice

Stone NJ, et al. J Am Coll Cardiol 2014; 63:2889

Top 10 Take-Home Tips

2. In **all patients with clinical ASCVD**, reduce LDL-C with **high-intensity statin therapy** (or maximum tolerated statin tx).
   - More LDL-C reduction → greater risk reduction.
   - Lower LDL-C by ≥50%.
3. In **very high-risk ASCVD,** consider adding non-statin if LDL-C is ≥70 mg/dL.
   - Add ezetimibe.
   - Consider PCSK9 inhibitor.

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (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 heart failure

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

Top 10 Take-Home Tips

4. In patients with **LDL-C ≥190 mg/dL begin high-intensity statin *w/out calculating ASCVD risk.***
   - If LDL-C still ≥100 mg/dL on a statin, adding ezetimibe is reasonable.
   - If LDL-C still ≥100 mg/dL on statin and ezetimibe & multiple ASCVD RFs, consider adding a PCSK9 inhibitor.

Severe Hypercholesterolemia

- Lifelong, usually genetic
- 1/200-500 in US
- 4-5x ASCVD risk over 10-20 yrs in men, 20-30 yrs in women
- Do not use risk scores
- Treat starting at age 20 years (some treat younger)

Grundy SM, et al. Circulation 2018.
DOI: 10.1161/CIR.0000000000000625

Top 10 Take-Home Tips

5. In patients 40-75 yrs old with **diabetes mellitus** and LDL-C ≥70 mg/dL, **start moderate intensity statin *w/out calculating ASCVD risk.***
   - If multiple ASCVD RFs or >50 yrs old, high-intensity statin is reasonable.
   - If 20-39 yrs old, moderate-intensity statin is reasonable if DM specific risk enhancers.

DM Specific Enhancers

- T2 DM ≥10, T1 DM ≥20 yrs
- Albuminuria ≥30 mcg/mg creat
- eGFR <60 mL/min/1.73 m^2
- Retinopathy
- Neuropathy
- ABI <0.9

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

Top 10 Take-Home Tips

6. In adults 40-75 yrs old evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.
   - Review major ASCVD RFs and 10-year risk
   - Presence of risk-enhancing factors (see #8)
   - Potential benefits of lifestyle and statin tx
   - Potential for adverse effects and drug–drug interactions
   - Consider costs of statin tx
   - Patient preferences & values in **shared decision-making**

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

The SHARE Approach

5 Essential Steps of Shared Decision Making

https://www.ahrq.gov/health-literacy/curriculum-tools/shareddecisionmaking/index.html

Top 10 Take-Home Tips

7. In adults 40-75 yrs old without DM but with LDL-C ≥70 mg/dL and 10-year ASCVD risk ≥7.5%, start a moderate-intensity statin, if discussion of tx options favors statin therapy.
   - If statins are indicated, reduce LDL-C by ≥30%.
   - If 10-year risk is ≥20%, reduce LDL-C by ≥50%.
   - Risk-enhancing factors favor statin tx (see #8).
   - If risk status is uncertain, consider coronary artery calcium screening to improve specificity (see #9).

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

Top 10 Take-Home Tips

8. In adults 40-75 yrs old without DM but with 10-year ASCVD risk 7.5-19.9% (intermediate risk), risk-enhancing factors favor initiation of statin tx.

ASCVD Risk Enhancers

- FHx premature ASCVD (M<55; F<65 yrs old)
- 1° hypercholesterolemia (LDL-C ≥160, non-HDL-C ≥190 mg/dL)
- Metabolic syndrome
- Chronic kidney disease (eGFR 15-59)
- Chronic inflammatory conditions (*i.e.*, psoriasis, RA, HIV)
- Premature menopause (<40 yrs)
- Pre-eclampsia, pregnancy-induced HTN, gestational DM
- South Asian ancestry
- Lipid/biomarkers
  - Persistent TG ≥175mg/dL
  - HsCRP ≥2.0 mg/L
  - Lp(a) ≥50 mg/dL or ≥125 nmol/L
  - ApoB ≥130 mg/dL
  - ABI <0.9

Top 10 Take-Home Tips

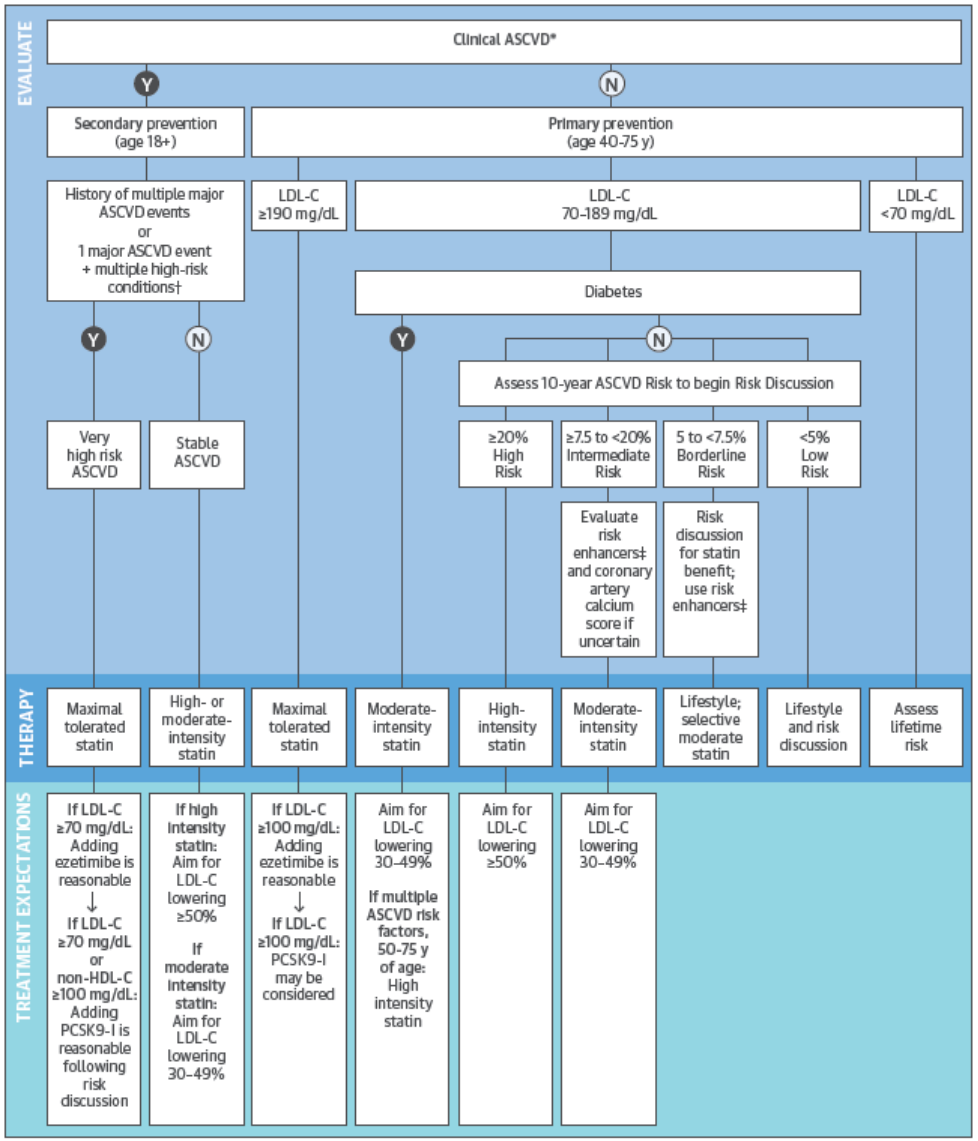
9. In adults 40-75 yrs old without DM but with 10-year ASCVD risk 7.5-19.9% (intermediate risk), if a decision about statin therapy is uncertain, consider measuring CAC.
   - If CAC = 0, statin tx may be withheld or delayed, **except in cigarette smokers, DM, or family hx of premature ASCVD.**
   - CAC = 1 to 99 favors statin tx, esp. if ≥55 yrs old.
   - CAC ≥100 or ≥75th percentile, statin indicated, unless deferred by shared-decision making.
   - **Other caveats**: $150-$180, radiation ≅ 10-20 CXRs, adventitious findings.

Top 10 Take-Home Tips

10. Assess adherence and percentage response to LDL-C lowering meds and lifestyle changes
    - **Repeat lipid measurements** 4-12 weeks after med initiation/dose adjustment, then q 3-12 mos.
    - Define responses to lifestyle and statin tx by % LDL-C reductions compared with baseline.
        - In ASCVD patients at very high-risk, add non-statin drug therapy if LDL-C ≥70 mg/dL (see #3).
        - If primary prevention with LDL-C ≥190 mg/dL, add non-statin drug therapy if LDL-C ≥100 mg/dL (see #4).

Grundy SM, et al. Circulation 2018. DOI: 10.1161/CIR.0000000000000625

2018 Cholesterol Guideline Summary



Statin-Associated Muscle Sx

- True incidence not known – heterogeneous sx and causes including a significant nocebo effect
  - Latin for “I will harm”
  - A nocebo effect is an ill effect caused by the suggestion or belief that something is harmful
- ASCOT – muscle-related adverse events
  - Blinded: 2.03 vs 2.0%/yr; median 2.3 years (p=0.72)
  - Unblinded: 41% higher in statin users (p=0.006)
- ODYSSEY-Alternative: among those who failed 2 statins, 78% tolerated blinded atorva 20 mg QD

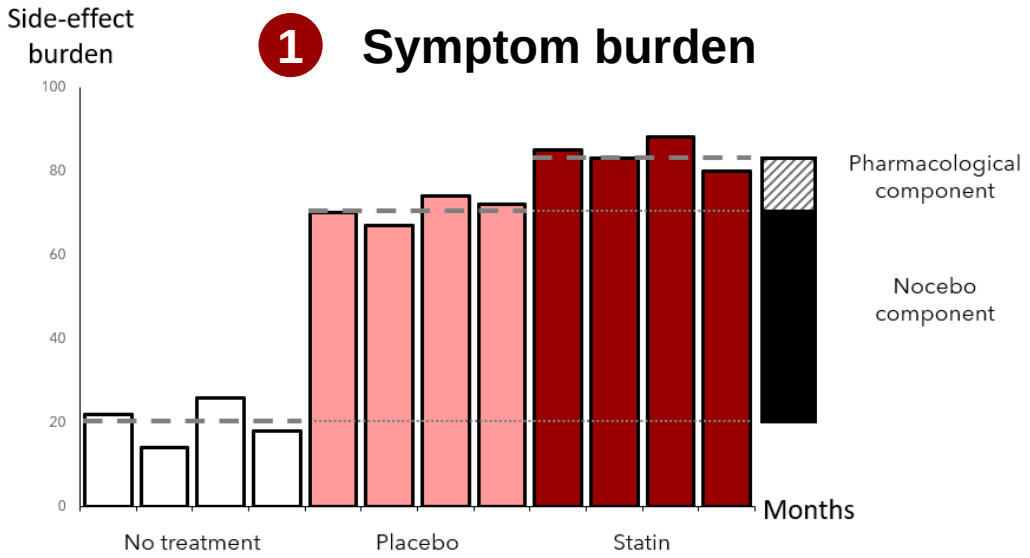
Gupta A, et al. Lancet 2017; 389:2473
Finegold J et al. Eur J Prev Cardiol 2014; 21:464
Moriarty P, et al. J Clin Lipidol 2015; 9:758

N-of-1 Trial of Patient Symptoms:
The SAMSON Trial

4 Empty

4 Placebo

4 Atorvastatin



1 **Symptom burden**

1 year

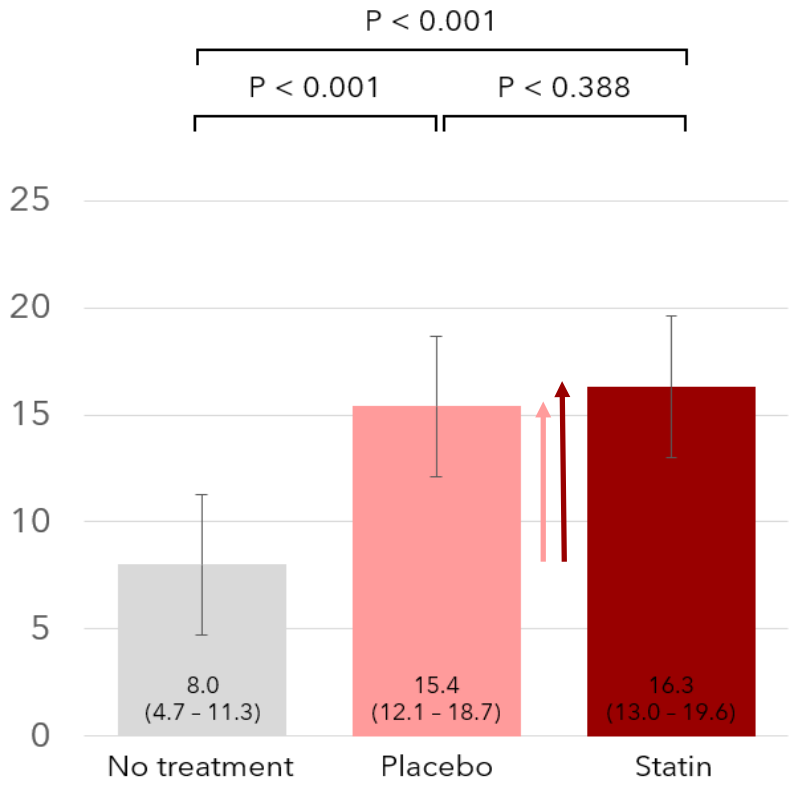
2 **% taking statins 6 months after completing trial**

Wood FA, et al. N Engl J Med 2020; 383:2182

N-of-1 Trial of Patient Symptoms: The SAMSON Trial

N = 60

Age (years)	65.5 (8.6)
Gender	
Male	35 (58.3)
Female	25 (41.7)
BMI	29.1 (6.7)
# previous statins tried	
1	17
2	20
3	11
4	7
5	3
Previous statin (yrs)	2.8 (4.7)
LDL-C (mmol/L)	161.0 (36.6)



Calculated nocebo proportion (↑÷↑) = 0.90

6 months later, 50% back on statin tx

Wood FA, et al. N Engl J Med 2020; 383:2182

StatinWISE

- N=200 who recently stopped or were considering stopping statin tx due to muscle sx
- Rdm: 5 double-blinded tx periods (2 months each) of atorvastatin 20 mg daily or placebo
- No difference in muscle symptom scores between the statin & placebo periods (mean Δ −0.11, 95% CI −0.36 to 0.14; P=0.40)
- Withdrawals because of intolerable muscle symptoms: 18 (9%) during a statin period vs. 13 (7%) during a placebo period

2/3 completing the trial restarted long-term statin tx

Herrett E, et al. BMJ 2021;372:n135

Treatment of Hyperlipidemia: Nutrition

- **All**
  - Fruits, vegetables, legumes, nuts, whole grains, low-fat dairy, poultry, fish, non-tropical vegetable oils
  - Limit sweets, sugar-sweetened beverages, red meats
  - Achieve ideal weight
- For lowering LDL-C
  - Reduce sat fat intake: goal <5%-6% of calories
  - Reduce percent of calories from trans fat
  - Add psyllium, stanol/sterol margarines
- For lowering triglycerides - ***Lose weight***
  - Reduce simple carbohydrates and sugars
  - Limit alcohol

Summary: Lipid Therapy Based on Lipid Pattern – All with Lifestyle Changes

Medication Sequence	Lipid Pattern		
	TG <200 mg/dL	TG 200-499 mg/dL	TG ≥500 mg/dL
First	Statin	Statin	Fibrate
Second	Add ezetimibe (consider resin)	Add ezetimibe or fish oils (EPA?)	Add fish oils
Third	Add PCSK9 inhibitor	Add PCSK9 inhibitor	Add statin
Fourth	*Consider:* resin, niacin, lomitapide, mipomersen, LDL apheresis	*Consider:* niacin, lomitapide, LDL apheresis	*Consider:* niacin, lomitapide, plasmapheresis

Guidelines in Cardiology

Richard Lehman @R... · 2h

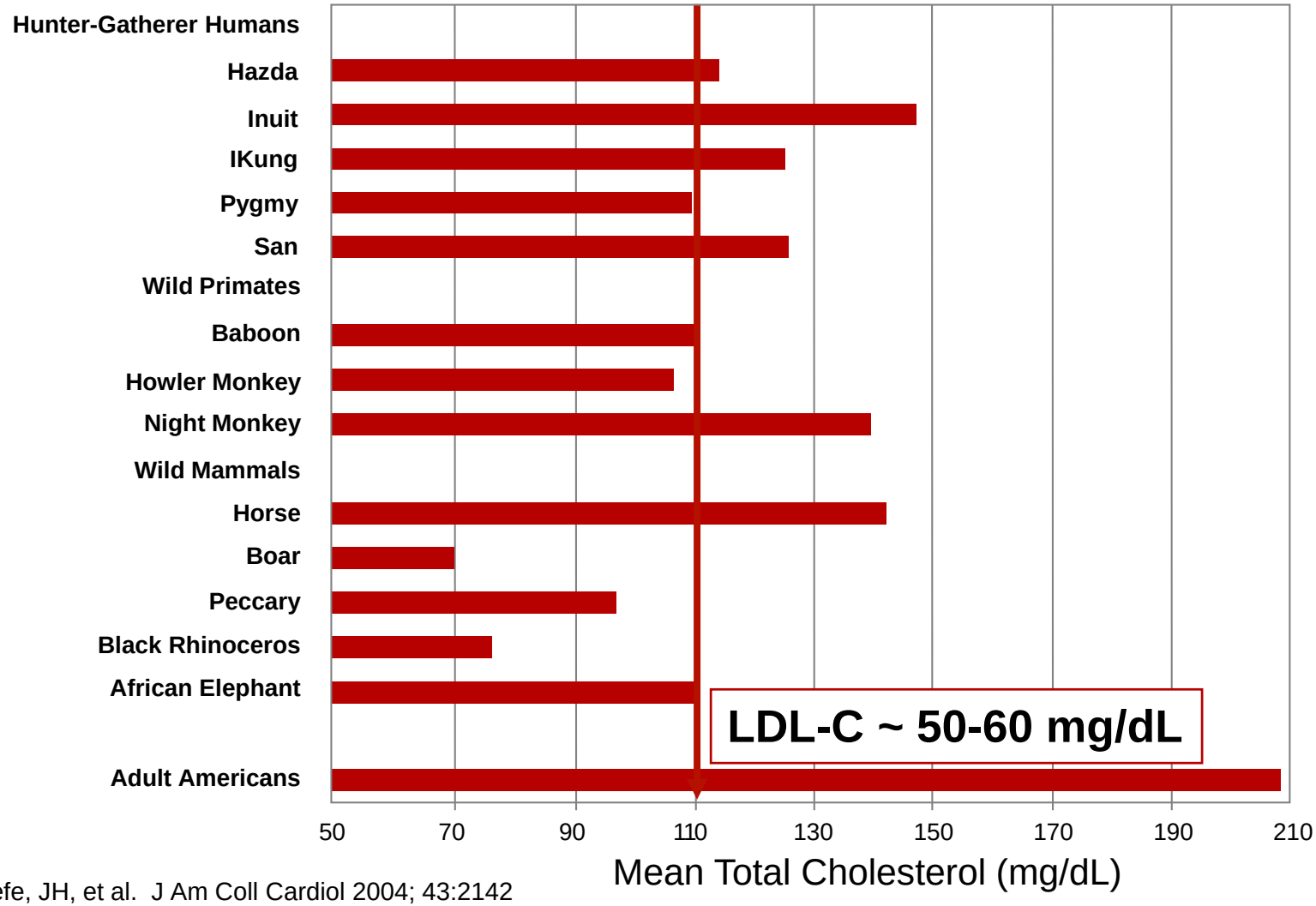
Replying to @bnallamo @CircOutcomes and...

I'm reminded of @cardiobrief a few years ago: "Guidelines are like declarations of war: they should only be issued if there is an overwhelming need and complete consensus."

The rest should be SDM informed by continuously updated evidence and patient goals.

6 16

Total Cholesterol Levels in Humans, Primates, and Mammals



O'Keefe, JH, et al. J Am Coll Cardiol 2004; 43:2142