2018 Update of Lipid Therapy for Coronary Patients

Bahman Nouri, MD FACC FSCAI

Office: (650) 306-2300

Cell: (415) 269-7852

No Disclosures

Outline

- Who should you screen?
- What tests should your order?
- Who should you treat?
- Which drugs should you use?
- What are the controversies?

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Major Risks Factors for ASCVD

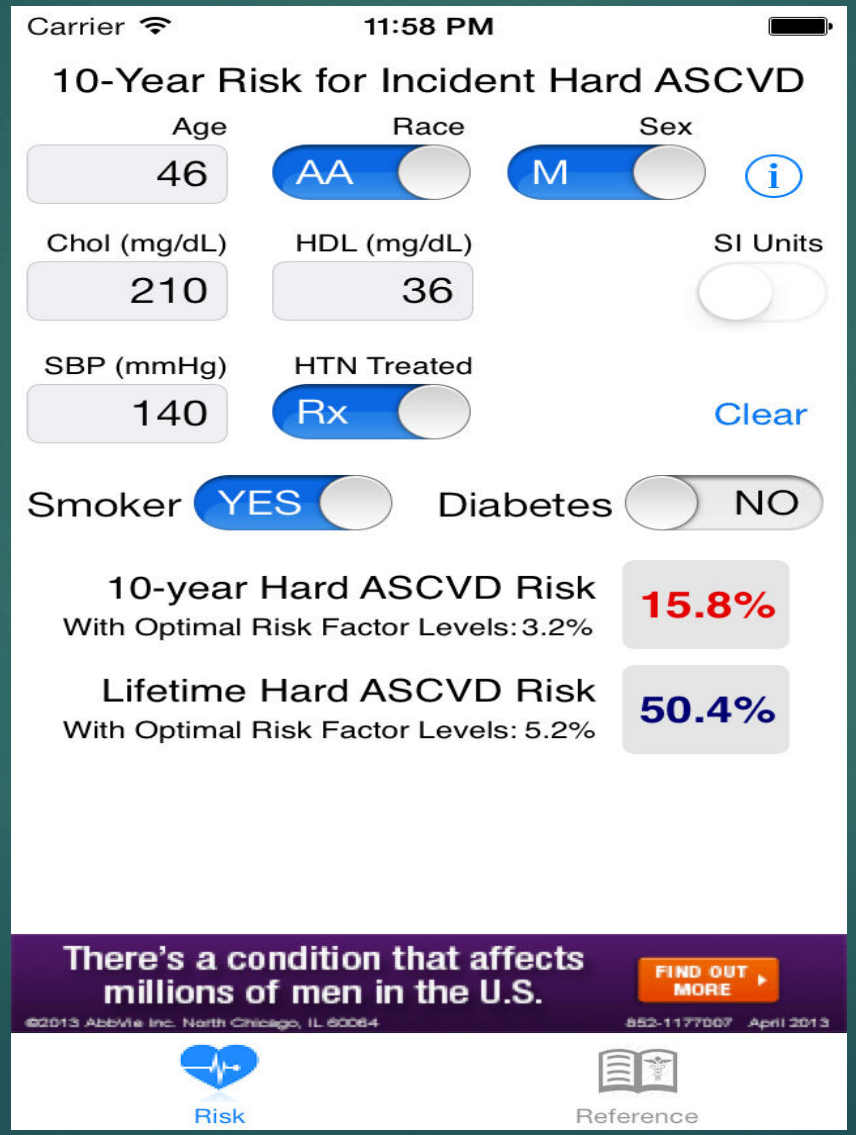
Major Risk Factors	Additional Risk Factors	Non-traditional Risk Factors
Advancing age	Obesity, abdominal obesity	↑ Lipoprotein (a)
↑ Total serum cholesterol	FHx hyperliidemia	↑ Clotting factors
↑ Non-HDL-C	↑ Small, dense, LDL-C	↑ Inflammatory markers (hsCRP, Lp-PLA2
↑ LDL-C	↑Apo B	↑ Homocysteine levels
Low HDL-C	↑ LDL particle concentration	↑ Uric acid
Diabetes mellitus	↑ Fasting/post-prandial hypertriglyceridemia	↑ TG-rich remnants
Hypertension	PCOS	
Chronic kidney disease, 3,4	Dyslipidemic triad	
Cigarette smoking		
Family history of ASCVD		

Endocrine Practice Vol 23 April 2017. AACE Guidelines

Burden of ASCVD

- US 2016:
  - 660,000 new coronary events
  - 305,000 recurrent events
- Annual incidence of MI: 550,000 new attacks
  200,000 recurrent attacks
- >100 million US adults >20 years have total cholesterol >200 mg/dL
  >30 million have total cholesterol >240 mg/dL

10-year risk calculators



ASCVD Risk Categories and LDL-C targets

Risk Category	Risk Factors/ 10-year risk	Treatment Goals		
		LDL	Non-HDL	Apo B
Extreme Risk	• Progressive ASCVD including unstable angina after achieving LDL <70 • CVD in patients with DM, CKD 3 or 4, HeFH • Hx premature ASCVD (<55 M, <65 F)	**<55**	**<80**	**<70**
Very High Risk	• Established CAD or recent hospitalization for ACS, carotid or peripheral intervention, **10-y risk >20%** • DM or CKD ¾ with 1 or more RFs • HeFH	**<70**	**<100**	**<80**

ASCVD Risk Categories and LDL-C targets

Risk Category	Risk Factors/ 10-year risk	Treatment Goals		
		LDL	Non-HDL	Apo B
High Risk	• ≥ 2 risk factors and 10-y risk 10-20% • DM or CKD 3/4 with no other RFs	**<100**	**<130**	**<90**
Moderate Risk	• ≤ 2 risk factors and 10-y risk <10%	**<100**	**<130**	**<90**
Low Risk	• 0 risk factors	**<130**	**<160**	**NR**

Who should be screened?

- Patient with suspicion for Familial Hypercholesterolemia
- Annual screening of all adults with type II diabetes
- Young adults (Men 20-45, Women 20-55):
  - Every 5 years
- Middle-Age Adults (Men 45-65, Women 55-65):
  - Without ASCVD RFs every 1-2 years
  - With ASCVD RFs every year
- Older adults (>65):
  - Annual screening if 0-1 ASCVD RFs
  - More frequent screening if more RFs

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The Fasting Lipid Panel

- Total Cholesterol
- HDL-C
- TG
- LDL –C (calculated)

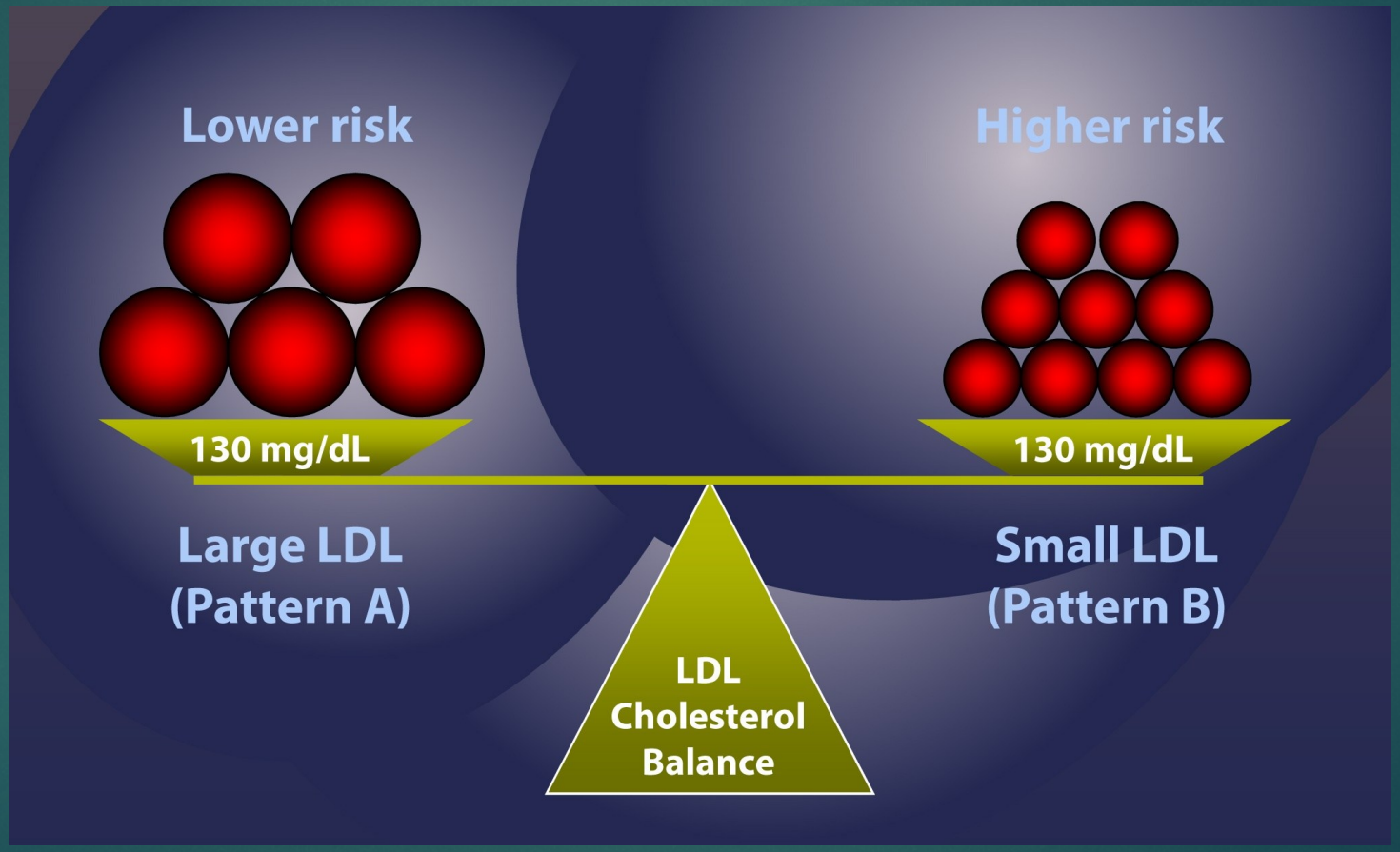
Beyond the Fasting Lipid Panel

- Direct LDL measurement
- **LDL particle number (LDL-P)**
- LDL particle size
- **Lp(a)**
- CAC score
- LPLA2
- **Apo B**
- Homocysteine
- hs-CRP

LDL particle number (LDL-P)

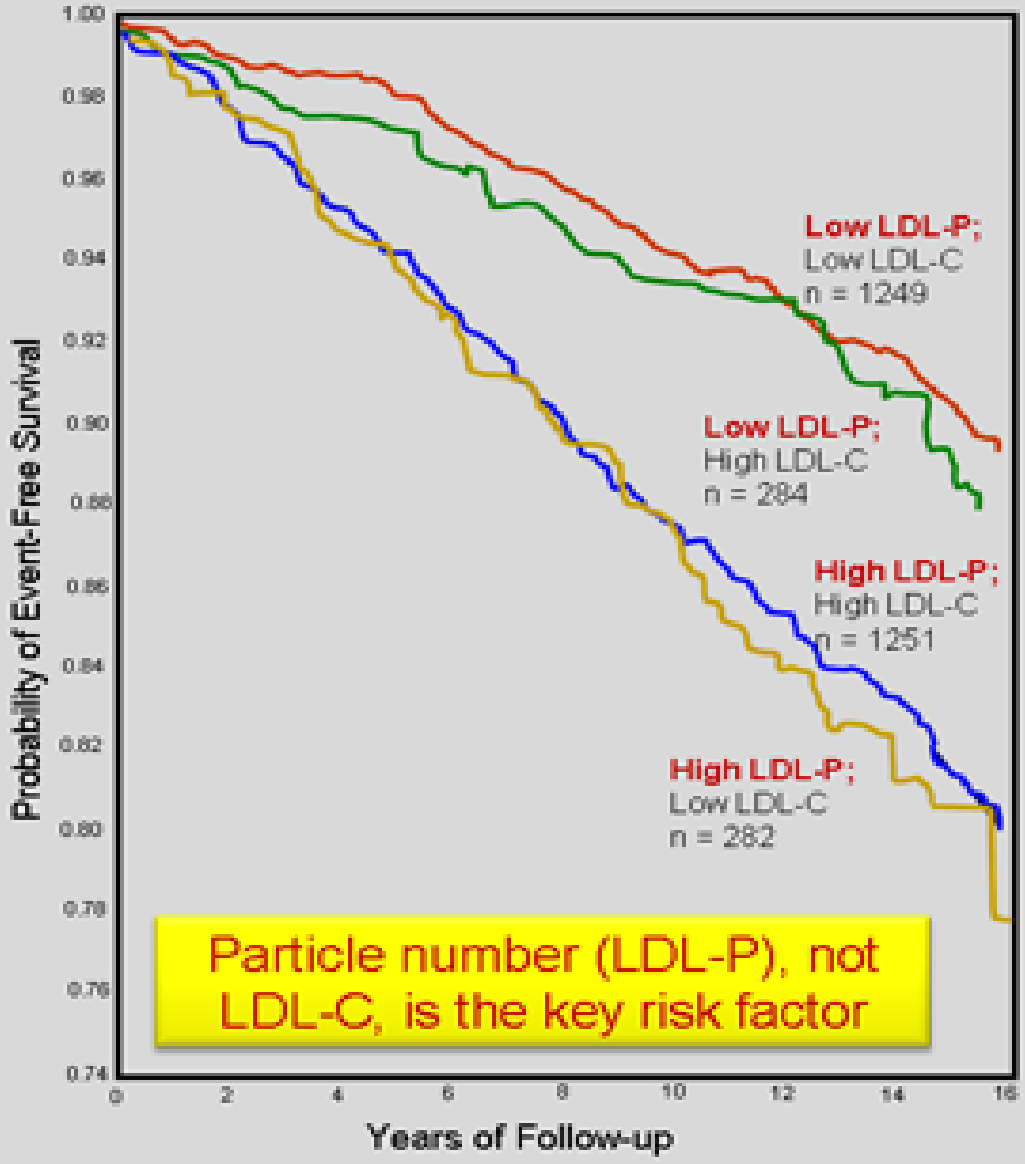
- Measured by one of 4 methods:
  - Gradient gel electrophoresis
  - NMR spectroscopy
  - VAP panel (ultracentrifugation)
  - Ion mobility
- Better predictor of cardiovascular disease than LDL-C
- Optimal is < 1000 nmol/L

Higher LDL-P (with similar LDL-C) confers higher cardiovascular risk



Framingham Heart Study Offspring Cohort

Event-free survival among participants with low-density lipoprotein cholesterol (LDL-C) and LDL particle number (LDL-P) above or below the median. Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.



LDL-P was strongly associated with increased CVD risk in both men and women ($p<0.0001$).

When data for men and women were combined, LDL-P was approximately twice as strongly related to CVD incidence as LDL-C.

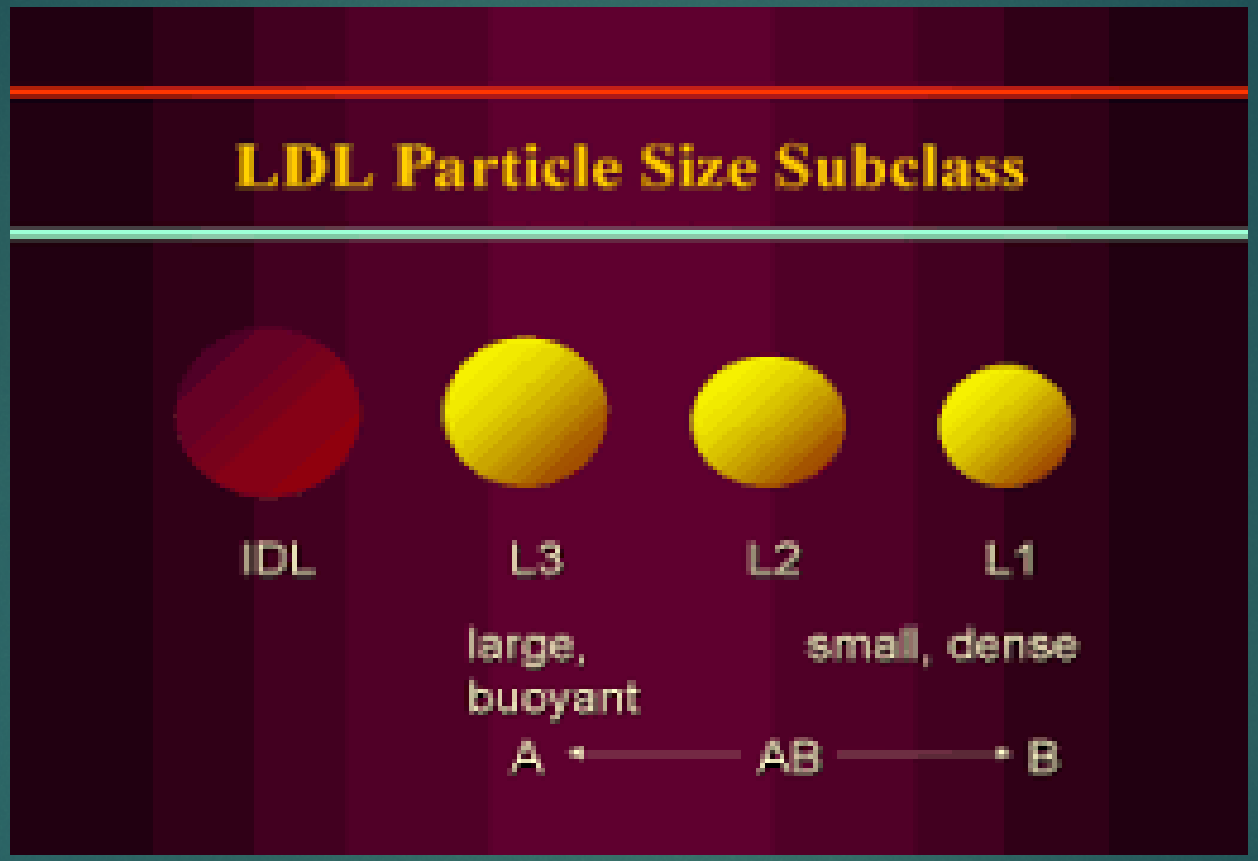
Reprinted with permission from Cromwell W et al. *J Clin Lipidol*. 2007;1:583-592.

Case

- 52 yo woman seen to assess her risk of CVD
- Healthy and fit, no significant PMH
- BMI 21, 112/70, normal exam
- Father died at 54 ("he was the picture of health")

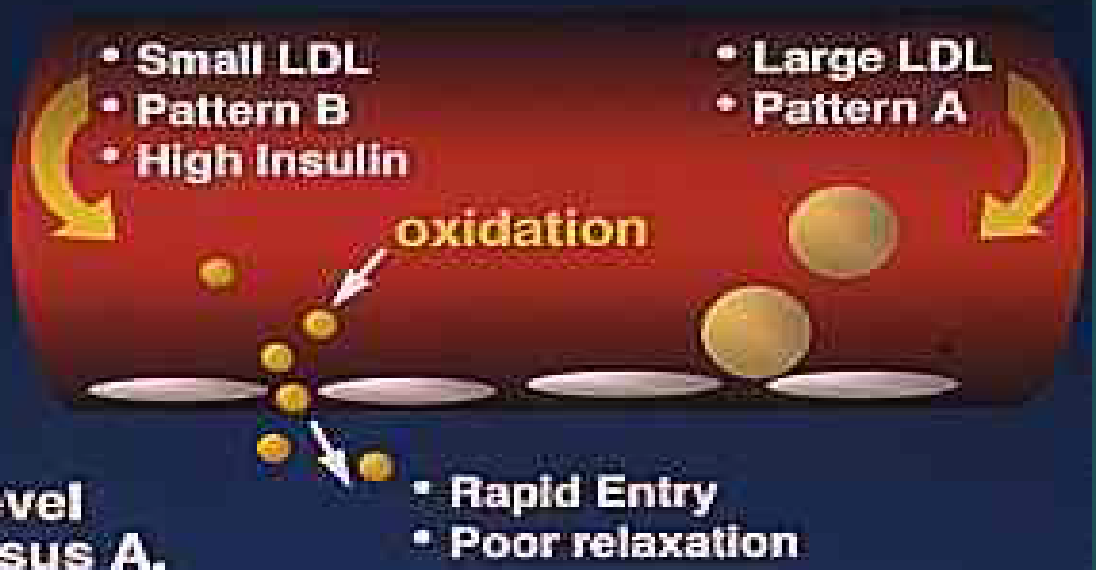
- Fasting labs **TCHOL 192, LDL 104, HDL 57, TG 26, 10-y risk 0.8%**
- **Would you treat?**

LDL-P 2100 nmol/L. Started on moderate-intensity statin


LDL Particle Size Subclass
IDL
L3
L2
L1
large, buoyant
small, dense
A
AB
B

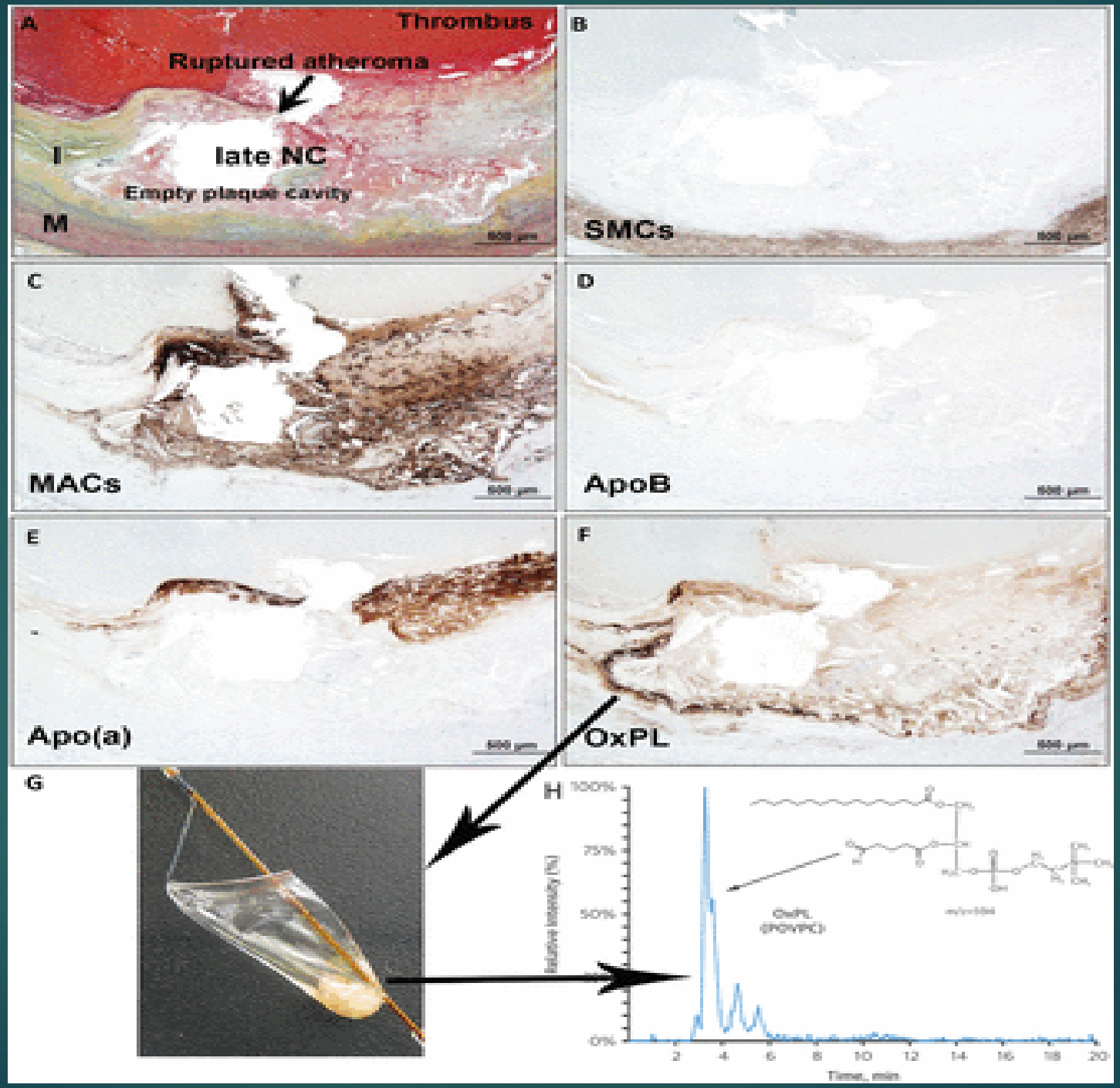
ALP (LDL Pattern B)
Why is it *Dangerous?*

1. Rapid entry into arterial wall.
2. Low vitamin E in lipoproteins.
3. More susceptible to oxidative damage.
4. High blood insulin.
5. After a meal, blood fat level doubles in pattern B versus A.
6. Poor blood vessel relaxation.



Lp(a)

- LDL-like particle where Apo B is covalently bound to Apo (a)
- Has physiologically evolved from the plasminogen gene
- Marked heterogeneity in concentration and isoforms
- Has atherogenic and prothrombotic properties
- Normal value <30 mg/dL, very high value >60 mg/dL
- Consider single-lifetime measure of Lp(a) in high risk patients, those with CVD despite controlled LDL, intermediate risk patients with intermediate LDL levels to better reclassify risk
- No targeted therapy. Statins raise Lp(a) 10-20%
- Lp(a) may be lowered by PCSK9 inhibitors.



JACC 69(6) Feb 2107

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Four Statin Benefit Groups

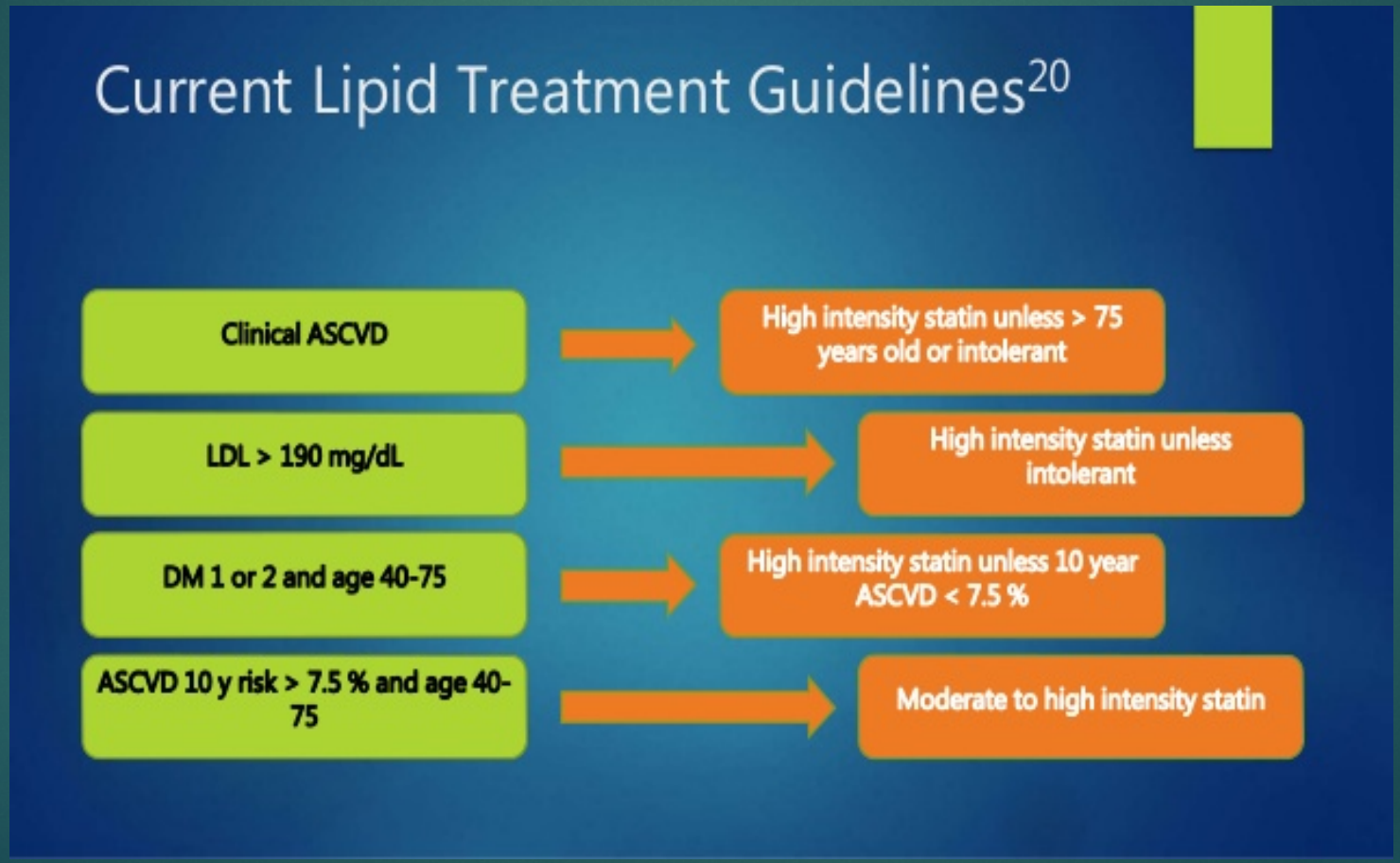
2013 ACC/AHA Guidelines for the treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

1. **Adults aged ≥ 21 years with clinical ASCVD**
   - Including hx of or concurrent ACS, MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD
     - MAJOR RECOMMENDATIONS:
       - **PATIENTS ≤ 75 years, high-intensity statin (or moderat- intensity if safety concern)**
       - **PATIENT > 75 years, moderate-intensity statin**
2. **Adults aged ≥ 21 years with LDL-C ≥ 190 mg/dL**
   - Not due to modifiable secondary causes
     - MAJOR RECOMMENDATIONS:
       - **High –intensity statin therapy to achieve a ≥ 50% reduction of LDL-C**
       - **May consider combining statin and non-statin therapy to further reduce LDL-C**
       - **Cascade screening of close biological relatives**

Four Statin Benefit Groups

- **3. Adults age 40-75 years without ASCVD but with diabetes and with LDL-C 70-189 mg/dL**
  - MAJOR RECOMMENDATIONS:
    - **Moderate-intensity statin**
    - **If 10-year ASCVD risk is ≥ 7.5%, consider high-intensity statin**
- **4. Adults aged 40-75 without ASCVD or diabetes, and with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥ 7.5%**
  - MAJOR RECOMMENDATIONS:
    - **If 10-year risk ≥ 7.5%, moderate or high-intensity statin**
    - **If risk ≥ 5 to 7.5%, consider moderate-intensity statin**
    - **Individualize decision based on presence of high risk factors: LDL>160, FHx early CAD, hs-CRP >2.0, CAC >300, ABI<0.9, high 10-year risk; and engage pt in risks about benefits, adverse reaction from drug-drug interations, and pt preferences.**

In a Nutshell



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Examples of High, Moderate, and Low Intensity Statin Therapy

High Intensity	Moderate Intensity	Low Intensity
Daily dose lowers LDL-C ≥ 50%	Daily dose lowers LDL-C 30- <50%	Daily dose lowers LDL-C < 30%
Atorvastatin 40-80 mg **Rosuvastatin 20-40 mg**	**Atorvastatin 10-20 mg** **Fluvastatin 40 mg bid** Fluvastatin XL 80 mg **Lovastatin 40 mg** Pitavastatin 2-4 mg **Pravastatin 40-80 mg** **Rosuvastatin 5-10 mg** **Simvastatin 20-40 mg**	Fluvastatin 20-40 mg **Lovastatin 20 mg** Pitavastatin 1 mg Pravastatin 10-20 mg Simvastatin 10 mg

Bold face indicates statins and doses that were evaluated in RCTs included In the 2013 ACC/AHA guidelines

Non-statin agents

- Ezetimibe (Zetia)
  - Reduces cholesterol absorption in small intestine
  - FDA-approved indications:
    - As adjunct to diet to ↓ TC, Apo B, LDL-C alone or in combination w/ statin
    - As adjunct to diet to ↓ TC, Apo B, LDL-C in combination w/ fibrate
  - Mean % reduction in LDL-C
    - Monotherapy - 18%
    - Combination with statin - 25%
  - CV outcome trial IMPROVE-IT
  - Considerations: usually well tolerated, increased risk of URI

Non-statin agents

- **Bile acid sequestrants**
  - Colesevalam (Welchol)
  - Cholestyramine (Questran)
  - Colestipol (Colestid)
  - Effect on LDL-C 15% with monotherapy
  - Considerations: High pill burden, constipation, nausea, ↑TG
- **Nicotinic acid (Niacin)** - ↓ LDL 5-25%, ↓ TG 20-50%, ↓ Lp(a) 30%, ↑ HDL 15-35%
  - Reduced insulin sensitivity, impaired glucose control in T2DM, ↑ myopathy
  - Neutral CVD outcomes, lack of impact on mortality
  - Recommended for statin intolerant pts who have not reached LDL targets
- Phytosterols – 5 to 10% decrease in LDL-C
- Viscous soluble fiber – 5 to 10% reduction in LDL-C

PCSK9 inhibitors

- Human monoclonal antibody to PCSK9, increases number of LDL receptors, increasing clearance of LDL
  - Alirocumab (Praluent) - Sanofi
  - Evolocumab (Repatha) - Amgen
- FDA-approved indications:
  - Adjunct to diet and maximally tolerated statin therapy to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction
- Dosing – Start (75 mg [A], 140 mg [E] SQ every 2 weeks, double dose every 2 weeks up to max dose (300 mg [A], 420 mg [E] once a month.
- Mean LDL reduction 45-58% alone or in addition to statin
- Outcomes trials: ODYSSEY, FOURIER
- Drug-drug interactions: none so far
- Considerations: Cost, SQ, robust LDL-C reduction, lack of myopathy, nasophyaryngitis, long term outcomes lacking, burdensome prior auth

Very novel agents

- Mipomersen (KYNAMRO)
  - Antisense human oligonucleotide (ASO) targeted to human Apo B-100 mRNA
    - Binds by Watson-Crick base pairing and inhibits translation of apo B-100
  - FDA-approved as an adjunct to other meds in patients with HoFH
  - Mean LDL-C reduction – 25%
  - Dose 200 mg SQ QWK
  - High risk of liver toxicity and even progression to cirrhosis
  - Only available through FDA REMS program

Very novel agents

- Lomitapide (Juxtapid)
  - Interferes with assembly of Apo B lipoproteins in the ER
  - Approves as adjunct to other strategies for HoFH
  - Dose: 5 mg po daily, titrate to 60 mg po daily
  - Mean LDL reduction – additional 40-50% reduction
  - High risk of liver disease and progression to cirrhosis/steatohepatitis
  - Inhibits CYP3A4 (grapefruit juice, atorvastatin, OCPs)
  - Only available through FDA REMS program

LDL apheresis

- For pts with LDL-C > 500
- Extracorporeal technique weekly or biweekly
- Robust LDL changes >50-60%
- Limited outcome date
- Considerations - access problems, inconvenient and time consuming, hypotension, hypocalcemia, iron deficiency due to regular phlebotomy, hypocalcemia, need to have a hematology program with interdisciplinary goals

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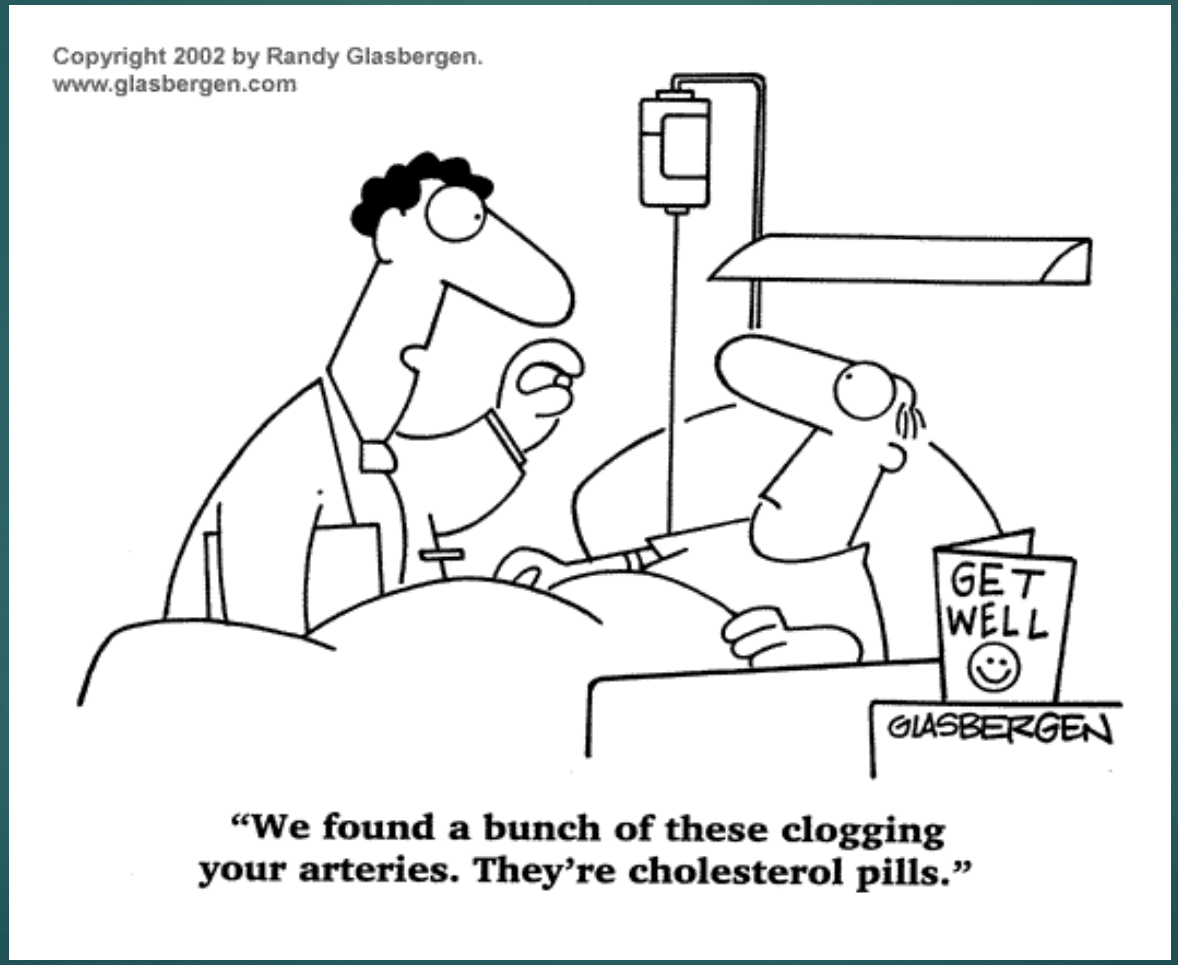
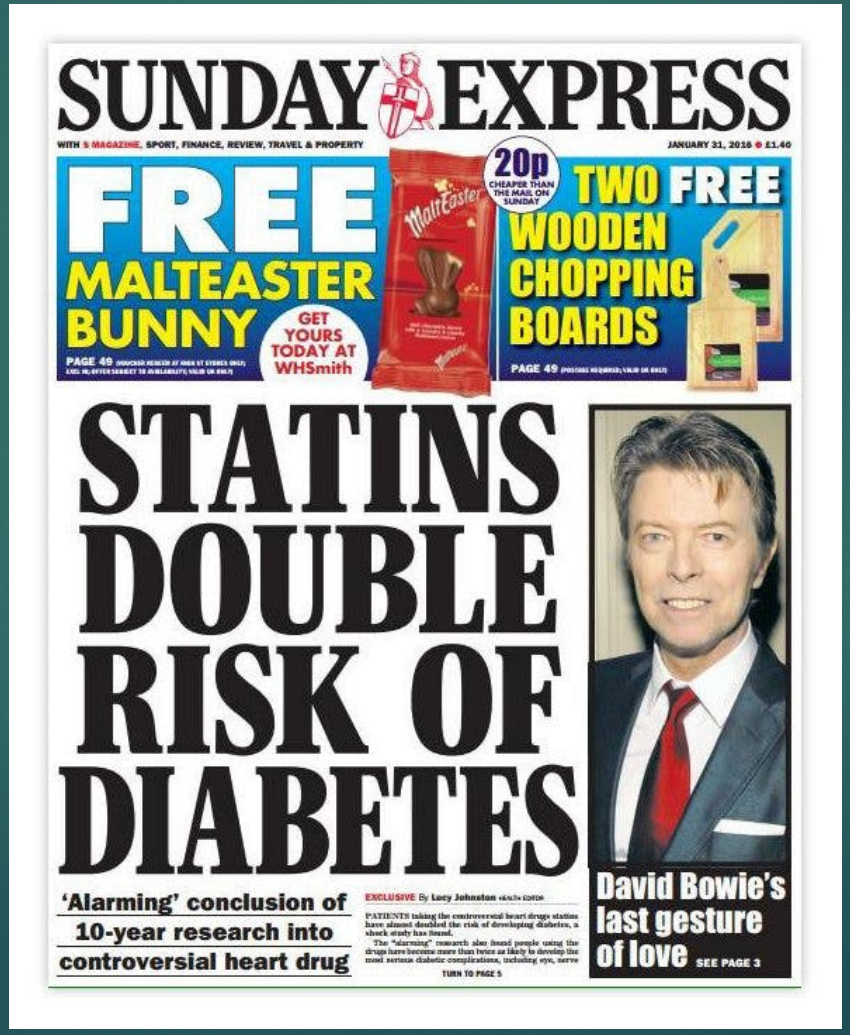
Are these drugs bad for us?

"We just made a big cancer breakthrough. Have a cigar."

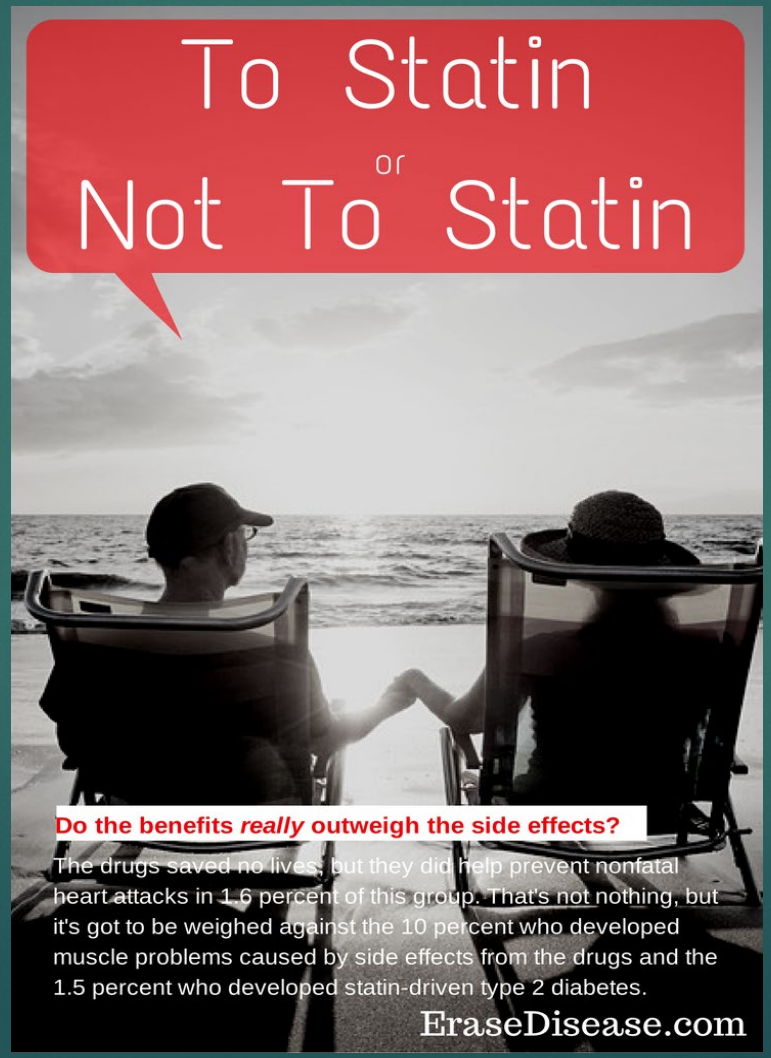
Are they hurting us?



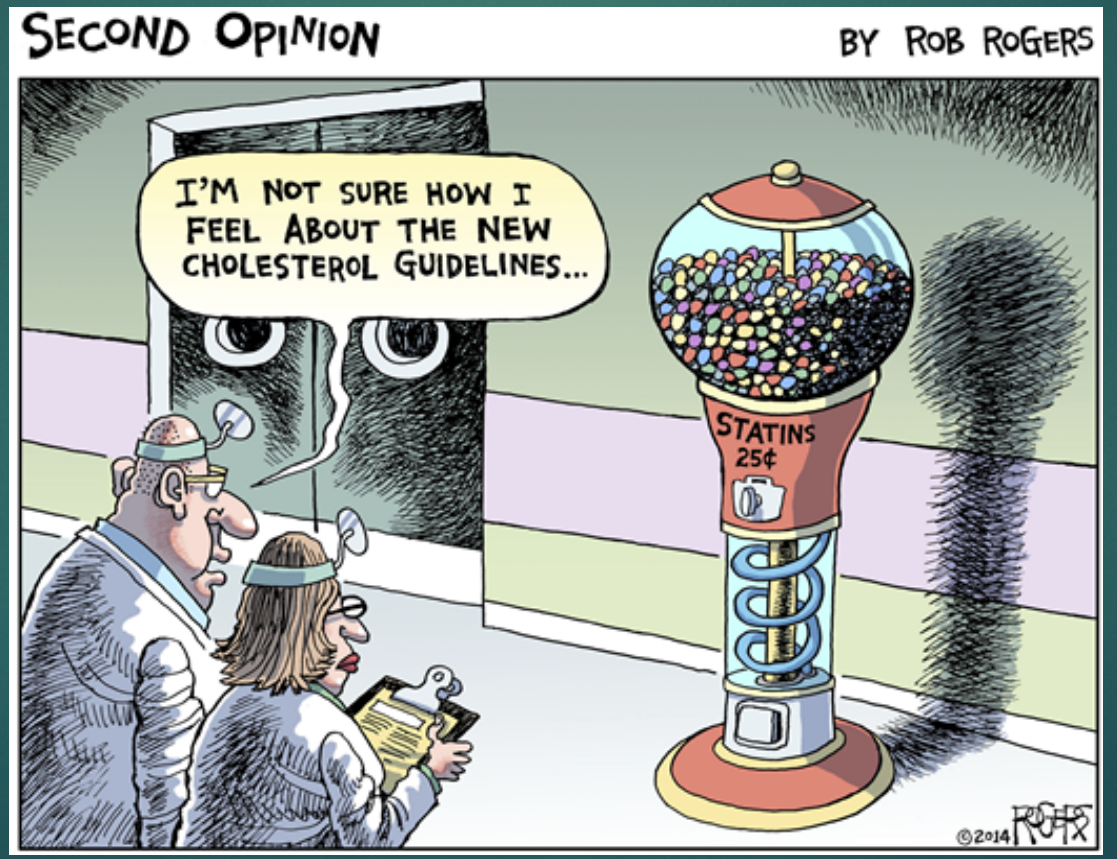
Bad Press: from the tabloids…



…to Shakespeare

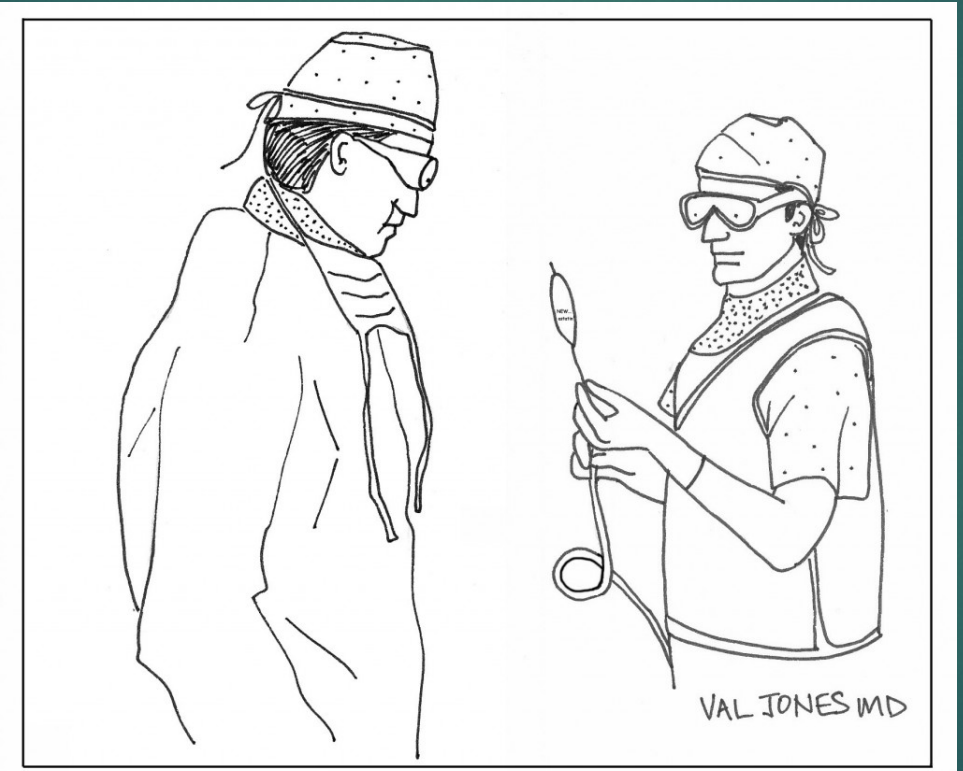


Are we over-prescribing these meds?



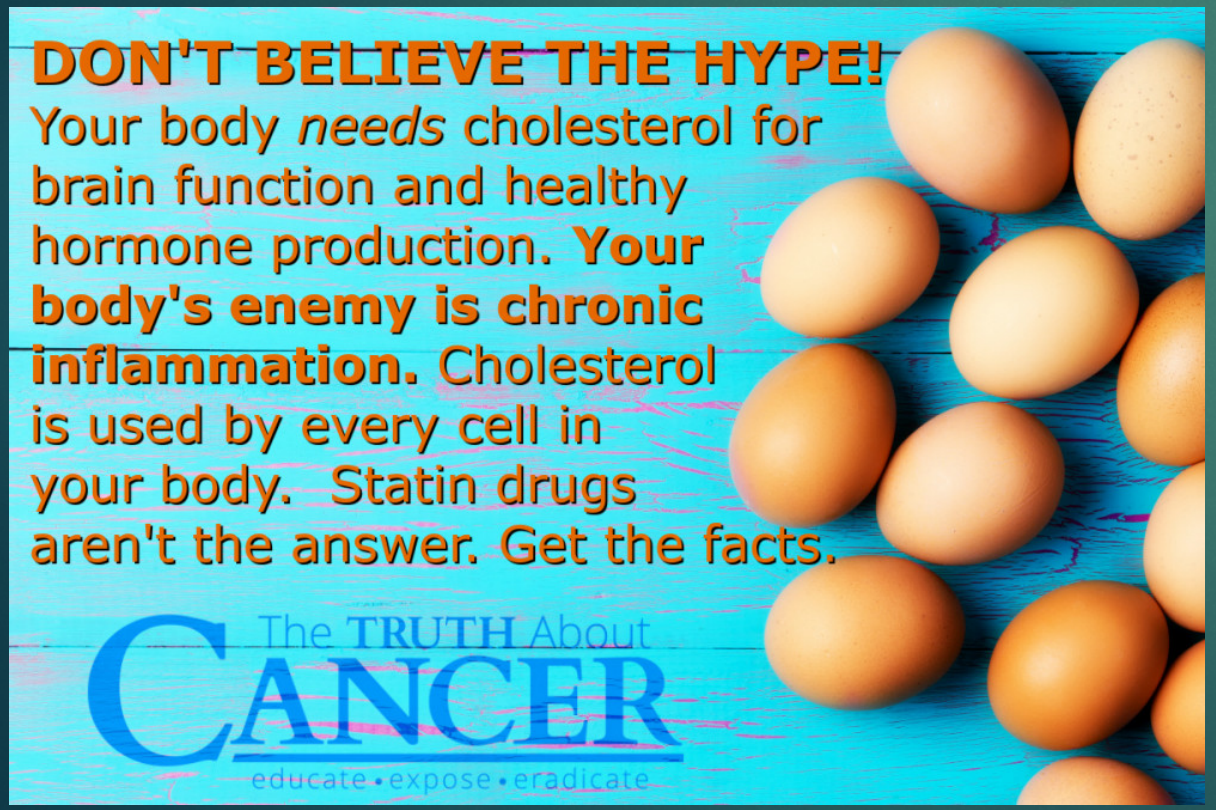
Statins and Diabetes

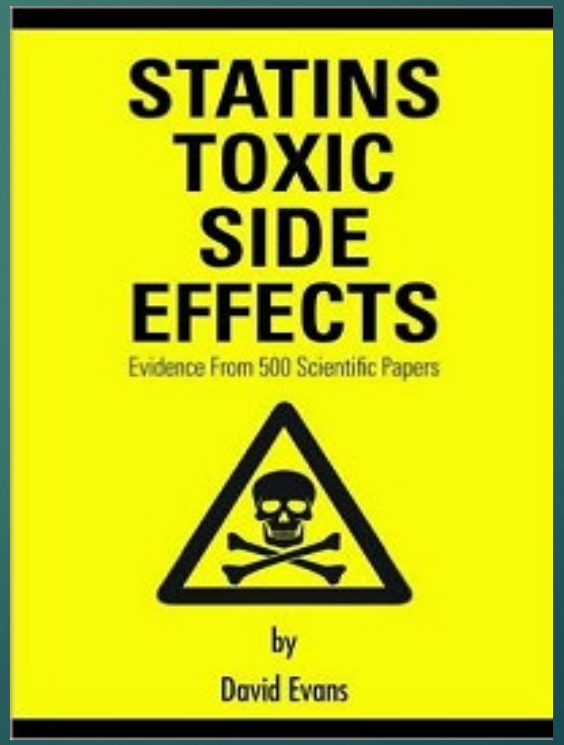
Are we being influenced by Pharma?

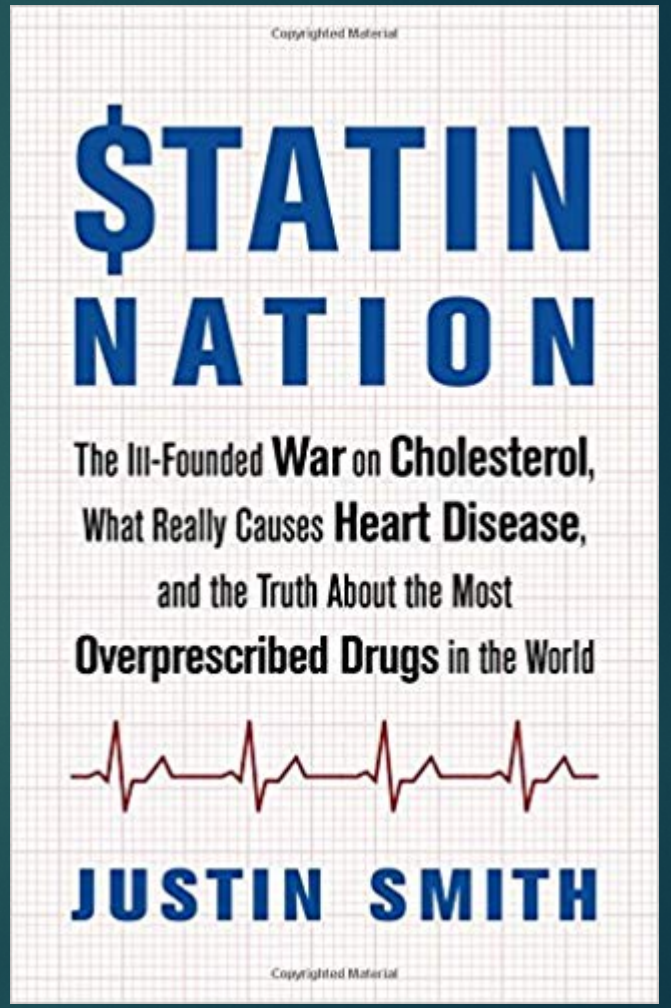


"Drs. Smith and Thompson noted that the new cardiac balloon catheter featured a microscopic statin advertisement.'"


Tablets
The Statin Disaster:
Biggest Fraud
in Medical History


DON'T BELIEVE THE HYPE!
Your body needs cholesterol for brain function and healthy hormone production. Your body's enemy is chronic inflammation. Cholesterol is used by every cell in your body. Statin drugs aren't the answer. Get the facts.
The TRUTH About
CANCER
educate • expose • eradicate


STATINS
TOXIC
SIDE
EFFECTS
Evidence From 500 Scientific Papers
by
David Evans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The Ill-Founded War on Cholesterol,
What Really Causes Heart Disease,
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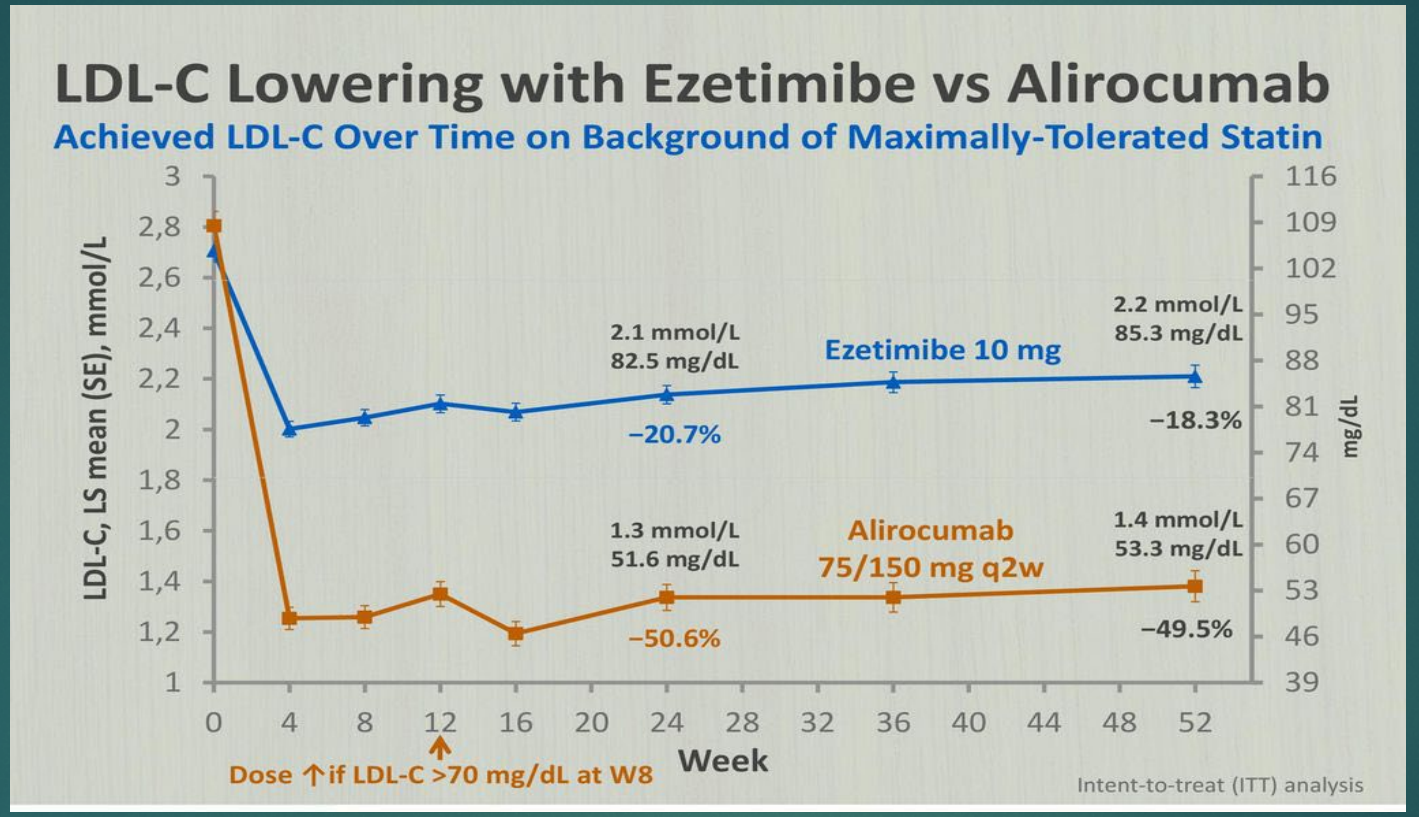
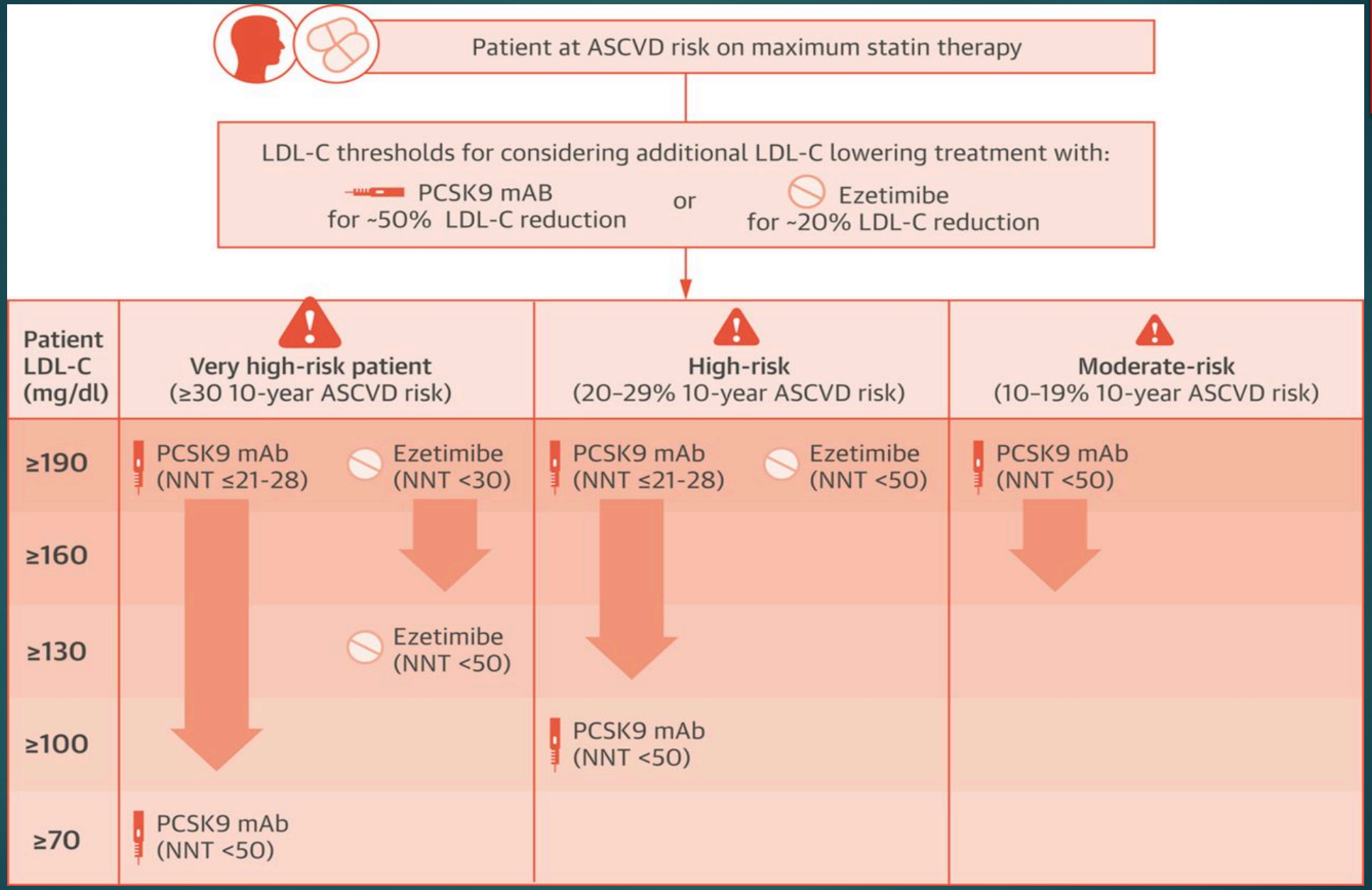
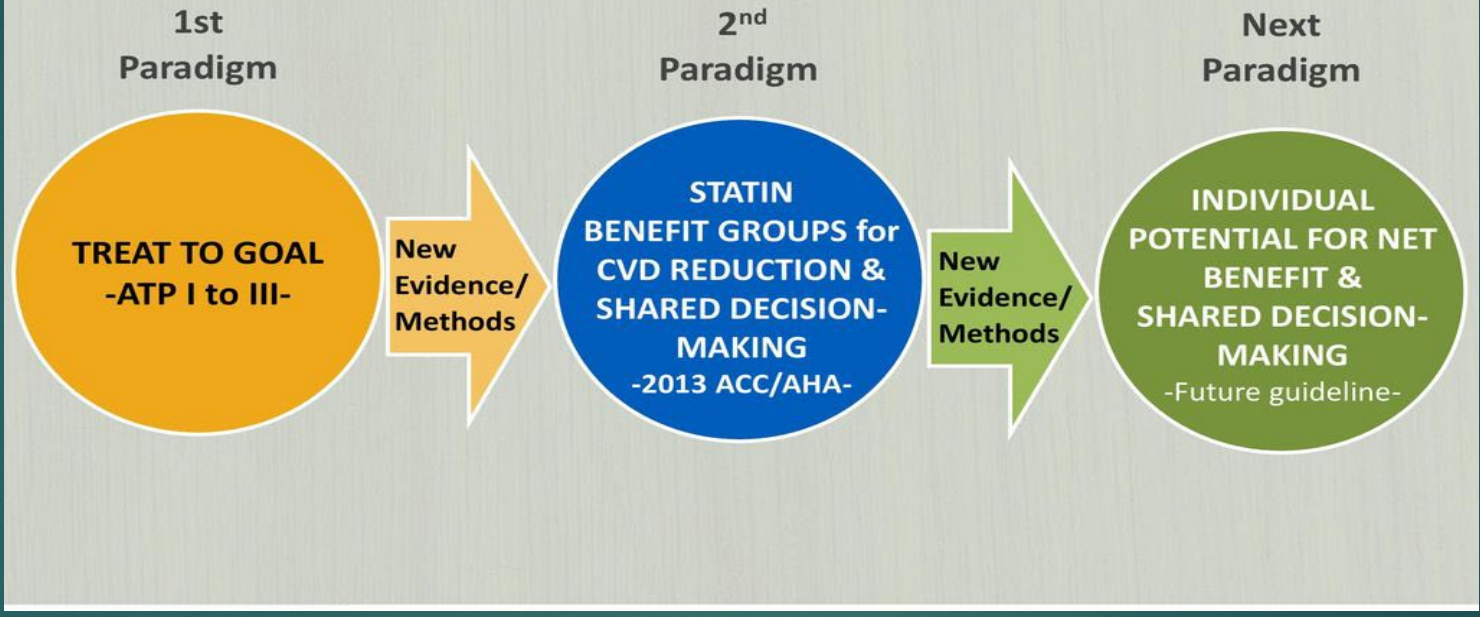


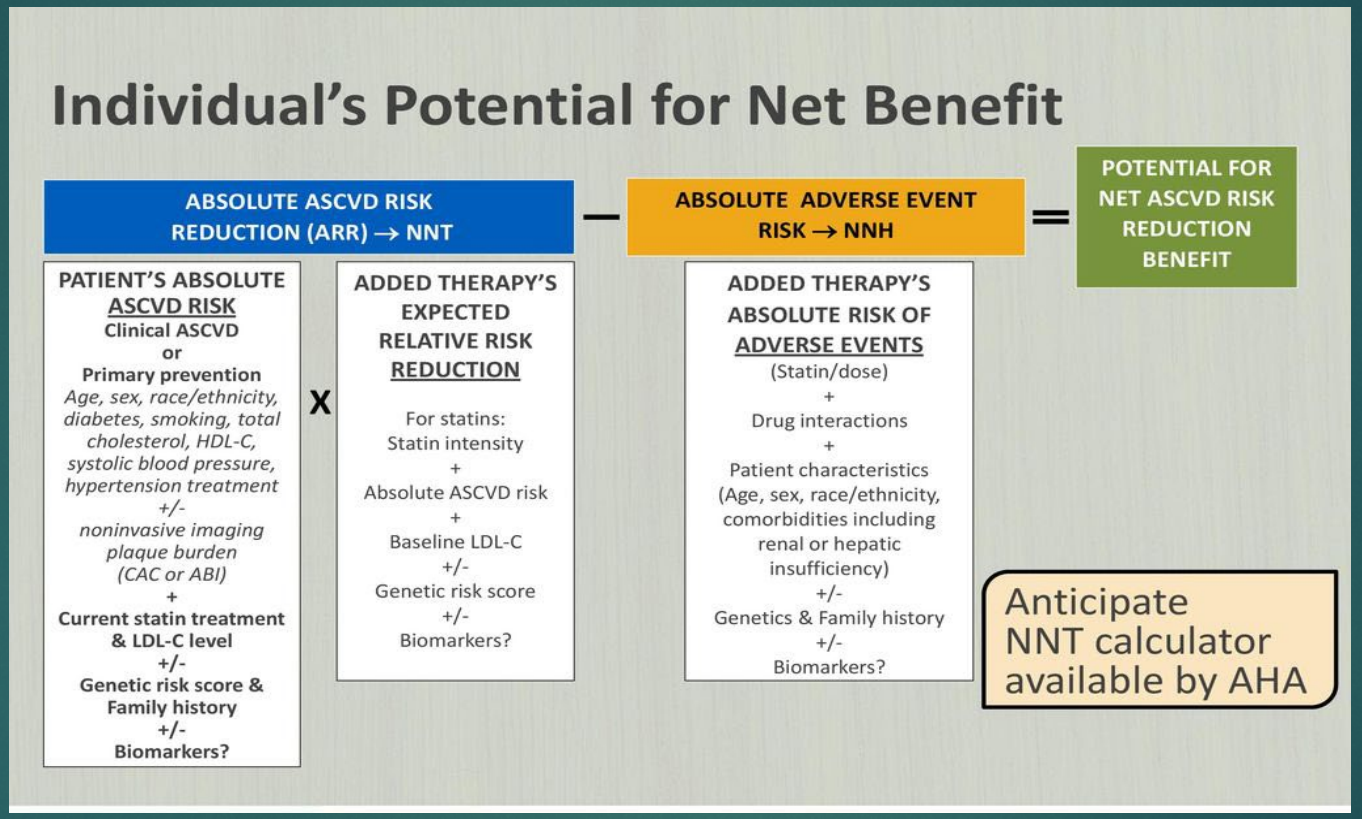
Cannon, C. Eur Heart J 2015;36



Robinson, JG JACC 2016, 68(22)

Evolving Paradigms for CVD Prevention





Circulation 2016,133

Some closing thoughts..

- Statins are the only class of drugs with substantial mortality and morbidity benefits.
- Ezetemibe and PCSK9 inhibitors have single RCT data to show mortality benefit
- No mortality benefit for niacin or fibrates
- 2013 guidelines
  - Shift away from LDL-lowering targets and focus on treatment groups with known benefit and statin dose classes with highest impact
- **We must customize the drug to the patient, and do a multivariate analysis for every patient incorporating patient risk factors, lab data, genomics, cost, benefit vs risk, to come up with a comprehensive model tailored for each patient.**

Thank You!