


## Dyslipidemia Across the Lifespan



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## Disclosures

- None relevant to this talk
- No consultation or speaking fees
- Institutional support in pituitary disease
  - ♦ Ionis currently

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## Objectives/Goals

- Leave time for questions
- Avoid topics of others! (No obesity, DM/ meds, triglycerides, HTN)
- Can't cover all of the major pediatric/adult guidelines (over 300 pages) or basic science
- Discuss risk factors for ASCVD in pediatrics and adulthood
- Discuss newest treatment guidelines and focus on LDL-C
- Hit a few favorite topics not covered elsewhere
  - Aspirin therapy
  - Statin safety and side effects
  - "Statin denialism"
  - Statins and liver disease

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### Statins: Mechanism of Action

The diagram illustrates the mechanism of action of statins. In the endoplasmic reticulum, HMG CoA reductase converts HMG CoA to Mevalonate acid. Statins inhibit this enzyme, leading to a decreased concentration of Mevalonate acid within the cell. This results in decreased synthesis of cholesterol and LDL. Simultaneously, statins increase the number of LDL receptors on the plasma membrane, which enhances the uptake of LDL from the blood. Additionally, statins increase the synthesis of VLDL and decrease the secretion of VLDL from the liver.

Thehealthgate.com: Syed Shoab  
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### PCSK9 Inhibitors

The diagram compares hypercholesterolemia (A) and the effect of monoclonal antibodies to PCSK9 (B). In hypercholesterolemia, PCSK9 binds to and degrades LDL receptors, leading to fewer receptors on the cell surface and increased LDL levels. PCSK9 inhibitors block PCSK9, preventing it from degrading LDL receptors. This results in more LDL receptors on the cell surface, which increases the clearance of LDL from the blood. The diagram also shows the recycling of LDL receptors and the role of clathrin-coated vesicles.

Mayo Clinic Website  
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### Pediatrics: Rare Risk Factors

- Homozygous and heterozygous familial hypercholesterolemia are the serious disorders but rare (?)
- Dutch screening turned up 1:250000 homozygous, 1:250 Heterozygous
- Homozygous: LDL 300 to over 800, CV events in first decade
- Heterozygous: LDL 160-300 typically, 50% of men and 25% of women have CV event by age 50

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Wiegman, A. Lipid Screening, Action and PU in Children. Current Card Reports 9 August 2018

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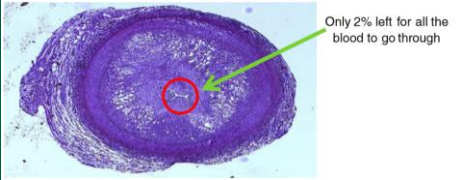
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### 4 year old with Homozygous FH



Only 2% left for all the blood to go through

Wayman, A. Lipid Screening, Action and FU in Children. Current Card Reports, 9 August 2018

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### Common Risk Factors in Pediatrics

- Bogalusa Heart Study
  - ♦ Lipids
  - ♦ Blood pressure
  - ♦ BMI
  - ♦ Tobacco Use

Benson, G. CV disease risk factor variables at the preschool age. The Bogalusa Heart Study. Circulation. 1979; 60:4-12, 1979

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### Common Risk Factors in Pediatrics

- PDAY Study: Risk Factors
  - ♦ Age
  - ♦ High LDL
  - ♦ Low HDL
  - ♦ Hypertension
  - ♦ Tobacco
  - ♦ DM
  - ♦ Obesity

Strong, JP et al. The PDAY Study: natural history, risk factors and pathobiology. Pathobiological Determinants of Atherosclerosis in Youth. Ann NY Acad Sci. 1997 April

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### Other Risk Factors

- None strong enough to form recommendations
  - ♦ Race
  - ♦ Socio-economic status
  - ♦ Fitness

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### Pediatric Atherosclerosis

Right Coronary Artery – Raised Lesions  
 Males by age group (years)

Number of Risk Factors: 0, 1, 2, 3+  
 Age Group: 15-24, 25-34

These computerized images from the Pathobiological Determinants of Atherosclerosis in Youth study are prevalence maps of fatty streaks and raised lesions, with color intensity reflecting the density and grade of the lesions for the two age groups and the number of risk factors. SOURCE: Edward E. Hesterick and C. Alex McMahan for the Pathobiological Determinants of Atherosclerosis in Youth Study Group, unpublished observation.

2011 Expert Panel on CV Health and Risk Reduction Full Report, NHLBI

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### Tracking of Risk Factors

- If present in childhood, do risk factors persist?:
  - ♦ Obesity: 84% of adults still obese if over 95% as a child
  - ♦ Hypertension and hyperlipidemia not as strong
  - ♦ Smoking: 50% quit
  - ♦ T1DM persists
  - ♦ T2DM no data
  - ♦ Physical activity variable

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**Challenges in Pediatric Research**

- Interventions (lifestyle especially) would have to be maintained into adulthood to get results
- Ethics of non-intervention
- Issues around withholding existing treatments or novel treatments
- Newer imaging modalities for adults (coronary CT, US for cIMT) may be useful in childhood research



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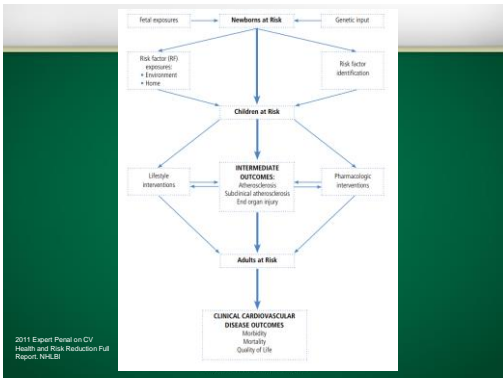
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**Pediatrics**

- Current Resources in Pediatrics
- 2008 ACP guidelines (90% awareness among pediatricians in 2015)
- 2011 NHLBI guidelines (endorsed by ACP) (60% Awareness among pediatricians in 2015)
- They are quite complicated
- I observe very few children or adolescents that are treated



Rodday et al. Pediatric Cholesterol Screening and Tx, 2015 Abstract.

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**2011 NHLBI Guidelines**

- I'll give you my "take home messages"
- I personally feel the guidelines are too complex
- Access to lipids specialists in childhood is very limited
- I've experienced a great reluctance to take statins in pediatric/adolescent/young adult patients
- The recommendations re: nutrition should be universal

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**2011 NHLBI Guidelines**

- Take home messages
  - ♦ Universal screen age 9-11 and 17-21
  - ♦ If LDL  $\geq$  190, possible heterozygotic FH, screen family. Treat.
  - ♦ LDL 130-190 and NO risk factors, healthy eating
  - ♦ LDL 130-159 and 160-190, detailed assessment of risk factors
  - ♦ Unlike adults, tx is universal in DM at LDL  $\geq$  160

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**Adults**

- 2013 ACC/AHA Lipid Guidelines
- Updated in October of 2018 (120 Pages)

Grundy SM et al. 2018. Cholesterol Clinical Practice Guidelines

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# Dyslipidemia Throughout the Lifespan

## Brooks Vaughan MD

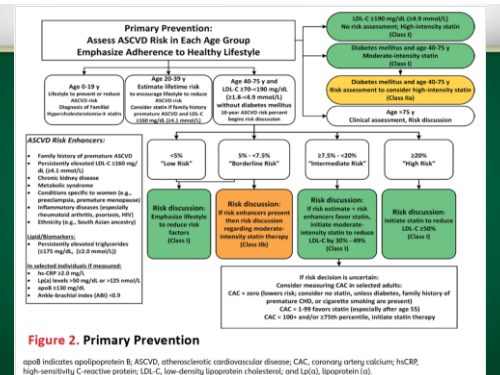


Figure 2. Primary Prevention

Legend: spgdl indicates spirogliprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).

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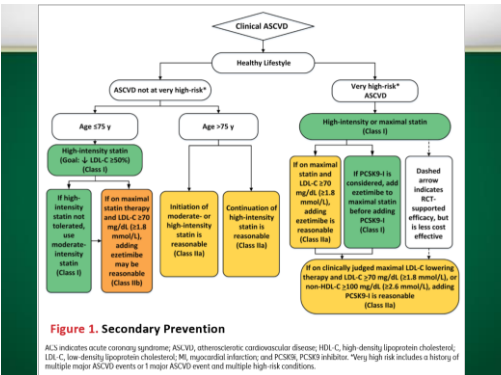


Figure 1. Secondary Prevention

Legend: ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9, PCSK9 inhibitor. \*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

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**Definition of Very High Risk ASCVD**  
**>1 Major ASCVD Event**

- Recent ACS (within past 12 months)
- History of MI (other than recent ACS above)
- History of ischemic stroke
- Symptomatic PAD (claudication with ABI < 0.85 or previous revascularization or amputation)

**Or**

**1 Major Event + >1 High Risk Conditions**

- Age > 65 years
- Familial hypercholesterolemia
- Prior CABG or PCI outside of the major ASCVD event
- Diabetes mellitus
- Hypertension
- CKD (eGFR 30-59 ml/min/1.73 m<sup>2</sup>)
- Current smoking
- Persistently elevated LDL-C > 100 mg/dl (> 2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF

Grundy SM et al. 2018 Cholesterol Clinical Practice Guidelines

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**Top 10 Take Home Messages #1**

- Emphasize a heart healthy lifestyle across the lifespan
  - ♦ Exercise
  - ♦ Healthy eating: lean protein, fruits, nuts and vegetables

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**Top 10 Take Home Messages #2**

- In patients with clinical ASCVD, reduce LDL-C with high intensity statin or maximally tolerated statin
  - ♦ Lower LDL-C levels by  $\geq 50\%$

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**Top 10 Take Home Messages #3**

- In very high-risk ASCVD use LDL-C threshold of 70 mg/dL to consider additions of non-statin to statin therapy
  - ♦ Ezetimibe
  - ♦ PCSK9 inhibitors

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**Top 10 Take Home Messages #4**

- In patients with severe primary hypercholesterolemia (LDL-C  $\geq$  190 mg/dL), begin high intensity statin regardless of 10 year risk calculation
  - ♦ May need ezetimibe plus statin or PCSK9

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**Top 10 Take Home Messages #5**

- In patients 40-75 with DM and LDL  $\geq$ 70, start moderate intensity statin without calculating 10 year ASCVD risk
  - ♦ Reasonable to use high-intensity statin in those with multiple risk factors

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**Top 10 Take Home Messages #6**

- In adults 40-75 being evaluated for primary prevention
  - ♦ Clinician-patient risk discussion before starting statin
  - ♦ Review major risk factors and calculate 10 year risks
  - ♦ Patient preference, cost, interactions, side effects

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**Top 10 Take Home Messages #7**

- In adults 40-75 without diabetes and with LDL over 70 and a 10 year ASCVD risk of  $\geq 7.5\%$ , start a moderate intensity statin if a discussion of treatment options favors statin therapy
  - ♦ Consider CAC score to improve specificity
  - ♦ If statins indicated, reduce LDL by  $\geq 30\%$  or more
  - ♦ If 10 year risk is  $\geq 20\%$  reduce levels by  $\geq 50\%$

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**Top 10 Take Home Messages #8**

- In adults 40-75 without DM and a 10 year risk of 7.5 to 19.9% (intermediate risk), risk enhancing factors favor initiation of statin therapy
  - FH premature ASCVD
  - LDL  $\geq 160$
  - Metabolic syndrome
  - CKD
  - H/o preeclampsia or early menopause under 40
  - Inflammatory dx
  - HIV
  - South Asian ethnicity
  - High triglycerides  $\geq 175$  mg/dL
  - Apo B  $\geq 130$  mg/dL
  - HS CRP  $\geq 2$  mg/L
  - LP(a)  $\geq 50$

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**Top 10 Take Home Messages #9**

- In adults 40 to 75 yo without DM and LDL  $\geq 70$ -189 mg/dL and 10 year risk 7.5-19.9% consider measuring CAC
  - ♦ If zero, can withhold delay unless smoker or strong family history
  - ♦ CAC score 1-99 favors therapy especially  $\geq 55$  years old
  - ♦ CAC  $\geq 100$  Agaston units or 75<sup>th</sup> percentile statin therapy is indicated

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### ADA Standards of Care

- Used to recommend aspirin therapy in certain groups as primary prevention
- Now: "May be considered in those with diabetes who are at increased cardiovascular risk"



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### Aspirin Cardiovascular Events Healthy Elderly

No. at Risk	
Aspirin	9525 9322 9068 7820 5827 3568 2234
Placebo	9589 9387 9119 7843 5839 3578 2223

McNeil et al. Effect of ASA on VC Events and Bleeding in Health Elderly. NEJM, Oct 18, 2018



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### Aspirin CV Events in Healthy Elderly: Bleeding

No. at Risk	
Aspirin	9525 9337 9094 7833 5826 3574 1248
Placebo	9589 9424 9192 7930 5935 3632 1244

McNeil et al. Effect of ASA on VC Events and Bleeding in Health Elderly. NEJM, Oct 18, 2018



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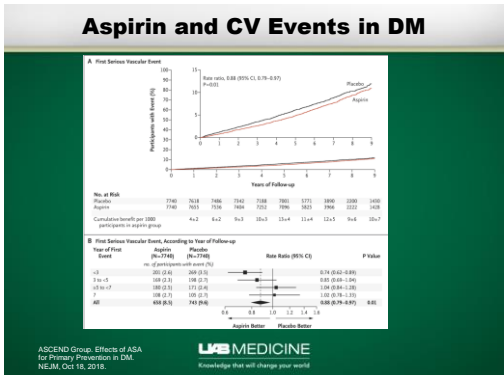
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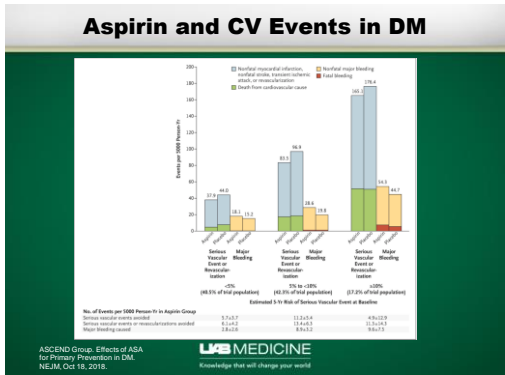
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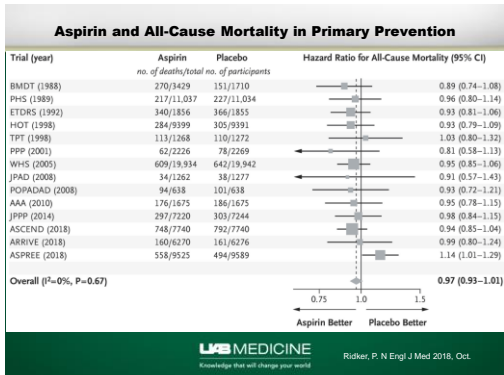




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## Aspirin and ASCVD

- What can we conclude about the use of aspirin for prophylaxis 150 years after its chemical synthesis? For secondary prevention, in which risk is determined largely by the extent of atherosclerotic disease, the benefits of aspirin outweigh the risks of bleeding. In contrast, for primary prevention, in which risk is determined largely by age and the presence or absence of diabetes, the benefit–risk ratio for prophylactic aspirin in current practice is exceptionally small. Thus, beyond diet maintenance, exercise, and smoking cessation, the best strategy for the use of aspirin in the primary prevention of cardiovascular disease may simply be to prescribe a statin instead.


Ridker, P. N. *Engl J Med* 2018, Oct.

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## Statins




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## Statins




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**Side Effects**

- Myalgias with normal CK: 1-5% in RCT, 5-10% observational
  - ♦ Bilateral proximal muscles
  - ♦ Leg cramps and joint pain very atypical
  - ♦ Re-challenge, altered dose or regimen often works
- LFT abnormalities rare, no recommendation now for serial monitoring
  - ♦ Tolerate up to 3x normal

Grundy SM et al. 2018. Cholesterol Clinical Practice Guidelines 

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**Statin Safety and Side Effects**

- No recommendation for routine CK or LFT monitoring
- FDA removed LFT monitoring from label in 2012, does recommend baseline testing and "as clinically indicated thereafter"
- No evidence to support coenzyme q10 in randomized studies

Grundy SM et al. 2018. Cholesterol Clinical Practice Guidelines 

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**Liver Disease**


Liver (2. Hep), Section Editor

**The Use of Statins in Patients With Chronic Liver Disease and Cirrhosis**

Carlos Mactenamo-Velázquez, MD  
Juan G. Abraldes, MD, MSc  
Aldo J. Montano-Loza, MD, PhD

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Email: aldolm@ual.es

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### Liver Disease

Statins

Platelet Activation  
Coagulation  
Angiogenesis  
Oxidative Stress  
Apoptosis  
Fibrosis  
Proliferation  
Endothelial Dysfunction

Moctezuma-Velazquez et al. Use of Statins in Patients with Liver Disease and Cirrhosis. Curr Treat Options Gastro 16: 220-240, 2018

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### Liver Disease

- Few situations where you can't / shouldn't use them
- Consult GI specialist if unsure
  - Beneficial in NASH / NAFLD
  - Beneficial in Hep C
  - Safe in compensated cirrhosis
  - Benefits:
    - Potential to lower HCC risk, less liver decompensation, infections, risk of progression, death

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### Questions/Discussion?

- Thank you for your attention and the opportunity to speak....

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