# Update in Lipid Management

Mark Steiner, MD

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# Update in Lipid Management

- General Risk Factor Management
- Lipid Guidelines
  - Take Home Points
  - Statin Therapy
- Non-statin Therapy
  - Ezetimibe
  - PCSK9 inhibitor
  - Alternative therapies

# Background

- ASCVD remains the leading cause of morbidity and mortality globally.
  - Much of this is attributable to suboptimal implementation of prevention strategies and uncontrolled ASCVD risk factors.
  - The most important way to prevent ASCVD is to promote a healthy lifestyle throughout life.
- 10-year absolute ASCVD risk enables matching the intensity of preventive interventions to the patient's absolute risk to maximize anticipated benefit and minimize potential harm from overtreatment.
- After the age of 20, it is reasonable to measure traditional risk factors at least every 4-6 years.

# General Risk Reduction Goals

- The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life.
  - Team-based care
  - Evaluation of 10 year ASCVD
  - Diet, exercise and weight loss.
  - Tobacco cessation.
- Guidelines stress lifestyle modification as first line therapy
  - Basis for initial intervention
  - Challenging to achieve


**"First we insert a balloon to open the clogged artery, then we fill the balloon with helium so you weigh less."**

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# Lipid Guidelines

- **Guidelines are long and complex**
- **New guidelines give numerical thresholds not goals**
- **Initial therapies are always lifestyle modification**
- **Risk factor and risk evaluation key to subsequent treatment recommendations**
- **This talk will highlight take home points**

# Lipid Guidelines – Take Home Points

**In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.**

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

# Lipid Guidelines – Take Home Points

**In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.**

- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L).
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost- effectiveness is low at mid-2018 list prices.

# Lipid Guidelines – Take Home Points

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

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

• If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) & the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.

# Lipid Guidelines – Take Home Points

**In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.**

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

# Lipid Guidelines – Take Home Points

**In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.**

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, (LDL-C), hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);

- the presence of risk-enhancing factors;
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.

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# Lipid Guidelines – Take Home Points

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

Risk-enhancing factors favor statin therapy (see next slide).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

# Lipid Guidelines – Take Home Points

**In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy.**

## Risk-enhancing factors include

- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;
- history of preeclampsia or premature menopause (age <40 yrs)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥ 175 mg/dL (≥1.97 mmol/L);

# Lipid Guidelines – Take Home Points

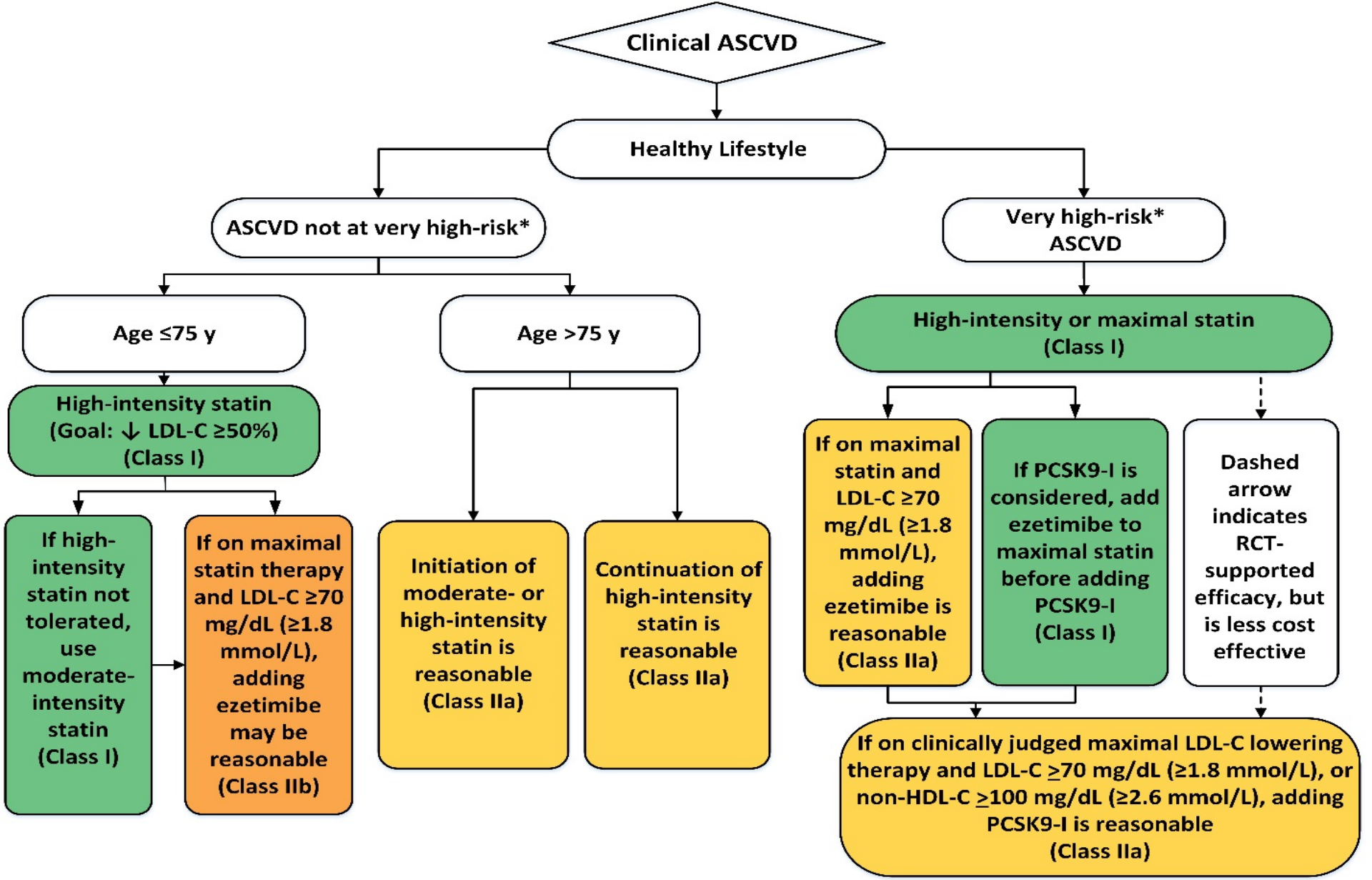
**In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.**

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

# Lipid Guidelines – Take Home Points

**Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.**

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy.


Clinical ASCVD
Healthy Lifestyle
ASCVD not at very high-risk*
Very high-risk* ASCVD
Age ≤75 y
Age >75 y
High-intensity or maximal statin (Class I)
High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)
If high-intensity statin not tolerated, use moderate-intensity statin (Class I)
If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)
Initiation of moderate- or high-intensity statin is reasonable (Class IIa)
Continuation of high-intensity statin is reasonable (Class IIa)
If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)
If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)
Dashed arrow indicates RCT-supported efficacy, but is less cost effective
If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)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# Ezetimibe

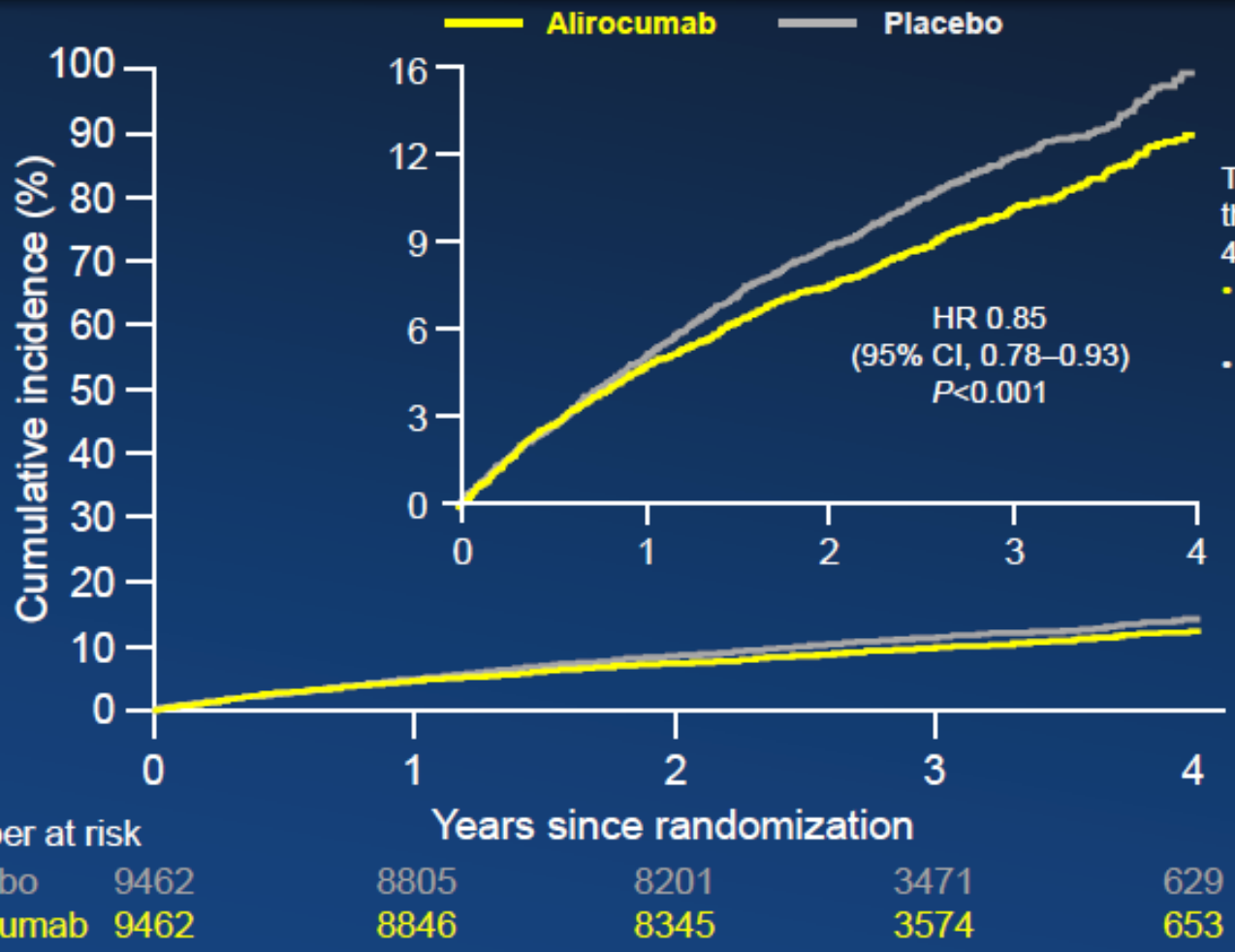
- Inhibits Niemann-Pick C1 like 1 Protein
- IMPROVE-IT and SHARP trials demonstrated benefit in cardiac endpoints in ACS and non-ACS patients
- Well tolerated and generic available
- Monotherapy gives ~ 18% reduction and combination with statins results in ~ 25% reduction in LDL levels


"Mr. Clark, lowering your cholesterol level NOW won't do you a bit of good."

# PCSK9 inhibitors

- Human monoclonal antibody to PCSK9 that increases number of LDL receptors.
- ODYSSEY and FOURIER studies revealed decreased cardiac events.
- Subcutaneous injections every 2-4 weeks
- LDL reductions from 45-64% depending on study.
- Adverse effects – nasopharyngitis and site reactions. Overall well tolerated.

# Cumulative Incidence of the Composite Primary Endpoint




The Kaplan–Meier rates for the primary endpoint at 4 years were:

- 12.5% (95% CI: 11.5–13.5) for alirocumab
- 14.5% (95% CI: 13.5–15.6) for placebo

To prevent one primary end point event, 49 patients (95% CI: 28–164) would need to be treated for 4 years

The inset shows the same data on an enlarged y-axis.
CI, confidence interval; HR, hazard ratio.

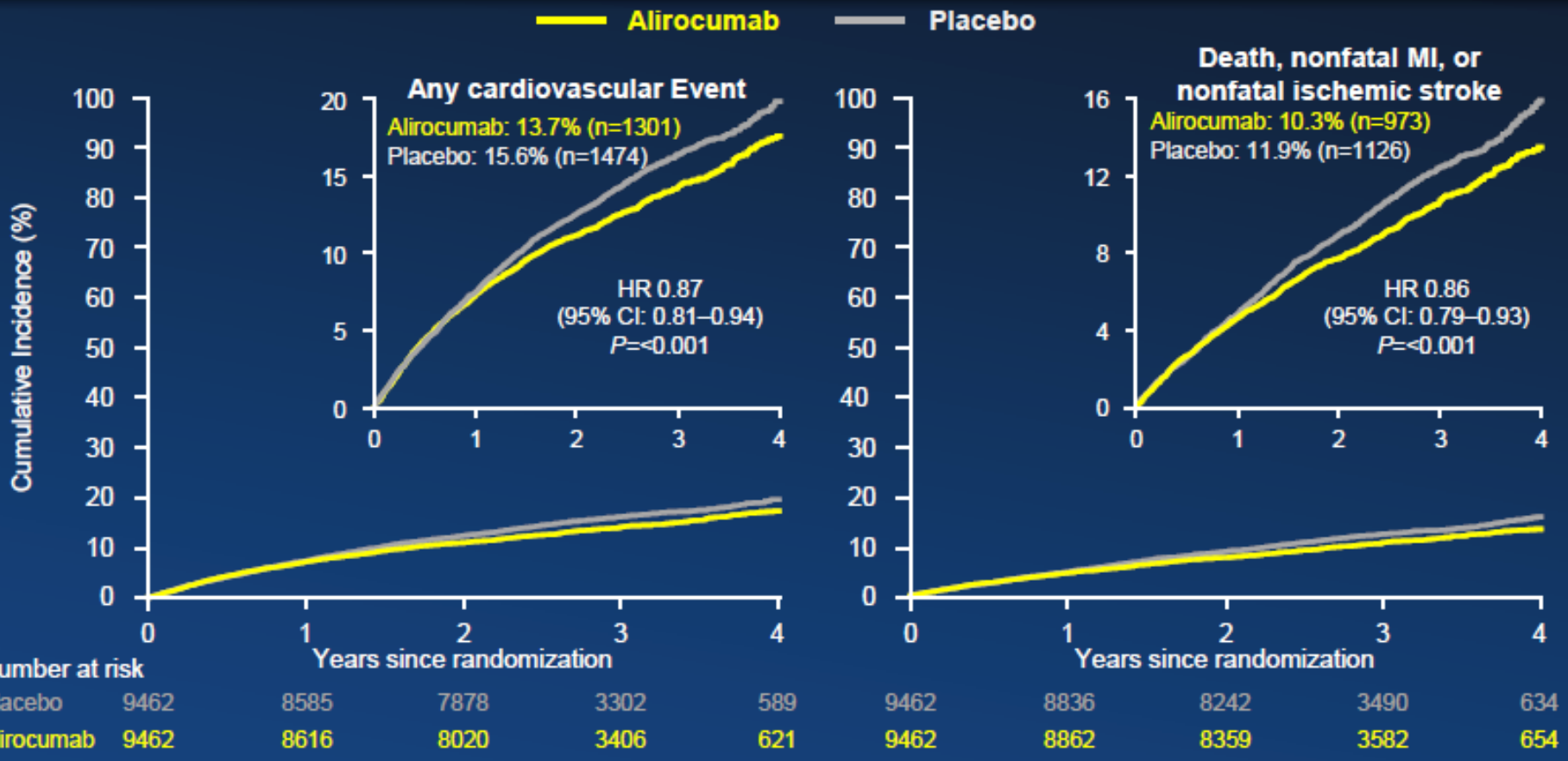
Schwartz GG et al. *N Engl J Med* 2018 (epub ahead of print).





ODYSSEY OUTCOMES

# Main Secondary Endpoints: Any Cardiovascular Event and Death, Nonfatal MI, or Nonfatal Ischemic Stroke




| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 9462 | 8585 | 7878 | 3302 | 589 | 9462 | 8836 | 8242 | 3490 | 634 |
| Alirocumab | 9462 | 8616 | 8020 | 3406 | 621 | 9462 | 8862 | 8359 | 3582 | 654 |

The insets shows the same data on an enlarged y-axis.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

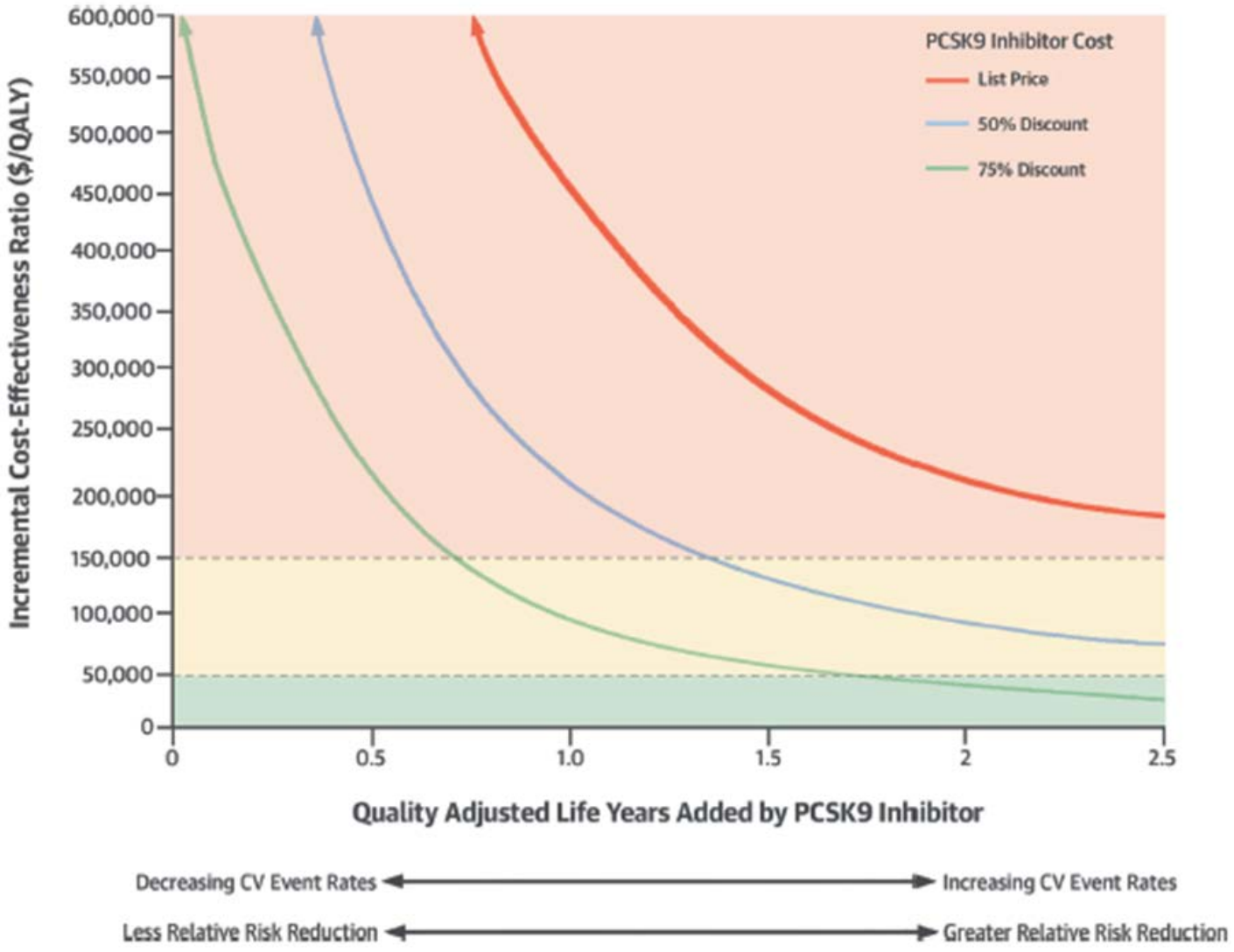
Schwartz GG et al. *N Engl J Med* 2018 (epub ahead of print).





ODYSSEY OUTCOMES

# Cost-Effectiveness Analysis for PCSK9 Inhibitors

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**"With this new drug, cholesterol forms *outside* of the body, where it can't clog the arteries."**

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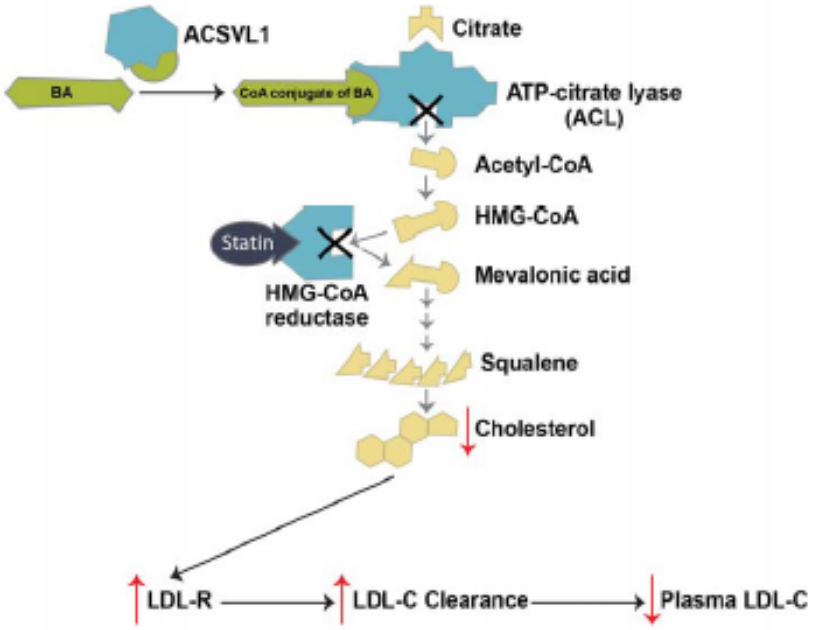
# Alternative therapies

- Bile acid sequestrants
  - May be beneficial in patients unable to take Ezetimibe
- Phytosterols
- Lomitapide
  - Inhibts microsomal triglyceride transfer protien
- LDL apheresis
  - Removes apo B-containing lipoproteins
- Inclisiran – siRNA compound
- Bempedoic Acid
  - See next slide

# Bempedoic Acid - Mechanism

## Bempedoic Acid Mechanism of Action

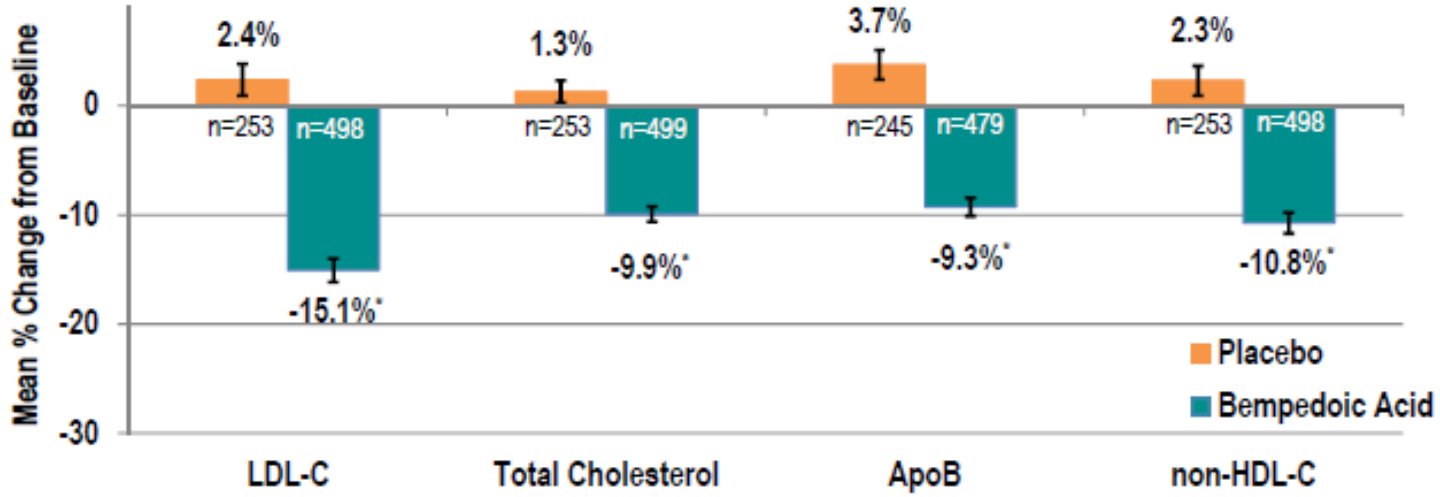



- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Bempedoic acid inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Bempedoic acid upregulates LDL receptors and lowers LDL-C
- Activated bempedoic acid is not present in skeletal muscle

# Bempedoic Acid - Data

## CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in Lipids and Lipoproteins




*P < .001 for all comparisons

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# Hypertriglyceridemia

- Diet therapy
  - Treat obesity, metabolic syndrome, hyperglycemia
- Treat underlying causes
  - Diabetes, triglyceride raising drugs, secondary disorders
- Statin therapy
  - Especially in patients with increased cardiac risk
- Fibrates or Omega-3 fatty acids
  - Especially in patients with trig > 500 mg/dl
  - Use fenofibrate rather then gemfibrozil for patients on statins

# Coronary artery calcium scoring

- For individuals with intermediate predicted risk (≥7.5% to <20%) CAC measurement can be a useful tool in refining risk assessment for preventive interventions (e.g., statin therapy).
  - In these groups, CAC measurement can reclassify risk upward (particularly if CAC score is ≥100 Agatston units or ≥75th age/sex/race percentile) or downward (if CAC is zero) in a significant proportion of individuals.
  - In such intermediate-risk adults, those with CAC ≥100 Agatston units or CAC ≥75th percentile have ASCVD event rates for which initiation of statin therapy is reasonable. Those with CAC scores of zero appear to have 10-year event rates in a lower range for which statin therapy may be of limited value.
- Clinicians should not down-classify risk in patients who have CAC scores of zero but who are persistent cigarette smokers, have diabetes, have a family history of ASCVD, or, possibly, have chronic inflammatory conditions.

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

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

**A couple were talking, and the wife says, “It’s my birthday tomorrow.”**

**Her husband responds with, “What do you want for your birthday?”**

**The wife says, “I want something that goes very fast.”**

**The next day, the husband comes home and says, “I have a gift for you, which goes from 0 to 300 in 3 seconds.”**

**The wife asks, “Is it a Ferrari? Or a Lamborghini?”**

**The husband says, “No, it’s a weighing scale!!!”**

**…The husband’s funeral is tomorrow.**

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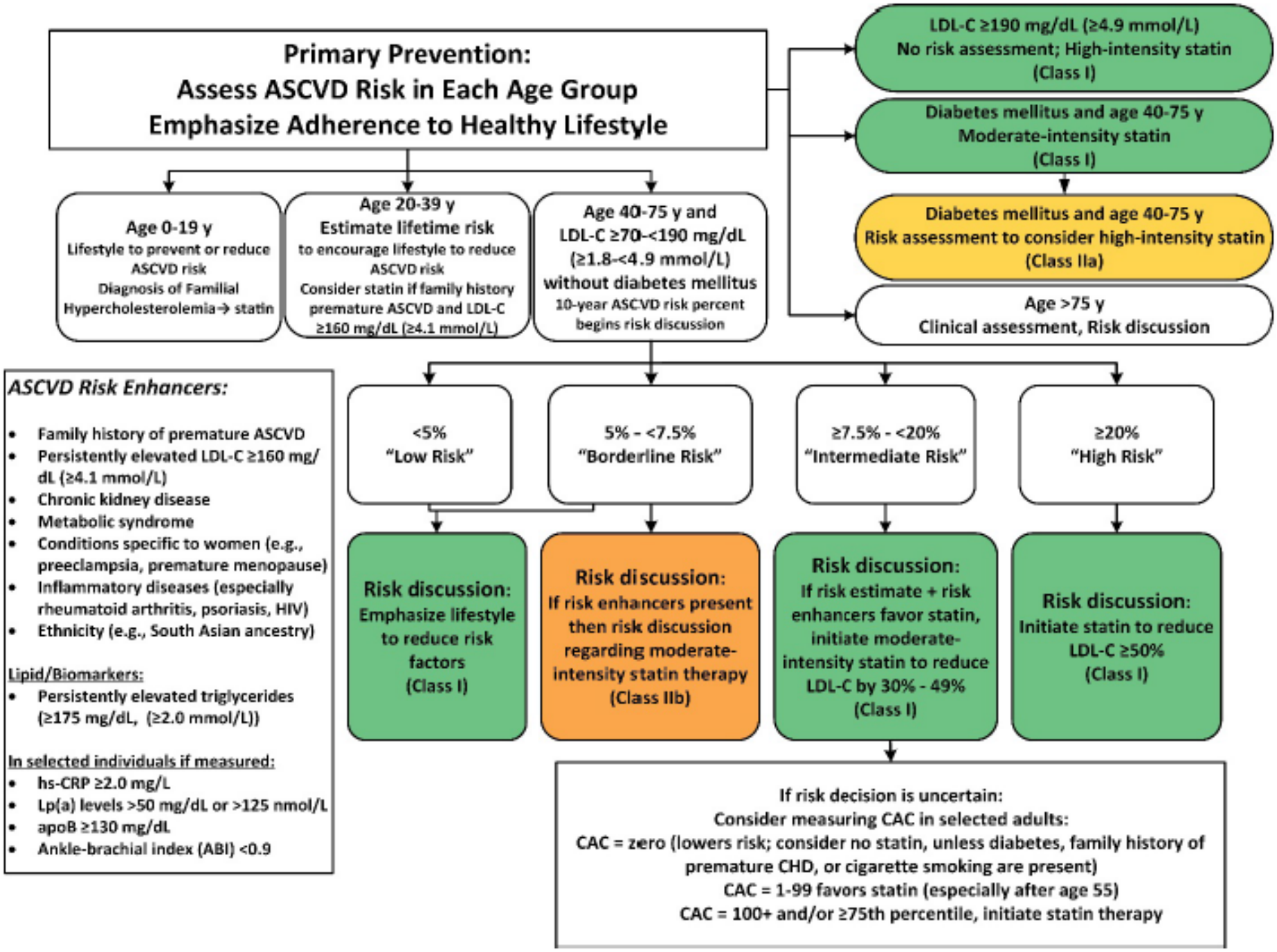
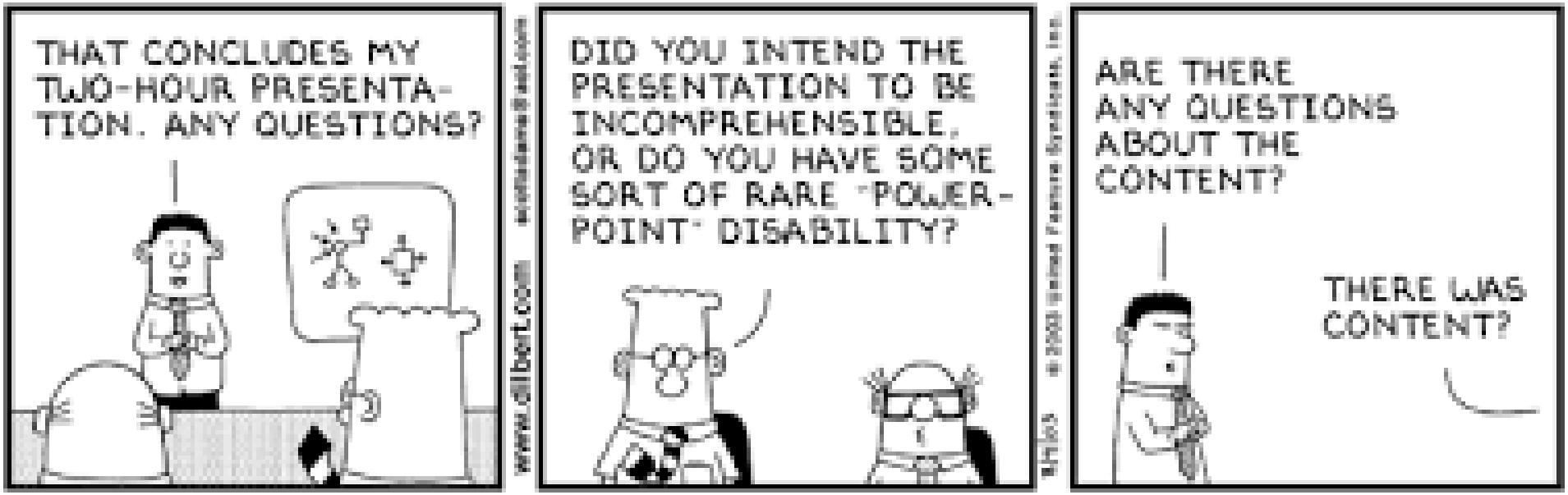

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; 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



# ??? QUESTIONS ???

Thank you for your attention…

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