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Fourth Annual Cardiovascular Symposium
at Hollis Cancer Center/Campisi Family Auditorium

Lipid management and risk panels for cardiovascular disease

Stephen L. Kopecky, M.D. FACC, FAHA, FASPC, FACP

8:00-8:35 am
Q&A 8:35- 8:40 am

 |

Conflict of Interest

Activity	Company	Explanation
Consulting	Prime Therapeutics	Pharmacy benefits manager. Discuss drug efficacy, safety, uniqueness
Consulting	Roche	
Research Support	True Health	Research in randomized trials
DSMB Member	Applied Clinical Intelligence	Member of Data Monitoring Cmte
Member	American Society for Men's Health	501c3 - Educational org. to improve men's health awareness and care
Board of Directors, Member	Mayo Clinic Support Services, Texas	Texas Non-Profit Health Organization
Member, Mayo Clinic CV P&T Task Force	Mayo Clinic	Discuss drug efficacy, safety, uniqueness

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Objectives

- Identify cardiovascular disease risk factors & use them to predict the risk of future coronary events
- Apply management strategies to the prevention of CAD, including therapies to reduce risk factors and appropriate counseling on lifestyle changes
- Initiate appropriate lipid lowering therapies to reduce risk of future events, recognizing potential side effects and drug-drug interactions

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Approach to Hyperlipidemia

1. Rule out secondary causes
2. Assess risk
3. Discuss options
4. Initiate treatment & monitor

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Secondary Causes of HLD Most Commonly Encountered

Secondary Cause	Elevated LDL-C	Elevated TG's
Diet	Saturated or *trans* fats, weight gain, anorexia	Weight gain, very low-fat diet, high refined carbs, excess alcohol
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, BAS, anabolic steroids, glucocorticoids, protease inh, retinoic acid, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders of metabolism	Low T4, obesity, pregnancy*	DM(poorly controlled), Low T4, obesity, pregnancy*

* Statin contraindicated (& w/ lactation)

How many of the 1st CV Events that occur are in 'High Risk' patients ?

<½ of the 1st CV Events that occur are in 'High Risk' patients

Wilson	CRP and reclassification of risk *Circ. Cardiovasc. Qual. Outcomes* 1, 92–97	(2008)
Polonsky	Coronary artery calcium score and risk classification *JAMA* 303, 1610–1616	(2010)
Elias-Smale	Calcium improves classification : Rotterdam study. *J. Am. Coll. Cardiol.* 56, 1407–1414	(2010)
Erbel	Heinz Nixdorf Recall study. *J. Am. Coll. Cardiol.* 56, 1397–1406	(2010)
Nambi	Carotid intima–media thickness : the ARIC study. *J. Am. Coll. Cardiol.* 55, 1600–1607	(2010)
Polak	Carotid intima–media thickness and cardiovascular events. *N. Engl. J. Med.* 365, 213–221	(2011)
Cooney	Re-evaluating the Rose approach *Eur. J. Cardiovasc. Prev. Rehabil.* 16, 541–549	(2009)
Wald	A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326, 1419	(2003)

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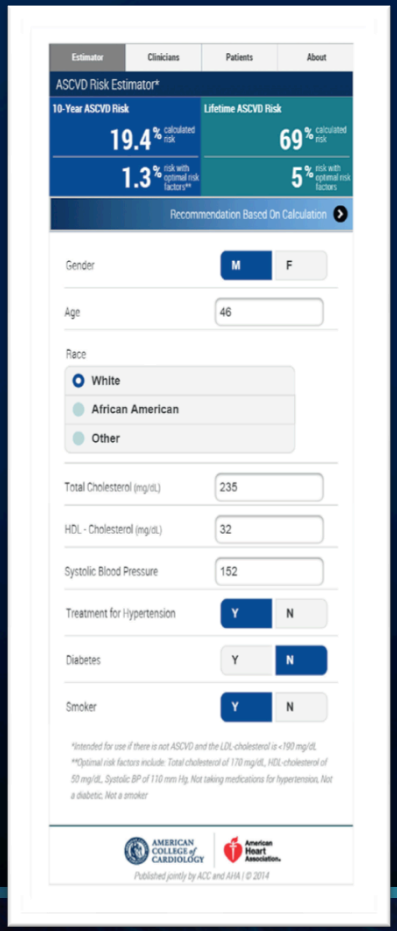
ACC/AHA ASCVD Risk Estimator Plus

Optimal risk factors
- → TC = 170 mg/dL
- → HDL-C = 50 mg/dL
- → Systolic BP = 110 mmHg
- → Not taking medications for HTN
- → Not a diabetic
- → Not a smoker



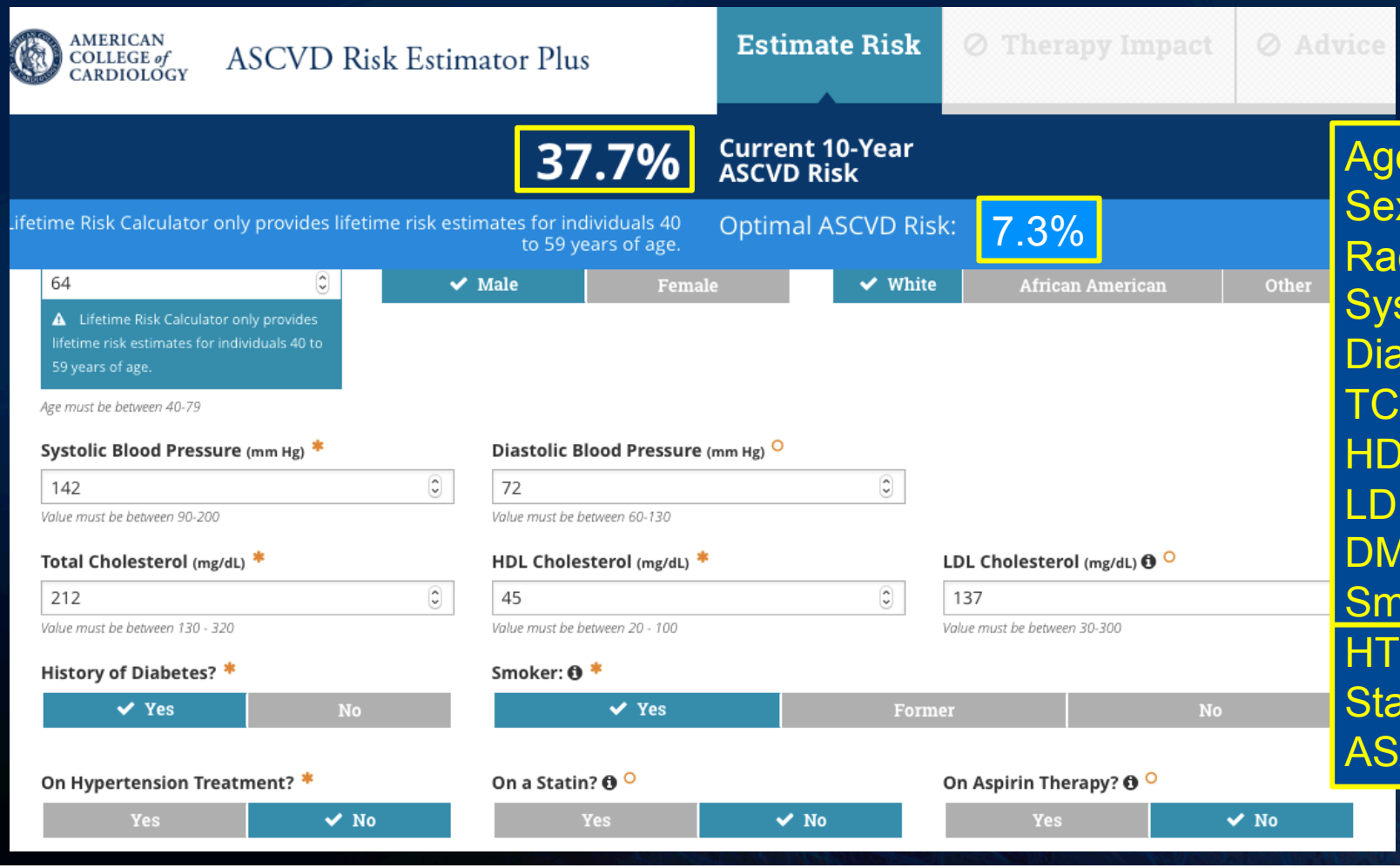
10-year risk of non-fatal MI, coronary heart disease death, and fatal and non-fatal stroke

Intended for use if no ASCVD and LDL-C is <190 mg/dL (~4.9 mmol/L)

Goff DC, et al. *J Am Coll Cardiol* 2014;63:2935-59

10 Year Risk Fatal/NF MI/CVA

If ≥7.5%, consider lipid lowering therapy



Age
Sex
Race
Sys BP
Dias BP
TC
HDL
LDL
DM
Smoker

HTN Rx
Statin Rx
ASA Rx

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Risk 37.7%

Therapy(s)	Projected ASCVD Risk for this patient if Therapy Initiated
Statin	28.3%
BP Drugs	27.6%
D/C Smoking	27.5%
ASA	33.9%
Statin + Aspirin	25.4%
BP drug(s) + Aspirin	24.9%
Statin + BP drug(s)	20.7%
Statin + Stop smoking	20.6%
Stop smoking + Aspirin	24.8%
BP drug(s) + Stop smoking	20.2%
Statin + BP drug(s) + Aspirin	18.6%
BP drug(s) + Stop smoking + Aspirin	18.2%
Statin + BP drug(s) + Stop smoking	15.1%
Statin + Stop smoking + Aspirin	18.6%
Statin/BP/Smoke/ASA	13.6%

28.3%

27.6%

27.5%

33.9%

13.6%

Projected ASCVD Risk if Therapy Initiated

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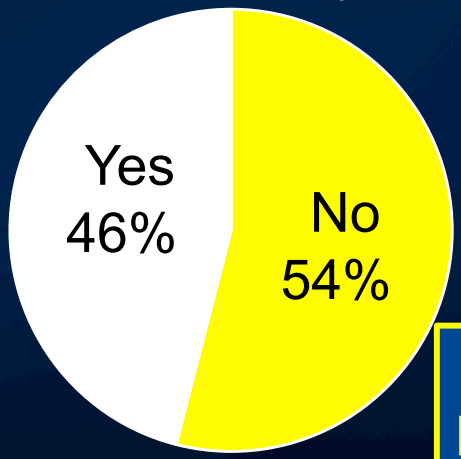
AHA/ACC Risk Calculator (MESA >7.5% 10-yr risk)

Who should take statin ?

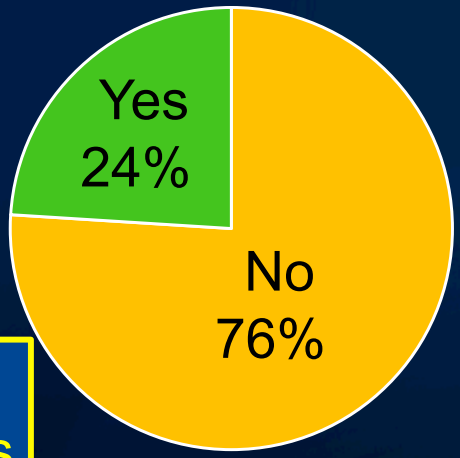
(MESA Study)



(Sensitivity 0.76, specificity 0.56)

Missed Rx Opportunities ?

Adverse Events in "No Statin"



Give statin to~ 50%,
Miss ~25% of CV events

Statins given to many patients that are not going to have CV events

Hard CVD Events in 'statin not recommended'

Hard CVD Events in 'statin recommended'

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Kakadiaris et al J Am Heart Assoc. 2018;7

2018 Cholesterol Guidelines

- Groups : 4 Groups based on clinical criteria
- Treatment Qualifiers :
  Based on “Very High Risk” (Secondary)
  or “Risk Enhancers” (Primary)

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2018 Cholesterol Guidelines : 4 Groups

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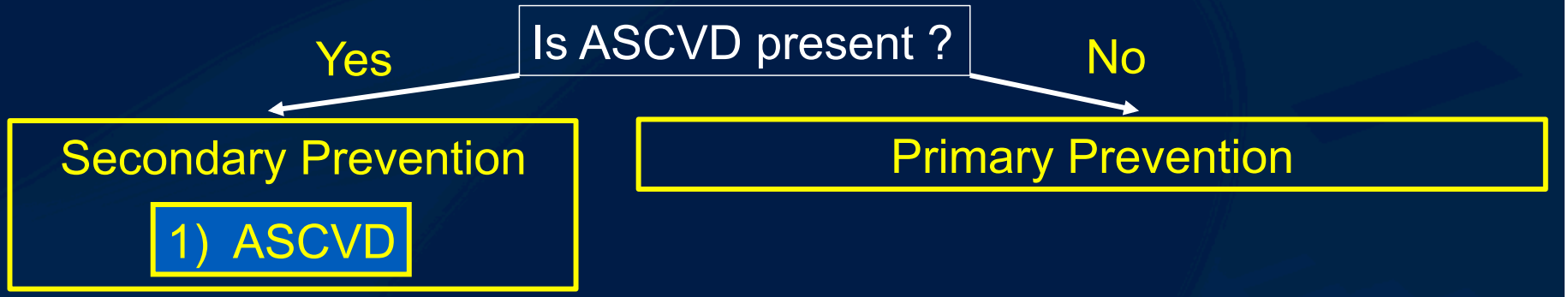
ASCVD : Any CAD/angina, Stroke/TIA, PAD, Aortic aneurysm (all of atherosclerotic origin), Any artery revascularization

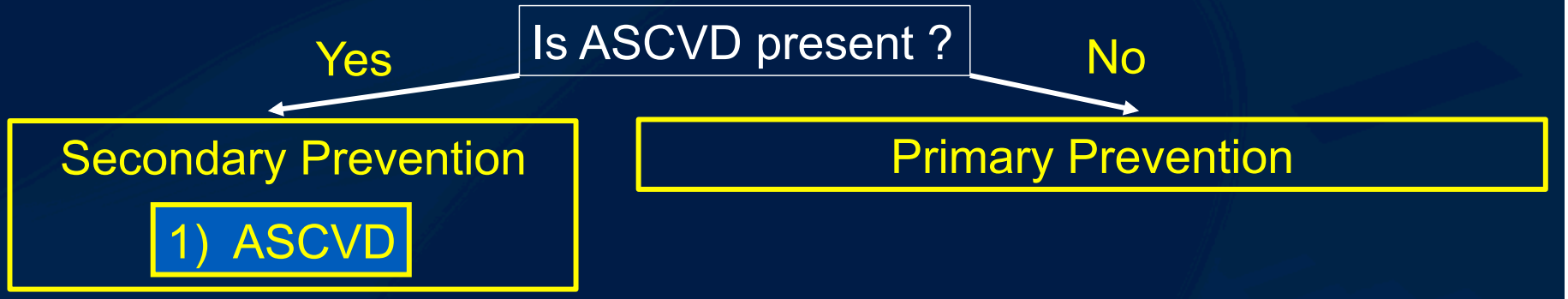
2018 Cholesterol Guidelines : 4 Groups



Rx : “Very High Risk"

ASCVD : Any CAD/angina, Stroke/TIA, PAD, Aortic aneurysm (all of atherosclerotic origin), Any artery revascularization

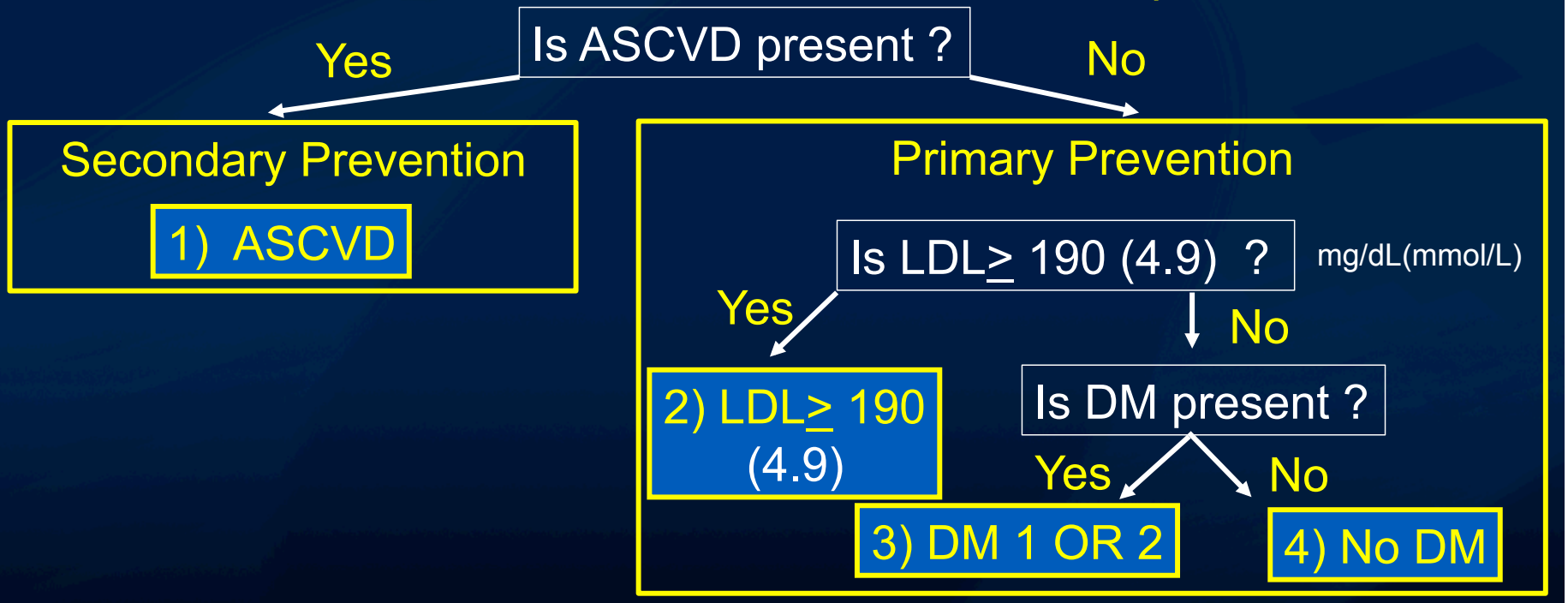
2018 Cholesterol Guidelines : 4 Groups



Rx : “Very High Risk"

ASCVD : Any CAD/angina, Stroke/TIA, PAD, Aortic aneurysm (all of atherosclerotic origin), Any artery revascularization

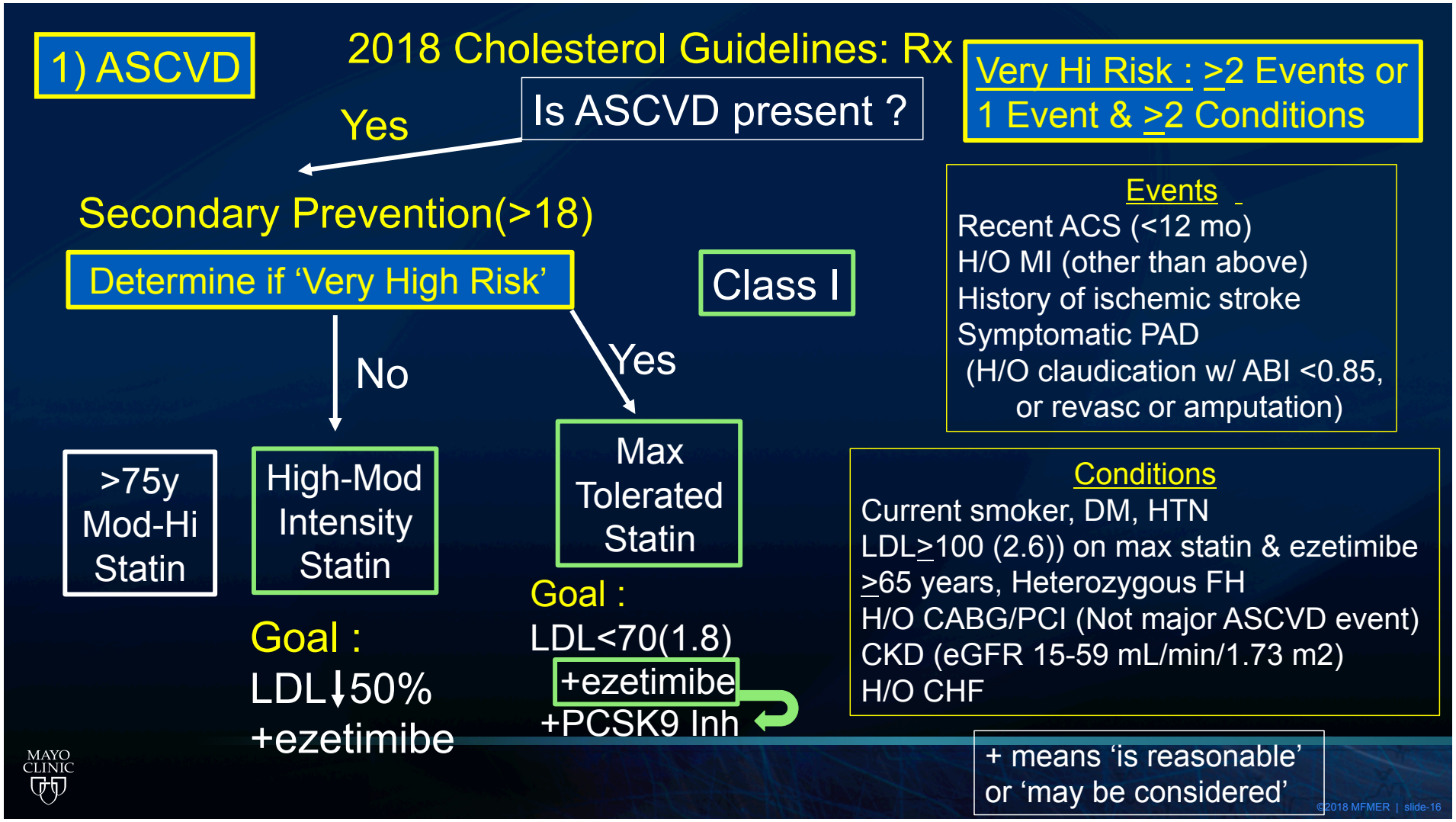
2018 Cholesterol Guidelines : 4 Groups



Rx : "Very High Risk"

Rx: "Risk Enhancers"

ASCVD : Any CAD/angina, Stroke/TIA, PAD, Aortic aneurysm (all of atherosclerotic origin), Any artery revascularization



2018 Cholesterol Guidelines:Rx

Primary Prevention
2) LDL≥190(4.9)

No Risk Assessment

Age 20-75y

Max Tolerated Statin → Class 1 Recommendation

Goal: 50% Reduction (or LDL<100)

If LDL < 50% Reduction

+Ezetimibe

(+PCSK9 Inh)

+ means 'is reasonable'
or 'may be considered'

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2018 Cholesterol Guidelines:Rx

Primary Prevention
3) DM (40-75y)

AHA/ACC Risk Assessment [If LDL ≥70(1.8)]

Risk ≥20%

Risk < 20%

High Intensity Statin

Yes

"Risk Enhancers" ?

- DM2 for 10 yr / DM1 20 yr
- Ur Albumin ≥30 mcg/mg creat
- eGFR <60 ml/min/1.73 m2
- Retinopathy, Neuropathy
- ABI <0.9

No

Mod Intensity Statin

LDL : mg/dl(mmol/L)

Primary Prevention
4) No DM

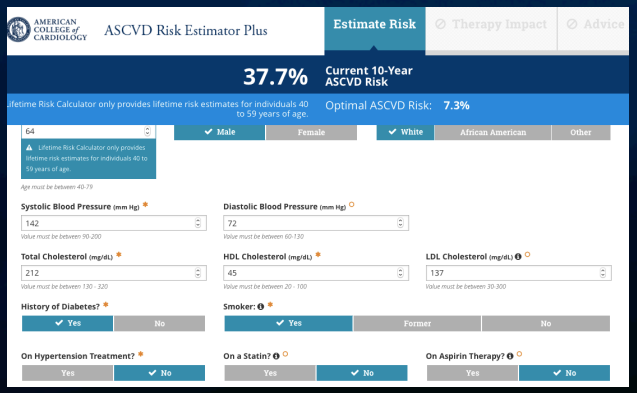
2018 Cholesterol Guidelines:Rx

LDL 70(1.8)-189(4.9)

0-19 yr
Lifestyle
If HeFH → Statin

20-39 yr
Lifestyle
If Fam Hx Early ASCVD+LDL>160(4.1):
+ statin

40-75 yr
↓
AHA/ACC ASCVD Risk Estimator Plus



+ means ‘is reasonable’
or ‘may be considered’

“Begin the risk discussion”

2018 Cholesterol Guidelines:Rx

Primary Prevention
4) No DM

LDL 70(1.8)-189(4.9)

AHA/ACC ASCVD Risk Estimator Plus

- ≥20% High → High Intensity Statin
- ≥7.5-<20% Intermed → Eval "Risk Enhancers" If +: Mod Statin
- 5-≤7.5% Borderline → Eval "Risk Enhancers" If +: Mod Statin (IIb)
- ≤5% Low → Lifestyle

CT CAC if uncertain

ASCVD 'Risk Enhancers' : Use in Primary Prevention

History & Co-Morbidities

Fam Hx premature ASCVD
Ethnicity (eg, South Asian ancestry)
Chronic Kidney Disease
Metabolic Syndrome
Conditions specific to women
(eg, Pre-eclampsia,
premature menopause)
Inflammatory diseases
(esp Rh Arthritis, psoriasis, HIV)

Lipid/Biomarkers

LDL-C ≥ 160(4.1)
Persistently elevated
TG's[≥175(2.0)]

In select individuals if measured-

hsCRP≥2.0
ABI<.9
Lp(a) >50 mg/dL or 125 nmol/L[1]
ApoB>130 mg/dL[2]

Formal recommendation to check :
1 Lipoprotein (a) if Fam Hx of
premature ASCVD
2 APO B if TG's > 200

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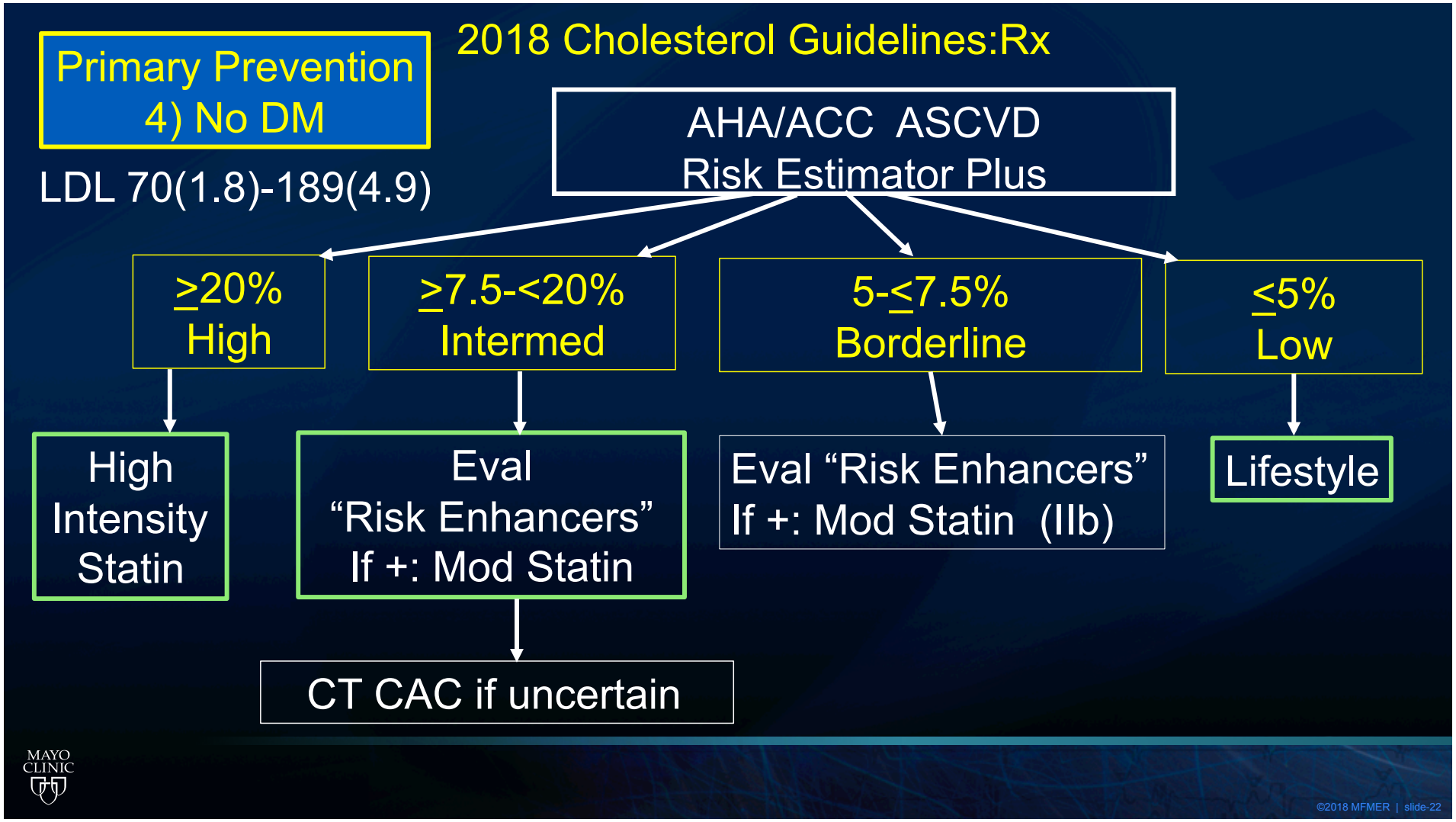

Primary Prevention
4) No DM

2018 Cholesterol Guidelines:Rx

LDL 70(1.8)-189(4.9)

How to use CT Scan
for Coronary Calcium (CAC)

Score 0 : Consider no statin (unless DM, FHx early CHD, smoking)
Score 1-99 : Favors statin (esp age> 55)
Score 100+ and/or 75th %tile : Initiate statin therapy

↓

Moderate Intensity Statin

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LDL Lowering with Hi, Mod, and Lo Intensity Daily Statin

	High	Moderate	Low
LDL ↓	≥50%	30%-<50%	<30%
	At (40*)-80	At 10 (20)	Si 10
	Ro 20 (40)	Ro (5) 10	Pr 10–20
		Si 20–40	Lo 20
		Pr 40 (80)	Fl 20–40
		Lo 40	Pi 1
		Fl XL 80	
		Fl 40 bid	
		Pi 2–4	

All doses in mg per day
*If unable to tolerate 80 mg
Ro=Rosuvastatin
At=Atorvastatin
Si=Simvastatin
Pr=Pravastatin
Lo=Lovastatin
Fl=Fluvastatin
Pi=Pitavastatin

2018 ACC/AHA Cholesterol Guideline

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Yellow : Evaluated in RCTs and Chol Treatment Trialists Meta-analysis of 170,000 participants
Lancet 2010;376:1670–1681; All demonstrated reduction in major CV events

1 Clinical ASCVD if any of the following :
All of atherosclerotic origin- H/O ACS, MI, any CAD, stable/unstable angina, any artery revasc, stroke/TIA, PAD, or aortic aneurysm

Secondary Prevention: Very High-Risk Factors for Future ASCVD Events

1) Major ASCVD Events

- Recent ACS (<12 mo)
- H/O MI (other than above)
- History of ischemic stroke
- Symptomatic PAD (H/O claudication w/ ABI<0.85 or revasc or amputation)

2) High-Risk Conditions

- Age ≥65 years, Current smoking
- DM, HTN
- LDL-C ≥100 mg/dL (2.6 mmol/L)) on
- max tolerated statin & ezetimibe
- Heterozygous FH
- H/O CABG/PCI (Not maj ASCVD event)
- CKD (eGFR 15-59 mL/min/1.73 m2)
- H/O CHF

Very High-Risk =>1 Event[1] OR 1 Event & >1 High Risk Conditions[2]

Primary Prevention Risk Enhancers

History
- Fam Hx premature ASCVD
- CKD
- Metabolic Syndrome
- Conditions specific to women (eg, Preeclampsia, premature menopause)
- Inflammatory diseases (esp Rh Arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asian ancestry)

Lipid/Biomarkers
- LDL-C ≥ 160(4.1)
- Persistently elevated TG's[≥175(2.0)]

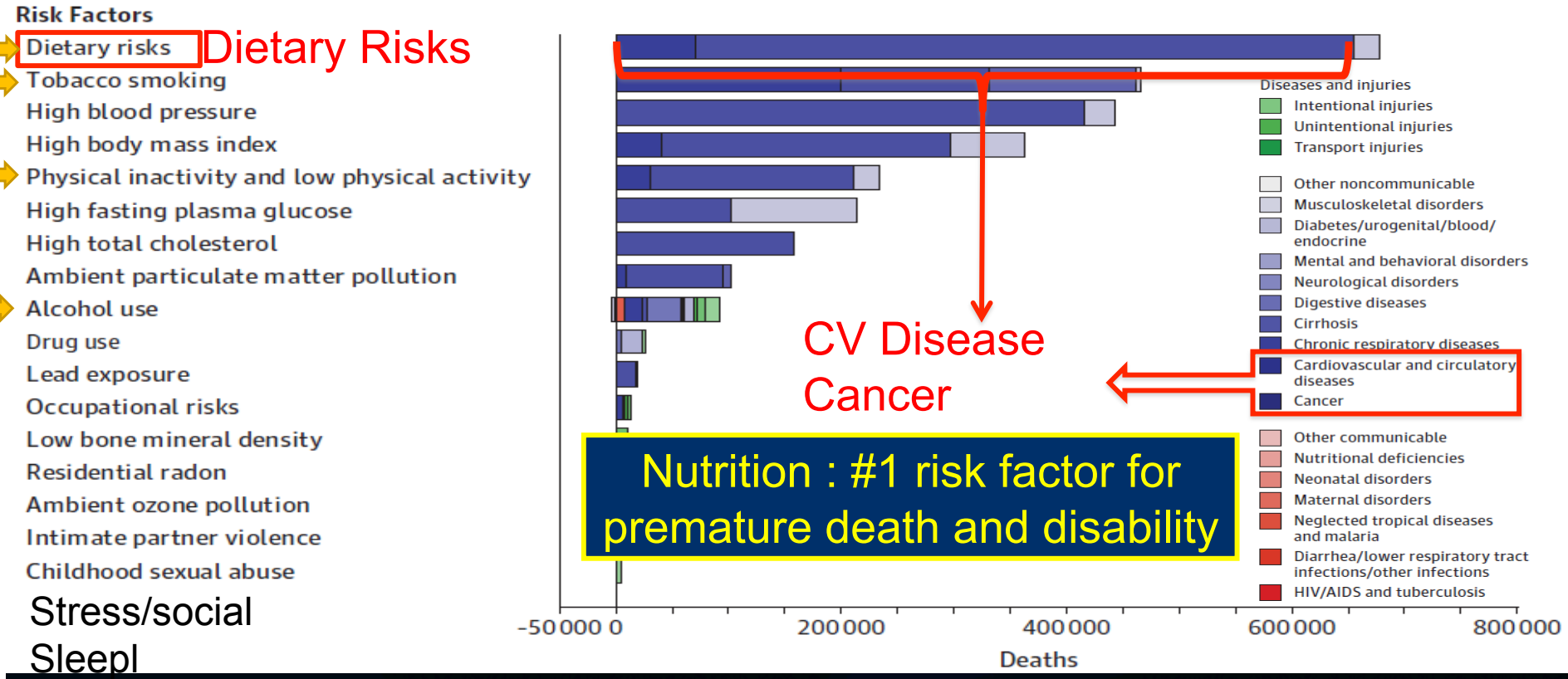
In select individuals if measured-
- hsCRP≥2.0
- ABI<.9
- Lp(a) >50 mg/dL or 125 nmol/L
- ApoB>130 mg/dL

DM-Specific Risk Enhancers that are Independent of Other Risk Factors in DM

- Long duration (DM2-10 yrs /DM1-20 yrs)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m2
- Retinopathy OR Neuropathy
- ABI <0.9

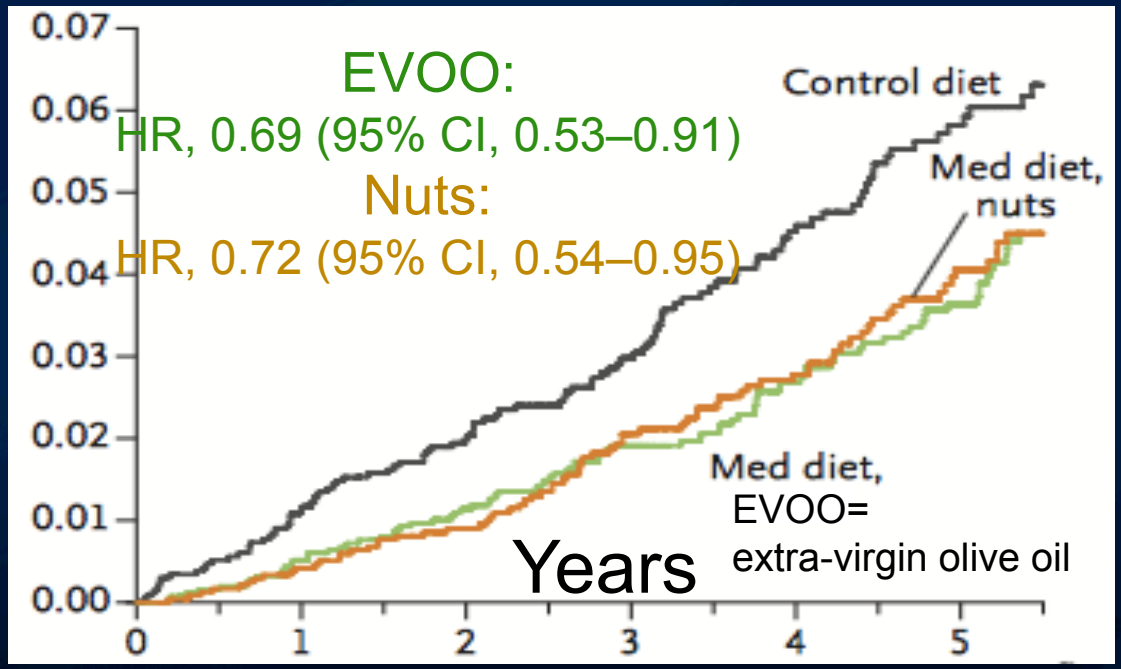
CAC = 0 (consider no statin, unless DM, FHx early CHD, smoking)
CAC = 1-99 favors statin (esp age> 55)
CAC = 100+ and/or 75th percentile, initiate statin therapy

US : Deaths Related to the 17 Leading Risk Factors



Murray et al. JAMA. 2013;310:591-608.

PREDIMED Study : Acute MI, Stroke, CV death



Study stopped at 4.8 yrs

Event Curves diverged early

Control = Low Fat Diet

- MI, Stroke, CV Death reduced w/ Mediterranean Diet
- Greater adherence = Greater reduction in events

PREDIMED Study NEJM 2018; 378:e34

Benefits of Mediterranean Diet

Lower risk of :

- Death from CV Disease and Stroke* !
- Death from Cancer*
- Diabetes*
- Alzheimer's Disease (dementia)*
- Arthritis*
- Parkinson's Disease*
- Macular Degeneration+ !
- Erectile Dysfunction#
- Female Sexual Dysfunction#

Mediterranean and DASH :
Only Nutritional patterns shown to reduce CV M/M

* PREDIMED NEJM. 2013;368:1279–129 and SubStudies
+ Ophthalmology. 2017;124:82–89.
# MEDITA Study Diabetes Care 2016;39:e143–e144

! HDL Related

Nuts

Almonds
12/d

Alcohol

M:5 Oz
W:3 Oz

Cola

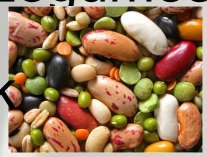
12 Oz/d

Fruit/Veg:Less cooked
Skin on
Fresh

Extra Virgin
Olive Oil

*Serving
=tennis
ball

Legumes*



3/wk

Fruits*

3/d

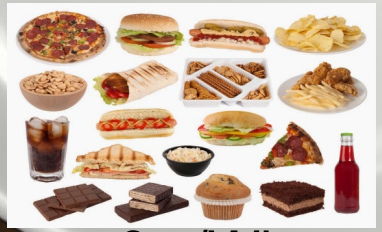
Vegetables*
2/d

White meat poultry
No skin

Fish/Seafood
4/wk

Limit
Intake

Processed Foods



3 x/Wk

Red Meat

1/d

1 Pad/d

Serving=
Deck of cards

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How beneficial is healthy eating when taking a statin ?

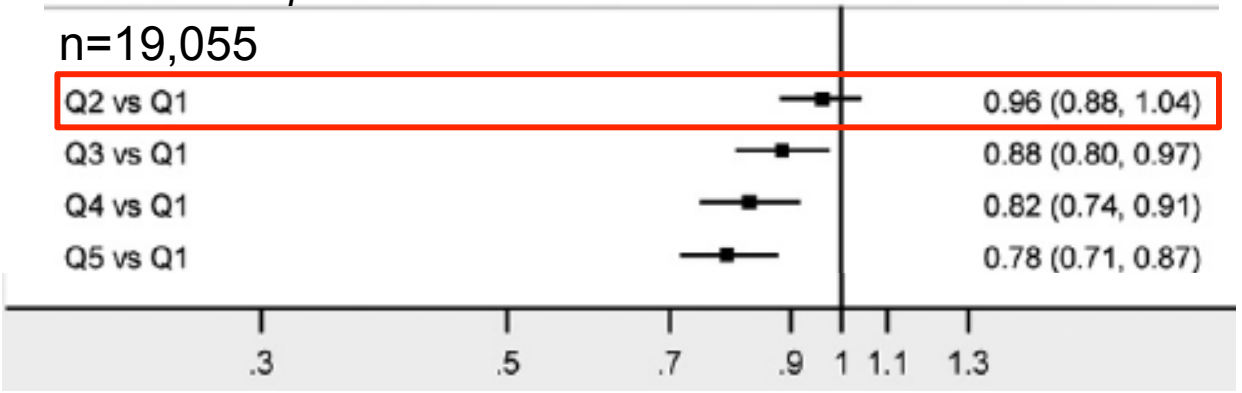
Quintile 5 Healthiest : *Mediterranean Style Diet**

Quintile 1 Unhealthiest : *Processed, sodium*

Primary outcome = CV Death, MI, Stroke, or CHF

*Modified Alternative Healthy Eating Index

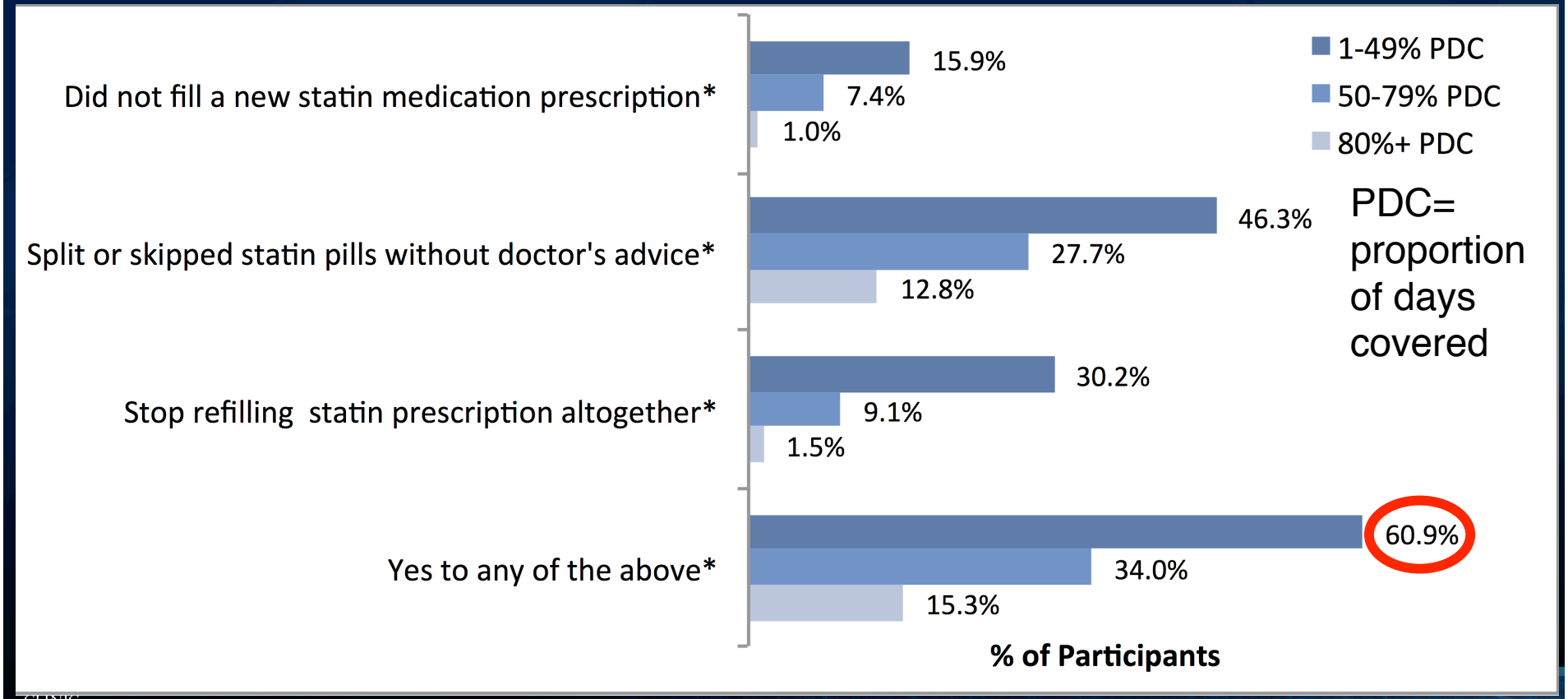
p<0.001 for Trend



If you're not eating healthy,
the benefits of a statin are significantly lessened

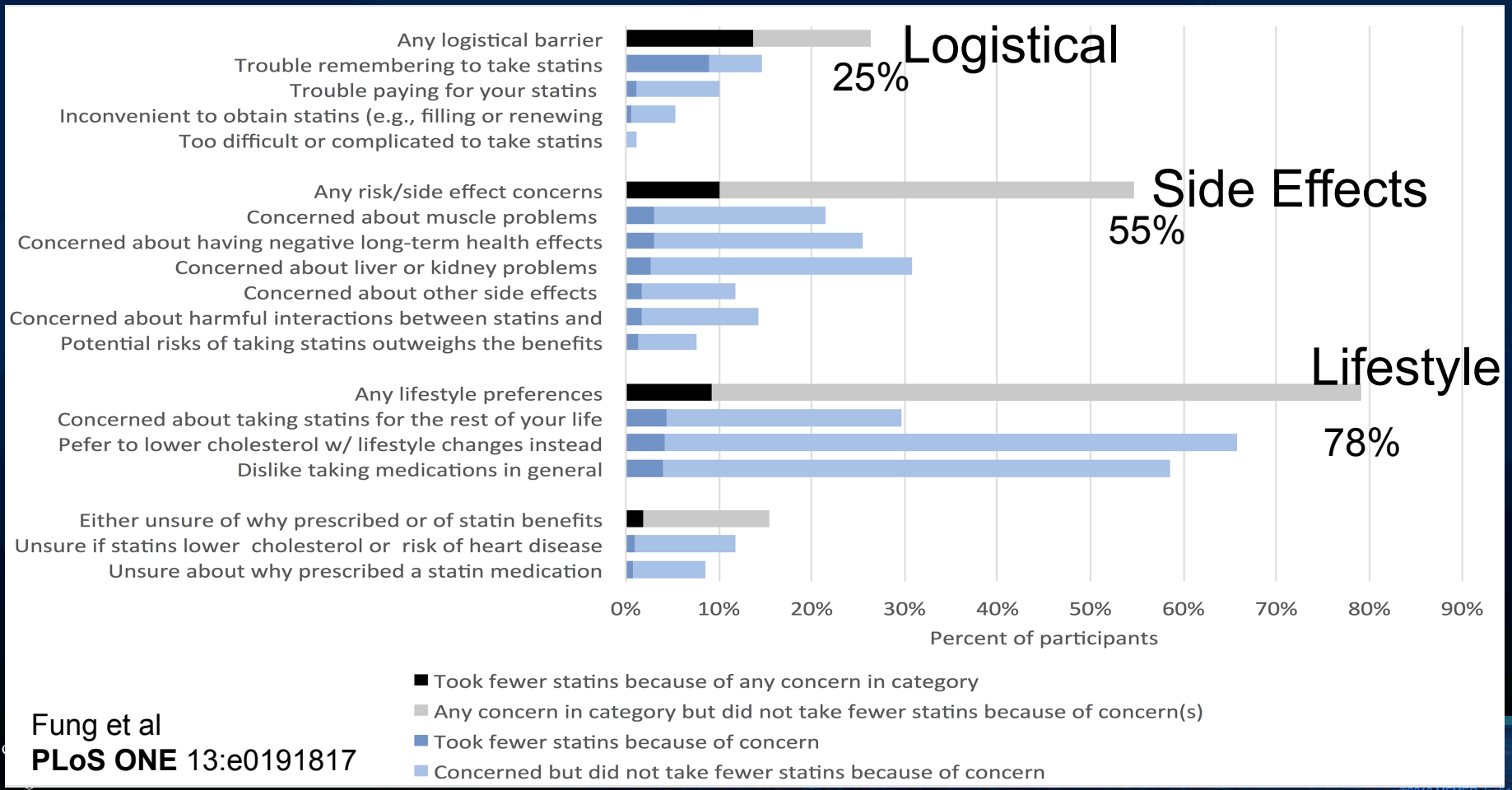
ONTARGET & TRANSCEND Trials Circ 2012;126:2705-2712

Real World data on Adherence



Fung V, Graetz I, Reed M and Jaffe MG **PLoS ONE** 13:e0191817

Reasons patients took fewer statins



Fung et al
PLoS ONE 13:e0191817

PATIENT EDUCATION

Alternative Therapies for Managing or Lowering Cholesterol

Cholesterol is a fat found in the bloodstream and in your body's cells. You need cholesterol for a healthy body, but too much cholesterol in the blood is a major risk factor for heart disease, high blood pressure, heart attack and stroke.

Low density lipoprotein (LDL) is often called "bad" cholesterol. Your health care provider looks at your LDL levels together with your other risk factors. For many people, an LDL under 100 mg/dL is considered healthy. For some people, an LDL between 100 and 130 may be of little concern. However, if you have heart disease or diabetes, you may be encouraged to lower your LDL cholesterol to 70 mg/dL or less.

Some people can lower their LDL levels and keep them in the healthy range through lifestyle habits, which include healthy physical activity and diet. Others may need prescription medications to lower cholesterol levels. Medications include statin drugs such as simvastatin, lovastatin, or pravastatin. Ask your health care provider to help you set a goal for your lipid levels. Work with your health care provider to achieve those levels.

Table 1. Use only one of these products. **Do not combine.**

Product	Effect on LDL cholesterol	How much to take
Plant stanols (found in products that contain sitostanol, such as Benecol™ Spreads and Smart Chews)	Blocks cholesterol absorption in the intestine	800 milligrams (mg) to 4,000 mg (4 grams) per day, divided and taken with meals (2 to 3 teaspoons Benecol™ Spreads or 2 to 4 Smart Chews)
Plant sterols (found in some products such as Promise activ™ Spreads)		
Plant stanol and sterol supplements (found in products like CholestOff™ and Centrum Cardio™)		

Table 2. You can use the products in the white table (Table 2) in combination with each other.

Product	Effects on LDL cholesterol	How much to take
Oat bran (Found in oatmeal and other oat bran products. Look for oat bran or whole oats as an ingredient on the label)	Stops the liver from making cholesterol	Up to 150 g of whole oat products per day (about the same as eating 1½ cups of cooked oatmeal)
Blonde psyllium (found in seed husks and products such as Metamucil™)	Increases loss of cholesterol by way of bile acid into the intestine	5 g seed husk twice per day, or 1 serving of a product such as Metamucil™

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Statin Intolerance - Myalgia : Does it exist ?

Definition :	Concept	Actuality	
Stop drug - symptom resolves	100%	25%	
Restart drug – symptom returns*	100%	50%	* Blinded
Start Placebo – return of symptoms*	0%	25%	
Able to tolerate some statin	0%	75%	

- Myalgias - comprise 90% of side effects
- DM – Usually in those at risk for DM (hi FBS, Metabolic Syn)
  5 CV events prevented for every 1 DM case occurs

No ‘Gold Standard’ for statin intolerance diagnosis

Lloyd-Jones et al ACC/AHA Update 2015

Moriarity et al Jrnl of Clin Lipid 2015; 9(6):758–769
Parker et al. *Circulation*. 2013;127(1):96-103.
Collins et al. [published online September 8, 2016]. *Lancet*. doi:10.1016/S0140 -6736(16)31357-5

Statin Intolerance – Patient Risk Factors

- History
  - Age >80 years, female sex, low BMI
  - Vigorous activity
  - FH of statin intolerance
  - FH of metabolic/inflammatory muscle disease
  - Osteoarthritis, Musculoskeletal disease
  - Fibromyalgia
  - Major surgery, trauma, infection < 6 weeks
  - Excess Alcohol
- Lab
  - High CK, Untreated hypothyroidism, Low vitamin D
- Drugs
  - Concomitant drug affecting statin metabolism

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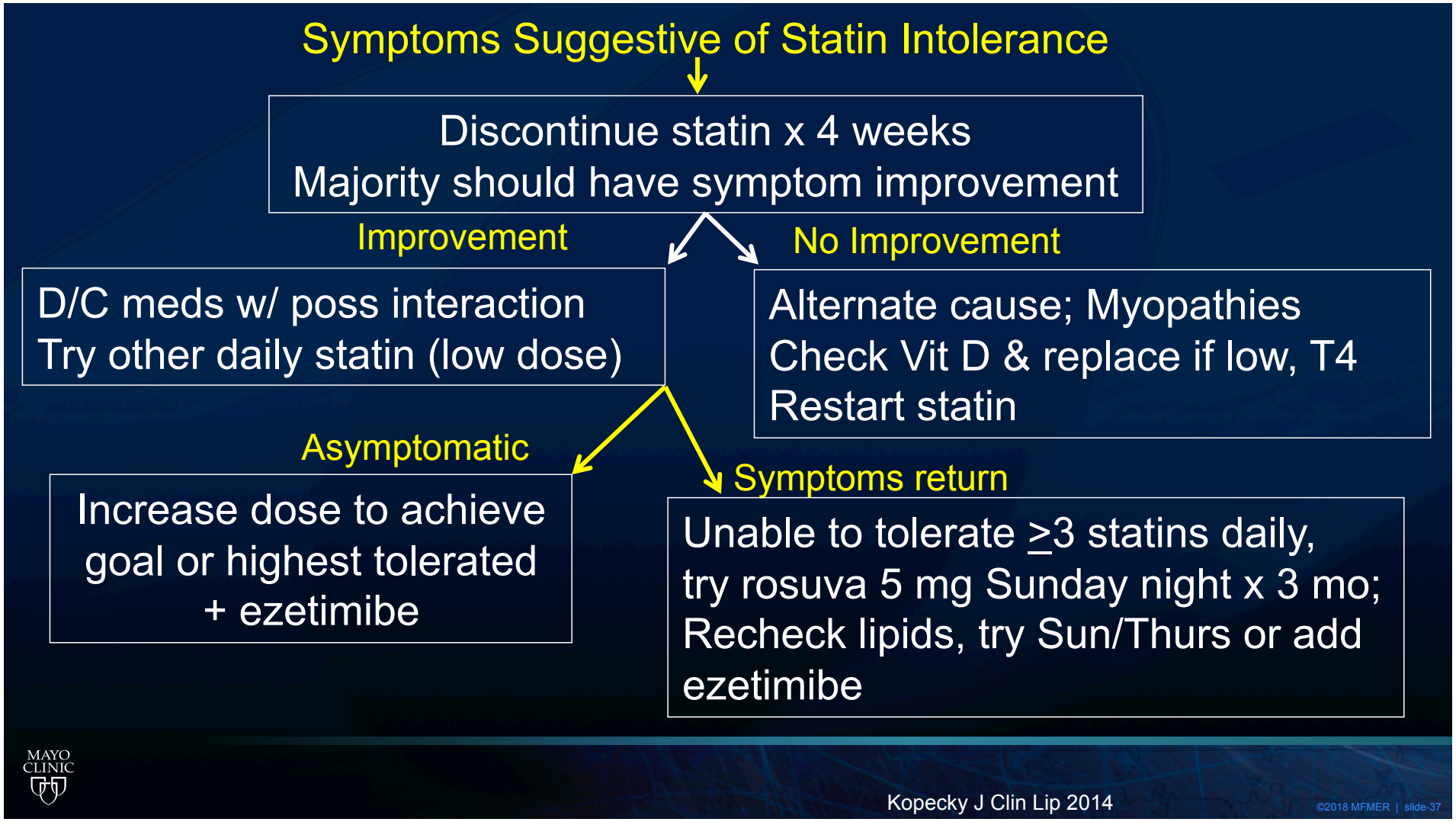

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Kopecky J Clin Lip 2014

Lipid Rx to Reduce Risk of Recurrent Events or ASCVD

1 Four Therapeutic Categories (ASCVD, LDL≥190, DM, Non-DM)
2 Determine ASCVD Risk w/ AHA/ACC Risk Estimator Plus
3 Consider Risk Enhancers, Cor Cal CT if Intermediate (5-20%) Risk
4 LDL Goals : Very Hi Risk ASCVD <70; if baseline LDL> 190, then < 100
5 Discuss Benefits & Risks, Side Effects
6 Consider drug-drug interactions
7 Try < daily dose if intolerant
8 Encourage Healthful Lifestyle & Food Patterns

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Questions & Discussion

