# Cardiovascular Disease : Identifying the Vulnerable Applying Evidence-based Prevention

Brett Nowlan, MD FACC ABCL

Non-invasive cardiologist and lipidologist - Cottage Grove Cardiology

System Director, Preventive Cardiology - Hartford Healthcare Heart and Vascular Institute

Director, Mens Cardiovascular Health - Hartford Healthcare Tallwood Institute

Assistant Professor - Frank Netter School of Medicine, Quinnipiac U.

# Summary of learning objectives

How best to predict cardiovascular risk - the ‘plaque-driven’ approach.

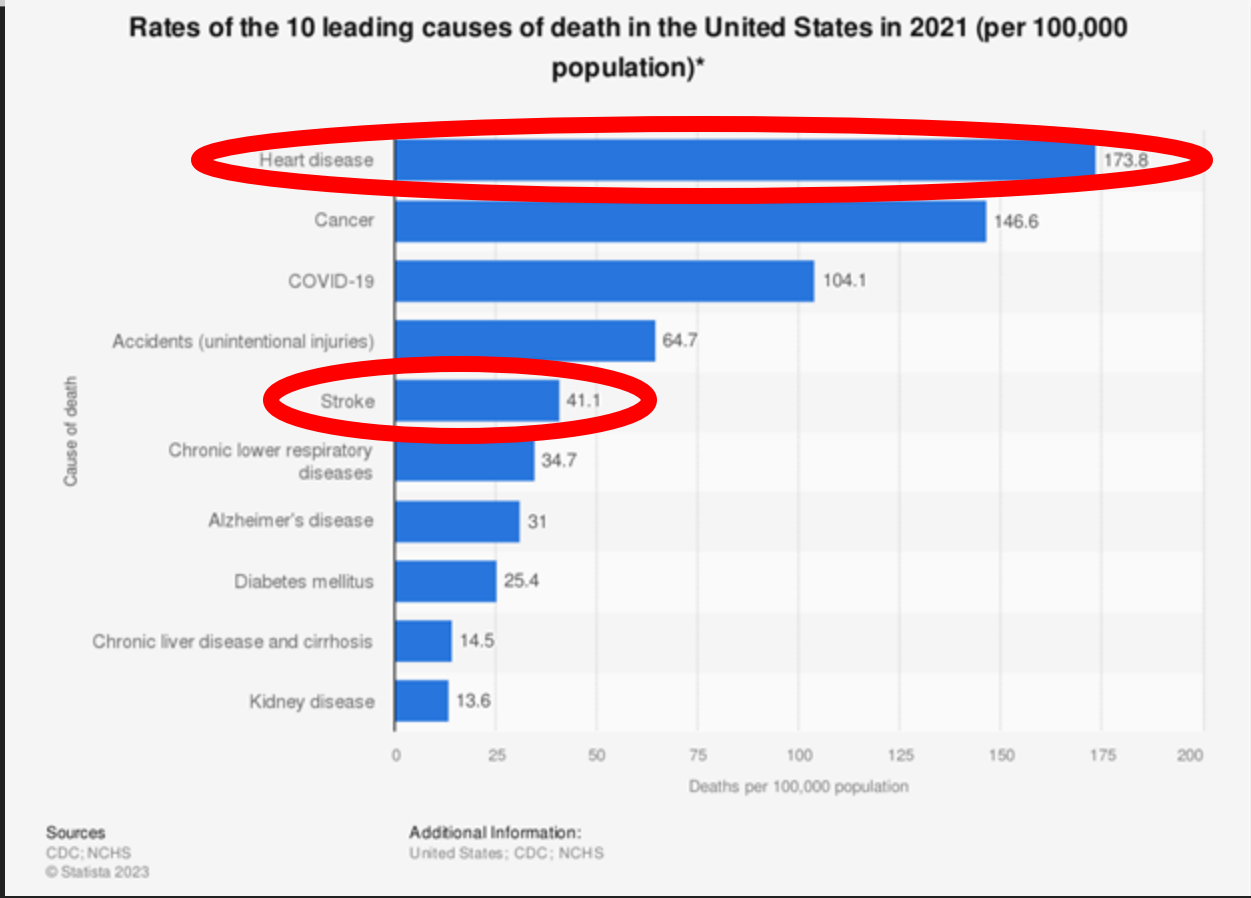
Avenues of risk reduction in 2023.

Getting to grips with dietary science pertaining to cardiovascular risk reduction.

# Deep thoughts

"Dad always thought laughter was the best medicine, which I guess is why several of us died of tuberculosis." - Jack Handy

# Cardiovascular disease is the leading cause of death



# ACC/AHA ASCVD Risk Estimator - “Pooled Cohort Equation”

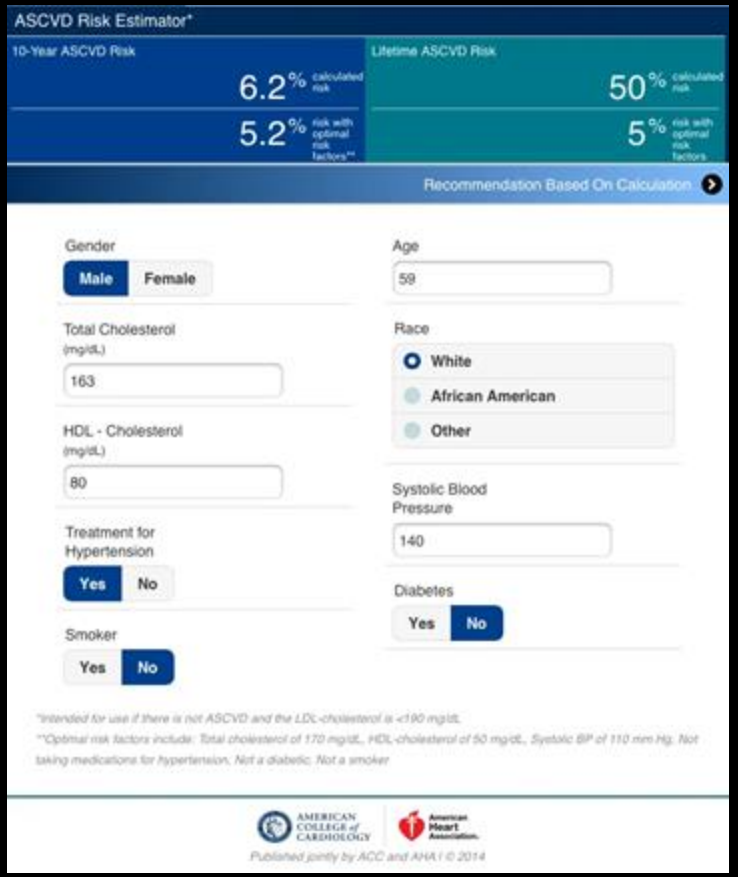



**Table 1: ASCVD Risk Enhancers**

- Family history of premature ASCVD
- Primary hypercholesterolemia
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g. preeclampsia, premature menopause)
- Chronic inflammatory conditions (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g. south Asian ancestry)

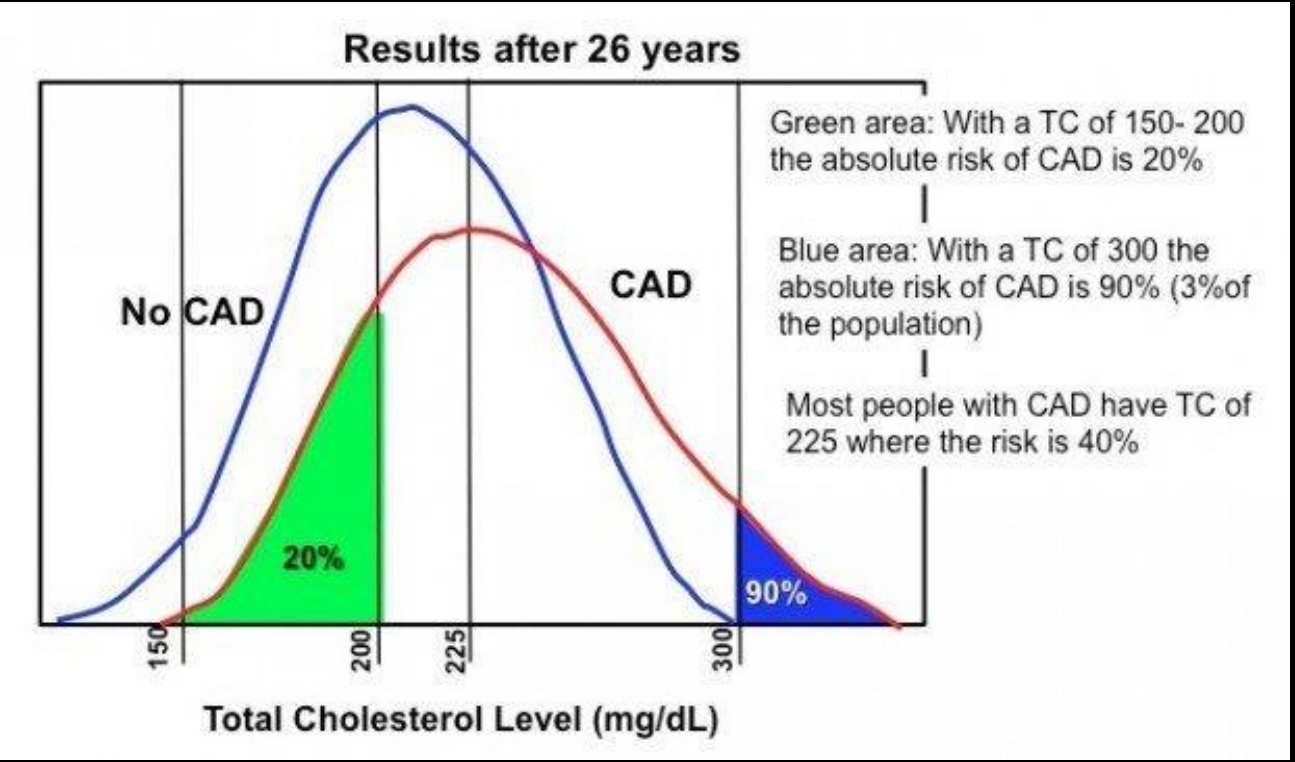
**Lipid/Biomarkers:**

- Persistently elevated triglycerides (≥175 mg/dL)

***In selected individuals if measured:***

- hsCRP ≥2 mg/L
- Lp(a) levels ≥50 mg/dL or ≥125 nmol/L
- ApoB levels ≥130 mg/dL
- Ankle-brachial index <0.9

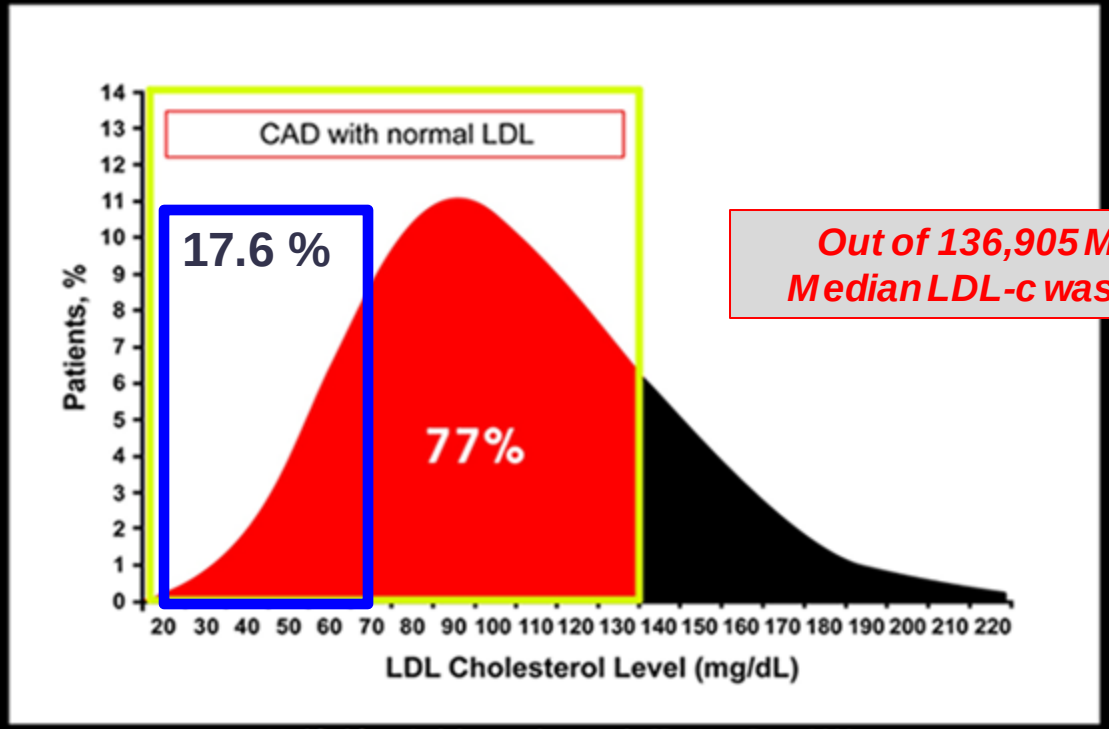
# Total cholesterol is a poor predictor




Framingham data

# LDL cholesterol is also a poor predictor

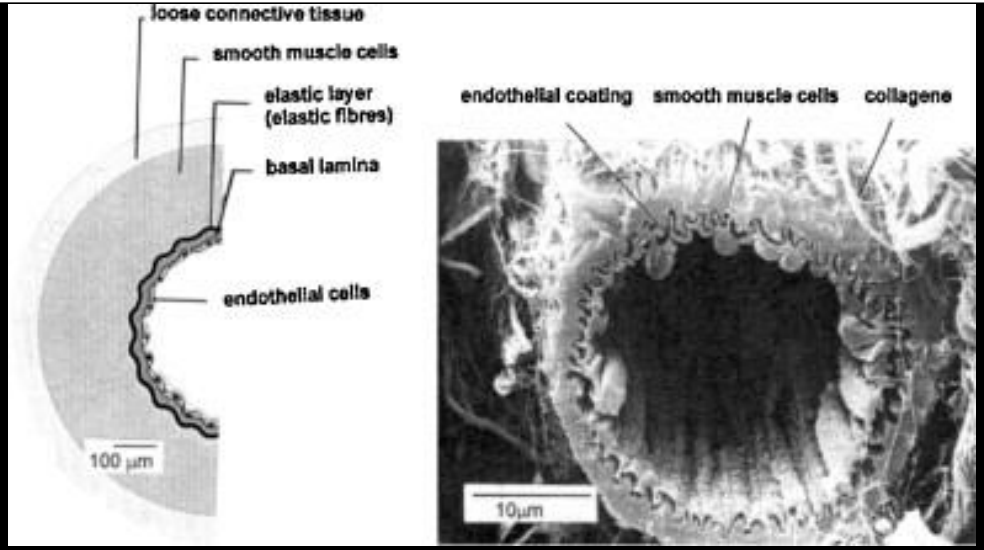
## 77% of patients with coronary artery disease have normal cholesterol

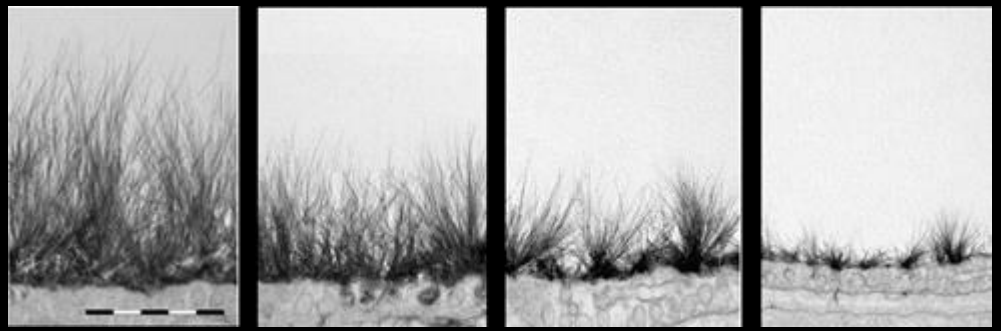


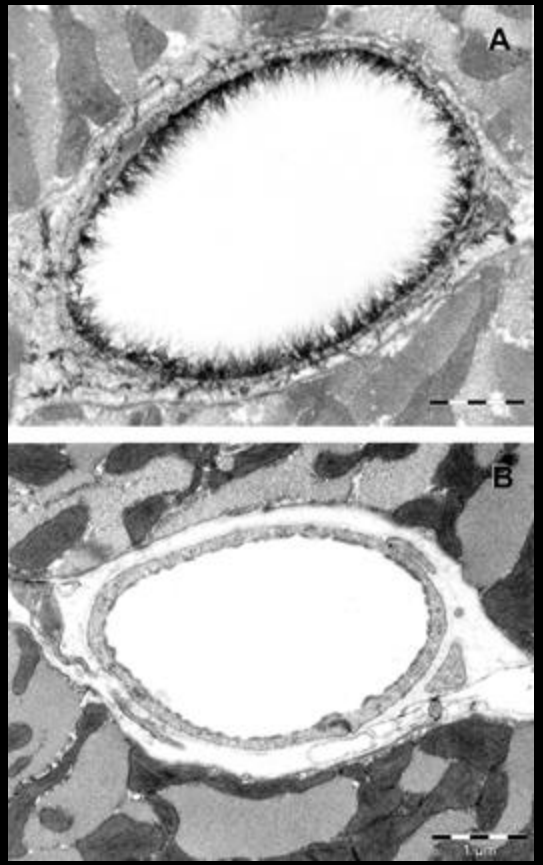

*Out of 136,905 MI patients*
*Median LDL-c was 105 mg/dL*

Modified from Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009

# We don’t understand endothelial vulnerability well





# Concept

Plaque develops as an interplay between one's biochemistry, and one's endothelial vulnerability

*We can't measure endothelial vulnerability*

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*We can't measure endothelial vulnerability*

So measure the endpoint of this interplay : **LOOK FOR PLAQUE**

# Concept

Plaque develops as an interplay between one's biochemistry, and one's endothelial vulnerability

*We can't measure endothelial vulnerability*

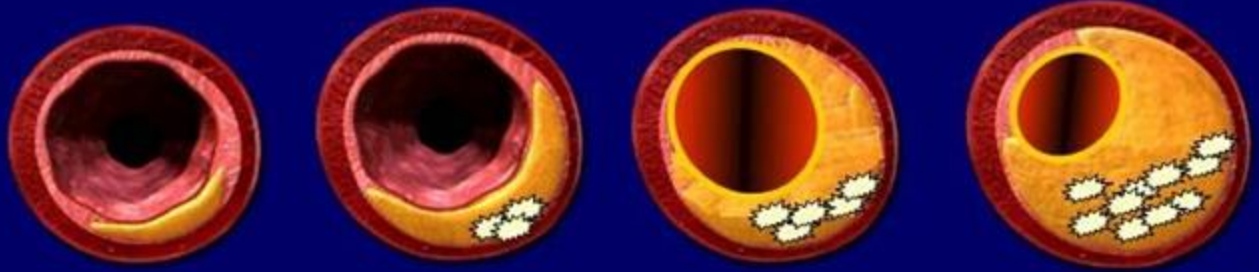
So measure the endpoint of this interplay : **LOOK FOR PLAQUE**

If there is no plaque, what are you treating? Just the numbers.

If there is plaque, you should treat, regardless of the numbers

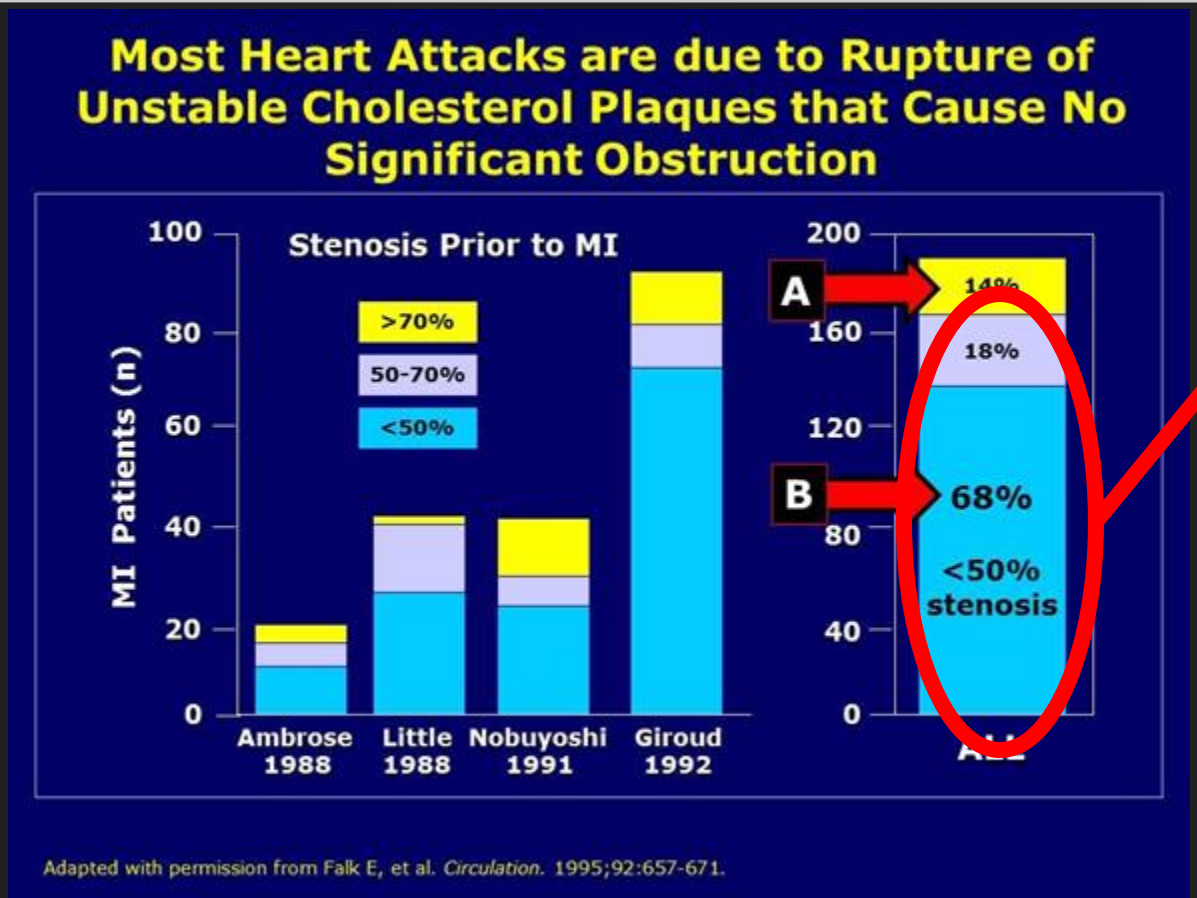
# Looking for plaque

# Symptom/stress test model looking for plaque is a LATE marker



| Stages >> | Early | Moderate | Advanced | Late |
|---|---|---|---|---|
| Obstruction | none | 20% | 50% | 70% |
| Symptoms | none | none | none | yes |
| Stress test | normal | normal | normal | abnormal |

# Late markers are often, well, late…




**86%** of plaque leading to MI *undetectable* by stress testing

# USA Statistics using this paradigm

805,000 suffer an MI yearly (605,000 are a first heart attack)

About **400,000 are fatal**
About **200,000 are fatal within the first 1 hour of symptom onset**

About 150,000 are silent

*2022 AHA Heart and Stroke Statistics*：
**356,000 out of hospital cardiac arrests; 90% are fatal**

# Deep thoughts

"To me, boxing is like a ballet, except there's no music, no choreography, and the dancers hit each other." - Jack Handy

# The ‘Plaque-driven’ approach

1) Start by looking for plaque, with the *correct tools.*

# So what is the best screen for plaque in asymptomatic people?

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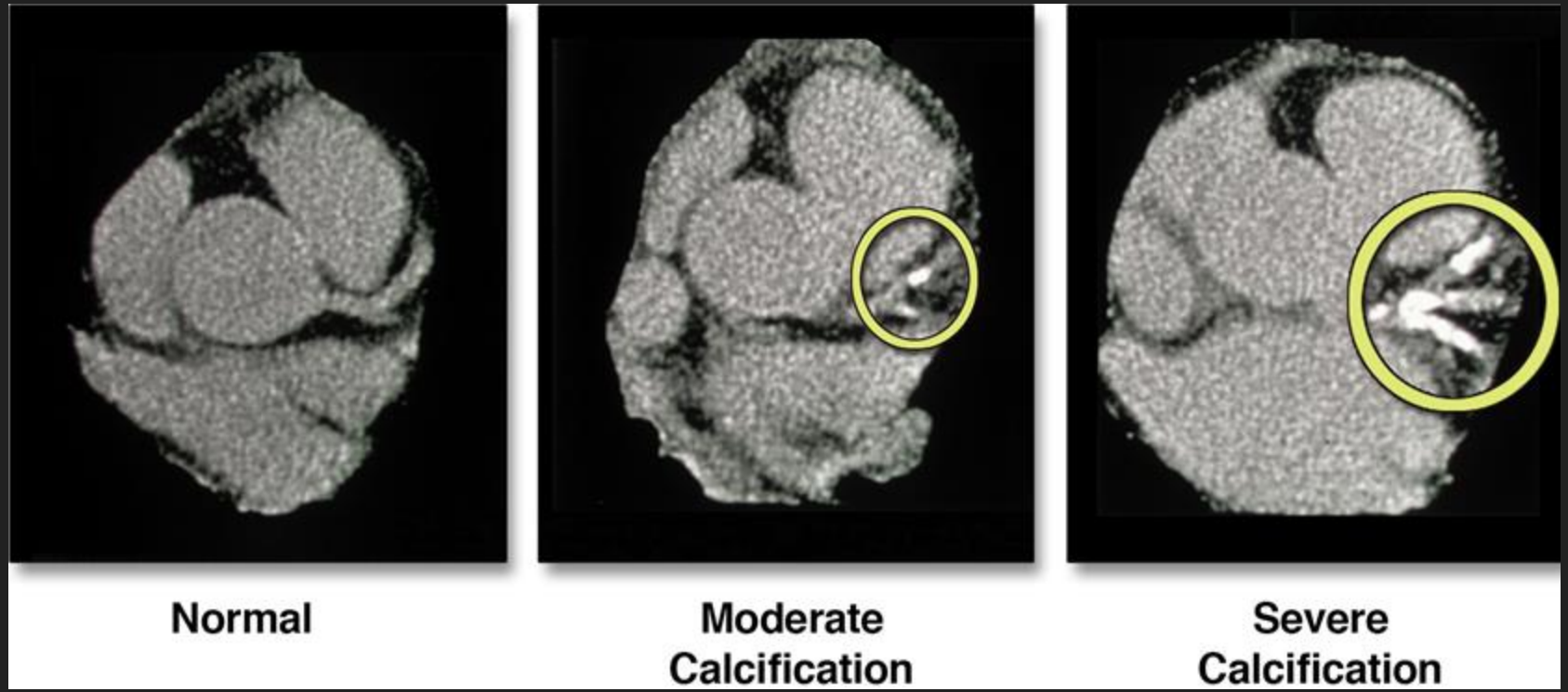
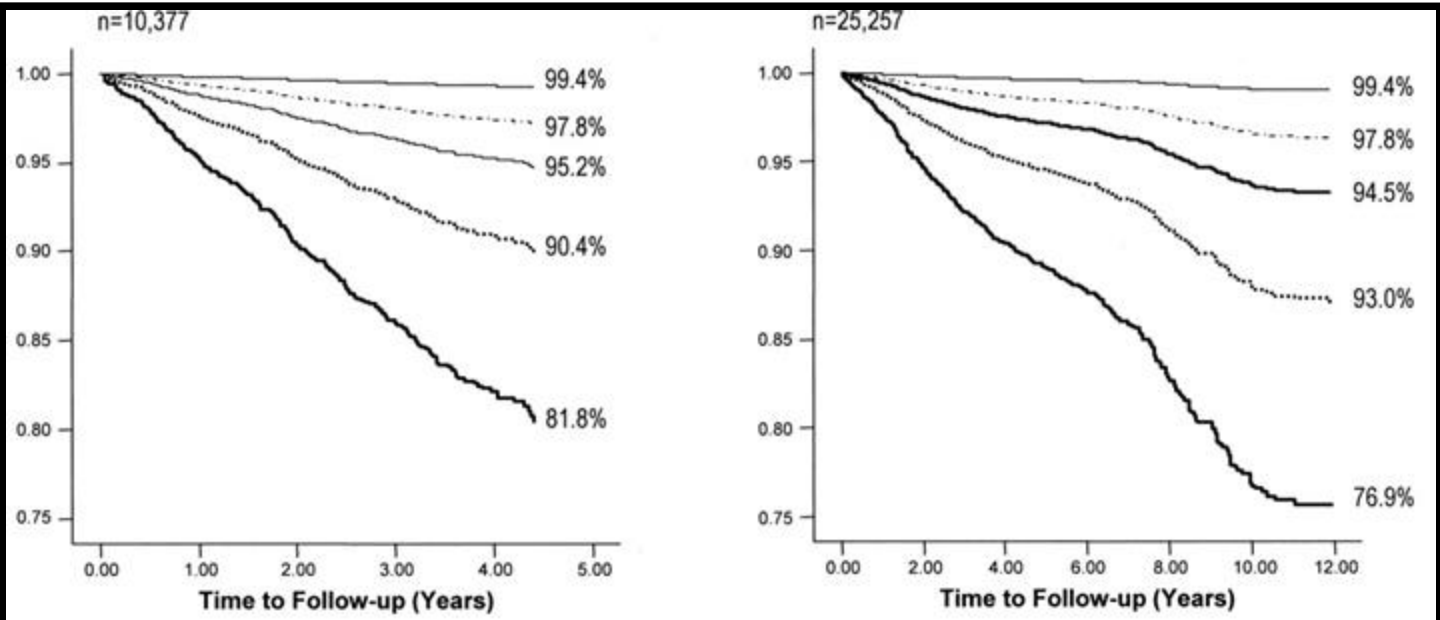
**Coronary calcium scan.**



# Coronary calcium scan

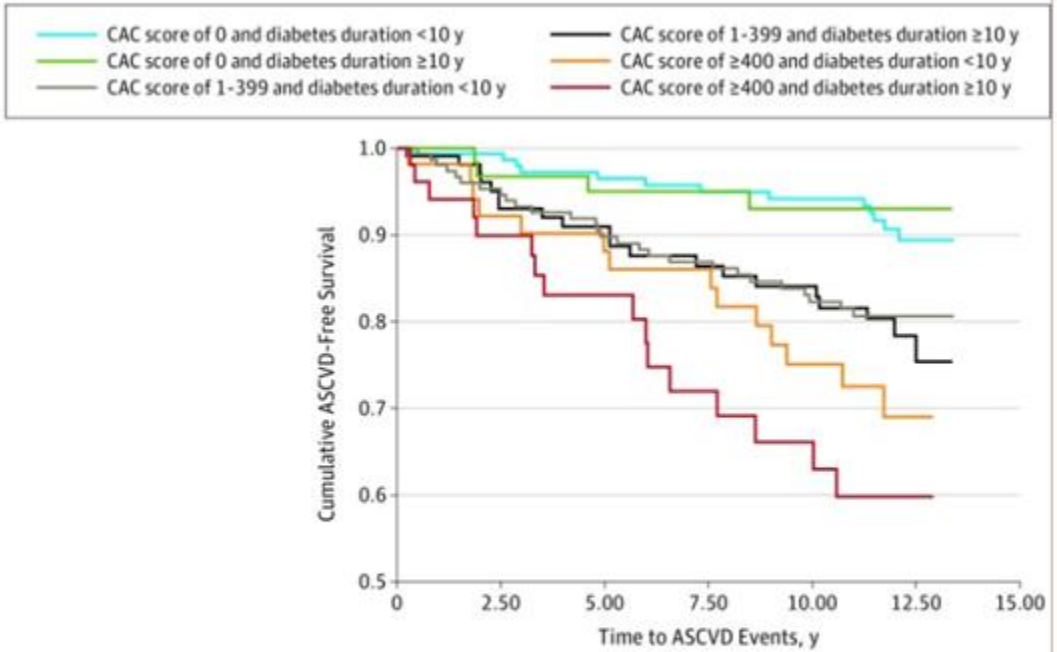



| CAC Score | (5 Yr Mortality = 1.2%) | (12-Yr Mortality = 2.1%) | Difference |
|---|---|---|---|
| 0-10 | 99.4% | 99.4% | 0.0% |
| 11-100 | 97.8% | 97.8% | 0.0% |
| 101-400 | 95.2% | 94.5% | 0.7% |
| 401-1,000 | 90.4% | 93.0% | 0.6% |
| >1,000 | 81.8% | 76.9% | 4.9% |

Budoff MJ et al; J Am Coll Cardiol 2007; 49 : 1860 - 1870

# CAC in diabetics

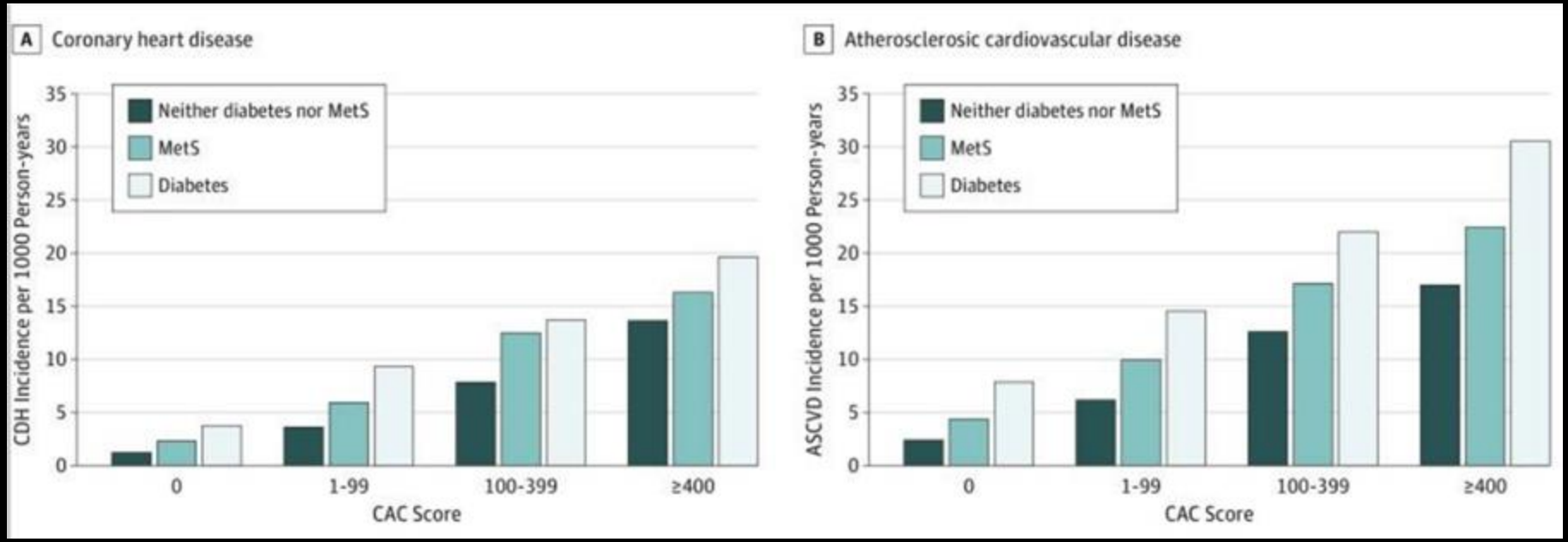
B Atherosclerotic cardiovascular disease




No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| CAC score of 0 and diabetes duration <10 y | 151 | 142 | 130 | 120 | 117 | 45 |
| CAC score of 0 and diabetes duration ≥10 y | 64 | 59 | 53 | 51 | 46 | 14 |
| CAC score of 1-399 and diabetes duration <10 y | 149 | 139 | 125 | 117 | 103 | 33 |
| CAC score of 1-399 and diabetes duration ≥10 y | 105 | 92 | 81 | 74 | 68 | 25 |
| CAC score of ≥400 and diabetes duration <10 y | 54 | 46 | 42 | 40 | 32 | 10 |
| CAC score of ≥400 and diabetes duration ≥10 y | 52 | 41 | 35 | 26 | 21 | 7 |

# CAC in diabetics




JAMA Cardiol. 2017 Dec; 2(12): 1332–1340.
Published online 2017 Nov 8. doi: 10.1001/jamacardio.2017.4191
PMCID: PMC5814996
NIHMSID: NIHMS946128
PMID: 29117273

Coronary Artery Calcium Score for Long-term Risk Classification in Individuals With Type 2 Diabetes and Metabolic Syndrome From the Multi-Ethnic Study of Atherosclerosis

Shaista Malik, MD, PhD, MPH,[1,2] Yanglu Zhao, MD, MS,[3] Matthew Budoff, MD,[4] Khurram Nasir, MD,[5,6] Roger S. Blumenthal, MD,[6] Alain G. Bertoni, MD, MPH,[7] and Nathan D. Wong, PhD, MPH[1]

# c-statistic

Concordance-statistic

Is equal to the area under a ROC (Receiver Operating Characteristic) curve; in clinical studies the c-statistic gives the probability a randomly selected patient who experienced an event had a higher risk score than a patient who had not experienced the event.

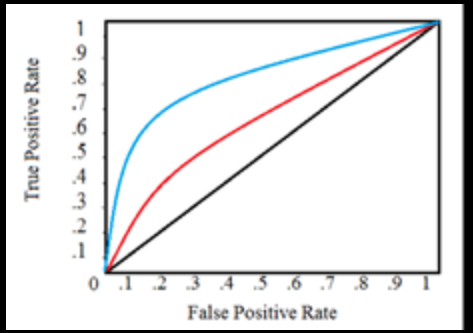
Ranges from 0.5 (completely random) to 1.0 (perfect risk prediction)

(IF CI includes 0.5, c-statistic is *not* significant)

*Rough rule* : **>0.80** **very good/strong models**

0.70-0.80 good models

**<0.70** **weak models**

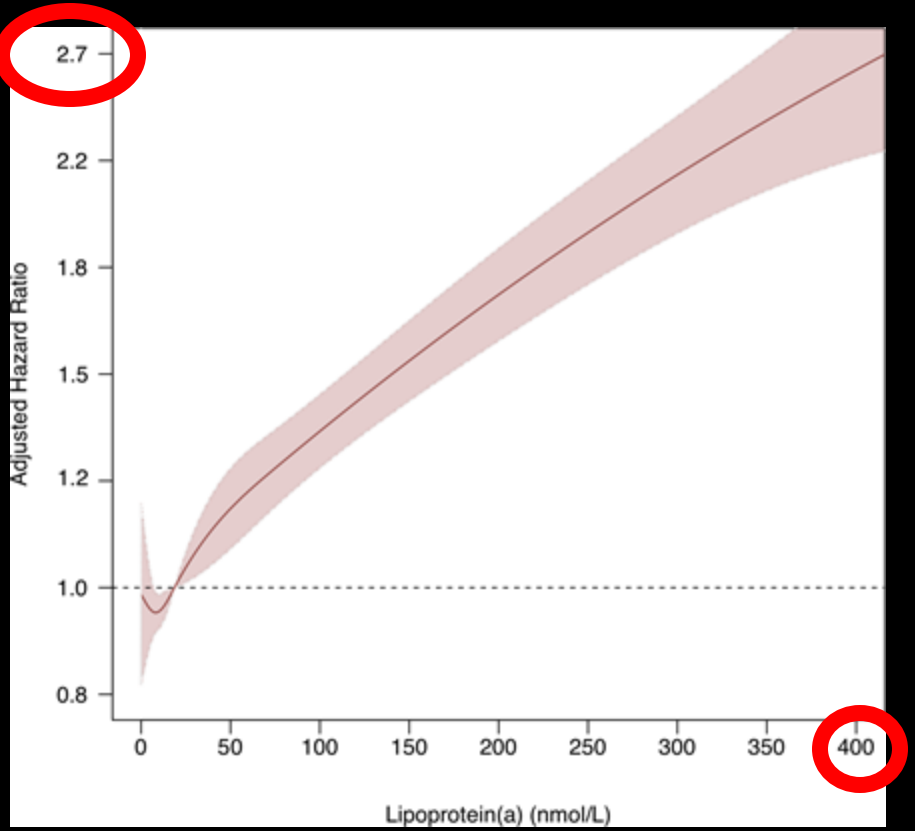


# Adding markers to risk prediction

For a binary risk marker considered in isolation, a univariate odds ratio of **9.0 or greater** would be required for excellent discrimination of cases from noncases.

When the marker is considered in the context of preexisting risk factors or a risk score, multivariable ("independent") odds ratios **in excess of 3.0** for the marker would typically be required to increase the c-statistic by an **additional 5%** or more.

# What helps risk prediction?




Lipoprotein (a)

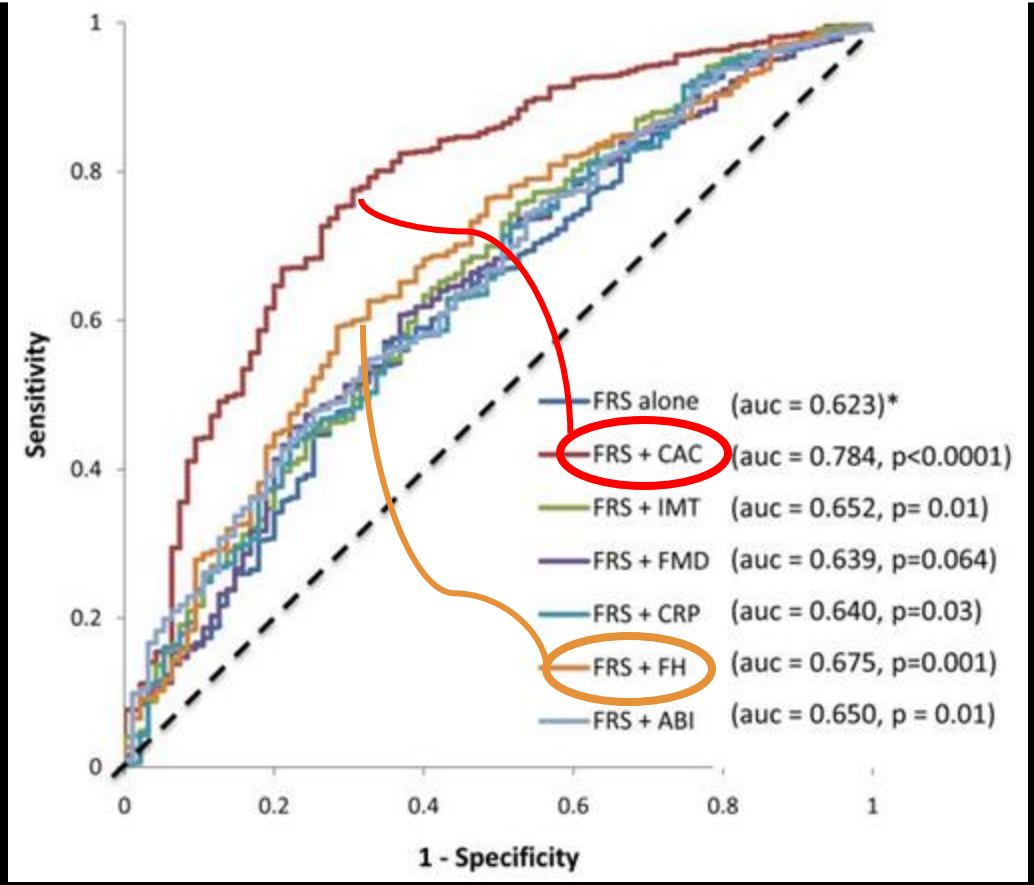
Phoebe Finneran. Journal of the American Heart Association. Lipoprotein(a) and Coronary Artery Disease Risk Without a Family History of Heart Disease, Volume: 10, Issue: 5, DOI: (10.1161/JAHA.120.017470) Feb 2021

# What helps risk prediction?

**Association of Risk Markers With Incident Coronary Heart Disease***

| Risk marker | Hazard ratio (95% CI) |
|---|---|
| Ankle-brachial index | 0.79 (0.66–0.96) |
| Brachial flow-mediated dilation | 0.93 (0.74–1.16) |
| Coronary artery calcium | 2.60 (1.94–3.50) |
| Carotid intima-media thickness | 1.17 (0.96–1.45) |
| Family history | 2.18 (1.38–3.42) |
| High-sensitivity CRP | 1.28 (1.00–1.64) |

# C-statistic of the coronary calcium scan




Almeida et al; Therapeutic Lipidology 16 Dec 2020; 585-603

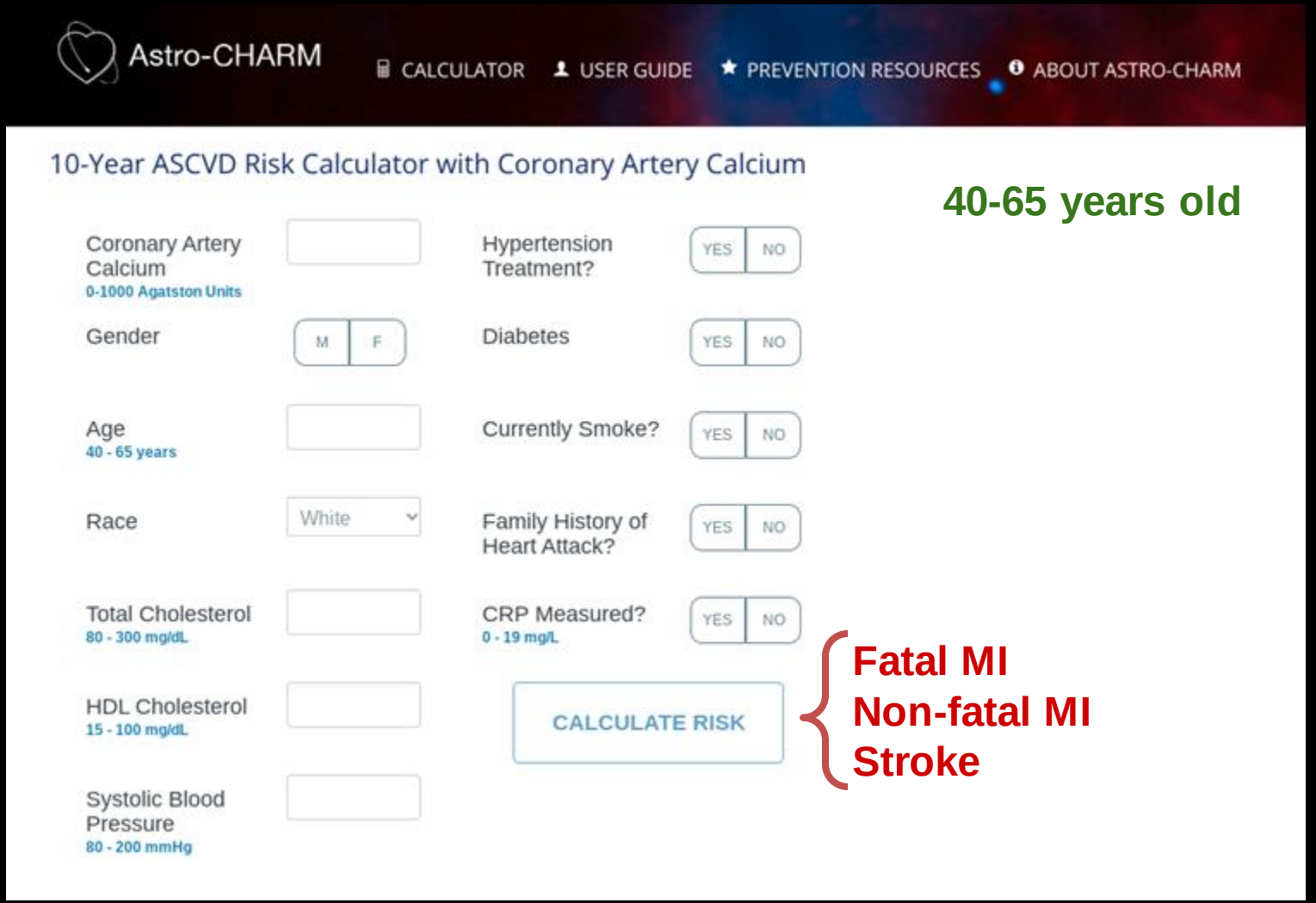
# Astro-CHARM

"Astronaut Cardiovascular Health and Risk Modification"

Stimulated by the National Aeronautics and Space Admin, for astronaut population
First ASCVD risk calculator to incorporate risk factors (incl hs-CRP) and CAC data

| | | |
|---|---|---|
| Risk-factor model c-statistic | 0.784 | |
| Astro-CHARM c-statistic | **0.817** | (p<0.0001) |

Khera, Budoff et al Circulation. 2018;138:1819-1827

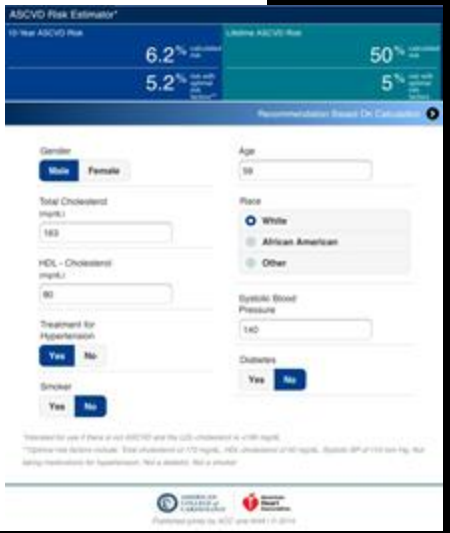

Astro-CHARM
CALCULATOR
USER GUIDE
PREVENTION RESOURCES
ABOUT ASTRO-CHARM
10-Year ASCVD Risk Calculator with Coronary Artery Calcium
Coronary Artery Calcium
0-1000 Agatston Units
Gender
M
F
Age
40 - 65 years
Race
White
Total Cholesterol
80 - 300 mg/dL
HDL Cholesterol
15 - 100 mg/dL
Systolic Blood Pressure
80 - 200 mmHg
Hypertension Treatment?
YES
NO
Diabetes
YES
NO
Currently Smoke?
YES
NO
Family History of Heart Attack?
YES
NO
CRP Measured?
0 - 19 mg/L
YES
NO
CALCULATE RISK
40-65 years old
Fatal MI
Non-fatal MI
Stroke

Astro-CHARM

CALCULATOR | USER GUIDE | PREVENTION RESOURCES | ABOUT ASTRO-CHARM

## 10-Year ASCVD Risk Calculator with Coronary Artery Calcium

| | | | |
|---|---|---|---|
| Coronary Artery Calcium<br>0-1000 Agatston Units | | Hypertension Treatment? | YES / NO |
| Gender | M / F | Diabetes | YES / NO |
| Age<br>40 - 65 years | | Currently Smoke? | YES / NO |
| Race | White | Family History of Heart Attack? | YES / NO |
| Total Cholesterol<br>80 - 300 mg/dL | | CRP Measured?<br>0 - 19 mg/L | YES / NO |
| HDL Cholesterol<br>15 - 100 mg/dL | | CALCULATE RISK | |
| Systolic Blood Pressure<br>80 - 200 mmHg | | | |



MESA The Multi-Ethnic Study of Atherosclerosis

## MESA 10-Year CHD Risk with Coronary Artery Calcification

Back to CAC Tools

**66-85 years old**

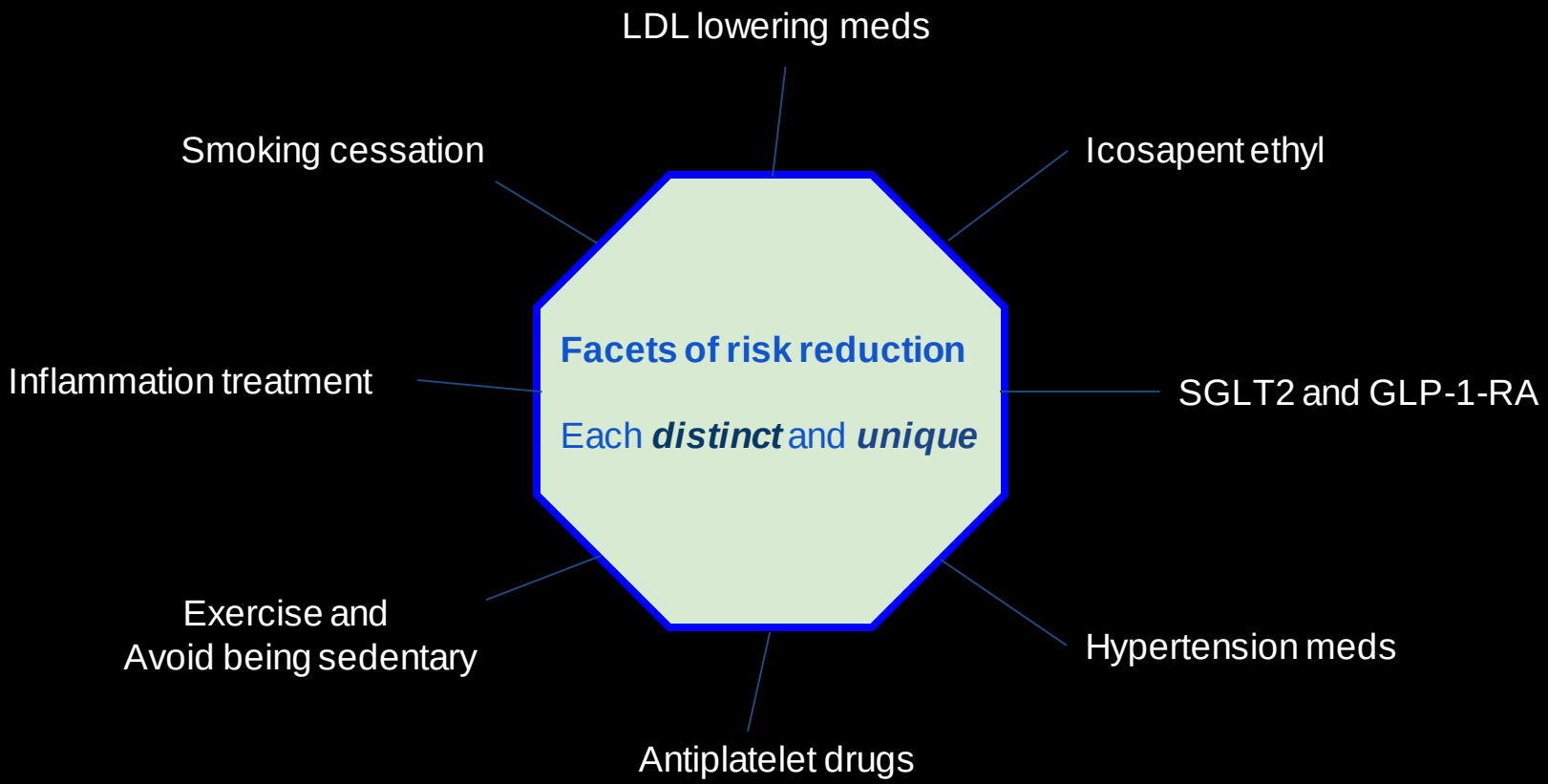
| | | | | | | |
|---|---|---|---|---|---|---|
| **1. Gender** | Male ○ | Female ○ | | | | |
| **2. Age (45-85 years)** | | Years | | | | |
| **3. Coronary Artery Calcification** | | Agatston | | | | |
| **4. Race/Ethnicity** | **Choose One** | | | | | |
| | Caucasian ○ | | | | | |
| | Chinese ○ | | | | | |
| | African American ○ | | | | | |
| | Hispanic ○ | | | | | |
| **5. Diabetes** | Yes ○ | No ○ | | | | |
| **6. Currently Smoke** | Yes ○ | No ○ | | | | |
| **7. Family History of Heart Attack** (History in parents, siblings, or children) | Yes ○ | No ○ | | | | |
| **8. Total Cholesterol** | | mg/dL | or | | mmol/L | |
| **9. HDL Cholesterol** | | mg/dL | or | | mmol/L | |
| **10. Systolic Blood Pressure** | | mmHg | or | | kPa | |
| **11. Lipid Lowering Medication** | Yes ○ | No ○ | | | | |
| **12. Hypertension Medication** | Yes ○ | No ○ | | | | |

Calculate 10-year CHD risk

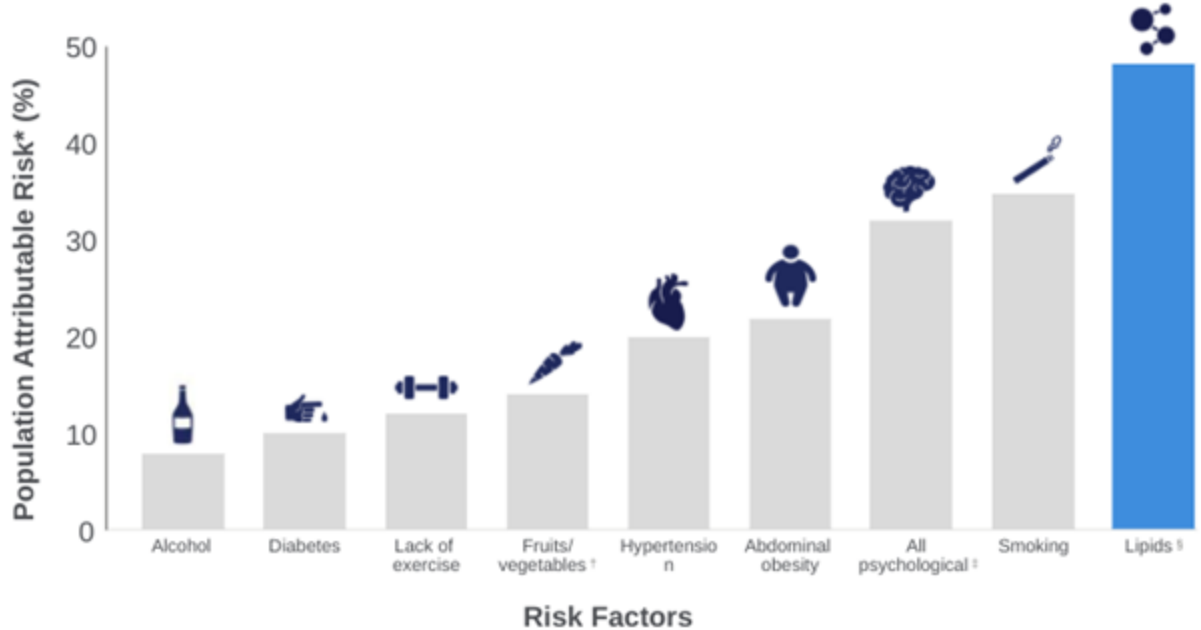
**CHD event**

# Concept

If you have plaque - **HAMMER EVERYTHING**


LDL lowering meds
Smoking cessation
Icosapent ethyl
Facets of risk reduction
Each distinct and unique
Inflammation treatment
SGLT2 and GLP-1-RA
Exercise and
Avoid being sedentary
Hypertension meds
Antiplatelet drugs

# Dyslipidemia is the most important risk factor for an MI




INTERHEART: A case control study designed to assess the importance of nine modifiable risk factors in MI in 52 countries. 15,152 cases and 14,820 controls were enrolled. Data above is based on population attributable risk data in men and women, adjusted for all risk factors.[1]

*Population attributable risk indicates the number or proportion of cases that would not occur in a population if the risk factor were eliminated.[2]

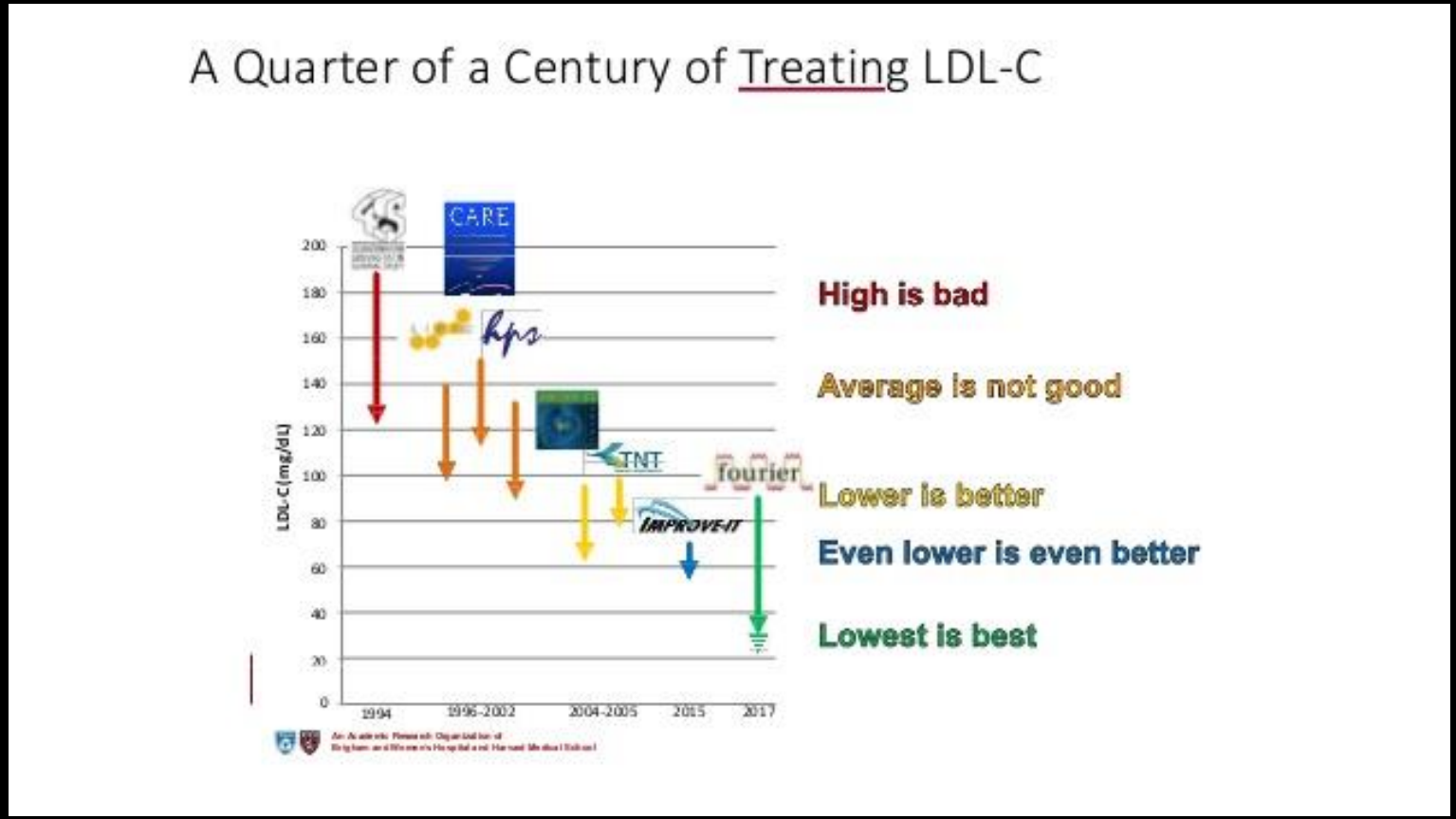
†Irregular consumption of fruits and vegetables.[1]

‡A model-dependent index combining positive exposure to depression, perceived stress at home or work (general stress), low focus of control, and major life events, all referenced against nonexposure for all 5 factors.

§ApoB/ApoA1 ratio[1]

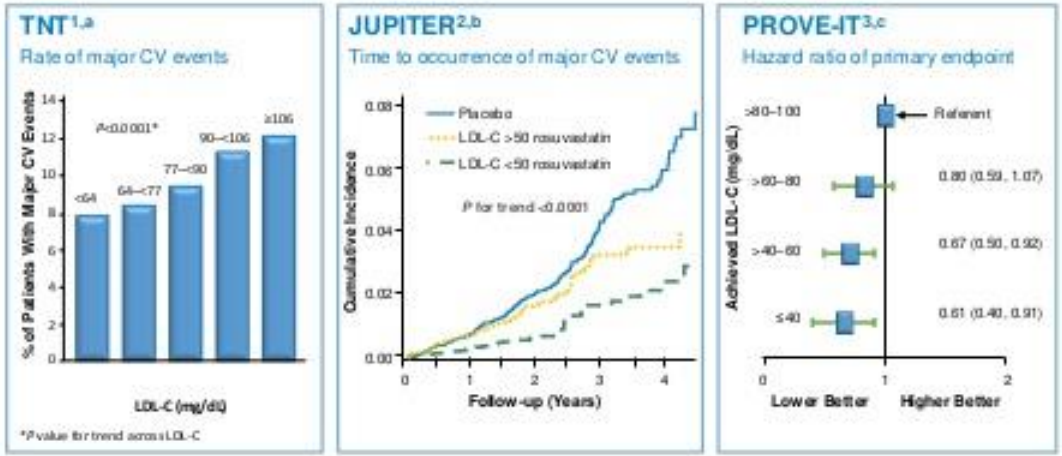
1. Yusuf S, et al. *Lancet*. 2004;364:937-952. 2. Rockhill B, et al. *Am J Public Health*. 1998;88:15-19

# Trials have shown progressive benefit with lower LDL-c



# Lower LDL-c WITHIN trials show progressive benefit

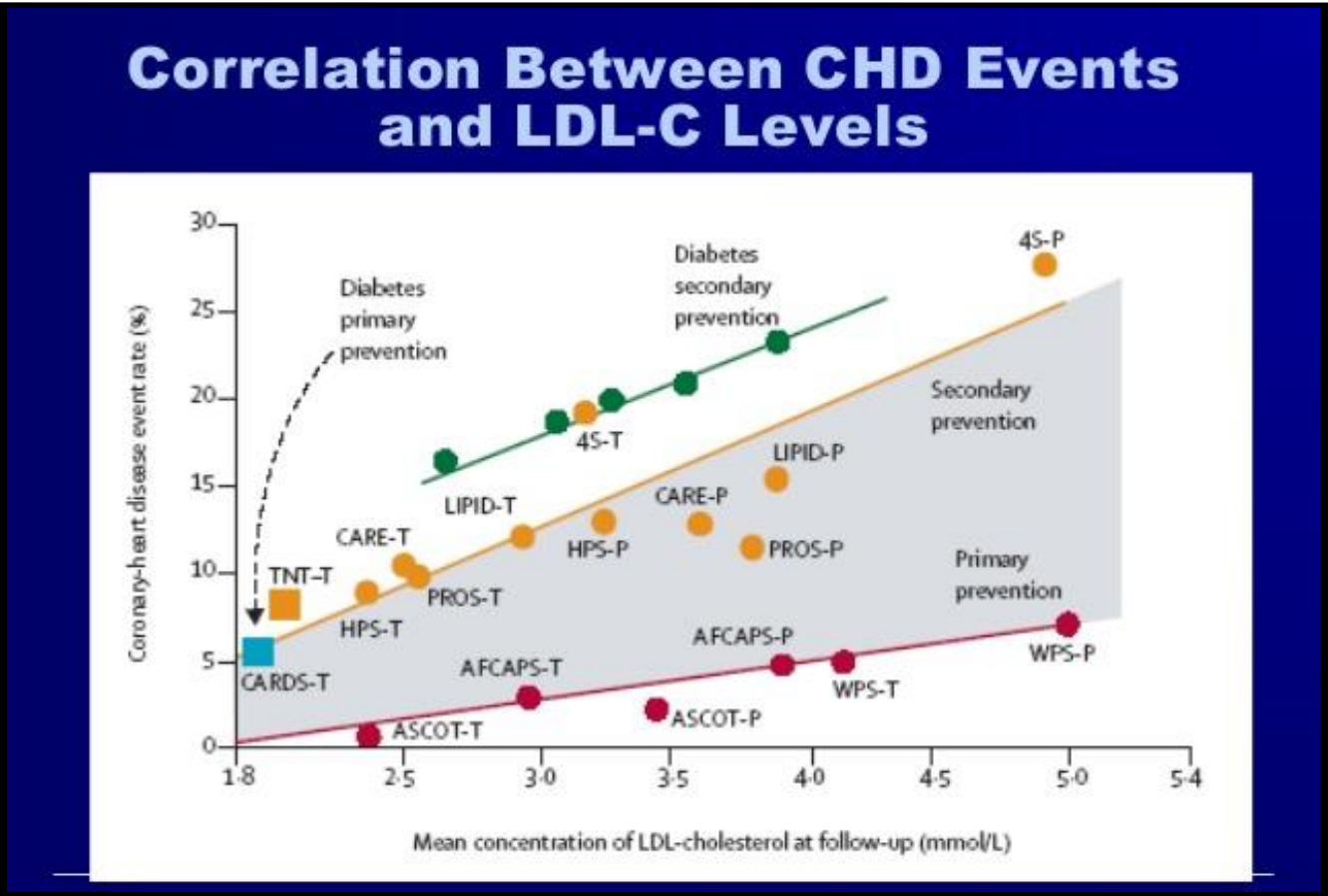
## The lower the LDL-C achieved, the lower the risk of CV events




[a]RCT in patients with stable coronary disease. Major CV Events = death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke. [b]RCT of patients with LDL-C <130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, and no history of CVD or diabetes mellitus. Major CV events = CV death, MI, stroke, arterial revascularization, or hospitalized UA. [c]post randomization LDL-C [c]RCT patients with stabilized ACS. Primary composite endpoint of death, MI, stroke, revascularization, and UA requiring hospitalization.
ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RCT, randomized controlled trial; UA, unstable angina.


1. LaRosa JC, et al. J Am Coll Cardiol 2007;100:747–52.
2. Hsia J, et al. J Am Coll Cardiol 2011;57:1666–75.
3. Wiviott SD, et al. J Am Coll Cardiol 2005;46:1411–6.

# Trials have shown progressive benefit with lower LDL-c



# Statins for LDL-c lowering

Cholesterol Treatment Trialists Collaborators
Meta-analysis of 27 randomised trials; n=134,537; Lancet 2010

For every **38 mg/dL** reduction in LDL with statins :

***10% reduction*** in any cause of death

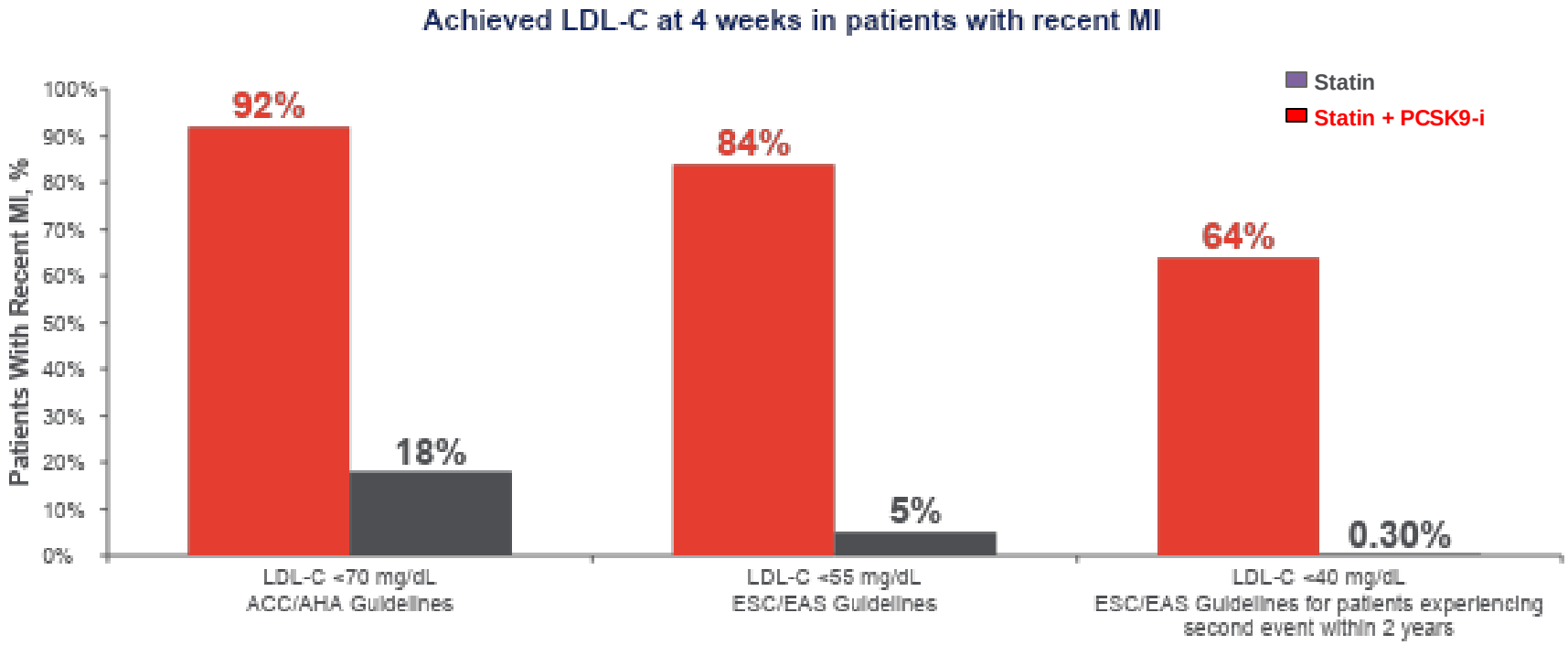
***14% reduction*** in any vascular death

***15% reduction*** in stroke

***21% reduction*** in any major vascular event

***24% reduction*** in any major cardiac event

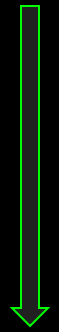
# How effective is statin monotherapy?




1. Grundy SM, et al. *Circulation*. 1999;100:1481-1492. 2. Mach F, et al. *Eur Heart J*. 2020;41:111-188. 3. Gencer B, et al. *JAMA Cardiol*. 2020 May 20. [Epub ahead of print.]

# Lowering LDL cholesterol

Statins
Ezetimibe
Bempedoic acid
PCSK9 Mab



PROVEN BENEFIT

PCSK9 siRNA

UNPROVEN BENEFIT

WITH DIET

?

# Understanding Nutrition Data

*This is the basis of most dietary recommendations :*

“Total cholesterol has been observed to be associated with higher CVD incidence.”

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“Eating fat, particularly saturated fat, has been observed to raise total cholesterol.”

# Understanding Nutrition Data

*This is the basis of the recommendation :*

“Total cholesterol has been observed to be associated with higher CVD incidence.”

“Eating fat, particularly saturated fat, has been observed to raise total cholesterol.”

“Surely eating less fat, to modify your total cholesterol, should modify CVD incidence.”

# Understanding Nutrition Data

Most dietary ‘evidence’ is based on prospective cohort data, not randomized trials.

*Summary of pitfalls of prospective cohort nutrition data :*

**Discusses correlation, not causation**

**Uses highly error-prone FFQ or 24-hr recall patient data**

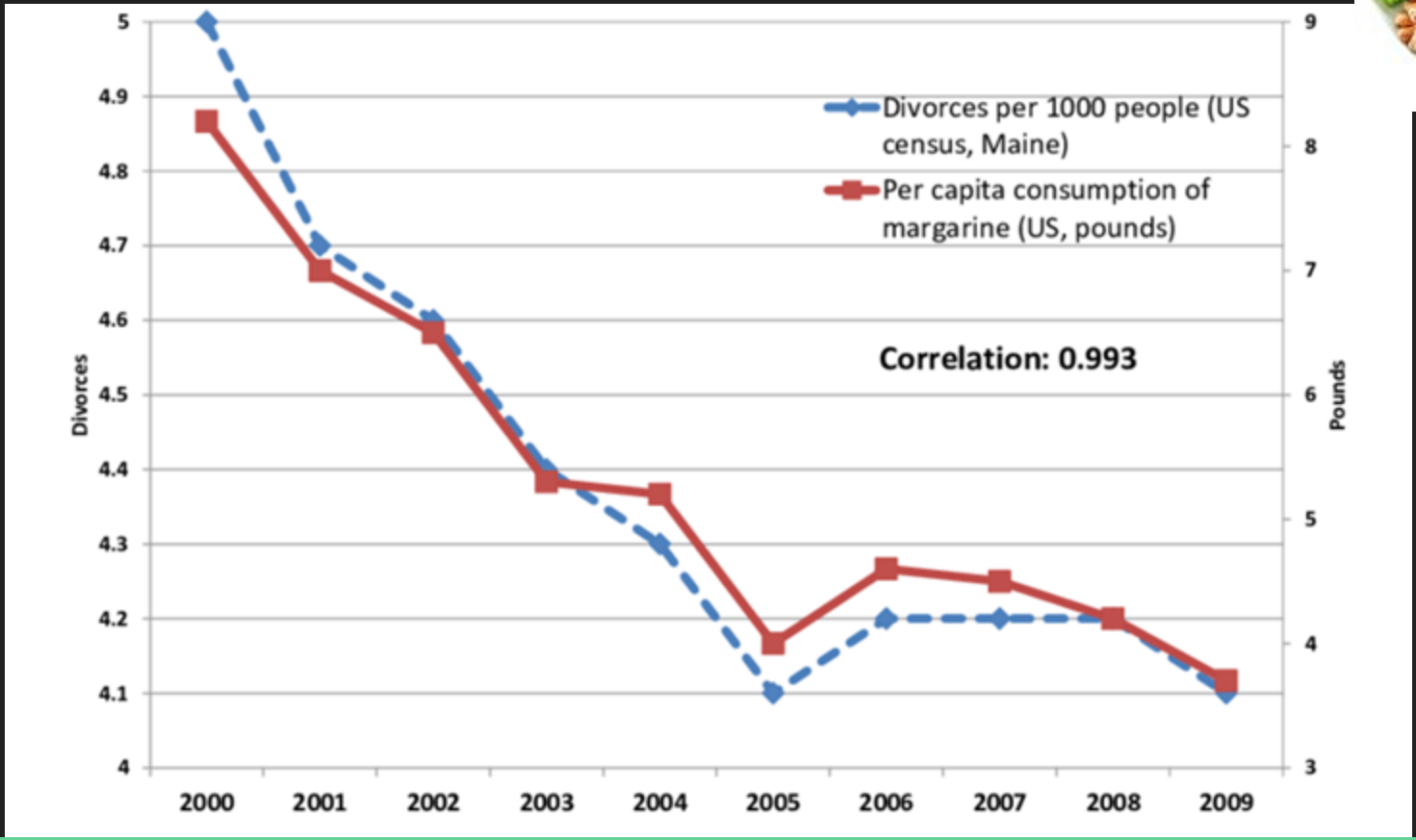
**Uses surrogates of outcomes (like LDL-c) frequently, not actual outcomes**

# Understanding Nutrition Data

Correlation is NOT causation.
Correlation is NOT definitive evidence. It is hypothesis-generating.
Correlation is prone to bias. If you draw enough statistical lines...

This is why we demand randomized control trials for medications.

# Understanding Nutrition Data - Correlation



# Example of observational vs randomized data

**HRT**

- ↓Total cholesterol
- ↓LDL cholesterol
- ↑HDL

- Observational studies suggest a 30-50% reduction in CVD amongst HRT users
- A meta-analysis of observational studies found a relative risk of CVD of 0.8 in women taking HRT compared with controls

*(Beral et al 2002)*

**WHI Study**

- ↑ risk of CVD seen in combined arm compared to placebo (HR 1.29, 1.02-1.63)

- Incidence of stroke increased in both combined HRT group (HR .131) and oestrogen only group (HR 1.39) of WHI Study
- Recent meta-analysis found ↑ risk of stroke, particularly ischaemic stroke with current HRT use (total stroke OR 1.29, 1.13-1.47) *(Bath & Gray 2005)*
- Do not forget risk of thromboembolism

# How are details about diets actually obtained?

## Food Frequency Questionnaires :

Total calorie intake underreported by a median of **30-40%**
Total protein intake underreported by a median of **30%**

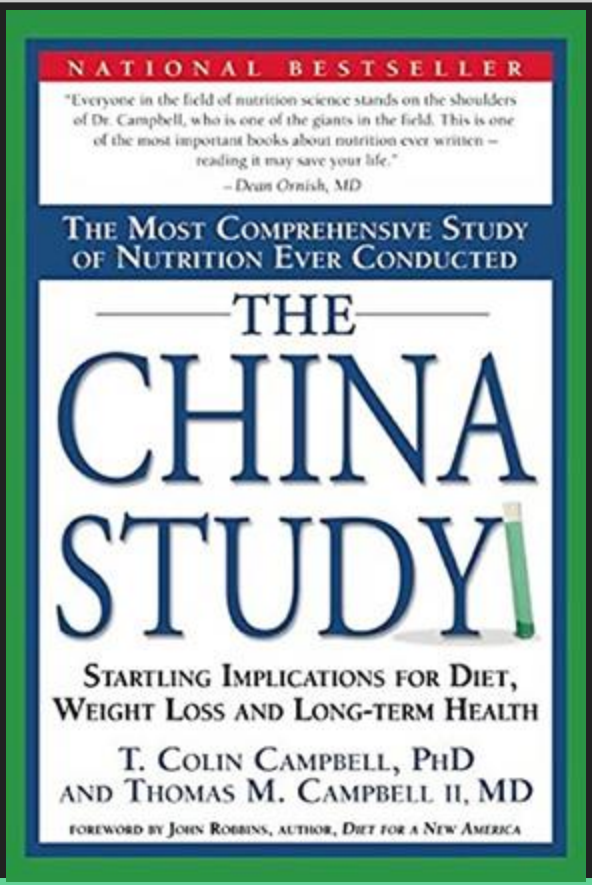
True RR of **2.0 : Reported RR of** **1.24-1.33**

True RR of **1.0 : Reported RR of** **1.30-1.40**

# Food Frequency Questionnaires

If any FFQ-based nutritional observational study reports a hazard ratio up to **1.40**,
this falls within the reporting error of that FFQ.

# Understanding Nutrition Data - Correlation




6,500 adults in rural China
3 days of dietary data collected (1983)
Mortality rates documented (from 1973-1975)

**8,000** *statistically* significant associations

# Not all cholesterol lowering is beneficial

The data for SPECIFIC MEDICATION LOWERING is clear...
The data for ANY CHOLESTEROL LOWERING is not...

- ⬇Total cholesterol
- ⬇LDL cholesterol
- ⬇Triglycerides
- ⬇Glucose
- ⬇BMI

→ ?

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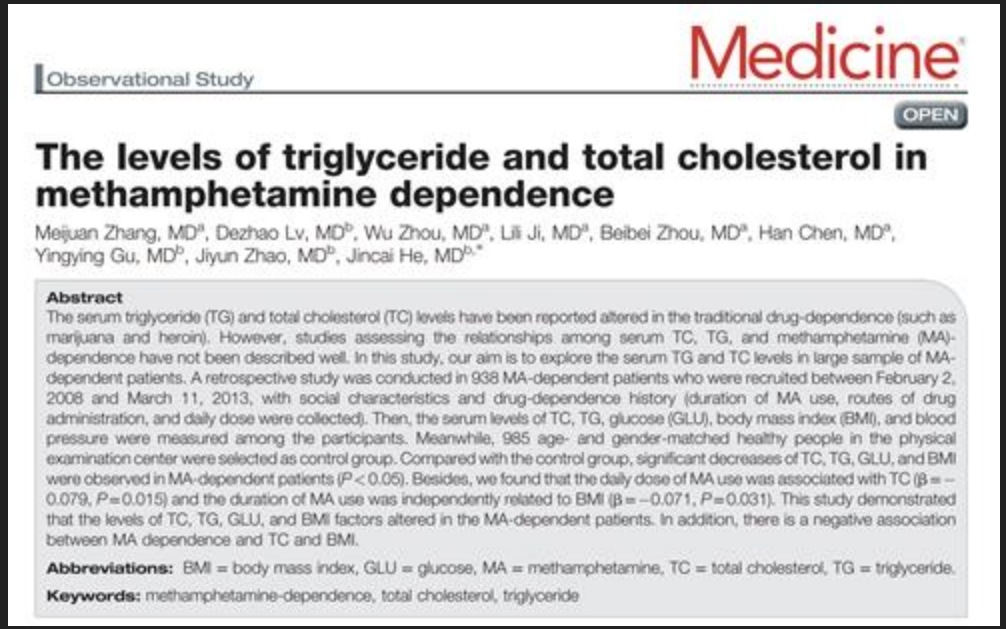


Observational Study

Medicine

OPEN

## The levels of triglyceride and total cholesterol in methamphetamine dependence

Meijuan Zhang, MD[a], Dezhao Lv, MD[b], Wu Zhou, MD[a], Lili Ji, MD[a], Beibei Zhou, MD[a], Han Chen, MD[a], Yingying Gu, MD[b], Jiyun Zhao, MD[b], Jincai He, MD[b,*]

**Abstract**

The serum triglyceride (TG) and total cholesterol (TC) levels have been reported altered in the traditional drug-dependence (such as marijuana and heroin). However, studies assessing the relationships among serum TC, TG, and methamphetamine (MA)-dependence have not been described well. In this study, our aim is to explore the serum TG and TC levels in large sample of MA-dependent patients. A retrospective study was conducted in 938 MA-dependent patients who were recruited between February 2, 2008 and March 11, 2013, with social characteristics and drug-dependence history (duration of MA use, routes of drug administration, and daily dose were collected). Then, the serum levels of TC, TG, glucose (GLU), body mass index (BMI), and blood pressure were measured among the participants. Meanwhile, 985 age- and gender-matched healthy people in the physical examination center were selected as control group. Compared with the control group, significant decreases of TC, TG, GLU, and BMI were observed in MA-dependent patients ($P < 0.05$). Besides, we found that the daily dose of MA use was associated with TC ($\beta = -0.079$, $P = 0.015$) and the duration of MA use was independently related to BMI ($\beta = -0.071$, $P = 0.031$). This study demonstrated that the levels of TC, TG, GLU, and BMI factors altered in the MA-dependent patients. In addition, there is a negative association between MA dependence and TC and BMI.

**Abbreviations:** BMI = body mass index, GLU = glucose, MA = methamphetamine, TC = total cholesterol, TG = triglyceride.

**Keywords:** methamphetamine-dependence, total cholesterol, triglyceride

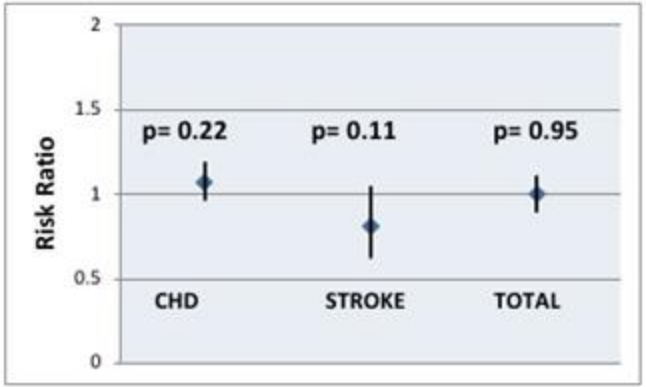
# Understanding Nutrition Data - Correlation

**Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease**

Siri-Tarino *et al* (2010) Am J Clin Nutr 91: 535-46

Meta-analysis of 21 studies including 347,747 subjects of whom 11,006 developed CHD or Stroke

**Author's Conclusion:** A meta-analysis of prospective epidemiological studies showed that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD



# Randomized Controlled Nutrition Trials

## Women's Health Initiative Study

Largest ever dietary RCT; n=48,835; mean 8.1 years follow-up

Intervention : low fat (20% of cal), 5+ servings fruit/vegetables, 6+ servings grains


# Randomized Controlled Nutrition Trials

## Women's Health Initiative Study

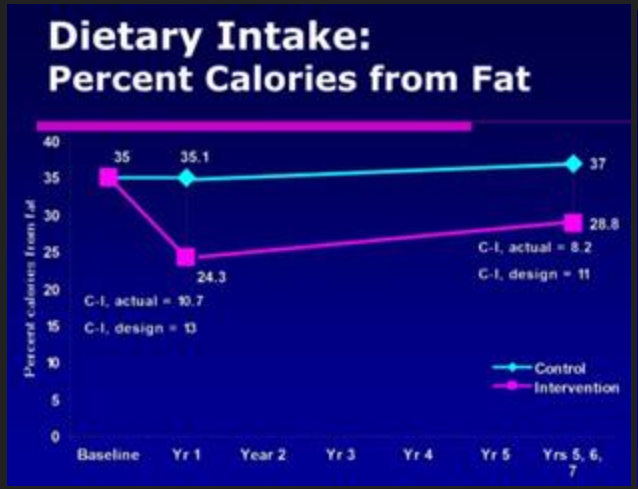
40% were randomly assigned to a low-fat dietary pattern intervention (target of 20% of energy from fat)

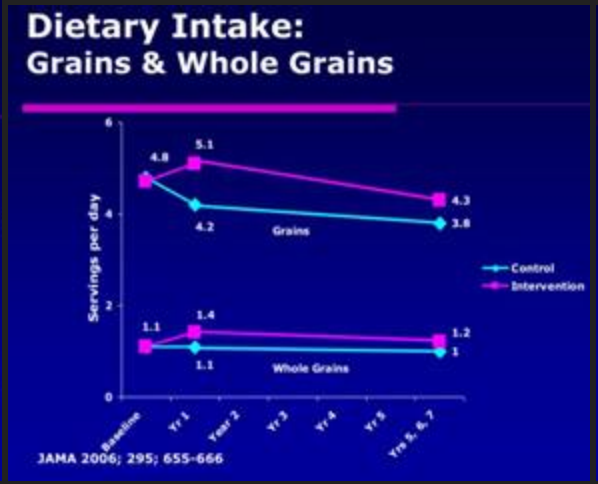
60% were randomly assigned to a usual diet comparison group.

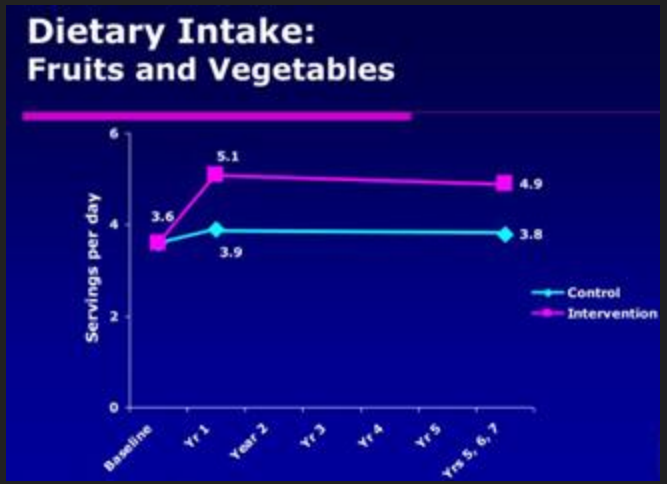
The 8.3-y intervention period ended in March 2005, after which >80% of surviving participants consented to additional active follow-up through September 2010; all participants were followed for mortality through 2013.

*The American Journal of Clinical Nutrition*, Volume 106, Issue 1, July 2017, Pages 35–43,

# Randomized Controlled Nutrition Trials



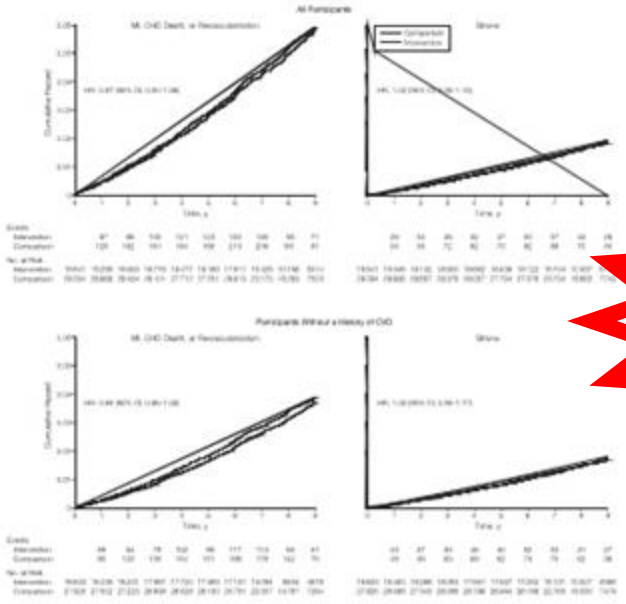



# Randomized Controlled Nutrition Trials

## The Women's Health Initiative Randomized Controlled Dietary Modification Trial

48835 post-menopausal women randomized to a low-fat* diet or usual diet for 8.1 years



- A dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains

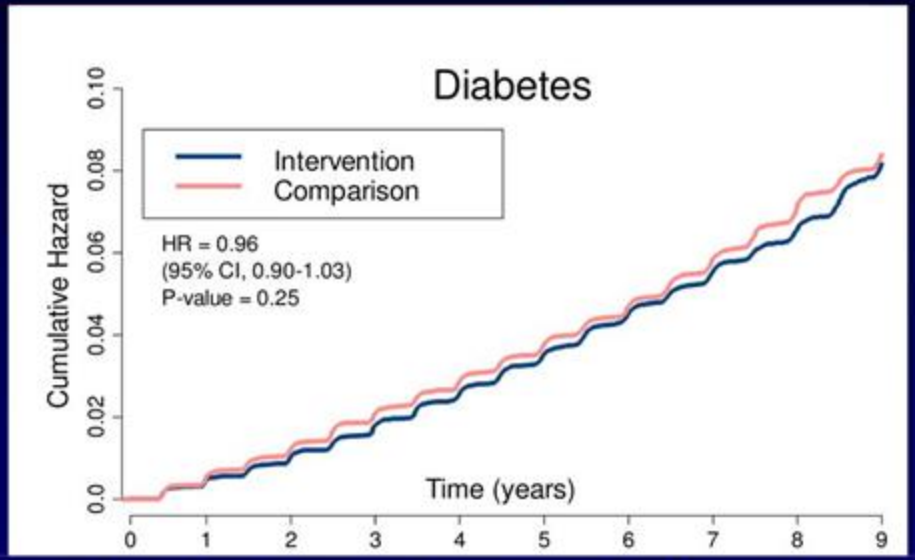
Low fat diet did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women

* Less then 20% of energy intake

Howard, B.V. et al. (2006). JAMA, 295, 655–666

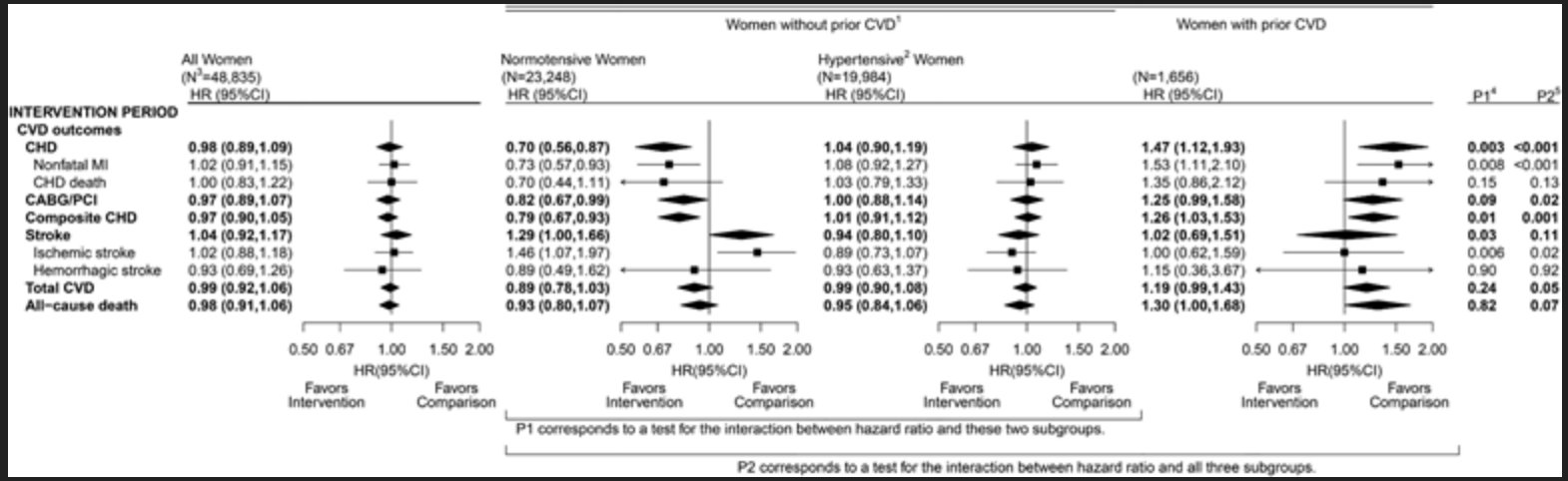
# Randomized Controlled Nutrition Trials

## Risk of Treated Diabetes in the WHI Dietary Modification Trial




Tinker et al, *Arch Intern Med. 2008;168(14):1500-1511*

# Randomized Controlled Nutrition Trials




*Healthy normotensive women* : CHD benefit offset by **increased ischemic stroke risk**

*Women with CVD at baseline (3.4%)* : **47% increased risk of CHD** during study duration
**61% increased risk** in the post-study follow-up

# Randomized Controlled Nutrition Trials

## Minnesota Coronary Experiment

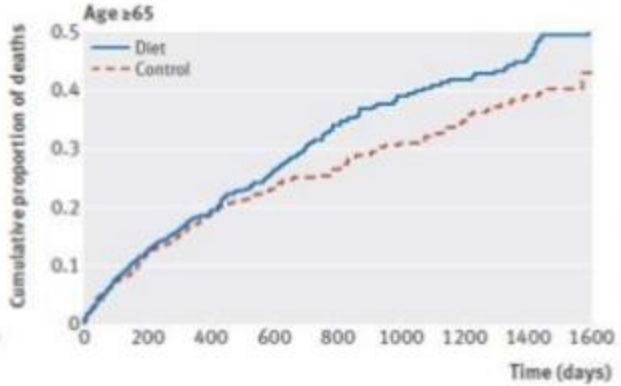
Second largest ever dietary RCT; n=9,570; 5 years follow-up

*Intervention :* exchanging saturated fat for PUFA (linoleic acid - corn oil and margarine)

The intervention group lowered cholesterol by **31 mg/dL**; and significantly lower than control group ($p < 0.001$)

# Randomized Controlled Nutrition Trials

## Minnesota Coronary Experiment




"Though the MCE intervention **lowered serum cholesterol**, this **did not translate to improved survival**"

"Paradoxically, MCE participants who had **greater reductions in serum cholesterol** had a **higher**, rather than lower, **risk of death**"

Source: Ramsden CE, Zamora D, Majchrzak-Hong S, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968–73). BMJ 2016;353:i1246

Myocardial infarction
**HR 1.86**

In survival analyses (table 4⇑), there was a robust association between decreasing serum cholesterol and increased risk of death, and this association did not differ between the intervention and control group (P>0.16 for all serum cholesterol × intervention interactions). Among both groups combined, a 30 mg/dL (0.78 mmol/L) decrease in serum cholesterol was associated with 22% higher risk of death from any cause (hazard ratio 1.22, 95% confidence interval 1.14 to 1.32) based on a Cox model adjusted for baseline serum cholesterol, age, sex, adherence to diet, BMI, and systolic blood pressure.

# Randomized Controlled Nutrition Trials

## Sydney Diet Heart Study

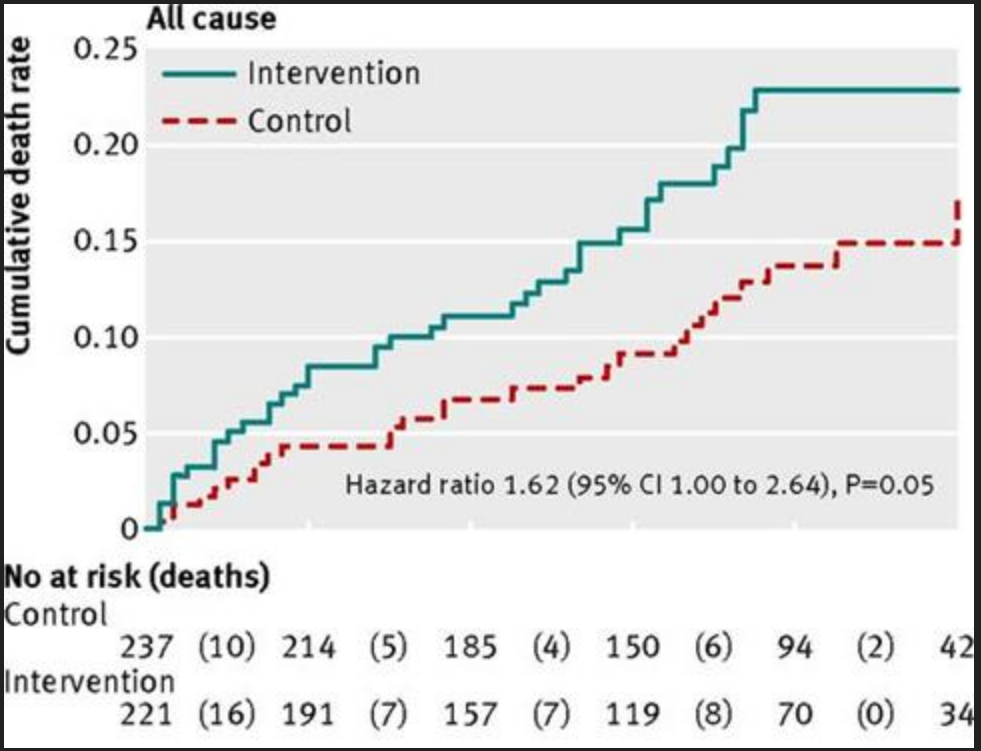
Dietary RCT; n=458; 5 years follow-up

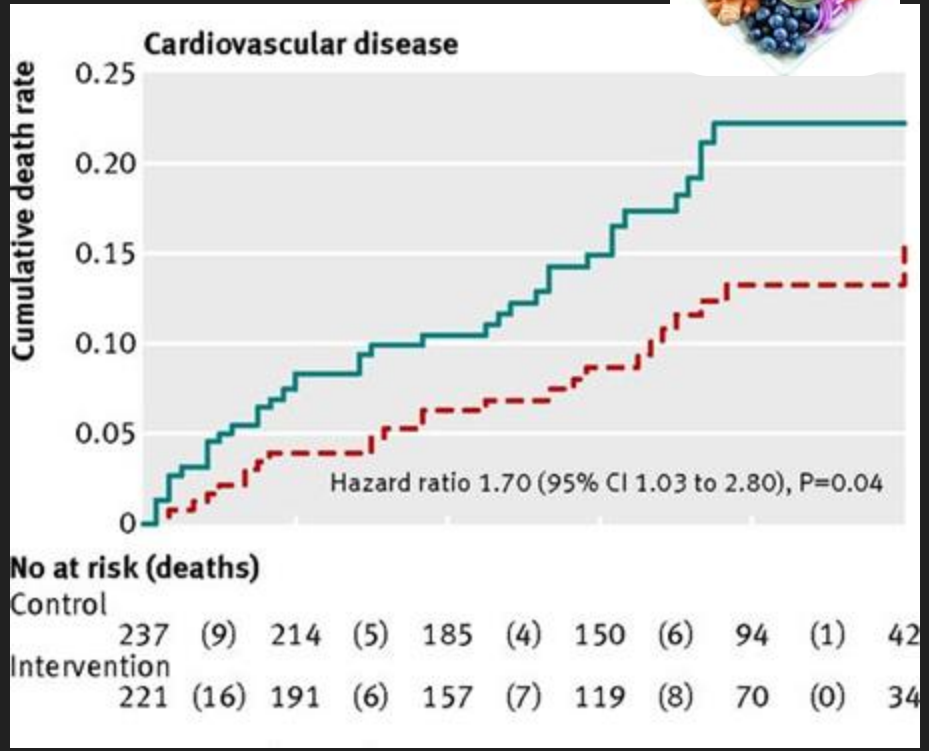
Number Needed to Kill
**17**

Intervention : exchanging saturated fat for PUFA (linoleic acid), in post-MI patients

Compared with the control group, the intervention group had an increased risk of all cause mortality (17.6% *v* 11.8%; hazard ratio 1.62 (95% confidence interval 1.00 to 2.64); P=0.051), cardiovascular mortality (17.2% *v* 11.0%; 1.70 (1.03 to 2.80); P=0.037), and mortality from coronary heart disease (16.3% *v* 10.1%; 1.74 (1.04 to 2.92); P=0.036) (fig 2⇓).

# Randomized Controlled Nutrition Trials



# Dietary lowering of cholesterol

In RANDOMIZED CONTROLLED DIETARY TRIALS

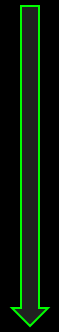
Eating to lower cholesterol *DID* lower cholesterol levels

But ***INCREASED*** cardiovascular and all-cause mortality risk

In a ***DOSE-DEPENDENT*** fashion.

# Lowering LDL cholesterol

Statins
Ezetimibe
Bempedoic acid
PCSK9 Mab



PROVEN BENEFIT

PCSK9 siRNA

UNPROVEN BENEFIT

WITH DIET

PROVEN HARM

# Deep thoughts

TO ME CLOWNS AREN'T FUNNY. IN FACT, THEY'RE KIND OF SCARY. I'VE WONDERED WHERE THIS STARTED AND I THINK IT GOES BACK TO THE TIME I WENT TO THE CIRCUS AND A CLOWN KILLED MY DAD.

# Concept

If you don’t have plaque - **CHILL OUT**

# Coronary calcium scan

Very powerful prognosticator

44,052 consecutive asymptomatic patients sent for CAC

mean follow-up 5.6 years

**19,898 had CAC : 0**

**All-cause mortality : 0.52%**

**2-fold risk** for CAC 1-10

**7.5-fold risk** for CAC >10

Blaha M et al JACC Cardiovasc Imaging 2009 June; 2 (6) : 692 - 700

# Coronary calcium scan

if CAC = 0 : **<0.1%/yr event rate**

at least 99% 5-yr survival (regardless of risk factors)

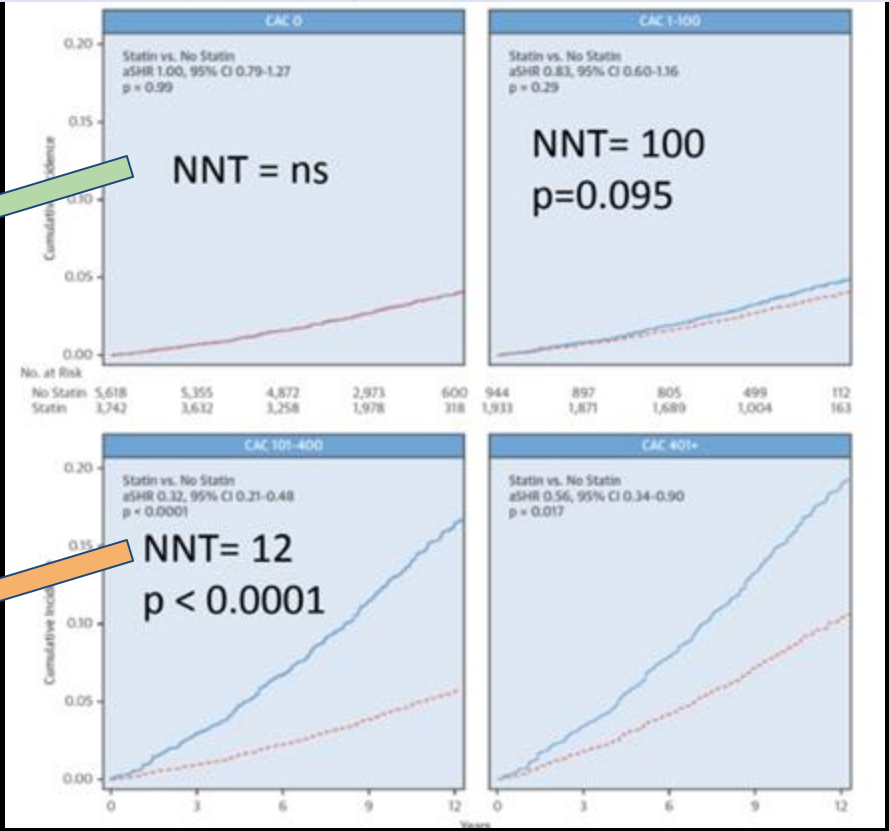
'warranty period' of about 5 years

*much more powerful risk stratification than biomarkers; arguably the best current risk assessor (and best negative risk predictor)*

Johns Hopkins Group, AHA Scientific Sessions

# Coronary Artery Calcium scan and statin benefits

**CENTRAL ILLUSTRATION: Cumulative Incidence of MACE Stratified by Statin Treatment and CAC Severity**



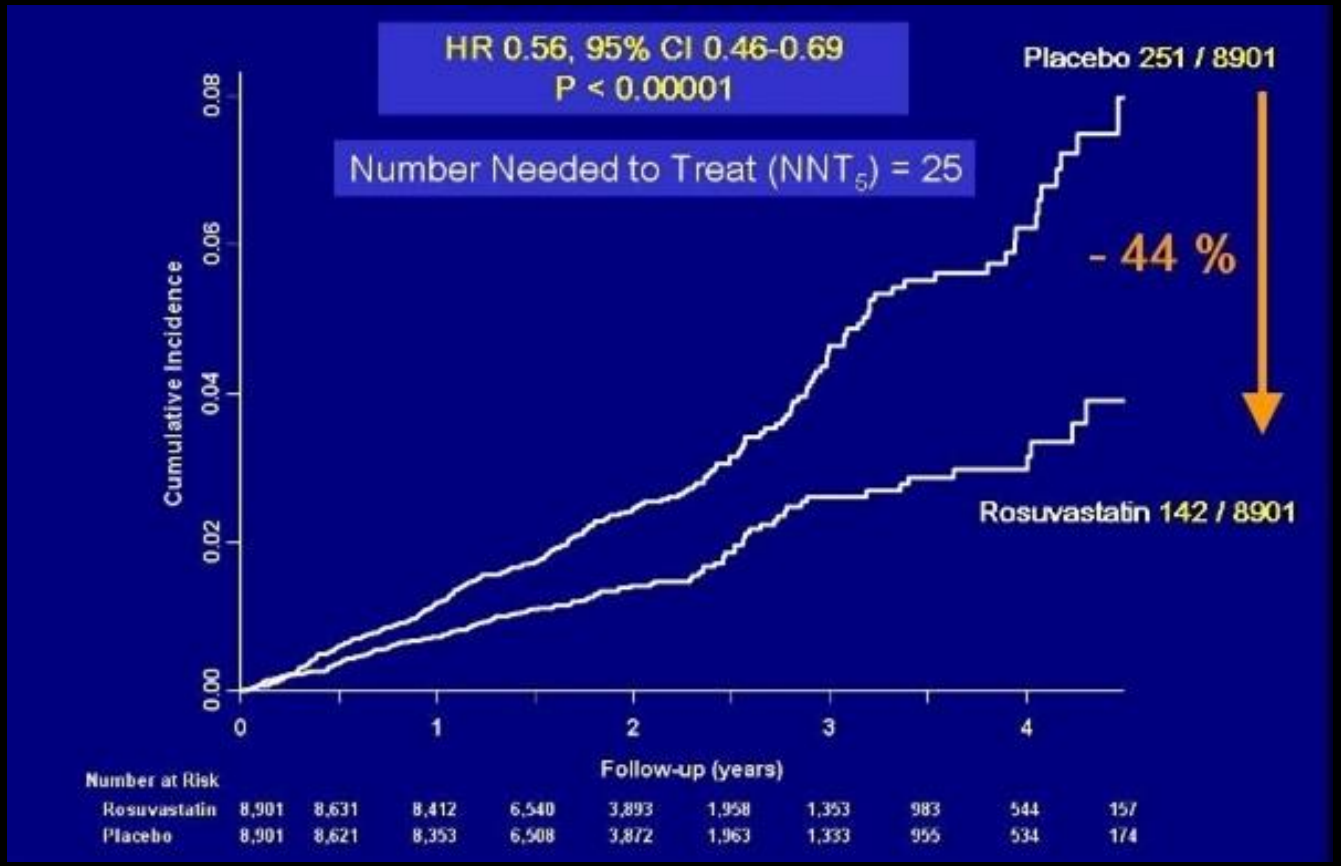

12 years of follow-up

**CAC = 0**
**"The power of zero"**

**CAC = 100-400**

Mitchell, J.D. et al. J Am Coll Cardiol. 2018;72(25):3233–42.

# Benefit of statins of there is no plaque




JUPITER Trial

Ridker PM et al, NEJM 2008 : 359; 2195-2207

# Benefit of statins if there is no plaque

Table 1: Effect of Statin Therapy by CAC score on Major Adverse Cardiovascular Events

| CAC Score | Therapy | N | Events/1000 Patient Years | NNT: 1 year | NNT: 5 years | NNT: 10 years |
|---|---|---|---|---|---|---|
| 0 | Statin | 5206 | 2.7 | 3950.9 | 790.2 | 395.1 |
| | No Statin | 5038 | 2.9 | | | |
| >0 | Statin | 3799 | 7.5 | 899.6 | 179.9 | 90.0 |
| | No Statin | 913 | 8.6 | | | |
| 1-100 | Statin | 2404 | 4.7 | 1185.5 | 237.1 | 118.6 |
| | No Statin | 763 | 5.5 | | | |
| 101-400 | Statin | 922 | 8.7 | 82.5 | 16.5 | 8.3 |
| | No Statin | 112 | 20.8 | | | |
| >400 | Statin | 473 | 19.8 | 45.3 | 9.1 | 4.5 |
| | No statin | 38 | 41.9 | | | |

# Concept

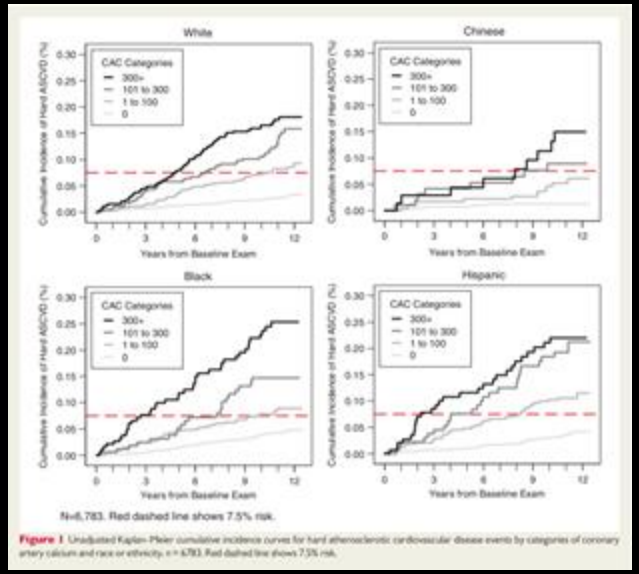
We are both over- and undertreating people

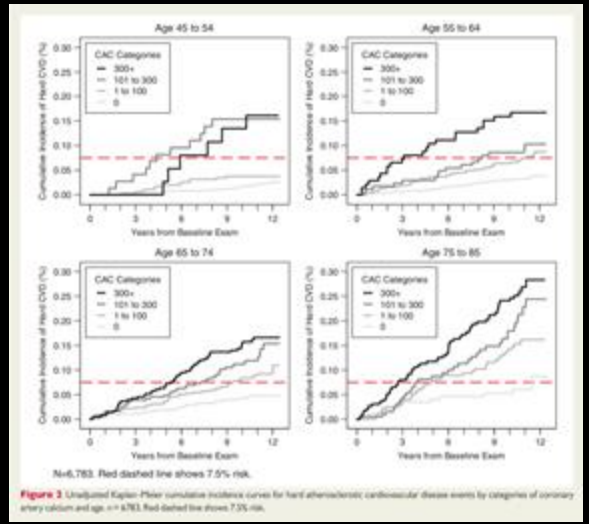
# Risk reclassification

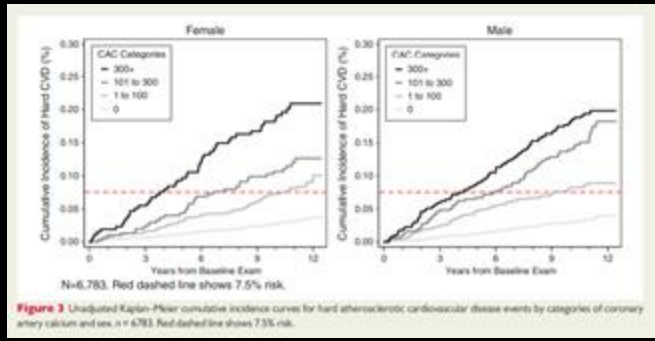
Relook at MESA, incorporating all ASCVD events (not just CHD); median 11.1 years

**CAC=0 all were <5% risk**

**CAC >100 all were >7.5% risk**




Budoff et al Eur Heart J. 2018 Jul 1;39(25):2401-2408

# Coronary calcium scans in severely elevated LDL

**Low-Density Lipoprotein Cholesterol Is Predominantly Associated With Atherosclerotic Cardiovascular Disease Events in Patients With Evidence of Coronary Atherosclerosis: The Western Denmark Heart Registry**

Martin Bødtker Mortensen ✉, Omar Dzaye, Hans Erik Bøtker, Jesper Møller Jensen, Michael Maeng, Jacob Fog Bentzen, Helle Kanstrup, Henrik Toft Sørensen, Jonathon Leipsic, Ron Blankstein, Khurram Nasir, Michael J. Blaha and Bjarne Linde Nørgaard

**Originally published** 9 Jan 2023 | https://doi.org/10.1161/CIRCULATIONAHA.122.061010 | Circulation. 2023;0

The percentage of individuals with a CAC score of 0 ranged from 46.2% (438 of 948) of patients with LDL-C levels ≥190 mg/dL to 54.9% (4370 of 7964) of patients with LDL-C levels of 77 to 112 mg/dL, and was associated with no detectable plaque in most patients, ranging from 77.2% in those with LDL-C levels ≥190 mg/dL to 88.6% in those with LDL-C levels <77mg/dL.

# Coronary calcium scans in severely elevated LDL

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**Originally published** 9 Jan 2023 | https://doi.org/10.1161/CIRCULATIONAHA.122.061010 | Circulation. 2023;0

Absence of CAC was associated with low rates of ASCVD and death across all LDL-C strata—6.3 (95%CI, 5.6-7.0) per 1000 person-years in the overall population. This held true even in the highest LDL-C strata (≥190 mg/dL), which exhibited an event rate of 6.9 (95%CI, 4.0-11.9) per 1000 person-years among those with a CAC of 0. The rates rose with increasing CAC scores. Among those with CAC scores of 1 to 99 and of ≥100, respectively, the rate was 11.1 [95%CI, 10.0-12.5] and 21.9 [95%CI, 19.9-24.4] events per 1000 person-years.[3]

# CAC as the gatekeeper

**CAC : 0** **Reasonable to withhold medication for most**

**CAC > 0** **Reasonable to treat with something**

*ESPECIALLY IF* CAC > 100
CAC > 75th percentile for age/gender/race (MESA)
CAC > 0 and age < 55 yrs

# CAC and deciding on aspirin use

MESA

6,814 primary prevention patients (45-84 yrs old)

followed for median of 7.6 years

**if CAC>100** : **9-fold risk** CHD events

**6.5-fold risk** of CVD event (compared to CAC : 0)

**Net benefit with ASA therapy** (regardless of risk factors)

Miedema et al (MESA subanalysis); Circ. Cardiovasc. Qual. Outcomes 2014 May

# What I do

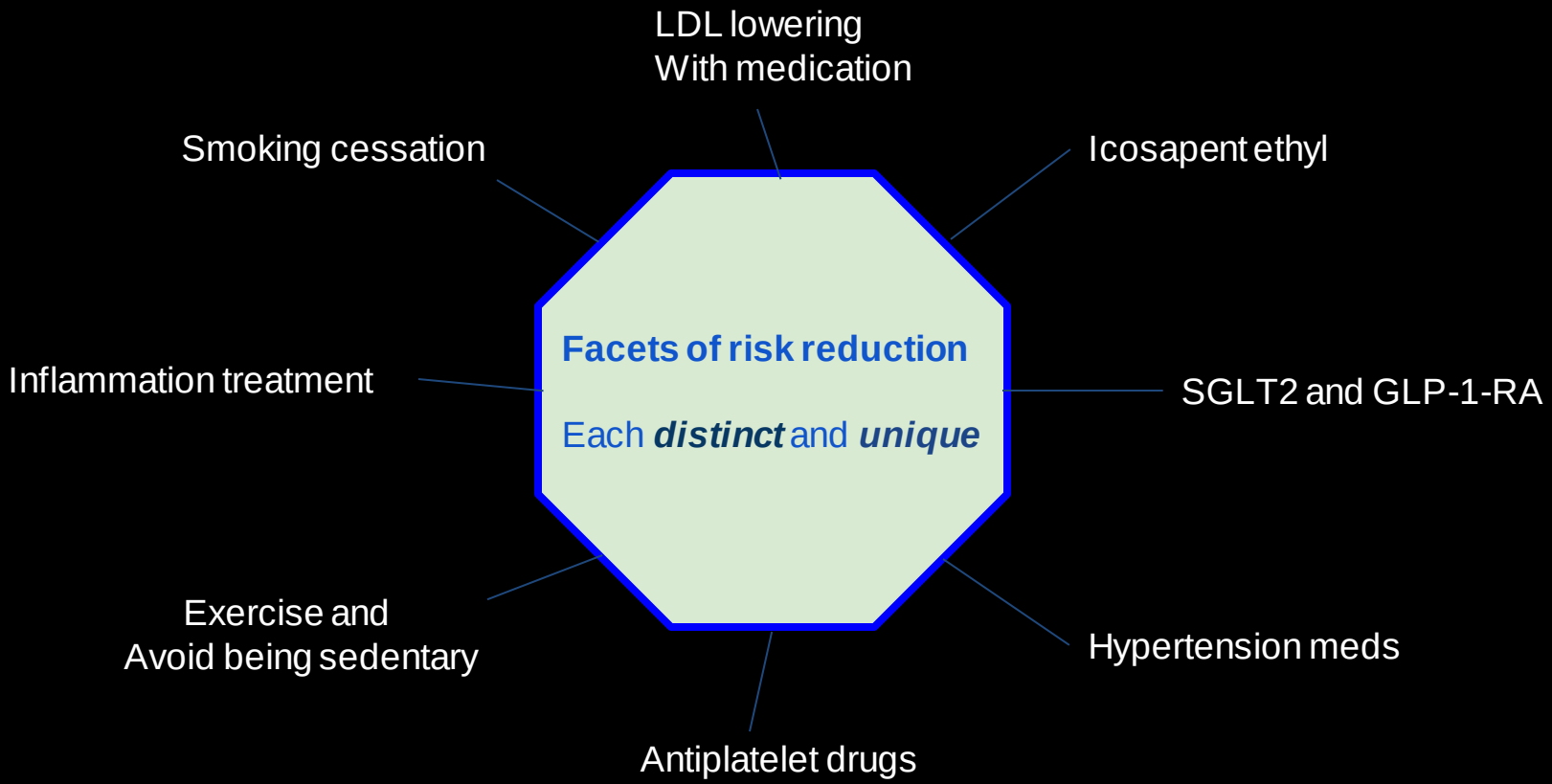
1 If someone has declared ASCVD, I treat aggressively.
2 If there is no known ASCVD, I trawl through CT chests, abdomens etc.
3 If no known plaque, I order a calcium scan, and advanced lipid panel.

4 **I calculate Astro-CHARM risk if 40-65 yrs old. MESA risk if 66-85 yrs old.**

5 If no CAC, and they are younger, I add a carotid U/S with IMT.

6 NO PLAQUE : I work on lifestyle optimization (exercise, insulin, TG/HDL ratio, inflammation, EPA)
I am unlikely to medicate, but I discuss the concept of lifetime risk, and give a choice.
Repeat CAC in 5 years.

7 PLAQUE : I work on lifestyle optimization (exercise, insulin, TG/HDL ratio, inflammation, EPA)
(CAC>0) I recommend at least some medication addition. Typically statins first.
Goal Apo-B <60 ideally. This is the job SOLELY OF MEDICATION.
Anti-platelets? ACE-I? SGLT-2i/GLP-1-RA? Icosapent ethyl? Colchicine? Rivaroxaban?
Repeat CAC in 3-5 years to 'audit' the treatment plan efficacy.
**If >15%/annum increase in plaque - intensify.**


LDL lowering
With medication
Smoking cessation
Icosapent ethyl
Facets of risk reduction
Each distinct and unique
Inflammation treatment
SGLT2 and GLP-1-RA
Exercise and
Avoid being sedentary
Hypertension meds
Antiplatelet drugs

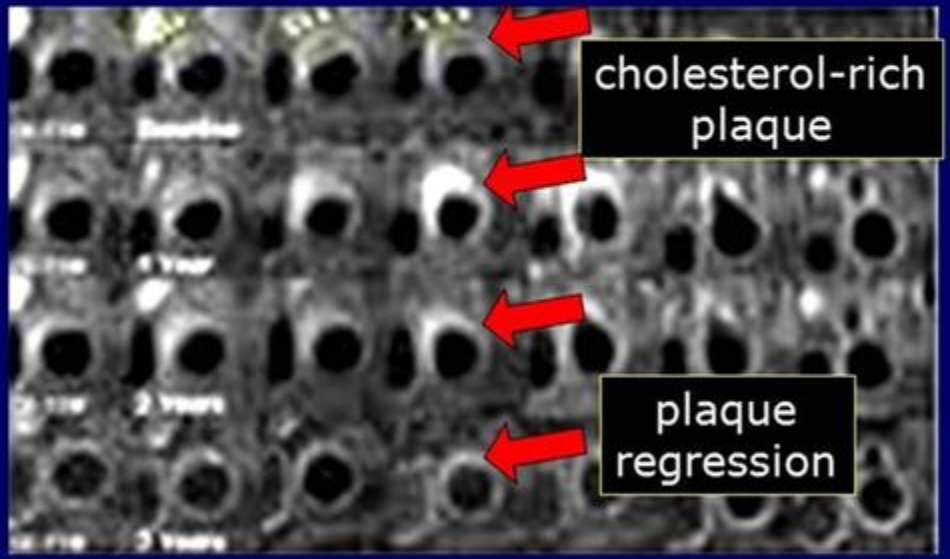
# High Resolution MRI Demonstrating Plaque Regression with Advanced Cholesterol Therapy

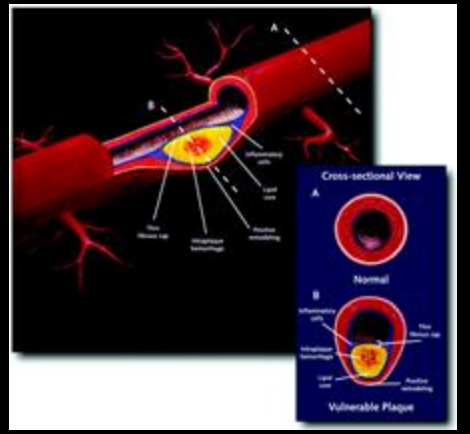
Pre-treatment

After 1 year

After 2 years

After 3 years




Zhao. JACC:Vascular Imaging 2011;4:977

# Summary

Best prediction of cardiovascular risk is plaque, using the coronary calcium scan.

If one has plaque, there are many avenues for risk reduction.
If one does not have plaque, your risk is very low already.

Cholesterol lowering has the biggest impact on risk reduction. There are many medication options to achieve this. Achieving this by diet is irrelevant/harmful.

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Best prediction of cardiovascular risk is plaque, using the coronary calcium scan.

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Cholesterol lowering has the biggest impact on risk reduction. There are many medication options to achieve this. Achieving this by diet is irrelevant/harmful.

QUESTIONS ?

# Cardiometabolic medications and mortality

1. Statins reduce CV mortality, compared to placebo (4S : **NNT 31; median 5.4 yrs)**
2. Increasing statin intensity/adding other LLT does not further lower CV mortality
3. ACE inhibitors lower all-cause mortality **(NNT 67; mean 4.3 yrs)**
4. Icosapent ethyl lowers all-cause mortality in USA cohort **(NNT 39; mean 4.9 yrs)**
5. Empagliflozin lowers CV mortality **(NNT 46; median 3.1 yrs)**
6. Liraglutide reduces CV and all-cause mortality **(NNT 77/72; median 3.8 yrs)**
7. Semaglutide reduces CV and all-cause mortality **(NNT 100/72; median 1.4 yrs)**
8. Rivaroxaban + ASA reduces all-cause mortality, esp in diabetics **(NNT 52; 1.9 yrs)**