Bale/Doneen Live Chat Session

9/11/2013

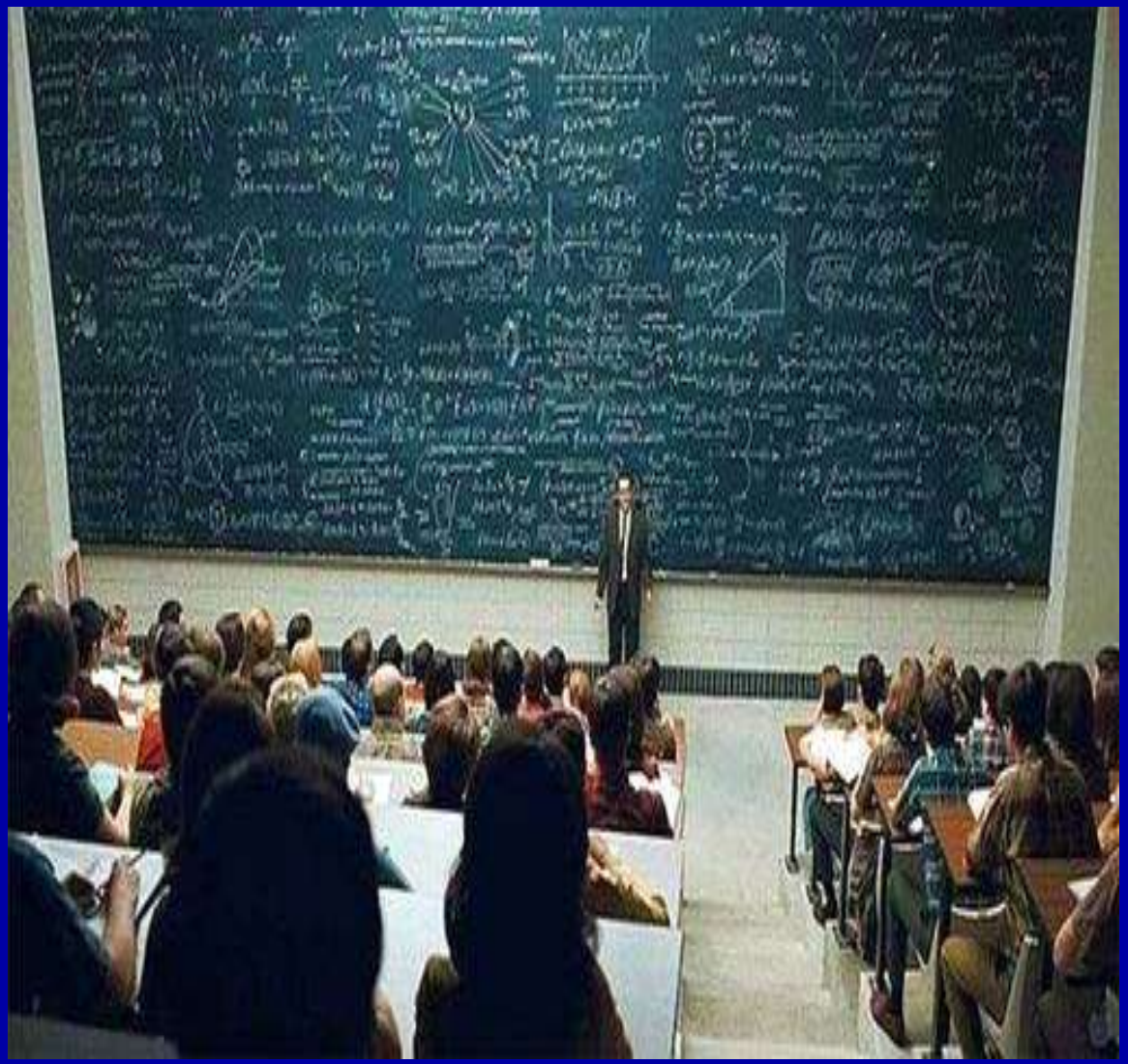
5:30-6:30 pm PST

Bradley Bale, MD

Outline

- New data and slides
- Review upcoming meetings
- Open discussion for remaining

New Data??!!!: OMG!: 26 studies



Bibliography

- Briffa, T. G., & Tonkin, A. (2013). Put Disease Prevention First. Circulation, 128(6), 573-575.
- Pletcher, M. J., et. al. (2013). Interpretation of the Coronary Artery Calcium Score in Combination with Conventional Cardiovascular Risk Factors: The Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. doi: 10.1161/CIRCULATIONAHA.113.002598
- Sabater-Lleal, et. al. (2013). A Multi-Ethnic Meta-Analysis of Genome-Wide Association Studies in Over 100,000 Subjects Identifies 23 Fibrinogen-Associated Loci but no Strong Evidence of a Causal Association between Circulating Fibrinogen and Cardiovascular Disease. Circulation. doi: 10.1161/circulationaha.113.002251
- Varbo, A., et. al. (2013). Elevated Remnant Cholesterol Causes Both Low-Grade Inflammation and Ischemic Heart Disease, While Elevated Low-Density Lipoprotein Cholesterol Causes Ischemic Heart Disease without Inflammation. Circulation. doi: 10.1161/CIRCULATIONAHA.113.003008
- Acharjee, S., et. al. (2013) Low Levels of High Density Lipoprotein Cholesterol and Increased Risk of Cardiovascular Events in Stable Ischemic Heart Disease Patients: A Post Hoc Analysis from the COURAGE Trial. J Am Coll Cardiol(0). doi: http://dx.doi.org/10.1016/j.jacc.2013.07.051

Bibliography

- van de Woestijne, A. P., et. al. (2013). Low HDL-cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid-lowering medication. J Am Coll Cardiol. doi: 10.1016/j.jacc.2013.04.101
- Boekholdt, S. M., et. al. (2013). Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events among Statin-Treated Patients: A Meta-Analysis. Circulation. doi: 10.1161/CIRCULATIONAHA.113.002670
- DiDonato, J. A., et. al. (2013). The Function and Distribution of Apolipoprotein A1 in the Artery Wall are Markedly Distinct from those in Plasma. Circulation. doi: 10.1161/circulationaha.113.002624
- Dietmann, A., et. al. (2013). Effects of Aggregatibacter actinomycetemcomitans leukotoxin on endothelial cells. Microb Pathog, 61-62, 43-50.

Bibliography

- Robinson-Cohen C, H. A. N. I. J. H., & et al. (2013). RAcial differences in the association of serum 25-hydroxyvitamin d concentration with coronary heart disease eventsrace and chd events associated with vitamin d race and chd events associated with vitamin d. JAMA, 310(2), 179-188.
- Ferreira, A. P., et. al. (2013). The effect of aerobic exercise intensity on attenuation of postprandial lipemia is dependent on apolipoprotein E genotype. Atherosclerosis, 229(1), 139-144.
- O'Keefe, J. H., Lavie, C. J. 9/17/(2013). Effects of Habitual Coffee Consumption on Cardiometabolic Disease, Cardiovascular Health, and All-cause Mortality. J Am Coll Cardiol. doi: 10.1016/j.jacc.2013.06.035
- Liu, J., Sui, X., Lavie, C. J. et. al. Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality. Mayo Clinic Proceedings(0). doi: http://dx.doi.org/10.1016/j.mayocp.2013.06.020

Bibliography

- Ros, E., & Hu, F. B. (2013). Consumption of Plant Seeds and Cardiovascular Health: Epidemiological and Clinical Trial Evidence. Circulation, 128(5), 553-565.
- Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. Bmj, 347, f5001. doi: 10.1136/bmj.f5001
- Daniel Cuevas-Ramos, et. al. Effect of tomato consumption on high-density lipoprotein cholesterol level: a randomized, single-blinded, controlled clinical trial. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 7/2013:6 263–273
- McDonnell, M. N. (2013). Physical Activity Frequency and Risk of Incident Stroke in a National US Study of Blacks and Whites. Stroke. 44:2519-2524
- Goldberg, R., et. al. (2013). Lifestyle and Metformin Treatment Favorably Influence Lipoprotein Subfraction Distribution in the Diabetes Prevention Program. Journal of Clinical Endocrinology & Metabolism. doi: 10.1210/jc.2013-1452

Bibliography

- Liao MT, Tsai CT, Lin JL. Statins reduce the incidence of dementia in patients with atrial fibrillation: A nationwide cohort study. European Society of Cardiology 2013 Congress; August 31, 2013; Amsterdam, the Netherlands. Abstract P4077.
- Wu C, Lin T. Statin use and the incidence of dementia in the elderly: A nationwide data survey. European Society of Cardiology 2013 Congress; August 31, 2013; Amsterdam, the Netherlands. Abstract 1609.
- Merwick, A., et. al. (2013). Reduction in Early Stroke Risk in Carotid Stenosis With Transient Ischemic Attack Associated With Statin Treatment. Stroke. doi: 10.1161/strokeaha.113.001576
- DeGorter, M. K., et. al. (2013). Clinical and Pharmacogenetic Predictors of Circulating Atorvastatin and Rosuvastatin Concentration in Routine Clinical Care. Circulation: Cardiovascular Genetics. doi: 10.1161/circgenetics.113.000099

Bibliography

- Nicholls, S. J. (2013). Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension. JAMA. doi: 10.1001/jama.2013.277169
- Althouse, A. D., et. al. (2013). Favorable Effects of Insulin Sensitizers Pertinent to Peripheral Arterial Disease in Type 2 Diabetes: Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Diabetes Care. doi: 10.2337/dc12-2265
- Bach, R. G., et. al. (2013). Rosiglitazone and Outcomes for Patients with Diabetes and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Circulation. doi: 10.1161/circulationaha.112.000678

Bibliography

- Woo, J. S., et. al. (2013). Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of Exenatide Myocardial Protection in Revascularization Study. Arteriosclerosis, Thrombosis, and Vascular Biology. doi: 10.1161/atvbaha.113.301586
- Scirica, B. M., et. al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. New England Journal of Medicine, 0(0), null. doi: doi:10.1056/NEJMoa1307684
- Ghebremariam, Y. T., Lependu, P., Lee, J. C., Erlanson, D. A., Slaviero, A., Shah, N. H., . . . Cooke, J. P. (2013). Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation, 128(8), 845-853.

Hang on to Your Hat

CVD is a Huge Global Issue

- ~ 6 million CVD deaths globally/year.
- 1/3 of those are in individuals aged <70 yo.
- ~ 50% of annual major coronary events are recidivistic.
- ~ 50% of these recurrent events are fatal.

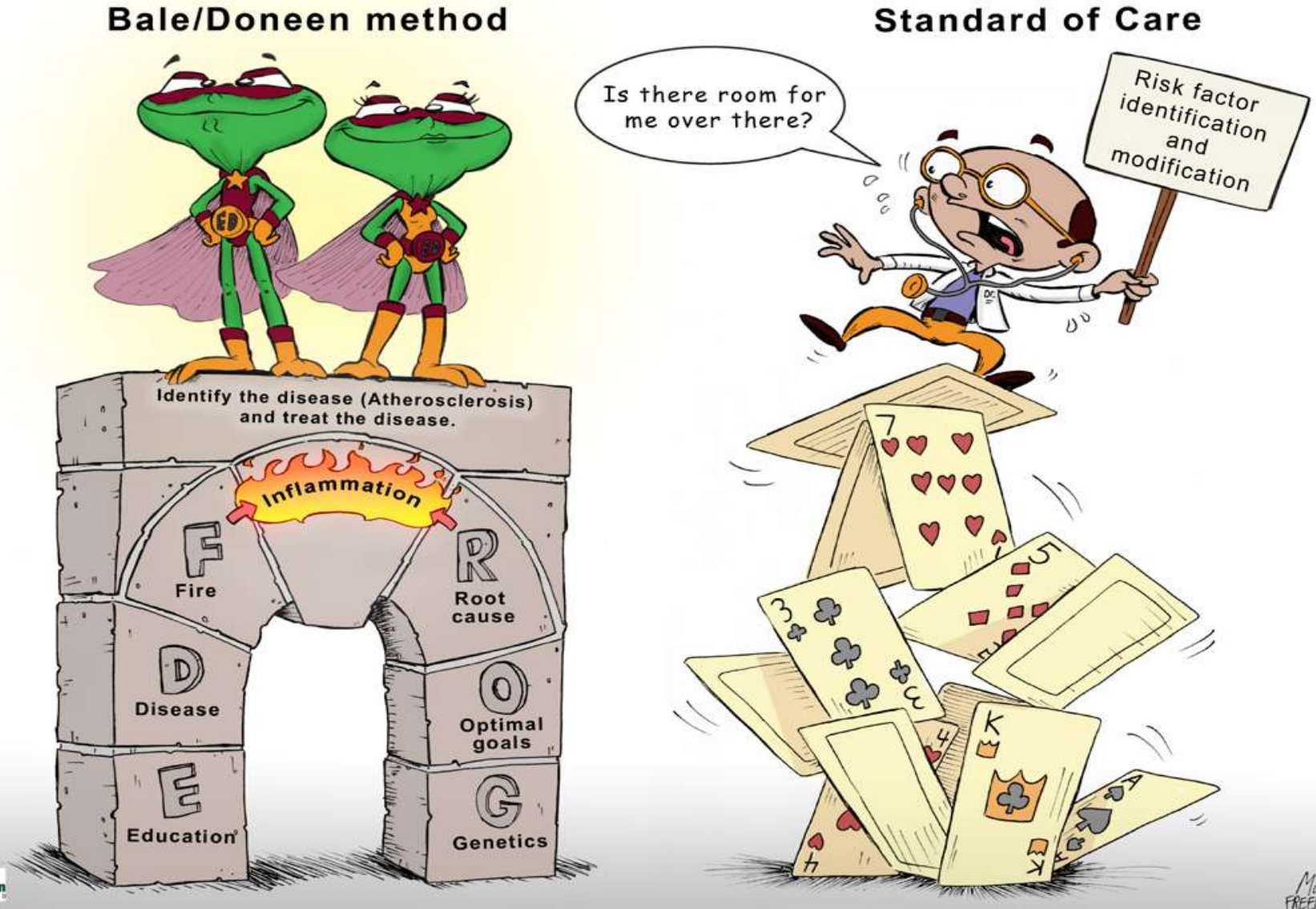
Briffa, T. G., & Tonkin, A. (2013). Put Disease Prevention First. *Circulation, 128*(6), 573-575.

Preventing Disease Should Rank Higher Than Treating Disease

Evidence-based management of CHD is critical to achieve optimal reductions in mortality and morbidity.

Briffa, T. G., & Tonkin, A. (2013). Put Disease Prevention First. *Circulation, 128*(6), 573-575.

What's the difference?



CACS Relative to Other CV Risk Factors

- 6,757 MESA pts.; 45 to 84 yo; utilizing risk factors devise a formula to derive a predicted score for an individual.

- Calculated: scenarios with a high expected CAC an actual score of 50 decreases FRS expected risk; when a low score is expected a score of 50 increases FRS expected risk.

(seems a bit ridiculous-based on math and not actual events!!!)

Pletcher, M. J., et. al. (2013). Interpretation of the Coronary Artery Calcium Score in Combination with Conventional Cardiovascular Risk Factors: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.002598

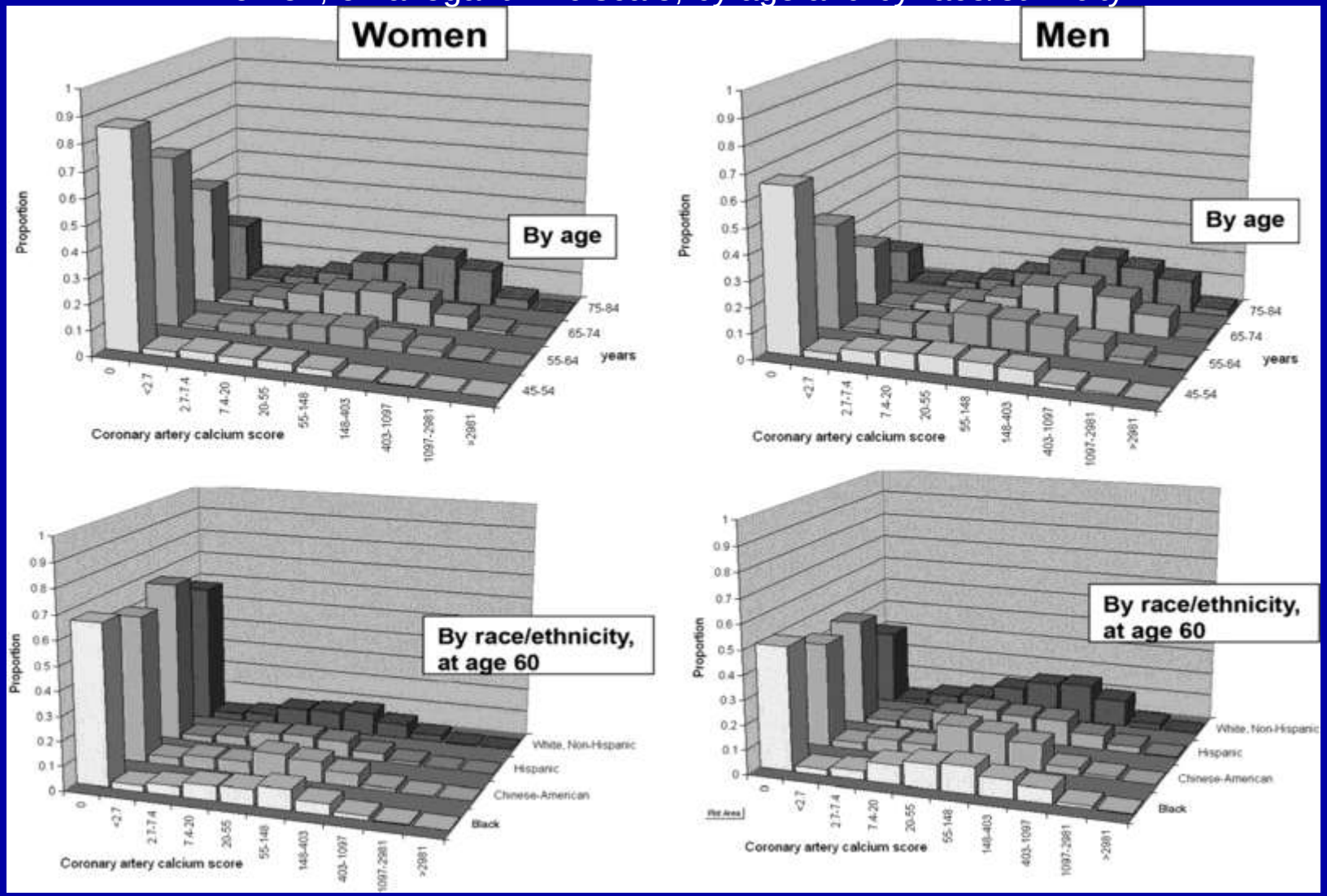
CACS Relative to Other CV Risk Factors

- §Posttest risk estimates were calculated by assuming that the pretest 10-year CHD risk estimate represented an average of persons with different CAC scores, weighted by the probability of having a CAC score in each category. The risk in each category was calculated algebraically using these relative risk estimates from Detrano et al2: CAC=0, reference; CAC=1–100, 3.61; CAC=101–300, 7.73; and CAC >300, 9.67. Resulting risk scores were rounded to the nearest whole percentage.

Pletcher, M. J., Sibley, C. T., Pignone, M., Vittinghoff, E., & Greenland, P. (2013). Interpretation of the Coronary Artery Calcium Score in Combination with Conventional Cardiovascular Risk Factors: The Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.002598

CACS Relative to Other CV Risk Factors

Distribution of coronary artery calcium (CAC) scores among men and women, on a logarithmic scale, by age and by race/ethnicity.

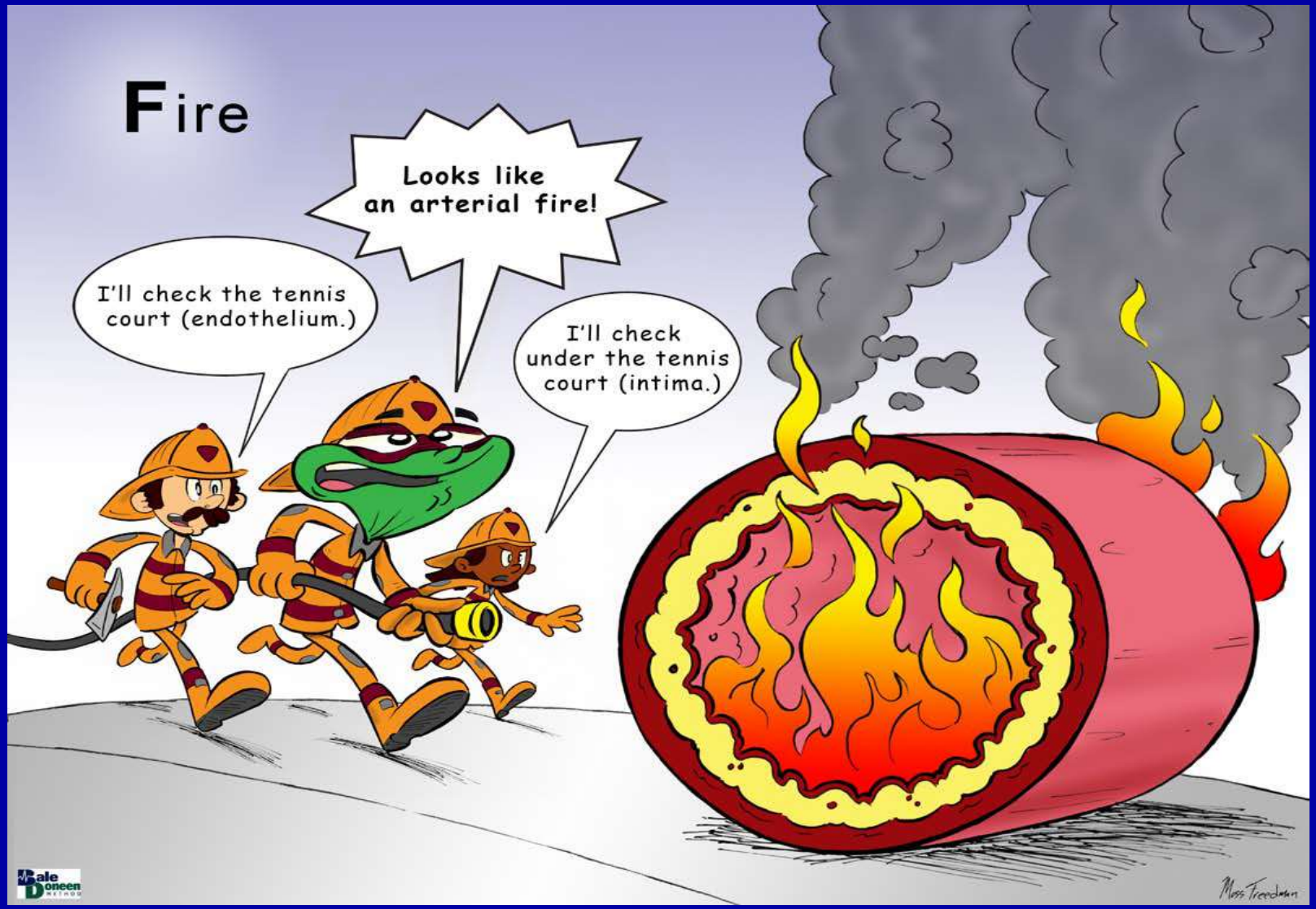


Pletcher M et al. Circulation 2013;128:1076-1084

Bale/Doneen Thoughts

- Distributions of CACS based on CV risk factors are interesting and might come in handy discussing with a patient.
- Nice to have ethnic data and gender breakdown.
- Bottom line: if you have a positive score, you have a ‘cat in the gutter’!

Inflammation



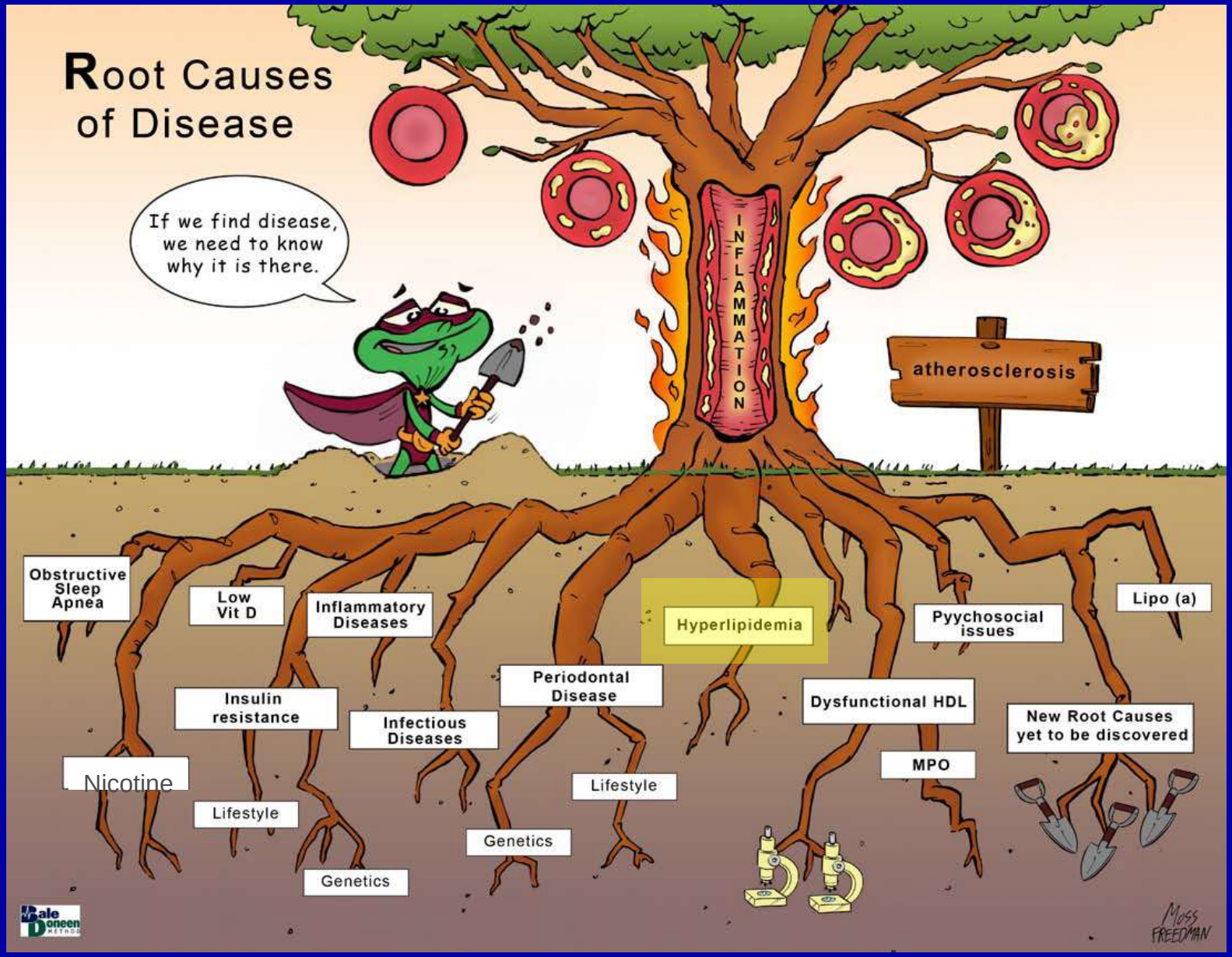
Fibrinogen is not Causal of ASVD

- Meta-analysis of 28 multi-ethnic GWA studies; ~ 100,000 individuals; identified 24 SNPs associated with fibrinogen levels (adjust. BMI & smoking); evaluated assoc. of these with CHD and stroke risk

- 40,695 CHD cases & 85,582 controls; 4,752 stroke cases & 24,030 controls

- Pooled association for the 24 SNPs was not significant for CHD or stroke

Sabater-Lleal, et. al. (2013). A Multi-Ethnic Meta-Analysis of Genome-Wide Association Studies in Over 100,000 Subjects Identifies 23 Fibrinogen-Associated Loci but no Strong Evidence of a Causal Association between Circulating Fibrinogen and Cardiovascular Disease. *Circulation*. doi: 10.1161/circulationaha.113.002251



Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- Remnant cholesterol is the cholesterol content of TG-rich lipoproteins composed of very low-density lipoproteins and IDL in the fasting state, and of these two lipoproteins together with chylomicron remnants in the non-fasting state.

- Remnant cholesterol and TG are two different types of fat and are components of the same lipoproteins, i.e. remnants, and levels of remnant cholesterol and TG are therefore highly correlated (R value=0.96).

Varbo, A., et. al. (2013). Elevated Remnant Cholesterol Causes Both Low-Grade Inflammation and Ischemic Heart Disease, While Elevated Low-Density Lipoprotein Cholesterol Causes Ischemic Heart Disease without Inflammation. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- Since many human cells can degrade TG and none can degrade cholesterol, it seems plausible that it is the cholesterol content of remnants that is causal for atherosclerosis development and not the TG content.

Varbo, A., et. al. (2013). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- 60,608 subjects; 10,668 with CHD; genotyped for variants affecting levels of 1) nonfasting remnant cholesterol 2) LDL-C 3) CRP by CRP alleles 4) CRP by IL6R alleles

- Investigated possible causal associations between the lipoproteins and C-reactive protein (inflammation), and between the lipoproteins and IHD.

Varbo, A., et. al. (2013). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- A 39 mg/dL higher level of nonfasting remnant cholesterol was associated causally with a 28%(10-48%) higher level of CRP.
- A 39 mg/dL higher level of LDL was not associated causally with CRP.
- CRP was not associated causally with lipoproteins

Varbo, A., et. al. (2013). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- A 39 mg/dL higher level of nonfasting remnant cholesterol was associated causally with a 3.3 higher risk ratio for CHD (95%CI: 2.1-5.2).

- A 39 mg/dL higher level of LDL-C was associated causally with a 1.8 higher risk ratio for CHD (95%CI: 1.5-2.2).

- Causal assoc. with CRP alleles was borderline; no assoc. with IL6R alleles

Varbo, A., et. al. (2013). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- A significant causal relationship for CHD remained for remnant cholesterol in subjects without diabetes or obesity.

- The possible causal relationship for CHD with LDL-C in subjects without diabetes or obesity was not tested. ☹

Varbo, A., et. al. (2013). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

Elevated Remnant Cholesterol Causes Arterial Inflammation and CHD: Elevated LDL-C Does Not Cause Inflammation

- LDL particles need to be oxidized before they can be taken up by macrophages, while remnants can be taken up by macrophages without oxidation.

- Residual risk of CHD even with low LDL may be partially explained by the association between non-fasting remnant cholesterol and low-grade inflammation.

Varbo, A., et. al. (2013). *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.003008

BD Method Thoughts

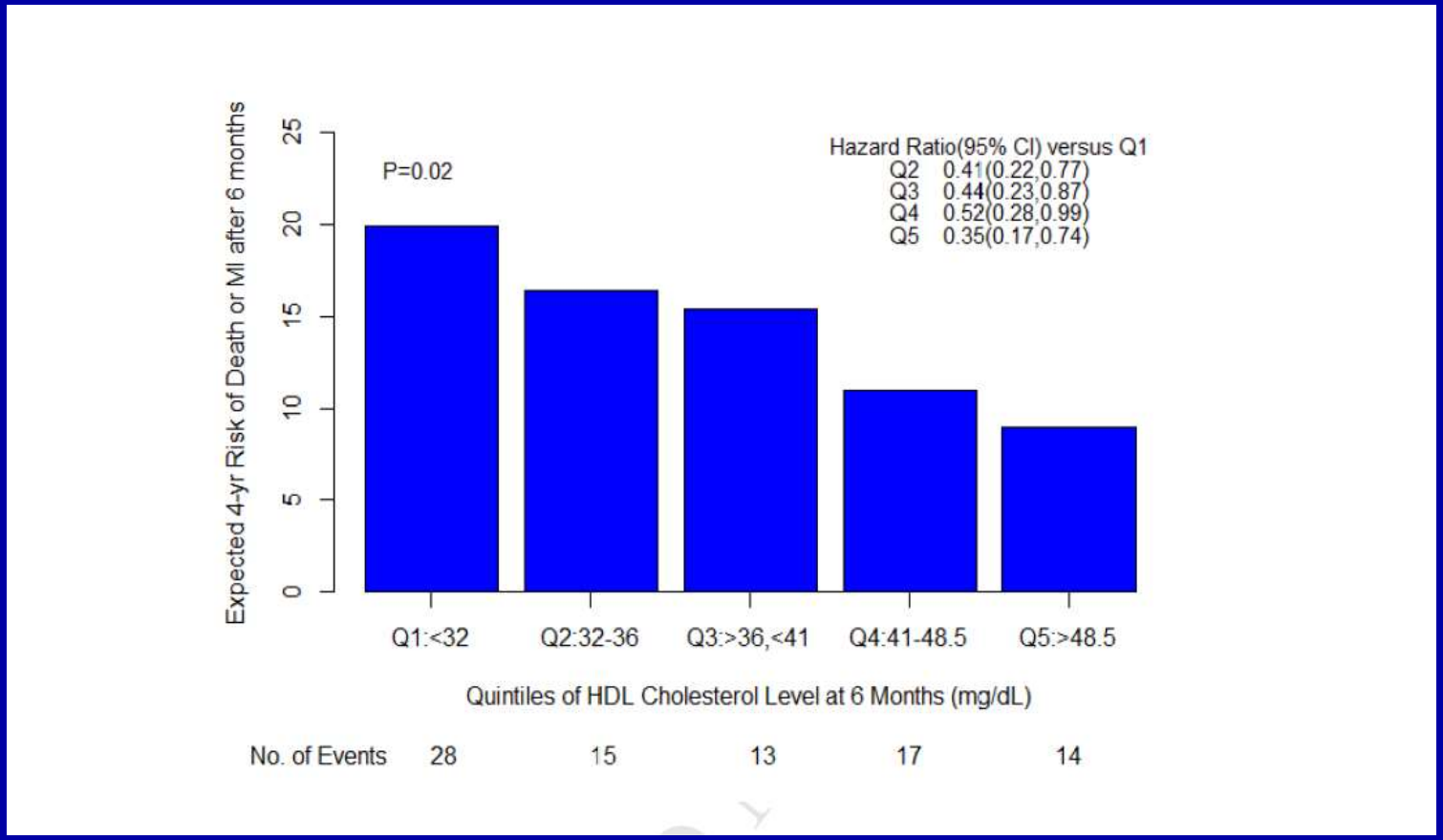
- Helps explain why apoB is predictive (contains VLDL & IDL).
- Helps explain why even aggressive statin rx may not be enough (no effect on remnants).
- Lends support for use of niacin; especially in pts with high TG (surrogate for remnants).
- Must wonder if LDL-C would be causal in non-obese & non-DM pts!
- This is a big deal study adding support to inflammation as cause of ASVD and explaining increased risk of people with increased TG.

HDL Remains Important in Stable CHD on Optimal LDL Therapy

- Post hoc analysis 2,193 COURAGE pts; HDL change in first 6 months as predictor of CV events at 4 yrs
- Quartile of HDL-C was a significant, independent predictor of death/MI (P = 0.05).
- Pts with LDL-C levels < 70 mg/dL, had 65% relative risk reduction in death/MI with HDL in the highest quintile compared to the lowest quintile, (P=0.02).

Acharjee, S., et. al. (2013) Low Levels of High Density Lipoprotein Cholesterol and Increased Risk of Cardiovascular Events in Stable Ischemic Heart Disease Patients: A Post Hoc Analysis from the COURAGE Trial. *J Am Coll Cardiol*(0). doi: http://dx.doi.org/10.1016/j.jacc.2013.07.051

HDL Remains Important in Stable CHD on Optimal LDL Therapy



Acharjee, S., et. al. (2013) *J Am Coll Cardiol*(0). doi: http://dx.doi.org/10.1016/j.jacc.2013.07.051

HDL is Predictive of CV Risk

- 6,111 pts with ASVD; either CDH, CVD, PVD or AAA; theoretical % of LDL-c reduction was determined based on particular medication used (~2/3 on lipid lowering rx); follow-up was q 6 months/pt questionnaire; end points were CV death; MI; stroke
- Baseline HDL evaluated as predictor of risk
- Followed mean of 5.4 yrs; 874 CV events

van de Woestijne, A. P., et. al. (2013). Low HDL-cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid-lowering medication. *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.04.101

HDL is Predictive of CV Risk

- Per 3.9 mg/dL increase in HDL-c the risk of vascular events decreased 5% in pts not on lipid rx

  HR- 0.95 (95%CI 0.92-0.99)

- Per 3.9 mg/dL increase in HDL-c the risk of vascular events decreased with 6% in pts on “usual” lipid rx

  HR- 0.94 (95%CI 0.90-0.98)

- If pt on “intensive” lipid rx, no relationship was seen

Adjusted for: age, sex, DM, BMI, TG, smoking, alcohol

van de Woestijne, A. P., et. al. (2013) *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.04.101

HDL is Predictive of CV Risk

- This study is rather worthless as lipids were only measured at baseline and medications used were only assessed at baseline.

- Really shocked that JACC even published this!! ?????

van de Woestijne, A. P., et. al. (2013) *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.04.101

HDL Remains Important After LDL Treatment

- Meta-analysis 8 statin trials; 38,153 statin rx'ed pts; followed one year; 5,387 MACEs

- HDL-C was assoc. with a reduced risk of MACE

  HR- 0.83 (95%CI- 0.81-0.86) per 1 standard deviation increment

- Assoc. remained even in pts achieving on-statin LDL-C levels < 50 mg/dL

Boekholdt, S. M., et. al. (2013). Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events among Statin-Treated Patients: A Meta-Analysis. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.002670

HDL Remains Important After LDL Treatment

- Pts in the top quintile of on-statin HDL-C had much less risk of MACE compared to bottom quintile

  multivariable adjusted HR-0.65 (95%CI 0.59-0.71)

- The strong inverse assoc. btw HDL-C and risk of MACE was virtually unaffected by LDL-C from >130 mg/dL to < 50mg/dL

Boekholdt, S. M., et. al. (2013). Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events among Statin-Treated Patients: A Meta-Analysis. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.002670

HDL Remains Important After LDL Treatment

- apoA-I was assoc. with a reduced risk of MACE

  HR- 0.79 (95%CI- 0.72-0.82)

- An increase in apoA-I was assoc. with reduced risk

  HR- 0.93 (95%CI- 0.90-0.97)

  this was not true for HDL

- Implies rx to raise apoA-1 will reduce CV risk

Boekholdt, S. M., et. al. (2013). Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events among Statin-Treated Patients: A Meta-Analysis. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.002670

HDL Remains Important After LDL Treatment

Trial	% Δ HDL & apoA1 control	% Δ HDL & apoA1 rx arm
4S	-3.3 -6.0	+4.4 -5.1
AFCAPS-TexCAPS	+1.3 +3.7	+6.2 +6.7
LIPID	-2.7 +2.8	+3.8 +5.8
CARDS	-2.7 -4.1	-1.5 -3.9
TNT*	-2.3 +0.1	-2.9 -3.0
IDEAL^	+2.4 +3.7	-0.7 -0.9
SPARCL	+1.2 +2.7	+3.4 +1.7
JUPITER	+1.8 -0.8	+6.3 +1.1

- *Atorvastatin 10mg instead of placebo
- ^ Simvastain 20mg instead of placebo

Boekholdt, S. M., et. al. (2013). Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events among Statin-Treated Patients: A Meta-Analysis. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.002670

ApoA1 in Arterial Wall Compared to Plasma is Distinctly Different in Distribution, Make-up and Function

- Antibody developed to recognize lipid-free and HDL-associated apoA1 in both native and oxidized forms.
- Examined homogenates of aorta – both atherosclerotic and non-atherosclerotic.

DiDonato, J. A., et. al. (2013). The Function and Distribution of Apolipoprotein A1 in the Artery Wall are Markedly Distinct from those in Plasma. *Circulation*. doi: 10.1161/circulationaha.113.002624

ApoA1 in Arterial Wall Compared to Plasma is Distinctly Different in Distribution, Make-up and Function

- >100-fold enrichment of apoA1 in ASVD tissue compared to normal aorta ($P<0.001$)
- <3% of apoA1 from normal or ASVD tissue was assoc. with HDL
- Functionally, wall apoA1 had ~80% lower cholesterol efflux activity and ~90% lower LCAT activity than plasma apoA1

DiDonato, J. A., et. al. (2013). The Function and Distribution of Apolipoprotein A1 in the Artery Wall are Markedly Distinct from those in Plasma. *Circulation*. doi: 10.1161/circulationaha.113.002624

ApoA1 in Arterial Wall Compared to Plasma is Distinctly Different in Distribution, Make-up and Function

Arterial wall apoA1 is markedly enriched within atherosclerotic-plaque, predominantly lipid-poor, not associated with HDL, extensively oxidatively cross-linked, and functionally impaired.

DiDonato, J. A., et. al. (2013). The Function and Distribution of Apolipoprotein A1 in the Artery Wall are Markedly Distinct from those in Plasma. *Circulation*. doi: 10.1161/circulationaha.113.002624

ApoA1 in Arterial Wall Compared to Plasma is Distinctly Different in Distribution, Make-up and Function

- This study along with others suggest that measurement in the circulation of HDL-C, apoA1, or even cholesterol efflux activity, may not adequately reflect what is happening within the artery wall.

- Development of a "dysfunctional HDL" assay that detects forms of apoA1 formed in the artery wall but which diffuse back out into the circulation may be what is needed to provide insights into the processes happening within the artery wall.

DiDonato, J. A., et. al. (2013). The Function and Distribution of Apolipoprotein A1 in the Artery Wall are Markedly Distinct from those in Plasma. *Circulation*. doi: 10.1161/circulationaha.113.002624

BD Method Thoughts: HDL & apoA1

- HDL is predictive - ? surrogate for remnant cholesterol (usual. low with IR & high TG).
- If trying to assess benefit of rx, perhaps should just measure apoA1.
- Hopefully a dysfunctional HDL measure will emerge.

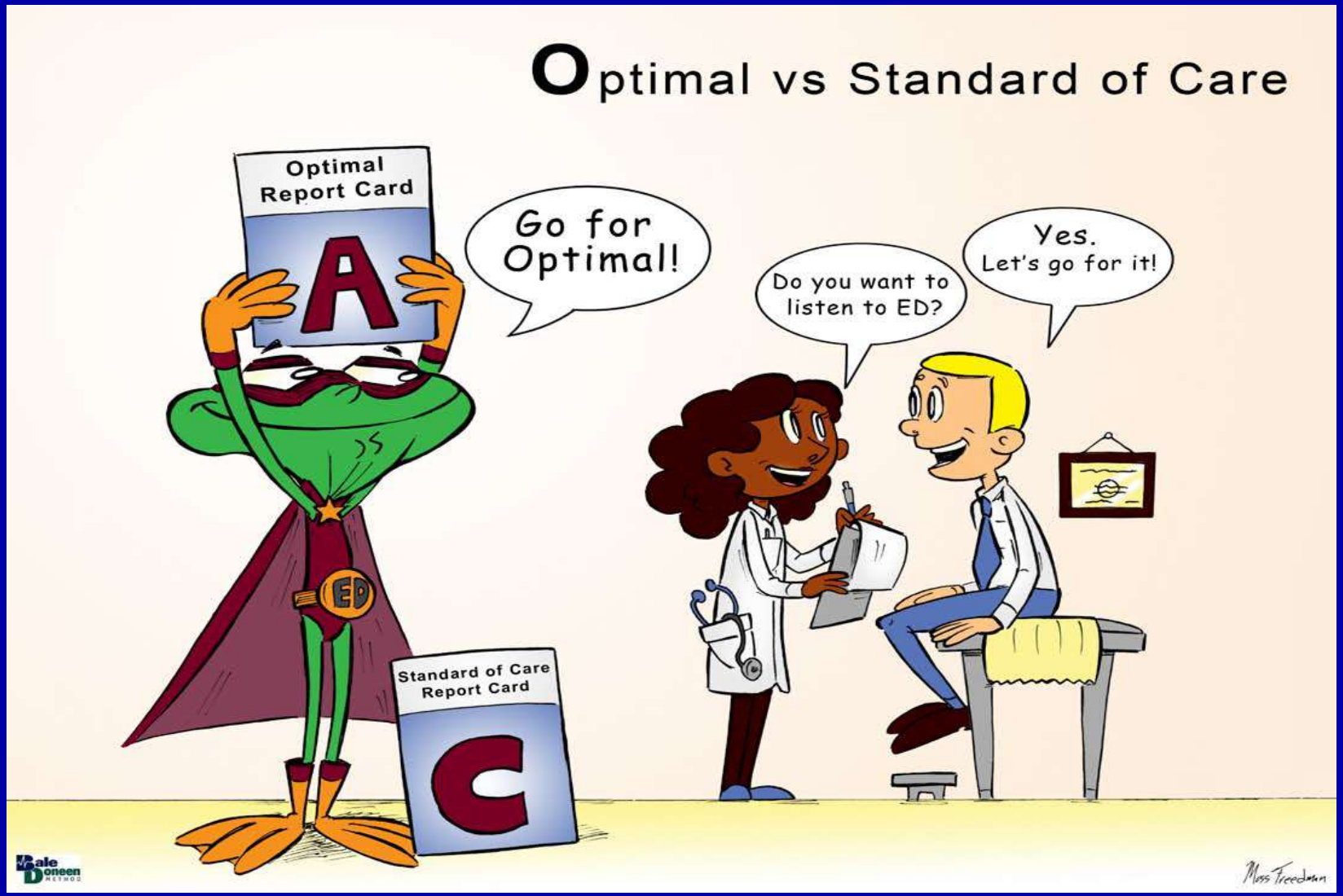
Aggregatibacter actinomycetemcomitans (A.a.) Leukotoxin Detrimental to Endothelial Cells

- *A.a.* generates leukotoxin; purified leukotoxin from *A.a.* was applied *in vitro* to human microvascular endothelial cells

- Numerous detrimental effects were noted:
  1) decreased proliferation
  2) apoptosis
  3) increased VCAM & ICAM

Dietmann, A., et. al. (2013). Effects of Aggregatibacter actinomycetemcomitans leukotoxin on endothelial cells. *Microb Pathog, 61-62*, 43-50.

Optimal Care



Vitamin D Deficiency More Important in Whites and Chinese

- 6,436 pts (MESA) no known CVD; followed 8.5 yrs.; 361 CHD events; evaluated baseline vit. D as predictor of risk

- Vit. D 1) low was <20 ng/mL (n=2131) 2) medium was 20-29 ng/mL (n=2224) 3) high was ≥30 ng/mL (n=2081)

- Results adjusted for known CHD risk factors.

Robinson-Cohen C, H. A. N. I. J. H., & et al. (2013). RAcial differences in the association of serum 25-hydroxyvitamin d concentration with coronary heart disease eventsrace and chd events associated with vitamin d race and chd events associated with vitamin d. *JAMA, 310*(2), 179-188.

Vitamin D Deficiency More Important in Whites and Chinese

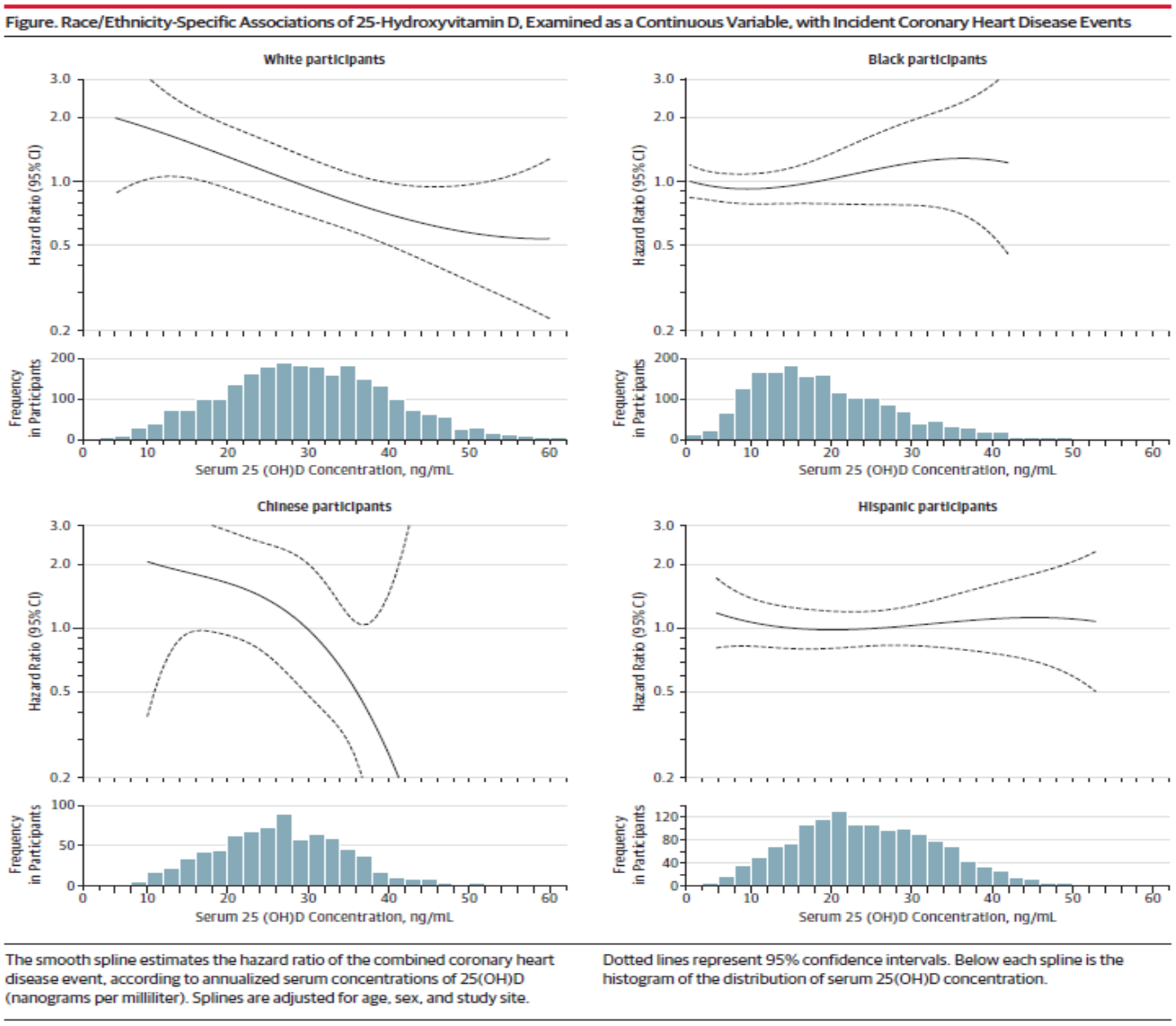
- Lower vit. D was associated with a greater risk in Whites: n = 167; HR-1.26 [95%CI, 1.06-1.49] for each 10-ng/mL decrement in 25(OH)D

- Lower vit. D was associated with a greater risk in Chinese: n=27; HR-1.67 [95%CI, 1.07-2.61]

- Lower vit. D not associated with risk in Blacks: n=94; HR -0.93 [95%CI, 0.73-1.20] or Hispanics: n=73; HR - 1.01 [95%CI, 0.77-1.33]

Robinson-Cohen C, H. A. N. I. J. H., & et al. (2013) *JAMA, 310*(2), 179-188. doi: 10.1001/jama.2013.7228

Vitamin D Deficiency More Important in Whites and Chinese



Robinson-Cohen C, H. A. N. I. J. H., & et al. (2013) *JAMA*, *310*(2), 179-188. doi: 10.1001/jama.2013.7228

Vitamin D Deficiency More Important in Whites and Chinese: Why????

- Low 25(OH)D may lead to 1,25 dihydroxyvitamin D deficiency with resulting inappropriate activation of RAAS and dysregulation of immune cell functions.

- Blacks have higher circulating concentrations of 1,25-dihydroxyvitamin D, despite lower 25 (OH)D.

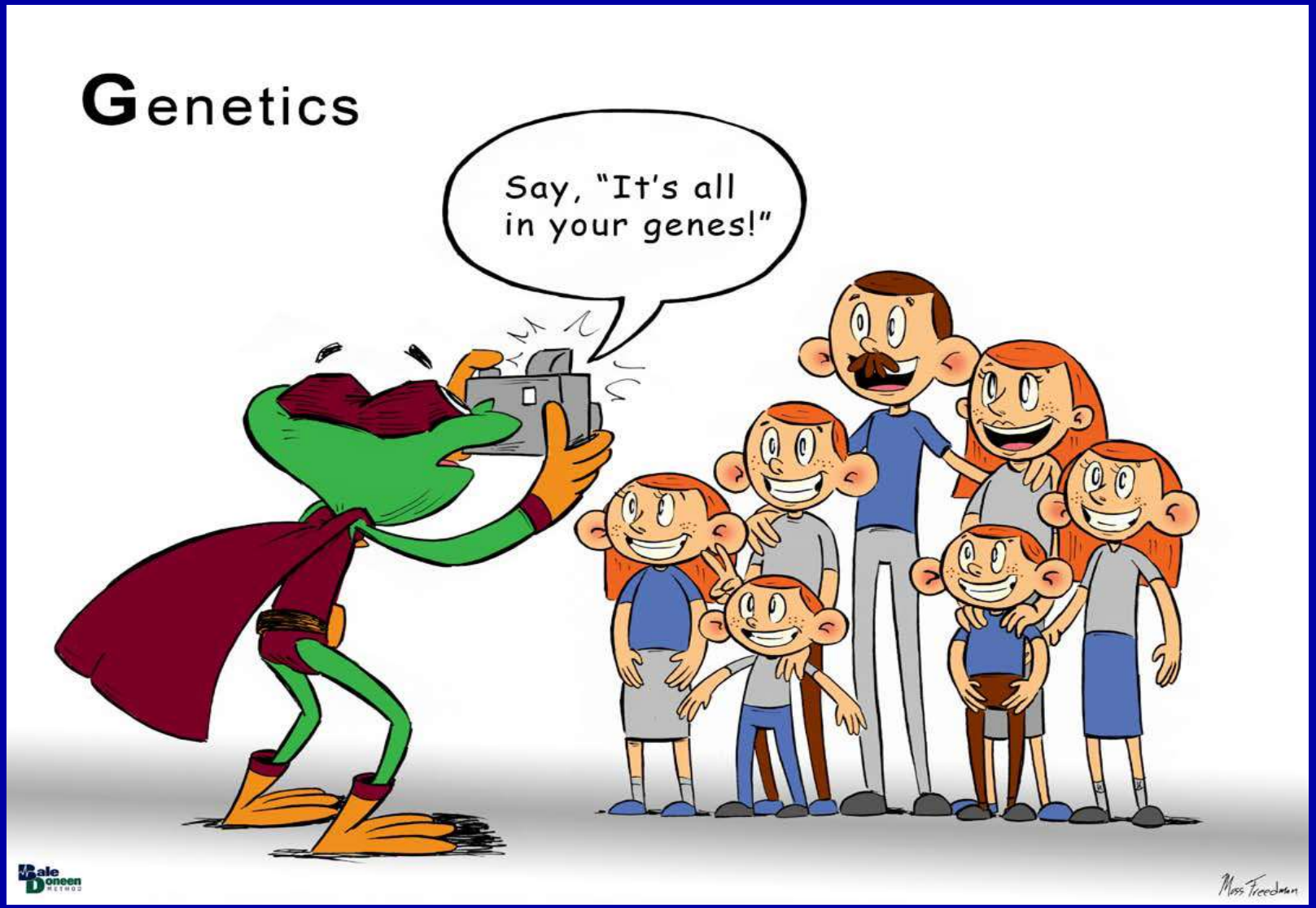
- Vitamin D receptor affinity for vitaminD metabolites may vary by race.

Robinson-Cohen C, H. A. N. I. J. H., & et al. (2013) *JAMA, 310*(2), 179-188. doi: 10.1001/jama.2013.7228

BD Methods Thoughts

- May help explain discrepancies for vit. D importance in various studies.
- ‘Optimal’ cut points will need to be determined for ethnicity.
- Should we stop measuring the levels in Blacks and Hispanics??

Genes



Bale Doneen METHOD

Apo E Genotype Influences Aerobic Exercise's Effect on Postprandial Lipid (PPL) Levels

- 30 healthy men equally divided btw ApoE 2/3, 3/3, 3/4; baseline lipids similar; postprandial lipidemia assessed in response to exercise

- Random sequence of exercise separated by a minimum 48 hrs, as follows: (a) no exercise (control), (b) intense intermittent exercise, (c) moderate continuous exercise.

500 Kcal was end point for exercise

- Each test series was completed 30-min before ingestion of a high-fat meal (1 g fat/kg). Lipids assessed at 1, 2, 3 and 4 h post meal.

Ferreira, A. P., et. al. (2013). The effect of aerobic exercise intensity on attenuation of postprandial lipemia is dependent on apolipoprotein E genotype. *Atherosclerosis, 229*(1), 139-144.

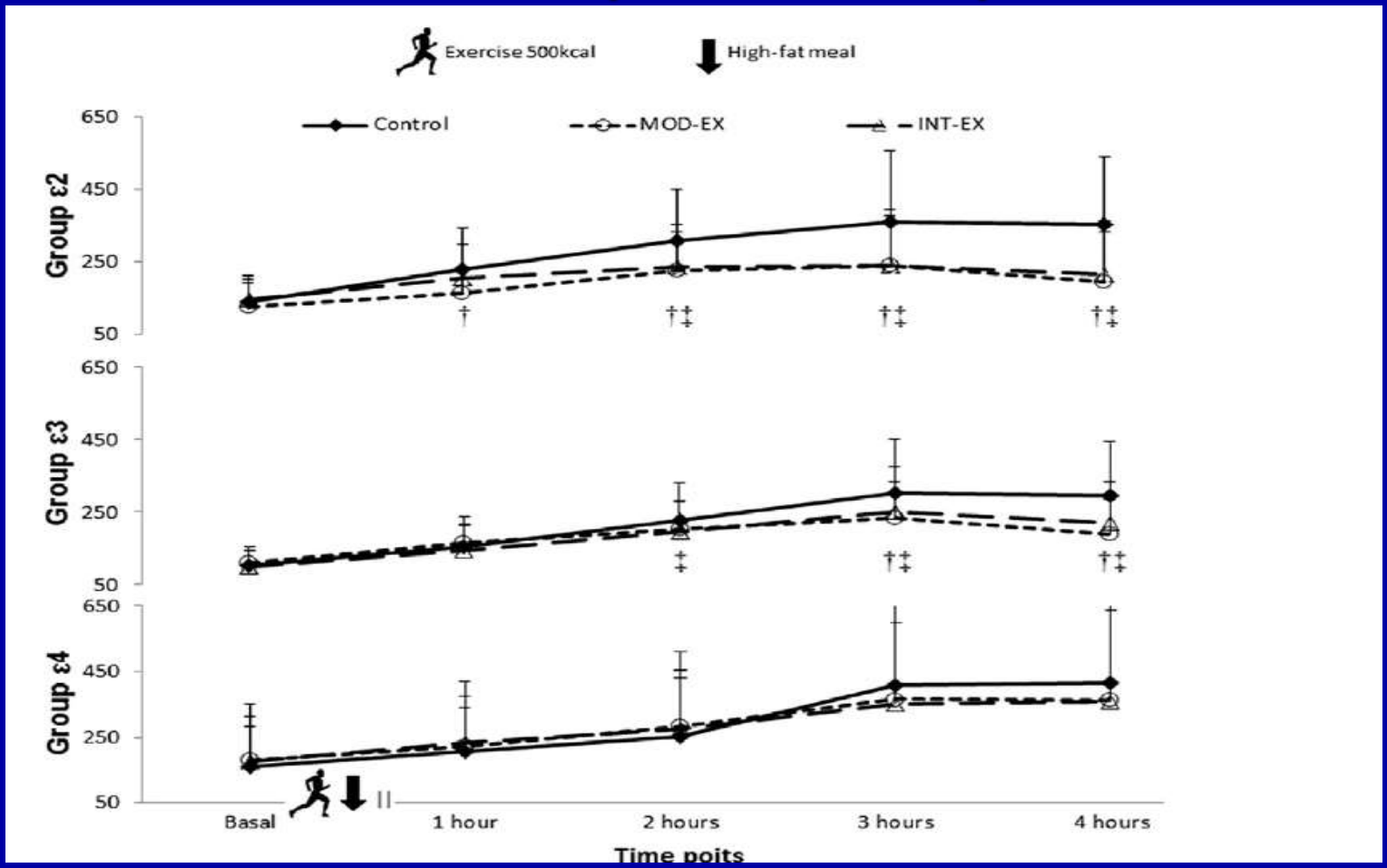
Apo E Genotype Influences Aerobic Exercise's Effect on Postprandial Lipid (PPL) Levels

- Moderate and intense exercise were effective in attenuating PPL in both apoE 2/3 & 3/3 subjects
- apoE 2/3's had greater benefit with moderate training than 3/3 subjects.
- apoE 3/4's showed no benefit with exercise for PPL

remember remnant cholesterol (i.e. PPL) data!!!

Ferreira, A. P., et. al. (2013). The effect of aerobic exercise intensity on attenuation of postprandial lipemia is dependent on apolipoprotein E genotype. *Atherosclerosis, 229*(1), 139-144.

Apo E Genotype Influences Aerobic Exercise's Effect on Postprandial Lipid Levels



Ferreira, A. P., et. al. (2013). The effect of aerobic exercise intensity on attenuation of postprandial lipemia is dependent on apolipoprotein E genotype. *Atherosclerosis, 229*(1), 139-144.

Apo E Genotype Influences Aerobic Exercise's Effect on Postprandial Lipid Levels

- BDM thoughts:

  even more important for apoE 4's to avoid high fat diets

  should avoid eating large meals

  ??dark chocolate even more important??

  ??women respond similarly???

Ferreira, A. P., et. al. (2013). The effect of aerobic exercise intensity on attenuation of postprandial lipemia is dependent on apolipoprotein E genotype. *Atherosclerosis, 229*(1), 139-144.

EDFROG IRA

Education	Genetics	Individual Management
Disease	Optimal	Risk factor response
Fire	Roots	Assess Disease Annually

Coffee can be Beneficial

- Coffee consumption may reduce the risk of type 2 DM and BP, as well as obesity and depression.

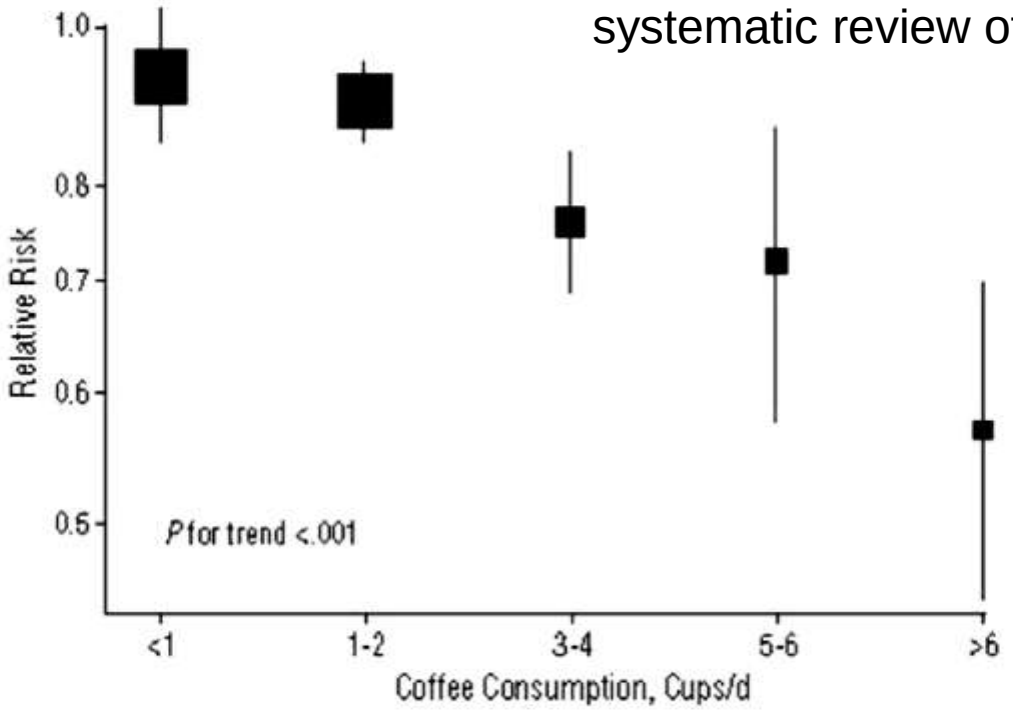
- Data suggests that habitual coffee consumption is neutral to beneficial regarding: CAD, CHF, arrhythmias and stroke.

- A daily intake of 2 to 3 cups appears to be safe and is associated with neutral to beneficial effects.

O'Keefe, J. H., Lavie, C. J. 9/17/(2013). Effects of Habitual Coffee Consumption on Cardiometabolic Disease, Cardiovascular Health, and All-cause Mortality. *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.06.035

Coffee can Reduce Risk DM

systematic review of 9 cohort studies



The Relationship Between Coffee Consumption and Subsequent Type 2 Diabetes Mellitus in Different Categories of Coffee Consumption

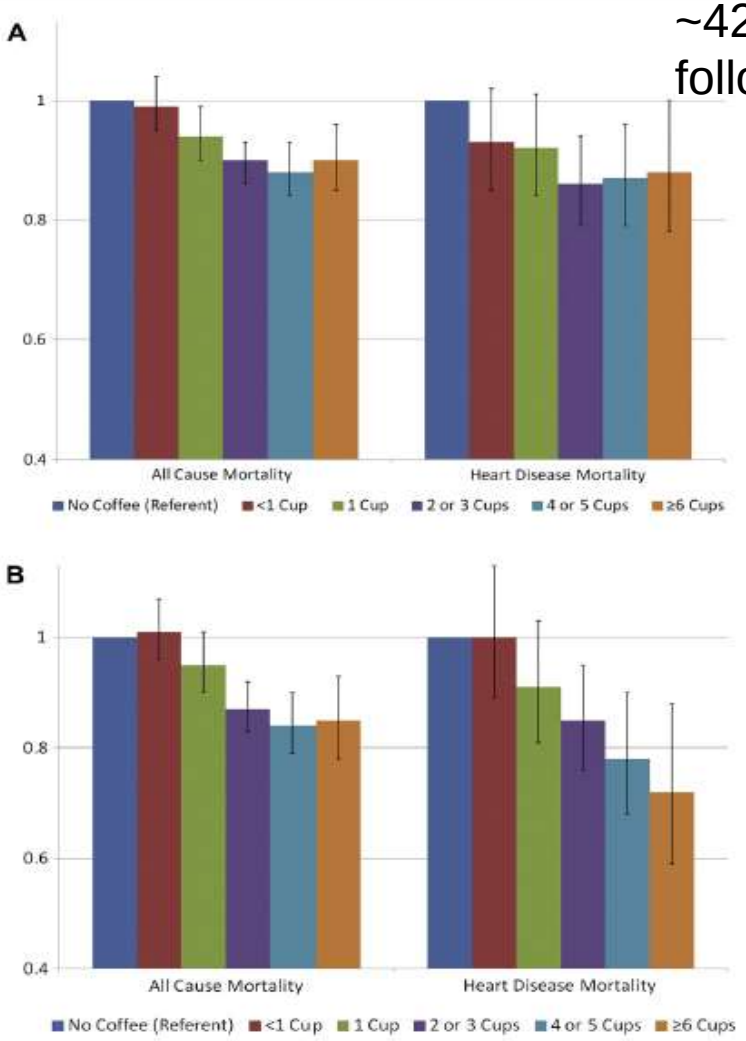
O'Keefe, J. H., Lavie, C. J. (2013). Effects of Habitual Coffee Consumption on Cardiometabolic Disease, Cardiovascular Health, and All-cause Mortality. *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.06.035

Coffee Reduces Mortality: CHD & All-cause

~420,000 pts
followed ~12 yrs.

unadjusted

Adjusted:
Smoking
EtoH
Dietary fat
BMI
Exercise



print & web 4C/FPO

Figure 2 Adjusted Hazard Ratios for Risk of Death as a Function of Coffee Consumption

O'Keefe, J. H., Lavie, C. J. (2013). *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.06.035

Coffee can Reduce HF Risk

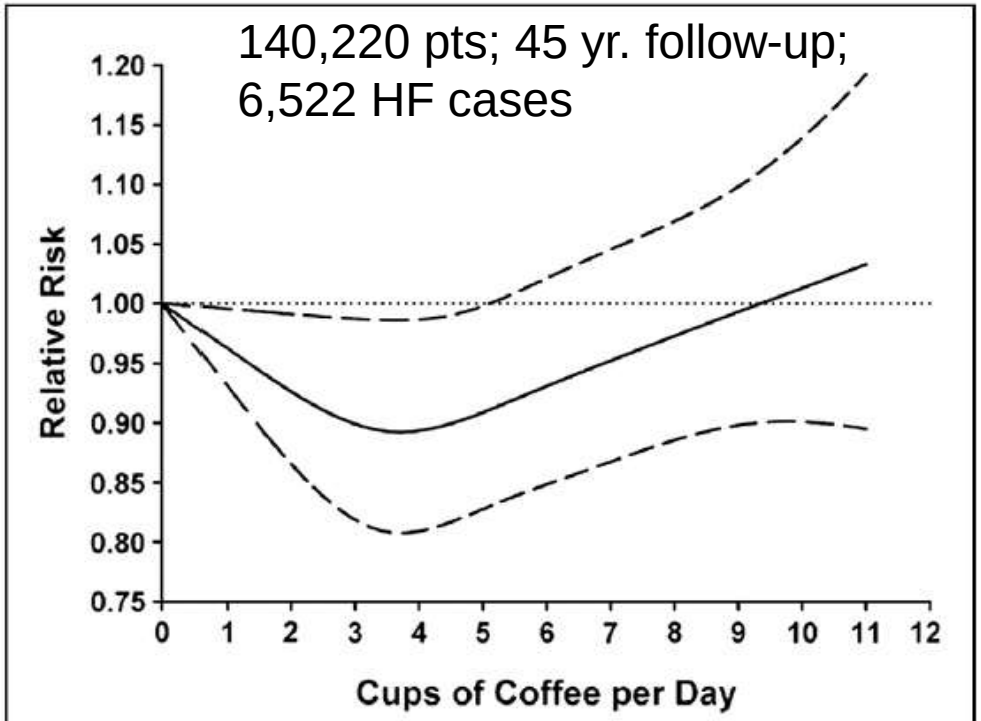


Figure 3 **Coffee and Risk of Heart Failure**

Association between heart failure and cups of coffee per day compared with no consumption. Relative risk **(solid line)** and 95% CI **(dashed lines)**. **Error bars** indicate 95% confidence interval. Adapted from Freedman et al. (25) and Mostofsky et al. (29).

O'Keefe, J. H., Lavie, C. J. (2013). *J Am Coll Cardiol*. doi: 10.1016/j.jacc.2013.06.035

Coffee: Too Much can be Deadly

- 43,727 pts.; 20-87 yo; 22% female; median follow-up 17 yrs.; 2,512 deaths (314 women) with 804 CVD; assessed coffee intake's association with mortality risk

- Consumption of regular coffee was grouped cups/wk: a) 0 b) 1- 7 c) 8-14 d)15-21 e)22-28 f) >28

- Multivariate models were adjusted for: age, baseline exam yr, decaffeinated use, tea use, decaffeinated tea use, physical inactivity, BMI, smoking, alcohol, DM, BP, lipids, parental hx of CVD, and CRF.

Liu, J., Sui, X., Lavie, C. J. et. al. Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality. *Mayo Clinic Proceedings*(0). doi: http://dx.doi.org/10.1016/j.mayocp.2013.06.020

Coffee: Too Much can be Deadly

- The only significant association found was with all-cause mortality in men and women <55 yo who consume >28 cups/wk

HR- 1.56 (95% CI, 1.30-1.87)

HR- 2.13 (95% CI, 1.26-3.59)

respectively

Liu, J., Sui, X., Lavie, C. J. et. al. Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality. *Mayo Clinic Proceedings*(0). doi: http://dx.doi.org/10.1016/j.mayocp.2013.06.020

Coffee: Too Much can be Deadly

There was no significant association with coffee intake and CVD mortality in men or women

Liu, J., Sui, X., Lavie, C. J. et. al. Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality. *Mayo Clinic Proceedings*(0). doi: http://dx.doi.org/10.1016/j.mayocp.2013.06.020

BD Method Thoughts

Seeds Reduce CV Risk

- Substantial evidence increased consumption of seeds, including whole grains, nuts, legumes, cocoa products, and coffee, is associated with lower risk of CVD and T2DM.

- Dietary recommendations should embrace a wide array of seeds as part of a plant-based dietary program.

Ros, E., & Hu, F. B. (2013). Consumption of Plant Seeds and Cardiovascular Health: Epidemiological and Clinical Trial Evidence. Circulation, 128(5), 553-565.

Seeds Reduce CV Risk

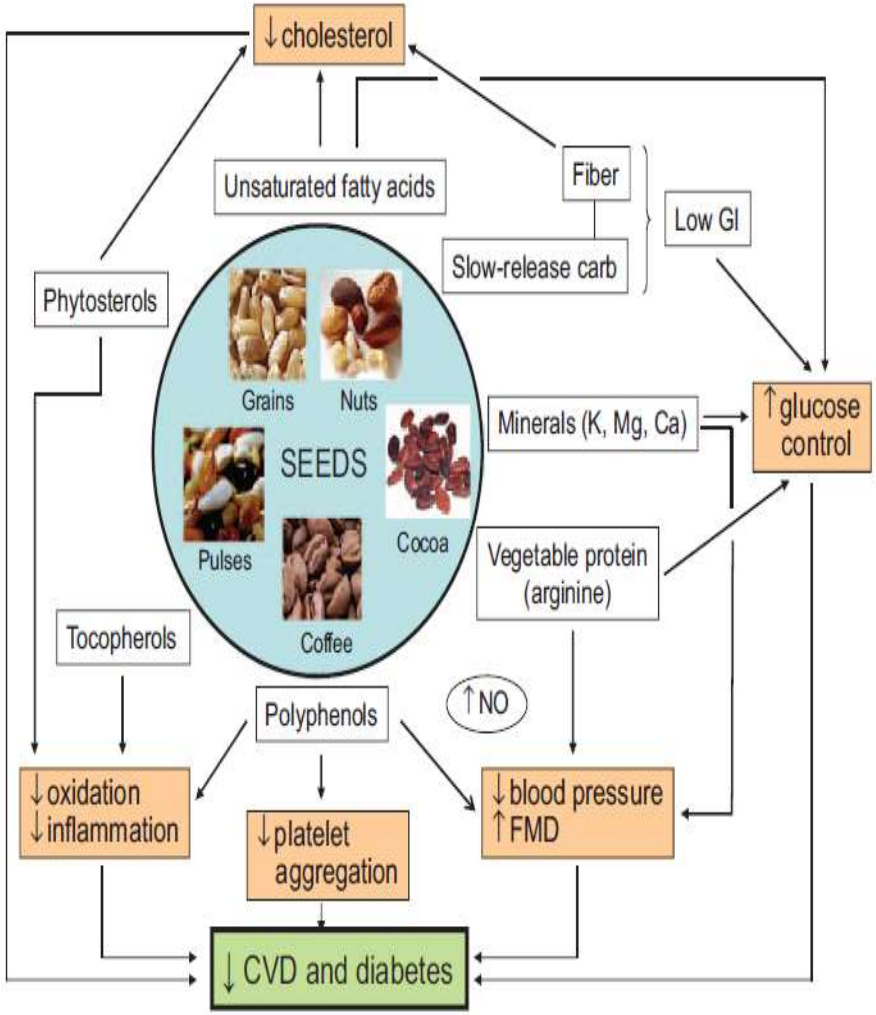


Figure. The consumption of seeds improves cardiovascular health because of their unique composition in bioactive nutrients and phytochemicals and a complex synergy among them for effects on metabolic and vascular physiology pathways. The main known nutrients of seeds are represented together with their principal biological targets (long-arrow connections). The net effects on intermediate markers of cardiovascular risk that have been demonstrated for most seed classes in clinical trials are cholesterol-lowering, improved glycemic control, decreased blood pressure, improved vasomotion, reduced platelet aggregation, and antioxidant and anti-inflammatory actions. The overall result is reduced CVD and T2DM, as suggested for all seeds in observational cohort studies and observed for nuts in clinical trials. See text for details. Ca indicates calcium; carb, carbohydrate; CVD, cardiovascular disease; FMD, flow-mediated vasodilation; GI, glycemic index; K, potassium; Mg, magnesium; NO, nitrous oxide; and T2DM, type 2 diabetes mellitus.

Ros, E., & Hu, F. B. (2013). *Circulation, 128*(5), 553-565.

Smart Gal

Fruit Reduces Risk of Diabetes

- 187,382 non-DM; 81% women; followed ~ 18 yrs.; 12,198 cases new-onset DM; evaluated fruit consumption as risk factor

- Adjusted for known personal, lifestyle and dietary risk factors for new-onset DM

- Every three servings/week of total whole fruit reduced the risk

HR-0.98 (95% CI, 0.96 to 0.99)

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

Fruit Reduces Risk of Diabetes

- Fruit juice consumption significantly increased the risk of DM

  HR-1.08 (95%CI, 1.05 - 1.11).

- Individual fruits differed significantly in their association with new-onset DM - $p<0.001$ in all cohorts.

  (the glycemic index/glycemic load values of fruits did not account for the differences)

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

Fruit Reduces Risk of Diabetes

Table 3| **Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole fruit consumption in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study**

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Cantaloupe								
Nurses' Health Study†:	1231/250 261	2292/516 604	2098/458 752	737/168 509				
Adjusted hazard ratio‡	1.00	1.00 (0.93 to 1.08)	1.06 (0.98 to 1.15)	1.07 (0.96 to 1.19)		1.08 (0.98 to 1.18)		
Nurses' Health Study II†:	890/345 001	1257/595 757	773/364 046	233/111 307				
Adjusted hazard ratio‡	1.00	0.99 (0.90 to 1.09)	1.05 (0.94 to 1.17)	1.11 (0.94 to 1.30)		1.12 (0.96 to 1.32)		
Health Professionals Follow-up Study†:	655/165 084	1230/292 381	562/137 179	240/59 759				
Adjusted hazard ratio‡	1.00	1.15 (1.03 to 1.27)	1.17 (1.03 to 1.34)	1.19 (1.01 to 1.40)		1.14 (0.98 to 1.34)		
Pooled results‡§	1.00	1.03 (0.98 to 1.08)	1.08 (1.02 to 1.14)	1.10 (1.02 to 1.19)		1.10 (1.02 to 1.18)	0.01	0.77

Significant increased risk with 2-4 servings/wk of Cantaloupe

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

Fruit Reduces Risk of Diabetes

Table 3| **Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole fruit consumption in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study**

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Apples and pears								
Nurses' Health Study†:	584/102 327	1375/275 896	1418/288 494	1861/437 158	1120/290 252			
Adjusted hazard ratio‡	1.00	0.94 (0.84 to 1.04)	0.94 (0.84 to 1.05)	0.85 (0.77 to 0.95)	0.82 (0.73 to 0.92)	0.91 (0.87 to 0.95)		
Nurses' Health Study II†:	334/98 142	835/322 737	688/303 354	881/463 781	415/228 096			
Adjusted hazard ratio‡	1.00	0.83 (0.72 to 0.95)	0.83 (0.72 to 0.96)	0.79 (0.68 to 0.91)	0.76 (0.64 to 0.90)	0.93 (0.86 to 0.99)		
Health Professionals Follow-up Study†:	251/50 846	631/144 067	527/123 440	786/203 567	492/132 482			
Adjusted hazard ratio‡	1.00	0.91 (0.78 to 1.06)	0.98 (0.83 to 1.16)	0.91 (0.77 to 1.07)	0.93 (0.78 to 1.11)	0.98 (0.92 to 1.06)		
Pooled results‡§	1.00	0.90 (0.83 to 0.96)	0.92 (0.85 to 0.99)	0.85 (0.78 to 0.92)	0.83 (0.76 to 0.90)	0.93 (0.90 to 0.96)	<0.001	0.19

Significant reduced risk with Apples and Pears

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

Fruit Reduces Risk of Diabetes

Table 3| **Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole fruit consumption in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study**

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Grapefruit								
Nurses' Health Study†:	2225/411 039	1873/426 864	1177/269 719	813/212 965	270/73 539			
Adjusted hazard ratio‡	1.00	0.91 (0.85 to 0.97)	0.95 (0.88 to 1.03)	0.88 (0.80 to 0.96)	0.86 (0.75 to 0.98)	0.92 (0.87 to 0.98)		
Nurses' Health Study II†:	1667/682 234	881/438 763	350/166 255	202/104 317	53/24 543			
Adjusted hazard ratio‡	1.00	1.00 (0.91 to 1.09)	1.06 (0.94 to 1.20)	0.97 (0.83 to 1.14)	0.91 (0.69 to 1.21)	0.97 (0.86 to 1.09)		
Health Professionals Follow-up Study†:	933/215 578	816/201 584	414/100 589	365/97 276	159/39 377			
Adjusted hazard ratio‡	1.00	1.03 (0.93 to 1.14)	1.09 (0.96 to 1.24)	0.93 (0.81 to 1.06)	1.08 (0.90 to 1.30)	0.99 (0.91 to 1.08)		
Pooled results‡§	1.00	0.96 (0.91 to 1.00)	1.00 (0.94 to 1.06)	0.91 (0.85 to 0.97)	0.93 (0.84 to 1.03)	0.95 (0.91 to 0.99)	0.02	0.42

Significant reduced risk with 2-4 servings/wk for Grapefruit

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

Fruit Reduces Risk of Diabetes

Table 3| **Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole fruit consumption in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study**

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Blueberries								
Nurses' Health Study†:	3711/720 706	1798/448 560	693/176 252	156/48 609				
Adjusted hazard ratio‡	1.00	0.90 (0.85 to 0.96)	0.89 (0.82 to 0.98)	0.82 (0.69 to 0.98)		0.77 (0.66 to 0.91)		
Nurses' Health Study II†:	2021/761 856	757/435 865	280/153 746	95/64 644				
Adjusted hazard ratio‡	1.00	0.83 (0.76 to 0.91)	0.90 (0.79 to 1.04)	0.69 (0.55 to 0.87)		0.67 (0.54 to 0.83)		
Health Professionals Follow-up Study†:	1687/383 033	779/207 202	165/45 628	56/18 540				
Adjusted hazard ratio‡	1.00	0.94 (0.85 to 1.03)	0.96 (0.80 to 1.15)	0.74 (0.55 to 1.00)		0.75 (0.58 to 0.98)		
Pooled results‡§	1.00	0.89 (0.85 to 0.93)	0.91 (0.84 to 0.97)	0.77 (0.67 to 0.87)		0.74 (0.66 to 0.83)	<0.001	0.57

Significant reduction in risk from Blueberries

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

Fruit Reduces Risk of Diabetes

- Further research is needed to confirm our findings on specific fruits in relation to type 2 diabetes.
- The results support recommendations on increasing consumption of a variety of whole fruits as a measure for diabetes prevention.
- Perhaps blueberries, grapes, pears and apples are the most effective in this regard.
- Bottom line: eating fruit does not cause diabetes!!!

Muraki, I., et. al. (2013). Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *Bmj, 347*, f5001. doi: 10.1136/bmj.f5001

HDL Increased with Tomato Consumption

- 50 pts.; 82% women; mean age of 42 ± 15.5 yrs; mean BMI of 27.6 ± 5.0 kg/m2; HDL<50mg/dL female or < 40mg/dL male; TG<150 mg/dL

- 2-wk run-in isocaloric diet; then randomized to 300 g of cucumber (control group) or two uncooked Roma tomatoes a day for 4 weeks.

- mean HDL-C increase was 5.0 ± 2.8 mg/dL (range 1–12 mg/dL)significant increase in HDL-C levels with tomato vs control

  36.5 ± 7.5 mg/dL to 41.6 ± 6.9 mg/dL, P <0.0001

Daniel Cuevas-Ramos, et. al. Effect of tomato consumption on high-density lipoprotein cholesterol level: a randomized, single-blinded, controlled clinical trial. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 7/2013:6 263–273

HDL Increased with Tomato Consumption

- Significant increase in HDL-C levels in tomato group

  36.5 ± 7.5 mg/dL to 41.6 ± 6.9 mg/dL, P <0.0001

- Tomato group- mean HDL-C increase was 5.0 ± 2.8 mg/dL (range 1–12 mg/dL)

- Non-significant change in HDL-C in control group

  36.8 ± 7.2 mg/dL to 35.8 ± 7.3 mg/dL, p=0.08

Daniel Cuevas-Ramos, et. al. Effect of tomato consumption on high-density lipoprotein cholesterol level: a randomized, single-blinded, controlled clinical trial. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 7/2013:6 263–273

Exercise Reduces Stroke Risk

- 27,348 Blacks & Whites ≥45 yo; evaluated impact of exercise frequency on stroke and TIA incidence over 5.7 yrs.

- 3 categories of physical activity (PA): a) none (1/3 of pts) b)1- 3X/wk c) ≥4X/wk

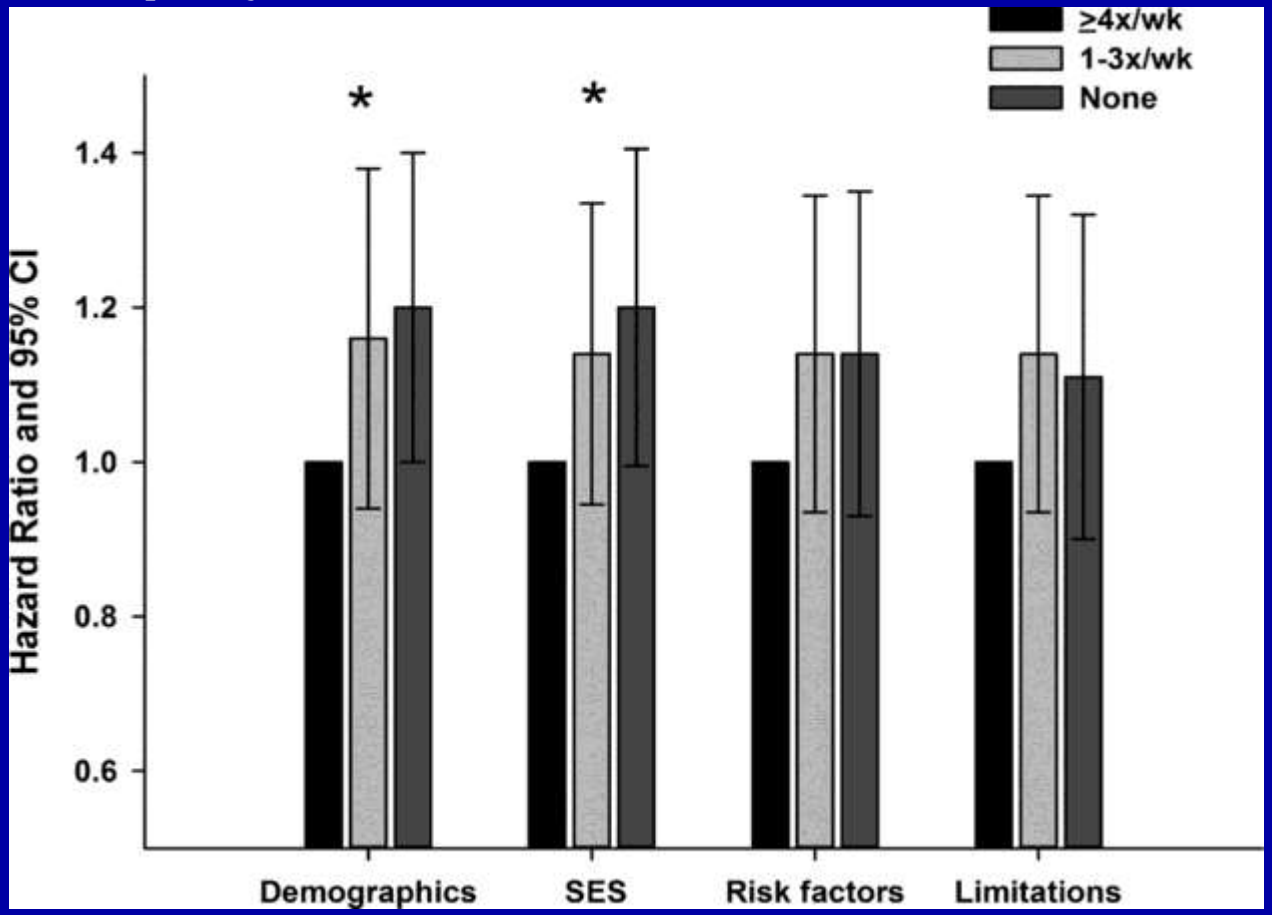
  (PA- based on sweating)

- Subjects would did not exercise were 20% more likely to suffer a stroke or TIA than those who exercised enough to break a sweat ≥4X/wk

McDonnell, M. N. (2013). Physical Activity Frequency and Risk of Incident Stroke in a National US Study of Blacks and Whites. *Stroke*. 44:2519-2524

Exercise Reduces Stroke Risk

PA frequency and risk of incident stroke/transient ischemic attack.



The initial regression model included adjustment for demographics (age, sex, race, and age–race interaction) and then further adjustments were performed for 3 additional models: socioeconomic status (including region, urban/rural residence), stroke risk factors (DM, BP, BMI, alcohol, smoking), presence of physical limitations (unable to climb stairs, perform moderate physical activities).

*Significant association between PA and stroke (Ptrend<0.05). CI indicates confidence interval.

McDonnell M et al. Stroke 2013;44:2519-2524

Diabetes Prevention with Lifestyle Superior to Metformin with Lipid Effects

- 1,645 randomized IR pts from the DPP; 3 rx arms (placebo, metformin 850mg bid, intensive lifestyle-ILS); assessed lipid changes at one year.

- ILS produced significant reductions in VLDL, small dense LDL and increased large HDL-P.

- Metformin had no effect on VLDL; decreased small dense LDL (less so than ILS); increased large and small HDL.

Goldberg, R., et. al. (2013). Lifestyle and Metformin Treatment Favorably Influence Lipoprotein Subfraction Distribution in the Diabetes Prevention Program. *Journal of Clinical Endocrinology & Metabolism*. doi: 10.1210/jc.2013-1452

Diabetes Prevention with Lifestyle Superior to Metformin with Lipid Effects

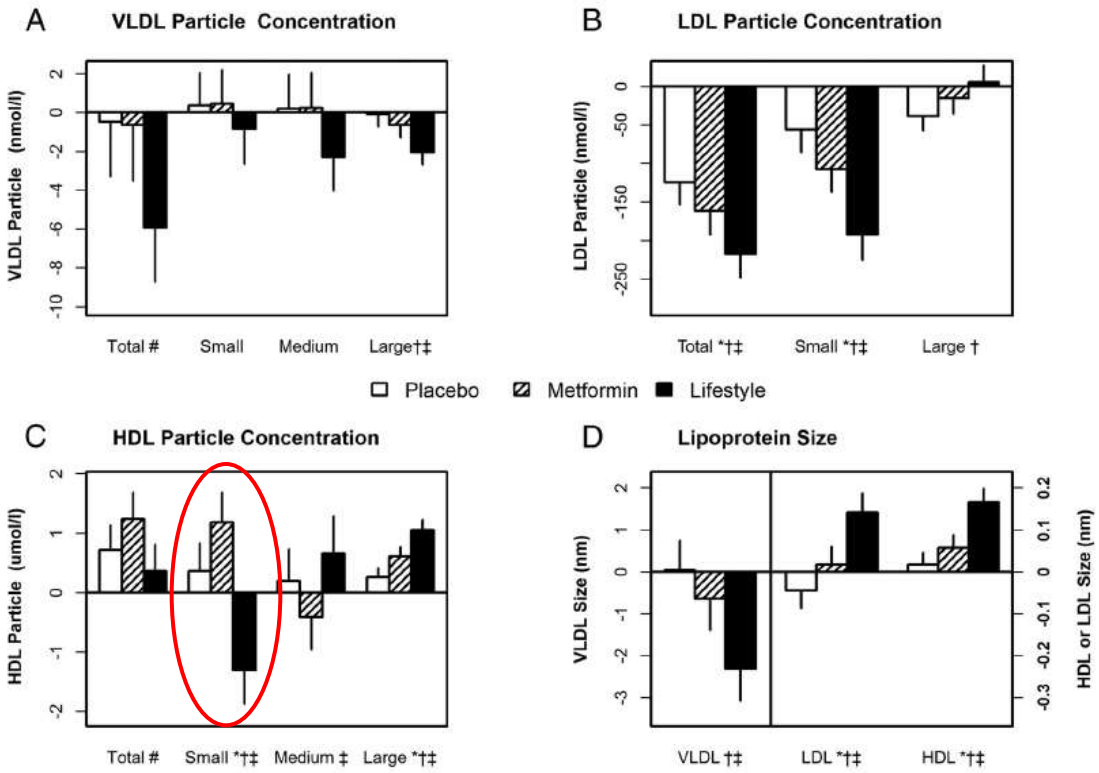


Figure 1. Changes from baseline in lipoprotein subfractions and size using NMR after 1 year according to treatment group. *, Adjusted $P < .01$ for placebo vs metformin; †, adjusted $P < .01$ for placebo vs lifestyle; ‡, adjusted $P < .01$ for metformin vs lifestyle; #, treatment group comparison not presented. Changes in subfractions were adjusted for baseline levels and use of lipid-lowering medications.

ILS- clear winner!!!!

Goldberg, R., et. al. (2013). Lifestyle and Metformin Treatment Favorably Influence Lipoprotein Subfraction Distribution in the Diabetes Prevention Program. *Journal of Clinical Endocrinology & Metabolism*. doi: 10.1210/jc.2013-1452

Statins Reduced Dementia Risk ~ 50% in AF Patients

- 5,221 AF pts; 1,652 on statins; followed 6 yrs.
- New onset dementia in 2.1% of statin pts versus 3.5% non-statin pts
- OR- 0.565 for new-onset dementia statin use versus non-use; p=0.002

Liao MT, Tsai CT, Lin JL. Statins reduce the incidence of dementia in patients with atrial fibrillation: A nationwide cohort study. European Society of Cardiology 2013 Congress; August 31, 2013; Amsterdam, the Netherlands. Abstract P4077.

Statins Reduce Dementia Risk

- 57,669 pts >65 yo; no hx of dementia; 15,200 on statins & divided into dose tertiles; followed 4.5 yrs.
- 5,516 cases of non-vascular dementia
- Found inverse relationship between statin use and dementia; risk reduced with increasing statin dose.

Wu C, Lin T. Statin use and the incidence of dementia in the elderly: A nationwide data survey. European Society of Cardiology 2013 Congress; August 31, 2013; Amsterdam, the Netherlands. Abstract 1609.

Statins Reduce Dementia Risk

Statin	Lowest-dose tertile	Mid-dose tertile	Highest-dose tertile	p for trend
Atorvastatin	0.680	0.543	0.305	<0.001
Rosuvastatin	0.365	0.134	0.129	0.011
Fluvastatin	0.971	0.578	0.255	0.058
Simvastatin	0.747	0.664	0.510	0.064
Pravastatin	0.662	0.933	0.491	0.422
Lovastatin	1.382	0.930	1.626	0.116
All statins	0.923	0.806	0.311	<0.001

Wu C, Lin T. Statin use and the incidence of dementia in the elderly: A nationwide data survey. European Society of Cardiology 2013 Congress; August 31, 2013; Amsterdam, the Netherlands. Abstract 1609.

Immediate Statin Treatment for TIA pts with Carotid Stenosis Yields Huge Stroke Reduction

- 245 TIA pts with ipsilateral carotid stenosis; evaluated stroke risk relative to acute initiation of statin rx versus no statin rx

- Statin rx was assoc. with reduced stroke risk

  OR for 90-day stroke-0.37 (95%CI, 0.17–0.82)

- Adjusted for: ABCD2 score, smoking, antiplatelet treatment, recent TIA, and diffusion weighted imaging hyperintensity.

Merwick, A., et. al. (2013). Reduction in Early Stroke Risk in Carotid Stenosis With Transient Ischemic Attack Associated With Statin Treatment. *Stroke*. doi: 10.1161/strokeaha.113.001576

Immediate Statin Treatment for TIA pts with Carotid Stenosis

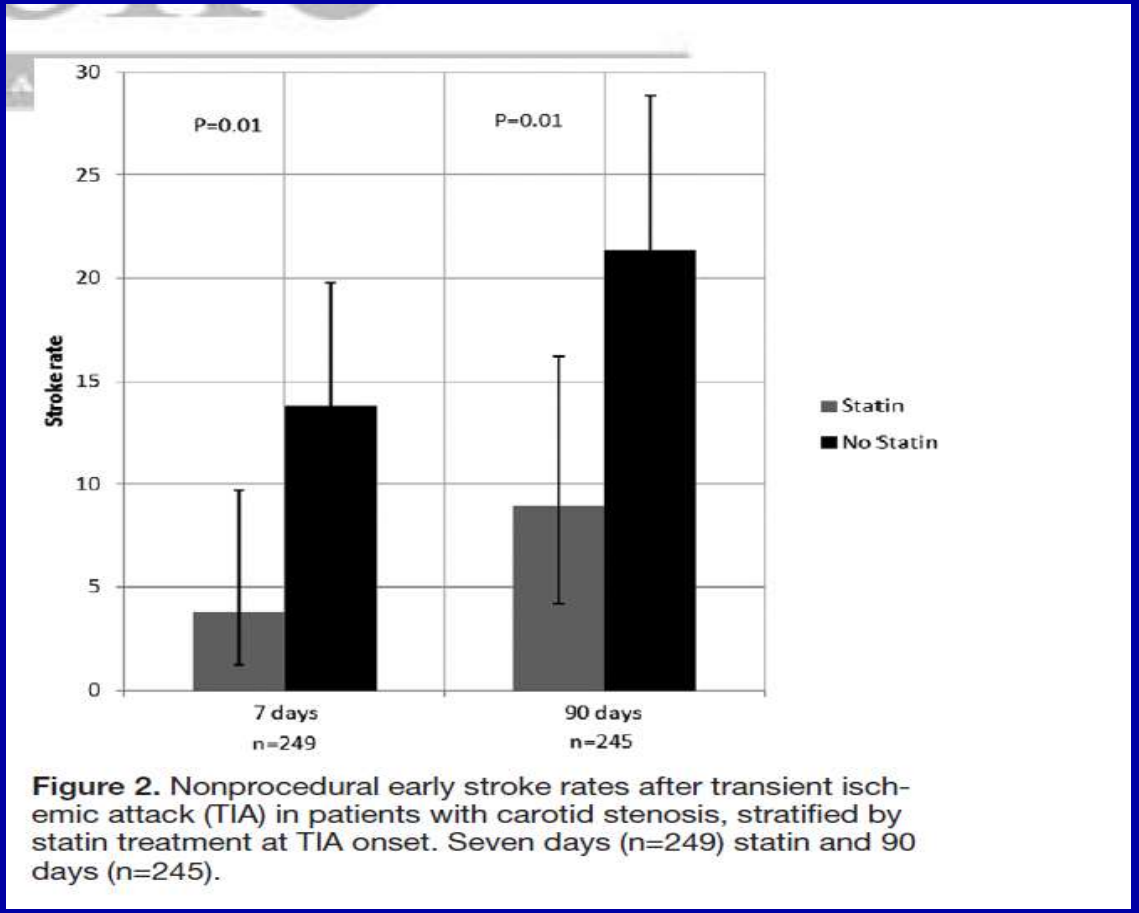


Figure 2. Nonprocedural early stroke rates after transient ischemic attack (TIA) in patients with carotid stenosis, stratified by statin treatment at TIA onset. Seven days (n=249) statin and 90 days (n=245).

Merwick, A., et. al. (2013). Reduction in Early Stroke Risk in Carotid Stenosis With Transient Ischemic Attack Associated With Statin Treatment. *Stroke*. doi: 10.1161/strokeaha.113.001576

Statin Hepatic versus Plasma Level Determines Lipid Effect

- Lathosterol is a late intermediate in cholesterol synthesis used to measure the efficacy of statin-mediated HMG-CoA reductase inhibition.
- Plasma concentrations of atorva and rosuva did not correlate with lathosterol levels.
- Suggests that statin concentration in the liver, not the plasma, is the most important factor in determining the inhibition of HMG-CoA reductase.

DeGorter, M. K., et. al. (2013). Clinical and Pharmacogenetic Predictors of Circulating Atorvastatin and Rosuvastatin Concentration in Routine Clinical Care. *Circulation: Cardiovascular Genetics*. doi: 10.1161/circgenetics.113.000099

Aliskiren Fails to Halt Progression of CAD

- 458 CAD pts with pre-BP & 2 additional risk factors; IVUS baseline and after 2 yrs rx; 225 Aliskiren 300mg & 233 placebo

- Primary end point: change in percent atheroma volume (PAV); only 1 coronary artery investigated/pt

- PAV, with aliskiren (−0.33%- 95%CI, −0.68%to 0.02%); placebo (0.11%; 95%CI, −0.24%to 0.45%)

  between-group difference, −0.43%

  (95%CI, −0.92%to 0.05%) p = .08

Nicholls, S. J. (2013). Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension. *JAMA*. doi: 10.1001/jama.2013.277169

Aliskiren Fails to Halt Progression of CAD: Does Prevent Events?-Hypothesis Generating

- Prespecified exploratory analysis revealed that fewer major CV events occurred in the aliskiren group:

  26 vs 50

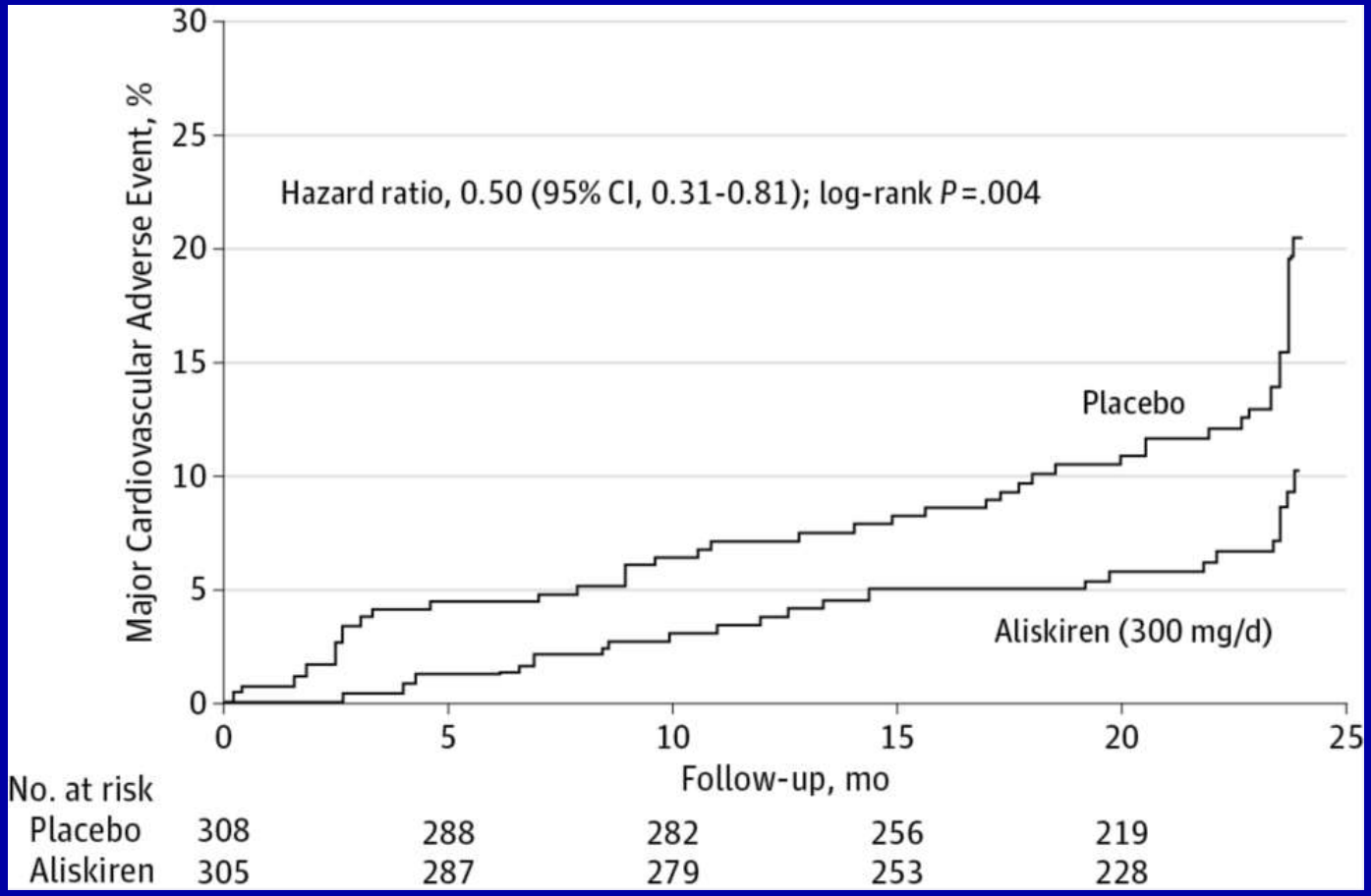
  HR- 0.50 (95%CI, 0.31 to 0.81) p = .004

- Definitive event benefit will require a larger, adequately powered clinical trial with CV events pre-specifed as the primary end point.

Nicholls, S. J. (2013). Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension. *JAMA*. doi: 10.1001/jama.2013.277169

Aliskiren Prevents Events

Incidence of Centrally Adjudicated Major Adverse Cardiovascular Events



Nicholls, S. J. (2013). Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension. *JAMA*. doi: 10.1001/jama.2013.277169

Aliskiren Prevents Heart Attacks??

	Aliskiren (n = 305)	Placebo (n = 308)	*P* Value[a]
Cardiovascular events			
Death	1 (0.3)	6 (1.9)	.07
Nonfatal myocardial infarction	1 (0.3)	8 (2.6)	.02
Nonfatal stroke	1 (0.3)	4 (1.3)	.19
Hospitalization for acute coronary syndrome	4 (1.3)	9 (2.9)	.18
Hospitalization for heart failure	0	1 (0.3)	.32
Arterial revascularization	24 (7.9)	35 (11.4)	.13
First major adverse cardiovascular event	26 (8.5)	50 (16.2)	.004

Nicholls, S. J. (2013). Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension. *JAMA*. doi: 10.1001/jama.2013.277169

Interesting 76% of Pts. on Aliskiren were on Combo RAAS Rx !!!

Table 1. Patient Demographics and Concomitant Medication Use at Baseline

	No. (%) of Patients[a]	
	Aliskiren (n = 305)	Placebo (n = 308)
Age, mean (SD), y	60.2 (9.4)	59.2 (8.3)
Men	228 (74.8)	239 (77.6)
White race	284 (93.1)	285 (92.5)
Body mass index, mean (SD)[b]	29.4 (5.2)	30.6 (5.3)
Medical history		
Diabetes	89 (29.2)	90 (29.2)
Hypertension	249 (81.6)	265 (86.0)
Smoking	91 (29.8)	97 (31.5)
Previous MI	95 (31.1)	101 (32.8)
Previous PCI	147 (48.2)	137 (44.5)
Medication use		
Statin	266 (87.2)	279 (90.6)
Antihypertensive agent use	266 (87.2)	266 (86.4)
Concomitant medication use		
Antiplatelet therapy	291 (95.4)	301 (97.7)
Statin	276 (90.5)	288 (93.5)
β-Blocker	239 (78.4)	245 (79.5)
ACE inhibitor	163 (53.4)	191 (62.0)
ARB therapy	69 (22.6)	70 (22.7)
Calcium channel blocker	125 (41.0)	136 (44.2)

76% in aliskiren group on combo rx

Nicholls, S. J. (2013). Effect of Aliskiren on Progression of Coronary Disease in Patients With Prehypertension. *JAMA*. doi: 10.1001/jama.2013.277169

Insulin Sensitizers can Mitigate PAD Risk

- 1,479 BARI 2D pts without PAD; age 61.9 yo ± 8.0 yrs; 72% male; 15% black; 735 given IS (TZD or met.); 744 given insulin providing (IP) rx; 4.6 yr. follow-up.

- 303 PAD-related outcomes: new ABI ≤0.9, a lower-extremity revascularization or amputation.

- IS rx significantly reduced PAD risk compared to IP rx

Althouse, A. D., et. al. (2013). Favorable Effects of Insulin Sensitizers Pertinent to Peripheral Arterial Disease in Type 2 Diabetes: Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Diabetes Care*. doi: 10.2337/dc12-2265

Insulin Sensitizers can Mitigate PAD Risk

Adjusted for A1c risk reduction was:

27% for new onset PAD

42% for revascularization

88% for amputation !!!

Althouse, A. D., et. al. (2013). *Diabetes Care*. doi: 10.2337/dc12-2265

Rosiglitazone Did Not Cause CV Risk

- Data from BARI-2D; 748 pts on rosi; 1,363 not on TZD rx; follow-up 4.5 yrs.; evaluated difference in CV outcomes

- After multivariable adjustment, there was no increased CV risk with rosi

Bach, R. G., et. al. (2013). Rosiglitazone and Outcomes for Patients with Diabetes and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Circulation*. doi: 10.1161/circulationaha.112.000678

Rosiglitazone Did Not Cause CV Risk

- Composite death, MI, and stroke HR 0.72 (95% (CI), 0.55 to 0.93)

Significantly better

- Stroke HR 0.36 (95% CI 0.16 to 0.86)
- MI HR 0.77 (95% CI, 0.54 to 1.10)
- CHF HR 1.22 (95%CI, 0.84 to 1.82)
- Fractures HR 1.62 (95% CI 1.05 to 2.51)

Significantly worse

Bach, R. G., et. al. (2013). Rosiglitazone and Outcomes for Patients with Diabetes and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Circulation*. doi: 10.1161/circulationaha.112.000678

Rosiglitazone Did Not Cause CV Risk

- Analyses did not detect any significant hazard of increased ischemic CV risk with rosiglitazone in this particularly vulnerable, higher risk population.

- Analysis showed a significantly lower incidence of the composite of death, MI and stroke; stroke

Bach, R. G., et. al. (2013). Rosiglitazone and Outcomes for Patients with Diabetes and Coronary Artery Disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Circulation*. doi: 10.1161/circulationaha.112.000678

Exenatide Beneficial in STEMI

- 58 STEMI pts.; 18 (25% DM) immediate administration of exenatide; 40 controls; assessed subsequent infarct size and LV function; 6 mo. follow-up

- Exenatide rx with primary PCI was associated with reduction of infarct size (~40%) and improvement of subclinical LV function.

Woo, J. S., et. al. (2013). Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of Exenatide Myocardial Protection in Revascularization Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.301586

Exenatide Beneficial in STEMI

- Exenatide group were treated with 10 μg subcutaneous and intravenous bolus 10 μg injection of exenatide 5 min before the onset of reperfusion.

- 10 μg subcutaneous injection was continued twice daily on the following 2 days.

Woo, J. S., et. al. (2013). Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of Exenatide Myocardial Protection in Revascularization Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.301586

Exenatide Beneficial in STEMI

- Mechanisms???

a) increase glucose update in myocardium for fuel yielding decreased oxygen demand vs FFAs

b) trigger molecules for initiating survival pathways in ischemic/reperfusion injuries

c) triggers endothelial nitric oxide synthase

d) several pathways associated with metabolism, contractility, reduction of apoptotic cell death, and anti-inflammatory effect.

Woo, J. S., et. al. (2013). Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of Exenatide Myocardial Protection in Revascularization Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.301586

DDP4I Saxagliptin Failed to Impact CV Risk

- 16,492 DM pts.; randomly assigned saxagliptin or placebo for 2 yrs.; otherwise care as usual
- primary end point was a composite of CV death, MI, or ischemic stroke.
- Primary end-point event occurred in 613 pts in the saxagliptin group and in 609 pts in the placebo group

Scirica, B. M., et. al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *New England Journal of Medicine, 0*(0), null. doi: doi:10.1056/NEJMoa1307684

DDP4I Saxagliptin Increased HF Risk

- Major secondary end points included HF

- Heart failure risk was significantly higher with rx

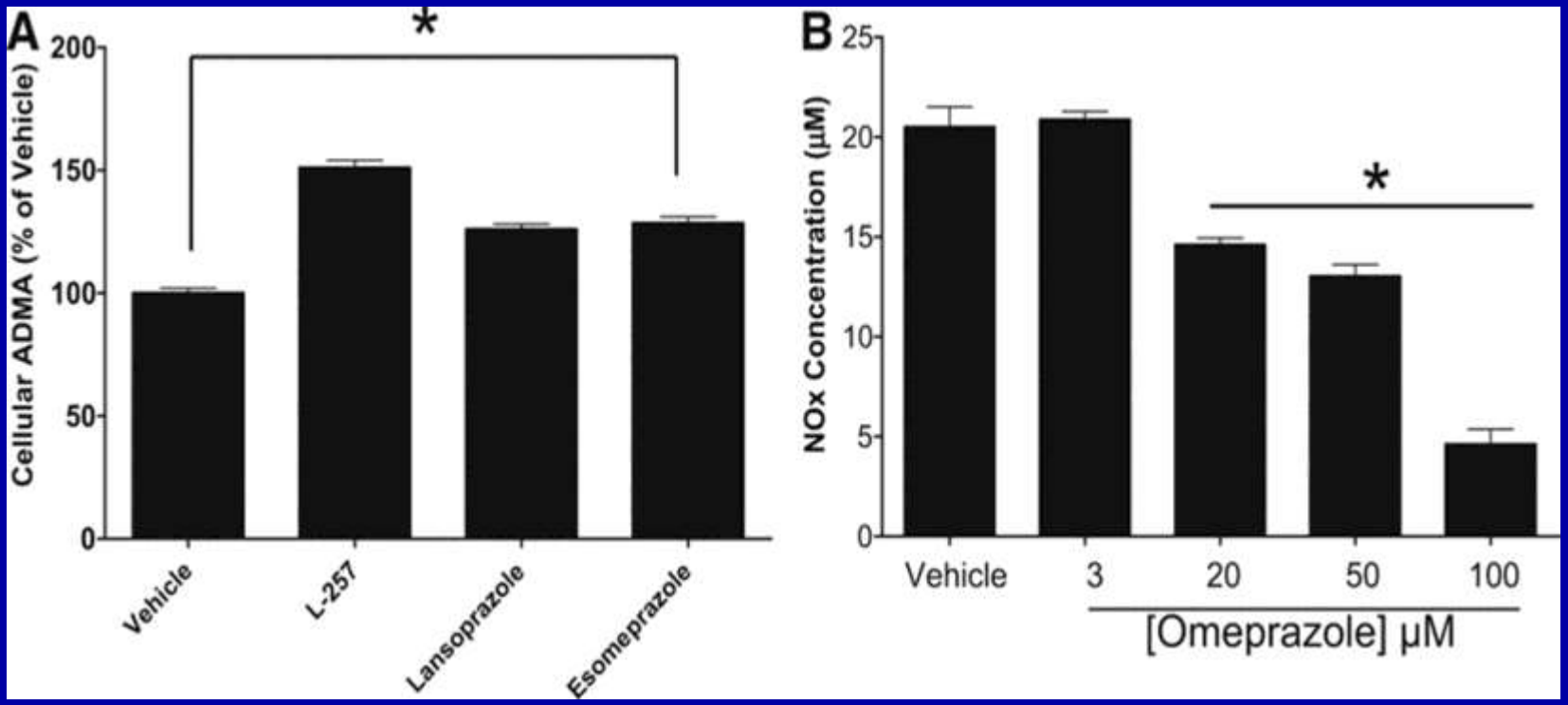
  HR-1.27 (95% CI, 1.07 to 1.51) p = 0.007

Scirica, B. M., et. al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *New England Journal of Medicine, 0*(0), null. doi: doi:10.1056/NEJMoa1307684

PPIs Increase ADMA and Decrease NO in Human Endothelial Cells

A. PPIs increase ADMA conc.

B. reduce NO



Ghebremariam, Y. T., Lependu, P., Lee, J. C., Erlanson, D. A., Slaviero, A., Shah, N. H., . . . Cooke, J. P. (2013). Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. *Circulation, 128*(8), 845-853.

Upcoming BD Method Activities

Fall- 2013 Bale/Doneen Activities

Preceptorship Programs remaining for 2013

Sept 14-15 Lubbock, TX

Nov 8-9 Nashville, TN

2013 lectures:

Sept 20-21 American Academy of Oral/Systemic Health- LV

Sept 30 American Osteopathic Association- LV

Oct 3 Academy of Comprehensive Esthetics- LV

Oct 11-12 Intern. Acad. of Biological Dentistry and Medicine- Houston

Oct 17-19 Bale/Doneen Reunion- Dallas

Oct 18-19 CHL symposium/ MD/VIP Meeting- Dallas

Dec 13 Partners In Complete Health “Say Ahhh”- NY

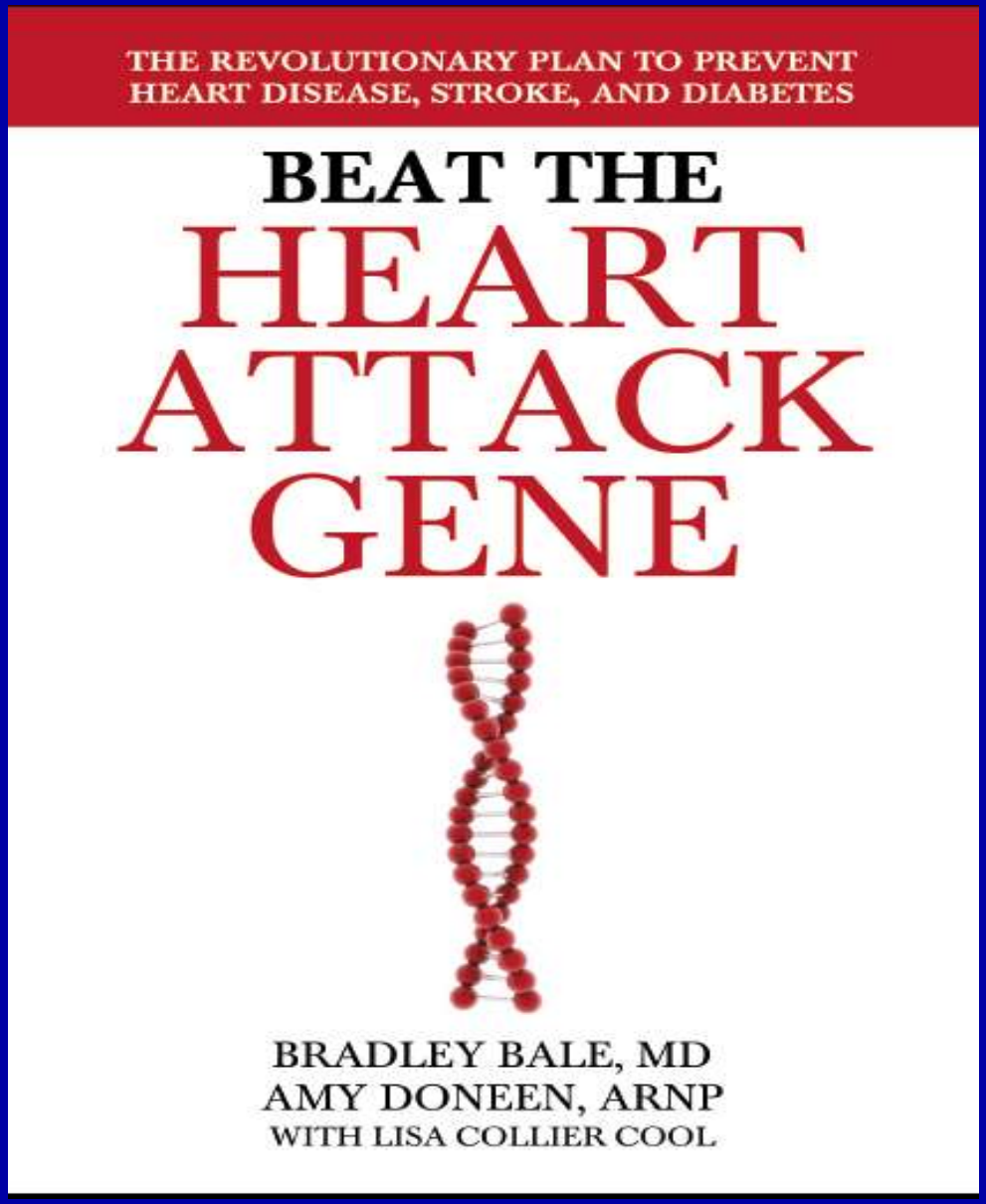
Other exciting happenings for 2013/2014

Beat The Heart Attack Gene – Turner Publishing – Jan 2014

Bale/Doneen Prospective Cohort – John Hopkins

Journal of Arteriology

Publisher: Turner Publishing
Release Date: January 2014



Open for Discussion