Bale/Doneen Live Chat Session

11/13/2013

5:30-6:30 pm PST

Bradley Bale, MD

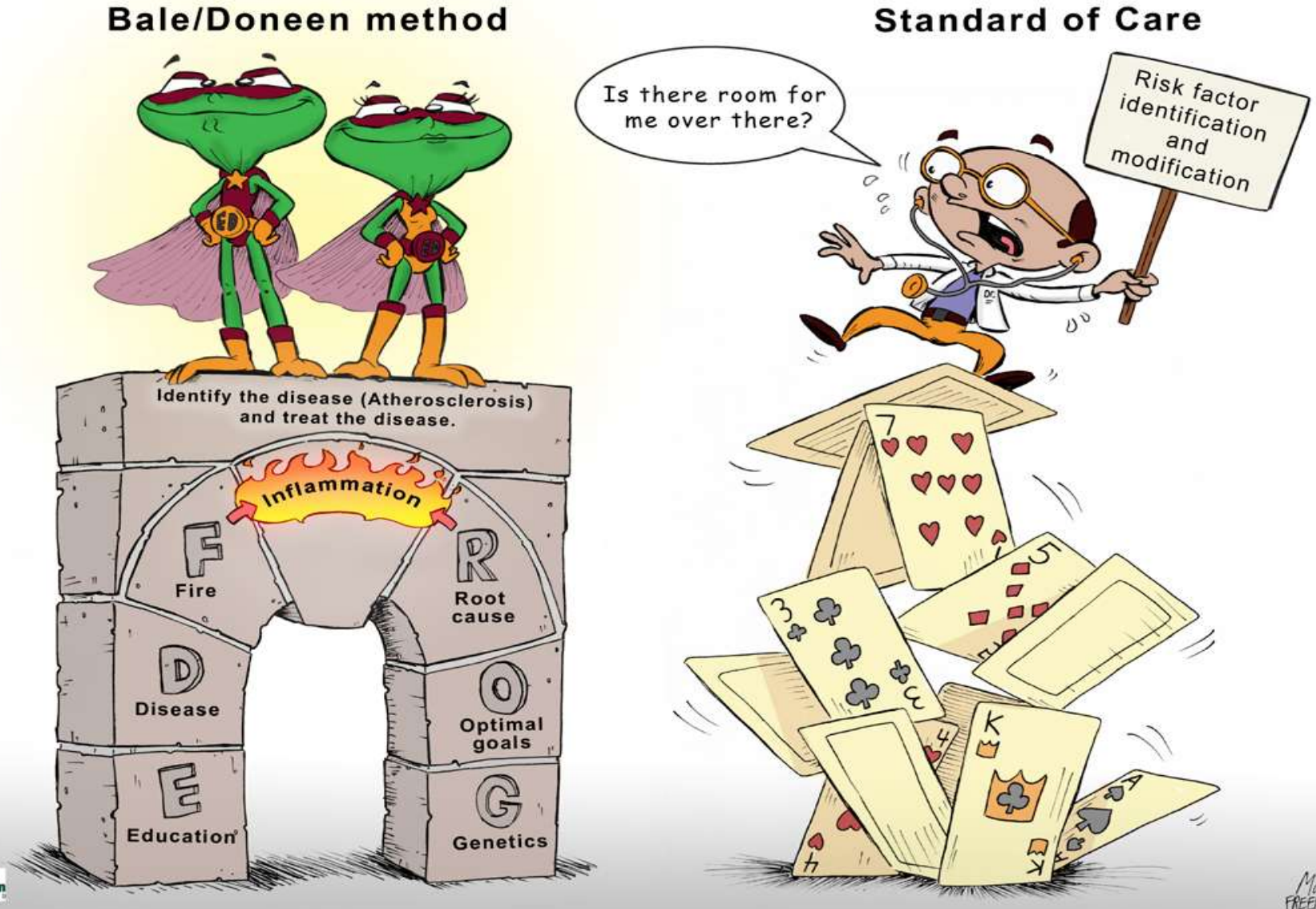
Intention of the live chats

- New data and slides
- Discuss “hot” topics
- Case study
- Review upcoming meetings
- Open discussion for remaining

Reality for 90% of Today's Chat!:OMG!

New Guidelines!!!

What's the difference?



CAC Out Predicts Lipids for CVD Risk

- 5,534 MESA pts without baseline statin rx; follow-up 7.6 yrs.; outcome CV events.
- Classified pts by CACS of zero; 1-99; ≥100; # lipid abnormalities (LA).
- Determine absolute CVD risk according to above categories.

Martin, S. S., Blaha, M. J., Blankstein, R., Agatston, A. S., Rivera, J. J., Virani, S. S., . . . Nasir, K. (2013). Dyslipidemia, Coronary Artery Calcium, and Incident Atherosclerotic Cardiovascular Disease: Implications for Statin Therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. doi: 10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

- 256 (5%) hard CVD events (excludes angina leading to revascularization) occurred during 7.6 yrs.
- 202 events (79%) were in subjects with a positive CACS; 65% in subjects with zero to 1 LA
- Overall, the absolute incident hard CVD event rates were: 1.8%, 5.3% and 11.1% among those with CACS=0, CACS 1-99 and ≥100, respectively.

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

- CAC stratifies CVD risk regardless of the burden of dyslipidemia.
- CACS ≥100 defines a CV event risk similar to a 'secondary' prevention population.

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

- Study examined two paradigms of risk assessment: dyslipidemia (risk factor) and CAC (measurable atherosclerosis).

- Atherosclerosis was superior.

Martin, S. S., Blaha, M. J., Blankstein, R., Agatston, A. S., Rivera, J. J., Virani, S. S., . . . Nasir, K. (2013). Dyslipidemia, Coronary Artery Calcium, and Incident Atherosclerotic Cardiovascular Disease: Implications for Statin Therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. doi: 10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk: but remember!

- Some events do occur when CAC=0
- CAC does not measure non-calcified plaques.
- However, even in the presence of three LA, when CACS=0, the absolute event rate was <5% over 7.6 years.

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not number of lipid abnormalities

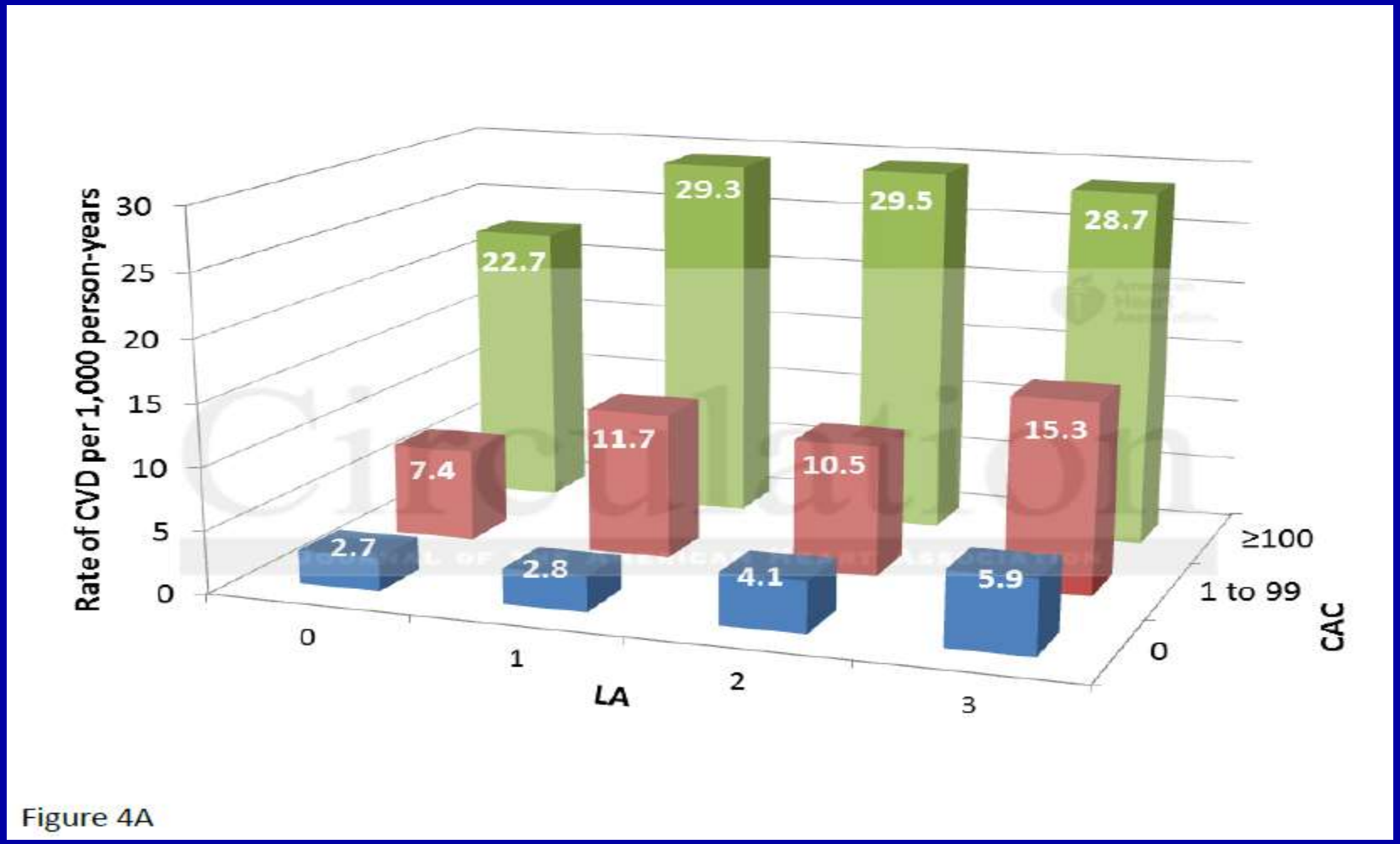


Figure 4A

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not by LDL-C

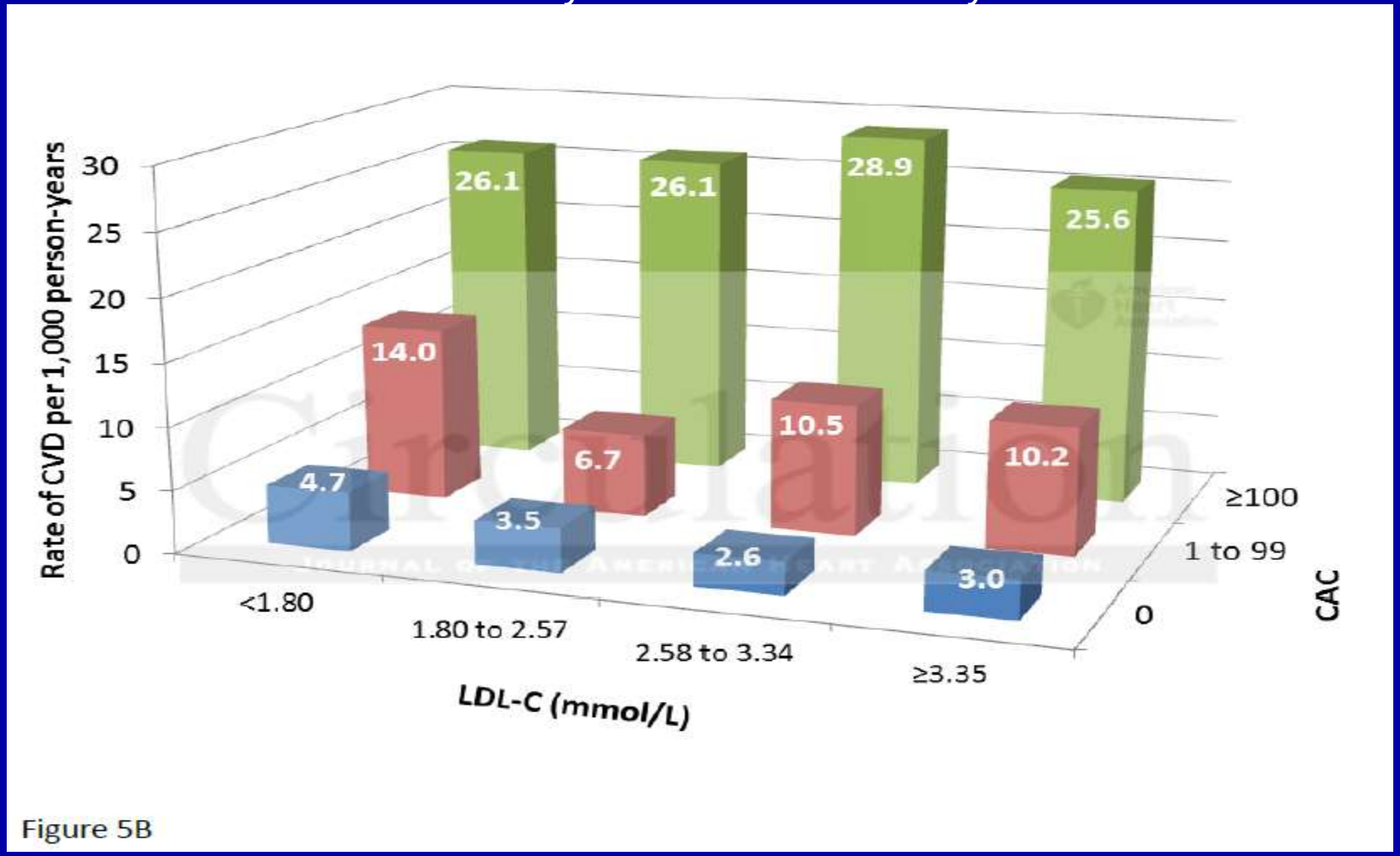


Figure 5B

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not TC/HDL

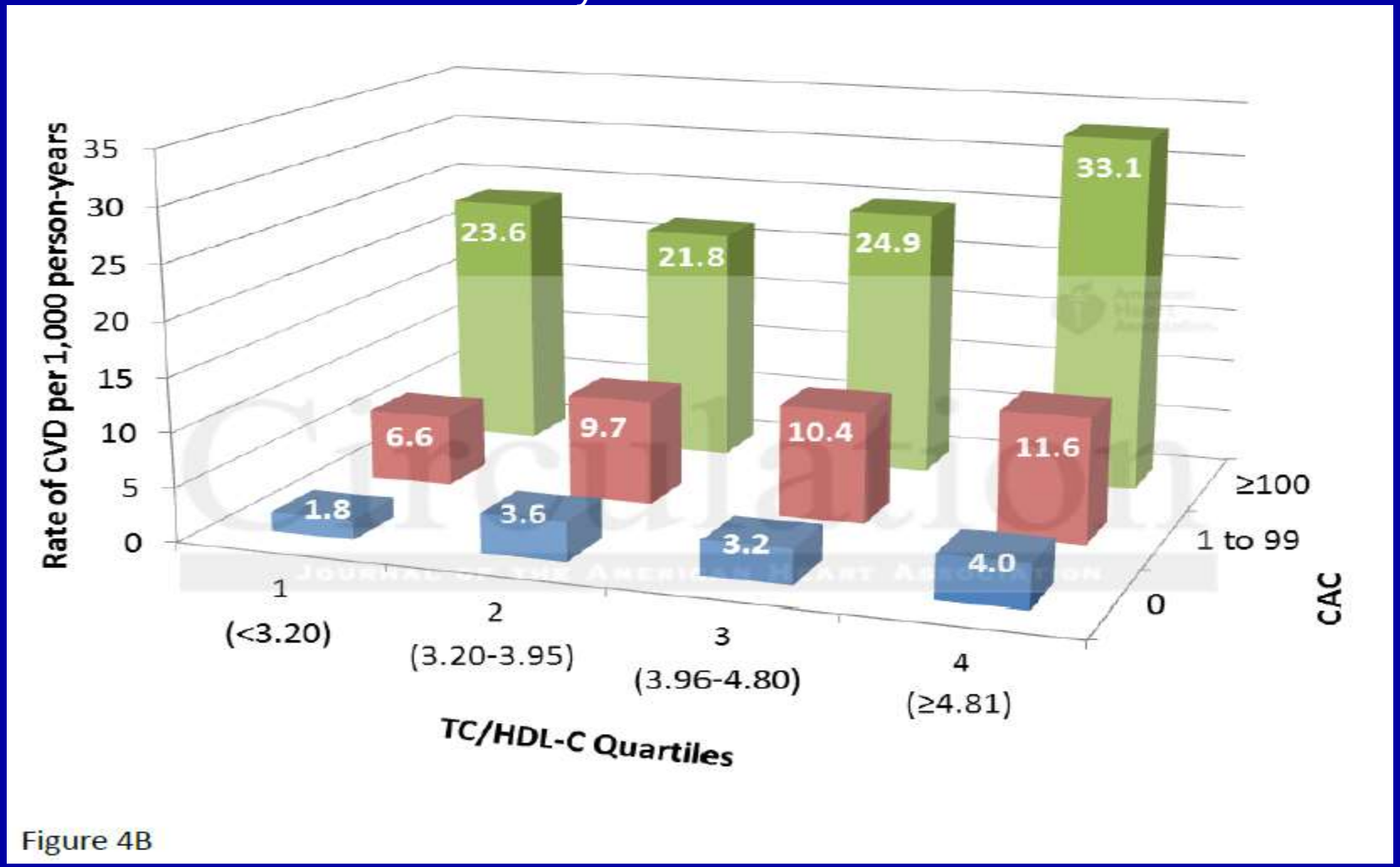


Figure 4B

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not non-HDL (apoB)

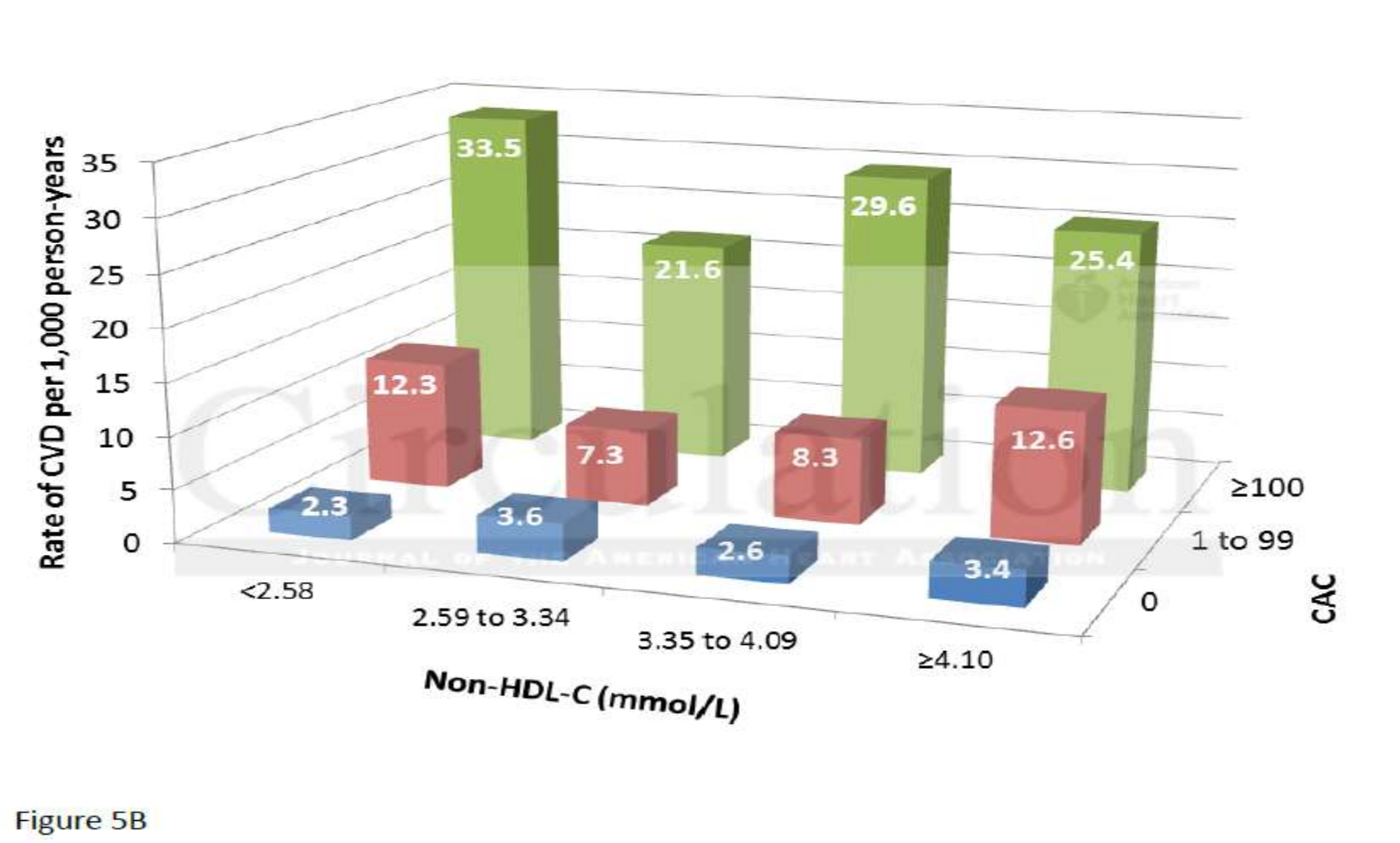


Figure 5B

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

Risk Assessment Guidelines: 12/12/2013

Risk Factor
Sex
Age
Race
Total Cholesterol
HDL-Cholesterol
Systolic Blood Pressure
Treatment for High Blood Pressure (if SBP >120)
Diabetes
Smoker

Your 10-Year ASCVD Risk (%)
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)

Goff, D. C., et. al. (2013). 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. doi: 10.1161/01.cir.0000437741.48606.98

Risk Assessment Guidelines: 12/12/2013

- If, after quantitative risk assessment, a risk based treatment decision is uncertain, assessment of 1 or more of the following—

family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.

Goff, D. C., et. al. (2013). Circulation. doi: 10.1161/01.cir.0000437741.48606.98

Risk Assessment Guidelines: 12/12/2013

CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event. *

Amazing!!!!!

Goff, D. C., et. al. (2013). Circulation. doi: 10.1161/01.cir.0000437741.48606.98
*Helfand M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Annals of internal medicine. 2009;151:496-507
*Peters SA, et. al. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart 2012;98:177-84.
*Den Ruijter HM, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 2012;308:796-803

CIMT can Enhance CV Event Risk Prediction

- 3,703 pts; median age 64.4 yrs; 48% men; followed 3 yrs.; 215 suffered a first CVE
- All measures of C-IMT and the interadventitia common carotid artery diameter (ICCAD) were associated with the risk of CVEs, after adjustment for FRFs and therapies with $p < 0.005$
- Average of 8 maximal IMT measurements (IMTmean-max), alone or combined with ICCAD, classified events and non-events better than the mean CCA-IMT

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- C-IMTs and ICCAD predict the risk of CVEs independently of each other
- C-IMT assesses atherosclerosis when plaques are incorporated in the measurements
- ICCAD (arterial diameter) reflects vascular remodeling in response to the growth of local atherosclerotic plaques & as a compensatory response to VRFs which associate fairly well with the coronary artery disease status

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- Findings provide new evidence to support the use of IMT variables and ICCAD, in addition to VRFs, for CV risk stratification in clinical practice, with a NRI of 12.1%.

- Assessment of composite IMT variables and ICCAD is time consuming compared with CC-IMT assessment alone (15 to 20 vs. 8 to 10 min).

- The benefits provided by a better risk classification may easily offset the additional costs.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT Can Help Detect Significant CAD in Asx'ic Diabetics

- 333 asx'ic type 2 diabetic pts without history of CAD
- 17 discovered to have severe CAD requiring revascularization; CIMT maximum value evaluated as a predictor
- Maximum IMT was an independent predictor of severe CAD even after adjustment for conventional risk factors

Irie, Y., et. al. The Utility of Carotid Ultrasonography in Identifying Severe Coronary Artery Disease in Asymptomatic Type 2 Diabetic Patients Without History of Coronary Artery Disease. *Diabetes Care, 36*(5), 1327-1334. doi: 10.2337/dc12-1327

CIMT Can Help Detect Significant CAD in Asx'ic Diabetics

- ROC curve analyses: addition of maximum IMT to conventional risk factors significantly improved the prediction ability for severe CAD (from area under the curve, 0.67 to 0.79; P = 0.039).

- The greatest sensitivity and specificity were obtained with cut-off value of 2.45 mm.

Irie, Y., et. al. The Utility of Carotid Ultrasonography in Identifying Severe Coronary Artery Disease in Asymptomatic Type 2 Diabetic Patients Without History of Coronary Artery Disease. *Diabetes Care, 36*(5), 1327-1334. doi: 10.2337/dc12-1327

CIMT Can Help Detect Significant CAD in Asx'ic Diabetics

- The greatest sensitivity and specificity were obtained with cut-off value of 1.55 mm, if pt < 65 yo
- The greatest sensitivity and specificity were obtained with cut-off value of 2.65 mm, if pt ≥ 65 yo

Irie, Y., et. al. The Utility of Carotid Ultrasonography in Identifying Severe Coronary Artery Disease in Asymptomatic Type 2 Diabetic Patients Without History of Coronary Artery Disease. *Diabetes Care, 36*(5), 1327-1334. doi: 10.2337/dc12-1327

CIMT Can Help Detect Significant CAD in Asx'ic Diabetics

- SPECT scan, CT angiography, and coronary angiography can determine disease severity.
- However, they have potential for significant adverse effects, technical difficulty, availability, and cost.
- CIMT is a noninvasive and inexpensive risk prediction tool for identifying asx'ic diabetics at high-risk for CAD.

Irie, Y., et. al. The Utility of Carotid Ultrasonography in Identifying Severe Coronary Artery Disease in Asymptomatic Type 2 Diabetic Patients Without History of Coronary Artery Disease. *Diabetes Care, 36*(5), 1327-1334. doi: 10.2337/dc12-1327

CIMT Strongly Predicts Heart Attack (MI) Risk

- 6,257 'healthy' 25-84 yo; 52% women; followed 15 ½ yrs.; evaluated CIMT as predictor of MI
- CIMT categorized as quartiles of IMT and total plaque area
- 894 incident MIs

Hald, E. M., et. al. (2013). Carotid Atherosclerosis Predicts Future Myocardial Infarction But Not Venous Thromboembolism: The Tromsø Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302162

CIMT Strongly Predicts Heart Attack Risk

- MI risk increased significantly across quartiles of mean intima-media thickness (P for trend <0.001) and with increasing total plaque area (P for trend <0.001).

- Carotid atherosclerosis was strongly associated with future MI.

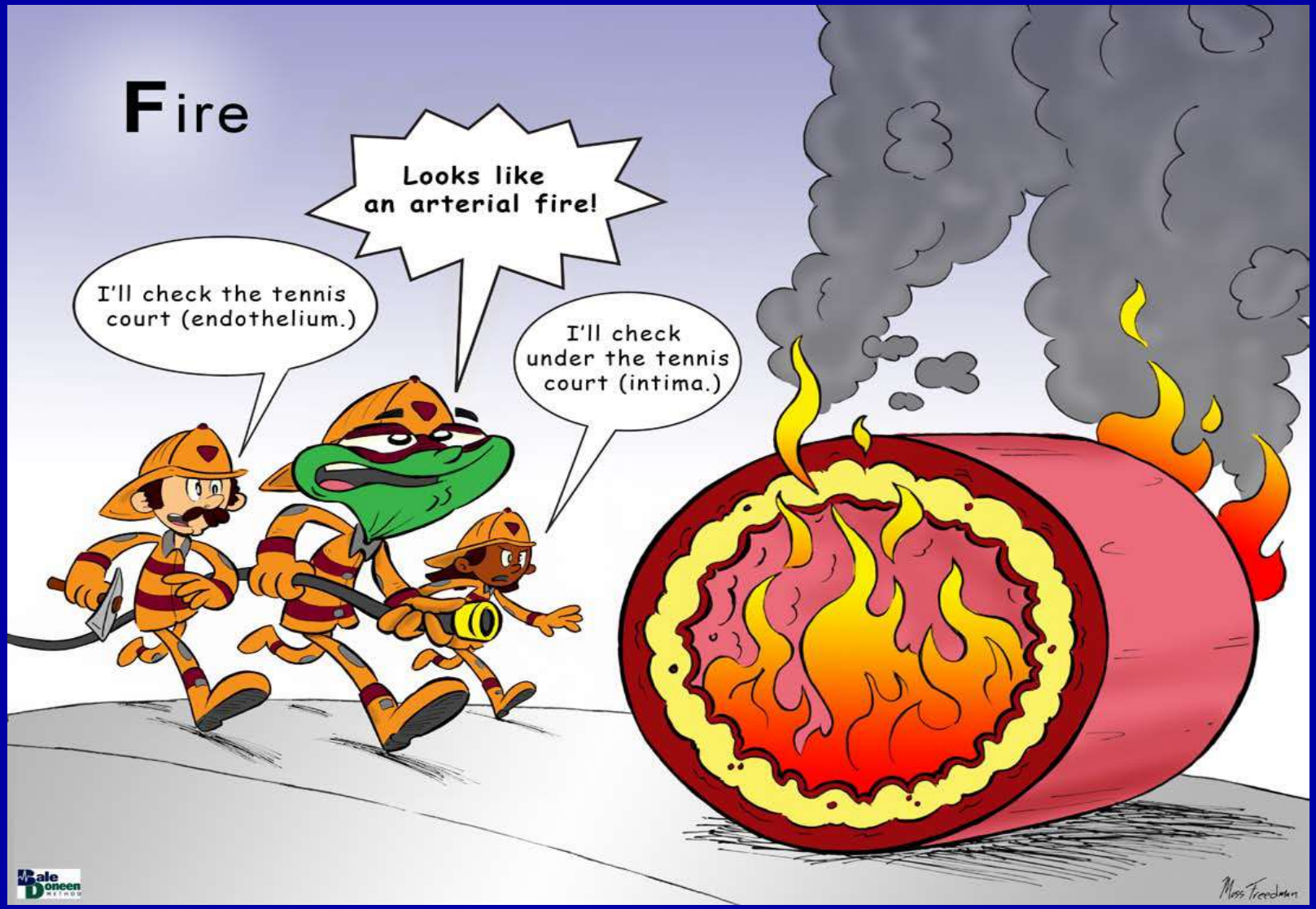
Hald, E. M., et. al. (2013). Carotid Atherosclerosis Predicts Future Myocardial Infarction But Not Venous Thromboembolism: The Tromsø Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302162

CIMT Strongly Predicts Heart Attack Risk

Study showed that carotid atherosclerosis is a strong risk factor for MI.

Hald, E. M., et. al. (2013). Carotid Atherosclerosis Predicts Future Myocardial Infarction But Not Venous Thromboembolism: The Tromsø Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302162

Inflammation



BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

- 3,635 stable CAD pts without ACS; coronary angiography; followed 3 yrs.; end point MACE
- Evaluated BNP, MPO & CRP as predictors of risk.
- These markers reflect myocardial dysfunction, plaque vulnerability, and systemic inflammation, respectively.

Tang, W. H., et. al. (2013) Usefulness of Cardiac Biomarker Score for Risk Stratification in Stable Patients Undergoing Elective Cardiac Evaluation Across Glycemic Status. *Am J Cardiol* 2013;111:465e470

BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

- All 3 biomarkers provided incremental risk prediction.
- After adjusting for traditional risk factors, including Framingham risk factors, BNP, MPO & hsCRP each remained independent predictors of MACE.

Tang, W. H., et. al. (2013) Usefulness of Cardiac Biomarker Score for Risk Stratification in Stable Patients Undergoing Elective Cardiac Evaluation Across Glycemic Status. *Am J Cardiol* 2013;111:465e470

BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

- A cardiac biomarker score (CBS) was developed using cutoffs for positive of BNP >100 pg/ml, MPO >322 pmol/L and hsCRP >2.0 ng/L.

- Scores were categorized as 0, 1, 2, or 3 depending on how many biomarkers positive.

Tang, W. H., et. al. (2013) Usefulness of Cardiac Biomarker Score for Risk Stratification in Stable Patients Undergoing Elective Cardiac Evaluation Across Glycemic Status. *Am J Cardiol* 2013;111:465e470

BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

- A higher CBS predicted future risk for MACEs at 3 yrs regardless of age, gender, BMI, DM, BP, renal insufficiency, or previous myocardial infarction.

- Use of the CBS on top of traditional risk factors was also shown to reclassify subjects (net reclassification index 12.86%, p <0.001; integrated discrimination improvement 12.0%, p <0.001; C-statistic 66.9% vs 71.1%, p <0.001).

Tang, W. H., et. al. (2013) Usefulness of Cardiac Biomarker Score for Risk Stratification in Stable Patients Undergoing Elective Cardiac Evaluation Across Glycemic Status. *Am J Cardiol* 2013;111:465e470

BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

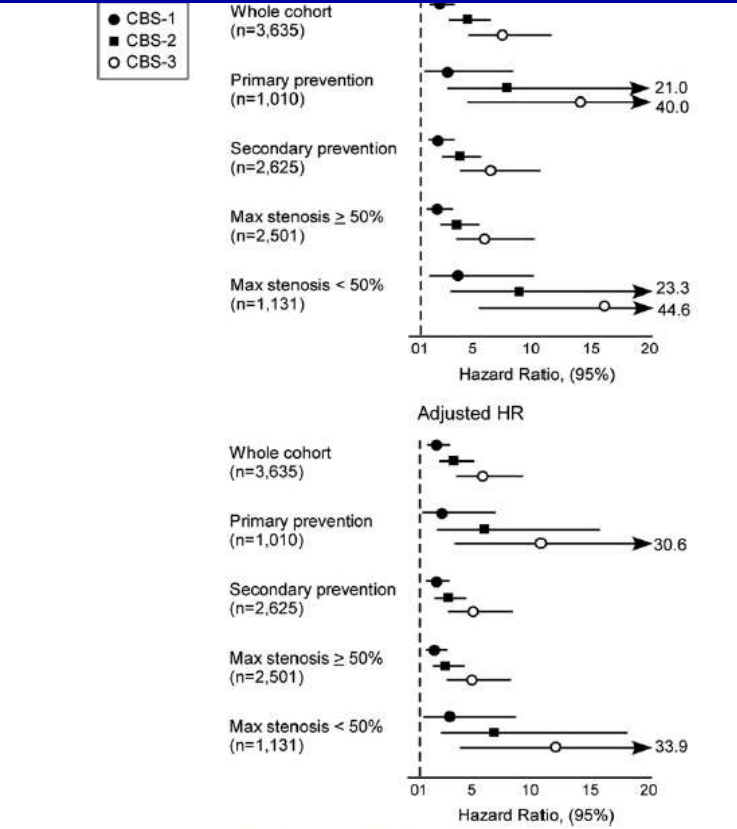


Figure 2. Forest plot of unadjusted and adjusted HRs for predicting future MACEs at 3-year follow-up according to CBS according to subgroups (zero score as reference, adjustments as in Table 3, model 1).

Tang, W. H., et. al. (2013) *Am J Cardiol* 2013;111:465e470

BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

Hazard Ratio, (95%)

Figure 2. Forest plot of unadjusted and adjusted HRs for predicting future MACEs at 3-year follow-up according to CBS according to subgroups (zero score as reference, adjustments as in Table 3, model 1).

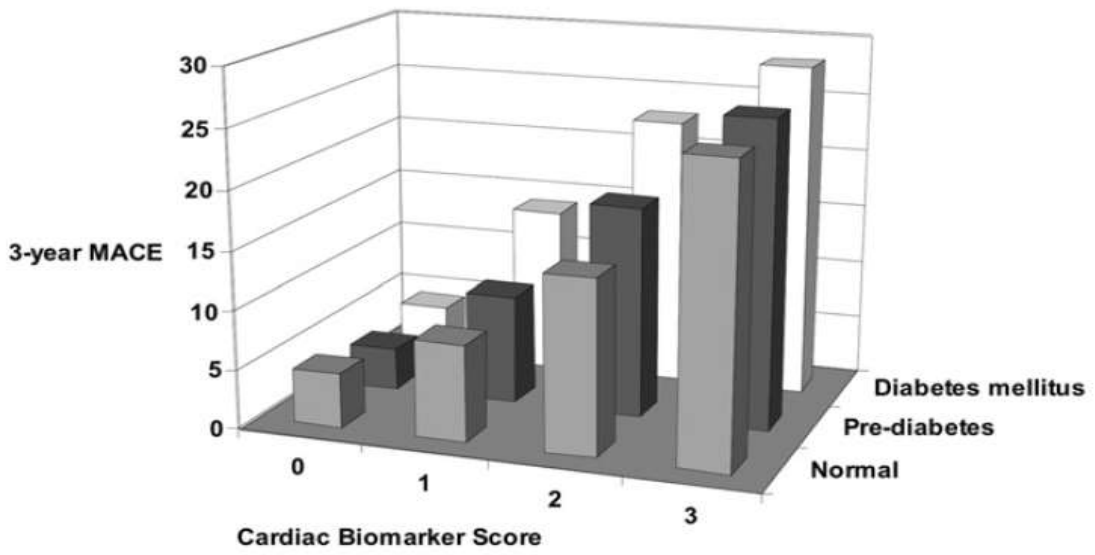


Figure 3. Event rates for future MACEs at 3-year follow-up according to glycemic status.

Tang, W. H., et. al. (2013) *Am J Cardiol* 2013;111:465e470

BNP, MPO, hs-CRP as Predictors of MACE in Stable CAD Patients

In summary, an integrated assessment of cardiac biomarkers may provide independent prognostic value for long-term adverse clinical events in stable cardiac patients.

Tang, W. H., et. al. (2013) Usefulness of Cardiac Biomarker Score for Risk Stratification in Stable Patients Undergoing Elective Cardiac Evaluation Across Glycemic Status. *Am J Cardiol* 2013;111:465e470

Reminder in Confirmation Genetic Studies for Inflammation Being Causal

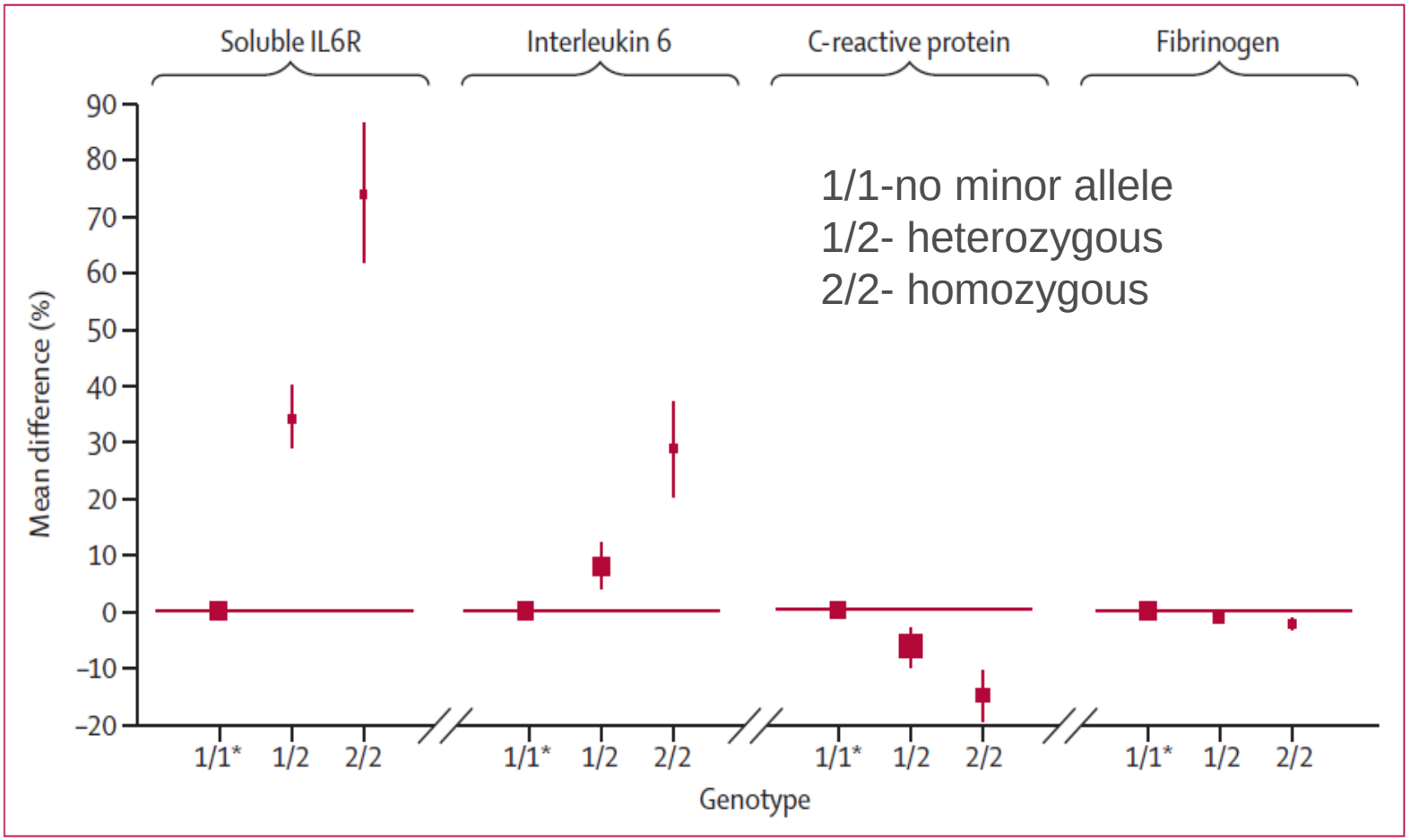


Figure 1: IL6R genotypes and circulating concentrations of inflammation markers

IL6R Genetics Consortium and Emerging Risk Factors Collaboration, Dr Nadeem Sarwar, Dr Adam S Butterworth, et. al. ***Lancet 3/31/2012; 379: 1205–13***

Was the Elevated IL-6 Just an Innocent Bystander in This Reduced Risk!!??

IL-6 Facilitates Reverse Cholesterol Transport (RCT)

- Stimulated aortic endothelial cells with IL-6.
- This increased endothelial lipase (EL) expression.
- EL facilitates the endothelial binding and transport of HDL into the intima.
- EL also reduced HDL particle size.
- IL-6 stimulates the translocation of HDL through the endothelium, the first step in RCT.

Robert, J., et. al. (2013). Interleukin 6 Stimulates Endothelial Binding and Transport of High-Density Lipoprotein Through Induction of Endothelial Lipase. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.301363

EDFROG IRA

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

Testosterone (T) Primarily Related to Lean Mass, Muscle Size & Strength

- 400 healthy men; 20 to 50 yo

- Cohort #1- 198 had suppression of (T) and estradiol; then 16 wk rx with placebo or supplemental test rx at various doses
  (net effect: low T & estradiol or 'norms' of T & estradiol)

- Cohort #2- 202 had suppression of T & estradiol; then supplemental rx with placebo or T along with hormonal suppression of estradiol conversion from the T supplement
  (net effect: low T & estradiol or 'norms' of T & low estradiol)

Finkelstein, J. S., et. al. (2013). Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men. *New England Journal of Medicine, 369*(11), 1011-1022.

Testosterone Primarily Related to Lean Mass, Muscle Size & Strength

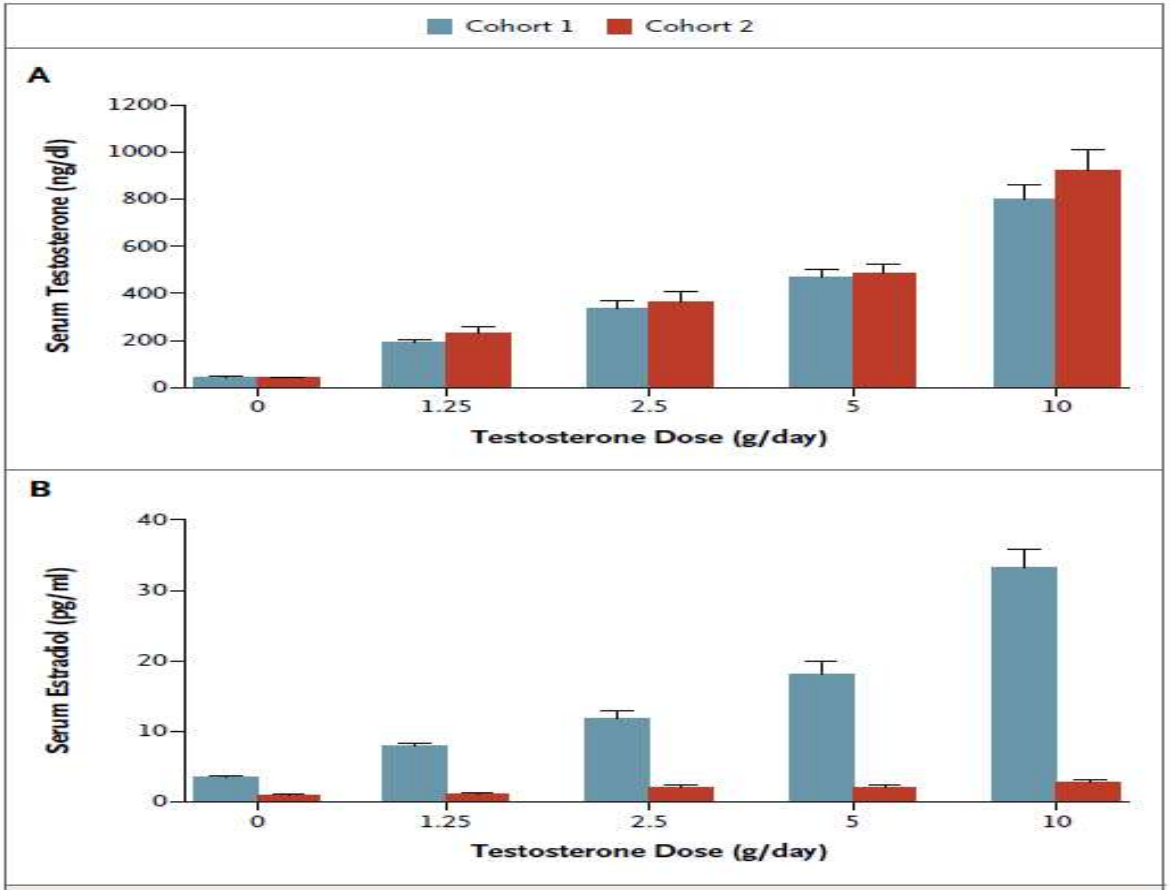


Figure 2. Mean Serum Testosterone and Estradiol Levels from Weeks 4 to 16, According to Testosterone Dose and Cohort.
T bars indicate standard errors.

Finkelstein, J. S., et. al. (2013). *New England Journal of Medicine*, *369*(11), 1011-1022.

Testosterone Primarily Related to Lean Mass, Muscle Size & Strength

- Primary outcomes were: changes in the % body fat and lean mass.

- Secondary outcomes were: subcutaneous-and intraabdominal-fat areas, thigh-muscle area and strength, and sexual function (desire & erection).

Finkelstein, J. S., et. al. (2013). *New England Journal of Medicine, 369*(11), 1011-1022.

Testosterone Primarily Related to Lean Mass, Muscle Size & Strength

- T deficiency accounted for decreases in lean mass, muscle size, and strength.
- Estrogen deficiency accounted for increases in body fat.
- T & estrogen deficiency contributed to sexual function.
- The amount of T required to maintain lean mass, fat mass, strength, and sexual function varied widely in men.

Finkelstein, J. S., et. al. (2013). *New England Journal of Medicine*, *369*(11), 1011-1022.

Testosterone Primarily Related to Lean Mass, Muscle Size & Strength

- >80% of circulating estradiol in men is derived from the aromatization of T.
- Consequences of male hypogonadism are routinely attributed solely to T deficiency.
- Despite clear evidence that bone loss in men is primarily due to estrogen deficiency.

Finkelstein, J. S., et. al. (2013). *New England Journal of Medicine*, *369*(11), 1011-1022.

Testosterone Primarily Related to Lean Mass, Muscle Size & Strength: Clinical Implications

- Interpret T levels considering physiology of muscles, body fat & sexual function.
- T deficiency leading to estrogen deficiency will result in visceral fat along with IR and IR CV complications
- T levels of approx. 200 ng/dL were associated with decreased lean mass, thigh-muscle area, and erectile function. Therefore, T supplementation may be justified with T levels in this range.

Finkelstein, J. S., et. al. (2013). *New England Journal of Medicine*, *369*(11), 1011-1022.

Testosterone Primarily Related to Lean Mass, Muscle Size & Strength

- In men with hypogonadism, measuring estradiol would be helpful in assessing the risk of sexual dysfunction, bone loss, or fat accumulation.
- Treatment with aromatizable androgens would be preferable to treatment with nonaromatizable androgens.
- This study should facilitate the development of more rational approaches to the dx and rx of hypogonadism in men.

Finkelstein, J. S., et. al. (2013). *New England Journal of Medicine*, *369*(11), 1011-1022.

Testosterone (T) May Cause CV Harm

- 8,709 men with low T; 1,223 put on T rx ~ 1 ½ yrs. post angiogram; followed ~ 3 yrs post cath
- Primary outcome: all cause mortality; MI; ischemic stroke.
- Outcome results: 19.9% in no T rx group vs 25.7% in T rx group - absolute risk difference of 5.8%.

Vigen, R., et. al. (2013). Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*, *310*(17), 1829-1836.

Testosterone (T) May Cause CV Harm

Models adjusting for the presence of CAD demonstrated that T rx as a time-varying covariate was associated with significant increased risk.

HR-1.29 (95%CI, 1.04 to 1.58)

Vigen, R., et. al. (2013). *JAMA, 310*(17), 1829-1836.

T Rx Group Had Fewer CV Risk Factors at Baseline

Table 1. Characteristics of Patients at Study Entry Who Did and Did Not Receive Testosterone Therapy

	Unweighted Covariates at Study Entry, No. (%) of Patients		
	No Testosterone Therapy (n = 7486)	Testosterone Therapy (n = 1223)	*P* Value
Age, mean (SD), y	63.8 (9.0)	60.6 (7.6)	<.001
Total testosterone, mean (SD), ng/dL	206.5 (73.8)	175.5 (62.3)	<.001
Coronary arteries			
Normal	900 (12.3)	197 (16.1)	<.001
Nonobstructed	2089 (27.9)	356 (29.1)	.64
Obstructed	4497 (60.1)	670 (54.8)	.001
Hypertension	6952 (92.9)	1101 (90.0)	.001
Hyperlipidemia	6611 (88.3)	1051 (85.9)	.02
Diabetes	4171 (55.7)	650 (53.2)	.09
Obesity	4033 (53.9)	703 (57.5)	.02
Depression	2641 (35.3)	448 (36.6)	.37
Prior PCI	2181 (29.1)	335 (27.4)	.22
Obstructive sleep apnea	1980 (26.4)	341 (27.9)	.30
Congestive heart failure	1826 (24.4)	222 (18.2)	<.001
Prior myocardial infarction	1816 (24.3)	248 (20.3)	.002
Chronic obstructive pulmonary disease	1622 (21.7)	228 (18.6)	.02
Peripheral vascular disease	1463 (19.5)	201 (16.4)	.01
Cerebrovascular disease	1222 (16.3)	136 (11.1)	<.001

Abbreviation: PCI, percutaneous coronary intervention.

SI conversion factors: To convert testosterone from ng/dL to nmol/L, multiply by 0.0347.

T rx'ed group had significantly: >normal coronaries; < obstructive CAD; < BP, cholesterol, CHF, hx MI, COPD, PAD, CVD; only worse issue was >obesity.

Vigen, R., et. al. (2013). *JAMA, 310*(17), 1829-1836.

No On Rx Differences in: BP, LDL, or Statin & Beta-blocker Use

Table 3. Blood Pressure, Low-Density Lipoprotein Levels, and Use of Statins and β-Blockers Among Patients After Coronary Angiography

	No Testosterone Therapy	Testosterone Therapy	*P* Value
Blood pressure, mean (SD), mm Hg[a]			
1 Year			
Systolic	130.9 (21.0)	129.2 (10.25)	.10
Diastolic	74.6 (13.1)	73.1 (6.9)	.02
2 Years			
Systolic	130.7 (20.7)	130.0 (14.2)	.47
Diastolic	74.5 (13.0)	73.4 (9.4)	.06
LDL, mean (SD), mg/dL[a]			
1 Year	85.4 (41.1)	83.7 (22.0)	.46
2 Years	85.6 (40.9)	85.9 (29.0)	.84
β-Blocker use, No./total (%)			
1 Year	6347.75/7075.87 (89.7)	105.85/119.09 (88.9)	.76
2 Years	4081.83/4527.06 (90.2)	249.23/280.14 (89.0)	.51
1 Year statin use, No./total (%)[b]	6649/7075.87 (94.0)	110.8/119.09 (93.0)	.67

Vigen, R., et. al. (2013). *JAMA*, *310*(17), 1829-1836.

Testosterone (T) May Cause CV Harm

- The association was consistent among pts with and without CAD.
- Risk with T rx not related to risk factor control or rates of secondary prevention medication.
- These findings raise concerns about the potential safety of T rx.

Vigen, R., et. al. (2013). *JAMA*, *310*(17), 1829-1836.

Testosterone (T) May Cause CV Harm: simple math is puzzling

7,486 non-T rx'ed: 681 died; 420 MI; 486 stroke = 1,587 primary outcomes = 21.2%

1,223 T rx'ed: 67 died; 23 MI; 33 stroke = 123 primary outcomes = 10.1%

Conclusion: T rx cuts primary outcome in half!!!

Vigen, R., et. al. (2013). *JAMA, 310*(17), 1829-1836.

Statistician explanation: Kaplan-Meier Curve

A Kaplan-Meier curve is estimated, each time that an event occurs the probability of remaining event free is calculated based on {100% minus [the number of events at that time divided by the number at risk of the event at that time] x100%}. The number of men at risk in the Testosterone Therapy (TT) group is always much smaller at any given time than the number of men at risk in the group that never receives TT. So one event in the TT group leads to a smaller % remaining event free compared to the % that would be calculated when one event occurs in the never treated group. Within each of the TT and no TT group, the % are then multiplied over all of the event times that occur separately in each group to arrive at the overall Kaplan-Meier curve in each group. The result is a lower cumulative % remaining event free in the TT group, or, conversely, a higher cumulative percentage of events in that group.

Hot Topics

Lipid Therapy Guidelines 12/12/2013

High-moderate intensity statin rx for all of the following:

a) 'Secondary' prevention – proven ASVD due to an event or need for an intervention. High intensity

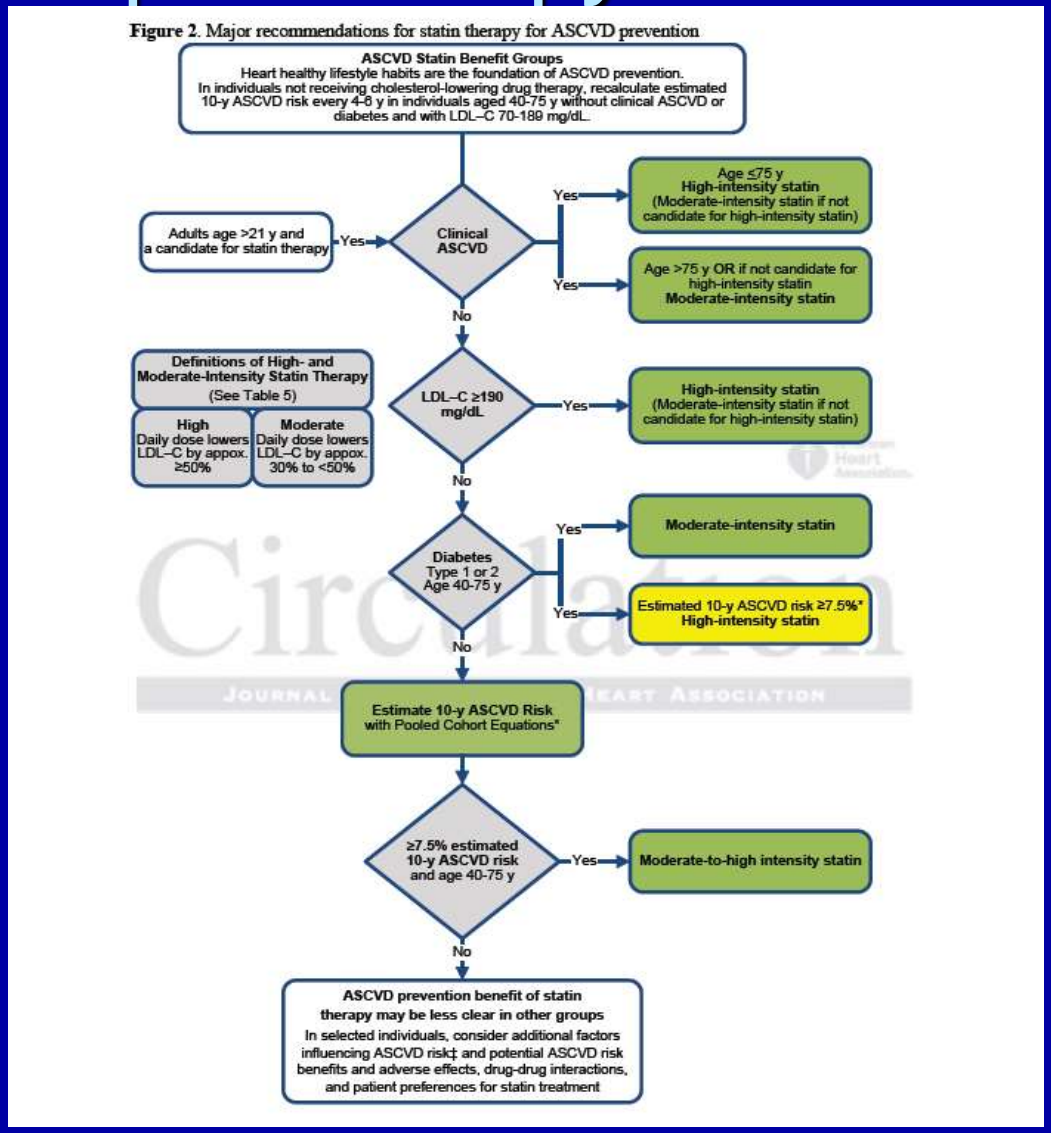
b) LDL-C ≥190 mg/dL – High intensity

c) Diabetic 40-75yo with LDL-C ≥70mg/dL ('primary') – moderate intensity; if 10 yr. risk >7.5% - High intens.

d) 'Primary' prevention with LDL-C ≥70mg/dL & 10 yr. risk ≥7.5% - high or moderate intensity

Stone, N. J., et. al. (2013). 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. doi: 10.1161/01.cir.0000437738.63853.7a

Lipid Therapy Guidelines 12/12/2013



Incredible: no mention of Inflammation playing a role in determining 'intensity' of statin therapy!

High intensity rx is now the SOC for all 'secondary' pts regardless of LDL-C level or inflammation! There are no longer any lipid 'targets'.

Pts. >70 yo automatically get statin rx as their estimated 10-year risk is still ≥7.5% simply due to age.

Stone, N. J., et. al. (2013). 2013 ACC/AHA Guidelines. Circulation. doi: 10.1161/01.cir.0000437738.63853.7a

Lipid Therapy Guidelines 12/12/2013

State: If statin not indicated with one of the four criteria, may consider additional factors influencing ASCVD risk.

a) LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias
a) Famhx: first degree relative with ASCVD <55yo male or <65yo female
b) C-reactive protein >2 mg/L
c) CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity
d) ankle-brachial index <0.9
e) elevated lifetime risk of ASCVD

At least a hint of inflammation consideration with CRP; CAC & PAD represent ASVD

Stone, N. J., et. al. (2013). 2013 ACC/AHA Guidelines. Circulation. doi: 10.1161/01.cir.0000437738.63853.7a

Lipid Therapy Guidelines 12/12/2013

- These guidelines are only focused on the treatment of cholesterol to reduce risk (not inflammation).
- They only acknowledge statins for lipid rx.
- No place for low intensity statin rx (<30% LDL-C reduction.
- Gave up treat-to-goal paradigm. This includes all lipid fractions (e.g. – LDL, HDL, lipo (a), TG,).

Stone, N. J., et. al. (2013). 2013 ACC/AHA Guidelines. Circulation. doi: 10.1161/01.cir.0000437738.63853.7a

Only focused on the treatment of cholesterol with a statin to reduce risk and not inflammation

Fails to recognize previous studies showing the statin's inflammation effect is at least as important as the lipid effect!

Inflammation More Important than LDL

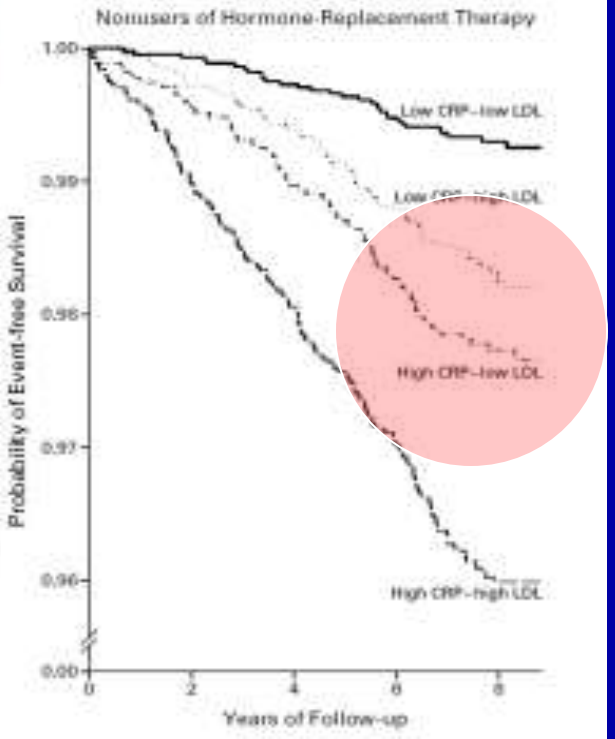
Clinical implications of hsCRP testing

Cardiovascular events (cont' d)

- hsCRP is a stronger predictor of cardiovascular events in women than LDL-C and adds prognostic information to Framingham risk scores[1]

Women's Health Study

- 28,345 women (8 yrs.; 15,745 were not on HRT)
- hsCRP and LDL-C measured at baseline



Ridker, P. M., et. al. (2002). Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events. *New England Journal of Medicine, 347*(20), 1557-1565.

CRP Change as Important as LDL Change

- 504 CAD pts; half prava 40mg & half atorva 80mg; 18 mos.; outcome- IVUS change in CAD

- After adjustment for reduction lipid, the decrease in CRP was independently and significantly correlated with the rate of progression.

- Pts with reductions in both LDL and CRP that were greater than the median had significantly slower rates of progression than pts with reductions in both biomarkers that were less than the median (P=0.001)

Nissen, S. E., et. al. (2005). Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*, *352*(1), 29-38.

CRP Change as Important as LDL Change

- Reduced rate of progression of atherosclerosis in CAD pts is significantly related to greater reductions in CRP.
- Study raises the provocative question of whether the effects of statins on CRP should be considered in decisions regarding therapy.

Nissen, S. E., et. al. (2005). Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*, *352*(1), 29-38.

CRP Matters in Statin Therapy

- PROVE IT/TIMI 22; ACS pts randomized to prava 40mg or atorva 80mg.
- What mattered in terms of outcome was achieving the "dual goals" of both LDL and CRP reduction.
- Which drug got you there did not matter.

Cannon, C. P., (2004). Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *New England Journal of Medicine*, *350*(15), 1495-1504.

CRP Predicts Events in Statin Trial Regardless of Lipids

- 15,548 healthy men and women; rosuvastatin 20 mg vs placebo; median follow-up 2 yrs.; CV outcomes.

- hsCRP concentrations were predictive of event rates irrespective of the lipid endpoint.

Ridker, P. M., et. al. (2009) Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *The Lancet*, *373*(9670), 1175-1182.

Lp-PLA2 Change Predicts CV Events in Statin Trial

- 7,863 CAD pts. ~ 16% female; randomized to pravastatin 40mg or placebo; 6 yr. follow-up for CHD (events & death); evaluate Lp-PLA2 as a predictor at baseline and with change at one yr.

- Lp-PLA2 was categorized in quartiles

White, H. D., et. al. (2013). Changes in Lipoprotein-Associated Phospholipase A2 Activity Predict Coronary Events and Partly Account for the Treatment Effect of Pravastatin: Results From the Long-term Intervention with Pravastatin in Ischemic Disease Study. *J Am Heart Assoc*, *2*(5), e000360.

Lp-PLA2 Change Predicts CV Events

- Change in Lp-PLA2 was a significant independent predictor of CHD events after adjustment for these 23 risk factors, including LDL-C and LDL-C changes.

P<0.001

White, H. D., et. al. (2013). *J Am Heart Assoc*, *2*(5), e000360.

Lp-PLA2 Change Predicts CV Events

- In a model looking at events after 1 year and adjusting for baseline BNP, cystatin C, D-dimer, troponin I, Lp-PLA2 activity, and change in these same biomarkers, there was still a strong association with change in Lp-PLA2 activity and CHD events.

  $P<0.001$

- Reducing Lp-PLA2 reduces CV event risk!!!

White, H. D., et. al. (2013). *J Am Heart Assoc*, *2*(5), e000360.

Lp-PLA2 Change Predicts CV Events

- Pravastatin reduced Lp-PLA2 by 16% compared with placebo ($P<0.001$).
- After adjustment for Lp-PLA2 change, the pravastatin rx effect was reduced from 23% to 10% with 59% of the rx effect accounted for by changes in Lp-PLA2.

White, H. D., et. al. (2013). *J Am Heart Assoc*, *2*(5), e000360.

Lp-PLA2 Change Predicts CV Events

- Showed that when baseline and change in LDL-C were included in the model and/or when baseline and change in Lp-PLA2 and LDL-C were fitted as continuous variables rather than quartiles, the strong association between change in Lp-PLA2 and CHD events was maintained, while change in LDL-C was not a predictor of outcomes.

White, H. D., et. al. (2013). *J Am Heart Assoc*, *2*(5), e000360.

Lp-PLA2 Change Predicts CV Events

- Novel finding of this study is that change in Lp-PLA2 levels accounted for at least as much of the pravastatin treatment effect on reducing CHD death and MI as did LDL-C reduction.

White, H. D., et. al. (2013). *J Am Heart Assoc*, *2*(5), e000360.

Only acknowledge statins for lipid rx

Ignores other known excellent therapies for lipids

Niacin Therapy

"*Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.*"

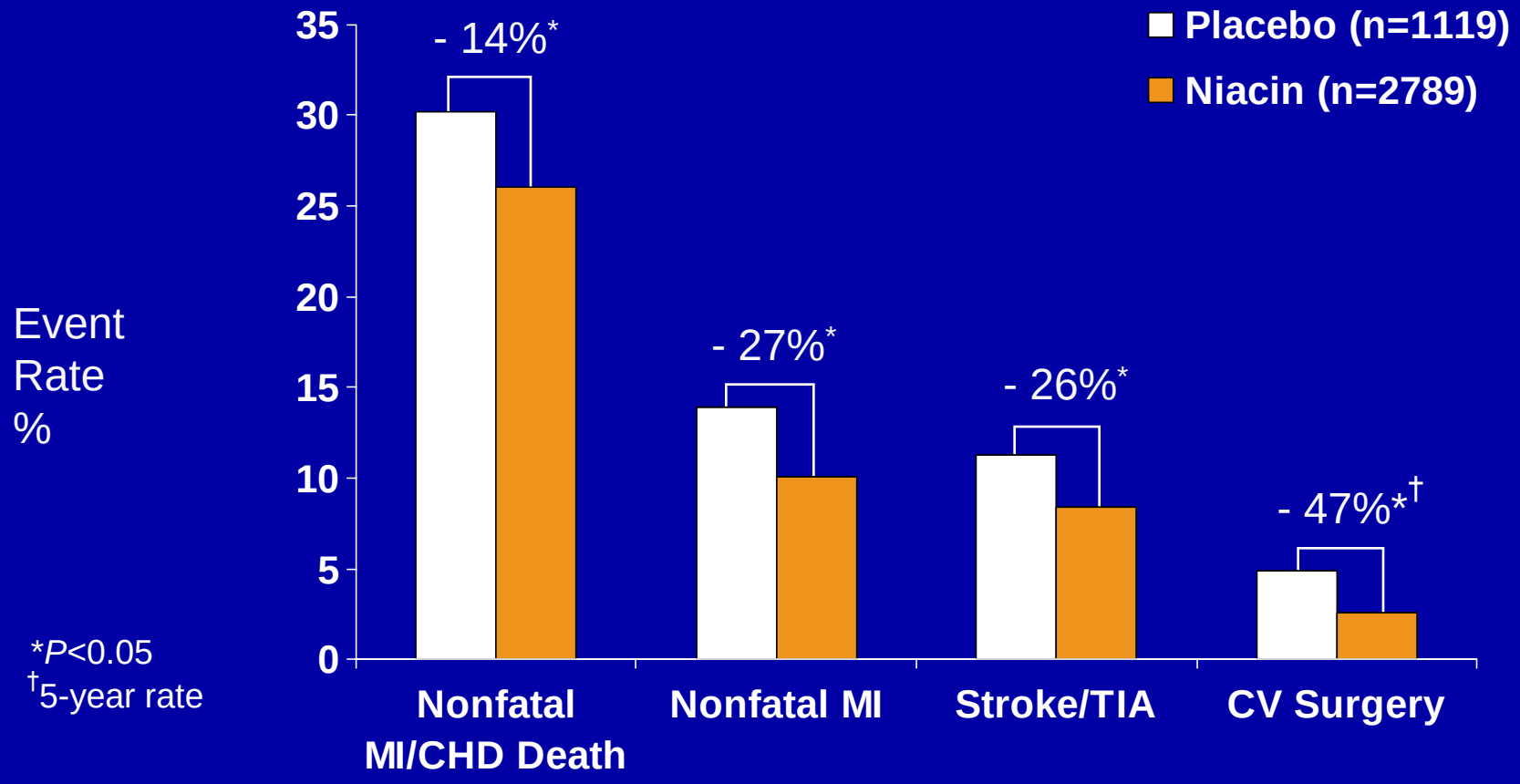
Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation*. 2002;106:3143-3421.

Niacin Mono Therapy: Coronary Drug Project

- Randomized, placebo-controlled
- 8,341 men with h/o MI, 30–64 y/o, 6 arms
  - Placebo
  - Niacin
  - Clofibrate
  - Low-dose estrogen (↑ non-fatal CV events)
  - High dose estrogen (↑ thromboembolism, cancer)
  - d-thyroxine (↑ deaths)
- Baseline lipids: TC 250 mg/dL, TG 177 mg/dL

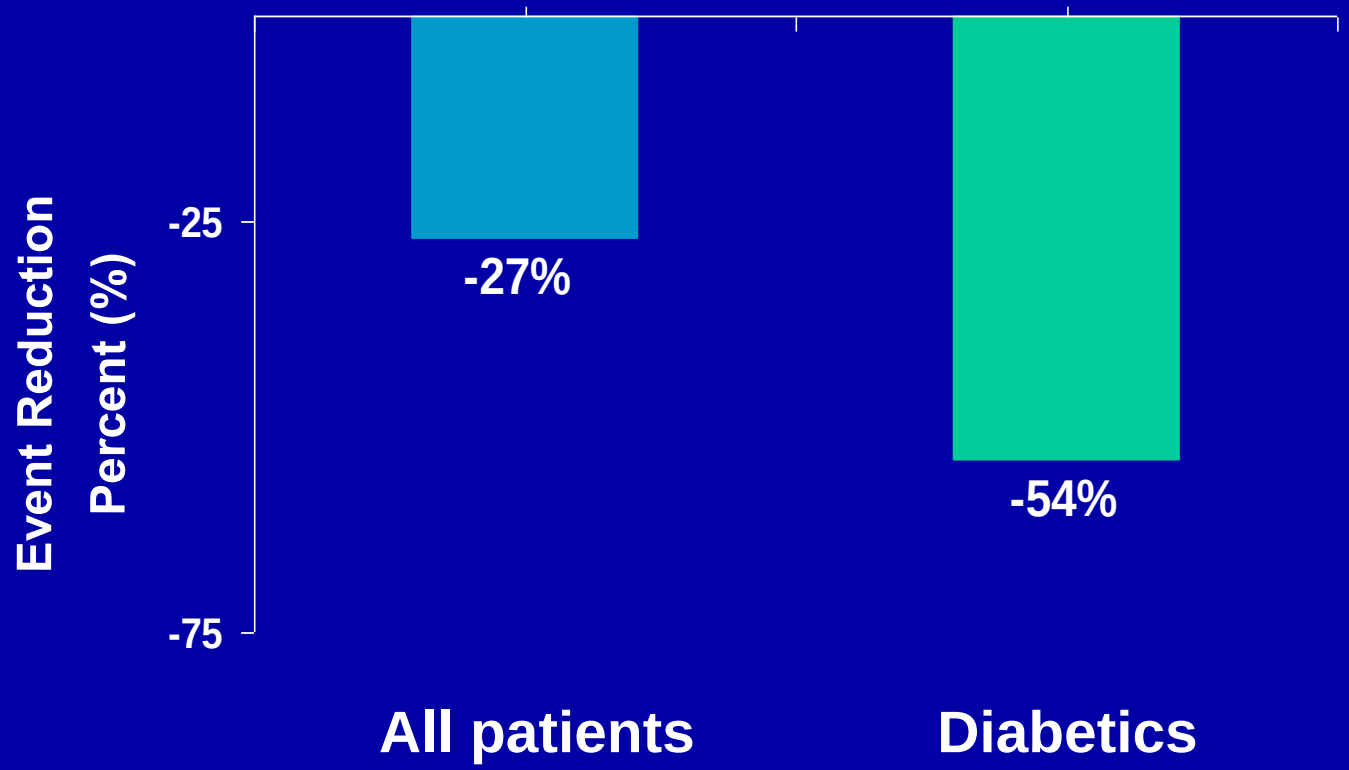
Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. (1975). *JAMA, 231*(4), 360-381.

Coronary Drug Project 5-Year Events



Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. (1975). JAMA, 231(4), 360-381.

CORONARY DRUG PROJECT
Non-fatal MI REDUCTION



November 20, 2002, Scientific Session of the 75th AHA Chicago, Il..

Lipoprotein effects of Fibrates

	Fibrates
LDL	↓ 5 – 20%
HDL	↑ 10 – 20%
Triglycerides	↓ 20 – 50%
Small,Dense LDL	Decrease

Third Report of the National Cholesterol Education Program Expert Panel. Executive Summary. NIH Publication No. 01-3670. May 2001.

Guerre-Millo M, et al. *J Biol Chem*. 2000;275:16638-16642.

Gembibrizil: Helsinki Heart Study

- A 5-year trial that tested the efficacy of gemfibrozil for decreasing the risk of coronary artery disease in hypercholesterolemic men without coronary artery disease.
- The study involved 4,081 men (40 to 55 years of age) with a non-HDL cholesterol level >200 mg/dL.
- Gemfibrozil use was associated with a 34% reduction in coronary artery events.

Frick, M. H., et. al. (1987). Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia. *New England Journal of Medicine, 317*(20), 1237-1245.

Gemfibrozil appears favorable in IR pts. according to 18 yr. follow-up from Helsinki HS

- Pts. In highest tertile for BMI & TG (IR) had:
  - 71% CHD mortality reduction
  - 33% all-cause mortality reduction

- If med started btw 40-47yo, did better than those who started btw 48-57yo

Tenkanen, L., et. al. (2006). Gemfibrozil in the treatment of dyslipidemia: An 18-year mortality follow-up of the helsinki heart study. *Arch Intern Med, 166*(7), 743-748.

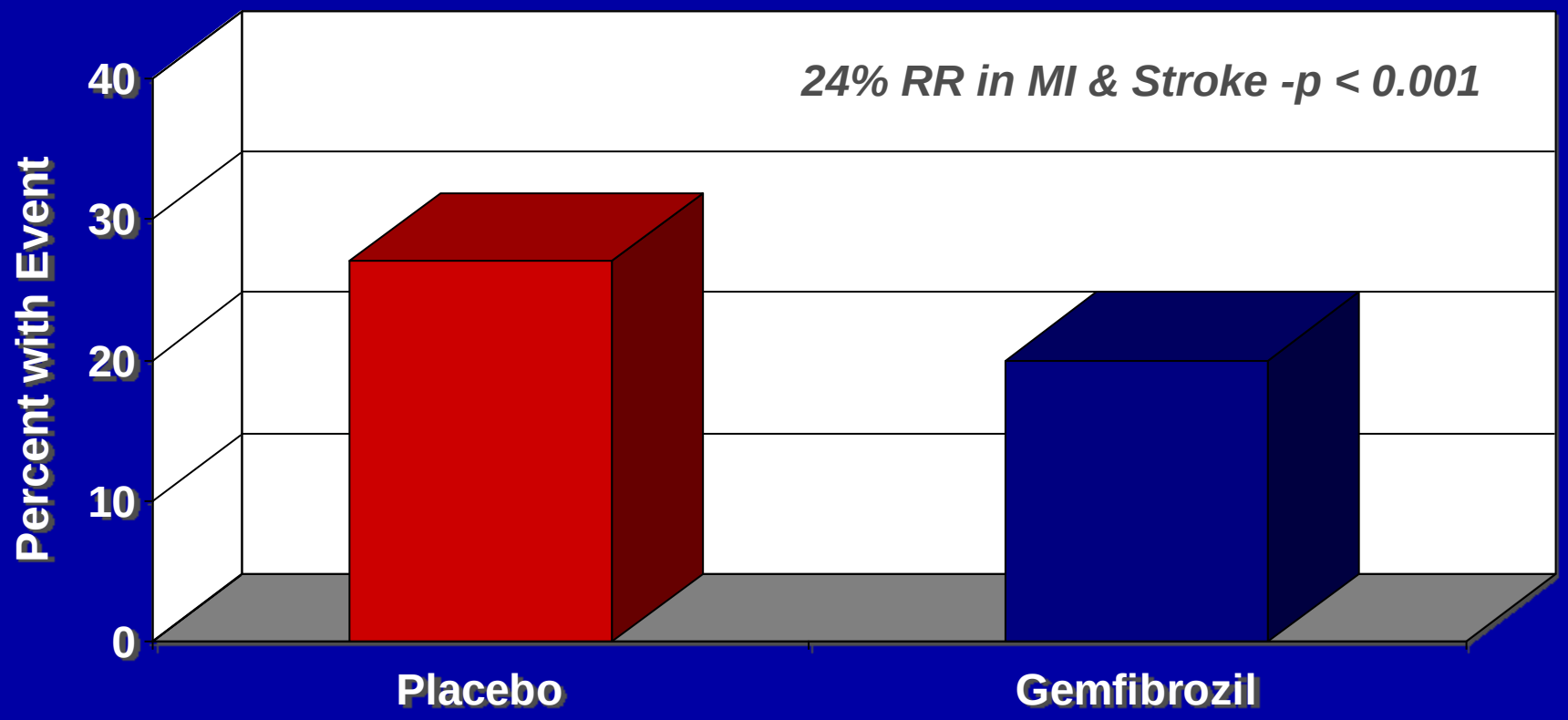
Gembibrizil: VA-HIT

- 5 yr. double blind trial; compared gemfibrozil (1200 mg/day) with placebo
- 2,531 men with CHD, HDL ≤40 mg/dL, and LDL ≤140 mg/dL
- The primary outcome was nonfatal MI or death from coronary causes

Rubins, H. B., et. al. (1999). Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men with Low Levels of High-Density Lipoprotein Cholesterol. *New England Journal of Medicine, 341*(6), 410-418.

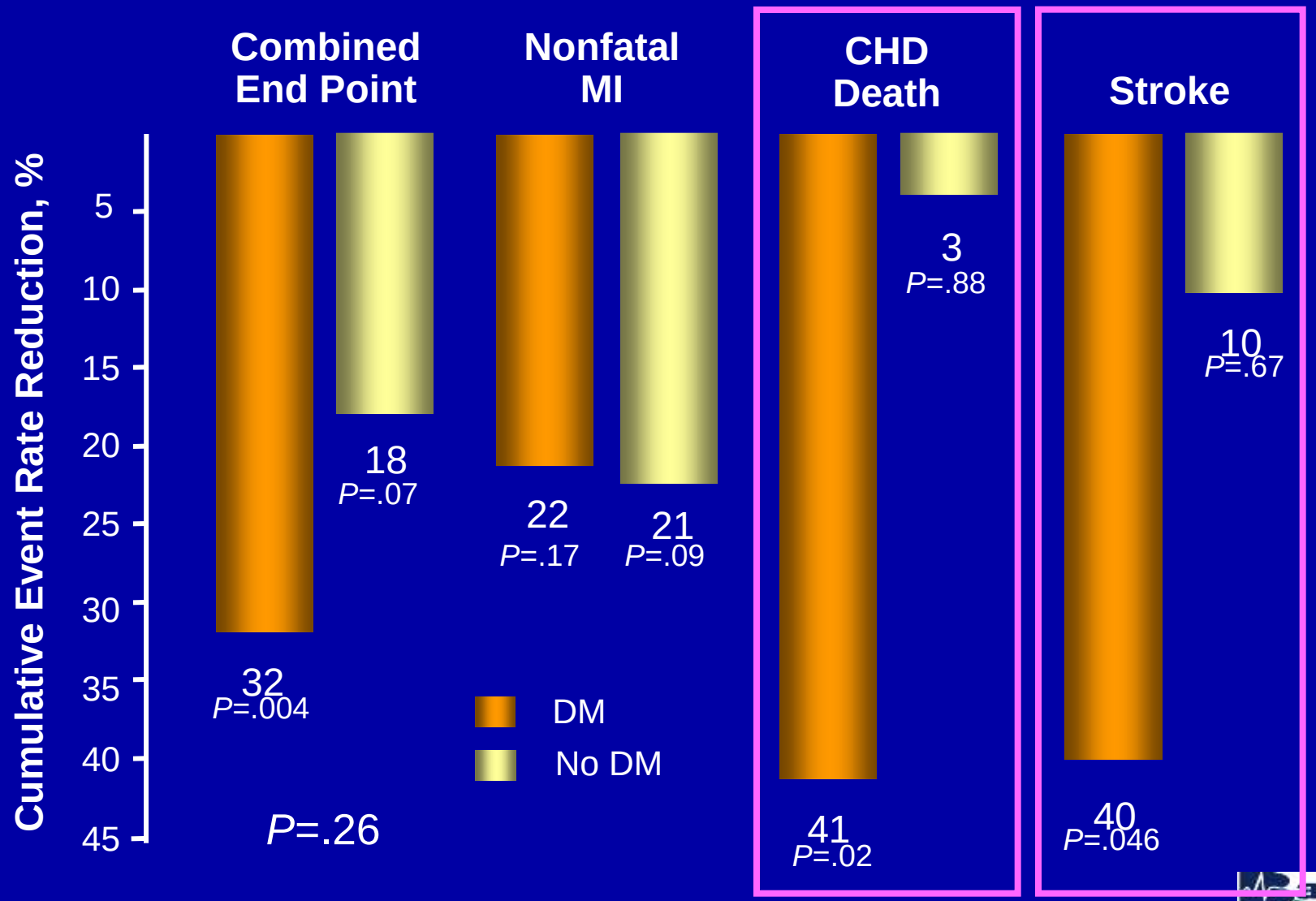
VA HIT

No change LDL; 6% increase HDL; 31% decrease TG



Rubins HB, et al. *N Engl J Med.* 1999;341:410-418

VA-HIT: CVD Risk Reduction in Diabetics Compared With Nondiabetics



Rubins HB, et al. *Arch Intern Med*. 2002;162:2597-2604.

Red Yeast Rice is as Effective as Pravastatin 20mg

Treatment BID dosing	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)	Triglycerides (mg/dL)
Red yeast rice 2400mg			
•Baseline	260.7	181.2	142.2
•12 wk	200.9	126.1	120.9
Pravastatin 20mg			
•Baseline	253.4	163.6	148.4
•12 wk	198.6	120.3	126.1

Discontinuation due to myalgia was equivalent
Red yeast rice is not regulated by the FDA, leading to a lack of consistency

Halbert SC et al. *Am J Cardiol 1/21/*2010; 105:198-204.
**Lu,Z, et.al. Am J Cardiol* 6/12/2008; 101:1689-1693

Red Yeast Rice Reduces CV Risk

- 5,000 CAD Chinese pts; randomly assigned either to placebo or red yeast rice; 4.5 years; CHD death or event
- 10.4% in the placebo group suffered primary end point versus 5.7% in treated group

RR reduction 45%, $p<0.001$

Lu, Z., et. al. (2008). Effect of Xuezhikang, an Extract From Red Yeast Chinese Rice, on Coronary Events in a Chinese Population With Previous Myocardial Infarction. *Am J Cardiol, 101*(12), 1689-1693.

Red Yeast Rice Reduces CV Risk

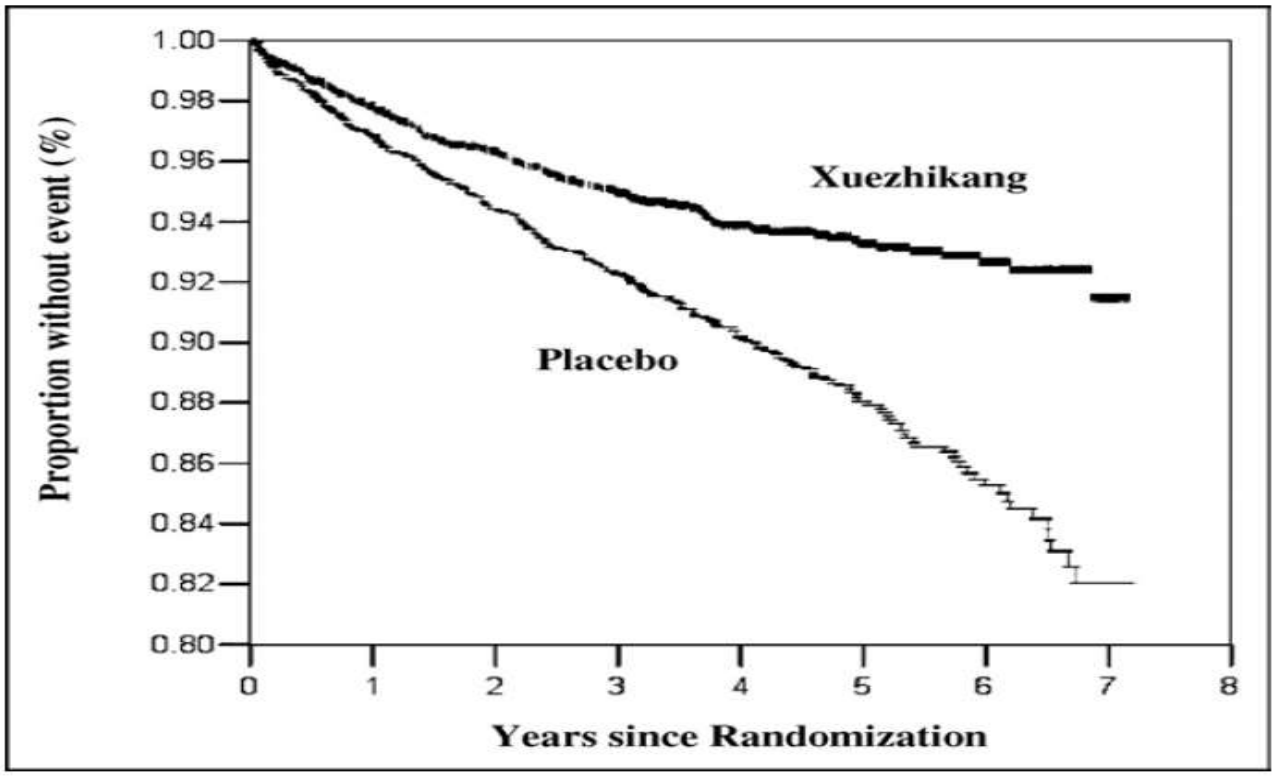


Figure 1. Kaplan-Meier curves for the proportion of patients without primary events in the XZK and placebo groups.

Lu, Z., et. al. (2008). Effect of Xuezhikang, an Extract From Red Yeast Chinese Rice, on Coronary Events in a Chinese Population With Previous Myocardial Infarction. *Am J Cardiol, 101*(12), 1689-1693.

No place for low intensity statin rx <30% LDL-C reduction.

This appears to be an oxymoron for statin therapy.

Several just reviewed plus some statin trials

Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

Atorva	Fluva	Pitava	Lova	Prava	Rosuv	Vytor	Simva	%↓ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----		-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%
	-----		-----	-----	40 mg	10/80 mg	-----	63%

FDA Safety Communication 6/8/2011

No place for low intensity statin rx <30% LDL-C reduction.

Implication is LDL must be significantly reduced to lower risk & one is better off with ‘stronger statins’.

Several just reviewed contradict that!

Plenty of statin data showing stronger is not necessarily better or needed.

Statins Beneficial Even if LDL is Very Low

- 4295 pts.; average age 65; 50% DM & or CAD; 2 yr. follow-up
- 60% of pts with LDL levels <60 mg/dL prescribed statins
- Statin rx reduced mortality 35%

Leeper, N. J., et. al. (2007). Statin Use in Patients With Extremely Low Low-Density Lipoprotein Levels Is Associated With Improved Survival. *Circulation, 116*(6), 613-618

Statins Beneficial Even if LDL is Very Low

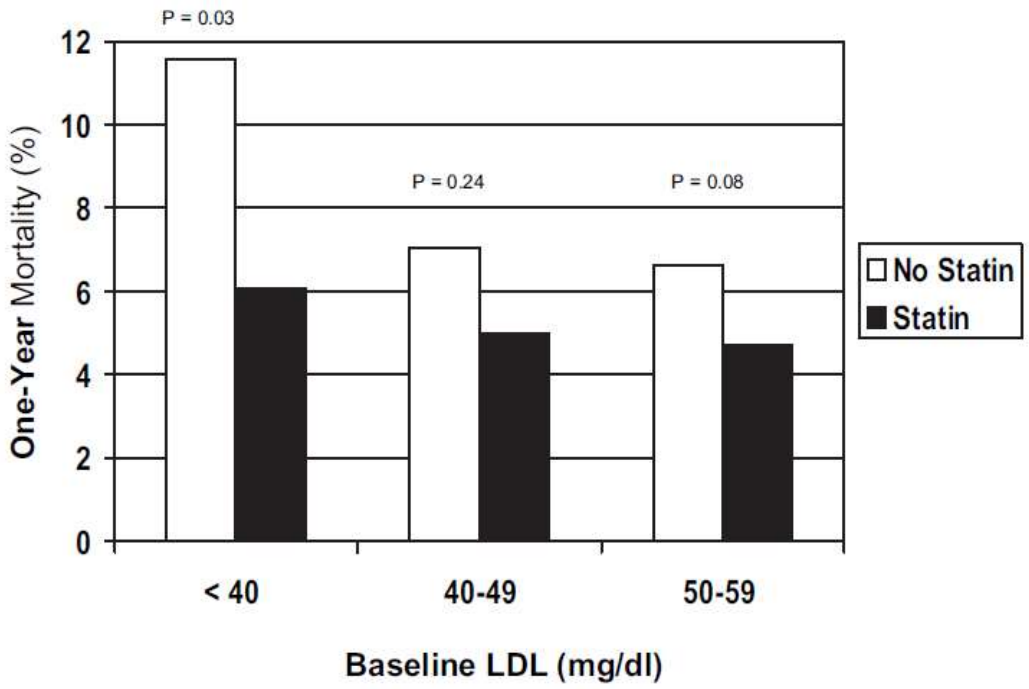


Figure 4. Mortality rates by LDL value. Statin use is associated with improved survival in subjects with LDL values below 40 mg/dL. Number of subjects by LDL level: <40 mg/dL: 247 taking a statin, 242 not on a statin; 40 to 49 mg/dL: 382 taking a statin, 355 not taking a statin; and 50 to 59 mg/dL: 1105 taking a statin, 772 not taking a statin.

"The mechanism by which therapy improves survival in patients with very low cholesterol levels is unclear"

Leeper, N. J., et. al. (2007). *Circulation, 116*(6), 613-618

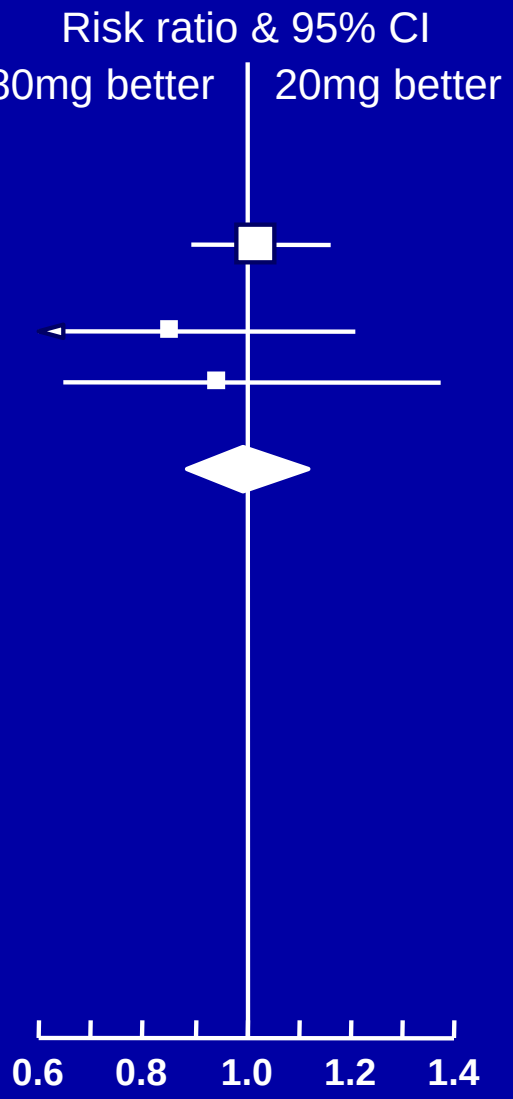
SEARCH: 12,064 Stable post-MI Patients

- Simvastatin 80mg vs 20mg
- Mean (SD) duration: 6.7 (1.5) years

Study of the Effectiveness of, A. (2010). Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. *The Lancet, 376*(9753), 1658-1669.

High Dose Statin No Better than Lower Dose in Stable CHD – SEARCH trial

Cause of death	Simvastatin allocation 80mg (n=6031)		20mg (n=6033)	
CHD	447	(7.4%)	438	(7.3%)
Stroke	57	(0.9%)	67	(1.1%)
Other vascular	53	(0.9%)	56	(0.9%)
All vascular	**557**	**(9.2%)**	**561**	**(9.3%)**



Study of the Effectiveness of, A. (2010). *The Lancet, 376*(9753), 1658-1669.

Gave up treat-to-goal paradigm. This includes all lipid fractions (e.g. – LDL, HDL, lipo (a), TG,).

Recent evidence argues this is not a wise idea!

Lipo (a) Baseline and One Year Follow-up Predict CV Risk in CAD Pts

- 7,863 post-MI pts; ~18% female; baseline and one year change in Lp (a) evaluated for predicting CV event risk; 6 yr. follow-up.

- The median conc. of Lp(a) at baseline was 13.9 (25th–75th percentiles, 6.6–44.05) mg/dL with the upper decile >73.7 mg/dL; none had values >90 mg/dL.

- Half the pts had values <13.9 mg/dL, which are 'normal'

Nestel, P. J., et. al. (2013). Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Baseline Predicts CV Risk in CAD Pts

- CHD events: Lp(a) >73.7 mg/dL
  HR- 1.24 (95%CI, 1.02-1.52)

- CVD events: Lp(a) >73.7 mg/dL
  HR- 1.21 (95%CI, 1.07-1.36)

- Non-fatal MI: Lp(a) 44.1-73.7 mg/dL
  HR- 1.28 (95%CI, 1.02-1.60)

Nestel, P. J., et. al. (2013) *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Change in One Year Follow-up Predict CV Risk in CAD Pts

- A relative change >13% from baseline to one yr is larger than can be accounted for by analytic variation.

- An increase >13% relative to a decrease of >13% generated a significant increased risk

  HR for CV event- 1.21 (95%CI,1.06–1.39) P=0.005

  HR for CHD event- 1.21 (95%CI,1.05–1.39) P=0.009

Nestel, P. J., et. al. (2013). Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Change in One Year Follow-up Predict CV Risk in CAD Pts

- If lipo (a) increased by ≥3.4 mg/dL versus decreased by ≥2.4 mg/dL, 23% more likely to have CV event

  HR-1.23 (95% CI, 1.07–1.39) P=0.002

Nestel, P. J., et. al. (2013). Plasma Lipoprotein(a) Concentration Predicts Future Coronary and Cardiovascular Events in Patients With Stable Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

Lipo (a) Baseline and One Year Follow-up Predict CV Risk

Study indicates lipo (a) should be a target of therapy!

Nestel, P. J., et. al. (2013) *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302479

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

- 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, 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. = LDL is not inflammatory !

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).

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.

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 needs to be oxidized before they can be taken up by macrophages, while triglyceride-rich lipoproteins or 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. = remnant cholesterol and inflammation should be 'targets' of therapy.

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

BDM Thoughts

Great that they include people with known ASVD for statin therapy regardless of LDL- problem.

a) For sub-clinical disease they only addressed CAC and even then the score had to be ≥300.

b) Carotid plaque should have been included.

c) Any sub-clinical ASVD found in any manner should have been included.

BDM Thoughts

Too bad they are still relying heavily on risk factors as opposed to actual ASVD.

Incredible that they failed to address inflammation and how that should play a critical role in the ‘intensity’ of therapy. Many individuals will now receive higher dose statin therapy which ups the risk of serious side effects.

BDM Thoughts

Cholesterol can be a driver of ASVD and statins are not the only medications to address those issues. As a matter of fact, other agents such as niacin may be more appropriate. Lipo (a) and remnant cholesterol should be targeted. Niacin is the most effective agent we have to do that.

BDM Thoughts

It is too bad these new guidelines are so slanted toward statin therapy. The public is already very suspicious of the motivation behind the push for statins. They are good drugs, but they can cause harm and we have other effective agents. These guidelines may make the public even more wary of 'experts' and drug companies! That would be justifiable as there does appear to be lack of acknowledgement of scientific evidence beyond statin therapy.

We are Prejudice Too!! ☺☺

BDM

New guidelines

Upcoming Presentations

Upcoming Presentations

- Watch for numerous press releases about **Beat the Heart Attack Gene**
- On-line basic BDM course by 1/1/2014
- Book release ~ Feb. 4th; can pre-order now
- Preceptorship LV,NV 3/21-22/2013

Open for Discussion