Bale/Doneen Live Chat Session

10/8/2014

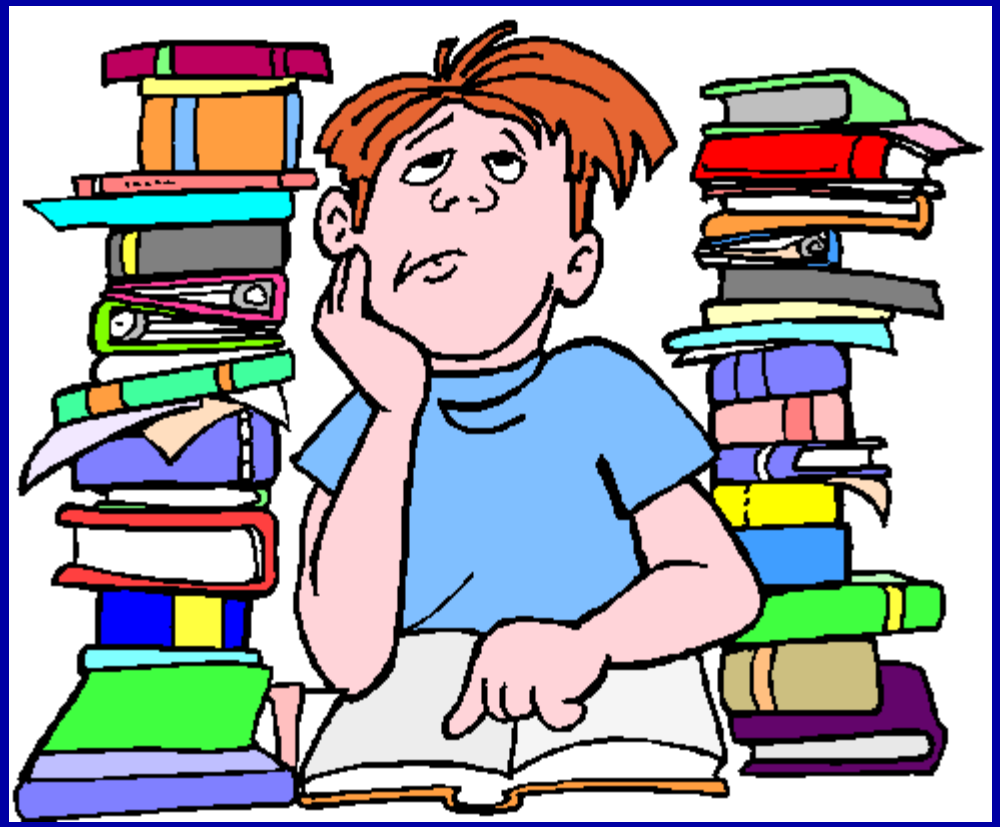
5:30-6:30 pm PST

Bradley Bale, MD

Intention of the live chats

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

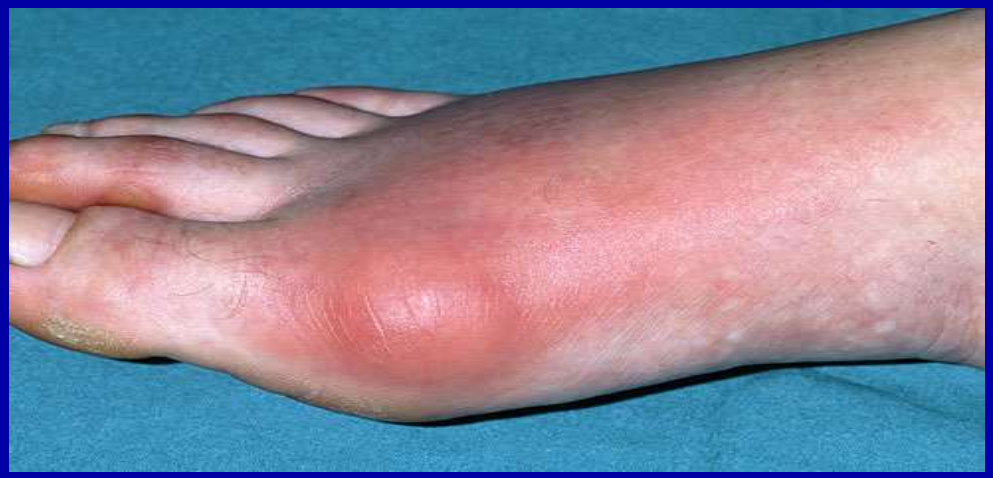
New Studies??!!!:

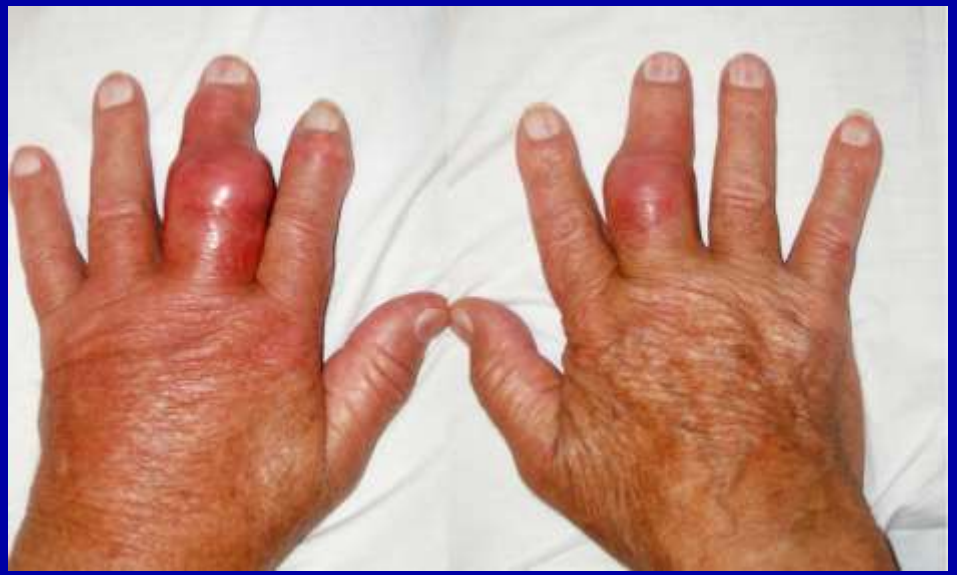


Will concentrate on a few of many.

Red Flag

The Pain of Gout May Pale Compared to What May Come Next





Gout Increases the Likelihood of New Onset Diabetes

35,339 gout pts; 72% men; mean age 63 yo; gender, age, BMI matched with 5 non-gout pts; investigated incidence of new onset DM over 1000 person-years.

Adjusted for: smoking, alcohol, physician visits, comorbidities and medication use.

Rho, Y. H., et. al. (2014). Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study. *Annals of the Rheumatic Diseases*. doi: 10.1136/annrheumdis-2014-205827

Gout Increases the Likelihood of New Onset Diabetes

Women with gout were 48% more likely to become diabetic.

HR- 1.48 (95% CI 1.29 to 1.68) p<0.001

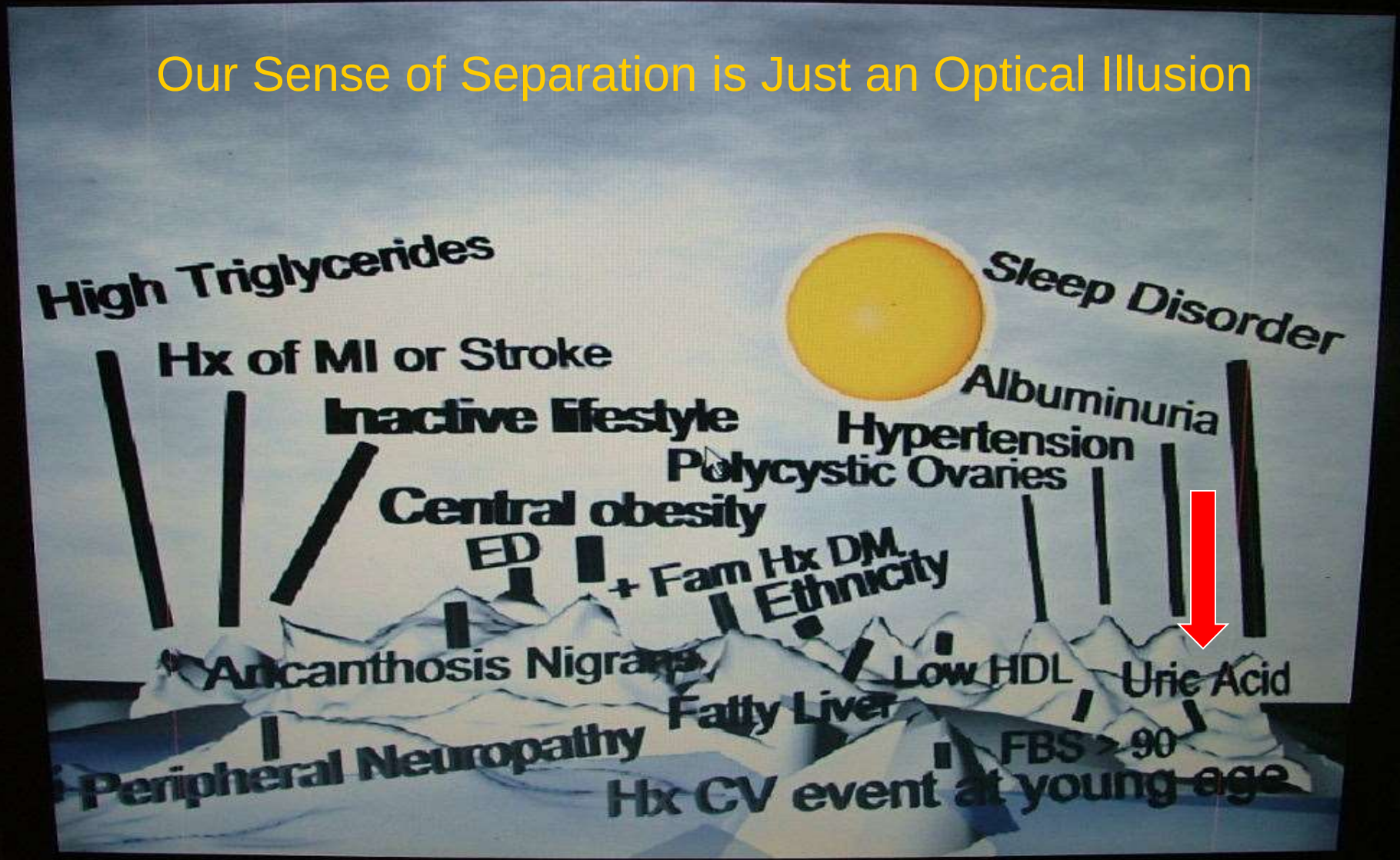
Men with gout were 15% more likely to become diabetic.

HR-1.15 (95% CI 1.06 to 1.24), p <0.001

"Screen for diabetes and aggressively manage risk factors in patients with gout"

Rho, Y. H., et. al. (2014). Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study. *Annals of the Rheumatic Diseases*. doi: 10.1136/annrheumdis-2014-205827

Our Sense of Separation is Just an Optical Illusion



Insulin resistant icebergs: created by Bradley F Bale, MD; produced by Jacob Bale June 2002

Insulin Resistance Inhibits Uric Acid Excretion

Hyperinsulinemia caused a significant decrease in urinary uric acid excretion.

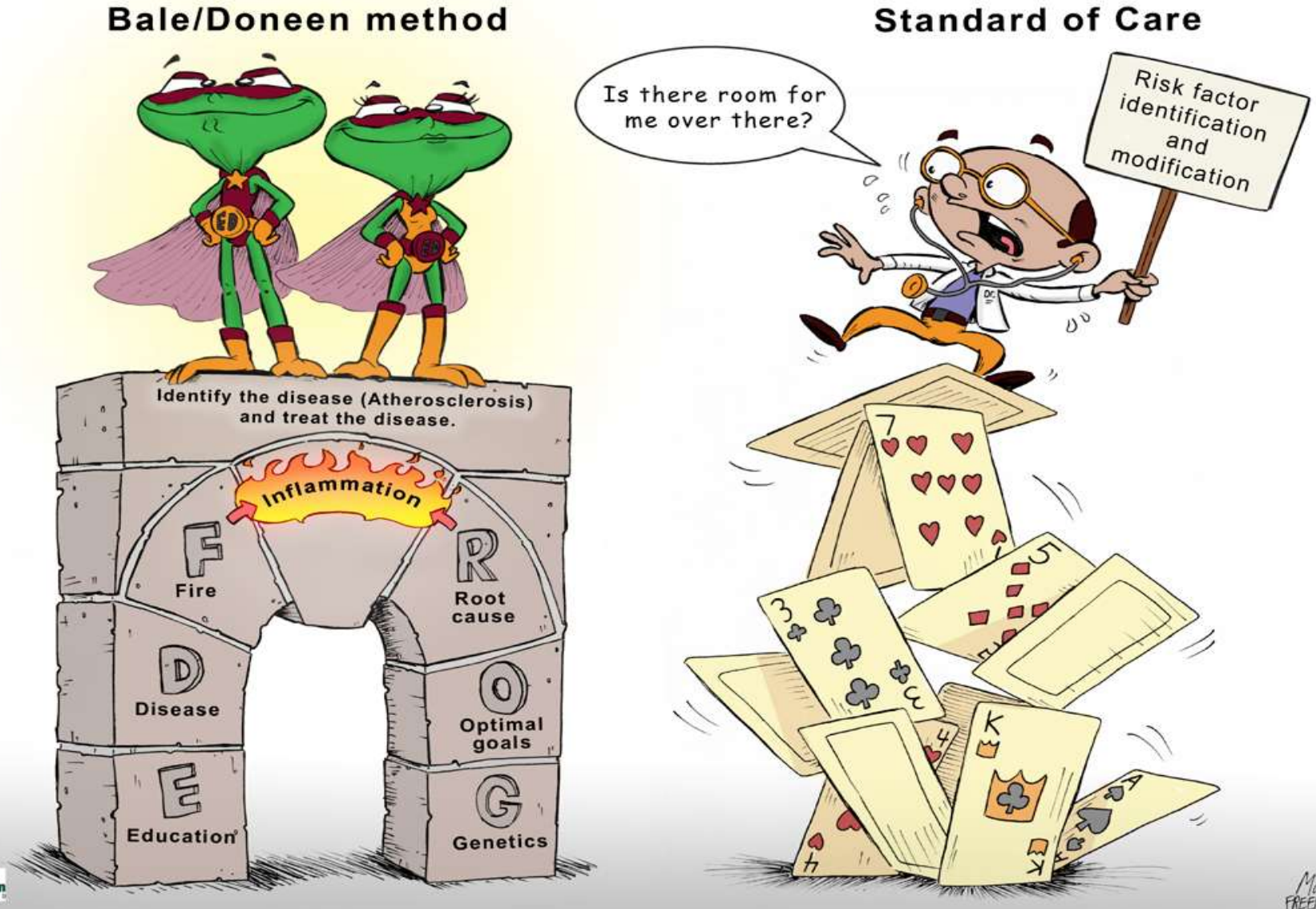
Absolute excretion rate-1.66 +/- 0.21 vs. 2.12 +/- 0.23 mumol/min; p = 0.03

Clearance rate 5.6 +/- 0.8 vs. 7.3 +/- 0.8 ml/min; p = 0.03

Fractional excretion 4.48 +/- 0.80 ml/min vs. 6.06 +/- 0.64%; p < 0.03

Quinones Galvan, A., Natali, A., Baldi, S., Frascerra, S., Sanna, G., Ciociaro, D., & Ferrannini, E. (1995). *Effect of insulin on uric acid excretion in humans. American Journal of Physiology - Endocrinology and Metabolism.* ***January 1995*** *Vol. 268 no. 1, E1-E5.*

What's the difference?



Favorable CV Biomarkers and Lower Burden of Subclinical ASVD Drive the Benefit Found in the AHA's 7 Essentials for Heart Health: Background

Key biological pathways are involved in the development of subclinical ASVD.

There are multiple biomarkers representing these biological pathways.

Subclinical atherosclerosis is a fundamental precursor to CV events.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

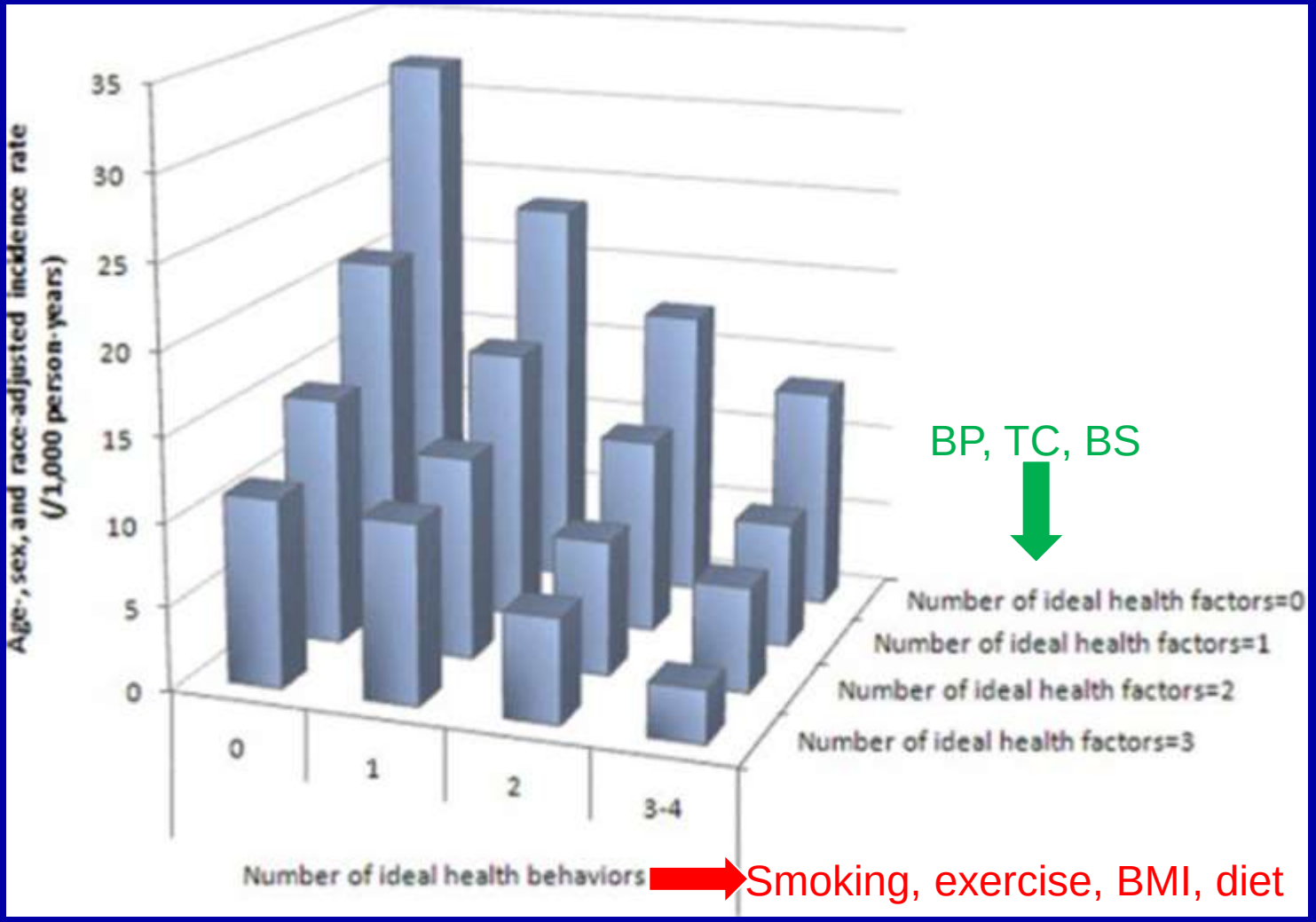
Favorable CV Biomarkers and Lower Burden of Subclinical ASVD Drive the Benefit Found in the AHA's 7 Essentials for Heart Health: Background

The AHA Cardiovascular Health score is inversely associated with the incidence of CV events.

Hypothesized that a better AHA Cardiovascular Health score is associated with: a) a more favorable biomarker profile b) a lower prevalence of subclinical CVD.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

Incidence of cardiovascular events according to the number of ideal health behaviors and health factors.



Go A et al. Circulation 2014;129:e28-e292

Favorable CV Biomarkers and Lower Burden of Subclinical ASVD Drive the Benefit Found in the AHA's 7 Essentials for Heart Health

2,680 Framingham offspring pts used to evaluate the association between the CVH score and each biomarker.

1,842 Framingham offspring pts used to assess the association between the CVH score and presence of subclinical disease.

1,826 of these pts used to assess the association between the CVH score and the incidence of CV events.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

Biomarker Tests: 12

CRP

NT-pro ANP & BNP

hs-cTnI

Fibrinogen

Homocysteine

PAI-1

D-dimer

ST-2

Renin

Aldosterone

growth differentiation factor-15 (GDF-15)

Xanthakis, V., Januzzi. J., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009273

Subclinical Disease Tests

Supplementary Table 3. Definition of Subclinical Cardiovascular Disease

Characteristic	Definition of subclinical disease component	Cut-points for subclinical disease presence used in the present study
1. LV hypertrophy by ECG/echocardiography		
LV hypertrophy by ECG	Sum of R in AVL plus S in V3	exceeding 2.8 mV in men and 2.0 mV in women
LV hypertrophy by echocardiography	LV mass was calculated as 0.8 { 1.04 [(IVS+LVEDD+PW)^3 - (LVEDD)^3] } + 0.6 g. LV mass values were then adjusted for height using the ratio of LV mass to height.	Value in the sex-specific top quintile
2. LV systolic dysfunction by echocardiography		
LV systolic dysfunction	LV fractional shortening was calculated as (LVEDD-LVESD)/LVEDD.	A fractional shortening of less than 0.29 by M-mode, or by evidence on two-dimensional echocardiography of mild or greater systolic dysfunction on visual assessment in multiple views (corresponding to ejection fraction less than 50%), or by both criteria.
3. Carotid ultrasound abnormality		
Increased carotid artery IMT	A composite measure that combined the maximal common carotid artery IMT and maximal internal carotid artery IMT was obtained by averaging these two measurements after standardization (subtraction of the mean and division by the standard deviation for the measurement).	1) A standardized carotid IMT that met or exceeded the sex-specific 80th percentiles in the sample; 2) An extreme increase of common carotid IMT; or 3) Presence of carotid artery stenosis ≥25%.
Extreme increase of common carotid artery IMT	An extreme increase of common carotid IMT ≥1 mm.	
Carotid artery stenosis ≥25%	Presence of a stenosis of ≥25% in the internal or common carotid artery.	
4. Peripheral arterial disease		
Ankle-brachial index ≤0.9	Defined as the ratio of the average systolic blood pressure at the ankle of each leg divided by the average systolic blood pressure in the arm with the highest blood pressure.	An ankle-brachial index at or below 0.9 in either leg.
5. Glomerular endothelial dysfunction		
Microalbuminuria	Urine albumin to urine creatinine ratio	≥25 μg/mg in men, and ≥35 μg/mg in women

Xanthakis, V., Januzzi. J., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009273

CV Events

myocardial infarction

coronary insufficiency

angina pectoris

stroke

transient ischemic attack

intermittent claudication

heart failure

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

Distribution of CV Health Scores

CVH score frequencies (%)	Women N=1485	Men N=1195
0 points	0.6	0.9
1 point	6.7	10.2
2 points	19.0	22.6
3 points	27.6	33.4
4 points	23.1	21.3
5 points	16.8	9.0
6 points	4.9	2.2
7 points	1.3	0.4

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

CV Biomarkers and CV Health Score Related

NT-proANP and BNP directly and linearly associated. P<0.001 (note all values were wnl; remember levels rise with lower BMI).

PAI-1, aldosterone, CRP, D-dimer, fibrinogen, homocysteine, GDF-15 inversely related. p<0.001

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

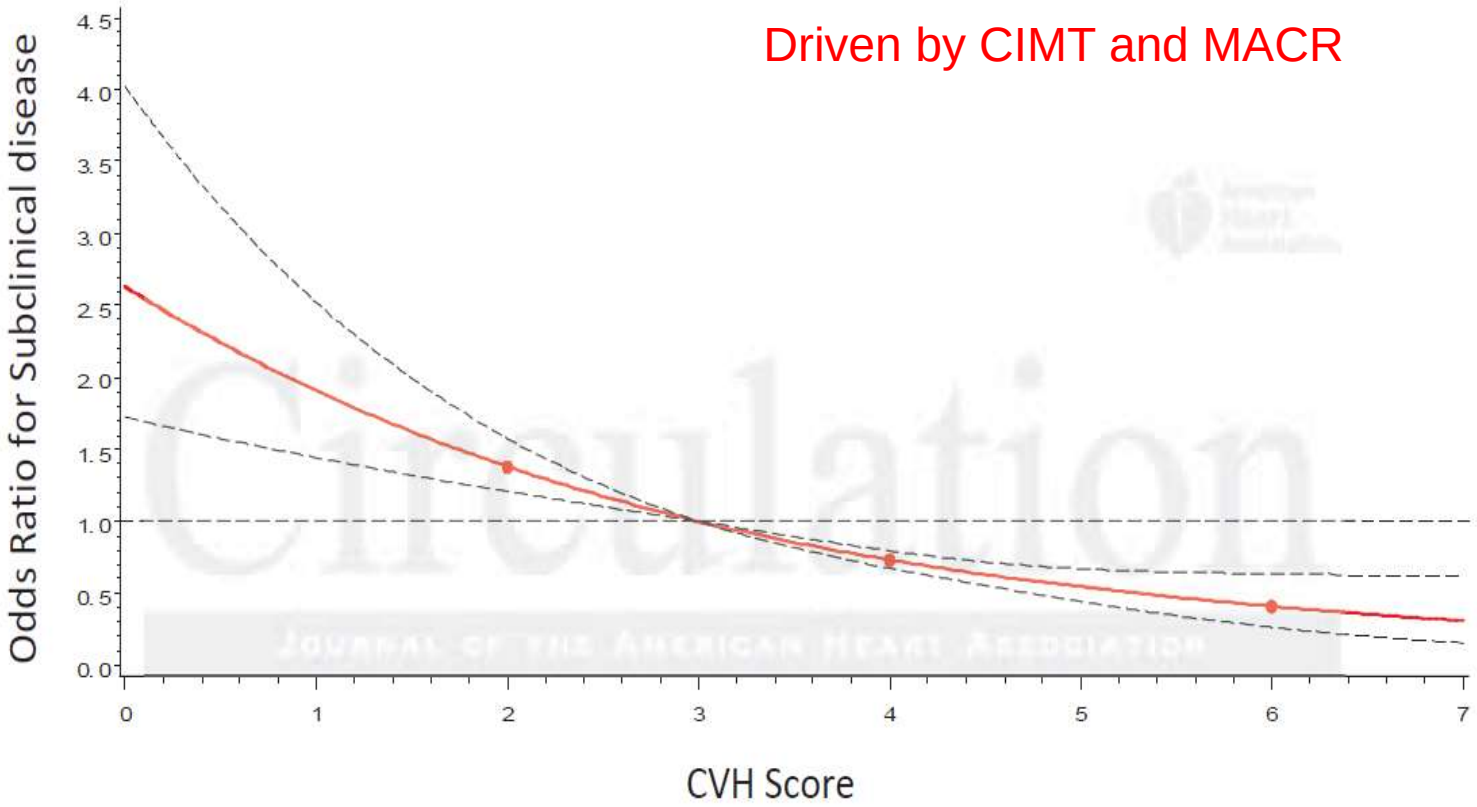
Subclinical Disease and CV Health Score

Statistically significant association $p<0.0001$

Higher CVH score was associated with lower odds of subclinical disease.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

Subclinical Disease and CV Health Score



Xanthakis, V., Januzzi. J., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009273

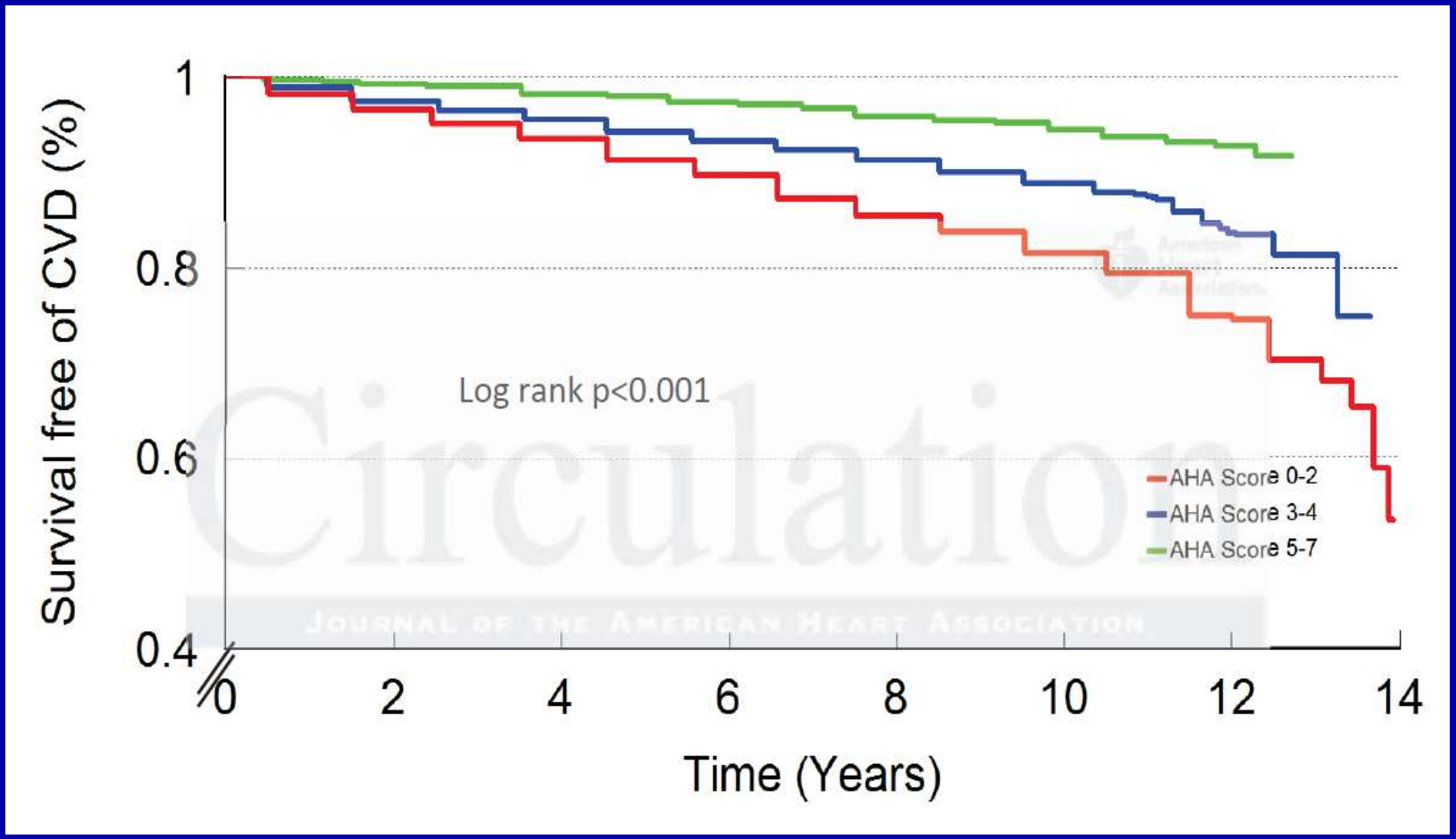
CV Events and CV Health Score

267 events: 150 CAD, 59 CVD, 36 HF, 22 intermittent claudication.

CVH score was inversely associated with the incidence of CV events in age- and sex-adjusted models.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

CV Events and CV Health Score



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Favorable CV Biomarkers and Lower Burden of Subclinical ASVD Drive the Benefit Found in the AHA's 7 Essentials for Heart Health

The association between the CVH score and the incidence of CV events was only partly mediated (~ 50% for each) by subclinical disease and select biomarkers.

Suggests that other biomarkers and subclinical disease measurements are needed to completely explain ideal cardiovascular health.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

Favorable CV Biomarkers and Lower Burden of Subclinical ASVD Drive the Benefit Found in the AHA's 7 Essentials for Heart Health

Need to identify additional biomarkers and subclinical mediators of the association between the CVH score and CV events.

Reasonable to expect a lower incidence of CV events in pts with favorable CVD biomarkers and a lower burden of subclinical atherosclerosis.

Xanthakis, V., Januzzi. J., et. al. (2014). Ideal Cardiovascular Health: Associations with Biomarkers and Subclinical Disease, and Impact on Incidence of Cardiovascular Disease in the Framingham Offspring Study. *Circulation*. doi: 10.1161/circulationaha.114.009273

Editorial to Xanthakis' et. al. Study

For each one point higher in the score, the odds of having any subclinical disease decreased 23%.

For each one point higher in the score, the odds of having a CV event decreased 23%.

After adjustment for the biomarkers and subclinical disease, the benefit was reduced to 13% per one point higher.

Lloyd-Jones, D. M. (2014). Cardiovascular Health and Protection Against CVD: More Than the Sum of the Parts? *Circulation*. doi: 10.1161/circulationaha.114.012869

Editorial to Xanthakis' et. al. Study

"where CVH score is poor, we must improve it; where it is intermediate, we must restore it; and where ideal, we must preserve it."

Lloyd-Jones, D. M. (2014). Cardiovascular Health and Protection Against CVD: More Than the Sum of the Parts? *Circulation*. doi: 10.1161/circulationaha.114.012869

BDM Thoughts

- Pts need to strive for a score of 7 with the essentials.
- Interesting that ST-2, hs-cTnI, renin not related to CVH score.
- CIMT and MACR gain more support from this study.
- Fibrinogen and CRP also gain support as biomarkers.
- NT pro-BNP in the upper end of normal may be fine.
- Missing biomarkers: Lp-PLA2, MPO, F2 isoprostane, T. bili.
- Nice study in support of assessing subclinical disease.
- Missing subclinical test: CAC; chart review.
- CVH score missing sleep and psychosocial issues.
- Also missing an essential ingredient – oral health! no wonder even pts with a perfect score had events.

AHA Conclusions

Level A evidence that PD is independently associated with arterial disease.

Peter B. Lockhart, et. al. *Circulation published online April 18, 2012*
DOI: 10.1161/CIR.0b013e31825719f3

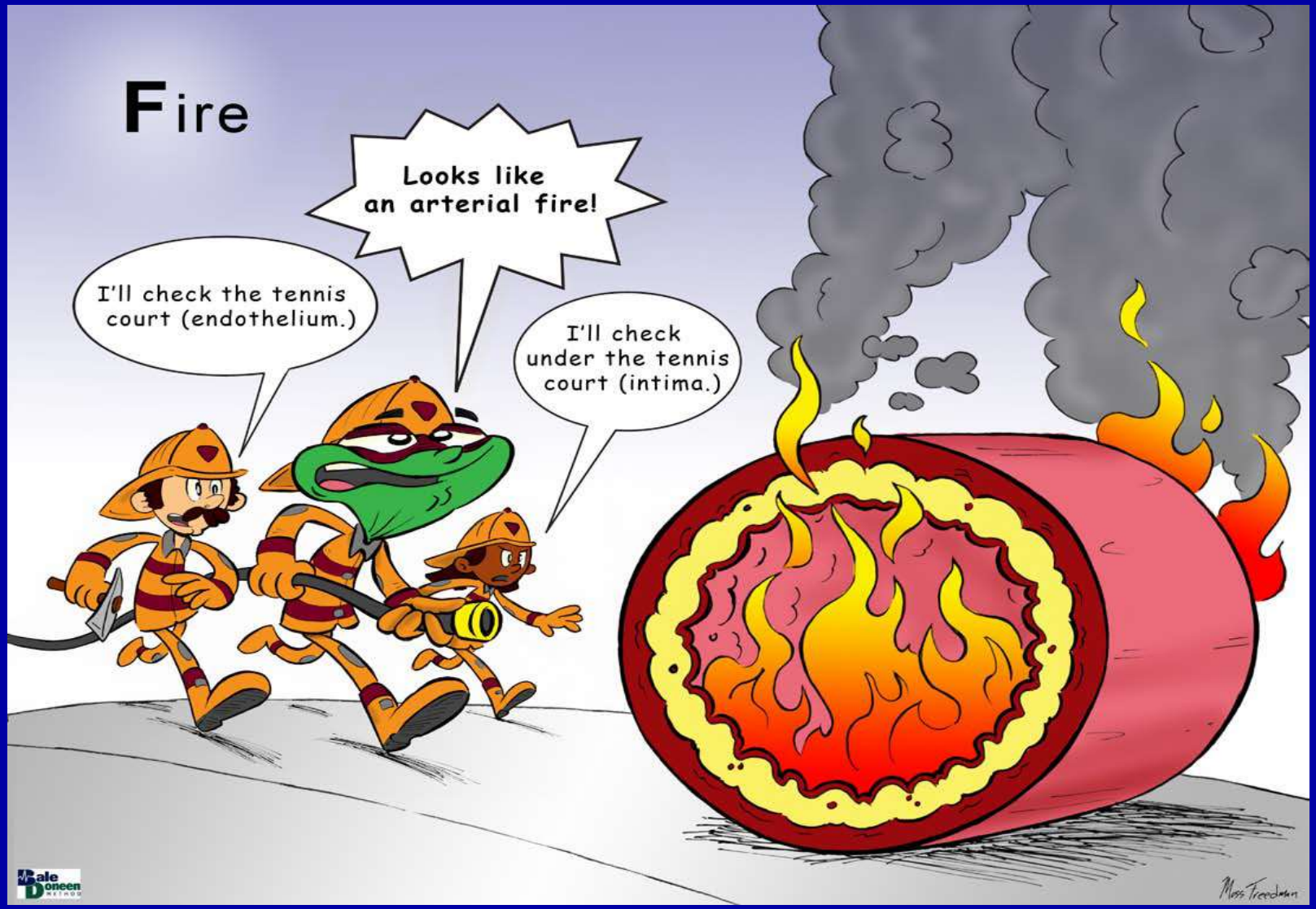
Oral Pathogens and Acute Heart Attack: Conclusions

Dental infection and oral bacteria are associated with the development of acute coronary thrombosis – heart attack!!!

Dental health and dental care should be one major element in preventing heart attacks!!!

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Inflammation



Microalbumin-creatinine ratio (MACR) Levels & Changes are Prognostic of CV Events: Background

Post hoc analysis of Losartan Intervention for End point Reduction in Hypertension (LIFE); Action in Diabetes Mellitus and Vascular Disease (ADVANCE); Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET); Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRASCEND) reported reduction in MACR is associated with decreased CV risk.

Pascual, J. M., et. al.(2014). Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin-creatinine ratio (MACR) is Prognostic of CV Events: Background

European Society of Hypertension and the European Society of Cardiology (ESH-ESC) guidelines in hypertension recommend the use of MACR to assess target organ damage.

US-released recommendations in 2014 for CV risk assessment qualify MACR as Grade N (no recommendation for or against) and recommendations for hypertension management 2014 do not mention its potential role.

Pascual, J. M., et. al.(2014). Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin-creatinine ratio (MACR) Changes are Prognostic of CV Events: Background

In 1989 it was demonstrated that the amount of albumin in the urine is dependent on endothelial permeability. *

Many CV risk factors can effect endothelial function with BP being an important one.

If these risk factors are managed well, MACR should improve and theoretically portend lower CV event risk.

Pascual, J. M., et. al.(2014). Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

*Deckert, T., et. al. (1989). Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia, 32*(4), 219-226.

Microalbumin Changes are Prognostic of CV Events

2,835 hypertensives without CVD; mean age 55; 53% women; 19% DM; ~ 2/3 of non-DM had low ten yr coronary risk; follow-up 4.7 yrs (range 6mos.-25 yrs).

BP rx to maintain BP <140/90; microalbumin-creatinine ratio (MACR) measured yearly. (microalbuminuria was defined as ≥22 mg/g in men and ≥31 mg/g in women)

Objective: Did MACR levels and changes predict CV events.

Pascual, J. M., et. al.(2014). Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin Changes are Prognostic of CV Events

294 CV events: 84 CAD; 82 stroke; 24 PAD;

74 HF; 30 CV death.

Adjusted for: LVH, CV risk, eGFR, rx with ACEi or ARBs at the beginning and SBP <140 mm Hg and LDL <100 mg/dL during the follow-up.

Pascual, J. M., et. al.(2014). Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

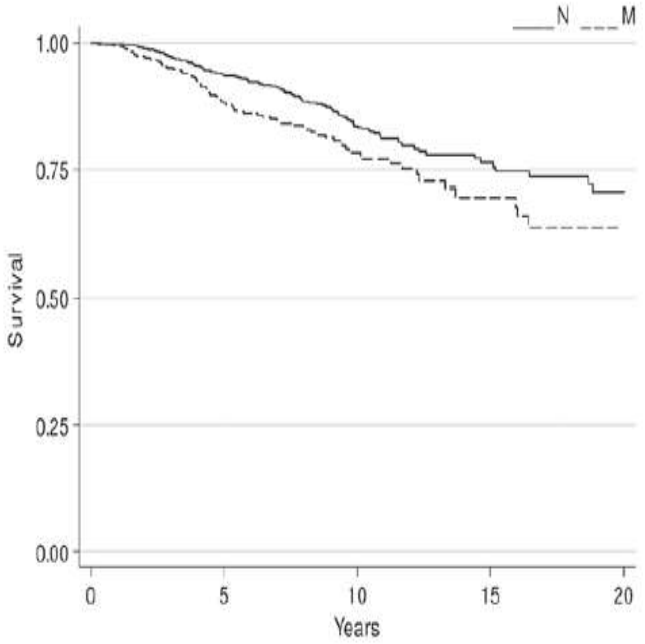
Microalbumin Changes are Prognostic of CV Events

Microalbuminuria (by their definition) at anytime during the study was a significant predictor of CV events.

HR- 1.49, (95% CI, 1.14–1.94)

Pascual, J. M., et. al.(2014). *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin Changes are Prognostic of CV Events



Number of patients at risk					
No microalbuminuria	2219	1035	362	91	41
Microalbuminuaria	616	300	118	39	16

Figure 1. Kaplan–Meier of event-free survival grouped by microalbuminuria at baseline in the study population. Normoalbuminuria (N) and microalbuminuria (M).

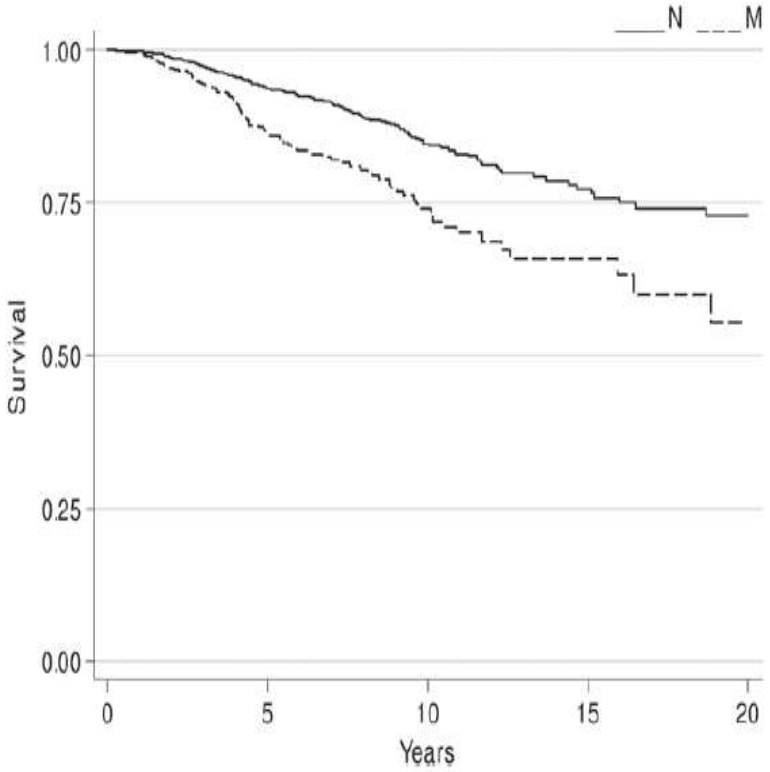


Figure 2. Kaplan–Meier of event-free survival grouped by microalbuminuria at follow-up in the study population. Normoalbuminuria (N) and microalbuminuria (M).

Pascual, J. M., et. al.(2014). *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin Changes are Prognostic of CV Events

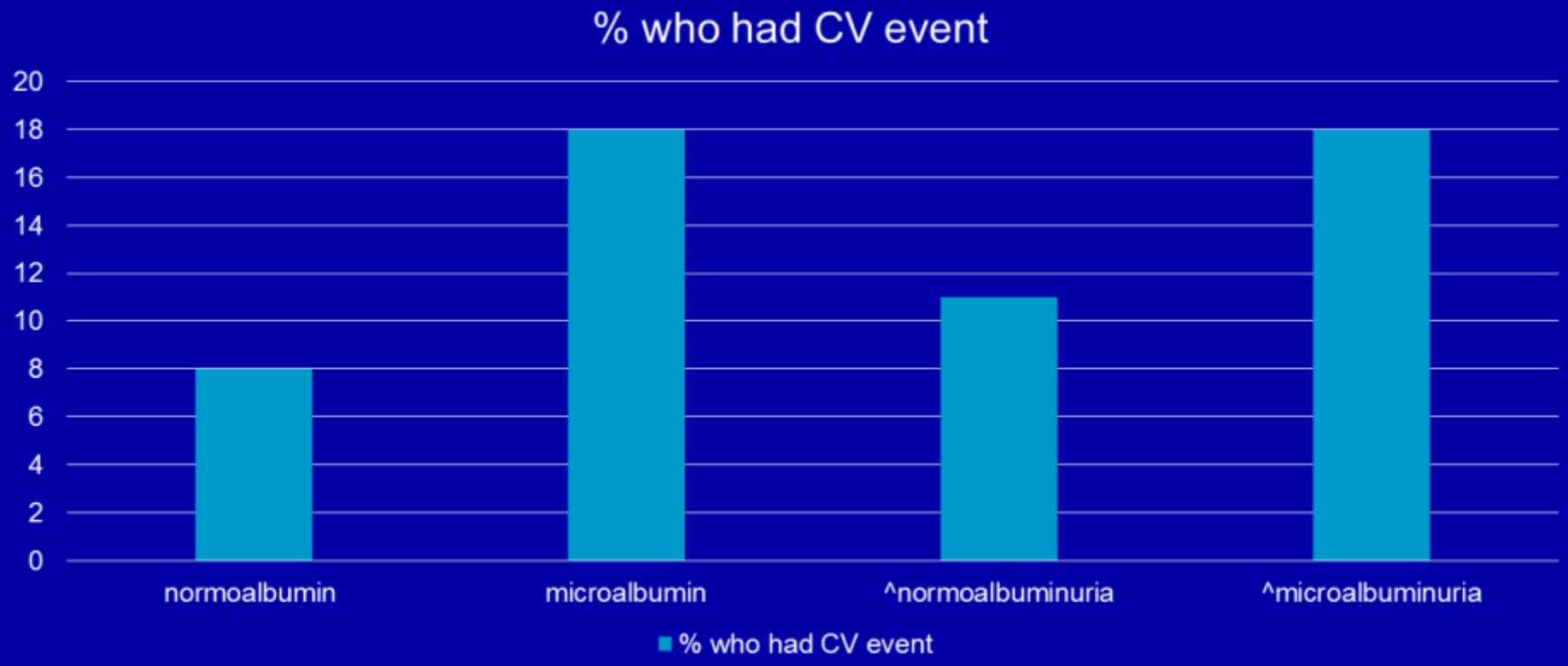
Change in MACR was predictive of risk:

a) worse prognosis, if going from normoalbuminuria to microalbuminuria

b) better prognosis, if going from microalbuminuria to normoalbuminuria.

Pascual, J. M., et. al.(2014). *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin Changes are Prognostic of CV Events



^ = change

Pascual, J. M., et. al.(2014). *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin Changes are Prognostic of CV Events

MACR represents a measurement of organ (endothelium) damage.

Clinically advantageous to evaluate simple organ damage markers, such as MACR, to refine CV risk assessments.

It is reasonable to search for asym'ic organ damage in hypertensive patients, for the initial stratification of CV risk and also during follow-up.

Pascual, J. M., et. al.(2014). *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

Microalbumin Changes are Prognostic of CV Events

It is reasonable to take information from changes in MACR to assess whether treatment is successful.

MACR is a valuable marker of CV risk in a population of hypertensives with low-moderate risk.

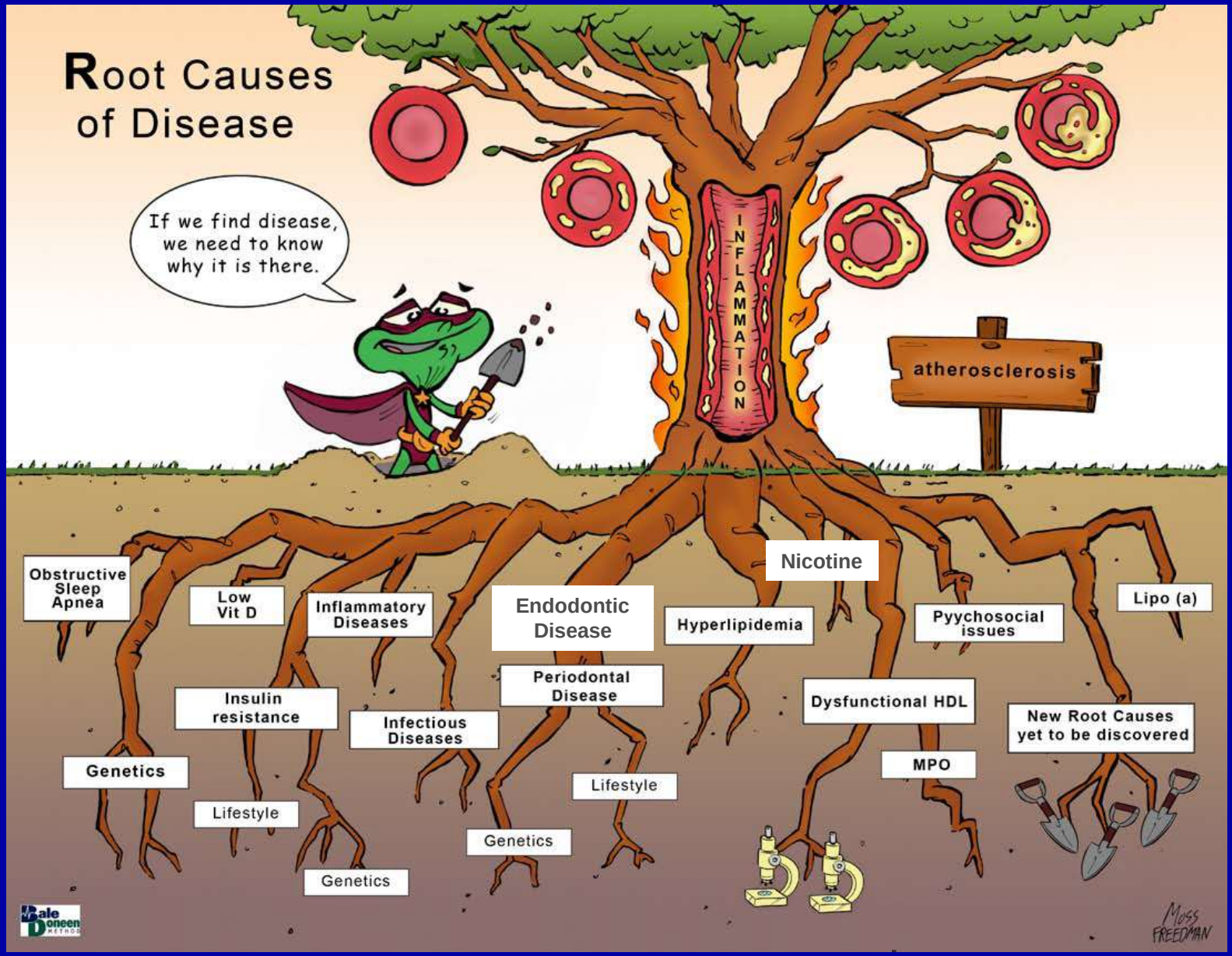
MACR predicts risk for CV events independent of other CV risk factors including coronary risk estimation.

Pascual, J. M., et. al.(2014). *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.04273

BDM Thoughts

- Study supports value of routine measurement of MACR.
- Unfortunate they did not use more sensitive levels for ‘microalbuminuria’; would expect even more dramatic results for predictability.
- Another great example of how deficient the US guidelines are and how long it takes for good science to be utilized clinically.
- Another illustration of how information regarding subclinical disease can enhance CV risk prediction; arguably the most important organ in the body is the endothelium.
- No test is fool proof. Remember other reasons MACR may be elevated: renal disease; inflammatory conditions like RA and Lupus; infectious diseases like hepatitis; drugs like NSAIDS; multiple myeloma; amyloidosis; toxins; trauma.

(Dr. John Lourie gave great presentation CHL sym.)



IR Associated with Subclinical Myocardial Damage: Backgroud

IR either as pre-diabetes or DM has an increased prevalence of ASVD/CIMT or CAC.

IR hyperglycemia may induce coronary microvascular dysfunction causing myocardial injury.

High-sensitivity cardiac troponin T (hs-cTnT) can detect subclinical myocardial injury associated with increased risk of heart failure and death.

IR pts should have higher hs-cTnT levels.

Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

IR Associated with Subclinical Myocardial Damage

9,331 ARIC pts. without known CVD; hs-cTnT measured at baseline and 6 years later; pts evaluated for IR with A1c or known DM.

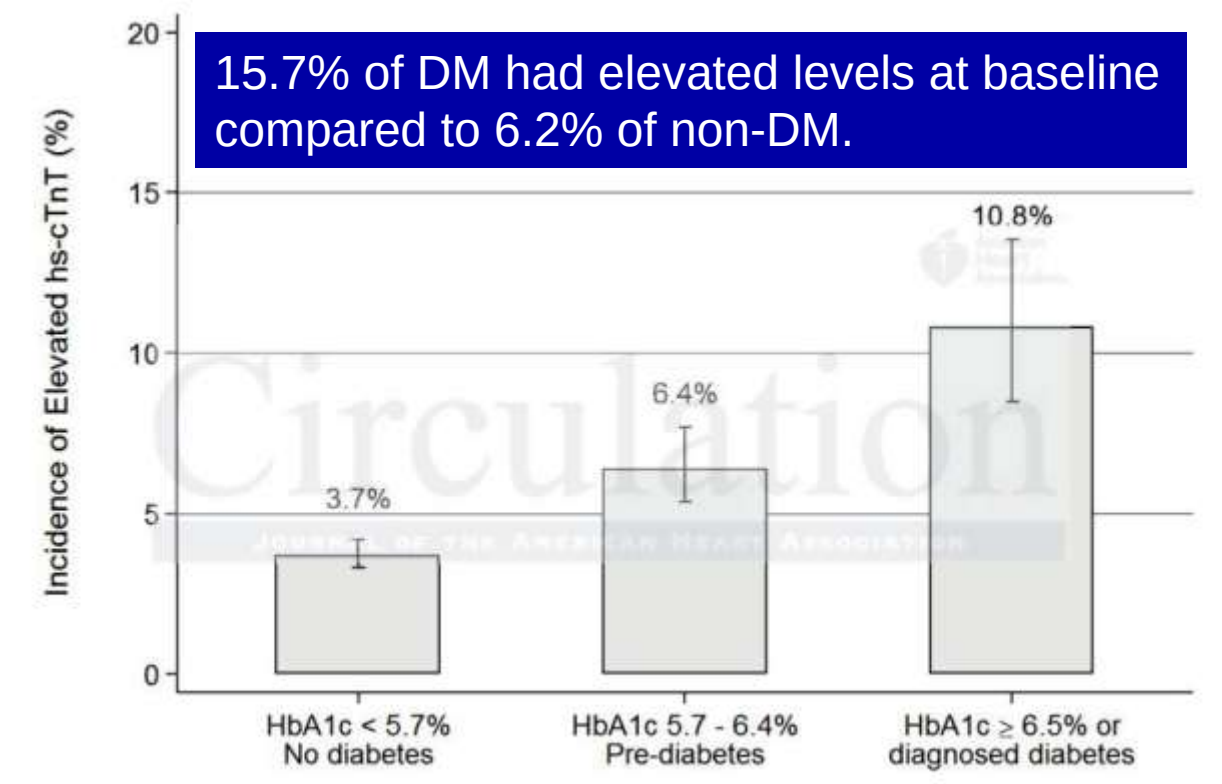
Outcome: incidence of developing elevated hs-cTnT.

Adjusted results for: age, sex, ethnicity, BMI, smoking, alcohol, LVH, syst. BP, lipids, eGFR, CRP, meds for BP and lipids.

Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

IR Associated with Subclinical Myocardial Damage

More likely to develop elevated hs-cTnT (<14 ng/L), if IR



Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

Hs-cTnT Associated with Risk of CAD, HF, Death

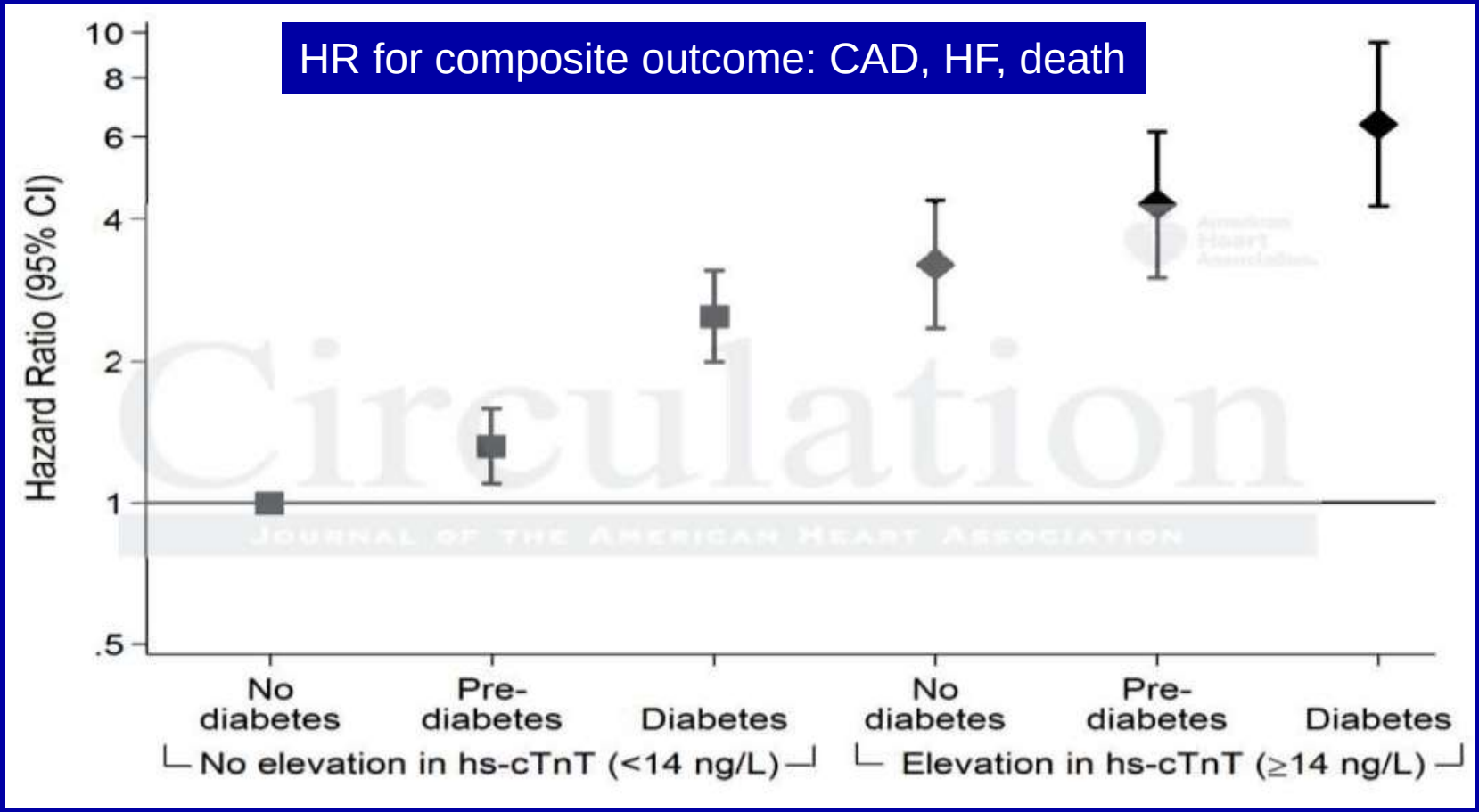
8,005 ARIC pts. without known CVD; evaluated for incident CAD, HF, and all-cause mortality 6 yrs later.

Outcome: RR associated with incidence of elevated hs-cTnT.

Adjusted results for these variables at yr 6: age, sex, ethnicity, BMI, smoking, alcohol, LVH, syst. BP, lipids, eGFR, CRP, meds for BP and lipids.

Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

Hs-cTnT Associated with Risk of CAD, HF, Death



Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

IR & hs-cTnT Associated with Risk of CAD, HF, Death

Supplemental Table 4. Adjusted* hazard ratios (95% confidence intervals) for the association of visit 2 (1990-1992) diabetes status and 6-year incident elevated (≥14 ng/L) highly sensitive cardiac troponin T (hs-cTnT) with incident coronary heart disease (CHD), heart failure and all-cause mortality (N=8,005)

			CHD		Heart Failure		Death	
Visit 4 hs-cTnT	HbA1c diagnostic criteria	N	Events	HR (95%CI)	Events	HR (95%CI)	Events	HR (95%CI)
hs-cTnT <14 ng/L	No diabetes (< 5.7%)	5,477	540	1 (reference)	370	1 (reference)	831	1 (reference)
	Pre-diabetes (5.7-6.4 %)	1,642	228	1.34 (1.14-1.58)	193	1.32 (1.10-1.59)	380	1.30 (1.15-1.48)
	Diabetes (diagnosis or ≥ 6.5 %)	506	109	2.31 (1.86-2.88)	115	2.49 (1.99-3.12)	150	1.71 (1.43-2.06)
hs-cTnT ≥14 ng/L	No diabetes (< 5.7%)	207	38	1.61 (1.15-2.26)	48	3.21 (2.35-4.39)	77	2.07 (1.62-2.64)
	Pre-diabetes (5.7-6.4 %)	110	34	2.92 (2.04-4.17)	36	4.30 (3.01-6.14)	56	2.61 (1.97-3.45)
	Diabetes (diagnosis or ≥ 6.5 %)	63	24	3.84 (2.52-5.84)	28	6.37 (4.27-9.51)	39	4.36 (3.14-6.07)

*Adjusted for age, race, sex, BMI, CRP, smoking, systolic BP, lipids, eGFR, BP and lipid meds, alcohol, LVH.

Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

IR Associated with Subclinical Myocardial Damage

IR pts are at risk for not only the subsequent development of DM, but also for the progression of subclinical cardiac damage and ensuing CV events.

No significant ethnical differences in risk were observed.

Selvin, E., et. al. (2014). Diabetes, Pre-Diabetes and Incidence of Subclinical Myocardial Damage. *Circulation*. doi: 10.1161/circulationaha.114.010815

BDM Thoughts

- Supports being aggressive with screening for IR and utilizing a hs-cTn test.
- Too bad they had to use A1c – they missed a lot of IR people and identified a few who were not IR.
- Results probably would have been more impressive with the OGTT, but they were impressive enough.
- IR and elevated hs-cTn need to be treated with the comprehensive BDM approach.
- Reading the authors' discussion is sad; since LDL was not related to anything, they hypothesize that hyperglycemia is causing microvascular disease. No mention of arterial inflammation from insulin resistance!!!!! Apparently they have not read the Decode study from 1999 – "the sugar doesn't matter"! Ballantyne was a co-author.

A1c!!!!!

A1c an Inaccurate Measurement for IR

73 yo female: FBS- 87; A1c- 5.6 = fine

OGTT- 1hr.- 218; 2 hr. –155 = IR

58 yo female: FBS- 87; A1c- 5.5 = fine

OGTT- 1hr. – 185; 2 hr.- 136 = IR

61 yo male: FBS- 82; A1c-5.9 = IR

OGTT- 1hr. – 123; 2hr.- 76 = fine

Two Dental Parameters Along with A1c Dx Pre-DM or DM with 92% Confidence

535 pts with no hx of pre-DM or DM

Used fasting blood glucose (FBG) to diagnose pre-DM and DM

If, > 25% of pockets depths were at least 5mm or ≥4 missing teeth plus an HbA1c ≥5.7% = 92% accuracy for identifying IR.

Lalla, E., et. al. 7/2011 J Dent Res 90(7):855-860

Two Dental Parameters Coupled with A1c Can Dx IR (united we stand, divided we fall)

	actual positives which are correctly identified	correctly identified as not having the condition		
	Sensitivity	**Specificity**	**PPV**	**NPV**
> 25% deep pockets, or ≥ 4 missing teeth	0.73	0.45	0.43	0.75
Point-of-care HbA1c ≥ 5.7%	0.75	0.56	0.49	0.80
≥ 26% deep pockets, or ≥ 4 missing teeth, along with point-of-care HbA1c ≥ 5.7%	0.92	0.28 many people with IR missed!	0.42	0.86

Optimal cut-offs were defined as those with the least (1-sensitivity) + (1-specificity).

Lalla, E., et. al. 7/2011 J Dent Res 90(7):855-860

Insulin Resistance (IR) is a Proatherogenic State

IR damages the arteries regardless of the sugar*

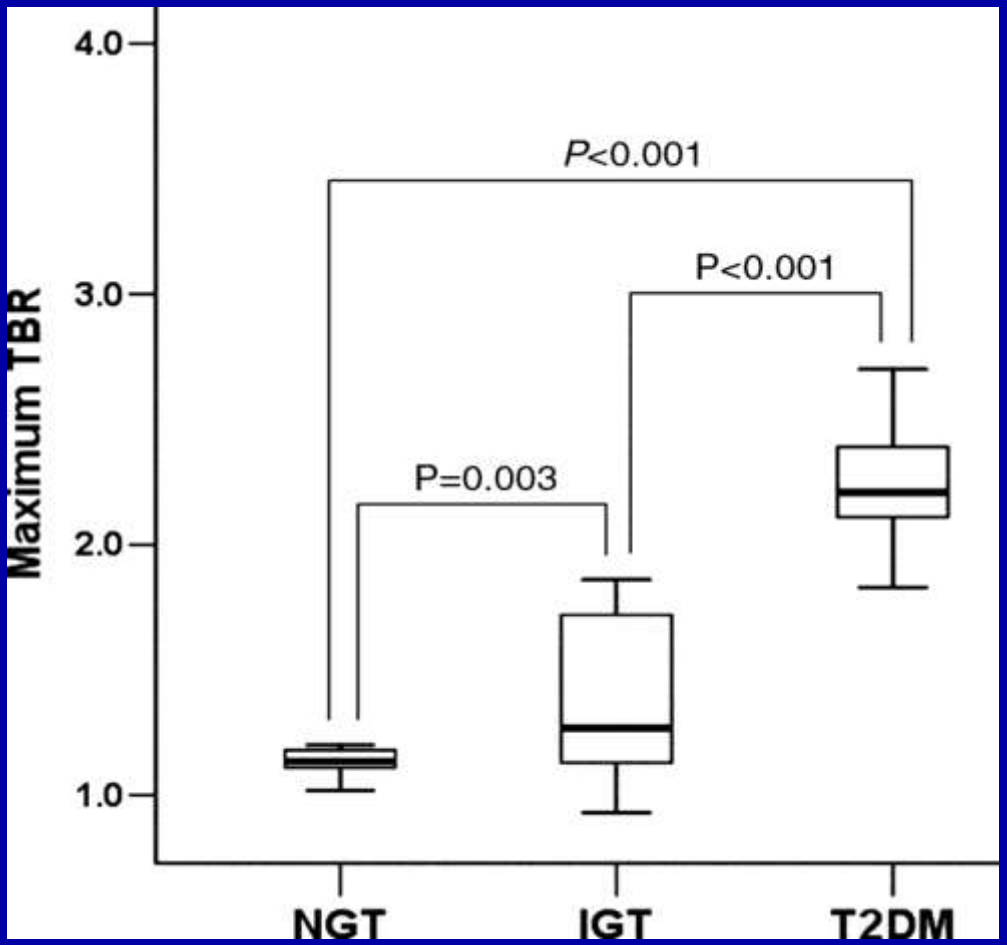
*DECODE Study Group. *Lancet* 1999;354:617–621.

Insulin Resistance Increases Arterial Inflammation

- Carotid inflammation assessed with FDG-PET
- 90 pts:30 normal GTT;30 impaired GTT; 30 T2DM
- Inflammation significantly increased with impaired GTT and T2DM

Kim T N et al. Circ Cardiovasc Imaging 2010;3:142-148

Carotid Artery Inflammation is Elevated in Insulin Resistant Individuals



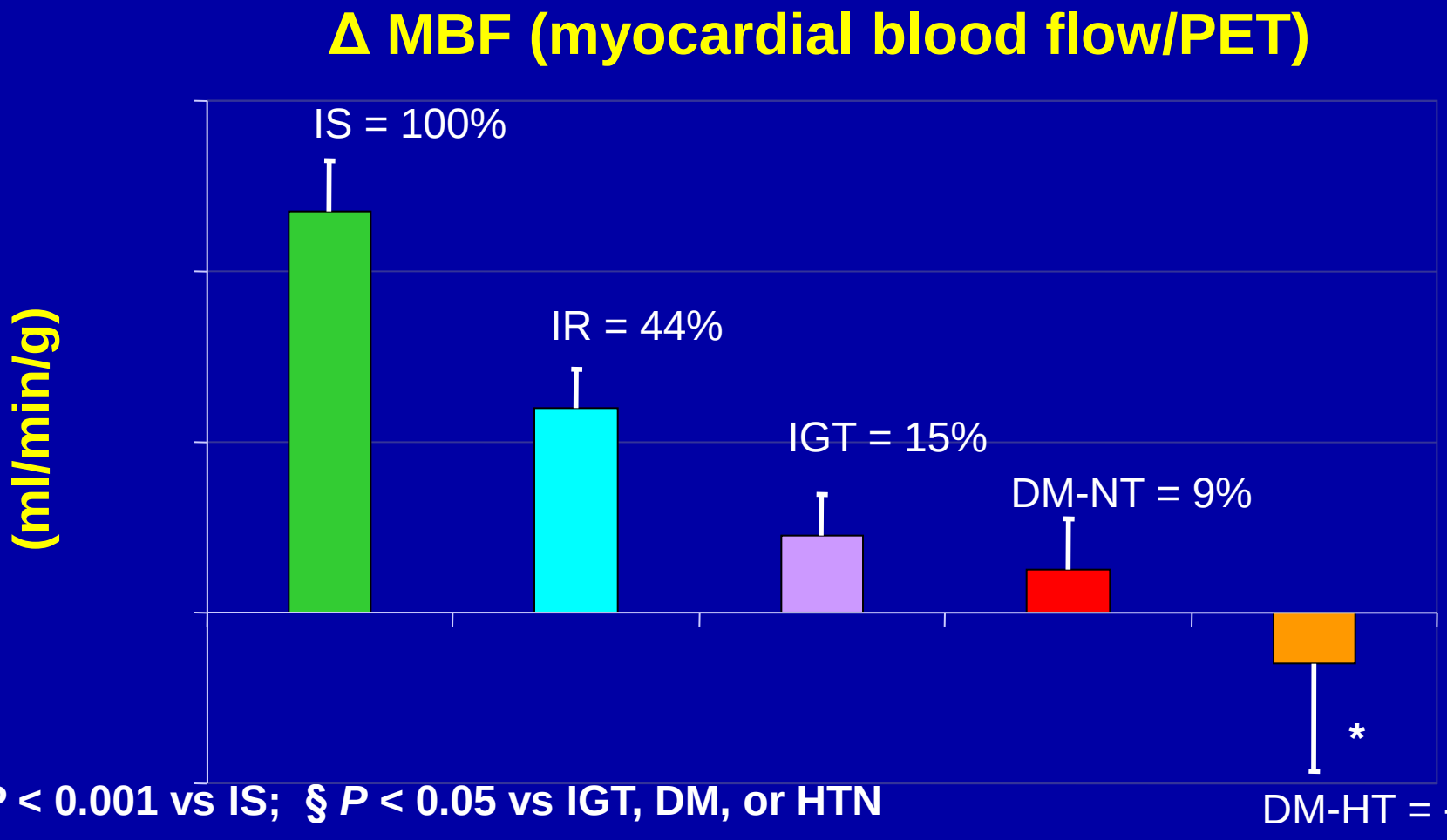
Maximum TBR by glucose tolerance group.

American Heart Association
Learn and Live

Kim T N et al. Circ Cardiovasc Imaging 2010;3:142-148

Dale Doneen METHOD

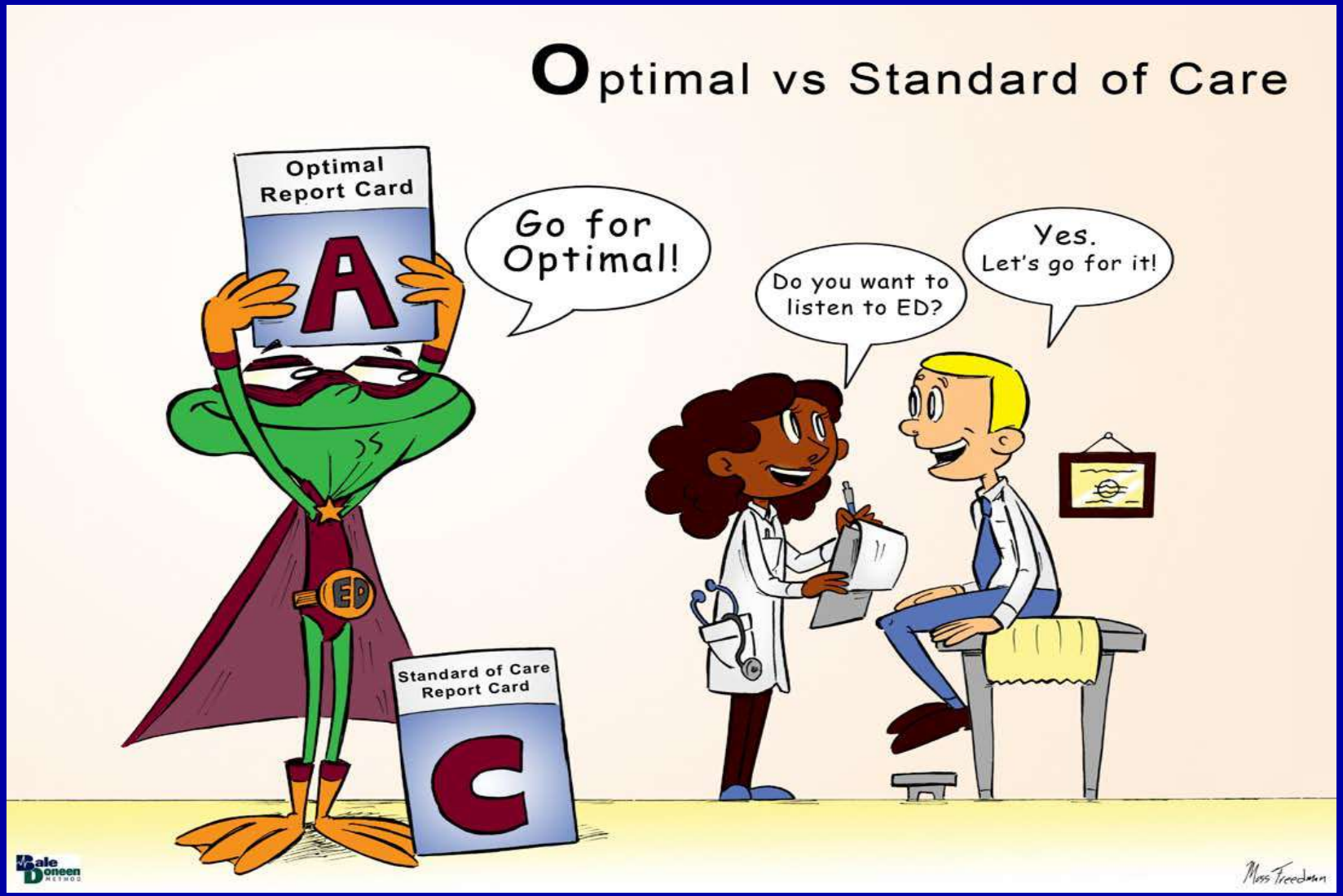
Blood Flow to the Heart Muscle Decreases as Insulin Resistance Progresses



*** *P* < 0.001 vs IS; § *P* < 0.05 vs IGT, DM, or HTN**

Prior, J. et al., *Circulation 5/14/*2005;111:2291-8.

Optimal Care



One Year Post MI Ischemic Stroke (IS) Risk: Incidence and Predictors

173,233 AMI pts.; mean age 71; btw 1998-2008.

Goal of study: a) 1 yr. post MI incidence of IS b) has modern AMI rx affected the risk of IS c) identify independent predictors of post MI IS.

Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

One Year Post MI Stroke Risk: Incidence and Predictors

Incidence of IS: 7,185 (4.1%) within one yr of AMI.

Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

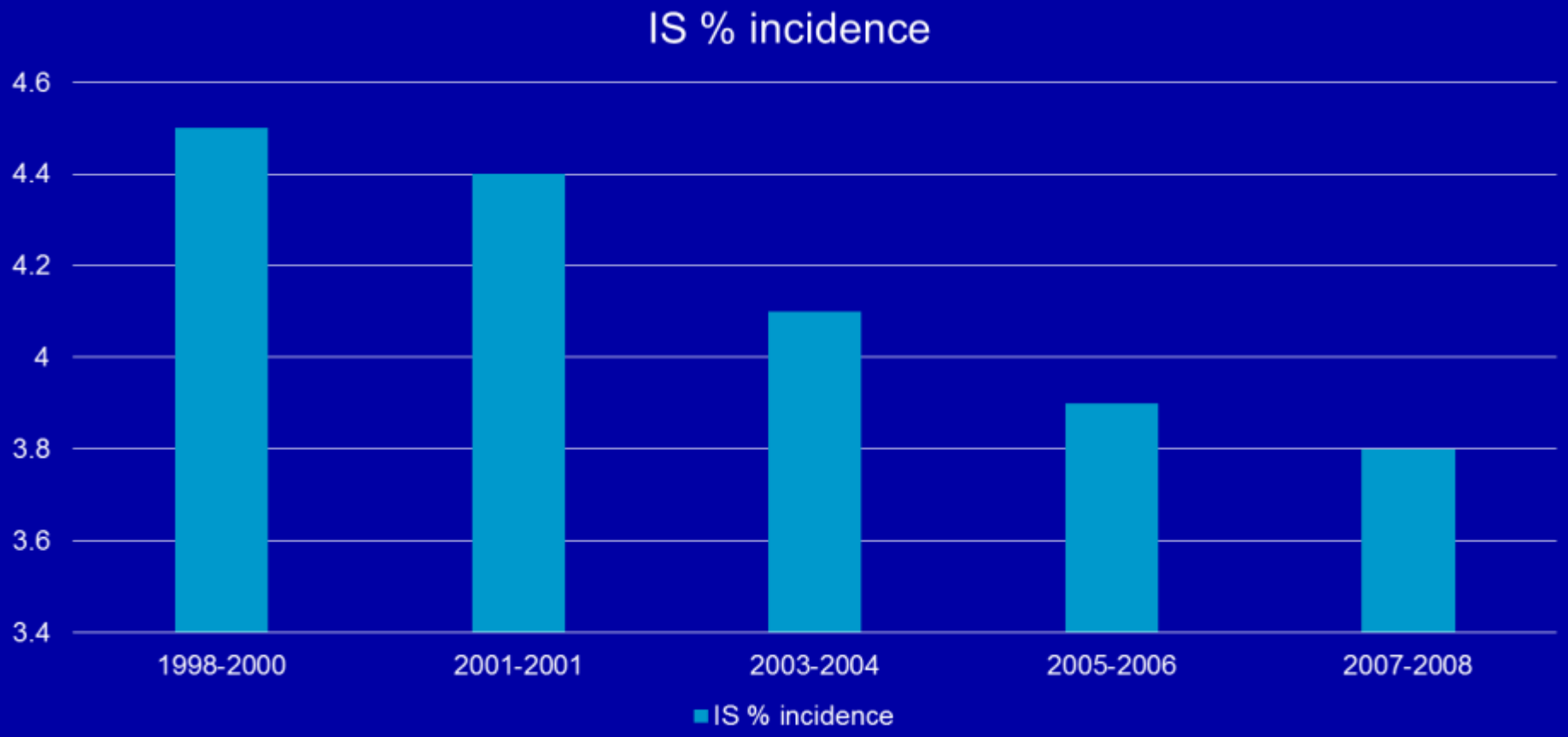
One Year Post MI Stroke Risk: Incidence is Decreasing - ☺

Divided the entire time into 5 periods: 1998 to 2000, 2001/2002, 2003/2004, 2005/2006, and 2007/2008.

Stroke incidence decreased 20% during yr 2007-2008 compared to yrs 1998-2000.

Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

One Year Post MI Stroke Risk: Incidence is Decreasing



Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

One Year Post MI Stroke Risk: Predictors

150,562 pts in the hunt for independent predictors utilizing a regression model and variables with >95% valid cases were included in the multivariate analysis.

Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

One Year Post MI Stroke Risk: Independent Predictors

Table 3. Predictors of Ischemic Stroke Among 150 562 Subjects 1 Year After Acute Myocardial Infarction, Multivariate Cox Regression Model

Predictor Variable	Hazard Ratio (95% CI)	*P* Value
Age	1.03 (1.03–1.03)	<0.001
Female sex	1.10 (1.04–1.16)	<0.001
Previous stroke	2.59 (2.45–2.75)	<0.001
Diabetes mellitus	1.30 (1.22–1.37)	<0.001
Atrial fibrillation	1.65 (1.56–1.75)	<0.001
Clinical signs of heart failure at admission	1.18 (1.11–1.24)	<0.001
ST-segment–elevation myocardial infarction	1.19 (1.12–1.27)	<0.001
ACEi treatment at discharge	1.14 (1.08–1.2)	<0.001
Fibrinolysis at presentation	0.88 (0.80–0.95)	<0.001
PCI during hospitalization	0.69 (0.64–0.74)	<0.001
Aspirin treatment at discharge	0.86 (0.80–0.92)	<0.001
Statin treatment at discharge	0.87 (0.82–0.92)	<0.001
P2Y12-inhibitor treatment at discharge	0.87 (0.82–0.93)	<0.001

ACEi indicates angiotensin-converting enzyme inhibitor; CI, confidence interval; and PCI, percutaneous coronary intervention.

What?!

ACEi association possibly explained by an association with HF. ?????????

Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

One Year Post MI Stroke Risk: Incidence and Predictors

The proportion of pts receiving aspirin, statins, and P2Y12-inhibitors increased markedly during the study period, coinciding with the observed risk reduction of stroke.

Uncontroversial to consider age, sex, AF, DM, previous stroke, STEMI, and HF as independent predictors of IS after AMI.

Ulvenstam, A., et. al. (2014). Incidence, Trends, and Predictors of Ischemic Stroke 1 Year After an Acute Myocardial Infarction. *Stroke*. doi: 10.1161/strokeaha.114.005770

BDM Thoughts

- MI pts need optimal management for stroke prevention.
- Dual anti-platelet rx and statins are critical.
- In light of a recent study, try to maintain K+ in the upper end of normal.
- Magnesium supplementation, especially if pt on PPI.
- Again, be thorough with IR assessment and rx.
- Remember coffee (may want CYP1A2 gene), white fruits & vegetables, dark chocolate, exercise, nicotine, waist, sleep, psychosocial issues.
- Make sure with DNA testing there is no periodontal disease; rule out endodontic disease (they just had an MI!).
- Measure lipo (a) !
- Optimize blood pressure.
- Monitor inflammation closely.

K+ Reduces Ischemic Stroke (IS) Risk in Women

90,137 stroke free postmenopausal women; 50-79 yo followed 11 yrs.; K+ dietary intake in quartiles; outcome: death and strokes.

Adjusted for potential confounding variables;

hypertensive and non-hypertensive pts analyzed separately.

Seth, A., et. al. (2014). Potassium Intake and Risk of Stroke in Women With Hypertension and Nonhypertension in the Women's Health Initiative. *Stroke*. doi: 10.1161/STROKEAHA.114.006046

K+ Reduces IS Risk in Women

Comparing highest to lowest quartile of potassium intake:

10% lower risk of death – signif.

16% reduced risk of ischemic stroke – signif.

NS relationship to hemorrhagic stroke

Non-hypertensive pts had a significant 27% lower risk of ischemic stroke.

Seth, A., et. al. (2014). Potassium Intake and Risk of Stroke in Women With Hypertension and Nonhypertension in the Women's Health Initiative. *Stroke*. doi: 10.1161/STROKEAHA.114.006046

Potassium Extremely Important in Cardiac Arrhythmias and Sudden Cardiac Death

Incidence of ventricular tachycardia is 3X higher in MI pts with low ‘normal’ potassium than in pts with a high ‘normal’ serum potassium.

In pts with known CAD, it is beneficial to maintain plasma potassium levels in the upper normal range.

Kjeldsen, K. (2010). Hypokalemia and sudden cardiac death. *Exp Clin Cardiol, 15*(4), e96-99.

Lower Magnesium Associated with Risk of AF

Age- and sex-adjusted incidence of AF

Serum magnesium, mg/dL	Events, n	Incidence rate per 1000 person-years
≤1.77	80	9.4
1.78-1.88	53	6.9
1.89-1.98	50	7.1
≥1.99	45	6.3

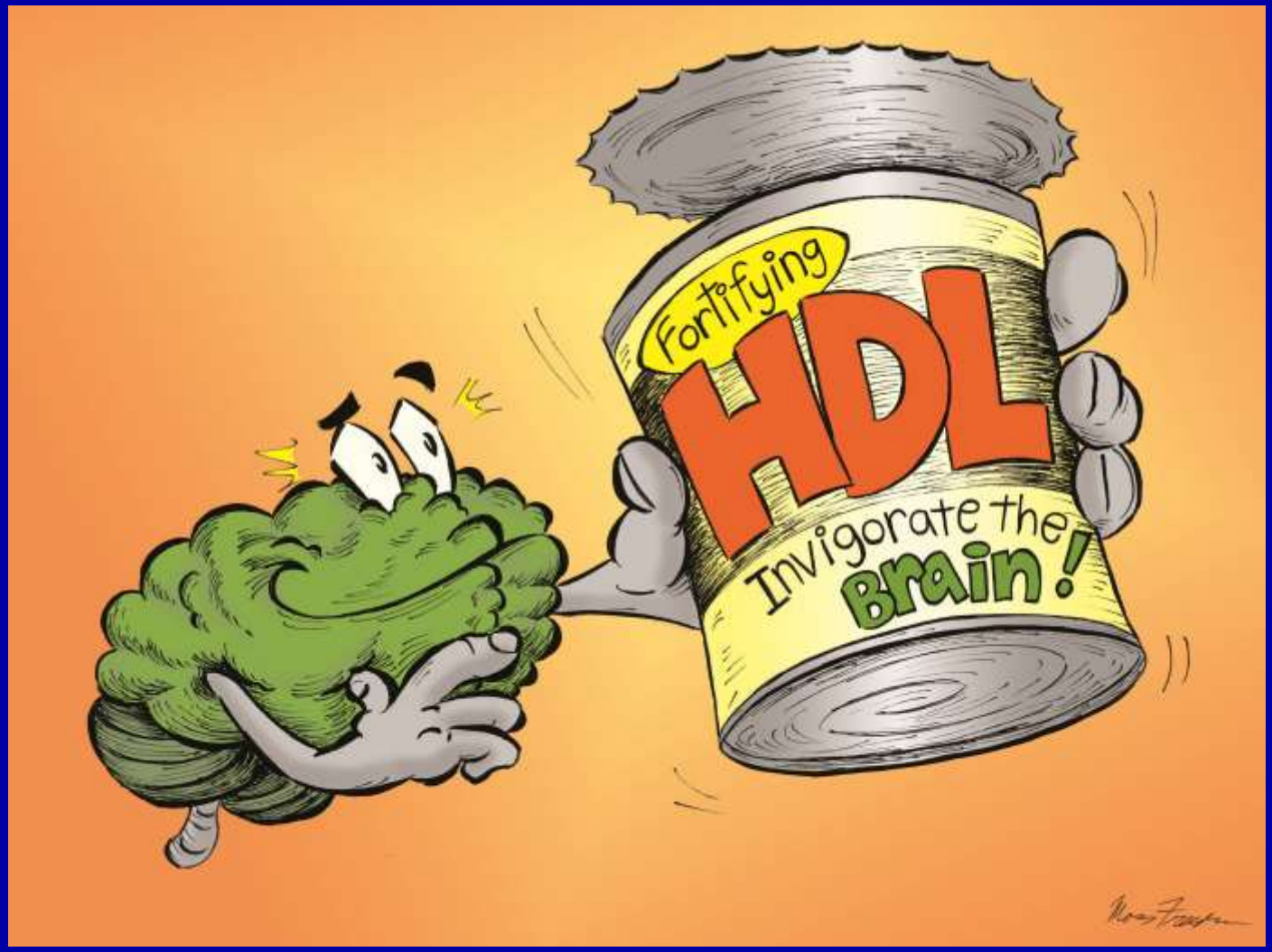
Khan AM, et al. *Circulation* 2012; DOI: 10.1161/CIRCULATIONAHA.111.082511. Available at: http://circ.ahajournals.org/.

Insulin resistance Significantly Increases Ischemic Stroke Risk in Non-diabetic Adults

- 1509 multiethnic group free from stroke and DM; followed 8.5 yrs.
- Those in top quartile of IR were 3X greater risk for ischemic stroke
- Independent of traditional risk factors and metabolic syndrome

Arch Neurol. 10/2010;67:1177-1178, 1195-1200

HDL is Brain Food



HDL & atherosclerotic stroke risk

Each 1 mg/dL increase in HDL yields:

1.9% reduction in stroke risk

Tirschwell DL, et. Al. ***Neurology*** 2004;63:1868-75

Lifestyle Has Huge Impact on Stroke Risk

23,927 subjects; followed 12.7 yrs.; 195 women (73% IS) and 356 (78% IS) men had incident stroke.

Evaluated impact of obesity, smoking, alcohol consumption, diet, and physical inactivity on stroke risk.

38% of strokes were estimated as preventable with adherence to a healthy lifestyle.

Tikk, K., et. al. (2014). Primary Preventive Potential for Stroke by Avoidance of Major Lifestyle Risk Factors: The European Prospective Investigation Into Cancer and Nutrition-Heidelberg Cohort. *Stroke, 45*(7), 2041-2046.

Stroke risk factors

Smoking. According to the National Stroke Association, smoking doubles the risk for stroke.

Texas Heart Institute Heart Information Center

Mediterranean Diet Reduces CV Risk

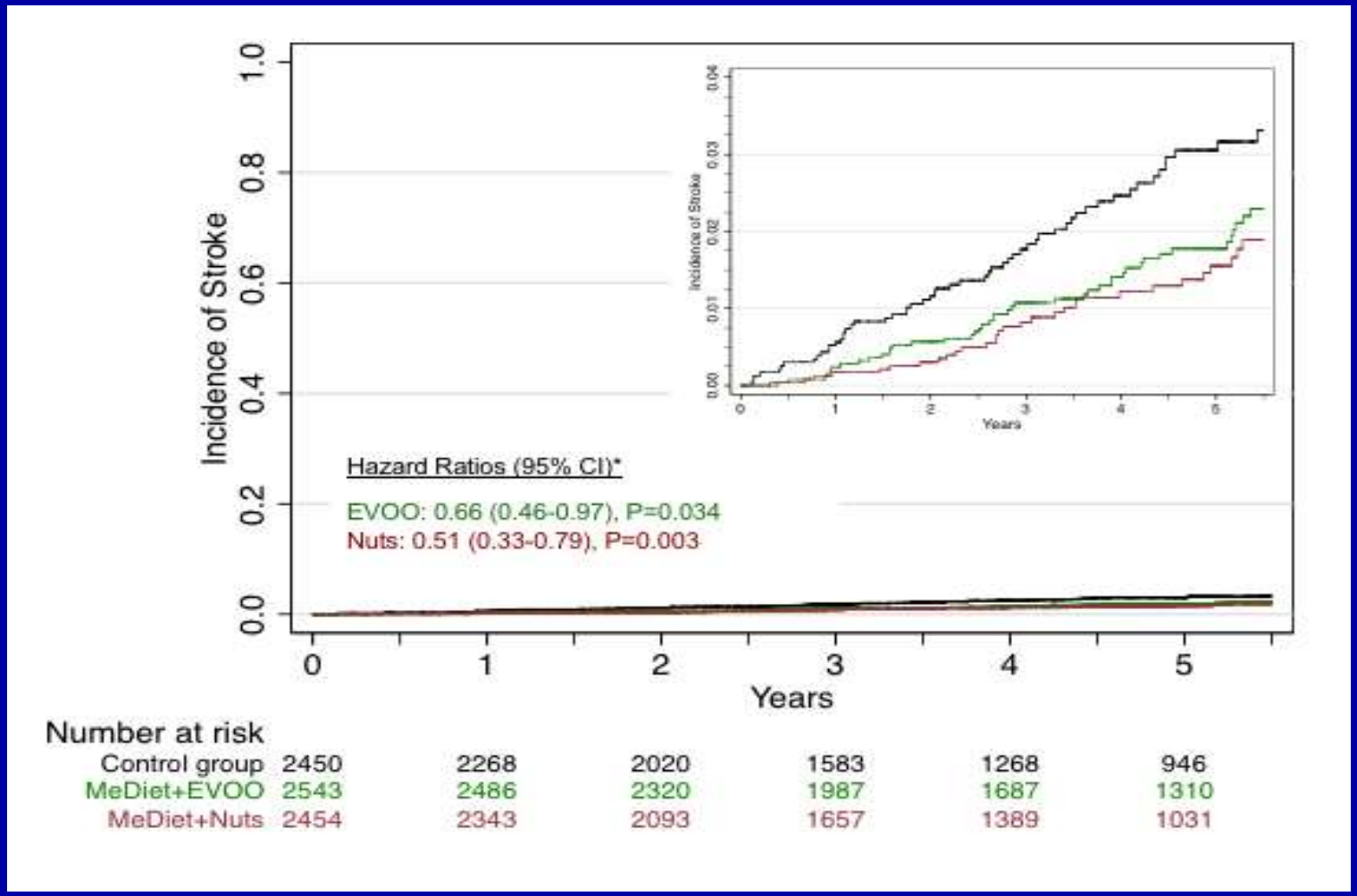
- 7,747 high CV risk pts.; 57% female; 55 - 80 yo; end points CV events and death; Mediterranean diet –a) extra virgin olive oil b) extra nuts versus low fat diet; unrestricted caloric diets; halted at 4.8 yrs.

- Multivariable-adjusted HRs were 0.70 (95% CI, 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group a) & b) respectively, versus the low fat diet

Estruch R et al. N Engl J Med 5/4/2013. Volume 368(14):1279-1290

Mediterranean Diet Clobbers Stroke Risk

Kaplan-Meier Estimates of Incidence of Stroke



Estruch R et al. N Engl J Med 5/4/2013. Volume 368(14):1279-1290

Keep the Rhythm

Fish Consumption Reduces Stroke Risk

- 38 studies; 794,000 subjects; 34,817 cerebrovascular events
- RR for CVD with consuming fish 2-4 servings a week versus ≤1 servings a week was 0.94 (95% CI-0.90 to 0.98)
- RR for CVD with consuming fish ≥5 servings a week versus 1 serving a week was 0.88 (95%CI-0.81 to 0.96)

Chowdhury, R., et. al., *BMJ 10/30/*2012;345:e6698 doi: 10.1136/bmj.e6698

White Fruits and Vegetables May Protect Against Stroke

- 20,069 healthy subj. 20-65 yo; followed 10yrs.
- Fruits and vegetables sorted into four color groups: green, orange/yellow, red/purple, white
- Only color associated with reducing stroke was white
- Each 25-g/d (1/6 medium apple) serving of white fruit and vegetable reduced stroke risk 9%

Linda M. Oude Griep, MSc, et. al. ***Stroke. 10/2011;42:3190-3195***

White fruits & veg

- Apples; pears; banana
- Cauliflower; cucumber; chicory; onions; cabbage

Flaxseed Lowers BP: Potential Mechanism

RDBPP study with 110 PAD pts.; 30 g of milled flaxseed/d for 6 mos lowered BP significantly:

10 mm Hg systolic; 7 mm Hg diastolic

Flaxseed contains the n3 fatty acid α-linolenic acid.

Plasma α-linolenic acid increased with ingestion of flaxseed and was inversely associated with BP

Caligiuri, S. P., et. al. (2014). Flaxseed Consumption Reduces Blood Pressure in Patients With Hypertension by Altering Circulating Oxylipins via an alpha-Linolenic Acid-Induced Inhibition of Soluble Epoxide Hydrolase. *Hypertension*. doi: 10.1161/HYPERTENSIONAHA.114.03179

Chocolate Associated with Lower Stroke Risk

- 33,372 women; 1,549 incident strokes in 10 yrs.

Multivariable stroke risk for a 50-g/week increase in chocolate

Stroke	Relative risk	95% CI
Total	0.86	0.77-0.96
Cerebral infarction	0.88	0.77-0.99
Hemorrhagic stroke	0.73	0.54-0.99

Larsson SC, et. al. *J Am Coll Cardiol* 10/18/2011; 58:1828-1829.

Coffee Protects Against Stroke

- 484,757 participants; follow-up two to 24 yrs; 272 strokes
- Habitual consumption of 1-3 cups of coffee/day was associated with decreased risk of stroke

  RR 0.86 (95% CI 0.75-0.98) $p<0.02$
- 3-6 cups/day had similar results
- >6 cups/day had no significant effect

D'Elia L, et al. J Hypertension 5/2012; 30 (e-Supplement A):e107.

Processed Meat will give You a Stroke!

- 40,291 Swedish men; followed 10 yrs.
- 2,409 strokes
- RR of stroke for those who had the highest intake of processed meat compared with those with the lowest intake

  1.23 (95% CI 1.07-1.40) p=0.004

Larsson SC, e. al. *Am J Clin Nutr 8/*2011; 94:417-421. _

Periodontal Wellness Reduces Risk of Stroke

- 510,762 PD & 208,674 non-PD pts; divided PD pts into prophylactic rx, intensive rx (subgingival curettage, root planning, periodontal flap or extraction), no rx
- Follow-up ~ 8 yrs.; 15,141 pts developed ischemic stroke
- Adjusted for age, sex and comorbidities (BP, DM, dyslipidemia, AF, CKD, subclinical ASVD) to assess incident risk of stroke (SR)

Lee, Y-L, DDS, et. al. Stroke 2/19/2013; 44: XXX-XXX
DOI: 10.1161/STROKEAHA.111.000076

Periodontal Wellness Reduces Risk of Stroke: Conclusions

- PD is an important risk factor for ischemic stroke
- PD treatment lowers risk of stroke, especially among young subjects

Lee, Y-L, DDS, et. al. Stroke 2/19/2013; 44: XXX-XXX
DOI: 10.1161/STROKEAHA.111.000076

Lipo (a) Associated with Carotid ASVD (CA) in Young Ischemic Stroke (IS) Adults

- 196 IS pts.; mean age 44; 40% female; 40% had plaque identified on carotid duplex
- Age, smoking, DM, BP, TG, statin therapy, and Lp(a) significantly associated with CA.
- Multinomial logistic regression analysis showed a significant graded association of Lp(a) with CA $p<0.001$

Nathalie Nasr, et. al. *Stroke published online September 22, 2011. available* http://stroke.ahajournals.org/content/early/2011/09/22/STROKEAHA.111.624684

Odds Ratio of Lipo (a) Independently Predicting Carotid Plaque

Lipo (a)	Non-stenotic CA	Stenotic CA	P value
≥30 mg/L	3.11	7.44	<0.001
≥50 mg/L	3.38	10.9	<0.001

Nathalie Nasr, et. al. *Stroke published online September 22, 2011. available* http://stroke.ahajournals.org/content/early/2011/09/22/STROKEAHA.111.624684

Stroke Risk Factors – Accounting for 90% of Strokes

INTERSTROKE: Population-attributable risk for common risk factors

Risk factor	Population-attributable risk, % (99% CI)
Hypertension	**34.6 (30.4–39.1)**
Regular physical activity	**28.5 (14.5–48.5)**
Waist-to-hip ratio (tertile 2 vs tertile 1)	**26.5 (18.8–36.0)**
Ratio of apolipoprotein B to A1 (tertile 2 vs tertile 1)	**24.9 (15.7–37.1)**
Smoking	**18.9 (15.3–23.1)**
Dietary risk score (tertile 2 vs tertile 1)	**18.8 (11.2–29.7)**
Cardiac causes	**6.7 (4.8–9.1)**
Diabetes	**5.0 (2.6–9.5)**
Psychological factors	
• **Stress**	**4.6 (2.1–9.6)**
• **Depression**	**5.2 (2.7–9.8)**

No assoc. with TC or 'bad cholesterol' & ischemic stroke but strong assoc. between HDL & ischemic stroke

O'Donnell MJ et al. *Lancet* 2010; available at: http://www.thelancet.com.

Bale

Pre-hypertension Independently Increases Stroke Risk About 50%

- 12 prospect. studies; 518,520 middle aged adults; 2.7 to 32 yrs
- RR of stroke: 1.55 (95% CI 1.35-1.79) p<0.001
  adjusted for age, sex, DM, BMI, smoking, cholesterol

Risk of stroke by prehypertension category

Prehypertension range (mm Hg)	Relative risk (95% CI)
SBP 120-129 or DBP 80-84	1.22 (0.95-1.57)
SBP 130-139 or DBP 85-89	1.79 (1.49-2.16)

Lee M, et. al. *Neurology* 9/28/2011; 77:1330-1337.

Therapy for Prehypertension Reduces Stroke Risk 22%

- 16 randomized trials; 70,664 pts with prehypertension

- Pts who received BP rx compared with those who received placebo, had significant stroke reduction:

  RR: 0.78 (95% CI 0.71-0.86) $p<0.000001$

- NNT to prevent one stroke- 169 pts for 4.3 yrs

- ACEI's and CCB's about 25%; ARB's about 15%

Sipahi I, et. al. Stroke 12/8/2011; DOI: 10.1161/STROKEAHA.111.636829

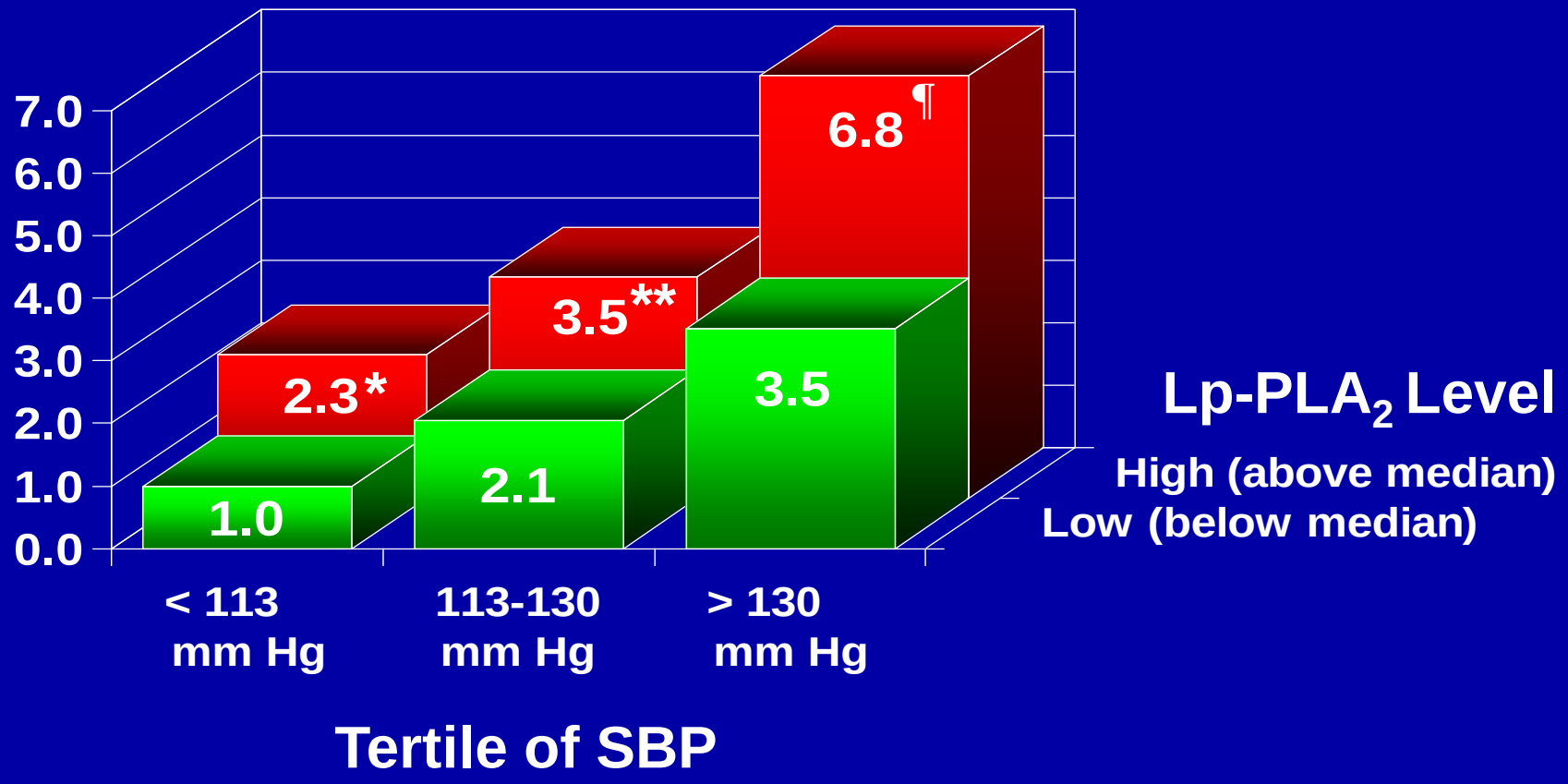
BP trial in elderly halted early due to reduced stroke and mortality risk

- 3845 patients aged ≥80
- Baseline: diastolic BP of 90 to 109 mm Hg and or systolic blood pressure of 160 to 199 mm Hg
- Rx: placebo or indapamide 1.5 mg and perindopril 2 mg or 4 mg a day if required
- Reductions so significant trial stopped two years early !

Imperial College, London. Trial stops after stroke and mortality significantly reduced by blood-pressure-lowering treatment for those aged 80 and over [press release]. August 7, 2007

The PLAC® Test Identifies Stroke-Prone Hypertensive Patients in ARIC

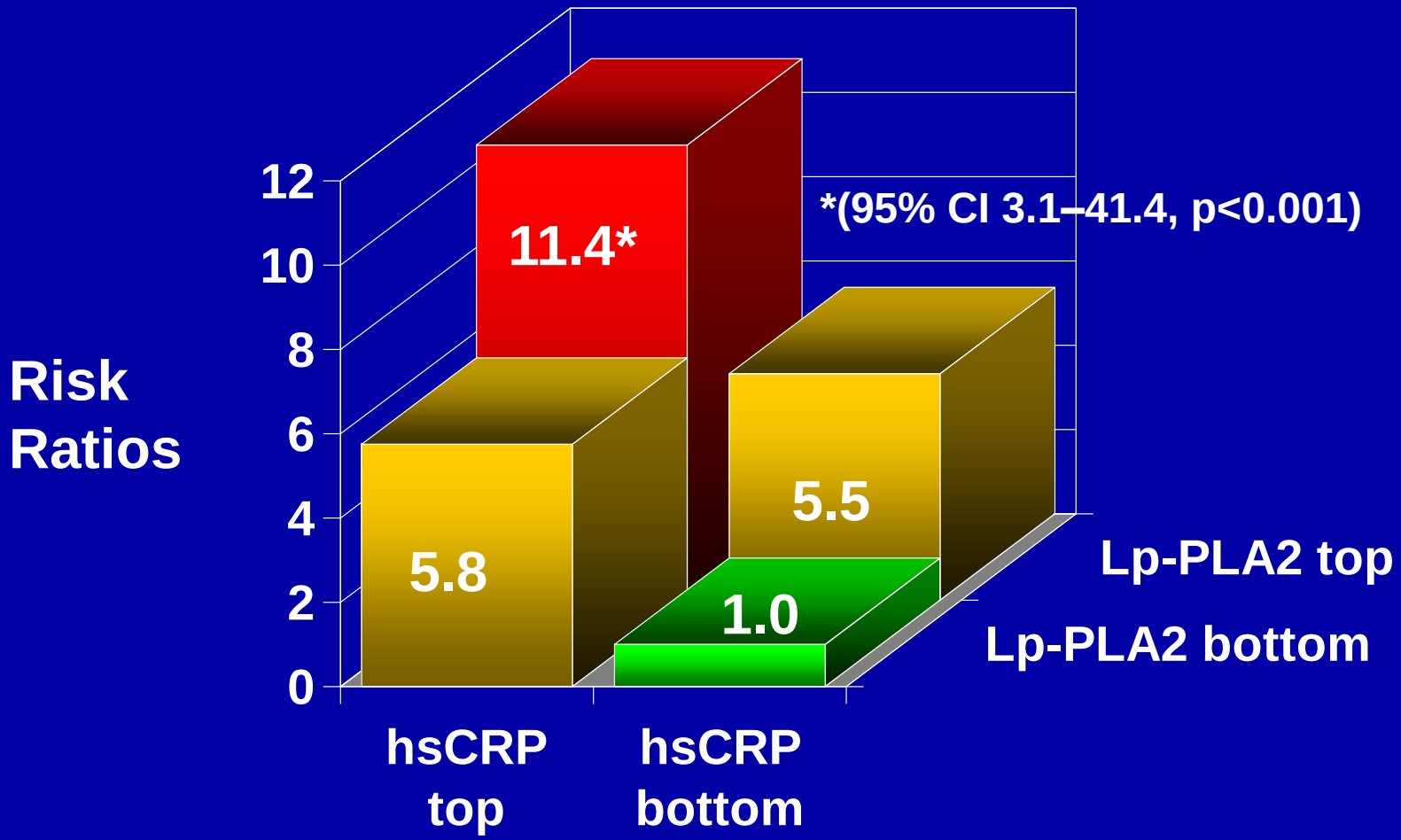
Risk Ratios for Ischemic Stroke Based on Lp-PLA_2 Level and SBP



(Data on file with FDA)

*p=0.03, **p≤ 0.005, ¶p<0.0001

Additive Risk for Incident Ischemic Stroke by Lp-PLA$_2$ and hsCRP Tertiles in ARIC



Adjusted for demographics, current smoking status, blood pressure, diabetes, LDL and HDL

(Data on file with FDA)

EDFROG IRA

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

Lifestyle to Prevent Myocardial Infarction (MI) in Men

20,721 healthy men 45-79 yo; followed 11 yrs.; 1,361 incident cases of MI.

Evaluated impact of diet, moderate alcohol, no smoking, physical activity and waist on risk of MI.

Akesson, A., et. al. (2014). Low-Risk Diet and Lifestyle Habits in the Primary Prevention of Myocardial Infarction in Men: A Population-Based Prospective Cohort Study. *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks

Having all 5 factors optimized compared with none:

RR of MI -0.14 (95% CI: 0.04 to 0.43)

Optimization of these healthy behaviors could prevent 79% (95% CI: 34% to 93%) of the MIs in men!

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

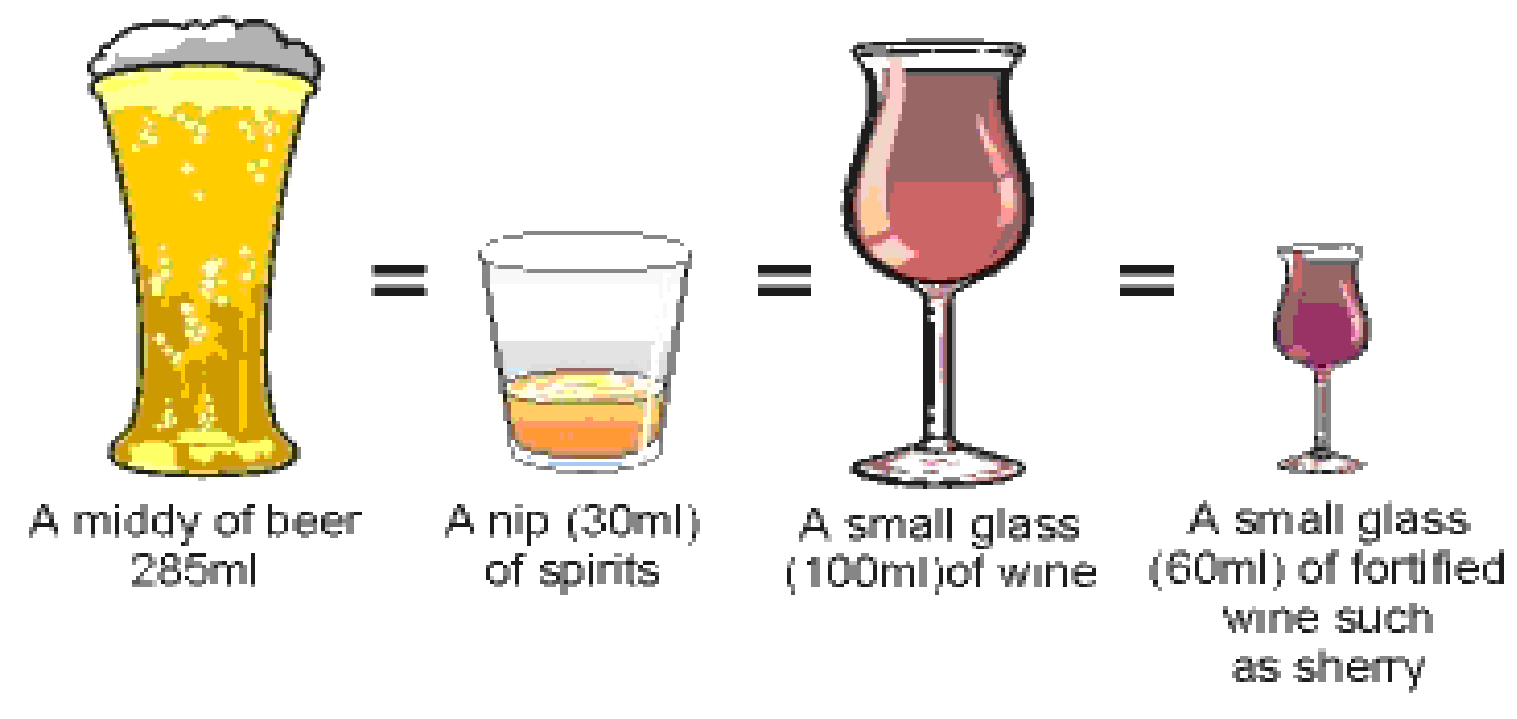
Lifestyle to Prevent Heart Attacks: diet

Healthy foods included: fruits, vegetables, legumes, nuts, reduced-fat dairy products, whole grains, and fish.

Unhealthy foods included: red and processed meat, fried potatoes, solid fats, full-fat cheese, white bread, refined cereals, and various sweets.

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks: alcohol



Optimal up to 30 grams of alcohol a day

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks: smoking

Non-smoker = never

≥ 20 years without

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks: physical activity

Walk or cycle ≥40 min/day and exercised ≥1 h/wk

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks: waist

Optimal = < 37.5 inches

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks

TABLE 3 Effect of Combined Low-Risk Behaviors in Relation to Risk of Myocardial Infarction*

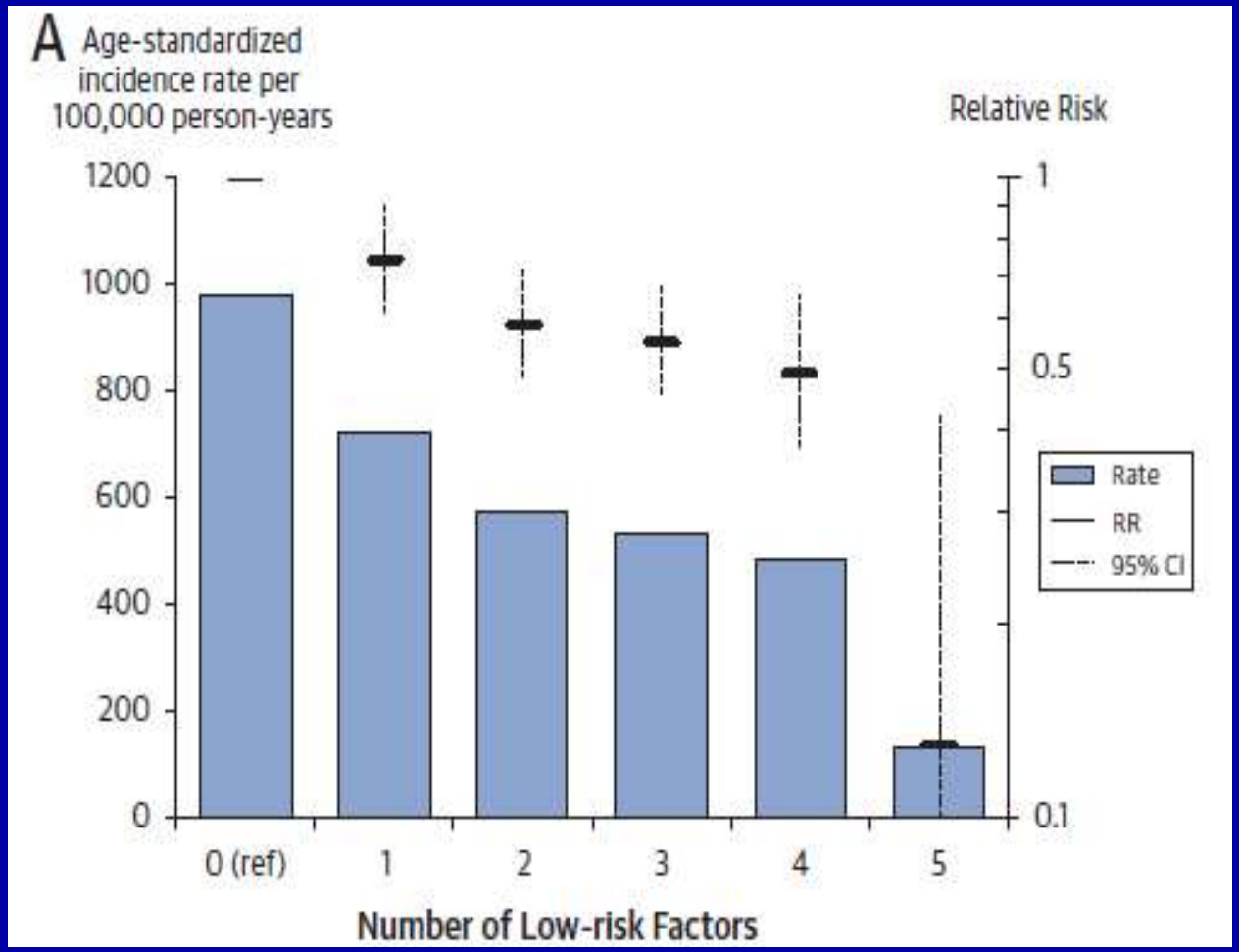
Group	Low-Risk Group No. of Events (% Men)	Age-Standardized Incidence Rate† (95% CI)	Compared With High-Risk Group‡ RR (95% CI)	Compared With the Remainder of the Study Population RR (95% CI)	Population Attributable Risk§ % (95% CI)
Diet (D)	177 (18)	495 (417-572)	0.74 (0.58-0.96)	0.82 (069-0.96)	16 (4-35)
D + alcohol (A)	74 (8.7)	429 (321-537)	0.65 (0.48-0. 87)	0.75 (0.59-0.95)	23 (4-39)
D + A + smoking (S)	36 (5.4)	321 (208-433)	0.36 (0.25-0.53)	0.54 (0.39-0.76)	44 (23-49)
D + A + S + physical activity (P)	9 (1.7)	218 (73-363)	0.24 (0.12-0.47)	0.36 (0.19-0.69)	64 (30-81)
D = A + S + P + waist	3 (1.0)	131 (0-279)	0.14 (0.04-0.43)	0.21 (0.07-0.66)	79 (34-93)

*All relative risks were adjusted for age (continuous), educational achievement (≤9, 10 to 12, >12 years), family history of myocardial infarction (yes/no), use of aspirin (yes/no), marital status (unmarried, married, divorced, widowed), non-Recommended Food Score (quintiles), and total energy intake (continuous). †Per 100,000 person-years. ‡The high-risk group (8.3% of the study population and 166 cases of myocardial infarction [age-standardized incidence rate 979 cases per 100,000 person-years]) included men with no low-risk factors and was characterized by the following: median 2.9 servings/day of vegetables and fruit, 3.0 servings/day of whole grains, and 1.4 servings/week of fish; 24 pack-years of tobacco smoking (55% reported to be current smokers); 36% reported neither ≥40 min of daily walking/bicycling nor ≥1 h per week of exercise; and a median waist circumference 101 cm. §Estimated compared with the remainder of the total study population, representing 91.3%, 94.6%, 98.3%, and 99%, respectively, for each additional low-risk factor. ||The model was also adjusted for smoking, physical activity, and waist circumference. ¶The model was also adjusted for physical activity and waist circumference. #The model was also adjusted for waist circumference.

RFS = Recommended Food Score; other abbreviations as in Table 2.

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks



MI Incidence for the Addition of Any Low-Risk Behavior

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

Lifestyle to Prevent Heart Attacks

Safe, economical, medication-free, lifestyle strategies can dramatically reduce the incidence of MI.

This type of prevention can be utilized globally.

Akesson, A., et. al. (2014). *J Am Coll Cardiol, 64*(13), 1299-1306.

BDM Thoughts

- Blends with our method very well.
- ‘Extreme’ diets not necessary.
- Fine tune diet and alcohol advice with apoE.
- Remember nicotine in any form is harmful – cigars, chew or e-cigarettes.
- Daily physical activity is important; try to acquire some of that with ‘work’.
- Central adiposity is dangerous.
- Try to be ‘perfect’, but realize each success with a lifestyle issue mitigates CV risk.

“Striving for perfection is a virtue unless encumbered with anxiety and condemnation.” Bradley Bale

New Offering from CHL

Hot Topics

Telomere Length in WBCs Associated with CV Risk: Background

Telomeres are protein structures at the end of chromosomes.

They shorten with each cell division eventually resulting in cellular senescence.

Senescence is linked to oxidative stress and inflammation.

This is a driver of arterial inflammation.*

Haycock, P. C., et. al. (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

*Bale, B. F. D. A. L. (2013). Autophagy, Senescence, and Arterial Inflammation: Relationship to Arterial Health and Longevity. *Alternative Therapies in Health & Medicine, 19*(4), 8-10.

Telomere Length in WBCs Associated with CV Risk: Background

Length varies considerably between individuals, including those of the same chronological age.

Telomere length within individuals is generally strongly correlated across tissue types.

Leucocytes, being easily accessible, can serve as a marker of telomere length in general within an individual.

Hypothesis: leucocyte telomere length is related to CV risk.

Haycock, P. C., et. al. (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

Telomere Length in WBCs Associated with CV Risk

Meta-analysis; 24 studies involving 43,725 pts; 8,400 with ASVD (5,566 CAD; 2,834 CVD); half prospective and half retrospective; mean age 60 yo; 47% female.

Weak inverse correlation between telomere length and chronological age.

r=−0.13, (95% CI−0.18 to −0.08)

Haycock, P. C., et. al. (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

Telomere Length in WBCs Associated with CAD Risk

Increased CAD risk comparing shortest third v longest third of telomere length.

RR-1.54 (95% CI, 1.30 - 1.83)

Four studies adjusted for conventional CV risk factors plus CRP and physical activity.

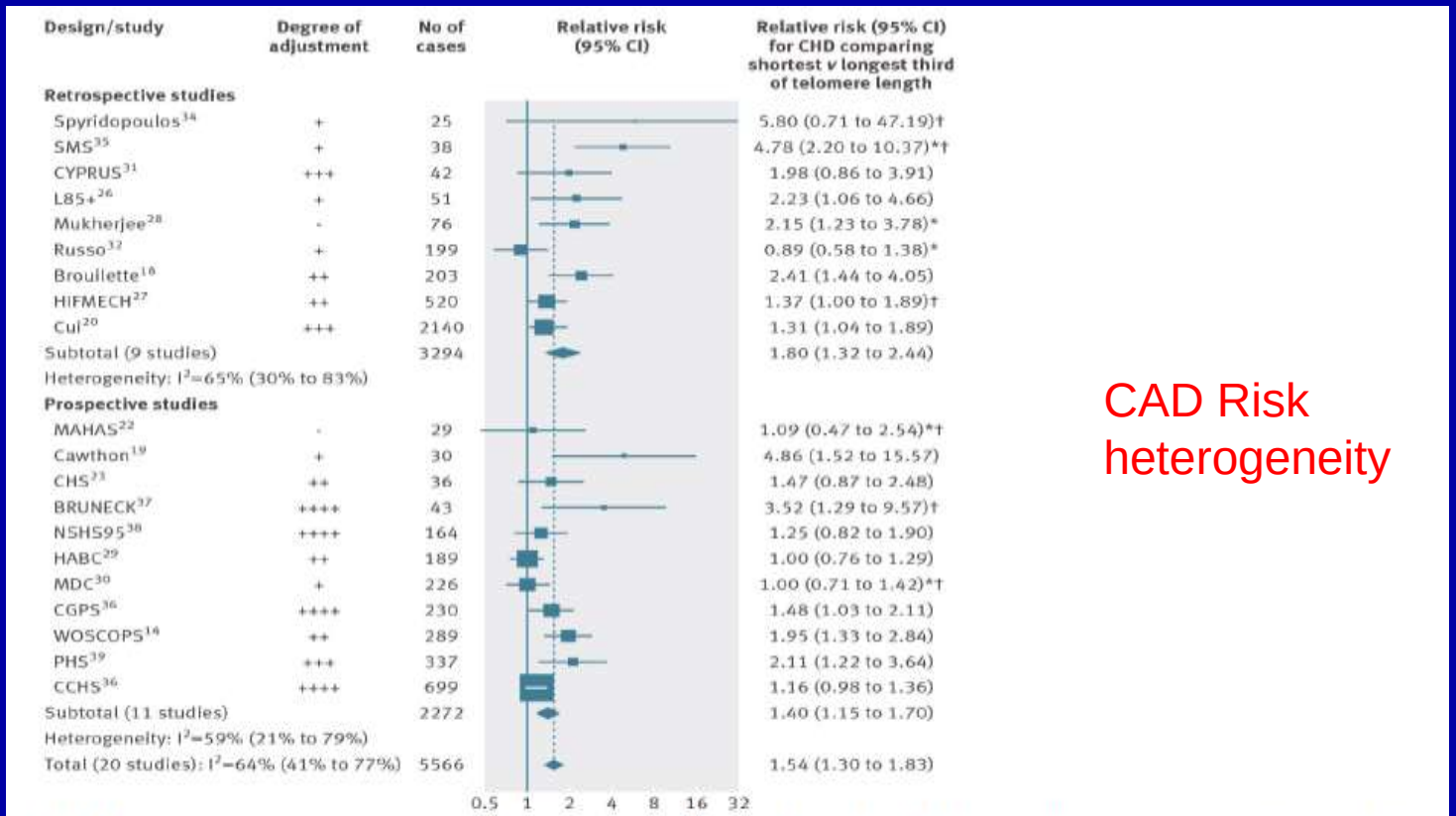
RR-1.42 (95% CI,1.17 to 1.73)

Adjusting for publication bias:

RR-1.34 (95% CI, 1.12 to 1.60) p=0.001

Haycock, P. C., et. al. (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

Telomere Length in WBCs Associated with CV Risk



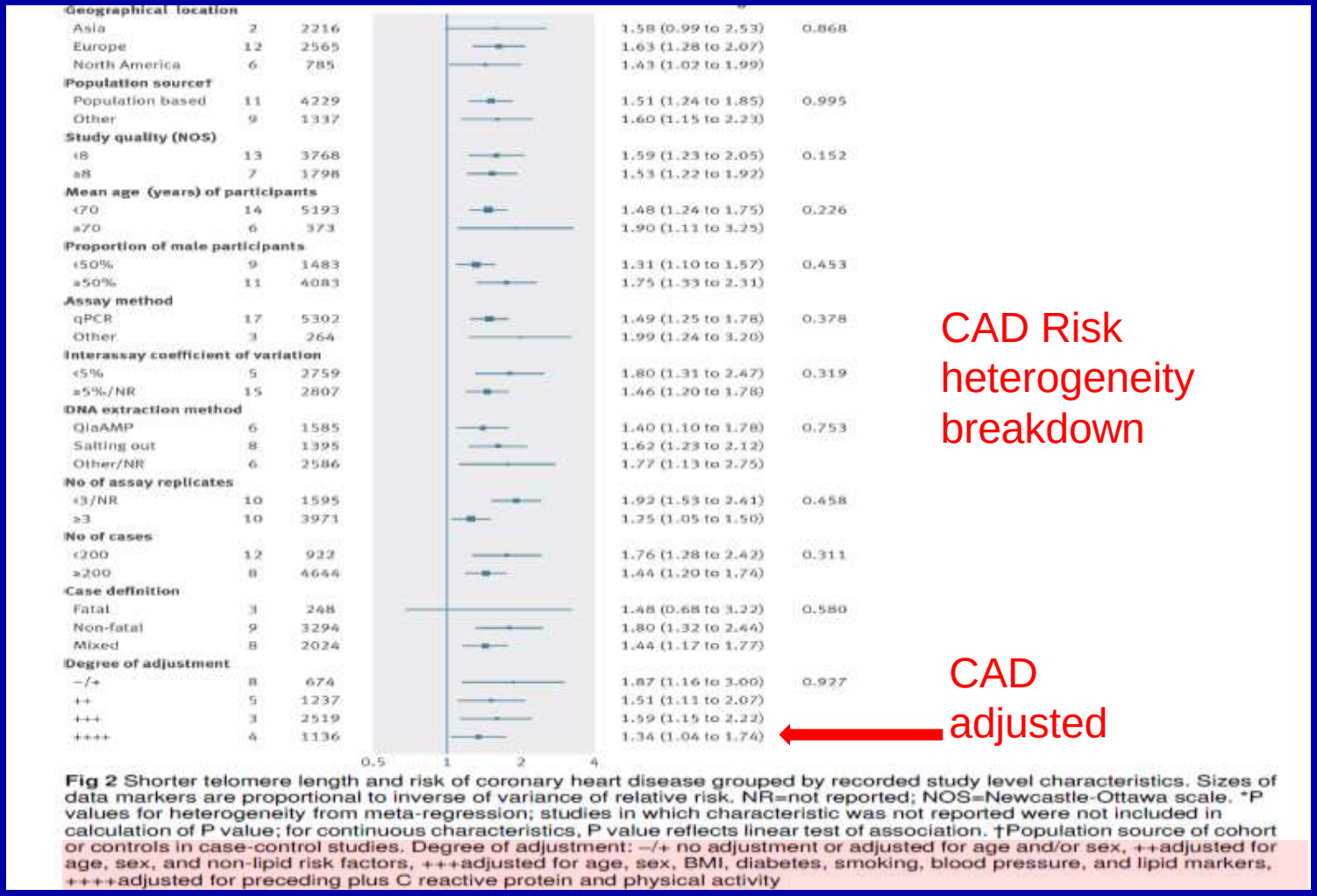
Design/study	Degree of adjustment	No of cases	Relative risk (95% CI) for CHD comparing shortest *v* longest third of telomere length
Retrospective studies			
Spyridopoulos[34]	+	25	5.80 (0.71 to 47.19)†
SMS[35]	+	38	4.78 (2.20 to 10.37)*†
CYPRUS[31]	+++	42	1.98 (0.86 to 3.91)
LBS+[26]	+	51	2.23 (1.06 to 4.66)
Mukherjee[28]	-	76	2.15 (1.23 to 3.78)*
Russo[32]	+	199	0.89 (0.58 to 1.38)*
Broullette[16]	++	203	2.41 (1.44 to 4.05)
HIFMECH[27]	++	520	1.37 (1.00 to 1.89)†
Cul[20]	+++	2140	1.31 (1.04 to 1.89)
Subtotal (9 studies)		3294	1.80 (1.32 to 2.44)
Heterogeneity: I^2=65% (30% to 83%)			
Prospective studies			
MAHAS[22]	-	29	1.09 (0.47 to 2.54)*†
Cawthon[19]	+	30	4.86 (1.52 to 15.57)
CHS[23]	++	36	1.47 (0.87 to 2.48)
BRUNECK[37]	++++	43	3.52 (1.29 to 9.57)†
NSHS95[38]	++++	164	1.25 (0.82 to 1.90)
HABC[29]	++	189	1.00 (0.76 to 1.29)
MDC[30]	+	226	1.00 (0.71 to 1.42)*†
CGPS[36]	++++	230	1.48 (1.03 to 2.11)
WOSCOPS[14]	++	289	1.95 (1.33 to 2.84)
PHS[39]	+++	337	2.11 (1.22 to 3.64)
CCHS[36]	++++	699	1.16 (0.98 to 1.36)
Subtotal (11 studies)		2272	1.40 (1.15 to 1.70)
Heterogeneity: I^2=59% (21% to 79%)			
Total (20 studies): I^2=64% (41% to 77%)		5566	1.54 (1.30 to 1.83)

Fig 1 Shorter telomere length and risk of coronary heart disease across 20 studies stratified by study design (see table for study acronyms). Study specific estimates were pooled with random effects meta-analysis. Sizes of data markers are proportional to inverse of variance within study. Degree of adjustment: – no adjustment, + adjusted for age and/or sex, ++ adjusted for age, sex, and non-lipid risk factors, +++ adjusted for age, sex, smoking, BMI, diabetes, blood pressure, and lipid markers; ++++ preceding plus adjusted for C reactive protein and physical activity. *Calculated from mean difference in telomere length between cases and controls; †obtained through correspondence. Summary associations for prospective and retrospective studies were not significantly different (P=0.32)

CAD Risk heterogeneity

Haycock, P. C., et. al. (2014). *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

Telomere Length in WBCs Associated with CV Risk



Geographical location				
Asia	2	2216	1.58 (0.99 to 2.53)	0.868
Europe	12	2565	1.63 (1.28 to 2.07)	
North America	6	785	1.43 (1.02 to 1.99)	
Population sourcef				
Population based	11	4229	1.51 (1.24 to 1.85)	0.995
Other	9	1337	1.60 (1.15 to 2.23)	
Study quality (NOS)				
‹8	13	3768	1.59 (1.23 to 2.05)	0.152
≥8	7	1798	1.53 (1.22 to 1.92)	
Mean age (years) of participants				
‹70	14	5193	1.48 (1.24 to 1.75)	0.226
≥70	6	373	1.90 (1.11 to 3.25)	
Proportion of male participants				
‹50%	9	1483	1.31 (1.10 to 1.57)	0.453
≥50%	11	4083	1.75 (1.33 to 2.31)	
Assay method				
qPCR	17	5302	1.49 (1.25 to 1.78)	0.378
Other	3	264	1.99 (1.24 to 3.20)	
Interassay coefficient of variation				
‹5%	5	2759	1.80 (1.31 to 2.47)	0.319
≥5%/NR	15	2807	1.46 (1.20 to 1.78)	
DNA extraction method				
QiaAMP	6	1585	1.40 (1.10 to 1.78)	0.753
Salting out	8	1395	1.62 (1.23 to 2.12)	
Other/NR	6	2586	1.77 (1.13 to 2.75)	
No of assay replicates				
‹3/NR	10	1595	1.92 (1.53 to 2.41)	0.458
≥3	10	3971	1.25 (1.05 to 1.50)	
No of cases				
‹200	12	922	1.76 (1.28 to 2.42)	0.311
≥200	8	4644	1.44 (1.20 to 1.74)	
Case definition				
Fatal	3	248	1.48 (0.68 to 3.22)	0.580
Non-fatal	9	3294	1.80 (1.32 to 2.44)	
Mixed	8	2024	1.44 (1.17 to 1.77)	
Degree of adjustment				
−/+	8	674	1.87 (1.16 to 3.00)	0.927
++	5	1237	1.51 (1.11 to 2.07)	
+++	3	2519	1.59 (1.15 to 2.22)	
++++	4	1136	1.34 (1.04 to 1.74)	

0.5 1 2 4

CAD Risk heterogeneity breakdown

CAD adjusted

Fig 2 Shorter telomere length and risk of coronary heart disease grouped by recorded study level characteristics. Sizes of data markers are proportional to inverse of variance of relative risk. NR=not reported; NOS=Newcastle-Ottawa scale. *P values for heterogeneity from meta-regression; studies in which characteristic was not reported were not included in calculation of P value; for continuous characteristics, P value reflects linear test of association. †Population source of cohort or controls in case-control studies. Degree of adjustment: −/+ no adjustment or adjusted for age and/or sex, ++adjusted for age, sex, and non-lipid risk factors, +++adjusted for age, sex, BMI, diabetes, smoking, blood pressure, and lipid markers, ++++adjusted for preceding plus C reactive protein and physical activity

Haycock, P. C., et. al. (2014). *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

Telomere Length in WBCs Associated with CVD Risk

Increased CVD risk comparing shortest third v longest third of telomere length.

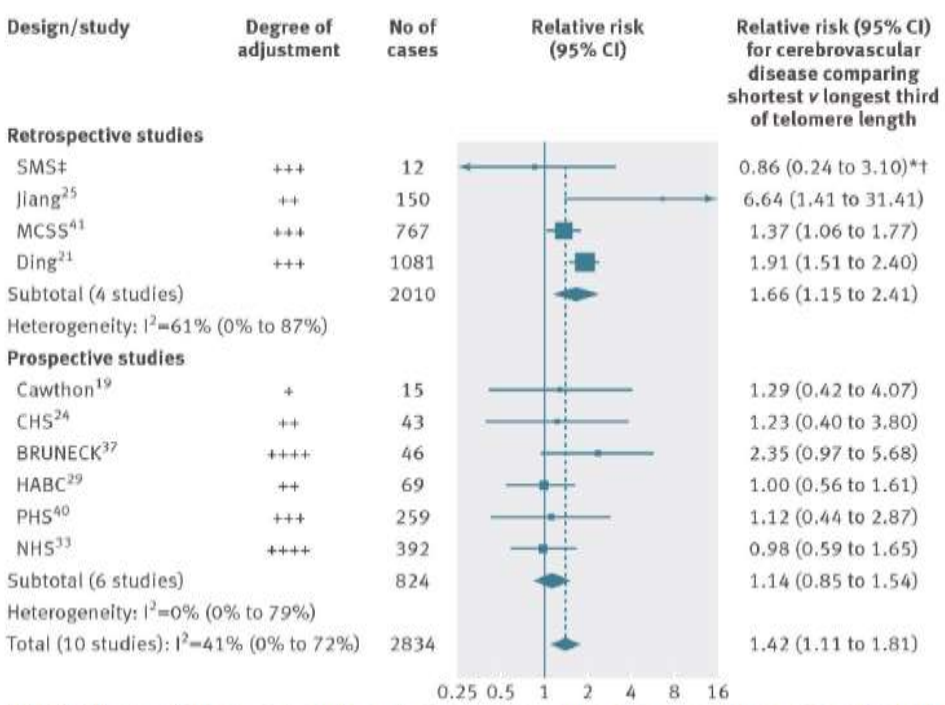
RR- 1.42 (95% CI, 1.11 to 1.81)

Results did not change significantly after adjusting for conventional CV risk factors or publication bias.

Results were insignificant in prospective studies & the higher quality studies.

Haycock, P. C., et. al. (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

Telomere Length in WBCs Associated with CV Risk



Design/study	Degree of adjustment	No of cases	Relative risk (95% CI) for cerebrovascular disease comparing shortest *v* longest third of telomere length
Retrospective studies			
SMS‡	+++	12	0.86 (0.24 to 3.10)*†
Jiang[25]	++	150	6.64 (1.41 to 31.41)
MCSS[41]	+++	767	1.37 (1.06 to 1.77)
Ding[21]	+++	1081	1.91 (1.51 to 2.40)
Subtotal (4 studies)		2010	1.66 (1.15 to 2.41)
Heterogeneity: I^2=61% (0% to 87%)			
Prospective studies			
Cawthon[19]	+	15	1.29 (0.42 to 4.07)
CHS[24]	++	43	1.23 (0.40 to 3.80)
BRUNECK[37]	++++	46	2.35 (0.97 to 5.68)
HABC[29]	++	69	1.00 (0.56 to 1.61)
PHS[40]	+++	259	1.12 (0.44 to 2.87)
NHS[33]	++++	392	0.98 (0.59 to 1.65)
Subtotal (6 studies)		824	1.14 (0.85 to 1.54)
Heterogeneity: I^2=0% (0% to 79%)			
Total (10 studies): I^2=41% (0% to 72%)		2834	1.42 (1.11 to 1.81)

Fig 3 Shorter telomere length and cerebrovascular disease risk across 10 studies stratified by study design (see table for study acronyms). Study specific estimates were pooled with random-effects meta-analysis. Sizes of data markers are proportional to inverse of variance within study. Degree of adjustment: +adjusted for age and/or sex, ++adjusted for age, sex, and non-lipid risk factors, +++adjusted for age, sex, smoking, BMI, diabetes, blood pressure, and lipid markers, ++++adjusted for preceding plus C reactive protein and physical activity. *Calculated from mean difference in telomere length between cases and controls; †obtained through correspondence; ‡previously unpublished. Summary associations for prospective and retrospective studies were not significantly different (P=0.15)

CVD risk

Haycock, P. C., et. al. (2014*Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

GWA Studies Indicate Telomere Length has Causal Relationship to CV Risk

Meta-analysis of 14 GWAS; 22,233 CAD pts & 64,762 controls.

7 SNPs found that each explained <1% of the variation in mean leucocyte telomere length.

Combined these SNPS into a single genetic risk score.

Codd, V., et. al. (2013). Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet, 45*(4), 422-427.

GWA Studies Indicate Telomere Length has Causal Relationship to CV Risk

Alleles associated with shorter telomere length were associated with increased CAD risk.

The genetic effect in the shortest versus longest third of the telomere length.

RR- 1.67 (95% CI, 1.12 to 2.56)

Codd, V., et. al. (2013). Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet, 45*(4), 422-427.

Atherosclerosis and Senescence

Endothelial senescence is associated with loss of function and a shift toward a proinflammatory and proapoptotic state.

VSMCs senescence generate a proinflammatory environment and have diminished ability to repair plaque. May promote the thinning of fibrous cap and the instability of atherosclerotic plaques.

Monocyte senescence generates a greater proinflammatory environment

Wang J C , Bennett M Circulation Research 7/2012;111:245-259

Atherosclerosis and Senescence:
Therapeutic measures to mitigate senescence

Exercise; diet with caloric restriction.

Agents which reduce ROS and oxidative DNA damage: antioxidants, statins, ACEI, ARBs.

Pioglitazone has actions which can help maintain telomeres; increasing telomerase expression.

Wang J C , Bennett M Circulation Research 7/2012;111:245-259

PPAR gamma Activation May Mitigate Senescence

Mouse study showing PPAR gamma activation can reduce senescence.

It does this via reducing oxidative stress, enhancing mitochondrial activity and increasing telomerase.

Xiong, S., et. al. (2013). Peroxisome proliferator-activated receptor gamma coactivator-1alpha is a central negative regulator of vascular senescence. *Arterioscler Thromb Vasc Biol, 33*(5), 988-998.

Should we use this new test??

Telomere Length in WBCs Associated with CV Risk

Whether telomere testing can provide reliable information about CV risk to individuals from the general population has not been firmly established.

Judgment on whether it is a clinically useful predictor of risk that can help guide treatment decisions will require formal evaluation.

Haycock, P. C., et. al. (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *Bmj, 349*, g4227. doi: 10.1136/bmj.g4227

BDM Thoughts

- This will be in the lay press.
- Many patients are interested in anti-aging solutions.
- Some patients will request this test.
- It is good to know CHL now offers it.
- If the result indicates significantly shortened telomeres, at minimum, we can offer lifestyle suggestions.
- If abnormal, remain vigilant with arterial inflammation and subclinical disease.

Upcoming Presentations

Upcoming Presentations

10/16-19/14 – BDM Reunion Canyon Ranch, Tucson, AZ

10/20/14 - Brad speaking in Knoxville, TN – CHL

11/7-8/14 – BDM Preceptorship San Antonio, TX - Marriott Riverwalk

11/14/14 - Brad speaking all day at DISH meeting – Brentwood, TN

11/17/14- Amy speaking at NP conference in Chicago, Ill.

12/1/14 - Brad speaking at NY Dental Society Meeting – NY,NY

Exciting Announcement!!

501c3 status

Mission: to advance the science of arteriology to the point every person has the opportunity to live out their life free of significant arterial disease.

Open for Discussion