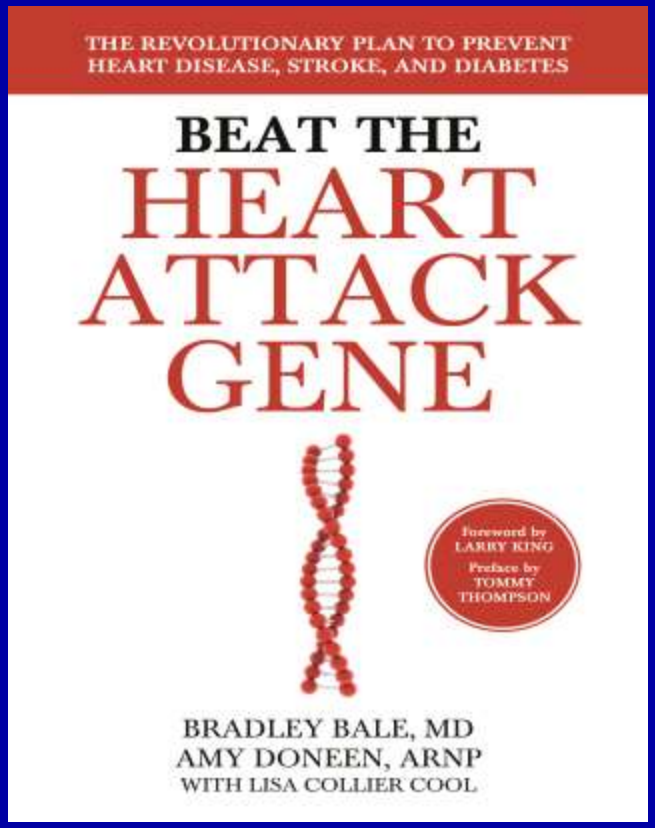
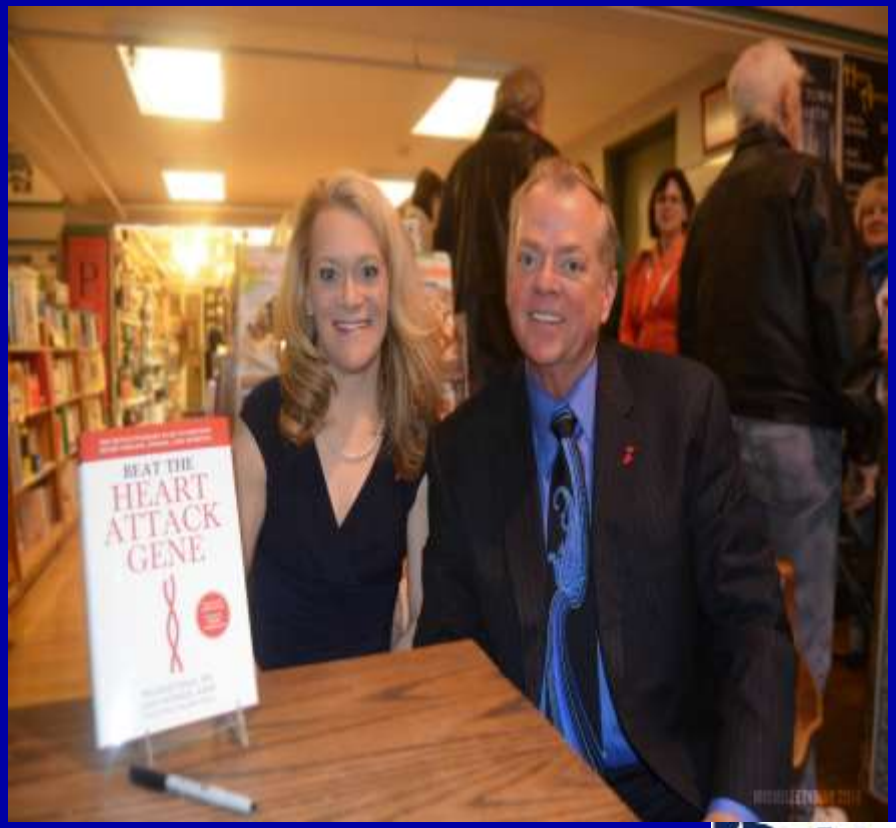
Bale/Doneen Live Chat Session

3/12/2014

5:30-6:30 pm PST

Bradley Bale, MD





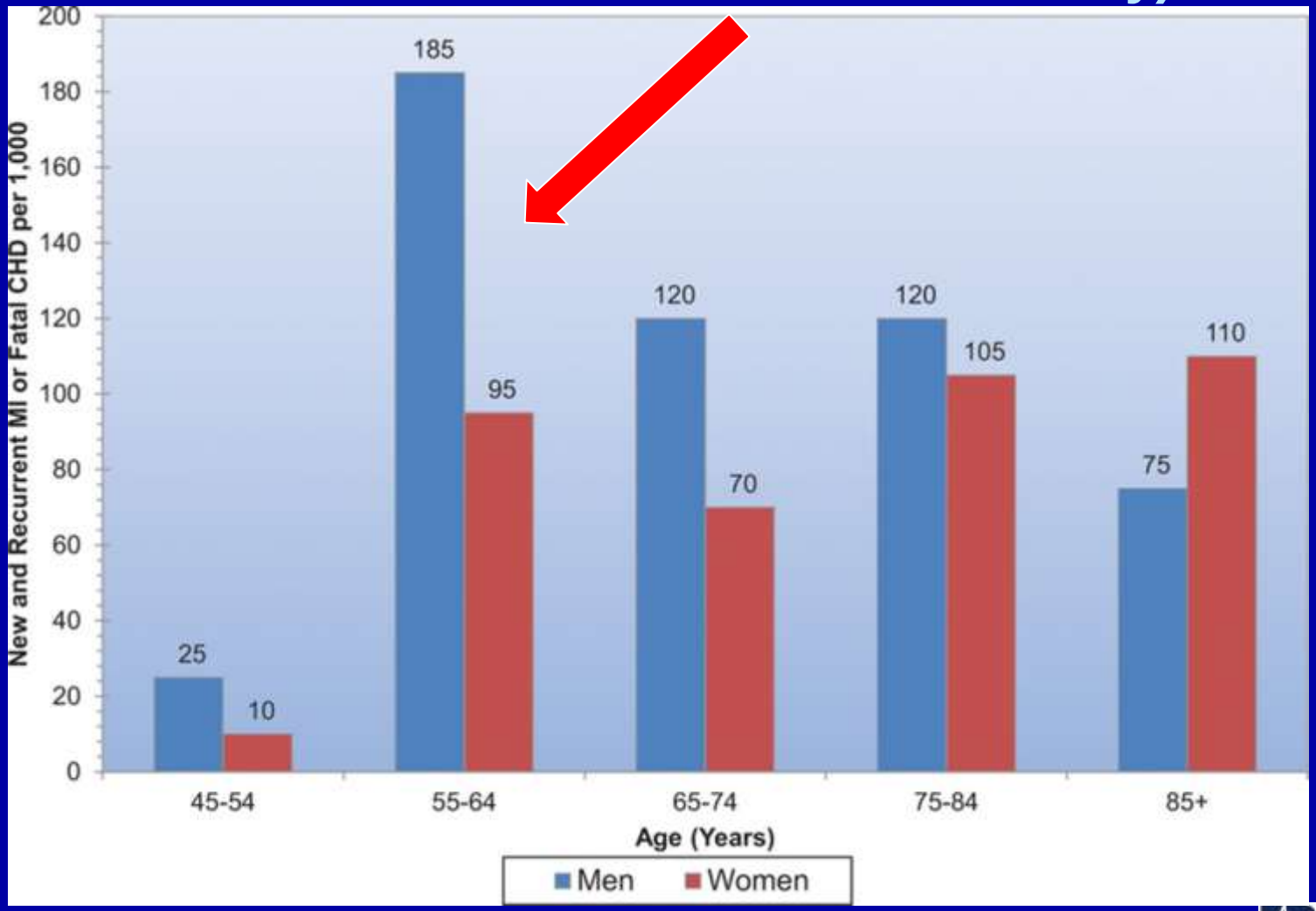
Live chat-outline

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

New Studies Just Keep Coming!

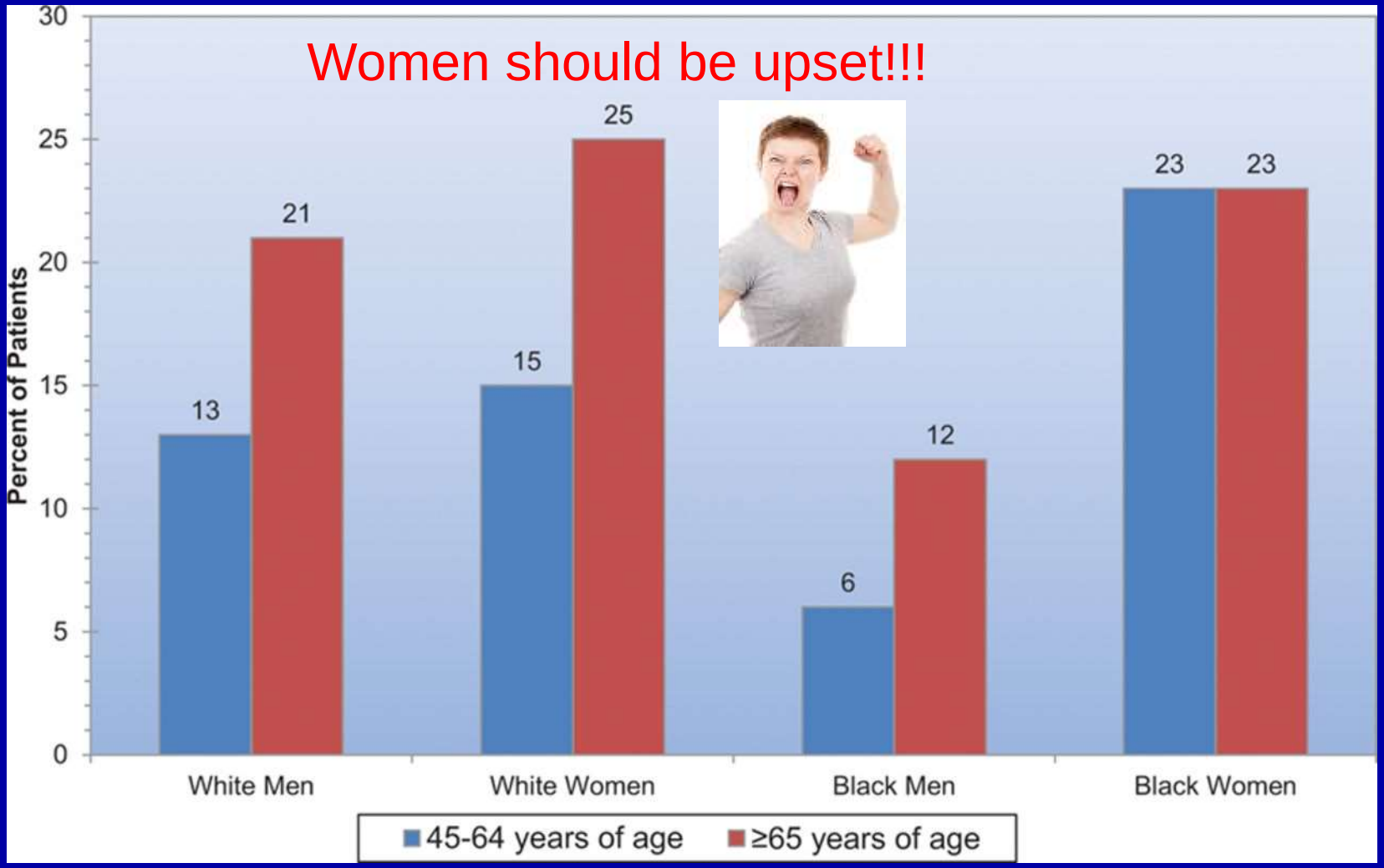
Just Published Stats

Annual number of adults per 1000 having diagnosed heart attack or fatal coronary heart disease (CHD) by age and sex (Atherosclerosis Risk in Communities Surveillance: 2005–2010 and Cardiovascular Health Study).



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

Proportion of patients with recurrent stroke within 5 years after first stroke.

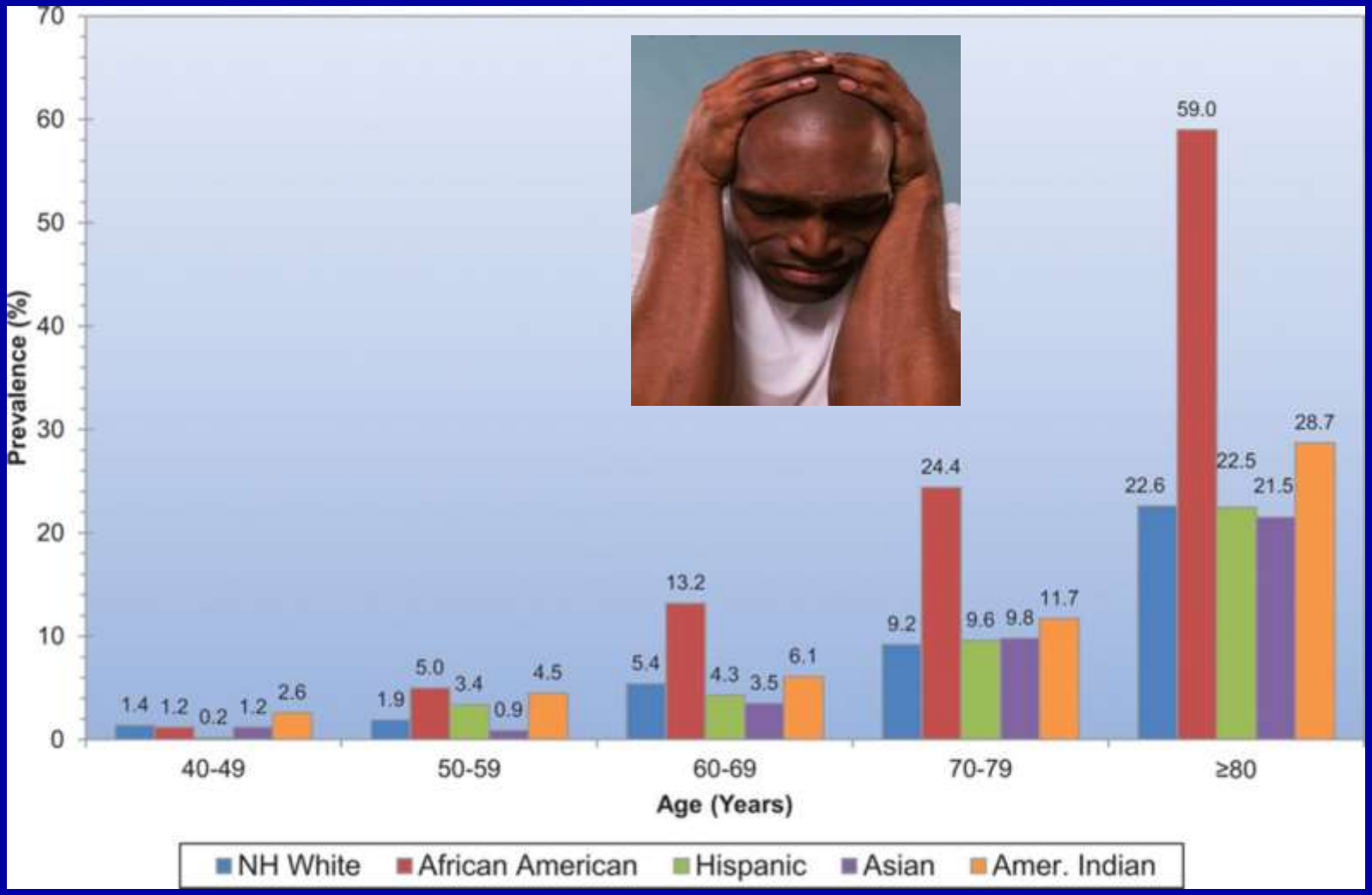


Go A et al. Circulation 2014;129:e28-e292

First acute decompensated heart failure annual event rates per 1000 (from ARIC Community Surveillance 2005–2010).

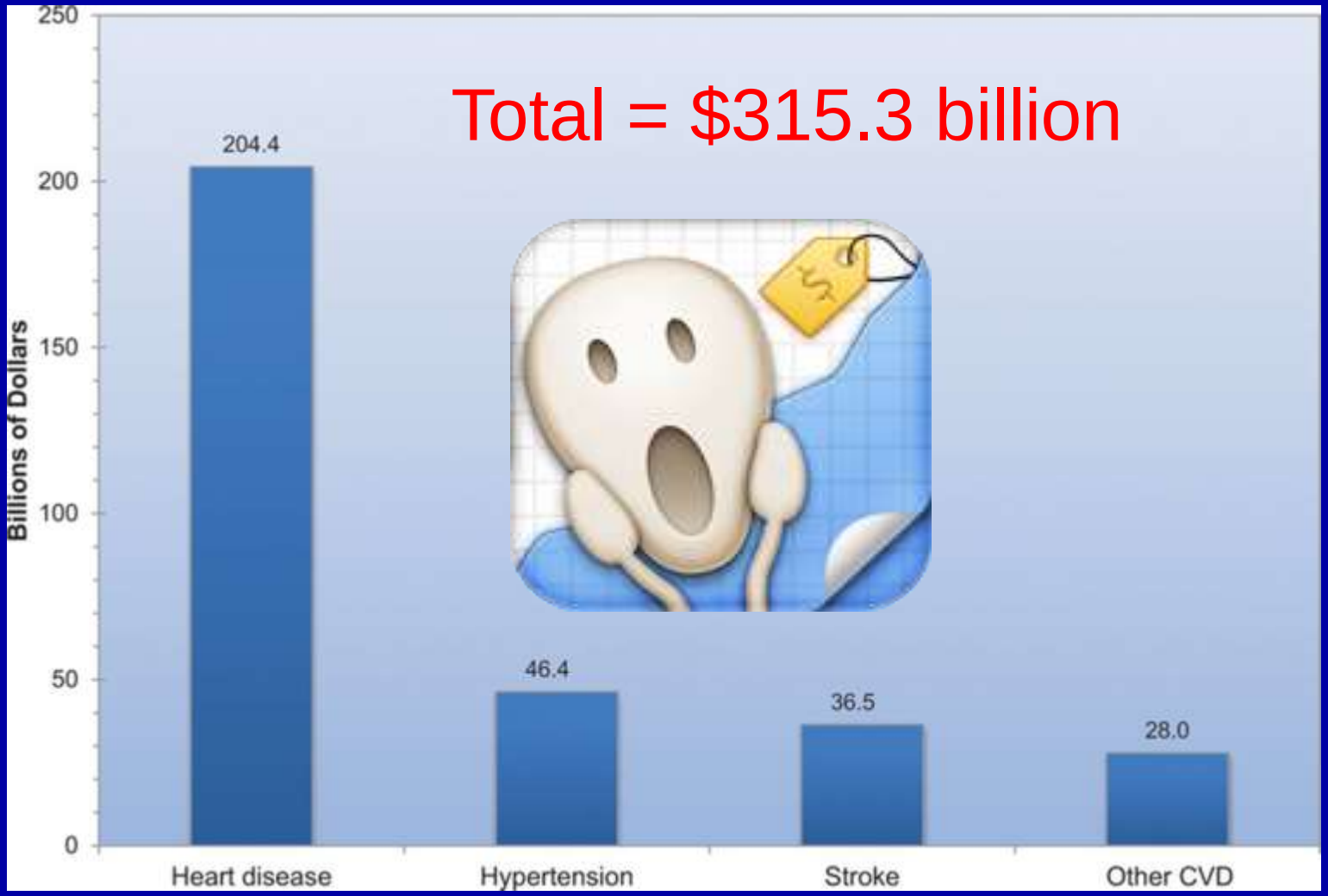
Go A et al. Circulation 2014;129:e28-e292

Prevalence estimates for peripheral arterial disease in males by age and ethnicity.



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

Direct and indirect costs of cardiovascular disease (CVD) and stroke (in billions of dollars), United States, 2010.



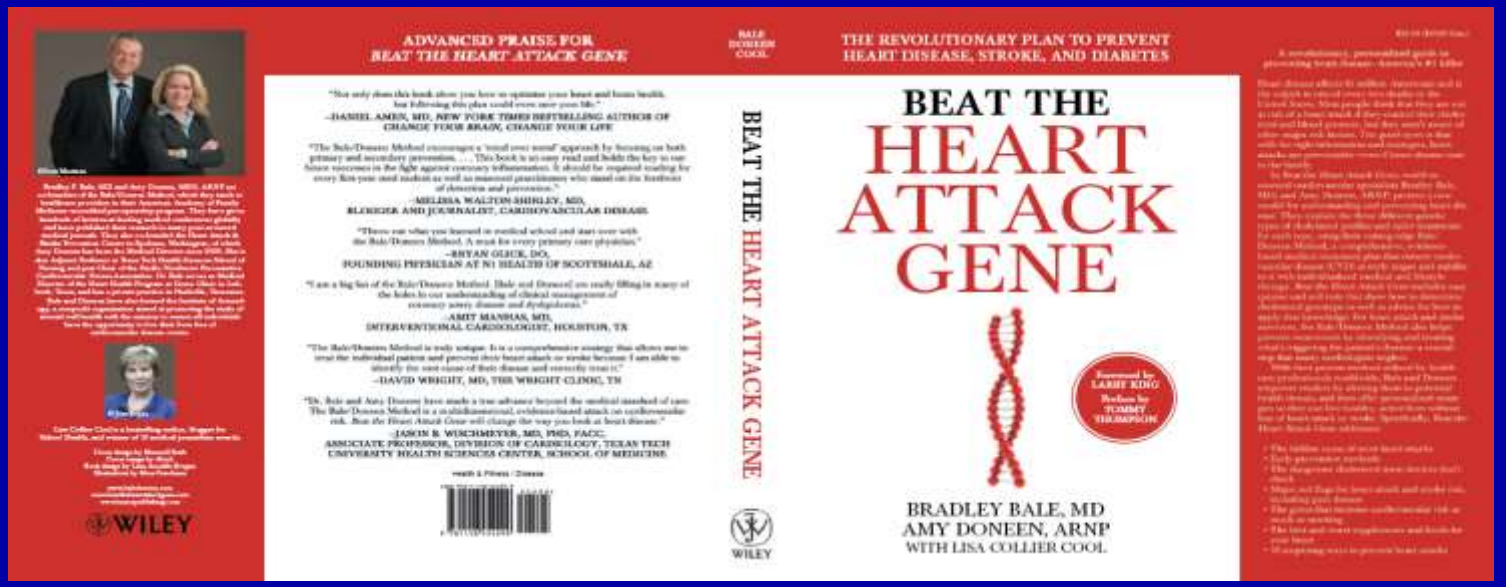
Go A et al. Circulation 2014;129:e28-e292

What is projected cost??

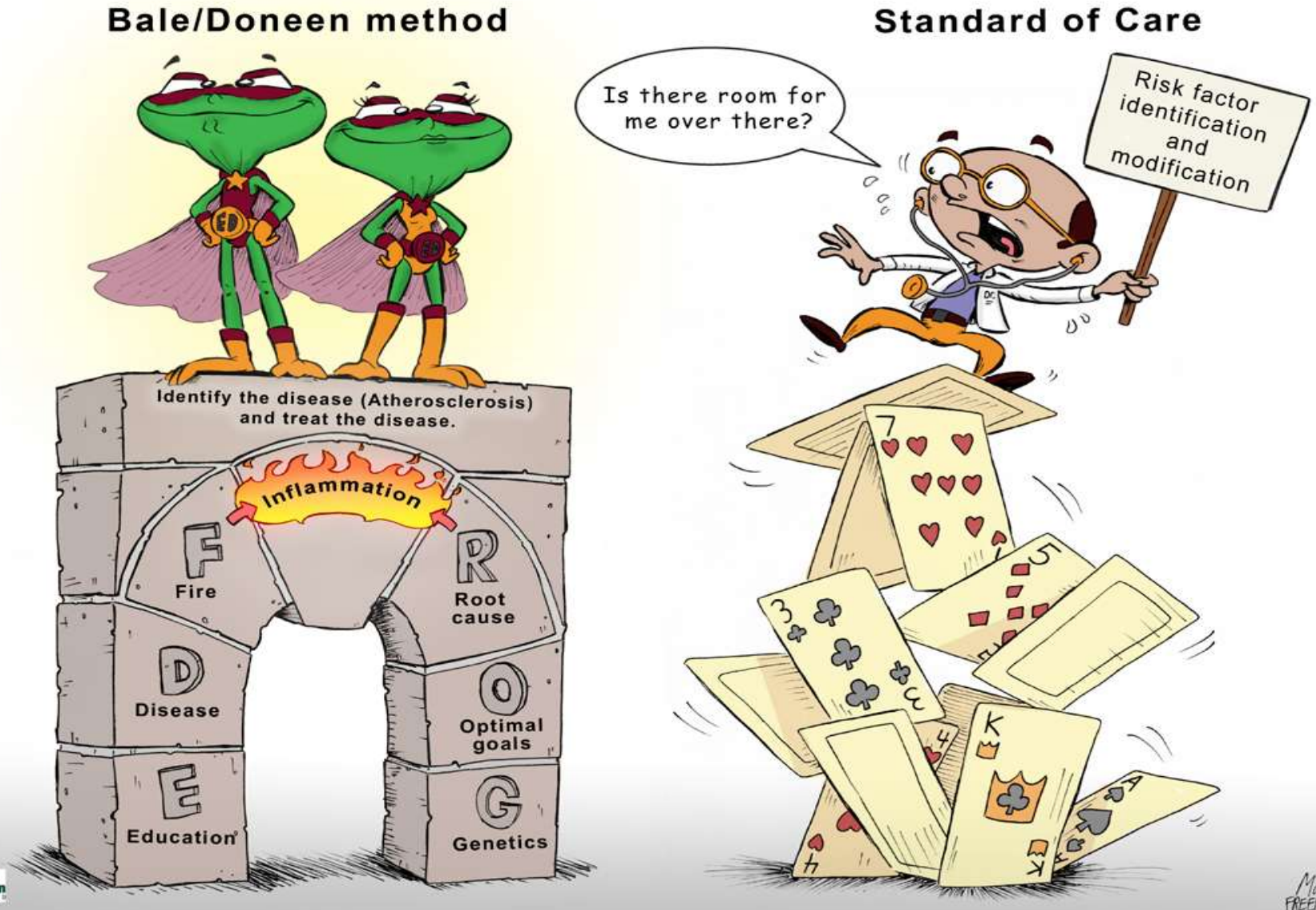
Projected total costs of cardiovascular disease (CVD), 2015 to 2030 (2012 $ in billions) in the United States.

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

Solution??



What's the difference?



Extent of Coronary Atheroma Burden Predictive of CV Death and MI Regardless of Degree of Stenosis

- 3,242 sx'ic pts; 43% female; mean age 56±13 yo; CTA; followed 3.6 yrs.

- CTA results classified for presence, severity and extent of coronary atheroma
  - a) stenosis: <50% or >50% obstructing
  - b) severity: 1, 2, 3 vessel disease or left main
  - c) extent: sum of segments with disease- ≤4 or >4

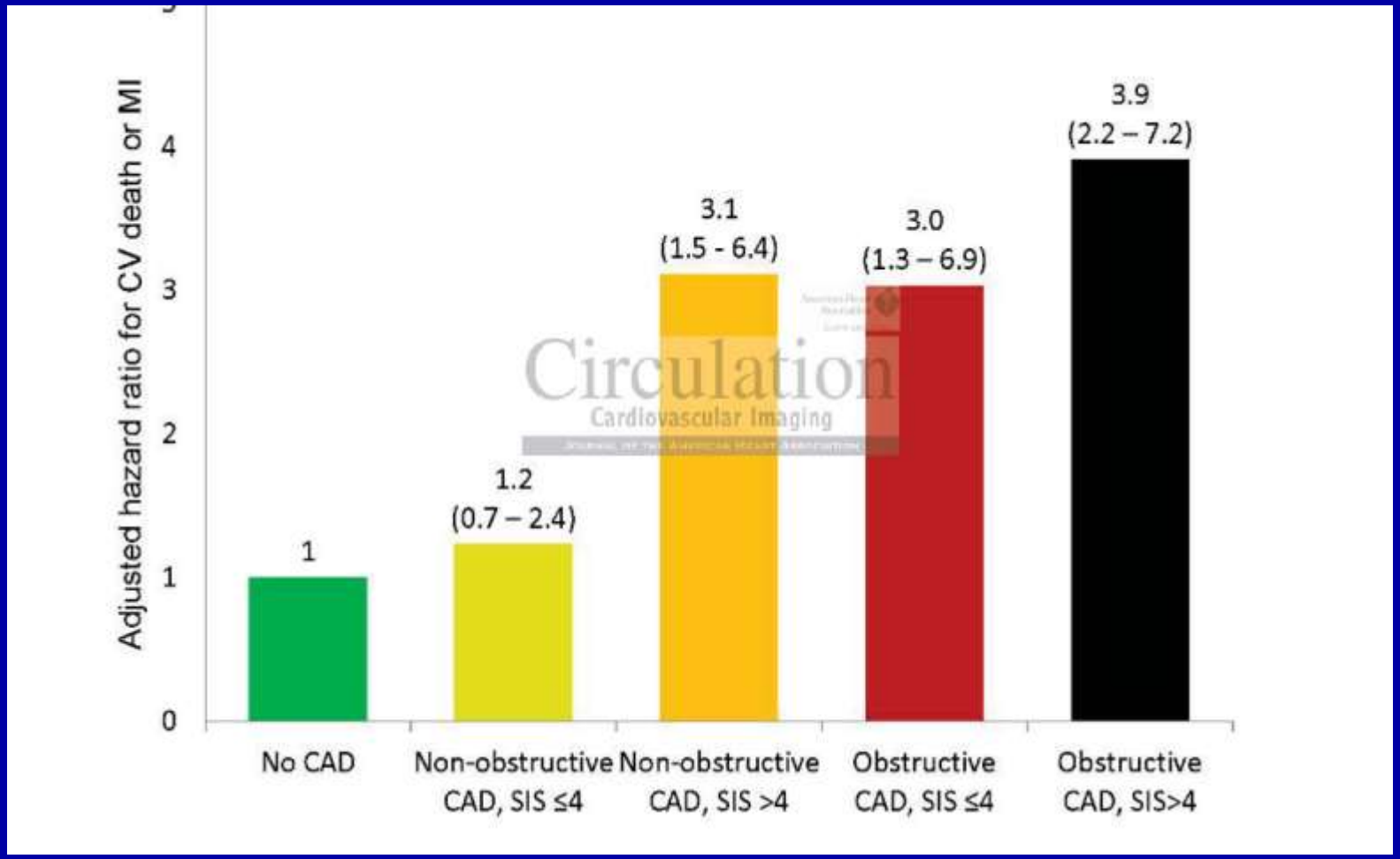
Bittencourt, M. S., et. al., (2014). Prognostic Value of Non-Obstructive and Obstructive Coronary Artery Disease Detected by Coronary Computed Tomography Angiography To Identify Cardiovascular Events. *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Extent of Coronary Atheroma Burden Predictive of CV Death and MI Regardless of Degree of Stenosis

- Primary outcome: CV death & non-fatal MI
- Secondary outcome: MACE
- Tertiary outcome: all-cause mortality

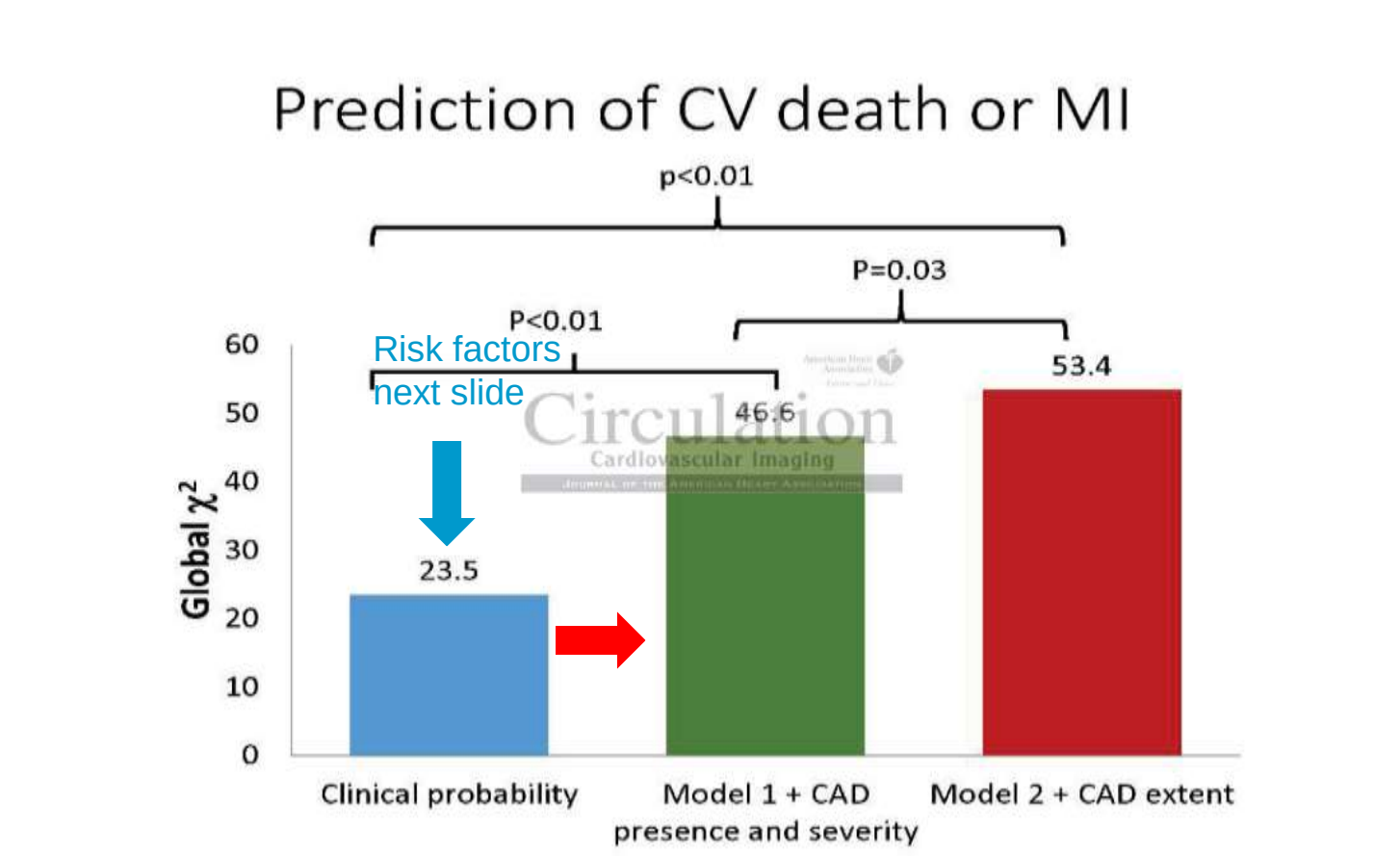
Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Extent of Coronary Atheroma Burden Predictive of CV Death and MI Regardless of Degree of Stenosis



Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Including Extent of Coronary Atheroma Enhances Predcition of CV Death and MI: presence of disease significantly out predicts risk factors and sx's



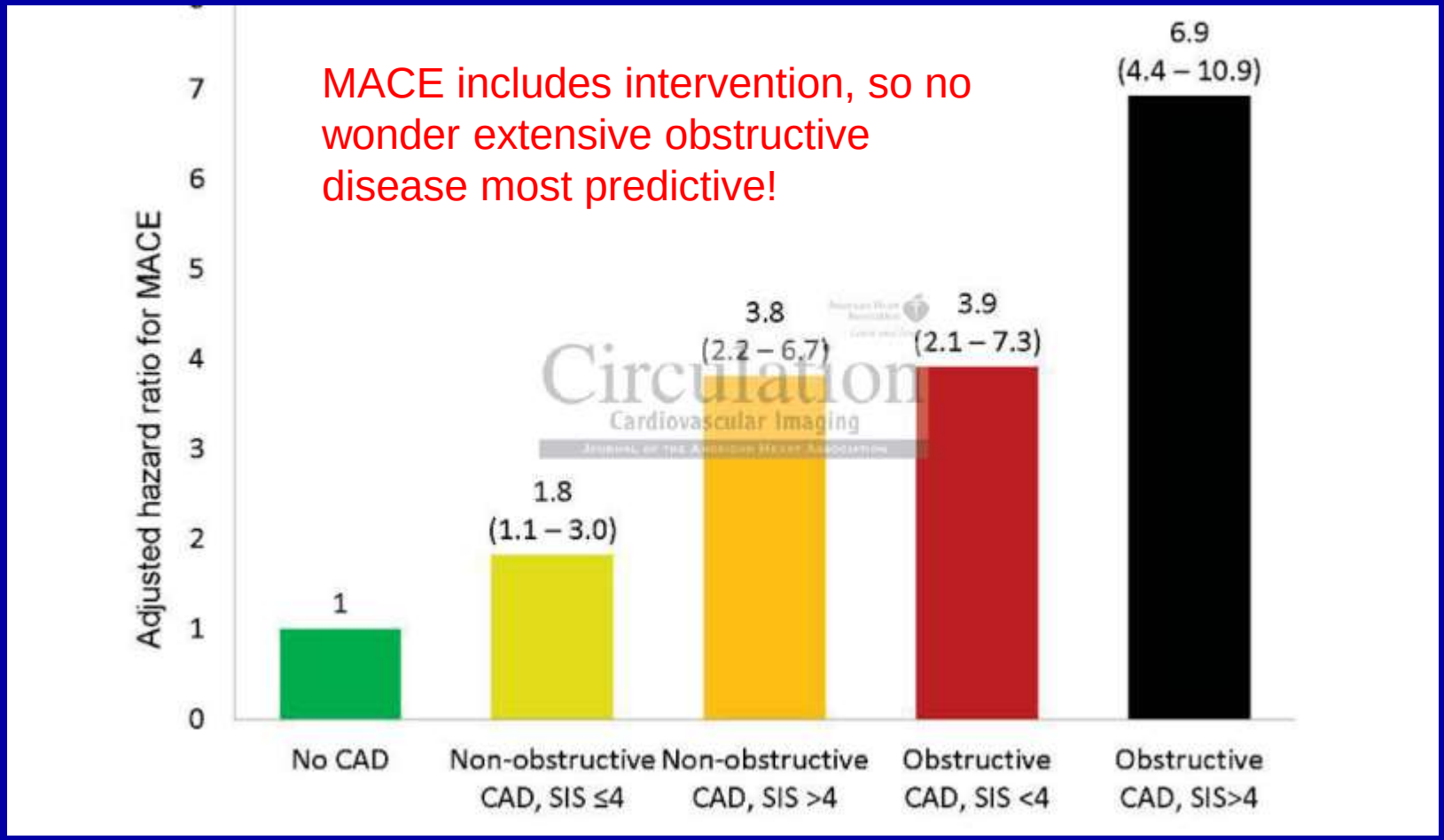
Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Risk Factors Utilized to Predict Risk: pale in predictability compared to presence of disease!

Variable			Choose response	Sum
Age	Men	Women		
	<40	<50	3	
	40–54	50–64	6	
	55	65	9	
Oestrogen status			Positive=−3	
Women only			Negative=+3	
Angina history			Typical=5	
Diamond method			Atypical=3	
			Non-anginal=1	
Diabetes?			2	
Hyperlipidaemia?			1	
Hypertension?			1	
Smoking? (any)			1	
First degree family history of CAD			1	
Obesity? BMI>27			1	
			Total score:	

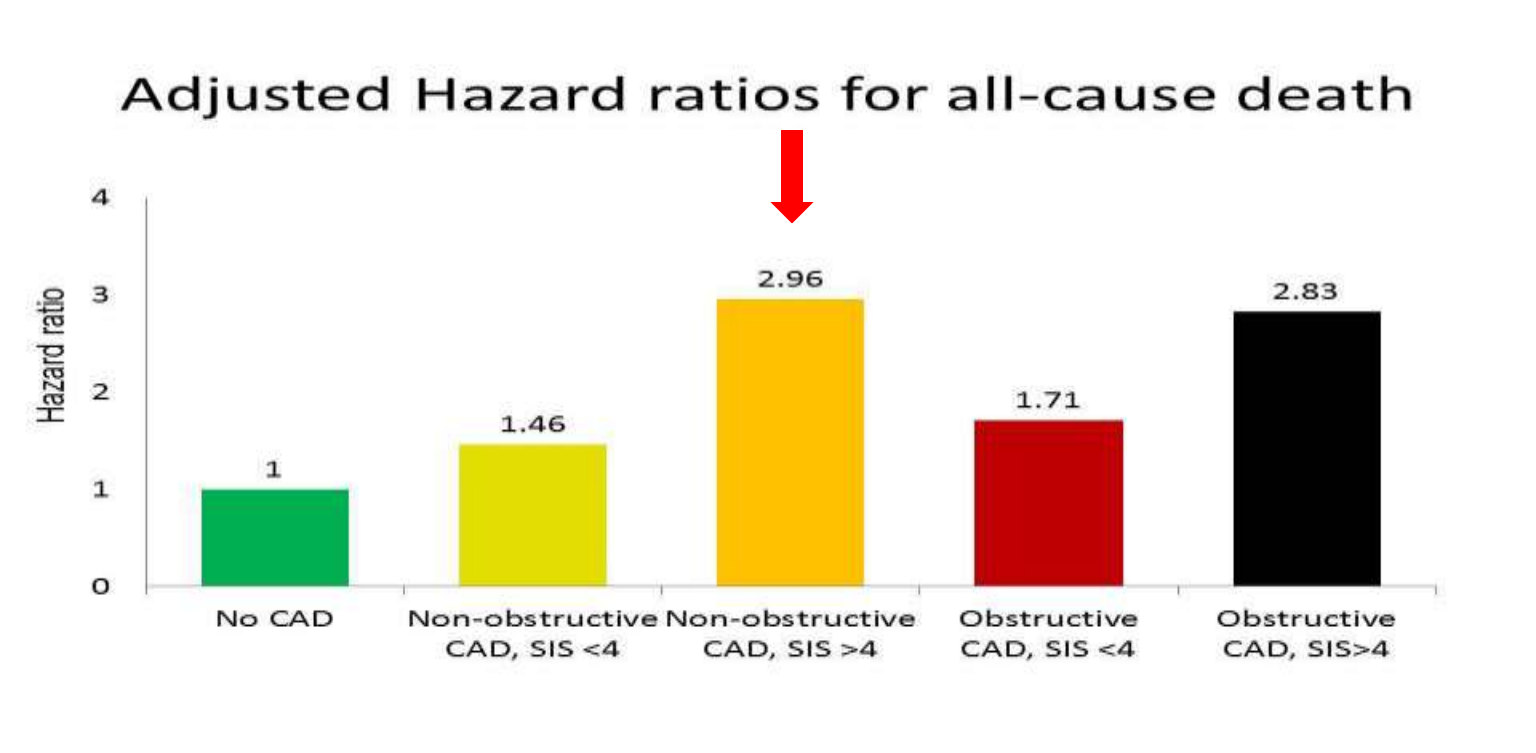
Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Extent of Coronary Atheroma Burden Predictive of MACE Regardless of Degree of Stenosis



Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Extent of Coronary Atheroma Burden Predictive of Dying Regardless of Degree of Stenosis



Adjusted hazard ratios for the incidence of all-cause death. Cox proportional hazard models adjusted for the clinical probability, which includes age, gender, risk factors and symptoms.

Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

Extent of Coronary Atheroma Burden Predictive of CV Death and MI Regardless of Degree of Stenosis

- Non-obstructive CAD is also associated with an increased risk of hard CV events, as well as, risk for revascularizations.

- There were coronary heart disease events even in pts with “no” (lumenology) CAD; 1% in 3.5 yrs.

- Presence of disease out predicts risk factors and sx’s! (BDM Platform appears strong and solid!)

Bittencourt, M. S., et. al., (2014). *Circulation: Cardiovascular Imaging*. doi: 10.1161/circimaging.113.001047

What about our position on calcification??

Coronary Calcification Pathophysiology

- SMC apoptosis results in fine microcalcification.
- Microcalcifications coalesce into larger masses involving the necrotic core and the surrounding collagen-rich extracellular matrix forming speckled fragmented calcification.
- Macrophage apoptosis exhibits large punctate, blocky appearing calcification.

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

Coronary Calcification Pathophysiology

- Progression of disease results in calcified sheets or plates.
- Calcified plates may fracture which results in the formation of nodular calcification accompanied by fibrin deposition.
- These nodules may protrude into the lumen or into the media.

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

Coronary Calcification Pathophysiology

- Luminal protrusion causes discontinuity of the collagen and endothelium with acute thrombosis.

- This only occurs in 2 to 7% of coronary thrombosis cases, but is more frequent (4%–14%) in the carotid plaques.

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

Coronary Calcification Clinical Implications

- Biomechanical models using coronary plaques from human autopsy cases suggest that calcification does not increase fibrous cap stress, whereas greater lipid area does.

- Autopsy studies have shown an inverse correlation between calcification and macrophage areas in coronary plaques from SCD victims.

- Imaging studies have demonstrated less calcification in ruptured or vulnerable plaques as compared with stable plaques.

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

Coronary Calcification Clinical Implications

- CT cannot identify microcalcification seen in early plaques.
- This includes calcification of both SMCs as well as macrophages.

Coronary calcification cannot see the early lesions

- CT can identify aggregated calcium which involves both large areas of adjoining necrotic core and collagen.

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

Coronary Calcification Clinical Implications

- Calcification is greater in men than in women especially in the premenopausal period.

- Blacks have less calcification than whites.

A zero coronary calcification score in women and Blacks may be misleading.

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

Coronary Calcification Clinical Implications

- There remain many unanswered questions, regarding the origin, mechanism, and purpose of calcification in human atherosclerosis.

- Current evidence, including statin treatment which results in increased calcification, suggests calcification is a marker of a stable, non-progressive atherosclerosis process.

The BDM position is supported

Otsuka, F., et. al. (2014). Has Our Understanding of Calcification in Human Coronary Atherosclerosis Progressed? *Arterioscler Thromb Vasc Biol*. doi: 10.1161/ATVBAHA.113.302642

What about the BDM Position that if you have any positive CACS, you have disease and risk; most of the plaque on first screening is un-calcified???

The Majority of Coronary Plaque Volume is Un-calcified

- 805 healthy adults with + famhx CAD;, mean age 51 ± 11 yrs.; 56% female; 39% African American; screened for CAD by CT angiography; plaque volumes (mm3) were quantified

- Prevalence of plaque was 58%-males; 36%-females

- Non-calcified plaque (NCP) accounted for most of the total plaque volume at all ages.

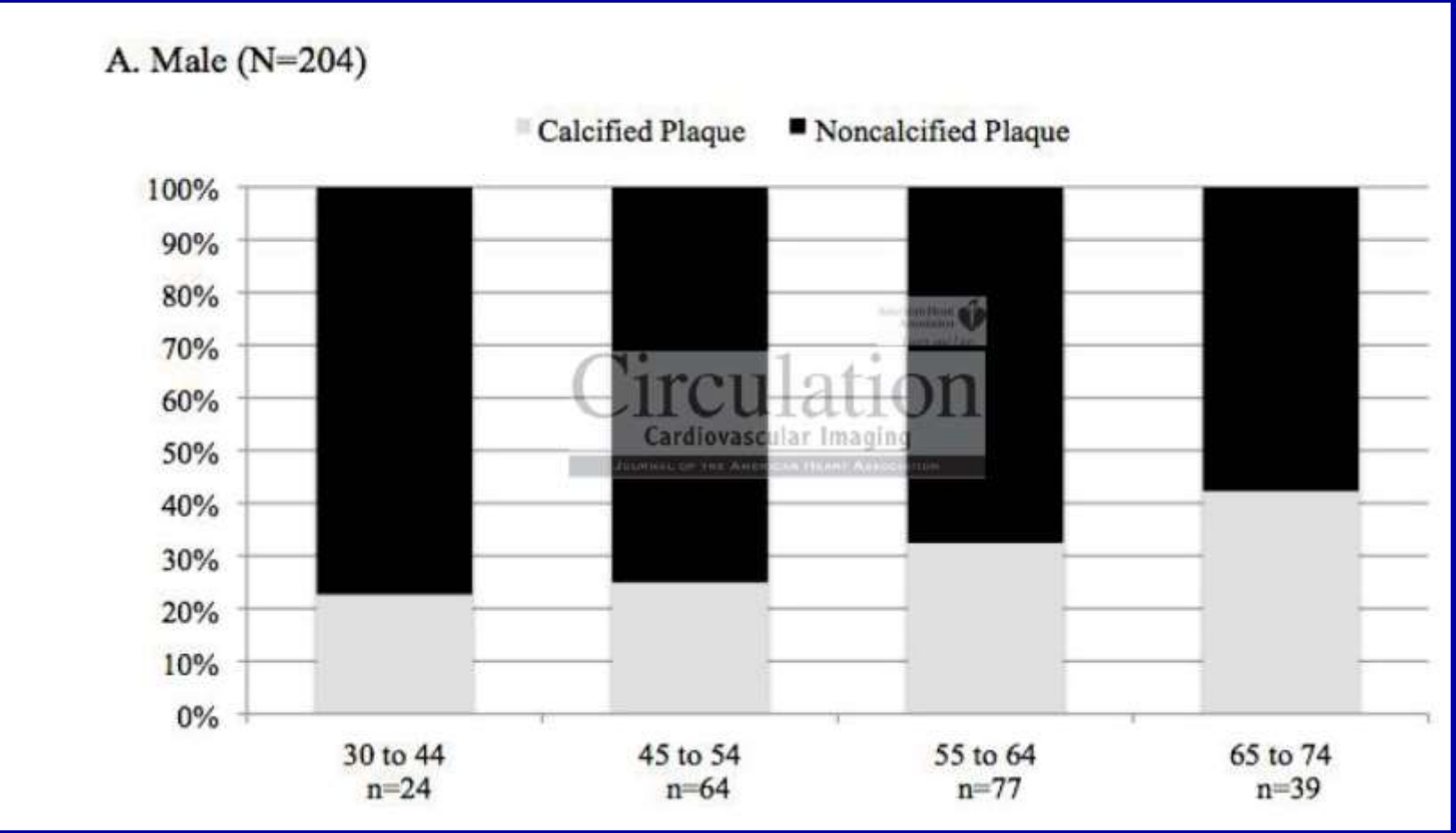
Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- NCP in subjects <55yo accounted for >70% of plaque in males; >80% females
- Coronary calcification is a late manifestation of atherosclerosis.

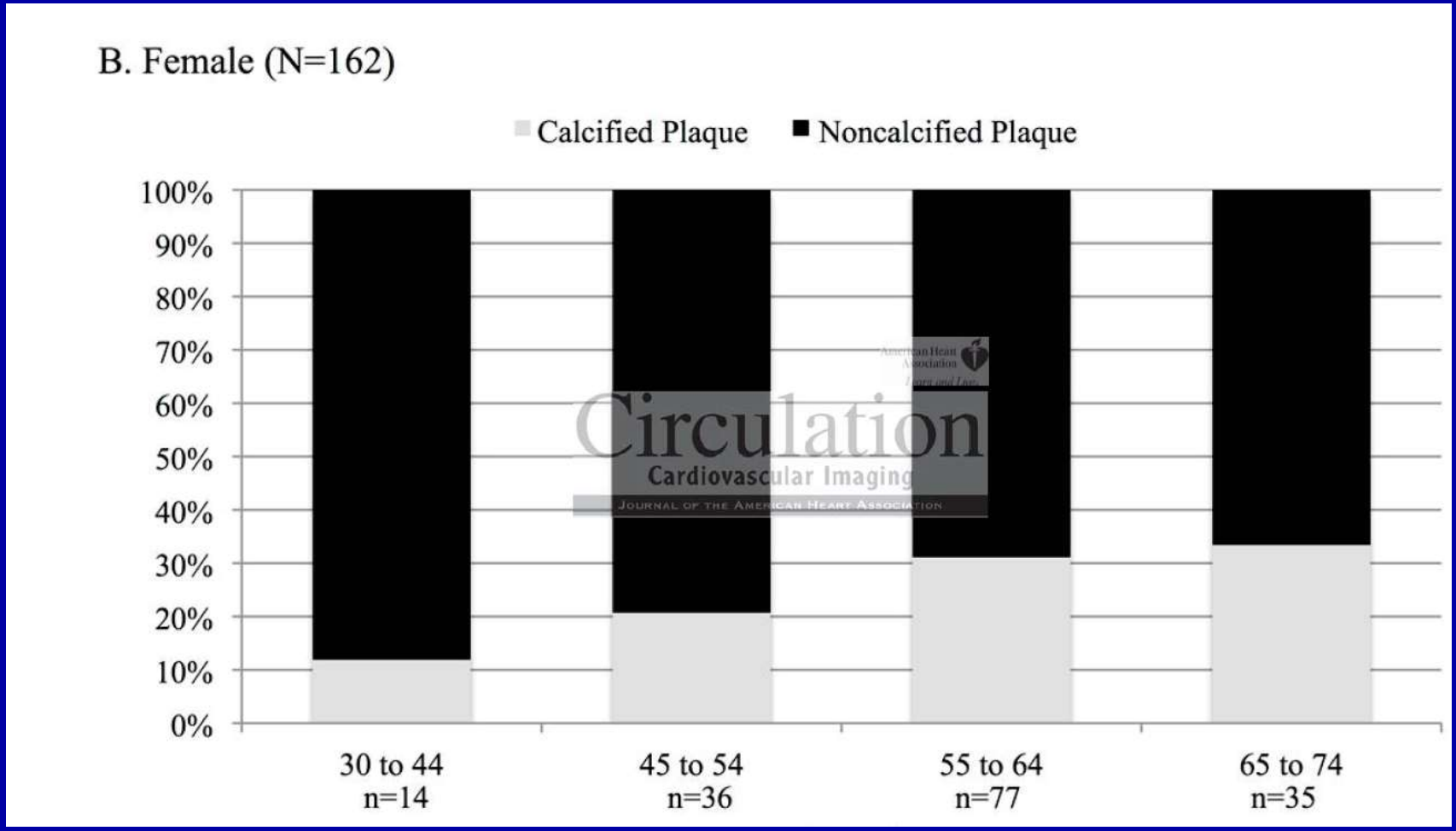
Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified



Kral, B. G., et. al. (2014). *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified



Kral, B. G., et. al. (2014). *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- Earlier stages of atherogenesis are represented by non-calcified or mixed composition plaques.
- These un-calcified plaques are particularly prone to plaque rupture, thrombosis, and acute CAD events.
- NCP volume was significantly associated with the presence of at least one stenosis >50% ($p<0.0001$), independent of all traditional risk factors.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- CAC cannot detect the true extent of coronary artery plaque.
- The extent of subclinical NCP, a putative precursor for CAD events, may have important implications for primary prevention.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- Females were twice as likely to have exclusively NCP compared to males, (16.8% vs 8.3%, p= 0.01).

- Subjects with a strong sibling history (n=49) were 3.0 times (95% CI 1.3–6.6) more likely to have any coronary plaque. That is I folks!!- thank goodness Amy manages my risk!

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

We are not done with this study!!

How well did FRS predict presence of CAD??

FRS was a Poor Predictor of Who had Coronary Plaque

FRS	Women with plaque	Men with plaque
Low	30%	50%
Intermediate	50%	75%

In intermediate risk women and men, LAD plaque was present in 50% and 70%, respectively!!!!

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

FRS was a Poor Predictor of Who had Coronary Plaque

- FRS failed to identify many patients with severe CAD-left main and/or 3-vessel disease

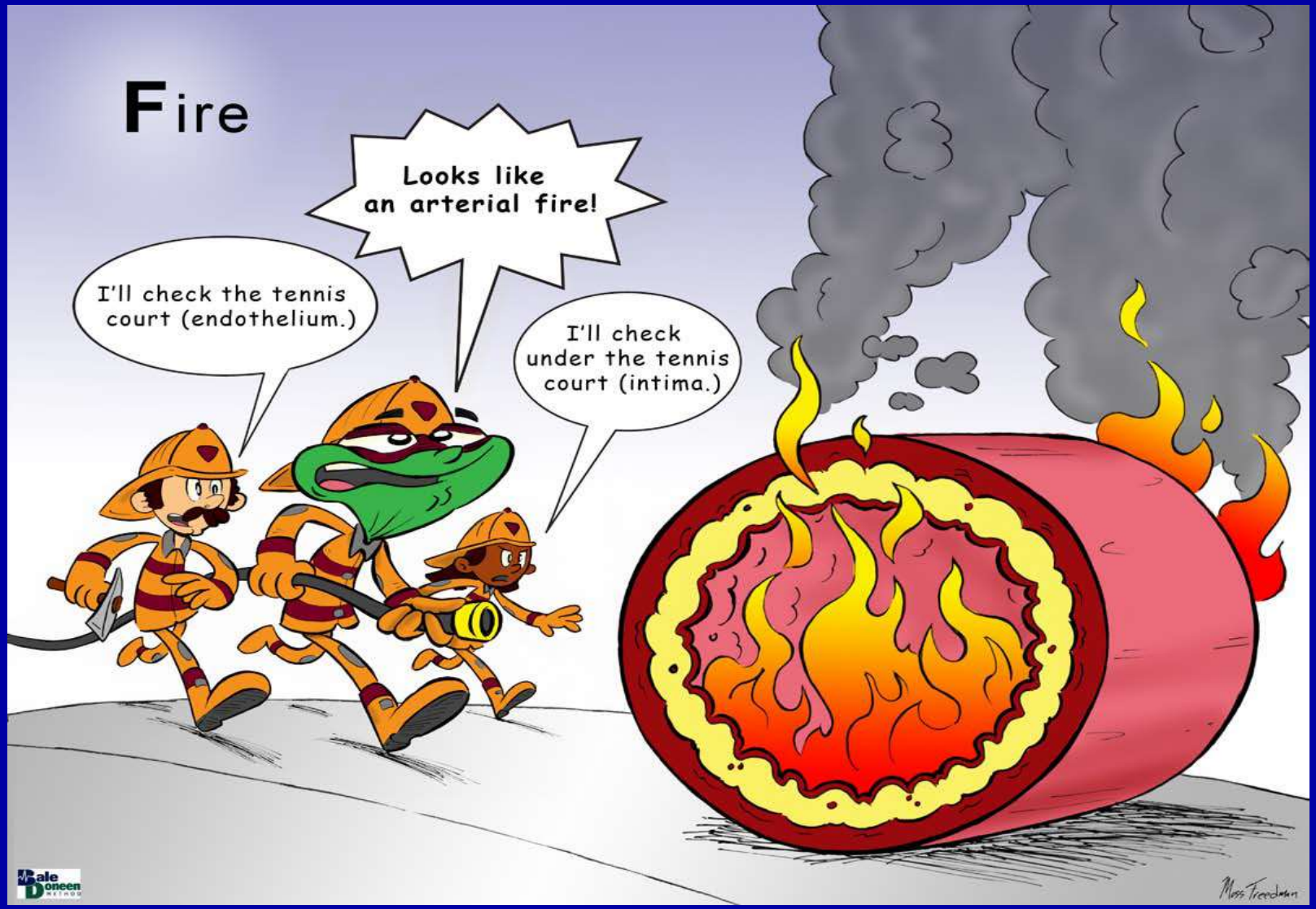
21% of females and 44% of males with this type of disease were intermediate FRS!!

The Majority of Coronary Plaque Volume is Un-calcified

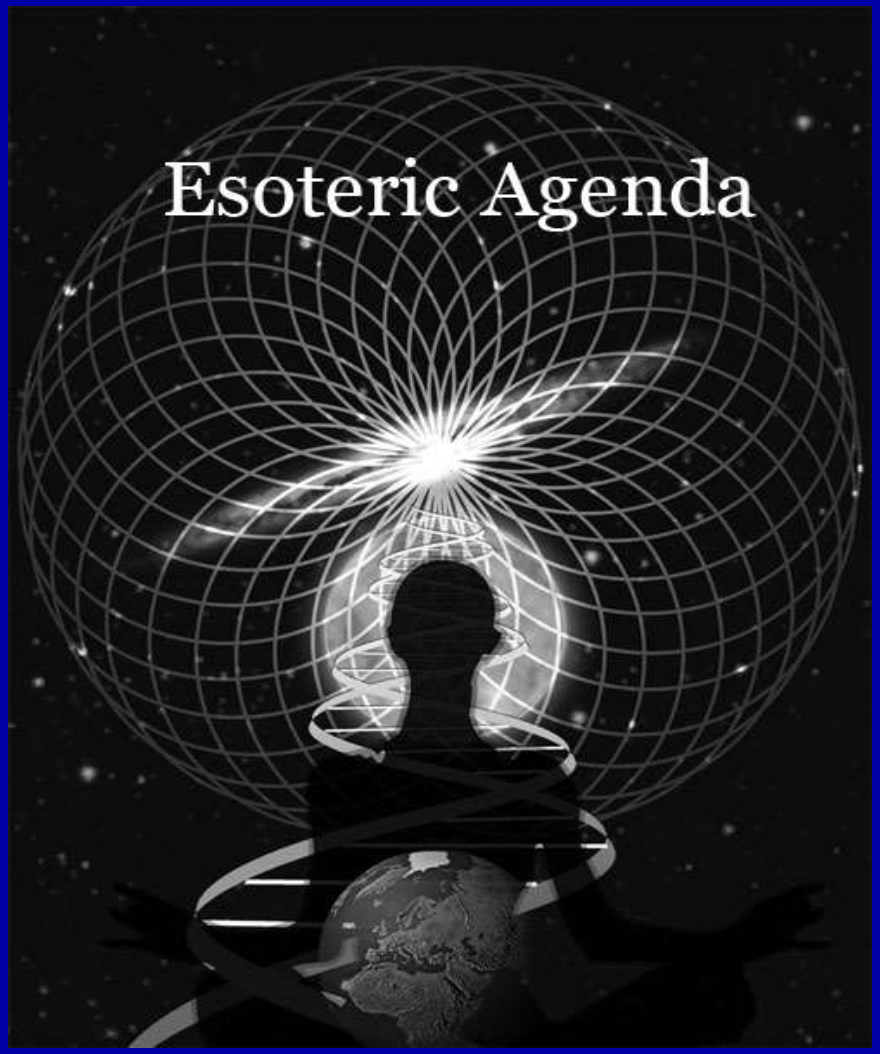
Study suggests that judging whether or not to administer aggressive primary prevention on CACS algorithms or on FRS may obviate appropriate risk reduction interventions.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

Inflammation



Not totally esoteric!



Atherosclerosis: Inflammation Regulation

- Endothelium (ECs) is a confluent monolayer barrier between the flowing blood and underlying tissue.
- When healthy it provides a non-adhesive and non-thrombotic surface.
- Interendothelial junctions tightly regulate permeability.
- ECs communicate chemically with the vascular smooth muscle cells (VSMC) to regulate vasomotor tone.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation-Krüppel-like factors

- Homeostasis depends on optimal EC function and laminar shear stress.
- Krüppel-like factors (KLFs) are central players in this homeostasis.
- KLFs are transcription factors located mainly in the nucleus of cells; currently 17 different KLFs.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation-Krüppel-like factors

- KLFs can act as either transcriptional activators or repressors.
- KLFs exert their effects via either direct DNA binding or through interaction with cofactors.
- KLF2 and KLF4 are highly expressed in ECs; increased with laminar flow and reduced at arterial branch points and other regions of turbulent flow.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation- KLFs & EC

- KLF2 and KLF4 are potent inducers of endothelial NO synthase and thrombomodulin.

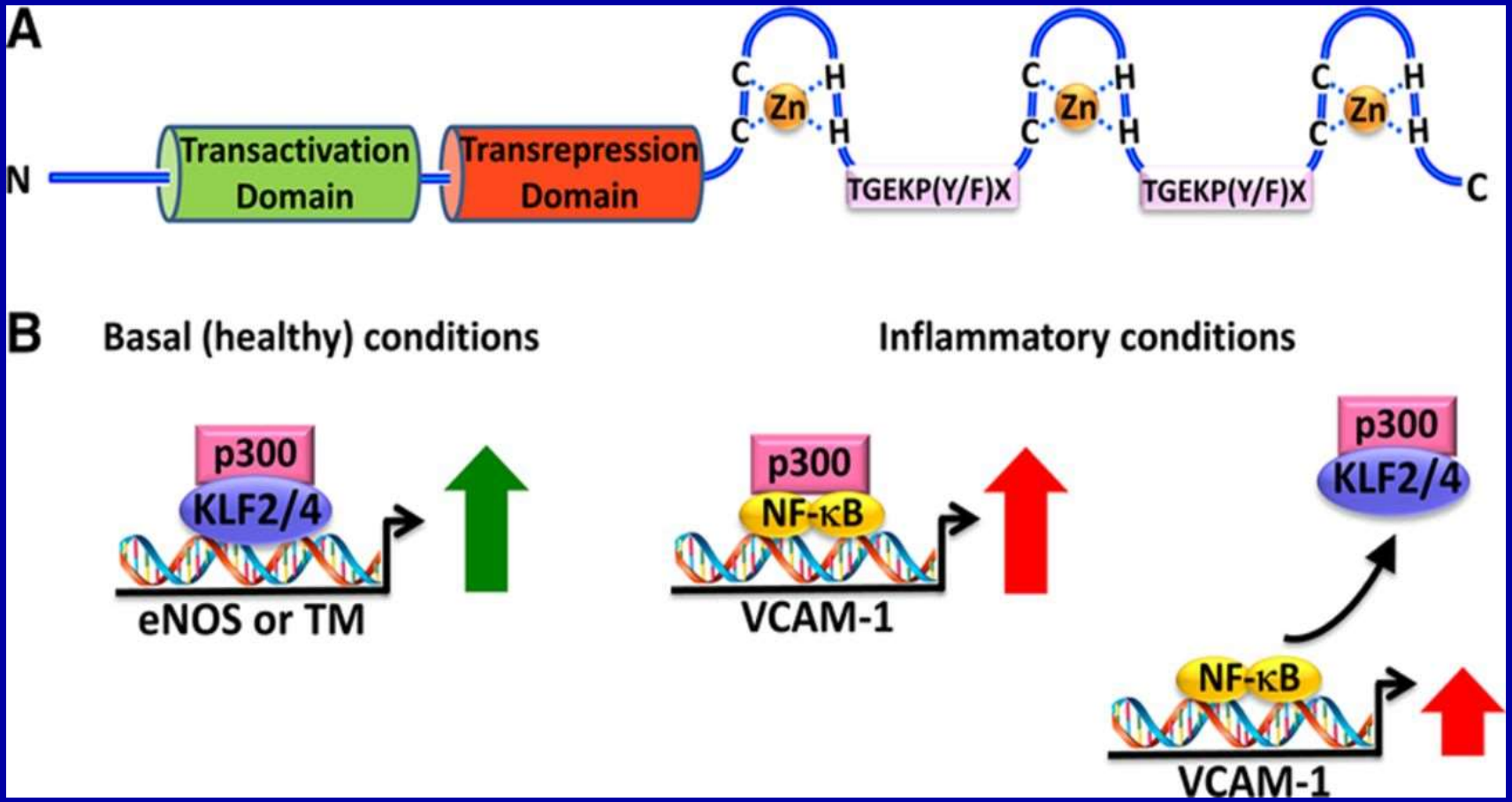
- They also inhibit cytokine-induced expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and other inflammatory mediators.

- KLF2 plays an essential role in EC permeability by regulating key junction proteins (ZO-1 and occludin).

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation Regulation

A, Schematic representation of common structure and functional domains for Krüppel-like factors (KLFs).



Jain M et al. Arterioscler Thromb Vasc Biol 2014;34:499-508

Atherosclerosis: Inflammation-KLFs & Immune Cells (ICs)

- KLF2 is a potent negative regulator of monocyte/macrophage proinflammatory activation.
- CAD pts have significantly lower KLF2 expression in circulating monocytes than do healthy subjects.
- KLF4 is a mediator of macrophage subset specification by regulating macrophage M1/M2 polarization.
- KLF4 levels are high in M2 and low in M1; response to IL-4 & IL-16 or LPS & interferon-γ, respectively.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation-KLFs & ICs

- Activation of naïve T cells can lead to induction of adaptive immunity and progression of atherosclerosis.
- KLF2 appears to help maintain T- lymphocyte quiescence.
- Studies suggest an anti-atherogenic role of KLF4 in regulating T-cell activation and proliferation.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation-VSMCs

- VSMCs are in the medial layer; the internal elastic lamina separates them from the intima and EC.
- VSMCs respond to blood-borne, EC-derived, and tissue metabolic signals; relaxing or contracting, controlling vasomotor tone.
- Synthetic activity and proliferative rate are low.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation- VSMCs

- In response to growth factors and cytokines produced by invading macrophages during atherogenesis, VSMCs migrate across the elastic lamina.

- They undergo a phenotypic switch from a relatively quiescent contractile cell to an inflammatory, proliferative cell.

- They take on characteristics of foam cells, elaborate inflammatory signals, and synthesize extracellular matrix proteins leading to the fibrous plaque cap.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Atherosclerosis: Inflammation-KLFs & VSMCs

- KLF4 & 5 seem to play a proatherogenic role in VSMC transformation.
- KLF15 is anti-atherogenic in terms of VSMC transformation.

Jain, M. K., Sangwung, P., & Hamik, A. (2014). Regulation of an Inflammatory Disease: Krüppel-Like Factors and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

Please tell me why this is not totally esoteric!!!

Atherosclerosis: Inflammation Regulation

- Exercise increases laminar shear stress and thus EC KLF2 and KLF4. - great
- Broccoli, grapes, red wine (resveratrol), and olive oil enhance KLF4 and KLF2 expression.
- Statins induce EC expression of KLF2 and KLF4.
- Cigarette smoke increases VSMC KLF4 expression.

Jain, M. K., *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 499-508.

CRP Does Not Cause Inflammation in Healthy Subjects

- Seven healthy adults; IV infusion of authentic natural purified human CRP; post-infusion exams & blood at 0.5, 4, 8, 24 hrs.; 2, 6 and 10 days.

- No increased proinflammatory cytokines; all acute phase reactants (other than CRP) remained normal throughout.

- No significant change in any of the clinical, physical, biochemical, coagulation, or hematologic parameters.

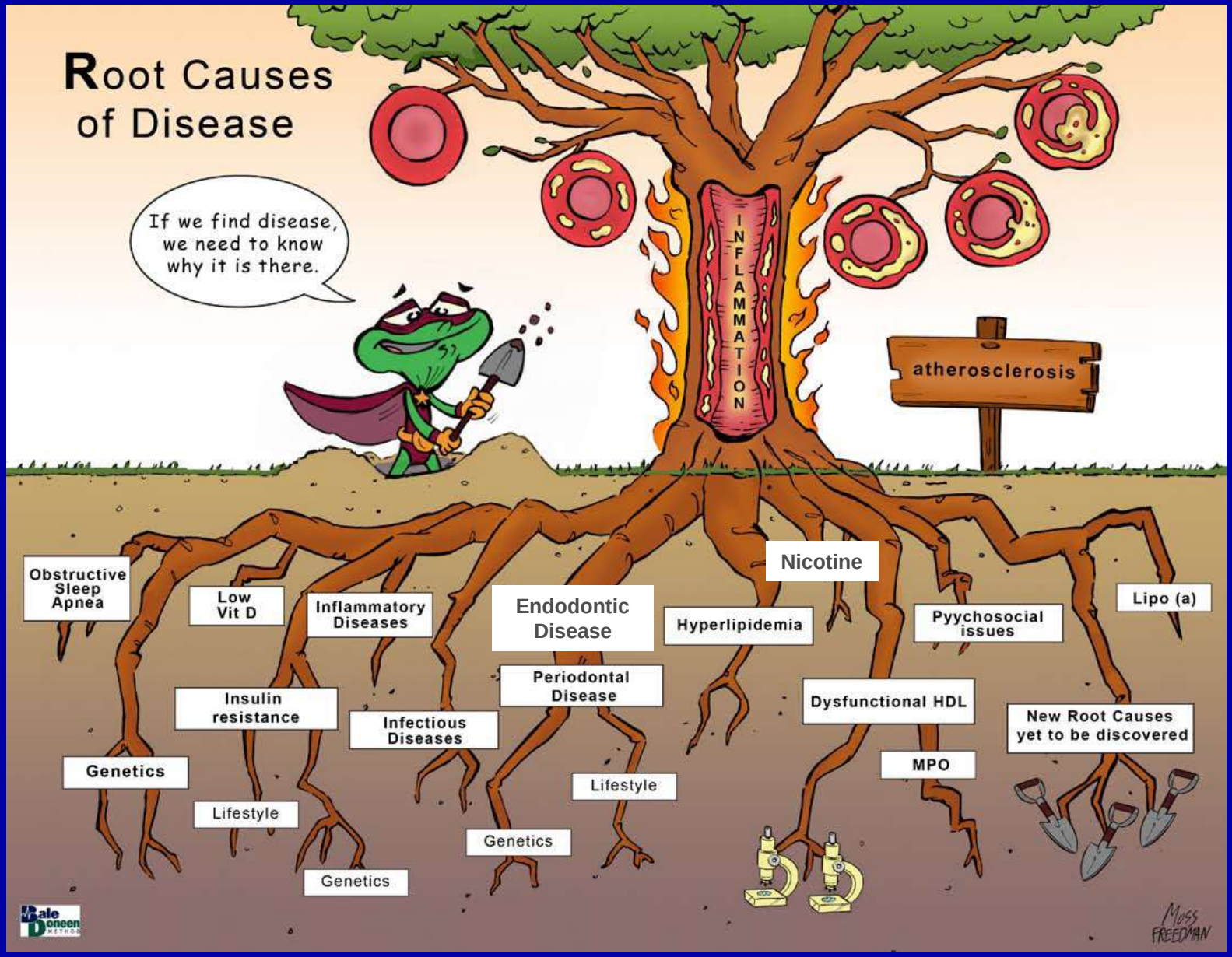
Lane, T., et. al. (2014). Infusion of pharmaceutical-grade natural human C-reactive protein is not proinflammatory in healthy adult human volunteers. *Circ Res, 114*(4), 672-676.

CRP Does Not Cause Inflammation in Healthy Subjects

- Conclusive demonstration that CRP itself does not have any proinflammatory effects in normal healthy adult subjects.

- There is no evidence to support a causative role of CRP in human atherosclerosis.

Lane, T., et. al. (2014). Infusion of pharmaceutical-grade natural human C-reactive protein is not proinflammatory in healthy adult human volunteers. *Circ Res, 114*(4), 672-676.



Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- 7,730 white Jupiter pts; median lipo (a) of 23 nmol/L at baseline; evaluated baseline and on-rx lipo (a) as independent risk for CVE.

- Mendelian randomization studies support a causal role of Lp(a) in CVD pathogenesis.

- Does this remain the case even in the face of potent statin therapy?

Khera, A. V., et. al. (2014). Lipoprotein(a) Concentrations, Rosuvastatin Therapy, and Residual Vascular Risk: An Analysis From the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- The median change in Lp(a) with rosuvastatin and placebo was zero.
- No relationship was noted between change in LDL cholesterol and change in Lp(a) with statin rx.
- During a median follow-up of 2.0 yrs, the primary and expanded (+all-cause mortality) CVD end points occurred in 210 and 283 pts; rosuva & placebo respectively

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- Baseline Lp(a) was associated with increased risk of CVD, with a fully adjusted HR per 1-SD increment in ln Lp(a) of 1.18 (95% CI, 1.03–1.35) and 1.21 (95% CI, 1.08–1.36) for the primary and expanded end point, respectively.

- Also a significant increased risk in the highest quartile Lp(a) (>50 nmol/L) compared to lowest.

adjusted HR of

1.64 (95% CI, 1.12–2.41) for the primary end point

1.61 (95% CI, 1.16–2.25) for the expanded end point.

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

The baseline Lp(a) association with CVD did not differ according to randomized treatment group.

Furthermore, the association was similar across clinically relevant clinical subgroups.

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- On-treatment with rosuva. Lp(a) concentrations were similarly associated with residual risk of CVD for each SD change in Lp(a)

adjusted HRs of 1.27 (95% CI, 1.01–1.59) for the primary end point

1.29 (95% CI, 1.07–1.56) for the expanded end point

adjustment for on-statin concentrations of HDL, LDL, TG, hsCRP did not alter the results

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

- Pts whose on-statin Lp(a) was ≥50 mg/dL

HR-1.67; (95% CI, 0.93–3.02) P=0.09

HR-1.54; (95% CI, 0.93–2.55) P=0.09

primary and expanded end points, respectively

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

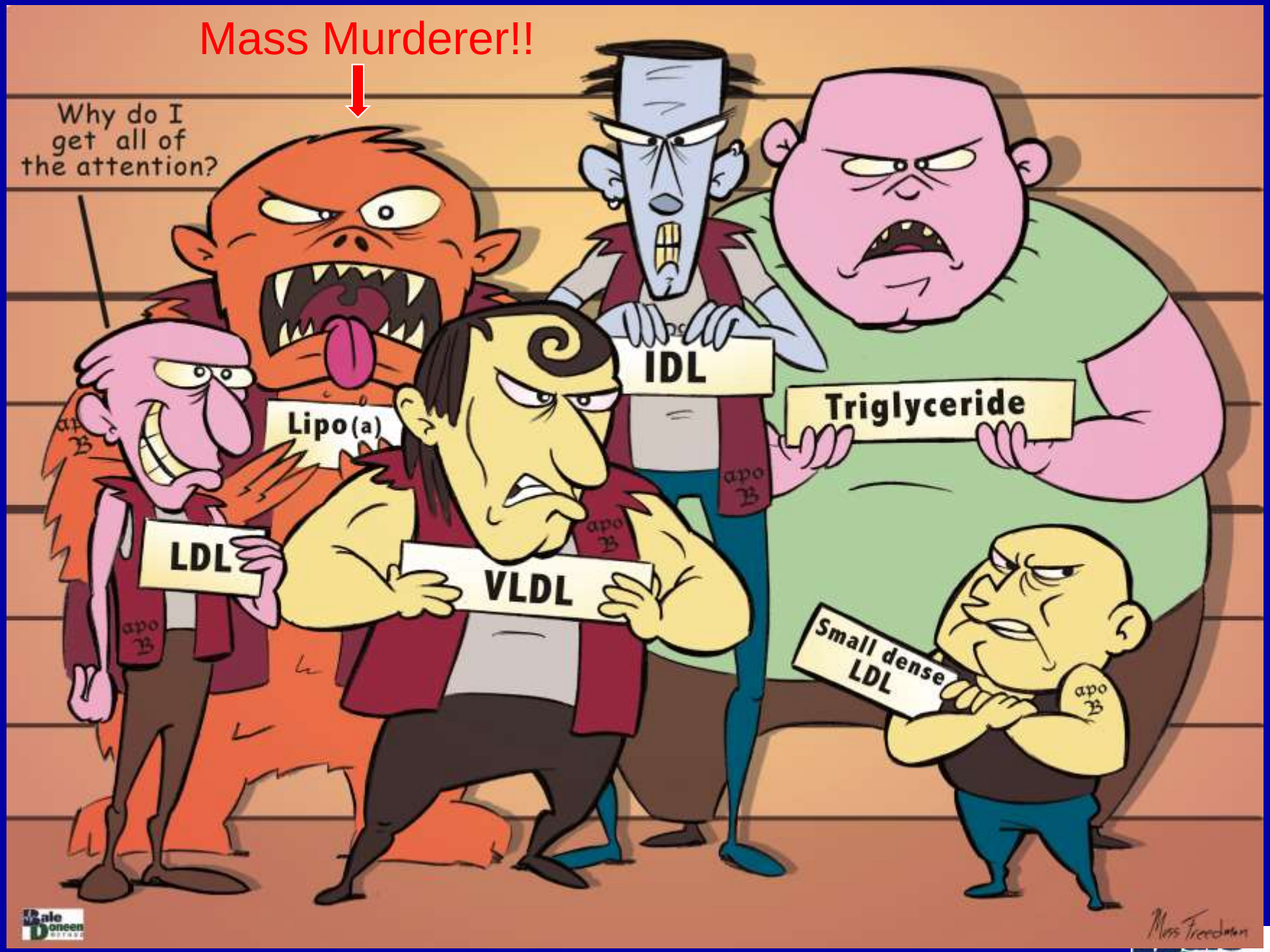
There was no evidence of interaction by ethnicity when the model involved all ethnic groups: total Jupiter population of 9,591

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.

Lipo (a) Continues to Drive CV Risk Despite Statin Therapy

Despite potent statin therapy with achievement of very low LDL cholesterol (median on-treatment LDL cholesterol 54 mg/dL), baseline and on-statin Lp(a) concentrations were associated with residual risk of CVD independent of other risk factors, including LDL cholesterol.

Khera, A. V., et. al. (2014). *Circulation, 129*(6), 635-642.


Mass Murderer!!
Why do I get all of the attention?
Lipo(a)
LDL
VLDL
IDL
Triglyceride
Small dense LDL
apo B

ABO Blood Type CV Risk Much More Involved Than Just Cholesterol

- 6,476 undergoing coronary angiography; observed increased risk of CAD in non-O blood types; evaluated data to determine contribution from cholesterol
- 4.9% difference in >50% stenosis in ≥1 coronary arteries between non-O type and O type p=.0004
- 3.5% difference in MI risk between non-O type and O type p=.008

Chen, Y., et. al. (2014). Analysis of Circulating Cholesterol Levels as a Mediator of an Association Between ABO Blood Group and Coronary Heart Disease. *Circulation: Cardiovascular Genetics, 7*(1), 43-48.

ABO Blood Type CV Risk Much More Involved Than Just Cholesterol

- 10% of difference in CAD risk was mediated by increased LDL-C
- 11% of difference in MI risk was mediated by increased LDL

Chen, Y., et. al. (2014). Analysis of Circulating Cholesterol Levels as a Mediator of an Association Between ABO Blood Group and Coronary Heart Disease. *Circulation: Cardiovascular Genetics, 7*(1), 43-48.

A1c Levels Independently Associated with White Matter Disease (WMD) in Stroke Patients

- 512 pts; 1st ischemic stroke; mean age, 68.5; 37.5% women; WMD dx'ed- MRI; 90% had WMD

- Assessed vascular risk factors (DM, HTN, atrial fibrillation, hypercholesterinemia, and current smoking) and labs (creat., lytes, RBC, leukocytes, lipids, A1c)

Rozanski, M., et. al. (2014). Elevated Levels of Hemoglobin A1c Are Associated With Cerebral White Matter Disease in Patients With Stroke. *Stroke*. doi: 10.1161/STROKEAHA.114.004740

A1c Levels Independently Associated with White Matter Disease (WMD) in Stroke Patients

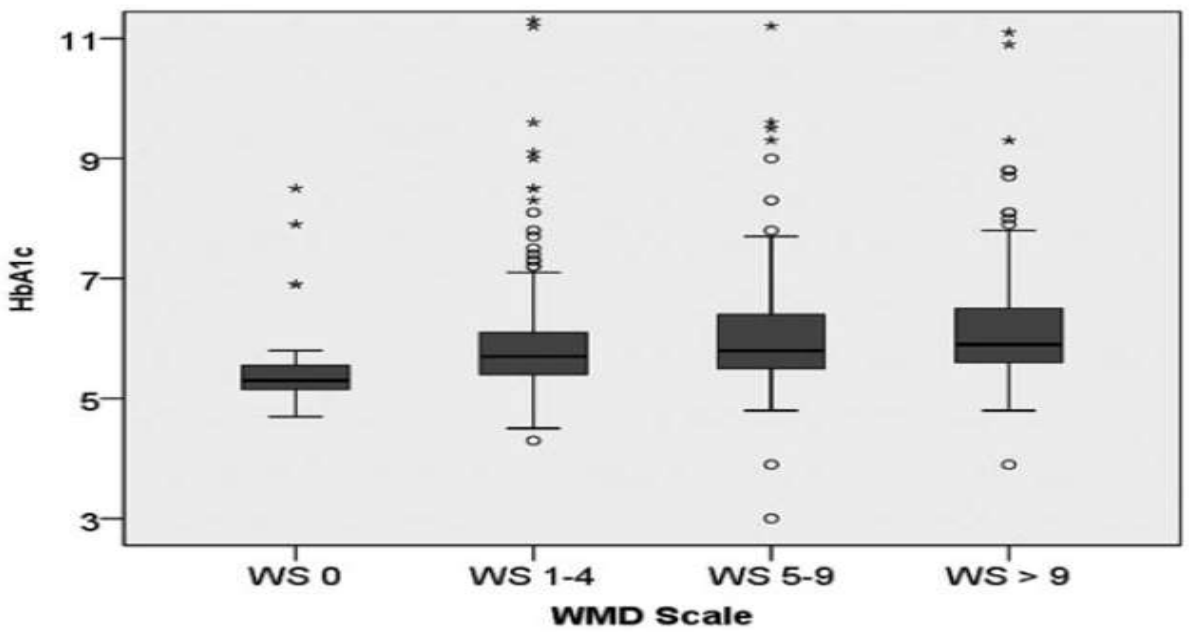


Figure 2. Association between levels of hemoglobin A1c (HbA1c) and extent of cerebral white matter disease (WMD). HbA1c ranges in percentages and extent of WMD (divided into groups according to Wahlund score [WS]). The difference in HbA1c ranges between patients without WMD (WS 0) and groups with any sign of WMD was statistically significant in multiple regression analysis (P=0.003).

Rozanski, M., et. al. (2014). *Stroke*. doi: 10.1161/STROKEAHA.114.004740

A1c Levels Independently Associated with White Matter Disease (WMD) in Stroke Patients

In multiple regression analysis, age, arterial hypertension, and elevated levels of HbA1c ($P<0.05$) remained independently associated with the extent of WMD.

Interesting: no association with lipids – mean HDL was 50.7 mg/dL in all groups

Rozanski, M., et. al. (2014). Elevated Levels of Hemoglobin A1c Are Associated With Cerebral White Matter Disease in Patients With Stroke. *Stroke*. doi: 10.1161/STROKEAHA.114.004740

Small Intestine is an Insulin Sensitive Organ

- 20 duodenal specimens; obese bariatric surgery pts; paired for age, sex, BMI & IR (HOMA)

- Insulin signaling, inflammatory biomarkers, oxidative stress, and lipoprotein assembly were assessed.

Veilleux, A., et. al. (2014). Intestinal Lipid Handling: Evidence and Implication of Insulin Signaling Abnormalities in Human Obese Subjects. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 644-653. doi: 10.1161/atvbaha.113.302993

Small Intestine is an Insulin Sensitive Organ

- The intestine of IR subjects showed defects in insulin signaling; high oxidative stress and inflammation.

- The intestine of IR subjects also demonstraged enhanced a lipogenesis rate and apolipoprotein B-48 biogenesis along with exaggerated triglyceride-rich lipoprotein production.

Veilleux, A., et. al. (2014). Intestinal Lipid Handling: Evidence and Implication of Insulin Signaling Abnormalities in Human Obese Subjects. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 644-653. doi: 10.1161/atvbaha.113.302993

Small Intestine is an Insulin Sensitive Organ

- The small intestine regulates lipid metabolism in fed and fasting states and may, therefore, be central in lipid homeostasis in both normal physiology and pathophysiological conditions.

- Lipid synthesis as well as lipoprotein assembly and secretion occur in this tissue, and these metabolic pathways are sensitive to several hormones such as insulin.

Veilleux, A., et. al. (2014). Intestinal Lipid Handling: Evidence and Implication of Insulin Signaling Abnormalities in Human Obese Subjects. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 644-653. doi: 10.1161/atvbaha.113.302993

Periodontal Disease (PD) Associated with CIMT Progression

- 420 pts; 68 yo ± 8 yrs.; perio probing depths and DNA for 11 pathogens; CIMT; baseline and 3 yr. follow-up measurements.

- Analyzed longitudinal change in the extent of sites with a ≥3-mm probing depth and longitudinal change in the relative predominance of causative bacteria of PD with amount of CIMT progression.

Desvarieux, M., et. al. (2013). Changes in clinical and microbiological periodontal profiles relate to progression of carotid intima-media thickness: the oral infections and vascular disease epidemiology study. *J Am Heart Assoc, 2*(6), e000254. doi: 10.1161/JAHA.113.000254

Periodontal Disease (PD) Associated with CIMT Progression

Eleven pathogens tested by DNA:

- *Aggregatibacter actinomycetemcomitans* -Aa
- *Porphyromonas gingivalis* –Pg
- *Tannerella forsythia* - Tf
- *Treponema denticola* - Td
- *Prevotella intermedia* – Pi
- *Fusobacterium nucleatum* – Fn
- *Micromonas micros* – Mm
- *Campylobacter rectus* – Cr
- *Eikenella corrodens* – Ec
- *Veillonella parvula* - Vp
- *Actinomyces naeslundii* - An

High Risk Etiologic

Intermediate Risk Putative

Healthy

Desvarieux, M., et. al. (2013). *J Am Heart Assoc, 2*(6), e000254. doi: 10.1161/JAHA.113.000254

Periodontal Disease (PD) Associated with CIMT Progression

- Longitudinal Δ in mean pocket depth (pd) or attachment loss (AL) was positively associated with IMT change:

pd- greatest worsening vs greatest improvement- +0.072 mm

AL- greatest worsening vs greatest improvement- +0.049 mm

- Baseline pd & AL did not predict progression; it was the change that predicted progression (good news ☺)

Desvarieux, M., et. al. (2013). Changes in clinical and microbiological periodontal profiles relate to progression of carotid intima-media thickness: the oral infections and vascular disease epidemiology study. *J Am Heart Assoc, 2*(6), e000254. doi: 10.1161/JAHA.113.000254

Periodontal Disease (PD) Associated with CIMT Progression

- Pathogen results demonstrated a significant relationship with CIMT progression solely in the high risk pathogen group.

- Changes in intermediate and or healthy pathogens was not related to amount of CIMT progression.

Desvarieux, M., et. al. (2013). Changes in clinical and microbiological periodontal profiles relate to progression of carotid intima-media thickness: the oral infections and vascular disease epidemiology study. *J Am Heart Assoc, 2*(6), e000254. doi: 10.1161/JAHA.113.000254

Periodontal Disease (PD) Associated with CIMT Progression

- ~0.1 mm difference in IMT change among pts with deteriorating vs improving periodontal health.
- Every 0.05 mm/yr increase=23% greater risk stroke*
- Every 0.03 mm/yr increase=2.3 fold increase in MI^

Desvarieux, M., et. al. (2013). *J Am Heart Assoc, 2*(6), e000254. doi: 10.1161/JAHA.113.000254

*Polak, J. F., et. al. (2011). Common Carotid Artery Intima-Media Thickness Progression as a Predictor of Stroke in Multi-Ethnic Study of Atherosclerosis. *Stroke, 42*(11), 3017-3021.

^Hodis, H. N., et. al. (1998). The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med, 128*(4), 262-269.

Periodontal Disease (PD) Associated with CIMT Progression

- Improvement in PD—defined both clinically and microbiologically—is associated with less progression in carotid atherosclerosis.

- Emphasizes the importance of periodontal care as a CV preventive health measure.

Desvarieux, M., et. al. (2013). *J Am Heart Assoc, 2*(6), e000254. doi: 10.1161/JAHA.113.000254

Bacteremia Increases CV Risk for Approximately One Month

- 4,389 hospitalized, + blood culture pts; matched for age, gender & time with ~40,000 community subjects & ~20,000 non-bacteremia acutely hospitalize pts.

- Followed one year for subsequent heart attacks and strokes; multivariable regression analyses for relative risk calculated

Dalager-Pedersen, M., et. al. (2014). Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006699

Bacteremia Increases CV Risk for Approximately One Month

- 158 bacteremia patients suffered a CV event within the first 30 days.

- Bacteremia pts compared to population controls were 20 times more likely to suffer an event

  RR- 20.86 (95% CI, 15.38-28.29)

- Bacteremia pts compared to hospitalized controls were twice as likely to suffer an event

  RR- 2.18 (95% CI, 1.80-2.65)

Dalager-Pedersen, M., et. al. (2014). Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006699

Bacteremia Increases CV Risk for Approximately One Month

- From 31 to 180 days, bacteremia pts were 64% more likely to have event than pop controls
- After 30 days there was no increased risk in bacteremia pts compared to hospital controls
- Community-acquired bacteremia is associated with increased short-term risk of MI and stroke.

Dalager-Pedersen, M., et. al. (2014). Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006699

Bacteremia Increases CV Risk for Approximately One Month

- Infections may increase CV event risk by inducing demand ischemia, decreasing myocardial contractility, or by causing endothelial dysfunction, coagulation disturbance, or direct platelet activation.

- The markedly increased risk only within the first 30 days after bacteremia supports a pathogenic link between acute inflammation associated with bacterial infection and vascular events.

keep in mind for dental procedures

Dalager-Pedersen, M., et. al. (2014). Risk for Myocardial Infarction and Stroke after Community-Acquired Bacteremia: A 20-Year Population-Based Cohort Study. *Circulation*. doi: 10.1161/CIRCULATIONAHA.113.006699

EDFROG IRA

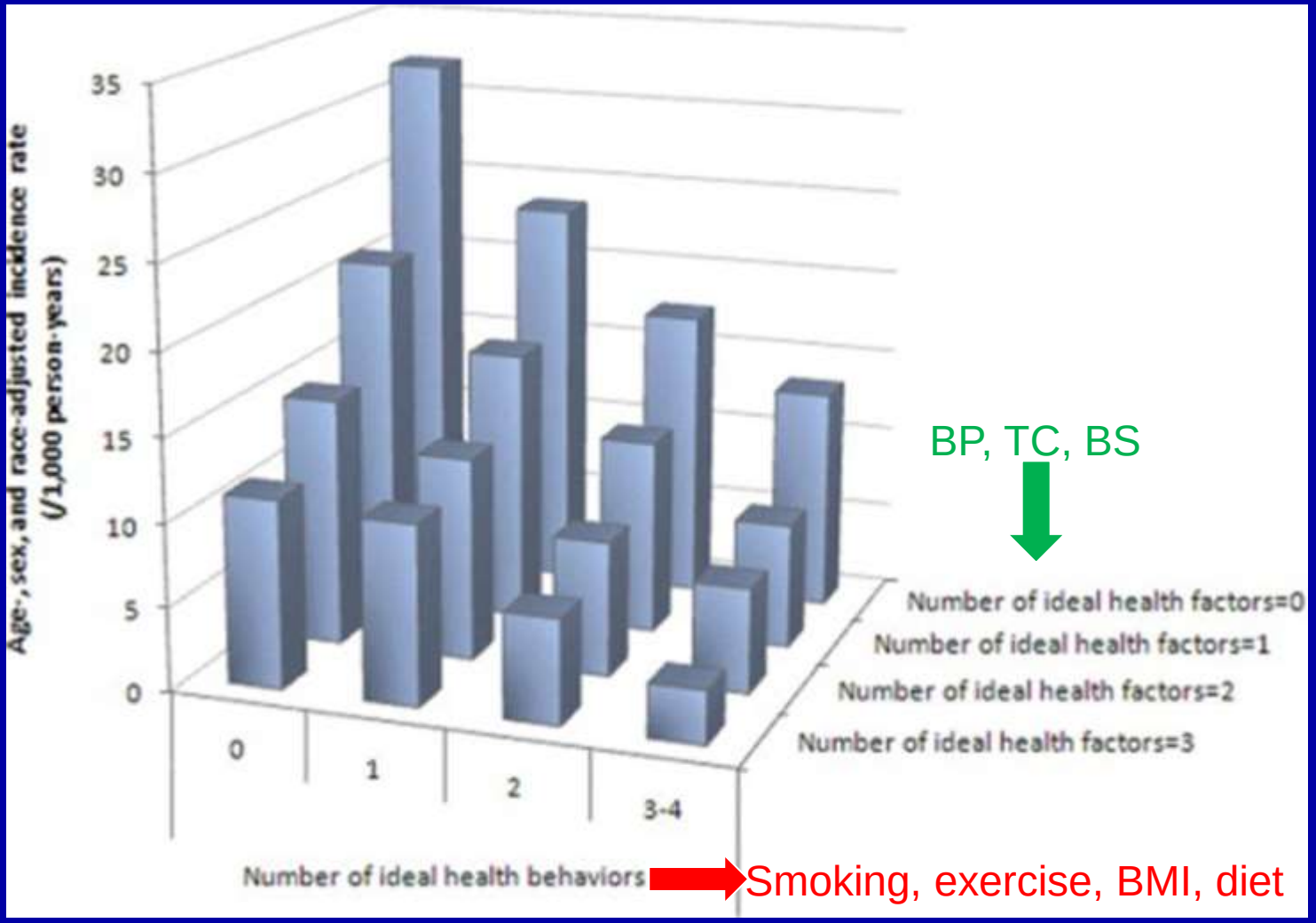
Education	Genetics	Individual Management
Disease	Optimal	Risk factor response
Fire	Roots	Assess Disease Annually

AHA 7 Essentials for Heart Health

- Do not smoke
- BMI ≤25
- 150’ moderate or 75’ vigorous exercise/wk
- Diet- at least four of these five: 1) 4 1/2 cups/day of fruit and vegetables; 2) ≥two 3.5-ounce fish/wk;
  3) ≤ three sugar-sweetened 12 oz. beverages/wk; 4) ≥ three 1-ounce servings of fiber-rich whole grains/day; 5) <1,500 milligrams salt/day
- TC <200 mg/dL
- BP < 120/80
- FBG <100 mg/dL

Published on line 1/20/2010: AHA ***Circulation***

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



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

Obesity

Obesity Incidence from 2003 to 2012 High and Static

- NHANES data; obesity = BMI ≥30
- The prevalence of obesity in the United States is still high at 16.9% in youth and 34.9% in adults.
- This is ~ same as 2003

Ogden, C. L., et. al. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA, 311*(8), 806-814.

Obesity Incidence from 2003 to 2012 High and Static

- Obesity prevalence in children 2 to 5 yo decreased from 14% in 2003-2004 to 8% in 2011-2012.

- Obesity prevalence in women ≥60 yo increased from 31.5% to more than 38%.

- These subgroup analyses did not adjust for multiple comparisons and should be interpreted with caution.

Ogden, C. L., et. al. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA, 311*(8), 806-814.

Upcoming Presentations

Upcoming Presentations

- 3/21-22/2014 – BDM Preceptorship & book signings LV, NV
- 3/26/14 – Brad speaking at Piedmont hospital – Atlanta, GA
- 3/28/14 – Brad speaking at Dental Institute for Systemic Health – Nashville, TN
- 4/18/14 – Brad delivering key note address at the International Clinical and Experimental Cardiology Conference – San Antonio, TX
- 4/26/14 – Amy and Brad speaking at PerioProtect meeting in LV,NV
- 5/15/14 – Brad speaking at dental meeting in Connecticut- TBA
- 6/7/14 – Brad speaking at DO 2014 Joint Annual Convention- San Antonio, TX

Open for Discussion