Bale/Doneen Live Chat Session

7/9/2014

5:30-6:30 pm PST

Bradley Bale, MD

Intention of the live chats

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

New Studies??!!!: OMG!

Supplement section at end!

Red Flags

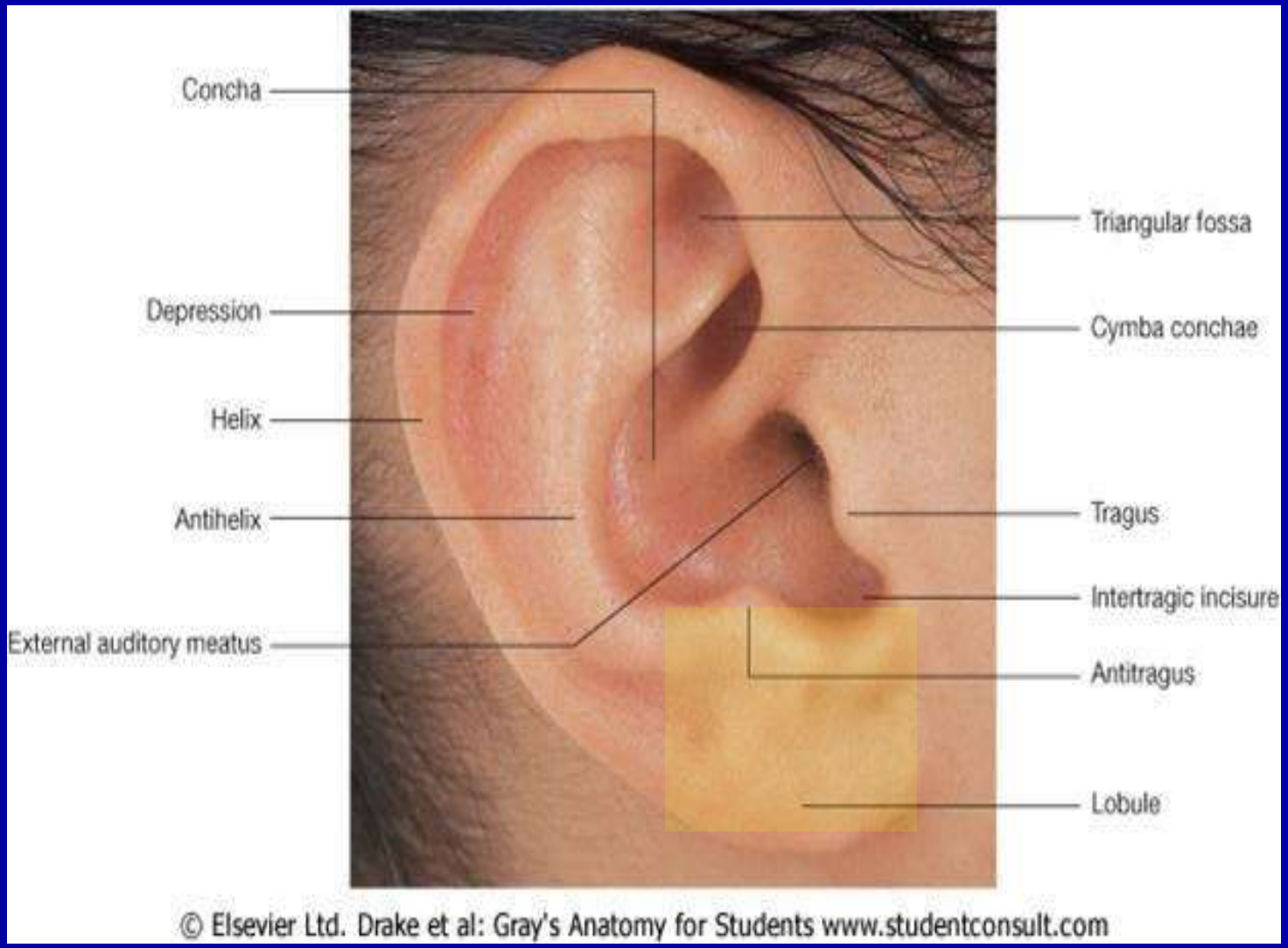
Ear Creases 'Frank's Sign' Associated with CVD Risk

Diagonal earlobe crease (DELC) in lobule, also known as Frank's sign, was first associated with CAD by Sanders T. Frank in 1973.

Since then has been shown to be associated with MACE, stroke and CIMT independently of traditional risk factors.

Qamar, A., Ioannides, K. L. H., Khetarpal, S. A., & Kiss, D. (2014). Bilateral Earlobe Creases and Coronary Artery Disease. *Circulation, 130*(1), 92-93.

Anatomy Refresher



Ear Creases ‘Frank’s Sign’ Associated with CVD Risk

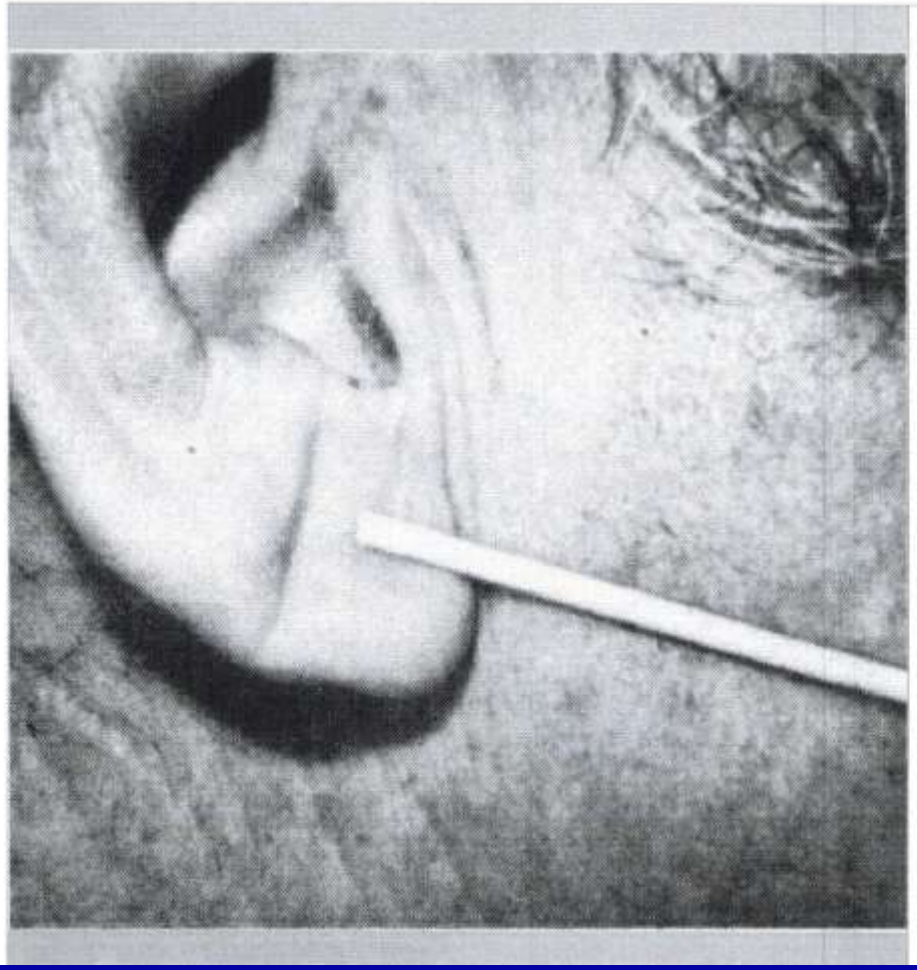
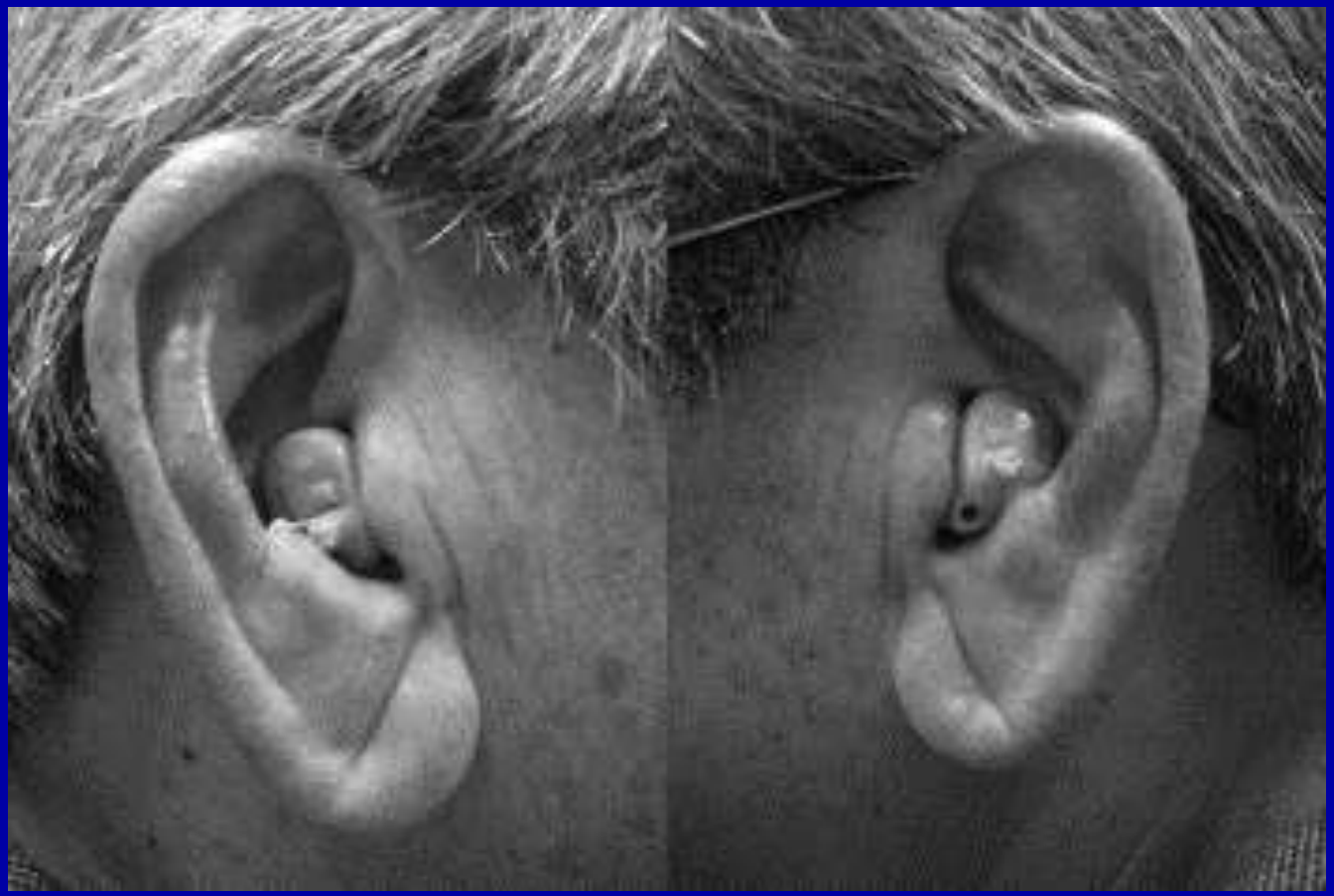


Figure 1. The Ear-Lobe Sign — a Deep Crease in the Lobule Portion of the Auricle.

Deep crease
lobule portion

Aural Sign of Coronary-Artery Disease. (1973). *New England Journal of Medicine, 289*(6), 327-328.

Ear Creases ‘Frank’s Sign’ Associated with CVD Risk

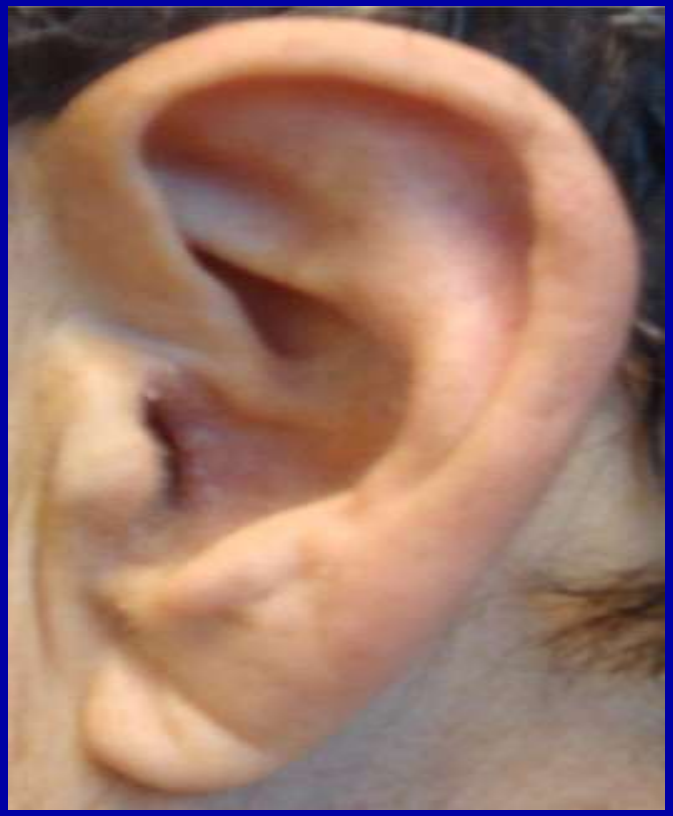


65 yo man with a calcified carotid artery atheroma on his panoramic radiograph and well-defined, bilateral diagonal earlobe creases.

Arthur H. Friedlander Association Between Clinically Identified Diagonal Earlobe Creases and Calcified Carotid Artery Atheromas Evidenced on Panoramic Radiography. Journal of Oral and Maxillofacial Surgery, Volume 68, Issue 1, 2010, 227 - 228

Dale Doneen METHOD

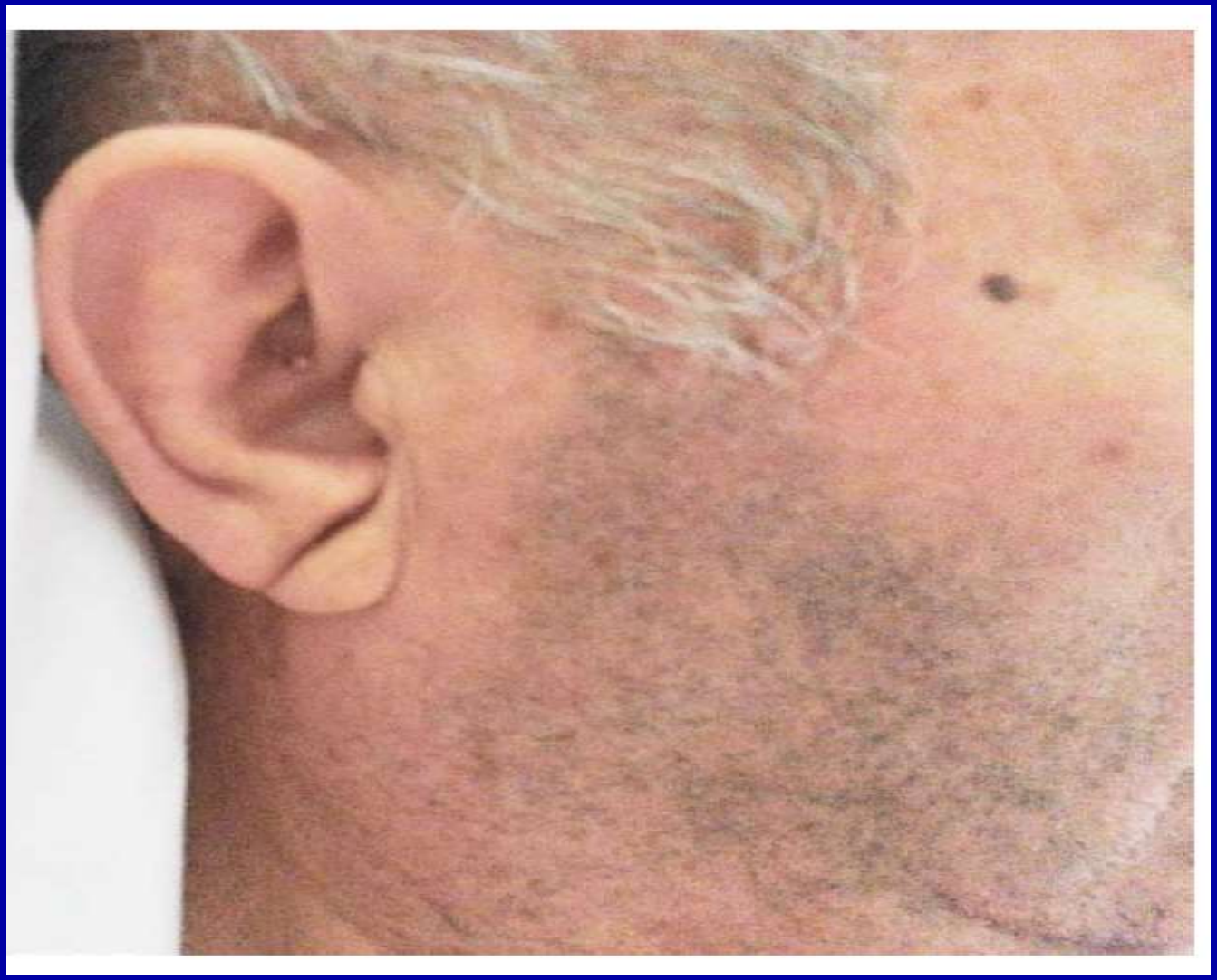
Ear Creases ‘Frank’s Sign’ Associated with CVD Risk



Diagonal ear lobe crease.

Haim Shmilovich , et. al. Relation of Diagonal Ear Lobe Crease to the Presence, Extent, and Severity of Coronary Artery Disease Determined by Coronary Computed Tomography Angiography The American Journal of Cardiology, Volume 109, Issue 9, 2012, 1283 - 1287

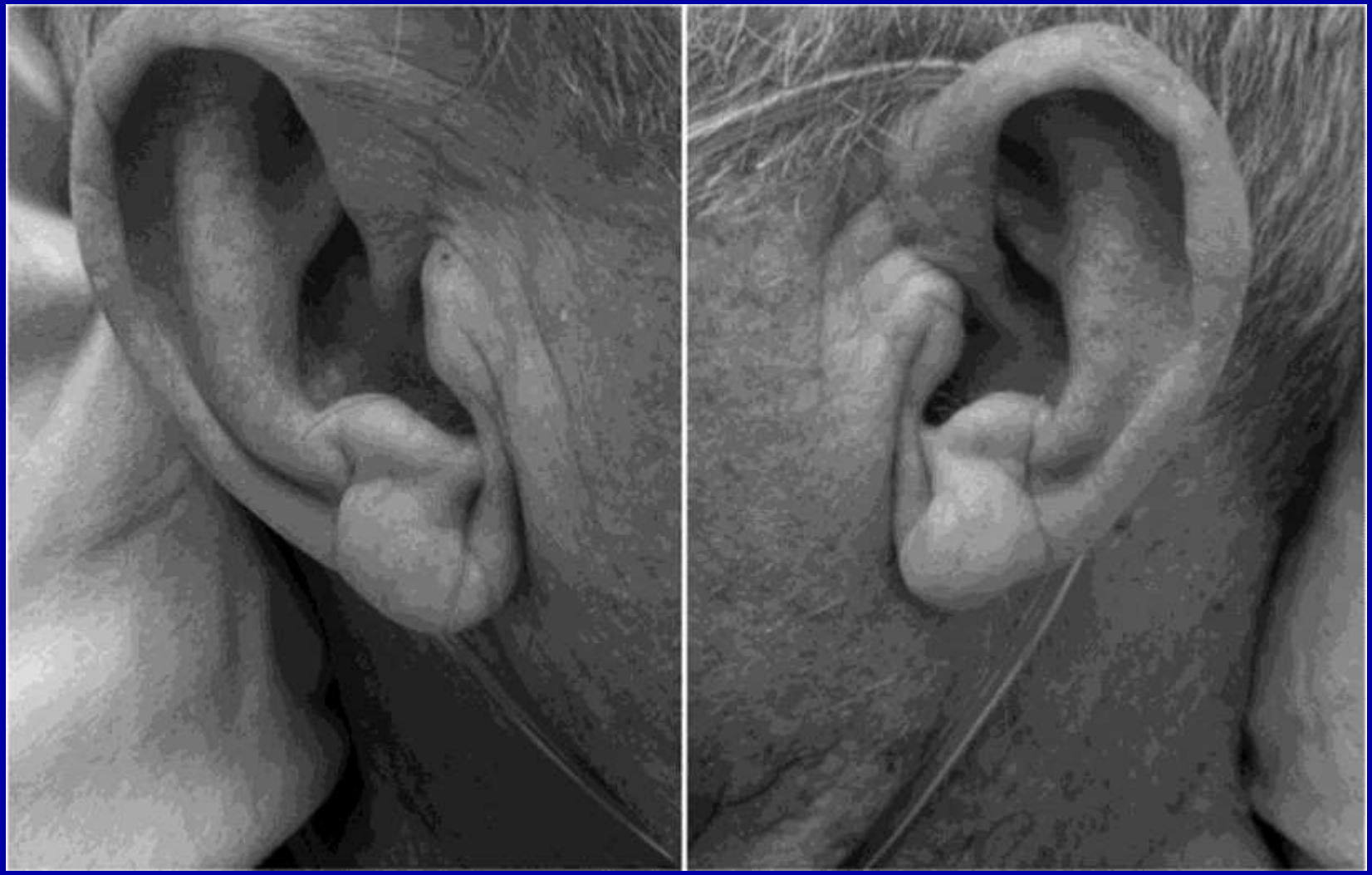
Ear Creases ‘Frank’s Sign’ Associated with CVD Risk



Zapata-Wainberg, G., & Vivancos, J. (2013). Bilateral Earlobe Creases. *New England Journal of Medicine, 368*(24), e32.

Ear Creases ‘Frank’s Sign’ Associated with CVD Risk

Bilateral earlobe crease (Frank’s sign).



Qamar A et al. Circulation. 2014;130:92-93

BDM Thoughts

Easy to note by all providers.

Regardless, everyone needs a ‘disease’ assessment.

? Could help sway some patients into a thorough CV risk work up.

Chronic Inflammatory Conditions Elevate CV Risk

- 156,108 chronic inflammatory disease pts (<3%had multiple diseases); 373,851 matched controls; >18 yo; prospective with follow-up maximum of 11 yrs.; mean CRP also evaluated -tertiles

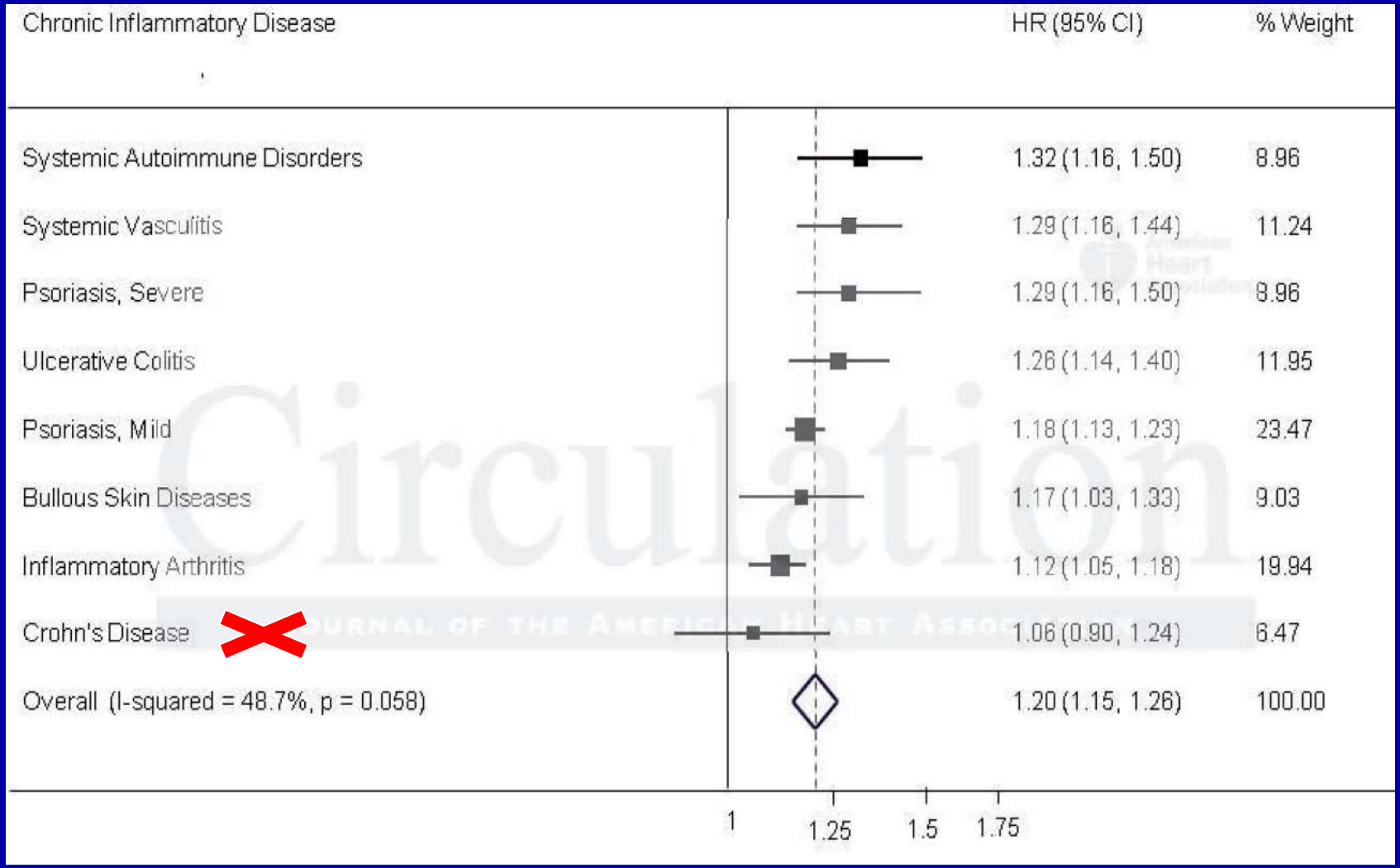
- Outcomes: new onset CVD, type 2 diabetes

- Overall a significant 20% increased risk of CVD or DM with a chronic inflammatory disease

Dregan, A., et. al. (2014). Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke: A Population-Based Cohort Study. *Circulation*. doi: 10.1161/circulationaha.114.009990

Chronic Inflammatory Conditions Elevate CV Risk

Forest plot displaying random effect meta-analysis of the influence of diverse chronic inflammatory conditions on multiple cardiovascular and type II diabetes



Dregan, A., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009990

Chronic Inflammatory Conditions: conditions included.

Chronic inflammatory disorders included in study.

Chronic Inflammatory disorder	Read code	Conditions included
Psoriasis and similar disorders (N=90,880)	**M16**	Psoriasis and similar disorders: including psoriatic arthropathy; other psoriasis; parapsoriasis; palmoplantar pustular psoriasis; other psoriasis and similar disorders; psoriasis and similar disorders NOS
Bullous Skin Diseases (N=4,284)	**M14**	Bullous dermatoses including: dermatitis herpetiformis; subcorneal pustular dermatosis; juvenile dermatitis derpetisformis; impetigo herpetiformis; pemphigus; pemphigoid; benign mucous membrane pemphigoid; erosive pustular dermatosis of the scalp; other specified bullous dematoses; bullous dermatoses NOS.
Crohn's Disease (N=7,628)	**J40**	Regional enteritis – Crohn's disease - including: regional enteritis of the small bowel; regional enteritis of the large bowel; regional ileocolitis; regional enteritis NOS
Ulcerative Colitis (N=12,203)	**J41**	Indiopathic proctocolitis including: ulcerative proctocolitis; ulcerative (chronic) enertocolitis; ulcerative (chronic) ileocolitis; ulcerative pancolitis; other idiopathic proctocolitis; idiopathic proctocolitis NOS
Inflammatory Arthritis (N=27,358)	**N04**	Rheumatoid arthritis and other inflammatory polyarthropathy including: rheumatoid arthritis; Felty's syndrome; other rheumatoid arthropathy and visceral/systemic involvement; juvenile rheumatoid arthritis, Still's disease; chronic post-rheumatic arthropathy; other juvenile arthritis; seropositive erosive rheumatoid arthritis; seropositive rheumatoid arthritis, unspecified; other specified inflammatory polyarthropathy; inflammatory polyarthropathy NOS.
Systemic Autoimmune Disorders (N=7,472)	**N00**	Diffuse diseases of connective tissue including: systemic lupus erythematosus; scleroderma; sicca (Sjogren's syndrome); dermatomyositis; polymyositis; adult Still's disease; antiphospholipid syndrome; other specified diffuse collagen diseases, collagen diseases NOS.
Systemic Vasculitis (N=6,283)	**G75**	Polyarteritis nodoa and allied conditions including: polyarteritis nodosa; acute febrile mucocutaneous lymph node syndrome; hypersensitivity angiitis; lethal midline granuloma; Wegener's granuloma; Giant cell arteritis; thrombotic microangiopathy; Takayasu's disease; Churg-Strauss vasculitis; Juvenile polyarteritis; microscopic polyangiitis; necrotising vasculopathy unspecified; polyarteritis nodosa and allied conditions NOS

Dregan, A., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009990

Chronic Inflammatory Conditions Elevate CV Risk: CRP was Related to Risk

Positive dose-relationship between mean CRP and study outcomes.

Evidence that risk is associated with severity of inflammation.

This data points supports role of systemic inflammation in CVD.

Dregan, A., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009990

Chronic Inflammatory Conditions Elevate CV Risk: CRP Related to Risk- Driven by CHD and DM

Table 4. Dose-response relationship between tertiles* mean CRP levels and study outcome.

	Multiple outcomes		CHD		Stroke		Diabetes	
	CI† cases	Controls	CI cases	Controls	CI cases	Controls	CI cases	Controls
N(%)								
	46,108(27)	40,644(13)	47,549(33)	44,116(15)	51,220(34)	48,076(16)	48,603(33)	45,576(15)
Median(IQR)								
	6(3,14)	4(2,8)	6(3,14)	4(2,8)	6(3,14)	4(2,9)	6(3,1.4)	4(2,9)
CRP tertiles – HR‡ (95%CI)								
Lowest	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Second	1.27 (1.14-1.41)	1.20 (1.07-1.36)	1.23 (1.05-1.45)	1.17 (0.97-1.40)	1.13 (0.91-1.42)	0.99 (0.77-1.27)	1.29 (1.12-1.49)	1.33 (1.13-1.59)
Highest	1.52 (1.37-1.68)	1.44 (1.30-1.60)	1.33 (1.14-1.56)	1.18 (1.00-1.30)	1.15 (0.91-1.40)	1.21 (0.98-1.49)	1.65 (1.44-1.89)	1.59 (1.38-1.84)
P for trend								
	<0.001	<0.001	<0.001	0.023	0.212	0.032	<0.001	<0.001

*Controls: Mean values, First tertile: 0-3 mg/L; Second tertile: 3.01-6 mg/L; Third tertile: >6.02 mg/L. Patients: Mean values, First tertile: 0-4 mg/L; Second tertile: 4.00-10 mg/L; Third tertile: >10.01 mg/L. †Chronic inflammation. ‡HR=Hazard ratios; CI=Confidence Intervals.

Dregan, A., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009990

Chronic Inflammatory Conditions Elevate CV Risk

This data strongly supports the hypothesis that virtually any source of chronic inflammation is associated with CVD and T2DM.

The observational nature of the present study precludes any definitive conclusion regarding causality or mechanism, but the CRP information indicates risk is associated with severity of inflammation.

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Dregan, A., et. al. (2014). Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke: A Population-Based Cohort Study. *Circulation*. doi: 10.1161/circulationaha.114.009990

Chronic Inflammatory Conditions Elevate CV Risk: Authors' Discussion

- Prevention of CVD and T2DM merits higher priority in the management of participants with chronic inflammatory disorders.
- Clinicians should have a lower threshold for starting preventive medical interventions in most chronic inflammatory conditions.
- Mean CRP values should be preferred to single baseline whenever possible.

Dregan, A., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009990

BDM Thoughts

- Pts with chronic inflammatory conditions should be considered at higher risk for CVD.
- BDM providers should network with providers handling such conditions.

- Supports the use of monitoring CRP over time as a biomarker indicating higher CV risk, in particular – CHD and new onset DM.
- More support for a critical role of inflammation in CVD.

Dregan, A., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.114.009990

Sjögren's Syndrome (SjS) Associated with 2X Increased Risk of Heart Attack

Retrospective matched cohort study; 1,176 new cases SjS; 11,879 non-SjS matched controls.

Incident rate of first time heart attack was 7.7/ 1,000 pt-yrs for SjS and 3.5/1,000 pt-yrs. for non-SjS.

RR for heart attack was 2.2 (95% CI 1.41- 3.32)

Yurkovich M, Sayre EC, Shojania K, Avina-Zubieta A. The risk of myocardial infarction and cerebrovascular accident in patients with Sjögren's syndrome: a general population-based cohort study. EULAR 7/1/2014; Paris: Abstract # OP0212

Sjögren's Syndrome Associated with Increased Heart Attack Risk

Adjusting for other relevant risk factors for CVD including medications made no significant difference. RR- 2.4 (1.5– 3.8)

Risk highest during 1st yr: RR- 3.6

Increased risk persisted up to five years

Trend for increased stroke, but not significant.

Yurkovich M, Sayre EC, Shojania K, Avina-Zubieta A. The risk of myocardial infarction and cerebrovascular accident in patients with Sjögren's syndrome: a general population-based cohort study. EULAR 7/1/2014; Paris: Abstract # OP0212

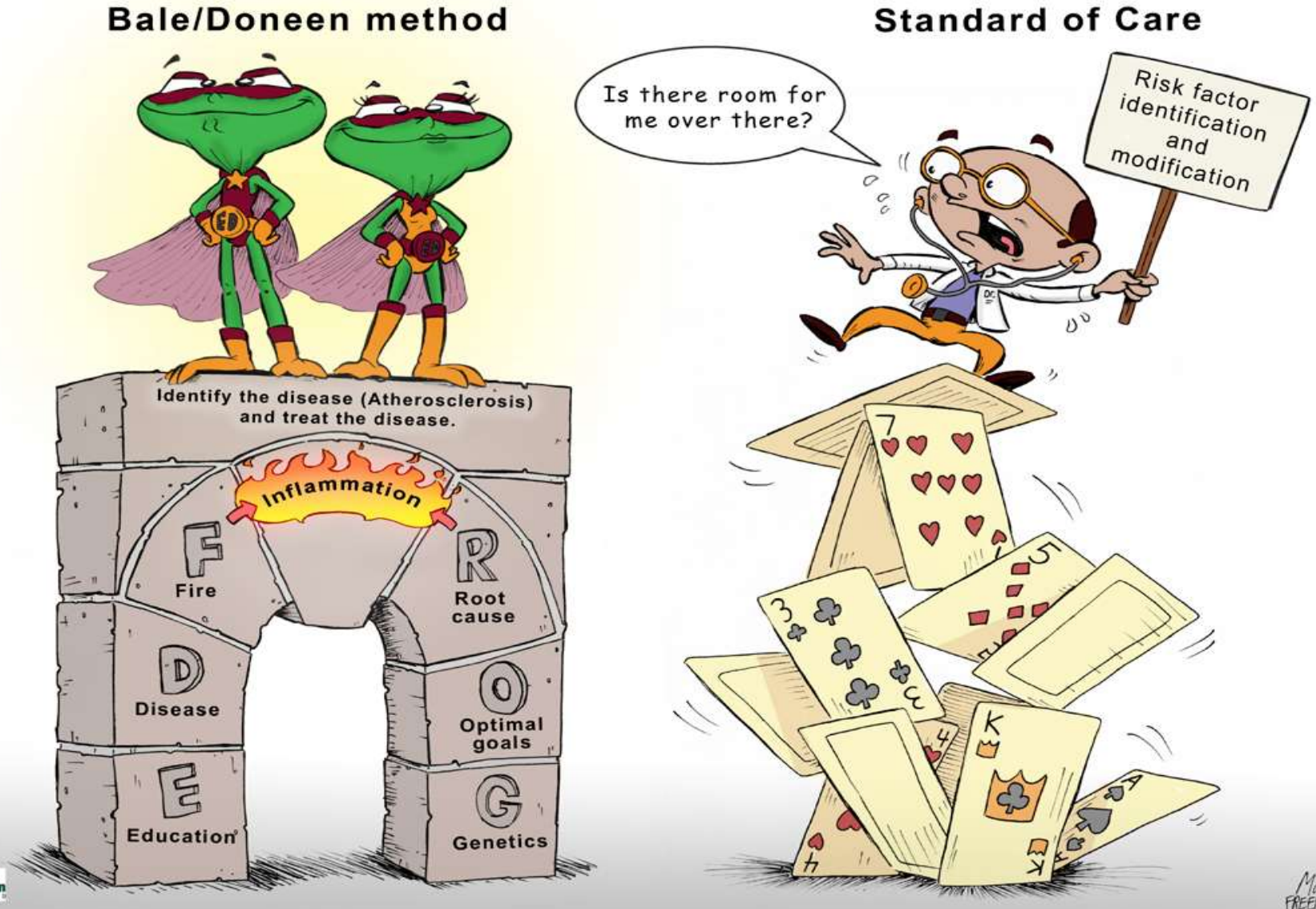
BDM Thoughts

- Principal investigator of the study, Dr. Antonio Aviña-Zubieta, "Our results support the role of inflammation in CVD and the need for increased monitoring for CAD in all pts with this condition, in addition to proper management and modification of their CV risk factors to reduce the risk of a future heart attack.“

- Yaahoo, Dr. Zubieta! Would just add all of these patients deserve testing for subclinical ASVD.

- This study also supports that the CV risk is being driven mainly by heart attack as opposed to stroke.

What's the difference?



Quantified AAC An Excellent Predictor of CV Events and Mortality: Background

Subclinical atherosclerosis as measured by CT quantified CAC improves CV risk predictions.

Purpose of current study is to investigate if AAC quantified by CT is related to CV outcomes; if so, is relationship independent of CAC.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

Abdominal Aorta Calcification (AAC) Quantified by CT is An Excellent Predictor of CV Events and Mortality

- 1,974 MESA pts; 45-84 yo; baseline AAC & coronary artery calcification (CAC); 5 ½ yr follow-up
- AAC & CAC: tertiles of Agatston score via percentiles
- Outcomes: CHD and CVD events; mortality CVD & all cause.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

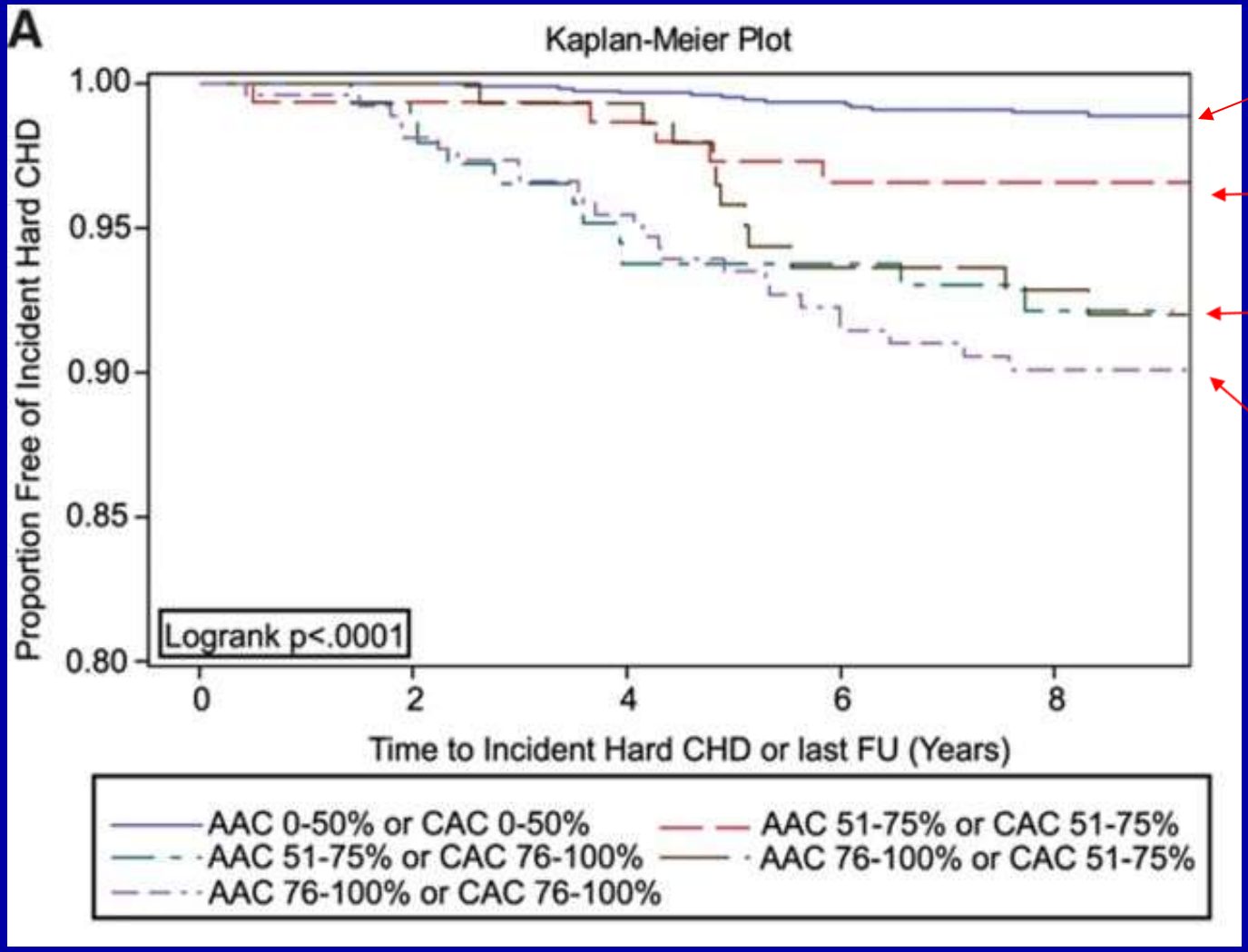
Quantified AAC An Excellent Predictor of CV Events and Mortality

	0-50 percentile	51-75 percentile	76-100 percentile
AAC Agatston score	0-241	242-1,437	1,438-20,952
CAC Agatston score	0-9	10-136	137-4,508

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

Abdominal Aorta Calcification An Excellent Predictor of CHD Events: on par with CAC

Kaplan–Meier curve for AAC and CAC categories and time to a CHD event.



Both low %

Both moderate %

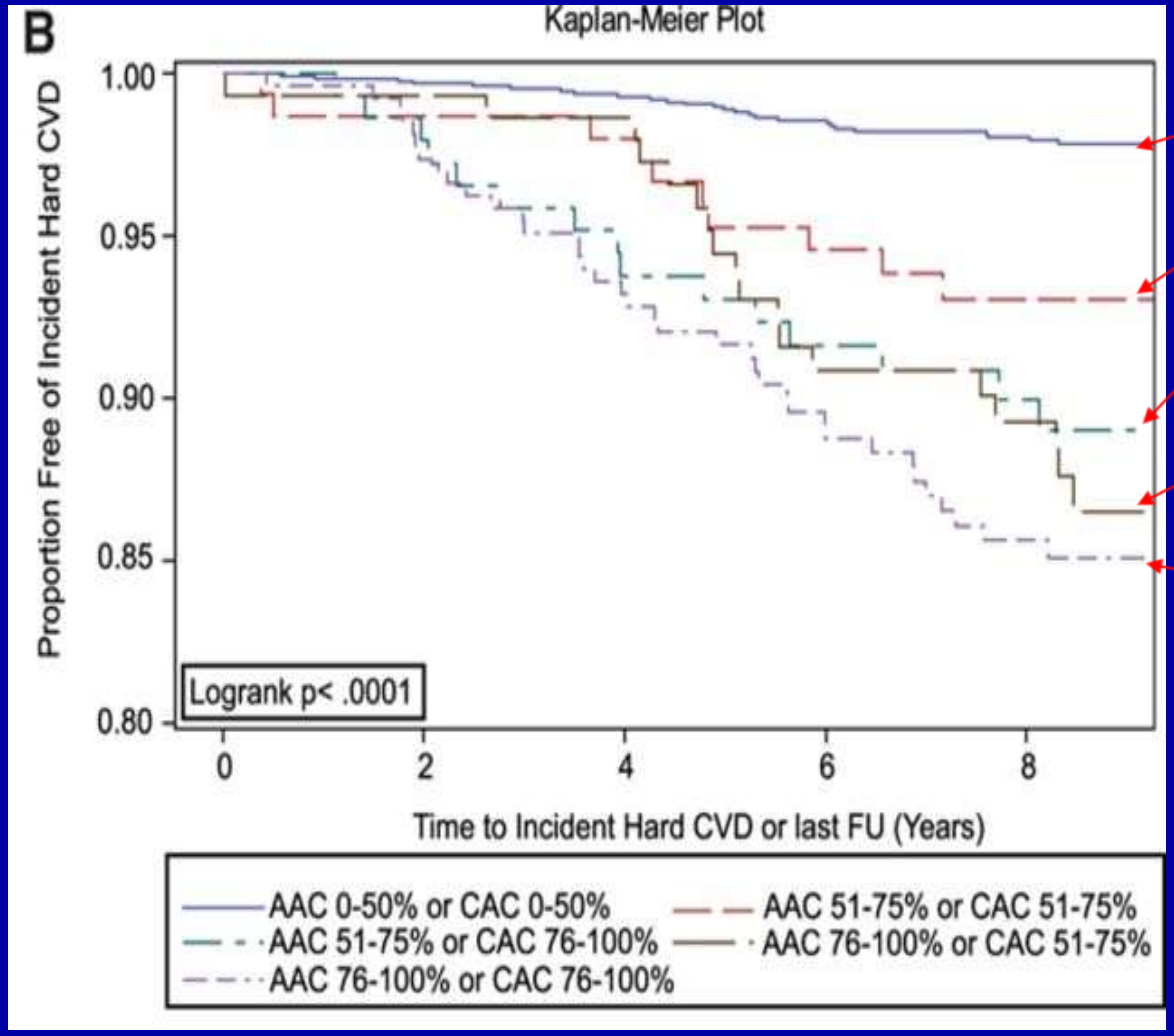
One moderate & one high%

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of CV Events: at least as good as CAC

Kaplan–Meier curve for AAC and CAC categories and time to a CVD event.



Both low %

Both moderate %

CAC high & AAC mod. %

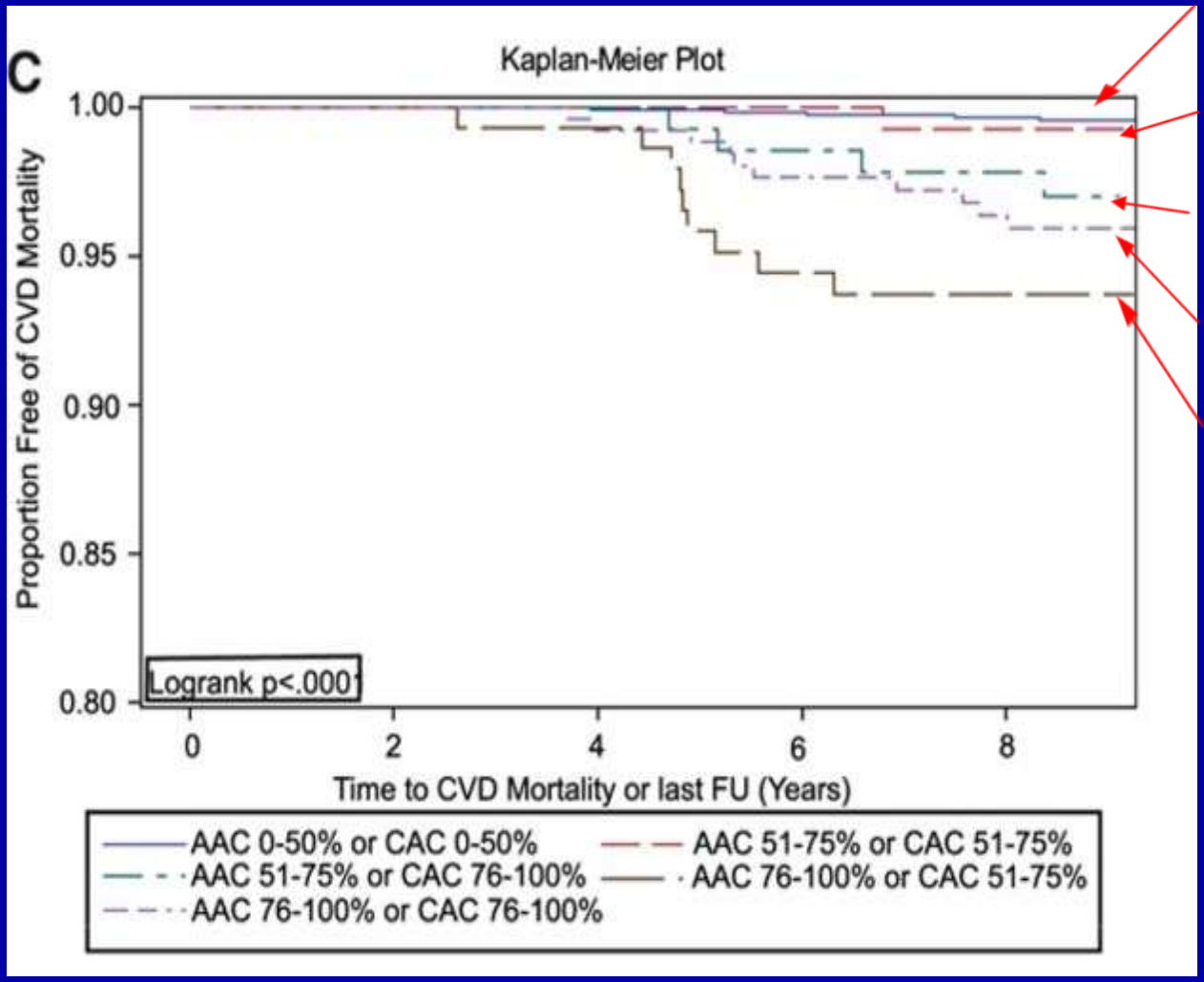
AAC high & CAC mod %

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of CV Mortality: at least as good as CAC

Kaplan–Meier curve for AAC and CAC categories and time to a CVD death.



Both low %

Both moderate %

CAC high & AAC mod. %

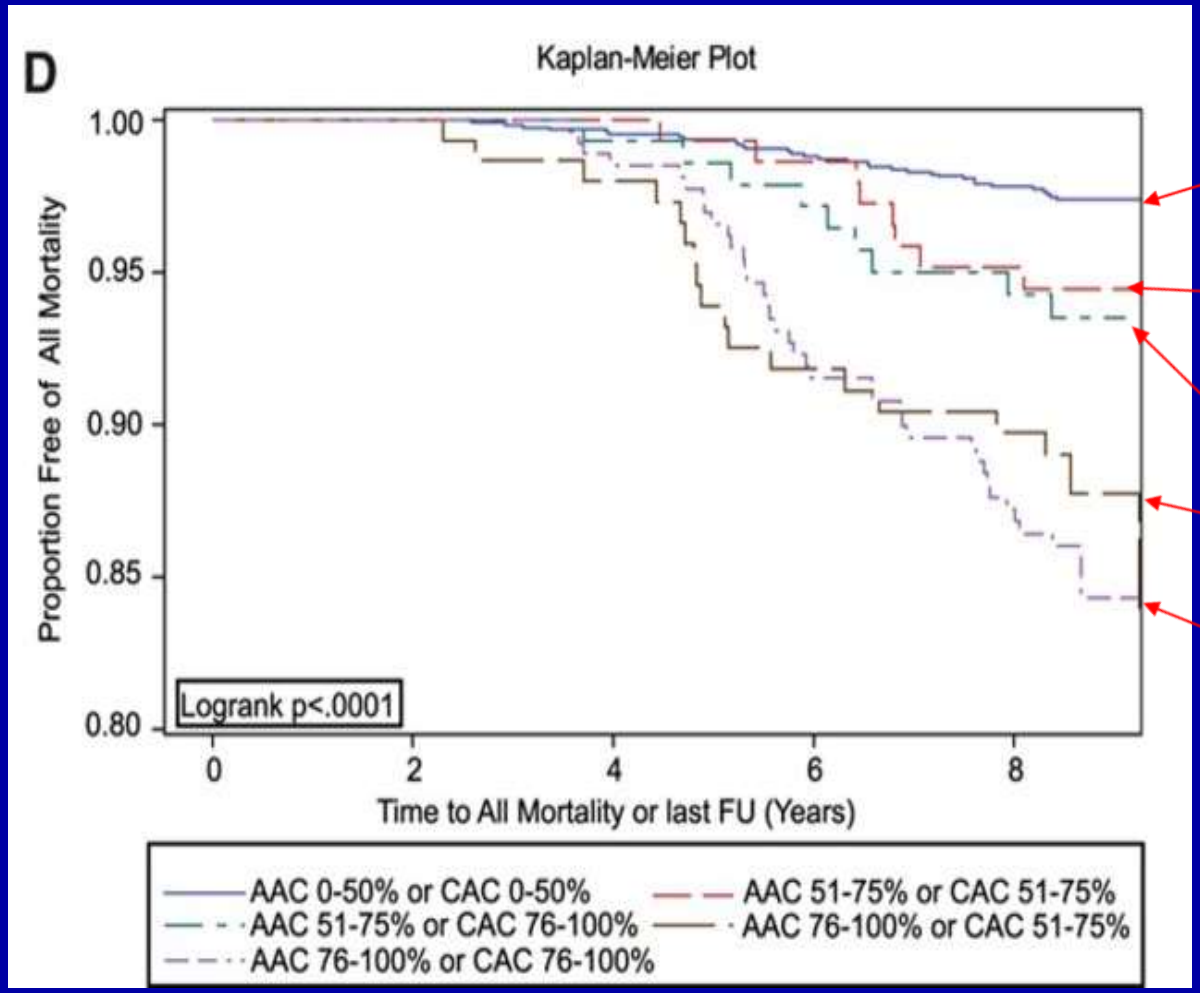
AAC high & CAC mod %

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of Death: better than CAC

Kaplan–Meier curve for AAC and CAC categories and time to all mortality.



Both low %

Both moderate %

CAC high & AAC mod. %

AAC high & CAC mod %

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of CV Events and Mortality

With AAC ≥85 %'tile (2,754 Ag) & CAC ≥85 %'tile (300 Ag) when adjusted for FRS and each other, only AAC remained significantly predictive of all four outcomes; CAC did not predict any of them.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

Abdominal Aorta Calcification An Excellent Predictor of CV Events and Mortality

AAC would add to CAC in predicting hard CVD events; is a stronger subclinical ASVD measure for predicting CVD mortality and all cause mortality.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

BDM Thoughts

- It is important to judge CV risk based on the presence of ASVD; study confirms that.
- If disease (calcium) is present, there is risk.
- Trying to judge risk based on quantifying the amount of ‘calcium’ in any arterial bed can be misleading.
- Calcium in any arterial bed is associated with increased CV risk; once found, follow inflammation.
- Quantified AAC may become an option instead of CAC.
- Imaging that can demonstrate the morphology of plaque would be more useful.

Plaque Structural Stress (PSS) Related to Event Risk and Plaque Composition

A mechanism for plaque rupture is intra-plaque structural stress.

When the stress exceeds the material strength of the fibrous cap there is a rupture.

PSS can be calculated and ex vivo data

demonstrate plaque rupture is associated with higher PSS.

Teng, Z., et. al. (2014). Coronary Plaque Structural Stress Is Associated With Plaque Composition and Subtype and Higher in Acute Coronary Syndrome: The BEACON I (Biomechanical Evaluation of Atheromatous Coronary Arteries) Study. *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

Plaque Structural Stress Related to Event Risk and Plaque Composition

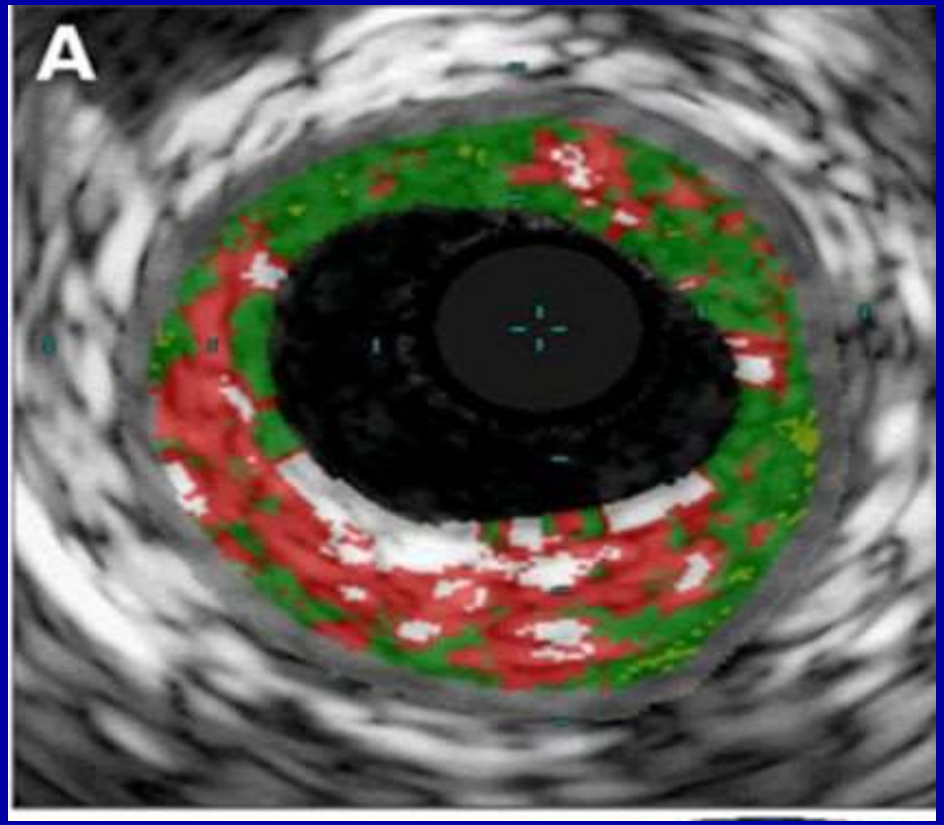
Virtual histology intravascular ultrasound (VH-IVUS) is a modality that uses backscatter to identify plaque composition.

It reliably identifies dense calcium, fibrofatty, fibrous tissue and necrotic core.

Methodology exists using finite element analysis (FEA) to calculate PSS from in vivo VH-IVUS data.

Teng, Z., et. al. (2014). *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

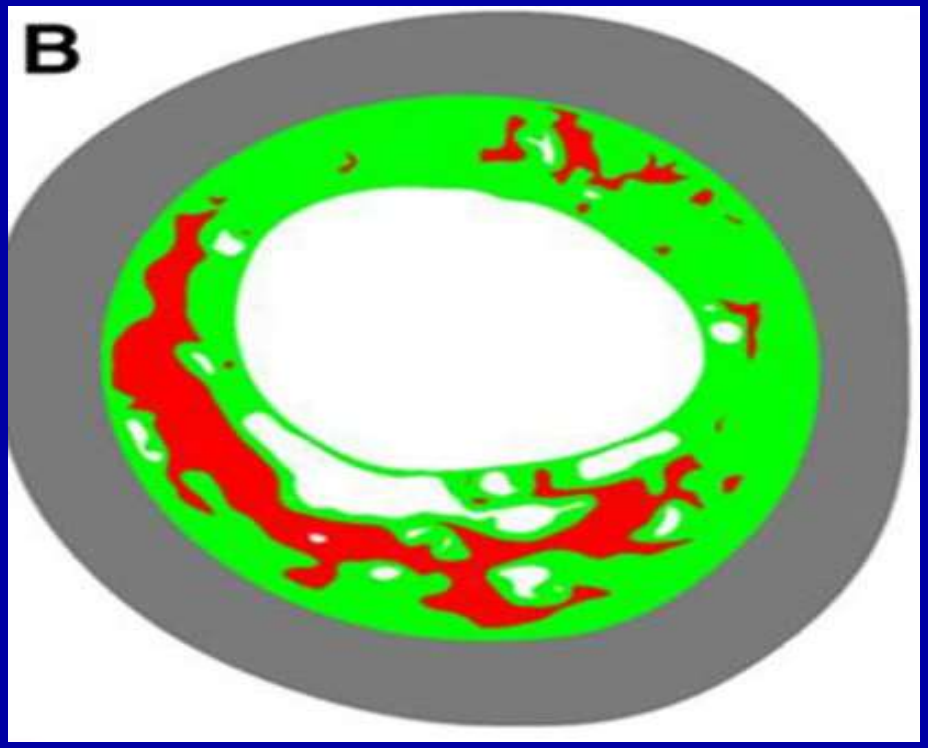
Stepwise calculation of plaque structural stress (PSS) through finite element analysis (FEA).



A, Virtual histology intravascular ultrasound image showing dense calcification (white), necrotic core (red), fibrous (green), and fibrofatty tissue (light green).

Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

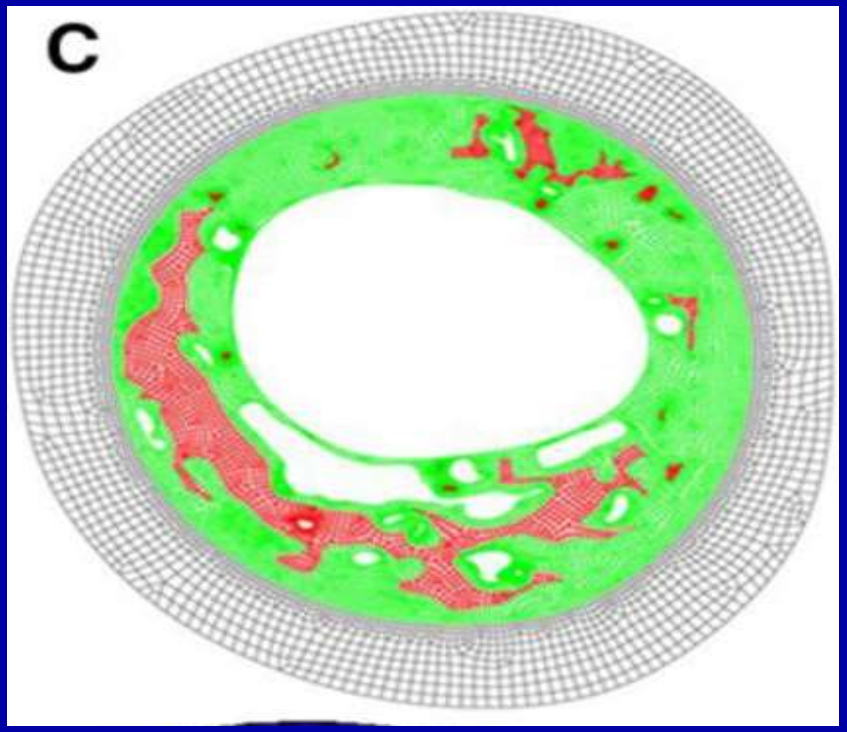
Stepwise calculation of plaque structural stress (PSS) through finite element analysis (FEA).



B, Reconstructed geometry and segmented plaque components used for FEA.

Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

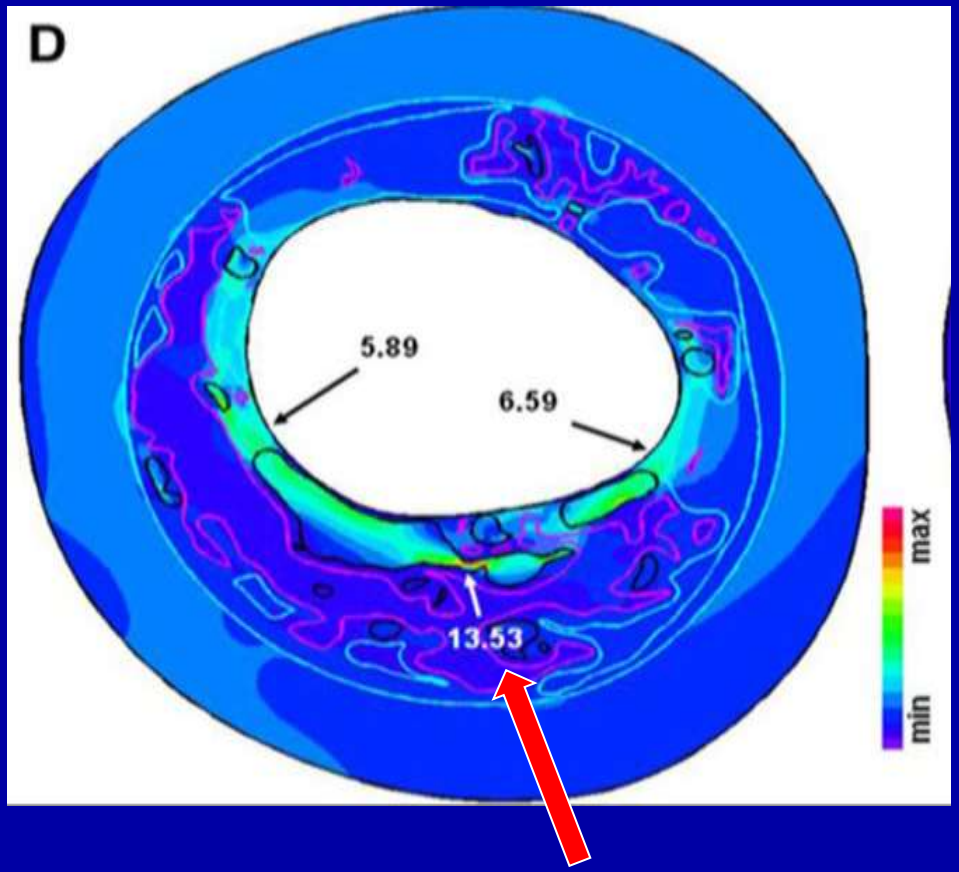
Stepwise calculation of plaque structural stress (PSS) through finite element analysis (FEA).



C, Nine-node quadrilateral mesh with ≈10 000 elements constructed.

Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

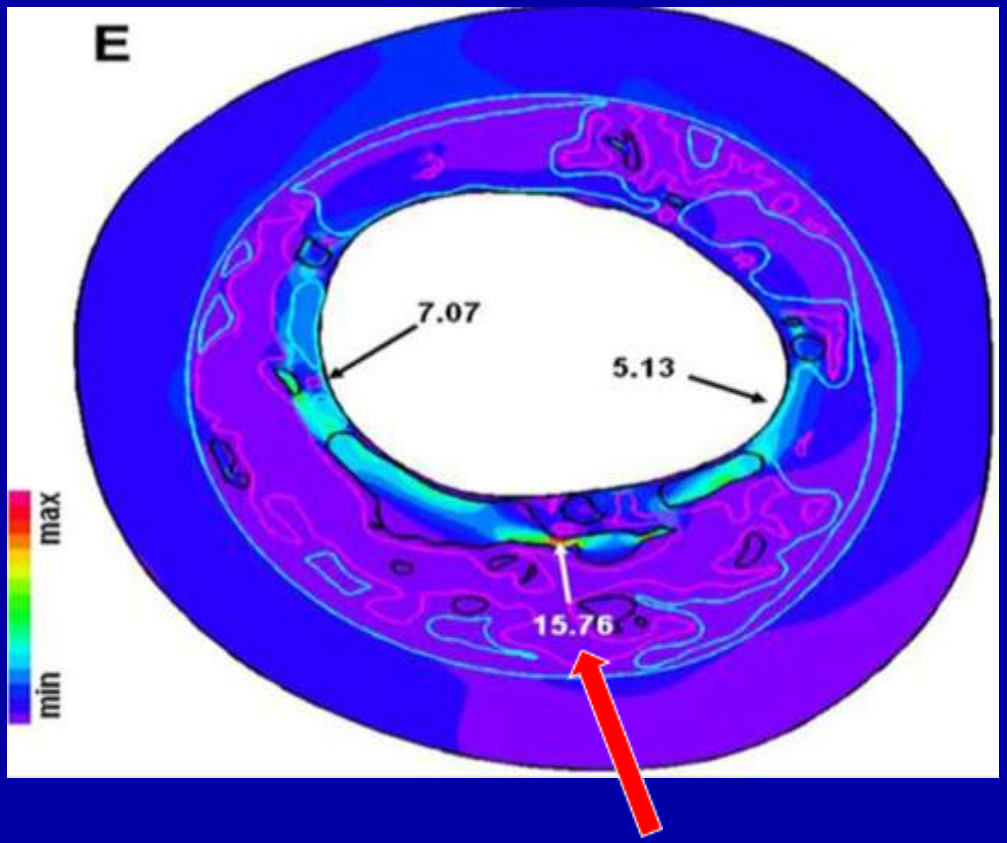
Stepwise calculation of plaque structural stress (PSS) through finite element analysis (FEA).



D, Band plot of PSS identifying regions with high stress concentration (arrows).

Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

Stepwise calculation of plaque structural stress (PSS) through finite element analysis (FEA).



E, Band plot of variation of PSS during 1 cardiac cycle, illustrating regions with high stress variation (arrows).

Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

Plaque Structural Stress Related to Event Risk and Plaque Composition

53 pts with LAD culprit lesions; 23 ACS; 30 stable angina (SAP); 118 plaques examined.

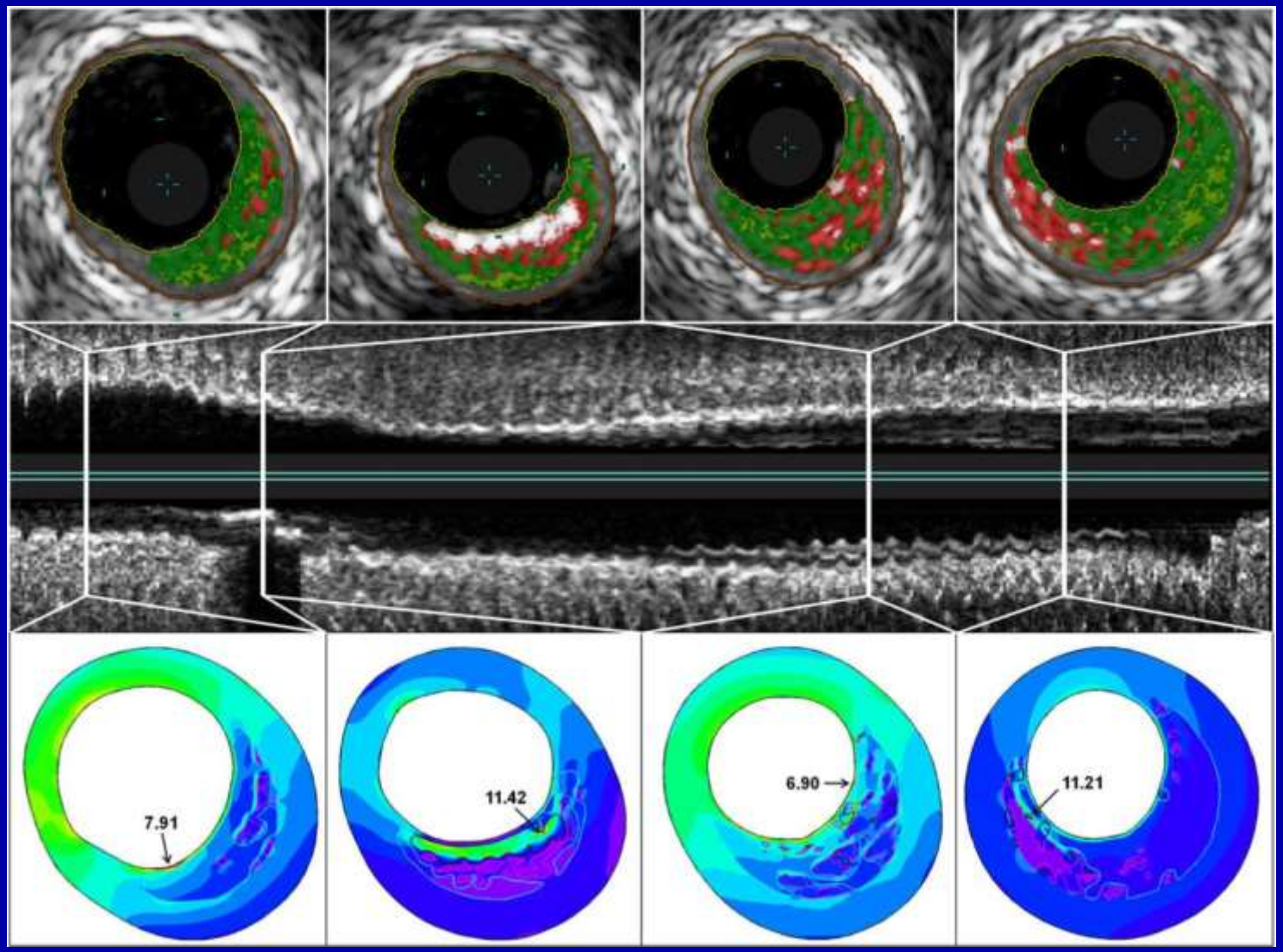
PSS values calculated showed a wide distribution, ranging from 2.81 to 29.03 (median, 9.04; Q1–Q3, 7.28–11.40).

PSS varied markedly over short distances within a plaque and in similar plaques.

Teng, Z., et. al. (2014). *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

PSS Varies Significantly Within a Plaque

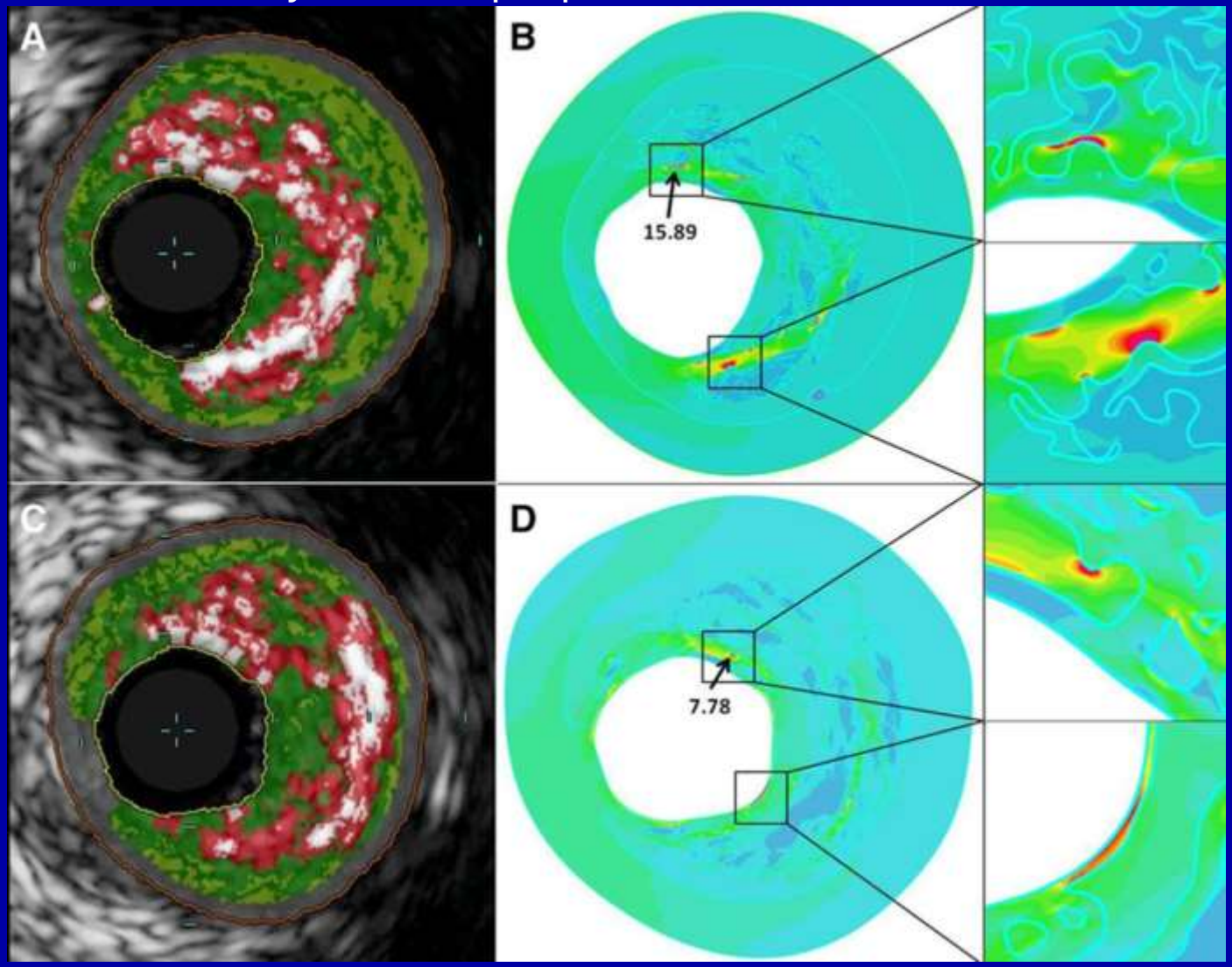
Longitudinal reconstruction illustrating PSS variability throughout a single plaque.



Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

Plaques Which can be Classified as Identical Can Have Very Different PSS

PSS variability between plaques with identical classification.



Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

Plaque Structural Stress Related to Event Risk and Plaque Composition

PSS was unequally distributed across vessels and plaques, indicating regions of plaque vulnerability may exist over an exceptionally short distance.

Plaque rupture is likely a focal event, occurring in specific areas of plaque weakness.

Summarized variables describing plaques may dilute their true overall risk of rupture.

Teng, Z., et. al. (2014). *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

Plaque Structural Stress Related to Event Risk and Plaque Composition

Marked variation of PSS highlight the heterogeneity of materials that comprise the plaque.

PSS increased with increasing calcification but then plateaued or even reduced when calcification became more extensive.

PSS increased with larger area/arc of necrotic core.

Teng, Z., et. al. (2014). *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

Plaque Structural Stress Related to Event Risk and Plaque Composition

ACS pts with minimal luminal area (MLA) ≤ 4mm², plaque burden >70% and non-calcified thin fibrous cap plaques (ncTFCA) had greater PSS than SAP with similar plaques.

Pronounced enhancement predicting ACS risk when coupled PSS values to ncTFCA

If PSS ≥10.22 - positive predictive value of 91.4%

Teng, Z., et. al. (2014). *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

BDM Thoughts

- Superb study with intriguing findings.
- Carotid plaques classified as ‘soft’ or ‘heterogeneous’ certainly must be considered dangerous! (?echogenic)
- Larger carotid plaques overall should be considered more dangerous - ? growth due to internal increased PSS causing intra-plaque hemorrhage and increased vaso vasorum.
- Structural tests utilized to augment ‘event predictability’ are currently not practical.
- If there is an atheroma, safest assumption is: there is ‘event’ risk.
- Monitoring bio-markers of inflammation are a practical means of tracking ‘event’ risk.

Carotid ASVD Strong Predictor of Adverse CAD Events

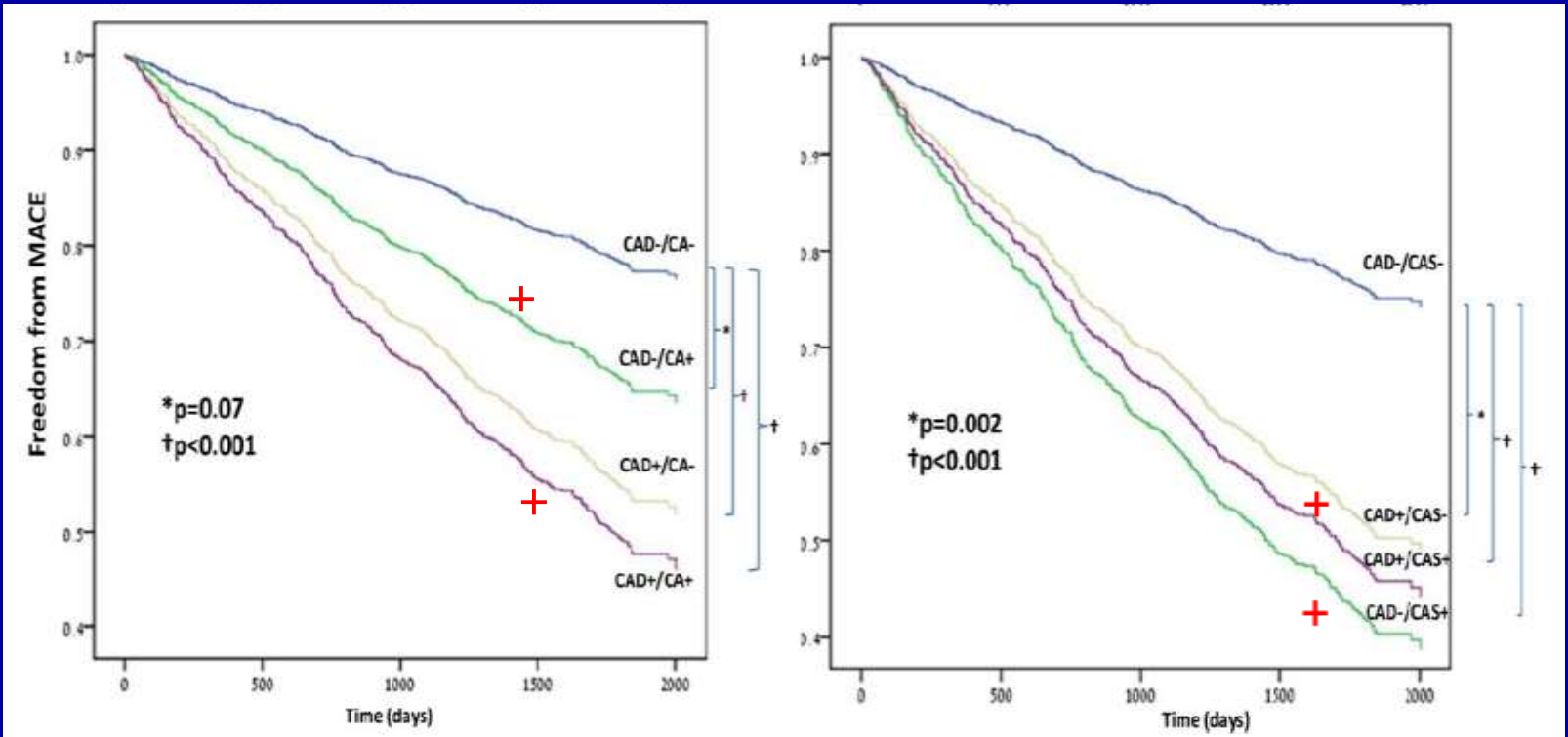
- 1,391 post angiogram pts; 79% + for CAD; same day carotid US; followed ~ 4 ½ yrs.
- Objective: is carotid ASVD & or stenosis associated with CV risk in pts with or without CAD?
- Primary end point: MACE- all-cause mortality, MI, stroke, and any coronary revascularization.

Steinvil, A., et. al. (2014). Impact of Carotid Atherosclerosis on the Risk of Adverse Cardiac Events in Patients With and Without Coronary Disease. *Stroke*. doi: 10.1161/STROKEAHA.114.005663

Carotid ASVD Strong Predictor of Adverse CAD Events

Carotid ASVD +

Carotid Stenosis +



Kaplan–Meir unadjusted curves stratified by presence of coronary artery disease (CAD), carotid atherosclerosis (CA), and carotid artery stenosis (CAS).

Steinvil, A., et. al. (2014). *Stroke*. doi: 10.1161/STROKEAHA.114.005663

Carotid ASVD Strong Predictor of Adverse CAD Events

Carotid disease predicts adverse cardiac events.

This is very important in pts without pre-existing CAD, who might otherwise be considered at low risk on the basis of negative coronary imaging.

Steinvil, A., et. al. (2014). *Stroke*. doi: 10.1161/STROKEAHA.114.005663

BDM Thoughts

Nice confirmation that carotid ASVD is associated with increased risk for heart attack, stroke and CV death.

This study utilized carotid duplex which is not as informative as CIMT and is not recommended for screening purposes.

Carotid 3D Imaging for Monitoring Disease

Method for analyzing serial 3D MRI images of the carotid artery.

Enables detailed visual inspection of local differences between time points, providing intuitive insight into the disease progression in an individual patient.

van ‘t Klooster, R., et. al. (2014). Visualization of Local Changes in Vessel Wall Morphology and Plaque Progression in Serial Carotid Artery Magnetic Resonance Imaging. *Stroke*. doi: 10.1161/strokeaha.114.004767

Carotid 3D Imaging for Monitoring Disease

- 71 yo post stroke male; ipsilateral carotid artery plaque with ≈30% luminal reduction.
- MRI of carotid 35 days post stroke and at 2 yrs.

van ‘t Klooster, R., et. al. (2014). Visualization of Local Changes in Vessel Wall Morphology and Plaque Progression in Serial Carotid Artery Magnetic Resonance Imaging. *Stroke*. doi: 10.1161/strokeaha.114.004767

Carotid 3D Imaging for Monitoring Disease

Vessel wall thickness

Baseline | Follow-up | VWT difference | Lipid rich core change

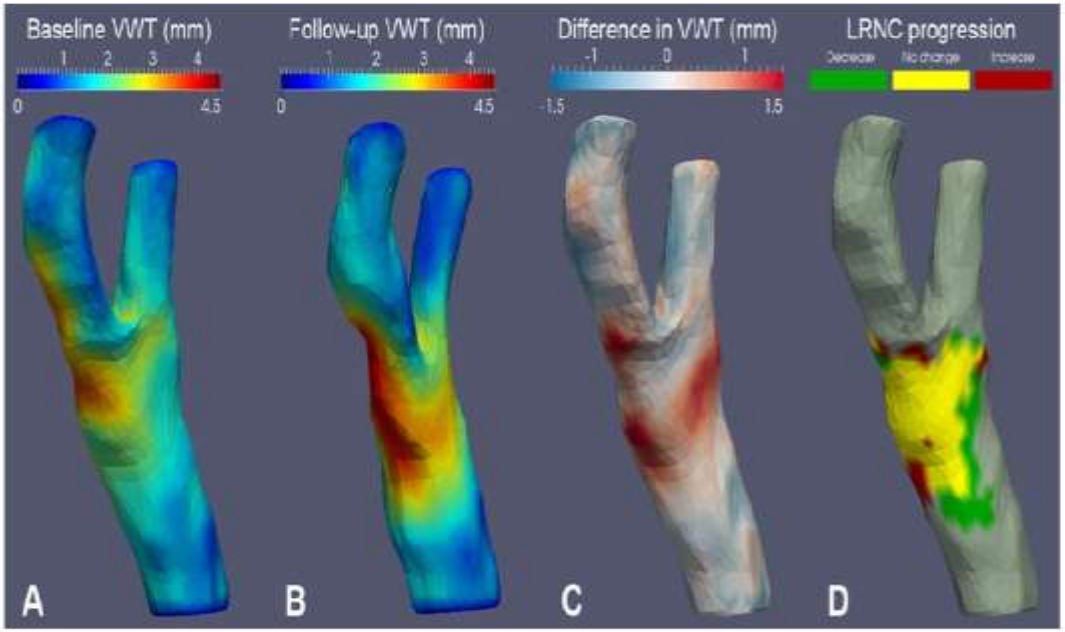


Figure 3. Three-dimensional (3D) surface meshes showing (**A** and **B**) local vessel wall thickness (VWT) at baseline and follow-up, respectively; (**C**) difference in VWT over time; and (**D**) progression or regression of lipid-rich necrotic core (LRNC) with or without intraplaque hemorrhage over time.

van 't Klooster, R., et. al. (2014). Visualization of Local Changes in Vessel Wall Morphology and Plaque Progression in Serial Carotid Artery Magnetic Resonance Imaging. *Stroke*. doi: 10.1161/strokeaha.114.004767

Carotid 3D Imaging for Monitoring Disease

This new visual data analysis tool can provide clinicians detailed views of the atherosclerotic disease evolution in individual patients.

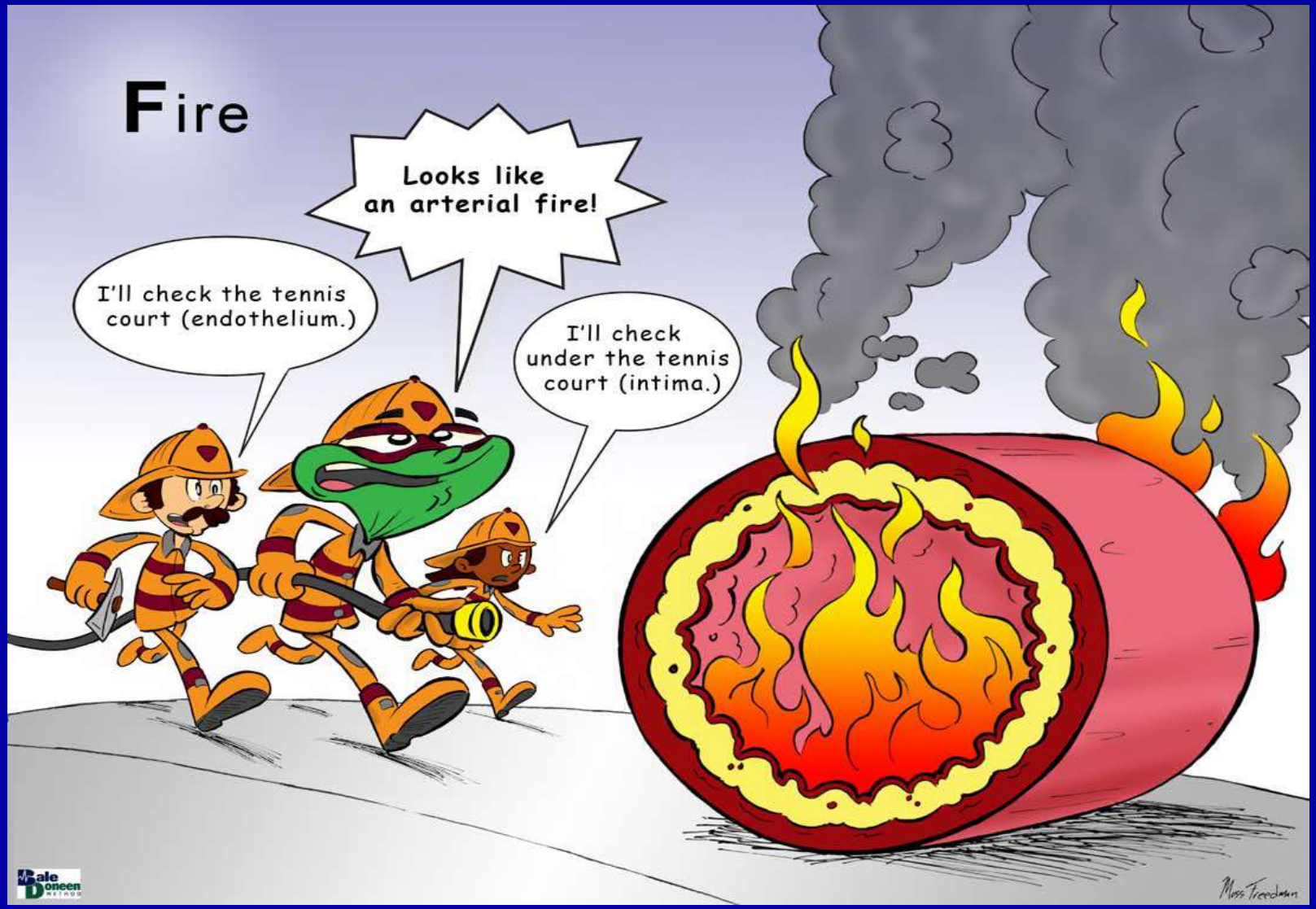
Further research on a larger cohort and multiple readers is warranted.

van ‘t Klooster, R., et. al. (2014). Visualization of Local Changes in Vessel Wall Morphology and Plaque Progression in Serial Carotid Artery Magnetic Resonance Imaging. *Stroke*. doi: 10.1161/strokeaha.114.004767

BDM Thoughts

- More expensive with a cost that can be >10× that of an ultrasound examination.
- MRI scanners less accessible.
- Contraindicated with to metallic foreign bodies in the orbit or near vital structures, cochlear implants, and pacemakers.
- Skin burns can occur from certain medicine patches, tattoos, or permanent cosmetics.
- Claustrophobia can be a significant issue.
- May be very useful in research!

Inflammation



Inflammatory Evidence During a Heart Attack

32 ACS, 33 chronic stable angina, 25 healthy pts; 18F-FDG PET scans of bone marrow, spleen and carotid.

Metabolic activity of the BM, spleen, and carotid was highest in pts with ACS, intermediate in patients with angina, and lowest in control subjects.

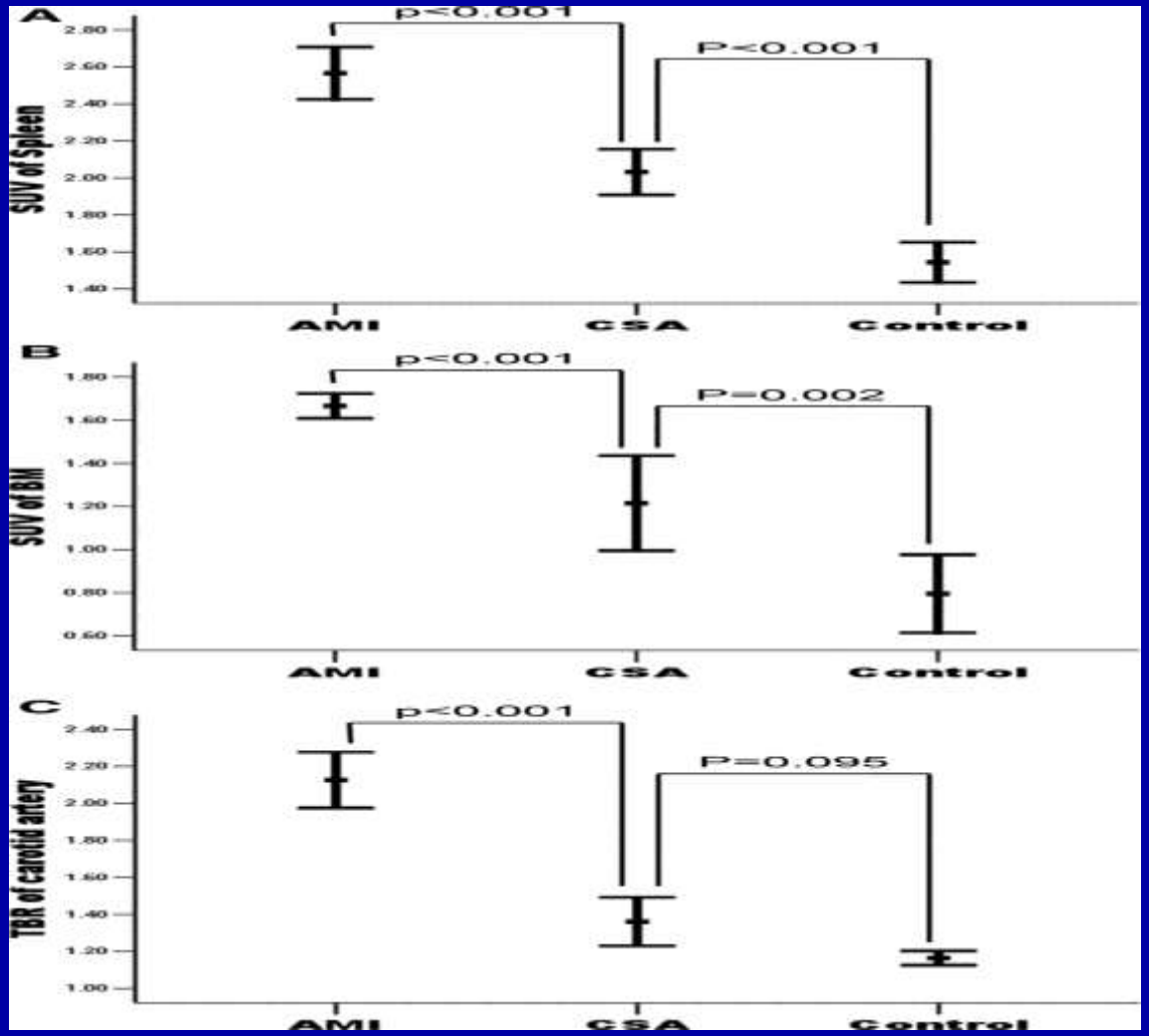
Kim, E. J., et. al. (2014). Metabolic Activity of the Spleen and Bone Marrow in Patients With Acute Myocardial Infarction Evaluated by 18F-Fluorodeoxyglucose Positron Emission Tomograpic Imaging. *Circulation: Cardiovascular Imaging, 7*(3), 454-460.

Inflammatory Evidence During a Heart Attack

Spleen-SUV

BM- SUV

Carotid TBR



Mean differences in spleen standard uptake value (SUV; A), bone marrow (BM) SUV (B), and the carotid artery target-to-background ratio (TBR; C) among the 3 study groups.

Kim E J et al. Circ Cardiovasc Imaging. 2014;7:454-460

Inflammatory Evidence During a Heart Attack

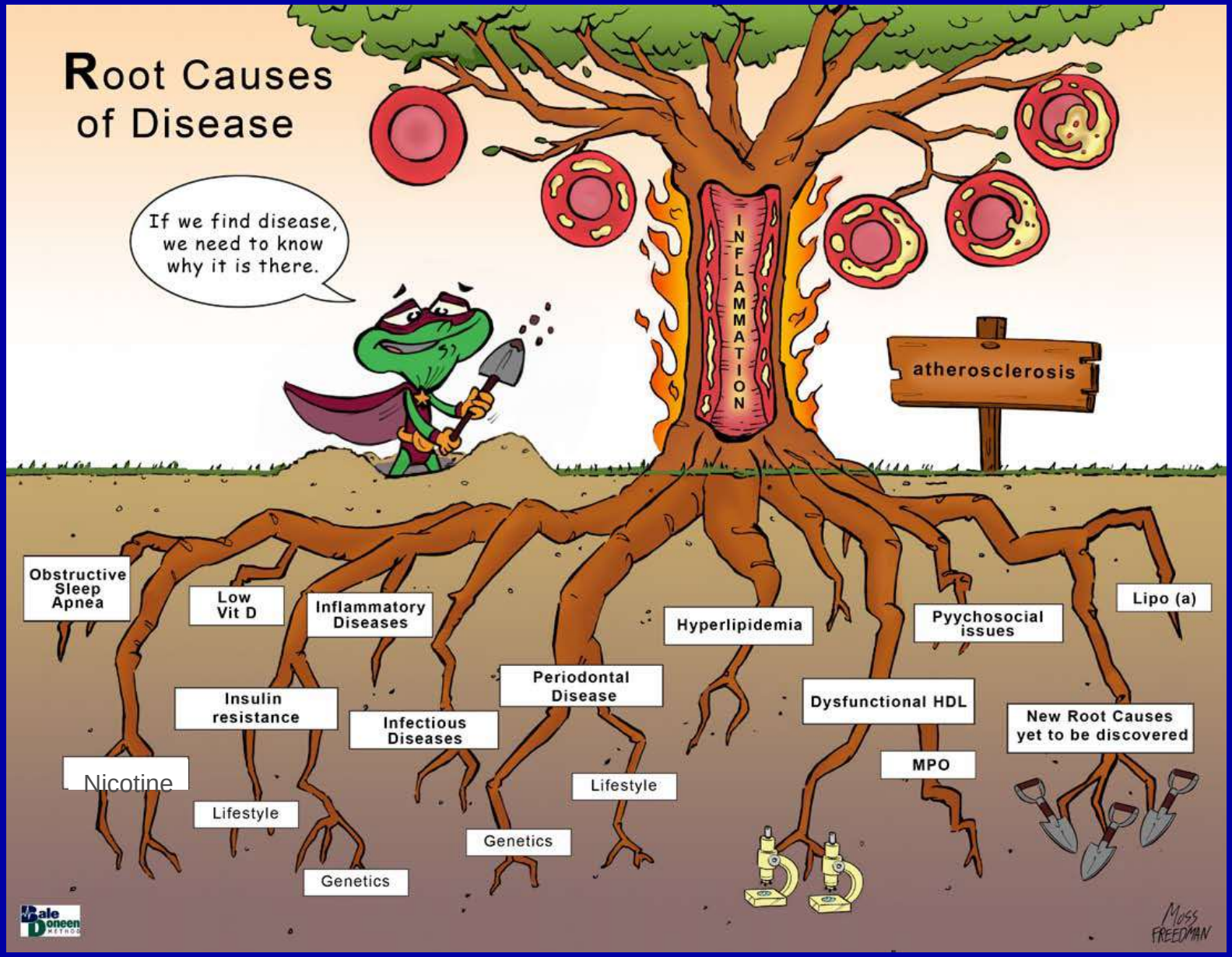
Inflammatory status of atherosclerosis is influenced by systemic inflammation modulated by the spleen and BM.

The relationship between these parameters and CAD status was independent of traditional CV risk factors (sex, waist, BP, DM, smoking, lipids, statins).

Kim, E. J., et. al. (2014). Metabolic Activity of the Spleen and Bone Marrow in Patients With Acute Myocardial Infarction Evaluated by 18F-Fluorodeoxyglucose Positron Emission Tomograpic Imaging. *Circulation: Cardiovascular Imaging, 7*(3), 454-460.

BDM Thoughts

- Many studies to support the association between inflammation and CV events with circulating biomarkers.
- This study adds another level of evidence for arterial inflammation's role in triggering events using a molecular imaging tool.
- This message will not disappear & the evidence for it will continue to strengthen.



TG's Relationship to Apolipoprotein C3 (APOC3) Genetics and Ischemic ASVD Risk: Background

TGs are surrogate markers of remnant cholesterol which cause arterial inflammation even without oxidation and which increase CAD substantially. *

APOC3, a component of remnant cholesterol, extracellularly it inhibits hydrolysis of TG-rich lipoproteins by lipoprotein lipase and it also decreases liver uptake of TG-rich remnant lipoproteins.

Intracellularly it promotes TG synthesis and VLDL assembly and secretion.

Net effect = increases plasma TG and remnants.

*Varbo, A., et. al. (2013). Elevated Remnant Cholesterol Causes Both Low-Grade Inflammation and Ischemic Heart Disease, -----.*Circulation, 128*(12), 1298-1309.

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

TG's Relationship to APOC3 Genetics and Ischemic ASVD Risk

75,725 subjects; median follow-up 4 yrs.; 10,797 developed ischemic ASVD (7,557 were CAD)

Two objectives:

1) were low levels of non-fasting TG associated with lower risk.
2) were loss of function APOC3 genetics associated with lower risk.

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

TG's Relationship to APOC3 Genetics and Ischemic ASVD Risk

Subjects with non-fasting TG <90 mg/dL vs. those with levels >350 mg/dL had significantly less risk

Ischemic ASVD: HR-0.43 (95% CI, 0.35-0.54)

Ischemic CAD: HR-0.40 (95% CI, 0.31- 0.52)

Adjusted for: age, sex, smoking, BP, physical activity and alcohol. (did not include BMI, DM, statin rx)

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

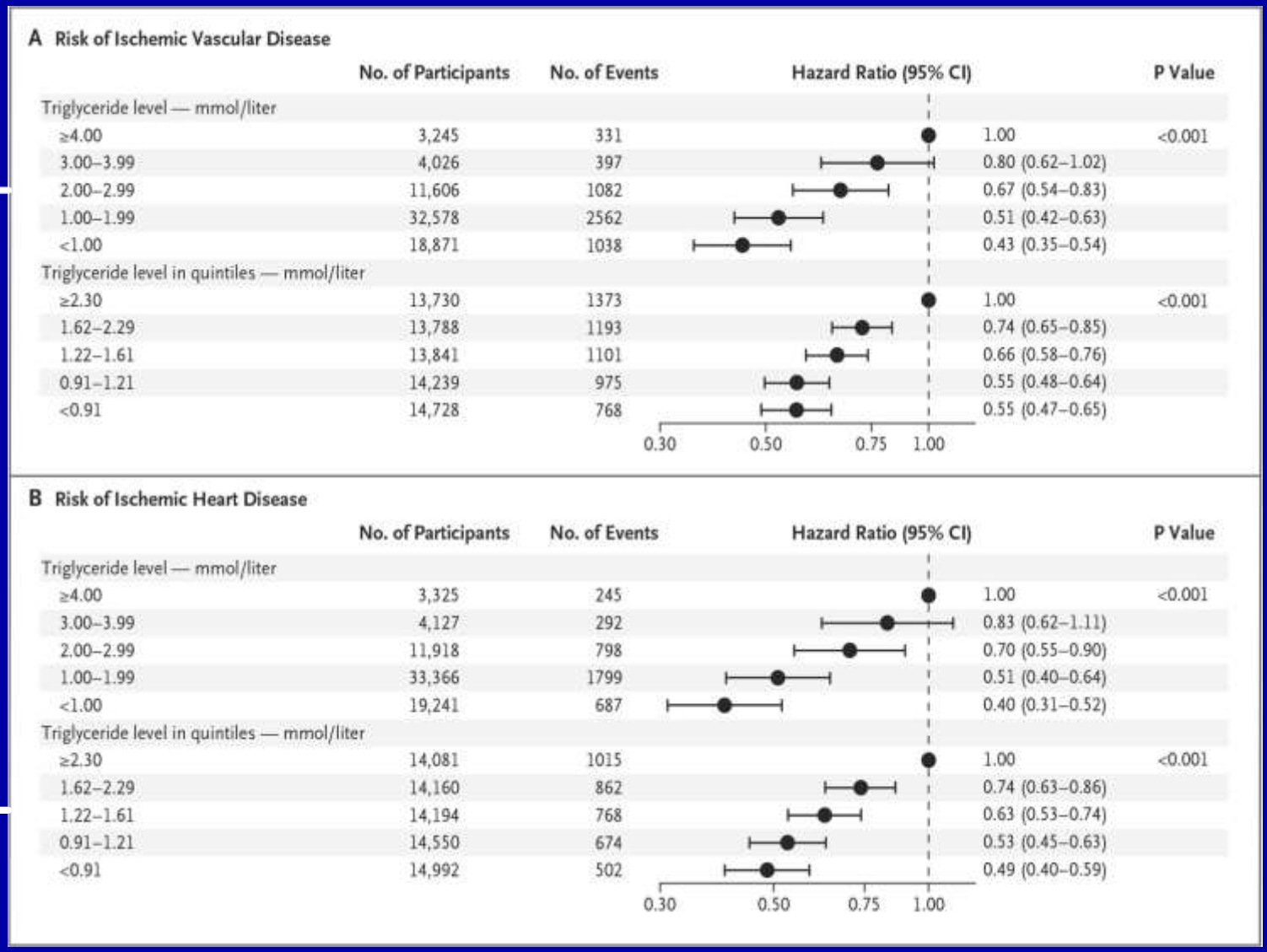
Non-fasting TG Related to Ischemic ASVD

Risks of Ischemic ASVD & CAD as a Function of Plasma Levels of Triglycerides.

mg/dL

≥348
261-347
174-346
87-345
<87

≥200
141-199
106-140
79-105
<79



A Risk of Ischemic Vascular Disease

	No. of Participants	No. of Events	Hazard Ratio (95% CI)	P Value
Triglyceride level — mmol/liter				
≥4.00	3,245	331	1.00	<0.001
3.00–3.99	4,026	397	0.80 (0.62–1.02)	
2.00–2.99	11,606	1082	0.67 (0.54–0.83)	
1.00–1.99	32,578	2562	0.51 (0.42–0.63)	
<1.00	18,871	1038	0.43 (0.35–0.54)	
Triglyceride level in quintiles — mmol/liter				
≥2.30	13,730	1373	1.00	<0.001
1.62–2.29	13,788	1193	0.74 (0.65–0.85)	
1.22–1.61	13,841	1101	0.66 (0.58–0.76)	
0.91–1.21	14,239	975	0.55 (0.48–0.64)	
<0.91	14,728	768	0.55 (0.47–0.65)	

0.30 0.50 0.75 1.00

B Risk of Ischemic Heart Disease

	No. of Participants	No. of Events	Hazard Ratio (95% CI)	P Value
Triglyceride level — mmol/liter				
≥4.00	3,325	245	1.00	<0.001
3.00–3.99	4,127	292	0.83 (0.62–1.11)	
2.00–2.99	11,918	798	0.70 (0.55–0.90)	
1.00–1.99	33,366	1799	0.51 (0.40–0.64)	
<1.00	19,241	687	0.40 (0.31–0.52)	
Triglyceride level in quintiles — mmol/liter				
≥2.30	14,081	1015	1.00	<0.001
1.62–2.29	14,160	862	0.74 (0.63–0.86)	
1.22–1.61	14,194	768	0.63 (0.53–0.74)	
0.91–1.21	14,550	674	0.53 (0.45–0.63)	
<0.91	14,992	502	0.49 (0.40–0.59)	

0.30 0.50 0.75 1.00

Jørgensen AB et al. N Engl J Med 2014;371:32-41

Relationship of Loss of Function APOC3 Genetics and Lipids

Three rare loss-of-function mutations for APOC3 were identified; no homozygotes found.

Heterozygosis for loss-of-function mutations in APOC3 was assoc. with a mean reduction in non-fasting TG of 44% ($P<0.001$).

Heterozygotes also had: 16% lower apoB; 24% higher HDL; 9% higher ApoA1.

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

Relationship of Loss of Function APOC3 Genetics and Other Known CV Risk Factors

Table S4. Characteristics of study participants by *APOC3* genotype.

nothing significant

	R19X			IVS2+1G>A			A43T			Any mutation		
	Noncarriers	Heterozygotes	P-value	Noncarriers	Heterozygotes	P-value	Noncarriers	Heterozygotes	P-value	Noncarriers	All heterozygotes	P-value
Number of subjects (%)	75,692 (99.96)	33 (0.04)	-	75,516 (99.72)	209 (0.28)	-	75,707 (99.98)	18 (0.02)	-	75,465 (99.66)	260 (0.34)	-
Age (years)	58 (47-67)	59 (48-67)	0.88	58 (47-67)	60 (49-68)	0.09	58 (47-67)	55 (46-74)	0.69	58 (47-67)	59 (48-69)	0.10
Female (%)	55	45	0.25	55	56	0.75	55	61	0.62	55	55	0.99
Body mass index (kg/m^2)	26 (23-28)	25 (24-27)	0.63	26 (23-28)	26 (24-28)	0.87	26 (23-28)	28 (23-29)	0.46	26 (23-28)	26 (24-28)	0.87
Diabetes (%)	4	0	0.25	4	6	0.16	4	6	0.71	4	5	0.35
Smoking (%)	24	21	0.73	24	28	0.18	24	11	0.21	24	26	0.46
Hypertension (%)	56	64	0.40	56	52	0.22	56	67	0.38	56	55	0.57
Physical inactivity (%)	7	9	0.70	7	10	0.21	7	11	0.54	7	10	0.16
Alcohol consumption (%)	72	73	0.92	72	74	0.58	72	78	0.58	72	74	0.50
Lipid lowering therapy (%)	9	3	0.21	9	7	0.29	11	0	0.17	9	6	0.08

Values are median and interquartile range or percentage. P-values by Mann-Whitney *U* test and chi-square test for continuous and categorical variables, respectively.

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

TG's Relationship to APOC3 Genetics and Ischemic ASVD Risk

Heterozygotes vs subjects with normal APOC3 genetics had significantly less risk.

Ischemic ASVD HR-0.59 (95% CI, 0.41-0.86) p=0.007

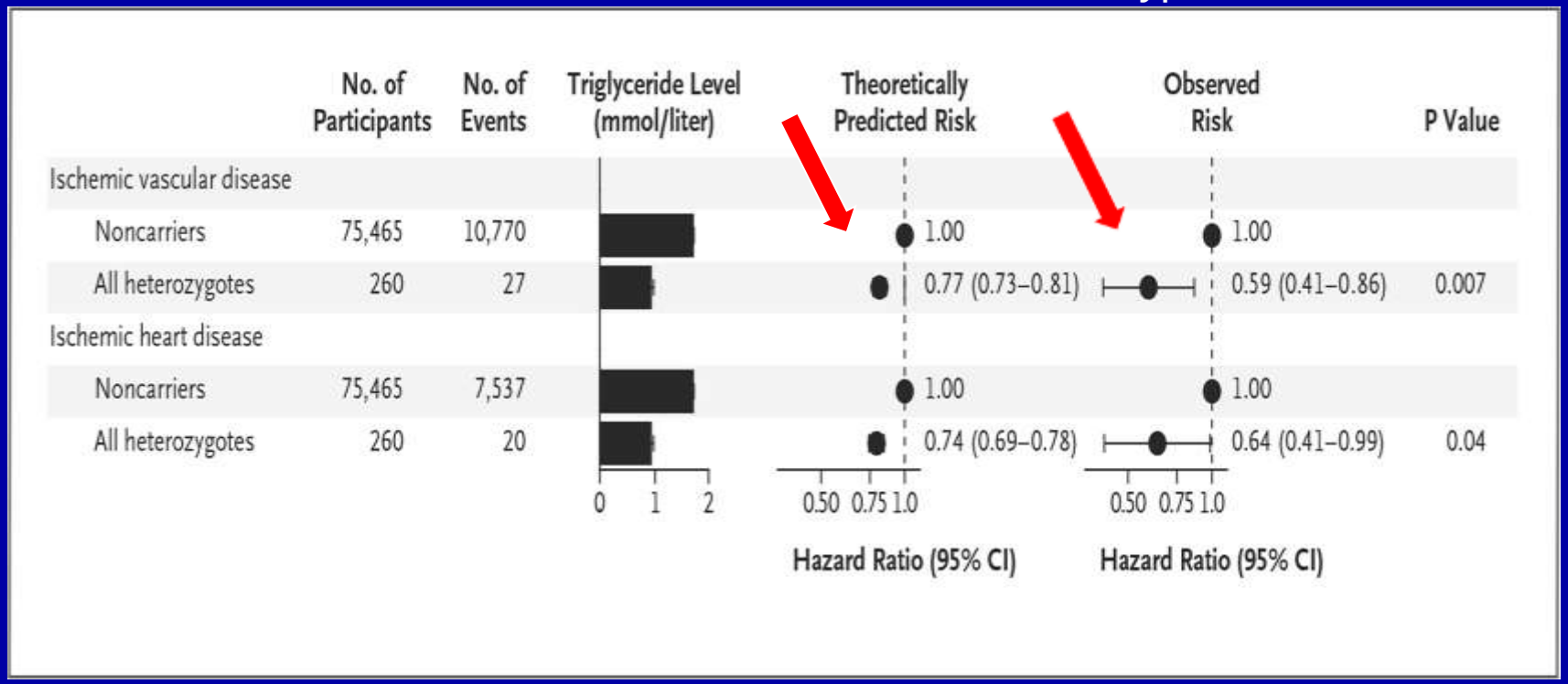
Ischemic CAD HR- 0.64 (95% CI,0.41-0.99) P =0.04

These reductions are greater than predicted based on TG

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

Risk Reduction Greater Than Predicted Based on TG Levels Alone

Mean Plasma Levels of Nonfasting TG and Hazard Ratios for Ischemic ASVD and CAD as a Function of APOC3 Genotype.



Authors' opinion this is most likely reflecting the beneficial effects of lifelong reductions in levels of triglycerides and remnant cholesterol.

BDM: what about the increase in HDL and apoA1 ?????

Jørgensen AB et al. N Engl J Med 2014;371:32-41

TG's Relationship to APOC3 Genetics and Ischemic ASVD Risk: Conclusion

Loss-of-function mutations in APOC3 associated with low levels of TG and a reduced risk of ischemic ASVD.

Inhibition of APOC3 by antisense oligonucleotides is potential therapy for reducing CV risk.

Jorgensen, A. B., et. al. (2014). Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease. *N Engl J Med*. Volume 371(1):32-41

Loss of Function APOC3 Genes, TG and CAD

4 mutations of APOC3 identified (3 loss of function & 1 a missense); 110,970 subjects evaluated for the mutations (1 in 150 had at least one) and risk of CAD (34,002 CAD pts).

There was a significant reduction in fasting TG and APOC3 levels in carriers: 39% & 46%, respectively.

(HDL 22% higher & LDL 16% lower)

Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease. *New England Journal of Medicine, 2014;371:22-31*

Loss of Function APOC3 Genes, TG and CAD

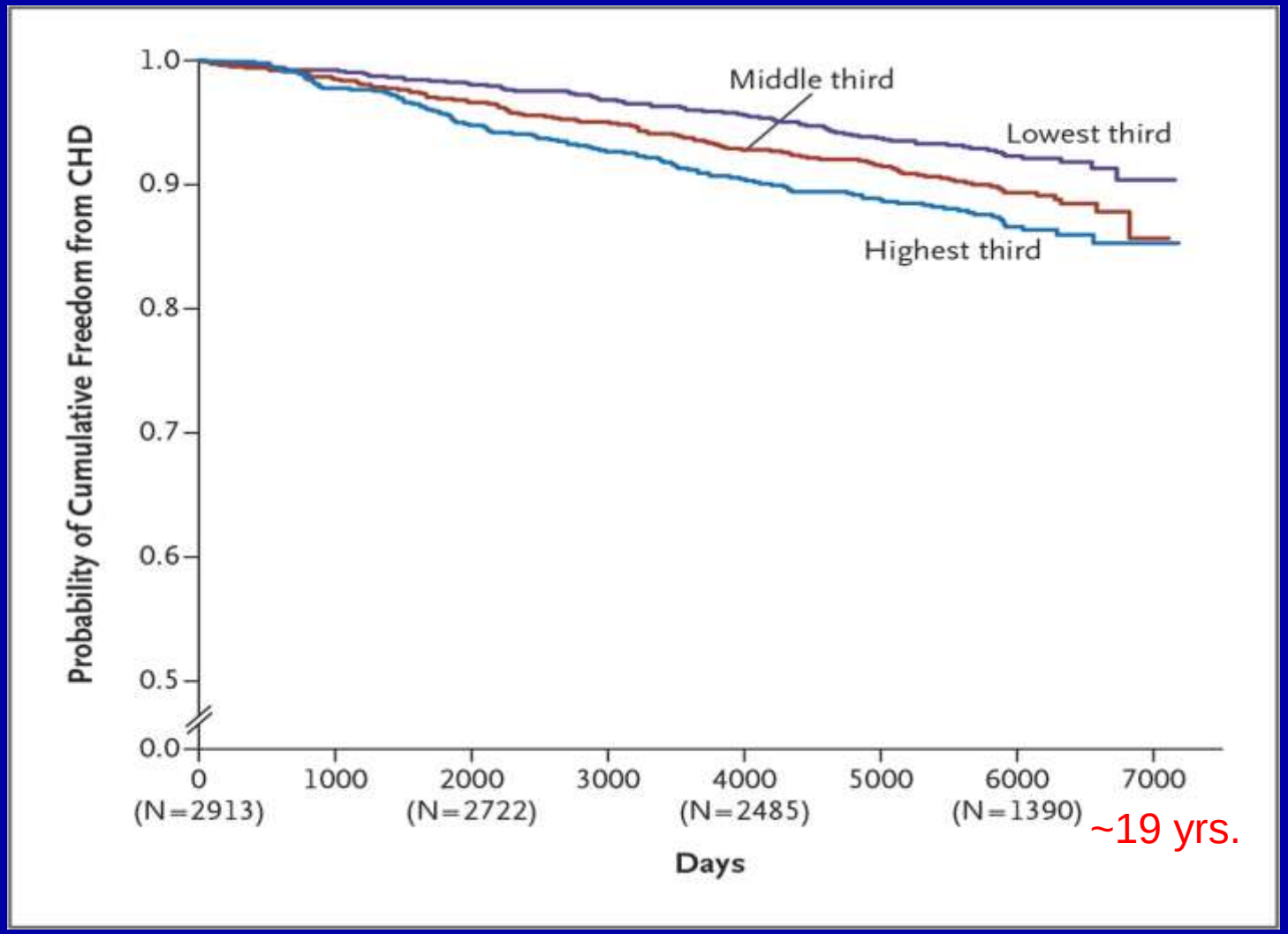
Risk of CAD among 498 carriers was 40% lower than noncarriers

OR-0.60; (95% CI, 0.47- 0.75) P =0.00004

Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease. *New England Journal of Medicine, 2014;371:22-31*

APOC3 Plasma Levels Associated with CAD Risk

Cumulative Probability of Freedom from CAD According to Plasma Level of APOC3 at Baseline in the FHS.



The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. N Engl J Med 2014;371:22-31

Loss of Function APOC3 Genes, TG and CAD

Loss of APOC3 function confers protection against CAD.

Our data provide confidence that an antisense oligonucleotide for APOC3 might reduce the risk of CAD.

Cannot determine the specific mechanism by which risk reduction was accomplished: TG lowered, HDL higher, LDL lower, APOC3 lower.

Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease. *New England Journal of Medicine, 2014;371:22-31*

BDM Thoughts

Exciting to see genetic studies leading to potential excellent novel therapies (i.e. PCSK9 monoclonal antibodies).

Remember marijuana and APOC3 – not good news especially in light of these studies.

Marijuana (MJ) Increases APOC3

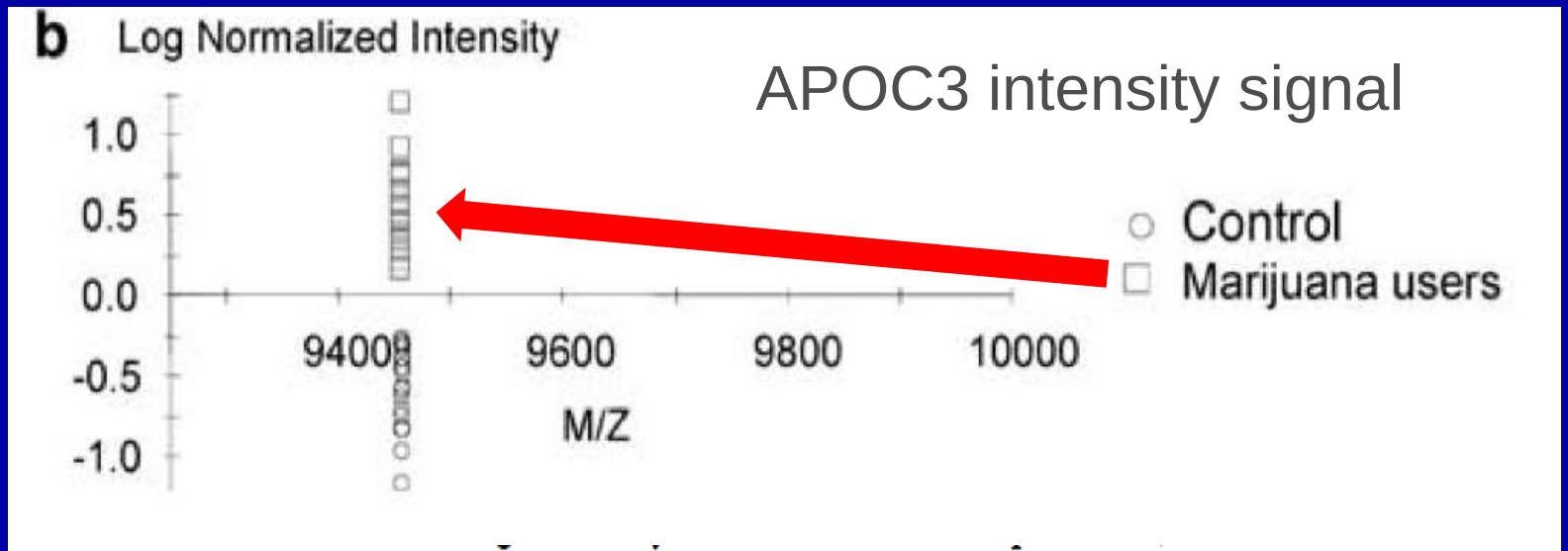
- 18 MJ users & 24 controls; use of other illicit drugs or heavy alcohol use excluded; joints/wk 78−350.

- Utilized a sophisticated proteomic approach to determine if MJ increased plasma APOC3

- Significantly higher APOC3 levels in MJ users

Jayanthi, S., et. al. (2010). Heavy marijuana users show increased serum apolipoprotein C-III levels: evidence from proteomic analyses. *Mol Psychiatry, 15*(1), 101-112.

Marijuana (MJ) Increases APOC3



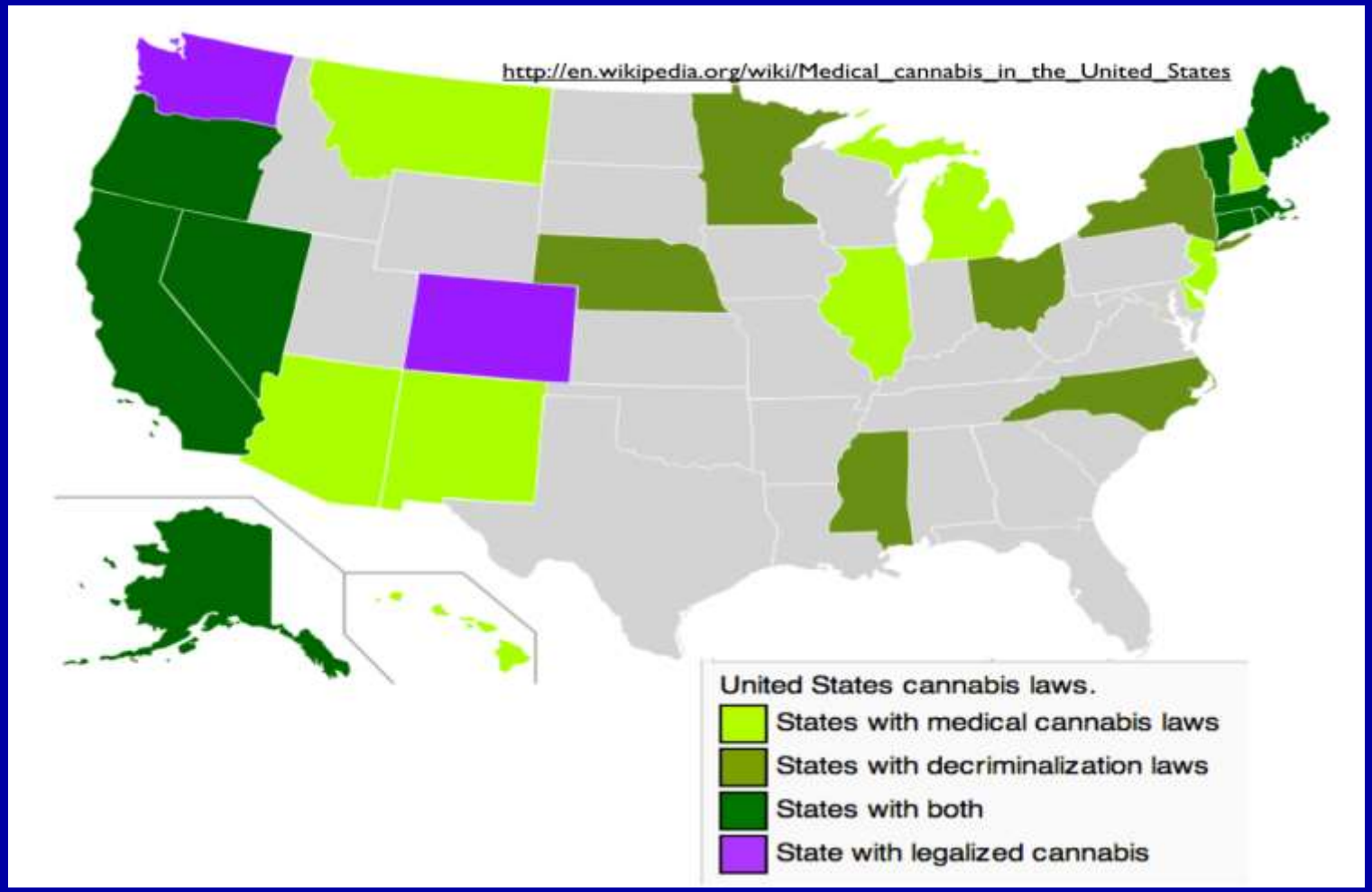
test). (b) Range of values for individual MJ users (on top of line) and controls (bottom of line). Note the lack of overlap between the two groups, with the MJ group showing higher values.

Jayanthi, S., et. al. (2010). Heavy marijuana users show increased serum apolipoprotein C-III levels: evidence from proteomic analyses. *Mol Psychiatry, 15*(1), 101-112.

Gov. Cuomo signed legislation 7/5/2014 legalizing medical marijuana.- 23rd State

FREDERIC J. BROWN/AFP/Getty Images

Happy Barely Belated Birthday Washington State-7/8/2014 !



BDM Thoughts

In light of the evidence with APOC3 and the current rather laissez faire attitude toward MJ, all patients should be asked about use of MJ.

Those who are using MJ should be educated on this potential risk.

PD Therapy Has a Positive Impact on the Atherosclerotic Disease Process

- 168 Australian Aboriginals; mean age 40; moderate PD; no known CVD or endodontic disease; all received oral hygiene instruction; 78 also received nonsurgical rx with Gracey hand scalers and piezoelectric US device.

- Multiple endpoints: one of which was one year change in maximum CIMT.

Kapellas, K., et. al. (2014). Effect of Periodontal Therapy on Arterial Structure and Function Among Aboriginal Australians: A Randomized, Controlled Trial. *Hypertension*. doi: 10.1161/hypertensionaha.114.03359

PD Therapy Has a Positive Impact on the Atherosclerotic Disease Process

Periodontal intervention produced a statistically significant reduction in maximum CIMT compared with the control group.

−0.02mm (95% CI, −0.05 to −0.002mm) p=0.03

Kapellas, K., et. al. (2014). Effect of Periodontal Therapy on Arterial Structure and Function Among Aboriginal Australians: A Randomized, Controlled Trial. *Hypertension*. doi: 10.1161/hypertensionaha.114.03359

PD Therapy Only Had a Positive Impact on Maximum CIMT and an Adverse Effect on ADMA

Table 3. Change in Pulse Wave Velocity, Carotid Intima-Media Thickness, and Inflammatory Markers (Complete Case Analysis) at 12 Months

	Treatment		Control		ANCOVA Least Squares	
Cardiovascular Risk Markers	Baseline	12 Mo	Baseline	12 Mo	Mean Δ (95% CI)	*P* Value
hsCRP, mg/L	4.68 (5.41)	5.28 (6.46)	4.84 (6.18)	4.25 (4.38)	0.84 (–0.63 to 2.32)	0.26
IL-6, pg/mL	3.24 (2.27)	1.87 (2.64)	1.99 (2.05)	2.22 (2.33)	–0.28 (–1.38 to 0.82)	0.62
Total cholesterol, mmol/L	5.01 (1.09)	4.97 (1.14)	5.04 (1.13)	4.82 (1.06)	0.07 (–0.11 to 0.24)	0.44
Non-HDL cholesterol, mmol/L	3.98 (1.11)	3.96 (1.10)	3.97 (1.14)	3.67 (1.09)	0.20 (–0.07 to 0.48)	0.15
HDL Cholesterol, mmol/L	1.03 (0.33)	1.04 (0.31)	1.08 (0.36)	1.11 (0.48)	0.00 (–0.07 to 0.06)	0.88
ADMA, mmol/L	0.42 (0.12)	0.48 (0.11)	0.43 (0.11)	0.44 (0.10)	0.05 (0.004 to 0.10)	0.03
HbA1c, mmol/mol	48.12 (19.61)	46.81 (19.30)	44.98 (15.40)	43.22 (12.08)	1.29 (–0.86 to 3.44)	0.24
PWV, m/s	8.27 (1.30)	8.44 (0.92)	8.37 (1.36)	8.33 (1.04)	0.21 (–0.01 to 0.43)	0.06
Maximum IMT, mm	0.79 (0.19)	0.76 (0.16)	0.79 (0.15)	0.78 (0.15)	–0.025 (–0.047 to –0.002)	0.03
Mean IMT, mm	0.64 (0.14)	0.63 (0.14)	0.64 (0.12)	0.65 (0.11)	–0.013 (–0.030 to 0.004)	0.13

Data for baseline/follow-up means presented as mean (SD). Reported values limited to those that have completed data at 12 months post-intervention. ADMA indicates asymmetrical dimethylarginine; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; IMT, intima-media thickness; and PWV, pulse wave velocity.

Kapellas, K., et. al. (2014). Effect of Periodontal Therapy on Arterial Structure and Function Among Aboriginal Australians: A Randomized, Controlled Trial. *Hypertension*. doi: 10.1161/hypertensionaha.114.03359

PD Therapy with One Time Scaling and US Treatment Failed at One Year

PD therapy resulted in modest improvements in PD parameters in the short-term, which were no longer significant by 12 months (consistent with PD recurrence).

Kapellas, K., et. al. (2014). Effect of Periodontal Therapy on Arterial Structure and Function Among Aboriginal Australians: A Randomized, Controlled Trial. *Hypertension*. doi: 10.1161/hypertensionaha.114.03359

PD Therapy Did Not Have a Positive Effect on Most PD Parameters

Table S3: Periodontal parameters at baseline and 12 months (Complete-Case Analysis)*

	Treatment		Control			
Periodontal health measures	Baseline	12 month	Baseline	12 month	ANCOVA least squares mean Δ (95% CI)	*P* value
Extent CAL ≥3mm	53.07 (25.84)	46.37 (25.71)	53.07 (27.59)	50.37 (24.20)	-4.00 (-8.01, 0.02)	0.05
Mean PD mm	2.38 (0.53)	2.26 (0.52)	2.41 (0.60)	2.37 (0.55)	-0.09 (-0.19, 0.01)	0.08
Extent PD ≥4mm (%)	13.38 (12.67)	11.69 (12.82)	14.26 (14.86)	13.61 (13.65)	-0.16 (-0.33, 0.01)	0.06
Extent PD ≥5mm (%)	4.45 (6.36)	4.24 (6.82)	5.45 (8.67)	5.25 (8.25)	-0.63 (-2.09, 0.84)	0.40
Extent CAL ≥3mm & PD ≥4mm	13.18 (12.50)	11.27 (12.28)	14.18 (14.62)	13.10 (13.19)	-1.27 (-2.87, 0.32)	0.12
Mean index teeth with calculus	4.11 (1.67)	2.97 (1.94)	4.06 (1.64)	3.94 (1.76)	-1.02 (-1.48, -0.56)	<0.01
Mean gingival bleeding score	1.44 (0.67)	1.35 (0.74)	1.43 (0.68)	1.50 (0.67)	-0.13 (-0.32, 0.05)	0.16
Mean index teeth with plaque	5.22 (1.25)	5.18 (1.37)	5.39 (1.06)	5.29 (1.23)	-0.06 (-0.05, 0.17)	0.30
Extent visible plaque (%)	28.66 (36.22)	28.54 (36.31)	25.25 (33.29)	32.14 (38.49)	-6.12 (-16.30, 4.05)	0.24

Data for means presented as mean (SD).

Reported mean (SD) values limited to those that have completed data 12-months post-intervention.

CAL= Clinical attachment loss; PD = probing pocket depth.

Mean gingival bleeding: modified from Löe & Silness scoring system (number of teeth with BOP / number of teeth periodontally assessed)[4];

Maximum score for index teeth with calculus & plaque=6;

Extent visible plaque limited to scores ≥2 indicative of moderate/abundant plaque visible with the naked eye.[4]

Kapellas, K., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03359

BDM Thoughts

- Surprised study got published: investigators not even blinded when doing repeat CIMTs.
- This study illustrates some form of ‘PD prophylactic rx’ is needed: many options such as q 3 mo. hygiene visits, PerioProtect, ozone rx, laser rx, daily solutions like Therasol, Closys, etc.
- There is a need for better research utilizing DNA salivary testing for bacterial burden as the primary marker for effective therapy. Dental parameters like pocket depth, bleeding on probing and clinical attachment loss should be secondary indicators of effective therapy.
- Studies like this one finding their way into a peer reviewed AHA journal probably weaken the oral systemic argument.

Oral Health Should be a Key Element in Healthcare Policies

Oral health is a critical component of overall health.

United Nations in 2011 recognized oral disease as an integral part of non-communicable diseases including CVD!

Oral health needs to be defined with objective measurements such as, salivary DNA of pathogens.

Glick, M., & Meyer, D. M. (2014). Defining oral health: A prerequisite for any health policy. *The Journal of the American Dental Association, 145*(6), 519-520.

Oral Health Should be a Key Element in Healthcare Policies

Oral health is essential to an individual's general health and quality of life.

Oral health professionals should be viewed as indispensable partners within primary health care.

Glick, M., & Meyer, D. M. (2014). Defining oral health: A prerequisite for any health policy. *The Journal of the American Dental Association, 145*(6), 519-520.

We have some work to do!

7/9/2014 (today) I received a call from a healthcare office from which we had requested records.

They said, “We noticed you are a medical provider. We are a dental office. Why would you want records from us?”

Chewing Tobacco (snus) Cessation Slashes Post MI Mortality Risk

2,474 snus using MI pts.; followed 2 yrs post MI.

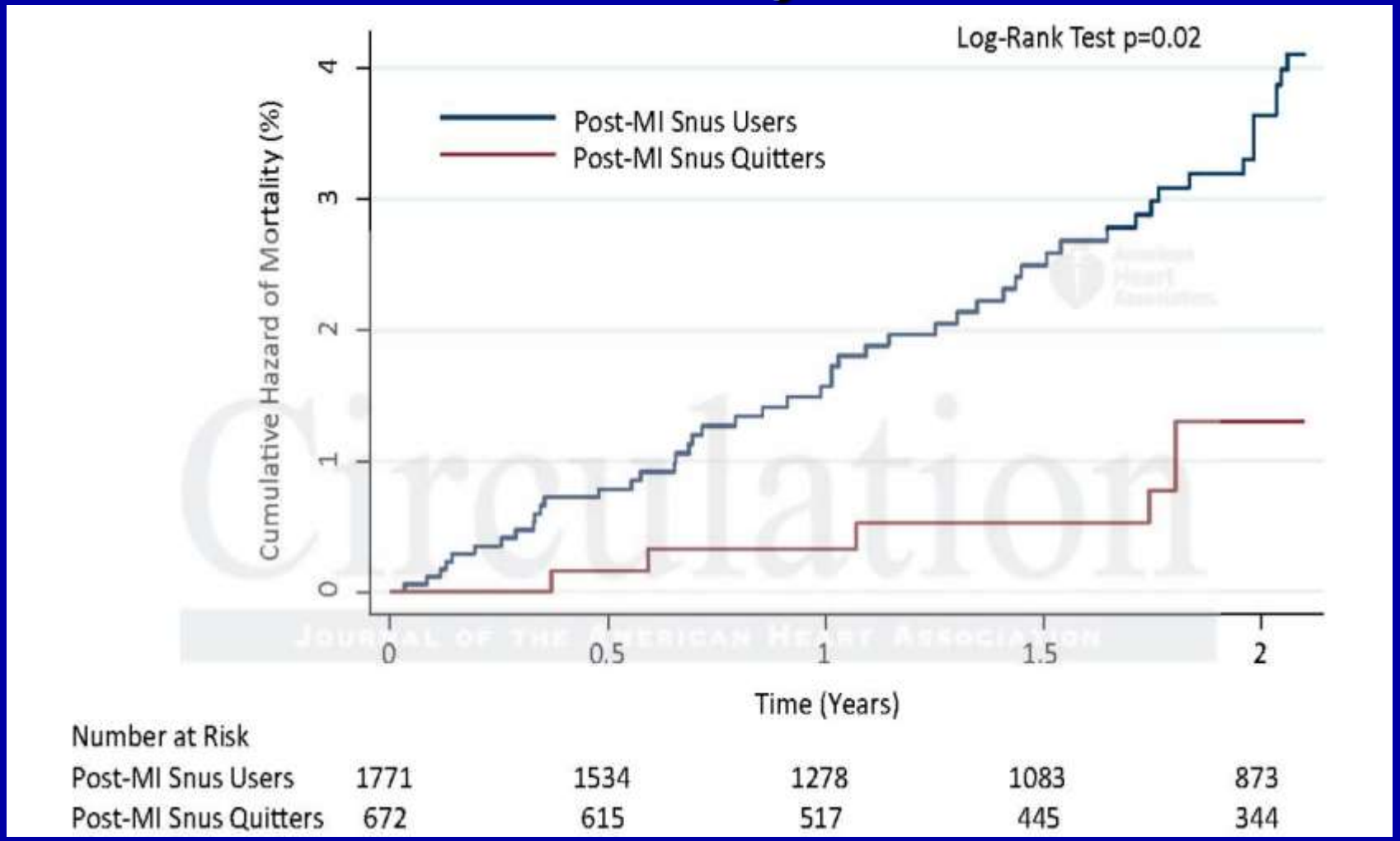
Objective: does quitting snus post MI (n-675) reduce risk of dropping dead?

Adjusting for age and gender, snus quitters had half the mortality risk

HR-0.51; (95% CI 0.29 to 0.91)

Arefalk, G., et. al. (2014). Discontinuation of Smokeless Tobacco and Mortality Risk after Myocardial Infarction. *Circulation*. doi: 10.1161/circulationaha.113.007252

Chewing Tobacco Cessation Slashes Post MI Mortality Risk



Arefalk, G., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.113.007252

BDM Thoughts

Glad to help with that message!

Depression Significant CV Risk in Younger Women

- 3,237 coronary angiogram pts; CAD either: present or absent; all assessed at baseline with Patient Health Questionnaire (PHQ)-9; followed 3 yrs. for CV events and death; pts segregated for age and gender.

- 34% of pts were women; mean age 62.5 ±11.8 yrs

- Two objectives: Is depression associated with:
  1) CAD?
  2) CV event risk and/or death?

Shah, A. J., et. al. (2014). Sex and Age Differences in the Association of Depression With Obstructive Coronary Artery Disease and Adverse Cardiovascular Events. *J Am Heart Assoc, 3*(3). doi: 10.1161/jaha.113.000741

Depression Significant CV Risk in Younger Women

After multivariable adjustment for CAD risk factors, depression was a significant predictor of CAD only in women ≤55yo

OR/1 point increase in PHQ-9 score =1.07

(95% CI, 1.02 to 1.13)

Shah, A. J., et. al. (2014). *J Am Heart Assoc, 3*(3). doi: 10.1161/jaha.113.000741

Depression Significant CV Risk in Younger Women

Highest adjusted hazard ratios of death and MACE were in young women.

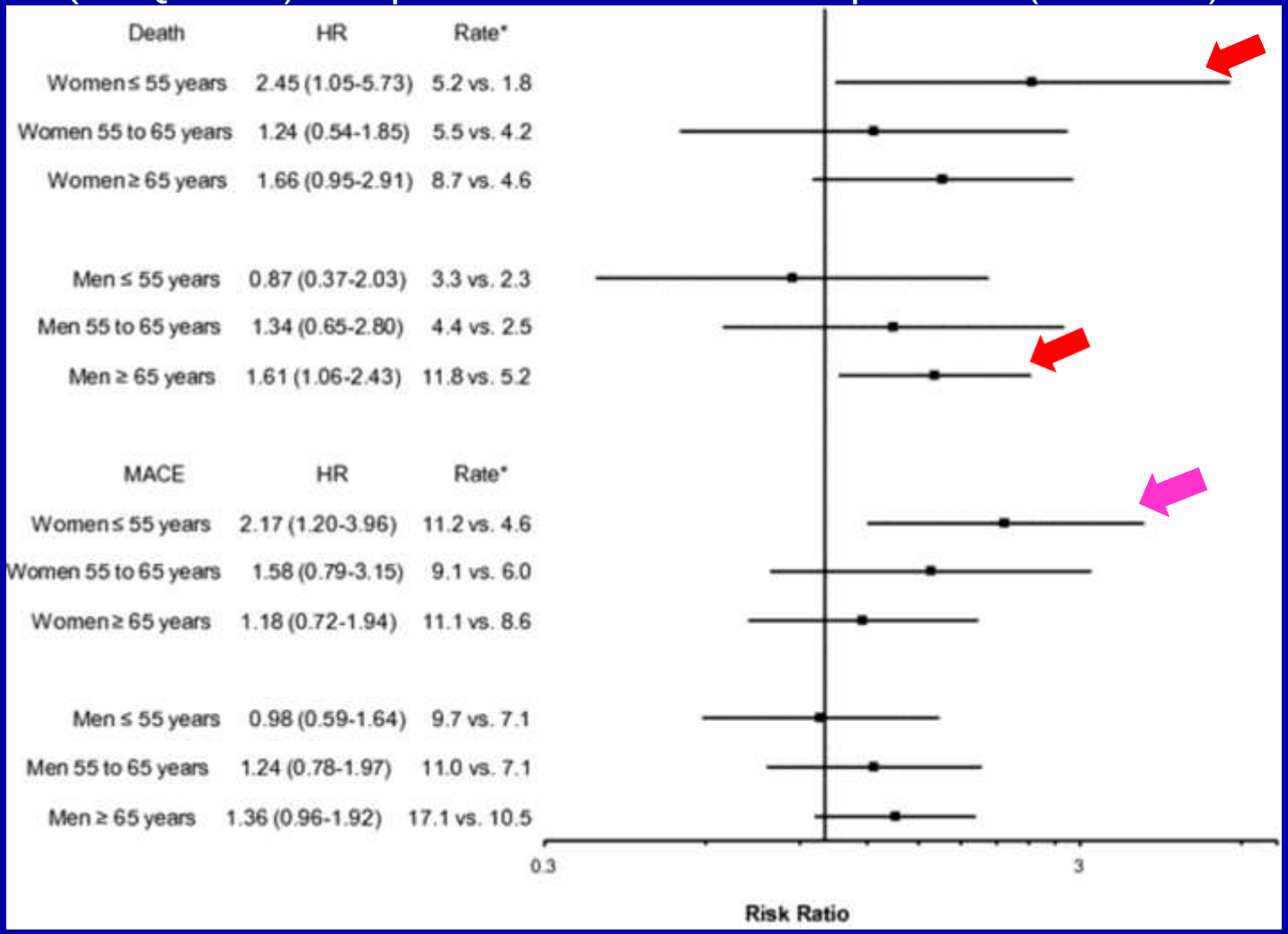
Adjusted hazard ratios of death and MACE only significant in young women.

Adjusted hazard ratio of death was also significant in older men.

Shah, A. J., et. al. (2014). *J Am Heart Assoc, 3*(3). doi: 10.1161/jaha.113.000741

Depression Significant CV Risk in Younger Women

Adjusted HR of death or MACE for moderate/severe depression (PHQ-9≥10) compared with no or mild depression (PHQ<10).



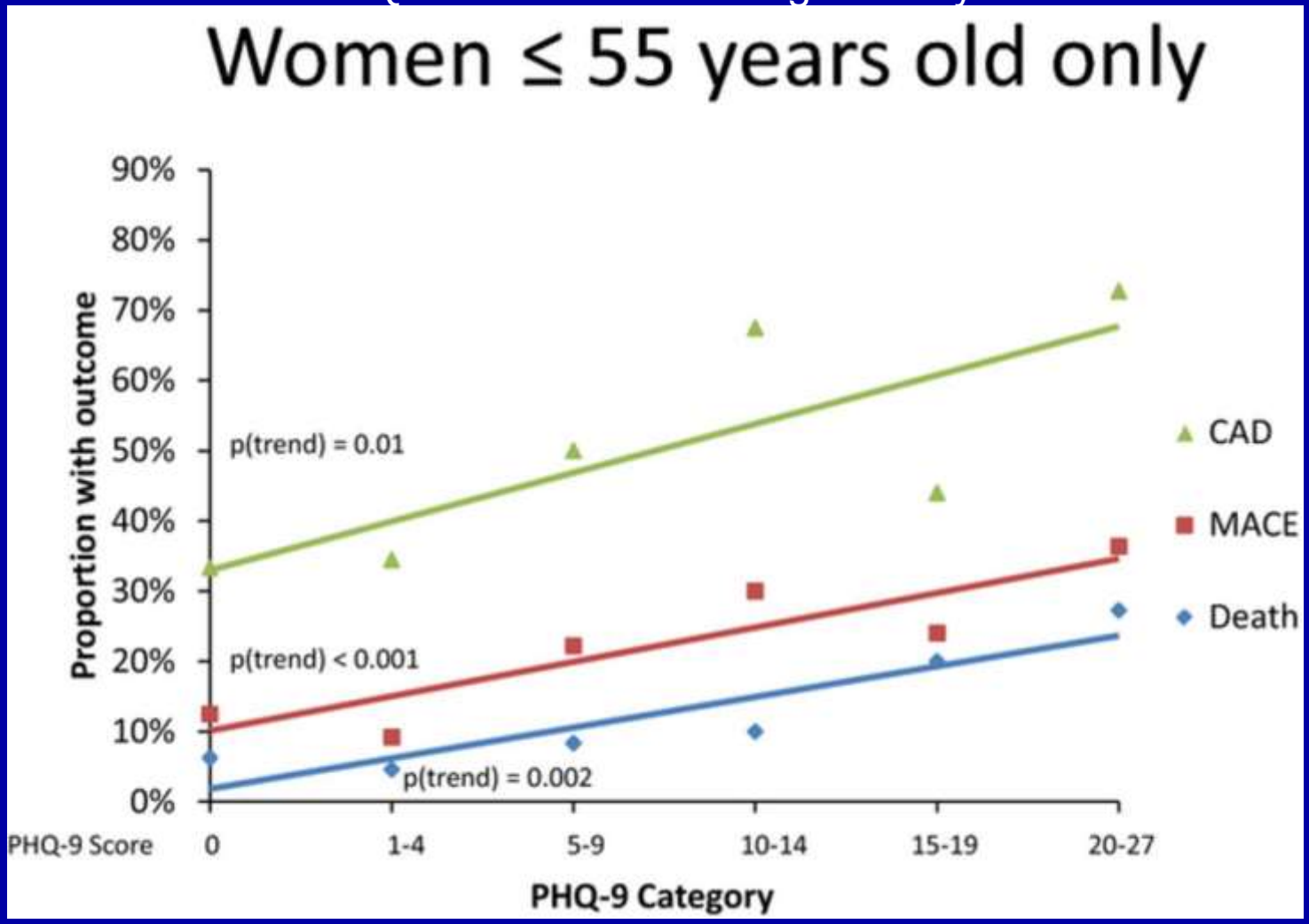
Death

MACE= death or coronary issues

Shah A J et al. J Am Heart Assoc 2014;3:e000741

Depression Significant CV Risk in Younger Women

Prevalence of CAD, as well as risk of death and MACE according to PHQ-9 score in women aged ≤55 years.



significant linear trend

Shah A J et al. J Am Heart Assoc 2014;3:e000741

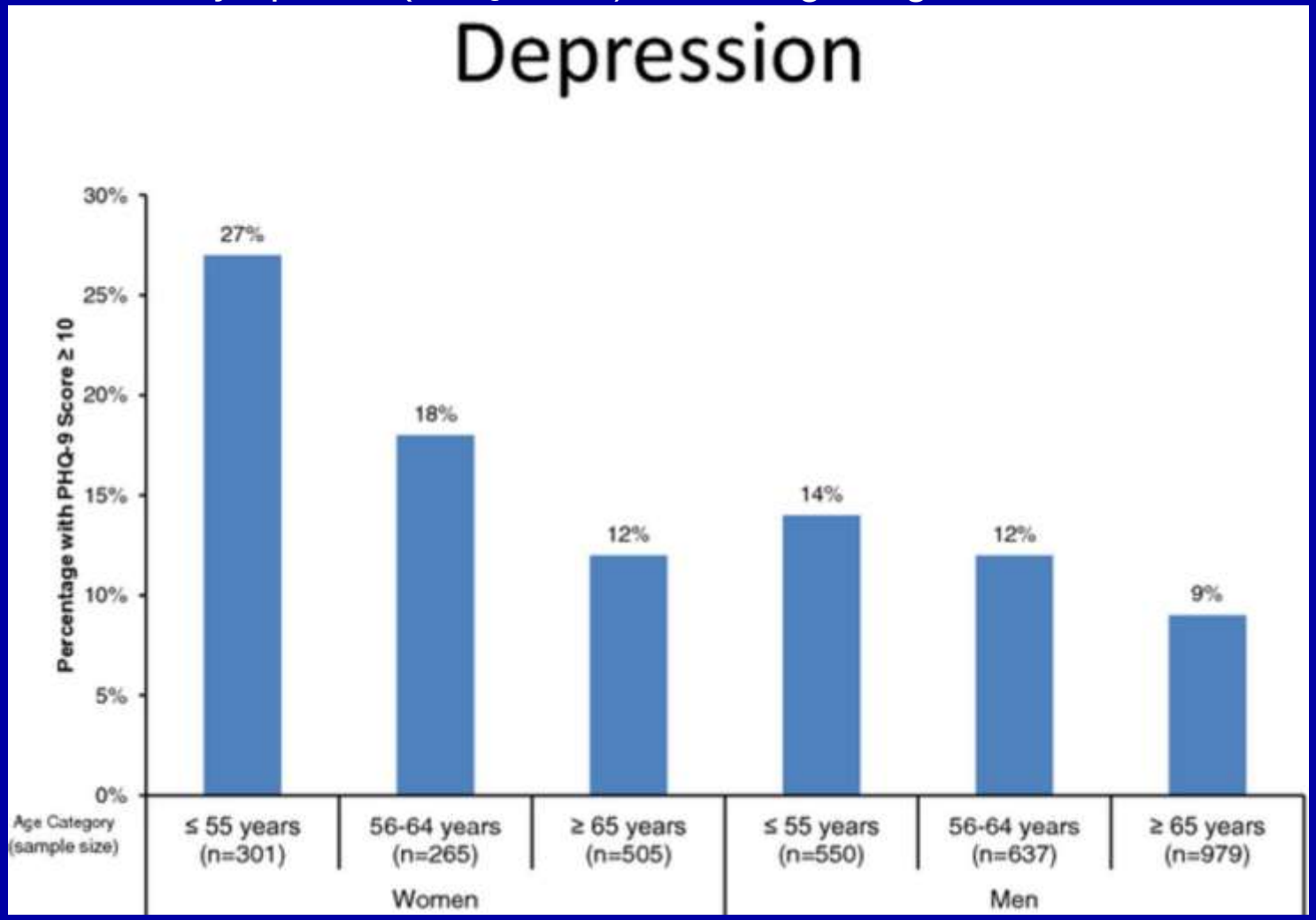
Depression Significant CV Risk in Younger Women

A concern in light of these findings is young women had the highest burden of depression & 27% had at least moderate depression.

Shah, A. J., et. al. (2014). *J Am Heart Assoc, 3*(3). doi: 10.1161/jaha.113.000741

Depression Significant CV Risk in Younger Women

Proportion of pts with moderate or higher severity depressive symptoms (PHQ-9≥10) according to age and sex.



Shah A J et al. J Am Heart Assoc 2014;3:e000741

Depression Significant CV Risk in Younger Women

Few women develop CVD at a young age, but the lifetime risk is over 50%.

Therefore, identification of risk factors in young populations may enhance early prevention efforts.

Serious attention should be paid to depression in this high-risk group.

Shah, A. J., et. al. (2014). *J Am Heart Assoc, 3*(3). doi: 10.1161/jaha.113.000741

BDM Thoughts

- Psychosocial issues are a CV risk factor and should be assessed in all patients.
- Depression in younger women also associated with increased stroke risk (Mishra, 2013).
- Anxiety is an independent risk factor for CHD and vascular inflammation (Roest, 2010 and Steptoe, 2011).
- Objective monitoring is essential – at baseline and at follow-up.

Jacksn, C, Mishra, G. Stroke Depression and Risk of Stroke. Published on-line May 16, 2013. Stroke 2013; 44:00-00.

Janzsky et al. June 28, 2010. Journal of Am Coll of Cardiology

Roest et al. Journal of the Am College of Cardiology, June 29, 2010

Ways to assess and monitor for depression and anxiety.

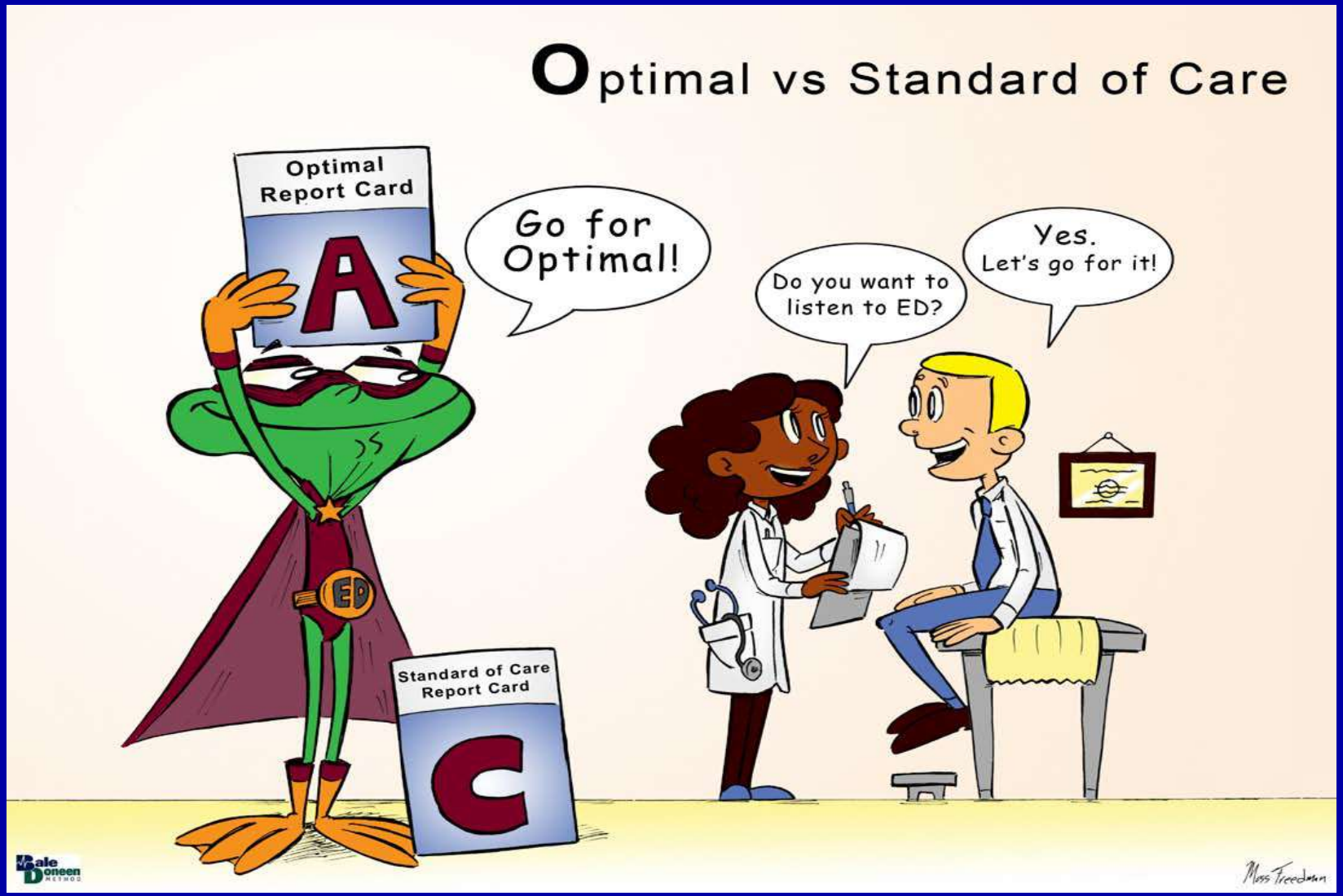
AssessMD –assesses depression with questions that encompass the PHQ-9, but is even more comprehensive and includes anxiety. Performed on an electronic tablet or iPAD.

42 questions; easy for patient to self administer. Usual provider reimbursement $28-$40.

Due to provider demand, can structure payment as 20 dollars per test or unlimited testing for $499 per month.

To sign up: www.AssessMD.com – use corporate code BaleDoneen60 and you will get a 60 day free trial.

Optimal Care



BP Goals in Elderly: Functional Limitations Should be Considered- Background

Elderly people ≥75 yo represent the fastest growing age group in the United States, and ≈2/3 are living with high blood pressure.

What is the optimal BP target in this age group to prevent CV events and death??

Currently some evidence indicating degree of disability should factor into goals.

Peralta, C. A., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BP Goals in Elderly: Functional Limitations Should be Considered

2,358 pts from CHS; mean age 78; assessed limitations in activities of daily living (ADL); 775 had ≥1 ADL; followed 10 yrs; 778 incident CV events.

(ADL: bed to chair; eating; bathing; dressing; toilet)

Evaluated BP's association with CV event risk and the potential impact of limitation with ADL on best BP targets to reduce risk.

Peralta, C. A., et. al. (2014). Systolic and Diastolic Blood Pressure, Incident Cardiovascular Events, and Death in Elderly Persons: The Role of Functional Limitation in the Cardiovascular Health Study. *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BP Goals in Elderly: Functional Limitations Should be Considered- BP ~ same in 2 groups

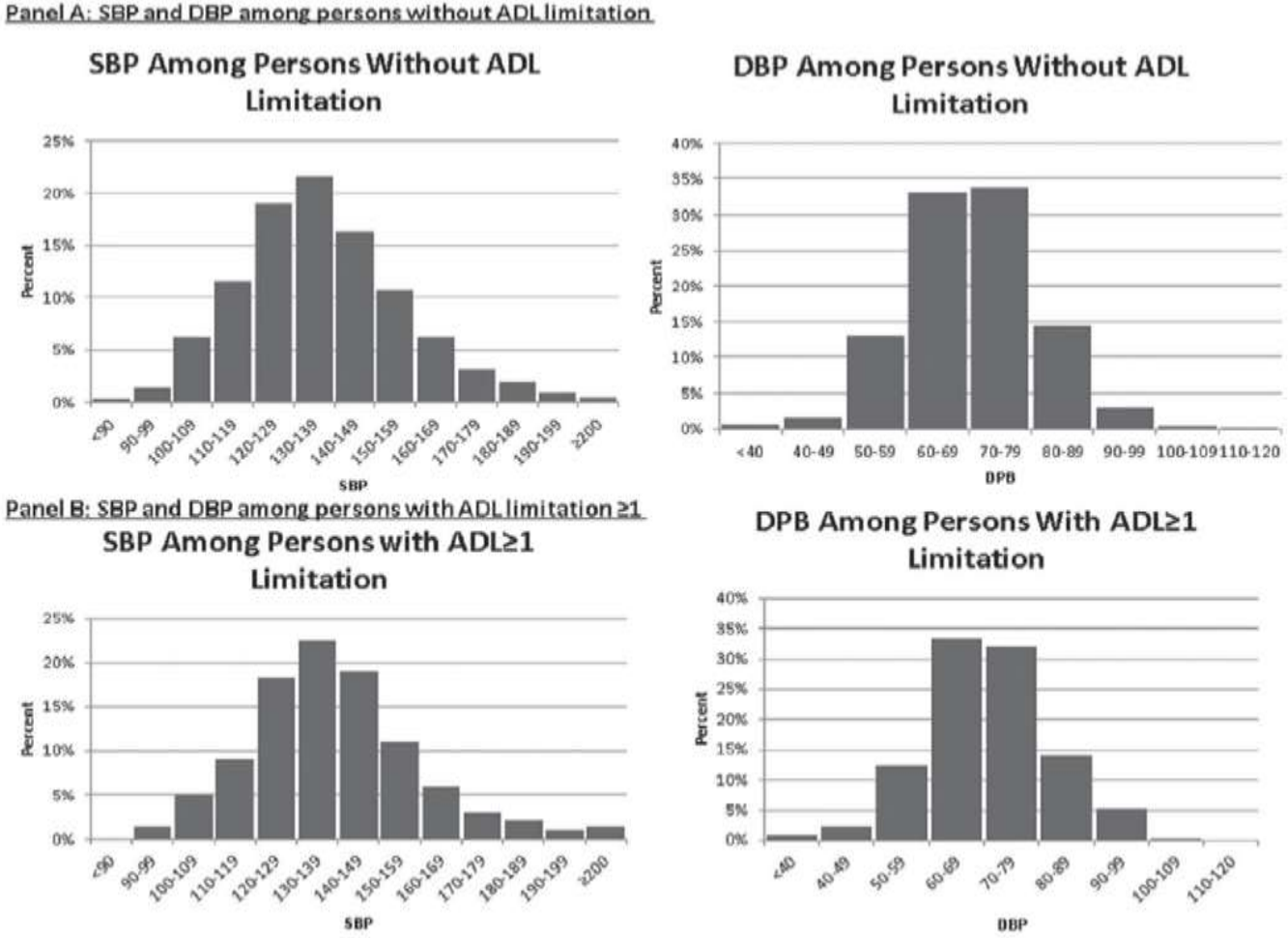


Figure 1. Distribution of systolic blood pressure (SBP) and diastolic blood pressure (DBP) among 3547 Cardiovascular Health Study Participants without (**A**) and with (**B**) activities of daily living (ADL) limitation.

Peralta, C. A., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BP Goals in Elderly: Functional Limitations Should be Considered- CV Events

Results fully adjustment for potential confounders and treatment with BP medications.

ADL limitation had no significant impact on systolic BP association with risk.

For every 10-mm Hg increase above 120-mm Hg CV risk rose 6-8%

Peralta, C. A., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BP Goals in Elderly: Functional Limitations Should be Considered- CV Events

ADL limitation was significant with diastolic BP.

For diastolic BP >80mm Hg vs ≤65 mm Hg

Individuals without ADL limitations had an insignificant 4% increased risk.

Individuals with ADL limitations had a significant 51% decreased risk.

Peralta, C. A., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BP Goals in Elderly: Functional Limitations Should be Considered Also for Death Risk

DBP Related to Risk of Death

DBP				
Without ADL limitation				
DBP (per 10-mm Hg increase)	2792	58.5	0.98 (0.93, 1.03)	1.07 (1.01, 1.14)‡
DBP				
≤65	941	63.6	1.00	1.00
66–80	1425	55.0	0.94 (0.83, 1.07)	1.11 (0.97, 1.27)
>80	426	59.4	0.99 (0.83, 1.18)	1.30 (1.06, 1.61)‡
With ADL limitation				
DBP (per 10-mm Hg increase)	755	102.9	0.93 (0.84, 1.02)	0.97 (0.88, 1.07)
DBP				
≤65	258	120.8	1.00	1.00
66–80	366	86.7	0.68 (0.54, 0.86)‡	0.72 (0.57, 0.91)‡
>80	131	120.7	0.87 (0.63, 1.20)	0.87 (0.61, 1.24)

Peralta, C. A., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BP Goals in Elderly: Functional Limitations Should be Considered

Study suggests ascertaining ADL limitations can identify a subgroup of elders in whom a low DBP should be avoided.

Therefore, among people with ADL limitations, the benefit of a lower SBP needs to be weighed against the associations of diastolic hypotension with higher risk of CVD and death.

Peralta, C. A., et. al. (2014). *Hypertension*. doi: 10.1161/hypertensionaha.114.03831

BDM Thoughts

- For healthy individuals regardless of age optimal BP is ~ <120/65 mm Hg.
- For pts with health issues ‘optimal’ BP varies significantly.
- This study indicates clinically it is important to question elderly pts about any ADL limitations.
- In elderly pts with limitations of ADL, BP therapy should target a systolic BP as low as possible without dropping the diastolic under 66 mm Hg.
- Big picture: need to individualize management; one size does not fit all.

EDFROG IRA

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

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.

Lifestyle Has Huge Impact on Stroke Risk

Table 2. Risk of Stroke Associated with Lifestyle Factors Among Men (m) and Women (w)

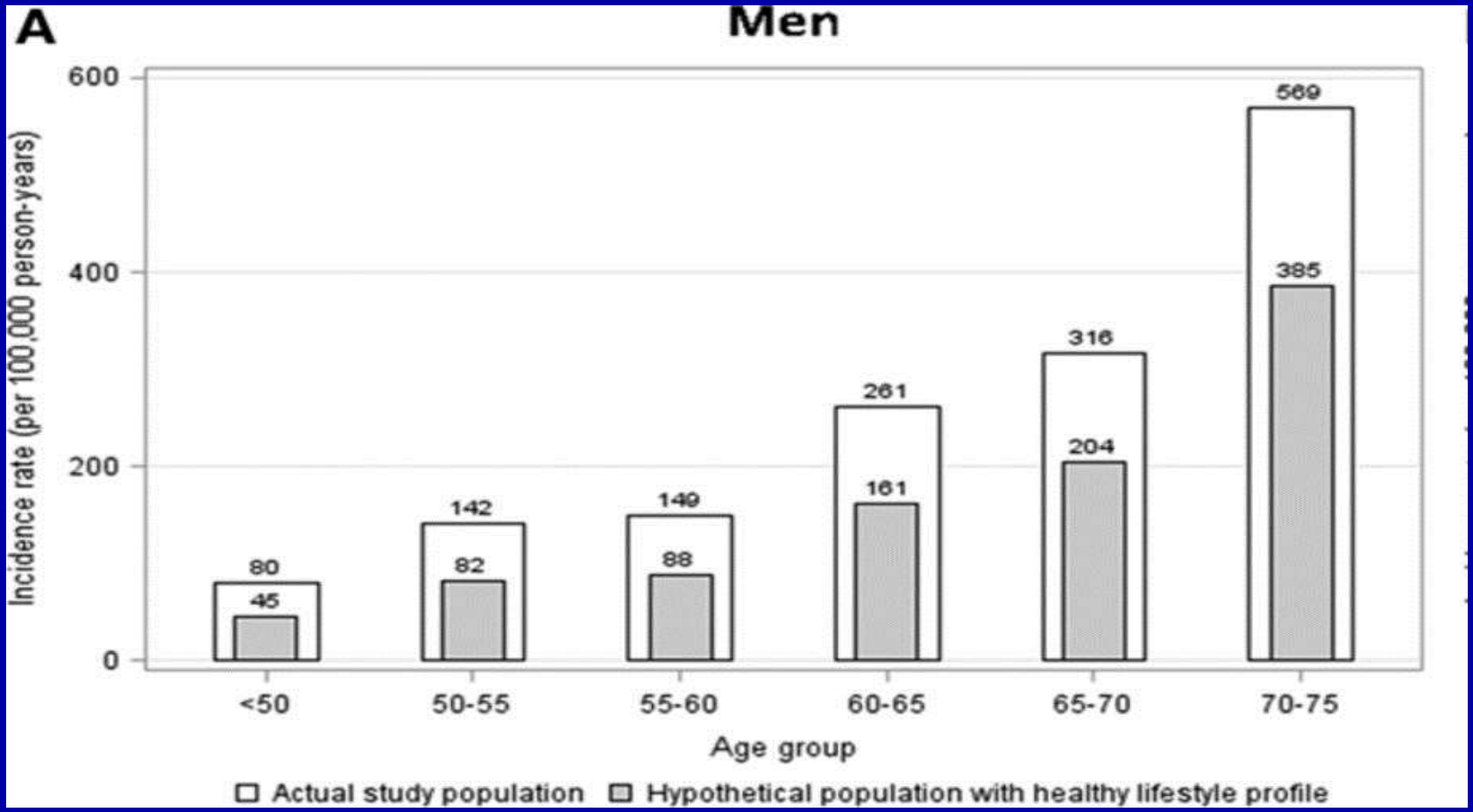
	Men			Women		
	No. of Stroke	Univariable Model HR (95% CI)	Multivariable Model* HR (95% CI)	No. of stroke	Univariable Model HR (95% CI)	Multivariable Model* HR (95% CI)
BMI categories, kg/m²						
<25.0	77	1.00	1.00	81	1.00	1.00
25.0–29.9	206	1.43 (1.10–1.86)	1.33 (0.96–1.83)	65	1.07 (0.77–1.49)	0.82 (0.54–1.24)
≥30	73	1.44 (1.05–1.99)	1.22 (0.79–1.89)	49	1.57 (1.09–2.25)	1.03 (0.63–1.76)
Waist circumference, cm						
<91 (m) <74.7 (w)	87	1.00	1.00	35	1.00	1.00
91–99.4 (m) 74.7–84.9 (w)	119	1.21 (0.92–1.60)	1.04 (0.75–1.43)	63	1.24 (0.82–1.88)	1.35 (0.87–2.10)
≥99.5 (m) ≥85 (w)	150	1.45 (1.11–1.90)	1.18 (0.82–1.70)	97	1.79 (1.20–2.6	1.92 (1.11–3.30)
Physical activity index						
Inactive	54	1.00	1.00	52	1.00	1.00
Moderately inactive	109	0.71 (0.51–0.98)	0.76 (0.54–1.05)	62	0.47 (0.33–0.6	0.49 (0.34–0.71)
Moderately active	95	0.74 (0.53–1.04)	0.81 (0.57–1.13)	47	0.49 (0.33–0.7	0.53 (0.35–0.79)
Active	98	0.84 (0.60–1.17)	0.92 (0.66–1.29)	34	0.47 (0.30–0.7	0.50 (0.32–0.77)
Smoking status						
Never smoker	101	1.00	1.00	98	1.00	1.00
Former smoker	154	1.00 (0.77–1.28)	0.98 (0.76–1.27)	39	1.00 (0.69–1.45)	0.87 (0.59–1.26)
Current smoker	101	2.15 (1.63–2.85	1.63 (1.23–2.17)	58	2.61 (1.87–3.6	2.04 (1.46–2.88)
Lifetime mean alcohol consumption, g/d						
<12 (m) >6 (w)	100	1.00	1.00	117	1.00	1.00
12–24 (m) 6–11 (w)	111	1.04 (0.79–1.36)	1.00 (0.76–1.31)	42	1.03 (0.72–1.47)	1.09 (0.76–1.56)
25–59 (m) 12–23 (w)	99	0.96 (0.73–1.27)	0.88 (0.66–1.16)	23	0.98 (0.63–1.54)	1.01 (0.64–1.59)
≥60 (m) ≥24 (w)	46	1.57 (1.11–2.23)	1.30 (0.91–1.86)	13	1.40 (0.79–2.49)	1.31 (0.73–2.34)
DASH-style diet score						
Unhealthy diet score	139	1.00	1.00	117	1.00	1.00
Intermediate diet score	125	0.91 (0.72–1.16)	0.97 (0.76–1.23)	78	1.00 (0.72–1.40)	1.14 (0.82–1.60)
Healthy diet score	92	0.58 (0.45–0.75	0.68 (0.52–0.89)	55	0.89 (0.62–1.27)	1.16 (0.79–1.68)

BMI indicates body mass index; CI, confidence interval; DASH, Dietary Approach to Stop Hypertension; and HR, hazard ratio.
*Multivariable model adjusted for BMI, waist circumference, physical activity, smoking status, alcohol consumption, and diet where appropriate.

Tikk, K., et. al. (2014). *Stroke, 45*(7), 2041-2046.

Lifestyle Has Huge Impact on Stroke Risk

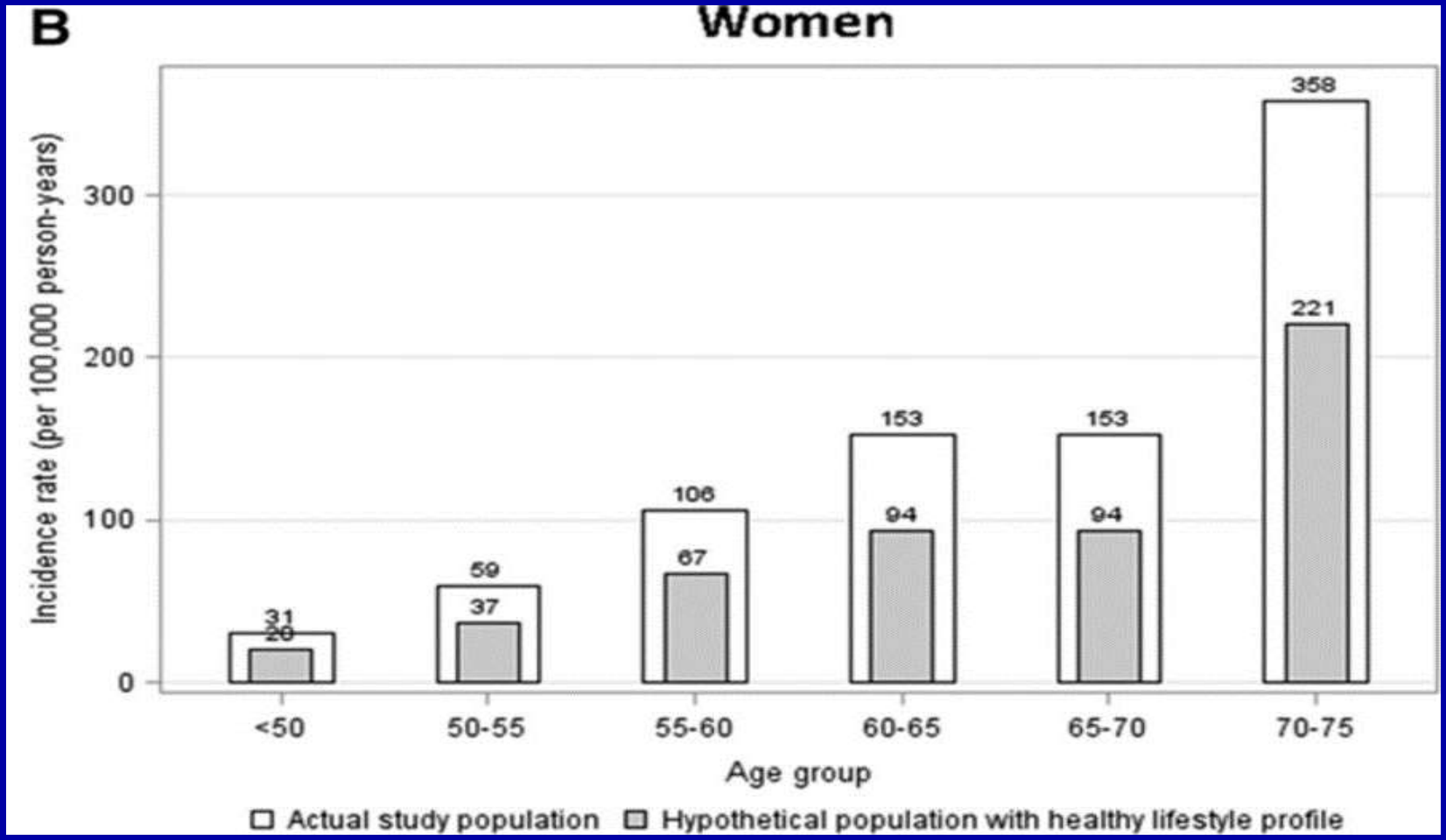
Five-year stroke incidence rates for men (A) predicted in the actual study population and in a hypothetical population with a healthier lifestyle profile (never smoker, optimal body weight and waist, physically active and moderate low alcohol consumption, healthy diet score).



Tikk K et al. Stroke. 2014;45:2041-2046

Lifestyle Has Huge Impact on Stroke Risk

Five-year stroke incidence rates for men women (B) predicted in the actual study population and in a hypothetical population with a healthier lifestyle profile (never smoker, optimal body weight and waist, physically active and moderate low alcohol consumption, healthy diet score).



Tikk K et al. Stroke. 2014;45:2041-2046

BDM Thoughts

Obesity, physical activity, smoking and diet are lifestyle issues having significant impact on stroke risk.

Alcohol was only significant when it was heavy use and then it increased stroke risk.

We need to continue to promote lifestyle as the most important means of reducing CV risk!

Fitness Related to Long Term CV Mortality Risk: Background

Tools for predicting long term (~lifetime) CV risk are lacking.

There is evidence that a one time measure of physical fitness is associated with CV event risk and mortality in the short and long term.

Is a one time measurement of fitness a significant covariate in long term prediction of CV death?

Wickramasinghe, C. D., et. al. (2014). *Circulation: Cardiovascular Quality and Outcomes*. doi: 10.1161/circoutcomes.113.000531

Fitness Related to Long Term CV Mortality Risk

16,533 Cooper Clinic pts (low-risk cohort); followed for 28 yrs.; 1,123 (6.8%) CV deaths during that time.

Pts had baseline sex-specific fitness testing: low, intermediate, high.

Sex-specific 30-yr risk estimates for CV death were calculated to see if fitness level was associated with the individuals who suffered a CV death.

Wickramasinghe, C. D., et. al. (2014). Prediction of 30-Year Risk for Cardiovascular Mortality by Fitness and Risk Factor Levels: The Cooper Center Longitudinal Study. *Circulation: Cardiovascular Quality and Outcomes*. doi: 10.1161/circoutcomes.113.000531

Fitness Related to Long Term CV Mortality Risk

Across all risk factor strata, the presence of low fitness was associated with a greater 30-year risk for CV death.

Wickramasinghe, C. D., et. al. (2014). *Circulation: Cardiovascular Quality and Outcomes*. doi: 10.1161/circoutcomes.113.000531

Fitness Related to Long Term CV Mortality Risk

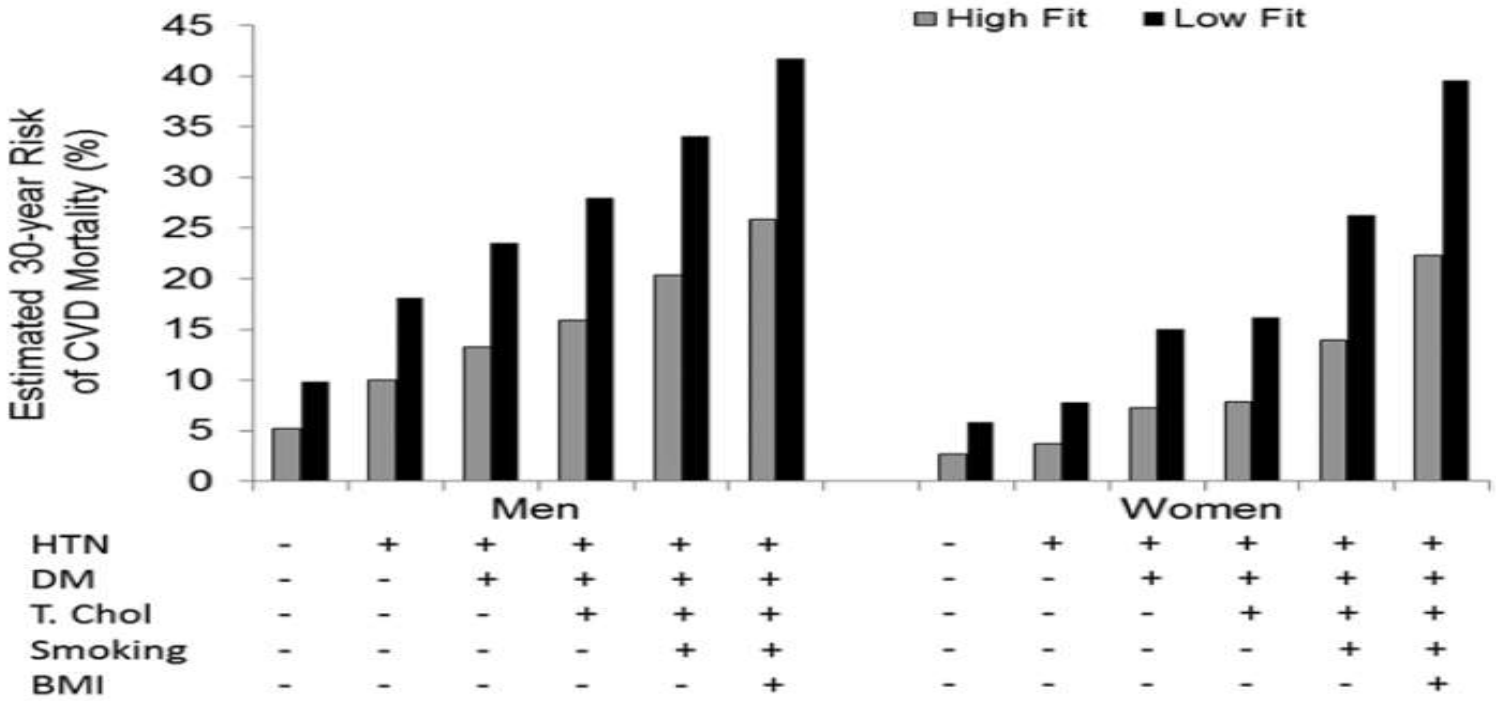


Figure 3. Estimated 30-year risk for cardiovascular disease (CVD) mortality for 50-year-old men and women by risk factor and fitness categories. Risk estimates are derived from risk calculator according to the presence (+) or absence (–) of risk factors (as defined below) and stratified by high fitness (men, 12 metabolic equivalents [METs]; women, 10 METs) or low fitness (men, 8 METs; women, 6 METs). BMI indicates body mass index (25 kg/m^2); DM, diabetes mellitus (present); HTN, hypertension (160 mm Hg); and T.Chol, total cholesterol (240 mg/dL).

Wickramasinghe, C. D., et. al. (2014). *Circulation: Cardiovascular Quality and Outcomes*. doi: 10.1161/circoutcomes.113.000531

Fitness Related to Long Term CV Mortality Risk

Cardiovascular Lifetime Risk Pooling Project: to determine the lifetime risks for CV death, fatal/non-fatal CAD, and fatal/non-fatal stroke for risk factors measured at four index ages: age 45-, 55-, 65-, and 75-years.

Includes: gender, age, sys BP, DM, TC, smoking, BMI, METS

Calculator available at: www.lifetimerisk.org

Wickramasinghe, C. D., et. al. (2014). *Circulation: Cardiovascular Quality and Outcomes*. doi: 10.1161/circoutcomes.113.000531

BDM Thoughts

- Supports physical fitness to reduce CV risk.
- Calculator is fun and may motivate some pts, but is based on a very limited number of risk factors.
- Evaluating for presence of disease should be an integral part of any risk assessment.
- Inflammation is the trigger for CV events; biomarkers of arterial inflammation determine current risk.
- Surprised how many people who attended the Cooper Clinic ended up having CV events- 1,123 fatal + 1,970 non-fatal CV events= 2,093 (12.7%).
- Bottom line: exercise!!!

Exercise Impacts Depression Favorably

Review of 39 randomized trials; 2,326 pts; 68% female; 22-88 yo; 14 countries; follow-up 1-4 mos.

Exercise vs either placebo, anti-depressants, psychological interventions

Outcomes: change in depression by Beck, Hamilton or Geriatric Depression Scale.

Cooney, G., Dwan, K., & Mead, G. (2014). EXercise for depression. *JAMA, 311*(23), 2432-2433.

Exercise Impacts Depression Favorably

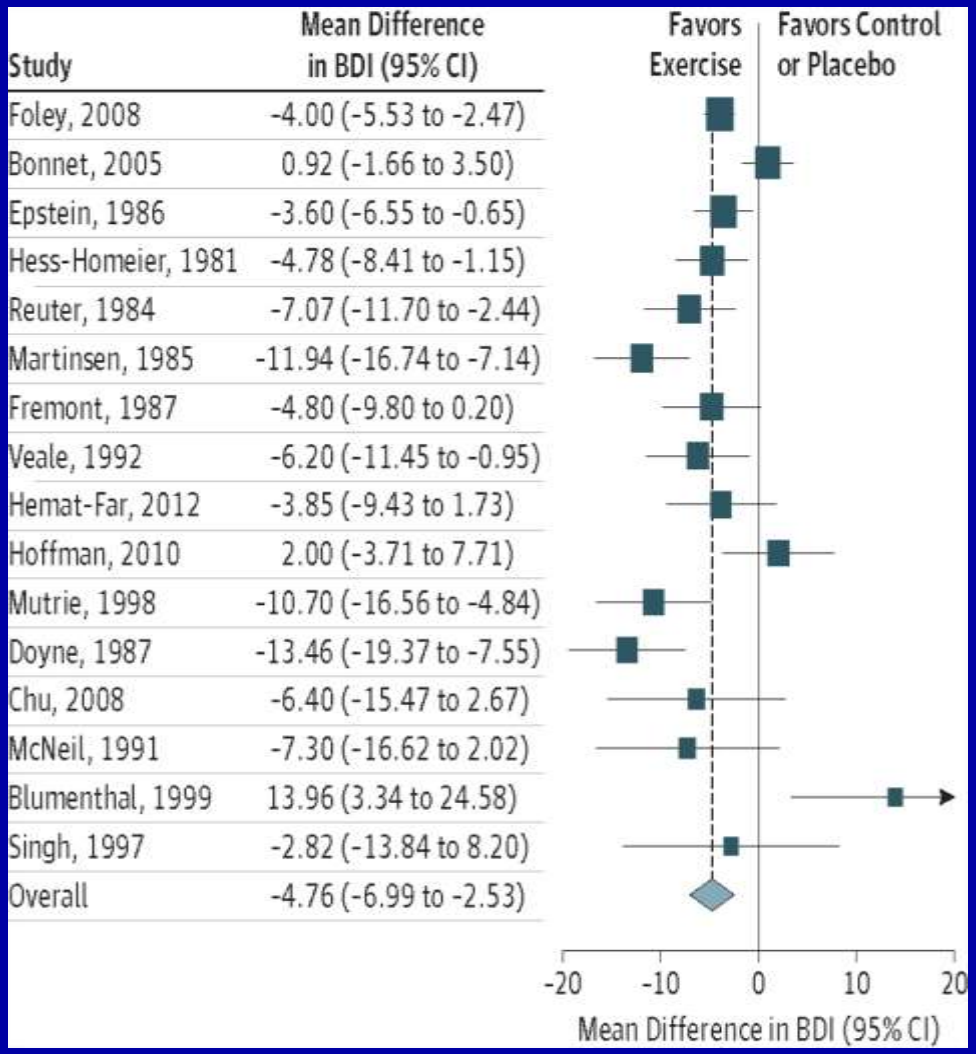
Exercise was associated with a greater reduction in depression by 38%

−0.62 (95% CI, −0.81 to −0.42)

Cooney, G., Dwan, K., & Mead, G. (2014). EXercise for depression. *JAMA, 311*(23), 2432-2433.

Exercise Impacts Depression Favorably

Mean Difference in Beck Depression Inventory Score for Exercise vs Control or Placebo Intervention. BDI indicates Beck Depression Inventory. Only 16 trials used the BDI score. The size of the data markers indicates the weight of the study. Meta-analysis used the random-effects method.



Cooney, G., Dwan, K., & Mead, G. (2014). EXercise for depression. *JAMA, 311*(23), 2432-2433.

BDM Thought

Did you exercise today??!!!

Mediterranean Diet Improves BP, Glucose & Lipids

- PREDIMED; 235 pts; 56.5% female; mean age 66.5 yrs; three dietary arms; change in one yr.

- Sys BP: significant decrease 2.3 mm Hg – EVOO; 2.6 mm Hg-Nuts; no significant change low fat.

- Dias BP: significant decrease 1.2 mm Hg both EVOO & Nuts; no significant change low fat.

Doménech, M., et. al. (2014). Mediterranean Diet Reduces 24-Hour Ambulatory Blood Pressure, Blood Glucose, and Lipids: One-Year Randomized, Clinical Trial. *Hypertension, 64*(1), 69-76.

Mediterranean Diet Improves BP, Glucose & Lipids

- Mean changes from baseline in fasting blood glucose were −6.1, −4.6, and 3.5 mg/dL in EVOO, Nuts, Low fat, respectively with p=0.016

- Mean changes from baseline for TC were −11.3, −13.6, and −4.4 mg/dL EVOO, Nuts, Low fat, respectively with p=0.043

Doménech, M., et. al. (2014). Mediterranean Diet Reduces 24-Hour Ambulatory Blood Pressure, Blood Glucose, and Lipids: One-Year Randomized, Clinical Trial. *Hypertension, 64*(1), 69-76.

BDM Thoughts

- Too bad they have not reported apoE genotypes.
- MD theoretically good for apoE 3's & 2's; low fat should be better of the 4's.
- Genetics allows more personalized care.

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

Flaxseed Lowers BP: Potential Mechanism

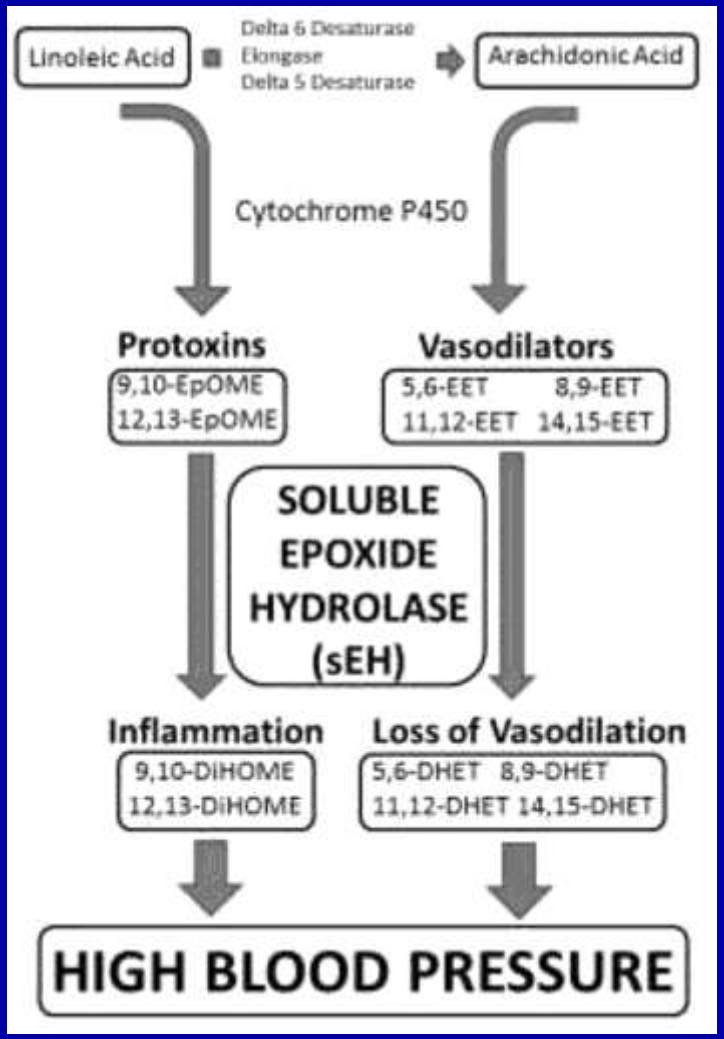
Epoxide hydrolase creates oxylipins which increase vascular tone and BP.

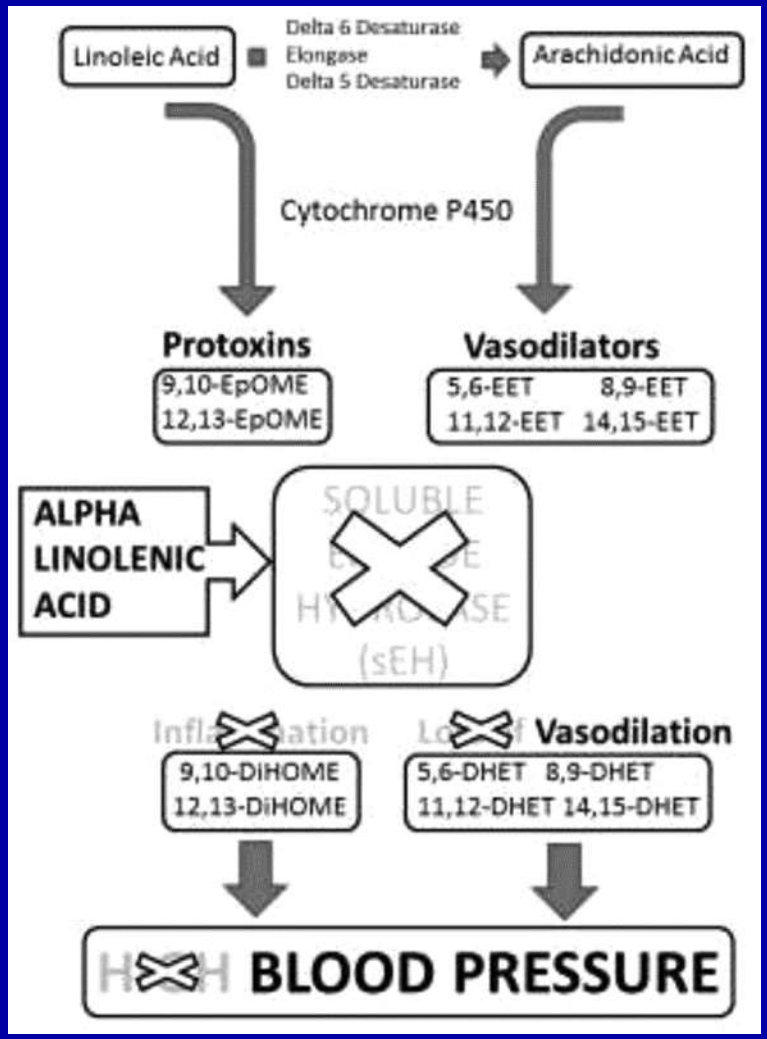
With pts' plasma it was demonstrated that α-linolenic acid significantly decreased soluble epoxide hydrolase activity.

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

Flaxseed Lowers BP: Potential Mechanism

Schematic of dihydroxyoctadecenoic acid (DiHOME) and dihydroxyeicosatrienoic acid (DHET) production by soluble epoxide hydrolase (sEH).





Caligiuri S P et al. Hypertension. 2014;64:53-59

Dark Chocolate Improves Peripheral Arterial Disease (PAD): Background

- PAD present in ~ 20% people ≥70 yo
- ASVD of PAD pts includes large arteries & the microcirculation.
- Impaired nitric oxide (NO) generation and oxidative stress play a role in claudication sx's.
- Dark chocolate lowers activation of NOX2 which increases NO and lowers reactive oxygen species.
- Theoretically, dark chocolate should rapidly enhance vasodilation.

Loffredo, L., (2014). Dark Chocolate Acutely Improves Walking Autonomy in Patients With Peripheral Artery Disease. *J Am Heart Assoc, 3*(4). doi: 10.1161/jaha.114.001072

Dark Chocolate Improves Peripheral Arterial Disease

- 20 PAD pts; 30% female; mean age: 69 ±9 years); random single blind cross-over study; 40 g of dark chocolate (>85% cocoa) or 40 g of milk chocolate (≤35% cocoa).

- Assessed numerous variables at baseline and 2 hours: FMD, isoprostanes, nitrite/nitrate (NOx), and sNOX2-dp, NOX2 activity (sNOX2-dp), maximal walking distance (MWD) and maximal walking time (MWT).

Loffredo, L., (2014). *J Am Heart Assoc, 3*(4). doi: 10.1161/jaha.114.001072

Dark Chocolate Improves Peripheral Arterial Disease

Dark Chocolate had significant favorable results: FMD, MWD (+11%; P<0.001), MWT (+15%; P<0.001), serum NOx (+57%; P<0.001), isoprostanes (-23%; P=0.01) and sNOX2-dp (-37%; P<0.001).

Milk chocolate produced no changes.

Loffredo, L., (2014). *J Am Heart Assoc, 3*(4). doi: 10.1161/jaha.114.001072

Dark Chocolate Improves Peripheral Arterial Disease

- Study suggests short term use of dark chocolate improves PAD claudication sx's perhaps mediated by reducing oxidative stress & increasing NO.

- Studies with long-term dark chocolate administration in a larger population are needed to see if this may be a novel therapy for PAD pts.

Loffredo, L., (2014). *J Am Heart Assoc, 3*(4). doi: 10.1161/jaha.114.001072

BDM Thoughts

Study helps substantiate recommending dark chocolate with the strength of a prescription medication.

Our normal amount is ~ 7 grams.

Perhaps it should be higher in someone with PAD?

CPAP Therapy Reduces BP: Background

- OSA is known to raise BP.
- Remains uncertain whether CPAP provides additional BP benefit beyond pharmacotherapy.
- Also unknown if hours of adherence are important.
- Repetitive cycles of hypoxemia and reoxygenation are thought to play a central role in the BP issue.
- Therefore, it has been proposed that nocturnal supplemental oxygen may serve as a potential alternative to CPAP.

Gottlieb, D. J., et. al. (2014). CPAP versus Oxygen in Obstructive Sleep Apnea. *New England Journal of Medicine, 370*(24), 2276-2285

CPAP Therapy Reduces BP

281 pts with OSA (15-50 AHI); 45-75 yo; under management for CVD with cardiologists; mean daytime BP 128/73; nocturnal 116/66.

(Interesting: average Epworth score 8-9)

Randomly rx'ed with healthy lifestyle & sleep education (HLSE), CPAP or oxygen.

The primary outcome was 24-hour mean arterial pressure change from baseline to 12 weeks.

Gottlieb, D. J., et. al. (2014). *New England Journal of Medicine, 370*(24), 2276-2285

CPAP Therapy Reduces BP

CPAP, but not nocturnal supplemental oxygen, resulted in a significant reduction in blood pressure.

Unfortunately, study was not powered to determine a critical adherence threshold.

Gottlieb, D. J., et. al. (2014). *New England Journal of Medicine, 370*(24), 2276-2285

CPAP Reduces BP

Effect of Treatment on 24-Hour Blood Pressure.

Table 2. Effect of Treatment on 24-Hour Blood Pressure.*

Variable	CPAP (N=90)	NSO (N=94)	HLSE (N=97)	CPAP vs. HLSE	NSO vs. HLSE	CPAP vs. NSO
24-Hr mean arterial blood pressure						
Baseline	89.5±8.6	88.6±10.0	87.7±9.3			
12 Wk	87.8±8.1	90.2±11.1	89.0±11.2	−2.4 (P=0.04)	0.4 (P=0.71)	−2.8 (P=0.02)
24-Hr mean systolic blood pressure						
Baseline	124.7±13.5	125.3±16.9	123.6±14.3			
12 Wk	123.4±12.8	126.9±16.5	124.7±16.4	−1.9 (P=0.25)	1.2 (P=0.45)	−3.1 (P=0.06)
24-Hr mean diastolic blood pressure						
Baseline	72.0±7.7	70.8±8.3	69.6±8.6			
12 Wk	69.8±7.5	71.7±9.8	70.9±10.1	−2.8 (P=0.005)	−0.1 (P=0.95)	−2.8 (P=0.006)

Remember a 2 mm-Hg reduction in diastolic BP 'usually' reduces CV risk ~ 14 to 20%

* Plus–minus values are means ±SD. The between-group differences are the mean differences at 12 weeks, adjusted for study site, presence or absence of coronary artery disease, and blood pressure as measured at baseline. CPAP denotes continuous positive airway pressure, NSO nocturnal supplemental oxygen, and HLSE healthy lifestyle and sleep education.

Gottlieb DJ et al. N Engl J Med 2014;370:2276-2285

Dale Doneen METHOD

CPAP Therapy Reduces BP

In pts with OSA & CVD or multiple CV risk factors on appropriate pharmaceutical therapy, CPAP generates further significant BP reduction.

Gottlieb, D. J., et. al. (2014). *New England Journal of Medicine, 370*(24), 2276-2285

BDM Thoughts

- CPAP must be regarded as preferred rx for OSA
- The additional BP reduction with CPAP is significant in terms of CV risk.
- Epworth sleep questionnaire scores of $\geq$8 are suggestive of an issue.

Aspirin (ASA) Reduces Pancreatic Cancer Risk

362 pancreas-cancer cases; matched to 690 controls.

Regular aspirin use was associated with half the risk of pancreatic cancer

OR=0.52; (95% CI, 0.39–0.69)

Streicher, S. A., et. al. (2014). Case–Control Study of Aspirin Use and Risk of Pancreatic Cancer. *Cancer Epidemiology Biomarkers & Prevention, 23*(7), 1254-1263.

Aspirin (ASA) Reduces Pancreatic Cancer Risk

Each year of low dose ASA (81mg- 325mg/d) use decreased the risk 6%

OR=0.94; (95%CI, 0.91–0.98)

Each year of high dose ASA (325mg- 1,200 mg q 4-6 hrs.) reduced the risk an insignificant 2%

OR=0.98; (95%CI, 0.96–1.01)

Streicher, S. A., et. al. (2014). *Cancer Epidemiology Biomarkers & Prevention, 23*(7), 1254-1263.

Aspirin (ASA) Reduces Pancreatic Cancer Risk

Table 5. Pancreatic cancer ORs for individuals ever regularly using aspirin during specific time intervals in the past

Interval during which aspirin was ever used (years in the past)	Any aspirin		Low-dose aspirin		Regular aspirin	
	Controls/cases	OR[a] (95% CI)	Controls/cases	OR[a] (95% CI)	Controls/cases	OR[a] (95% CI)
Never used	345/218	1	345/218	1	345/218	1
Use in current year	288/128	0.51 (0.37–0.69)	189/82	0.53 (0.38–0.75)	100/39	0.46 (0.30–0.72)
>1, ≤3	252/114	0.56 (0.41–0.76)	167/78	0.57 (0.40–0.81)	88/37	0.52 (0.32–0.82)
>3, ≤5	233/105	0.54 (0.40–0.75)	152/69	0.54 (0.38–0.79)	84/37	0.56 (0.34–0.86)
>5, ≤7	190/89	0.57 (0.41–0.80)	116/53	0.55 (0.36–0.82)	74/36	0.59 (0.37–0.96)
>7, ≤10	98/51	0.62 (0.41–0.95)	75/30	0.44 (0.27–0.73)	58/34	0.74 (0.44–1.23)
>10, ≤20	101/50	0.65 (0.42–0.98)	56/21	0.44 (0.25–0.79)	45/29	0.90 (0.52–1.55)
>20	42/16	0.43 (0.22–0.83)	13/6	0.39 (0.12–1.19)	29/10	0.45 (0.20–0.99)

[a]ORs for ever having regularly used aspirin (yes/no) in the time windows shown. Adjusted as in Table 2.

Keep in mind the latency of pancreatic cancer is on average at least 10 years

Streicher, S. A., et. al. (2014). *Cancer Epidemiology Biomarkers & Prevention, 23*(7), 1254-1263.

Aspirin (ASA) Reduces Pancreatic Cancer Risk

Study suggests that a daily low dose aspirin regimen may provide chemoprophylaxis against pancreatic cancer.

?? Prevention (use ≥10yrs) and or slowing tumorigenesis process (use <10 yrs).

Streicher, S. A., et. al. (2014). *Cancer Epidemiology Biomarkers & Prevention, 23*(7), 1254-1263.

BDM Thoughts

Always nice to see potential good side effects to ‘foundation’ rx for ASVD!!

Glucagon-like peptide-1 receptor agonist (GLP-1) Attractive From CV Perspective: Background

DM increases risk of heart attack and stroke ~ 2X.

CV events remain the largest morbidity and mortality risk for diabetics.

Novel therapies are needed which enhance glycemic control, BP reduction, lipid control & weight loss.

Smilowitz, N. R., Donnino, R., & Schwartzbard, A. (2014). Glucagon-Like Peptide-1 Receptor Agonists for Diabetes Mellitus: A Role in Cardiovascular Disease. *Circulation, 129*(22), 2305-2312.

GLP-1 Attractive From CV Perspective

Table 2. Clinical Effects of GLP-1 Agonists

GLP-1 Agonists	Clinical Effects
Glycemic control	
Hemoglobin A1C	Mean A1C reduction of 1.1%–1.6%
Postprandial effects	Reduced postprandial hyperglycemia
Gastric emptying and appetite	Reduced appetite and delayed gastric emptying
Established cardiovascular risk factor effects	
Body weight	Weight loss of 2.0–2.4 kg relative to placebo and 4.8 kg of weight loss vs insulin
Lipid profile	Reductions in total cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B levels
Blood pressure	Reductions in systolic blood pressure of 2–4 mm Hg
Cardiovascular benefits under Investigation	
Heart failure	Hemodynamic improvements in heart failure
Coronary artery disease	Improved vascular endothelial function
	Improved ischemic conditioning
Risks and concerns*	
Common ADRs	Nausea, vomiting, diarrhea
Uncommon ADRs	Hypoglycemia
Safety concerns	Pancreatitis
	Pancreatic cancer
	Medullary thyroid cancer
	Increased heart rate (2 bpm)

Smilowitz, N. R., et. al. (2014). *Circulation, 129*(22), 2305-2312.

GLP-1 Attractive From CV Perspective

Table 1. Prescribing GLP-1 Agonists

	Exenatide (Twice Daily)	Exenatide (Once Weekly)	Liraglutide	Lixisenatide
Brand	Byetta	Bydureon	Victoza	Lyxumia
Availability	USA, EU	USA, EU	USA, EU	EU
Initial dose	5 μg subQ twice daily (60 min before a meal)	2 mg subQ once weekly (without regard to meals)	0.6 mg subQ daily once weekly, then increase to 1.2 mg daily	10 μg daily for 14 days, then increase to 20 μg daily
Maximal dose	10 μg subQ twice daily	2 mg subQ once weekly	1.8 mg subQ once daily	20 μg daily
Renal adjustment	Caution with eGFR 30–50 Avoid if eGFR <30	Caution with eGFR 30–50 Avoid if eGFR <30	Caution with renal impairment[27]	Caution with eGFR 30–50 Avoid if eGFR <30
Half-life	2.4 h	2 wk	13 h	3 h
Common ADRs	Nausea, vomiting, diarrhea, constipation, local injection site reactions, hypoglycemia, headache			

ADR indicates adverse drug reaction; eGFR, estimated glomerular filtration rate; EU, European Union; GLP-1, glucagon-like peptide-1; and subQ, subcutaneous.

Smilowitz, N. R., et. al. (2014). *Circulation, 129*(22), 2305-2312.

GLP-1 Attractive From CV Perspective

In conclusion, cardiovascular risk factor reduction offers a compelling rationale to incorporate GLP-1 agonist therapy early in the management of diabetes mellitus in patients at risk for cardiovascular disease.

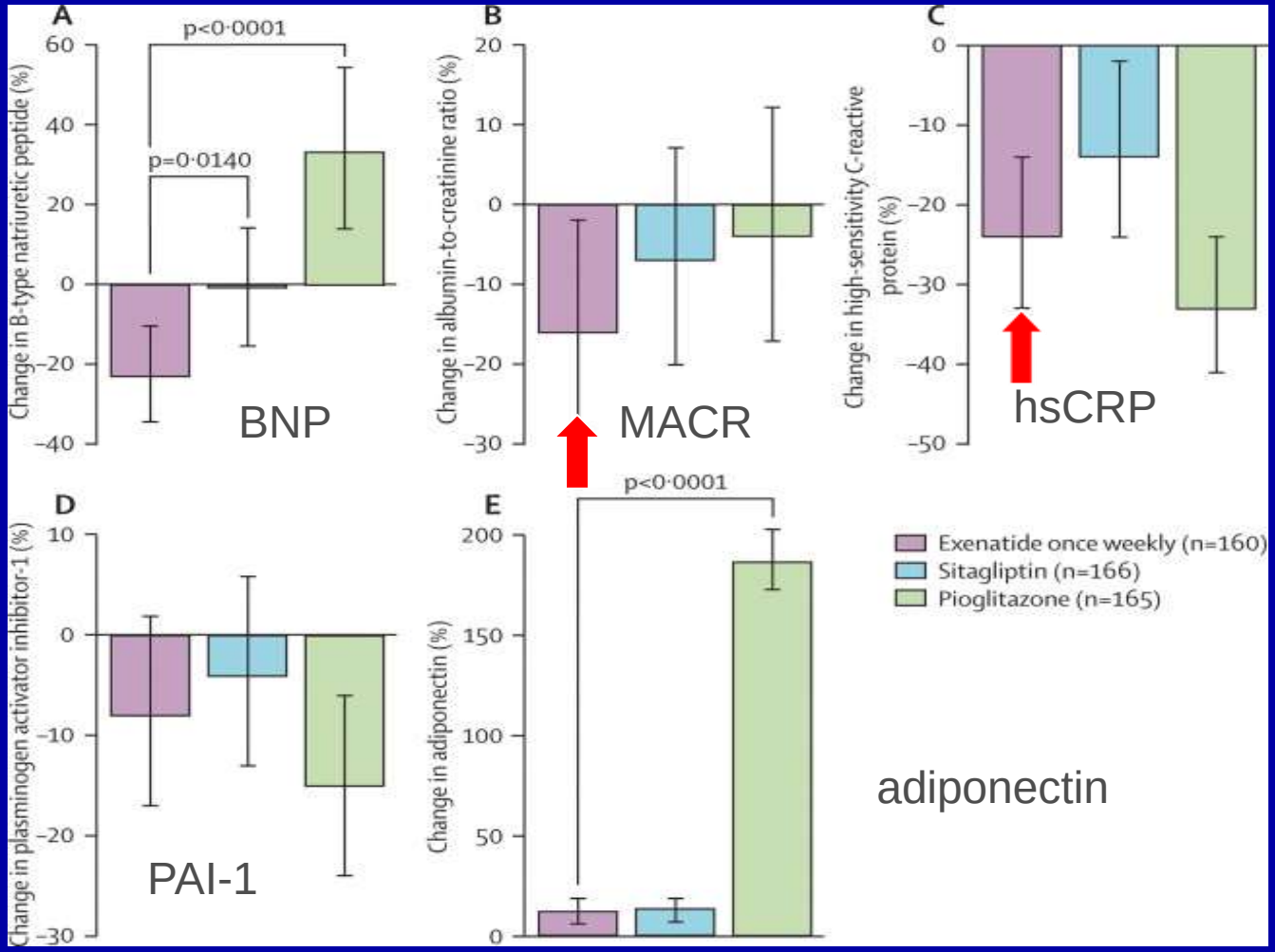
Smilowitz, N. R., et. al. (2014). *Circulation, 129*(22), 2305-2312.

BDM Thoughts

Nice review and we agree this is an attractive option in many patients.

Amazing they did not discuss inflammation which is an important consideration for their use (see next slide).

DURATION-2: CV Risk Factors



Richard M Bergenstal, Carol Wysham, et. al. ***Lancet 2010; 376: 431***

Adding Insulin to Metformin May Increase Mortality Risk

178,341~ 14 mos. of metformin monotherapy VA pts; 2,948 added insulin & 39,990 added a sulfonylurea then followed ~ 14 mos.

Composite outcome of AMI, stroke hospitalization, or all-cause death.

HR calculated after adjusting for multiple known risk factors including other meds.

Roumie, C. L., et. al. (2014). Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes. *JAMA, 311*(22), 2288-2296.

Adding Insulin to Metformin May Increase Mortality Risk

Comparing insulin to sulfon. for composite outcome
HR-1.30; (95%CI, 1.07-1.58) P = .009

Same comparison for heart attack and stroke showed insignificant benefit:

HR-0.88; (95%CI, 0.59-1.30) P = 0.52

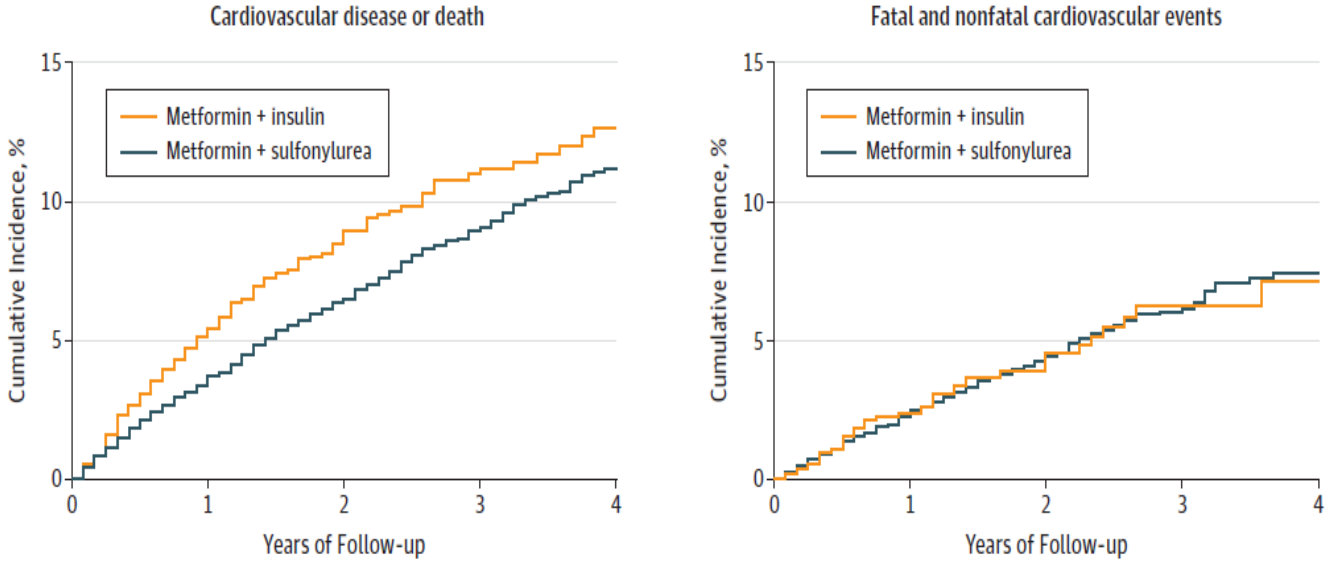
Same coparison for all-cause death

HR, 1.44; (95%CI, 1.15-1.79) P = 0.001

Roumie, C. L., et. al. (2014). *JAMA, 311*(22), 2288-2296.

Adding Insulin to Metformin May Increase Mortality Risk

Figure 2. Cumulative Incidence of Cardiovascular Events and Mortality



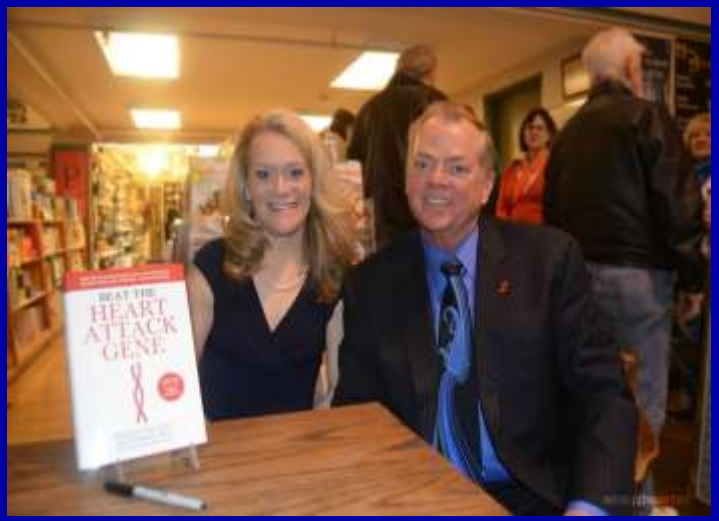
No. at risk										
Metformin + insulin	2436	1362	805	430	213	1865	889	413	184	60
Metformin + sulfonylurea	12180	6742	3693	2003	974	9145	4441	1942	875	330
No. of events										
Metformin + insulin		105	40	14	5		33	14	5	1
Metformin + sulfonylurea		353	150	76	35		164	58	26	9

A, Cumulative incidence of cardiovascular disease (acute myocardial infarction, stroke) or death among a propensity score–matched cohort of patients taking metformin + sulfonylurea vs patients taking metformin + insulin. All follow-up is through September 30, 2011. Events are the composite of cardiovascular disease or all-cause death that occurred in the 12 months between each point. B, Cumulative incidence of fatal and nonfatal cardiovascular events (acute myocardial infarction, stroke, or cardiovascular deaths) among a propensity score–matched cohort of patients taking metformin + sulfonylurea vs patients taking metformin + insulin. All follow-up is through September 30, 2009. Events are the composite of fatal and nonfatal cardiovascular events that occurred in the 12 months between each point.

Roumie, C. L., et. al. (2014). *JAMA, 311*(22), 2288-2296.

Cases???- Dr. Doneen Next Month!!!

Upcoming Presentations



3rd Edition Now Out!!!

Thank you!!!!

- 7/9/2014- Amy in Portland for CHL presentation
- 7/14/2014- BDM 8.5 CME course on line enduring material !
- 8/6/2014- Brad in Dallas area for CHL presentation
- 9/12-13 - Amy speaking in Cleveland, OH at CHL Symp.
- 9/26-27 - Amy and Brad speaking in St. Louis at AAOSH
- 10/17-19 - Bale/Doneen Reunion at Canyon Ranch, Tucson, AZ – launching BDM Speaker's Bureau
- 11/7-9 - Bale/Doneen Preceptorship in San Antonio, TX

Open for Discussion

Abdominal Aorta Calcification An Excellent Predictor of CV Events and Mortality

Risk Factors	AAC 0–50th Percentile	AAC 51st–75th Percentile	AAC 76th–100th Percentile	AAC *P* Value Test for Trend	CAC 0–50th Percentile	CAC 51st–75th Percentile	CAC 76th–100th Percentile	CAC *P* Value Test for Trend
Hard CHD*, per 1000 person-years	1.8 (10)	3.9 (10)	12.1 (30)		1.1 (6)	6.5 (17)	11.1 (27)	
Hard CVD, per 1000 person-years†	3.0 (16)	7.9 (20)	19.2 (47)		2.4 (13)	11.2 (29)	17.1 (41)	
CVD mortality, per 1000 person-years‡	0.5 (3)	2.9 (8)	7.0 (19)		0.7 (4)	3.9 (11)	5.5 (15)	
Total mortality, per 1000 person-years	4.4 (25)	8.0 (22)	21.3 (58)		4.2 (24)	11.4 (32)	18.0 (49)	

*Hard CHD indicates myocardial infarction, resuscitated cardiac arrest, and coronary heart disease death.

†Hard CVD indicates myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death, and stroke death.

‡CVD mortality indicates death from atherosclerotic coronary heart disease, stroke, atherosclerotic disease other than coronary disease or stroke, or other cardiovascular disease not defined.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

AAC and CAC Predict Risk After Adjusting for FRS

Table 2. Cox Models for Hard CHD, Hard CVD, CVD Mortality, and Total Mortality for Categorical Definition of AAC and CAC, Adjusted for the General Framingham Risk Score and Ethnicity

	Hard CHD		Hard CVD		CVD Mortality		Total Mortality	
Events	50		83		30		105	
Total	1930		1930		1966		1966	
Percentile categories	HR	*P* Value	HR	*P* Value	HR	*P* Value	HR	*P* Value
AAC only, percentile								
0–50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
51st–75th	1.49	0.383	1.87	0.069	3.77	0.054	1.43	0.232
>75th	4.06	<0.001	4.00	<0.001	7.83	0.002	3.51	<0.001
CAC only, percentile								
0–50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
51st–75th	4.74	0.001	3.67	<0.001	4.03	0.019	2.28	0.003
>75th	6.14	<0.001	4.21	<0.001	3.92	0.021	2.79	<0.001

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

AAC and CAC Predict Risk After Adjusting for FRS and Either CAC or ACC: Independent Predictors

Table 2. Cox Models for Hard CHD, Hard CVD, CVD Mortality, and Total Mortality for Categorical Definition of AAC and CAC, Adjusted for the General Framingham Risk Score and Ethnicity

	Hard CHD		Hard CVD		CVD Mortality		Total Mortality	
Events	50		83		30		105	
Total	1930		1930		1966		1966	
Percentile categories	HR	*P* Value	HR	*P* Value	HR	*P* Value	HR	*P* Value
AAC and CAC, percentile								
AAC 0–50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
AAC 51st–75th	1.08	0.875	1.46	0.279	3.11	0.104	1.23	0.506
AAC >75th	2.38	0.038	2.66	0.003	5.89	0.009	2.71	<0.001
CAC 0–50th	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
CAC 51st–75th	3.91	0.006	2.92	0.003	2.75	0.096	1.82	0.037
CAC >75th	4.35	0.004	2.90	0.003	2.10	0.231	1.85	0.036

Criqui, M. H., et. al. (2014). *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

Prevalence of Abdominal Aortic Plaque in Older Framingham Subjects via CT Scan

- 1,016 FR Offspring pts; mean age ~ 64 yo ±9 yrs.; 53% women; all had CT
- 84.1% men + ; 76.5% women +
- Also had MRI for plaque of abd aorta
  - Amazingly, only 44.7% men +; 49.1% women +

What???!!!!!

Chuang, M. L., et. al. (2014). Risk Factor Differences in Calcified and Noncalcified Aortic Plaque: The Framingham Heart Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1580-1586.

Prevalence of Abdominal Aortic Plaque in Older Framingham Subjects via CT Scan

MRI plaque defined as luminal protrusions of ≥1mm in the radial direction.

Smaller luminal irregularities may not be optimally depicted because of respiratory or other motion.

Did not assess generalized aortic wall thickening.

Possible that we failed to capture some of the total noncalcified plaque! - Hello!!!!

Chuang, M. L., et. al. (2014). Risk Factor Differences in Calcified and Noncalcified Aortic Plaque: The Framingham Heart Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1580-1586.

BDM Thoughts: Should have been rejected!!

- This study is severely flawed as they are trying to draw conclusions about calcified and non-calcified aortic plaque and the MRI obviously missed about half of the plaque.
- Most all calcified plaque would have non-calcified areas!
- Most plaque is remodeled and would be invisible to their definition of plaque via MRI.
- The study goes on to try to find risk factor differences for the two types of plaque. – worthless conculsions!
- In their next study they are going to see if there is a difference in 'event' risk based on this data!!!! – ridiculous!
- Only take away is by retirement age the vast majority of Caucasians have abdominal aortic plaque = risk.
- Realize their next study will be worthless!!!

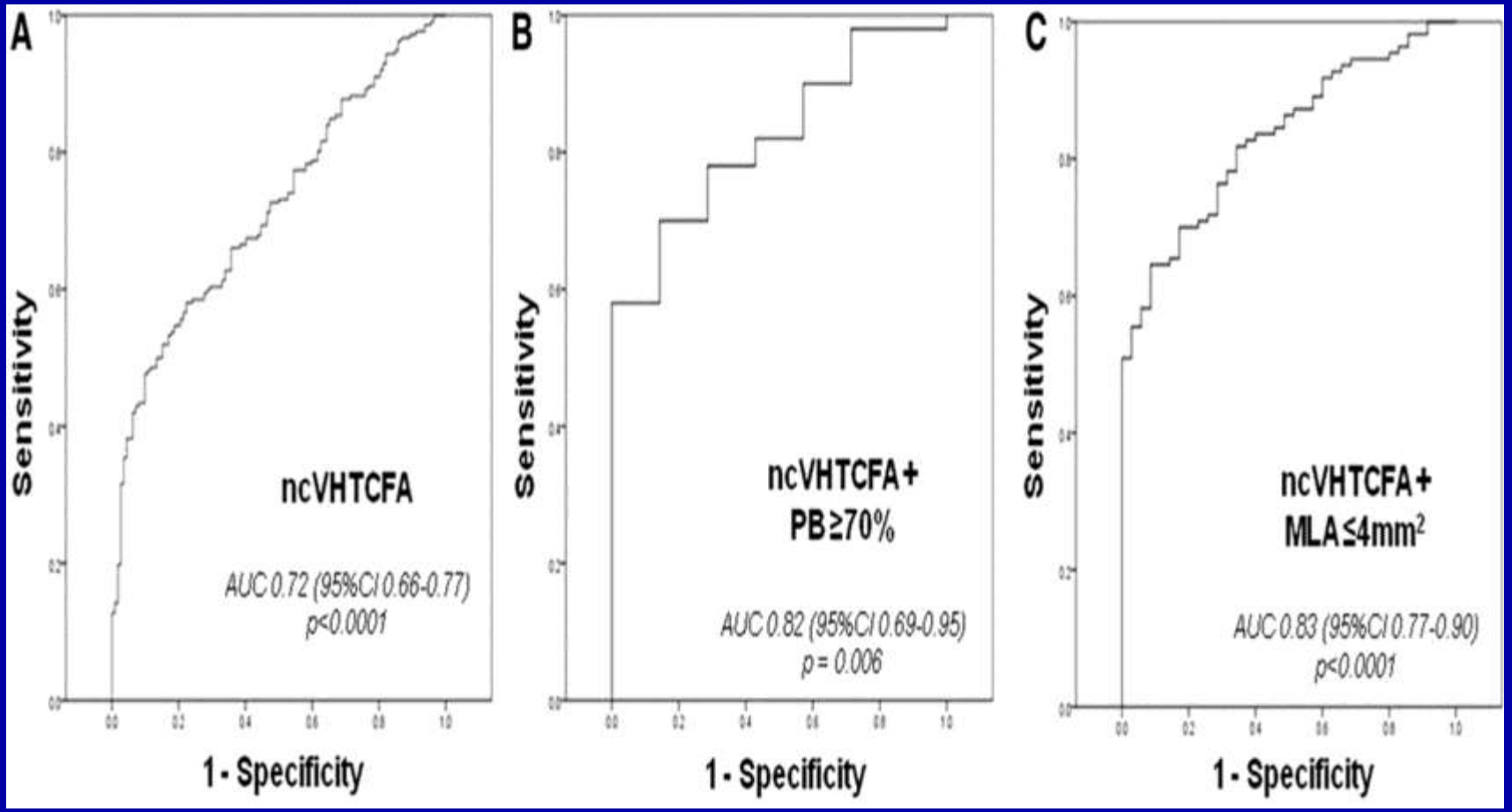
Plaque Structural Stress Related to Event Risk and Plaque Composition

- PSS alone had poor discriminatory power to predict ACS.

However, when combined with ncVHTCFA alone or in combination with PB ≥70% or MLA <4mm^2, the power was substantial.

Teng, Z., et. al. (2014). *Circulation: Cardiovascular Imaging, 7*(3), 461-470.

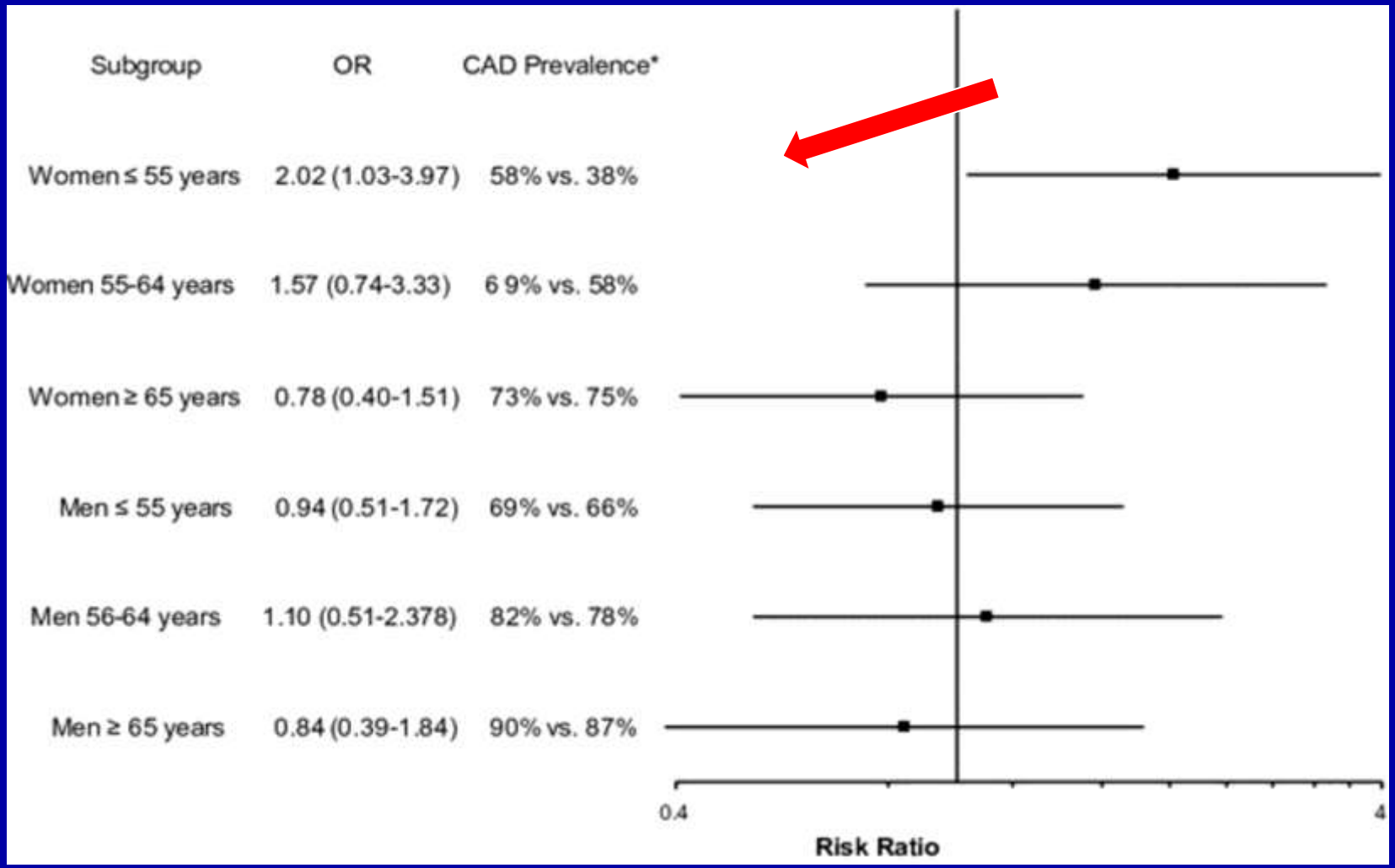
Receiver operating characteristic (ROC) curves illustrating the discriminatory power of combined virtual histology intravascular ultrasound (VH-IVUS) and plaque structural stress (PSS) to identify clinical presentation.



Teng Z et al. Circ Cardiovasc Imaging. 2014;7:461-470

Depression Significant CV Risk in Younger Women

Adjusted odds ratio of CAD for moderate/severe depression (PHQ-9≥10) compared with no or mild depression (PHQ<10).



Shah A J et al. J Am Heart Assoc 2014;3:e000741

IR Does Not Increase Stroke Risk in Blacks

- 12,366 white & 6,782 black pts; IR by HOMA; followed for 5.7 yrs.; outcome ischemic stroke (IS) and hemorrhagic stroke (HS)

- 364 incident IS and 41 incident HS

Howard, G., et. al. (2014). Racial Differences in the Association of Insulin Resistance With Stroke Risk: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Stroke*. doi: 10.1161/strokeaha.114.005306

IR Does Not Increase IS Risk in Blacks

- 17% increased risk of IS in Whites with each log increase in IR

[HR]ln(IR)=1.17; (95% CI, 1.00–1.38)

- No increased risk of IS in Blacks

HRln(IR)=1.01; (95% CI, 0.81–1.25)

Howard, G., et. al. (2014). Racial Differences in the Association of Insulin Resistance With Stroke Risk: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Stroke*. doi: 10.1161/strokeaha.114.005306

IR Does Not Increase HS Risk in Blacks

- IR yielded a non-significant reduced risk of HS in Whites

  HRln(IR)=0.61; (95% CI, 0.35–1.04)

- IR yielded a non-significant increased risk of HS in Blacks

  HRln(IR)=1.20; (95% CI, 0.60–2.39)

Howard, G., et. al. (2014). Racial Differences in the Association of Insulin Resistance With Stroke Risk: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Stroke*. doi: 10.1161/strokeaha.114.005306

IR Does Not Increase Stroke Risk in Blacks

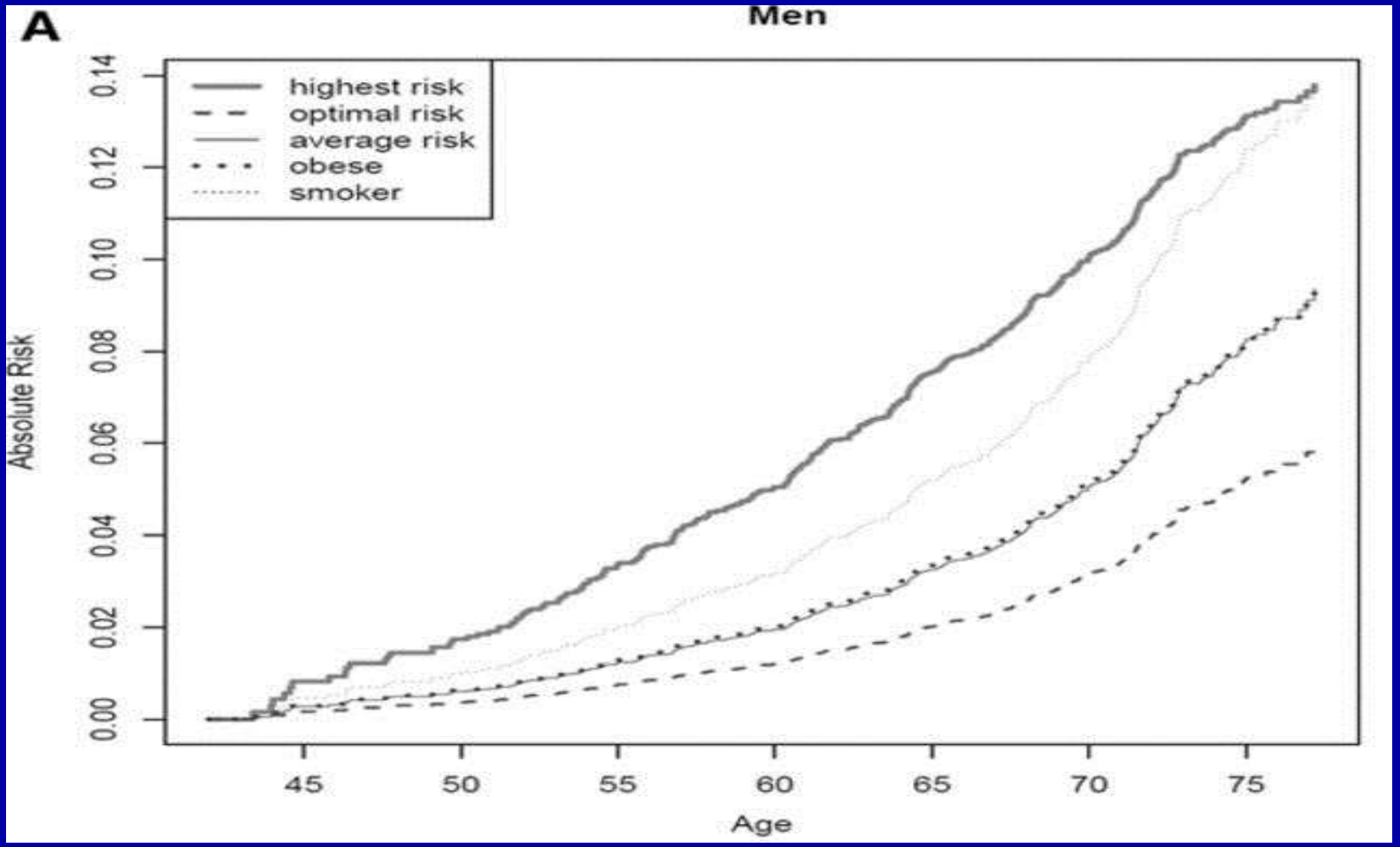
- Data suggest that IR, as measured by the HOMA, may be playing a larger role in white than black populations.

- Further research is needed.

Howard, G., et. al. (2014). Racial Differences in the Association of Insulin Resistance With Stroke Risk: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Stroke*. doi: 10.1161/strokeaha.114.005306

Lifestyle Has Huge Impact on Stroke Risk

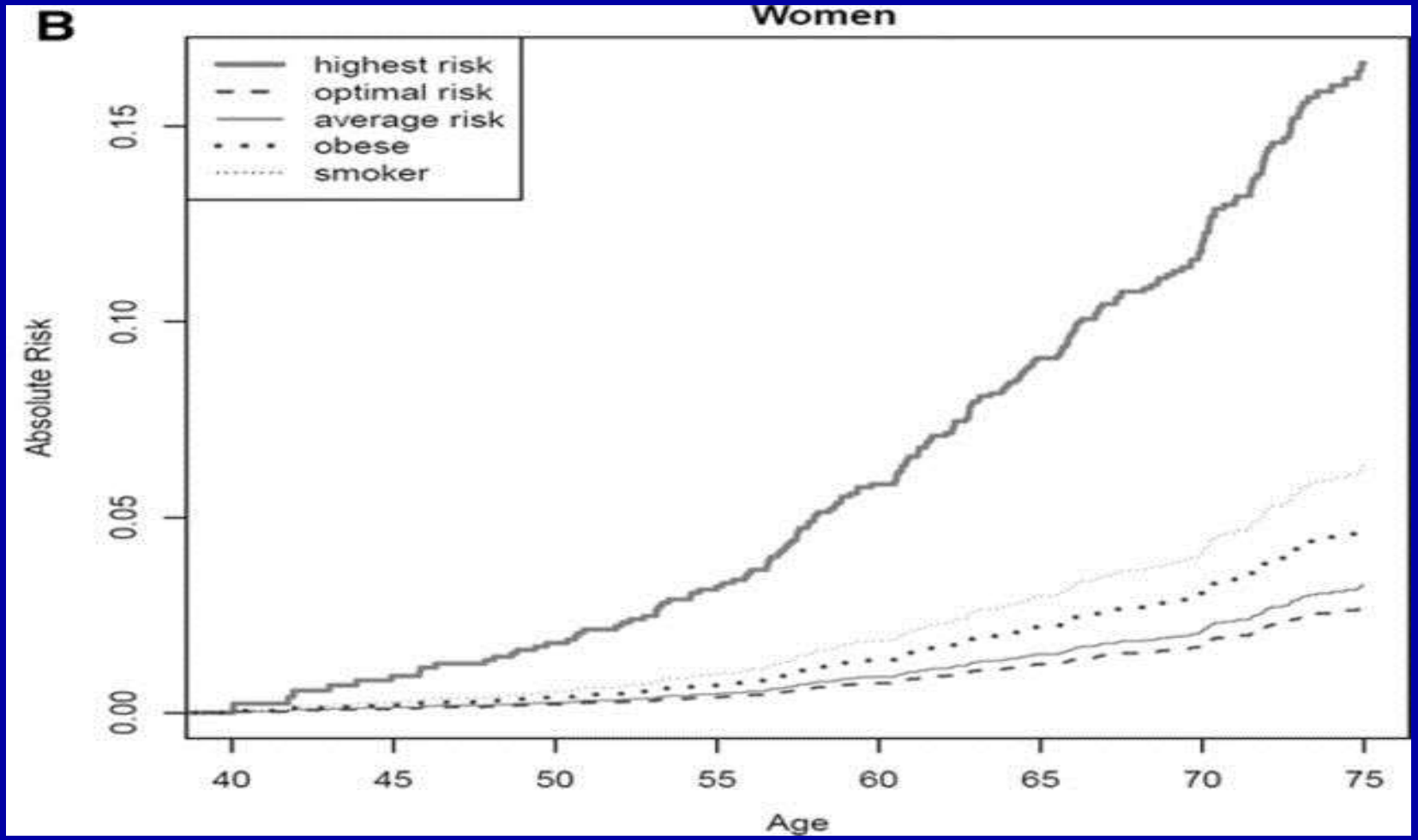
Absolute risk to develop stroke for a men at age 42 with a given lifestyle profile who is disease free.



Tikk K et al. Stroke. 2014;45:2041-2046

Lifestyle Has Huge Impact on Stroke Risk

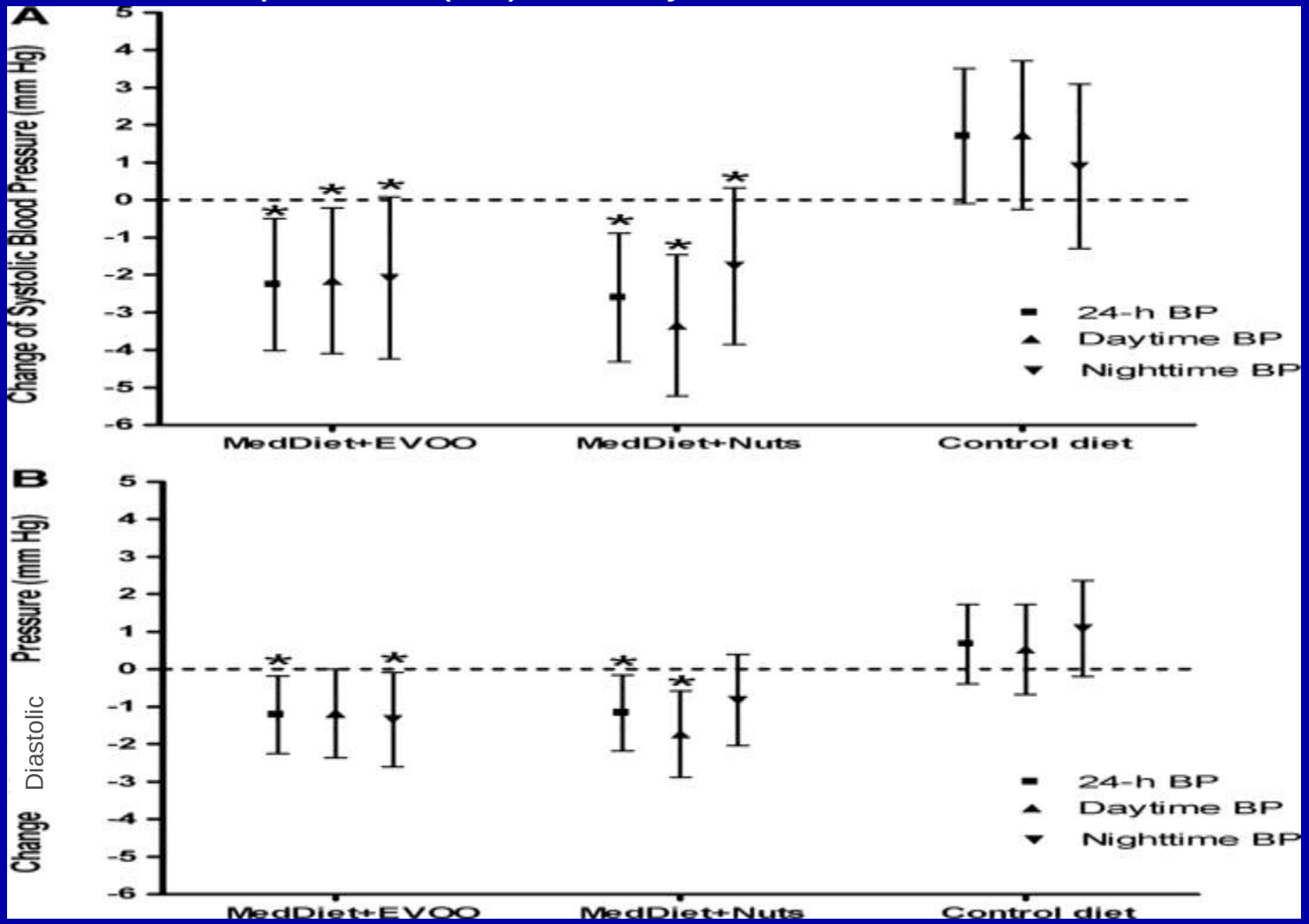
Absolute risk to develop stroke for a women at age 38 with a given lifestyle profile who is disease free.



Tikk K et al. Stroke. 2014;45:2041-2046

Mediterranean Diet Improves BP, Glucose & Lipids

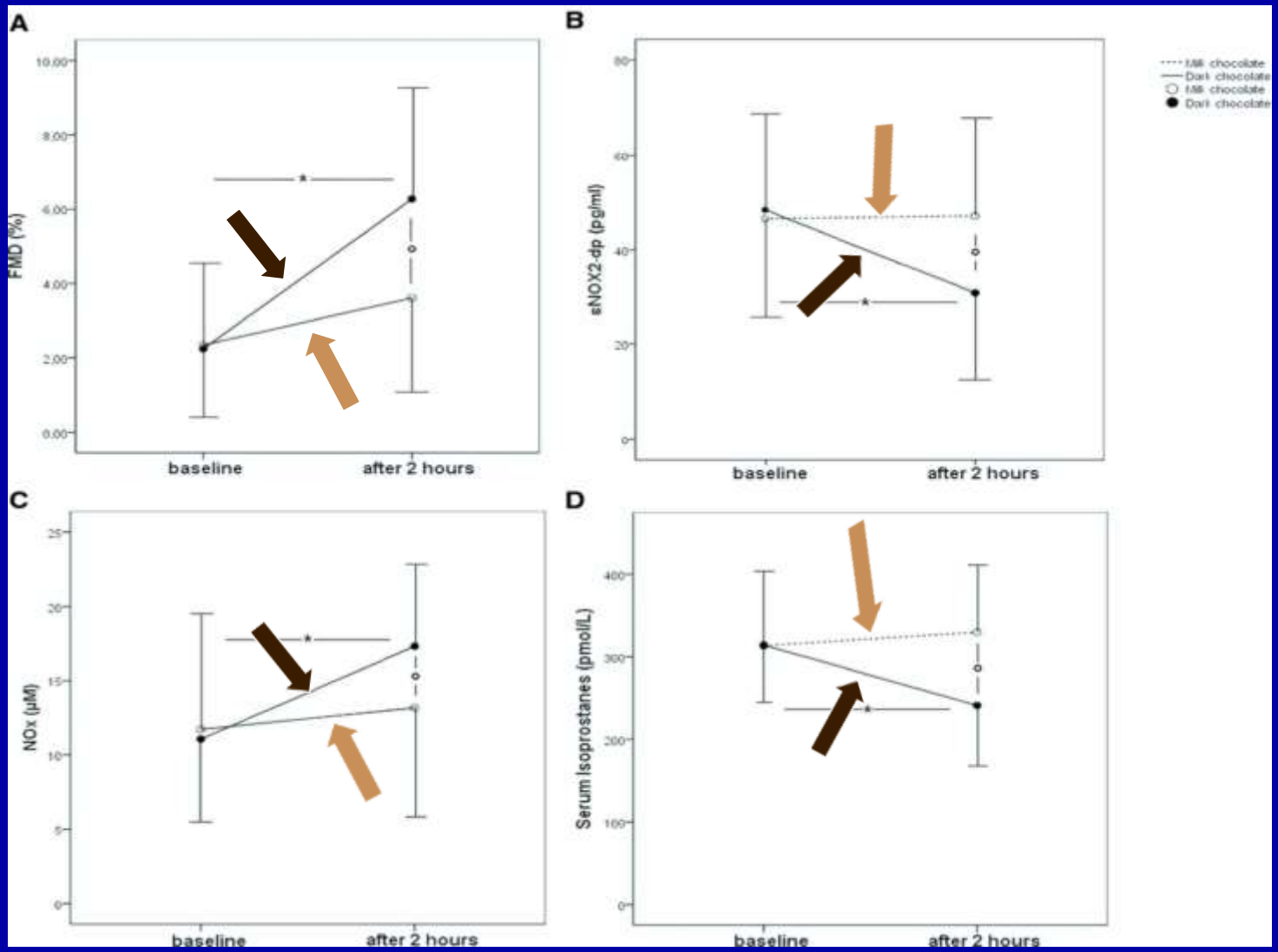
Adjusted changes in ambulatory systolic (A) and diastolic (B) 24-hour blood pressure (BP) after 1 year of diet intervention.



Doménech M et al. Hypertension. 2014;64:69-76

Dark Chocolate Improves PAD

(A) FMD, (B) sNOX2-dp, (C) nitrite/nitrate, and serum isoprostanes (D) isoprostanes before and 2 hours after intake



Loffredo L et al. J Am Heart Assoc 2014;3:e001072

Alcohol and Abdominal Aortic Aneurysm (AAA) Risk: Background

- AAA's account for ~ 11,000 deaths/yr. in US.
- AAA is not ASVD, however, BDM recommends screening and also testing 9p21 which is associated with increased risk.
- Pts with risk should be informed of behaviors that might mitigate the risk (i.e. lowering homocysteine*; fruit^).

Stackelberg, O., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.113.008279
*Liu, Z., et. al. (2012). Hyperhomocysteinemia exaggerates adventitial inflammation and angiotensin II-induced abdominal aortic aneurysm in mice. *Circ Res, 111*(10), 1261-1273.
^Stackelberg, O., (2013). Fruit and vegetable consumption with risk of abdominal aortic aneurysm. *Circulation, 128*(8), 795-802

Alcohol and Abdominal Aortic Aneurysm (AAA) Risk

80,284 subjects; 44% women; 46-84 yo; 14 yr. follow-up; 1,214 AAAs (194 female).

Examined alcohol consumption (self-reported) and risk of developing AAA; ‘control’ amount was 12 grams (one glass) per week.

Stackelberg, O., et. al. (2014). Alcohol Consumption, Specific Alcoholic Beverages, and Abdominal Aortic Aneurysm. *Circulation*. doi: 10.1161/circulationaha.113.008279

Alcohol and Abdominal Aortic Aneurysm (AAA) Risk

Men who consumed 120 gms/wk vs ‘control’ had a 20% lower risk of AAA

HR-0.80 (95% CI, 0.68–0.94)

Women who consumed 60 gms/wk vs control had a 43% lower risk of AAA

HR-0.57 (95% CI, 0.40–0.82)

Results unchanged when compared to never drinkers; intake beyond above.

Stackelberg, O., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.113.008279

Alcohol and Abdominal Aortic Aneurysm (AAA) Risk: By Type of Alcohol

- Men: 50% beer, 26% wine, and 24% liquor.
- Women: 34% beer, 54% wine, and 12% liquor.
- Significant inverse relationship with beer in men and wine in women: not significant for the others.

Stackelberg, O., et. al. (2014). *Circulation*. doi: 10.1161/circulationaha.113.008279

BDM Thoughts

- Alcohol advice needs to be couched in light of numerous variables for an individual pt
- Variables run the gamut from religion to laws to genetics.
- In women always remember the known cancer risk.
- In apoE 4's remember the potential advese lipid effects.