Bale/Doneen Live Chat Session

11/12/2014

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!

Way too many to discuss. Will concentrate on a few.

Red Flags

Male Pattern Baldness is Associated with Increased Risk of Heart Attack

10,885 CAD-free pts.; 20 - 93 yo; 35 yr follow-up

Frontoparietal baldness (FPB) & crown top baldness (CTB) were associated with increased risk of heart attack.

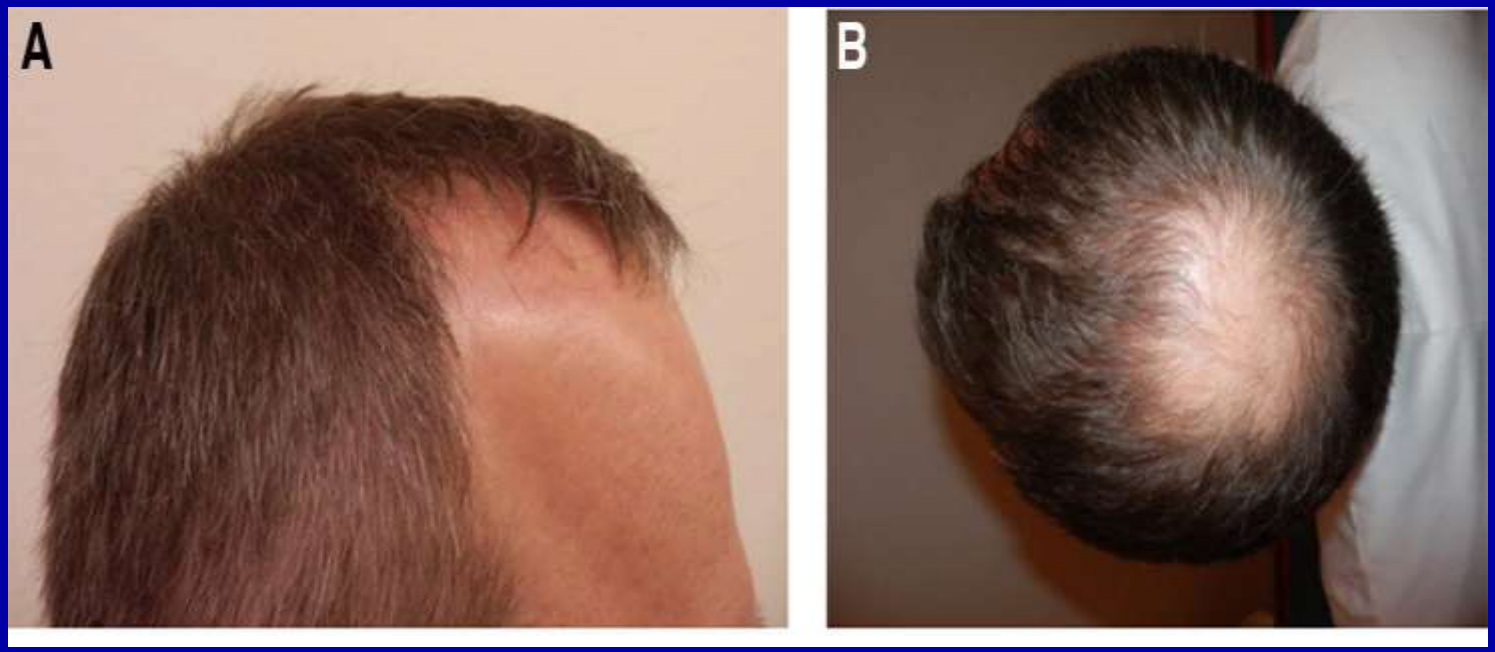
After multiple adjustments both independently predicted risk in men; similar but less significant in women.

40% increased with FPB

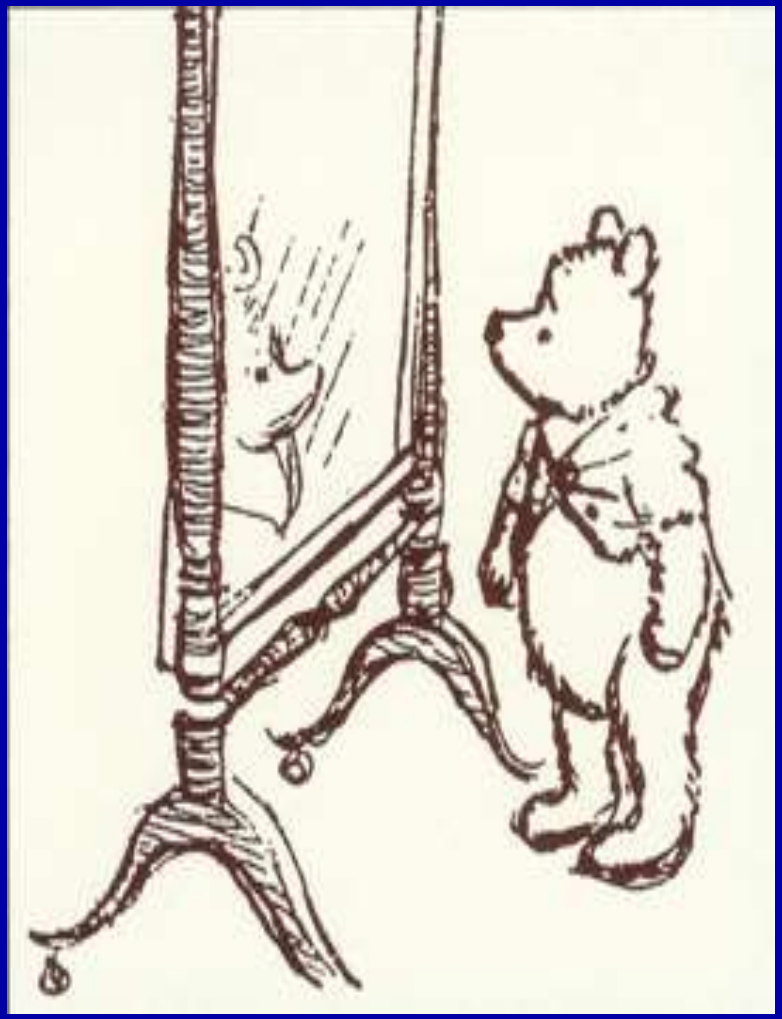
13% increased with CTB

Christoffersen, M., et. al. (2014). Visible age-related signs and risk of ischemic heart disease in the general population: a prospective cohort study. *Circulation, 129*(9), 990-998.

A. Frontoparietal baldness
B. Crown top baldness



I looked in the mirror! Help, Amy!!!



Polycystic Ovarian Syndrome (PCOS) Associated with Increased Risk of Subclinical ASVD: Background

Prevalence of PCOS 6-10%

PCOS is associated with obesity, IR, DM, and lipid abnormalities.

Some evidence connecting PCOS with subclinical CVD.

Calderon-Margalit, et. al. (2014). Prospective Association of Polycystic Ovary Syndrome With Coronary Artery Calcification and Carotid-Intima-Media Thickness: The Coronary Artery Risk Development in Young Adults Women's Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.304136

Polycystic Ovarian Disease Associated with Increased Risk of Subclinical ASVD

985 young women followed for 20 yrs.; baseline information on PCOS; at a mean follow-up age of 45yo, assessed for subclinical ASVD with CIMT and CAC.

PCOS defined as having both anovulation and hyperandrogenism.

Calderon-Margalit, et. al. (2014). Prospective Association of Polycystic Ovary Syndrome With Coronary Artery Calcification and Carotid-Intima-Media Thickness: The Coronary Artery Risk Development in Young Adults Women's Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.304136

Polycystic Ovarian Disease Associated with Increased Risk of Subclinical ASVD

Adjusted for: age, race, education, smoking, menopausal status, BMI, systolic BP, TG, and HOMA-IR.

Women with PCOS were ~ 3X more likely to have CAC

OR- 2.70 (95% CI, 1.31–5.60)

Women with PCOS were significantly more likely to have increased bulb and internal carotid-IMT measurements.

Calderon-Margalit, et. al. (2014). Prospective Association of Polycystic Ovary Syndrome With Coronary Artery Calcification and Carotid-Intima-Media Thickness: The Coronary Artery Risk Development in Young Adults Women's Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.304136

Polycystic Ovarian Disease Associated with Increased Risk of Subclinical ASVD

Study suggests that women in their twenties with PCOS are at increased risk for the development of subclinical CVD.

Calderon-Margalit, et. al. (2014). Prospective Association of Polycystic Ovary Syndrome With Coronary Artery Calcification and Carotid-Intima-Media Thickness: The Coronary Artery Risk Development in Young Adults Women's Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.304136

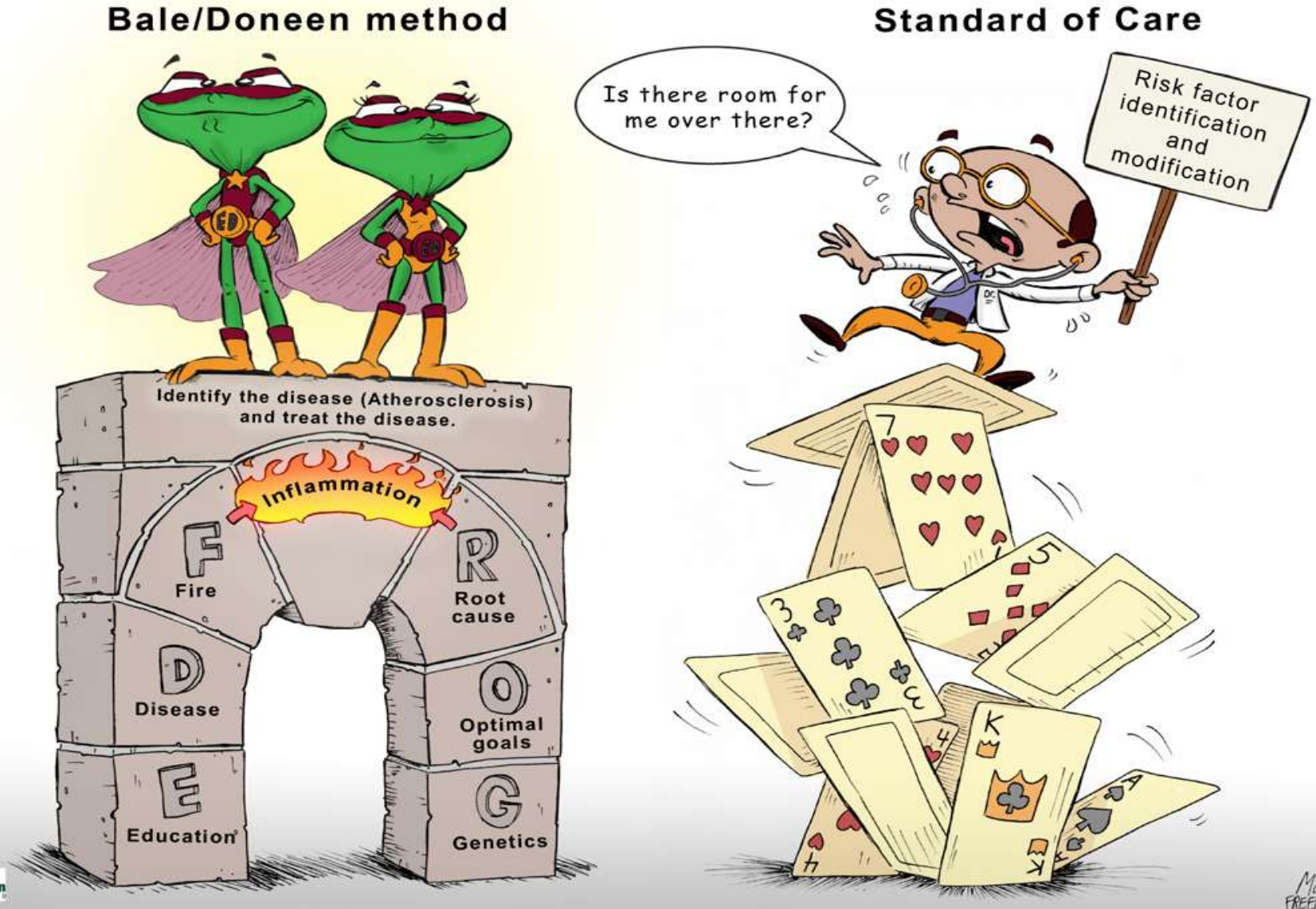
BDM Thoughts

These young ladies need early assessment of arterial inflammation and potential root causes.

Optimal management should begin at an early age.

This certainly needs to include excellent oral hygiene and routine care in a dental practice.

What's the difference?



Left Sided Carotid Plaque Overall More Dangerous Than on Right Side: Background

ASVD disease in the carotid arteries is a major cause of ischemic cerebrovascular events.

Ischemic stroke is more often diagnosed in the left hemisphere than in the right.

This may be due to a higher prevalence, severity, or vulnerability of left carotid artery plaque.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side

1,414 stroke-free Rotterdam pts; at least one carotid plaque ≥2.0mm; mean age 72yo; 47% female; MRI of carotids.

MRI determined: prevalence, stenosis, thickness and predominant component (ie, lipid core, intraplaque hemorrhage, calcification, or fibrous tissue).

Purpose: any significant differences by side.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side

85% of pts had bilateral plaque.

If unilateral, left side was 2X as common as right.

No gender difference in left vs right unilateral plaque, but left sided pts were younger

with mean age 68yo vs 71yo.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side

Thickness was greater in left vs right plaque.

No difference in plaque stenosis or calcification left vs right.

Lipid core and intraplaque hemorrhage were more frequent in left sided plaque.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side

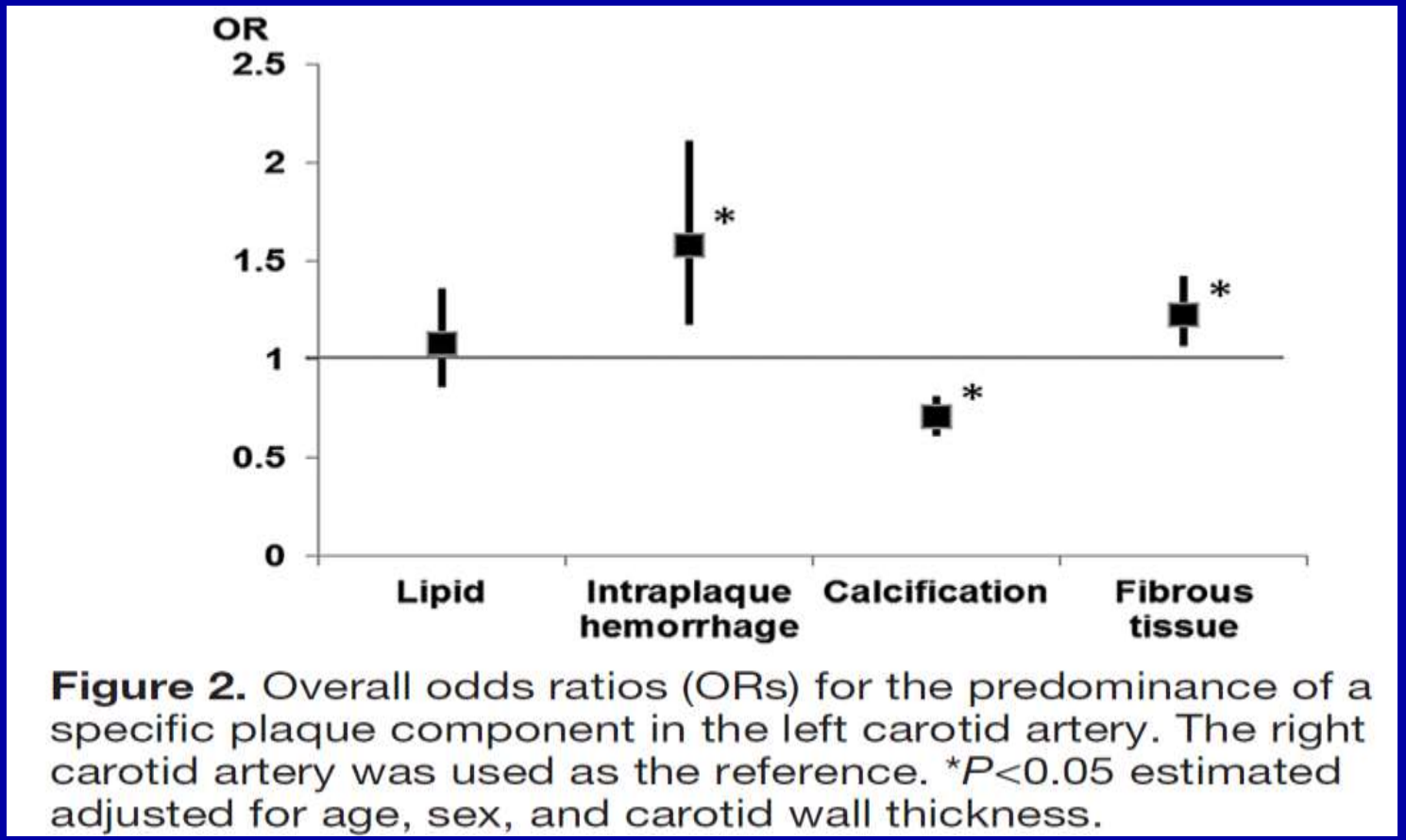


Figure 2. Overall odds ratios (ORs) for the predominance of a specific plaque component in the left carotid artery. The right carotid artery was used as the reference. *$P<0.05$ estimated adjusted for age, sex, and carotid wall thickness.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side

Plaque prevalence, severity, and composition are not equally distributed among the left and right carotid arteries.

Left-sided plaques have a more vulnerable composition.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side: Mechanism?

Geometric factors: bifurcation angle; direct connection of the left carotid artery to the aortic arch.

Hemodynamic forces: left carotid artery exposed to potentially higher arterial pressures.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Sided Carotid Plaque Overall More Dangerous Than on Right Side

Differences found were relatively small and may not explain higher incidence of left hemisphere strokes.

In most people the left hemisphere is dominant for language processing facilitating recognition of an infarct.

Infarcts in the right hemisphere can result in occult cognitive deficit or apraxia.

Selwaness, M., et. al. (2014). Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke, 45*(11), 3226-3230.

Left Internal Carotid Stenosis Associated with Dementia

- Autopsy exam 112 dementia and 577 controls
- Left internal carotid stenosis (≥70%) was associated with dementia

  OR, 2.30 (95% CI, 1.14–4.74) p=0.02 - after multivariate logistic regression models
- Right internal carotid stenosis showed

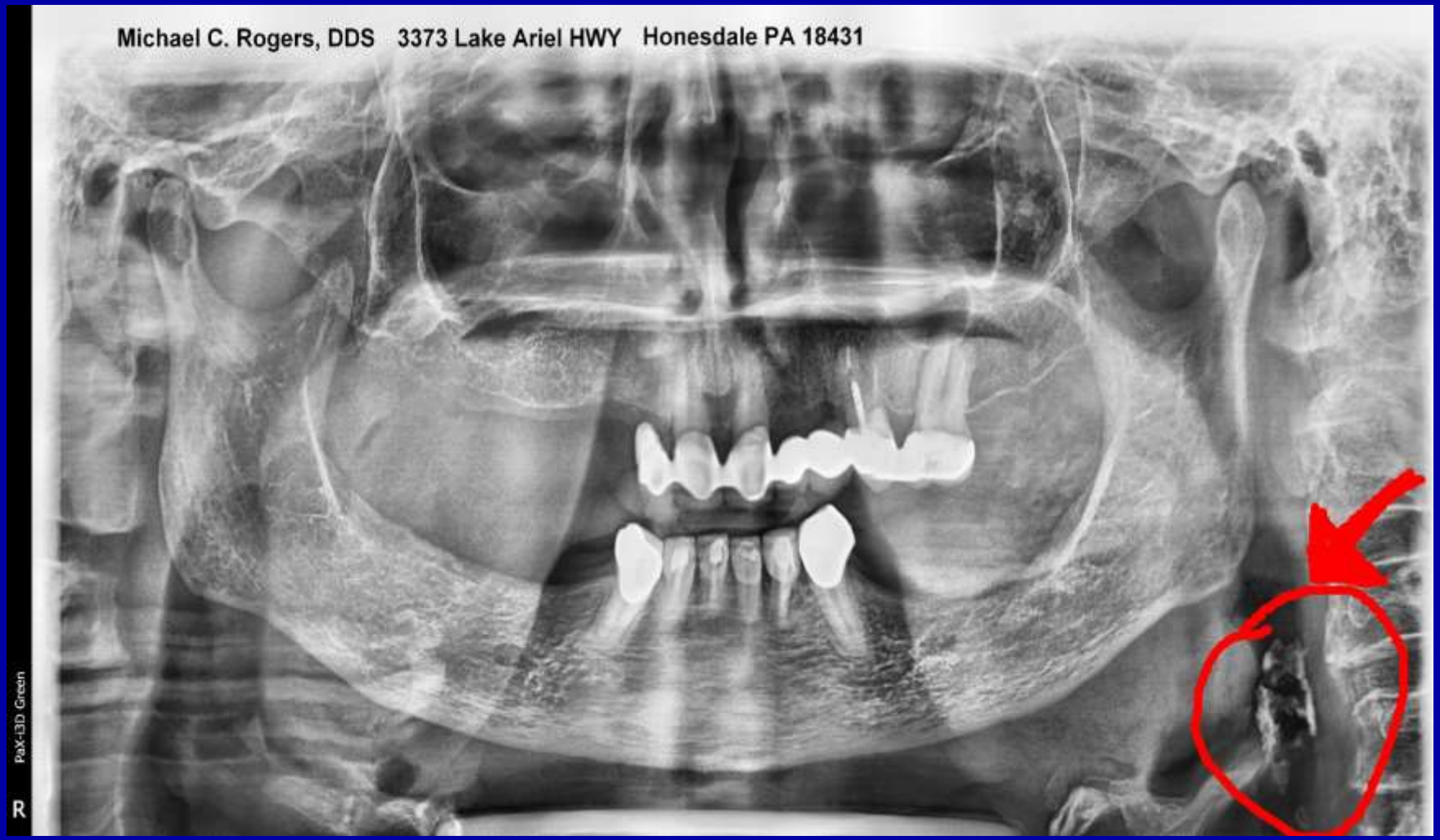
  non-significant trend

  OR, 1.96 (95% CI, 0.94–4.08) p=0.07

Suemoto, C. K., et. al. (2011). Atherosclerosis and Dementia: A Cross-Sectional Study With Pathological Analysis of the Carotid Arteries. *Stroke*. doi: 10.1161/strokeaha.111.628156

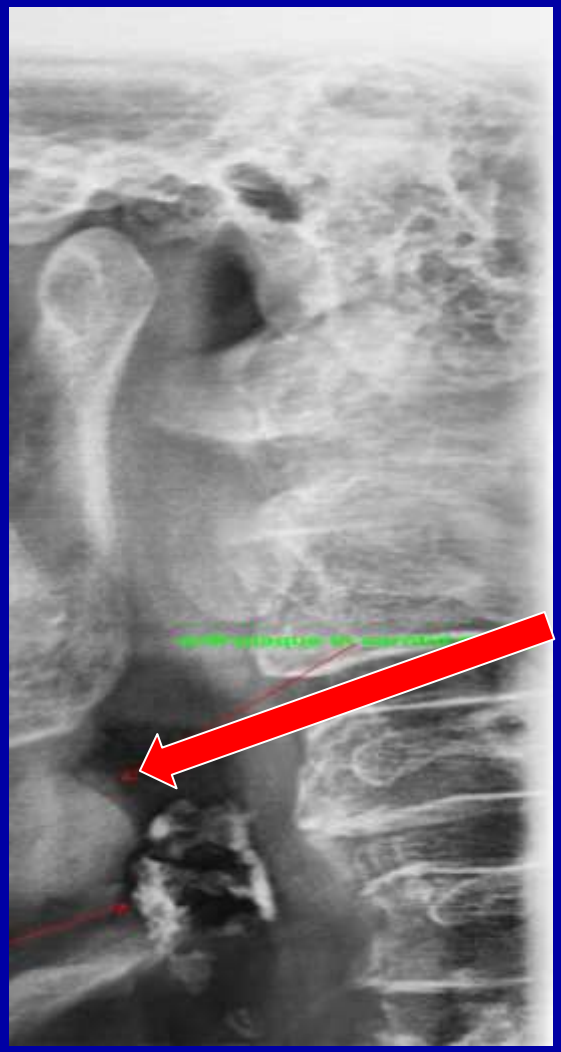
Illusion

Panorex: Left Carotid Calcification



Courtesy Dr. Mike Rogers

Panorex: Left Carotid Plaque



Soft carotid plaque

Courtesy Dr. Mike Rogers

Left Internal Carotid Plaque with Thrombus

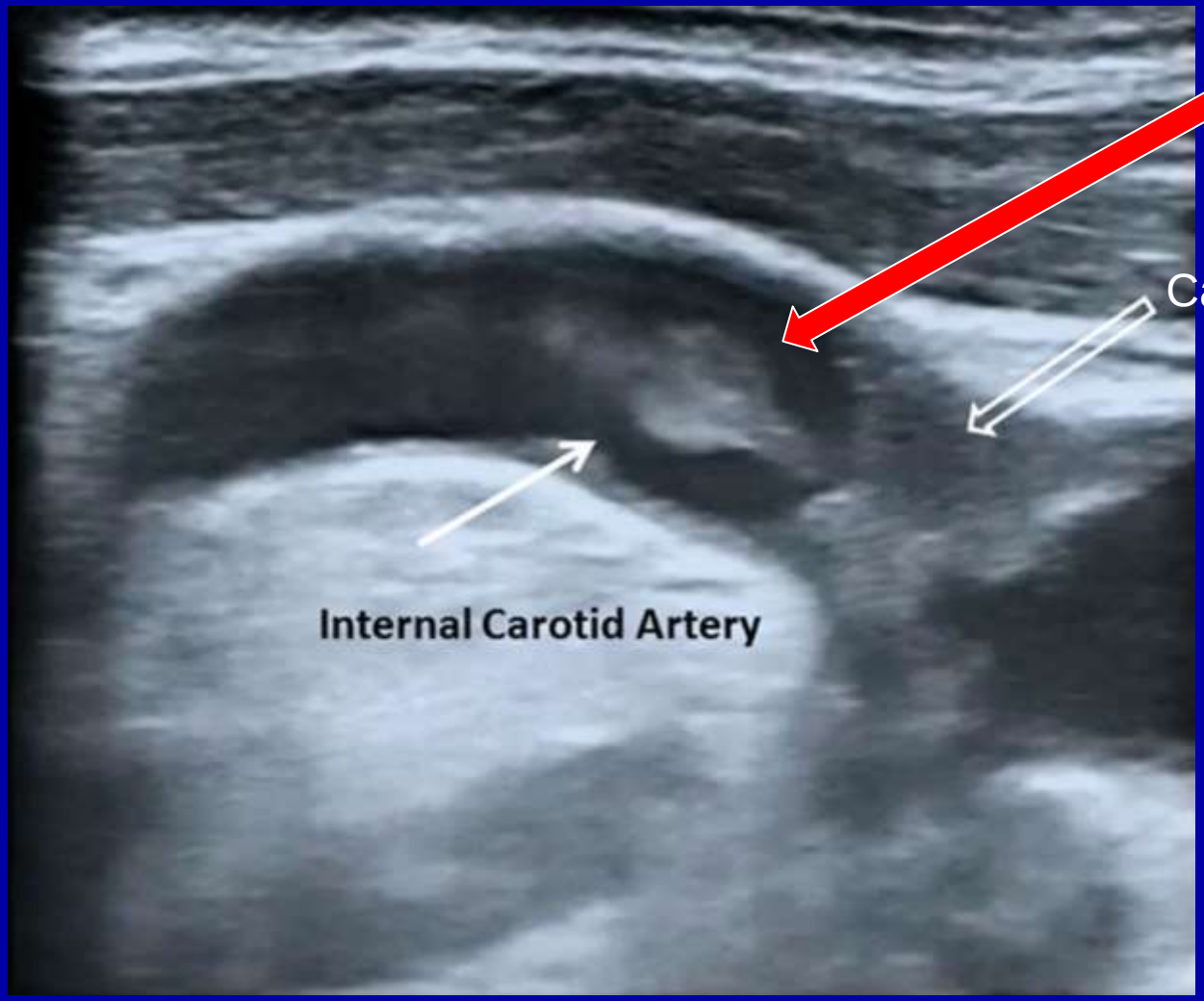
88 yo male with hx of left hemisphere TIA 1 mo. ago.

Admitted with B-cell lymphoma intestinal infiltration and perforation.

Four days after admission, aphasia and right hemiplegia; diagnosis of left middle cerebral artery stroke.

Delgado, M. G., et. al. (2013). Threatening Internal Carotid Artery Floating Thrombus: Left Middle Cerebral Artery Stroke in a Patient With Lymphoma. *Circulation, 127*(8), e463.

Carotid duplex ultrasonography of a longitudinal section of the left internal carotid artery showed an atherosclerotic carotid plaque (black arrow) with a floating thrombus (white arrow).



Delgado M G et al. Circulation 2013;127:e463-e463

Left Internal Carotid Plaque with Thrombus

Anticoagulation treatment with low-molecular-weight heparin was initiated.

Neurological status remained unchanged.

The patient was discharged under anticoagulant treatment.

Later readmitted and died 24 hours later.

Delgado, M. G., et. al. (2013). Threatening Internal Carotid Artery Floating Thrombus: Left Middle Cerebral Artery Stroke in a Patient With Lymphoma. *Circulation, 127*(8), e463.

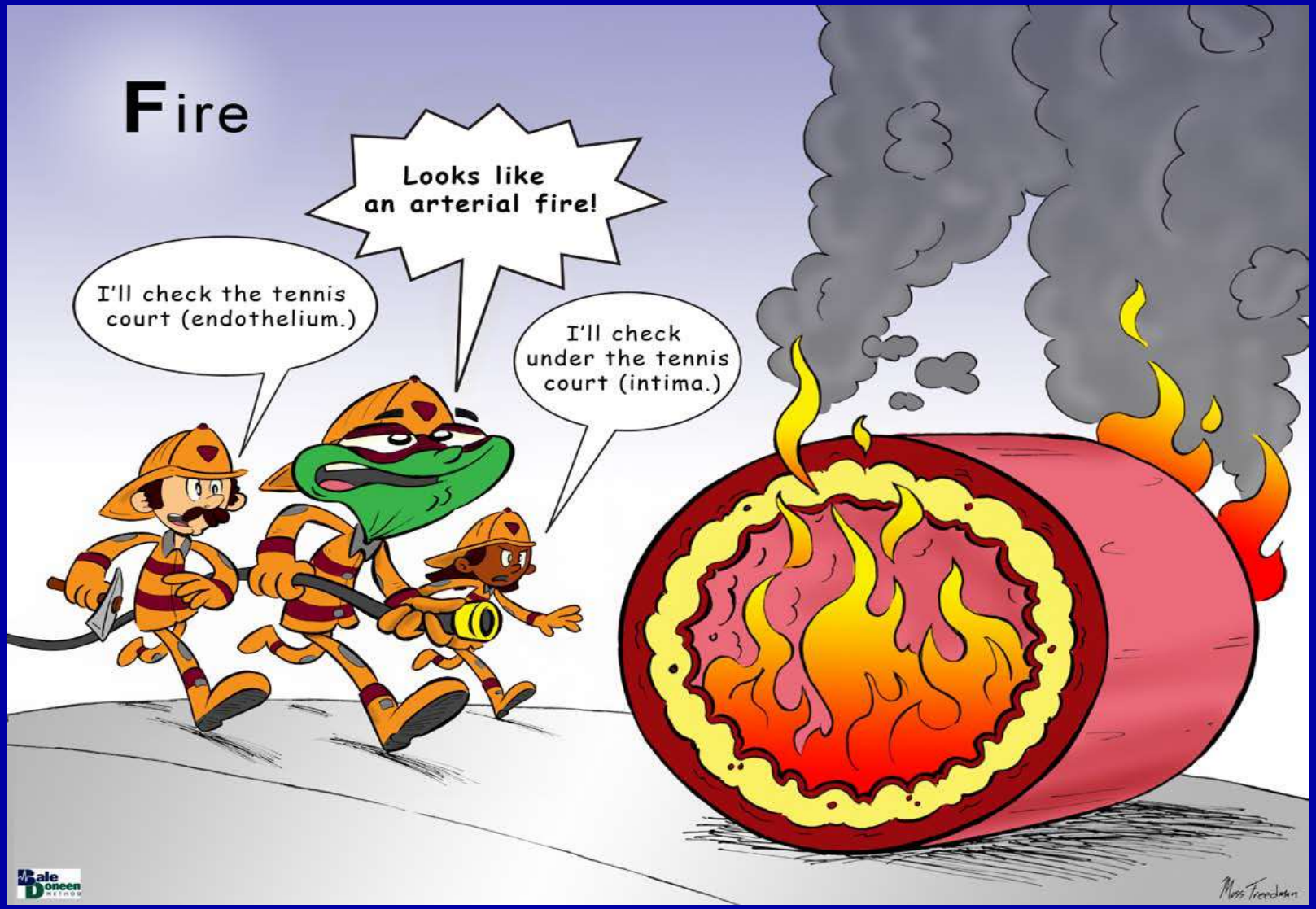
BDM Thoughts

All carotid plaques must be considered dangerous regardless of ‘side’.

Perhaps side does matter in terms of likelihood of events.

Inflammation is the ultimate determinant of risk!

Inflammation



18FDG-PET-CT of Carotid Correlates with Event Risk: Background

High levels of glucose metabolism are seen in tissue with inflammatory activity.

Studies have documented the degree of plaque inflammation depicted by 18FDG uptake is significantly correlated with histopathologic findings.

18FDG-PET-CT can image inflammatory cell activity within the carotid plaque.

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk: Background

Unstable carotid plaque has a thin fibrous cap and contains large numbers of macrophages and T lymphocytes (inflammation).

Therefore, 18FDG-PET-CT should be able to differentiate which stenotic carotid plaques are generating cerebral symptoms and microemboli.

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk

Examined 123 stenotic carotid plaques derived from 110 pts; 60 symptomatic; 63 asymptomatic.

Target to background ratio (TBR) calculated with maximum uptake of carotid plaque and mean uptake of jugular veins.

Correlated findings with clinical symptoms and presence of microembolic signals (MES) detected by transcranial Doppler.

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk

TBR values were higher in symptomatic compared with asymptomatic ($p<0.0018$) and in MES+ compared with MES− plaques ($p<0.008$).

TBR also accurately identified MES+ plaques not only within the symptomatic (11/14, 79%) but also within the asymptomatic group (4/5, 80%).

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk

18FDG-PET-CT accurately detected high-risk carotid plaques.

Inflammatory activity within the carotid plaque was able to discriminate between symptomatic and asymptomatic plaques.

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk

Inflammation was predominant in the soft component of the plaque compared with the calcified one.

Calcification and inflammation rarely overlap.

Remember: a plaque classified as predominantly calcified may still have highly inflamed soft components.

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk

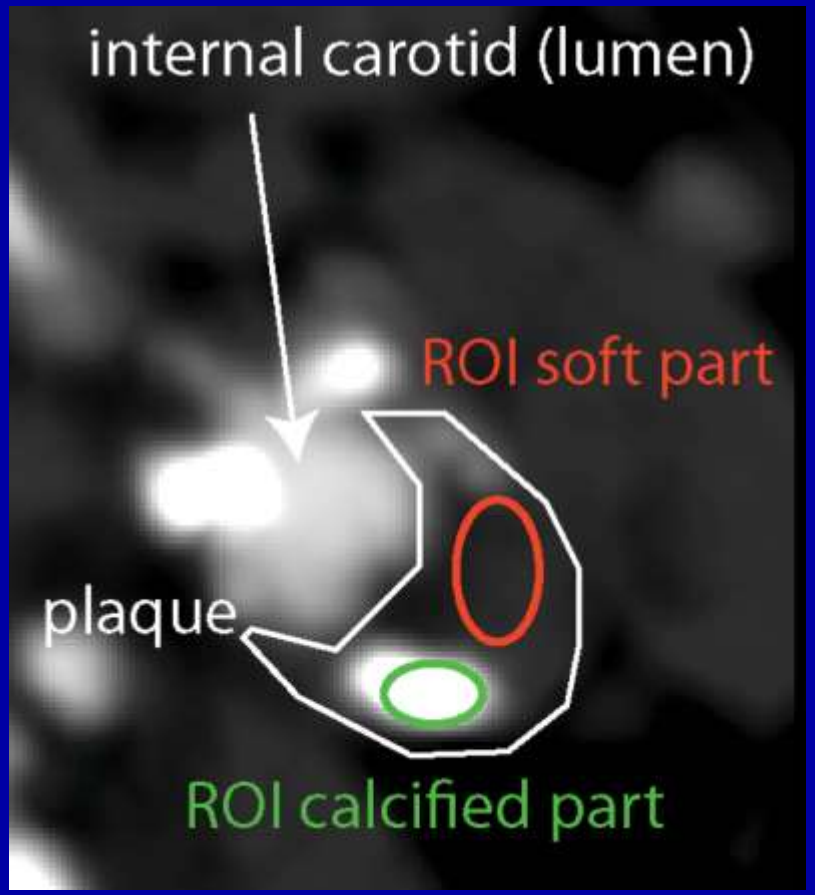
18FDG-PET-CT as imaging biomarker may be a useful tool in clinical practice.

It could become a part of the standard exam to select pts for intervention or for more aggressive medical treatment.

Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

18FDG-PET-CT of Carotid Correlates with Event Risk

Standardized uptake values (SUV) measurement in the region of interest (ROI) of the different plaque components.



Müller, H. F. G., et. al. (2014). 18FDG-PET-CT: An Imaging Biomarker of High-Risk Carotid Plaques. Correlation to Symptoms and Microembolic Signals. *Stroke*. doi: 10.1161/strokeaha.114.006488

BDM Thoughts

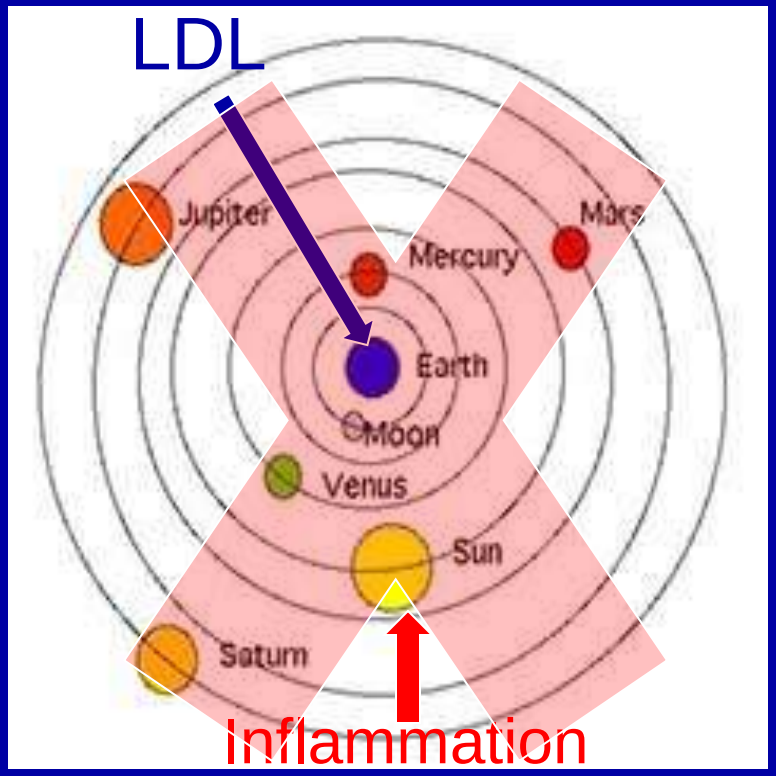
Superb study validating inflammation as the trigger of CV events.

Emphasizes the importance of monitoring inflammation in pts with plaque (asymptomatic lesions can be seeding damaging microemboli).

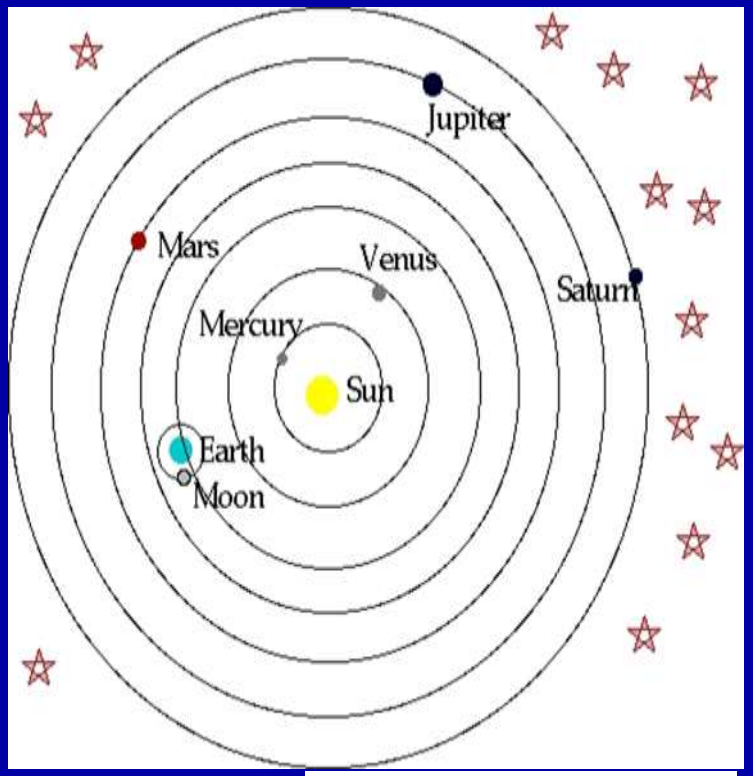
Fortunately, we have less expensive ways to detect inflammation in plaque than PET-CT.

Inflammatory Message

The Sun (inflammation) is at the center; not the Earth (lipids) . Many scientists for a long time thought it was the other way!



Standard of Care!
antiquated



BDM

Carotid Inflammation Predicts Stroke Risk: Background

Microwave radiometry (MWR) noninvasively measures the temperature of carotid plaques.

This temperature (“fire”) reflects plaque inflammatory activity.

Higher inflammation is associated with plaque vulnerability.

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

Carotid Inflammation Predicts Stroke Risk: Background

Hypothesized that in pts with acute ischemic stroke, culprit carotid arteries will exhibit higher temperature compared with the contralateral carotid arteries.

"Carotids causing strokes are on fire!"*

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

*BDM

Carotid Inflammation Predicts Stroke Risk

50 consecutive pts with acute ischemic stroke due to large artery ASVD; carotids evaluated with carotid ultrasound and MWR.

Three segments of 20 mm studied in each carotid artery; middle segment was bifurcation; segment with the highest plaque thickness was target for MWR.

Ipsilateral carotid artery was assigned as culprit.

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

Carotid Inflammation Predicts Stroke Risk

MWR measurements were performed in both culprit and non-culprit carotid arteries over the segments.

Temperature difference (ΔT) of each carotid artery was assigned as the temperature of the target segment minus the minimal temperature of each carotid.

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

Carotid Inflammation Predicts Stroke Risk

Culprit carotid arteries had higher ΔT compared with asymptomatic carotid arteries.

0.93±0.58 versus 0.58±0.35°C; $p<0.001$

After adjustment for: sex, age, vascular risk factors, and max plaque thickness, the chance of having a hotter culprit carotid were 6X greater!

OR- 5.94 (95% CI,1.56–22.63) p=0.01

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

Carotid Inflammation Predicts Stroke Risk

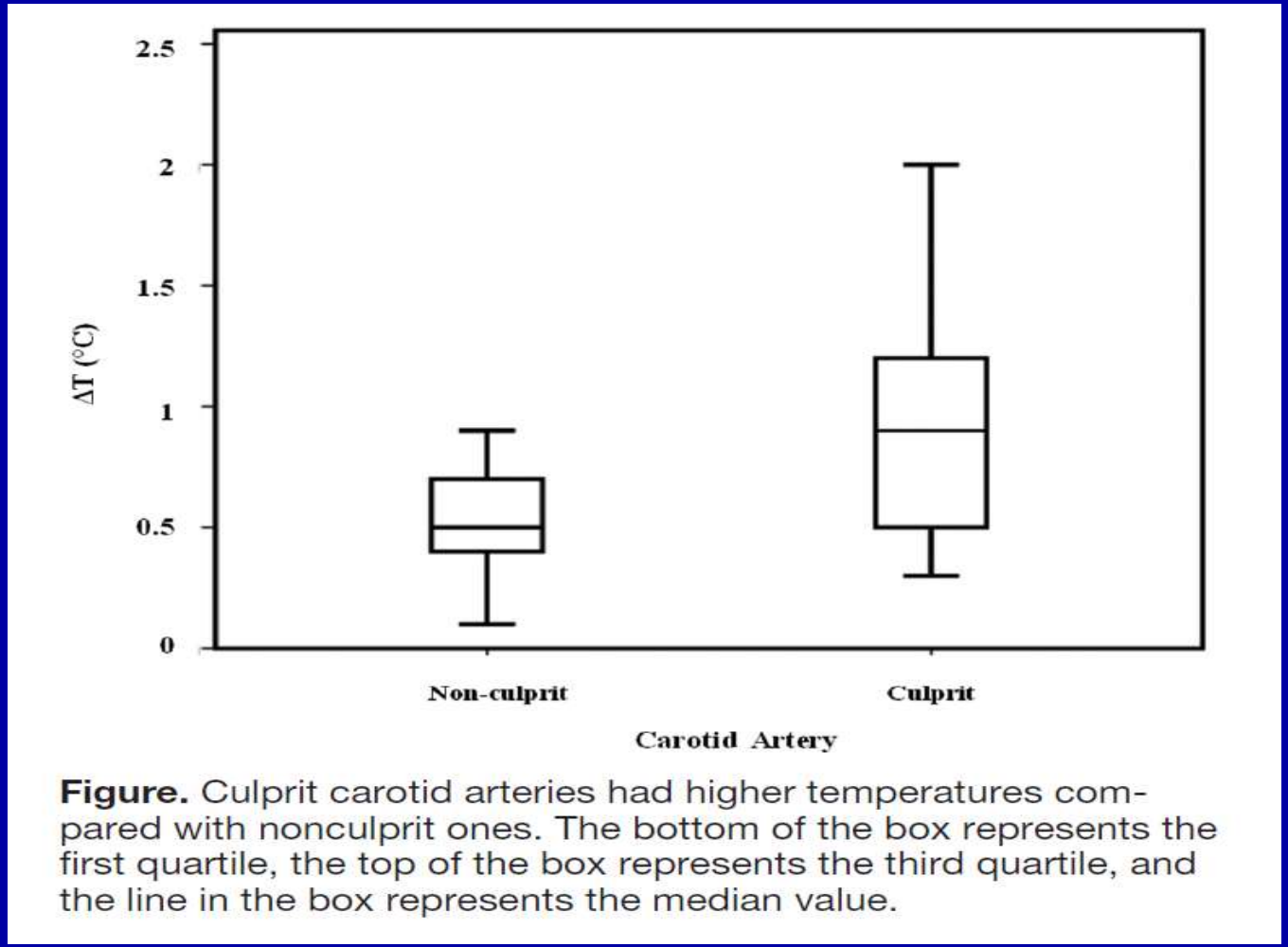


Figure. Culprit carotid arteries had higher temperatures compared with nonculprit ones. The bottom of the box represents the first quartile, the top of the box represents the third quartile, and the line in the box represents the median value.

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

Carotid Inflammation Predicts Stroke Risk

The findings with MWR regarding the inflammatory status of the culprit carotid artery are in accordance with the studies using 18FDG-PET-CT.

Confirms previous studies demonstrating inflammatory activity of plaque significantly interferes progression and destabilization of ASVD.

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

Carotid Inflammation Predicts Stroke Risk

Diagnostic algorithms to accurately assess ASVD inflammation will increase the accuracy of identifying vulnerable plaque.

A new simple noninvasive method, such as MWR, may be useful in primary and secondary prevention of stroke..

Toutouzas, K., et. al. (2014). Incremental Predictive Value of Carotid Inflammation in Acute Ischemic Stroke. *Stroke*. doi: 10.1161/strokeaha.114.007526

BDM Thoughts

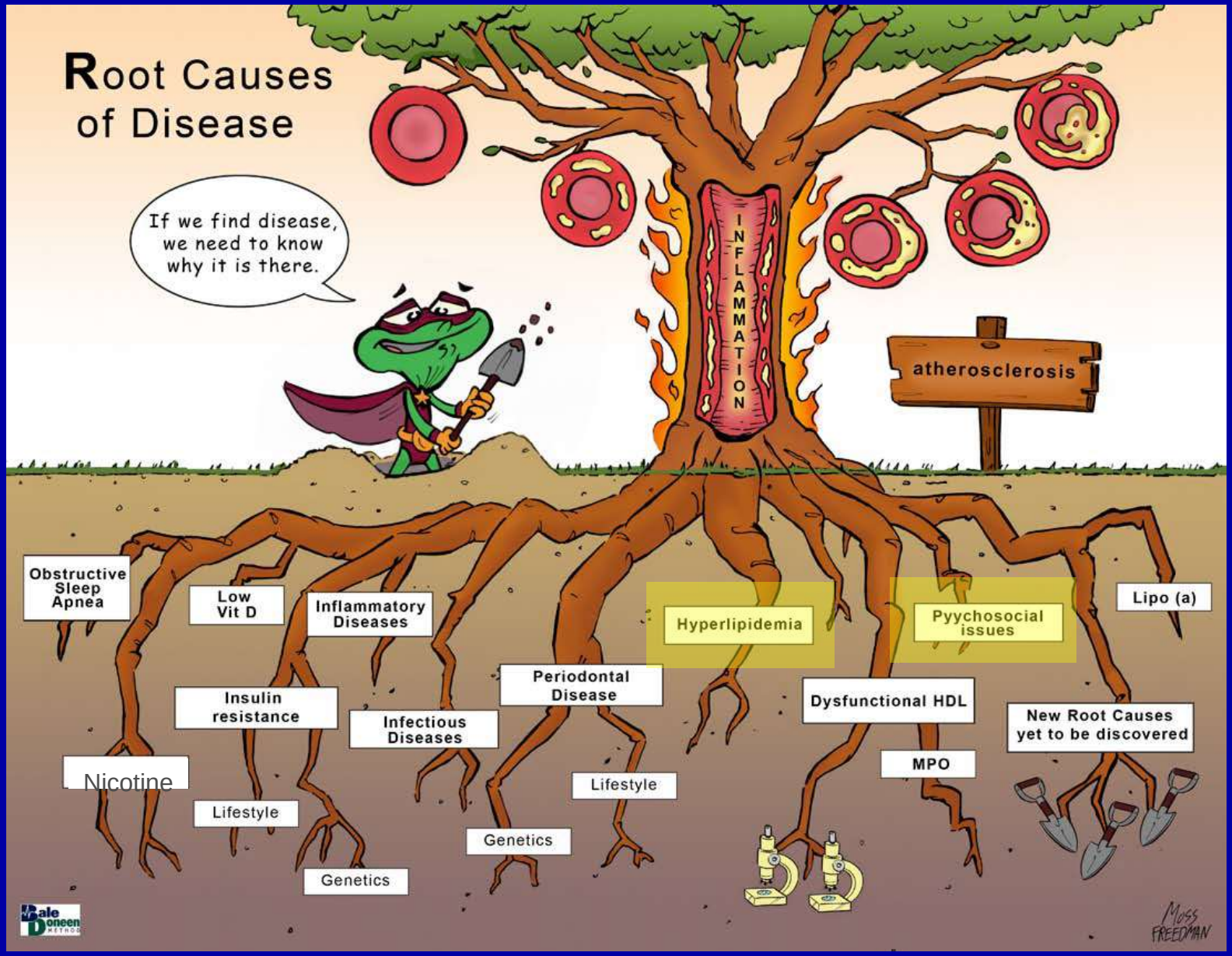
Love this study that literally looks at heat; the F of EDFROG!!!!

Again helps confirm the ‘sun’ at the center of the ASVD solar system!!

Again, fortunately we have simple serum and urine biomarkers to detect ‘fire’! ☺

Fire in the Hole!!!

Hs-CRP
Fibrinogen
Lp-PLA2
MPO
F2 isoprostane
MACR



Stress Alters Circulatory Nanoparticles-Proteins and mi-RNAs

Heat shock proteins (Hsp) and microRNA (miRNA) are biologically active nanoparticles (40–100 nm) released by cells .

Murine induced stress through the sympathetic nervous system modified Hsp and miRNA levels.

Beninson, L. A., et. al. (2014). Acute Stressor Exposure Modifies Plasma Exosome-Associated Heat Shock Protein 72 (Hsp72) and microRNA (miR-142-5p and miR-203). *PLoS One, 9*(9), e108748. doi: 10.1371/journal.pone.0108748

What???: Epigenetics

Psychosocial Issues Alter Epigenetics Which Influence Arterial Inflammation

Psychological stress engenders a pro-inflammatory epigenetic signature, which increases risk for heart attack and stroke.

Hsp can mediate inflammation; miRNAs key regulators of gene expression.

Epigenetics may bridge the psycho-social environment with inflammation and risk for CVD.

Saban, K. L., et. al. (2014). Epigenetics and social context: implications for disparity in cardiovascular disease. *Aging Dis, 5*(5), 346-355.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke: Background

Guidelines recommend LDL-C as the primary lipid target for recurrent stroke risk reduction.

However, evidence indicates other lipids are superior predictors of stroke.

If that is true they should be therapeutic targets to reduce stroke and recurrent stroke risk.

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke

3,385 recent ischemic stroke (IS) pts.; ~62% male; mean age ~ 66yo; 80% white; baseline lipids with TC/HDL & TG/HDL available; follow-up 2 yrs.

Primary outcome was recurrent IS. (n-272)

Secondary outcome: composite of all MACE. (n-564)

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke

Recurrent stroke was highest in the upper quintile of TG/HDL ratio

HR- 1.68 (95%CI, 1.16-2.45)

MACE was highest in the upper quintile of TG/HDL & TC/HDL ratio

HR- 1.57 (95%CI, 1.21−2.03)

HR- 1.51 (95%CI, 1.17−1.95), respectively

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke

After adjusting for multiple confounders and comparing upper quintile to lower quintile:

Upper quintile TG/HDL ratio had 56% increased risk of IS and 39% increased risk of MACE.

Lowest quintile $\leq$1.93

Highest quintile $\geq$6.22

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke

After adjusting for multiple confounders and comparing upper quintile to lower quintile:

Upper quintile TC/HDL ratio had insignificant 35% increased risk of IS and a significant 45% increased risk of MACE.

Lowest quintile ≤3.50

Highest quintile ≥5.98

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke

After adjusting for multiple confounders and comparing upper quintile to lower quintile:

LDL/HDL ratio showed no association with risk.

Non-HDL showed no association with risk.

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

TG/HDL Ratio Most Predictive Lipid Measure for Recurrent Stroke

Results suggest that TG/HDL ratio should be a target of therapy to reduce recurrent stroke.

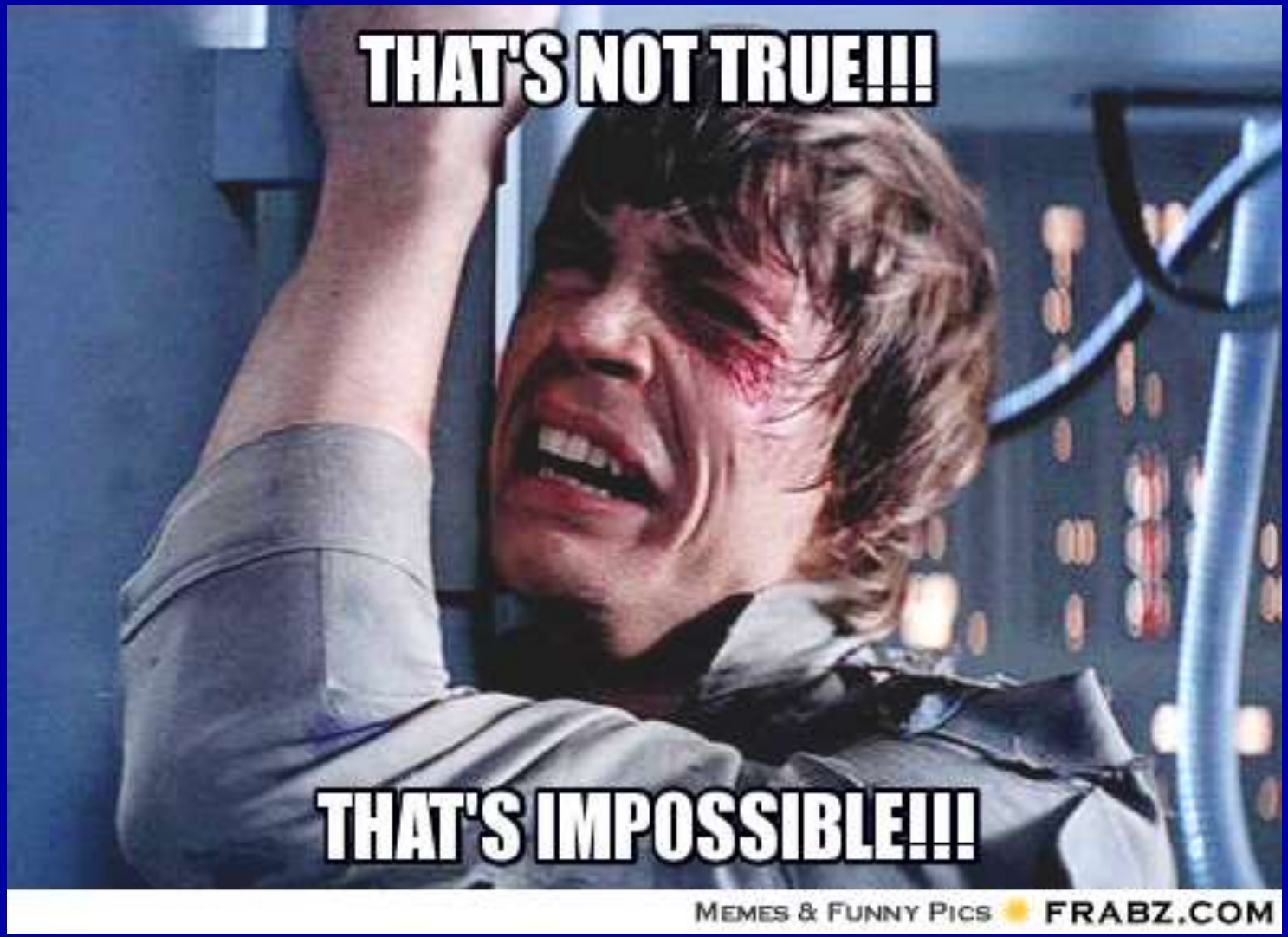
In addition, data suggests in stroke victims TG/HDL and TC/HDL ratios should be targets of therapy to reduce MACE.

Park, J.-H., et. al. (2014). Nontraditional Serum Lipid Variables and Recurrent Stroke Risk. *Stroke, 45*(11), 3269-3274.

BDM Thoughts

- Results consistent with evidence that LDL-C does not predict stroke risk.
- Another study showing serious fallacy with current guidelines recommending LDL-C as primary lipid target of therapy.
- Results consistent with evidence that HDL-C is important in stroke risk as is TG (remnant cholesterol).
- Helps explain why stroke recidivism is shockingly high.
- Helps explain recent results reported in BARI-2D trial with rosiglitazone and stroke.
- Supports BDM goal for TC/HDL as <3.0; TG/HDL goals of <3.5 Whites; <3.0 Hispanics; <2.0 Blacks (IR = stroke risk).

LDL-C Does Not Predict CV Risk!



HDL is most predictive of stroke

Age- and gender-adjusted for all strokes (n=1111)

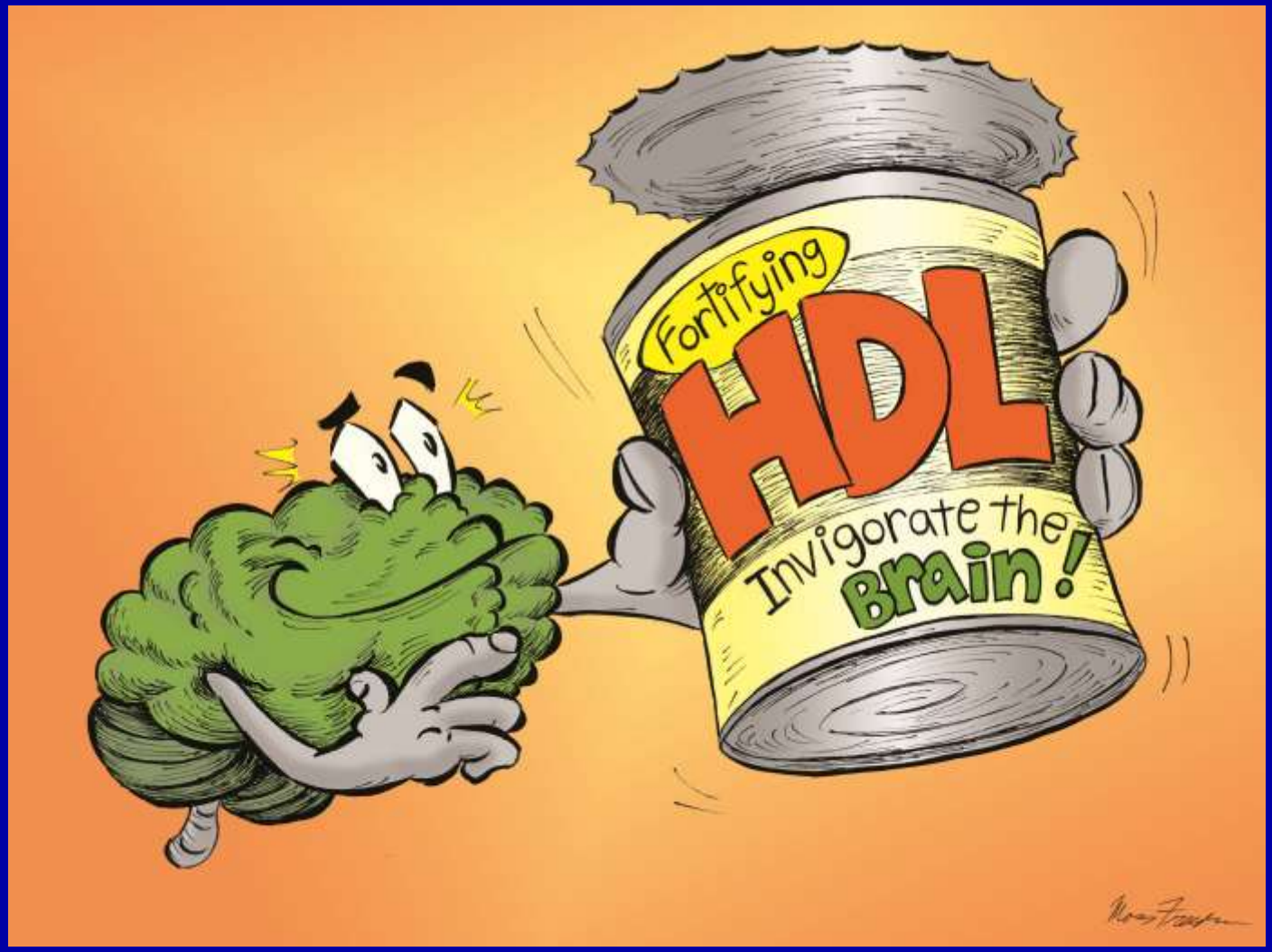
Variable	Relative risk/standard deviation	95% CI
ApoB/apoA-1	1.14	1.07-1.20
ApoB	1.03	0.97-1.10
ApoA-1	0.84	0.79-0.89
LDL/HDL	1.07	1.03-1.10
TC/HDL	1.08	1.05-1.12
LDL	0.98	0.92-1.05
Non-HDL	1.03	0.96-1.10
HDL cholesterol	0.81	0.77-0.86

AMORIS trial: 175000 men and women followed 10.3 yrs.

The risk of stroke was calculated as a relative risk for 1 standard-deviation unit change (RR/SD). Subjects having the highest apoA-1 and lowest apoB values were used as the reference.

Walldius G et al. *J Intern Med* 3/2006; 259: 259-266.

HDL is Brain Food



HDL & atherosclerotic stroke risk

Each 1 mg/dL increase in HDL yields:

1.9% reduction in stroke risk

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

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

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

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

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

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

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

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

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

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

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

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

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

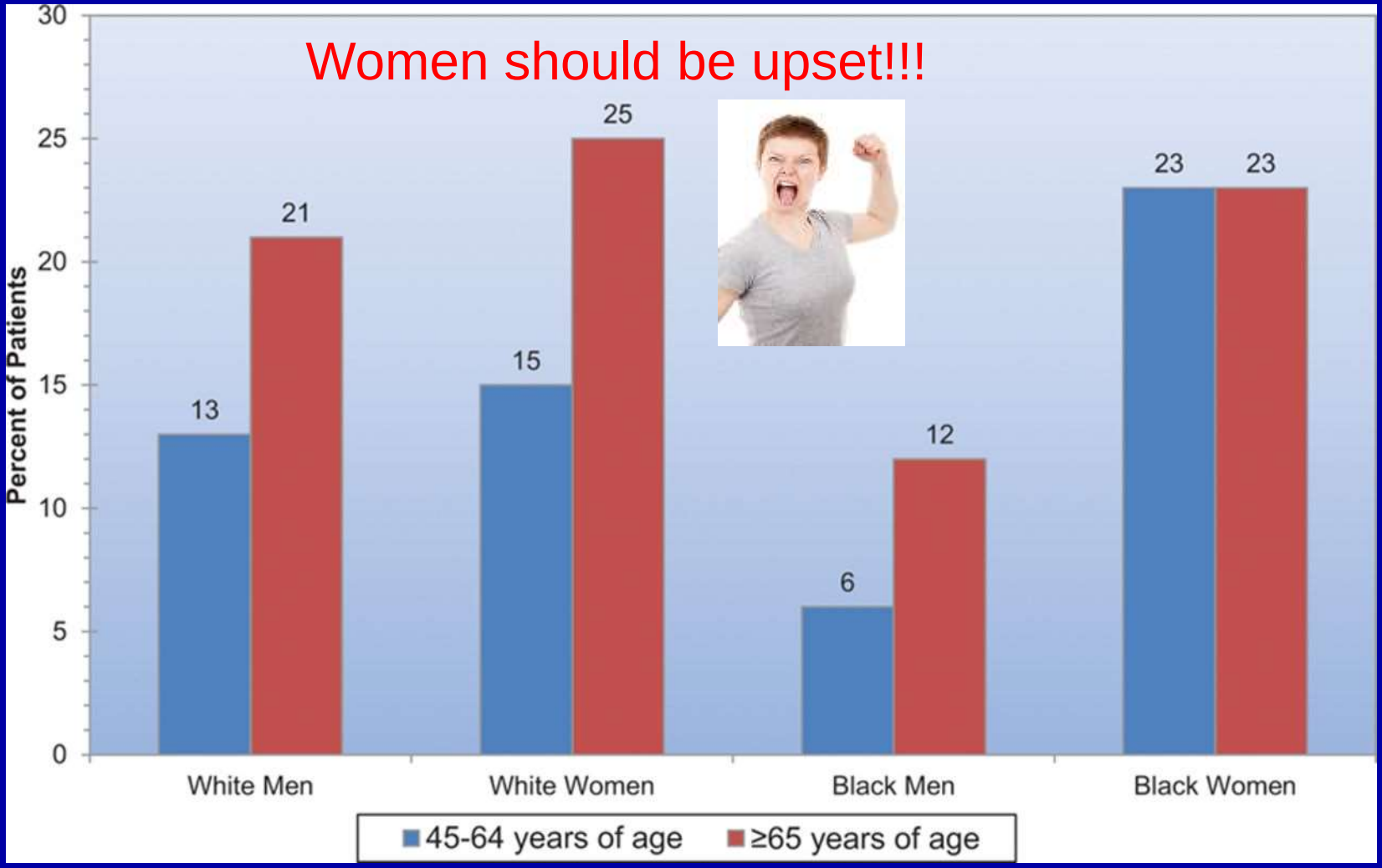
AHA 2013 Statistics

23% of strokes are recidivistic!

Every 4 minutes someone dies from a stroke

Go, A. S., et. al. (2013). Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation, 127*(1), e6-e245.

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



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

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

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

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

Pioglitazone Improved CAD via Reducing TG/HDL

- Post hoc analysis 360 subjects in PERISCOPE
- Improved TG/HDL independently predicted change in total atheroma volume p=0.02
- adjusted for: sex, BP, history of PCI, hypercholesterolemia, **metformin** use, baseline HbA_{1C}, and baseline apoA-1.

Nicholls, S. J., et. al. (2011). Lowering the Triglyceride/High-Density Lipoprotein Cholesterol Ratio Is Associated With the Beneficial Impact of Pioglitazone on Progression of Coronary Atherosclerosis in Diabetic Patients: Insights From the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) Study. *J Am Coll Cardiol, 57*(2), 153-159.

Rosiglitazone Reduced Stroke Risk 64%

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

Stroke HR 0.36 (95% CI 0.16 to 0.86)

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

MI HR 0.77 (95% CI, 0.54 to 1.10)

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

TG/HDL > 3.5 = IR in Caucasians

Ethnicity is Important

Dr. Gerald Reaven 1/2001

McLaughlin, Reaven, et.al., ***Am J Cardiol***. 8/1/2005;96:399-404

TG/HDL Ratio in Ethnic Groups

Mexican Americans: ≥3.0

Non-Hispanic Blacks: ≥2.0

Chaoyang Li, Earl S. Ford, Yuan-Xiang Meng, Ali H Mokdad, Gerald Reaven
Cardiovascular Diabetology 2/28/2008, 7:4 doi:10.1186/1475-2840-7-4

A1c Misses ~Half of Patients with Pre-diabetes

501 pts screened for pre-diabetes with 75 gram OGTT; also had A1c drawn.

193 pts had IFG and or IGT

A1c missed 90 of the pre-diabetics

Chilelli, N. C., et. al. (2014). Screening with HbA1c identifies only one in two individuals with diagnosis of prediabetes at oral glucose tolerance test: findings in a real-world Caucasian population. *Acta Diabetol, 51*(5), 875-882.

EDFROG IRA

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

RAAS Plus Trimethoprim/Sulfamethoxazole May Kill People

1,027 sudden death cases in ≥66yo pts on RAAS med; occurring within 7 days of exposure to an antibiotic; matched to 3,733 controls (sudden death; on RAAS, but no antibiotic).

Antibiotics were: co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin.

Amoxicillin was reference antibiotic.

Fralick, M., et. al. (2014). *Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study* BMJ 2014;349:g6196 doi: 10.1136/bmj.g6196.

RAAS Plus Trimethoprim/Sulfamethoxazole Maybe Deadly

Co-trimoxazole associated with increased risk

OR-1.38 (95% CI, 1.09 to 1.76)

Ciprofloxacin was also associated with risk

OR- 1.29 (95% CI, 1.03 to 1.62)

No increased risk with norfloxacin or nitrofurantoin.

Fralick, M., et. al. (2014). *Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study* BMJ 2014;349:g6196 doi: 10.1136/bmj.g6196.

RAAS Plus Trimethoprim/Sulfamethoxazole Maybe Deadly

Trimethoprim has structural and pharmacologic similarities to amiloride.

Trimethoprim blocks the epithelial sodium channel (ENaC) in the distal nephron, impairing renal potassium elimination.

~80% of pts receiving co-trimoxazole develop increases in serum potassium concentrations of at least 0.36 mEq/L and 6% develop frank hyperkalemia.

Fralick, M., et. al. (2014). *Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study* BMJ 2014;349:g6196 doi: 10.1136/bmj.g6196.

RAAS Plus Trimethoprim/Sulfamethoxazole Maybe Deadly

Suggest when clinically appropriate, clinicians either choose alternate antibiotics or limit the dose and duration of co-trimoxazole treatment.

When co-trimoxazole is prescribed, close monitoring of serum potassium is advisable in susceptible pts.

Fralick, M., et. al. (2014). *Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study* BMJ 2014;349:g6196 doi: 10.1136/bmj.g6196.

BDM Thoughts

Reinforces previous warning.

Also makes you wonder about ciprofloxacin.

Remember to monitor K+ closely when initiating therapy with amiloride.

Amiloride: K+ Sparing Diuretic

Inhibits of Na+ reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct.

This decreases the net negative potential of the tubular lumen reducing both K+ & H- secretion and subsequent excretion.

It is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

Usual dose is 5-10mg; may go up to 20mg; comes in 5 mg tablets.

Anna J. Stears, et. al. ***Hypertension. 5/2012;59:934-942***

Potassium Extremely Important in Cardiac Arrhythmias and Sudden Cardiac Death

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

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

(4.5-5.0)

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

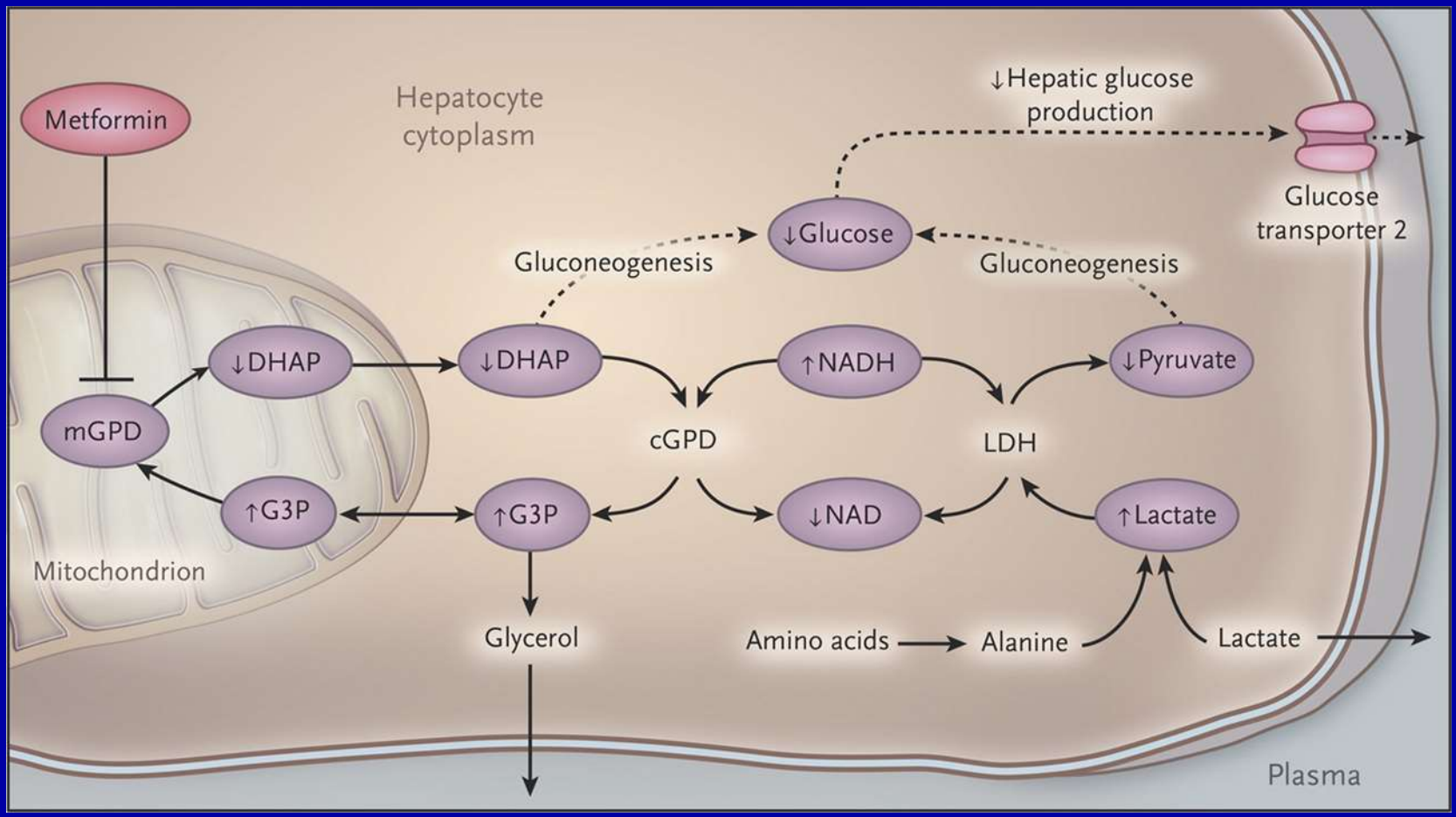
Want More from Amiloride!!!

Amiloride Did Not Cause Any Impairment in Glucose Tolerance

- Two double-blind, placebo-controlled, crossover studies; total 78 pts.; outcome was change in 2hr. GTT after 4 wks. rx with Hctz or amiloride
- Thiazide diuretic significantly impaired glucose tolerance; no impairment was seen with K-sparing diuretic
- Substitution or addition of amiloride may be the solution to preventing thiazide-induced diabetes mellitus

Anna J. Stears, et. al. ***Hypertension. 5/2012;59:934-942***

Metformin: How It Works



"Doc, how is this pill supposed to help me?"

"Sir, it blocks an enzyme that makes the liver put out too much sugar into your blood."

Ferrannini, E. (2014). The Target of Metformin in Type 2 Diabetes. *New England Journal of Medicine, 371*(16), 1547-1548.

Cases !!!

9/2014: 82 yo Caucasian Male

- Known CAD/CT angio; subclinical carotid and femoral ASVD.
- Been plugged into BDM since 2009; cold arteries for several years.
- Routine follow-up labs drawn 9/11/2014.

- Current meds: (no changes in several years)

  Niaspan – 1500 mg

  Fish oil - 1 gram

  Actos - 45 mg

  vit D3 - 5,000 IU

  CoQ10 - 200 mg

  ASA - 81 mg

  Indapamide - 1.25 mg

  Dark choc. - 7 grams

  Dexilant

  Magnesium - 200mg

9/2014: 82 yo Caucasian Male

Routine follow-up labs drawn 9/11/2014.

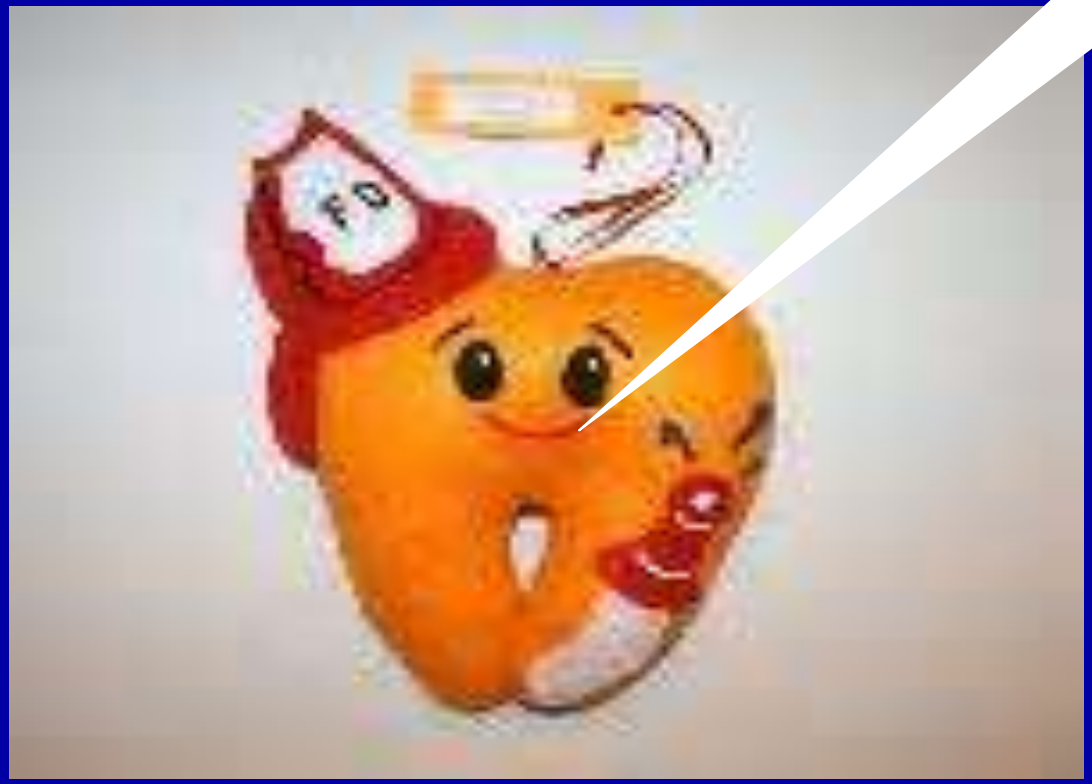
Nurse gets results on 9/18:

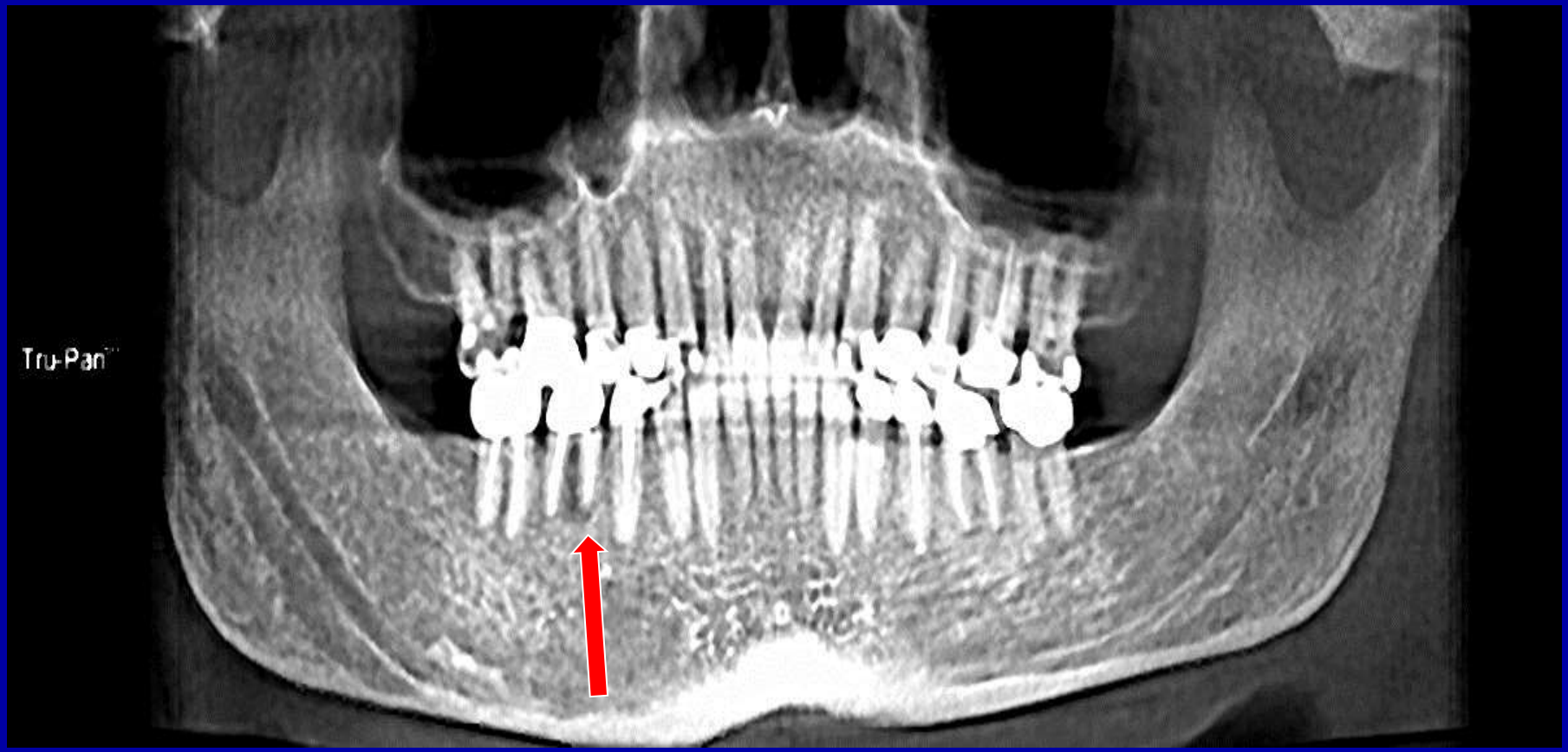
	09	10	11	12	13	5/14	9/11/14
TC	202	152	251	209	205	188	185
TG	59	54	71	65	50	74	58
HDL	97	73	90	90	80	85	89
LDL	93	68	147	106	115	88	84
TC/HDL	2.1	2.1	2.8	2.3	2.6	2.2	2.1
hsCRP	0.8	5.4	1.1	0.9	2.6	0.6	24.5
MACR	6.2	5.2	9.0	3.6		15.6	35.6
PLAC2	146	195	130	126	162	155	185
MPO	1847	221			138	163	283
F2 isopros	1.82	1.08			0.55	0.54	0.27
Pro-BNP	55		35			64	220
	No Niacin Lifestyle issues	GI Issue fever					9/18 call Tooth Ache!

9/2014: 82 yo Caucasian Male

We have your results back.

“ I bet you do not like my results. I have a molar that is hurting and the gum tissue around it seems swollen.”





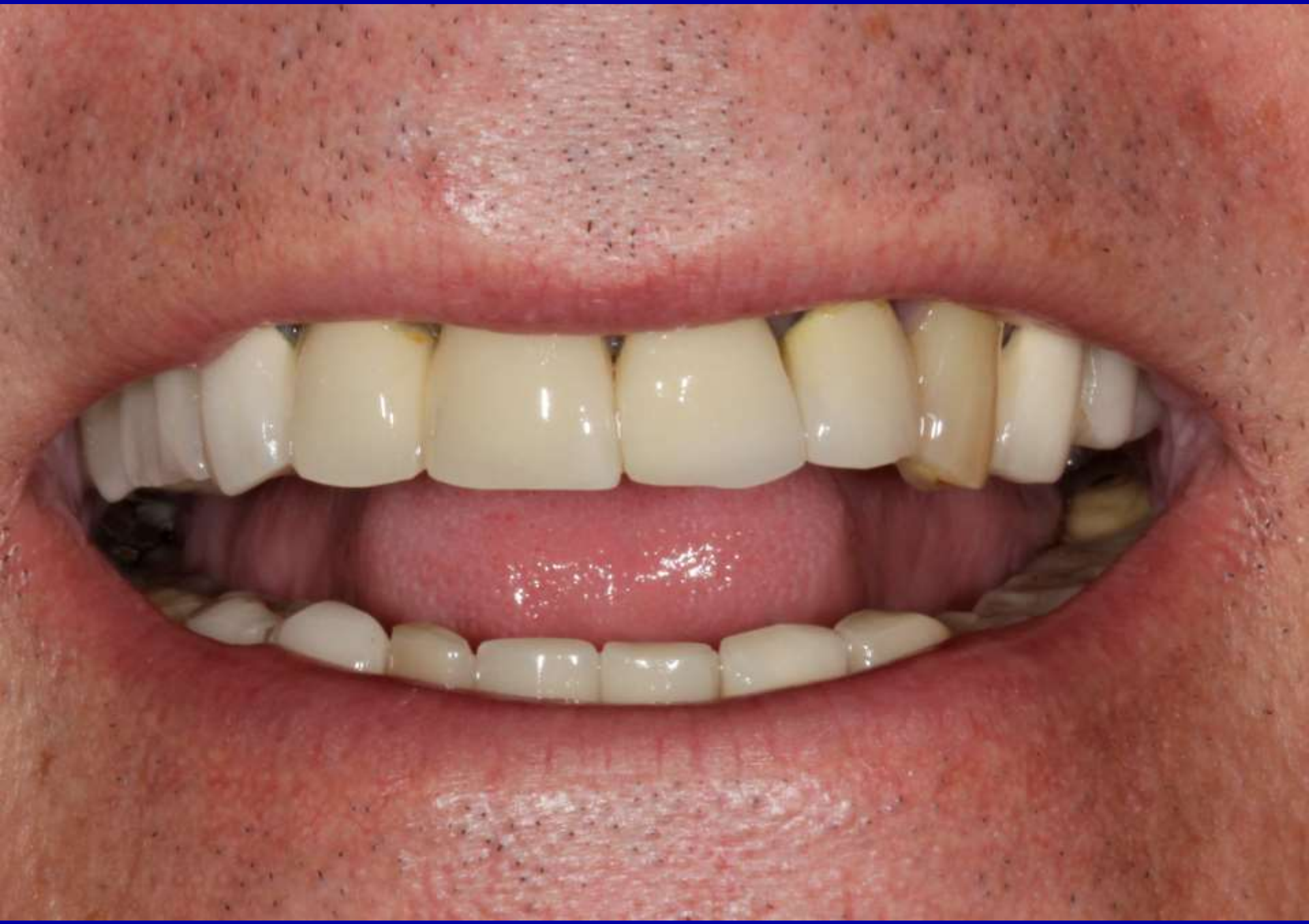
They got it out!!

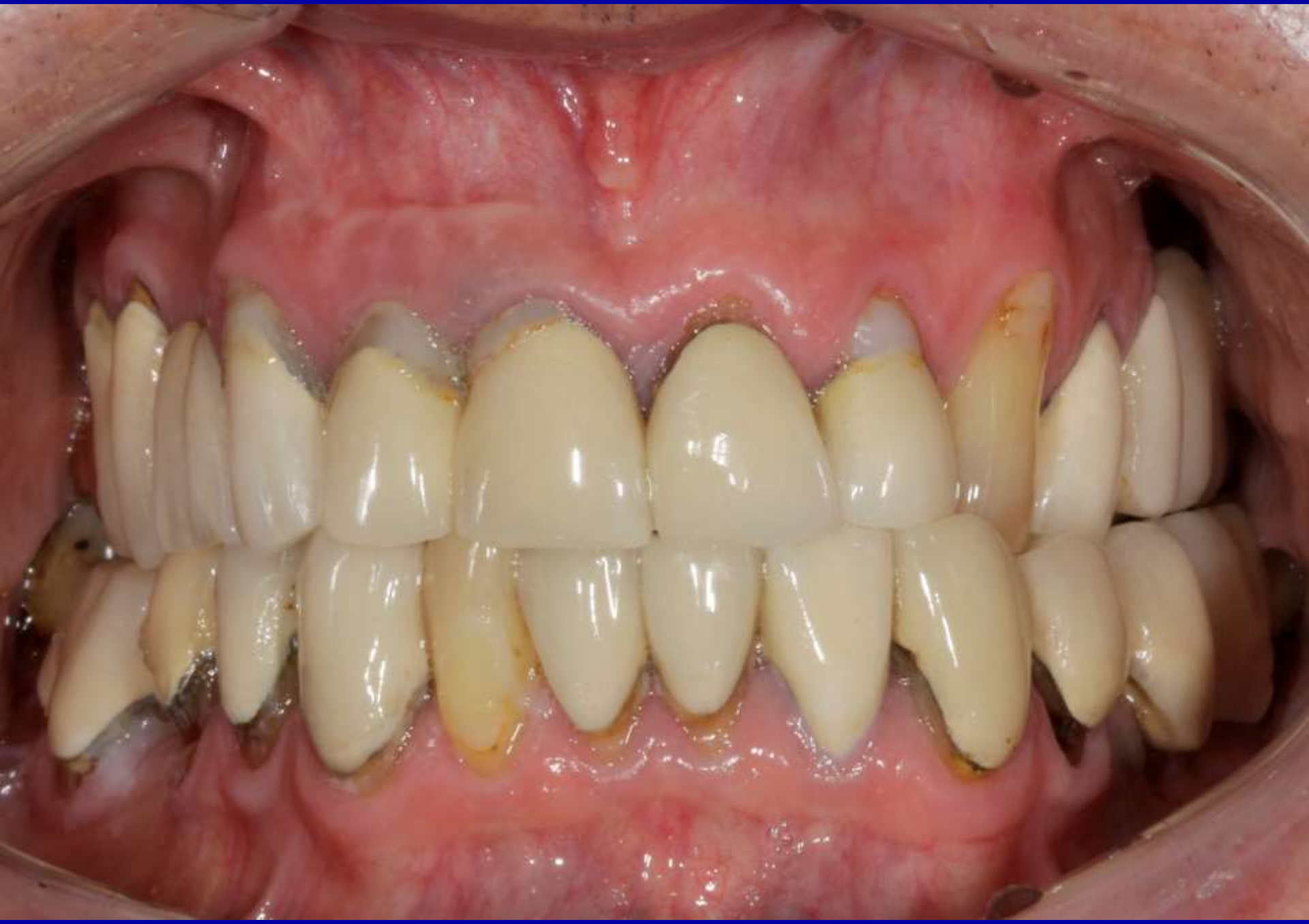
	9/11/14	10/2/14
TC	185	
TG	58	
HDL	89	
LDL	84	
TC/HDL	2.1	
hsCRP	24.5	0.6
MACR	35.6	7.7
PLAC2	185	167
MPO	283	134
F2 isopros	0.27	
Pro-BNP	220	41
	9/18 Tooth Ache!	9/24 Tooth extract.

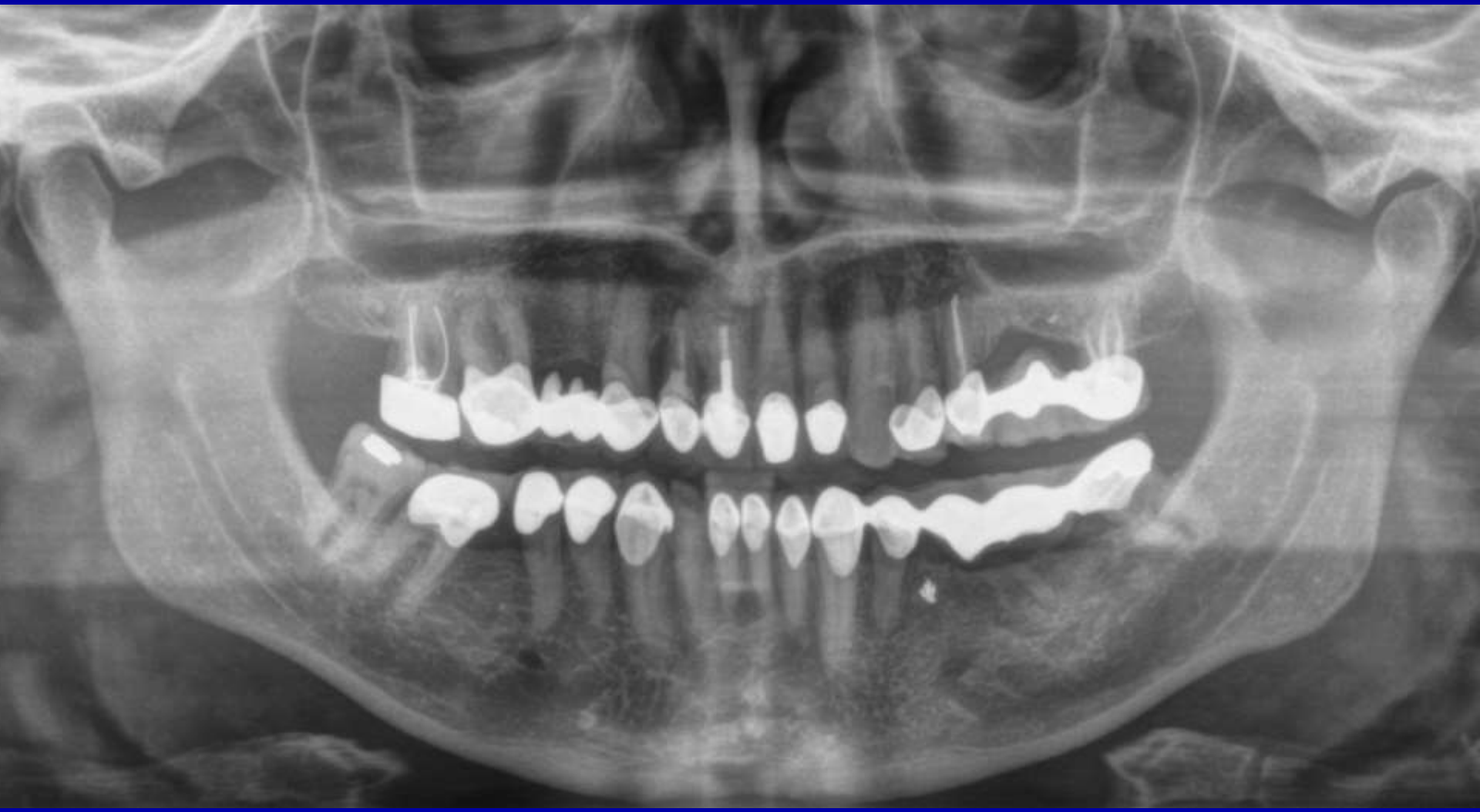
Close call !!!

New Patient Requiring Extensive Restorative Care

- **Medical** issues affecting dental decisions:
- 65 y.o. male, 5,9”, 190 lbs, waist 38”
- Presents for extensive dental restorative care
- Has history of periodontal disease but current disease is stable (no bleeding on periodontal chart)
- Has a structural fracture of upper right front tooth that cannot be saved.
- Two stents placed at 54 years old. No evidence of advanced lipid testing.
- No evidence by history that he is doing anything differently now than he was before stent placement.
- Concern as a dental provider is how inflamed is he and is he stable enough for us to begin invasive work?

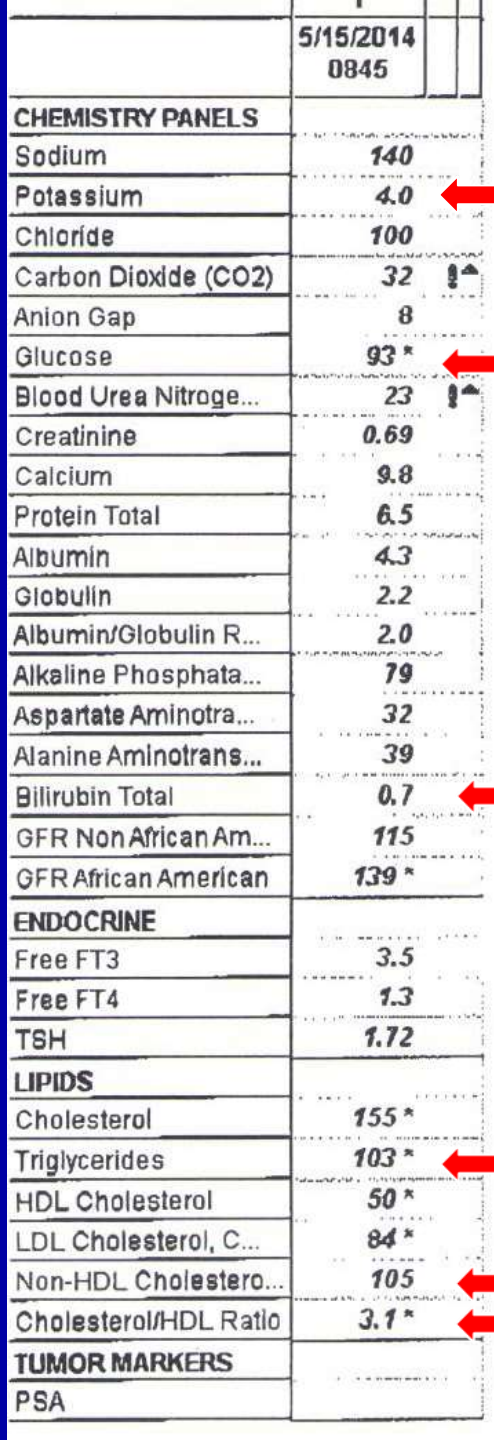






Asked for Any Current Labs

Recommended collecting a more comprehensive collection of information



	5/15/2014 0845
CHEMISTRY PANELS	
Sodium	140
Potassium	4.0
Chloride	100
Carbon Dioxide (CO2)	32
Anion Gap	8
Glucose	93 *
Blood Urea Nitroge...	23
Creatinine	0.69
Calcium	9.8
Protein Total	6.5
Albumin	4.3
Globulin	2.2
Albumin/Globulin R...	2.0
Alkaline Phosphata...	79
Aspartate Aminotra...	32
Alanine Aminotrans...	39
Bilirubin Total	0.7
GFR Non African Am...	115
GFR African American	139 *
ENDOCRINE	
Free FT3	3.5
Free FT4	1.3
TSH	1.72
LIPIDS	
Cholesterol	155 *
Triglycerides	103 *
HDL Cholesterol	50 *
LDL Cholesterol, C...	84 *
Non-HDL Cholestero...	105
Cholesterol/HDL Ratio	3.1 *
TUMOR MARKERS	
PSA	

Dale Doneen METHOD

3rd PARTY REQUISITION FORM

ClevelandHeartLab®
Know your risk.

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p 866.358.9828 | f 866.869.0148
www.clevelandheartlab.com

LAB USE ONLY

INSTRUCTIONS
1. Please complete all highlighted areas in their entirety.
2. Please provide all specimen information (draw date/time).

Initials: Time: Draw Date:

PRACTITIONER INFORMATION

Client ID		
Practitioner ID		
Practice Name		
Practitioner Name		
NPI		
Address		
City	State	ZIP
Phone	Fax	

PATIENT INFORMATION

DOB	☐ Male ☐ Female	
Last Name		
First Name	Middle Initial	
Ht. Wt. BMI	Fasting? ☐ Yes ☐ No	
Race ☐ American Indian/Alaskan Native ☐ Asian ☐ Black/African-American ☐ White/Caucasian (Non-Hispanic) ☐ Hispanic/Latino ☐ Other		
☐ Patient Demographics Sheet Attached		
Address		
City	State	ZIP
Phone		
Other Patient ID	Last Four Digits of SSN	

TEST MENU (Please fill in box completely)

INFLAMMATION
- ☐ Myeloperoxidase (83876)
- ☐ Lp-PLA$_2$ (The PLAC® Test) (83698)
- ☐ High-Sensitivity CRP (hs-CRP) (86141)
- ☐ Microalbumin/Creat Ratio (82043/82570)
- ☐ Oxidized LDL (83516)
- ☐ F$_2$-Isoprostanes/Creat Ratio (83789/82570)

OTHER INFLAMMATION TESTS
- ☐ Galectin-3 (82777)
- ☐ Fibrinogen Mass (85385)
- ☐ Homocysteine (83090)

LIPIDS
- ☐ Standard Lipid Panel *(Includes non-HDL cholesterol)* (80061)
  - ☐ If TGs >400 mg/dL reflex to a Direct LDL (83721)
- ☐ ApoB (82172)
- ☐ ApoA1 (82172)
- ☐ sdLDL (83701)
- ☐ Lp(a) (83695)
- ☐ HDL2b (82664)
- ☐ *NMR LipoProfile®* with Lipids (83704/80061)*
- ☐ *NMR LipoProfile®* without Lipids (83704)*

METABOLIC
- ☐ Glucose (82947)
- ☐ Insulin (83525)
  - ☐ Reflex to Adiponectin if indicated (83516)
- ☐ OGTT (82951)
- ☐ GlycoMark® (84378)
- ☐ HbA1c (83036)
  - ☐ Reflex to GlycoMark® if indicated (84378)
- ☐ Adiponectin (83516)
- ☐ Fructosamine (82985)
- ☐ C-Peptide (84681)
- ☐ Cystatin C (82610)

CARDIAC
- ☐ NT-proBNP (83880)*
- ☐ Creatine Kinase (82550)

VITAMINS/SUPPLEMENTS
- ☐ Coenzyme Q10 (83789)*
- ☐ Vitamin D, 25 OH (82306)
- ☐ Vitamin D2/D3 (82306)

FATTY ACIDS
- ☐ OmegaCheck™ (82541)

HORMONES
- ☐ Testosterone, Total (84403)
- ☐ Estradiol (82670)
- ☐ FSH (83001)
- ☐ Luteinizing Hormone (83002)
- ☐ Progesterone (84144)

THYROID FUNCTION
- ☐ T4, Free (84439)
- ☐ T4, Total (84436)
- ☐ T3, Free (84481)
- ☐ T3, Total (84480)
- ☐ TSH (84443)
  - ☐ Reflex to T4, Free if indicated (84439)
  - ☐ Reflex to T3, Free if indicated (84481)

ANEMIA/IRON METABOLISM
- ☐ Ferritin (82728)
- ☐ Iron (83540)
- ☐ Serum Iron & IBC (83540/83550)
- ☐ Folate (82746)
- ☐ RBC Folate (82747)
- ☐ Vitamin B12 (82607)

CANCER
- ☐ PSA, Total (84153)
  - ☐ Reflex to PSA, Free if indicated (84154)
- ☐ PSA, Total (G0103; Medicare)
  - ☐ Reflex to PSA, Free if indicated (84154)

PLATELET FUNCTION
- ☐ AspirinWorks® (84431/82570)

GENETICS
- ☐ CYP2C19 (81225)
- ☐ ApoE (81401)
- ☐ MTHFR (81291)

ROUTINE PANELS†
- ☐ Basic Metabolic Panel (80048)
- ☐ Comprehensive Metabolic Panel (80053)
- ☐ Hepatic Function Panel (80076)
- ☐ Renal Function Panel (80069)
- ☐ Electrolyte Panel (80051)

STANDARD LABORATORY TESTS
- ☐ CBC/Auto Diff (85025)*
- ☐ CBC (85027)*
- ☐ Urinalysis (81001)*
- ☐ Uric Acid (84550)

CLEVELAND CLINIC WELLNESS PROGRAMS
- ☐ Go!® Foods for You
- ☐ Stress Free Now
- ☐ Go!® to Sleep

OTHER
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____
- ☐ _____ _____

* Sample must be shipped the same day collected.
† Individual tests for each panel are available upon request.

BILLING INFORMATION (Check only one billing option)

COPY OF FRONT & BACK OF PATIENT'S MEDICARE OR INSURANCE CARD MUST BE ATTACHED TO THIS FORM

Note: A patient approved Medicare ABN Form required for ApoE, MTHFR or CYP2C19 and all V70 diagnostic codes; otherwise testing will not be performed.

☐ **Medicare#** _____

☐ **Medicare HMO Provider#** _____

☐ **Insurance Provider:** _____
Policy ID# _____
Patient Relation: ☐ Self ☐ Spouse ☐ Dependent

☐ **Patient Self-Pay:** By checking the box, the patient will receive a direct bill.

DIAGNOSIS (ICD-9 Code)

☐ Acquired Hypothyroidism, spec.	244.8	☐ Other Malaise and Fatigue	780.79
☐ Acquired Hypothyroidism, unspec.	244.9	☐ Shortness of Breath	786.05
☐ Diabetes Type II	250.00	☐ Impaired Fasting Glucose	790.21
☐ Diabetes Type II, uncontrolled	250.02	☐ Impaired Glucose Tolerance	790.22
☐ Vitamin D deficiency	268.9	☐ Abnormal Chemistry	790.6
☐ Pure Hypercholesterolemia	272.0	☐ Abnormal Clinical Findings	796.4
☐ Pure Hyperglyceridemia	272.1	☐ Family Hx of CVD	V17.3
☐ Mixed Hyperlipidemia	272.2	☐ Family Hx of Other CVDs	V17.49
☐ Unspec. Hyperlipidemia	272.4	☐ Family Hx of Diabetes	V18.0
☐ Metabolic Syndrome	277.7	☐ Long-term Use of Aspirin	V58.66
☐ Unspec. Iron deficiency anemia	280.9	☐ Long-term Medication Use	V58.69
☐ Hypertension, malignant	401.0	☐ PSA Screening	V76.44
☐ Hypertension, benign	401.1	☐ Other _____	_____
☐ Hypertension, unspec.	401.9	☐ Other _____	_____
☐ Intermediate Coronary Syndrome	411.1	☐ Other _____	_____
☐ Coronary Atherosclerosis of unspec. type of vessel, native or graft	414.00	☐ Other _____	_____
☐ Coronary Atherosclerosis, native coronary artery	414.01	☐ Other _____	_____
☐ Congestive heart failure, unspec.	428.0	☐ Other _____	_____

Note: The provided ICD-9 codes are listed as a convenience. Ordering practitioners should report the diagnosis code that best describes the reason for performing the test, regardless of whether the code is listed above or not. Ordering practitioners must provide the 4th or 5th ICD-9 digit as appropriate. Only tests that are medically reasonable and necessary for the diagnosis or treatment of a Medicare or Medicaid patient will be reimbursed. The Office of the Inspector General takes the position that a physician who orders medically unnecessary tests for Medicare or Medicaid reimbursement may be subject to civil penalties under the False Claims Act.

COMMENTS:

Practitioner's Signature: X Date: X

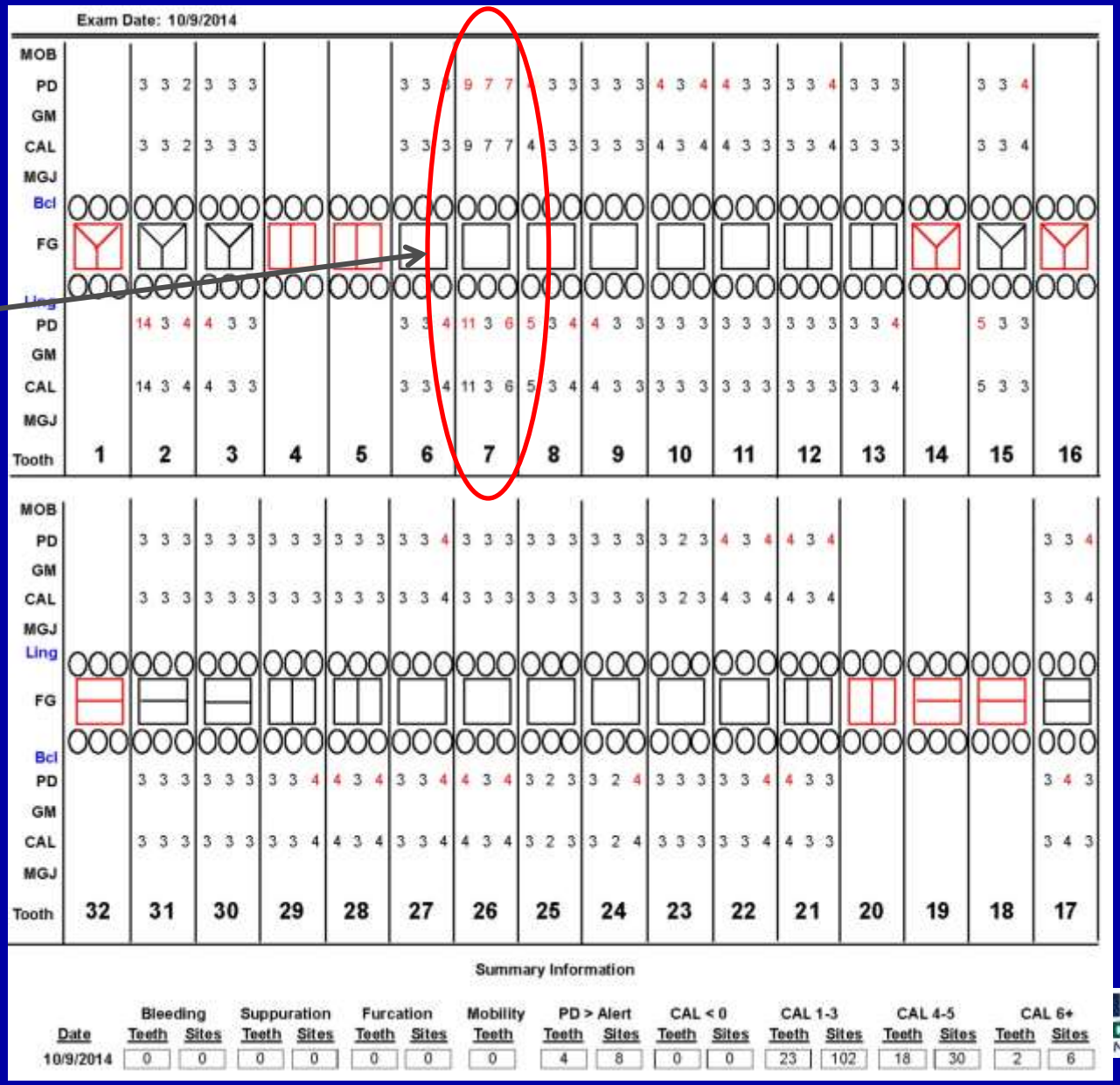
Dale Doneen METHOD

Current Meds

Prescriptions	Vitamins
Atorvastin 40 mg **PM**	Multi vitamin & minerals **AM**
Zetia 10 mg **PM**	Fish oil 1000mg **pm**
Allopurinol 300mg **AM**	Saw Palmetto+ 160 mg **AM**
Indapamide (Lozol) 2.5 mg **AM**	Coenzyne Q10 100 mg **AM**
Pot Citrate Er tabs 10 MEQ **AM & PM 23.08**	DMAE 500mg **AM**
Flutiticasone (as needed) **AM** – 1 SPRAY	Alpha Lipoic Acid 100 mg **AM**
Montelukast 10 mg **AM**	Biotin 5 mg **AM**
	B12 1000mcg **AM**
	Slo Niacin 500mg **AM**

Periodontal Chart

Fractured tooth



Desired Information

- Oral DNA
- Cone Beam Image
- Inflammatory Biomarkers to determine stability
- Advanced Lipids
- Bale/Doneen Method Info

Oral DNA Pending

Cone Beam Image Report

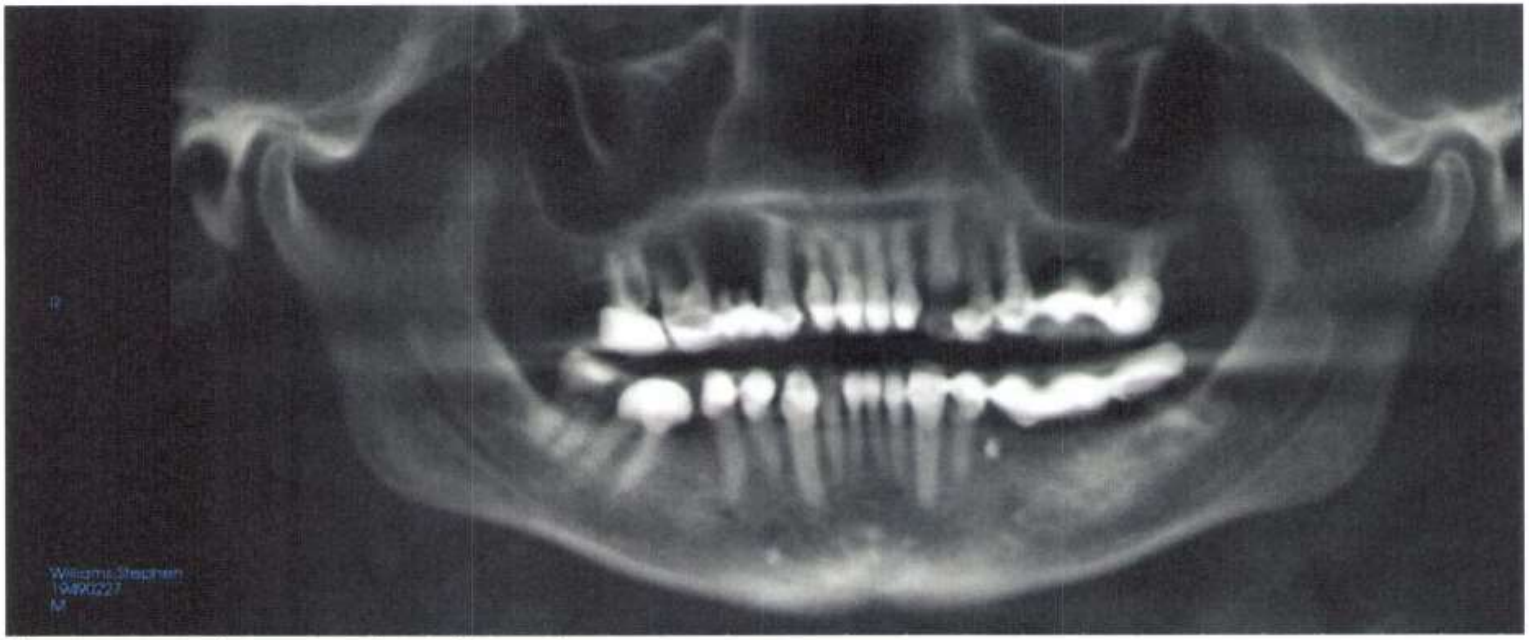
Images provided: Cone Beam CT images in the bone window. Axial, coronal and sagittal planes. FOV:

Clinical Info: Implant analysis requested. Relevant History: Implants planned Client Notes: Implants planned

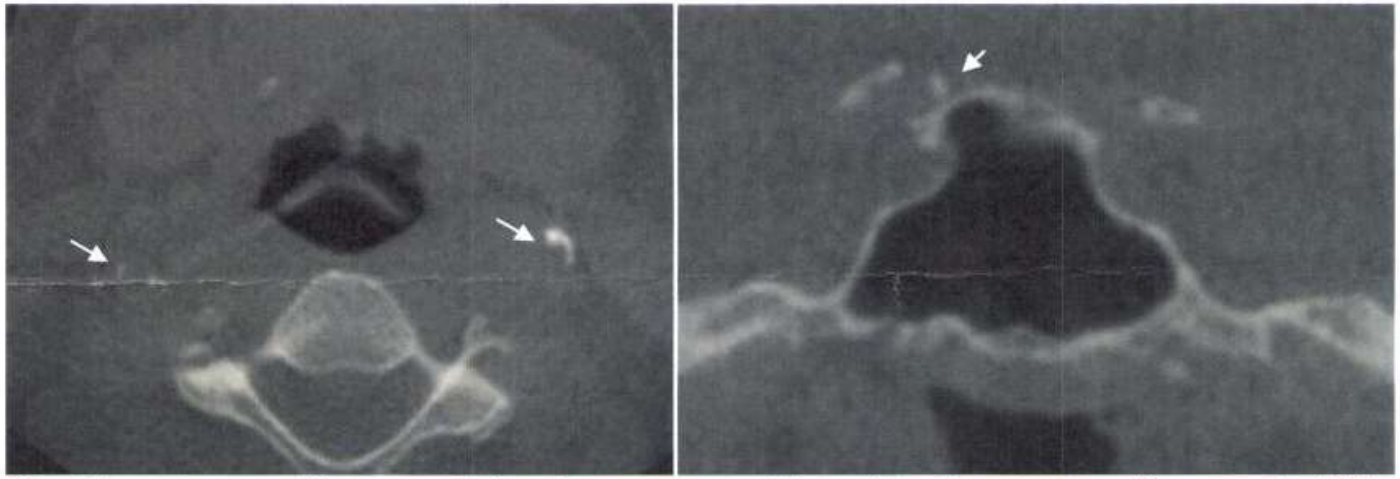
Diagnostic Objectives:
1. Implant Planned
2. Rule Out Pathology

Findings:
Maxilla: no abnormalities detected
Sinuses: no abnormalities detected, the right and left osteomeatal complexes were patent.
Nasal Cavity: a mild deviation the nasal septum was noted.
Mandible: no abnormalities detected
Air Space: no abnormalities detected
TMJs: no abnormalities detected
Other findings: 1) Curvilinear areas of increased density were noted lateral to the pituitary fossa and within the lower neck in areas anatomically associated with the carotid arteries; these areas appear to be consistent with calcification carotid artery. 2) sclerosis and small osteophytes were noted C-1 C-2 cervical vertebra. 3) An ovoid area of increased density was noted in the midline of the middle cranial fossa in an area associated with the pineal gland. The area appears consistent with calcification of the pineal gland. The
Dental findings: cross-sections illustrating several dental findings have been provided below.

The following are selected images from the volume illustrating major findings



Reconstructed panoramic radiograph



Curvilinear areas of increased density were noted lateral to the pituitary fossa and within the lower neck in areas anatomically associated with the carotid arteries; these areas appear to be consistent with calcification carotid artery.

INFLAMMATION

	In Range	Out of Range	Flag**	Relative Risk	Reference Range	Units	Previous Result	Date
Myeloperoxidase (5)	276			LOW	<420	pmol/L		
Based on a recent study of a high risk population, defined as stable patients without acute coronary syndrome who underwent elective diagnostic coronary angiography1, Cleveland HeartLab has defined the following cut-offs for MPO: A cut-off of <420 pmol/L defines an "apparently healthy" population at low risk for a cardiovascular event, 420-479 pmol/L defines a population at intermediate risk for a cardiovascular event, and >=480 pmol/L defines a high risk population based on the 97.5%ile." (Reference: 1Tang et al. Am J Cardiol. 111:465-70, 2013).								
Lp-PLA$_2$ (The PLAC® Test)	146			LOW	≤ 200	ng/mL		
High-sensitivity CRP	0.8			LOW	<1.0	mg/L		
Microalbumin/Creatinine ratio	See Below				<30.0	mg/g		
Microalbumin in patient's urine sample is below assay detection; therefore, the Microalbumin/Creatinine ratio cannot be calculated. Persistent Microalbumin/Creatinine ratios of 30-300 mg/g has been shown to be an early indicator of diabetic nephropathy (1). A 3-fold increase in CVD has been found in men with Microalbumin/Creatinine ratios >=3.9 mg/g and in women with values >=7.5 mg/g in the Framingham Heart Study (2). (References: 1. Diabetes Care 2011;34:S33A; 2. Arnlov et al. Circulation 2006;112:969).								
Microalbumin	<3.0					mg/L		
Creatinine, Urine	70.4				20.0-300.0	mg/dL		
OxLDL	34			LOW	<60	U/L		
Based on a recent study of an 'apparently healthy' and non-metabolic syndrome population-1, the following cut-offs have been defined for OxLDL: A cut-off of <60 U/L defines a population with a low relative risk of developing metabolic syndrome, a range of 60 to 69 U/L defines a population with a moderate relative risk (2.8 fold) and >=70 U/L defines a population with a high relative risk (3.5-fold). (Reference: 1-Holvoet et al. JAMA. 2008; 299: 2287-2293.)								
F$_2$-Isoprostane/Creatinine Ratio (5)	0.57			LOW	<0.86	ng/mg		
F$_2$-Isoprostane	0.40					ng/mL		
Creatinine, Urine	70.4				20.0-300.0	mg/dL		
Homocysteine	7.7				<15.0	umol/L		

LIPIDS

	In Range	Out of Range	Flag**	Relative Risk	Reference Range	Units	Previous Result	Date
Lp(a)		131		HIGH	<30	mg/dL		

	In Range	Out of Range	Flag**	Relative Risk	Reference Range	Units	Previous Result	Date
NMR LIPOPROFILE								
LDL Particle Number (LIPO)		1463		HIGH	<1000	nmol/L		
LDL Cholesterol, Calculated (LIPO)	75			LOW	<100	mg/dL		
LDL-C is inaccurate if patient is nonfasting.								
HDL-C (LIPO)	56			LOW	≥40	mg/dL		
Triglycerides (LIPO)		227		HIGH	<150	mg/dL		
Cholesterol, Total (LIPO)	176			LOW	<200	mg/dL		
HDL-Particle Number (LIPO)	49.7			LOW	≥30.5	umol/L		
Small LDL-Particle Number (LIPO)		1084		HIGH	≤527	nmol/L		
LDL Size (LIPO)		20.1		HIGH	> 20.5	nm		
Large VLDL-P (LIPO)		11.0		HIGH	≤2.7	nmol/L		
Large HDL-P (LIPO)		3.3		HIGH	≥4.8	umol/L		
VLDL Size (LIPO)		54.1		HIGH	≤46.6	nm		
Small LDL-P, LDL Particle Size, Large HDL-P, Large VLDL-P VLDL Size, HDL Size, HDL Particle, and LP-IR Score have been validated by LipoScience but not cleared by US FDA; the clinical utility of these test results has not been fully established.								
HDL Size (LIPO)		8.6		HIGH	≥9.2	nm		
LP-IR Score (LIPO)		81		HIGH	≤45			

METABOLIC

	In Range	Out of Range	Flag**	Relative Risk	Reference/ Optimal Range	Units	Previous Result	Date
OxLDL	34			LOW	<60	U/L		
Based on a recent study of an 'apparently healthy' and non-metabolic syndrome population-1, the following cut-offs have been defined for OxLDL: A cut-off of <60 U/L defines a population with a low relative risk of developing metabolic syndrome, a range of 60 to 69 U/L defines a population with a moderate relative risk (2.8 fold) and >=70 U/L defines a population with a high relative risk (3.5-fold). (Reference: 1-Holvoet et al. JAMA. 2008; 299: 2287-2293.)								
Fructosamine (CCF)	228							
Reference range: 170 to 285 Unit: umol/L (NOTE) INTERPRETIVE INFORMATION: Fructosamine Variations in levels of serum proteins (albumin and immunoglobulins) may affect fructosamine results. Test performed by: ARUP Labs, 500 Chipeta Way, Salt Lake City, UT,84108, unless otherwise specified.								
Cystatin C	0.74				0.47-1.09	mg/L		

VITAMINS/SUPPLEMENTS

	In Range	Out of Range	Flag**	Relative Risk	Reference Range	Units	Previous Result	Date
Coenzyme Q10 [1]	3.02			LOW		ug/mL		
Population reference range: 0.36 to 1.69 ug/mL. Studies have suggested that serum levels of Coenzyme Q10 at > 2.0 ug/mL show an anti-hypertensive effect.								
Vitamin D, 25-Hydroxy by LC-MS/MS [4]	42.1			LOW	30.0-80.0	ng/mL		
Incidence of 25-OH Vitamin D toxicity increases when total Vitamin D is above 100 ng/mL and the majority of individuals with toxicity have total Vitamin D levels at >150 ng/mL. (Reference: Jones G Am J Clin Nutr 2008;88:582S).								

FATTY ACIDS

	In Range	Out of Range	Flag**	Relative Risk	Optimal	Units	Previous Result	Date
OmegaCheck™ (Whole Blood: EPA+DPA+DHA) [3]	6.4			LOW	≥5.5	% by wt		
The risk categories for OmegaCheck are based on the top (75th percentile) and bottom (25th percentile) quartiles of the CHL reference population. Consumption of foods rich in omega-3 fatty acids or supplements containing omega-3 fatty acids (EPA, DHA or DPA) may increase omega-3 fatty acid levels measured by OmegaCheck, and decrease the risk of sudden death due to cardiovascular disease.* The totality of the scientific evidence demonstrates that when consumption of fish oils is limited to 3 g/day or less of EPA and DHA, there is no significant risk for increased bleeding time beyond the normal range. A daily dosage of 1 gram of EPA and DHA lowers the circulating triglycerides by about 7-10% within 2 to 3 weeks. *Albert CM et al. N Engl J Med. 2001; 346: 1113-1118.								
Arachidonic Acid/EPA Ratio		7.7	H		<5.0			
Omega-6/Omega-3 Ratio		5.2	H		<4.5			
Omega-3 total	6.4					% by wt		
EPA		1.5	L		>2.0	% by wt		
DPA	1.5				>1.0	% by wt		
DHA		3.4	L		>4.0	% by wt		
Omega-6 total	33.00					% by wt		
Cleveland HeartLab measures a number of omega-6 fatty acids with AA and LA being the two most abundant forms reported.								
Arachidonic Acid		11.5	H		<9.0	% by wt		
Linoleic Acid	18.1				<20.0	% by wt		

GENOTYPING

	Genotype	Risk	Interpretation
MTHFR [2]	677TT, 1298AA	HIGH	This patient displays the homozygous mutation at position 677 (TT) and no mutation at position 1298 (AA) of MTHFR. Homozygous mutations at 677 (TT) and no mutation at position 1298 (AA) are associated with greatly decreased MTHFR activity, high levels of homocysteine and increased risk for coronary artery disease and venous thrombosis, particularly in the setting of low folate status.

**Flags: H = Out of Range High; L = Out of Range Low; CH = Critical High; CL = Critical Low

Dale Doneen METHOD

OUT OF RANGE RESULTS SUMMARY

	Result	Flag**	Relative Risk	Reference/ Optimal Range	Units	Previous Result	Date
LIPIDS							
Lp(a)	131		HIGH	<30	mg/dL		
LDL Particle Number	1463		HIGH	<1000	nmol/L		
Triglycerides	227		HIGH	<150	mg/dL		
Small LDL-Particle Number	1084		HIGH	≤527	nmol/L		
LDL Size	20.1		HIGH	> 20.5	nm		
Large VLDL-P	11.0		HIGH	≤2.7	nmol/L		
Large HDL-P	3.3		HIGH	≥4.8	umol/L		
VLDL Size	54.1		HIGH	≤46.6	nm		
HDL Size	8.6		HIGH	≥9.2	nm		
LP-IR Score	81		HIGH	≤45			
FATTY ACIDS							
Arachidonic Acid/EPA Ratio	7.7	H		<5.0			
Omega-6/Omega-3 Ratio	5.2	H		<4.5			
EPA	1.5	L		>2.0	% by wt		
DHA	3.4	L		>4.0	% by wt		
Arachidonic Acid	11.5	H		<9.0	% by wt		

Patient Name [redacted]

Date	10-7-14		
Age			
WT/Waist/ B/P			
Last Flu/pnm Vaccine			

INFLAMMATION Ok for dental

hs CRP	<1.0 mg/L	.8		
Myeloperoxidase	<420 pmol/L	276		
Lp-PLA2 PLAC Test	≤ 200 ng/mL	146		
Urinary MicroAlb/Creat	<3.5 mg/g M <7.5 W	–		
F2-Isprostanes/Creat	<0.86 ng/mg	.57		
Oxidized LDL	<45 U/L	34		
Bilirubin	>0.8 mg/dL	.7		
Fibrinogen	175-400 mg/dL			

LIPIDS

Total Cholesterol	<200 mg/dL	176		
Triglycerides =VLDL + IDL	<150 mg/dL	* 227		
LDL-C	<100 mg/dL	75		
HDL-C	>50 mg/dL W >40 mg/dL M	58		
Non-HDL Cholesterol	<130 mg/dL			
Apo B	<100 mg/dL			
Apo A	>130 mg/dL W >120 mg/dL M			
Apo B/Apo A1 Ratio	<0.70 W <0.75 M			
sdLDL	<40.0 mg/dL			
Lp (a)	<30 mg/dL	* 131		
HDL2b (%)	>25 %			
A1c	≤5.6 %			
TG/HDL IR Indicator	<3.5mg/dL	* 3.91		

LP-IR score 81 should be ≤45

OTHER ADVANCED TESTS

NT pro-BNP				
hs Cardiac Troponin	>7.9			
Galectin 3				
FBS	70-99 mg/dL			

Has particle # and size issues managed by Dr. Isaken

Date				

OGTT	1 hour and 2 hour			
Vit D	>30 sufficient	42.1		
Potassium	4.6 - 5.0			
Alt/Ast	0-55 U/L / AST 5-34 U/L			
CBC				
CoQ10	.36-1.59 µg/ml	3.02		
TSH				
Omega 3		6.4		
Aspirin Response	<1500			
Perio Disease	Active or Stable			

GENETICS 40% of Risk

Apo E			
9p21			
KIF6			
IL-Beta			
Haptoglobin			
CYP2C19 Plavix			
4q25 Atrial Fibriliation Risk			
CYP1A2 Caffiene Metabolism			
TCF7L2 Diabetes and IR Risk			
MTHFR	* GTT 1298A	High Risk	

OTHER IMAGING +/- Arteriosclerosis

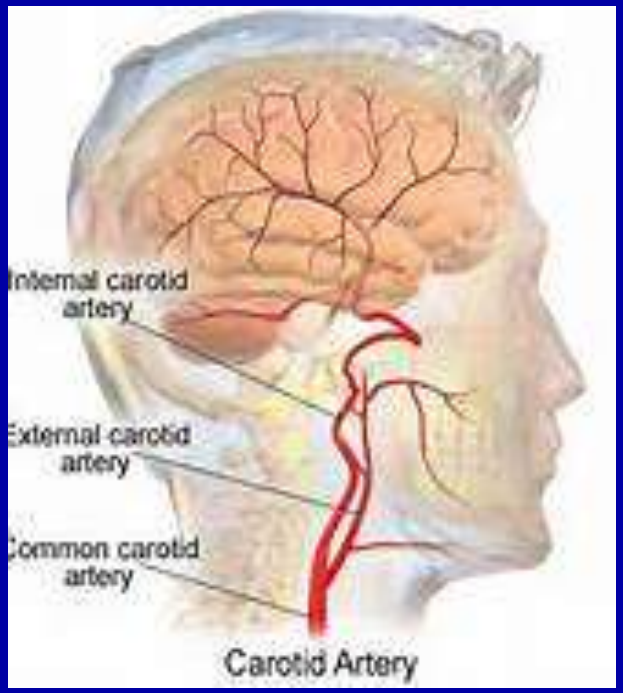
VH-IVUS			
Panorex			
Cone Beam Results			
CACS			
CIMT			

Discussion

- Inflammation ok
- Lifestyle – diet, sleep, exercise
- Lipid Management – multiple adjustments on BD Method

- Ok to start dental treatment and work with medical team on CVD management

The carotid arteries serve as a window to systemic atherosclerosis

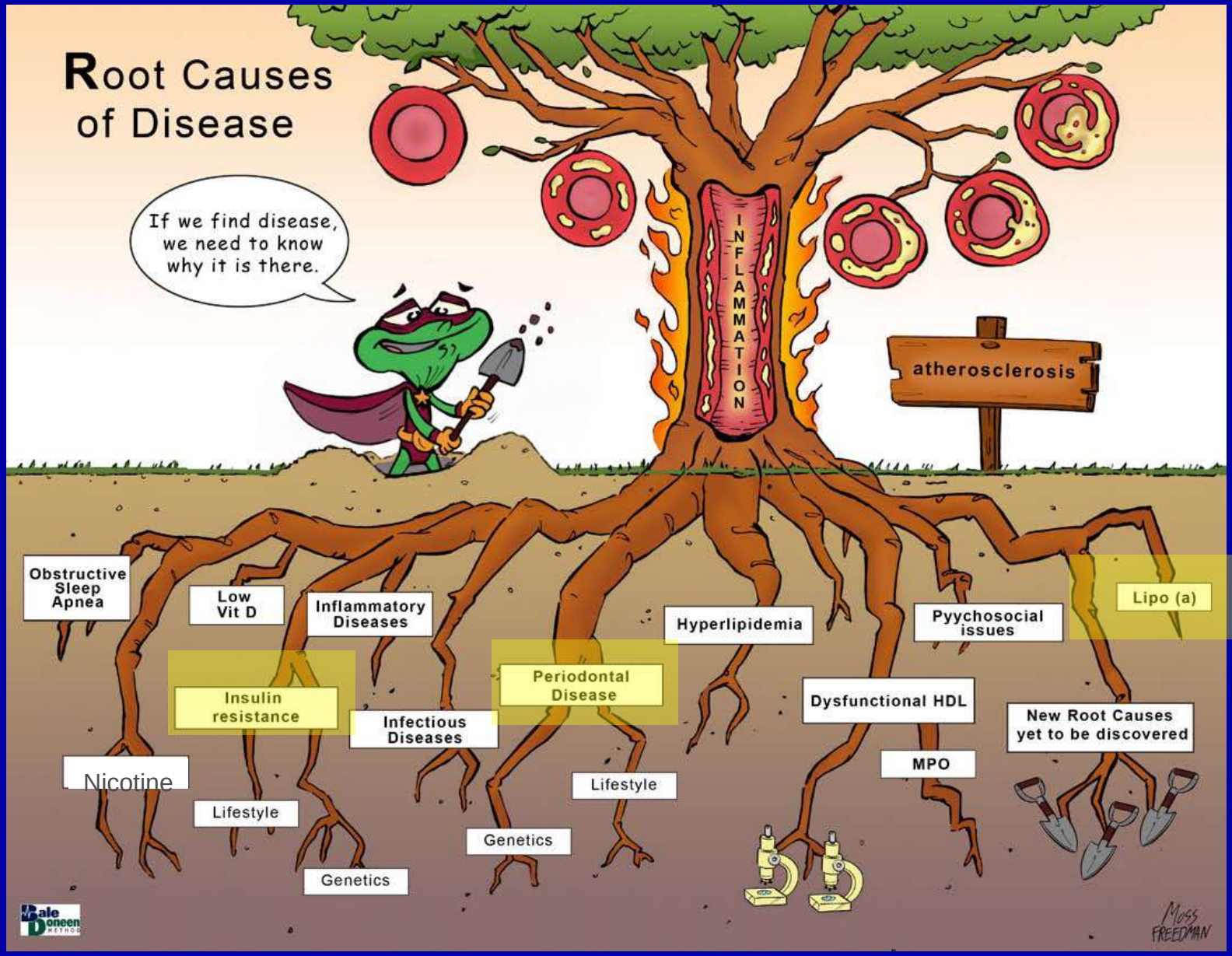


Willeit, K., et. al. (Sept 12, 2013). Carotid Atherosclerosis and Incident Atrial Fibrillation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302272

IMT of Carotid (CIMT) American Heart Association

safe, non-invasive, inexpensive, valid and reliable

AHA Expert Panel Statement of Prevention V Conference – Circulation 2000



Bale Doneen METHOD

Moss Freedman

Gout Increases the Likelihood of New Onset Diabetes

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

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

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

Gout is Associated with Increased CV Risk

5,926 subjects; 25 to 74 yo; followed 16 yrs.

For each 59.48-µmol/L increase in uric acid level, ischemic heart disease mortality increased 17% in men and 30% in women.

Adjusted for: age, race, BMI, smoking, alcohol, cholesterol, BP, DM and diuretic use.

Fang, J., & Alderman, M. H. (2000). Serum uric acid and cardiovascular mortality: The nhanes i epidemiologic follow-up study, 1971-1992. *JAMA, 283*(18), 2404-2410.

TG/HDL > 3.5 = IR in Caucasians

Ethnicity is Important

Needs OGTT to define beta cell function loss

Dr. Gerald Reaven 1/2001

McLaughlin, Reaven, et.al., ***Am J Cardiol***. 8/1/2005;96:399-404

Who is the Worst Hombre?

Lipo (a) Causes Heart Attacks

Copenhagen Data: >41,000 subjects over 13 years, 2800 MI's

Looked at risk of MI from lipo (a) levels by assessing the levels genetically

Consistent increase in MI risk with higher lipo (a) levels

Risk starts around 40-50 mg/L; each doubling of the level increases the risk about 20%

Dr Pia R Kamstrup,PR,et. Al., JAMA 6/10/09

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

Baseline and on-statin Lp(a) concentrations were associated with residual risk of CVD independent of other risk factors, including LDL cholesterol.

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

European Atherosclerosis Society

- Recommend screening for lipo (a)
- Treat if levels over 50 mg/dL
- Advise 1 to 3 g of niacin daily

Would d/c Zetia and increase a good OTC niacin (Endur-acin)

Nordestgaard, B. G., et. al. (2010). Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. doi: 10.1093/eurheartj/ehq386

Ezetimibe Yields Paradoxical Results with CIMT: Possible Mechanisms

- Ezetimibe predominately inhibits the scavenger receptor B1, involved in intracellular translocation of cholesterol
- This receptor binds to the ligand apoprotein A1, the principal apoprotein component of HDL-C in the process of reverse cholesterol transport
- Ezetimibe is also known to cause transcriptional down-regulation of key lipid transport proteins including the ATP binding cassette transporter (ABCA1) and SRB1.

Taylor, A. J., et. al. *European Heart Journal*
doi:10.1093/eurheartj/ehs105

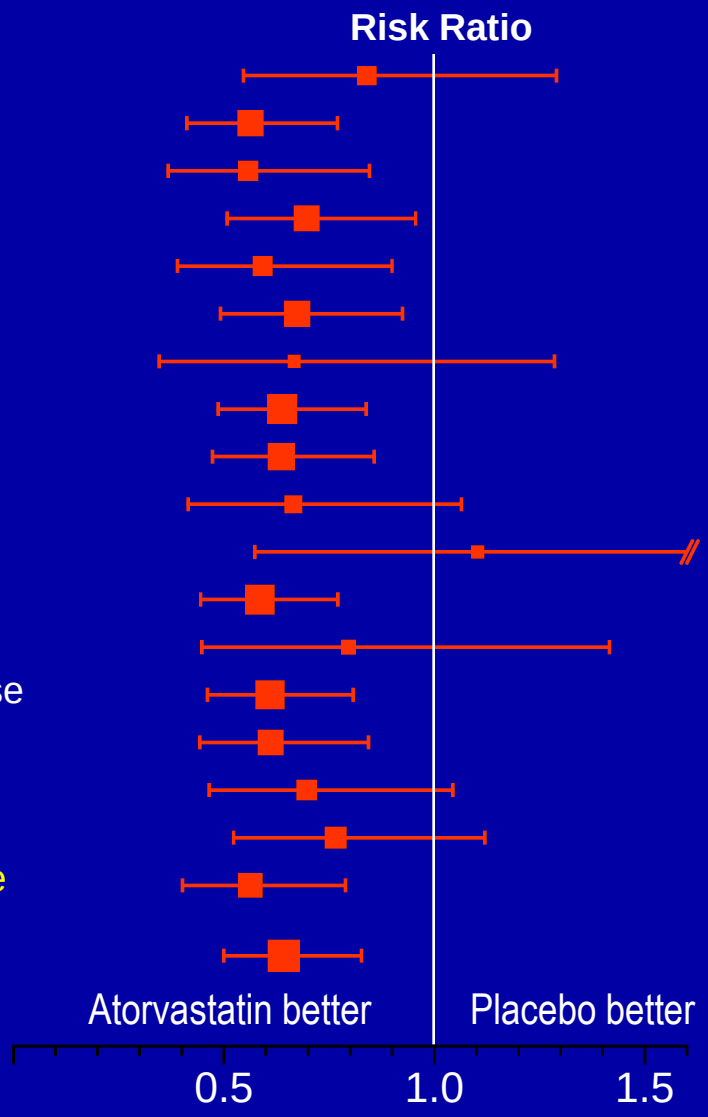
Ezetimibe Yields Paradoxical Results with CIMT: Possible Mechanisms

- Recent studies also suggest that the effect on the lipid particle profile is an absolute or relative increase in the proportion of small dense LDL-C.

- Endothelial function: 8 of 11 trials showed blunting of improvement combined with statin; 2 largest trials showed no effect as mono-rx despite LDL reduction = statin

Taylor, A. J., et. al. *European Heart Journal*
doi:10.1093/eurheartj/ehs105

ASCOT Pre-specified Subgroups: Primary End Point



	Hazard Ratio
Diabetes	0.84 (0.55-1.29)
Nondiabetes	0.56 (0.41-0.77)
Current smoker	0.56 (0.37-0.85)
Noncurrent smoker	0.70 (0.51-0.96)
Obese	0.59 (0.39-0.90)
Nonobese	0.67 (0.49-0.92)
LVH	0.67 (0.35-1.29)
No LVH	0.64 (0.49-0.84)
Older (>60 years)	0.64 (0.47-0.86)
Younger (≤60 years)	0.66 (0.41-1.06)
Female	1.10 (0.57-2.12)
Male	0.59 (0.44-0.77)
Previous vascular disease	0.80 (0.45-1.42)
No previous vascular disease	0.61 (0.46-0.81)
Renal dysfunction	0.61 (0.44-0.84)
No renal dysfunction	0.70 (0.47-1.04)
With metabolic syndrome	0.77 (0.52-1.12)
Without metabolic syndrome	0.56 (0.40-0.79)
All patients	0.64 (0.50-0.83)

Area of squares is proportional to the amount of statistical information

Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

Atorvastatin Increases Insulin Resistance

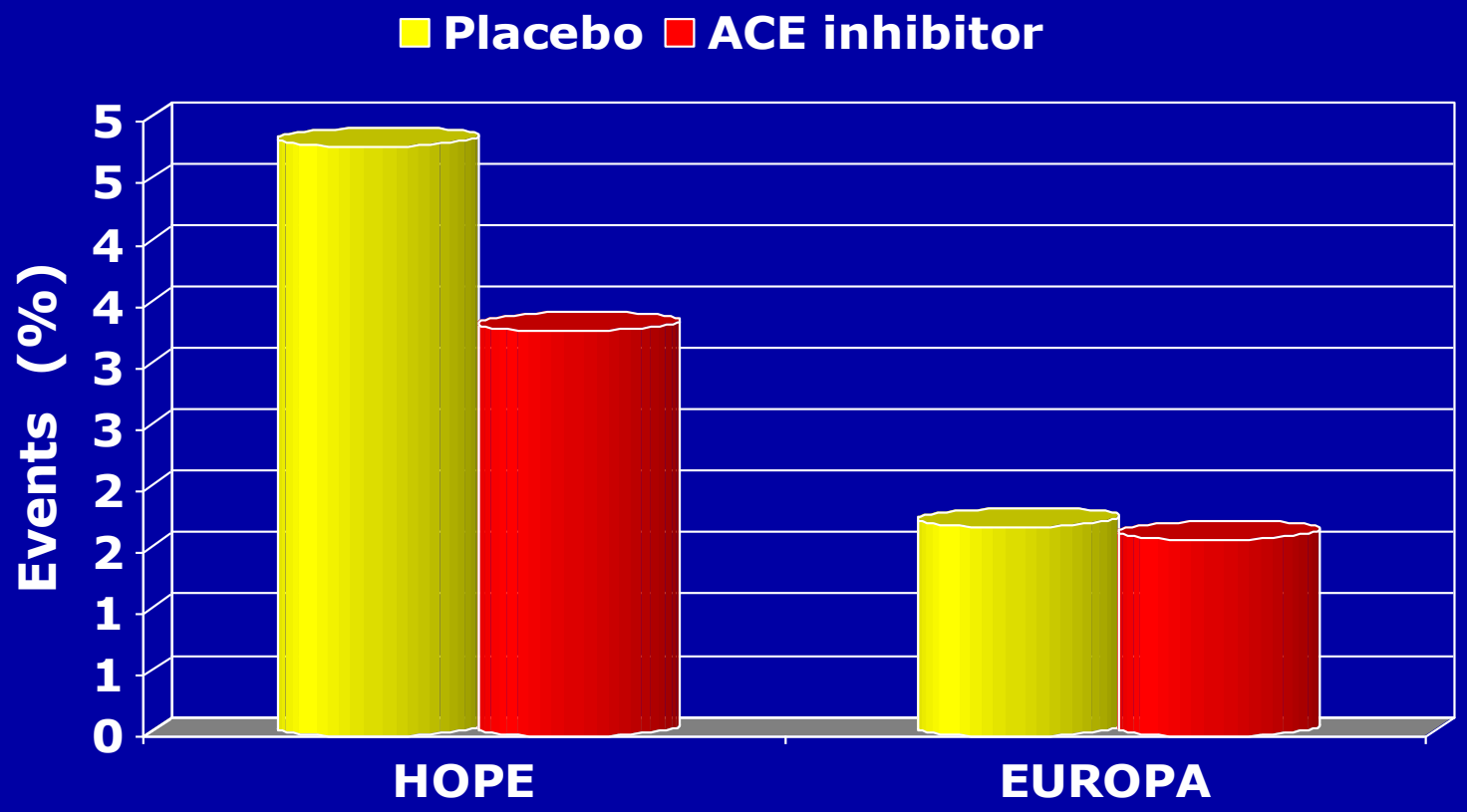
- Randomized, blinded, placebo-controlled; 213 subjects; placebo or atorva 10,20,40,80mg; two months

- Atorva significantly increased fasting insulin (mean changes: 25%, 42%, 31%, and 45%, respectively) and A1c (2%, 5%, 5%, and 5%, respectively); compared baseline $p<0.05$ or placebo ($p=0.009$ for insulin and $p=0.008$ for A1c

Would switch to Crestor, if KIF6 +, could consider pravastatin.

Koh, K. et al., *J Am Coll Cardiol 9/*2010;55:1209-16

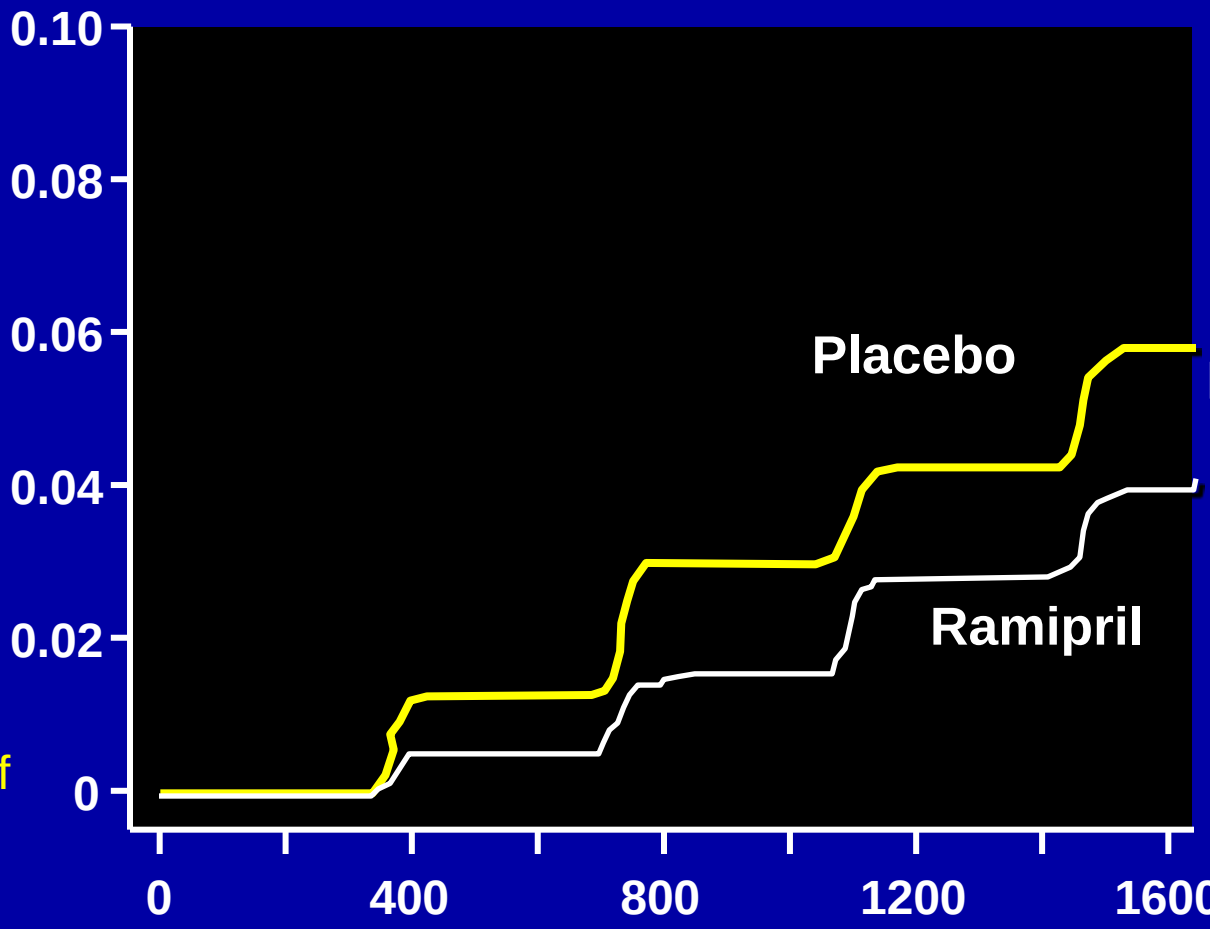
Stroke results
HOPE (ramipril) 32%
EUROPA (perindipril): NS 6%



HOPE NNT 4.5yrs to prevent one major CV event = 26

EUROPA NNT 4 yrs. to prevent one major CV event = 50

HOPE: Ramipril and the Risk of Type 2 Diabetes



Cumulative Risk for Self-Reported Diabetes

This persisted in 2.6 yr. extension of HOPE-TOO*

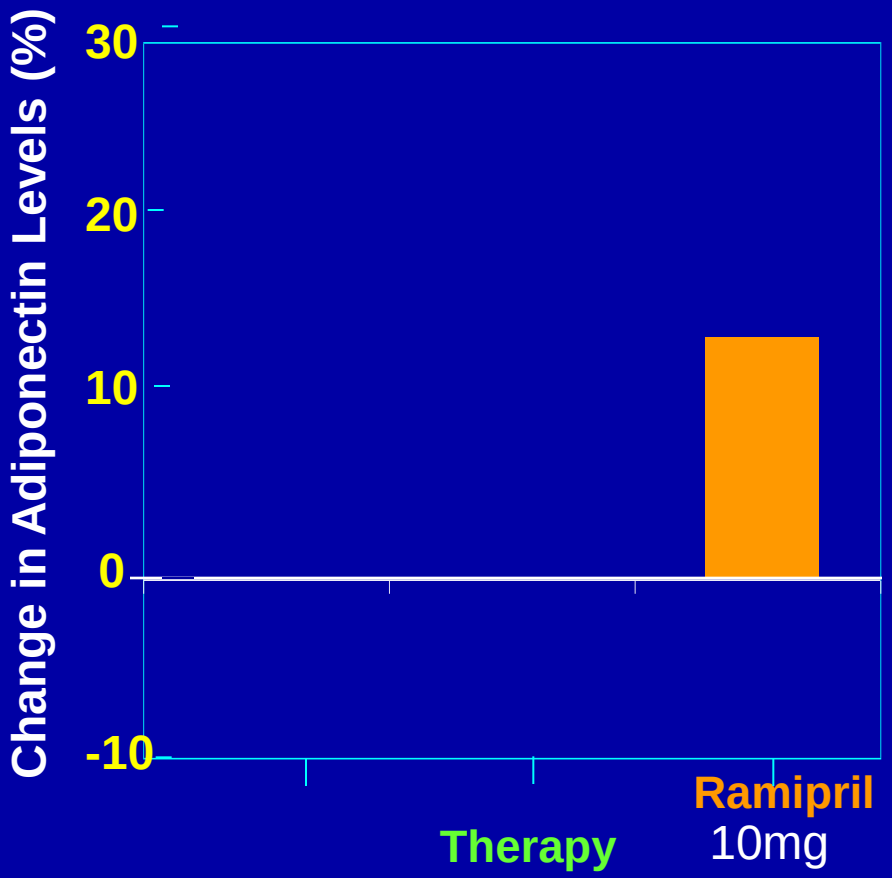
Yusuf S et al. JAMA 2001;286:1882-85

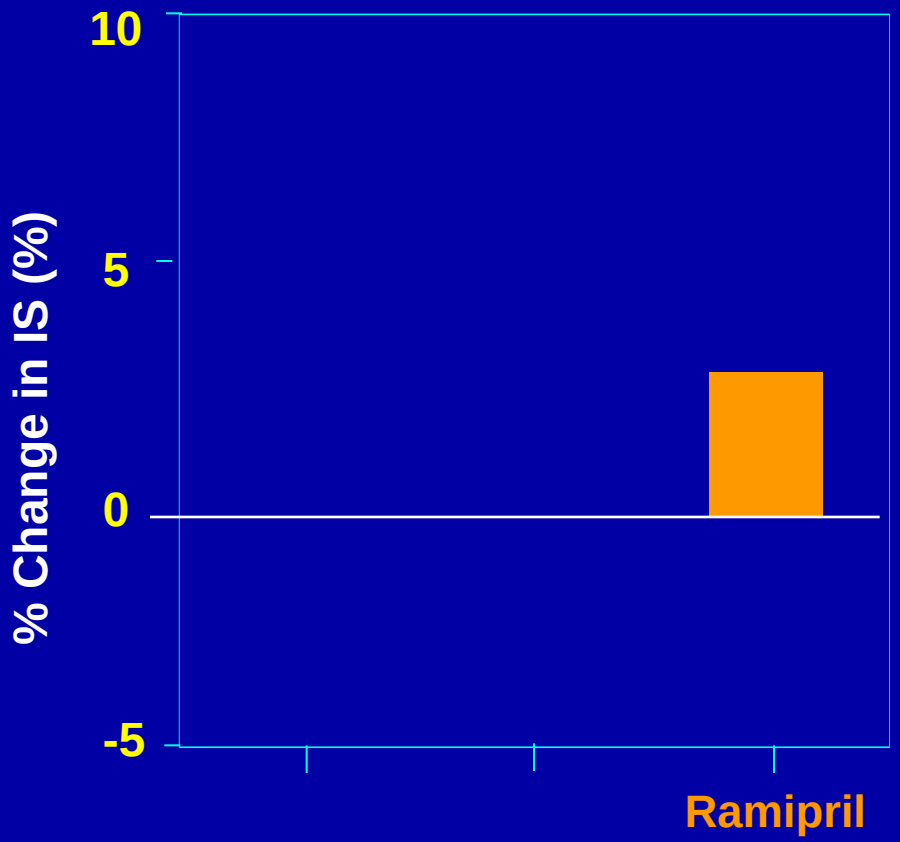
Days of Follow-up

* ***Circulation***.8/2005;112:1339-1346.

Percent Change in Adiponectin Levels and Percent Change in Insulin Sensitivity

50 pts. With DM





KK Koh, et. Al.,Hypertension 2005 5;():*Posted on* May 17, 2005

The Direct Effects of the ACE Inhibitors, on Isolated Human Pancreatic Islets

- RAS molecules are present in human islets and their expression is sensitive to glucose concentration
- ACE inhibitors protect human islets from glucotoxicity

Lupi, R. et al., *Eur J Endocrinol* 2006;154:355-61.

Potassium Extremely Important in Cardiac Arrhythmias and Sudden Cardiac Death

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

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

4.6-5.0

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

Foods High in K+

- Sweet Potato – 1 cup cooked – 950 mg potassium
- Butternut squash – 1 cup cooked – 582 mg potassium
- Figs – 4 large – 541 mg potassium
- Cantaloupe – 1 cup – 494 mg potassium
- Lentils – 1/2 cup cooked – 475 mg potassium
- Avocado – 1/2 medium – 439 mg potassium
- Bananas – 1 medium – 422 mg potassium
- Spinach – 2 cups raw – 334 mg potassium
- Blackberries – 1 cup 282 mg potassium
- Strawberries – 1 cup 252 mg potassium
- Almonds – 1 ounce raw – 198 mg potassium

Amiloride: K+ Sparing Diuretic

Inhibits of Na+ reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct.

This decreases the net negative potential of the tubular lumen reducing both K+ & H- secretion and subsequent excretion.

It is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

Usual dose is 5-10mg; may go up to 20mg; comes in 5 mg tablets.

Anna J. Stears, et. al. ***Hypertension. 5/2012;59:934-942***

Amiloride Did Not Cause Any Impairment in Glucose Tolerance

- Two double-blind, placebo-controlled, crossover studies; total 78 pts.; outcome was change in 2hr. GTT after 4 wks. rx with Hctz or amiloride
- Thiazide diuretic significantly impaired glucose tolerance; no impairment was seen with K-sparing diuretic
- Substitution or addition of amiloride may be the solution to preventing thiazide-induced diabetes mellitus

Anna J. Stears, et. al. ***Hypertension. 5/2012;59:934-942***

Lifestyle to Prevent Myocardial Infarction (MI) in Men

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

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

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

Lifestyle to Prevent Heart Attacks

Having all 5 factors optimized compared with none:

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

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

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

Lifestyle 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.

Exercise to Prevent Diabetes

Burning an extra 500 kcal/wk can reduce the risk of developing type 2 diabetes by 6%.

Helmrich SP, et al. *N Engl J Med.* 1991; 325:147-152

Improving Fitness Level Reduces Type 2 DM Incidence up to 70%

- 4,187 healthy men; fitness assessed 4X over 7 yrs. (1979-1985)

- HR for DM comparing lowest to highest fitness trend quartile, after adjustment for: age, initial fitness, BMI, syst BP, smoking, alcohol and Famhx DM

  0.33 (95% CI- 0.21-0.50)

Sawasa, S. S., PhD, et. al. Diabetes Care 6/2010, Vol. 33, No. 6:1353-1357

Interval Training: Beneficial for Metabolic Syndrome (MS)

- 32 MS subjects; three groups: interval training (IT), continuous moderate exercise (CME) or control

- IT: warm up 10 mins. at 70% MHR , four 4-min. sessions 90% MHR, with 3 min. recovery periods at 70% MHR, 5 min. cool-down, 3X/wk for 16 wks

- CME 45 mins. at 70% MHR, 3X/wk for 16 wks

- IT > insulin sensitivity; HDL levels increased 25%; lower FBG; decrease waist

Tjonnas AE, Lee SJ, Rogonmo O, et al. *Circulation*. 8/1/2008;doi:10.1161/circulationaha.108.772822.

Lifestyle to Prevent Heart Attacks: diet

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

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

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

Cinnamon Reuces Glucose and Improves Lipids

- Meta-analysis of 10 RCTs; 543 diabetic pts; cinnamon 120 mg/d to 6 g/d for 4 to 18 wks

- Cinnamon showed statistically significant decrease in levels of fasting plasma glucose, TC, LDL-C, TG and increased HDL-C.

Allen, R. W., et. al. (2013). Cinnamon Use in Type 2 Diabetes: An Updated Systematic Review and Meta-Analysis. *Ann Fam Med, 11*(5), 452-459.

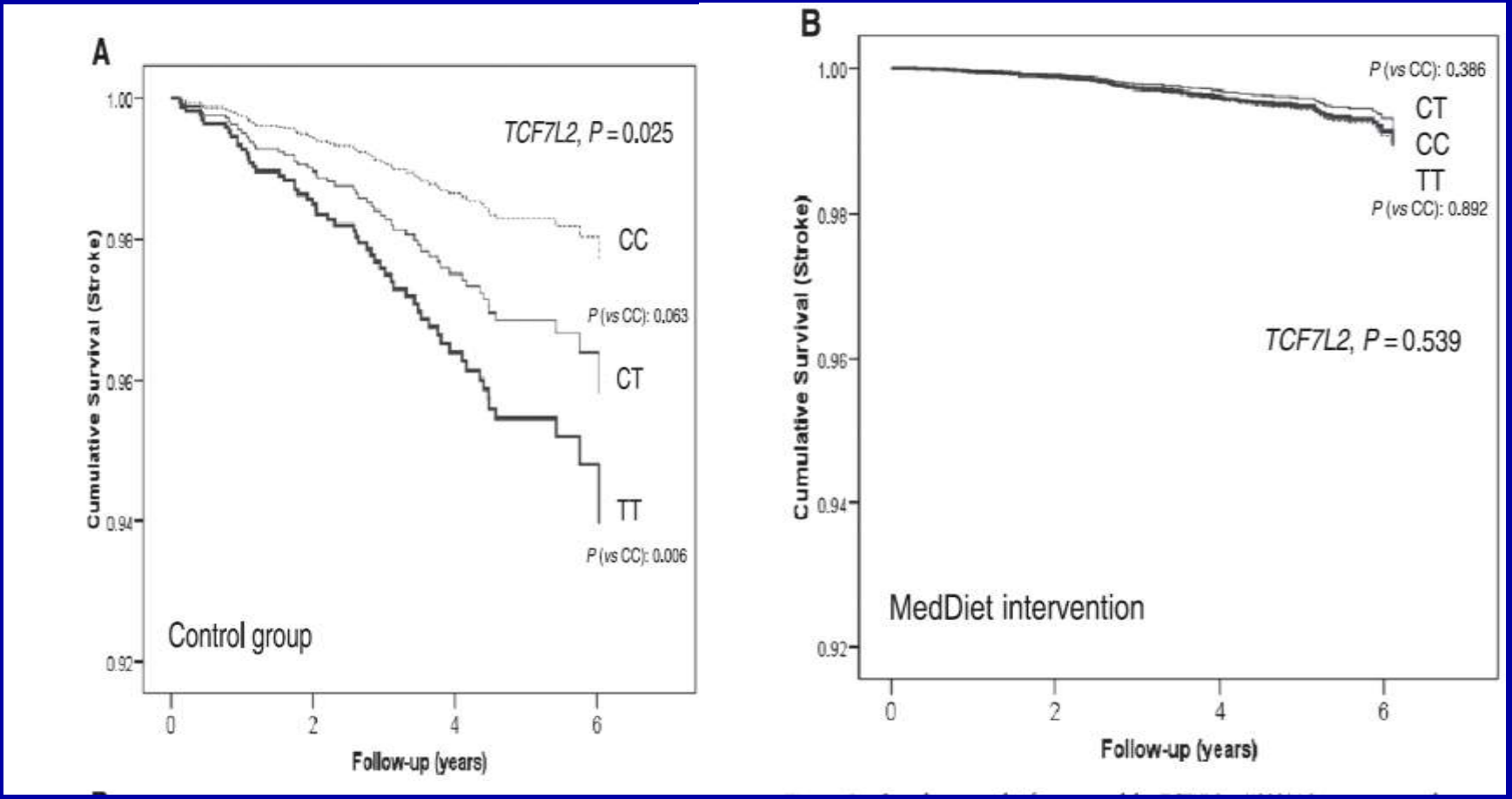
Mediterranean Diet (MD) Modulates Glycemic and Stroke Risk Generated by TCF7L2 Gene

- 7,018 pts. all genotyped for TCF7L2; 14.2% were (+)-TT; randomized 3 dietary arms (2- MD); followed 4.8 yrs; end points glycemic levels, lipids and CV events

- Homozygotes (TT) on MD had significant improvement in fasting glucose (FG) and lipids; the MD also negated their increased stroke risk

Corella, D., et. al. (2013). Mediterranean Diet Reduces the Adverse Effect of the TCF7L2-rs7903146 Polymorphism on Cardiovascular Risk Factors and Stroke Incidence: A randomized controlled trial in a high-cardiovascular-risk population. *Diabetes Care*. doi: 10.2337/dc13-0955

Mediterranean Diet Mitigates Stroke Risk Generated by TCF7L2 Gene



Cumulative stroke free-survival by TCF7L2-rs7903146 genotypes in the control group (A) (n = 2,291) and in the MedDiet intervention groups (B) (n = 4,827).

Corella, D. et al. (2013). *Diabetes Care*. doi: 10.2337/dc13-0955

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EPA and DHA levels Predictability of risk for ACS

Analyzed whole blood of 94 ACS patients and 94 age-gender matched controls

Omega 3 associations with ACS were made (adjusted for smoking, BMI, DM, lipids, hx MI or revascularization)

EPA and DHA content was 29% lower in ACS group vs control ($1.7 \pm 1.9\%$ vs $2.4 \pm 1.4\%$, $p < 0.0001$)

Low blood levels of EPA and DHA is an independent predictor of increased risk for ACS

W. Harris, K. Read, et al. Am J. Cardiology 8.31.2007;99:154-158

Fish Consumption Reduces Stroke Risk

- RR for CVD with long chain omega 3 fatty acids measured as circulating biomarkers and self reported dietary exposures were 1.04 (95%CI-0.90 to 1.20) and 0.90 (0.80 to 1.01), respectively

- The beneficial effect of fish intake on cerebrovascular risk is likely mediated through the interplay of a wide range of nutrients abundant in fish.

- The lack of assoc. with risk reduction for long chain omega 3 fatty acids was consistent in primary or secondary prevention

- Findings suggest that single nutrients may have limited effects on chronic disease outside of their original food sources.

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

Dark Chocolate Mitigates the Negative Arterial Effects of Hyperglycemia

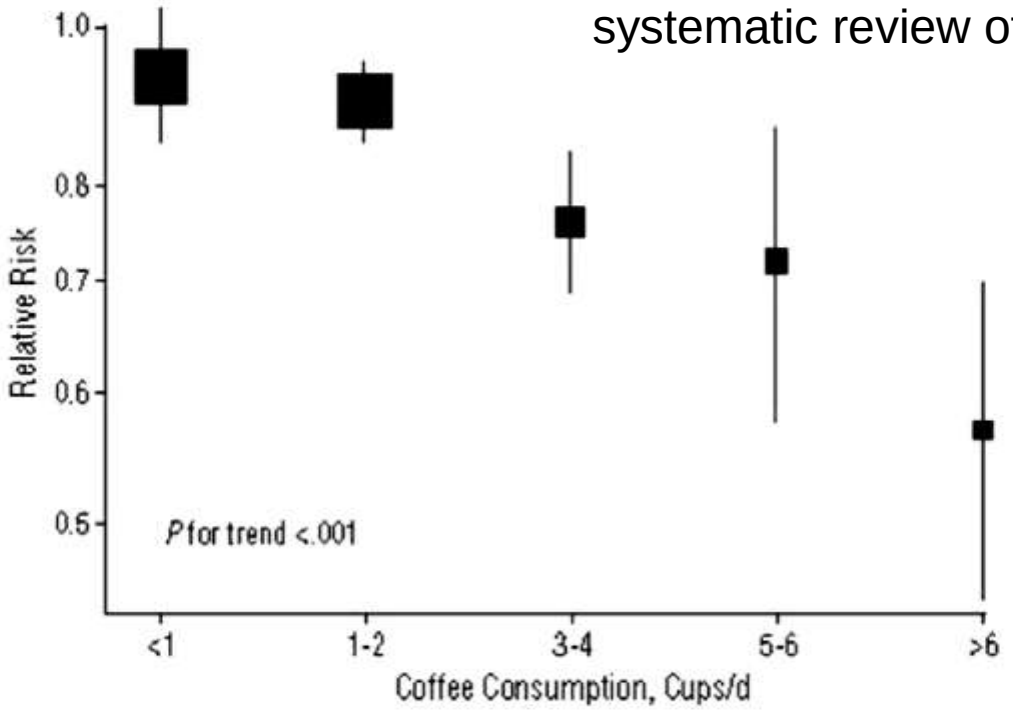
- 12 healthy young adults; mean age 28; treated with 100mg dark flavanol rich dark chocolate & flavanol free white chocolate for 3 days with 7 day wash out in-between.

- At end of each treatment phase subjects underwent OGTT and endothelial function and oxidative tests were performed.

Grassi, D., et. al. ***Hypertension. 8/2012;60:*****00-00**
DOI: 10.1161/HYPERTENSIONAHA.112.193995

Coffee can Reduce Risk DM

systematic review of 9 cohort studies



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

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

Coffee May Increase the Risk of DM ?!

1,180 stage 1 BP non-DM pts; 18-45 yo; 639 CYP1A2 (caffeine) genotyping; followed 6 yrs.

58% were slow metabolizers of caffeine

24% developed pre-diabetes defined by FBG

Dr Lucio Mos ‘results from the HARVEST study’ presented at ESC Congress Sept. 2, 2014

Coffee May Increase the Risk of DM ?!

The risk of prediabetes associated with coffee intake was increased only in slow caffeine metabolizers.

HR for >3 cups/d -2.78 (95% CI,1.32-5.88) p=0.0076

Carriers of the slow *1F allele (slow caffeine metabolizers) should abstain from drinking caffeinated coffee.

Dr Lucio Mos ‘results from the HARVEST study’ presented at ESC Congress Sept. 2, 2014

Take Back to the Trenches

- Consider genetic testing for all patients
- Tests to arguably get on everyone:

  9p21, apo E, KIF6
- Tests that are useful in certain patients:

  4q25, CYP2C19, Hp
- If testing for MTHFR, realize the ‘high risk’ genotype (*TT*) is actually ‘low risk’ for CVD

Upcoming Presentations

My Last Chat of 2014

Congratulations Again to Dr. Amy Lynn Doneen!!!!

Upcoming Presentations

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

11/17/14- Amy giving Key Note Address at 2nd International Conference on Nursing & Healthcare -Chicago, Ill.

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

1/9-10/15- Amy and Brad giving BDM training at TT SON.

2/13/15- Brad speaking at Second Annual Private Wealth Summit – Phoenix, AR

2/20-21/15- BDM Preceptorship in LV, NV.

Getting Close to Announcing a CEO for IOA!!

501c3 status

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

Open for Discussion