Bale/Doneen Live Chat Session

7/10/2012

5:30-6:30 pm PST

Bradley Bale, MD

Intention of the live chats

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

88 yo Jack Swinging!!

- http://webmedia.apqc.org/il80web20025/Marketing/Webinars/Jack_swing.wmv

Green Flag! ☺

Gilbert Syndrome: Cardioprotective

- Gilbert synd incidence is 5-10%; mild unconjugated hyperbilirubinemia; bilirubin at low concentrations is a potent endogenous antioxidant
- 216 healthy young men; half with Gilbert's
- Evaluated oxidative stress with urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG)
- Evaluated endothelial function with FMD brachial artery

Maruhashi, T., et. al. *Circulation. published online July 6, 2012*
DOI: 10.1161/CIRCULATIONAHA.112.105775

Gilbert Syndrome: Cardioprotective

- 8-OHdG levels were 7.8±2.4 vs. 10.4±3.2 ng/mg creatinine, for Gilbert vs control subjects: P=0.001
- FMD was 7.2±2.2% vs. 5.9±1.7% for Gilbert vs control: P<0.001
- Patients with Gilbert syndrome have lower levels of oxidative stress and enhanced endothelial function

Maruhashi, T., et. al. *Circulation. published online July 6, 2012*
DOI: 10.1161/CIRCULATIONAHA.112.105775

Education

As an adult, you need to understand the importance of CV wellness!

Racial and Gender Differences in First Events: CV vs non-CVD Death

- Examined incidence of ‘first events’ – CV event vs non-CV death; 3 populations – no known CVD
- ARIC- 14,569; 45-64 yo; 27% Black; 10.5 yrs.
- CHS – 4,237; 65-84 yo; 16% Black; 8.5 yrs.
- MESA – 2,000; 45-85 yo; 27% Black; 5.4 yrs.

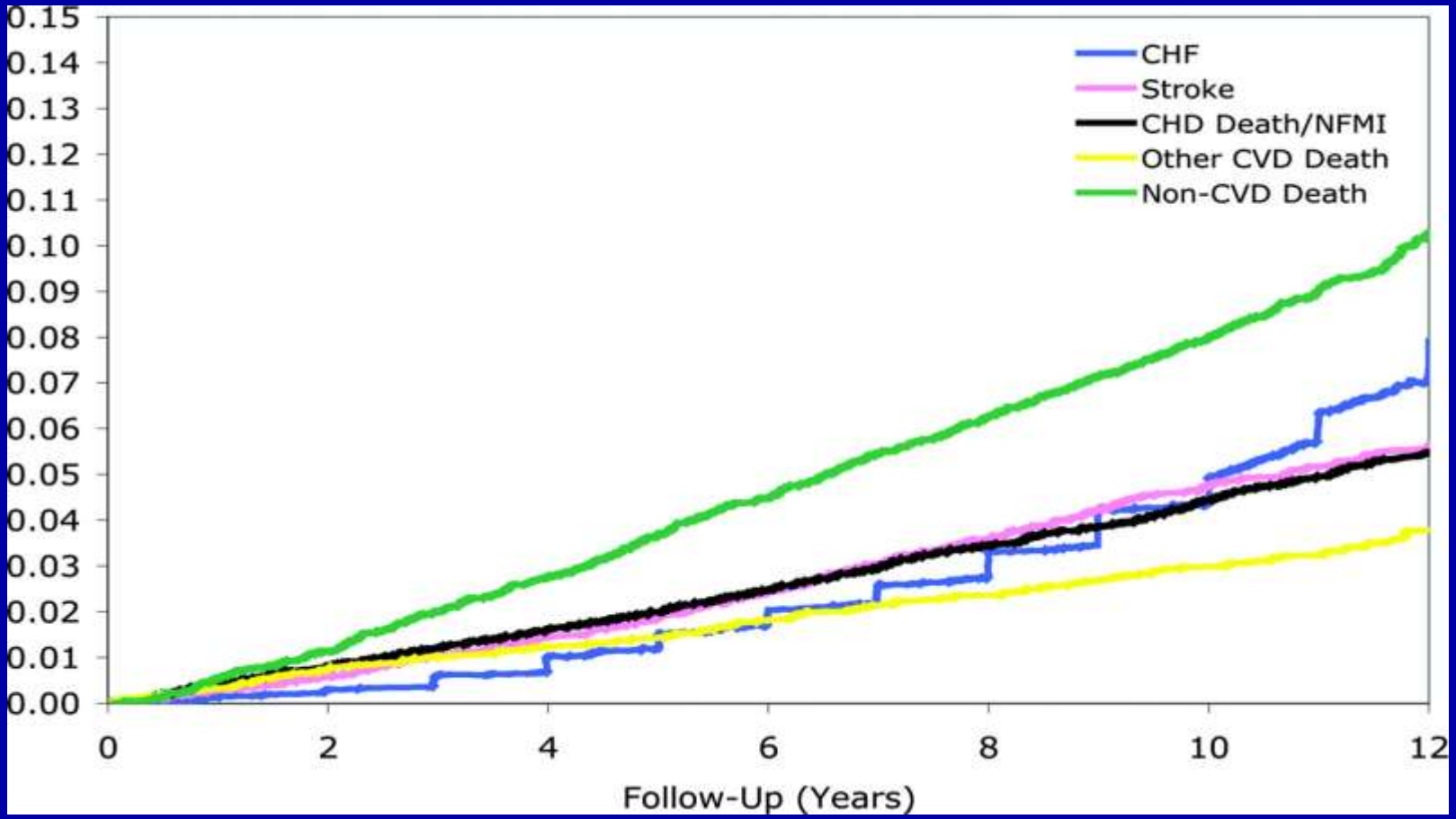
Feinstein M et al. Circulation 7/2012;126:50-59

Competing Risks for First CVD Events Versus Non-CVD Death: ARIC

- CVD occurred 2 times more frequently than non-CVD death in both black and white women & black men
- CVD occurred 3 times more frequently than non-CVD death for white men

Feinstein M et al. Circulation 7/2012;126:50-59

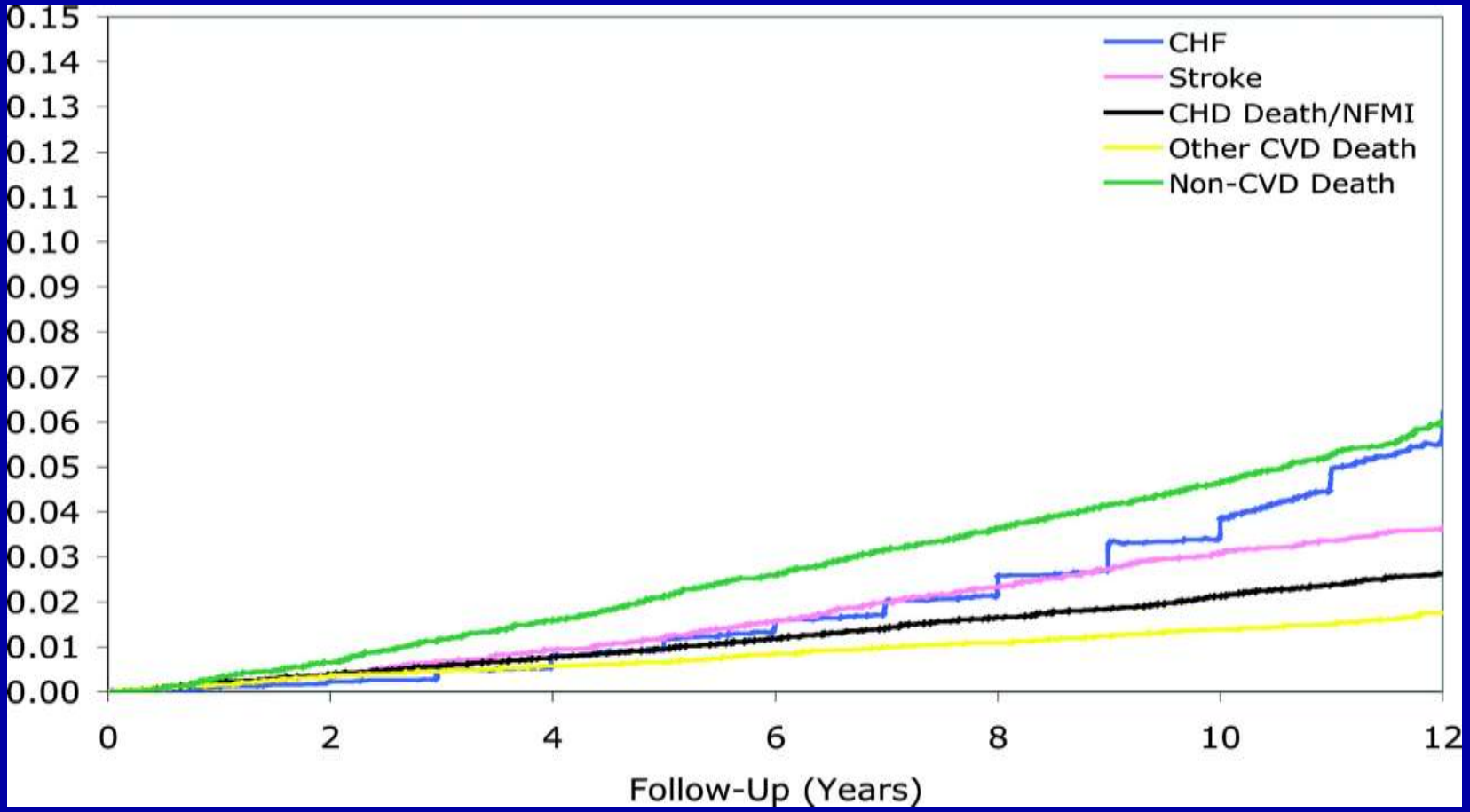
ARIC- Black Males: similar risk of CV events – CHF, stroke, MI



Competing cumulative incidences of CVD events and non-CVD death among black male ARIC participants.

Feinstein M et al. Circulation 2012;126:50-59

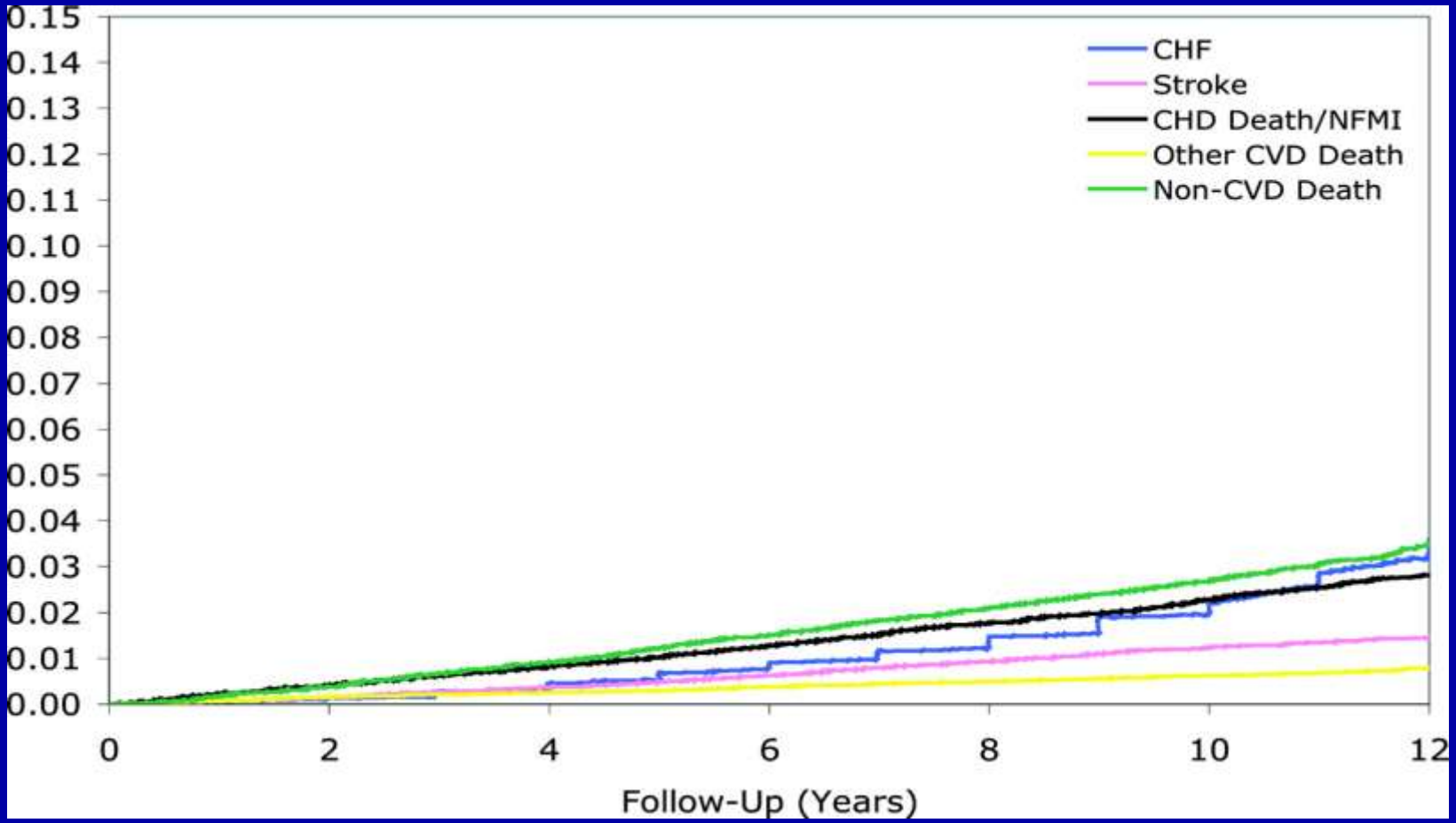
ARIC-Black Females: higher risk CHF and stroke vs MI



Competing cumulative incidences of CVD events and non-CVD death among black female ARIC participants.

Feinstein M et al. Circulation 2012;126:50-59

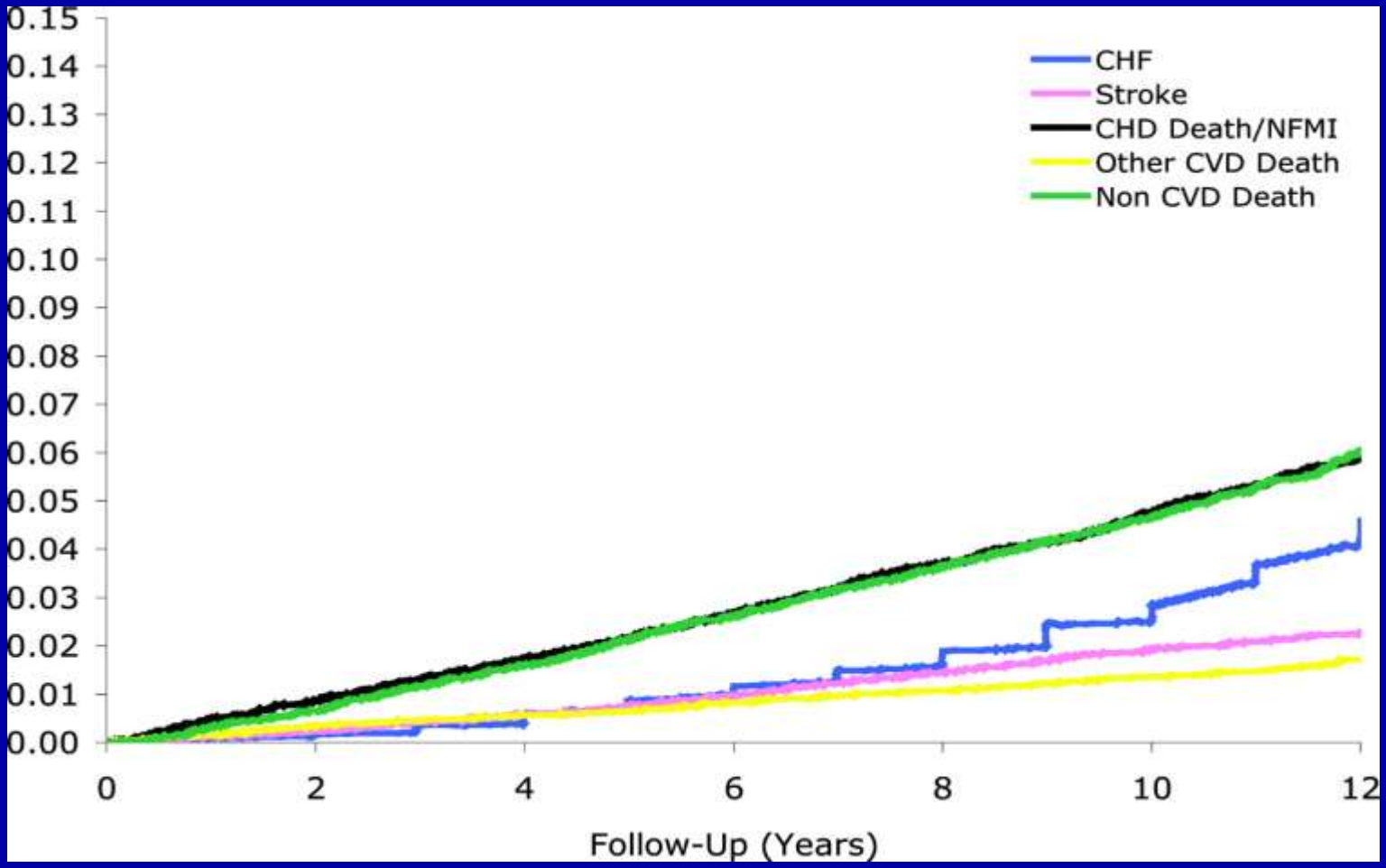
ARIC-White females: higher risk CHF and MI



Competing cumulative incidences of CVD events and non-CVD death among white female ARIC participants.

Feinstein M et al. Circulation 2012;126:50-59

ARIC- White males: higher risk of MI !!



Competing cumulative incidences of CVD events and non-CVD death among white male ARIC participants.

Feinstein M et al. Circulation 2012;126:50-59

Competing Risks for First CVD Events Versus Non-CVD Death: CHS (65-84 yo)

- CVD occurred 3 times more frequently than non-CVD death in all groups

Feinstein M et al. Circulation 7/2012;126:50-59

Competing Risks for First CVD Events Versus Non-CVD Death: MESA

- Younger cohort 45-64: CVD occurred 3.5 times more frequently than non-CVD death in all groups
- Older cohort >65: CVD occurred 2.5 times more frequently than non-CVD death in all groups

Feinstein M et al. Circulation 7/2012;126:50-59

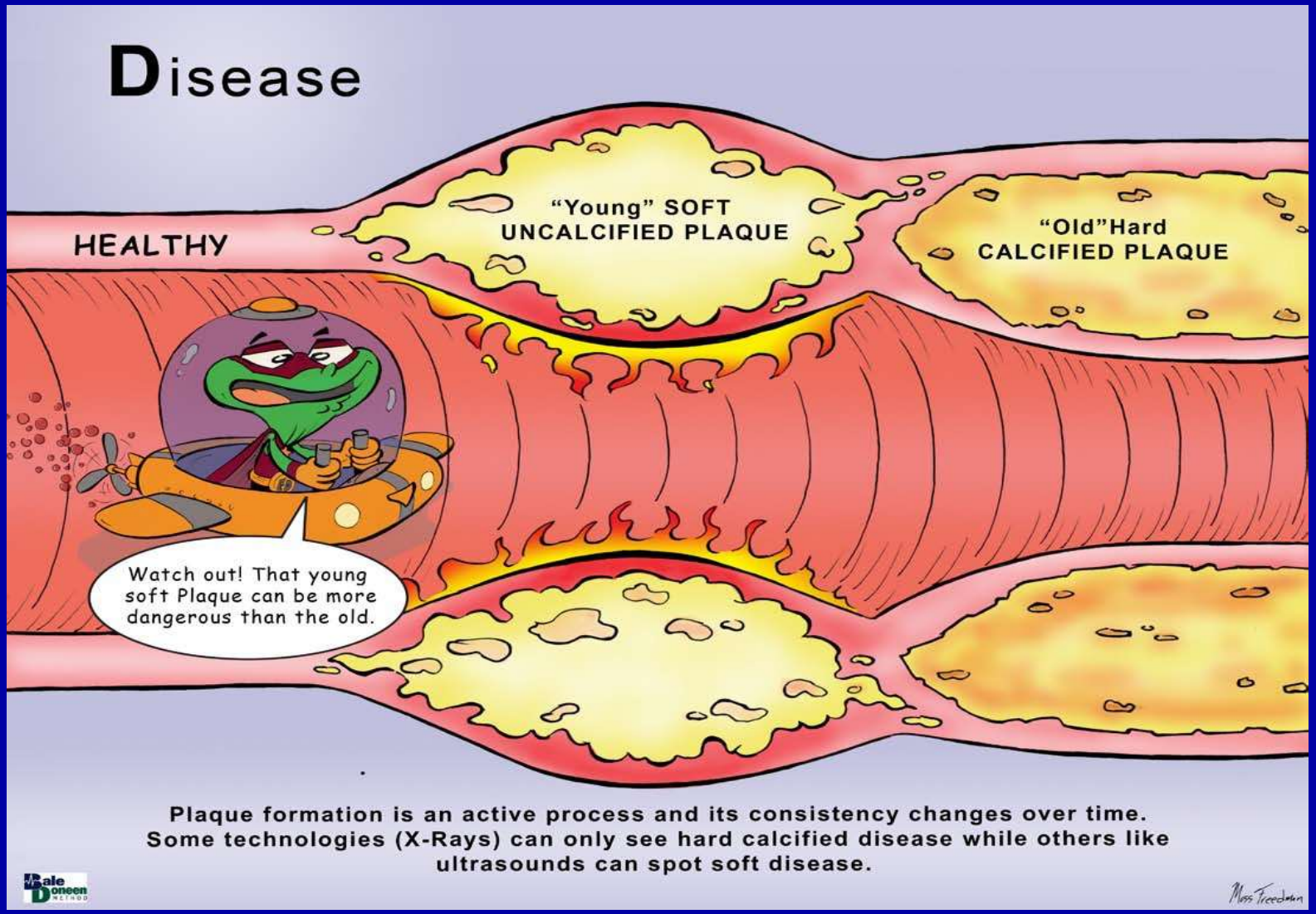
Racial and Gender Differences in First Events: CV vs non-CVD Death - Summary

- Adults regardless of sex or ethnicity are 2 to 3 times more likely to suffer a CV event fatal or non-fatal rather than a non-CVD death

- Clinical utility – good marketing tool for your program; may help with educating individual patients about the importance of your prevention program.

Feinstein M et al. Circulation 7/2012;126:50-59
BD Method

Disease: endothelial function??



Noninvasive Determination of Endothelial Function

- Brachial artery FMD correlates with endothelial function in the coronaries, relates to traditional risk factors, improves with targeted treatment, and predicts risk of future CV events.

- Viewed as the gold standard for noninvasive interrogation of peripheral artery vaso-reactivity

Noyan Gokce, **Circ Cardiovasc Imaging 2011;4:348-350**

Noninvasive Determination of Endothelial Function

- Limitations of FMD: requires extensive sonographer training, expensive equipment, labor-intensive image analysis, no standard methodology
- Above issues have precluded its integration into clinical practice
- Thus, there is interest in techniques inherently faster and easier to perform - digital pulse amplitude tonometry (PAT) & fingertip photoplethysmography (PulseTrace)

Noyan Gokce, **Circ Cardiovasc Imaging 2011;4:348-350**

Noninvasive Determination of Endothelial Function: PAT

- Measures volumetric changes in the fingertip, using a probe that quantifies pulse amplitude in response to reactive hyperemia using a commercially available device (EndoPAT)
- Signals in the contralateral hand not experiencing hyperemia are simultaneously recorded, controlling for systemic effects.
- Provides a reactive hyperemia PAT ratio in relation to the control arm that is expressed after natural log transformation owing to skewed variable distribution.
- The potential advantage of this technique relates to use of an automated, computerized analysis system that minimizes operator dependency and interobserver variability

Noyan Gokce, **Circ Cardiovasc Imaging 2011;4:348-350**

Noninvasive Determination of Endothelial Function: Pulse Trace

- Quick and simple utilizing infrared light transmission photoplethysmography on fingertip
- Performs digital pulse volume waveform analysis and generates an automated reflection index (RI)
- The RI shows decrement with cardiac risk factors but exhibits somewhat low reproducibility, and its ability to detect changes with intervention is unknown.

Noyan Gokce, **Circ Cardiovasc Imaging 2011;4:348-350**

Comparing Non-invasive Endothelial Function Tests

- 5,000 subjects; mean age 55.5 ±10.9 yo; 50% women; simultaneous FMD, PAT, Pulse Trace at baseline and post 5 min. brachial artery occlusion
- Reference group: no known CVD or classical CV risk factors; mean age 50.2+10.4 yo; 60% women
- Three tests correlated weakly with each other
- Three tests differed significantly in their relation to traditional risk factors

Schnabel R B et al. Circ Cardiovasc Imaging 2011;4:371-380

Comparing Non-invasive Endothelial Function Tests

- Strongest clinical correlates of all vascular function tests were age and sex
- FMD also correlated with BMI, BP, DM, dyslipidemia, and hsCRP
- PAT was additionally associated with smoking and IR
- Pulse trace demonstrated the weakest relationship with measured risk factors

Schnabel R B et al. Circ Cardiovasc Imaging 2011;4:371-380

Comparing Non-invasive Endothelial Function Tests

- For the entire study, measured risk factors explained only 16% of the variability in hyperemic responses for any of the 3 techniques
- Traditional risk factors were a poor predictor of physiological responses

Schnabel R B et al. Circ Cardiovasc Imaging 2011;4:371-380

Comparing Non-invasive Endothelial Function Tests

- Fasting blood glucose was markedly related to PAT
- Indicating changes in the microvasculature
- IR reduces vasoreactivity of small vessels; induces vascular complications such as retinopathy, microalbuminuria, and neuropathy

Schnabel R B et al. Circ Cardiovasc Imaging 2011;4:371-380

Noninvasive Determination of Endothelial Function

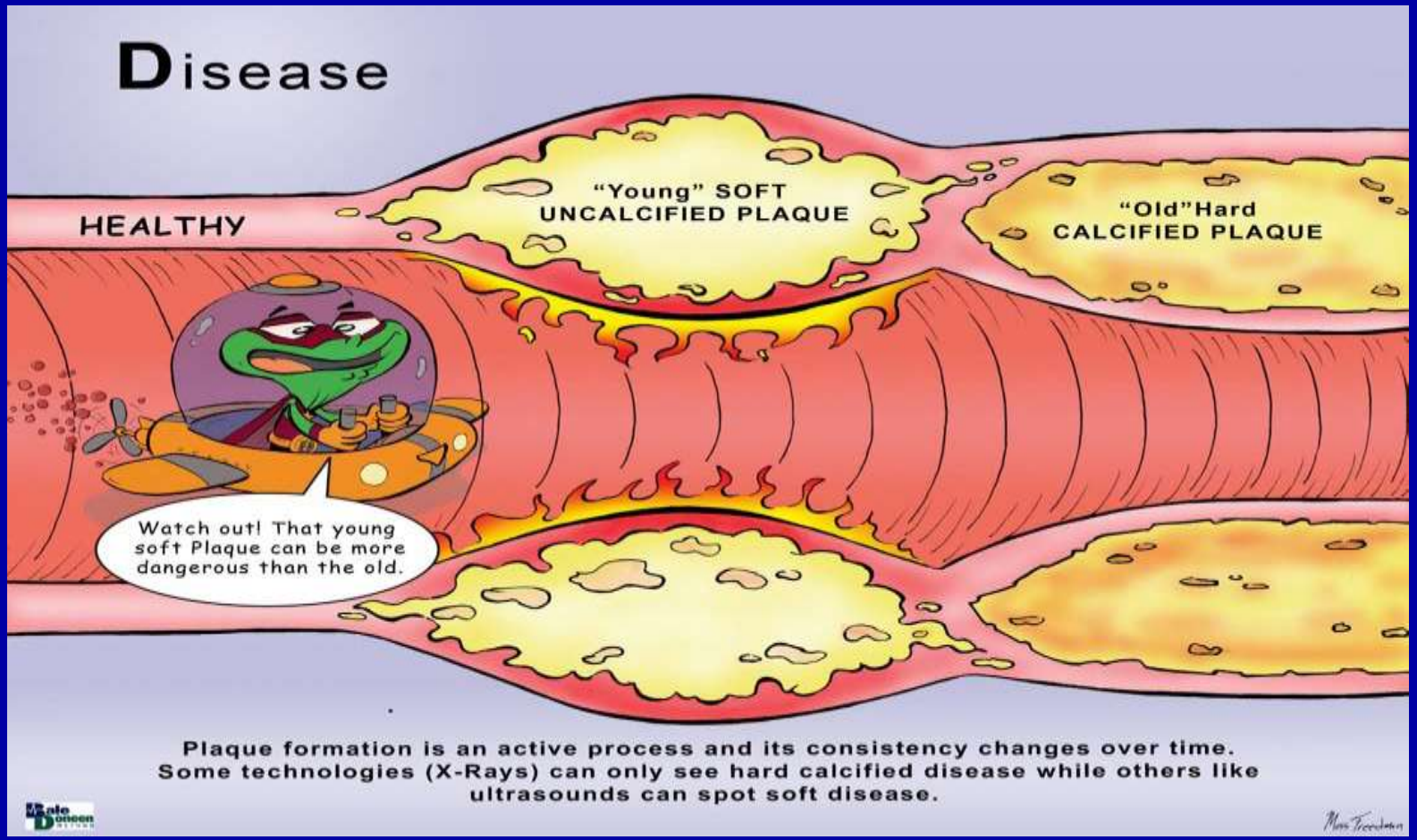
- FMD and PAT lack correlation and show different association to risk factors
- FMD examines macrovascular disease and PAT measures microvascular disease
- Different stages of CV disease processes may have different effects on macro vs micro vasculature
- Robust epidemiological outcome data are needed to assess the value of dynamic arterial changes for risk screening beyond classical risk factors

Noyan Gokce, **Circ Cardiovasc Imaging 2011;4:348-350**

EndoPAT for Clinical Use??

- ?? More sensitive for IR than OGTT, TC/TG, met synd. ???
- How does it help with management??
- Is cost an issue??
- Other comments or concerns??

Disease: what is really going on in the wall???



Molecular Imaging of Atherosclerosis

- Need imaging approaches that reach beyond the visualization of stenosis.
- Carotid ultrasound has improved the observation of plaques by detecting qualitative differences in plaque composition.
- However this technique does not inform specifically on the active cellular and molecular processes that drive the evolution of atherosclerotic lesions.

Thibaut Quillard, Peter Libby, ***Circulation Research 7/***2012;111:231-244

Molecular Imaging of Atherosclerosis

- The metabolic activity of macrophages in inflamed lesions, as reflected by uptake of glucose analogs, furnishes a target for imaging.
- Cells take up fluorine-labeled 2-deoxy-D-glucose (FDG) at the same rate as glucose.
- After phosphorylation, FDG accumulates inside the cell and can be detected by PET
- F-FDG imaging combines PET with CT for precisely identifying the anatomic source of the PET signal

Thibaut Quillard, Peter Libby, ***Circulation Research 7/***2012;111:231-244

Molecular Imaging of Atherosclerosis

- F-FDG imaging first used in atherosclerotic pts to assess inflammation and macrophage load in the symptomatic carotid artery versus the contralateral asymptomatic control vessel.

- Higher PET signal in the symptomatic vessel correlated with macrophage staining and expression of inflammatory markers in the retrieved endarterectomy specimen.

Thibaut Quillard, Peter Libby, ***Circulation Research 7/***2012;111:231-244

Molecular Imaging of Atherosclerosis

- Plaques contain myeloperoxidase (MPO) generated from macrophages.
- MPO can serve as a marker of inflammatory cells and an indirect marker of ROS production.
- An MR-dedicated probe for MPO (MPO[Gd]) was able to identify inflammation in rabbit atherosclerotic plaques

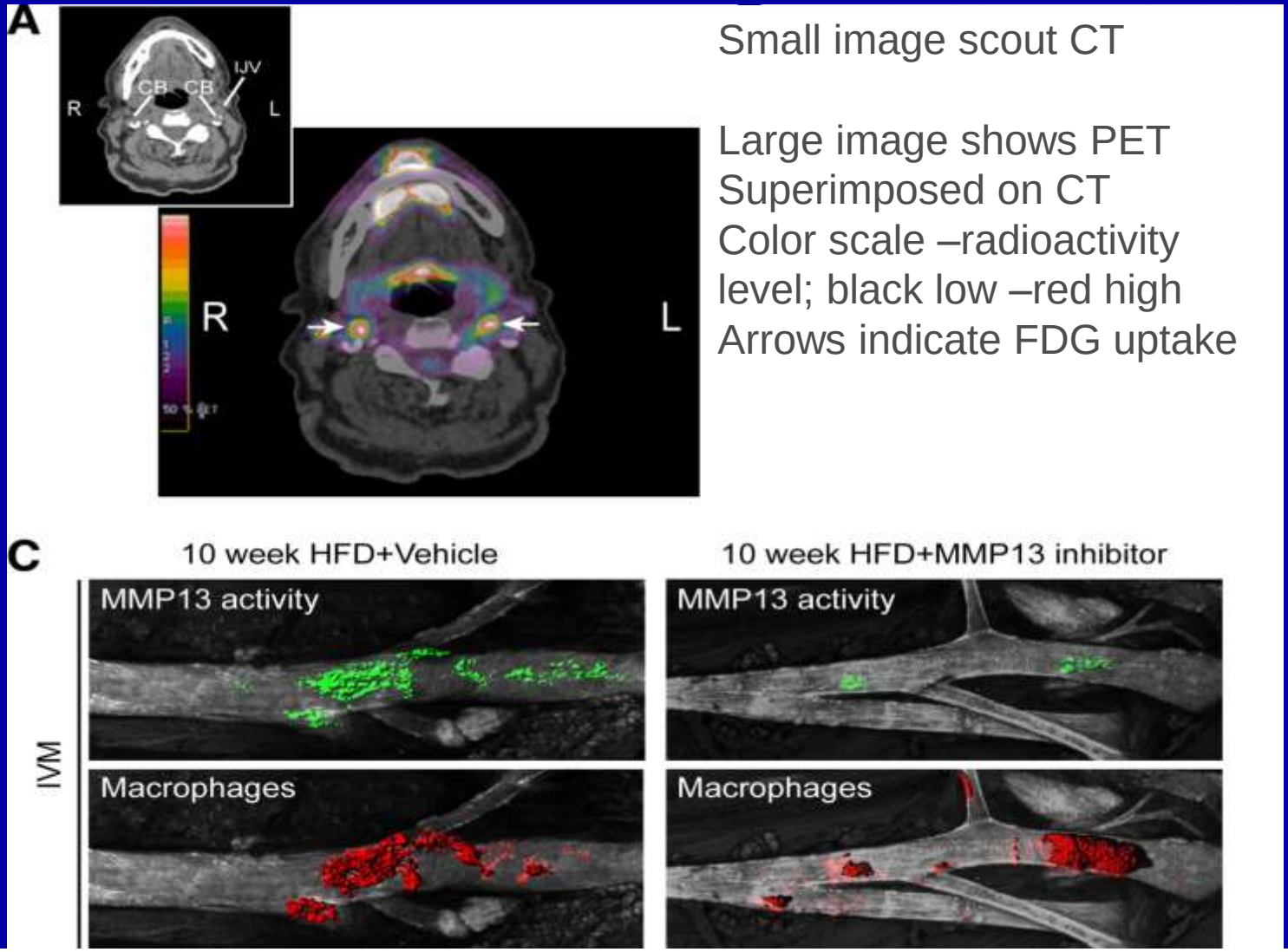
Thibaut Quillard, Peter Libby, ***Circulation Research 7/***2012;111:231-244

Molecular Imaging of Atherosclerosis

- Markers of cell death; necrotic core
- Markers of angiogenesis
- Markers of proteinases; affect virtually all aspects of atherosclerotic plaque formation, growth, and complications, in part by degrading extracellular matrix
- Markers of extracellular matrix – collagen
- Markers of intraplaque hemorrhage
- Markers of microcalcification

Thibaut Quillard, Peter Libby, ***Circulation Research 7/***2012;111:231-244

F-FDG-PET/CT and Microscopic Images



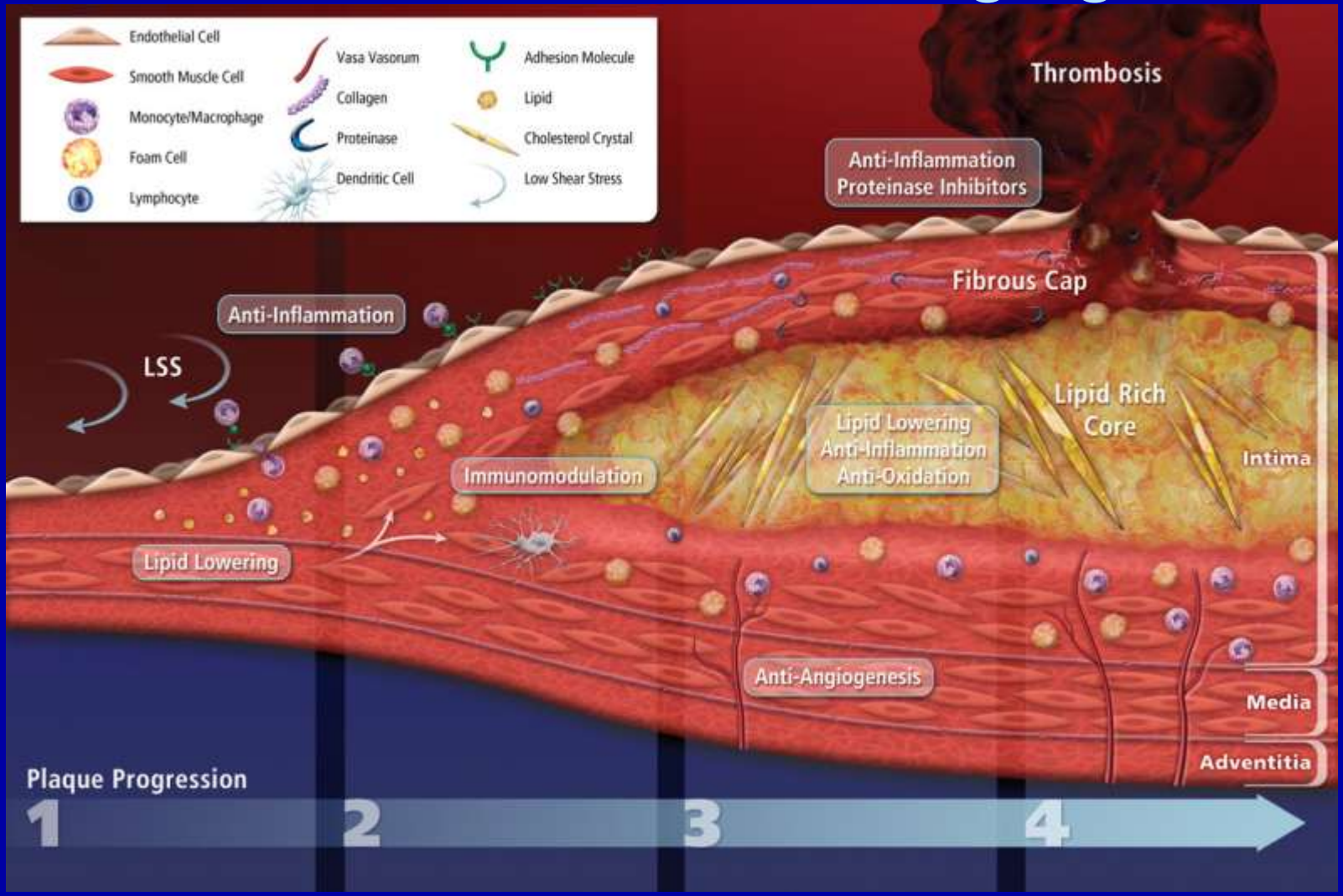
Small image scout CT

Large image shows PET Superimposed on CT
Color scale –radioactivity level; black low –red high
Arrows indicate FDG uptake

Intravascular microscopy with MMP probes and nanoparticles for Macrophages

Quillard T , Libby P Circulation Research 7/2012;111:231-244

Atherosclerotic Plaque with Areas of Potential Molecular Imaging



Quillard T , Libby P Circulation Research 7/2012;111:231-244

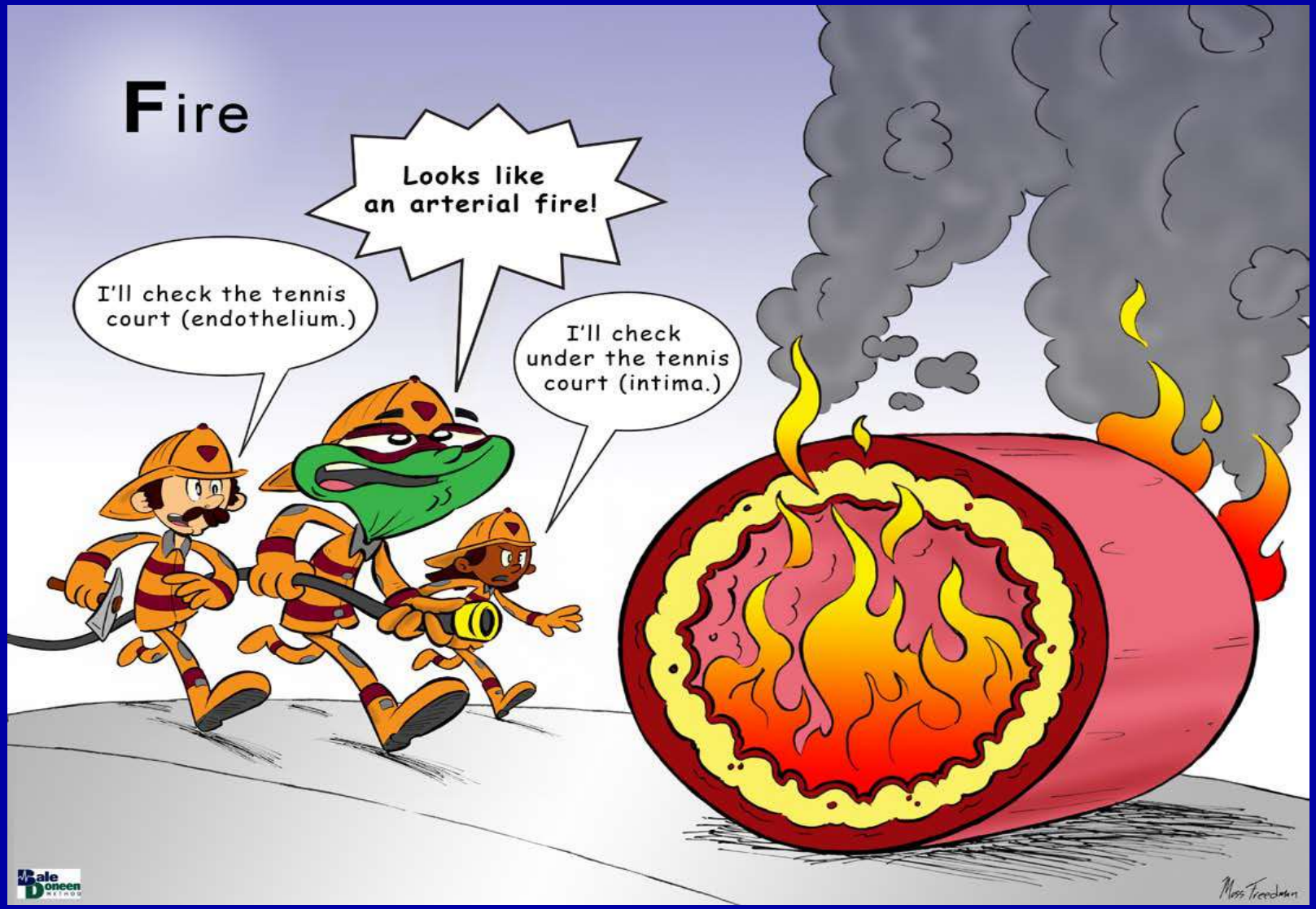
Molecular Imaging of Atherosclerosis

- Research benefits: aid elucidating the key processes involved in plaque formation, progression and disruption which will facilitate discovery of novel therapeutics

- Potential clinical benefits: monitoring ongoing therapy

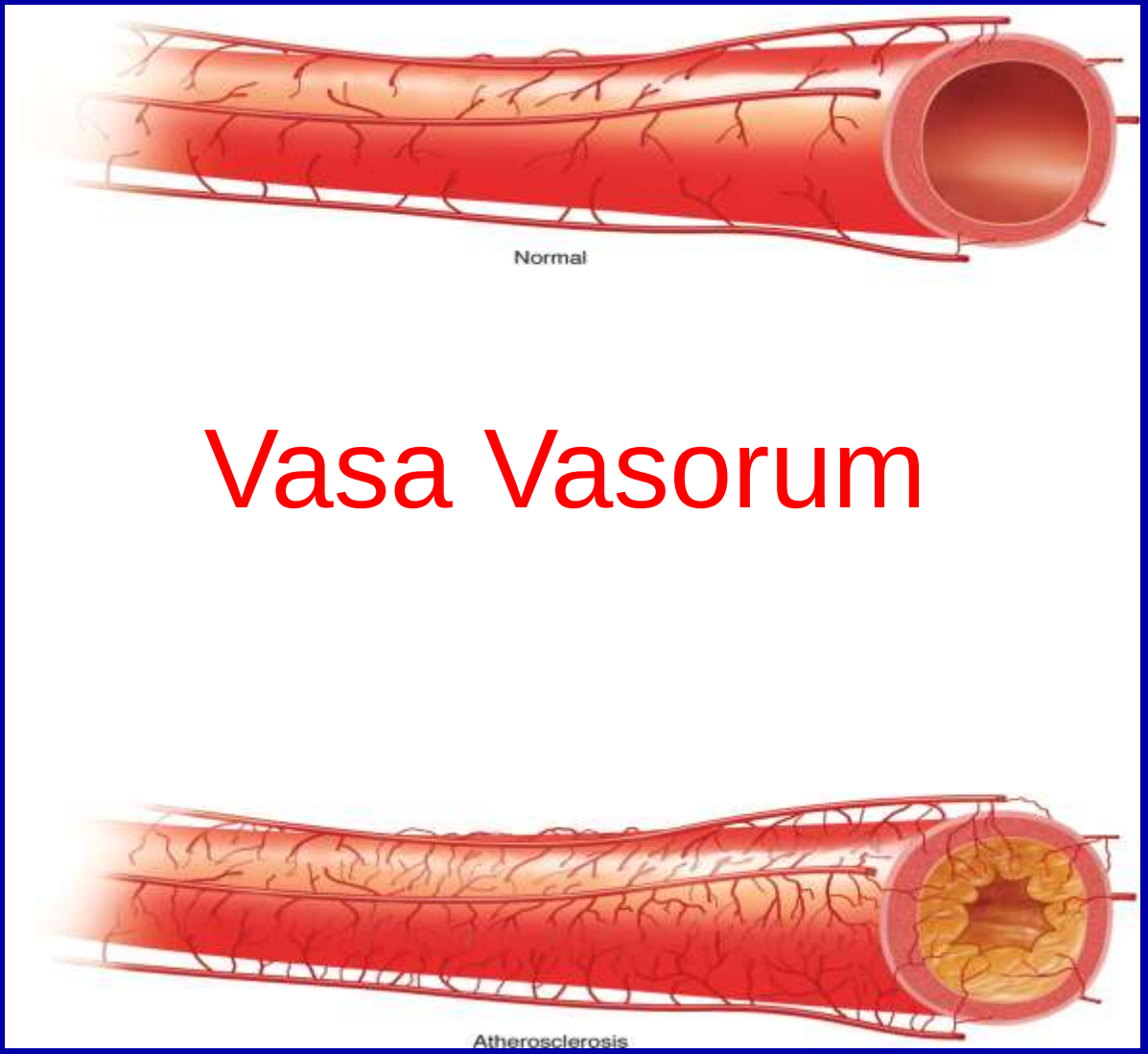
Thibaut Quillard, Peter Libby, ***Circulation Research 7/***2012;111:231-244

Inflammation



The Other Side of the Story!

Healthy artery



Atherosclerotic artery

JACC -- Doyle and Caplice 49 (21): 2073 Figure IG1

Micro-endothelial Cells: Importance in Arterial Inflammation

- It has been demonstrated that neovascularization (vaso vasorum) is associated with plaque destabilization.
- Plaques with moderate and severe inflammation have significantly increased neovessel content.
- Ruptured plaques exhibited the highest degree of neovascularization.

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- Endothelial cells (Ecs):
  1) macrovascular (MAC ECs) - line large- or medium-sized vessels
  2) microvascular (MIC ECs) - line small-sized vessels and capillaries

- MIC ECs develop from the vasa vasorum; penetrate into plaque to supply oxygen and nutrients; contribute to intraplaque hemorrhage, lipid core expansion, and plaque rupture.

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- Toll like receptor 4 (TLR4) plays a significant role in arterial inflammation
- Sophisticated *in vitro study* to investigate the TLR4-mediated upregulation of cytokine production between MIC and MAC ECs
- Focused on the secretion of IL-6, a key inflammatory cytokine, in response to lipopolysaccaride (LPS), a potent ligand for TLR4

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- Found baseline expression of TLR4 was ≈3-fold greater in MIC vs MAC Ecs
- NF-κB transcriptional activity that is responsible for the upregulation of inflammatory cytokines
- TLR4 activation increased NF-κB transcriptional activity by 10- and 3-fold, respectively, in MIC and MAC Ecs

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- Amount of IL-6 secreted by LPS-treated MIC ECs was 150,916 pg/mL versus 501 pg/mL for MAC ECs (300 fold difference!!)
- Demonstrated in aortic and cardiac tissue
- Demonstrated the secretion was due to TLR4

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- Also investigated the increase in gene expression for cytokines, chemokines, growth factors, and adhesion molecules with activation of TLR4 comparing MIC Ecs with MAC ECs

- Multiple fold increase in most comparing MIC vs MAC ECs

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- Investigated if inflammatory cytokines released by MIC ECs in response to TLR4 stimulated MMP expression by mononuclear cells.
- Striking augmentation of MMP-1 secretion: 10-fold
- No increase in MMP from monocytes when MAC ECs had TLR4 stimulation

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Micro-endothelial Cells: Importance in Arterial Inflammation

- This study elucidates a novel mechanism potentially involved in neovascularization-associated plaque vulnerability.

- MIC ECs may play an important role in plaque destabilization through TLR4- dependent mechanisms.

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

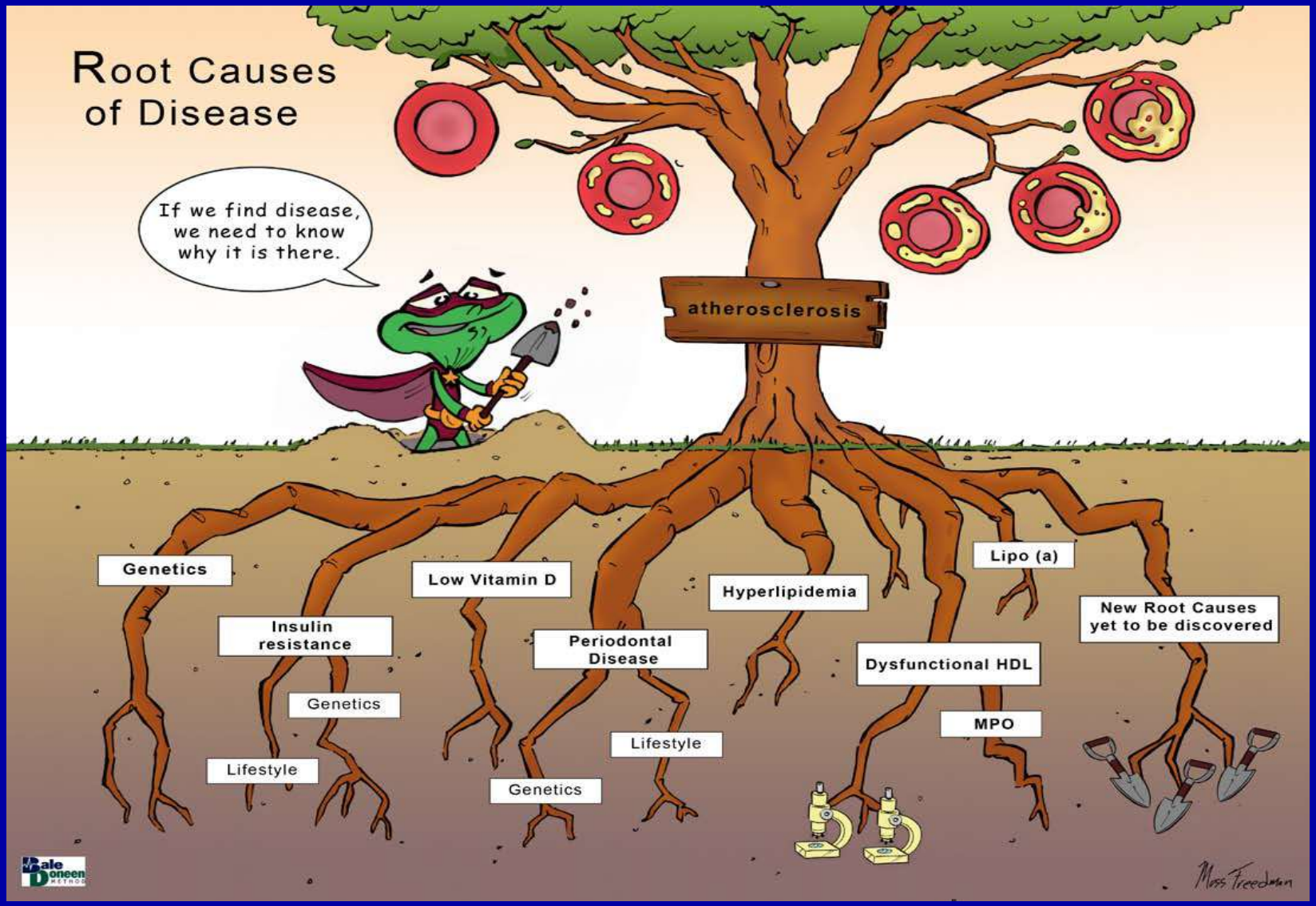
Micro-endothelial Cells: Remember Periodontal Disease !

- Periodontal disease has been implicated in the progression of atherosclerosis.

- PD pathogens such as, Porphyromonas gingivalis, generate LPS which stimulate an inflammatory response by engaging TLR4.

Lu, Z.,et. al. ***Arterioscler Thromb Vasc Biol. 6/2012;32:1696–1706***

Roots



Atherosclerosis and Senescence

- Cell senescence = irreversible loss of the ability of cells to divide. Two types.

- 1)- replicative senescence; occurs with exhaustion of proliferative lifespan over time; ‘aging’; shortened telomeres induce DNA damage

- 2) stress-induced premature senescence (SIPS); triggered by external stimuli, including oxidizing agents and radiation; not usually characterized by telomere shortening

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

Atherosclerosis and Senescence

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

- VSMCs senescence generate a proinflammatory environment and have diminished ability to repair plaque.

- Monocyte senescence generates a greater proinflammatory environment

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

Atherosclerosis and Senescence

- Mechanisms underlying cellular senescence in atherosclerosis are likely to be multiple and cumulative

- Telomere shortening leading to replicative senescence will interact with nuclear and mitochondrial DNA damage due to free radicals.

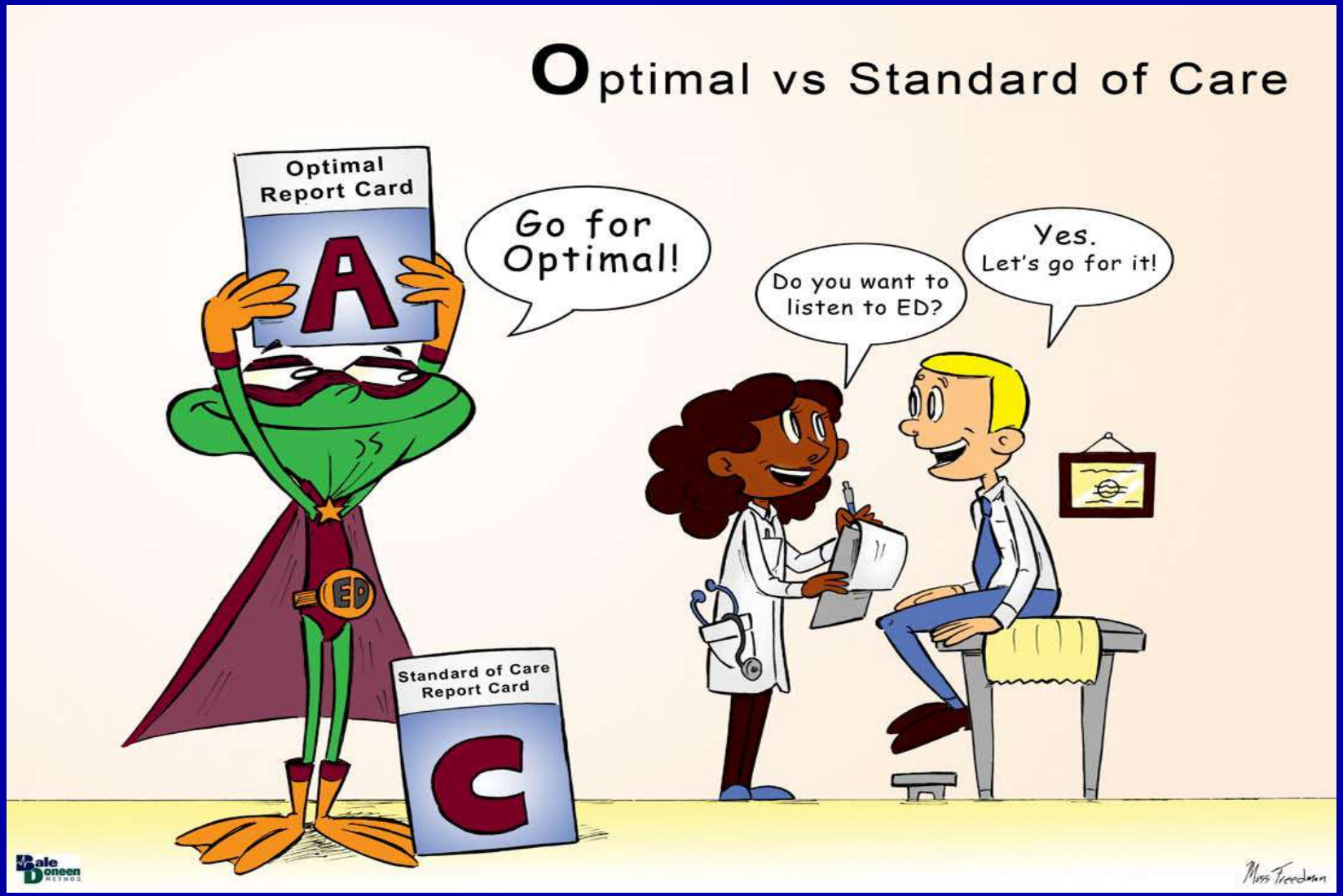
Wang J C , Bennett M Circulation Research 7/2012;111:245-259

Atherosclerosis and Senescence:
Therapeutic measures to mitigate senescence

- Exercise, diet (caloric restriction), resveratrol ?
- Agents which reduce ROS and oxidative DNA damage: antioxidants, statins, ACEI, ARBs, chloroquine ?
- Pioglitazone has actions which can help maintain telomeres; increasing telomerase expression which may cause increased risk for cancer ??

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

Optimal Care



BP- Long Term Mean Control is Predictive of CIMT and CV Events

- Mild-moderate hypertensive pts.; 1,521 evaluated visit to visit (6 mos.) variation in syst. BP; 1,264 evaluated yearly 24hr. BP monitoring variation; 4 yr. study

- Objective: which BP variable predicts CV events and change in CIMT – short term variation or long term mean BP control??

- The long term mean BP was predictive of CIMT and CV events; on treatment short term BP changes were not predictive of CIMT change or CV events

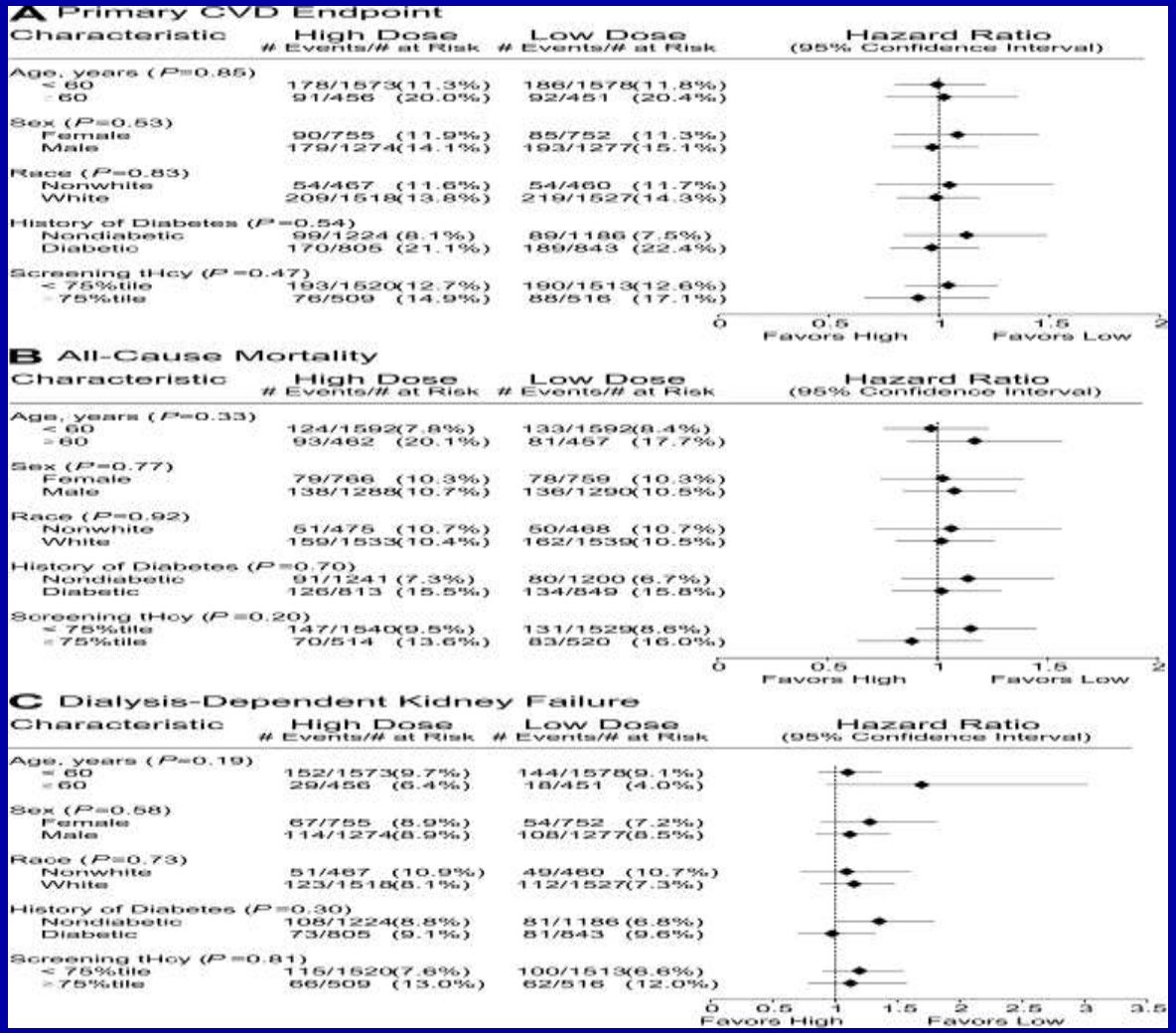
Mancia, G., et. al. *Circulation. published online July 3, 2012*
DOI: 10.1161/CIRCULATIONAHA.112.107565

Homocysteine Lowering in Kidney Transplant Pts has no CV Benefit

- 4,110 kidney transplant pts.; randomized to low or high dose rx for homocysteine for 4 yrs.; eval. CV outcomes
- Mean treatment Hcy levels (mol/L) of 11.8 for high dose and 15.9 for low dose
- High dose rx did not reduce CV outcomes or risk of going on to kidney failure

Bostom A G et al. Circulation 5/2011;123:1763-1770

Hazard ratios for treatment group comparisons from primary and secondary outcome subgroup analyses.

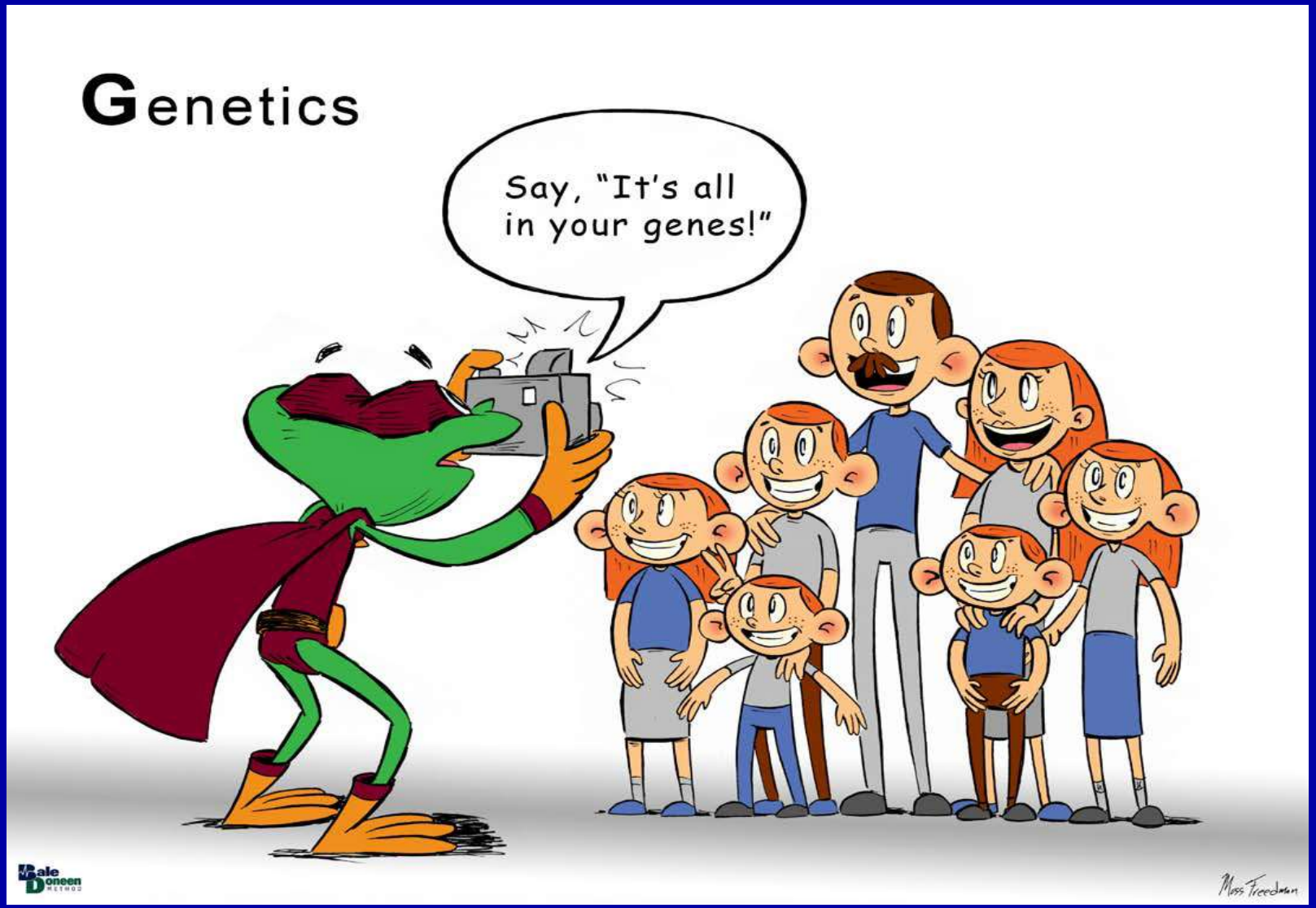


Favors high= lower Hcy
Favors low = higher Hcy

Bostom A G et al. Circulation 5/2011;123:1763-1770

Bale Doneen METHOD

Genes



Genetics: AHA Statements

- Genetic testing can complement standard clinical evaluation.

- The power of genetics lies in:

  1) exquisite diagnostic accuracy

  2) preclinical identification of at-risk individuals and family members

Ashley, E. A., et.al. *Circulation. 7/2012;126:142-157*

Genetics: AHA Statements

- Coronary artery disease, MI, ischemic stroke, and atrial fibrillation have heritable contributions
- In the clinical setting genetic testing may permit better identification of inherited risk than family history
- The patient interview as routinely performed suffers from limited reliability

Ashley, E. A., et.al. *Circulation. 7/2012;126:142-157*

Genetics: AHA Statements - Challenges

- The minor changes in risk prediction from individual SNPs, or even panels, create skepticism about the clinical utility.
- New SNPs associated with CVDs are being identified rapidly which dampens enthusiasm for genotyping “now”.
- No clinical trials have been performed that demonstrate clinical outcome benefit of genotyping.
- Interpretation of results can be challenging and time consuming for clinicians and patients alike.
- Genotyping healthy individuals carries potential risks, such as limiting qualification for life or long-term disability insur.
- Unclear how payers will react to covering the costs of “predictive genotyping”.
- Despite this, knowledgeable clinicians might reasonably choose to perform genotyping.

Ashley, E. A., et.al. *Circulation. 7/2012;126:142-157*

Genetics: AHA Statements

- The rapid pace of advancement in genetic technology offers great promise in its potential to transform patient care.

- As a result, policies, systems, and processes designed for an earlier era of medicine will be forced to adapt.

- The American Heart Association is committed to support innovative research in CV genetics and its safe and efficient translation to patient care.

Ashley, E. A., et.al. *Circulation. 7/2012;126:142-157*

Genetic Risk Score for CAD/MI is Predictive

- 2,597 cardiac cath pts.; sorted out ones with hx MI <70yo and ones without hx MI >70yo; followed for 2.5 yrs. for incident MI
- Genotyped for 11 known CAD/MI SNPs; combined into a weighted risk ‘score’
- Score was associated with pts. with hx of MI <70yo versus without hx >70yo; $p<0.001$; replicated in another cohort with $p<0.001$
- Score improved c-statistic in traditional risk models
- Score did not predict events in 2.5 yr. follow-up

Patel, R. S.,et.al. *Circ Cardiovasc Genet published online July 5, 2012*
DOI: 10.1161/CIRCGENETICS.111.960229

EDFROG IRA

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

Niacin: Encourage Wider Use

- Niacin-containing regimens have demonstrated reduced atherosclerosis progression and CV events
- Uncomfortable side effects limit use

- Effective counseling by clinicians can improve compliance
- Encourage wider use of the cardioprotective agent

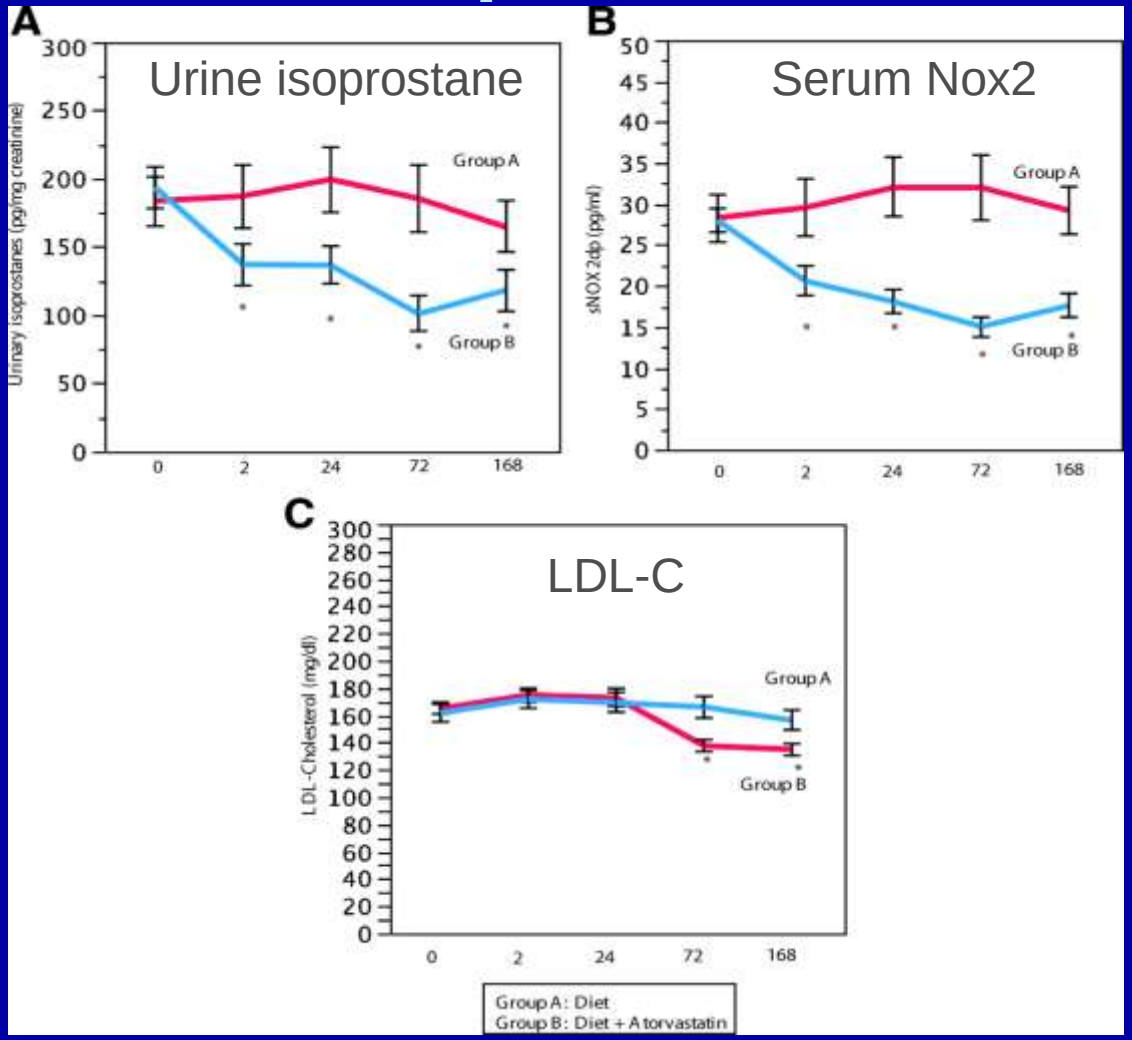
Carol M. Mason, ARNP, CLS, FAHA, FNLA, FPCNA; Amy L. Doneen, MSN, ARNP. *Journal of Cardiovascular Nursing* 7&8/2012 Vol. 27, No. 4: 303-316

Atorvastatin has Antiplatelet and Antioxidant Effects

- 30 hyperlipidemic pts; half Med. Diet or atorva 40mg; assessed oxidative stress and platelet activation at baseline, 2 hrs., 1, 3 & 7 days
- Med. Diet demonstrated no effect
- Atorvastatin immediately and progressively reduced oxidative stress and platelet activation
- Additional reason to utilize statins in all secondary and tertiary patients

Pignatelli P et al. Circulation 7/2012;126:92-103

Atorvastatin Reduces Oxidative Stress Independent of LDL-C

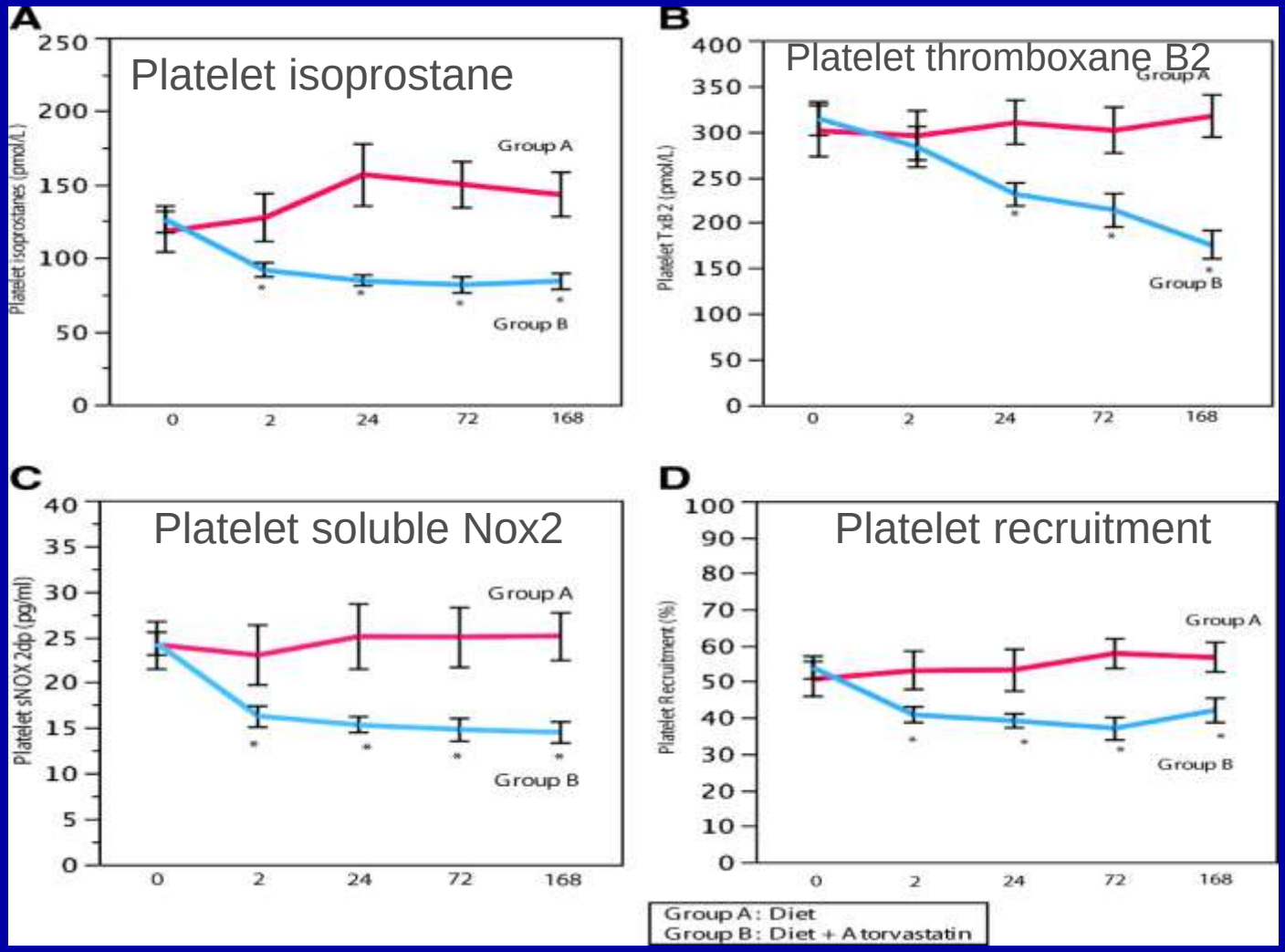


Diet
Atrova

*p<0.005

Pignatelli P et al. Circulation 7/2012;126:92-103

Atorvastatin Reduces Platelet Activation



Diet
Atrova

*P<0.005

Pignatelli P et al. Circulation 2012;126:92-103

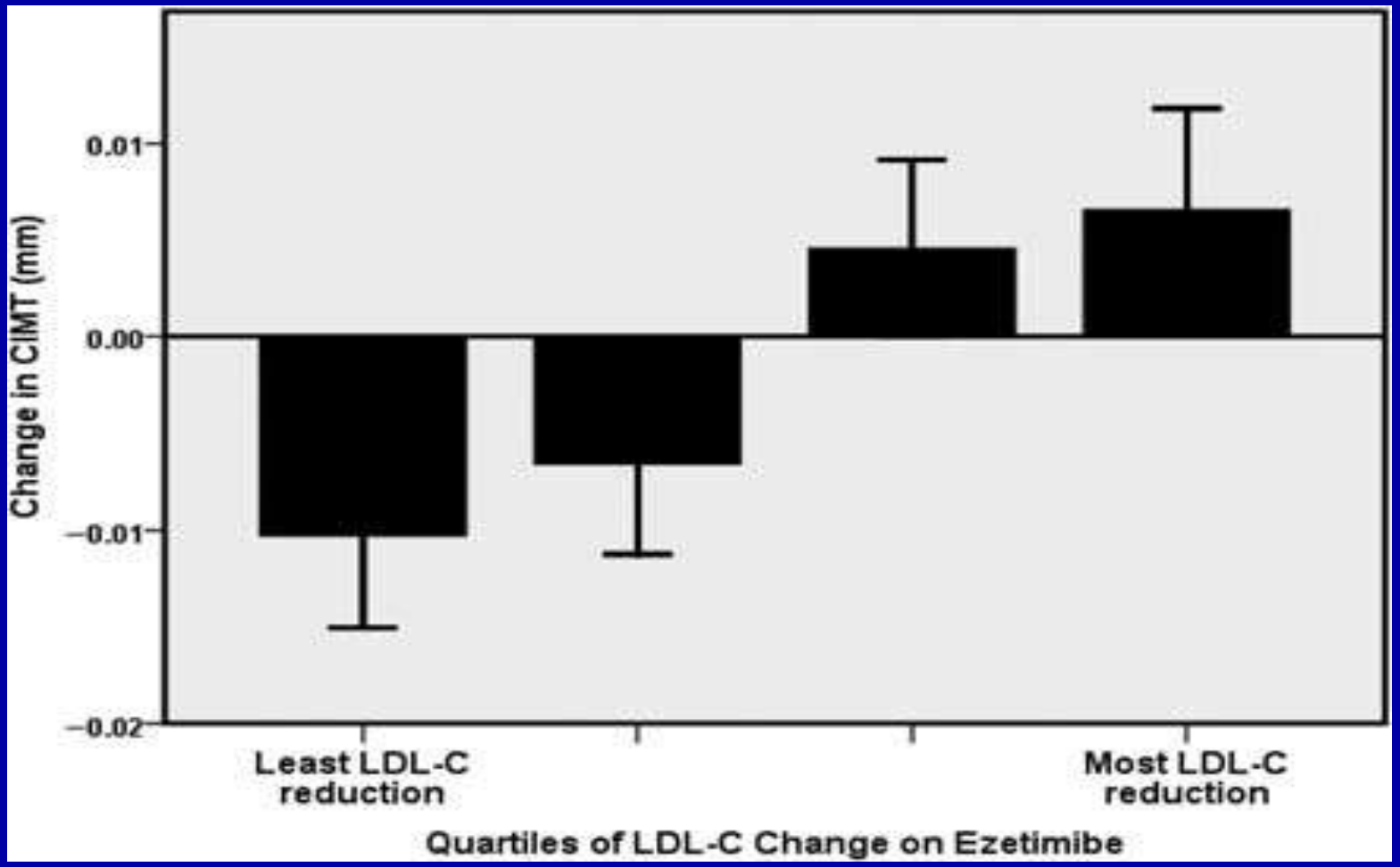
Ezetimibe Yields Paradoxical Results with CIMT

- 159 CAD or high CV risk pts.; on statin with LDL<100mg/dL; HDL <50 or 55 mg/dL – men –women; ezetimibe added to rx
- Ezetimibe reduced LDL-C from 84±23 to 66±20 mg/dL
- Multivariable models controlling for change in LDL-C, cumulative ezetimibe exposure, and baseline and on-treatment variables showed:

  greater LDL reduction & drug exposure were associated with CIMT progression with p=0.005 and =0.02, respectively
- Suggests the presence of off-target actions of ezetimibe.

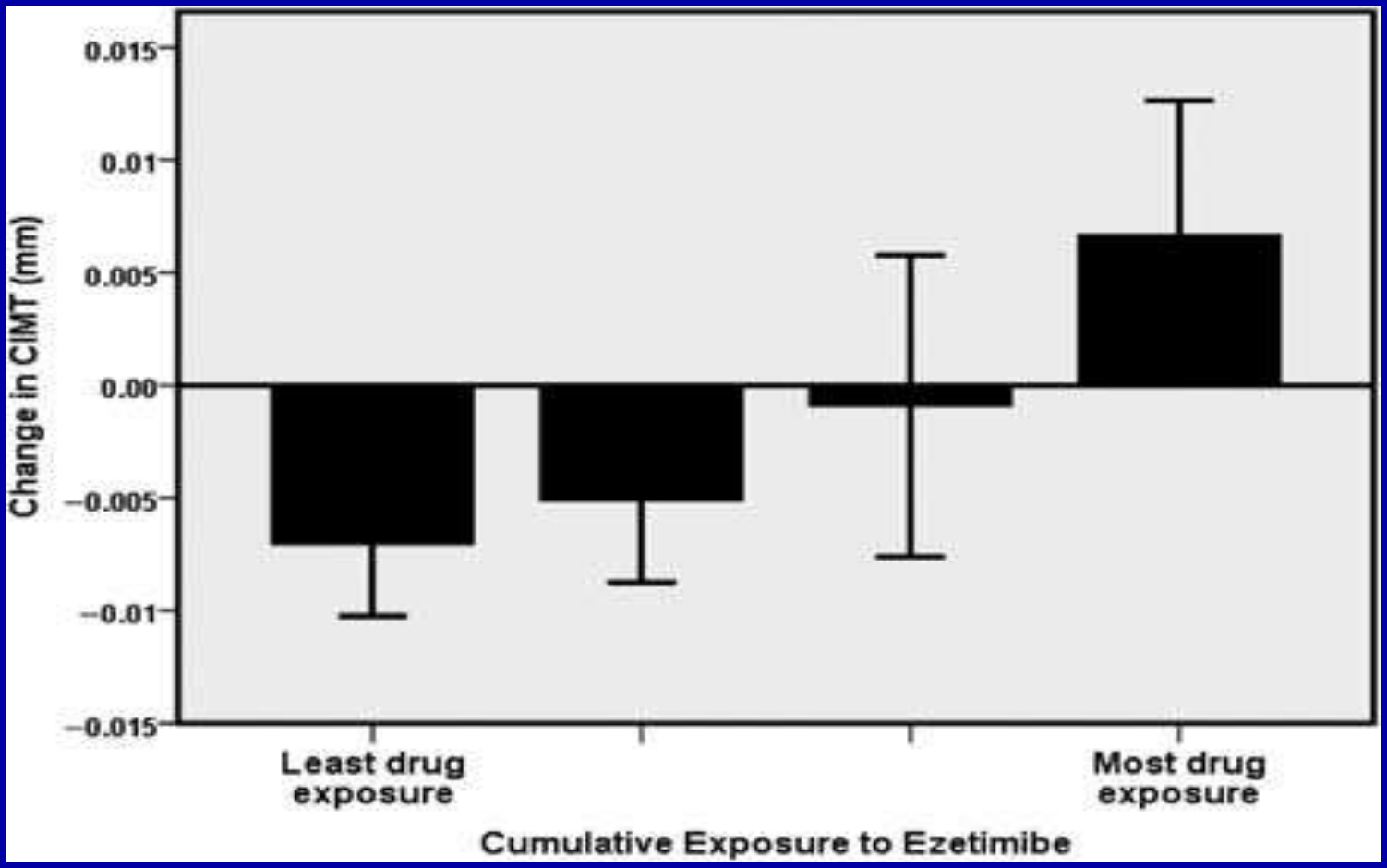
Taylor, A. J., et. al. *European Heart Journal 5/7/2012*
doi:10.1093/eurheartj/ehs105

Ezetimibe Yields Paradoxical Results with CIMT



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

Ezetimibe Yields Paradoxical Results with CIMT



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

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

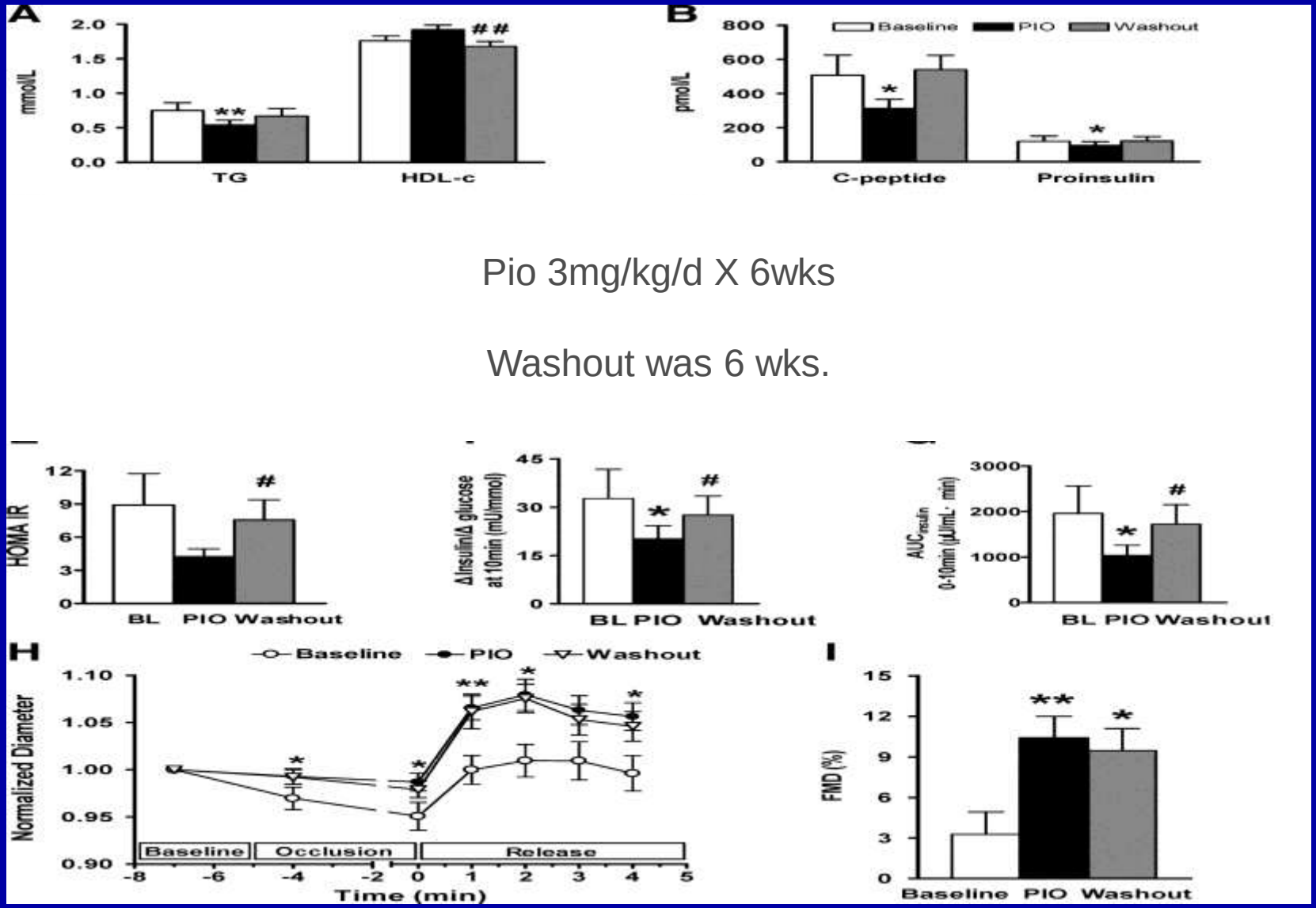
Taylor, A. J., et. al. *European Heart Journal*
doi:10.1093/eurheartj/ehs105

Pioglitazone Normalizes Endothelial Function in Metabolic Syndrome(MetS.)

- 408 Rhesus monkeys; 35 predisposed to MetS followed for 18 months; 18 progressed to MetS
- FMD decreased 60%
- Pioglitazone rx for six weeks (n=12) improved dyslipidemia & IR; completely normalized FMD

Zhang X et al. Circulation 7/2011;124:77-86

Effects of Pioglitazone in MetS Monkeys



Pio 3mg/kg/d X 6wks

Washout was 6 wks.

Zhang X et al. Circulation 2011;124:77-86

Pioglitazone Normalizes Endothelial Function in Metabolic Syndrome(MetS.)

- Normalization of FMD in the MetS rhesus monkey suggests that treatment of MetS before frank T2D develops may have profound effects on vascular function and risk for atherogenesis

- Persistent improvement despite washout of drug was an unexpected finding that would be fascinating to replicate in humans

Zhang X et al. Circulation 7/2011;124:77-86

Hot Topics

Inflammatory Testing: “IT”

TED MED review on www.theheart.org

Please see our white paper posted on our website: www.baledoneen.com

Case

Upcoming Presentations

- 7/21/2012– ***Bale/Doneen Method Highlighting Inflammatory Testing for the Reduction of Cardiovascular*** **Events. ;5 hr. CME; Baltimore, Maryland**
- 9/7/2012 – Amy and Brad speaking– U. of Nevada Medical School – Diabetic Conference
- 9/14-15/2012 – BD Method Preceptorship; San Antonio, TX
- 9/20/2012 – BD Method Reunion; Las Vegas, NV
- 9/21-22/2012 – Amy and Brad speaking – CHL Symposium; Las Vegas, NV
- New CME opportunity!!! – 11/2/2012 – ***Vascular Inflammation: The Systemic / Oral Connection***; 6.5 hr. CME; Las Vegas, NV

Open for Discussion