Bale/Doneen Live Chat Session

8/8/2012

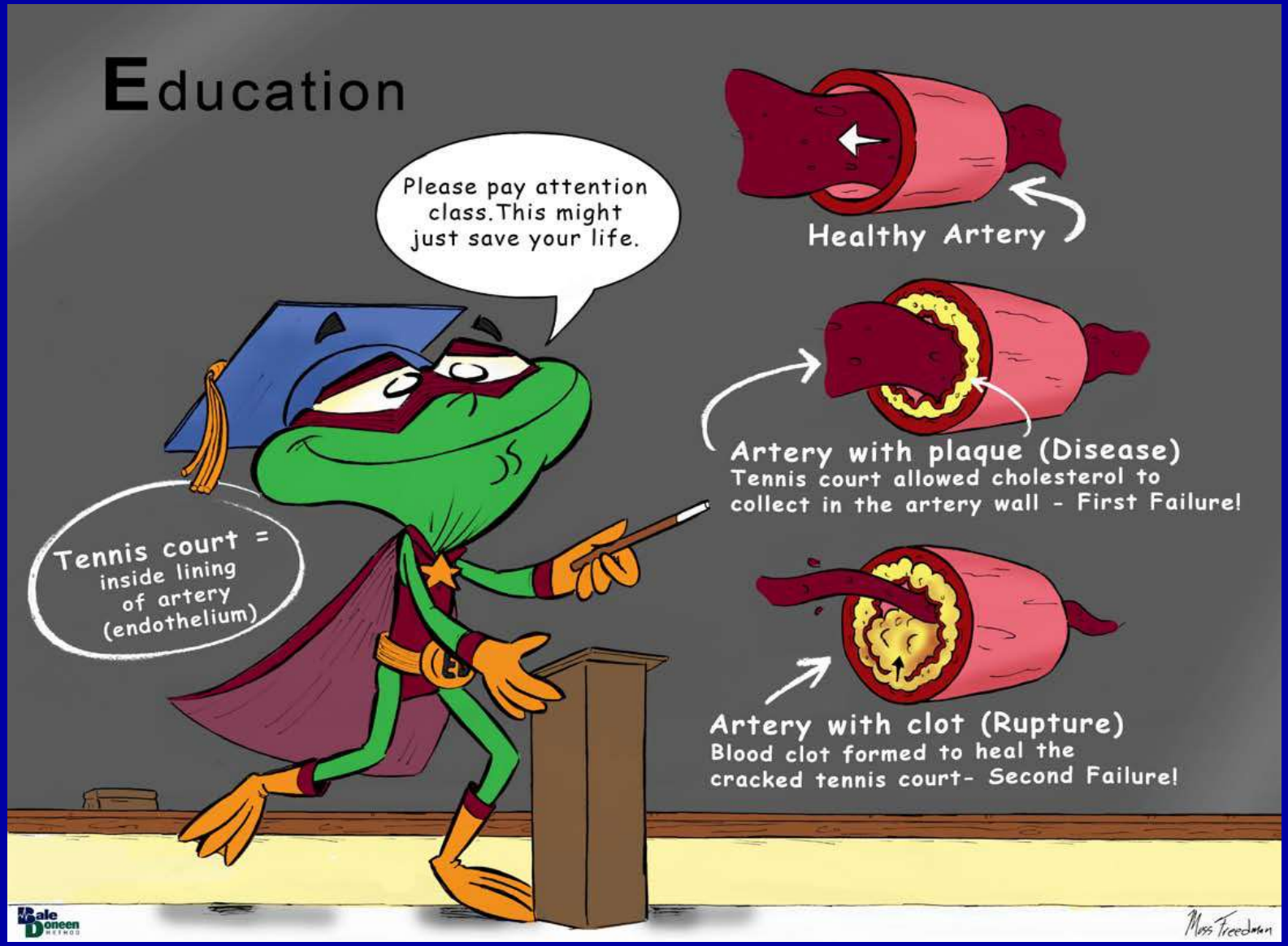
5:30-6:30 pm PST

Bradley Bale, MD

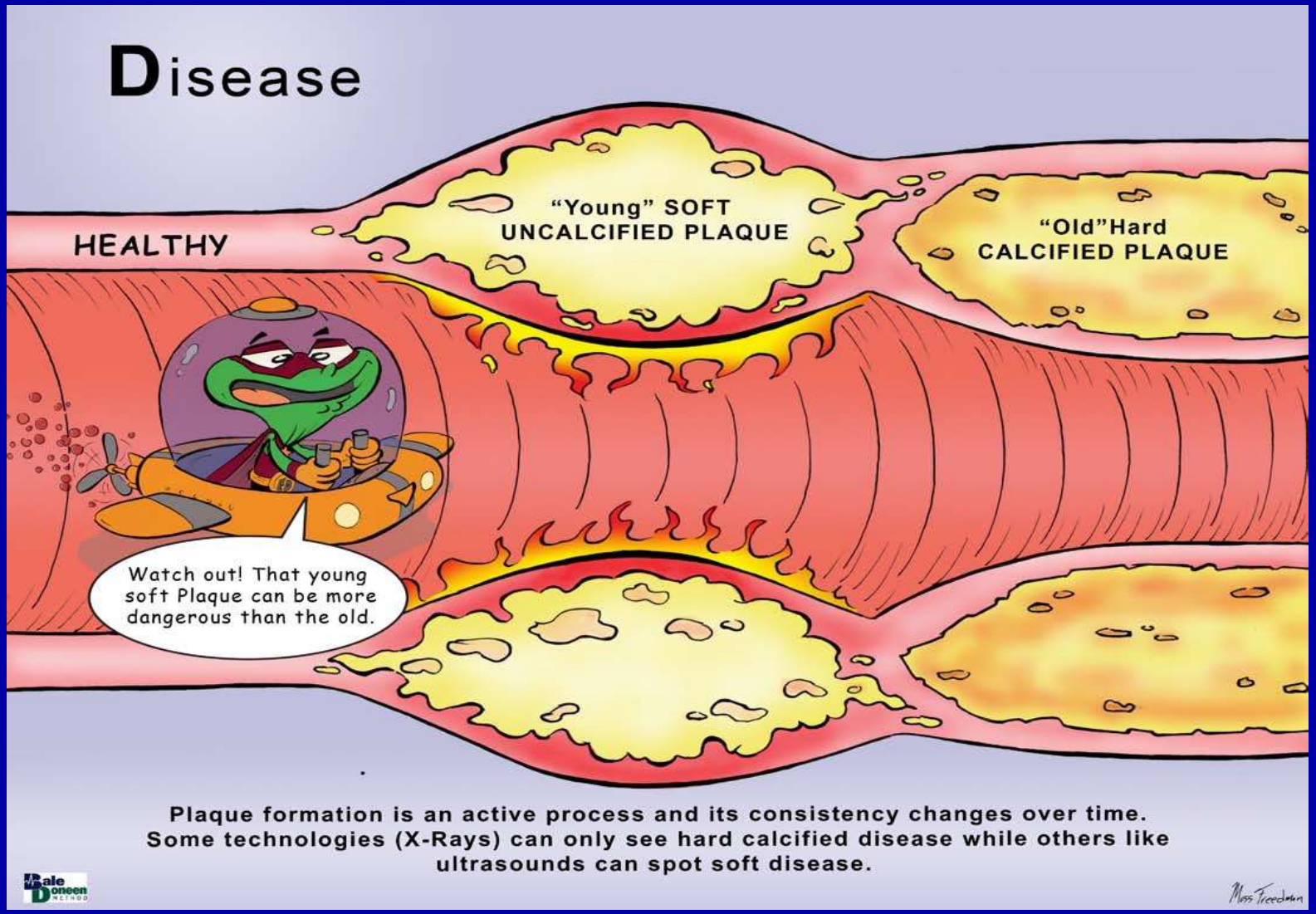
Intention of the live chats

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

Education



Disease: inflammation??



“Non-culprit” Plaques in ACS vs Stable CAD Pts Differ Significantly

- ACS from a ruptured plaque is not merely an isolated vascular accident, but reflects a pan-vascular process with the potential to unstable plaques in nonculprit areas.

- 17 ACS & 87 stable CAD pts.; 3 vessel optical coherence tomograpy (OCT); “non-culprit” plaques compared: 45 ACS; 203 non-ACS

Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

Optical Coherence Tomography (OCT) Effective for Detecting Vulnerable CAD

- 48 CAD pts: performed IVUS, (virtual histology) VH-IVUS, and OCT
- OCT detected vulnerable plaque with thin cap, large lipid core, thrombus and fissures -four to five times better than the other modalities; can identify neovascularization
- OCT's resolution is almost 10 times greater than IVUS
- OCT’s limitations are the need for “a blood-clear zone and the low penetrating depth

Published on Oct 13, 2008: to be presented at the 20th Annual Transcatheter Cardiovascular Therapeutics scientific symposium

“Non-culprit” Plaques in ACS vs Stable CAD Pts Differ Significantly

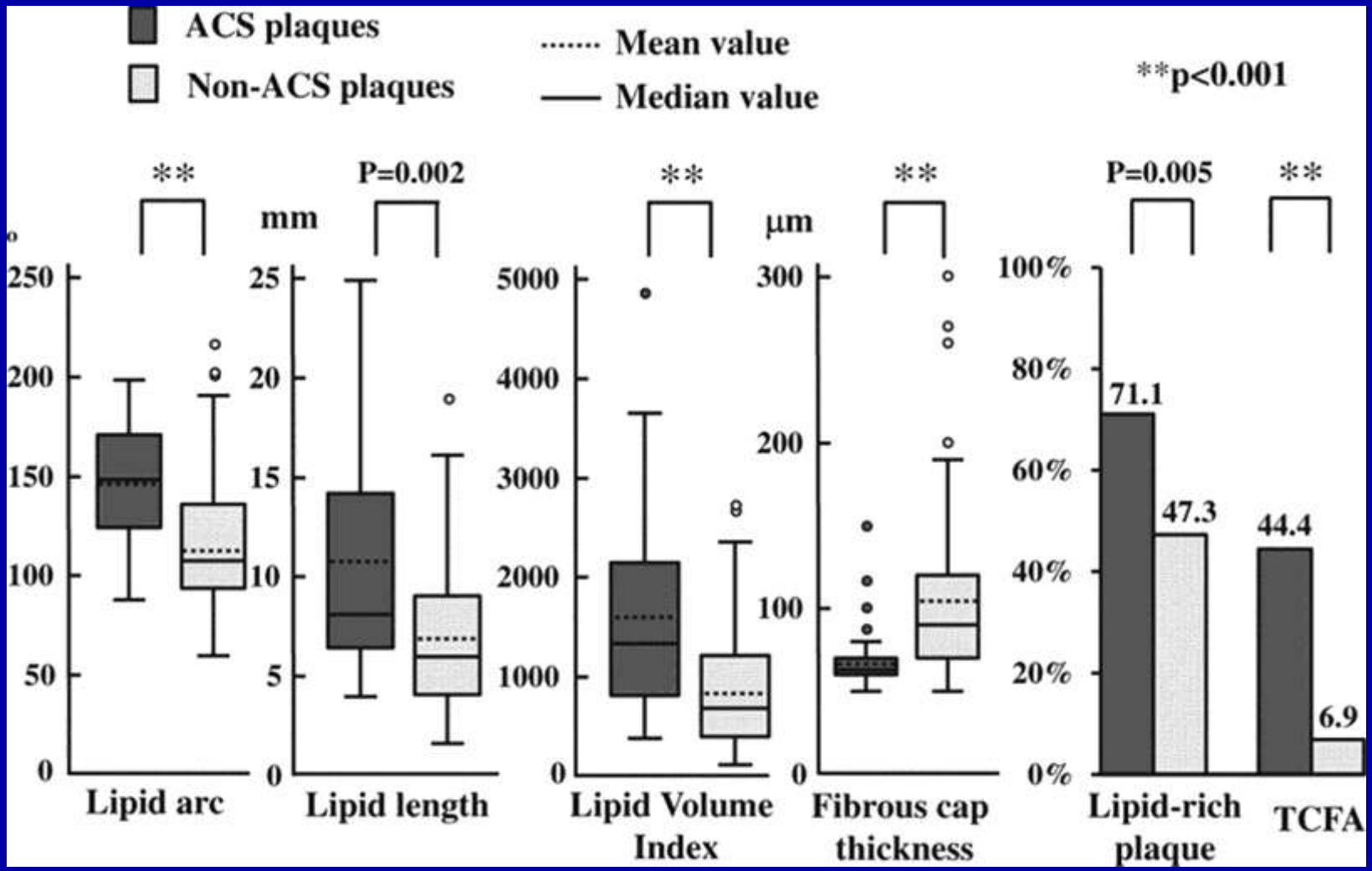
- 17 ACS & 87 stable CAD pts.; 3 vessel optical coherence tomograpy (OCT); non-culprit plaques compared: 45 ACS; 203 non-ACS

- Number of plaques per patient did not differ (~2.5/pt)

- All of the following were significantly greater in ACS pts: wider lipid arc; *longer lipid length; larger lipid volume; thinner fibrous cap; thrombus (29.4% versus 1.1%, P<0.001).*

Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

Plaque-based comparison of optical coherence tomography findings between acute coronary syndrome (ACS) and non-ACS plaques.



Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

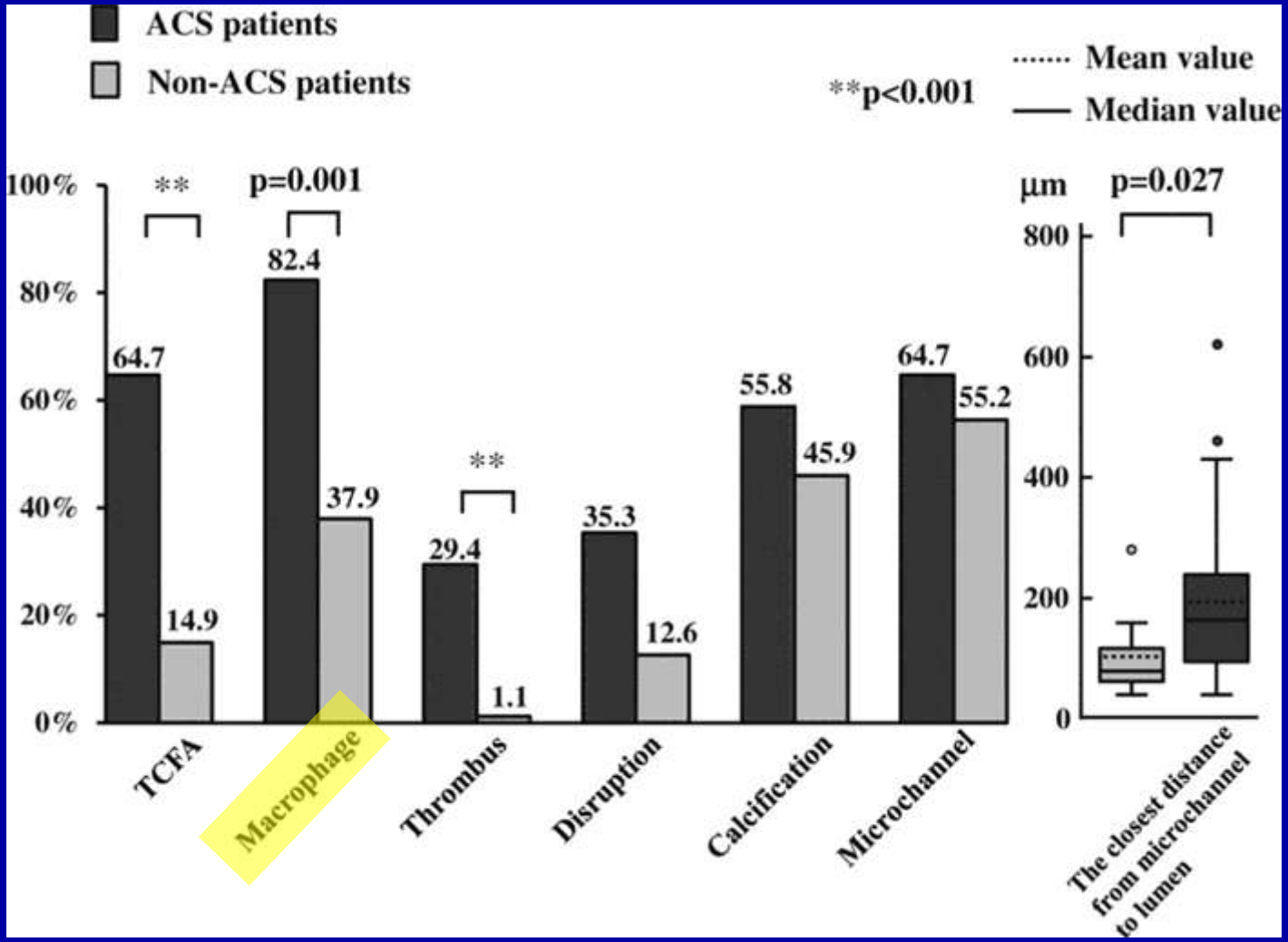
ACS Pts have more Inflamed Non-culprit Plaques and Vaso Vasorum Closer to Lumen

- *ACS vs stable CAD: macrophage 82.4% versus 37.9% - p=0.001*
- Prevalence of vaso vasorum did not differ between the groups, but the neovasculature was much closer to the lumen in ACS subjects

Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

ACS Pts have more: thin cap fibroatheroma; inflammation; thrombus; vaso vasorum close to lumen

plaque characteristics in ACS vs Stable CAD



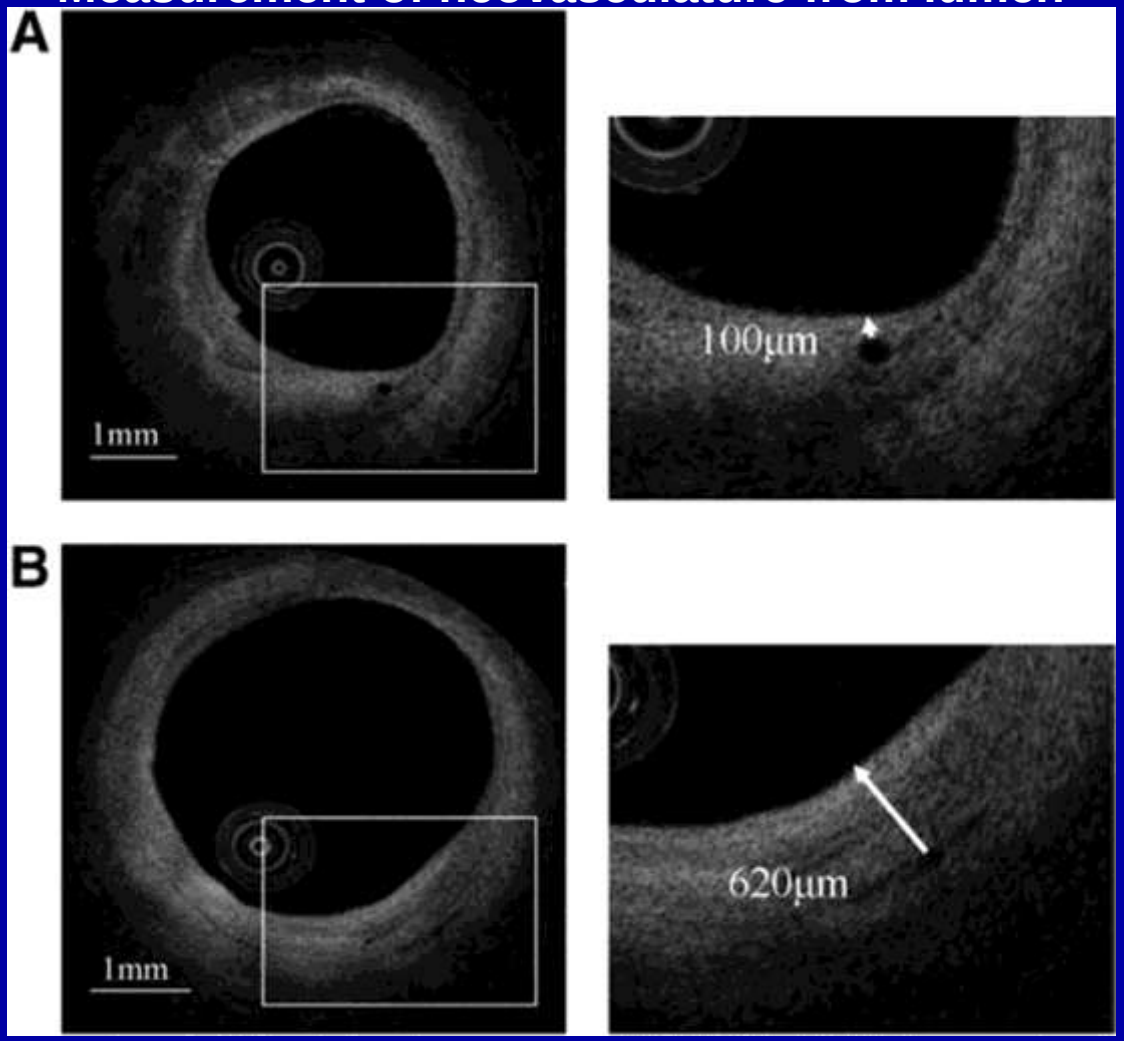
Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

Vaso Vasorum is Much Closer to Lumen in ACS Pt's Plaque

Measurement of neovasculature from lumen

ACS non-culprit plaque

Stable CAD plaque



Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

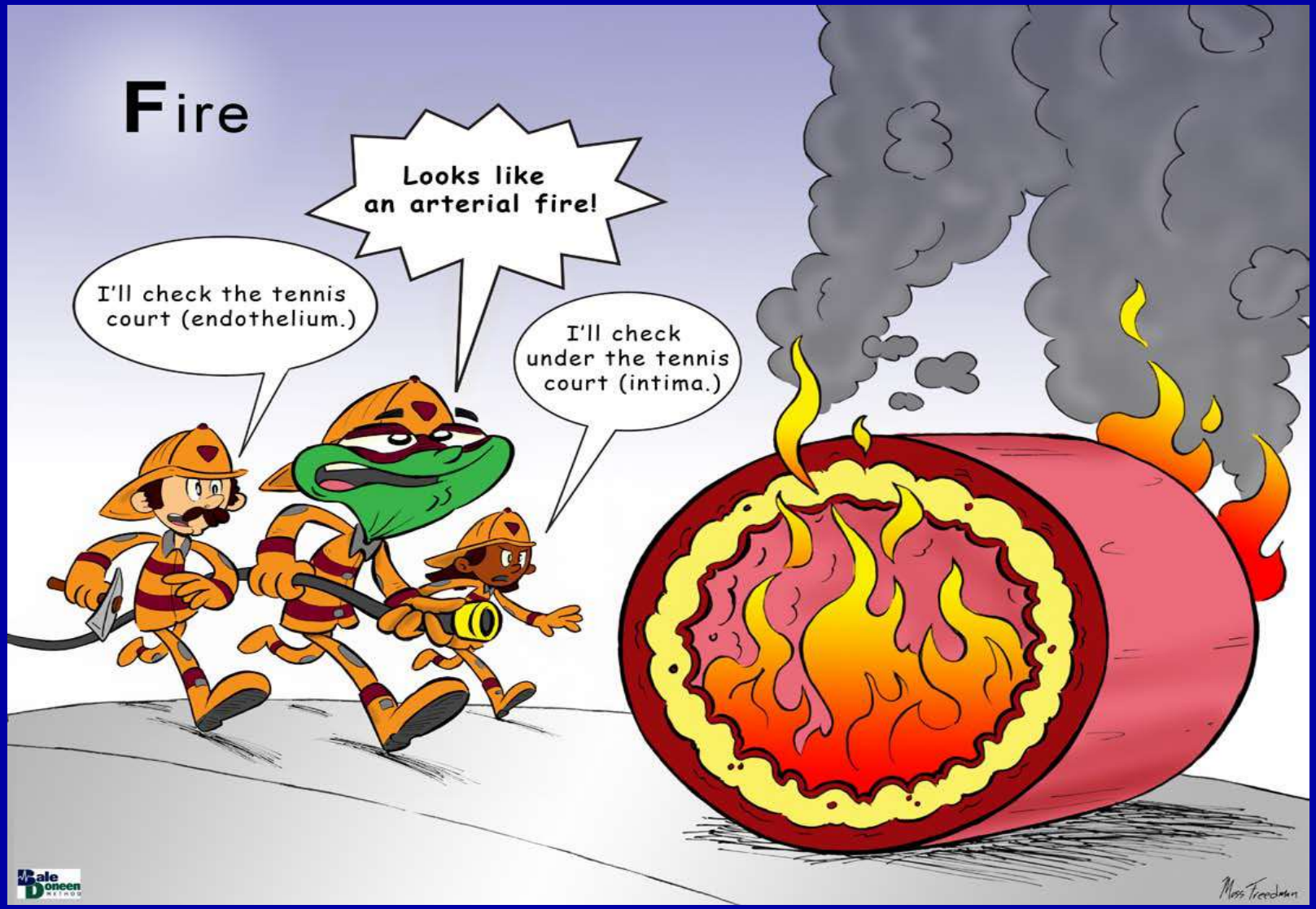
Discussion Points

- Helps explain high recidivism – a stent in culprit lesion is not going to stabilize other lesions
- Supports that a lot of ruptures (thrombi) do not cause symptomatic events (~ a third of ACS non-culprits!!)
- Supports inflammation as driver of ASVD
- Supports importance of vaso vasorum and micro-endothelial cells
- Illustrates unreliability of calcification

- Bottom line: ACS pts are “hotter” –inflammation; need to put the “fires” out!!!! – stents do not do that!!

Kato K et al. Circ Cardiovasc Imaging 7/2012;5:433-440

Inflammation



Oxidative Stress Increases Risk of Thrombosis

- Oxidant stress is associated with platelet activation
- Isoprostanes significantly increase platelet aggregation via activation of the glycoprotein IIb/IIIa.

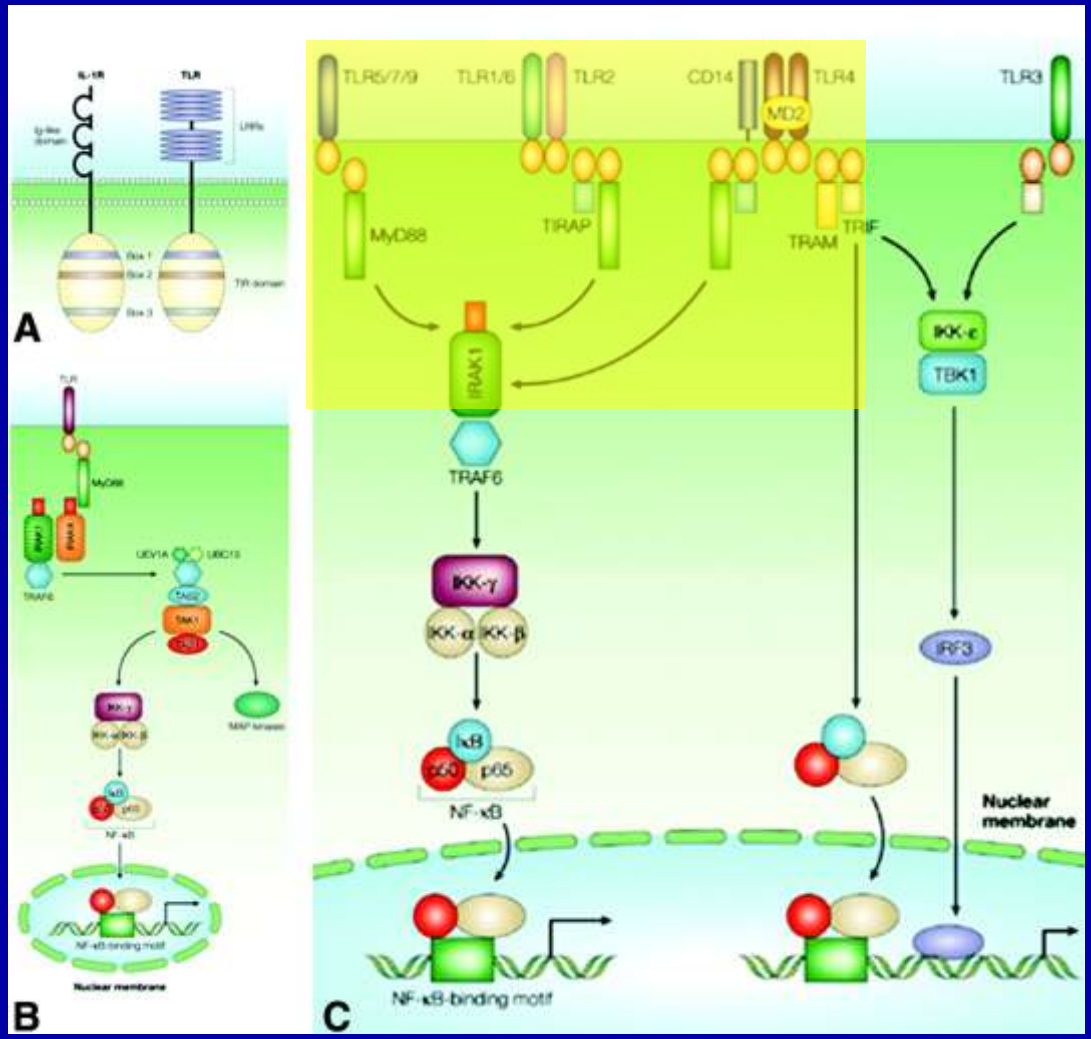
Pignatelli P et al. Circulation 7/2012;126:92-103

Toll Receptors Key in Inflammation Driving Atherosclerosis

- TLRs act like a bridge connecting the extracellular activity to the interior of the cell.
- The TLR intracellular component (TInterleukinR=TIR) communicates with the protein: myeloid differentiation factor 88 (MyD88)
- With TLR2 and TLR4 MyD88-dependent signaling requires an adaptor protein termed TIRAP (TIR domain-containing adaptor protein).
- When stimulated, MyD88 sequentially recruits interleukin (IL)-1 receptor associated kinases 4, 1 and 2 (IRAK4, IRAK1 and IRAK2) to the receptor complex.

Mann D L *Circulation Research* **2011;108:1133-1145**

TLR Structure and Signaling.



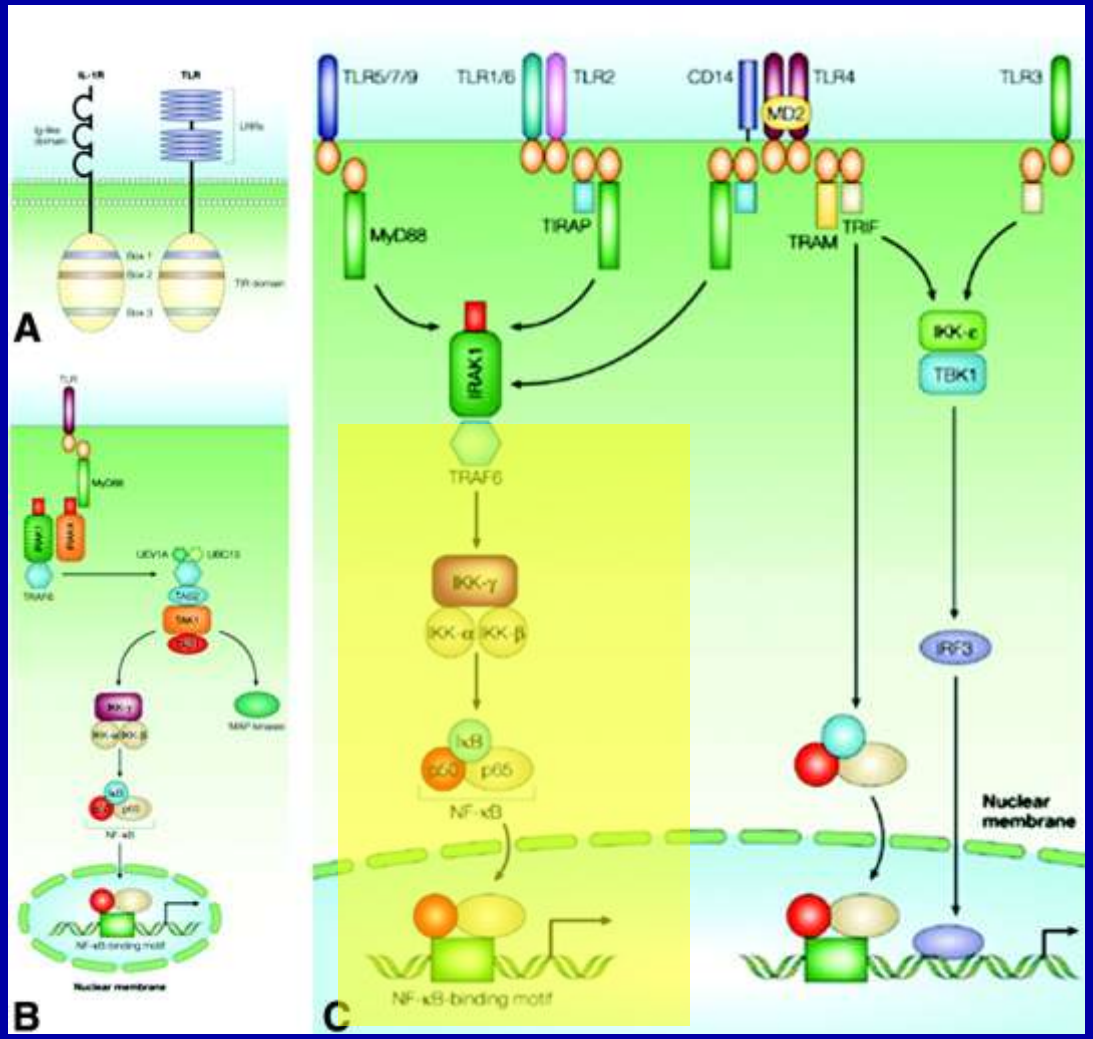
Mann D L Circulation Research 2011;108:1133-1145

Toll Receptors Key in Inflammation Driving Atherosclerosis

- Through a series of complex chemical reactions with the IL-1 receptor kinases nuclear factor kappa beta is activated.
- NF-kB then translocates to the nucleus and induces the expression of its target genes
- NF-kB regulates the expression of cell adhesion molecules and chemokines, which in turn recruit macrophages and neutrophils

Mann D L *Circulation Research* **2011;108:1133-1145**

TLR Structure and Signaling.



Mann D L Circulation Research 2011;108:1133-1145

TLRs Play a Key Role in Inflammation Driving Atherosclerosis

- TLR signaling upregulates proinflammatory cytokines (IL-1, IL-6, TNF), cell adhesion molecules by vascular endothelial cells, and enhances the release of matrix metalloproteinase by macrophages.

Mann D L *Circulation Research* **2011;108:1133-1145**

Toll Receptors Key in Inflammation Driving Atherosclerosis

- The biological response following TLR activation is similar whether it be endogenous or exogenous
- If the activating stimulus persists, chronic inflammation will ensue. Sustained TLR activation is maladaptive.
- The resulting inflammatory response can lead to progression of atherosclerosis and instability of atheroma.

Mann D L *Circulation Research* **2011;108:1133-1145**

Toll Receptors (TLRs) Key in Inflammation Driving Atherosclerosis

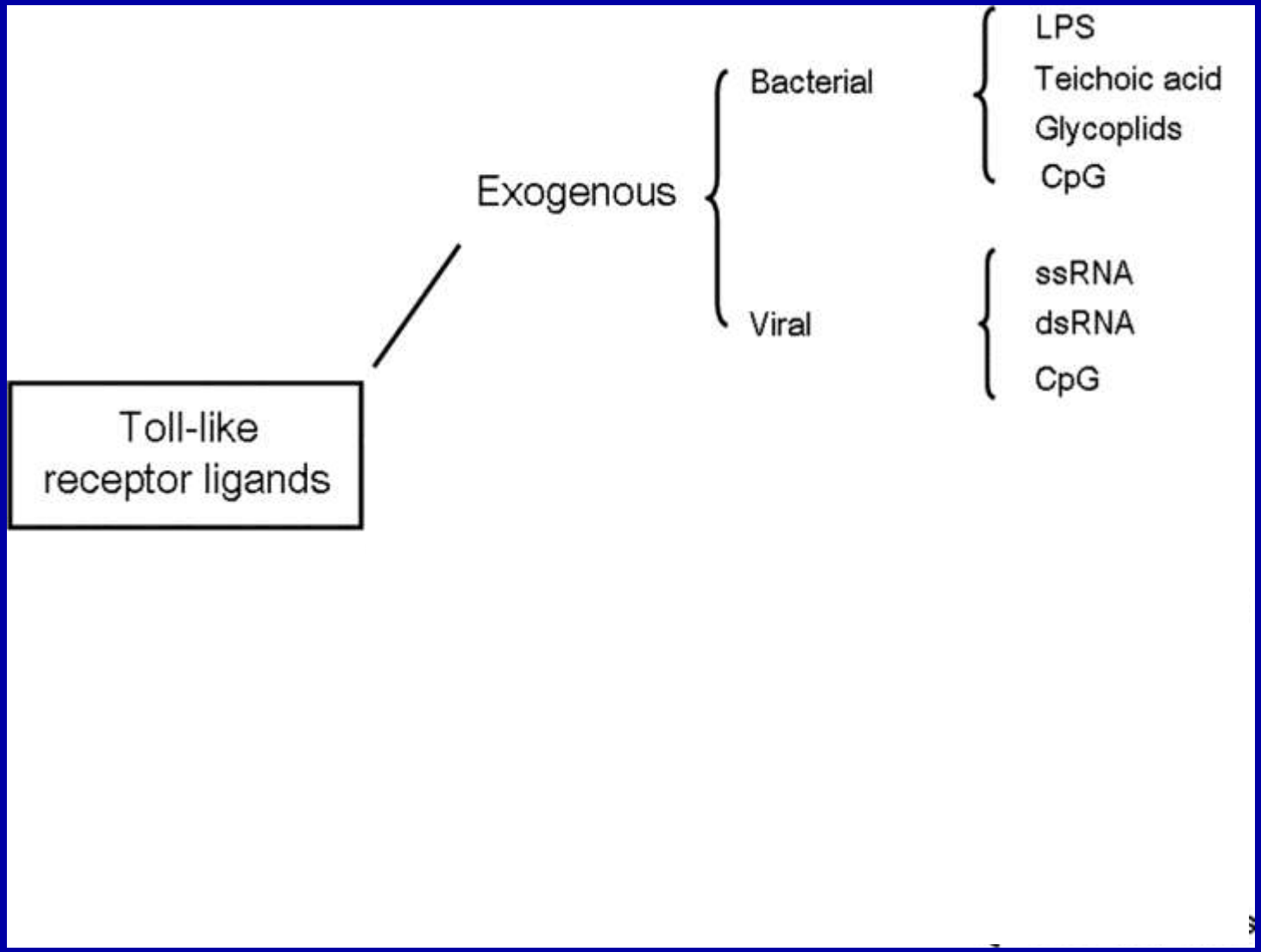
- Quintessential feature of the innate immune system is to serve as an “early warning system” enabling the host to accurately discriminate self from non-self

- TLRs assist in this regard by recognizing patterns conserved on pathogens

- Examples include the lipopolysaccharides (LPSs) of gram-negative organisms, the teichoic acids of gram- positive organisms, the glycolipids of mycobacterium, the zymosans of yeast, and the double-stranded RNAs of viruses.

Mann D L *Circulation Research* **2011;108:1133-1145**

Potential Exogenous TLR Ligands



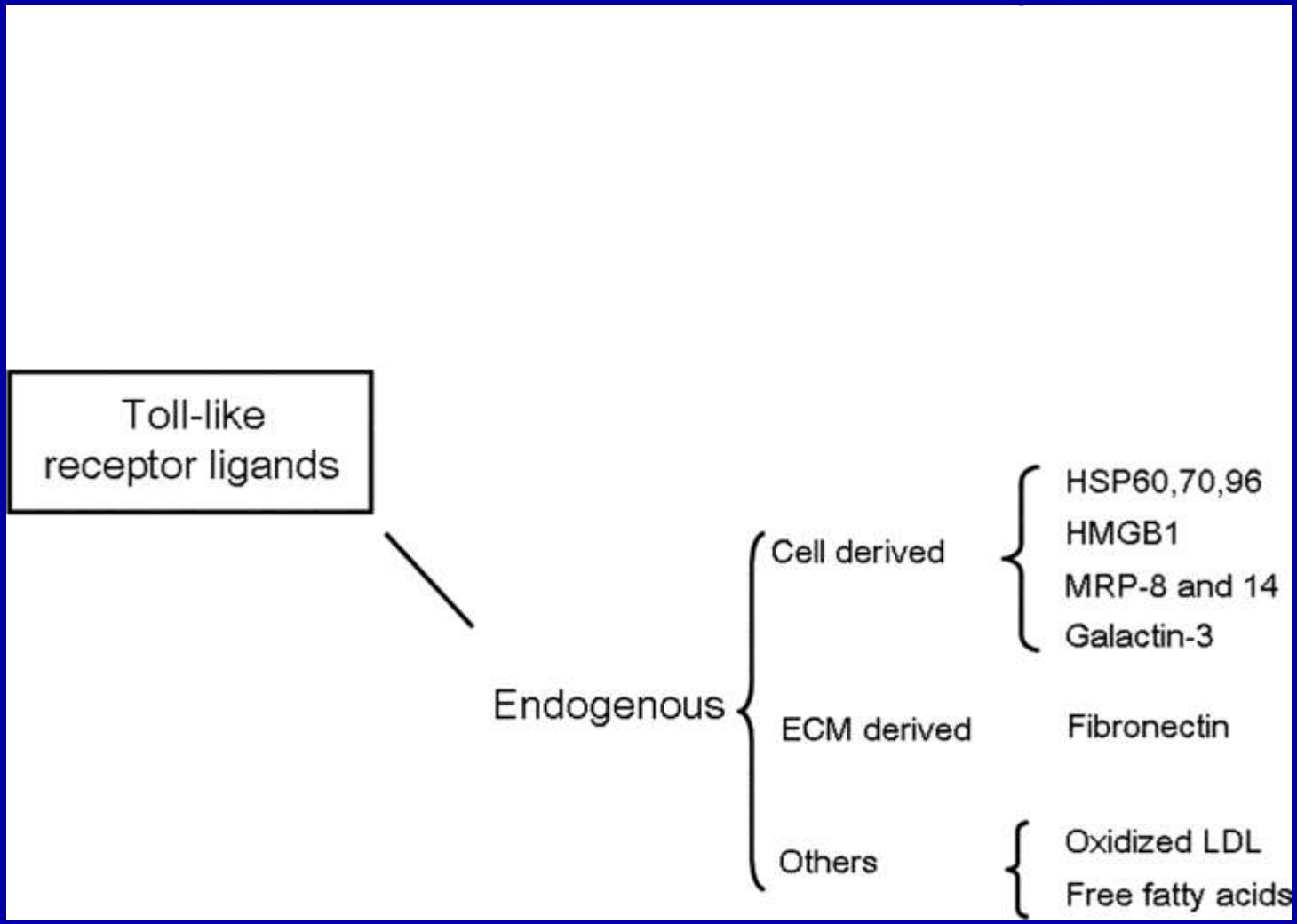
Mann D L Circulation Research 2011;108:1133-1145

Toll Receptors Key in Inflammation Driving Atherosclerosis

- Also important for innate immune system to identify damaged host material
- TLRs recognize host damage-associated molecular patterns (DAMPs) which can arise from injured cells, extracellular matrix and oxidized proteins

Mann D L *Circulation Research* **2011;108:1133-1145**

Potential Endogenous TLR Ligands.



Mann D L Circulation Research 2011;108:1133-1145

Evidence that TLRs Play a Key Role in Inflammation Driving Atherosclerosis

- TLR4 or TLR2 knockout mice crossed with atherosclerosis-prone *mice,* had reduced atherosclerosis *even* though cholesterol levels did not differ.
- Mice lacking MyD88 had reduced plaque burden when compared with appropriate controls.
- TLRs 1, 2, 4, and 5 are expressed in atherosclerotic plaques by resident cells and leukocytes.
- TLR4 is upregulated and concentrated in the shoulder region of the plaque.

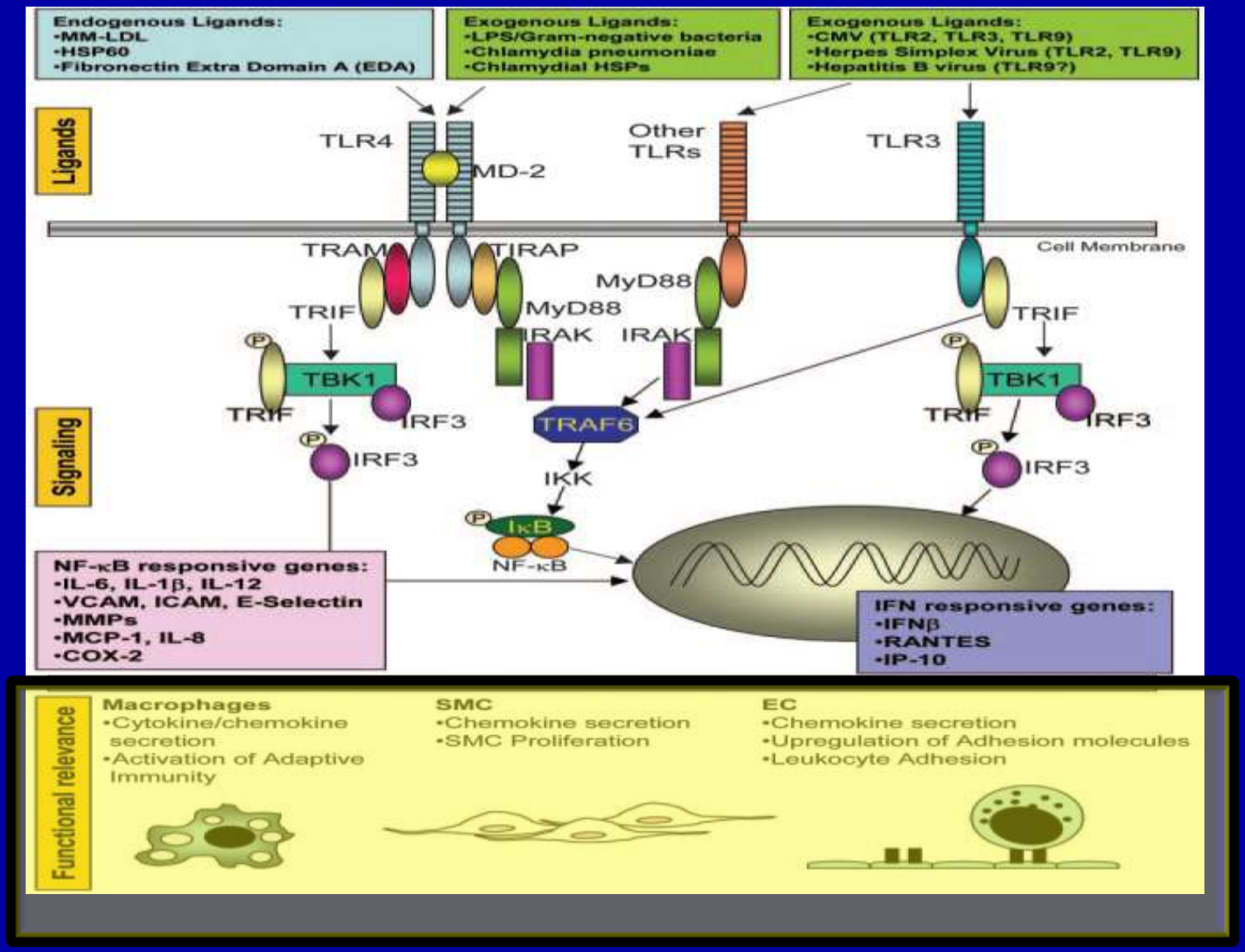
Mann D L *Circulation Research* **2011;108:1133-1145**

Evidence that TLRs Play a Key Role in Inflammation Driving Atherosclerosis

- Several TLR gene polymorphisms have been described
- Pts either heterozygous or homozygous for two different SNPs (Asp299Gly and Thr399Ile) that map to the extracellular domain of TLR4 are hyporesponsive to a challenge with LPS
- A population-based epidemiologic study did show subjects carrying the Asp299Gly were less susceptible to carotid ASVD.
- Other studies have reported that this polymorphism imparts protection from carotid and femoral ASVD and ACS, as well as, greater benefit from statin therapy.
- There are several other small studies with discordant results

Michelsen, K. S., et. al. *J Immunol 2004; 173:5901-5907*

TLRs Basic Diagram: Highlighting Clinical Relevance



Michelsen, K. S., et. al. *J Immunol 2004; 173:5901-5907*

Potential Therapies for TLRs in Atherosclerosis

- OPN-305 is a fully humanized anti-TLR2-specific monoclonal antibody that is a potent inhibitor of TLR2-mediated proinflammatory cytokine production.

- OPN-305 was granted orphan status for the prevention of the ischemia and reperfusion injury associated with organ transplantation, and planning for the first human trials as a potential treatment of inflammatory diseases are underway.

Mann D L *Circulation Research* **2011;108:1133-1145**

Potential Therapies for TLRs in Atherosclerosis

- Eritoran (E5564), which reduces the binding of lipid-A (the biologically active part of the LPS molecule), reduced mortality by 6.4% compared with the placebo group in a phase II sepsis trial, and is currently undergoing evaluation in phase III sepsis trials.

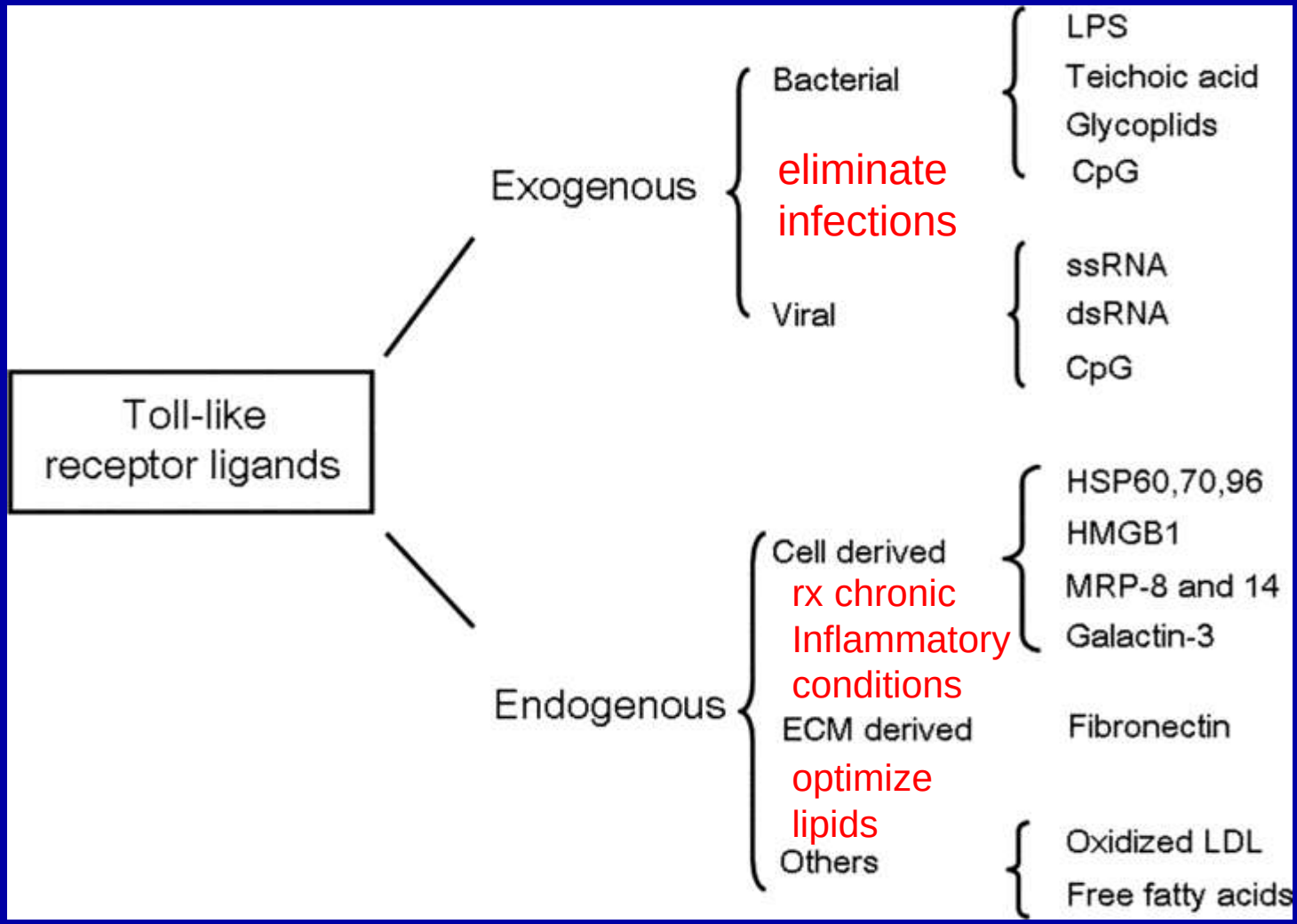
- Ibudilast (AV411) is a novel TLR4 antagonist that suppresses proinflammatory cytokines such as TNF and IL-6. It may also induce the antiinflammatory cytokine IL-10. Ibudilast is undergoing phase II trials for opioid dependence (NCT00723177).

Mann D L *Circulation Research* **2011;108:1133-1145**

BD Method Idea Regarding Therapies for TLRs in Atherosclerosis

- Treat the underlying reasons for sustained TLR activation!

Potential Exogenous and Endogenous TLR Ligands.



Mann D L Circulation Research 2011;108:1133-1145

TLR4 an Integral Component of Insulin Resistance (IR)

- Obesity generates increased FFAs which are linked to inflammation and IR
- FFAs are a ligand for TLR4
- TLR4 is thought to be the mediator for the inflammation and IR associated with obesity

Kim F et al. Circulation Research 2007;100:1589-1596

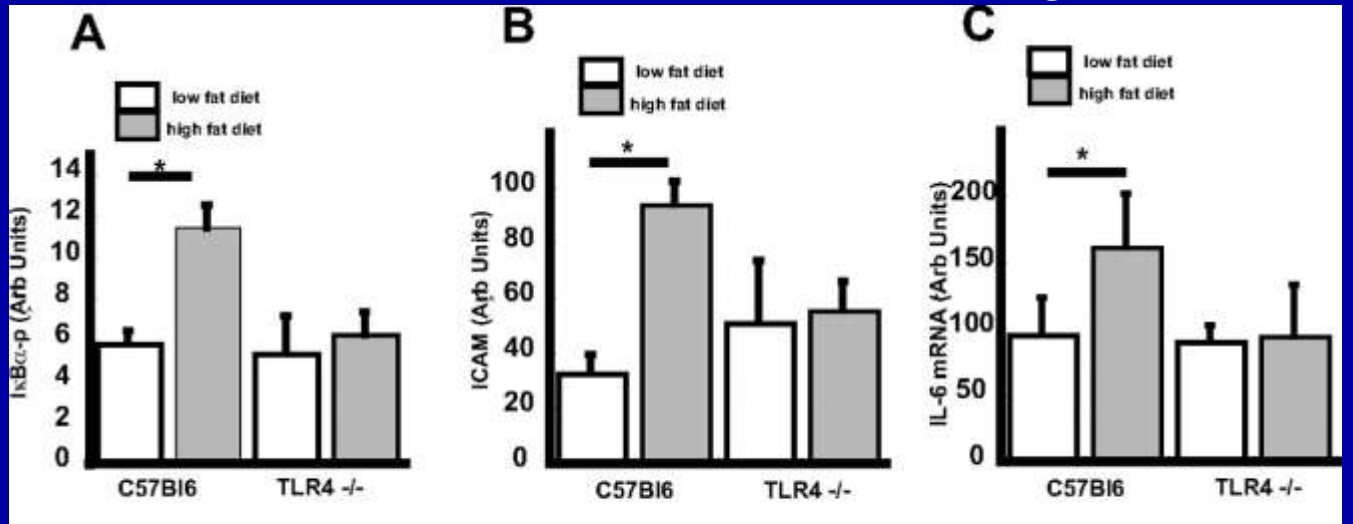
TLR4 an Integral Component of Driving the Inflammation of Insulin Resistance

- Fed high fat diet to normal mice and mice devoid of TLR4
- Lysated thoracic aorta samples after eight weeks
- Despite same weight gain, the mice without TLR4 did not develop increased levels of IKKbeta, ICAM, IL-6
- These are elements known to be involved with the development of inflammation associated with IR

Kim F et al. Circulation Research 2007;100:1589-1596

TLR4 an Integral Component of Insulin Resistance

Effect of 8 weeks of HF feeding



A) IKKbeta did not go up in mice without TLR4
(Activation of IKKbeta is associated with NF-kB activation)
B) Chemo-attractant proteins did not go up in mice without TLR4
C) Cytokine IL-6 did not go up in mice without TLR4

Strong signal that TLR4 plays a vital role in the inflammation associated with IR

Kim F et al. Circulation Research 2007;100:1589-1596

TLR4 an Integral Component of Creating the Resistance to Insulin

- To assess whether or not TLR4s are involved in the development of IR in vascular tissue, a subset of mice from each group received IP injections of either placebo or insulin (2 U in 300 L of normal saline) and 15 minutes later, the thoracic aorta was removed and lysated

- IR impairs activation of phosphorylation of Akt (pAkt) and eNOS (peNOS)

- The samples were analyzed for levels of pAkt and peNOS

Kim F et al. Circulation Research 2007;100:1589-1596

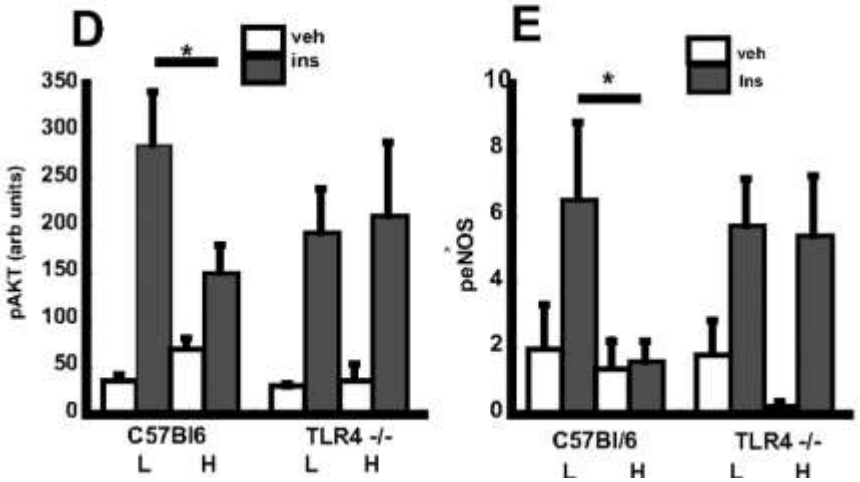
TLR4 an Integral Component of Insulin Resistance

Effect of IP insulin on markers of insulin sensitivity

When you are sensitive to insulin, insulin administration will immediately increase pAKT and phosphorylated eNOS

Normal mice on LF diet remain sensitive to insulin and have expected increases in pAKT and peNOS
Normal mice on HF diet develop IR and do not get as much increase in pAKT or peNOS

Mice without TLR4 appear to remain sensitive to insulin regardless of LF or HF diet



Strong signal TLR4 is involved in development of IR

Kim F et al. Circulation Research 2007;100:1589-1596

TLR4 an Integral Component of Insulin Resistance: Inflammation & IR

- Thoracic aortic cultures from both type of mice; exposed to three hours of FFAs; analyzed change in IKKbeta (inflammation) and peNOS (IR)

- In the mice without TLR4s, there was no increase in the levels

Kim F et al. Circulation Research 2007;100:1589-1596

TLR4 an Integral Component of Insulin Resistance

- Incubated human microvascular endothelial cells (HMECs) in the presence of FFAs.
- FFAs caused activation of IKKb; NF-kB; increased ICAM and IL-6; induced IR
- All of these effects were prevented either by decreasing TLR4 expression or by inhibiting MyD88 signaling.

Kim F et al. Circulation Research 2007;100:1589-1596

TLR4 an Integral Component of Insulin Resistance

- These findings implicate the TLR4 pathway as a critical factor in the deleterious effects of FFAs on endothelial insulin signaling, NO production and arterial inflammation.

- Documents the key role for TLR4 in the mechanism for obesity inducing vascular inflammation and IR.

Kim F et al. Circulation Research 2007;100:1589-1596

Toll Like Receptor 7 (TLR7) is Anti-inflammatory

- TLR7 is protective in atherosclerosis by shaping monocyte/macrophage function towards an ‘alternatively activated’ anti-atherogenic phenotype.

- This challenges the current paradigm that all TLRs are pathogenic in atherosclerosis

Salagianni, M., et. al. *Circulation. published online July 11, 2012*
http://circ.ahajournals.org/content/early/2012/07/11/CIRCULATIONAHA.111.067678

Toll Like Receptor 7 (TLR7) is Anti-inflammatory

- Functionally inactivated TLR7 mice (FI) developed more extensive atherosclerosis than their controls despite having lower cholesterol levels.
- FI mice developed more vulnerable plaques: increased necrotic core, increased macrophages, decreased collagen, thinner fibrous cap.
- FI mice had higher levels of circulating M1 macrophages and MCP-1
- FI mice responded with greater inflammation when TLR2 &4 were stimulated.

Salagianni, M., et. al. *Circulation. published online July 11, 2012*
http://circ.ahajournals.org/content/early/2012/07/11/CIRCULATIONAHA.111.067678

Toll Like Receptor 7 (TLR7) is Anti-inflammatory

- Genome-wide expression studies were carried out in human carotid plaque samples
- 127 carotid endarterectomy and 10 carotid control specimens were analyzed
- TLR7 was consistently up-regulated at the mRNA level in atherosclerotic lesions
- TLR7 expression was reduced in active cigarette smoking and unaffected by DM, BP, obesity, gender, or medication

Salagianni, M., et. al. *Circulation. published online July 11, 2012*
http://circ.ahajournals.org/content/early/2012/07/11/CIRCULATIONAHA.111.067678

Toll Like Receptor 7 (TLR7) is Anti-inflammatory

- Examined whether TLR7 expression was functionally important by stimulating cell cultures of endarterectomy specimens with the TLR7 agonist imiquimod

- Stimulation reduced inflammation, decreased presence of platelets and increased deposition of collagen and extracellular matrix

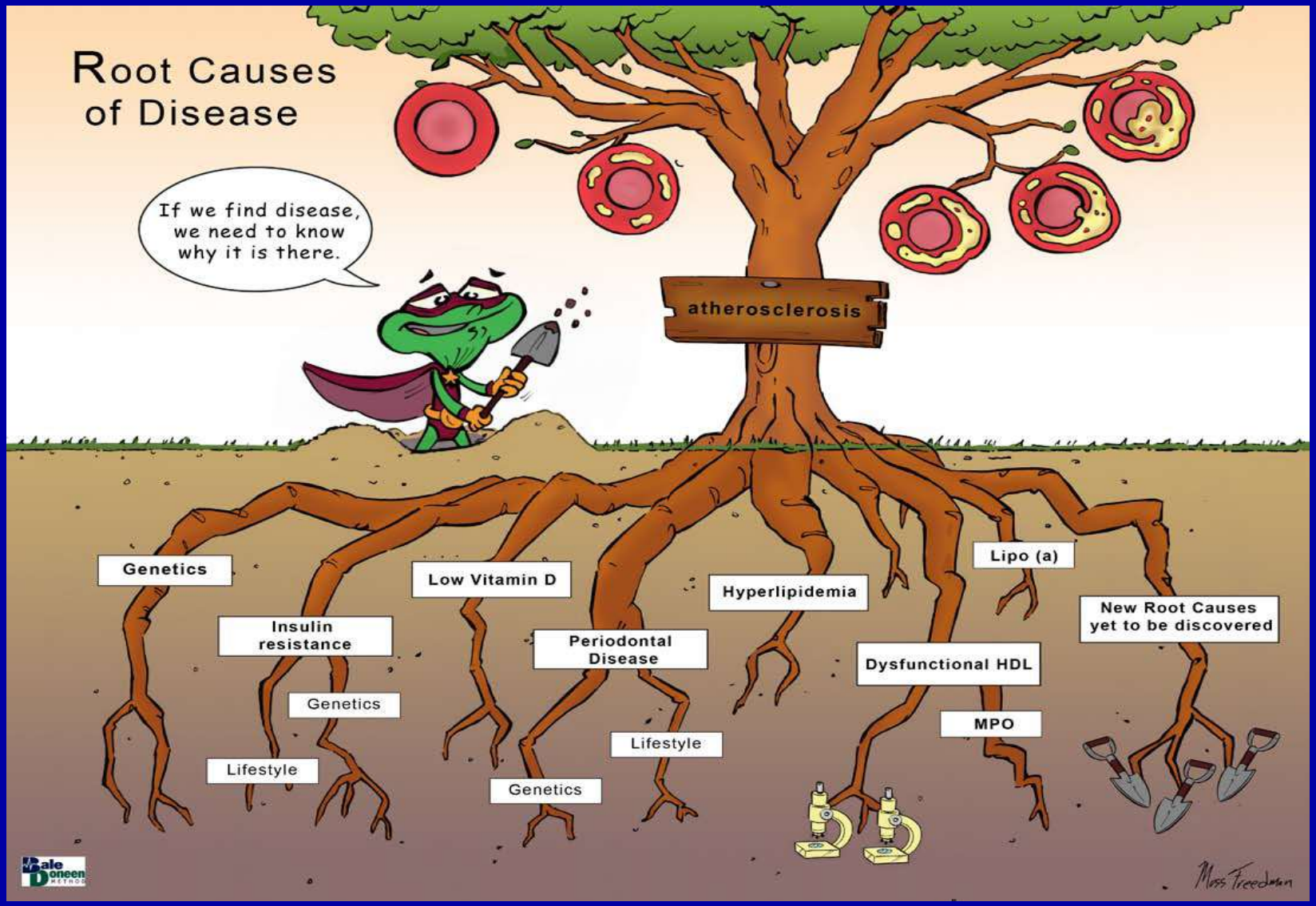
Salagianni, M., et. al. *Circulation. published online July 11, 2012*
http://circ.ahajournals.org/content/early/2012/07/11/CIRCULATIONAHA.111.067678

Toll Like Receptor 7 (TLR7) is Anti-inflammatory

- Well established that TLR2 and TLR4 respond to ‘danger’ signals induced during hypercholesterolemia or tissue stress to promote macrophage accumulation and inflammation in the vessel wall.
- We now expand this scheme by adding TLR7, a receptor that senses viral and self single stranded RNA.
- In the context of atherosclerosis TLR7 favors the generation of M2 macrophages aimed at restoring homeostasis.
- TLR7 inhibits atherosclerosis and promotes plaque stabilization.

Salagianni, M., et. al. *Circulation. published online July 11, 2012*
http://circ.ahajournals.org/content/early/2012/07/11/CIRCULATIONAHA.111.067678

Roots



Red Meat Increases Risk of Ischemic Stroke

- Meta-analysis 4 prospective studies with 6,420 ischemic & 1,276 hemorrhagic strokes and 289,076 pts; analyzed risk for each daily severing of red meat (fresh, processed and total)

- One serving equals 50 g (~2oz.) of processed meat and 100 to 120 g of fresh red meat and total red meat (11-22 yr follow-up).

- Adjusted relative risk for ischemic stroke

  ‘fresh’ RR- 1.13 (95% CI, 1.00 –1.27)

  ‘processed’ RR- 1.15 (95% CI, 1.06 –1.24)

  ‘total’ RR- 1.12 (95% CI, 1.05–1.19)

- No significant associations for hemorrhagic stroke

Kaluza, J., PhD, et. al. ***Stroke. 7/31/2012;43:00-00***

OSA Increases CV Risk

- Meta-analysis showed greater likelihood of stroke or CV events with increasing apnea-hypopnea index values
- 5 studies with 8,435 OSA pts - significant risk for stroke:

  OR- 2.24 (95% CI, 1.57–3.19)
- 6 studies with 8,785 OSA pts - non-significant for ischemic heart disease (IHD)

  OR- 1.56 (95% CI, 0.83–2.91)
- 5 studies that recruited mainly men - significance for IHD

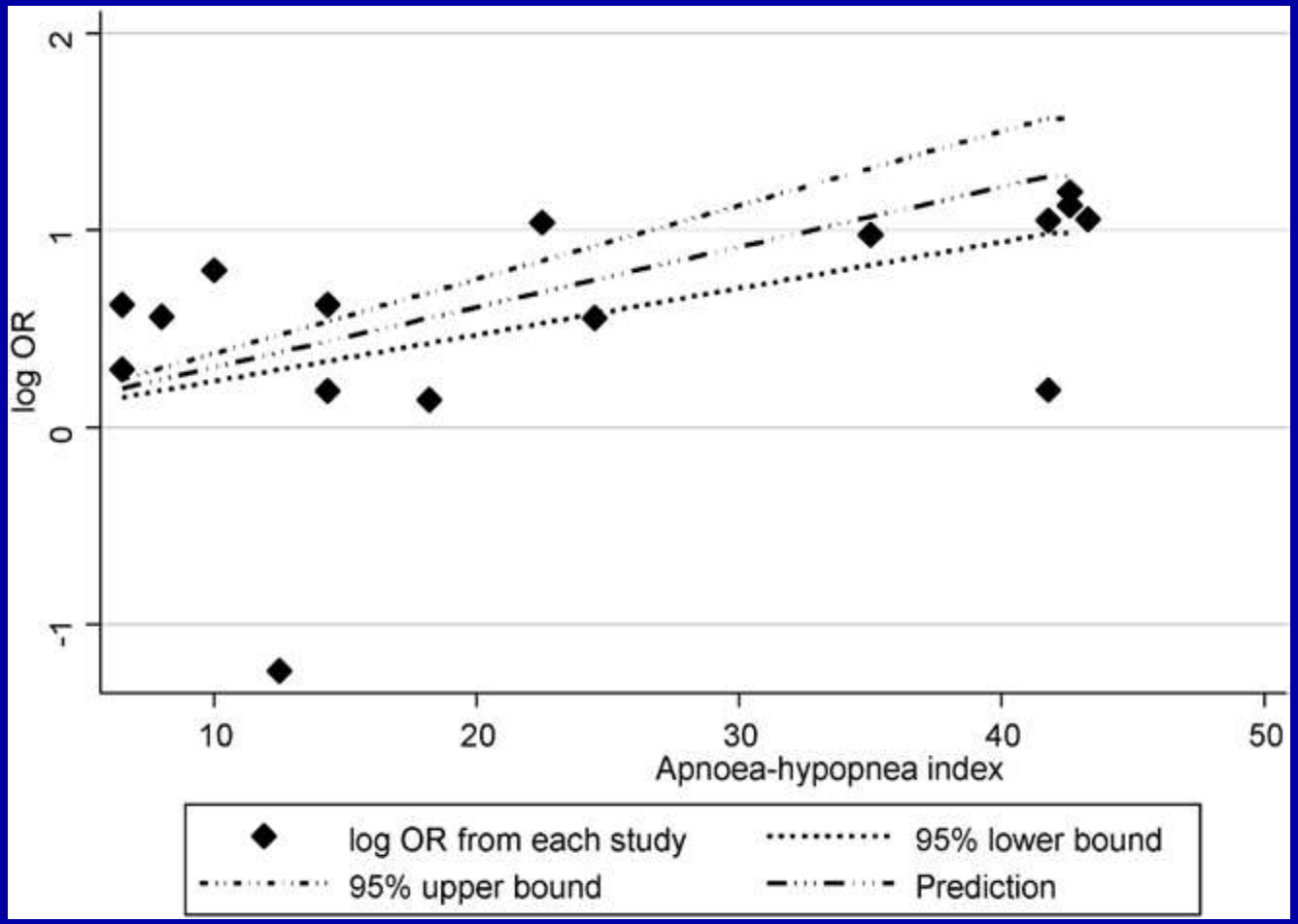
  OR -1.92 (95% CI, 1.06–3.48)
- 2 studies with 2,446 OSA pts – significant CV death

  OR- 2.09 (95% CI, 1.20–3.65)

Follow-up 3-12 yrs.; up to 50% of pts. were treated for OSA

Loke, Y. K., MD, et. al. ***Circ Cardiovasc Qual Outcomes. 8/2012;5:00-00*** online before print July 24, 2012, doi: 10.1161/CIRCOUTCOMES.111.964783

OSA Increases CV Risk



Regression analysis for odds ratio of stroke or serious cardiovascular events according to degree of apnea-hypopnoea index (AHI).

Loke, Y. K., MD, et. al. ***Circ Cardiovasc Qual Outcomes. 8/2012;5:00-00*** online before print July 24, 2012, doi: 10.1161/CIRCOUTCOMES.111.964783

Heart Acts as an Endocrine Organ Through Natriuretic Peptides (NPs)

- Atrial and B NPs effect natriuresis, diuresis and vasodilitation via renal and endothelial receptors
- Recently discovered that adipose tissue receptors also exist for NPs
- The cardiac NPs effect the metabolism of fat cells

Bordicchia, M., et. al., J *Clin Invest. 2012;122(3):1022–1036*

BNP and Atrial NP from the Heart Act on Adipose Cells to Increase Brown Fat and Reduce Weight

- In adipose tissue, the NPs increase lipolysis
- NPs also increase in the expression of brown adipocyte–associated genes
- Brown adipocytes promote increased energy utilization and heat generation (thermogenesis)
- Net effect is to protect against weight gain and glucose intolerance

Thomas J. Wang, *NEJM* 7/26/2012. 367;4: 377-8

Bordicchia, M., et. al., J *Clin Invest. 2012;122(3):1022–1036*

BNP and Atrial NP from the Heart Act on Adipose Cells to Increase Brown Fat and Reduce Weight

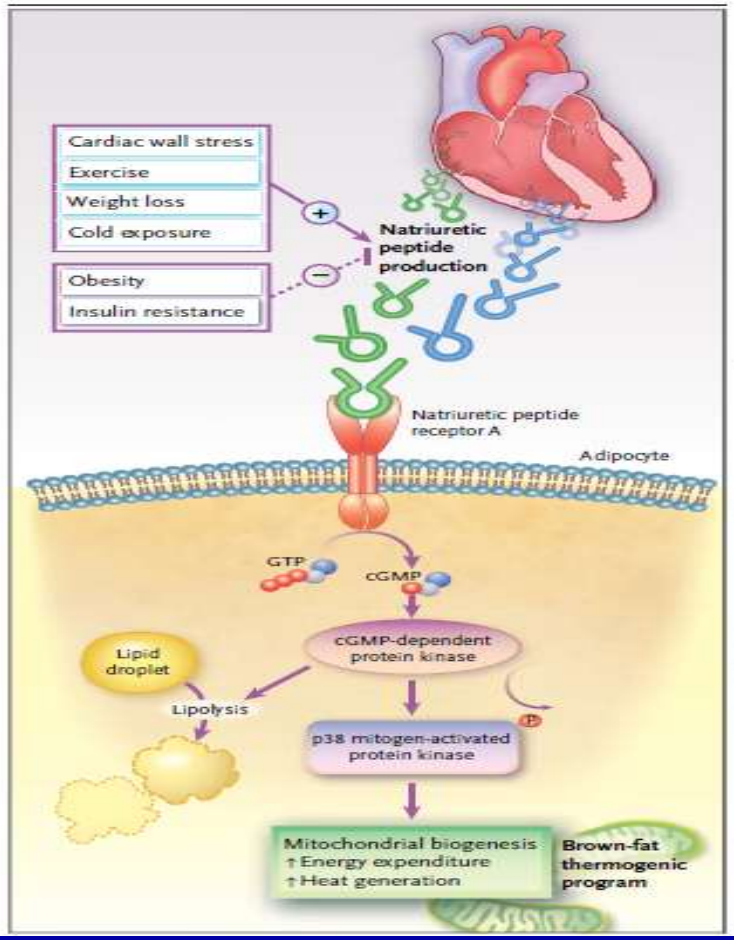


Figure 1. Natriuretic Peptides, Metabolic Traits, and Adipocyte Function.

The heart synthesizes peptide hormones known as the natriuretic peptides. Expression of natriuretic peptides is up-regulated by cardiac wall stress, weight loss, exercise, and exposure to cold and appears to be suppressed by obesity and insulin resistance. A recent study by Bordicchia and colleagues[1] shows that the natriuretic peptides are important regulators of adipocyte function. The receptor target for circulating natriuretic peptides is natriuretic peptide receptor A (NPR-A), a membrane-bound guanylyl cyclase. Binding of natriuretic peptides to NPR-A on adipocytes leads to the production of intracellular second messenger cyclic guanosine monophosphate (cGMP). The cGMP activates cGMP-dependent protein kinase (PKG). PKG-mediated phosphorylation triggers a cascade that includes enhanced lipolysis and activation of p38 mitogen-activated protein kinase, turning on the brown-fat thermogenic program. GTP denotes guanosine triphosphate.

NPs increase with exercise, wt. loss, cold exposure and cardiac stress

NPs decrease with IR and obesity

Thomas J. Wang, *NEJM* 7/26/2012. 367;4: 377-8

Observed BNP Paradox is Solved!!

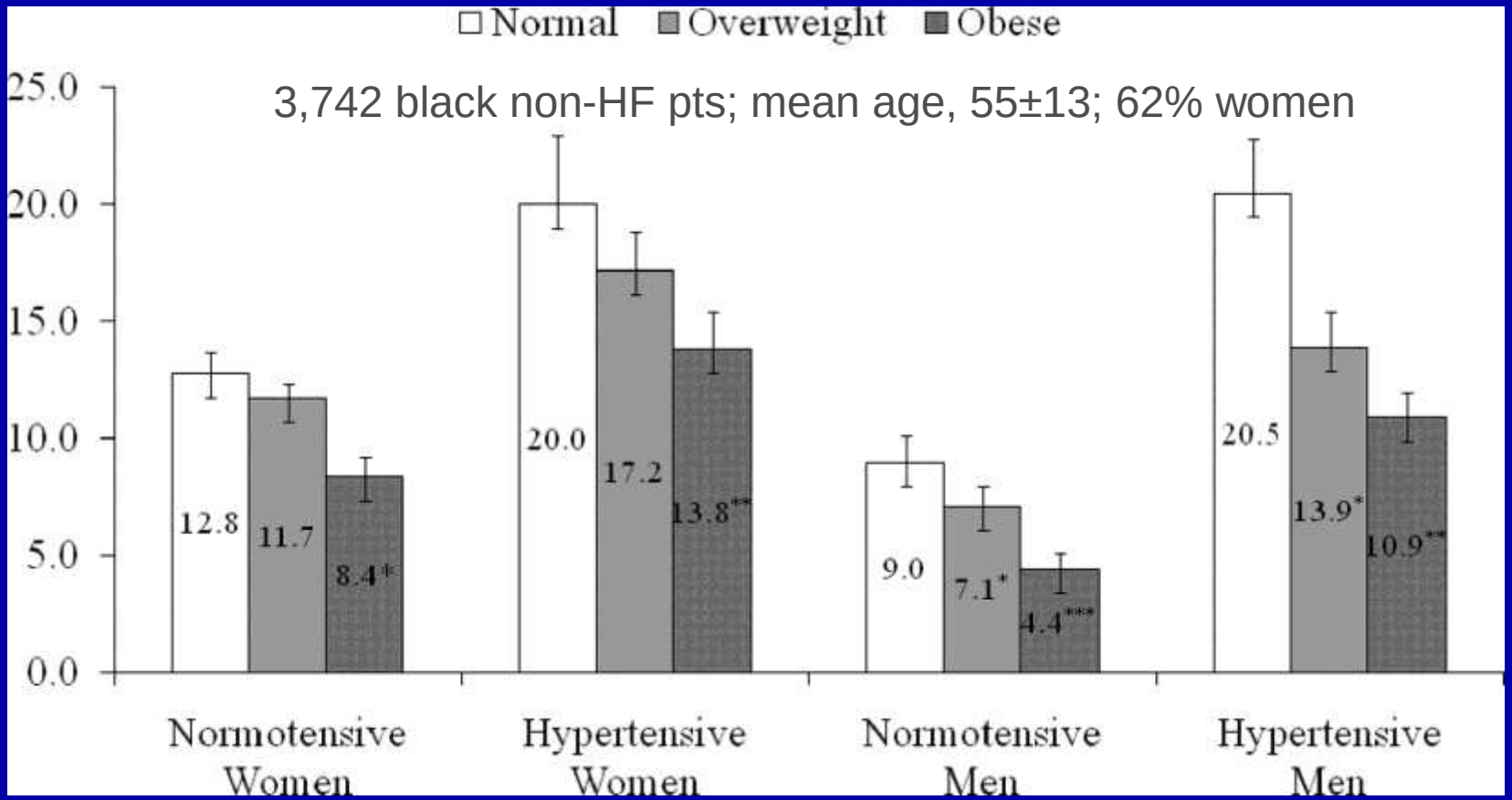
BNP Paradox ("natriuretic handicap") : Lower BNP with Higher BMI

- Observed in obese non-hispanic's from Framingham Offspring Study and now in obese blacks from Jackson Heart Study

Fox E., MD, MPH, et. al. ***Circulation.***, *8/2011; 124: 1021-1027*

BNP Levels Lower with Obesity

Sex-specific adjusted means and SEs for BNP by BMI and hypertension status.



adjusted for age, MI, DM, smoking, BP stages, creatinine, echo findings

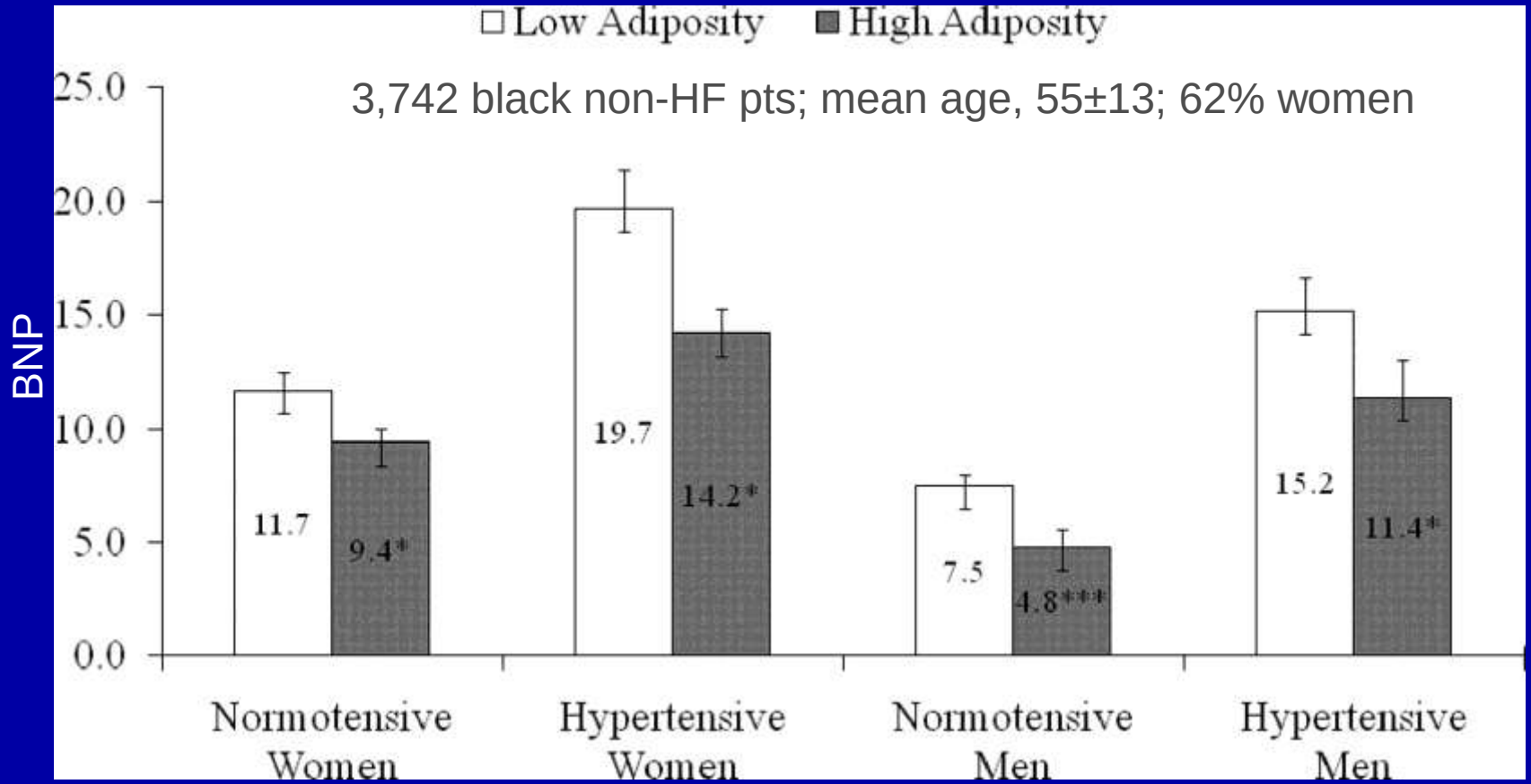
Fox E R et al. Circulation 2011;124:1021-1027

American Heart Association
Learn and Live

Bale Doneen METHOD

BNP Levels Lower with Obesity

Sex-specific adjusted means and SEs for BNP by adiposity (waist) and BP status.



Fox E R et al. Circulation 2011;124:1021-1027

American Heart Association
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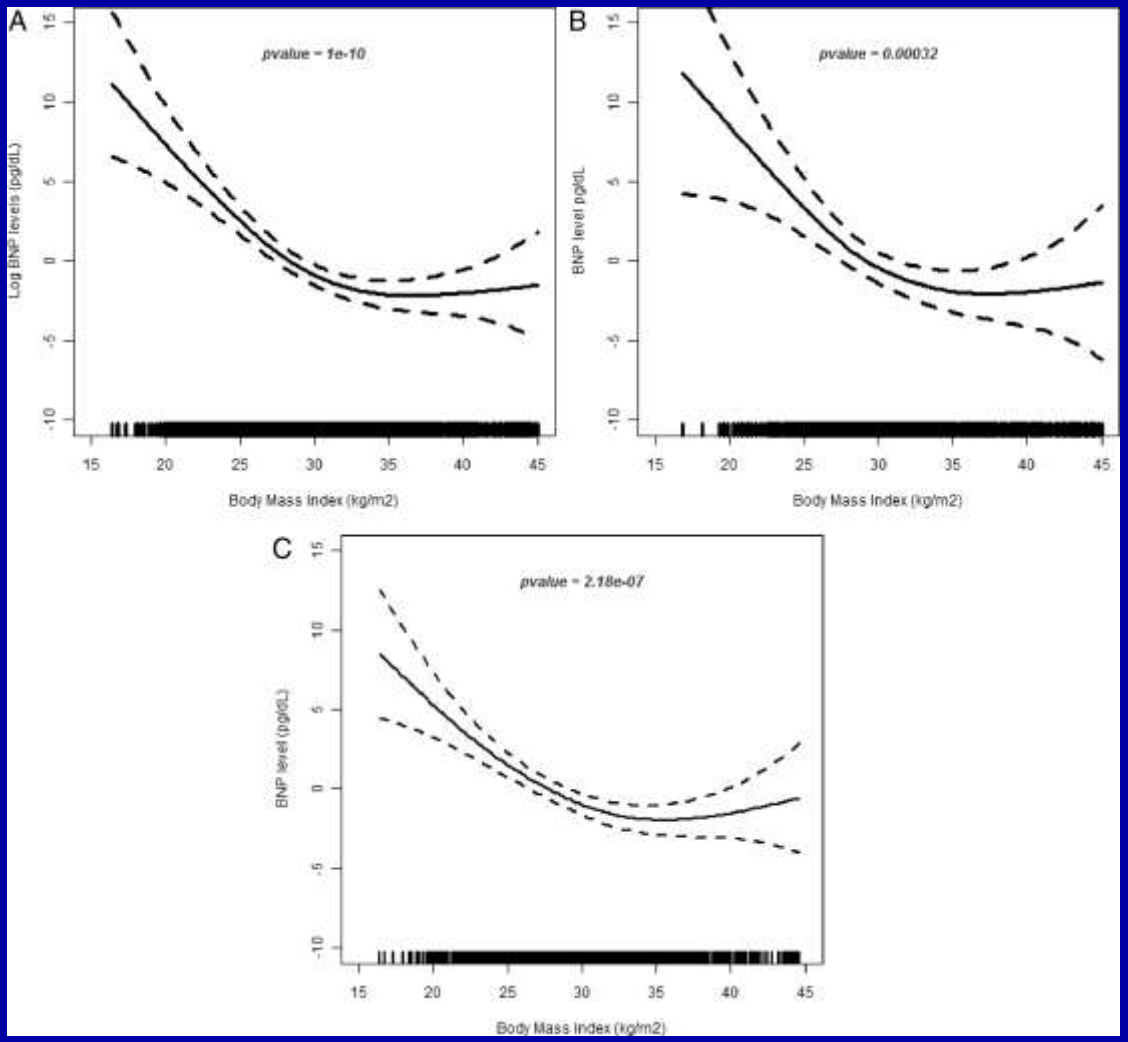
BNP Levels Lower with Obesity: flattens once BMI ≥40

A through C, Relation of (BNP) to (BMI).



Fox E R et al. Circulation 2011;124:1021-1027

American Heart Association
Learn and Live

Dale Doneen Method

Normal Weight New Onset Diabetics at Higher Mortality Risk

- 2,625 pts >40 yo with incident diabetes; 27,125 person-yrs of follow-up; 12% with BMI 18.5 to 24.99 (normal); 449 deaths

- Hazard ratio for death was higher in normal BMI pts

  For CV : 1.52 (95% CI, 0.89-2.58)

  For non-CVD: 2.32 (95% CI, 1.55-3.48)

  above HRs adjusted for: demographic characteristics, BP, lipid levels, waist and smoking

Carnethon, M. R., PhD. *JAMA*. 8/8/2012;308(6):581-590

Normal Weight New Onset Diabetics at Higher Mortality Risk

- "obesity paradox" has been observed in asso. with several chronic conditions, including HF, CKD, and BP
- Paradox refers to evidence that overweight and obese pts have better outcomes than do leaner individuals

Carnethon, M. R., PhD. *JAMA*. 8/8/2012;308(6):581-590

BDM Hypothesis

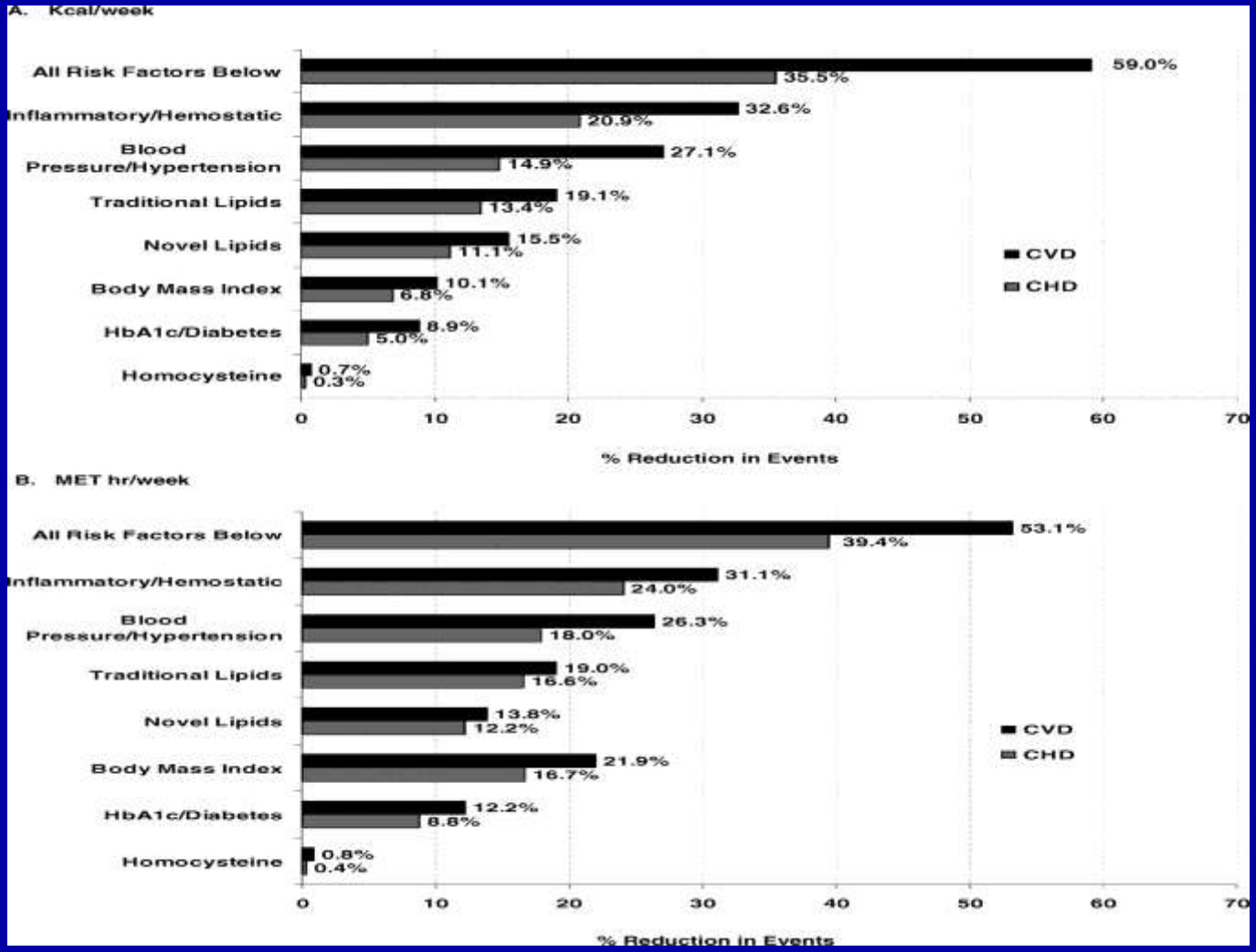
- 'Normal' BMI new onset diabetics have 'higher' BNP levels
- BNP was one of only two independent predictors of CV events in Framingham
- Many of these 'normal' BMI diabetics may have HF, CKD and hypertension

EDFROG IRA

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

Exercise: Greatest Benefit Rests with Reducing Arterial Inflammation

Percentage reduction in CVD events associated with physical activity that is explained by risk factors.



27,055 women WHS
followed 11 yrs
hsCRP; fibrinogen

Mora S et al. Circulation 2007;116:2110-2118

Caffeine Reduces Atherosclerosis

- Caffeine's metabolites, 1-methylxanthine and 1-methyluric acid, are potent antioxidants.
- The activity of these antioxidants are comparable to glutathione and significantly greater than ascorbic acid.
- This property of caffeine might reduce atherosclerosis

Mercer, J. R., et. al. ***Arterioscler Thromb Vasc Biol. 2012;32:00-00***
http://atvb.ahajournals.org/content/early/2012/08/02/ATVBAHA.112.251322

Caffeine Reduces Atherosclerosis

- ROS promote atherosclerosis via: inflammatory gene expression; oxidation of LDL; decreasing NO; cell proliferation, apoptosis and migration; DNA damage.

Mercer, J. R., et. al. ***Arterioscler Thromb Vasc Biol. 2012;32:00-00***
http://atvb.ahajournals.org/content/early/2012/08/02/ATVBAHA.112.251322

Caffeine Reduces Atherosclerosis

- Utilizing murine VSMCs which were stimulated to form ROS, it was demonstrated that caffeine and its most powerful anti-oxidant metabolite (1-MUA) significantly reduced ROS concentrations

- 1-MUA was 100 fold more effective than caffeine µmol/L / µmol/L

Mercer, J. R., et. al. ***Arterioscler Thromb Vasc Biol. 2012;32:00-00***
http://atvb.ahajournals.org/content/early/2012/08/02/ATVBAHA.112.251322

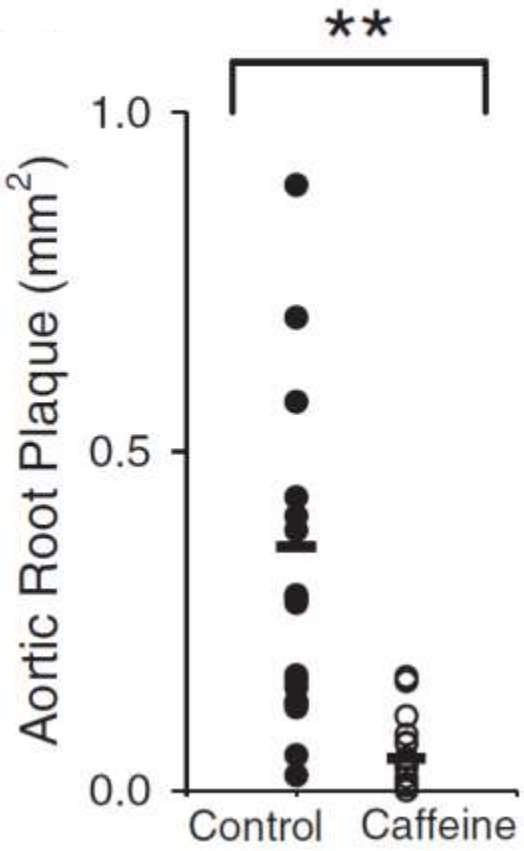
Caffeine Reduces Atherosclerosis

- Mice consumed a dose of caffeine required to reduce ROS in vitro for 14 weeks
- Tissues were examined; it was found that dose was effective
- Mice were then fed an atherogenic diet for 6 to 20 wks; some got caffeine at above dose and some received no caffeine
- Caffeine did not effect BP, weight gain or lipids
- Caffeine inhibited atherogenesis

Mercer, J. R., et. al. ***Arterioscler Thromb Vasc Biol. 2012;32:00-00***
http://atvb.ahajournals.org/content/early/2012/08/02/ATVBAHA.112.251322

Caffeine Reduces Atherosclerosis

Aortic root plaque area in control (n=18) or caffeine-treated mice (n=15) (***P≤0.01).*



Mercer, J. R., et. al. ***Arterioscler Thromb Vasc Biol. 2012;32:00-00***
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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.

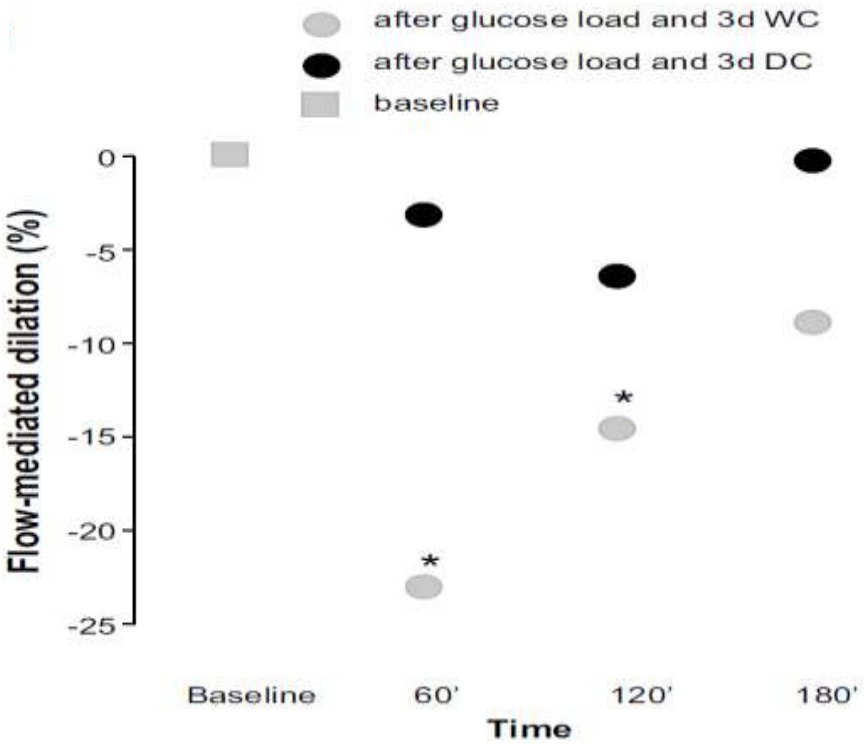
- At end of each treatment phase subjects underwent OGTT and endothelial function and oxidative tests were performed.

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

Dark Chocolate Mitigates the Negative Arterial Effects of Hyperglycemia: ET Dysfunction

Dark chocolate greatly reduced the decrease in FMD.

Essentially protected the subject from the endothelial dysfunction following a sugar load.



White chocolate did not protect subjects from endothelial dysfunction

Also DC compared with the WC increased baseline FMD 8.51±0.69 versus 7.88±0.68% with *P=0.03*

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

Dark Chocolate Mitigates the Negative Arterial Effects of Hyperglycemia: Oxidative Stress

- Oxidative stress, as measured by the total isoprostanes, improved at baseline with DC

  233.9±34.2 versus 208.1±22.8 pg/L; *P=0.04*

- Isoprostanes increased significantly at 30 & 60 mins. following glucose load after WC; no change after DC

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

Dark Chocolate Mitigates the Negative Arterial Effects of Hyperglycemia: BP

- DC prevented the increase in BP induced by the glucose load SBP: $p<0.0001$ and DBP: *P=0.019*
- With WC increases were in range of 4-8 mm/Hg

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

Hot Topics

Temperatures in July broke records set over 135 years ago!!

Case

None submitted. Please send cases to Amy for our reunion and for the CHL symposium!!

Upcoming Presentations

- 9/7/2012 – Amy and Brad speaking– U. of Nevada Medical School – Diabetic Conference
- 9/14-15/2012 – BD Method Preceptorship; San Antonio, TX – new one hour ethics course !
- 9/20/2012 – BD Method Reunion; Las Vegas, NV
- 9/21-22/2012 – Amy and Brad speaking – CHL Symposium; Las Vegas, NV
- 10/5 – Amy and Brad speaking AAPP – Ft. Lauderdale, FL
- 10/6- ***Bale/Doneen Method Highlighting Inflammatory Testing for the Reduction of Cardiovascular*** **Events. ;5 hr. CME; Chicago, ILL.**
- 11/2 New CME opportunity!!! — ***Vascular Inflammation: The Systemic / Oral Connection***; 6.5 hr. CME; Las Vegas, NV
- **11/6 -** *Independent Effects of Risk Factors and Treatment on Carotid Intima-Media Thickness Progression in a Community Practice*; **Birju Patel**, Michael Blaha, Steven Jones, Johns Hopkins Univ, Baltimore, MD; AHA Scientific Sessions; LA, CA

Open for Discussion