

Bale/Doneen Live Chat Session

4/11/2012

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

Complexity of Coronary Events

- One million Americans suffer acute coronary events annually and 400,000 die from those events
- Due to increasing obesity, DM and age of the population, it is estimated that over the next two decades healthcare dollars spent for CVD will triple: from \$273 billion to \$818 billion
- More effective solutions for prevention are needed

Arbab-Zadeh A et al. Circulation 3/6/2012;125:1147-1156

Complexity of Coronary Events

- 100 ACS deaths 76% had intraluminal thrombus
- 50% of those without a thrombus had evidence of healed myocardial infarctions
- This suggests that a coronary event in the past eventually led to myocardial scar formation and lethal arrhythmia.
- Thus, the vast majority (80% to 90%) of sudden coronary deaths are either the immediate result or a sequela of acute coronary arterial thrombosis.

Arbab-Zadeh A et al. Circulation 3/6/2012;125:1147-1156

Copyright Bale/Doneen Paradigm



Complexity of Coronary Events

- 623 pts followed for 3 yrs for occurrence of MI; all had Virtual Histology IVUS at baseline
- 313 had 595 thin cap fibroatheromas ; 26 resulted in events
- Suggests identification of potentially vulnerable plaque confers some increase in event risk, but it is less than generally assumed.

Complexity of Coronary Events

- Lots of clinical and pathological evidence that most plaque ruptures do not result in an 'event'
- Estimated that only about 10% of 'event' ruptures occur in 'virgin' ruptures
- These 'silent' ruptures lead to progression of plaque volume
- Plaque ruptures produce the majority of events, but the majority of plaque ruptures do not cause events

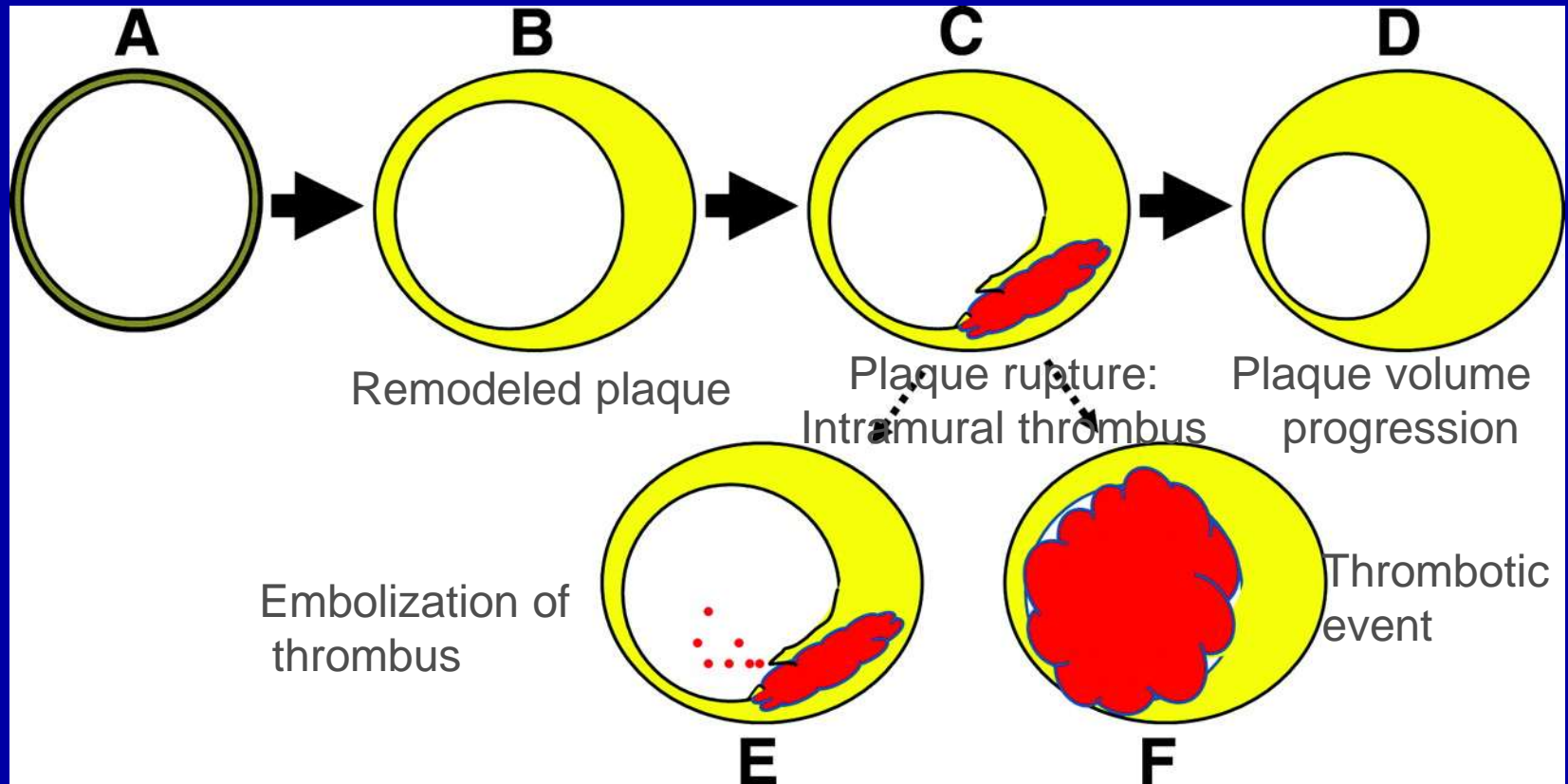
Arbab-Zadeh A et al. Circulation 3/6/2012;125:1147-1156

Copyright Bale/Doneen Paradigm



Complexity of Coronary Events

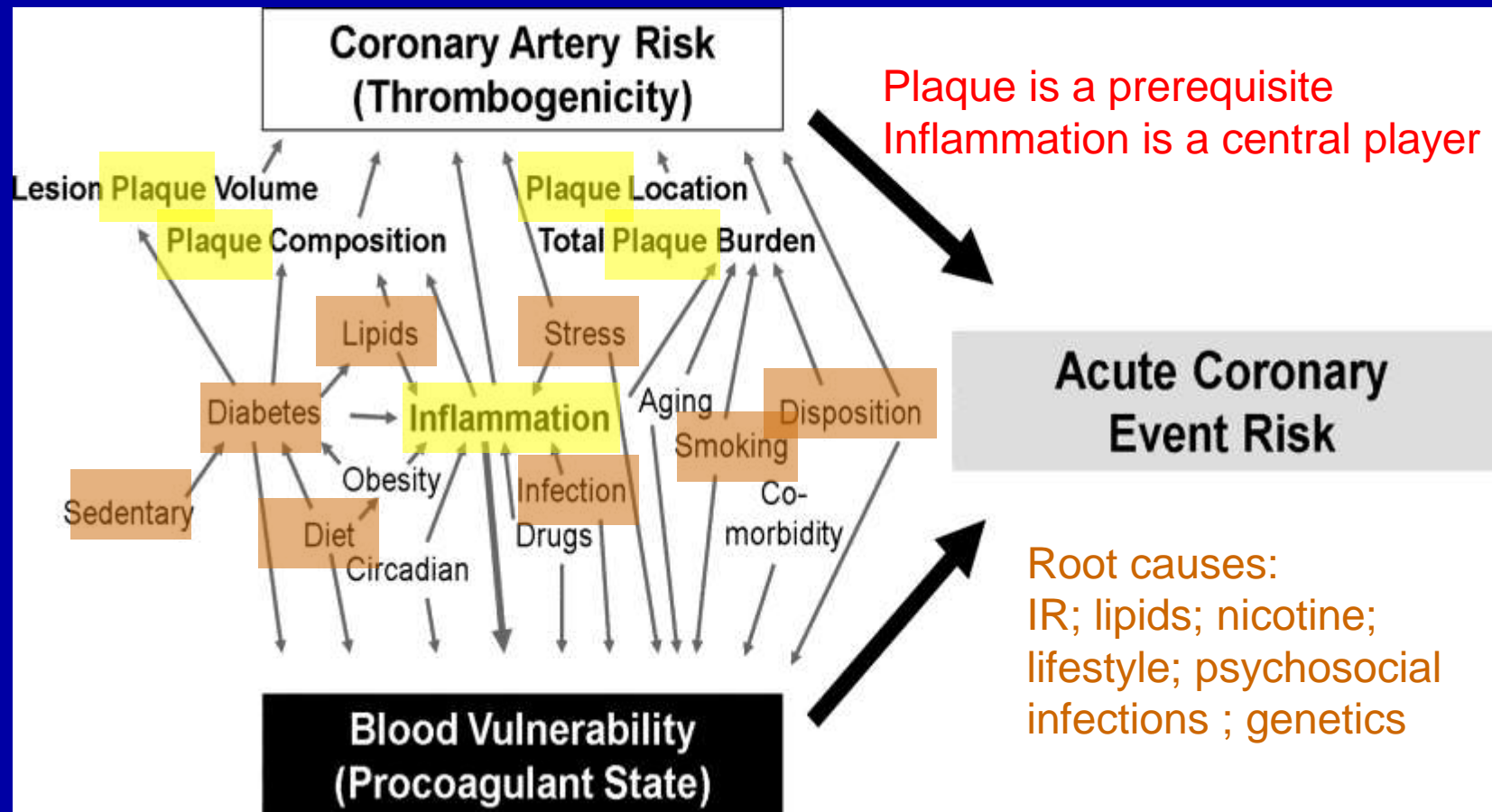
The progression of coronary artery disease.



Arbab-Zadeh A et al. *Circulation* 3/6/2012;125:1147-1156

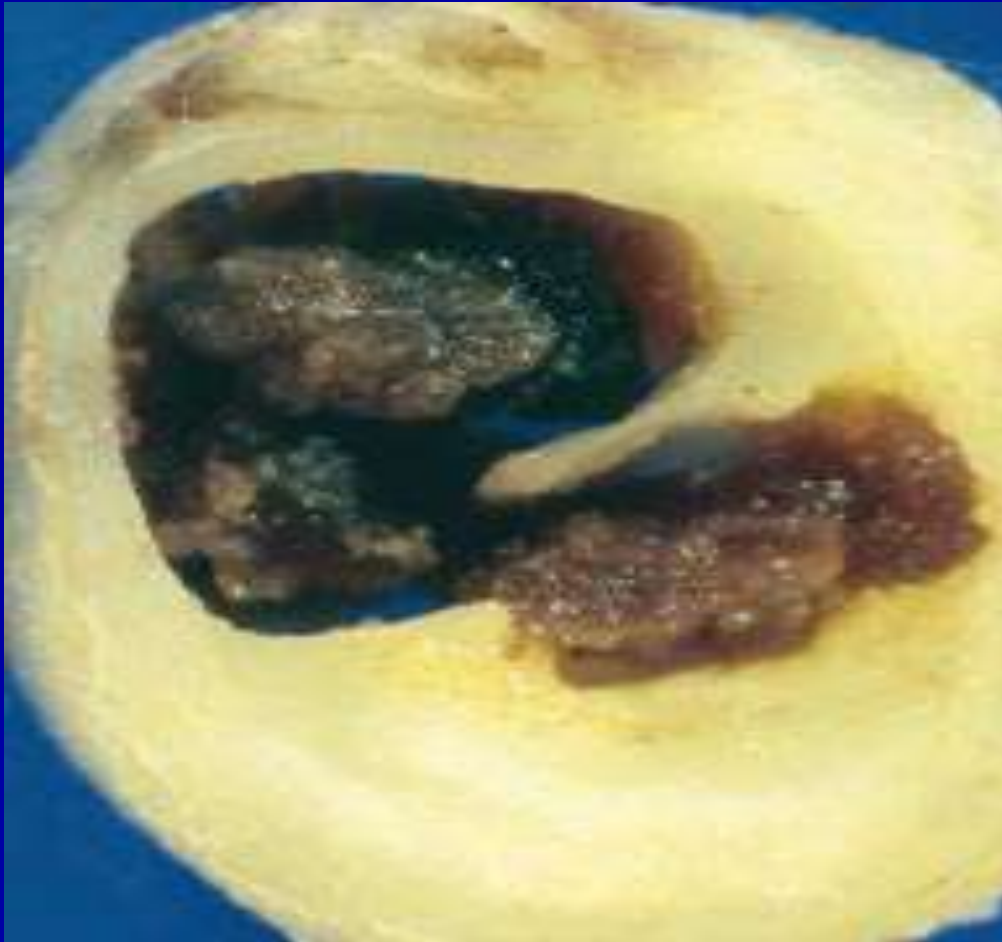
Complexity of Coronary Events

The complex interplay of factors contributing to ACS risk.



Arbab-Zadeh A et al. *Circulation* 3/6/2012;125:1147-1156

Typical Lesion of Acute Myocardial Infarction



Thrombosis caused by disruption. The cap of the plaque has torn and thrombus within the lipid core extends into and occludes the lumen.

Michael J Davies

Heart 2000;**83:361–366**

Copyright Bale/Doneen Paradigm

Complexity of Coronary Events

- In general, the greater the plaque burden and the activity of the CAD, the more plaque ruptures/erosions will occur.
- This increases the chance that one of these ruptures/erosions will coincide with a state that may permit the development of a vascular occlusive thrombus.

Complexity of Coronary Events

- Coronary atherosclerosis essentially is a *conditio sine qua non*.
- Therefore, *assessing its extent, severity, and location* must be considered fundamental for risk estimates

Complexity of Coronary Events

- Noninvasive vascular imaging has the potential to substantially affect our ability to identify and manage patients at risk of acute coronary events.
- A staged approach is likely necessary, with the least costly and most benign techniques applied to pts of seemingly low risk for screening purposes
- For example, ultrasound imaging of carotid artery (CIMT)

Complexity of Coronary Events

- The activity of CAD (rate of progression) appear to be promising for estimating coronary event risk.
- Factors influencing coagulation, eg, inflammatory states, must be considered to maximize **ability to predict events.**
- Intervening exclusively on single, potentially vulnerable plaques is unlikely to reduce the incidence of acute coronary events.
- Must address atherosclerosis as a systemic disease.

Complexity of Coronary Events

- Numerous biomarkers reflecting inflammatory and metabolic processes are associated with increased acute coronary event risk.
- Their role for evaluating individuals for their coronary event risk appears to be supportive rather than leading.

Arbab-Zadeh A et al. Circulation 3/6/2012;125:1147-1156

Complexity of Coronary Events

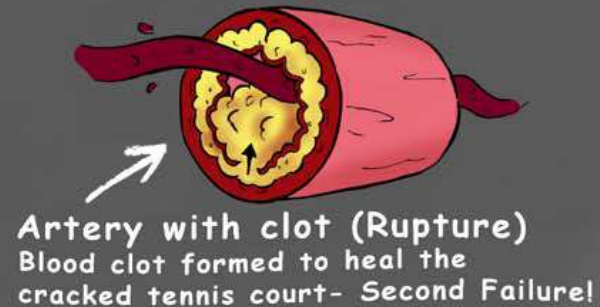
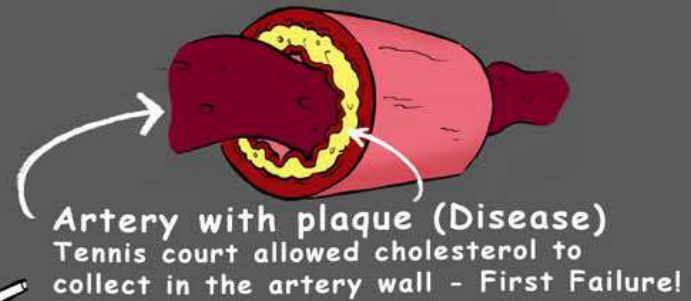
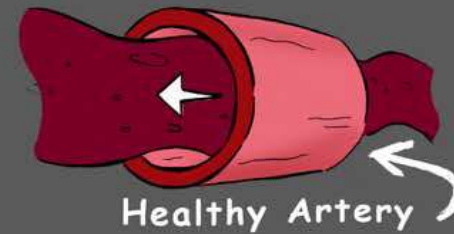
- Prevention takes a global approach and needs to be anchored in the disease
- EDFROG-IRA appears to fit extremely well with the recent article in Circulation:
Arbab-Zadeh A et al. Circulation 3/6/2012;125:1147-1156

Event Reality

Education

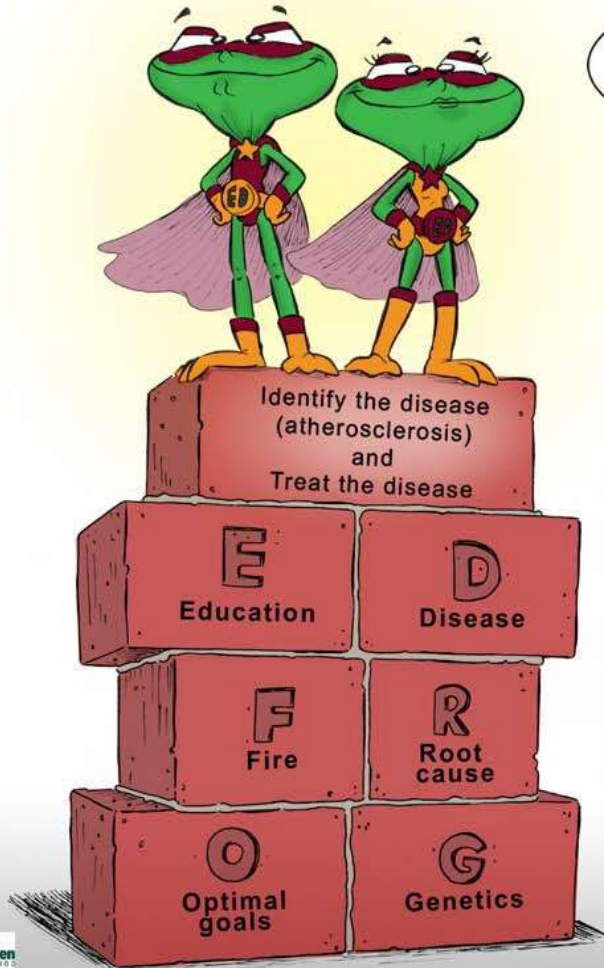
Please pay attention class. This might just save your life.

Tennis court =
inside lining
of artery
(endothelium)



What's the difference?

Bale/Doneen method

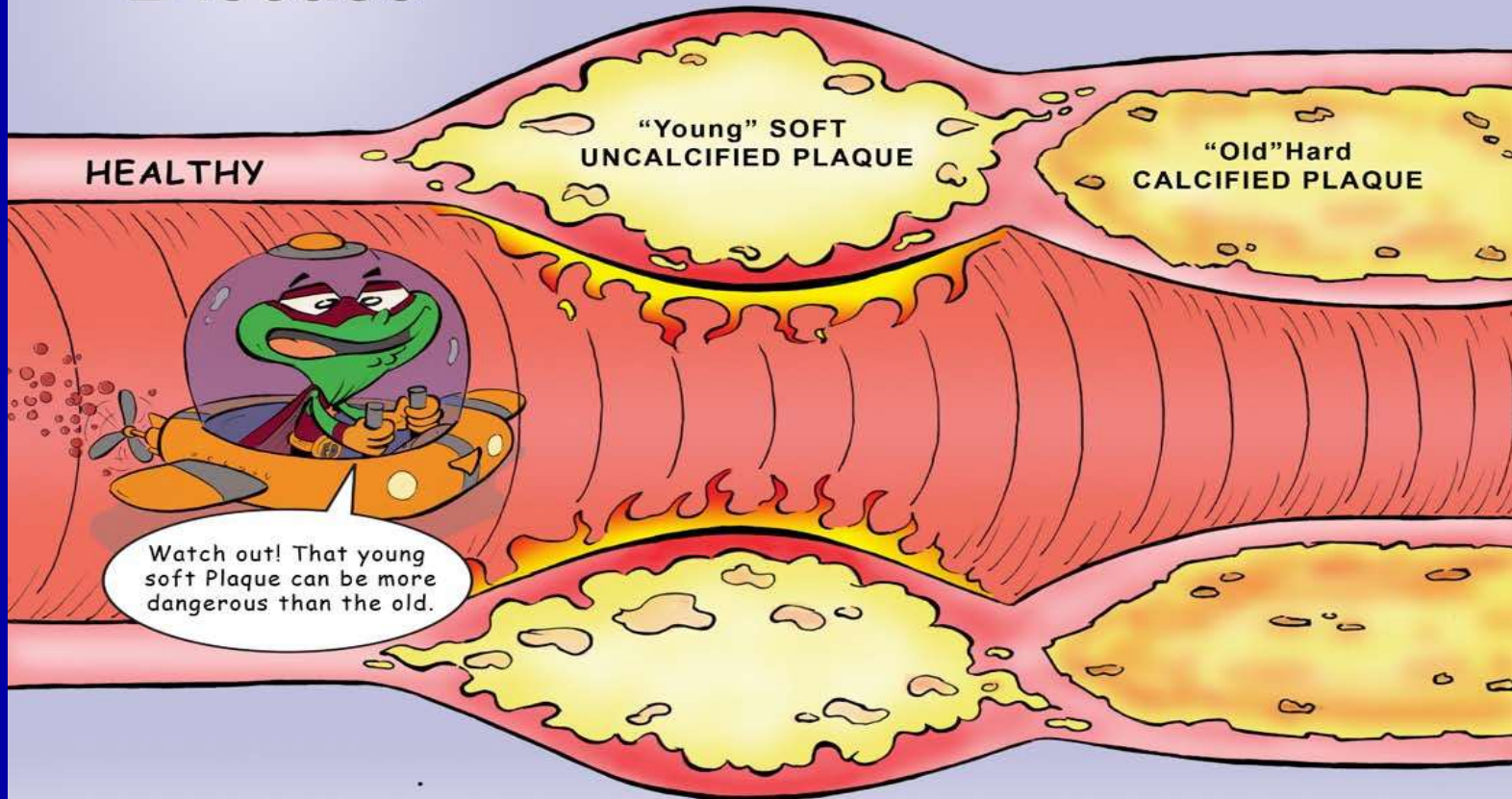


Standard of Care



Disease

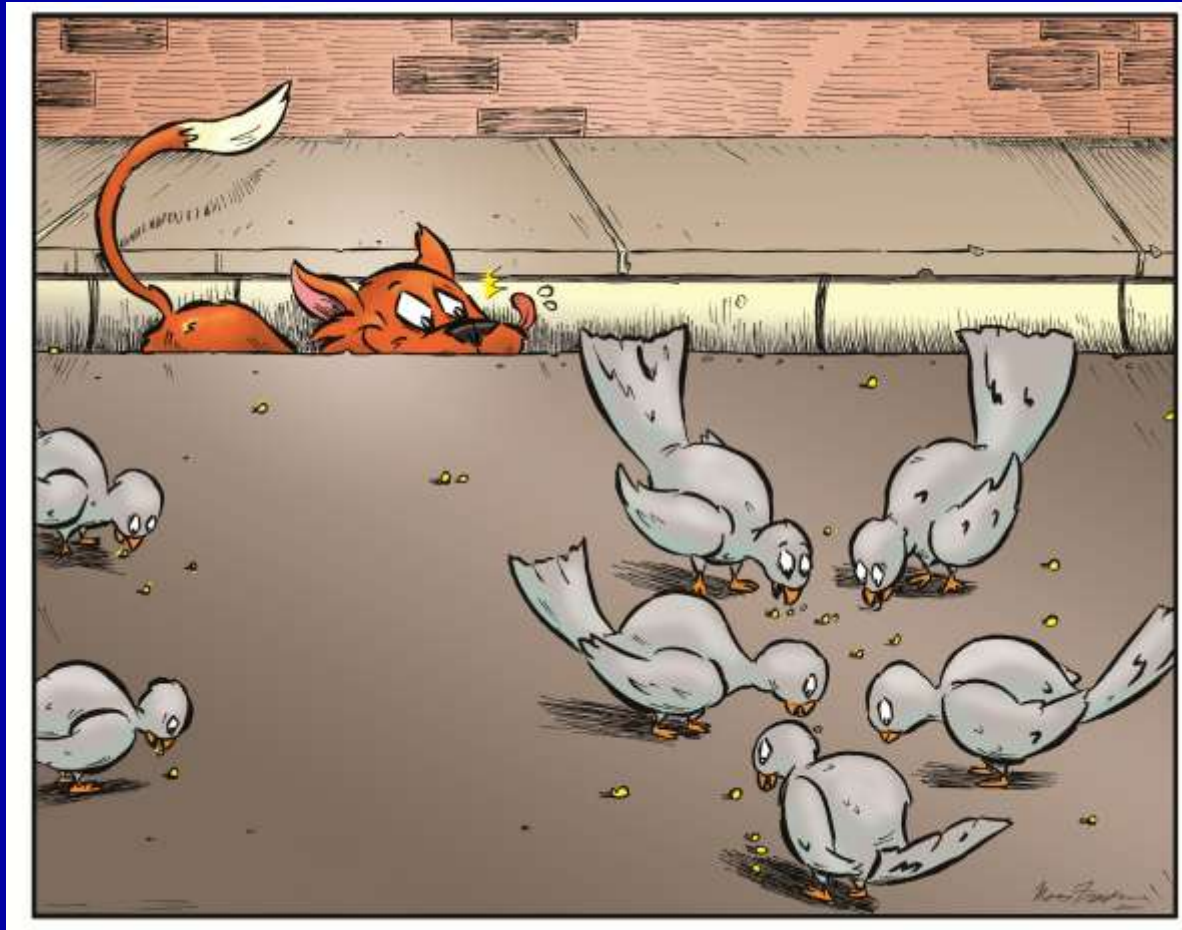
Disease



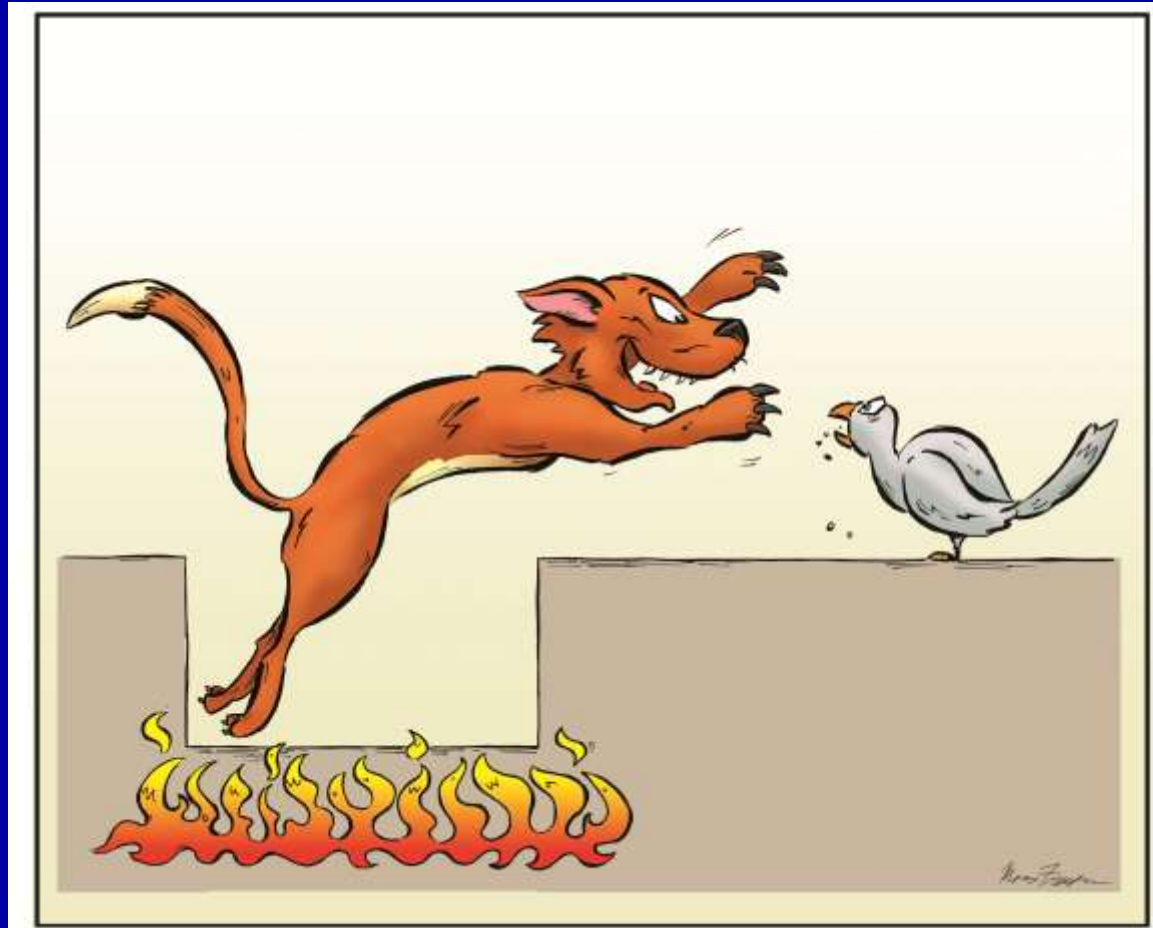
Plaque formation is an active process and its consistency changes over time. Some technologies (X-Rays) can only see hard calcified disease while others like ultrasounds can spot soft disease.



Miss Freedman

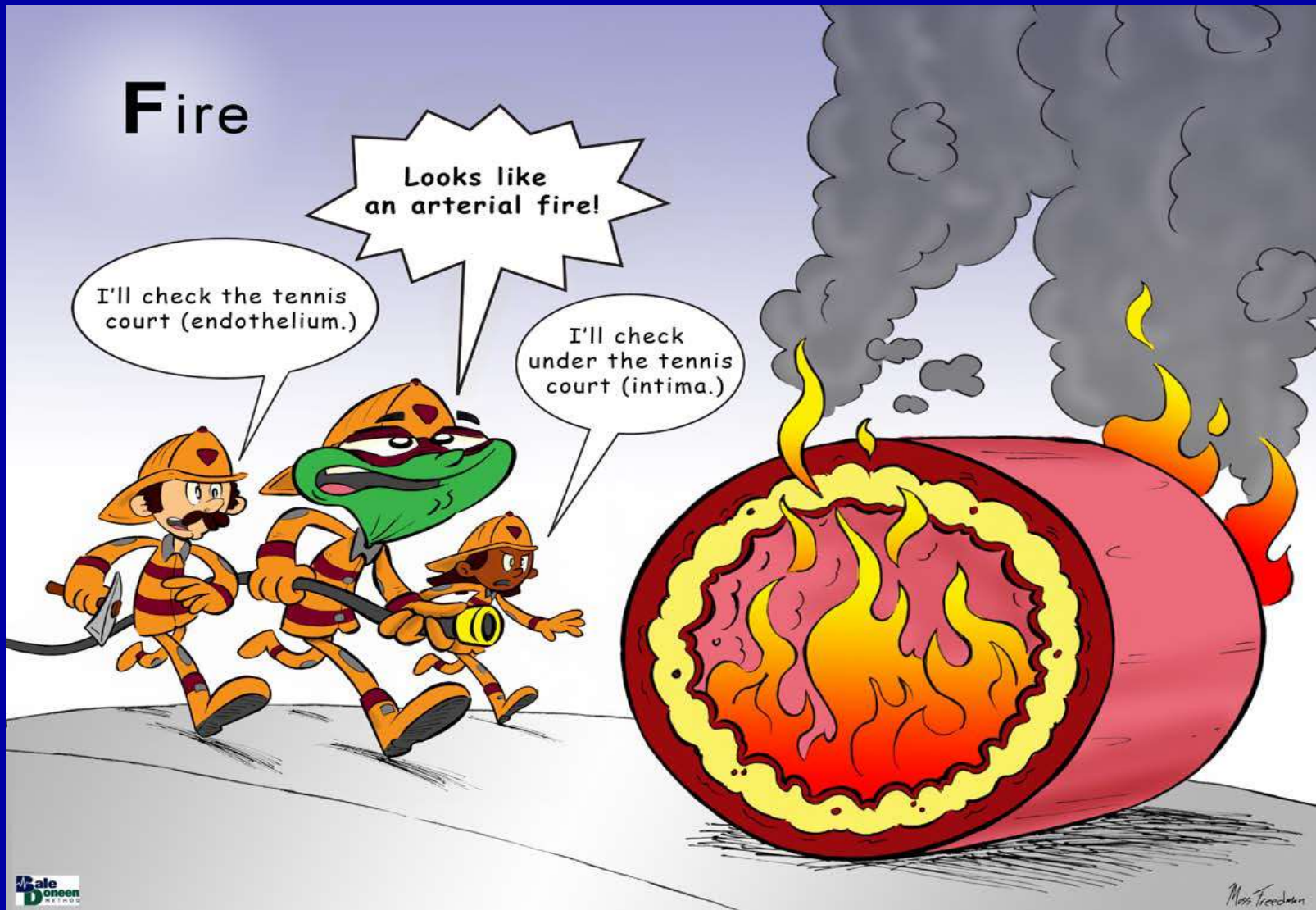


Copyright Bale/Doneen Paradigm



Copyright Bale/Doneen Paradigm

Inflammation



We need to keep those arteries cold so we can keep your body warm.

I know those hot arteries will make my body cold!



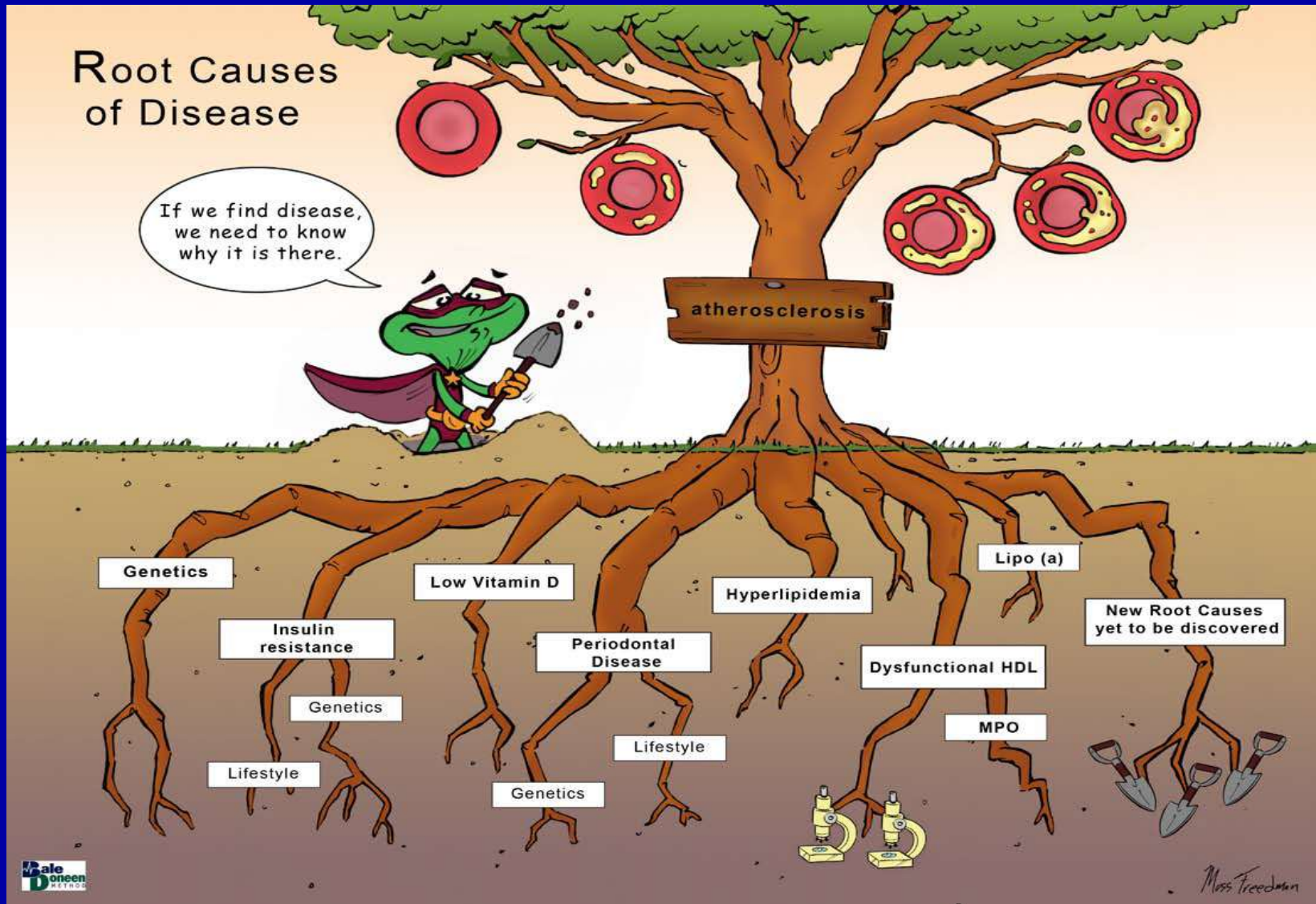
Bale
Doneen
PARADIGM

Miss Freedman

Roots

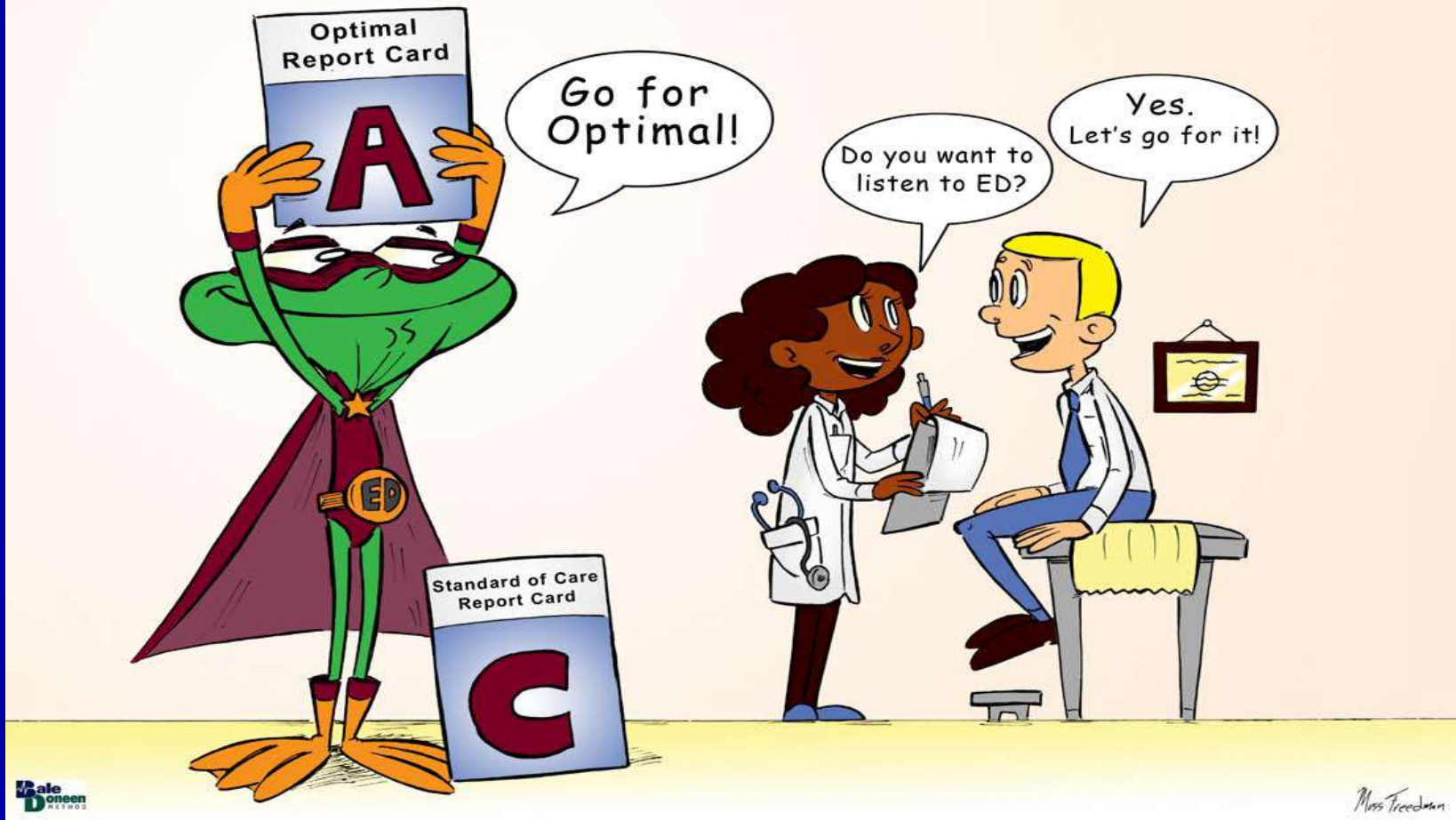
Root Causes of Disease

If we find disease, we need to know why it is there.



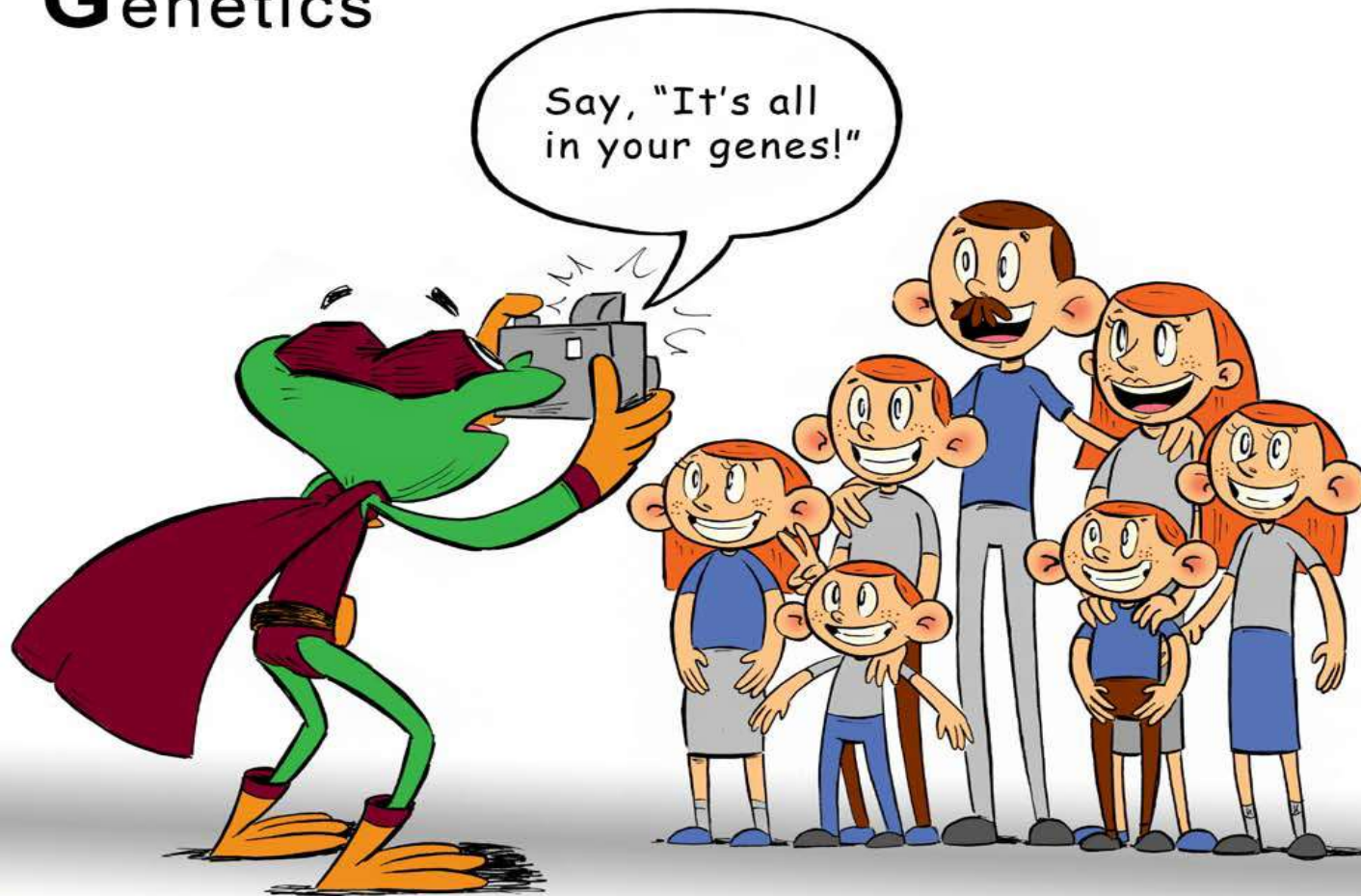
Optimal Care

Optimal vs Standard of Care



Genes

Genetics



Bale
Doneen
METHOD

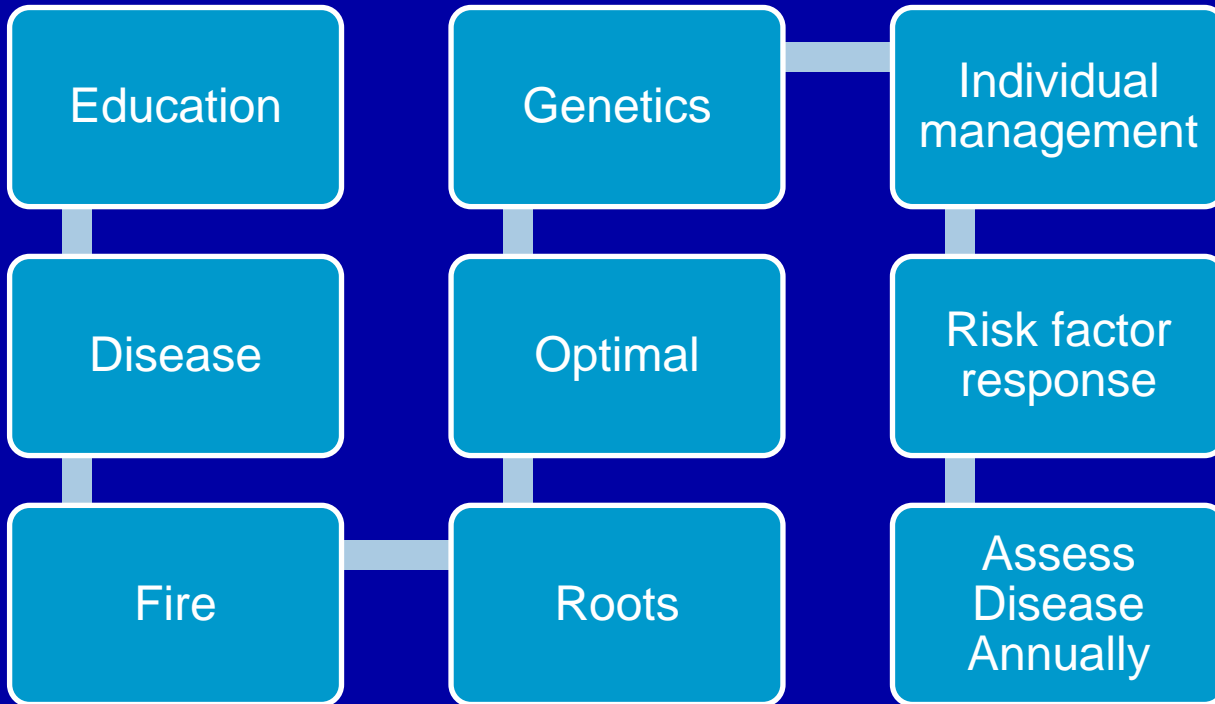
Miss Freedman



Copyright Bale/Doneen Paradigm



EDFROG IRA



Reynolds Risk Score is Superior to FRS

- Case-cohort sample 1722 cases of major CVD and a random sub-cohort of 1994 women without prior CVD (121 were also cases); followed 10yrs or until an event.
- ATP-III model (FRS) was calculated for those without diabetes mellitus
- The Reynolds Risk Score additionally includes hsCRP, Famhx and hemoglobin A1c among diabetics.
- Reynolds model demonstrated improved overall net reclassification index (NRI) of 4.9% with $p=0.02$

Cook N R et al. Circulation 4/2012;125:1748-1756

Reynolds Risk Score is Superior to FRS

The great majority of women destined to suffer a CV event had FRS scores $<10\%$; they would not qualify for statin rx under current guidelines

Reynolds (RRS) would reclassify 44% with ATP-III 5-10% risk:

- 15% into a lower risk category
- 29% to a higher risk category
 - Including 5% with an estimated risk $>20\%$ per RRS

Cook N R et al. Circulation 4/2012;125:1748-1756

Reynolds Risk Score is Superior to FRS

- 28.7% of women with a FRS score <5% had events
- 24% of women with a FRS score 5-<10% had events
- 42% of women with a FRS score 10-<20% had events
- 27.9% of women with a FRS score 20%+ had events

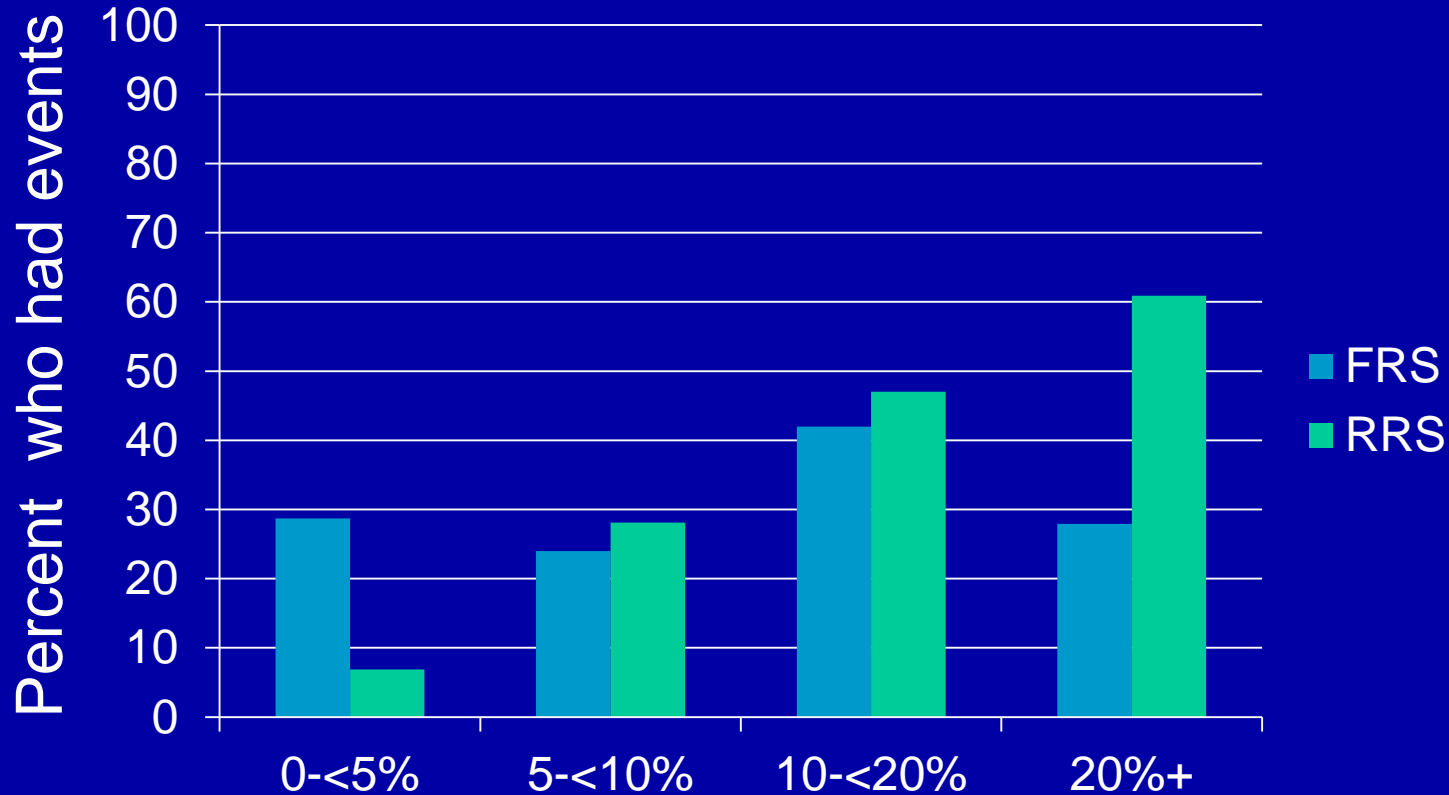
Cook N R et al. Circulation 4/2012;125:1748-1756

Reynolds Risk Score is Superior to FRS

- 6.9% of women with a RRS score <5% had events
- 28.1% of women with RRS score 5-<10% had events
- 47.0% of women with RRS score 10-<20% had events
- 60.9% of women with RRS score 20%+ had events

Cook N R et al. Circulation 4/2012;125:1748-1756

FRS and RRS Frequently Fail to Indentify Who Will Have an Event



Cook N R et al. *Circulation* 4/2012;125:1748-1756

Copyright Bale/Doneen Paradigm



Bale/Doneen Method Advice

- Calculate the RRS instead of the FRS
- Realize a 'non-high risk' score does not rule out the chance of an event
- The presence of an atheroma is essentially a conditio sine qua non for an event.
- Screen for subclinical atherosclerosis

Sibling (Sib) History of Ischemic Stroke (IS) Increases Stroke Risk 60%

- 30,735 sibs with sib hx of IS compared to 152,391 sibs without sib hx IS; 20 yr look
- RR 1.61 (95% CI 1.48-1.75) $p < 0.001$
- If full sib, RR 1.64 (95% CI 1.50-1.81) $p < 0.001$
- If half sib, RR 1.41 (95% CI 1.10-1.82) $p = 0.007$
- If IS ≤ 55 yo, RR 1.94 (95% CI 1.41-2.67) $p < 0.001$

Katherine Kasiman, et. al. *Circ Cardiovasc Genet* published online March 9, 2012;
<http://circgenetics.ahajournals.org/content/suppl/2012/04/03/CIRCGENETICS.111.962241.DC1>

Spouses Who Care for Their Partners with Cancer have Higher CV Risk

- 1,352,656 couples with children; cancers dx'ed btw 1987-2008; prospective design; Swedish population
- 122,683 women dx'ed with cancer; median yr of dx was 2000; median age of their spouses was 66 yo
- 161,287 men dx'ed with cancer; median yr of dx was 2002; median age of their wives was 67 yo
- Follow-up was divided into: 1 yr, 1 to 4 yrs, ≥ 5 yrs; expected # of CVD cases was calculated according to the incidence rate for all individuals without an affected spouse

Jianguang Ji, et. al. *Circulation* 4/2012, 125:1742-1747

Copyright Bale/Doneen Paradigm



Spouses Who Care for Their Partners with Cancer have Higher CV Risk

- Husband's risk by follow-up interval:

CHD: <1 yr. - 1.18 (95% CI, 1.10 –1.25); 1-4 yrs.- 1.20 (95% CI, 1.16 –1.25); \geq 5yrs. - 1.05 (CI, 1.02–1.09)

Ischemic stroke: <1 yr. - 1.28 (95% CI, 1.18 –1.38); 1-4 yrs. - 1.30 (95% CI, 1.25–1.36); \geq 5yrs.- 1.19 (95% CI, 1.14-1.23)

Hemorrhagic stroke: <1 yr. - 1.27 (95% CI, 1.07–1.51); 1-4 yrs. - 1.30 (95% CI, 1.18 –1.43); \geq 5yrs. - 1.21 (95% CI, 1.12–1.31)

Jianguang Ji, et. al. *Circulation* 4/2012, 125:1742-1747

Spouses Who Care for Their Partners with Cancer have Higher CV Risk

- Wife's risk by follow-up interval:

CHD: <1 yr. - 1.12 (95% CI, 1.04 –1.21); 1-4 yrs. - 1.17 (95% CI, 1.12–1.21); \geq 5yrs.- 1.11 (95% CI, 1.06 –1.15)

Ischemic stroke: <1 yr. -1.20 - (95% CI, 1.11–1.29); 1-4 yrs. -1.24 (95% CI, 1.19 –1.29); \geq 5yrs.-1.36 (; 95% CI, 1.31–1.41)

Hemorrhagic stroke: <1 yr. -1.19 -(95% CI, 0.99 –1.42); 1-4 yrs. -1.25 (95% CI, 1.13–1.37); \geq 5yrs. -1.30 (95% CI, 1.19 –1.42)

Jianguang Ji, et. al. *Circulation* 4/2012, 125:1742-1747

Spouses Who Care for Their Partners with Cancer have Higher CV Risk

- CV risk was more pronounced with cancers with high mortality rates, such as pancreatic, lung, and liver cancers
- Findings suggest that psychological distress after the cancer dx may play an important role in the risk of CHD and stroke
- Studies have shown that behavioral interventions can significantly reduce the stress and distress in family caregivers of pts with chronic and fatal diseases; decreasing their subsequent risk of CVD.
- Clinical attention and support are needed for spouses caring for partners with cancer

Jianguang Ji, et. al. *Circulation* 4/2012, 125:1742-1747

CHD Risk Increase with Consumption of Sugar Sweetened Beverages

- Health Professionals Follow-Up Study, prospective study >42,833 men; 22 yrs. follow-up
- Sugar-sweetened beverage consumption was associated with a higher risk of CHD
- The association was independent of: BMI, DM, and other established CV risk factors. (artificially sweetened beverages did not show this association).
- Each additional serving per day was associated with a 19% increased risk of CHD.

Sugar-sweetened beverages were statistically associated with:

Increased triglycerides

Increased hsCRP

Increased interleukin-6

Increased tumor necrosis factor receptors 1 and 2

Decreased HDL

Decreased lipo(a)

Decreased leptin.

Lawrence de Koning, et. al. *Circulation* 4/2012, 125:1735-1741

Table 4. Cross-Sectional Associations Between the Cumulative Average (1986–1994) Intake of Sugar-Sweetened and Artificially Sweetened Beverages and Biomarkers

	n	Mean	Change per 1 Sugar-Sweetened Beverage per Day	P	Change per 1 Artificially Sweetened Beverage per Day	P
Total cholesterol, mg/dL	3746	207 (43)	0.51 (–2.24 to 3.27)	0.72	–0.43 (–2.21 to 1.35)	0.63
Triglycerides, mg/dL	2064	164 (107)	12.7 (4.2–21.2)	0.01	0.01 (–5.59 to 5.62)	1.00
LDL, mg/dL	3025	130 (34)	–0.84 (–3.3 to 1.59)	0.50	–0.82 (–2.49 to 0.85)	0.34
HDL, mg/dL	3025	46 (16)	–1.87 (–2.70 to –1.03)	<0.01	0.04 (–0.48 to 0.56)	0.88
Lp(a), mg/dL	1594	20 (28)	–2.81 (–4.90 to –0.72)	0.01	0.11 (–1.59 to 1.81)	0.90
HbA _{1c} , %	2339	5.85 (1.10)	0.05 (–0.06 to 0.16)	0.41	0.03 (–0.03 to 0.09)	0.43
CRP, mg/L*	3217	1.20 (2.94)	0.12 (0.02–0.23)	0.02	–0.05 (–0.10 to 0.01)	0.11
IL-6, pg/mL*	1314	1.52 (2.41)	0.16 (0.03–1.65)	0.02	–0.05 (–0.13 to 1.60)	0.22
TNFr1, pg/mL	729	1493 (511)	78.5 (23.5–133.5)	0.01	45.3 (–4.1 to 94.7)	0.07
TNFr2, pg/mL	1613	2889 (872)	99.3 (11.4–187.2)	0.03	–16.0 (–69.3 to 37.3)	0.56
VCAM, ng/mL	1407	1283 (381)	5.61 (–26.3 to 37.5)	0.73	2.44 (–20.5 to 25.4)	0.83
ICAM, ng/mL	1407	352 (95)	3.70 (–4.19 to 11.59)	0.36	–1.88 (–7.84 to 4.07)	0.54
Adiponectin, ng/mL	1849	12761 (7936)	–458 (–1235 to 319)	0.25	–304 (–694 to 87)	0.13
Leptin, pg/mL	608	7526 (5797)	–796 (–1442 to –149)	0.02	132 (–356 to 620)	0.60

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein(a); HbA_{1c}, hemoglobin A_{1c}; CRP, C-reactive protein; IL-6, interleukin-6; TNFr1, tumor necrosis factor- α receptor 1; TNFr2, tumor necrosis factor- α receptor 2; VCAM, vascular cell adhesion molecule-1; and ICAM, intracellular adhesion molecule-1. Models are adjusted for the same covariates as in Table 2 except for mediators (high cholesterol, high blood pressure, type 2 diabetes mellitus).

*CRP and IL-6 were log transformed because of highly skewed distributions. Changes in CRP and IL-6 are calculated from parameter estimates representing percent change in the geometric mean (shown). Blood samples were provided in 1994.

elimination of CHD cases in the first 4 years (n=272), and in a unfavorable changes in blood lipids independently of BMI. In a

TC & HDL are Related to Stroke Risk

- Prospective investigation of assoc. of TC, HDL, TC/HDL ratio with total and type-specific stroke incidence; 58,235 Finnish 25-74 yo; no known CVD at baseline; follow-up 20 yrs.
- Strokes: 3085 ischemic, 497 intracerebral hemorrhage, and 332 subarachnoid hemorrhage
- Low levels of HDL cholesterol and high TC/HDL ratio were associated with increased risks of total and ischemic stroke in both men and women
- After adjustment for BMI, BP, and hx of DM, the association in men was no longer significant

Yurong Zhang, et. al. **Stroke** 5/2012;**43:00-00**

<http://stroke.ahajournals.org/content/early/2012/04/10/STROKEAHA.111.646778>

TC Related to Stroke Risk

- TC after full adjustment predicted the risk of **intracerebral hemorrhagic stroke in women**
- TC after full adjustment did not predict the risk of total or ischemic stroke in women or men, intracerebral hemorrhagic stroke in men, or subarachnoid hemorrhage in either men or women.

Yurong Zhang, et. al. **Stroke** 5/2012;**43:00-00**

<http://stroke.ahajournals.org/content/early/2012/04/10/STROKEAHA.111.646778>

HDL Related to Stroke Risk

- The multivariable-adjustment for: age, study year, education, physical activity, smoking, alcohol consumption, and family hx of stroke inverse associations of HDL-C with risks of **total and ischemic stroke** were found in both men (*P*_{trend} <0.05) and women (*P*_{trend} <0.001).
- **After additional adjustment** for: BMI, DM, BP the association **remained statistically significant in women** (*P*_{trend} <0.01) but **no longer significant in men** (*P*_{trend} >0.2).

Yurong Zhang, et. al. **Stroke** 5/2012;**43:00-00**

<http://stroke.ahajournals.org/content/early/2012/04/10/STROKEAHA.111.646778>

TC/HDL Related to Stroke Risk

- The multivariable-adjustment for: age, study year, education, physical activity, smoking, alcohol consumption, and family hx of stroke inverse associations of HDL-C with risks of **total and ischemic stroke** were found in both men (*P*_{trend} <0.05) and women (*P*_{trend} <0.001).
- **After additional adjustment** for: BMI, DM, BP the association **remained statistically significant in women** (*P*_{trend} <0.05) but **no longer significant in men** (*P*_{trend} >0.1).
- No significant association between TC/HDL ratio and the risk of hemorrhagic stroke was observed in either men or women

Yurong Zhang, et. al. **Stroke** 5/2012;**43:00-00**

<http://stroke.ahajournals.org/content/early/2012/04/10/STROKEAHA.111.646778>

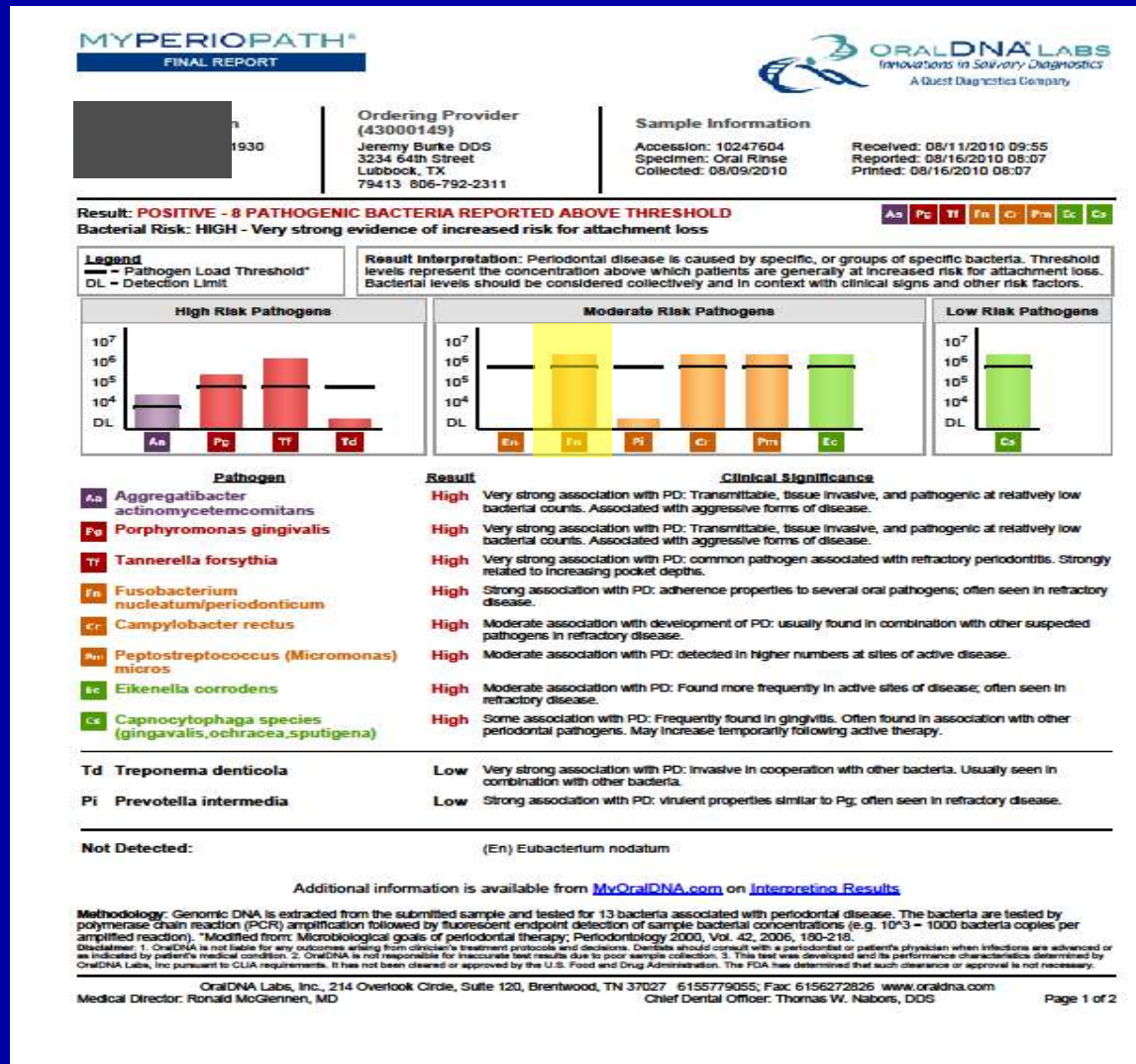
TC/HDL Related to Stroke Risk

- The present study provides further evidence for a positive association of TC/HDL ratio with the risks of total and ischemic stroke in both men and women
- People with dyslipidemia often have high BMI, high blood pressure, and diabetes
- The attenuation of stroke risk after adjusting for the above factors indicates that dyslipidemia may be part of the mechanism by which these other factors may increase the risk of stroke

Yurong Zhang, et. al. **Stroke** 5/2012;**43:00-00**

<http://stroke.ahajournals.org/content/early/2012/04/10/STROKEAHA.111.646778>

Do not forget OralSystemic Connection



PD Pathogens Found in Carotid Atheroma

- 42 carotid endarterectomy specimens analyzed via DNA for PD pathogens
- *Porphyromonas gingivalis* (78.57%, 33/42),
- *Aggregatibacter actinomycetemcomitans* (66.67%, 28/42)
- *Tannerella forsythia* (61.90%, 26/42)
- *Eikenella corrodens* (54.76%, 23/42)
- *Fusobacterium nucleatum* (50.00%, 21/42)
- *Campylobacter rectus* (9.52%, 4/42)
- *All had at least one; many had multiple pathogens*

Figuro, E., DDS, et. al. Journal of Periodontology; 8/2011. DOI: 10.1902/jop.2011.100719

Fusobacterium nucleatum (Fn)

Increases Permeability of Endothelium

- Fn adheres to and invades endothelial cells via a novel surface adhesin -FadA
- Vascular endothelial (VE)-cadherin is a cell–cell junction molecule
- This molecule is the receptor for Fn’s FadA
- The union of cadherin & FadA causes a relocation of VE-cadherin away from the cell–cell junctions.
- As a result, endothelial permeability increases allowing the bacteria to enter the arterial wall
- Fn may serve as an ‘enabler’ for other microorganisms explaining why Fn is often found in mixed infections.

Yann Fardini, et. al. *Molecular Microbiology* 11/2011 82(6):1468–1480

Klotho: Greek Goddess Regulating CV Health

- Klotho spins the thread of life
- Klotho gene discovered in 1997 - controls aging
- Klotho is a protein found in both tissue and extracellular fluid
- Klotho is expressed in human arteries
- Klotho prevents VSMC from differentiating to an osteoblast like phenotype (decreased Klotho yields increased arterial calcification)
- Klotho is upregulated through vitamin D receptor activation by calcitriol or paricalcitol (vit. D)

Sharon Moe,

<http://circ.ahajournals.org/content/early/2012/04/02/CIRCULATIONAHA.112.104828>

Kenneth Lim, et. al. CIRCULATIONAHA.111.053405

Published online before print April 5, 2012

Klotho: Greek Goddess Regulating CV Health

- Klotho is involved in vascular health through other mechanisms
 - a) improves endothelial dilatation in mice
 - b) protects against endothelial cell apoptosis in cell cultures
 - c) decreases TNF alpha induced intracellular adhesion molecule-1 (ICAM-1) and VCAM-1
 - d) reduced intracellular superoxide production and decreased angiotensin II oxidative stress

Sharon Moe,

<http://circ.ahajournals.org/content/early/2012/04/02/CIRCULATIONAHA.112.104828>

Kenneth Lim, et. al. CIRCULATIONAHA.111.053405

Published online before print April 5, 2012

Klotho: Greek Goddess Regulating CV Health

- In human kidney biopsies, decreased Klotho expression is found very early in the course of CKD, at stage 2, (estimated glomerular filtration rates of 60 to 90ml/min)

Sharon Moe,

<http://circ.ahajournals.org/content/early/2012/04/02/CIRCULATIONAHA.112.104828>

Kenneth Lim, et. al. CIRCULATIONAHA.111.053405

Published online before print April 5, 2012

Klotho: Greek Goddess Regulating CV Health

- Is decreased Klotho in the arteries a risk factor because it is an indicator of kidney disease or calcitriol (vit. D) deficiency?
- Are studies demonstrating reduced mortality with the administration of calcitriol in pts on dialysis due to a direct effect from the upregulation of Klotho in the vasculature?
- Is Klotho deficiency simply a biomarker of early kidney disease, or can a reduction in Klotho due to inflammation be a cardiovascular risk factor independent of kidney disease?

Sharon Moe,

<http://circ.ahajournals.org/content/early/2012/04/02/CIRCULATIONAHA.112.104828>

Kenneth Lim, et. al. CIRCULATIONAHA.111.053405 Published online before print April 5, 2012

K⁺ Sparing Diuretic 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

Hot Topic

- Statins in primary prevention !

Patient Identification



Primary

No disease.

Your gutter is cat free and we work to keep it that way.



Secondary

Disease but no heart attack or stroke.

The cat is in the gutter. We need to make sure it doesn't get out



Tertiary Prevention

Patient has had a heart attack or stroke.

The cat has gotten out of the gutter once before; we need to make sure it doesn't happen again.

Need to Adopt BDM Definitions

- Primary— no known ASVD
statins may or may not be appropriate
- Secondary – subclinical ASVD
statins are appropriate - inflammation
- Tertiary – ASVD which has caused an event
statins are appropriate - inflammation

Case

Upcoming Presentations

- 4/19/2012– Brad and Amy CHL Seattle, WA
- 4/24/2012– Brad and Amy El Paso, TX
- 4/30/2012 – Brad and Amy Atlanta, GA – documentary
- 5/3/2012 – Amy, Lake Chelan, WA oral systemic health- Richardson Group
- 5/18-19/2012- BD Method Preceptorship in Seattle, WA
- Reminder ! : BDM Reunion and CHL Symposium – Las Vegas, NV 9/20-22/2012

Open for Discussion