Live January 2012 Chat

- January 11, 2012
- Host: Amy Doneen MSN, ARNP
- Welcome to 2012!!

2012 Preceptorships

- Feb 10-11: Las Vegas
- May 18-19: Seattle
- Sept 14-15: San Antonio
- Nov 9-10: Atlanta

Beat The Heart Attack Gene

Wiley and Sons

Bradley Bale & Amy Doneen
with Lisa Collier Cool

Finalized September 1, 2012!

Outline for Today January 11, 2012

- New study information
  - Vitamin D and HsCRP
  - Fitness and Longevity
  - CPAP and Metabolic Syndrome
  - CPAP withdrawal and OSA return
  - Smoking and pregnancy – arterial damage to child
  - Aliskerin combined with ACE/ARB
  - ELEVATE TIMI 56
- New labs available
  - Galectin 3 - CHL
  - Co-Q-10 - CHL
- Questions from dental graduates
- Case Application

Vitamin D and hsCRP
What is an optimal level?

NHANES (2001-2006). Mean age 46, 52% women. Smokers, obese and non-whites all had lower Vit D levels at baseline.

Median serum 25-hydroxyvitamin D 21 ng/mL and CRP 0.21mg/dL.

hsCRP levels decreased as Vitamin D levels increased up until the 21 ng/mL.

Vit D supplementation in asymptomatic subjects with baseline vitamin D > 21 ng/mL might nave no additional inflammatory benefit as measured by hsCRP.

Amer, Qayyum. Am J Cardiol January 2012; 109: 226-230

Fitness and Longevity

14 345 men (mean age 44 years) with at least 2 medical examinations. METS and BMI were calculated. 11.4 year follow-up after the last exam. 914 all-cause and 300 CVD death occurred.

Changes in fitness and BMI between the baseline and last examinations over 6.3 years were classified into loss, stable, or gain groups. (95% CI)

Every 1-MET improvement was associated with 15% and 19% lower risk of all-cause and CVD mortality, respectively.

BMI change was not associated with all-cause or CVD mortality. Men who lost fitness had higher all-cause and CVD mortality risks regardless of BMI change.

Lee D., et al. Long-Term effects of changes in CV fitness and BMI on all-cause and CVD mortality. Circulation. 10/2011: DOI 10.1161/Circulationaha.111.038422

CPAP improves Metabolic Syndrome in Apnea patients

86 patients, mean age 45 (90% men). Mean BMI 32, mean waist 50 inches. ½ patients with HTN, DM, mean FBS 106. >80% with dyslipidemia. Pts randomized to 3 months of CPAP or "sham" CPAP followed by a one month wash-out then cross over x 3 more months.

<u>CPAP compared to sham treatment:</u>

- SBP -3.07 vs +0.79 mmHg, p=0.001
- DBP -2.81 vs -0.33 mmHg, p<0.001
- A1C -0.03% vs +0.19%, p=0.003
- TG -18.86 vs =0.21, p=.02
- TC -9.36 vs +3.90, p=0.005
- Non-HDL -9.32 vs +3.98 mg/dL, p=0.009
- Reversal of Metabolic Syndrome: 13% vs 1%, p=0.003

Sharma SK, et al New Engl J Med 12/2011; 365: 2277-2286

CPAP withdrawal to OSA

- 40 Patients used CPAP for >12 months with average compliance of at least 4 hr/noc. Randomized to continue CPAP or subtherapeutic CPCP for 2 weeks. Evaluated: Epworth, driving test, FMD, BP. Pulse, lipids,

Average arousal incidents:	+20.7h/ vs -0,6/h	P<0.001
Apnea-hypopnea events:	+33.8/h vs 0.4/h	P<0.001
Epworth score:	+2.0 vs -0.7	P=0.001
Morning BP:	+6.2/+4.4 vs -2.3/-2.5 mmHg	P=0.008
Morning heart rate:	+6.3 vs 0.0 bpm	P=0.035
FMD:	-3.2% vs -1.7%	P<0.001

NS: lipids and psychomotor changes

- Dr. Kohler: Withdrawl of CPAP was associated with a return of OSA by the first night.

Kohler, et al. Effects of CPAP Withdrawl. Am J respir Crit Care med January 2011.

Smoking and Pregnancy: Arterial damage in offspring

Prospective data 259 children (evaluated at 5 years with cIMT and endothelial vasodilation)

Children of prenatal smoking mothers had a cIMT thickness 18.8 um thicker than those with no prenatal smoke exposure (95% CI 1.1 to 36.5, P=0.04)

Children of prenatal smoking mothers had arterial distensibility that was 15% lower than other 5 year old children (95% CI -0.3 to -0.02, P=0.02)

The highest increase in cIMT was observed in children with two parents who smoked during the pregnancy, at 27.7 um (95% CI 0.2 to 55.3)

Geerts C, et al "Parental smoking and vascular damage in their five-year-old Children" Pediatrics 2012; 129: 46-55.

Aliskiren added to ACE, ARB a Bad Idea

- Renally impaired diabetes; ACEI or ARB rx with aliskiren or placebo
- During a 18 – 24 mo. follow-up group, aliskiren arm had increased incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension compared to placebo
- Trial halted due to potential harm

Novartis announces termination of ALTITUDE study with Rasilez/Tekturna in high-risk patients with diabetes and renal impairment [press release]. December 20, 2011

ELEVATE-TIMI 56: CYP2C19: overcome by dosing?

333 pts, stable CVD, 75gm clopidogrel, asa

74% noncarriers, 24% heterozygous, 2% homozygous

Each tx period 14 days – 4 tx groups

Heterozygous Carriers: ($p<0.001$ for trend) 225 mg dose of clopidogrel achieved a level of platelet reactivity comparable to that of noncarriers taking the 75mg dose

Homozygous Carriers: Although escalating doses were associated with declines in platelet ($P=0.003$ for trend), platelet reactivity remained high even at 300mg/day.

Mega J, et al "Dosing clopidogrel based on CYP2C19 and effects on platelet reactivity." JAMA 11/29/2011.

Cleveland HeartLab: 2 new tests Both currently: Soft Launch stage

- Galectin -3 – “Improving Management of the Hypertensive Patient”- CHL
- Co-Q-10 – who to test and why.
- Hard launch of both – within next month.

Cleveland HeartLab :

- ✓ Chronic inflammation with resultant fibrosis, loss of tissue architecture, and subsequent organ failure is a massive health-care burden worldwide
- ✓ Galectin-3 is intimately involved in the inflammatory process and subsequent fibrosis
- ✓ Measurement of galectin-3 levels in a hypertensive patient population may help to improve patient management and guide therapy

ClevelandHeartLab®

Bale Doneen METHOD

Inflammation to scarring…….

- Inflammation is typically a beneficial and protective response to tissue injury in the body promoting and healing and repair of damaged tissues
- Problems arise when this process becomes dysregulated and chronic inflammation ensues
- Chronic inflammation contributes to scarring and subsequent organ failure in many disease states and increases morbidity and mortality

ClevelandHeartLab®

Dale Doneen METHOD

Dr. Marc Penn, January 2012

- Inflammation plays a key role in various cardiovascular-related conditions including
  - ✓ Development of atherosclerosis – F_2-IsoPs
  - ✓ Formation of vulnerable plaque – MPO/Lp-PLA_2
  - ✓ Left ventricular remodeling – Galectin-3

Cleveland HeartLab – a tool for hypertension management.

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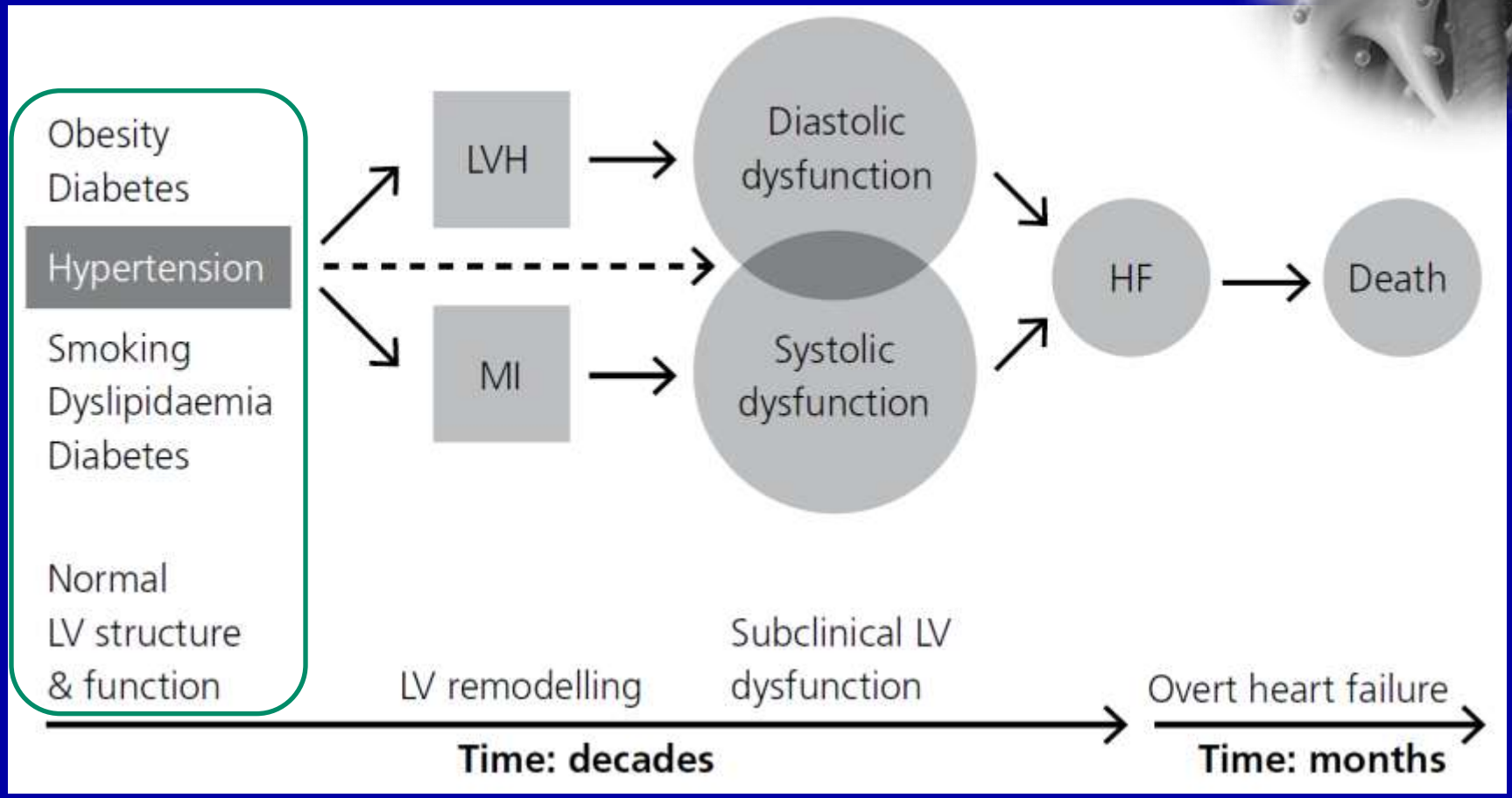
Bale Doneen METHOD

The hypertension continuum



CHL: If you interrupt this process by appropriately controlling blood pressure, you can prevent fibrosis and subsequent organ damage.

Meredith PA et al. JRAAS. 2006; 7: 64-73.

ClevelandHeartLab®

Bale Doneen METHOD

Ca^{2+} Channel blockers
Prevent calcium from entering the cells of the heart and blood vessel walls, resulting in lower blood pressure

Diuretics
Help rid the body of salt and water

Treatment of hypertension

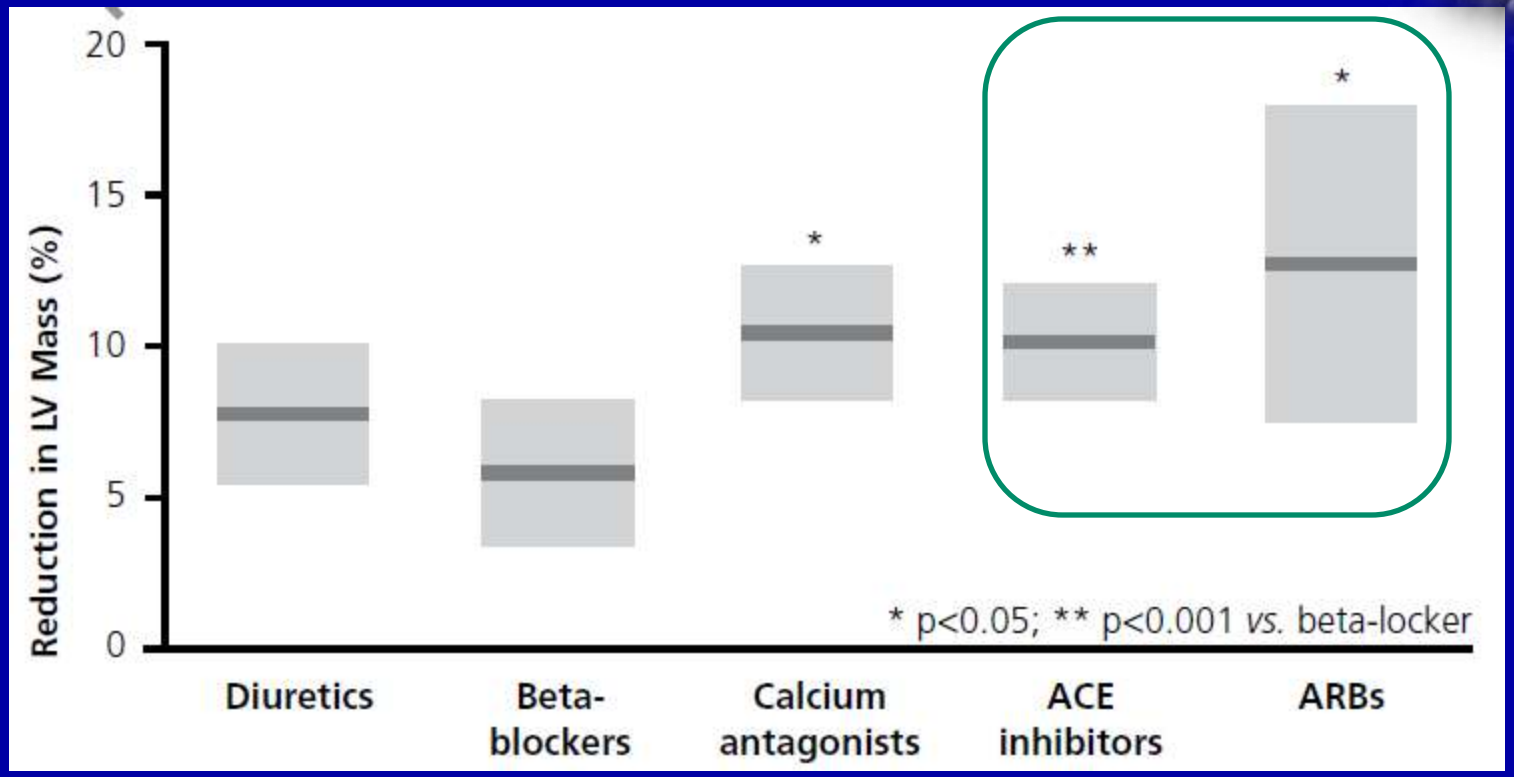
Beta-blockers
Reduce blood pressure by blocking the effects of the hormone epinephrine (adrenaline)

ACE inhibitors
Relax blood vessels by blocking production of angiotensin II

ARBs
Block the action of angiotensin II (blocks the receptor)

Dale Doneen METHOD

The affect of LV mass using various HTN medications:



Meta-analysis of regression of left ventricular hypertrophy with antihypertensive therapy by drug class.[3] Mean % change in left ventricular mass from baseline (with 95% CIs) adjusted for change in diastolic BP and duration of treatment.

Meredith PA et al. JRAAS. 2006; 7: 64-73.

ClevelandHeartLab®

Bale Doneen METHOD

Management of hypertensive individuals using galectin-3 testing

ClevelandHeartLab®

Hypertensive Individual

Low
galectin-3

Treat with your preferred hypertension treatment

Moderate/High
galectin-3

Treat with an ACE or ARB first to help reverse LV remodeling

Bale/Doneen: ACI-1 in presence of atherosclerosis first

Bale Doneen METHOD

Measurement galectin-3 levels

- Galectin-3 levels may be elevated in individuals with:
  - Advanced cancer
  - Other conditions associated with organ fibrosis
  - Known human anti-mouse antibodies (HAMA) or rheumatoid factor (RF)
- Galectin-3 levels should be interpreted with caution in individuals with known autoimmune disorders
- Additionally, specimens with high levels of gamma globulins (> 2.5 g/dL) may cause false elevation in results.

ClevelandHeartLab®

Dale Doneen METHOD

Conclusions

- Hypertension acts as a major determinant of endothelial dysfunction and vascular damage, but can also contribute to adverse cardiac remodeling
- Galectin-3 mediated-inflammation can contribute to fibrosis and subsequent adverse cardiac remodeling
- Measurement of galectin-3 levels in hypertensive individuals can guide therapy in an effort to reduce adverse cardiac remodeling and improve outcomes

ClevelandHeartLab®

Dale Doneen METHOD

Endurance Athletes and Heart Damage

40 endurance athletes (mean age 37) participating in endurance event. All trained for >10 hrs/week and finished in top ¼ of the race. All asymptomatic with no known CV risk factors. 2-3 wks before, right after, 6-11 d post race.

Compared with baseline – all measures of right vent function worsened immediately post race. Left vent function was unaffected.

Cardiac troponin and NT BNP both sign increased post race, decreased right vent EF but unrelated to left vent EF.

39 had MRI – 5 showed subclinical myocardial fibrosis - these athletes had long endurance history and lower right vent EFs

La Gerche A, et al. Eur Heart J 2011: DOI: 10.1093/euroheartj/ehr397.

Co-Q-10

Why offer CoQ10 Testing?

- ✓ A significant inter-product variability in the absorption and bioavailability of CoQ10 exists within OTC preparations
- ✓ May be depleted in certain acute and chronic disease states
- ✓ Demonstrated clinical utility
- ✓ Significant lay press interest in CoQ10 and patients routinely ask physicians about testing and supplementation

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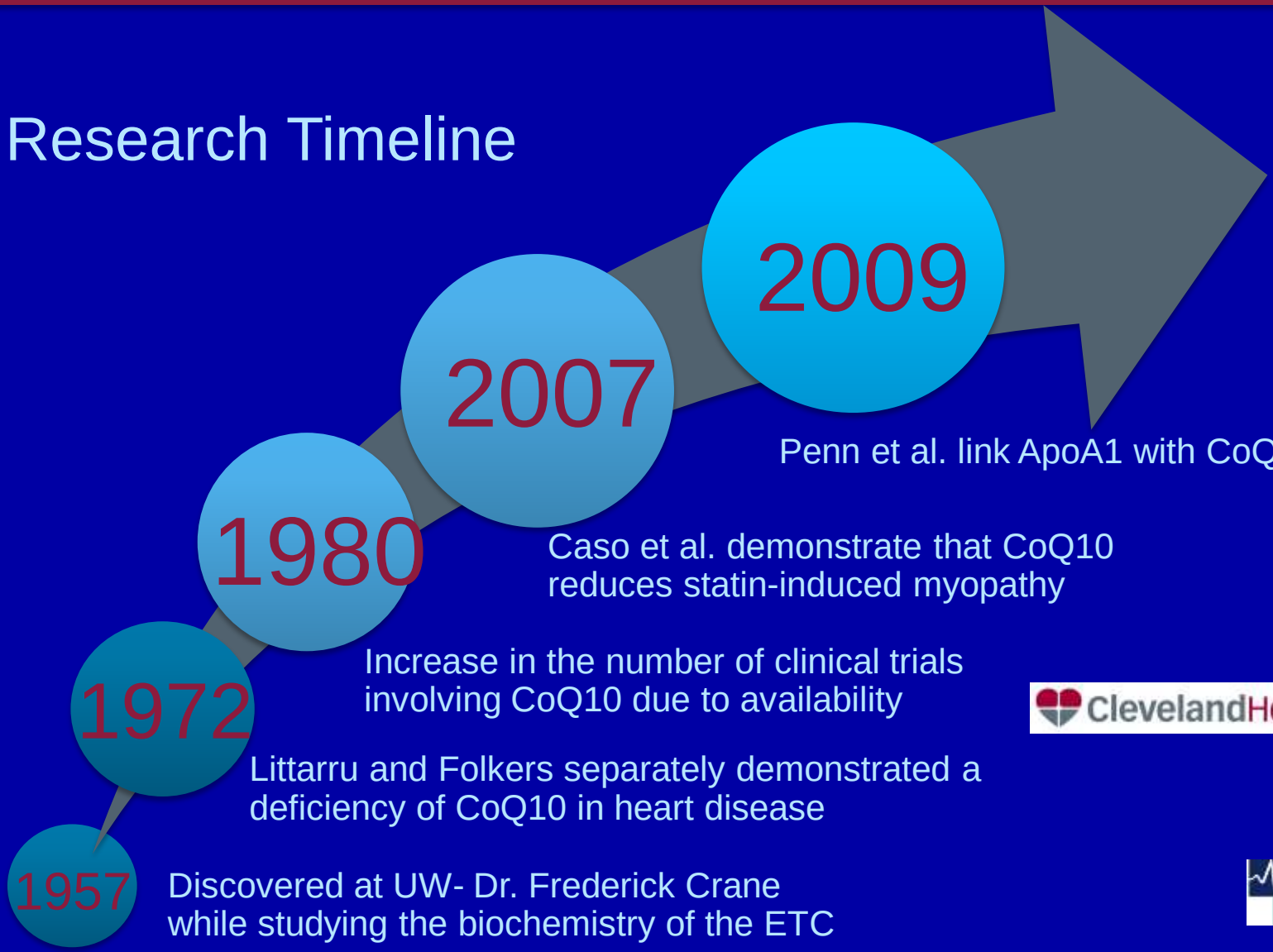
Michelle Beidelschies, PhD

Dale Doneen METHOD

Introduction

Research Timeline



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Dale Doneen METHOD

Clinical indications for CoQ10 testing

CoQ10 deficiency

CoQ10 deficiency contributes to:

Mitochondrial dysfunction

Muscle dysfunction without myonecrosis

Statin-induced myopathy

Statins have various adverse effects including:

Myotoxicity (myopathy)
Liver damage
Rhabdomyolysis

Low ApoA1 levels

Recent data demonstrates that:

ApoA1 levels may predict CoQ10 levels

ApoA1 may be involved in CoQ10 absorption

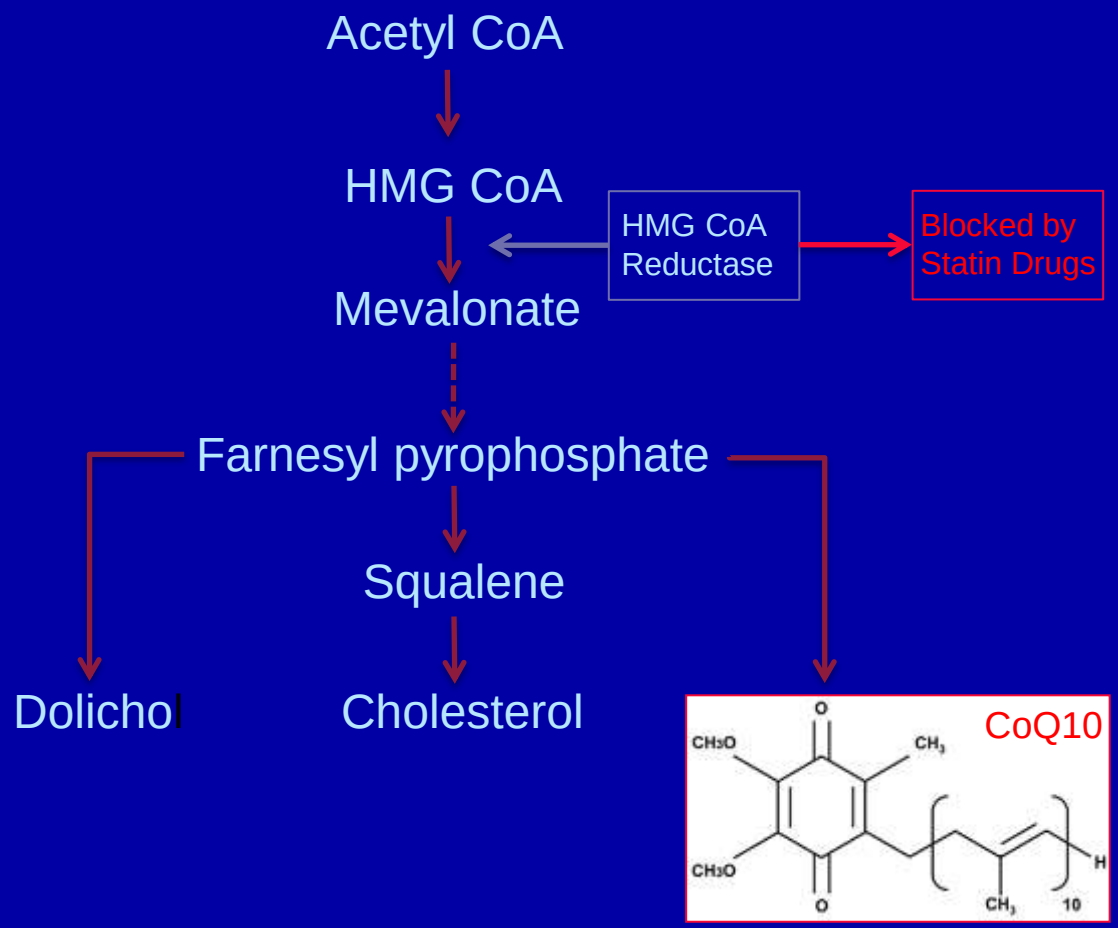
CoQ10 supplementation reduces infarct size

ClevelandHeartLab®

Bale Doneen METHOD

Statins inhibit the production of cholesterol and CoQ10

- CoQ10 shares a common biosynthetic pathway with cholesterol
- Synthesis of the intermediate precursor, mevalonate, is inhibited by various drugs (β-blockers, BP meds, and statins)



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Bale Doneen METHOD

Evidence of Plasma CoQ10-Lowering Effect by HMG-CoA Reductase Inhibitors: A Double-Blind, Placebo-Controlled Study

G. Ghirlanda, MD, A. Oradei, MD, A. Manto, MD, S. Lippa, MD, L. Uccioli, MD, S. Caputo, MD, A. V. Greco, MD, and G. P. Littarru, MD

J Clin Pharmacol 1993;33:226–229

	Group A	Group B
No. of participants	10	30
History	Asymptomatic	Hypercholesterolemic
Treatment	20 mg/day Prava/Simva	20 mg/day Prava/Simva/Placebo
Duration of study	1 month	3 months

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Dale Doneen METHOD

CoQ10 levels are **reduced approximately 50%** in **hypercholesterolemic individuals** on statin therapy

	Placebo		
	Basal	Week 12	%
CoQ10	1.1 ± 0.2	0.9 ± 0.2•	−17
CHO	0.64 ± 0.4	6.17 ± 0.7•	−7
HDL-CHO	1.39 ± 0.4	1.34 ± 0.4•	−4
LDL-CHO	4.26 ± 0.6	3.82 ± 0.8•	−11
TG	1.84 ± 0.72	1.81 ± 0.84•	−0.5

J Clin Pharmacol 1993;33:226–229

	Pravastatin		
	Basal	Week 12	%
CoQ10	1.23 ± 0.3	0.6 ± 0.2***	−50
CHO	6.35 ± 1.1	4.93 ± 1.3**	−23
HDL-CHO	1.29 ± 0.3	1.34 ± 0.36•	+1
LDL-CHO	3.92 ± 0.5	3.12 ± 31**	−21
TG	1.59 ± 0.84	1.32 ± 0.42•	−17

	Simvastatin		
	Basal	Week 12	%
CoQ10	1.2 ± 0.1	0.6 ± 0.2***	−54
CHO	6.92 ± 0.5	5.32 ± 0.6**	−27
HDL-CHO	1.34 ± 0.4	1.34 ± 0.4•	0
LDL-CHO	4.2 ± 0.4	3.0 ± 0.5***	−29
TG	1.43 ± 0.57	1.07 ± 0.26•	−26

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Bale Doneen METHOD

Myotoxicity (myopathy) Liver damage Rhabdomyolysis

Effect of Coenzyme Q10 on Myopathic Symptoms in Patients Treated With Statins

Giuseppe Caso, MD, MSc, PhD[a,*], Patricia Kelly, DO[b], Margaret A. McNurlan, PhD[a], and William E. Lawson, MD[b]

Am J Cardiol 2007;99:1409–1412

Double-Blinded Protocol		
	CoQ10 group	Vitamin E
No. of participants	18	14
History	Myopathic symptoms	Myopathic symptoms
Treatment	100 mg/day	400 IU/day
Duration of study	30 days	30 days

Muscle pain assessed before and after treatment

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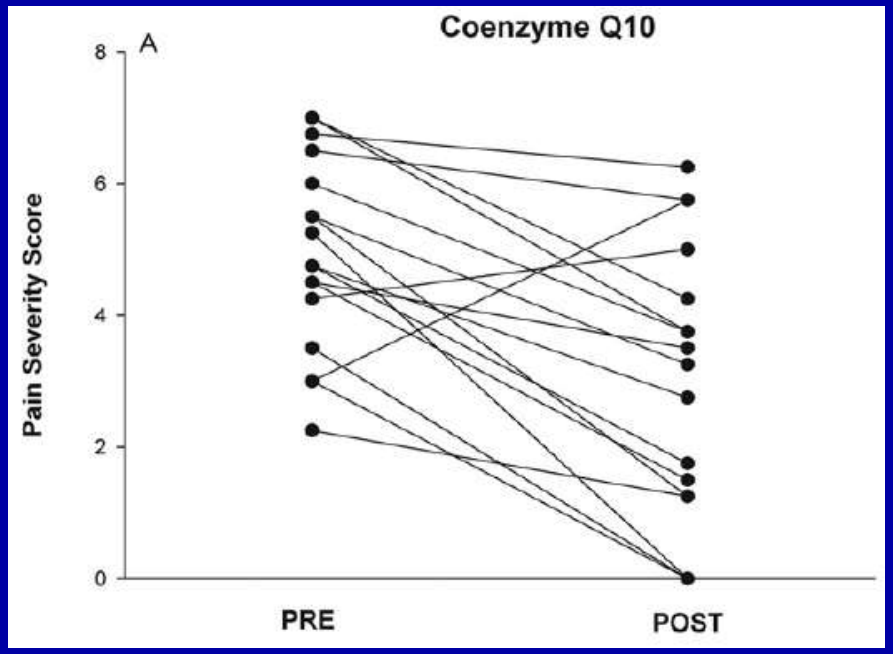
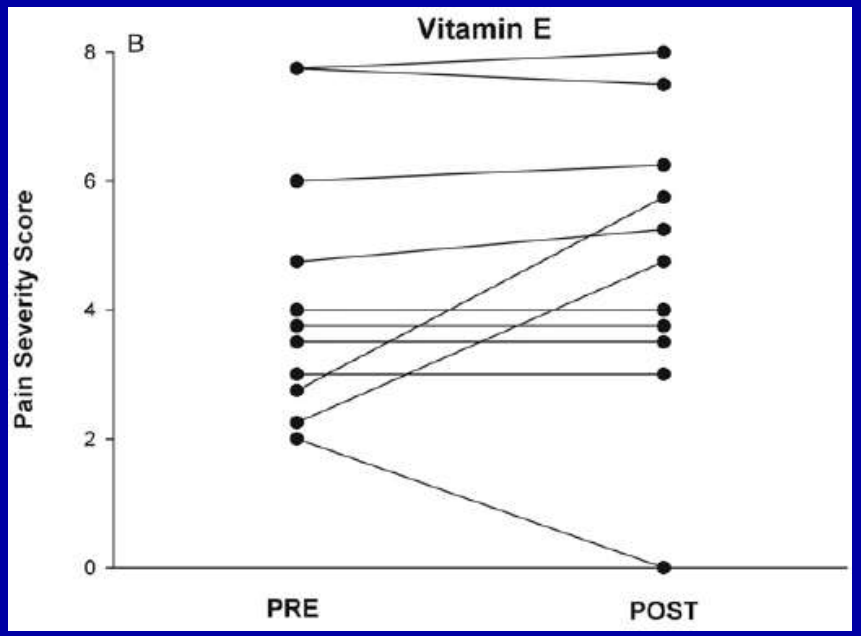
Dale Doneen METHOD

CoQ10 supplementation can **reduce the degree of muscle pain by 40%** in individuals on statin therapy





Am J Cardiol 2007;99:1409–1412

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Bale Doneen METHOD

Effect of Coenzyme Q_{10} Supplementation on *Simvastatin*-Induced Myalgia

Joanna M. Young, BSc[a,*], Christopher M. Florkowski, MBBS, MD[a,b], Sarah L. Molyneux, PhD[b], Roberta G. McEwan, RN[a], Christopher M. Frampton, PhD[c], Peter M. George[b], and Russell S. Scott, MBChB, PhD[a]

Am J Cardiol 2007;100:1400–1403

Double-Blind, Placebo-Controlled		
	Severe myalgia	Moderate myalgia
History	Inability to tolerate a statin dose of 20-40 mg/day within 1 month of Tx	Development of myalgic symptoms at doses ≥20 mg/day after >1 month of Tx
No. of participants	19	25
	Within each group, patients were randomized to Tx with CoQ10 200mg/day or placebo for 12 weeks + Simvastatin (titrated from 10-20 mg/day to 40 mg/day)	

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Bale Doneen METHOD

CoQ10 supplementation **improves Simvastatin tolerance**

Simvastatin dose tolerated at 12 weeks

Tolerated Dose (mg/day)	Coenzyme Q_{10} and Simvastatin Therapy (n = 22)	Simvastatin Alone (n = 22)
40	16 (73%)	13 (59%)
20	0	3 (14%)
10	0	2 (9%)
0	6 (27%)	4 (18%)

Data are expressed as number (percentage) of patients.

p = 0.34 for comparison of the number of patients who tolerated simvastatin 40 mg/day (chi-square test); p = 0.47 for comparison of the number of patients remaining on simvastatin (chi-square test).

Am J Cardiol 2007;100:1400–1403

Still a number of individuals who are able to tolerate the statin alone.

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Bale Doneen METHOD

CoQ10 supplementation **improves myalgia symptoms**

	Coenzyme Q_{10} and Simvastatin Therapy (n = 22)	Simvastatin Alone (n = 21)	p Value*
Δ Myalgia score (mm)	6.0 (2.1–8.8)†	2.3 (0–12.8)†	0.63
Δ Coenzyme Q (μmol/L)	1.7 (0.3 to 2.2)†	−0.5 (−0.6 to −0.3)†	<0.001

Am J Cardiol 2007;100:1400–1403

There is an improvement in the myalgia score, but it is not statistically significant

Suggests that not everybody needs CoQ10 supplementation and warrants an analysis of a subpopulation of patients

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Bale Doneen METHOD

Clinical indications for CoQ10 testing

CoQ10 deficiency

CoQ10 deficiency contributes to:

Mitochondrial dysfunction

Muscle dysfunction without myonecrosis

Statin-induced myopathy

Statins have various adverse effects including:

Myotoxicity (myopathy)
Liver damage
Rhabdomyolysis

Low ApoA1 levels

Recent data demonstrates that:

ApoA1 levels may predict CoQ10 levels

ApoA1 may be involved in CoQ10 absorption

CoQ10 supplementation reduces infarct size

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Bale Doneen METHOD

Rosuvastatin combined with regular exercise preserves coenzyme Q10 levels associated with a significant increase in high-density lipoprotein cholesterol in patients with coronary artery disease

Kensuke Toyama[a,b], Seigo Sugiyama[a,*], Hideki Oka[b], Yuri Iwasaki[c], Hitoshi Sumida[d], Tomoko Tanaka[e], Shinji Tayama[b,e], Hideaki Jinnouchi[e], Kunihiko Matsui[f], Hisao Ogawa[a]

[a] *Department of Cardiovascular Medicine, Faculty of Life Science, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan*
[b] *Division of Cardiology, Health Insurance Hitoyoshi General Hospital, Kumamoto, Japan*
[c] *Clinical Research Center, Health Insurance Hitoyoshi General Hospital, Kumamoto, Japan*
[d] *Division of Interventional Cardiology, Department of Cardiovascular Medicine, Kumamoto University Hospital, Kumamoto, Japan*
[e] *Division of Preventive Cardiology, Department of Cardiovascular Medicine, Kumamoto University Hospital, Kumamoto, Japan*
[f] *Department of General Internal Medicine, Yamaguchi University Hospital, Yamaguchi, Japan*

Atherosclerosis 217 (2011) 158–164

Prospective, open labeled randomized trial		
	Atorvastatin	Rosuvastatin
No. of participants	14	14
History	CAD	CAD
Treatment	10-40 mg/day	2.5- 20 mg/day
Duration of study	20 weeks	20 weeks

Both groups underwent exercise training

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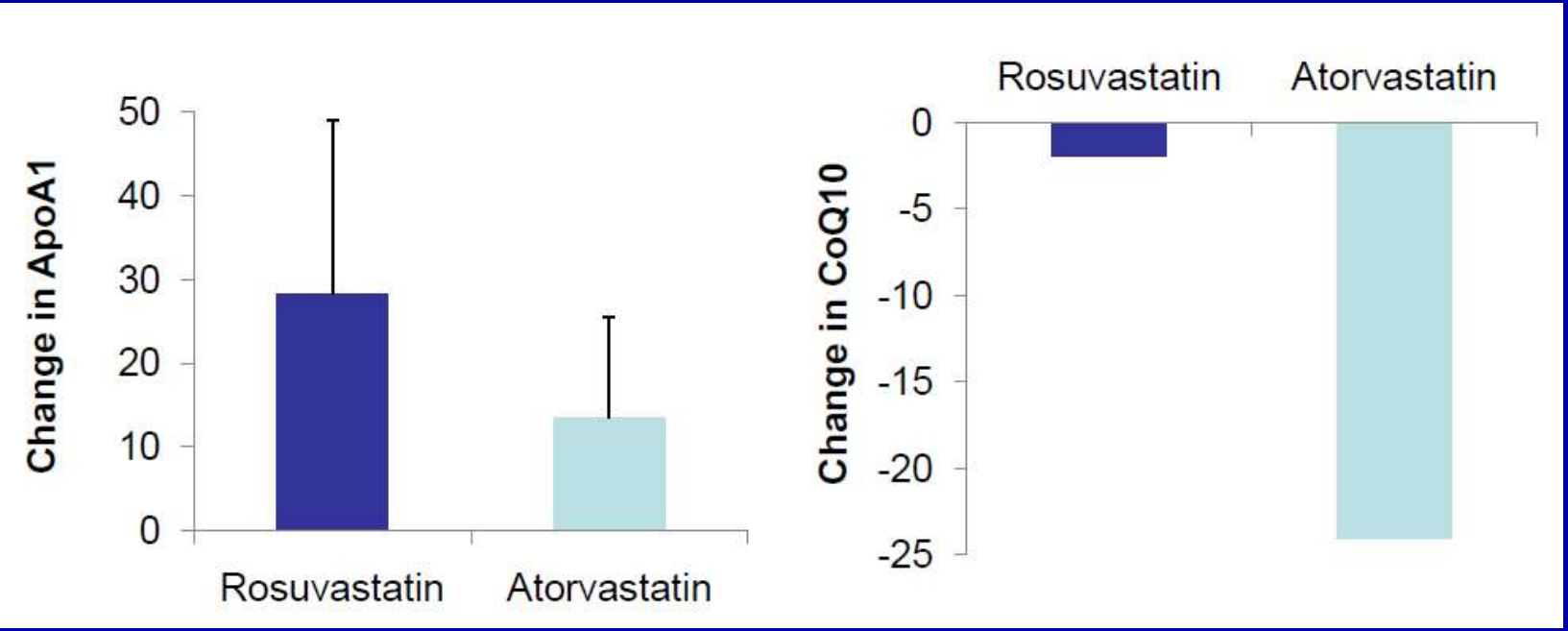
Dale Doneen METHOD

ApoA1 levels may predict CoQ10 levels



Exercise in combination with Rosuvastatin therapy improved HDL levels and preserved CoQ10 levels

Atherosclerosis 217 (2011) 158–164

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Dale Doneen METHOD

New! ApoA1 and CoQ10 data

From the laboratory of Marc S. Penn, MD, PhD
Animal model

If ApoA1 is absent or low, CoQ10 levels are low

Supplementation restores CoQ10 levels and reduces infarct size

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Dale Doneen METHOD

Who should get CoQ10 testing?

Individuals on statin therapy

If myalgia symptoms are present/intolerable

- Consider pretreatment with CoQ10 and reinitiation of current or alternative statin therapy
- CoQ10 supplementation may help to improve compliance

Target ApoA1/HDL and monitor CoQ10 levels

If at increased risk for acute coronary syndrome

- Test CoQ10 levels to determine if supplementation may be necessary to decrease infarct size

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Dale Doneen METHOD

Recent Publication -

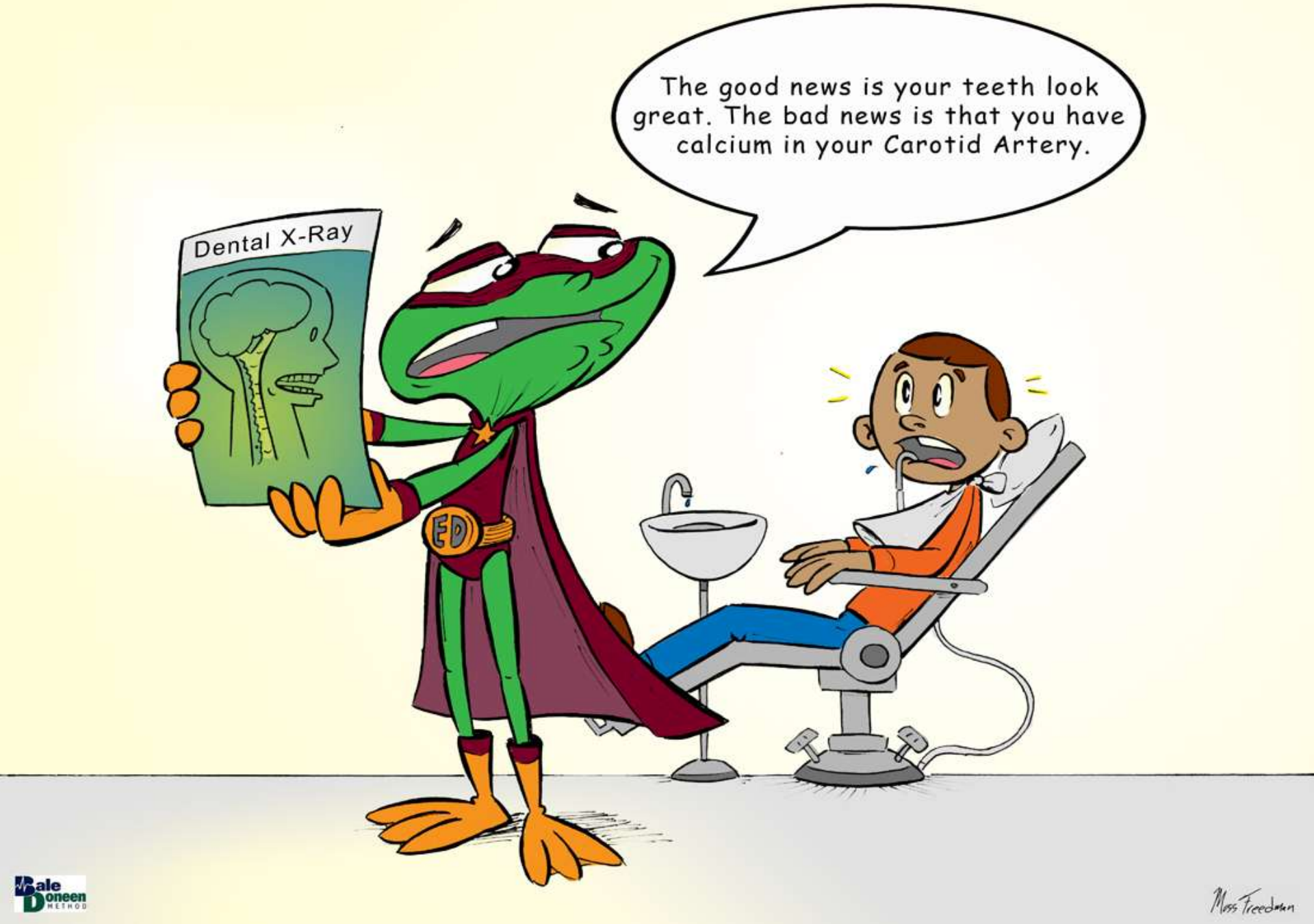
expert roundtable: Cardiology | Fall 2011 (4) | 2011

- Clinician Perspective on the Benefits of Niacin Therapy for the Treatment of Dyslipidemia and Strategies to Improve Long-Term Adherence to Therapy

- **ARTICLE ID:** CV9266
- **MODERATOR:** Peter H. Jones, MD[1]
- **PARTICIPANTS:** Bradley Bale, MD[2] and Amy Doneen, RN, BSN, MSN, ARNP[3]

3 main points – to get across.

- TC/HDL
- Inflammation
- What is the REAL value…..


The good news is your teeth look great. The bad news is that you have calcium in your Carotid Artery.
Dental X-Ray
ED

Patti DeMatteis
Dental Hygiene Excellence, L.L.C.

- If a dental patient with a history of stroke or heart attack is diagnosed with active periodontal disease, we would recommend ideal, full mouth periodontal treatment. If the patient accepts ideal periodontal treatment, as a prerequisite to starting periodontal treatment we would recommend Oral DNA testing to start patient on systemic antibiotic the day of treatment. We would also utilize locally applied antibiotics, and antimicrobial agents. When would you recommend a consultation with the patient's primary care physician or specialist?

- If the same patient refuses Oral DNA testing, would your above recommendation change?

- What if the above patient refuses the recommended periodontal treatment all together? Should we consult with the primary care physicians and or specialists?

- In your opinion, what other general health conditions would merit need for a consultation with the primary care physician or specialists before starting full mouth periodontal treatment?

- I have a 77 yo male retired lawyer patient with a chronic degree of periodontal disease and I could see him having other health challenges (he can barely walk) and I was concerned for his heart disease and stroke risk. He was trying to let me allow him to come in every 4 months instead of every three so I said I would feel better about it if you passed a couple of medical tests . So I recommended CIMT and PLAC for him and his internal medicine doc said that those tests were unnecessary as they would not impact any clinical outcomes nor change the approach for risk factor reduction. I was shocked to hear this. Next week I will be talking to this doc and I will try and defend the need for those tests. Anything else I can say to help him understand the importance? Any help will be very much appreciated.

- *Dr. Chris Kammer, President American Academy for Oral Systemic Health*

Consultation with J.C. 35 year old male

J.C. was referred to me by a PCP in town. He suffered an "event" of some kind that seems to be "like a TIA" but no atherosclerosis found. Bubble echo normal….normal lipids, slightly high BP….quit chewing at time of "event"…..watch and wait…..

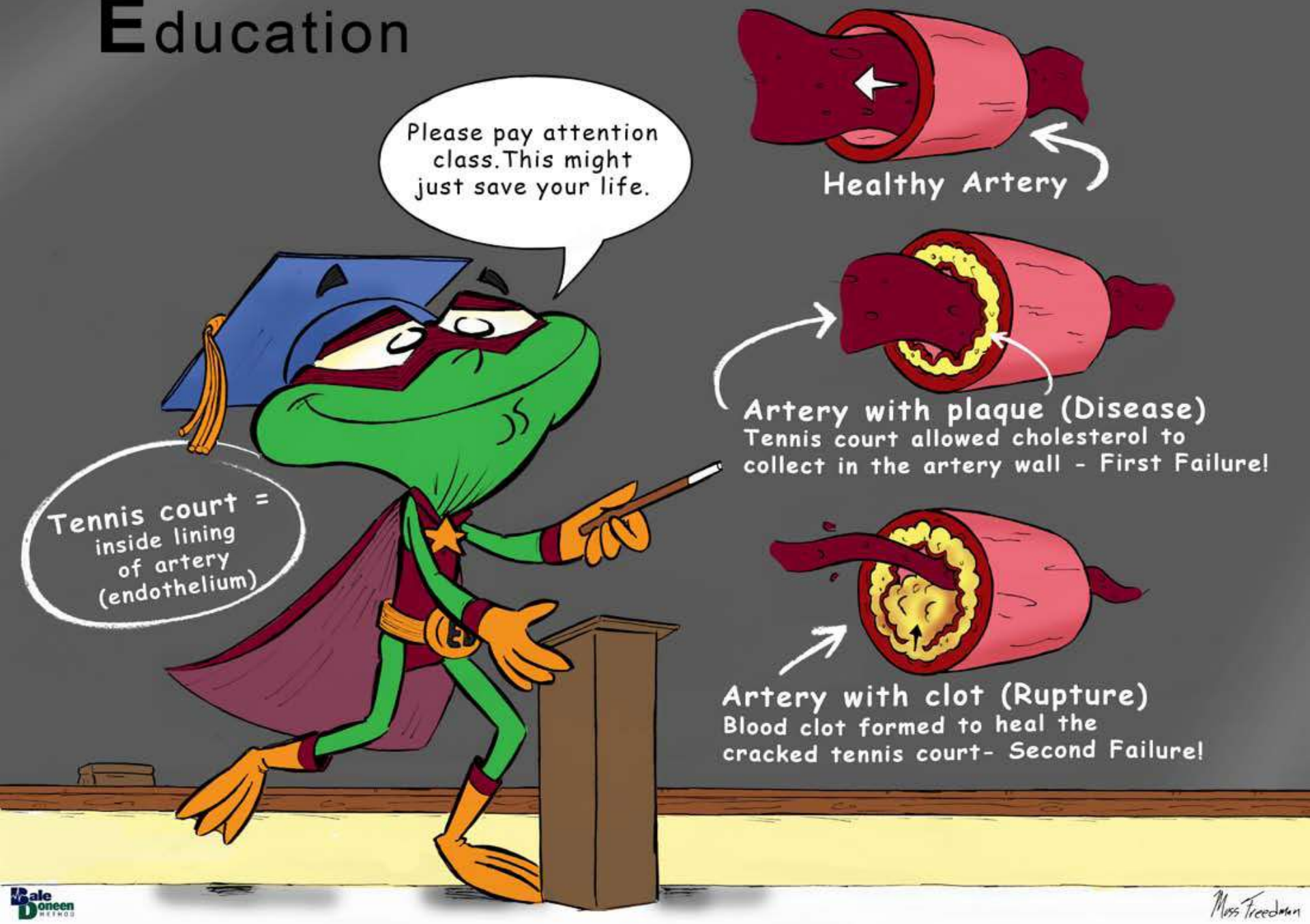
Amy Doneen

January 10, 2012

Understanding = Participation

EVENT REALITY Cartoons: created by Bale/Doneen Method; illustrated by Moss Freedman June 2010

Education



Carotid Intima-Media Thickness

Your arterial wall average thickness is normal.

Highly predictive of development of stroke, transient ischemic attack (TIA), heart attack

Transcript July 2003 ACCEL interview with Pam Douglass (President of American Society of Echocardiography and Cardiology Dept. Chair at the University of Wisconsin School of Medicine, Madison

Carotid artery plaque predicts CV events better than stenosis

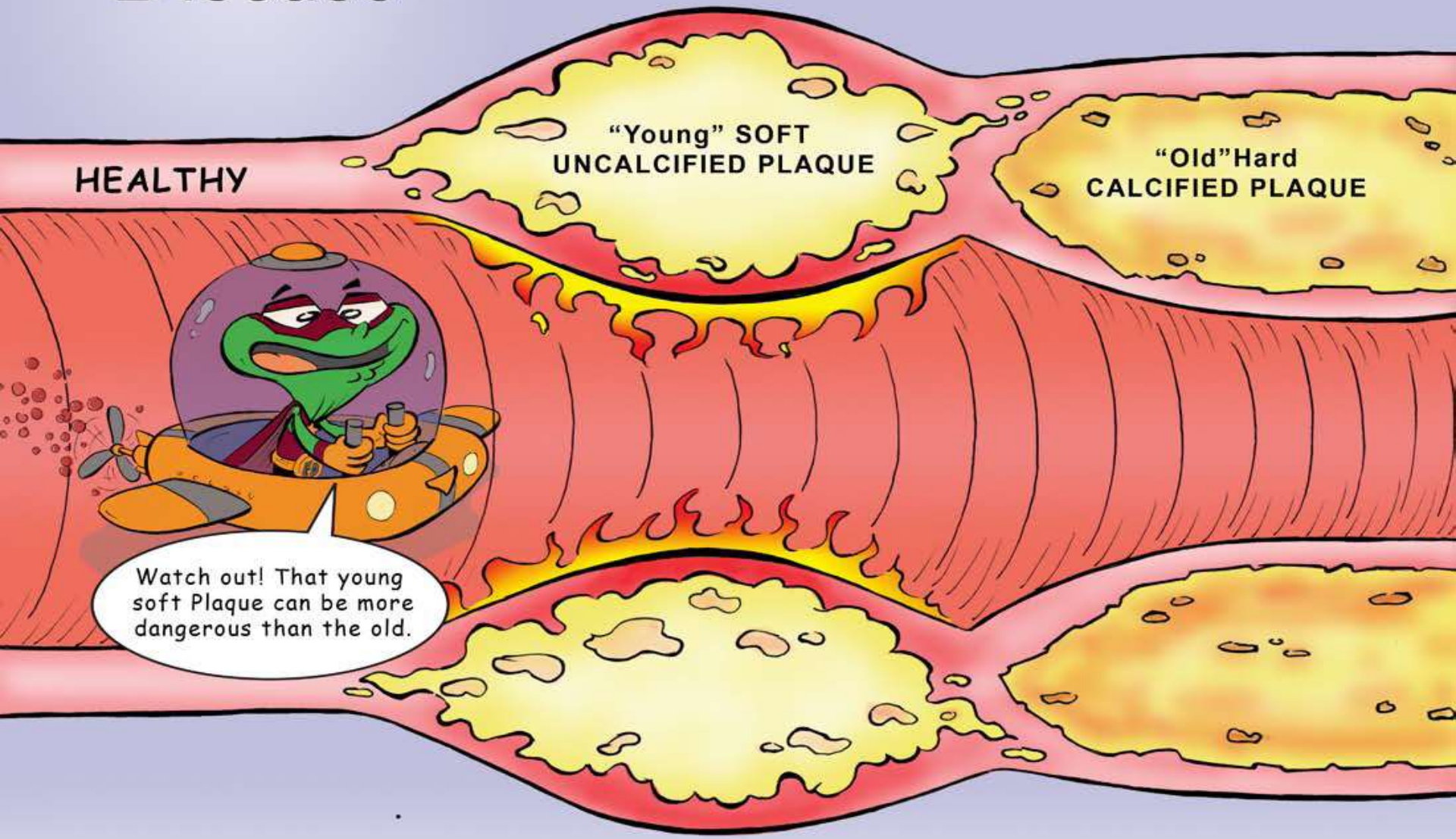
Plaque was ten times more predictive

7.4mm soft plaque – internal carotid bilaterally

(2.8 mm soft bilaterally internal carotid)

Iemolo F et al. *Stroke* 1/22/2004. Available at: http://stroke.ahajournals.org.

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.

Dale Doneen METHOD

Moss Freedman

Carotid-Wall Intima–Media Thickness and Cardiovascular Events

Hypothesized that the IMT of the CCA and ICA would add to the predictive value of FRS regarding new-onset cardiovascular events.

Increased IMT of the CCA represents a form of atherosclerosis that is manifested as diffuse arterial-wall thickening, whereas increased IMT of the proximal ICA is a surrogate for focal atherosclerotic plaque.

Joseph F. Polak, M.D., M.P.H., Michael J. Pencina, Ph.D., Karol M. Pencina, Ph.D., Christopher J. O'Donnell, M.D., M.P.H., Philip A. Wolf, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

Polak JF et al. N Engl J Med July 21, 2011;365:213-221

Results

The results showed that the Framingham risk factors were all significant predictors of cardiovascular disease.

Addition of mean CCA IMT: was significantly associated with the risk of cardiovascular disease: HR per 1-SD increase in thickness, 1.13; 95% [CI], 1.02 to 1.24; P=0.02

Addition of maximum IMT of ICA was also significantly associated with the risk of cardiovascular disease: HR per 1-SD increase in thickness, 1.21; 95% CI, 1.13 to 1.29; P<0.001

When ICA IMT was added to the model, the predictability sign increased by 0.010 (95% CI, 0.003 to 0.016; P=0.003), from 0.748 (95% CI, 0.719 to 0.776) to 0.758 (95% CI, 0.730 to 0.785).

Polak JF et al. N Engl J Med July 21, 2011;365:213-221

Intracranial Artery Calcification (IAC) Assoc. with CV Events in Post Stroke Patient

- 302 post IS pts; follow-up 2 yrs.; 45 CV events

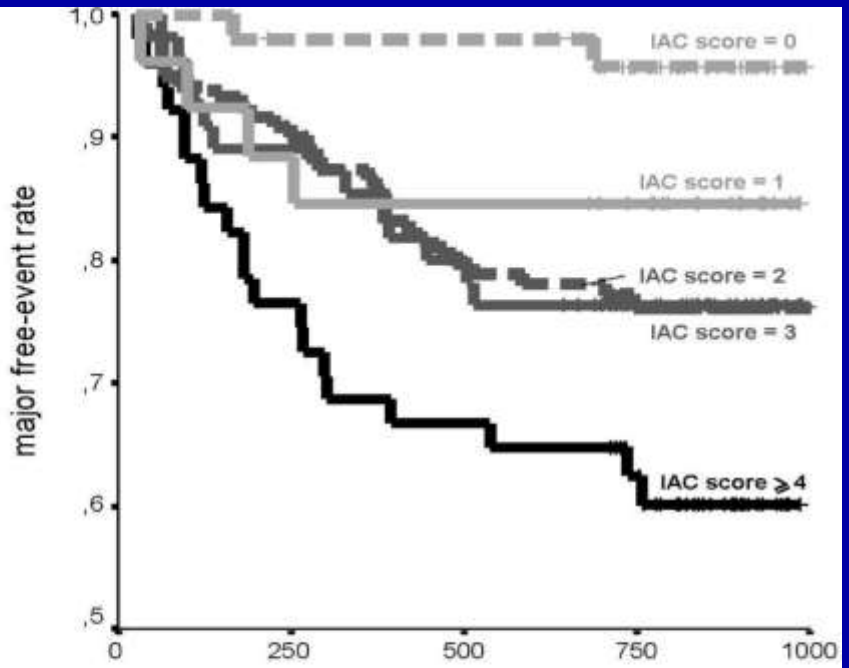
- IAC score was significantly associated with CV events

  HR 1.39; (95% CI, 1.10 –1.76) *p=0.007*

Bugnicourt, Jean-Marc, et. al.*Stroke* 10/2011
http://stroke.ahajournals.org/content/early/2011/09/22/STROKEAHA.111.618652

Intracranial Artery Calcification (IAC) Assoc. with CV Events in Post Stroke Pts

Kaplan–Meier analysis of the incidence of major clinical events in patients with ischemic stroke according to the IAC scores.
Patients with the highest IAC scores had significantly higher rates of death and vascular events than those with the Scores
(log rank test, *P0.029).*



Cumulative events					
IAc score = 0	0	1	1	2	2
IAC score = 1	0	4	4	4	4
IAC score = 2	0	12	25	28	28
IAC score = 3	0	7	13	13	13
IAC score ≥ 4	0	13	17	19	20

Bugnicourt, Jean-Marc, et. al.*Stroke* 10/2011
http://stroke.ahajournals.org/content/early/2011/09/22/STROKEAHA.111.618652

Sub-clinical Atherosclerosis Predicts CV Risk

- 10,000 healthy subjects followed 10 yrs.; 40% female; aged 35-65 yo; base line B-mode US carotids and femorals

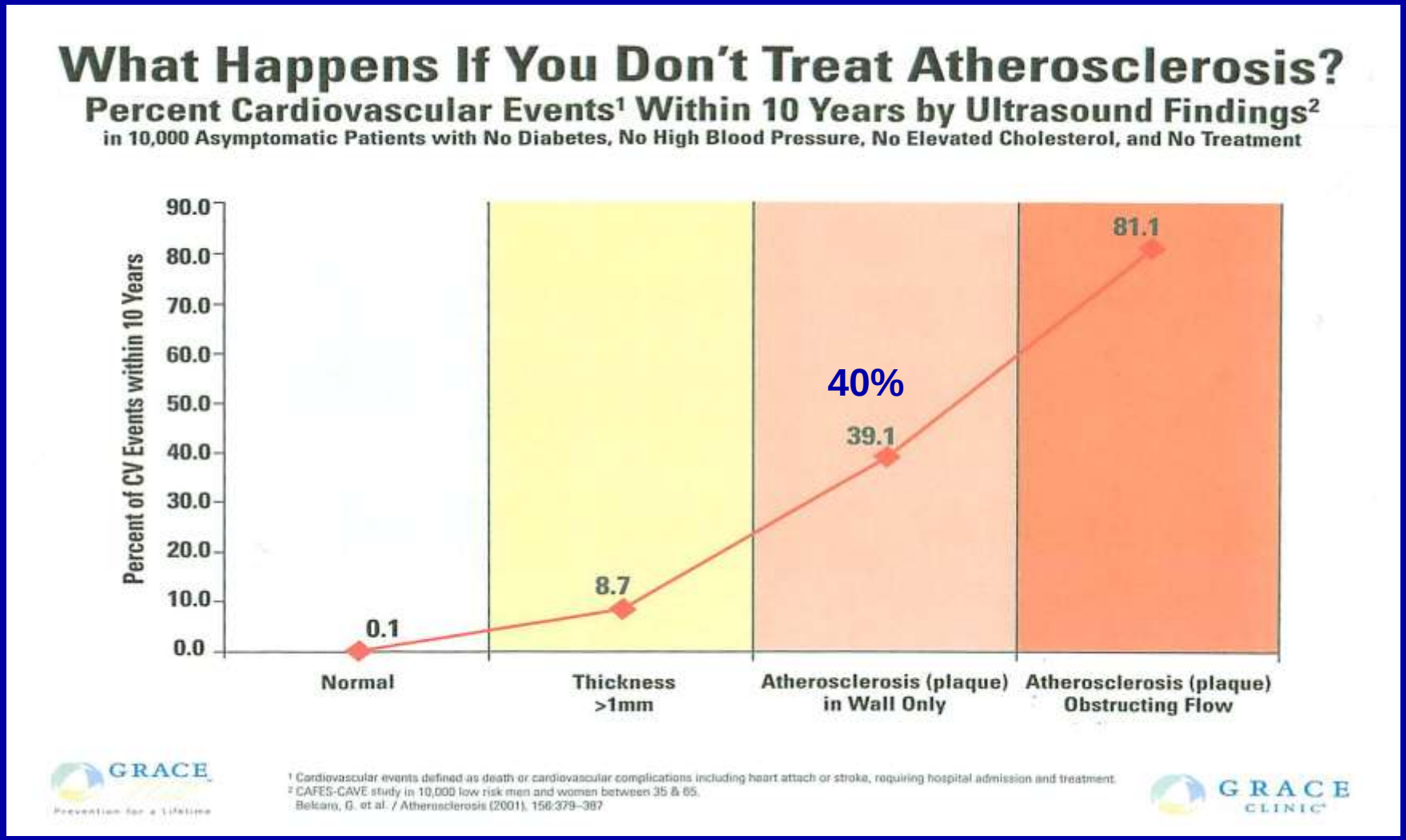
- No treatment allowed over 10 years -

- Class 1 (normal artery): 7989 subjects – 10 CV events
- Class 2 (wall thickening): 930 subjects - 81 CV events
- Class 3 (disease present): 611 subjects – 239 CV events
- Class 4 (stenotic disease): 470 subjects – 381 CV events

- Respective incidence: 0.1%; 8.6%; 39.8%; 81.1%

Belcaro, G., et. al. CAFES-CAVE Study. ***Atherosclerosis*** 2001. 156:379-387

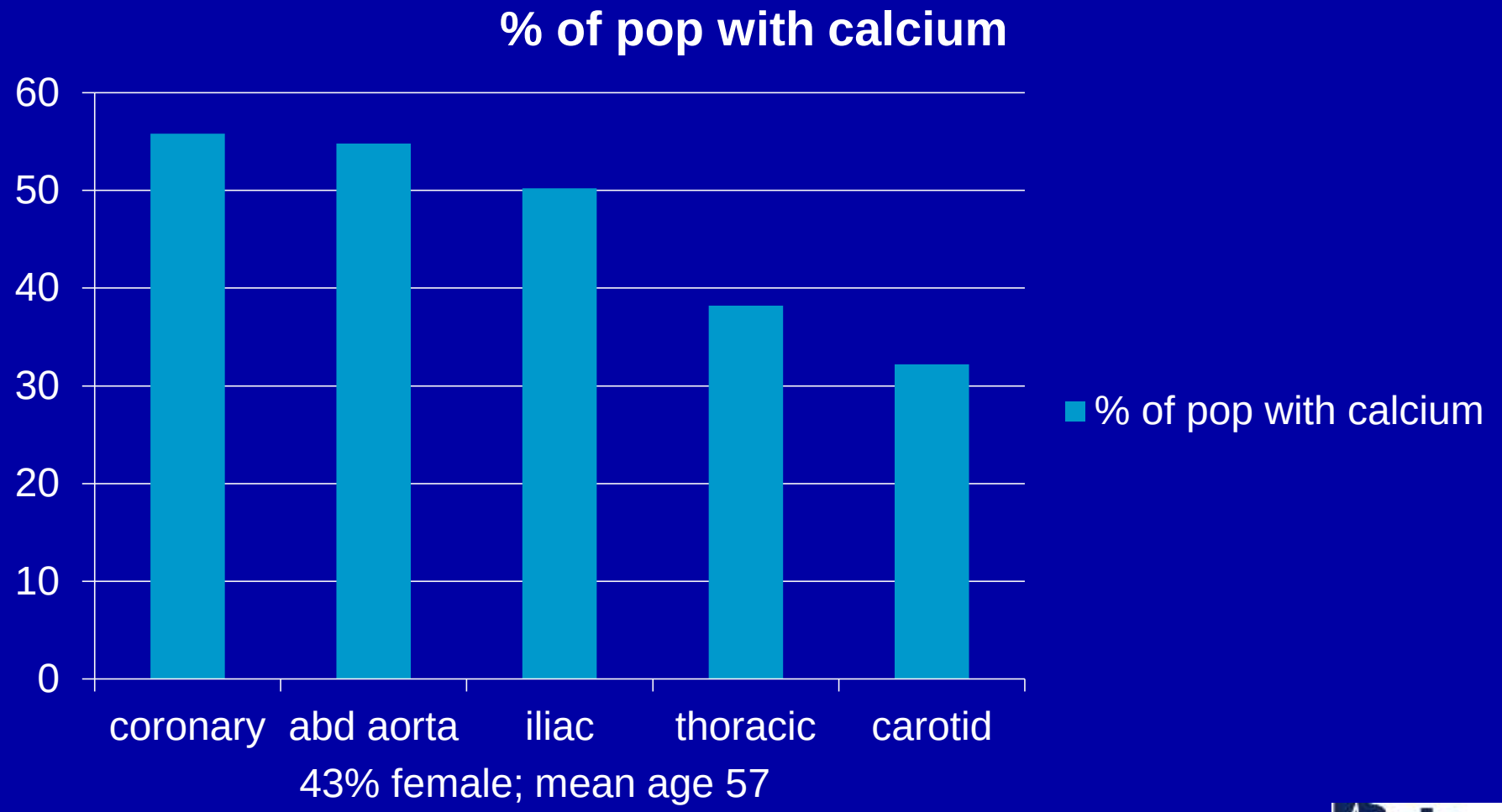
The Risk of Not Treating Plaque



Belcaro, G., et. al. ***Atherosclerosis*** 2001. Vol. 156:379-387

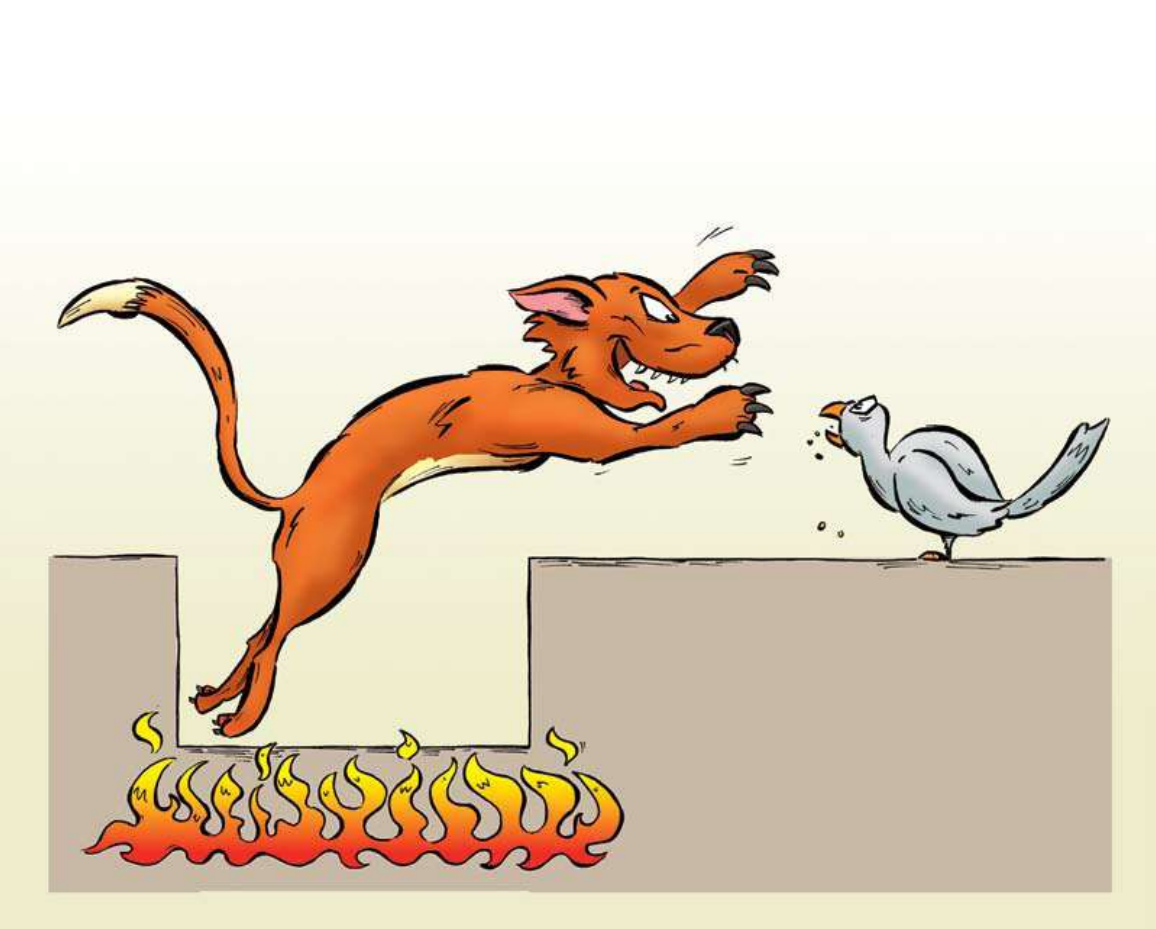
Calcium Revealed by Total Body CT Scans in Various Arterial Beds

Not everyone has plaque

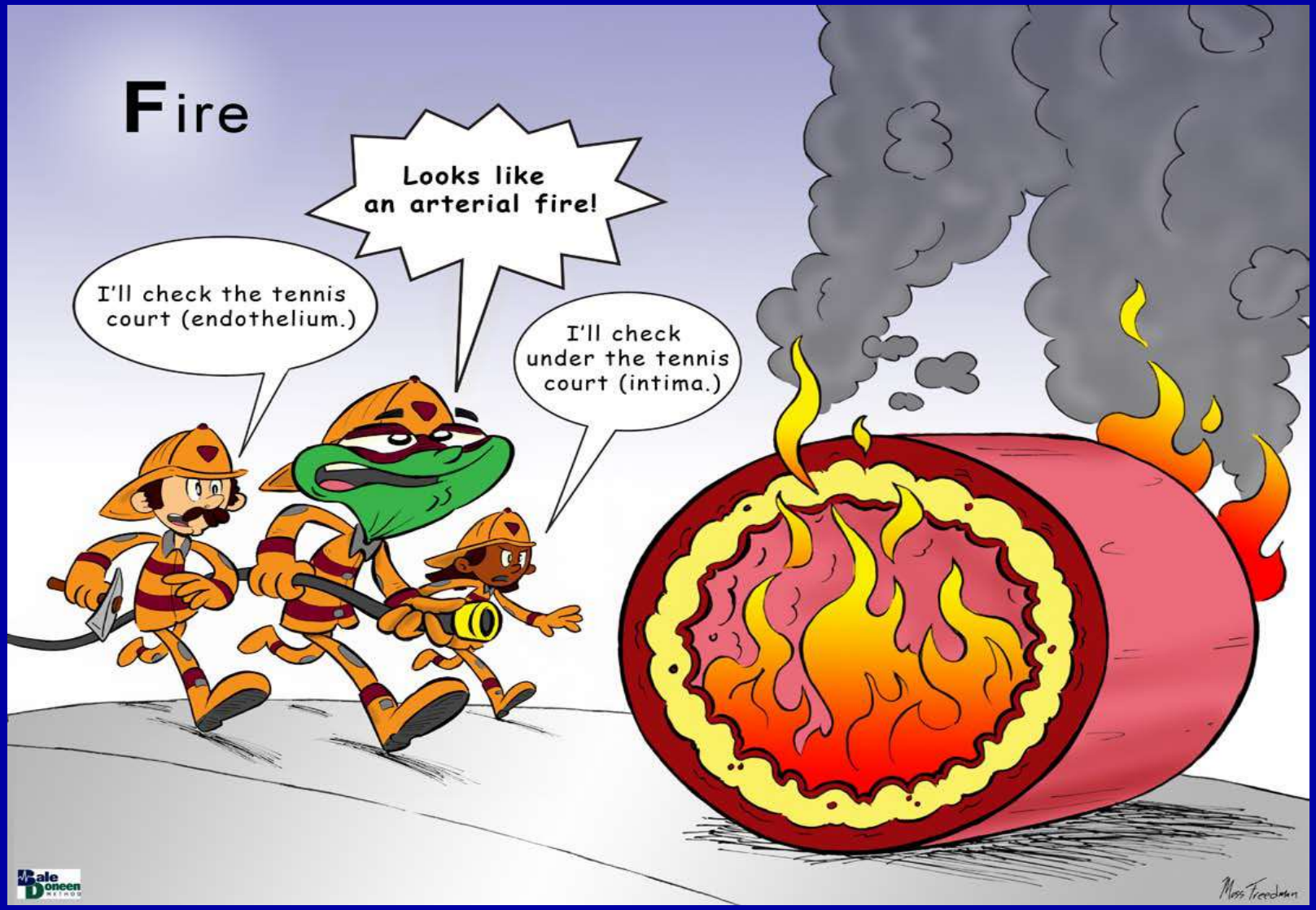


Allison M A., et.al. ***Arterioscler Thromb Vasc Biol. 1/2012;32:00-00***

Fire Makes the Cat Jump



Inflammation



Is This Happening to You??!!

Broad View - Oxidation

- Many age-related diseases (cardiovascular) seem to be mediated, at least in part, by oxidative stress

- Reactive Oxygen Species (ROS) generation and the corresponding response to oxidative stress are key factors in determining longevity

- F2 isoprostane considered gold standard test

Yours is 0.18; want < 0.86

Toren Finkel and Nikki J. Holbrook, Nature 2000; 408:239-47

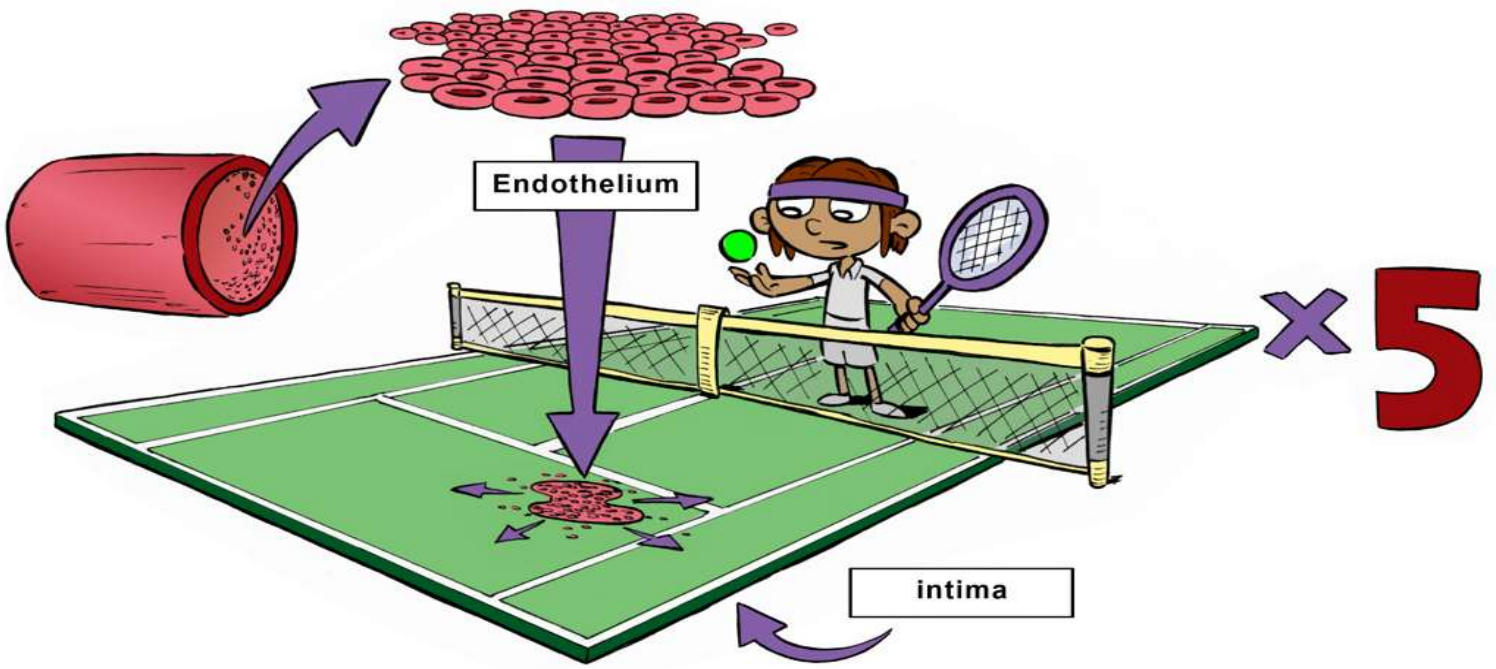
Myeloperoxidase (MPO), predicts future risk of coronary artery disease in healthy people

Regardless of other known risk factors !

Yours was 335; want < 480

Meuwese MC et al. *J Am Coll Cardiol* 7/2/2007; available at: http://content.onlinejacc.org.

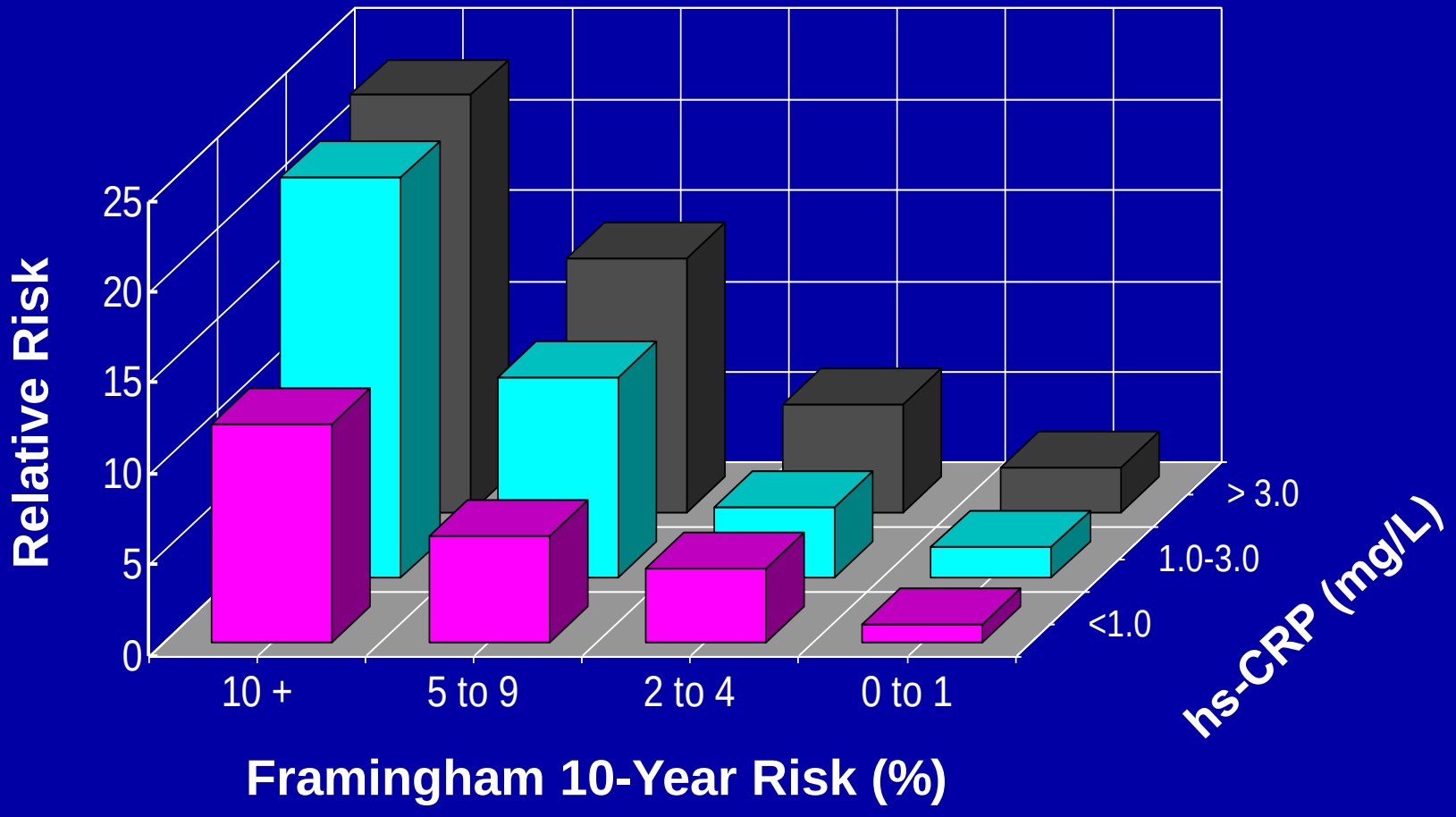
‘Tennis Court’



The endothelial cells which line our arteries are so numerous that, if taken out of your body, they would cover the surface of five tennis courts. These endothelial cells “tennis court” create a vital protective wall against heart attacks and strokes.

CRP: how hot is your tennis court????

Your level is 1.2 ; goal is <0.6



Ridker P et al. *N Engl J Med.* 2002;347:1557-1565.

MACR above 7.5 ug/mg females or 4.0 ug/mg males marks increased risk

End point	Hazard ratio	p
CVevent	2.92	<0.001

Fram. Offspring pts. ; mean age 55; 58% women

No baseline BP, DM, CVD; followed 6 yrs.

Cut off of 30 ug/mg is for risk of end stage renal disease!

Your level: 6.0

Ärnlöv J et al. *Circulation* 8/16/2005; 112:969-975.

How hot is it under your tennis court ??!!

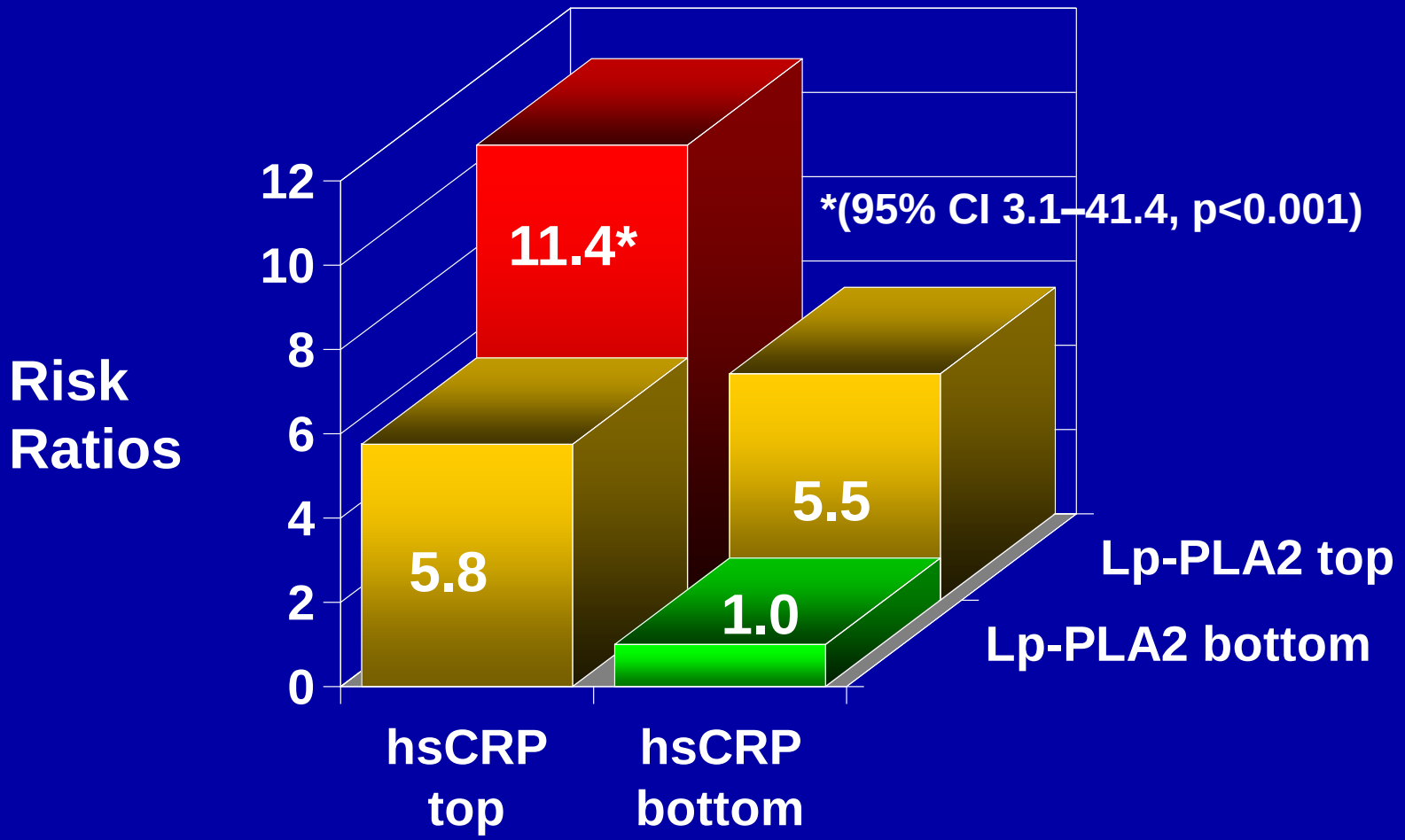
Your level is 241 ; want < 180

PLAC-2

What is this?

Let’s look at this animation !

Additive Risk for Incident Ischemic Stroke by Lp-PLA$_2$ and hsCRP Tertiles in ARIC



Adjusted for demographics, current smoking status, blood pressure, diabetes, LDL and HDL

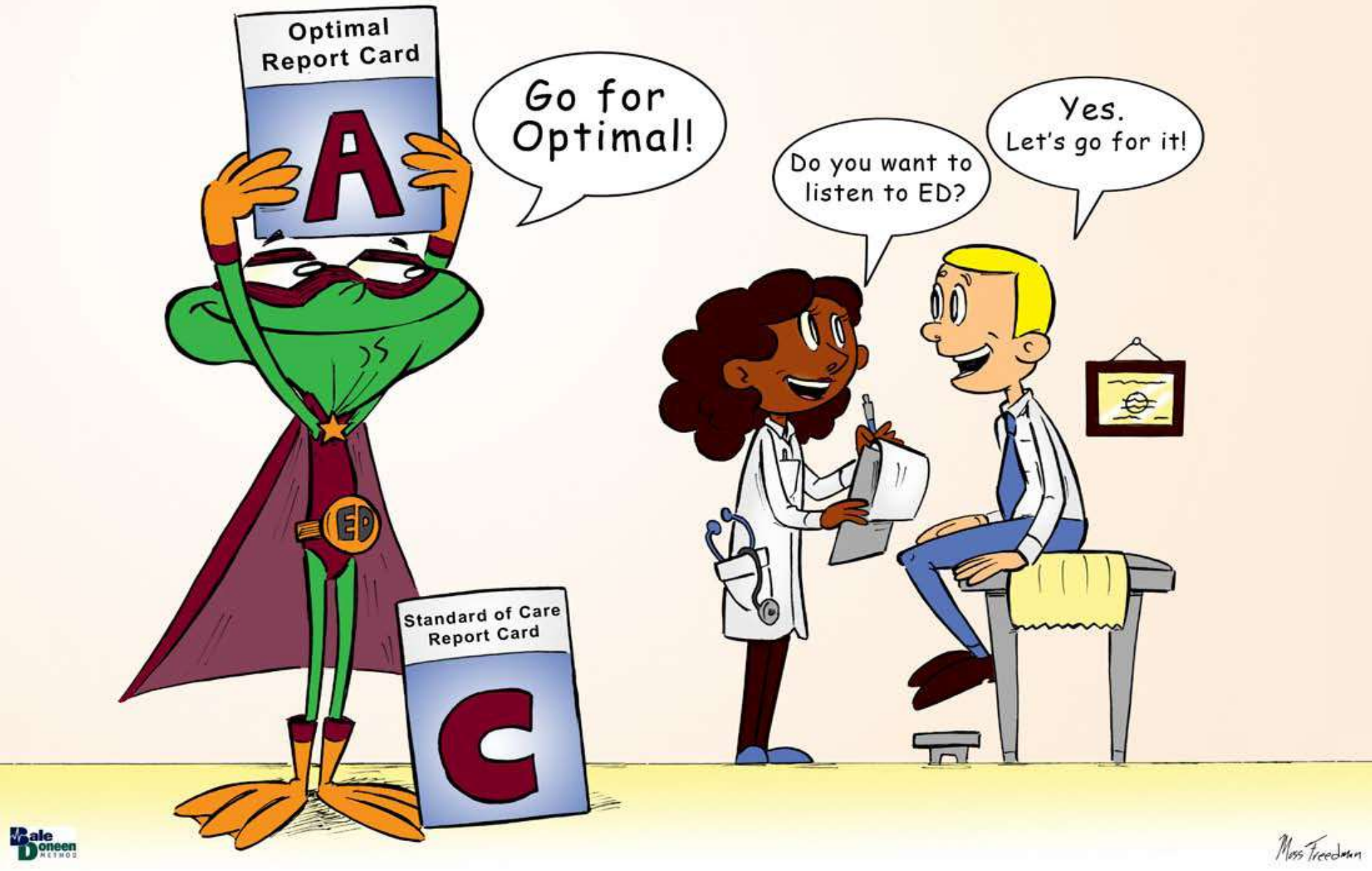
(Data on file with FDA)

Periodontal Disease Associated with Elevated Levels of Lp-PLA2

- 421 ‘healthy’ adults
- Those with PD were 1.8 times more likely to have Lp-PLA2 levels >215 ng/mL
- 37% of individuals with no CV risk factors except PD had elevated Lp-PLA2
- Suggests oral health exams can identify people at risk for CVD

Am J Cardiol 12/1/2008; 102:1509-1513

Optimal vs Standard of Care



Pre-hypertension vs BP > 120/80 Triples Risk for a Heart Attack over 10 years

I want your BP 115/75 or less (currently 130/90)

Outcome	Relative risk* (95% CI)
MI**	3.5 (1.6-7.5)

***Adjusted for age, gender, smoking, obesity, diabetes, hypercholesterolemia, and study period**
**** statistically significant**

5181 people from FHS; mean age 44yo; 55% female
Followed 10 years

Qureshi AI et al. *Stroke* 9/2005; available at http://stroke.ahajournals.org.

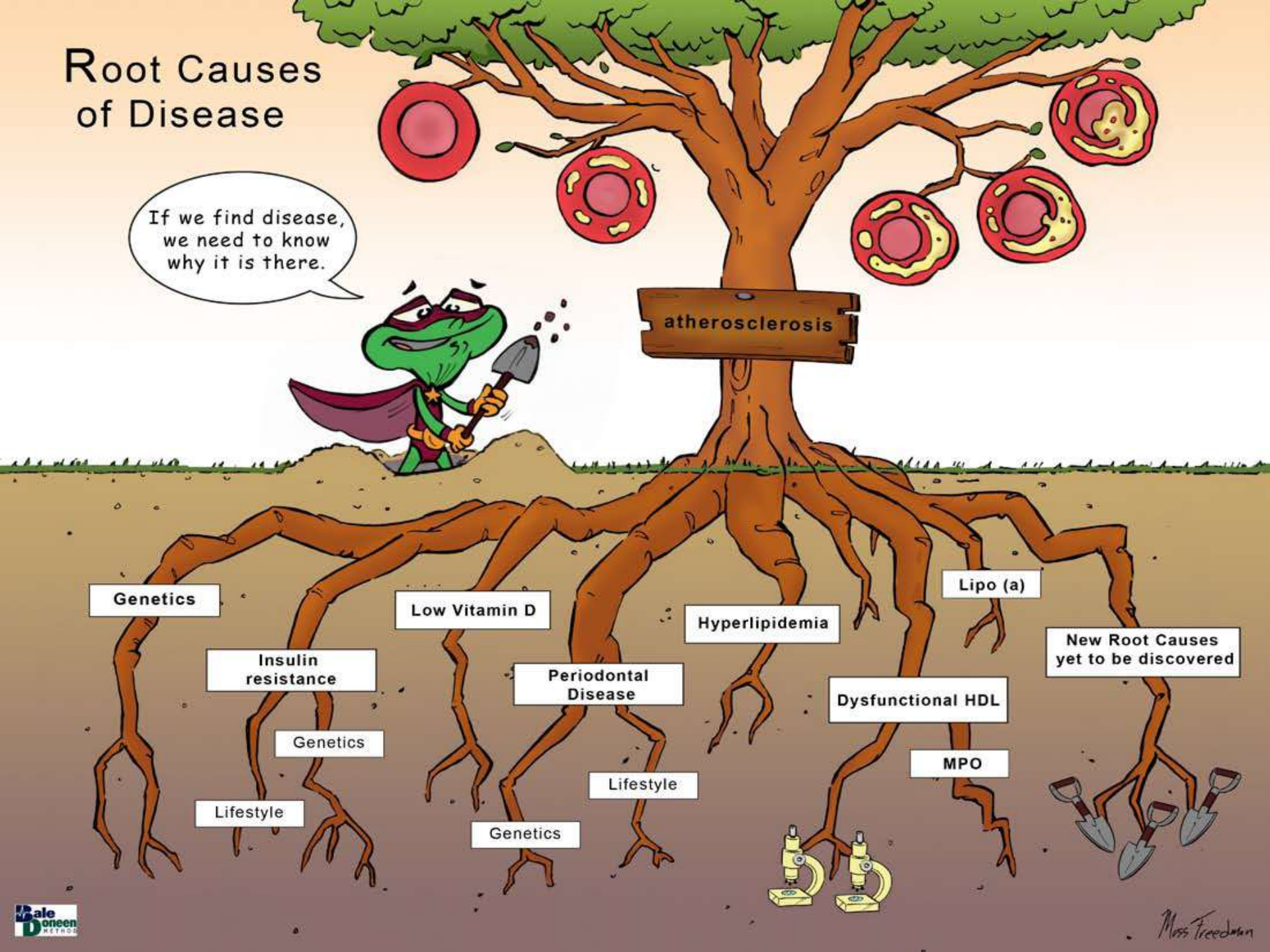
Pre-hypertension Independently Increases Stroke Risk About 50%

- 12 prospect. studies; 518,520 middle aged adults; 2.7 to 32 yrs
- RR of stroke: 1.55 (95% CI 1.35-1.79) p<0.001
  adjusted for age, sex, DM, BMI, smoking, cholesterol

Risk of stroke by prehypertension category

Prehypertension range (mm Hg)	Relative risk (95% CI)
SBP 120-129 or DBP 80-84	1.22 (0.95-1.57)
SBP 130-139 or DBP 85-89	1.79 (1.49-2.16)

Lee M, et. al. *Neurology* 9/28/2011; 77:1330-1337.


Root Causes of Disease
If we find disease, we need to know why it is there.
atherosclerosis
Genetics
Insulin resistance
Genetics
Lifestyle
Low Vitamin D
Periodontal Disease
Lifestyle
Genetics
Hyperlipidemia
Lipo (a)
Dysfunctional HDL
MPO
New Root Causes yet to be discovered
Dale Boneen METHOD
Moss Freedman

Standard Lipid Panel

Total Cholesterol:	147	(goal <200)	
Triglycerides:	62	(goal <100)	
HDL (good):	43	(goal >60)	HDL 2b: 12%
LDL (bad):	92	(goal <70)	LDL 3a+3b: 11.5%
Apo B (all bad):	71	(goal <60)	

*Dr. Gerald Reaven 1/2001; McLaughlin, Reaven, et.al., ***Am J Cardiol***. 8/1/2005;96:399-404

Lipoprotein Sub-classes Predict Multiple Invasive Cardiac Procedures

5.5 yrs.	Single PCI # 58	Repeat PCI # 21	P
HDL 2b < 20%	6%	94%	0.01
LDL 3a & 3b > 20%	10%	90%	0.007
LDL 4b > 10%	30%	70%	0.0004
HDLC < 40	40%	60%	0.05
TG > 200	55%	45%	0.12
LDLC > 100	85%	15%	0.24
LDL 4b > 10% & or HDL 2b <20%	0%	100%	

James Margolis, Charles Brown, Kristi Picardi, H. Robert Superko
AHA Meeting 2002, Chicago, IL

TC/HDL Best Predictor of CAD Death in Men

- 5,344 men aged 40 to 69; followed about 30 yrs.
- 447 CAD deaths; 215 in without hx; 232 in with hx ;only 8% of those with known CVD were on a statin
- TC / HDL ratio significantly predicted ischemic heart disease mortality in all men, with a HR of 1.57 (95% CI, 1.32-1.86)
- Associations did not change significantly after adjustment for other cardiovascular risks – including age, known CVD, statin use

Yours is TC/HDL 3.4 want < 3.0

Robert Clarke, MD, FRCP, Cardiology Review. May 2008

Dale Doneen METHOD

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

Definitions of Vit. D Status

Serum 25-Hydroxyvitamin D, ng/ml	Vitamin D Status
10	**Severe deficiency**
10-20	**Deficiency**
20-30	**Mild-moderate deficiency**
30	**Sufficient**
40-50	**Ideal**
50-150	**Intermediate data***
>150	**Toxicity**
Institute of Medicine Definitions†	
12	At risk of deficiency
12-19	At risk of inadequacy
20-50	Sufficient
>50	Possibly harmful

*Some data suggest increased falls, fractures, certain cancers, and even cardiovascular risk at values >50 ng/ml.

†Definitions adapted from Looker et al.

Lavie, C. J., et. al. *J. Am. Coll. Cardiol. 10/4/2011;58;1547-1556*

Periodontal Disease (PD) and CV Risk

- 3.8 X more likely to have a heart attack
- 2X more likely to have a stroke

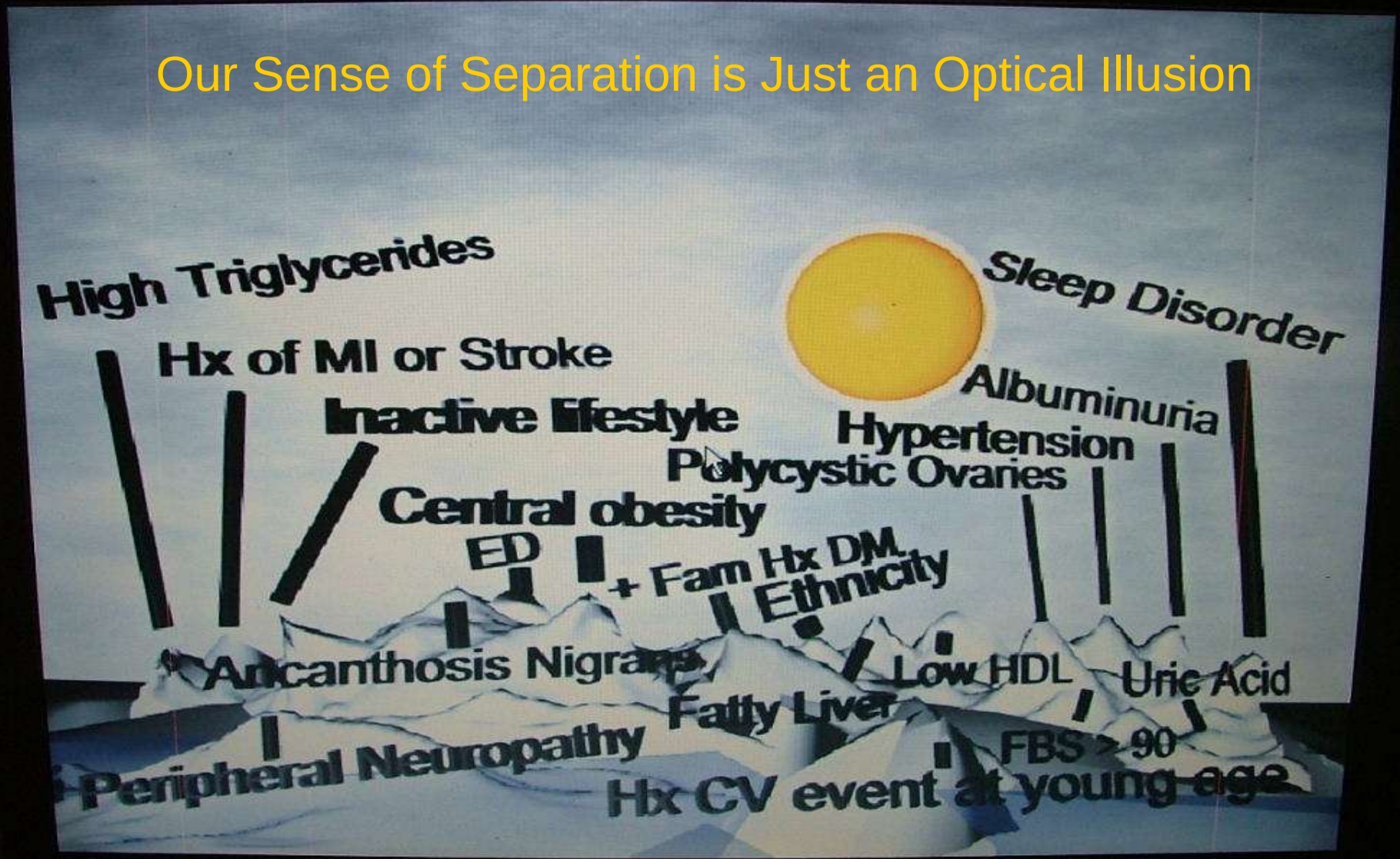
Connections: Oral & Systemic Health Review, July 2005, Vol. 1 No. 1:1-8

Insulin Resistance (IR) is a Proatherogenic State

IR damages the arteries regardless of the sugar*

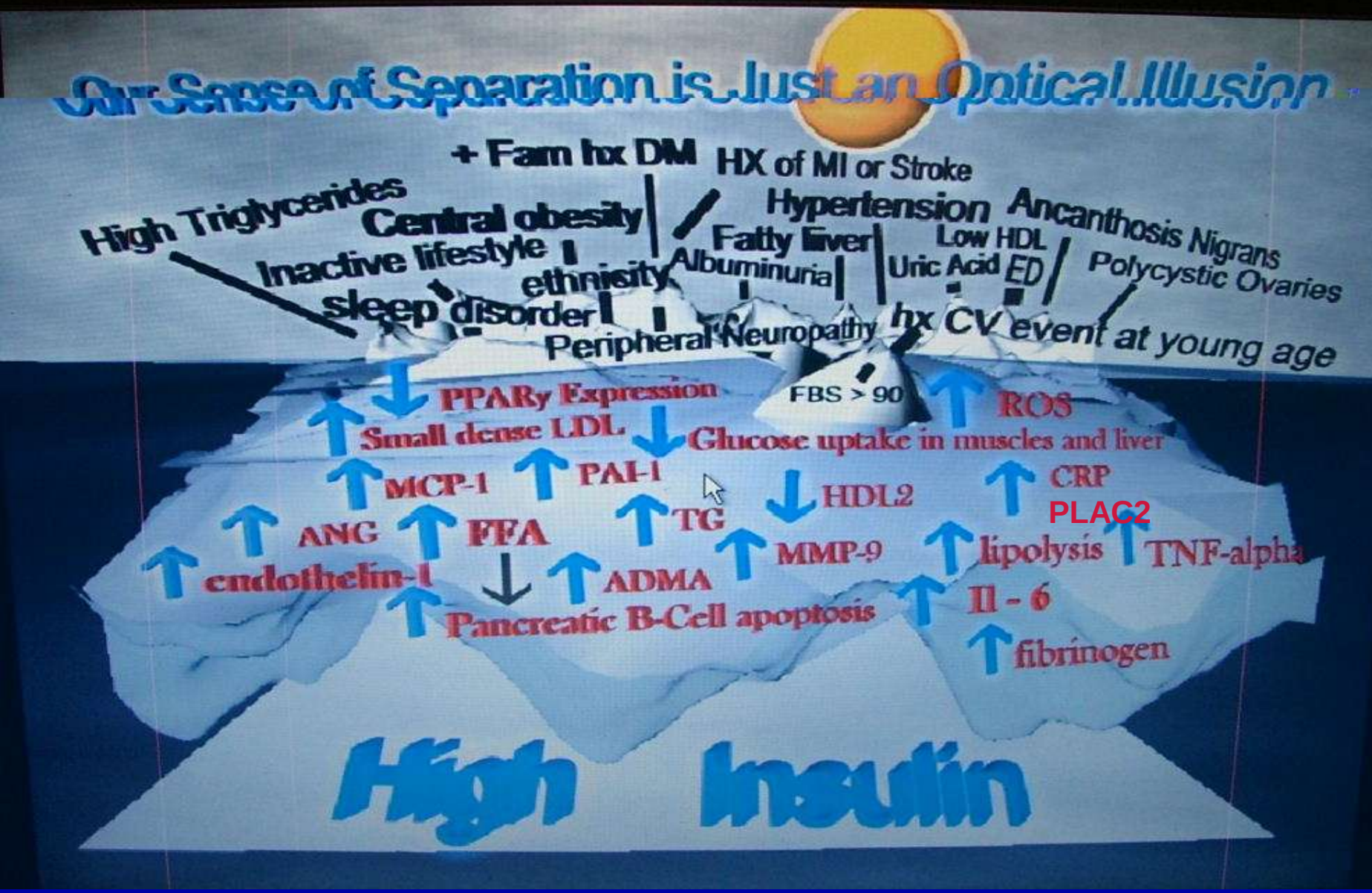
*DECODE Study Group. *Lancet* 1999;354:617–621.

Our Sense of Separation is Just an Optical Illusion



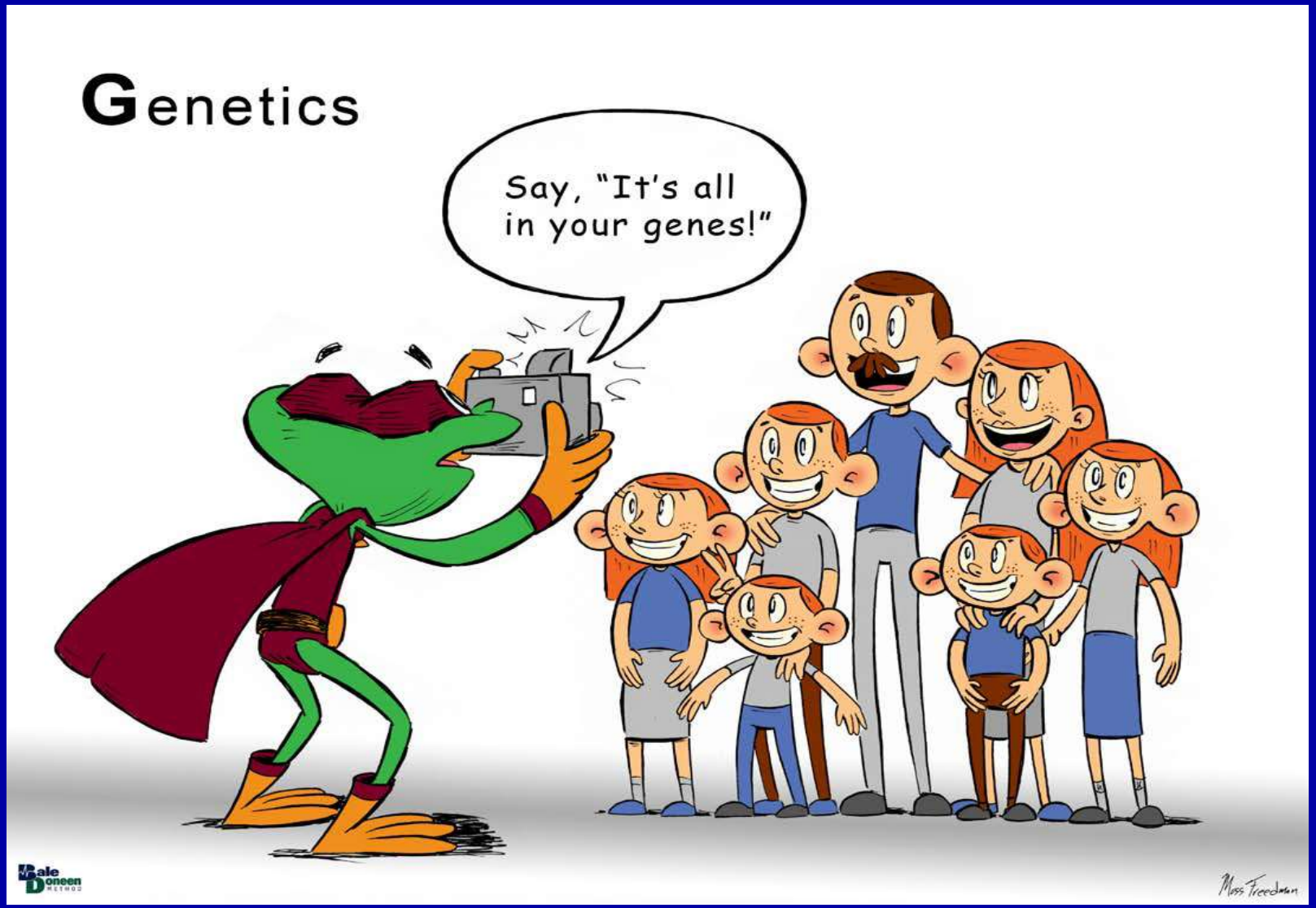
Insulin resistant icebergs: created by Bradley F Bale, MD; produced by Jacob Bale June 2002

Bale Doneen METHOD

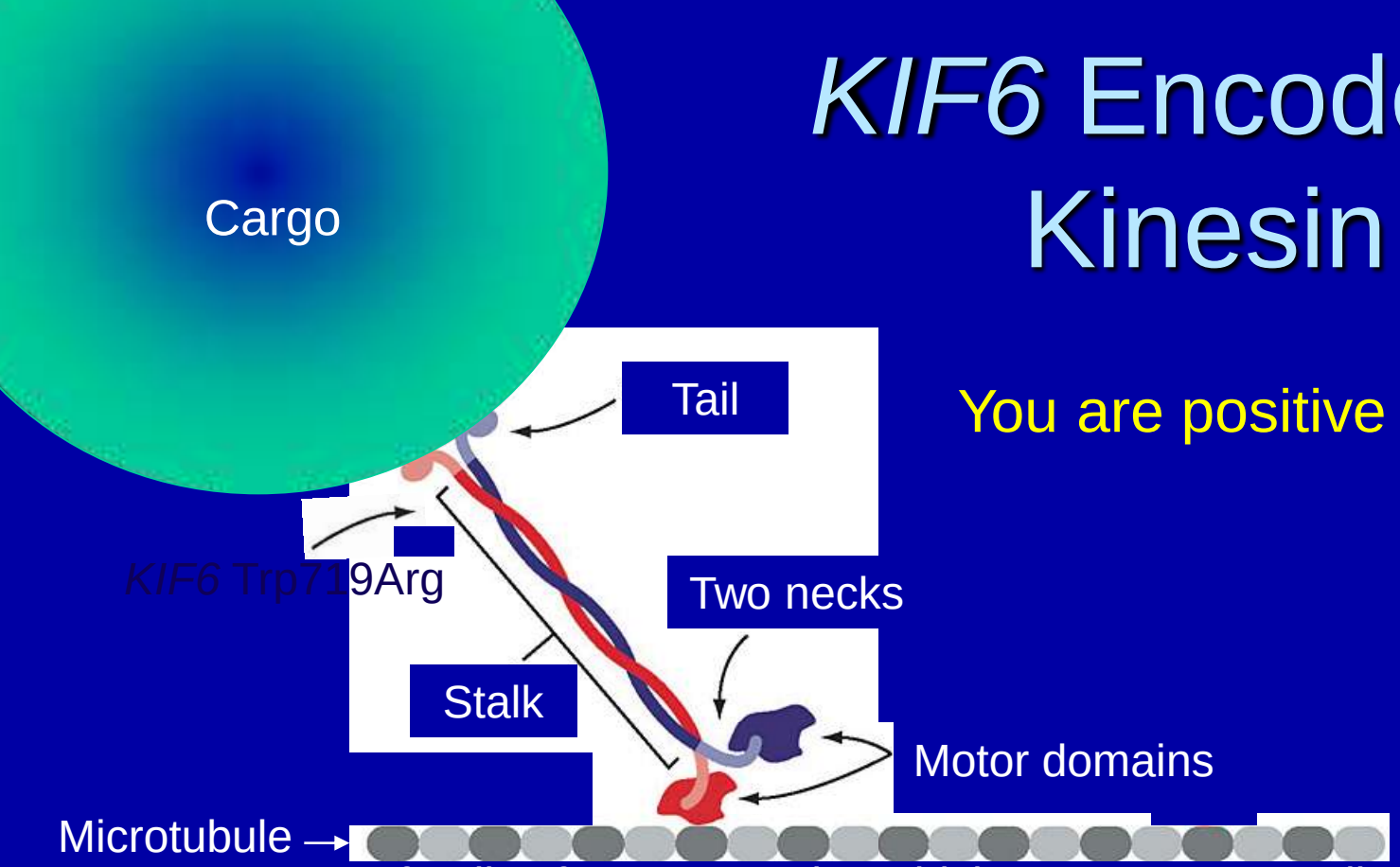


Insulin resistant icebergs: created by Bradley F Bale, MD; produced by Jacob Bale June 2002

Genes



KIF6 Encodes a Kinesin



You are positive for this gene

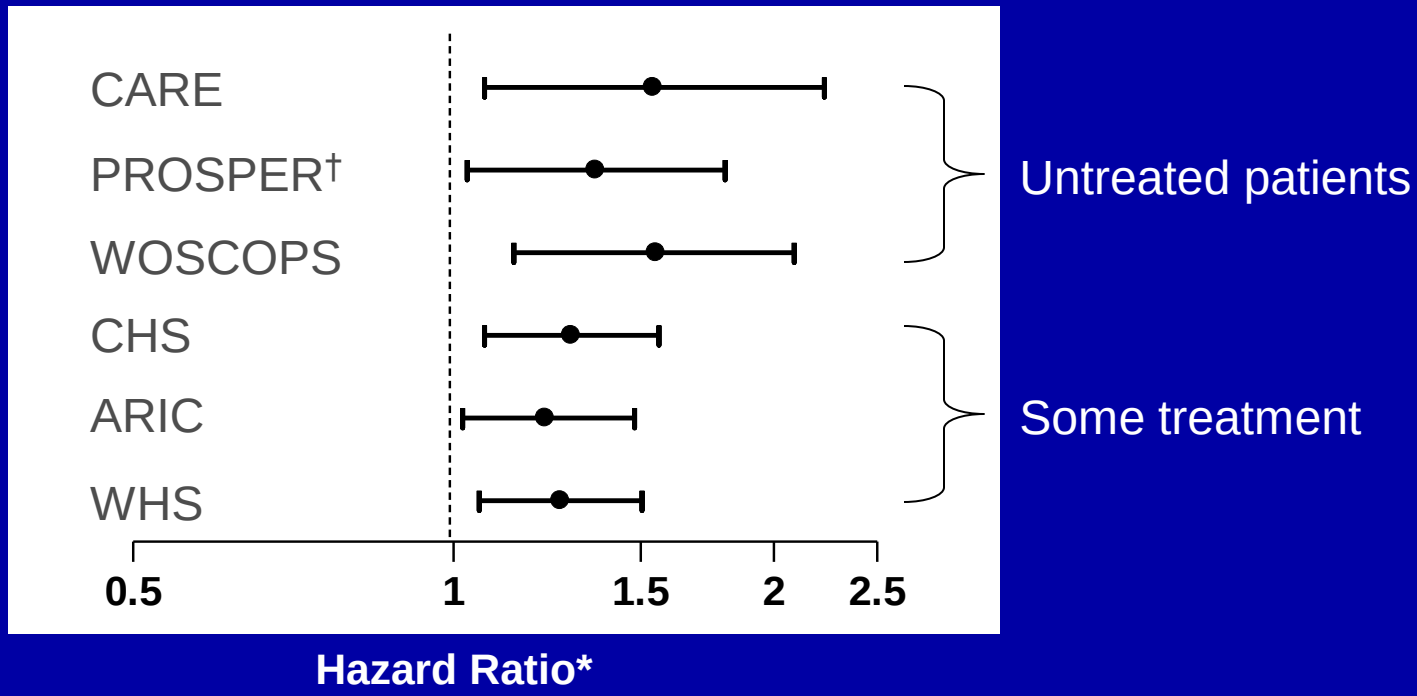
- Kinesins: a family of motor proteins which transport organelles, protein complexes and mRNAs within a cell
- The genetic variant changes tryptophan to an arginine
- This change results in a non-polar residue replacing a basic residue in the tail domain which may affect cargo binding or regulation in the motor domain

Asbury *et al*. *Science* **302**: 2130 (2003)

Asbury *et al*. *Science* **302**: 2130 (2003)

KIF6 Variant is Associated with CHD

Increased Risk in Untreated Populations



- *KIF6* variant predicts risk of CHD
- Up to 55% increased risk in untreated populations

**Adjusted for traditional risk factors*

†PROSPER patients with prior vascular disease

Clinical Significance of *KIF6* Testing

KIF6 carriers- may have higher life time CV risk

1. Maintain a disease treatment platform. (EDFROG)
2. Disease = absolute risk
3. Monitor for “cats in the gutter”? Routine evaluation
4. Any statin is beneficial

KIF6 noncarriers

1. Still can be at risk: monitor for disease
2. If using pravastatin or atorvastatin, consider treatment beyond mono-statin therapy
3. May want to favor statin therapy with simvastatin or rosuvastatin

Bale/Doneen Method Clinical Application

9p21

You inherited this gene from both of your parents.

- 50% of Caucasians and Asians are heterozygotes

  ~ 25% ⇧ risk of MI/CHD, 49% ⇧ risk of young age MI, 36% ⇧ risk of AAA compared non-carriers

- 23% of Caucasians and Asians are homozygotes

  ~ 56% risk of MI/CHD, 102% risk of young age MI, 74% risk of AAA compared to non-carriers

1. Helgadottir, A, et al. Science 316 (5830): 1491-1493.
2. Helgadottir,A, et al. Nature Genetics 40 (2): 217-224.

Treatment for arterial disease:

Foundation Treatment for Vascular Disease:

1. Lifestyle advice – Guided by your apo E 3/3 genotype
2. Omega 3 therapy: 2 gm per day
3. Antiplatelet therapy – Aspirin 81mg with resistance testing
4. ACE-I: Ramipril 10mg – goal <115/75
5. Statin Therapy – Simcor – combo definitely due to inflammation and IR dyslipidemia.

Foundation 1: Lifestyle

White Fruits and Vegetables May Protect Against Stroke

- Prospective 20,069 healthy subj. 20-65 yo; 55% women; followed 10yrs.; 233 strokes occurred
- Fruits and vegetables sorted into four color groups: green, orange/yellow, red/purple, white
- Only color associated with stroke was white
- Each 25-g/d (1/6 medium apple) increase in white fruit and vegetable reduced stroke risk 9%

HR, 0.91 (95% CI, 0.85– 0.97)

adjusted for age, sex, lifestyle, and dietary factors

Linda M. Oude Griep, MSc, et. al. ***Stroke. 10/2011;42:3190-3195***

Chocolate Associated with Lower Stroke Risk

- 33,372 women; 1,549 incident strokes in 10 yrs.

Multivariable stroke risk for a 50-g/week increase in chocolate

Stroke	Relative risk	95% CI
Total	0.86	0.77-0.96
Cerebral infarction	0.88	0.77-0.99
Hemorrhagic stroke	0.73	0.54-0.99

Larsson SC, et. al. *J Am Coll Cardiol* 10/18/2011; 58:1828-1829.

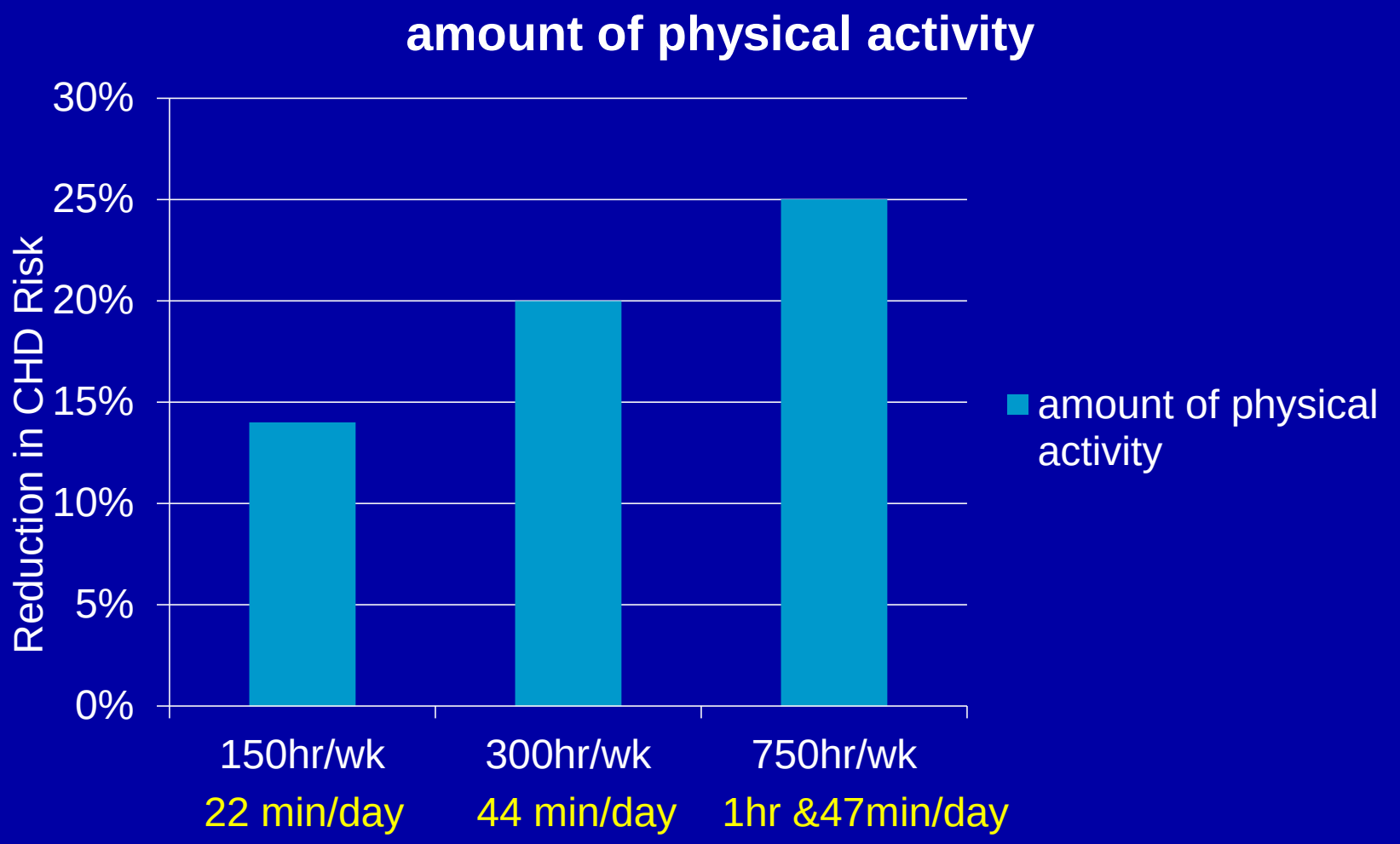
Oral Hygiene Associated with CV Event Risk

- 11,869 subjects; mean age 50; followed 8 yrs.
- 555 CV events (74% CAD)
- Poor oral hygiene = never or rarely brushed

  HR -1.7 (95% CI- 1.3 to 2.3) p<0.001

Oliveira, C., et. al. ***BMJ*** 5/27/2010;340:c2451

Exercise Amount Related to CHD Risk



Sattelmair J, et. al. *Circulation* 8/1/2011; DOI: 10.1161/CIRCULATIONAHA.110.010710. Available at: **http://circ.ahajournals.org**

Resistance training for CVD health

- lifting weights or exerting force against resistance
- resistance training has moderate effects on lean body mass and major effects on muscle strength
- aerobic exercise has no effect on lean body mass and minimal effects on mm strength
- both have small effects on HDL and LDL cholesterol
- Proper instruction and technique is essential

7/16/2007. *Circulation* 2007; DOI: 10.1161/CIRCULATIONAHA.107.185214. Available at: http://www.circulationaha.org.

Less Than Six Hours of Sleep a Night More Than Quadruples the Risk of Pre-diabetes

- 364 individuals followed for six years; 91 developed IFG; 273 controls who did not develop IFG
- Three sleep categories: < 6hrs. (25); 6-8 hrs. (314); > 8hrs. (24)
- If in group of < 6hrs., 4.7 times more likely to develop IFG
- Adjusted for: age, baseline glucose; BP; smoking; famhx of DM; weight change; depression

Lisa Rafalson, Ph.D. presented at the AHA Epidemiology and Prevention Meeting April, 2009

Foundation 3: Antiplatelet

"Aspirin resistance" raises risk of recurrent CV events

- meta-analysis 1813 patients with CVD from 12 prospective studies
- varied in the patients' CV conditions, aspirin dosages, tests for aspirin resistance, end points, and follow-up time
- average prevalence of ‘resistance” was 27%.
- odds ratio for CV events among patients with aspirin resistance was 3.8 (95% CI 2.3-6.1)

Arch Intern Med 8/13-27/2007; 167:1593-1599.

Foundation 3: ACE-I

BP Medications Lower CV Risk Regardless of Hypertension Diagnosis

- Meta-analysis of 147 randomized trials that involved 464,000 patients
- Approx. 50% reduction in CHD and CVD events for every 10 mm Hg diastolic reduction
- This held true for subjects without hypertension: even for BP's as low as 110/70

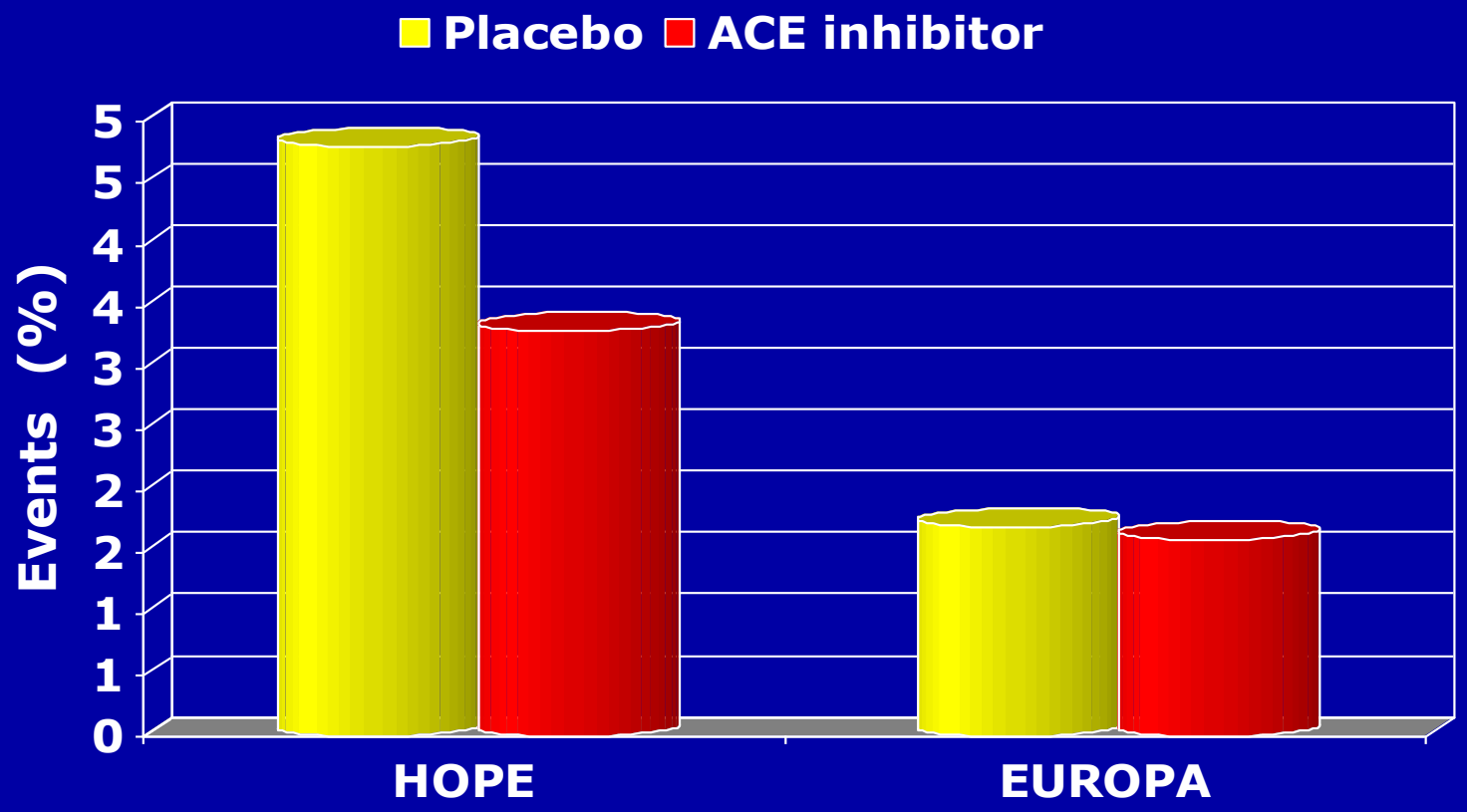
Law, M.R., et. al. ***BMJ*** 5/19/2009;338:b1665

American College of Physicians:

- Recommend all patients with CAD be on an angiotensin blocking agent

Annals of Internal Medicine, Oct. 2004

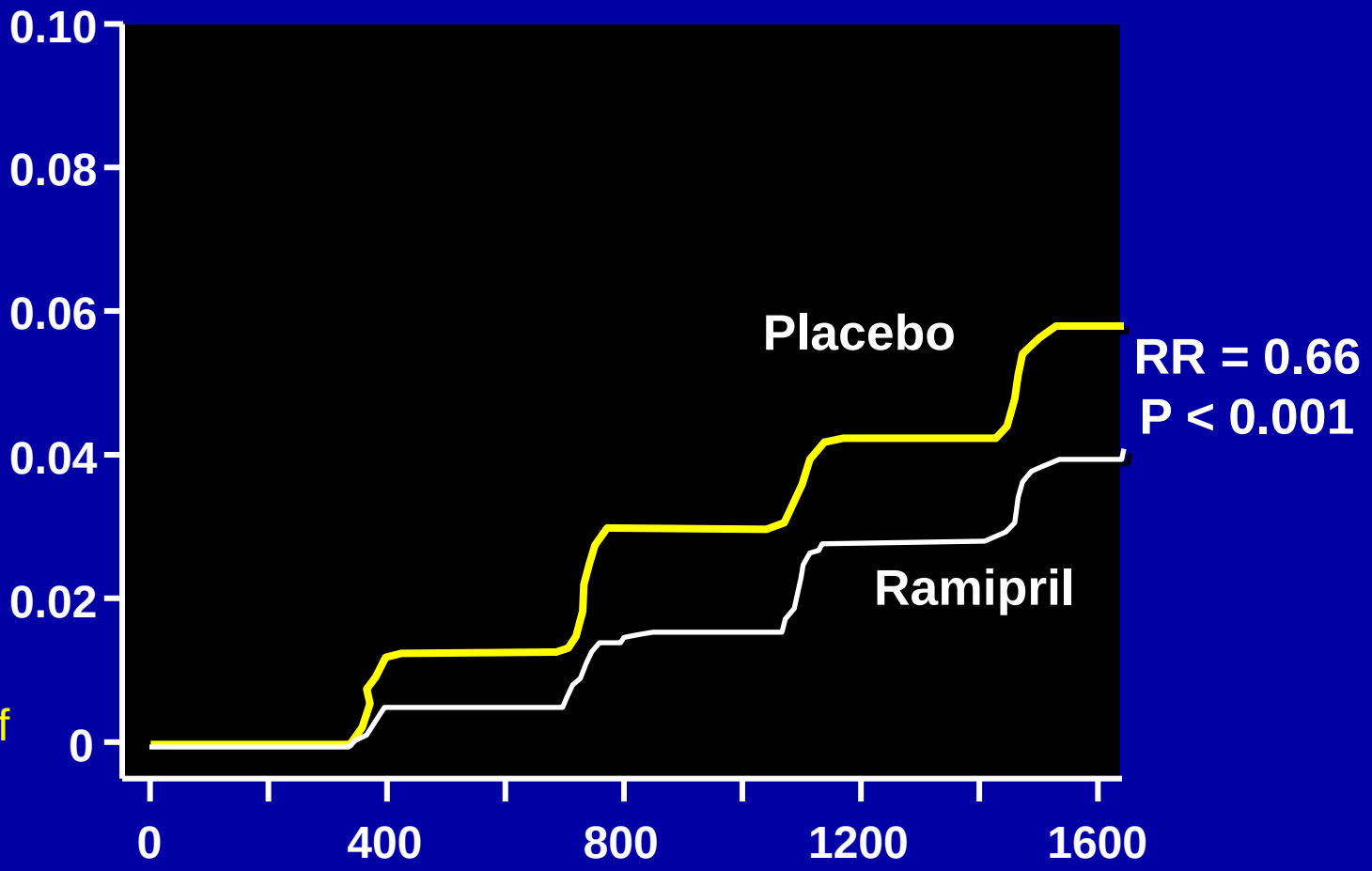
Stroke results
HOPE (ramipril) 32%
EUROPA (perindipril): NS 6%



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



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

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

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

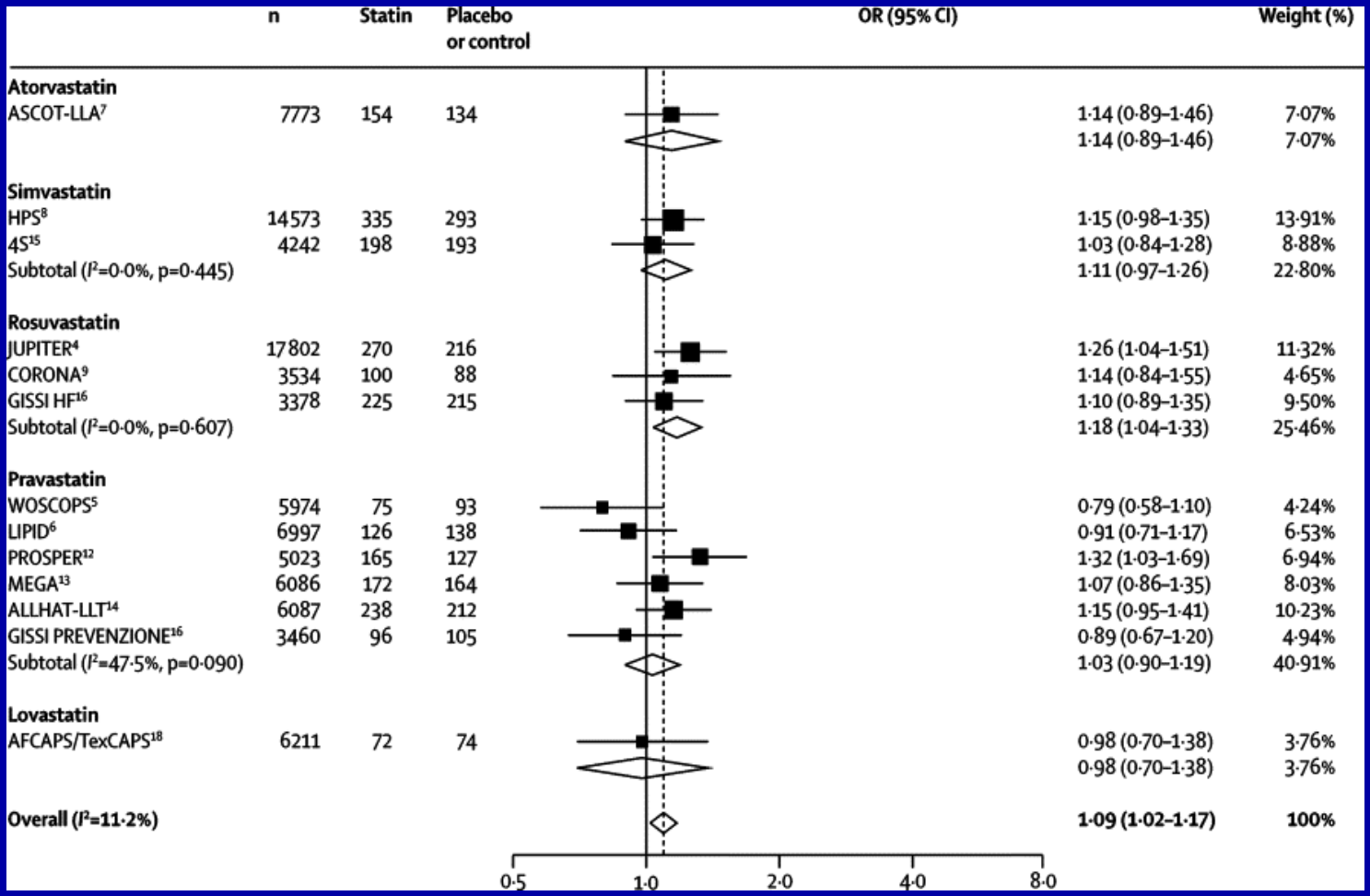
Foundation 5: Statin Therapy

Statins Beneficial Even if LDL is Very Low

- 4295 pts.; average age 65; 50% DM & or CAD; 2 yr. follow-up
- 60% of pts with LDL levels <60 mg/dL prescribed statins
- Statin rx reduced mortality 35%

Circulation 7/30/2007; 116:613-618

Statin RX and Incident DM

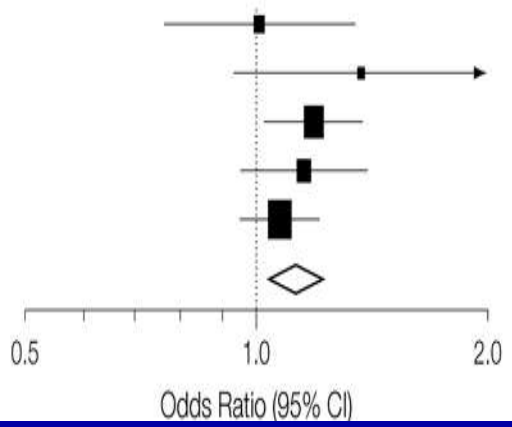


Only two trials met significance!!! Jupiter and Prosper !!!

Sattar N., ProfPhD, et. al. *Lancet*. 3/2010 Vol. 375, Issue 9716:735-742

Meta-analysis of New-Onset DM Comparing Intensive-Dose to Moderate-Dose Statin Rx

Incident Diabetes	Cases/Total, No. (%) Intensive Dose	Moderate Dose	OR (95% CI)
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16 408 (8.8)	1300/16 344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2 = 0\%$; $P = .60$			



32,752 pts without diabetes at baseline; 2,749 developed diabetes in a year
1,449 high dose statin ; 1,300 low to moderate-dose statin
Only one of the five trials was significant !!
Surprised more did not become diabetic as at least 70% were IR at baseline!!

Preiss, D. et al. JAMA 6/22/2011;305:2556-2564

Baseline Data From Trials Comparing Intensive-Dose to Moderate-Dose Statin Rx

Table 2. Baseline Data From Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

Source	BMI, Mean (SD)[a]	Age, Mean (SD), y	HDL, Mean (SD), mg/dL	LDL, Mean (SD), mg/dL	LDL Reduction, Relative %[b]	ln Triglycerides, Mean (SD), mg/dL	FPG, Mean (SD), mg/dL	FPG Measured After Baseline
Cannon et al (PROVE IT–TIMI 22),[18] 2004	29 (5)	58 (11)	39 (12)	109 (31)	22	5.05 (0.44)	104 (11)[c]	Not specified[c]
de Lemos et al (A to Z),[17] 2004	NA	60 (11)	39 (12)	113 (27)	15	5.00 (0.39)	NA	NA
LaRosa et al (TNT),[15] 2005[d]	28 (4)	61 (9)	47 (12)	98 (20)	22	4.89 (0.42)	97 (11)	Annually
Pedersen et al (IDEAL),[16] 2005[d]	27 (4)	62 (10)	47 (12)	125 (35)	16	4.87 (0.44)	99 (11)	Final visit
Armitage et al (SEARCH),[5] 2010	28 (4)	64 (9)	43 (16)[e]	98 (23)[e]	12	4.97 (0.54)[e]	NA	NA

Abbreviations: A to Z, Aggrastat to Zocor trial; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; LDL, low-density lipoprotein cholesterol; NA, not available; PROVE IT–TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets study.

SI conversion factors: To convert HDL and LDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Calculated as [LDL(intensive-dose group)–LDL(moderate-dose group)]/LDL(baseline).

[c] For baseline FPG level, there were 315 results from the PROVE IT–TIMI 22 participants, which were similarly distributed between treatment groups.

[d] Excluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.

[e] Nonfasting.

Unclear whether statin rx is associated with a tendency for an increase in DM or whether these individuals are just at higher risk.

Preiss, D. et al. JAMA 2011;305:2556-2564

National Guidelines: Niacin Therapy

NCEP ATP III Guidelines[1]

- "*Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.*"

ADA/AHA 2007 Scientific Statement[2]

- *"The most effective available drug for raising HDL-cholesterol levels is nicotinic acid.*"

[1]Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation*. 2002;106:3143-3421.
[2]Buse JB, et al. *Diabetes Care.* 2007;30:162-172.

Flu vaccine recommended for all patients with CVD

Manufacturer	How to order for the 2006/2007 influenza season
GlaxoSmithKline	Call Flurix Service Center at 1-866-475-8222 (choose option 1)
Novartis (formerly Chiron)	Call 1-800-244-7668 (choose option 2) to receive a list of vaccine distributors in your area
Sanofi Pasteur	Set up a provider account and then place order at http://www.vaccineshoppe.com.

50% reduction in CV deaths in vaccinated pts.

Up to 91,000 pts. A year die from CV events triggered by the flu

Use inactivated influenza vaccine

Davis MM et al. *Circulation* 9/18/2006; 114:1549-1553.

In summary

Dear Jason,

I am very pleased you are here. Your plaque is driven by an underlying insulin resistance condition and genetics that include KIF 6 and 9P21. Your low vitamin D level is also a contributor. Already, the simcor, omega 3, ramipril and baby aspirin are protecting you. We need to move forward with treating your insulin resistance but first I want to see how your inflammation has settled.

Warmly,

Amy

Treatment: 1 med at a time

1. Lifestyle – see dietician, 22min exercise, sleep, stress management.
2. Cinnamon 2gm/day, dark chocolate 7 gm/d
3. Vitamin D3 5000 iu day
4. Omega 3 2000mg /day
5. Simcor 40/1000 (titrate)
6. Ramipril 10mg (titrate)
7. Aspirin 81 mg – follow up aspirin test
8. Dental exam – IL-1 and Myperiopath
9. Eye exam – complete – send me report.
10. Next visit: 1 month, evaluate inflammatory and safety labs and discuss IR and treatment.