Bale/Doneen Live Chat Session

Amy Doneen MSN, ARNP

February 6, 2014

5:30-6:30 pm PST

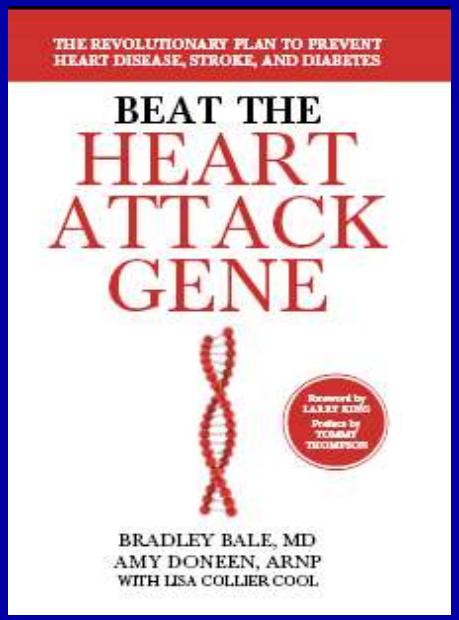
February 5, 2014

- **Amazon Best Sellers Rank:** out of 10,315 in Books (See Top 100 in Books)

#1 in Books > **Genetic**

#6 in Books> **Cardiovascular**

#7 in Books > **Cardiology**



Outline for today's discussion

New Guidelines

- JNC 8 HTN Guidelines
- Women and Stroke AHA/ASA Guidelines
- Obesity in childhood

Red Flags:

- Trigeminal Neuralgia
- NAFLD
- Psoriasis

Root Causes:

- Smoking

Treatment:

- Physical Exercise – when is it too much?
- Exercise in youth – protective later
- Omega 3 fatty acids and reduction of T2DM
- Influenza Vaccine

Case presentations

Review of Slide deck to preceptors – if time.

JNC 8 – Feb 2014

Box. Recommendations for Management of Hypertension

Recommendation 1

In the general … pharmacologic treatment to lower … pressure (SBP) ≥150 mm Hg or dias… Hg and treat to a goal SBP <150 mm … ng Recommendation – Grade A)

>60 years
BP Treat/goal: 150/90

Corollary Recommendation

In the general population aged ≥60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140 mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

Recommendation 2

In the general p… …cologic treatment to lower BP at DBP … 90 mm Hg. (For ages 30-59 years, St… For ages 18-29 years, Expert Opinion …

<60 years old
DBP Treat/goal: 90

Recommendation 3

In the general p… …cologic treatment to lower BP at SBP … <140 mm Hg. (Expert Opinion – Grade…

<60 years old
SBP Treat/goal: 140

Recommendati…

In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

James, P., Oparil, S. et al. 2014 Evidence-based guidelines for the management of HTN in adults (JNC8). JAMA. Doi:10.1001/jama12/2013

Dale Doneen METHOD

JNC 8

Recommendation 5

In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

Recommendation 7

In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population: Moderate Recommendation – Grade B; for black patients with diabetes: Weak Recommendation – Grade C)

Recommendation 8

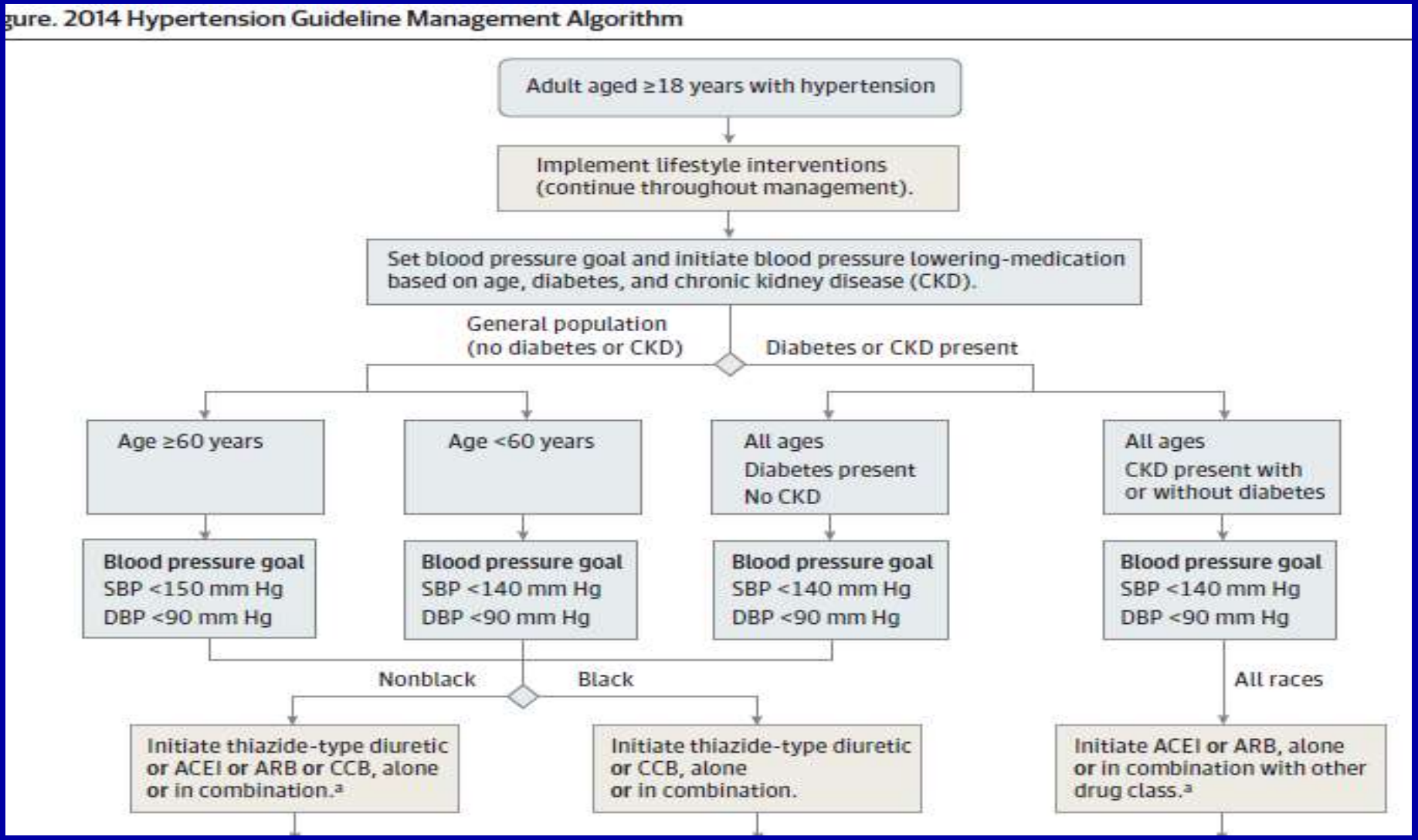
In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

Recommendation 9

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in

James, P., Oparil, S. et al. 2014 Evidence-based guidelines for the management of HTN in adults (JNC8). JAMA. Doi:10.1001/jama12/2013

JNC 8



James, P., Oparil, S. et al. 2014 Evidence-based guidelines for the management of HTN in adults (JNC8). JAMA. Doi:10.1001/jama12/2013

Bale Doneen METHOD

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.

Stroke and women

Guidelines for the Prevention of Stroke in Women AHA/ASA

Study embargoed for: 3 pm CT/4p.m. ET Thursday Feb 6, 2014

The Aim of this statement is to summarize data on stroke risk factors that are unique to women and provide cardiovascular prevention guidelines for women.

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Guidelines for the Prevention of Stroke in Women AHA/ASA

The guidelines focus on the risk factors unique to women and stroke r/t preeclampsia, oral contraceptives, menopause, HRT, obesity/metsynd, AF, migraine with aura.

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Statistics – U.S. Stats

Estimated 6.8 million (2.8%) of people in the US are living after having a stroke – 3.8 million women and 3 million men.

Stroke is the 5th leading cause of death for men and 3rd leading cause of death for women. Nearly half of stroke survivors have residual deficits

Formal guidelines for women and stroke have not been published.

53.5% of stroke occur in women vs men. 60% of stroke deaths in women.

87% strokes are ischemic (IS) and 10% are hemorrhagic (ICH) and 3% subarachnoid (SAH)

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Stroke Awareness

Delayed hospital arrival is the single most important reason for the failure to administer thrombolytic treatment (3-4.5 hours)

Women have longer pre-hospital delay than men despite women showing more knowledge and awareness of stroke symptoms.

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Stroke & Prehypertension

INTERSTROKE - women had a higher risk of stroke with self-reported BPs of 160/90mm Hg [OR] 4.89 than men (CI, 3.79-6.32)

Older women (mean age 63 years) with prehypertension had a 93% increased risk of stroke compared with normotensive women in the WHI cohort – implies that early and sustained treatment of HTN is critical.

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Stroke and issue unique to women

Pregnancy induced hypertension

Preecclampsia and stroke

Oral Contraceptives and stroke

HRT and stroke

Migraine with Aura and stroke

Metabolic syndrome, obesity and stroke

AF and Stroke

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Risk factor stratification

Table 16. Risk Factors and Points Included in the Framingham Stroke Risk Score for 10-Year Stroke Risk Prediction in Women*

Predictors	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Age, y	54–56	57–59	60–62	63–64	65–67	68–70	71–73	74–76	77–78	79–81	82–84
SBP (untreated), mm Hg		95–106	107–118	119–130	131–143	144–155	156–167	168–180	181–192	193–204	205–216
SBP (treated), mm Hg		95–106	107–113	14–119	120–125	126–131	132–139	140–148	149–160	161–204	204–216
Diabetes mellitus	No			Yes							
Cigarette smoking	No			Yes							
Prior cardiovascular disease†	No		Yes								
Atrial fibrillation	No						Yes				
LVH on ECG	No				Yes	Yes					

ECG indicates electrocardiogram; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Risk factor stratification

Table 17. Ten-Year Stroke Probability in Women According to Framingham Stroke Risk Score

Points	10-y Probability, %	Points	10-y Probability, %	Points	10-y Probability, %
1	1	11	8	21	43
2	1	12	9	22	50
3	2	13	11	23	57
4	2	14	13	24	64
5	2	15	16	25	71
6	3	16	19	26	78
7	4	17	23	27	84
8	4	18	27		
9	5	19	32		
10	6	20	37		

Bushnell, C., McCullough, L., et al. Guidelines for the prevention of stroke in women. AHA/SASA Guidelines. Stroke. 2014;45:000-000.

Obesity and children

Incidence of Childhood Obesity in the United States

Solveig A. Cunningham, Ph.D., Michael R. Kramer, Ph.D., and K.M. Venkat Narayan, M.D.

N Engl J Med, Volume 370(5):403-411
January 30, 2014

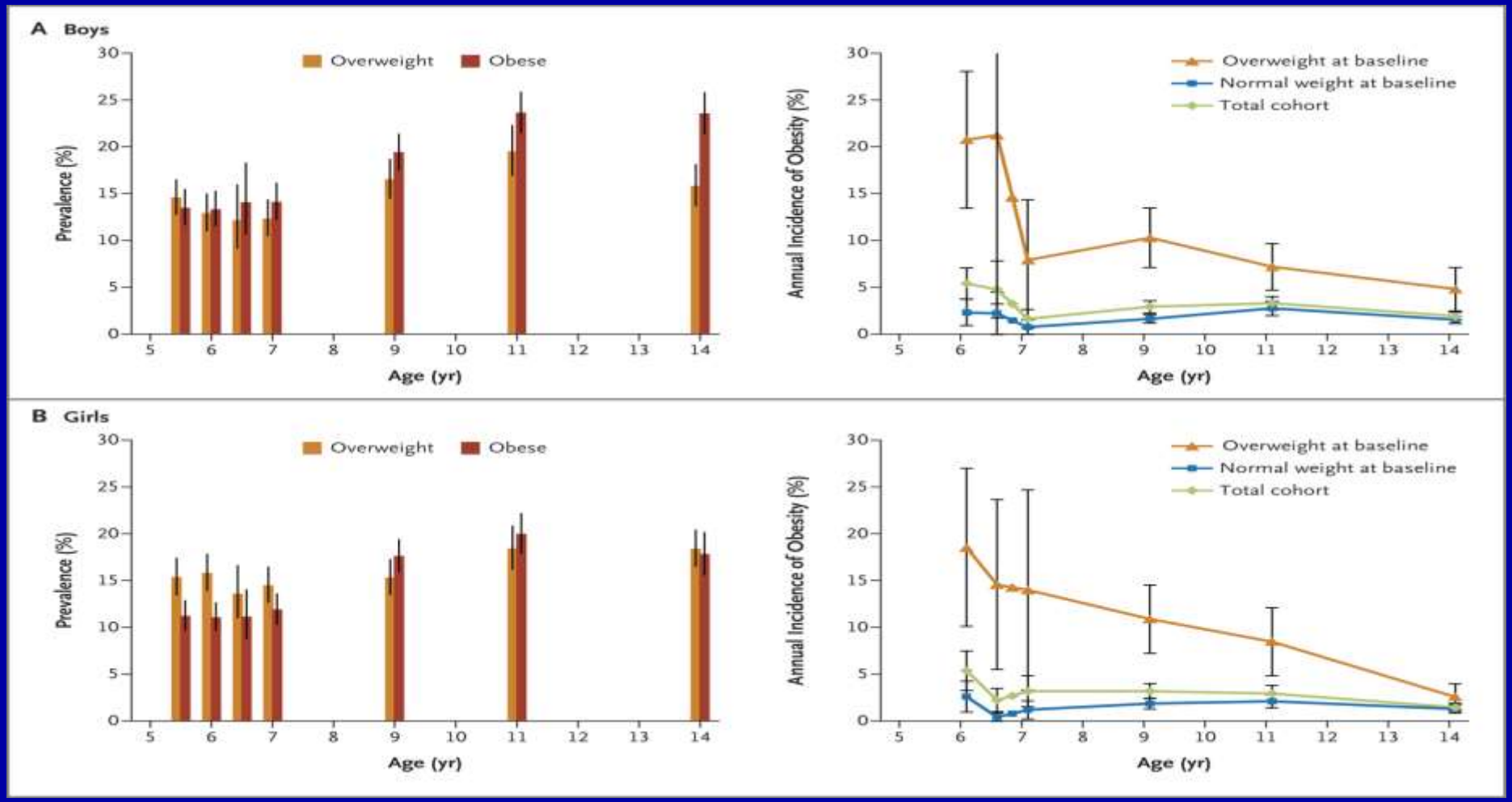
Incidence of Childhood Obesity in the United States

According to this report, nearly half of children who became obese between the ages of 5 and 14 years had been overweight and 75% had been above the 70th percentile for BMI at the start of kindergarten.

Focusing on early childhood obesity may be important in stemming the epidemic.

N Engl J Med, Volume 370(5):403-411
January 30, 2014

Prevalence and Incidence of Obesity between Kindergarten and Eighth Grade.



Cunningham SA et al. N Engl J Med 2014;370:403-411

The NEW ENGLAND JOURNAL of MEDICINE

Probability of Obesity in Eighth Grade, Mean Age, 14.1 Years, According to z Score and Percentile of Body-Mass Index at Earlier Ages.

Table 3. Probability of Obesity in Eighth Grade, Spring Semester (Mean Age, 14.1 Years), According to z Score and Percentile of Body-Mass Index at Earlier Ages.*

Weight Category and z Score	Percentile of Body-Mass Index	Probability of Obesity in Eighth Grade, Spring Semester					
		Kindergarten, Fall Semester: Mean Age, 5.6 Yr	Kindergarten, Spring Semester: Mean Age, 6.1 Yr	First Grade, Fall Semester: Mean Age, 6.6 Yr	First Grade, Spring Semester: Mean Age 7.1 Yr	Third Grade, Spring Semester: Mean Age, 9.1 Yr	Fifth Grade, Spring Semester: Mean Age, 11.1 Yr
		percent					
Normal weight							
0.00	50	6	6	5	5	2	<1
0.25	60	9	9	8	8	3	1
0.52	70	13	13	12	12	5	1
0.84	80	19	20	19	19	11	4
Overweight							
1.04	85	25	25	25	24	16	7
1.28	90	33	34	33	33	25	16
Obese							
1.64	95	47	49	48	48	44	39
2.33	99	72	75	75	76	80	87

* Data are from the Early Childhood Longitudinal Study, Kindergarten Class of 1998–1999.[8]

Cunningham SA et al. N Engl J Med 2014;370:403-411

Dale Doneen METHOD

Conclusions

Incident obesity between the ages of 5 and 14 years was more likely to have occurred at younger ages, primarily among children who had entered kindergarten overweight.

Cunningham SA et al. N Engl J Med 2014;370:403-411

Red Flags

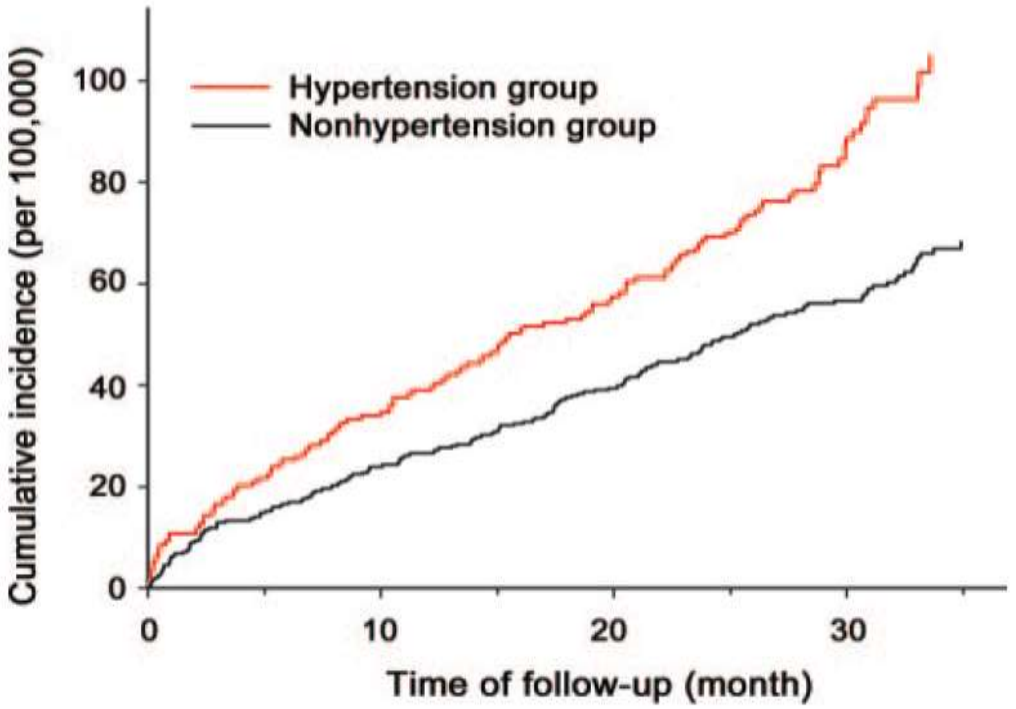
Hypertension (HT) Associated with Increased Risk of Trigeminal Neuralgia (TN)

- 138,492 HT pts; 276,984 non-HT pts. age- and sex-matched; followed 3 yrs for incidence of TN

- Adjusted hazard ratio for TN was 1.51 in HT pts. (95% CI 1.19–1.90) p <0.0006

Pan, S. L., et. al. (2011). Increased risk of trigeminal neuralgia after hypertension: a population-based study. *Neurology, 77*(17), 1605-1610.

Hypertension (HT) Associated with Increased Risk of Trigeminal Neuralgia (TN)



Cumulative risk of developing trigeminal neuralgia over time for the hypertension group (red line) and nonhypertension group (black line).

Pan, S. L., et. al. (2011). Increased risk of trigeminal neuralgia after hypertension: a population-based study. *Neurology, 77*(17), 1605-1610.

Stroke Risk Increased in Patients with Trigeminal Neuralgia (TN)

- 1,453 TN pts & 5,812 non-TN pts; followed 2 yrs. for incidence on stroke; 54.7% women; mean age 55.7 yrs.

- Hazard ratio was 1.76 after adjusting for demographic characteristics and comorbid medical disorders.

  (95% CI, 1.33–2.33); $p<0.0001$

Pan, S. L., et. al. (2011). Increased risk of stroke after trigeminal neuralgia--a population-based follow-up study. *Cephalalgia, 31*(8), 937-942.

Stroke Risk Increased in Patients with Trigeminal Neuralgia

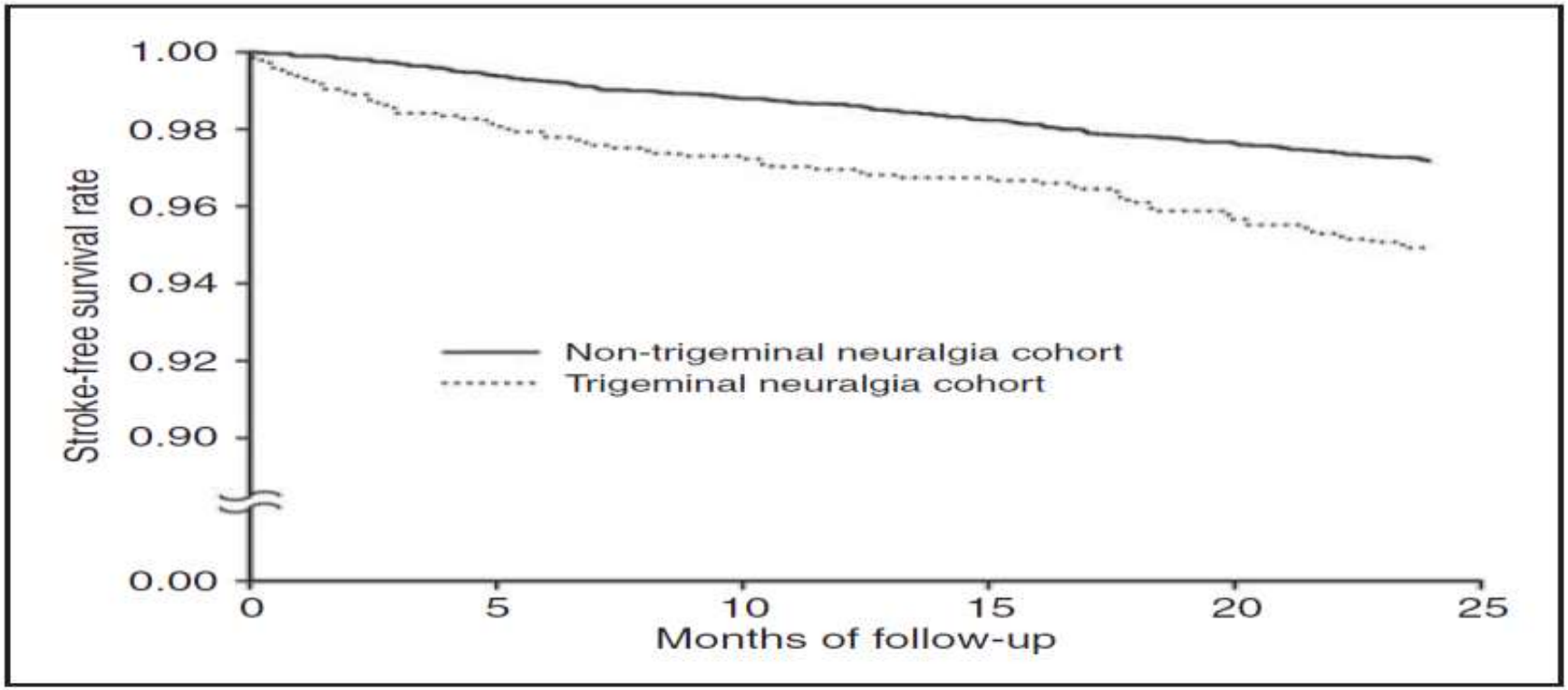


Figure 1. Two-year stroke-free survival rate for the trigeminal neuralgia cohort and the non-trigeminal neuralgia cohort.

Pan, S. L., et. al. (2011). Increased risk of stroke after trigeminal neuralgia--a population-based follow-up study. *Cephalalgia, 31*(8), 937-942.

Non-Alcoholic Fatty Liver Disease - NAFLD

NAFLD independently associated with 1.4-2-fold risk of CVD

Death in NAFLD: CVD - 25% of death; liver - 13% of death

NAFLD independently associated with 2-fold risk of DM

T2DM with NAFLD compared to nonT2DM with NAFLD

higher mortality risk (RR 3.30, p=0.002)

liver related mortality (RR 22.83, p=0.003)

Stepanova,M, Younossi, ZM. Independent association between NAFLD and CVD in the US population. Clin. Gastroenterol. Hepatol 10(6). 646-650 (2012)

Psoriasis

Case control 133 patients:

72 with psoriasis; 61 controls

Carotid atheroma plaques in 34.7% of psoriatic patients vs 8.7% controls (p=0.001)

Metabolic Syndrome diagnosed in 40.3% of psoriatic patients vs 13.1% controls (p<0.001)

Arias-Santiago, S., Orgaz-Molina J. et al. Eur J. Dermatol. 2012;22(3):337-44

TNF Inhibitors Reduce CVD in patients with Psoriasis- pilot study

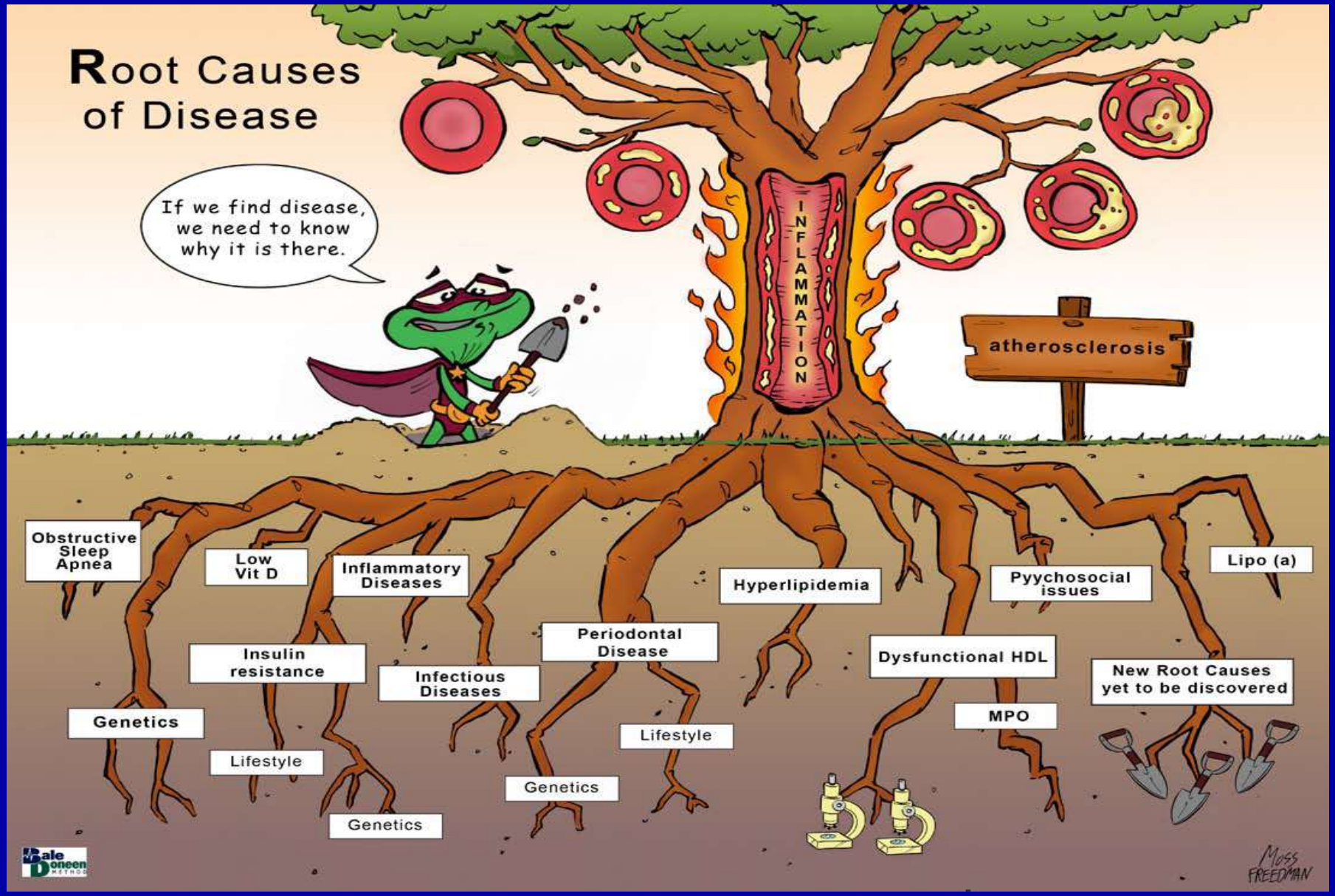
Measured carotid IMT in 16 pts (13 men and 3 women – mean age range 24-56) with severe psoriasis before & after 6 months of TNF alpha inhibitors

Baseline: 3 of 16 with calcified plaque, 13 of 16 no plaque.

cIMT findings:

1. 11/13 pts with no plaque had baseline carotid IMT > age
2. Those without plaque: 13/16 showed a significant decrease in IMT after 6 mo of anti-TNF therapy (P=.0002)
3. Pts with calcified plaque at baseline (3/16) showed no sign IMT changes after 6 months of therapy.

Szakonyi, J., Kontar, O et al. Impact of TNF-a inhibitor on arerial IMT: Pilot study. J Am Acad Dermatol. 2013:69:523-529



The Health Consequences of Smoking – 50 years in progress

Now determined that the link between smoking and impaired glucose and development of diabetes is INDEPENDENT of other factors such as physical inactivity and poor diet.

Cigarettes Cause Diabetes!

The Health Consequences of Smoking – 50 years of Progress.
Published online January 17, 2014

The Health Consequences of Smoking – 50 years in progress

Meta analysis of 24 prospective cohort studies – in total 3.9 million subjects, none with DM at baseline.

140,813 developed diabetes

Compared with nonsmokers, risk of developing T2DM was 1.37

adjusted for: age, BMI, physical activity, diet, ETOH, fmhx, gender, race/ethnicity, education level.

The Health Consequences of Smoking – 50 years of Progress.
Published online January 17, 2014

The Health Consequences of Smoking – 50 years in progress

A dose-response analysis proved further causation:

Compared to never-smokers:

RR for developing DM increased:

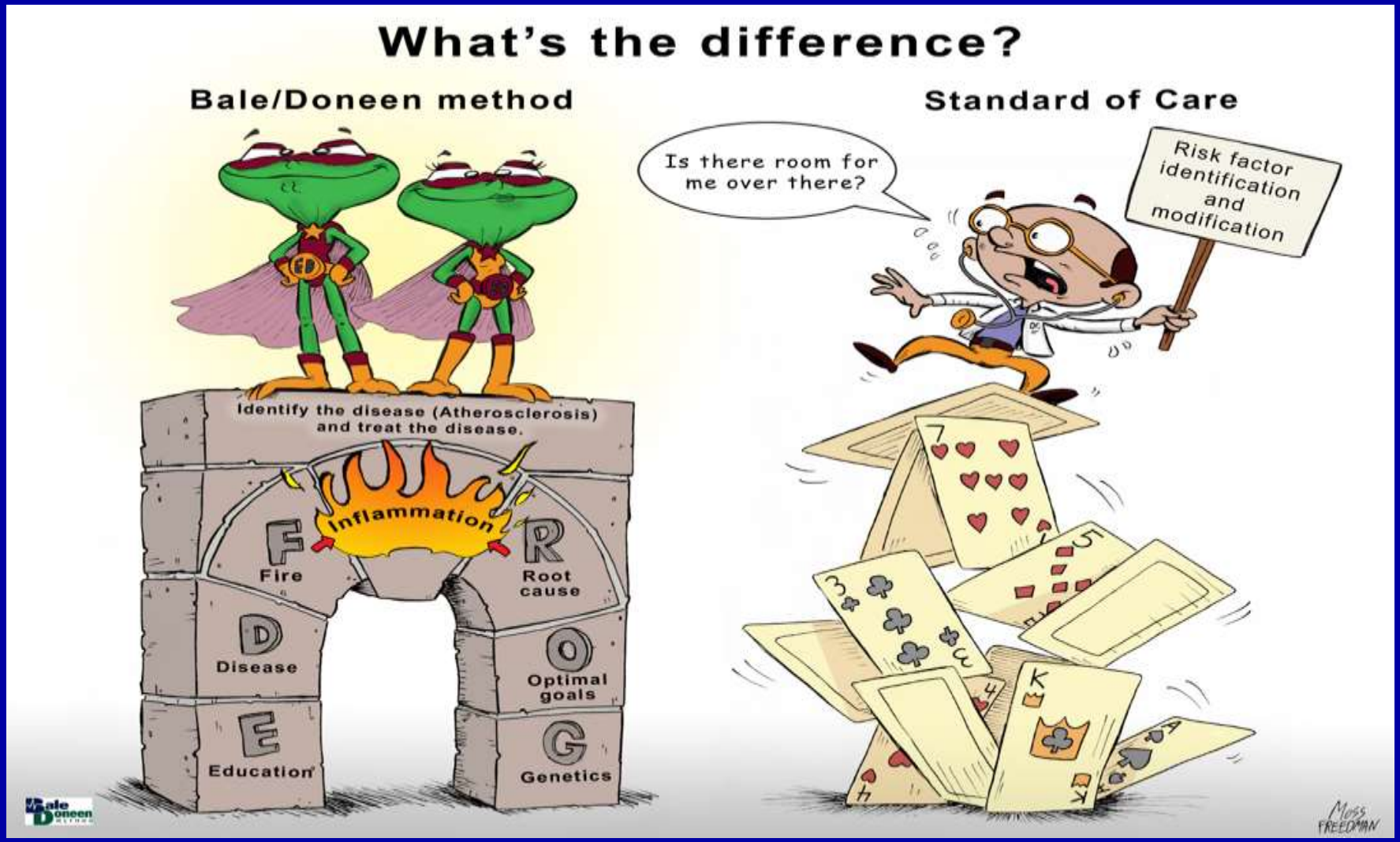
1.14 for former smokers

1.25 for light smokers (1-19 or 1-15 cig/d)

1.54 for heavy smokers (≥ 15 or ≥ 20 cig/d)

The Health Consequences of Smoking – 50 years of Progress.
Published online January 17, 2014

Treatment



Running – everyone is doing it…

Exercise: More is Better…??

Marathon running – in past 3 decades – participation has gone from 25,000 runners in 1976 to 2 million in 2010.

The paradox: “An expansion in the number of habitually sedentary individuals paralleling a concomitant increase in unprecedented hours of vigorous exercise.”

Franklin, B. Preventing Exercise-related CV Events. Circulation: published online January 13, 2014; http://circ.ahajournals.org.

Exercise: More is Better…??

Jan 2000 – May 2010: CV outcomes of CV events among 10.9 million registered marathon runners.

Of the 59 cases of cardiac arrest (mean + SD age: 42+13 years; 51 men); 42 (71%) were fatal.

Overall incidence of cardiac arrest was 1 per 184,000 participants, and the SCD was 1 per 259,000 participants which translates to 0.2 cardiac arrests and 0.14 SCDs per 100,000 estimated runner hours.

The relative risk is inversely related to the habitual level of activity – the long term cardioprotective effect of regular physical activity is substantial.

Franklin, B. Preventing Exercise-related CV Events. Circulation: published online January 13, 2014; http://circ.ahajournals.org.

Exercise: More is Better…??

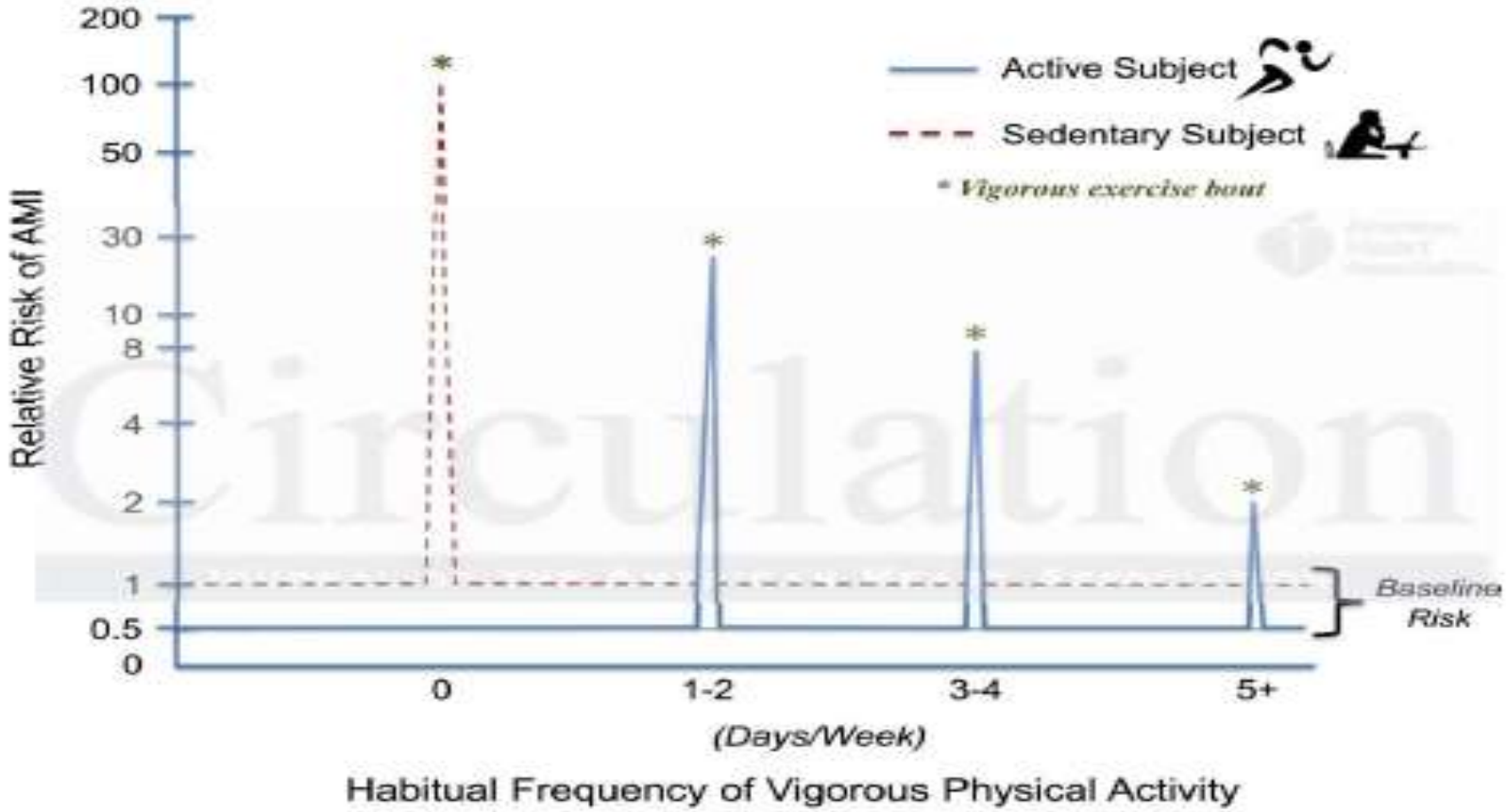
The risk of AMI associated with each bout of physical activity is approximately doubled for an individual who engages in vigorous exercise ≥ 5 times per week for approximately 1 hour per session.

During or soon after an acute bout of vigorous exercise, the risk of AMI would be approximately 50 times higher for the least active than for the most active cohort.

The net effect of Regular exercise does reduce overall CVD

Franklin, B. Preventing Exercise-related CV Events. Circulation: published online January 13, 2014; http://circ.ahajournals.org.

Exercise: More is Better…??



Franklin, B. Preventing Exercise-related CV Events. Circulation: published online January 13, 2014; http://circ.ahajournals.org.

Exercise: More is Better…??

Bale/Doneen Take-Away:

For Inactive patients who need to start exercising:

1. Consider preliminary exercise testing and monitoring to evaluate safety for new program.
2. Cardiac Rehab where people can be monitored and encouraged.
3. Start low and GO SLOW.

For Active Patients:

1. Consistency is key.
2. Regular, daily exercise is the valuable.
3. Stay in shape – hard to get back in shape.

Franklin, B. Preventing Exercise-related CV Events. Circulation: published online January 13, 2014; http://circ.ahajournals.org.

Exercise and Youth

Exercise in youth linked with lower MI risk later in life.

743,498 Swedish men – examined at 18 y.o. during 1969-1984. Aerobic fitness (Wmax) and muscle strength measured.

MIs were tracked through national registers during follow-up of 34 years, 11,526 MI's were registered in the cohort.

Adjusted for age, BMI, diseases, education, blood pressure and socio-economic factors.

Hogstrom, G., Nordstrom, A., High aerobic fitness in late adolescence is associated with a reducted Risk of MI later in life. Eur Heart J Jan 2014;.

Exercise in youth linked with lower MI risk later in life.

Each one standard deviation increase in the level of physical fitness (Wmax) was associated with an 18% decreased risk of later MI

[(HR) 0.82, 95% CI 0.80-0.85]

The beneficial effects of baseline Wmax were significant across all BMI groups, ranging from lean (BMI <18.5) to obese (BMI >30) (P<0.05 for all).

Hogstrom, G., Nordstrom, A., High aerobic fitness in late adolescence is associated with a reducted Risk of MI later in life. Eur Heart J Jan 2014;.

Increased Risk of Non-Fatal MI following Testosterone Therapy Prescription in men

http://health.yahoo.net/experts/dayinhealth/testosterone-therapy-overhyped

Cohort study of the risk of nonfatal MI following initial TT prescription (n=55,593) compared with incidence rate of MI in the 90 days following (post prescription interval) compared with one year prior to the initial prescription.

Finkle, W., Greenland, S., et al. Increased risk of nonfatal MI following testosterone Therapy prescription in men. PLoS ONE 9(1): January 29,2014. DOI: 10.137

Increased Risk of Non-Fatal MI following Testosterone Therapy Prescription in men

55,593 men received TT script compared with 167,279 who filled PDE5 inhibitor script as comparison group.

Compared rate of MI in the 90 day post-prescription interval with the incidence rate in the one year pre-prescription interval

Men with hx of MI prior to first prescription of TT or PDE51 were excluded from post-prescription analysis

Finkle, W., Greenland, S., et al. Increased risk of nonfatal MI following testosterone Therapy prescription in men. PLoS ONE 9(1): January 29,2014. DOI: 10.137

Increased Risk of Non-Fatal MI following Testosterone Therapy Prescription in men

Results:

In all subjects:

the post/pre-prescription RR for TT prescription was 1.36 (1.03,1.81). RRR compares 2 groups (95% CI)

Men >55: RR 0.95 (0.54,1.67)

Men 55-64: RR 1.17 (0.84,1.63)

Men <65 with CAD: RR 2.07 (1.05,4.11)

Men >65: RR 2.19 (1.27,3.77)

Men >75: RR 3.43 (1.54,7.66)

Finkle, W., Greenland, S., et al. Increased risk of nonfatal MI following testosterone Therapy prescription in men. PLoS ONE 9(1): January 29,2014. DOI: 10.137

Increased Risk of Non-Fatal MI following Testosterone Therapy Prescription in men

Bale/Doneen Take-Away:

This evidence supports an association between testosterone therapy and risk of CV events. Likewise, evidence does exist that low endogenous testosterone levels have also been associated with cardio/metabolic risk.

The effects of exogenous TT may differ from the endogenous effects of testosterone. Evaluate each patient individually and reassess inflammation and disease carefully.

Remember – we are treating the n of 1 = the patient!

Finkle, W., Greenland, S., et al. Increased risk of nonfatal MI following testosterone Therapy prescription in men. PLoS ONE 9(1): January 29,2014. DOI: 10.137

Serum Omega 3 and risk of incident T2DM in men

Prospective, population based trial: Investigated serum EPA, DPA, DHA, ALA, hair mercury, and risk of incident T2DM in 2,212 Finnish men aged 42-60 years.

Serum PUFA and hair mercury were used as biomarkers for exposure. Dietary intakes assessed with 4-day food diary.

T2DM assessed by self questionnaire and fasting and 2hr OGTT at regular intervals at 4, 11, 20 years from baseline.

Virtanen, J., Mursu, J., et al. Serum Omega-3 Polyunsaturated Fatty Acids and Risk of Incident T2DM in Men. Diabetes Care. Jan 2014; 37:189-196

Serum Omega 3 and risk of incident T2DM in men

During average follow-up of 19.3 years, 422 men developed T2DM (19%)

Men in highest vs lowest serum EPA+DPA+DHA quartile had 33% lower multivariate-adjusted risk for T2DM

(95% CI 13-49; p trend 0.01)

No statistical association were observed with serum or dietary ALA, dietary fish or EPA+DHA, or hair mercury.

Virtanen, J., Mursu, J., et al. Serum Omega-3 Polyunsaturated Fatty Acids and Risk of Incident T2DM in Men. Diabetes Care. Jan 2014; 37:189-196

Flu Shot

Influenza Vaccine and CV Outcomes in High Risk patients

Systematic Review and meta-analysis (1946-2013). RCTs comparing influenza vaccine vs placebo. 6735 patients, mean age 67 years, 51.3% women, 36.2% with cardiac history, mean follow-up 7.9 months.

Analyses were stratified by sub groups of patients with and without a history of ACS within 1 year of randomization

Influenza vaccine was associated with a lower risk of CV events 2.9% vs 4.7%;RR, 0.64 [95%CI, 0.48-0.86], p=.003

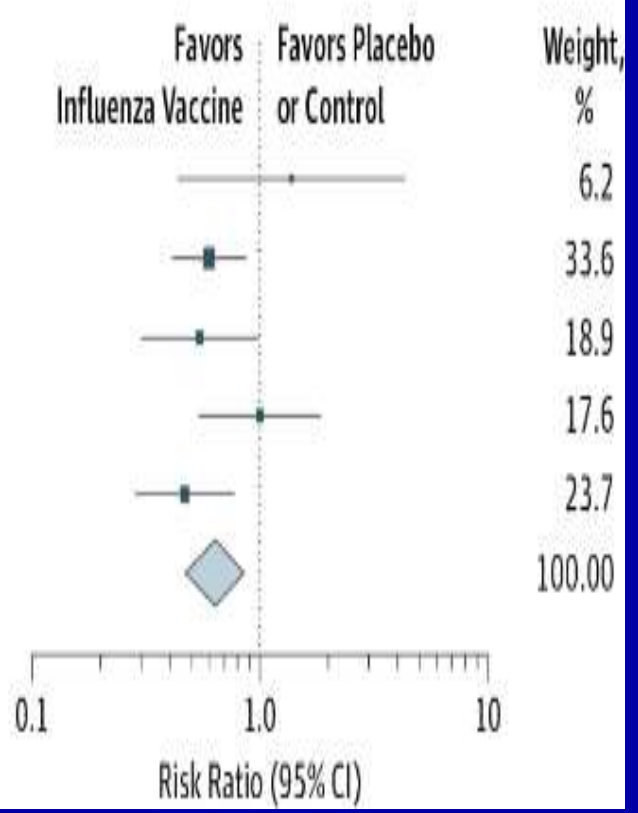
Udell, J., Zawi, R., et al. Association between influenza vaccination and CV Outcomes In high-risk patients. JAMA. 2013;310(16):1711-1720

Major Adverse Cardiovascular Events Comparing Influenza Vaccine vs Control

Study	Influenza Vaccine: No. of Events	Influenza Vaccine: Total Participants	Placebo or Control: No. of Events	Placebo or Control: Total Participants	Risk Ratio (95% CI)	Weight, %
Govaert et al,[41] 1994	7	927	5	911	1.38 (0.44-4.32)	6.2
FLUVACS,[20,21] 2004	32	145	54	147	0.60 (0.41-0.87)	33.6
FLUCAD,[22,23] 2008	16	325	30	333	0.55 (0.30-0.98)	18.9
De Villiers et al,[42] 2009	20	1620	20	1622	1.00 (0.54-1.85)	17.6
Phrommintikul et al,[24] 2011	20	221	42	218	0.47 (0.29-0.77)	23.7
Total (95% CI)	95	3238	151	3231	0.64 (0.48-0.86)	100.00

Heterogeneity: $\tau^2 = 0.03$; $\chi^2_4 = 5.59$, ($P = .23$); $I^2 = 28\%$

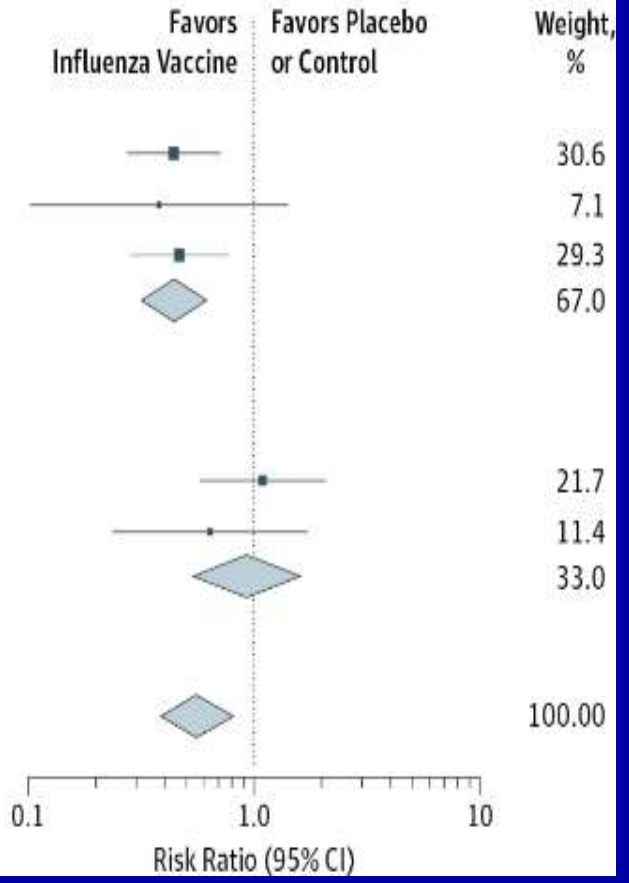
Test for overall effect: $Z = 2.93$ ($P = .003$)



Udell, J., Zawi, R., et al. Association between influenza vaccination and CV Outcomes In high-risk patients. JAMA. 2013;310(16):1711-1720

Major Adverse CV Events Comparing Influenza Vaccine vs Control Stratified by Timing of ACS

Study	Influenza Vaccine: No. of Events	Influenza Vaccine: Total Participants	Placebo or Control: No. of Events	Placebo or Control: Total Participants	Risk Ratio (95% CI)	Weight, %
Recent ACS						
FLUVACS,[20,21] 2004	18	96	41	97	0.44 (0.28-0.71)	30.6
FLUCAD,[22,23] 2008	3	83	7	74	0.38 (0.10-1.42)	7.1
Phrommintikul et al,[24] 2011	20	221	42	218	0.47 (0.29-0.77)	29.3
Subtotal (95% CI)	41	400	90	389	0.45 (0.32-0.63)	67.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_2 = 0.09$, ($P = .96$); $I^2 = 0\%$						
Test for overall effect: $Z = 4.68$ ($P < .001$)						
Stable CAD						
FLUVACS,[20,21] 2004	14	49	13	50	1.10 (0.58-2.09)	21.7
FLUCAD,[22,23] 2008	6	242	10	259	0.64 (0.24-1.74)	11.4
Subtotal (95% CI)	20	291	23	309	0.94 (0.55-1.61)	33.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.81$, ($P = .37$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.23$ ($P = .82$)						
Total (95% CI)	61	691	113	698	0.57 (0.39-0.82)	100.00
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_4 = 6.01$, ($P = .20$); $I^2 = 33$						
Test for overall effect: $Z = 3.00$ ($P = .003$)						
Test for subgroup differences: $\chi^2_1 = 5.11$, ($P = .02$); $I^2 = 80.4\%$						



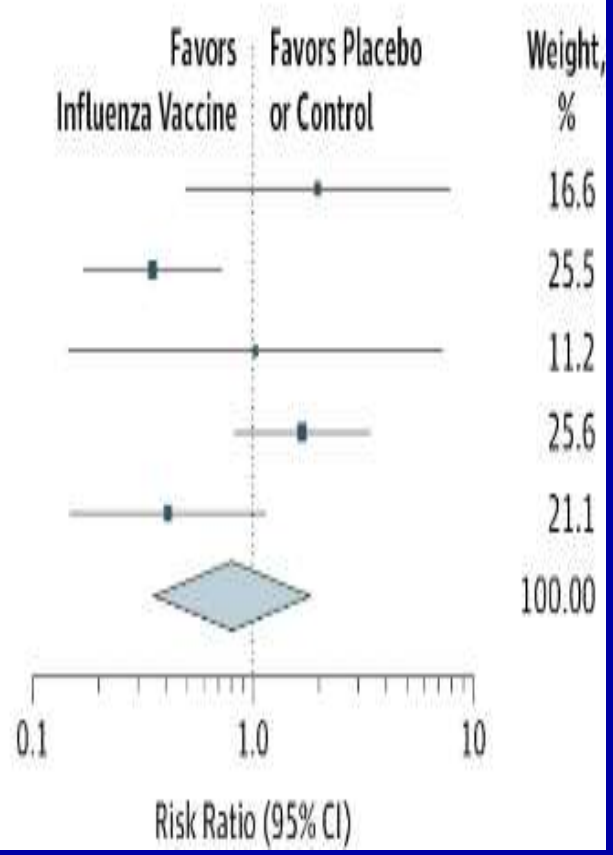
Udell, J., Zawi, R., et al. Association between influenza vaccination and CV Outcomes In high-risk patients. JAMA. 2013;310(16):1711-1720

Cardiovascular Mortality Comparing Influenza Vaccine vs Control

Study	Influenza Vaccine: No. of Events	Influenza Vaccine: Total Participants	Placebo or Control: No. of Events	Placebo or Control: Total Participants	Risk Ratio (95% CI)	Weight, %
Govaert,[41] 1994	6	927	3	911	1.97 (0.49-7.84)	16.6
FLUVACS,[20,21] 2004	9	145	26	147	0.35 (0.17-0.72)	25.5
FLUCAD,[22,23] 2008	2	325	2	333	1.02 (0.15-7.23)	11.2
De Villiers et al,[42] 2009	20	1620	12	1622	1.67 (0.82-3.40)	25.6
Phrommintikul et al,[24] 2011	5	221	12	218	0.41 (0.15-1.15)	21.1
Total (95% CI)	42	3238	55	3231	0.81 (0.36-1.83)	100.00

Heterogeneity: $\tau^2 = 0.54$; $\chi^2_4 = 12.36$, ($P = .01$); $I^2 = 68\%$

Test for overall effect: $Z = 0.50$ ($P = .61$)



Udell, J., Zawi, R., et al. Association between influenza vaccination and CV Outcomes In high-risk patients. JAMA. 2013;310(16):1711-1720

Cases Submitted

Case submitted by Jon on February 3rd with the following questions:

1. What is the etiology of patient's coronary disease?
2. What can I do for him moving forward?
3. What is the data correlating CACS and Event risk?

History Provided:

67 year old healthy man with history of:

1. dyslipidemia
2. nephrolithiasis
3. gluten enteropathy (on gluten free diet)
4. borderline elevated PSA
5. History of increased FFA and A1C of 6.3% in the past now AIC is 5.2%, FBS 78, 2hr OGTT 74
6. Elevated uric acid without hx of gout.

Presents with progressive atherosclerotic changes on his limited carotid studies.

Family History & Personal hx

Mother – CAD – resulting in AMI in her 70's, CVA in her 70's.

Meds: Niaspan 750, Prava 10, ASA 325, Vitamin D3 1000, Cranberry, Centrum Silver, Iron

Personal history –

- Nonsmoker
- Apo E 3/4- follows low fat diet – watches
- Father, grandfather
- Runs 5 miles/day
- Dentition is good, no OSA

Scans and reported labs

"Stable IMT with progressive plaque burden"

"CAC score was 800 – January 2014" – after this scan cardiologist recommended increasing statin and lowering LDL from 70's to 50's

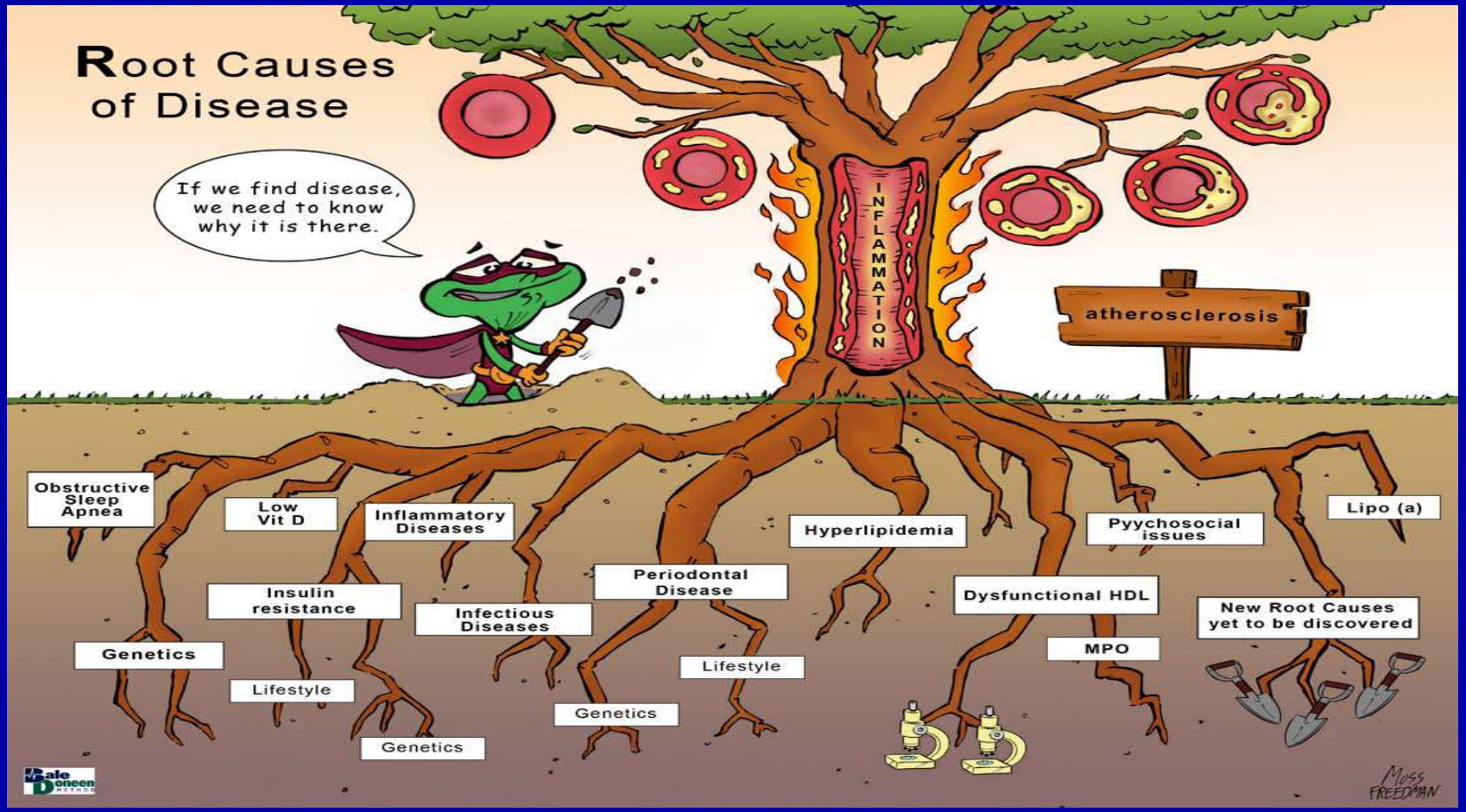
"lipids at target"

"indices of inflammation are all quiet"

"Cystatin C is elevated but improved and stable renal functions in normal range"

"Blood Pressure is normal and not on blood pressure meds"

Question 1:What is the etiology of patient's coronary disease?



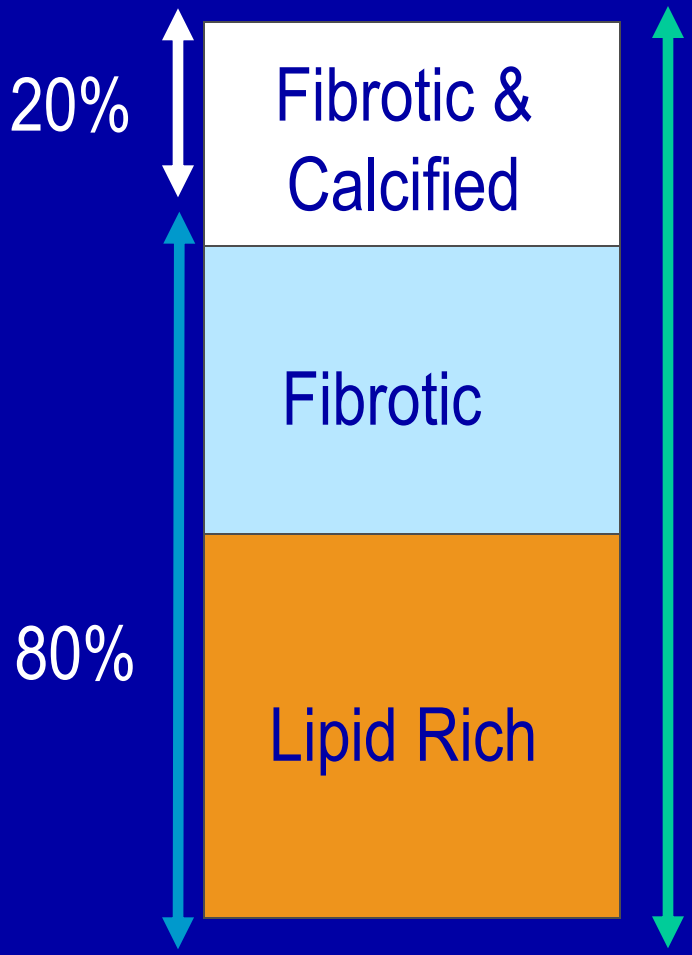
Bale Doneen METHOD

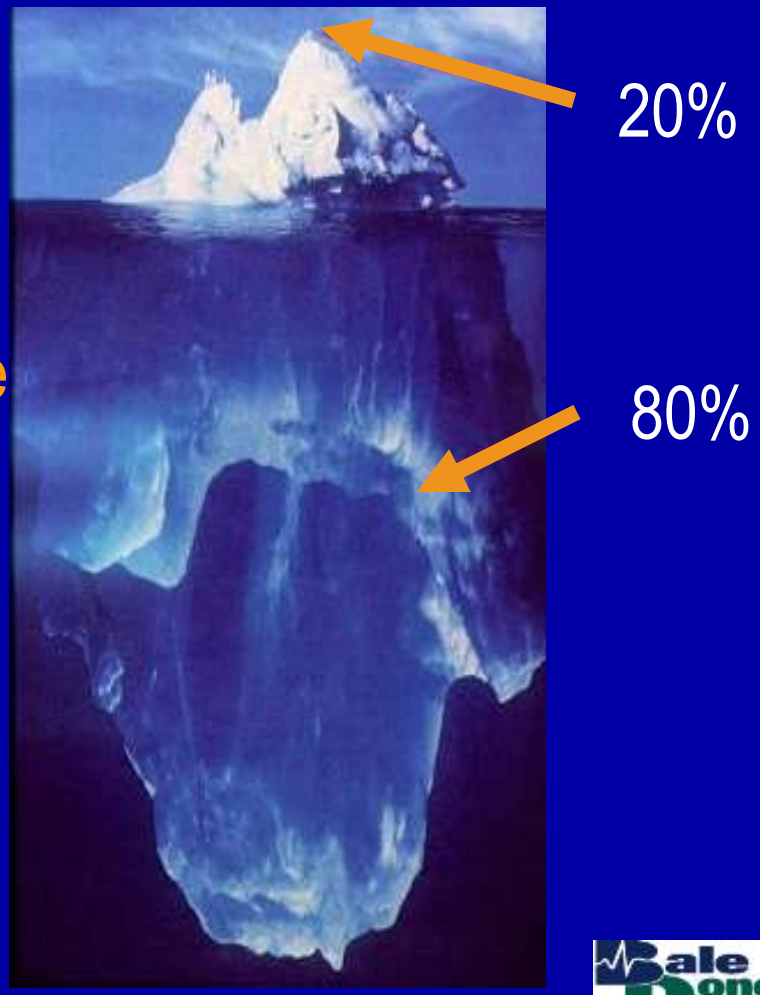
Question 2: What can I do for him moving forward?

1. Identify ALL root causes – treat all optimally.
2. Treatment for vascular disease should include: ASA 81, ACE-I (even with normal BP), Omega 3, Statin (dose based on inflammation).
3. Monitor inflammation quarterly
4. Health maintenance – including vaccines

Question 3: What is the data correlating CACS and Event risk?

Coronary Artery Calcium Testing - CACS





Coronary Artery Calcification

- CACS documents presence of coronary ASVD -
- Identifies patients at increased risk for MI & CV death
- Adds predictive ability to FRS
- 2A recommendation by the ACC/AHA to refine the CV risk assessment.
- Now available: SAIP radiation exposure guidelines

ACC/AHA 2010 recommendations
J of Cardiovascular CT (2011) s. 75-83.

Calcium in Ruptured Plaques

- 101 IVUS detected ruptured plaques with 101 matched control plaques without rupture
- Ruptured plaques had quantitatively less calcium

Am J Cardiol. 2005;96:352-357.

CACS Significantly Enhances FRS in Intermediate Risk Subjects

- 1,330 non-DM, intermediate risk, MESA subjects; followed ~7.6 yrs.
- Compare CACS, CIMT, ABI, brachial FMD, hsCRP and Famhx in enhancing FRS for predicting CV events
- 123 CVD events occurred (94 CHD)

Yeboah, J. MD, MS, et. al. *JAMA*. 8/21/2012;308(8):788-795

CACS Significantly Enhances FRS in Intermediate Risk Subjects

- Independent significant predictors:

  CAC – HR- 2.60 (95% CI, 1.94-3.50)
  Famhx- HR- 2.18 (95% CI, 1.38-3.42)
  hsCRP- HR- 1.28 (95% CI, 1.00-1.64)
  ABI - HR- 0.79 (95% CI, 0.66-0.95)

- CAC provided superior discrimination and risk reclassification compared with other risk markers

Yeboah, J. MD, MS, et. al. *JAMA*. 8/21/2012;308(8):788-795

CAC predicts stroke risk

4180 subjects from the Heinz Nixdorf Recall Study (45-75 years of age; 47.1% men) without previous stroke, coronary heart disease, or MI were Evaluated for stroke events over 94.9 $\pm$ 19.4 months.

Determine whether CAC is a stroke predictor in addition to established vascular risk factors (age,
Sex, SBP, LDL, HDL, DM, smoking and AF).

92 subjects (55 men and 37 women) developed a stroke during follow-up period (82 ischemic and 10 hemorrhagic).

Hermann, D., Gronewold, J., et al. Stroke. March 25, 2013;44:1008-1013.

CAC predicts stroke risk

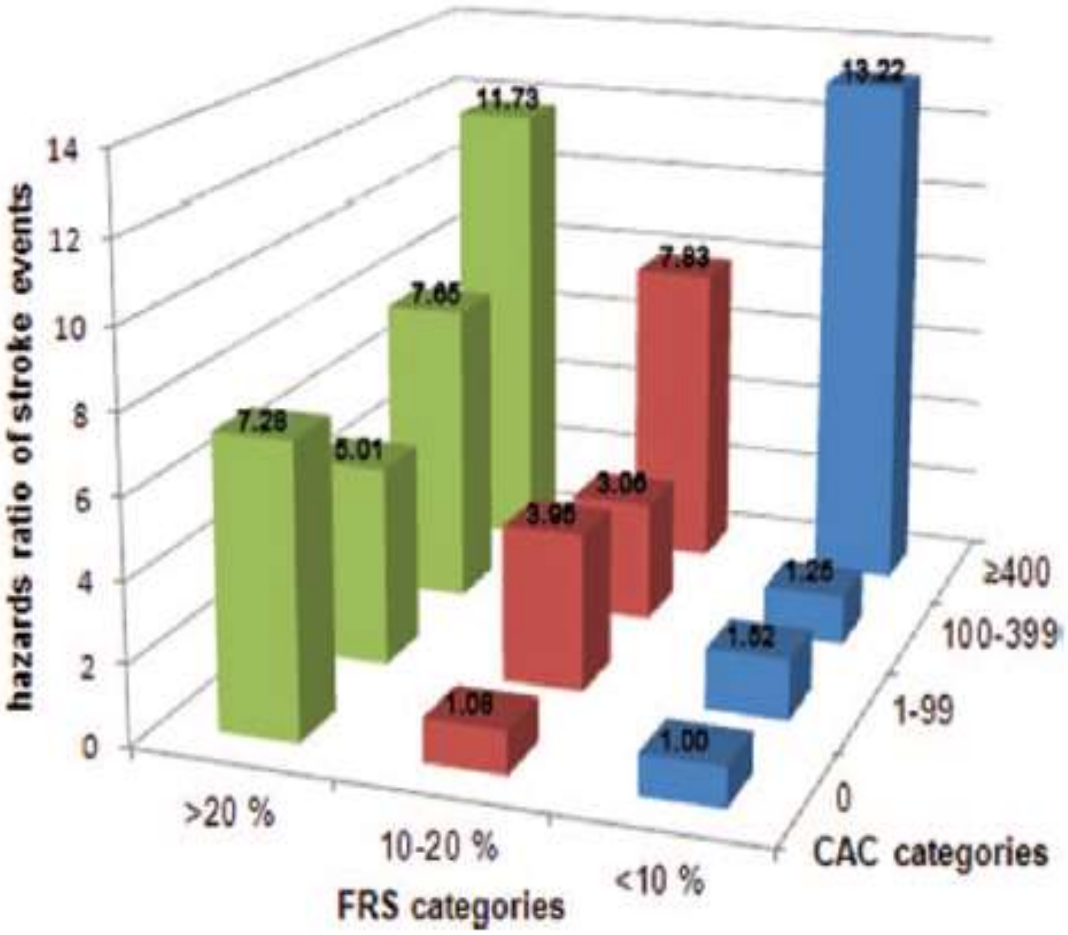


Figure 2. Stroke risk in subjects belonging to the Heinz Nixdorf Recall study stratified on Framingham risk score (FRS) and coronary artery calcification (CAC) categories. Hazards ratios of stroke events in the different combinations of FRS and CAC categories are shown, with the lowest CAC and FRS category as reference. For the low and intermediate FRS categories, log-rank tests for trends revealed significant differences between CAC categories, indicating that CAC discriminates stroke hazard in subjects at low and intermediate vascular risk.

Hermann, D., Gronewold, J., et al. Stroke. March 25, 2013;44:1008-1013.

CAC predicts stroke risk

CAC is an independent predictor of future stroke events in the general population.

CAC predicted stroke in men and women – more significantly in subjects < 65 yrs.

CAC predicted stroke independent of AF

CAC discriminated stroke risk specifically in subjects with FRS <10% and FRS 10-20%.

Hermann, D., Gronewold, J., et al. Stroke. March 25, 2013;44:1008-1013.

CAC predicts stroke risk

BD Take-Away:

Disease ANYWHERE in the vascular system documents risk for a vascular EVENT!

Atherosclerosis = risk for an event.

This discussion goes both ways –

plaque in the coronary tree = risk for stroke.

plaque in the carotid bed = risk for MI.

Hermann, D., Gronewold, J., et al. Stroke. March 25, 2013;44:1008-1013.

CAC Out Predicts Lipids for CVD Risk

- 5,534 MESA pts without baseline statin rx; follow-up 7.6 yrs.; outcome CV events.
- Classified pts by CACS of zero; 1-99; ≥100; # lipid abnormalities (LA).
- Determine absolute CVD risk according to above categories.

Martin, S. S., Blaha, M. J., Blankstein, R., Agatston, A. S., Rivera, J. J., Virani, S. S., . . . Nasir, K. (2013). Dyslipidemia, Coronary Artery Calcium, and Incident Atherosclerotic Cardiovascular Disease: Implications for Statin Therapy from the Multi-Ethnic Study of Atherosclerosis. *Circulation*. doi: 10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

- CAC stratifies CVD risk regardless of the burden of dyslipidemia.
- CACS ≥100 defines a CV event risk similar to a ‘secondary’ prevention population.

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not by LDL-C

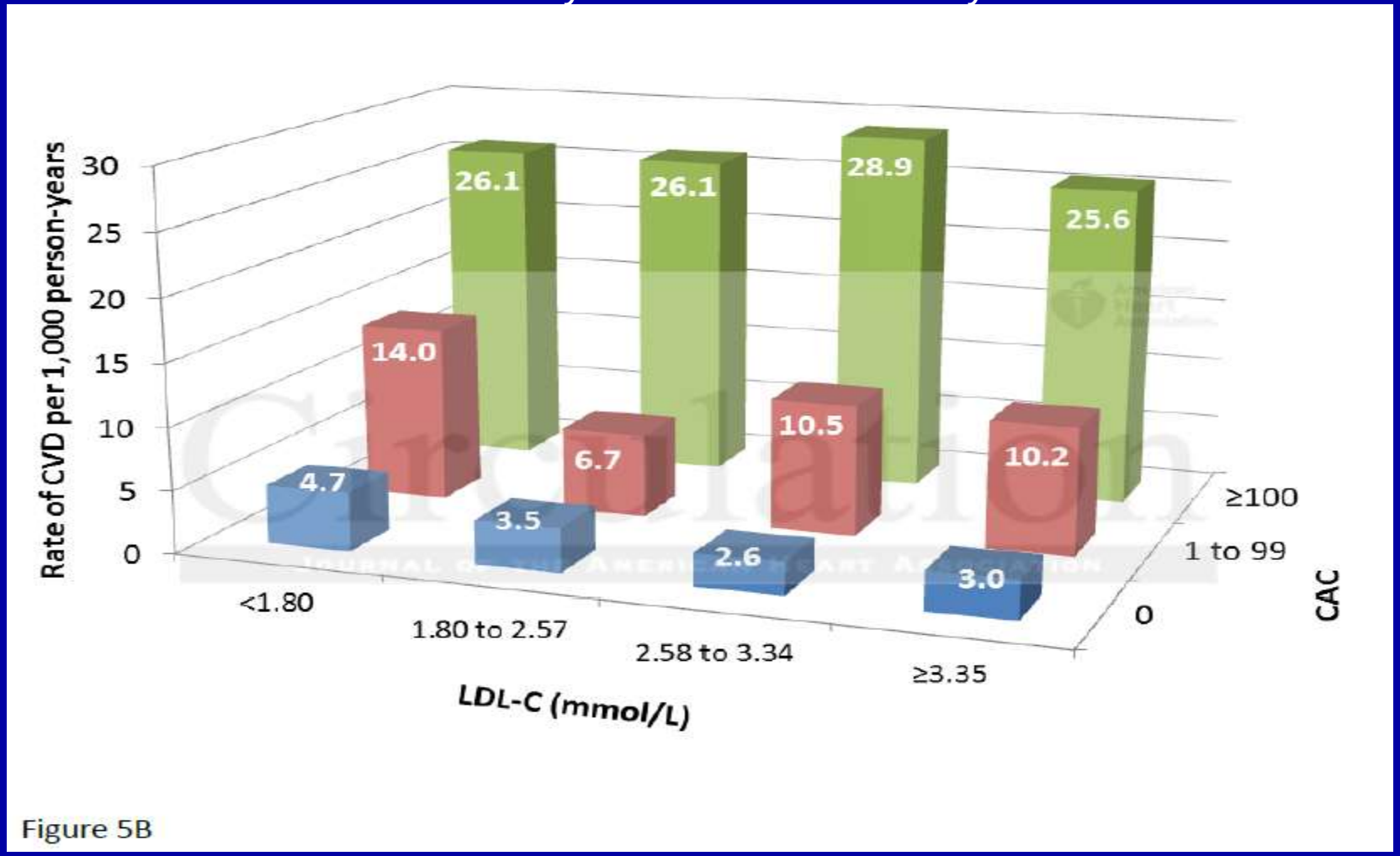


Figure 5B

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

CAC Out Predicts Lipids for CVD Risk

Events driven by atherosclerosis not TC/HDL

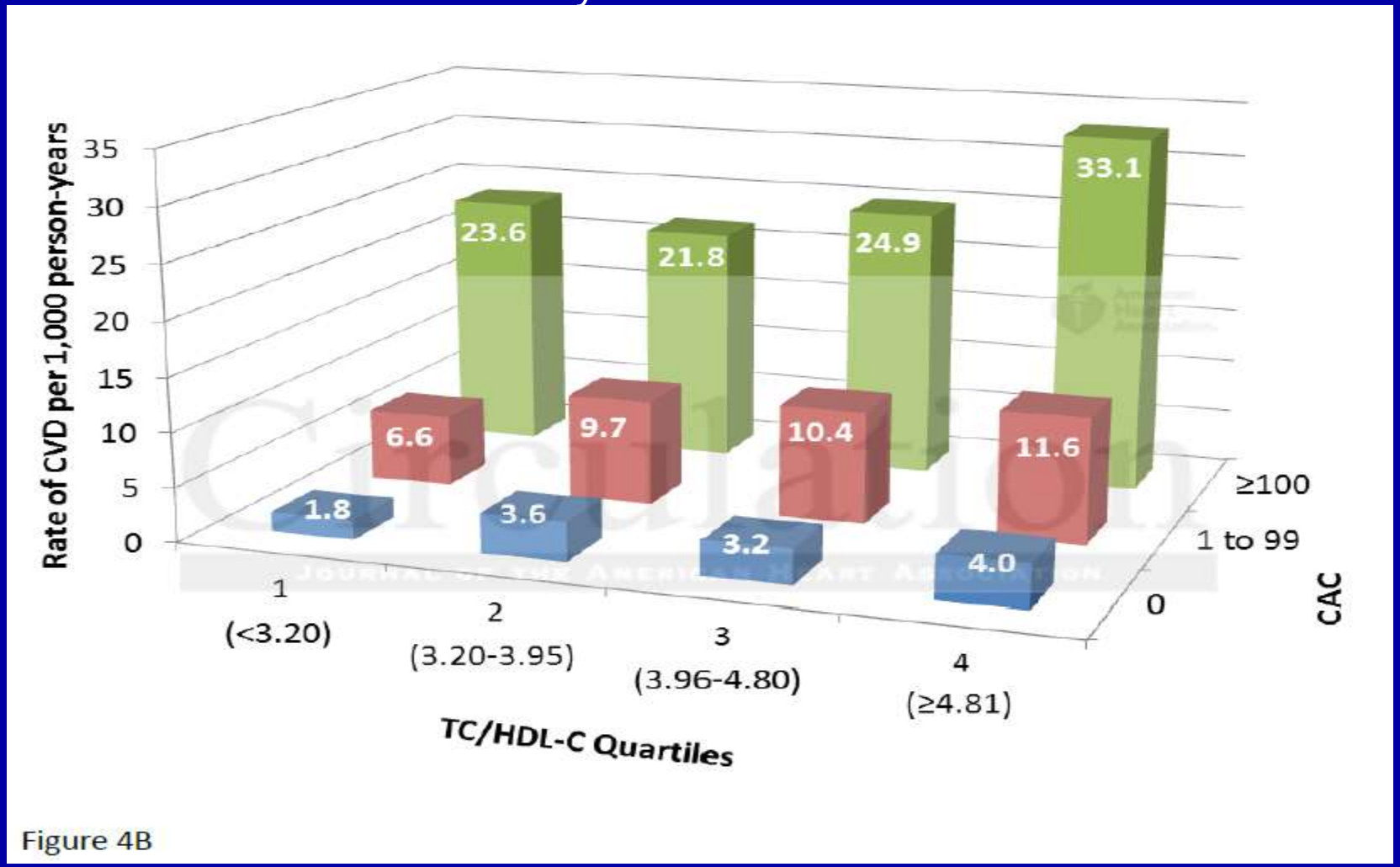


Figure 4B

Martin, S. S., et. al. (2013). *Circulation*. doi:10.1161/circulationaha.113.003625

Arterial Inflammation Precedes Calcification

- 137 pts; age-61±13 yrs; 48.1% men; serial PET/CT scans 1–5 yrs apart; thoracic aorta focal arterial inflammation was prospectively (baseline) determined by PET/FDG

- A blinded investigator evaluated calcium deposition on the baseline and follow-up computed tomographic scans along the same standardized sections of the aorta.

- A vascular segment was classified as either with or without subsequent calcification.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

- Across all patients, subsequent Ca deposition was associated with the underlying inflammatory signal, measured as standardized uptake value with OR of 2.94 (95%CI- 1.27-6.89) or as TBG ratio with OR 2.59 (95% CI, 1.18-5.70) p values of 0.01 and 0.02 respectively – adjusted for CV risk factors.

- First-in-human evidence that arterial inflammation precedes subsequent Ca deposition.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

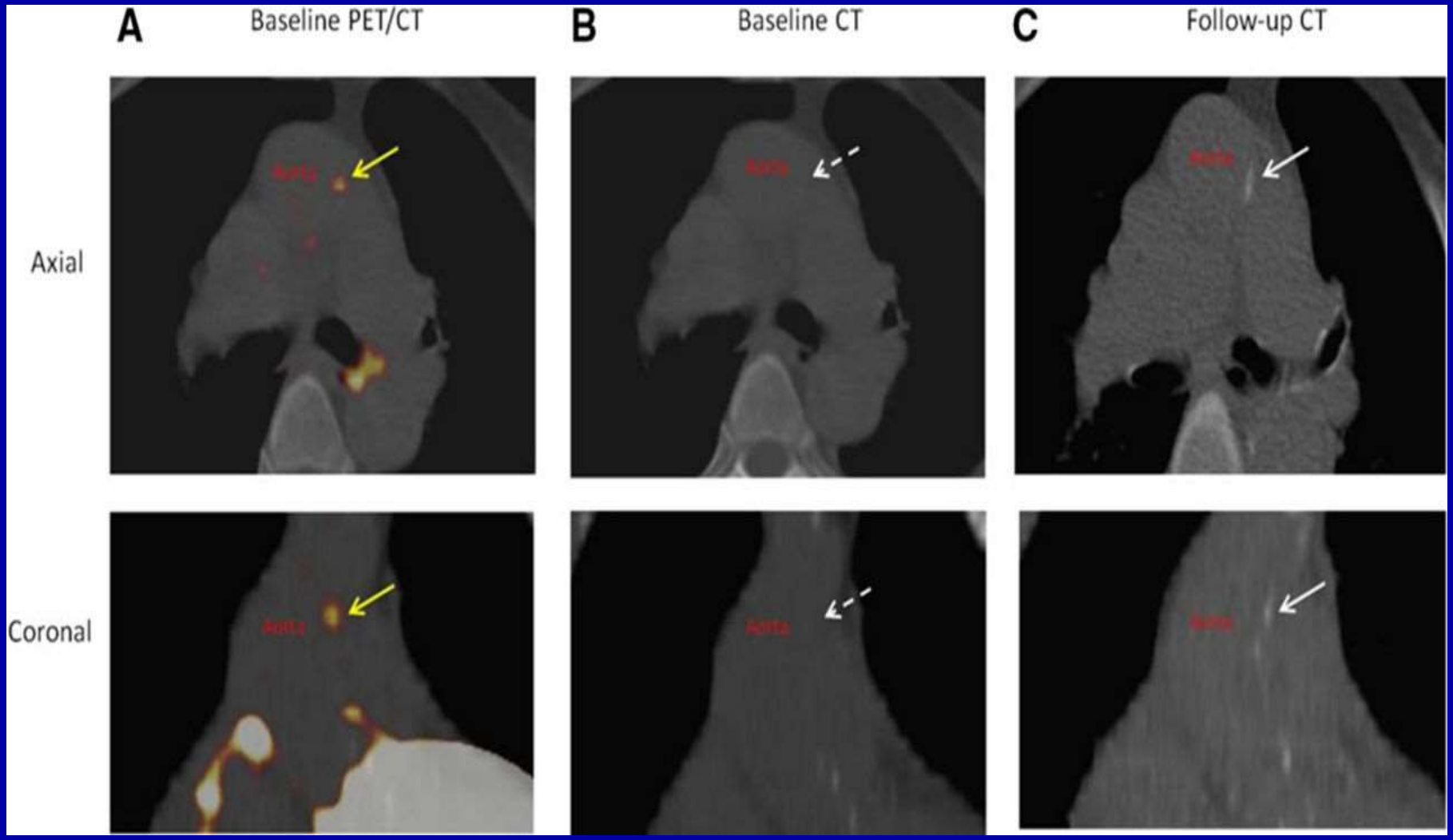
Inflammation is an important driver of plaque progression.

Human studies have shown that high aortic and carotid FDG uptake is related to subsequent risk of plaque rupture and clinical events.

Abdelbaky, A., et. al. (2013). Focal Arterial Inflammation Precedes Subsequent Calcification in the Same Location: A Longitudinal FDG-PET/CT Study. *Circulation: Cardiovascular Imaging*, *6*(5), 747-754.

Arterial Inflammation Precedes Calcification

Baseline (PET) and sequential (CT) images of incident calcium deposition.



Abdelbaky A et al. Circ Cardiovasc Imaging 2013;6:747-754

CACS is not Useful for Tracking Atherosclerosis

- Meta-analysis of 10 randomized trials (n=2612)
- CAC was measured at baseline and again at least one year later in pts with CVD or CKD
- Rx: statins (n=1370), placebo (n=564), and antihypertensives (n=201);
- Change in CACS did not reach statistical significance btw rx and control arms in any studies

McCullough P, Chinnaiyan K. Annual progression of coronary calcification in trials of preventative therapies: a systematic review. *Arch Intern Med* Jan 2010; 169:2064-2070.

So – for this patient

1. Having an isolated CACS of 800 in an asymptomatic individual who runs 5 miles per day doesn't necessarily mean that treatment should be changed.

2. He does have CACS and ASVD (cIMT) – is he on adequate treatment for atherosclerosis? ASA 81 –check, ACE

3. However – step back and make sure ALL root causes are being treated.

4. Measure inflammation to determine adequacy of treatment and safety of the patient.

5. Continue to use IMT to follow his disease annually.