Bale/Doneen Live Chat Session

Amy Doneen MSN, ARNP

April 9, 2014

5:30-6:30 pm PST

Since Release: February 5, 2014

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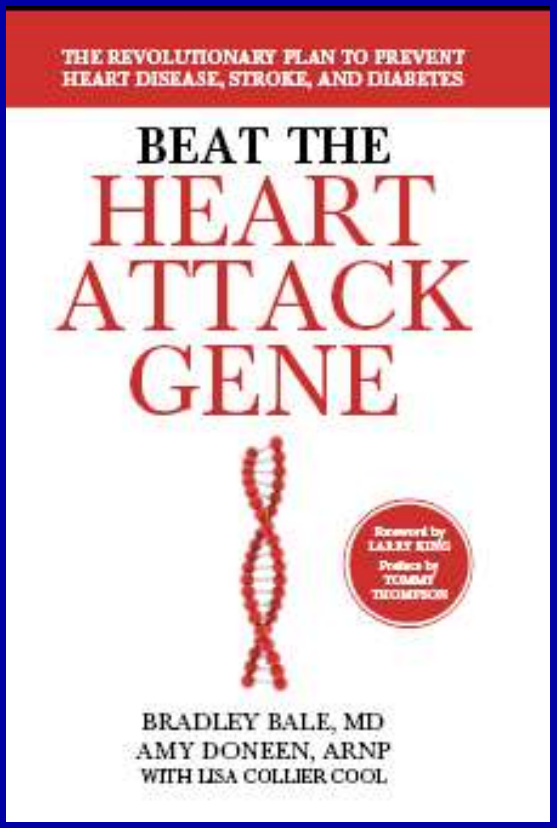


Outline for today's discussion

Red Flags:

- Cognitive Impairment
- Air Pollution
- Obesity trends in children thru 2012

Disease:

- STEMI thrombi symptoms
- Stress imaging post PCI not helpful
- Stroke Risk 30 days post MI

Root Causes:

- Psychosocial: Depression and post MI
- IR: Sugar Promotes CV death
- IR: HgA1C not predictive

Treatment:

- Fruit and vegetables reduce mortality
- Metformin
- ASA in noncardiac surgery - POISE
- ACE better than ARBs
- ACE advantage ang 1-7 and enhance insulin sensitivity
- Ramipril and PAD – why?

Red Flags

Cognitive Impairment and Stroke Risk

Cognitive Impairment and Stroke Risk

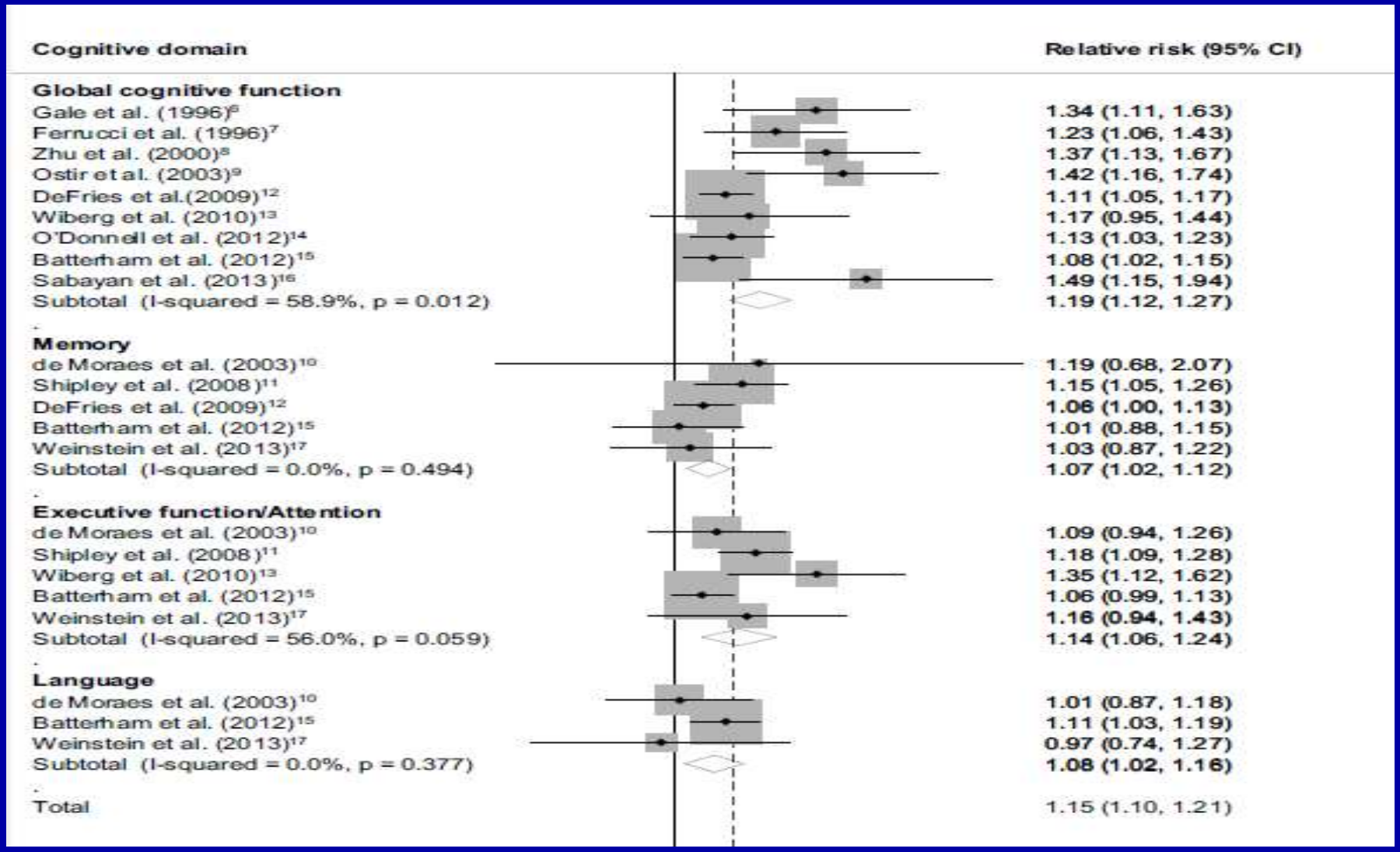
- Prospective cohort studies with 95% CI were included – between 1/1/80-10/1/13
- Risk of Stroke per SD lower performance in cognitive tests was calculated.
- 12 studies – 82,899 participants, 3043 CVA.
  - f/u 3-21 years, men and women > 65 years old.

Pooled RR per each SD yielded a higher risk of stroke:

lower global performance:	1.19 (95% CI, 1.12-1.27)
lower executive function:	1.14 (95% CI, 1.06-1.24)
lower memory scores:	1.07 (95% CI, 1.02-1.12)
lower language scores:	1.08 (95% CI, 1.02-1.16)

Rostamian. Cognitive Impairment and Risk of Stroke. Stroke, 4.7.2014;45:00-00

Cognitive Impairment and Stroke Risk



Rostamian. Cognitive Impairment and Risk of Stroke. Stroke, 4.7.2014;45:00-00

Cognitive Impairment and Stroke Risk

Bale/Doneen Take-Away:

Agree with authors of study – suggest that cognitive assessment, particularly in older subjects, might be an easily accessible tool in daily practice to identify subjects at high risk of stroke and require further analysis

Further analysis……disease/inflammation!

Rostamian. Cognitive Impairment and Risk of Stroke. Stroke, 4.7.2014;45:00-00

Air Pollution and CVD

Air Pollution and CVD

- Associated between hourly changes in air pollution on CVD morbidity.
- Cross over design 10,949 residents in Okayama Japan, aged ≥ 65 taken to hospital b/t 1/2006-12/2010 for onset of CVD events.
- Calculated hourly average city air pollutants from monitoring statins – focus on 'suspended particulate matter' & disease onset.
- Interesting note: researchers did control for weekly flu cases and excluded.

Yorifuji. CV Emergency hospital visits and hourly changes in air pollution. Published online April 1, 214. Stroke

Air Pollution and CVD

Table 1. Characteristics of Emergency Hospital Visits for Patients >65 Years With Cardiovascular Disease and Residing in Okayama City, Japan, 2006 to 2010 (n=10 949)

	Patients
Age, y, mean (SD)	80 (8.1)
Patients ≥75 y*	7930 (72.4)
Women*	5801 (53)
Medical history*	
Hypertension	1933 (18)
Arrhythmia	245 (2.2)
Coronary heart disease	965 (8.8)
Cerebrovascular disease	1829 (17)
Diabetes mellitus	726 (6.6)
Malignant neoplasms	274 (2.5)
Types of cardiovascular disease*	
Ischemic heart disease	1597 (15)
Arrhythmia	813 (7.4)
Cerebrovascular disease	5851 (54)
Hemorrhagic stroke	1452 (13)
Ischemic stroke	2726 (25)
Transient ischemic attack	1047 (9.6)

*No. (%) of participants is shown. Percentages may not sum to 100% due to rounding.

Yorifuji. CV Emergency hospital visits and hourly changes in air pollution. Published online April 1, 214. Stroke

Air Pollution and CVD

Table 3. Adjusted OR* per Interquartile Range Increase in SPM by Exposure Period Before Emergency Call

SPM	Cardiovascular Disease	Cerebrovascular Disease	Hemorrhagic Stroke	Ischemic Stroke	TIA
0–6 h	1.04 (1.01–1.06)	1.04 (1.00–1.08)	1.05 (0.97–1.13)	1.04 (0.98–1.09)	1.04 (0.95–1.13)
0–12 h	1.02 (0.99–1.05)	1.03 (0.99–1.07)	1.05 (0.97–1.13)	1.02 (0.96–1.08)	1.01 (0.92–1.11)
0–24 h	1.00 (0.97–1.04)	1.01 (0.96–1.05)	1.03 (0.95–1.12)	0.99 (0.92–1.06)	1.00 (0.90–1.10)
24–48 h	0.97 (0.94–1.00)	0.96 (0.92–1.00)	1.03 (0.95–1.12)	0.92 (0.86–0.98)	0.88 (0.79–0.98)
48–72 h	1.00 (0.97–1.03)	0.99 (0.95–1.03)	1.08 (1.00–1.16)	0.95 (0.89–1.01)	0.92 (0.83–1.01)
72–96 h	0.97 (0.95–1.00)	1.00 (0.96–1.04)	1.05 (0.97–1.13)	0.97 (0.91–1.03)	0.94 (0.85–1.03)

OR indicates odds ratio; SPM, suspended particulate matter; and TIA, transient ischemic attack.

*Adjusted for ambient temperature (degrees of freedom=6) and humidity (degrees of freedom=3). Interquartile range=20.6 μg/m^3.

Yorifuji. CV Emergency hospital visits and hourly changes in air pollution. Published online April 1, 214. Stroke

Air Pollution and CVD

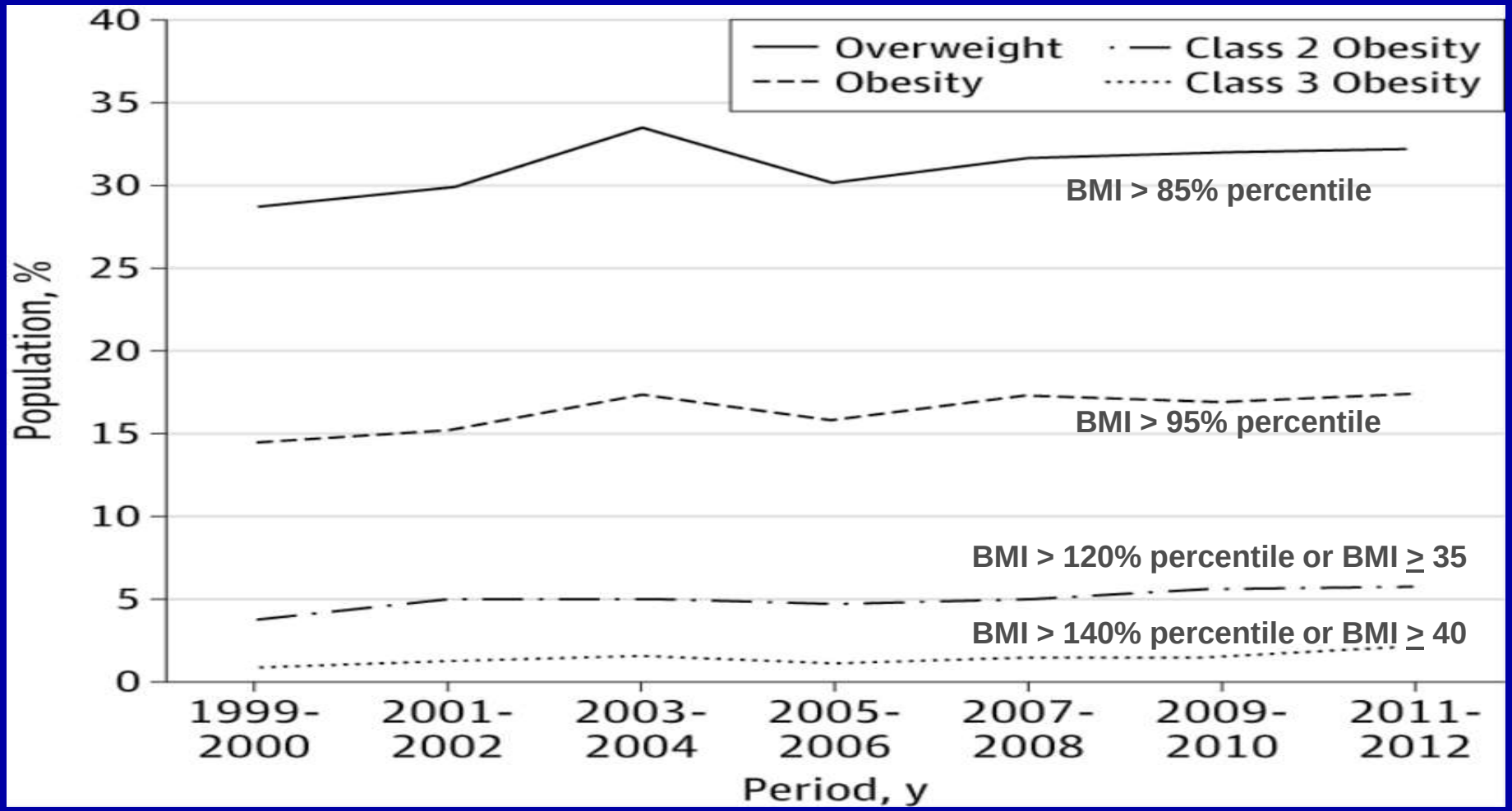
Bale/Doneen Take Away:

- Study has weaknesses due to lack of control for various CVD risk factors. However, it does appear that during the first 6 hours of heavy air pollutant exposure (SPM) that the vulnerable patient is at risk for vascular events.
- Solution:
  - Make sure inflammatory markers are mitigated prior to exposure. Follow a disease/inflammatory paradigm.

Yorifuji. CV Emergency hospital visits and hourly changes in air pollution. Published online April 1, 214. Stroke

Prevalence and Trends in Obesity and Severe Obesity Among Children in the United States, 1999-2012

Prevalence and Trends in Obesity and Severe Obesity Among Children in the United States, 1999-2012



JAMA Pediatr. April 4, 2014. doi:10.1001/jamapediatrics.2014.21

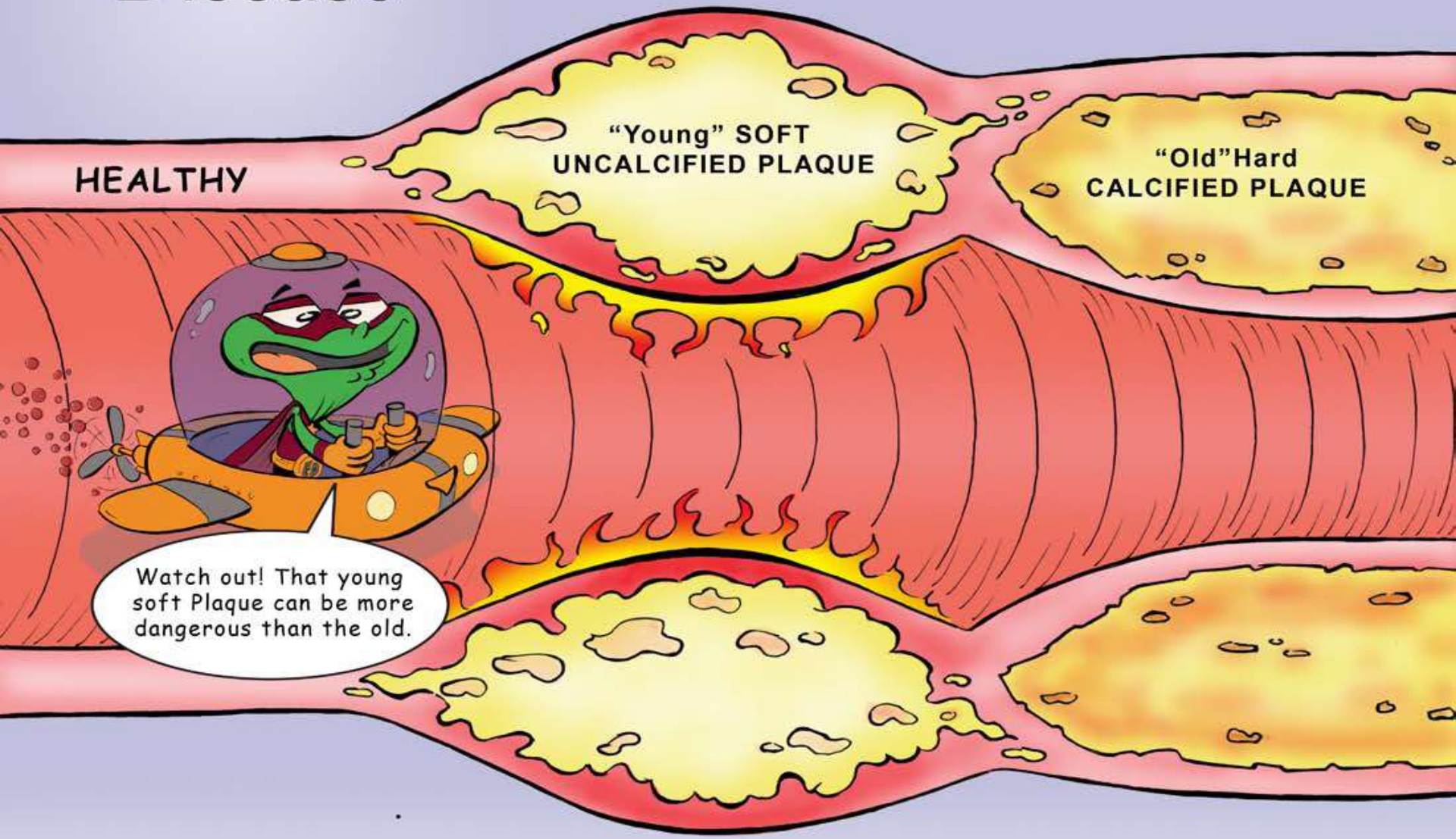
Prevalence and Trends in Obesity and Severe Obesity Among Children in the United States, 1999-2012

Table 1. Distribution of Demographic Characteristics and Obesity Prevalence by Demographic Characteristics for All Participants, 1999 to 2012

Characteristic	Full Population, No. (%)	Overweight		Obesity		Class 2 Obesity		Class 3 Obesity	
		% (95% CI)	*P* Value[a]	% (95% CI)	*P* Value[a]	% (95% CI)	*P* Value[a]	% (95% CI)	*P* Value[a]
Total No.	26 690	8979		4902		1671		518	
Total prevalence		31.2 (30.1-32.2)		16.4 (15.6-17.2)		5.1 (4.6-5.5)		1.5 (1.3-1.7)	
Population[b]	71 898 377	22 403 078		11 781 596		3 645 60		155 791	
Age, y									
2-5	5963 (21.1)	23.8 (22.2-25.4)		11.1 (9.9-12.2)		2.1 (1.6-2.6)		0.5 (0.2-0.7)	
6-11	7987 (33.5)	33.1 (31.5-34.7)	<.001	17.5 (16.3-18.7)	<.001	5.0 (4.5-5.6)	<.001	1.2 (0.9-1.4)	<.001
12-19	12 740 (45.4)	33.2 (31.8-34.5)		18.0 (16.9-19.1)		6.5 (5.7-7.3)		2.1 (1.8-2.5)	
Sex									
Female	13 154 (48.8)	30.7 (29.4-32.0)	.24	15.6 (14.6-16.6)	.005	4.8 (4.2-5.3)	.10	1.4 (1.1-1.7)	.47
Male	13 536 (51.2)	31.6 (30.3-32.9)		17.1 (16.2-18.1)		5.4 (4.7-6.0)		1.5 (1.3-1.8)	
Race/ethnicity									
White	7317 (58.2)	28.7 (27.1-30.3)		14.3 (13.0-15.6)		3.9 (3.2-4.5)		1.0 (0.7-1.3)	
Black	7733 (14.6)	35.1 (33.8-36.4)	<.001	20.3 (19.3-21.4)	<.001	8.5 (7.7-9.3)	<.001	3.3 (2.8-3.9)	<.001
Hispanic	9875 (19.9)	37.7 (36.5-39.0)		20.9 (19.8-22.0)		6.6 (5.9-7.3)		1.8 (1.4-2.1)	
Other	1765 (7.2)	24.6 (21.9-27.3)		12.7 (10.8-14.6)		3.6 (2.5-4.7)		0.7 (0.1-1.4)	

JAMA Pediatr. April 4, 2014. doi:10.1001/jamapediatrics.2014.21

Disease

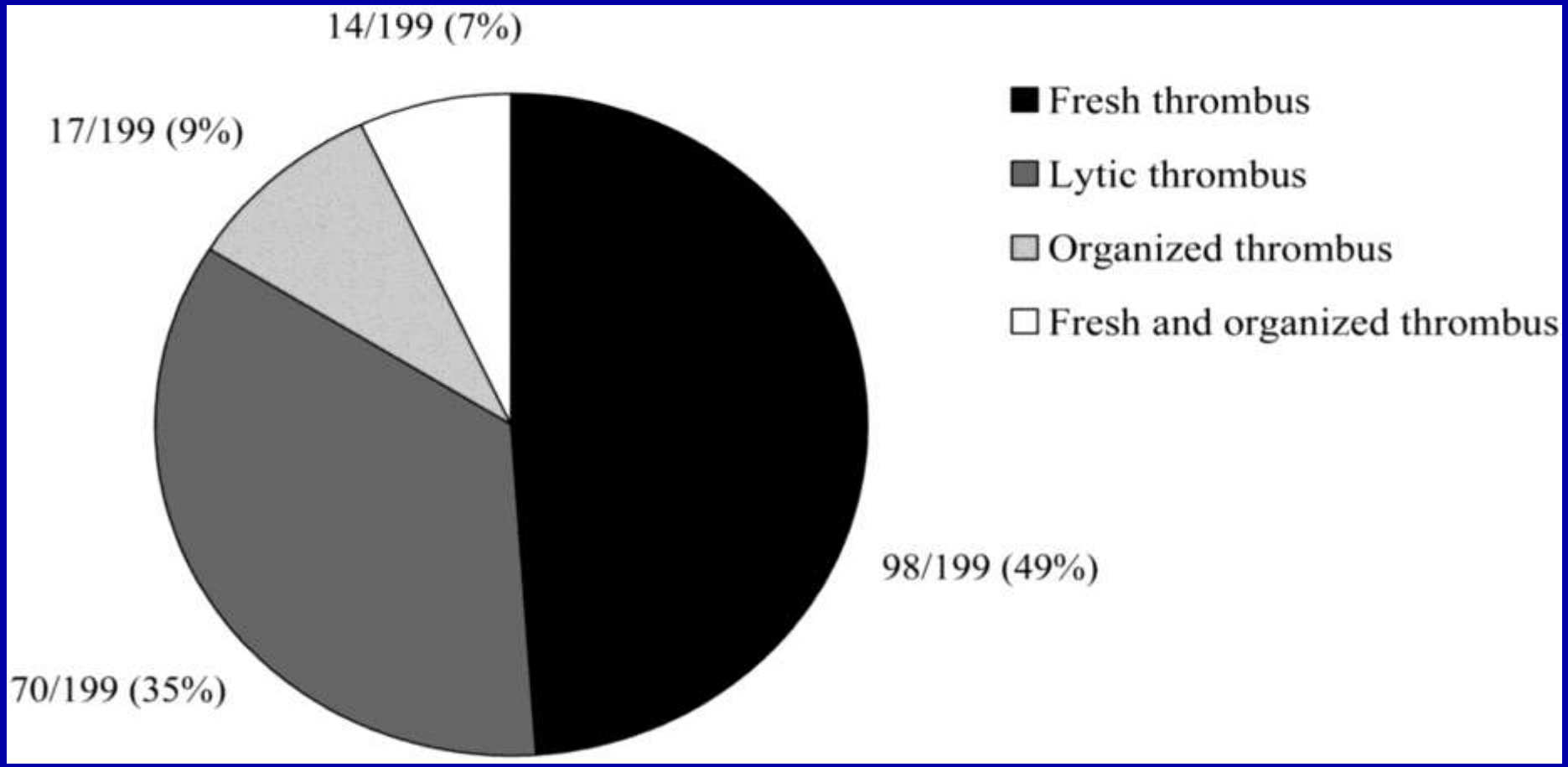


Plaque formation is an active process and its consistency changes over time. Some technologies (X-Rays) can only see hard calcified disease while others like ultrasounds can spot soft disease.

Dale Doneen METHOD

Moss Freedman

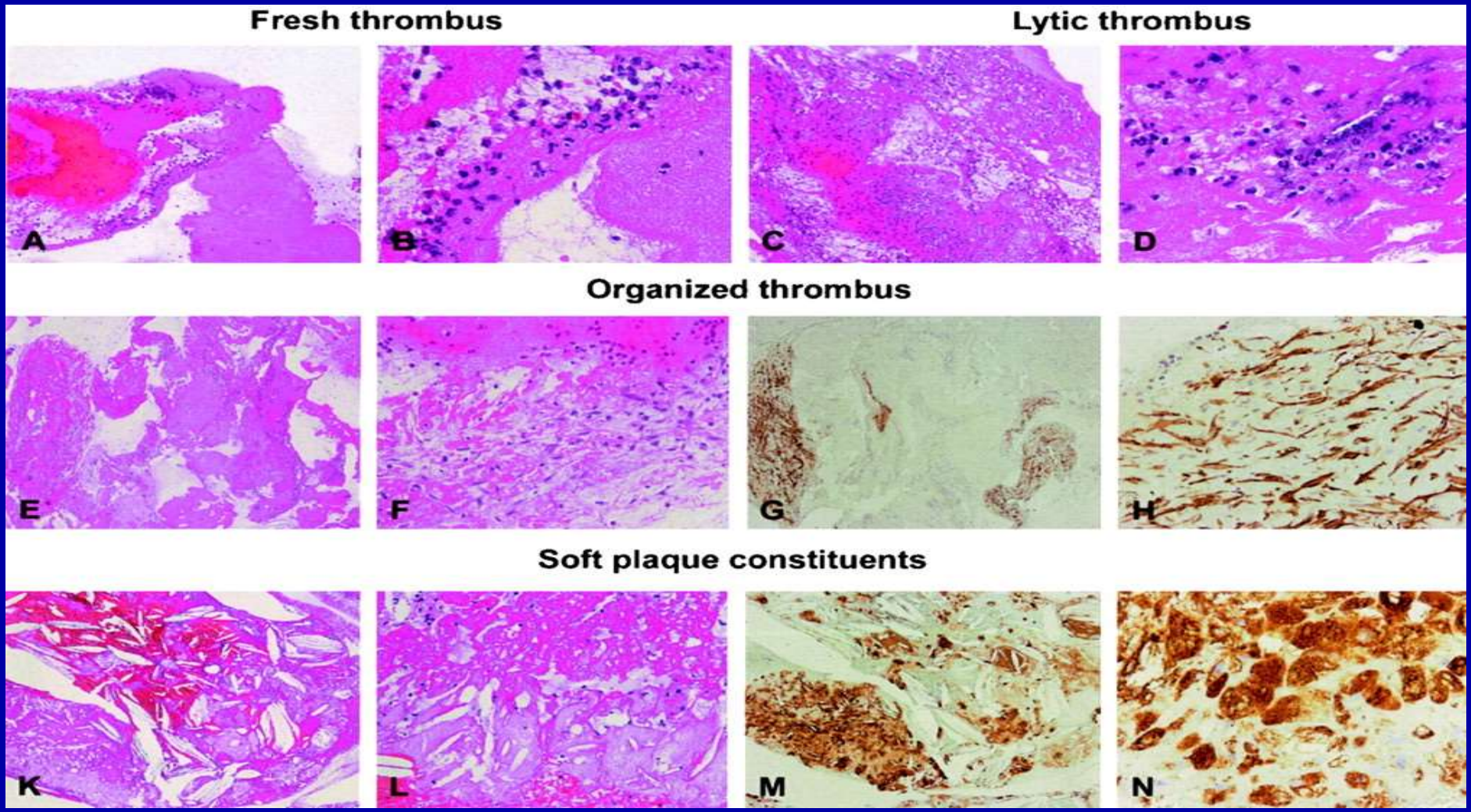
Plaque Instability Frequently Occurs Days or Weeks Before Occlusive Coronary Thrombosis



Saskia Z.H. Rittersma, Allard C. van der Wal, Karel T. Koch, Jan J. Piek, José P.S. Henriques, Karla J. Mulder, Johanna P.H.M. Ploegmakers, Martin Meesterman, and Robbert J. de Winter

Circulation Volume 111(9):1160-1165 March 8, 2005

Histological spectrum of thrombus and atherosclerotic plaque tissue retrieved by intracoronary thrombectomy.



Circulation Volume 111(9):1160-1165 March 8, 2005

Histological spectrum of thrombus and atherosclerotic plaque tissue retrieved by intracoronary thrombectomy.

Authors Conclusion in 2005:

Results validate that the absence of complete healing of aging. Thrombus may play an important role in acute coronary thrombosis.

Also suggestive that microvascular plaque rupture/healing can occur in asymptomatic individuals.

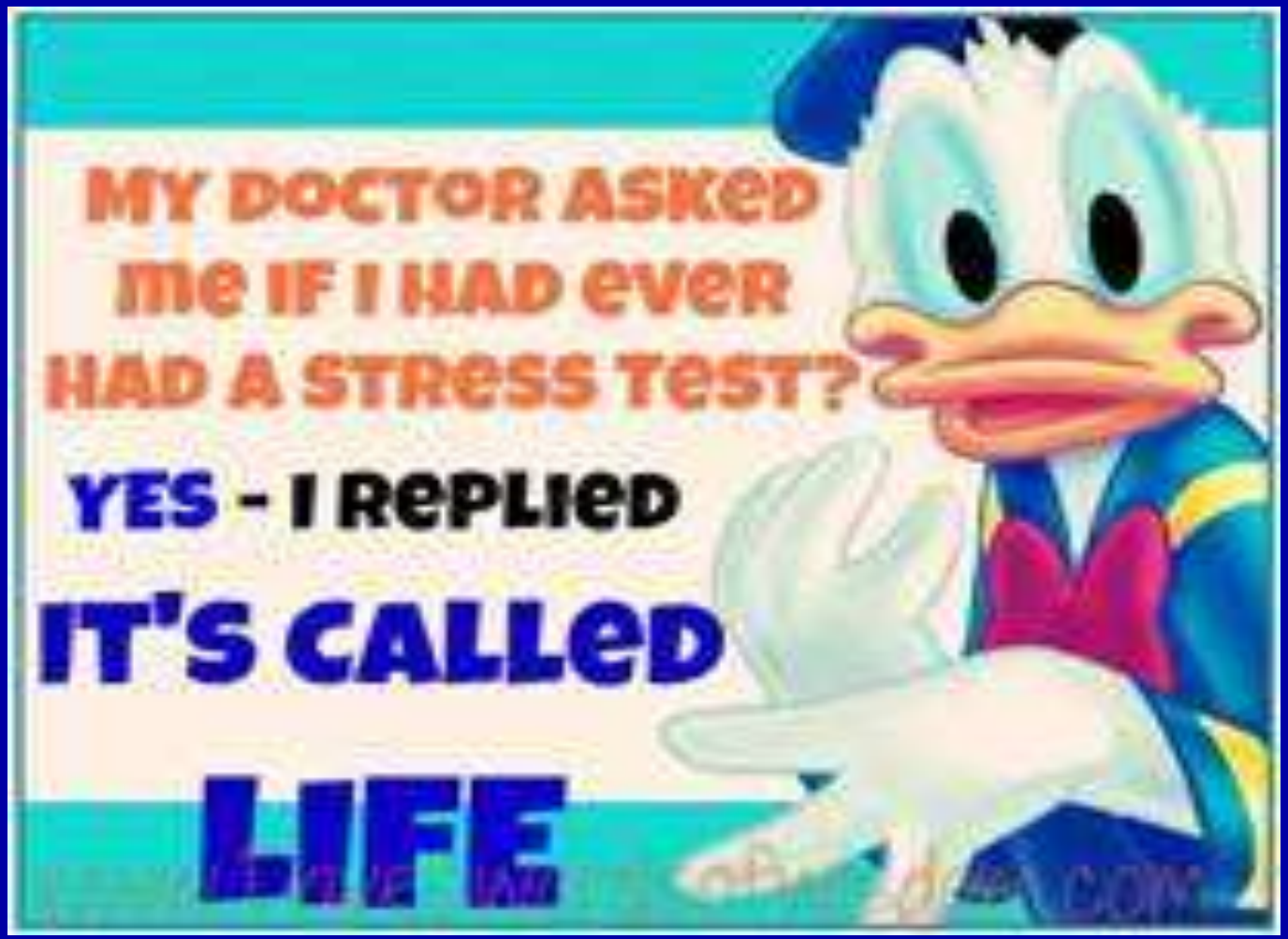
Bale/Doneen Solution:

- Follow a disease/inflammatory paradigm!
- Monitor inflammatory markers regularly.
- Goal of treatment: Atherosclerosis stabilization.
- Remember: Define “event” globally.

Circulation Volume 111(9):1160-1165 March 8, 2005

Bale Doneen METHOD

Stress Imaging in Asymptomatic Patients Post PCI



Stress Imaging in Asymptomatic Patients Post PCI

Olmsted County, MN, residents who underwent PCI were followed for stress nuclear or stress echo, coronary angiography, or CABG as initial procedure post PCI.

Pts whose first follow-up procedure was a stress imaging test were evaluated for symptom status at the time of the study and whether they underwent PCI or CABG within 90 days.

Peterson, T. The low yield of stress imaging in a population-based study of asymptomatic patients post PCI. Circ Cardiovasc Imaging Published online 3/31/14

Stress Imaging in Asymptomatic Patients Post PCI

Of 1848 patients who underwent PCI during study period:

710 (38%) had stress imaging as their initial procedure after PCI.

241 (13%) were asymptomatic at time of testing. 207 (86%) of these underwent PCI for ACS or unstable angina.

Within 90 days of stress imaging, 16 of the 241 asymptomatic patients underwent angiography and two patients were revascularized.

Stratified for timing, 0/138 asymptomatic patients tested within two years of PCI underwent revascularization. 2/103 asymptomatic patients had revascularization

Peterson, T. The low yield of stress imaging in a population-based study of asymptomatic patients post PCI. Circ Cardiovasc Imaging Published online 3/31/14

Stroke risk 30 days post MI

Stroke risk 30 days post MI

Aim of trial: investigate whether changes in AMI treatment corresponded to a lower incidence of ischemic stroke and which risk factors predicted ischemic stroke after AMI.

Patients with AMI b/t 1998-2008 – divided population into 5 time periods.

173,233 patients with AMI,, 3571 (2.1%) developed ischemic stroke within 30 days.

Kajermo, U. et al. Stroke 30 days post MI. Stroke. 4/1/2014:45:00-00

Stroke risk 30 days post MI

Statistically significant:
Age (76 vs 71)

Female % (45 vs 36)

Previous stroke % (29 vs 11)

Diabetic % (25 vs 19)

Table 1. Baseline Characteristics of 173 233 Patients With AMI Between the Years 1998 to 2008 According to the Occurrence of Ischemic Stroke Within 30 Days

Ischemic Stroke	No Stroke (n=169 662)	Stroke (n=3571)	*P* Value
Age (mean)	71.1	76.1	<0.001
Women, %	36.6	45.0	<0.001
BMI (mean) n=valid cases	26.6 n=61 809	25.7 n=1063	<0.001
Heart rate, bpm n=valid cases	81.0 n=73 504	85.5 n=1475	<0.001
Systolic BP, mm Hg n=valid cases	145.1 n=75 099	146.6 n=1491	0.043
Diastolic BP, mm Hg n=valid cases	82.5 n=73 796	82.4 n=1460	0.919
P-cholesterol, mmol/L n=valid cases	5.1 n=85 684	4.9 n=1483	<0.001
P-LDL, mmol/L n=valid cases	3.2 n=76 832	3.0 n=1338	<0.001
P-glucose, g/L n=valid cases	8.2 n=91 147	8.9 n=1796	<0.001
Prior AMI, %	15.8	17.8	0.001
Prior stroke, %	10.7	29.0	<0.001
Prior ischemic stroke, %	8.2	24.6	<0.001
Prior renal failure, %	2.2	2.2	0.993
Prior dialysis, %	0.5	0.4	0.404
Prior COPD, %	8.3	7.9	0.425
Prior heart failure, %	11.9	14.9	<0.001
Prior diabetes mellitus, %	19.2	25.2	<0.001
Prior peripheral arterial disease, %	5.6	8.0	<0.001
STEMI, %	35.4	35.4	0.999
Atrial fibrillation during hospitalization, %	16.8	31.7	<0.001
Clinical signs of heart failure during hospitalization, %	34.9	51.9	<0.001
PCI during hospitalization, %	35.6	18.7	<0.001
Fibrinolysis during hospitalization, %	15.3	13.6	0.005
CABG during hospitalization, %	1.9	2.6	0.003

Kajermo, U. et al. Stroke 30 days post MI. Stroke. 4/1/2014:45:00-00

Stroke risk 30 days post MI

Table 5. Predictor of Ischemic Stroke at 30 Days After AMI in a Multivariate Cox Regression Model

Predictor Variable	Hazard Ratio (95% CI)	*P* Value
Age	1.02 (1.01–1.02)	<0.001
Female sex	1.17 (1.09–1.26)	<0.001
Prior stroke	2.52 (2.33–2.73)	<0.001
Diabetes mellitus	1.20 (1.10–1.30)	<0.001
Atrial fibrillation	1.53 (1.41–1.66)	<0.001
Clinical signs of heart failure in hospital	1.24 (1.15–1.34)	<0.001
ST-segment–elevation myocardial infarction	1.38 (1.27–1.50)	<0.001
Fibrinolysis	0.84 (0.74–0.94)	0.002
Percutaneous coronary intervention during hospitalization	0.69 (0.62–0.76)	<0.001
CABG during hospitalization	1.64 (1.32–2.03)	<0.001
ASA treatment at discharge	0.65 (0.60–0.71)	<0.001
Statin treatment at discharge	0.88 (0.81–0.96)	0.002
P2Y12 inhibitor treatment at discharge	0.83 (0.75–0.91)	<0.001
ACE inhibitor treatment at discharge	1.10 (1.02–1.18)	0.011

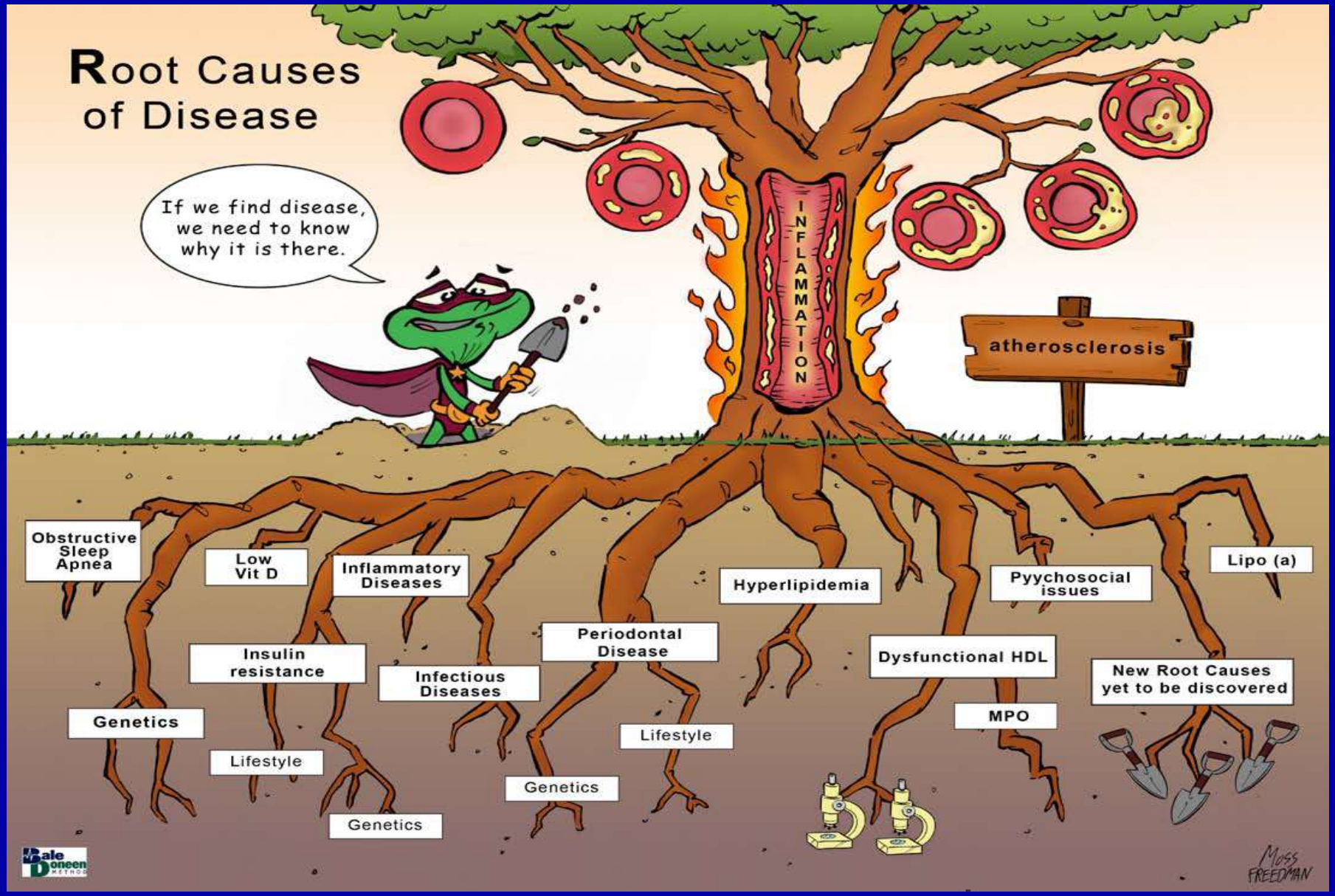
ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; and CI, confidence interval.

Kajermo, U. et al. Stroke 30 days post MI. Stroke. 4/1/2014:45:00-00

Stroke risk 30 days post MI

- Bale/Doneen Take Away:
  - Ischemic Stroke is a manifestation of an atherosclerotic thrombotic accident.
  - Treat atherosclerosis as a systemic disease.
  - Monitor inflammatory markers and disease annually to know if treatment is effective.

Kajermo, U. et al. Stroke 30 days post MI. Stroke. 4/1/2014:45:00-00



Depression and CAD

Systematic review of literature on depression and medical outcomes after ACS – Included all-cause mortality, cardiac mortality, and composite outcomes for mortality and nonfatal events.

Total of 53 individual studies and 4 meta-analyses met inclusion criteria.

Depression and depressive symptoms are common among the estimated 15.4 million US adults with CHD.

Approximately 20% of patients hospitalized for ACS meet the DMS criteria for major depression, and an even larger percentage show subclinical levels of depressive symptoms.

Leifheit-Limson, E. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: symptomatic review and recommendations. Circulation 4.4.2014. 129:1350-1369.

Depression and CAD

Mechanisms postulated/discussed in the paper linking depression and CVD events:

- neuroendocrine dysfunction
- disturbances in autonomic cardiac control
- enhance platelet activity
- endothelial dysfunction
- inflammation

Mechanisms involving high risk behaviors linking depressing and CVD events:

- smoking, sedentary lifestyle, delay in seeking tx, nonadherence to prevention measures, poor self care.

Leifheit-Limson, E. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: symptomatic review and recommendations. Circulation 4.4.2014. 129:1350-1369.

Depression and CAD

Still lack evidence of cause/effect showing that treatment of depression improves survival of ACS or prevents disease however…worsening depression is associated with worse clinical outcomes.

Bale/Doneen Take Away: Proper screening for depression is essential for all patients with vascular disease. Psychosocial remains a root cause of CVD (INTERHEART TRIAL)

Leifheit-Limson, E. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: symptomatic review and recommendations. Circulation 4.4.2014. 129:1350-1369.

Added Sugar intake and CV Mortality

Added Sugar intake and CV Mortality

NHANES, 1988-1994 (III), 1999-2004, and 2005-2010 [n=31,147].

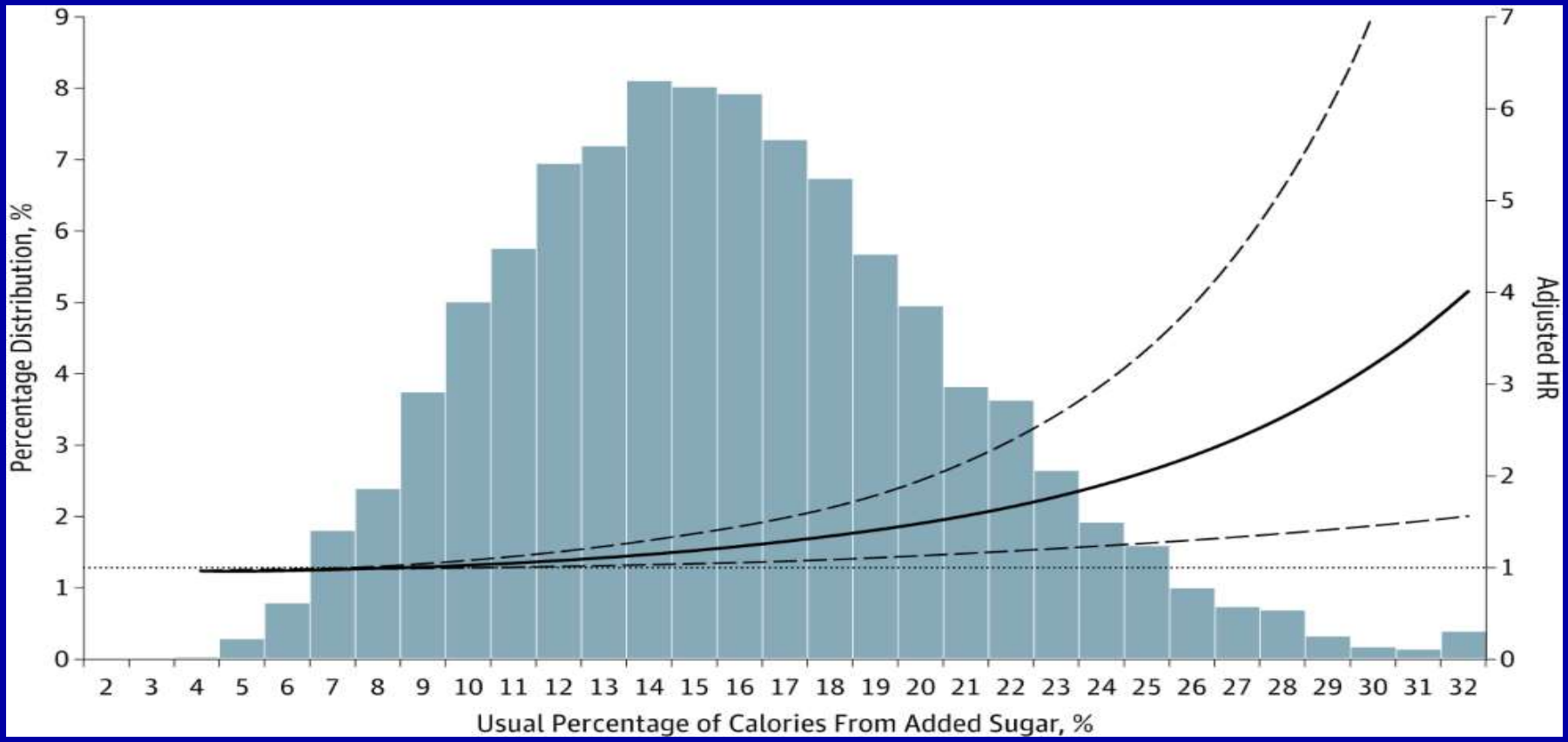
For this analysis, NHANES III linked mortality cohort (1988-2006 [n=11,733], a prospective cohort of nationally representative sample of US adults.

Among US adults, the adjusted mean percentage of daily calories from added sugar increased from 15.7% (95% CI,15.0%-16.4%) in 1988-1994 to 16.8% (16.0%-17.8%; p=.02) in 1999-2004 and decreased to 14.9% (14.2%-15.5%;p=.001) in 2005-2010.

During 14.6 years – 831 CVD deaths during 163,039 person-years.

JAMA Intern Med. JAMA Intern Med 2014;(3/31/2014):.doi:10.1001/jamainternmed.13563

Added Sugar intake and CV Mortality

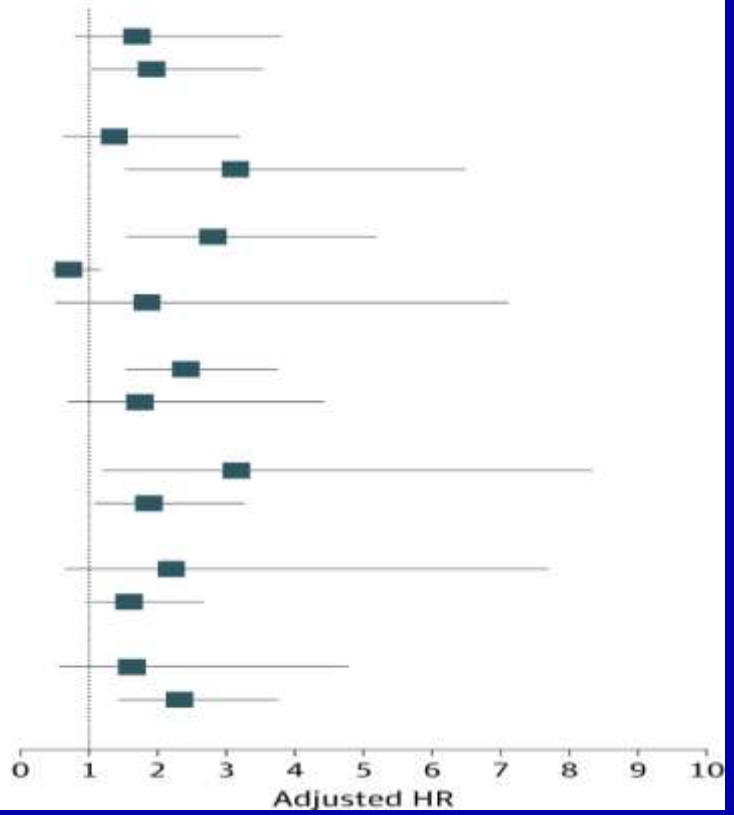


Adjusted HR of the Usual % of Calories From Added Sugar for CVD Mortality Among US Adults 20 Years or Older: National Health and Nutrition Examination Survey Linked Mortality Files, 1988-2006 Histogram of the distribution of usual percentage of calories from added sugar in the population.

JAMA Intern Med. 2014;(3/31/2014):. doi:10.1001/jamainternmed

Added Sugar intake and CV Mortality

Subgroup	No. of Participants (Deaths)	Adjusted HR (95% CI)
Age, y		
<60	8835 (144)	1.67 (0.78-3.58)
≥60	2898 (687)	1.83 (1.01-3.31)
Sex		
Male	5639 (434)	1.34 (0.60-3.00)
Female	6094 (397)	2.95 (1.48-5.91)
Race/ethnicity		
Non-Hispanic white	4802 (494)	2.67 (1.48-4.80)
Non-Hispanic black	3233 (187)	0.71 (0.44-1.15)
Mexican American	3217 (134)	1.76 (0.49-6.39)
Education, y		
<12	4318 (455)	2.29 (1.49-3.50)
≥12	7415 (376)	1.67 (0.67-4.18)
Healthy Eating Index		
≥Top 50%	5673 (457)	2.96 (1.15-7.63)
<Top 50%	6060 (374)	1.80 (1.05-3.07)
Physical activity		
High	4407 (287)	2.12 (0.63-7.18)
Low	7326 (544)	1.54 (0.93-2.53)
Body mass index		
<25	4697 (320)	1.55 (0.56-4.34)
≥25	7036 (511)	2.23 (1.40-3.55)



For the Healthy Eating Index score, the top 50% or higher included the participants with a score of 63.5 or more; high physical activity included the participants who had moderate intensity to vigorous activities 5 or more times per week. Limit lines indicate 95% CI.

JAMA Intern Med. 2014;(3/31/2014):. doi:10.1001/jamainternmed

Added Sugar intake and CV Mortality Percentage of calories from Sugar

eTable 3. Adjusted Hazard Ratio of Cardiovascular Disease Mortality According to Percentage of Calories From Added Sugar Based on First-Day 24 Hour Dietary Recall Among US Adults Aged ≥20 Years—NHANES Linked Mortality Files, 1988-2006

		Mid-value of Quintiles of Percentage of Calories from Added Sugar for US Adults [a]					
Characteristics		Q1 3.5%	Q2 9.3%	Q3 14.6%	Q4 20.7%	Q5 31.5%	p-value[b]
CVD deaths/participants/ total person years	831/11,733/ 163,039,						
Range/Usual percentage (%)	0%-100%	0- <6.6%	6.6- <11.5%	11.5- <16.6%	16.6- <23.6%	≥23.6%	
HR adjusted for age, sex and race/ethnicity only		1.06 (0.95 - 1.20)	1.0	1.00 (0.92 - 1.08)	1.09 (0.96 - 1.23)	1.50 (1.21 - 1.87)	0.006
Fully adjusted HR[c]		1.05 (0.92 - 1.19)	1.0	1.00 (0.92 - 1.10)	1.08 (0.93 - 1.26)	1.43 (1.10 - 1.86)	0.027

Adjusted for: age, sex, race, ethnicity, educational attainment, smoking status, alcohol consumption, physical activity level, antihypertensive meds, fmhx CVD, health eating index score, BMI, SBP, TC and total calorie intake.

JAMA Intern Med. 2014;(3/31/2014):. doi:10.1001/jamainternmed

Added Sugar intake and CV Mortality Sugar Sweetened Beverage

eTable 7. Adjusted Hazard Ratio of Cardiovascular Disease Mortality According to Categories of Sugar Sweetened Beverage Consumption Among US Adults Aged ≥20 Years—NHANES Linked Mortality Files, 1988-2006

		Servings of Sugar Sweetened Beverage Consumption per week[a]			
Characteristics		<1	1 to <3	3 to <7	≥7
CVD deaths/participants	831/11,733	468/4,348	97/1,288	83/1,829	183/4,268
Total person years	163,039	58,219	17,925	26,199	60,696
HR adjusted for age, sex and race/ethnicity only		1.00	1.01 (0.72 - 1.41)	1.00 (0.72 - 1.35)	1.38 (1.10 - 1.72)
Fully adjusted HR[b]		1.00	1.03 (0.73 - 1.44)	1.04 (0.75 - 1.45)	1.29 (1.04 - 1.60)

Adjusted for: age, sex, race, ethnicity, educational attainment, smoking status, alcohol consumption, physical activity level, antihypertensive meds, fmhx CVD, health eating index score, BMI, SBP, TC and total calorie intake.

JAMA Intern Med. 2014;(3/31/2014):. doi:10.1001/jamainternmed

HgA1C did not add predictability for CV Events

To determine whether adding HgA1C values to conventional CV risk factors is predictive of CVD risk.

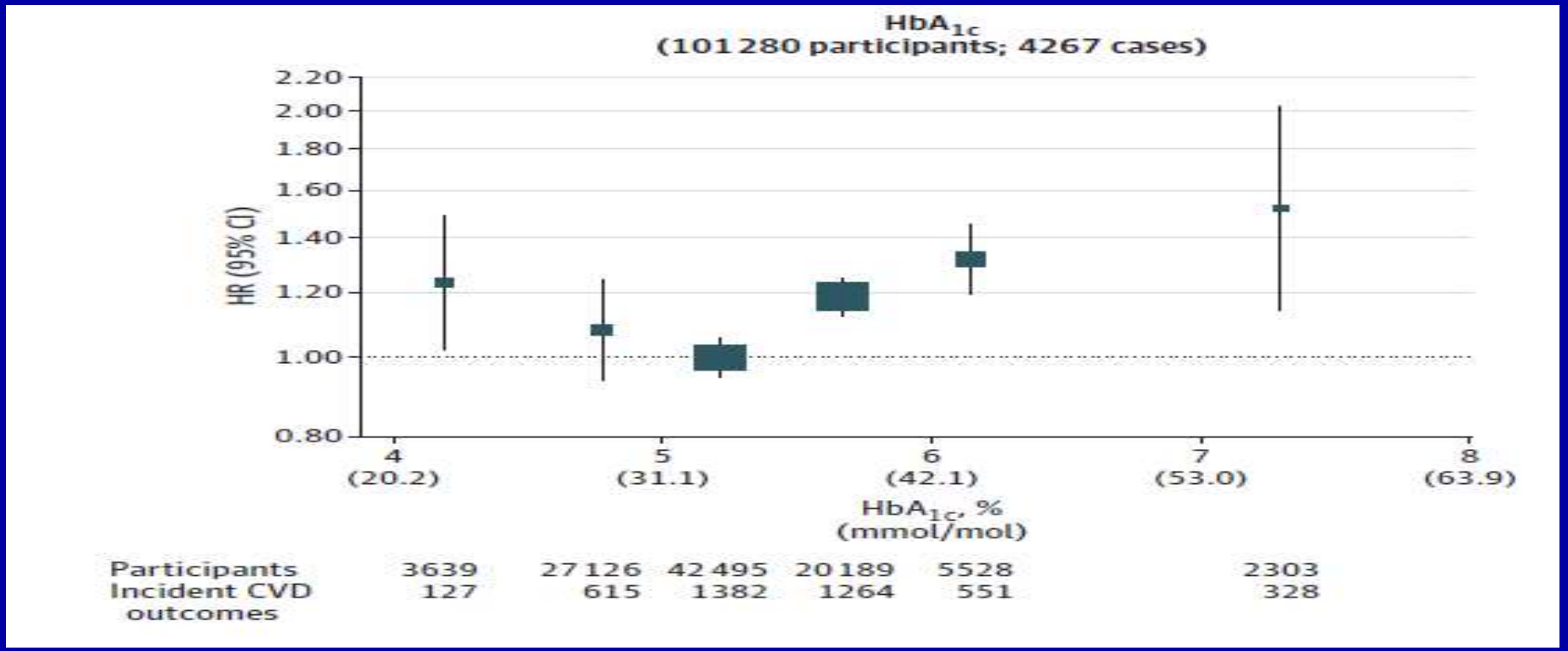
Analysis of 73 prospective studies involving 294,998 participants without Known DM or CVD at baseline

Primary outcome was first-onset CVD, defined as fatal or nonfatal coronary Heart disease event or any stroke.

Mean age 58 (SD,9), 49% women, 86% lived in Europe or North America

Danesh, J. JAMA. March 26, 2014; 311(12):1225-1233.

HgA1C did not add predictability for CV Events



Adjusted for: age, sex, smoking status, SBP and TC, HDL

Danesh, J. JAMA. March 26, 2014; 311(12):1225-1233.

HgA1C did not add predictability for CV Events

Conclusions by Authors:

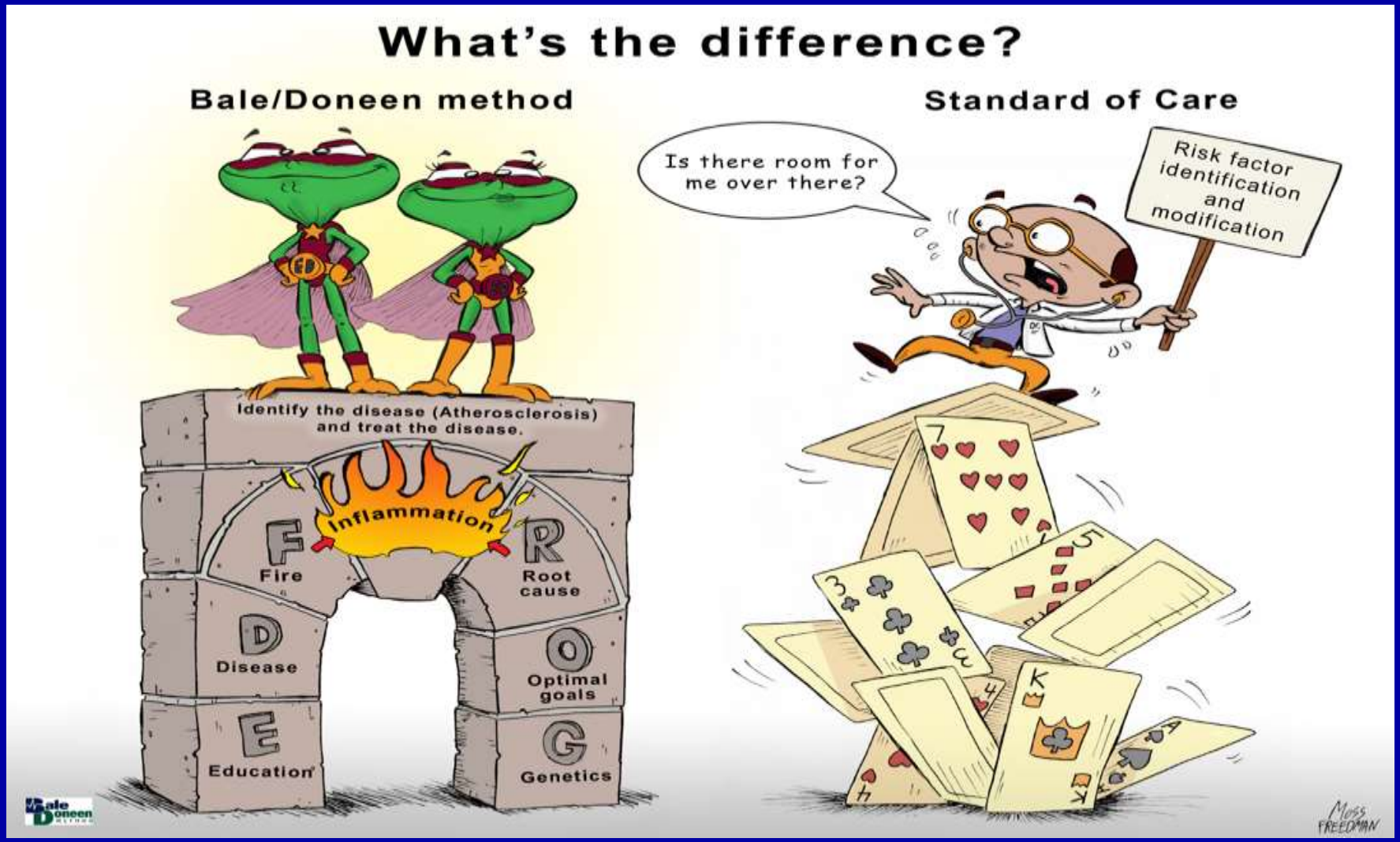
1. Current analysis of almost 300,000 people without known DM and CVD at baseline indicates that HgA1C is not associated with clinically meaningful improvement in assessment of CVD risk
2. Adding information with HgA1C was not associated with sign improvement in reclassification of participants across clinical risk categories

Bale/Doneen Take Away –

1. This study did not assess for screening for diabetes and diabetes specific microvascular complications.
2. We do not advocate using A1C to diagnose IR – use OGTT.

Danesh, J. JAMA. March 26, 2014; 311(12):1225-1233.

Treatment



Fruit & Vegetable Consumption and all-cause cancer and CVD mortality

Fruit & Vegetable Consumption and all-cause cancer and CVD mortality

Cox regression used to estimate association between fruit and vegetable consumption and all-cause, cancer and CV mortality adjusting for age, sex, social class, education, BMI, alcohol consumption and physical activity.

65, 226 age 35+ ears in 2001-2008 Health Surveys for England, annual surveys, random samples, median follow-up: 7.7 years.

Fruit and vegetable consumption was associated with decreased:

(reference category 7+ portions vs < 1 portion/day)

All-cause mortality	HR 0.67 (95% CI 0.58-0.78)
Reduced Cancer	HR 0.75 (95% CI 0.59-0.96)

Oyebode O., et al. J Epidemiology Community health. April 2014:0:1-7.

Fruit & Vegetable Consumption and all-cause cancer and CVD mortality

Table 3 Association between fruit and vegetable consumption and cancer or CVD-specific mortality

	Portions of fruit and vegetables consumed in the previous day HRs (95% CI)				
Model	0–<1*	1–<3	3–<5	5–<7	7+
Cancer					
Number of participants (deaths)	*10 607 (169)*	*28 805 (485)*	*24 968 (400)*	*13 082 (187)*	*7885 (95)*
Model 1†	1	0.87 (0.75 to 1.02)	0.78 (0.66 to 0.92)	0.71 (0.58 to 0.86)	0.70 (0.55 to 0.90)
Model 2‡	1	0.89 (0.76 to 1.04)	0.81 (0.69 to 0.95)	0.75 (0.62 to 0.91)	0.75 (0.59 to 0.96)
CVD					
Number of participants (deaths)	*10 607 (189)*	*28 805 (553)*	*24 968 (449)*	*13 082 (208)*	*7885 (83)*
Model 1†	1	0.88 (0.77 to 1.03)	0.78 (0.66 to 0.91)	0.74 (0.61 to 0.89)	0.63 (0.49 to 0.80)
Model 2‡	1	0.91 (0.78 to 1.05)	0.82 (0.70 to 0.95)	0.80 (0.66 to 0.96)	0.69 (0.53 to 0.88)

*Reference category.
†Adjusted for age-group, sex, social class, cigarette smoking and BMI.
‡Adjusted for age-group, sex, social class, cigarette smoking, BMI and additionally adjusted for physical activity, education and alcohol intake.
CVD, cardiovascular disease.

Oyebode O., et al. J Epidemiology Community health. April 2014:0:1-7.

Fruit & Vegetable Consumption and all-cause cancer and CVD mortality

Table 5 Association between variety of fruit and vegetable consumed and risk of death, from all causes

Type of fruit or vegetable consumed	HR per portion adjusted for age, sex, social class, cigarette smoking and BMI	p Value	HR per portion adjusted for age, sex, social class, cigarette smoking, BMI and all other fruit and vegetable variables	p Value
Vegetables	0.84 (0.81 to 0.88)	<0.001	0.85 (0.81 to 0.89)	<0.001
Salad	0.87 (0.82 to 0.92)	<0.001	0.87 (0.82 to 0.92)	<0.001
Vegetables in composites	0.92 (0.82 to 1.02)	0.10	0.92 (0.82 to 1.02)	0.10
Pulses	0.95 (0.88 to 1.03)	0.20	0.95 (0.88 to 1.03)	0.20
Fresh Fruit	0.96 (0.95 to 0.98)	<0.001	0.96 (0.95 to 0.98)	<0.001
Dried fruit	0.91 (0.84 to 0.99)	0.03	0.91 (0.84 to 0.99)	0.03
Fruit in composites	0.93 (0.84 to 1.03)	0.17	0.93 (0.84 to 1.03)	0.17
Fruit juice	0.97 (0.91 to 1.04)	0.40	0.97 (0.91 to 1.04)	0.40
Frozen/canned fruit	1.17 (1.07 to 1.28)	0.001	1.17 (1.07 to 1.28)	0.001

Oyebode O., et al. J Epidemiology Community health. April 2014:0:1-7.

Fruit & Vegetable Consumption and all-cause cancer and CVD mortality

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What this study adds?

- Fruit and vegetable consumption is inversely associated with all-cause, cancer and cardiovascular mortality in a nationally representative non-institutionalised population.
- Those eating seven or more portions of fruit and vegetables daily have the lowest risk of mortality from any cause.
- Consumption of vegetables, salad and fresh or dried fruit is robustly associated with decreased mortality.

Oyebode O., et al. J Epidemiology Community health. April 2014:0:1-7.

Metformin not beneficial post MI

Metformin not beneficial post MI

Animal studies shows metformin showing preservation of Left ventricular function.

Objective: evaluate the effect of metformin on preservation of LVF in non-DM presenting with STEMI.

Design: double-blind, placebo study with 380 pts undergoing PCI for STEMI Netherlands between 1/1/2011 -5/26/2013

Intervention: Metformin 500mg (n=119) placebo (n=189) BID x 4 months.

Endpoint: Incidence of major cardiac events (MACE). LVEF obtained by MRI is an established efficacy measure because it predicts MACE.

Lexis, C. et al. Effect of Metformin on LVEF after MI in non-DM. JAMA. 3.31, 2014.

Metformin not beneficial post MI

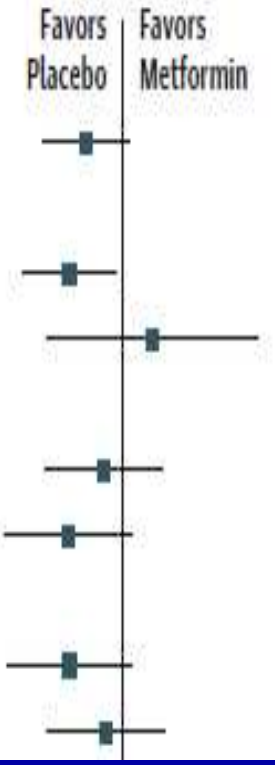
Outcome[a]	Total (n = 379)	Metformin (n = 191)	Placebo (n = 188)	*P* Value
Primary end point, % (95% CI)				
LVEF	53.9 (52.9-55.0)	53.1 (51.6-54.6)	54.8 (53.5-56.1)	.10
Secondary end point, median (IQR)				
NT-proBNP, ng/L	167 (72-390)	167 (65-393)	167 (74-375)	.66
Creatinine, μmol/L	79 (71-88)	79 (70-87)	79 (72-89)	.61
Glucose, mmol/L	5.7 (5.2-6.2)	5.7 (5.2-6.3)	5.6 (5.2-6.2)	.96
HbA_{1c}, %	5.9 (5.7-6.1)	5.9 (5.6-6.1)	5.9 (5.7-6.1)	.15

Lexis, C. et al. Effect of Metformin on LVEF after MI in non-DM. JAMA. 3.31, 2014.

Metformin not beneficial post MI

Figure 2. Estimated Effect of Metformin Compared With Placebo on Left Ventricular Ejection Fraction (LVEF) According to Prespecified Subgroups

Variable	No. of Patients		LVEF (95% CI), %		Difference in LVEF in Percentage Points (95% CI)	P for Interaction
	Metformin	Placebo	Metformin	Placebo		
Overall	135	136	53.09 (51.56-54.61)	54.80 (53.46-56.14)	-1.71 (-3.73 to 0.31)	
Sex						
Male	107	106	52.35 (50.76-53.94)	54.89 (53.37-56.41)	-2.54 (-4.73 to -0.36)	.11
Female	30	28	55.91 (51.70-60.12)	54.48 (51.45-57.50)	1.43 (-3.58 to -6.44)	
Age, y						
Below median (≤58.0)	71	65	53.81 (51.74-55.87)	54.69 (52.85-56.52)	-0.88 (-3.63 to 1.88)	.40
Above median (>58.0)	64	71	52.28 (49.98-54.58)	54.90 (52.92-56.89)	-2.62 (-5.61 to 0.38)	
BMI						
Below median (≤26.6)	69	67	52.21 (49.98-54.44)	54.77 (52.84-56.70)	-2.56 (-5.49 to 0.37)	.40
Above median (>26.6)	66	69	54.00 (51.89-56.11)	54.83 (52.92-56.74)	-0.83 (-3.64 to 1.99)	



Lexis, C. et al. Effect of Metformin on LVEF after MI in non-DM. JAMA. 3.31, 2014.

Metformin not beneficial post MI

Bale/Doneen Take-Away:

4 months metformin 500 mg BID:

- Did not have sign effect on FBS or Hg A1C
- Did not effect LVEF in non diabetic patients post MI

In previous meta-analysis metformin:

- Has not shown an impact on the prevention of new onset DM.

Metformin does not have a proven role to protect the heart in post MI, non-diabetic patients.

Lexis, C. et al. Effect of Metformin on LVEF after MI in non-DM. JAMA. 3.31, 2014.

POISE-2 PeriOperative Ischemic Evaluation-2 Trial

POISE-2 PeriOperative Ischemic Evaluation-2 Trial

Aspirin in patients undergoing noncardiac surgery

200 million adults worldwide undergo non-cardiac surgery annually. 10 million suffer major vascular complications (MI most common)

Surgery is associated with: inflammation, platelet activation, potential thrombosis perioperatively. Evidence that aspirin prevents perioperative VTE

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

POISE-2 PeriOperative Ischemic Evaluation-2 Trial

Design: Blinded 2x2 factorial RCT

Aspirin vs Placebo (200mg just before surgery, then 100mg x 30 d)

Clonidine vs Placebo.

Eligibility: undergoing noncardiac surgery, ≥ 45 yrs, at risk for vascular complication.

Exclusion Criteria:

BMS <6 weeks before surgery

DES <1 year before surgery

Took Aspirin within 72 hours before surgery.

Primary Outcome: Death or nonfatal MI at 30 days.

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

POISE-2 PeriOperative Ischemic Evaluation-2 Trial

Characteristics	**Aspirin (N=4998)**	**Placebo (N=5012)**
Age – (mean yrs)	68.6	68.6
Male (%)	52.0	53.6
Known vascular disease	32.7	32.6
History of PCI	4.7	4.7

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

POISE-2 PeriOperative Ischemic Evaluation-2 Trial

Surgery	**Aspirin** (N=**4998)**	**Placebo (N=5012)**
Orthopedic	38.2	39.2
General	26.8	26.8
Urologic or gynecologic	16.7	16.8
Vascular	6.2	5.9
Other	12.1	11.3

65% of patients received prophylactic anticoagulant

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

Poise: 1^{O} and 2^{O} outcome results

Outcome	Aspirin (4998)	Placebo (5012)	HR (95% CI)	P
1^{O} outcome: death or nonfatal MI	351 (7.0)	355 (7.1)	0.99 (0.86-1.15)	0.92
2^{O} outcomes: death, MI, or stroke	362 (7.2)	370 (7.4)	0.98 (0.85-1.13)	0.80
death, MI, revasc, PE, DVT	402 (8.0)	407 (8.1)	0.99 (0.86-1.14)	0.90

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

Poise: Tertiary outcome results

Outcome	Aspirin (4998)	Placebo (5012)	HR (95% CI)	P
Mortality	65 (1.3)	62 (1.2)	1.05 (0.74-1.49)	0.78
MI	309 (6.2)	315 (6.3)	0.98 (0.84-1.15)	0.85
Periph arterial thrombosis	13 (0.3)	15 (0.3)	0.87 (0.41-1.83)	0.71
PE	33 (0.7)	31 (0.6)	1.07 (0.65-1.74)	0.79
DVT	25 (0.5)	35 (0.7)	0.72 (0.43-1.20)	0.20
acute kidney injury, dialysis	33 (0.7)	19 (0.4)	1.75 (1.00-3.09)	0.05

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

Poise: Safety outcome results

Outcome	Aspirin (4998)	Placebo (5012)	HR (95% CI)	P
Major bleed	229 (4.6)	187 (3.7)	1.23 (1.01-1.49)	0.04
Life-threat bleed	87 (1.7)	73 (1.5)	1.19 (0.88-1.63)	0.26
Stroke	16 (0.3)	19 (0.4)	0.84 (0.43-1.64)	0.62

- Primary and 2nd outcome results similar in both aspirin strata
- Multivariable regression – life-threatening or major bleed independent predictor of periop MI

  HR, 1.82; (95% CI, 1.40-2.36); P<0.001

Devereaux, PJ et al. PIOSE-2. Population Health Research Institute, New England Journal med. 3/31/2014

Poise: Conclusion and Take-Away

Bale/Doneen Take-Away:

For patients on long term ASA therapy, the most effective time to restart ASA following:

1. Non-emergency surgery is 8-10 days post procedure when bleeding risk diminished considerably.

2. If ASA introduced after surgery to treat a thrombotic event (CVA or MI), expect an absolute increase of 1.0-1.3 percentage points in the risk of life-threatening or major bleeding.

3. If ASA administered within first 2 days post surgery, risks must be weighed between high risk of death from the thrombotic event and the potential benefits of aspirin.

4. Measure Inflammatory markers prior and post surgery! No surprises

, PJ et al. PIOSE-2. Population Health Research Institute, New England DevereauxJournal med. 3/31/2014

ACEIs Superior to ARBs in DM for Reducing CV Risk

ACEIs significantly reduced the risk of:

a) all-cause mortality	-13% (95%CI, 0.78-0.98)
b) CV deaths	-17% (95% CI, 0.70-0.99)
c) major CVEs	-14% (95% CI, 0.77-0.95)
d) MI	-21% (95% CI, 0.65-0.95)
e) HF	-19% (95% CI, 0.71-0.93)
f) Stroke	N/S

Cheng, J., et. al. (2014). *JAMA Intern Med*. doi: 10.1001/jamainternmed.2014.348

ACEIs Superior to ARBs in DM for Reducing CV Risk

ARBs significantly reduced the risk of:

HF -30% (95% CI, 0.59-0.82)

ARBs did not significantly reduce the risk of: all cause mortality; CV death; major CVEs; MIs or Strokes

Cheng, J., et. al. (2014). *JAMA Intern Med*. doi: 10.1001/jamainternmed.2014.348

ACEIs Superior to ARBs in DM for Reducing CV Risk

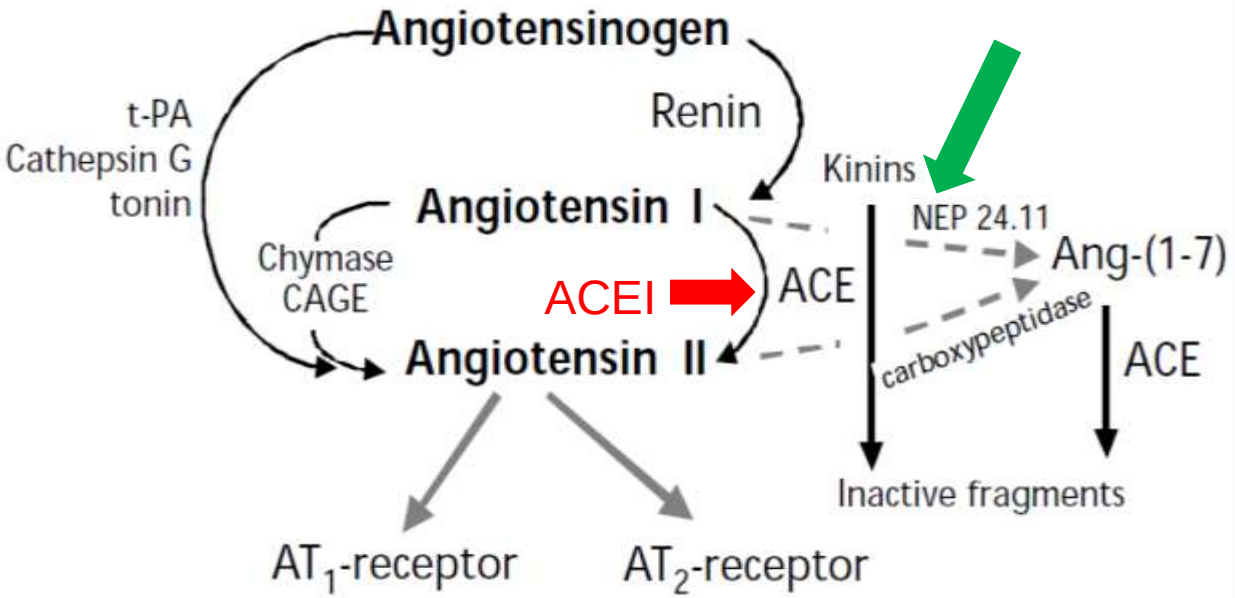
- ARB therapy was associated with a trend to more fatal CV events compared with placebo (RR, 1.90).

- A possible biological rationale for the benefit of ACEIs, but not ARBs, on cardioprotective effects seems to be related to angiotensin-(1-7) and bradykinin antagonism.

Cheng, J., et. al. (2014). *JAMA Intern Med*. doi: 10.1001/jamainternmed.2014.348

ACEI Can Enhance Production of Ang-(1-7)

Figure 2 The renin-angiotensin-aldosterone system enzyme cascade depicting ACE and non-ACE pathways involved in the generation of Ang II. CAGE, chymostatin-sensitive Ang II-generating enzyme; t-PA, tissue plasminogen activator; NEP 24.11, neutral endopeptidase



Weinberg, M. S., et. al. (2000).
J Renin Angiotensin Aldosterone Syst, 1(3), 217-233.

Ang 1-7 Enhance Insulin Sensitivity

- Muscle accounts for 70% to 80% of insulin-stimulated whole-body glucose disposal during insulin infusion.

- 40% of insulin's metabolic action in muscle is dependent upon its delivery to the connective tissue of the muscle.

- This is regulated by the skeletal muscle microvasculature.

Fu, Z., et. al. (2014). Angiotensin-(1–7) Recruits Muscle Microvasculature and Enhances Insulin's Metabolic Action via Mas Receptor. *Hypertension*. doi: 10.1161/hypertensionaha.113.03025

Ang 1-7 Enhance Insulin Sensitivity

- Insulin regulates its own delivery in muscle by increasing muscle microvascular blood volume (MBV) and stimulating its own transendothelial transport.

- RAS also effects the skeletal muscle MBV.

- Ang-(1–7) induces arterial relaxation and increases skeletal muscle MBV up to 80%.

(from this elaborate rat study)

Fu, Z., et. al. (2014). Angiotensin-(1–7) Recruits Muscle Microvasculature and Enhances Insulin's Metabolic Action via Mas Receptor. *Hypertension*. doi: 10.1161/hypertensionaha.113.03025

Ang 1-7 Enhance Insulin Sensitivity

- This increase in MBV can enhance insulin-mediated whole-body glucose disposal ~ 30%.
- This effect of Ang-(1-7) may contribute to the CV protective response seen with ACEI and help explain their insulin-sensitizing action.

Fu, Z., et. al. (2014). Angiotensin-(1–7) Recruits Muscle Microvasculature and Enhances Insulin's Metabolic Action via Mas Receptor. *Hypertension*. doi: 10.1161/hypertensionaha.113.03025

ACEIs Superior to ARBs in DM for Reducing CV Risk

ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in diabetics.

Cheng, J., et. al. (2014). *JAMA Intern Med*. doi: 10.1001/jamainternmed.2014.348

Ramipril and PAD

Ramipril and PAD

Previously reported that Ramipril induced a 123% increase in maximum walking time when administered for 24 weeks in patients with intermittent claudication (Ahimastos, 2013).

This study (2014) asks why??

Ahimastos and colleagues explore the effects of Ramipril on circulating biomarkers of angiogenesis/arteriogeneis, thrombosis, inflammation, and leukocyte adhesion in these patients.

Ahimastos, A et al. Vascular mechanisms of Ramipril. Circ Research. 2014;114:1144-1155.

Ramipril and PAD

It has been suggested that ACE inhibitors may modify inflammation and thrombosis – both of which are critical in the complications of atherosclerosis and in the decline of worsening PAD.

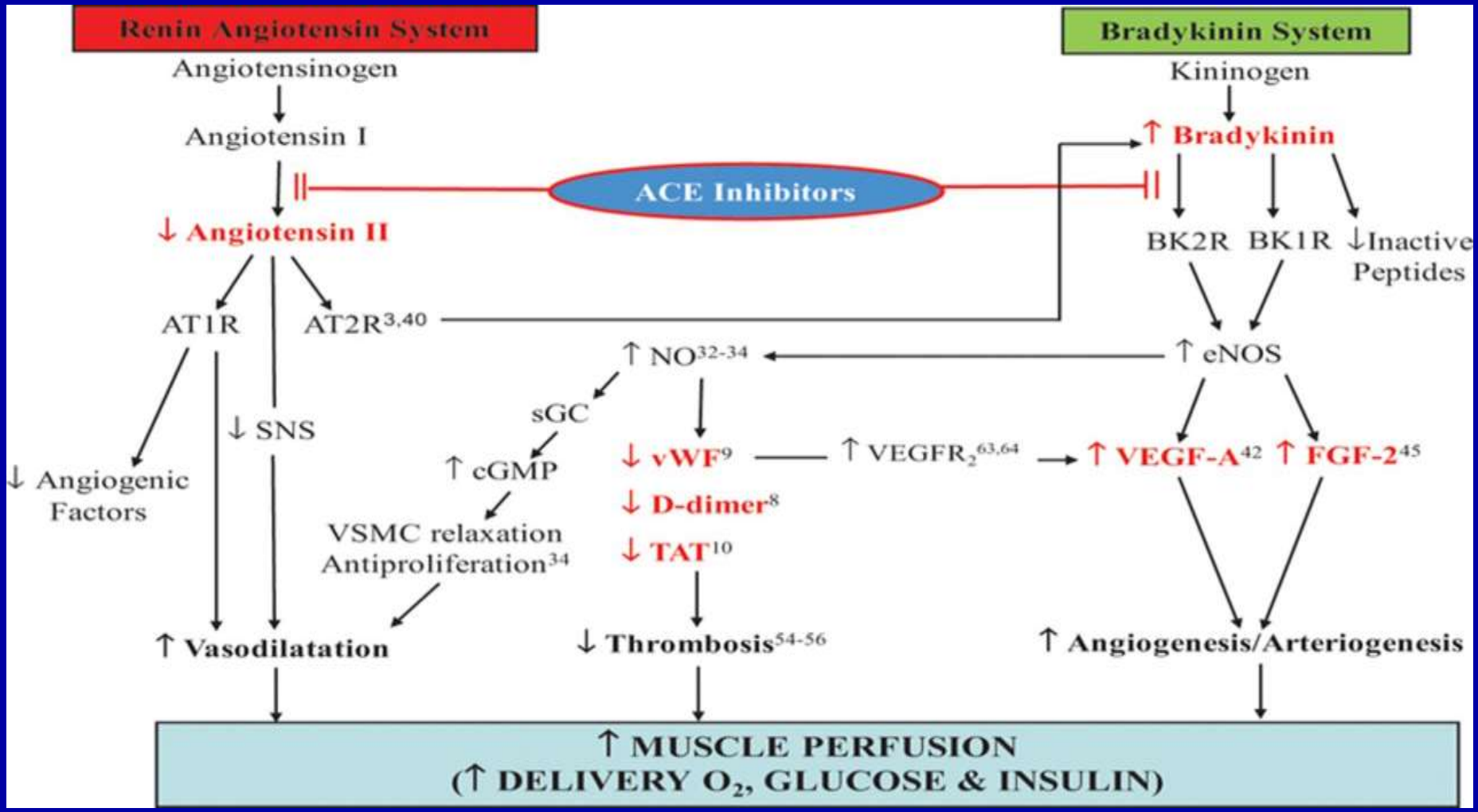
Original Study involved 3 centers – this trial only utilized a single site (165 participants).

Inclusion Criteria: ABI <0.9 at rest in at least 1 leg, history of intermittent claudication, stable meds for ≥ 6 months.

Exclusion Criteria: resting BP ≥ 160/100, use of ACE/ARB in last 6 months, use of K+ diuretics in last 6 months, renal issues, condition other than PAD that limits walking.

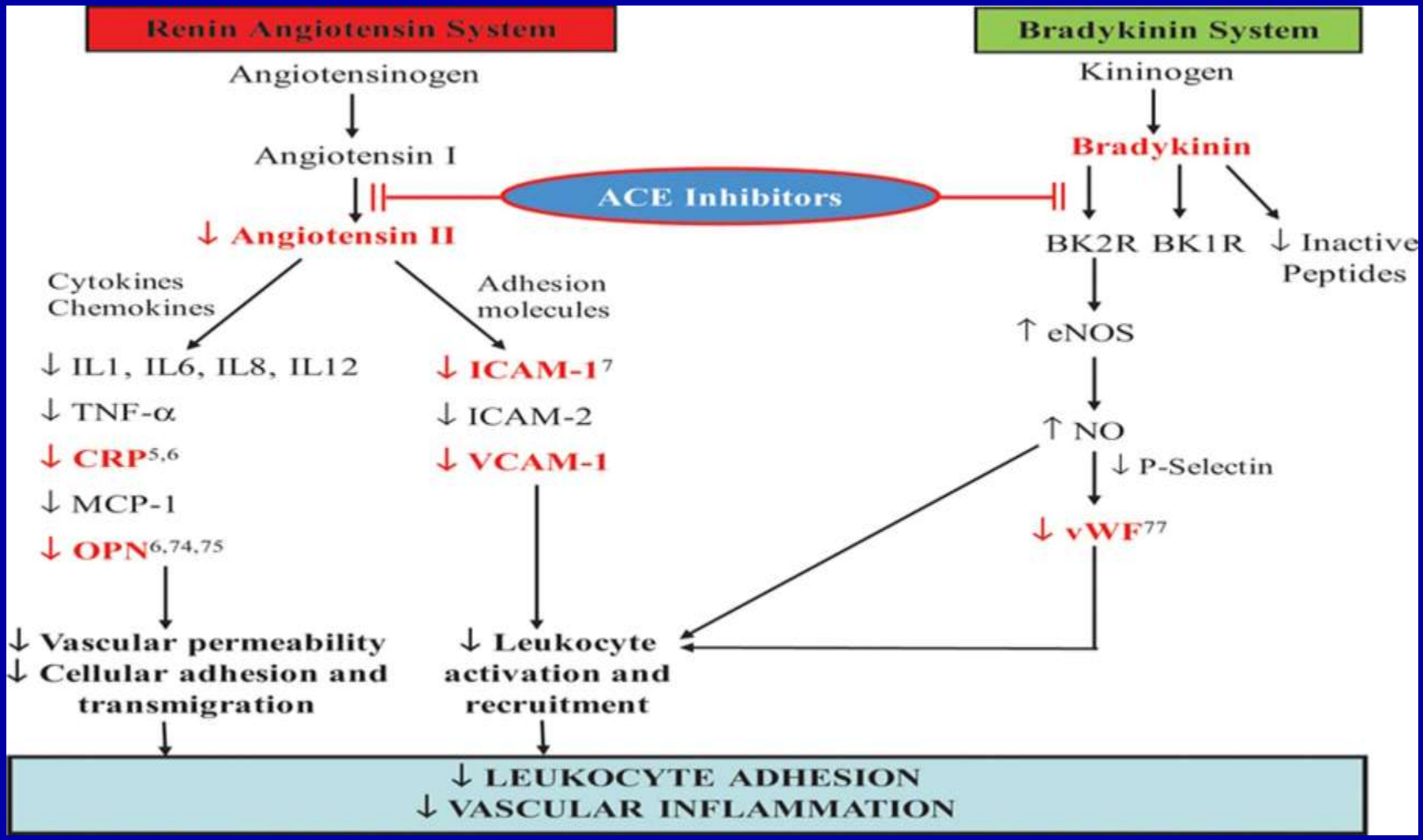
Ahimastos, A et al. Vascular mechanisms of Ramipril. Circ Research. 2014;114:1144-1155.

Ramipril increases lower limb profusion



Ahimastos, A et al. Vascular mechanisms of Ramipril. Circ Research. 2014;114:1144-1155.

Ramipril reduces vascular inflammation



Ahimastos, A et al. Vascular mechanisms of Ramipril. Circ Research. 2014;114:1144-1155.

Ramipril improves PAD by:

Increasing lower limb perfusion:

1. angiogenesis/arteriogenesis through the renin-angiotensin system and bradykinin system.
2. Reduction in thrombosis via NO mechanisms mediated by the preservation of bradykinin
2. Vasodilation through reduction in angiotensin II.

Reducing vascular inflammation:

A reduction in angiotensin II levels results in:

reduced expression of adhesion molecules

reduced chemokines & cytokines,

leukocyte margination (rolling and adhesion)

transmigration through vascular wall.

Ahimastos, A et al. Vascular mechanisms of Ramipril. Circ Research. 2014;114:1144-1155.

Ramipril improves PAD by:

Conclusion: Ramipril was associated with an increase in markers of angiogenesis/arteriogenesis and a reduction in the markers of thrombosis, inflammation and leukocyte adhesion – suggests multiple contribution for patients with PAD.

Bale/Doneen Take Away:

Ramipril has pleotropic effects that go beyond BP – protection of the arterial system.

Ahimastos, A et al. Vascular mechanisms of Ramipril. Circ Research. 2014;114:1144-1155.

Upcoming lectures

- 4/17: Washington State District Dental Meeting
- 4/24: Tri Cities – Oral/Systemic meeting
- 4/25: Seattle – Washington State Dental Hygeine
- 4/26: Dr. Duane Keller – Las Vegas

- More to come…. ☺

Sent 4/9/14 at 4:40 pm PST

Dear Amy

I'm asking tonight about a case of a 70 yo female (Boston qualifier) marathon runner whose cholesterol was 193, LDL 95 and HDL 85 in2002. 2003 her liposcience profile was all in the optimum boxes. It was still optimum 2005 with LDL particle number of 760. In 2010 lipids are not available, but apolipoprotein A1 was 193, Apo B 68, B/A1 0.35 and Cardio CRP 0.7. Then her lipids began to creep up. LDL particles were 1340 in 2012 with direct LDL of 87 (HDL labs). In the late summer 2013 she both retired and developed a stress fracture in her foot. She stopped running for 3 months. Her lipids rose to TC 222, HDL 94, TG 58 , LDL 116 and non-HDL of 128. HS-CRP was 1.6. She agreed to pravastatin 20 mg daily and with a return to running this spring her lipids were down to TC of 195,HDL 101, TG 70, LDL 80 with non-HDL of 94. HS-CRP dropped to 0.8.

She's been healthy, and hasn't taken any medications other than HRT Jintel 1mg - 5mcg (since menopause I believe from her gynecologist). Her father had diabetes, hypertension and either heart disease or a stroke but lived to 86. Her mother was doing well in her middle 80s last time I asked. None of her siblings had vascular disease last I asked. Her exam is normal and BMI is 20.5.

When she had the stress fracture last summer the x ray also showed vascular calcifications. This prompted a calcium score which was very high at 1133, about 92nd percentile. A stress echo was negative and showed good conditioning. She has not repeated the CIMT. She has also become aware of adverse heart effects of excessive exercising, and has decided to not focus on marathons. She decided to drop her running from 45 miles a week to 30 miles a week. She also agreed to continue pravaststin 20 mg indefinitely.

With her long history of "good" lipid values, exercise and conditioning and lack of strong FH for vascular disease we were floored with the cardiac calcium score. Is there an explaination? What lipid values should we target? Should she stop the HRT?

Thanks, Stan