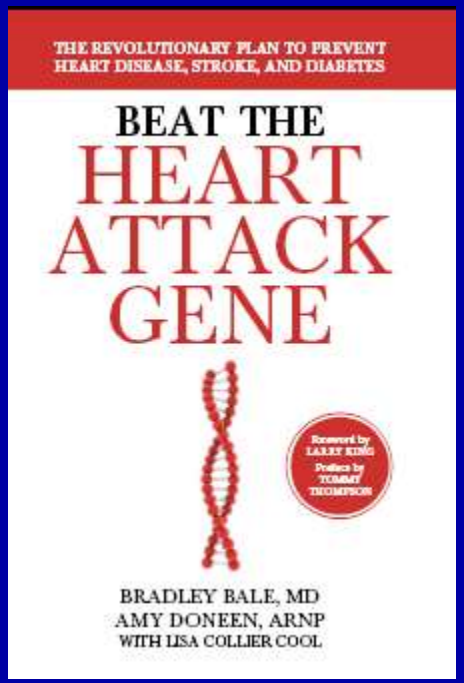
Bale/Doneen Live Chat Session

Amy Doneen DNP(c), ARNP



June 11, 2014

5:30-6:30 pm PST

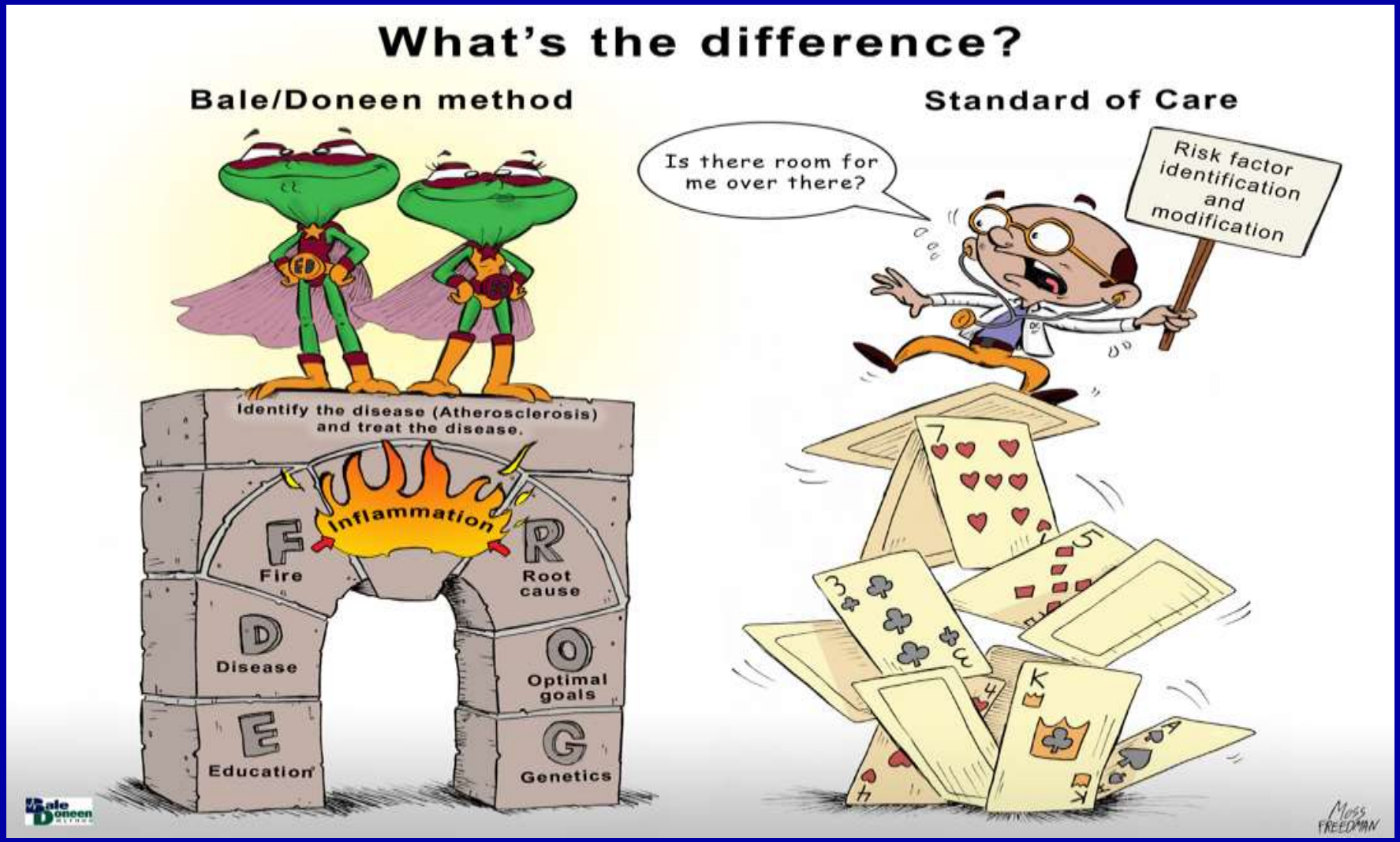
Busy time of year at the Doneen household ☺

Congrats to Sydney
June 9, 2014

Outline for 6/11/2014 Live Chat Session

- Prevention
  - BD: Outcome Data
  - Diabetes Statistics
- Red Flags
  - Atrial Fib
- Disease
  - microvascular/renal
  - CACs and Risk Factors
  - CACS – uncalcified
- Inflammation
  - Vitamin D
  - Inflammatory Markers for CKD
  - Estrogen and older women
- Treatment
  - Shingles Vaccine
  - Influenza Vaccine
  - Fatty fish and memory loss prevention
  - High Dose Statin and DM risk
  - Statin and tooth loss

The Bale/Doneen Difference



We have a choice…

Prevention – The Bale/Doneen Method

OR

Retail Therapy – Shopping for new shirts…

Heart-Shocking ‘Shirt’

Sandya Subramanian, et. al. Department of Biomedical Engineering:
Center for Bioengineering Innovation and Design:
Whiting School of Engineering: http://engineering.jhu.edu
Johns Hopkins School of Medicine:
http://www.hopkinsmedicine.org/som/Reference

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8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events

A Growth-Curve Analysis

Du Feng, PhD; M. Christina Esperat, PhD, RN, FAAN; Amy L. Doneen, RN, BSN, MSN, ARNP; Bradley Bale, MD; Huaxin Song, PhD; Alexia E. Green, PhD, RN, FAAN

Background: Early identification of cardiovascular diseases allows us to prevent the progression of these diseases. The Bale/Doneen Method, a prevention and treatment program for heart attacks and ischemic strokes, has been adopted nationally in primary care and specialty clinics. **Objectives:** The main purpose of this study was to evaluate the effect of the Bale/Doneen Method on lipoproteins and carotid intima-media thickness (IMT) for cardiovascular disease prevention and reduction. A secondary purpose was to illustrate the use of latent growth-curve analysis in studying trajectories of clinical outcomes and biomarkers in individual patients over time. **Method:** This retrospective analysis is based on 576 patients at a nurse-managed ambulatory clinic who received the heart attack prevention and treatment program from 2000 to 2008. All patients were white; 61% were men; mean age was 55.5 years. Outcome measures include hemoglobin A_{1c}, fasting blood sugar, plaque burden score (PBS), high-density lipoprotein, low-density lipoprotein (LDL), mean carotid artery IMT, and lipoprotein-associated phospholipase A_2 test results. Latent growth-curve analysis was used in modeling changes in these outcome measures. **Results:** On average, mean IMT score decreased by 0.01 per year ($P < .001$), PBS decreased by 0.17 per year ($P < .001$), LDL decreased by 5.19 per year ($P < .001$), and lipoprotein-associated phospholipase A_2 decreased by 3.6 per year ($P < .05$). Hemoglobin A_{1c} increased by 0.04 per year ($P < .001$). Significant sex and age differences in the initial level and/or rate of change of mean IMT, PBS, fasting blood sugar, high-density lipoprotein, and LDL scores were found. **Discussion:** The current findings suggest that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.

KEY WORDS: cardiovascular disease, early prevention, treatment program

Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

Retrospective analysis 576 pts; treated in prevention clinic 2000-2008; mean age 55.5 yrs; 39% female.

Latent growth-curve analysis was used in modeling changes in outcome measures.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

TABLE 2 Baseline Patient Demographic Characteristics (N = 576)

Characteristic	n (%) or Mean ± SD
Age, y	55.5 ± 10.2
BMI, kg/m^2	27.5 ± 5.0
Male	344 (61)
White	576 (100)
Current or past smoker	209 (36)
Diabetes	25 (5)
Hyperlipidemia	512 (89)
Hypertension	325 (58)
CAD/CAD equivalent	143 (25)
Metabolic syndrome	321 (56)
Insulin resistant	417 (73)
Adjusted Framingham Risk Score	
<10%	370 (66)
10%–20%	141 (24)
>20%	58 (10)
Carotid plaque—PBS score ≥1.2 mm	(85)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; PBS, plaque burden score.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

TABLE 1 Components of the Bale/Doneen Method

Components	Description
1. Education	Each patient is educated about the disease state of atherosclerosis and understands how myocardial infarctions and ischemic strokes occur.
2. Disease	Each patient is evaluated for the presence of atherosclerosis, using noninvasive office-based techniques, to find asymptomatic vascular disease, and is monitored annually with an intima-media thickness (IMT) test to follow the individual trajectory of atherosclerotic disease. In addition, all patients are monitored annually with a carotid IMT test to follow the atherosclerotic disease over time in the individual patient.
3. Inflammation	Biomarkers are used to routinely determine the inflammatory state of the vascular system. Endothelial markers include hs-C-reactive protein, microalbumen/creatinine urine ratio, and fibrinogen. Lipoprotein-associated phospholipase A_2 is evaluated for intima activity. Patients were instructed to have these assessed at least biannually.
4. Root causes	The root cause or causes of the atherosclerotic process are determined and managed for each patient. Root causes of atherosclerosis can include insulin resistance, lipo(a), familial hyperlipidemia, potentially myeloperoxidase, and vitamin D deficiency.[51] Appropriate follow-up testing for effective management of a root cause was done on average quarterly to semiannually.
5. Optimal goals	Goals of therapy are set based on peer-reviewed, reliable research and guidelines, with optimal targets in an attempt to minimize risk and often going beyond the values set for the standard of care. Attainment of goals was evaluated, on average, every 3–6 months.
6. Genetics	Genetic information is obtained on patients to aid in the assessment of their cardiovascular risk and to help guide therapy. These tests were never repeated. Their clinical utility never expires, unlike other biomarkers. This makes them arguably the least expensive tests performed.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

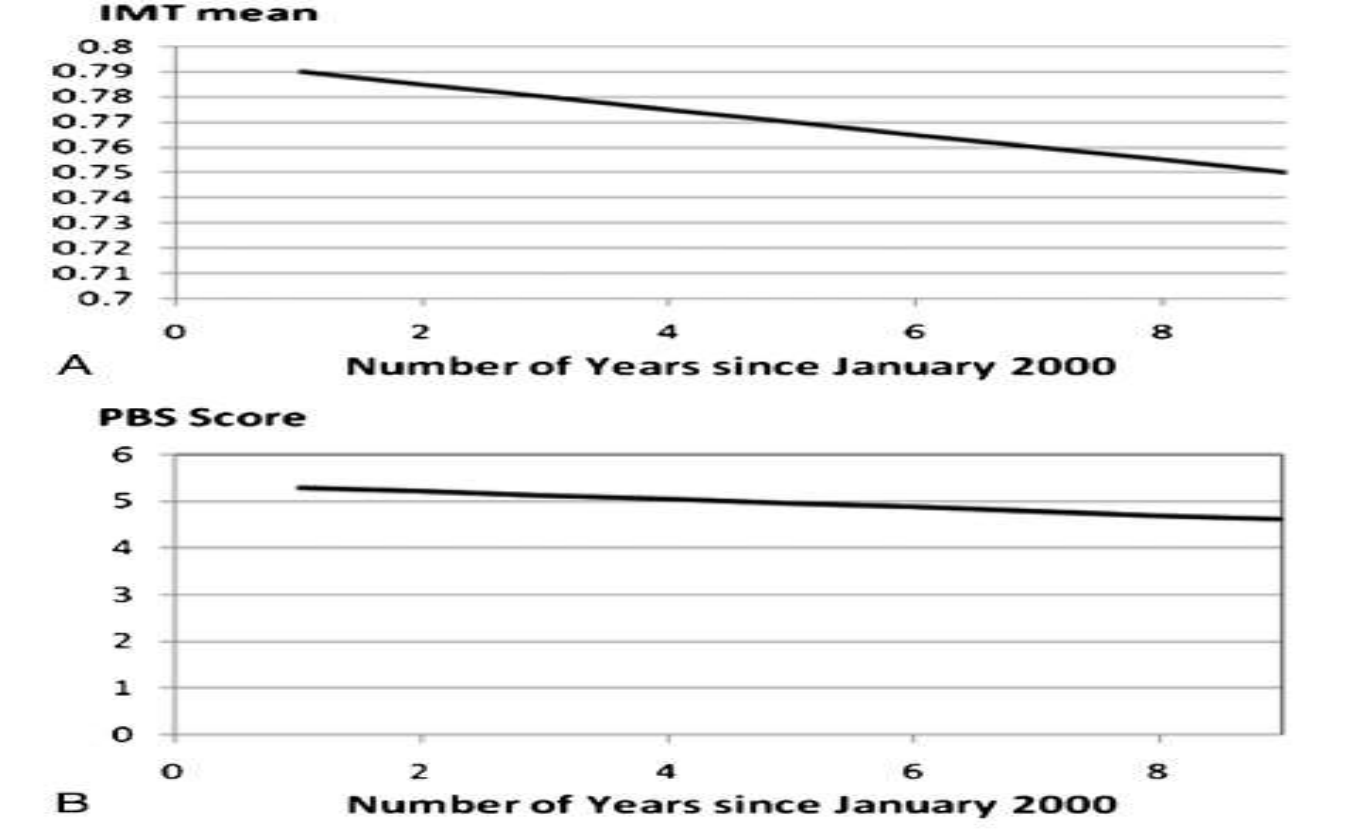
Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

Mean cIMT score decreased by 0.01mm/yr – $p<0.001$

cIMT plaque burden score decreased by 0.17mm/yr- $p<0.001$

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process



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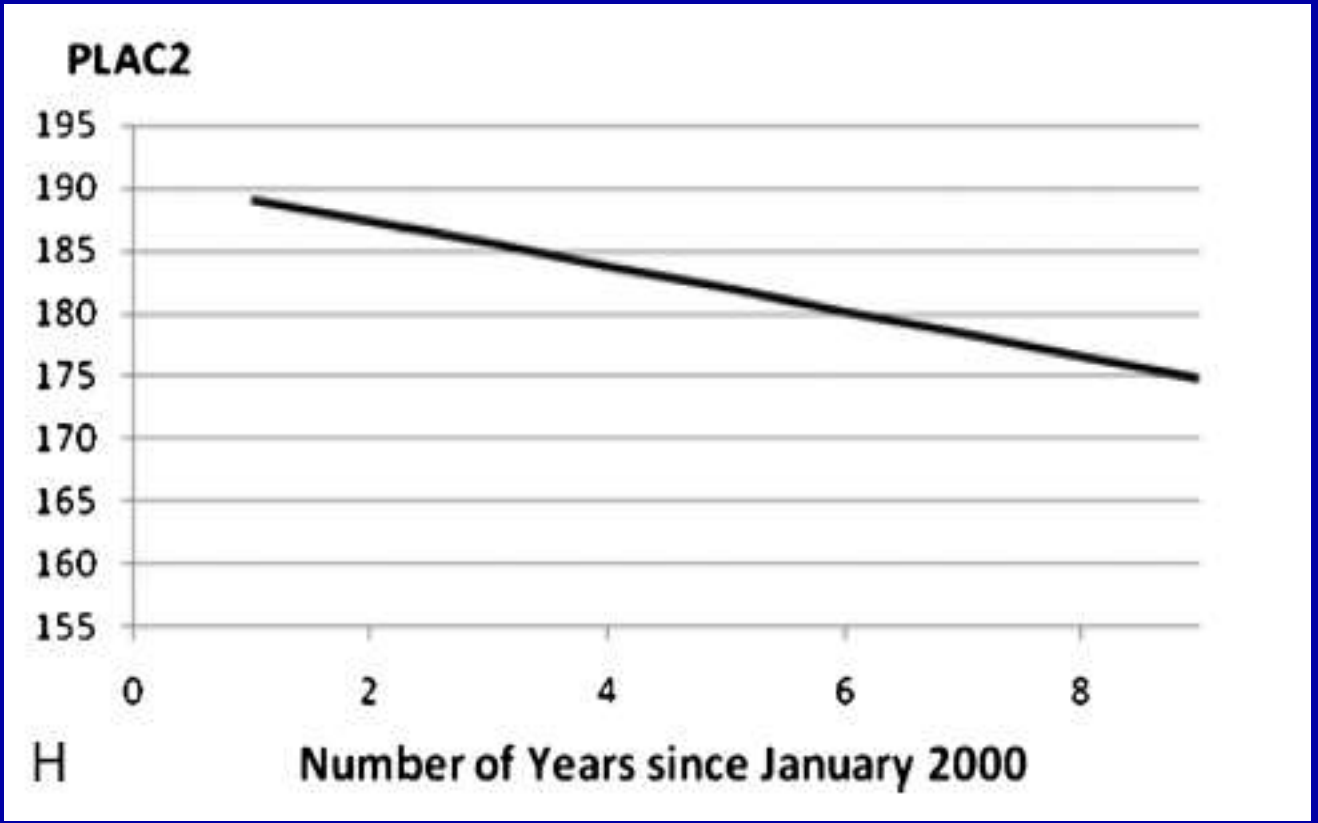

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What's New and Important

- The Bale/Doneen Method rests on a platform of assessing and monitoring arterial disease. It is anchored in inflammation being causal of atherosclerosis. The method comprehensively evaluates known sources for arterial inflammation and promotes optimal management of all identified contributors to the arterial ''fire.'' The methods of assessing and treating patients used by the Bale/Doneen Methods are available to any practitioner.
- Previous studies have indicated that patients who receive prevention and treatment of CVD through the Bale/Doneen Method show stabilization of the atherosderotic disease process, a significant conversion of plaque morphology to 100% echogenic lesions by the fifth year of follow-up, and that echogenic carotid plaque is significantly less inflamed than nonecogenic plaque. Consistent with past studies, this article shows that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.
- The use of growth-curve modeling in examining changes in markers such as IMT and other biomarkers associated with CVD can improve the accuracy of CVD risk prediction and help identify effective treatments.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

Findings suggest that the Bale/Doneen Method is effective in generating a positive effect on the atherosclerotic disease process by achieving regression of disease in the carotid arteries.

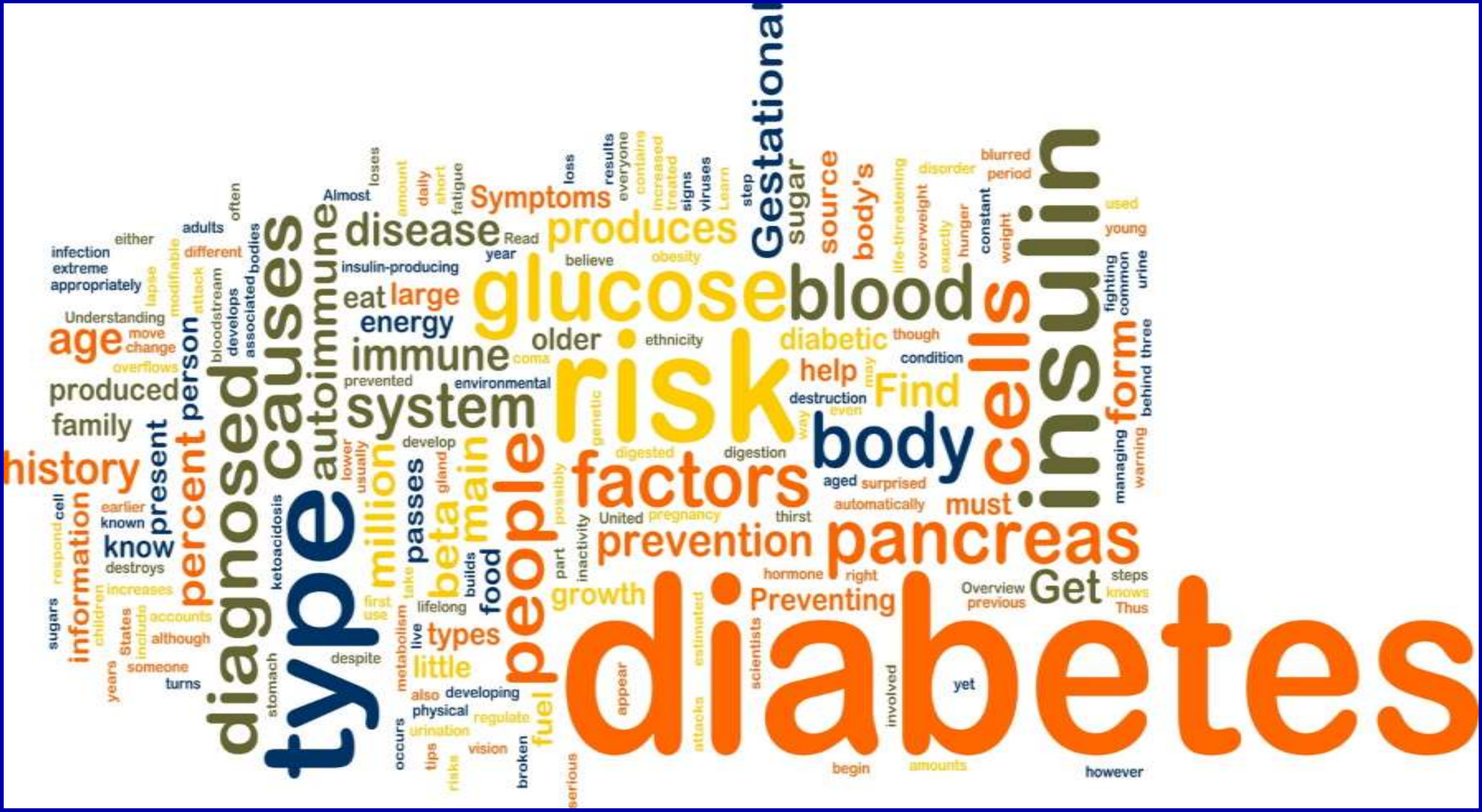
Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

Bale/Doneen Method is Effective in Generating a Positive Effect on the Atherosclerotic Disease Process

The Bale/Doneen Method is a method of delivering evidence- and outcome-based medical care using a system anchored in the disease of atherosclerosis rather than the standard practice of delivering preventative care based solely on risk factors.

Feng, D., Esperat, M. C., Doneen, A. L., Bale, B., Song, H., & Green, A. E. (2014). 8-Year Outcomes of a Program for Early Prevention of Cardiovascular Events: A Growth-Curve Analysis. *J Cardiovasc Nurs*. doi: 10.1097/jcn.0000000000000141

2014 Diabetes Statistics



National Diabetes Statistics Report, 2014

National Diabetes Statistics Report, 2014

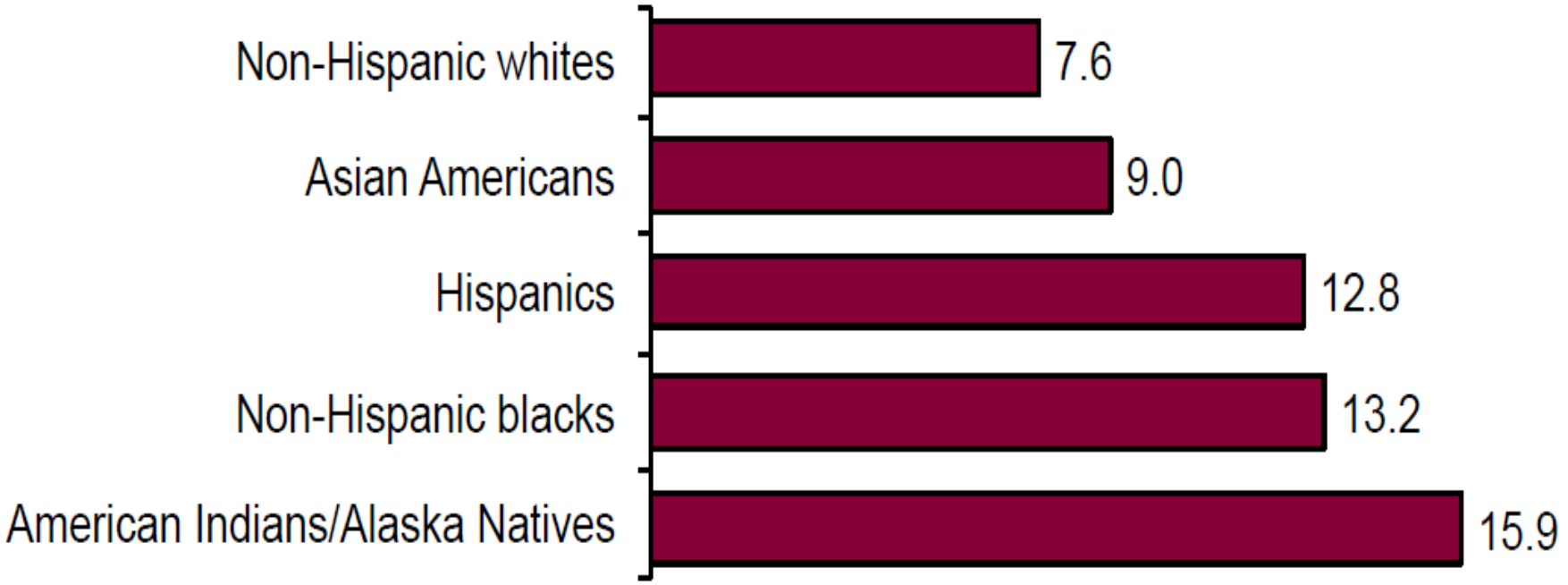
Diagnosed and undiagnosed diabetes among people aged 20 years or older, United States, 2012

	Number with diabetes (millions)	Percentage with diabetes (unadjusted)
Total		
20 years or older	28.9	12.3
By age		
20–44	4.3	4.1
45–64	13.4	16.2
65 years or older	11.2	25.9
By sex		
Men	15.5	13.6
Women	13.4	11.2

Source: 2009–2012 National Health and Nutrition Examination Survey estimates applied to 2012 U.S. Census data.

National Diabetes Statistics Report, 2014

Age-adjusted* percentage of people aged 20 years or older with diagnosed diabetes, by race/ethnicity, United States, 2010–2012



*Based on the 2000 U.S. standard population.
Source: 2010–2012 National Health Interview Survey and 2012 Indian Health Service's National Patient Information Reporting System.

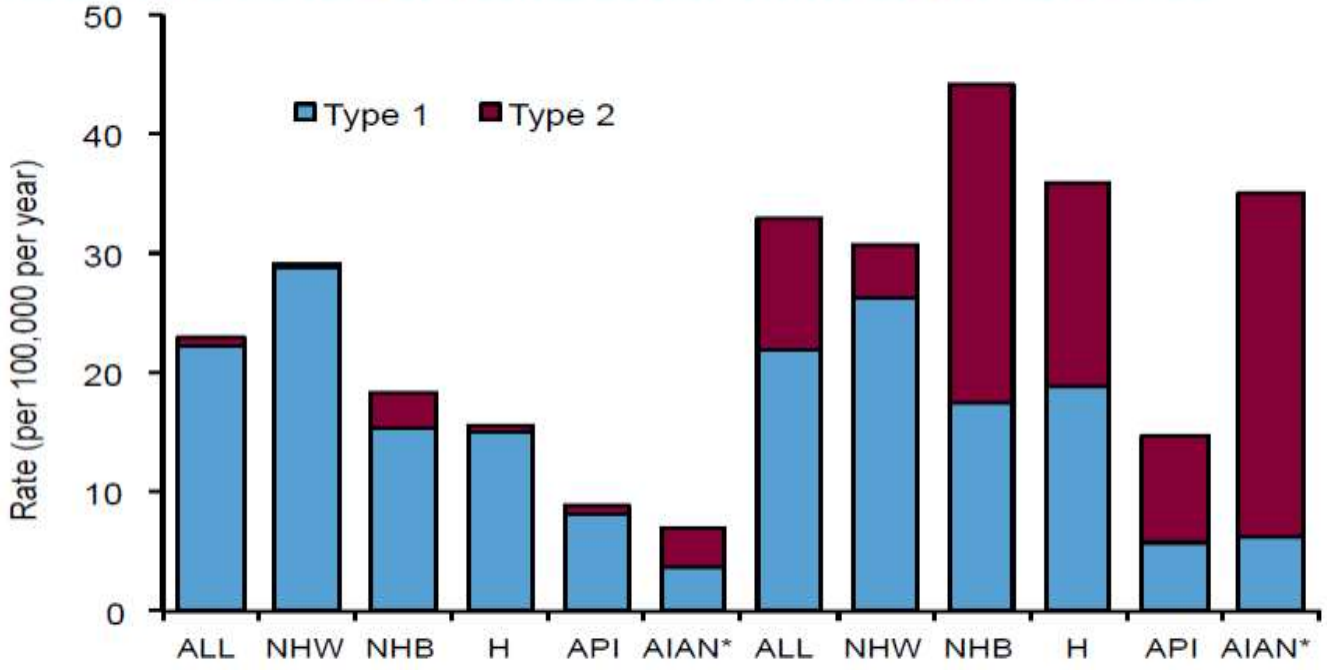
National Diabetes Statistics Report, 2014

Prediabetes among people aged 20 years or older, United States, 2012

- In 2009–2012, based on fasting glucose or A1C levels, 37% of U.S. adults aged 20 years or older had prediabetes (51% of those aged 65 years or older). Applying this percentage to the entire U.S. population in 2012 yields an estimated 86 million Americans aged 20 years or older with prediabetes.

National Diabetes Statistics Report, 2014

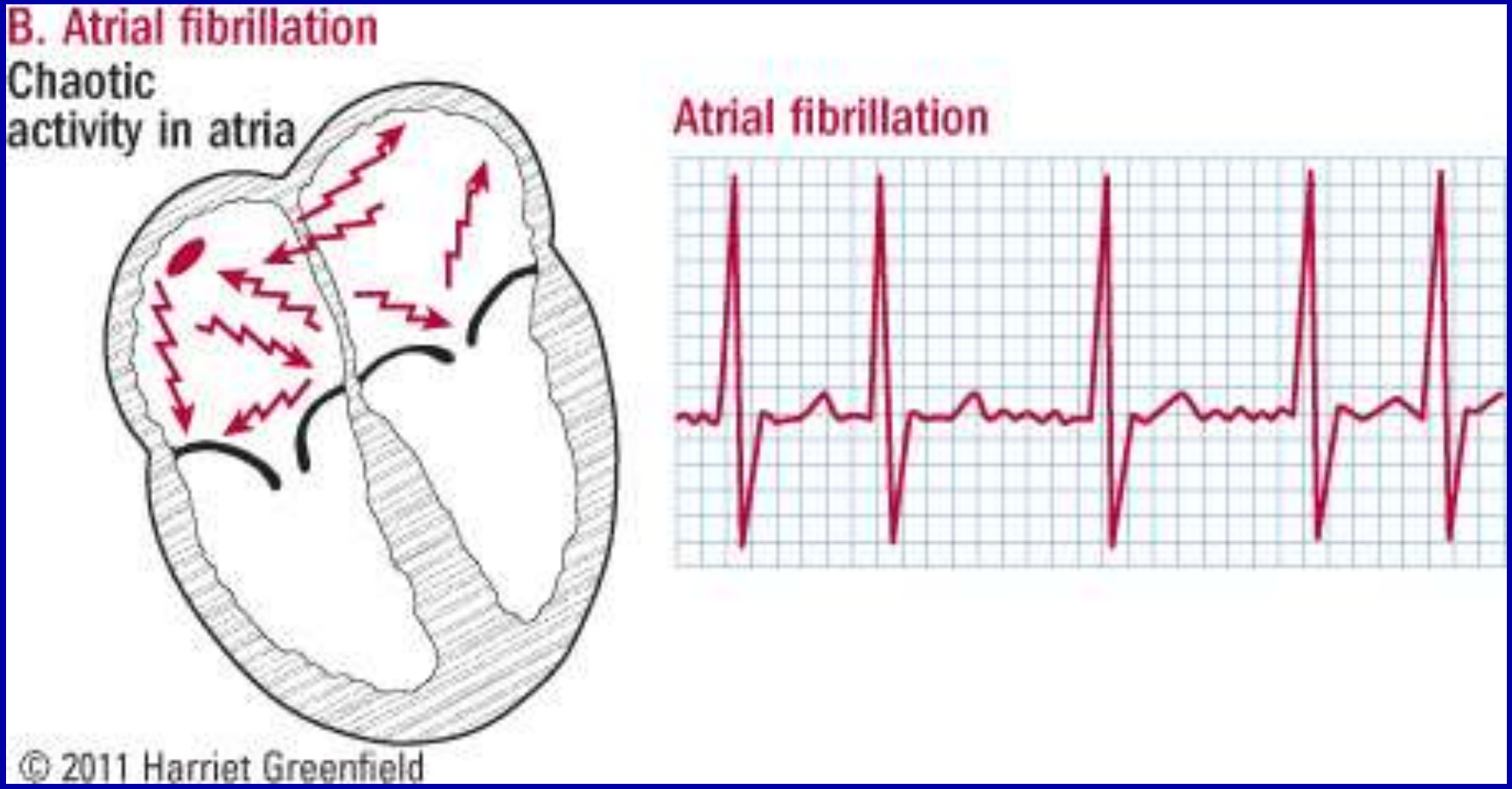
Rate of new cases of type 1 and type 2 diabetes among people younger than 20 years, by age and race/ethnicity, 2008–2009



* The American Indian/Alaska Native (AI/AN) youth who participated in the SEARCH study are not representative of all AI/AN youth in the United States. Thus, these rates cannot be generalized to all AI/AN youth nationwide.
Source: SEARCH for Diabetes in Youth Study
NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AIAN=American Indians/Alaska Natives.

Red Flags

Atrial fibrillation



Atrial fibrillation is associated with different levels of physical activity levels at different ages in men

Risk of developing AF in large cohort of Swedish men.

Information about physical activity was obtained from 44,410 AF-free men, aged 45-79 years (mean age 60) who had completed a self-administered questionnaire at baseline in 1997.

Reported retrospectively their time spent on leisure-time exercise and on walking or bicycling though out their lifetime at 15, 30 and 50 years of age and at baseline.

Drca, N., Wolk, A. et al. Heart. BMJ May 26, 2014. http://dx.doi.org/10.1136/heartjnl.

Atrial fibrillation is associated with different levels of physical activity levels at different ages in men

Participants reported their time spent walking or bicycling for everyday transportation purposes and leisure-time exercise (such as running, soccer, bicycling, swimming, floor ball, gymnastics, cross-country skiing, etc) at 15, 30, and 50 years.

Definitions of exercise:

Low-intensity to moderate-intensity physical activity:

Walking/bicycling for transportation

Leisure-time exercise:

moderate-intensity to high-intensity physical activity.

Drca, N., Wolk, A. et al. Heart. BMJ May 26, 2014. http://dx.doi.org/10.1136/heartjnl.

Atrial fibrillation is associated with different levels of physical activity levels at different ages in men

During f/u of 12 years 4568 cases of AF were diagnosed. Observed a RR of 1.19 (95% CI 1.05-1.36) of developing AF in men who at the age of 30 years had exercised for >5 h/week compared with <1 h/week.

Risk higher (RR 1.49, 95%%CI 1.14 to 1.95) among the men who exercised >5 h/week at age 30 and quit exercising later in life (<1 h/week at baseline).

Drca, N., Wolk, A. et al. Heart. BMJ May 26, 2014. http://dx.doi.org/10.1136/heartjnl.

Atrial fibrillation is associated with different levels of physical activity levels at different ages in men

Table 1 Age-standardized baseline characteristics for the lowest and highest categories of leisure-time exercise and walking/bicycling, in the cohort of Swedish men

	Exercise at age 30 years		Exercise last year		Walking/bicycling at age 30 years		Walking/bicycling last year	
Characteristic	<1 h/week	>5 h/week	<1 h/week	>5 h/week	Almost never	>1 h/day	Almost never	>1 h/day
Age, mean (years)	57.1	60.9	57.9	63.6	55.9	62.8	59.9	62.8
Height, mean (cm)	177	178	177	177	177	177	177	177
Body Mass Index, mean (kg/m^2)	25.9	25.9	26.3	26.2	26.1	25.9	26.5	25.5
Postsecondary education (%)	13.2	14.7	13.7	10.7	14.8	12.7	14.2	12.5
Current smoking (%)	27.5	23.9	30.8	23.2	29.6	25.8	32.7	25.0
Aspirin use (%)	36.9	35.0	37.5	34.1	37.2	35.8	38.4	34.4
History of coronary heart disease or heart failure (%)	8.1	8.9	9.4	8.5	10.0	8.9	10.7	8.2
History of hypertension (%)	24.0	21.5	26.2	22.0	26.1	23.6	27.8	21.6
History of type 2 diabetes (%)	9.7	7.8	10.8	8.4	10.8	8.7	12.0	8.2
Family history of myocardial infarction (%)	14.0	15.7	14.9	18.2	15.6	15.3	15.6	15.1
Alcohol intake, mean (g/day)	9.8	10.7	10.2	10.8	10.4	10.1	10.7	9.9

Drca, N., Wolk, A. et al. Heart. BMJ May 26, 2014. http://dx.doi.org.

Atrial fibrillation is associated with different levels of physical activity levels at different ages in men

Drca, N., Wolk, A. et al. Heart. BMJ May 26, 2014. http://dx.doi.org/10.1136/heartjnl.

Atrial fibrillation is associated with different levels of physical activity levels at different ages in men

Increased risk of AF with a high level of leisure-time exercise at a younger ag is in agreement with the Physicians' Health Study (showed a 74% increased risk of AF associated with a high frequency of vigorous exercise (5-7 days/week) in men < 50 years of age).

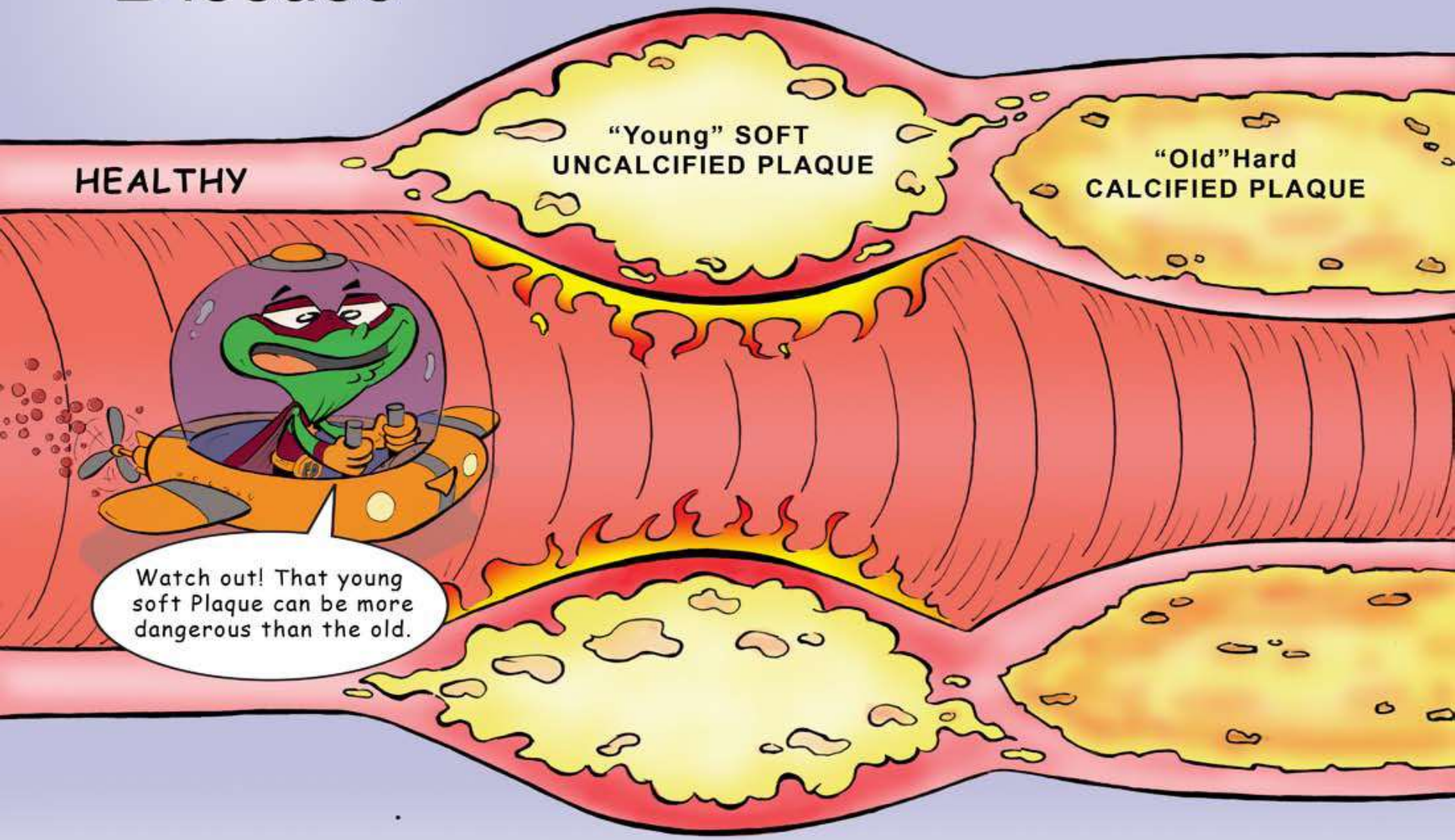
Why? Definition of "leisure-time" activity at younger age is different than at older age.

Data did NOT show that leisure-time exercise in older age (60 years) increased the risk of AF.

No increase risk of AF with walking or bicycling at any age.

Drca, N., Wolk, A. et al. Heart. BMJ May 26, 2014. http://dx.doi.org/10.1136/heartjnl.

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

Microcirculatory maker for prediction of renal end points

Central Retinal Artery Occlusion (CRAO)

Microcirculatory Marker for the Prediction of Renal End Points

Retinal arteriolar narrowing reflects aging, CKD and HTN.

Prospective Cohort Study in patients with CKD stage 2 to 4 – 164 men and women (60 ± 13.8 years) underwent retinal photography and determination of albuminuria.

Cases of incident renal end points defined as 50% renal function loss and start of renal replacement therapy were identified.

Over 1410 days – 25 patients with CKD had incident renal end points.

Baumann, M., Burkhardt, K, Uwe, H. (May 27, 2014). Hypertension.doi:10.1161

Narrow retinal arterioles for the Prediction of Renal End Points

164 Stage 2-4 CKD patients from nephrology centers.
Final Analysis – 141 patients with CKD – all patients had retinal vessels analyzed for retinal vessel diameter, BP and renal function assessed.

Diabetes	(n=45; 32%)
Glomerulonephritis	(n=31; 22%)
Hypertension/renovascular disease	(n=27; 19%)
Reflux nephropathy and other	(n=9; 6%)
Polycystic kidney disease	(n=8; 6%)
Cancer or unknown	(n=21; 15%)

CKD Stage 2 = 30%
CKD Stage 3 = 45%
CKD Stage 4 = 25%

Mean GFR of the group – 45 mL/min (16-88)

Baumann, M., Burkhardt, K, Uwe, H. (May 27, 2014). Hypertension.doi:10.1161

Narrow arterioles for the Prediction of Renal End Points

Table 1. Characterization of Total CKD Cohort and According to CKD Stages

Characteristics	CKD Cohort (n=141)	CKD 2 (n=43)	CKD 3 (n=63)	CKD4 (n=35)	*P* Value
Age, y	60.8±13.8	57.5±11.8	62.0±15.5	62.5±13.0	
Women, %	43	42	51	30	
BMI, kg/m^2	28.1±5.8	27.2±3.5	29.4±7.2	27.8±4.7	
eGFR, mL/min	47.8±23.2	76.7±11.0	45.6±10.8	21.6±6.5	<0.001
ACR, mg/g	170 (90–682)	92 (50–133)	155 (90–385)	361 (150–1120)	<0.001
Albuminuria, %	21	10	24	34	
Hemoglobin, g/dL	12.7±1.8	14.2±1.5	12.8±1.3	11.1±1.5	<0.001
Parathormone, pg/mL	87.1 (51.0–129.5)	52.3 (29.7–107.2)	82.8 (52.6–129.5)	107.4 (60.6–165.2)	<0.05
SBP, mm Hg	136.8±18.3	134.8±15.2	136.5±19.4	138.7±18.2	
DBP, mm Hg	76.3±10.6	77.7±7.6	76.2±10.7	74.2±10.6	

Baumann, M., Burkhardt, K, Uwe, H. (May 27, 2014). Hypertension.doi:10.1161

Narrow Arterioles for the Prediction of Renal End Points

Predictors of renal disease progression:

Narrow arterioles reflect a state of vascular remodeling
Albuminuria reflects microcirculatory damage

After adjusting for age and eGFR, the combination of narrow retinal arterioles and albuminuria had the worst prognosis for renal failure.

Retinal Arterioles is a quantitative measure in predicting renal progress in CKD stage 2 to 4.

Baumann, M., Burkhardt, K, Uwe, H. (May 27, 2014). Hypertension.doi:10.1161

Narrow Arterioles for the Prediction of Renal End Points

To measure retinal vessel diameters from digitized photographs, a standardized protocol was adopted:

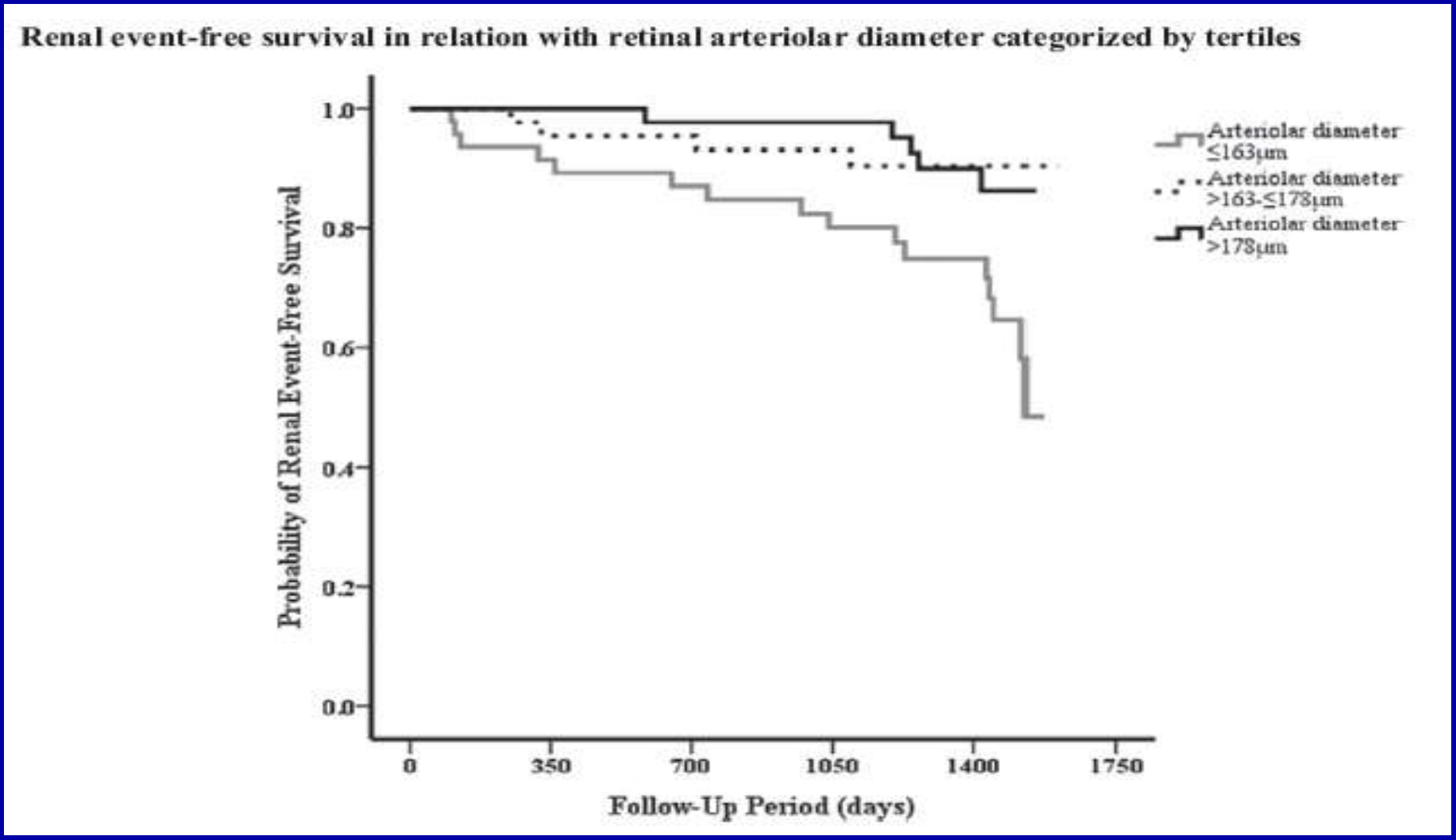
Two 30 degree color retinal photographs of the left eye and 2 photographs of the right eye were taken at baseline.

Images digitized using a high-resolution scanner with standard settings. Using a computer program, the diameters of the arterioles were and venules in a specified zone surrounding the optic disc were measured. Reproducibility was established.

Term: central retinal arteriolar equivalent (CRAE)

Baumann, M., Burkhardt, K, Uwe, H. (May 27, 2014). Hypertension.doi:10.1161

Narrow Arterioles for the Prediction of Renal End Points



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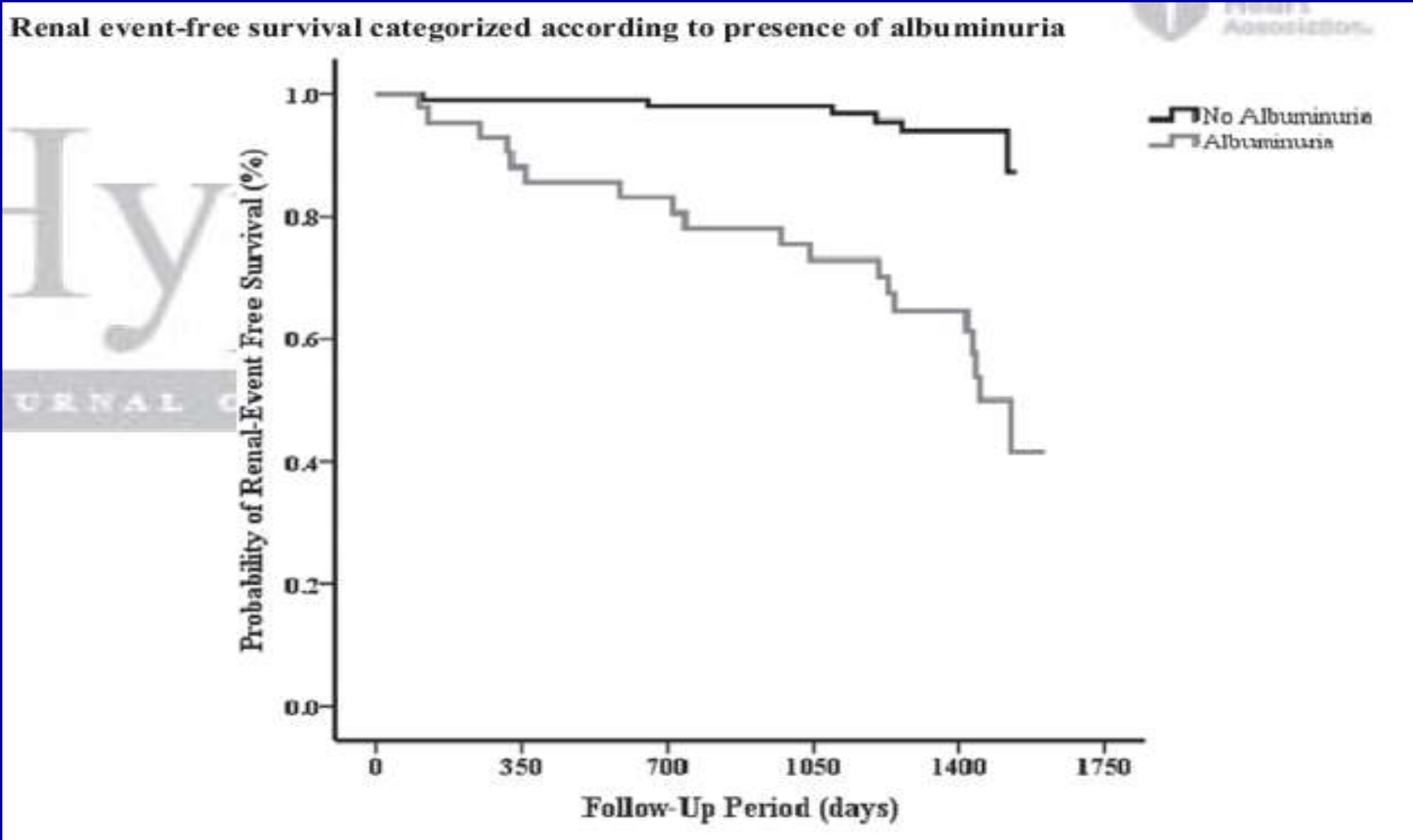
Narrow Arterioles for the Prediction of Renal End Points



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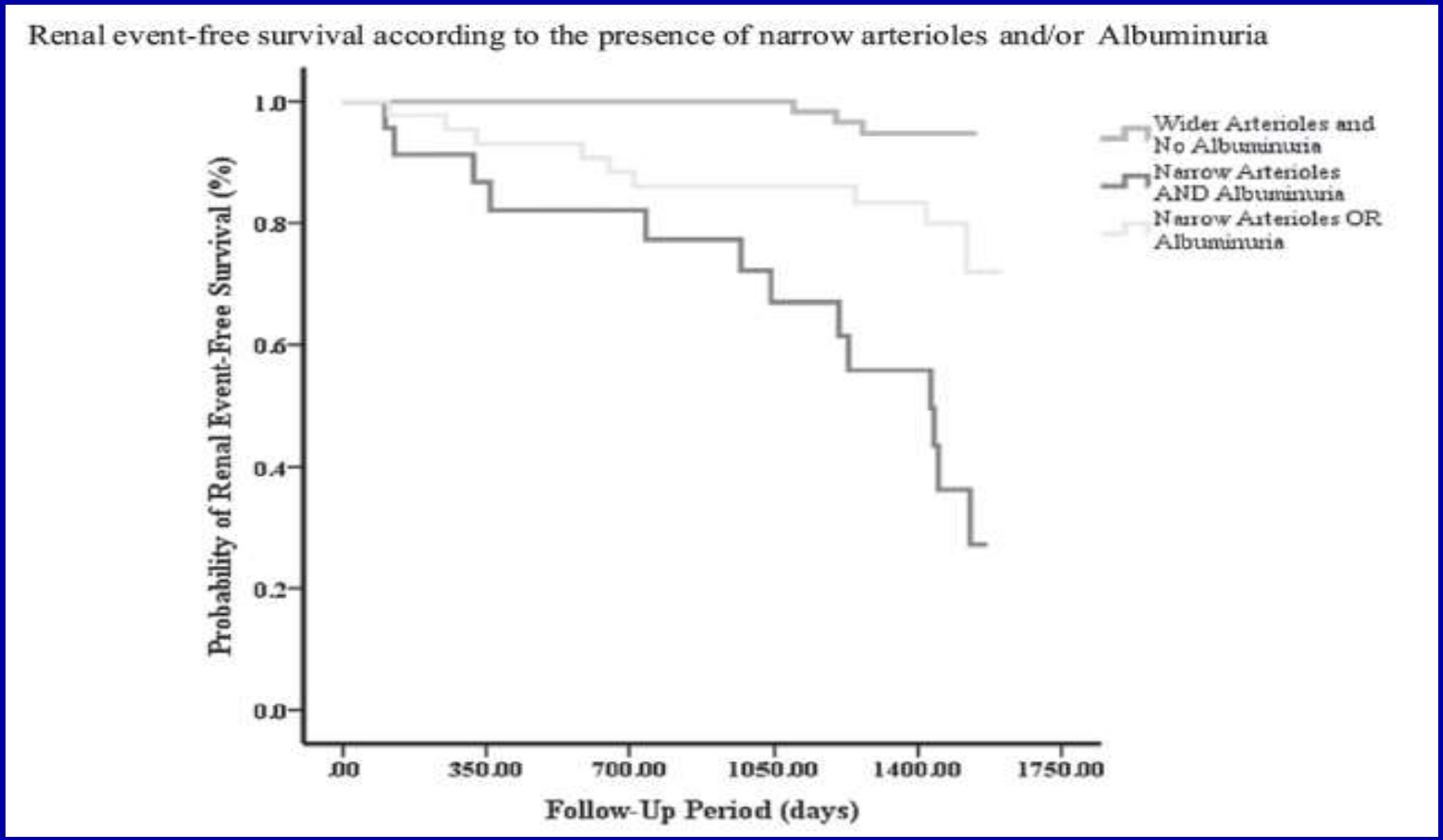
Narrow Arterioles for the Prediction of Renal End Points



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Narrow Arterioles for the Prediction of Renal End Points

Bale/Doneen Implications:

Patients in Stage 2-4 CKD with narrow retinal arterioles have increased risk for vascular endpoints.

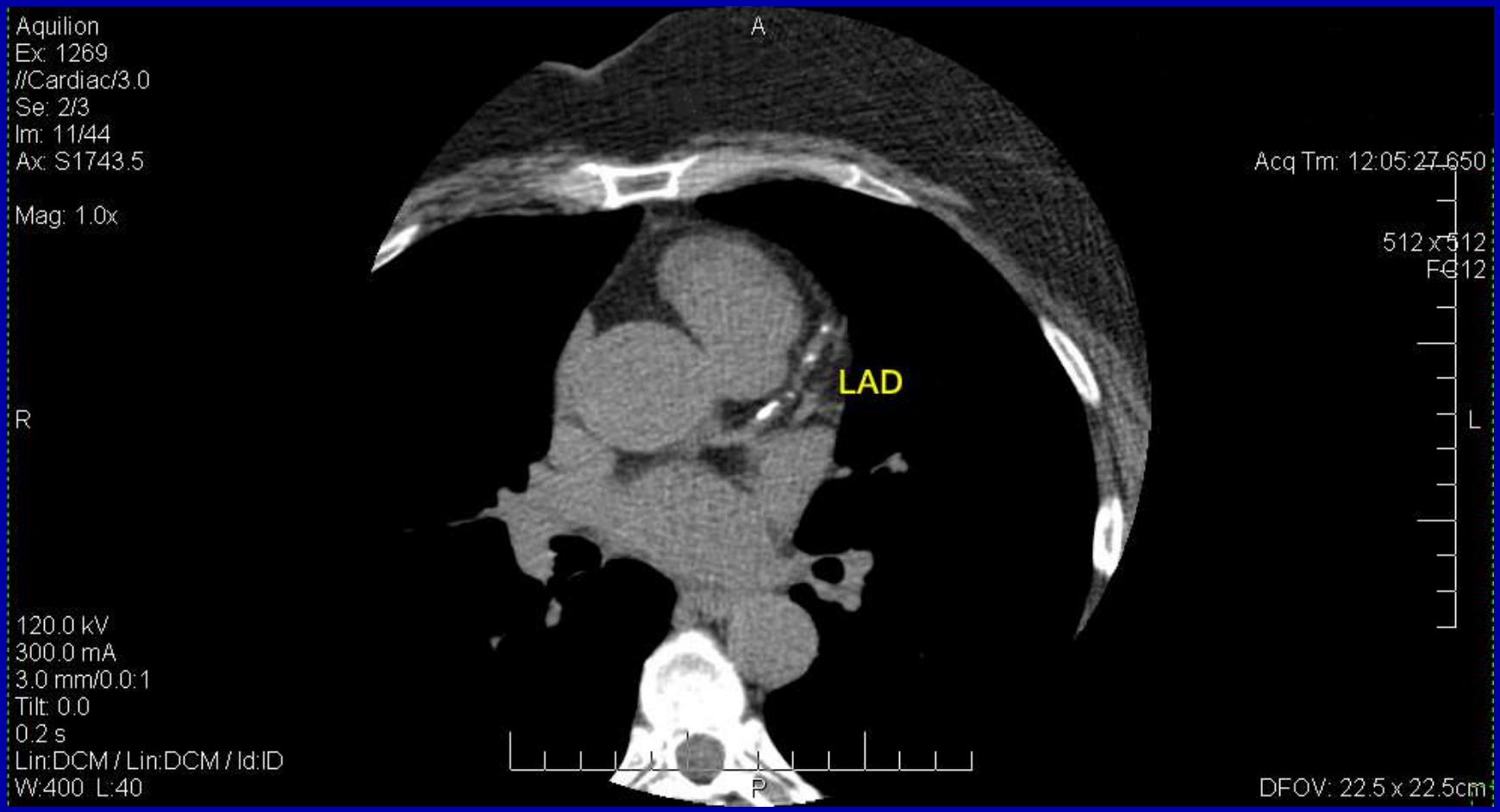
This provides another avenue for risk stratification and implications for aggressiveness of therapy to prevent disease progression.

Highest risk – narrow arterioles coupled with albuminuria.

Protocol for retinal imaging is standardized and reproducible.

Baumann, M., Burkhardt, K, Uwe, H. (May 27, 2014). Hypertension.doi:10.1161

Paradoxical relationship of traditional risk factors and CACS



Paradoxical Relationship of Traditional Risk Factors for CV Events and Coronary Calcification

- 6,355 MESA pts.; mean age 62 yo; 53% women; 12% DM; 13% smokers; followed 7.5 yrs.; 539 CAD events; baseline CACS

- Risk factors: age, gender, syst. BP, TC, HDL-C, smoking, BMI and DM.

- Only measured at baseline and treatment effects could not be well accounted for.

Yeboah, J., et. al. (2014). Mediation of Cardiovascular Risk Factor Effects Through Subclinical Vascular Disease: The Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.303753

Paradoxical Relationship of Traditional Risk Factors for CV Events and Coronary Calcification

- All risk factors had a significant effect mediated through CAC.
- The continuous measure of CACS was modified by the traditional risk factors.
- The event risk associated with a 10% increase in the FRS score was greater when the CACS was low than when the CACS was high.

Yeboah, J., et. al. (2014). Mediation of Cardiovascular Risk Factor Effects Through Subclinical Vascular Disease: The Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.303753

Paradoxical Relationship of Traditional Risk Factors for CV Events and Coronary Calcification

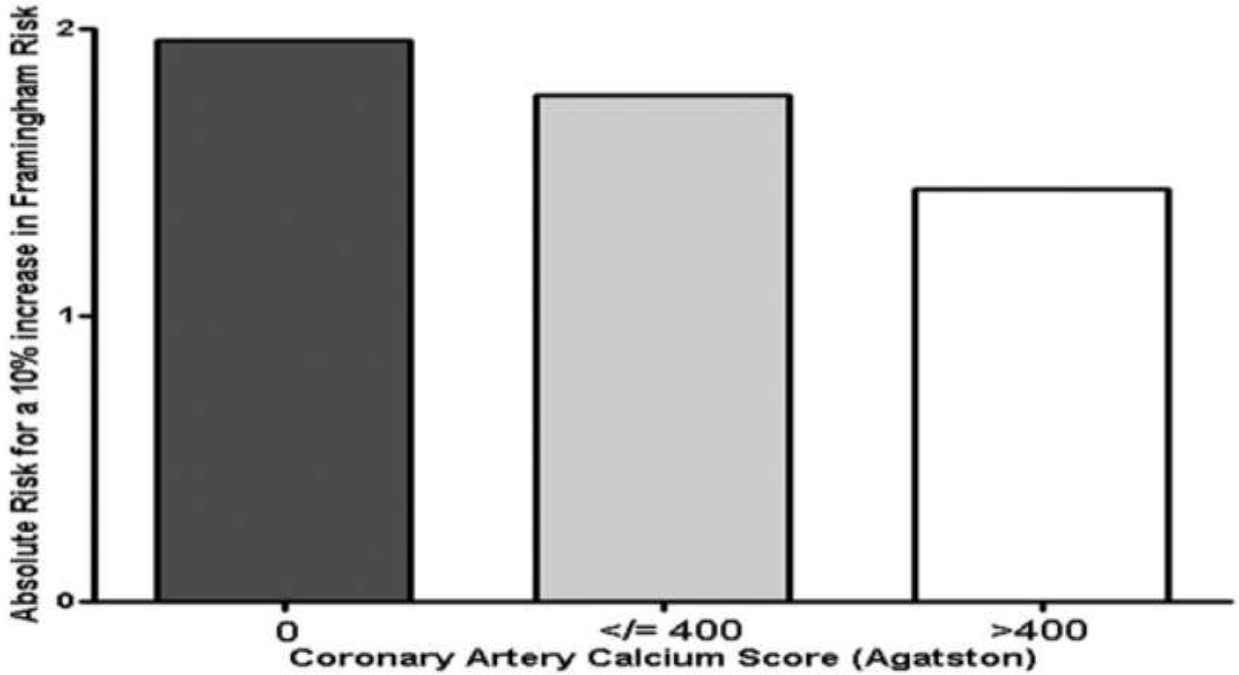


Figure 2. The absolute increase in risk for every 10% increase in the Framingham generalized clinical cardiovascular disease risk score in Multi-Ethnic Study of Atherosclerosis participants with coronary artery calcium scores of zero, ≤400, and >400 Agatston.

Yeboah, J., et. al. (8/2014).. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.303753

Paradoxical Relationship of Traditional Risk Factors for CV Events and Coronary Calcification

- Evidence suggests that the effects of any risk factor cannot be discounted because of the absence of subclinical disease.

- Calls into question the use of subclinical disease measures as intermediate or surrogate markers of disease risk attributed to the risk factors themselves.

Yeboah, J., et. al. (2014). Mediation of Cardiovascular Risk Factor Effects Through Subclinical Vascular Disease: The Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.303753

BDM Thoughts

- CACS of zero does not rule out subclinical CAD.
- There is not a paradox with these findings according to our method.
- A higher CACS can be a surrogate marker for ‘stabilizing’ disease.
- It is inflammation which triggers ‘events’; ASVD is a prerequisite not a ‘trigger’.

Yeboah, J., et. al. (2014). *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.114.303753

The majority of Coronary Plaque is uncalcified

CCS (Agaston)	Risk	Description
0	Non-identified	Negative test. Findings are consistent with a low risk of having a cardiovascular event in the next 5 years.
1-10	Minimal	Minimal atherosclerosis is present. Findings are consistent with a low risk of having a cardiovascular event in the next 5 years.
11-100	Mild	Mild coronary atherosclerosis is present. There is likely mild or minimal coronary stenosis. A mild risk of having CAD exists.
101-400	Moderate	Moderate calcium is detected in the coronary arteries and confirms the presence of atherosclerotic plaque. A moderate risk of having a cardiovascular event exists.
>400	High	A high calcium score may be consistent with significant risk of having a cardiovascular event within the next 5 years

Picture – taken from: Rotterdam Coronary Artery Algorithm Evaluation Framework Walsum, T., Niessen, W. Retrieved online June 10, 2014

The Majority of Coronary Plaque Volume is Un-calcified

- 805 healthy adults with + famhx CAD;, mean age 51 ± 11 yrs.; 56% female; 39% African American; screened for CAD by CT angiography; plaque volumes (mm3) were quantified

- Prevalence of plaque was 58%-males; 36%-females

- Non-calcified plaque (NCP) accounted for most of the total plaque volume at all ages.

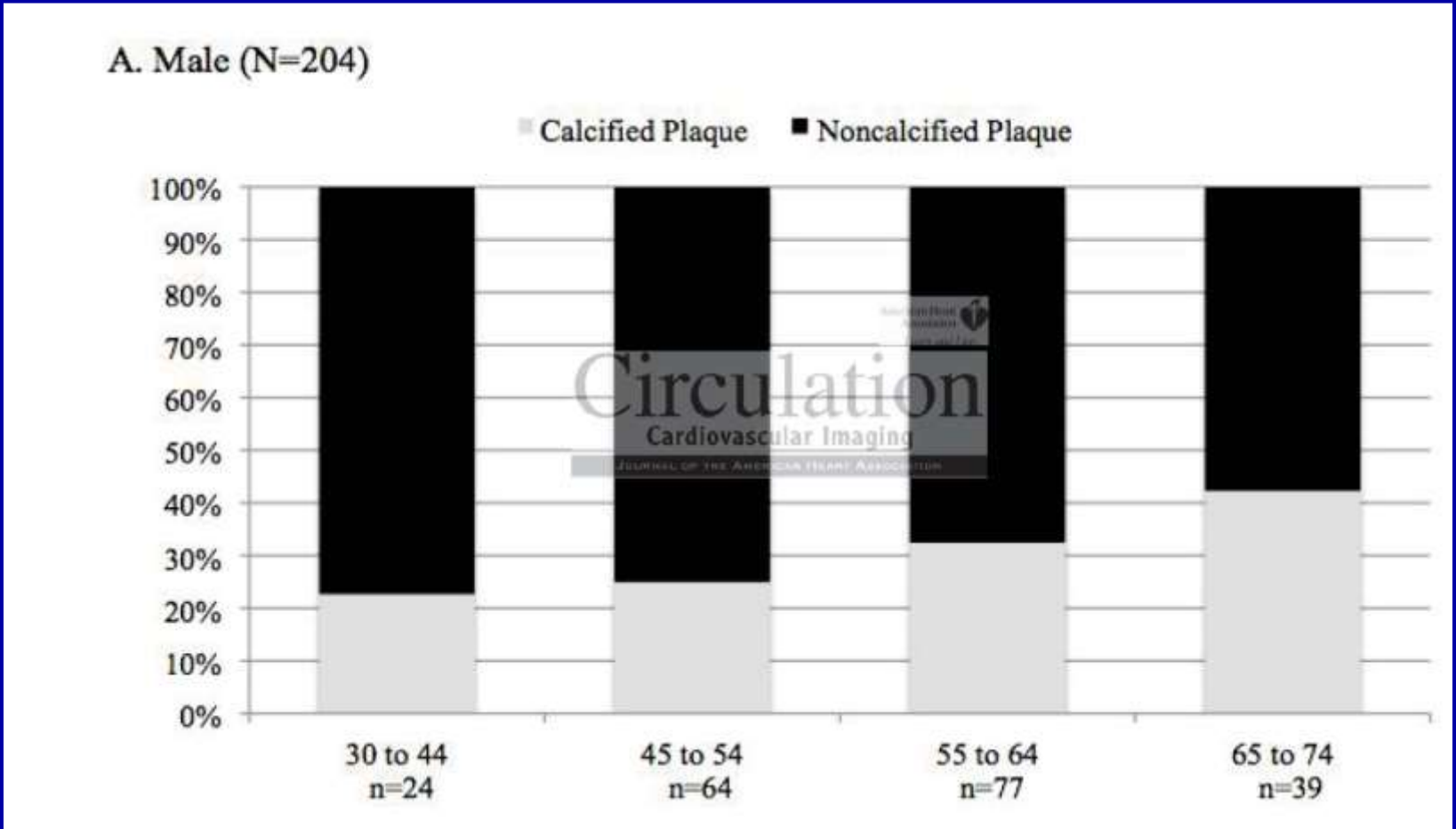
Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- NCP in subjects <55yo accounted for >70% of plaque in males; >80% females
- Coronary calcification is a late manifestation of atherosclerosis.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified



Kral, B. G., et. al. (2014). *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

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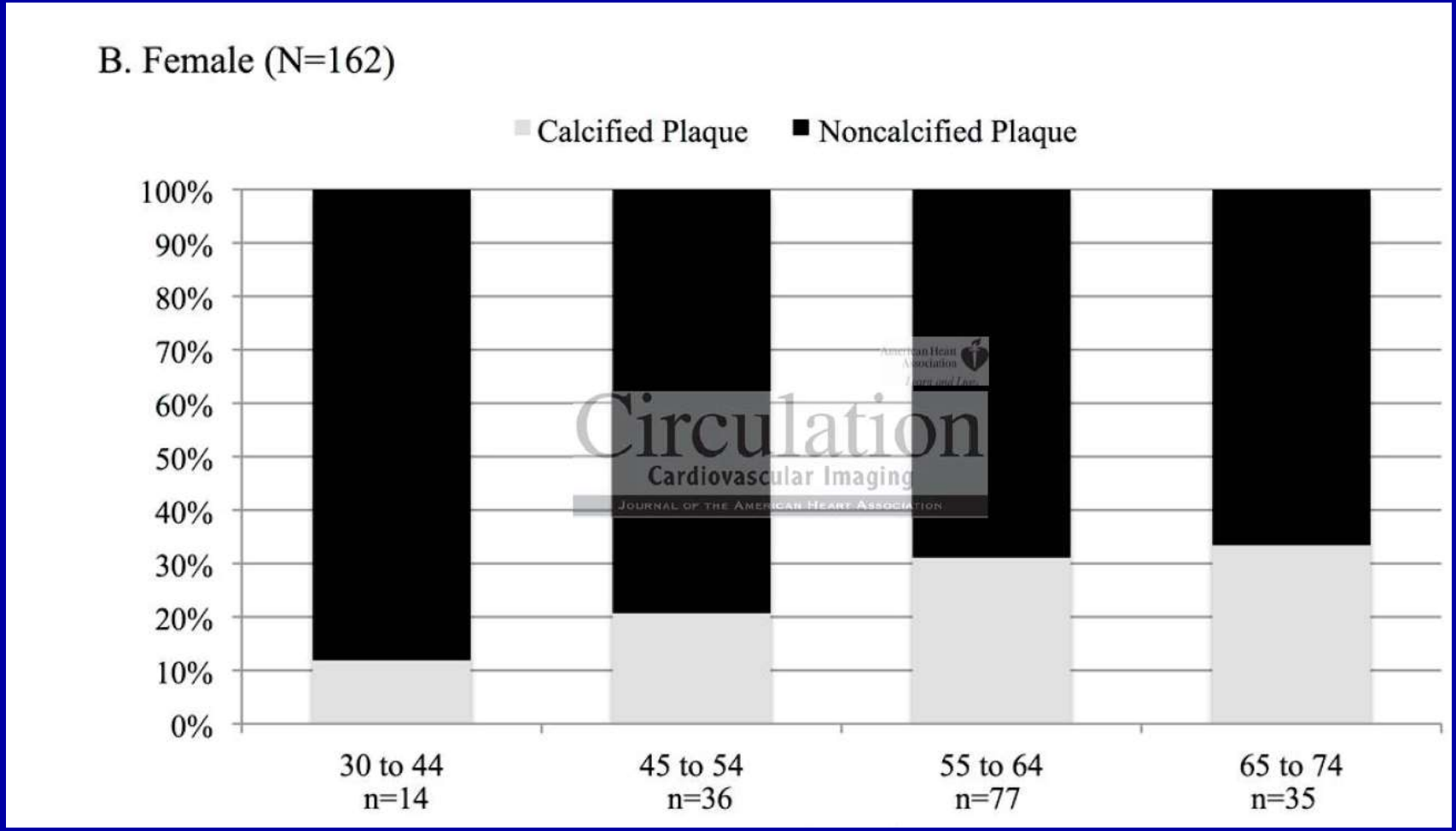


Kral, B. G., et. al. (2014). *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- Earlier stages of atherogenesis are represented by noncalcified or mixed composition plaques.
- These un-calcified plaques are particularly prone to plaque rupture, thrombosis, and acute CAD events.
- NCP volume was significantly associated with the presence of at least one stenosis >50% ($p<0.0001$), independent of all traditional risk factors.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- CAC cannot detect the true extent of coronary artery plaque.
- The extent of subclinical NCP, a putative precursor for CAD events, may have important implications for primary prevention.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

The Majority of Coronary Plaque Volume is Un-calcified

- Females were twice as likely to have exclusively NCP compared to males, (16.8% vs 8.3%, p= 0.01).

- Subjects with a strong sibling history (n=49) were 3.0 times (95% CI 1.3–6.6) more likely to have any coronary plaque.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

FRS was a Poor Predictor of Who had Coronary Plaque

FRS	Women with plaque	Men with plaque
Low	30%	50%
Intermediate	50%	75%

In intermediate risk women and men, LAD plaque was present in 50% and 70%, respectively!!!!

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

FRS was a Poor Predictor of Who had Coronary Plaque

FRS failed to identify many patients with severe CAD-left main and/or 3-vessel disease

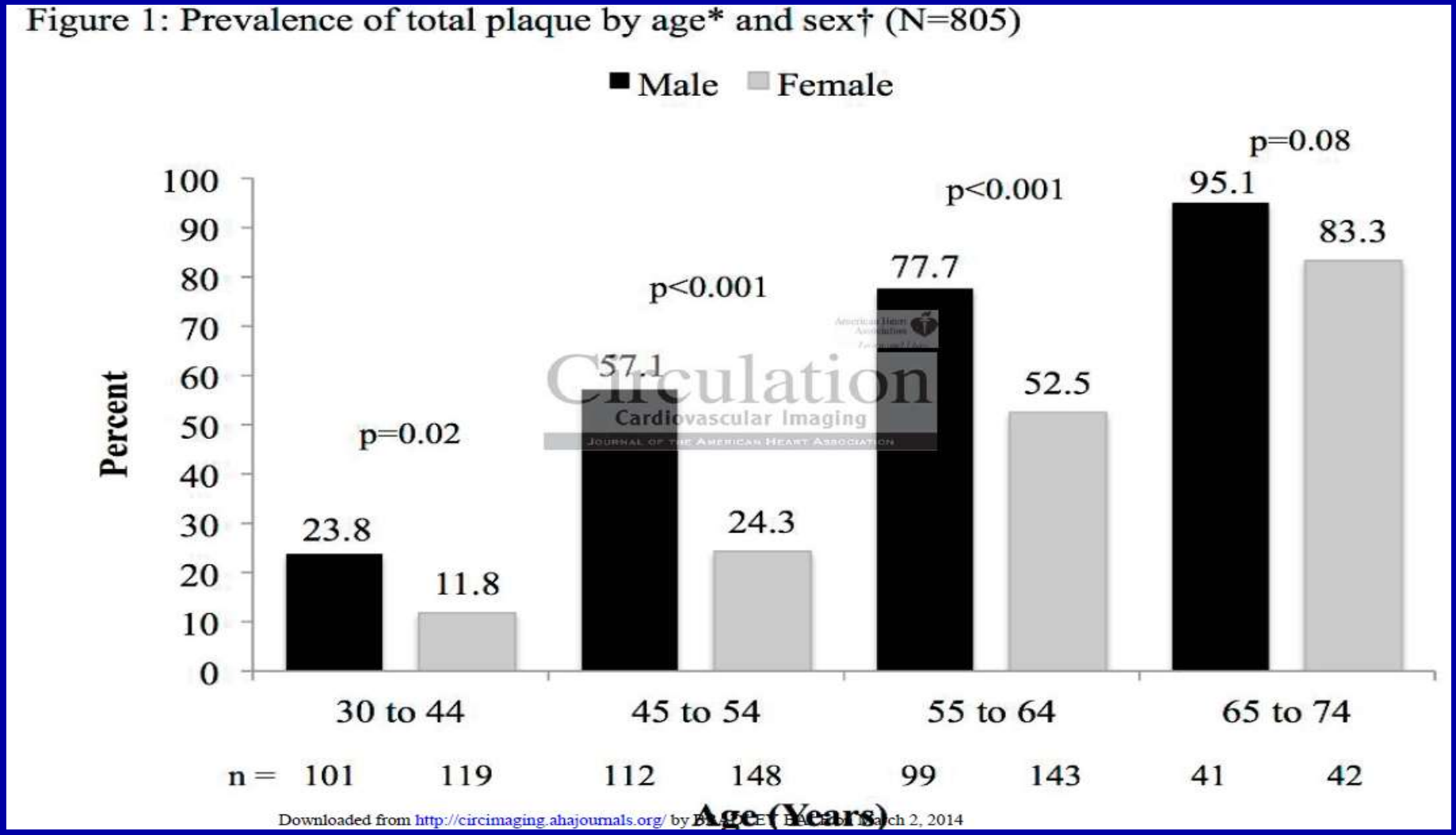
21% of females and 44% of males with this type of disease were intermediate FRS!

The Majority of Coronary Plaque Volume is Un-calcified

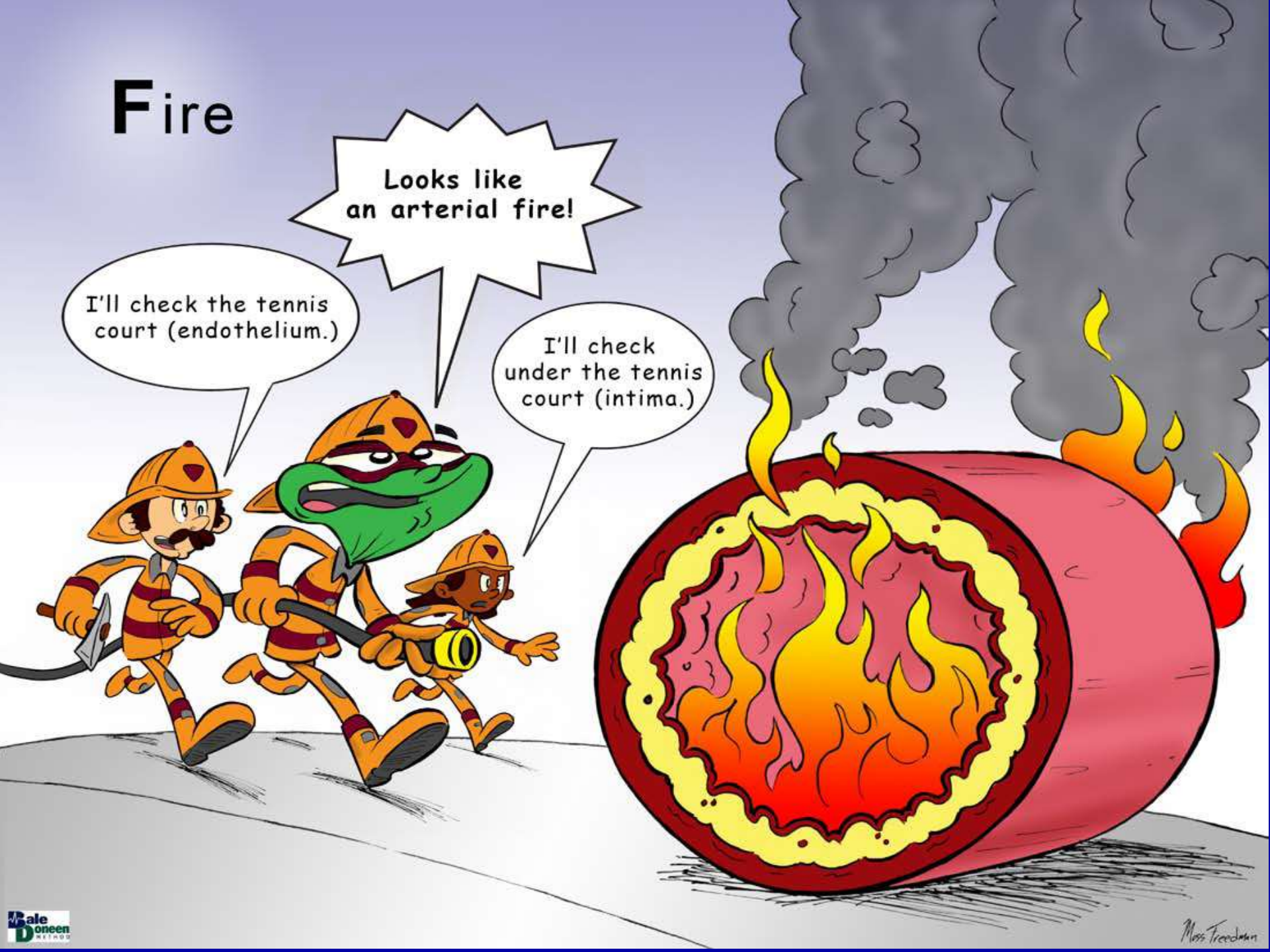
Study suggests that judging whether or not to administer aggressive primary prevention on CACS algorithms or on FRS may obviate appropriate risk reduction interventions.

Kral, B. G., et. al. (2014). Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease. *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980

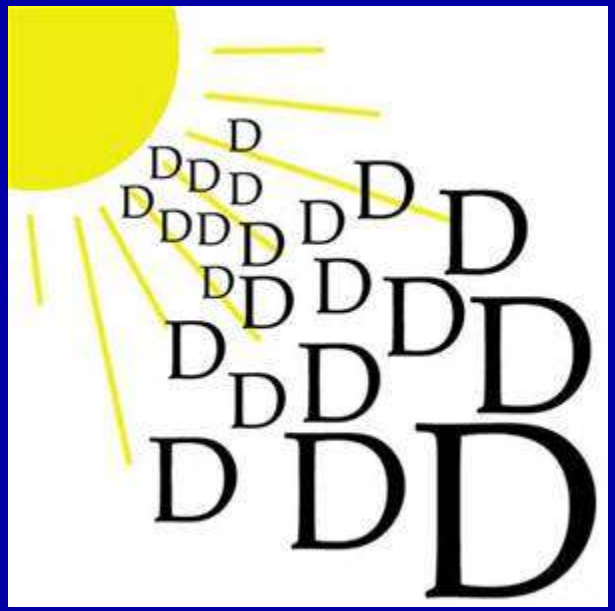
Overall Prevalence of Coronary Plaque



Kral, B. G., et. al. (2014). *Circ Cardiovasc Imaging*. doi: 10.1161/CIRCIMAGING.113.000980


Fire
Looks like an arterial fire!
I'll check the tennis court (endothelium.)
I'll check under the tennis court (intima.)
Bale Doneen METHOD
Moss Freedman

Vitamin D and Inflammation



Vitamin D & Inflammatory Diseases

Discuss the potential mechanisms of
vitamin D in regulating immune/inflammatory responses in:

Vitamin D signaling & immune/inflammation system
Vitamin D and inflammatory diseases
Atherosclerosis-related CVD
Asthma
Inflammatory bowel diseases
Chronic kidney disease
Liver inflammatory disease
Multiple sclerosis
Other inflammation/immune-related disorders

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

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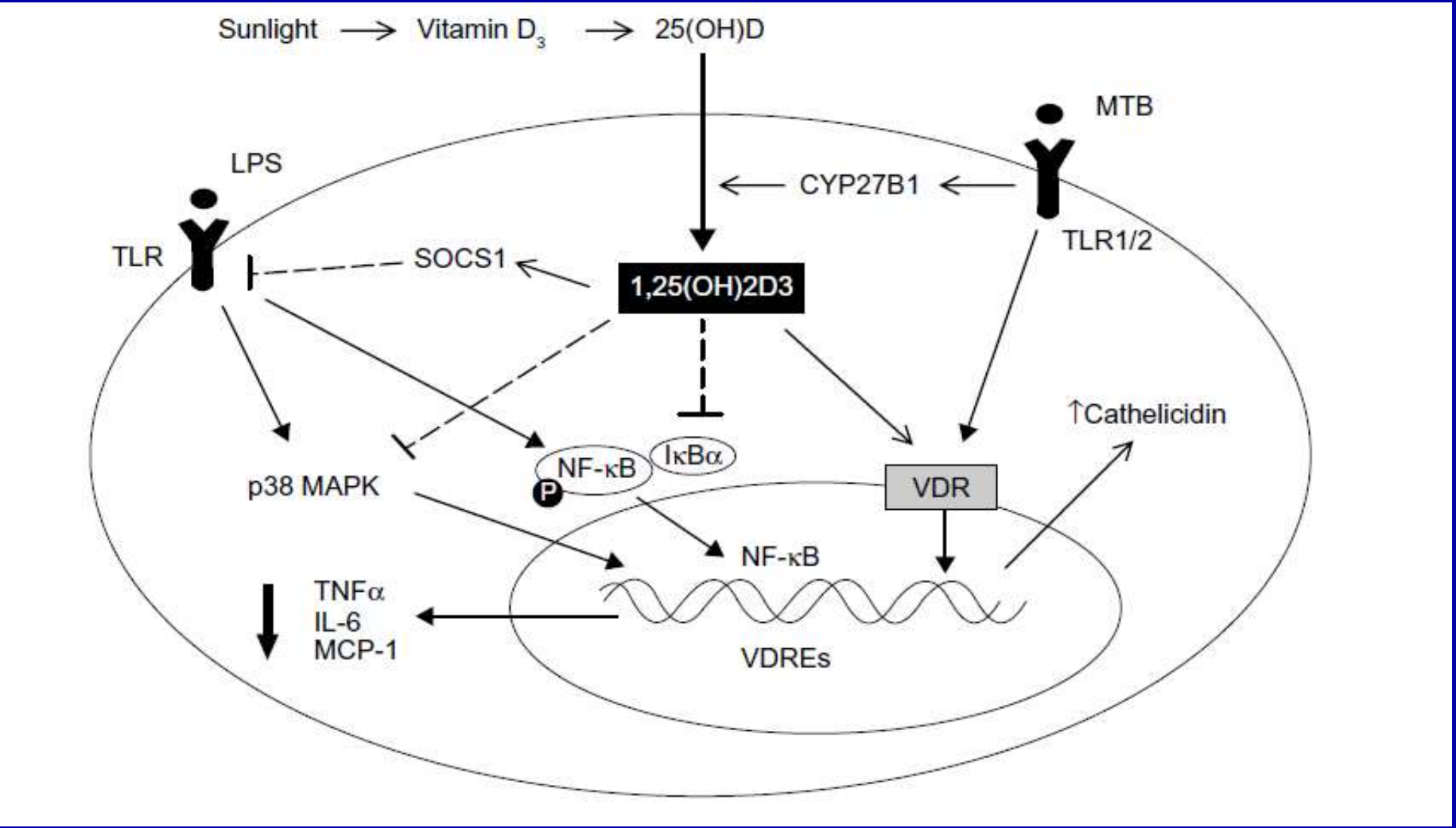
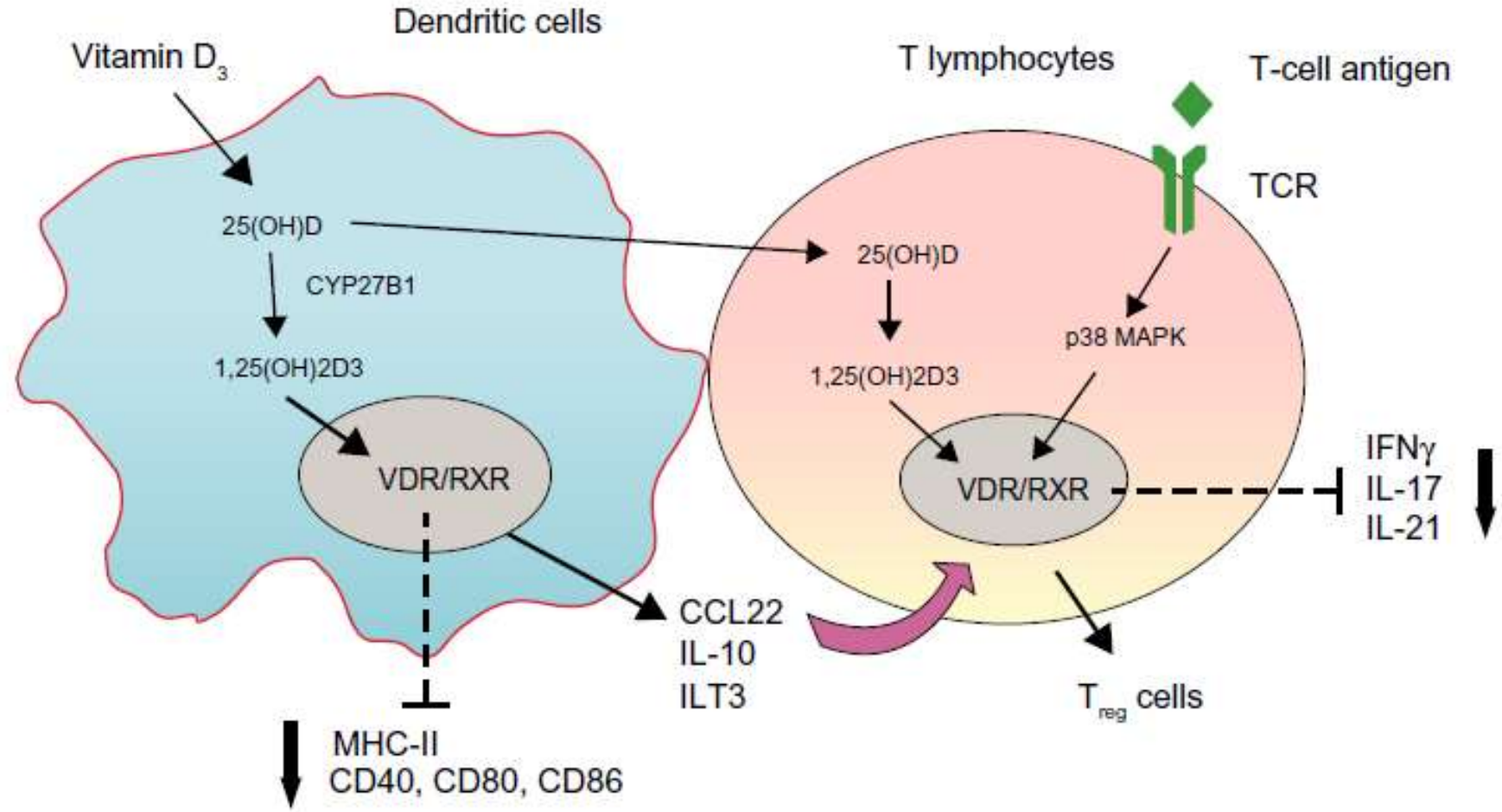
Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates macrophage-mediated innate immune response.



Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates dendritic cells (DCs) and T-lymphocyte function.



Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates Atherosclerotic Cardiovascular disease.

Clinical studies indicate an inverse association between 25(OH)D3 levels and CHD risk.

Significant increase for all-cause mortality when serum 25(OH)D3 concentration <30.

Low 25(OH)D3 15-30 vs >30 had higher risk of coronary artery stenosis.

RCTs show intake of VitD associated with lower risk of CVD, due to improvement of vascular endothelial function and decrease in inflammation.

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Vitamin D status and CVD Risk

Table 2 Summary of major clinical studies evaluating the relationship between vitamin D status and cardiovascular disease (CVD) risk

Source	Study design	Condition	Population (cases)	Main outcome(s)
Martins et al[65]	Retrospective study (secondary analysis of the US NHANES III data)	Mean $25(OH)D_3$ levels =30 ng/mL	15,088 participants in the US	Serum $25(OH)D_3$ levels were negatively associated with important CVD risk factors, including hypertension, diabetes mellitus, obesity, and high serum TG levels
Ponda et al[17]	Cross-sectional (retrospective study)	$25(OH)D_3$ levels <20 ng/mL	107,811 participants in the US	Vitamin D deficiency was associated with an unfavorable lipid profile, including higher TC, LDL, TG, and lower HDL
Park and Lee[64]	Cross-sectional (retrospective study)	$25(OH)D_3$ levels <25 nmol/L	5,559 Korean participants	Vitamin D insufficiency was associated with increased prevalence of CVD, accompanied by higher waist circumference, fasting glucose, LDL, and TG levels and lower HDL cholesterol levels
Wang et al[69]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <15 ng/mL	1,739 Framingham offspring	Vitamin D deficiency was associated with incident CVD
Dobnig et al[70]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <13.3 ng/mL	3,258 participants in Austria	Low $25(OH)D_3$ and $1,25(OH)_2D_3$ levels were independently associated with all-cause and cardiovascular mortality
Semba et al[68]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <10.5 ng/mL	1,006 participants in Italy	Older community-dwelling adults with low serum $25(OH)D_3$ levels were at higher risk for all-cause and CVD mortality
Zhao et al[66]	Cohort study (prospective study)	$25(OH)D_3$ levels <29 ng/mL	2,609 participants with hypertension in the US	Concentrations of $25(OH)D_3$ were inversely associated with all-cause and CVD mortality among adults with hypertension in the US
Wasson et al[67]	Cross-sectional (prospective study)	The $25(OH)D_3$ levels <15 ng/mL	1,844 ischemic heart disease (IHD) patients	Vitamin D Levels of <15 ng/mL were associated with a hazard ratio of 2.30 (P=0.035) for IHD events compared to levels ≥30 ng/mL
Lim et al[71]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <30 ng/mL	921 participants with hypertension in the US	Low $25(OH)D_3$ concentrations were independently associated with higher risk of coronary artery stenosis

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates Atherosclerotic Cardiovascular disease.

Mechanism of action – vitamin D can:

Protect against endothelial dysfunction by stimulating nitric oxide production and inhibiting oxidative stress.

Reduce levels of prostaglandins and suppress pro-inflammatory cytokine expression

May alter macrophage function and gene expression (crucial in the formation of foam cells and vascular inflammation response)

In T2DM – inhibit foam cell formation and suppress macrophage cholesterol efflux.

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Vitamin D – Cause and Effect – root cause

Table 3 Summary of interventional studies evaluating the effect of vitamin D supplements on cardiovascular disease (CVD) risk

Source	Study design	Condition	Population (cases)	Main outcome(s)
Harris et al[72]	Randomized, placebo-controlled trial	Vitamin D (2,000 IU/day) for 16 weeks	57 African American adults	Vitamin D supplements (2,000 IU/day) for 16 weeks were effective at improving vascular endothelial function in African American adults
Zittermann et al[73]	Randomized, placebo-controlled trial	Vitamin D (83 μg/day) for 1 year	200 overweight subjects (mean 25[OH]D_3 levels =12 ng/mL)	Vitamin D supplements enhanced the beneficial effects of weight loss on CVD risk, including decreasing lipid levels and inflammation
Sun et al[74]	Cross-sectional (prospective study)	Vitamin D (≥600 IU/day) or vitamin D (<100 IU/day)	2,280,324 person-years of follow-up	Higher intake of vitamin D was associated with a lower risk of CVD in men but not in women
Cauley et al[75]	Cross-sectional (prospective study)	Calcium plus vitamin D supplementation	29,862 postmenopausal women	There was no difference in CVD morbidity between groups
Ponda et al[77]	Randomized, placebo-controlled trial	Vitamin D (50,000 IU/week) for 8 weeks	151 vitamin D-deficient (25[OH]D levels <20 ng/mL) patients	Correcting vitamin D deficiency in the short term did not improve the lipid profile
Yiu et al[78]	Randomized, placebo-controlled trial	Vitamin D (5,000 IU/day) for 12 weeks	100 type 2 diabetes mellitus patients	12 weeks of oral supplementation with vitamin D did not significantly affect vascular function or serum biomarkers of inflammation and oxidative stress
Stricker et al[168]	Randomized, placebo-controlled trial	Vitamin D (100,000 IU/single oral dose)	76 patients with peripheral arterial disease	Vitamin D supplementation did not influence endothelial function, arterial stiffness, coagulation, or inflammation parameters
Gepner et al[76]	Randomized, placebo-controlled trial	Vitamin D (2,500 IU/day) for 4 months	114 subjects	Vitamin D supplementation did not improve endothelial function, arterial stiffness, or inflammation

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates Chronic Kidney Disease

20-85% of CKD disease patients have Vitamin D deficiency.

Chronic low-grade inflammation is a hallmark of CKD (important factor to progression of CKD and high cardiovascular mortality).

Vit D deficient (<10 ng/mL) vs >30 ng/mL were 3.79 (1.71-8.43) more likely to die from all-cause and 5.61 for CV mortality – linking CKD, Vitamin D and CHD

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates Chronic Kidney Disease

Table 6 Summary of major clinical studies evaluating the relationship between vitamin D status and chronic kidney disease (CKD) risk

Source	Study design	Objective	Population (cases)	Main outcome(s)
Pilz et al[116]	Prospective cohort study	To investigate the relationship between the vitamin D status and mortality of CKD	444 CKD patients	Low $25(OH)D_3$ levels were associated with increased all-cause and cardiovascular mortality in CKD patients
Santoro et al[117]	Cross-sectional study	To investigate the relationship between the vitamin D status and mortality of CKD	104 CKD patients	Vitamin D has been shown to reduce the probability of cardiovascular or renal events; vitamin D intake for more than 12 months can reduce the probability of such events by 11.42%
London et al[119]	Cross-sectional study	To investigate the relationship between vitamin D status and cardiovascular risk factors	104 CKD patients (end stage)	Vitamin D deficiency and low $1,25(OH)_2D_3$ could be associated with arteriosclerosis and endothelial dysfunction in hemodialysis patients
Isakova et al[114]	Cross-sectional study	To investigate the relationship between vitamin D level, inflammation, and albuminuria	1,847 participants	Low $25(OH)D_3$ and $1,25(OH)_2D_3$ levels were independently associated with albuminuria; vitamin D deficiency may contribute to inflammation and subsequent albuminuria
Petchey et al[115]	Cross-sectional study	To investigate the relationship between vitamin D status and maximum aerobic-exercise capacity in patients with CKD	85 CKD participants	Vitamin D was independently associated with aerobic capacity in CKD patients
Satirapoj et al[113]	Cross-sectional study	To investigate the relationship between vitamin D status and the staging of CKD	2,895 CKD patients	$25(OH)D_3$ insufficiency and deficiency were more common and associated with level of kidney function in the Thai CKD population, especially in advanced-stage CKD
Schaible et al[121]	Cross-sectional study	To investigate the effect of vitamin D status on fetuin-A in CKD patients	112 pediatric patients	Cumulative intake of $25(OH)D_3$ and calcitriol were significantly correlated with fetuin-A in CKD patients
Seeherunvong et al[118]	Cross-sectional, retrospective study	To assess the prevalence of abnormal vitamin D status in children and adolescents with CKD	258 patients with early CKD	Vitamin D insufficiency and deficiency may contribute to growth deficits during the earliest stages of CKD

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Primary mechanism through which vitamin D regulates Liver Inflammatory Disease

NAFLD – presence of hepatic steatosis without significant alcohol use or other known liver disease.

Recent studies – indicate: IR, metSynd, proinflammatory cytokines in the development and progression of NAFLD.

Inverse relationship with Vit D and IR and MetSynd.

Vit D may be involved in NAFLD through its ability to modulate the immune/inflammation system.

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Vitamin D and inflammation

Conclusion and remaining question –

Vitamin D deficiency IS associated with several inflammatory diseases –

However, the question remains whether or not vitamin D deficiency contributes to the etiology of inflammatory disease OR if vitamin D deficiency is a manifestation of these diseases.

Yin, Kai. June 4 2014. Vitamin D and inflammation. Journal of Inflammation Research 2014:7 69-87.

Cardiac Markers and CKD

Cardiac and Kidney Markers for CV Prediction in Individuals with Chronic Kidney Disease

8622 participants aged 52-75 years old in ARIC Study –

- cardiac troponin T
- NT-proBNP
- Cystatin C
- B2-macroglobulin
- B-trace protein

Compared for improvement in predicting incident CVD after stratifying by CKD status.

Median f/u of 11.9 years – 1672 CVD events including MI, CVA and HF (336 cases in CKD).

Matsushita, K, Sang, Y et al. May 15, 2014. Cardiac and kidney markers for CV Prediction In individuals with CKD. ATVB. DOI:10.1161/ATVBAHA.114.303465

Cardiac and Kidney Markers for CV Prediction in Individuals with Chronic Kidney Disease

Every marker was independently associated with incident CVD in participants with and without CKD.

HR were larger for cardiac markers than for kidney markers- particularly in CKD:

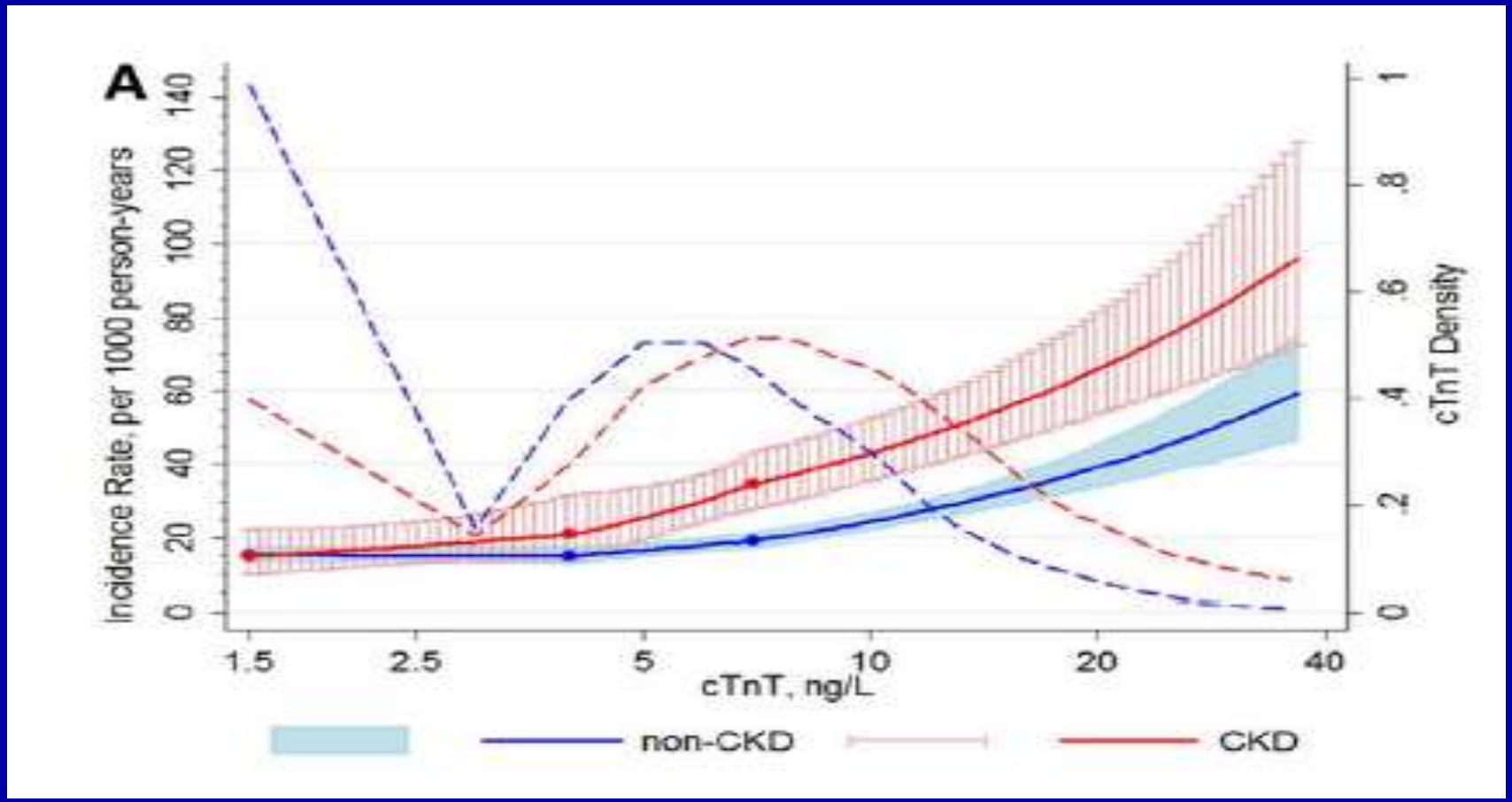
troponin T: OR 1.61, CI 1.43-1.81

NT-pro-BNP: OR 1.50, CI 1.34-1.68

Kidney markers included: cystatin C, B2M, and B-trace protein. Also – Troponin T and Nt-ProBNP higher than hsCRP

Matsushita, K, Sang, Y et al. May 15, 2014. Cardiac and kidney markers for CV Prediction In individuals with CKD. ATVB. DOI:10.1161/ATVBAHA.114.303465

Cardiac and Kidney Markers for CV Prediction in Individuals with Chronic Kidney Disease



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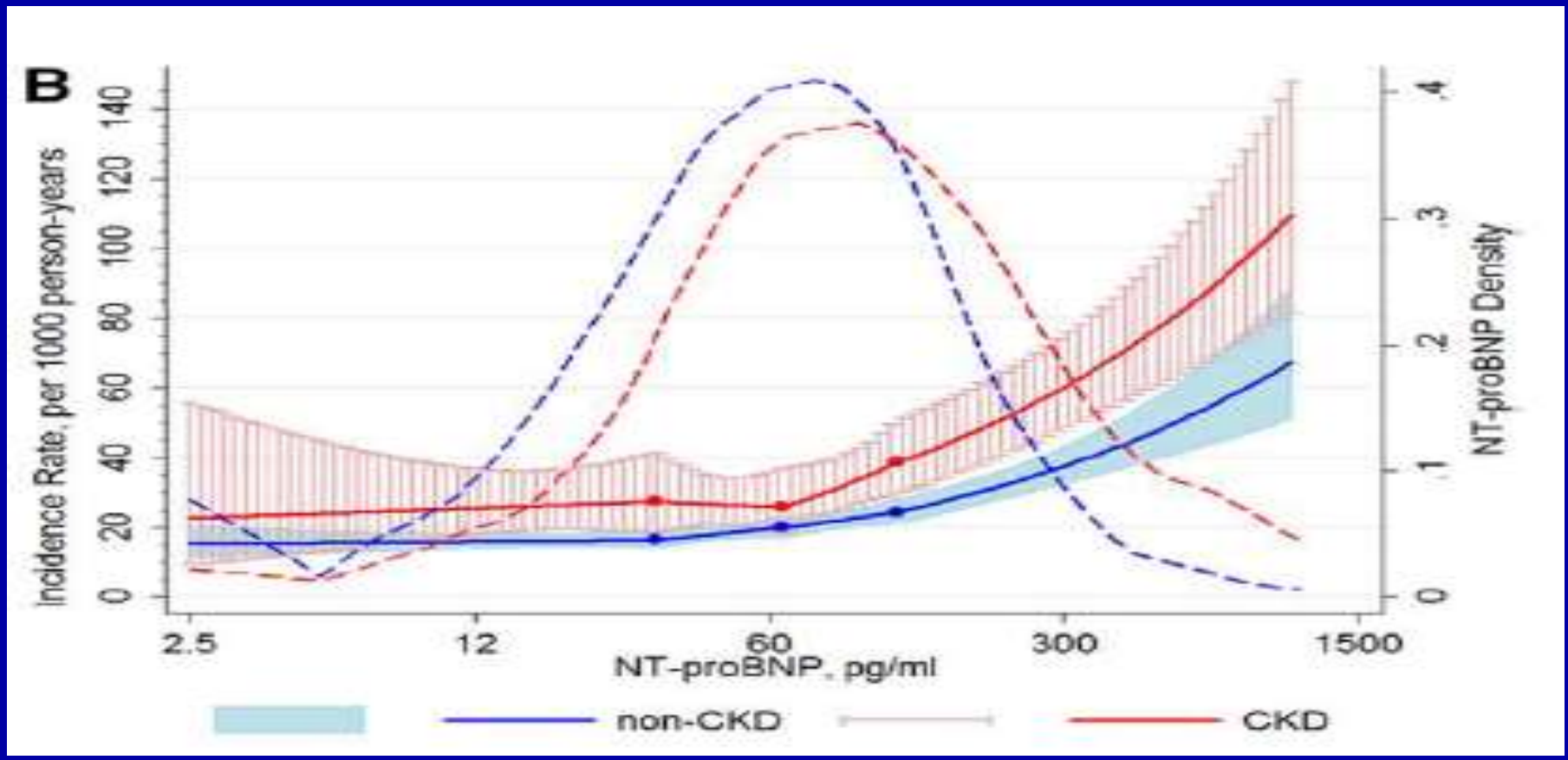
Cardiac and Kidney Markers for CV Prediction in Individuals with Chronic Kidney Disease



Matsushita, K, Sang, Y et al. May 15, 2014. Cardiac and kidney markers for CV Prediction In individuals with CKD. ATVB. DOI:10.1161/ATVBAHA.114.303465

Cardiac and Kidney Markers for CV Prediction in Individuals with Chronic Kidney Disease

1. cTnT and NT-proBNP with CVD were independent of kidney function and even stronger in those with CKD than those without.

2. Prediction improvement for CVD by cTnT and NT-proBNP was larger than previously/recently reported with TC, HDL and hsCRP for CHD prediction in meta-anlaysis.

3. cTnT and NT-proBNP improved risk prediction independently of each other and gained more power if combined.

Matsushita, K, Sang, Y et al. May 15, 2014. Cardiac and kidney markers for CV Prediction In individuals with CKD. ATVB. DOI:10.1161/ATVBAHA.114.303465

Cardiac and Kidney Markers for CV Prediction in Individuals with Chronic Kidney Disease

4. Contribution to improved CVD prediction were largest for HF, followed by CHD and CVA.

5. Confirmed prediction values of these cardiac markers in people without history of CVD

6 These markers outperformed nontraditional kidney markers, including cystatin C, for CVD prediction.

Matsushita, K, Sang, Y et al. May 15, 2014. Cardiac and kidney markers for CV Prediction In individuals with CKD. ATVB. DOI:10.1161/ATVBAHA.114.303465

ESTROGEN & INFLAMMATION

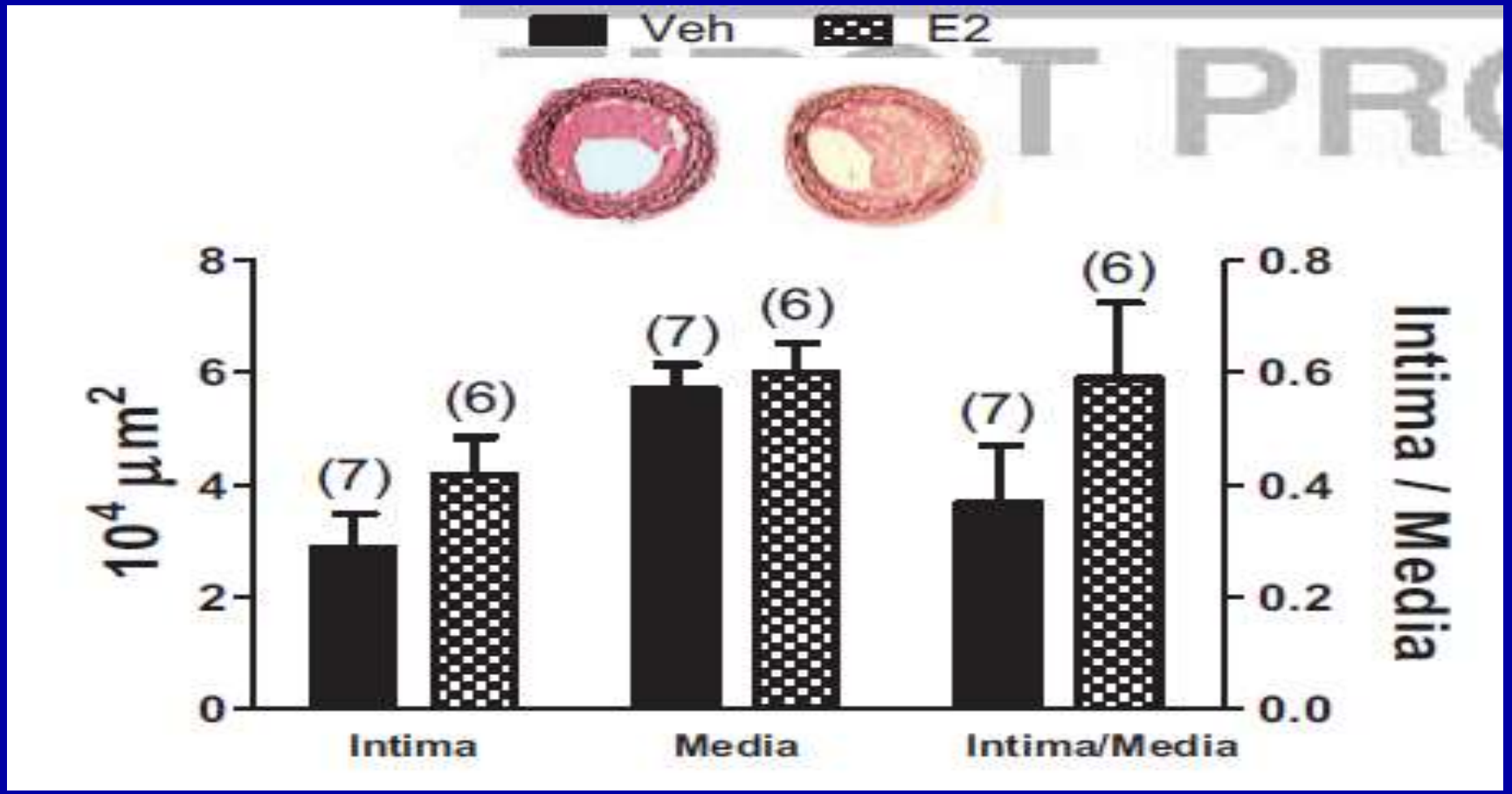
Estrogen Effects on Vascular Inflammation are Age Dependent

Estradiol (E2) pretreatment of cells derived from young mice attenuated C-reactive protein (CRP)-induced expression of inflammatory mediators.

Young (10 weeks) and aged (52 weeks) female mice were used as source for primary cultures of cells derived from young mice attenuated CRP induced expression of inflammatory mediators.

Bowling, M, Xing, D et al. ATVD April 21, 2014. DOI:10.1161/ATVBAHA.114.303629

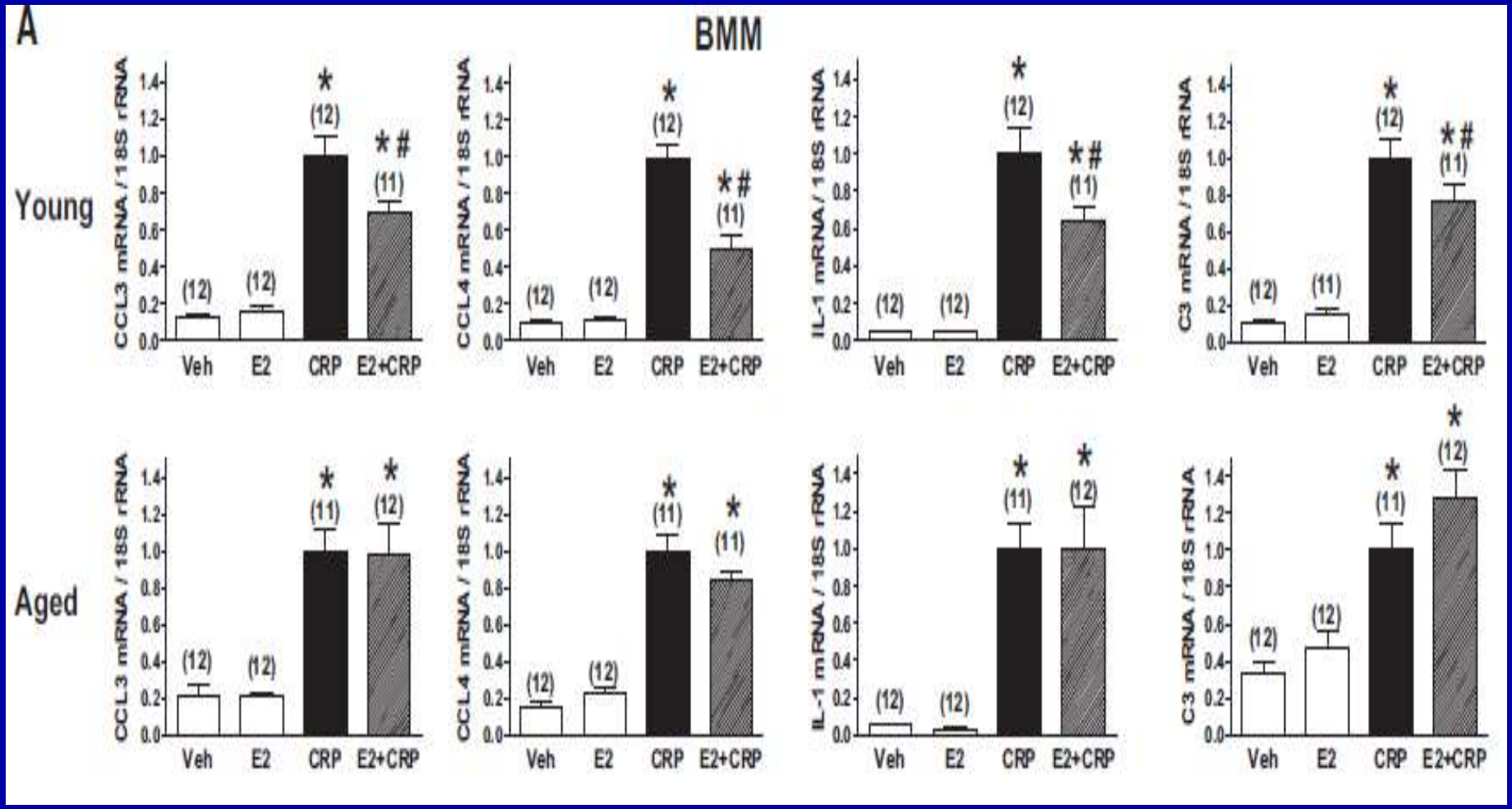
Estrogen Effects on Vascular Inflammation are Age Dependent -



Carotid arteries harvested from 50-54 week old mice

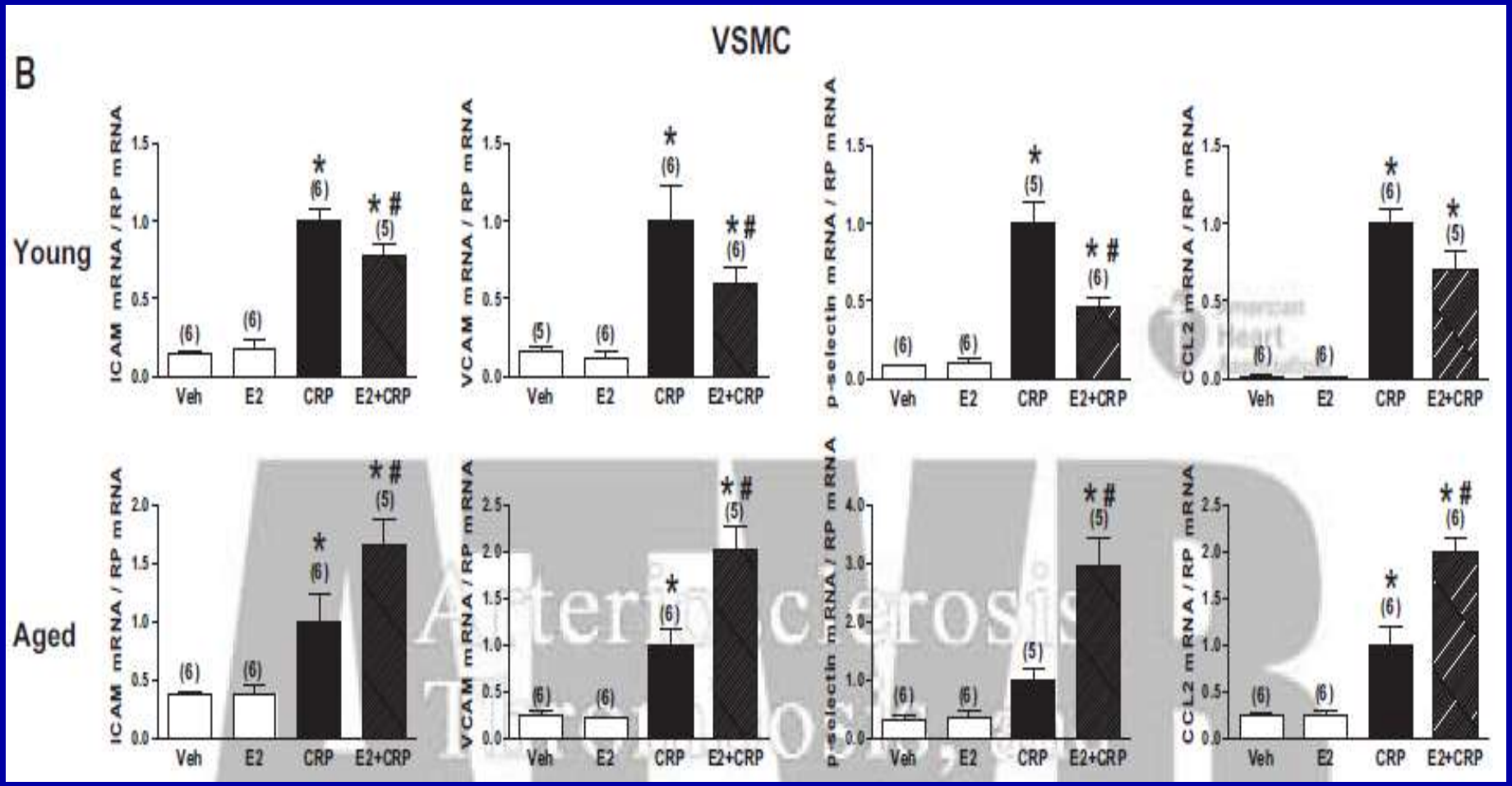
Bowling, M, Xing, D et al. ATVD April 21, 2014. DOI:10.1161/ATVBAHA.114.303629

Estrogen Effects on Vascular Inflammation are Age Dependent
Bone Marrow-derived macrophages (BMM)



Bowling, M, Xing, D et al. ATVD April 21, 2014. DOI:10.1161/ATVBAHA.114.303629

Estrogen Effects on Vascular Inflammation are Age Dependent – Vascular Smooth Muscle Cell (VSMC)



Bowling, M, Xing, D et al. ATVD April 21, 2014. DOI:10.1161/ATVBAHA.114.303629

Estrogen Effects on Vascular Inflammation are Age Dependent – Vascular Smooth Muscle Cell (VSMC)

Conclusion:

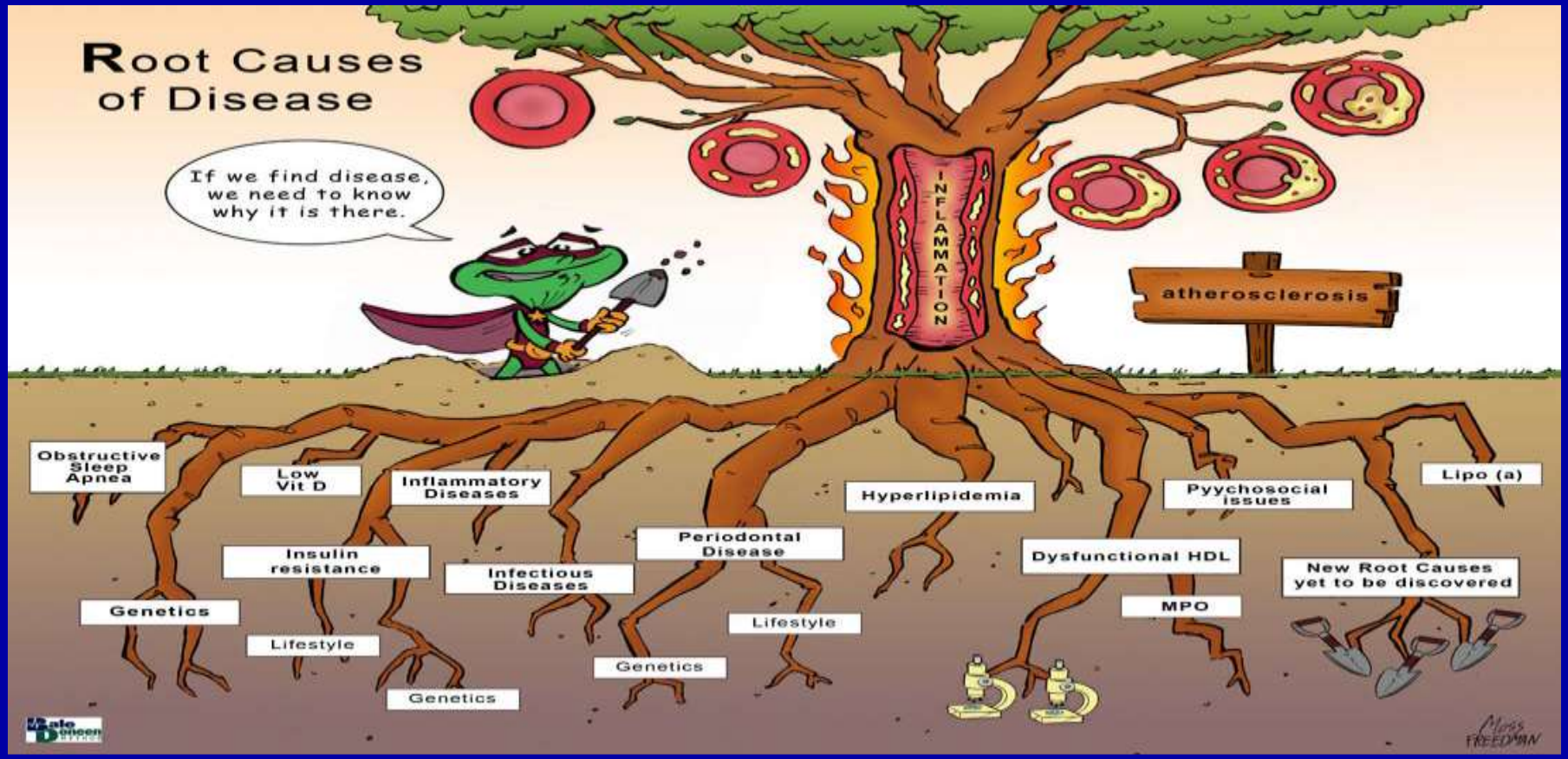
In animal models Estrogen (E2) attenuates inflammatory response to CRP in bone marrow macrophages and vascular smooth muscle cells in older models.

Bale/Doneen Take-Away:

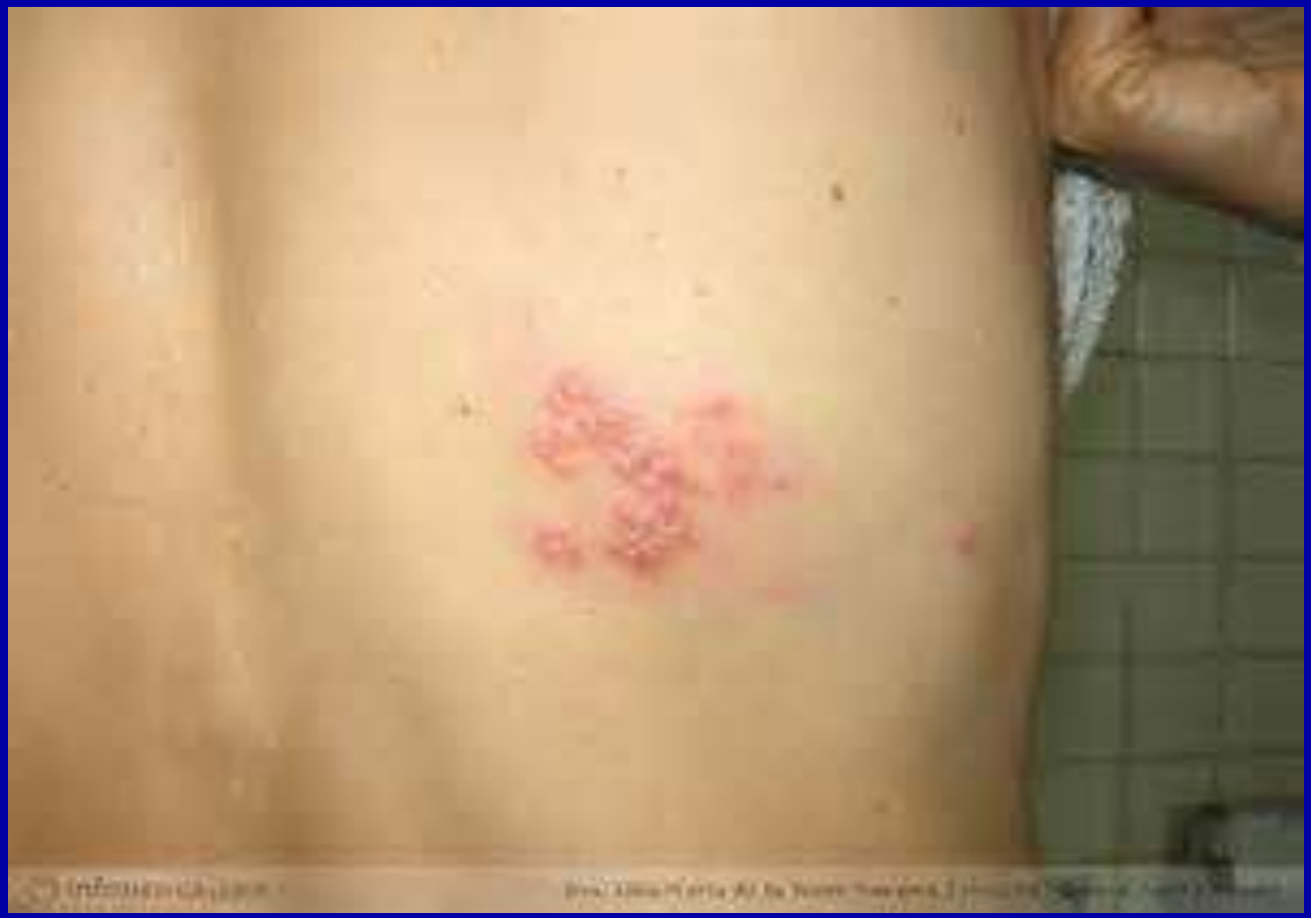
When utilizing hormone therapy – monitor inflammatory cascade/response for safety.

Bowling, M, Xing, D et al. ATVD April 21, 2014. DOI:10.1161/ATVBAHA.114.303629

Treatment



HERPES ZOSTER



Herpes Zoster (HZ)Increases Risk of Stroke

- 31,140 subjects; 7,760 had HZ outbreak; within one yr. 31% greater risk of stroke and four times higher risk, if had HZ ophthalmicus*
- 2,632 subjects; 658 had HZ outbreak; HZ had 4.52 – fold higher risk of stroke. #
- About 19% of zoster occurs between ages 50 and 59; consider it for those individuals too
- BDM- adults over age 50 with plaque or vascular inflammation – consider vaccination

D. Gilden, J of Internal Med doi: 10.1111/j.1365-2796.2011.02359.x
*Kang JH, et. al. Stroke 2009;40:3443–8.
#Lin H-C, et. al. Neurology 2010;74:792–7.

Quantification of risk factors for herpes zoster: population based case-control study

Purpose: Quantify the effects of possible risk factors for herpes zoster at different ages.

144,959 adults diagnosed with zoster between 2000-2011 – age/sex matched controls

Median age of case control – 62 years old

Forbes, H, Bhaskaran, K. (May 13, 2014). Quantification of risk factors for herpes Zoster. BMJ 2014;348:g2911 doi:10.1136/bmj.g2911

Quantification study of Zoster

Increased risk of zoster: 99% confidence intervals

Leukemia*:	OR 3.90. CI [3.21-4.74]
Myeloma*:	OR 2.16. CI [1.84-2.53]
SLE:	OR 1.72. CI [1.45-2.04]
Rheumatoid Arthritis:	OR 1.46. CI [1.38-1.55]
Inflammatory Bowel Disease:	OR 1.36. CI [1.26-1.46]
COPD:	OR 1.32. CI [1.27-1.37]
T1DM (not T2DM):	OR 1.27. CI [1.07-1.50]
Asthma:	OR 1.21. CI [1.17-1.25]
Depression:	OR 1.15. CI [1.10-1.20]
Chronic Kidney Disease:	OR 1.14. CI [1.08-1.18]

*current vaccine contraindicated in these groups

Forbes, H, Bhaskaran, K. (May 13, 2014). Quantification of risk factors for herpes Zoster. BMJ 2014;348:g2911 doi:10.1136/bmj.g2911

Quantification of risk factors for herpes zoster: population based case-control study

Increased risk was proportionally greater in younger age groups.

Approximately 45% of zoster cases occurred in patients under 60 years and 65% in those under 70 years.

Those at highest risk (immunocompromised) are contraindicated to get the vaccine – alternate strategies needed

People under agge 60 are at increased risk as well – below age for insurance coverage for the vaccine.

Forbes, H, Bhaskaran, K. (May 13, 2014). Quantification of risk factors for herpes Zoster. BMJ 2014;348:g2911 doi:10.1136/bmj.g2911

Influenza vaccination and CV risk in patients with recent TIA and stroke

Influenza vaccination and CV risk in patients with recent TIA & CVA

OPTIC registry (n=3,625)and the AMISTAD study (n=618) and the PERFORM trial (n=19,120) – all included pts with recent CVA and TIA. (total n= 23,363)

Influenza vaccination status was determined in 23,110 patients.

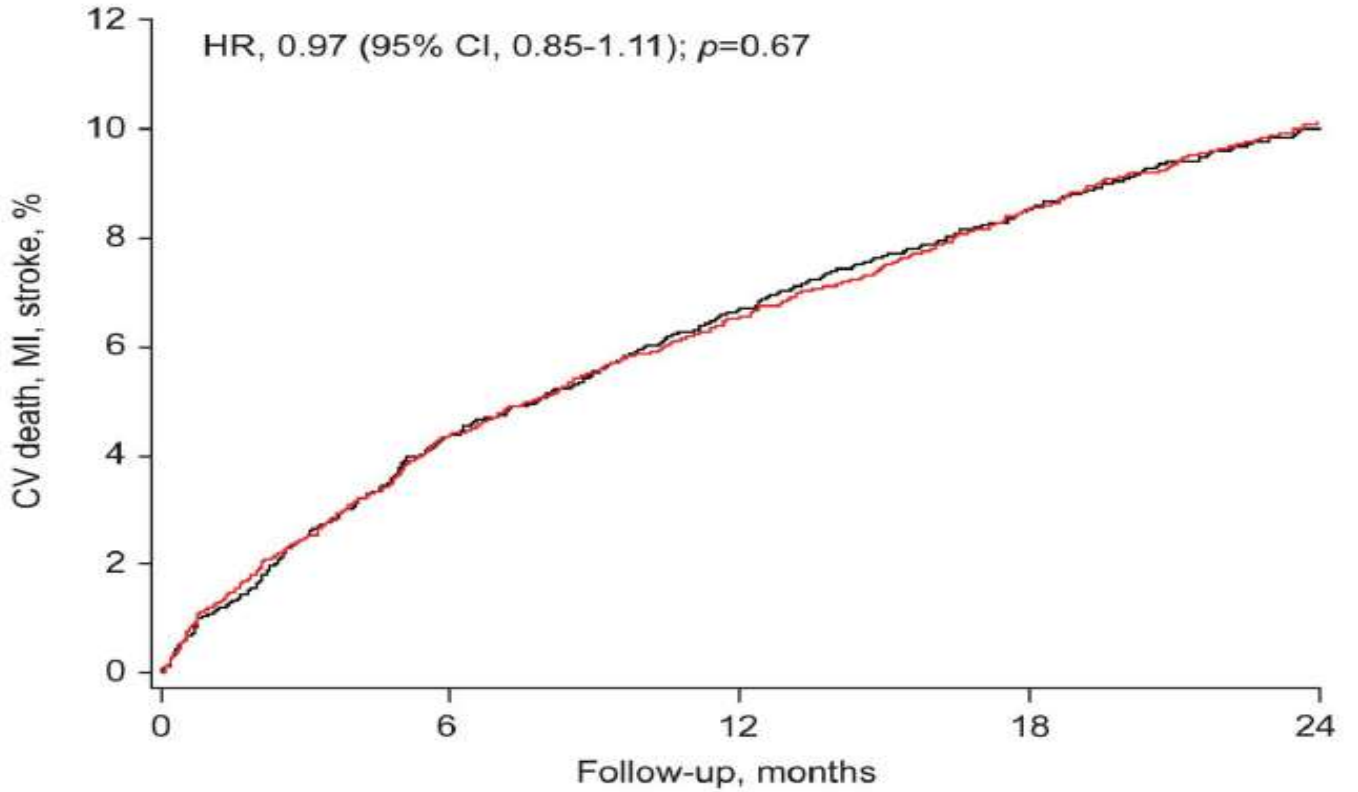
Primary outcome: composite of nonfatal myocardial infarction, nonfatal stroke, or vascular death up to 2 years.

Secondary outcome: myocardial infarction and stroke separately

Lavallee, P, Labreuche, J. et al. Neurology June 2014;82:1905-1913

Influenza vaccination and CV risk in patients with recent TIA & CVA

Figure 2 Cumulative incidence curve of cardiac death, myocardial infarction, and stroke by influenza vaccination use in propensity score–matched sample

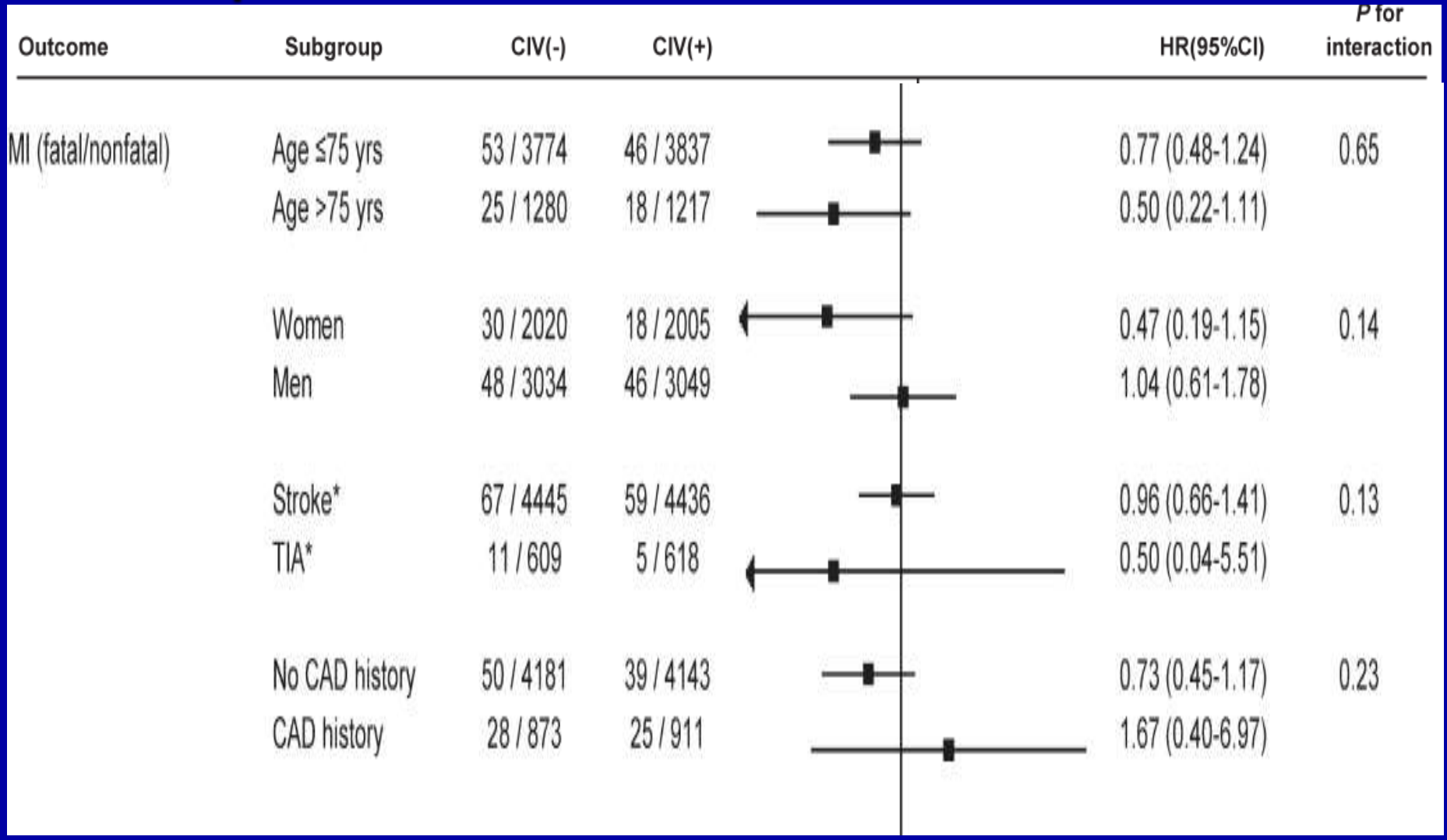


Number of patients at risk:

No influenza vaccination	5054	4730	4566	4406	3251
Influenza vaccination	5054	4753	4590	4435	3271

Lavallee, P, Labreuche, J. et al. Neurology June 2014;82:1905-1913

Influenza vaccination and CV risk in patients with recent TIA & CVA



Outcome	Subgroup	CIV(-)	CIV(+)	HR(95%CI)	*P* for interaction
MI (fatal/nonfatal)	Age ≤75 yrs	53 / 3774	46 / 3837	0.77 (0.48-1.24)	0.65
	Age >75 yrs	25 / 1280	18 / 1217	0.50 (0.22-1.11)	
	Women	30 / 2020	18 / 2005	0.47 (0.19-1.15)	0.14
	Men	48 / 3034	46 / 3049	1.04 (0.61-1.78)	
	Stroke*	67 / 4445	59 / 4436	0.96 (0.66-1.41)	0.13
	TIA*	11 / 609	5 / 618	0.50 (0.04-5.51)	
	No CAD history	50 / 4181	39 / 4143	0.73 (0.45-1.17)	0.23
	CAD history	28 / 873	25 / 911	1.67 (0.40-6.97)	

Lavallee, P, Labreuche, J. et al. Neurology June 2014;82:1905-1913

Influenza vaccination and CV risk in patients with recent TIA & CVA

Bale/Doneen Discussion Points of this observational study –

1. No information on lifestyle or socioeconomic status

2. Previously – ONTARGET and TRANSCENT (n=31,546) with history of vascular disease and 20% with TIA or CVA or DM showed a 31-48% reduction of major vascular events with the influenza vaccine

3. In this study – cardioembolic stroke was an exclusion criteria in both the PERFORM and OPTIC registry – cannot exclude influenza vaccine benefit in that group.

4. Majority taking antithrombotic therapies, antihypertensive therapies and lipid-lowering drugs and had regular follow-up visits – well controlled so question if vaccine would show additive benefit.

Lavallee, P, Labreuche, J. et al. Neurology June 2014;82:1905-1913

Fatty Fish and dementia risk

Fatty Fish reduces memory loss risk in non Apo E 4 carriers

Compare lean fish vs fatty fish (tuna or other fish) intake with dementia, Alzheimer disease (AD) and vascular dementia (VaD) in relation to Apo E 4 status in the cardiovascular health Cognition Study (CHCS). Ave f/u 5.4 yrs, mean age 64 years.

Lean fish had no benefit but fatty fish more than twice per week was associated with a 28% reduction in risk of dementia and a 41% in AD compared to those who ate it only once per month.

Huang, T.L., Zandi, P.P. et al. Neurology 2005, 65:1409-1414.

Fatty Fish reduces memory loss risk in non Apo E 4 carriers

No. of servings/wk	n	Events/person-yr	Model 1* HR	Model 1* 95% CI	Model 2† HR	Model 2† 95% CI
APOE ε4 positive						
<0.25	59	14/311	1		1	
0.25–2	160	40/775	1.07	0.58–1.98	1.23	0.66–2.30
2–4	151	34/805	0.99	0.52–1.89	1.06	0.55–2.05
≥4	104	23/553	0.91	0.44–1.88	1.03	0.49–2.16
APOE ε4 negative						
<0.25	206	41/1022	1		1	
0.25–2	561	76/3064	0.72	0.46–1.12	0.85	0.54–1.33
2–4	490	69/2691	0.59‡	0.36–0.95	0.72	0.44–1.17
≥4	313	33/1791	0.54‡	0.31–0.95	0.69	0.91–1.22

* Model 1: controlling for age at baseline, minority status, sex, presence of *APOE* ε4, energy, BMI, region, fried fish.
† Model 2: controlling also for education and income.
‡ $p < 0.05$.

Huang, T.L., Zandi, P.P. et al. Neurology 2005. 65:1409-1414.

High Dose Statins and DM Risk

High Potency Statins Increase New Onset DM Risk Greater Than Lower Potency Statins

- 136,966 recently hospitalized for CVD pts; ≥40 yo; new statin rx btw 1/97-4/11.
- Compared new-onset DM incidence in users of higher vs. lower potency statins.

Dormuth, C. R., et. al. (2014). Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *Bmj, 348*. doi: 10.1136/bmj.g3244

High Potency Statins Increase New Onset DM Risk Greater Than Lower Potency Statins

- High potency statin defined as: rosuvastatin ≥10mg, atorvastatin ≥20 mg, simvastatin ≥40 mg
- DM dx by hospitalization or diabetic medication

Dormuth, C. R., et. al. (2014). Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *Bmj, 348*. doi: 10.1136/bmj.g3244

High Potency Statins Increase New Onset DM Risk Greater Than Lower Potency Statins

- Propensity scores utilized an algorithm that prioritizes thousands of drug, diagnostic, procedure, and demographic variables according to their potential to cause bias in the estimate of an exposure-outcome association.

- After estimating propensity scores, patient with the smallest 5% and largest 5% propensity scores were trimmed from the analysis.

Dormuth, C. R., et. al. (2014). Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *Bmj, 348*. doi: 10.1136/bmj.g3244

High Potency Statins Increase New Onset DM Risk Greater Than Lower Potency Statins

- First 2 years there was a significant increase risk of new onset diabetes with higher vs lower potency

  RR-1.15 (95% CI-1.05 to 1.26)

- Highest risk was in the first 4 months

  RR- 1.26 (95% CI-1.07 to 1.47)

Dormuth, C. R., et. al. (2014). Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *Bmj, 348*. doi: 10.1136/bmj.g3244

High Potency Statins Increase New Onset DM Risk Greater Than Lower Potency Statins

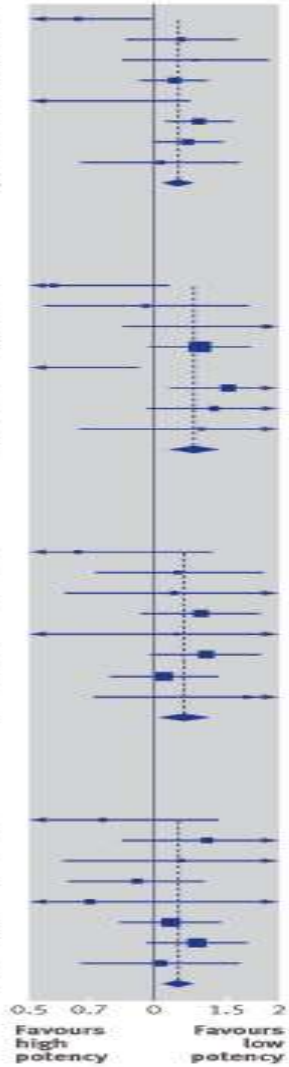
Authors point out that in stable CAD patients there is no difference in serious adverse events or all cause mortality comparing high potency to lower potency statins.

There is a harmful association between statin potency and new diabetes which should be considered when starting statin rx in patient with known CVD.

Dormuth, C. R., et. al. (2014). Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *Bmj, 348*. doi: 10.1136/bmj.g3244

High Potency Statins Increase New Onset DM Risk

Subgroup	Low dose statins Cases	Low dose statins Controls	High dose statins Cases	High dose statins Controls	Rate ratio (95% CI)	Weight (%)	Rate ratio (95% CI)
≤2 years of current therapy							
Alberta	68	531	90	944		5.2	0.66 (0.44 to 0.98)
CPRD	103	1064	247	2266		9.2	1.17 (0.87 to 1.57)
Manitoba	47	447	170	1514		5.2	1.27 (0.85 to 1.88)
Marketscan	180	1853	502	4652		25.3	1.12 (0.94 to 1.34)
Nova Scotia	18	125	23	216		1.3	0.54 (0.24 to 1.21)
Ontario	236	2658	675	6196		26.5	1.29 (1.08 to 1.53)
Quebec	260	2775	507	4681		23.1	1.21 (1.00 to 1.46)
Saskatchewan	42	378	188	1585		4.3	1.04 (0.67 to 1.61)
Total	954	9831	2402	22 054		100.0	1.15 (1.05 to 1.26)
Test for heterogeneity: χ^2=13.32, df=7, P=0.06, I^2=47%							
Test for overall effect: z=3.00, P=0.003							
≤120 days of current therapy							
Alberta	26	159	31	306		6.3	0.57 (0.30 to 1.07)
CPRD	30	282	50	495		7.9	0.96 (0.55 to 1.69)
Manitoba	9	113	52	425		3.9	1.89 (0.85 to 4.20)
Marketscan	86	773	195	1452		33.0	1.29 (0.98 to 1.70)
Nova Scotia	9	46		56		1.1	0.20 (0.04 to 0.91)
Ontario	62	758	197	1696		23.8	1.52 (1.10 to 2.11)
Quebec	57	550	123	959		18.7	1.40 (0.97 to 2.02)
Saskatchewan	17	137	69	442		5.3	1.31 (0.66 to 2.60)
Total	296	2818	720	5831		100.0	1.26 (1.07 to 1.47)
Test for heterogeneity: χ^2=15.22, df=7, P=0.03, I^2=54%							
Test for overall effect: z=2.84, P=0.004							
>120 to ≤365 days of current therapy							
Alberta	16	178	20	285		4.2	0.66 (0.31 to 1.38)
CPRD	37	387	91	849		10.7	1.15 (0.72 to 1.83)
Manitoba	21	177	60	541		6.4	1.12 (0.62 to 2.04)
Marketscan	53	625	177	1625		21.7	1.30 (0.94 to 1.80)
Nova Scotia		34	9	70		0.9	1.13 (0.23 to 5.47)
Ontario	75	888	242	2262		26.1	1.33 (0.99 to 1.80)
Quebec	99	951	174	1609		26.9	1.06 (0.79 to 1.42)
Saskatchewan	11	147	54	509		3.2	1.68 (0.72 to 3.94)
Total	315	3387	827	7750		100.0	1.19 (1.02 to 1.38)
Test for heterogeneity: χ^2=4.62, df=7, P=0.71, I^2=0%							
Test for overall effect: z=2.20, P=0.03							
>365 to ≤730 days of current therapy							
Alberta	26	194	39	353		5.5	0.75 (0.40 to 1.41)
CPRD	36	395	106	922		9.7	1.35 (0.84 to 2.17)
Manitoba	17	157	58	548		5.3	1.16 (0.61 to 2.21)
Marketscan	41	455	130	1575		15.8	0.91 (0.63 to 1.32)
Nova Scotia	6	45	10	90		1.5	0.70 (0.21 to 2.34)
Ontario	99	1012	236	2238		28.9	1.10 (0.84 to 1.45)
Quebec	104	1274	210	2113		29.2	1.27 (0.97 to 1.67)
Saskatchewan	14	94	65	634		4.0	0.55 (0.26 to 1.15)
Total	343	3626	854	8473		100.0	1.08 (0.93 to 1.25)
Test for heterogeneity: χ^2=8.05, df=7, P=0.33, I^2=13%							
Test for overall effect: z=0.98, P=0.33							



CPRD=UK Clinical Practice Research Datalink

Rate ratios for new onset diabetes within two years of starting higher potency or lower potency statins after a major cardiovascular event or procedure (as-treated analysis)

Dormuth, C. R., et. al. (2014). *Bmj, 348*. doi: 10.1136/bmj.g3244

BDM Thoughts – statins & DM

Higher potency statins do appear to slightly increase the risk of new-onset DM. Lower potency statins are reasonable choices when initiating rx in CVD pts without significant inflammation.

Lower potency statins should be preferred in BDM defined 'primary' prevention. This is another issue with the current guidelines.

Higher incidence of new onset DM during the first four mos indicates poor screening for IR during hospitalization; statin isn't going to trigger DM that quickly.

Dormuth, C. R., et. al. (2014). *Bmj, 348*. doi: 10.1136/bmj.g3244

Statins and decreased risk of tooth loss

Statins associated with less tooth loss

5 year population-based follow-up study of tooth loss comparing participants treated with statins (n=134) with those not on statins.

Adjusted for age and sex.

Statins associated with reduced tooth loss during the follow-up period 0.70, 95%CI [0.52-1.01], P=0.04

Long term statin use may have beneficial effect of protecting against tooth loss.

Meisel, P.,, Kroemer, H et al. Statins and tooth loss. J. Periodontaol June 2014.

Statins associated with less tooth loss

Limitations:

All statin use grouped together

Baseline statin use assessed and again a 5 years

BDM Conclusions:

-CRP was assessed – if >2 – risk was sign. higher for tooth loss by 22%

-inflammatory cascade is a systemic issue

-statins are (by class) and excellent anti-inflammatory medication.

-tooth loss is often a manifestation of system ill health and periodontal health.

Meisel, P.,, Kroemer, H et al. Statins and tooth loss. J. Periodontaol June 2014.

Conclusion/Upcoming Events

Washington State Dental Association

Friday June 13th – Belleview, WA

CHL Symposium

September 12-13 – Cleveland, OH

AAOSH Conference

September 26-27 – St. Louis, MO

Bale/Doneen Reunion

October 17-19 – Canyon Ranch, Tucson, AZ

Bale/Doneen Preceptorship

November 7-9 – San Antonio, TX