Bale/Doneen Live Chat Session

December 7, 2011

5:30-6:30 pm PST

Bradley Bale, MD

Intention of the live chats

- New data and slides
- Discuss “hot” topics
- Case studies from attendees
- Review upcoming meetings
- Open discussion for remaining

HPV Cancer Genotype Associated with History of CV Events

- 2,450 women mean age 38; 60 were post MI or stroke; 47% + for HPV on vaginal swab
- OR **for hx of CV event being + for HPV vs. –**

  2.30 (1.27-4.16) p=0.006
- Compared risk with HPV cancer and non-cancer genotypes: only significant for cancer genotype

  OR -2.86 (1.43-5.70), 0.003
- Adjusted for: age, race, smoking, alcohol, sex behavior, lung, liver, thyroid disease, eGFR, STD, cancer , BP, DM, met synd, CRP, MACR, BP and lipid meds

Kuo H-K, et. al. *J Am Coll Cardiol* 11/1/2011; 58: 2001-2006.

Presence of Plaque Predicts Event Risk

- 480 acute chest pain pts; mean age 55 years; 65% female; all received contrast-enhanced CTA; followed 1 yr for MACE

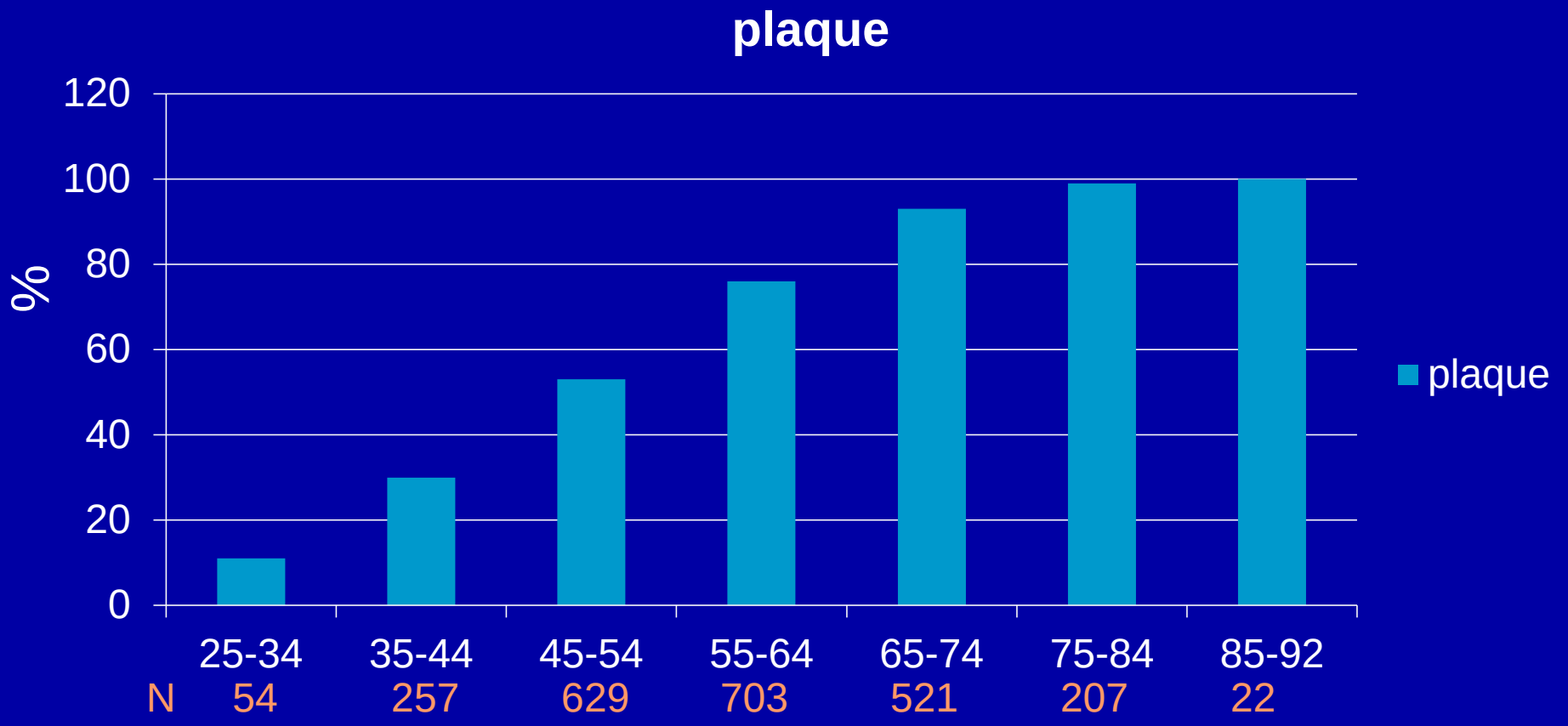
- 70 pts. suffered MACE

- HR using pts. with no plaque as reference – women vs men:
  with >4 coronary segments 113.9 vs 66.9, $p<0.01$
  with any plaque 49.3 vs 39.1, $p<0.001$

- Chest pain coupled with plaque at greatly increased risk for a major cardiovascular event

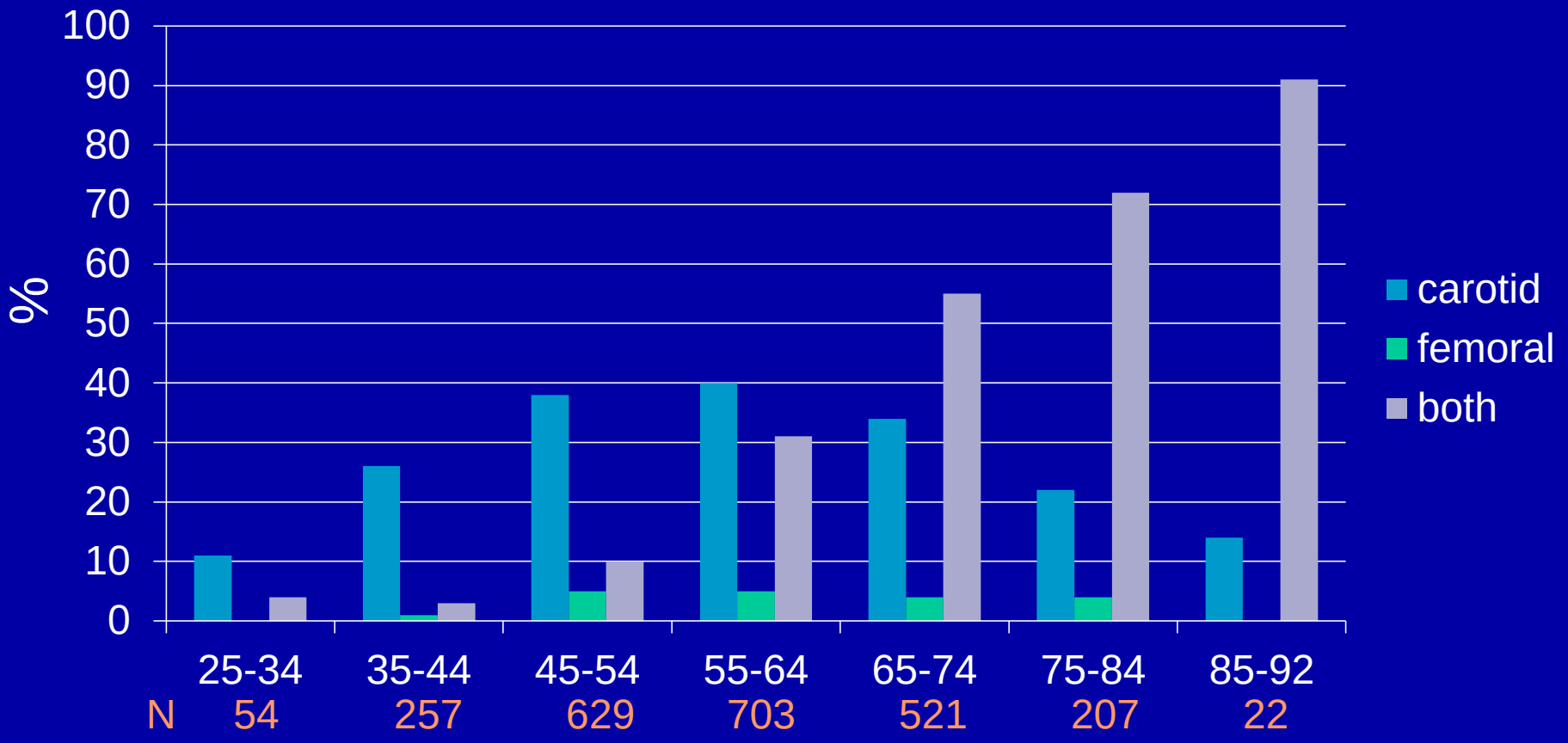
Nance JW Jr, et al. Radiological Society of North America 2911 Scientific Assembly and Annual Meeting; December 1, 2011; Chicago, IL. Abstract MSVA51-17.

Prevalence of Plaque in Carotid and Femoral Beds



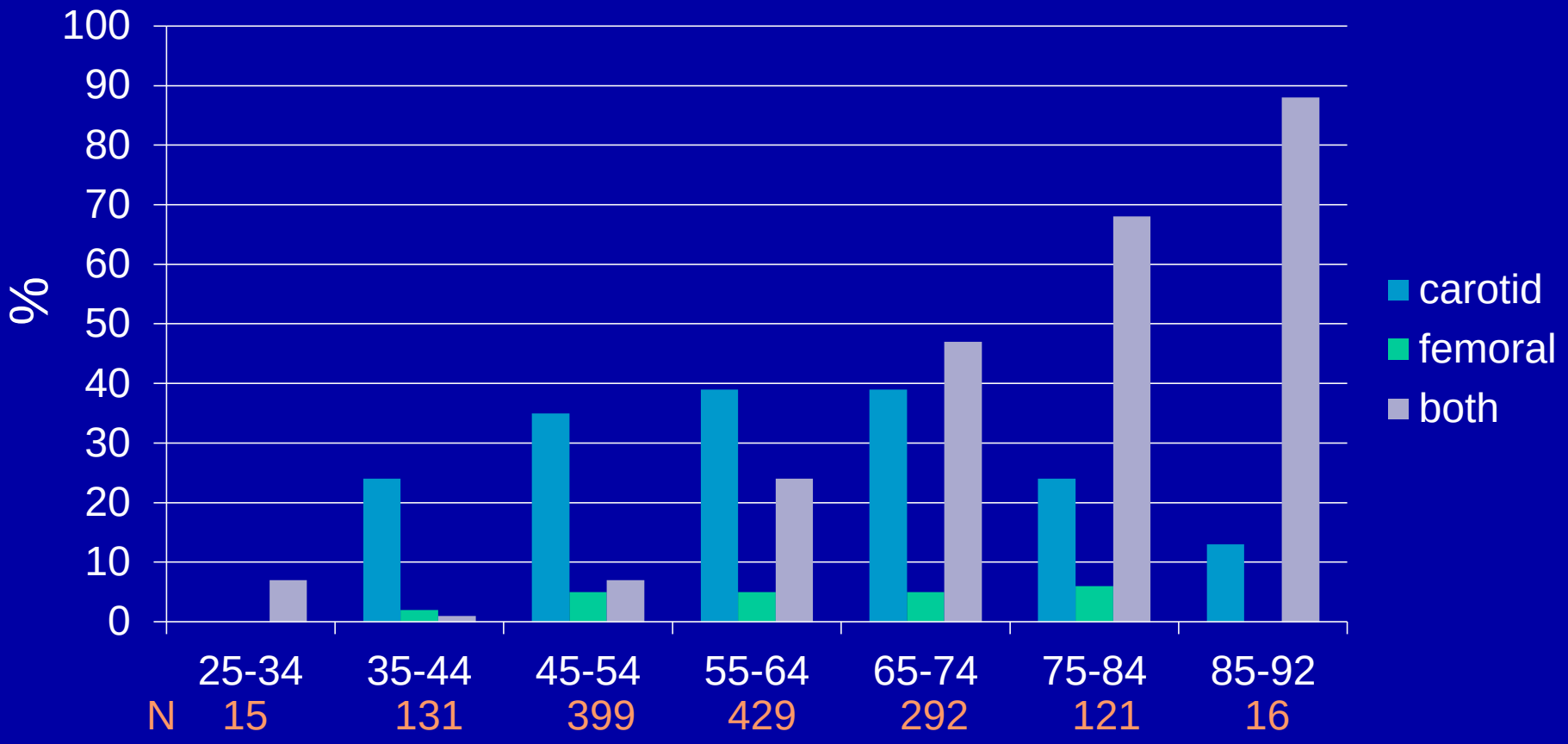
2,393 asx'ic patients (59% female) from a multispecialty clinic sent in for screening

Prevalence of Plaque Relative to Carotid and Femoral Beds



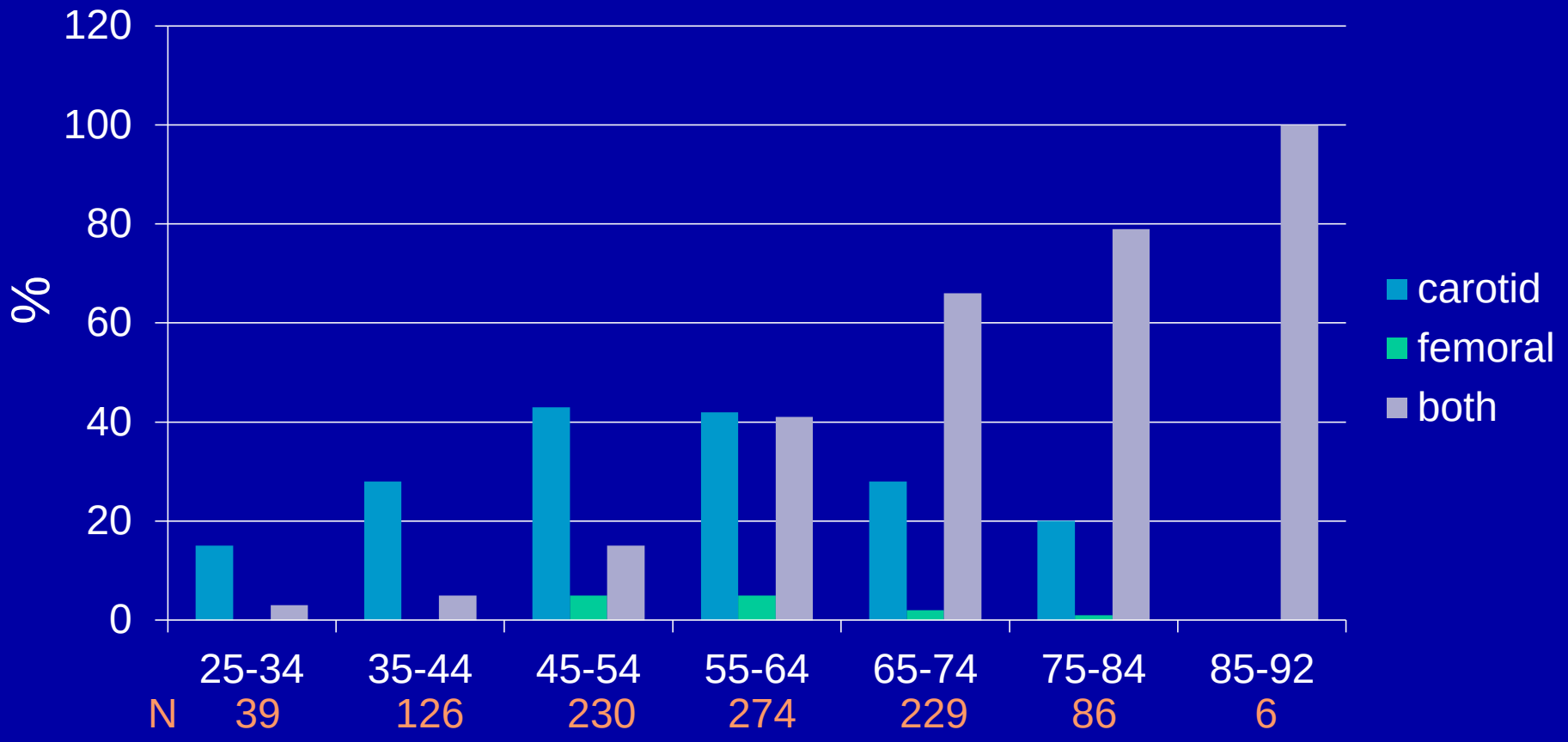
2,393 asx'ic patients (59% female) from a multispecialty clinic sent in for screening

Prevalence of Plaque Relative to Carotid and Femoral Beds - Females



1,403 asx'ic female pts from a multispecialty clinic sent in for screening

Prevalence of Plaque Relative to Carotid and Femoral Beds - Males



990 asx'ic male pts from a multispecialty clinic sent in for screening

CCA IMT Progression Predicts Stroke Risk

- 5,028 MESA subjects; CCA IMT taken in area free of plaque; rate of change (mm/year)= first result minus second result divided by number of months btw measurements
- 42 -1st strokes; median 3 yr. ; average age 64; 52% female
- IMT rate of change significantly associated with incident stroke
  HR - 1.23 per 0.05 mm/year (95%CI, 1.02–1.48)
- CCA IMT progression is associated with incident stroke

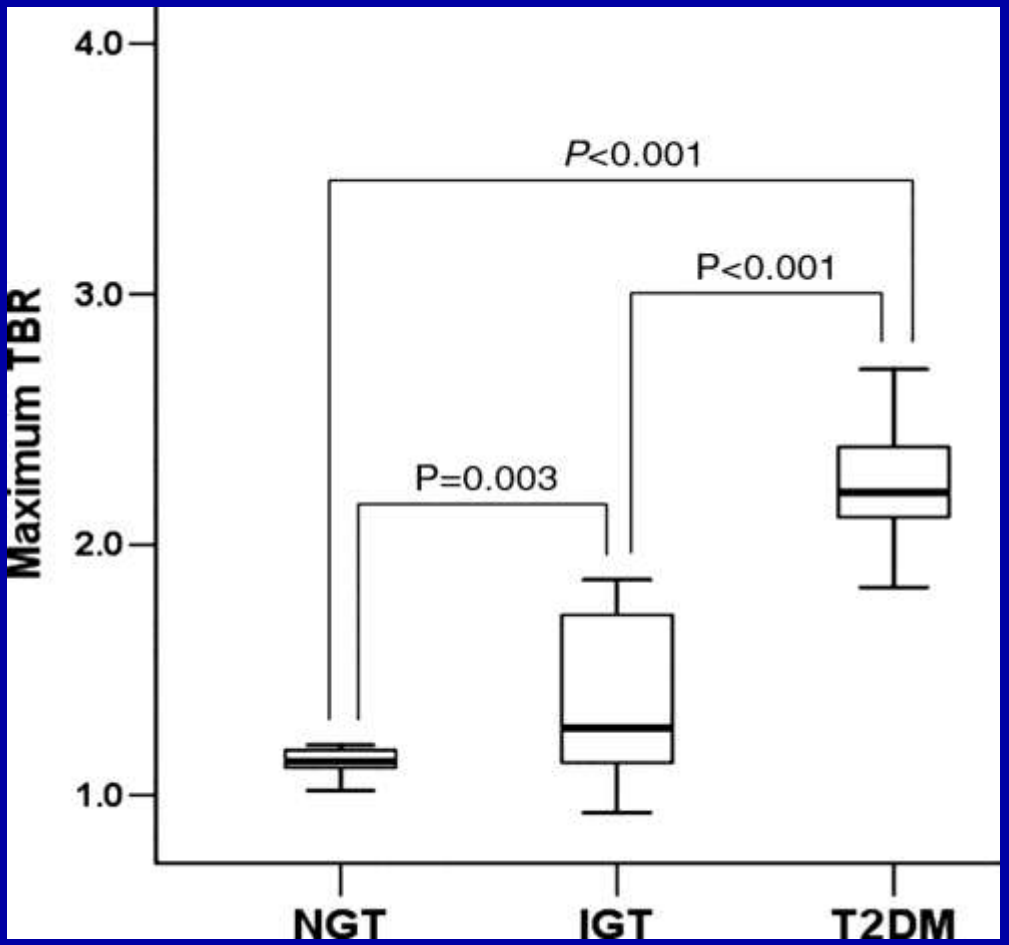
Polak J F et al. Stroke 10/2011;42:3017-3021

Vascular Inflammation in Patients With Impaired Glucose Tolerance & DM

- Inflammation assessed with FDG-PET in carotids; 90 pts;30 normal GTT;30 impaired GTT; 30 T2DM
- The inflammatory values were significantly increased in pts with impaired GTT and T2DM compared with normal
- Pts with metabolic syndrome also had increased values compared with those without metabolic syndrome
- Impaired GTT and T2DM are associated with vascular inflammation in carotid atherosclerosis

Kim T N et al. Circ Cardiovasc Imaging 2010;3:142-148

Carotid Artery Inflammation is Elevated in Insulin Resistant Individuals



Maximum TBR by glucose tolerance group.

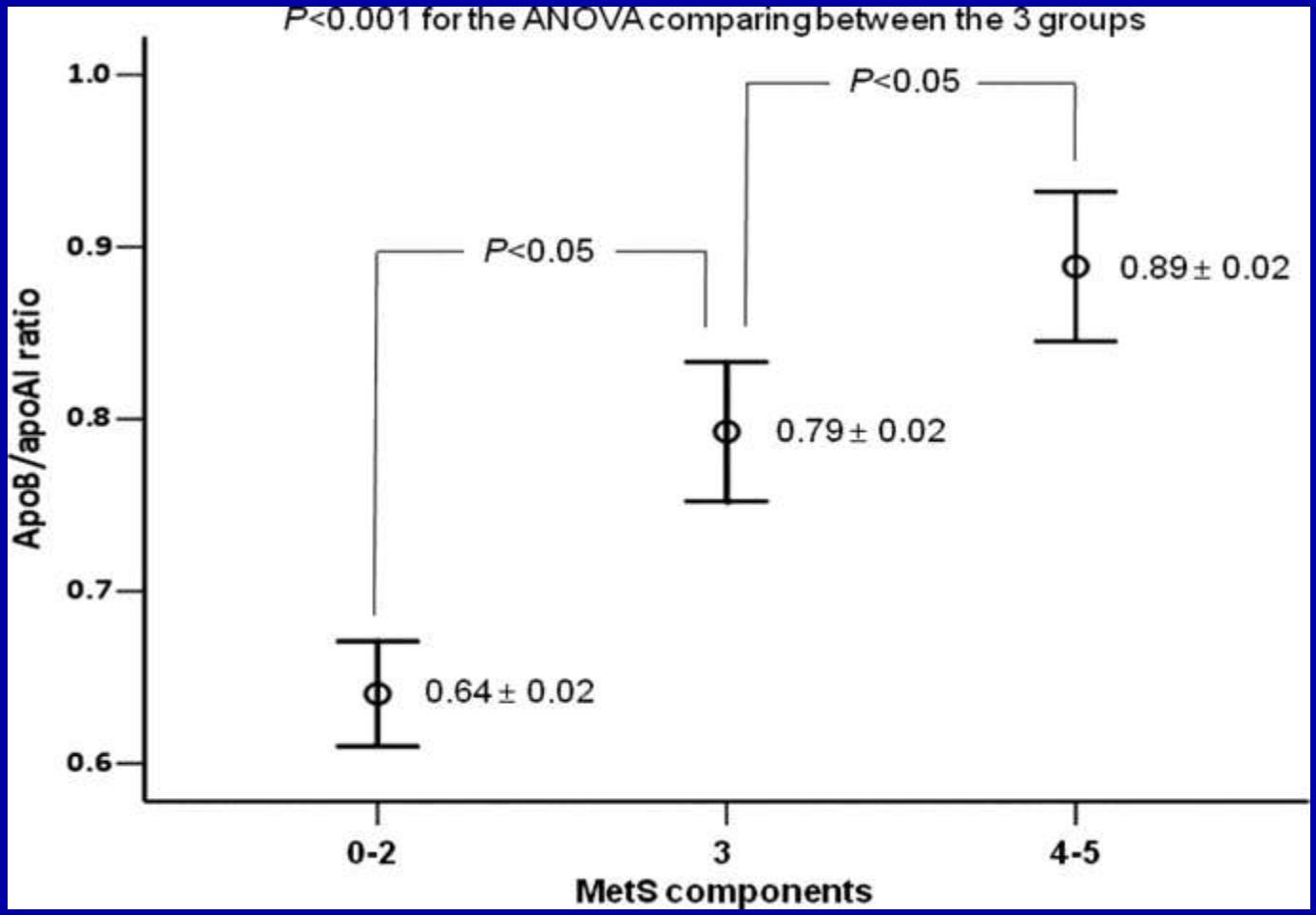
American Heart Association
Learn and Live

Kim T N et al. Circ Cardiovasc Imaging 2010;3:142-148

Dale Doneen METHOD

apoB/ApoA1 Ratio Increases with Metabolic Syndrome Components

apoB/AI ratio according to the severity of MetS components.



Park J et al. Stroke 2011;42:3040-3046

Lp (a) Associated with Increased CV Risk in African Americans (AA)

- ARIC data; lipo (a) 3,467 AA; 9,851 Caucasians; followed 20 years
- 676 CVD events in AA; 1,821 in whites
- Lipo (a) was at least as predictive in AA; there was a wider range of levels in AA

Virani SS, et. al. *Circulation* 11/29/2011; DOI:10.1161/?CIRCULATIONAHA.111.045120. Available at: http://circ.ahajournals.org

Lp (a) Associated with Increased CV Risk in African Americans

Table 2: Hazard ratios* for incident CVD events for race-specific Lp(a) quintiles.

African Americans:

	HR (95% CI); Number of Events					
Incident Events	Quintile 1 0.1–≤6.1 mg/dl	Quintile 2 >6.1–≤10.3 mg/dl	Quintile 3 >10.3–≤15.8 mg/dl	Quintile 4 >15.8–≤24 mg/dl	Quintile 5 >24 mg/dl	p for linear trend
CVD	Reference; 122	1.008 (0.78–1.31); 115	1.21 (0.95–1.55); 142	1.10 (0.85–1.41); 131	1.35 (1.06–1.74); 166	0.0004
CHD	Reference; 87	1.03 (0.76–1.39); 82	1.24 (0.92–1.66); 104	1.07 (0.79–1.44); 93	1.27 (0.94–1.71); 115	0.009
Ischemic strokes	Reference; 49	0.95 (0.63–1.43); 45	1.21 (0.82–1.78); 57	1.09 (0.73–1.63); 53	1.60 (1.10–2.34); 79	0.0004

Caucasians:

	HR (95% CI); Number of Events					
Incident Events	Quintile 1 0.1–≤1.5 mg/dl	Quintile 2 >1.5–≤3.1 mg/dl	Quintile 3 >3.1–≤6.0 mg/dl	Quintile 4 >6.0–≤13.5 mg/dl	Quintile 5 >13.5 mg/dl	p for linear trend
CVD	Reference; 383	0.94 (0.81– 1.09); 327	1.01 (0.87–1.17); 339	1.05 (0.90–1.22); 363	1.27 (1.10–1.47); 409	0.001
CHD	Reference; 330	0.91 (0.78–1.08); 274	0.99 (0.84–1.16); 285	1.09 (0.93–1.28); 322	1.28 (1.10–1.50); 353	0.002
Ischemic strokes	Reference; 77	1.03 (0.74–1.44); 72	1.17 (0.85–1.62); 81	0.87 (0.62–1.23); 64	1.27 (0.92–1.76); 86	0.25

*Adjusted for age, gender, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.
HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

Virani SS, et. al. *Circulation* 11/29/2011; DOI:10.1161/?CIRCULATIONAHA.111.045120.
Available at: http://circ.ahajournals.org

Lp (a) Associated with Increased CV Risk in African Americans

Table 4: Hazard ratios* for incident CVD events per 10-mg/dl increase in Lp(a).

African Americans:

	HR (95% CI); Number of Events				
Incident Events	≤10 mg/dl	>10–≤20 mg/dl	>20–≤30 mg/dl	>30 mg/dl	p for linear trend
CVD	Reference; 228	1.08 (0.89–1.30); 217	1.16 (0.92–1.46); 120	1.58 (1.24–2.01); 111	<0.0001
CHD	Reference; 164	1.06 (0.85–1.32); 155	1.17 (0.89–1.53); 88	1.33 (1.00–1.78); 74	0.008
Ischemic strokes	Reference; 90	1.14 (0.85–1.54); 89	1.15 (0.80–1.64); 49	2.12 (1.48–3.03); 55	<0.0001

Caucasians:

	HR (95% CI); Number of Events				
Incident Events	≤10 mg/dl	>10–≤20 mg/dl	>20–≤30 mg/dl	>30 mg/dl	p for linear trend
CVD	Reference; 1265	1.25 (1.11–1.41); 340	1.27 (1.06–1.51); 137	1.42 (1.12–1.79); 79	0.014
CHD	Reference; 1078	1.29 (1.13–1.47); 300	1.35 (1.12–1.63); 124	1.35 (1.04–1.75); 62	0.14
Ischemic strokes	Reference; 270	1.05 (0.79–1.39); 61	1.11 (0.74–1.67); 27	1.65 (1.04–2.61); 22	0.014

*Adjusted for age, gender, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.
Abbreviations as in Table 2.

Virani SS, et. al. *Circulation* 11/29/2011; DOI:10.1161/?CIRCULATIONAHA.111.045120. Available at: http://circ.ahajournals.org

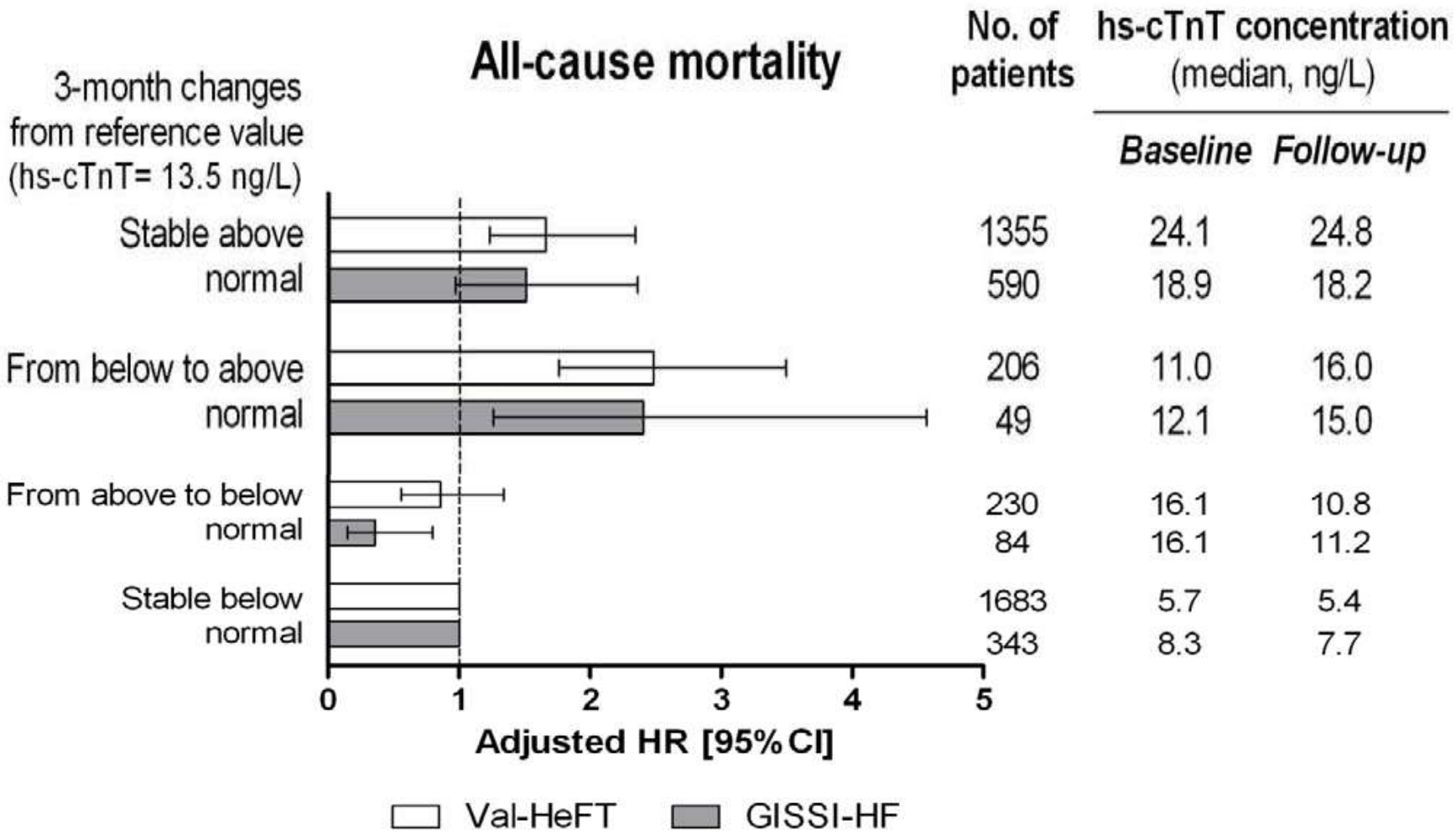
High Sensitivity Cardiac Troponin T (hscTnT) Predicts Mortality Risk in HF Patients

- 5,284 HF pts.; hscTnT measured at baseline and 3-4 mos. later
- All cause mortality rates calculated per 100 person-years; 820 deaths within 2-4 yrs.
- Increased hscTnT levels were associated with mortality:

  HR 1.88 (95% CI1.50-2.35) - after adjustment for conventional risk factors and baseline levels of hs-cTnT and NT-proBNP.

Serge Masson, et. al. Circulation 12/1/2011
http://circ.ahajournals.org/content/early/2011/12/02/CIRCULATIONAHA.111.044149

High Sensitivity Cardiac Troponin T (hscTnT) Predicts Mortality Risk in HF Patients



Serge Masson, et. al. Circulation 12/1/2011
http://circ.ahajournals.org/content/early/2011/12/02/CIRCULATIONAHA.111.044149

PD Pathogens Found in Carotid Atheroma

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

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

PD Pathogens Found in Carotid Atheroma

- Potential mechanisms of enhancing atherosclerosis
- Increasing adherence of leukocytes to the vascular endothelium by increasing (VCAM)-I, (ICAM)-I and E-selectine
- Increasing the migration of monocytes through endothelial cells via increased MCP-1
- *Promoting the transformation of macrophages into foam cells*
- *Inducing a pro-coagulant effect*
- *Favoring the rupture of plaque through the release of metalloproteinases*

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

9p21 Increases Mortality Risk in Elderly

- 1,095 deceased pts > 70; without known CAD prior to death
- Examined relationship of possessing 9p21 *rs1333049 allele* and risk of dying
- This *allele* was associated with all-cause mortality

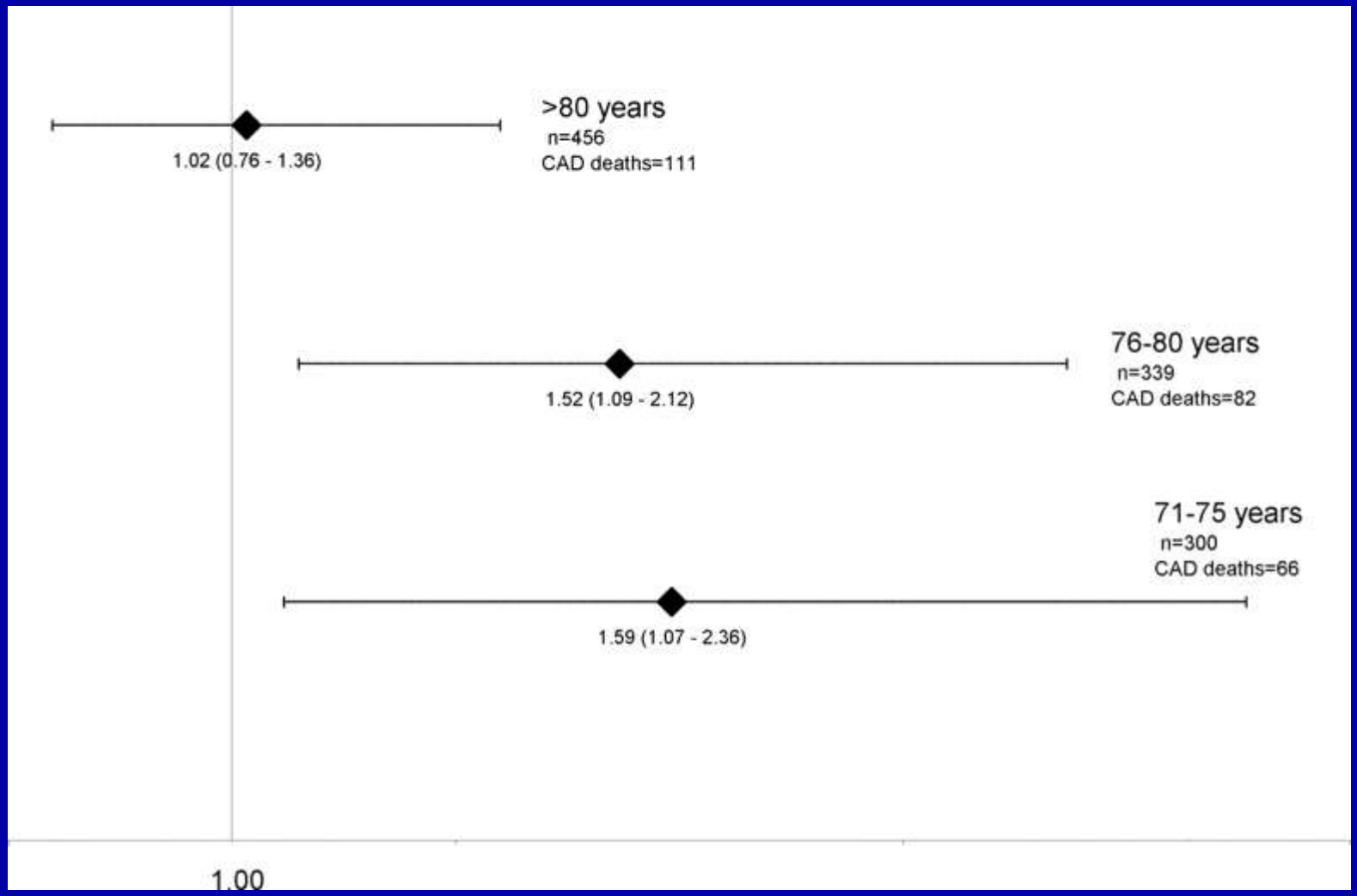
  HR 1.19 (95% CI, 1.08 –1.30)
- Also associated with CAD mortality

  HR 1.29 (95% CI, 1.08 –1.56) independent of CAD risk factors.
- Those 71 – 80 yo at enrollment who died of CAD, FRS predicted 21%; adding the allele predicted 27%

Dutta A et al. *Circ Cardiovasc Genet. 10/2011;4:542-548.*

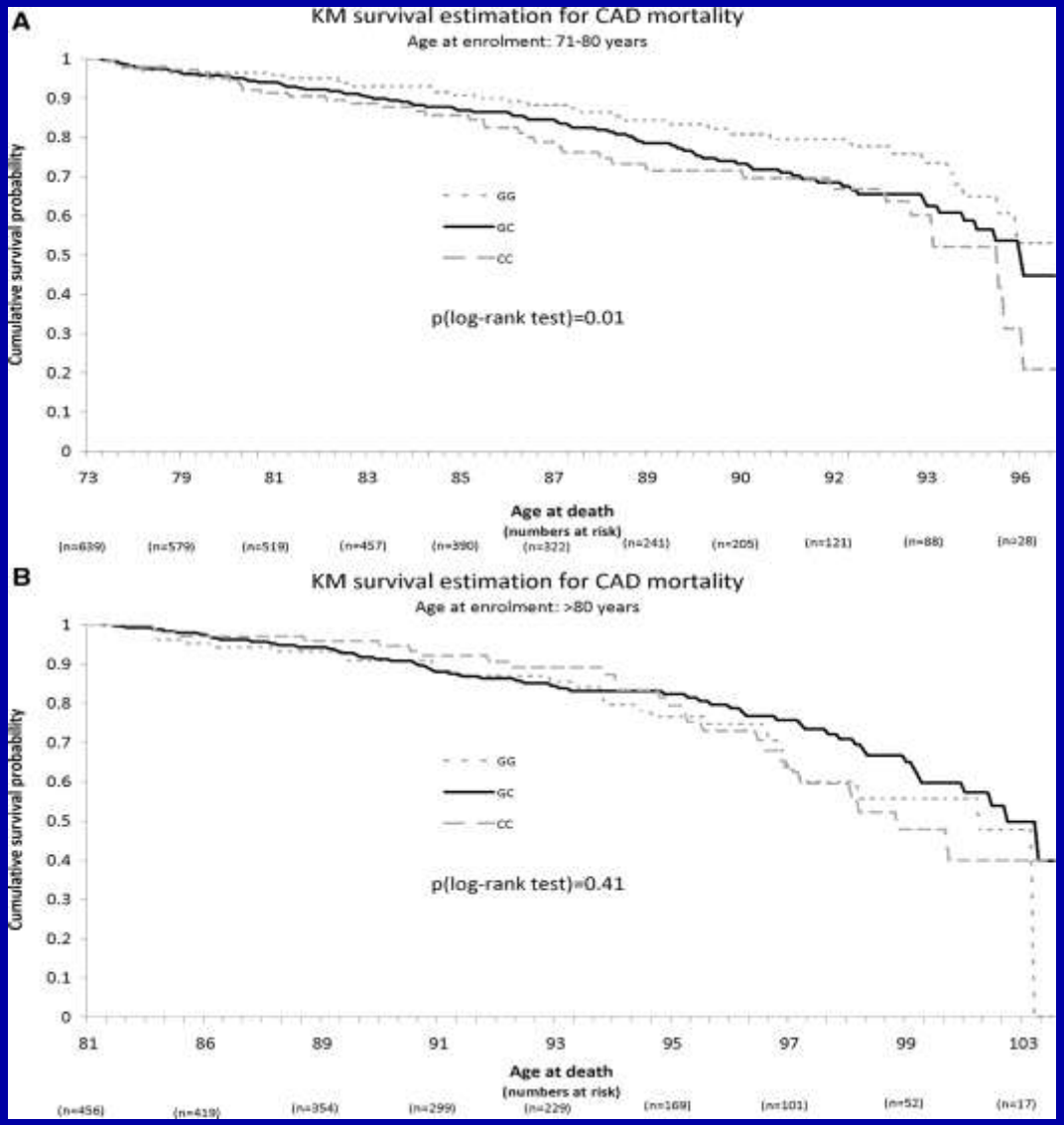
9p21 Increases CAD Mortality Risk in Elderly

Age group–specific hazard ratio (HR) per C allele of rs1333049.



Dutta A et al. Circ Cardiovasc Genet 2011;4:542-548

Kaplan–Meier survival estimation (for coronary artery disease [CAD]–specific mortality) across genotypes of rs1333049 in different age groups.



Dutta A et al. Circ Cardiovasc Genet 2011;4:542-548

9p21 Associated with Stroke Risk

- 1,657 stroke pts (724 atherothrombosis, 466 lacunar infarction, and 462 hemorrhagic) ;1,664 controls; followed for median 4.5 yrs (317 recurrent strokes)
- After adjustment for vascular risk factors, homozygote GG had significant increased risk for strokes

  atherothrombotic 1.47-fold (95% CI, 1.11–1.89) *p=0.05*

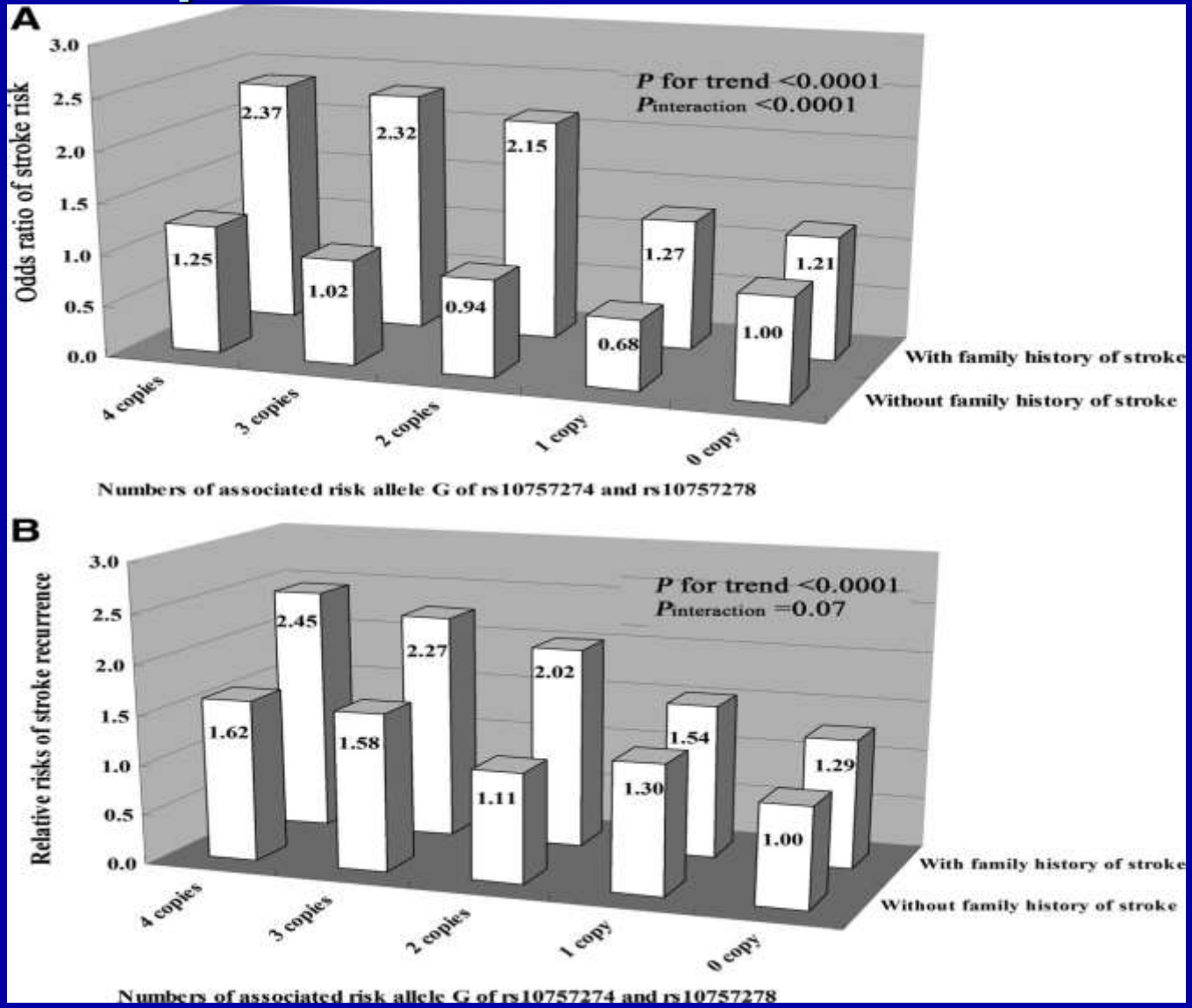
  hemorrhagic 1.60-fold (95% CI, 1.16 –2.15)p=0.04
- *Homozygote GG also a significant risk for recurrent stroke*

  RR 1.56 (95% CI,1.15–2.12) *p=0.005*
- Homozygote GG increased cardiovascular mortality

  RR 2.0 (95% CI, 1.26 –3.18)*p=0.003*
- *Family history was very influential in risk*

Weili Zhang, MD, PhD, et. al. ***Stroke. 2012;43:00-00***
doi: 10.1161/STROKEAHA.111.625442

9p21 and Stroke Risk



Weili Zhang, MD, PhD, et. al. ***Stroke. 2012;43:00-00***
doi: 10.1161/STROKEAHA.111.625442

Chocolate Associated with Lower Stroke Risk

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

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

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

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

White Fruits and Vegetables May Protect Against Stroke

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

HR, 0.91 (95% CI, 0.85– 0.97)

adjusted for age, sex, lifestyle, and dietary factors

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

Stroke Risk and Dietary Antioxidants

- 31,035 CVD-free & 5,680 with CVD; Swedish women; 49 to 83 yo; assessed antioxidant dietary intake; followed 12 yrs
- In CVD-free group: 988 ischemic, 226 hemorrhagic, 108 unspecified strokes
- In CVD group: 796 ischemic, 100 hemorrhagic, 111 unspecified strokes
- Multivariable HR of total stroke comparing the highest with the lowest quintile of antioxidant consumption:

  CVD-free 0.83 (95% CI, 0.70–0.99) *P for trend0.04*

  CVD - 0.90 (95% CI, 0.75–1.07) *P for trend0.30*
- *Multivariable HR for hemorrhagic stroke:*

  CVD - 0.55 (95% CI, 0.32– 0.95) *P for trend0.03*

Susanne Rautiainen, et. al. ***Stroke. 2012;43:00-00***
http://stroke.ahajournals.org/content/early/2011/11/30/STROKEAHA.111.635557

Stroke Risk and Dietary Antioxidants

Table 3. Relative Risk of Stroke by Quartiles of Total Antioxidant Capacity of Diet Among Women With a Cardiovascular Disease History at Baseline in the Swedish Mammography Cohort (n=5680)

Total Antioxidant Capacity of the Diet*					
Cohort With a CVD History	Q1	Q2	Q3	Q4	*P* for Trend
Total stroke					
No. of cases	272	248	233	245	
Person-time, y	13 780	14 370	14 445	14 529	
Age-adjusted HR	1.00	0.85 (0.71–1.00)	0.81 (0.68–0.97)	0.90 (0.76–1.07)	0.31
Multivariable HR†	1.00	0.86 (0.72–1.02)	0.82 (0.68–0.98)	0.90 (0.75–1.07)	0.30
Cerebral infarction					
No. of cases	206	197	188	205	
Age-adjusted HR	1.00	0.88 (0.73–1.08)	0.87 (0.71–1.06)	0.96 (0.79–1.17)	0.80
Multivariable HR†	1.00	0.90 (0.74–1.10)	0.87 (0.71–1.06)	0.96 (0.79–1.18)	0.82
Hemorrhagic stroke					
No. of cases	39	20	18	23	
Age-adjusted HR	1.00	0.48 (0.28–0.82)	0.44 (0.25–0.76)	0.56 (0.34–0.94)	0.03
Multivariable HR†	1.00	0.47 (0.27–0.82)	0.43 (0.25–0.76)	0.54 (0.32–0.93)	0.03

CVD indicates cardiovascular disease; Q, quartile; HR, hazard ratio.

*Total antioxidant capacity intake (μmol Trolox equivalents/d) was measured with the oxygen radical absorbance capacity assay.

†Adjusted for age, education, smoking, body mass index, physical activity, stroke, myocardial infarction, angina pectoris, atrial fibrillation, hypertension, hypercholesterolemia, diabetes, family history of myocardial infarction, aspirin use, dietary supplement use, and intakes of total energy, alcohol, and coffee.

Susanne Rautiainen, et. al. ***Stroke. 2012;43:00-00***
http://stroke.ahajournals.org/content/early/2011/11/30/STROKEAHA.111.635557

Effects of Weight Loss and Long-Term Weight Maintenance With Diets on CV Risk Factors

- 932 overwt. pts; 8wk. low cal diet for wt. loss; then 26 wk wt. maintenance diets; mix glycemic & protein high or low with control diet (five diet groups)
- Weight loss improved lipids, BP and hsCRP:

  wt. lost was 11.23 kg (95% CI 11.54 - 10.92) *P<0.001*
  hsCRP reduction was 1.15mg/L (95% CI 1.30-0.41) P<0.001
- Low vs high glycemic diet reduced hsCRP more:

  0.46 mg/L (95% CI 0.79-0.13) P<0.001
- Low vs high protein diet reduced hsCRP more:

  0.25 mg/L (95% CI 0.59- 0.17) P<0.001
- Diets had no significant effect on lipids or BP

Özlem Gögebakan, et. al. *Circulation 12/6/*2011;124:00-00
http://circ.ahajournals.org/content/early/2011/11/15/CIRCULATIONAHA.111.033274

Weight loss reduces CRP regardless of how the weight is lost

- 33 studies: 28 lifestyle and 5 surgical; lipo-suction not included

- Every one pound lost yields a 0.06 mg/L decrease in CRP; current study is 1 pound yields 0.05 mg/L

- Weight loss is an effective non-pharmacologic strategy to lower CRP

Selvin E et al. *Arch Intern Med 1/8*/2007; 167:31-39.

Effects of Long-Term Weight Maintenance With Diets on hsCRP

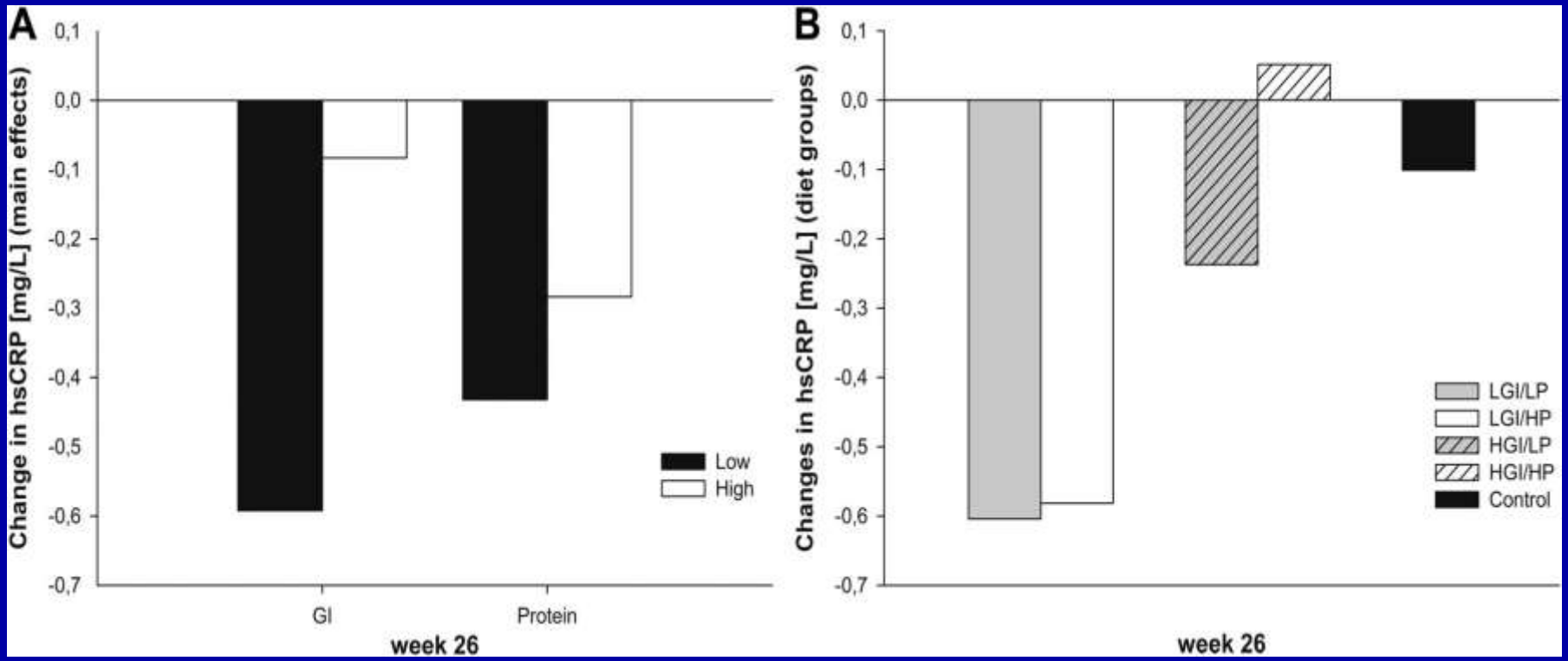


Figure 2. A, Changes of high-sensitivity C-reactive protein (hsCRP) between post–low-calorie diet (week 0) and postintervention (week 26). The values were normalized to post–low-calorie diet. For absolute values, see Tables I and II in the online-only Data Supplement. **B, Changes of hsCRP between post–low-calorie diet (week 0) and postintervention (week 26) for the combined low-glycemic-index** (LGI) diets (HP/LGI and LP/LGI) vs high-glycemic-index (HGI) diets (HP/HGI and LP/HGI) and for the combined high-protein (HP) (HP/ HGI and HP/LGI) vs the low-protein (LP) diets (LP/LGI and LP/HGI).

Özlem Gögebakan, et. al. *Circulation 12/6*/2011;124:00-00

http://circ.ahajournals.org/content/early/2011/11/15/CIRCULATIONAHA.111.033274

Bedtime Dosing of BP Medications Reduces Cardiovascular Risk in CKD

- 661 CKD pts.; randomized to all BP meds upon awakening or at least one at hs; follow-up 5.4 yrs.

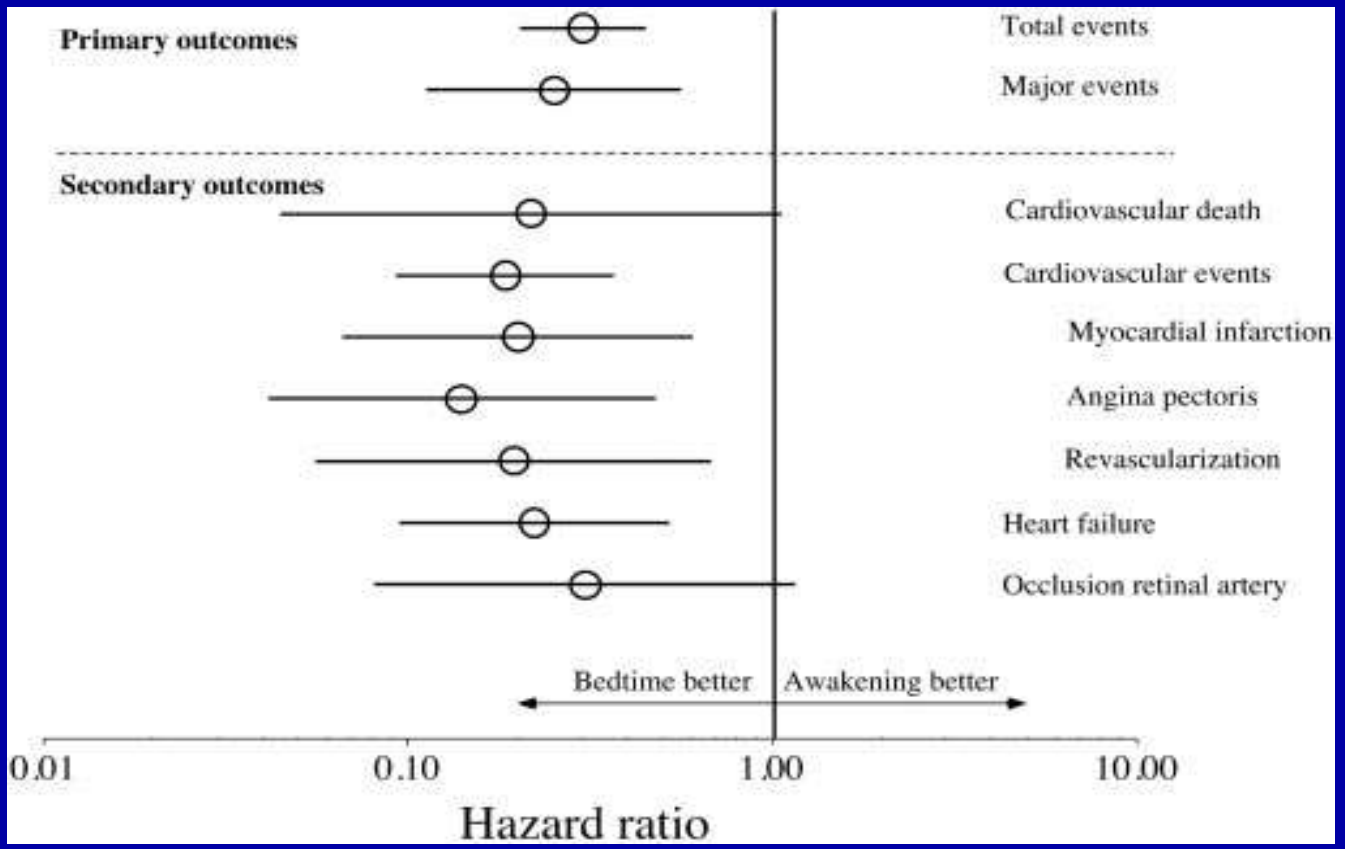
- Risk of a CV death, MI and stroke was dramatically lower in hs group

  adjusted HR 0.28 (95% CI 0.13 to 0.61) *p=0.001*

- Each 5-mmHg decrease in mean sleep-time systolic BP - 14% reduction CV event risk – *p=0.001*

Hermida RC, et. al. *J Am Soc Nephrol* 2011; DOI:10.1681/ASN.2011040361

Bedtime Dosing of BP Medications Reduces Cardiovascular Risk in CKD



Hermida RC, et. al. *J Am Soc Nephrol* 2011; DOI:10.1681/ASN.2011040361

High Dose Rosuvastatin versus Atorvastatin and CAD Regression

- 1,039 CAD pts; baseline & 2 yr. IVUS; rx either atorvastatin 80 mg or rosuvastatin 40 mg daily
- End of study lipid difference rosuva versus atorva:

  LDL - 62.6 vs. 70.2 mg/dL P<0.001

  HDL - 50.4 vs. 48.6 mg/dL P = 0.01

  TC/HDL – 2.8 vs. 3.0

End of study hsCRP % decrease difference:

1.7 to 1.1 = 55%

1.5 to 1.0 = 50%

Stephen J. Nicholls, M.B., B.S., Ph.D., et. Al. ***N Engl J Med*** 11/2011;365:2078-87

High Dose Rosuvastatin versus Atorvastatin and CAD Regression

- The primary end point, change in percent atheroma volume (PAV), was significant in both groups- rosuva vs atorva:

  decrease 1.22% (95% CI, -1.52 to -0.90)

  decrease 0.99% (95% CI, -1.19 to -0.63)

  difference was not significant with P=0.17

- The secondary end point, normalized total atheroma volume (TAV), was significant:

  −6.39 mm3 (95% CI, −7.52 to −5.12)

  −4.42 mm3 (95% CI, −5.98 to −3.26)

  difference in favor of rosuva was signif. with P = 0.01

Stephen J. Nicholls, M.B., B.S., Ph.D., et. Al. ***N Engl J Med*** 11/2011;365:2078-87

High Dose Rosuvastatin versus Atorvastatin and CAD Regression

- Greater regression of PAV with rosuva in women −1.76% vs. −0.71%, P = 0.01
- Incidence of elevated Ast/Alt:

  atorva 2.0% vs.0.7% with rosuva; P = 0.04
- Incidence of proteinuria:

  atrova 1.7% vs. 3.8% with rosuva; P=0.02
- A1c did not change significantly in either group

Stephen J. Nicholls, M.B., B.S., Ph.D., et. Al. ***N Engl J Med*** 11/2011;365:2078-87

Prespecified Subgroup Analysis for Change in PAV from baseline to 2 yrs.

The NEW ENGLAND JOURNAL of MEDICINE

Characteristic	No.	Median (95% CI)	P Value for Treatment	P Value for Interaction
Age				0.22
<Median			0.95	
Atorvastatin	252	−1.06 (−1.43 to −0.46)		
Rosuvastatin	253	−1.12 (−1.60 to −0.73)		
≥Median			0.07	
Atorvastatin	267	−0.84 (−1.28 to −0.46)		
Rosuvastatin	267	−1.35 (−1.68 to −0.90)		
Sex				0.03
Male			1.00	
Atorvastatin	386	−1.03 (−1.32 to −0.70)		
Rosuvastatin	379	−1.09 (−1.44 to −0.72)		
Female			0.01	
Atorvastatin	133	−0.71 (−1.38 to −0.25)		
Rosuvastatin	141	−1.76 (−2.39 to −1.02)		
Diabetes				0.63
Yes			0.95	
Atorvastatin	87	−0.50 (−1.30 to 0.01)		
Rosuvastatin	72	−0.86 (−1.86 to −0.31)		
No			0.16	
Atorvastatin	432	−1.04 (−1.35 to −0.70)		
Rosuvastatin	448	−1.31 (−1.53 to −0.91)		

Regression Progression

Stephen J. Nicholls, M.B., B.S., Ph.D., et. Al. ***N Engl J Med*** 11/2011;365:2078-87

High Dose Rosuvastatin versus Atorvastatin and CAD Regression

Event rate still extremely high despite regression !!

Table 4. Clinical and Biochemical Adverse Events and Reasons for Discontinuation of Treatment.

Event	Atorvastatin (N=689)	Rosuvastatin (N=691)
Cardiovascular event — no. (%)		
Death from cardiovascular causes	2 (0.3)	2 (0.3)
Nonfatal myocardial infarction	11 (1.6)	11 (1.6)
Nonfatal stroke	2 (0.3)	3 (0.4)
Hospitalization for unstable angina	13 (1.9)	16 (2.3)
Arterial revascularization	41 (6.0)	42 (6.1)
First major adverse cardiovascular event	49 (7.1)	52 (7.5)

One third of the patients did not get regression. Article does not specify, if the patients with events had regression.

Stephen J. Nicholls, M.B., B.S., Ph.D., et. Al. ***N Engl J Med*** 11/2011;365:2078-87

Hot Topic

- AIM-HIGH

AIM-HIGH

- 3,414 stable CVD pts.; 85% male; mean age 64; 92% Caucasian; 80% met. synd; 33% DM; 20% current smokers; 5 yr. follow-up (stopped early)
- Two arms: 1) statin plus ezetemibe – LDL 40-80

  2) above plus ER niacin
- 94% on statin at base line with mean lipids:

  TC- 141; LDL- 71; HDL- 35; TG – 161

  TC/HDL=4.0
- Hypothesis: adding ER niacin 1.5-2 grams will reduce CV event risk an additional 25%

AIM-HIGH, Am Heart J 2011;161:471-477

May 26, 2011: AIM HIGH

- Trial halted May 25, 2011 for futility

- CV events: 249 (15%) 1° events in the simva arm

  262 (15%) in the niacin arm

  (p=0.561)

- Horrible residual risk in both arms !!!

AIM-HIGH Clinical Update: Data Safety Monitoring Board 5/26/2011

AIM-HIGH

Dose used in trial

	Monotherapy	Combo therapy
Simvastatin < 40 mg	11%	19%
Simvastatin 40 mg	50%	50%
Simvastatin > 40 mg	25%	18%
On ezetimibe	22%	10%

AIM-HIGH

Lipid changes in study

- HDL increased 25% in combination arm and 9% in simvastatin monotherapy. Difference 4.5 mg/dl at end of study
- Triglyceride decreased 29% in combination and 4.5% in simvastatin monotherapy
- LDL in combination arm fell during the study from 74 to 62 and 74 to 68 in simvastatin monotherapy

Study not Properly Powered

- The end of study difference in HDL of 4 mg/dL and 6 mg/dL in favor on the niacin arm should generate a 10% advantage

- Study not powered to show that small of a benefit

AIM-HIGH did not AIM-LOW Enough

- apoB/ApoA1 or ‘poor man’s’ TC/HDL is best predictor of risk
- Trials with regression results: ASTEROID; ARBITOR-6 had end point TC/HDL – 2.8
- End ratio in AIM-HIGH niacin arm – 3.1; statin 3.7

Inflammation

- Events are triggered by inflammation.

- Eradication of arterial inflammation may require therapy beyond statin and niacin.

- It will be interesting to see the trial results in regards to biomarkers of inflammation.

Conclusion

- Study neither confirms nor negates niacin as a valuable therapy
- Study certainly demonstrates that atherosclerosis involves much more than the lipids
- A holistic individualized approach is needed to prevent events

BD Conclusions Regarding Niacin

- Study does not affect our use of niacin
- Continue to prescribe niacin
- Good candidates:
  - patients who are statin intolerant
  - patients with the lipo (a) issue
  - patients with MPO issue
  - patients with IR dyslipidemia
  - patients with TC/HDL levels > 3.0
  - patients with persistent arterial inflammation

Case

Case

- 56 yo WM; executive physical; no CV c/o's
- PMhx: obestiy with BMI 37.5 – resolved yrs. ago; gout in past; SAFD – self diagnosed
- Meds: vit. D3 1,000 IU; full spectrum light one hr./day
- Habits: no nicotine, alcohol, drugs; ?? Soda
  exercise: 3-4 X/wk; ?? how long and what kind
  vegetarian diet
  sleep ??
  stress ??
- ROS: urinary freq., urgency, nocturia
- FamHx: Mother alive in 90's- overwt.; BP
  Father died 91 from injury
  Negative for any CAD or CVD or DM

- PE: waist 41”; 205 lbs.; HR -72; BP- 122/78
  negative except BPH
- Basic Labs: TC- 139; TG – 57; HDL – 55; LDL- 73
  CMP wnl except FBS – 104
  CBC, thyroid, testosterone, uric acid, vit. D – normal
  PSA – 2.9
- Advanced Labs: hsCRP- 1.1; fibrinogen- 400; MACR – 2.8; Lp-PLA2 – 183; MPO- 185; F2 -0.28
  lipo (a), LDL subs, apoB – normal
  HDL2b – 19%
  NT pro-BNP - 61

- FRS- 4%
- RRS- 3%
- ABI – 1.45 R; 1.36 L
- CIMT

  mean thickness – 1.005 = 85 yo

  plaques in R and L CCA ; >ist 2.5mm; H
- Stress test

  excellent fitness level; asx'ic

  significant ST depressions; >ist 4.3mm in V5 at 11.7 METs; fully recovered at 6 mins.

Diagnoses

- Subclinical carotid ASVD
- Abnormal stress test - ? obstructing CAD
- Abnormal ABI
- Overweight
- Borderline hsCRP and Lp-PLA2
- IFG – he is IR
- Pre-hypertension
- BPH with PSA 2.9

Recommendations

- Refer to cardiologist
- ASA 81 mg
- Fish oil 1-2 gr
- Weight loss

Questions

- What is etiology of ASVD?
- Any further testing?
- Any prescription drugs?

- IR ??

  MS – no; TG/HDL – no; A1c – 4.6 – no

  FBS – 104

  2 hr. glucose – 106

  1 hr. glucose – 139

Fasting blood sugar

- Yours was 108

  ADA guidelines > 100 is abnormal = IR= pre-diabetes

  > 125 = diabetes

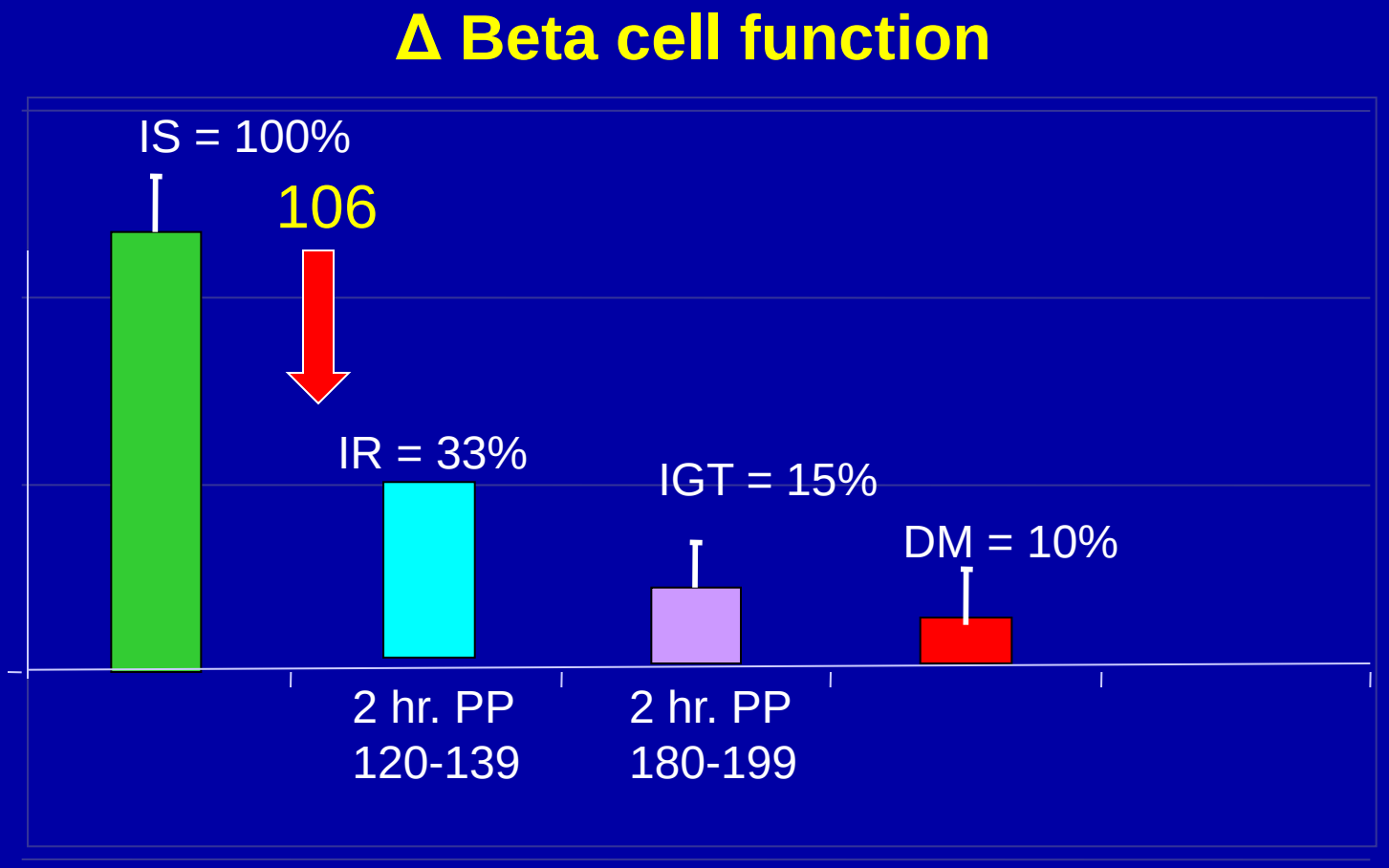
One Hour Glucose Post 75 g Challenge Best Test to Indentify 'At Risk for Diabetes'

- 3,450 subjects; 2 hr. post 75 gram glucose <140mg/dL; followed 7-8 yrs.
- One hour glucose is best predictor
- Increased incidence from 125mg/dL on up; marked increase at ≥150mg/dL
- FBG < 126mg/dL NOT predictive, if 1 hr. < 125mg/dL
- 1 hr. G >150mg/dL 13 times greater risk for DM in next 6-7 yrs. !!!

Your one hour was 139

Abdul-Ghani, M.A., DeFronzo, R.A., et. al. *Diabetes Care* 3/2010. Vol.33, No.3:557-561

Beta cell function as Insulin Resistance Progresses

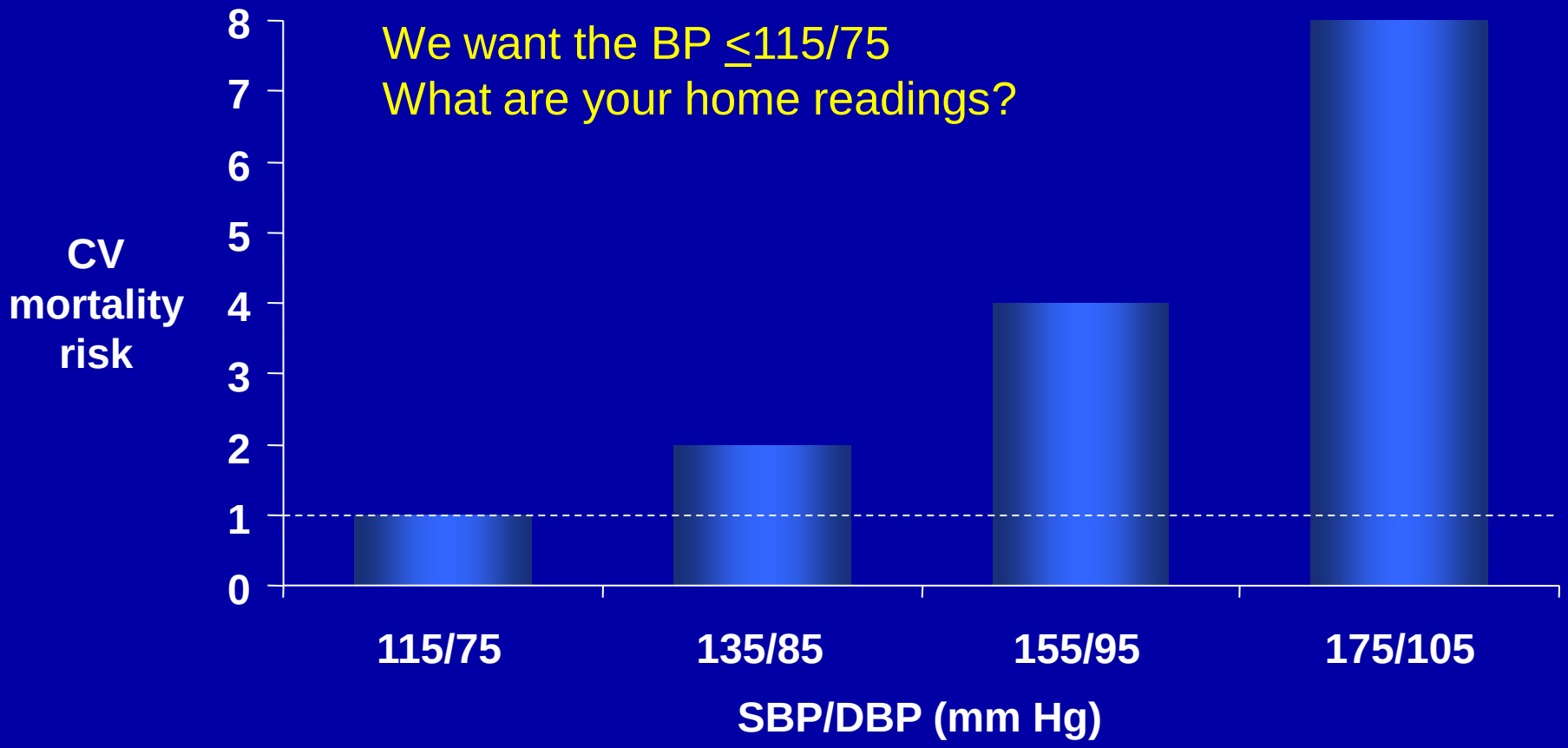


DeFronzo, R. Diabetes, Vol. 58, April 2009

Root Causes??

- BP – pre-hypertension
- Lipo (a) – 12
- Vit. D – 72
- KIF6 - ???
- 9p21- ???
- LPA - ???
- apoE - ???
- IL-1 ???
- PD - ???
- Sleep and psychosocial ???

CV Mortality Risk Doubles with Each 20/10 mm Hg BP Increment*



*Individuals aged 40-70 years, starting at BP 115/75 mm Hg.
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure
Lewington S, et al. *Lancet*. 2002; 60:1903-1913.
JNC 7. *JAMA.* 2003;289:2560-2572.

Pre-hypertension Independently Increases Stroke Risk About 50%

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

Risk of stroke by prehypertension category

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

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

Further testing?

Further testing?

- KIF6
- 9p21
- LPA
- apoE
- IL-1
- MyPerioPath
- Sleep and psychosocial ???
- ABI with exercise
- CoQ10

Prescription Meds??

The patient has ASVD

How should we treat them??

Normal foundation

- Lifestyle advice –plug into BHL educator
- Anti-platelet rx–- ASA 81mg

Statin

Inhibition of angiotensin-renin-aldosterone system

Effects of Statins Beyond Cholesterol

- Reduces the inflammation inside the artery
- Reduces ability of LDL to get eaten by the WBCs

- Reduces risk of forming a clot

- Reduces WBCs sticking to artery wall

- Makes plaque less likely to rupture
  - Decreased content of cholesterol in plaque
  - Reduces inflammation in the plaque
  - Strengthens the surface over the plaque

Rosenson R, et al. *JAMA*. 1998;279:1643-1650;
Gotto AM, et al. *Curr Opin Lipidology*. 2001;12:391-394;
Maron DJ, et al. *Circulation.* 2000;101:207-213;
White CM. *J Clin Pharmacol*. 1999;39:111-118.

ACEI CV Benefits

- Arteries
  - dilate arteries
  - reduce inflammation
  - reduce clotting
  - improve endothelial function
  - decrease CIMT progression
- Heart
  - improve LV function
- Kidneys
  - improve renal function
- Insulin resistance
  - reduce risk of new onset diabetes (increase adiponectin)*

Eur Heart J. 2003;5;A43-A48
J Am Coll Cardiol. 2004;43:220-2206
Circulation.2001;103:919-925
J Am Coll Cardiol. 2005;45:409A Abstr.
N Engl J Med. 2005;352:937-938
Hypertension* 2005 5;():*Posted on* May 17, 2005

Any additional OTC Therapy??

- Emphasize fruits and veg- white
- Hammer home exercise!!
- Make sure eliminate soda pop
- Dark chocolate
- Cinnamon
- Reduce vit. D intake

White Fruits and Vegetables May Protect Against Stroke

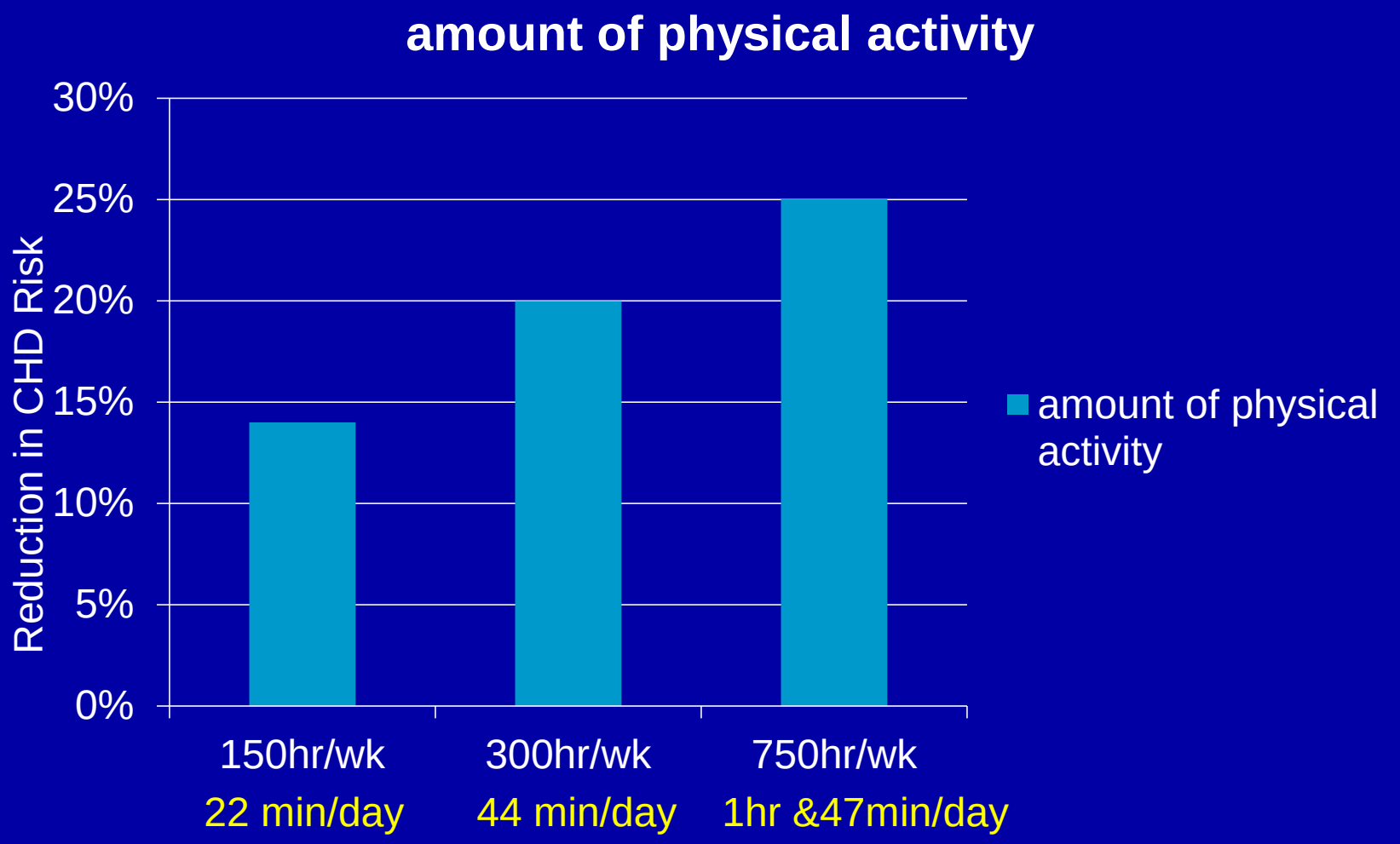
- Prospective 20,069 healthy subj. 20-65 yo; 55% women; followed 10yrs.; 233 strokes occurred
- Fruits and vegetables sorted into four color groups: green, orange/yellow, red/purple, white
- Only color associated with stroke was white
- Each 25-g/d (1/6 medium apple) increase in white fruit and vegetable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

HR, 0.91 (95% CI, 0.85– 0.97)

adjusted for age, sex, lifestyle, and dietary factors

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

Exercise Amount Related to CHD Risk



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

Exercise to Prevent Diabetes

Burning an extra 500 kcal/wk can reduce the risk of developing type 2 diabetes by 6%.

Helmrich SP, et al. *N Engl J Med.* 1991; 325:147-152

Improving Fitness Level Reduces Type 2 DM Incidence up to 70%

- 4,187 healthy men; fitness assessed 4X over 7 yrs. (1979-1985)
- 274 incident cases of DM (1985-1999)
- Segregated fitness level trends into quartiles
- HR for DM comparing lowest to highest fitness trend quartile, after adjustment for: age, initial fitness, BMI, syst BP, smoking, alcohol and Famhx DM

  0.33 (95% CI- 0.21-0.50)

Sawasa, S. S., PhD, et. al. Diabetes Care 6/2010, Vol. 33, No. 6:1353-1357

Diet Soda Daily Increased Vascular Events 50% Over 9 Years

2500 people from the multiethnic cohort study self reported soda intake.

Follow-up 9.3 years, there were 559 vascular events, including both ischemic and hemorrhagic strokes.

After controlling for metabolic syndrome, PAD, CAD, daily consumption of diet soda increased RR 1.48 (95% CI 1.03-2.12) for CV event compared to no soda intake

Gardener H, Rundek T, Wright C, et al. Soda Consumption and risk of vascular events in the Northern Manhattan Study. International Stroke Conference 2011; February 9, 2011.

Chocolate Lowers BP and CV Mortality Risk

- Observational survey data of 19,357 people; aged 35 to 65; 8-12 yr. follow-up
- Divided into quartiles of average daily chocolate consumption: top ≥7.5 grams to bottom ≤1 gram
- 166 MIs (24 fatal) and 136 strokes (12 fatal)
- Top quartile compared to bottom: 27% less likely to die of heart attack and 48% less likely die from a stroke
- Why????: flavanols release nitric oxide, which lowers BP and improves platelet function
- Survey of 1,500 subjects: 57% ate milk chocolate, 24% dark chocolate, and 2% white chocolate

cocoa content is important; the higher the cocoa content the better; i.e. dark chocolate; 100 g of dark chocolate contains roughly 500 calories; less dark the more calories

Buijsse, B, et al. *Eur Heart J* 3/2010: DOI:10.1093/eurheartj/ehq068. Available at: http://eurheartj.oxfordjournals.org.

Chocolate Associated with Lower Stroke Risk

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

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

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

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

Effects of 6-g cinnamon capsules daily on glucose levels

Group	Baseline (mmol/L)	After 40 days (on cinnamon or placebo; mmol/L)	After 20-day washout (mmol/L)
6-g cinnamon	13.0	9.2	11.4
6-g placebo	16.7	16.8	17.0

60 poorly controlled type 2 DM in Pakistan

Six arms: 1g, 3g, 6g, placebos

No dose related differences

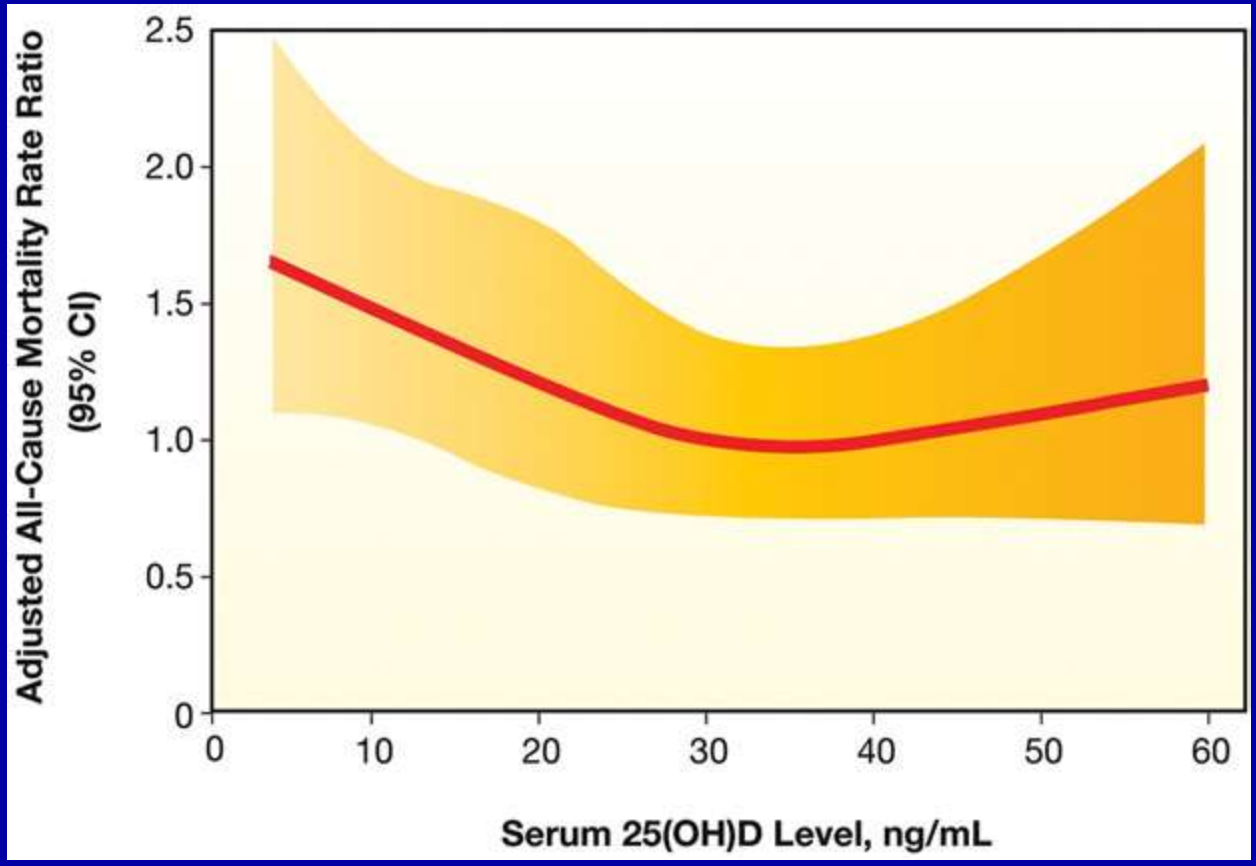
Why????: spices affect insulin activity

Intriguing but: small study; poor diabetic control;

capsules; Pakistan cinnamon; diet?; exercise?; interactions

Khan A et al. *Diabetes Care* 2003 Dec; 26(12):3215-8.

Impact of Vitamin D on Mortality in the NHANES III Study



Restricted cubic spline showing the fully adjusted associations between serum 25-hydroxyvitamin D (25[OH]D) levels and all-cause mortality in 13,331 participants of the Third National Health and Nutrition Examination Survey. CI confidence interval. Reproduced with permission from Melamed et al.

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

Do not forget the potential significance of an ABI ≥ 1.40

- 4420 pts. with ABI btw 0.90 & 1.40; 296 with an ABI ≥1.40
- If the ABI ≥1.40 there was a significantly higher prevalence of foot ulcers

  -after adjustment for age, gender, race, smoking, diabetes, hypertension, dyslipidemia, and BMI

  (OR 2.67, 95% CI 1.42-5.02)

- There was also a marginally significant association with CHF, stroke, and neuropathy

- Diabetes, male gender, and waist circumference were associated with an ABI ≥1.40

Allison MA, Hiatt WR, Hirsch AT, et al. *J Am Coll Cardiol* 4/1/2008; 51:1292-8

Upcoming Presentations

- 1/19/2012 – Brad CHL San Antonio, TX
- 1/21/2012 – Brad and Amy BHL mini-course in Atlanta, GA – still a ???
- 2/4/2012 – Brad and Amy AAPP in Scottsdale, AZ
- 2/10-11- BD Method Preceptorship in Las Vegas, NV

Open for Discussion