Bale/Doneen Live Chat Session

1/9/2013

5:30-6:30 pm PST

Bradley Bale, MD

Happy New Year!

Intention of the live chats

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

Red Flags

ED Predicts CV Risk & Mortality

- 92,757 pts from 16 studies; mean follow-up, 6.1 yrs
- Evaluated relative risk in men with and without ED
- Analyzed for risk difference based on FRS
- Analyzed for risk difference of ED being dx'ed by a single question or a questionnaire

Vlachopoulos, C. V., MD, et. al.; ***Circ Cardiovasc Qual Outcomes*. 1/8/2013;6:1-11**

ED Predicts CV Risk & Mortality: Single Question

		RR	95% CI
CV Events:	n= 91,831	1.44	1.27–1.63
CV Mortality:	n= 34,761	1.19	0.97–1.46
MI:	n= 35,523	1.62	1.34–1.96
Stroke:	n= 27,689	1.39	1.23–1.57
All Cause Mortality:	n= 17,869	1.25	1.12–1.39

Vlachopoulos, C. V., MD, et. al.; ***Circ Cardiovasc Qual Outcomes*. 1/8/2013;6:1-11**

ED Predicts CV Risk & Mortality: RR Increased Only with ≥10% FRS

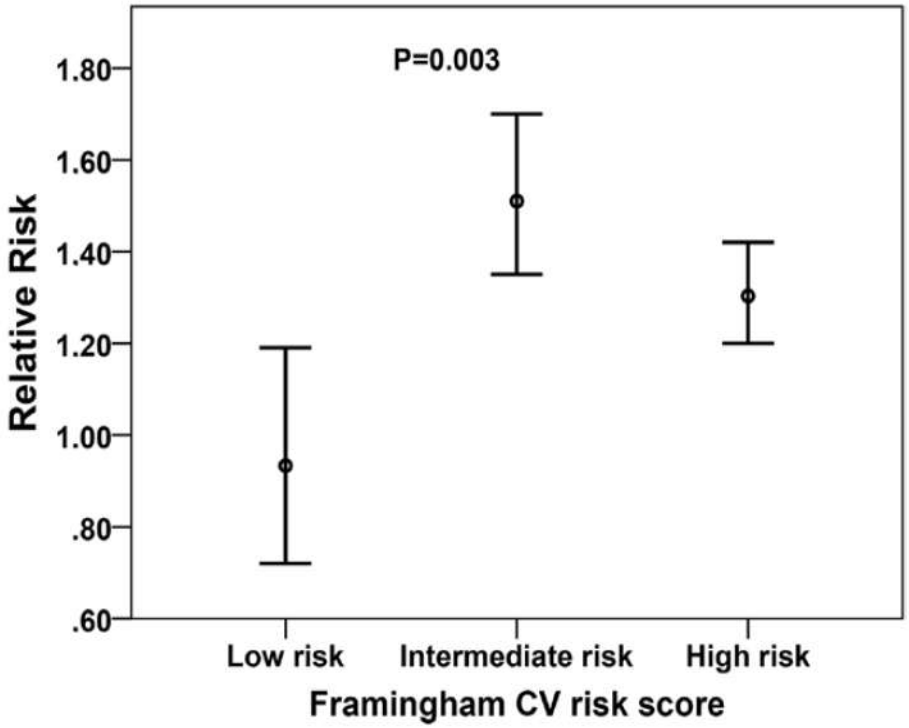


Figure 3. Pooled relative risk (RR) and 95% confidence interval for erectile dysfunction and total cardiovascular (CV) events, according to CV risk assessed by Framingham Risk Score. The center circle of the bar denotes the pooled RR; the extremes of the bars, the upper and lower limits of 95% of the data. Value by test for interaction.

Vlachopoulos, C. V., MD, et. al.; ***Circ Cardiovasc Qual Outcomes*. 1/8/2013;6:1-11**

ED Predicts CV Risk & Mortality:
RR of Total CV Events Increased with Questionnaire

- RR- 1.61 (95% CI, 1.38–1.86) versus 1.27 (95% CI, 1.18–1.37) *P*=0.006

- International Index of Erectile Function questionnaire (IIEF): 15 item questionnaire, validated as a brief and reliable self administered scale for assessing erectile function.*

Vlachopoulos, C. V., MD, et. al.; ***Circ Cardiovasc Qual Outcomes*. 1/8/2013;6:1-11**
* Rosen RC, et. al., Urology. 1997 Jun;49(6):822-30

ED Predicts CV Risk & Mortality

- CV risk conferred by ED is similar in magnitude to hypertension and dyslipidemia
- RR was higher in the younger pts., smoker, dyslipidemics and known CVD
- Highlight the role of ED as a potential low-cost biomarker calling for more aggressive CV risk factor modification

Vlachopoulos, C. V., MD, et. al.; ***Circ Cardiovasc Qual Outcomes*. 1/8/2013;6:1-11**

BD Method Thoughts

- Should utilize IIEF questionnaire
- Always remain anchored in looking for disease: remember according to Cafés to Cave Study, anyone with plaque is equivalent to FRS high risk and an IMT of >1mm is close to intermediate risk at 8.7% ten yr. risk
- Network with urologists

Stroke History Predicts Future Stroke Risk

- 30,239 black and white Americans ≥45 yo; ~50% Black and ~ female; followed 5 yrs.; 737 incident strokes
- Evaluated baseline self reported history of stroke sx's, TIA, distant stroke, recent stroke as predictors of stroke & death
- Adjusted for: age, race, sex, income, education, alcohol, smoking, DM, BP, MI, AF and dyslipidemia

Judd S E et al. Stroke 2013;44:55-60

Stroke History Predicts Future Stroke Risk

- Sx's (sudden loss strength, vision, sensation, understanding, expression) were not a significant predictor after full adjustment

- Hx TIA – 1.7 X more likely

- Hx distant stroke – 2.2 X more likely

- Hx recent stroke – 2.9 X more likely

Judd S E et al. Stroke 2013;44:55-60

Stroke History Predicts Future Stroke Risk

Table 2. Risk of Future Stroke After Self-Reported Stroke, TIA, or Stroke Symptoms in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

	No Report of Stroke Symptoms, TIA, or Stroke	Stroke Symptoms	TIA	Distant Stroke*	Recent Stroke*	*P* Value (trend)
No.	22795	3871	1096	807	846	
Number of adjudicated strokes	456	104	56	50	71	
Adjusts for age, race, and sex	ref	1.32 (1.07–1.64)	2.15 (1.62–2.84)	2.74 (2.05–3.68)	3.72 (2.89–4.78)	<0.001
Adjusts for above plus region, income, and education	ref	1.26 (1.02–1.57)	2.11 (1.59–2.79)	2.61 (1.95–3.51)	3.49 (2.71–4.50)	<0.001
Adjusts for above plus comorbidities†	ref	1.20 (0.96–1.51)	1.73 (1.27–2.36)	2.23 (1.61–3.09)	2.85 (2.16–3.76)	<0.001

TIA indicates transient ischemic attack.

*A recent stroke is defined as a stroke within 5 years of the baseline interview. A distant stroke is defined as a stroke that occurred ≥5 years from baseline interview. Recent stroke, distant stroke, TIA, and stroke symptoms were all ascertained by self-report.

†Comorbidities include alcohol intake, current smoking, and a history of diabetes mellitus, hypertension, history of coronary artery disease, atrial fibrillation, dyslipidemia, and the racial difference in retrieving medical records.

Judd S E et al. Stroke 2013;44:55-60

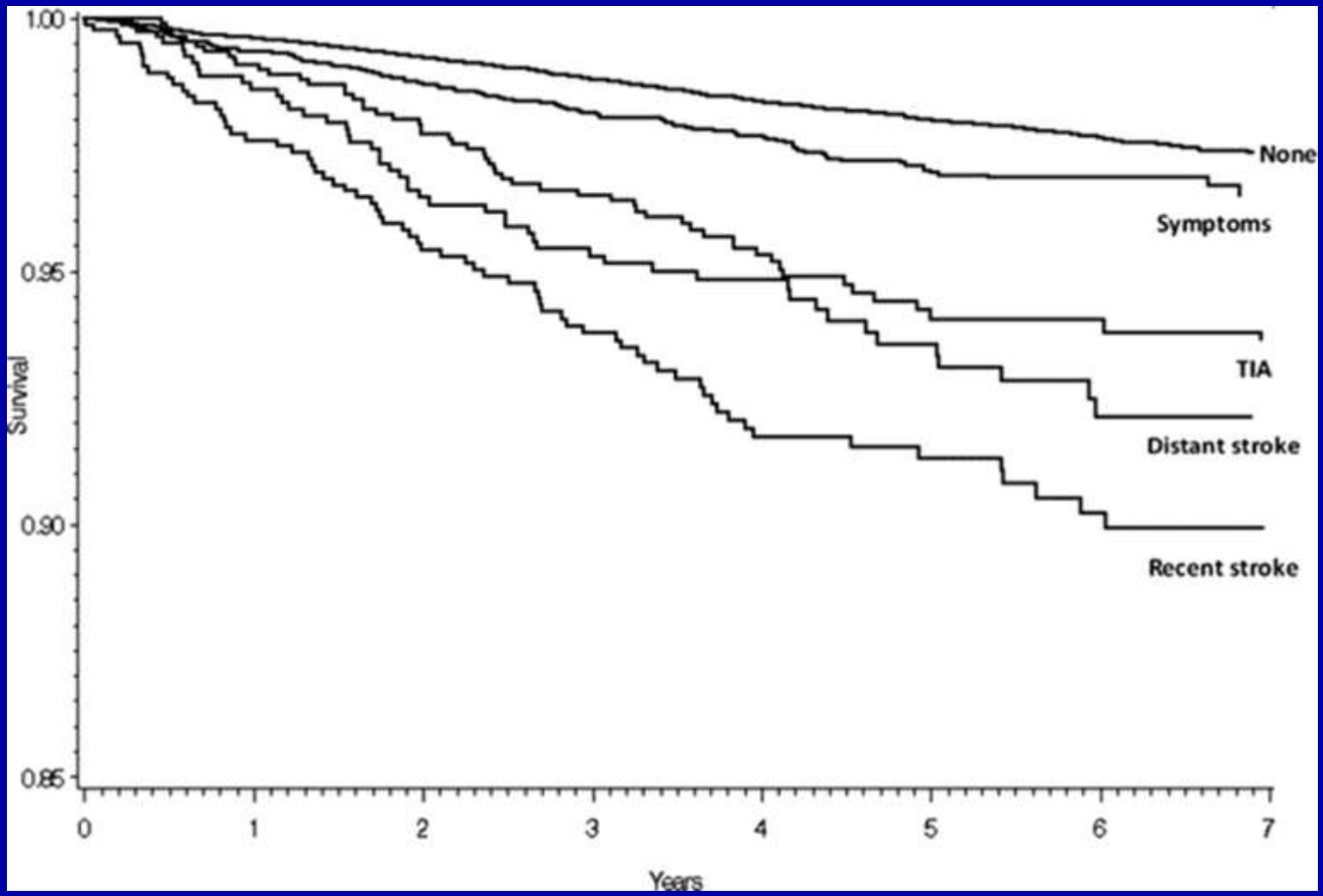
Stroke History Predicts Future Stroke Risk

Distant stroke almost as predictive as recent stroke

Judd S E et al. Stroke 2013;44:55-60

Stroke History Predicts Future Stroke Risk

Risk of future stroke after self-report stroke, transient ischemic attack (TIA), or stroke.



Judd S E et al. Stroke 2013;44:55-60

Stroke Symptoms & History Predict Risk of Being Dead in Five Years

Table 3. Risk of Death After Self-Reported Stroke, TIA, or Stroke Symptoms in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

	No Report of Stroke Symptoms, TIA, or Stroke	Stroke Symptoms	TIA	Distant Stroke*	Recent Stroke*	*P* Value (trend)
No.	22795	3871	1096	807	846	
No. deaths	1844	529	213	196	211	
Adjusts for age, race, and sex	ref	1.63 (1.47–1.79)	2.01 (1.74–02.32)	2.51 (2.16–2.91)	2.47 (2.14–2.85)	<0.001
Adjusts for above plus income and education	ref	1.45 (1.33–1.60)	1.88 (1.63–2.18)	2.07 (1.78–2.42)	2.07 (1.78–2.39)	<0.001
Adjusts for above plus comorbidities†	ref	1.33 (1.19–1.48)	1.58 (1.35–1.85)	1.86 (1.58–2.20)	1.79 (1.53–2.09)	<0.001

TIA indicates transient ischemic attack.

*A recent stroke is defined as a stroke within 5 years of the baseline interview. A distant stroke is defined as a stroke that occurred ≥5 years from baseline interview. Recent stroke, distant stroke, TIA, and stroke symptoms were all ascertained by self-report.

† Comorbidities include alcohol intake, current smoking, and a history of diabetes mellitus, hypertension, myocardial infarction, atrial fibrillation, and dyslipidemia.

Judd S E et al. Stroke 2013;44:55-60

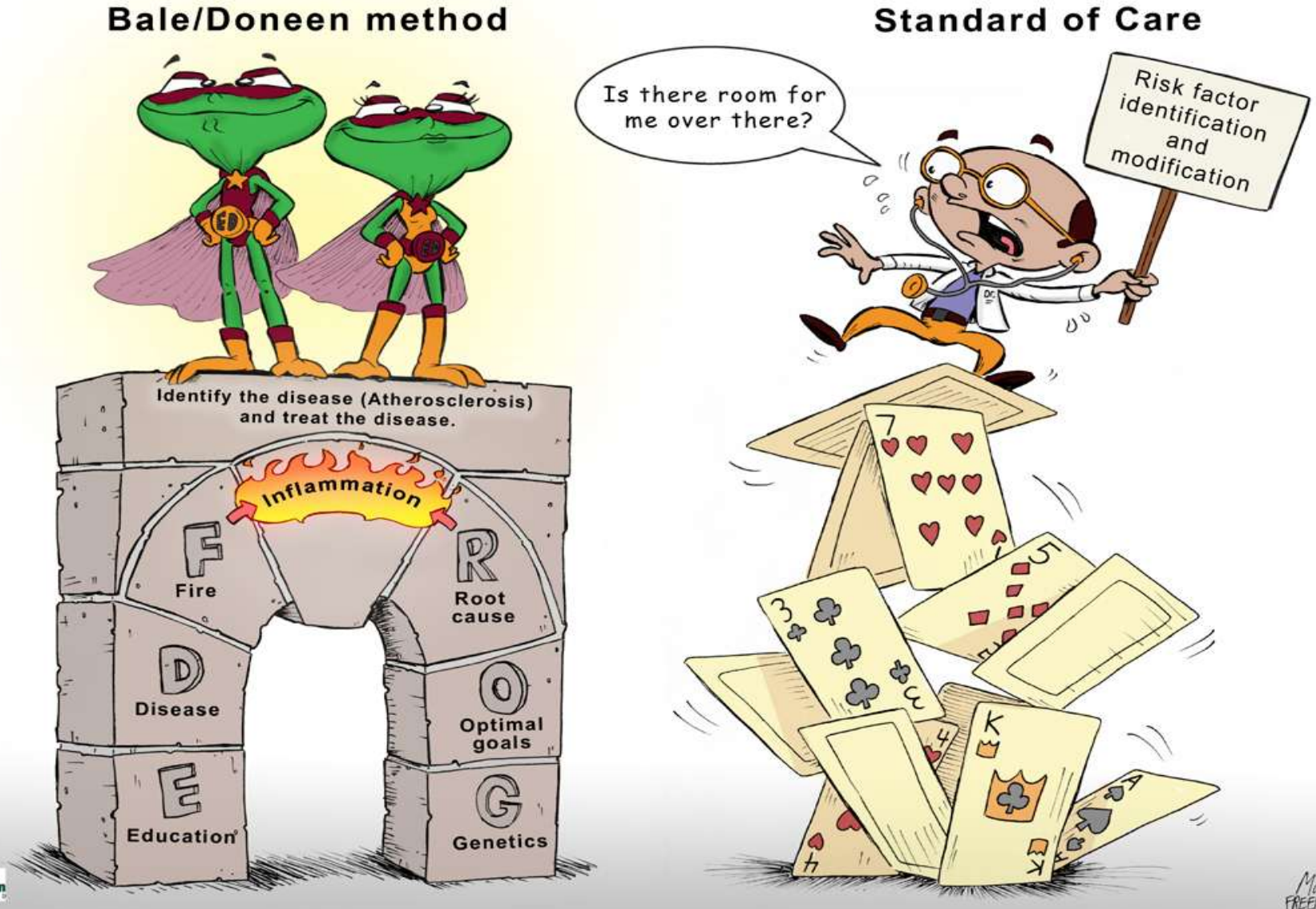
BD Method Thoughts

- Patient history needs to include ‘stroke’ sx’s: sudden loss strength, vision, sensation, understanding, expression

- Stroke sx’s independently predict 5 year mortality after adjusting for: age, race, sex, income, education, alcohol, smoking, DM, BP, MI, AF and dyslipidemia

Judd S E et al. Stroke 2013;44:55-60

What's the difference?



ADA: Screening for CAD in DM

- Risk factor–based approach fails to identify who will have silent ischemia on screening tests.
- Asymptomatic diabetic pts found to have CAD via CACS have more future cardiac events.
- Routine use of CACS leads to radiation exposure and may result in unnecessary invasive testing
- The balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA: Screening and Managing CHD Risk

- Assess CV risk factors annually (basic lipids, BP, smoking, MACR, famhx)

BD Method Thoughts: Incredible!!!!!

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

Progression of Asymptomatic Carotid Stenosis Predicts CV Event Risk

- 523 pts; unilateral asx'ic carotid stenosis- 50% to 69%; repeat US ~ 9 months for ? progression; then followed ~ 3 ½ yrs. for CV events
- 129 had progression; 53.7% had CV events
- 394 did not have progression; 3.3% had CV events

Balestrini, S., et. al. ***Stroke*. 1/3/2013;44:XXX-XXX**
http://stroke.ahajournals.org/content/early/2013/01/03/STROKEAHA.112.671461

Progression of Asymptomatic Carotid Stenosis Predicts CV Event Risk

- After adjustment for: age, smoking, DM, BP, antidiabetics, and the interaction term age and analysis time

- HR for CV events in progressor's:

  21.57 (95% CI, 11.81–39.39) $p<0.001$

- HR for ipsolateral stroke in progressor's:

  31.97 (95% CI, 9.83–103.91) $p<0.001$

Balestrini, S., et. al. ***Stroke*. 1/3/2013;44:XXX-XXX**
http://stroke.ahajournals.org/content/early/2013/01/03/STROKEAHA.112.671461

Progression of Asymptomatic Carotid Stenosis Predicts CV Event Risk

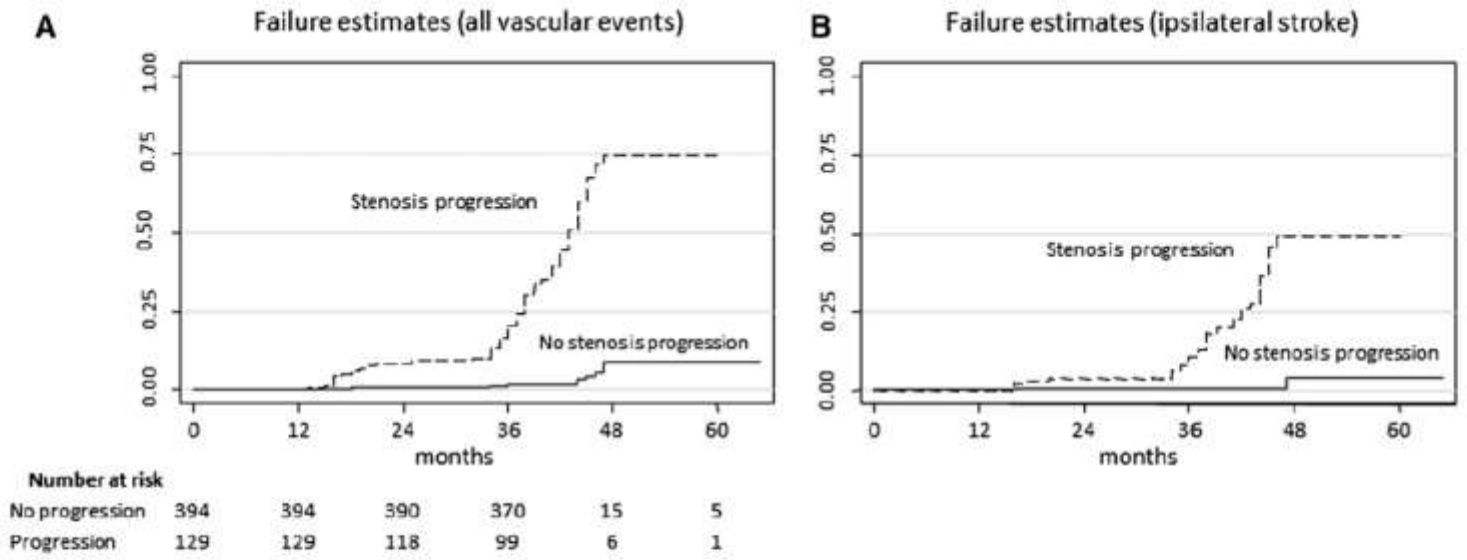


Figure. **A**, Failure estimates for combined vascular events. **B**, Failure estimates for ipsilateral strokes.

% of progressor's who had a heart attack: 6.2%
% of non=progressor's who had a heart attack: 1.5%

Balestrini, S., et. al. ***Stroke*. 1/3/2013;44:XXX-XXX**
http://stroke.ahajournals.org/content/early/2013/01/03/STROKEAHA.112.671461

Progression of Asymptomatic Internal Carotid Stenosis Predicts CV Event Risk

- All subjects received the best treatment available for each vascular risk condition and education about lifestyle modifications.
- Strategies for monitoring ***disease progression*** to guide therapeutic decisions are not available.

Balestrini, S., et. al. ***Stroke*****. 1/3/2013;44:XXX-XXX**
http://stroke.ahajournals.org/content/early/2013/01/03/STROKEAHA.112.671461

Progression of Asymptomatic Carotid Stenosis Predicts CV Event Risk

Monitoring the disease was a significant predictor of CV events!

Risk factors and rx were not!!!

Table 2. Univariate Cox Regression Analyses Considering as Outcome Variable the Incidence of Combined Vascular Events

Variables	Hazard Ratio	SE	95% Confidence Interval
Age	1.03	0.02	0.995–1.055
Sex	1.22	0.27	0.783–1.893
Smoking	1.52	0.36	0.959–2.416
Diabetes mellitus	1.36	0.32	0.856–2.170
Dyslipidemia	0.92	0.21	0.595–1.428
Hypertension	1.64	0.45	0.959–2.797
CAD	0.87	0.24	0.503–1.502
Antihypertensives	1.33	0.32	0.824–2.139
Antidiabetics	1.38	0.34	0.854–2.218
Statins	0.81	0.19	0.516–1.272
Antiplatelets	1.33	0.31	0.845–2.083
Progressive carotid stenosis	20.90	6.34	12.535–37.880

CAD indicates coronary artery disease.

Balestrini, S., et. al. ***Stroke*. 1/3/2013;44:XXX-XXX**
http://stroke.ahajournals.org/content/early/2013/01/03/STROKEAHA.112.671461

Progression of Asymptomatic Carotid Stenosis Predicts CV Event Risk

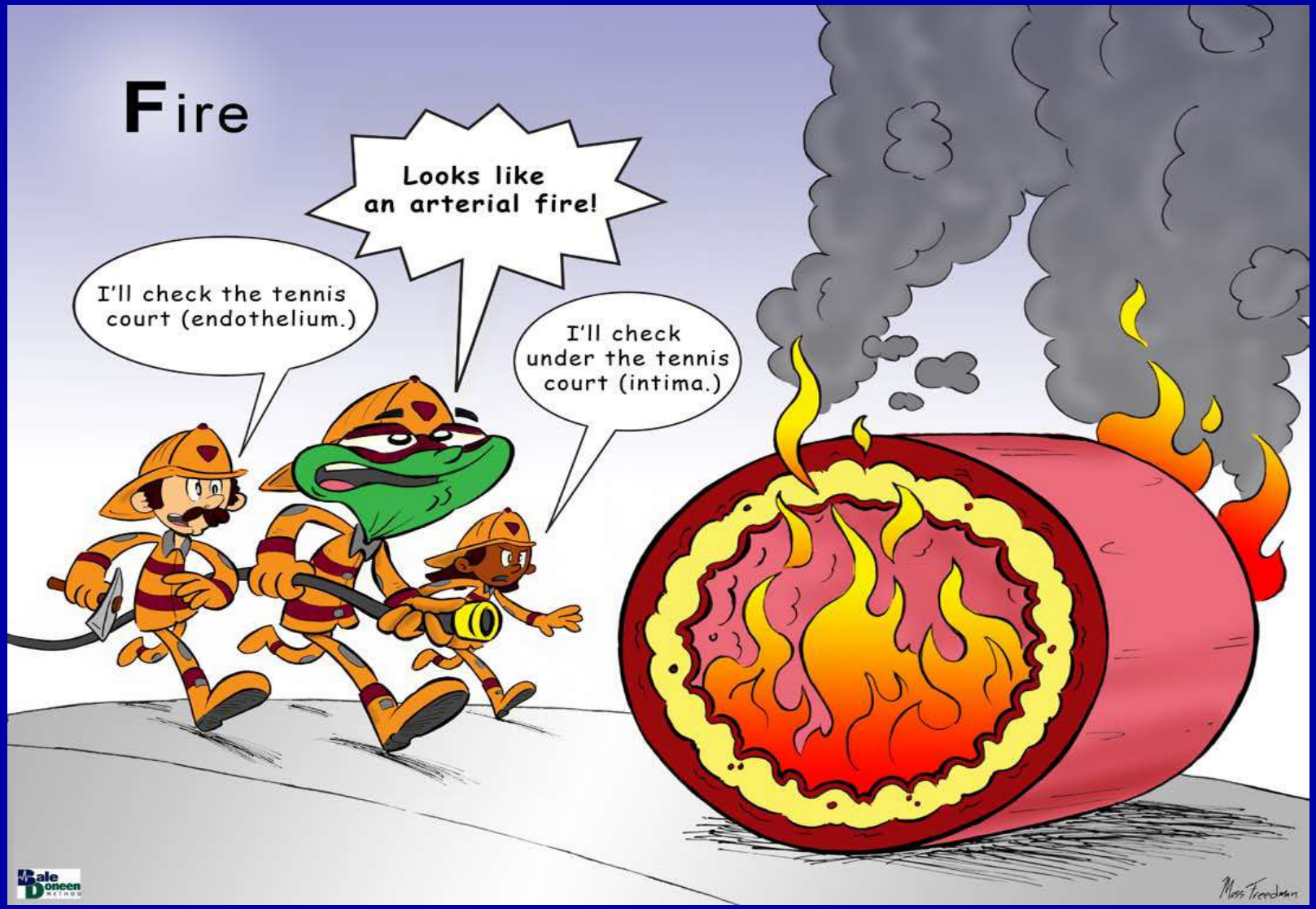
- Study shows that ~ 9 mo. US monitoring of moderate atheroma can identify subjects at higher vascular risk.
- Carotid ASVD should be considered as part of a generalized atherosclerosis process. (signif. MI risk)
- Progressor's need more aggressive treatment strategies.

Balestrini, S., et. al. ***Stroke*. 1/3/2013;44:XXX-XXX**
http://stroke.ahajournals.org/content/early/2013/01/03/STROKEAHA.112.671461

BD Method Thoughts

- Supports concept of being anchored in disease
- Supports value of monitoring disease to help direct management
- Supports concept that arterial beds other than the coronaries can predict risk of heart attacks
- Supports stabilizing plaque prevents events

Inflammation



Oxidative Stress is Related to ASVD

- 31 females (~40 yo) genetically deficient in NOX2; 31 matched controls and 31 matched, but obese females
- FMD and CIMT utilized as markers of atherosclerotic burden
- Oxidative stress measured by: 1) serum activity of NOX2 2) serum nitrite/nitrate 3) urinary isoprostane 4) ex vivo platelet production of nitrite/nitrate & isoprostane

Violi, F., et. al. ***Arterioscler Thromb Vasc Biol*. 1/2013;33:1-7**

Oxidative Stress is Related to ASVD

- Markers of oxidative stress significantly lower in females genetically deficient in NOX2 (GDF)

	GDF	Control	p GDF vs C	Obese	p C vs O
Serum NOX2 pg/mL	12.8±11.9	24.9±19.3	0.004	36.1±18.6	0.008
Serum N/N µmol/L	30.5±6.3	23.8±7.6	<0.001	12.6±4.2	<0.001
Urine isopr pg/mg creat.	82.3±46.0	132.6±87.3	0.007	182.2±84.6	0.008
Platelet N/N µmol/L	X	<X	<0.001	<<X	<0.001
Platelet isopr pg/mg	<<X	<X	<0.001	X	<0.001

Violi, F., et. al. ***Arterioscler Thromb Vasc Biol*. 1/2013;33:1-7**

Oxidative Stress is Related to ASVD

- CIMT significantly lower in females genetically deficient in NOX2 (GDF)

GDF – 0.50 ±0.11mm

Controls – 0.60 ±0.11mm

Obese – 0.71 +0.15mm

$p<0.001$

Violi, F., et. al. ***Arterioscler Thromb Vasc Biol*. 1/2013;33:1-7**

Oxidative Stress is Related to ASVD

- FMD significantly higher in females genetically deficient in NOX2 (GDF)

GDF – 9.2 ±5.0%

Controls – 5.7 ±3.0%

Obese – 3.2 ±2.1%

$p<0.001$

Violi, F., et. al. ***Arterioscler Thromb Vasc Biol*. 1/2013;33:1-7**

Oxidative Stress is Related to ASVD

FMD demonstrated moderate correlation with intima-media thickness (r=–0.433; P<0.001), serum NOX2 activity (r=–.325; P<0.001), and urinary isoprostanes (r=–0.314; P=0.002)

Violi, F., et. al. ***Arterioscler Thromb Vasc Biol*. 1/2013;33:1-7**

BD Method Thoughts

- Additional evidence to support oxidative stress as a cause of ASVD
- Oxidative stress relates to inflammation via senescence (endothelium, macrophage, VSMC); oxidized LDL & FFA
- Oxidation creates pro-thrombotic conditions
- Supports monitoring urinary isoprostane in all stages of CV prevention

Violi, F., et. al. ***Arterioscler Thromb Vasc Biol*. 1/2013;33:1-7**

Seasonal Affective Disorder (SAD)

- ~ 2% of pop.; up to 10% in northern latitudes; sx's ~ 40% of yr.; 4:1 women to men; < with age
- Depression with seasonality
- Biological mechanisms??: circadian phase shift; retinal sensitivity; neurotransmitter dysfunct.; genetic influences; serotonin levels
- Treatment: light rx; cognitive behavior rx; pharmacotherapy

Kurlansik, S. L., PhD, Ibay, A.D., MD. Am Fam Physician 12/2012;86(11):1037-1041

Seasonal Affective Disorder (SAD) and Bilirubin

- 9 pts with SAD; 7 matched controls; assessed nocturnal bilirubin levels baseline
- SAD pts received two weeks light therapy and nocturnal levels were reassessed in 7 pts.

Oren, D. A., et. al. *BIOL PSYCHIATRY* 2002;51:422–425

Seasonal Affective Disorder (SAD) and Bilirubin: SAD pts. have lower levels

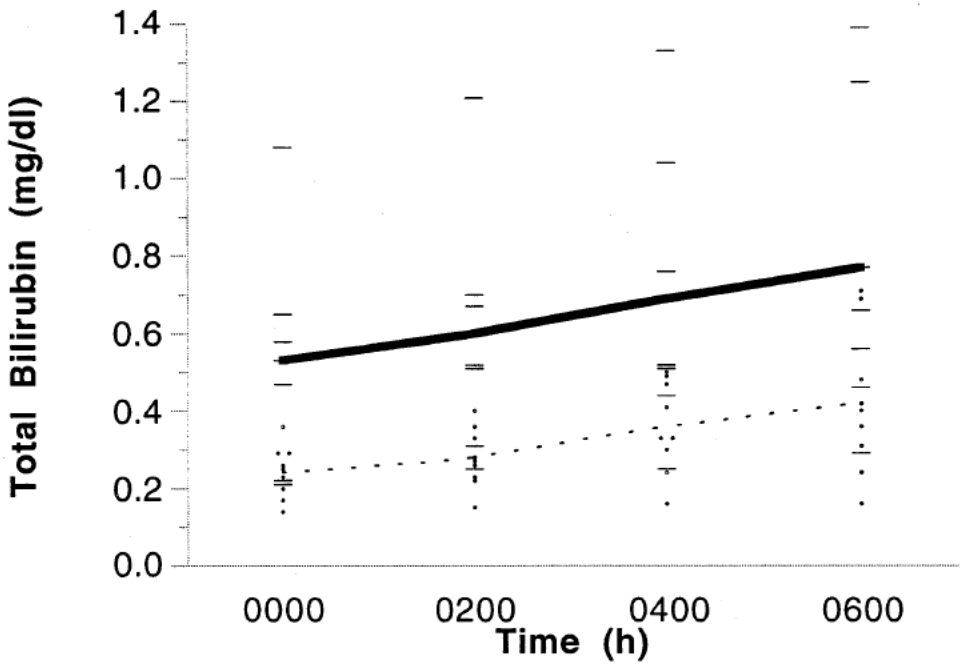


Figure 1. Nocturnal serum bilirubin levels in patients (dots) and normal volunteers (lines). Dotted connecting line depicts mean levels in patients; solid line depicts mean levels in normal volunteers.

0000=midnight

P<0.02

Oren, D. A., et. al. *BIOL PSYCHIATRY* 2002;51:422–425

Seasonal Affective Disorder (SAD) and Bilirubin: Light rx increases levels

Table 3. Mean ± SD of Total Serum Bilirubin Levels (mg/dL) in Seven Patients Before and After Light Therapy at Each Time Point

	Time (hour)			
Group	0000	0200	0400	0600
Patients (depressed)	.24 ± .05	.28 ± .05	.37 ± .09	.41 ± .14
Patients (after light treatment)	.31 ± .07	.35 ± .06	.41 ± .10	.47 ± .12
p	< .003	< .001	> .02	< .08
t	−4.869	−6.053	−1.344	−2.167
df	6	6	6	6

Statistics associated with paired *t* tests.

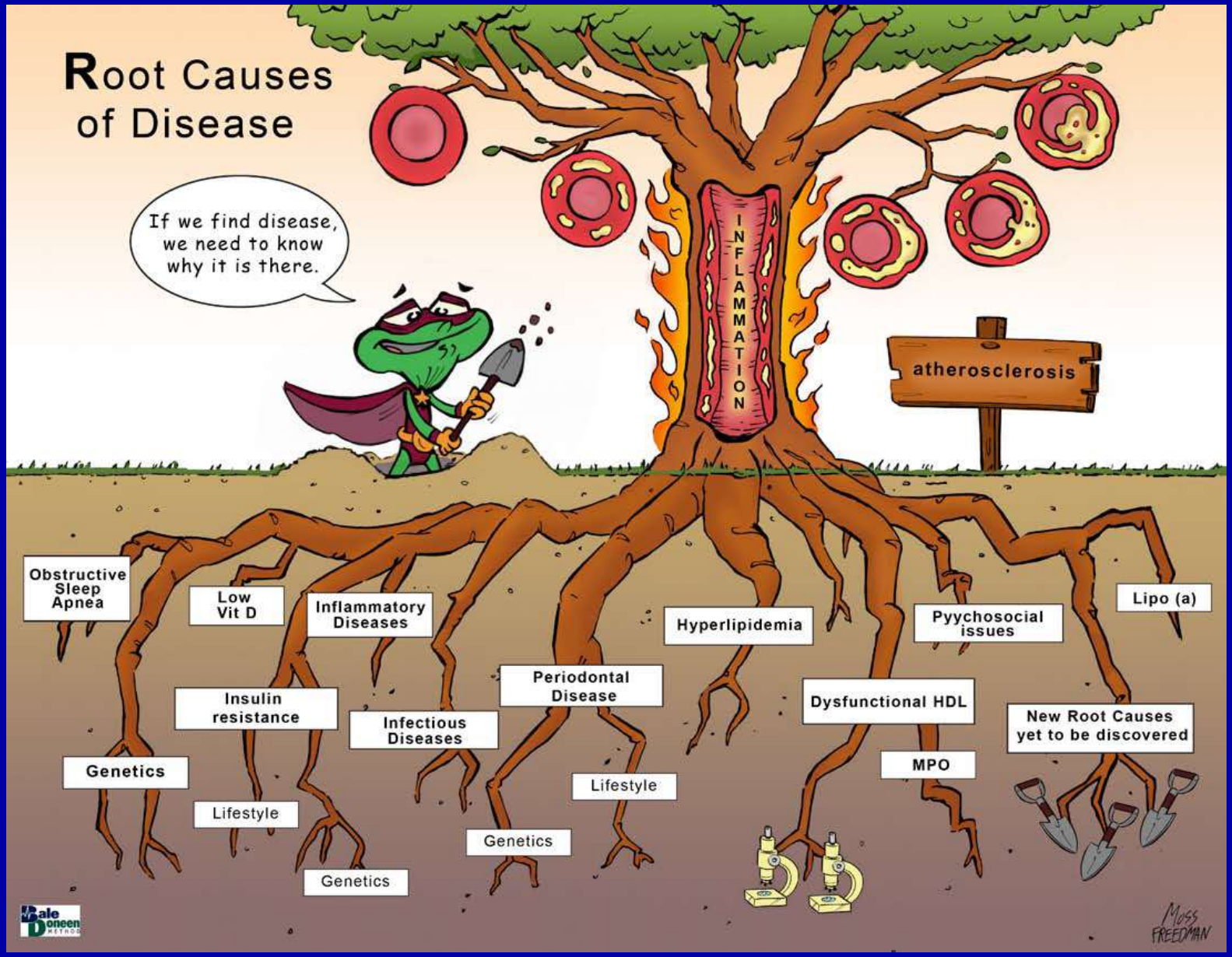
?? due to circadian phase shift (~2 hr. advance)

Depression scores improved ~50%

Oren, D. A., et. al. *BIOL PSYCHIATRY* 2002;51:422–425

BD Method Thoughts

- Now that we are paying more attention to bilirubin realize low levels may signal SAD
- Light therapy can improve SAD and bilirubin levels
- ???? Translate to reduced CV risk ????



ADA: Who to Test for Prediabetes & DM

Table 4—*Criteria for testing for diabetes in asymptomatic adult individuals*

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2*) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - women with polycystic ovary syndrome
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. In the absence of the above criteria, testing for diabetes should begin at age 45 years.
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

*At-risk BMI may be lower in some ethnic groups.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA: Who to Test for Prediabetes & DM

Table 5—*Testing for type 2 diabetes in asymptomatic children**

Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus any two of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
- Maternal history of diabetes or GDM during the child's gestation

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

*Persons aged 18 years and younger.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA: Criteria for Diagnosing Pre-DM

Table 3—*Categories of increased risk for diabetes (prediabetes)

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h plasma glucose in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA: Criteria for Diagnosing DM

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

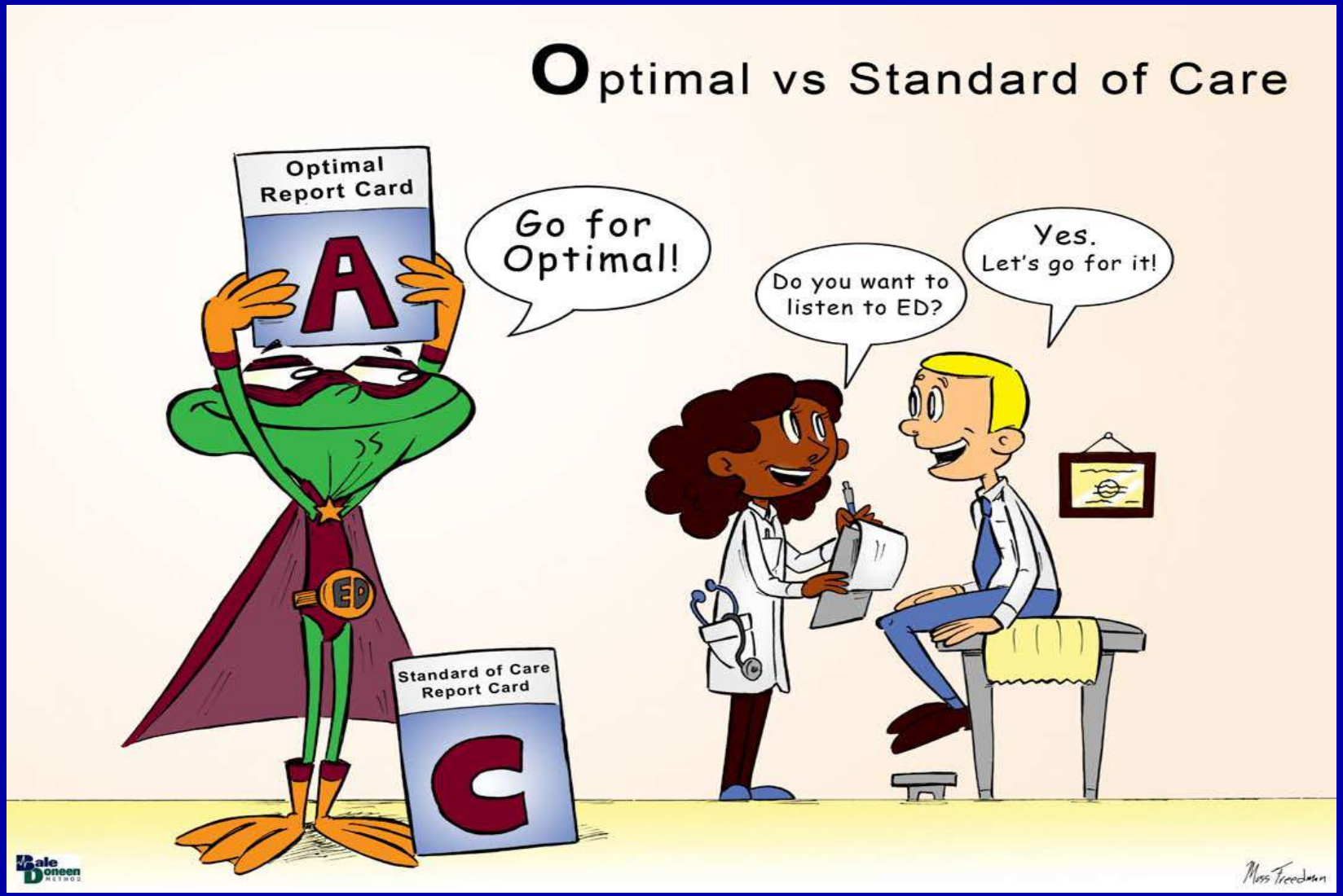
OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

Optimal Care



ADA: Management of Prediabetes

- Screen for and treat modifiable CVD risk factors
- Refer to a program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking. (based on the cost-effectiveness of DM prevention, such programs should be covered by third-party payers.)
- Metformin may be considered especially for those with BMI $\geq$35 kg/m2, < 60 yo and hx GDM.
- At least annual monitoring for the development of diabetes

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA: Screening and Managing CHD Risk

- Assess CV risk factors annually (basic lipids, BP, smoking, MACR, famhx)
- Pts at increased for CHD risk should receive ASA, statin, ACEI or ARB if hypertensive.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA BP Recommendations

- BP >120/80 mmHg - advise lifestyle changes to reduce BP
- BP ≥140/80 mmHg – start pharm. rx; start ACEI or ARB; @HS
- BP >115/75 mmHg is associated with increased CV events and mortality in individuals with diabetes
- Systolic BP >120mmHg predicts long-term end-stage renal disease (ESRD).

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA Changes BP Goal

- Recommend systolic BP <140; diastolic <80 mm Hg

- Lower levels may be appropriate for some patients
  - a) younger
  - b) longer life expectancy
  - c) higher risk of stroke
  - d) if can be achieved without excessive rx and without significant side effects

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

ADA: Comorbidities

- Periodontal disease- briefly mentioned – concluded- more severe, but not more prevelant; should be assessed and rx'ed, but no definite benefit with glycemic control
- OSA – briefly mentioned – obesity focused
- Low testosterone – briefly mentioned- obesity focused
- Cognitive impairment – stated is increased, but not related to sugar; more research needed
- Depression – stated is higher incidence

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

BD Method Thoughts

- Like screening criteria; very few pts <25 BMI; CVD; IR
- Incredible that still anchoring in risk factors and not disease!!
- Let down that Dx criteria still using A1c and 140mg/dL
- Disappointed, but not surprised, pio & GLP1 not emphasized
- Amazed still using 30 as cut point with MACR
- Saddened that other significant CV risk factors got little or no attention: lipo (a); psychosocial issues; PD; sleep; inflammatory conditions; tests for arterial inflammation and oxidation; bilirubin; vitamin D; genetics (9p21 & haptoglobin)
- Disillusioned by their myopic approach
- Bottom line: they have much to learn and gain from the BD Method

Oxidized LDL (oxLDL) Influenced by Genetics

- Genetic factors do affect the susceptibility of LDL to oxidation
- Three separate populations (>8,000 subjects) demonstrated a genetic link with higher oxLDL levels
- apoB rs676210 SNP influences levels

Kari-Matti Mäkelä, BM, BSc, et. al. Circulation Genetics on line 12/20/2012
DOI: 10.1161/CIRCGENETICS.112.964965

Oxidized LDL (oxLDL) Influenced by Genetics

- Mutation of leucine to proline increases plasma oxLDL levels in a stepwise manner
- The variation in apoB probably changes the 3D structure of apoB in a way that makes LDL less prone to oxidation in homozygous apoB (Leu/Leu)

Kari-Matti Mäkelä, BM, BSc, et. al. Circulation Genetics on line 12/20/2012
DOI: 10.1161/CIRCGENETICS.112.964965

Oxidized LDL (oxLDL) Influenced by Genetics

- Pro/Pro individuals (higher oxLDL) did not have higher risk for CAD & heart attacks

- Results are in line with large non-genetic studies showing that serum oxLDL levels are not independently predictive of CV end points.

Kari-Matti Mäkelä, BM, BSc, et. al. Circulation Genetics on line 12/20/2012
DOI: 10.1161/CIRCGENETICS.112.964965

Serum Oxidized LDL not as Predictive of CV Risk as apoB or TC/HDL

- 18,140 men followed 6 yrs.; 32,826 women followed 8 yrs.; 501 fatal and non-fatal MIs; each case matched with two controls; evaluated oxLDL (via 4E6 antibody) as predictor for events
- After adjustment for other standard lipid values, oxLDL was not predictive
- Ox-LDL was less predictive in development of CHD than apoB and TC/HDL-C ratio.

Wu, T., MD, PHD, et. al. J Am Coll Cardiol 2006;48:973–9

Serum Oxidized LDL not as Predictive of CV Risk as apoB or TC/HDL

- oxLDL is present in atherosclerotic lesions
- The importance of circulating oxLDL as a superior predictor of subsequent coronary events was not substantiated
- Antibody 4E6 is specific for oxidized apoB; it was found not to add prognostic information beyond apoB itself.

Wu, T., MD, PHD, et. al. J Am Coll Cardiol 2006;48:973–9

Serum Oxidized LDL not as Predictive of CV Risk as apoB or TC/HDL

Table 4. OxLDL in Comparison With Mutually Adjusted ApoB or Total/HDL Cholesterol Ratio in Multivariate Models

	Mutually Adjusted Marker 1			Mutually Adjusted Marker 2		
	Marker	RR (95% CI)	p_{LRT}	Marker	RR (95% CI)	p_{LRT}
Men	OxLDL	1.31 (0.67–2.57) p for linear trend = 0.3	0.5	ApoB	2.80 (1.44–5.44) p for linear trend = 0.0003	0.004
	OxLDL	1.70 (0.93–3.13) p for linear trend = 0.03	0.1	Total/HDL cholesterol ratio	2.82 (1.48–5.38) p for linear trend = 0.0001	0.002
Women	OxLDL	1.75 (0.77–4.01) p for linear trend = 0.1	1.0	ApoB	2.67 (1.09–6.53) p for linear trend = 0.02	0.06
	OxLDL	1.17 (0.51–2.68) p for linear trend = 0.3	0.2	Total/HDL cholesterol ratio	4.30 (1.76–10.52) p for linear trend = 0.0004	0.002

Multivariates included: body mass index, physical activity, alcohol consumption, history of high blood pressure, high cholesterol and diabetes, family history of myocardial infarction, and use of aspirin. The p value of the likelihood ratio test (LRT) is for adding the corresponding marker to the model; it compares the model with corresponding marker with the model without the corresponding marker with 4 def. Each marker is added to the model in quintiles with 4 dummy variables.

RR = relative risk in the highest compared with the lowest quintile of each marker; Ox = oxidized; other abbreviations as in Tables 1 to 3.

Wu, T., MD, PHD, et. al. J Am Coll Cardiol 2006;48:973–9

Serum Oxidized LDL not as Predictive of CV Risk as apoB or TC/HDL

- This data has clinical implications by raising the question of whether we should add additional costs to measure oxLDL
- Total cholesterol and HDL-C are standard lipid measures, and TC/HDL-C ratio can be calculated at no incremental cost
- TC/HDL-C ratio is a more powerful predictor of CHD than oxLDL

Wu, T., MD, PHD, et. al. J Am Coll Cardiol 2006;48:973–9

Leptin Predicts Stroke Risk in Older Men

- 3,411 men; no known CVD; aged 60 to 79; followed 9 yrs.; 192 incident strokes
- Leptin was a significant predictor:
  adjusted HR top quartile vs bottom - 1.73 (95%CI 1.06–2.83)
- Adjusted for: age, BMI, waist, hsCRP, known CV risk factors including systolic BP, fibrinolytic activity, von Willebrand

Wannamethee, G. S., PhD, et. al. ***Stroke.*** **2013;44:3-8**

Leptin Predicts Stroke Risk in Older Men

- Sensitivity analysis restricting incident cases to confirmed ischemic strokes (n=62 cases).

- Leptin was significantly associated with risk:

HR 2.31 (95% CI, 1.03–5.17)

adjusted for age, BMI, DM, angina, AF, smoking, social class, alcohol, physical activity, lung function, systolic BP, BP meds

Wannamethee, G. S., PhD, et. al. ***Stroke.*** **2013;44:3-8**

Leptin Predicts Stroke Risk in Older Men

- BMI and waist were not significantly associated with risk of stroke
- BMI >30 kg/m^2 vs <25 showed the lowest risk of stroke; after adjustments was significant with p=0.04 (??NT pro-BNP levels)
- Adiponectin did not predict stroke risk

Wannamethee, G. S., PhD, et. al. ***Stroke.*** **2013;44:3-8**

Leptin Predicts Stroke Risk in Older Men: Mechanisms??

- Endothelial dysfunction, inflammation and coagulation/fibrinolysis balance ???

- In this study not explained by endothelial dysfunction (vWF) inflammation (CRP or IL-6), or fibrinolytic activity (D-dimer). (?MACR, Lp-PLA2, MPO)

- Other mechanisms??: oxidative stress, platelet aggregation, and proliferation of vascular smooth muscle cells (?F2 isoprostane)

Wannamethee, G. S., PhD, et. al. ***Stroke.*** **2013;44:3-8**

BD Method Thoughts

- These measurements are dynamic; study assumes no change over 9 years
- Would be nice to know all levels measured at time of events
- Would be nice to know MACR, fibrinogen, Lp-PLA2, MPO, F2 isoprostane and NT pro-BNP at baseline and at time of event
- Perhaps leptin will turn out to be an independent valuable marker of stroke risk

Wannamethee, G. S., PhD, et. al. ***Stroke.*** **2013;44:3-8**

EDFROG IRA

Education	Genetics	Individual Management
Disease	Optimal	Risk factor response
Fire	Roots	Assess Disease Annually

Physical Activity Improves Cardio-metabolic Risk Factors

- 16 sex matched twins with 30 yr difference in physical activity; 1037 age and sex matched pairs of physically active versus inactive individuals for ≥5 yrs; evaluated differences in cardio-metabolic risk factors; adjusted for BMI

- Significant difference favoring activity for the following: isoleucine (stabilizers glucose, +), α1-acid glycoprotein (acute phase reactant), glucose, VLDL, large HDL

- Fatty acids were also shifted towards less saturated with activity

Kujala, U. M., et. al. *Circulation* online 12/20/2012
http://circ.ahajournals.org/content/early/2012/12/19/CIRCULATIONAHA.112.105551

Physical Activity Improves Cardio-metabolic Risk Factors

Decreased in active pts.

Increased in active pts.

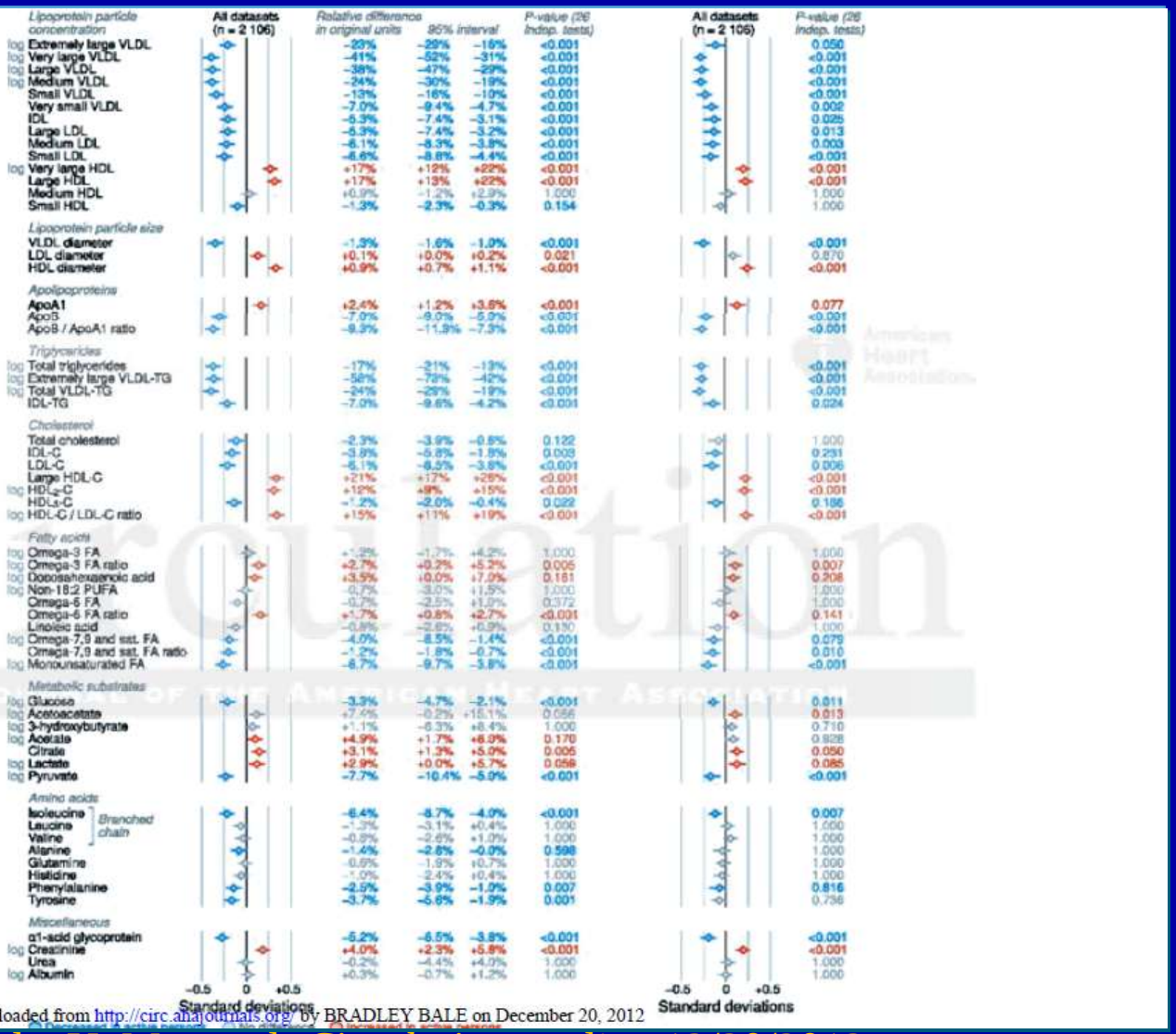


Figure 2

Kujala, U. M., et. al. *Circulation* online 12/20/2012

http://circ.ahajournals.org/content/early/2012/12/19/CIRCULATIONAHA.112.105551

Physical Activity Improves Cardio-metabolic Risk Factors

- Findings indicate that persistently physically active individuals have a healthier circulating metabolic profile than their inactive counterparts.

- Supports efforts for increased physical activity to reduce the public health burden of complex cardio-metabolic diseases

Kujala, U. M., et. al. *Circulation* online 12/20/2012
http://circ.ahajournals.org/content/early/2012/12/19/CIRCULATIONAHA.112.105551

BD Method Thoughts

- No surprises- supports lipid benefits of exercise
- Most interesting finding was alpha 1-acid glycoprotein which is an acute-phase serum protein mainly produced by the liver in response to proinflammatory cytokines
- Unfortunately numerous other inflammatory biomarkers were not done: isoprostane; hsCRP; fibrinogen; MACR; Lp-PLA2; myeloperoxidase; bilirubin

Kujala, U. M., et. al. *Circulation* online 12/20/2012
http://circ.ahajournals.org/content/early/2012/12/19/CIRCULATIONAHA.112.105551

Exercise Increases Bilirubin

- 11 marathon males; 38yo ±18 yrs.; BMI~21.7; ran 4 hrs. ~ 29 miles; 10 hr. fast prior to run

- Bilirubin (mol/l) before 11.1 ±4.0 & after 15.1 ±3.7 $p<0.05$

- "it is well established that plasma antioxidant molecules such as bilirubin increase after exercise."*

S. Ben´ıtez et al. / Atherosclerosis 160 (2002) 223–232
*Vasankari, T.J., et. al. *Free Radic Biol Med 1997;22:509–13*
*Viguie, C.A., et. al. *J Appl Physiol* 1993;75:566–72

Testosterone Increases Bilirubin

- 123 hypogonadal men; AndroGel (T gel) 1% CIII per day; ~ 3 ½ yrs.
- Serum total bilirubin showed a small (0.02 to 0.09 mg/dl) increase - $p<0.001$

WANG, C., et. al. *The Journal of Clinical Endocrinology & Metabolism* 89(5):2085–2098

Ischemic Stroke Risk Factors for Younger Population

- 4,467 ischemic stroke pts; aged 18 to 55 yo; median age 47 yo; investigated risk factor prevalence
- ~ 60% male; ~25% of strokes were TIAs
- ~10% of ischemic strokes occur <45 yo & with major long-term socioeconomic consequences
- Cost-effective preventive strategies are needed & require precise knowledge of modifiable risk factors for age

von Sarnowski B et al. Stroke 2013;44:119-125

Ischemic Stroke Risk Factors for Younger Population

- Non-modifiable risk factors: age, sex, history of CVE, and family history of CVD
- Well-documented and modifiable risk factors: CAD, PAD, HF, MI, valvular disease, AF, DM, BP, dyslipidemia, smoking, obesity, physical activity
- Less well-documented or potentially modifiable risk factors: migraines, OSA, short sleep duration, high alcohol consumption

von Sarnowski B et al. Stroke 2013;44:119-125

Ischemic Stroke Risk Factors for Younger Population

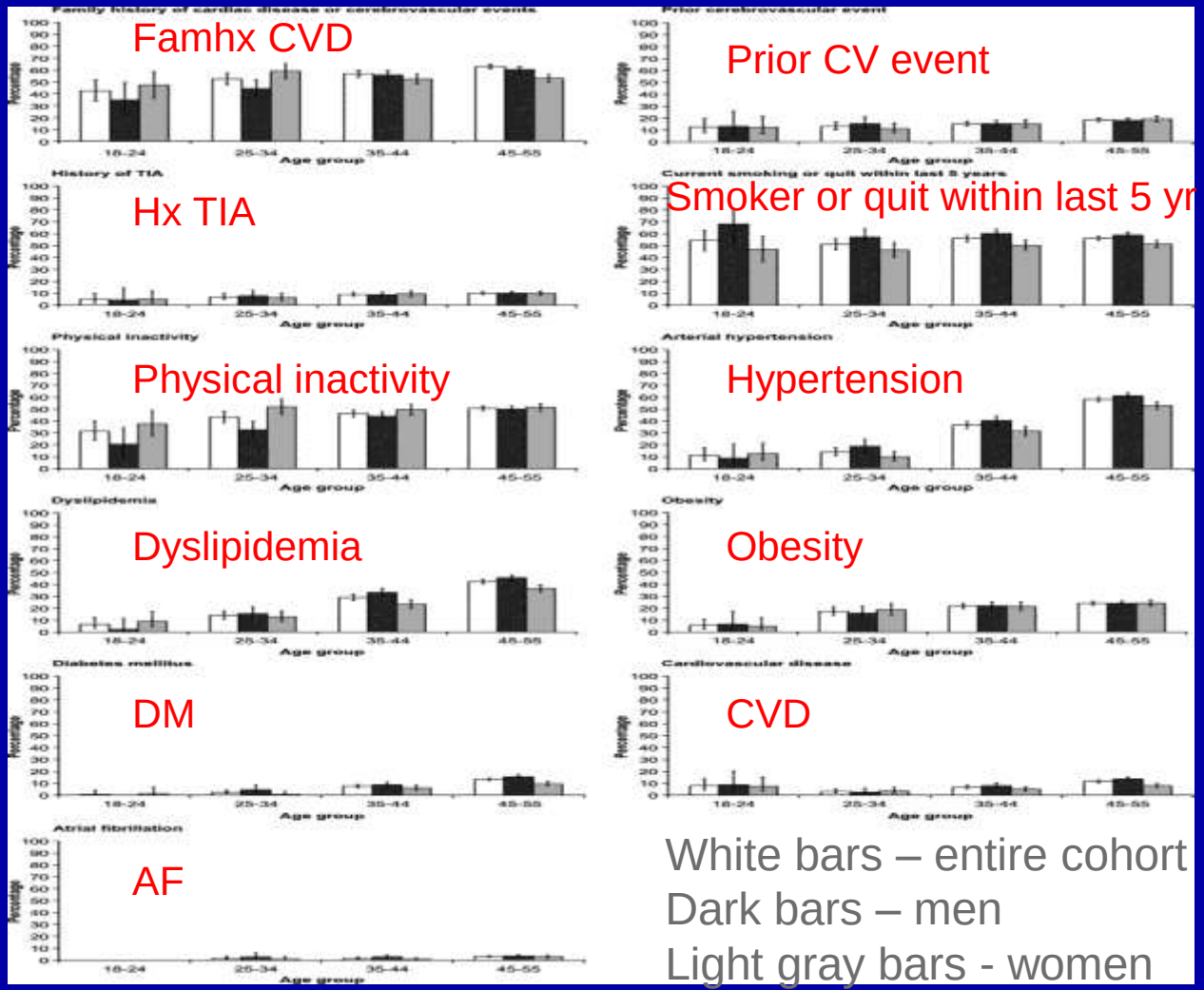
- Most frequent well-documented and modifiable risk factors were smoking (55.5%), physical inactivity (48.2%), arterial hypertension (46.6%), dyslipidemia (34.9%), and obesity (22.3%).

- Most frequent less well-documented modifiable risk factors were high-risk alcohol consumption (33.0%), short sleep duration (20.6%) and migraines (26.5%)

von Sarnowski B et al. Stroke 2013;44:119-125

Ischemic Stroke Risk Factors for Younger Population

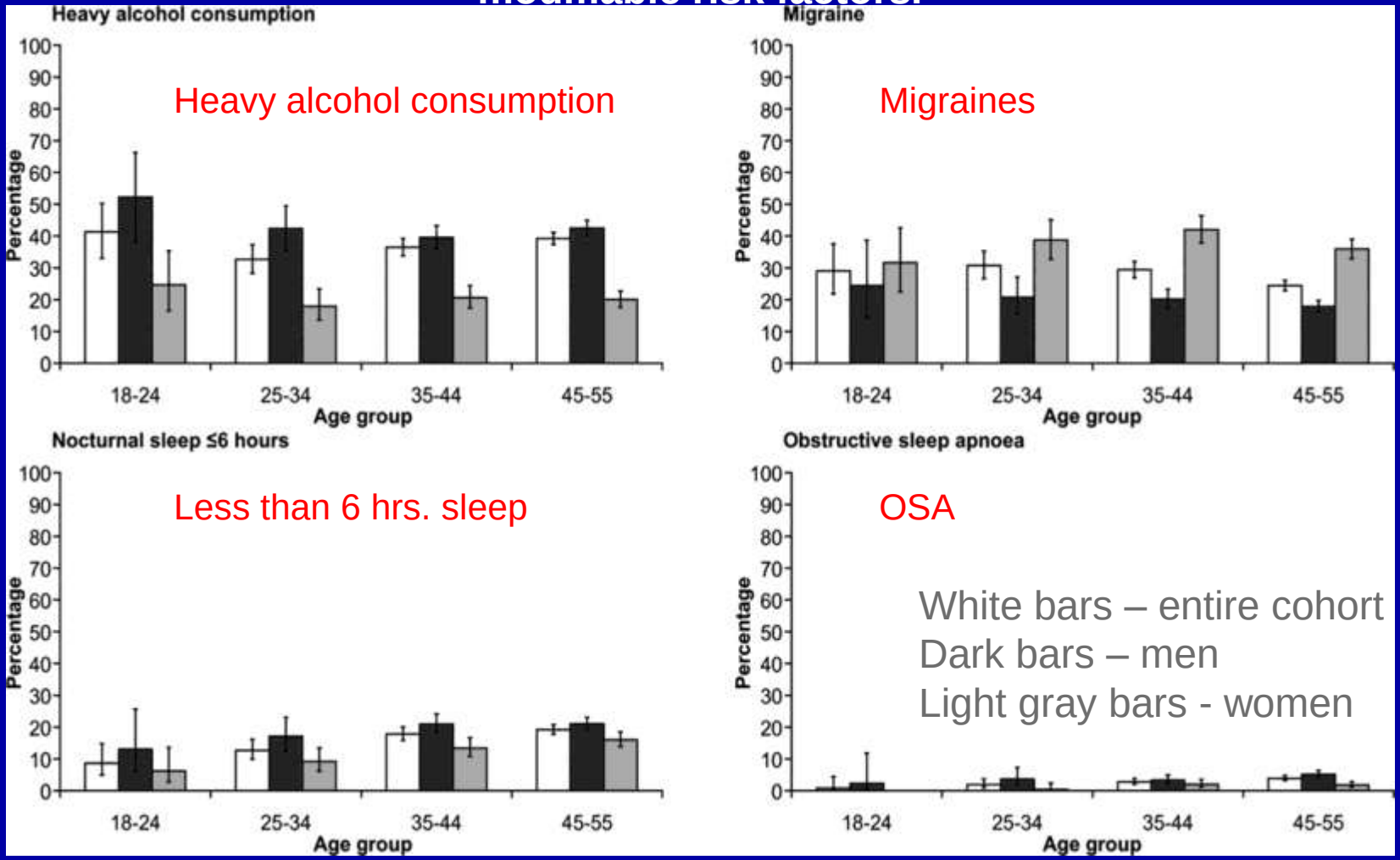
Age- and sex-specific proportions of nonmodifiable and modifiable risk factors.



von Sarnowski B et al. Stroke 2013;44:119-125

Ischemic Stroke Risk Factors for Younger Population

Age- and sex-specific proportions of less well-documented or potentially modifiable risk factors.



von Sarnowski B et al. Stroke 2013;44:119-125

Ischemic Stroke Risk Factors for Younger Population

- The well-documented vascular risk factors of BP, DM and hyperlipidemia are adversely influenced by lifestyle behaviors of smoking, physical inactivity, obesity, lack of sleep, high alcohol intake.

- The high prevalence of the above unhealthy choices in this group of stroke victims emphasizes the importance of adhering to healthy lifestyle behavior

- Physical inactivity, obesity along with BP, DM and dyslipidemia increased with age.

von Sarnowski B et al. Stroke 2013;44:119-125

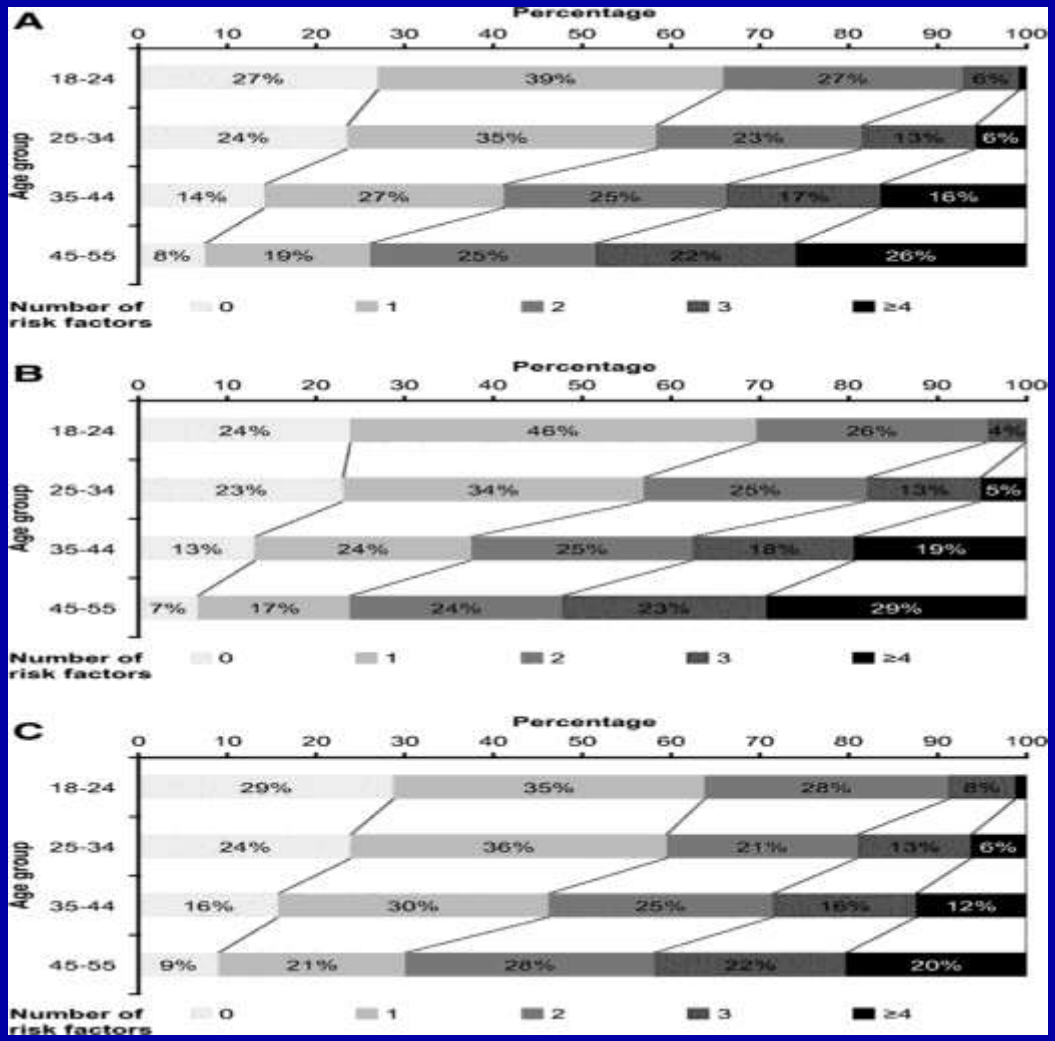
Ischemic Stroke Risk Factors for Younger Population

Proportions with none to ≥4 modifiable risk factors according to age

Entire cohort

Men

Women



von Sarnowski B et al. Stroke 2013;44:119-125

BD Method Thoughts

- A substantial % of stroke victims <35 yo had zero modifiable risk factors!!!
- This implies either a high prevalence of genetic influence and or missing some significant risk factors
- Potential missing risk factors: oral health; poor diet, psychosocial issues, vit. D, lipo (a), systemic infections, systemic inflammatory conditions, illicit drug use – cannabis*
- Definitely supports: not smoking, being physically active, maintaining a healthy weight, sleeping at least 6 hrs.; avoid binge drinking

von Sarnowski B et al. Stroke 2013;44:119-125

***Wolff Valérie, et. al. *Stroke.* published online December 27, 2012

Dale Doneen METHOD

Bariatric Surgery In Obese Type 2 DM Reduces CV Risk

- 15,951 obese DM pts.; 2,580 had bariatric surgery; average follow-up 20 mos.
- Rate of new-onset macro- or microvascular events was 2% in surgery pts vs 11% in non-surg. pts
- Rate of an incident CV event was 2% in surgery pts vs 13% in non-surg pts
- Multivariate-adjusted analysis showed significant RR reductions for CV events of 75% with bariatric surgery

Dr. John D. Scott. Annual Southern Surgical Association Meeting 12/12/2012

ADA: Bariatric Surgery

- Bariatric surgery may be considered for DM adults with BMI ≥35 kg/m2, especially if the DM or associated comorbidities are difficult to control with lifestyle and pharmacological therapy.

- Patients who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring.

ADA. *Diabetes Care* **January 2013 vol. 36 no. Supplement 1 S11-S66**
doi: 10.2337/dc13-S011

Barbaric or Civilized??

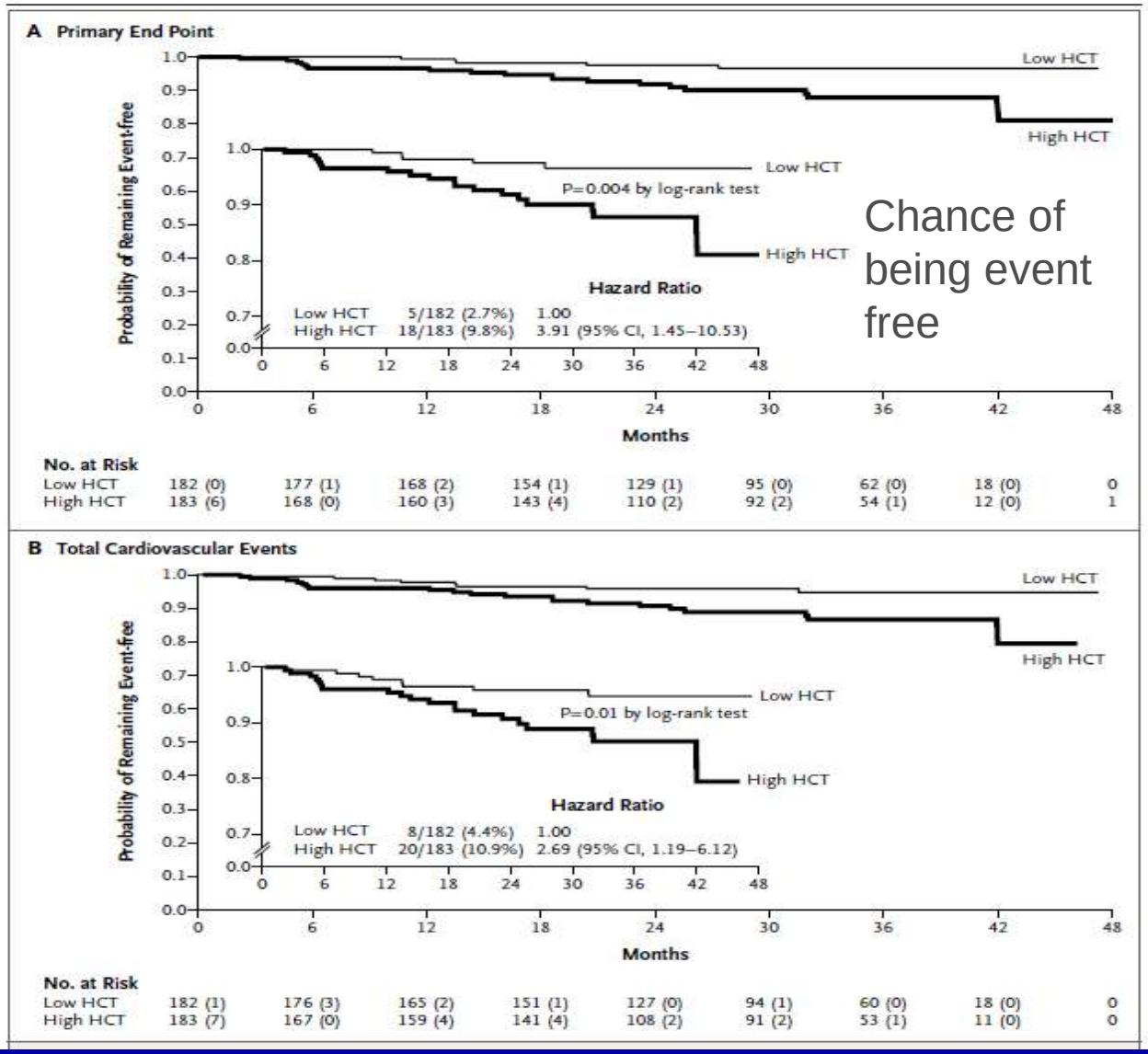
Polycythemia Vera (PCV): Hct <45% Lowers CV Risk

- 365 JAK2 + PCV pts.; either rx'ed to Hct <45% or 45 to 50%; end point: CV death or major thrombotic event; followed 2 ½ yrs

- HR in high-hematocrit group vs low group

  3.91; (95% CI, 1.45 to 10.53) P = 0.007

Marchioli, R. M.D, et. al. ***N Engl J Med* 12/8/2012.**
DOI: 10.1056/NEJMoa1208500



Chance of being event free

Total CV Events = Primary plus superficial venous thrombosis

Marchioli, R. M.D, et. al. ***N Engl J Med* 12/8/2012**

Rats!!

Pioglitazones Mitigates Aortic Value Stenosis (AVS)

- Mice prone to AVS; fed unhealthy diet; half rx'ed with pio ; 6 month trial; end points: histology and echo
- Pio attenuated lipid deposition, calcification, and apoptosis of aortic valves and improved aortic valve function
- Suggests pio may be useful for early intervention to prevent or slow stenosis of aortic valves

Chu, Y., et. al. ***Arterioscler Thromb Vasc Biol*. 2/2013;33:00-00**

Pioglitazones Mitigates Aortic Value Stenosis (AVS): ? Why ?

- PPARγ in the vascular wall protects against development of atherosclerosis.
- PPARγ impairs differentiation of progenitor cells into osteoblasts
- PPARγ is antiinflammatory; inflammation plays an important role in vascular calcification and aortic stenosis

Chu, Y., et. al. ***Arterioscler Thromb Vasc Biol*. 2/2013;33:00-00**

Hot Topics

ER Niacin-Laropriprant Failed to Reduce CV Risk

- 25,673 high CV risk pts; two rx arms: statin or statin plus ER niacin-laropriprant; followed 4 yrs.; primary endpoint: coronary deaths, non-fatal MI, strokes or revascularizations
- No significant benefit found
- There was a significant increase in serious non-fatal events
- Details to follow in first quarter of 2013

Merck announces HPS2-THRIVE study of Tredaptive (extended-release niacin/laropiprant) did not achieve primary endpoint. December 20, 2012

ER Niacin-Laropriprant Failed to Reduce CV Risk

- TREDAPTIVE/CORDAPTIVE is approved in approximately 70 countries
- Currently sold in approximately 40 countries.
- Also sold under the brand names PELZONT in Italy and TREVACLYN in Italy and Portugal.
- Sales through the first three quarters of 2012 were approximately $13 million.

Merck announces HPS2-THRIVE study of Tredaptive (extended-release niacin/laropiprant) did not achieve primary endpoint. December 20, 2012

Concern with new ER niacin (Cordaptive)

- Uses an investigational PGD2 receptor antagonist (laropriprant) to reduce flushing (blocks PGD2)
- PDG2 leads to 15-deoxyprostaglandin J2 which is potent ligand of PPAR-gamma*
- Potential CV benefits of stimulating PPAR-gamma include: reduction in MMP-9; MCP; HsCRP; PAI-1; fibrinogen; tumor necrosis factor alpha; ADMA^

*Journal of Clinical Lipidology 8/2007 Vol 1, No. 4:248-255
^ Bale/Doneen Method 3/7/2008

Cases???

Upcoming Presentations

Upcoming Presentations

- 2/22-23/2013 – BD Method Preceptorship; 17 hr. CME; LV, NV
- 3/8/2013 – Keynote Speakers – American Academy of Dental Practice Administration Conference; LV,NV
- 4/24/2013 – Keynote Speakers – Delta Dental Executive National Program; St. Louis, MO
- 5/17-18/2013 – BD Method Preceptorship; 17 hr. CME; Washington, DC

Open for Discussion