Bale/Doneen Live Chat Session

10/10/2012

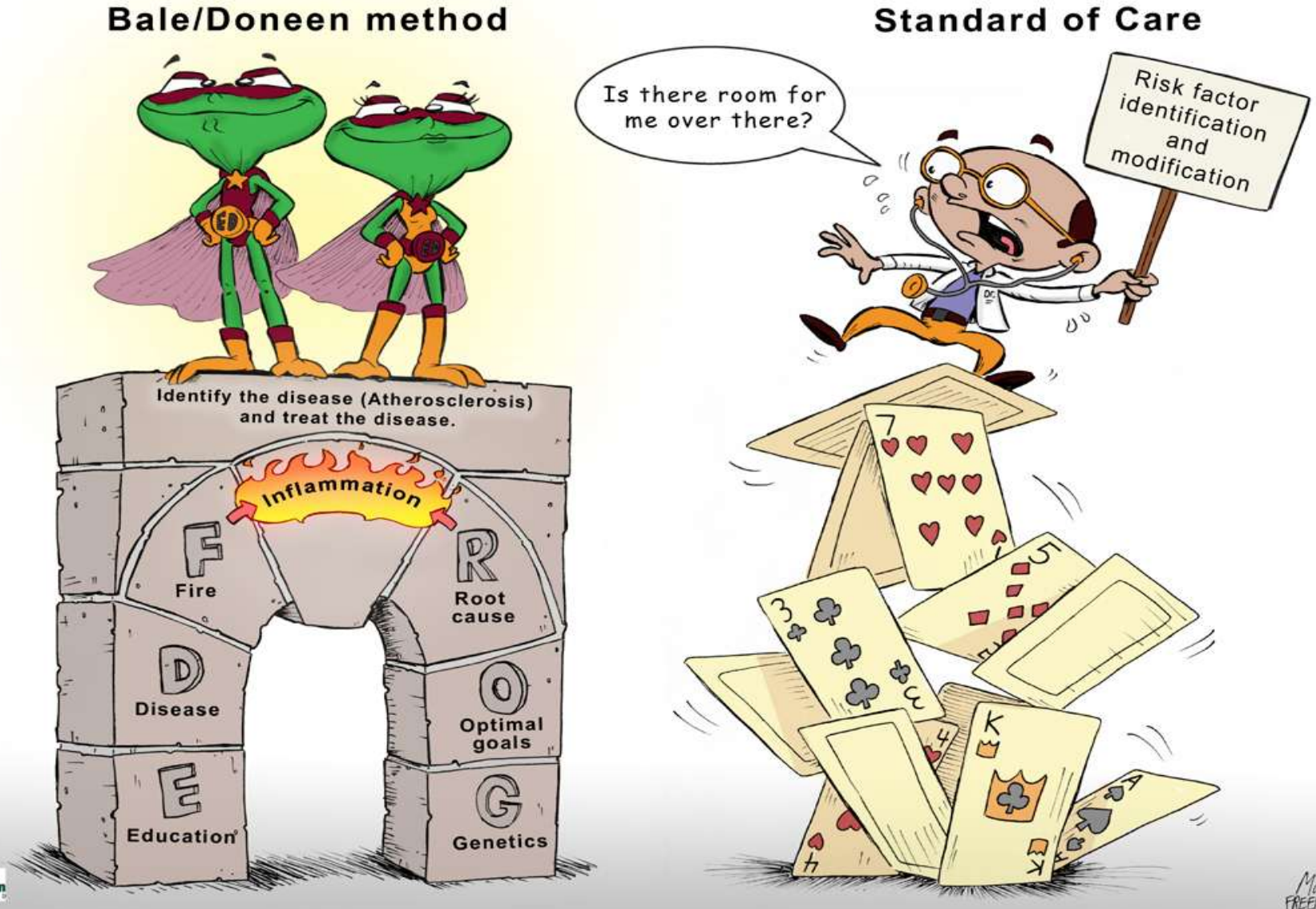
5:30-6:30 pm PST

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

What's the difference?



Coronary Calcium Score Relates to Mortality Risk Differently in Smokers

- 44,042 asympt. pts; ~54 yo; cardiac CT for CACS; followed ~5.6 years; 14% (6020) active smokers; 901 died
- 42 times more likely to die if, CACS >400 coupled with smoking compared to zero CACS in non-smoker!!

McEvoy JW, et al. JACC Cardiovasc Imaging 10/2012; 5:1037-1045

Coronary Calcium Score Relates to Mortality Risk Differently in Smokers

- Smokers with a zero score are 3 to 4 times more likely to die in five to six years than a non-smoker with a zero score

- Smokers risk of death is higher at any given CACS, but becomes less so as the score goes up

McEvoy JW, et al. JACC Cardiovasc Imaging 10/2012; 5:1037-1045

Coronary Calcium Score Relates to Mortality Risk Differently in Smokers

All-cause mortality hazard ratios for smokers vs nonsmokers

CAC score	HR for smoking vs nonsmoking (95% CI)
0	3.62 (2.28-5.75)
1-100	3.84 (2.82-5.22)
101-400	3.54 (2.57-4.89)
>400	2.71 (2.12-3.48)

McEvoy JW, et al. JACC Cardiovasc Imaging 10/2012; 5:1037-1045

Coronary Calcium Score Relates to Mortality Risk Differently in Smokers

- Any score above zero portents increased mortality risk (Amy's: "either pregnant or not")
- In non-smokers an advancing score increases the chance of death to a greater degree than in a smoker

McEvoy JW, et al. JACC Cardiovasc Imaging 10/2012; 5:1037-1045

Coronary Calcium Score Relates to Mortality Risk Differently in Smokers

All-cause mortality hazard ratios (95% CI) comparing subjects with elevated coronary calcium and those with zero coronary calcium

CAC score	Non-smokers, n=38 022	Smokers, n=6020
0	Reference	reference
1-100 vs 0	2.62 (1.99-3.45)	2.04 (1.10-2.83)
101-400 vs 0	4.15 (3.11-5.54)	2.57 (1.62-4.05)
>400 vs 0	8.04 (6.09-10.61)	4.25 (2.72-6.63)

McEvoy JW, et al. JACC Cardiovasc Imaging 10/2012; 5:1037-1045

Coronary Calcium Score Relates to Mortality Risk Differently in Smokers

- Does this sound like Amy!! ☺

- "---------- studies have shown that --- lung-cancer scans can also identify those with coronary calcium. It can give you extra information with no extra cost," coinvestigator Dr Khurram Nasir

McEvoy JW, et al. JACC Cardiovasc Imaging 10/2012; 5:1037-1045

CIMT can Enhance CV Event Risk Prediction

- 3,703 pts; median age 64.4 yrs; 48% men; followed 3 yrs.; 215 suffered a first CVE

- All measures of C-IMT and the interadventitia common carotid artery diameter (ICCAD) were associated with the risk of CVEs, after adjustment for FRFs and therapies with $p < 0.005$

- Average of 8 maximal IMT measurements (IMTmean-max), alone or combined with ICCAD, classified events and non-events better than the mean CCA-IMT

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

Table 1 Definitions of Carotid IMT Ultrasonographic Variables

Name	Definitions	Absolute Differences (Mean ± SD)		ICCs	
		Intra	Inter	Intra	Inter
1^{st}CC-IMT$_{mean}$	Average of 6 mean IMT values obtained by measuring left and right CC (1-cm length) in the first centimeter proximal to the bifurcation in the 3 scan angles (lateral, anterior, and posterior)	0.031 ± 0.03	0.045 ± 0.041	0.95	0.89
1^{st}CC-IMT$_{max}$	The highest among all the maximal IMT values measured in each 1 of the 6 first centimeters of the CC segments	0.039 ± 0.041	0.079 ± 0.072	0.92	0.83
CC-IMT$_{mean}$	Average of all mean IMT values obtained from left and right CC visualized in their entire length (excluding the first centimeter) with sequential probe movements of 1-cm length, in the 3 scan angles. The total number of segments visualized ranged from 6 to 24 according to the length of the subject's neck. In each segment, the software automatically provided the maximal IMT value	0.089 ± 0.161	0.101 ± 0.081	0.92	0.95
CC-IMT$_{max}$	The highest of all the maximal IMT values detected in the 6–24 CC segments	0.067 ± 0.101	0.138 ± 0.307	0.96	0.52
Bif-IMT$_{mean}$	Average of 6 mean IMT values obtained by measuring left and right Bif (1-cm length) in the 3 scan angles (lateral, anterior, and posterior)	0.09 ± 0.114	0.139 ± 0.178	0.93	0.76
Bif-IMT$_{max}$	The highest maximal IMT value measured in the 6 Bif segments	0.093 ± 0.122	0.204 ± 0.26	0.84	0.68
ICA-IMT$_{mean}$	Average of 6 mean IMT values obtained by measuring left and right ICAs (the first cm proximal to bifurcations) in the 3 scan angles (lateral, anterior, and posterior)	0.17 ± 0.204	0.195 ± 0.153	0.95	0.94
ICA-IMT$_{max}$	The highest maximal IMT value measured in the 6 ICA segments	0.195 ± 0.283	0.331 ± 0.459	0.91	0.60
IMT$_{mean}$	Average of 1^{st}CC-IMT$_{mean}$, CC-IMT$_{mean}$, Bif-IMT$_{mean}$, and ICA-IMT$_{mean}$, left and right carotid arteries	0.038 ± 0.05	0.054 ± 0.095	0.96	0.87
IMT$_{max}$	Highest value out of 1^{st}CC-IMT$_{max}$, CC-IMT$_{max}$, Bif-IMT$_{max}$, and ICA-IMT$_{max}$ of left and right carotid arteries	0.164 ± 0.227	0.239 ± 0.238	0.95	0.89
IMT$_{mean\text{-}max}$	Average of maximal IMT measured in 8 segments (1^{st}CC, CC, Bif, and ICA in left and right carotid arteries)	0.096 ± 0.109	0.134 ± 0.145	0.95	0.88
ICCAD	Average of left and right interadventitia common carotid artery diameters	0.037 ± 0.037	0.031 ± 0.023	0.99	0.99

Reproducibility data between 125 intrasonographer and 32 intersonographer duplicate scans are also reported. Composite variables (IMT$_{mean}$, IMT$_{max}$, and IMT $_{mean\text{-}max}$) refer to the whole carotid tree. 1^{st}CC = first centimeter of the common carotid; Bif = bifurcation; CC = common carotid; ICA = internal carotid artery; ICC = intraclass correlation coefficient; IMT = intima-medial thickness.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- Interadventitia common carotid artery diameter (ICCAD), is assessed in plaque-free areas; ‘arterial diameter’
- ICCAD increases during atherogenesis and enlargement is associated with VRFs and subclinical atherosclerosis
- Studies specifically designed to assess the prognostic value of ICCAD are few
- ICCAD represents ‘remodeling’ (process to maintain good lumen despite developing atherosclerosis)

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- Compared with classification based on FRFs alone, the NRI resulting from the combination of FRFs +ICCAD +IMTmean-max was +12.1% ($p < 0.01$).

- Pts with a FRS > 22.6% (cohort average), and both IMTmean-max and ICCAD above the median, had a 6.5% risk to develop a CVE over 3 years versus a 3.4% risk for those with the same FRS, and both IMTmean-max and ICCAD below the median

- Risk stratification based on C-IMT and ICCAD as an adjunct to FRFs is a rational approach for prevention of CVD

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

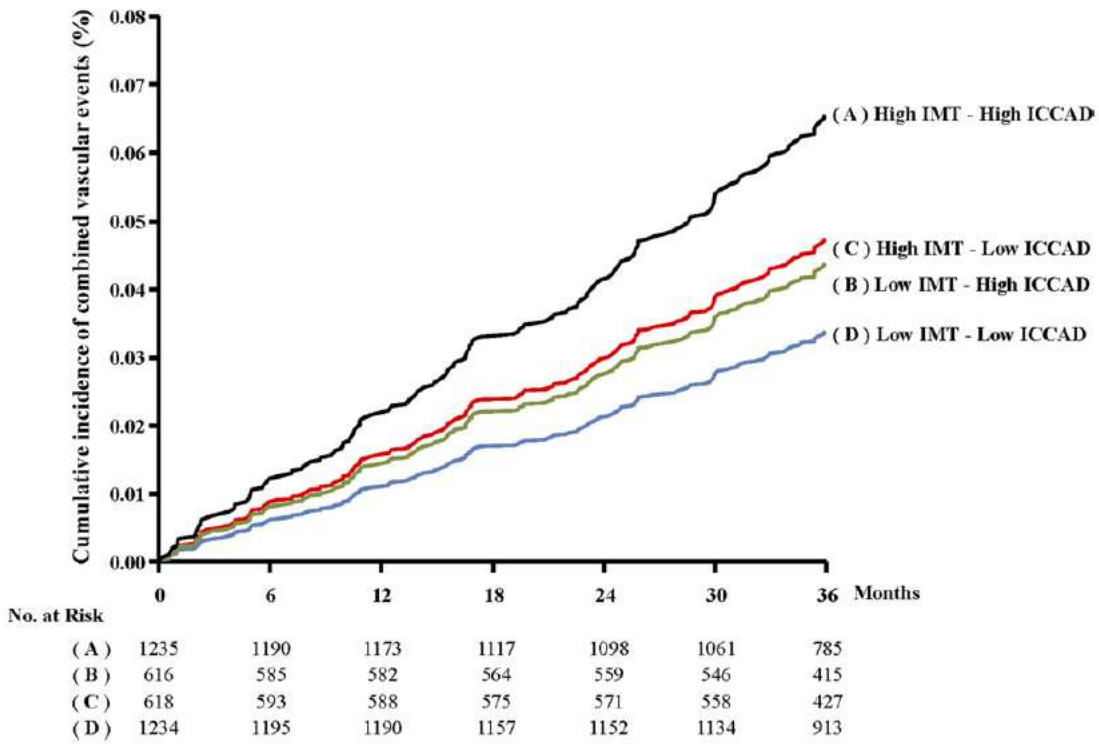


Figure 1 **FRS-Adjusted Kaplan-Meier Incidence Curves**

The study population was stratified according to $IMT_{mean\text{-}max}$ and ICCAD values above or below their respective medians (1.34 mm and 7.74 mm, respectively). Curves were computed for the mean value of FRS (22.6%). FRS = Framingham Risk score; ICCAD = interadventitia common carotid artery diameter; $IMT_{mean\text{-}max}$ = mean–maximum intima-media thickness.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

Table 2 Baseline Characteristics of IMPROVE Study Participants With and Without Vascular Events

	Entire Sample (N = 3,703)	Without Event (n = 3488)	With Event (n = 215)	p Value
Kuopio (pooled)	1,048 (28.3)	972 (27.9)	76 (35.3)	
Stockholm	532 (14.4)	508 (14.6)	24 (11.2)	
Groningen	527 (14.2)	478 (13.7)	49 (22.8)	<0.0001
Paris	501 (13.5)	476 (13.6)	25 (11.6)	
Milan	553 (14.9)	533 (15.3)	20 (9.30)	
Perugia	542 (14.6)	521 (14.9)	21 (9.77)	
Anthropometric variables				
Male	1,774 (47.9)	1,641 (47.0)	133 (61.9)	<0.0001
Age, yrs	64.2 ± 5.4	64.1 ± 5.40	65.4 ± 5.84	0.0012
BMI, kg/m^2	27.3 ± 4.27	27.2 ± 4.25	28.0 ± 4.56	0.023
Waist/hip ratio	0.92 ± 0.09	0.92 ± 0.09	0.94 ± 0.08	<0.0001
Diastolic blood pressure, mm Hg	82.0 ± 9.8	81.9 ± 9.75	82.8 ± 10.4	0.32
Systolic blood pressure, mm Hg	142.0 ± 18.5	141.7 ± 18.3	145.8 ± 20.5	0.010
Smoking habits				
Current smokers	549 (14.8)	501 (14.4)	47 (21.9)	
Former smokers	1,371 (37.0)	1,272 (36.5)	96 (44.7)	<0.0001
Never smokers	1,783 (48.2)	1,712 (49.1)	71 (33.0)	
Pack-years*	18 (8–30)	18 (8–30)	21 (11–30)	0.06
Biochemical markers				
Total cholesterol, mmol/l	5.49 ± 1.13	5.49 ± 1.13	5.50 ± 1.05	0.75
HDL cholesterol, mmol/l	1.26 ± 0.36	1.27 ± 0.36	1.18 ± 0.30	0.0007
Triglycerides, mmol/l	1.3 (0.93, 1.89)	1.3 (0.92, 1.87)	1.48 (1.09, 2.17)	0.0001
LDL cholesterol, mmol/l	3.54 ± 1.01	3.55 ± 1.01	3.53 ± 0.94	0.75
Uric acid, μmol/l	310 (263–360)	309 (263–359)	329 (274–390)	0.0003
hs-CRP, mg/l	2.06 (0.96–3.80)	2.05 (0.95–3.75)	2.30 (1.22–4.63)	0.012

Not significant

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Blood glucose, mmol/l	5.92 ± 1.64	5.91 ± 1.65	6.05 ± 1.42	0.013
Creatinine, μmol/l	79 (68–91)	79 (68–90)	84 (74–97)	<0.0001
Personal history				
Hypercholesterolemia	2,581 (69.7)	2,450 (70.2)	131 (60.9)	0.004
Hypertriglyceridemia	954 (25.8)	893 (25.6)	61 (28.4)	0.37
Low HDL	488 (13.2)	449 (12.9)	39 (18.1)	0.027
Hypertension	2,552 (68.9)	2,391 (68.5)	161 (74.9)	0.053
Diabetes	913 (24.7)	846 (24.3)	67 (31.2)	0.023
Framingham risk score	22.6 (14.3–34.4)	22.2 (14.2–33.8)	30.8 (19.1–47.6)	<0.0001
≤5%	43 (1.20)	42 (1.2)	1 (0.5)	
>5, ≤10%	354 (9.6)	347 (9.9)	7 (3.3)	
>10, ≤15%	570 (15.4)	546 (15.7)	24 (11.2)	
>15, ≤20%	564 (15.2)	539 (15.5)	25 (11.6)	
>20%	2,021 (54.6)	1,875 (53.8)	146 (67.9)	<0.0001
Family history				
CHD	2,315 (62.5)	2,165 (62.1)	146 (67.9)	0.062
CVD	1,322 (35.7)	1,240 (35.6)	81 (37.7)	0.53
PVD	443 (12.0)	412 (11.8)	29 (13.5)	0.42
Therapies				
Statins	1,483 (40.0)	1,408 (40.4)	75 (34.9)	0.11
Fibrates	284 (7.7)	274 (7.86)	12 (5.58)	0.23
Fish oil	125 (3.4)	120 (3.44)	5 (2.33)	0.38
Other lipid-lowering drugs	23 (0.62)	21 (0.60)	2 (0.93)	0.55
Beta blockers	878 (23.7)	815 (23.4)	64 (29.8)	0.03
Calcium antagonists	603 (16.3)	558 (16.0)	45 (20.9)	0.06
ACE inhibitors	722 (19.5)	683 (19.6)	39 (18.1)	0.60
Alpha-2 inhibitors	45 (1.22)	42 (1.20)	3 (1.40)	0.80
Sartans	562 (15.2)	529 (15.2)	33 (15.3)	0.94
Diuretics	857 (23.1)	804 (23.1)	53 (24.7)	0.59
Antiplatelet agents	618 (16.7)	561 (16.1)	57 (26.5)	<0.0001
Insulin	141 (3.81)	131 (3.76)	10 (4.65)	0.51
Estrogen supplement	226 (11.7)	220 (6.31)	6 (2.79)	0.04

Not significant

Worsened risk

Beneficial

CIMT can Enhance CV Event Risk Prediction

Ultrasonographic variables, mm				
CC-IMT$_{mean}$	0.71 (0.65–0.80)	0.71 (0.65–0.79)	0.77 (0.69–0.88)	<0.0001
1stCC-IMT$_{mean}$	0.76 (0.69–0.87)	0.76 (0.69–0.86)	0.81 (0.73–0.96)	<0.0001
Bif-IMT$_{mean}$	1.06 (0.85–1.34)	1.05 (0.84–1.33)	1.17 (0.94–1.55)	<0.0001
ICA-IMT$_{mean}$	0.75 (0.64–1.00)	0.75 (0.63–0.98)	0.89 (0.68–1.23)	<0.0001
CC-IMT$_{max}$	1.07 (0.96–1.30)	1.06 (0.95–1.30)	1.15 (1.03–1.48)	<0.0001
1stCC-IMT$_{max}$	1.08 (0.96–1.30)	1.08 (0.96–1.27)	1.18 (1.01–1.48)	<0.0001
Bif-IMT$_{max}$	1.67 (1.30–2.22)	1.67 (1.30–2.22)	1.93 (1.45–2.59)	<0.0001
ICA-IMT$_{max}$	1.17 (0.93–1.76)	1.16 (0.92–1.74)	1.48 (1.02–2.20)	<0.0001
IMT$_{mean}$	0.85 (0.74–1.00)	0.84 (0.74–0.99)	0.95 (0.81–1.13)	<0.0001
IMT$_{max}$	1.85 (1.39–2.50)	1.85 (1.39–2.48)	2.31 (1.65–2.89)	<0.0001
IMT$_{mean-max}$	1.34 (1.12–1.65)	1.33 (1.12–1.63)	1.52 (1.28–1.89)	<0.0001
Plaque†, No.(%)	2,576 (69.5)	2,397 (68.7)	179 (83.2)	<0.0001
ICCAD	7.74 (7.22–8.32)	7.72 (7.20–8.30)	8.13 (7.53–8.66)	<0.0001

Values are n (%), mean ± SD, or median (interquartile range). p Values were calculated by Wilcoxon test or by chi-square as appropriate. To convert biochemical markers in mg/dl, divide values of total and HDL cholesterol by 0.0259016, values of triglycerides by 0.0113815, values of uric acid by 59.48, values of blood glucose by 0.0556122, and values of creatinine by 87.777778. The Framingham risk score was not calculated in 151 patients because of missing data in 1 of the variables included in the algorithm. *Calculated excluding never smokers. †Plaque = presence of at least 1 plaque.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; other abbreviations as in Table 1.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- Significant advantage in using IMTmean or IMTmean-max over CC-IMT—for predicting stroke events
- CC-IMT was as good as composite IMT variables in improving the prediction of coronary events -?? Because atherosclerosis in the bifurcation or in the internal carotid may actually cause cerebrovascular events, whereas it is merely a marker of coronary atherosclerosis.
- Interestingly, composite IMTs that incorporate plaques in their measurement performed significantly better than the presence of plaque.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- The best reclassification was obtained by combining IMTmean-max and ICCAD.
- The NRI using this combination was 19% for combined and cerebrovascular events and 9.8% for coronary events.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

Table 8 Risk Reclassification Comparing the Extrapolated 10-Year Risk According to FRFs Before and After Adding ICCAD and $IMT_{mean\text{-}max}$ in the Prediction of Combined Vascular Events

	10-Year Risk Categories for FRFs Plus ICCAD Plus $IMT_{mean\text{-}max}$			
10-Year Risk Categories for FRFs	<10%	10%–20%	>20%	Reclassified, n (%)
<10%*				
n = 680 (20%)	571 (84%)	109 (16%)	0 (0%)	109 (16.0%)
Observed risk (95% CI)	8 (4.3–12.9)	9.7 (2–23.3)	NA	
10%–20%*				
n = 1,697 (50%)	364 (21.4%)	1087 (64.1%)	246 (14.5%)	610 (35.9%)
Observed risk (95% CI)	7.7 (3.3–13.9)	12.1 (8.5–16.3)	40.6 (26.8–57.4)	
>20%*				
n = 1,007 (30%)	2 (0.2%)	265 (26.3%)	740 (73.5%)	267 (26.5%)
Observed risk (95% CI)	NA	21.7 (12.4–33.6)	39.7 (31.5–48.9)	
NRI: 12.1%; p = 0.003				

*To be noticed, these categories differ from those predicted by the Framingham risk score (see Table 2) due to a recalibration of the risk estimation in our cohort.
NA = not applicable; other abbreviations as in Tables 1, 3, 5, and 7.

Baldassarre, D., PHD, et. al. J Am Coll Cardiol 10/16/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- C-IMTs and ICCAD predict the risk of CVEs independently of each other
- C-IMT assesses atherosclerosis when plaques are incorporated in the measurements
- ICCAD (arterial diameter) reflects vascular remodeling in response to the growth of local atherosclerotic plaques & as a compensatory response to VRFs which associate fairly well with the coronary artery disease status

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/2012;60:1489–99

CIMT can Enhance CV Event Risk Prediction

- Findings provide new evidence to support the use of IMT variables and ICCAD, in addition to VRFs, for CV risk stratification in clinical practice, with a NRI of 12.1%.

- Assessment of composite IMT variables and ICCAD is time consuming compared with CC-IMT assessment alone (15 to 20 vs. 8 to 10 min).

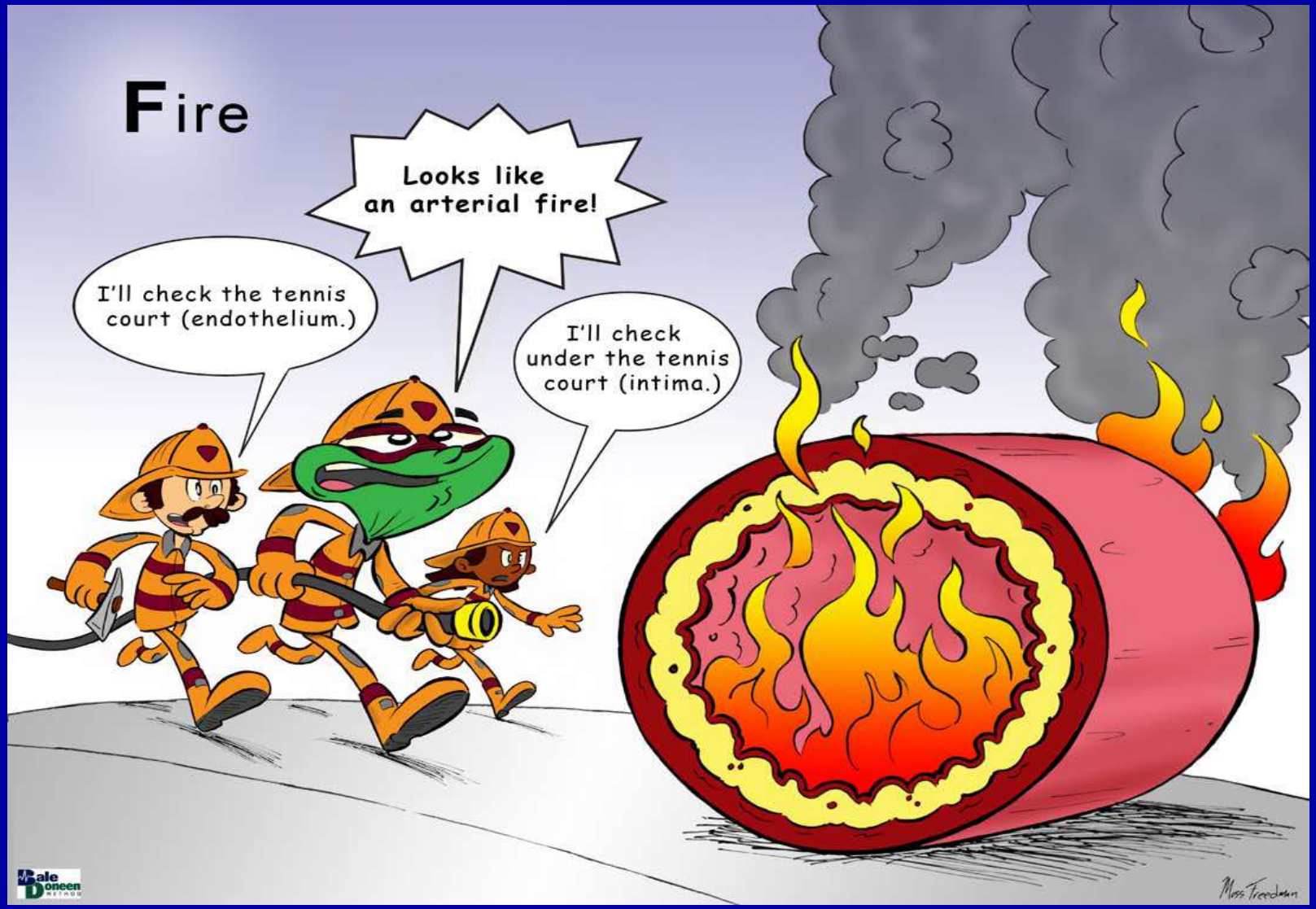
- The benefits provided by a better risk classification may easily offset the additional costs.

Baldassarre, D., PHD, et. al. *J Am Coll Cardiol* 10/16/2012;60:1489–99

BD Method Thoughts

- Supports utilizing CIMT
- Albeit for a given FRS those with above median IMT mean-max and ICCAD were almost double the risk for an event, remember many of the ones with okay US findings had an event
- Do not forget CAFE to CAVES study
- Do your composite IMT measurements incorporate plaque??
- Do you know the correlation coefficients and absolute differences in IMT measurements??
- Perhaps the ICCAD should be added to the testing?

Inflammation



C-Reactive Protein & Fibrinogen Add Predictive Value to Traditional Risk Factors for Predicting First Cardiovascular Events

- Pooled analysis of data from ~250,000 people without CVD
- Adding CRP and or fibrinogen significantly improved risk assessment for a first event.
- Estimated the addition of this information in intermediate risk pts could help prevent one additional event over a period of 10 years for every 390 men & 740 women screened
- This is based on a 20% reduction from statin therapy

The Emerging Risk Factors Collaboration. N Engl J Med. October 4, 2012 Volume 367(14):1310-1320

The NEW ENGLAND JOURNAL of MEDICINE

Hazard Ratio for First CV Event Utilizing CRP and Fibrinogen on Par with TC and HDL

Table 1. Baseline Characteristics and Hazard Ratios for First-Onset Cardiovascular Disease.*

Characteristic	Participants with Assessment of C-Reactive Protein (N = 166,596)	Hazard Ratio (95% CI)†	Participants with Assessment of Fibrinogen (N = 185,892)	Hazard Ratio (95% CI)†
Mean age at time of survey — yr	59.7±8.6	1.90 (1.86–1.94)	59.3±8.4	1.81 (1.77–1.85)
Male sex — no. (%)	82,077 (49)	NA‡	100,530 (54)	NA‡
Current smoker — no. (%)	35,779 (21)	1.64 (1.58–1.71)	46,799 (25)	1.71 (1.64–1.78)
Systolic blood pressure — mm Hg	136±19	1.26 (1.24–1.28)	137±18	1.30 (1.28–1.32)
History of diabetes — no. (%)	10,802 (6)	1.74 (1.64–1.85)	11,287 (6)	1.89 (1.79–2.00)
Total cholesterol — mmol/liter	5.86±1.06	1.17 (1.15–1.19)	5.80±1.08	1.19 (1.17–1.21)
HDL cholesterol — mmol/liter	1.32±0.38	0.86 (0.84–0.88)	1.32±0.39	0.85 (0.83–0.87)
Log_e CRP — mg/liter	0.59±1.09	1.20 (1.18–1.22)	—	—
Fibrinogen — g/liter	—	—	3.15±0.74	1.15 (1.13–1.17)

* Plus–minus values are means ±SD. Data on C-reactive protein are from 38 studies in which 13,568 participants had a first-ever cardiovascular disease outcome during follow-up, and data on fibrinogen are from 40 studies in which 12,021 participants had a first-ever cardiovascular disease outcome during follow-up. Dashes indicate that summary statistics are not applicable for either CRP or fibrinogen because the models used were based on two separate sets of data to maximize the information on each marker. CRP denotes C-reactive protein.

† The hazard ratios were calculated per 1-SD increment in the measured level or as compared with the relevant reference category. Where appropriate, hazard ratios were adjusted for age, sex, smoking status, systolic blood pressure, diabetes status, and levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and C-reactive protein or fibrinogen.

‡ Hazard ratios according to sex are not available (NA) because these models were stratified by sex.

The Emerging Risk Factors Collaboration. N Engl J Med 10/4/2012;367:1310-1320

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Bale/Doneen Discussion Points:

C-Reactive Protein and fibrinogen evaluated as continual variables (no cut points & hsCRP not utilized)

Simply evaluated baseline values and then followed for 10 years; no ongoing monitoring to direct therapy which is what is done with BP,DM, lipids; logical to believe monitoring would have value.

Estimated risk reduction accomplished only with statins assuming a 20% reduction;

High risk patients should have much more therapy which could approach a 100% risk reduction. This would mean:

One event avoided for every 80 men screened & 150 women screened.

If you assume an event costs at least $100,000, the cost of CRP or fibrinogen would have to be about $1,000 to break even (Reality: tests cost pennies).

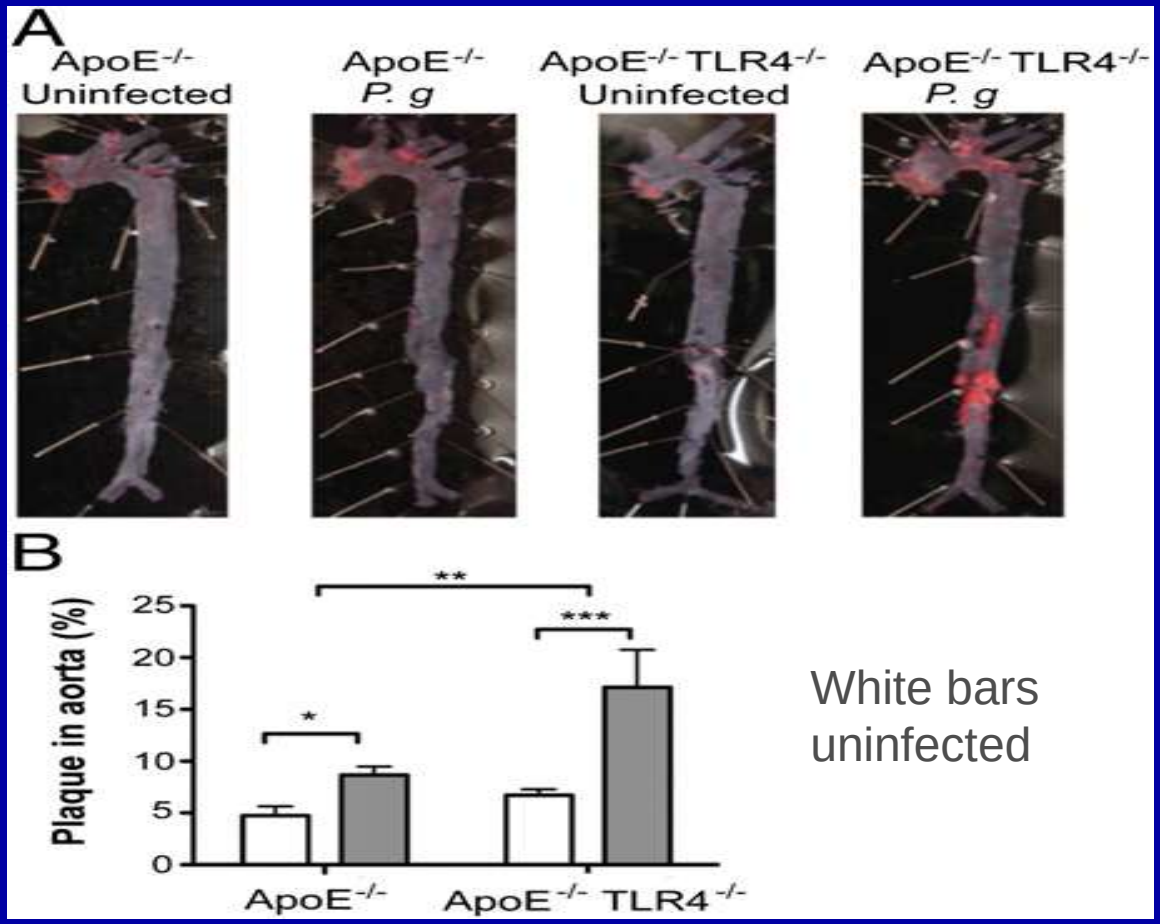
Porphyromonas gingivalis (Pg) and TLRs 2 & 4

- Pg induces proinflammatory responses primarily through fimbriae-mediated signaling via TLR2 that is MyD88- dependent
- Through a separate mechanism Pg stimulates increased endothelial adhesion via TLR2
- If there is a deficiency of TLR4, TLR2 expression is increased with Pg infection which leads to an enhanced atherosclerotic disease state
- In addition, studies indicate that in the absence of TLR4 there can be a failure to develop protective Th1 immunity

Hayashi, C., et. al. *J Immunol* 10/2012; 189:3681-3688

Porphyromonas gingivalis (Pg) and TLRs 2 & 4

Hayashi, C., et. al. J Immunol 10/2012; 189:3681-3688



TLR4 deficiency confers enhanced susceptibility to atherosclerosis in the aorta after infection with P. gingivalis. (A) Sudan IV staining of aorta en face lesions 16 wk after first infection with P. gingivalis. (B) Quantification of lipid content within the total aorta of uninfected (white bars) and P. gingivalis-infected mice (gray bars) (n = 10–13/group). Percentage of aorta occupied by lipids was calculated using IPLab software (Becton Dickinson). *p , 0.05, **p , 0.01, ***p , 0.001.

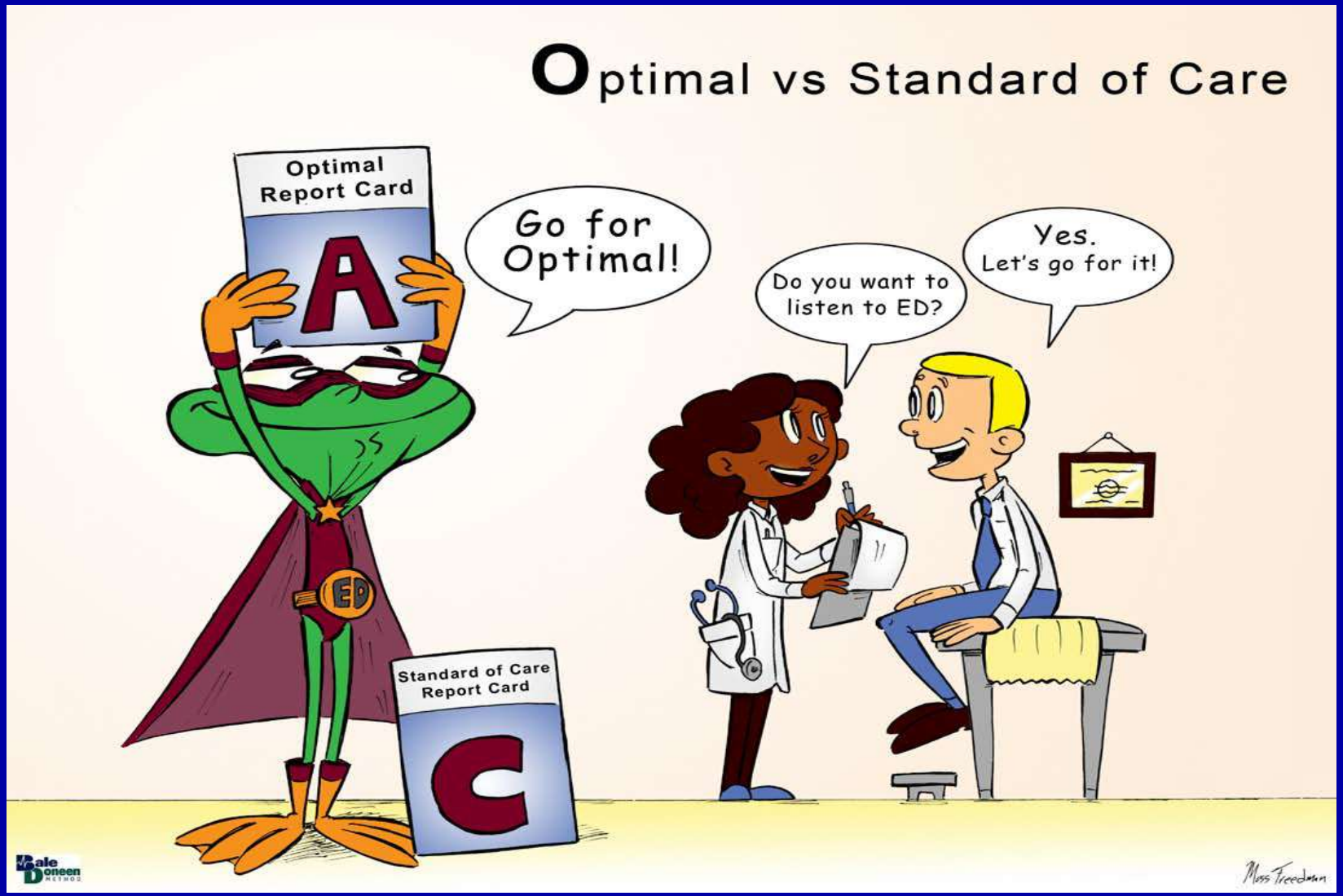
Porphyromonas gingivalis (Pg) and TLRs 2 & 4

- Plausible that common human TLR4 polymorphisms can attenuate receptor signaling leading to an increased risk of atherosclerosis associated with bacterial infection

- Results raise caution for the safety and efficacy of TLR4 antagonists for the treatment of atherosclerosis, especially in patients with comorbid conditions including periodontal disease and other infectious diseases

Hayashi, C., et. al. J Immunol 10/2012; 189:3681-3688

Optimal Care



Prospective Urban Rural Epidemiology (PURE) Study

- Purpose: assess the prevalence, awareness, and control of BP worldwide; 153,000 pts.; 17 countries; 5 continents; 528 urban and rural communities

- Mean age 50.4; 60% female; 46% rural communities

- 40% high BP; 30% pre-hypertension

- Of hypertensives:

  a) 54% unaware of it

  b) 40% being treated

  c) 13% were controlled

Dr Rafael Diaz, European Society of Cardiology (ESC) Congress 8/2012

BP Related to Brain Volume and Cognitive Decline

- 183 pts; mean age 65; 62.4% women; brain MRI; 24 hr. BP monitor.

- Found a significant BP related decrease in gray matter volume of the left supplementary motor areas (Brodmann area 6) and of the left superior and middle frontal gyrus (Brodmann area 8).

- The decrease in gray matter volume was significantly associated with a decline in executive function performance.

Celle, S., et. al. Hypertension. 2012;60:00-00
http://hyper.ahajournals.org/content/early/2012/10/08/HYPERTENSIONAHA.112.193409

BP Related to Brain Volume and Cognitive Decline

- High BP levels were associated with smaller gray matter volume in the supplementary motor area (BA6), regardless of the type of BP measures
- Only high 24-hour and awake SBPs were associated with smaller gray matter volume in the superior frontal gyrus (BA8)
- High-sleep SBP and DBP were significantly associated with smaller gray matter volume in the middle frontal gyrus (BA8).

Celle, S., et. al. Hypertension. 2012;60:00-00
http://hyper.ahajournals.org/content/early/2012/10/08/HYPERTENSIONAHA.112.193409

BP Related to Brain Volume and Cognitive Decline

- Decreases in gray matter volume in supplementary motor areas were significantly associated with decline in all ESDs performance.

- Decreases in superior and middle frontal gyrus were associated with a decline in mental shifting performance.

- Decreases in gray matter volume were shown only on the left side

Celle, S., et. al. Hypertension. 2012;60:00-00
http://hyper.ahajournals.org/content/early/2012/10/08/HYPERTENSIONAHA.112.193409

Comparison of Baseline Characteristics Between the Subset of Participants (n=183) and Other Participants From the PROOF Study (n=828)

Participants From the PROOF Study (n=828)

Baseline Characteristics	VBM+ (n=183)	VBM− (n=828)	*P* Value*
Men/women	68/115	332/496	0.73
Age, mean±SD, y	65.3±0.6	65.8±2.3	0.12
BMI, mean±SD, kg/m²	25.3±3.3	25.3±4.1	0.92
Duration of hypertension, mean±SD, y	9.9±7.5	10.8±7.5	0.34
Use antihypertensive drugs, n (%)†	61(33.3)	301(36.4)	0.45
Type 2 diabetes mellitus, n (%)	11 (6)	48 (5.8)	0.95
Smoking, n (%)‡	44 (24)	207 (25)	0.69
High total cholesterol, n (%)§	66 (36.1)	300 (36.2)	0.89
Alcohol daily use, n (%)‖	70 (38.3)	362 (43.7)	0.12
Education level¶			
Mean±SD, y	11.2±3.3	11.0±3.0	0.06
Level 1, n (%)	18 (10)	62 (9)	0.23
Level 2, n (%)	71 (39)	329 (40)	0.45
Level 3, n (%)	52 (28)	226 (27)	0.29
Level 4, n (%)	42 (23)	211 (24)	0.28
MMSE score (/30), mean±SD	28.7±1.4	28.5±1.5	0.31
Executive subdomains performance			
Digit span score, mean±SD#	7.9±2..6	8.3±2.8	0.16
TMTB score, mean±SD**	100.7±49.2	106.4±51.1	0.20
Ratio of Stroop score, mean±SD††	2.2±0.6	2.2±0.6	0.93
Clinical blood pressure measures, mm Hg‡‡			
SBP, mean±SD	141.7±14.7	143.1±19.1	0.42
DBP, mean±SD	86.6±9.5	87.7±10.5	0.20
24-h ambulatory blood pressure measures, mm Hg			
24-h SBP, mean±SD	119.1±11.4	119.2±13.9	0.91
24-h DBP, mean±SD	76.1±7.5	76.1±8.0	0.97
Awake SBP, mean±SD	123.6±14.7	123.7±14.4	0.88
Awake DBP, mean±SD	78.9±8.2	78.9±8.3	0.97
Sleep SBP, mean±SD	106.1±11.4	106.3±15.3	0.84
Sleep DBP, mean±SD	67.9±7.9	68.9±8.9	0.66
Dip SBP, mean±SD	0.139±0.077	0.139±0.079	0.99
PP, mean±SD	42.8±10.9	43.0±9.7	0.82
MAP, mean±SD	90.1±8.8	90.2±9.2	0.87

Mean ‘clinical’ BP 142/87

Mean 24 BPM BP 119/76

BDM Thoughts

- Should we be using 24 hr. BPM routinely
- Best BP is “just above syncope”
- For that to be a goal, we must maintain CV wellness at young ages to avoid obstructive CVD which precludes the above goal

Preeclampsia by 34 Weeks Carries Long Term CV Consequences for Mother and Offspring

- 45 women with early onset preeclampsia (prior 34 wks); 45 women with late-onset; 50 women with normotensive; 6 to 13 yrs after pregnancy; 47 offspring included

- Early onset preeclampsia:

  1) higher diastolic 6 wks postnatal -(86.25 ± 13.46 vs 75.00 ± 5.00 mm Hg) $p<0.05$

  2) greater increase in BP over subsequent 6 to 13 yrs

  3) higher nocturnal systolic and diastolic BPs in later life (111.07 ± 13.18 versus 101.13 ± 11.50 mm Hg) $p=0.04$,

  (67.00 ± 7.25 versus 58.60 ± 5.79 mm Hg) $p=0.002$

Lazdam, M., et. al. *Hypertension*. published online October 8, 2012
http://hyper.ahajournals.org/content/early/2012/10/08/HYPERTENSIONAHA.112.198366

Preeclampsia by 34 Weeks Carries Long Term CV Consequences for Mother and Offspring

6 to 13 years after pregnancy

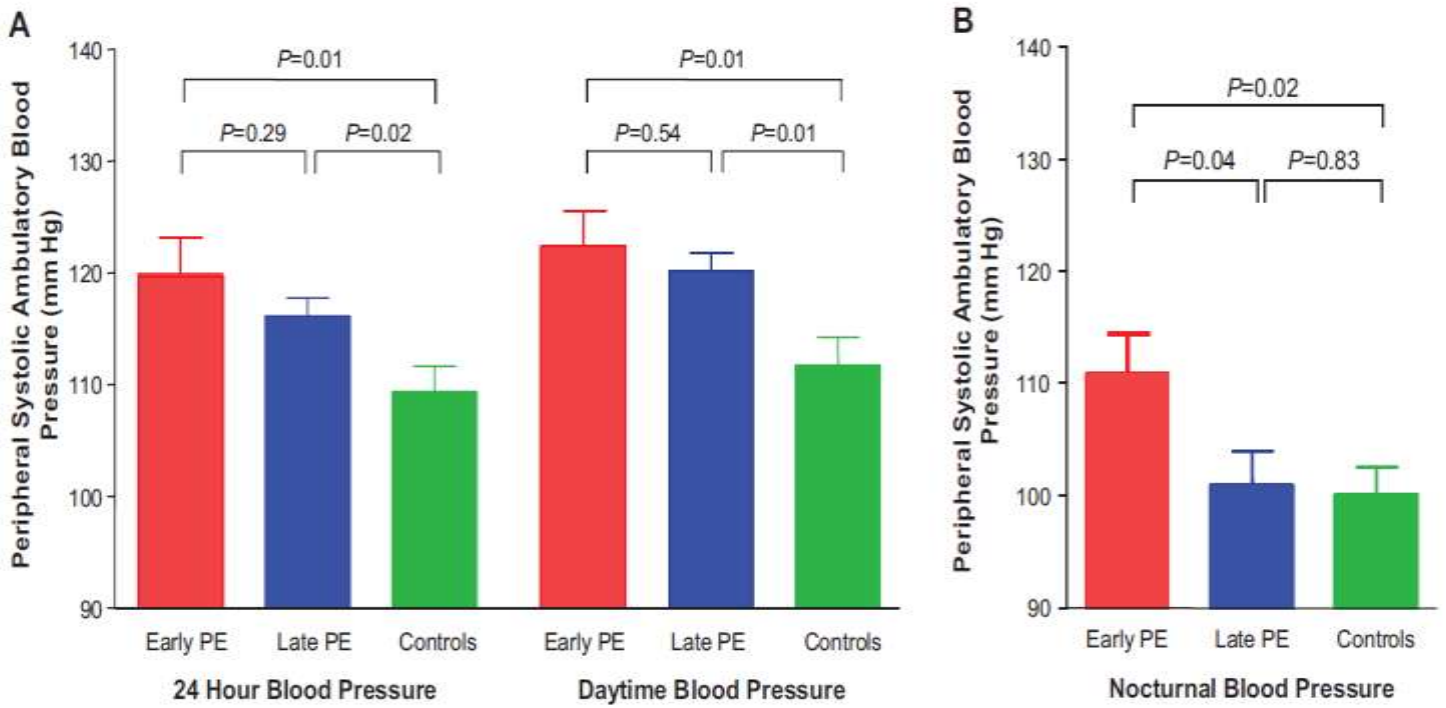


Figure 2. Ambulatory blood pressure. **A**, Women with both early onset (**red bars**) and late-onset preeclampsia (PE) (**blue bars**) had significantly greater 24-hour and daytime systolic blood pressure (SBP) compared with controls (**green bars**). **B,** However, only women with early onset preeclampsia had significantly higher nocturnal SBP compared with both women with uncomplicated pregnancies and late-onset preeclampsia (The **bar graph** represents mean SBP±SEM).

Preeclampsia by 34 Weeks Carries Long Term CV Consequences for Mother and Offspring

- Offspring: 14 were controls, 15 early onset, 18 were to late onset

- Offspring of early onset preeclampsia pregnancies display specific adverse BP characteristics later in life.

- SBP was significantly higher in offspring of early onset preeclampsia compared with those born after late-onset disease

  (96.27 ± 7.30 versus 88.39 ± 7.57 mm Hg) p=0.005

Lazdam, M., et. al. *Hypertension*. published online October 8, 2012
http://hyper.ahajournals.org/content/early/2012/10/08/HYPERTENSIONAHA.112.198366

BDM Thoughts

- All post preeclampsia women deserve close CVD follow-up
- They maybe candidates for aggressive BP rx
- Should follow periodically with CIMT
- Offspring of early onset preeclampsia pregnancies should be watched closely for hypertension

Minnesota Heart Survey: BP Trends 1980-2009

- Surveys Minneapolis/St. Paul; 11,192 men & 12,795 women; age 25 to 74; series of six surveys five years apart; in home and ‘at sites’ visits

- Hypertension = ≥140 syst & or ≥90 diasotlic; controlled = <140/90

Luepker R V et al. Circulation 10/2012;126:1852-1857

Minnesota Heart Survey: BP Trends 1980-2009

- % men with uncontrolled BP fell from 20.3% to 5.8% ($P<0.001$) and women from 13.1% to 2.7% ($P<0.0001$)
- Majority of the decline in mean population BP was the result of aggressive use of antihypertensive drugs.
- Stroke mortality in this population fell in parallel.

Luepker R V et al. Circulation 10/2012;126:1852-1857

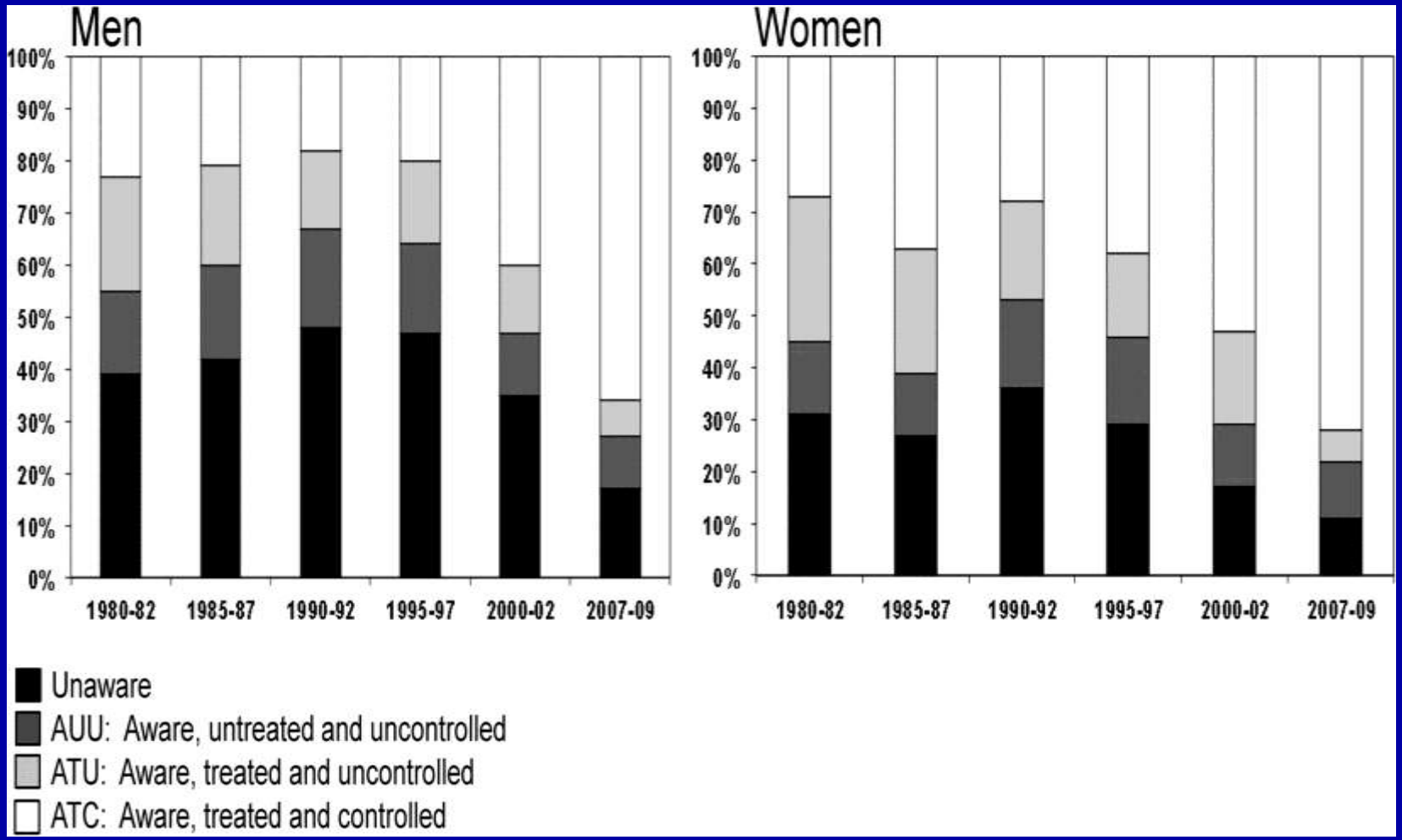
Minnesota Heart Survey: BP Trends 1980-2009

- Declining numbers of hypertensive persons were unaware, untreated, or inadequately treated.
- This trend, first noted in 2000 to 2002, has accelerated despite rising levels of overweight and obesity in this population.
- The rates of hypertension detection and control observed in MHS exceed the 61.2% proposed goal for the national Healthy People 2020.

Luepker R V et al. Circulation 10/2012;126:1852-1857

Minnesota Heart Survey: BP Trends 1980-20

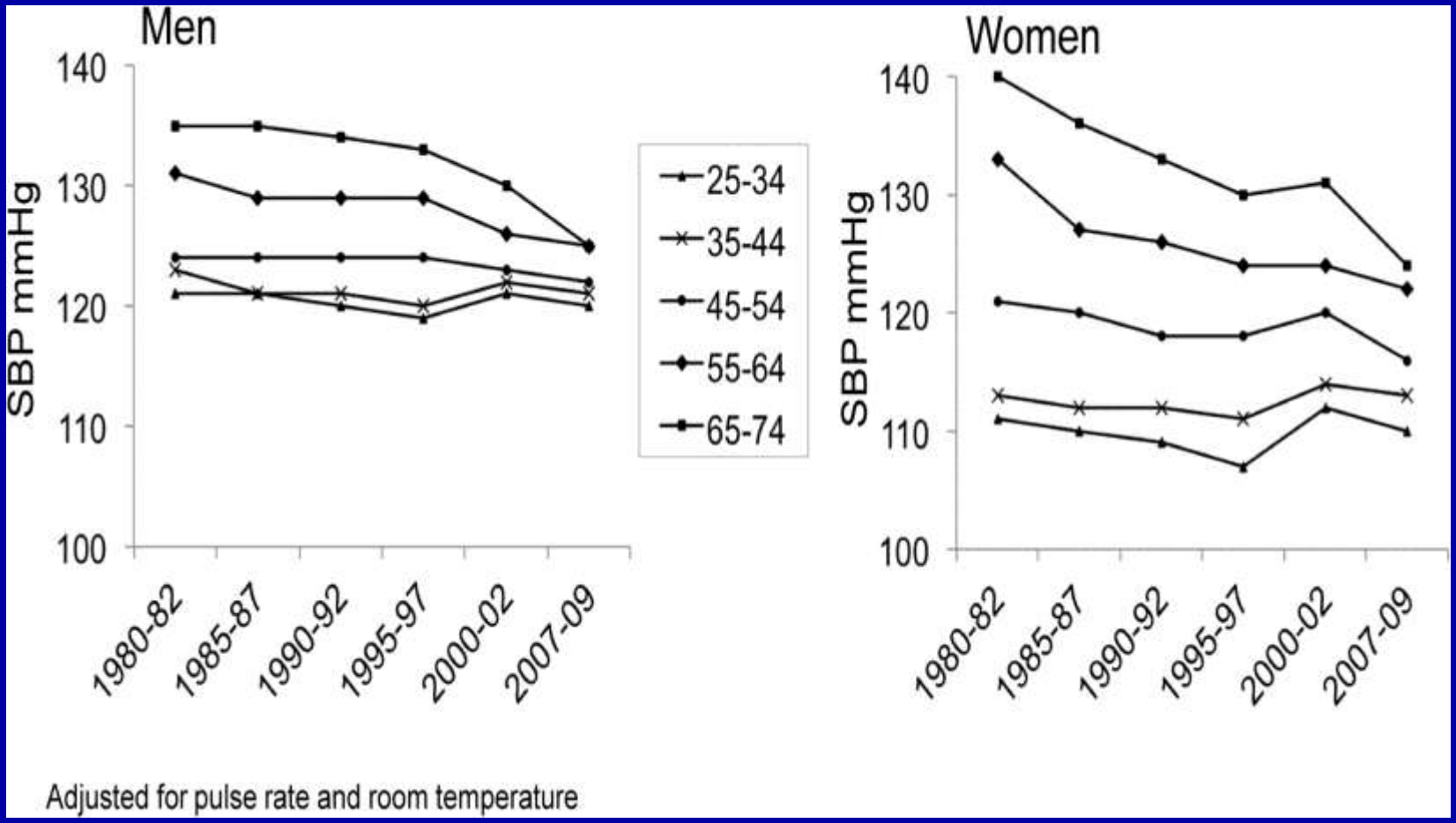
Trends in detection, treatment, and control of hypertension from 1980 to 1982 to 2007 to 2009 for men and women



Luepker R V et al. Circulation 2012;126:1852-1857

Minnesota Heart Survey: BP Trends 1980-20

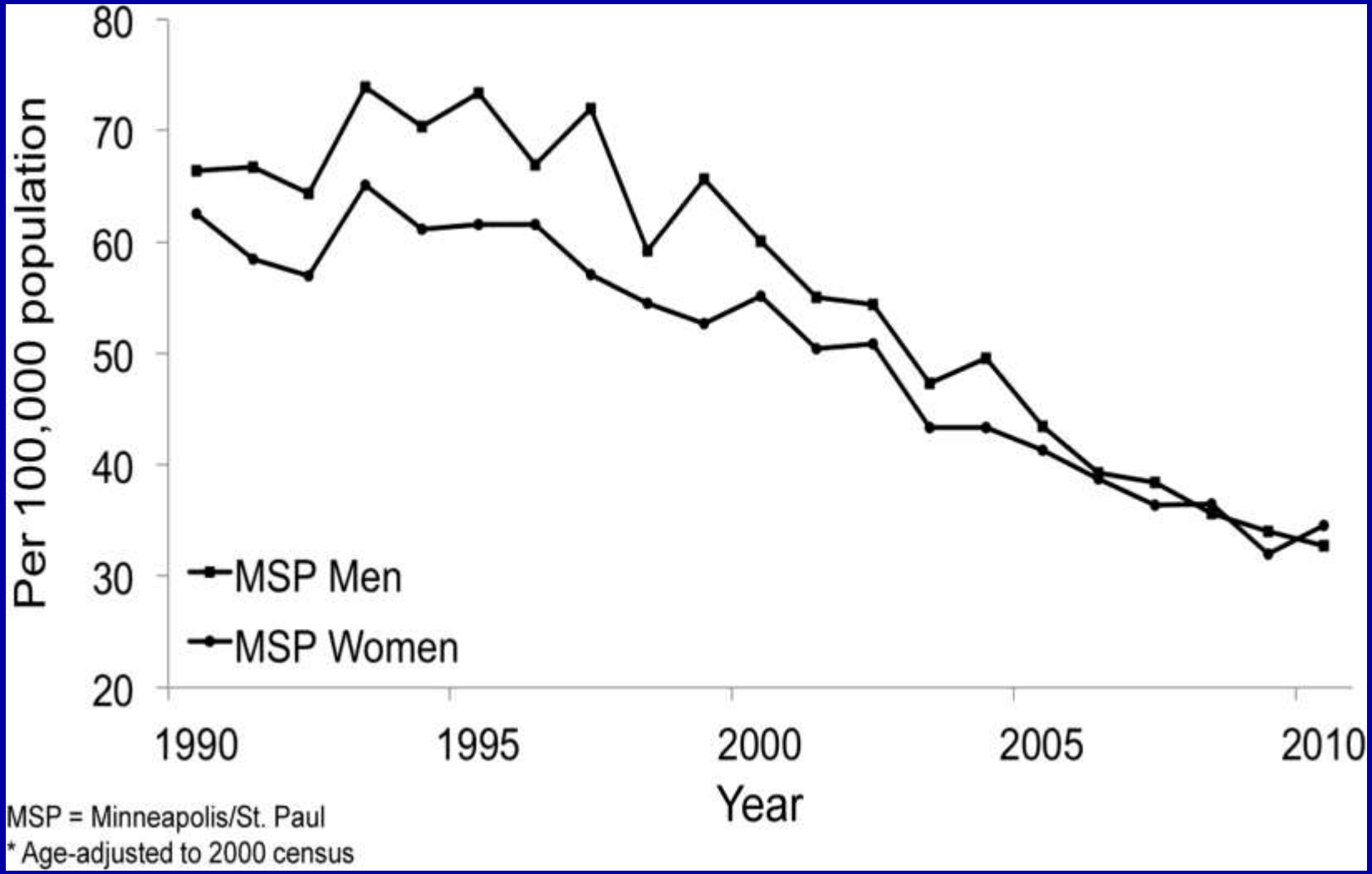
Systolic blood pressure (SBP) by sex and age decade, adjusted for pulse rate and room temperature.



Luepker R V et al. Circulation 2012;126:1852-1857

Minnesota Heart Survey: BP Trends 1980-20

Age-adjusted mortality for stroke 1990 to 2009.



Luepker R V et al. Circulation 2012;126:1852-1857

Minnesota Heart Survey: BP Trends 1980-2009 Reasons??

- Minnesota has among the highest levels of health insurance coverage
- Has a well developed healthcare system.
- Greater levels of high school and college education.
- Higher family incomes, and fewer people in poverty than the national figure

Luepker R V et al. Circulation 10/2012;126:1852-1857

EDFROG IRA

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

Serum Lycopene Decreases the Risk of Stroke in Men

- 1,031 Finnish men aged 46−65 yrs; 12 yr. follow-up; 67 strokes (50 ischemic)
- Evaluated risk against serum concentrations of lycopene, α-carotene, β-carotene, α-tocopherol, and retinol
- Highest quartile of lycopene compared to lowest had HR:
  any stroke - 0.45 (95% CI 0.25−0.95) p = 0.036
  ischemic stroke - 0.41 (95% CI 0.17−0.97) p = 0.042
  adjusted for age, BMI, syst. BP, smoking, LDL, DM, and history of stroke
- α-Carotene, β-carotene, α-tocopherol, and retinol were not related to risk

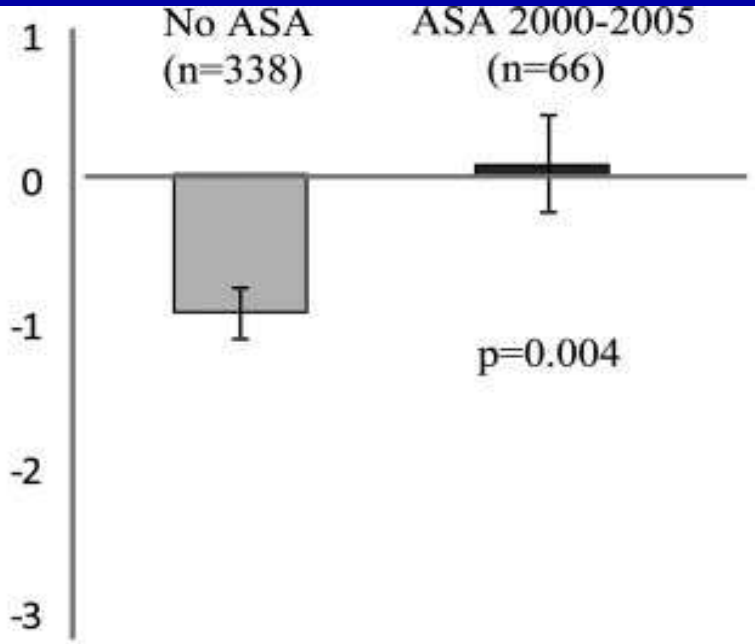
Karppi, J., PhD, et. al. *Neurology* October 9, 2012 vol. 79 no. 15 1540-1547

Low Dose Aspirin Reduces Memory Loss in Women with High CV Risk

- Prospective 5 yr. follow-up; 681 non-demented women; 70-92yo; 601 high CV risk; 129 on low dose aspirin
- Cognition was measured using the Mini Mental State Examination (MMSE), word fluency, naming ability and memory word tests
- MMSE declined on average: −0.88 for the whole sample; −0.95 for ASA non-users; −0.05 for those using ASA in 2000 and 2005 (N=66).

Kern S, Skoog I, Östling S, et al. BMJ Open 10/8/2012; 2:e001288. doi:10.1136/bmjopen-2012-001288

Low Dose Aspirin Reduces Memory Loss in Women with High CV Risk



1. Mini Mental State Examination.
2. Acetylsalicylic acid.

P-values (Mann-Whitney U-tests) compare MMSE change between ASA-users versus non-users.

Kern S, Skoog I, Östling S, et al. BMJ Open 10/8/2012; 2:e001288. doi:10.1136/bmjopen-2012-001288

Low Dose Aspirin Reduces Memory Loss in Women with High CV Risk

- Stratified into: using ASA in 2000 and 2005 (N=66); in 2000 but not in 2005 (N=18); not in 2000 but in 2005 (N=67); not using ASA at either examination (N=338).

- Women using ASA at both examinations increased in MMSE score (p=0.004 compared to never users)

- Women with FRS ≥10% (95% of all the women) on ASA decreased less in MMSE scores than those without ASA (−0.33 SD 3.3 vs −0.95 SD 2.9; p=0.028

Kern S, Skoog I, Östling S, et al. BMJ Open 10/8/2012; 2:e001288. doi:10.1136/bmjopen-2012-001288

Mechanism by which Aspirin Might Protect the Brain

- "We think it's possible that aspirin might influence cognitive decline by enhancing cerebral blood flow through a reduction in platelet aggregation”*

- "adds to evidence that there may be some neuroprotective effects of aspirin”^

- Supports theory that most events are ‘silent’; cognitive decline can result from ‘silent strokes’; individuals with disease are at risk for this; ASA can prevent these Æ

*Study's lead author, Dr Silke Kern
^Dr Christopher M Reid (Monash University, Melbourne Australia)
Æ Bale/Doneen Method

Pioglitazone: Latest Rumblings

- PROactive study six yr post termination:
  1) only 13.5% of pio pts in trial stayed on med
  2) this precludes statistically sound conclusions
  3) no persistent reduced CV risk in pio “arm” pts
  4) no signal of increased bladder CA in pio “arm”

- Two posters looked at CV event risk in pts taking pio vs. metformin or placebo. There was no increase in CV events and some reduction in MACE

- Pio lost US patent protection; opened to generics in Aug.

European Association for the Study of Diabetes 2012 Meeting; October 4, 2012 Berlin, Germany

KEEPS Says HRT Early is Fine

- RDBPCT; 4 yrs.; 727 healthy women 42-58 yo; within 3 yrs. post menopause; either:o-CEE (Premarin®) 0.45 mg/d or t-E2 (Climara®) patch, 50 µg/day or placebo. All received cyclical micronized progesterone (Prometrium®)
- No significant BP effect in rx arms
- o-CEE, but not t-E2, increased in HDL
- o-CEE decreased LDL, but increased in TG
- t-E2 had neutral effects on these biomarkers.

S. Mitchell Harman, MD PhD; JoAnn Manson MD Dr DrPH, FAHA; Sanjay Asthana MD
Press release 10/3/2012: KRONOS Longevity Research Center

KEEPS Says HRT Early is Fine

- t- E2 improved insulin sensitivity - “HOMA-IR.”
- During 48 mos. of rx vs placebo, no apparent effects assessed by carotid ultrasound and a non-significant trend toward less accumulation of coronary artery calcium (CAC).
- Conclude that HRT at the doses employed in this population neither significantly reduced nor accelerated progression of CVD

S. Mitchell Harman, MD PhD; JoAnn Manson MD Dr DrPH, FAHA; Sanjay Asthana MD
Press release 10/3/2012: KRONOS Longevity Research Center

KEEPS Says HRT Early is Fine

- Improvements in hot flashes, night sweats, mood, sexual function, and bone density were observed with HT vs placebo.
- No significant differences in adverse events (breast cancer, endometrial cancer, myocardial infarction, TIA, stroke, or venous thromboembolic disease) were found among groups.
- However, the absolute numbers of such events were extremely small in all three treatment groups, making definitive conclusions impossible.

S. Mitchell Harman, MD PhD; JoAnn Manson MD Dr DrPH, FAHA; Sanjay Asthana MD
Press release 10/3/2012: KRONOS Longevity Research Center

Hot Topics

Will revive one!

Statins do not Increase Risk of Diabetes

- 2,798 pre-diabetics; 484 took statins; 1-year follow-up
- 31 statin users developed DM; 126 non-users became DM
- There was no significant risk for DM with statin use

  OR 1.17- (95% CI 0.78 to 1.76) p=0.442

Rautio N, Jokelainen J, Oksa H, et al. BMJ Open 10/2012;2:e001472. doi:10.1136/bmjopen-2012-001472

Statins do not Increase Risk of Diabetes: Baseline Values were Significantly Different

Table 1 Cardio-metabolic risk factors at the baseline according to use of statins in a high-risk cohort of the FIN-D2D

	Use of statins				
	User		Non-user		
Variable	N	Mean (SD)	N	Mean (SD)	p Value
Age (years)	484	59.0 (8.59)	2314	53.7 (10.6)	<0.001
Weight (kg)	484	87.2 (14.9)	2314	87.8 (16.9)	0.442
BMI (kg/m^2)	484	31.0 (4.58)	2302	31.5 (5.30)	0.027
Systolic BP (mm Hg)	472	140 (16.5)	2276	139 (17.5)	0.166
Diastolic BP (mm Hg)	472	85 (9.00)	2276	86 (9.45)	0.002
Total cholesterol (mmol/l)	429	4.78 (0.99)	2051	5.26 (0.95)	<0.001
HDL cholesterol (mmol/l)	425	1.38 (0.37) 54	2028	1.43 (0.43) 56	0.019*
LDL cholesterol (mmol/l)	415	2.65 (0.87)	1979	3.14 (0.84)	<0.001
Triglycerides (mmol/l)	424	1.68 (0.90) 146	2019	1.56 (0.95) 136	0.001*
Fasting glucose (mmol/l)	424	5.84 (0.55) 105	2008	5.77 (0.58) 104	0.016
2 h glucose (mmol/l)	421	7.11 (1.81) 128	1999	6.91 (1.82) 124	0.046

p Values for independent sample t test.
*Log-transformed triglyceride values are used in the statistical test.
BP, blood pressure; BMI, body mass index; FIN-D2D, Implementation project of the national diabetes prevention programme in Finland; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Rautio N, Jokelainen J, Oksa H, et al. BMJ Open 10/2012;2:e001472. doi:10.1136/bmjopen-2012-001472

Statins do not Increase Risk of Diabetes

Lifestyle effect with weight changes generated anticipated changes in glucose tolerance.
If anything the statin seemed to enhance the beta cell recovery despite the fasting glucose not responding as well if on a statin = ???? some increase in hepatic IR with statins???
Bottom line: no sign of impairment with beta cell function which is required for development of DM!!!

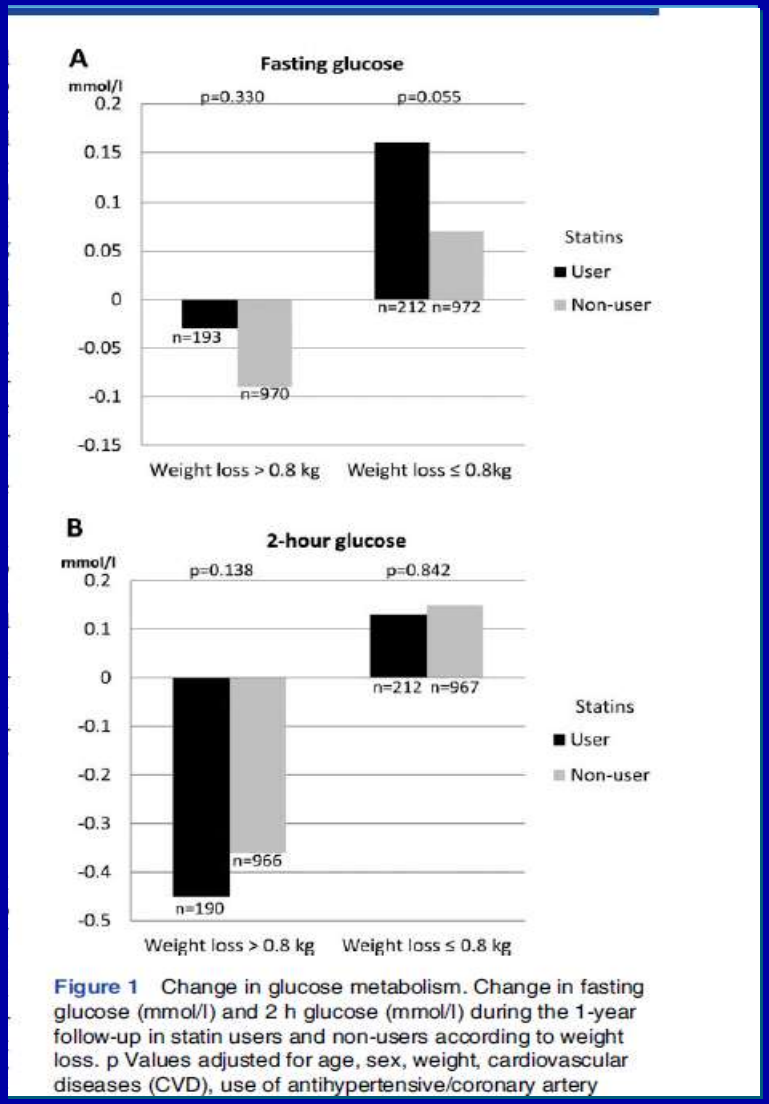


Figure 1 Change in glucose metabolism. Change in fasting glucose (mmol/l) and 2 h glucose (mmol/l) during the 1-year follow-up in statin users and non-users according to weight loss. p Values adjusted for age, sex, weight, cardiovascular diseases (CVD), use of antihypertensive/coronary artery

Rautio N, Jokelainen J, Oksa H, et al. BMJ Open 10/2012;2:e001472. doi:10.1136/bmjopen-2012-001472

Statins do not Increase Risk of Diabetes

- Incredible conclusion by authors!!!

- The finding that fasting glucose slightly increased (1.3 mg/dL) in statin users in spite of lifestyle interventions suggests the view that the use of statins might have unfavorable effects on glucose metabolism and that statins might hamper beneficial effects of lifestyle intervention in people at high risk of T2D.

- Yikes!! They need to read DeFronzo's work !!!!

Rautio N, Jokelainen J, Oksa H, et al. BMJ Open 10/2012;2:e001472. doi:10.1136/bmjopen-2012-001472

Cases???

45 yo male IT executive
PMHx - unremarkable
Meds: omega 3 1 cap per day, Vit E 400iu, Ginko Biloba, Calcium + Vit D supplement
Fam Hx - Father 67, mother 68, 3 kids - all healthy
Social: nonsmoker, alcohol: 2 wine, 2 beer per week, exercise: cycling 2-3 times per week, 20-40 miles
ROS- negative except Achilles soreness
Exam : 70", 194lbs, 135/78, BMI 27.83, Body fat 24.3 by DEXA, waist 36.5"
Normal examination
CIMT, distal common carotid: 0.7 and 0.6mm
Lab: HS CRP 3.1
FBS 95
Fasting insulin 2
Standard Lipids: trig 81, TC 183, HDL 63, LDL 104, ratio 2.9
Vitamin D 40
Advanced Cardiovascular Risk Markers
LDL IIIa+b (%) 8.8
LDL IVb(%) 0.8
IHDLZb(%) 14
ApoB(mg/dL) 88
Lp(a), Extended Range (mg/dL) 48
Lp-PLA2(ng/mL) 254

- Interesting case; Let's try dissecting it with EDFROG.

- I assume he is educated on 'event reality'; the fact that most events occur due to non-obstructing asymptomatic atheroma.

- Excellent that you did an IMT. The thickness seems fine, but what is most important is whether or not there is plaque present. Apparently, none was seen and I assume the technician is well trained to look for plaque. Since the patient is 45 and a male, I would recommend doing a coronary calcification test. As you know, generally the carotid is the last place to develop plaque. I would still consider this patient 'guilty' of harboring atheroma. If he has a zero score, I would then assume (albeit not absolute) he is a true 'primary' prevention patient.

- He has evidence of arterial inflammation with the hsCRP and Lp-PLA2. This places him at high risk for developing atheroma, if he is primary prevention; high risk for an event, if he is secondary prevention. There are missing data points in regard to inflammation. Does he have the 'joker'?? Is the hsCRP marking endothelial inflammation?? The microalbumin-creatinine ratio would help sort that out. Is he compliant enough with lifestyle?? The F2 isoprostane would help answer that very important question.

- He possesses a very important root cause for early heart attack and stroke (lipo (a))! His fasting blood sugar of 95 is very suspect of underlying insulin resistance and he should undergo an OGTT. His low % of HDL 2b would reinforce that possibility. I assume you have ruled out other possible roots such as psychosocial, sleep and dental.

- If his BP is really 135/78, that is not optimal and places him at significant increased risk over time for CV events and CKD. Is he already in stage two CKD (what is his eGFR)? Is his heart happy (NT pro-BNP)? His vit. D is borderline low.

- What are his genetics? 9p21, KIF6, apoE (is the alcohol okay?), LPA gene

- Current management: evidence tells us vit. E increases mortality; calcium increases CV risk

- Did the CIMT myself, no plaque
- Have ordered a calcium CT
- He wanted to work on diet and weight loss for 3 months and recheck and so I will check MPO, Microalbumin/creat, F2 isoprostane, OGTT then, get genetic markers if he can pay for them
- Estimated GFR was 71

Upcoming Presentations

Upcoming Presentations

- 10/20- Bale/Doneen Method Highlighting Inflammatory Testing for the Reduction of Cardiovascular Events. ;5 hr. CME; Jacksonville, FL
- 11/2 New CME opportunity!!! — ***Vascular Inflammation: The Systemic / Oral Connection***; 6.5 hr. CME; Las Vegas, NV
- 11/3- Bale/Doneen Method Highlighting Inflammatory Testing for the Reduction of Cardiovascular Events. ;5 hr. CME; Phoenix, AZ
- 11/6 - Independent Effects of Risk Factors and Treatment on Carotid Intima-Media Thickness Progression in a Community Practice; Birju Patel, Michael Blaha, Steven Jones, Johns Hopkins Univ, Baltimore, MD; AHA Scientific Sessions; LA, CA
- 11/9-10/2012 – BD Method Preceptorship; Atlanta, GA
- 11/30 --1:45 pm – 2:45 pm Arteriology: Where Arterial Disease and Inflammation Collide; NC Winter AAFP Meeting; Asheville, NC
- 12/15/2012- Bale/Doneen Method Highlighting Inflammatory Testing for the Reduction of Cardiovascular Events. ;5 hr. CME; Dallas, TX

Open for Discussion