Bale/Doneen Live Chat Session

12/5/2012

5:30-6:30 pm PST

Bradley Bale, MD

Intention of the live chats

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

New Red Flag!!!

Low Bilirubin Increases CV Risk

- 130,052 pts starting statin rx; without known liver or CVD; followed for 3 ½ yrs.; 7,850 CV events
- Evaluated baseline bilirubin as predictor of risk
- After adjusting for conventional CV risk factors, as bilirubin decreased below 0.6 mg/dL, the CV risk increased

Horsfall L J et al. Circulation 11/2012;126:2556-2564

Low Bilirubin Increases CV Risk

- Comparing pts with a similar CVD risk profile and a bilirubin level of 0.6 mg/dL versus 0.3mg/dL, the lower bilirubin pts had the following increased risk:

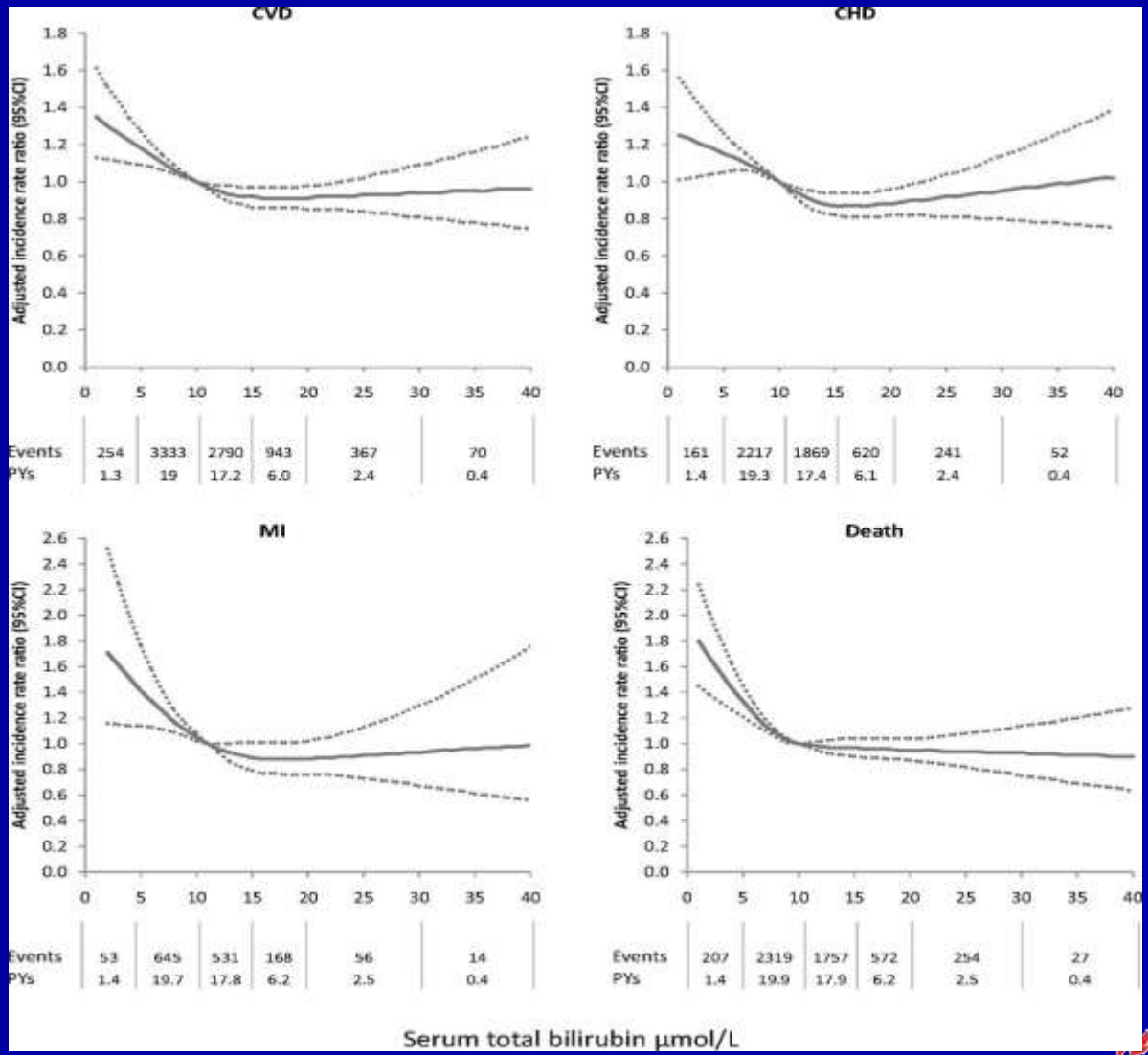
CVD event	+ 18% (95% CI, 9–27)
MI	+ 34% (95% CI, 13–56)
All cause death	+ 33% (95% CI, 21–46)

- Bilirubin prior to a statin is an independent risk factor for CVD and death in both men and women

Horsfall L J et al. Circulation 11/2012;126:2556-2564

Low Bilirubin Increases CV Risk

Estimated relationship between serum bilirubin level, coronary heart disease, stroke, and death with the median level of 10 µmol/L (0.6 mg/dL) used as the reference value.



Horsfall L J et al. Circulation 11/2012;126:2556-2564

American Heart Association
Learn and Live

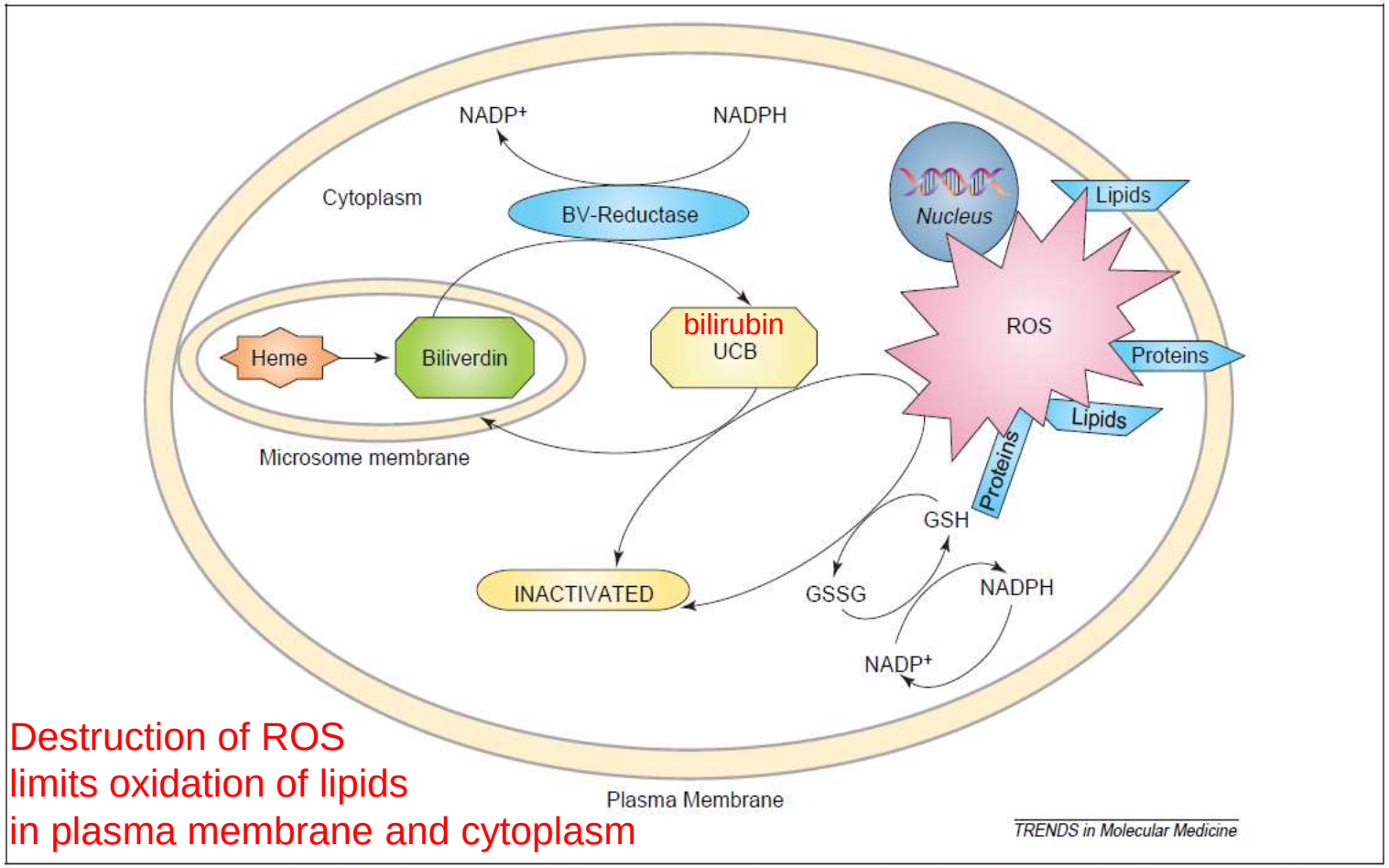
Bale Doneen METHOD

Low Bilirubin Increases CV Risk: *potential mechanisms*

- Bilirubin is a potent antioxidant and anti-inflammatory agent
- Bilirubin is particularly effective at suppressing the oxidation of LDL
- Bilirubin directly applied to the endothelium improves markers of oxidative stress and cellular dysfunction

Horsfall L J et al. Circulation 11/2012;126:2556-2564

Bilirubin as an Anti-0xidant

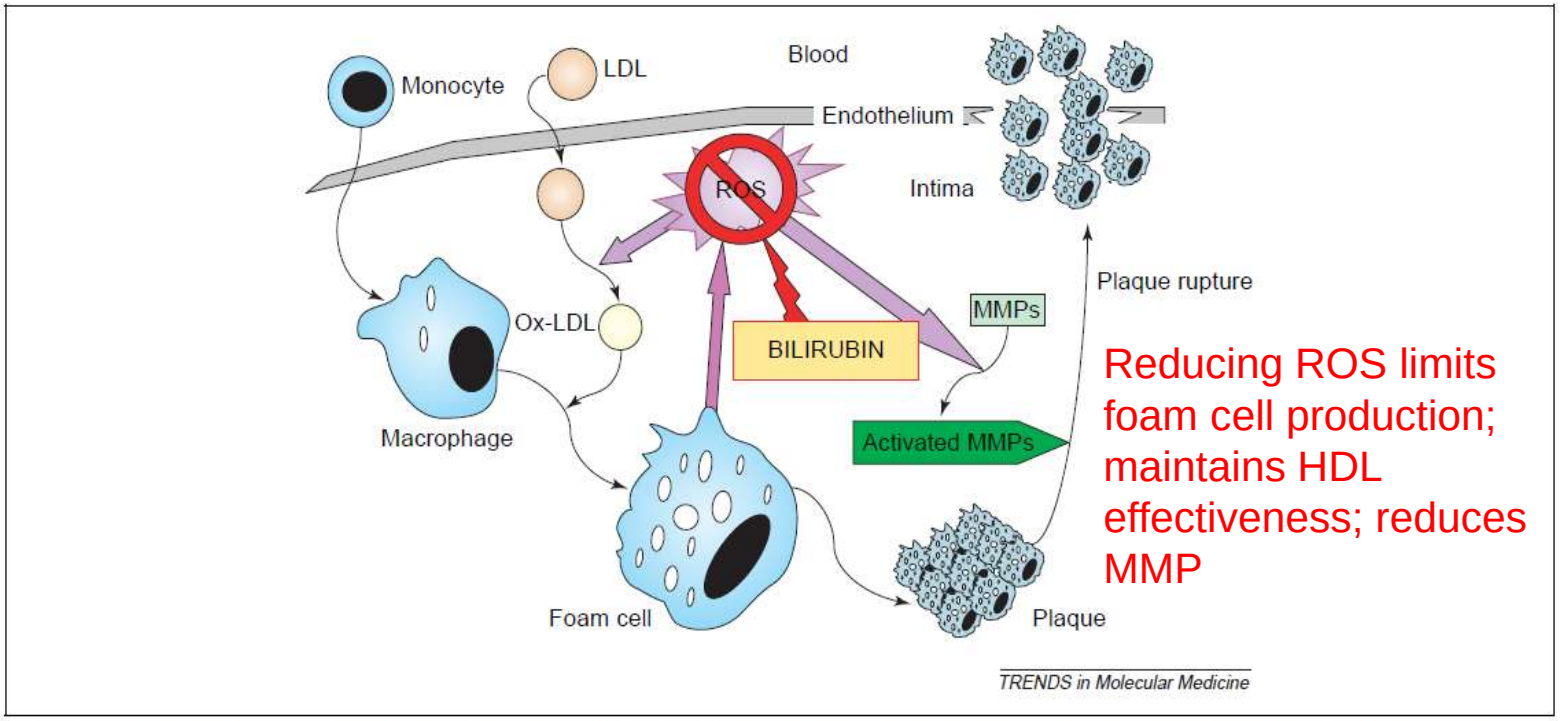


Destruction of ROS
limits oxidation of lipids
in plasma membrane and cytoplasm

Figure 1. The protective antioxidant effects of UCB and GSH in cells. In the cell, unconjugated bilirubin (UCB) and glutathione (GSH) act as scavengers of reactive oxygen species (ROS), being oxidized to biliverdin and GSSG, respectively. In each case, the regeneration of UCB and GSH by cytoplasmic biliverdin reductase and glutathione reductase, respectively, maintains the concentrations of these scavengers. This process is especially important for UCB, which is present in cells in only nanomolar concentrations, compared with millimolar concentrations for GSH. By destroying ROS, the UCB and GSH systems limit the oxidation of DNA in the nucleus, and of proteins and lipids in the plasma membrane and cytoplasm. The heme-oxygenase reaction occurs in the microsomal membrane.

Rigato, I., et. al. TRENDS in Molecular Medicine Vol.11 No.6 June 2005

Bilirubin as an Anti-0xidant



Reducing ROS limits foam cell production; maintains HDL effectiveness; reduces MMP

Figure 2. Potential anti-atherogenic mechanisms of bilirubin. LDL that has penetrated the intimal layer of arteries can be converted by reactive oxygen species (ROS) to oxidized LDL (Ox-LDL). Monocytes can migrate from the blood into the intima, where they undergo phenotypic modification into macrophages. Macrophages can take up the oxidized LDL, which stimulates their production of ROS, amplifying the oxidation of LDL. This leads to further lipid accumulation and the formation of foam cells, one of the main components of the atherosclerotic plaque. ROS can also activate the matrix metalloproteinases (MMPs) that cause plaque rupture. Bilirubin, by acting as an ROS scavenger, might limit oxidation of LDL, decreasing foam-cell plaque formation and the activation of MMPs. The oxidation of HDL, which impairs the function of HDL in limiting lipid accumulation in macrophages, can also be inhibited by bilirubin (not shown).

Rigato, I., et. al. TRENDS in Molecular Medicine Vol.11 No.6 June 2005

Low Bilirubin Increases CV Risk: *interesting findings*

- The addition of LDL reduction to the model made no material difference in the associations
- The addition of other covariates potentially on the causal pathway did not alter the associations
- About one in five patients starting a statin will have a bilirubin <0.36 mg/dL
- When bilirubin levels are <0.6-0.9 mg/dL, every 0.06 mg/dL increase in bilirubin decreases CV risk ~3% to 5%

Horsfall L J et al. Circulation 11/2012;126:2556-2564

Low Bilirubin Increases CV Risk: *reasons for higher levels*

- Genetic variations of UGT1A1 enzyme (Gilbert's)
- Younger age
- Male sex
- Lower BMI
- Nonsmoking status
- Niacin via stimulating heme oxygenase activity
- Statins increase bilirubin 10 to 20%
- Antihypertensives ?????
- Hepatobiliary disease, alcoholism, hemolytic anemia – all excluded from study

Horsfall L J et al. Circulation 11/2012;126:2556-2564

Low Bilirubin Increases CV Risk:
reasons for lower levels

- Genetic variations of UGT1A1 enzyme
- Corticosteroid prescriptions
- Seasonal affective disorder- can be 50% lower*

Horsfall L J et al. Circulation 11/2012;126:2556-2564

*Rigato, I., et. al. TRENDS in Molecular Medicine Vol.11 No.6 June 2005

Bale/Doneen Thoughts

- Fits with ‘inflammation’ message
- Pay more attention to bilirubin – lab flow sheet
- Observe changes with management
- Another reason for lower BMI
- A reason why alcohol shows benefit?
- Another reason to quit smoking
- More reason for niacin and statin rx
- Another source of referrals: GI docs who have patients with levels below 0.6 mg/dL

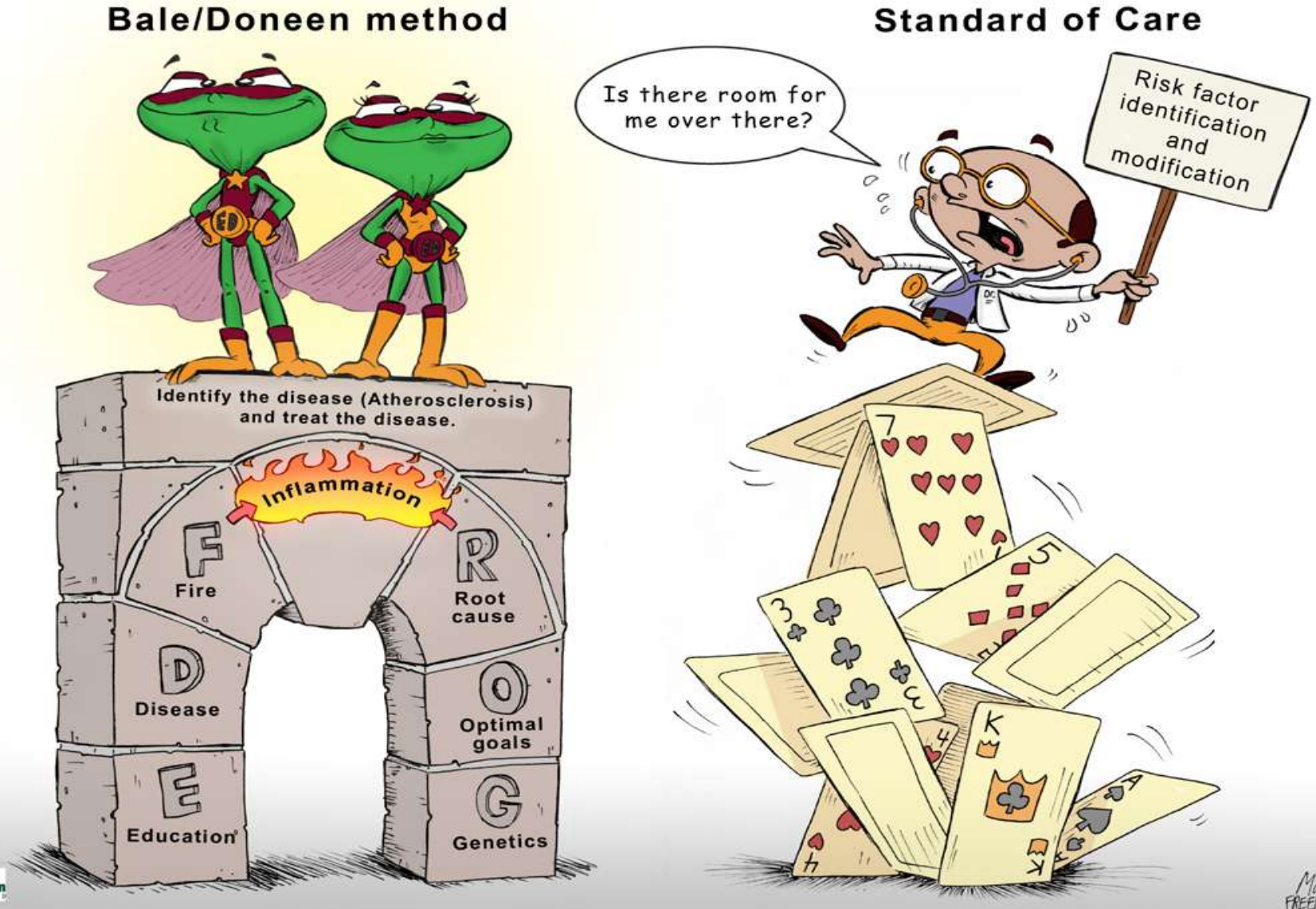
Green Flags: Gilbert's Make Sense

Gilbert Syndrome: Cardioprotective

- Gilbert synd incidence is 5-10%; mild unconjugated hyperbilirubinemia
- Patients with Gilbert syndrome have lower levels of oxidative stress and enhanced endothelial function

Maruhashi, T., et. al. *Circulation. published online July 6, 2012*
DOI: 10.1161/CIRCULATIONAHA.112.105775

What's the difference?



CT Angio Identifies Non-obstructing Plaques Which Might Explain Some MIs

- 50 pts. with documented MI but 'normal' coronaries on angiogram; all underwent 64 slice CT angiography
- 60 additional (41 <50% stenotic found on angio in 25 pts) plaques found with CT; 60% in infarcted related arteries (IRA)
- IRA plaques (61): 22 calcified; 22 non-calcified; 17 heterog.
- Non-IRA plaques (40): 27 calcified; 5 non-calcified; 8 heterog.

Aldrovandi, A., et. al. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.117598

CT Angio Identifies Non-obstructing Plaques Which Might Explain Some MIs

- IRA (infarct arteries) vs non-IRA plaques:

  a) mean percentage stenosis not different

  (33.5%±14.6 *vs* 31.7%±12.2), p=0.59

  b) mean plaque area was different

  (6.1±5.4mm_2 *vs* 4.2±2.1 mm_2: p=0.03)

  c) mean remodeling index was different

  (1.25±0.41 *vs* 1.08±0.21, p=0.01)

Aldrovandi, A., et. al. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.117598

CT Angio Identifies Non-obstructing Plaques Which Might Explain Some MIs

- CT angio detects non-stenotic coronary plaques that are underestimated by conventional angiograms
- IRA plaques are more remodeled, occupied greater area and had less calcified

Aldrovandi, A., et. al. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.117598

CT Angio Identifies Non-obstructing Plaques Which Might Explain Some MIs: Coronary Calcification Findings

- Median Agatston CAC score was 6 (range 0-4937)
  (16 scores were between 1 & 6)

- 17 patients (34%) had a CAC score of zero
  (33 out of 50 MI pts. had CACS 0 to 6)

Aldrovandi, A., et. al. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.117598

CT Angio Identifies Non-obstructing Plaques Which Might Explain Some MIs

- Normal coronary angiography can be seen in 9-31% of the women and 4-14% of the men experiencing an AMI
- Technique does not provide any information concerning the vessel wall and plaques.
- Mechanism of AMI in this setting may include prolonged coronary artery spasm, coronary embolism and, more probably, transient coronary thrombosis

Aldrovandi, A., et. al. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.117598

CT Angio Identifies Non-obstructing Plaques Which Might Explain Some MIs

- Studies supports the pathophysiology of MI due to atherosclerosis, with the disruption of mild coronary plaques

- Absence of coronary atherosclerosis at CTCA may be more indicative of an alternative etiology such as embolic MI and possibly asymptomatic arrhythmias such as AF; (embolization of plaque contents also possible)*

Aldrovandi, A., et. al. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.117598
*Jason C. Kovacic and Valentin Fuster. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.150425

Atherosclerosis a Pre-requisite for Vast Majority of Heart Attacks

- "disruption of a mild, moderate *or angiographically insignificant* atherosclerotic plaque with resultant thrombosis formation and total or subtotal occlusion, *with or without spasm or embolization*, probably explains *most cases* of MI."

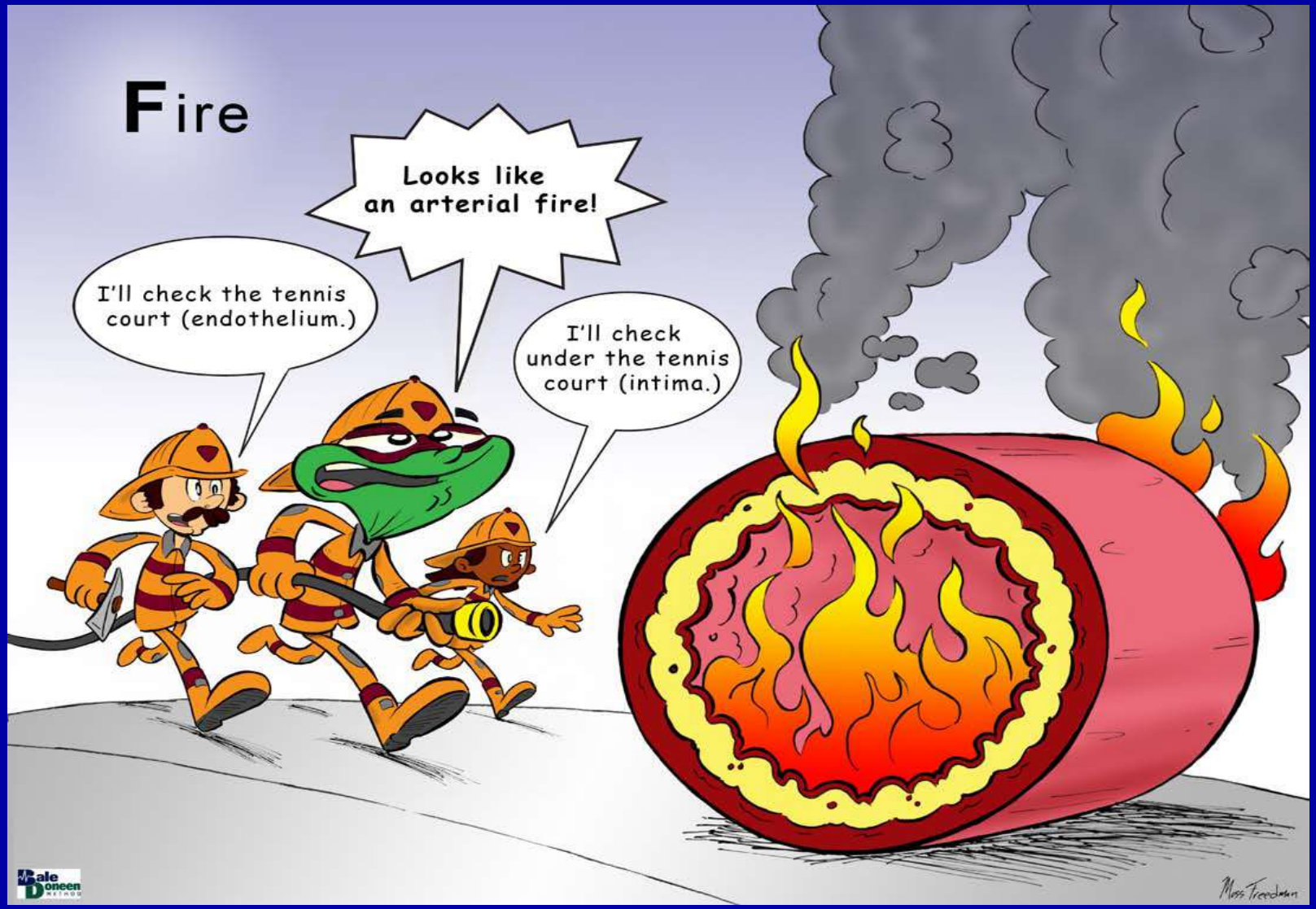
Jason C. Kovacic and Valentin Fuster. *Circulation.* published online November 20, 2012
http://circ.ahajournals.org/content/early/2012/11/19/CIRCULATIONAHA.112.150425

BD Method Thoughts

- Findings add further support to basing risk assessment on disease and not risk factors

- Also reinforces concept that any positive CACS score creates some risk and a zero score does not eliminate risk

Inflammation



IL-6 Coupled with Silent Lacunar Strokes Associated with Risk of First Stroke Event

- 464 pts with CV risk factors; ~ 69 yo; followed 5 yrs.; end point first cerebrovascular (CV) event; 25 new onset of CVEs (16 ischemic, 5 hemorrhagic, and 4 invasive interventions after TIA)

- Baseline: MRI for silent lacunar infarct (SLI); CIMT; hsCRP; IL-6; IL-18

- IL-6 was associated with risk for first CV event:

HR 1.80 per 1-SD increase in log IL-6, P=0.03 adjusted for age, sex, conventional risk factors, CIMT, SLI

Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* **2013;33:00-00**

http://atvb.ahajournals.org/content/early/2012/11/21/ATVBAHA.112.300350

IL-6 Coupled with Silent Lacunar Strokes Associated with Risk of First Stroke Event

- Pts. with IL-6 levels above the median coupled with SLI compared to those with levels below median and no SLI were four times more likely to have a first cerebrovascular event

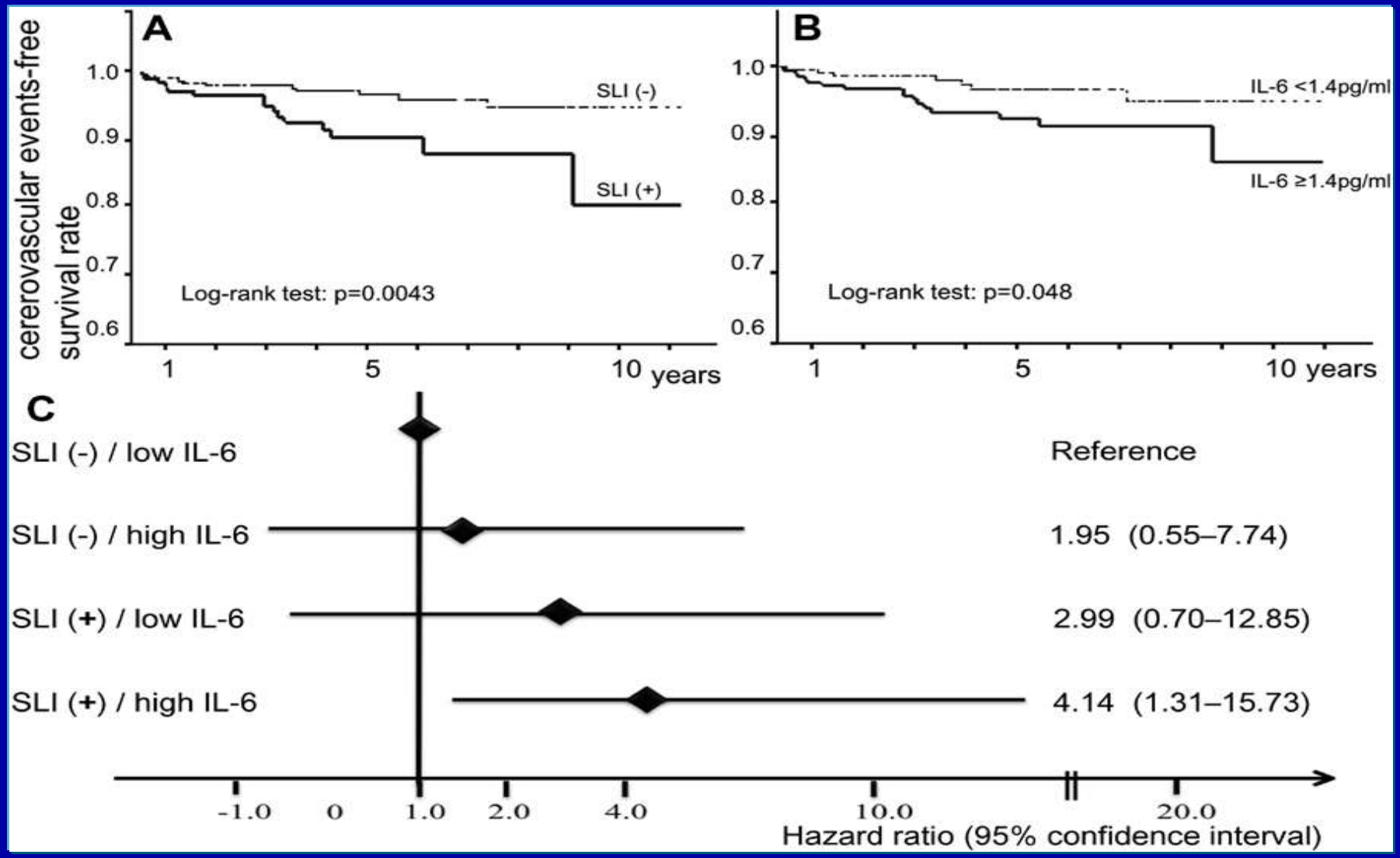
HR - 4.14, P=0.0014

net reclassification improvement of 14.3% (P=0.04)

Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* **2013;33:00-00**

http://atvb.ahajournals.org/content/early/2012/11/21/ATVBAHA.112.300350

IL-6 Coupled with Silent Lacunar Strokes Associated with Risk of First Stroke Event



Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* **2013;33:00-00**

IL-6 Coupled with Silent Lacunar Strokes Associated with Risk of First Stroke Event

- Risk of stroke was significantly higher in males, SLI, higher IMT and higher IL-6 levels.
- IL-6 levels showed borderline significance (*P*=0.054) with atherothrombotic stroke (n=11)
- Risk of stroke was not significantly greater with higher blood pressure, cholesterol, fasting glucose, HbA1c, white blood cell counts, hsCRP and IL-18.

Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* 2013;33:00-00

http://atvb.ahajournals.org/content/early/2012/11/21/ATVBAHA.112.300350

Baseline Values Significantly Associated with Risk of First Stroke Event

	All, n=464	(-) CVE n=439	(+)CVE n=25	P value
Sex,% male	49	48	71	0.04
IMT, mm	1.14+0.61	1.11+0.57	1..69+1.05	0.01
SLI, %	28	34	58	0.01
IL-6, pg/mL	1.40 (0.84-2.31)	1.38 (0.82-2.24)	2.46 (1.14-4.18)	0.006
hsCRP, mg/dL	0.05 (0.02-0.11)	0.05 (0.02-0.11)	0.055(0.033-0.183)	0.06

Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* 2013;33:00-00

http://atvb.ahajournals.org/content/early/2012/11/21/ATVBAHA.112.300350

IL-6 Coupled with Silent Lacunar Strokes Associated with Risk of First Stroke Event

- IL-6 marginally added to the risk of first stroke when coupled with conventional risk factors and surrogate markers (ie, IMT, SLI).

- Results suggest IL-6 measurement should not routinely be performed in the general population because the overall added value may be small and unlikely to be a clinical importance at the moment.

Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* **2013;33:00-00**

http://atvb.ahajournals.org/content/early/2012/11/21/ATVBAHA.112.300350

IL-6 Coupled with Silent Lacunar Strokes Associated with Risk of First Stroke Event: *Issues*

- Small number of end points; end points included hemorrhagic stroke; TIA not included unless intervention needed
- Inflammatory markers only evaluated at baseline (they are very dynamic!)
- Pts were being treated

Miwa. K., et. al. online November 21, 2012 *Arterioscler Thromb Vasc Biol.* **2013;33:00-00**

http://atvb.ahajournals.org/content/early/2012/11/21/ATVBAHA.112.300350

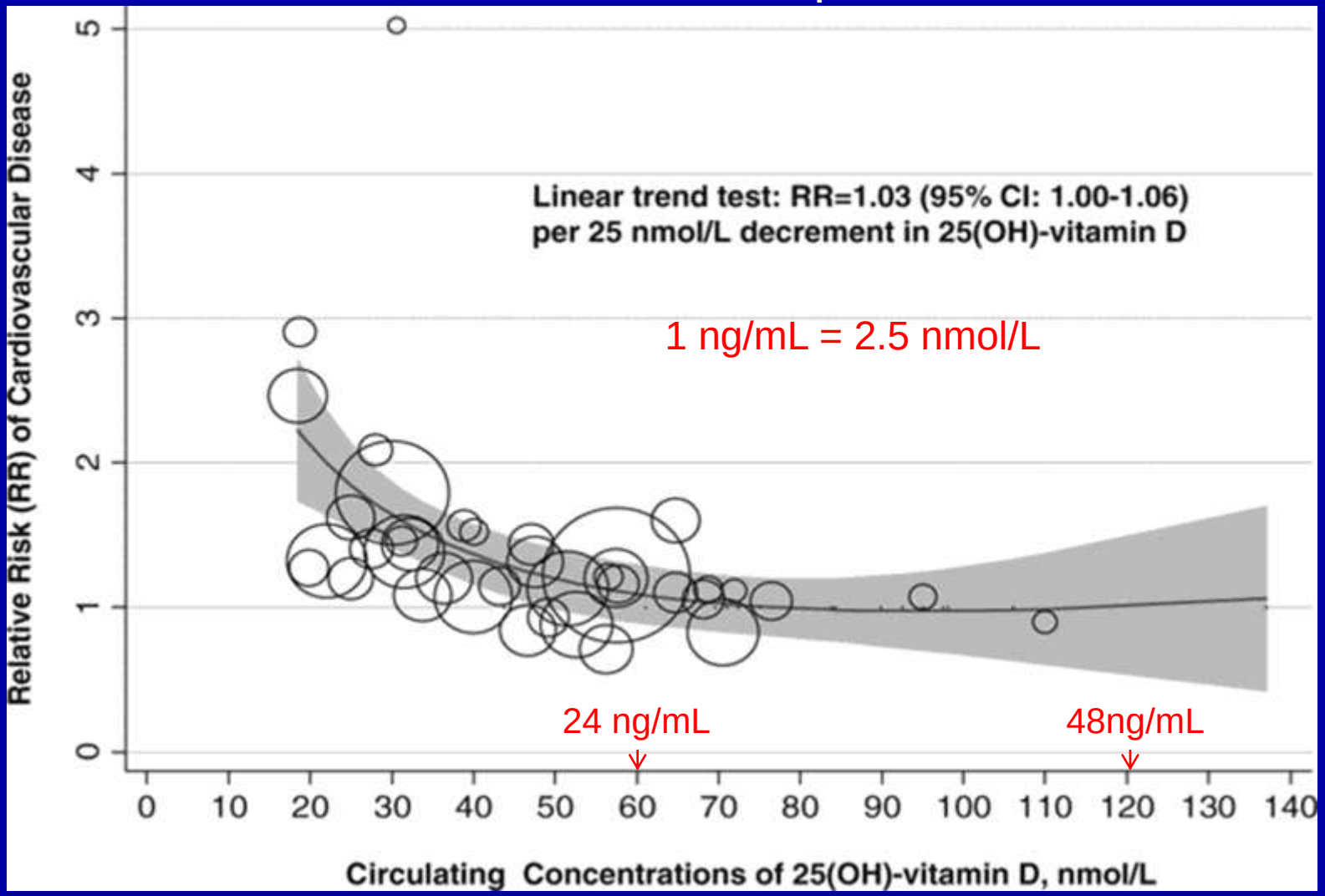
Vitamin D Levels Below 24 ng/mL Increase CV Risk

- Meta-analysis (19 prospective trials) 65,994 pts; 6,123 CVD cases
- Definite increased risk when levels below 24 ng/mL
- For every 10 ng/mL decrease there was a significant 3% increase risk of a CV event (95% CI, 1.00–1.06)

Wang L et al. Circ Cardiovasc Qual Outcomes 11/2012;5:819-829

Vitamin D Levels Below 24 ng/mL Increase CV Risk

Dose–response association between circulating 25(OH)-vitamin D and risk of cardiovascular disease in 16 independent studies.



Wang L et al. Circ Cardiovasc Qual Outcomes 2012;5:819-829

American Heart Association
Learn and Live

Bale Doneen METHOD

Optimal Dose of Vitamin D for CV Risk Reduction

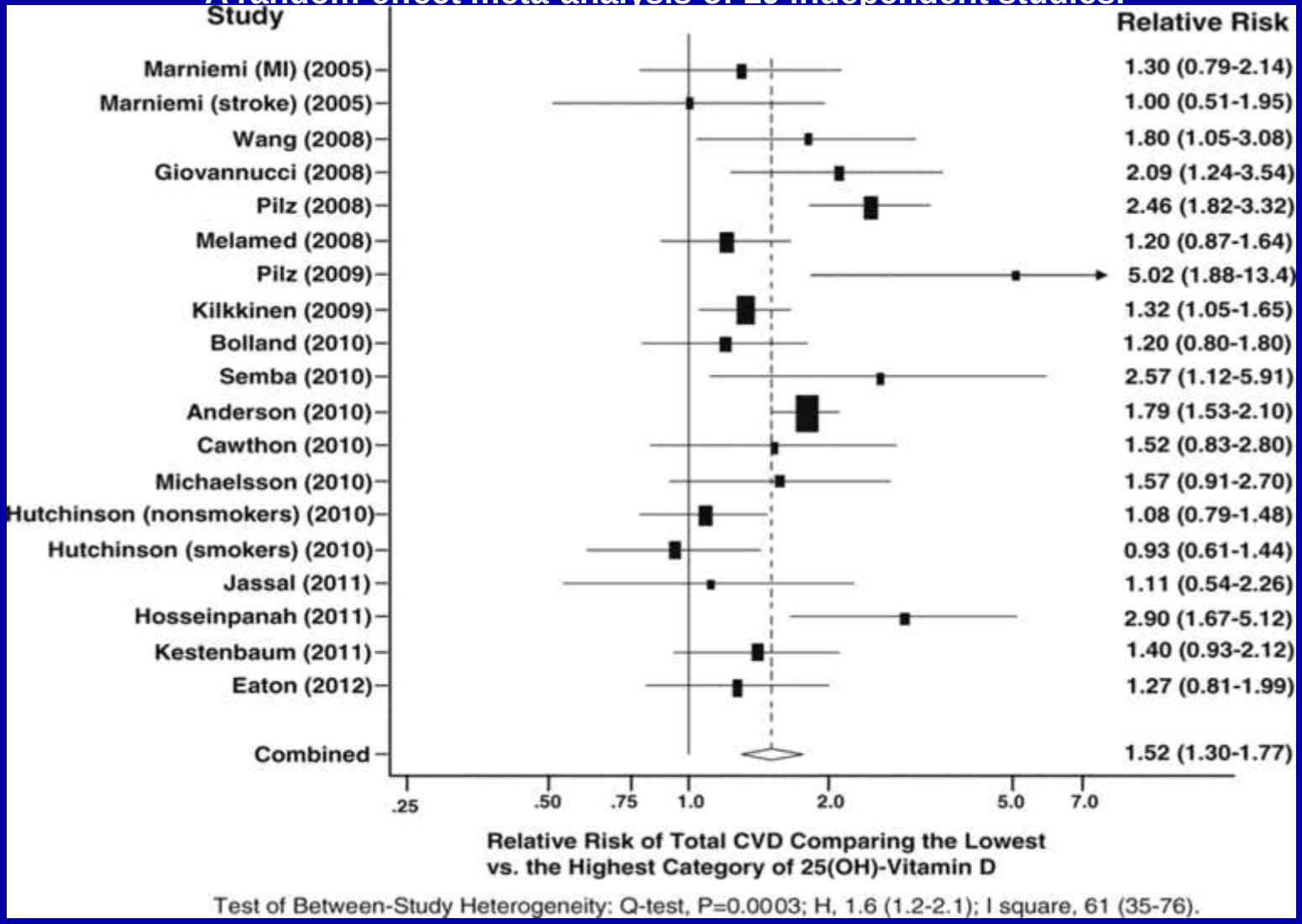
- Comparing lowest with the highest 25(OH)-vitamin D categories for CV risk:

Total CVD	RR 1.52 (95%CI-1.30-1.77)
CVD mortality	RR 1.42 (95% CI-1.19-1.71)
CHD	RR 1.38 (95% CI-1.21-1.57)
Stroke	RR 1.64 (95% CI-1.27-2.10)

Wang L et al. Circ Cardiovasc Qual Outcomes 11/2012;5:819-829

Highest Vitamin D Levels Compared to Lowest Reduce Total CVD Risk ~ 52%

A random-effect meta-analysis of 19 independent studies.



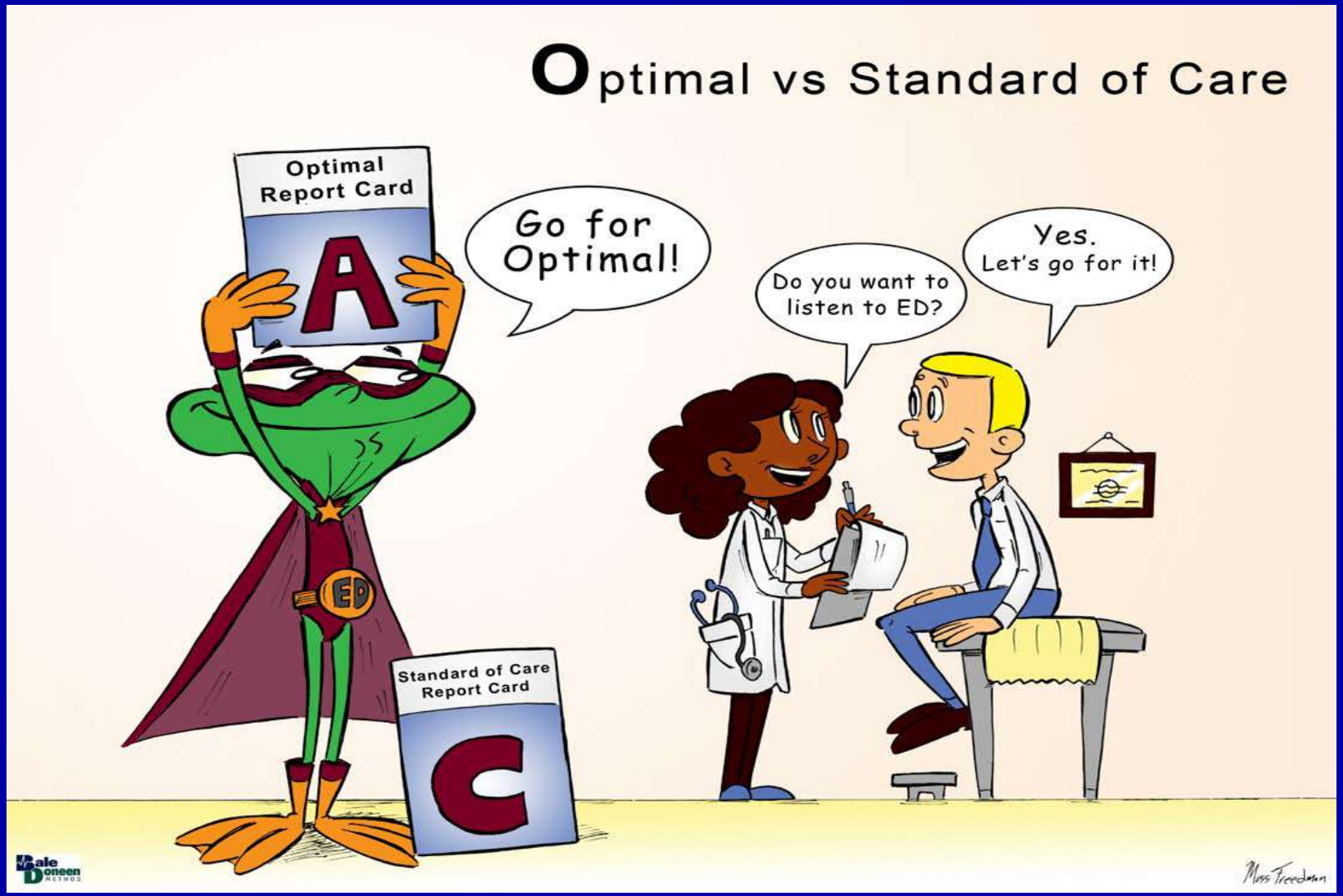
Wang L et al. Circ Cardiovasc Qual Outcomes 2012;5:819-829

Vitamin D Levels Below 24 ng/mL Increase CV Risk: BD Thoughts

- Vitamin D levels should be assessed for CV risk
- Levels should be maintained above 24 ng/mL
- “Optimal” level is still unknown

Wang L et al. Circ Cardiovasc Qual Outcomes 11/2012;5:819-829

Optimal Care



Management of Stable Ischemic Heart Disease: Goals

- Prevent premature CV death, nonfatal acute MI & HF

- Maintain or restore a quality of life that is satisfactory to the patient while eliminating unnecessary tests and treatments and preventing hospital admissions

Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

Management of Stable Ischemic Heart Disease: 1st Step Lifestyle

- Physical activity
- Weight – emphasize waist
- Diet
- Smoking – include 2nd hand exposure
- Oral health
- Sleep
- Psychosocial

Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011
Bale/Doneen Method

Management of Stable Ischemic Heart Disease: Pharmaceutical

- Anti-platelet rx
- Lipid lowering agents
- ACEI–BP, CKD, DM or LV dysfunction
- Beta-blocker
- Glycemic control in DM

Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

Management of Stable Ischemic Heart Disease: Intervention

- Survival
- Symptom relief

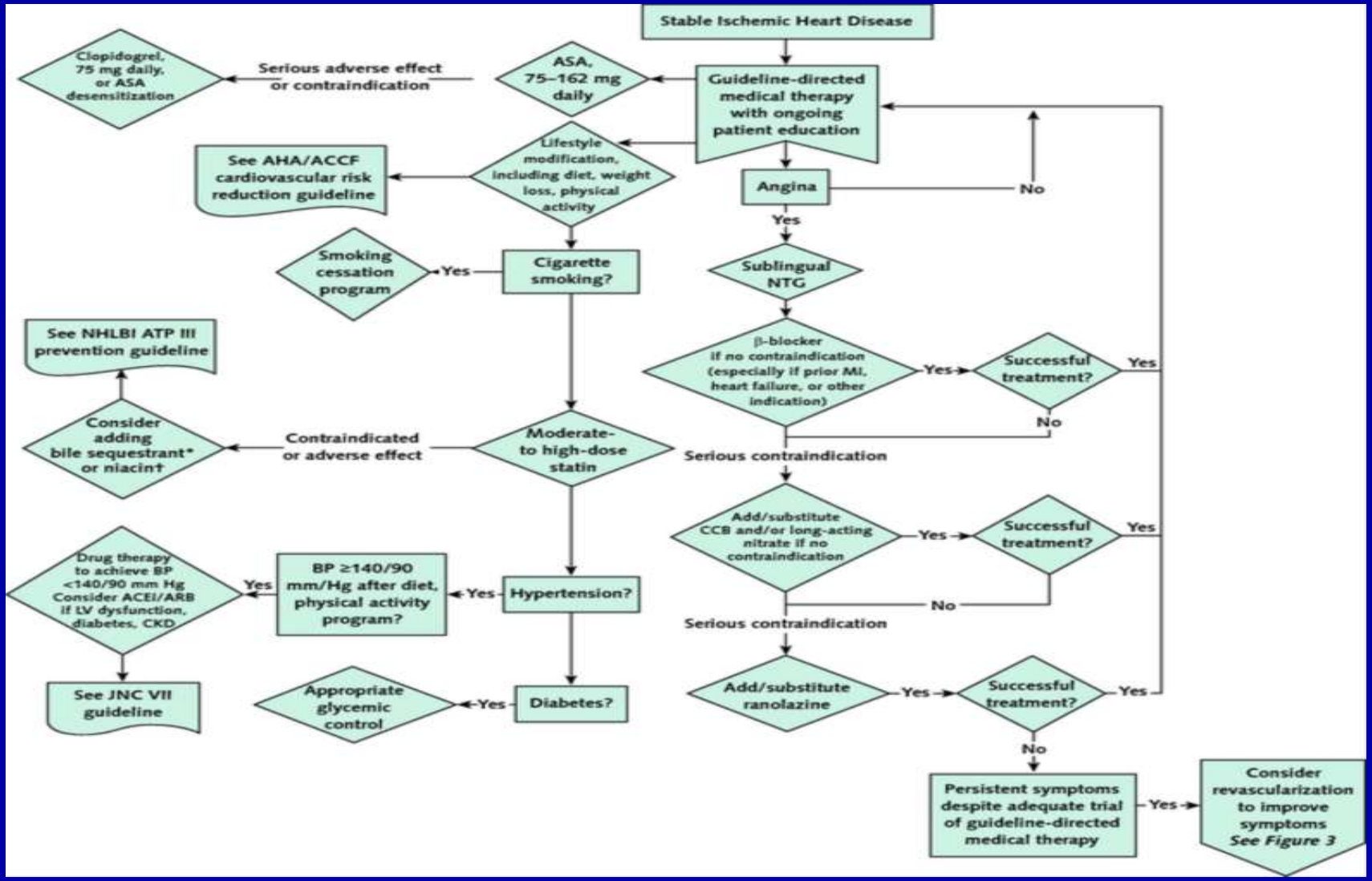
Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

Management of Stable Ischemic Heart Disease: Follow-up at least annual

- Sx's and function
- ? HF and arrhythmias
- Risk factor monitoring
- Compliance with lifestyle and meds

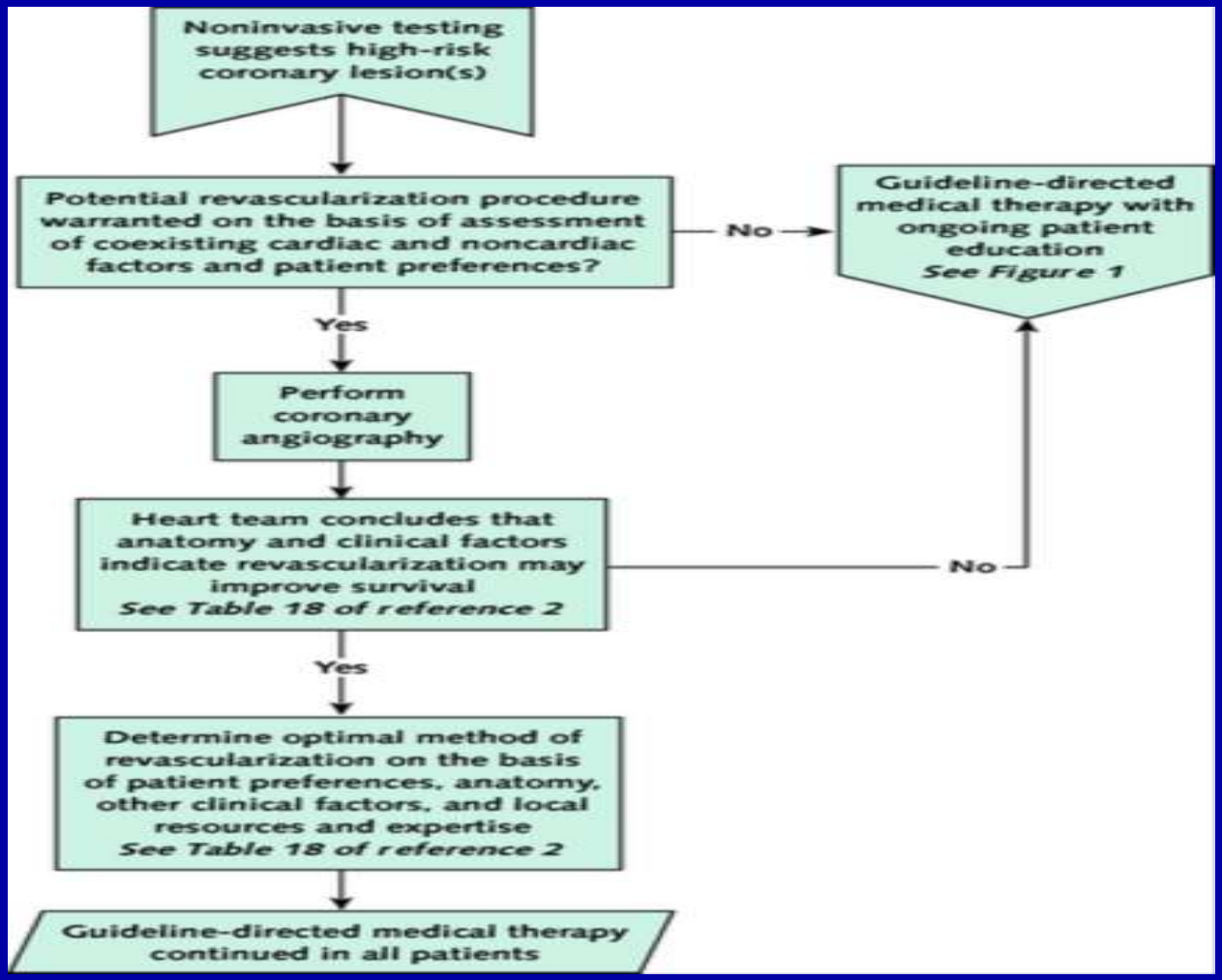
Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

Management of Stable Ischemic Heart Disease: Summary of a Clinical Practice Guideline From the American College of Physicians/ ACCF/AHA/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons



Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

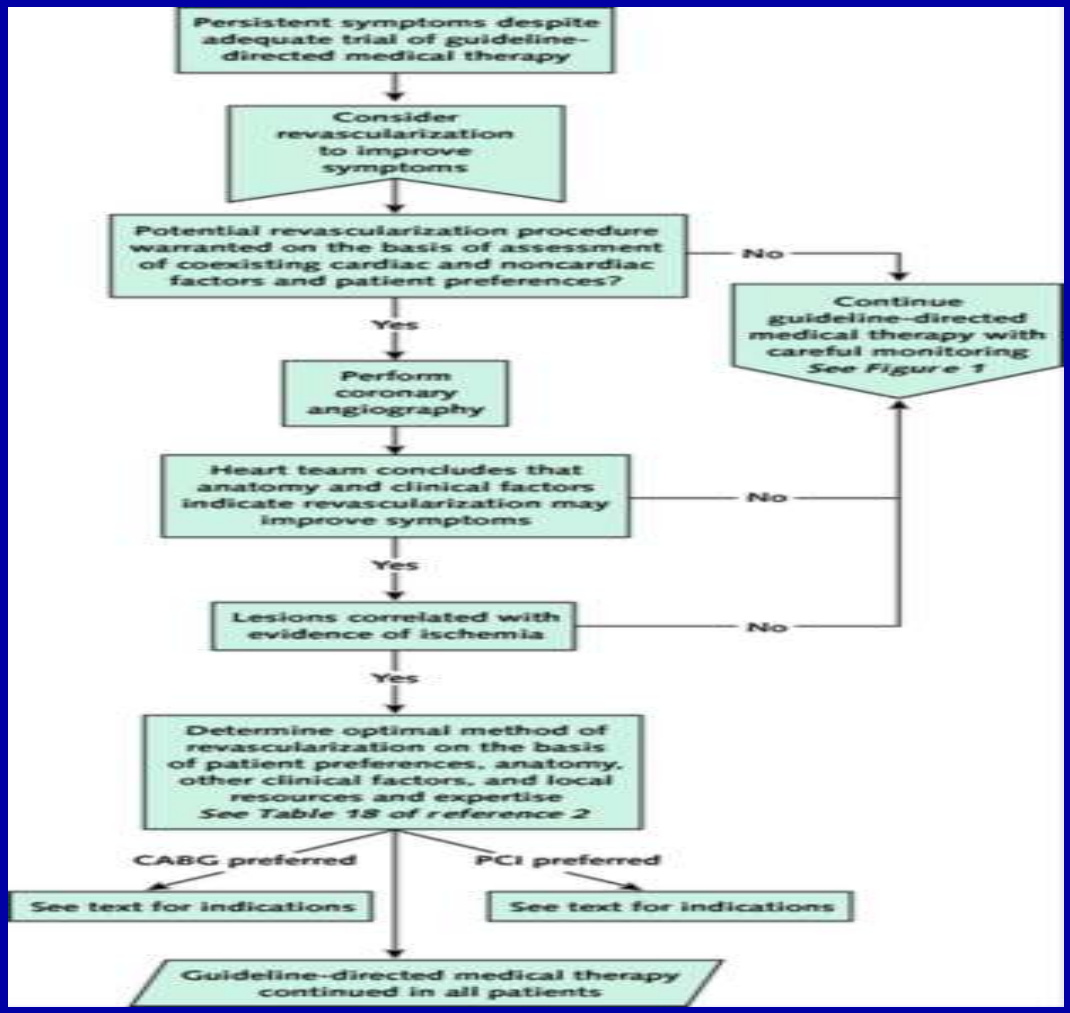
Management of Stable Ischemic Heart Disease: Summary of a Clinical Practice Guideline From the American College of Physicians/ ACCF/AHA/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons



Revascularization to improve survival of patients with stable ischemic heart disease.

Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

Management of Stable Ischemic Heart Disease: Summary of a Clinical Practice Guideline From the American College of Physicians/ ACCF/AHA/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons



Revascularization to improve symptoms of patients with stable ischemic heart disease.
CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Ann Intern Med.2012;157(10):735-743.
doi:10.7326/0003-4819-157-10-201211200-00011

EDFROG IRA

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

Second Hand Smoke Increases Systolic BP

- 2889 never smokers; 1004 with elevated BP; measured serum cotinine levels; evaluated cotinine level relationship to BP

- After adjusting for: age, sex, ethnicity, education, alcohol drinking, body mass index, glycohemoglobin, total cholesterol, and other confounders, cotinine levels of >0.218 ng/mL vs <0.025 ng/mL had OR for hypertension of 1.44 (95%CI, 1.01–2.04)

- Relationship was with systolic and not diastolic pressure

Alshaarawy, O., et. al. ***Hypertension.*** **2013;61:000-000**
DOI:10.1161/HYPERTENSIONAHA.112.198218

Second Hand Smoke Increases Systolic BP

- 0.01-ng/mL increase in serum cotinine in never smokers is independently associated with a 1-mm Hg increase in systolic BP.
- Systolic BP has been shown to be more important than the diastolic BP in estimating the risk of CVD
- May help explain reduction in CV risk with smoking bans
- Mechanisms underlying the observed association remain unknown

Alshaarawy, O., et. al. ***Hypertension.*** **2013;61:000-000**
DOI:10.1161/HYPERTENSIONAHA.112.198218

Lower Magnesium Associated with Risk of AF

- 3,530 ‘healthy’pts.; 44 yo – mean; 52% women; 20 yr. follow-up; 228 developed AF; evaluated baseline Mg as risk factor for AF
- Lowest quartile ≤1.77 mg/dL; highest quartile ≥1.99 mg/dL
- In multivariable-adjusted models, HR for AF lowest quartile vs highest quartile was:

  1.52- (95%CI- 1.00 to 2.31) *P*=0.05)

Khan AM, et al. *Circulation* 2012; DOI: 10.1161/CIRCULATIONAHA.111.082511. Available at: http://circ.ahajournals.org/.

Lower Magnesium Associated with Risk of AF

Age- and sex-adjusted incidence of AF

Serum magnesium, mg/dL	Events, n	Incidence rate per 1000 person-years
≤1.77	80	9.4
1.78-1.88	53	6.9
1.89-1.98	50	7.1
≥1.99	45	6.3

Khan AM, et al. *Circulation* 2012; DOI: 10.1161/CIRCULATIONAHA.111.082511. Available at: http://circ.ahajournals.org/.

Lower Magnesium Associated with Risk of AF

- Association is not linear; excess risk is primarily in lowest quartile
- Causality cannot be inferred
- Mg was only measured at baseline and levels fluctuate over time
- Alcohol consumption was self-reported; binge drinking not addressed

Khan AM, et al. *Circulation* 2012; DOI: 10.1161/CIRCULATIONAHA.111.082511. Available at: http://circ.ahajournals.org/.

Magnesium

- Mg rich foods: beans, whole grains, nuts, green leafy vegetables*
- Alcohol acts acutely as a Mg diuretic; chronic intake of alcohol deplete Mg stores^

* Chacko, S. A., MPH, et. al. Diabetes Care 2/2010, Vol 33, No. 2:304-310
^ Rivlin. R. S. *J Am Coll Nutr October 1994 vol. 13 no. 5 416-423*

Hemorrhagic Risk with Warfarin use in AF

- Population-based cohort study; 125,195 AF pts. ≥66 yo; 13 yr. span of time; end point hospitalized hemorrhagic event

- Rate of hemorrhage was 3.8% (95% CI- 3.8%–3.9%) per person-year

- Risk was highest during first 30 days at:

  11.8% (95% CI 11.1%–12.5%) per person-year

Gomes, T., MHSc, et. al. ***CMAJ* 11/2012. DOI:10.1503/cmaj.121218**

Hemorrhagic Risk with Warfarin use in AF

- During a 5 year follow-up, the following occurred:

  8.7% (10,840) had hemorrhages

  18.1% of the above (1,963) died in hospital or within 7 days of discharge

Gomes, T., MHSc, et. al. ***CMAJ* 11/2012. DOI:10.1503/cmaj.121218**

Hemorrhagic Risk with Warfarin use in AF: Related to CHADS2 and Age

- CHADS2 estimates stroke risk in patients with AF (congestive heart failure, hypertension, age ≥75 yr, DM and prior stroke, TIA or thromboembolism)

$CHADS_2$ Score	Patients,no. (%)* *n* = 125 195
O	8,655 (6.9%)
1	30,108 (24.0%)
2	44,716 (35.7%)
3	29.713 (23.7%)
4	9,599 (7.7%)
5	1,860 (1.5%)
6	544 (0.4%)

Gomes, T., MHSc, et. al. ***CMAJ* 11/2012. DOI:10.1503/cmaj.121218**

Hemorrhagic Risk with Warfarin use in AF Based on CHADS2

$CHADS_2$ score	Major bleed rate (% per person-year)
0	1.8
1	2.5
2-3	4.3
4-6	6.7

Gomes, T., MHSc, et. al. ***CMAJ* 11/2012. DOI:10.1503/cmaj.121218**

Hemorrhagic Risk with Warfarin use in AF Based on Age

Age (y)	Major bleed rate (% per person-year)
≤75 or under	2.9
>75	4.6

Gomes, T., MHSc, et. al. ***CMAJ* 11/2012. DOI:10.1503/cmaj.121218**

Hemorrhagic Risk with Warfarin use in AF

- ~ Two thirds of hemorrhages were GI
- Only 5% of hemorrhages were intracranial (overall risk 0.2%)

Gomes, T., MHSc, et. al. ***CMAJ* 11/2012. DOI:10.1503/cmaj.121218**

Hemorrhagic Risk with Warfarin use in AF: *what is risk of a stroke without rx?*

- The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year, 2 to 7 times that of people without AF; rate of brain ischemia accompanying nonvalvular AF exceeds 7% per year*

*Fuster, V., et. al. JACC Volume 57, Issue 11, 15 March 2011, Pages e101–e198

BD Method Thoughts

- Risk of stroke in AF patients demands anti-coagulant therapy
- Extra caution if pt. >75yo and or CHADS2 score ≥2; any hx of GI bleeding
- Watch very closely first 30 days; educate patients
- Follow emerging hemorrhagic data with newer agents
- Continue to try to actually eliminate the AF – look for cause

Pioglitazone Reduces CIMT Progression in Pre-diabetics

- 382 pre-diabetic pts.; 188 randomized to pio 45mg; mean follow-up 2.3 yrs.; progression of CIMT was 49% less in pio group with $p<0.01$

- After adjustment for all of the putative mediators of this difference and for concomitant medications, the annualized rate of CIMT progression with pio was 47% less than placebo – $p<0.01$

Saremi, A., et. al. online 11/26/2012. ***Arterioscler Thromb Vasc Biol.*** **2013;33:00-00**

http://atvb.ahajournals.org DOI: 10.1161/ATVBAHA.112.300346

Pioglitazone Reduces CIMT Progression for Unknown Reasons

- After adjustment for age, sex, race and ethnicity, study site, and history of CVD at baseline, pioglitazone reduced CIMT-progression rates to similar degrees, regardless of whether risk factors improved or worsened.

- The mechanisms by which pio reduced progression of atherosclerosis was not determined by any of the putative mediators examined.

Saremi, A., et. al. online 11/26/2012. ***Arterioscler Thromb Vasc Biol.*** **2013;33:00-00**

http://atvb.ahajournals.org DOI: 10.1161/ATVBAHA.112.300346

Pioglitazone has Numerous Possible Direct Positive Effects on Atherosclerosis

- PPAR-γ is abundant in endothelial cells, vascular smooth muscle cells, and monocytes/macrophages, providing a direct pathway for antiinflammatory and antioxidant effects.

- In addition, improvements in insulin signaling increases endothelial NO, decreases smooth muscle cell migrationand reduces macrophage uptake of LDL and formation of foam cells.

- Identifying the direct vascular mechanisms by which pio reduces atherosclerosis may help refine targets for therapy

Saremi, A., et. al. online 11/26/2012. ***Arterioscler Thromb Vasc Biol.*** **2013;33:00-00**

http://atvb.ahajournals.org DOI: 10.1161/ATVBAHA.112.300346

Pioglitazone had Numerous Positive Effects on CV Risk Factors in Pre-diabetics

Table 2. Risk Factors at Baseline and End of the Study

	Placebo		Pioglitazone		*P* Values for Change Between Groups
	Baseline	Absolute Change	Baseline	Absolute Change	
BMI, kg/m^2	33.40 (5.60)	0.09 (1.88)	32.80 (4.80)	1.56 (2.03)	<0.001*
Waist, cm	106 (13)	1 (6)	105 (12)	4 (6)	<0.001*
Systolic BP, mm Hg	127 (17)	−2.33 (15.20)	125 (16)	0.07 (14.98)	0.121
Diastolic BP, mm Hg	73 (11)	−0.52 (9.17)	73 (9)	−1.88 (9.47)	0.165
Total cholesterol, mg/dL	173 (33)	1 (33)	167 (33)	2 (31)	0.771
LDL-C, mg/dL	107 (30)	−1 (30)	103 (30)	−2 (29)	0.627
HDL-C, mg/dL	41 (10)	3 (8)	40 (10)	7 (9)	<0.001*
Triglycerides, mg/dL	112 (84–154)	−4 (57)	107 (84–146)	−10 (52)	0.12
Total cholesterol/HDL-C	4.4 (1.2)	−0.29 (0.99)	4.4 (1.2)	−0.59 (1.06)	0.004
Triglyceride/HDL-C	3.3 (2.0)	−0.34 (1.88)	3.3 (2.1)	−0.67 (1.54)	0.057
Fasting glucose, mg/dL	105 (8)	−5 (13)	105 (12)	−10 (11)	<0.001*
2-hour glucose, mg/dL	169 (19)	−7 (37)	170 (22)	−26 (37)	<0.001*
HbA_{1c}, %	5.4 (0.4)	0.19 (0.36)	5.5 (0.4)	0.08 (0.32)	<0.001*
Fasting insulin, mU/L	8.1 (4.2–13.5)	0.96 (6.80)	7.8 (4.1–12.7)	−3.67 (8.85)	<0.001*
Matsuda index	3.3 (2.1–5.5)	1.52 (3.90)	3.0 (2.1–5.1)	3.98 (4.56)	<0.001*
SI	2.4 (1.7–3.3)	0.68 (2.70)	2.3 (1.6–3.4)	2.22 (6.42)	0.019
Adiponectin, μg/mL	10 (7–15)	2 (9)	10 (6–14)	29 (35)	<0.001*
Leptin, pg/mL	29 (14–47)	2 (12)	27 (14–43)	6 (17)	0.005
CRP, mg/L	2.0 (0.9–4.2)	0.06 (5.88)	1.9 (0.6–4.6)	−0.38 (6.56)	0.508
IL-6, ng/mL	1.5 (0.9–2.1)	0.46 (3.08)	1.3 (0.9–2.2)	−0.77 (7.57)	0.057
PAI-1, ng/mL	14 (10–20)	1.83 (10.38)	13 (9–19)	−2.19 (8.18)	<0.001*
MCP-1, pg/mL	128 (97–165)	9 (38)	136 (100–173)	12 (44)	0.556
TNF-α, pg/mL	3.8 (2.9–4.7)	0.52 (1.24)	3.8 (2.9–5.1)	0.16 (1.61)	0.024

BMI indicates body mass index, calculated as weight in kilogram divided by height in m^2; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, glycosylated hemoglobin; SI, insulin sensitivity index determined from a frequently sampled intravenous glucose tolerance test; CRP, C-reactive protein; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemotactic protein-1; TNF-α, tumor necrosis factor-α. Values are mean (SD) or median (25th–75th percentiles). No statistically significant differences were identified between the groups at baseline. Paired and unpaired *t*

Saremi, A., et. al. online 11/26/2012. ***Arterioscler Thromb Vasc Biol.*** **2013;33:00-00**

BD Method Thoughts: Pioglitazone Benefit Might be Elucidated by Bio-markers not Evaluated:

(the only inflammatory marker measured that we use was hsCRP)

- Microalbumin-creatinine ratio
- Lp-PLA2
- Myeloperoxidase
- F2 isoprostane
- Fibrinogen
- NT pro-BNP – known independent predictor

Saremi, A., et. al. online 11/26/2012. ***Arterioscler Thromb Vasc Biol.*** **2013;33:00-00**

http://atvb.ahajournals.org DOI: 10.1161/ATVBAHA.112.300346

Hot Topics

Statins Increase CK and Cause Myalgia

- 420 healthy statin naïve pts.; 50% women; ages 20 to 55+; atorva 80mg or placebo times 6 mos;
- CK average increased 20.8 ± 141.1 U/L ($p<0.0001$) with atorvastatin
- Myalgia occurred significantly more with atorva – 19 vs 10 with $p=0.05$ (~10% incidence); CK not related
- No difference in strength or exercise capacity

Parker, B. A., et. al. *Circulation.* published online November 26, 2012
http://circ.ahajournals.org/content/early/2012/11/26/CIRCULATIONAHA.112.136101

Statins Increase CK and Cause Myalgia

- Atorvastatin also increased average ALT values 15.7 ± 27.4 U/L ($p < 0.0001$)
- There was no effect on Vitamin D
- Statin myalgia came on in ~ 1 month
- Atorva pts with myalgia did demonstrate reductions in muscle strength in 5 of 14 measured variables

Parker, B. A., et. al. *Circulation.* published online November 26, 2012
http://circ.ahajournals.org/content/early/2012/11/26/CIRCULATIONAHA.112.136101

BD Method Thoughts

- Reinforces taking myalgia complaints seriously regardless of CK levels
- Wonder about long term mm damage (loss of strength) since the average CK did increase; coupled with biopsy studies showing tissue damage
- Reinforces avoiding high dose statin rx
- Curious about bilirubin changes – they did not measure it - ☹

Cases???

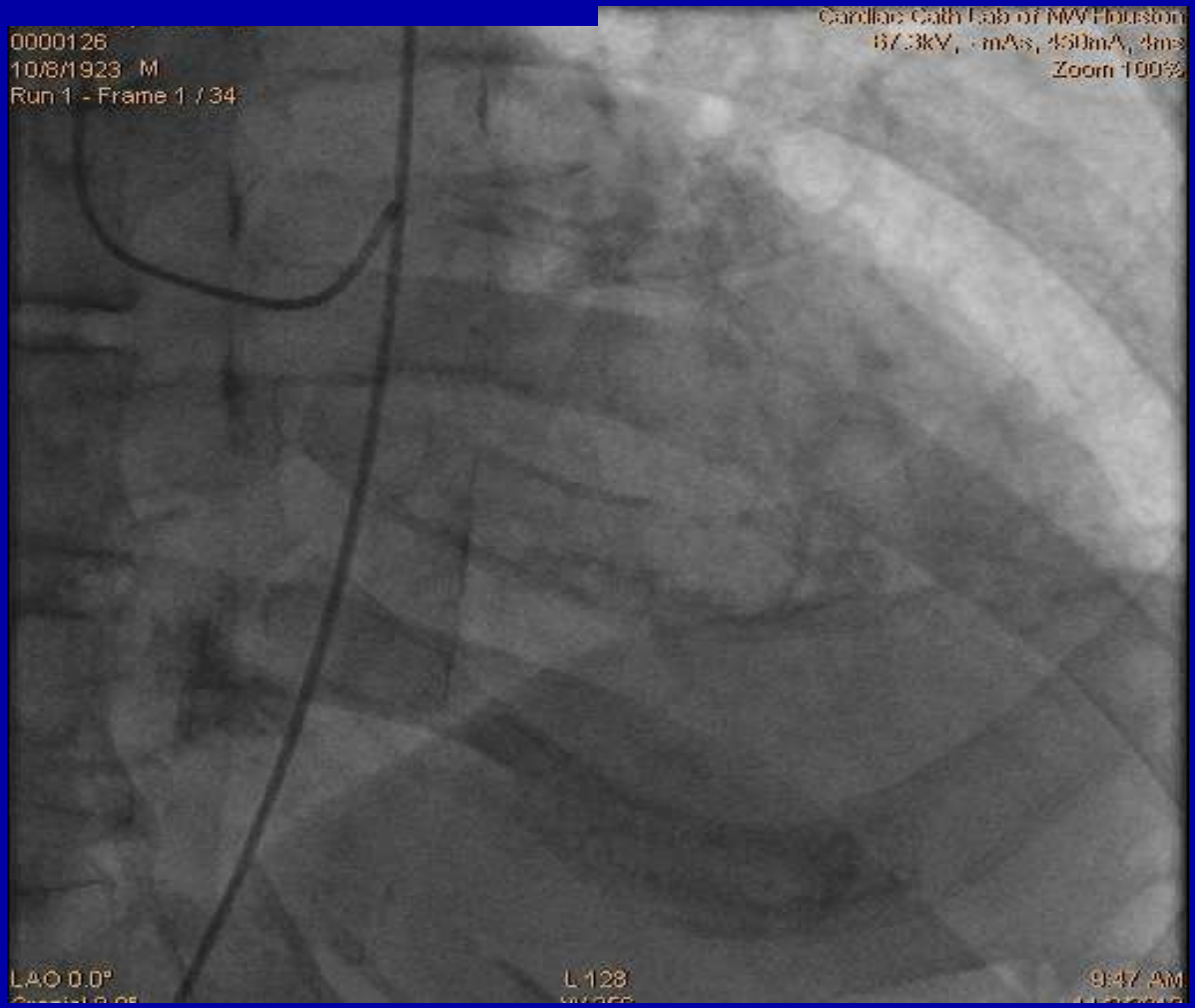
OMT to Stabilize CHD

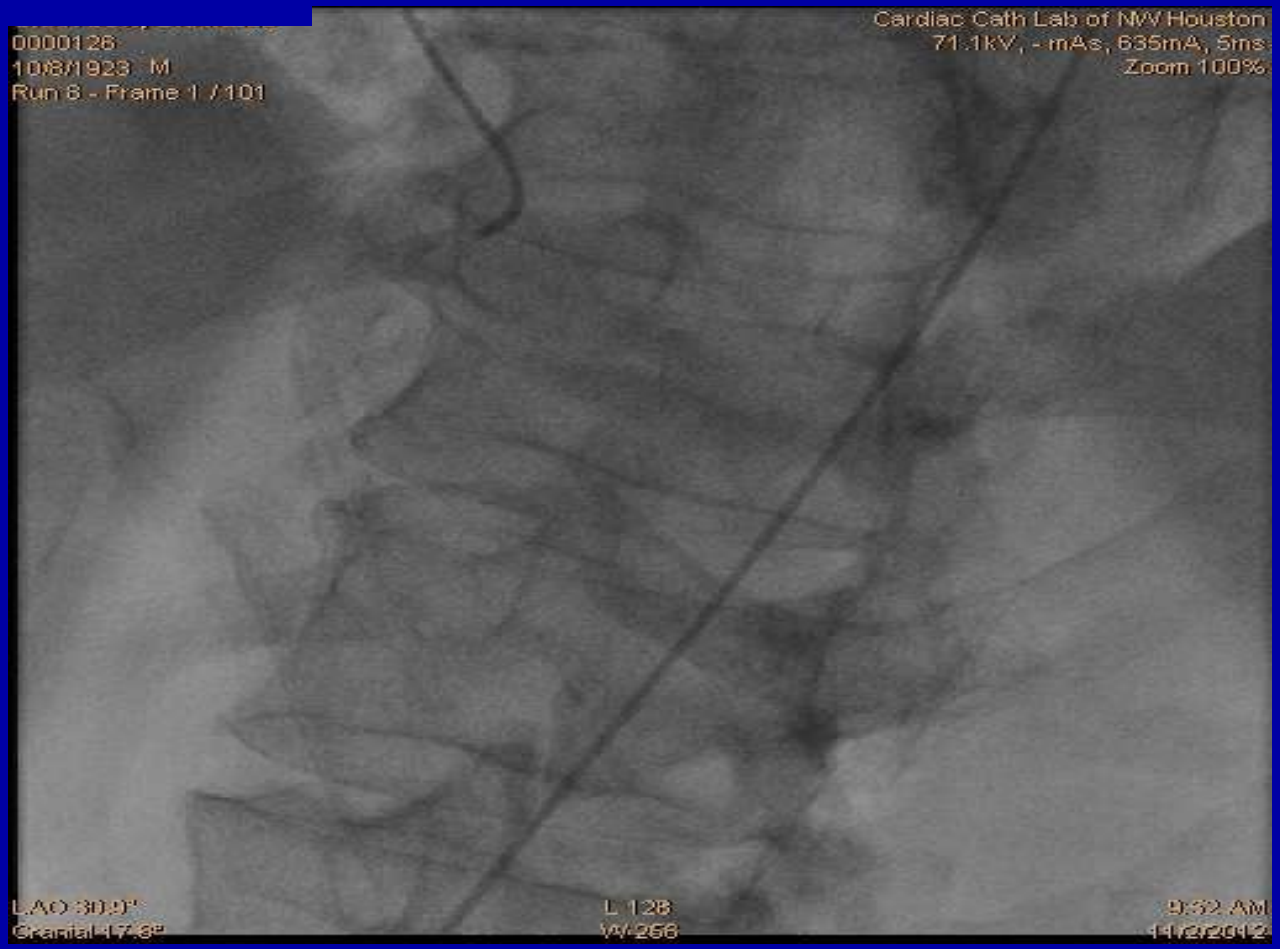
- 83 yo Caucasian male
- Dyspnea on exertion lead to angiogram
- 100% occlusion circumflex; 95% L main; 50% proximal LAD; 20% RCA; EF 65%
- CABG or multiple stents recommended
- Declined; started BD Method instead
- Lifestyle, ASA 81mg; vit. D3 2,000 IU; fish oil one cap 2-3 X/wk; rosuvastatin 20mg; niacin ER 1 gram; valsartan 80mg; carvedelol CR 10mg

- 89 yo now; still some dyspnea if walks too fast; arteries kept on “ice” last five years

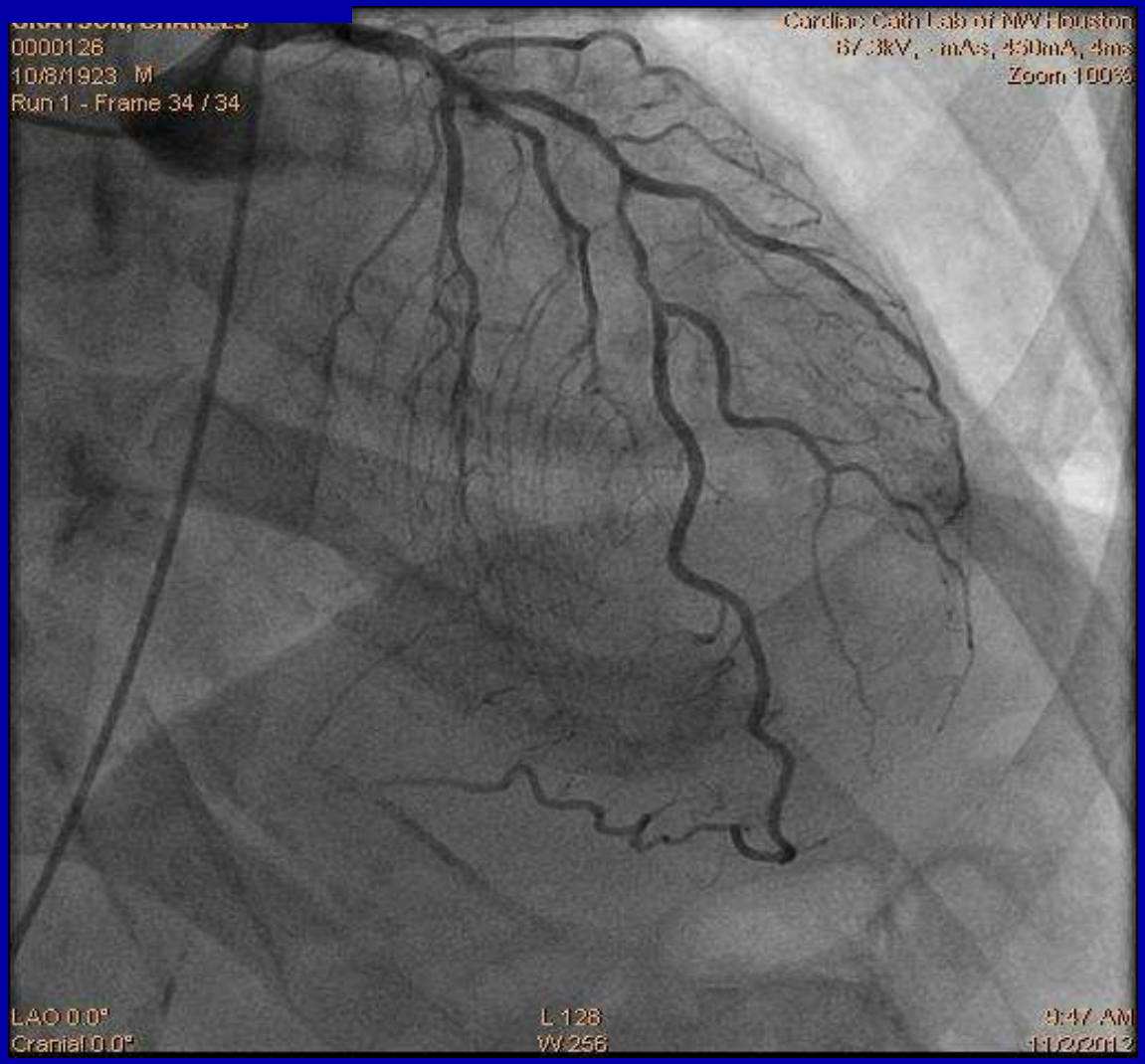
- Repeat angiogram 11/2012: 100% occlusion circumflex; 30% L main (was 95%); proximal LAD 30-40% (was 50%); RCA mild plaquing (was 20%); EF 65%; no evidence of any infarctions; numerous collateral vessels (angiogenesis) from RCA and distal LAD

- Cardiologist’s statement: *“big fan of the Bale/Doneen Method, you are really filling in many of the holes in our understanding of clinical management of cad and dyslipidemia.”*





OMT Works



Upcoming Presentations

Upcoming Presentations

- 12/15/2012- Bale/Doneen Method Highlighting Inflammatory Testing for the Reduction of Cardiovascular Events. ;5 hr. CME; Dallas, TX
- 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

Happy Holidays!

Open for Discussion