Bale/Doneen Live Chat Session

Amy Doneen DNP, ARNP

August 13, 2014

5:30-6:30 pm PST

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Happy Summer from Washington!

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Outline for today's discussion

1. New On-line Course Offering!
2. Bale/Doneen Reunion – Register Now!
3. HPS 2-Thrive (we can't seem to leave this topic) ☺
4. Alcohol in the INTERHEART Trial
5. Radiation Exposure with various coronary testing
6. Pschyological factors and Stroke/TIA risk
7. Xylitol and Pg
8. Cases x 3

Bale/Doneen On-Line Course

New On-Line Feature!

8.5 Category 1 CME – AAFP Approved

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21 video tutorials with 50 question exam requiring an 85% correct to receive certification of completion.

Purpose: Increase access to the Bale/Doneen Method for all medical and dental providers to gain a basic understanding of our disease/inflammatory approach to CVD Prevention.

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JOURNAL OF Arteriology

PRODUCED BY THE BALE/DONEEN METHOD

NEW ONLINE FEATURE!

Bradley Bale, MD

Amy L. Doneen, DNP, ARNP

We are proud to introduce our 8.5 hour CME Online course!

The cost of the 8.5 hour Category 1 CME course is $399.

To access this course, please go to: https://ioa.digitalchalk.com/dc/guest/login

Please share this site with your colleagues and friends.

This Enduring Material activity, Bale/Doneen Method Preceptorship Online Program, has been reviewed and is acceptable for up to 8.50 Prescribed credit(s) by the American Academy of Family Physicians. AAFP certification begins 07/14/2014. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Bale/Doneen On-Line Course

Completion of BOTH COURSES:

1. Allows ability to register for the referral directory on our website

2. Requirements to apply for Bale/Doneen speaker's bureau.

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Bale/Doneen Reunion

October 17-19, 2014 at the Canyon Ranch in Tucson, AZ

THIS WILL BE A WEEKEND OF FRIENDSHIP, LEARNING, SHARING, PHYSICAL AND INTELLECTUAL NOURISHMENT. WE ARE LAUNCHING THE SPEAKER'S BUREAU AND REVIEWING NEW DATA AND CASE STUDIES AND DISCUSSING MANY EXCITING OPPORTUNITIES. PLEASE JOIN US!

JOURNAL OF Arteriology
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Bale/Doneen public review of The New England of Medicine, July 17, 2014, Volume 371 No 3

"Effects of Extended-Release Niacin with Laropiprant in high risk patients. The HPS2-Thrive Collaborative Group."

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Bale/Doneen public review of HPS2-Thrive

What was the trial testing?

First, and most importantly, this was NOT a trial testing the value and safety of niacin (Vitamin B3). It was a trial testing an experimental product called, Laropiprant, which was coupled with niacin to block flushing. Tolerability of niacin has been limited due to flushing.

Therefore, Merck formulated a new drug which combined extended release niacin with laropiprant. This produce was given the name Cordaptive. It was denied approval by the FDA in April of 2008, but was approved in Europe. Merck was able to proceed with their investigational study utilizing this new drug. This study is HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events).

Bale/Doneen public review of HPS2-Thrive

HPS2-Thrive: The trial included 25,673 high risk patients who were randomized to either placebo or extended-release niacin plus laropiprant in addition to background therapy with simvastatin or simvastatin/ezetimibe (Vytorin).

Baseline demographics – 83% men, mean age 64.9 years, 78% with coronary disease (CAD), 32% with cerebrovascular disease (CVD), 13% with peripheral arterial disease (PAD), and 32% with diabetes (DM). It was a 4 year trial.

How does Laropiprant block the flushing? Laropiprant blocks a receptor, DP-1, to reduce the annoying dilation of arteries from niacin responsible for the flush. Blocking the receptor DP-1 by laropiprant could be projected to have adverse consequences.

Bale/Doneen public review of HPS2-Thrive

Beneficial effects of stimulating DP-1:

Turning on DP-1 directly dilates airways as well as arteries which improve blood flow and can enhance erections. DP-1 stimulation has anti-inflammatory effects with the asthmatic condition and it can enhance sleep and provide neuroprotection for the brain.

DP-1 activation has numerous indirect benefits as a result of increasing a substance called prostaglandin D2 (PGD2). This hormone like product improves the body's ability to fight viral lung infections. PGD2 also increases the production of substance which can stimulate peroxisome proliferator-activated receptor-gamma (PPAR gamma). These nuclear receptors regulate gene expression which favors lower blood sugar, prevention of diabetes, reduced arterial inflammation, reduced blood pressure and improved cholesterol.

Blocking the stimulation of DP-1 could have numerous serious detrimental effects.

Bale/Doneen public review of HPS2-Thrive

Are there any potential direct adverse effects of laropiprant?

Laropiprant works against a substance called tissue plasminogen (TP). Blocking the effect of TP inhibits the activation of platelets. This activity is critical for the formation of blood clots. The net result of laropiprant blocking the TP receptor would be to enhance the potential for hemorrhagic bleeding.

Bale/Doneen public review of HPS2-Thrive

Do the results of HPS2-Thrive match these anticipated side effects of Laropiprant blocking the pathway that Niacin stimulates?

The investigators reported that numerous serious side effects were seen in the study which had not been observed with niacin before.

They included: diabetic complications increased 3.7%, new onset diabetes increased 1.8%, infections (mainly lower respiratory) by 1.4%, gastrointestinal 1% increase, heart failure 0.4%, bleeding 0.7% and skin 0.3%. It is important to point out that major high blood sugar problems were increased 3 fold and any diabetic complications were up by 55% leading to the halting of this trial at 3.9 years.

We would argue these 'new' side effects seen with this novel drug, Cordaptive, can be attributed for the most part to the laropiprant component. The aforementioned science regarding this agent fits nicely with these novel adverse reactions.

Bale/Doneen public review of HPS2-Thrive

What did the investigators conclude?

Unfortunately, the investigators blamed these side effects entirely on niacin.

This conclusion was reached despite their statement that the study identified significant hazards, some of which had not been reported previously with niacin.

Niacin has over thirty years of trials which demonstrate its ability to improve all of the cholesterol substances. Some of these trials also demonstrate niacin's ability to halt arterial disease as well as its ability to regress disease and prevent heart attacks.

Bale/Doneen public review of HPS2-Thrive

What conclusions did we make from HPS2-THRIVE?

The number one conclusion is a clinical judgment regarding niacin CANNOT be derived from this trial. This trial did not involve mono-niacin therapy.

The therapeutic arm with niacin contained an intruder, laropiprant, which science tells us cannot be considered an innocent bystander.

Rather, we can infer that blocking the DP1 pathway in order to prevent the flushing from niacin is not a good idea.

Bale/Doneen public review of HPS2-Thrive

What conclusions did we make from HPS2-THRIVE?

We predicted in 2008 when Cordaptive was proposed that it would not generate cardiovascular benefit and probably would create harm.

We told the students in our CME course that if it got approved by the FDA, we would not recommend using it. We feel HPS2-THRIVE validated our stance. In our opinion, niacin got "thrown under the bus!"

Thus, this trial DOES NOT deter our use of niacin. It is still a wonderful natural therapy for patients who are statin intolerant; have sub-optimal cholesterol after statin treatment; are not at TC/HDL goal; have the inherited lipo (a) cholesterol issue; have insulin resistant dyslipidemia; have persistent arterial inflammation. Because flushing is of no threat to one's health and because niacin can promote better health, we will continue to prescribe niacin for the situations list above.

TABLE 2 Efficacy and Tolerability Findings From Major Randomized Controlled Trials of Niacin-Containing Therapies

Study[a]	Population	Follow-up, y	Treatment, g (n)[b]	Changes From BL in Lipids (Active Treatment), %	Changes From BL in Clinical/Angiographic/ Imaging Endpoints, % (Niacin vs Placebo or Other Comparator)	Frequency of Flushing (ever), % Adherence (Niacin vs Pbo or Other Comparator)
CDP[22,23]	Men 30–64 y post-MI	5–15	NIR 3.0 (1119) Pbo (2789)	TC, −10 TG, −19	−27 nonfatal MI (5 y) ($P < .05$) −11 total mortality (15 y) ($P = .0004$)	Flushing: 92 vs 4 ($P < .05$) Mean adherence: 66 vs 78
CLAS[24,29]	Men 40–59 y post-CABG	2–4	NIR 3.0–12.0 (mean, 4.3) + BAR (80) Pbo (82)	TG, −22 LDL-C, −43 HDL-C, +37	Atherosclerotic regression: 16 NIR vs 2 pbo ($P = .002$)	Flushing: 91 vs 6 ($P < .01$)
FATS[16]	Men ≤62 y with high Apo B + CHD	2.5	NIR 0.25–6.0 g + BAR 15–30 (36) Pbo-BAR (46)	TG, −29 HDL-C, +43 LDL-C, −32	Atherosclerotic regression: 39 NIR-BAR vs 11 pbo ($P < .005$) Clinical events[c]: 4 NIR-BAR vs 19 pbo-BAR −78 ($P < .01$)	Adherence: 86 NIR-BAR vs 89 pbo-BAR
HATS[17]	Adults <70 y with CHD + low HDL-C + ≥3 coronary arteries with ≥30% stenosis	3	NSR 0.5–2.0 → NIR 3–4 g if inadequate ↑HDL (mean, 2.4) + SA (+ 0.1 g niacin) (33) Pbo (34)	TG, −36 LDL-C, −42 HDL-C, +26	Atherosclerotic regression: by 0.4 on niacin vs progression by 3.9 on pbo ($P < .001$) Clinical events[d]: 3 vs 24 (−90%; $P = .03$)	Flushing: 30 vs 23 ($P = .35$) Adherence: 80 NSR-SA vs 80 pbo
ARBITER 2[28]	Adults >30 y with CHD + low HDL-C on statin	1	NER 0.5–1.0 + statin (87) Pbo + statin (80)	TG, −13 LDL-C, −2 HDL-C, +21	CIMT progression: −0.004 vs +0.044 mm in euglycemics ($P = .026$)	Flushing: 69 vs 13 ($P < .001$) Adherence: 90–95 ($P > .05$ vs pbo)
AFREGS[18]	Adults <76 y with CHD + low HDL-C	2.5	GF 1.2 NIR 0.25–3 BAR 16 (71) Pbo + TLC (72)	TG, −46 LDL-C, −22 HDL-C, +38	% Stenosis: −0.8 vs +1.4 ($P < .05$) Clinical events[e]: 13 vs 26 ($P = .04$)	Flushing: 92 vs 25 ($P < .001$) Adherence: 87–90 vs 88–92
ARBITER 6-HALTS[26]	Adults with atherosclerotic CHD or vascular disease, CHD risk equivalent or 10-y Framingham absolute CHD risk ≥20%, and LDL-C <100 mg/dL and HDL-C <50 mg/dL (men) or <55 mg/dL (women)	1.2	NER 2.0 (target, or MDT) (97) or EZ 10 mg (111) + ongoing statin at stable dose	NER/statin: LDL-C, −12.4 HDL-C, +17.6 EZ/statin: LDL-C, −21.0 HDL-C, −6.5 ($P \leq .01$ for each between-group comparison)	CIMT progression: NER/statin: −0.0142 mm EZ/statin: −0.0007 mm ($P = .01$) Clinical events[e]: NER/statin: 1% incidence EZ/statin: 5% incidence ($P = .04$)	Flushing: 36 vs NA Adherence: 88 vs 95 ($P < .001$)

AFREGS, Armed Forces Regression Study; Apo B, apolipoprotein B; ARBITER, Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ARBITER-6-HALTS, Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol: HDL and LDL Treatment Strategies; BAR, bile acid resin (sequestrant); BL, baseline; CABG, coronary artery bypass graft; CDP, Coronary Drug Project; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CLAS, Cholesterol-Lowering Atherosclerosis Study; EZ, ezetimibe; FATS, Familial Atherosclerosis Treatment Study; GF, gemfibrozil; HATS, High-Density Lipoprotein Atherosclerosis Treatment Study; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDT, maximum dose tolerated; MI, myocardial infarction; NER, niacin extended-release; NIR, niacin immediate-release (ie, crystalline niacin); NSR, niacin sustained-release; pbo, placebo; SA, simvastatin; TC, total cholesterol; TG, triglyceride; TLC, therapeutic lifestyle counseling.

[a]Study reports presented in ascending order of date published for major clinical trials reporting data on both efficacy and tolerability/adherence.

[b]Number randomized.

[c]Death, MI, revascularization, or worsening ischemia.

[d]Coronary death, MI, stroke, revascularization for worsening ischemia.

[e]Death from CHD, hospitalization for acute coronary syndrome, revascularization, MI.

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So – let's discuss the science behind HPS2-Thrive…

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HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease.

Jane Armitage on behalf of the

HPS2-THRIVE Collaborative Group

These slides were shown 3/2013 when trial was released online – this is a review…

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HPS2-THRIVE: Eligibility

Men and women

Aged 50-80 years

Prior history of: myocardial infarction;
ischaemic stroke or TIA;
peripheral arterial disease; or
diabetes with other CHD

No contra-indication to study treatments

No significant liver, kidney or muscle disease

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hps2 THRIVE

Dale Doneen METHOD

HPS2-THRIVE: Active pre-randomization run-in

Screened (51,698)

High cardiovascular risk patients screened in 245 sites within 6 countries

LDL lowering phase (36,059)

Standardise background LDL-lowering therapy with simvastatin 40 mg (+/- ezetimibe) daily (to total cholesterol target of 135 mg/dL)

Active ER niacin plus laropiprant (38,369)

Test compliance with ER niacin 2 grams plus laropiprant 40 mg (ERN/LRPT) daily for 1 month

Randomization (25,673)

ER niacin 2g plus laropiprant 40 mg daily vs. matching placebo tablets

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Characteristics of randomized participants

% or mean (SD)	ERN/LRPT (12,838)	Placebo (12,835)	All
Men	83%	83%	21,229 (83%)
Age (years)	64.9	64.9	64.9 (7.5)
Prior disease			
Coronary	78%	78%	20,137 (78%)
Cerebrovascular	32%	32%	8170 (32%)
Peripheral arterial	13%	12%	3214 (13%)
Diabetes	32%	32%	8299 (32%)

Too bad not many females

Baseline LIPIDS on statin-based therapy

	Mean (SD) baseline	
	mg/dL	mmol/L
Total cholesterol	128 (22)	3.32 (0.57)
Direct-LDL	63 (17)	1.64 (0.44)
HDL	44 (11)	1.14 (0.29)
Triglycerides*	125 (74)	1.43 (0.84)

*64% fasted for >8 hours

TC/HDL=2.9=optimal ; going to be tough to show benefit from a lipid perspective !!!!

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THRIVE

Dale Doneen METHOD

Effects of ER niacin/laropiprant on lipids

Year of FU	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)
1	-12	6	-35
4	-7	6	-31
STUDY AVERAGE	-10	6	-33

No ‘niacin creep’ observed
The change in the TC/HDL ratio would be minimal going from 2.9 to ~ 2.5
Going from optimal to optimal should not improve risk significantly

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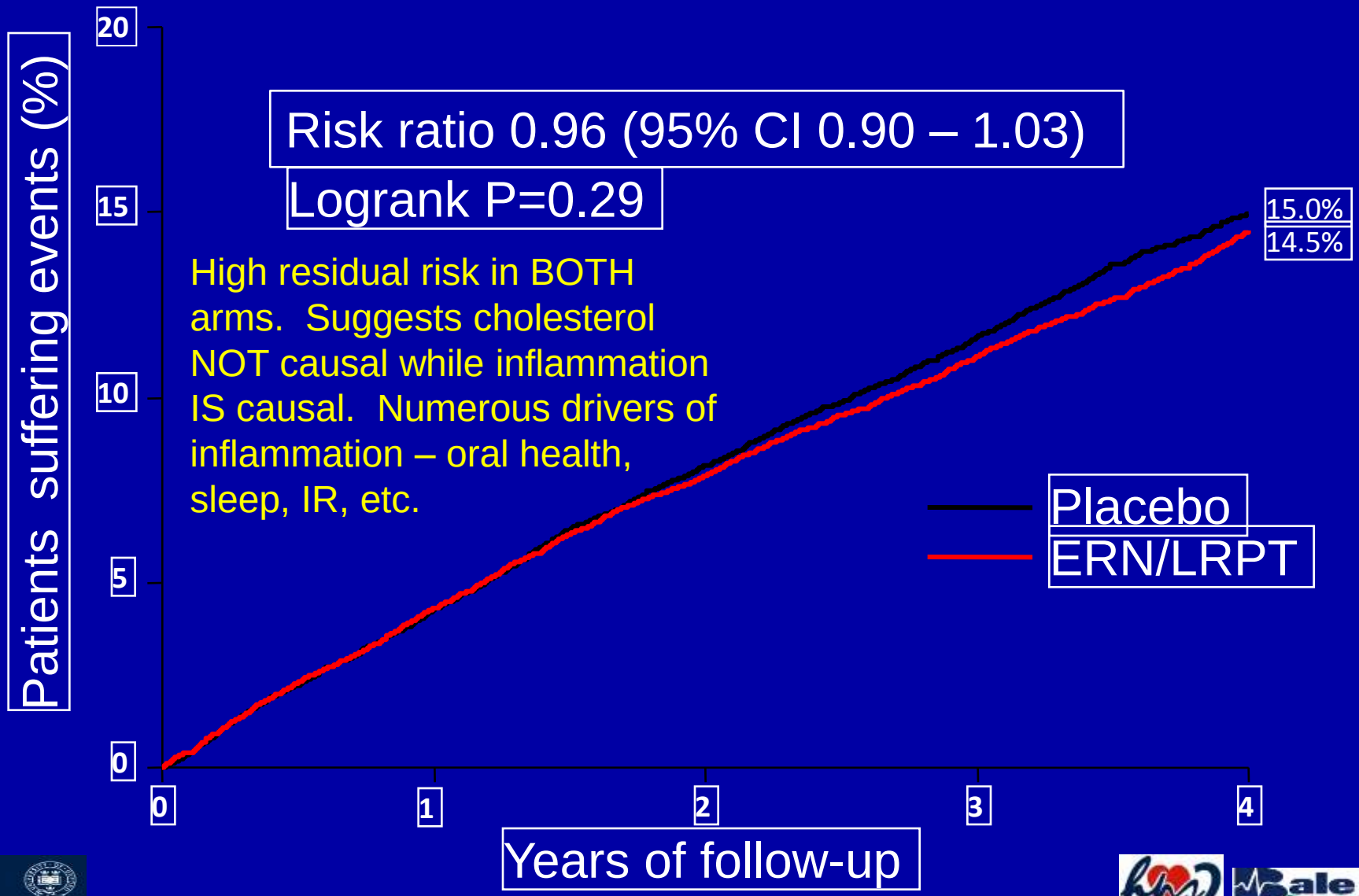
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS



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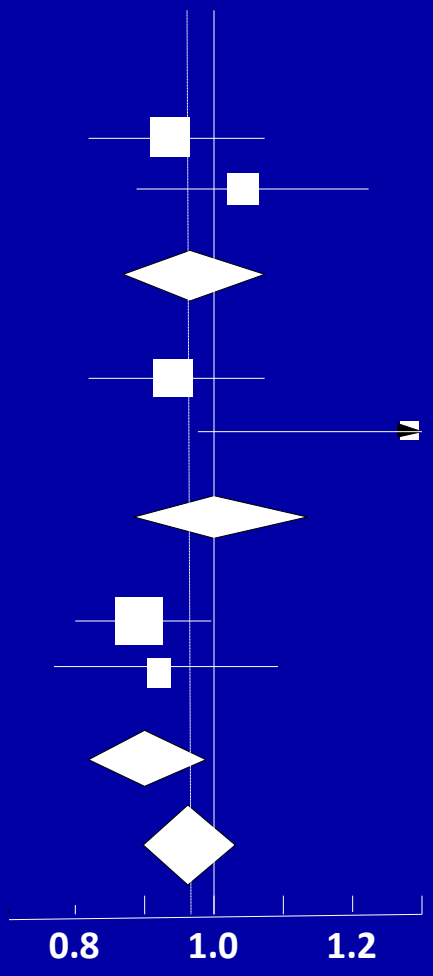
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Event	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	p
Non-fatal MI	402 (3.1%)	431 (3.4%)	0.93 (0.82-1.07)	0.33
Coronary death	302 (2.4%)	291 (2.3%)	1.04 (0.89-1.22)	0.63
Major coronary event	**668 (5.2%)**	**694 (5.4%)**	**0.96 (0.87-1.07)**	**0.51**
Ischaemic stroke	389 (3.0%)	415 (3.2%)	0.94 (0.82-1.08)	0.37
Haemorrhagic stroke	114 (0.9%)	89 (0.7%)	1.28 (0.97-1.69)	0.08
Any stroke	**498 (3.9%)**	**499 (3.9%)**	**1.00 (0.88-1.13)**	**0.56**
Coronary revasc	591 (4.6%)	664 (5.2%)	0.89 (0.80-0.99)	0.04
Non-coronary revasc	236 (1.8%)	258 (2.0%)	0.92 (0.77-1.09)	0.33
Any revascularization	**807 (6.3%)**	**897 (7.0%)**	**0.90 (0.82-0.99)**	**0.03**
Major vascular event	**1696 (13.2%)**	**1758 (13.7%)**	**0.96 (0.90-1.03)**	**0.29**



Certainly no signal of CV harm other than hemorrhagic stroke

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hps2 THRIVE

Dale Doneen METHOD

BD Method Concern with new ER niacin (Cordaptive): 2008 !

- Uses an investigational PGD2 receptor antagonist (laropriprant) to reduce flushing (blocks DP1 receptor)
- 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

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Laropiprant: Numerous Potential Adverse Effects from Blocking DP1

- Evidence supports DP1 receptor mediated effects of PGD2 are anti-inflammatory
- In asthma, signaling through DP1 appears anti-inflammatory
- DP1 signaling in bronchial smooth muscle causes bronchodilation

Vosper, H. Clin Med Insights Cardiol. 2011; 5: 85–101

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Laropiprant: Numerous Potential Adverse Effects from Blocking DP1

- PGD2 enhances sleep and this appears to be at least partially a DP1 mediated effect
- DP1 receptor mediates the erectile response in men (as studied in humans)
- DP1 mediated-effect enhancing insulin sensitivity has not been ruled out

Vosper, H. Clin Med Insights Cardiol. 2011; 5: 85–101

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Laropiprant: no reason to believe it will block niacin's adverse skin reactions

- Co-administration of niacin and DP1 antagonists assumed to be appropriate step to enhance tolerability.
- Evidence suggests the dermal effects of niacin are much more complex.
- A number of cell types are involved in the adverse effects of niacin on the skin: there is certainly evidence for a role for macrophages and platelets.

Vosper, H. Clin Med Insights Cardiol. 2011; 5: 85–101

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Laropiprant Might Cause more Bleeding

- Laropiprant has been shown to be an antagonist of the TP receptor.
- It is the TP receptor that mediates the powerful activation driven by thromboxane A2
- It may be that laropiprant acting in this capacity would inhibit platelet activation

Vosper, H. Clin Med Insights Cardiol. 2011; 5: 85–101

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Laropiprant Might Cause more Infection by Increasing Levels of PGD2

- Increase in PGD2 in mice led to diminished respiratory dendritic cell migration resulting in defects in virus-specific T-cell responses in vivo.
- Administration of PGD2 antagonist reversed this defect resulting in migration of dendritic cells with enhancement of T-cell antivirus response with increased clearance and survival
- These data suggest that similar to allergic airway disease PGD2 may have immunosuppressive effects in viral infections.

Myungsoo Joo, M., et. al.
Mediators Inflamm. 2012; 2012: 503128.
Published online 2012 June 25. doi: 10.1155/2012/503128

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Stimulation of DP1 Receptor is Neuroprotective

- Ischemia injury was produced by a 90-min occlusion of the right middle cerebral artery followed by a 4-day reperfusion.
- Infarct size was 49.0 ± 11.0% larger in DP1−/− mice (n = 11; $P < 0.01$) than in WT mice
- Corticostriatal neuronal cultures were exposed to DP1-selective agonist; provided dose-dependent protection against excitotoxicity induced by glutamate.
- DP1 receptor is neuroprotective in both in vivo and in vitro paradigms

Saleem, S., et. al. ***Eur J Neurosci***. 2007 July ; 26(1): 73–78

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Laropiprant May Effect Levels of 15 deoxyprostaglandin J2 (15 d-PGJ2)

- 15 deoxy-PGJ2 is produced in sufficient quantities by PGD2 to activate PPARγ
- Many of the anti-inflammatory effects of niacin may well be mediated by this receptor
- If PGD2 cannot bind to DP1, various metabolite levels could be affected

Vosper, H. Clin Med Insights Cardiol. 2011; 5: 85–101

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If laropiprant causes defects in virus-specific T-cell responses, decreases bronchial dilatation, increases inflammation, inhibits platelet aggregation, causes more stimulation of DP2 receptor and reduces the stimulation of PPAR gamma, what side effects might you expect??

- Increased infection – especially respiratory
- Increases GI and cerebral bleeding
- Increased peptic ulcer
- More hyperglycemia in diabetics
- Increased risk of new onset diabetes
- Less CV benefit

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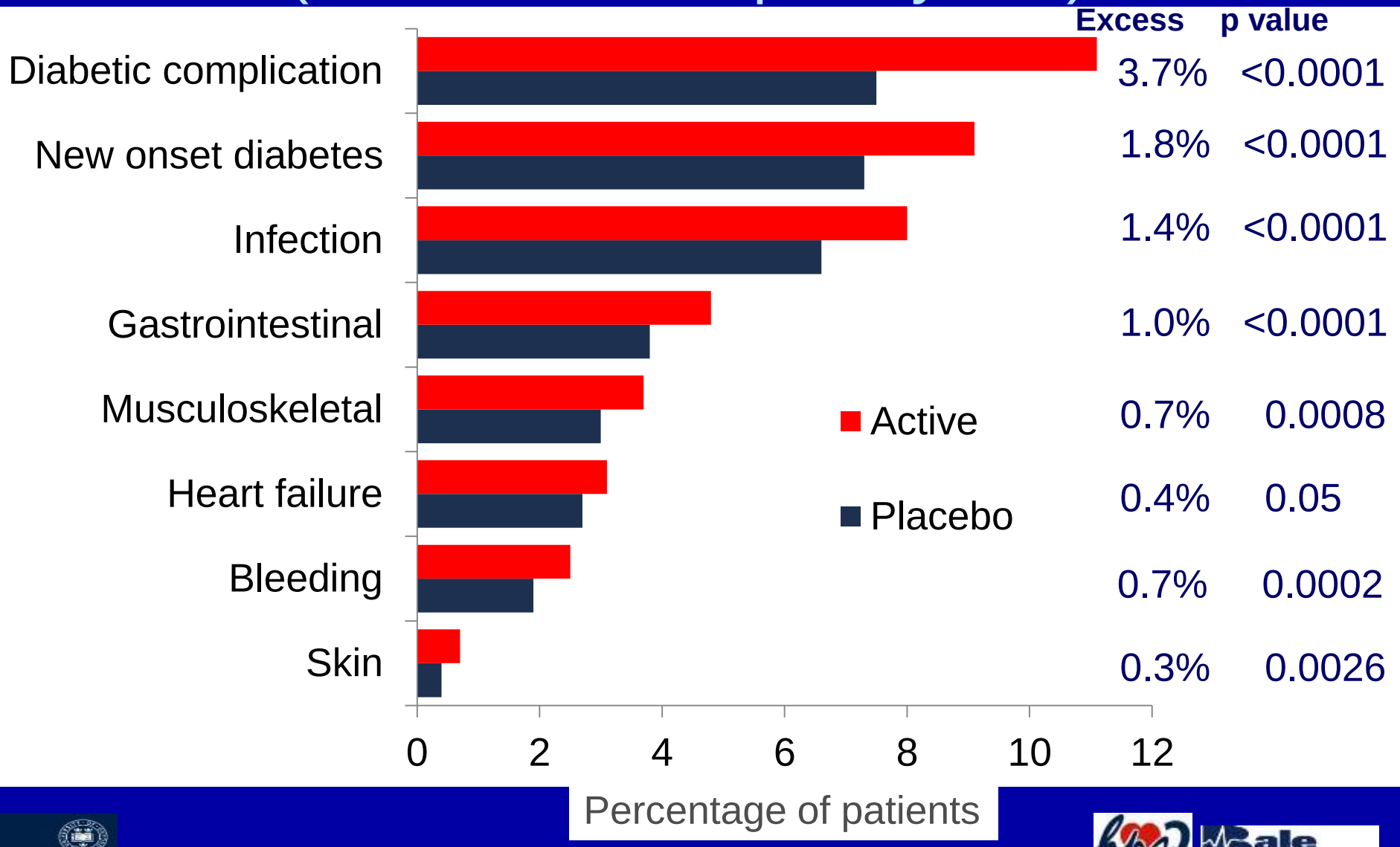
Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)



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THRIVE

Bale Doneen METHOD

Effect of ERN/LRPT on glucose related SAEs

Serious adverse event	ERN/LRPT	Placebo	Risk ratio (95% CI)
Participants with diabetes at randomization (n= 8299)			
Minor hyperglycaemic problem	8.7%	5.8%	1.55 (1.32-1.82)
Major hyperglycaemic problem	1.0%	0.3%	3.09 (1.81-5.27)
Hypoglycaemia	1.1%	0.7%	1.50 (0.96-2.35)
Other diabetic complication	1.1%	1.2%	0.93 (0.62-1.40)
Any diabetic complication	**460 (11.1%)**	**311 (7.5%)**	**1.55 (1.34-1.78)**
Participants without diabetes at randomization (n= 17,374)			
New-onset diabetes mellitus	**792 (9.1%)**	**632 (7.3%)**	**1.27 (1.14-1.41)**

This should have been expected due to laropiprant !!

AIM-HIGH (ER niacin without laro) & Hyperglycemia

- 1,696 placebo; 1,718 ER niacin; 85% (83%*) men; 34% (32%*) DM; follow-up ~ 3 years (3.9 yrs*)

- "Adverse effects were rare and included:
  liver-function abnormalities (0.5% in the placebo & 0.8% in the niacin)
  muscle symptoms or myopathy (0.3% of the patients overall)
  rhabdomyolysis (1 patient in the placebo & 4 in the niacin group)."

- New onset DM not even mentioned in AIM HIGH

The AIM-HIGH Investigators. N Engl J Med 12/15/2011. 365;24:2255-2267
* HPS-THRIVE

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Effect of ERN/LRPT on infection and bleeding

Serious Adverse Event	ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio (95% CI)
Infection			
Lower respiratory	4.3%	3.7%	1.17 (1.03-1.32)
Urinary tract	0.9%	0.8%	1.07 (0.82-1.39)
Abdominal/gastrointestinal	0.6%	0.5%	1.26 (0.91-1.75)
Skin	0.5%	0.3%	1.66 (1.14-2.43)
Other	2.4%	1.7%	1.38 (1.16-1.63)
Any infection SAE	**1031 (8.0%)**	**853 (6.6%)**	**1.22 (1.12-1.34)**
Bleeding			
Gastrointestinal	0.8%	0.6%	1.53 (1.14-2.05)
Intracranial	1.1%	0.9%	1.17 (0.92-1.50)
Other	0.6%	0.4%	1.66 (1.18-2.34)
Any bleeding SAE	**326 (2.5%)**	**238 (1.9%)**	**1.38 (1.17-1.62)**

UNIVERSITY OF OXFORD

THRIVE

Study stopped early due to SAEs; it was not due to CV Risk!

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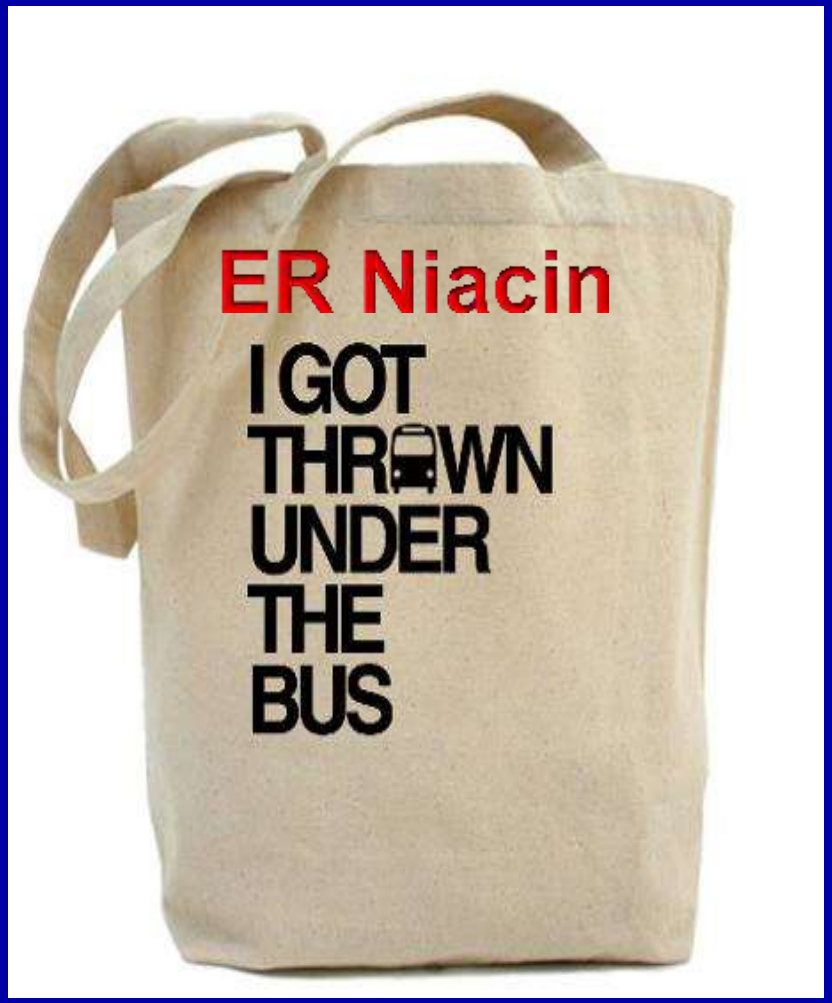
HPS2-THRIVE: SUMMARY



Niacin Can Be Good Medicine

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Moving on…..

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So – in celebration to moving forward – let's discuss the latest trial involving alcohol and CV Health☺

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Alcohol – INTERHEART Trial

12,195 cases of first MI and 15,583 age-and sex-match controls from 52 countries.

Current alcohol use was associated with a reduced risk of MI (compared with nonusers):

Adjusted odds ration, 0.87:95% CI, 0.80-0.94; P=0.001).

Not uniform across different regions (P<0.001)

Leong, D., Smyth, A., Teo, K. et al. Patterna of alcohol consumption and myocardial infarction risk: INTERHEART. Circulation. June 13, 2014: 130:390-398.

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Alcohol – INTERHEART Trial

In most participants, low levels of alcohol use are associated with a moderate reduction In the risk of MI.

Alcohol categories analyzed:

- <1 time/month
- <1 time/week
- 1-2 times/week
- 3-4 times/week
- 5-6 times/ week
- Daily consumption
- Consumption: Defined as ≥ 1 drink in last 12 months.
- Heavy use at time of MI: ≥ 6 drinks within 24 hrs of MI

Leong, D., Smyth, A., Teo, K. et al. Patterna of alcohol consumption and myocardial infarction risk: INTERHEART. Circulation. June 13, 2014: 130:390-398.

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Alcohol – INTERHEART Trial

Heavy episodic drinking (≥ 6 drinks) within the preceding 24 hours was associated with an increased risk of MI (odds ratio, 1.4; 95% CI, 1.1-1.9; P=0.01).

This risk was particularly elevated in older individuals >65 yrs (odds ratio, 5.3; 95% CI, 1.6-18; P=0.008).

In most participants, low levels of alcohol use are associated with a moderate reduction In the risk of MI. However, strength of association may not be uniform across different countries.

Leong, D., Smyth, A., Teo, K. et al. Patterna of alcohol consumption and myocardial infarction risk: INTERHEART. Circulation. June 13, 2014: 130:390-398.

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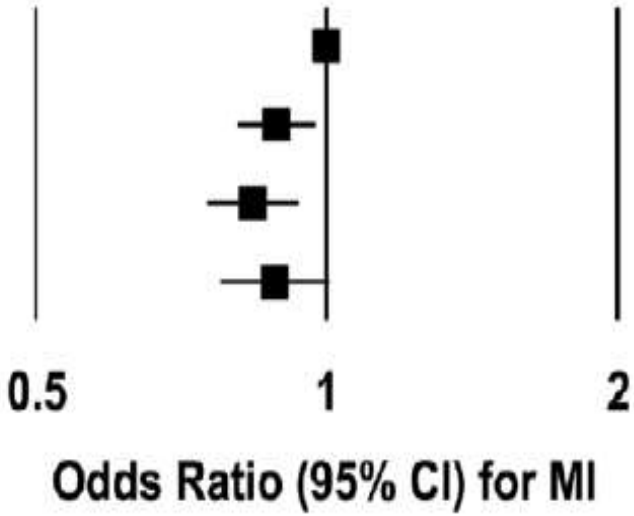
ETOH – INTERHEART Trial

B

	n	Odds ratio	Lower limit	Upper limit
Non-Drinker	10,056	1		
<1x/week	3,747	0.888	0.808	0.975
1-4x/week	2,527	0.839	0.751	0.937
>4x/week	1,596	0.884	0.775	1.007



Adjusted for: age (<45, 45-65, >65), sex, geographic region, dietary risk score, exercise Smoking, marital status, employment, education level, depression, stress at work or at home, financial stress , body mass index, and waist-to-hip ratio, serum ratio of Apo B/ Apo A1, TC, HDL, LDL, TG, history of HTN or diabetes.

Leong, D., Smyth, A., Teo, K. et al. Patterna of alcohol consumption and myocardial infarction risk: INTERHEART. Circulation. June 13, 2014: 130:390-398.

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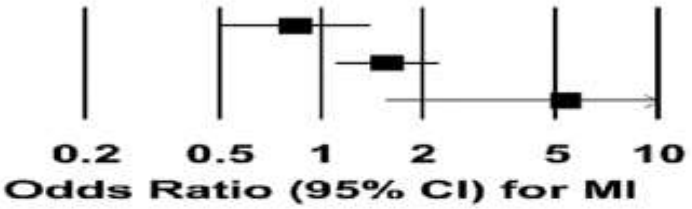
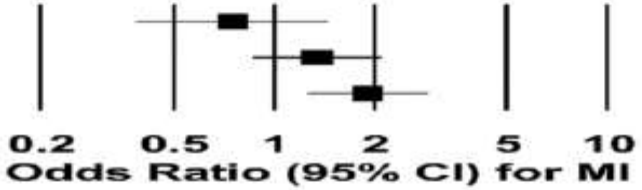
ETOH – INTERHEART Trial

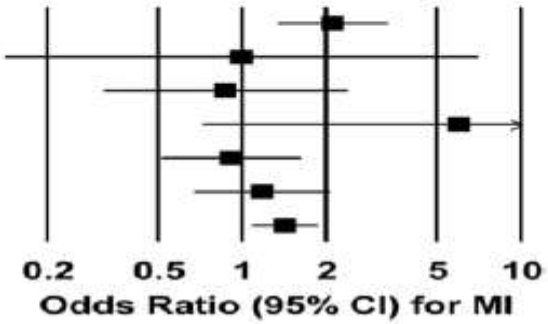
A HEAVY DRINKING	n	Odds ratio	Lower limit	Upper limit
Age (p<0.001)				
<45 years	1,957	0.844	0.506	1.408
45-65 years	6,331	1.571	1.098	2.248
>65 years	3,350	5.333	1.554	18.303



B	n	Odds ratio	Lower limit	Upper limit
Alcohol Frequency (p=0.02)				
<1x/week	2,528	0.750	0.384	1.465
1-4x/week	1,764	1.344	0.850	2.123
>4x/week	1,143	1.906	1.243	2.924



C	n	Odds ratio	Lower limit	Upper limit
Region (p=0.049)				
Europe/North America/Aus/NZ	2,934	2.111	1.336	3.337
Middle East	1,546	1.000	0.141	7.099
Africa	519	0.875	0.317	2.413
South Asia	1,643	6.000	0.722	49.837
China, SE Asia	3,923	0.917	0.514	1.635
South America	1,082	1.182	0.670	2.085
Total	11,652	1.429	1.081	1.888



Leong, D., Smyth, A., Teo, K. et al. Patterna of alcohol consumption and myocardial infarction risk: INTERHEART. Circulation. June 13, 2014: 130:390-398.

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ETOH – INTERHEART Trial

Bale/Doneen Take Away:

In most countries, low levels of alcohol use (<4 drinks/week) appears to be associated with a lower risk of MI, but such protective effect was not observed in South Asian Countries.

Episodic heavy drinking can precipitate acute MI, particularly in older individuals (over age 65).

Apo E was not assessed in the INTERHEART Trial

Leong, D., Smyth, A., Teo, K. et al. Patterna of alcohol consumption and myocardial infarction risk: INTERHEART. Circulation. June 13, 2014: 130:390-398.

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Radiation Exposure with various CV Tests

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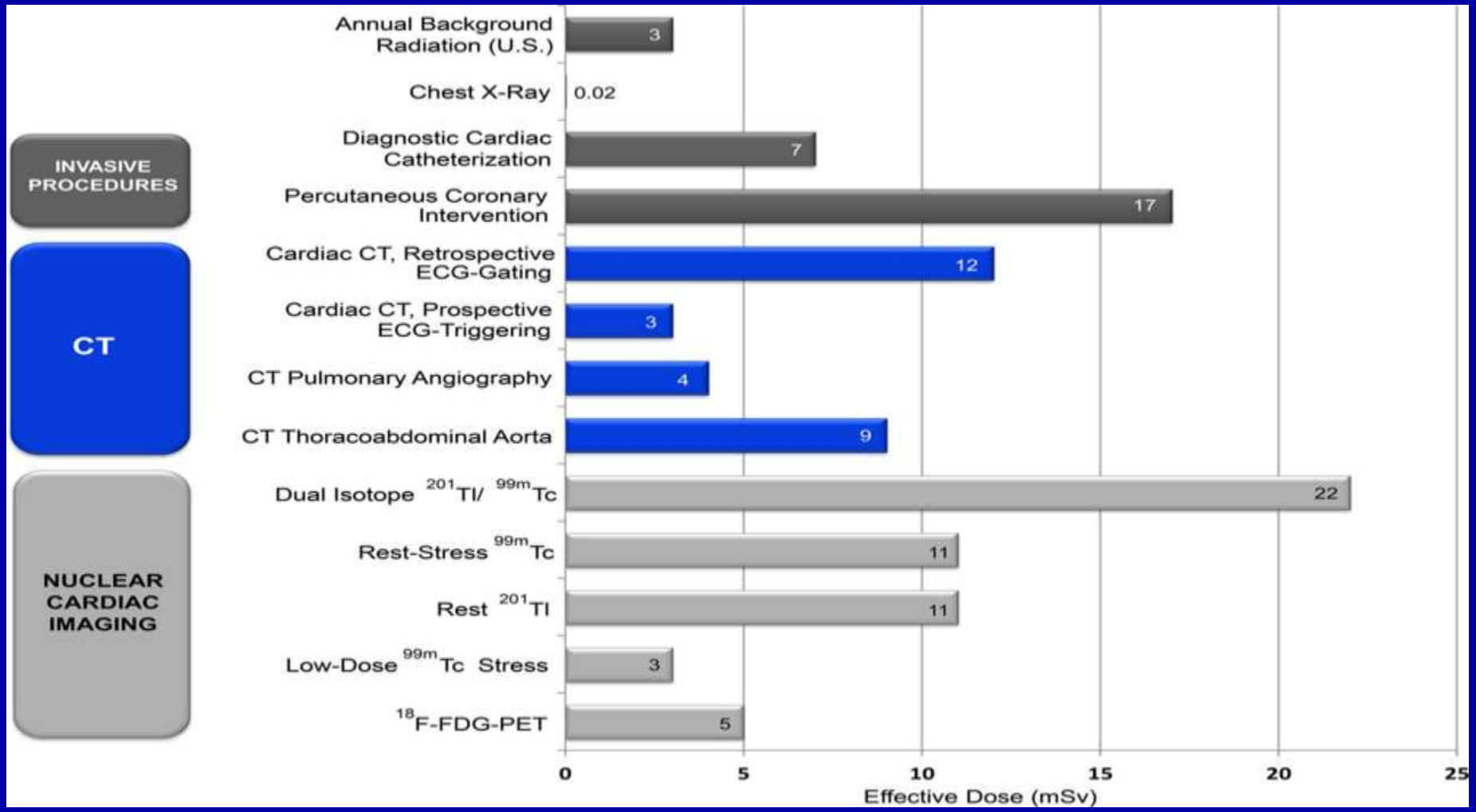
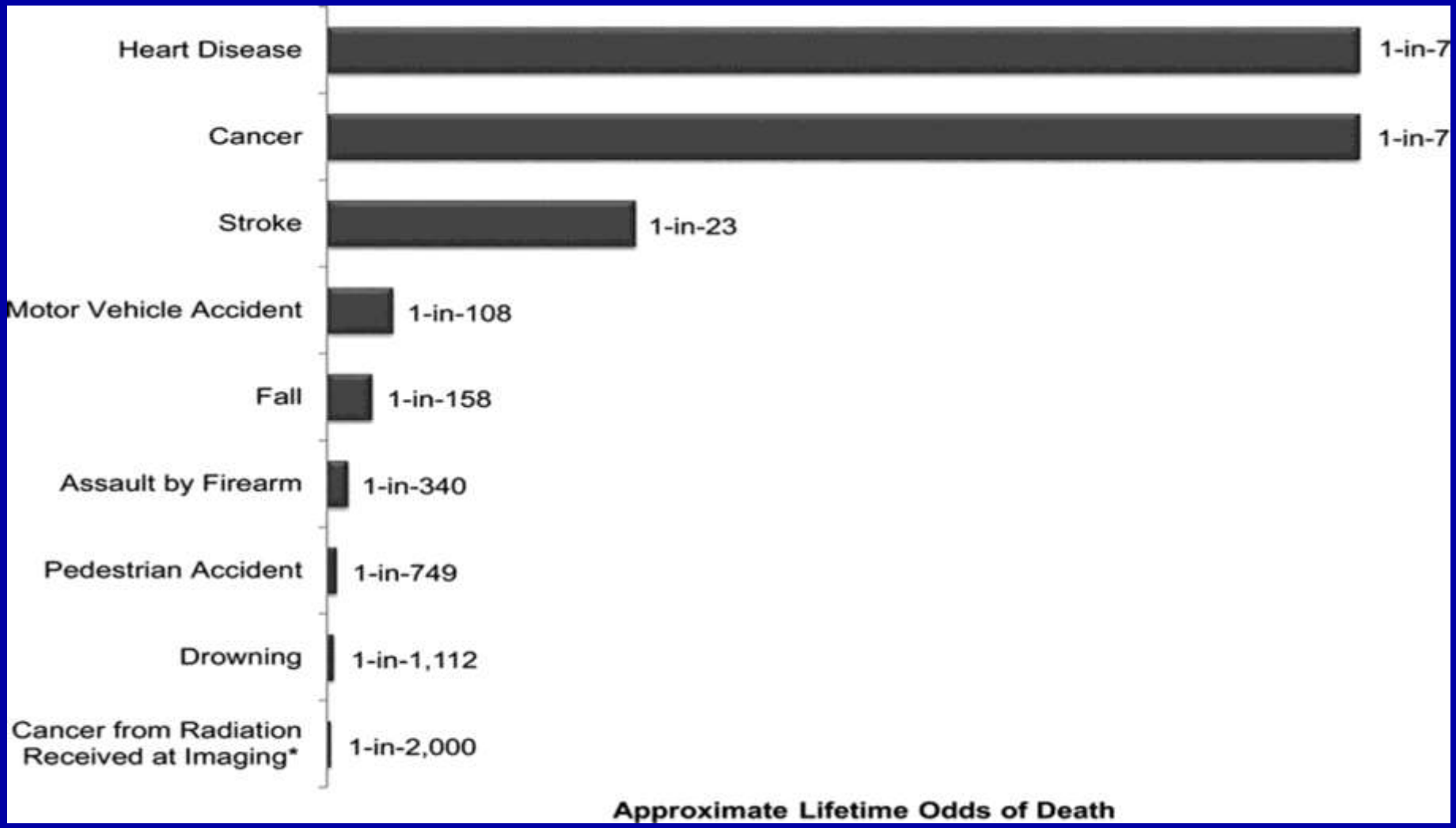
Radiation Risks from CV Imaging Tests



Meinel, F., Nance, J., Harris, B., DeCecco, C., et al. Radiation Risks from Cardiovascular Imaging Tests. Circulation. Volume 130(5):442-445. July 29, 2014

Radiation Risks from CV Imaging Tests



Meinel, F., Nance, J., Harris, B., DeCecco, C., et al. Radiation Risks from Cardiovascular Imaging Tests. Circulation. Volume 130(5):442-445. July 29, 2014

"Psychiatric and neurodevelopmental disorders are being thought of more and more as systemic illnesses in which inflammation is involved," noted Eric Hollander,

Eric Hollander, MD of Montefiore Medical Center and Albert Einstein College of Medicine NY.
Raison CL et al, JAMA Psychiatry. 2013:70(1):31-41.

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Early studies have shown that patients with depression, regardless of physical health status exhibit inflammation – increases in inflammatory cytokines: IL-6, TNF, and hsCRP.

Proof of concept study – Miller et al gave infusions of TNF antagonists to 60 adults with major tx resistant Depression .

Hypothesis: the TNF strategy might be effective only in patients with high inflammation before treatment – measured CRP and other biomarkers.

Infliximab did not prove to be more effective than placebo in treating TRD in study except in patients with baseline of higher CRP concentrations (>5mg/L)

Results indicate that inflammation might predict which patients would respond to immune-targeted therapy for depression – one of first studies in psychiatry connecting biomarkers and treatment response.

1. Eric Hollander, MD of Montefiore Medical Center and Albert Einstein College of Medicine NY. 2. Raison CL et al, JAMA Psychiatry. 2013:70(1):31-41.

Psychosocial Factors and Stroke & TIA Risk

Chronic stress, depressive symptoms, anger, and hostility in relation to incident stroke and TIA in middle-aged and older adults.

Data from Multi-Ethnic Study of Atherosclerosis (MESA) – population based cohort study of 6749 adults aged 45-84 years and free of clinical CVD at baseline, conducted in 6 US sites.

Primary outcome was clinically adjudicated incident stroke or TIA during a medium follow-up of 8.5 years.

Everson-Rose, S., Rostker, N., Lutsey, P., et al. Chronic stress, Depression, Anger, hostility, Risk Of stroke and TIA in MESA. Stroke. July 30, 2014. 452; 2318-2323.

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Psychosocial Factors and Stroke & TIA Risk

147 strokes, 48 TIA occurred during follow-up – A gradient of increasing risk was observed for depressive symptoms, chronic stress, and hostility (P for trend $\leq$0.02) but not for trait anger (P >0.10).

Higher levels of stress, hostility, and depressive symptoms are associated with significantly increased risk of incident stroke or transient ischemic attacks in middle-aged and older adults.

Associations are not explained by known stroke risk factors.

Everson-Rose, S., Rostker, N., Lutsey, P., et al. Chronic stress, Depression, Anger, hostility, Risk Of stroke and TIA in MESA. Stroke. July 30, 2014. 452; 2318-2323.

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Psychosocial Factors and Stroke & TIA Risk

Bale/Doneen Take-Away

1. ALWAYS assess for psychological health – include chronic stress and hostility in your assessment.
2. ASK about stress management techniques, especially in patients who have already had a stroke or TIA – perhaps their current coping mechanisms are not adequate.
3. DISCUSS the relationship between psychological health and stroke risk – it is strong and powerful association.
4. MESA forms available: http://www.mesa-nhlbi.org/ex1forms.aspx.

Everson-Rose, S., Rostker, N., Lutsey, P., et al. Chronic stress, Depression, Anger, hostility, Risk Of stroke and TIA in MESA. Stroke. July 30, 2014. 452; 2318-2323.

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Xylitol shows beneficial effect on Pg

Cytokine expression stimulated in human monocyte derived macrophages by live Porphyromanas gingivalis (Pg).

Purpose: To determine the effects of xylitol on live Pg-induced production of cytokine.

Live Pg infection increased the production of representative proinflammatory cytokines – such as TNF-a and IL-1B, in a multiplicity of infection and time dependent manner.

Live Pg also enhanced the release of cytokines and chemokines

Park, Na, Kim et al. Potent inhibitions of inflammation response with Xylitol. J. Periodontology August 2014. 85e212-e223.

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Xylitol shows beneficial effect on Pg

The pretreatment of xylitol significantly inhibited the P.gingivalis induced cytokines production and nitric oxide production.

Xylitol inhibited the attachment of live P. gingivalis on THP-1-derived macrophages.

Xylitol exerted antiphagocytic activity against both Escherichia coli and P. gingivalis.

Conclusion: Findings suggests that xylitol acts as an anti-inflammatory agent in THP-1-derived macropahges infected with live Pg, which supports it use in periodontitis.

Park, Na, Kim et al. Potent inhibitions of inflammation response with Xylitol. J. Periodontology August 2014. 85e212-e223.

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Xylitol shows beneficial effect on Pg

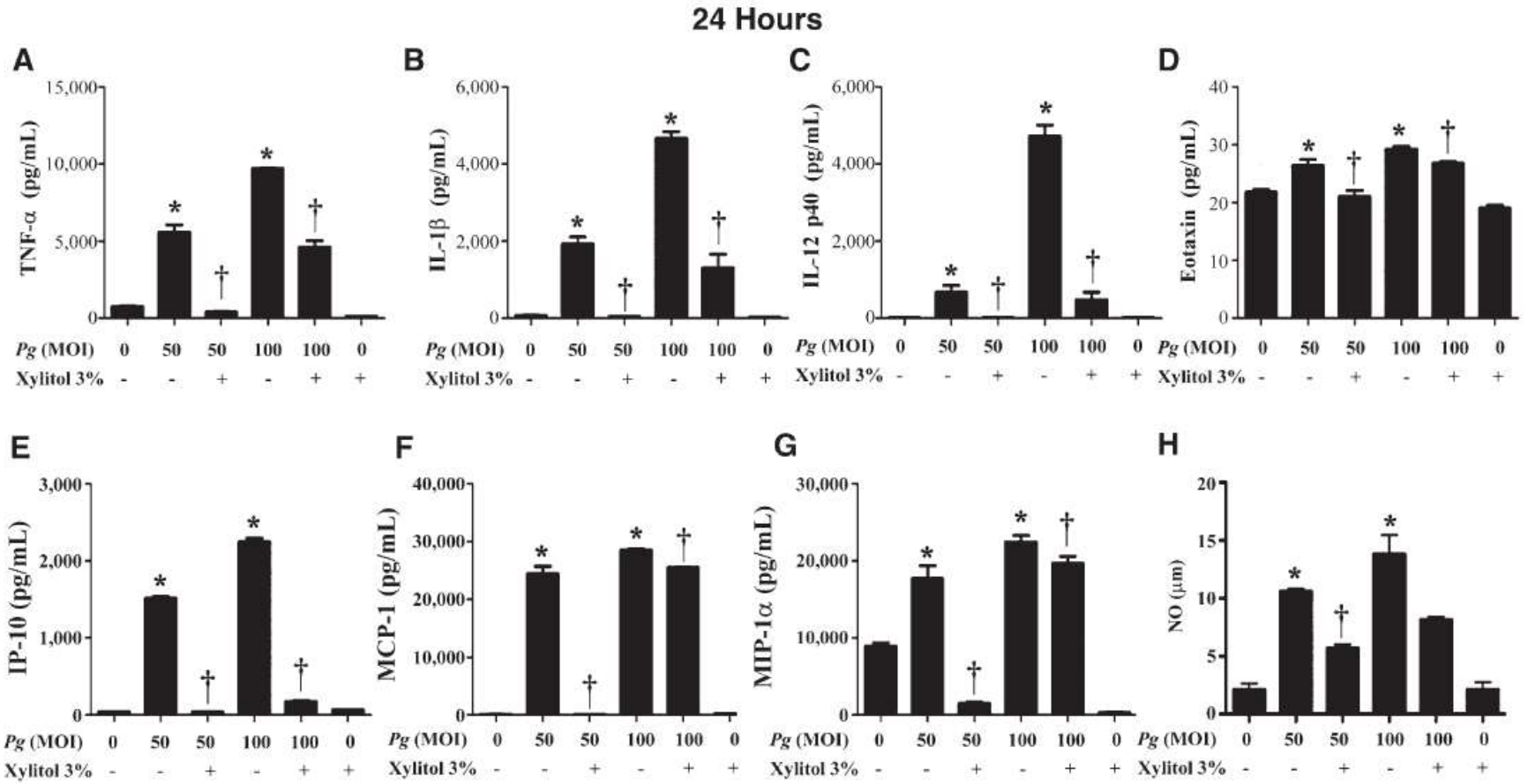

Figure 5.

*Cytokines **(A,B**, and **C)**, chemokines **(D,E,F** and **G)**, and NO **(H)** induced by live P. gingivalis (Pg) infection were inhibited by xylitol treatment in a dose-dependent manner. The THP-1-derived macrophages were pretreated with 3% xylitol for 30 minutes before infection with live P. gingivalis (MOI of 50 or 100) for 24 hours. The cytokines and chemokines concentrations in the culture supernatants were analyzed using a multiplex assay kit. For NO concentration, culture supernatant was assayed using a Griess reagent system. *P <0.05 compared to the control cells. †P <0.05 compared to the P. gingivalis–infected cells.*

Park, Na, Kim et al. Potent inhibitions of inflammation response with Xylitol. J. Periodontology August 2014. 85e212-e223.

Xylitol shows beneficial effect on Pg

Bale/Doneen Take Away:

Xylitol offers a cost-effective and non-invasive way to reduce the inflammatory effects of the dangerous inflammatory cascade associated with the Pg infection.

This does not replace optimal dental therapy but it does seem to be a fair augmentation to periodontal therapy – just like flossing and sonicare and regular dental cleanings every 3 months.

Remember – Xylitol is very toxic and dangerous for dogs.

Park, Na, Kim et al. Potent inhibitions of inflammation response with Xylitol. J. Periodontology August 2014. 85e212-e223.

Cases

1. **John:** Fatty liver or Liver disease?
2. **Adam:** Pioglitazone off label for MPO
3. **Marji:** Calcification – what is significant?

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Case 1: John
Increased Liver Enzymes

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Fatty Liver or Liver Disease?

First Appointment : Jan 8, 2014

45 year old male – 6'1'' 205 lbs, non-smoker, father of 2 boys

Dx: Depression since 1996 – Effexor 150mg

Meds: MVI, Vit D3 5000, Red Omega, Fish Oil 2000, RYR 600

Reason for visit: Father MI at 64 s/p CABG – current age 72.

Personal hx: snoring, fatigue, obesity, hyperlipidemia with high TG, wife PA and concerned.

Lipids and FBS from 2013 and 2011:

TC 247, 257

TG 278, 217

HDL 37, 31

LDL 154, 183

FBS 100, 93

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Fatty Liver or Liver Disease?

Social history:

- ETOH: 2-3 beer/week
- Caffeine: no coffee, Soda – 1 regular/day
- Stress: College PhD – currently home raising boys, wife is a PA and works long hours.
- Children: Boys – ages 14 and 11 – gifted program
- Exercise: Trying – not regularly – bike, swim, wts

ROS:

- Snoring – yes with daytime fatigue – never sleep study
- Dental – Q 6 months, Sonicare, floss, 2-3mm, no bleed
- Eye – Last exam 15-20 years ago

Fm Hx:

- Dad MI at 64 – CABG
- Mom – blood clots and obesity
- MGM – AD
- PGM – Dementia
- PGF – suicide/bipolar

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Fatty Liver or Liver Disease?

Physical Exam:

6’1”, 205 pounds,
Neck 15.5 inches,
Waist 38.5 inches
Body Fat: 22.7%
Central Adiposity 10%
Muscle Mass: 152.4 pounds
Hydration: 54.5%

EKG – WNL
Heart – WNL
Lungs – WNL
Abdomen – WNL
ABI – 1.0 bilateral

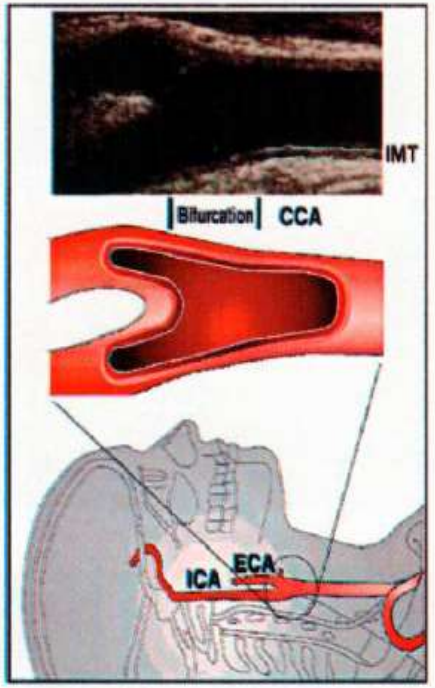
Genetics:

Apo E: 3/3
KIF 6: negative
9P21: +/-
LPA: negative

CardioRisk™ Scan Patient Results

Patient Name: , JOHN
Gender: M
Date of Exam 12/5/2013
Date of Birth: 7/18/1968
Referring Physician: HEART ATTACK PREVENTION CLINIC

Patient Age	45	Patient IMT	0.70 mm
Arterial Age	55	Normal IMT	<.50 mm



CV Event Risk

All measurements in mm

Test Criteria:	Normal	Moderate	High	Last Visit*	Alert Value*
Early Event Risk**	1.0				1.4
Average CCA Mean IMT	0.70				0.73
Average CCA Max Region		0.79			0.75
Plaque Burden**	NONE				

Comments:

The following values are the largest intima-media thickness (IMT) measurements found in each carotid artery segment. Any measurement equal to or 1.3mm is defined as 'plaque' and is characterized as being: **S = Soft; H = Heterogeneous; or E = Echogenic** (includes mineral deposits like calcium). All measurements are in millimeters.

Right CCA .7; Bulb 1.0; Internal Carotid .7
Left CCA .8; Bulb 1.0; Internal Carotid .8
Doppler was used bilaterally.

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What next?

I still want to know: Am I treating disease or an accelerated thickness or risk?

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PATIENT: [redacted], JOHN
EXAM DATE: Feb-06-2014
REFERRING: DONEEN, AMY L, ARNP
507 S WASHINGTON ST #170
SPOKANE, WA 99204

TELEPHONE: (509) 499-7804
CLINIC-ALL ORGANIZATIONS

Inland Imaging at Holy Family Hospital - Computed Tomography

CT CORONARY ARTERY CALCIUM STUDY

CLINICAL INFORMATION:
Screening for coronary artery disease.

COMPARISON:
None.

PROCEDURE:
Helical CT acquisition was obtained during prospective cardiac gating from the carina through the apex of the heart. Images were reconstructed in the axial plan at 2.5 mm intervals.

FINDINGS:
CORONARY ARTERY CALCIFICATION
Left Main Coronary Artery: 0
Left Anterior Descending Artery: 0
Left Cirumflex Artery: 0
Right Coronary Artery: 0
Posterior Descending Artery: 0

Total Calcium Score: 0

No pulmonary parenchymal, hilar, cardiac, pericardiac, chest wall, or osseous abnormalities are seen. Severe hepatic steatosis.

IMPRESSION:
1. Total calcium score is 0.
2. Severe hepatic steatosis.

COMMENT:
A zero score implies no identifiable plaque and a very low cardiovascular risk. Scores between 1 and 10 imply a minimal plaque burden with low cardiovascular risk. Scores from 11-100 imply a mild or minimal coronary stenosis and moderate cardiovascular risk. Scores between 101-400 imply a definite plaque burden and high likelihood of obstructive disease. A score of over 400 indicates an extensive plaque burden with a high likelihood of significant coronary stenosis (Rumberger, Mayo Clinic Proceedings 1999; 74; 243).

MRN: 10-02-01-74
EXAM#: 11885624

DOB: Jul-18-1968
AGE: 45 Years

DICTATED BY:
NACKOS, JEFFREY MD
TRANSCRIBED ON:
Feb-06-2014
RELEASED BY:
NACKOS, JEFFREY MD
INTERPRETED AND AUTHENTICATED BY:
NACKOS, JEFFREY MD
2/6/14 2:38 pm

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Fatty Liver or Liver Disease?

	12/30/13
TC TG HDL LDL	221 284 31 133
TC/HDL TG/HDL	7.1 9.2

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Fatty Liver or Liver Disease?

	12/30/13
ALT/AST GGT	132/53 62

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Fatty Liver or Liver Disease?

	12/30/13
FBS	96
A1C	5.1
1 hour	216
2 hour	118

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Fatty Liver or Liver Disease?

	12/30/13
hsCRP	2.3
MACR	3.0
PLAC2	135

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RE: John
DOB: 7-18-68

Dear Amy:

It was my pleasure to see Mr. Gregg in regards to his established diagnosis of fatty liver. I have identified the following problems:

1. Abnormal liver function tests in the face of a CT scan showing severe steatosis.
2. Elevated triglyceride with overweight status contributing to problem #1.

RECOMMENDATION: I told John that I thought we could go slow on his situation, allowing him to try to lose some weight (15-20 pounds) and to continue his medications to lower his triglycerides. We could then look at his liver function tests in 6 months and see if he still had elevation of his inflammatory indices. If he does, I would consider sending him to Virginia Mason for a FibroScan of his liver which would replace the need for liver biopsy. It also would give him a pretty good prognosis if the FibroScan was negative. This is a new test for which Virginia Mason just put into their diagnostic test regimen for liver disease and it is as sensitive as liver biopsy for fibrosis. They are charging $300 for those patients whose insurance do not cover the exam and that is a bargain considering what it costs for liver biopsy. There is also no risk in doing a noninvasive test as opposed to an invasive one. To start with, I am going to get a panel of tests to rule out hepatitis, autoimmune hepatitis, problems with regards to copper or iron storage, etc. He will call me in a week for the results of those and I will send him a copy. His alcohol consumption is not an issue with regards to his liver function and I did not spend much time in terms of telling him to be a teetotaler but just mentioned that for the next 6 months to stay of alcohol completely and also away from Tylenol but he could use aspirin or Advil, etc.

Fatty Liver or Liver Disease?

	12/30/13	Meds 1/21/14
TC TG HDL LDL	221 284 31 133	Simcor 1000/40
TC/HDL TG/HDL	7.1 9.2	
ALT/AST GGT	132/53 62	Liver eval
FBS A1C	96 5.1	Cinn 2gm Dk choc
1 hour 2 hour	216 118	
hsCRP MACR PLAC2	2.3 3.0 135	Sleep Dental Exercise

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Fatty Liver or Liver Disease?

	12/30/13	Meds 1/21/14	3/18/14
TC TG HDL LDL	221 284 31 133	Simcor 1000/40	129 149 39 60
TC/HDL TG/HDL	7.1 9.2		3.3 3.8
ALT/AST GGT	132/53 62	Liver eval	108/46 42
FBS A1C	96 5.1	Cinn 2gm Dk choc	96 5.1
1 hour 2 hour	216 118		
hsCRP MACR PLAC2	2.3 3.0 135	Sleep Dental Exercise	1.4 3.0 150

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Fatty Liver or Liver Disease?

	12/30/13	Meds 1/21/14	3/18/14	meds	6/16/14	Next med
ALT/AST GGT	132/53 62	Liver eval	108/46 42		62/29	

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Fatty Liver or Liver Disease?

	12/30/13	Meds 1/21/14	3/18/14	meds	6/16/14	Next med
TC TG HDL LDL	221 284 31 133	Simcor 1000/40	129 149 39 60	No Rx changes	143 234 38 58	Actos next
TC/HDL TG/HDL	7.1 9.2		3.3 3.8		3.8 6.2	
ALT/AST GGT	132/53 62	Liver eval	108/46 42		62/29	
FBS A1C	96 5.1	Cinn 2gm Dk choc	96 5.1	lifestyle	108 5.2	
1 hour 2 hour	216 118				246 141	
hsCRP MACR PLAC2	2.3 3.0 135	Sleep Dental Exercise	1.4 3.0 150	Still working on scans	1.1 2.0 119	

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Case 2: Adam
Elevated MPO and Lipo(a)

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MPO, Lipo(a) and CAD

Adam – first visit to A. Doneen: Nov 6, 2012

9/3/2012: running (regular since age 20) dull chest pressure radiated into back which resolved once stopped running – seemed similar to flu symptoms. Next day – 100% resolved.

9/5/2012: after walking and having coffee – pressure abruptly returned with intensity – called 911 – taken to Emergency - Cath lab –

Received Stent LAD – also found to have stenosis of the circumflex artery which was scheduled to be treated in a staged procedure

9/9/2012: with recurrent chest pain – small dissection at the proximal portion of the LAD – stented both LAD and circumflex.

2 weeks later – pain upper right leg – proximal external iliac artery – subsequently stented.

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MPO, Lipo(a) and CAD

Fm Hx:

Father: died a 89 CVA

Mother: died a 96 CHF

Brother: currently 68 – CAD with 2 stents and similar symptoms

Secondary hx: Grandparents lived to be in 80s and 90s – CHF, resp.

Treatment upon entry:

Aspirin 81mg

Plavix 75mg

Lisinopril 5mg BID

Metoprolol 12.5 BID

Simvastatin 40mg

Vitamin D 10,000iu weekly

Habits:

non-smoker

good diet

Regular exerciser

Sleep – 6-8 hrs

2 red wine/day

exercise: daily x 60 min

Social – married, one daughter, retired Priest, teaching at local university.

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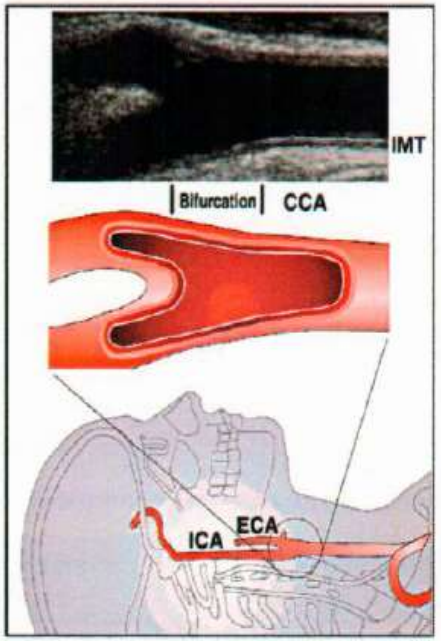
MPO, Lipo(a), and CAD

CardioRisk™ Scan Patient Results

Patient Name: BARTHOLOMEW, ADAM
Gender: M
Date of Exam 11/15/2012
Date of Birth: 5/11/1943
Referring Physician: HEART ATTACK PREVENTION CLINIC

Patient Age	69	Patient IMT	0.93 mm
Arterial Age	79	Normal IMT	<.50 mm



CV Event Risk

All measurements in mm

Test Criteria:	Normal	Moderate	High	Last Visit+	Alert Value*
Early Event Risk++	2.3				2.5
Average CCA Mean IMT			0.93		0.73
Average CCA Max Region			1.02		0.75
Plaque Burden**			3.6		

Comments:

The following values are the largest intima-media thickness (IMT) measurements found in each carotid artery segment. Any measurement equal to or 1.3mm is defined as 'plaque' and is characterized as being: **S = Soft; H = Heterogeneous; or E = Echogenic** (includes mineral deposits like calcium). All measurements are in millimeters.

Right CCA .9; Bulb .7; Internal Carotid 1.1
Left CCA 1.1; Bulb 2.3 H; Internal Carotid 1.3 E
Doppler was used bilaterally.

Pioglitazone: Off-label for MPO

	2/6/13	med
TC TG HDL LDL	146 104 50 75	
Apo B Lipo(a)	68 80	Niacin 1 gm
F2-ISO hsCRP Fibrinogen MACR PLAC-2 **MPO**	.62 2.1 403 2.0 113 **1158**	Actos 15mg
FBS/A1C 1 hr/1 hr	89/5.1 111/83	
hematuria		

Pioglitazone: Off-label for MPO

	2/6/13	med	5/2/13
TC TG HDL LDL	146 104 50 75		140 60 58 70
Apo B Lipo(a)	68 80	Niacin 1 gm	58
F2-ISO hsCRP Fibrinogen MACR PLAC-2 **MPO**	.62 2.1 403 2.0 113 **1158**	Actos 15mg	.40 0.2 <1.0 <100 **463**
FBS/A1C 1 hr/1 hr	89/5.1 111/83		82/5.3
hematuria			neg

Pioglitazone: Off-label for MPO

	2/6/13	med	5/2/13	8/6/13	11/7/13
TC TG HDL LDL	146 104 50 75		140 60 58 70	149 71 66 69	159 128 56 77
Apo B Lipo(a)	68 80	Niacin 1 gm	58	59	72
F2-ISO hsCRP Fibrinogen MACR PLAC-2 **MPO**	.62 2.1 403 2.0 113 **1158**	Actos 15mg	.40 0.2 <1.0 <100 **463**	0.2 10 84	0.60 0.6 346 <1.0 67 **275**
FBS/A1C 1 hr/1 hr	89/5.1 111/83		82/5.3	87/5.1	95/5.3
hematuria			neg	neg	neg

MPO, Lipo(a) and CAD

	2/6/13	med	5/2/13	8/6/13	11/7/13	4/21/14	7/8/14
TC TG HDL LDL	146 104 50 75		140 60 58 70	149 71 66 69	159 128 56 77	154 84 79 58	148 76 64 69
Apo B Lipo(a)	68 80	Niacin 1 gm	58	59	72		54 40
F2-ISO hsCRP Fibrinogen MACR PLAC-2 **MPO**	.62 2.1 403 2.0 113 **1158**	Actos 15mg	.40 0.2 <1.0 <100 **463**	0.2 10 84	0.60 0.6 346 <1.0 67 **275**	0.3 <1.0 80 **355**	.52 0.4 <1.0 88 **298**
FBS/A1C 1 hr/1 hr	89/5.1 111/83		82/5.3	87/5.1	95/5.3	99/5.2	87/5.2
hematuria			neg	neg	neg	neg	neg

MPO, Lipo(a) and CAD

	2/6/13	med	5/2/13	8/6/13	11/7/13	4/21/14	7/8/14
Lipo(a)	80	Niacin 1 gm					40
MPO	**1158**	Actos 15mg	**463**		**275**	**355**	**298**
hematuria			neg	neg	neg	neg	neg

MPO, Lipo(a) and CAD

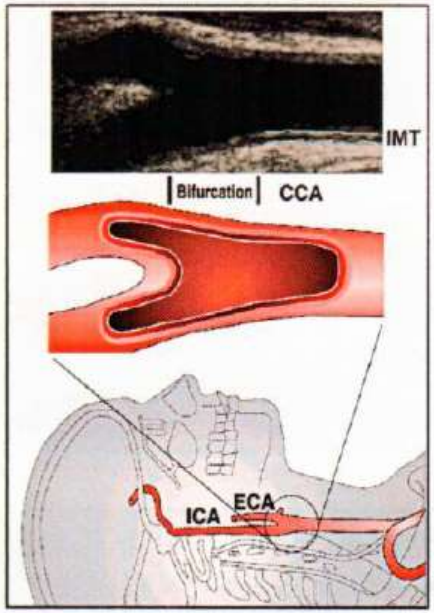
	2/6/13	med	5/2/13	8/6/13	11/7/13	4/21/14	7/8/14
TC TG HDL LDL	146 104 50 75		140 60 58 70	149 71 66 69	159 128 56 77	154 84 79 58	148 76 64 69
Apo B Lipo(a)	68 80	Niacin 1 gm	58	59	72		54 40
F2-ISO hsCRP Fibrinogen MACR PLAC-2 **MPO**	.62 2.1 403 2.0 113 **1158**	Actos 15mg	.40 0.2 <1.0 <100 **463**	0.2 10 84	0.60 0.6 346 <1.0 67 **275**	0.3 <1.0 80 **355**	.52 0.4 <1.0 88 **298**
FBS/A1C 1 hr/1 hr	89/5.1 111/83		82/5.3	87/5.1	95/5.3	99/5.2	87/5.2
hematuria			neg	neg	neg	neg	neg

MPO, Lipo(a), and CAD

CardioRisk™ Scan Patient Results

Patient Name: ADAM
Gender: M
Date of Exam 11/12/2013
Date of Birth: 5/11/1943
Referring Physician: HEART ATTACK PREVENTION CLINIC

Patient Age	70	Patient IMT	0.91 mm
Arterial Age	77	Normal IMT	<.50 mm



CV Event Risk

All measurements in mm

Test Criteria:	Normal	Moderate	High	Last Visit+	Alert Value*
Early Event Risk++	2.2				2.5
Average CCA Mean IMT			0.91	.93	0.73
Average CCA Max Region			1.01	1.02	0.75
Plaque Burden**			3.5		

Comments:

The following values are the largest intima-media thickness (IMT) measurements found in each carotid artery segment. Any measurement equal to or 1.3mm is defined as 'plaque' and is characterized as being: **S = Soft; H = Heterogeneous; or E = Echogenic** (includes mineral deposits like calcium). All measurements are in millimeters.

Right CCA 1.0; Bulb .9; Internal Carotid .9
Left CCA .9; Bulb 2.2 H; Internal Carotid 1.3 E
Doppler was used bilaterally.

plaque ⇒ IMT ≥ 1.3 mm

Marji: Calcification Reframing the importance for patients.

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Tower Heart Check Medical Group

465 N. Roxbury Drive, Beverly Hills, CA 90210

Patient Name:		**Patient ID:**	64083
Study:		**Study Date:**	11-JUL-00
Date of Birth:		**Patient Age:**	61
Referring Physician:		**Reading Physician:**	J. MADDAHI

HISTORY:
The patient is 61 years old, weighs 170 lbs, with a height of 67 inches.
The patient has gone through menopause, has had both ovaries removed and has had estrogen replacement. Low fat compliance of the patient's diet is moderate. The patient's stress level is high. The patient's general health is good. The patient reported moderate exercise 3 days a week for 10 - 19 mins. The patient does\did reside in a smoking environment at home and has/had been in this environment for 10 years.
The patient reported suffering from high cholesterol. The patient's motivations for getting scanned were have risk factors, getting older and wanted information about my heart.

Lipid Results:

	Results	REFERENCE RANGE
Cholesterol Level	274	140 - 200 mg/dl
HDL	35	32 - 96 mg/dl
LDL	189	68 - 130 mg/dl
Triglycerides	251	30 - 200 mg/dl
Cholesterol HDL Ratio	7.8	

TECHNIQUE: The patient underwent high resolution, volume mode, axial cardiac gated Electron Beam Computed Tomography of the chest with attention devoted to the coronary arteries only. Forty contiguous 3 millimeter slices of the heart were obtained at 100 millisecond scan times, in conjunction with ECG gating in diastole. 2D volume roam and 3D reconstructed images were analyzed interactively. Coronary calcification was analyzed using ScImage's Volumetric calcified plaque analysis software.

Your patient's Coronary Calcium score is 0.

Impression:
The EBCT examination has shown no measurable coronary atherosclerotic plaque. This suggests a very low (<5%) likelihood of significant coronary artery disease.

Recommendations:
1. No further cardiac testing is suggested at this time, unless directed by the family or personal physician.
2. Despite the results of the study, adherence to a healthy life style is always recommended. This includes regular exercise, weight control, proper diet, and avoidance of tobacco. These efforts will assist in lowering the chance of development of atherosclerosis. The family or personal physician is in the best position to provide more specific advice on risk factor modification.

Marji: Calcification

Your patient's Coronary Calcium score is 0.

Impression:
The EBCT examination has shown no measurable coronary atherosclerotic plaque. This suggests a very low (<5%) likelihood of significant coronary artery disease.

Recommendations:

1. No further cardiac testing is suggested at this time, unless directed by the family or personal physician.
2. Despite the results of the study, adherence to a healthy life style is always recommended. This includes regular exercise, weight control, proper diet, and avoidance of tobacco. These efforts will assist in lowering the chance of development of atherosclerosis. The family or personal physician is in the best position to provide more specific advice on risk factor modification.

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Marji – Calcification

RESULTS 2/22/2007

Location	# Calcified Lesions	Calcified Plaque Volume (mm3)	Calcium Score
Left Anterior Descending	1	0.9	0.9
Descending Aorta*	8	331.8	383.7
Ascending Aorta*	1	3.2	3.6
Total Aorta	**9**	**335**	**387.3**
Total Coronaries	**1**	**0.9**	**0.9**

* Indicates categories that are not included in the total coronaries

Scanner **RESULTS 05/30/2014**

Location	# Calcified Lesions	Calcified Plaque Volume (mm3)	Calcium Score
Left Anterior Descending	1	3.2	3.6
Descending Aorta*	12	1565.5	1916.4
Ascending Aorta*	1	17.2	20.1
Total Aorta*	**13**	**1582.7**	**1936.5**
Total Coronaries	**1**	**3.2**	**3.6**

* Indicates categories that are not included in the total

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Marji – Calcification

The total Coronary Calcium Score of 3.6 places this patient in the 27th percentile (Circulation, 2000;101:850-855) for an apparently healthy person of the same age and gender. This does not mean that the patient has 27% narrowing in the coronary arteries, but rather that 26% of apparently healthy persons of this age and gender have lower coronary calcium scores.

IMPRESSION: Minimal coronary atherosclerosis
Coronary Artery Calcium Score: 3.6 (27th percentile for age/gender)
There is also moderate to extensive atherosclerosis of the aorta. In comparison with the previous test of 2/22/2007, the coronary calcium score has not increased significantly and there no new coronary plaques. The thoracic aortic calcification has increased.

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Marji – Calcification

CT Calcium Score Interpretation Guides

Coronary Calcium Score	Diagnosis	Clinical Interpretation	Gender & Age Issues	Recommended Clinical Action
0	No identifiable atherosclerotic plaque. Very low CVD risk.	A 'negative' examination. NPV > 90-95% for absence of 'significant' CAD	Applicable to men and women over 40, but with caution in younger subjects.	Reassure patient while discussing public health guidelines for primary CVD prevention.
1-10	Minimal plaque burden. Low CVD risk.	'Significant' CAD very unlikely	Applicable to men and women over 40 but note general recommendation*	Discuss general public health guidelines for primary CVD prevention.
11-100	Mild, plaque burden. Moderate CVD risk.	Likely mild or minimal coronary stenosis	**Greater clinical significance** when score is above 75th percentile for age and sex (table1) or if calcium present in 2 or more vessels.	Counseling and risk factor modification are indicated. Following NCEP guidelines for cholesterol-lowering.
101-400	Moderate plaque burden. High CVD risk.	Moderate non-obstructive CAD highly likely.	**Greater clinical significance** when score is above 75th percentile for age and sex (table1) or if calcium present in 2 or more vessels.	Institute risk factor modification and clinical follow up. Ensure strict adherence to NCEP cholesterol-lowering guidelines. Recommend an appropriate exercise programme.
Over 400	Extensive plaque burden. Very high CVD risk.	High likelihood of at least one 'significant' coronary stenosis (>50% diameter)	**Greater clinical significance** when score is above 75th percentile for age and sex (table1) or if calcium present in 2 or more vessels.	Very aggressive risk factor modification using NCEP guidelines as for established CAD. Consider non-invasive stress test to rule out ischemia.

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This is what we know from Marji's three coronary scans

Calcium	2000	2007	2014
coronary	0	0.9	3.6
aorta	n/a	387.3	1936.9

1-10	Minimal plaque burden. Low CVD risk.	'Significant' CAD very unlikely	Applicable to men and women over 40 but note general recommendation*	Discuss general public health guidelines for primary CVD prevention.

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Abdominal Aorta Calcification (AAC) Quantified by CT is An Excellent Predictor of CV Events and Mortality

- 1,974 MESA pts; 45-84 yo; baseline AAC & coronary artery calcification (CAC); 5 ½ yr follow-up
- AAC & CAC: tertiles of Agatston score via percentiles
- Outcomes: CHD and CVD events; mortality CVD & all cause.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

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Quantified AAC An Excellent Predictor of CV Events and Mortality

	0-50 percentile	51-75 percentile	76-100 percentile
AAC Agatston score	0-241	242-1,437	1,438-20,952
CAC Agatston score	0-9	10-136	137-4,508

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

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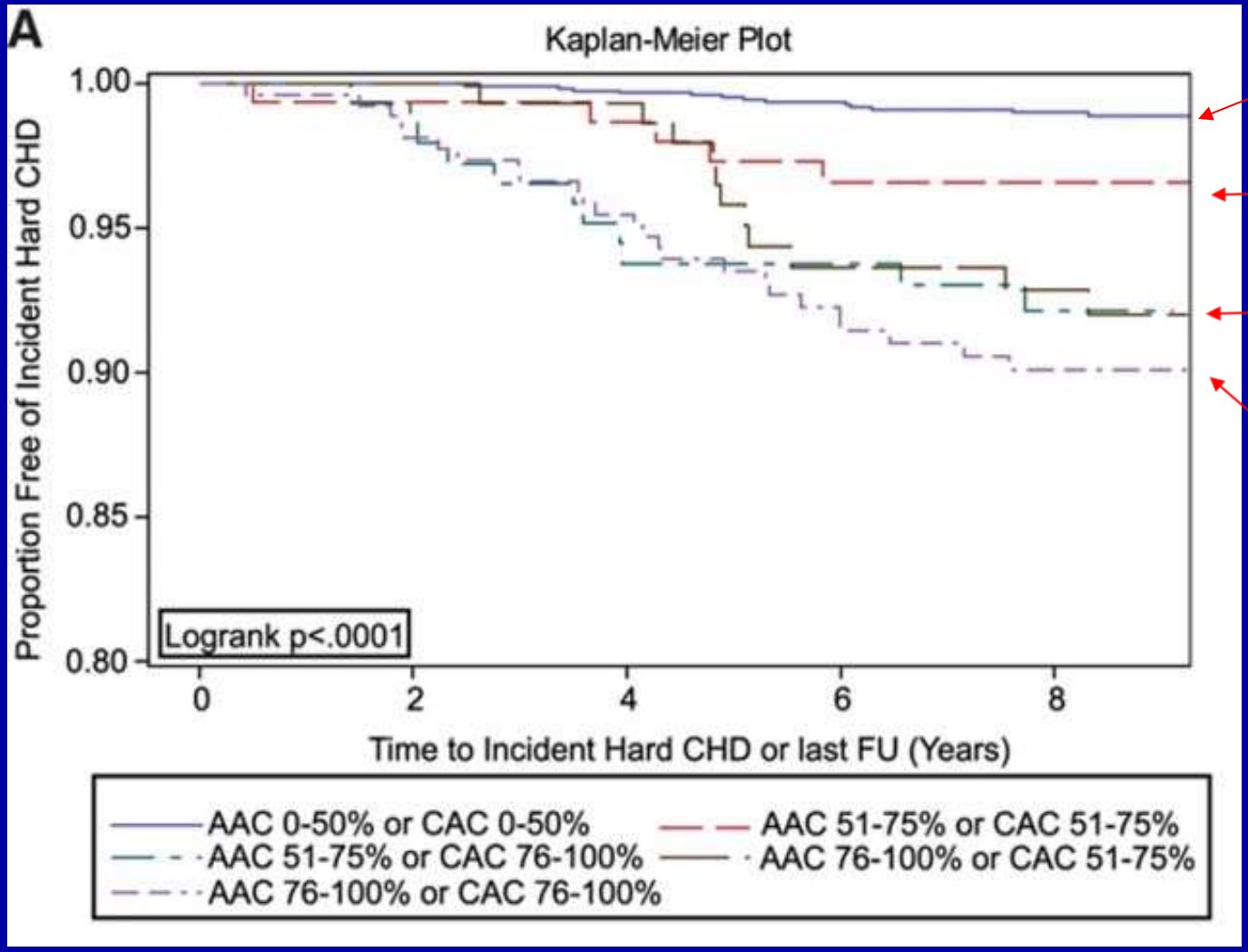
Abdominal Aorta Calcification An Excellent Predictor of CHD Events: on par with CAC

Kaplan–Meier curve for AAC and CAC categories and time to a CHD event.



Both low %

Both moderate %

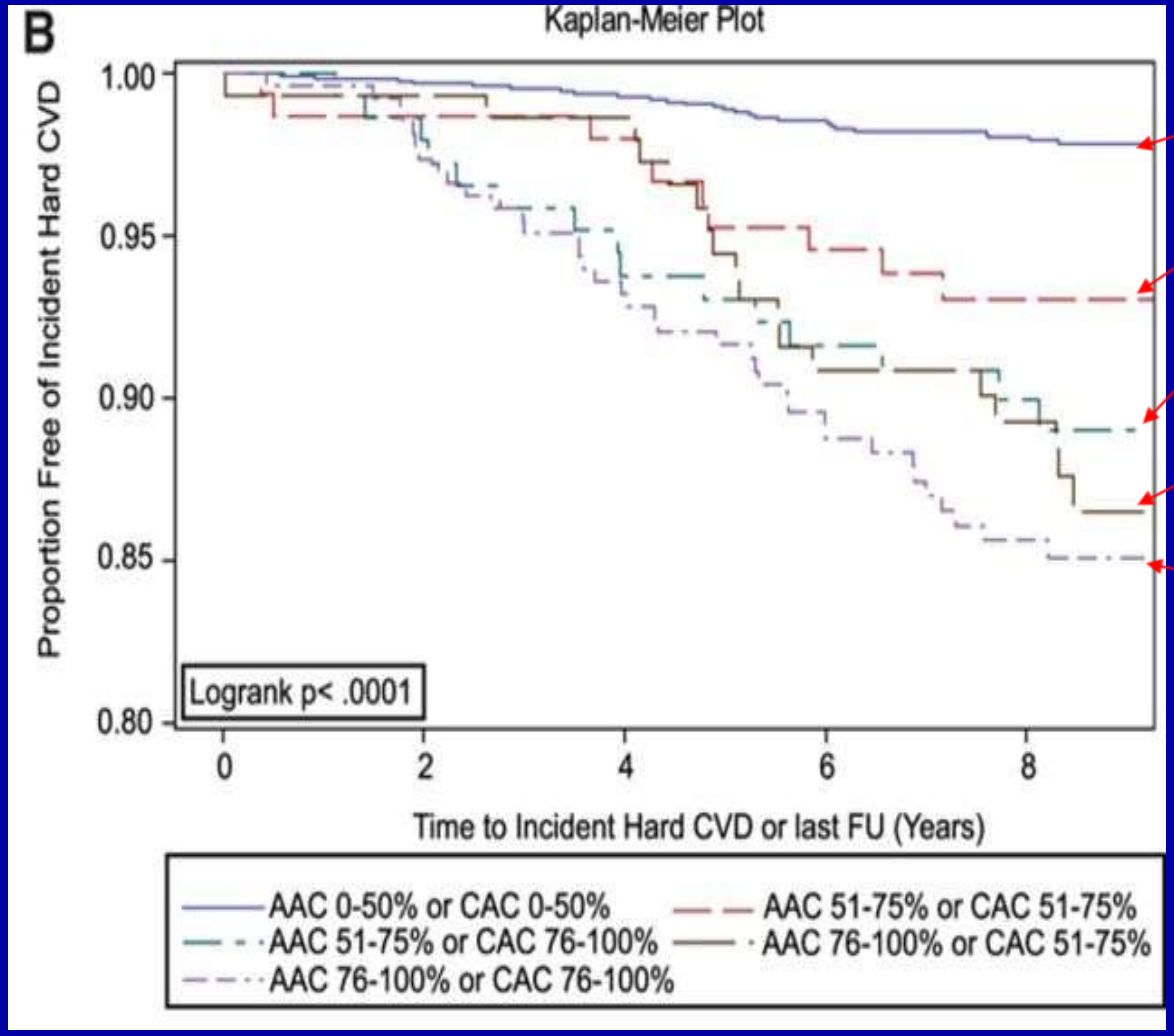
One moderate & one high%

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of CV Events: at least as good as CAC

Kaplan–Meier curve for AAC and CAC categories and time to a CVD event.



Both low %

Both moderate %

CAC high & AAC mod. %

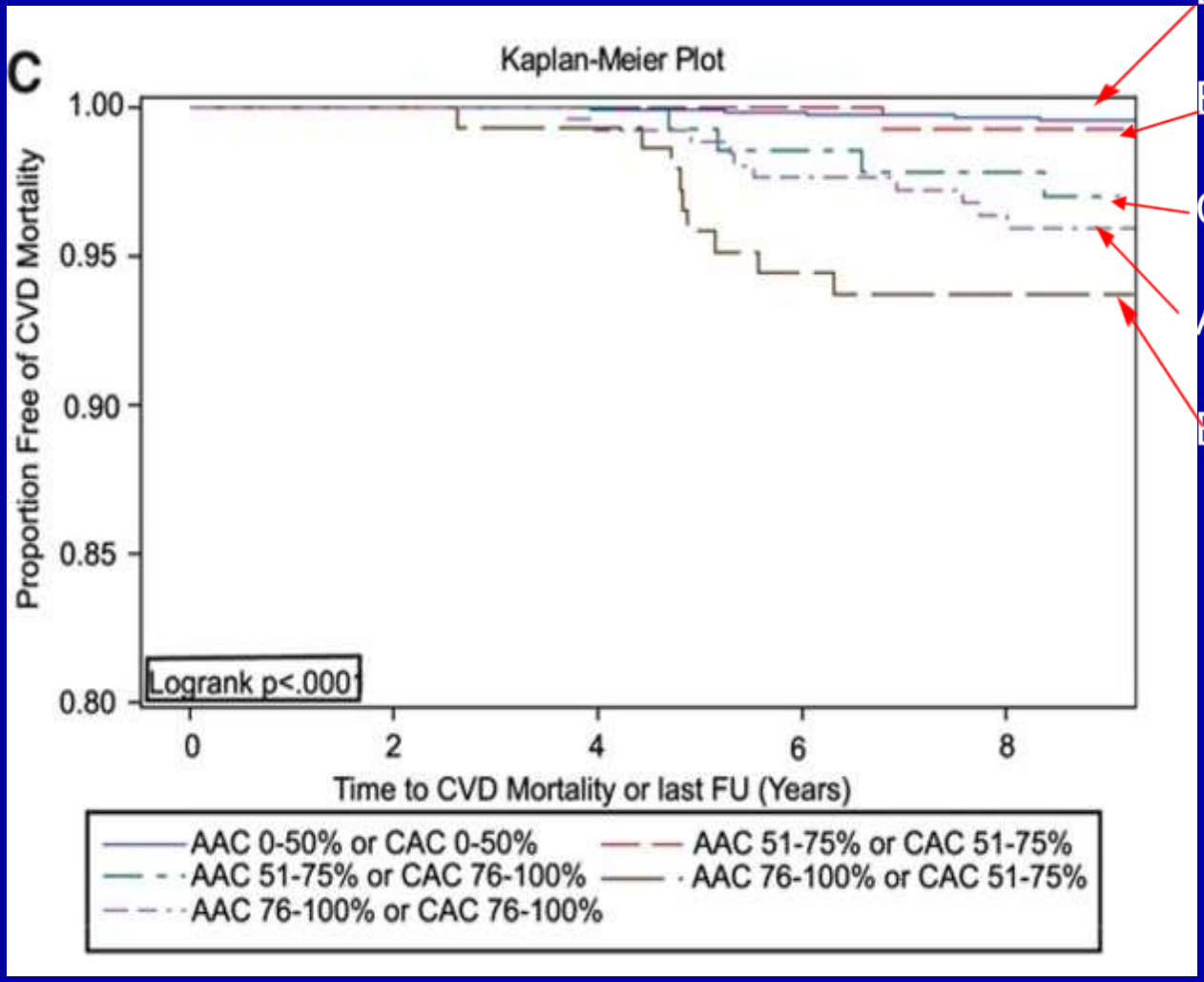
AAC high & CAC mod %

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of CV Mortality: at least as good as CAC

Kaplan–Meier curve for AAC and CAC categories and time to a CVD death.



Both low %

Both moderate %

CAC high & AAC mod. %

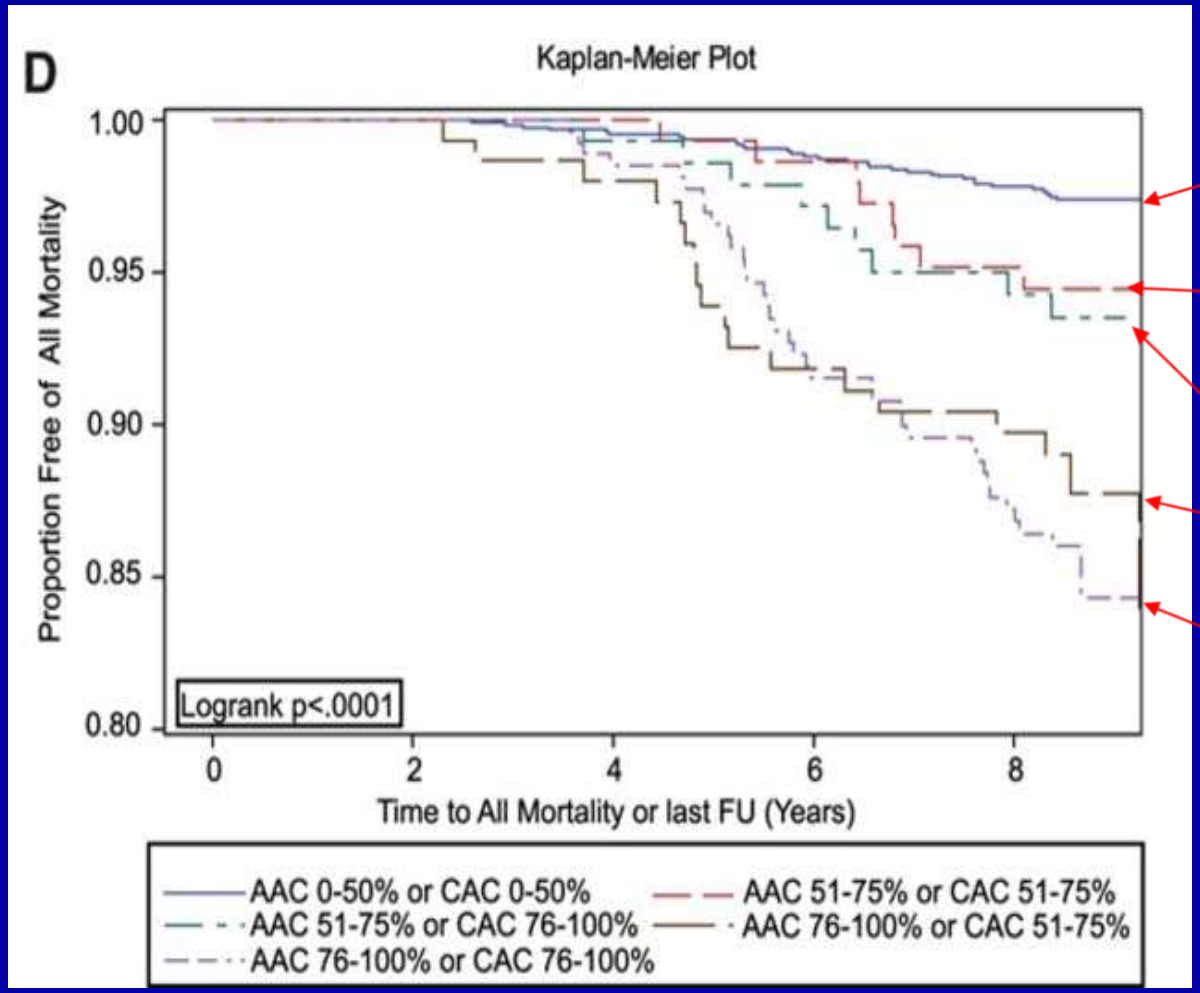
AAC high & CAC mod %

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of Death: better than CAC

Kaplan–Meier curve for AAC and CAC categories and time to all mortality.



Both low %

Both moderate %

CAC high & AAC mod. %

AAC high & CAC mod %

Both high %

Criqui M H et al. Arterioscler Thromb Vasc Biol. 2014;34:1574-1579

Abdominal Aorta Calcification An Excellent Predictor of CV Events and Mortality

With AAC ≥85 %'tile (2,754 Ag) & CAC ≥85 %'tile (300 Ag) when adjusted for FRS and each other, only AAC remained significantly predictive of all four outcomes; CAC did not predict any of them.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

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Abdominal Aorta Calcification An Excellent Predictor of CV Events and Mortality

AAC would add to CAC in predicting hard CVD events; is a stronger subclinical ASVD measure for predicting CVD mortality and all cause mortality.

Criqui, M. H., et. al. (2014). Abdominal Aortic Calcium, Coronary Artery Calcium, and Cardiovascular Morbidity and Mortality in the Multi-Ethnic Study of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(7), 1574-1579.

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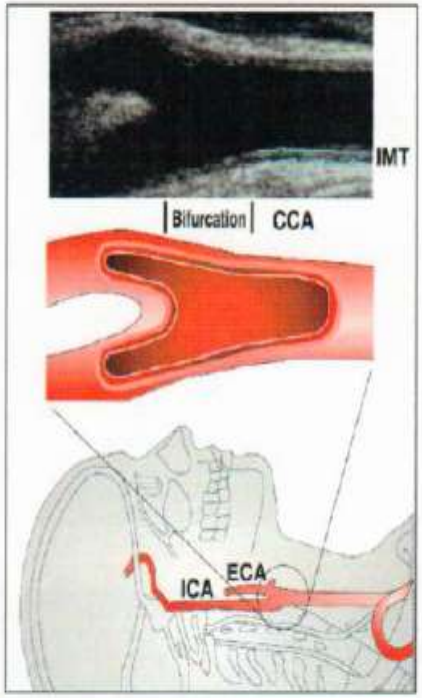
CardioRisk™ Scan Patient Results

Patient Name: MARJORIE
Gender: F
Date of Exam 7/16/2014
Date of Birth: 4/1/1939
Referring Physician: HEART ATTACK PREVENTION CLINIC

Patient Age	75	Patient IMT	0.76 mm
Arterial Age	67	Normal IMT	<.50 mm



CV Event Risk

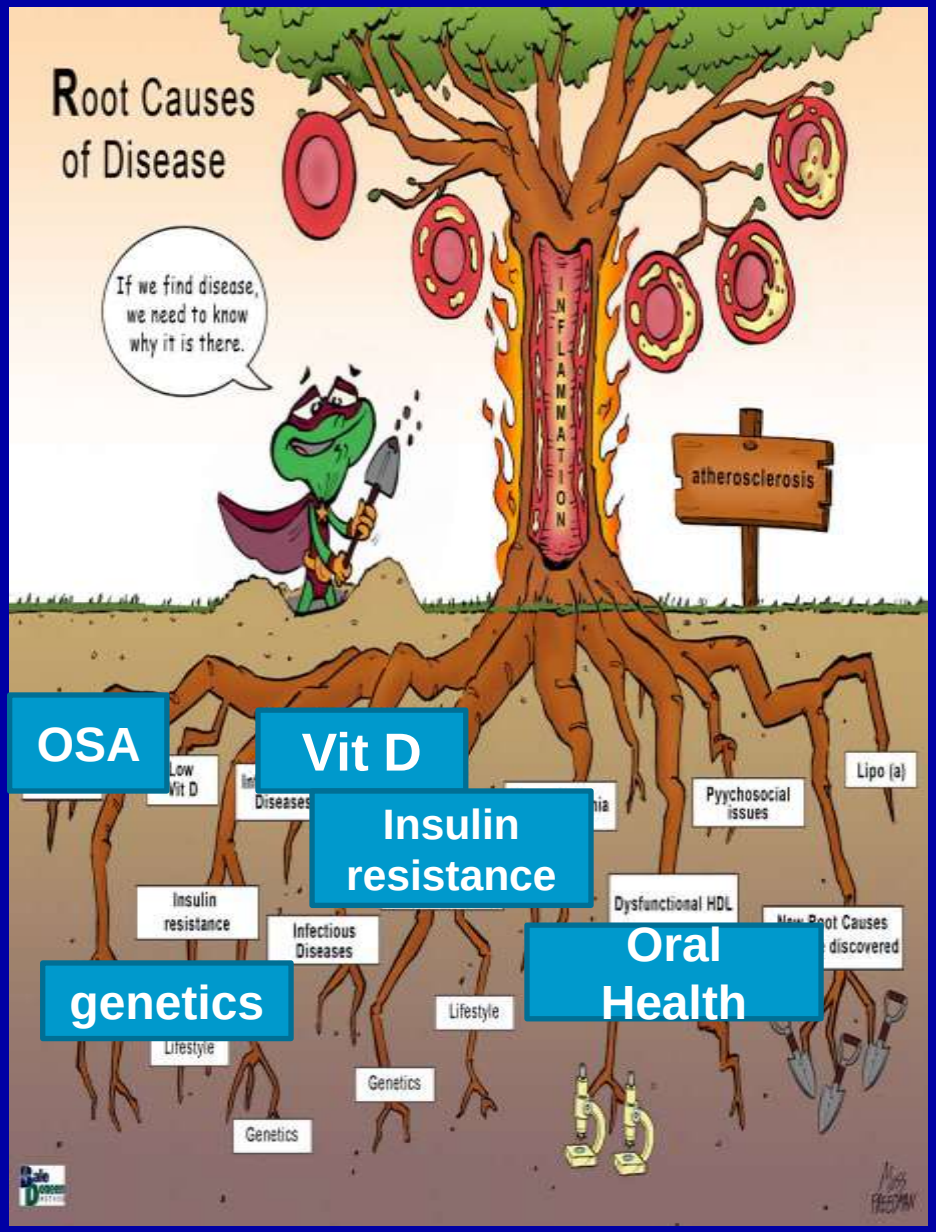
All measurements in mm

Test Criteria:	Normal	Moderate	High	Last Visit+	Alert Value*
Early Event Risk++	2.0				3
Average CCA Mean IMT		0.76			0.73
Average CCA Max Region		0.87			0.75
Plaque Burden**			3.7		

Comments:

The following values are the largest intima-media thickness (IMT) measurements found in each carotid artery segment. Any measurement equal to or 1.3mm is defined as 'plaque' and is characterized as being: **S = Soft; H = Heterogeneous; or E = Echogenic** (includes mineral deposits like calcium). All measurements are in millimeters.

Right CCA .8; Bulb 2.0 E; Internal Carotid 1.7 H
Left CCA .8; Bulb .5; Internal Carotid .5
Doppler was used bilaterally.



Bale Doneen METHOD

Marji's Inflammation & Roots:

Age: 75
Waist: 38"
BP: 132/86
HR: 76

TC: 180
TG: 184
HDL: 57
LDL: 86

FBS: 87
A1C: 5.7
1hr OGTT: 172
2hr OGTT: 51

Vitamin D: 25

MACR: 19
Lp-PLA2: 202

Apo E: 3/3
KIF6: negative
9P21: +/-

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Marji

Further testing:

1. Formal dental evaluation – Oral DNA and xrays
2. AAA Screen and formal sleep study
3. Labs: hsTroponin, F2-Iso and MPO
4. Vaccines – flu annually, Shingles (done), Pneumonia (done)

Optimize Lifestyle:

5. Visit with dietician regarding Apo E 3/3 and IR
6. Dark Chocolate at 7 gm/day
7. Cinnamon 2 gm/day
8. Exercise is a daily medication for IR and bone health
9. Dental every 3 months, floss twice day and sonicare
10. Stress Management: music, laughter, social, meditation, laughter yoga, Tai Chi

Marji

Medications/Supplements to treat inflammation & root causes:

11. Omega 3 fatty acid to 2 gm/day (fish oil)
12. Vitamin D3 to 5000 iu daily
13. Aspirin 81mg daily with f/u aspirin check
14. Ramipril 2.5 – titrate to 10mg at bedtime
15. Switch from Simvastatin to Crestor 10mg (IR & dyslipidemia)
16. Niacin (B3) at 1 gm per day

Marji – these are my recommendations at this point –

1.Items 1-10 can be initiated immediately.

2. If you continue care with me, we will work together and move forward on items 11-16 in a step-wise fashion which will involve regular blood work, visits, and annual IMT.

Upcoming talks

9/12-13: Amy speaking in Cleveland, OH at CHL Symposium

9/26-27: Amy and Brad speaking in St. Louis at AAOSH

10/17-19: Bale/Doneen Reunion at Canyon Ranch, Tucson,

11/7-9: Bale/Doneen Preceptorship in San Antonio, TX

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