Bale/Doneen Live Chat Session

3/13/2013

5:30-6:30 pm PST

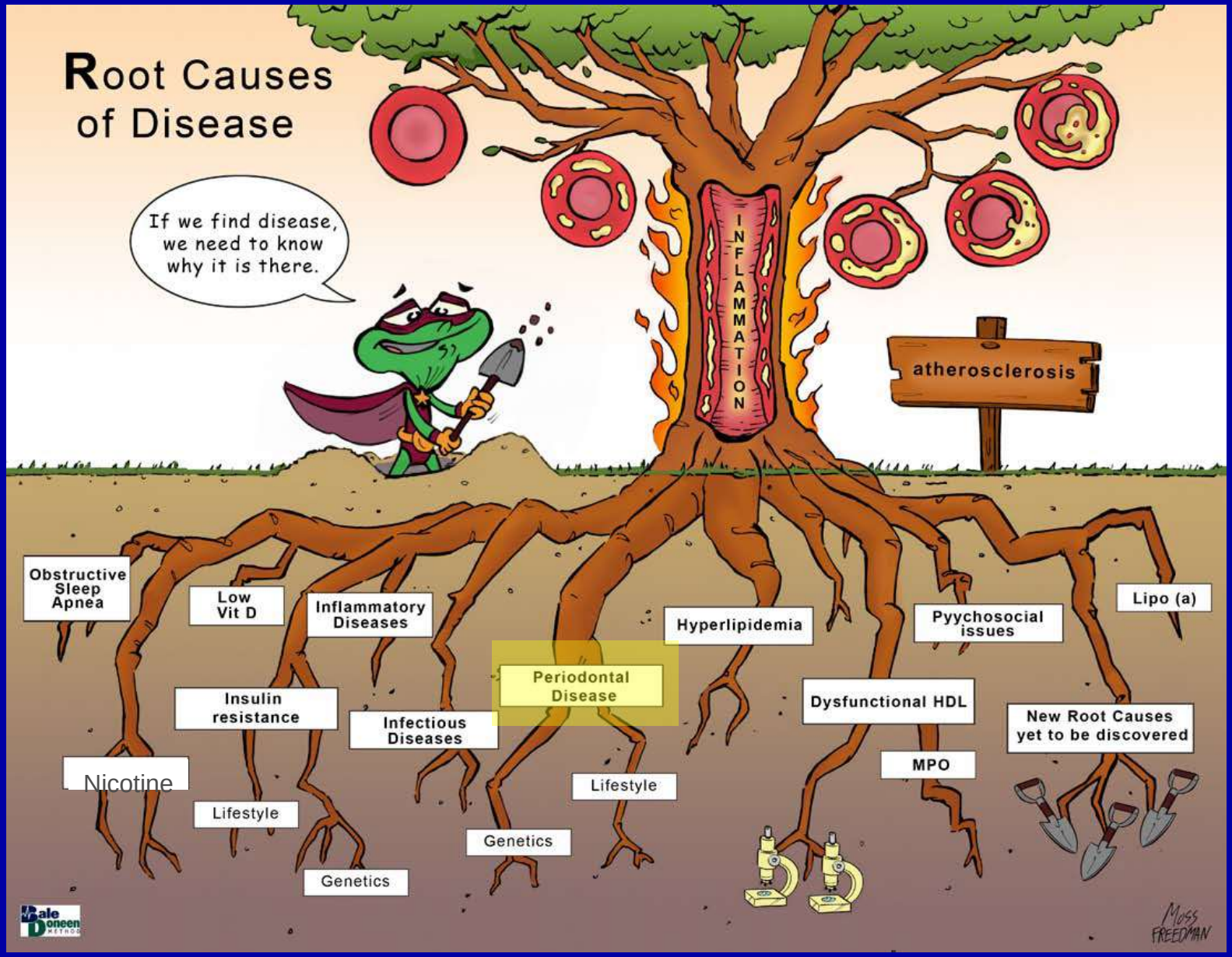
Bradley Bale, MD

Intention of the live chats

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

New Studies??!!!: OMG!

Way too many to discuss. Will concentrate on four only.



Periodontal Disease & Treatment Related to Risk of Stroke

- 510,762 PD & 208,674 non-PD pts; divided PD pts into prophylactic rx, intensive rx (subgingival curettage, root planning, periodontal flap or extraction), no rx
- Follow-up ~ 8 yrs.; 15,141 pts developed ischemic stroke
- Adjusted for age, sex and comorbidities (BP, DM, dyslipidemia, AF, CKD, subclinical ASVD) to assess incident risk (IR) of stroke

Lee, Y-L, DDS, et. al. Stroke 2/19/2013; 44: XXX-XXX
DOI: 10.1161/STROKEAHA.111.000076

Periodontal Wellness Reduces Risk of Stroke

- IR for PD prophylactic rx was 0.14%/year
- IR for non-PD pts. was 0.32%/year
- IR for intensive rx was 0.39%/year
- IR for no rx was 0.48%/year

Lee, Y-L, DDS, et. al. Stroke 2/19/2013; 44: XXX-XXX
DOI: 10.1161/STROKEAHA.111.000076

Periodontal Wellness Reduces Risk of Stroke

- After adjustment for confounders, the dental prophylaxis and intensive treatment groups had a significant lower hazard ratios for stroke than the non-PD group

  HR-0.78 & 0.95 (95% CI 0.75–0.81 & 0.91–0.99)

- PD without rx compared to non-PD group

  HR-1.15 (95% CI 1.07–1.24)

  among the youngest (20–44) age group

  HR-2.17 (95% CI 1.64–2.87)

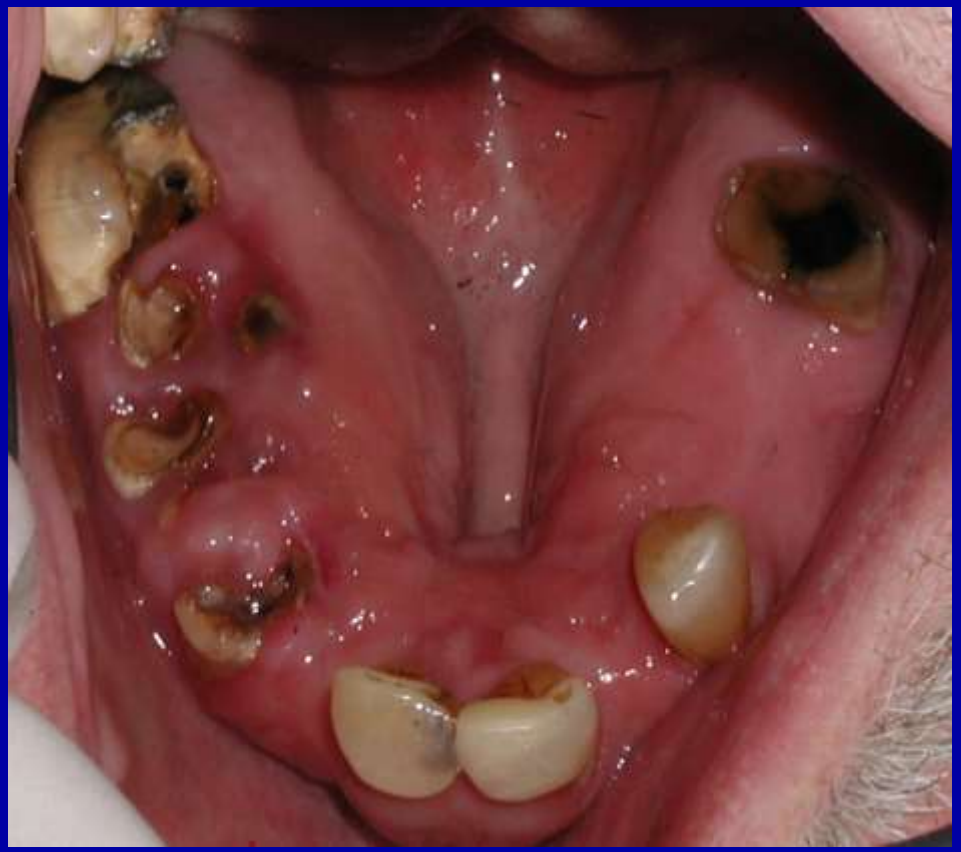
Lee, Y-L, DDS, et. al. Stroke 2/19/2013; 44: XXX-XXX
DOI: 10.1161/STROKEAHA.111.000076

Periodontal Wellness Reduces Risk of Stroke: Conclusions

- PD is an important risk factor for ischemic stroke
- PD patients who received treatment have a lower risk of stroke, especially among young subjects

Lee, Y-L, DDS, et. al. Stroke 2/19/2013; 44: XXX-XXX
DOI: 10.1161/STROKEAHA.111.000076

What About Endodontic Disease?



Oral Pathogens and Acute Heart Attack

- 101 acute heart attack pts; 76% male; ~63 yo
- Obstructing thrombi and arterial blood analyzed by PCR for oral pathogens
- Bacterial DNA load 16 times greater in the thrombi than the arterial blood sample
- ***Oral viridans streptococci*** found in 78% of thrombi; ***PD pathogens*** found in 35% of thrombi

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack

- Most frequently found bacterial DNA was from *Streptococcus sp*. mainly *Str. mitis-group* (72.3%)
- Most frequently found PD pathogens were: *Aggregatibacter actinomycetemcomitans* (5.9 %) and *Porphyromonas gingivalis* (5.0 %)

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack

- Viridans streptococci traditionally are assumed to be the most important organisms in periapical lesions.

- Oral viridans group streptococci are capable of invading human aortic endothelial cells and triggering the production of inflammatory cytokines and monocyte chemoattractant proteins

- Oral streptococci may initiate or contribute to platelet aggregation in coronaries – clot formation !!

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack

- Bacteremia originating from the oral cavity is common
- Happens following tooth brushing, tooth extraction and root canal treatment
- They are phagocytosed and may be translocated into the atherosclerotic plaque, or may end up in the plaque directly through the endothelium or via vasa vasorum

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack

- 30 pts had panoramic CT imaging
- ~50% showed periapical abscess
- If pt's thrombus was positive for strep viridans DNA, they were 13 times more likely to have a periapical abscess

OR 13.2 (95% CI 2.11 – 82.5) p=0.004

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack

- Electron microscopy performed on 9 thrombi
- Bacteria-like structures detected in all 9; whole bacteria in 3/9
- Immunohistochemistry for substances indicative of bacteria performed in 8 thrombi: CD 14 (bacteria recognition in monocyte/macrophage) and CD68 (inflammation from bacteria)
- CD14 and CD68 detected in all 8

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack: Conclusions

- Dental infection and oral bacteria are associated with the development of acute coronary thrombosis – heart attack!!!

- Dental health and dental care should be one major element in preventing heart attacks!!!

Pessi, T., PhD, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

Oral Pathogens and Acute Heart Attack

- Bale/Doneen Method Thoughts

1) Endodontic infection appears very common in heart attack pts; may trigger up to half of the heart attacks!!

2) All patients suffering a heart attack need a thorough oral health exam which includes PD pathogen testing as well as panoramic tomography.

3) This evaluation should be performed by an oral medicine specialist

4) This needs to become the standard of care

Pessi, T., P4D, et. al. *Circulation.* published online February 15, 2013
http://circ.ahajournals.org/content/early/2013/02/14/CIRCULATIONAHA.112.001254

EDFROG IRA

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

Laziness: it is a natural occurrence

This happened in the Shamattawa Dump in Manitoba, Canada

What to Consume??

Mediterranean Diet Reduces CV Risk

- 7,747 high CV risk pts.; 57% female; 55 - 80 yo; end points CV events and death; Mediterranean diet –a) extra virgin olive oil b) extra nuts versus low fat diet; unrestricted caloric diets; halted at 4.8 yrs.

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduces CV Risk

- Inclusion criteria ensuring high CV risk
  - a) type 2 diabetes or
  - b) three or more of the following:
    - 1) smoking
    - 2) hypertension
    - 3) LDL ≥ 160 mg/dL
    - 4) HDL ≤ 40 mg/dL
    - 5) BMI ≥ 25
    - 6) +Famhx
    - 7) if HDL ≥ 60mg/dL, subtract one

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduces CV Risk

- Exclusion criteria:
  - a) known CVD
  - b) major co-morbid conditions
  - c) inability to follow either diet plan
  - d) drug abusers

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Baseline Medications

Characteristic	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	
Medication use — no. (%)				
ACE inhibitors	1236 (48.6)	1223 (49.8)	1216 (49.6)	
Diuretics†	534 (21.0)	477 (19.4)	562 (22.9)	
Other antihypertensive agents	725 (28.5)	710 (28.9)	758 (30.9)	
Statins	1039 (40.9)	964 (39.3)	983 (40.1)	
Other lipid-lowering agents	121 (4.8)	145 (5.9)	126 (5.1)	
Insulin	124 (4.9)	126 (5.1)	134 (5.5)	
Oral hypoglycemic agents†	768 (30.2)	680 (27.7)	757 (30.9)	P<0.05
Antiplatelet therapy	475 (18.7)	490 (20.0)	513 (20.9)	
Hormone-replacement therapy‡‡	42 (2.8)	35 (2.6)	39 (2.7)	Women only
Score for adherence to Med diet§§	8.7±2.0	8.7±2.0	8.4±2.1	

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Basic Dietary Advice

Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/wk
Lean fish and seafood	≥3 servings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving /wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups¶	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduces CV Risk

- Objective biomarkers of adherence to the supplemental foods in random samples of:

a) urinary hydroxytyrosol, the main phenolic compound in extra-virgin olive oil, by gas chromatography–mass spectrometry

b) the plasma proportion of alpha-linolenic acid by gas-chromatography, as a measure of adherence to walnut consumption

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduced Cholesterol Intake Less

Table S8. Mean Baseline Values and Changes in Energy, Nutrient and Supplemental Food Intake by Study Arm.

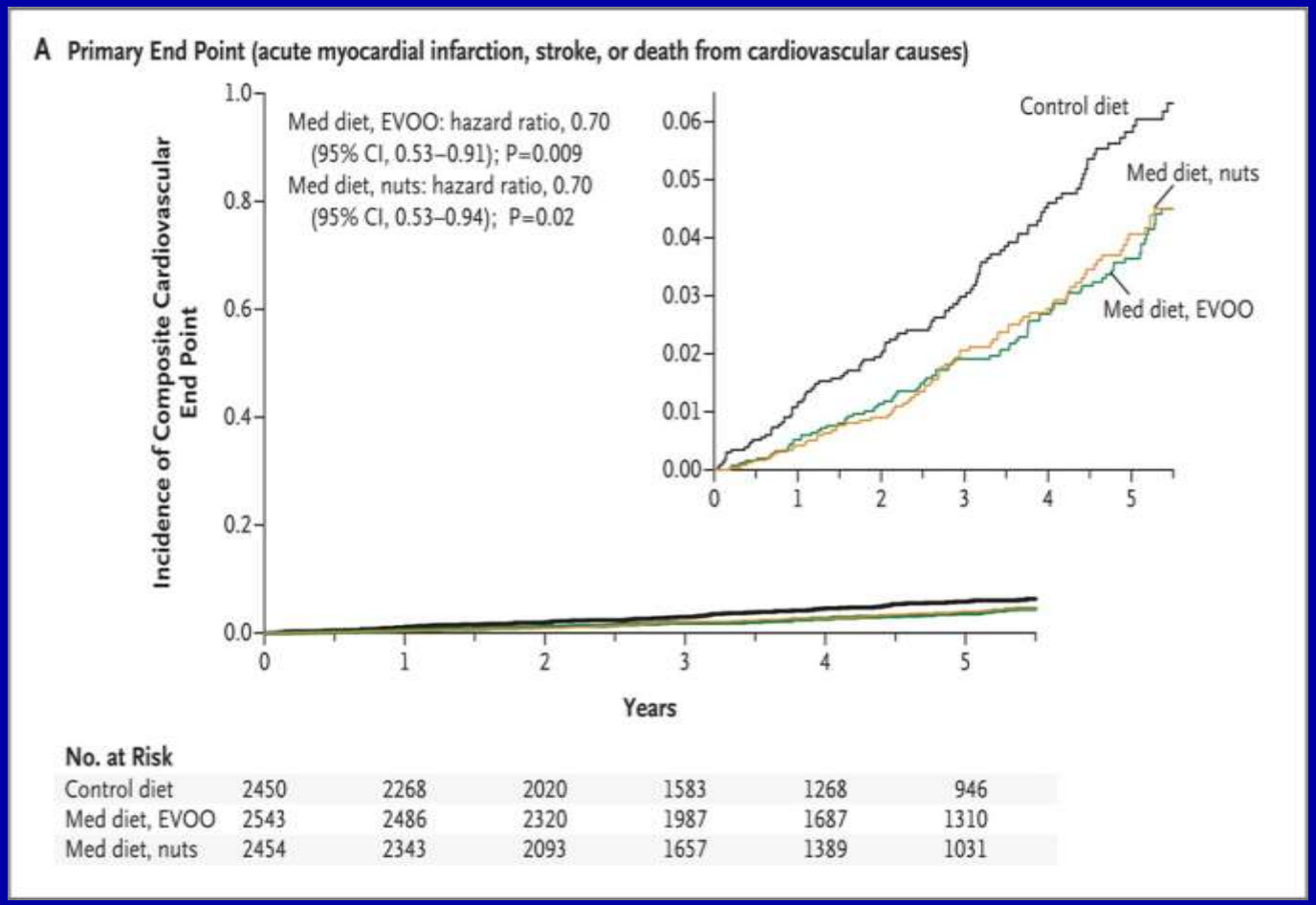
Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean diet intervention (versus the control diet) are shown. The change is follow-up minus baseline; hence a positive sign indicates increase over time (the last available follow-up food frequency questionnaire of each participant was used).

	Within-group mean changes					Between-group changes (differences vs. control)				
	MeDiet + Extra-virgin Olive Oil (n = 2364)		MeDiet + Nuts (n = 2108)		Control Diet (n = 1941)	MeDiet + Extra-Virgin Olive Oil vs. Control Diet			MeDiet + Nuts vs. Control Diet	
			Mean (95% CI)			*Mean (95% CI)*		P value*	*Mean (95% CI)*	P value*
Cholesterol (mg/d)	-24.89	(-30.5, -19.2)	-28.4	(-33.9, -22.9)	-32.3 (-38.1, -26.6)	7.48	(-2.34, 17.30)	0.19	3.97 (-5.69, 13.62)	0.70

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduces CV Events

Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.



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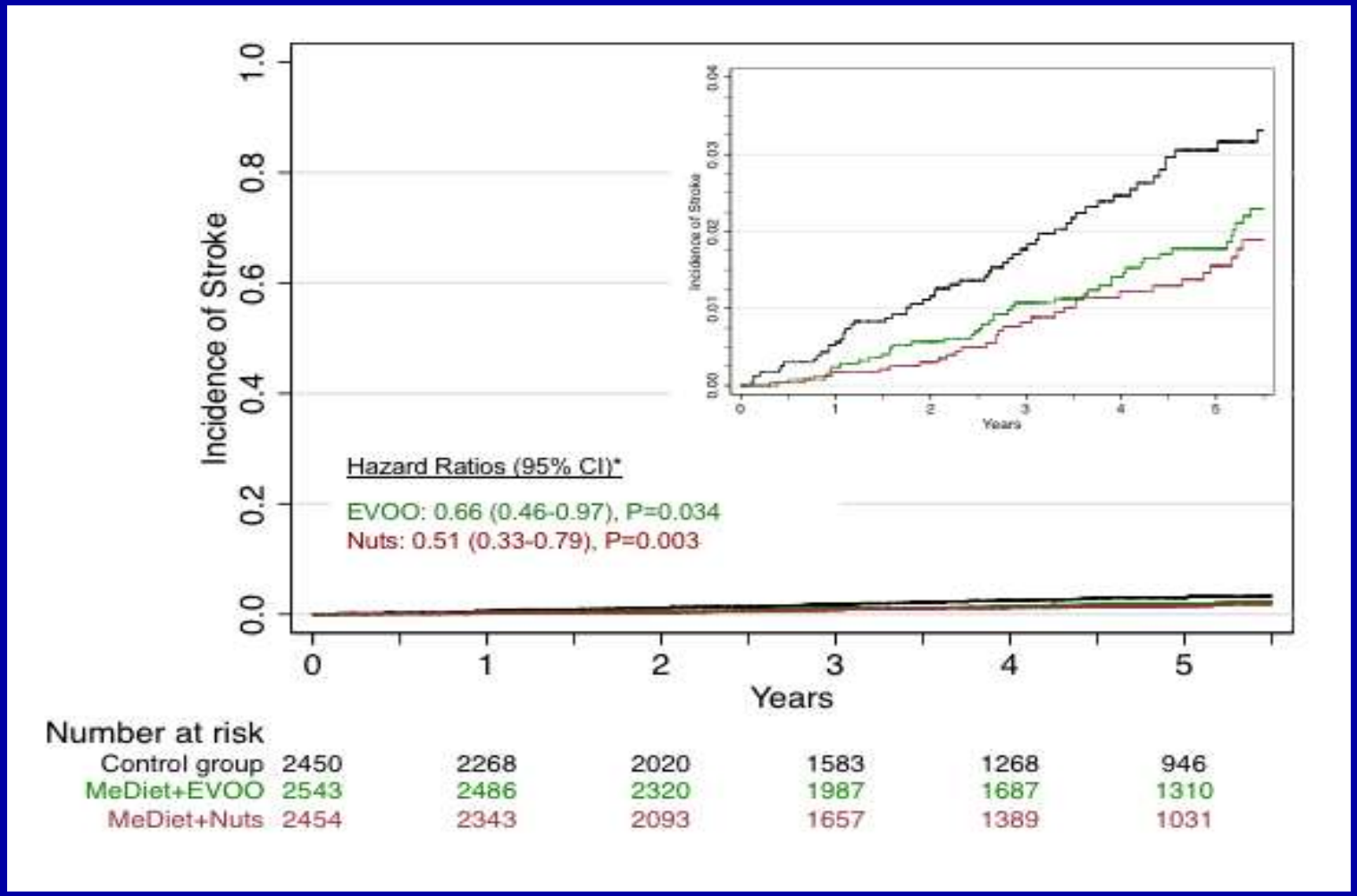
Mediterranean Diet Clobbers Stroke Risk

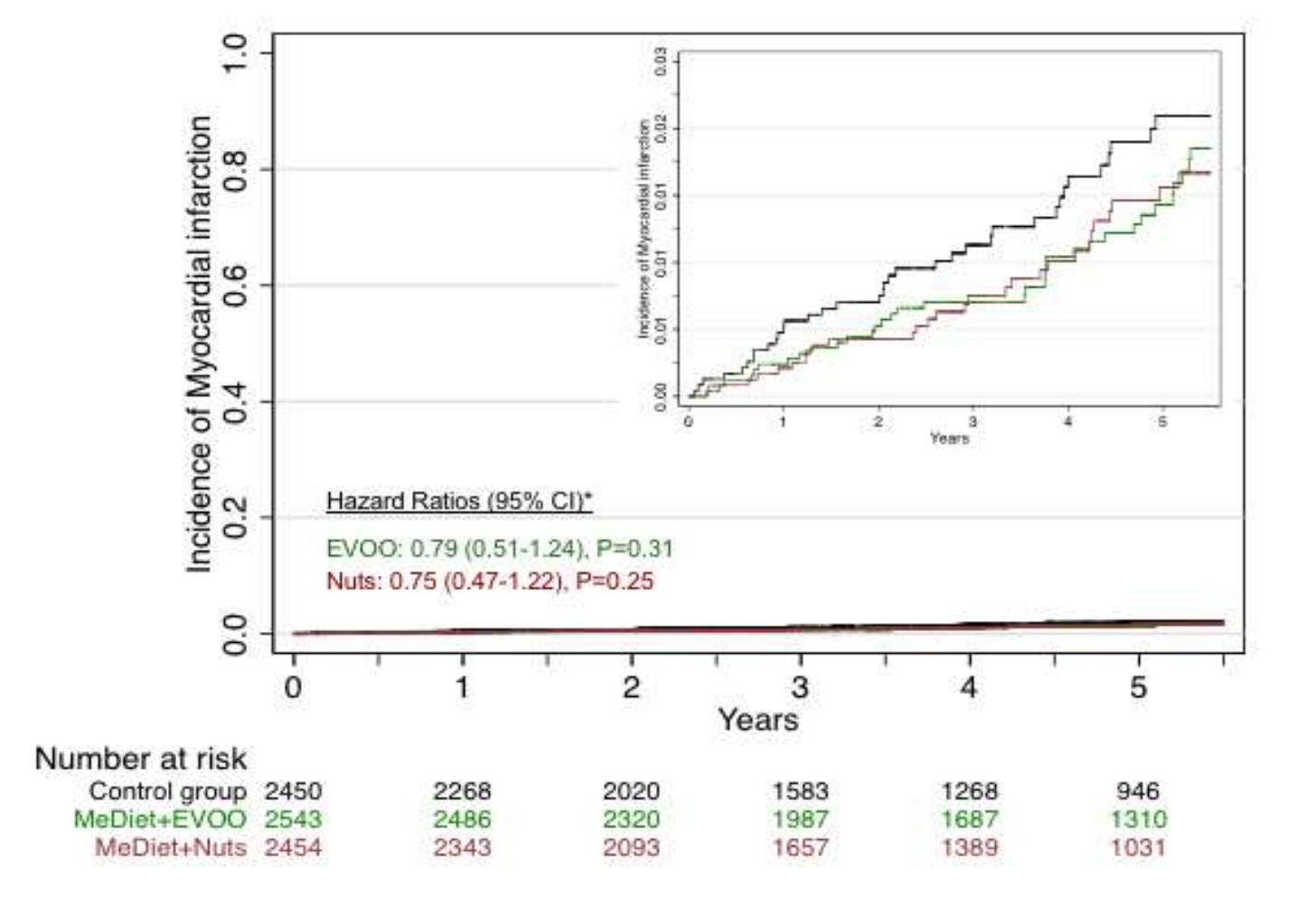
Kaplan-Meier Estimates of Incidence of Stroke



Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet did not Significantly Reduce Heart Attack Risk

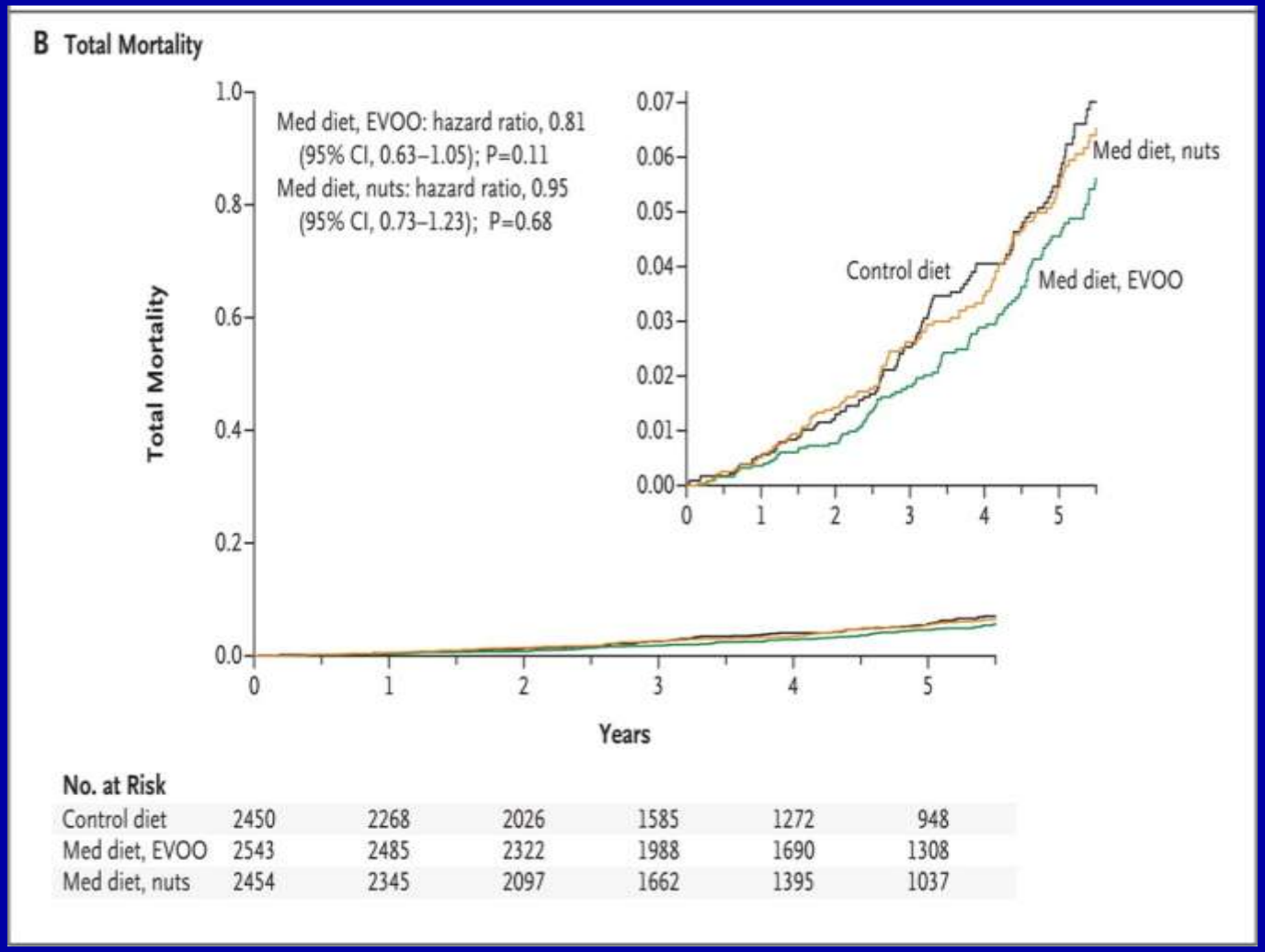
Kaplan-Meier Estimates of Incidence of Heart Attack



Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet did not Reduce Overall Mortality

Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.



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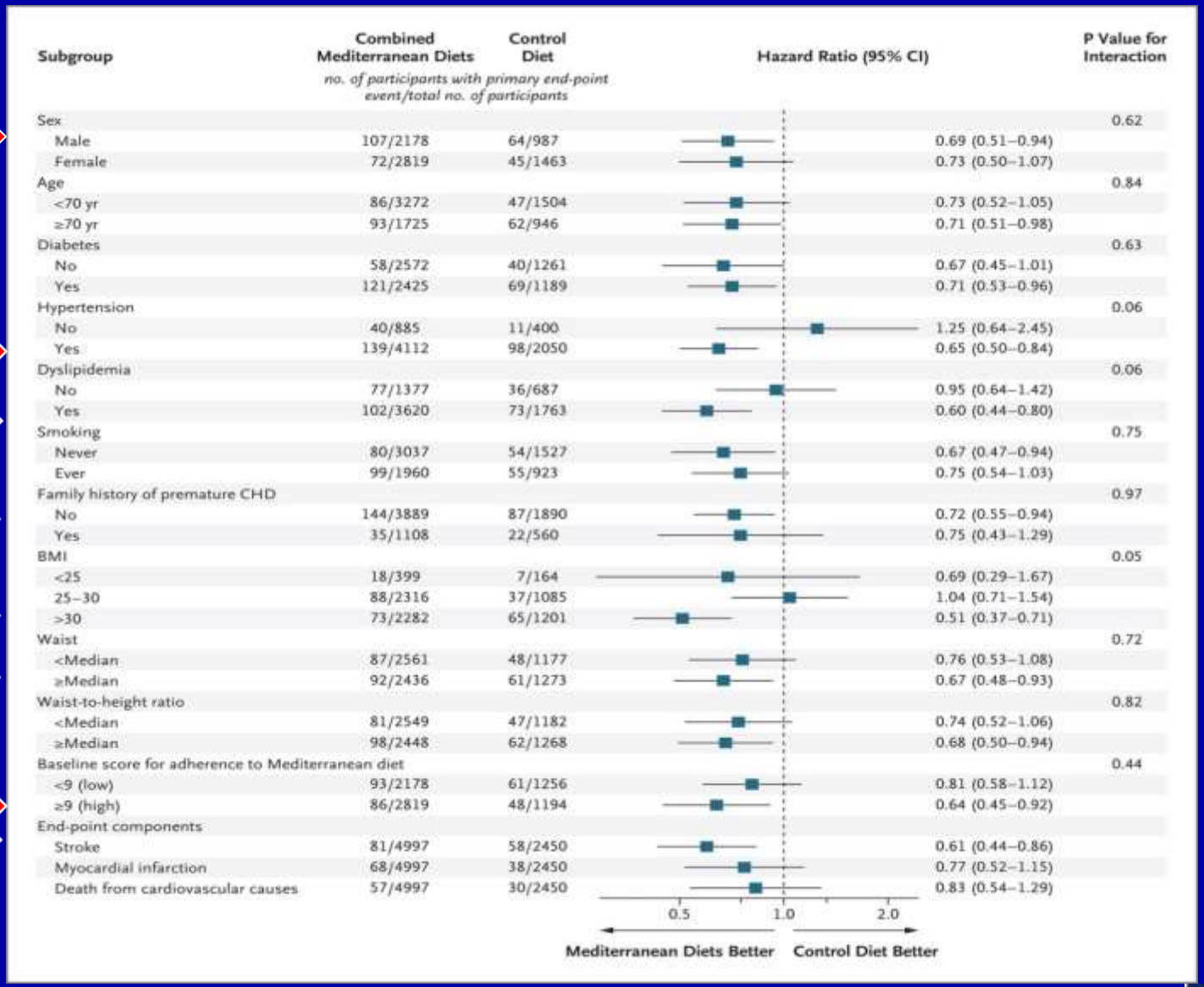
Mediterranean Diet Reduces CV Risk

Subgroup Analyses.



Subgroup	Combined Mediterranean Diets	Control Diet	Hazard Ratio (95% CI)	P Value for Interaction
	no. of participants with primary end-point event/total no. of participants			
Sex				0.62
Male	107/2178	64/987	0.69 (0.51–0.94)	
Female	72/2819	45/1463	0.73 (0.50–1.07)	
Age				0.84
<70 yr	86/3272	47/1504	0.73 (0.52–1.05)	
≥70 yr	93/1725	62/946	0.71 (0.51–0.98)	
Diabetes				0.63
No	58/2572	40/1261	0.67 (0.45–1.01)	
Yes	121/2425	69/1189	0.71 (0.53–0.96)	
Hypertension				0.06
No	40/885	11/400	1.25 (0.64–2.45)	
Yes	139/4112	98/2050	0.65 (0.50–0.84)	
Dyslipidemia				0.06
No	77/1377	36/687	0.95 (0.64–1.42)	
Yes	102/3620	73/1763	0.60 (0.44–0.80)	
Smoking				0.75
Never	80/3037	54/1527	0.67 (0.47–0.94)	
Ever	99/1960	55/923	0.75 (0.54–1.03)	
Family history of premature CHD				0.97
No	144/3889	87/1890	0.72 (0.55–0.94)	
Yes	35/1108	22/560	0.75 (0.43–1.29)	
BMI				0.05
<25	18/399	7/164	0.69 (0.29–1.67)	
25–30	88/2316	37/1085	1.04 (0.71–1.54)	
>30	73/2282	65/1201	0.51 (0.37–0.71)	
Waist				0.72
<Median	87/2561	48/1177	0.76 (0.53–1.08)	
≥Median	92/2436	61/1273	0.67 (0.48–0.93)	
Waist-to-height ratio				0.82
<Median	81/2549	47/1182	0.74 (0.52–1.06)	
≥Median	98/2448	62/1268	0.68 (0.50–0.94)	
Baseline score for adherence to Mediterranean diet				0.44
<9 (low)	93/2178	61/1256	0.81 (0.58–1.12)	
≥9 (high)	86/2819	48/1194	0.64 (0.45–0.92)	
End-point components				
Stroke	81/4997	58/2450	0.61 (0.44–0.86)	
Myocardial infarction	68/4997	38/2450	0.77 (0.52–1.15)	
Death from cardiovascular causes	57/4997	30/2450	0.83 (0.54–1.29)	

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduces CV Risk

- Diet had significant benefit in older, overweight, hypertensive, dyslipidemic, metabolic syndrome type males without a positive famhx of CVD, if they had higher adherence to the diet
- The decreased CV risk was driven by reduction in stroke; not heart attack

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Mediterranean Diet Reduces CV Risk

- Findings are consistent with smaller trials assessing effects of Mediterranean diet, olive oil and nuts on risk factors, such as BP and markers of oxidation, inflammation and endothelial dysfunction.

- Why huge reduction in stroke in ‘nut’ arm??

Estruch R et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1200303

Walnuts improve endothelial function in hypercholesterolemic subjects

Variable	Baseline	Control diet	Walnut diet	p
Endothelium-dependent vasodilation (%)	3.4	3.6	5.9	0.043
Intracellular adhesion molecule-1 (µmol/L)	355	370	343	>0.1
Vascular cell adhesion molecule-1 (µmol/L)	474	465	378	0.045

18 subjects; cross-over study; four week periods

Mediterranean diet vs. medit. diet with walnuts substituted for olive oil, olives, avocados

Ros E et al. *Circulation* 2004 Mar 22; 109:1609-14.

Pistachios reduce BP

28 adults with dyslipidemia completed a randomized, crossover, controlled-feeding study. All meals provided and calories controlled. On diet for 4 weeks.

Reductions in SBP after diet containing 1 serving/day: 6.2 ±1.9 mmHg
2 servings/day: 5.0 ±1.9

in DBP after diet containing 1 serving/day: 1.7 ±1.0
2 servings/day: 2.3 ±1.0

West S.G, Gebaurer S.Kl, et al. Hypertension. May 3, 2012; 60:58-63.

BD Method Thoughts

- Supports inflammation as causal of ASVD
- Supports importance of BP in stroke reduction
- Supports a very palatable diet can be beneficial
- The Mediterranean diet alone is not a panacea and did not reduce mortality risk
- Would anticipate even better results with some caloric restriction and monitoring of oxidation and inflammation

Hot Topics

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

UNIVERSITY OF OXFORD

hps2 THRIVE

Bale Doneen METHOD

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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hps2 THRIVE

Dale Doneen METHOD

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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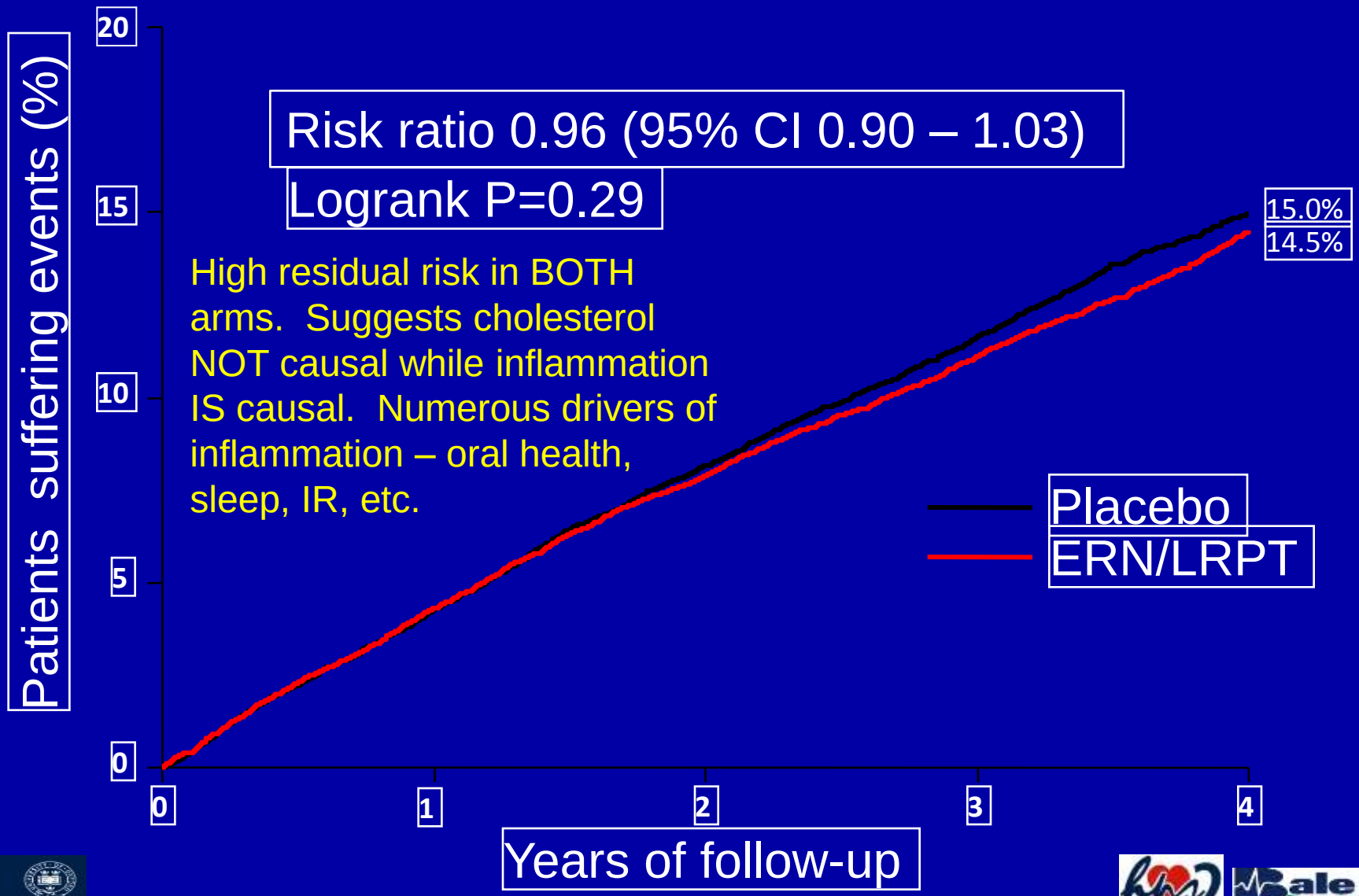
hps2 THRIVE

Dale Doneen METHOD

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS



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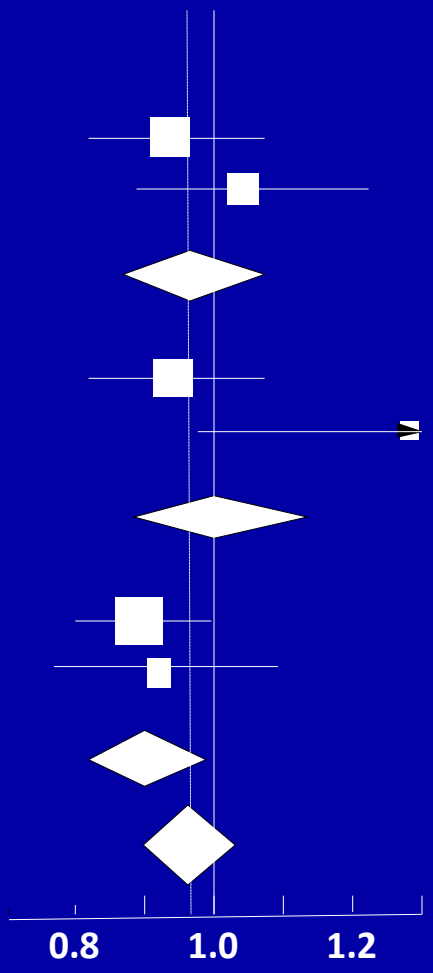
hps2 THRIVE

Dale Doneen METHOD

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

This trial was not an ER niacin trial: there was an intruder!!

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

Laropiprant: Numerous Potential Adverse Effects from Blocking PD1

- 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

Laropiprant: Numerous Potential Adverse Effects from Blocking PD1

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

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

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

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

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

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

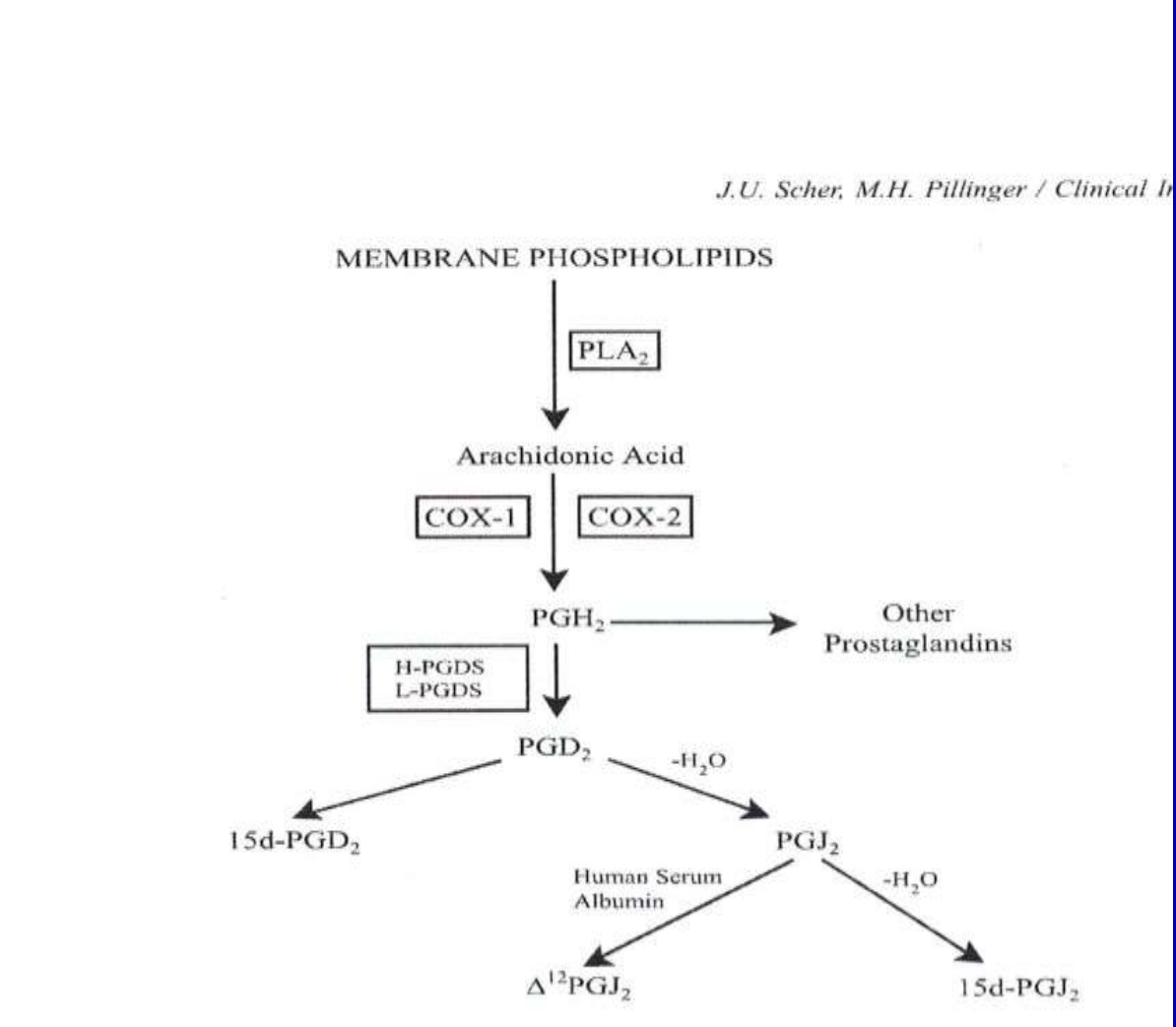
Saleem, S., et. al. ***Eur J Neurosci***. 2007 July ; 26(1): 73–78

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

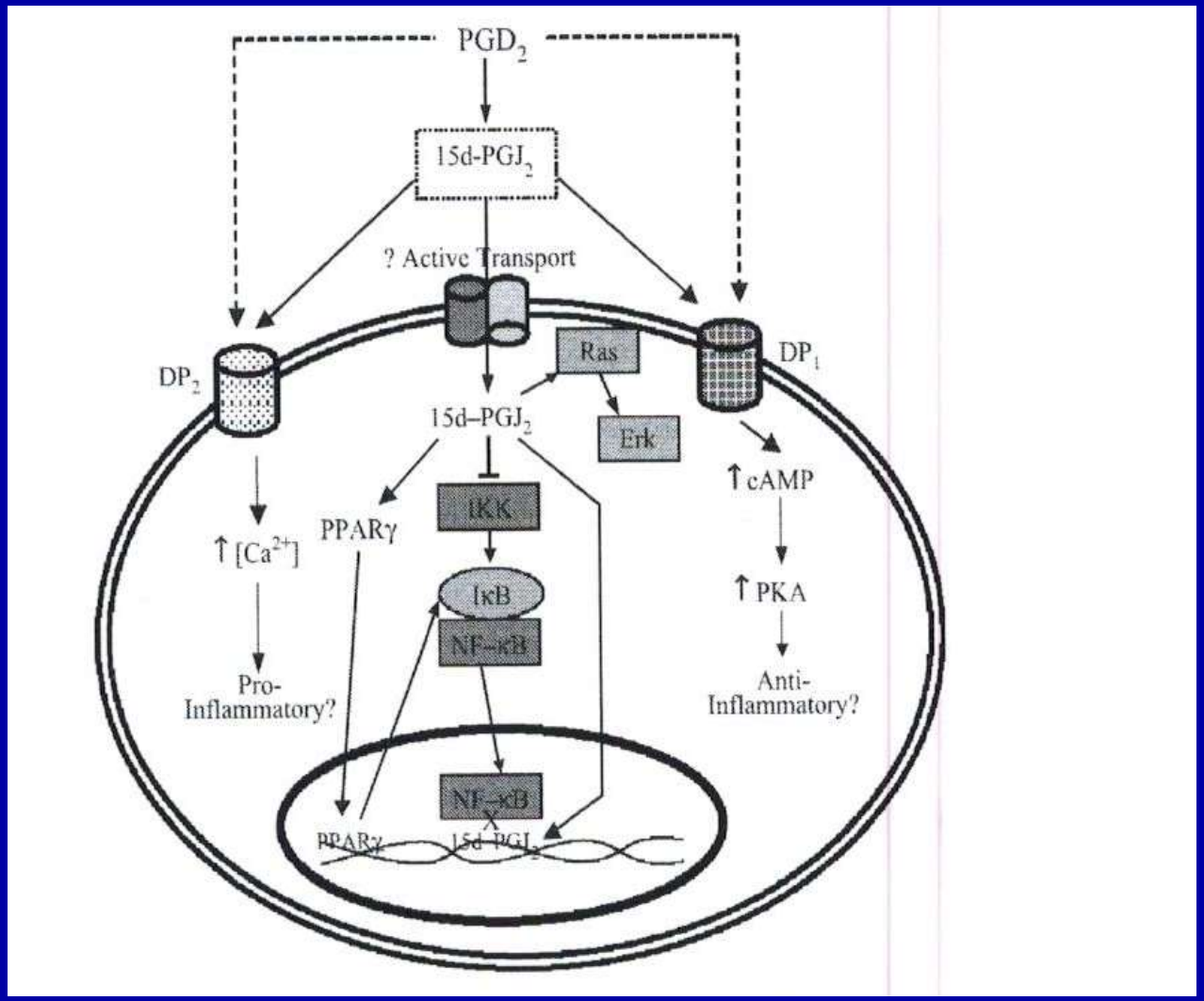
Vosper, H. Clin Med Insights Cardiol. 2011; 5: 85–101

Could Blocking DP1 Result in Greater 15d-PGD2 and Less 15d-PGJ2 ???



J.U. Scher, M.H. Pillinger / Clinical Immunology 114 (2005) 100–109

Blocking DP1 May not be a Good Idea!



J.U. Scher, M.H. Pillinger / Clinical Immunology 114 (2005) 100–109

15 d-PGJ2 Questions Remain

- 15d-PGJ2 is an endogenous PPARg ligand as well as a direct inhibitor of several other signal transduction pathways.
- The consequences of these activities are complex & likely to play a role in the prevention and/or resolution of inflammation.
- Many questions remain, including the possible existence of a specific 15d-PGJ2 membrane receptor.
- Additional research will be needed to elucidate both the biology and importance of 15d-PGJ2

J.U. Scher, M.H. Pillinger / Clinical Immunology 114 (2005) 100–109

Other Potential Benefits from PPAR gamma which would be lost if laropiprant decreases this stimulation

HDL Ability to Perform Reverse Cholesterol Transport Enhanced with Pioglitazone

- 39 met. synd. pts; 16 pio for 12 wks. & 23 placebo; pio 30mg 6wks. then increased to 45mg

Rx	N	% change efflux	95% CI	p vs baseline	P vs placebo
Pio	16	11.3	1.8-20.8	0.02	0.04
Placebo	23	0.0	-6.2-6.1	0.99	

Increased HDL-C 14% : no significant association with change in efflux capacity ($r = 0.22$; $P = 0.18$

Khera, A. V., M.D., et. al. N Engl J Med 1/2011;364:127-35.

Pioglitazone Decreases ADMA and Improves Endothelial Function

- 17 non-DM subjects with CAD; mean age 58; rx pio 30mg X 12 wks. followed 12 wks. without rx
- Urine ADMA levels decreased with rx (30%), 1.27 ± 0.5 µmol/ml to 0.97 ± 0.3, p = 0.017; returned to the initial values after the wash-out period
- Endothelium-dependent vasodilation improved significantly with the treatment from 4.4 ± 3.9 to 8.4 ± 4.1%, a relative increase of 91%; p<0.001

Staniloae, C., et. al. *Cardiology* 2007;108:164-169

Pioglitazone Lowers MACR

- 63 DM with BP on RAAS rx & elevated MACR; 32- pio 15-30mg/d or 31-metformin 500-750mg/d; X one year
- Similar glycemic and BP changes
- MACR decreased 8.3% in pio group and increased 4.2% in metformin group p=0.01

Morikawa, A., et. al. Clin Exp Nephrol (2011) 15:848–853

Pioglitazone Favors Anti-inflammatory Macrophages

- Inflammation initiates recruitment of neutrophils and monocytes to the damaged tissue.
- This process can rapidly terminated via anti-inflammatory cytokines.
- An imbalance of inflammation initiation and arrest results in chronic inflammatory diseases (atherosclerosis).
- Macrophages in atherosclerotic plaques are heterogeneous:
  1) proinflammatory “classical” M1
  2) anti-inflammatory “alternative” M2
- PPAR gamma (Pioglitazone) favors M2 polarization

Mandy Bloch, et. al., Circulation Research. *2/2012;110: 394-405*

Pioglitazone Slashes Risk of Diabetes Conversion 72%

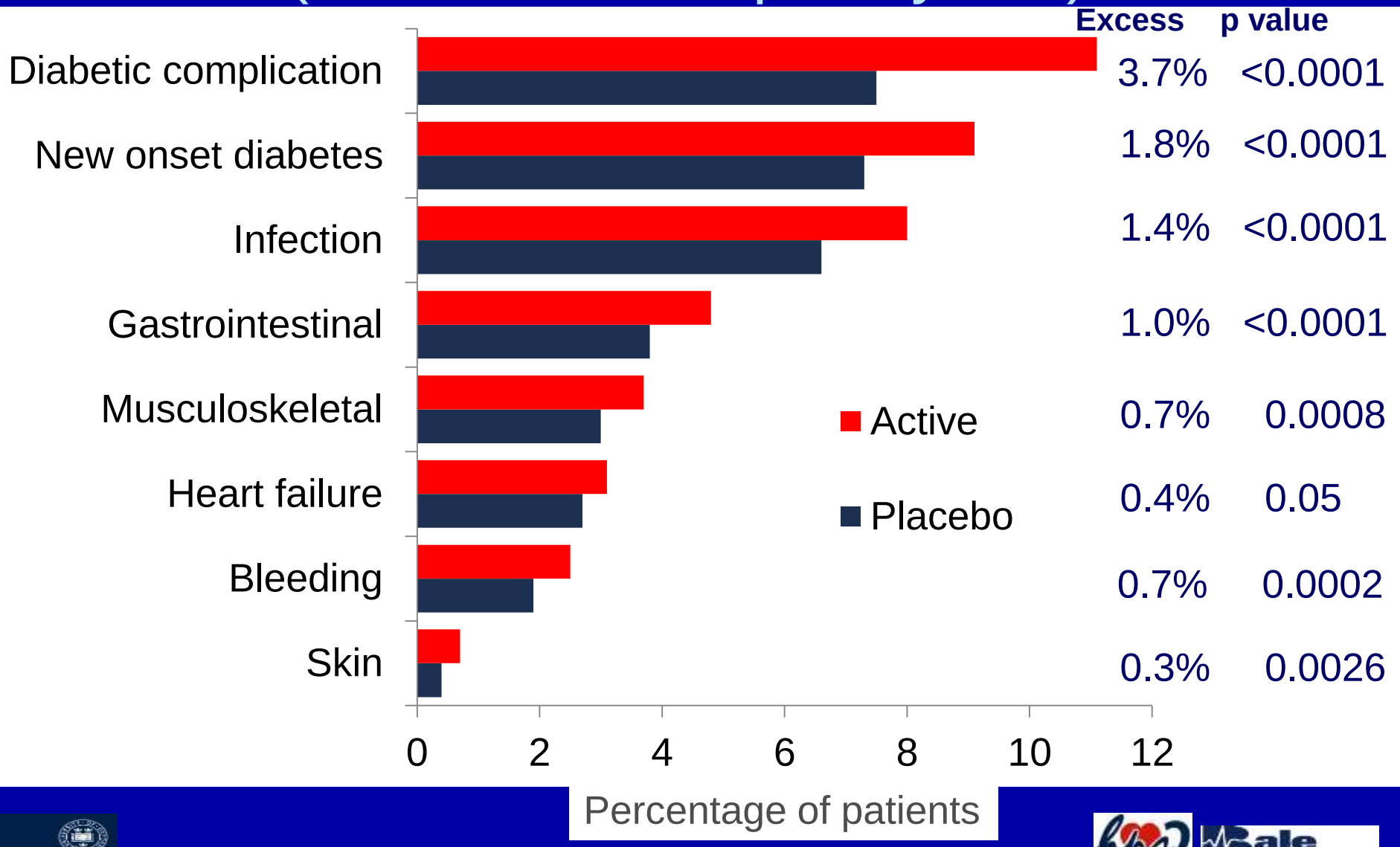
- 602 patients with IGT (FG 95-125mg/dL & or OGTT 140-199 mg/dL); Median follow-up 2.4 yrs.
- Randomized pioglitazone 30 -45 mg or placebo
- HR for DM -0.28; p<0.00

DeFronzo RA, et al. *N Engl J Med* 3/24/2011; 12:1104-1115

If laropiprant causes defects in virus-specific T-cell responses, decreases bronchial dilitation, 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

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 group and 0.8% in the niacin group), muscle symptoms or myopathy (0.3% of the patients overall), and rhabdomyolysis (1 patient in the placebo group and 4 in the niacin group)."

- New onset DM not even mentioned!!!!

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

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)**

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THRIVE

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

HPS2-THRIVE: SUMMARY

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hps2 THRIVE

Dale Doneen METHOD

HPS2-THRIVE: SUMMARY

- Significant excesses of serious adverse events (SAEs) due to known and unrecognised side-effects of niacin. Over 4 years, ER niacin/laropiprant caused SAEs in ~30 patients per 1000
- No significant benefit of ER niacin/laropiprant on the primary outcome of major vascular events when added to effective statin-based LDL-lowering therapy
- No clear evidence of differences in efficacy or safety in different types of patient (except for an excess of statin-related myopathy in Chinese patients)
- Findings are consistent with previous niacin trials. ??? The role of ER niacin for the treatment and prevention of cardiovascular disease needs to be reconsidered

BD Method HPS-THRIVE Conclusions

- Study supports optimal TC/HDL <3.0
- Study supports inflammation as causal and simply taking care of lipids as inadequate to halt the disease in many individuals (too bad no biomarkers available!)
- ER niacin plus laropiprant is not the same as ER niacin !!
- Conclusions about using ER niacin cannot be derived from this trial !!!
- It probably is not a good idea to block DP1: the 'flush' is probably good!

BD AIM HIGH Conclusions

- Study does not affect our use of niacin
- Continue to prescribe niacin
- Good candidates:

  patients who are statin intolerant

  patients who are not at TC/HDL goal

  patients with the lipo (a) issue

  patients with IR dyslipidemia

  patients with persistent arterial inflammation

Case

Kindly submitted by Dr. Linda Groene

- “young” 75 yo female
- Meds: crestor 10mg; niacin 500mg bid; losartan (intolerant of ACEI); atenolol; fish oil; ASA low dose; vit. D; folic acid
- Exercise daily; low fat diet
- Quit smoking seven yrs ago
- Disease: ABI wnl; abd US ‘08- wnl; +CAD on angio 3/11 with 30-40% stenotic plaque mid-RCA; + CIMT in 1/10 with mean CCA 1.37 mm; 1/13 with mean CCA 1.41 mm + – right CCA-2.1H, bulb-2.3H, ICCA-2.0E; left CCA-3.6H, bulb-2.7mmH, ICCA-3.8H (worse now than in 2010 ??)
- TC-183, TG-67, HDL-68, LDL-73; TC/HDL=2.7 ; lipo (a)- 20
- F2 isoprostane-0.4; MACR-22.2; hsCRP-1.1; LpPLA2-314; MPO-282 in 8/12

What to do next?? Guess saliva test is in order.

- Disease: we do not know that she is worse. The margin of error in the best of hands for the mean CCA thickness is + or – 0.06mm. Therefore, going from 1.37 mm to 1.41 mm is not any significant change. Unfortunately, the first CIMT did not contain any plaque data. Her current CIMT shows significant plaque. Fortunately, there is some echogenicity in all of the plaques which indicates some stabilization of the disease. Next year's CIMT will be interesting in terms of the plaque and you would hope some of the H goes to E.

- Fire: assume she is currently high risk for a CV event with evidence of endothelial and intimal inflammation.

- Roots:

  IR – any info on OGTT?

  Sleep – any issues?

  Psychosocial –pt claims no issue

  Oral health – absolutely salivary testing and referral ASAP to an oral medicine specialist

- Optimal: BP ?

- Genetics: ?; will want salivary IL-1 beta

- Management:
  - consider increasing niacin or crestor
  - if IR, consider low dose pioglitazone
  - why atenolol ?
  - why folic acid ?

Upcoming Presentations

Upcoming Presentations

- 4/13/2013 – Brad (Amy running Boston Marathon on 15th ! ☺)-21st Annual World Congress on Anti-aging and Aesthetic Medicine; Orlando, FL
- 4/24/2013 – Keynote Speakers – Delta Dental Executive National Program; St. Louis, MO
- 4/27/2013 – BD Method Inflammation 5 hr. CME – sponsored by CHL; Denver, CO
- 5/17-18/2013 – BD Method Preceptorship; 17 hr. CME; Washington, DC
- 8/11/2013 – Brad (Amy enjoying her lake place with family!☺) – Florida Endocrine Society “2013 Post Graduate Update”; Orlando, FL
- 9/13-14/2013 – BD Method Preceptorship; 17 hr. CME; Lubbock, TX

Open for Discussion