March 7, 2012 Chat Session

Amy Doneen MSN, ARNP

March 7, 2012

Outline for Today
March 7, 2012

- Recent FDA statement and Bale/Doneen response regarding:
  - Statins and memory,
  - Statins and diabetes risk
  - Statins and monitoring liver function
- Microvascular dementia – the past and present
- Periodontal disease and Alzheimer's risk – inflammation and spirochete
- Actos and Alzheimer's disease
- Actos and CAD regression
- Lp-PLA2 data

FDA statement 2.28.2012

- The Food and Drug Administration (FDA) added new safety warnings to cholesterol-reducing statin drugs on Wednesday, noting increased risks of Type 2 diabetes and memory loss for patients who take the medications. Additionally, it is stated that it is not necessary to regularly monitor liver function.

Read more: http://healthland.time.com/2012/02/29/fda-warns-statin-users-of-memory-loss-and-diabetes-risks/#ixzz1oPE2mCXM

BD Response to FDA statement on Statins and Dementia

Statins reduce the incidence of dementia

- 1,674 older (>60 yo) Mexican Americans; 27% took statins; 5-year follow-up
- 130 participants developed dementia
- HR = 0.52 (95% CI 0.34 - 0.80) if took statin

adjusted for: education, smoking, presence of at least one APOE 4 allele, and hx of stroke or DM

C. Cramer, PhD, et. al., ***NEUROLOGY*** 7/2008;71:344-350

Statins offer no protection against Alzheimer's disease

- **Religious Orders Study**, an ongoing prospective clinical-pathologic study of dementia
- 119 statin users (67 lipophilic); median age 75 yo; free of dementia; followed average of 12 years.
- 16 developed AD.

- After adjustment for age, sex, and education, baseline statin use was not associated with AD risk
- Type of statin also did not influence cognition

- 47 had brain autopsy at time of death; no influence found on the classic AD pathology or cerebral infarction

Arvanitakis Z, Schneider JA, Wilson RS, et al. *Neurology* 1/18/2008: DOI:10.1212/01.wnl.0000288181.00826.63. Available at: http://www.neurology.org.

Simvastatin linked to reduced incidence of dementia, Parkinson's disease

- Population-based 4.5 million subjects, 94.4% male
- 835,049 people taking statin (87% on Simvastatin Therapy)
- Incidence of dementia and PD among subjects who had continuously used a statin for at least seven months
- > 50% reduction in adjusted models for simvastatin; N/S others
- Why?
- ?statins protect the brain through an anti-inflammatory mechanism
- ?statins neuroprotective effect may be related to their ability to increase growth factors in the brain

BMC Med 7/19/2007; DOI:10.1186/1741-7015-5-20. Available at: http://www.biomedcentral.com/1741-7015/5/20

Statin Use Is Associated with Reduced Risk of Alzheimer's Disease

Case-control study of 2581 subjects enrolled at 15 research centers from 1996-2001. Subjects included 912 with AD and 1669 without AD or dementia.

The association between statin use and risk of AD was evaluated using generalized estimating equations, adjusting for age, sex, ethnicity, education, history of heart disease, stroke, diabetes and APOE genotype.

Robert C. Green, Sally E. McNagny, Parimala Jayakumar, L. Adrienne Cupples, Kelly Benke, Lindsay Farrer, for the MIRAGE Study Group Boston, MA

Statin Use Is Associated with Reduced Risk of Alzheimer's Disease

Statin use was associated with reduced risk of AD
(OR = 0.21, 95% (CI) 0.14 to 0.33).

Non-statin cholesterol lowering medications were not significantly associated with reduced risk of AD
(OR = 0.73, 95% CI 0.30 to 1.8).

APOE genotype did not alter the association between risk of AD and statin use.

The protective effect of natural statins was not significantly different from that of synthetic statins.

- *Robert C. Green, Sally E. McNagny, Parimala Jayakumar, L. Adrienne Cupples, Kelly Benke, Lindsay Farrer, for the MIRAGE Study Group Boston, MA*

Statin Use Is Associated with Reduced Risk of Alzheimer's Disease

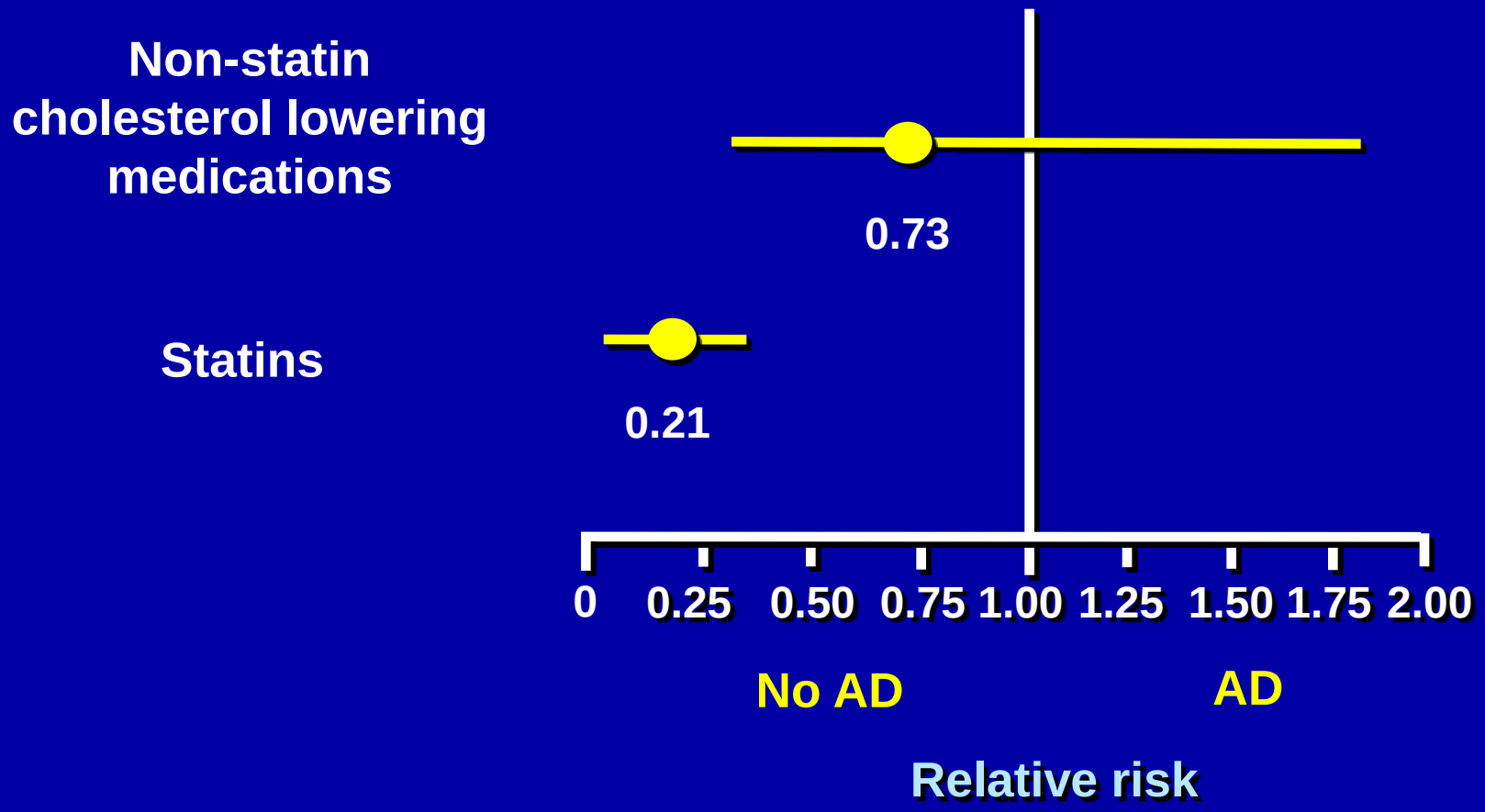
Statin medications are associated with reduced risk of AD.

African American ethnicity or the presence of the APOE e4 allele modifies the statin-AD risk association.

This is the largest study to demonstrate a protective effect of statin medications and the first to examine the impact of African American ethnicity and APOE genotype.

Robert C. Green, Sally E. McNagny, Parimala Jayakumar, L. Adrienne Cupples, Kelly Benke, Lindsay Farrer, for the MIRAGE Study Group Boston, MA

Statin Use is Associated with Reduced Risk of Alzheimer's Disease



Green et. al. Abstract presented at the American Academy of Neurology 2002

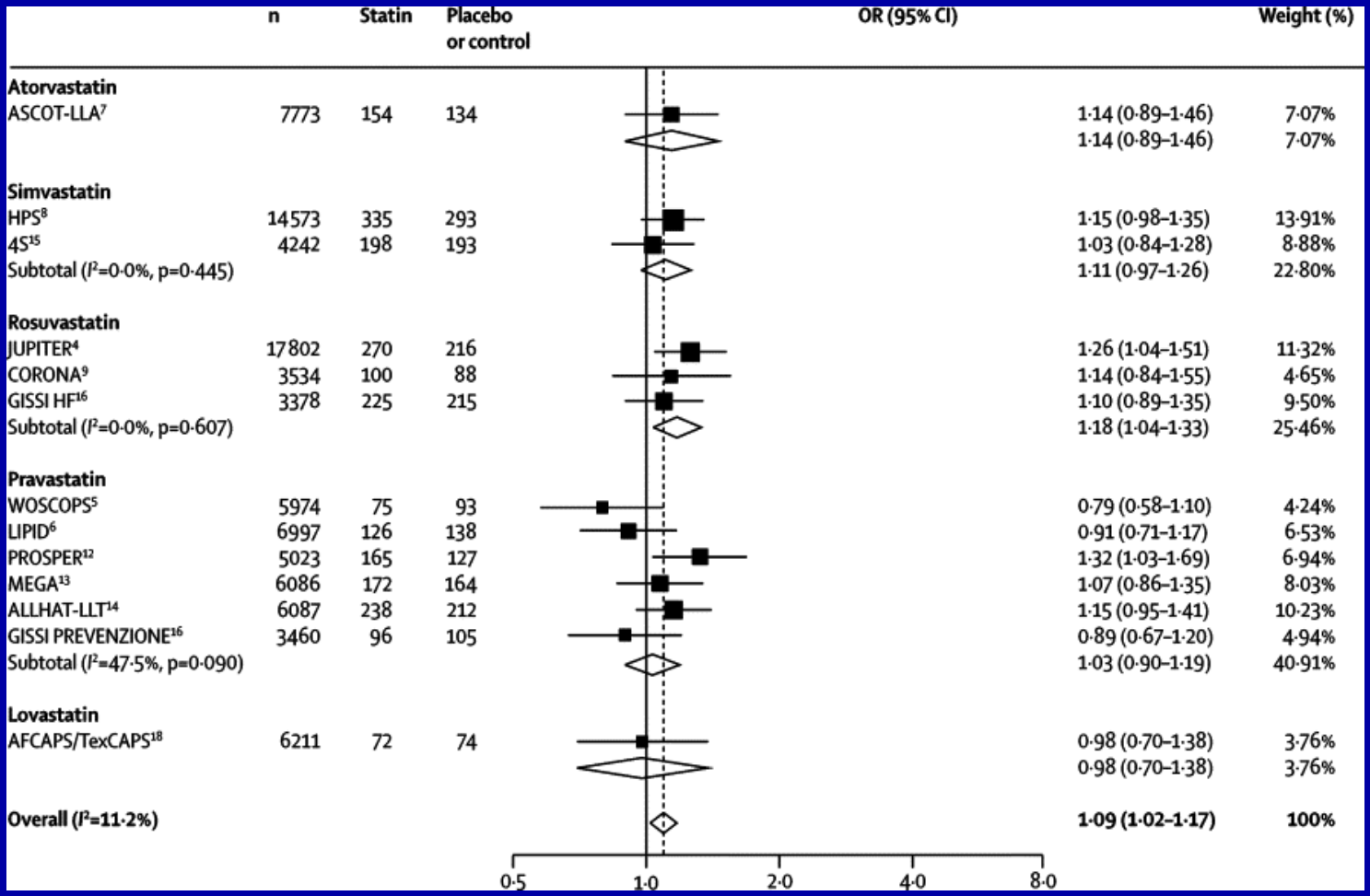
BD Response to FDA statement on Statins and diabetes

Rosuvastatin Significantly Reduces CV Morbidity and Mortality in Pts with LDLs <130

- double-blind, placebo-controlled, randomized clinical trial
- 15,000 healthy males ≥50 years and females ≥60 years with LDL-cholesterol levels <130 mg/dL; elevated HsCRP
- rosuvastatin 20 mg/day or placebo
- Trial stopped early due to unequivocal evidence of a reduction in cardiovascular morbidity and mortality

AstraZeneca. Crestor outcomes study JUPITER closes early due to unequivocal evidence of benefit [press release]. March 31, 2008

Statin RX and Incident DM

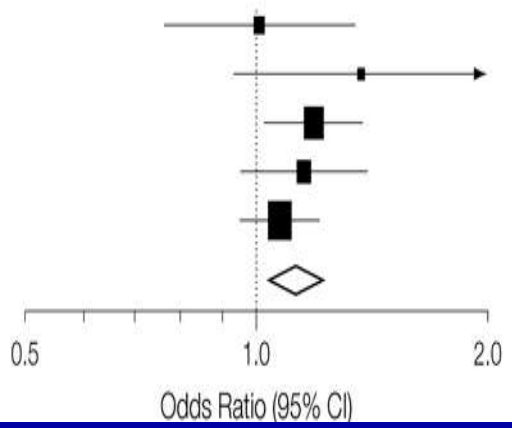


Only two trials met significance!!! Jupiter and Prosper !!!

Sattar N., ProfPhD, et. al. *Lancet*. 3/2010 Vol. 375, Issue 9716:735-742

Meta-analysis of New-Onset DM Comparing Intensive-Dose to Moderate-Dose Statin Rx

Incident Diabetes	Cases/Total, No. (%) Intensive Dose	Moderate Dose	OR (95% CI)
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	**1449/16 408 (8.8)**	**1300/16 344 (8.0)**	**1.12 (1.04-1.22)**
Heterogeneity: $I^2 = 0\%$; $P = .60$			



32,752 pts without diabetes at baseline; 2,749 developed diabetes in a year
1,449 high dose statin ; 1,300 low to moderate-dose statin
Only one of the five trials was significant

Surprised more did not become diabetic as at least 70% were IR at baseline!!

Preiss, D. et al. JAMA 6/22/2011;305:2556-2564

Baseline Data From Trials Comparing Intensive-Dose to Moderate-Dose Statin Rx

Table 2. Baseline Data From Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

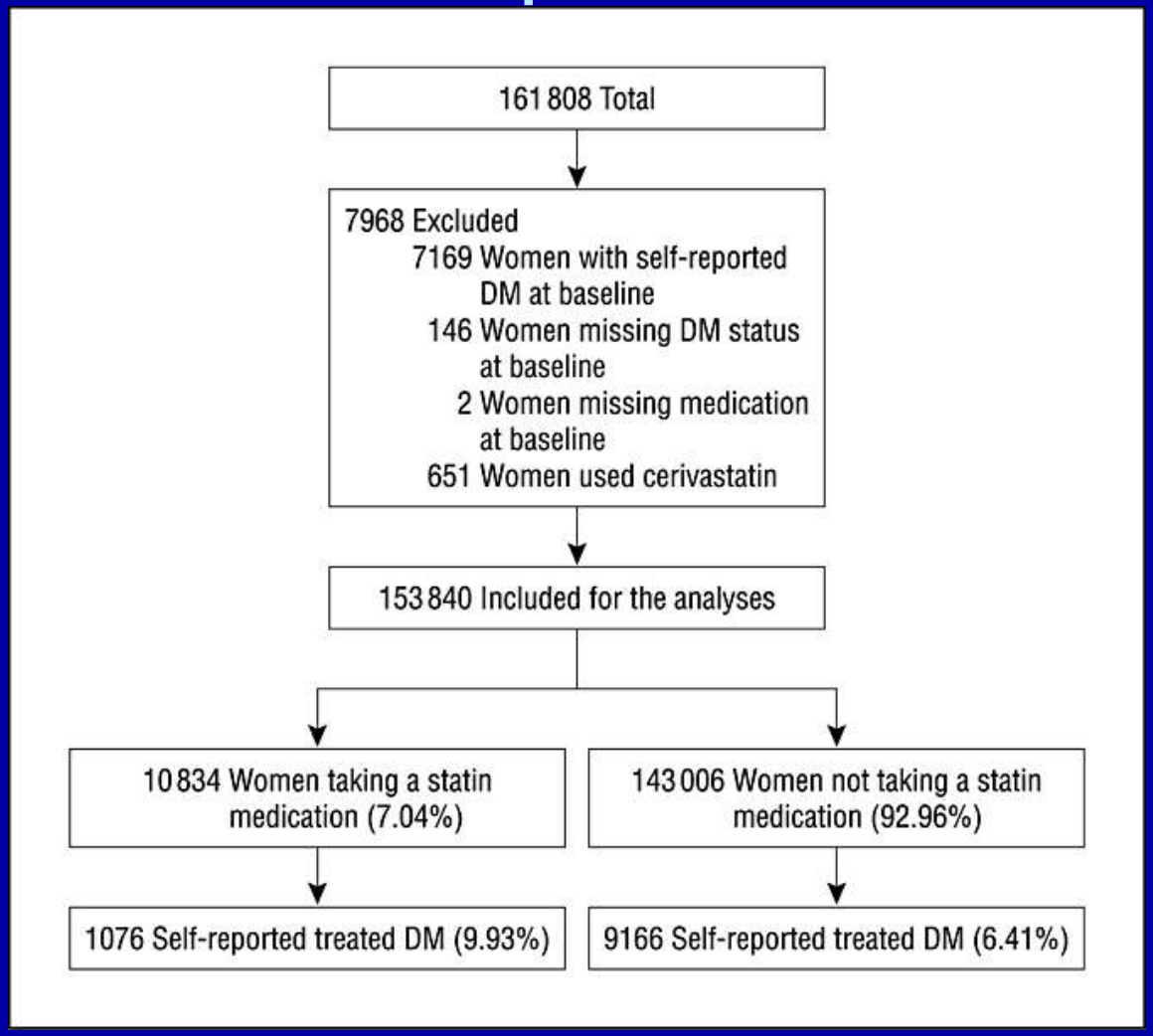
Source	BMI, Mean (SD)[a]	Age, Mean (SD), y	HDL, Mean (SD), mg/dL	LDL, Mean (SD), mg/dL	LDL Reduction, Relative %[b]	ln Triglycerides, Mean (SD), mg/dL	FPG, Mean (SD), mg/dL	FPG Measured After Baseline
Cannon et al (PROVE IT–TIMI 22),[18] 2004	29 (5)	58 (11)	39 (12)	109 (31)	22	5.05 (0.44)	104 (11)[c]	Not specified[c]
de Lemos et al (A to Z),[17] 2004	NA	60 (11)	39 (12)	113 (27)	15	5.00 (0.39)	NA	NA
LaRosa et al (TNT),[15] 2005[d]	28 (4)	61 (9)	47 (12)	98 (20)	22	4.89 (0.42)	97 (11)	Annually
Pedersen et al (IDEAL),[16] 2005[d]	27 (4)	62 (10)	47 (12)	125 (35)	16	4.87 (0.44)	99 (11)	Final visit
Armitage et al (SEARCH),[5] 2010	28 (4)	64 (9)	43 (16)[e]	98 (23)[e]	12	4.97 (0.54)[e]	NA	NA

Abbreviations: A to Z, Aggrastat to Zocor trial; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering study; LDL, low-density lipoprotein cholesterol; NA, not available; PROVE IT–TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction study; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT, Treating to New Targets study.
SI conversion factors: To convert HDL and LDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Calculated as [LDL(intensive-dose group)–LDL(moderate-dose group)]/LDL(baseline).
[c] For baseline FPG level, there were 315 results from the PROVE IT–TIMI 22 participants, which were similarly distributed between treatment groups.
[d] Excluded patients with known diabetes, FPG level of 126 mg/dL or greater, or both at baseline.
[e] Nonfasting.

Unclear whether statin rx is associated with a tendency for an increase in DM or whether these individuals are just at higher risk.

Preiss, D. et al. JAMA 2011;305:2556-2564

Statins Associated with New Onset DM in Post-menopausal Women



Culver, A. L. et al. Arch Intern Med 1/2012; 0:archinternmed.2011.625v2-9.

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Statins Associated with New Onset DM in Post-menopausal Women

Table 1. Characteristics of 153 840 Study Participants, Women's Health Initiative[a]

Variable	Total (N = 153 840)	Statin Users (n = 10 834)	Non–Statin Users (n = 143 006)	*P* Value
Age, y	63.17 (7.25)	65.66 (6.48)	62.98 (7.27)	<.001
BMI	27.77 (5.81)	28.56 (5.32)	27.70 (5.84)	<.001
Dietary variable				
Energy intake, kcal/d	1625.24 (711.56)	1541.81 (690.42)	1631.56 (712.75)	<.001
Carbohydrate, % of energy	50.34 (9.37)	52.12 (9.34)	50.21 (9.36)	<.001
Protein, % of energy	16.71 (3.21)	17.06 (3.31)	16.68 (3.20)	<.001
Fat, % of energy	32.53 (8.39)	30.79 (8.37)	32.66 (8.38)	.81
Saturated fat, % of energy	10.84 (3.33)	9.94 (3.15)	10.91 (3.34)	<.001
Trans fat, g/d	4.29 (3.22)	4.02 (3.08)	4.31 (3.23)	<.001
Fiber, g/d	15.88 (7.14)	15.63 (7.07)	15.90 (7.14)	.18
Alcohol intake, g/d	5.32 (10.58)	4.47 (9.44)	5.38 (10.65)	<.001
Physical activity				
Minutes of recreational physical activity per week[b]	183.40 (180.53)	177.50 (167.28)	183.86 (181.52)	<.001
Categorical variable, No. (%)				
Race/ethnicity				
Asian or Pacific Islander	3922 (2.56)	401 (3.71)	3521 (2.47)	<.001
African American	12 772 (8.32)	862 (7.97)	11 910 (8.35)	
Hispanic/Latino	5978 (3.90)	322 (2.98)	5656 (3.96)	
European American, not of Hispanic origin	128 458 (83.71)	9065 (83.87)	119 393 (83.69)	
Education				
<High school	7711 (5.05)	651 (6.05)	7060 (4.97)	<.001
High school/GED	25 955 (17.0)	2241 (20.83)	23 714 (16.71)	
>High school, <4 y college	57 740 (37.81)	4205 (39.08)	53 535 (37.72)	
≥4 y college	61 285 (40.14)	3663 (34.04)	57 622 (40.60)	
Smoking status				
Never	77 364 (50.94)	5178 (48.48)	72 186 (51.13)	<.001
Former	63 893 (42.07)	4858 (45.49)	59 035 (41.81)	
Current	10 605 (6.98)	644 (6.03)	9961 (7.06)	
Hormone therapy use				
Never	49 198 (32.94)	3654 (34.42)	45 544 (32.83)	<.001
Former	34 430 (23.05)	2633 (24.80)	31 797 (22.92)	
Current	65 720 (44.0)	4330 (40.78)	61 390 (44.25)	
Family history of DM				
Yes	47 329 (30.93)	3653 (33.91)	43 676 (30.70)	<.001
No	98 686 (64.48)	6599 (61.26)	92 087 (64.73)	
Type of statin medication use at baseline				
Lovastatin	2957 (27.29)	2957 (27.29)	NA	NA
Simvastatin	3282 (30.29)	3282 (30.29)	NA	NA
Fluvastatin	1316 (12.15)	1316 (12.15)	NA	NA
Atorvastatin	839 (7.74)	839 (7.74)	NA	NA
Pravastatin	2440 (22.52)	2440 (22.52)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development; HR, hazard ratio; NA, not applicable.

[a] Data are continuous variables given as means (SDs) except where noted. Numbers and percentages may not add up to 153 840 and 100% owing to missing data.

[b] Geometric means (SDs) were presented.

Culver, A. L. et al. Arch Intern Med 1/2012; 0:archinternmed.2011.625v2-9.

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Bale Doneen METHOD

Significant Differences ($p<0.001$) in the Two Groups

- Age – statin - older
- BMI – statin - higher
- % caloric intake from carbo.– statin –higher
- Alcohol intake – statin – lower
- Physical activity – statin – lower
- % Asian & Pacific Islander – statin – higher
- % never smoked – statin – lower
- Fam hx of DM - statin - higher

Culver, A. L. et al. Arch Intern Med 1/2012; 0: archinternmed.2011.625v2-9.

Statins Associated with New Onset DM in Post-menopausal Women

- Compared 10,834 women taking statins to 143,006 women not taking statins
- Huge fallacy with this study: two significantly different groups of women
- To prove validity, would need to take the 10,834 ‘selected’ for statin therapy and give half of them a statin for three years and the other half placebo for three years!!

Culver, A. L. et al. Arch Intern Med 1/2012; 0:archinternmed.2011.625v2-9.

Association Between Diabetes Mellitus (DM) Risk and Statin Use Status at Baseline in 153 840 Participants

Table 2. Association Between Diabetes Mellitus (DM) Risk and Statin Use Status at Baseline in 153 840 Participants

Variable	Patients, No.	Cases of New-Onset DM	Unadjusted HR	Age- and Race/Ethnicity-Adjusted HR[a]	Multivariate-Adjusted HR[b]
Taking statin medications at baseline					
Yes	10 834	1076 (9.93)	1.71 (1.61-1.83)	1.69 (1.58-1.80)	1.48 (1.38-1.59)
No	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Years of statin medication use					
<1.0	3614	360 (9.96)	1.74 (1.57-1.94)	1.71 (1.54-1.90)	1.46 (1.30-1.64)
1.0-2.9	3650	365 (10.00)	1.72 (1.55-1.91)	1.67 (1.51-1.86)	1.42 (1.26-1.59)
≥3.0	3570	351 (9.83)	1.68 (1.51-1.87)	1.68 (1.51-1.87)	1.57 (1.40-1.77)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Type of statin medications at baseline					
Lovastatin					
Yes	2949	281 (9.53)	1.52 (1.35-1.71)	1.51 (1.33-1.70)	1.35 (1.19-1.55)
Other statins	7885	795 (10.08)	1.85 (1.72-1.99)	1.82 (1.69-1.97)	1.56 (1.43-1.69)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Simvastatin					
Yes	3247	310 (9.55)	1.71 (1.52-1.92)	1.72 (1.53-1.93)	1.41 (1.25-1.61)
Other statins	7587	766 (10.10)	1.77 (1.64-1.91)	1.73 (1.61-1.87)	1.54 (1.41-1.67)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Fluvastatin					
Yes	1313	145 (11.04)	1.99 (1.69-2.35)	1.90 (1.61-2.24)	1.61 (1.35-1.92)
Other statins	9521	931 (9.78)	1.72 (1.60-1.84)	1.71 (1.59-1.83)	1.48 (1.37-1.60)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Atorvastatin					
Yes	839	79 (9.42)	1.99 (1.58-2.49)	1.99 (1.58-2.49)	1.61 (1.26-2.06)
Other statins	9995	997 (9.97)	1.74 (1.63-1.86)	1.72 (1.61-1.84)	1.49 (1.39-1.61)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Pravastatin					
Yes	2423	256 (10.57)	1.87 (1.65-2.13)	1.83 (1.61-2.07)	1.63 (1.43-1.87)
Other statins	8411	820 (9.75)	1.71 (1.59-1.84)	1.70 (1.58-1.83)	1.46 (1.34-1.58)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]
Potency of statin at baseline					
Low potency: lovastatin, fluvastatin and pravastatin	6701	682 (10.18)	1.68 (1.56-1.82)	1.64 (1.52-1.78)	1.48 (1.36-1.61)
High-potency: simvastatin and atorvastatin	4133	394 (9.53)	1.74 (1.58-1.93)	1.75 (1.58-1.93)	1.45 (1.36-1.61)
Nonuser	143 006	9166 (6.41)	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: HR, hazard ratio; PH, proportional hazards.
[a]The HRs were estimated from Cox PH models adjusting for age and race/ethnicity.
[b]The HRs were estimated from Cox PH models, adjusting for age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of DM, hormone therapy use, study arms, and self-report of cardiovascular disease at baseline.

Another challenge with this data:

- Length of time on statin
- Which statin
- Dose of statin

Made no difference in incidence of diabetes.

Culver, A. L. et al. Arch Intern Med 1/2012; 0:archinternmed.2011.625v2-9.

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BD Response to FDA statement on Statins and liver function

- NASH: Individuals on statin therapy have been shown to have a marked improvement in NASH – Athyros, V. et al., Lancet 2010;376:1916-1922. "Statins can reduce CV Morbidity and improve liver function in patients with abnormal liver tests potentially secondary to NASH".

- CYT P450 3A4 pathway may interacts with many medications.
- Most people treated for atherosclerosis are on multiple medications.
- **Bottom Line: Measure the Liver Function!!!**

Can CV Prevention help preserve our memory?

Microvascular dementia

Examining the pathology of microvascular dementia

Are vascular dementia and Alzheimer's disease the same?

Can treatment of vascular disease prevent memory loss by improving microvascular blood flow?

Cerebrovascular disease (CVD) and dementia

CVD is a major contributor to later-life dementia, accounting for up to 20% of cases of dementia. Atherosclerotic and arteriolosclerotic mechanisms account for most of the burden of disease. Cerebrovascular disease may take several forms.

Macrovascular disease in the form of large vessel and larger arteriole infarcts produce a wide spectrum of clinical syndromes. Single strategic infarctions, multiple bilateral infarctions and multiple lacunar infarctions can lead to cognitive dysfunction that spans a large range of both severity and type of cognitive deficits.

Microvascular which is not evident radiographically, often coexists with macrovascular disease and also with Alzheimer's disease. Amyloid angiopathy is relevant in cognitive disorders in the elderly and causes microhaemorrhages and large haemorrhages.

D S Knopman, Department of Neurology, Mayo Clinic 2007

Microvascular responses to CV risk factors

D. Neil Granger et al. Department of Molecular & Cellular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA 71130-3932

NIH: Granger, et al. Microcirculation. 2010 April ; 17(3): 192–205.

CVD risk factors are well known to enhance the development of atherosclerotic lesions in large arteries, there is evidence that the structure and function of microscopic blood vessels can be profoundly altered by these conditions.

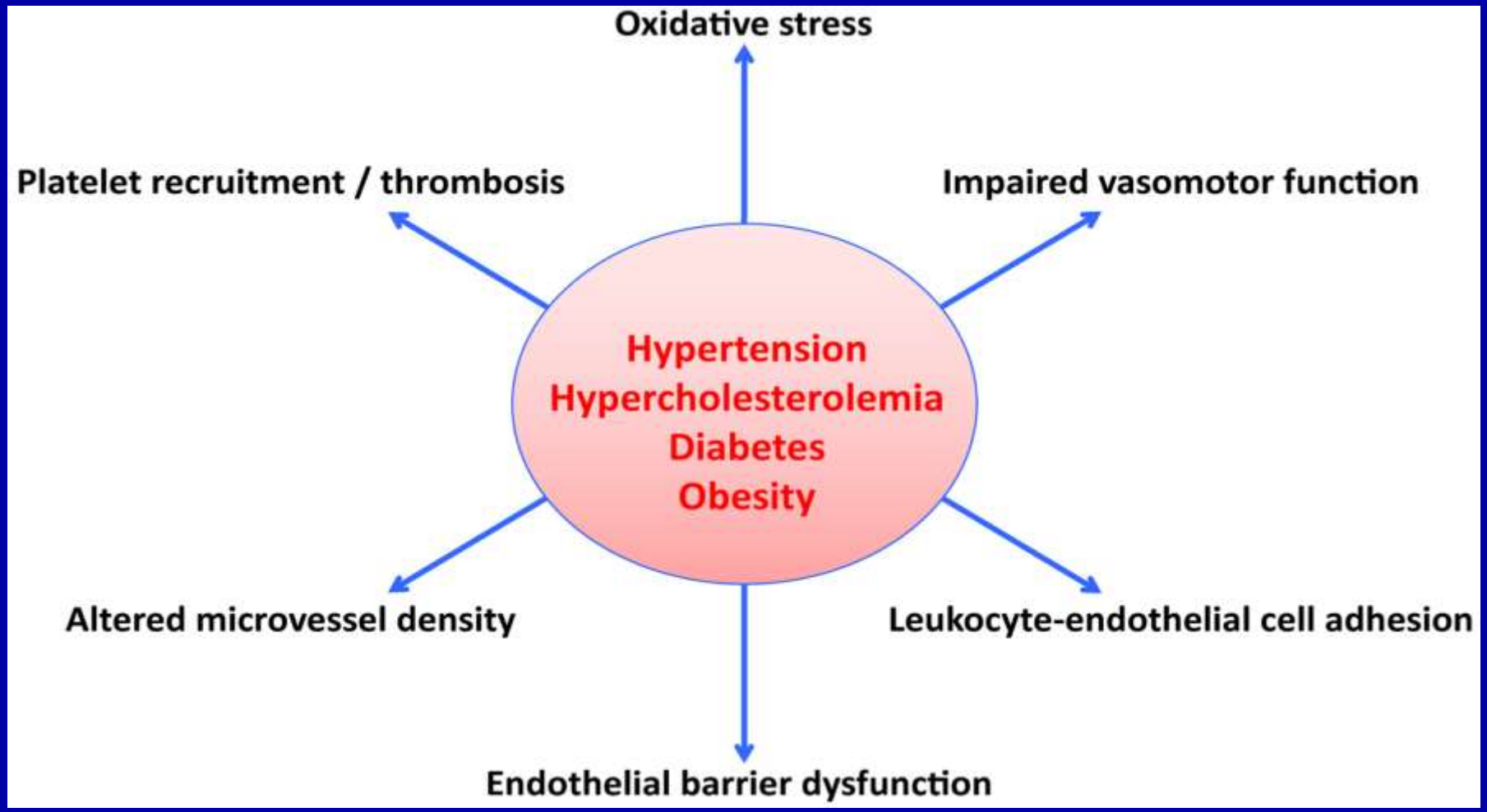
- The diverse responses of the microvasculature to CVD risk factors include oxidative stress, enhanced leukocyte- and platelet-endothelial cell adhesion, impaired endothelial barrier function, altered capillary proliferation, enhanced thrombosis, and vasomotor dysfunction.

- Emerging evidence indicates that a low-grade systemic inflammatory response that results from risk factor-induced cell activation and cell-cell interactions may underlie the phenotypic changes induced by risk factor exposure.

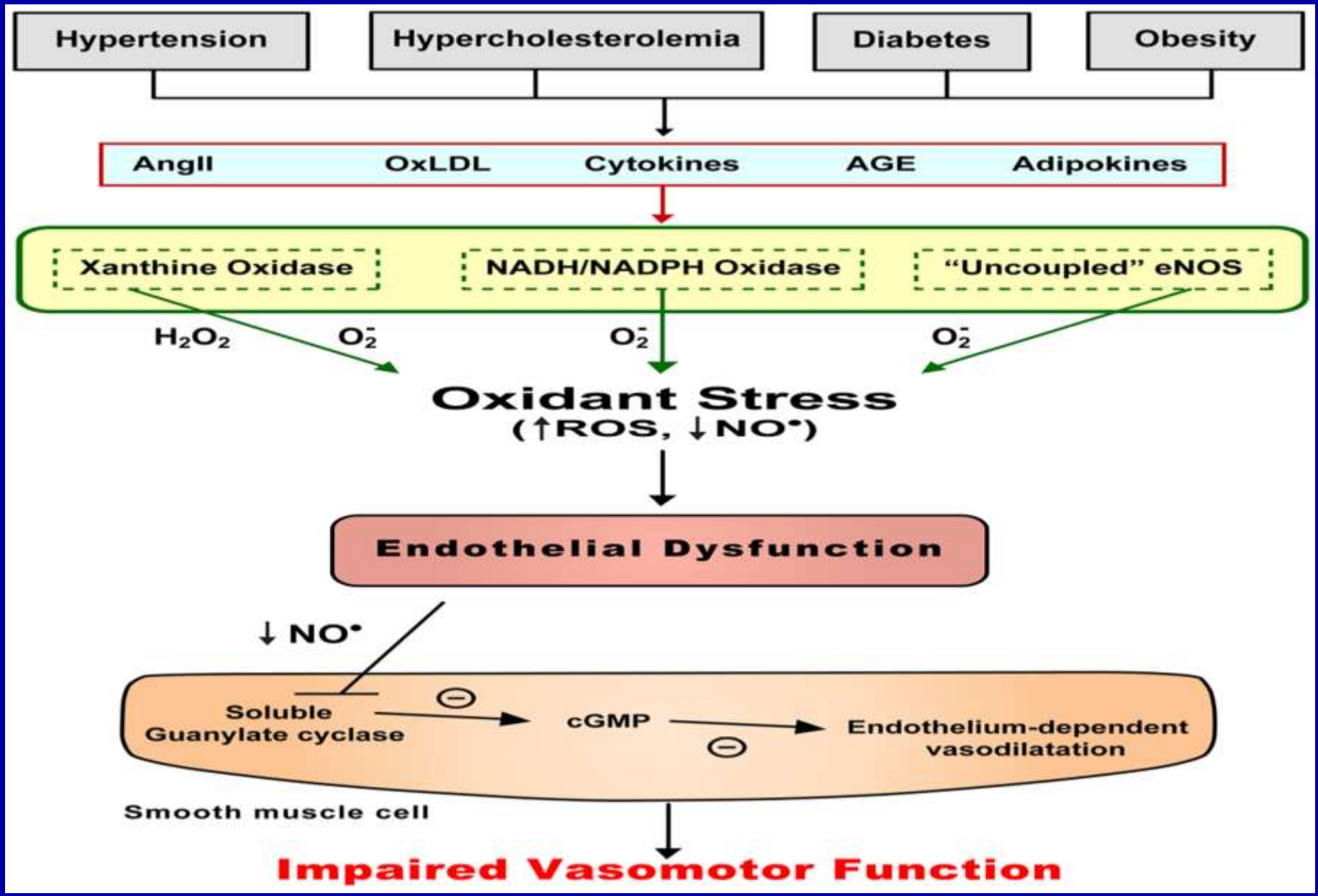
- Future efforts to develop therapies that prevent the harmful effects of risk factor-induced inflammation should focus on the microcirculation.

NIH: Granger, et al. Microcirculation. 2010 April ; 17(3): 192–205

Microvascular responses to cardiovascular risk factors.



Granger et al *Microcirculation*. available in PMC 2011 April 6.



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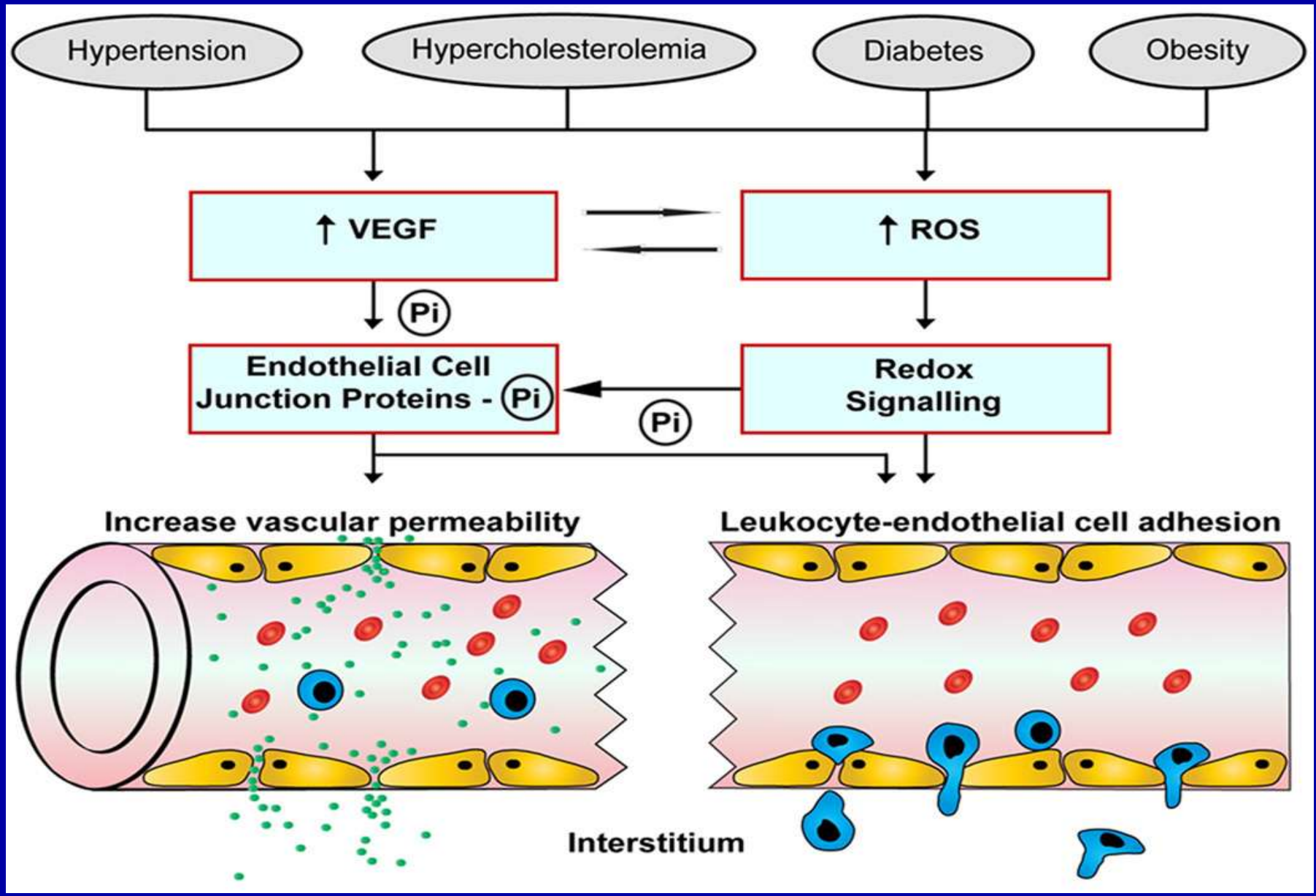

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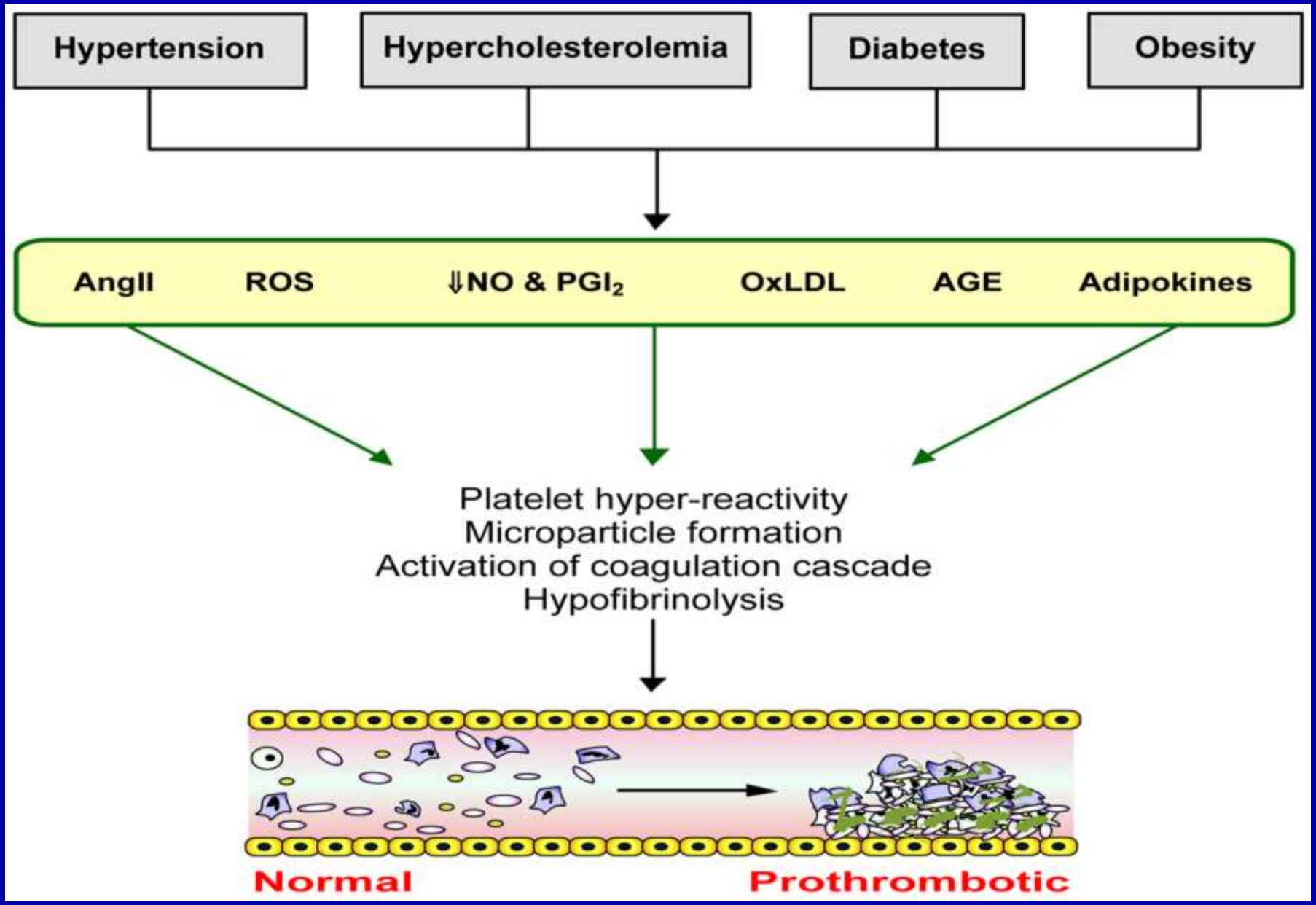
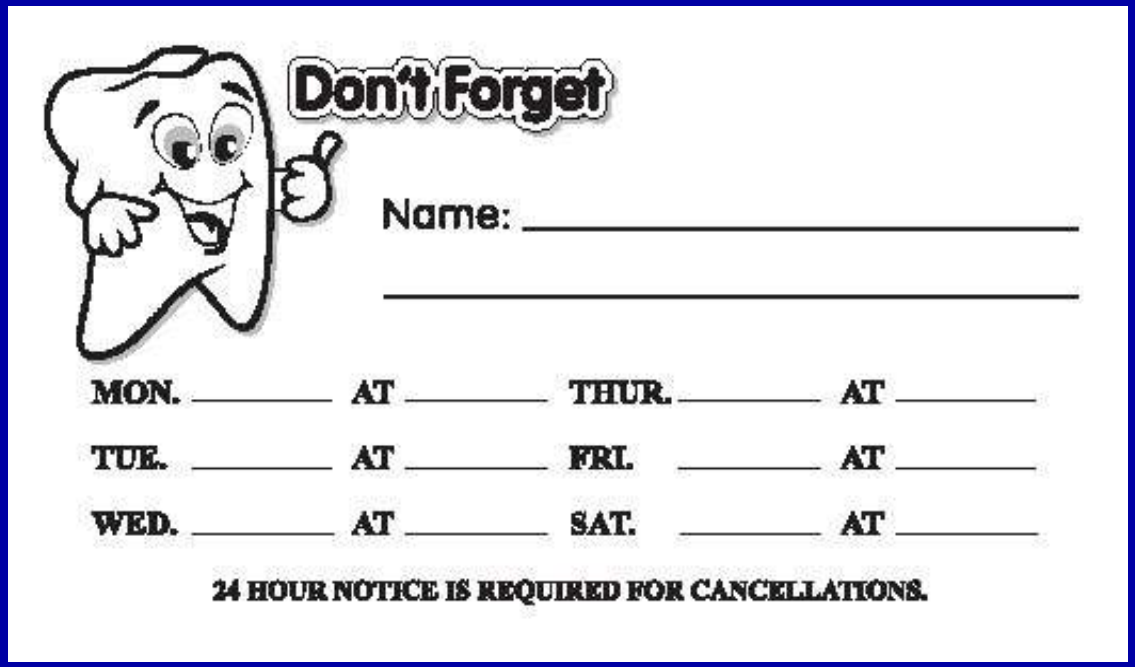


Granger et al *Microcirculation*. available in PMC 2011 April 6..

Alzheimers and periodontal disease

- Inflammation
- Spirochete



Inflammation as a potential mediator for the association between periodontal disease and Alzheimer's Disease

Amber Watts, Eileen Crimmins, Margaret Gatz. Neuropsychiatric Disease and Treatment 2008:4(5)865-876

Inflammation is the mediator

This model proposes possible links between oral infection and the pathology of Alzheimer Diesase.

Authors propose that they may contribute to, exacerbate, and share risk factors with AD

Pathogenic bacteria in the oral cavity can lead to periodontal infection. Individuals vary in susceptibility to infection, due to oral hygiene and particular genotypes (IL-1) that are more vulnerable to infection and have elevated inflammatory responses

Amber Watts et al Neuropsychiatric Disease and Treatment 2008:4(5)865-876

Bacteria and AD

- Bacteria becomes systemic via periodontal compromise
- Pathogens may cross the BBB and enter the brain – contribute to development of Alzheimer's by:
  - 1. Direct Effects of Pathogen Products
  - 2. Inflammatory response to the pathogens
  - 3. Effect the vascular integrity

Amber Watts et al Neuropsychiatric Disease and Treatment 2008:4(5)865-876

Another relationship between AD/brain function and PD

Quote from Dr. Tom Nabors….”Never trust a Spirochete!”

Alzheimer's disease – a neurospirochetosis

It is established that chronic spirochetal infection can cause slowly progressive dementia, brain atrophy and amyloid deposition in late neurosyphilis.

Recently, suggested that various type of spirochetes could cause dementia and be involved in pathogenesis of Alzheimer's disease (AD)

Reviewed all data in literature on detection of spirochetes in AD following established criteria of Koch and Hill.

Source: Judith Miklossy, Alzheimer's disease – a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria; Journal of Neuroinflammation, Aug., 2011, 8:90; doi:10.1186/1742-2094-8-90

Alzheimer's disease – a neurospirochetosis

- Results:
  - N=247
  - OR=20 (95% CI = 8-60)
- Recognizing all types of spirochetes detected in brains
  - >90% of AD cases

Source: Judith Miklossy, Alzheimer's disease – a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria; Journal of Neuroinflammation, Aug., 2011, 8:90; doi:10.1186/1742-2094-8-90

Alzheimer's disease – a neurospirochetosis

- *Borrelia burgdorferi:* Lyme Disease
  - 25.3% of AD cases analyzed
  - 13 times more frequent in AD compared to controls

Source: Judith Miklossy, Alzheimer's disease – a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria; Journal of Neuroinflammation, Aug., 2011, 8:90; doi:10.1186/1742-2094-8-90

Alzheimer's disease – a neurospirochetosis

- Periodontal pathogen Treponemas:
  - *T. denticola, T. pectinovorum, T. amylovorum, T. lecithinolyticum, T. maltophilum, T. medium, T. socranskii*
    - Revealed to be invasive *in vivo* and *in vitro*
  - At least one oral Treponema species was detected in 14 of 16 AD cases
  - Six different Treponema species detected in brain in one AD
  - Periodontal pathogen spirochetes in an identical way *to T. pallidum* have the ability to invade the brain, persist in the brain and cause dementia.

Source: Judith Miklossy, Alzheimer's disease – a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria; Journal of Neuroinflammation, Aug., 2011, 8:90; doi:10.1186/1742-2094-8-90

TZD's and Alzheimer's

TZD's provide Alzheimer's protection in diabetics??

- 142,328 DM subjects; mean age 66; followed 6 yrs.
- TZDs – 74,525; insulin – 67,803
- 3,191 new cases of Alzheimer's
- Relative risk reduction with TZD was a significant 19%
  remained significant after controlling for confounders

Donald Miller, Sc.D.; 10th International Conference on Alzheimer's Disease
Family Practice News; August 15, 2006:4

TZDs effect Alzheimer's risk in non-diabetics ?

- Randomized controlled trial; 30 non-diabetic probable Alzheimer's pts. on anti-dementia medication
- 15 received Actos 45mg; 15 – placebo; followed 18 mos.
- Trend toward better cognitive function- constructing a larger trial

Dr. Geldmacher, U. of Virginia; reported at 10th International Alzheimer's Conference
Family Practice News; August 15,2006:4

IR Increases Risk of Brain Dysfunction: possible explanation of why pioglitazone may reduce Alzheimer's risk

- 23 non-DM IR subjects; mean age 74; cerebral PET scanning
- Reduced glucose metabolism in frontal pariotemporal and cingulate regions (AD pattern)

Baker, L, Cross, D, ***Arch Neurol.*** 1/2011:68(1):51-71.

Pioglitazone and CAD regression

Pioglitazone Regressed CAD, Reduced Inflammation and Improved Endothelial Function in Pre-diabetics

- 30 pre-diabetic (2hr. -140-200 mg/dL) pts; 40-70% CAD lesions with thin caps and large necrotic core; randomized to 6 mos. pio 15mg/d or placebo; both got ‘standard’ rx

- CAD results via IVUS beneficial for pio:

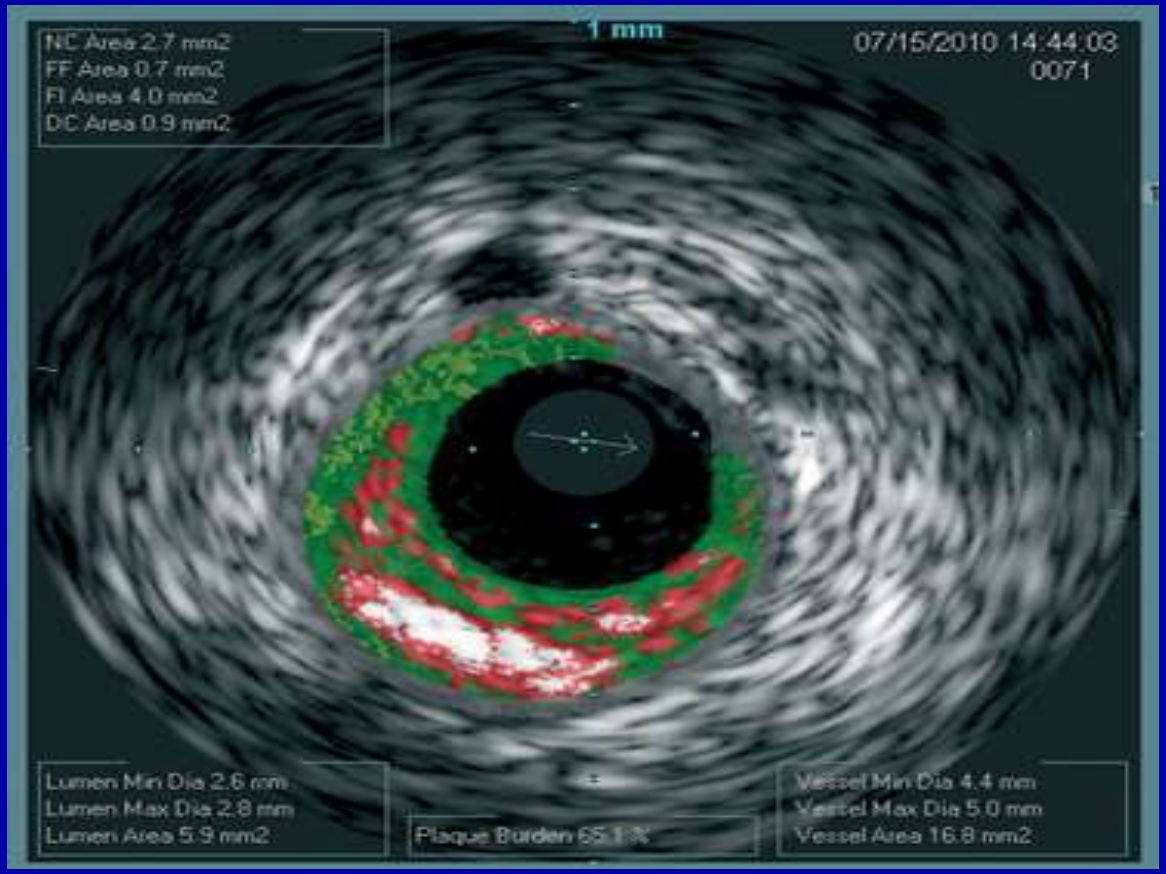
  plaque burden decreased 10.3% $p < 0.05$

  thin-cap fibroatheroma prevalence 11% vs. 22% $p < 0.05$

  necrotic core area 16.8% vs. 31.7% $p < 0.05$

Yang, H.-B., et. al. Diabet. Med. 3/1/2012. 29:359–365

Virtual Histology IVUS Utilized



White (dense calcium), **Red** (necrotic core),
Light green (fibro-fatty), **Dark green** (fibrotic tissue)

Yang, H.-B., et. al. Diabet. Med. 3/1/2012. 29:359–365

Pioglitazone Reduced Inflammation and Improved Endothelial Function in Pre-diabetics 6 months of therapy

	Pioglitazone group (n=15)		Control group (n=13)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
hsCRP mg/L	12.6 ± 9.1	3.8 ±2.9*^	13.2 ±8.9	4.7 ± 1.8*
Adiponectin mcg/ml	6.2 ± 0.9	13.5 ± 2.1*^	5.9 ± 0.8	6.1 ± 1.1
Endothelin-1 pg/ml	1.2 ± 0.1	0.7 ± 0.2*^	1.1 ± 0.1	1.0 ± 0.1
Data are means ± SD * p <0.05 vs baseline ^ p<0.05 vs. control				

Note: no significant lipid differences in two groups

Yang, H.-B., et. al. Diabet. Med. 3/1/2012. 29:359–365

Pioglitazone Regressed CAD, Reduced Inflammation and Improved Endothelial Function in Pre-diabetics in 6 months

- CAD regressed and stabilized with pio despite no significant lipid changes in two groups.
- Pio has now demonstrated this type of benefit in diabetics and pre-diabetics.
- Insulin resistant individuals are high risk for coronary events; pio appears to be a beneficial agent

Yang, H.-B., et. al. Diabet. Med. 3/1/2012. 29:359–365

Markers vs Players

A **Marker** is an indicator of risk but treating it does no good.

A **Player** is an indicator of risk and it also has an active role in the process of atheroscerosis.

Dale Doneen METHOD

Moss Freedman

New data on Lp-PLA2

Lp-PLA2 is manufactured in macrophages within the wall of the artery.

What is measured in the serum is a ‘surrogate’ marker for the amount of damaging enzyme within the wall.

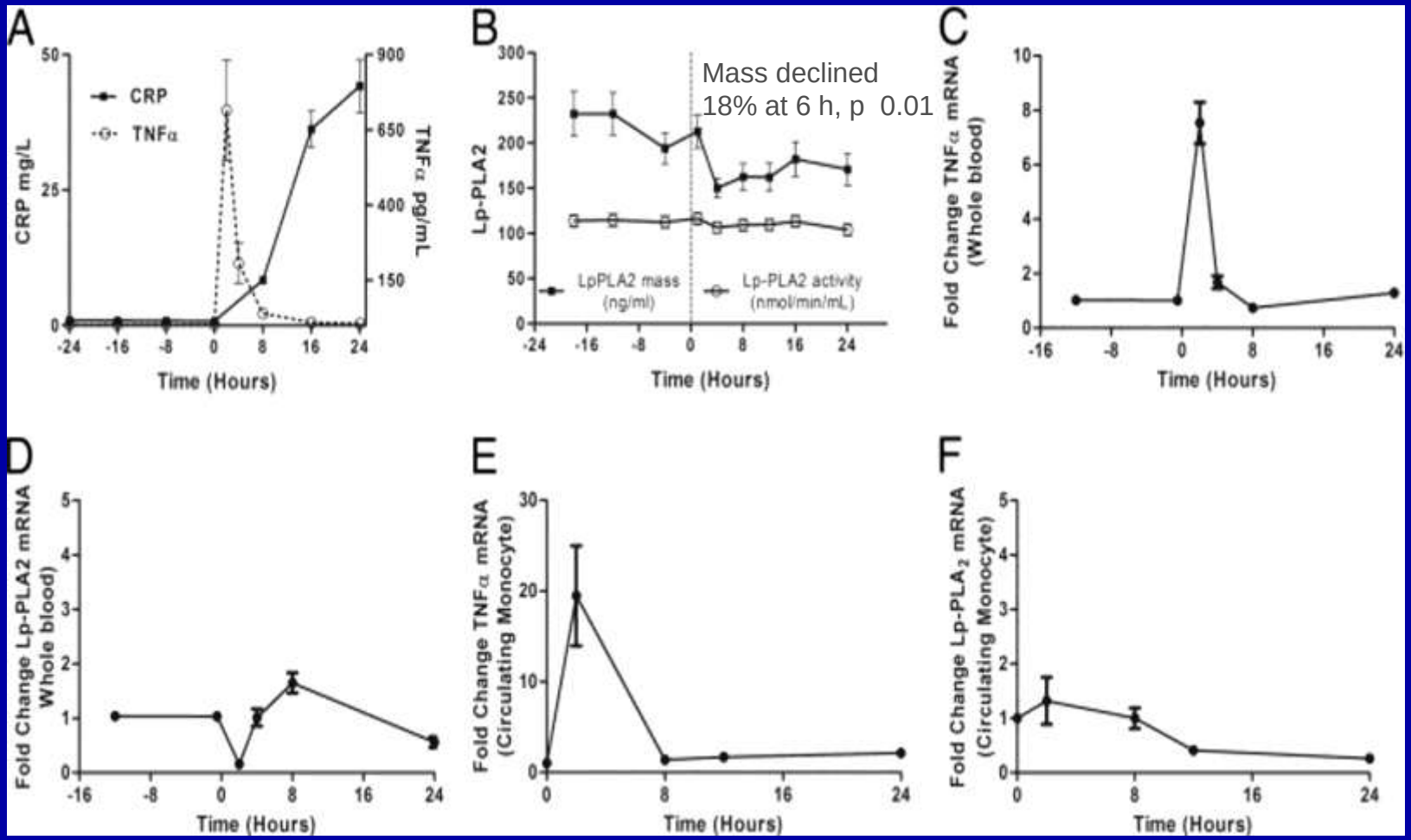
Implication: How good is a surrogate plasma?

Lp-PLA2 is not an Acute Phase Reactant as Opposed to CRP and TNF-alpha

- 32 healthy subjects; 50% female; mean age 26 ± 4 yrs.; infused with 3 ng/kg endotoxin; blood samples taken before and after infusion
- Endotoxin produced an acute febrile illness
- Resulted in an immediate transient rise in TNF-alpha and a 100 fold increase in CRP at 24 hours
- No significant change in Lp-PLA2

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Human Endotoxemia In Vivo Response: CRP, TNF alpha, Lp-PLA2



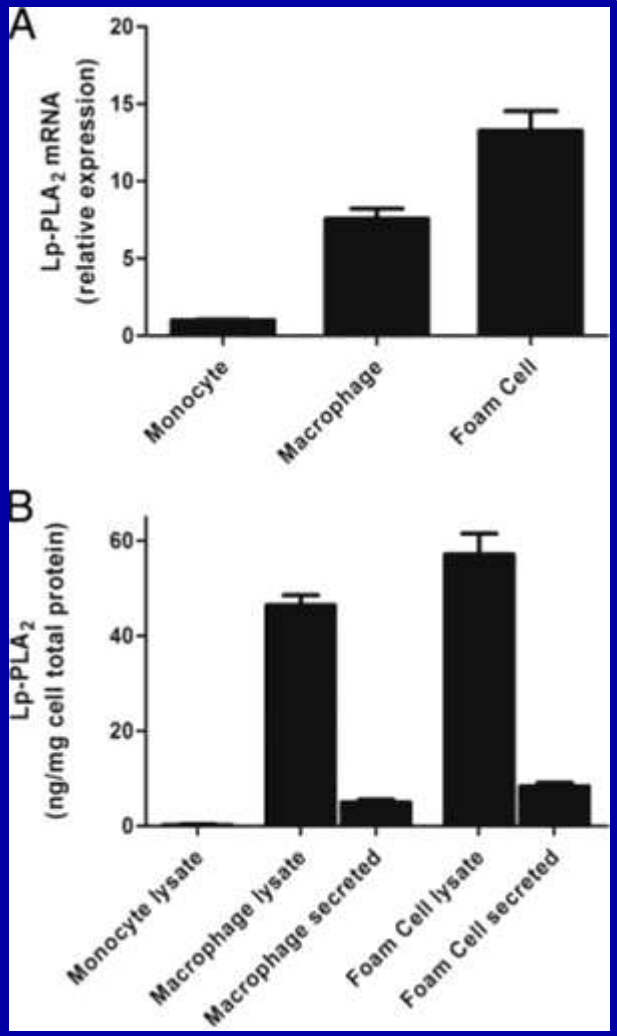
Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Lp-PLA2 Increases in ‘Foam Cells’ in Vitro

- Macrophages were exposed to acetylated LDL-cholesterol for 48 hrs to induce ‘foam cell’ production

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Lp-PLA2 Up-Regulated in Human Foamlike Cells In Vitro



The lack of in vivo increase in plasma or monocyte levels of Lp-PLA2 during acute inflammation coupled with this data suggests that, in human atherosclerosis, Lp-PLA2 may be generated by macrophages and foam cells rather than by circulating leukocytes

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

JACC
Journal of the American College of Cardiology

Genetics with Lp-PLA2 Signal It is Causal, but not due to Plasma Levels

- 2,061 European ancestry subjects without known CVD; all genotyped for *PLA2G7;* CACS via EBT; 1,581 with known plasma PLAC2 mass and activity

  SNP (rs1805017) had an association with Lp-PLA2 mass with p= 0.02

- Multiple *PLA2G7 SNPs had associations* with CAC-

  11 with p <0.05; lowest p <0.0001 for rs1421378
- Including plasma Lp-PLA2 mass or activity in the model did not attenuate the association

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Conclusions

- Lp-PLA2 does not contribute to acute phase response.
- The majority of Lp-PLA2 in atherosclerotic plaque is derived from local biosynthesis by inflammatory macrophage and foam cells
- Variants in *PLA2G7 are associated with CAC, but had* limited relation to plasma levels of Lp-PLA2 supporting an atherogenic role for *Lp-PLA2* independent of circulating Lp-PLA2 mass or activity.

Ferguson, J. F. et al. J Am Coll Cardiol 2/2012;59:764-772

Upcoming meetings

April 15:	Boston Marathon lecture!
May 18-19:	Seattle – BD CME
June 22-23:	AAOSH – Cleveland OH
Sept 8:	Diabetic Conference Reno, NV
Sept 14-15:	San Antonio – BD CME
Sept 20:	BD Reunion!!! Las Vegas
Sept 21-22:	CHL Symposium – Las Vegas
Nov 9-10:	Atlanta – BD CME

Open for discussion